A Formal Total Synthesis of (+)-Gephyrotoxin

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SUPPORTING INFORMATION

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General information:

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF was distilled from sodium/benzophenone ketyl immediately prior to use. Thin layer chromatography analyses were performed on Merck precoated silica gel (60 F_{254}) plates and column chromatography on silica gel Gerudan SI 60 (40–60 μm) (Merck). Melting points are uncorrected. Gas chromatography (GC) analyses were performed on capillary Chrompack CP-SIL5 columns. NMR spectra were recorded using 250 MHz spectrometer. Chemical shifts (δ) are expressed in ppm relative to TMS at δ = 0 ppm for ^{1}H NMR and to $CDCl_3$ at δ = 77.16 ppm for ^{13}C NMR.

5-(6*H*-[1,3]Dioxin-4-yl)-3-oxo-pentanoic acid methyl ester (11)

To a solution of diisopropylamine (13.4 mL, 96 mmol) in THF (90 mL) at –20 °C was added *n*-BuLi (2.5 M in hexane, 36.5 mL, 91.5 mmol). The solution was stirred at –20 °C for 20 min. The mixture was then warmed to –10 °C and methylacetoacetate (4.7 mL, 43.5 mmol) in THF (15 mL) was added dropwise. The solution was stirred at -10 °C for 1 h. To the resulting solution was added bromide **10**[1] (7.8 g, 43.5 mmol) in THF (10 mL). The solution was warmed to room temperature and stirred overnight. The mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with ether (3×20 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel column chromatography (ethyl acetate-cyclohexane, 3:7) provided compound **11** as a yellow oil (7.4 g, 79%).

IR (neat) 1746, 1717, 1683 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.38 (t, *J* = 7.5 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 3.48 (s, 2 H), 3.74 (s, 3H), 4.20 (d, *J* = 2.5 Hz, 2H), 4.71 (t, *J* = 2.5 Hz, 1H), 5.02 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 27.6, 39.8, 49.1, 52.5, 63.9, 90.6, 97.6, 152.6, 167.6, 201.7; HRMS (ESI) *m/z* calcd for $C_{10}H_{14}O_5Na$ (MNa^+) 237.0733, found 237.0734.

8-Hydroxy-3,6-dioxo-octanoic acid methyl ester (5a)

To a solution of **11** (0.20 g, 0.93 mmol) in a mixture of CH_2Cl_2 (9 mL) and H_2O (3 mL) at 0°C was added *p*-TsOH (54 mg, 0.27 mmol). The solution was warmed to room temperature and stirred overnight. The mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined extracts were dried (Na_2SO_4) and

concentrated. Purification by silica gel column chromatography (ethyl acetate-cyclohexane, 6:4) provided compound **5a** as a yellow oil (70 mg, 37%).

IR (neat) 3405, 1741, 1712 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.67-2.75 (m, 4H), 2.80-2.85 (m, 2H), 3.50 (s, 2 H), 3.71 (s, 3H), 3.83 (t, *J* = 5.0 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 36.4, 36.6, 44.8, 49.0, 52.5, 57.9, 167.6, 201.7, 209.5; HRMS (ESI) *m/z* calcd for $C_9H_{14}O_5Na$ (MNa^+) 225.0733, found 225.0730.

8-Acetoxy-3,6-dioxo-octanoic acid methyl ester (5b)

To a solution of **11** (0.20 g, 0.93 mmol) in CH_2Cl_2 (10 mL) was added at 0 °C acetic anhydride (0.17 mL, 1.86 mmol) followed by *p*-TsOH (18 mg, 0.09 mmol). The solution was warmed to room temperature and stirred overnight. The mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel column chromatography (ethyl acetate-cyclohexane, 1:1) provided compound **5b** as a yellow oil (0.12 g, 52%).

IR (neat) 1741, 1717 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.01 (s, 3H), 2.71-2.85 (m, 6H), 3.50 (s, 2H), 3.72 (s, 3H), 4.30 (t, *J* = 5.0 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.0, 36.3, 36.5, 41.4, 49.1, 52.5, 59.2, 167.6, 171.0, 201.4, 206.0; HRMS (ESI) *m/z* calcd for $C_{11}H_{16}NaO_6$ (MNa^+) 267.0839, found 267. 0834.

3,6-Dioxo-8-(tetrahydro-pyran-2-yloxy)-octanoic acid methyl ester (5c)

To a solution of **11** (0.90 g, 4.2 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added 3,4-dihydro-*2H*-pyran (0.76 mL, 8.4 mmol) followed by *p*-TsOH (80 mg, 0.42 mmol). The solution was warmed to room temperature and stirred overnight. The mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel column chromatography (ethyl acetate-cyclohexane, 1:1) provided compound **5c** as a yellow oil (1 g, 83%).

IR (neat) 1715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.41-1.76 (m, 7H), 2.73 (t, *J* = 5.0 Hz, 2H), 2.79-2.81 (m, 3H), 3.45-3.52 (m, 3H), 3.56-3.63 (m, 1H), 3.73 (s, 3H), 3.78-3.85 (m, 1H), 3.94-4.03 (m, 1H), 4.45-4.52 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.5, 25.4, 30.5,

36.2, 36.8, 42.8, 49.1, 52.3, 62.3, 62.5, 99.1, 167.5, 201.4, 207.3; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_6Na$ (MNa^+) 309.1308, found 309.1308.

(3*S*, 7a*S*)-[7a-(2-Acetoxy-ethyl)-3-phenyl-tetrahydro-pyrrolo[2,1-*b*]oxazol-5-ylidene]-acetic acid methyl ester (4b)

To a solution of β-keto ester **5b** (0.13 g, 0.454 mmol) in CH_2Cl_2 (10 mL) was added (*S*)-phenylglycinol (0.18 g, 1.36 mmol) followed by $ZnClO_4$, $6H_2O$ (10 mg, 0.023 mmol) and $MgSO_4$ (16 mg, 0.136 mmol). The mixture was stirred at room temperature for 24 h. The resulting mixture was filtered and concentrated. Purification by silica gel column chromatography (ethyl acetate-cyclohexane, 3:7) afforded pure **4b** (55 mg, 35%) as yellow oil.

IR (neat) 1739, 1695, 1613 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.98-2.10 (m, 6H), 2.30-2.39 (m, 1H), 2.89-3.04 (m, 1H), 3.53 (s, 3H), 3.69-3.85 (m, 1H), 3.89 (t, *J* = 7.5 Hz, 1H), 4.10-4.16 (m, 2H), 4.45-4.52 (m, 3H), 7.12-7.30 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.1, 32.6, 34.3, 34.9, 50.6, 60.6, 63.4, 75.0, 85.7, 105.0, 125.5, 127.9, 129.2, 139.3, 166.5, 169.0, 171.0; HRMS (ESI) *m/z* calcd for $C_{19}H_{23}NO_5Na$ (MNa^+) 368.1468, found 368.1477; $[\alpha]^{20}_D$ + 156 (*c* 1.10, $CHCl_3$).

(2*S*, 5*R*)- [5-(2-Hydroxy-ethyl)-1-(2-hydroxy-1-(*S*)-phenyl-ethyl)-pyrrolidin-2-yl]-acetic acid methyl ester (13).

To a solution of **12** (0.20 g, 0.51 mmol) in MeOH (15 mL) was added *p*-TsOH (126 mg, 0.66 mmol). The solution was stirred for 24 h at room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (10 mL). Then, methanol was partially evaporated. The crude product was dissolved in CH_2Cl_2 (10 mL) and the organic layer was washed with saturated aqueous NaCl (5 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel column chromatography (ethyl acetate-cyclohexane, 7:3) provided pure **13** as a yellow oil (50 mg, 30%).

IR (neat) 3384, 1731 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.26-1.77 (m, 6H), 2.37 (dd, *J* = 15.0, 10.0 Hz, 1H), 2.59 (dd, *J* = 15.0, 5.0 Hz, 1H), 3.32-3.41 (m, 4H), 3.63 (s, 3H), 3.69-3.81 (m, 2H), 3.85-4.10 (m, 3H), 7.28-7.33 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 29.1, 30.5, 35.3, 42.7, 51.7, 55.1, 60.3, 61.4, 62.9, 65.8, 128.0, 128.6, 128.9, 137.1, 172.9; HRMS (ESI) *m/z* calcd for $C_{17}H_{26}NO_4$ (MH^+) 308.1856, found 308.1852; $[\alpha]^{20}_D$ + 26 (*c* 0.80, $CHCl_3$).

(2*R*, 5*S*)- 3-[2-(2-Benzyloxy-ethyl)-5-(2-hydroxy-ethyl)-pyrrolidin-1-yl]-cyclohex-2-enone (17)

To a solution of **3** (0.32 g, 1.26 mmol) in toluene (20 mL) was added 1,3-cyclohexanedione (0.18 g, 1.66 mmol) followed by *p*-TsOH (73 mg, 0.38 mmol). The reaction mixture was stirred and refluxed using a Dean Stark trap for 6 h and solvent was evaporated**.** Purification by silica gel column chromatography (ethyl acetate-methanol, 8:2) provided **17** as an orange oil (0.40 g, 91%).

IR (neat) 3357, 1595, 1537 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.30-1.70 (m, 2H), 1.75-2.15 (m, 9H), 2.25-2.35 (m, 2H), 2.40-2.65 (m, 2H), 3.45-3.50 (m, 2H), 3.60-3.80 (m, 2H), 3.85-4.15 (m, 2H), 4.44-4.55 (m, 2H), 5.17 (s, 1H), 7.28-7.35 (m, 5 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.5, 27.8, 29.6 , 35.8, 35.9, 38.0, 56.9, 57.4, 59.5, 67.3, 73.3, 98.6, 127.7, 127.8, 128.5, 138.2, 163.8, 196.7; HRMS (ESI) *m/z* calcd for $C_{21}H_{30}NO_3$ (MH^+) 344.2220, found 344.2216; $[\alpha]^{20}$ + 47 (*c* 0.90, $CHCl_3$).

(1*S*, 3a*S*)- 1-(2-Benzyloxy-ethyl)-2,3,3a,4,5,7,8,9-octahydro-1*H*-pyrrolo[1,2-*a*]quinolin-6-one (18)

To a solution of **17** (100 mg, 0.29 mmol) in CH_2Cl_2 (5 mL) at –20 °C was added PBr_3 (54 µL, 0.58 mmol). The solution was refluxed for 4 h. Then the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed successively with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried (Na_2SO_4), evaporated under vacuum to afford the bromide intermediate (0.12 g, 0.296 mmol). The latter was refluxed in CH_3CN (5 mL) in the presence of NaI (0.22 g, 1.47 mmol) overnight. The reaction was quenched by addition of a saturated aqueous $NaHCO_3$ (5 mL) solution then washed with saturated aqueous NaCl (5 mL). The organic layer was dried (Na_2SO_4) and concentrated under vacuum. Purification by silica gel column chromatography (ethyl acetate-methanol, 95:5) provided **18** as a colorless oil (126 mg, 96%).

IR (neat) 1608, 1547 cm^{-1};^1H NMR (250 MHz, $CDCl_3$) δ 1.18-1.25 (m, 1 H), 1.50-1.64 (m, 2H), 1.79-1.96 (m, 5H), 2.02-2.20 (m, 3H), 2.30-2.36 (t, *J* = 7.5 Hz, 2H), 2.45 (t, *J* = 5 Hz, 1H), 2.60-2.68 (m, 2H), 3.25-3.27 (m, 1H), 3.42-3.54 (m, 2H), 4.01 (t, *J* = 7.5 Hz, 1H), 4.50-4.52 (m, 2H), 7.29-7.35 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.5, 22.0, 27.3, 28.4, 29.1,

29.6, 36.1, 36.3, 56.2, 59.4, 67.5, 73.2, 107.1, 127.5, 127.8, 128.5, 138.2, 159.1, 193.9; HRMS (ESI) *m/z* calcd for $C_{21}H_{28}NO_2$ (MH^+) 326.2114, found 326.2109; $[\alpha]^{20}$ + 322 (*c* 1.00, $CHCl_3$).

(1*S*, 3a*S*)-1-(2-Hydroxy-ethyl)-2,3,3a,4,5,7,8,9,-octahydro-1*H*-pyrrolo[1,2-*a*]quinolin-6-one (2).[2]

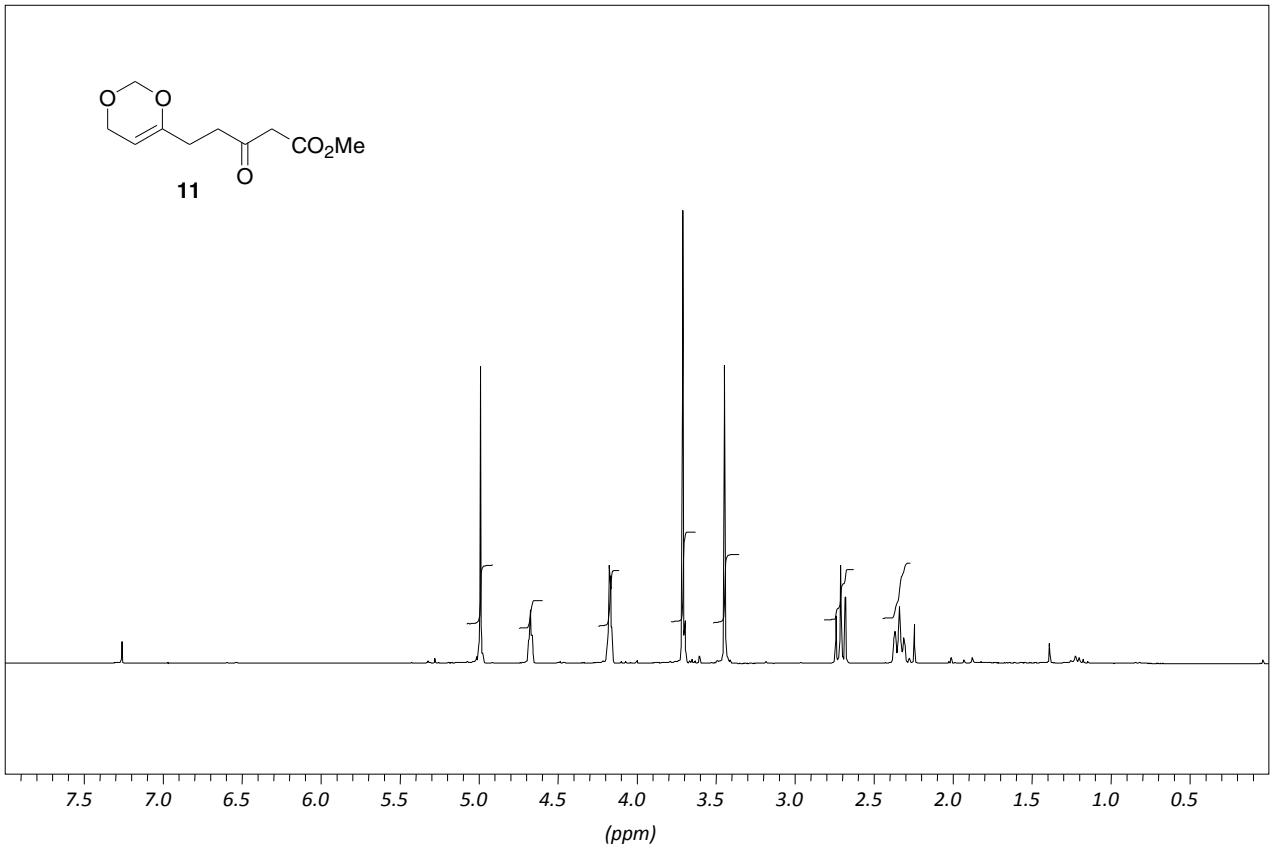
A solution of **18** (100 mg, 0.31 mmol) in MeOH (6 mL) was subjected to hydrogenation (1 atm) in the presence of 5% Pd/C (50 mg) and perchloric acid (60%, 33 µL, 0.31 mmol) at room temperature for 18 h. The reaction mixture was filtered over a Celite® pad and methanol was partially removed under vacuum. The crude product was diluted in CH_2Cl_2 (10 mL), washed successively with saturated aqueous Na_2CO_3 (5 mL) and brine (5 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification by silica gel column chromatography (ethyl acetate-methanol, 9:1) provided **2** as a white solid (60 mg, 86%).

mp 175-177 °C (from Cyclohexane-AcOEt,1:1) {lit.[2] : mp 176-179°C}; IR (neat) 3358, 1596 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.17-1.24 (m, 1H), 1.46-1.66 (m, 2H), 1.79-1.93 (m, 5H), 2.02-2.17 (m, 4H), 2.29 (t, *J* = 5 Hz, 2H), 2.36-2.48 (m, 1H), 2.56-2.70 (m, 2H), 3.19-3.26 (m, 1H), 3.60-3.74 (m, 2H), 3.98-4.07 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.4, 22.0, 27.4, 28.3, 29.0, 29.6, 36.2, 38.6, 55.9, 59.4, 59.8, 106.8, 159.7, 193.8; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}NO_2$ (MH^+) 236.1645, found 236.1644; $[\alpha]^{20}_D$ + 537 (*c* 2.00, EtOH) {lit.[2] : $[\alpha]^{20}_D$ + 538 (*c* 1.40, EtOH)}.

References

1. Greshock, T. J. ; Funk, R. L. *J. Am. Chem. Soc*. **2002**, *124*, 754-755.

2. Fujimoto, R. ; Kishi, Y. *Tetrahedron Lett.* **1981**, *42*, 4197-4198.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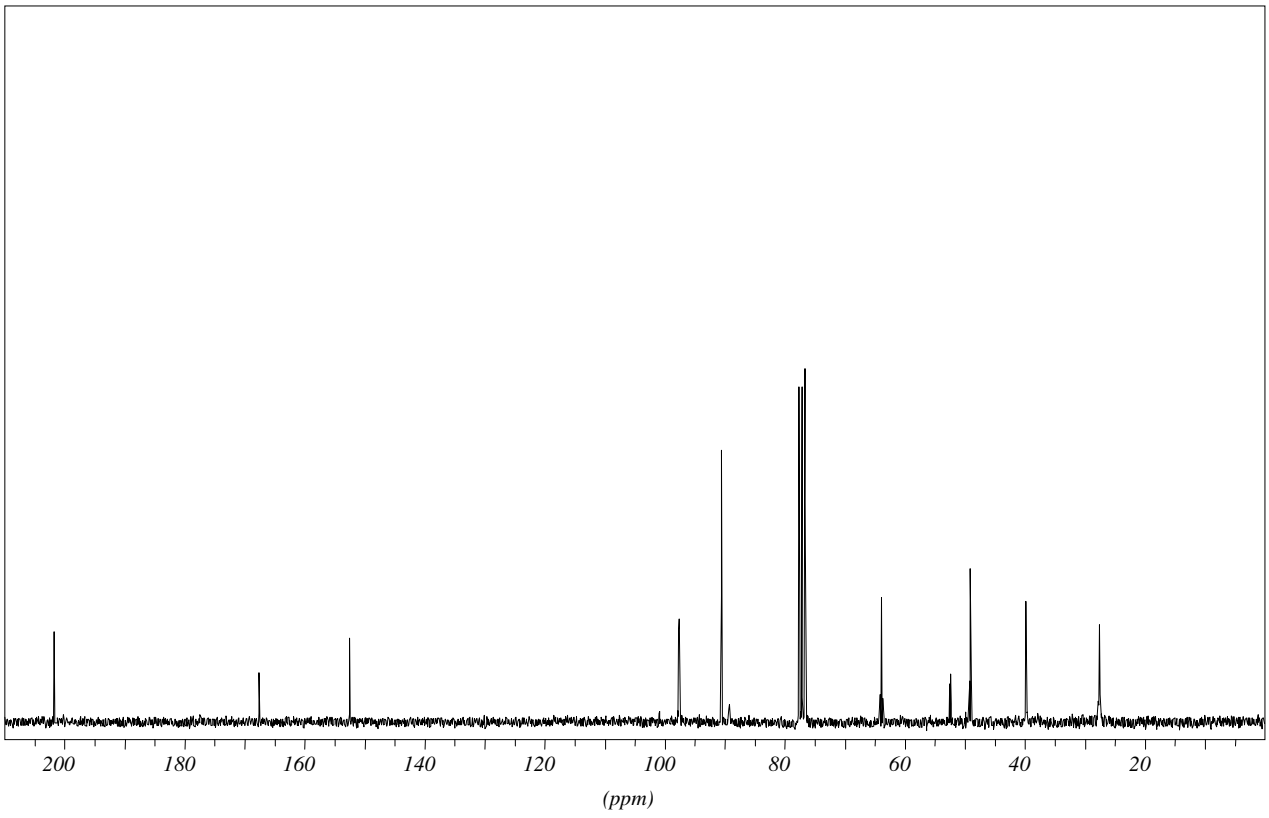
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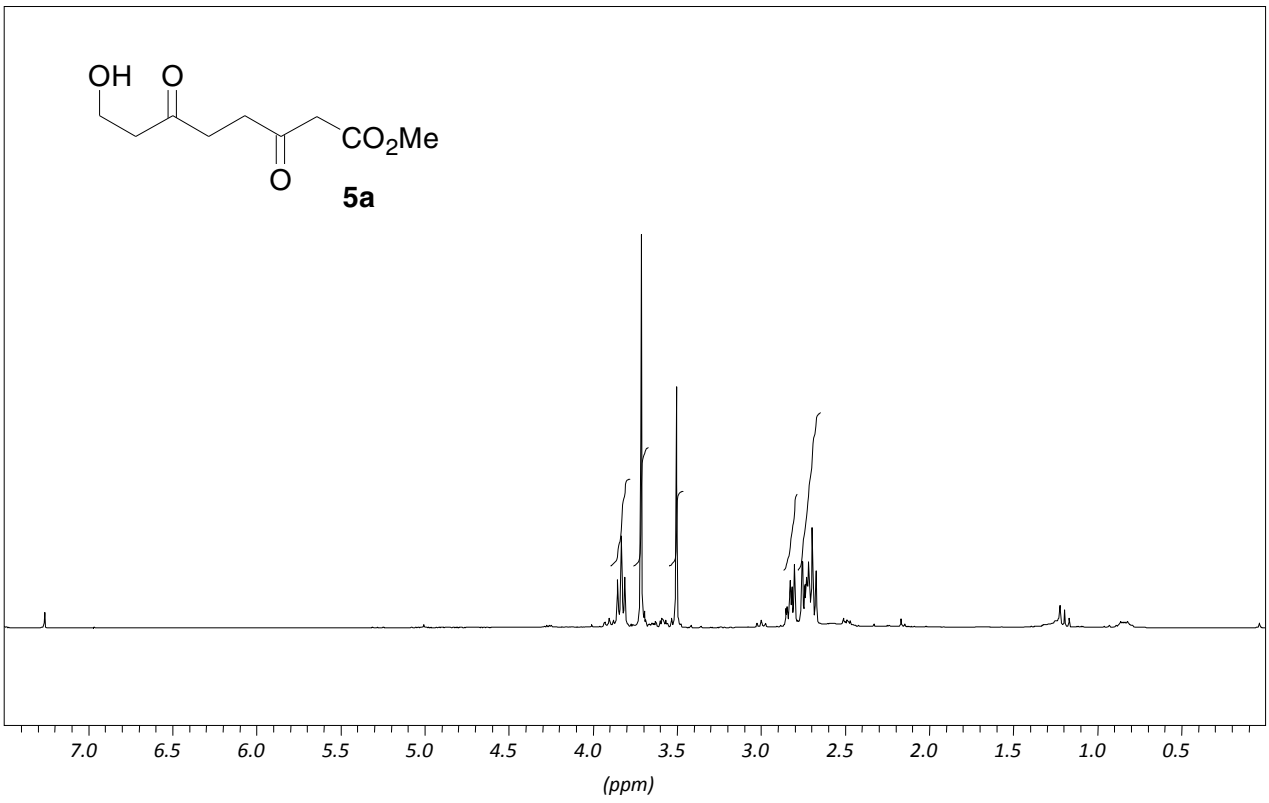
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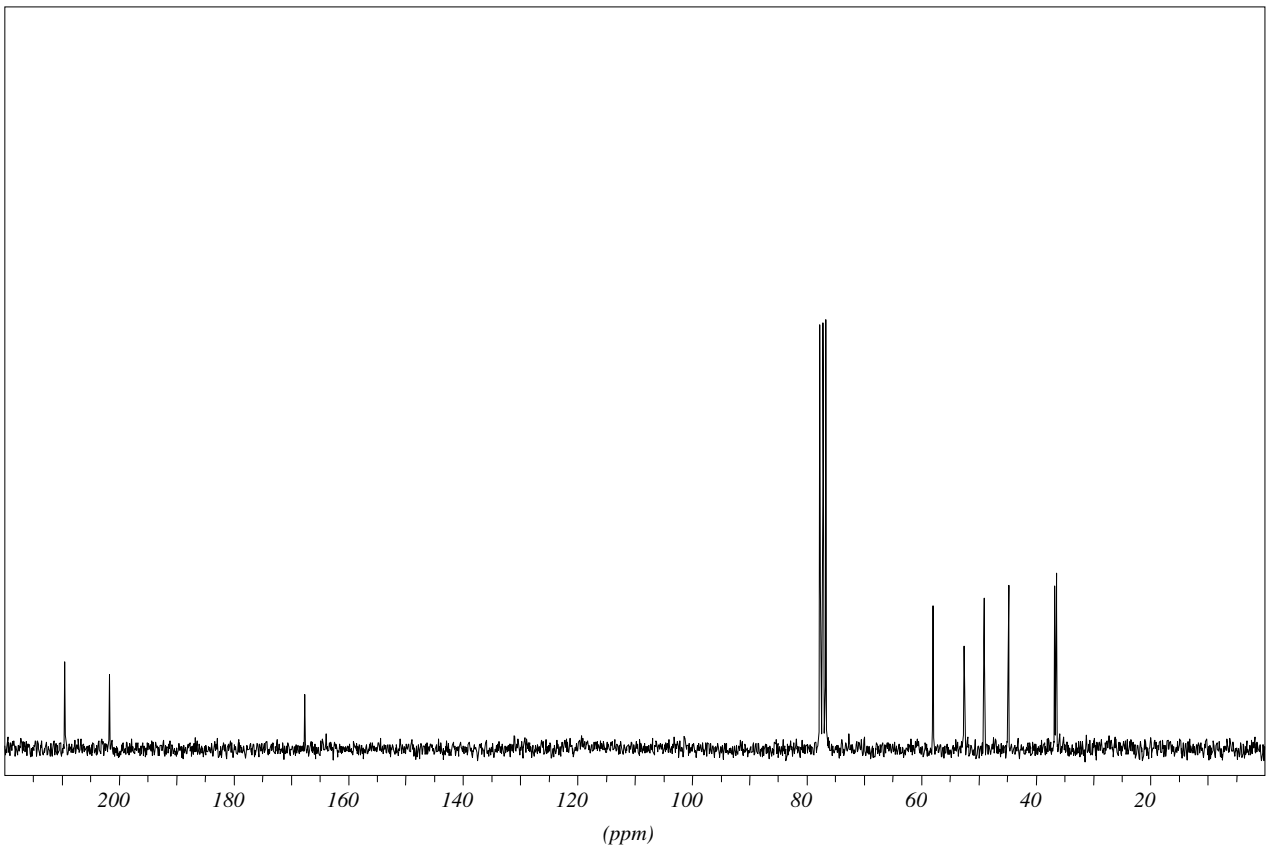
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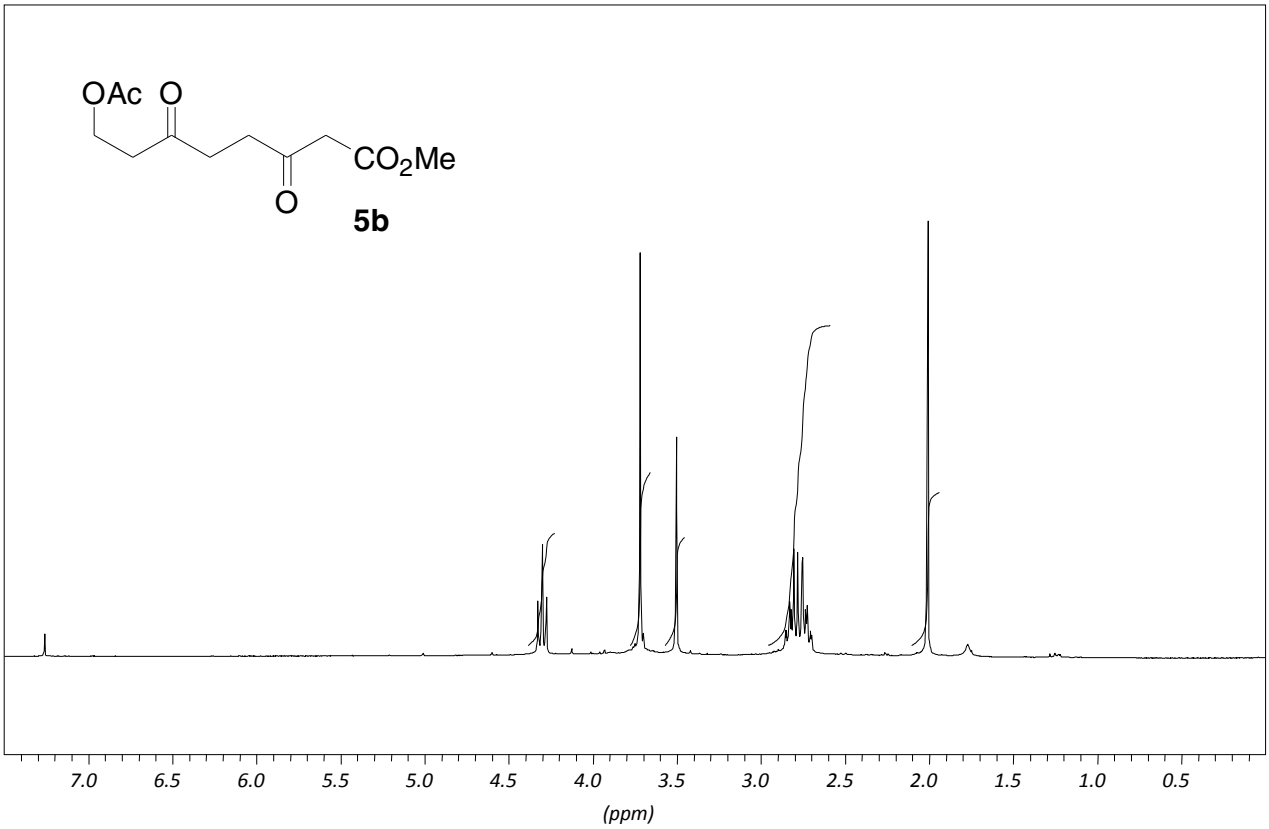
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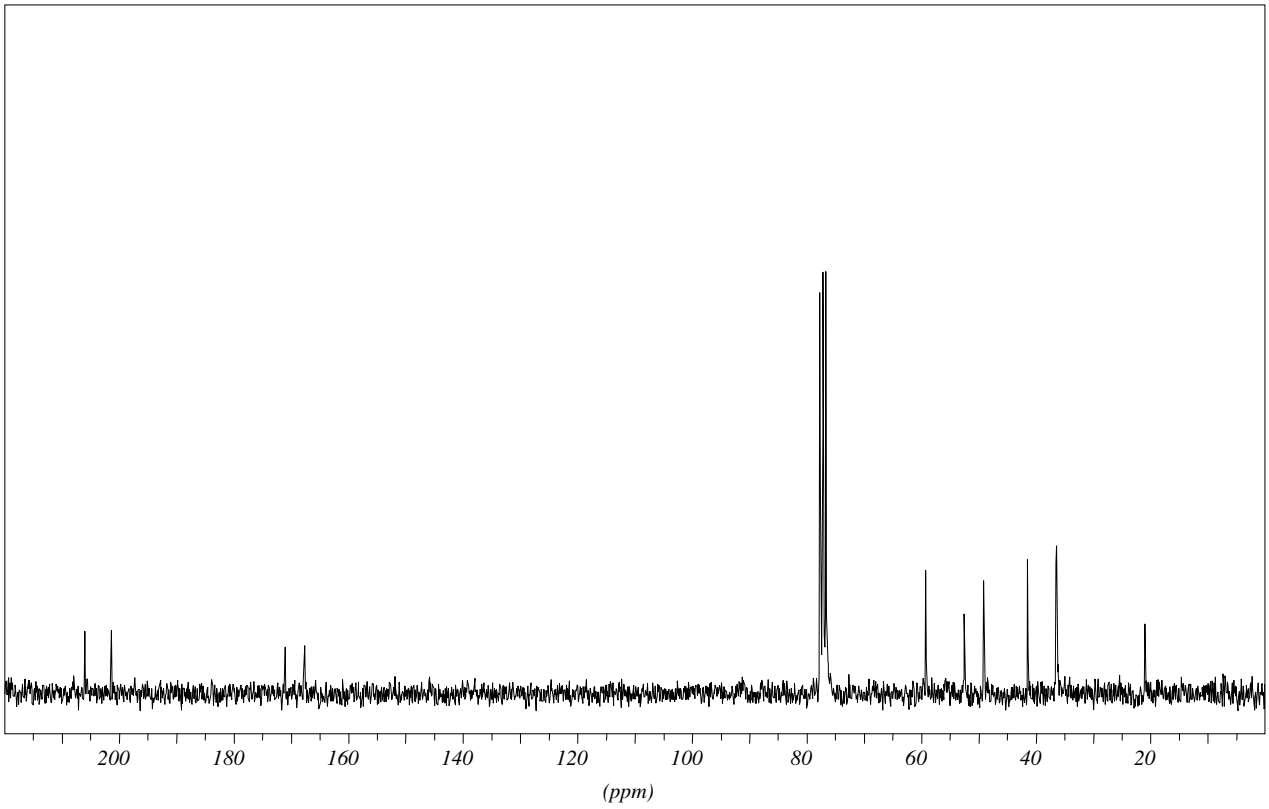
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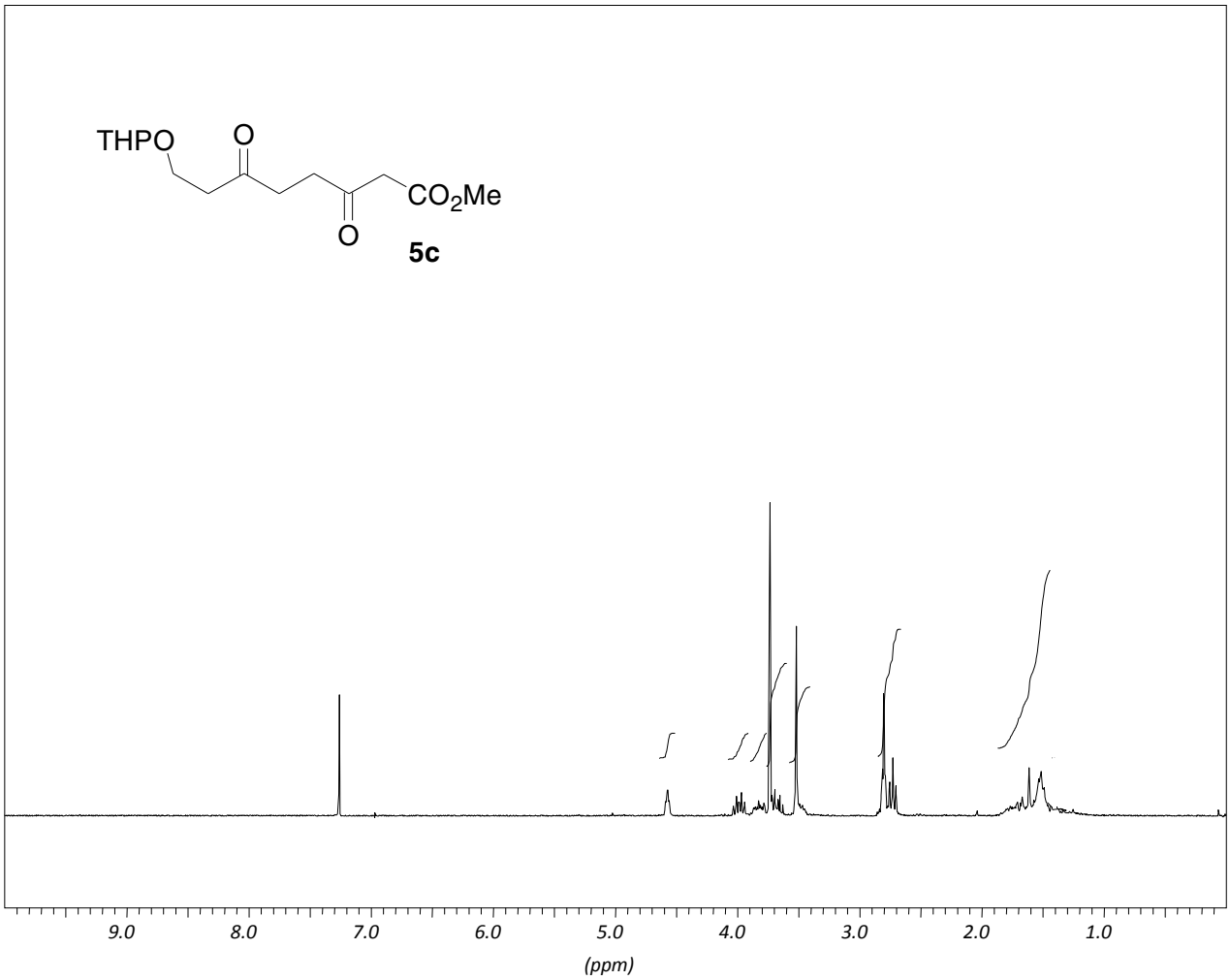
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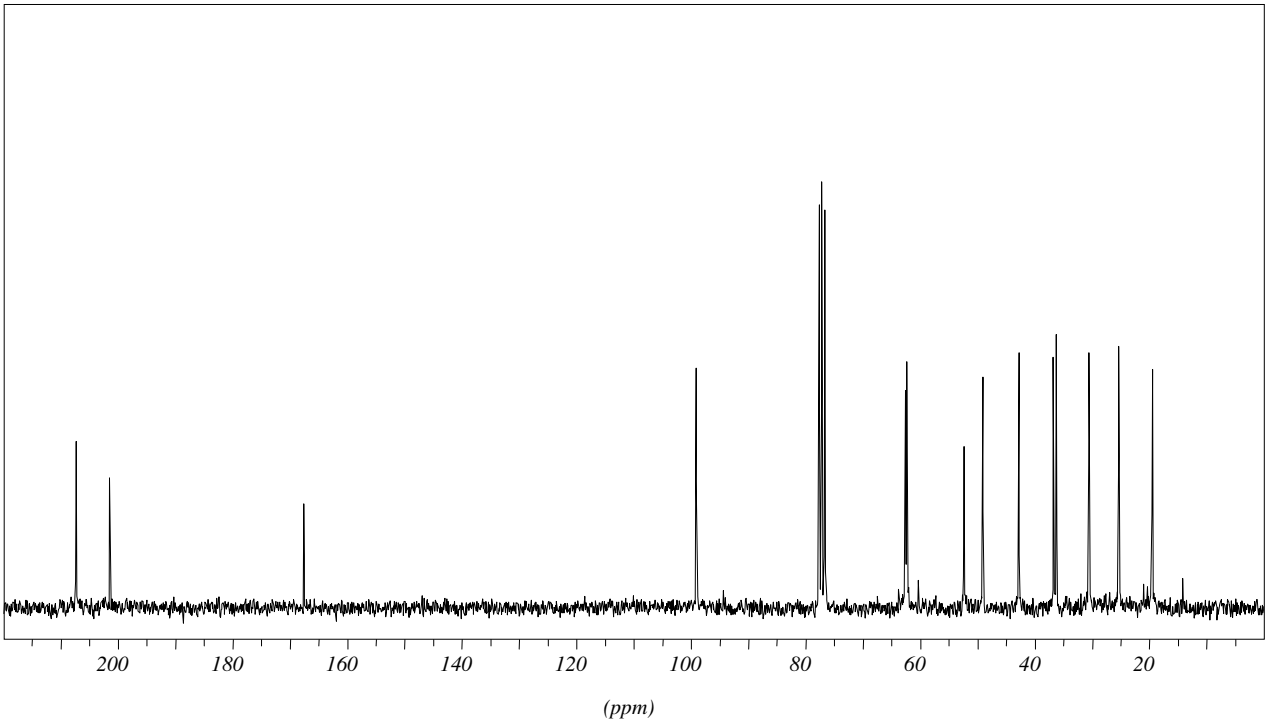
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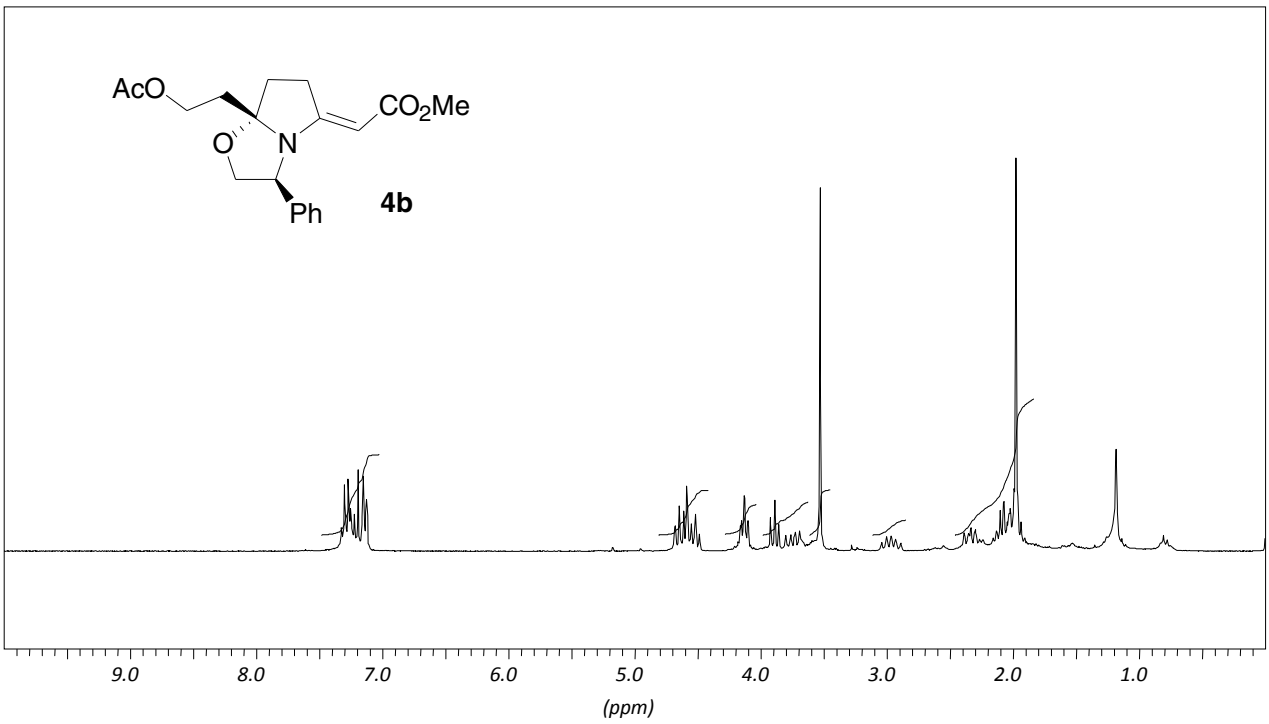
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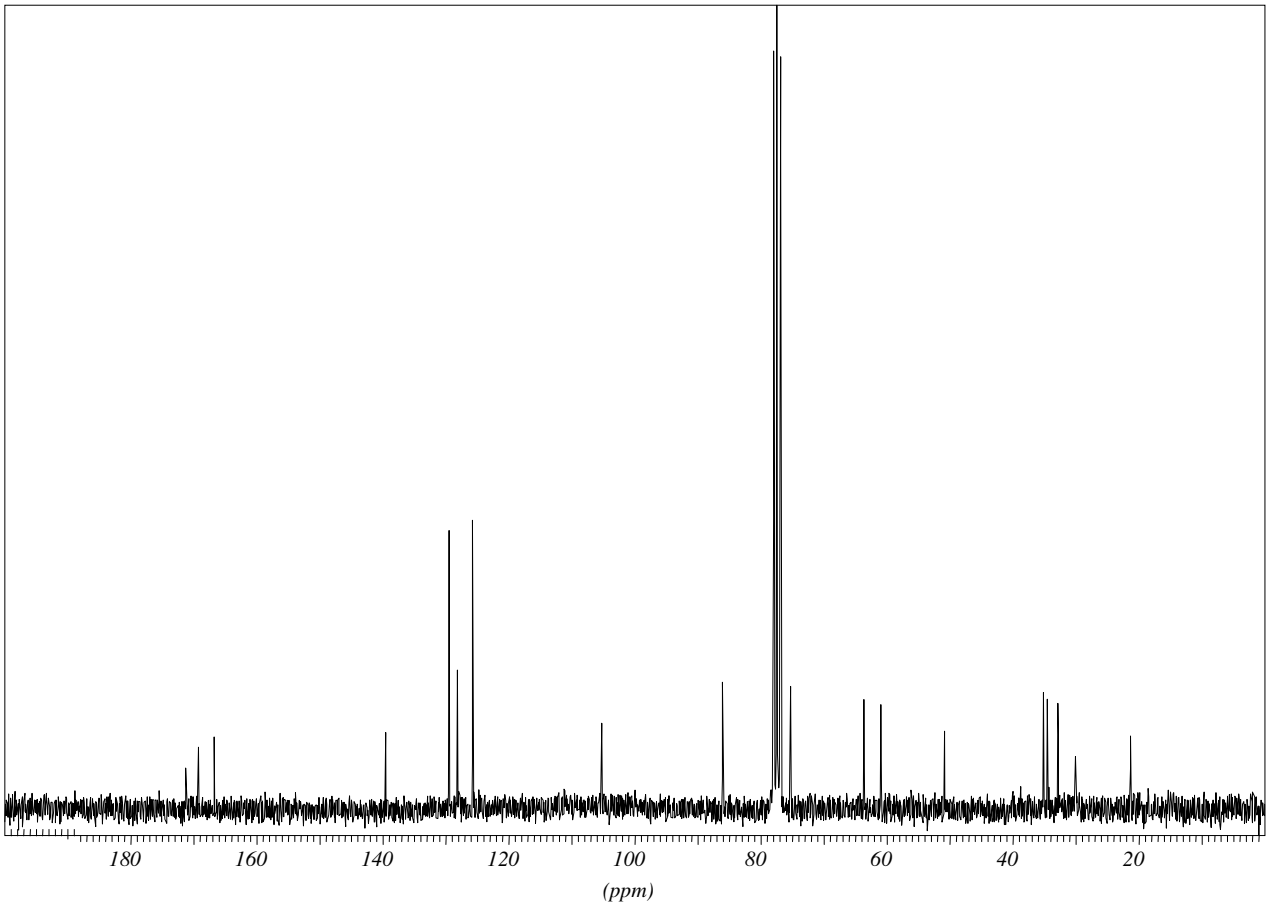
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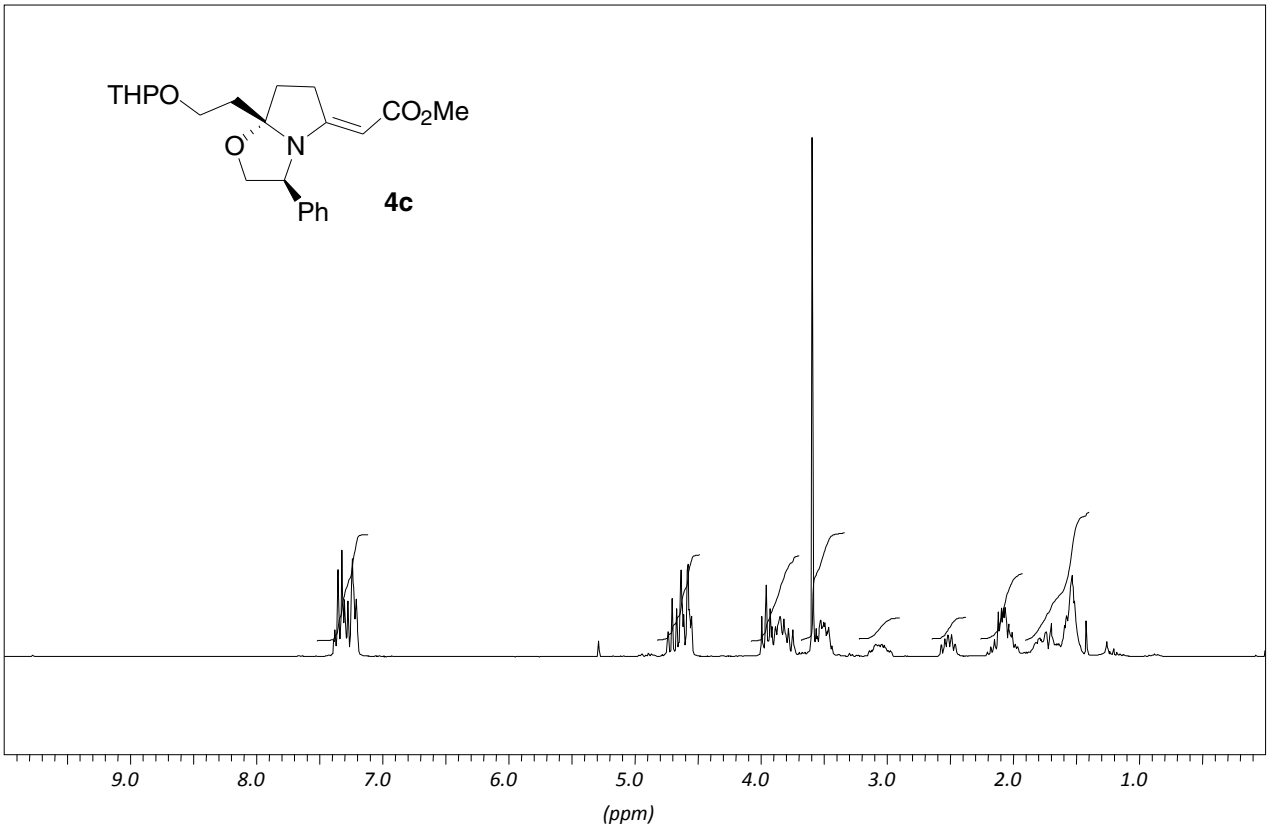
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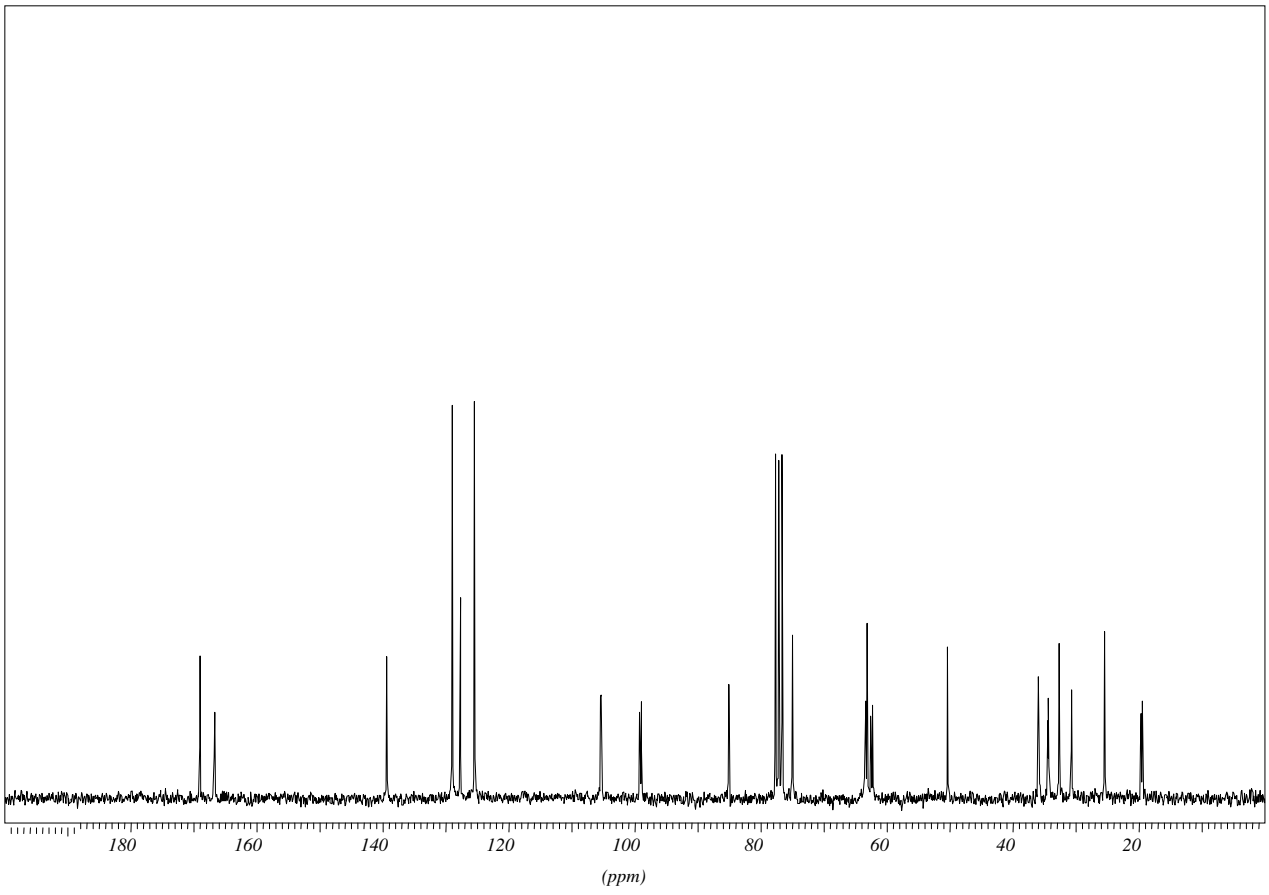
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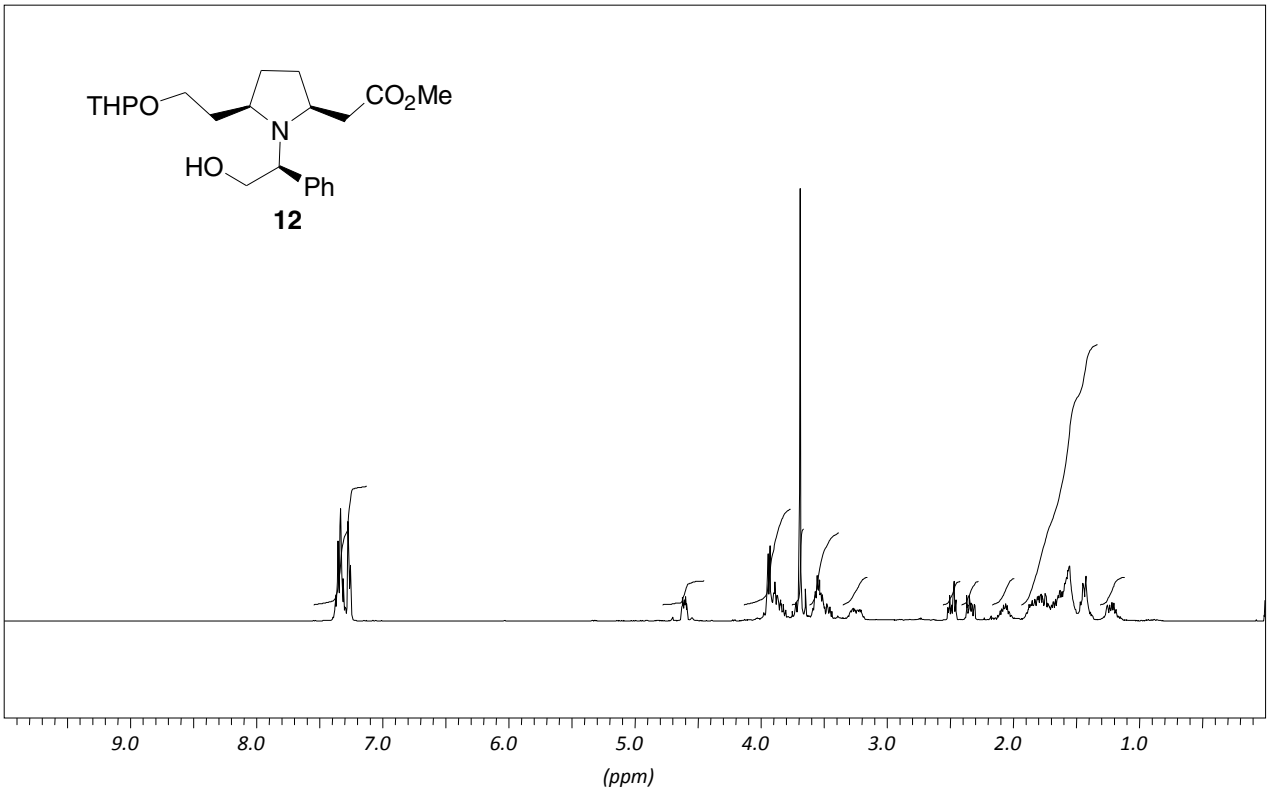
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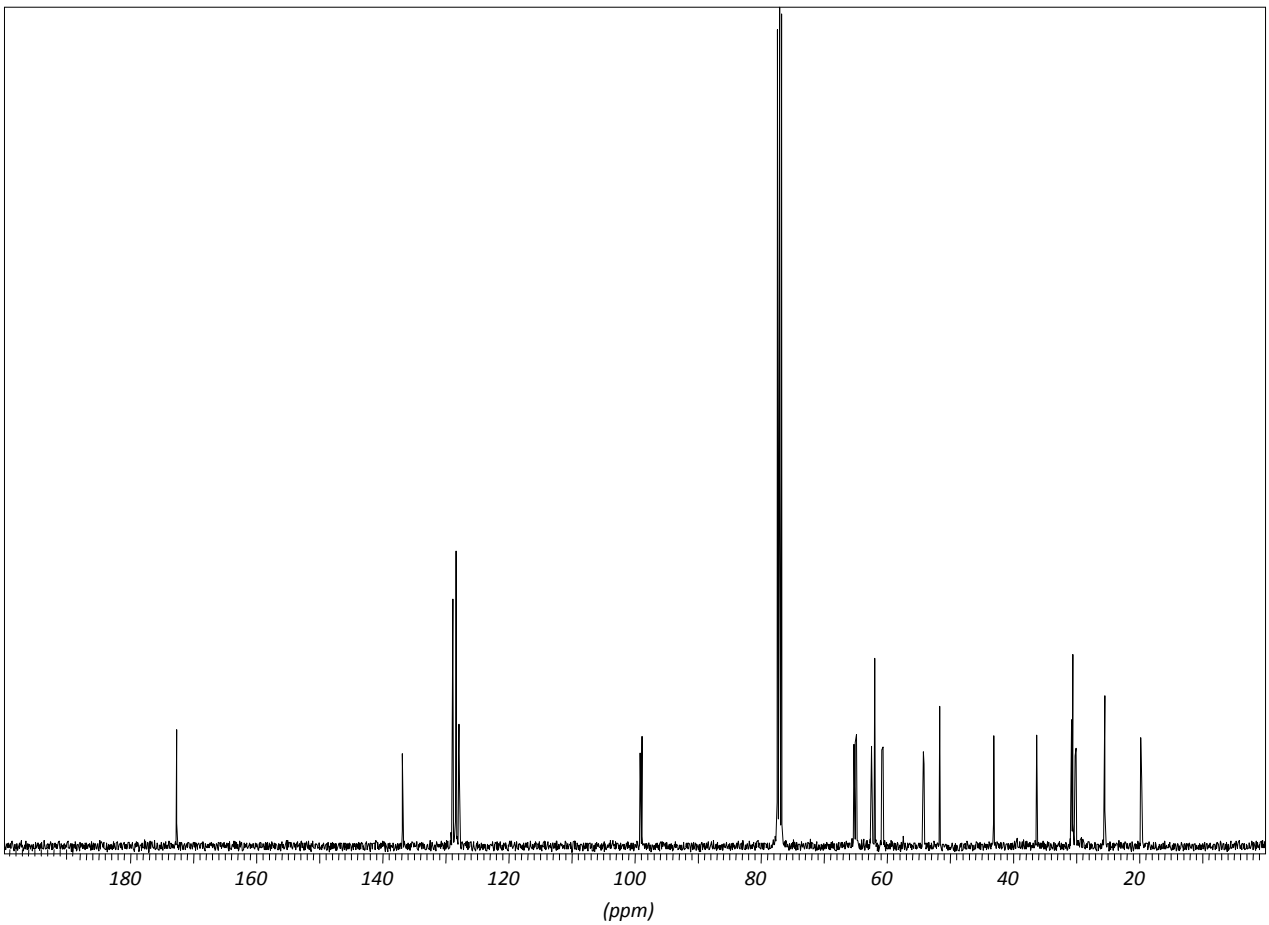
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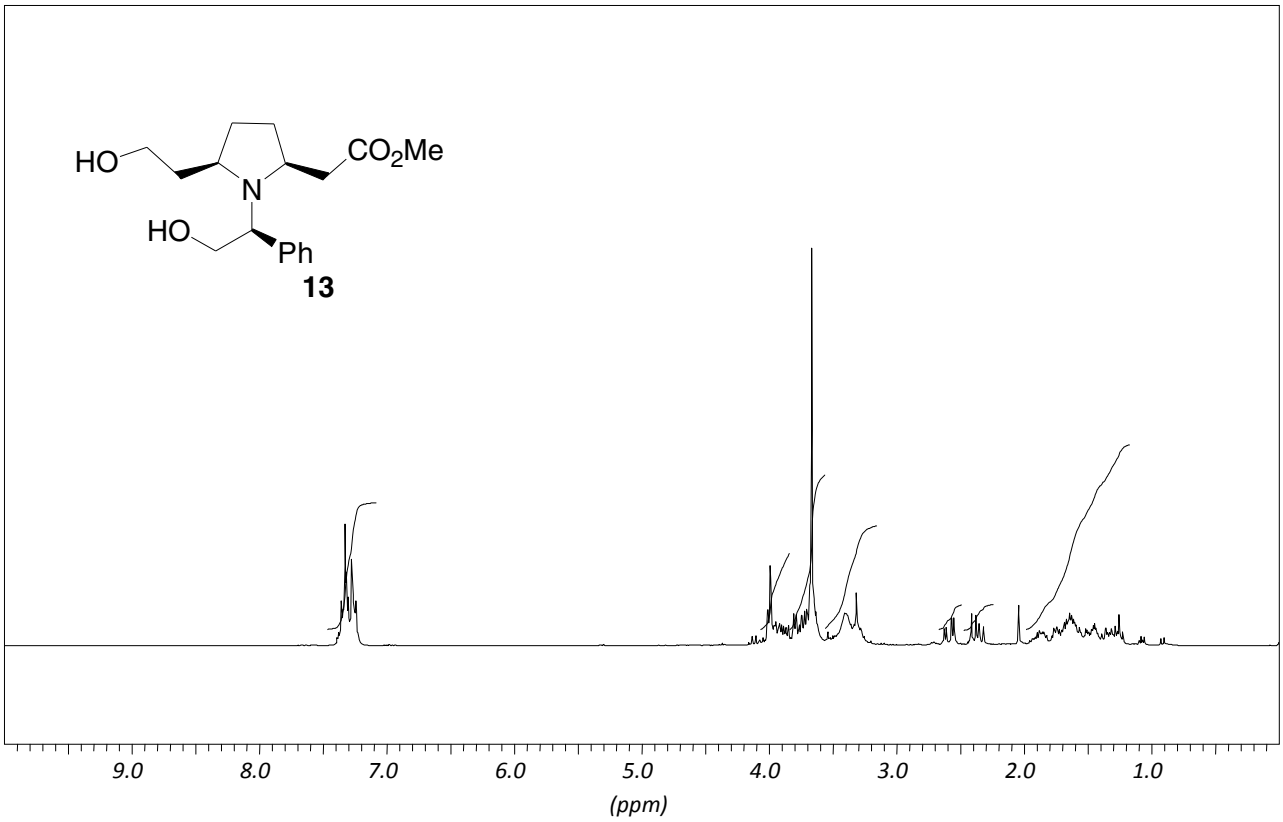
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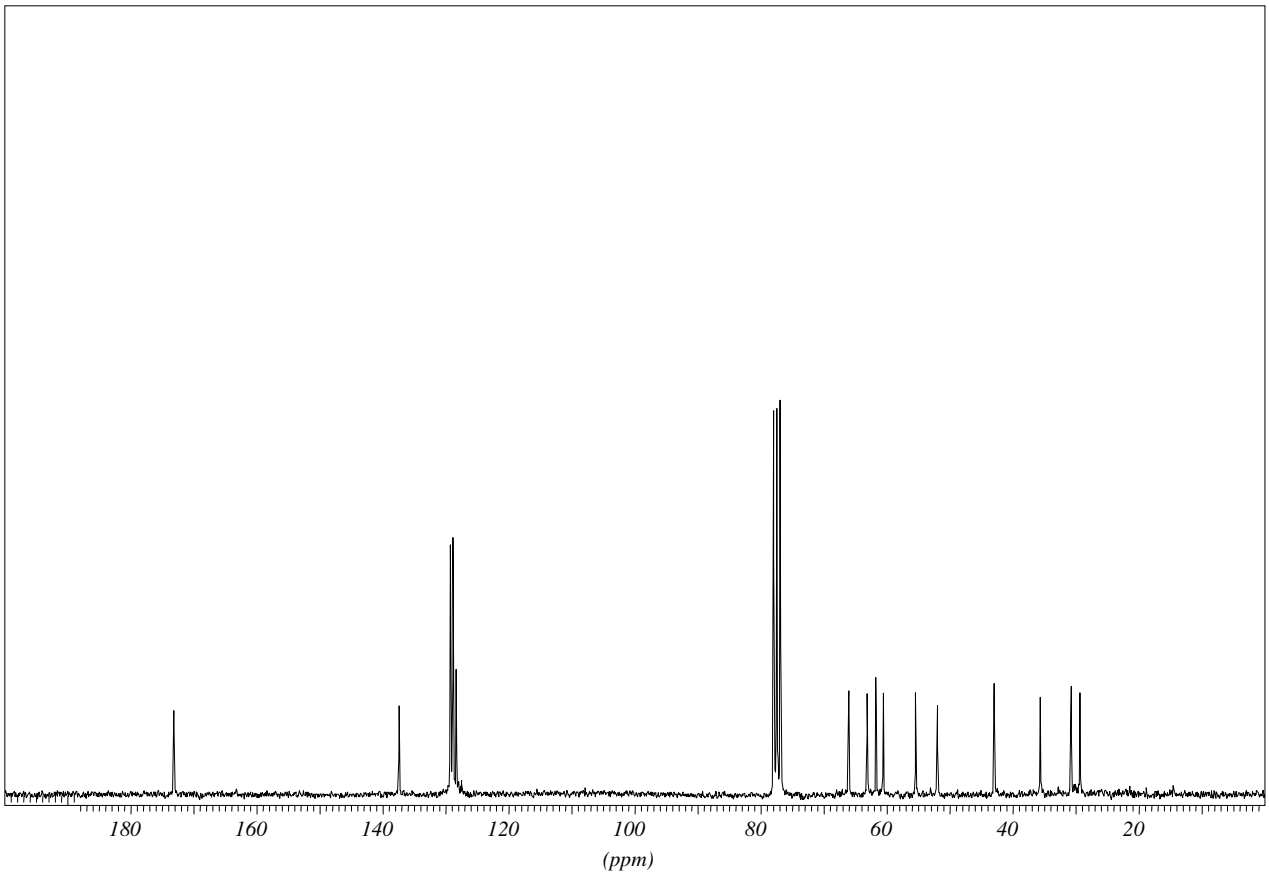
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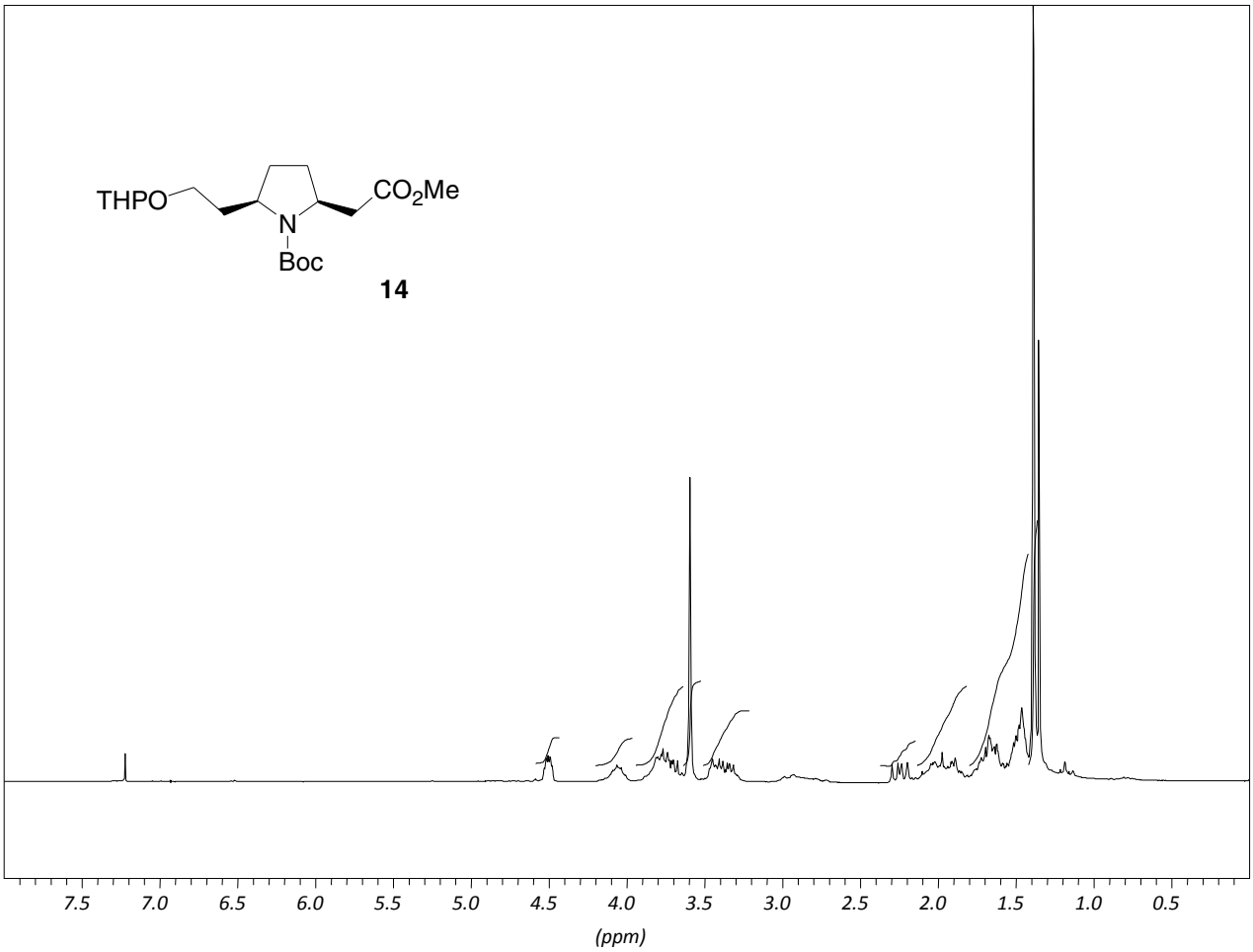
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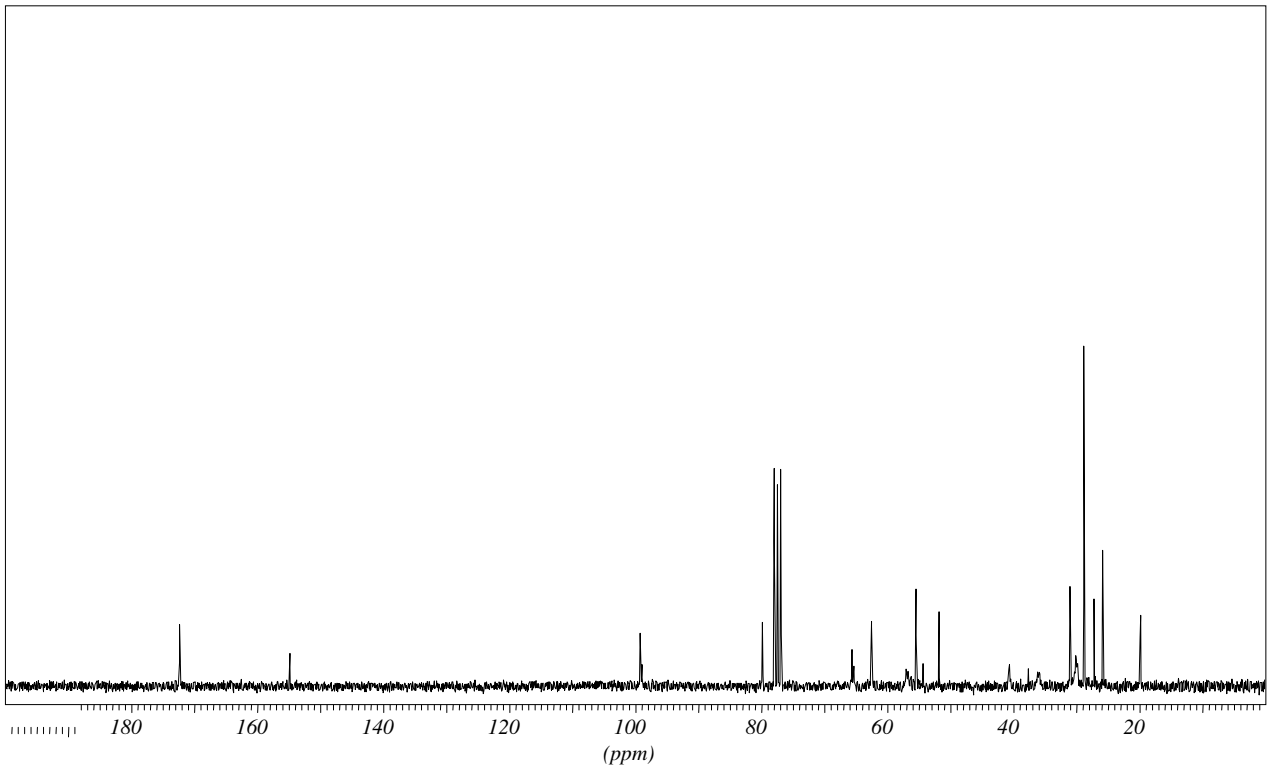
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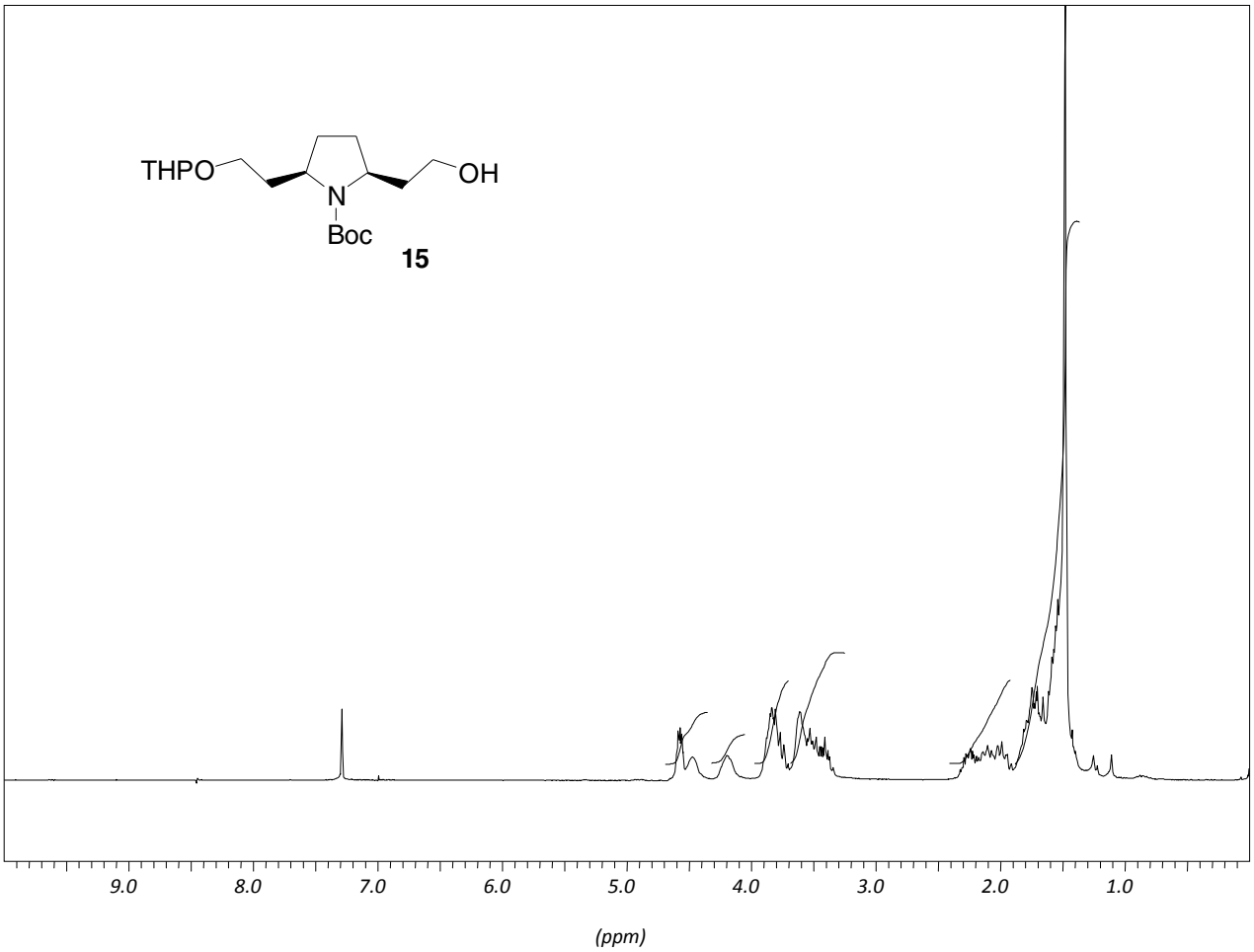
(ppm)


THPO
OH
N
Boc
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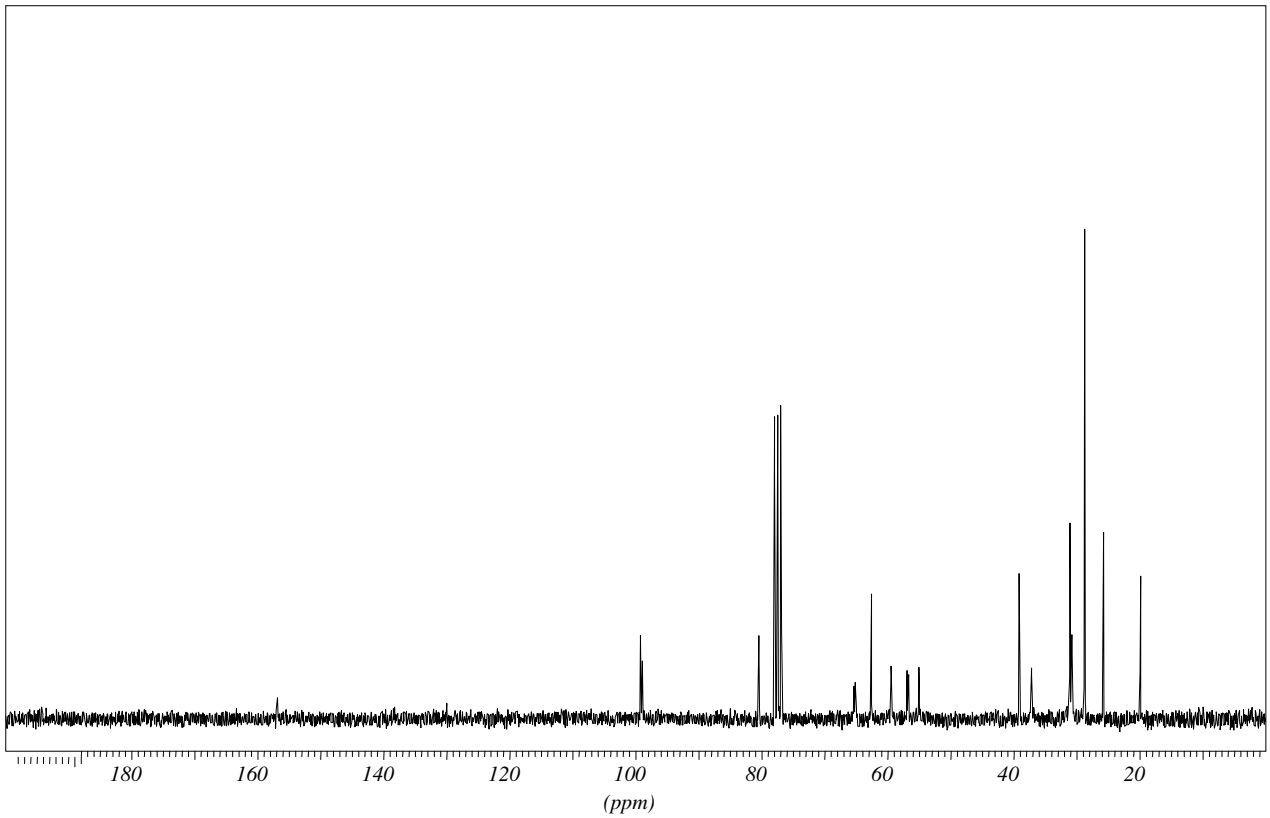
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)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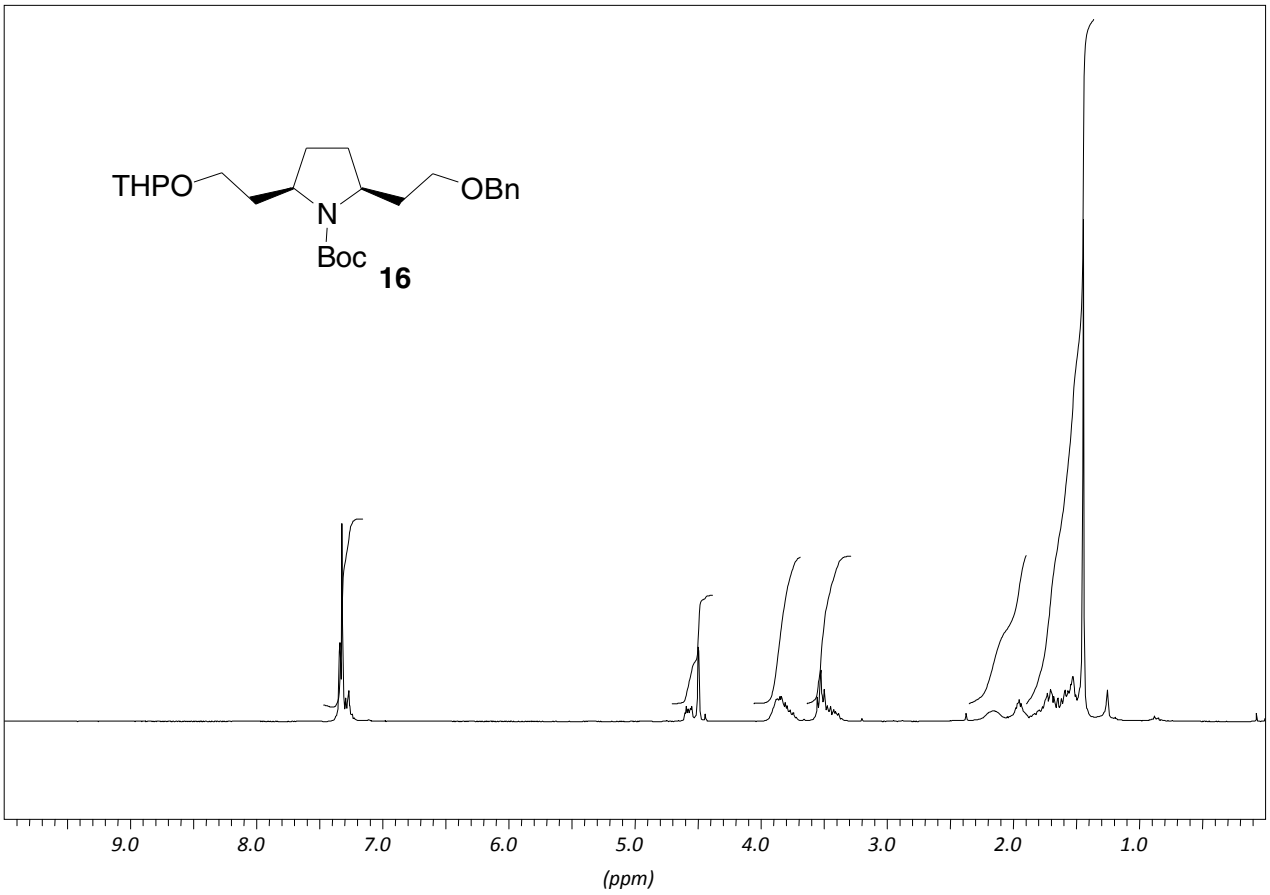
20
(ppm)


THPO
N
Boc
OBn
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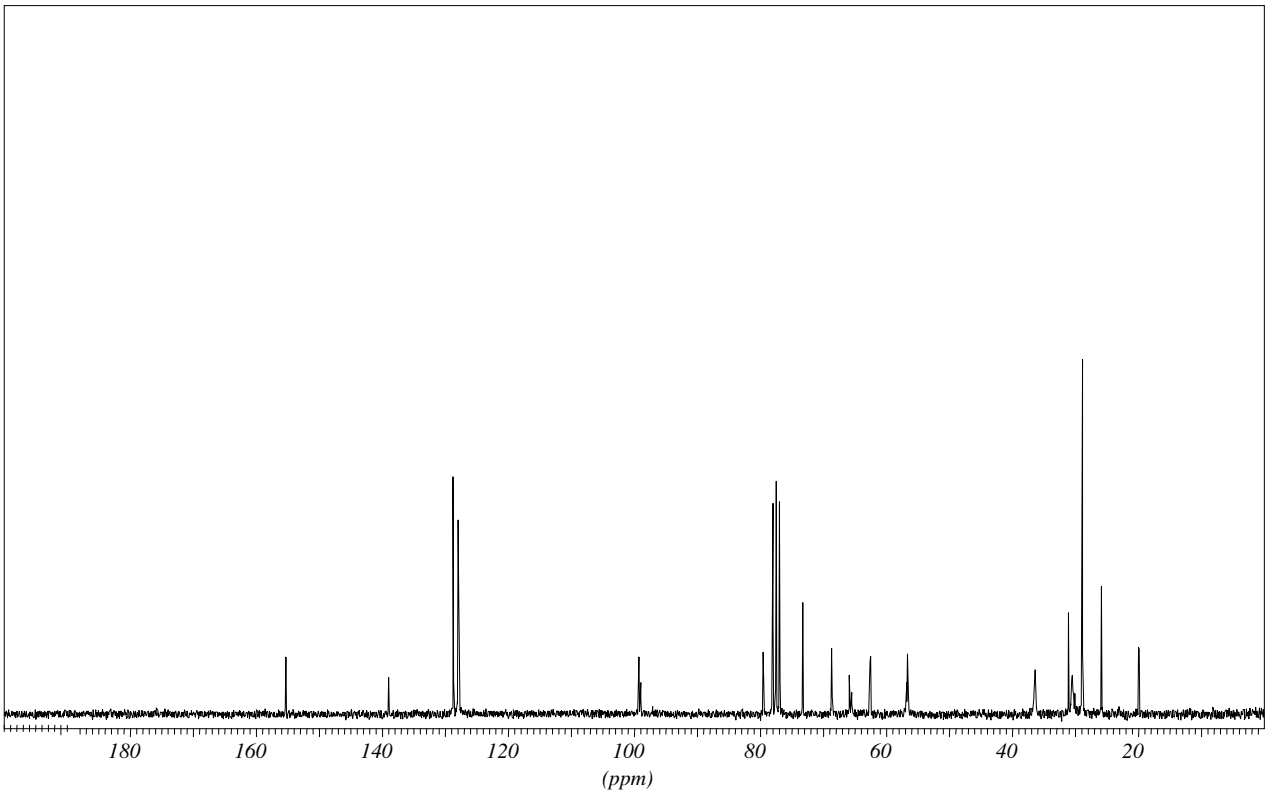
3.0
2.0
1.0
(ppm)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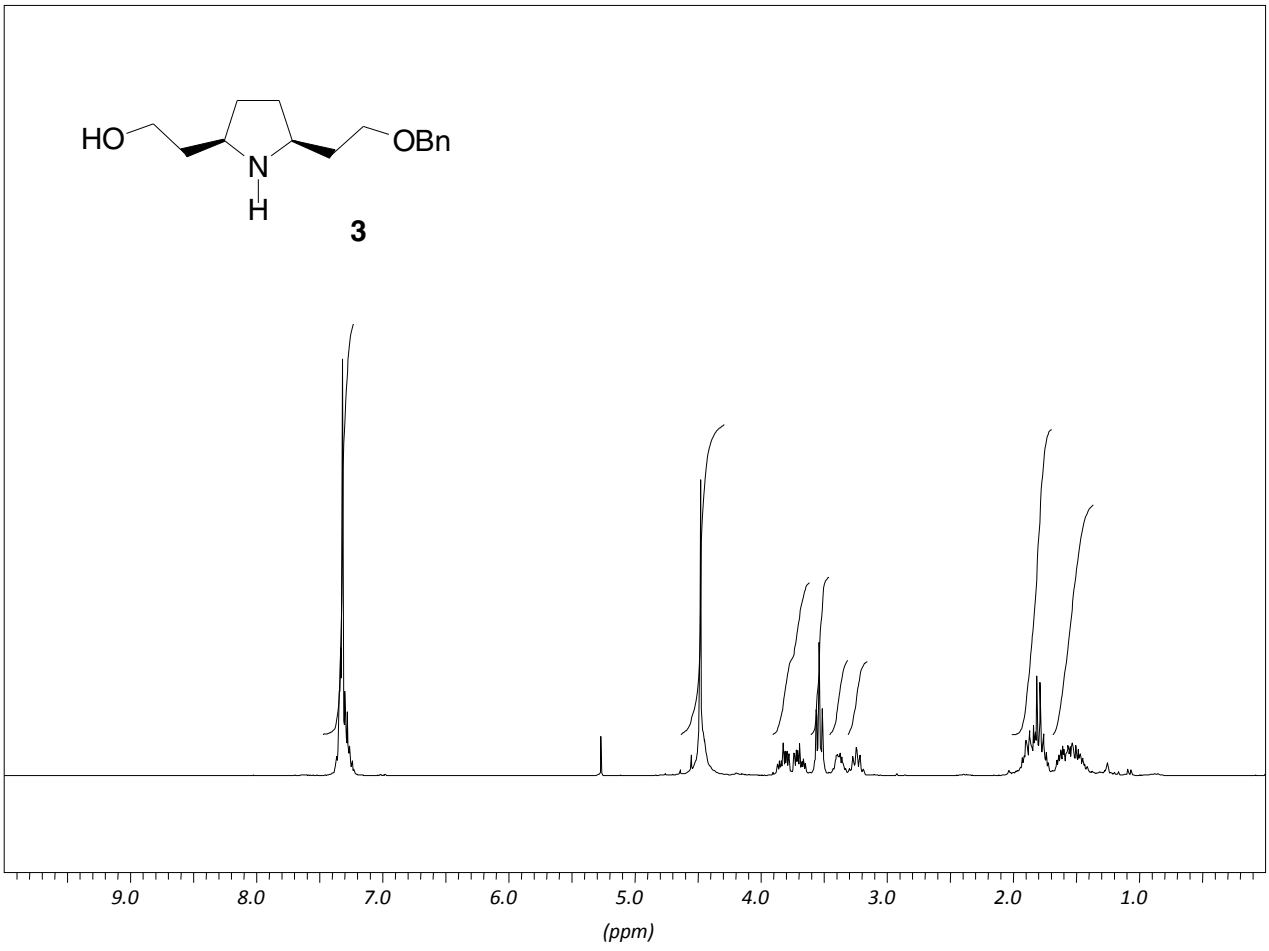
(ppm)


HO
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H
OBn
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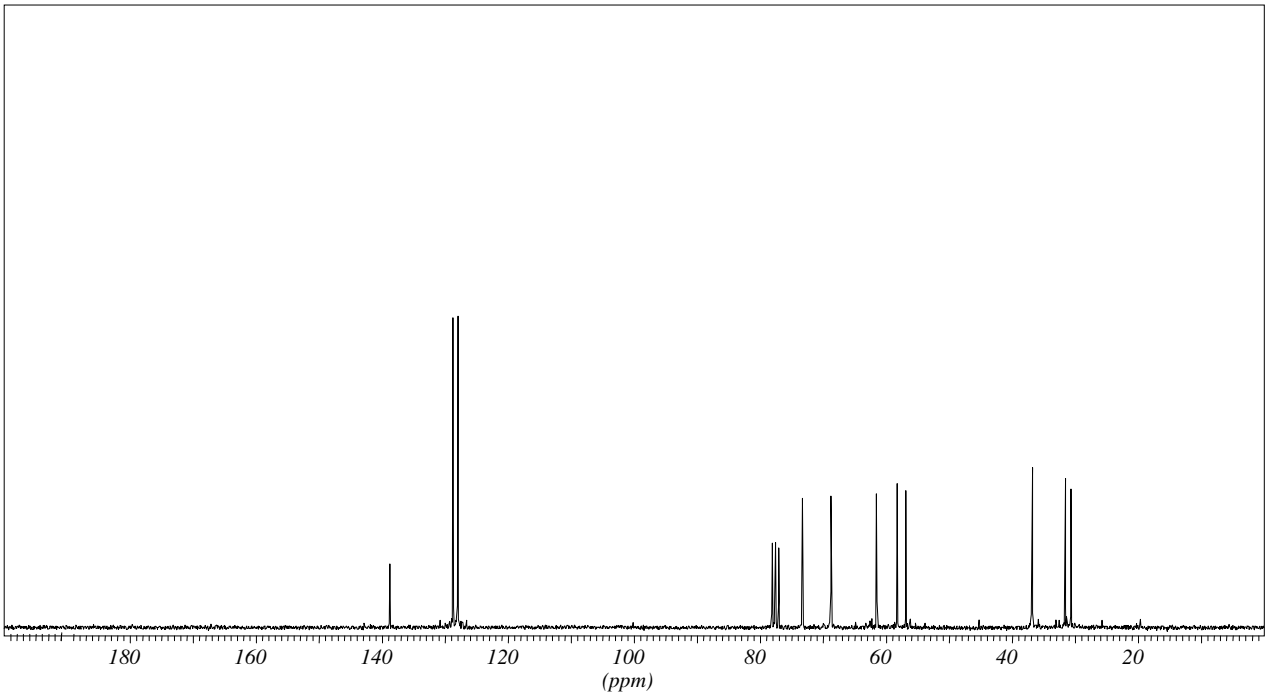
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)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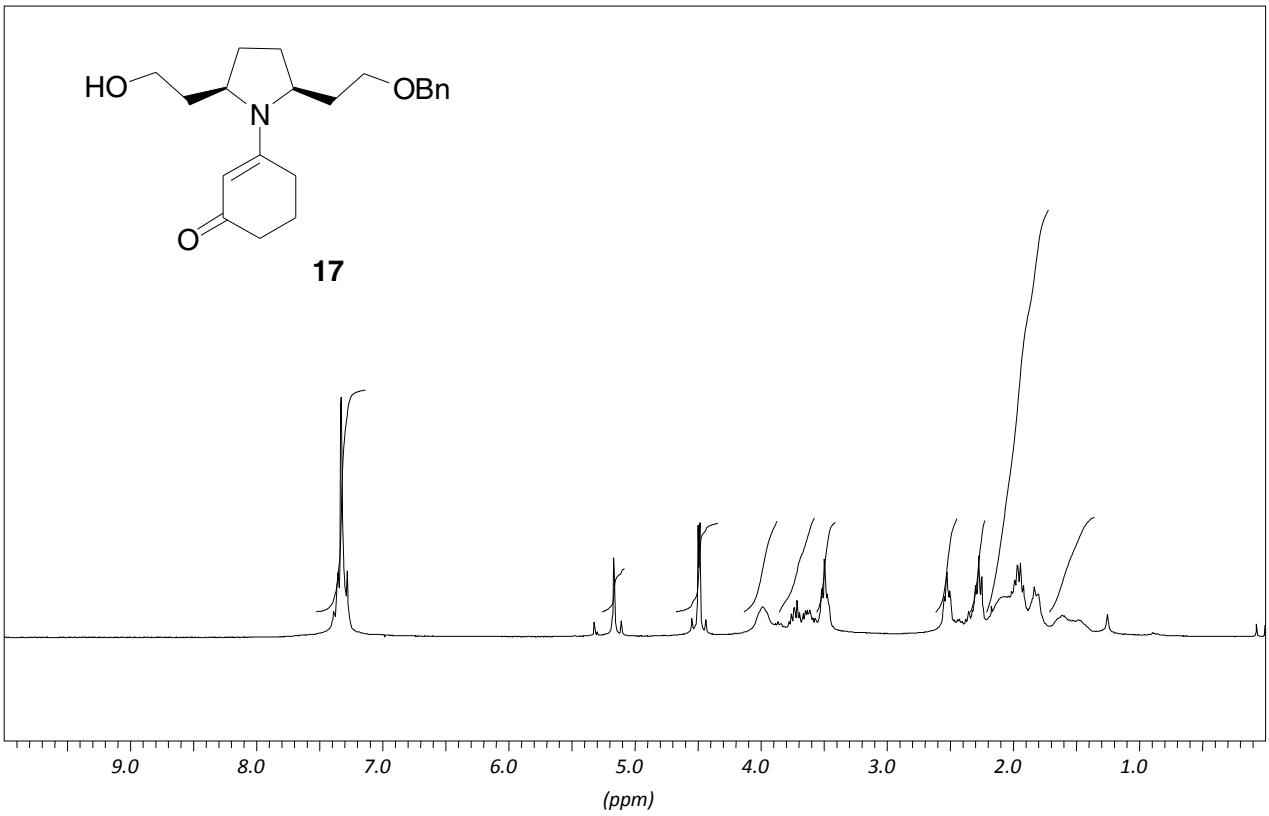
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OBn
O
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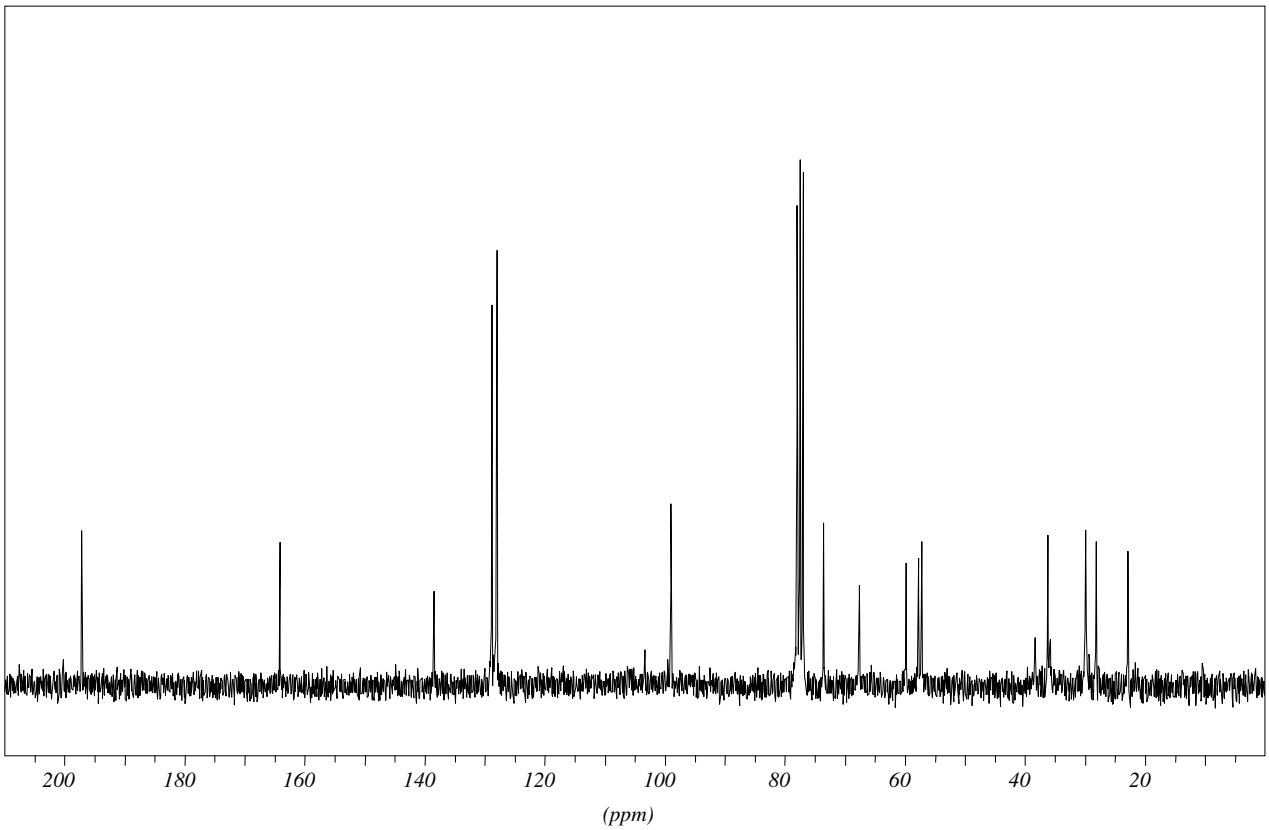
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)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60
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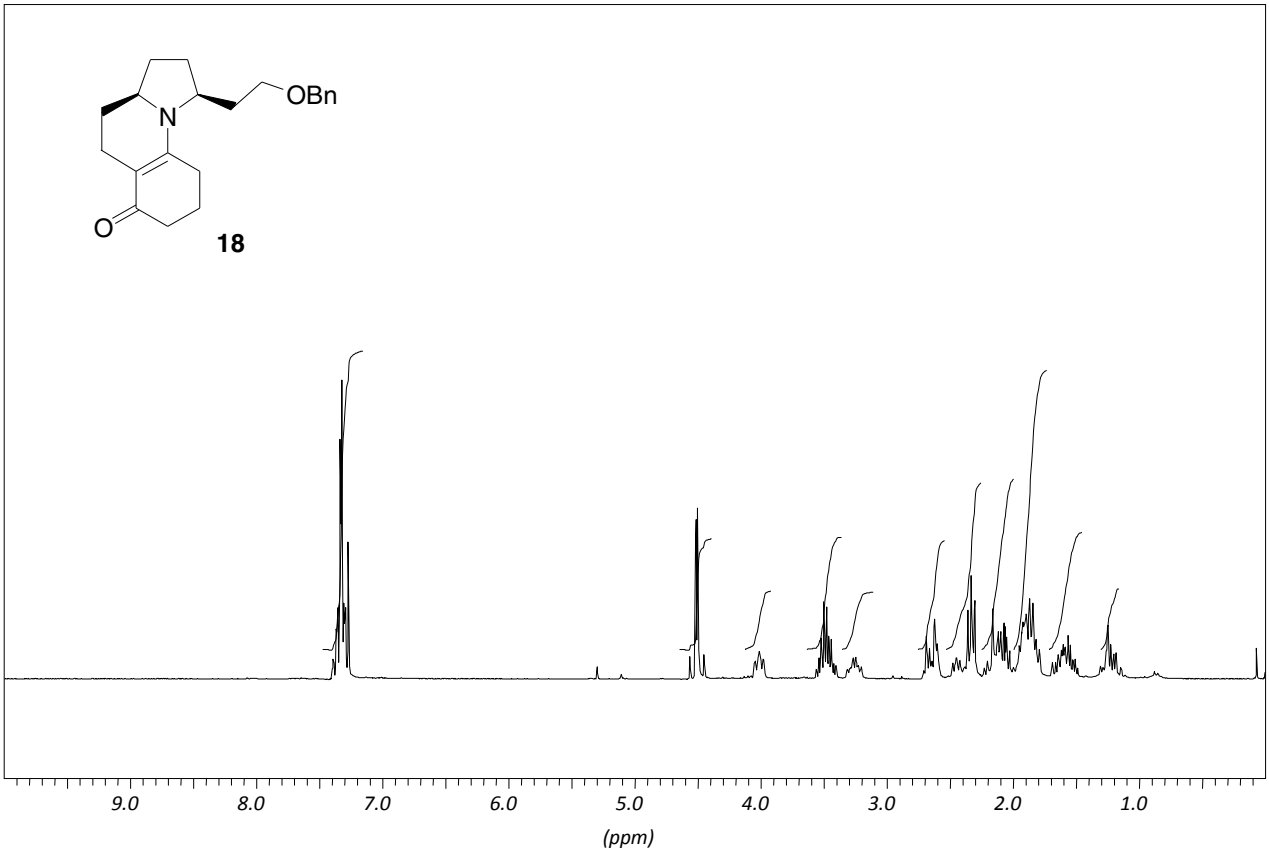
(ppm)


OBn
N
O
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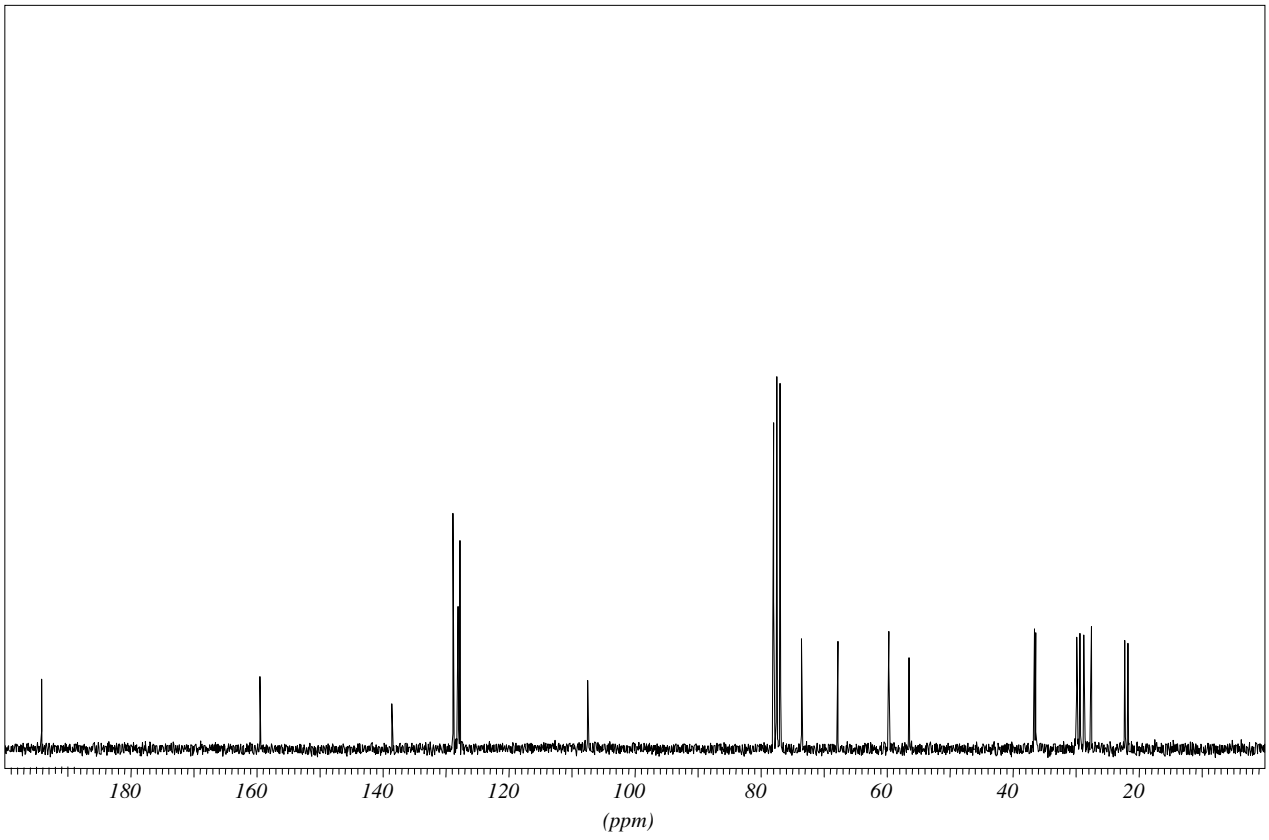
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)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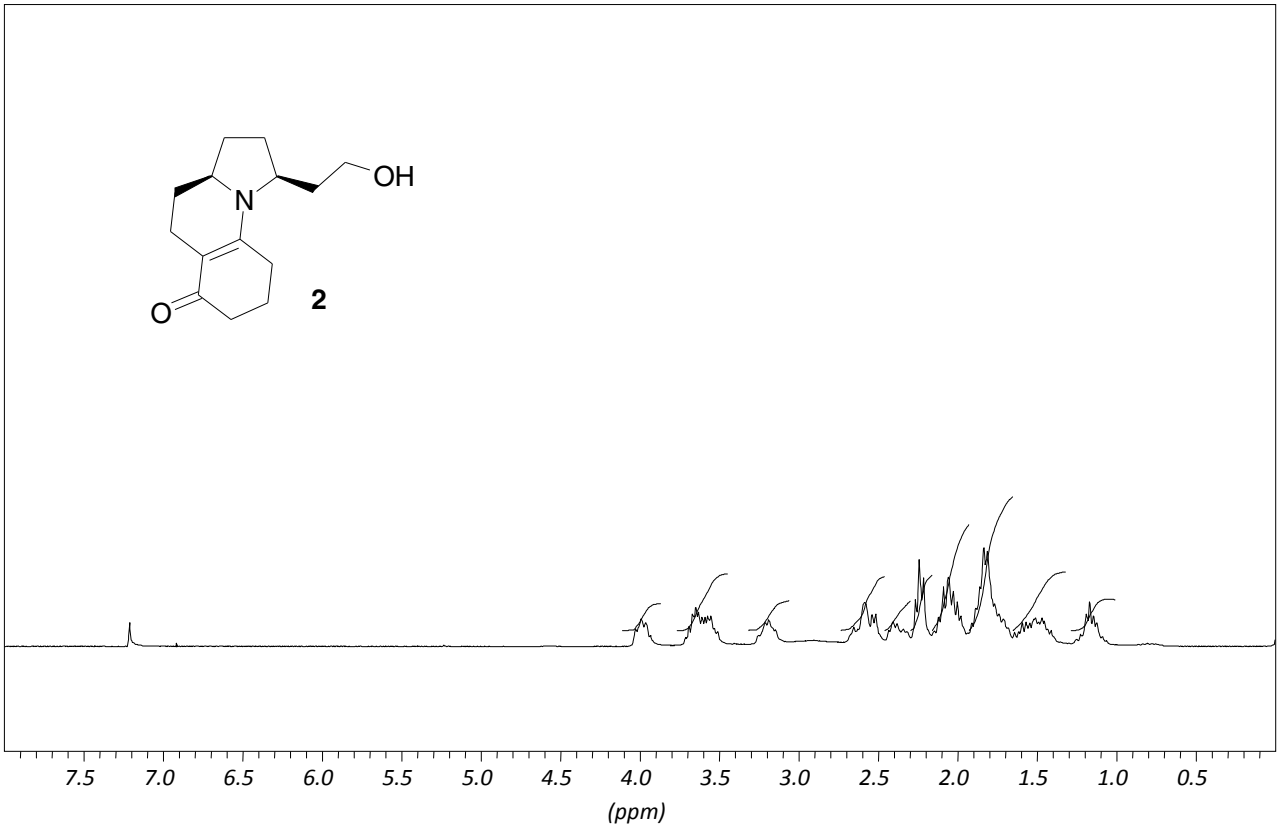
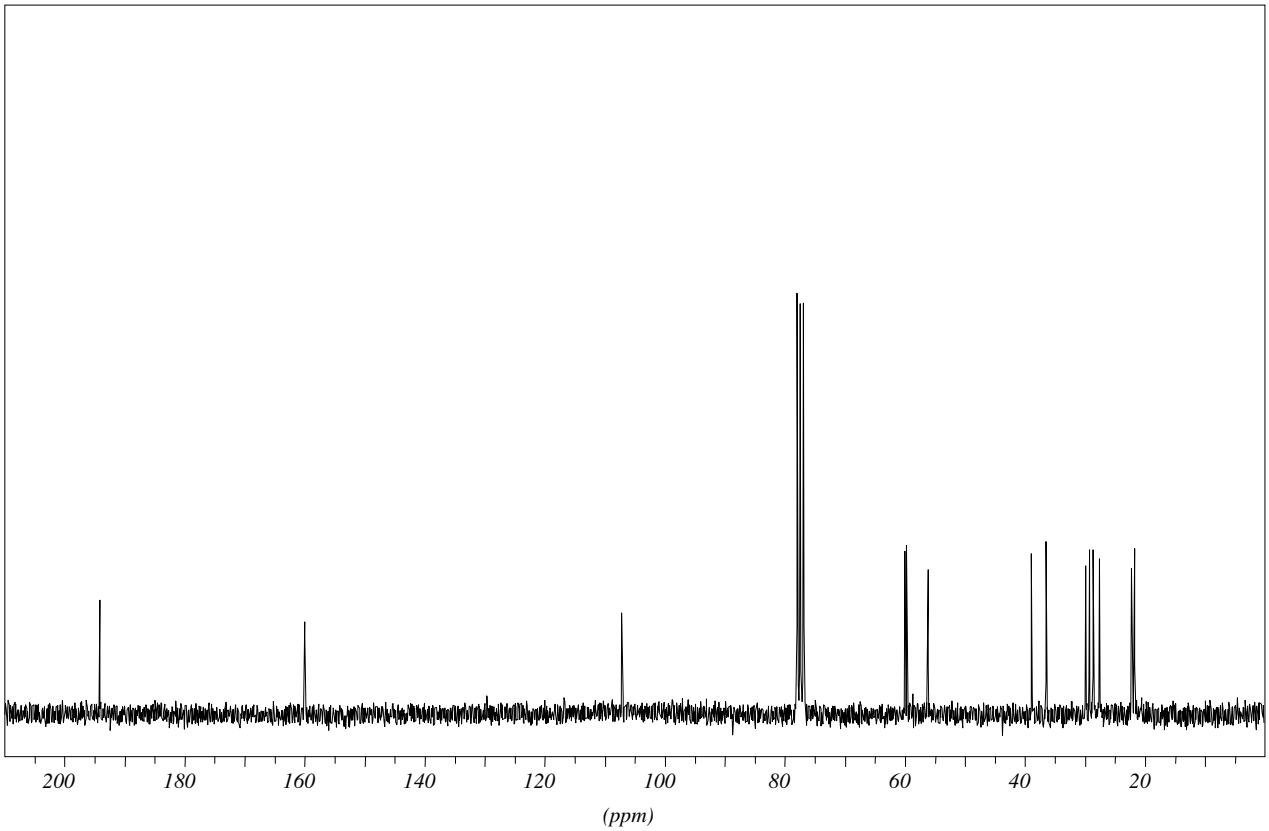
20
(ppm)


OH
N
O
2
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


200
180
160
140
120
100
80
60
40
20
(ppm)