A Short Total Synthesis of (±)-Aspidospermidine

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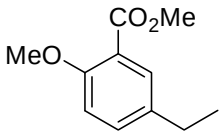
Supporting Information

Content

General Experimental

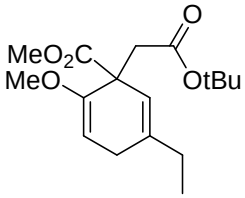
All reactions were carried out under an inert atmosphere. Commercial reagents were used as received without further purification. NMR spectra were recorded using a Bruker AMX400 operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Residual benzene (δ 7.15) and chloroform (δ 7.26) were used as internal references for ^{1}H NMR spectra measured in these solvents. Residual benzene (δ 128.1) and chloroform (δ 77.0) were used as internal references for ^{13}C NMR spectra. Coupling constants are in Hertz (*J* Hz). Mass spectra were recorded with a HP 5989B mass spectrometer using electron impact (EI). Infra-red spectra were recorded with a Perkin-Elmer 1600 Fourier Transform Spectrophotometer and are reported in terms of frequency of absorption (cm^{-1}). Analytical TLC was carried out on Merck silica gel plates using short wave (254 nm) UV light, $KMnO_4$ and anisaldehyde staining to visualise components. Silica gel (Silice 60, A C.C 40-63, SDS) was used for flash chromatography.

Methyl 5-ethyl-2-methoxybenzoate (4)



To a solution of methyl 5-ethyl-2-hydroxybenzoate (1.8 g, 10 mmol) in acetone (50 mL) at room temperature was added potassium carbonate (2 g, 15 mmol) and methyl iodide (1.3 mL, 20 mmol). After 6 hours the reaction mixture was concentrated then diluted with diethyl ether and water. The organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (1:9 ethyl acetate/hexanes) to yield the title compound as a colourless oil (1.65 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, d, J = 2.8 Hz), 7.23 (1H, dd, J = 6.2, 2.8 Hz), 6.80 (1H, d, J = 6.2 Hz), 3.84 (6H, s), 2.63 (2H, q, J = 7.4 Hz), 1.32 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 158.6, 133.2, 131.8, 130.1, 113.8, 113.5, 56.4, 52.4, 33.6, 15.2; IR (thin film) ν_{max} 3027, 2940, 1680, 1437, 1260, 1102 cm^{-1}; MS (CI): *m/z* (%) 195 $[M + H]^+$, 212 $[M + NH_3]^+$; HRMS (EI) calcd for $C_{11}H_{14}O_3$ $[M]^+$ 194.0943, found 194.0937

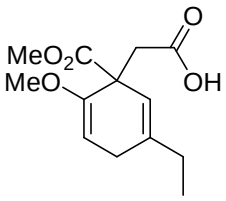
(±)- Methyl 5-Ethyl-2-methoxy-1-(*tert*-butoxycarbonylmethyl)cyclohexa-2,5-diene carboxylate (6)



To a solution of the ester **4** (5.0 g, 25.6 mmol) in THF (8.8 mL), *t*-butanol (2.1 mL) and ammonia (250 mL) at −40 ºC was added lithium (448 mg, 74 mmol, 3 equiv). A permanent blue colour resulted and after 5 minutes, *tert*-butylbromoacetate (7.3 mL, 49.4 mmol, 1.9 equiv) was added slowly. After a further 5 minutes the ammonia was allowed to evaporate at room temperature. The residue was neutralised with 2M HCl and the aqueous layer was extracted with diethyl ether. The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (1:5 diethyl ether/hexanes) to yield the title compound **6** as a colourless oil (5.36 g, 21.8 mmol, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33-5.31 (1H, m), 4.81 (1H, t, J = 3.5 Hz), 3.64 (3H, s), 3.52 (3H, s), 2.80-2.72 (3H, m), 2.67 (1H, dd, J = 22.0, 3.7 Hz), 2.01 (2H, qd, J = 7.9, 3.5 Hz), 1.34 (9H, s), 1.00 (3H, t, J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$)

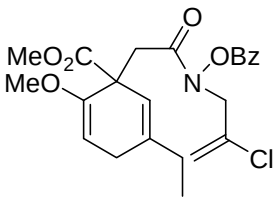
δ 173.1, 169.9, 152.3, 139.4, 119.2, 93.5, 79.8, 54.4, 52.5, 50.9, 41.9, 29.5, 28.9, 27.9, 12.0; IR (thin film) ν_{max} 3040, 2951, 1752, 1739, 1638, 1392, 1208, 1093 cm^{-1}; MS (CI): *m/z* (%) 311 $[M + H]^+$, 328 $[M + NH_3]^+$; HRMS (EI) calcd for $C_{13}H_{18}O_5$ $[M]^+$ 254.1154, found 254.1142.

(±)-2-(1-(Methoxycarbonyl)-5-ethyl-2-methoxycyclohexa-2,5-dienyl)acetic acid(7)



To solution of the *tert*-butyl ester **6** (438 mg, 1.5 mmol) in dichloromethane (15 mL) at 0 ºC was added 2,6-lutidine (700 µL, 3.2 mmol) and trimethylsilyltrifluoromethane sulfonate (700 µL, 3.4 mmol). After 1 hour water was added, the aqueous phase was acidified and extracted with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo* to leave the acid **7** as a colourless oil (372 mg, 98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.2 (1H, br s), 5.40-5.36 (1H, m), 4.85 (1H, t, *J* = 3.5 Hz), 3.69 (3H, s), 3.55 (3H, s), 3.01 (1H, d, *J* = 14.9 Hz), 2.82 (1H, d, *J* = 14.9 Hz), 2.77 (2H, s), 2.07 (2H, qd, *J* = 7.3, 3.5 Hz), 1.03 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 157.1, 139.5, 131.1, 119.4, 93.5, 65.7, 54.6, 51.6, 41.7, 29.0, 27.6, 11.3; IR (thin film) ν_{max} 3051, 2936, 1746, 1692, 1408, 1361, 1207, 1104 cm^{-1}; MS (CI): *m/z* (%) 255 $[M + H]^+$, 272 $[M + NH_3]^+$; HRMS (EI) calcd for $C_{17}H_{26}O_5$ $[M]^+$ 310.1780, found 310.1793.

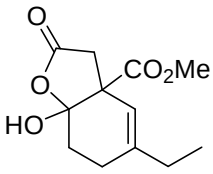
(±)-Methyl 1-[(*N*-2-Chloroallyl-*N*-benzyloxycarbomoyl)methyl]-5-ethyl-2-methoxy-cyclohexa-2,5-diene carboxylate (9)



A solution of the acid **7** (960mg, 4.02 mmol) and *N*-(2-chloroallyl) hydroxylammonium trifluoroacetate **8** (1.83g) in tetrahydrofuran (18 mL) and water (18 ml) was adjusted to pH 5. EDC (1.30 g, 6.78 mmol, 1.7 equiv) as added and the resulting mixture was stirred at rt for 2 hours. The mixture was diluted with diethyl ether, the aqueous phase was separated and extracted with diethyl ether and the combined organic extracts were washed with water. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (1:5 diethyl ether/hexanes) to yield the hydroxylamine (960 mg, 2.79 mmol, 69%). This hydroxylamine (800 mg, 2.33 mmol)

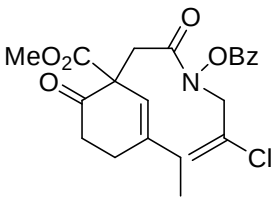
was dissolved in dichloromethane (44 mL) and triethylamine (3.3 mL, 20 mmol, 10equiv) and benzoyl chloride (1.16 mL, 10 mmol, 4.3 equiv) were added at rt. The mixture was stirred at rt for 15 minutes then was washed with water. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (3:7 diethyl ether/hexanes) to yield the title compound **9** as a colourless oil (810 mg, 1.88 mmol, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (2H, d, J = 7.2 Hz), 7.66 (1H, t, J = 7.2 Hz), 7.51 (2H, t, J = 7.6 Hz), 5.53 (1H, s), 5.43 (1H, s), 5.37 (1H, s), 4.84 (1H, s), 4.64 (1H, d, J = 16.4 Hz), 4.50 (1H, d, J = 16.4 Hz), 3.67 (3H, s), 3.50 (3H, s), 3.20 (1H, d, J = 15.6 Hz), 2.85-2.74 (3H, m), 2.07 (2H, q, J = 7.6 Hz), 1.04 (3H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 170.8, 164.1, 152.1, 139.5, 135.5, 134.4, 130.1, 128.8, 126.7, 119.3, 115,4, 94.0, 54.6, 53.3, 52.6, 50.3, 37.8, 29.2, 12.1; IR (thin film) ν_{max} 2963, 1766, 1735, 1640, 1452, 1219 cm^{-1}; MS (CI): *m/*z (%) 448 $[M + H]^+$.

Methyl 5-ethyl-2,3,3a,6,7,7a-hexahydro-7a-hydroxy-2-oxobenzofuran-3a-carboxylate (10)



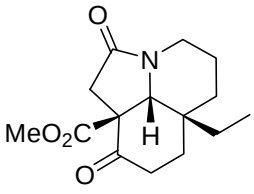
To a solution of the ester **4** (3.00 g, 15.4 mmol) in ammonia (150 mL), tetrahydrofuran (5.3 mL) and *tert*-butanol (1.3 mL) at −40 ºC was added lithium (270 mg, 44.8 mmol, 3 equiv). A permanent blue colour resulted and after 5 minutes, *tert*-butylbromoacetate (7.3 mL, 49.4 mmol, 3.2 equiv) was added slowly. After a further 5 minutes the ammonia was allowed to evaporate at room temperature then tetrahydrofuran (100 mL) and hydrochloric acid (2M, 100 mL) were added. The reaction mixture was stirred for an additional 2 hours then hydrochloric acid (6M, 50 mL) was added. After a further 4 hours the reaction mixture was diluted with water and diethylether. The organic phase was separated, the aqueous phase was extracted with diethylether and the combined organic extracts were dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (1:1 diethyl ether/hexanes) to provide the title compound **10** as a colourless oil (3.31 g, 13.9 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (1H, s), 3.72 (3H, s), 3.47 (1H, d, J = 17.2 Hz), 2.48 (1H, d, J = 17.2 Hz), 2.38-2.08 (4H, m), 2.02 (2H, q, J = 7.2 Hz), 0.98 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 170.9, 143.4, 118.4, 54.8, 52.9, 38.2, 29.7, 26.0, 11.8; IR (thin film) ν_{max} 3409, 2965, 1769, 1738, 1434, 1281, 1238 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{16}O_5$ $[M]^+$ 240.0978, found 240.1002.

Second Radical Precursor (11)



To a solution of the acid **10** (200 mg, 0.84 mmol) in tetrahydrofuran (11 mL) at 0 ºC was added triethylamine (146 µL, 1.04 mmol, 1.2 equiv) and isobutylchloroformate (125 µL, 0.96 mmol, 1.1 equiv). The reaction mixture was stirred for 15 minutes then additional triethylamine (282 µL, 2.00 mmol, 2.4 equiv) was added followed by a solution of the *N*-(2-chloroallyl) hydroxylammonium trifluoroacetate (400 mg) in tetrahydrofuran (2 mL). After 2 hours the reaction mixture was diluted with diethylether and was washed with 2M hydrochloric acid. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (7 mL) and triethylamine (490 µL, 3.48 mmol, 4.4 equiv) and benzoyl chloride (300 µL, 2.59 mmol, 3 equiv) were added. After 15 minutes the reaction mixture was washed with water and the organic phase was separated and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (3:10 diethyl ether/hexanes) to provide the title compound **11** as a colourless oil (255 mg, 0.56 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (2H, d, J = 7.6 Hz), 7.56 (1H, t, J = 7.2 Hz), 7.49 (2H, t, J = 7.6 Hz), 5.42 (1H, s), 5.36 (1H, s), 5.32 (1H, s), 4.56 (1H, d, J = 16.4 Hz), 4.47 (1H, d, J = 16.4 Hz), 3.63 (3H, s), 3.18 (1H, d, J = 17.2 Hz), 3.03 (1H, d, J = 17.2 Hz), 2.85-2.76 (1H, m), 2.64-2.56 (1H, m), 2.55-2.48 (1H, m), 2.46-2.38 (1H, m), 2.09 (2H, q, J = 7.6 Hz), 1.01 (3H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 170.7, 170.5, 163.9, 144.3, 135.0, 134.6, 130.0, 128.8, 126.2, 119.8, 115.6, 56.5, 53.2, 52.7, 38.0, 37.2, 30.0, 28.5, 11.9; IR (thin film) ν_{max} 2965, 1767, 1739, 1717, 1688, 1452, 1434, 1228 cm^{-1}; MS (CI): *m/z* (%) 434 $[M + H]^+$, 451 $[M + NH_3]^+$.

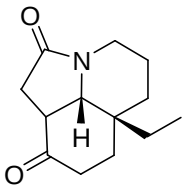
Methyl 6a-ethyl-nonahydro-2,9-dioxo-1*H*-pyrrolo[3,2,1-*ij*]quinoline-9a-carboxylate (12)



To a degassed solution of **11** (120 mg, 0.20 mmol) in trifluorotoluene (5 mL) was added a solution of tributyltin hydride (126 µL, 0.46 mmol, 2.3 equiv) and ACCN (10 mg, 0.041 mmol, 0.02 equiv) in trifluorotoluene (5 mL) over a period of 12 hours. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (diethyl ether) to provide the tricycle **12** as a colourless oil (35 mg, 0.106 mmol, 53%) and the bicycle **13** as a colourless oil (18 mg, 0.057 mmol, 29%). Data for tricycle **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (1H, d, J = 12.8 Hz), 3.82 (1H, d, J = 2.4 Hz), 3.74 (3H, s), 3.14 (1H, d, J = 17.2 Hz),

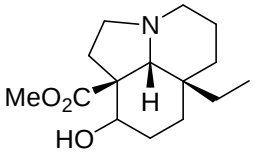
2.71 (1H, d, J = 17.2 Hz), 2.63 (1H, ddd, J = 16.4, 14.8, 6.4 Hz), 2.58-2.50 (1H, m), 2.42 (1H, ddd, J = 16.4, 4.8, 2.4 Hz), 2.02 (1H, t, 14.4, 4.8), 1.75 (1H, d, J = 13.6 Hz), 1.65 (2H, qd, J = 7.6, 7.6 Hz), 1.69-1.50 (3H, m), 1.38-1.30 (1H, m), 0.90 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 171.5, 171.5, 69.1, 57.4, 53.3, 40.7, 38.0, 34.9, 34.8, 32.9, 28.6, 24.8, 18.7, 6.8; IR (thin film) ν_{max} 2952, 1704, 1434 cm^{-1}; MS (CI): *m/*z (%) 280 $[M + H]^+$, 297 $[M + NH_3]^+$; HRMS (EI) calcd for $C_{15}H_{21}O_4N$ $[M]^+$ 279.1471, found 279.1464. Data for bicycle **13**:^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (1H, t, J = 2.0 Hz), 4.41 (1H, s), 4.32 (1H, d, J = 16.0 Hz), 3.78 (3H, s), 3.68 (1H, d, J = 16.0 Hz), 3.21 (1H, d, J = 16.8 Hz), 3.10 (1H, d, J = 16.8 Hz), 2.65 (1H, ddd, J = 16.8, 8.4, 5.6 Hz), 2.33 (1H, ddd, J = 16.8, 7.2, 4.8 Hz), 2.00-1.88 (3H, m), 1.71 (2H, dq, J = 14.4, 7.6 Hz), 0.98 (3H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 170.2, 169.4, 150.7, 108.2, 69.7, 59.7, 53.4, 46.5, 45.8, 41.0, 35., 31.6, 28.7, 8.4; IR (thin film) ν_{max} 2929, 1714, 1434, 1242 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{20}O_4NCl$ $[M]^+$ 313.1081, found 313.1074.

(±)-(4*S*,6a*R*)-6a-Ethyl-hexahydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline-2,9(9a*H*)-dione (14)



A solution of the ester **12** (10mg, 0.036 mmol) and lithium chloride (3 mg, 0.072 mmol, 2 equiv) in DMF (145 µL) was heated to 140 ºC overnight. The mixture was cooled, diluted with dichloromethane and was washed with water. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (6:4 diethyl ether/hexanes) and the title compound **14** was isolated as a colourless solid (6 mg, 0.027 mmol, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (1H, d, J = 12.8 Hz), 3.42 (1H, dd, J = 6.4, 2.0 Hz), 2.96 (1H, d, J = 17.2 Hz), 2.88 (1H, dd, J = 9.2, 6.4 Hz), 2.57-2.48 (1H, m), 2.47-2.31 (3H, m), 2.28 (1H, d, J = 17.2 Hz), 2.01 (1H, td, J = 13.6, 5.6 Hz), 1.90-1.80 (2H, m), 1.62-1.25 (5H, m), 0.97 (3H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 174.5, 65.8, 42.5, 40.5, 35.4, 34.1, 33.0, 32.6, 30.3, 29.2, 24.0, 18.8, 6.9; IR (thin film) ν_{max} 2952, 1704, 1434 cm^{-1}; MS (CI): *m/*z (%) 222 $[M + H]^+$, 239 $[M + NH_3]^+$; HRMS (EI) calcd for $C_{13}H_{19}O_2N$ $[M]^+$ 221.1416, found 221.1418.

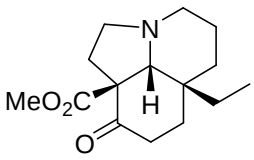
(±)-(4*R*,6a*R*,9a*S*)-Methyl 6a-ethyl-nonahydro-9-hydroxy-1*H*-pyrrolo[3,2,1-*ij*]quinoline-9a-carboxylate (15)



To a solution of the lactam **12** (10 mg, 36 µmol) in tetrahydrofuran (216 µL) was added borane-dimethylsulfide complex (36 µL, 2M in THF, 72

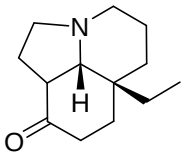
μmol, 2 equiv). The reaction mixture was brought to reflux for 1 hour, cooled and methanol was added. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (1:1 diethyl ether/hexanes) to yield the title compound **15** as a colourless oil (8.2 mg, 30.7 μmol, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (3H, s), 3.70-3.60 (1H, m), 3.17-3.10 (1H, m), 2.99 (1H, d, *J* = 10.8 Hz), 2.30-2.20 (3H, m), 1.98-1.86 (2H, m), 1.86-1.77 (1H, m), 1.77-1.62 (2H, m), 1.50-1.37 (3H, m), 1.25 (1H, d, *J* = 11.2 Hz), 1.10-0.98 (2H, m), 0.76 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 76.1, 74.3, 53.9, 53.3, 53.3, 51.7, 35.6, 33.1, 32.7, 29.6, 28.8, 26.6, 21.5, 7.0; IR (thin film) ν_{max} 3400, 2934, 1708, 1443 cm^{-1}; MS (CI): *m/z* (%) 268 $[M + H]^+$; HRMS (EI) calcd for $C_{15}H_{25}O_3N$ $[M]^+$ 267.1835, found 267.1828.

(±)-(4*R*,6a*R*,9a*S*)-Methyl 6a-ethyl-nonahydro-9-oxo-1*H*-pyrrolo[3,2,1-*ij*]quinoline-9a-carboxylate (16)



To a solution of the lactam **12** (35 mg, 0.106 mmol) in THF (500 μL) was added 9-BBN (464 μL, 0.5M in THF, 0.23 mmol, 2.2 equiv) and the mixture was brought to reflux. After 1 hour the mixture was cooled, ethanolamine was added and the solvent was removed *in vacuo*. The residue was treated with hexane and the solid was filtered and washed with hexane. The filtrate evaporated and the residue was purified by flash chromatography (3:7 diethyl ether/ hexanes) to yield the title compound **16** was isolated as a colourless oil (26 mg, 0.098 mmol, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (3H, s), 3.01 (2H, td, *J* = 8.8, 2.8 Hz), 2.86-2.79 (1H, m), 2.72 (1H, td, *J* = 14.4, 6.0 Hz), 2.49 (1H, s), 2.40-2.25 (2H, m), 2.23-2.16 (1H, m), 1.94-1.80 (2H, m), 1.72-1.60 (2H, m), 1.52-1.44 (2H, m), 1.40-1.10 (3H, m), 0.89 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 173.8, 53.2, 52.7, 52.6, 36.4, 35.8, 32.5, 29.8, 29.2, 27.3, 21.0, 7.1; IR (thin film) ν_{max} 2936, 1734, 1716, 1447 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{23}O_3N$ $[M]^+$ 265.1678, found 265.1673.

(±)-(4*S*,6a*R*)-6a-Ethyl-octahydro-9a*H*-pyrrolo[3,2,1-*ij*]quinolin-9-one (17)



A solution of the ester **16** (16mg, 0.060 mmol) and lithium chloride (5 mg, 0.120 mmol, 2 equiv) in DMF (242 µL) was heated to 140 ºC for 3 hours. The mixture was cooled, diluted with dichloromethane and was washed with water. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (6:4 diethyl ether/hexanes) and the title compound **17** was isolated as a colourless oil (11 mg, 0.053 mmol, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04-2.97 (2H, m), 2.66 (1H, ddd, *J* = 9.2, 5.2, 2.0 Hz), 2.45-2.20 (3H, m), 1.98-1.85 (3H, m), 1.79 (1H, dd, *J* = 10.8, 2.0 Hz), 1.76-1.57 (2H, m), 1.52-1.45 (2H, m), 1.37-1.26 (2H, m), 1.10 (1H, td, *J* = 13.2, 4.4 Hz), 0.93 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 73.6, 53.3, 53.0, 48.2, 36.9, 34.8, 32.9, 30.3, 30.1, 26.1, 21.3, 7.2; IR (thin film) ν_{max} 2931, 1712, 1448 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{21}ON$ $[M]^+$ 207.1623, found 207.1614

(±)-Dehydroaspidospermidine

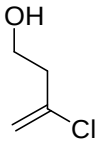
The title compound was prepared according to the procedure of Gnecco *et al.*[1w] (±)-(4*S*,6a*R*)-6a-Ethyl-octahydro-9a*H*-pyrrolo[3,2,1-*ij*]quinolin-9-one **17** (8.0mg, 39 µmol) was converted into the title compound (6.7 mg, 0.024 mmol, 62%). All spectral data corresponded to that quoted in ref. 1w.

(±)-Aspidospermidine (1)

The title compound was prepared according to the procedure of Gnecco *et al.*[1w] Dehydroaspidospermidine (4.0 mg, 14 µmol) was converted into the title compound (3.4 mg, 12.3 µmol, 88%). All spectral data corresponded to that quoted in ref. 1w.

Synthesis of Hydroxylamine 20

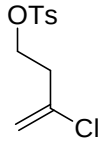
3-Chlorobut-3-enol



To a solution of paraformaldehyde (1.17 g) and 2-chloropropene (3 g, 2.70 mL, 39 mmol) in dichloromethane (94 mL) at 0 ºC was added diethylaluminium chloride (39 mL, 1.0 M in hexanes, 39 mmol, 1 equiv.). The reaction mixture was stirred overnight then was quenched by addition of saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (2:3 diethyl ether/hexanes) to yield 3-chlorobut-3-enol as a colourless oil (1.05 g, 9.9 mmol, 25%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, d, *J* = 0.8 Hz), 5.22 (1H, d, *J* = 0.8 Hz), 3.79 (2H, t,

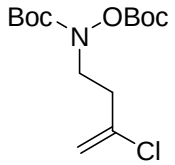
J = 6.0 Hz), 2.55 (2H, t, J = 6.0 Hz), 2.36 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 114.5, 59.4, 42.2; IR (thin film) ν_{max} 3358, 2957, 1636 cm^{-1}; HRMS (EI) calcd for C_4H_7OCl $[M]^+$ 106.0186, found 106.0185.

3-Chlorobut-3-enyl 4-methylbenzenesulfonate



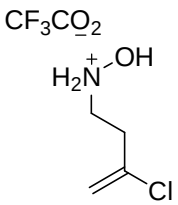
To a solution of the 3-chlorobut-3-enol (1.05 g, 9.9 mmol) and DMAP (catalytic) in acetonitrile (9.9 mL) and triethylamine (2.0 mL) was added *p*-toluenesulfonyl chloride (2.79 g, 14.6 mmol, 1.5 equiv). The misture was stirred at rt for 2h then was diluted with diethyl ether and washed with saturated aqueous sodium hydrogen carbonate then 2M HCl. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (1:4 diethyl ether/hexanes) and the tosylate was isolated as a colourless oil (1.61 g, 6.2 mmol, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (2H, d, J = 8.0 Hz), 7.32 (2H, d, J = 8.0 Hz), 5.19 (1H, s), 5.18 (1H, s), 4.17 (2H, t, J = 6.4 Hz), 2.62 (2H, t, J = 6.4 Hz), 2.41 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 136.6, 132.6, 129.9, 127.7, 115.4, 66.5, 38.4, 21.5; IR (thin film) ν_{max} 1637, 1598, 1360, 1177 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{13}O_3SCl$ $[M]^+$ 260.0274, found 260.0280.

***N*-(3-chloro-3-propenyl)[*N*,*O*-bis(*tert*-butyl-oxycarbonyl)] hydroxylamine**



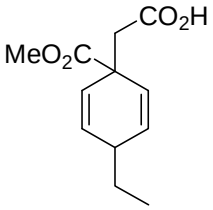
To a solution of the tosylate (1.61 g, 6.2 mmol) and *N*,*O*-bis(*tert*-butyl-oxycarbonyl) hydroxylamine (1.45 g, 6.25 mmol) in DMF (6.4 mL) was added potassium carbonate (920 mg). The reaction mixture was stirred for 24 h then was diluted with diethyl ether and was washed with water. The organic phase was separated and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (1:9 diethyl ether/hexanes) to yield the title compound as a colourless oil (1.45 g, 4.36 mmol, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (1H, d, J = 1.2 Hz), 5.20 (1H, d, J = 1.2 Hz), 3.80 (2H, br s), 2.62 (2H, t, J = 6.8 Hz), 1.50 (9H, s), 1.45 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 152.1, 138.9, 114.4, 84.9, 47.9, 36.9, 28.0, 27.5; IR (thin film) ν_{max} 2981, 1785, 1719, 1395, 1370 cm^{-1}; MS (CI): *m/z* (%) 322 $[M + H]^+$, 339 $[M + NH_3]^+$; HRMS (EI) calcd for $C_{14}H_{25}O_5NCl$ $[M]^+$ 322.1421, found 322.1431.

_N_-(3-chloro-3-propenyl) hydroxylammonium trifluoroacetate



A solution of the *N*-(3-chloro-3-propenyl)[*N*,*O*-bis(*tert*-butyl-oxycarbonyl)] hydroxylamine (740 mg, 2.3 mmol) in dichloromethane (4.4 mL) was treated with trifluoroacetic acid (1.89 mL). The reaction mixture was stirred at rt for 6 h then the solvent was removed *in vacuo* to yield the title compound **20** as a colourless oil (550 mg, 2.3 mmol, 100%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (2H, s), 3.53 (2H, t, *J* = 7.2 Hz), 2.84 (2H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 116.9, 49.0, 33.1.

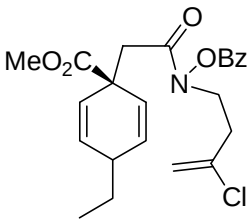
2-(1-(Methoxycarbonyl)-4-ethylcyclohexa-2,5-dienyl)acetic acid (19a/b)



To solution of methyl *p*-ethylbenzoate **18** (5.8 g, 0.035 mol) in ammonia (341 mL), THF (12 mL) and *t*-BuOH (2.86 mL) at −40 ºC was added lithium (614 mg, 0.102 mol, 3 equiv.). The mixture was stirred at the same temperature for 15 minutes then *t*-butylbromoacetate (16 mL, 0.108 mol, 3.1 equiv.) was added. After a further 15 minutes the ammonia was allowed to evaporate, the residue was neutralised with 2M HCl and the aqueous layer was extracted with diethyl ether. The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (50 mL) and was treated with trifluoroacetic acid (10 mL) at room temperature. After 2 h the solvent was removed and the title compound was purified by flash chromatography (3:10 diethyl ether/hexanes with 0.05% acetic acid) yielding the mixture of diastereomers **19a/b** (3.0 g, 0.0134 mol, 38%). The mixture of diastereomeric acids was dissolved in isopropanol and benzylamine (1.44 g, 1.46 mL, 1 equiv) was added. Crystallisation gave separation of the diastereomeric salts which were dissolved in ethyl acetate and washed with 2M HCl to recover the free acid. **19a:** ^{1}H NMR (400 MHz, C_6D_6) δ 5.94 (2H, dd, *J* = 10.2, 2.0 Hz), 5.55 (2H, dd, *J* = 10.2, 3.2 Hz), 3.35 (3H, s), 2.74 (2H, s), 2.49-2.44 (1H, m), 1.18 (2H, qd, *J* = 7.6, 6.0 Hz), 0.68 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 177.2, 173.9, 131.2, 127.1, 52.5, 46.6, 45.3, 37.1, 28.2, 10.8; IR (thin film) ν_{max} 2962, 1732, 1434 cm^{-1}; MS (CI): *m*/z (%) 225 $[M + H]^+$, 242 $[M + NH_3]^+$, MS HRMS (EI) calcd for $C_{12}H_{15}O_4$ $[M\text{-}H]^+$ 223.0970, found 223.0970; **19b:** ^{1}H NMR (400 MHz, C_6D_6) δ 5.74-5.66 (4H, m), 3.58 (3H, s), 2.66 (2H, s), 2.57-2.52 (1H, m), 0.98 (2H, qd, *J* = 7.6, 6.0 Hz), 0.48 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (100

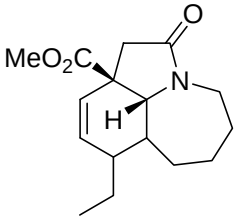
MHz, C_6D_6) δ 175.9, 173.7, 131.1, 127.0, 53.5, 52.3, 46.5, 37.0, 28.4, 10.7; IR (thin film) ν_{max} 2962, 1731, 1434 cm^{-1}; MS (CI): *m/z* (%) 225 $[M + H]^+$, 242 $[M + NH_3]^+$; MS HRMS (EI) calcd for $C_{12}H_{16}O_4$ $[M]^+$ 224.1049, found 224.1060

Radical Precursor 21a



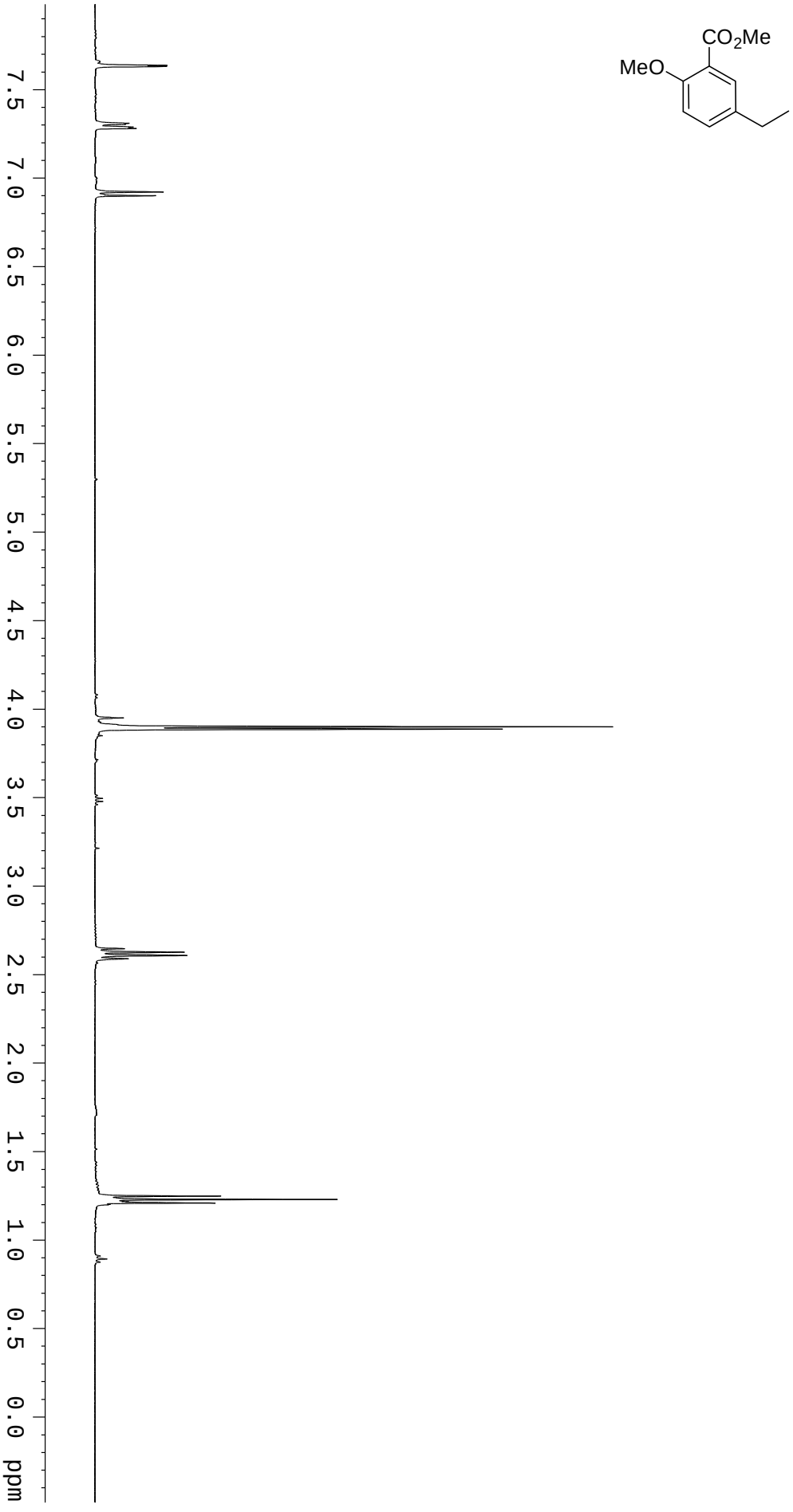
To a solution of the acid **19a** (35 mg, 0.16 mmol) in tetrahydrofuran (2.2 mL) at 0 ºC was added triethylamine (27.1 µL, 0.17 mmol, 1.1 equiv) and isobutylchloroformate (23.0 µL, 0.17 mmol, 1.1 equiv). The reaction mixture was stirred for 15 minutes then additional triethylamine (52.4 µL, 0.33 mmol, 2.1 equiv) was added followed by a solution of the *N*-(3-chloro-3-butenyl) hydroxylammonium trifluoroacetate **20** (36 mg) in tetrahydrofuran (2 mL). After 2 hours the reaction mixture was diluted with diethylether and was washed with 2M hydrochloric acid. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (1.2 mL) and triethylamine (91.1 µL, 0.54 mmol, 3.4 equiv) and benzoyl chloride (56.1 µL, 0.40 mmol, 2.5 equiv) were added. After 15 minutes the reaction mixture was washed with water and the organic phase was separated and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (3:10 diethyl ether/hexanes) to provide the title compound **21a** as a colourless oil (36 mg, 0.083 mmol, 52%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (2H, d, J = 7.6 Hz), 7.67 (1H, t, J = 7.2 Hz), 7.52 (2H, t, J = 7.6 Hz), 5.89-5.73 (4H, m), 5.26 (1H, s), 5.24 (1H, s), 4.02 (2H, t, J = 6.4 Hz), 3.73 (3H, s), 2.67-2.60 (5H, m), 1.50-1.40 (2H, m), 0.83-0.75 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 170.6, 164.1, 139.1, 134.6, 130.8, 130.0, 129.8, 126.6, 126.5, 114.4, 52.6, 46.3, 45.7, 43.1, 38.6, 36.5, 27.7, 10.4; IR (thin film) ν_{max} 2962, 1766, 1727, 1684, 1451 cm^{-1}; MS (CI): *m/z* (%) 432 $[M + H]^+$, 468 $[M + NH_3]^+$.

(4*R*,7a*R*)-Methyl 10-ethyl-1,2,3,4,4,6,7,7a,10,10a-decahydro-6-oxoazepino[3,2,1-*hi*]indole-7a-carboxylate (22a)



To a degassed solution of **21a** (36 mg, 0.083 mmol) in trifluorotoluene (2 mL) was added a solution of tributyltin hydride (52.3 µL, 0.19 mmol, 2.3 equiv) and ACCN (4.1 mg, 0.017 mmol, 0.02 equiv) in trifluorotoluene (2 mL) over a period of 12 hours. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (diethyl ether) to

provide the tricycle **22a** as a colourless oil (9 mg, 0.032 mmol, 39%) and the bicycle **23a** as a colourless oil (2 mg, 6.4 μmol, 8%). Data for tricycle **22a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74-5.68 (2H, m), 3.93 (1H, d, *J* = 10.8 Hz), 3.88 (1H, ddd, *J* = 11.2, 7.6, 5.2 Hz), 3.72 (3H, s), 3.09-3.02 (1H, m), 2.98 (1H, d, *J* = 16.8 Hz), 2.48 (1H, d, *J* = 16.8 Hz), 2.19 (1H, d, *J* = 14.8 Hz), 2.05-1.87 (3H, m), 1.70-1.52 (3H, m), 1.30-1.23 (2H, m), 1.15-1.02 (1H, m), 0.85 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 172.3, 133.2, 125.7, 64.1, 53.0, 50.7, 42.5, 42.3, 41.4, 40.4, 33.3, 26.6, 25.3, 24.5, 9.3; IR (thin film) ν_{max} 2929, 1734, 1692, 1437 cm^{-1}; MS (CI): *m/*z (%) 278 $[M + H]^+$; HRMS (EI) calcd for $C_{16}H_{23}O_3N$ $[M]^+$ 277.1678, found 277.1667.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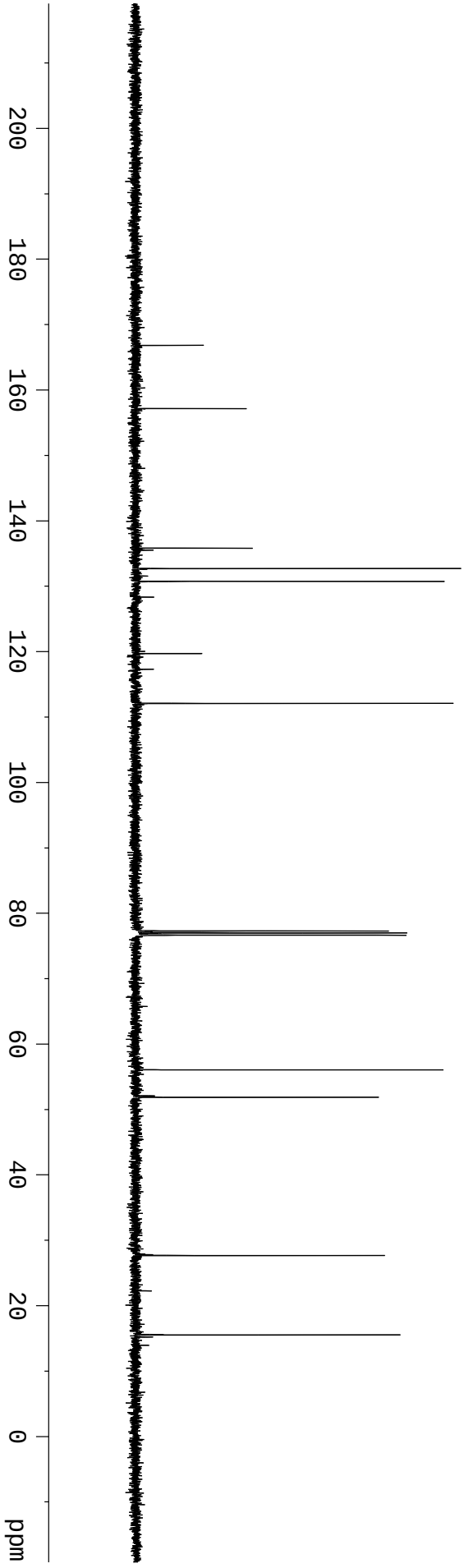
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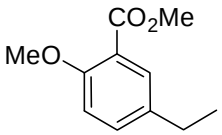
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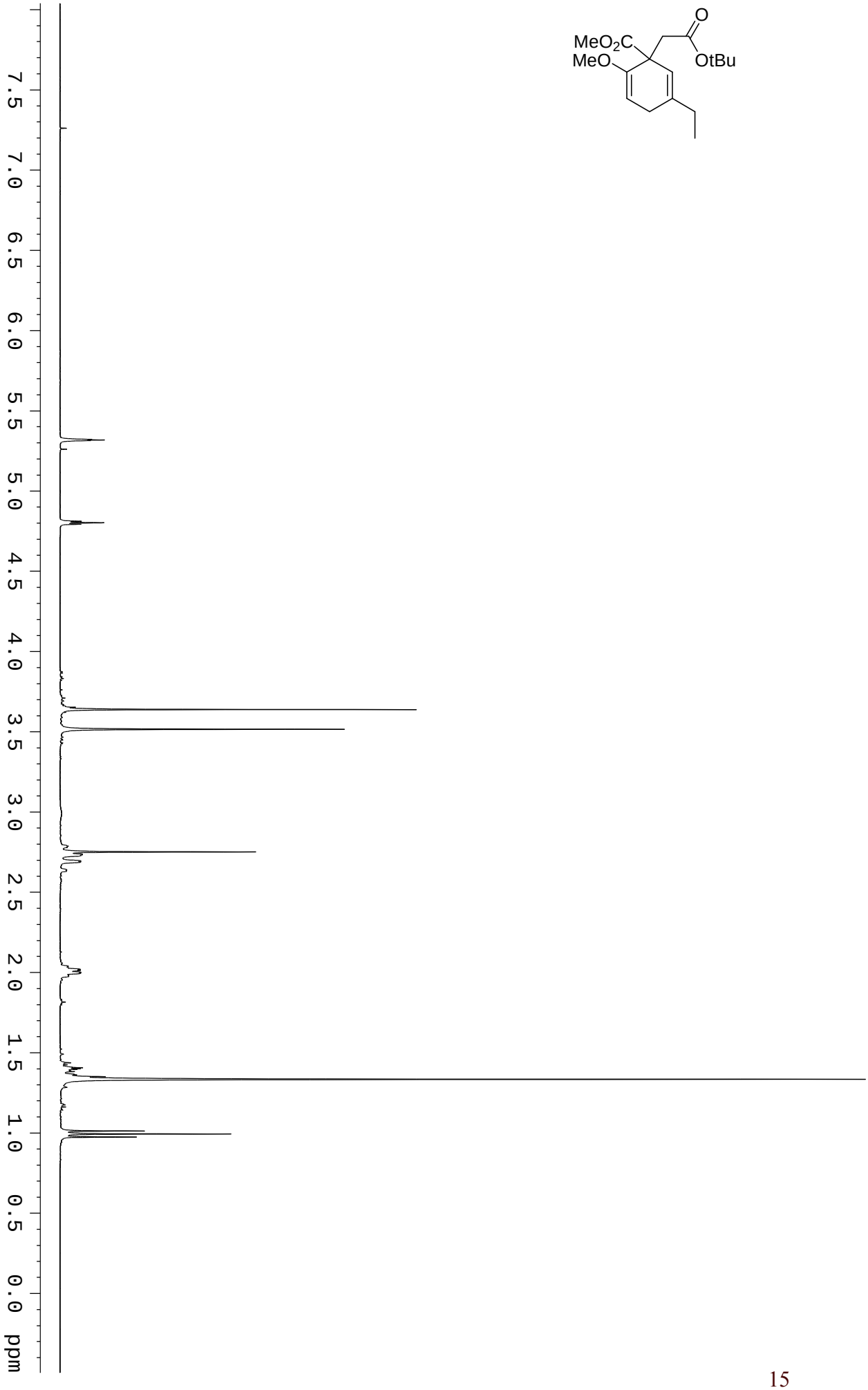
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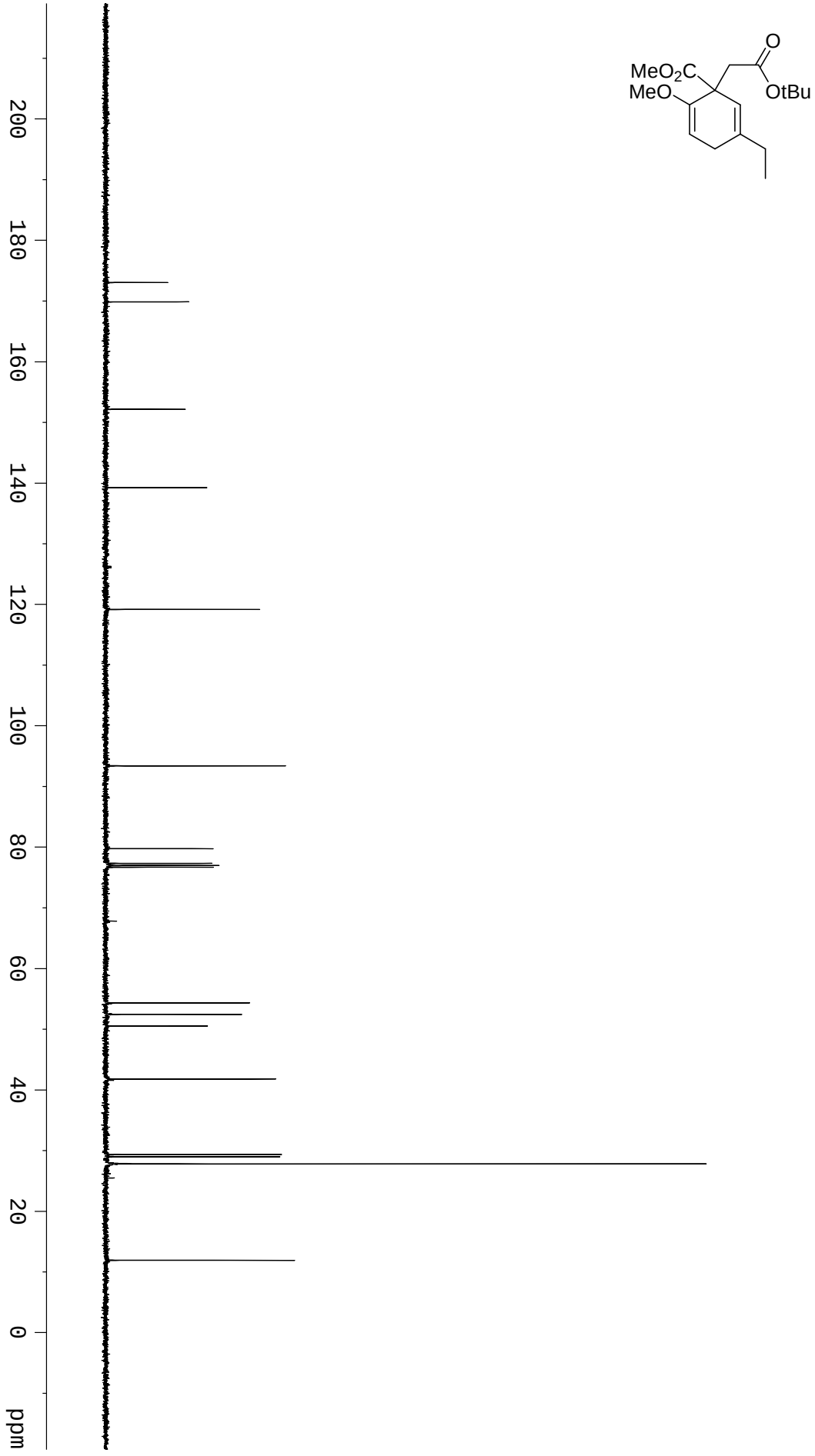
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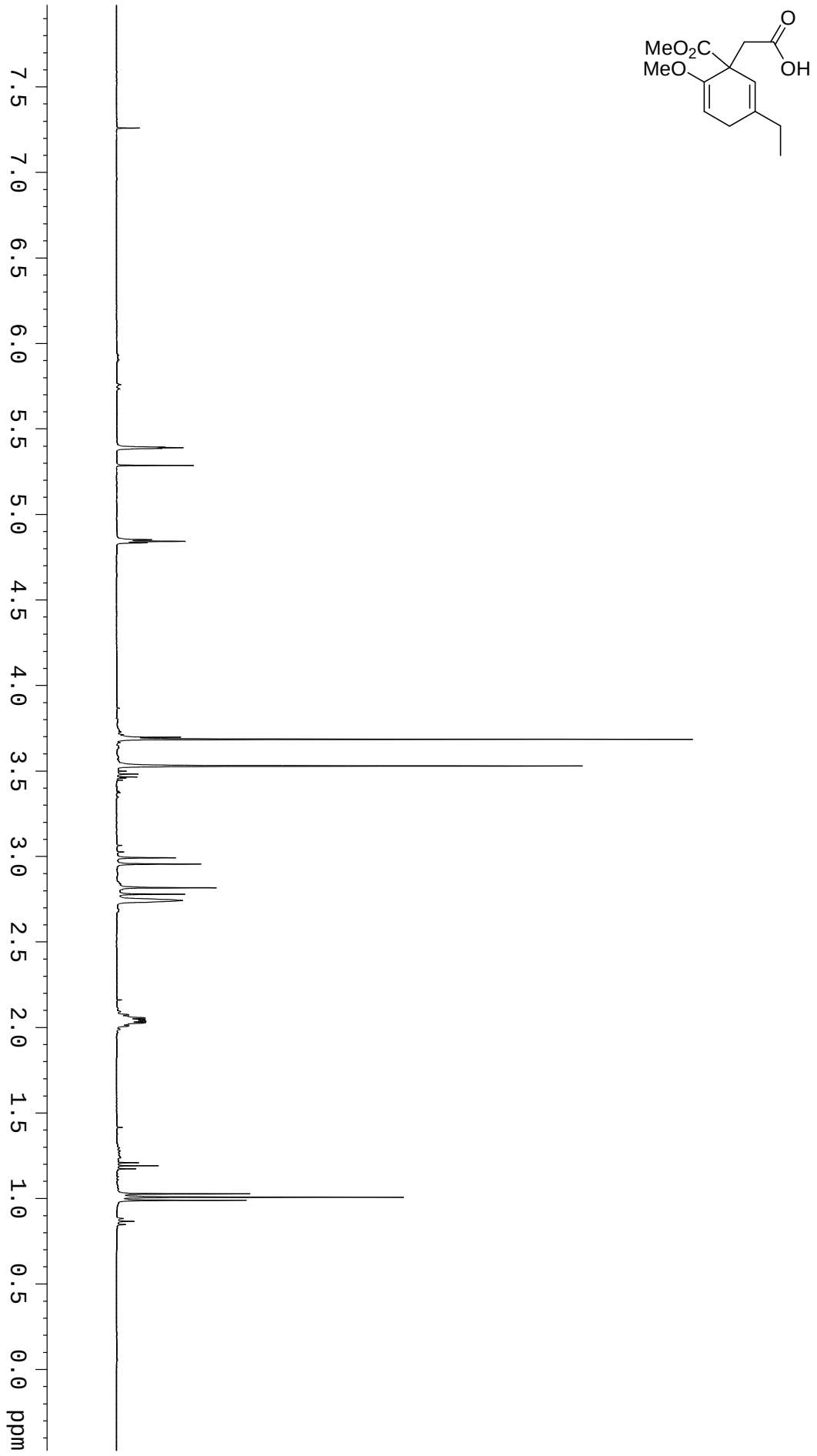
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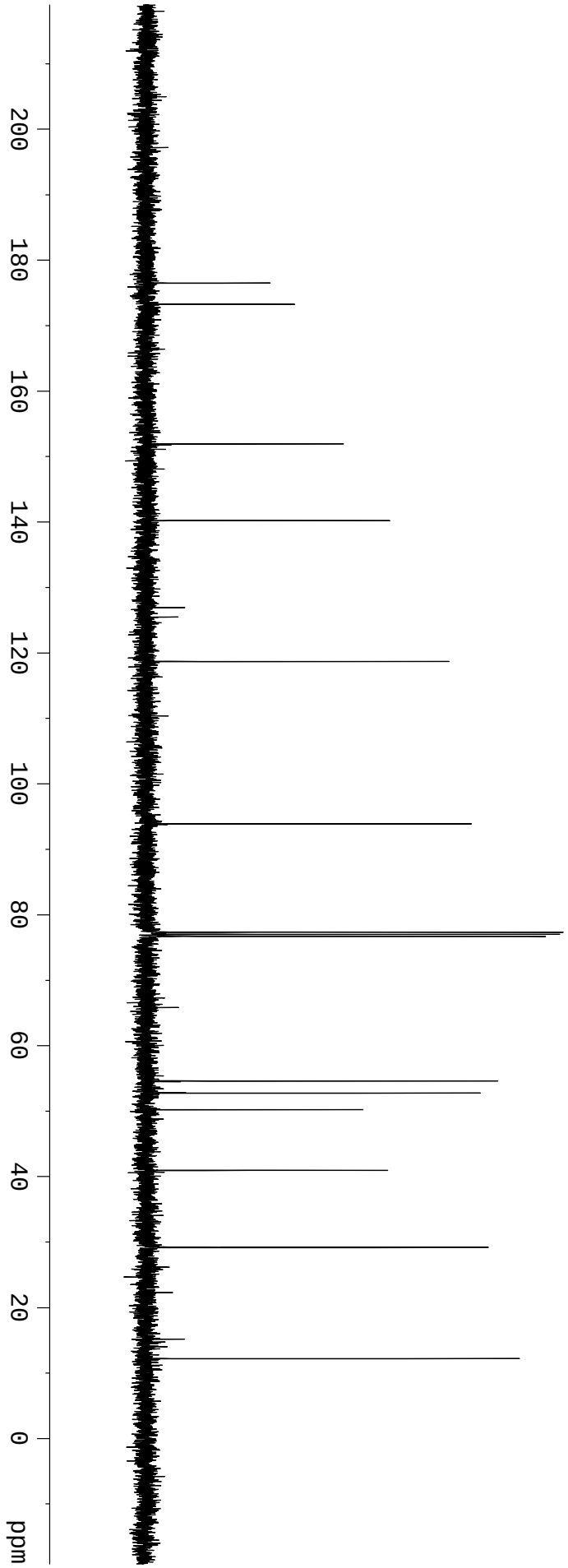
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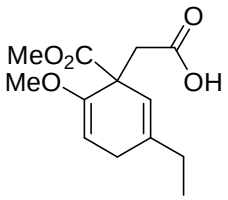
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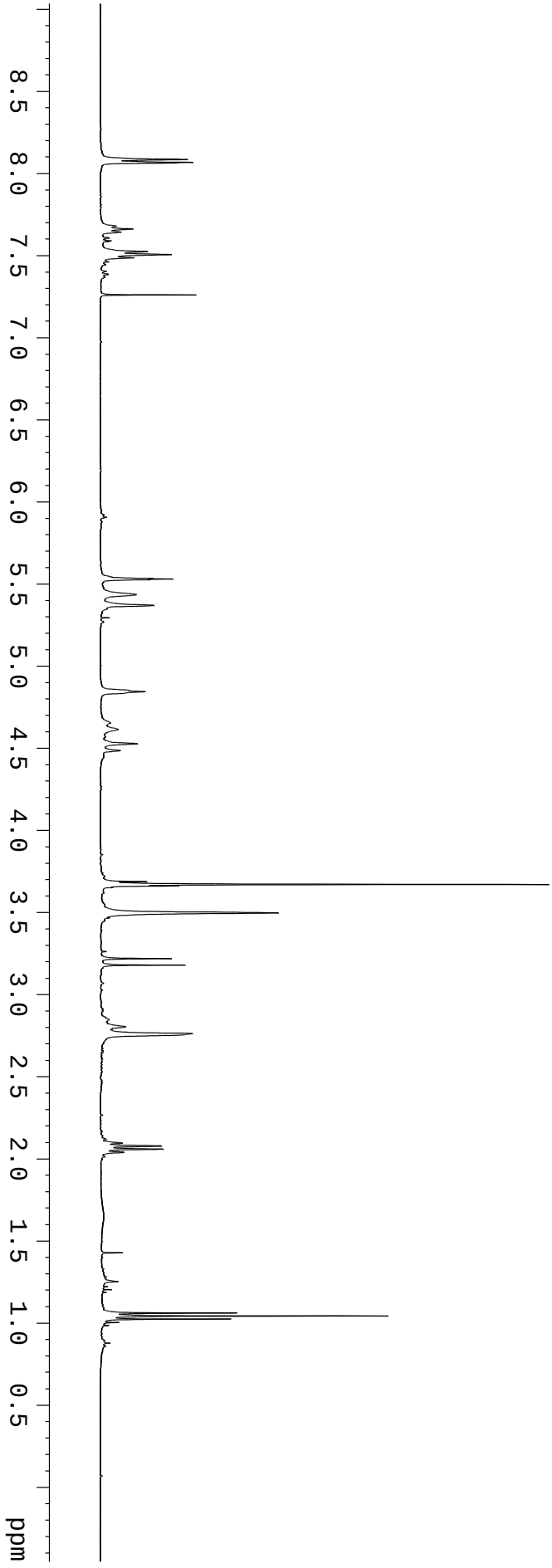
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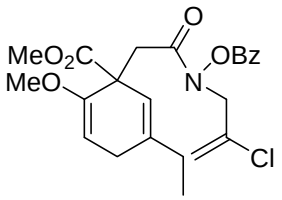
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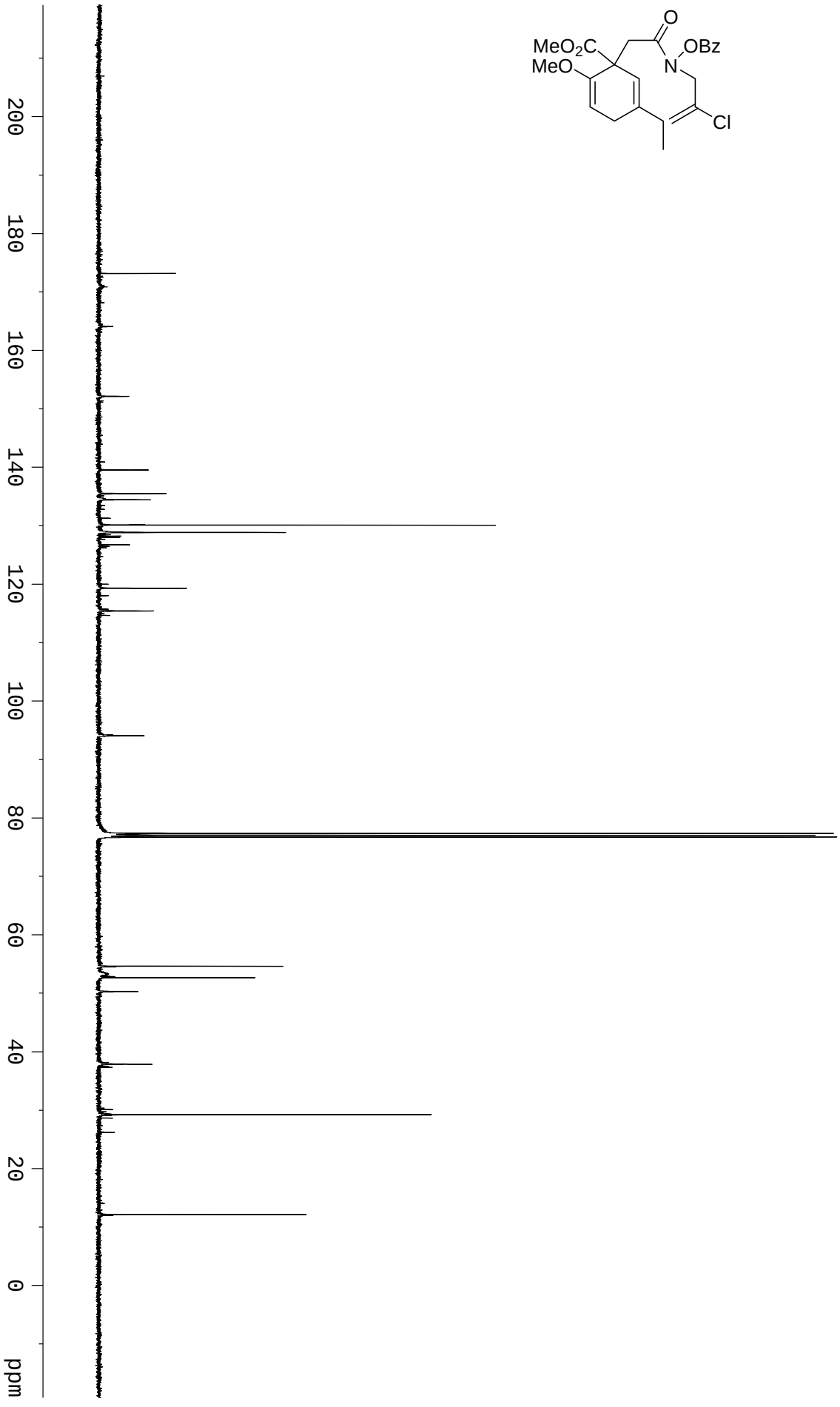
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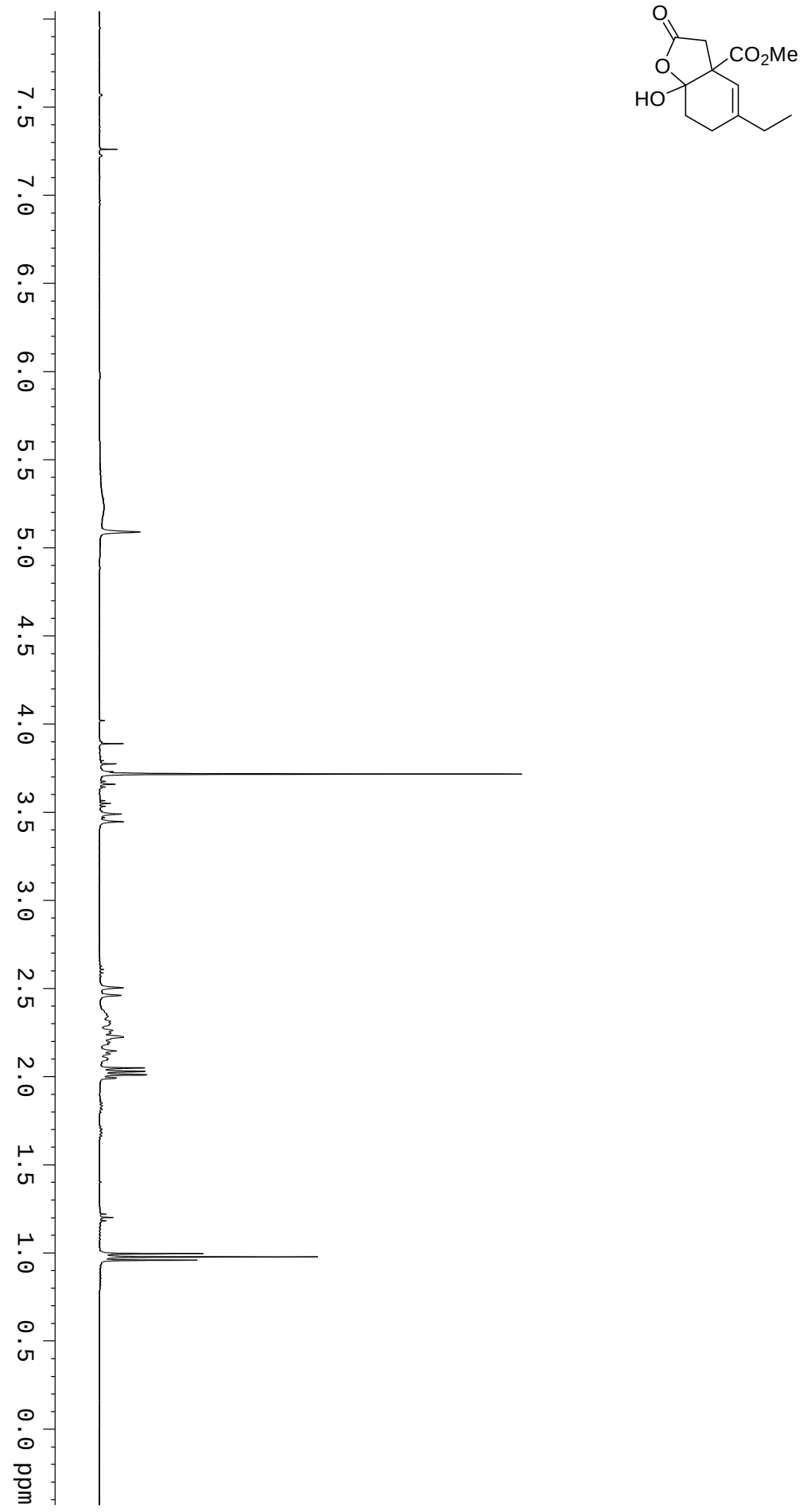
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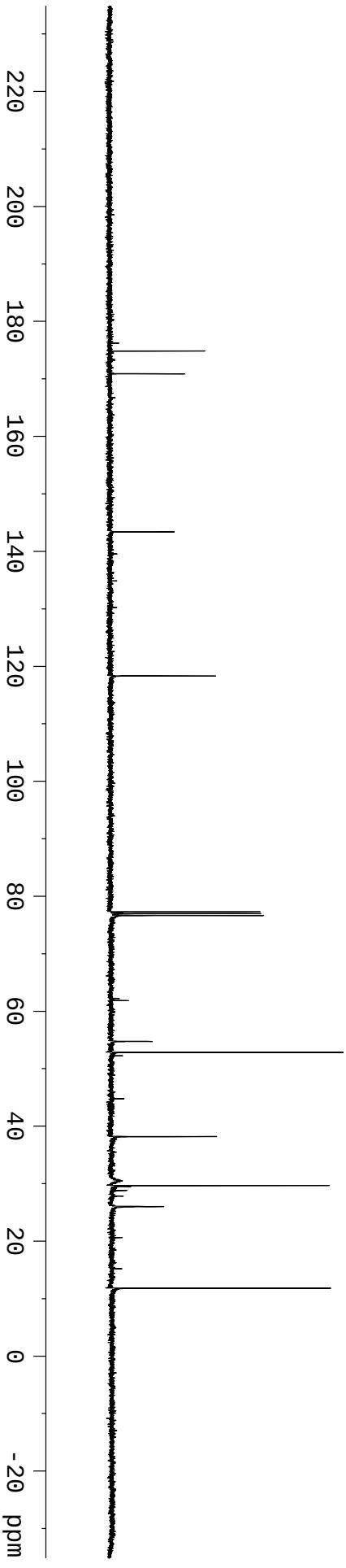
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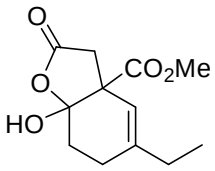
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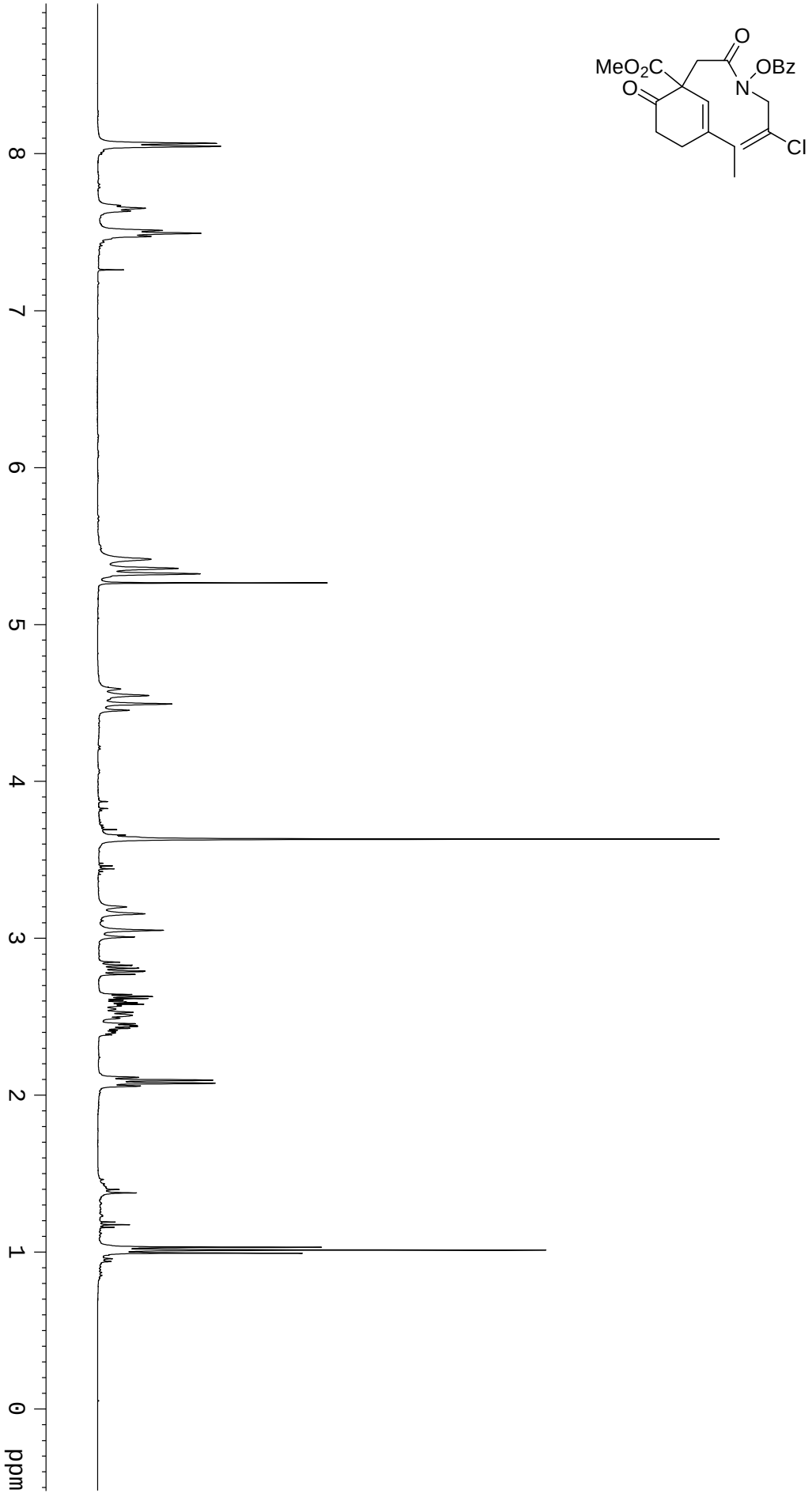
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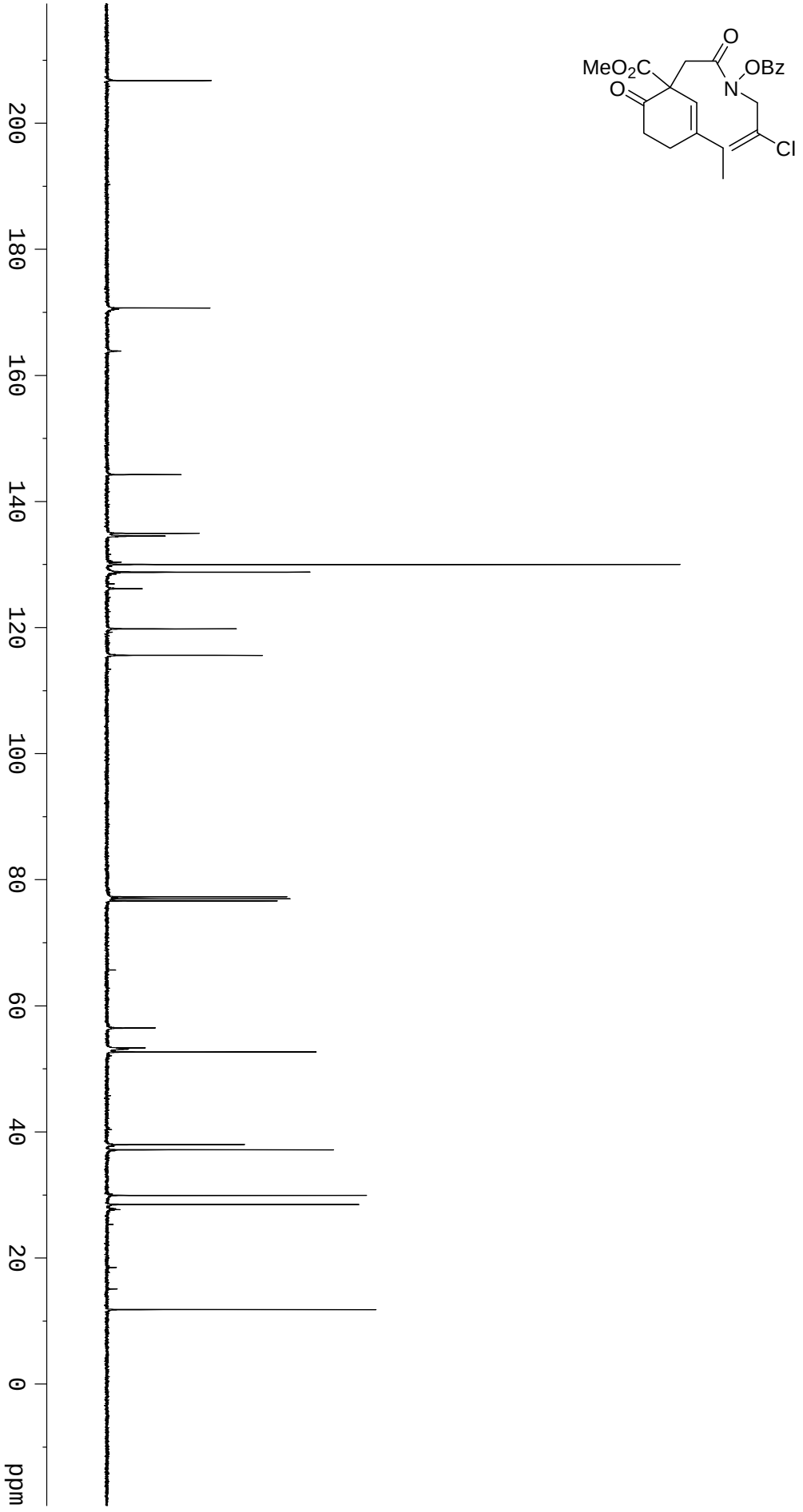
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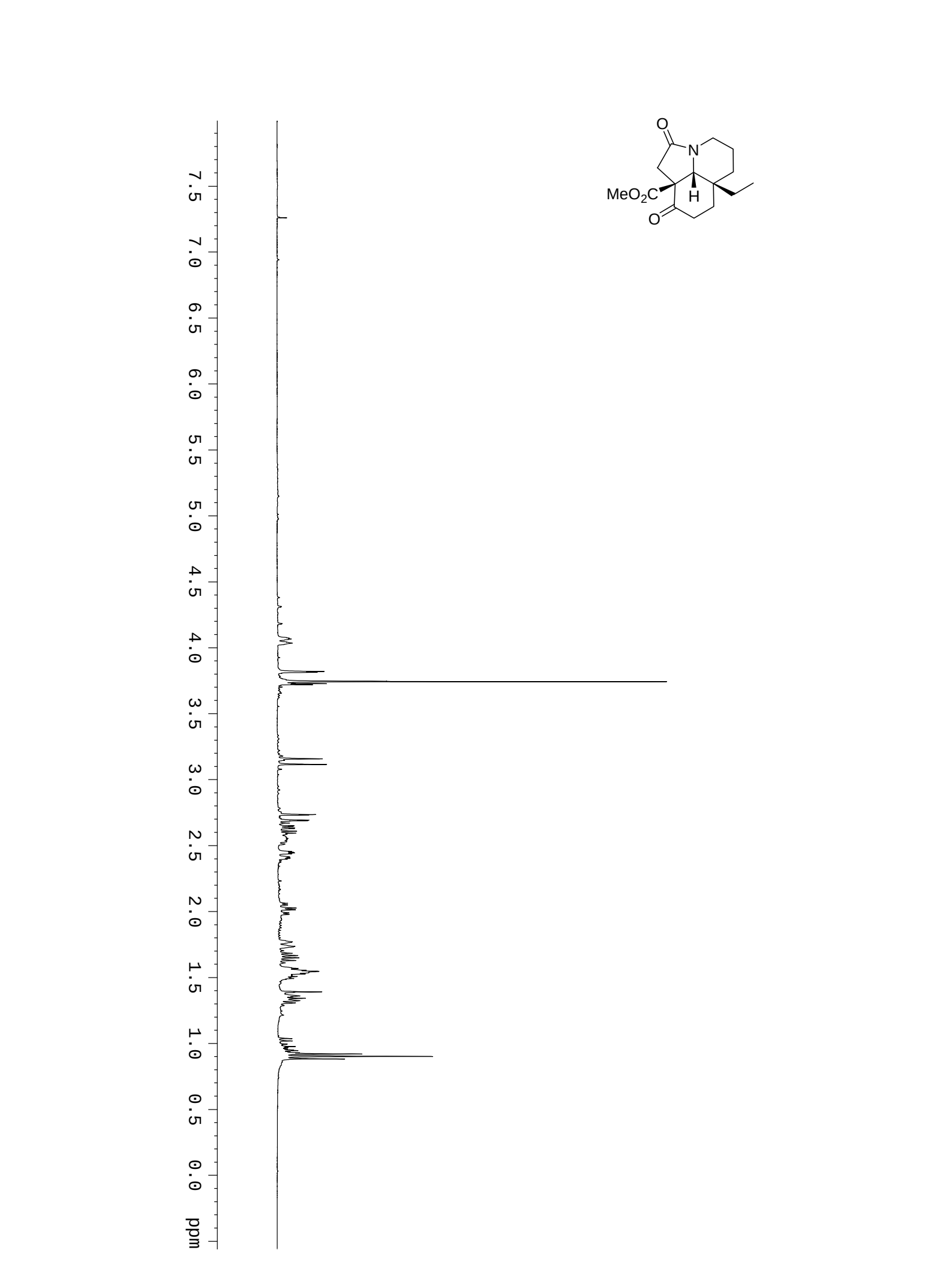
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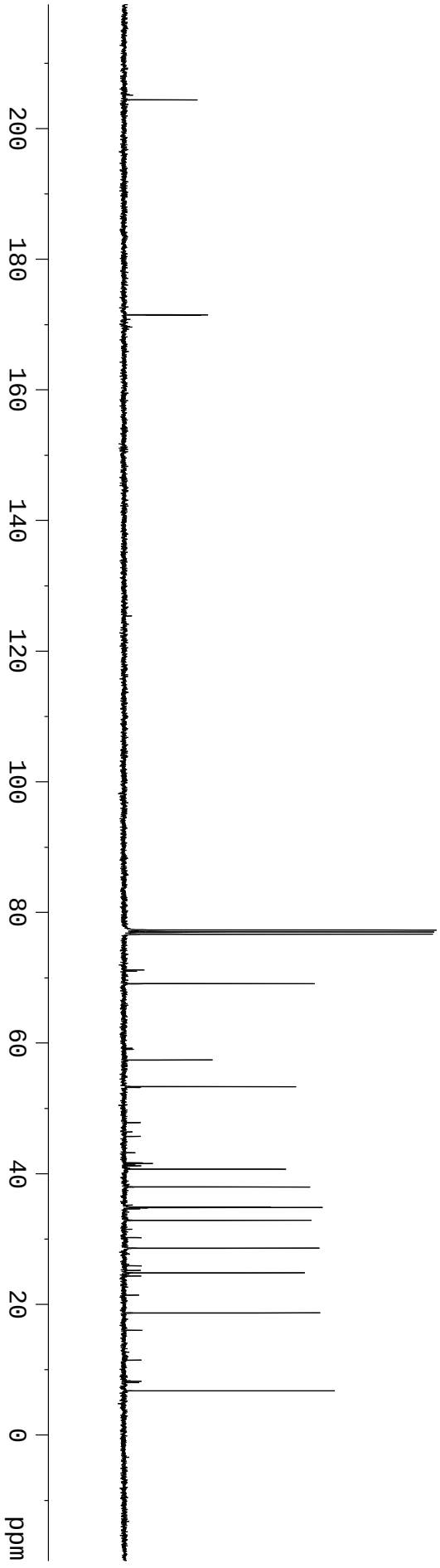
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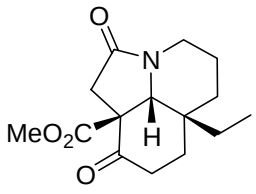
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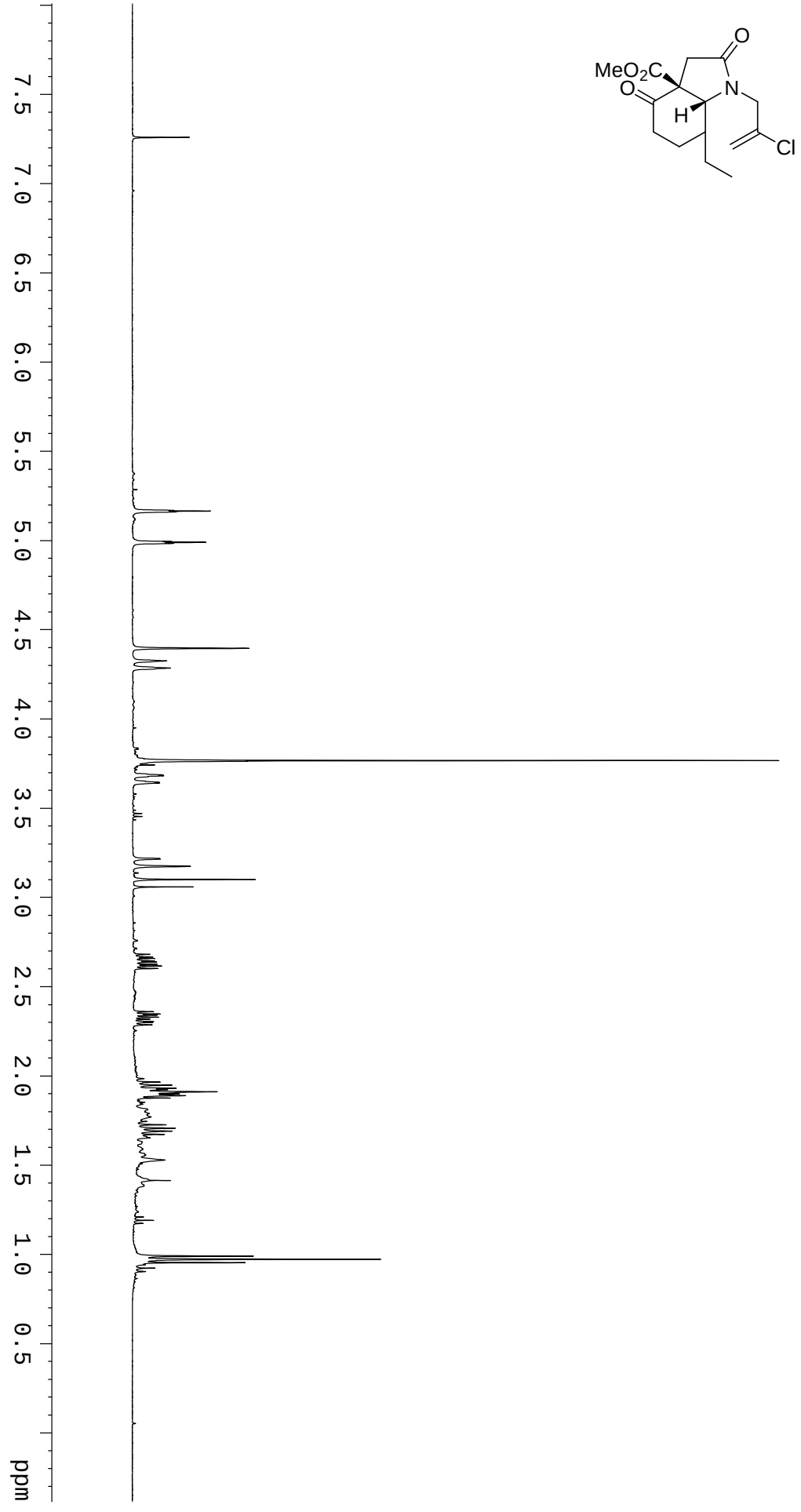
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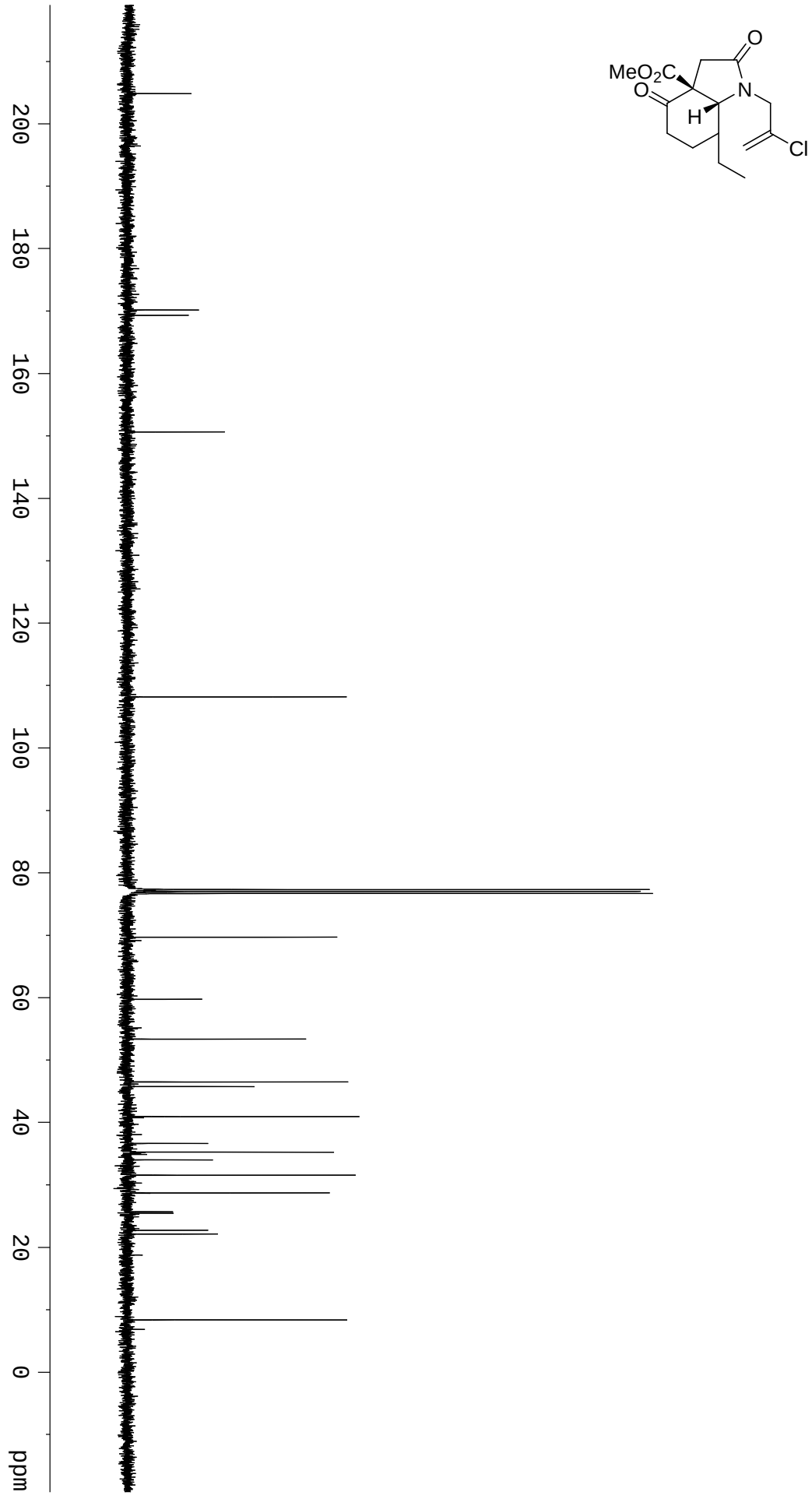
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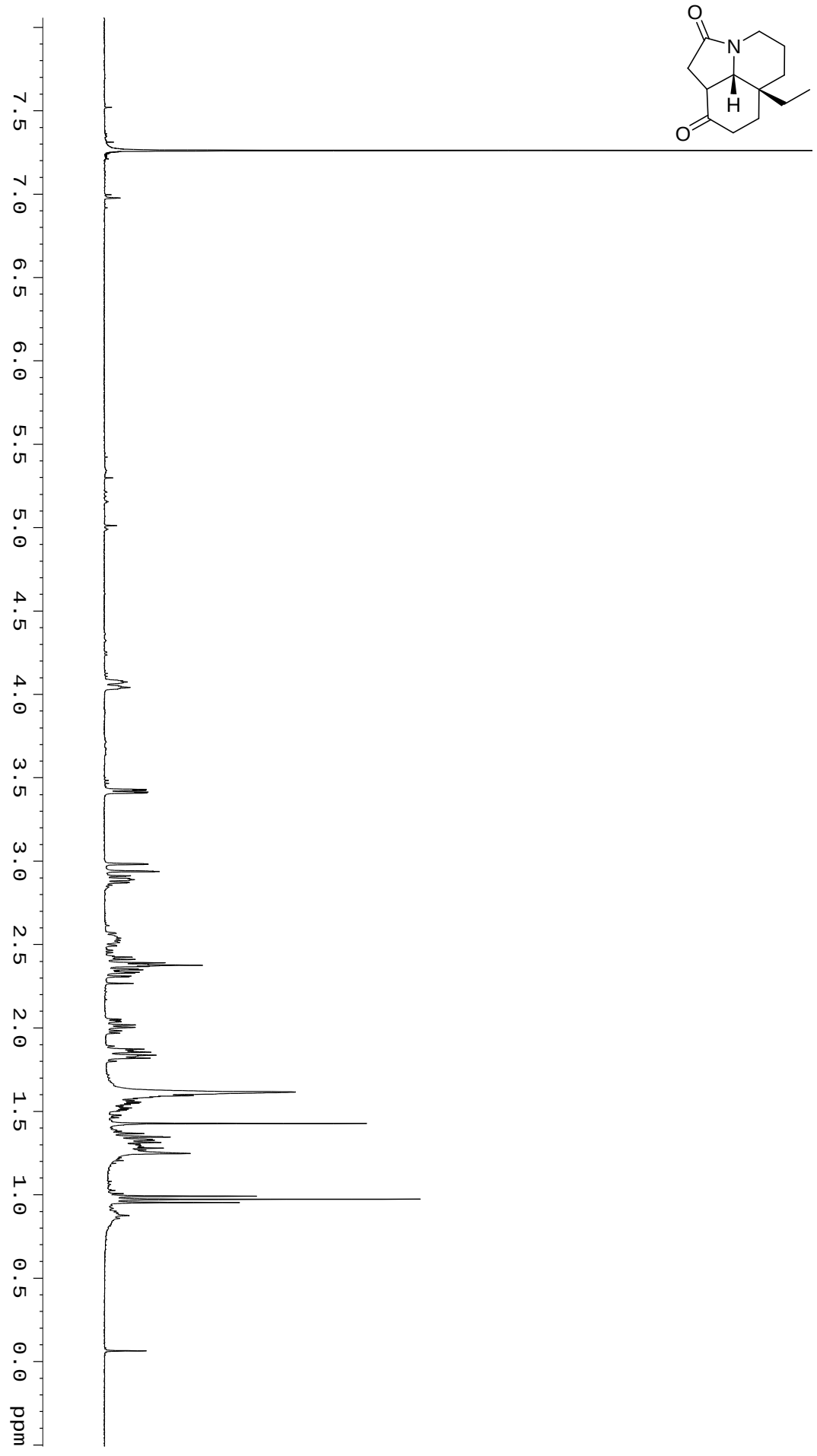
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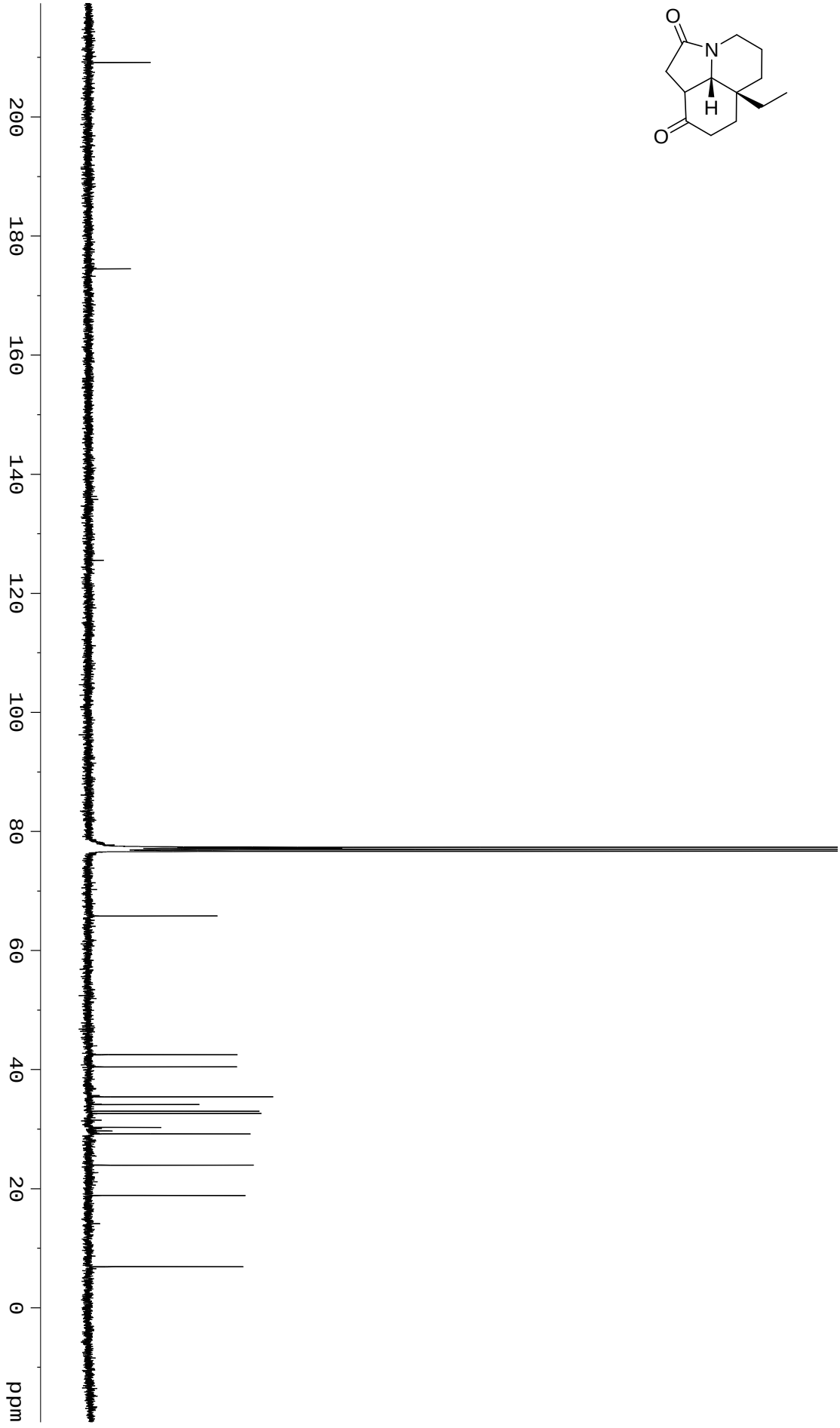
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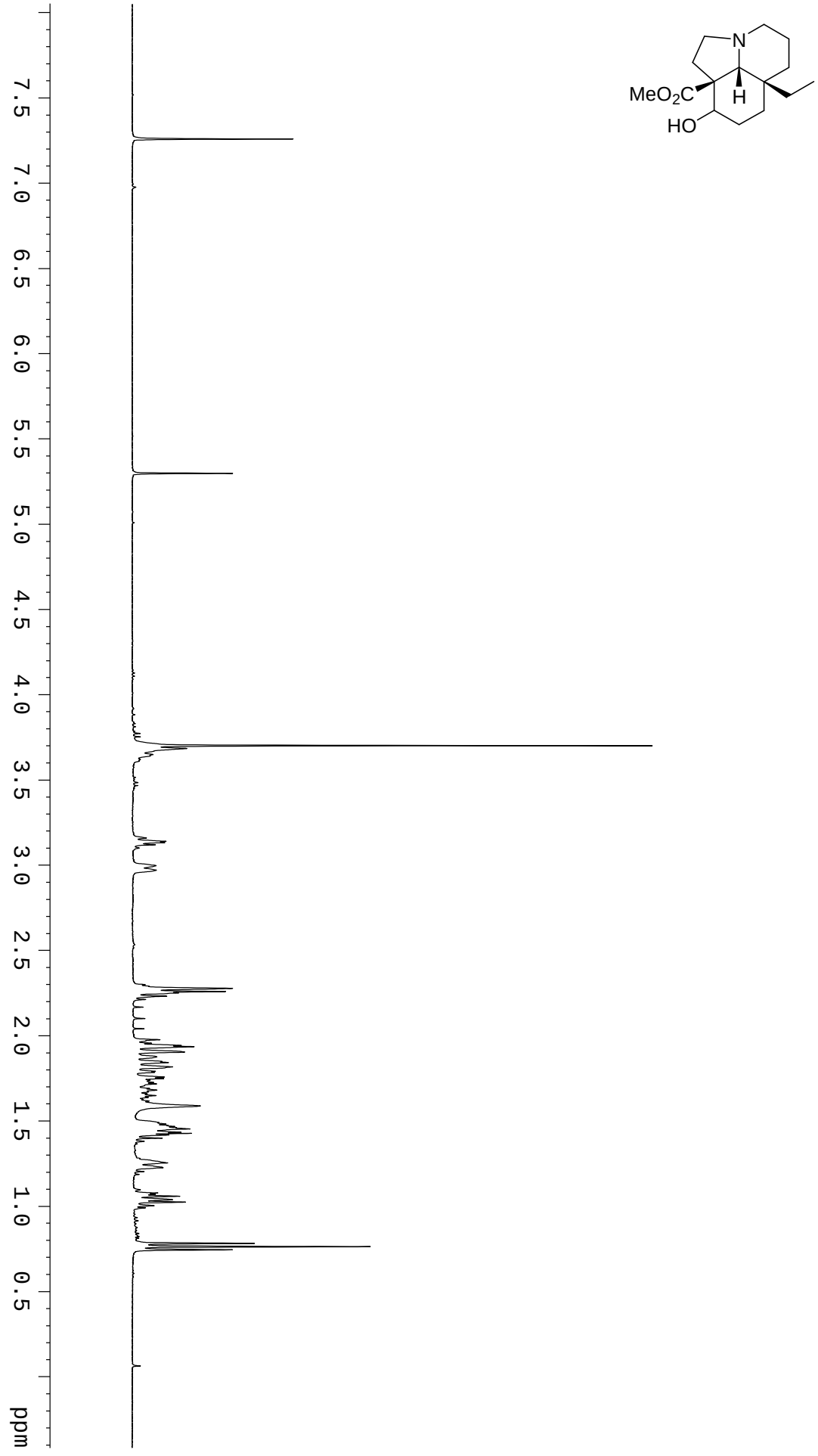
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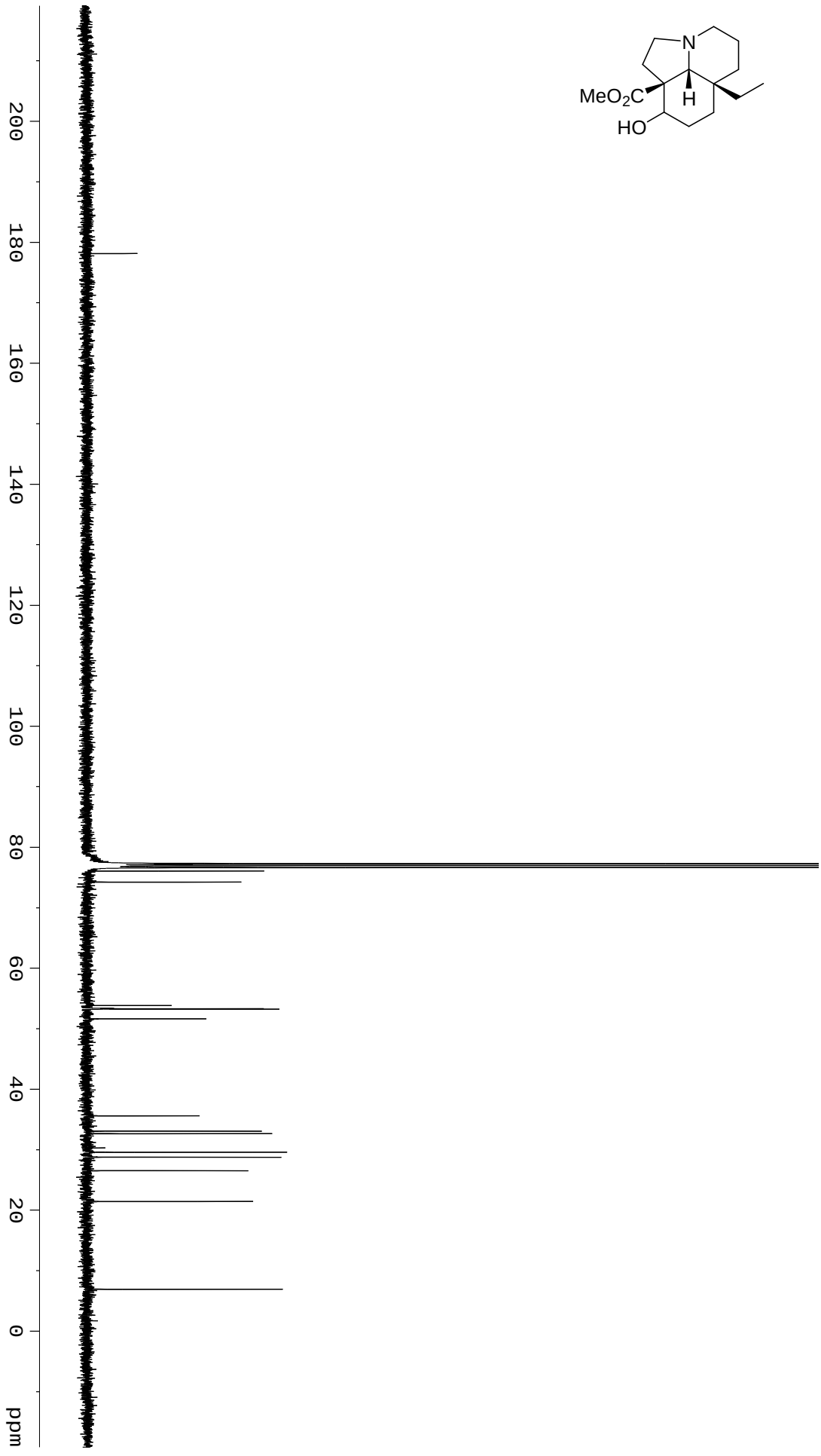
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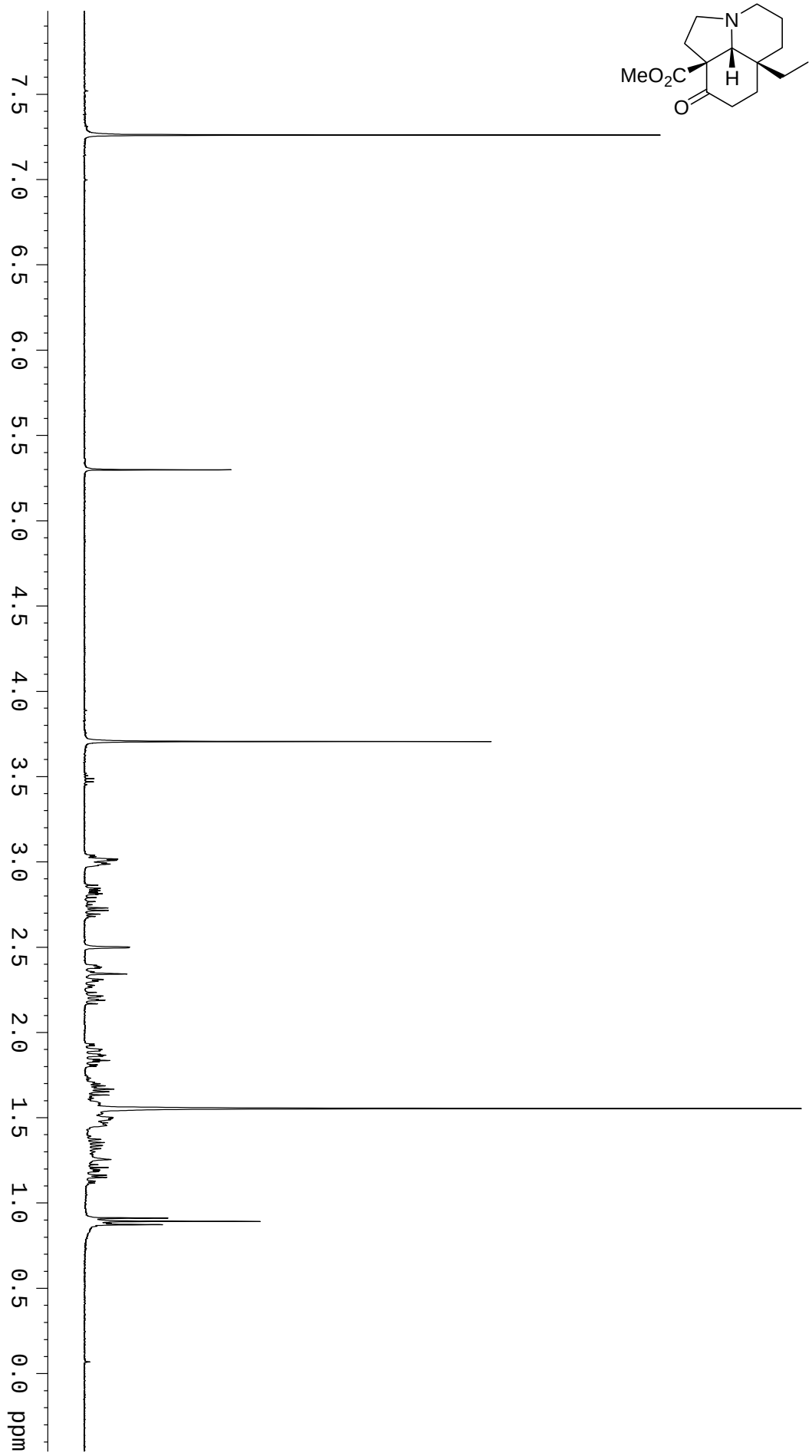
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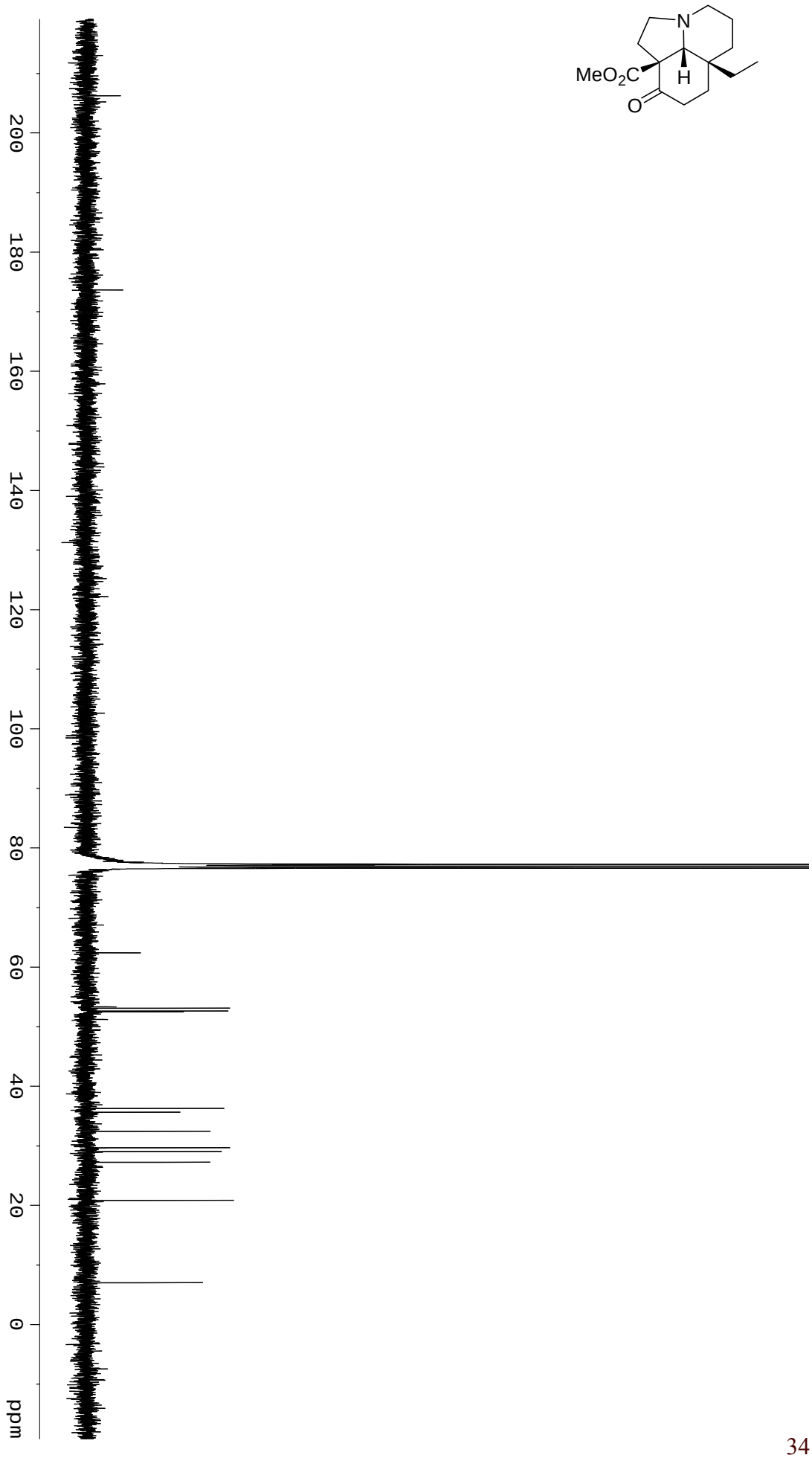
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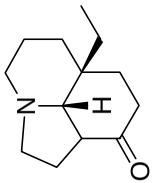
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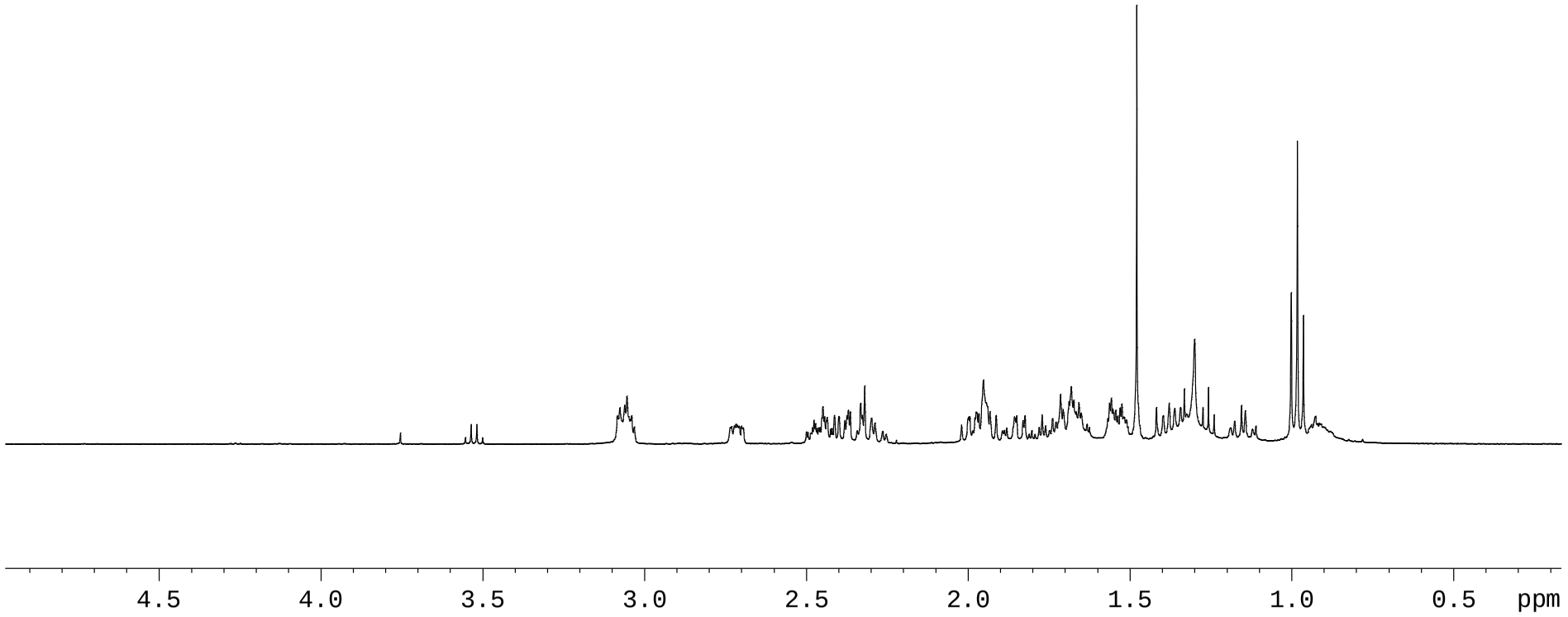
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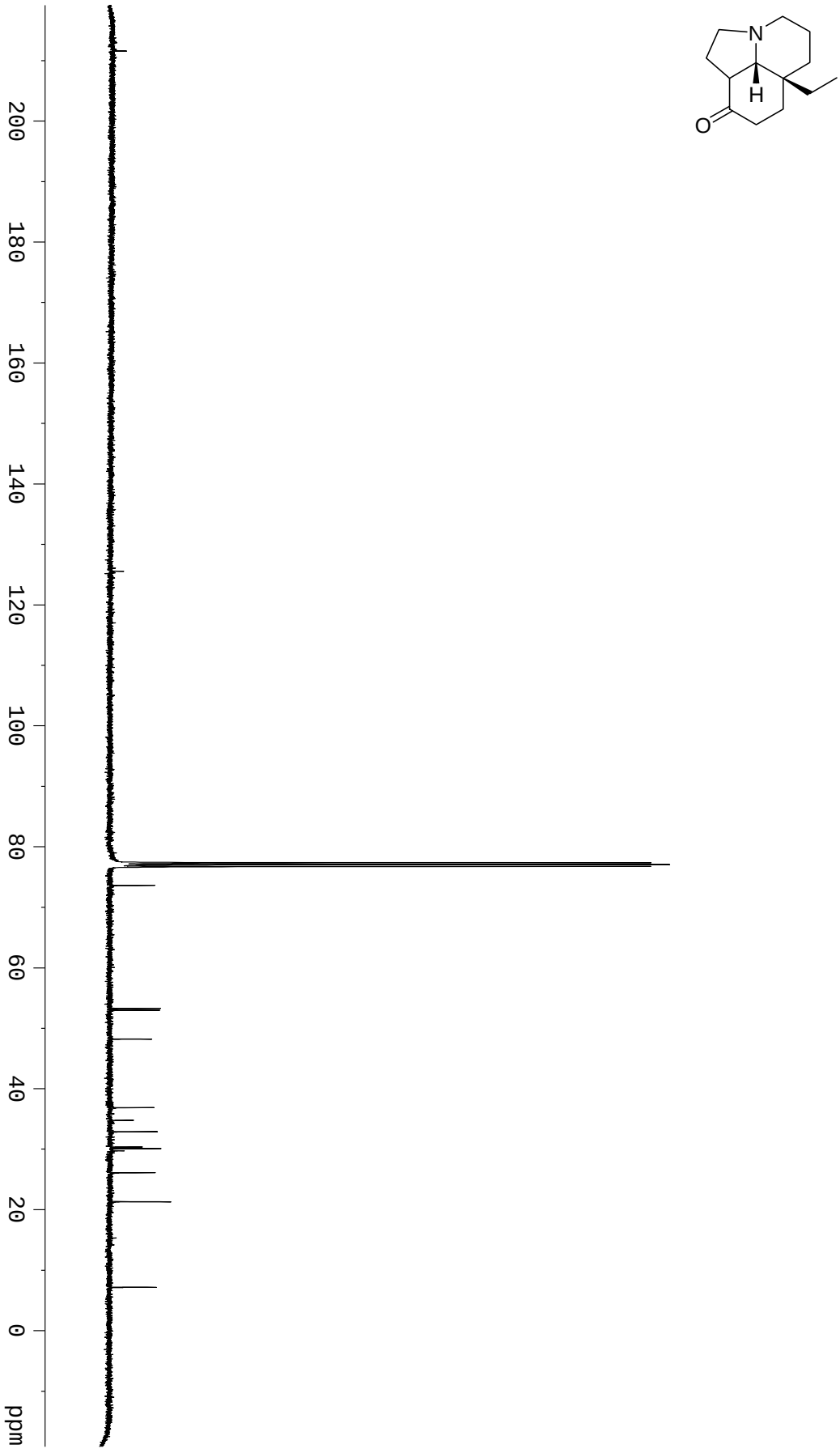
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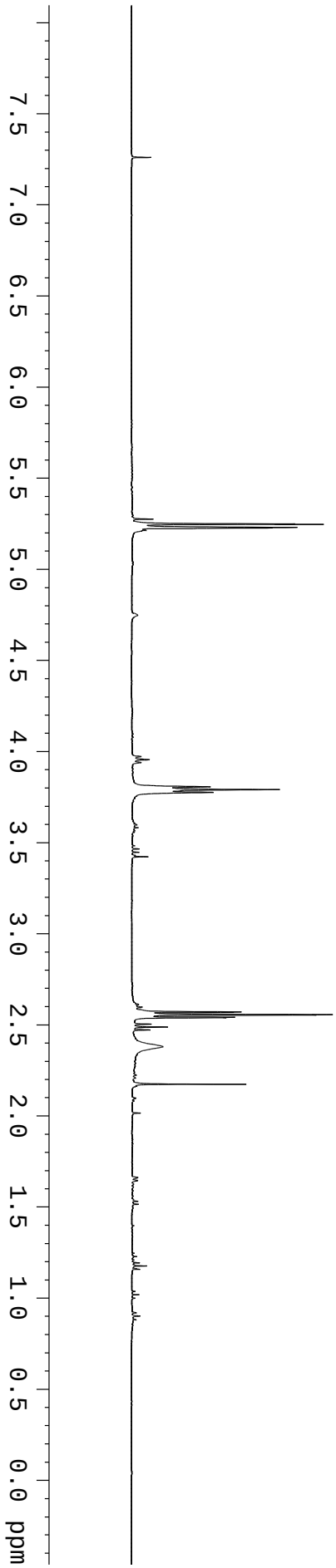
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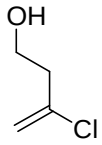
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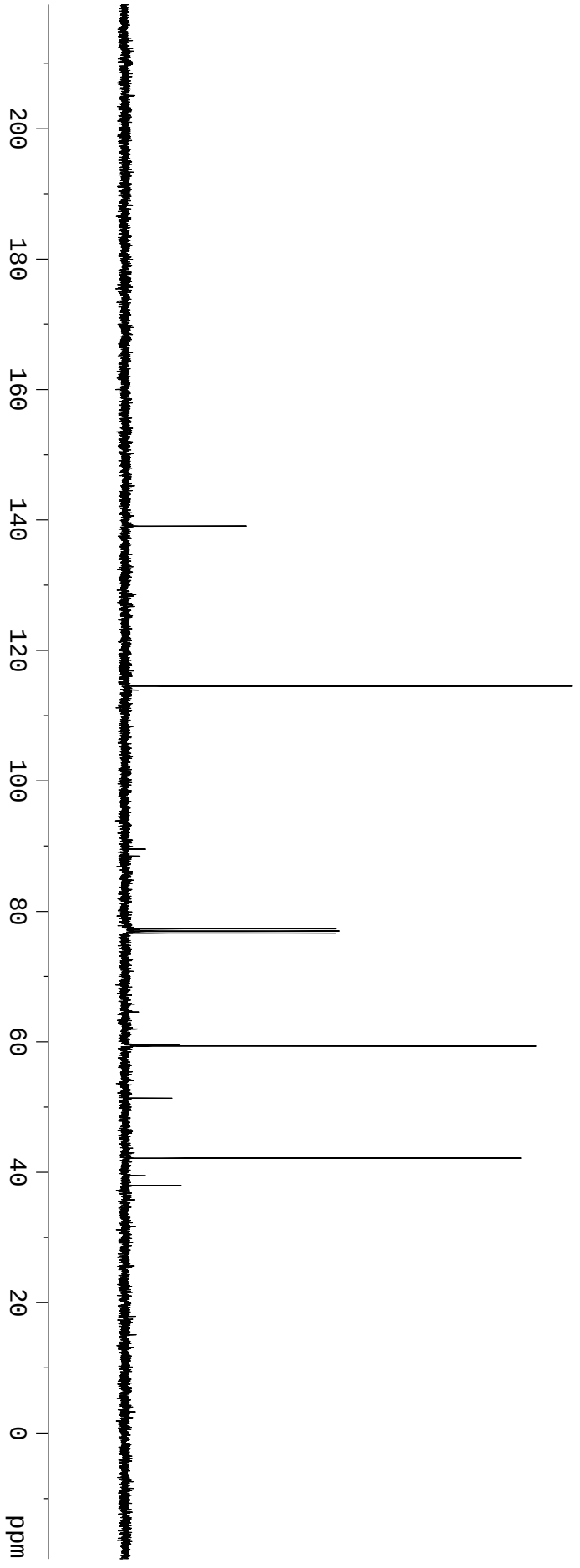
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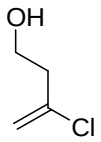
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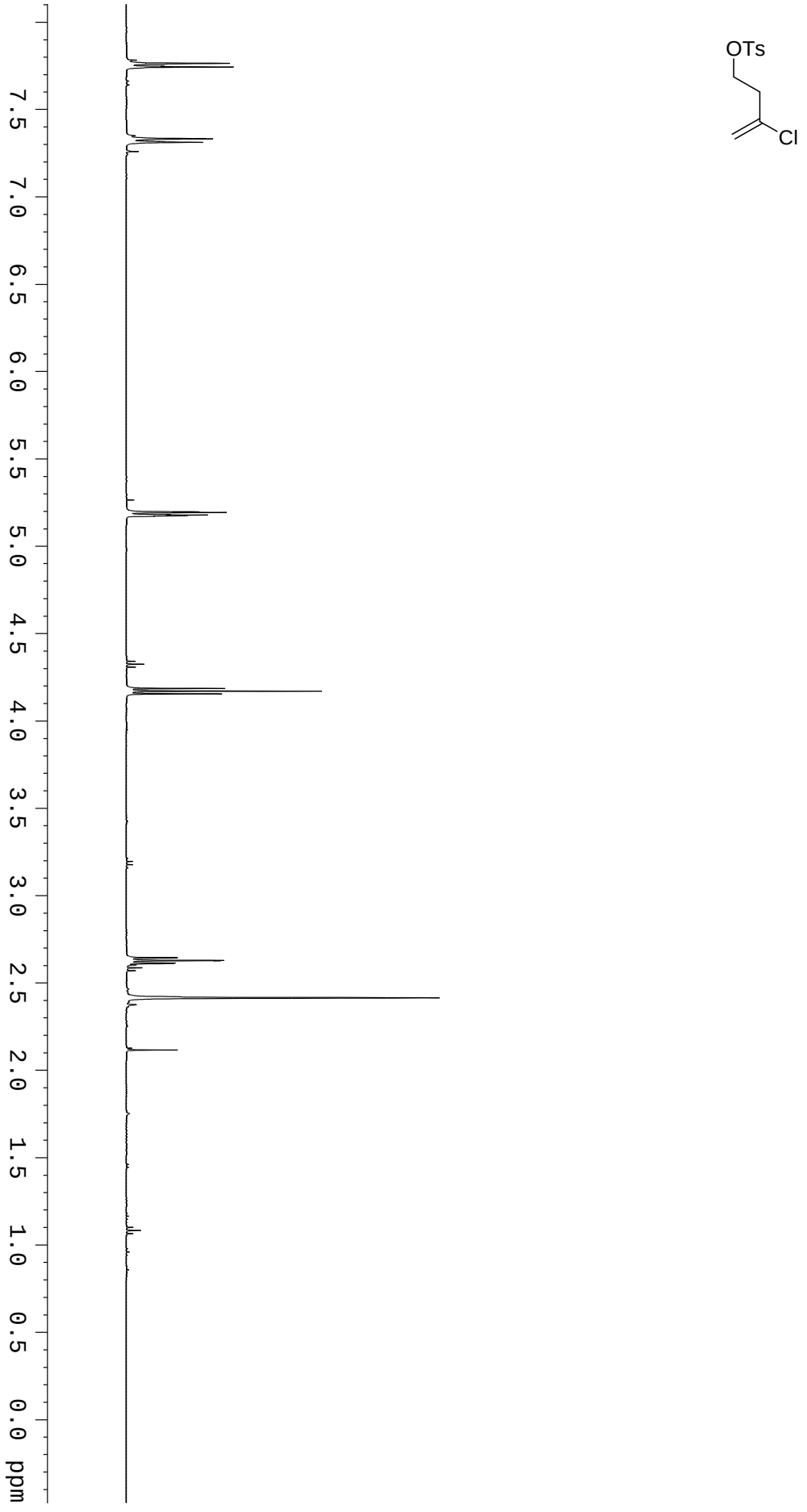
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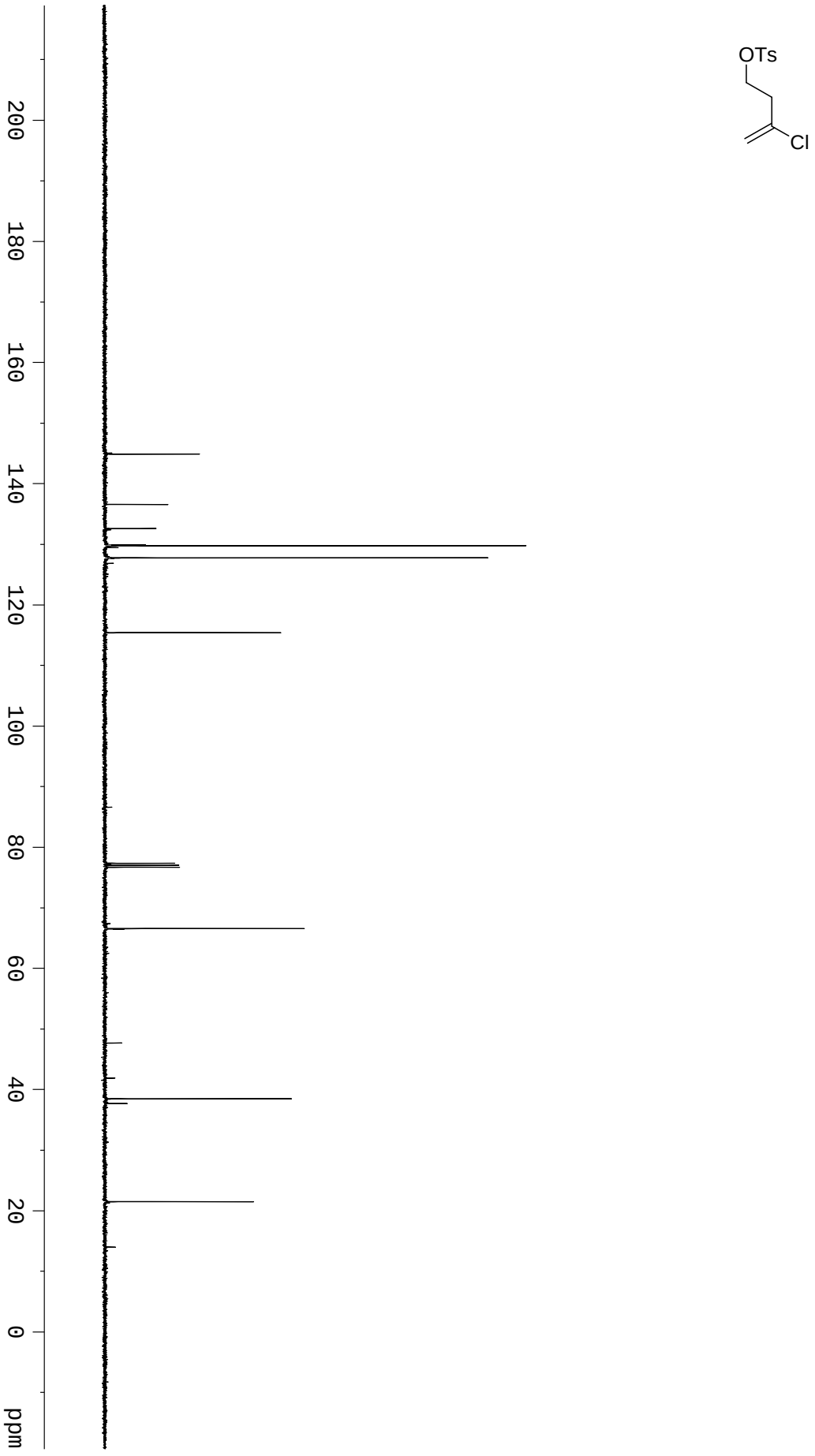
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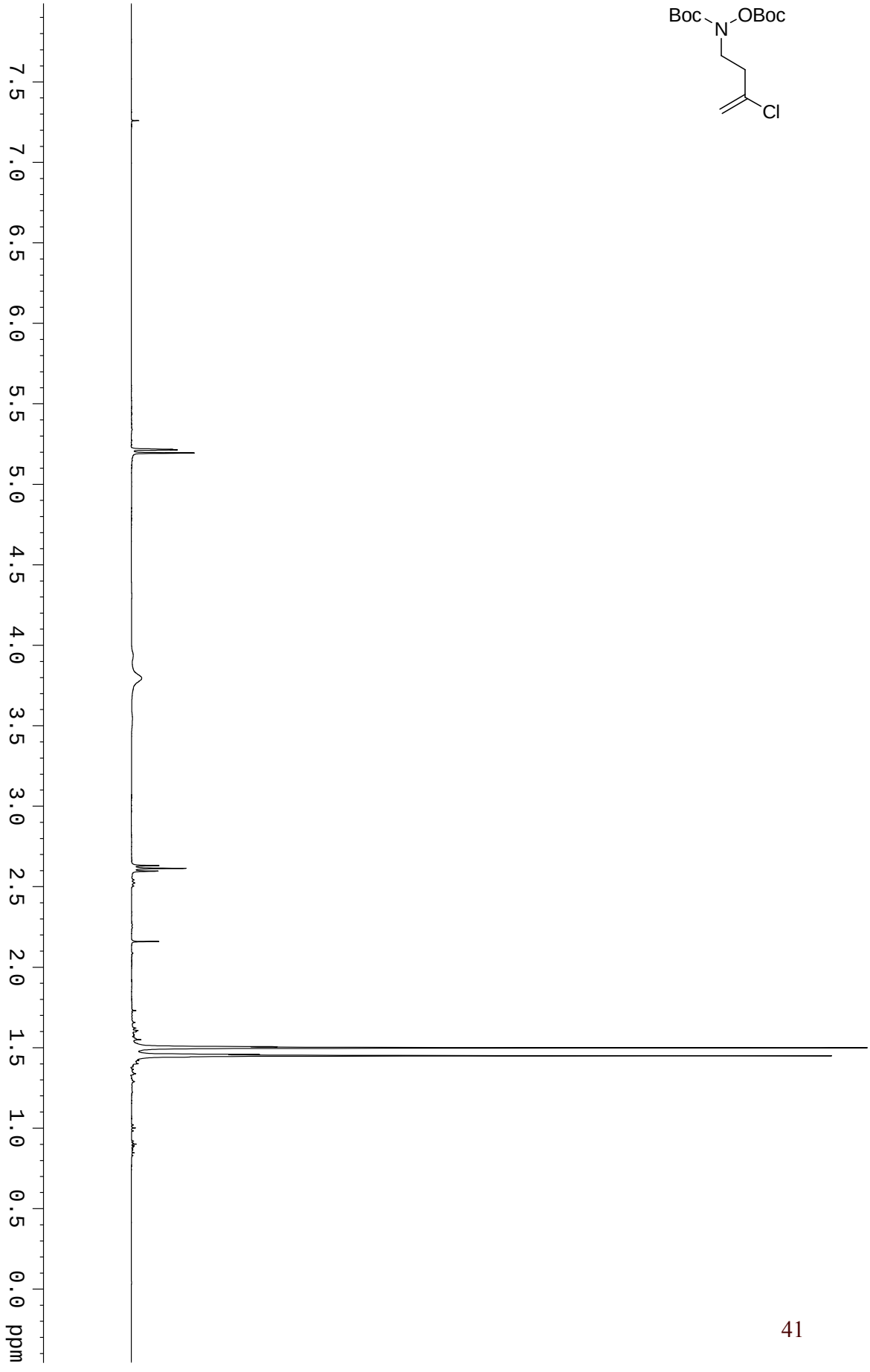
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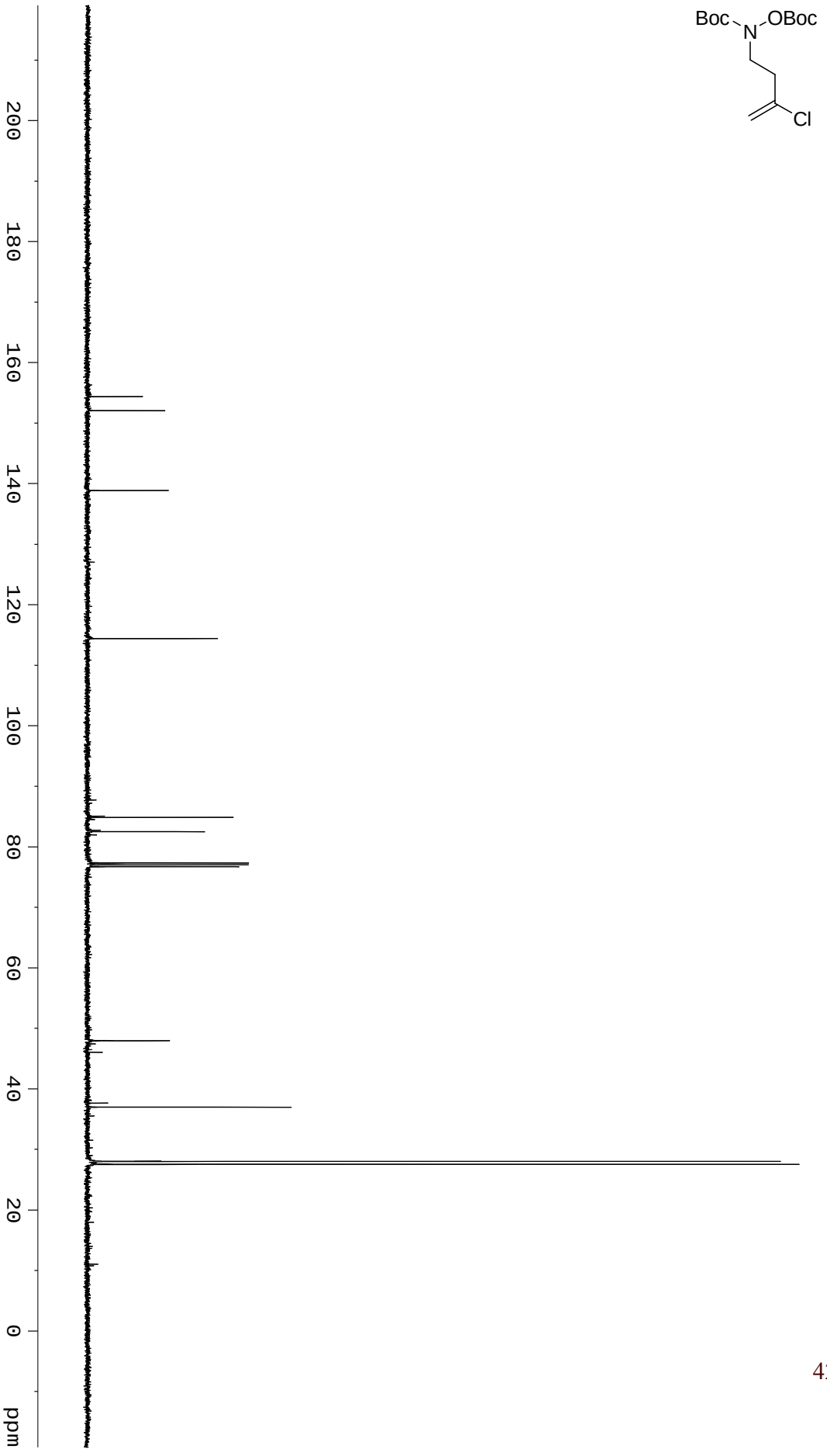
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Cl
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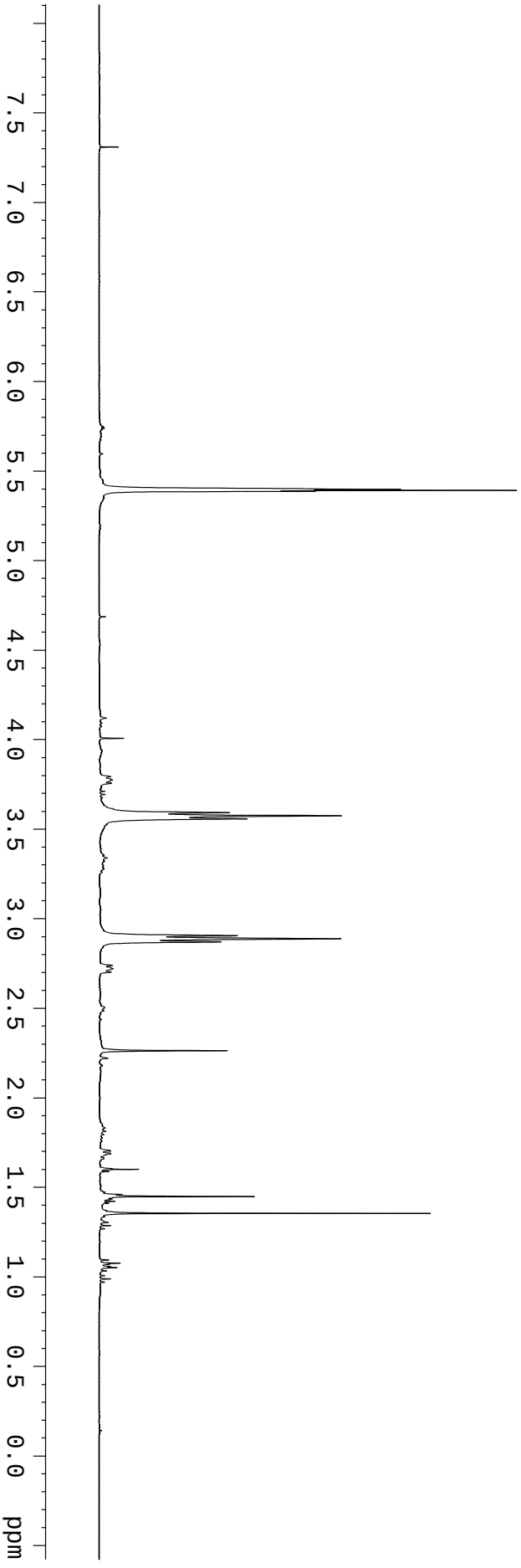
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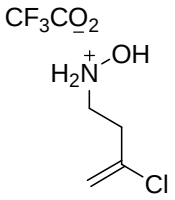
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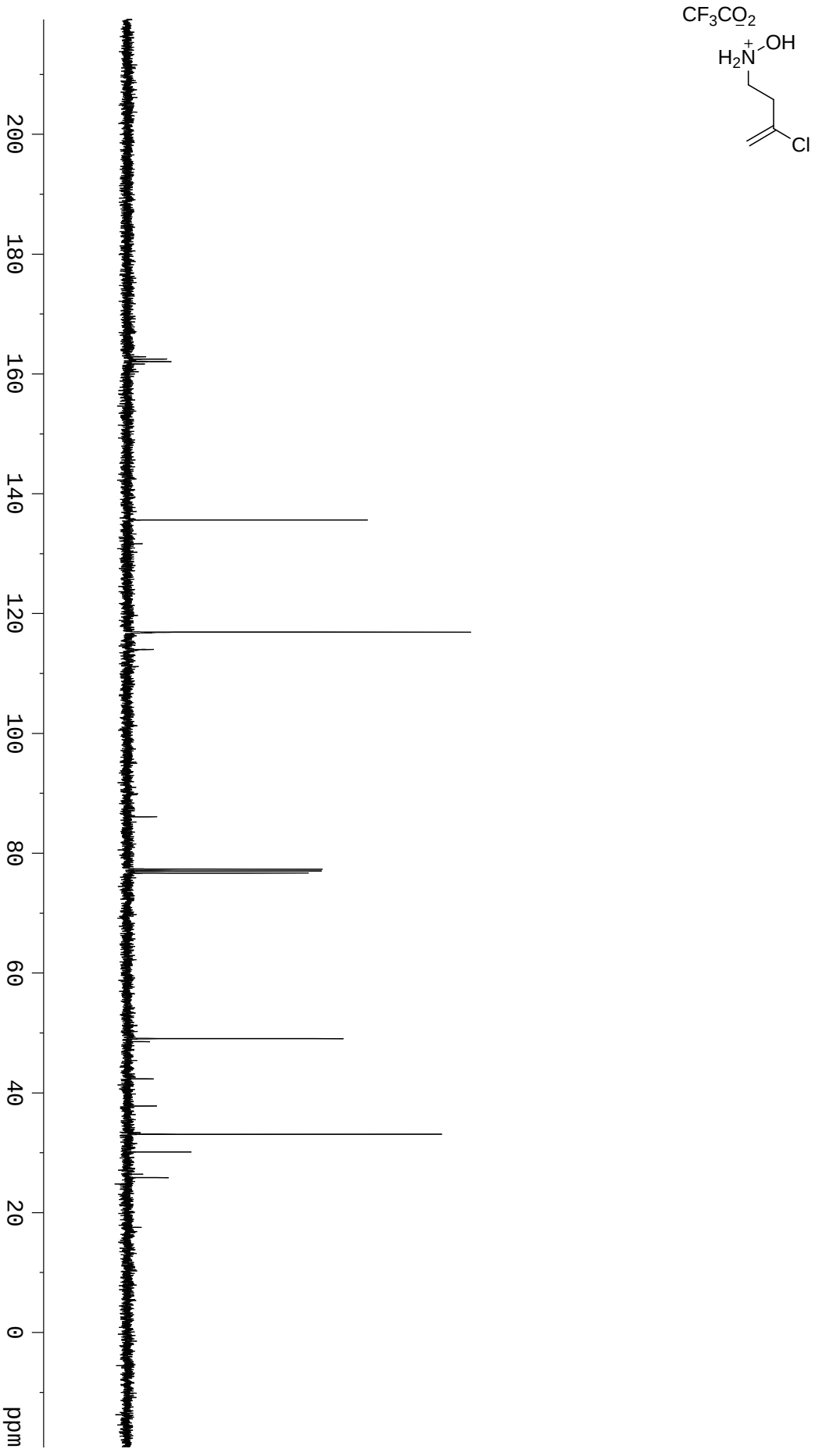
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CF3CO2
H2N
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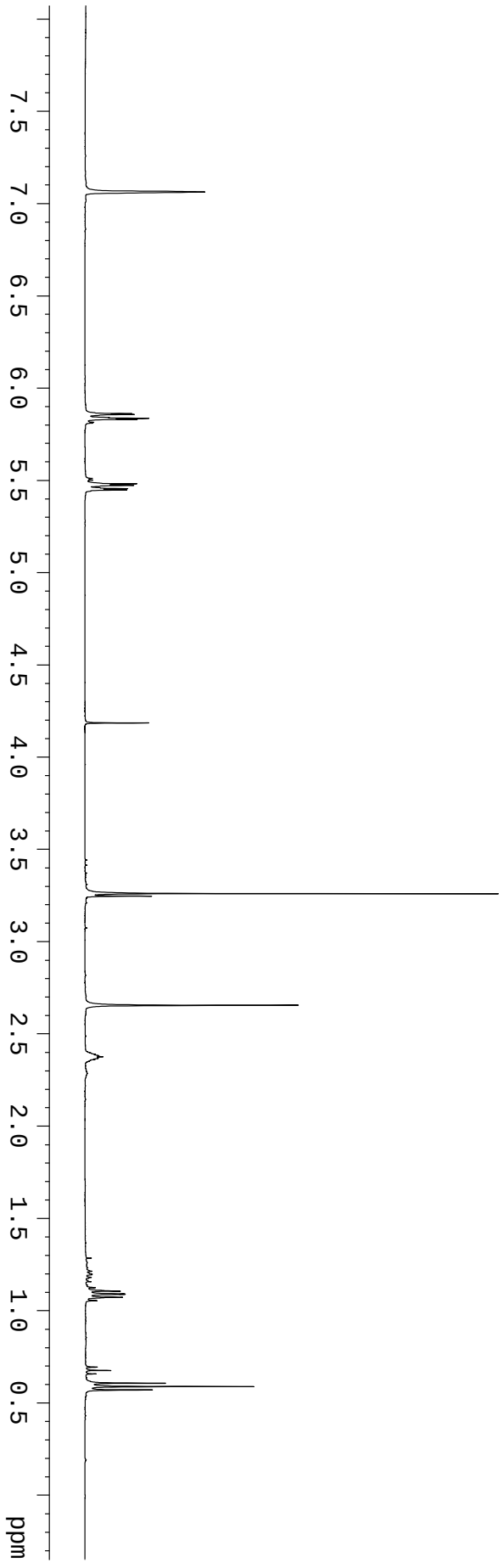
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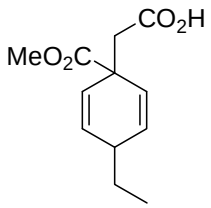
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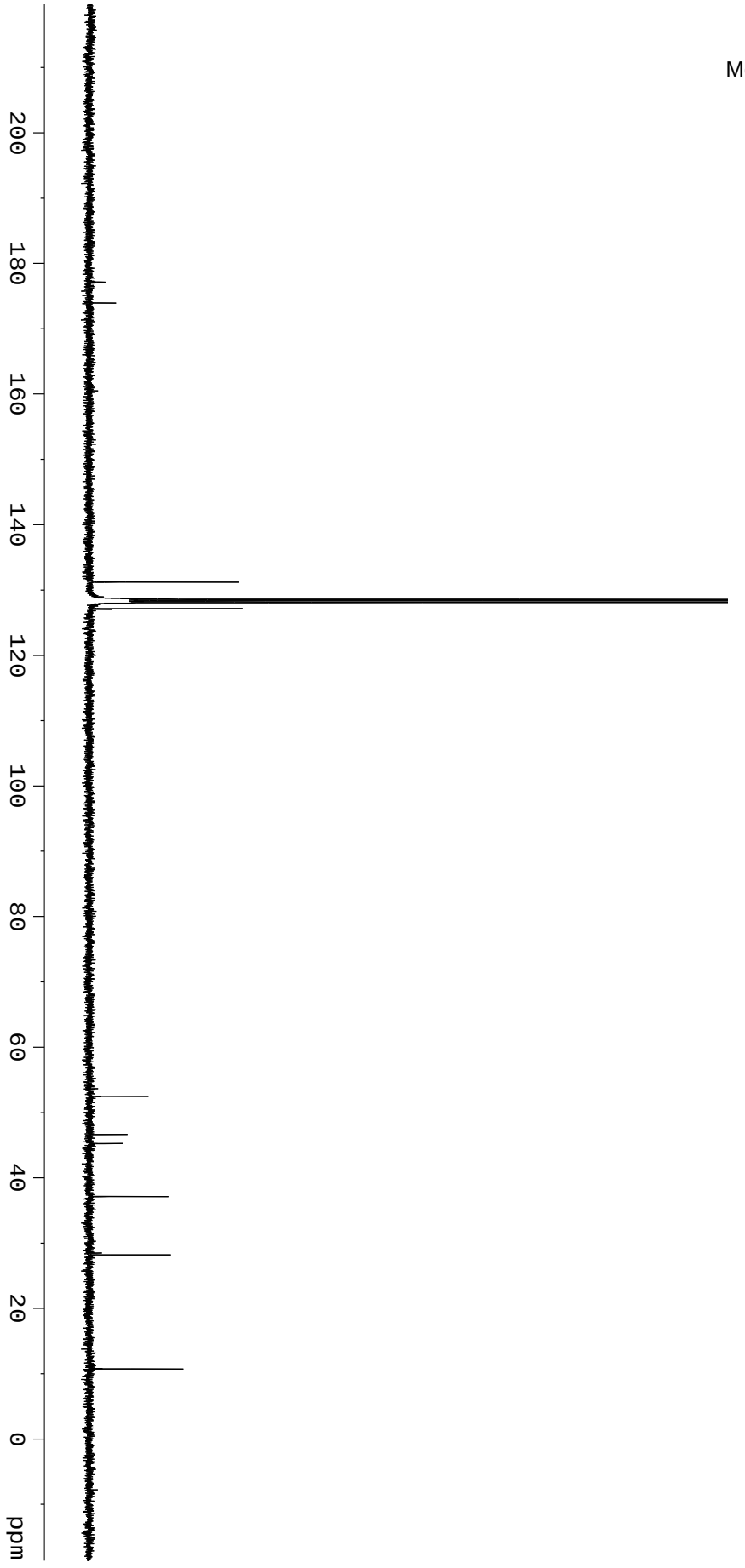
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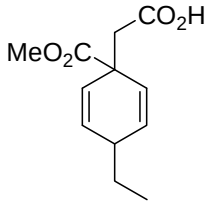
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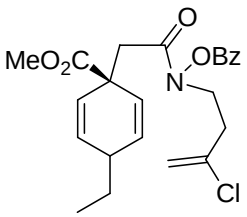
MeO2C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OBz
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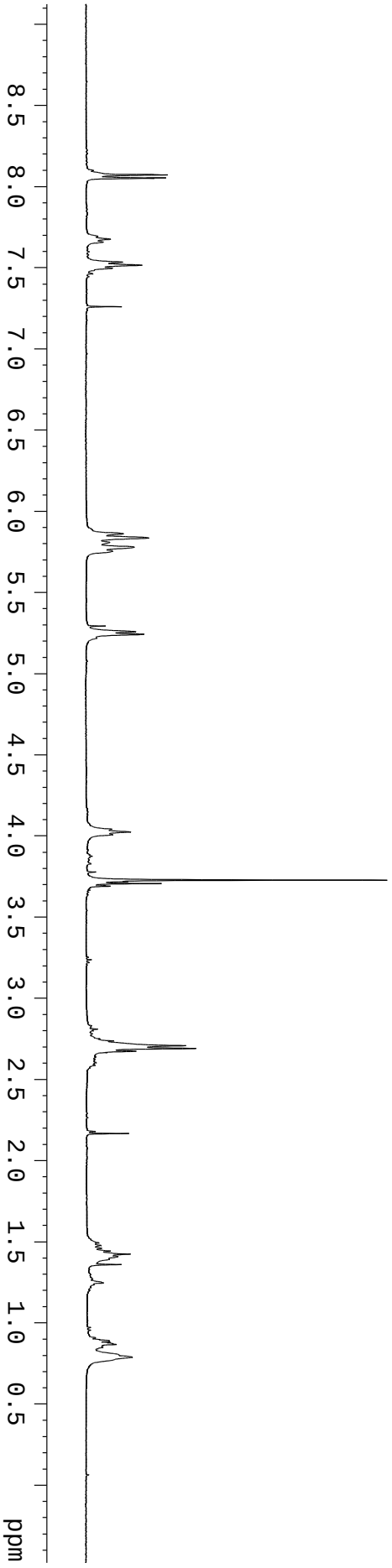
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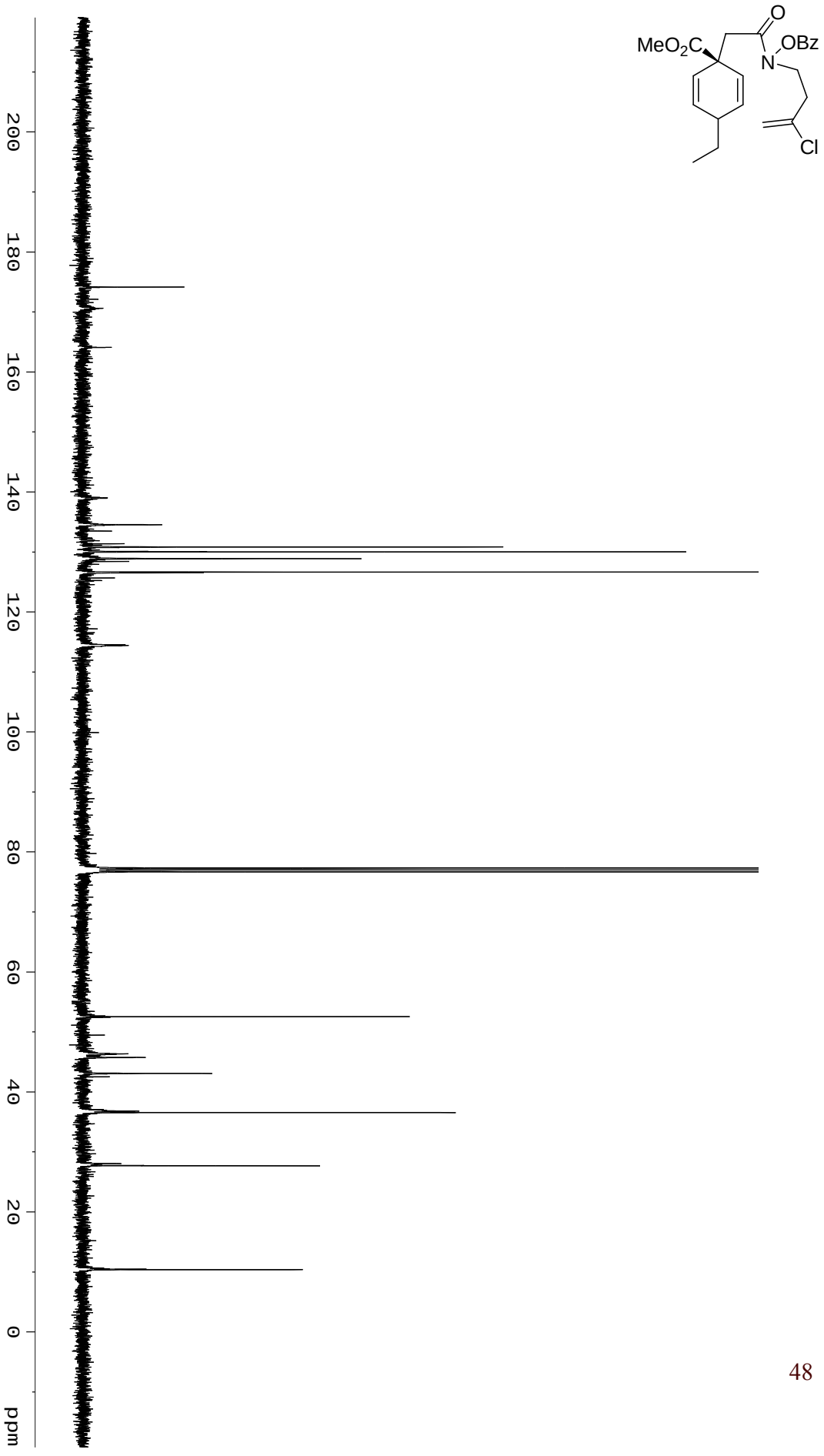
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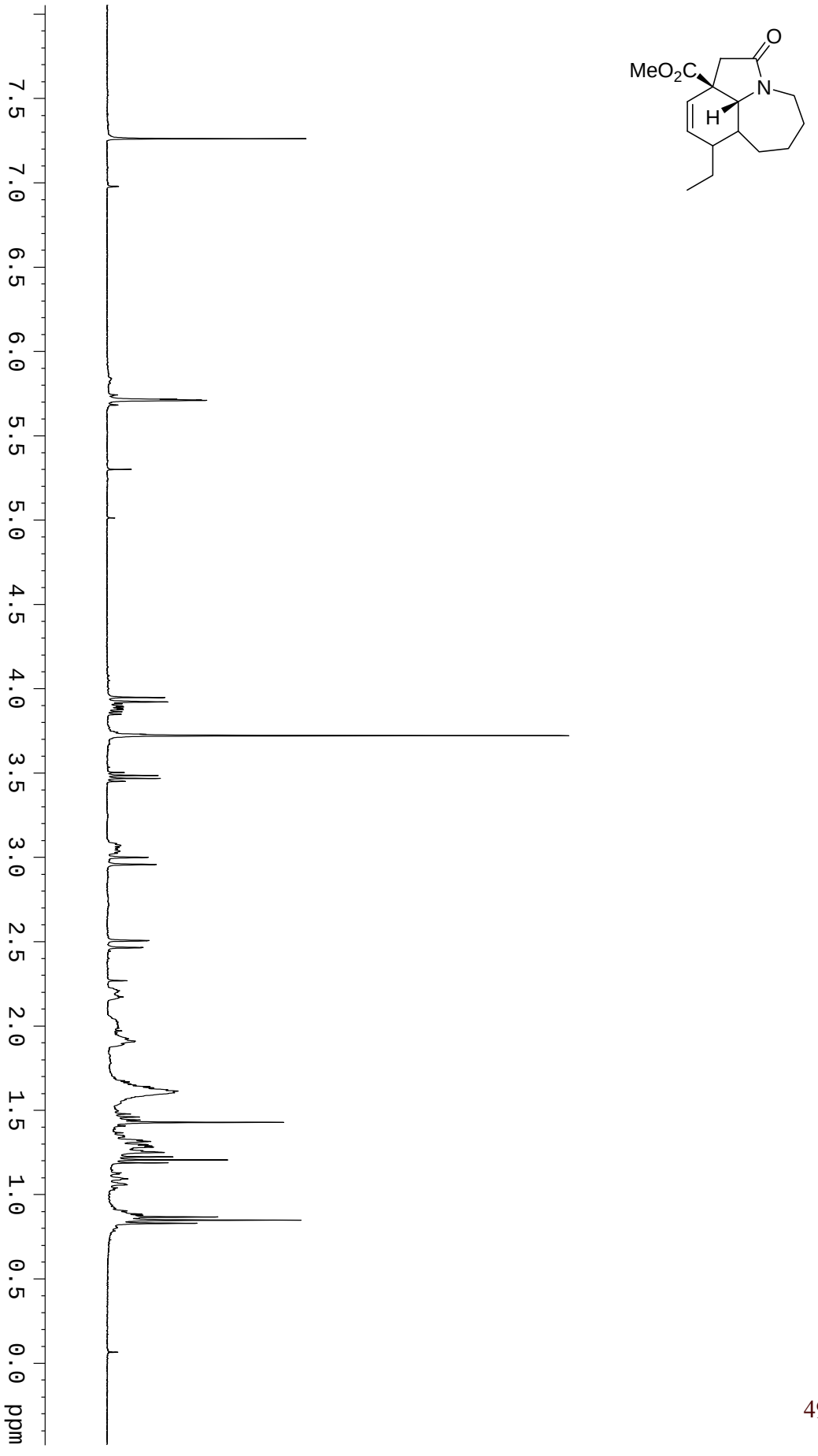
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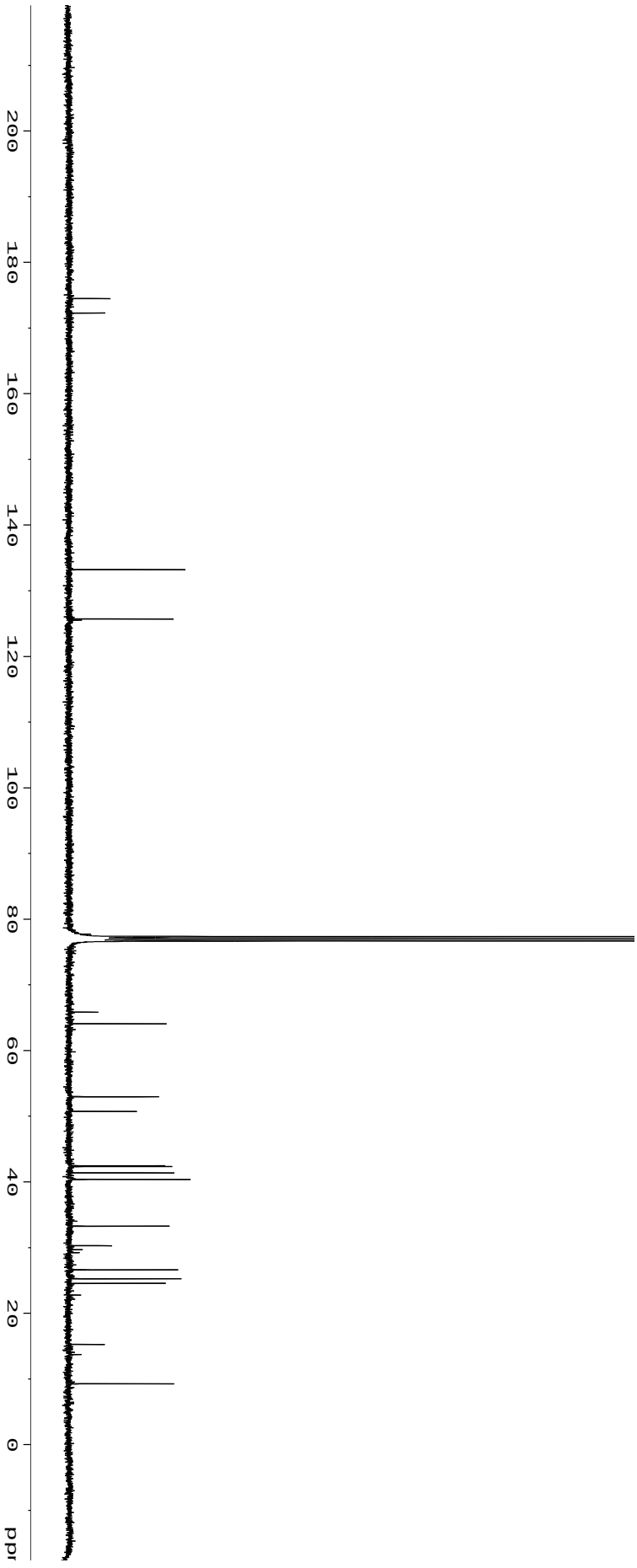
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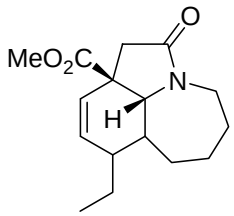
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