Electrochemical Synthesis of Phthalides via Anodic Activation of Aromatic Carboxylic Acids.

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Supporting Information

Contents

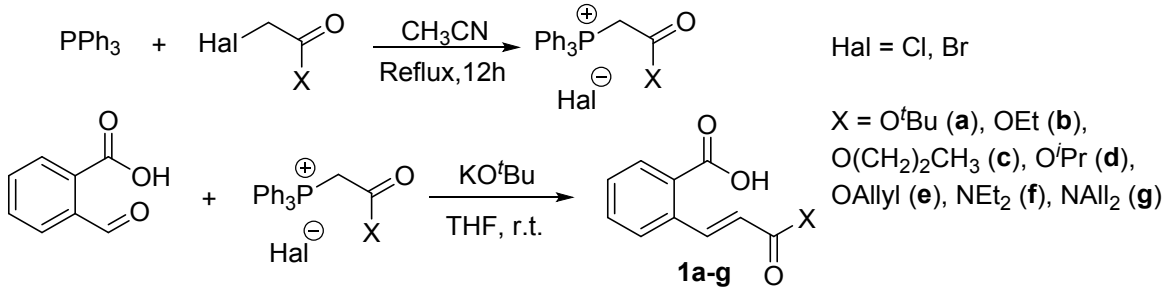
1. General information

- All reagents and solvents were purchased from Acros or Sigma-Aldrich and used directly as received without any further purification.
- Thin layer chromatography was performed on prepared thin layers precoated plates: Silicagel Merck 60 F_{254}. The visualisation of spots on TLC plates was effected by exposure to UV or by using basic $KMnO_4$ solution. Column chromatography was performed over ROCC Silica gel 60 (40 – 63μ mesh) using relevant eluent.
- JEOL JNM-ECX400 and ECA500 spectrometers were used for NMR measurements. Chloroform (δ = 7.24) was used as an internal standard for ^{1}H NMR and $CDCl_3$ (δ = 77.0) for ^{13}C NMR. Coupling constants are reported and expressed in Hz, splitting patterns are designated as br (broad), s (singlet), d (doublet), dd (double doublet), q (quartet), dt (double triplet), ddd (doublet of doublet of doublet), m (multiplet). Structures of known compounds were confirmed by comparison with data reported in literature.

- NMR Fourier transform, integration and pick picking were done with MestRenova software or ACD NMR software.
- Infrared spectra were recorded on Shimadzu FTIR-8400S spectrometer and the absorption bands are reported in reciprocal centimeters (cm-1).
- The mass spectra were recorded on a Finigan TSQ 7000 or Varian Matt 44S or Finnigan Exactive Orbitrap
- HPLC separations were performed with a reversed phase C18 LiChroCART® column (250 mm × 4 mm i.d.; particle size: 5 m) (Merck, Darmstadt, Germany), a HPLC Waters 2690 separation module (Waters, Milford, MA, USA) coupled to a UV spectrophotometric detector Kromaton (Angers, France); all controlled by Borwin software (Borwin, Rostock, Germany). The column was maintained at 30 ◦C.
- The electrochemical cells were purchased from the Institute of Creative Chemistry Japan. The 10ml cells were double jacketed and equipped with a stir bar and two 2.0 cm^2 platinum sheet electrodes separated apart by 5 mm.

2. Synthesis of starting materials

General procedure for synthesis of 2-(2-carboxyvinyl)-benzoic acid derivatives 1



Scheme S1

Phosphonium salts. To a solution of triphenylphosphine (10.2g, 42mmol, 1.15 eq.) in acetonitrile (100mL) ester or amide of halogenacetic acid (38mmol, 1eq.) was added and the mixture was refluxed for 12h. The solvent was evaporated under reduced pressure, to the residue THF (100mL) was added and sonicated for 30 minutes. The precipitate was filtered off, washed with THF and dried in vacuo to afford pure phosphonium salt in 60-96% yield.

2-(2-Carboxyvinyl)-benzoic acid derivatives 1. The appropriate phosphonium salt (20mmol, 1eq.) was suspended in THF and KO^{t}Bu (2.24g, 20mmol, 1eq.) was added portionwise and the mixture was stirred for 1 hour at ambient temperature. 2-Carboxybenzaldehyde (3.00g, 20mmol, 1eq.) was added and the mixture was stirred overnight. The solvent was removed under reduced pressure, the residue was dissolved in DCM (100mL), extracted with 10% K_2CO_3 (4x50mL), the combined aqueous phases were washed with DCM (4x50mL), and carefully acidified with 5% HCl

to pH 3. In case of precipitation the product was filtered off, washed with water and dried in vacuo. In case of oil formation the aqueous phase was extracted with DCM (3x50mL), the combined organic phases were washed with water, dried over Na_2SO_4, evaporated and dried in vacuo.

(E)-2-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)benzoic acid(1a). Yield 70%, white powder. **^{1}H NMR (500 MHz, $CDCl_3$)** δ = 8.48 (d, *J* =16.0Hz, 1H), 8.09 (dd, *J* =7.7, 1.4Hz, 1H), 7.63-7.62 (m, 1H), 7.58-7.55 (m, 1H), 7.47-7.44 (m, 1H), 6.27 (d, *J* =16.0Hz, 1H), 1.54 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ = 172.3, 166.2, 142.8, 137.4, 133.3, 131.7, 129.4, 128.7, 128.2, 123.3, 80.9, 28.3 ppm. **IR (neat, cm^{-1})** 1708, 1691, 1149, 762.**HRMS (ESI)**calcd for $C_{14}H_{16}O_4Na$ ($M+Na^+$) 271.09408, found: 271.09387

(E)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)benzoic acid (1b). E/Z = 85:15. Yield 76%. Although such a mixture is sufficient for lactonisation reaction, pure **E** isomer can be obtained after recrystallisation from hexane/ethyl acetate. White powder. **^{1}H NMR (500 MHz, $CDCl_3$)** δ = 8.55 (d, *J* =16.0Hz, 1H), 8.11 (d, *J* =7.4Hz, 1H), 7.62-7.57 (m, 2H), 7.49-7.45 (m, 1H), 6.33 (d, *J* =15.5Hz, 1H), 4.28 (q, *J* =7.3Hz, 2H), 1.34 (t, *J* =7.2Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ =172.1, 166.8, 143.9, 137.4, 133.4, 131.8, 129.6, 128.7, 128.3, 121.5, 60.8, 14.4 ppm. **IR (neat, cm^{-1})**1694, 1214, 748, 668.**HRMS(ESI)**calcd for $C_{12}H_{13}O_4$($M+H^+$) 221.08084, found: 221.08086

(E)-2-(3-oxo-3-propoxyprop-1-en-1-yl)benzoic acid (1c). Yield 65%,white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ = 8.55 (d, *J* =15.5Hz, 1H), 8.11 (d, *J* =7.4Hz, 1H), 7.64-7.58 (m, 2H), 7.49-7.46 (m, 1H), 6.34 (d, *J* =16.0Hz, 1H), 4.19 (t, *J* =6.6Hz, 2H), 1.74 (sxt, *J* =7.1Hz, 2H), 1.00 (t, *J* =7.4Hz, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ = 171.9, 166.9, 143.9, 137.4, 133.4, 131.8, 129.6, 128.6, 128.3, 121.5, 66.4, 22.2, 10.6 ppm. **IR (neat, cm^{-1})**1713, 1687, 1270, 1176, 762. **HRMS (ESI)**calcd for $C_{13}H_{15}O_4$($M+H^+$) 235.09649, found: 235.09645

(E)-2-(3-isopropoxy-3-oxoprop-1-en-1-yl)benzoic acid (1d). Yield 64%, white solid.**^{1}H NMR (500 MHz, $CDCl_3$)**δ = 8.53 (d, *J* =16.0Hz, 1H), 8.11-8.10 (m, 1H), 7.63-7.57 (m, 2H), 7.49-7.46 (m, 1H), 6.31 (d, *J* =16.0Hz, 1H), 5.15 (spt, *J* =6.3, 1H), 1.32 (d, *J* =6.3Hz, 6H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**δ = 171.9, 166.3, 143.6, 137.4, 133.3, 131.8, 129.5, 128.6, 128.3, 122.0, 68.2, 22.0 ppm. **IR (neat, cm^{-1})**1694, 1214, 1106, 750, 668.**HRMS (ESI)**calcd for $C_{13}H_{15}O_4$($M+H^+$) 235.09649, found: 235.09639

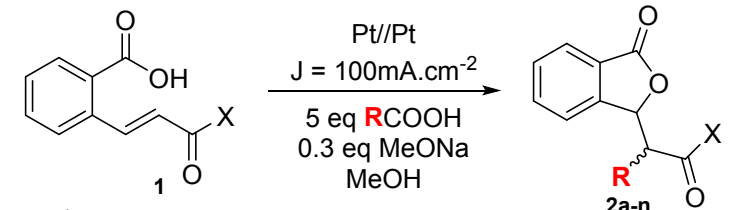
(E)-2-(3-(allyloxy)-3-oxoprop-1-en-1-yl)benzoic acid (1e). Yield 55%, white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ = 8.59 (d, *J* =16.0 Hz, 1H), 8.12 (d, *J* =7.4Hz, 1H), 7.64-7.59 (m,2H), 7.51-7.47 (m, 1H), 6.36 (d, *J* =16.0Hz, 1H), 6.00 (ddt, *J* =16.8, 11.0, 5.6Hz, 1H), 5.42-4.38 (m, 1H), 5.29-5.27 (m, 1H), 4.74 (d, *J* =5.7Hz, 2H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ = 172.2 ,166.4, 144.4, 137.3, 133.5, 132.3, 131.9, 129.7, 128.6, 128.3,121.1, 118.4, 65.4 ppm. **IR (neat, cm^{-1})** 1715, 1274, 1175, 764. **HRMS(ESI)**calcd for $C_{13}H_{13}O_4$($M+H^+$) 233.08084, found: 233.08083

(E)-2-(3-(diethylamino)-3-oxoprop-1-en-1-yl)benzoic acid (1f). Yield 87%, white powder. **^{1}H NMR (500 MHz, $CDCl_3$)** δ = 8.63 (d, *J* =15.5Hz, 1H), 7.99 (dd, *J* =8.0, 1.1Hz, 1H), 7.58-7.56 (m, 1H), 7.49-7.46 (m, 1H), 7.40-7.37 (m, 1H), 6.71 (d, *J* =15.5Hz, 1H), 3.54-3.51 (m, 4H), 1.28-1.23 (m, 6H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ =169.3, 166.8, 143.1, 137.1, 131.9, 131.2, 131.2, 129.0, 127.6, 119.6, 42.8, 41.6, 15.0, 13.2 ppm. **IR (neat, cm^{-1})** 2976, 2932, 1710, 1640, 1571, 1486, 1449, 1246, 1139, 1074, 966, 756. **HRMS (ESI)**calcd for $C_{14}H_{18}O_3N(M+H^+)$ 248.12812, found: 248.12812

(E)-2-(3-(diallylamino)-3-oxoprop-1-en-1-yl)benzoic acid (1g). Yield 84%, after recrystallisation from ethyl acetate white needles. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 8.62 (d, J = 15.6 Hz, 1H), 8.00 (dd, J = 7.8, 1.4 Hz, 1H) 7.54-7.52 (m, 1H), 7.48, (td, J = 7.4, 1.1 Hz, 1H), 7.41-7.37 (m, 1H), 6.65 (d, J = 15.6 Hz, 1H), 5.91-5.81 (m, 2H), 5.29-5.18 (m, 4H), 4.15 (d, J = 6.0 Hz, 2H), 4.05-4.04 (m, 2H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 169.5, 167.6, 143.4, 137.0, 133.1, 132.9, 132.1, 131.3, 130.9, 129.1, 127.6, 119.8, 118.1, 117.3, 49.4, 49.2 ppm**HRMS (ESI)**calcd for $C_{16}H_{18}O_3N(M+H^+)$ 272.128120, found: 272.12833

3. Electrochemical lactonisation reaction

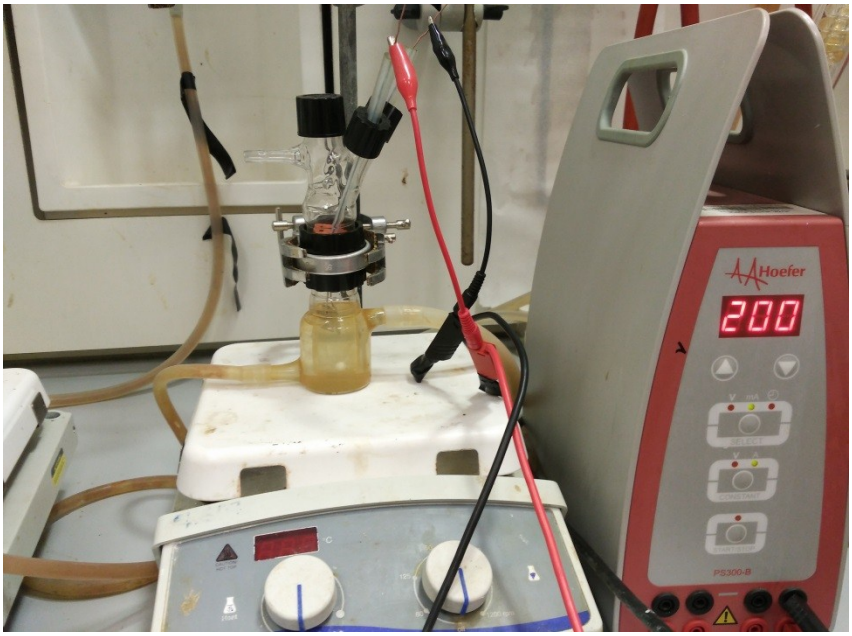
General procedure for electrochemical lactonisation reaction



X = O^{t}Bu (**a**), OEt (**b**), O^{n}Pr (**c**), O^{i}Pr (**d**), OAllyl (**e**), NEt_2 (**f**)

Scheme S2

Standard electrolysis procedure: A pre-cooled to 10°C 10mL undivided electrochemical cell, equipped with two platinum electrodes (2 cm^2 – separated from each other by 5 mm) was charged with a solution of 2-(2-carboxyvinyl)-benzoic acid derivative **1** (0.4mmol) in 10 mL of methanol and with an aliphatic carboxylic co-acid (2.0 mmol, 5 equivalents). Then, MeONa (0.12 mmol, 0.3 equivalent, 40 µL of 3M solution in MeOH) was added and the solution was electrolyzed at a constant current of 200 mA. The mixture was vigorously stirred and electrolysed until full consumption of starting material 1 as shown by TLC. Typically, 30-40 minutes (9.3-12.3 F/mol) was required for complete transformation. The solvent was then removed under reduced pressure and the residue was dissolved in DCM, washed with water, in the case of acetic acid, or with 10% K_2CO_3 for higher aliphatic acids. The organic solution was then dried with Na_2SO_4 and the solvent was removed under reduced pressure. The diastereoisomeric ratio was determined directly from the crude mixture by ^{1}H NMR analysis. The mixture was then purified over silica gel using column chromatography along with a petroleum ether/ethyl acetate mixture as the eluent in order to yield the pure lactones **2**.



Picture S1. Electrochemical setup with 10mL undivided cell, Pt 2 cm^2 electrodes and power source

2a. Following the general procedure from **1a** and acetic acid, yield 58%, dr = 1:1R_f = 0.13 (petroleum ether/EtOAc 9:1), colourless oil.**^{1}H NMR (500 MHz, $CDCl_3$)**δ = 7.88 (d, *J* =7.4 Hz, 1H), 7.55-7.51 (m, 1H), 7.67-7.63 (m, 1H), 7.48 (d, *J* =7.4Hz, 0.52H), 7.45 (d, *J* =8.0 Hz, 0.57H), 5.78-5.75 (m, 1H), 3.09 (qd, *J* =7.1, 4.6 Hz, 0.49H), 2.83-2.78 (m, 0.56H), 1.44 (s, 4.73H), 1.37 (s, 4.27H), 1.13 (d, *J* =6.9Hz, 1.59H), 1.06 (d, *J* =6.9Hz, 1.41H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)δ = 171.8, 171.3, 170.3, 170.4, 148.3, 147.6, 134.3, 134.1, 129.5, 129.4, 127.0, 126.5, 125.8, 125.7, 122.9, 122.3, 81.8, 81.7, 81.5, 81.4, 44.8, 43.8, 28.1, 28.0, 12.0, 11.6 ppm.**IR (neat, cm^{-1})**1765, 1726, 1154, 138.**HRMS (ESI)**calcd for $C_{15}H_{19}O_4$ ($M+H^+$) 263.12779, found: 263.12775

Gram scale synthesis of 2a: A pre-cooled to 10°C 50mL undivided electrochemical cell, equipped with two platinum electrodes (2 cm^2 – separated from each other by 5 mm) was charged with a solution of (*E*)-2-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)benzoic acid **(1a)** (8.0 mmol, 1.99g) and acetic acid (40 mmol, 2.4 g, 2.3 mL) in 46 mL of methanol. Then, MeONa (2.4 mmol, 0.3 equivalent, 0.8 mL of 3M solution in MeOH) was added and the mixture was vigorously stirred while being electrolyzed at a 200 mA constant current during 10 hours (9.3 F/mol of substrate). The solvent was removed under reduced pressure and the residue was dissolved in DCM. The solution was then washed with water, dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified over silica gel using column chromatography along with a petroleum ether/ethyl acetate 9:1 mixture as the eluent to afford 1.09g of pure **2a** as colorless oil with a yield of 52%.

2b. Following the general procedure from **1a** and propionic acid, yield 45%, dr = 1:1, R_f = 0.15, 0.20 (petroleum ether/EtOAc 9:1), colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$)** δ = 7.87 (d, J= 7.4 Hz, 1H), 7.66-7.62 (m, 1H), 7.53-7.44 (m, 2H), 5.63-5.61 (m, 1H), 2.78 (dt, *J* =9.7, 4.9 Hz, 0.46H), 2.53-1.49 (m, 0.53H), 1.92-1.62 (m, 2H), 1.43 (s, 4.72H), 1.25 (s, 4.08H), 0.98 (t, *J* =7.4 Hz) and 0.98 (t, *J* =7.4 Hz, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**δ = 171.6, 170.6, 170.3, 170.2, 148.6, 147.8, 134.2, 133.9, 129.5, 129.4, 126.9, 126.2, 125.8, 125.6, 122.9, 122.8, 81.9, 81.5, 80.8, 80.6, 52.7, 51.7, 28.1, 27.8, 22.5, 21.3, 12.0, 11.4 ppm. **IR (neat, cm^{-1})** 1765, 1723, 1153, 1157.**HRMS (ESI)**calcd for $C_{16}H_{21}O_4$ ($M+H^+$) 277.14344, found: 277.14341

2c. Following the general procedure from **1a** and isovaleric acid, yield 46%, dr = 1:1, R_f = 0.13, 0.18 (petroleum ether/EtOAc 20:1), white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ =7.90-7.88 (m, 1H), 7.67-7.63 (m, 1H), 7.55-7.44 (m, 2H), 5.60-5.58 (m, 1H), 2.98-2.94 (m, 0.48H), 2.70 (ddd, *J* =10.9, 7.2, 3.7 Hz, 0.52H), 1.85 (ddd, *J* =13.5, 10.6, 4.6 Hz, 0.55H), 1.75-1.59 (m, 2), 1.47-1.42 (m) and 1.42 (s) (5H), 1.35-1.28 (m, 1H), 1.25 (s, 4.28H), 0.91 (d, *J* =6.9 Hz) and 0.86 (d, *J* =6.3 Hz) (6H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**δ = 171.7, 170.8, 170.3, 170.2, 148.3, 147.7, 134.1, 133.9, 129.6, 129.5, 127.0, 126.4, 125.9, 125.7, 123.0, 122.7, 81.9, 81.6, 81.5, 81.0, 49.3, 48.2, 38.0, 36.8, 28.1, 27.8, 26.1, 23.6, 23.2, 21.9, 21.4 ppm. **IR (neat, cm^{-1})**1769, 1726, 1153.**HRMS (ESI)**calcd for $C_{18}H_{24}O_4Na$($M+Na^+$) 327.15668, found: 327.15656

2d. Following the general procedure from **1a** and 3,3-dimethylbutyric acid, yield 31%, dr = 1:1, R_f = 0.13(petroleum ether/EtOAc 20:1), white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ = 7.90 (d, *J* =4.6Hz) and 7.88 (d, *J* =4.6 Hz) (1H), 7.67-7.64 (m, 1H), 7.55-7.47 (m, 2H), 5.58 (d, *J* =5.7Hz, 0.52H), 5.56 (d, *J* =4.6 Hz, 0.47H), 3.00 (ddd, *J* =10.0, 4.3, 1.7 Hz, 0.48H), 2.82 (ddd, *J* =9.6, 5.6, 1.4 Hz, 0.51H), 1.96 (dd, *J* =14.3, 9.7 Hz, 0.52H), 1.85 (dd, *J* =14.3, 10.3 Hz, 0.49H), 1.39 (s, 4.53H), 1.26 (s, 4.52H), 0.89 (s, 4.45H), 0.85 (s, 4.59H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**δ = 171.9, 171.3, 170.2, 170.1, 147.8, 147.3, 133.9, 133.8, 129.6, 129.5, 127.1, 126.8, 125.8, 125.6, 123.1, 122.8, 82.4, 81.9, 81.8, 81.4, 47.2, 46.5, 40.7, 40.4, 30.7, 29.5, 29.4, 28.0, 27.7 ppm.**IR (neat, cm^{-1})**2955, 1766, 1727, 1467, 1367, 1286, 1146, 1061, 742. **HRMS (ESI)**calcd for $C_{19}H_{27}O_4$ ($M+H^+$) 319.19039, found: 319.19057

2m. Following the general procedure from **1a** and mono-methyl-hydrogen succinate, yield 55%, dr = 1:1, R_f = 0.15, 0.22 (petroleum ether/EtOAc 4:1), colourless oil, after column chromatography dr = 2.0:1**^{1}H NMR (500 MHz, $CDCl_3$)** δ = 7.90-7.88 (m, 1H), 7.68-7.64 (m, 1H), 7.55-7.46 (m, 2H), 5.70 (d, *J* =6.3Hz) and 5.65 (d, *J* =4.6 Hz) (1H), 3.66 (s) and 3.64 (s) (3H), 3.02-2.99 (m, 0.35H), 2.77 (ddd, *J* =10.0, 6.6, 4.0 Hz, 0.64H), 2.52-2.27 (m, 2H), 2.10-1.87 (m, 2H), 1.44 (s, 5.84H), 1.24 (s, 3.11H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**δ = 173.4, 173.2, 173.1, 170.8, 170.1, 170.0, 169.8, 148.0, 147.5, 134.3, 134.1, 129.7, 129.6, 126.8, 126.3, 125.9, 125.8, 122.8, 122.6, 82.4, 82.0, 81.0, 80.6, 51.9, 51.8, 49.5, 48.8, 31.6, 31.4, 28.1, 27.8, 23.2, 23.1 ppm. **IR (neat, cm^{-}**

1)2978, 1768, 1730, 1368, 1149, 1060, 742. **HRMS (ESI)**calcd for $C_{18}H_{23}O_6$ ($M+H^+$) 335.14891, found: 335.14898

2n. Following the general procedure from **1a** and 3-chloropropionic acid, yield 42%, dr = 1:1, R_f =0.12(petroleum ether/EtOAc 9:1), white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ =7.92-7.88 (m, 1H), 7.72-7.65 (m, 1H), 7.58-7.47 (m, 2H), 5.83(d, *J* = 5.0 Hz, 0.48H), 5.68 (d, *J* = 3.7Hz, 0.52H), .3.74-3.56 (m, 2H), 3.34-3.28 (m, 0.5H), 3.07-3.03 (m, 0.5H), 2.31-2.22 (m, 1H), 2.04-1.95 (m, 0.5H), 1.76-1.68 (m, 0.5H), 1.48 (s, 3.5H), 1.44 (s, 1.1H), 1.22 (s, 4.5H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 170.2, 169.7, 169.1, 168.1, 147.5, 147.3, 134.0, 129.7, 129.5, 126.6, 126.3, 125.8, 125.6, 122.6, 122.3, 82.5, 81.9, 80.8, 80.0, 47.0, 46.5, 42.6, 42.4, 30.6, 29.6, 28.0, 27.6 ppm.**HRMS (ESI)** calcd for $C_{12}H_{12}O_4{}^{35}Cl$($M+H^+$, deprotected COOH) 255.041863, found: 255.04175

2e. Following the general procedure from **1b** and acetic acid, yield 65%, dr = 1:1, R_f = 0.13 (petroleum ether/EtOAc 9:1), colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$)** δ = 7.91-7.89 (m, 1H), 7.69-7.64 (m, 1H), 7.56-7.53 (m, 1H) 7.48-7.42 (m, 1H), 5.86-5.84 (m, 1H), 4.25-4.17 (m, 2H), 3.21-3.16 (m, 0.5H), 3.92-3.87 (m, 0.5H), 1.28 (td, *J* =7.2, 1.1Hz, 1.5H), 1.25-1.22 (m, 1.5H), 1.15-1.14 (m, 1.5H), 1.06 (d, *J* =8.0Hz, 1.5H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ = 172.6, 172.4, 170.2, 148.1, 134.4, 134.1, 129.6, 129.6, 126.5, 126.0, 125.9, 123.0, 122.2, 81.2, 80.9, 61.4, 61.3, 44.1, 43.0, 14.3, 14.2, 11.6, 11.1 ppm. **IR (neat, cm^{-1})**1763, 1730, 1466, 1190, 1039, 743.**HRMS (ESI)** calcd for $C_{13}H_{15}O_4$ ($M+H^+$) 235.09649, found: 235.09645
The analytical data matches those reported in the literature: S. W. Youn, H. S. Song and J. H. Park, *Org. Biomol. Chem.,* **2014**, *12*, 2388–93.

2f. Following the general procedure from **1b** and propionic acid, yield 55%, dr = 1:1, R_f = 0.16 (petroleum ether/EtOAc 9:1), colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$)** δ = 7.87-7.86 (d, *J* =7.4Hz, 1H), 7.66-7.61 (m, 1H), 7.53-7.49 (m, 1.5H), 7.37 (d, *J* =6.9Hz, 0.5H), 5.68-5.65 (m, 1H), 4.21 (qd, *J* =7.3, 1.7Hz, 1H), 4.07 (q, *J* =6.9Hz, 1H), 2.87-2.84 (m, 0.5H), 2.59 (ddd, *J* =9.2, 8.0, 4.0Hz, 0.5H), 1.95-1.85 (m, 0.5H), 1.83-1.75 (m, 0.5H), 1.73-1.59 (m, 1H), 1.25 (t, *J* =7.2Hz, 1.6H), 1.11 (t, *J* =6.9Hz, 1.4H), 0.97-0.93 (m, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ = 172.3, 171.7, 170.1, 170.1, 148.3, 147.4, 134.3, 134.0 129.6, 126.8, 126.1, 125.9, 125.8, 123.0, 122.5, 80.6, 80.4, 61.1, 61.0, 52.0, 50.8, 22.2, 20.9, 14.3, 14.1, 12.0, 11.5 ppm. **IR (neat, cm^{-1})**1765, 1728, 1215, 908, 752. **HRMS (ESI)**calcd for $C_{14}H_{17}O_4$ ($M+H^+$) 249.11214, found: 249.11200
The analytical data matches those reported in the literature: S. W. Youn, H. S. Song and J. H. Park, *Org. Biomol. Chem.,* **2014**, *12*, 2388–93.

2g. Following the general procedure from **1b** and butyric acid, yield 52%, dr = 1:1, R_f = 0.19 (petroleum ether/EtOAc 9:1), colourless oil. **^{1}H NMR (500MHz, $CDCl_3$)** δ = 7.90 (d, *J* =7.4Hz, 1H) , 7.68-7.63 (m, 1H), 7.56-7.51 (m, 1.5H), 7.38 (d, *J* =8.0Hz, 0.5H), 5.69 (d, *J* =5.2Hz) + 5.67 (d, *J* =8.0Hz) (1H), 4.24-4.20 (m, 1H), 4.09 (q, *J* =6.9Hz, 1H), 2.97 (dt, *J* =9.9, 5.1 Hz, 0.5H),

2.68 (ddd, *J* =9.9, 7.9, 4.0Hz, 0.5H), 1.93-1.85 (m, 0.5H), 1.74-1.65 (m, 1H), 1.55-1.31 (m, 2.5H), 1.27 (t , *J* =7.2Hz, 1.5H) 1.15 (t, *J* =7.2H, 1.5H), 0.92-0.89 (m, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ = 172.5, 171.9, 170.1, 148.3, 147.4, 134.3, 134.0, 129.6, 129.6, 126.8, 126.2, 126.0, 125.8, 123.0, 122.5, 80.9, 80.6, 61.1, 61.0, 50.5, 49.1, 31.0, 29.5, 20.7, 20.4, 14.3, 14.2, 14.0, 13.9 ppm. **IR (neat, cm^{-1})**1765, 1730, 1215, 752. **HRMS (ESI)**calcd for $C_{15}H_{19}O_4$ ($M+H^+$) 263.12779, found: 263.12773

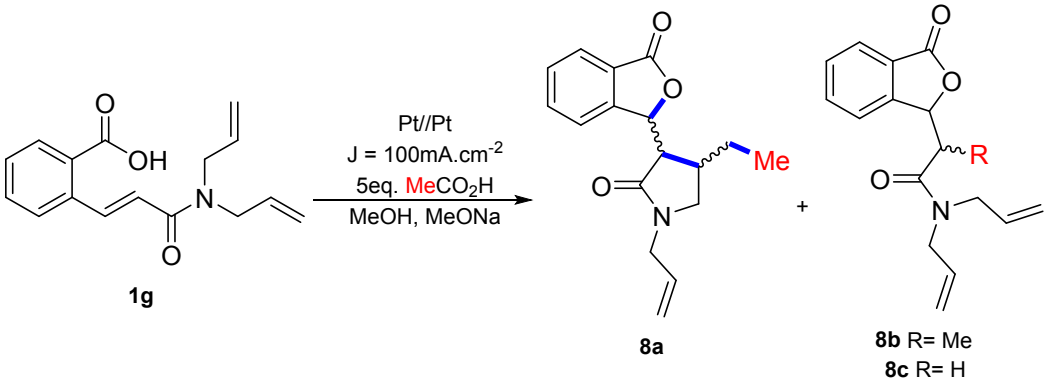
2h. Following the general procedure from **1c** and acetic acid, yield 42%, dr = 1:1, Rf = 0.10 (petroleum ether/EtOAc 9:1), colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$)** δ =7.90 (d, *J* =8.0 Hz, 1H), 7.69-7.64 (m, 1H), 7.56-7.52 (m, 1H), 7.47-7.41 (m, 1H), 5.86-5.84 (m, 1H), 4.13 (td, *J* =6.6, 1.1 Hz, 1H), 4.10-4.08 (m, 1H), 3.20 (qd, *J* =7.2, 4.9Hz, 0.5H), 2.93-2.87 (m, 0.5H), 1.71-1.59 (m, 2H), 1.14 (d, *J* =6.9 Hz, 1.5H), 1.05 (d, *J* =6.9 Hz, 1.5H), 0.93 (dt, *J* =14.5, 7.4 Hz, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ = 172.6, 172.4, 170.2, 148.0, 147.1, 134.4, 134.1, 129.6, 129.5, 126.9, 126.4, 125.9, 125.8, 123.0, 122.2, 81.2, 80.9, 67.0, 66.9, 44.1, 43.0, 22.0, 21.9, 11.6, 11.1, 10.5, 10.5 ppm.**IR (neat, cm^{-1})**2969, 1766, 1732, 1466, 1287, 1213, 1192, 1066, 1040, 744.**HRMS (ESI)**calcd for $C_{14}H_{17}O_4$ ($M+H^+$) 249.11214, found: 249.11204

2i. Following the general procedure from **1d** and acetic acid, yield 54%, dr = 1:1, R_f = 0.12 (petroleum ether/EtOAc 9:1), colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$)** δ =7.88 (d, *J* =7.4 Hz, 1H), 7.67-7.62 (m, 1H), 7.54-7.51 (m, 1H), 7.47-7.42 (m, 1H), 5.81 (d, *J* =5.2Hz, 0.5H), 5.79 (d, *J* =4.6Hz, 0.5H), 5.10-5.04 (m, 0.5H, 5.03-4.97 (m, 0.5H), 3.13 (qd, *J* =7.3, 4.6 Hz, 0.5H), 2.85 (qd, *J* =7.2, 5.4 Hz, 0.5H), 1.25 (d, *J* =6.3 Hz, 1.5H), 1.21 (d, *J* =6.3Hz, 1.5H), 1.18 (d, *J* =5.7Hz, 1.5H), 1.15 (d, *J* =6.3Hz, 1.5H), 1.13 (d, *J* =6.9Hz, 1.5H), 1.06 (d, *J* =7.4Hz, 1.5H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ = 172.1, 171.7, 170.3, 170.2, 148.1, 147.3, 134.3, 134.1, 129.6, 129.5, 126.9, 126.5, 125.9, 125.8, 123.0, 122.2, 81.3, 81.1, 68.9, 68.8, 44.1, 43.2, 21.8, 21.7, 11.7, 11.4 ppm. **IR (neat, cm^{-1})**2982, 1766, 1728, 1466, 1287, 1213, 1107, 744.**HRMS (ESI)**calcd for $C_{14}H_{17}O_4$ ($M+H^+$) 249.11214, found: 249.11207

2j. Following the general procedure from **1e** and acetic acid, yield 43%, dr = 1:1, R_f = 0.11 (petroleum ether/EtOAc 9:1), colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$)** δ =7.90 (d, *J* =6.9 Hz, 1H), 7.69-7.63 (m, 1H), 7.56-7.52 (m, 1H), 7.47-7.41 (m, 1H), 5.95-5.83 (m, 2H), 5.36-5.23 (m, 2H), 4.67 (d, *J* =5.7Hz, 1H), 4.63 (dt, *J* =5.7, 1.4 Hz, 1H), 3.22 (qd, *J* =7.2, 4.9 Hz, 0.5H), 2.94 (qd, *J* =7.1, 5.2Hz, 0.5H), 1.14 (d, *J* =6.9Hz, 1.5H), 1.06 (d, *J* =7.4Hz, 1.5H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ = 172.2, 172.0, 170.1, 147.9, 147.0, 134.4, 134.2, 131.7, 131.6, 129.7, 129.6, 126.9, 126.4, 126.0, 125.9, 123.1, 122.2, 119.1, 119.0, 81.1, 80.8, 66.0, 65.9, 44.0, 43.0 ppm. **IR (neat, cm^{-1})**1766, 1735, 1466, 1287, 1190, 1041, 744.**HRMS (ESI)**calcd for $C_{14}H_{15}O_4$ ($M+H^+$) 247.09649, found: 247.09639

2k. Following the general procedure from **1f** and acetic acid, yield 33%, dr = 1:1, R_f = 0.18, 0.28 (petroleum ether/EtOAc 2:1), after column chromatography dr = 2.33:1, colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$)** δ = 7.88 (d, *J* =7.4Hz) and 7.85 (d, *J* =8.0Hz) (1H), 7.77 (d, *J* =7.4Hz, 0.3H), 7.66-7.63 (m, 0.3H), 4.58-7.47 (m, 2H), 7.43-7.41 (m, 0.7H), 5.73 (d, *J* =6.3Hz, 0.3H), 5.68 (d, *J* =9.7Hz, 0.7H), 3.51-3.43 (m, 1H), 3.41-3.28 (m, 1.8H), 3.20-3.12 (m, 0.7H), 3.08-3.01 (m, 1H), 2.64 (dq, *J* =9.7, 6.7Hz, 0.7H), 1.51 (d, *J* =6.9Hz, 2H), 1.19-1.10 (m, 5H), 0.83 (t, *J* =7.2Hz, 2H) ppm.**^{13}C NMR (125 MHz, $CDCl_3$)** δ = 172.3, 172.1, 170.5, 170.2, 149.0, 147.9, 134.1, 133.9, 129.5, 129.4, 126.9, 125.8, 125.7, 125.7, 124.6, 123.6, 83.3, 82.5, 42.8, 42.4, 42.1, 40.7, 40.6, 16.7, 14.9, 14.7, 13.2 ppm. **IR (neat, cm^{-1})**1763, 1630, 1465, 1285, 1215, 1061, 993, 757, 689.**HRMS (ESI)**calcd for $C_{15}H_{20}O_3N(M+H^+)$ 262.14377, found: 262.14387

2l. Following the general procedure from **1f** and propionic acid, yield 40%, dr = 1:1, R_f = 0.22, 0.29 (petroleum ether/EtOAc 2:1), after column chromatography dr = 1.43:1, colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$)** δ = 7.89 (d, J =7.4Hz) and 7.86 (d, *J* =8.0Hz) (1H), 7.72-7.71 (m, 0.6H), 7.67-7.64 (m, 0.6H), 7.59-7.48 (m, 1.6H), 7.40-7.39 (m, 0.4H), 5.66 (d, *J* =9.2Hz, 0.4H), 5.62 (d, *J* =6.9Hz, 0.6H), 3.66-3.53 (m, 1H), 3.40-3.30 (m, 2H), 3.26-3.18 (m, 1H), 3.02-2.91 (m, 1H), 2.63 (td, *J* =9.2, 4.6Hz, 0.4H), 2.15-2.01 (m, 0.9H), 1.80-1.71 (m, 0.6H), 1.61-1.53 (m, 0.6H), 1.21-1.14 (m, 5H), 0.99 (t, *J* =7.4Hz, 1.2H), 0.86 (t, *J* =7.4Hz, 1.8H), 0.70 (t, *J* =7.2Hz, 1.2H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ = 171.3, 171.0, 170.5, 170.1, 148.8, 147.9, 133.9, 133.8, 129.5, 129.4, 126.8, 125.8, 125.7, 124.4, 123.7, 82.6, 82.3, 48.9, 47.1, 42.5, 42.1, 41.1, 40.7, 24.9, 21.3, 14.9, 14.4, 13.2, 13.1, 11.5, 11.2 ppm. **IR (neat, cm^{-1})**1765, 1632, 1465, 1288, 1068. **HRMS (ESI)**calcd for $C_{16}H_{22}O_3N(M+H^+)$ 276.15943, found: 276.15961



Scheme S3

Double cyclization experiment. Following the general procedure from **1g** (0.40 mmol, 108.5 mg) and acetic acid (5eq.) after workup 113.0 mg of complex mixture of compounds was obtained The mixture was analysed by ^{1}H NMR (**Fig S-1**), TLC and HPLC (**Fig S-2**) and subsequently subjected to preparative HPLC. Three major fractions were isolated and analysed by NMR and HRMS.
The complexity of the crude mixture due to the presence of several diastereoisomers makes the identification and assignation of each NMR signals a complex task and that even in the enriched

fractions. Nevertheless, we are confident in the formation of the product **8a** (as a mixture of diastereoisomers) due to:

1) The presence of appropriate high resolution mass spectrum m/z ratios that correspond to **8a** as well as **8b**
2) The preseice of multiplets at 0.79 and 1.17 ppm that can be assigned to Me group of **8b** (it matches very well the signals for a similar Me group in **2k**)
3) The presence of a characteristic highly shielded triplet at 0.63 ppm (3H) that corresponds to the aliphatic ethyl fragment of **8a** as well as a doublet at 6.10 ppm (1H) that could be assigned to the benzylic proton of **8a**.

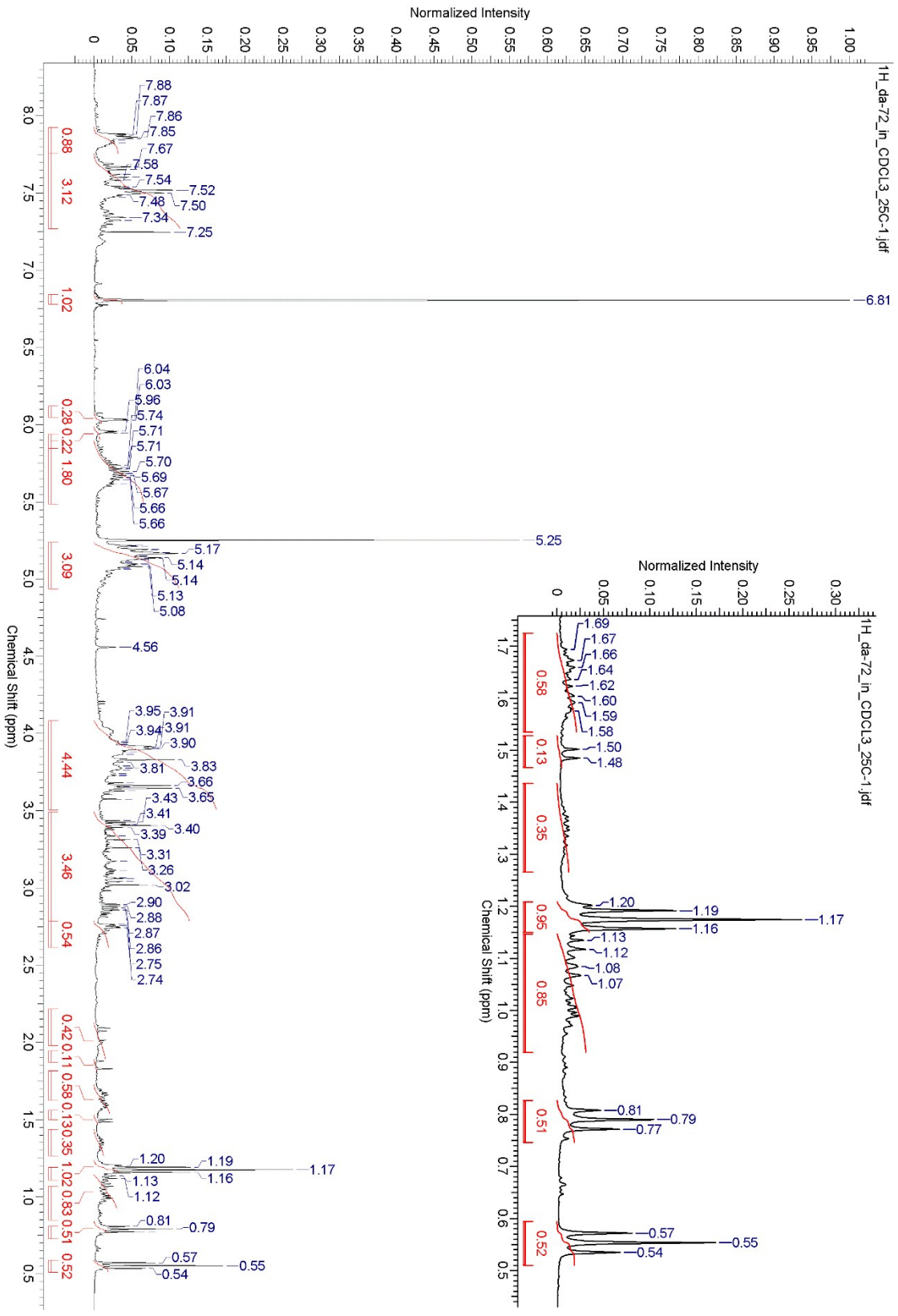
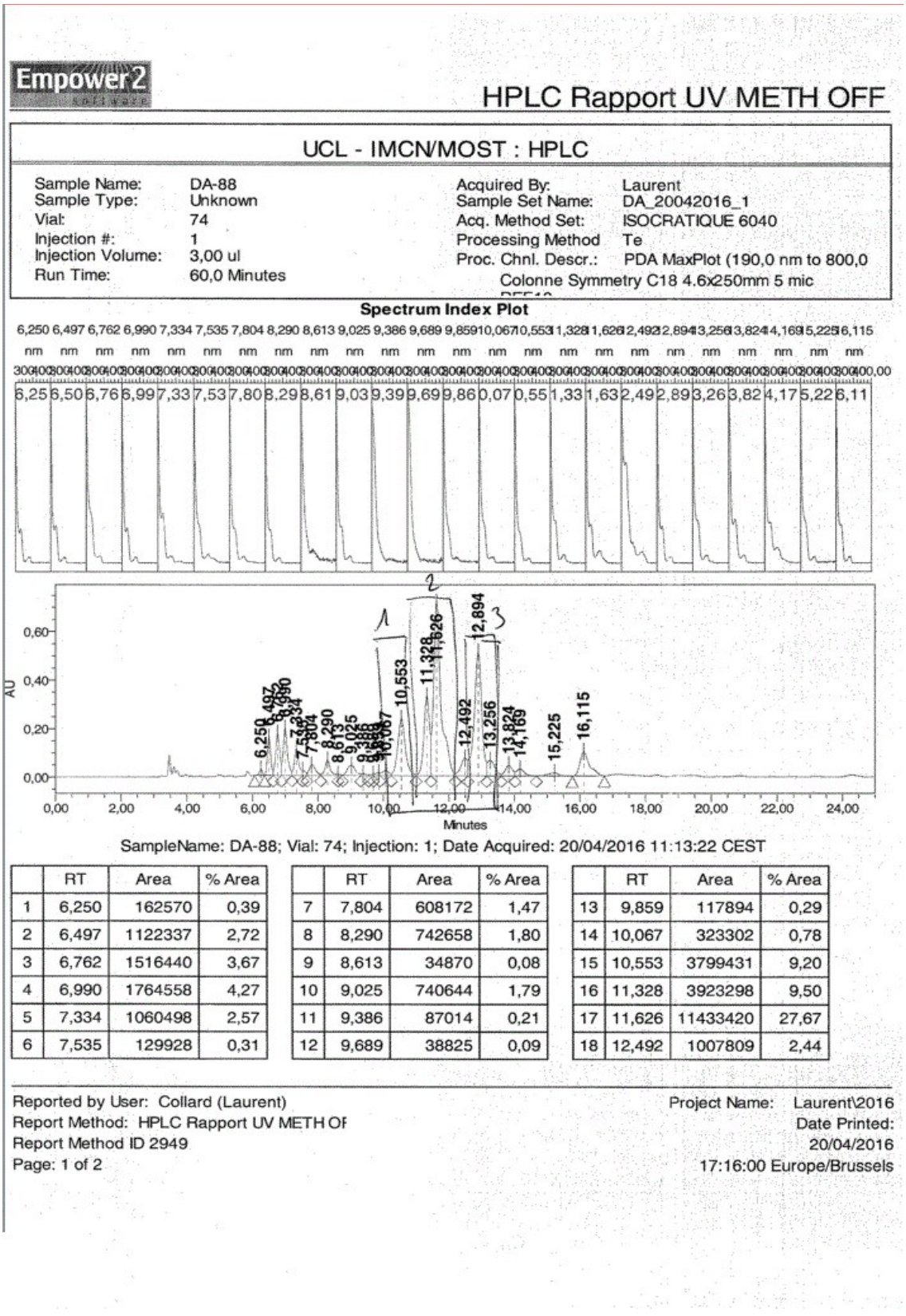


Fig S-1. ^{1}H NMR spectrum of the crude mixture from double cyclization experiment.

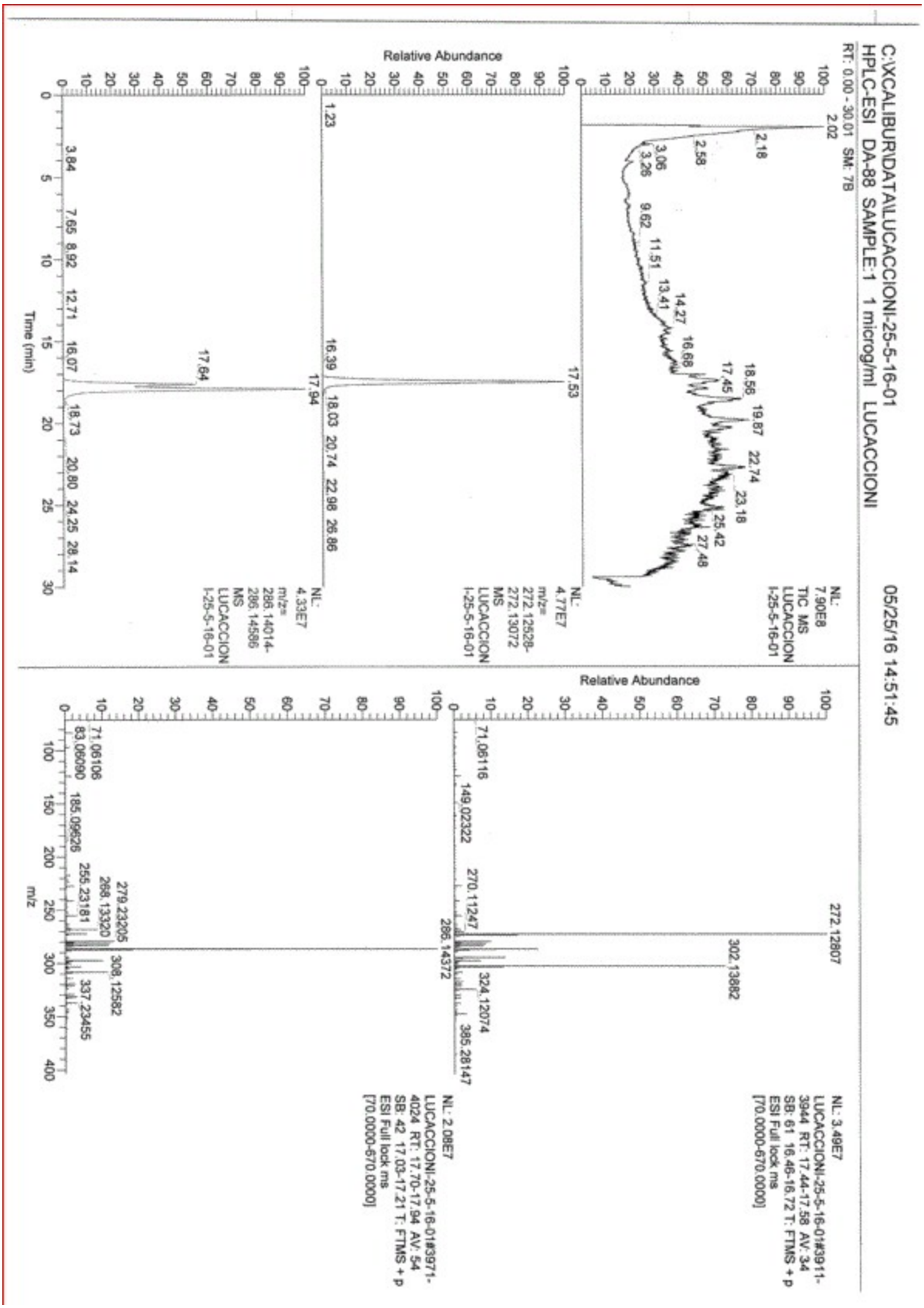


	RT	Area	% Area
1	6,250	162570	0,39
2	6,497	1122337	2,72
3	6,762	1516440	3,67
4	6,990	1764558	4,27
5	7,334	1060498	2,57
6	7,535	129928	0,31

	RT	Area	% Area
7	7,804	608172	1,47
8	8,290	742658	1,80
9	8,613	34870	0,08
10	9,025	740644	1,79
11	9,386	87014	0,21
12	9,689	38825	0,09

	RT	Area	% Area
13	9,859	117894	0,29
14	10,067	323302	0,78
15	10,553	3799431	9,20
16	11,328	3923298	9,50
17	11,626	11433420	27,67
18	12,492	1007809	2,44

Fig S-2. HPLC analysis of the crude mixture from double cyclization experiment.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05/25/16 14:51:45
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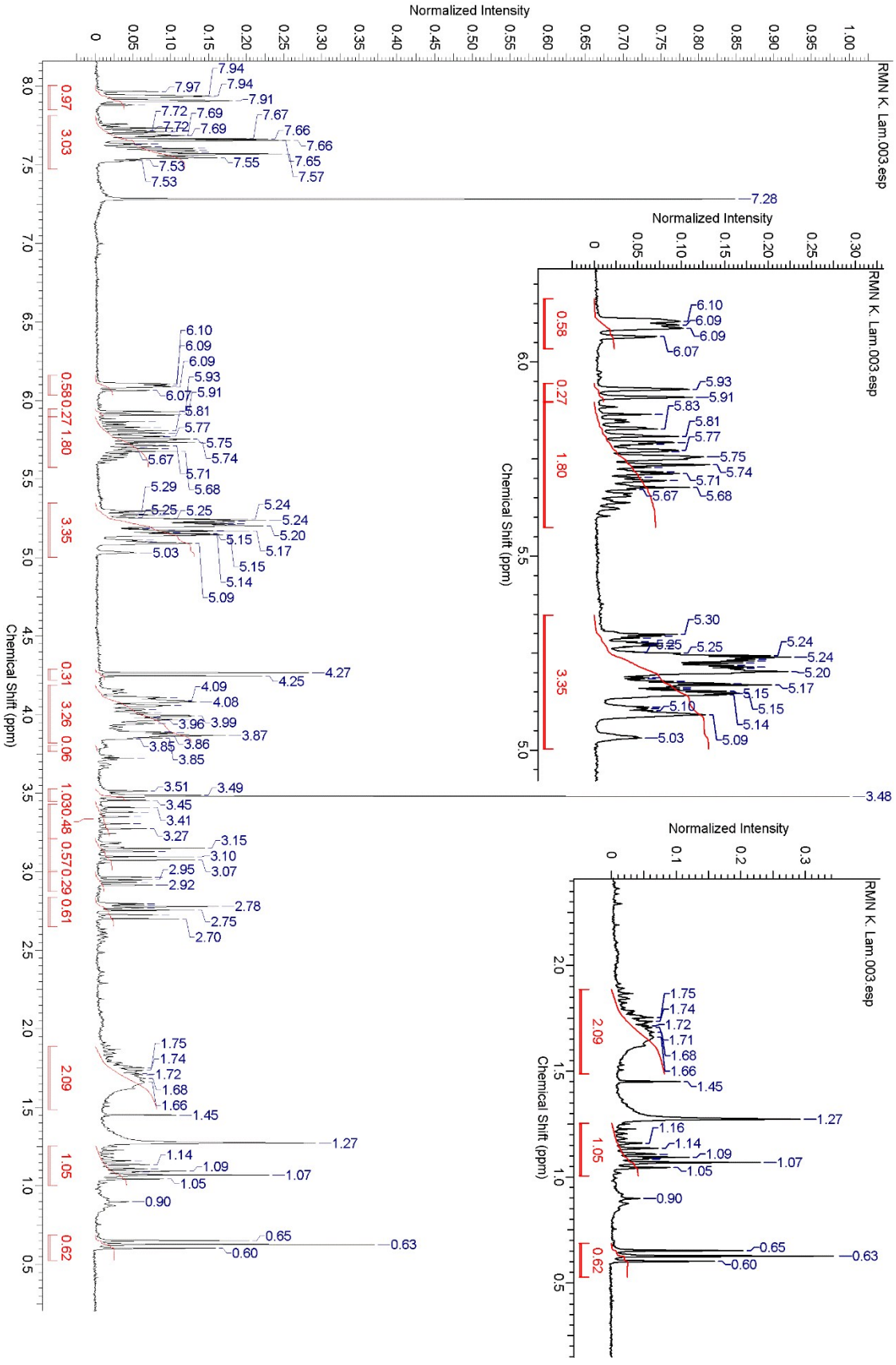
NL: 7.90E8 TIC MS LUCACCION I-25-5-16-01
NL: 4.77E7 m/z= 272.12528-272.13072 MS LUCACCION I-25-5-16-01
NL: 4.33E7 m/z= 286.14014-286.14586 MS LUCACCION I-25-5-16-01
Relative Abundance
Time (min)
NL: 3.49E7 LUCACCIONI-25-5-16-01#3911-3944 RT: 17.44-17.58 AV: 34 SB: 61 16.46-16.72 T: FTMS + p ESI Full lock ms [70.0000-670.0000]
NL: 2.08E7 LUCACCIONI-25-5-16-01#3971-4024 RT: 17.70-17.94 AV: 54 SB: 42 17.03-17.21 T: FTMS + p ESI Full lock ms [70.0000-670.0000]
m/z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5.77
5.75
5.74
5.67
5.71
5.68
5.29
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5.15
5.20
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1.74
1.72
1.68
1.66
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1.27
1.14
1.09
1.07
1.05
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0.97
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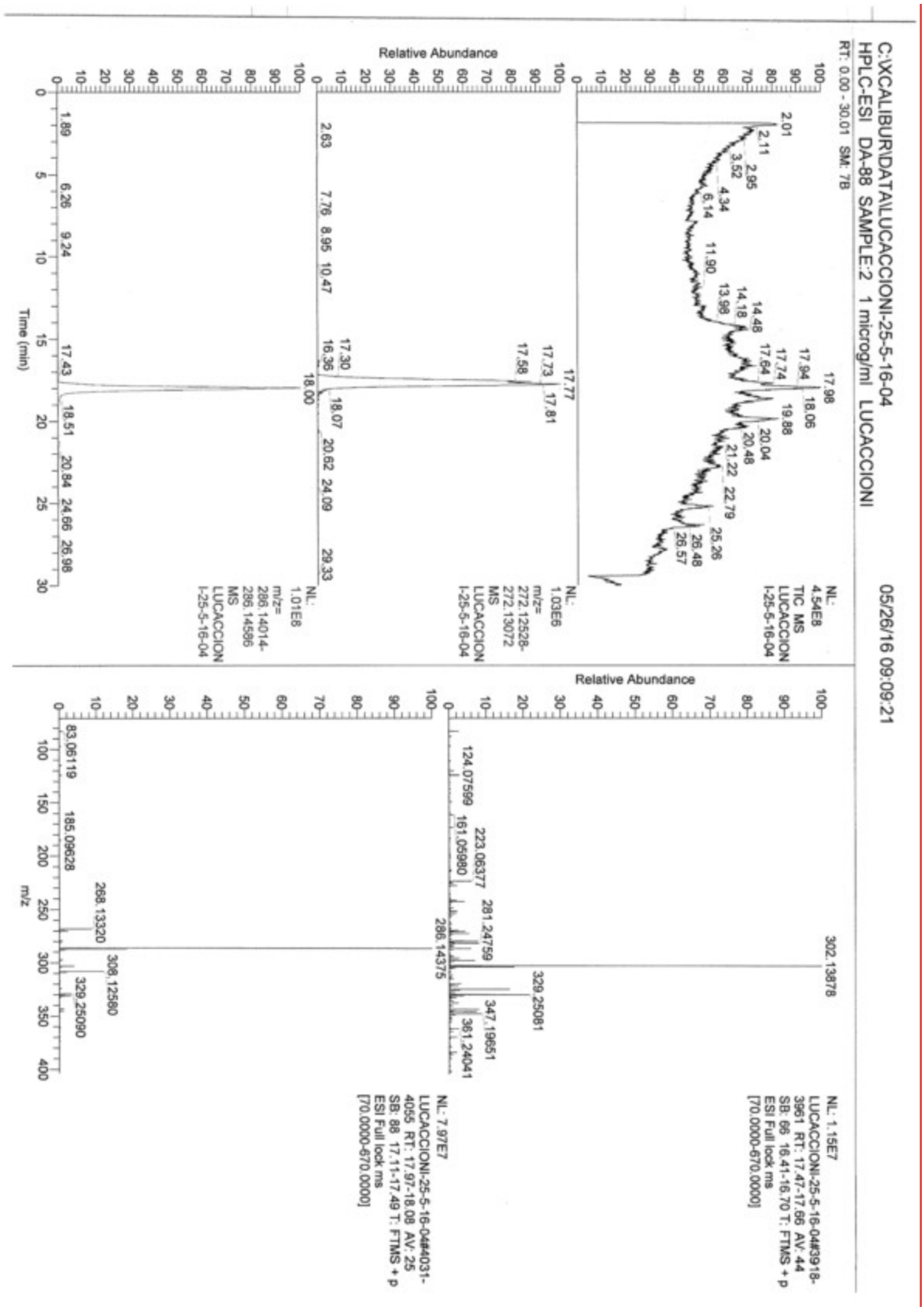
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NL: 1.01E6 m/z= 286.14014-286.14586 MS LUCACCION I-25-5-16-04
Relative Abundance
Time (min)
NL: 1.15E7 LUCACCIONI-25-5-16-04#3918-3961 RT: 17.47-17.66 AV: 44 SB: 66 16.41-16.70 T: FTMS + p ESI Full lock ms [70.0000-670.0000]
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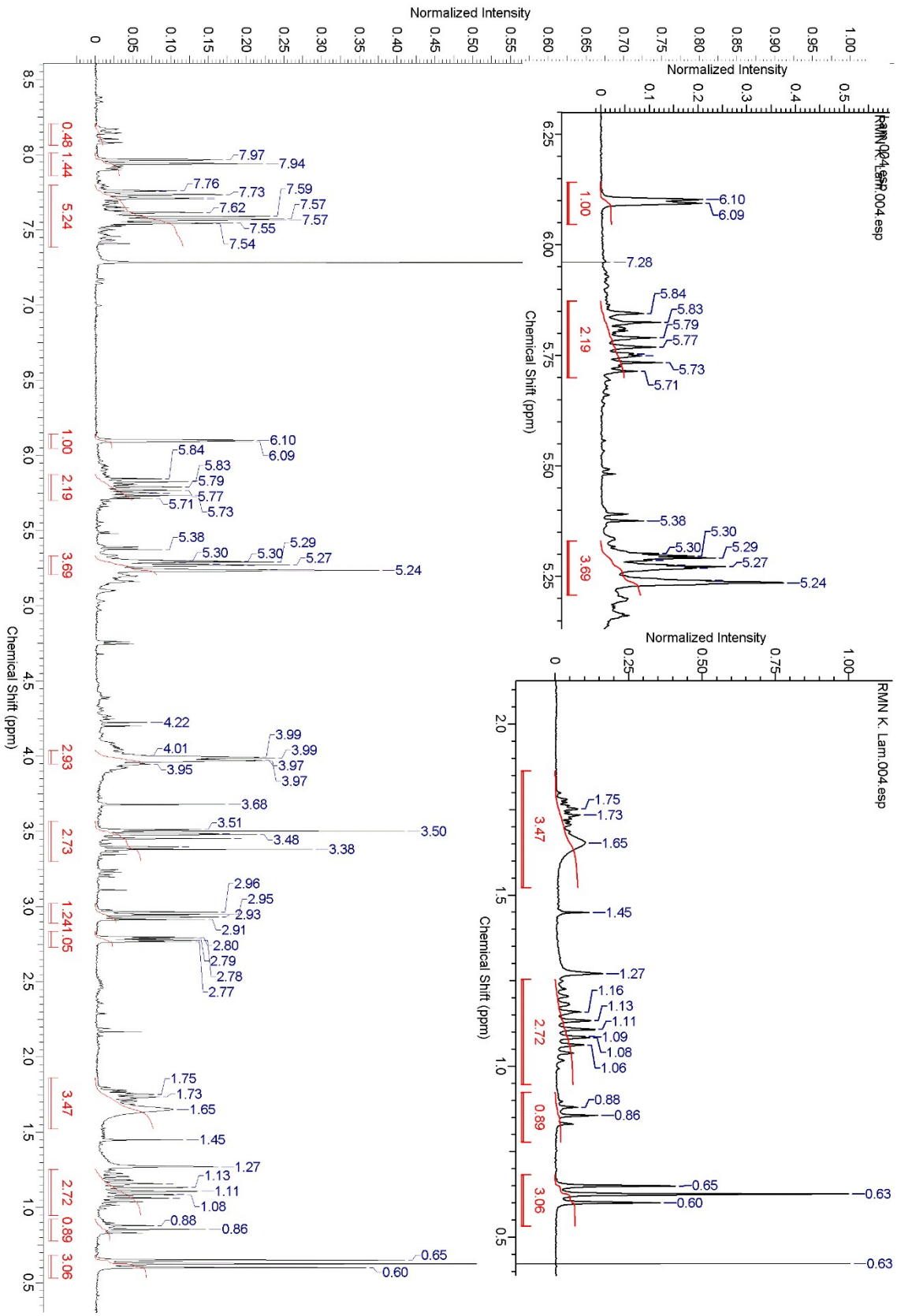
Normalized Intensity
Chemical Shift (ppm)
RMN K. Lam.004.esp
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1.73
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1.45
1.27
1.13
1.11
1.08
0.88
0.86
0.65
0.60
0.48
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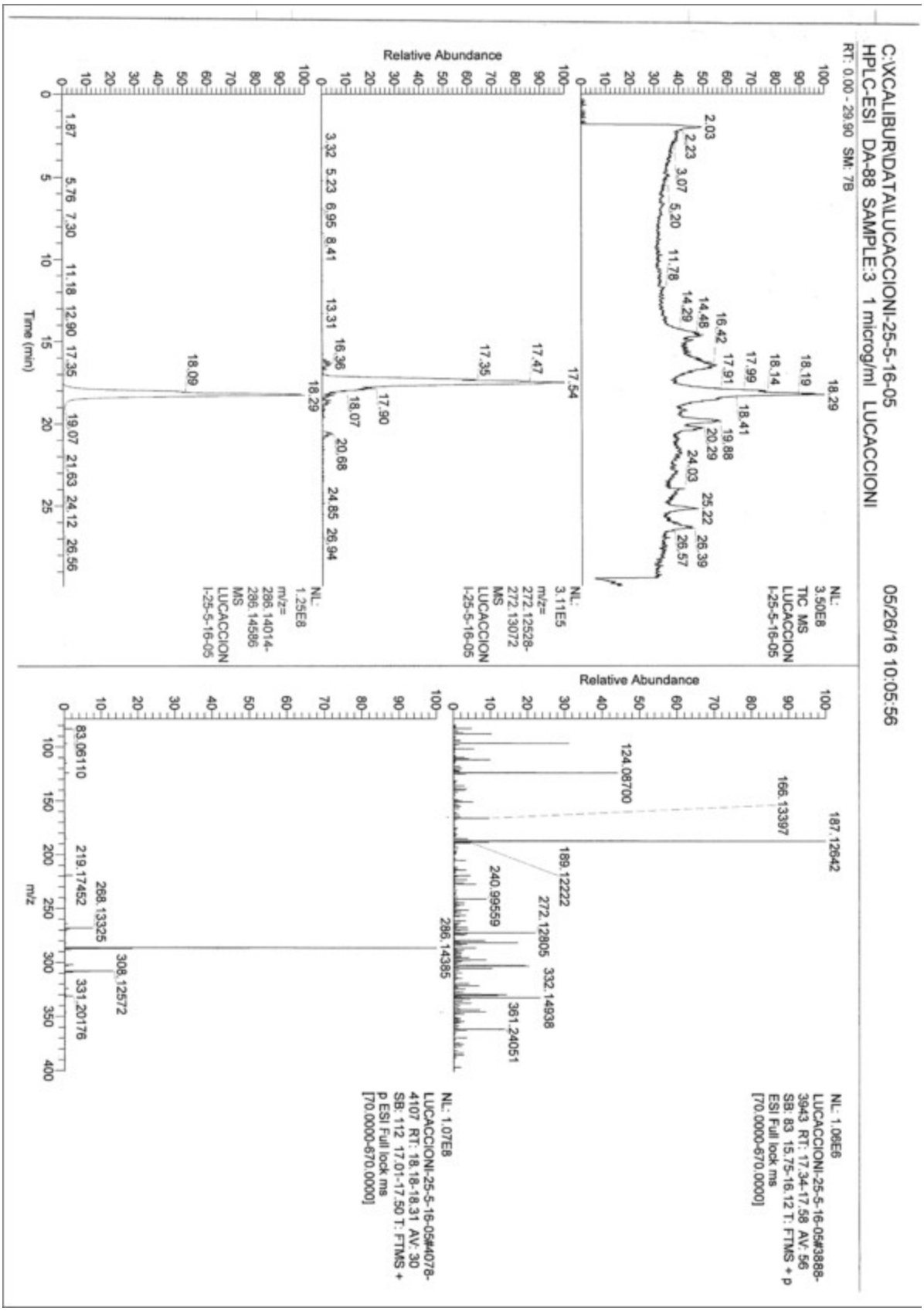
3.06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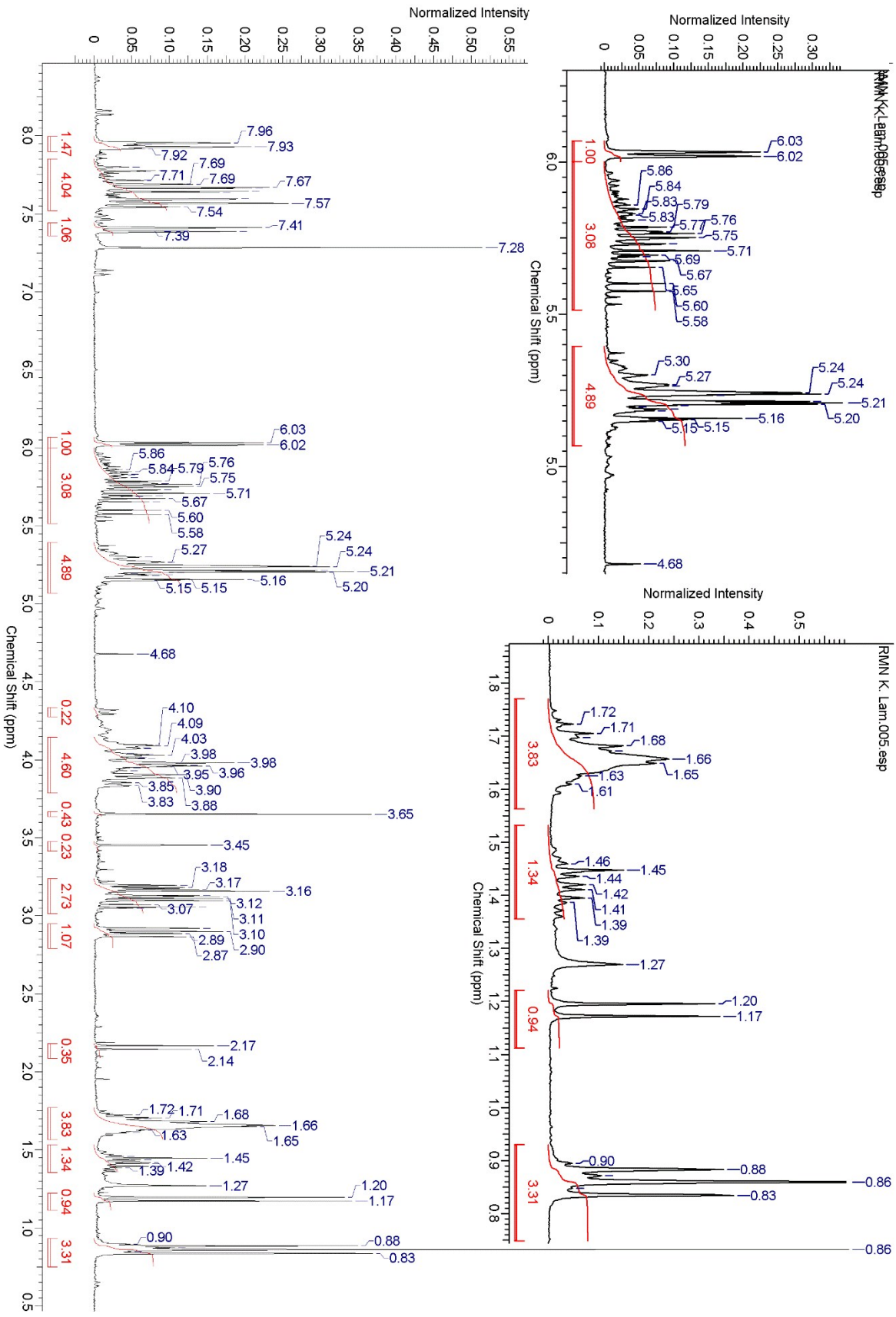
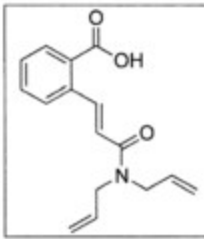
HPLC-ESI DA-88 SAMPLE:3 1 microg/ml LUCACCIONI
RT: 0.00 - 29.90 SM: 7B
Relative Abundance
Time (min)
NL: 3.50E8 TIC MS LUCACCION I-25-5-16-05
NL: 3.11E5 m/z= 272.12528-272.13072 MS LUCACCION I-25-5-16-05
NL: 1.25E8 m/z= 286.14014-286.14586 MS LUCACCION I-25-5-16-05
NL: 1.06E6 LUCACCIONI-25-5-16-05#3888-3943 RT: 17.34-17.58 AV: 56 SB: 83 15.75-16.12 T: FTMS + p ESI Full lock ms [70.0000-670.0000]
NL: 1.07E8 LUCACCIONI-25-5-16-05#4078-4107 RT: 18.18-18.31 AV: 30 SB: 112 17.01-17.50 T: FTMS + p ESI Full lock ms [70.0000-670.0000]
m/z

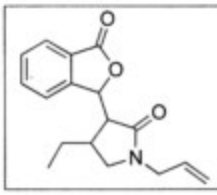

Normalized Intensity
Chemical Shift (ppm)
RMN K. Lam.005.esp
7.96
7.93
7.92
7.69
7.71
7.69
7.67
7.57
7.54
7.41
7.39
7.28
6.03
6.02
5.86
5.84
5.79
5.76
5.75
5.71
5.67
5.60
5.58
5.24
5.27
5.24
5.21
5.15
5.15
5.16
5.20
4.68
4.10
4.09
4.03
3.98
3.98
3.95
3.96
3.90
3.85
3.83
3.88
3.65
3.45
3.18
3.17
3.16
3.07
3.12
3.11
3.10
2.89
2.87
2.90
2.17
2.14
1.72
1.71
1.68
1.66
1.63
1.65
1.45
1.39
1.42
1.27
1.20
1.17
0.90
0.88
0.83
0.86
1.47
4.04
1.06
1.00
3.08
4.89
0.22
4.60
0.43
0.23
2.73
1.07
0.35
3.83
1.34
0.94
3.31

Produit de départ :



Chemical Formula: $C_{16}H_{17}NO_3$
Exact Mass: 271.12084
Molecular Weight: 271.31600

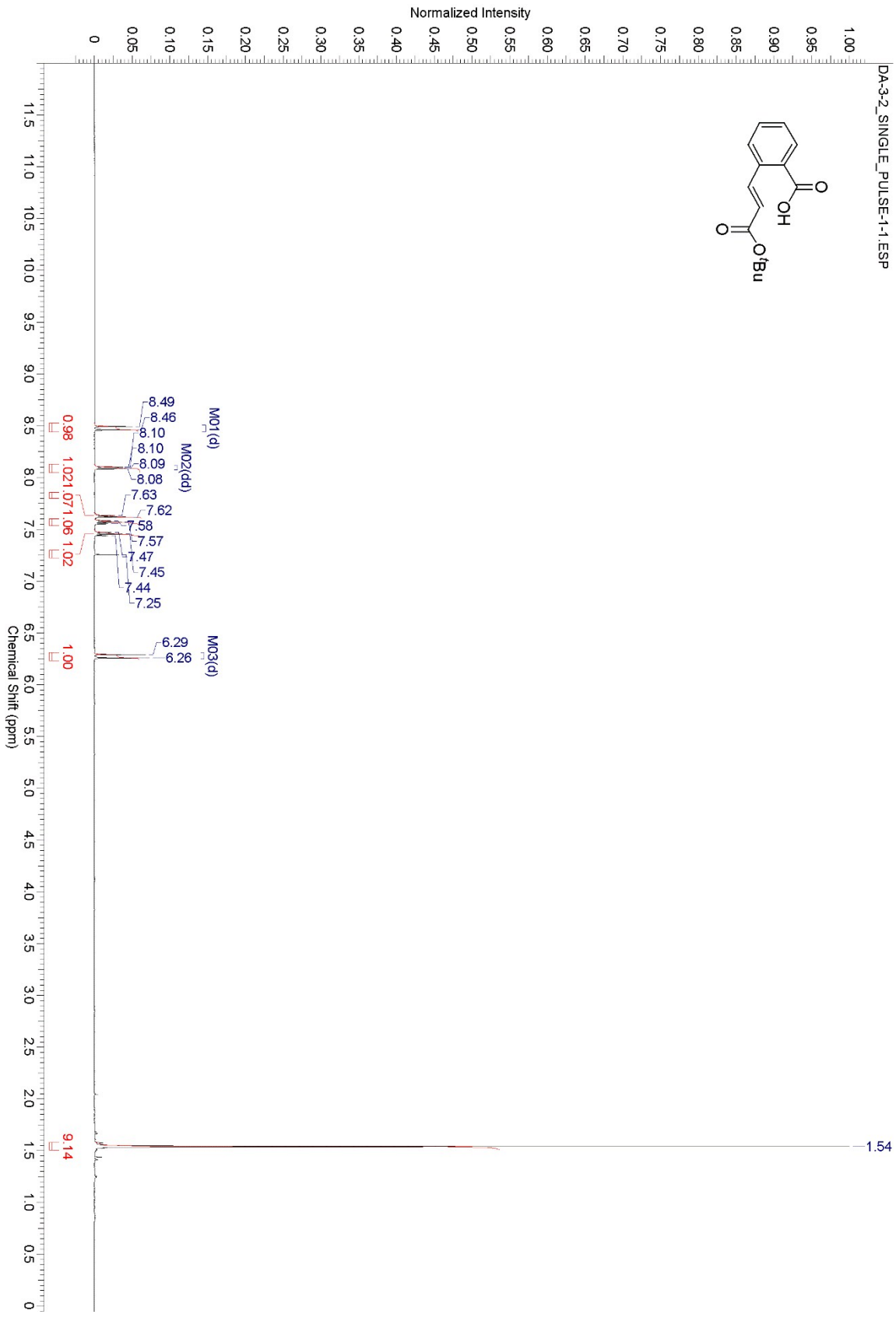
Produit d'arrivée :



Chemical Formula: $C_{17}H_{19}NO_3$
Exact Mass: 285.13649
Molecular Weight: 285.34300

Présents également toute une série d'intermédiares de réaction...

3 fractions contenant chaque fois entre 2 et 4 composés : pré-séparation réalisée en HPLC semi-préparative.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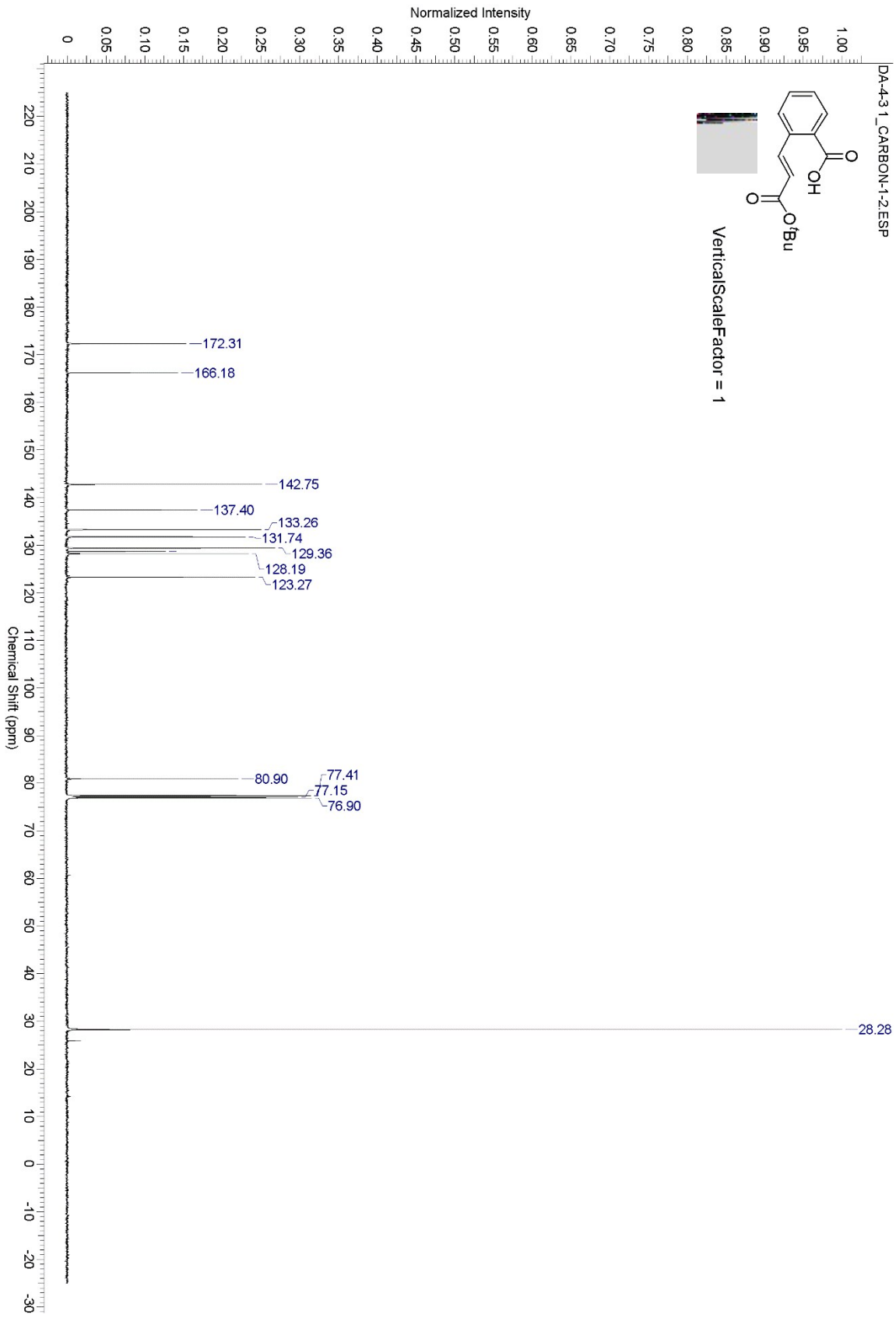
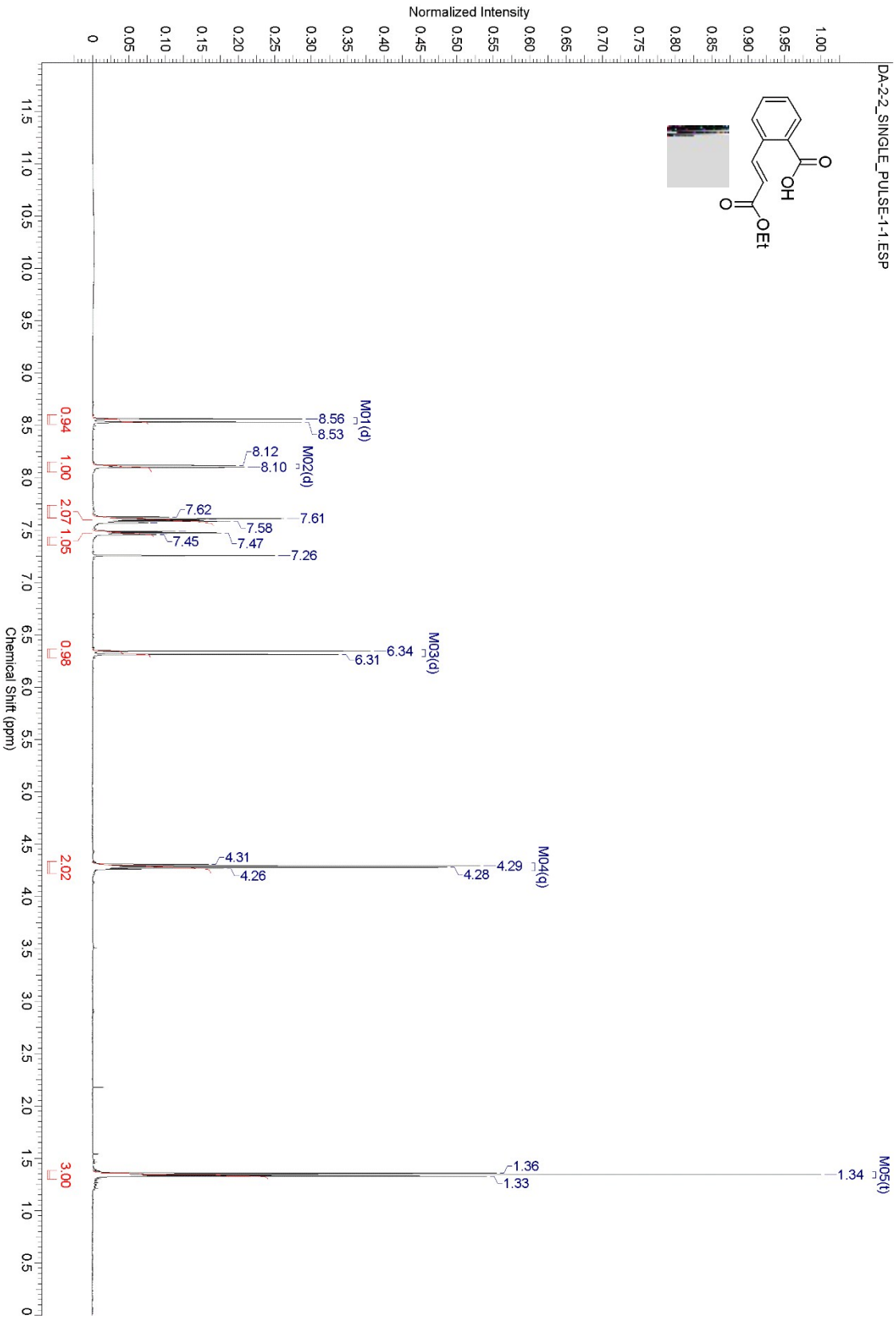
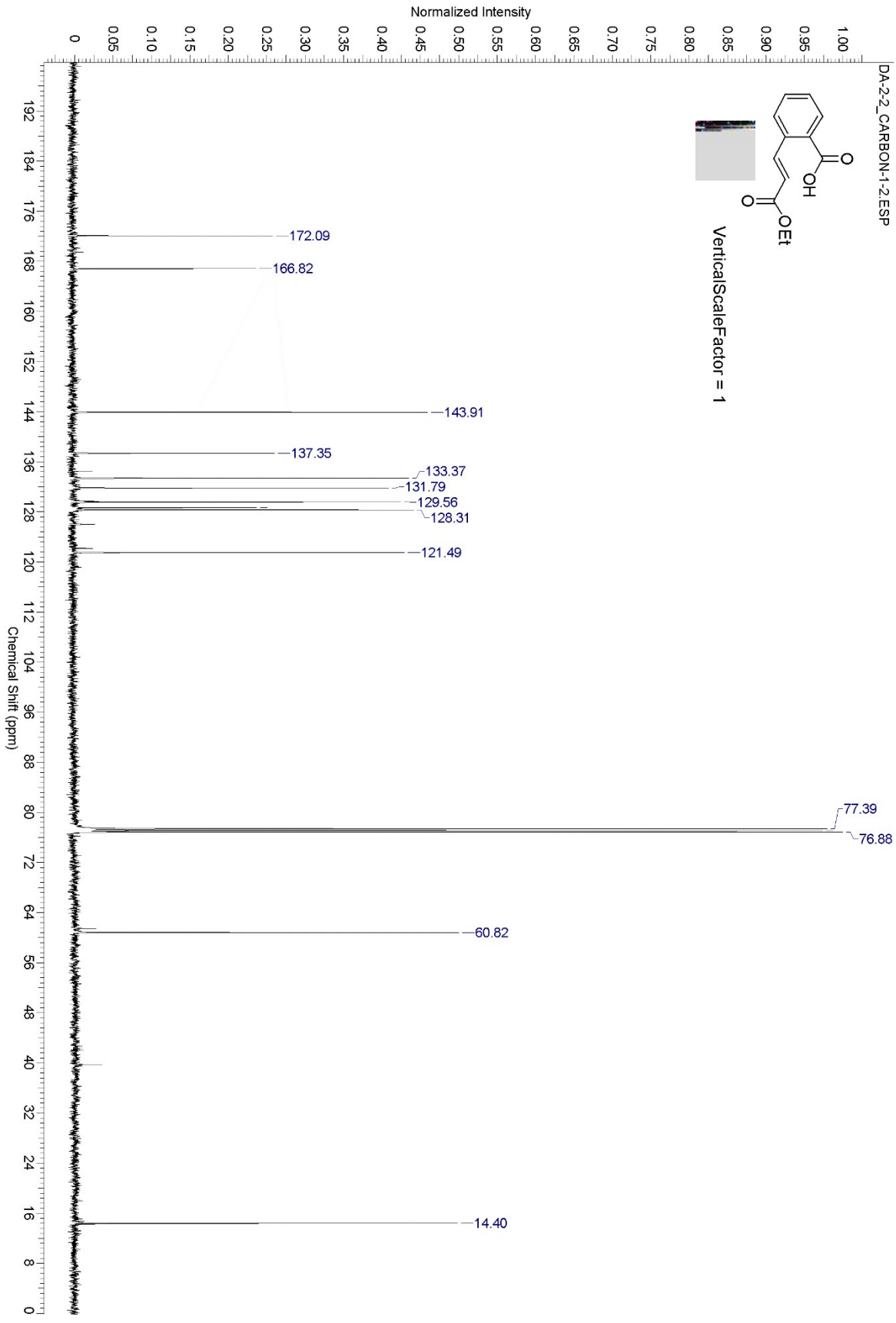
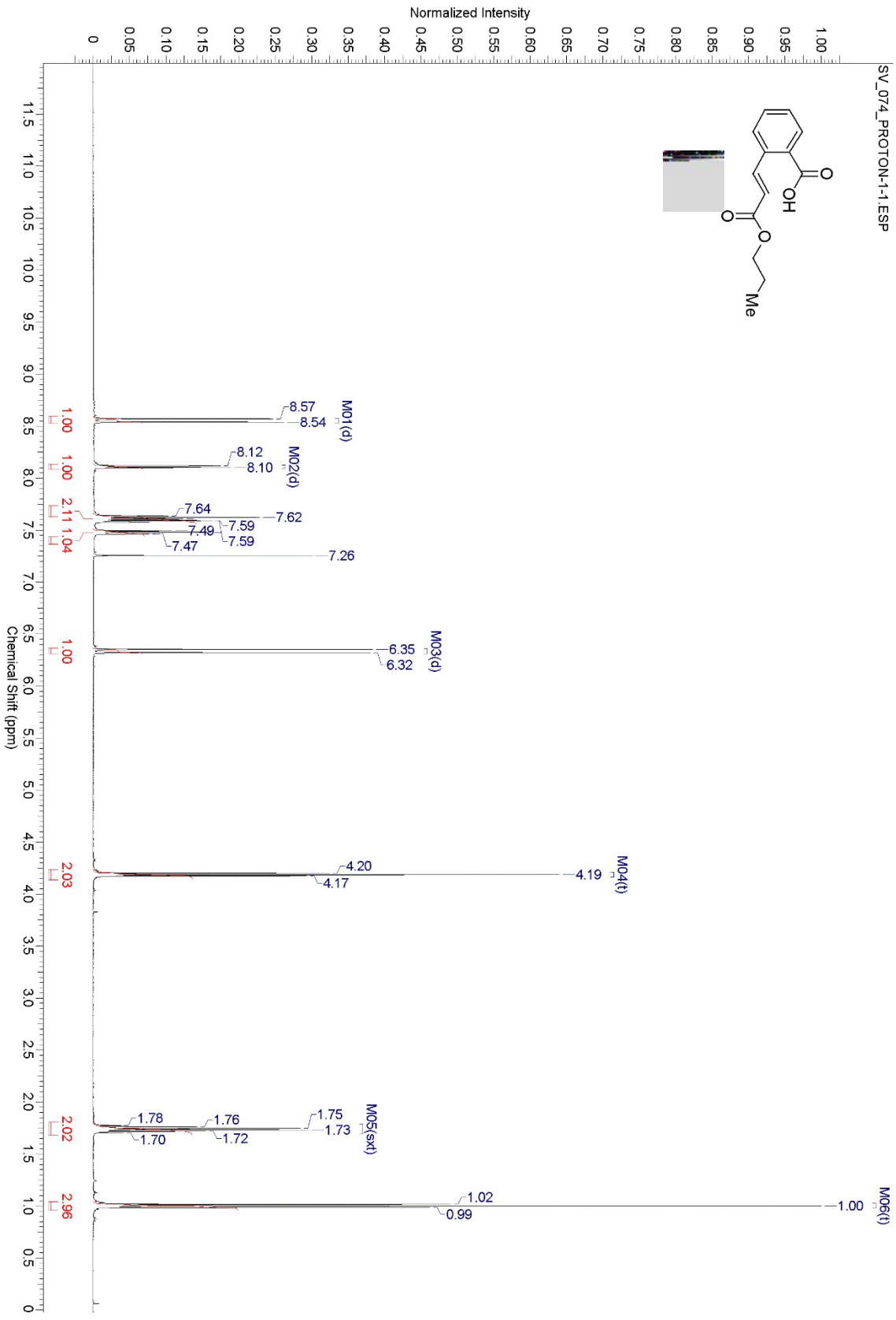
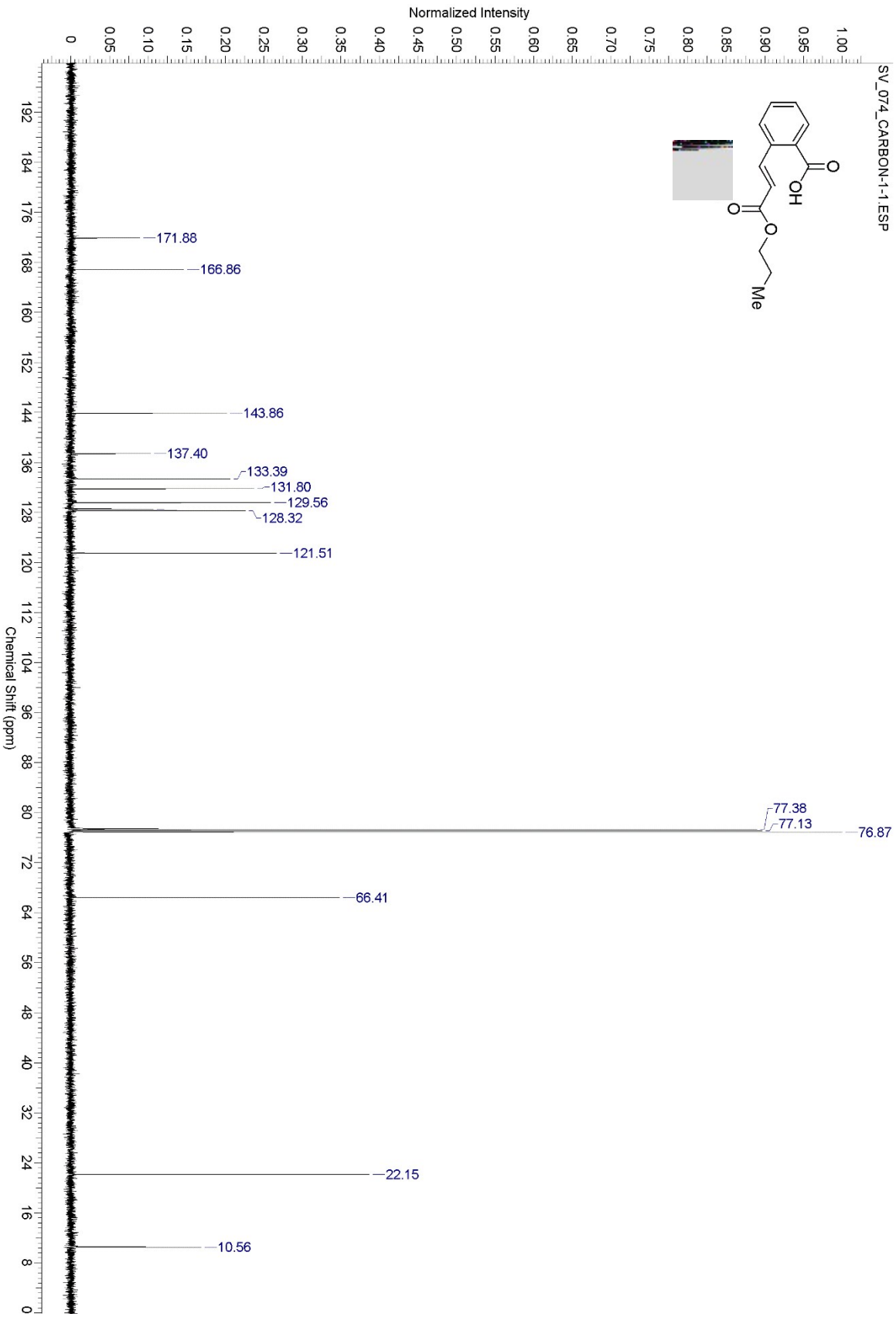
Normalized Intensity
Chemical Shift (ppm)
OH
O
O
O
tBu
8.49
8.46
8.10
8.10
8.09
8.08
7.63
7.62
7.58
7.57
7.47
7.45
7.44
7.25
6.29
6.26
M01(d)
M02(dd)
M03(d)
0.98
1.02
1.07
1.06
1.02
1.00
9.14
1.54

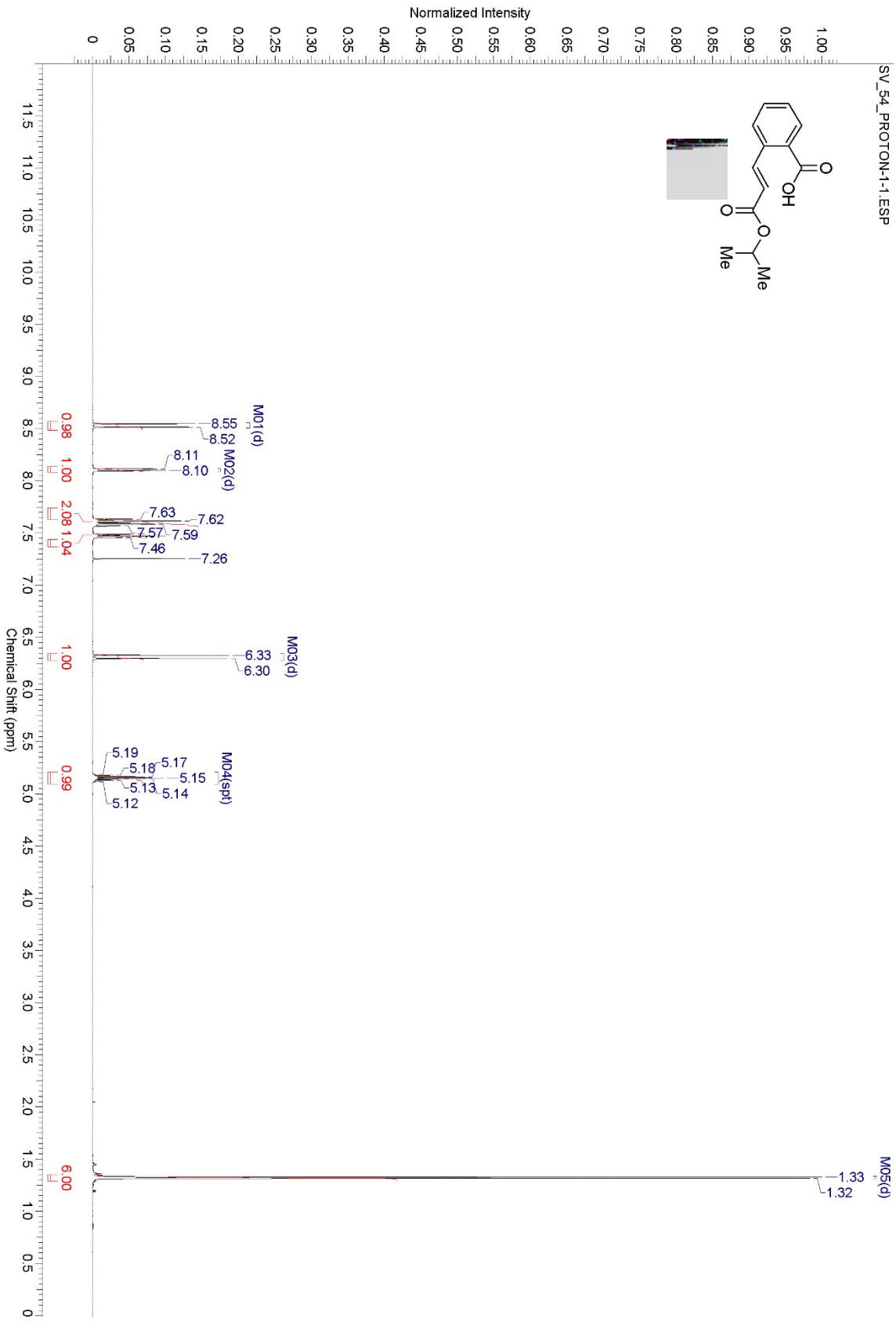

Normalized Intensity
0
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
0.50
0.55
0.60
0.65
0.70
0.75
0.80
0.85
0.90
0.95
1.00
DA-4-31_CARBON-1-2.ESP
VerticalScaleFactor = 1
O
OH
O
O
tBu
Chemical Shift (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
172.31
166.18
142.75
137.40
133.26
131.74
129.36
128.19
123.27
80.90
77.41
77.15
76.90
28.28

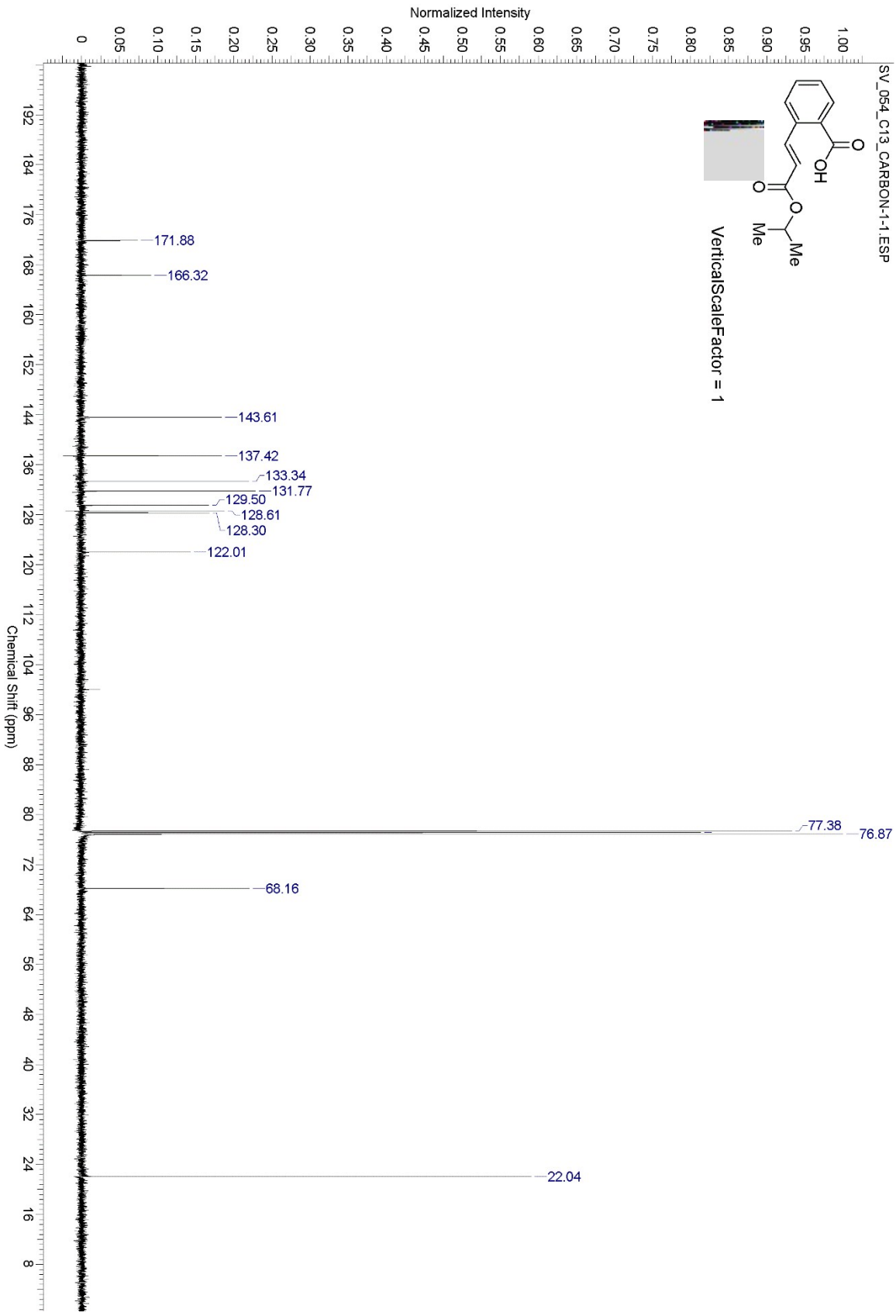

DA-2-2_SINGLE_PULSE-1-1.ESP
Normalized Intensity
Chemical Shift (ppm)
OH
O
O
OEt
M01(d)
M02(d)
M03(d)
M04(q)
M05(t)
8.56
8.53
8.12
8.10
7.62
7.61
7.58
7.45
7.47
7.26
6.34
6.31
4.31
4.29
4.28
4.26
1.36
1.34
1.33
0.94
1.00
2.07
1.05
0.98
2.02
3.00

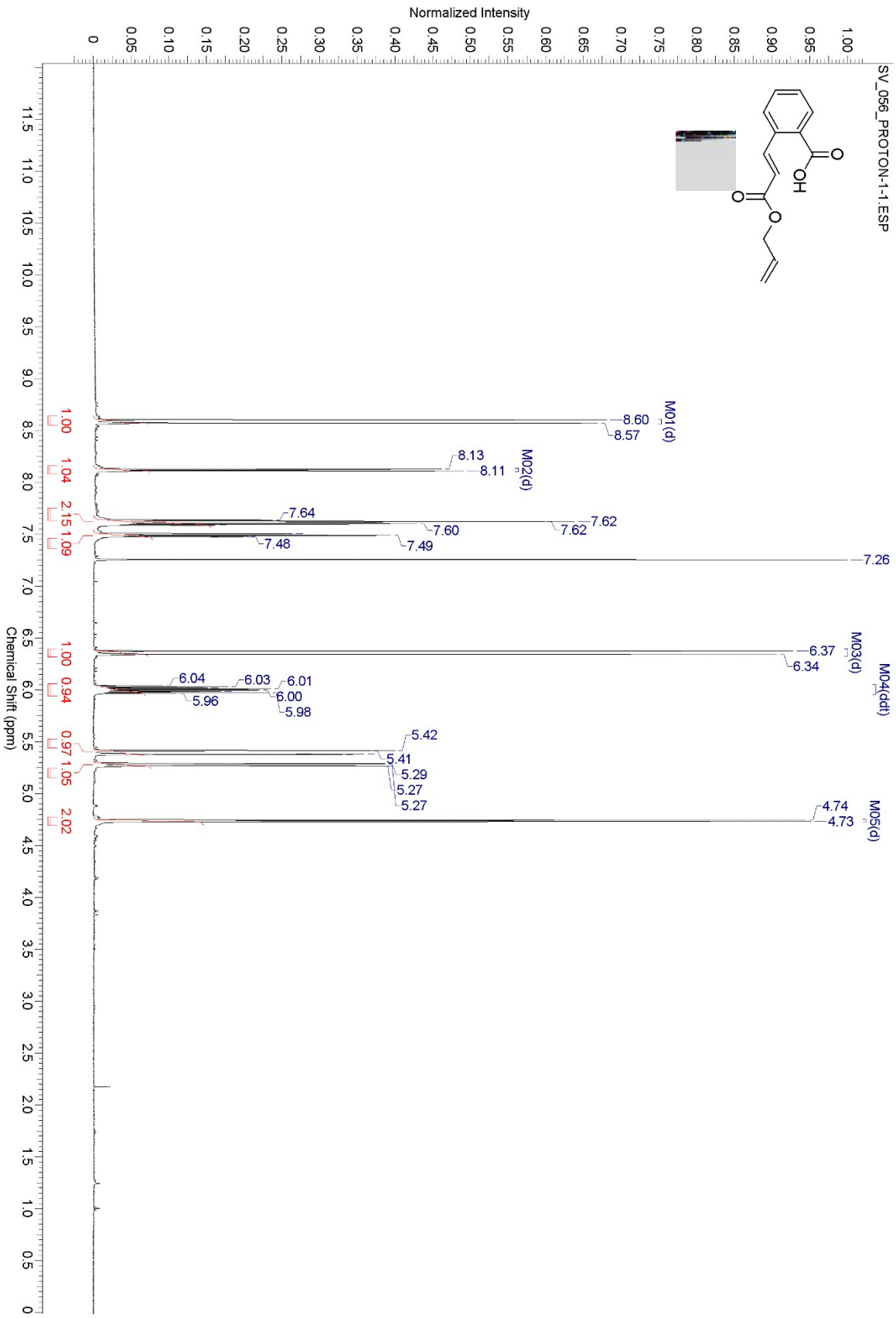

Normalized Intensity
0
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
0.50
0.55
0.60
0.65
0.70
0.75
0.80
0.85
0.90
0.95
1.00
DA-2-2_CARBON-1-2.ESP
VerticalScaleFactor = 1
OH
O
OEt
O
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
172.09
166.82
143.91
137.35
133.37
131.79
129.56
128.31
121.49
77.39
76.88
60.82
14.40


SV_074_PROTON-1-1.ESP
Normalized Intensity
Chemical Shift (ppm)
OH
O
O
O
Me
8.57
8.54
M01(d)
8.12
8.10
M02(d)
7.64
7.62
7.59
7.49
7.59
7.47
7.26
6.35
6.32
M03(d)
4.20
4.19
4.17
M04(t)
1.78
1.76
1.75
1.73
1.72
1.70
M05(sxt)
1.02
1.00
0.99
M06(t)
1.00
1.00
2.11
1.04
1.00
2.03
2.02
2.96


Normalized Intensity
0
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
0.50
0.55
0.60
0.65
0.70
0.75
0.80
0.85
0.90
0.95
1.00
SV_074_CARBON-1-1.ESP
O
OH
O
O
Me
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
171.88
166.86
143.86
137.40
133.39
131.80
129.56
128.32
121.51
77.38
77.13
76.87
66.41
22.15
10.56


SV_54_PROTON-1-1.ESP
Normalized Intensity
Chemical Shift (ppm)
M01(d)
8.55
8.52
M02(d)
8.11
8.10
7.63
7.62
7.57
7.59
7.46
7.26
M03(d)
6.33
6.30
M04(spt)
5.19
5.18
5.17
5.15
5.13
5.14
5.12
M05(d)
1.33
1.32
0.98
1.00
2.08
1.04
1.00
0.99
6.00
OH
O
Me
Me


Normalized Intensity
0
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
0.50
0.55
0.60
0.65
0.70
0.75
0.80
0.85
0.90
0.95
1.00
SV_054_C13_CARBON-1-1.ESP
VerticalScaleFactor = 1
O
OH
O
O
Me
Me
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
171.88
166.32
143.61
137.42
133.34
131.77
129.50
128.61
128.30
122.01
77.38
76.87
68.16
22.04


Normalized Intensity
SV_056_PROTON-1-1.ESP
Chemical Shift (ppm)
8.60
8.57
M01(d)
8.13
8.11
M02(d)
7.64
7.62
7.60
7.62
7.48
7.49
7.26
6.37
6.34
M03(d)
6.04
6.03
6.01
6.00
5.98
5.96
M04(ddt)
5.42
5.41
5.29
5.27
5.27
4.74
4.73
M05(d)
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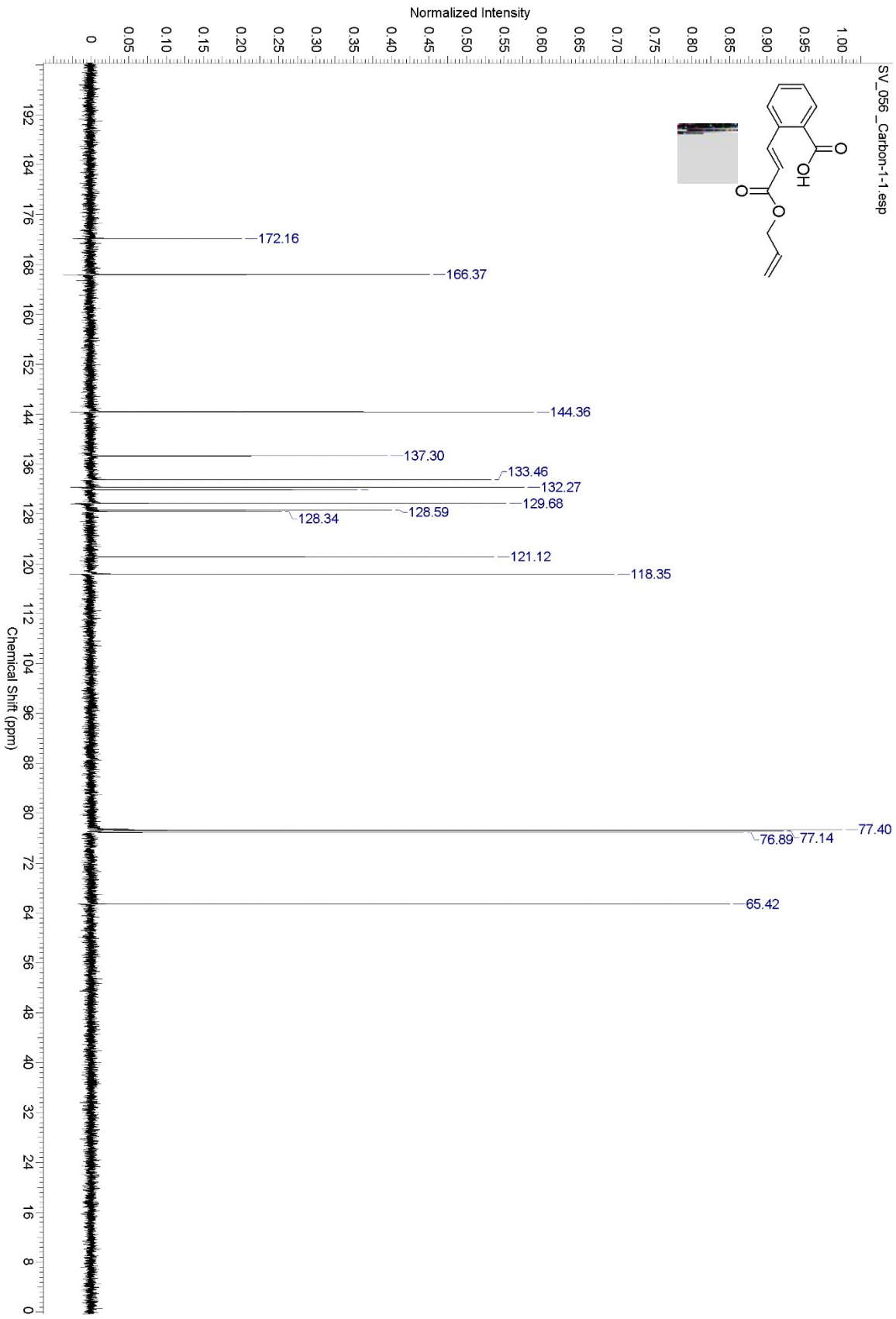
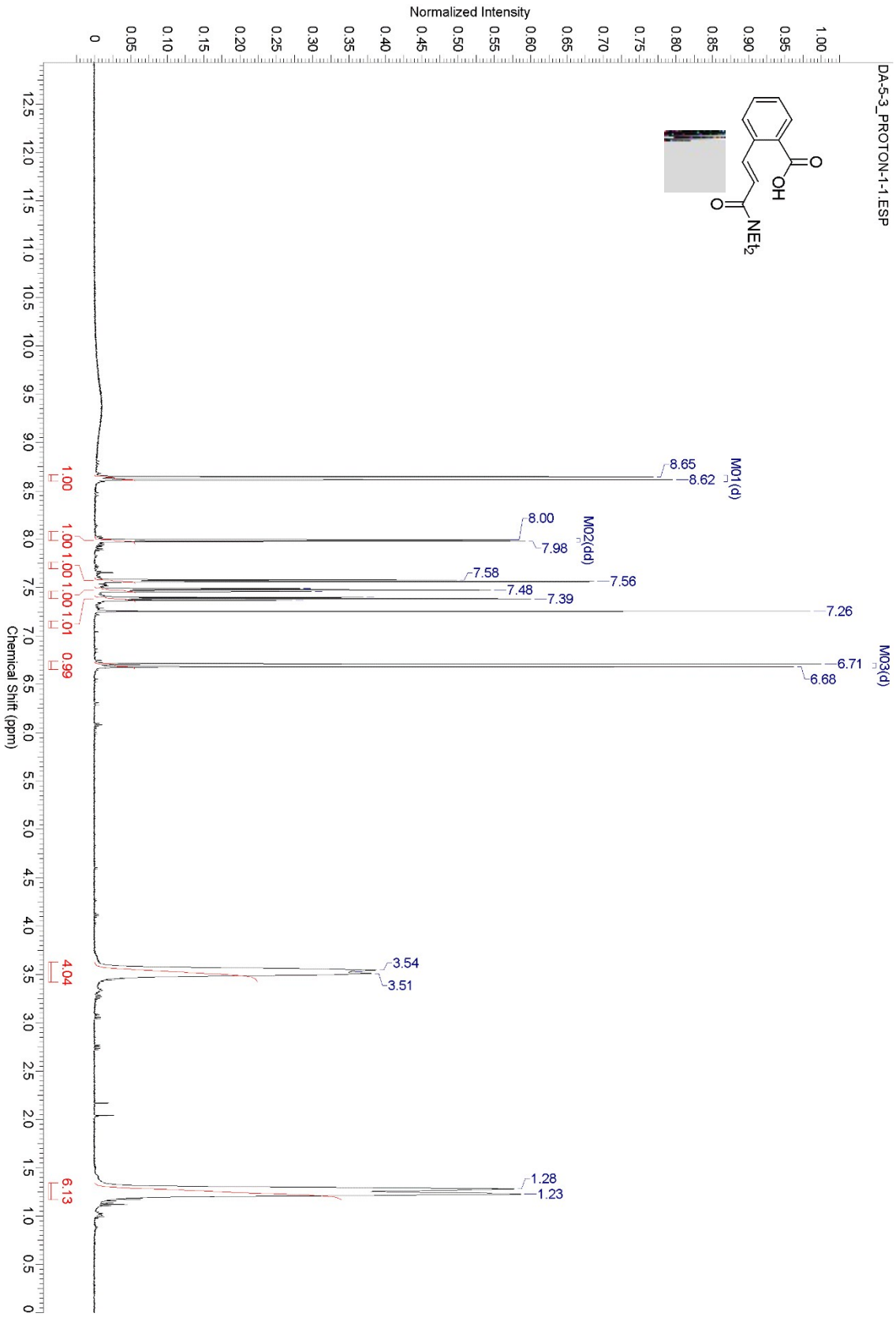
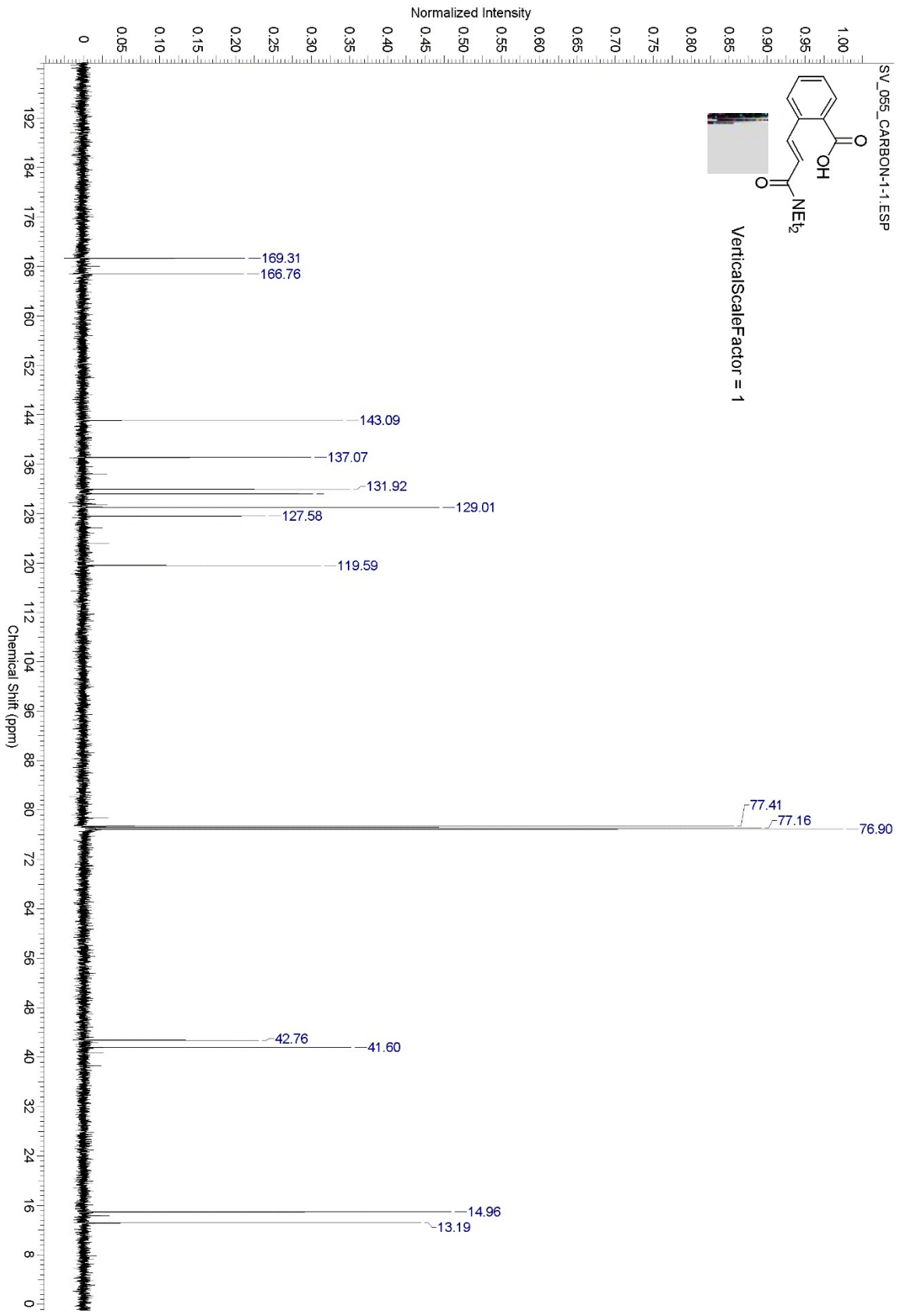
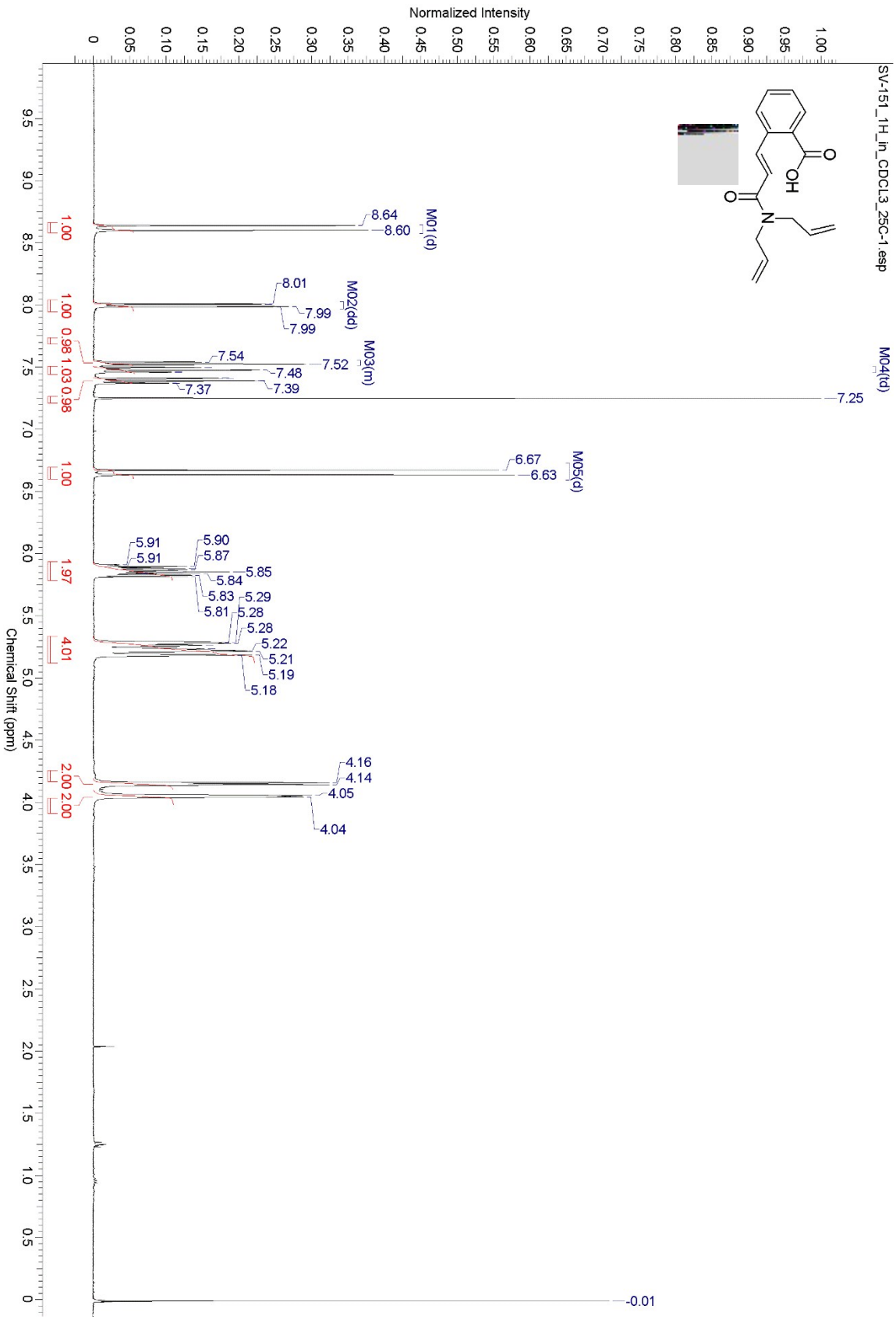
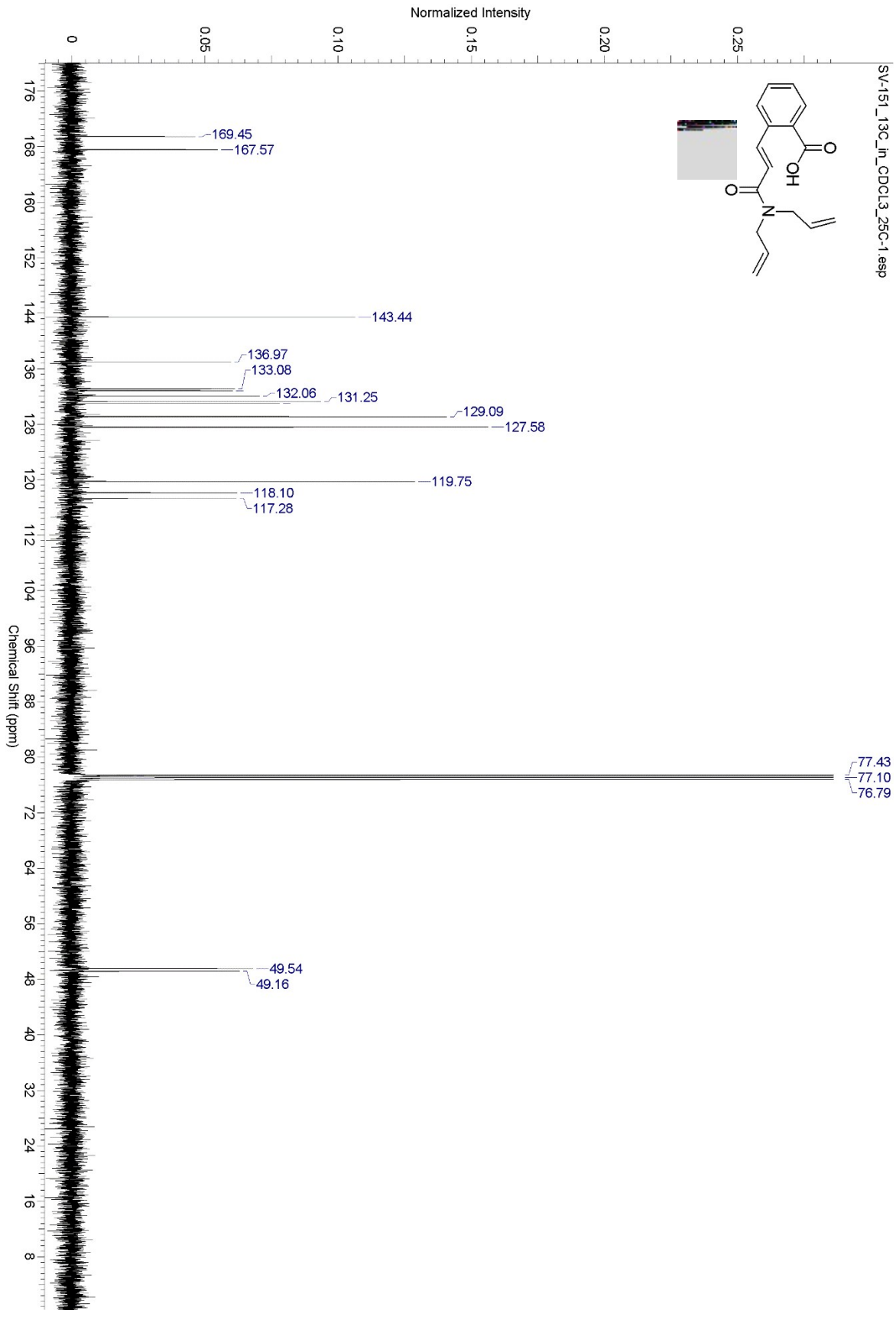
1.04
2.15
1.09
1.00
0.94
0.97
1.05
2.02
OH
O

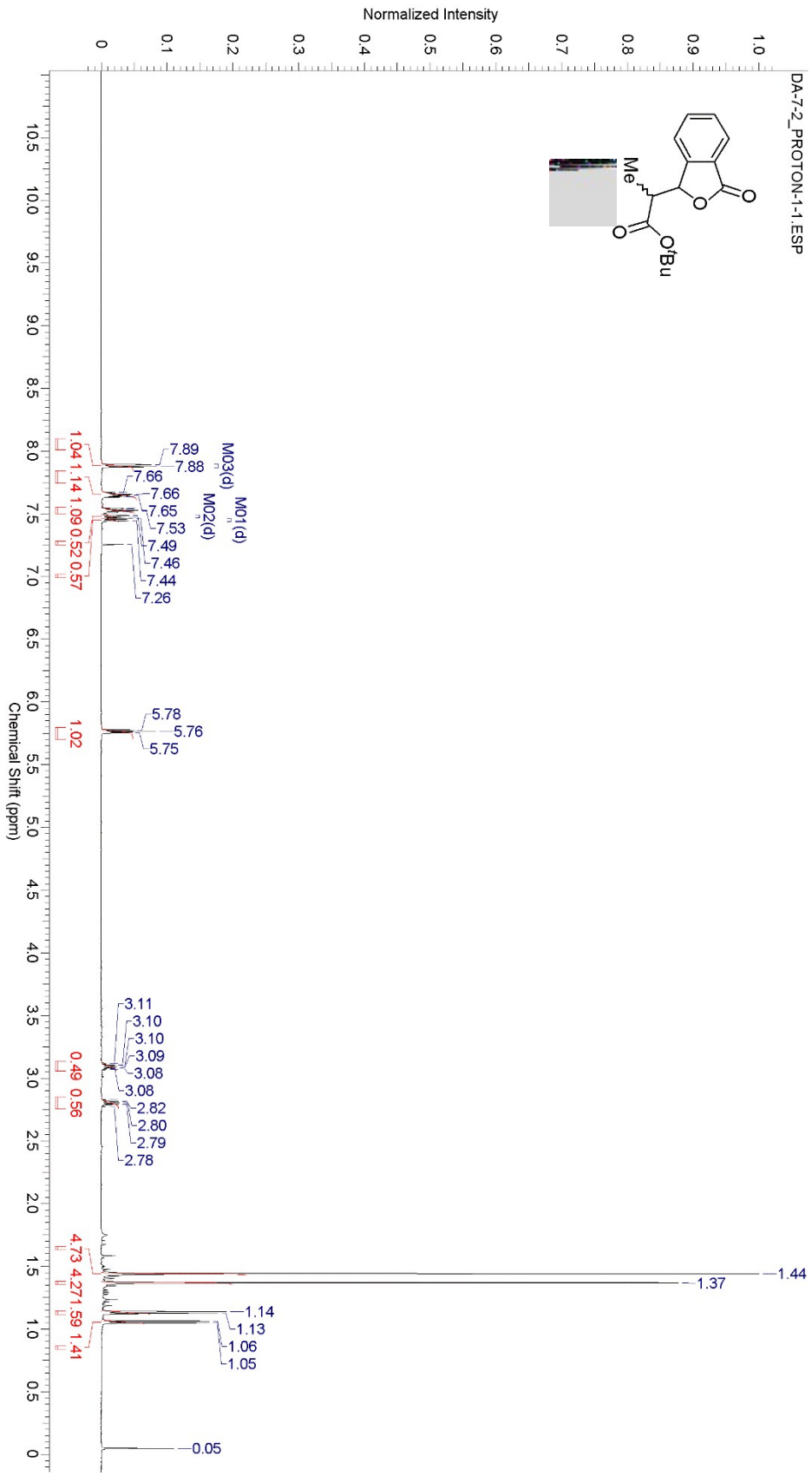

Normalized Intensity
0
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
0.50
0.55
0.60
0.65
0.70
0.75
0.80
0.85
0.90
0.95
1.00
SV_056_Carbon-1-1.esp
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
172.16
166.37
144.36
137.30
133.46
132.27
129.68
128.59
128.34
121.12
118.35
77.40
77.14
76.89
65.42
O
OH
O
O

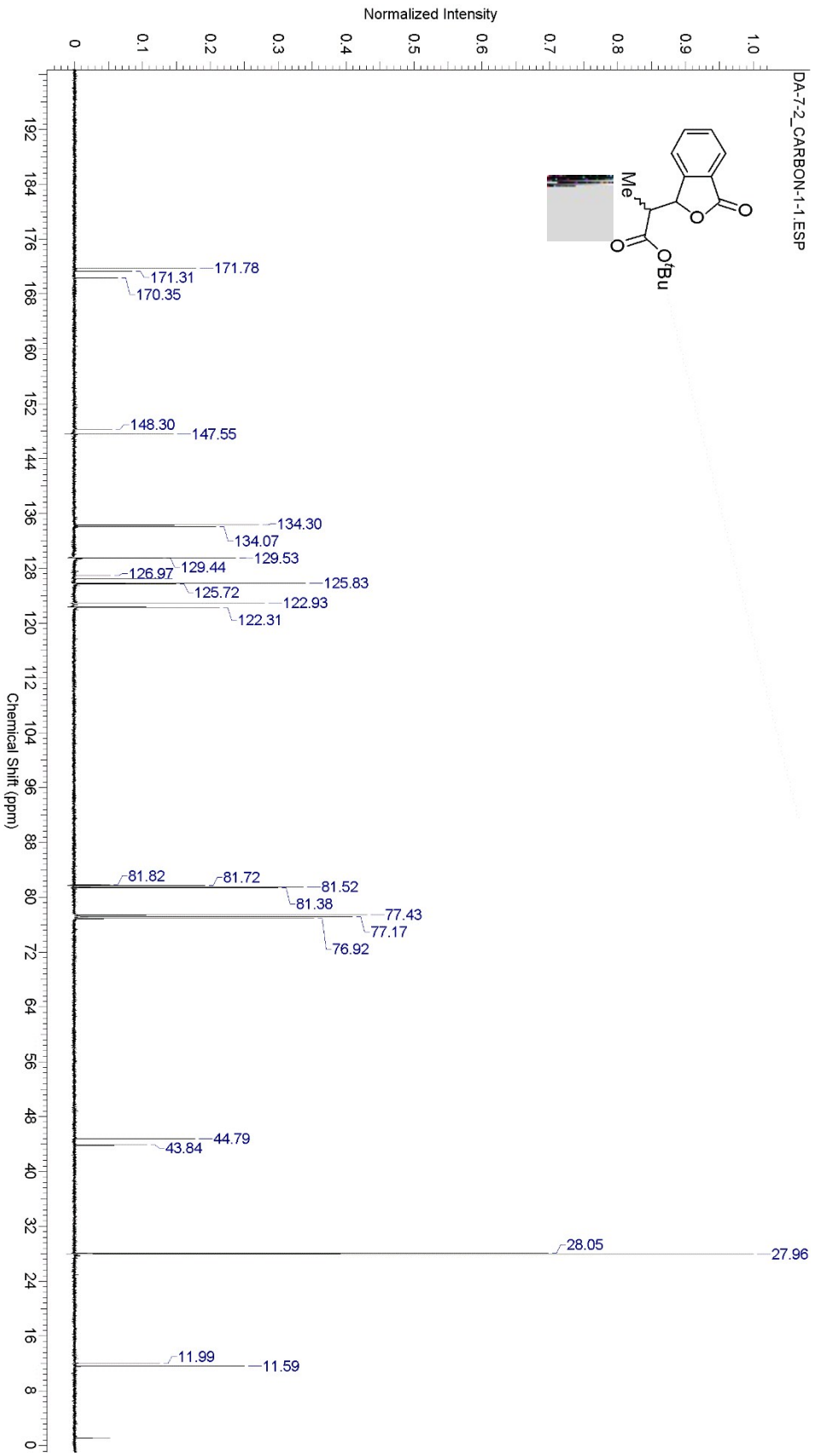

DA-5-3_PROTON-1-1.ESP
Normalized Intensity
Chemical Shift (ppm)
8.65
8.62
M01(d)
8.00
7.98
M02(dd)
7.58
7.56
7.48
7.39
7.26
6.71
6.68
M03(d)
3.54
3.51
1.28
1.23
1.00
1.00
1.00
1.00
1.00
1.01
0.99
4.04
6.13
OH
O
O
NEt2

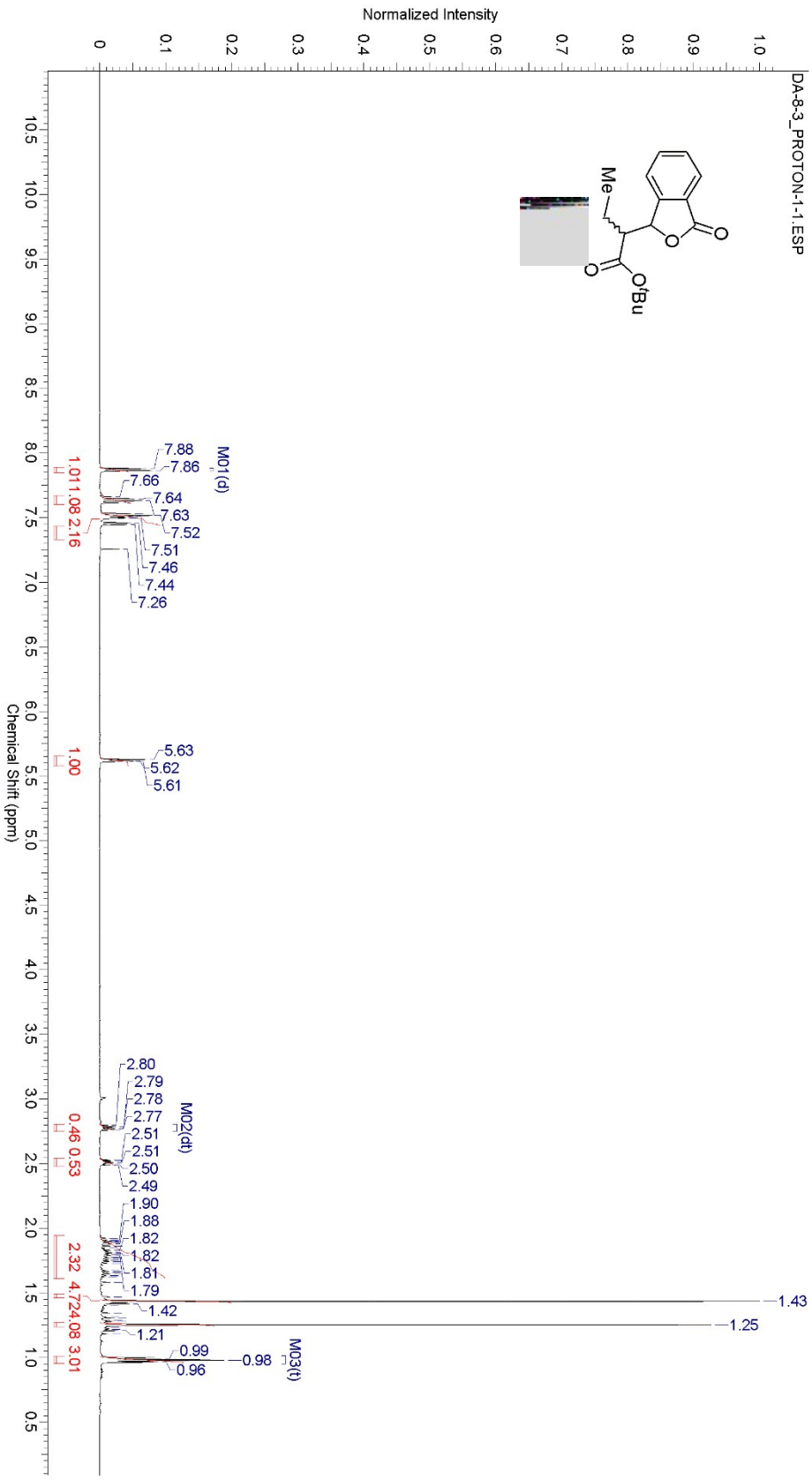

Normalized Intensity
0
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
0.50
0.55
0.60
0.65
0.70
0.75
0.80
0.85
0.90
0.95
1.00
SV_055_CARBON-1-1.ESP
O
OH
O
NEt2
VerticalScaleFactor = 1
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
169.31
166.76
143.09
137.07
131.92
129.01
127.58
119.59
77.41
77.16
76.90
42.76
41.60
14.96
13.19

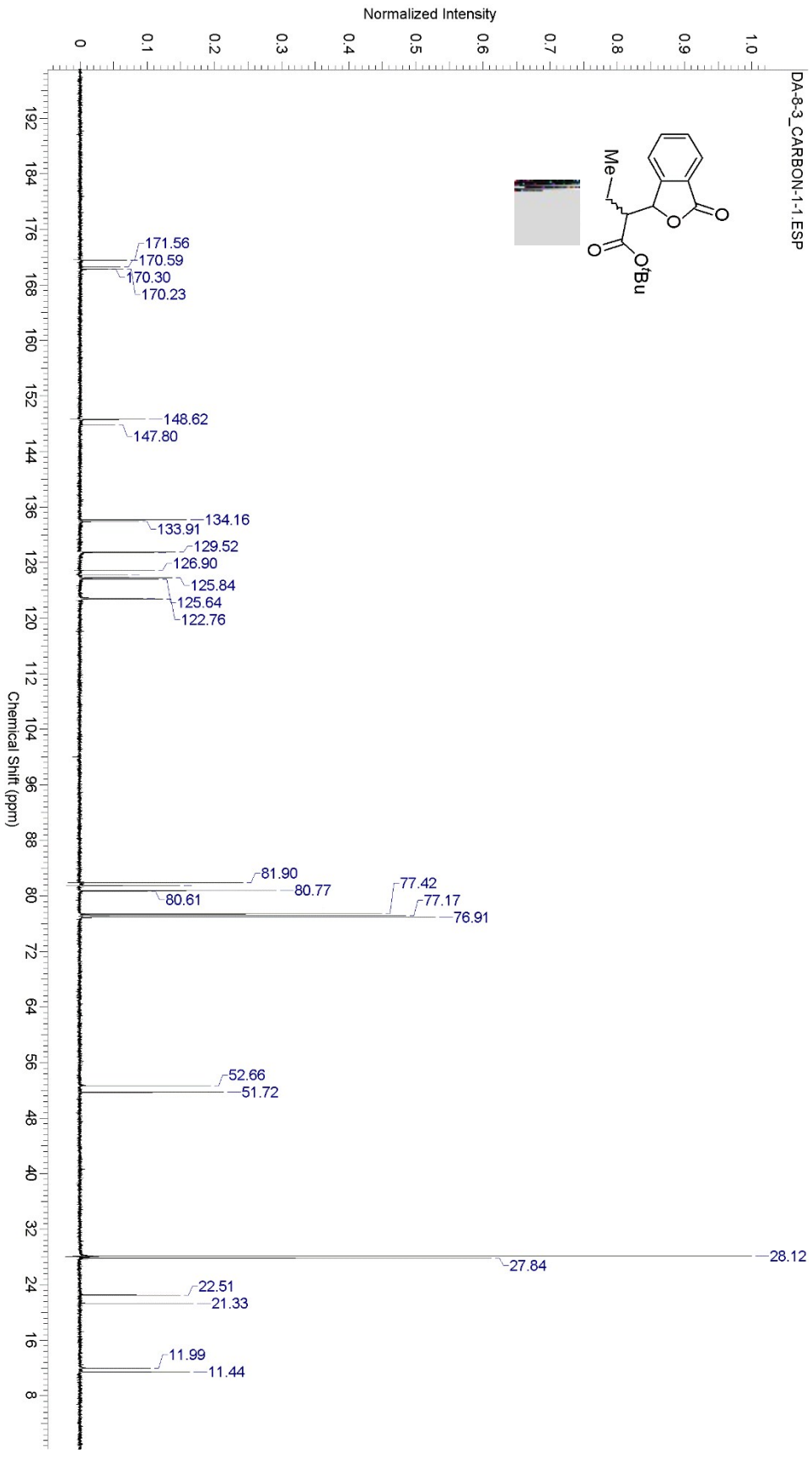

Normalized Intensity
Chemical Shift (ppm)
SV-151_1H_in_CDCL3_25C-1.esp
M01(d)
M02(dd)
M03(m)
M04(d)
M05(d)
8.64
8.60
8.01
7.99
7.99
7.54
7.52
7.48
7.39
7.37
7.25
6.67
6.63
5.91
5.91
5.90
5.87
5.85
5.84
5.83
5.81
5.29
5.28
5.28
5.22
5.21
5.19
5.18
4.16
4.14
4.05
4.04
-0.01
1.00
1.00
0.98
1.03
0.98
1.00
1.97
4.01
2.00
2.00
OH
O
N

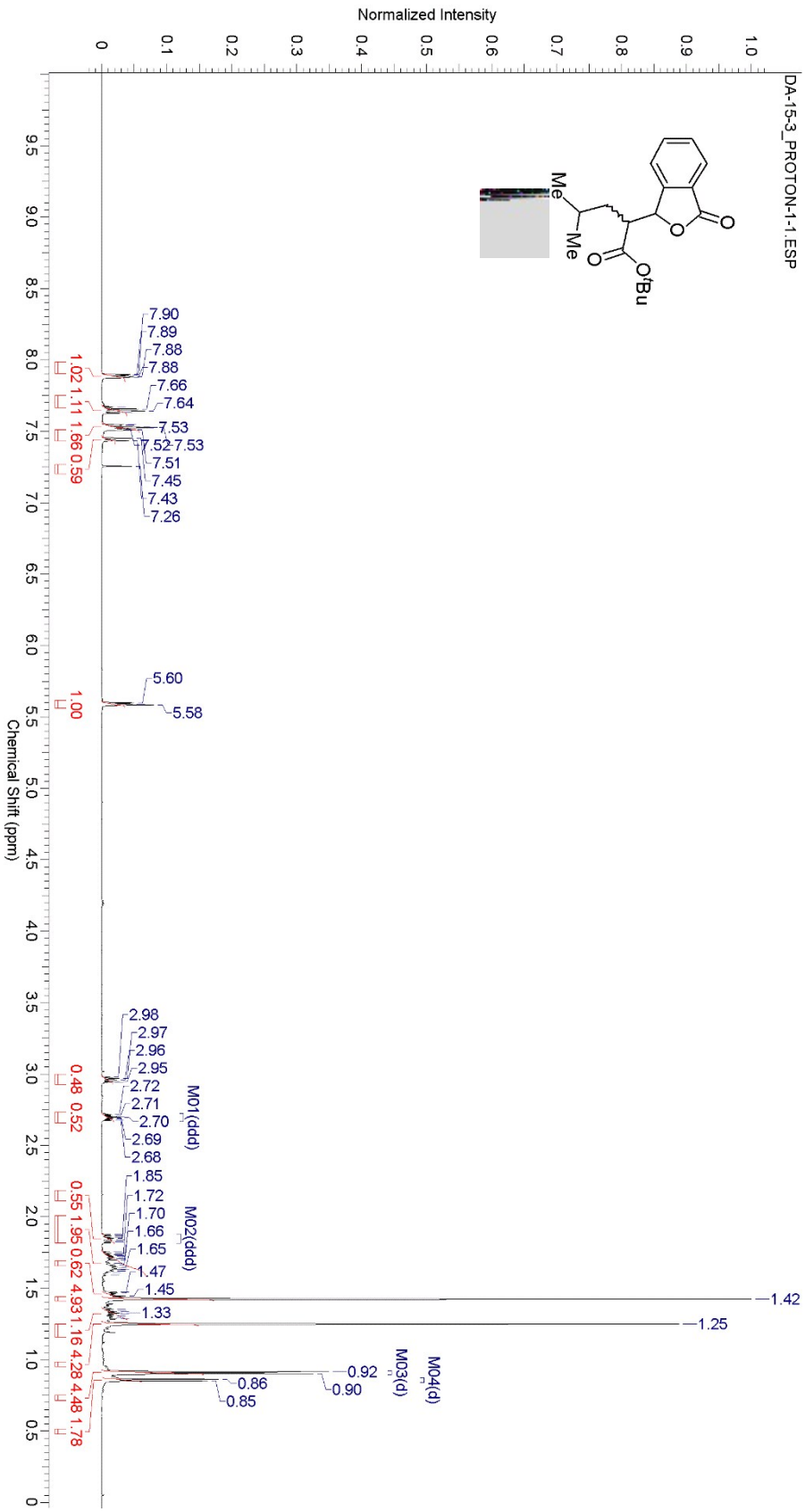

Normalized Intensity
0
0.05
0.10
0.15
0.20
0.25
SV-151_13C_in_CDCL3_25C-1.esp
Chemical Shift (ppm)
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
169.45
167.57
143.44
136.97
133.08
132.06
131.25
129.09
127.58
119.75
118.10
117.28
77.43
77.10
76.79
49.54
49.16
O
OH
O
N

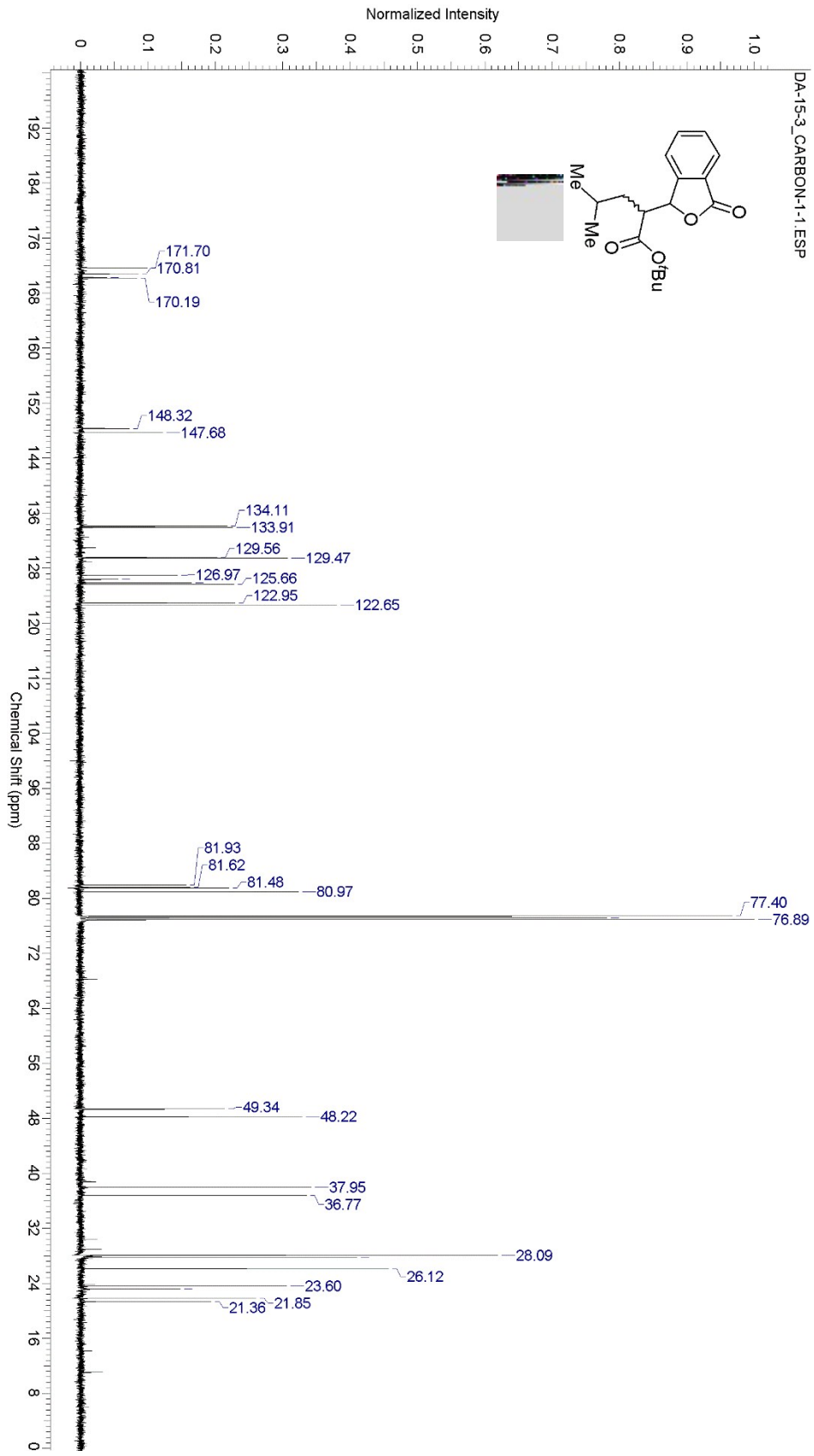

Normalized Intensity
DA-7-2_PROTON-1-1.ESP
Chemical Shift (ppm)
Me
O
O
O
O'Bu
M03(d)
M02(d)
M01(d)
7.89
7.88
7.66
7.66
7.65
7.53
7.49
7.46
7.44
7.26
1.04 1.14 1.09 0.52 0.57
5.78
5.76
5.75
1.02
3.11
3.10
3.10
3.09
3.08
3.08
2.82
2.80
2.79
2.78
0.49 0.56
4.73 4.27 1.59 1.41
1.44
1.37
1.14
1.13
1.06
1.05
0.05

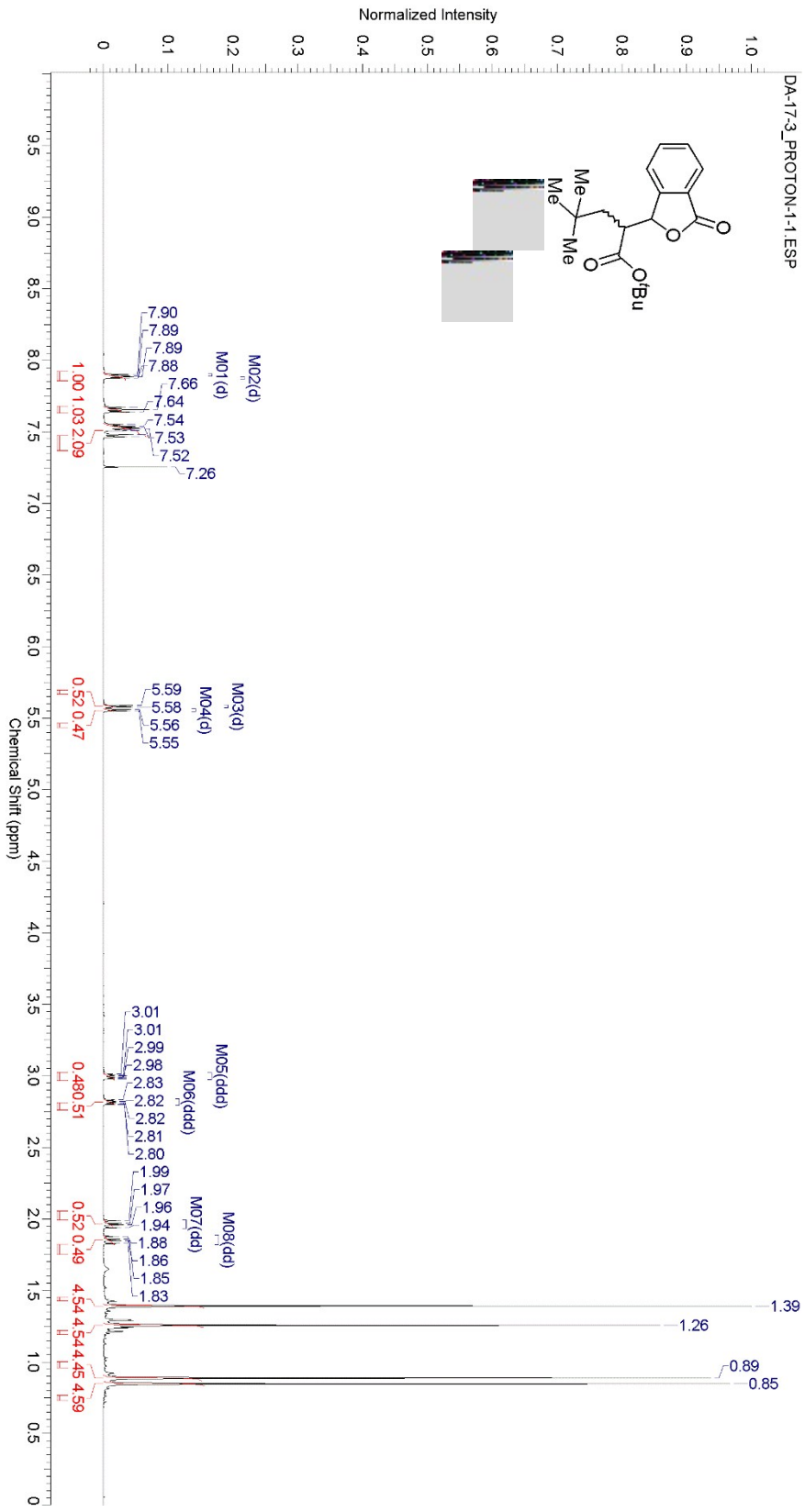

Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
DA-7-2_CARBON-1-1.ESP
Me
O
O
O
OtBu
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
171.78
171.31
170.35
148.30
147.55
134.30
134.07
129.53
129.44
126.97
125.83
125.72
122.93
122.31
81.82
81.72
81.52
81.38
77.43
77.17
76.92
44.79
43.84
28.05
27.96
11.99
11.59

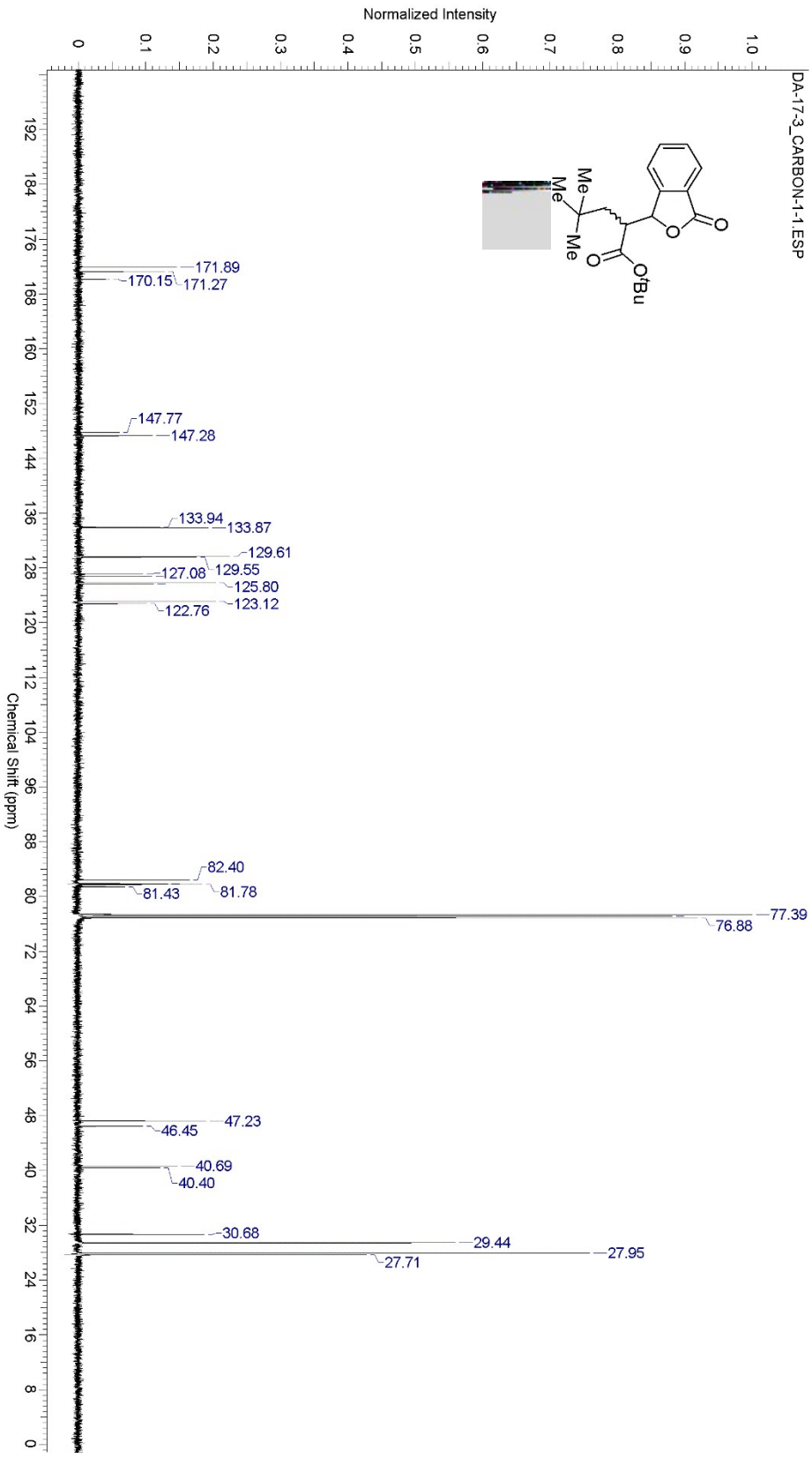

Normalized Intensity
DA-8-3_PROTON-1-1.ESP
Chemical Shift (ppm)
Me
O
O
O
O'Bu
7.88
7.86
7.66
7.64
7.63
7.52
7.51
7.46
7.44
7.26
M01(d)
1.01 1.08 2.16
5.63
5.62
5.61
1.00
2.80
2.79
2.78
2.77
2.51
2.51
2.50
2.49
M02(dt)
0.46 0.53
1.90
1.88
1.82
1.82
1.81
1.79
1.42
1.21
0.99
0.96
0.98
M03(t)
2.32 4.72 4.08 3.01
1.43
1.25

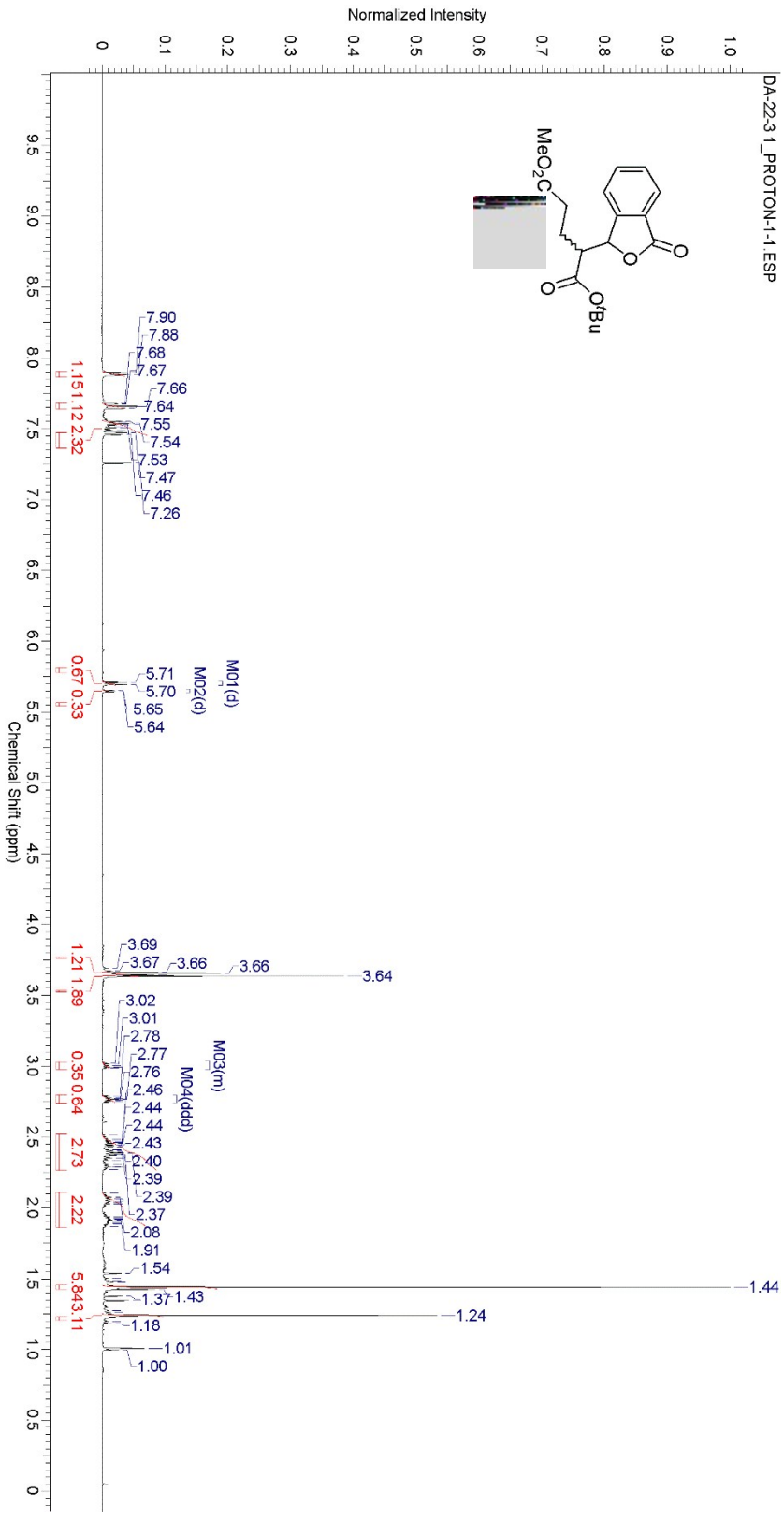

Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
DA-8-3_CARBON-1-1.ESP
Me
O
O
O
O
tBu
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
171.56
170.59
170.30
170.23
148.62
147.80
134.16
133.91
129.52
126.90
125.84
125.64
122.76
81.90
80.77
80.61
77.42
77.17
76.91
52.66
51.72
28.12
27.84
22.51
21.33
11.99
11.44

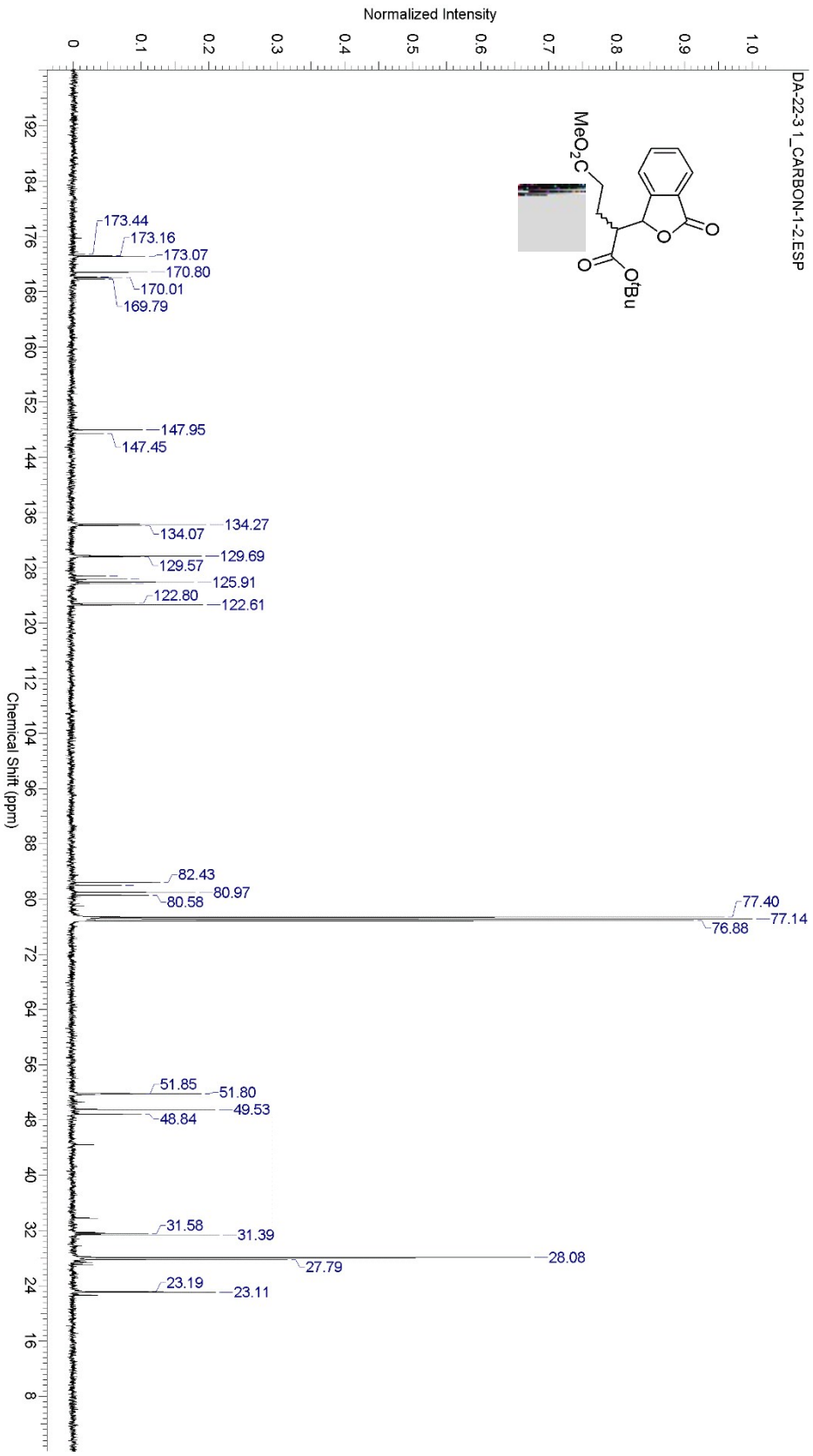

Normalized Intensity
DA-15-3_PROTON-1-1.ESP
Chemical Shift (ppm)
Me
Me
O
O
O
tBu
7.90
7.89
7.88
7.88
7.66
7.64
7.53
7.52-7.53
7.51
7.45
7.43
7.26
5.60
5.58
2.98
2.97
2.96
2.95
2.72
2.71
2.70
2.69
2.68
1.85
1.72
1.70
1.66
1.65
1.47
1.45
1.33
1.42
1.25
0.92
0.90
0.86
0.85
M01(ddd)
M02(ddd)
M03(d)
M04(d)
1.02 1.11 1.66 0.59
1.00
0.48 0.52
0.55 1.95 0.62 4.93 1.16 4.28 4.48 1.78


Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
DA-15-3_CARBON-1-1.ESP
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Me
Me
O
O
O
OtBu
171.70
170.81
170.19
148.32
147.68
134.11
133.91
129.56
129.47
126.97
125.66
122.95
122.65
81.93
81.62
81.48
80.97
77.40
76.89
49.34
48.22
37.95
36.77
28.09
26.12
23.60
21.36
21.85


Normalized Intensity
DA-17-3_PROTON-1-1.ESP
Chemical Shift (ppm)
Me
Me
Me
O
O
O
O
tBu
7.90
7.89
7.89
7.88
7.66
7.64
7.54
7.53
7.52
7.26
M01(d)
M02(d)
1.00 1.03 2.09
5.59
5.58
5.56
5.55
M03(d)
M04(d)
0.52 0.47
3.01
3.01
2.99
2.98
2.83
2.82
2.82
2.81
2.80
M05(ddd)
M06(ddd)
0.48 0.51
1.99
1.97
1.96
1.94
1.88
1.86
1.85
1.83
M07(dd)
M08(dq)
0.52 0.49
4.54 4.54 4.44 4.45 4.59
1.39
1.26
0.89
0.85


Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
DA-17-3_CARBON-1-1.ESP
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Me
Me
O
O
O
O
tBu
171.89
170.15
171.27
147.77
147.28
133.94
133.87
129.61
127.08
129.55
125.80
123.12
122.76
82.40
81.43
81.78
77.39
76.88
47.23
46.45
40.69
40.40
30.68
29.44
27.95
27.71


Normalized Intensity
DA-22-3 1_PROTON-1-1.ESP
MeO2C
O
O
O
O'Bu
Chemical Shift (ppm)
7.90
7.88
7.68
7.67
7.66
7.64
7.55
7.54
7.53
7.47
7.46
7.26
1.15 1.12 2.32
5.71
5.70
5.65
5.64
M01(d)
M02(d)
0.67 0.33
3.69
3.67
3.66
3.66
3.64
1.21 1.89
3.02
3.01
2.78
2.77
2.76
2.46
2.44
2.44
2.43
2.40
2.39
2.39
2.37
2.08
1.91
M03(m)
M04(ddd)
0.35 0.64
2.73
2.22
1.54
1.44
1.37
1.43
1.24
1.18
1.01
1.00
5.84 3.11


Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
DA-22-3 1_CARBON-1-2.ESP
MeO2C
O
O
O
OtBu
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
173.44
173.16
173.07
170.80
170.01
169.79
147.95
147.45
134.27
134.07
129.69
129.57
125.91
122.80
122.61
82.43
80.97
80.58
77.40
77.14
76.88
51.85
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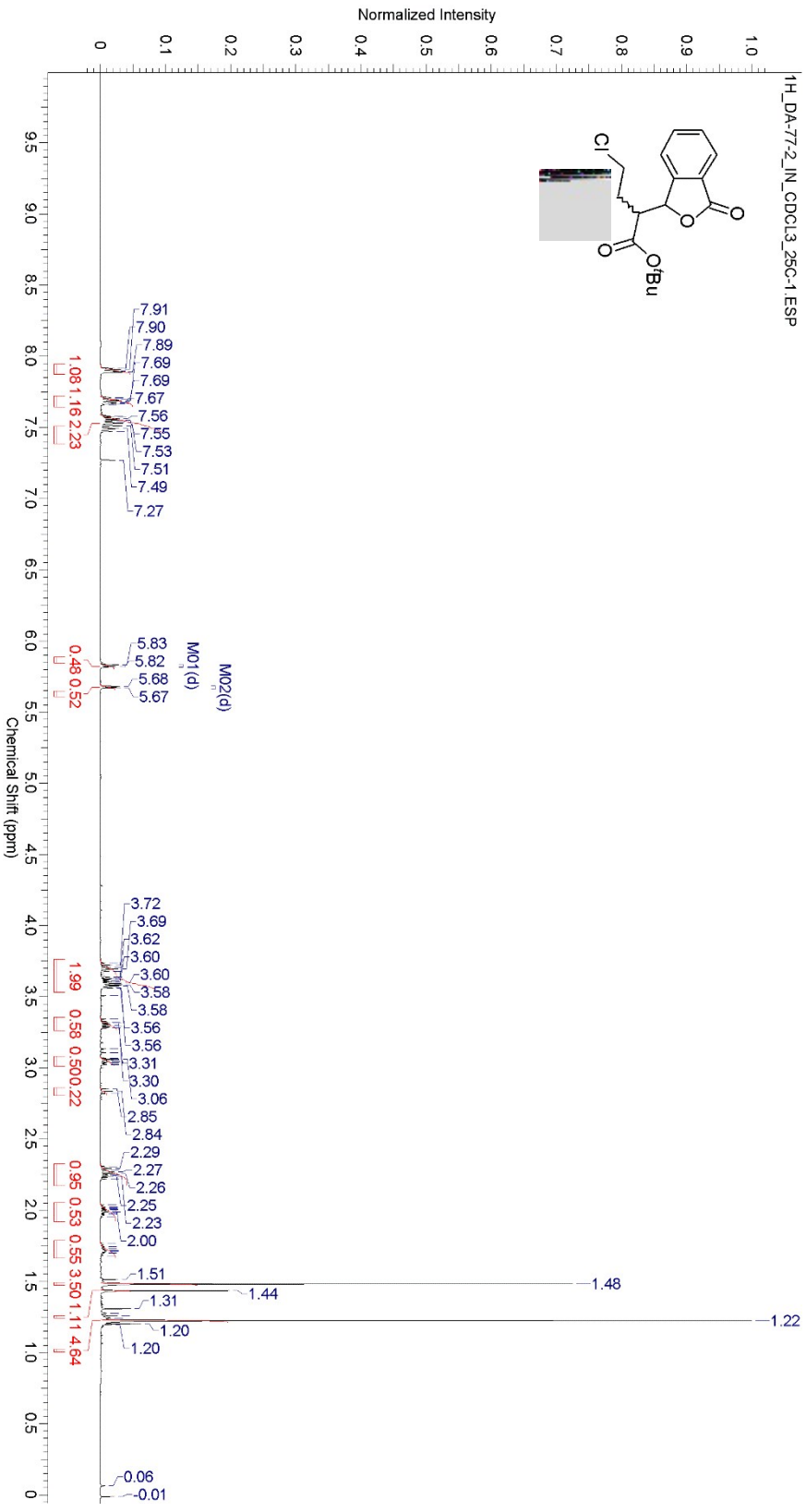
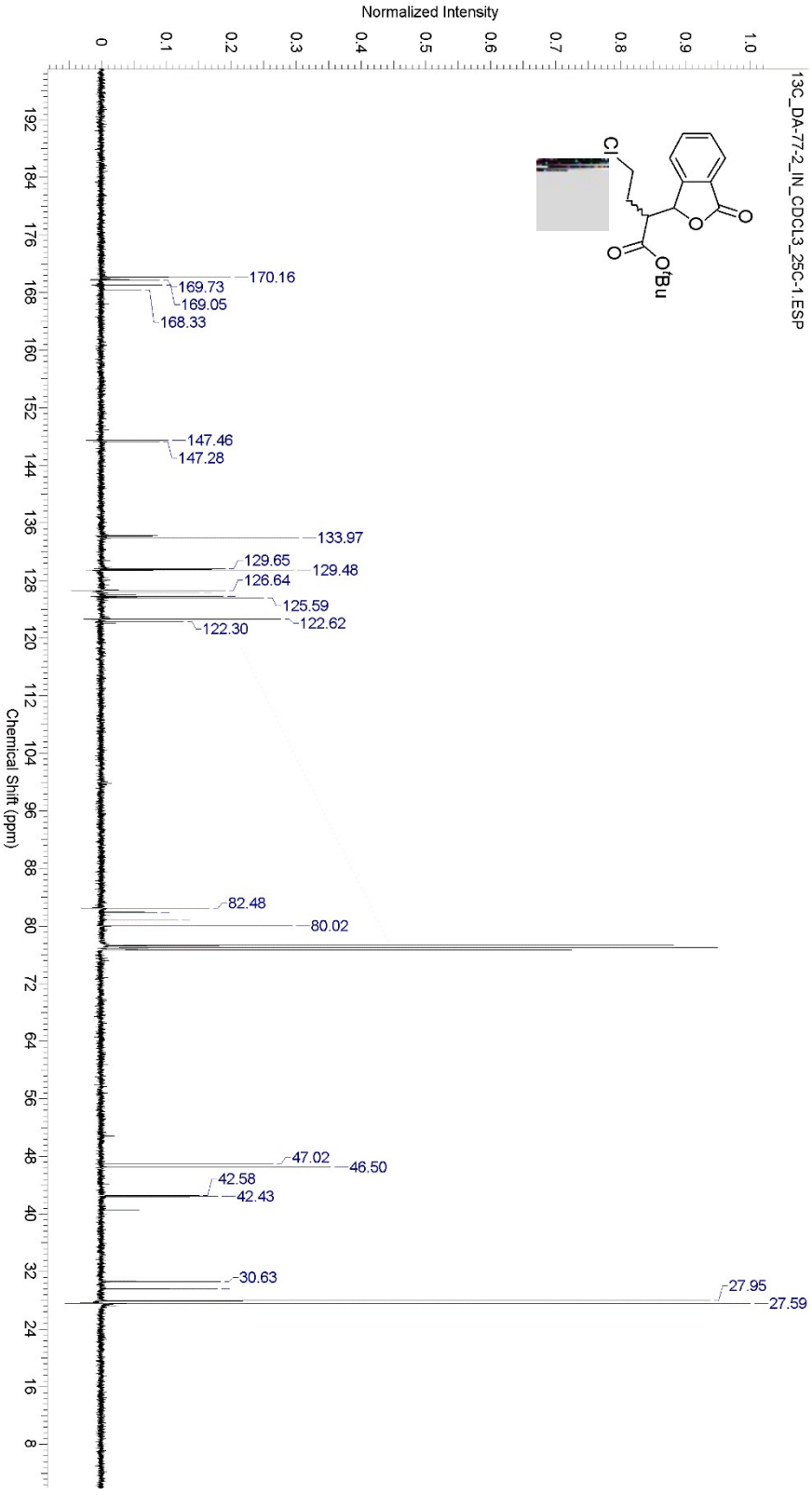
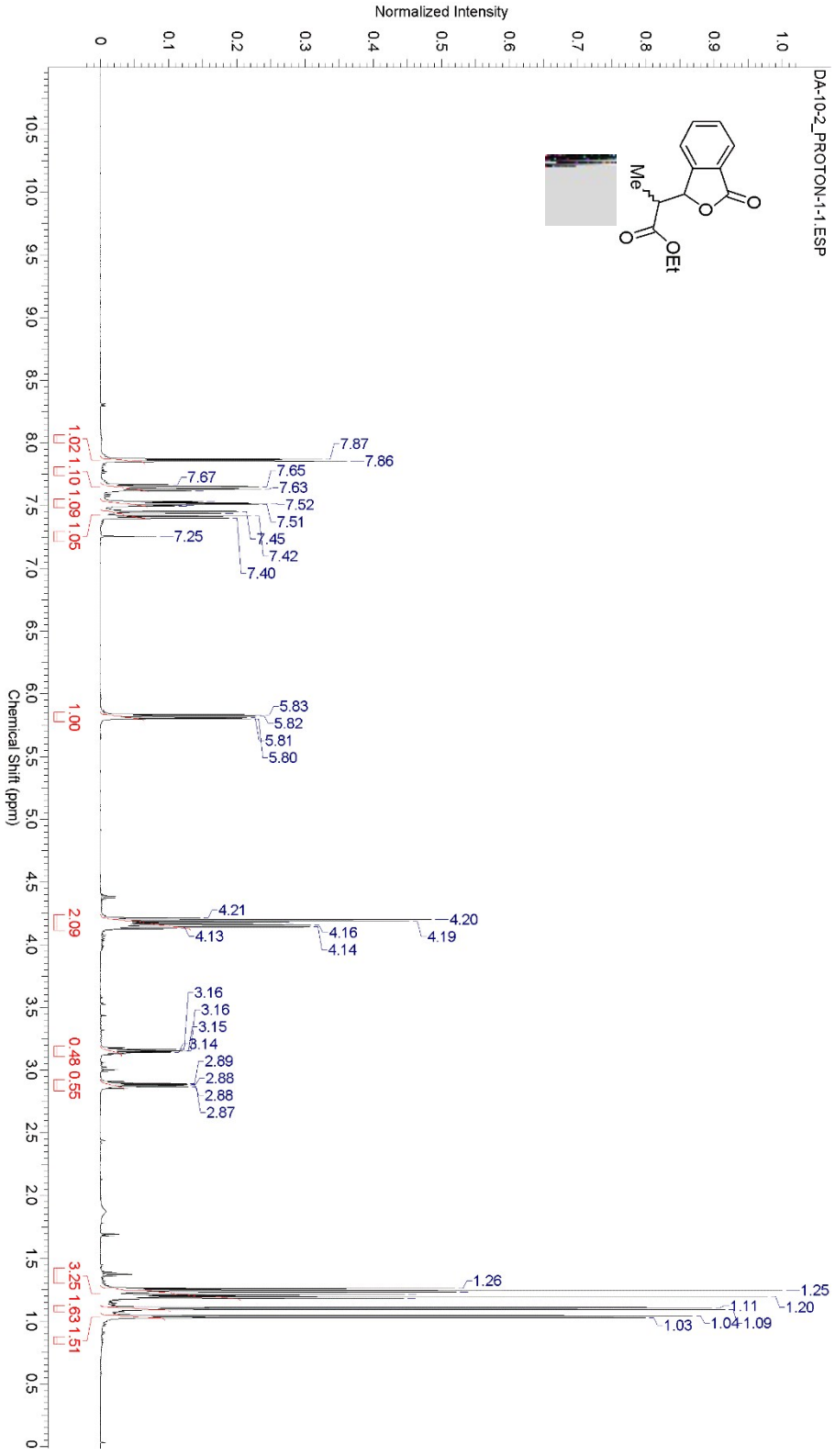
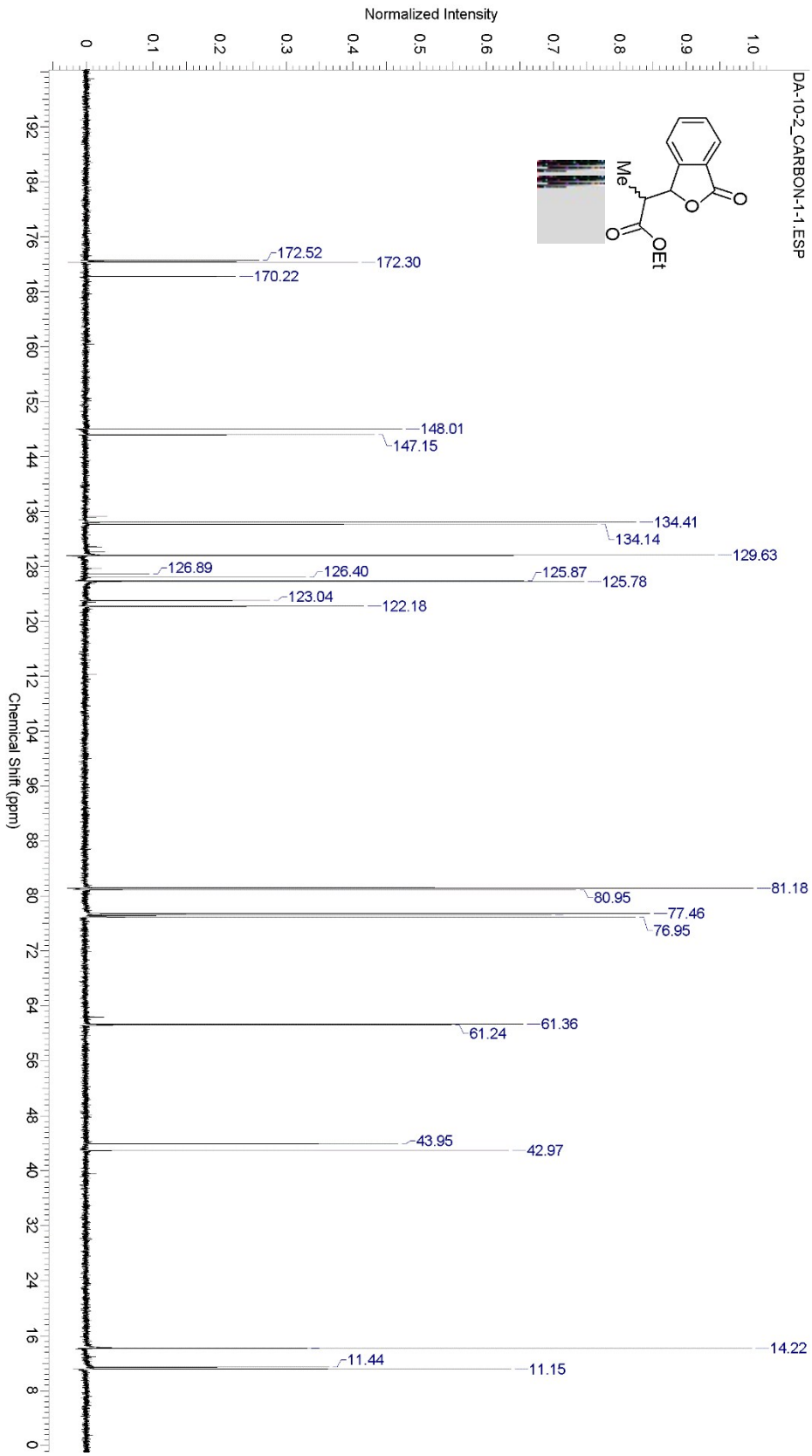
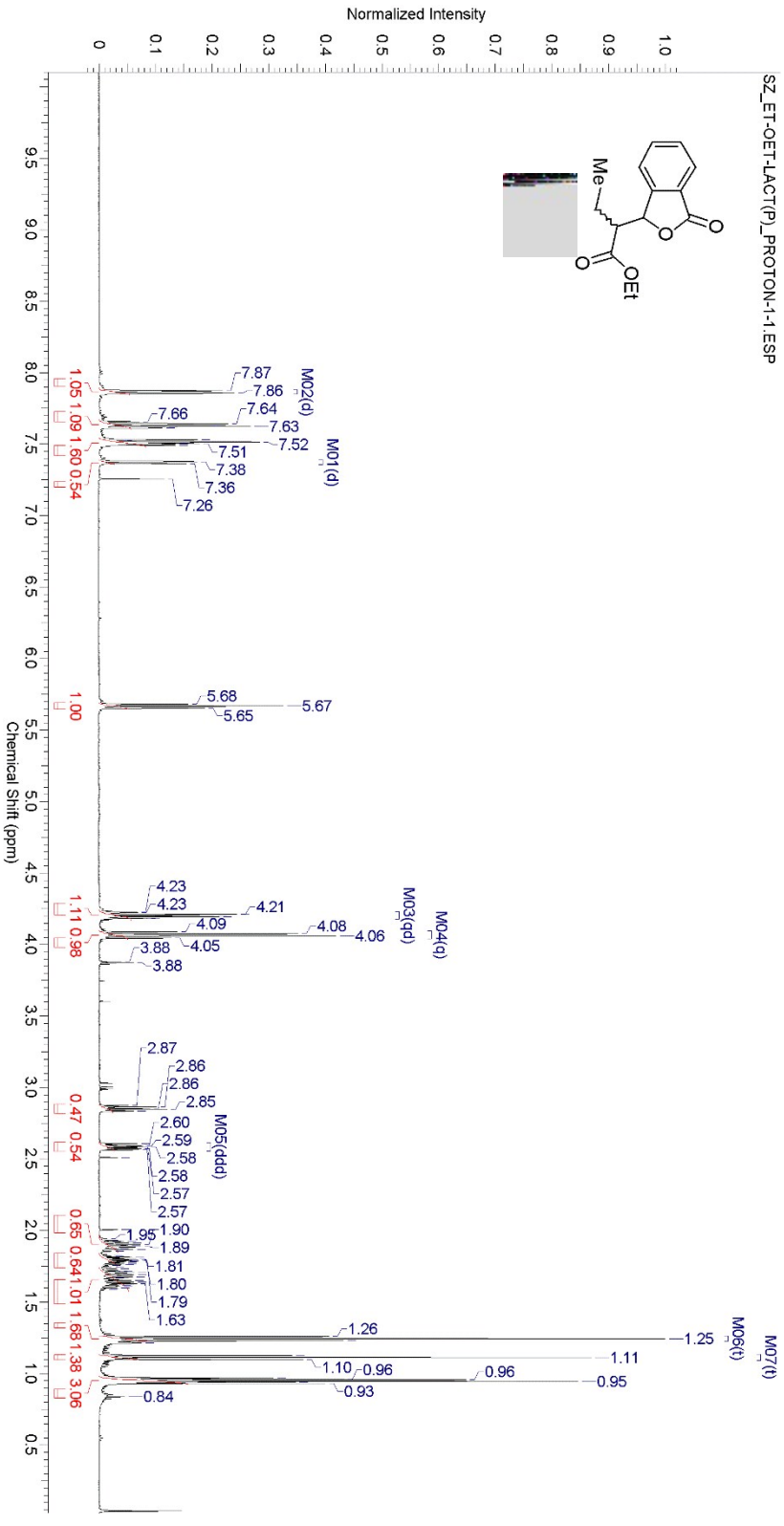
31.58
31.39
28.08
27.79
23.19
23.11

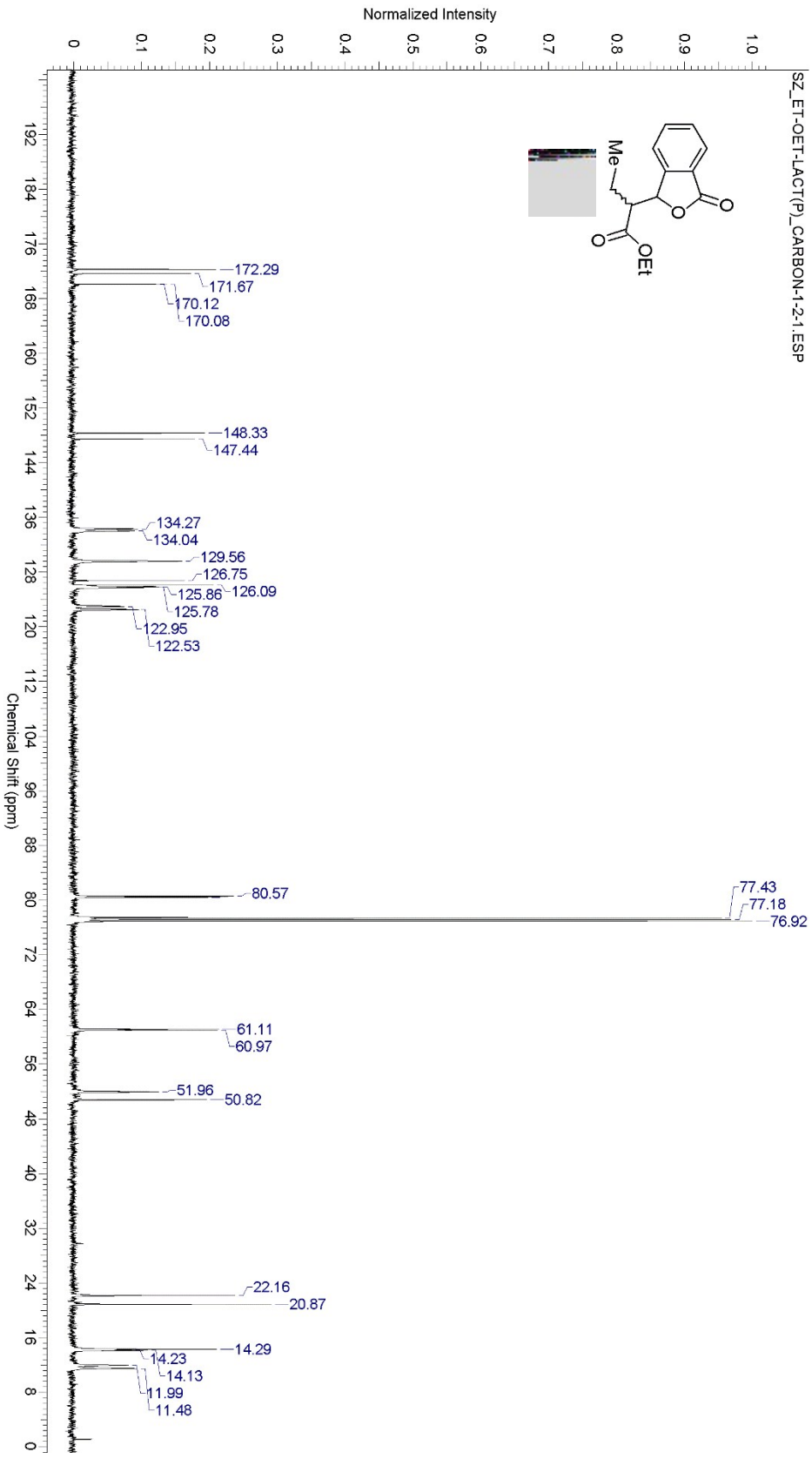

Normalized Intensity
1H_DA-77-2_IN_CDCl3_25C-1.ESP
Cl
O
O
O
O'Bu
Chemical Shift (ppm)
M01(d)
M02(d)
7.91
7.90
7.89
7.69
7.69
7.67
7.56
7.55
7.53
7.51
7.49
7.27
1.08 1.16 2.23
5.83
5.82
5.68
5.67
0.48 0.52
3.72
3.69
3.62
3.60
3.60
3.58
3.58
3.56
3.56
3.31
3.30
3.06
2.85
2.84
2.29
2.27
2.26
2.25
2.23
2.00
1.99 0.58 0.50 0.22
0.95 0.53 0.55 3.50 1.11 4.64
1.51
1.48
1.44
1.31
1.22
1.20
1.20
0.06
-0.01

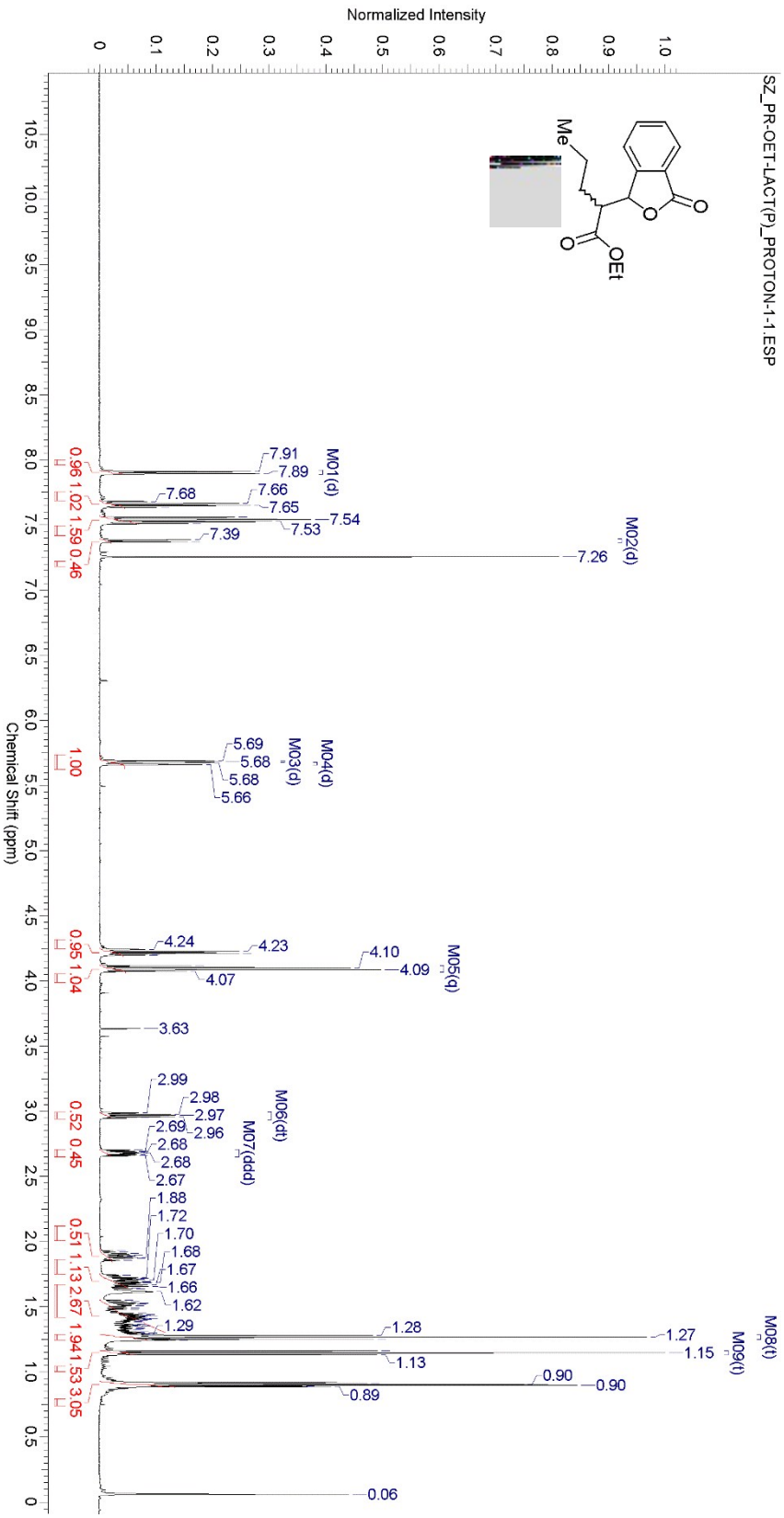

Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
13C_DA-77-2_IN_CDCL3_25C-1.ESP
Cl
O
O
O
O'Bu
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
170.16
169.73
169.05
168.33
147.46
147.28
133.97
129.65
129.48
126.64
125.59
122.62
122.30
82.48
80.02
47.02
46.50
42.58
42.43
30.63
27.95
27.59

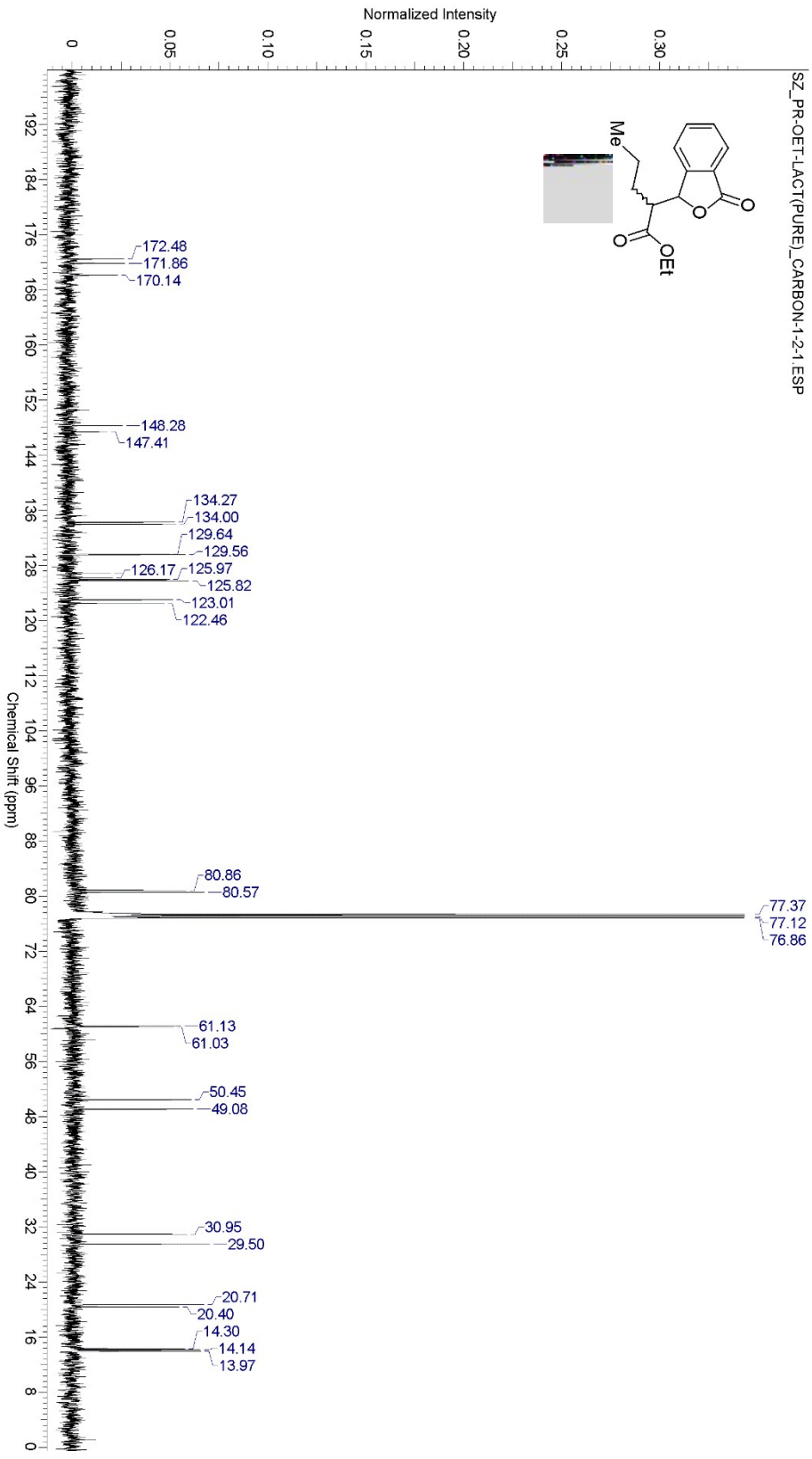

Normalized Intensity
DA-10-2_PROTON-1-1.ESP
Chemical Shift (ppm)
Me
OEt
7.87
7.86
7.67
7.65
7.63
7.52
7.51
7.45
7.42
7.40
7.25
5.83
5.82
5.81
5.80
4.21
4.20
4.19
4.16
4.14
4.13
3.16
3.16
3.15
3.14
2.89
2.88
2.88
2.87
1.26
1.25
1.20
1.11
1.04
1.09
1.03
1.02 1.10 1.09 1.05
1.00
2.09
0.48 0.55
3.25 1.63 1.51

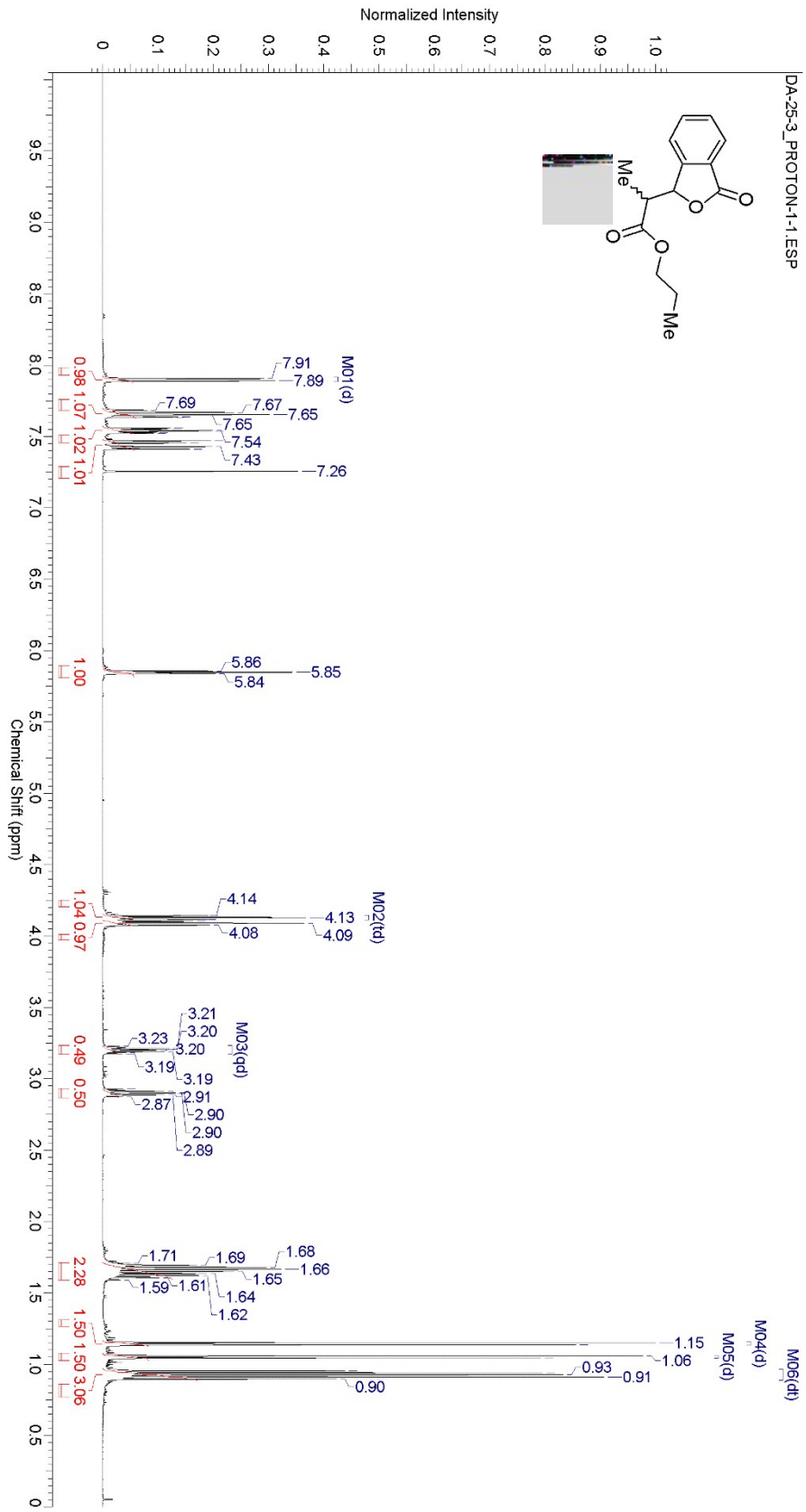

Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
DA-10-2_CARBON-1-1.ESP
Me
O
O
O
OEt
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
172.52
172.30
170.22
148.01
147.15
134.41
134.14
129.63
126.89
126.40
125.87
125.78
123.04
122.18
81.18
80.95
77.46
76.95
61.36
61.24
43.95
42.97
14.22
11.44
11.15

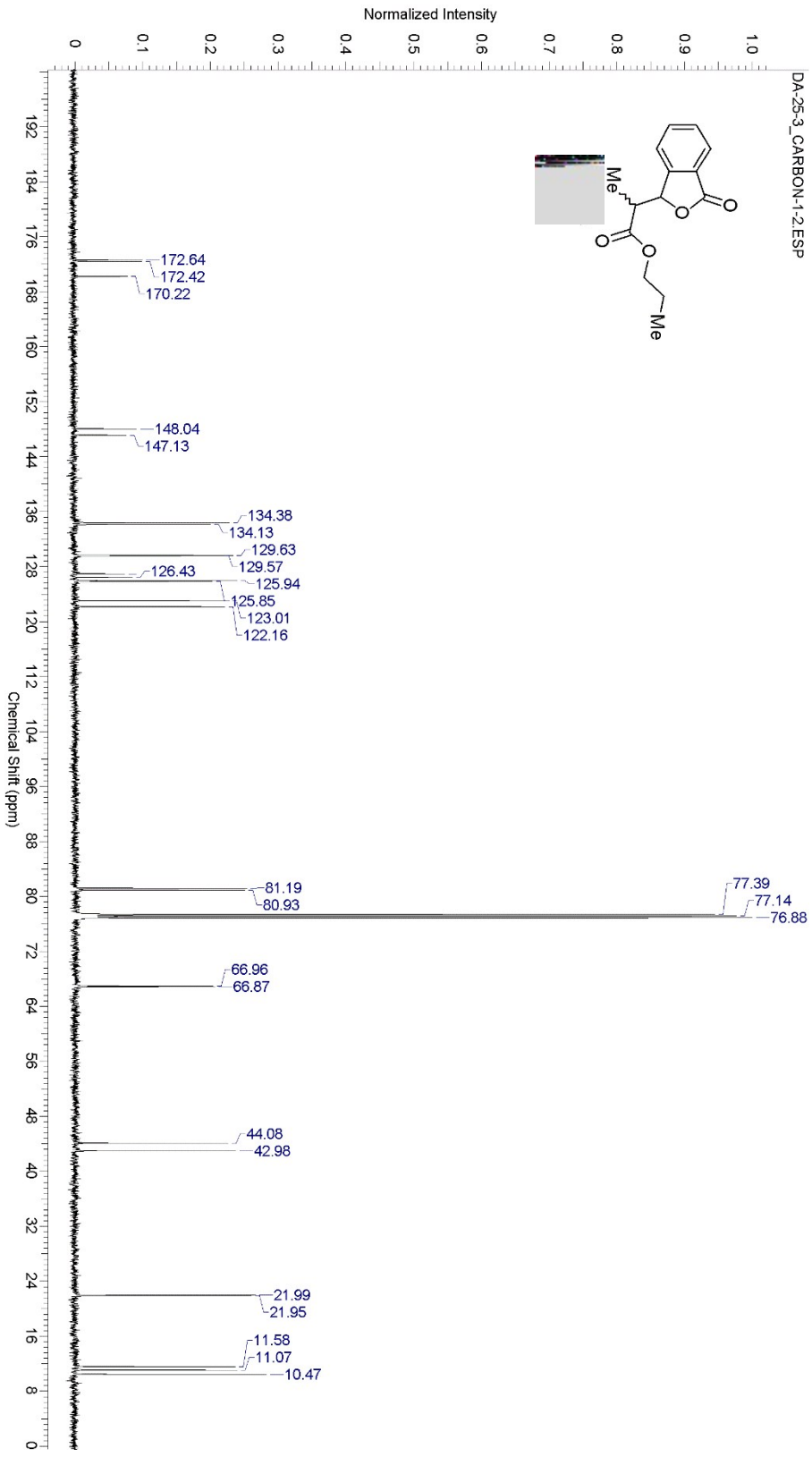

Normalized Intensity
SZ_ET-OET-LACT(P)_PROTON-1-1.ESP
Chemical Shift (ppm)
Me
OEt
M01(d)
M02(d)
M03(qd)
M04(q)
M05(ddd)
M06(t)
M07(t)

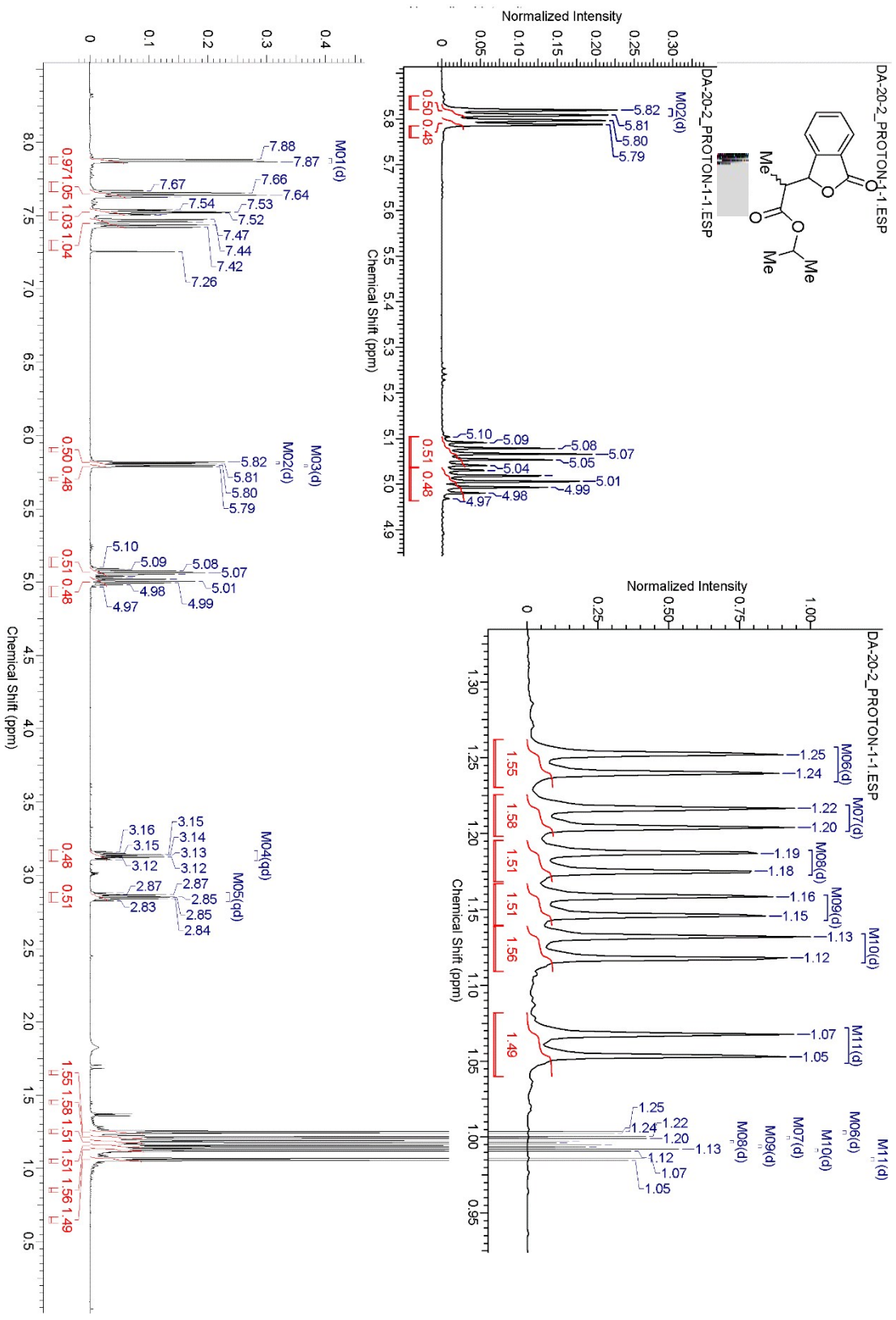

Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
SZ_ET-OET-LACT(P)_CARBON-1-2-1.ESP
Me
O
O
OEt
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
172.29
171.67
170.12
170.08
148.33
147.44
134.27
134.04
129.56
126.75
125.86
126.09
125.78
122.95
122.53
80.57
77.43
77.18
76.92
61.11
60.97
51.96
50.82
22.16
20.87
14.29
14.23
14.13
11.99
11.48

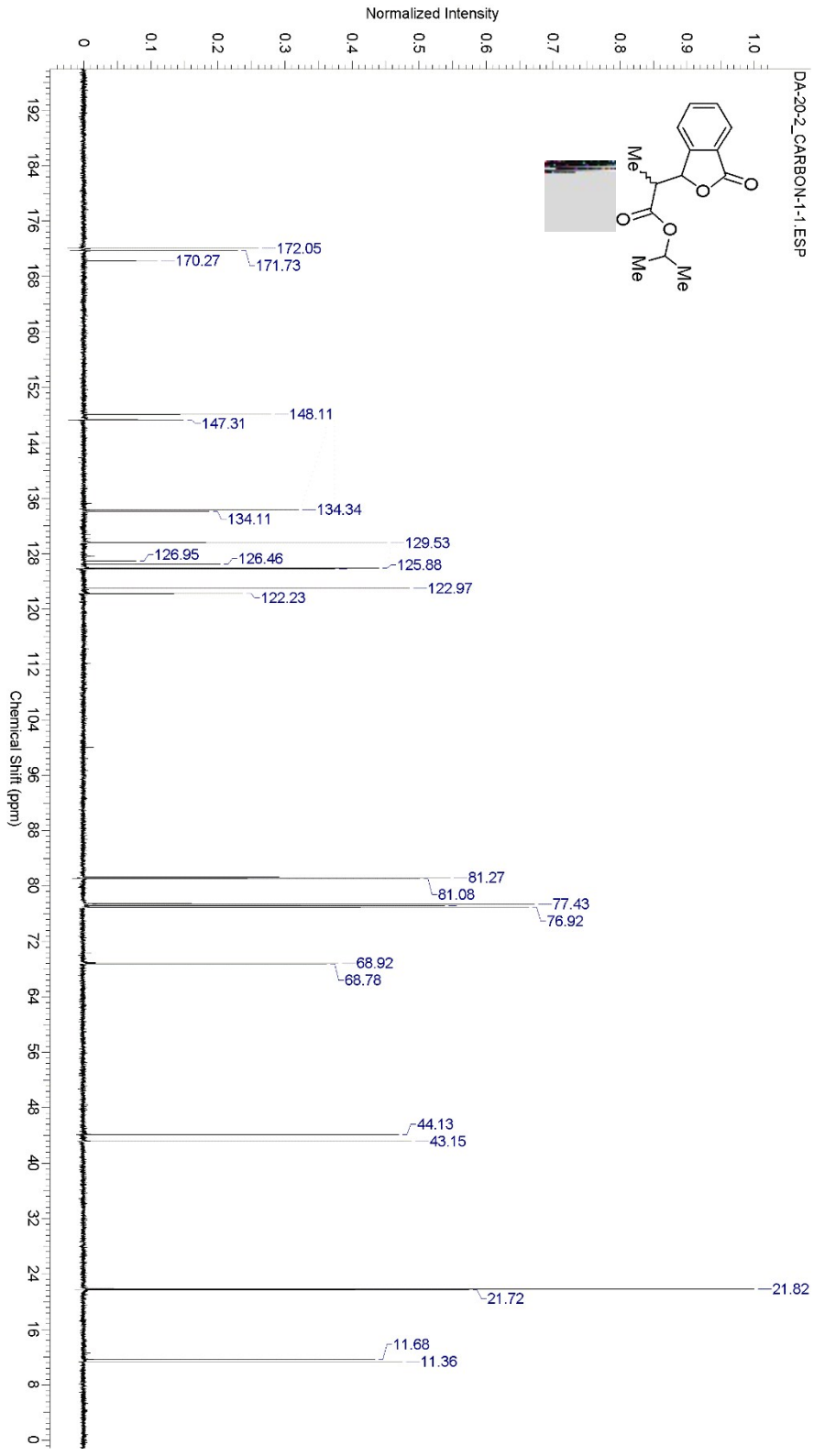

Normalized Intensity
SZ_PR-OET-LACT(P)_PROTON-1-1.ESP
Me
OEt
Chemical Shift (ppm)
M01(q)
M02(d)
M03(d)
M04(d)
M05(q)
M06(dt)
M07(ddd)
M08(t)
M09(t)
7.91
7.89
7.68
7.66
7.65
7.54
7.53
7.39
7.26
5.69
5.68
5.68
5.66
4.24
4.23
4.10
4.09
4.07
3.63
2.99
2.98
2.97
2.69
2.96
2.68
2.68
2.67
1.88
1.72
1.70
1.68
1.67
1.66
1.62
1.29
1.28
1.27
1.15
1.13
0.90
0.90
0.89
0.06
0.96 1.02 1.59 0.46
1.00
0.95 1.04
0.52 0.45
0.51 1.13 2.67 1.94 1.53 3.05

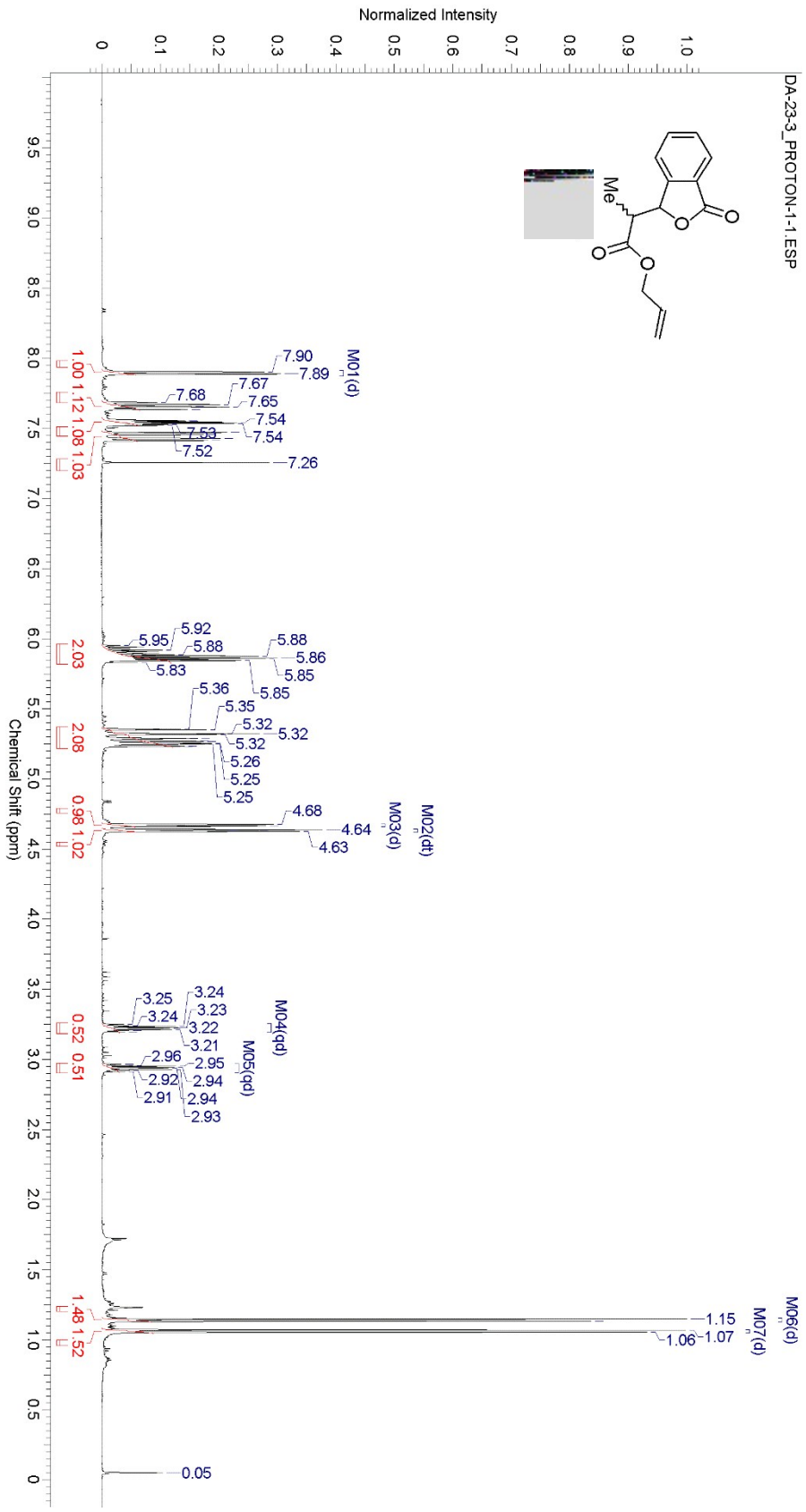

Normalized Intensity
0
0.05
0.10
0.15
0.20
0.25
0.30
SZ_PR-OET-LACT(PURE)_CARBON-1-2-1.ESP
Me
O
O
O
OEt
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
172.48
171.86
170.14
148.28
147.41
134.27
134.00
129.64
129.56
126.17
125.97
125.82
123.01
122.46
80.86
80.57
77.37
77.12
76.86
61.13
61.03
50.45
49.08
30.95
29.50
20.71
20.40
14.30
14.14
13.97

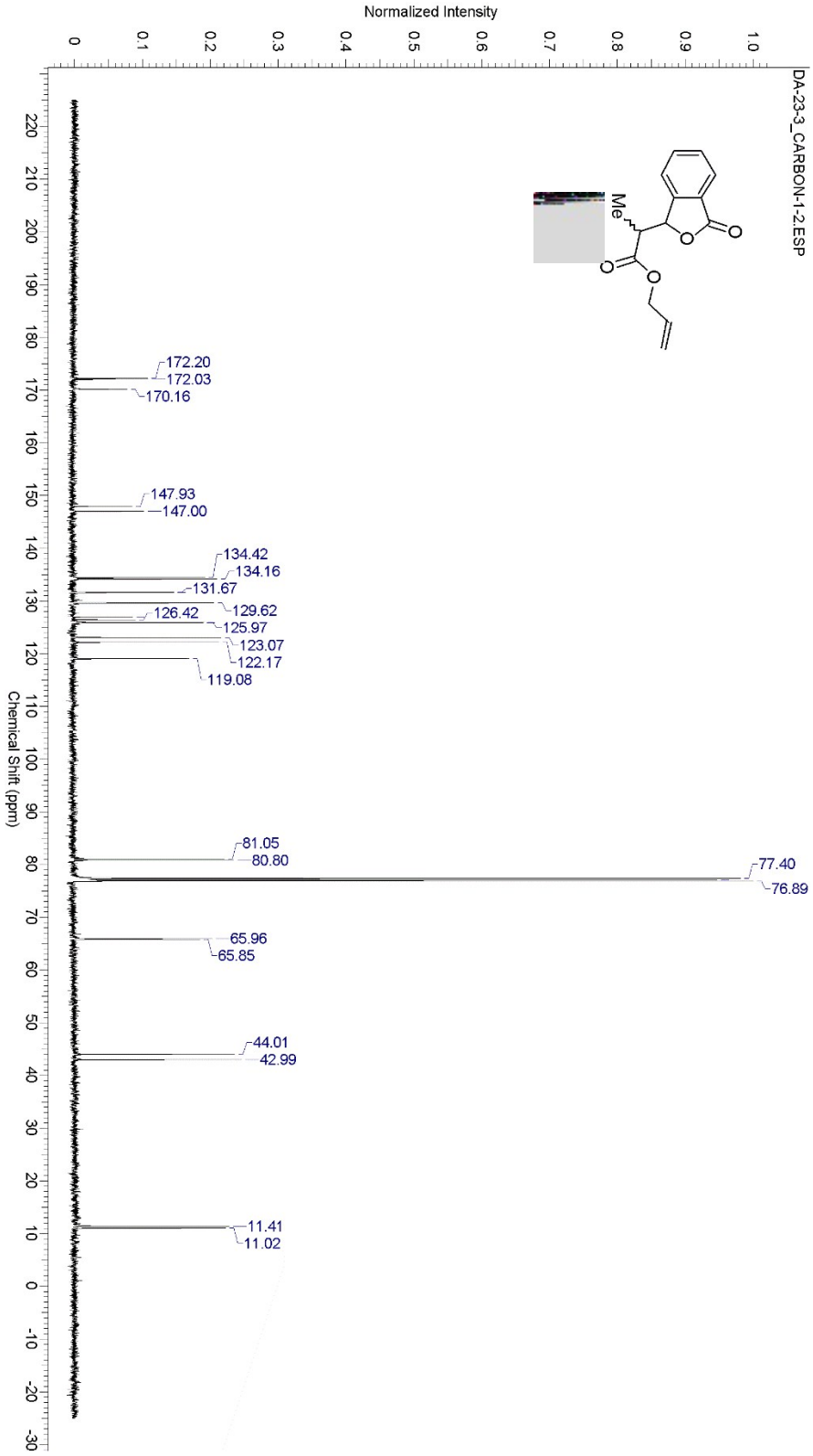

Normalized Intensity
DA-25-3_PROTON-1-1.ESP
Chemical Shift (ppm)
M01(d)
M02(td)
M03(qd)
M04(d)
M05(d)
M06(dt)
Me
Me

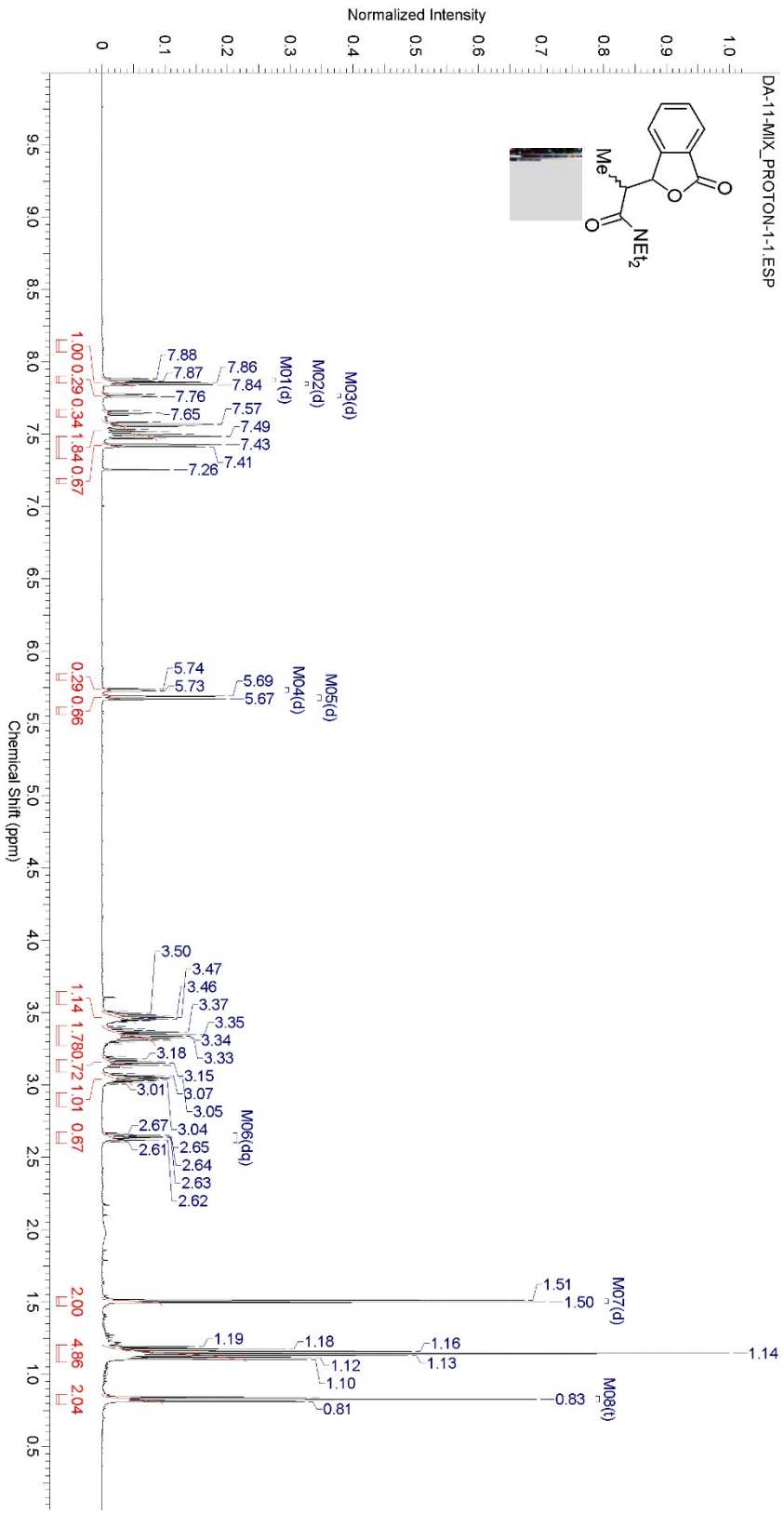

Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
DA-25-3_CARBON-1-2.ESP
Me
O
O
O
O
Me
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
172.64
172.42
170.22
148.04
147.13
134.38
134.13
129.63
129.57
126.43
125.94
125.85
123.01
122.16
81.19
80.93
77.39
77.14
76.88
66.96
66.87
44.08
42.98
21.99
21.95
11.58
11.07
10.47

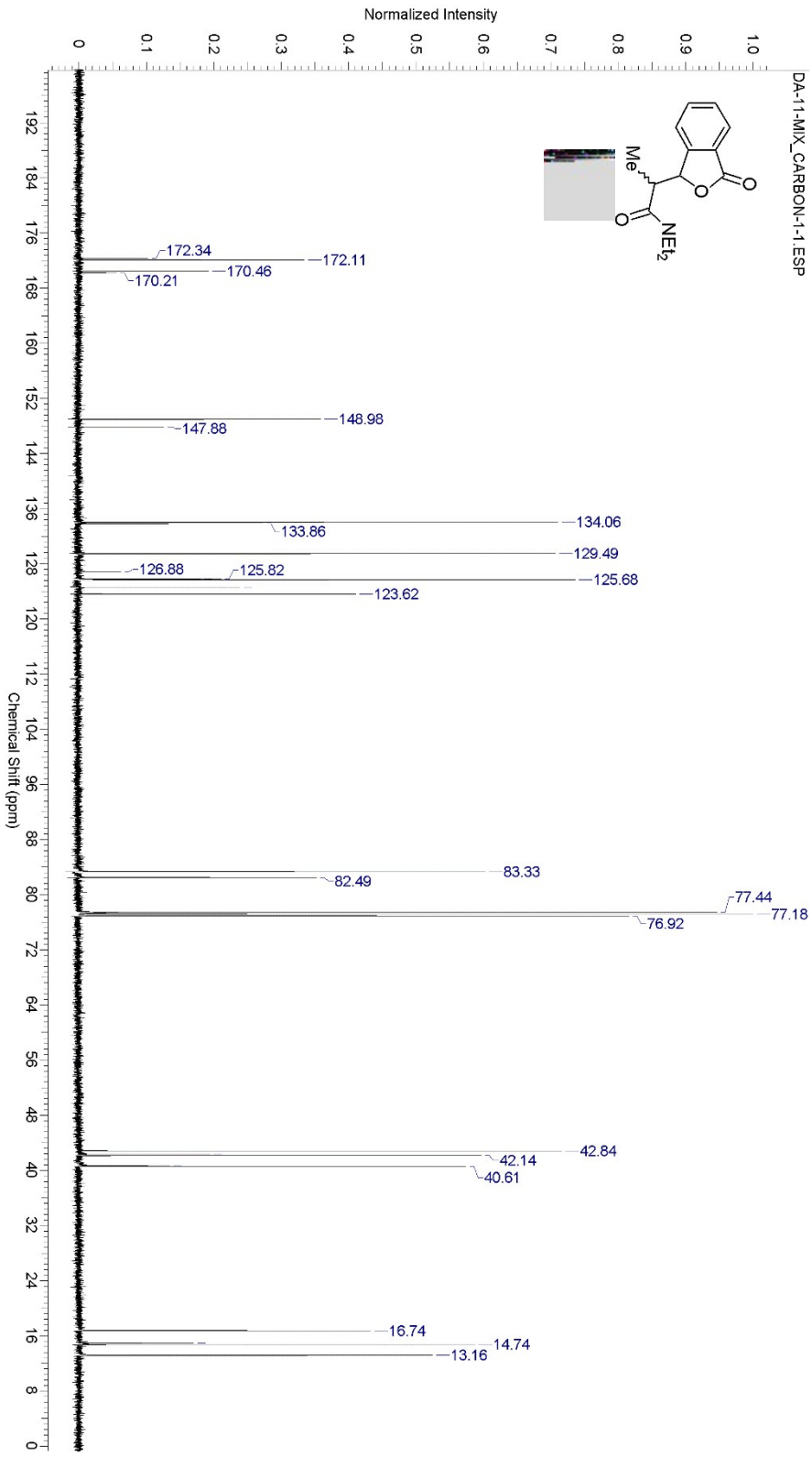

DA-20-2_PROTON-1-1.ESP
Normalized Intensity
Chemical Shift (ppm)
M01(d)
M02(d)
M03(d)
M04(qd)
M05(qd)
M06(d)
M07(d)
M08(d)
M09(d)
M10(d)
M11(d)
Me
Me
Me
O
O
O
O

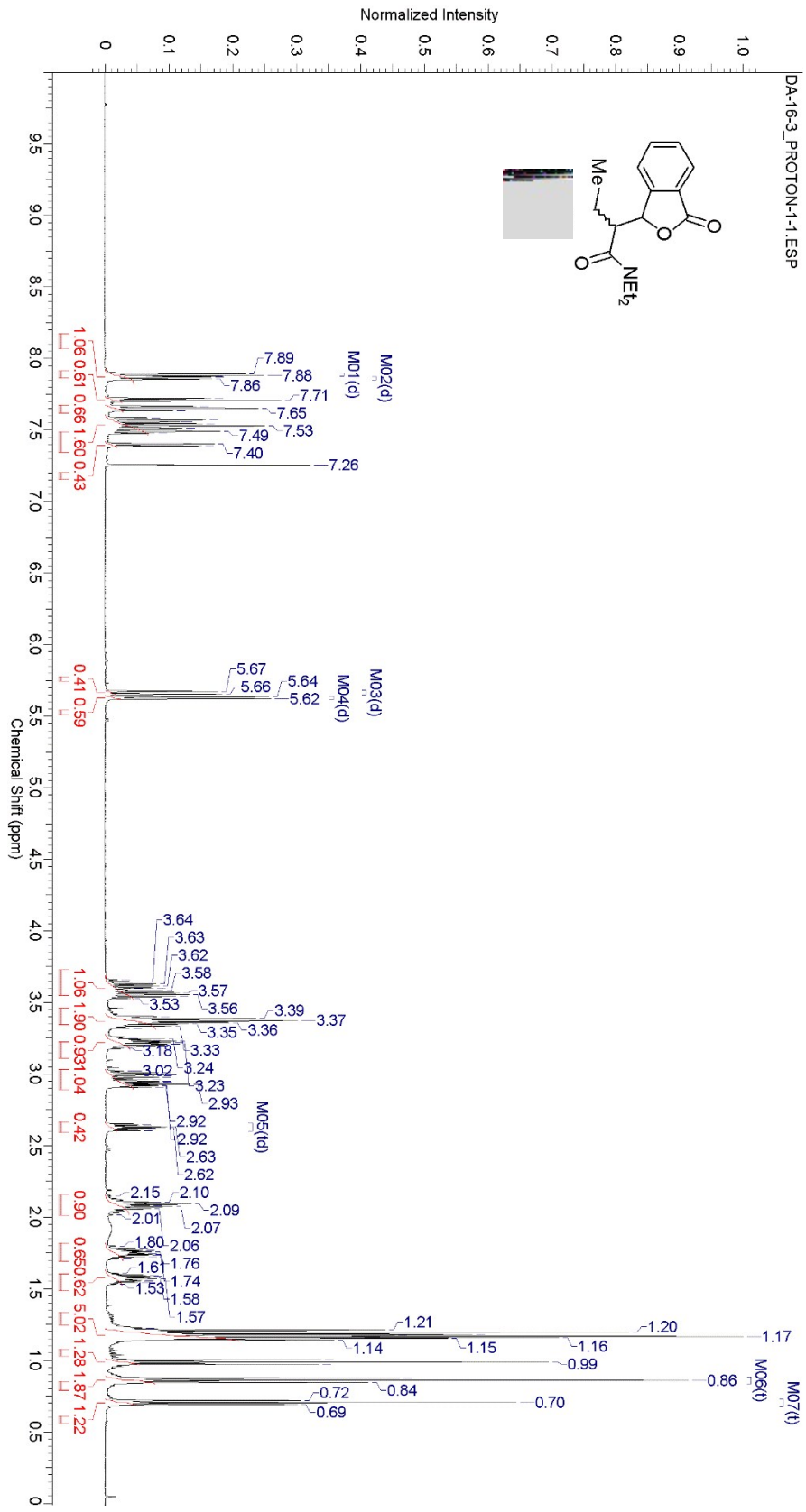

Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
DA-20-2_CARBON-1-1.ESP
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
172.05
170.27
171.73
148.11
147.31
134.34
134.11
129.53
126.95
126.46
125.88
122.97
122.23
81.27
81.08
77.43
76.92
68.92
68.78
44.13
43.15
21.82
21.72
11.68
11.36
Me
Me
Me
O
O
O
O

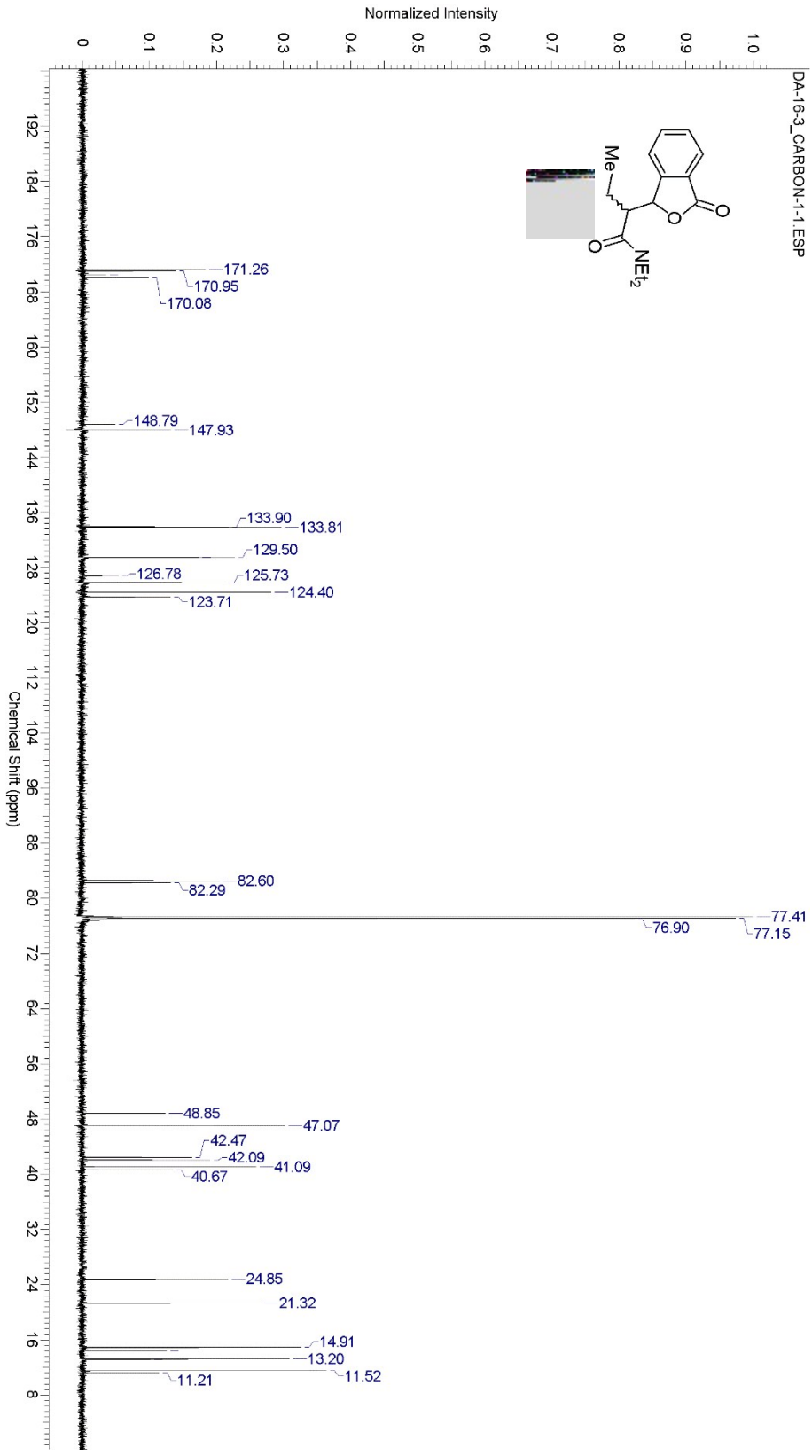

Normalized Intensity
DA-23-3_PROTON-1-1.ESP
Chemical Shift (ppm)
Me
M01(d)
M02(dt)
M03(d)
M04(qd)
M05(qd)
M06(d)
M07(d)
7.90
7.89
7.68
7.67
7.65
7.54
7.54
7.53
7.52
7.26
5.95
5.92
5.88
5.88
5.86
5.85
5.85
5.83
5.36
5.35
5.32
5.32
5.32
5.26
5.25
5.25
4.68
4.64
4.63
3.25
3.24
3.24
3.23
3.22
3.21
2.96
2.95
2.94
2.94
2.93
2.92
2.91
1.15
1.07
1.06
0.05
1.00 1.12 1.08 1.03
2.03
2.08
0.98 1.02
0.52 0.51
1.48 1.52


Normalized Intensity
DA-23-3_CARBON-1-2.ESP
Chemical Shift (ppm)
Me
O
O
O
O
172.20
172.03
170.16
147.93
147.00
134.42
134.16
131.67
129.62
126.42
125.97
123.07
122.17
119.08
81.05
80.80
77.40
76.89
65.96
65.85
44.01
42.99
11.41
11.02


Normalized Intensity
DA-11-MIX_PROTON-1-1.ESP
Chemical Shift (ppm)
Me
NEt2
7.88
7.87
7.86
7.84
7.76
7.65
7.57
7.49
7.43
7.41
7.26
M01(d)
M02(d)
M03(d)
5.74
5.73
5.69
5.67
M04(d)
M05(d)
3.50
3.47
3.46
3.37
3.35
3.34
3.33
3.18
3.15
3.07
3.05
3.04
3.01
2.67
2.65
2.64
2.63
2.62
2.61
M06(dq)
1.51
1.50
M07(d)
1.19
1.18
1.16
1.14
1.13
1.12
1.10
0.83
0.81
M08(t)
1.00 0.29 0.34 1.84 0.67
0.29 0.66
1.14 1.78 0.72 1.01 0.67
2.00
4.86
2.04


Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
DA-11-MIX_CARBON-1-1.ESP
Me
O
O
O
NEt2
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
172.34
172.11
170.46
170.21
148.98
147.88
134.06
133.86
129.49
126.88
125.82
125.68
123.62
83.33
82.49
77.44
77.18
76.92
42.84
42.14
40.61
16.74
14.74
13.16


Normalized Intensity
DA-16-3_PROTON-1-1.ESP
Chemical Shift (ppm)
Me
NEt2
M01(d)
M02(d)
M03(d)
M04(d)
M05(td)
M06(t)
M07(t)


Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
DA-16-3_CARBON-1-1.ESP
Me
O
O
O
NEt2
Chemical Shift (ppm)
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
171.26
170.95
170.08
148.79
147.93
133.90
133.81
129.50
126.78
125.73
124.40
123.71
82.60
82.29
77.41
77.15
76.90
48.85
47.07
42.47
42.09
41.09
40.67
24.85
21.32
14.91
13.20
11.52
11.21