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Supporting Information

Total Synthesis of (-)-Amathaspiramide A *via* One-pot Aldol Addition/Transamidification Reaction

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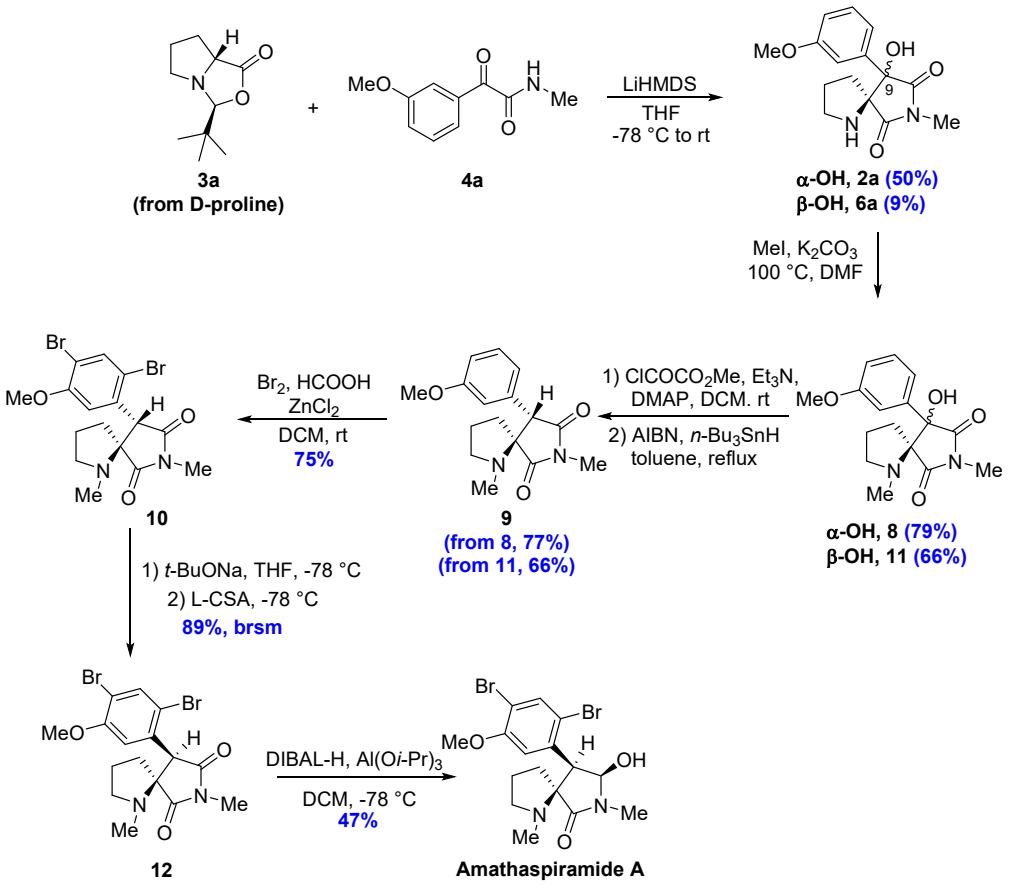
1. General Information

All anhydrous reactions were run under a positive pressure of nitrogen. Anhydrous solvents were obtained using standard drying techniques. Commercial grade reagents were used without further purification. Flash chromatography was performed on 300-400 mesh silica gel with the indicated solvent systems. ^{1}H NMR spectras were recorded on a Brüker Avance-600 HD (600 MHz) spectrometeror and chemical shifts are reported in ppm down field from TMS, using TMS (0.00 ppm) , residual $CDCl_3$ (7.26 ppm), residual CD_3OD (3.31 ppm) or residual DMSO-*d6* (2.50 ppm) as an internal standard. Datas are reported as: (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet; J = coupling constant in Hz, integration.). ^{13}C NMR spectras were recorded on a Bruker Avance-600 HD (150 MHz) spectrometer, using proton decoupling unless otherwise noted. High-resolution mass spectras were determined on an Aglient 6545 Accurate-Mass Q-TOF spectrometer. Optical rotations were measured on a Anton Paar MCP 5500 automatic polarimeter. Infrared spectras were recorded on a Shimadzu Fourier Transform Infrared Spectrophotometer IRAffinity-1. Melting points were determined on a digital melting point apparatus and temperatures were uncorrected. X-ray structure was determined on a Bruker D8 Venture X-ray Diffraction meter.

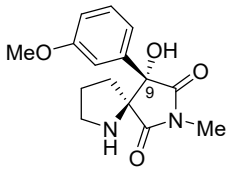
2. Experimental Procedures and Spectral Data

Synthesis of Amathaspiramide A

The Synthetic Route:



(5*S*,9*S*)-9-hydroxy-9-(3-methoxyphenyl)-7-methyl-1,7-diazaspiro[4.4]nonane-6,8-dione (2a)

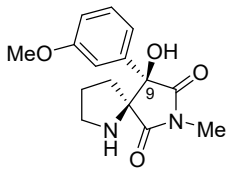


The acetal derived **3a** was prepared according to the literature[1]. In a 500 ml flask, LiHMDS (1.0 M solution in THF, 52 ml, 52.0 mmol） was added to THF (80 ml). After the solution cooled down to -78 °C, compound **3a** (6.40 g，34.8 mmol) in THF (80 ml) was added dropwise over 10 min and the mixture was stirred at the temperature for 30 min. Compound **4a** (3.36 g, 17.4 mmol) in THF (136 ml) was added dropwise over 20 min. After stirring at -78 °C for 2.5 h, the mixture was gradually warmed to room temperature for a period over 1.5 h and stirred for another 2 h. A saturated solution of NH_4Cl was

added, followed by removal of THF under reduced pressure. The residue was extracted with CH_2Cl_2 for three times. The combined organic layers were dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. The residual was subjected to flash chromatography on silica gel (PE/EtOAc = 1/1) to give **2a** in 50% yield (2.52 g), **6a** in 9% yield (0.45 g) and **7a** in 10% yield (0.65 g).

[α]25 D +0.46 (c = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29-7.25 (m, 1H), 6.91-6.89 (m, 1H), 6.86 (dd, *J* = 7.8, 2.4 Hz, 1H), 6.74 (dd, *J* = 7.8, 0.6 Hz, 1H), 3.80 (s, 3H), 3.16 (s, 3H), 3.09-3.04 (m, 1H), 2.90-2.85 (m, 1H), 2.57-2.52 (m, 1H), 1.97-1.85 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 180.1, 177.5, 159.9, 139.8, 129.9, 117.2, 113.8, 111.7, 82.0, 74.2, 55.3, 47.2, 33.2, 25.3, 25.2; **IR** (thin film): 2951, 1705, 1598, 1433, 1382, 1290, 1062, 788 cm^{-1}; **LRMS** (ESI): 291 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{19}N_2O_4$ $(M+H)^+$: 291.1339, found: 291.1338; mp: 85-87 °C.

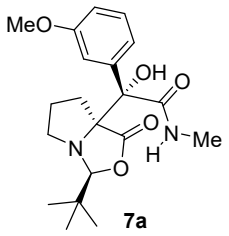
(5*S*,9*R*)-9-hydroxy-9-(3-methoxyphenyl)-7-methyl-1,7-diazaspiro[4.4]nonane-6,8-dione (6a)



6a

[α]25 D +13.02 (c = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.8 Hz, 1H), 6.98-6.96 (m, 1H), 6.86 (dd, *J* = 7.8, 2.4 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 3.81 (s, 3H), 3.20-3.15 (m, 1H), 3.14 (s, 3H), 3.01-2.96 (m, 2H), 1.99-1.92 (m, 1H), 1.85-1.78 (m, 1H), 1.58-1.53 (m, 1H), 1.44-1.36 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 179.1, 177.1, 159.7, 139.5, 129.4, 118.2, 113.6, 112.0, 78.1, 72.8, 55.3, 47.7, 32.3, 26.4, 25.4; **IR** (thin film): 3325, 2949, 1780, 1707, 1600, 1583, 1431, 1379, 1290, 1049 cm^{-1}; **LRMS** (ESI): 291 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{19}N_2O_4$ $(M+H)^+$: 291.1339, found: 291.1338; mp: 98-100 °C.

(*S*)-2-((3*S*,7a*S*)-3-(*tert*-butyl)-1-oxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-7a(5*H*)-yl)-2-hydroxy-2-(3-methoxyphenyl)-*N*-methylacetamide (7a)

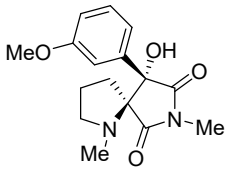


7a

7a: Orange solid (10% yield) **[α]**25 D +81.16 (c = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 7.38-7.36 (m, 1H), 7.29-7.26 (m, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.81 (dd, *J* = 7.8, 1.8

Hz, 1H), 4.72 (s, 1H), 4.12 (s, 1H), 3.80 (s, 3H), 3.18-3.12 (m, 1H), 2.90 (d, J = 4.8 Hz, 3H), 2.82-2.76 (m, 1H), 2.41-2.34 (m, 1H), 2.17-2.11 (m, 1H), 1.81-1.74 (m, 1H), 1.71-1.66 (m, 1H), 0.67 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 178.1, 172.9, 159.4, 140.6, 128.9, 119.4, 113.9, 113.5, 103.7, 81.6, 80.0, 56.9, 55.3, 35.9, 35.6, 26.9, 24.2, 24.1; **IR** (thin film): 3410, 2958, 1772, 1654, 1581, 1483, 1363, 1253, 1193, 1041, 779 cm^{-1}; **LRMS** (ESI): 377 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{20}H_{29}N_2O_5$ $(M+H)^+$: 377.2071, found: 377.2073; mp: 90-92 °C

(5*S*,9*S*)-9-hydroxy-9-(3-methoxyphenyl)-1,7-dimethyl-1,7-diazaspiro[4.4]nonane-6,8-dione (8)



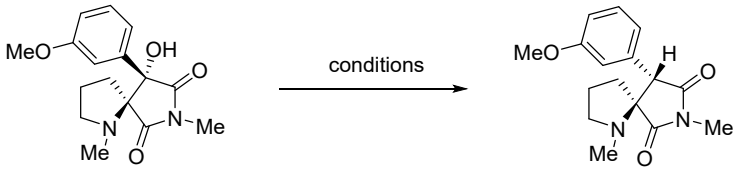
8

MeI (0.36 mL, 5.8 mmol) was added dropwise to a 100 ml flask charged with compound **2a** (1.12g, 3.9 mmol), K_2CO_3 (1.06 g, 7.8 mmol) and DMF (39 mL). After stirring at 100 °C for 5 h, the suspension was filtered, and the filtrate was concentrated under reduced pressure, diluted with EtOAc, washed with water and brine, and dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. The residue was purified *via* flash chromatography on silica gel (PE/EtOAc = 3/1) to give **8** (0.94 g, 79%) as a yellow solid.

[α]25 D -49.85 (c = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.21 (dd, J = 8.4, 7.8 Hz, 1H), 6.92-6.90 (m, 1H), 6.86 (ddd, J = 8.4, 1.8, 0.6 Hz, 1H), 6.79 (ddd, J = 7.8, 1.8, 0.6 Hz, 1H), 3.80 (s, 3H), 3.15 (s, 3H), 3.12 (s, 1H), 3.02-2.97 (m, 1H), 2.84-2.79 (m, 1H), 2.72-2.67 (m, 1H), 2.03-1.97 (m, 1H), 1.95-1.89 (m, 1H), 1.88-1.83 (m, 1H), 1.76 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 178.2, 177.8, 159.3, 140.4, 128.9, 119.0, 113.7, 113.6, 81.3, 76.1, 56.6, 55.3, 36.2, 35.0, 24.4, 24.2; **IR** (thin film): 3446, 2949, 1701, 1600, 1489, 1431, 1379, 1290, 1045, 792 cm^{-1}; **LRMS** (ESI): 305 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{16}H_{21}N_2O_4$ $(M+H)^+$: 305.1496, found: 305.1496; mp: 70-72 °C.

The Detailed Investigation of Deoxygenation

Table 1 Deoxygenation of Tertiary Alcohol 8

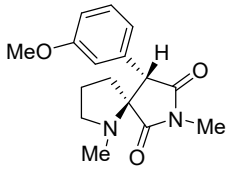


8 **9**

Entry	Conditions	Isolate yield
1	Me_3SiH, TFA, DCM, 0 to 25 °C	n.r.[a]
2	$Pd(OH)_2/C$, MeOH, H_2, 65 °C, 50 psi	n.r.
3	$SnCl_2 \cdot 2H_2O$, AcOH/HCl, 80 °C	n.r.
4	1) NaH, CS_2, MeI, THF, 0 to 25 °C 2) AIBN, *n*-Bu_3SnH, toluene, reflux	n.d.[b]
5	1) $ClCOCO_2Me$, Et_3N, DMAP, DCM 2) AIBN, *n*-Bu_3SnH, toluene, reflux	50%

[a] n.r. stands for no reaction. [b] n.d. stands for not detected.

(5*S*,9*S*)-9-(3-methoxyphenyl)-1,7-dimethyl-1,7-diazaspiro[4.4]nonane-6,8-dione (9)



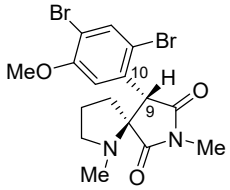
9

To a solution of **8** (610 mg, 2.0 mmol) and DMAP (25 mg, 0.2 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (0.42 mL, 3.0 mmol) slowly at 0 °C. Then methyl chlorooxalate (0.28 mL, 3.0 mmol) was added dropwise, and the mixture was stirred at room temperature for 1 h. The resulting solution was washed with water, dried over anhydrous Na_2SO_4, and concentrated to give yellow oil, which was used in the next step without further purification. To a solution of the crude product in degassed toluene (30 mL) was added AIBN (33 mg, 0.2 mmol) and *n*-Bu_3SnH (1.35 mL, 5.0 mmol). The solution was heated to 110 °C in an oil bath under nitrogen and stirred for 10 h. Then the resulting mixture was cooled to room temperature and evaporated. The residue was purified *via* flash chromatography (10% w/w anhydrous K_2CO_3-silica[2]; PE/EA = 3/1) to give **9** (288 mg, 50%, 77% brsm) as yellow oil and recovered **8** (210 mg, 34%). For **9**, NMR spectra of NOESY were given to assign its stereochemistry.

[α]25 D +6.70 (c = 0.50, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.8 Hz,

1H), 6.84 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.67-6.65 (m, 1H), 3.91 (s, 1H), 3.79 (s, 3H), 3.10 (s, 3H), 3.06-3.02 (m, 1H), 2.99-2.93 (m, 1H), 2.40 (s, 3H), 1.88-1.78 (m, 2H), 1.58-1.47 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 179.2, 176.5, 159.8, 136.2, 129.8, 121.2, 115.2, 112.9, 73.0, 55.3, 54.6, 54.2, 34.8, 32.6, 24.5, 21.9; **IR** (thin film): 2931, 1770, 1697, 1539, 1506, 1456, 1377, 1271, 1028, 785 cm^{-1}; **LRMS** (ESI): 289 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{16}H_{21}N_2O_3$ $(M+H)^+$: 289.1547, found: 289.1546.

(5*S*,9*S*)-9-(2,4-dibromo-5-methoxyphenyl)-1,7-dimethyl-1,7-diazaspiro[4.4]nonane-6,8-dione (10)

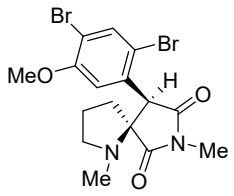


10

To a suspension of **9** (0.33 g, 1.13 mmol), zinc chloride (1.27 g, 9.3 mmol) and formic acid (0.88 mL, 23.3 mmol) in DCM (3.00 mL) was added bromine (0.24 mL, 4.7 mmol) in DCM (4.7 mL) dropwise over a period of 10 min at room temperature. After stirring for 10 h, the reaction mixture was quenched with a saturated solution of Na_2SO_3, extracted with CH_2Cl_2 for 3 times, dried over anhydrous Na_2SO_4, concentrated, and purified *via* flash chromatography on silica gel (PE/EA = 1/1) to give **10** (0.38 g, 75%) as yellow oil, which was a mixture of atropisomers (1.1:1).

Atropisomers at C9-C10 bond[3]; **[α]**25 D -21.74 (c = 1.00, $CHCl_3$); **Major**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.78 (s, 1H), 6.36 (s, 1H), 4.60 (s, 1H), 3.81 (s, 3H), 3.12 (s, 3H), 3.11-3.08 (m, 1H), 3.00-2.96 (m, 1H), 2.44 (s, 3H), 2.33-2.28 (m, 1H), 1.95-1.79 (m, 1H), 1.65-1.52 (m, 2H); **Minor**: **^{1}H NMR** (600 MHz, $CDCl_3$) 7.72 (s, 1H), 6.74 (s, 1H), 3.92 (s, 3H), 3.84 (s, 1H), 3.07 (s, 3H), 3.04-3.01 (m, 1H), 2.93-2.88 (m, 1H), 2.36 (s, 3H), 1.95-1.79 (m, 2H), 1.65-1.52 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 179.0, 178.6, 176.0, 175.1, 155.6, 155.4, 137.7, 136.7, 135.3, 135.1, 117.8, 117.0, 113.6, 112.9, 112.9, 112.3, 73.5, 71.8, 57.8, 56.7, 56.6, 54.5, 54.1, 53.1, 34.9, 34.6, 33.0, 31.0, 24.7, 24.7, 22.2, 21.9; **IR** (thin film): 2933, 2850, 1699, 1471, 1379, 1288, 1247, 1056 cm^{-1}; **LRMS** (ESI): 447 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{16}H_{19}Br_2N_2O_3$ $(M+H)^+$: 446.9736, found: 446.9738.

(5*S*,9*R*)-9-(2,4-dibromo-5-methoxyphenyl)-1,7-dimethyl-1,7-diazaspiro[4.4]nonane-6,8-dione (12)



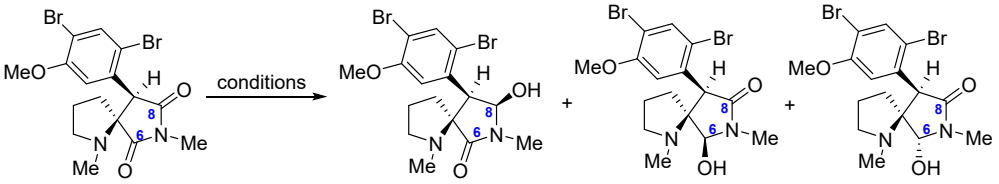
12

To a suspension of *t*-BuONa (54 mg, 0.562 mmol) in THF (4.5 mL) was added **10** (152 mg, 0.34 mmol) in THF (3 mL) dropwise over a period of 5 min at -78 °C. After stirring at this temperature for 1 h, the mixture was added precooled L-camphorsulfonic acid (174 mg, 0.75 mmol) in THF (7.5 mL) slowly. After the mixture was stirred for another 1 h at -78 °C, the reaction was quenched with saturated aqueous NH_4Cl. The resulting mixture was then allowed to warm to room temperature, extracted with EtOAc for 3 times, dried over anhydrous Na_2SO_4, concentrated, and purified *via* flash chromatography on silica gel (PE/EtOAc = 5/1) to give **12** (76 mg, 50%, 89% brsm) as a white solid, along with recovered **10** (67 mg, 44%). For **12**, NMR spectra of NOESY was given to assign its stereochemistry.

[α]25 D -16.30 (c = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76 (s, 1H), 6.56 (s, 1H), 4.56 (s, 1H), 3.82 (s, 3H), 3.13 (s, 3H), 2.91 (t, *J* = 7.6 Hz, 1H), 2.77-2.71 (m, 1H), 2.57-2.50 (m, 1H), 2.50-2.44 (m, 1H), 2.16 (s, 3H), 1.87-1.77 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 178.4, 176.6, 154.7, 136.2, 134.0, 117.1, 114.7, 111.9, 72.6, 57.2, 56.9, 56.5, 37.9, 37.0, 24.9, 23.8; **IR** (thin film): 2926, 1703, 1454,1367, 1286, 1246, 1056, 1026 cm^{-1}; **LRMS** (ESI): 447 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{16}H_{19}Br_2N_2O_3$ $(M+H)^+$: 446.9736, found: 446.9741; mp: 91-93 °C.

The Detailed Investigation of Reduction of Cyclic Imide 12

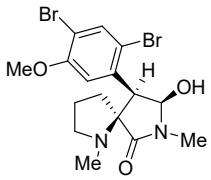
Table 2 Carbonyl Reduction of Cyclic Imide 12



Entry	Conditions	T.M. (%)[a]	13 (%)	14 (%)
1	DIBAL-H, DCM, -78 °C	30	43	n.d.[b]
2	DIBAL-H, Al(O*i*-Pr)$_3$, DCM, -78 °C	47	43	n.d.
3	DIBAL-H, THF, -78 °C	30	61	n.d.
4	DIBAL-H, toluene, -78 °C	20	60	n.d.
5	DIBAL-H, DCM, -30 °C	15	37	n.d.
6	$LiAlH_4$, THF, -78 °C	n.d.	53	n.d.
7	$NaBH_4$, MeOH/THF, 0 °C	n.d.	53	14
8	L-selectride, THF, -78 °C	8	26	8

[a] H^1NMR yield. [b] n.d. stands for not detected.

(5*S*,8*R*,9*R*)-9-(2,4-dibromo-5-methoxyphenyl)-8-hydroxy-1,7-dimethyl-1,7-diazaspiro[4.4]nonan-6-one

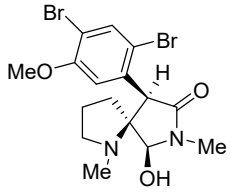

Amathaspiramide A

To a solution of **12** (45 mg, 0.1 mmol) and Al(O*i*-Pr)$_3$ (41 mg, 0.2 mmol) in DCM (2 mL) at –78 °C was added DIBAL-H (1.0 M in THF, 1 mL, 1 mmol) dropwise over a period of 15 min at –78 °C. After stirring at the same temperature for 2 h, the reaction mixture was quenched with MeOH (50 μL), a saturated solution of NH_4Cl (0.5 mL) and saturated aqueous Rochelle's salt (1 mL). The reaction was allowed to warm to room temperature and stirring was continued for 2 h. The resulting mixture was then extracted with DCM for 3 times, dried over anhydrous Na_2SO_4, concentrated, and purified *via* flash chromatography on silica gel (PE/EtOAc = 1/1) to give amathaspiramide A (21 mg, 47%) as a white solid and **13** (19 mg, 43%) as yellow oil.

[α]25 D +1.30 (c = 0.20, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76-7.73 (m, 2H), 5.17 (d, *J* = 5.4 Hz, 1H), 3.92 (d, *J* = 5.4 Hz, 1H), 3.87 (s, 3H), 3.00 (s, 3H), 2.97-2.93

(m, 1H), 2.85-2.79 (m, 1H), 2.52 (s, 3H), 2.44-2.37 (m, 1H), 1.92-1.85 (m, 1H), 1.80-1.73 (m, 1H), 1.41-1.32 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 174.9, 154.3, 135.2, 134.5, 118.0, 117.0, 111.1, 82.6, 71.2, 57.4, 56.2, 51.3, 37.1, 36.6, 27.7, 23.7.; **IR** (thin film): 3305, 2927, 1666, 1462, 1371, 1249, 1093, 1051, 740 cm^{-1}; **LRMS** (ESI): 449 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{16}H_{21}Br_2N_2O_3$ $(M+H)^+$: 448.9893, found: 448.9894; mp: 174-176 °C.

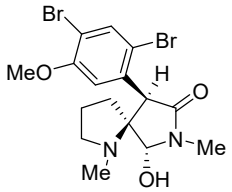
(5*S*,6*S*,9*R*)-9-(2,4-dibromo-5-methoxyphenyl)-6-hydroxy-1,7-dimethyl-1,7-diazaspiro[4.4]nonan-8-one (13)



13

[α]25 D -3.12 (c = 0.50, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.26 (s, 1H), 4.77 (s, 1H), 4.21 (s, 1H), 3.85 (s, 3H), 3.05 – 2.96 (m, 4H), 2.57-2.51 (m, 1H), 2.44-2.37 (m, 4H), 2.03-1.96 (m, 1H), 1.89-1.82 (m, 1H), 1.79-1.73 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 172.1, 155.0, 136.3, 135.8, 117.3, 115.5, 111.7, 86.4, 72.9, 56.5, 55.5, 55.4, 37.5, 35.7, 27.4, 21.6; **IR** (thin film): 2957, 2922, 1663, 1456, 1373, 1260, 1096, 1018, 799 cm^{-1}; **LRMS** (ESI): 449 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{16}H_{21}Br_2N_2O_3$ $(M+H)^+$: 448.9898, found: 448.9893

(5*S*,6*R*,9*R*)-9-(2,4-dibromo-5-methoxyphenyl)-6-hydroxy-1,7-dimethyl-1,7-diazaspiro[4.4]nonan-8-one (14)

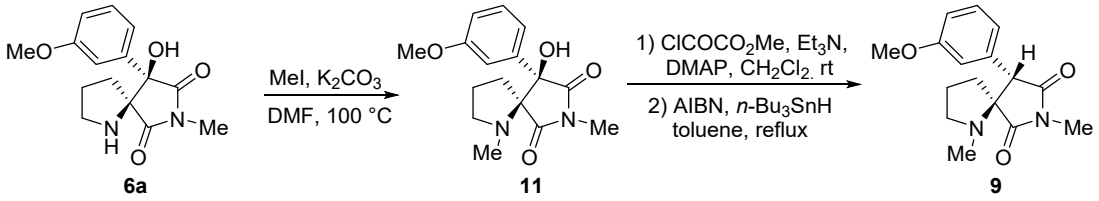


14

To a solution of **12** (45 mg, 0.1 mmol) in THF (2.5 mL) and MeOH (2.5 mL) at 0 °C was added $NaBH_4$ (11 mg, 0.3 mmol). After stirring at the same temperature for 1 h, the reaction was quenched with water. Then the mixture was extracted with DCM for 3 times, dried over anhydrous Na_2SO_4, concentrated, and purified *via* flash chromatography on silica gel (PE/EtOAc = 1/2) to give **13** (24 mg, 53%) and **14** (6 mg, 14%) as yellow oil. **[α]**25 D -12.40 (c = 0.10, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.72 (s, 1H), 6.77 (s, 1H), 4.84 (s, 1H), 4.49 (s, 1H), 3.84 (s, 3H), 3.00 (s, 3H), 2.88-2.82 (m, 1H), 2.60-2.53 (m, 1H), 2.38 (s, 3H), 2.24-2.13 (m, 2H), 1.66-1.58 (m, 1H), 1.43-1.37 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.5, 154.5, 135.6, 134.3, 117.2, 116.3, 111.3, 84.7, 72.7,

56.3, 55.6, 53.0, 36.1, 32.5, 27.3, 22.0; **IR** (thin film): 3331, 2924, 1682, 1584, 1462, 1368, 1260, 1057, 800, 735; **LRMS** (ESI): 449 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{16}H_{21}Br_2N_2O_3$ $(M+H)^+$: 448.9898, found: 448.9890

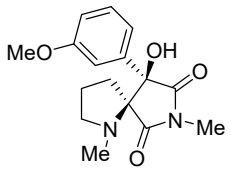
Methylation and Dehydroxylation from 6a



MeI (22 μL, 0.35 mmol) was added dropwise to a 25 ml flask charged with compound **6a** (67 mg, 0.23 mmol), K_2CO_3 (63 mg, 0.46 mmol) and DMF (2.3 mL). After stirring at 100 °C for 5 h, the suspension was filtered, and the filtrate was concentrated under reduced pressure, diluted with EtOAc, washed with water and brine and dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. The residue was purified *via* flash chromatography on silica gel (PE/EtOAc = 3/1) to give **11** (46 mg, 66%) as a yellow solid.

To a solution of **11** (30 mg, 0.1 mmol) and DMAP (3 mg, 0.02 mmol) in DCM (1 mL), was added triethylamine (21 μL, 0.15 mmol) slowly at 0 °C. Then methyl chlorooxalate (14 μL, 0.15 mmol) was added dropwise, and the mixture was stirred at room temperature for 1 h. The resulting solution was washed with water, dried over anhydrous Na_2SO_4, and concentrated to give yellow oil, which was used in the next step without further purification. To a solution of the crude product in degassed toluene (1.4 mL) was added AIBN (8 mg, 0.05 mmol) and *n*-Bu_3SnH (67 μL, 0.23 mmol). The solution was heated to 110 °C in an oil bath under nitrogen and stirred for 2 h. Then the resulting mixture was cooled to room temperature and evaporated. The residue was purified *via* flash chromatography (10% w/w anhydrous K_2CO_3-silica[2]; PE/EA = 3/1) to give **9** (14 mg, 47%, 55% brsm) as yellow oil and recovered **11** (5 mg, 15%).

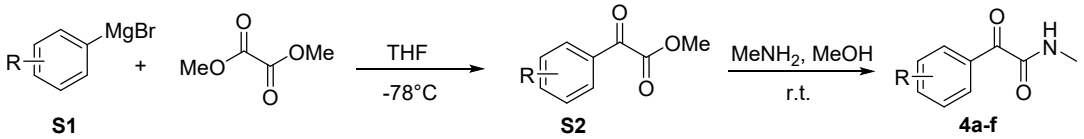
(5*S*,9*R*)-9-hydroxy-9-(3-methoxyphenyl)-1,7-dimethyl-1,7-diazaspiro[4.4]nonane-6,8-dione (11)



11

[α]25 D -49.85 (c = 1.00, $CDCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.8 Hz, 1H), 7.00 (s, 1H), 6.83 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.76 (br s, 1H), 3.80 (s, 3H), 3.25-3.21 (m, 1H), 3.17 (s, 3H), 2.80-2.75 (m, 1H), 2.34 (s, 3H), 2.19-2.12 (m, 1H), 1.78-1.73 (m, 1H), 1.58-1.50 (m, 1H), 1.45-1.39 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 177.7, 176.4, 160.0, 140.9, 129.8, 116.9, 113.5, 111.1, 77.3, 74.9, 56.8, 55.3, 36.8, 30.9, 24.7, 23.5; **IR** (thin film): 2953, 1782, 1712, 1583, 1487, 1456, 1429, 1377, 1288, 1261, 1172, 1047, 792 cm^{-1} **LRMS** (ESI): 305 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{16}H_{21}N_2O_4$ $(M+H)^+$: 305.1496, found: 305.1497; mp: 95-97 °C

Preparation of Ketoamides 4a-f

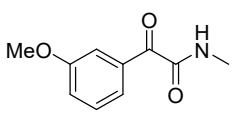


S1 S2 4a-f

To a solution of dimethyl oxalate (2.6 g, 22 mmol) was added Grignard reagent **S1** (1.0 M solution in THF, 20 ml, 20 mmol) dropwise at –78 °C. After stirring at -78 °C for 2.5 h, the mixture was quenched with aq. HCl (2 M, 6 mL), warmed to room temperature, and concentrated to remove THF. The residue was extracted with CH_2Cl_2 for three times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give yellow liquid, which was used in the next step without further purification.

To a solution of the crude product in MeOH (40 mL) was added $MeNH_2$ (27% in MeOH, 3.7 mL, ca. 26 mmol), and the mixture was stirred for 24-72 h until TLC control indicated the completed consumption of the substrate. Then the solvent was removed under reduced pressure and the residual was subjected to flash chromatography on silica gel (PE/EtOAc = 5/1) to give corresponding ketoamides **4a-f**.

2-(3-methoxyphenyl)-*N*-methyl-2-oxoacetamide (4a)

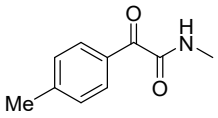


4a

4a: Yellow solid (63% yield); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.8z Hz, 1H), 7.85 (s, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.18 (dd,

J = 7.8, 2.4 Hz, 1H), 7.11 (br s, 1H), 3.87 (s, 3H), 2.98 (d, J = 5.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 187.4, 162.4, 159.5, 134.5, 129.6, 124.2, 121.6, 114.6, 55.5, 26.1; **IR** (thin film): 3320, 2950, 1664, 1286, 1255, 1197, 1039, 779 cm^{-1}; **LRMS** (ESI): 194 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{10}H_{12}NO_3$ $(M+H)^+$: 194.0812, found: 194.0814; mp: 30-32 °C

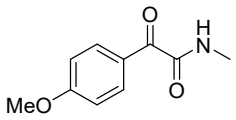
_N_-methyl-2-oxo-2-(_p_-tolyl)acetamide (4b)



4b

4b: White solid (70% yield); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.27 (d, J = 7.8 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 7.12 (br s, 1H), 2.98-2.95 (m, 3H), 2.43 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 187.2, 162.7, 145.6, 131.4, 130.8, 129.3, 26.0, 21.9; **IR** (thin film):3251, 3101, 1670, 1653, 1635, 1575, 1558, 1541, 1417, 759 cm^{-1}; **LRMS** (ESI): 200 $(M+Na)^+$; **HRMS** (ESI): m/z calcd for $C_{10}H_{11}NO_2Na$ $(M+Na)^+$: 200.0682, found: 200.0684; mp: 72-74 °C

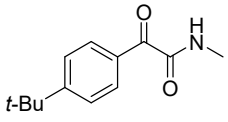
2-(4-methoxyphenyl)-_N_-methyl-2-oxoacetamide (4c)



4c

4c: Yellow solid (37% yield); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.43 (d, J = 7.8 Hz, 2H), 7.15 (br s, 1H), 6.95 (d, J = 7.8 Hz, 2H), 3.89 (s, 3H), 2.98-2.95 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 185.6, 164.7, 162.9, 134.0, 126.4, 113.8, 55.6, 26.0; **IR** (thin film): 3381, 1683, 1647, 1598, 1533, 1301, 1261, 1172, 1068, 1022, 846, 802, 534 cm^{-1}; **LRMS** (ESI): 216 $(M+Na)^+$; **HRMS** (ESI): m/z calcd for $C_{10}H_{11}NO_3Na$ $(M+Na)^+$: 216.0631, found: 216.0636; mp: 95-97 °C

2-(4-(_tert_-butyl)phenyl)-_N_-methyl-2-oxoacetamide (4d)

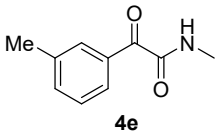


4d

4d: White solid (43% yield); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.29 (d, J = 7.2 Hz, 2H), 7.50 (d, J = 7.2 Hz, 2H), 7.13 (br s, 1H), 2.99-2.96 (m, 3H), 1.34 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 187.2, 162.7, 158.4, 131.2, 130.7, 125.5, 35.3, 31.0, 26.0; **IR** (thin film): 3325, 2962, 1662, 1602, 1527, 1409, 1292, 1224, 1188, 1111, 935 cm^{-1}; **LRMS** (ESI): 220 $(M+H)^+$; **HRMS** (ESI): m/z calcd for $C_{13}H_{18}NO_2$ $(M+H)^+$: 220.1332, found: 220.1338; mp: 60-

62 °C

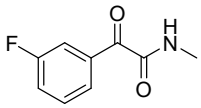
_N_-methyl-2-oxo-2-(_m_-tolyl)acetamide (4e)



4e

4e: White solid (57% yield); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.16-8.11 (m, 2H), 7.46-7.42 (m, 1H), 7.39-7.35 (m, 1H), 7.11 (br s, 1H), 3.00-2.95 (m, 3H), 2.42 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 187.9, 162.6, 138.3, 135.3, 133.3, 131.5, 128.4, 128.4, 26.0, 21.3; **IR** (thin film): 3307, 2922, 1662, 1558, 1411, 1303, 1244, 1174, 775, 669 cm^{-1}; **LRMS** (ESI): 200 $(M+Na)^+$; **HRMS** (ESI): m/z calcd for $C_{10}H_{11}NO_2Na$ $(M+Na)^+$: 200.0682, found: 200.0686; mp: 47-49 °C

2-(3-fluorophenyl)-_N_-methyl-2-oxoacetamide (4f)

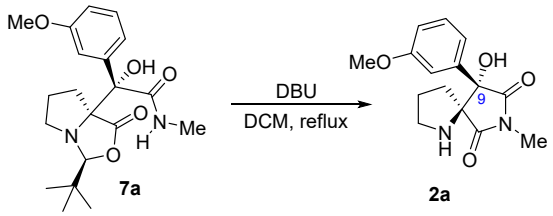


4f

4f: White solid (45% yield); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.19 (d, J = 7.2 Hz, 1H), 8.08 (d, J = 9.6 Hz, 1H), 7.50-7.44 (m, 1H), 7.37-7.31 (m, 1H), 7.13 (br s, 1H), 3.01-2.96 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 186.3 (d, J = 1.5 Hz), 162.4 (d, J = 247.5 Hz), 161.8, 135.1 (d, J = 7.5 Hz), 130.2 (d, J = 7.5 Hz), 127.2 (d, J = 3.0 Hz), 121.5 (d, J = 21.0 Hz), 117.9 (d, J = 22.5 Hz), 26.1; **IR** (thin film): 3372, 1668, 1541, 1436, 1411, 1305, 1240, 1168, 777, 686 cm^{-1}; **LRMS** (ESI): 182 $(M+H)^+$; **HRMS** (ESI): m/z calcd for $C_9H_9FNO_2$ $(M+H)^+$: 182.0612, found: 182.0613; mp: 57-59 °C

Substrate Scope of Aldol Addition/Transamidification

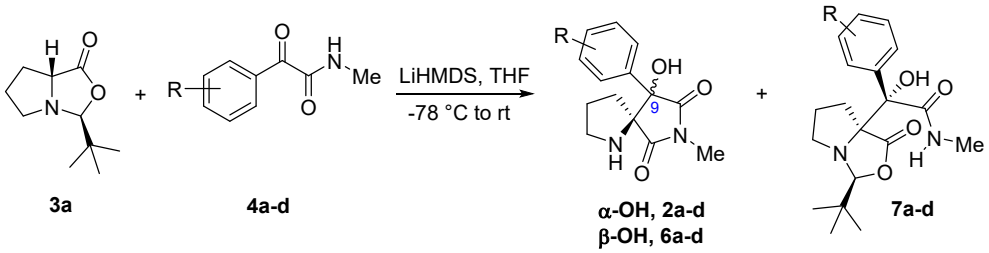
Transamidification of 7a to Obtain Spirocyclic Product



To a solution of **7a** (38 mg, 0.1 mmol) in DCM (2 mL) was added DBU (15 μL, 0.1 mmol) at 45 °C. After stirring at the same temperature for 30 h, the mixture was quenched with a saturated solution of NH_4Cl, extracted with DCM for 3 times, dried over anhydrous Na_2SO_4 and concentrated. The residual was subjected to flash chromatography on silica gel (PE/EtOAc = 1/1) to give **2a** in 65% yield (19 mg).

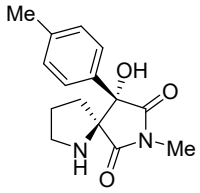
The Substrate Scope of 3 and 4

Procedure for Reaction of 3a and Ketoamides 4a-d



In a 100 ml flask, LiHMDS (1.0 M solution in THF, 3 ml, 3 mmol） was added to THF (20 ml). After the solution cooled down to -78 °C, the crude product of **3a** (367 mg, 2 mmol) in THF (20 ml) was added dropwise over 5 min and the mixture was stirred at the temperature for 1.5 h. After ketoamide **4** (1 mmol) in THF (10 ml) was added dropwise over 20 min, the mixture was stirred at the temperature for 2.5 h. Then the mixture was gradually warmed to room temperature for a period over 1.5 h and stirred for another 2 h. After a saturated solution of NH_4Cl was added, THF was removed under reduced pressure. The residue was extracted with DCM for 3 times, dried over anhydrous Na_2SO_4, concentrated, and purified *via* flash chromatography on silica gel (PE/EtOAc = 1/1) to give **2** , **6** and **7**.

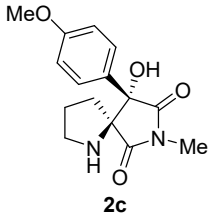
(5*S*,9*S*)-9-hydroxy-7-methyl-9-(*p*-tolyl)-1,7-diazaspiro[4.4]nonane-6,8-dione (2b)



2b

2b: Yellow oil (48% yield) **[α]**25 D -23.28 (c = 1.00, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.17-7.08 (m, 4H), 3.75 (br s, 1H), 3.13 (s, 3H), 3.05-3.00 (m, 1H), 2.85-2.80 (m, 1H), 2.54-2.49 (m, 1H), 2.33 (s, 3H), 1.95-1.84 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 180.2, 177.8, 138.6, 135.1, 129.5, 125.3, 81.9, 74.1, 47.1, 32.9, 25.4, 25.1, 21.1; **IR** (thin film): 3419, 2949, 1707, 1435, 1379, 1292, 1062, 815 cm^{-1}; **LRMS** (ESI): 275 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{19}N_2O_3$ $(M+H)^+$: 275.1390, found: 275.1393.

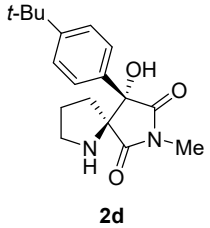
(5*S*,9*S*)-9-hydroxy-9-(4-methoxyphenyl)-7-methyl-1,7-diazaspiro[4.4]nonane-6,8-dione (2c)



2c

2c: Orange oil (39% yield) **[α]**25 D -22.28 (c = 1.00, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.18 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H), 3.13 (s, 3H), 3.05-3.00 (m, 1H), 2.86-2.77 (m, 1H), 2.54-2.47 (m, 1H), 1.96-1.82 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 180.1, 178.0, 159.8, 129.9, 126.9, 114.1, 81.6, 74.1, 55.3, 47.2, 32.6, 25.5, 25.1; **IR** (thin film): 3358, 2922, 1707, 1512, 1436, 1296, 1251, 1178, 1062, 831 cm^{-1}; **LRMS** (ESI): 291 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{19}N_2O_4$ $(M+H)^+$: 291.1339, found: 291.1342.

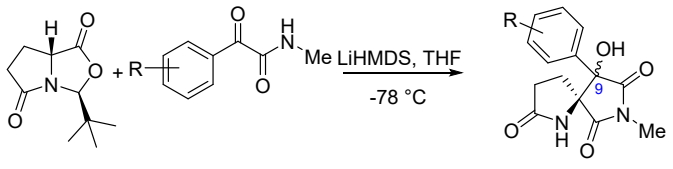
(5*S*,9*S*)-9-(4-(*tert*-butyl)phenyl)-9-hydroxy-7-methyl-1,7-diazaspiro[4.4]nonane-6,8-dione (2d)



2d

2d: Yellow oil (35% yield) **[α]**25 D -9.90 (c = 1.05, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 3.15 (s, 3H), 3.10-3.05 (m, 1H), 2.92-2.87 (m, 1H), 2.57-2.50 (m, 1H), 1.98-1.93 (m, 1H), 1.93-1.85 (m, 2H), 1.29 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 180.2, 177.7, 151.8, 135.0, 125.8, 125.1, 81.9, 74.1, 47.2, 34.6, 33.1, 31.2, 25.3, 25.1; **IR** (thin film): 3412, 2960, 1707, 1433, 1381, 1282, 1062, 833, 559 cm^{-1}; **LRMS** (ESI): 317 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{18}H_{25}N_2O_3$ $(M+H)^+$: 317.1860, found: 317.1873.

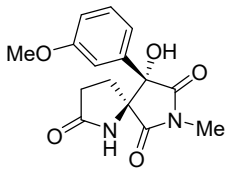
Procedure for Reaction of 3b and Ketoamides 4a-f



3b **4a-f** **α-OH, 2e-j** **β-OH, 6e-j**

The acetal derived **3b** was prepared according to the literature[4]. In a 100 ml flask, LiHMDS (1.0 M solution in THF, 3 ml, 3 mmol） was added to THF (20 ml). After the solution cooled down to -78 °C, **3b** (394 mg, 2 mmol) in THF (20 ml) was added dropwise over 20 min and the mixture was stirred at the temperature for 2 h. Ketoamide **4** (1 mmol) in THF (10 ml) was added dropwise over 15 min and the mixture was stirred at the temperature for 14 h. After a saturated solution of NH_4Cl was added, the mixture was allowed to warm to room temperature, followed by removal of THF under reduced pressure. The residue was extracted with DCM for 3 times, dried over anhydrous Na_2SO_4, concentrated, and purified *via* flash chromatography on silica gel (PE/EtOAc = 1/1) to give **2** and its epimer **6** at C9.

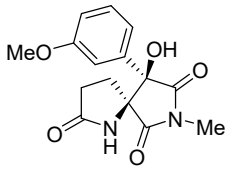
(5*S*,9*S*)-9-hydroxy-9-(3-methoxyphenyl)-7-methyl-1,7-diazaspiro[4.4]nonane-2,6,8-trione (2e)



2e

2e: White solid (39% yield) **[α]**25 D +79.01 (c = 0.97, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.78 (s, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 5.31 (s, 1H), 4.26 (s, 1H), 3.77 (s, 3H), 3.19 (s, 3H), 2.94-2.86 (m, 1H), 2.56-2.42 (m, 2H), 2.13-2.07 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 177.6, 176.3, 176.1, 160.4, 138.7, 130.7, 116.4, 114.5, 111.3, 80.5, 70.6, 55.4, 29.5, 28.3, 25.3; **IR** (thin film): 3305, 1708, 1600, 1490, 1431, 1290, 1259, 1047, 732 cm^{-1}; **LRMS** (ESI): 305 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{17}N_2O_5$ $(M+H)^+$: 305.1132, found: 305.1136; mp: 195-197 °C

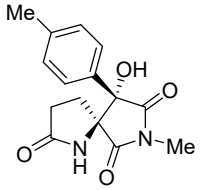
(5*S*,9*R*)-9-hydroxy-9-(3-methoxyphenyl)-7-methyl-1,7-diazaspiro[4.4]nonane-2,6,8-trione (6e)



6e

6e: White solid (11% yield) **[α]**25 D -20.20 (c = 0.50, $CHCl_3$);**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.8 Hz, 1H), 6.96 (s, 1H), 6.93-6.89 (m, 2H), 6.88 (br s, 1H), 5.16 (s, 1H), 3.79 (s, 3H), 3.13 (s, 3H), 2.35-2.26 (m, 1H), 2.05-1.97 (m, 1H), 1.76-1.62 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 178.2, 176.7, 175.4, 159.8, 136.4, 130.0, 118.6, 114.8, 112.3, 79.0, 69.3, 55.4, 29.0, 28.5, 25.5; **IR** (thin film): 3311, 2926, 1708, 1381, 1292, 1269, 1120, 1016, 794, 736 cm^{-1}; **LRMS** (ESI): 305 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{17}N_2O_5$ $(M+H)^+$: 305.1132, found: 305.1135. mp: 219-221 °C

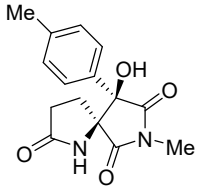
(5*S*,9*S*)-9-hydroxy-7-methyl-9-(*p*-tolyl)-1,7-diazaspiro[4.4]nonane-2,6,8-trione (2f)



2f

2f: White solid (54% yield) **[α]**25 D +48.18 (c = 1.00, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 5.36 (s, 1H), 4.33 (s, 1H), 3.17 (s, 3H), 2.91-2.84 (m, 1H), 2.54-2.40 (m, 2H), 2.32 (s, 3H), 2.12-2.06 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 177.7, 176.4, 176.4, 139.4, 134.1, 130.1, 124.8, 80.6, 70.6, 29.5, 28.2, 25.2, 21.1; **IR** (thin film): 3219, 2924, 1707, 1431, 1375, 1296, 1053, 732 cm^{-1}; **LRMS** (ESI): 289 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{17}N_2O_4$ $(M+H)^+$: 289.1183, found: 289.1185; mp: 173-175 °C

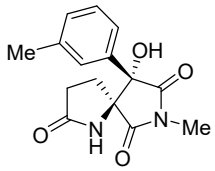
(5*S*,9*R*)-9-hydroxy-7-methyl-9-(*p*-tolyl)-1,7-diazaspiro[4.4]nonane-2,6,8-trione (6f)



6f

6f: White solid (16% yield) **[α]**25 D -12.18 (c = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 6.72 (s, 1H), 4.89 (s, 1H), 3.14 (s, 3H), 2.36 (s, 3H), 2.30-2.22 (m, 1H), 2.03-1.95 (m, 1H), 1.69-1.59 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 178.1, 176.8, 175.5, 139.5, 131.7, 129.5, 126.4, 79.0, 69.3, 28.9, 28.7, 25.4, 21.2; **IR** (thin film): 3331, 2924, 1712, 1435, 1381, 1298, 1045, 867, 734, 430 cm^{-1}; **LRMS** (ESI): 289 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{17}N_2O_4$ $(M+H)^+$: 289.1183, found: 289.1186; mp: 226-228 °C

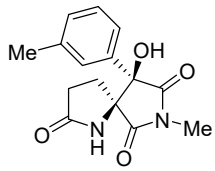
(5*S*,9*S*)-9-hydroxy-7-methyl-9-(*m*-tolyl)-1,7-diazaspiro[4.4]nonane-2,6,8-trione (2g)



2g

2g: White solid (49% yield) **[α]**25 D -0.38 (c = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28-7.24 (m, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.00 (s, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 5.04 (s, 1H), 3.66 (s, 1H), 3.23 (s, 3H), 2.96-2.89 (m, 1H), 2.58-2.47 (m, 2H), 2.34 (s, 3H), 2.15-2.09 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 177.3, 176.4, 176.2, 139.7, 137.1, 130.4, 129.5, 125.4, 121.7, 80.5, 70.4, 29.5, 28.3, 25.4, 21.7; **IR** (thin film): 3250, 2924, 1712, 1435, 1379, 1294, 1055, 802, 732 cm^{-1}; **LRMS** (ESI): 289 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{17}N_2O_4$ $(M+H)^+$: 289.1183, found: 289.1185; mp: 233-235 °C

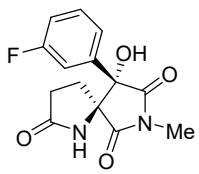
(5*S*,9*R*)-9-hydroxy-7-methyl-9-(*m*-tolyl)-1,7-diazaspiro[4.4]nonane-2,6,8-trione (6g)



6g

6g: White solid (15% yield) **[α]**25 D -18.93 (c = 1.10, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29-7.25 (m, 1H), 7.20-7.18 (m, 2H), 7.15 (d, *J* = 7.8 Hz, 1H), 6.94 (s, 1H), 5.36 (s, 1H), 3.13 (s, 3H), 2.35 (s, 3H), 2.31-2.24 (m, 1H), 2.01-1.95 (m, 1H), 1.70-1.58 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 178.4, 176.8, 175.6, 138.6, 134.9, 130.1, 128.7, 127.0, 123.5, 79.1, 69.4, 29.0, 28.5, 25.4, 21.6; **IR** (thin film): 3309, 2924, 1707, 1431, 1379, 1120, 1020, 798, 734 cm^{-1}; **LRMS** (ESI): 289 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{17}N_2O_4$ $(M+H)^+$: 289.1183, found: 289.1184; mp: 219-221 °C

(5*S*,9*S*)-9-(3-fluorophenyl)-9-hydroxy-7-methyl-1,7-diazaspiro[4.4]nonane-2,6,8-trione (2h)

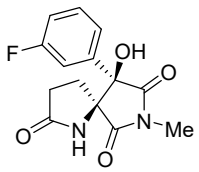


2h

2h: White solid (34% yield) **[α]**25 D +66.98 (c = 1.00, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38-7.33 (m, 1H), 7.08 (t, *J* = 7.8, 1H), 7.00-6.96 (m, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 5.25 (s, 1H), 3.97 (s, 1H), 3.23 (s, 3H), 2.95-2.88 (m, 1H), 2.58-2.45 (m, 2H), 2.17-2.10 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 177.3, 176.0, 175.6, 163.3 (d, *J* = 250.0 Hz), 139.7 (d, *J* = 6.0 Hz), 131.4 (d, *J* = 9.0 Hz), 120.2 (d, *J* = 3.0 Hz), 116.7 (d, *J* = 21.0 Hz), 112.8

(d, *J* = 24.0 Hz), 80.4, 70.5, 29.3, 28.4, 25.5; **IR** (thin film): 3207, 2924, 1708, 1435, 1379, 1296, 1053, 732 cm^{-1}; **LRMS** (ESI): 293 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{14}H_{14}FN_2O_4$ $(M+H)^+$: 293.0932, found: 293.0938; mp: 187-189 °C

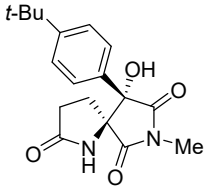
(5*S*,9*R*)-9-(3-fluorophenyl)-9-hydroxy-7-methyl-1,7-diazaspiro[4.4]nonane-2,6,8-trione (6h)



6h

6h: White solid (15% yield) **[α]**25 D -13.67 (c = 0.60, MeOH); **^{1}H NMR** (600 MHz, CD_3OD) δ 7.47-7.42 (m, 1H), 7.31-7.25 (m, 2H), 7.18-7.13 (m, 1H), 3.11 (s, 3H), 2.22 (ddd, *J* = 16.8, 9.8, 5.5 Hz, 1H), 2.06 (ddd, *J* = 13.4, 9.8, 6.5 Hz, 1H), 1.70 (ddd, *J* = 13.4, 9.6, 5.6 Hz, 1H), 1.59 (ddd, *J* = 16.3, 9.6, 6.5 Hz, 1H); **^{13}C NMR** (150 MHz, CD_3OD) δ 179.3, 177.1, 174.9, 162.6 (d, *J* = 245.4 Hz), 138.6 (d, *J* = 7.1 Hz), 129.9 (d, *J* = 8.1 Hz), 122.8 (d, *J* = 2.9 Hz), 115.3 (d, *J* = 21.3 Hz), 114.0 (d, *J* = 23.5 Hz), 78.3, 70.1, 28.7, 28.1, 24.0; **IR** (thin film): 3323, 2924, 1712, 1589, 1381, 1301, 1269, 1118, 1049, 1018, 738 cm^{-1}; **LRMS** (ESI): 293 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{14}H_{14}FN_2O_4$ $(M+H)^+$: 293.0932, found: 293.0935; mp: 206-208 °C

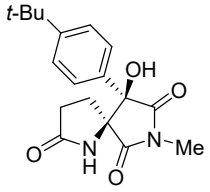
(5*S*,9*S*)-9-(4-(*tert*-butyl)phenyl)-9-hydroxy-7-methyl-1,7-diazaspiro[4.4]nonane-2,6,8-trione (2i)



2i

2i: White solid (54% yield) **[α]**25 D +21.98 (c = 1.00, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 5.22 (s, 1H), 3.97 (s, 1H), 3.19 (s, 3H), 2.94-2.86 (m, 1H), 2.57-2.43 (m, 2H), 2.15-2.07 (m, 1H), 1.29 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 177.6, 176.3, 176.2, 152.8, 134.0, 126.5, 124.6, 80.6, 70.5, 34.7, 31.2, 29.5, 28.3, 25.3; **IR** (thin film): 2960, 1712, 1435, 1381, 1286, 1103, 1053, 734 cm^{-1}; **LRMS** (ESI): 331 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{18}H_{23}N_2O_4$ $(M+H)^+$: 331.1652, found: 331.1651; mp: 244-246 °C

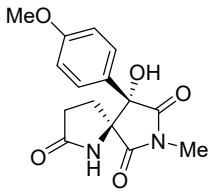
(5*S*,9*R*)-9-(4-(*tert*-butyl)phenyl)-9-hydroxy-7-methyl-1,7-diazaspiro[4.4]nonane-2,6,8-trione (6i)



6i

6i: White solid (18% yield) **[α]**25 D -2.20 (c = 0.20, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 6.43 (s, 1H), 3.91 (s, 1H), 3.17 (s, 3H), 2.33-2.25 (m, 1H), 2.06-1.98 (m, 1H), 1.71-1.63 (m, 2H), 1.32 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 177.6, 176.8, 175.2, 153.0, 131.2, 126.3, 125.9, 79.0, 69.0, 34.8, 31.2, 29.1, 28.8, 25.5; **IR** (thin film): 3257, 2960, 1793, 1712, 1431, 1291, 1020, 800, 580 cm^{-1}; **LRMS** (ESI): 331 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{18}H_{23}N_2O_4$ $(M+H)^+$: 331.1652, found: 331.1652; mp: 260-262 °C

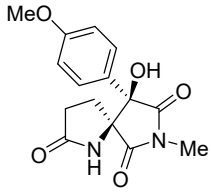
(5*S*,9*S*)-9-hydroxy-9-(4-methoxyphenyl)-7-methyl-1,7-diazaspiro[4.4]nonane-2,6,8-trione (2j)



2j

2j: White solid (31% yield) **[α]**25 D -17.92 (c = 0.25, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 5.03 (s, 1H), 3.81 (s, 3H), 3.54 (s, 1H), 3.22 (s, 3H), 2.95-2.88 (m, 1H), 2.59-2.47 (m, 2H), 2.16-2.10 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 177.2, 176.3, 176.3, 160.4, 128.9, 126.3, 114.9, 80.4, 70.5, 55.4, 29.5, 28.3, 25.3; **IR** (thin film): 3290, 2924, 1705, 1508, 1292, 1251, 1180, 1053, 732 cm^{-1}; **LRMS** (ESI): 305 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{17}N_2O_5$ $(M+H)^+$: 305.1132, found: 305.1139; mp: 220-222 °C

(5*S*,9*R*)-9-hydroxy-9-(4-methoxyphenyl)-7-methyl-1,7-diazaspiro[4.4]nonane-2,6,8-trione (6j)

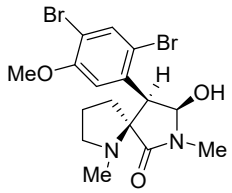


6j

6j: Yellow oil (11% yield) **[α]**25 D -13.25 (c = 0.40, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.47 (s, 1H), 4.30 (br s, 1H), 3.83 (s, 3H), 3.16 (s, 3H), 2.32-2.24 (m, 1H), 2.04-1.97 (m, 1H), 1.71-1.62 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 177.7, 176.7, 175.4, 160.4, 128.0, 126.2, 114.3, 78.8, 69.1, 55.4, 29.1, 28.8, 25.5; **IR** (thin film): 3365, 2926, 1707, 1514, 1436, 1255, 1180, 1016, 802 cm^{-1}; **LRMS** (ESI): 305 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{17}N_2O_5$ $(M+H)^+$: 305.1132, found: 305.1140

3. Comparison of NMR Data of Synthetic and Natural amathaspiramide A

Table 3 Comparison of ^{1}H NMR Data of Synthetic and Natural Amathaspiramide A



amathaspiramide A

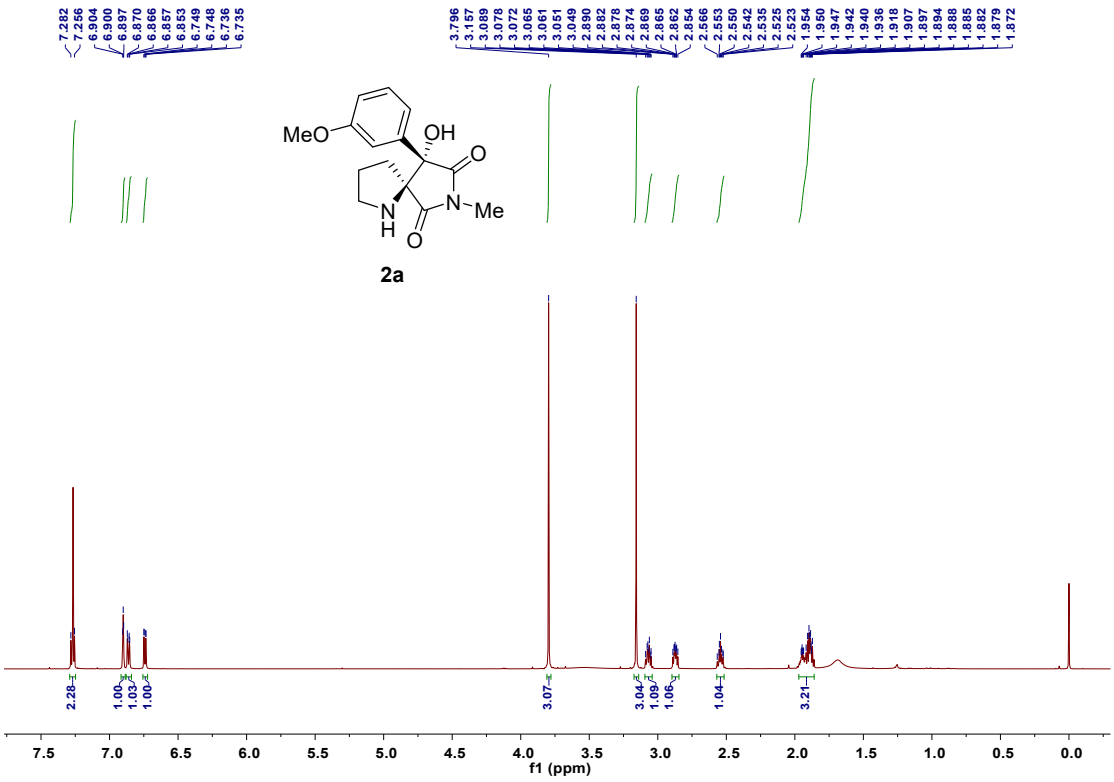
	Synthetic (600 MHz, $CDCl_3$)		Natural (300 MHz, $CDCl_3$)	
1	7.76-7.73	m, 2H	7.70	s, 1H
2			7.67	s, 1H
3	5.17	d, *J* = 5.4 Hz, 1H	5.15	d, *J* = 5.5 Hz, 1H
4	3.92	d, *J* = 5.4 Hz, 1H	3.90	d, *J* = 5.5 Hz, 1H
5	3.87	s, 3H	3.84	s, 3H
6	3.00	s, 3H	2.94	s, 3H
7	2.97-2.93	m, 1H	2.90	m, 1H
8	2.85-2.79	m, 1H	2.73	m, 1H
9	2.52	s, 3H	2.48	s, 3H
10	2.44-2.37	m, 1H	2.31	m, 1H
11	1.92-1.85	m, 1H	1.86	m, 1H
12	1.80-1.73	m, 1H	1.69	m, 1H
13	1.41-1.32	m, 1H	1.32	m, 1H

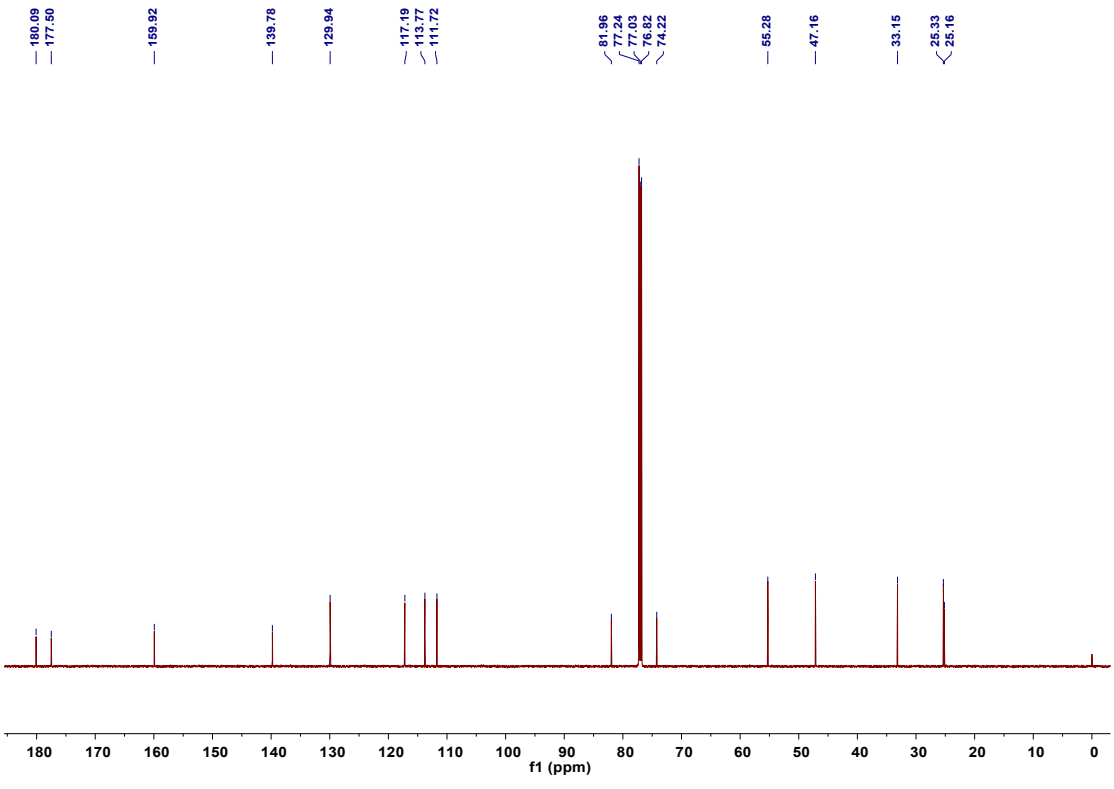
Table 4 Comparison of ^{13}C NMR Data of Synthetic and Natural Amathaspiramide A

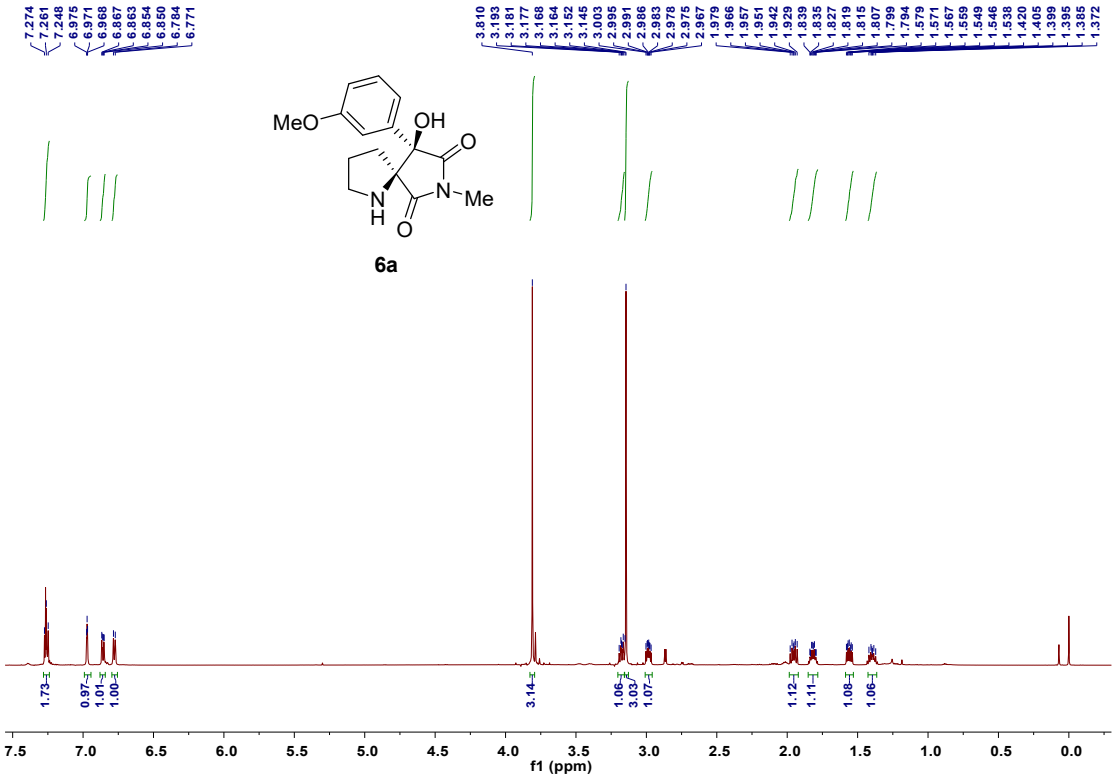
	Synthetic (150 MHz, $CDCl_3$)	**Natural (100 MHz, $CDCl_3$)**
1	174.9	175.2
2	154.3	154.1
3	135.2	135.0
4	134.5	134.6
5	118.0	118.3
6	117.0	117.1
7	111.1	111.0
8	82.6	82.6
9	71.2	71.3
10	57.4	57.4
11	56.2	56.2
12	51.3	51.3
13	37.1	37.0
14	36.6	36.5
15	27.7	27.7
16	23.7	23.6

* Data for natural amathaspiramide A were obtained from the literature[5]

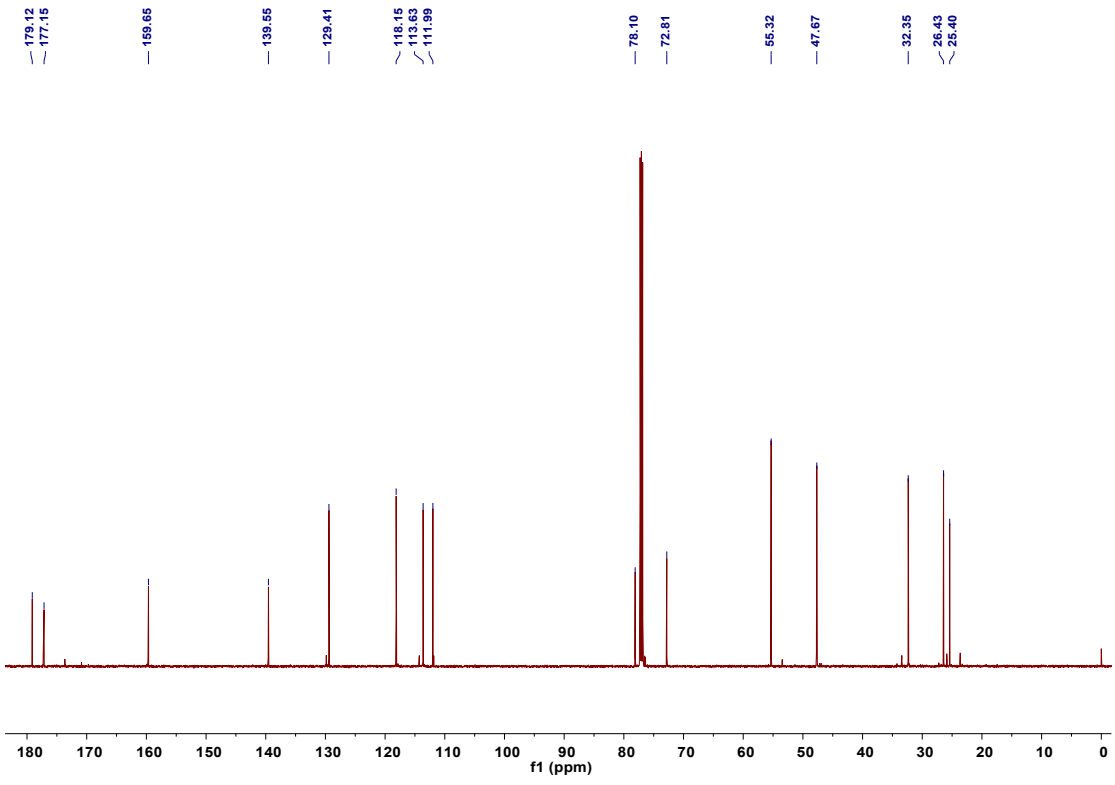
4. NMR Spectra

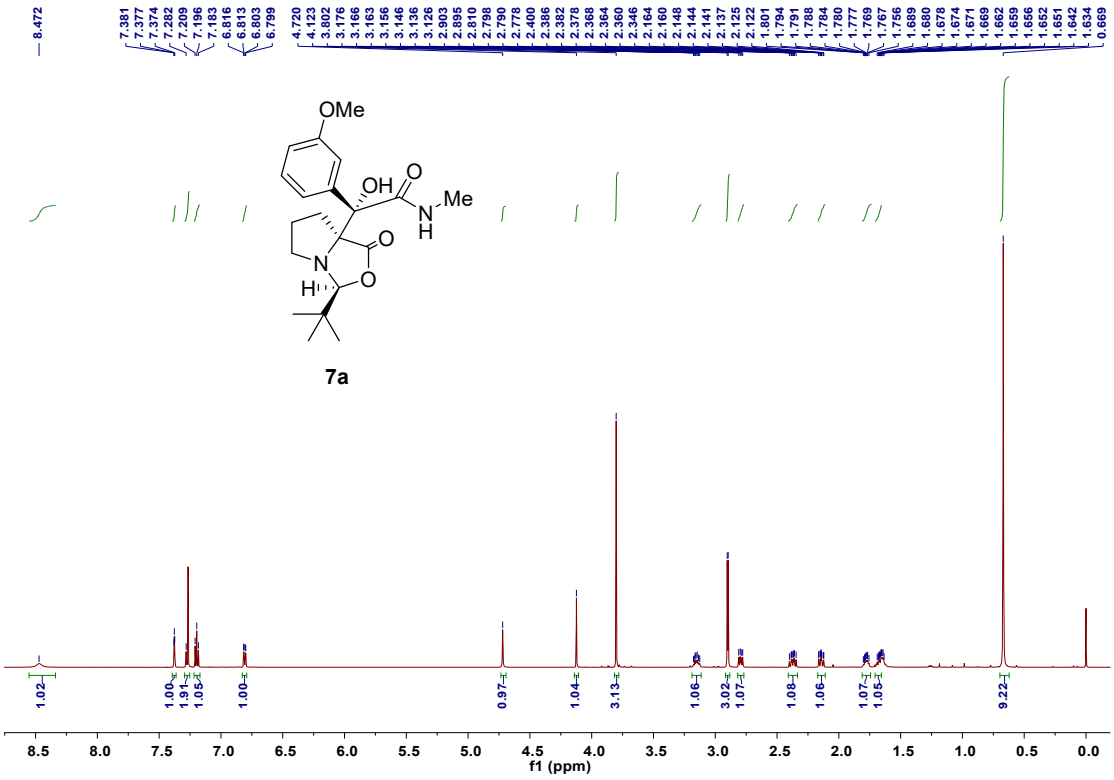


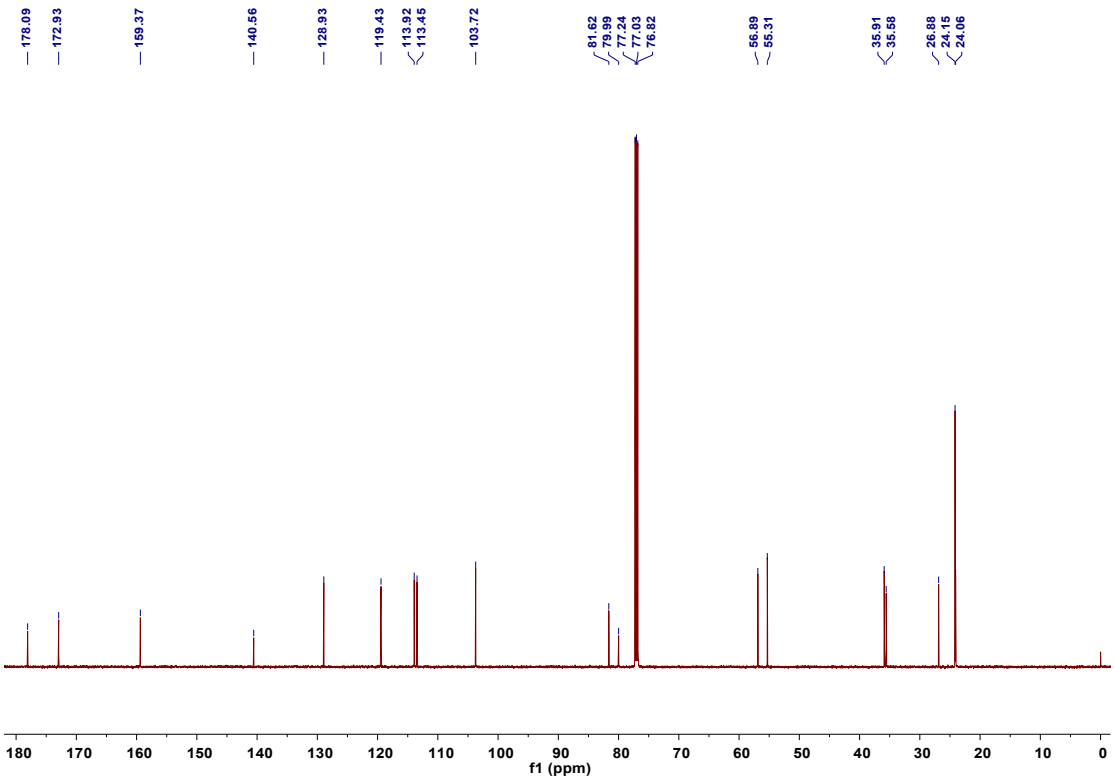


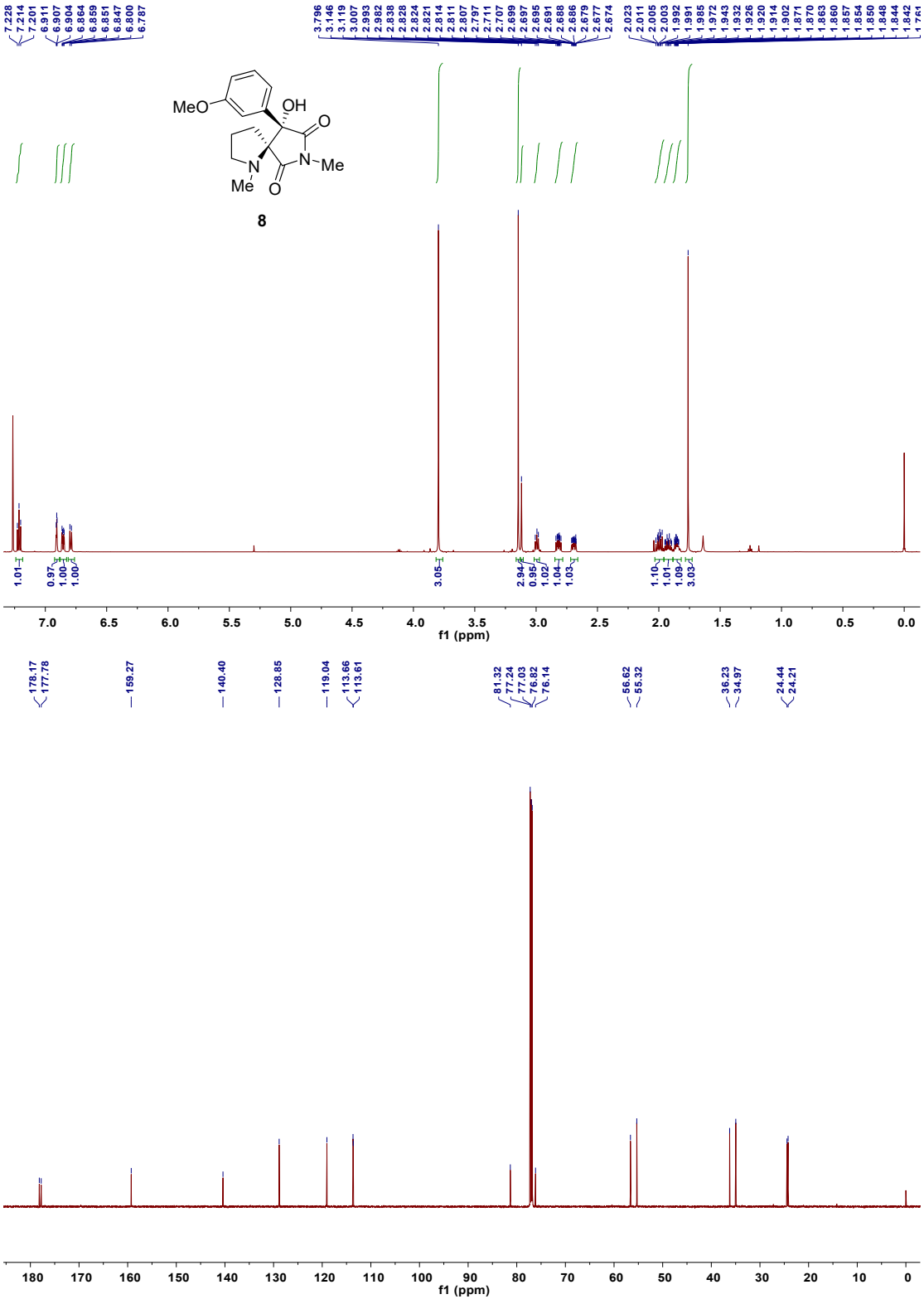

7.274
7.261
7.248
6.975
6.971
6.968
6.867
6.863
6.854
6.850
6.784
6.771
3.810
3.193
3.181
3.177
3.168
3.164
3.152
3.145
3.003
2.995
2.991
2.986
2.983
2.978
2.975
2.967
1.979
1.966
1.957
1.951
1.942
1.929
1.839
1.835
1.827
1.819
1.815
1.807
1.799
1.794
1.579
1.571
1.567
1.559
1.549
1.546
1.538
1.420
1.405
1.399
1.395
1.385
1.372
MeO
OH
O
N
Me
N
H
O
1.73
0.97
1.01
1.00
3.14
1.06
3.03
1.07
1.12
1.11
1.08
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

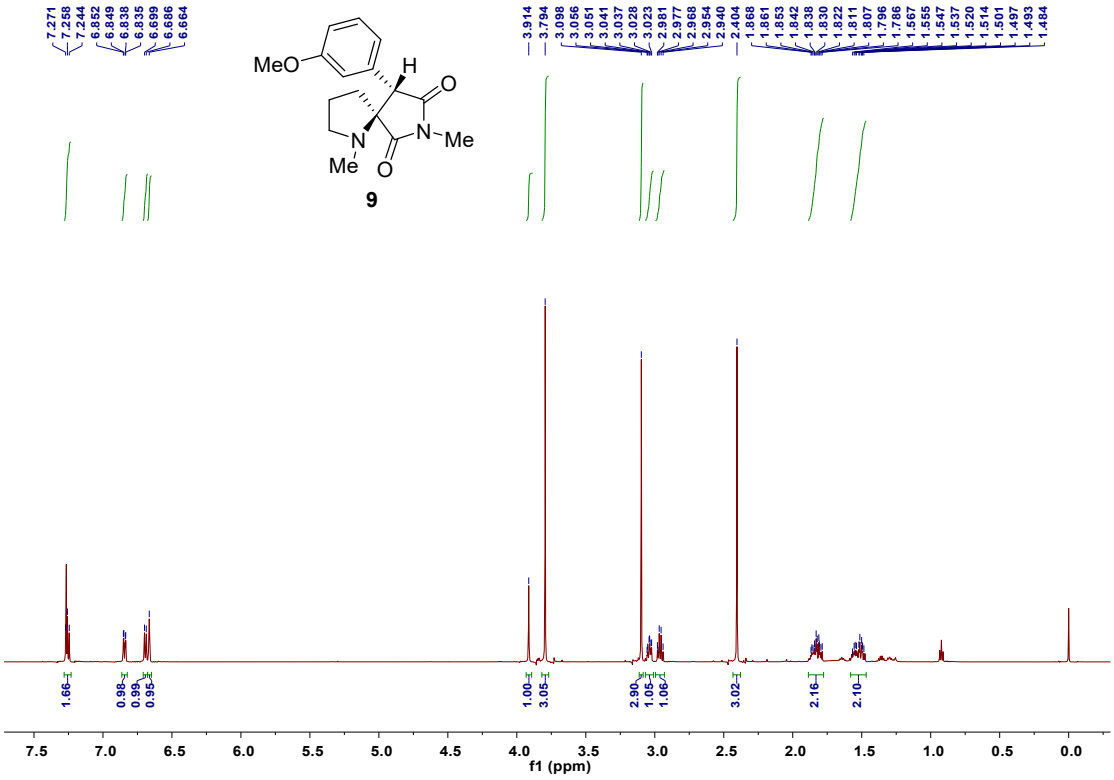
6a

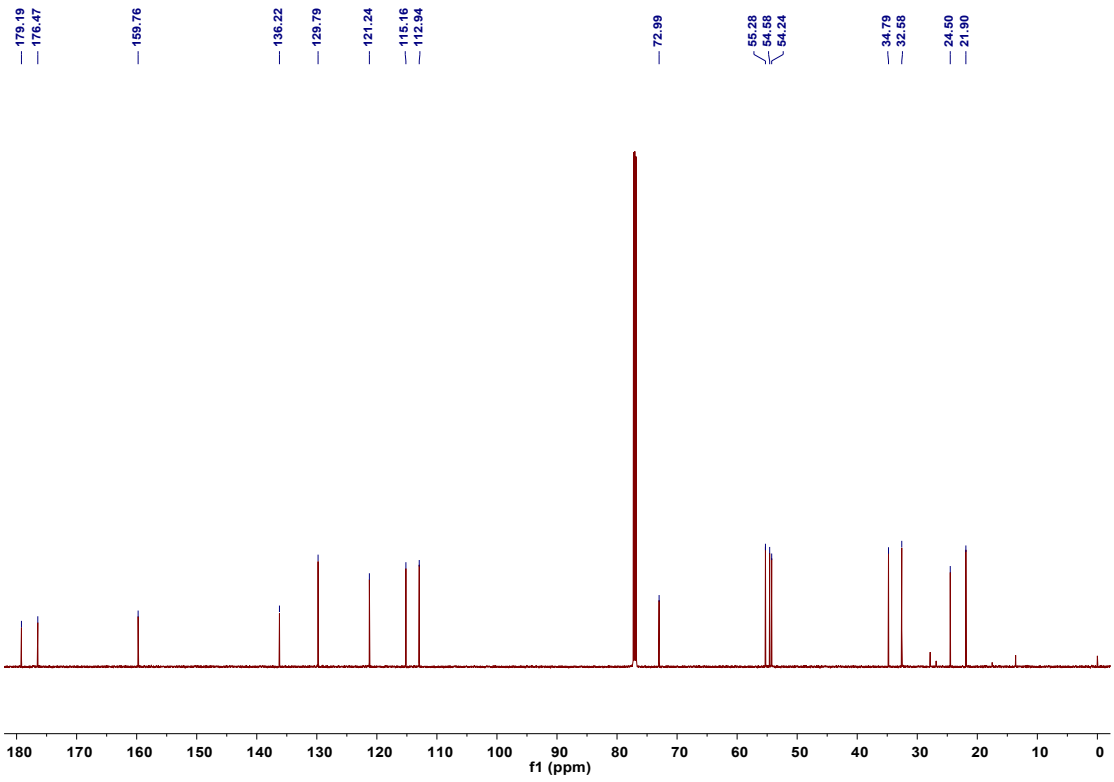

179.12
177.15
159.65
139.55
129.41
118.15
113.63
111.99
78.10
72.81
55.32
47.67
32.35
26.43
25.40
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

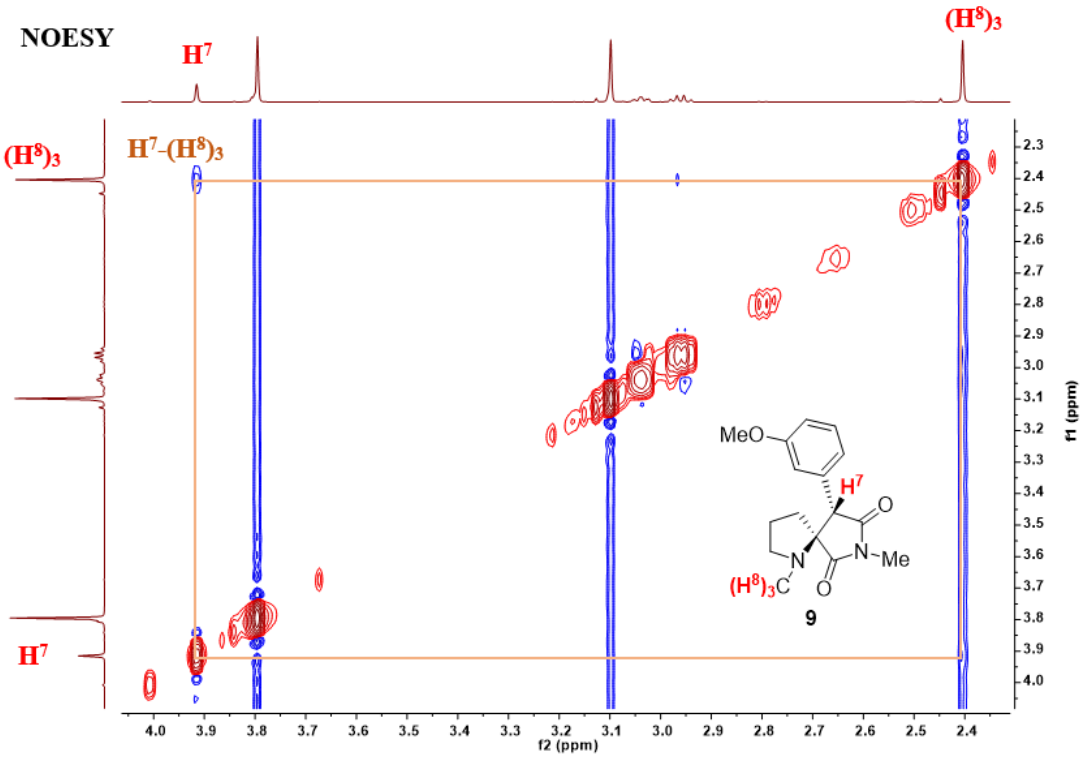

8.472
7.381
7.377
7.374
7.282
7.209
7.196
7.193
6.816
6.813
6.803
6.799
4.720
4.123
3.802
3.176
3.166
3.163
3.156
3.146
3.136
3.126
2.903
2.895
2.810
2.798
2.790
2.778
2.400
2.386
2.382
2.378
2.368
2.364
2.360
2.346
2.164
2.160
2.148
2.144
2.141
2.137
2.125
2.122
1.801
1.794
1.791
1.788
1.784
1.780
1.777
1.769
1.767
1.756
1.689
1.680
1.678
1.674
1.671
1.669
1.662
1.659
1.656
1.652
1.651
1.642
1.634
0.669
OMe
OH
O
N
Me
H
O
N
H
O
7a
1.02
1.00
1.91
1.05
1.00
0.97
1.04
3.13
1.06
3.02
1.07
1.08
1.06
1.07
1.05
9.22
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

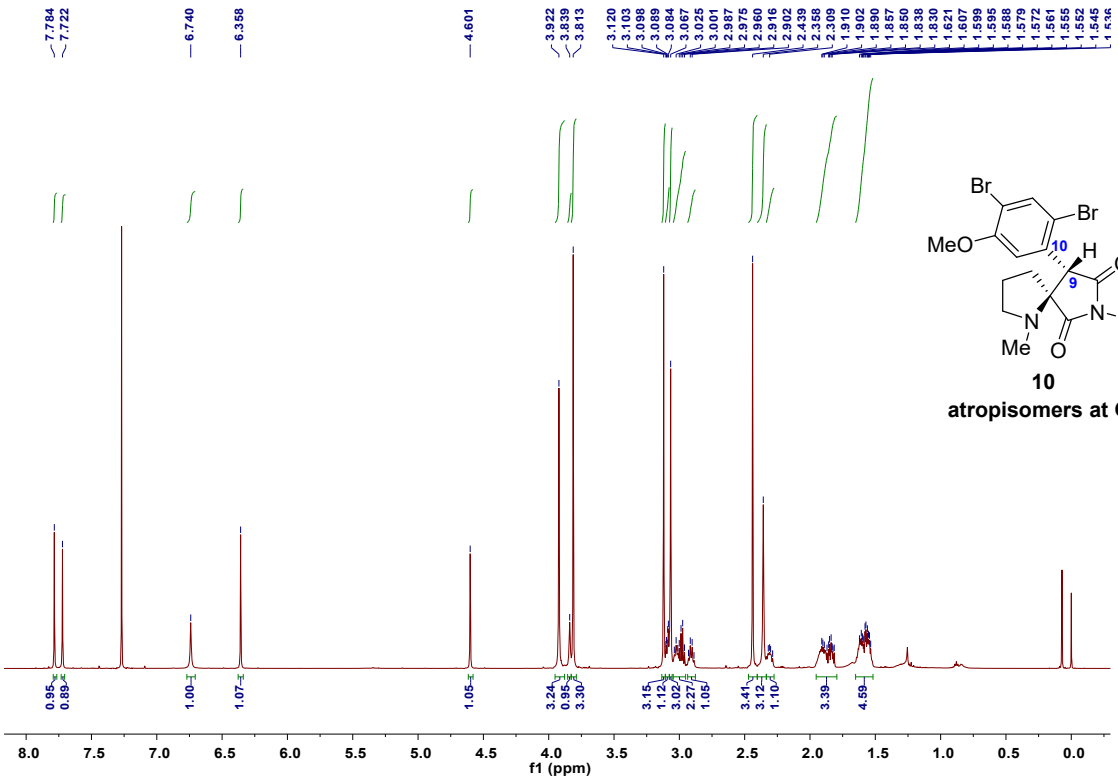

178.09
172.93
159.37
140.56
128.93
119.43
113.92
113.45
103.72
81.62
79.99
77.24
77.03
76.82
56.89
55.31
35.91
35.58
26.88
24.15
24.06
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MeO
OH
O
N
Me
N
Me
O
8
f1 (ppm)
f1 (ppm)


7.271
7.258
7.244
6.852
6.849
6.838
6.835
6.699
6.686
6.664
3.914
3.794
3.098
3.056
3.051
3.041
3.037
3.028
3.023
2.981
2.977
2.968
2.954
2.940
2.404
1.868
1.861
1.853
1.842
1.838
1.830
1.822
1.811
1.807
1.796
1.786
1.567
1.555
1.547
1.537
1.520
1.514
1.501
1.497
1.493
1.484
MeO
H
O
N
Me
N
Me
O
9
1.66
0.98
0.99
0.95
1.00
3.05
2.90
1.05
1.06
3.02
2.16
2.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

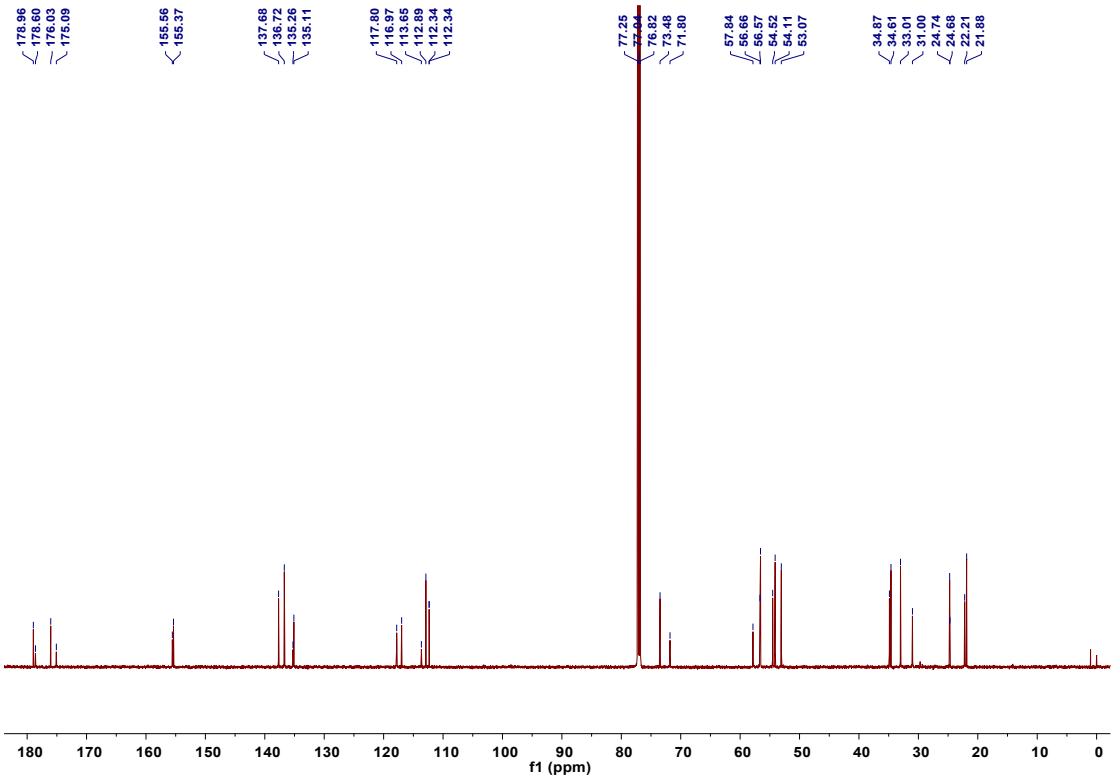

179.19
176.47
159.76
136.22
129.79
121.24
115.16
112.94
72.99
55.28
54.58
54.24
34.79
32.58
24.50
21.90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


NOESY
H7
(H8)3
(H8)3
H7-(H8)3
H7
MeO
H7
O
N
N-Me
(H8)3C
O
9
f1 (ppm)
f2 (ppm)

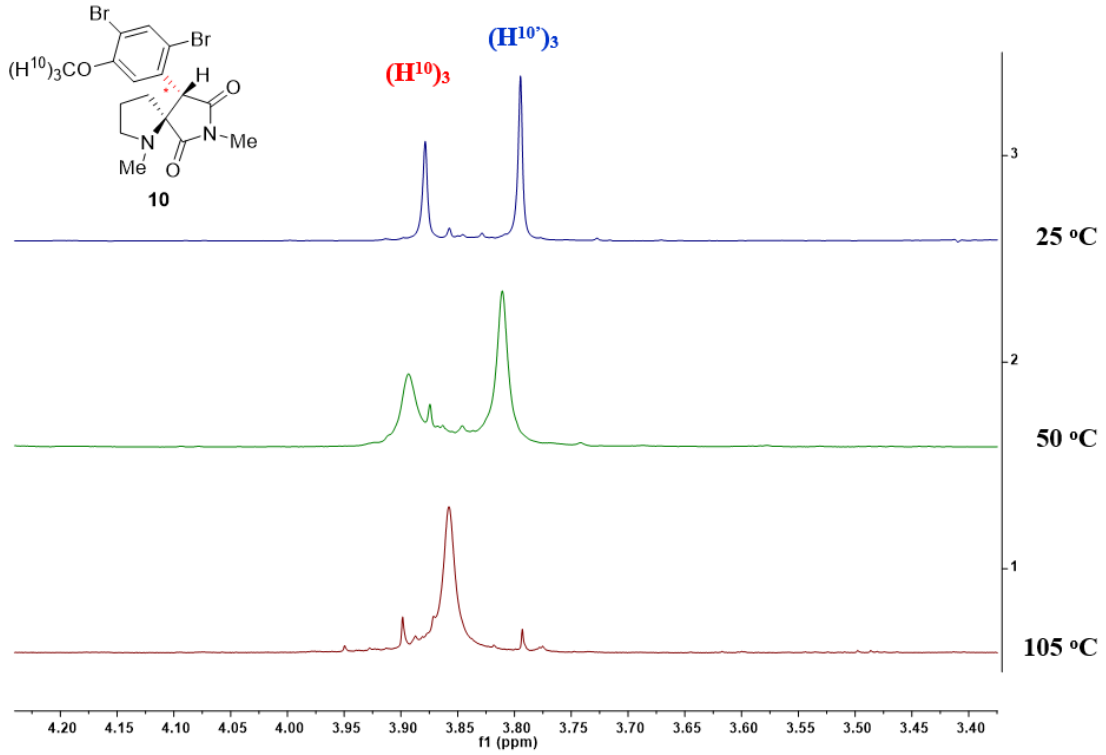


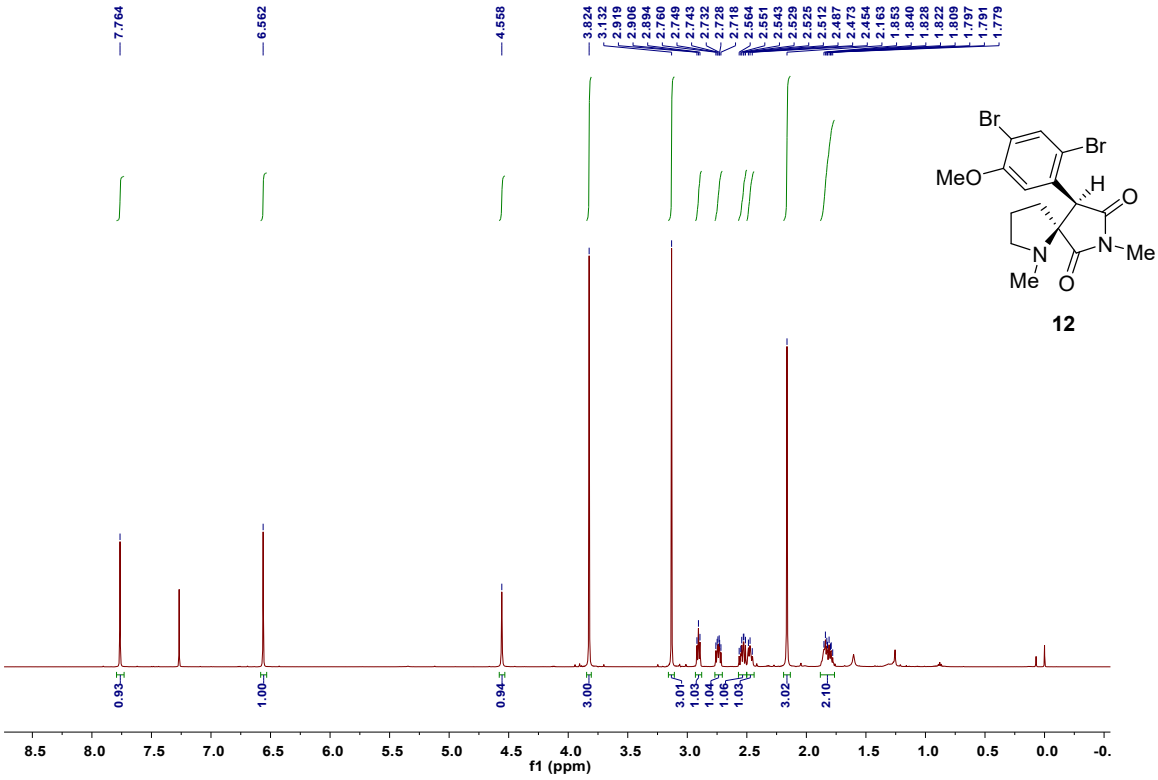
10

atropisomers at C9-C10 bond



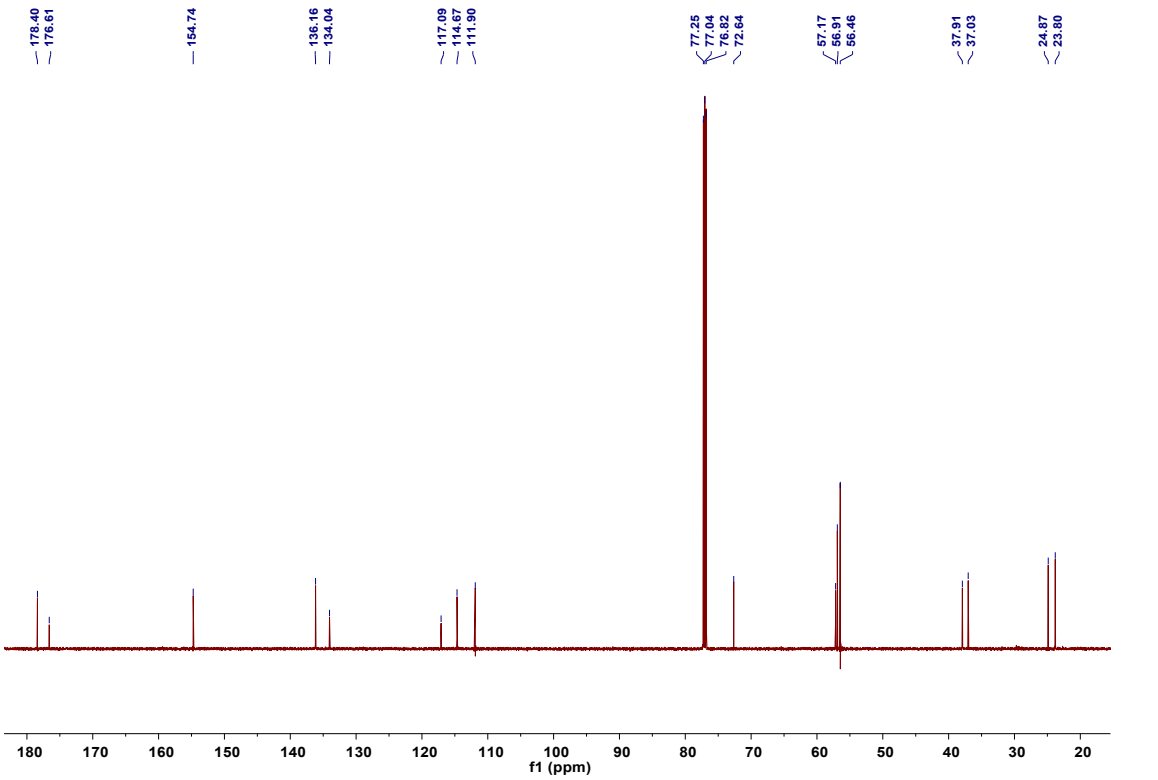
Variable-temperature NMR spectroscopy in DMSO-*d6* was used to investigate the atropisomers of **10**, in which two sets of signals in ^{1}H NMR spectra were observed at room temperature and coalesced over 105 °C.

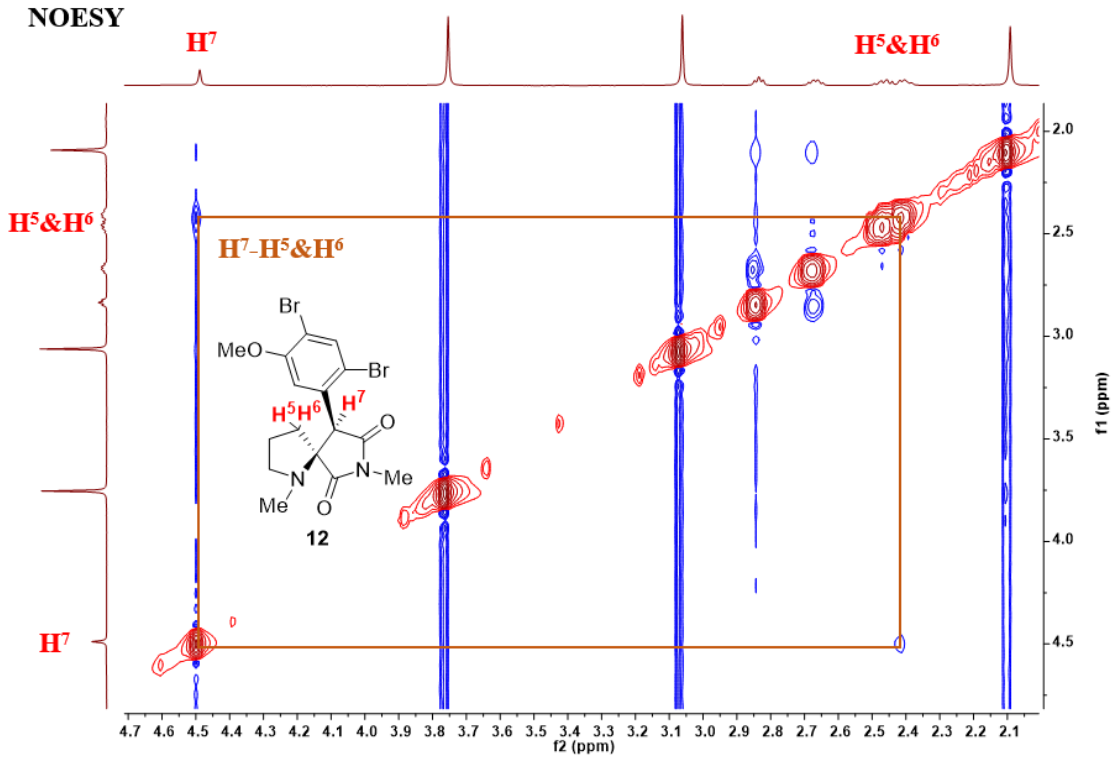


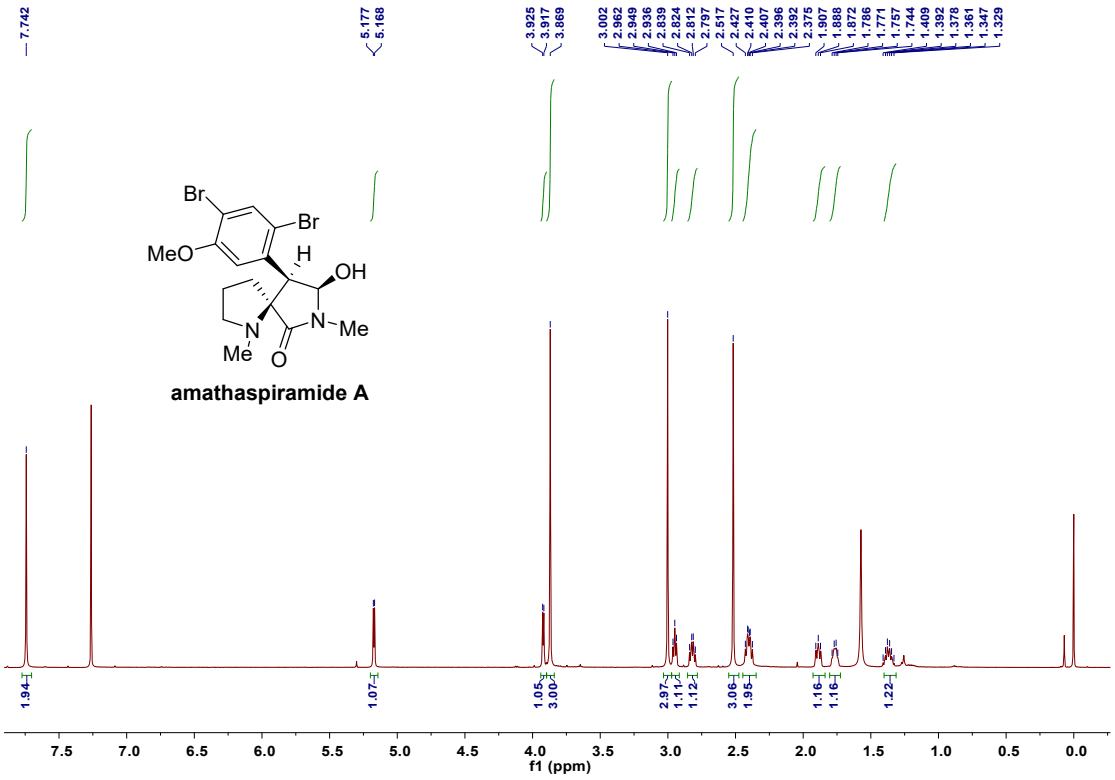

7.764
6.562
4.558
3.824
3.132
2.919
2.906
2.894
2.760
2.749
2.743
2.732
2.728
2.718
2.564
2.551
2.543
2.529
2.525
2.512
2.487
2.473
2.454
2.163
1.853
1.840
1.828
1.822
1.809
1.797
1.791
1.779
0.93
1.00
0.94
3.00
3.01
1.03
1.04
1.06
1.03
3.02
2.10
f1 (ppm)

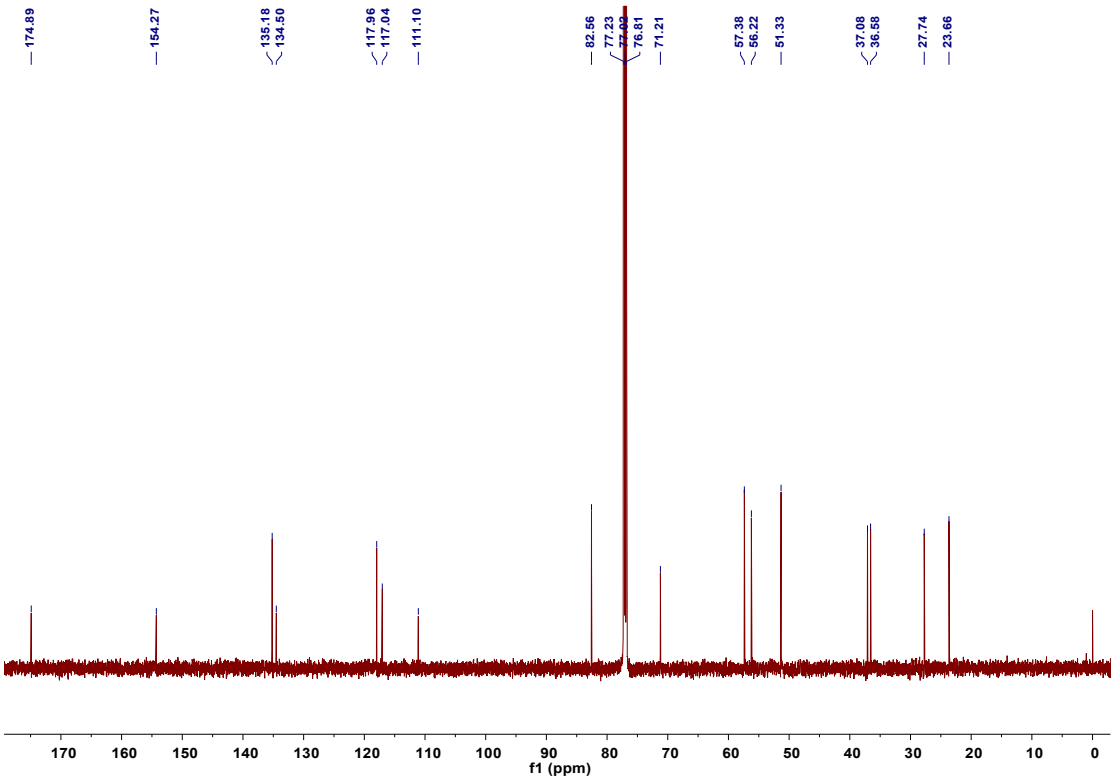
Br
Br
MeO
H
O
N
Me
N
Me
O

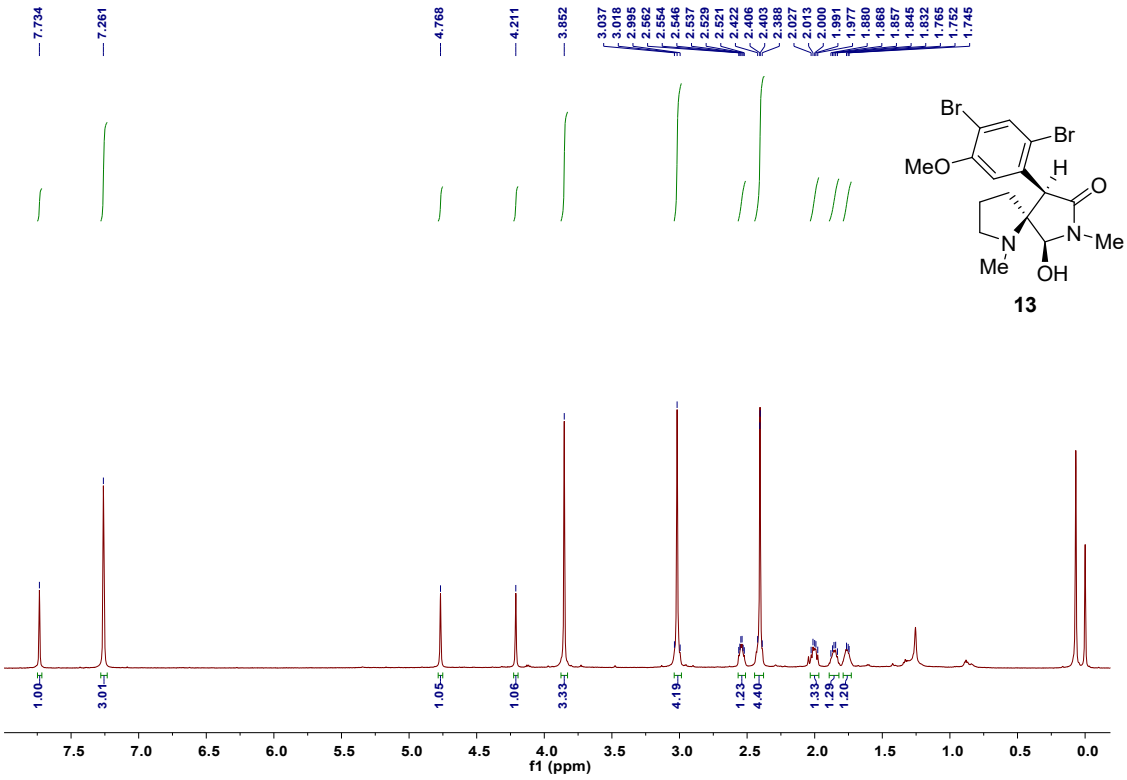
12


178.40
176.61
154.74
136.16
134.04
117.09
114.67
111.90
77.25
77.04
76.82
72.64
57.17
56.91
56.46
37.91
37.03
24.87
23.80
f1 (ppm)

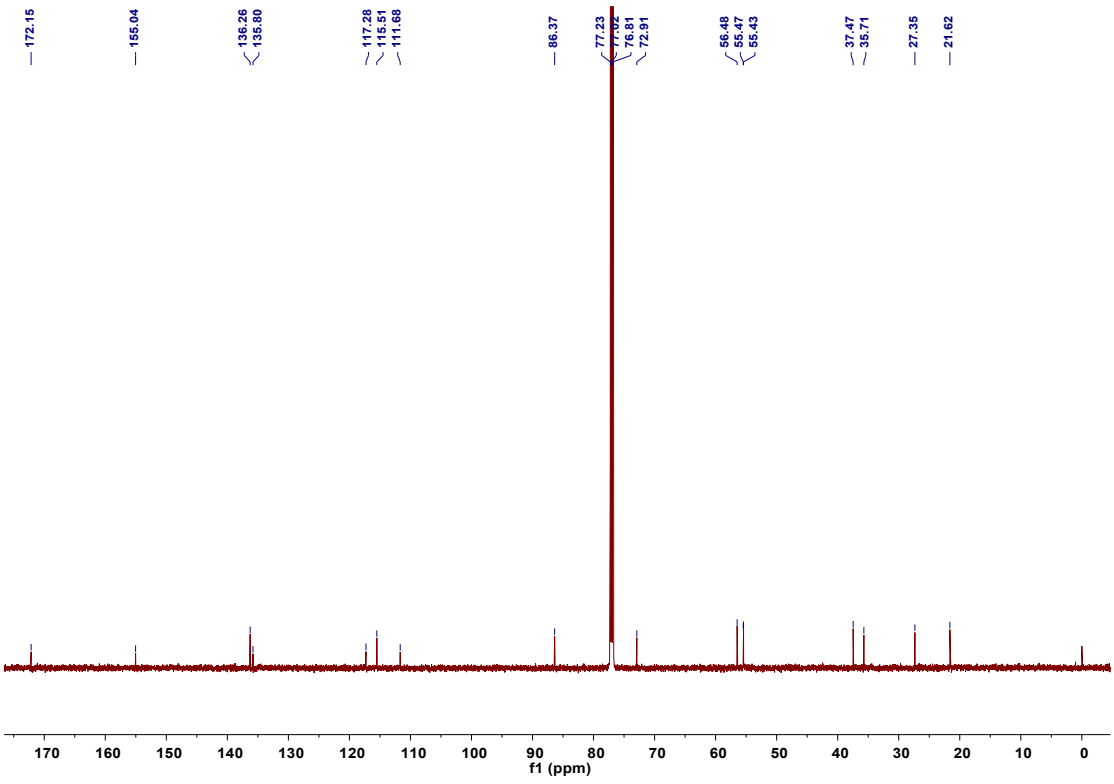

NOESY
H7
H5&H6
H5&H6
H7-H5&H6
Br
MeO
Br
H5H6
H7
O
N
Me
Me
N
O
12
H7
2.0
2.5
3.0
3.5
4.0
4.5
f1 (ppm)
4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1
f2 (ppm)

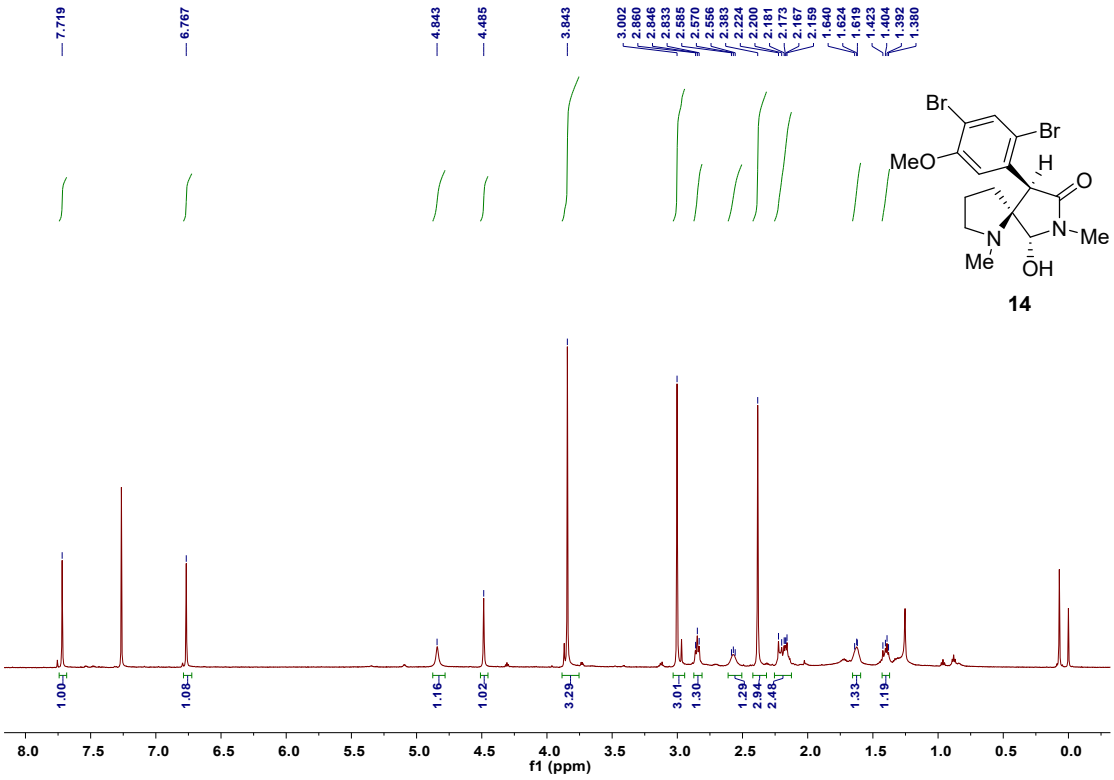

7.742
5.177
5.168
3.925
3.917
3.869
3.002
2.962
2.949
2.936
2.839
2.824
2.812
2.797
2.517
2.427
2.410
2.407
2.396
2.392
2.375
1.907
1.888
1.872
1.786
1.771
1.757
1.744
1.409
1.392
1.378
1.361
1.347
1.329
Br
Br
MeO
H
OH
N
N
Me
Me
O
amathaspiramide A
1.94
1.07
1.05
3.00
2.97
1.11
1.12
3.06
1.95
1.16
1.16
1.22
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


174.89
154.27
135.18
134.50
117.96
117.04
111.10
82.56
77.23
77.02
76.81
71.21
57.38
56.22
51.33
37.08
36.58
27.74
23.66
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

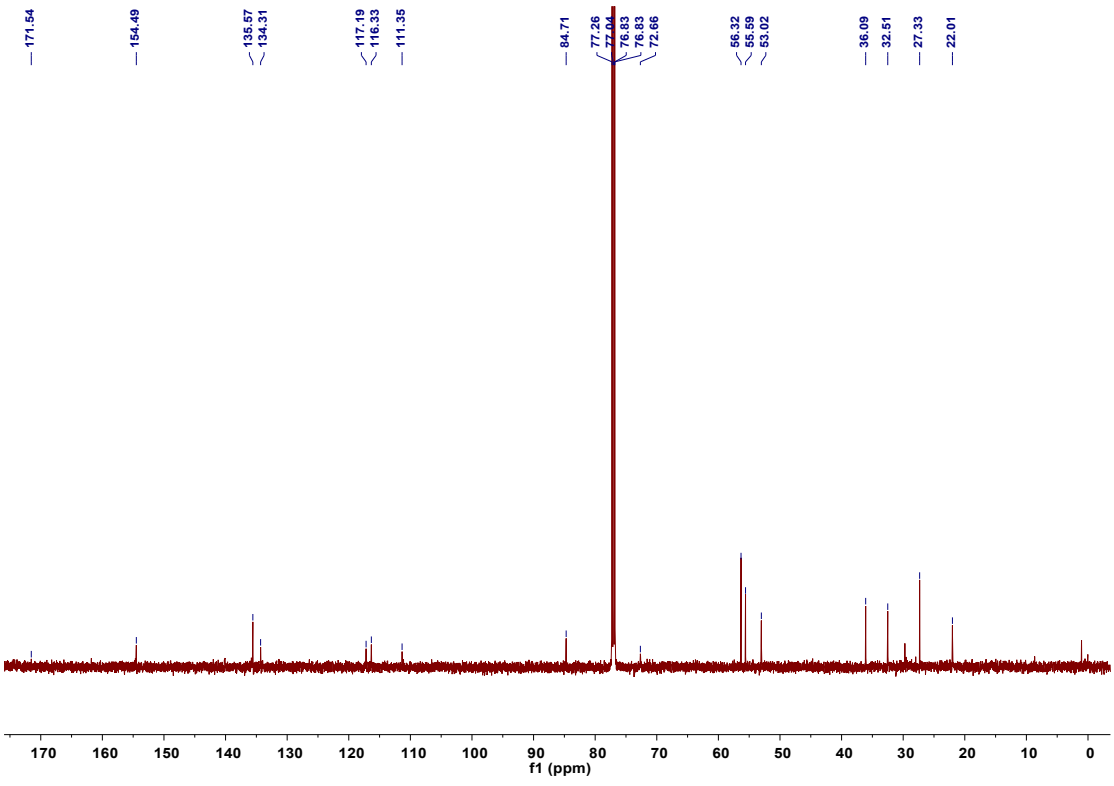

7.734
7.261
4.768
4.211
3.852
3.037
3.018
2.995
2.562
2.554
2.546
2.537
2.529
2.521
2.422
2.406
2.403
2.388
2.027
2.013
2.000
1.991
1.977
1.880
1.868
1.857
1.845
1.832
1.765
1.752
1.745
Br
Br
MeO
H
O
N
Me
Me
N
OH
1.00
3.01
1.05
1.06
3.33
4.19
1.23
4.40
1.33
1.29
1.20
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

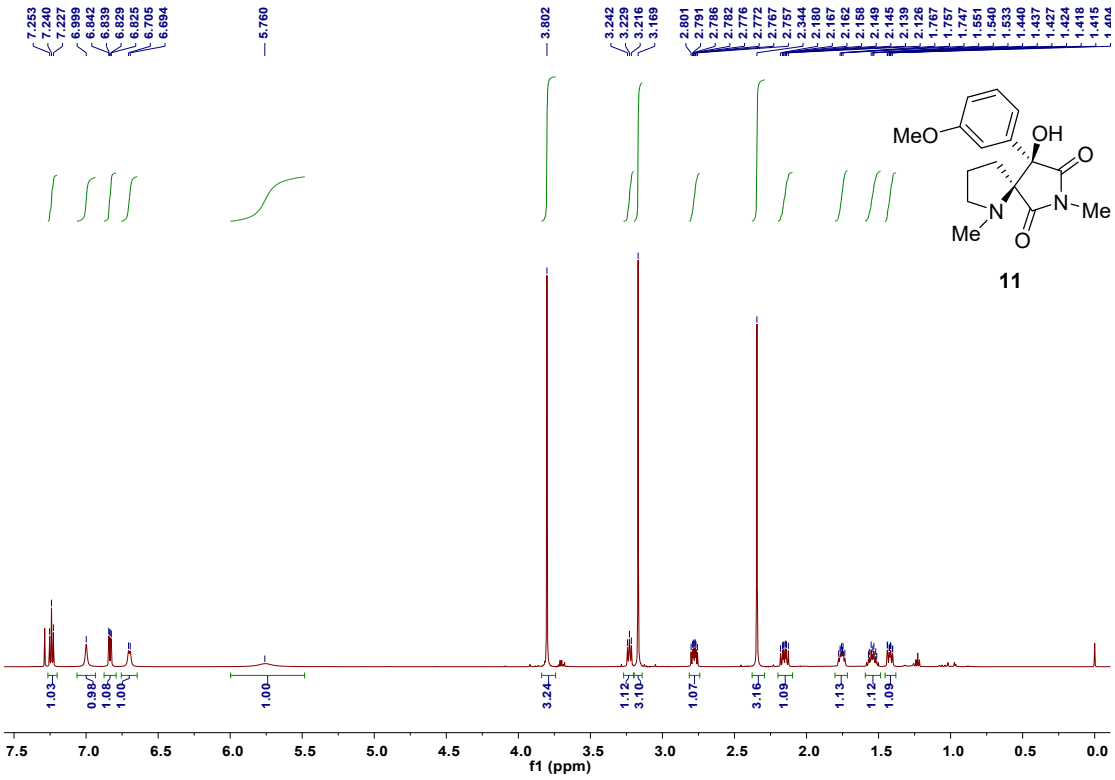
13

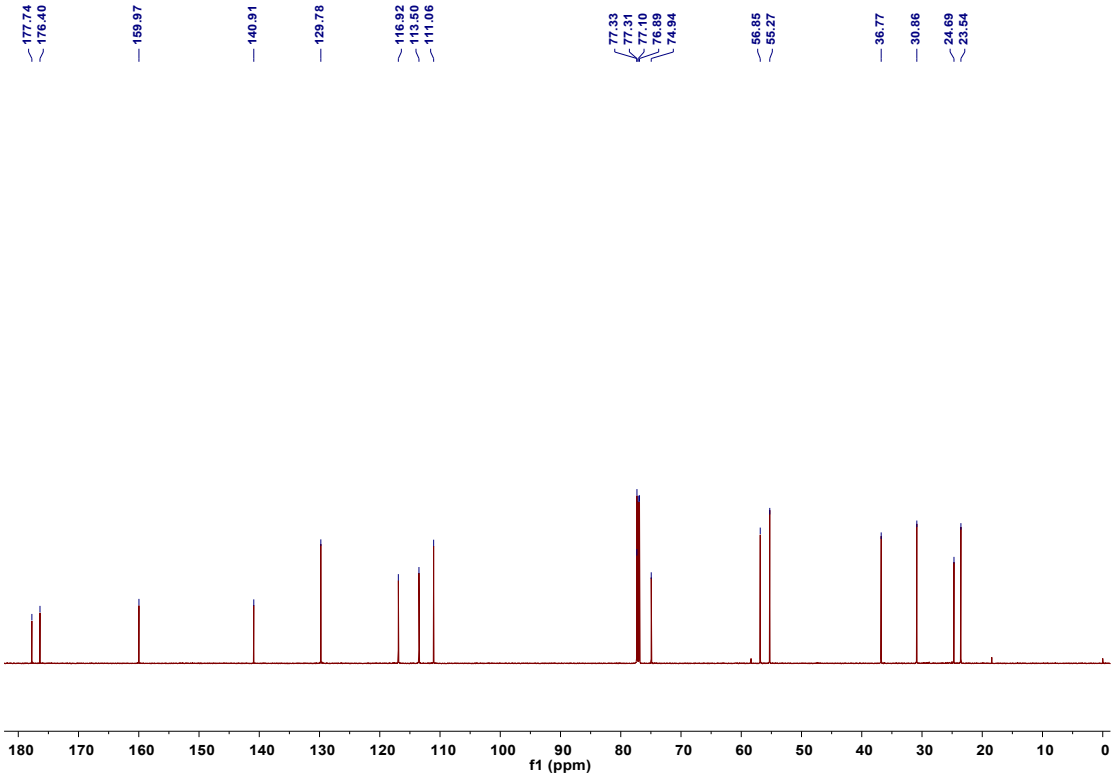

172.15
155.04
136.26
135.80
117.28
115.51
111.68
86.37
77.23
77.02
76.81
72.91
56.48
55.47
55.43
37.47
35.71
27.35
21.62
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

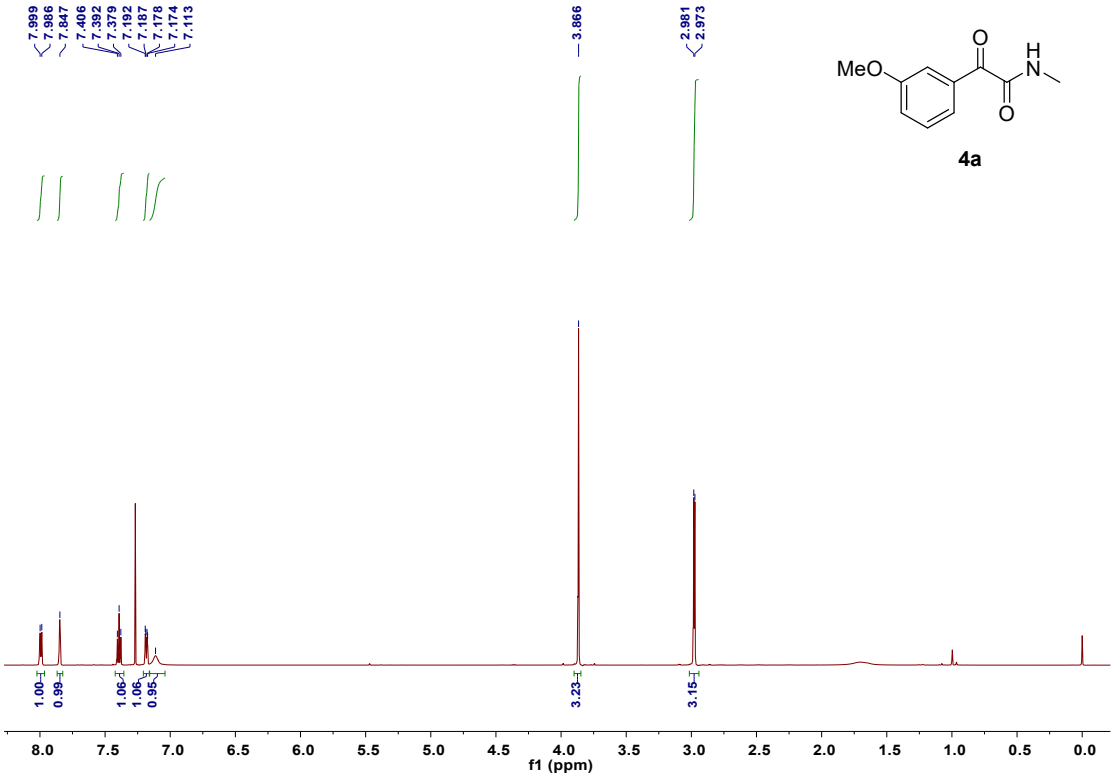

7.719
6.767
4.843
4.485
3.843
3.002
2.860
2.846
2.833
2.585
2.570
2.556
2.383
2.224
2.200
2.181
2.173
2.167
2.159
1.640
1.624
1.619
1.423
1.404
1.392
1.380
Br
Br
MeO
H
O
N
Me
N
Me
OH
1.00
1.08
1.16
1.02
3.29
3.01
1.30
1.29
2.94
2.48
1.33
1.19
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

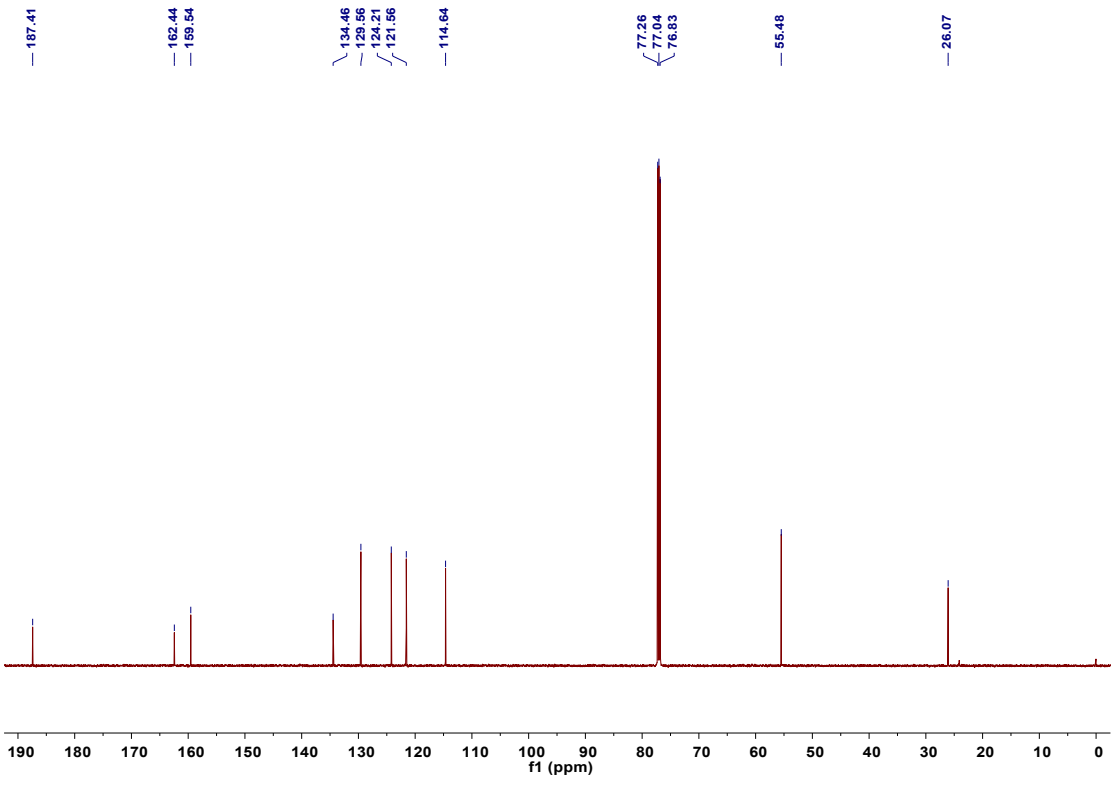
14

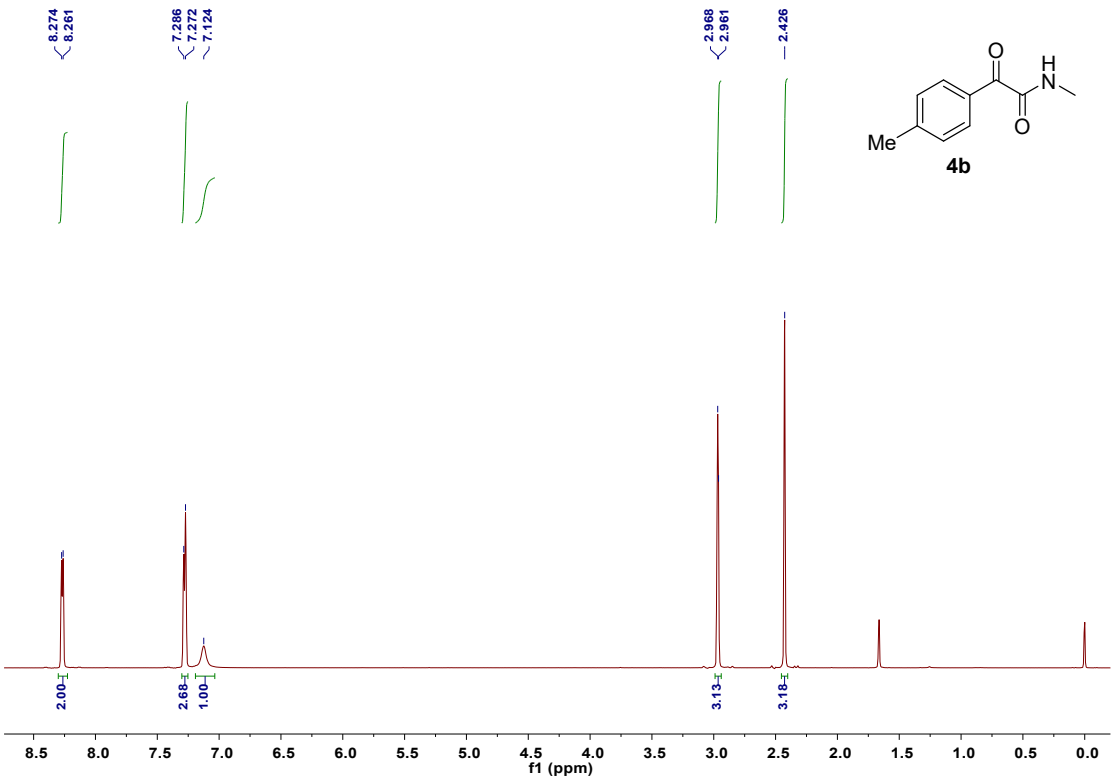

171.54
154.49
135.57
134.31
117.19
116.33
111.35
84.71
77.26
77.04
76.83
76.83
72.66
56.32
55.59
53.02
36.09
32.51
27.33
22.01
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

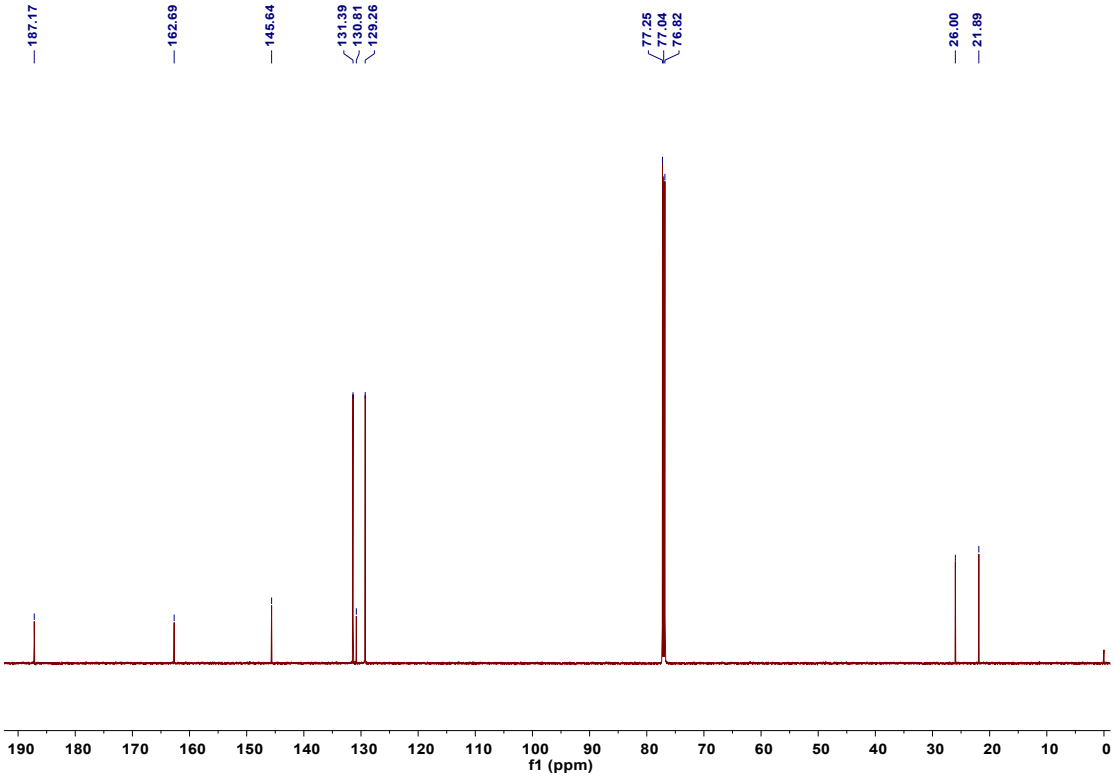

MeO
OH
O
N
Me
N
Me
O
11
f1 (ppm)

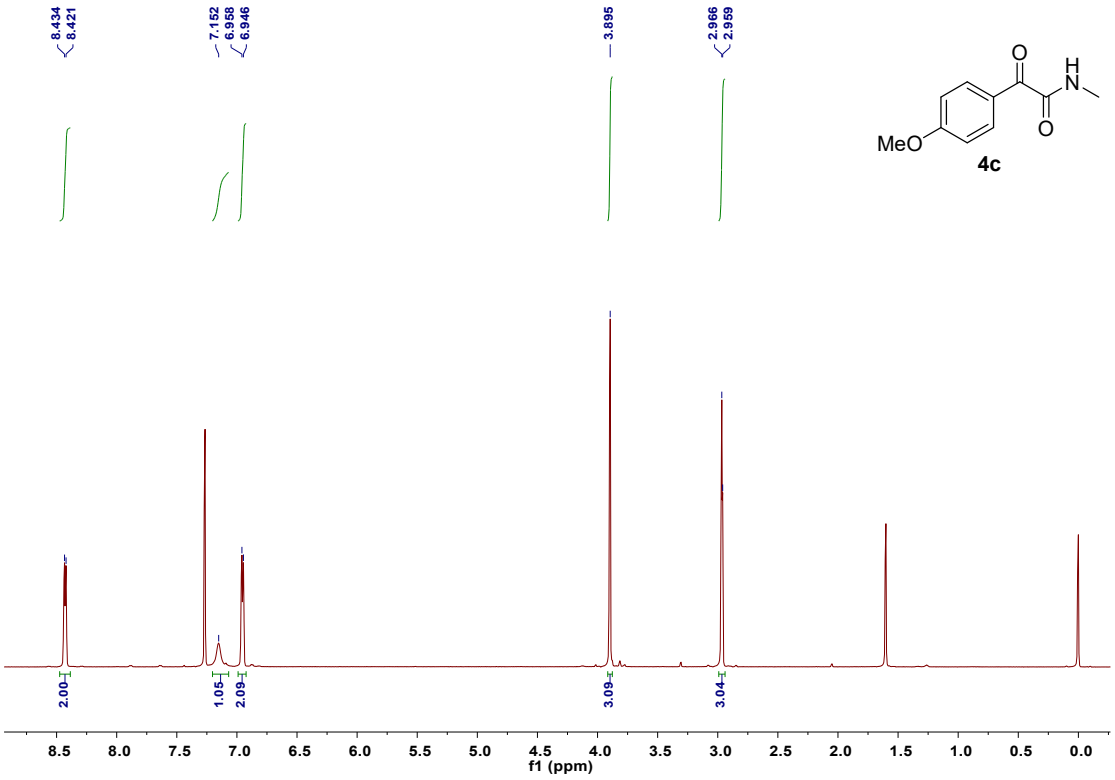

f1 (ppm)

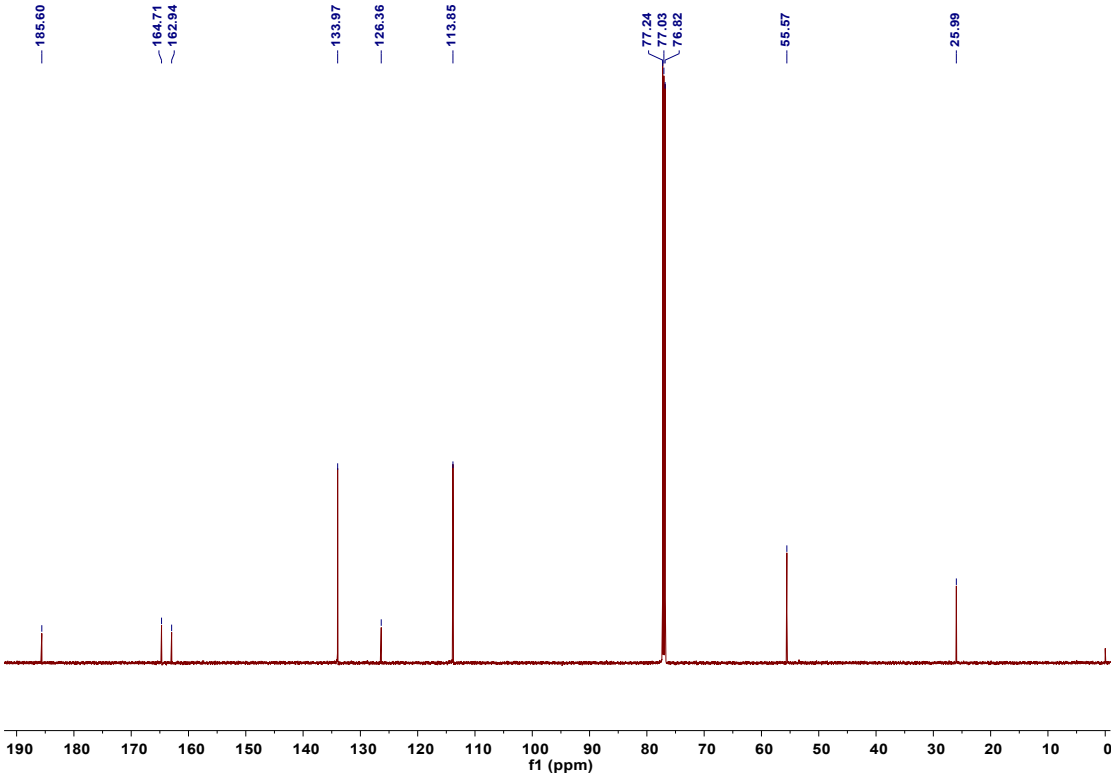

7.999
7.986
7.847
7.406
7.392
7.379
7.192
7.187
7.178
7.174
7.113
3.866
2.981
2.973
MeO
O
H
N
O
4a
1.00
0.99
1.06
1.06
0.95
3.23
3.15
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


187.41
162.44
159.54
134.46
129.56
124.21
121.56
114.64
77.26
77.04
76.83
55.48
26.07
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.274
8.261
7.286
7.272
7.124
2.968
2.961
2.426
O
H
N
O
Me
4b
2.00
2.68
1.00
3.13
3.18
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


187.17
162.69
145.64
131.39
130.81
129.26
77.25
77.04
76.82
26.00
21.89
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.434
8.421
7.152
6.958
6.946
3.895
2.966
2.959
O
H
N
O
MeO
4c
2.00
1.05
2.09
3.09
3.04
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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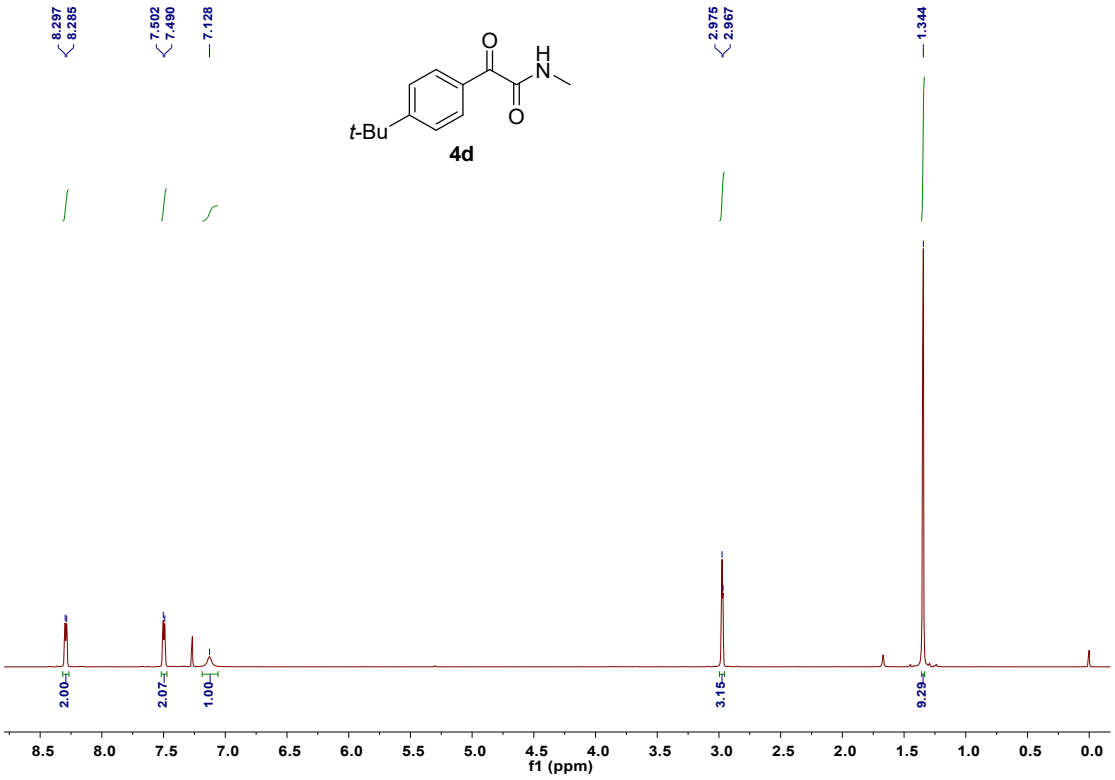
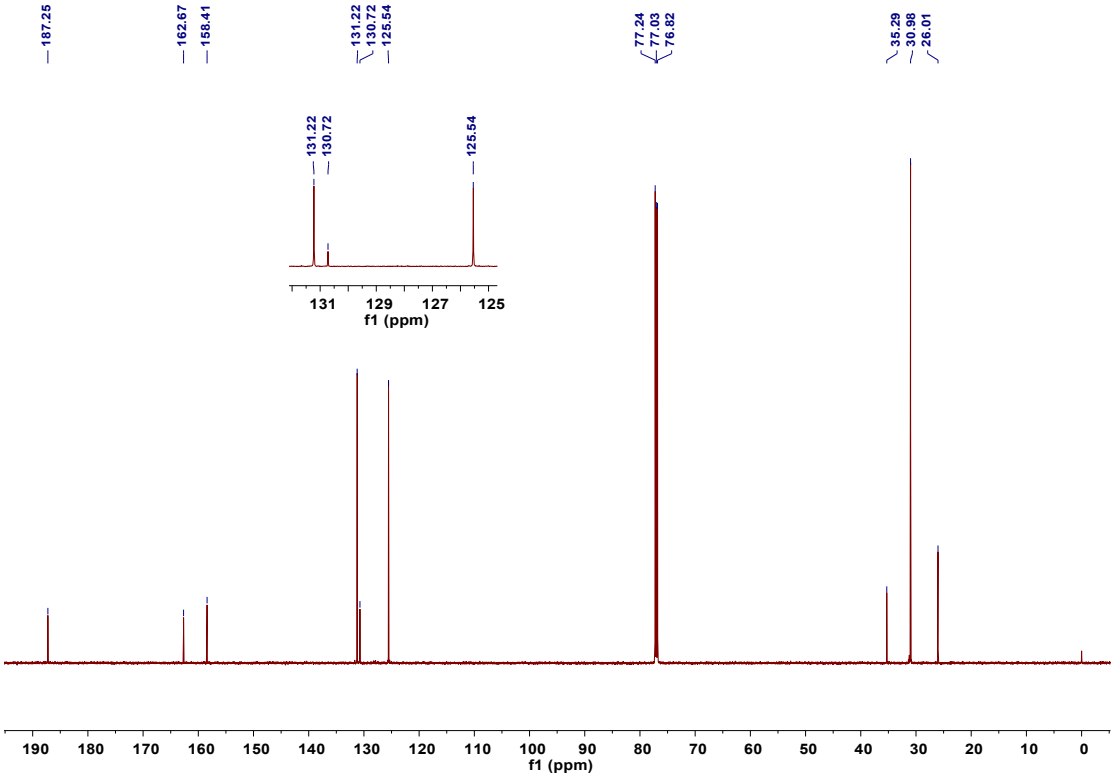
164.71
162.94
133.97
126.36
113.85
77.24
77.03
76.82
55.57
25.99
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.297
8.285
7.502
7.490
7.128
2.975
2.967
1.344
O
H
N
O
t-Bu
4d
2.00
2.07
1.00
3.15
9.29
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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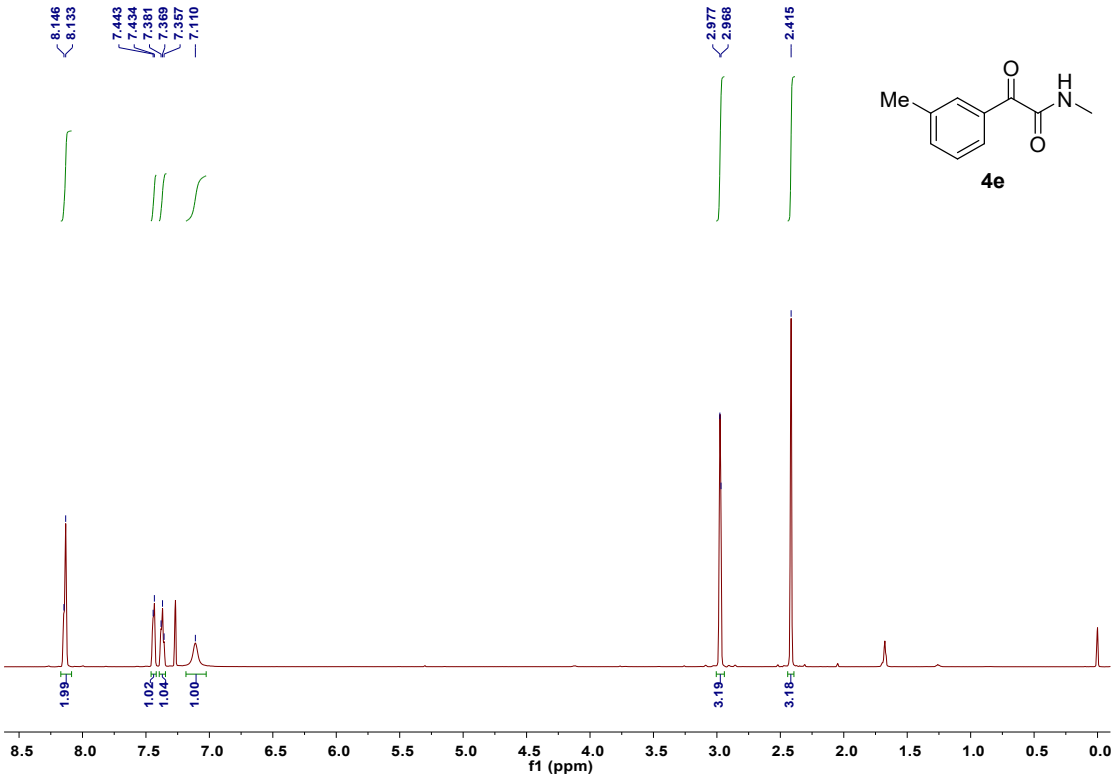
162.67
158.41
131.22
130.72
125.54
77.24
77.03
76.82
35.29
30.98
26.01
131.22
130.72
125.54
131 129 127 125
f1 (ppm)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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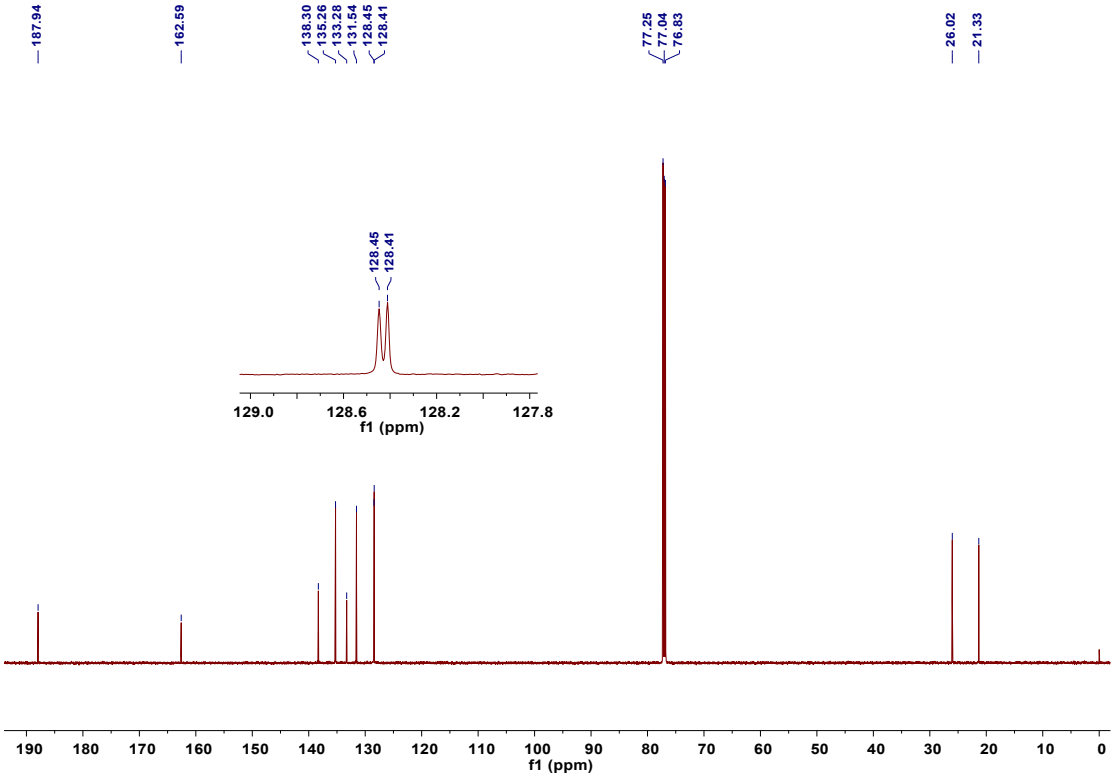
8.133
7.443
7.434
7.381
7.369
7.357
7.110
2.977
2.968
2.415
Me
O
H
N
O
4e
1.99
1.02
1.04
1.00
3.19
3.18
f1 (ppm)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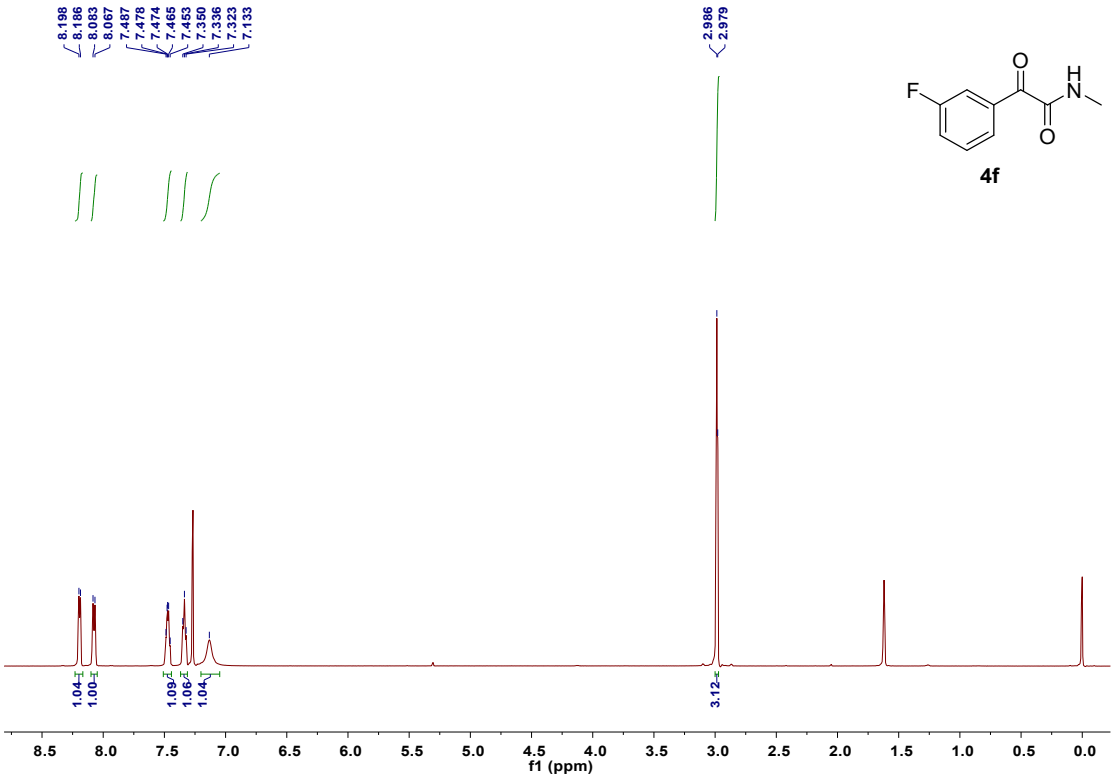
162.59
138.30
135.26
133.28
131.54
128.45
128.41
77.25
77.04
76.83
26.02
21.33
128.45
128.41
f1 (ppm)
f1 (ppm)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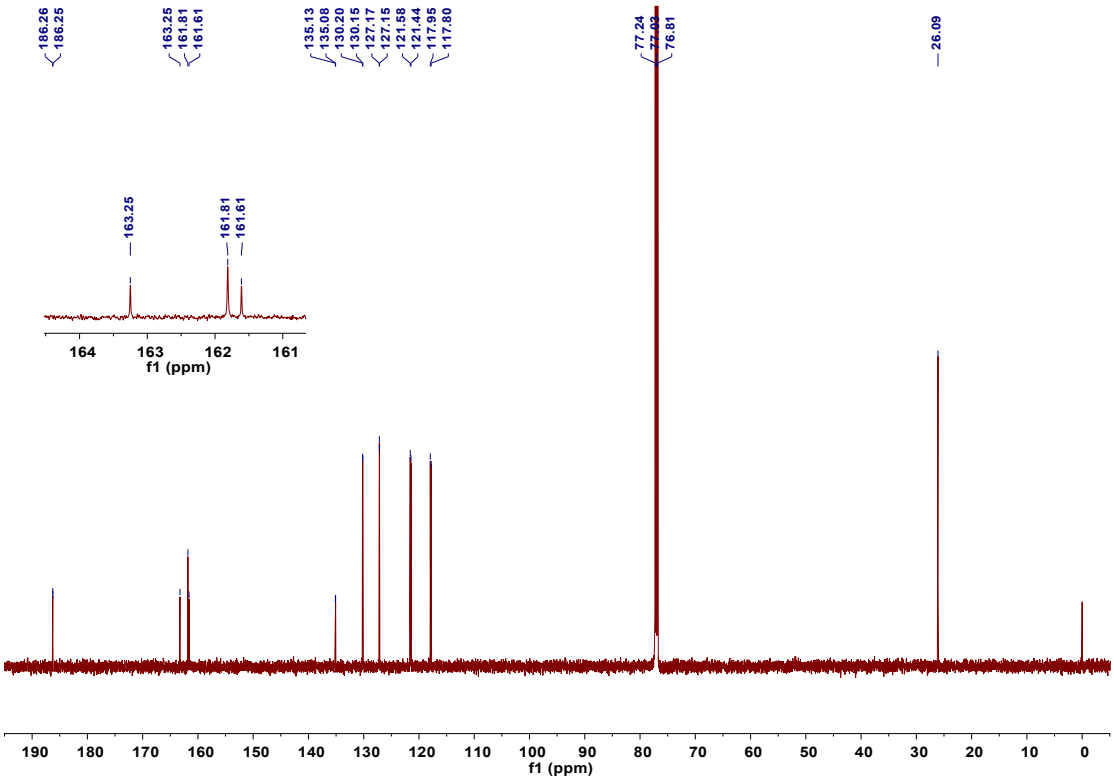
8.186
8.083
8.067
7.487
7.478
7.474
7.465
7.453
7.350
7.336
7.323
7.133
2.986
2.979
F
O
H
N
O
4f
1.04
1.00
1.09
1.06
1.04
3.12
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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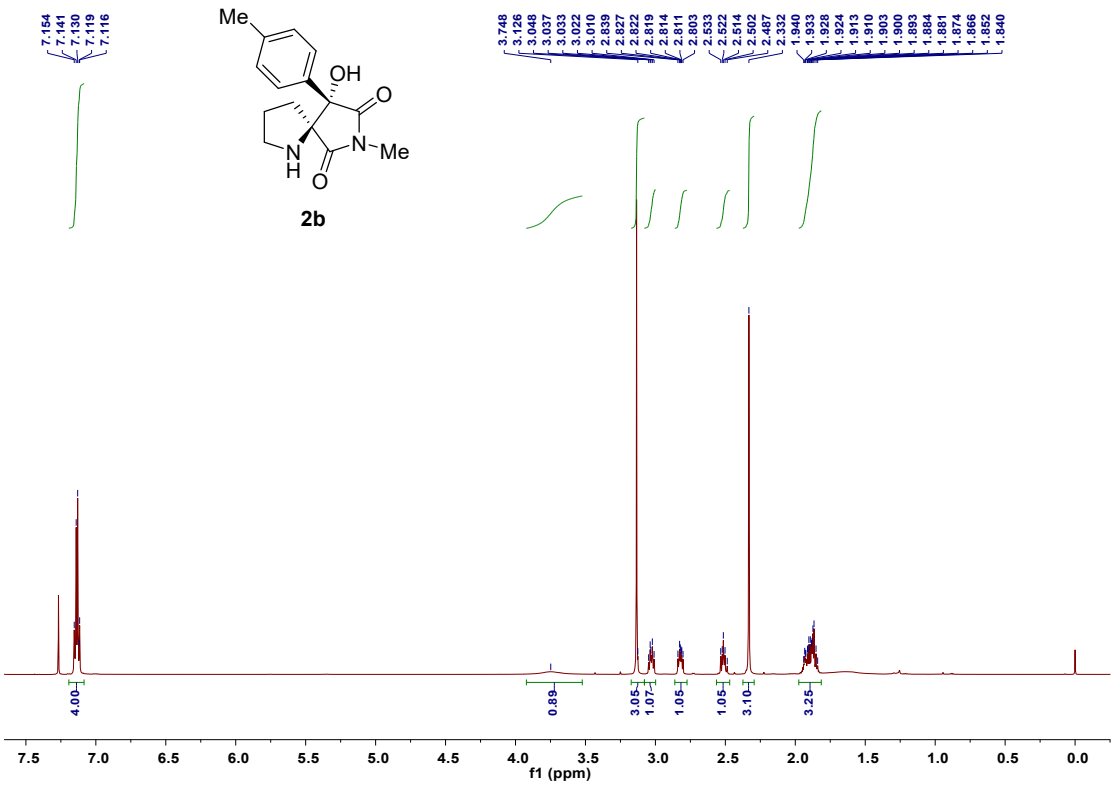
186.25
163.25
161.81
161.61
135.13
135.08
130.20
130.15
127.17
127.15
121.58
121.44
117.95
117.80
77.24
77.02
76.81
26.09
163.25
161.81
161.61
164 163 162 161
f1 (ppm)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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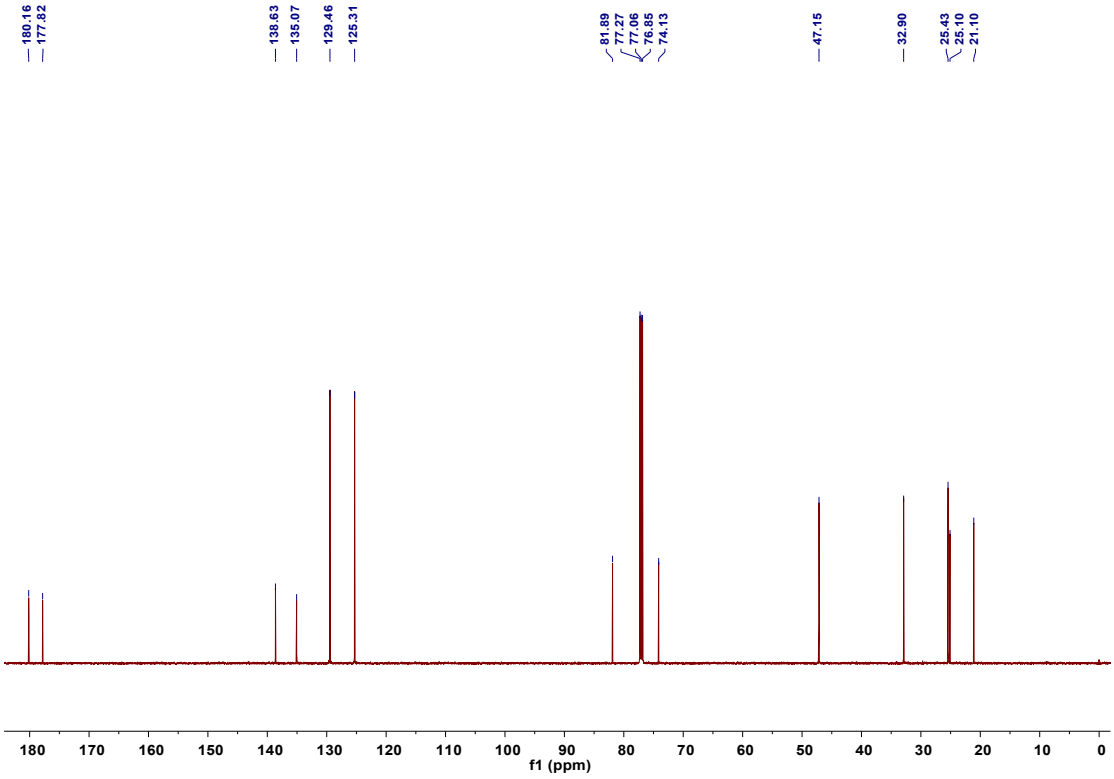
7.141
7.130
7.119
7.116
3.748
3.126
3.048
3.037
3.033
3.022
3.010
2.839
2.827
2.822
2.819
2.814
2.811
2.803
2.533
2.522
2.514
2.502
2.487
2.332
1.940
1.933
1.928
1.924
1.913
1.910
1.903
1.900
1.893
1.884
1.881
1.874
1.866
1.852
1.840
Me
OH
O
N
Me
H
O
2b
4.00
0.89
3.05
1.07
1.05
1.05
3.10
3.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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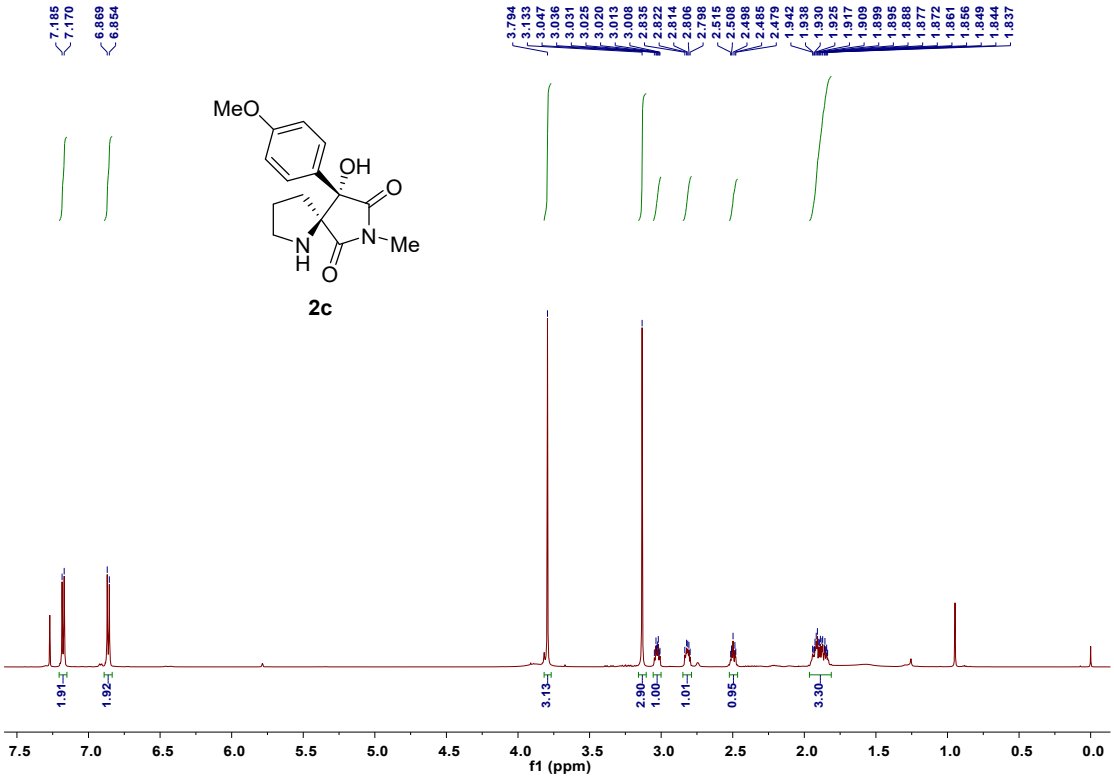
177.82
138.63
135.07
129.46
125.31
81.89
77.27
77.06
76.85
74.13
47.15
32.90
25.43
25.10
21.10
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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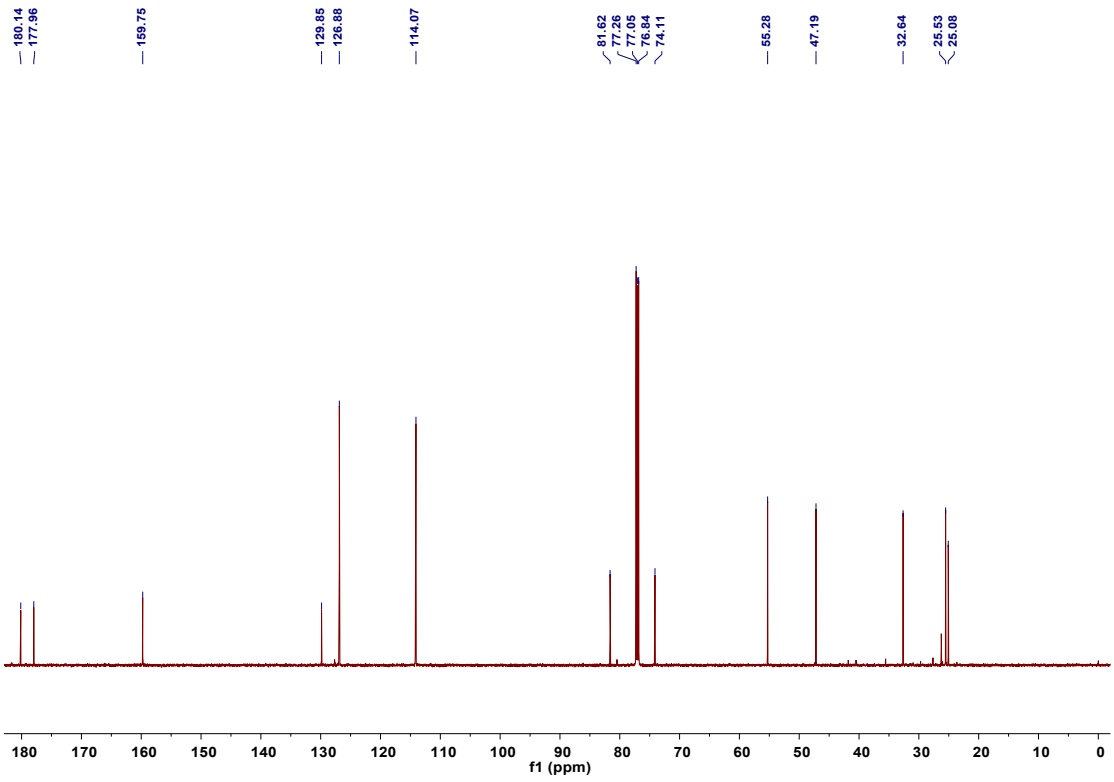
7.170
6.869
6.854
3.794
3.133
3.047
3.036
3.031
3.025
3.020
3.013
3.008
2.835
2.822
2.814
2.806
2.798
2.515
2.508
2.498
2.485
2.479
1.942
1.938
1.930
1.925
1.917
1.909
1.899
1.895
1.888
1.877
1.872
1.861
1.856
1.849
1.844
1.837
MeO
OH
O
N
Me
N
H
O
2c
1.91
1.92
3.13
2.90
1.00
1.01
0.95
3.30
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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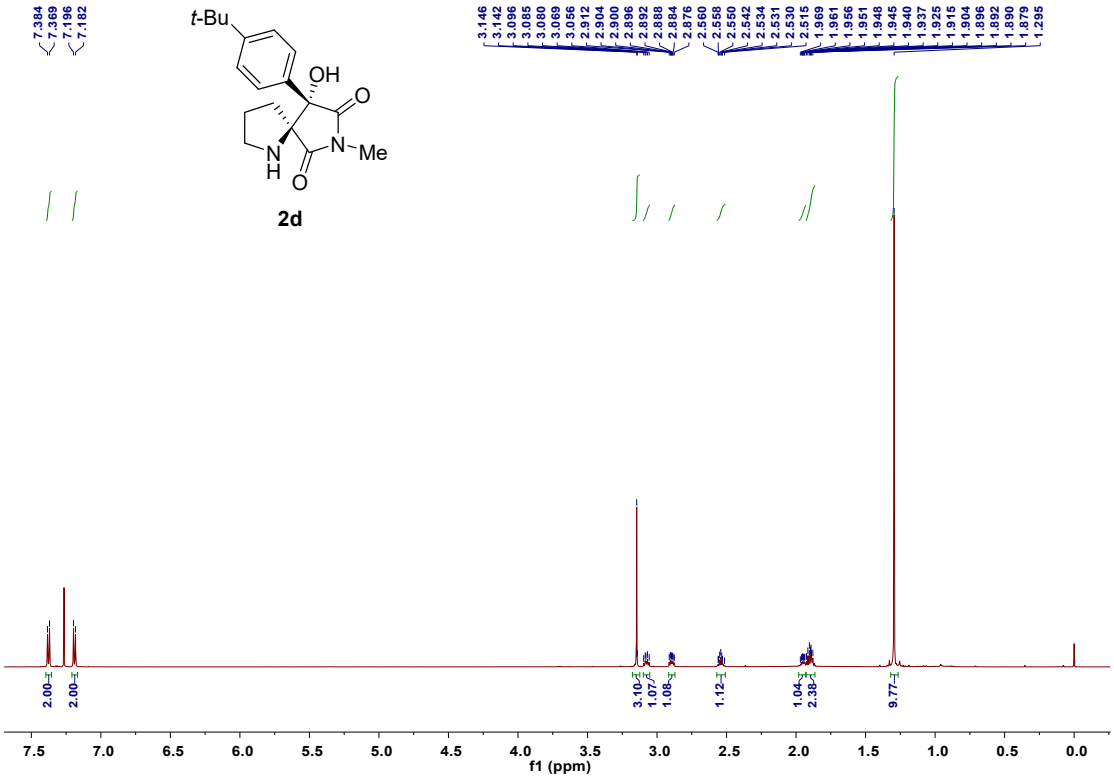
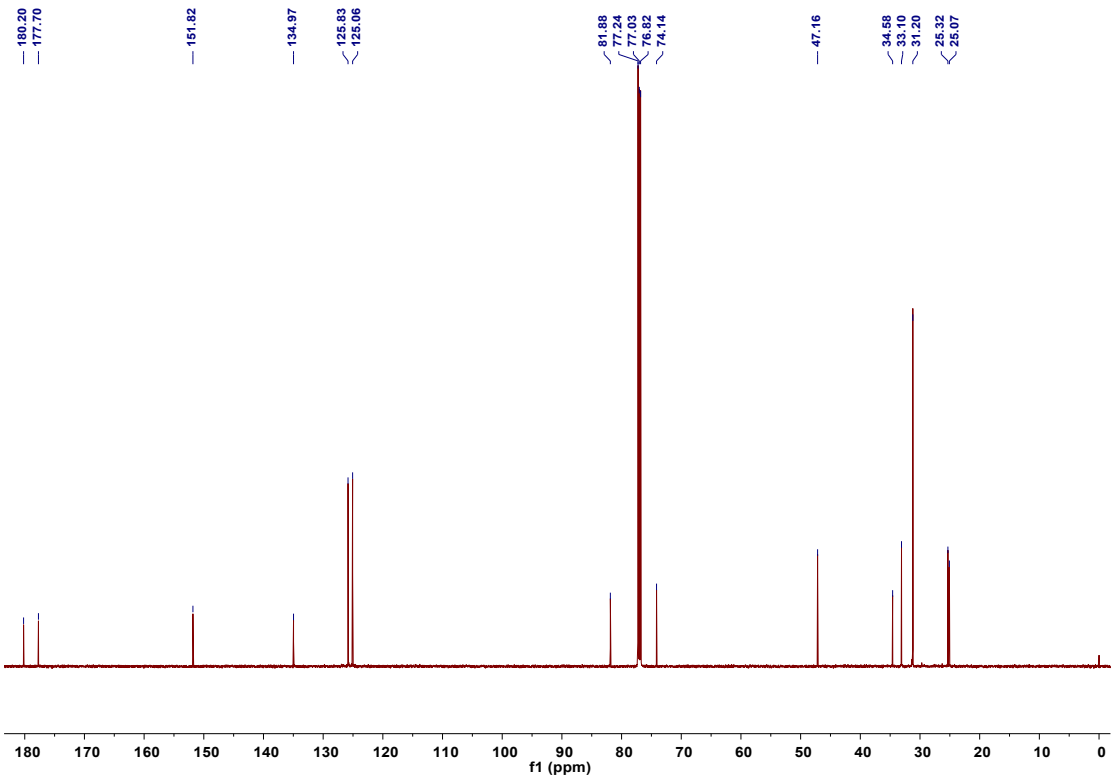
159.75
129.85
126.88
114.07
81.62
77.26
77.05
76.84
74.11
55.28
47.19
32.64
25.53
25.08
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.384
7.369
7.196
7.182
t-Bu
OH
O
N
Me
N
H
O
2d
3.146
3.142
3.096
3.085
3.080
3.069
3.056
2.912
2.904
2.900
2.896
2.892
2.888
2.884
2.876
2.560
2.558
2.550
2.542
2.534
2.531
2.530
2.515
1.969
1.961
1.956
1.951
1.948
1.945
1.940
1.937
1.925
1.915
1.904
1.896
1.892
1.890
1.879
1.295
2.00
2.00
3.10
1.07
1.08
1.12
1.04
2.38
9.77
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


180.20
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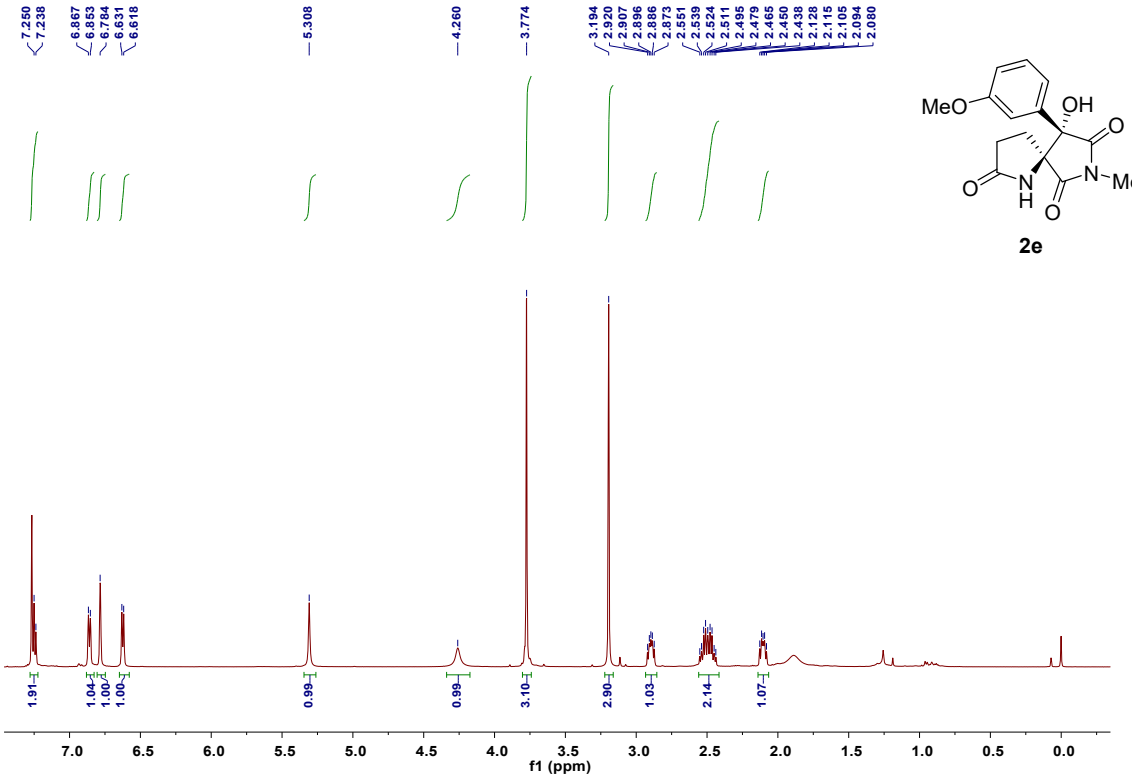
151.82
134.97
125.83
125.06
81.88
77.24
77.03
76.82
74.14
47.16
34.58
33.10
31.20
25.32
25.07
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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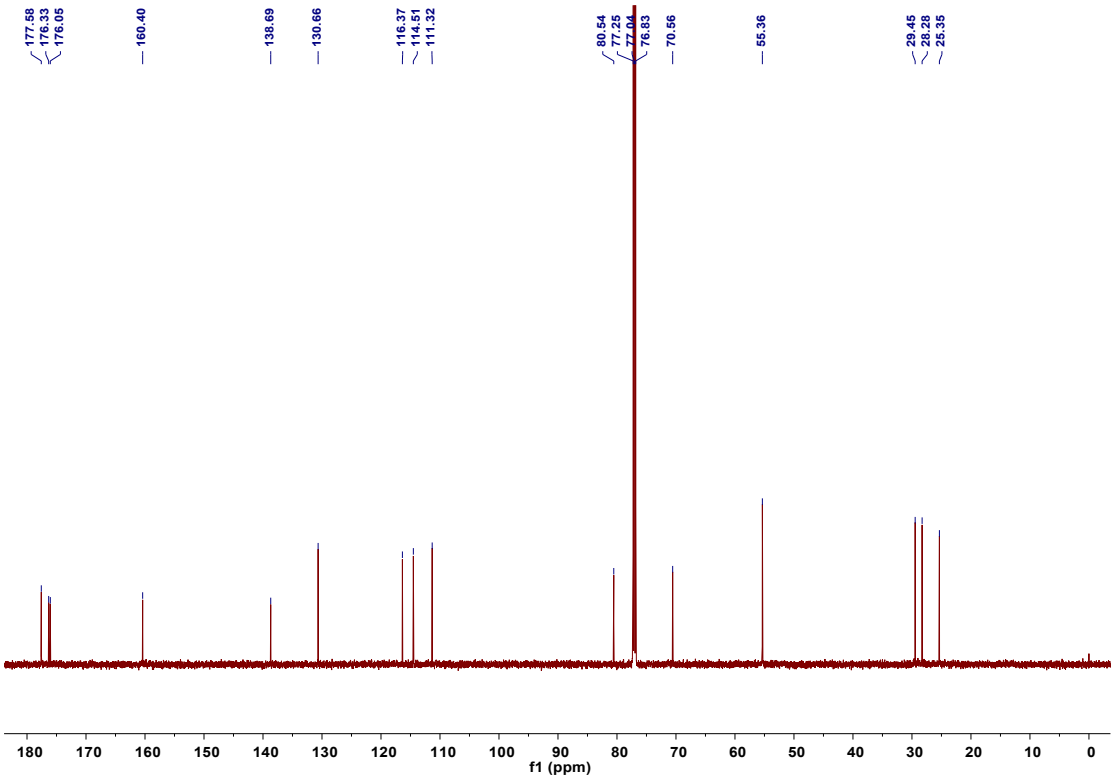
7.238
6.867
6.853
6.784
6.631
6.618
5.308
4.260
3.774
3.194
2.920
2.907
2.896
2.886
2.873
2.551
2.539
2.524
2.511
2.495
2.479
2.465
2.450
2.438
2.128
2.115
2.105
2.094
2.080
MeO
OH
O
N
Me
O
N
H
O
2e
1.91
1.04
1.00
1.00
0.99
0.99
3.10
2.90
1.03
2.14
1.07
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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176.33
176.05
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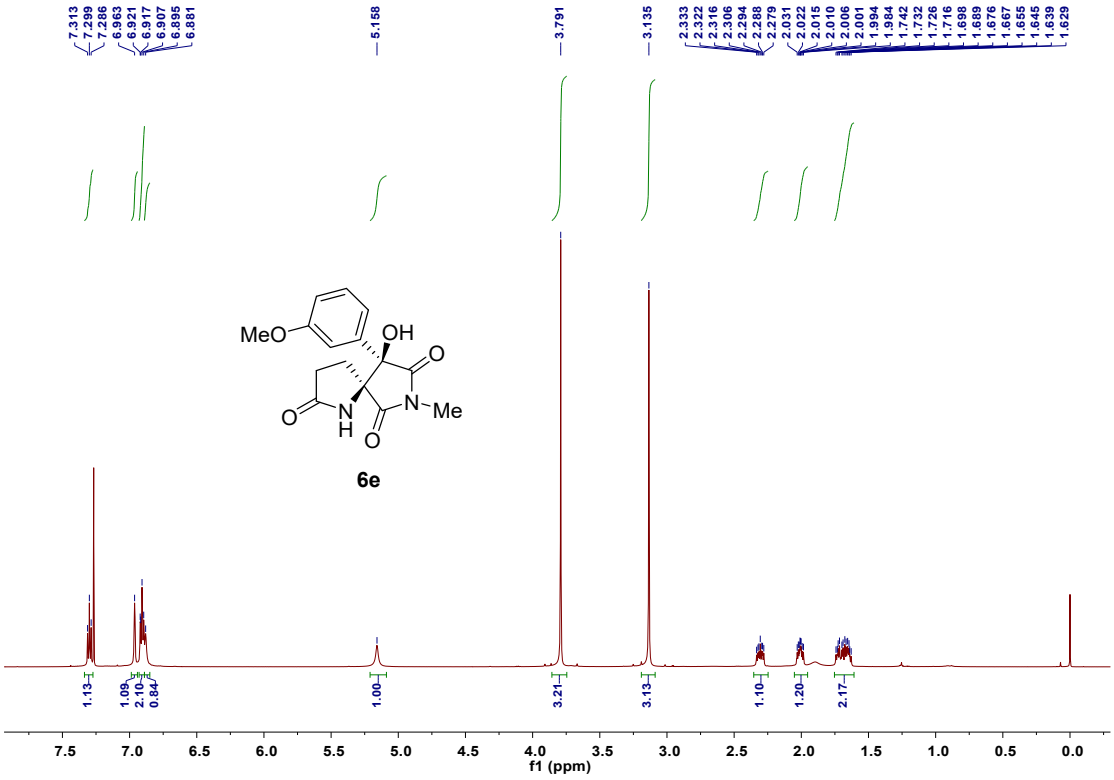
130.66
116.37
114.51
111.32
80.54
77.25
77.04
76.83
70.56
55.36
29.45
28.28
25.35
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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6.895
6.881
5.158
3.791
3.135
2.333
2.322
2.316
2.306
2.294
2.288
2.279
2.031
2.022
2.015
2.010
2.006
2.001
1.994
1.984
1.742
1.732
1.726
1.716
1.698
1.689
1.676
1.667
1.655
1.645
1.639
1.629
MeO
OH
O
N
Me
O
N
H
O
1.13
1.09
2.10
0.84
1.00
3.21
3.13
1.10
1.20
2.17
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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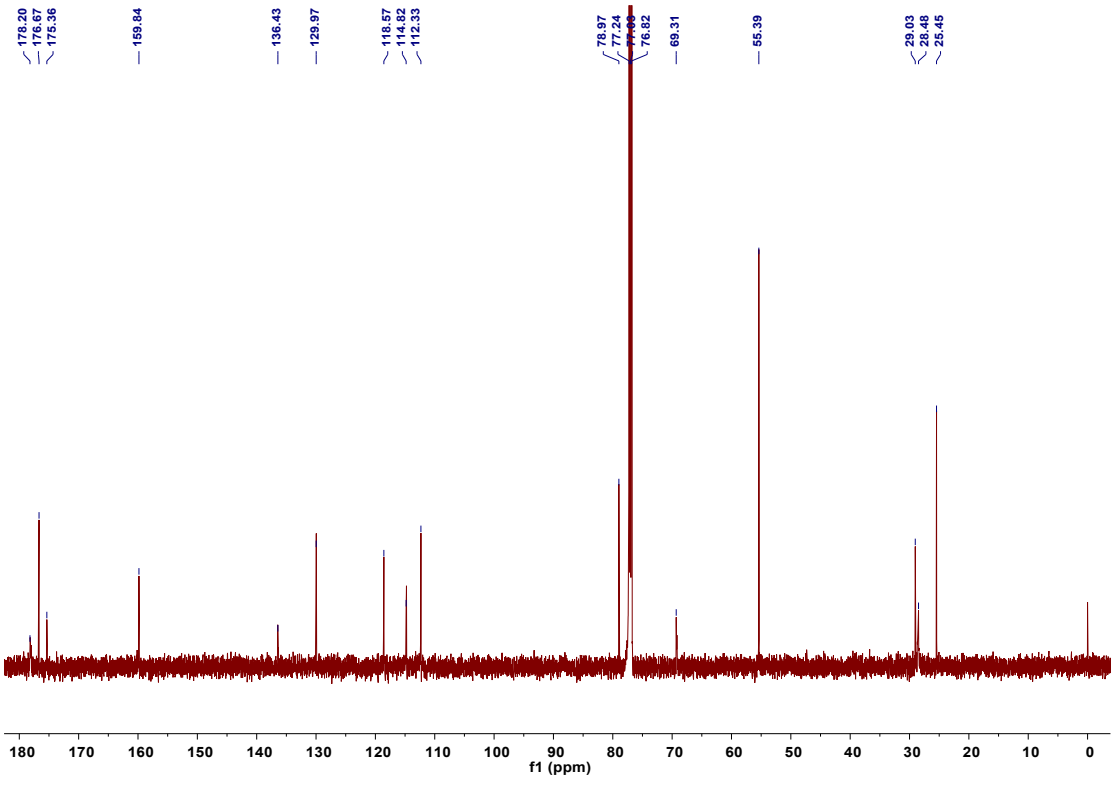
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

6e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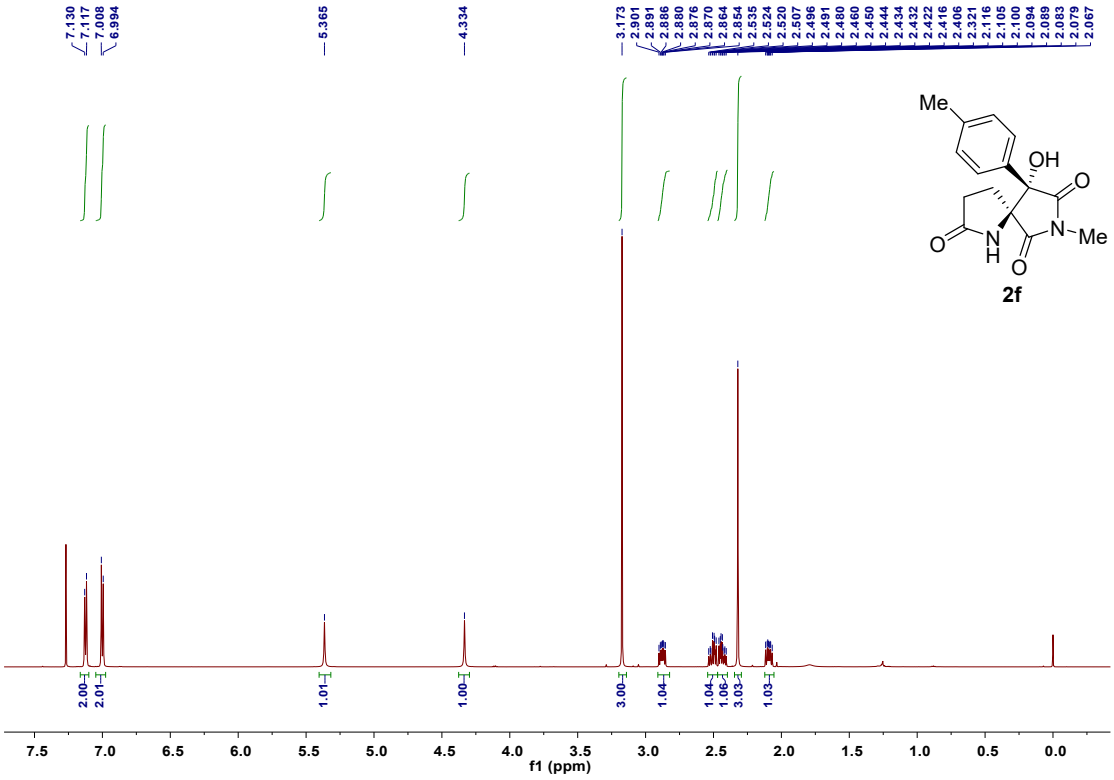
136.43
129.97
118.57
114.82
112.33
78.97
77.24
76.82
69.31
55.39
29.03
28.48
25.45
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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4.334
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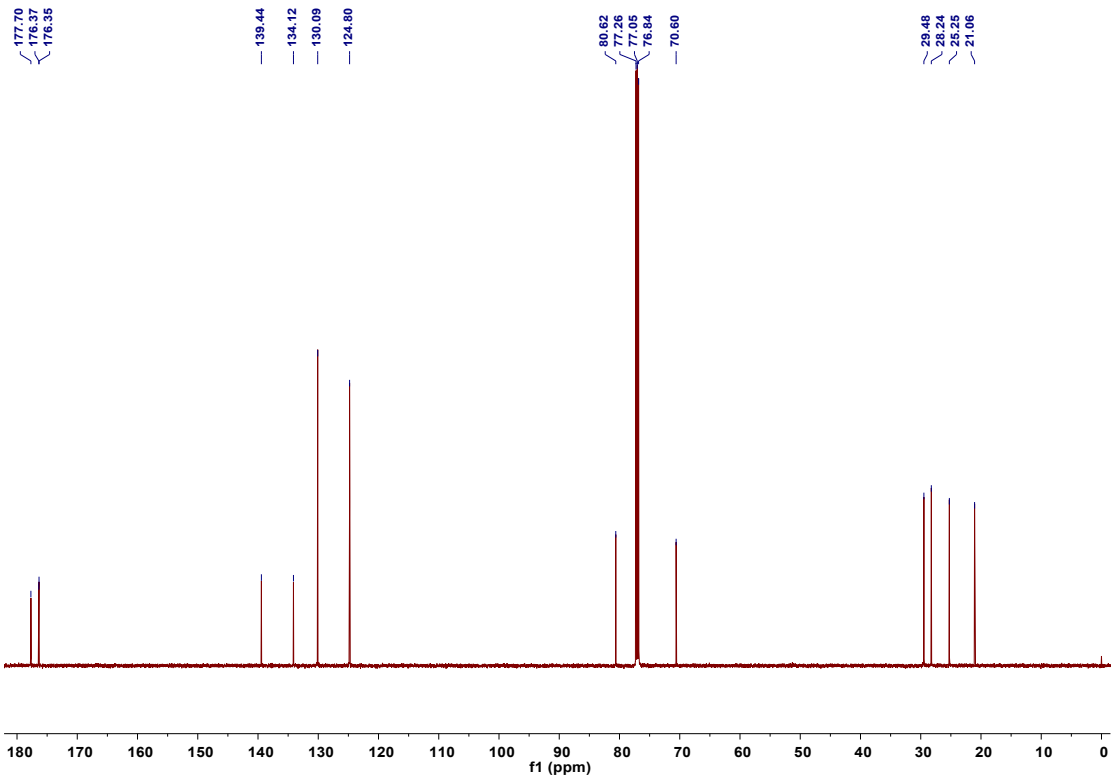
2.901
2.891
2.886
2.880
2.876
2.870
2.864
2.854
2.535
2.524
2.520
2.507
2.496
2.491
2.480
2.460
2.450
2.444
2.434
2.432
2.422
2.416
2.406
2.321
2.116
2.105
2.100
2.094
2.089
2.083
2.079
2.067
Me
OH
O
O
N
Me
H
N
O
2f
2.00
2.01
1.01
1.00
3.00
1.04
1.04
1.06
3.03
1.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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80.62
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77.05
76.84
70.60
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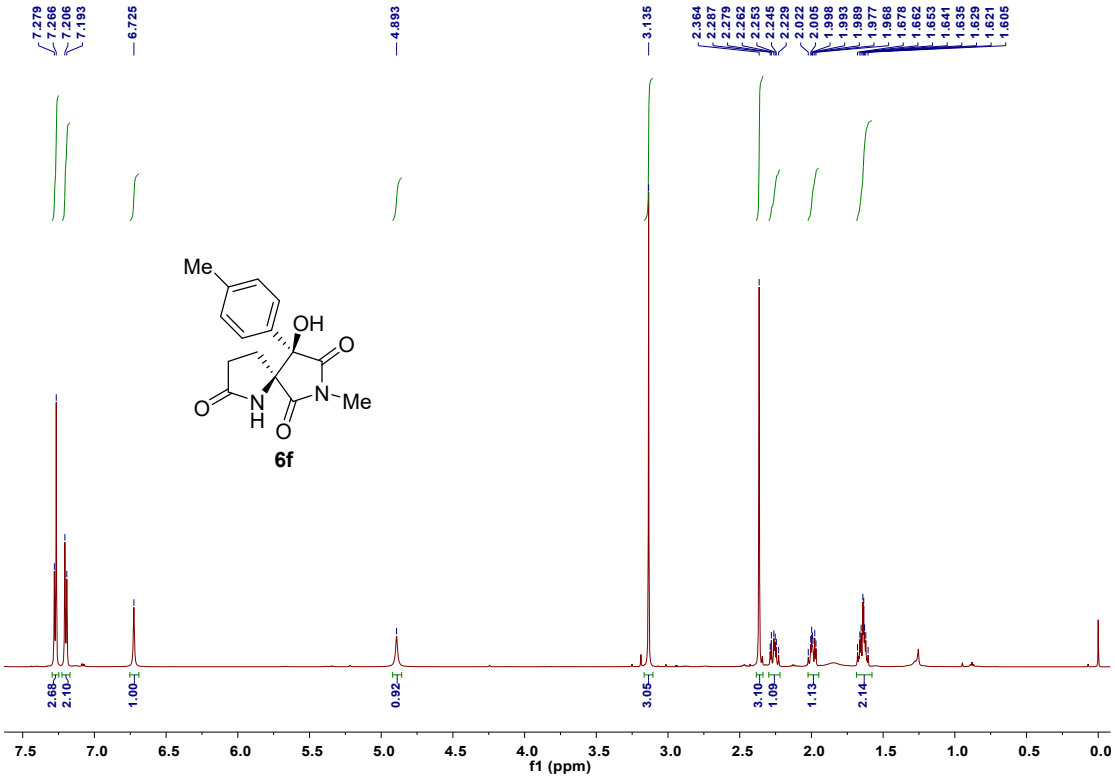
28.24
25.25
21.06
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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2.279
2.262
2.253
2.245
2.229
2.022
2.005
1.998
1.993
1.989
1.977
1.968
1.678
1.662
1.653
1.641
1.635
1.629
1.621
1.605
Me
OH
O
O
N
H
N
Me
O
2.68
2.10
1.00
0.92
3.05
3.10
1.09
1.13
2.14
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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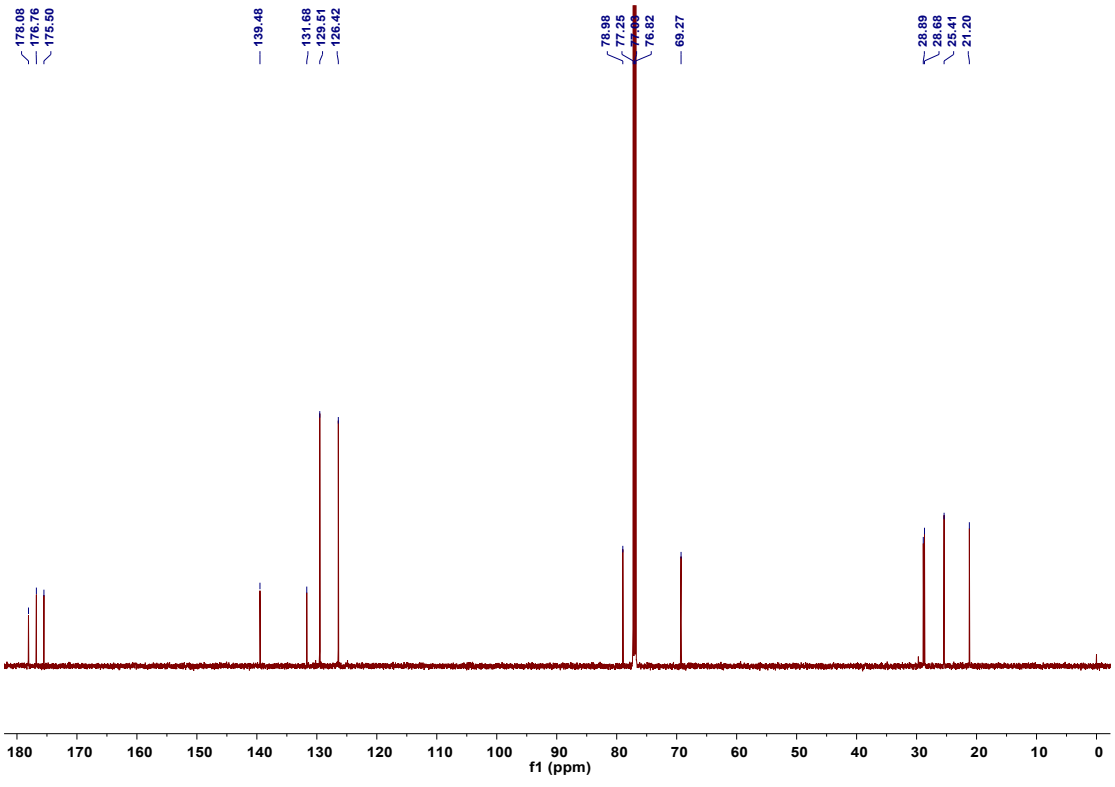
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

6f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131.68
129.51
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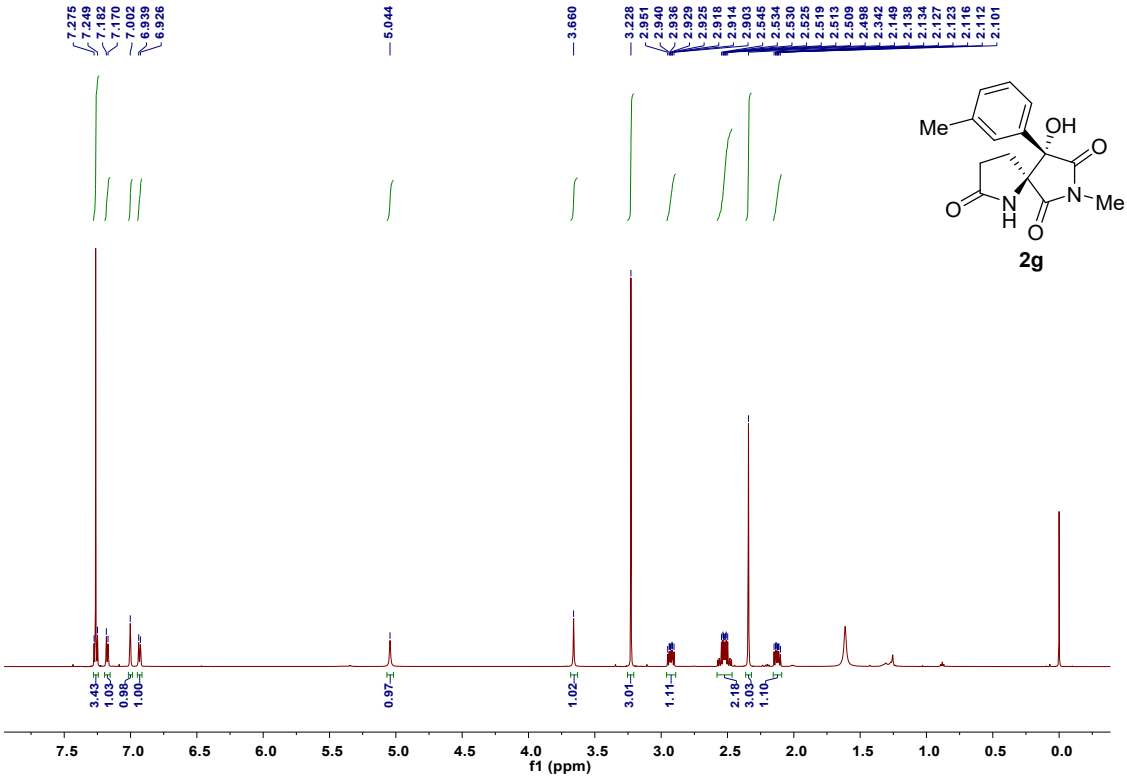
78.98
77.25
77.00
76.82
69.27
28.89
28.68
25.41
21.20
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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5.044
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2.936
2.929
2.925
2.916
2.914
2.903
2.545
2.534
2.530
2.525
2.519
2.513
2.509
2.498
2.342
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2.123
2.116
2.112
2.101
Me
OH
O
N
Me
O
N
H
O
2g
3.43
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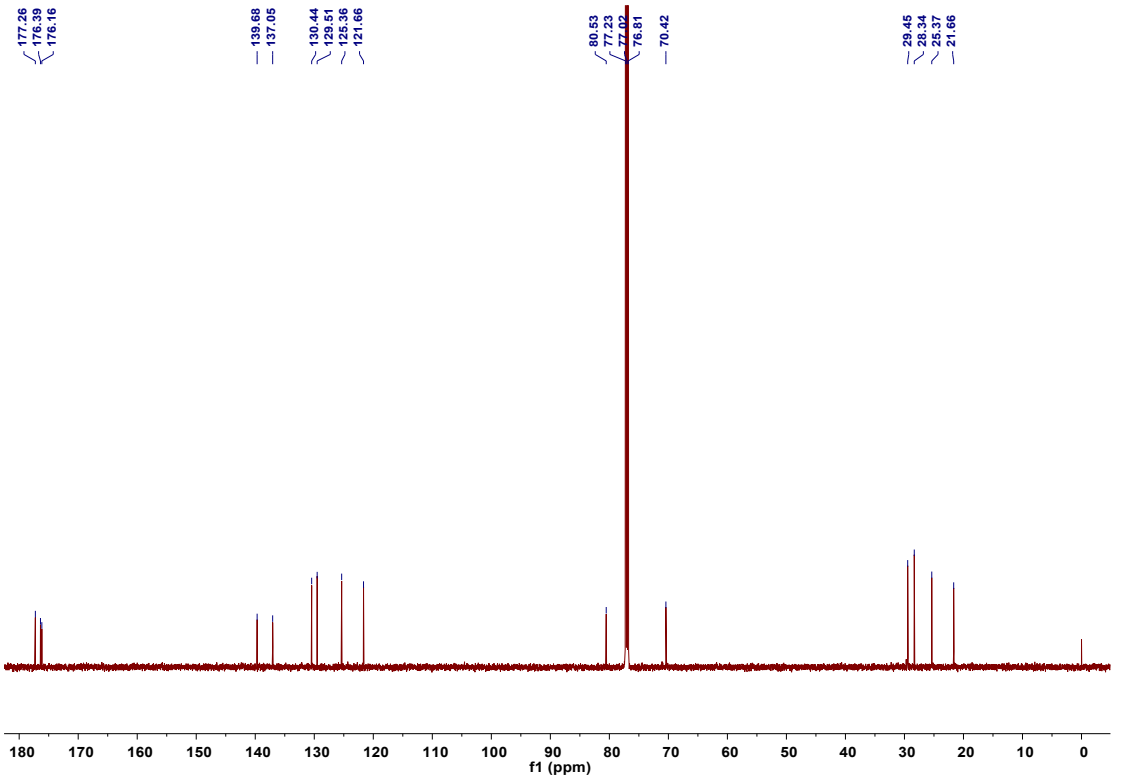
0.98
1.00
0.97
1.02
3.01
1.11
2.18
3.03
1.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


177.26
176.39
176.16
139.68
137.05
130.44
129.51
125.36
121.66
80.53
77.23
77.02
76.81
70.42
29.45
28.34
25.37
21.66
180
170
160
150
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130
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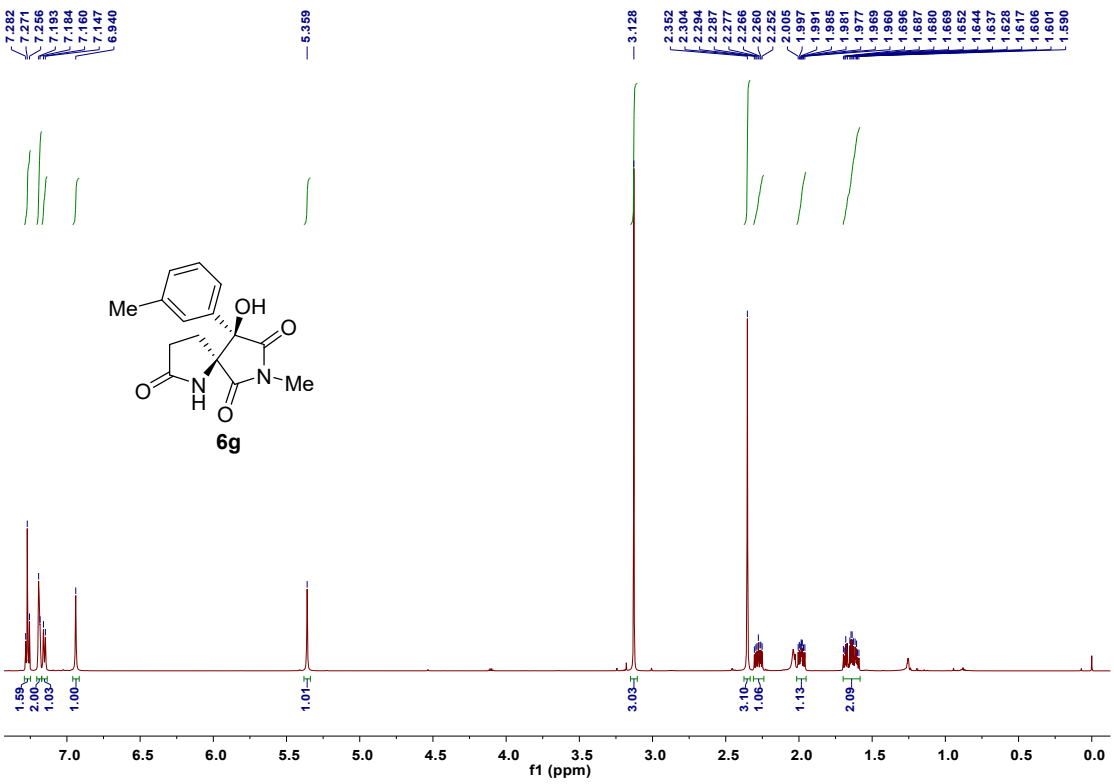
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.282
7.271
7.256
7.193
7.184
7.160
7.147
6.940
5.359
3.128
2.352
2.304
2.294
2.287
2.277
2.266
2.260
2.252
2.005
1.997
1.991
1.985
1.981
1.977
1.969
1.960
1.696
1.687
1.680
1.669
1.652
1.644
1.637
1.628
1.617
1.606
1.601
1.590
Me
OH
O
N
Me
O
N
H
O
6g
1.59
2.00
1.03
1.00
1.01
3.03
3.10
1.06
1.13
2.09
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
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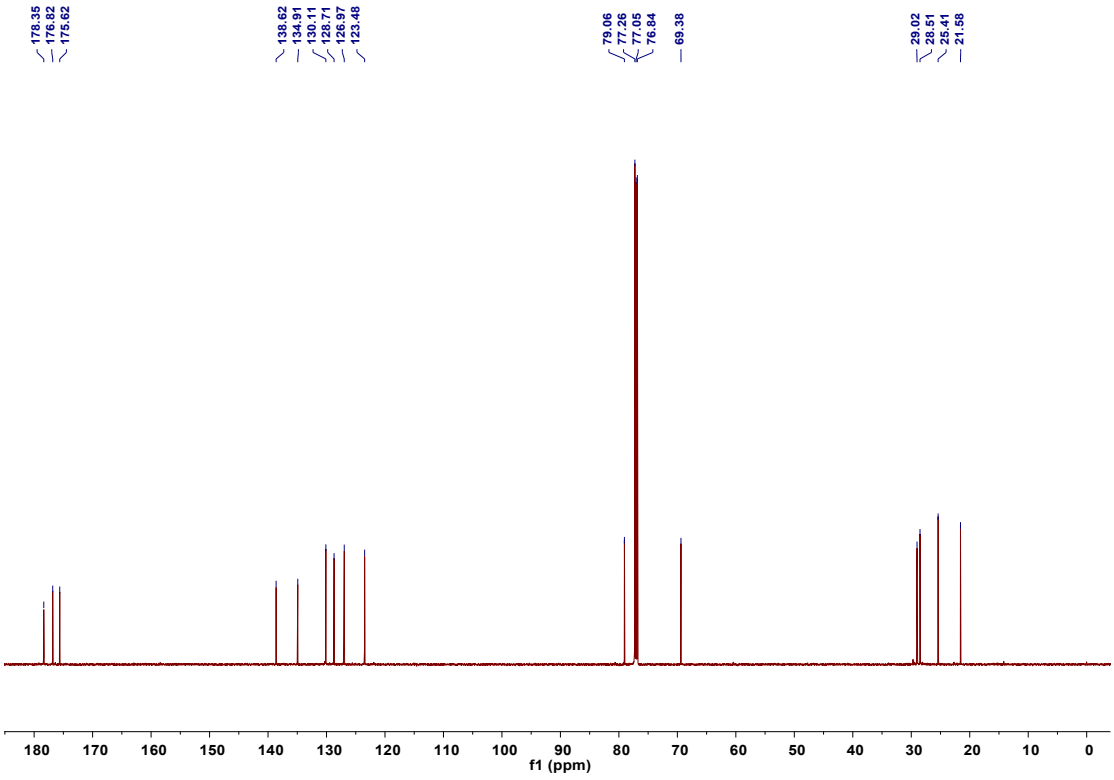
0.0
f1 (ppm)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77.05
76.84
69.38
29.02
28.51
25.41
21.58
180
170
160
150
140
130
120
110
100
90
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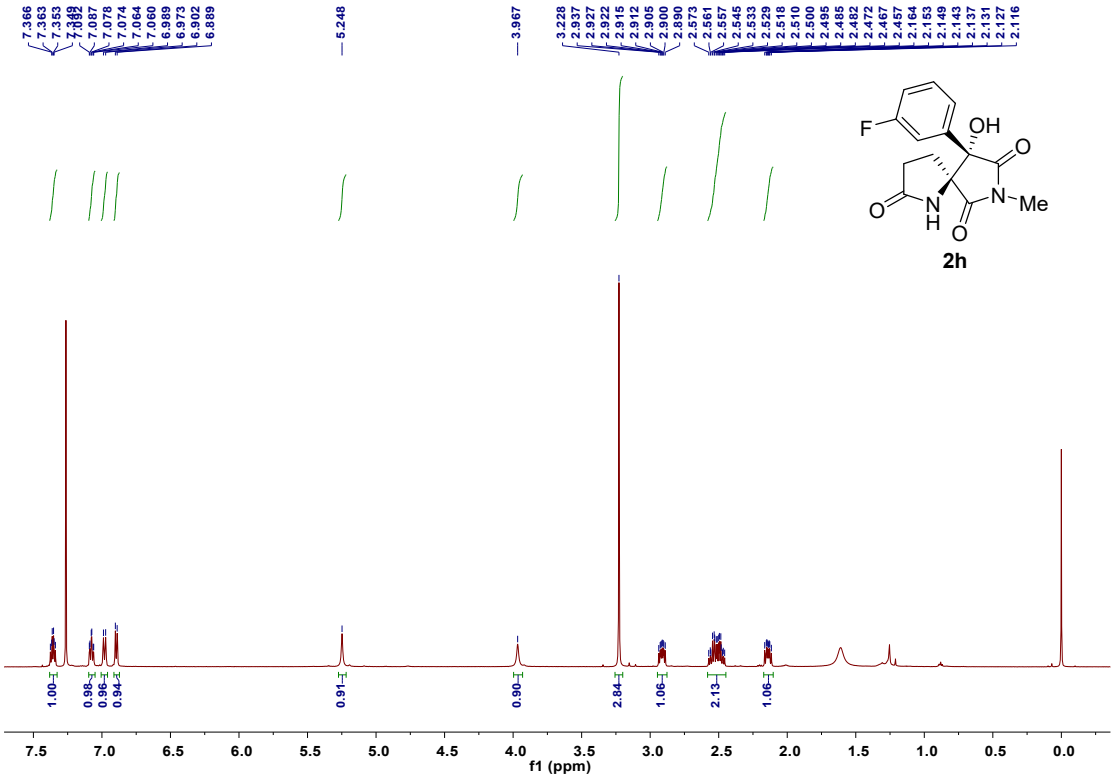
70
60
50
40
30
20
10
0
f1 (ppm)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7.078
7.074
7.064
7.060
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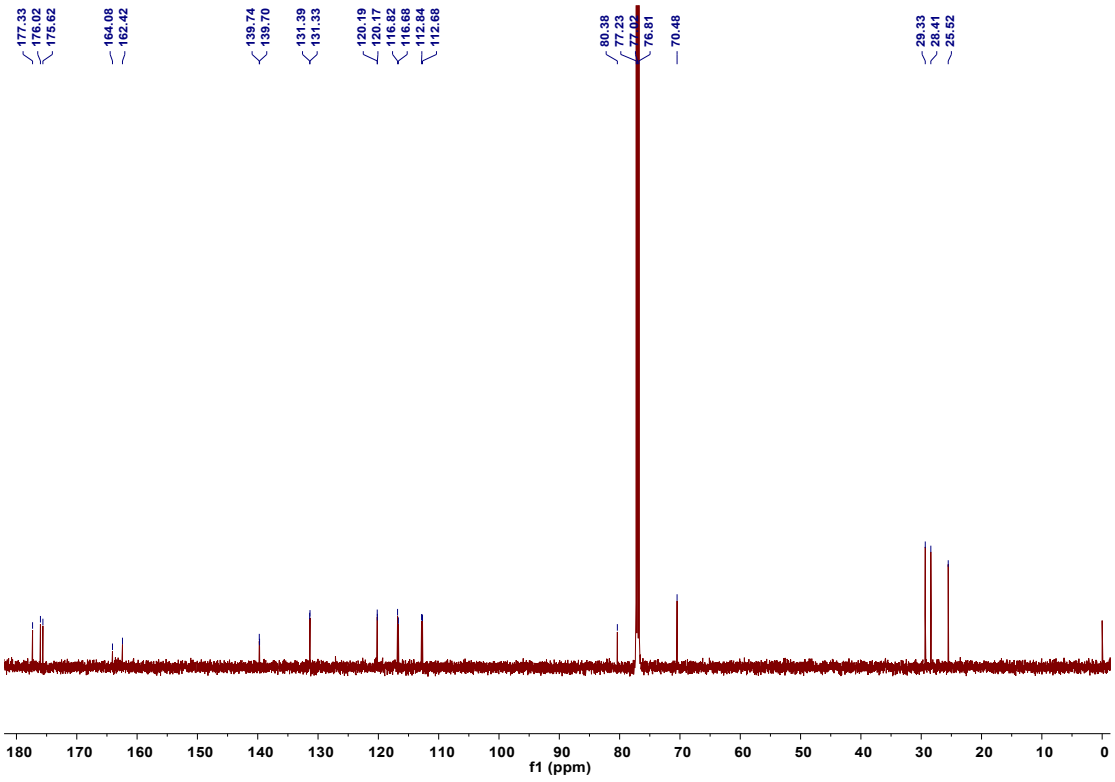
6.902
6.889
5.248
3.967
3.228
2.937
2.927
2.922
2.915
2.912
2.905
2.900
2.890
2.573
2.561
2.557
2.545
2.533
2.529
2.518
2.510
2.500
2.495
2.485
2.482
2.472
2.467
2.457
2.164
2.153
2.149
2.143
2.137
2.131
2.127
2.116
F
OH
O
O
N
H
N
Me
O
2h
1.00
0.98
0.96
0.94
0.91
0.90
2.84
1.06
2.13
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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131.39
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120.19
120.17
116.82
116.68
112.84
112.68
80.38
77.23
77.02
76.81
70.48
29.33
28.41
25.52
180
170
160
150
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130
120
110
100
90
80
70
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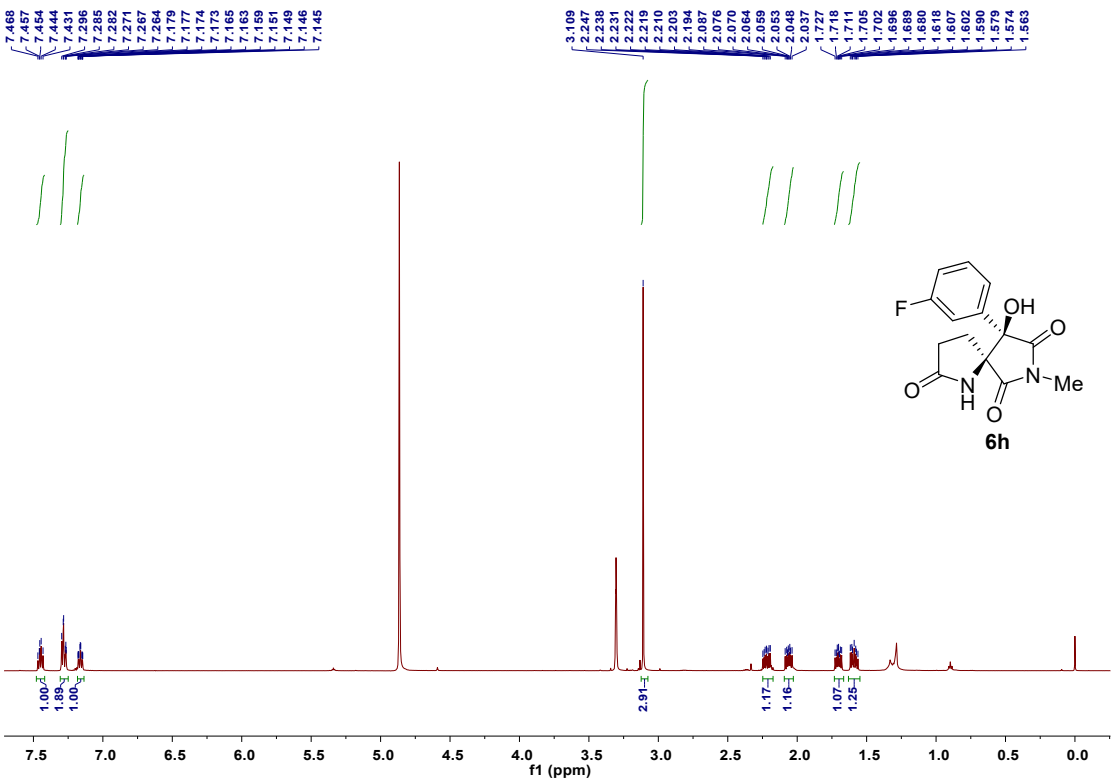
50
40
30
20
10
0
f1 (ppm)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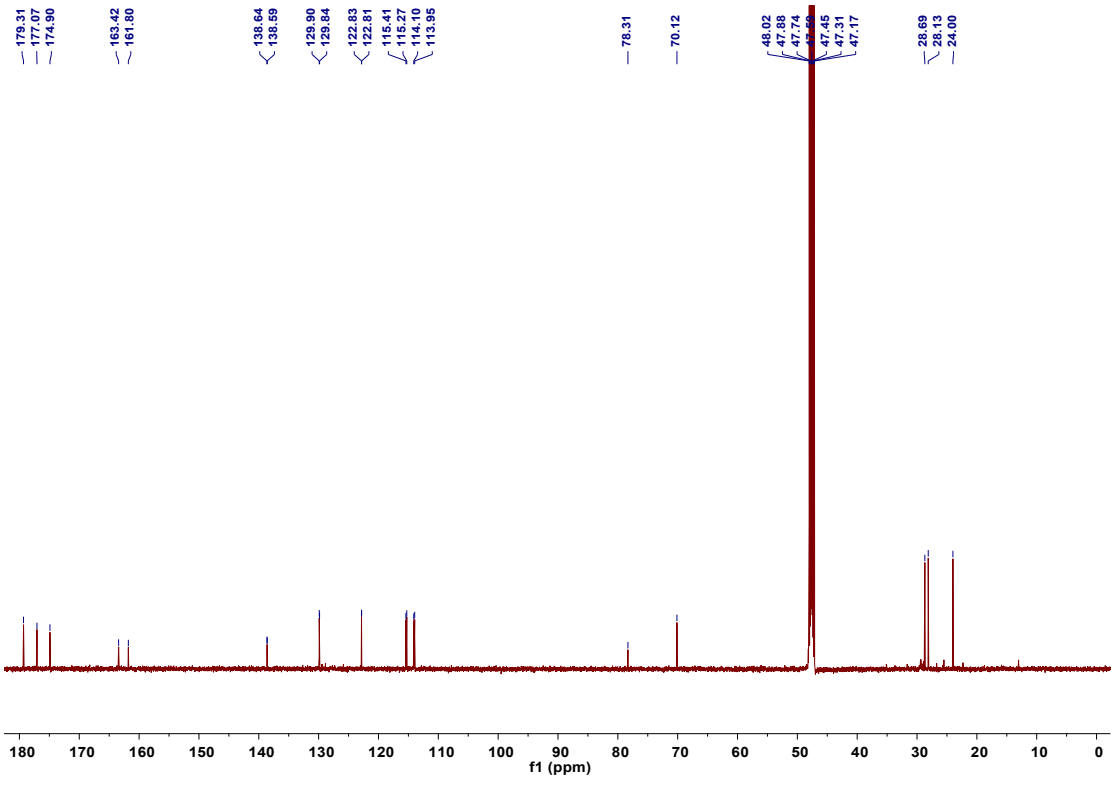
7.267
7.264
7.179
7.177
7.174
7.173
7.165
7.163
7.159
7.151
7.149
7.146
7.145
3.109
2.247
2.238
2.231
2.222
2.219
2.210
2.203
2.194
2.087
2.076
2.070
2.064
2.059
2.053
2.048
2.037
1.727
1.718
1.711
1.705
1.702
1.696
1.689
1.680
1.618
1.607
1.602
1.590
1.579
1.574
1.563
F
OH
O
N
Me
O
N
H
O
6h
1.00
1.89
1.00
2.91
1.17
1.16
1.07
1.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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177.07
174.90
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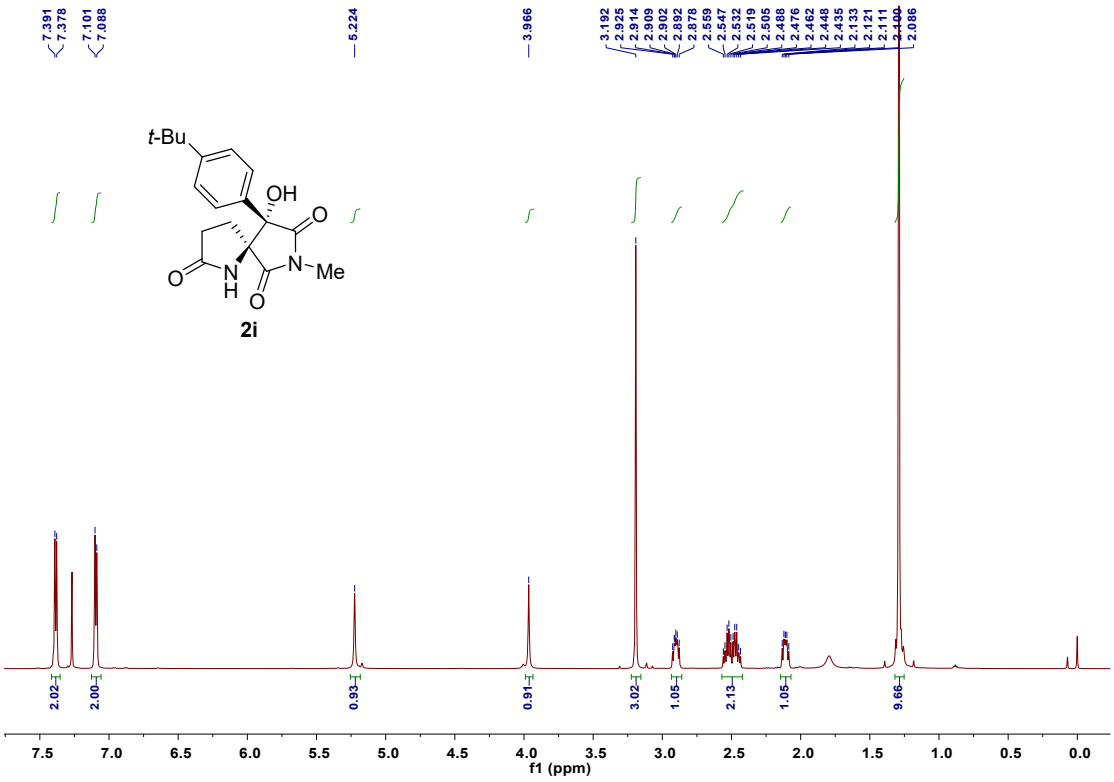
161.80
138.64
138.59
129.90
129.84
122.83
122.81
115.41
115.27
114.10
113.95
78.31
70.12
48.02
47.88
47.74
47.45
47.31
47.17
28.69
28.13
24.00
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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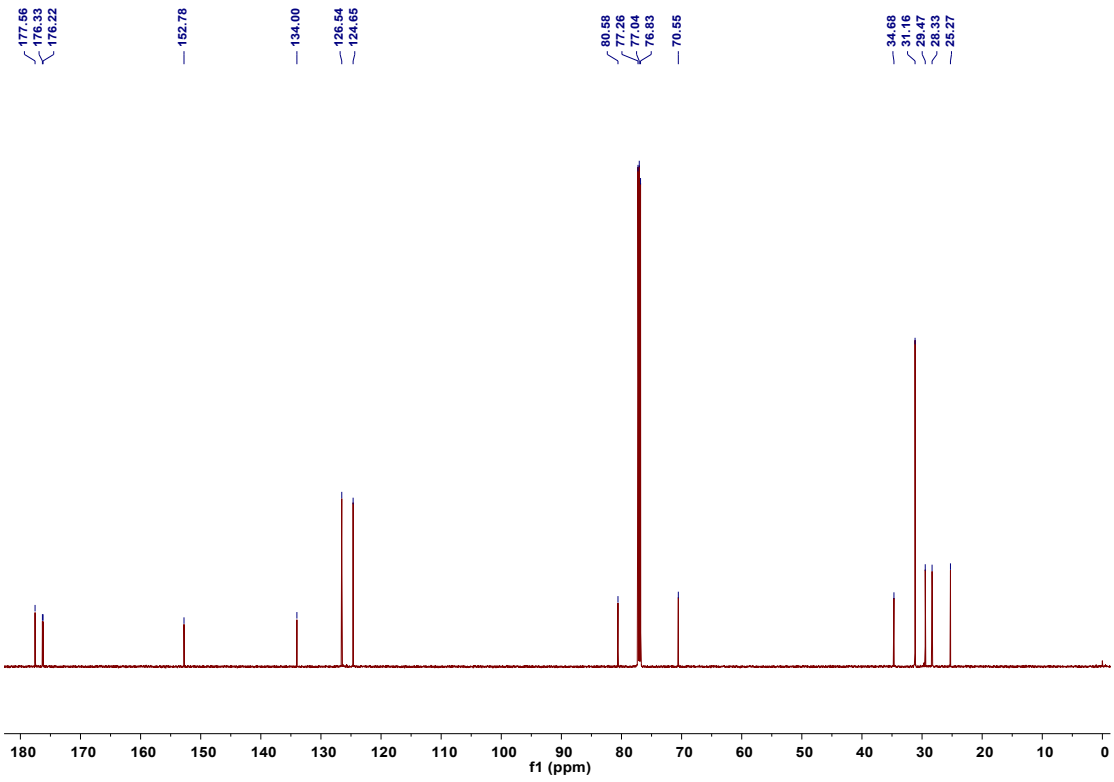
2.909
2.902
2.892
2.878
2.559
2.547
2.532
2.519
2.505
2.488
2.476
2.462
2.448
2.435
2.133
2.121
2.111
2.100
2.086
t-Bu
OH
O
N
H
O
N
Me
O
2i
2.02
2.00
0.93
0.91
3.02
1.05
2.13
1.05
9.66
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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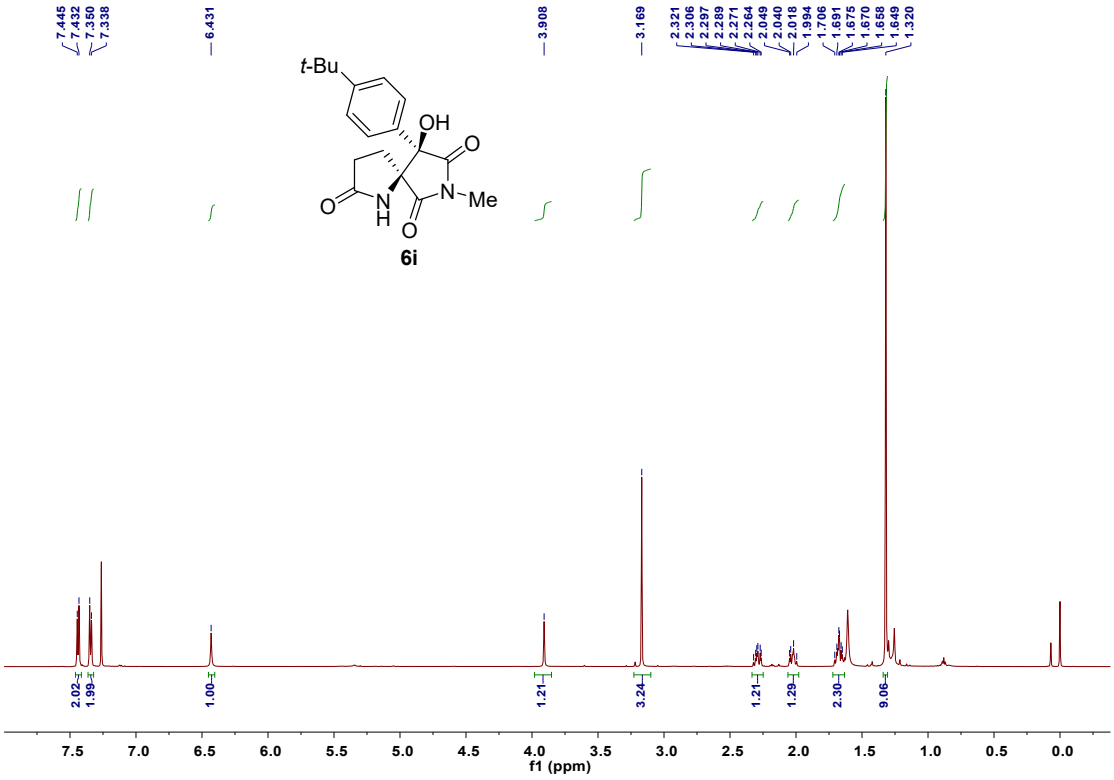
176.22
152.78
134.00
126.54
124.65
80.58
77.26
77.04
76.83
70.55
34.68
31.16
29.47
28.33
25.27
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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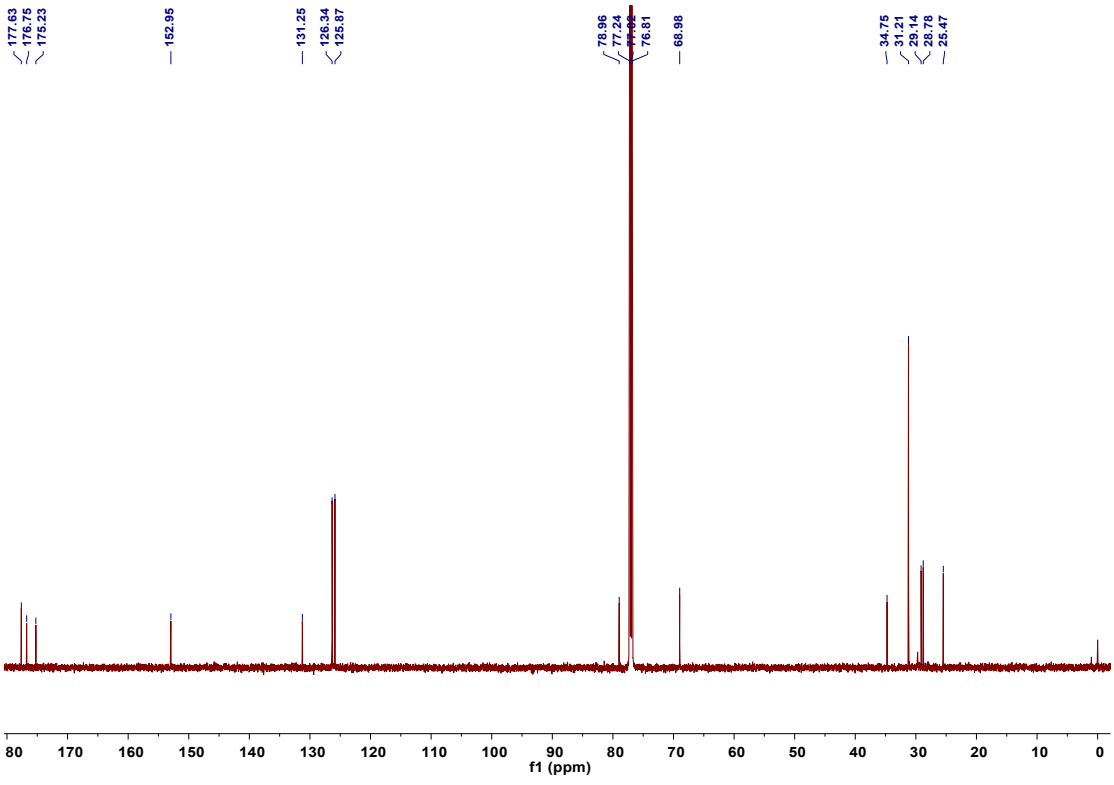
7.338
6.431
3.908
3.169
2.321
2.306
2.297
2.289
2.271
2.264
2.049
2.040
2.018
1.994
1.706
1.691
1.675
1.670
1.658
1.649
1.320
t-Bu
OH
O
N
Me
O
N
H
O
6i
2.02
1.99
1.00
1.21
3.24
1.21
1.29
2.30
9.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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152.95
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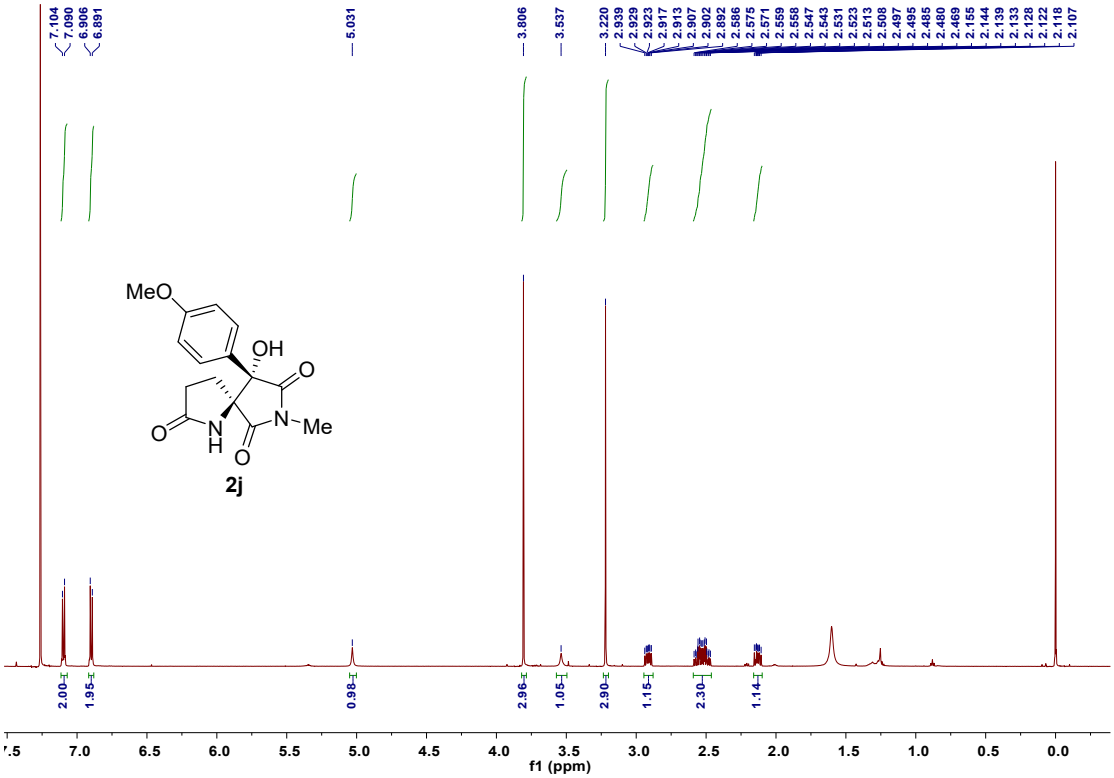
77.24
76.81
68.98
34.75
31.21
29.14
28.78
25.47
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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5.031
3.806
3.537
3.220
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2.929
2.923
2.917
2.913
2.907
2.902
2.892
2.586
2.575
2.571
2.559
2.558
2.547
2.543
2.531
2.523
2.513
2.508
2.497
2.495
2.485
2.480
2.469
2.155
2.144
2.139
2.133
2.128
2.122
2.118
2.107
MeO
OH
O
N
Me
O
N
H
O
2j
2.00
1.95
0.98
2.96
1.05
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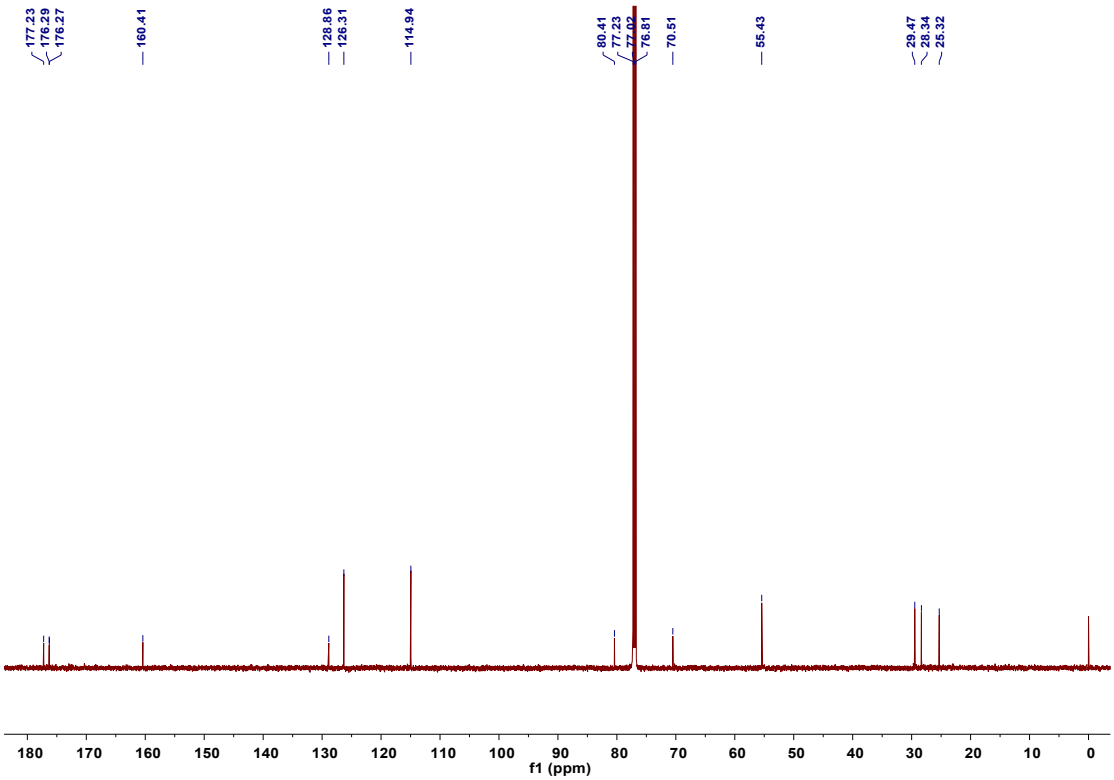
1.15
2.30
1.14
f1 (ppm)


177.23
176.29
176.27
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128.86
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77.02
76.81
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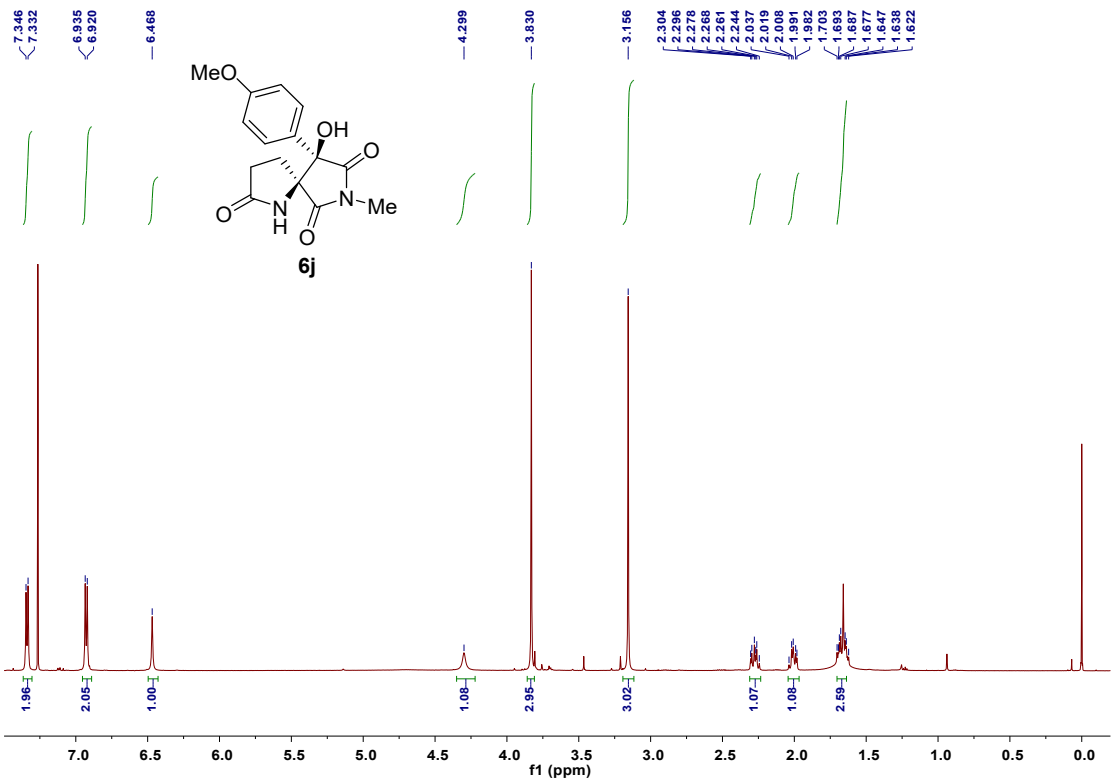
55.43
29.47
28.34
25.32
f1 (ppm)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3.156
2.304
2.296
2.278
2.268
2.261
2.244
2.037
2.019
2.008
1.991
1.982
1.703
1.693
1.687
1.677
1.647
1.638
1.622
MeO
OH
O
O
N
Me
N
H
O
6j
1.96
2.05
1.00
1.08
2.95
3.02
1.07
1.08
2.59
7.0
6.5
6.0
5.5
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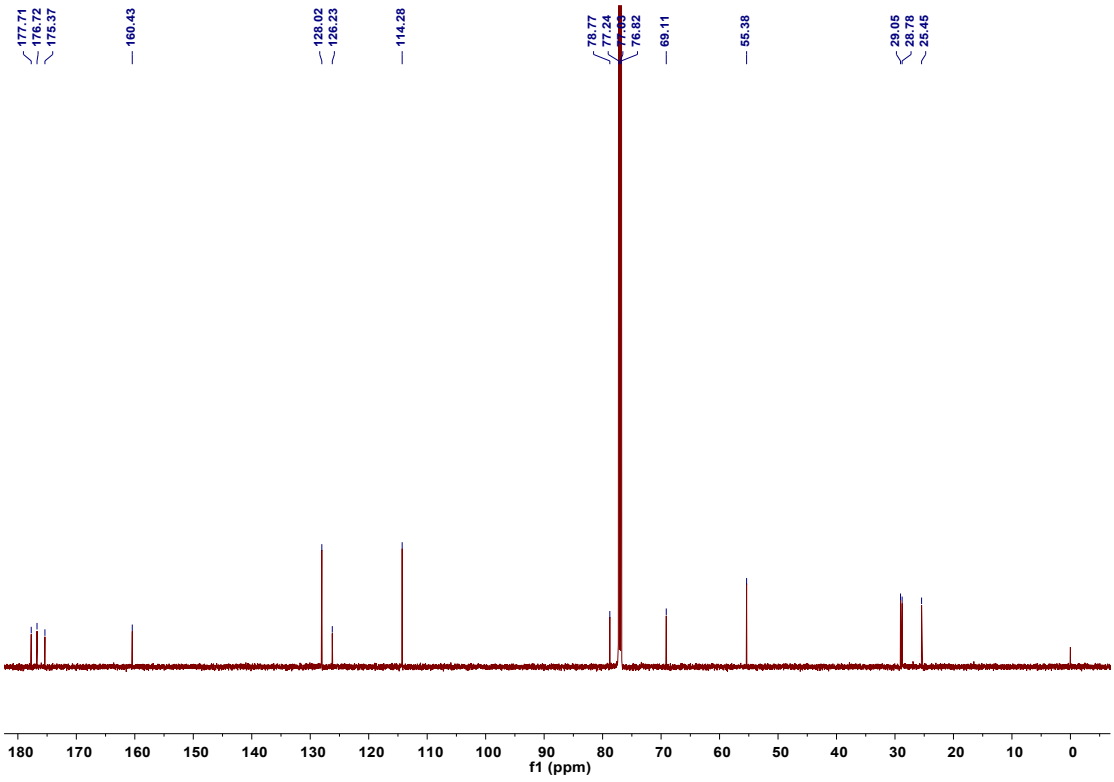
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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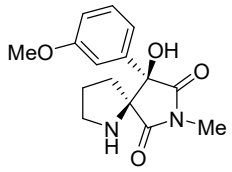
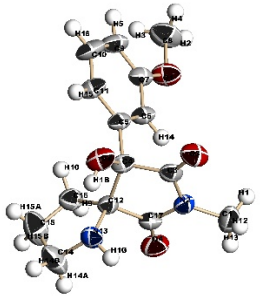
128.02
126.23
114.28
78.77
77.24
76.82
69.11
55.38
29.05
28.78
25.45
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

5. X-Ray Structure of 6a (CCDC-2133176)



6a



Identification code	cu_2021052788D2_0m
Empirical formula	$C_{15}H_{17}N_2O_4$
Formula weight	289.30
Temperature	305(2) K
Wavelength	1.54178 A
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 7.42380(10) A alpha = 90 deg.
	b = 9.5641(2) A beta = 90 deg.
	c = 20.7146(4) A gamma = 90 deg.
Volume	1470.78(5) A^3
Z, Calculated density	4, 1.307 Mg/m^3
Absorption coefficient	0.795 mm^-1
F(000)	612
Crystal size	0.200 x 0.200 x 0.150 mm
Theta range for data collection	5.093 to 65.164 deg.
Limiting indices	-8<=h<=7, -11<=k<=11, -24<=l<=24
Reflections collected / unique	15248 / 2505 [R(int) = 0.0423]
Completeness to theta = 65.164	99.6 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2505 / 0 / 198
Goodness-of-fit on F^2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0391, wR2 = 0.1109
R indices (all data)	R1 = 0.0408, wR2 = 0.1132
Absolute structure parameter	0.20(7)
Extinction coefficient	n/a
Largest diff. peak and hole	0.271 and -0.180 e.A^-3

6. References and Notes

1 E. R. Humphreys, J.-B. Hong and K. L. Green, Chiral Synthesis of an α-Tetrasubstituted Proline Derivative. *Synth. Commun.* 2011, **41**, 2256-2264.

2 D. C. Harrowven, D. P. Curran, S. L. Kostiuk, I. L. Wallis-Guy, S. Whiting, K. J. Stenning, B. Tang, E. Packard and L. Nanson, Potassium Carbonate-Silica: a Highly Effective Stationary Phase for the Chromatographic Removal of Organotin Impurities. *Chem. Commun*. 2010, **46**, 6335-6337.

3 Compound **10** had the phenomenon of atropisomer, which was not reported in the previous literature. We speculated that the steric hindrance of the N-1 methyl group prevented the free rotation of the C9-C10 bond.

4 W. Xu, J. Zhao, C. Tao, H. Wang, Y. Li, B. Cheng and H. Zhai, Collective Total Synthesis of (−)-Lundurines A–C. *Org. Lett.* 2018, **20**, 1509-1512.

5 B. D. Morris and M. R. Prinsep, Amathaspiramides A-F, Novel Brominated Alkaloids from the Marine Bryozoan Amathia Wilsoni. *J. Nat. Prod.* 1999, **62**, 688-693.