Synthetic Studies on Palau'amine. Construction of the Cyclopentane Core via an Asymmetric [1,3]-Dipolar Cycloaddition

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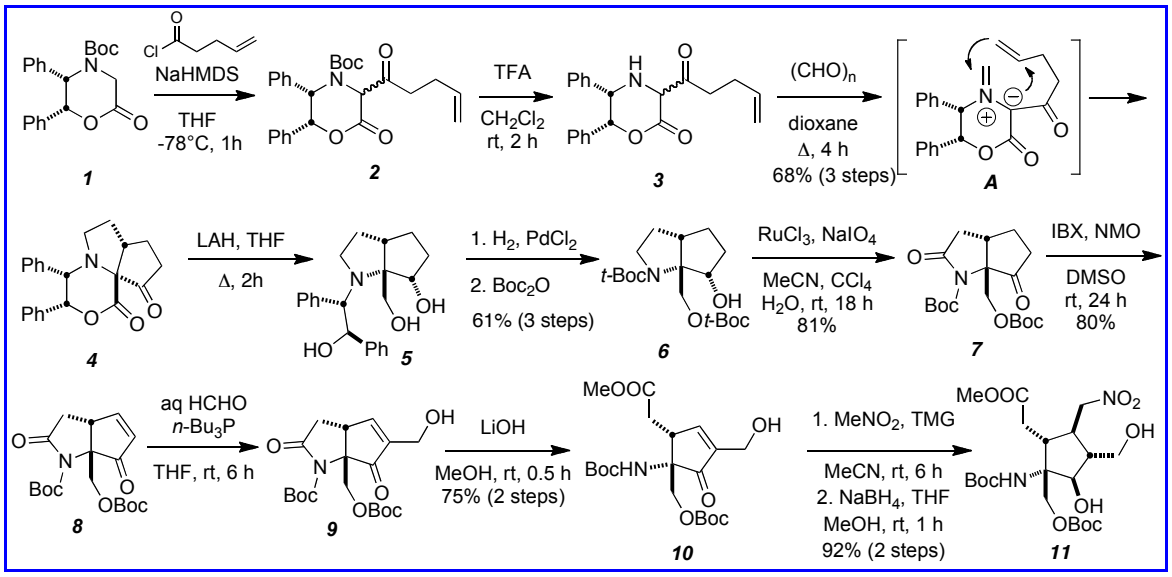
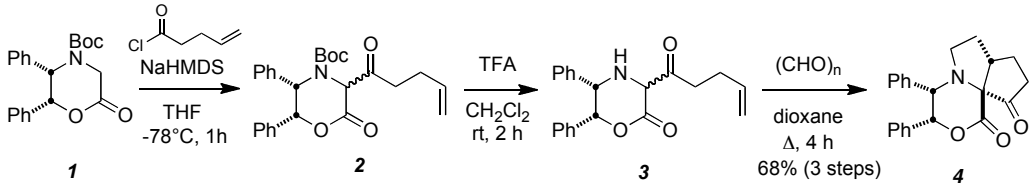
Supporting Information



Synthesis of Compound **4**



To a solution of **1** (1.00 g, 2.38 mmol) in THF (60 mL) was added NaHMDS (3.2 mL of 1M in THF, 3.2 mmol) at -78 °C. The resulting mixture was stirred at same temperature for 1 h. Then, 4-pentenoyl chloride (380 mL, 3.4, mmol) was added at -78 °C. The resulting mixture was stirred at same temperature for 1h. Then, H_2O were added at -78 °C and the mixture was extracted with EtOAc (x3).

The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was passed through a short silica gel column chromatography (*n*-hexane/EtOAc=10/1 to 5/1) to afford **2** as a mixture of inseparable diastereomers. This mixture **2** was carried on to the following step without further purification.

To a stirred solution of the crude mixture of **2** in CH_2Cl_2 (30 mL) was added TFA (8 mL) at room temperature. The resulting mixture was stirred at same temperature for 2 h. The mixture was concentrated under reduced pressure and the crude material including **3** was applied to following reaction without further purification.

To a stirred solution of the crude material including **3** in dioxane (100 mL) was added paraformaldehyde (310 mg, 10.2 mmol) at room temperature. The resulting mixture was heated to reflux temperature for 4 h, cooled to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 9/1 to 4/1 to 2/1) to afforded **4** (562 mg, 68%, 3 streps) as colorless solid.

$[\alpha]^{25}_D$ + 115.5 (c 0.87, $CHCl_3$)

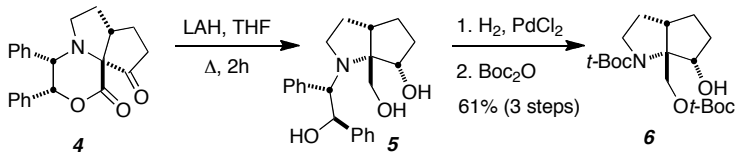
IR (thin film, cm^-): 3064, 2949, 2882, 1755, 1714, 1455, 1381, 1220, 1122, 701.

^{1}H NMR (400 MHz, CDCl3) δ: 7.30-7.05 (m, 8H), 6.92 (m, 2H), 5.46 (d, *J* = 4.0 Hz, 1H), 4.15 (d, *J* = 4.0 Hz, 1H), 3.36 (dt, *J* = 9.6, 4.8 Hz, 1H), 2.94-2.79 (m, 2H), 2.76 (ddd, *J* = 18.8, 9.6, 2.4 Hz, 1H), 2.52 (m, 1H), 2.38 (dd, *J* = 18.8, 9.6 Hz, 1H), 2.23 (ddd, *J* = 18.8, 13.6, 4.8 Hz, 1H), 2.00 (m, 1H), 1.49 (m, 1H).

^{13}C NMR (75 MHz, CHCl3) δ: 213.4, 168.3, 135.5, 134.2, 128.9, 128.5, 128.2, 127.9, 127.5, 84.4, 78.5, 64.5, 53.1, 46.5, 35.8, 29.7, 24.3.

HRMS (FAB+) *m/z* calcd. For $C_{22}H_{21}NO_3$ $(M+H)^+$ 348.1600; found 348.1595.

Synthesis of Compound **6**:



To a stirred solution of **4** (540 mg, 0.1.55 mmol) in THF (10 mL) was added LAH (391 mg, 10.3 mmol) at 0 °C. The resulting mixture was heated to reflux temperature for 2 h. Next, H_2O (390 μL), 10% aq NaOH (390 μL) and H_2O (1.2 mL) were sequentially added at 0 °C. The mixture was dried over $MgSO_4$, filtered through a pad of Celite and concentrated under reduced pressure. The crude material including **5** was used directly for the next step without further purification.

To a stirred solution of the crude material including **5** in EtOH (10 mL) was added $PdCl_2$ (400 mg) at room temperature. The resulting mixture was stirred at same temperature for 48 h under H_2 atmosphere (80 psi). Then, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude product was directly used for the next step without further purification.

To a stirred solution of the crude product obtained above in DMF (10 mL) were added Boc_2O (891 mg, 4.08 mmol), triethyl amine (860 mL, 6.20 mmol) and DMAP (99.2 mg, 0.81 mmol) at room temperature. The resulting mixture was stirred at same temperature for 12 h. Then, sat. NH_4Cl(aq) was added at room temperature and the mixture was extracted with EtOAc (x3). The combined organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 9/1 to 4/1 to 2/1) to afforded **6** (354 mg, 61%, 3 steps) as sticky oil.

$[\alpha]^{25}_D$ + 32.9 (c 1.02, $CHCl_3$)

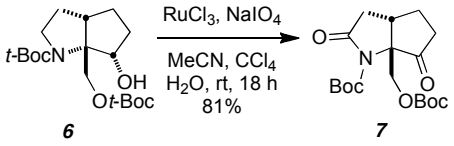
IR (thin film, cm^-): 3460, 2976, 2874, 1744, 1696, 1671, 1394, 1281, 1254, 1164, 860.

^{1}H NMR (300 MHz, CDCl3) δ: 4.73 (d, *J* = 11.4 Hz, 1H), 4.25 (brs, 1H), 4.08 (m, 1H), 4.04 (d, *J* = 11.4 Hz, 1H), 3.60-3.40 (m, 2H), 2.59 (m, 1H), 2.10-1.60 (m, 5H), 1.46 (s, 9H), 1.44 (s, 9H).

^{13}C NMR (75 MHz, CHCl3) δ: 156.7, 153.6, 82.3, 81.5, 80.7, 75.1, 67.4, 49.4, 47.3, 33.8, 29.3, 28.7, 28.1, 27.9.

HRMS (FAB+) *m/z* calcd. For $C_{18}H_{32}NO_6$ $(M+H)^+$ 358.2230; found 358.2225.

Synthesis of Compound **7**:



6 ***7***

To a stirred solution of **6** (350 mg, 0.98 mmol) in a mixture of MeCN, CCl_4 and H_2O = 1:1:1.2 (total 14 mL) were added $RuCl_3 \cdot 3H_2O$ (52 mg, 0.20 mmol) and $NaIO_4$ (860 mg, 4.02 mmol) at room temperature. The resulting mixture was stirred at same temperature for 18 h. Then, H_2O was added at room temperature and the mixture was extracted with EtOAc (x3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 4/1 to 21 to 1/1) to afforded **7** (293 mg, 81%, 2 steps) as sticky oil.

$[\alpha]^{25}_{D}$ – 42.7 (c 1.91, $CHCl_3$)

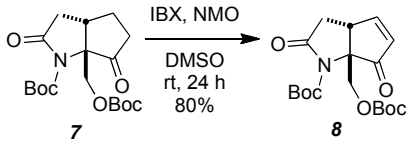
IR (thin film, cm^{-}): 2980, 1789, 1752, 1370, 1282, 1254, 1155.

^{1}H NMR (400 MHz, CDCl3) δ: 4.69 (d, *J* = 12.0 Hz, 1H), 4.24 (d, *J* = 12.0 Hz, 1H), 2.90 (dd, *J* = 17.6, 8.0 Hz, 1H), 2.74 (m, 1H), 2.60 (ddd, *J* = 18.0, 11.2, 5.2 Hz, 1H), 2.38-1.80 (m, 2H), 2.32 (d, *J* = 17.6 Hz, 1H), 1.68 (m, 1H), 1.47 (s, 9H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, CHCl3) δ: 207.9, 174.0, 153.1, 149.0, 84.8, 83.2, 65.5, 38.8, 36.4, 35.5, 28.0, 25.1.

HRMS (FAB+) *m/z* calcd. For $C_{18}H_{27}NNaO_7$ $(M+Na)^+$ 392.1680; found 392.1687.

Synthesis of Compound **8**:



To a stirred solution of **7** (20 mg, 0.054 mmol) in DMSO (1.0 mL) were added IBX (45.4 mg, 0.162 mmol) and NMO (19 mg, 0.16 mmol) at room temperature. The resulting mixture was stirred at same temperature for 24 h. Then, sat. $NaHCO_3$ was added at room temperature and the mixture was extracted with EtOAc (x3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 1/1) to afforded **9** (16 mg, 80%) as colorless oil.

$[\alpha]^{25}_{D}$ + 10.6 (c 0.98, $CHCl_3$)

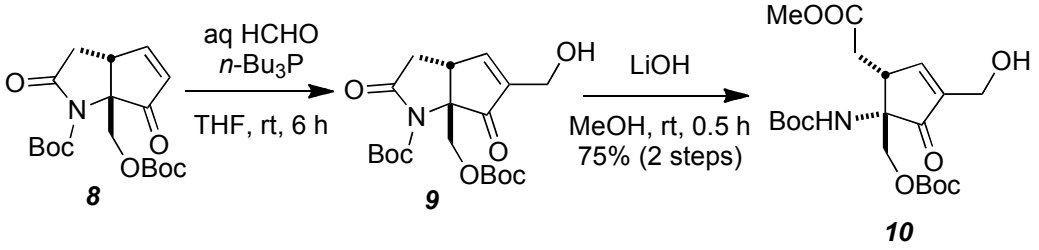
IR (thin film, cm^{-}): 2982, 1786, 1745, 1370, 1281, 1255, 1156.

^{1}H NMR (300 MHz, CDCl3) δ: 7.44 (dd, *J* = 6.4, 2.4 Hz, 1H), 6.25 (dd, *J* = 6.0, 1.8 Hz, 1H), 4.96 (d, *J* = 11.7 Hz, 1H), 4.27 (d, *J* = 11.7 Hz, 1H), 3.50 (dddd, *J* = 11.2, 2.4, 2.4, 1.8 Hz, 1H), 2.94 (dd, *J* = 18.0, 11.2 Hz, 1H), 2.45 (dd, *J* = 18.0, 2.4 Hz, 1H), 1.55 (s, 9H), 1.46 (s, 9H).

^{13}C NMR (100 MHz, CHCl3) δ: 199.8, 172.6, 161.1, 153.1, 149.1, 132.8, 84.9, 83.3, 69.0, 65.6, 42.1, 34.8, 28.0, 27.8.

HRMS (FAB+) *m/z* calcd. For $C_{18}H_{25}NNaO_7$ $(M+Na)^+$ 390.1532; found 390.1526.

Synthesis of Compound **10**:



To a stirred solution of **8** (375 mg, 1.02 mmol) in THF (20 mL) were added 37% aq HCHO (255 mL) and *n*-Bu_3P (53 mL, 0.226 mmol) at room temperature. The resulting mixture was stirred at same temperature for 6 h. Then, the mixture was concentrated under reduced pressure. The residue was passed through a short silica gel column chromatography (*n*-hexane/EtOAc= 1/1 to 0/1) to afford the crude material including **9**. The crude product **9** was directly used for the next step without further purification.

To a stirred solution of the crude material including **9** in MeOH (10 mL) was added $LiOH \cdot H_2O$ (21.3 mg, 0.51 mmol) at room temperature. The resulting mixture was stirred at same temperature for 0.5 h. Then, sat. NH_4Cl was added at room temperature and the mixture was extracted with EtOAc (x3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 1/2 to 0/1) to afforded **10** (323 mg, 75%, 2 steps) as colorless oil.

$[\alpha]^{25}_D$ – 31.7 (c 0.58, $CHCl_3$)

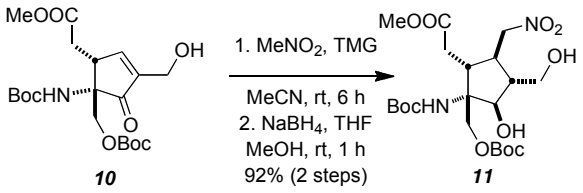
IR (thin film, cm^-): 3367, 2980, 1734, 1369, 1278, 1255, 1163.

^1H NMR (300 MHz, CDCl3) δ: 7.46 (s, 1H), 5.28 (brs, 1H), 4.435-4.25 (m, 3H), 4.07 (d, *J* = 11.0 Hz, 1H), 3.66 (s, 3H), 3.40-3.29 (m, 1H), 2.76 (dd, *J* = 16.6, 7.7 Hz, 1H), 2.34 (dd, *J* = 16.6, 8.4 Hz, 1H), 1.94 (brs, 1H), 1.44 (s, 9H), 1.38 (s, 9H).

^{13}C NMR (75 MHz, CHCl3) δ: 202.4, 172.5, 157.3, 155.2, 153.5, 142.9, 83.5, 80.7, 69.0, 65.1, 57.4, 52.0, 43.8, 34.1, 28.4, 27.8

HRMS (FAB+) *m/z* calcd. For $C_{20}H_{31}NO_9$ $(M+Na)^+$ 452.1891; found 452.1892.

Synthesis of Compound **11**:



To a stirred solution of **10** (415 mg, 0.966 mmol) in MeCN (30 mL) were added $MeNO_2$ (138 mL, 2.55 mmol) and TMG (185 mL, 1.47 mmol) at room temperature. The resulting mixture was stirred at same temperature for 6 h. Then, sat. NH_4Cl was added at room temperature and the mixture was extracted with EtOAc (x3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 1/1) to afforded the nitromethane addition product (436 mg, 92%) as colorless oil.

$[\alpha]^{25}_D$ + 56.9 (c 0.55, $CHCl_3$)

IR (thin film, cm^-): 3524, 2270, 2981, 1740, 1700, 1553, 1370, 1279, 1255, 1160.

^{1}H NMR (300 MHz, CDCl3) δ: 5.10 (brs, 1H), 4.64 (d, *J* = 5.9 Hz, 2H), 4.26-4.00 (m, 3H), 3.78 (dd, *J* = 11.4, 5.1 Hz, 1H), 3.68 (s, 3H), 3.10-2.95 (m, 1H), 2.70-2.35 (m, 4H), 1.61 (brs, 1H), 1.43 (s, 9H), 1.36 (s, 9H).

^{13}C NMR (75 MHz, CHCl3) δ: 211.4, 173.1, 156.0, 152.8, 83.7, 81.9, 68.9, 67.8, 64.3, 59.4, 52.5, 52.2, 40.3, 39.6, 34.7, 27.7, 27.5.

HRMS (FAB+) *m/z* calcd. For $C_{21}H_{34}N_2NaO_{11}$ $(M+Na)^+$ 513.2055; found 513.2058.

To a stirred solution of the nitromethane addition product obtained immediately above, (333 mg, 0.679 mmol) in a mixture of THF and MeOH = 1:1 (total 15 mL) was added $NaBH_4$ (84 mg, 2.22 mmol) at room temperature. The resulting mixture was stirred at same temperature for 1 h. Next, sat. NH_4Cl(aq) was added at room temperature and the mixture was extracted with EtOAc (x3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 1/1) to afforded **11** (334 mg, quant.) as colorless oil.

$[\alpha]^{25}_D$ – 21.3 (c 1.05, $CHCl_3$)

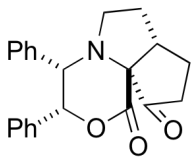
IR (thin film, cm^-): 3394, 2981, 1739, 1553, 1370, 1282, 1255, 1163.

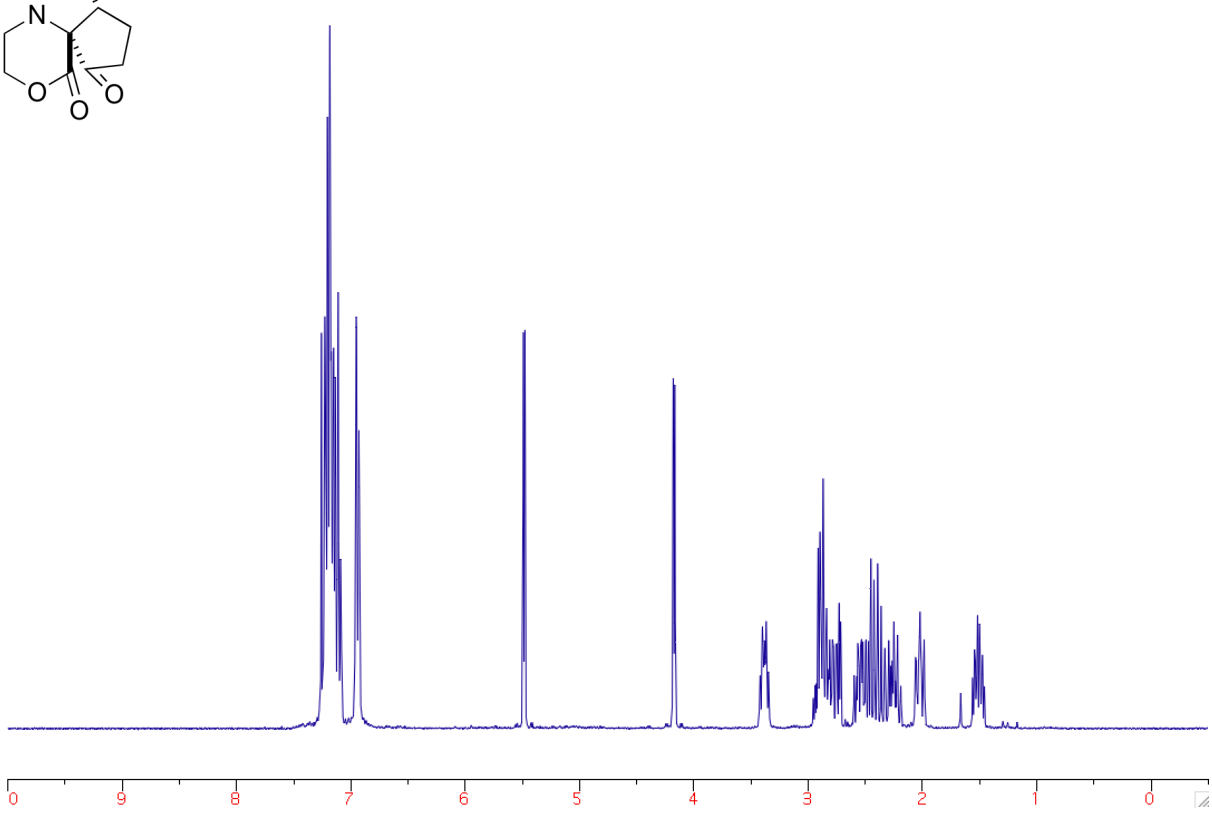
^{1}H NMR (300 MHz, CDCl3) δ: 5.28 (brs, 1H), 5.02 (brs, 1H), 4.55 (d, *J* = 5.5 Hz, 2H), 4.40-4.05 (m, 2H),

3.75 (d, *J* = 4.4 Hz, 1H), 3.66 (s, 3H), 2.55-2.65 (m, 1H), 2.52-2.25 (m, 3H), 2.05-1.90 (m, 2H), 1.42 (s, 9H), 1.35 (s, 9H).

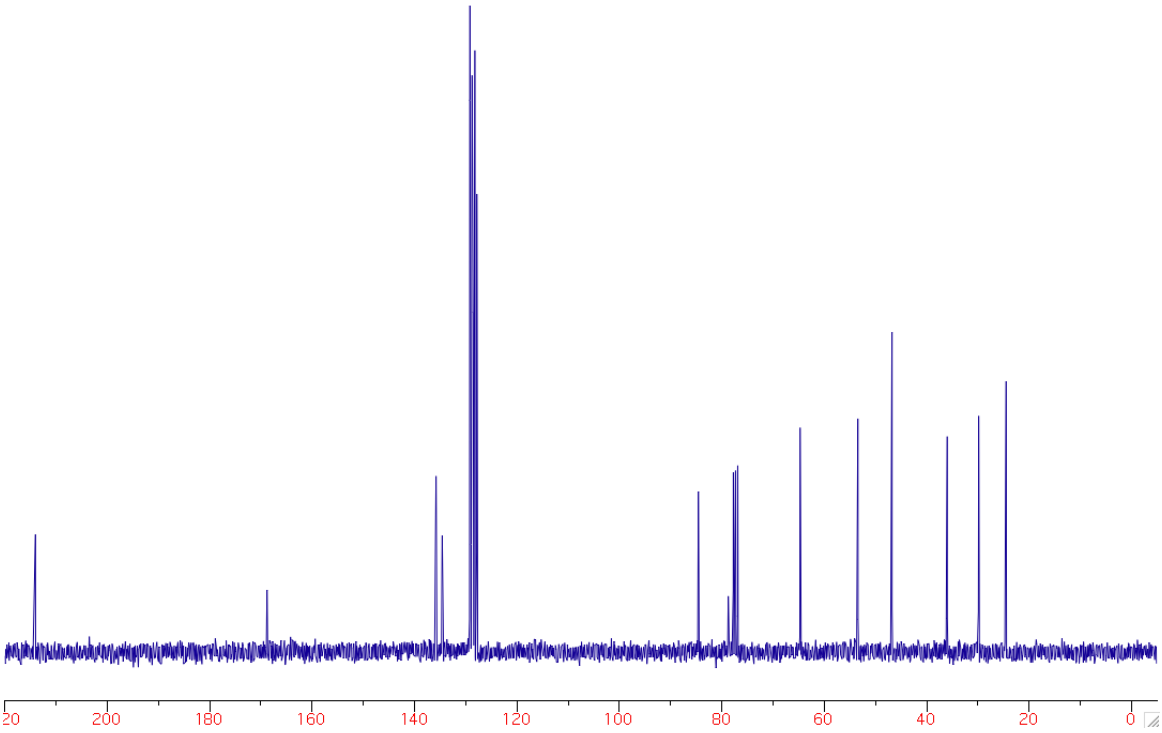
^{13}C NMR (75 MHz, CHCl3) δ: 173.7, 157.0, 153.6, 83.0, 80.9, 78.3, 68.0, 64.3, 63.0, 52.5, 47.9, 43.6, 41.3, 36.2, 28.5, 27.9.

HRMS (FAB+) *m/z* calcd. For $C_{21}H_{36}N_2NaO_{11}$ $(M+Na)^+$ 515.2211; found 515.2218.





^{1}H NMR (300 MHz, $CDCl_3$)



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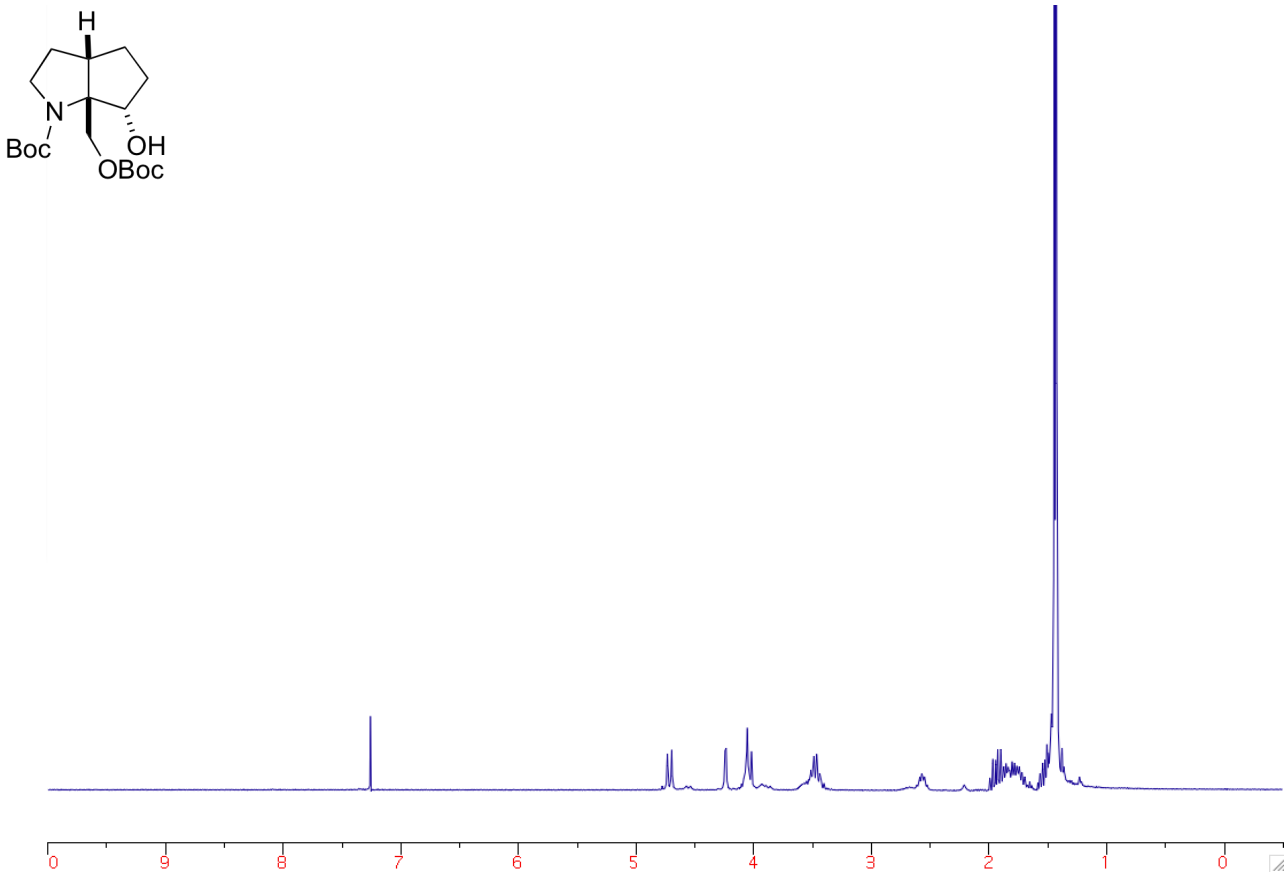

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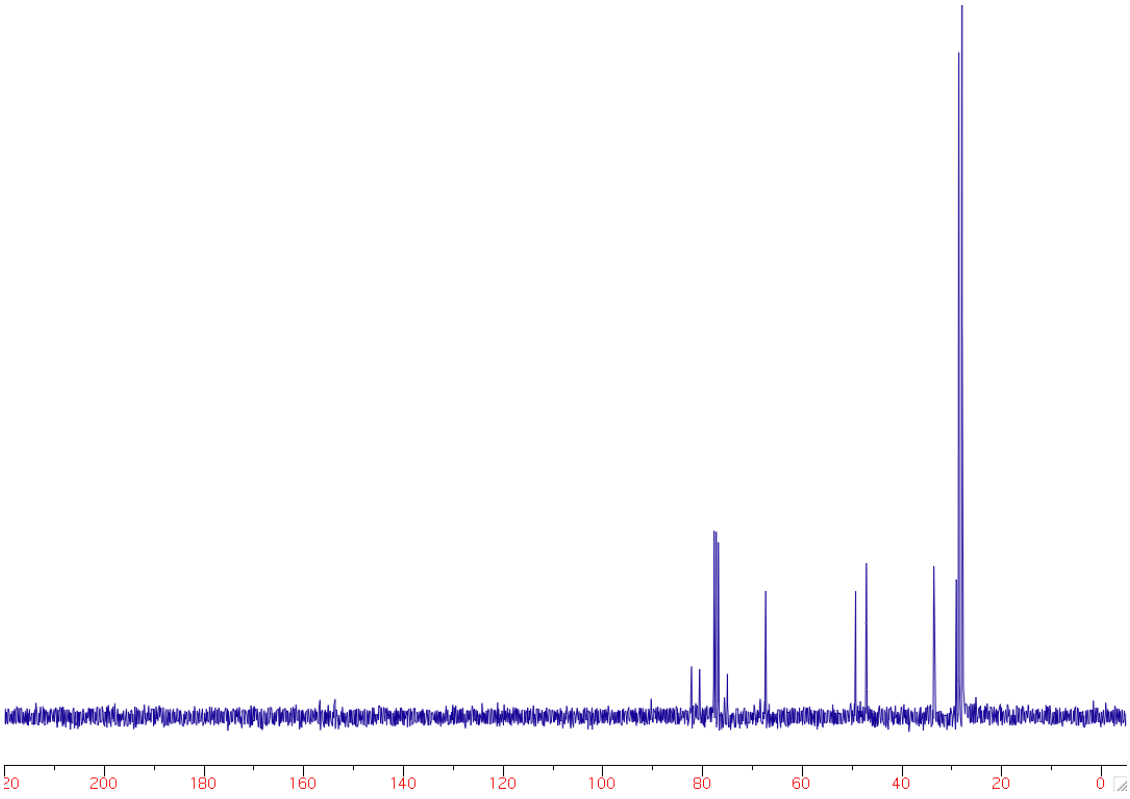
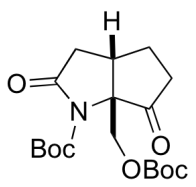
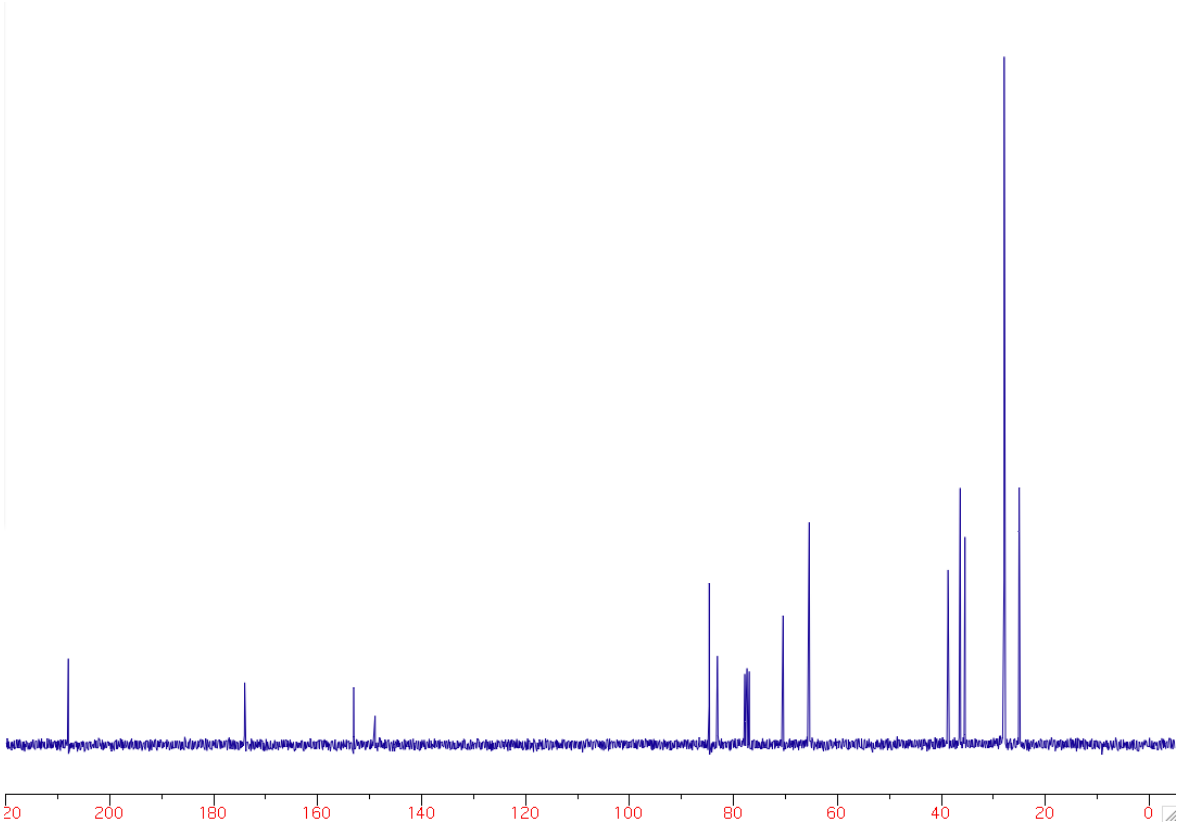


^{13}C NMR (75 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, $CDCl_3$)



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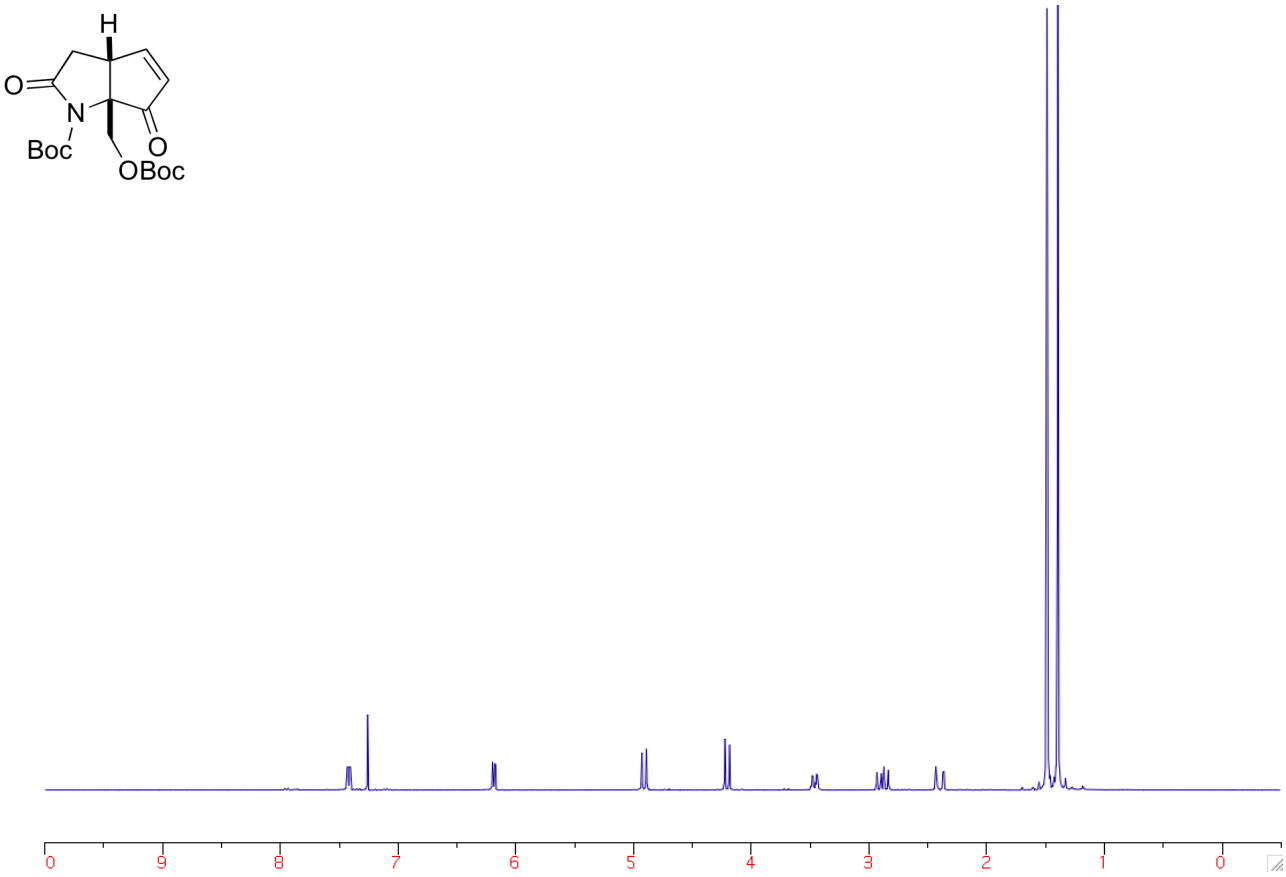
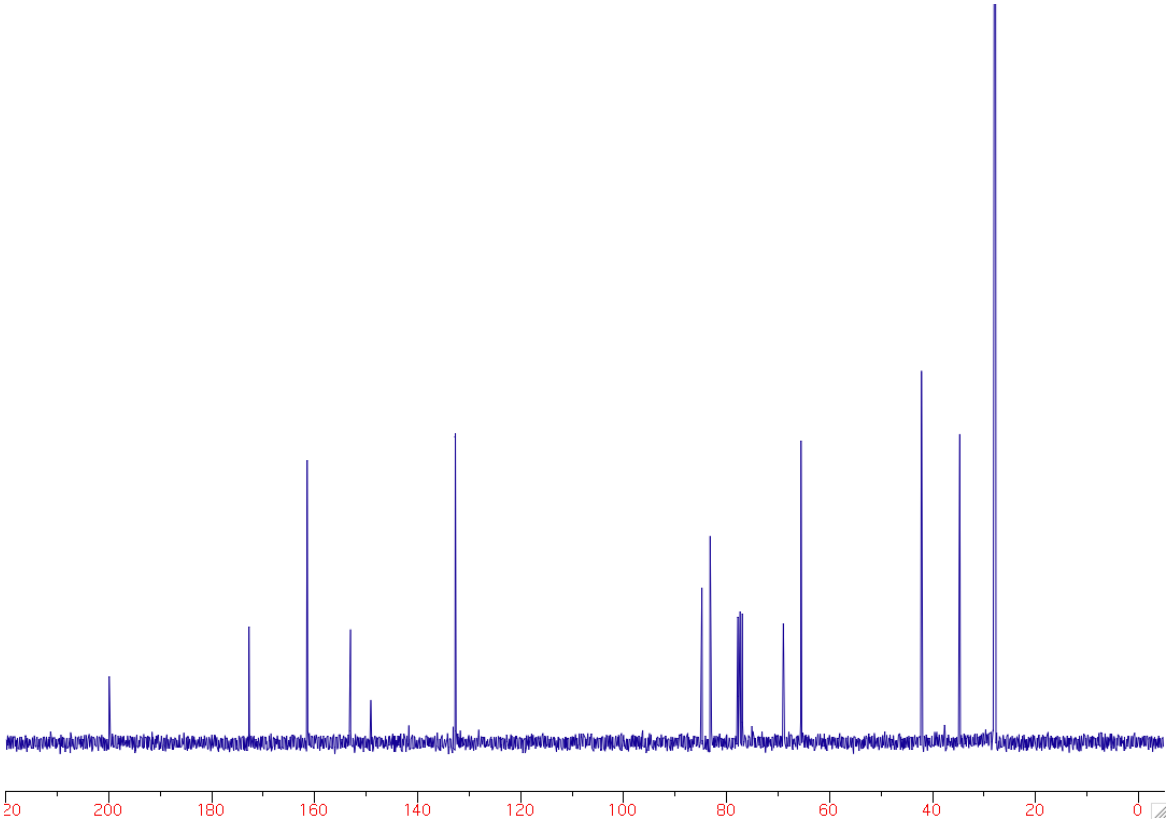
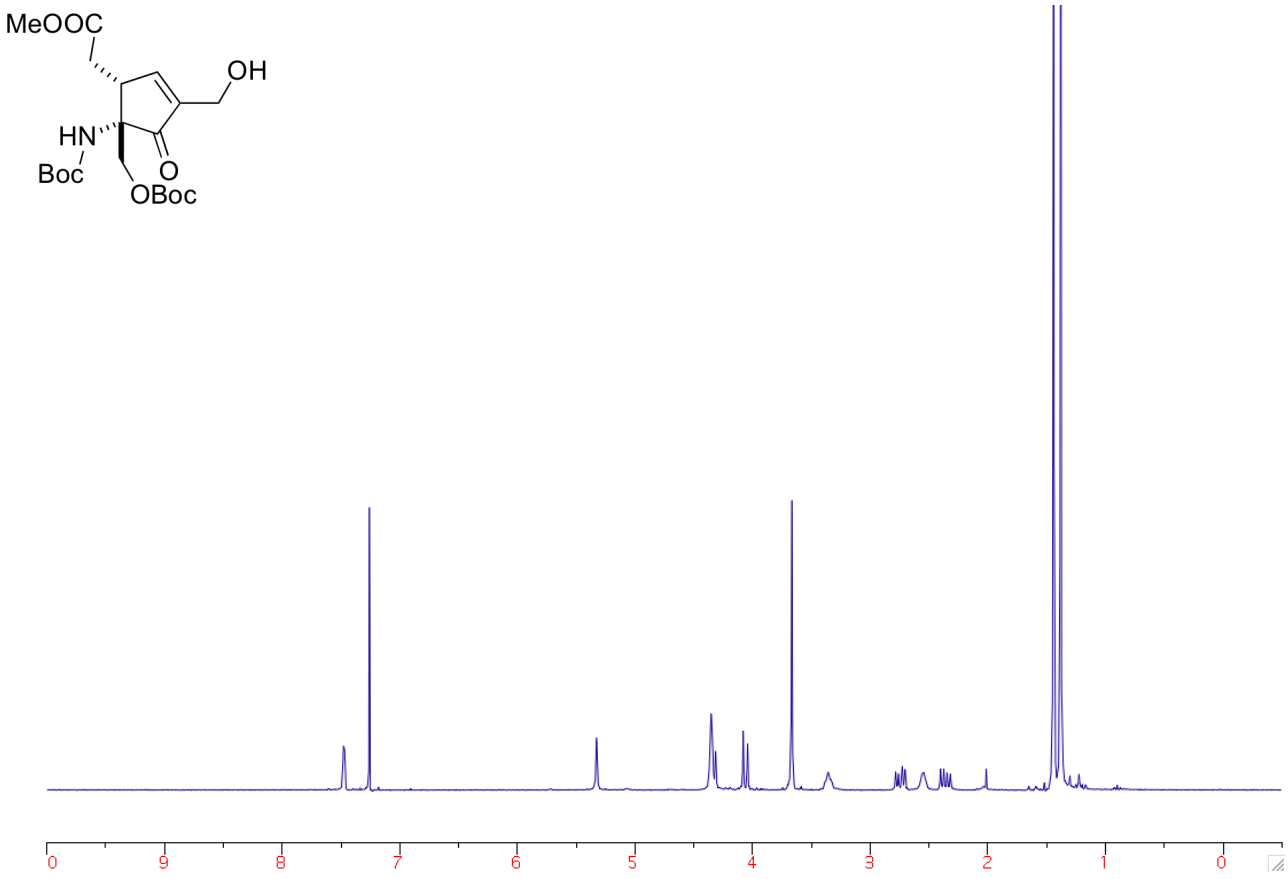


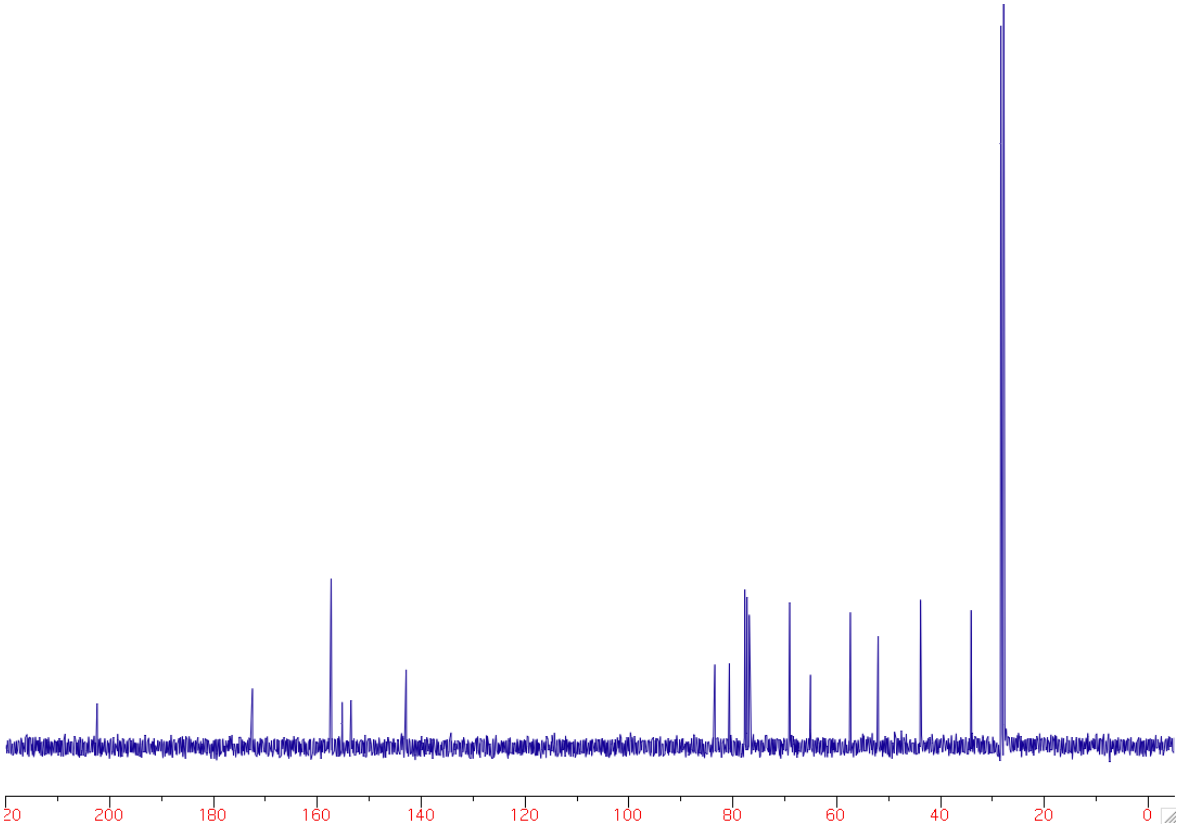
^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, $CDCl_3$)



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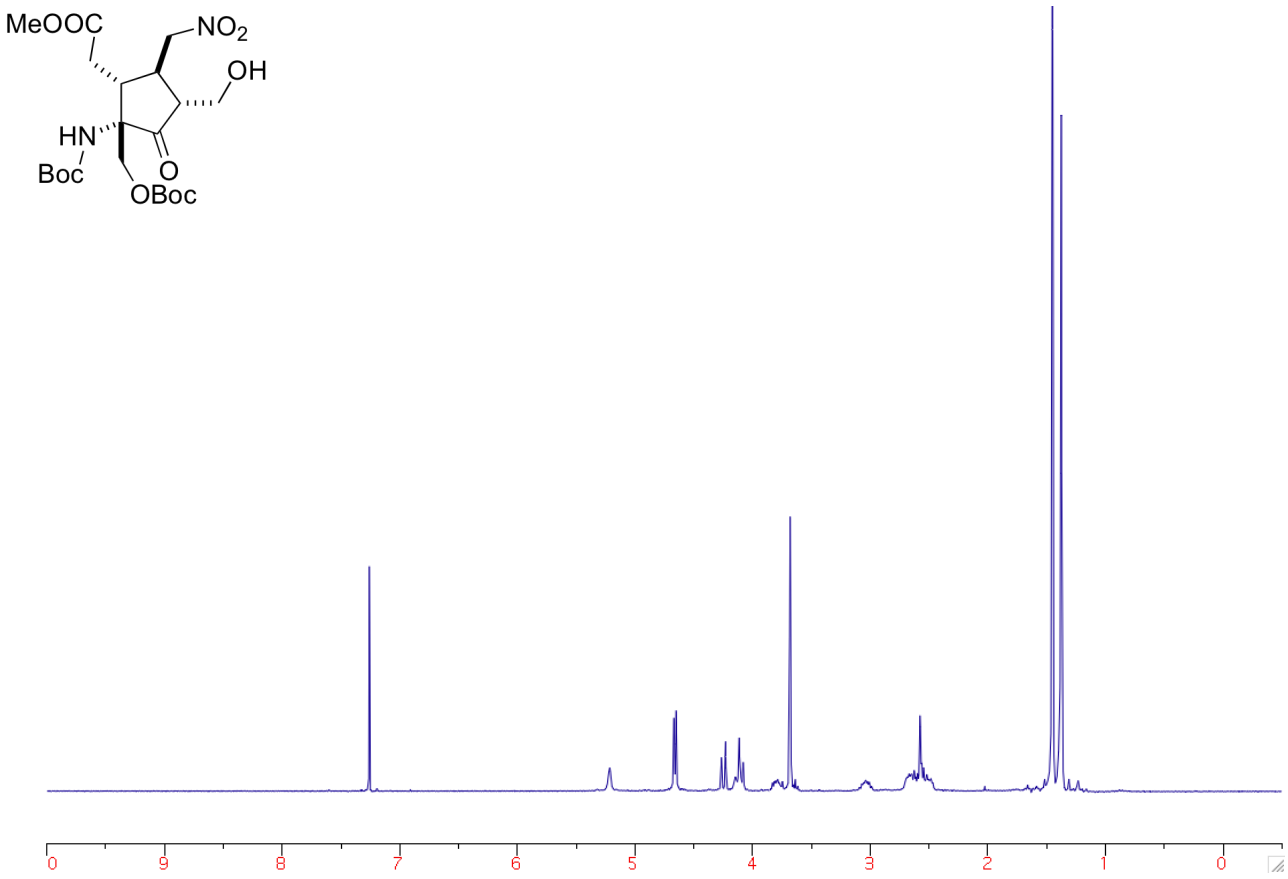
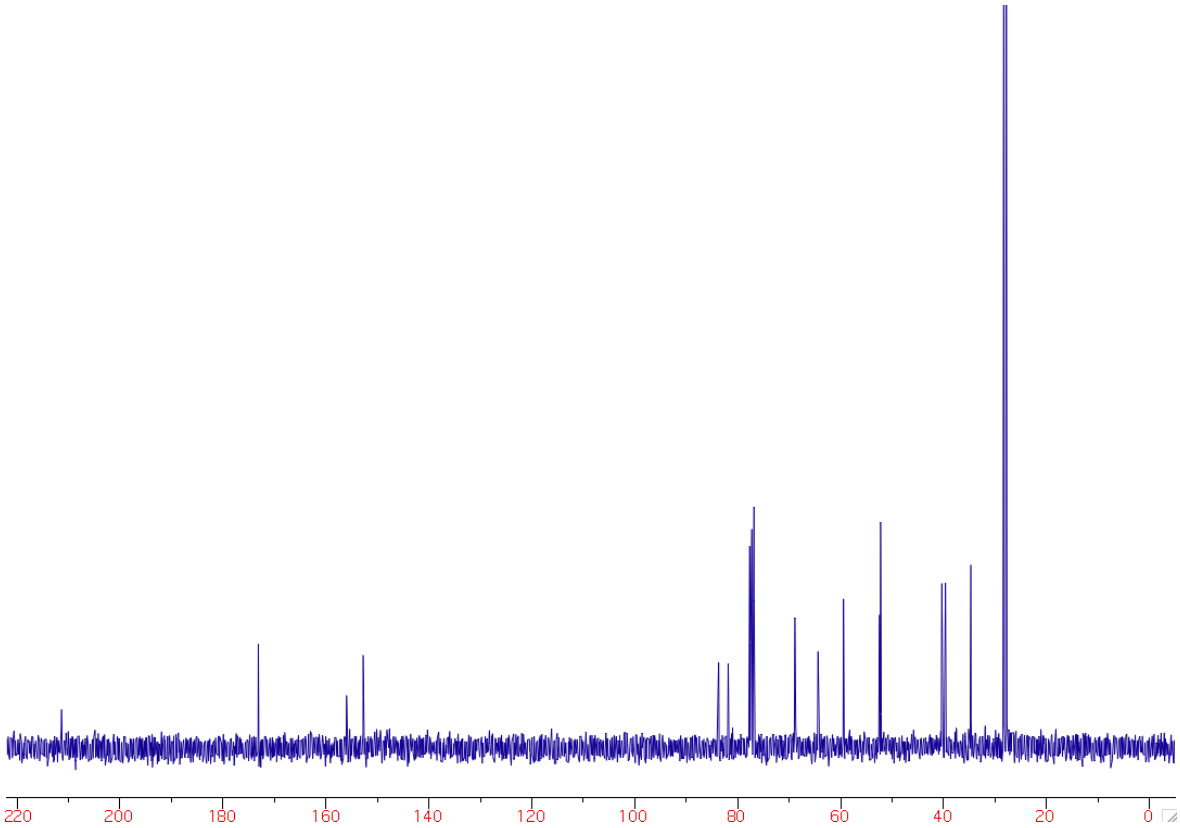
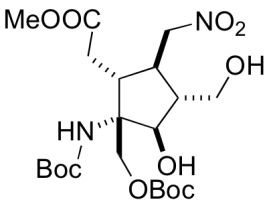
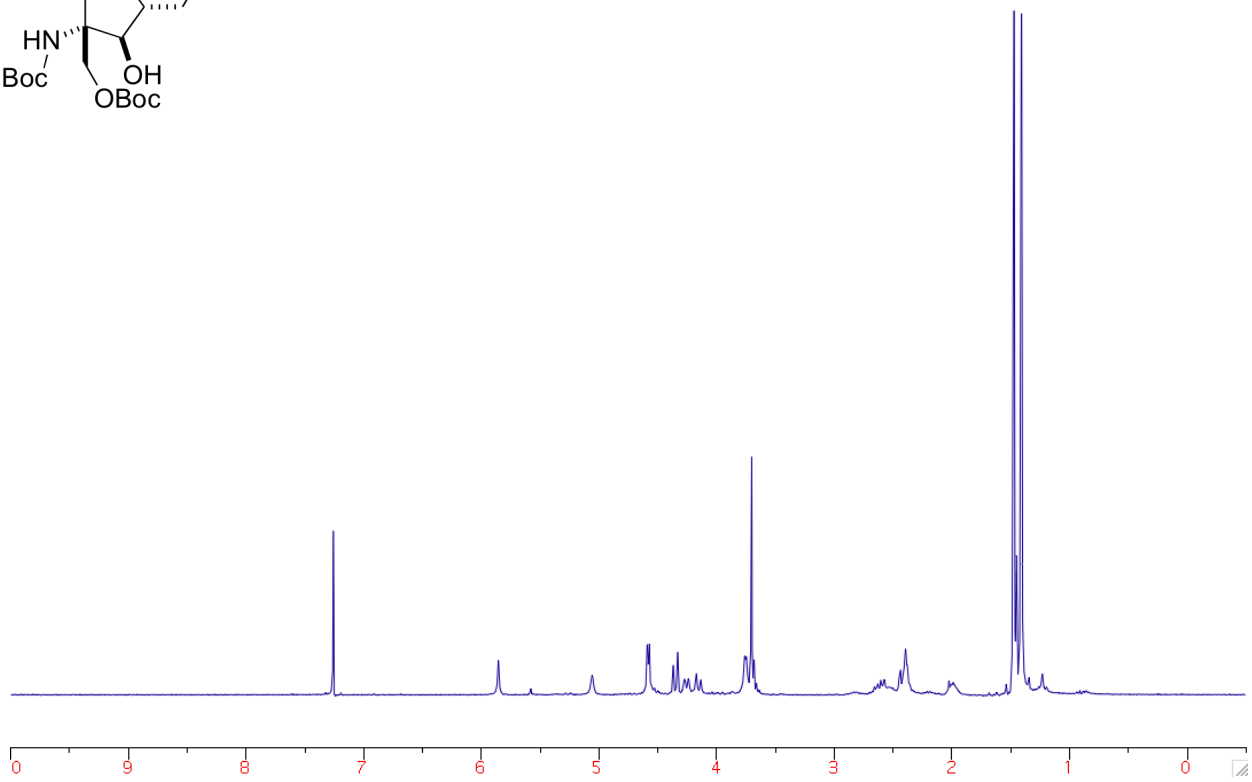


^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)





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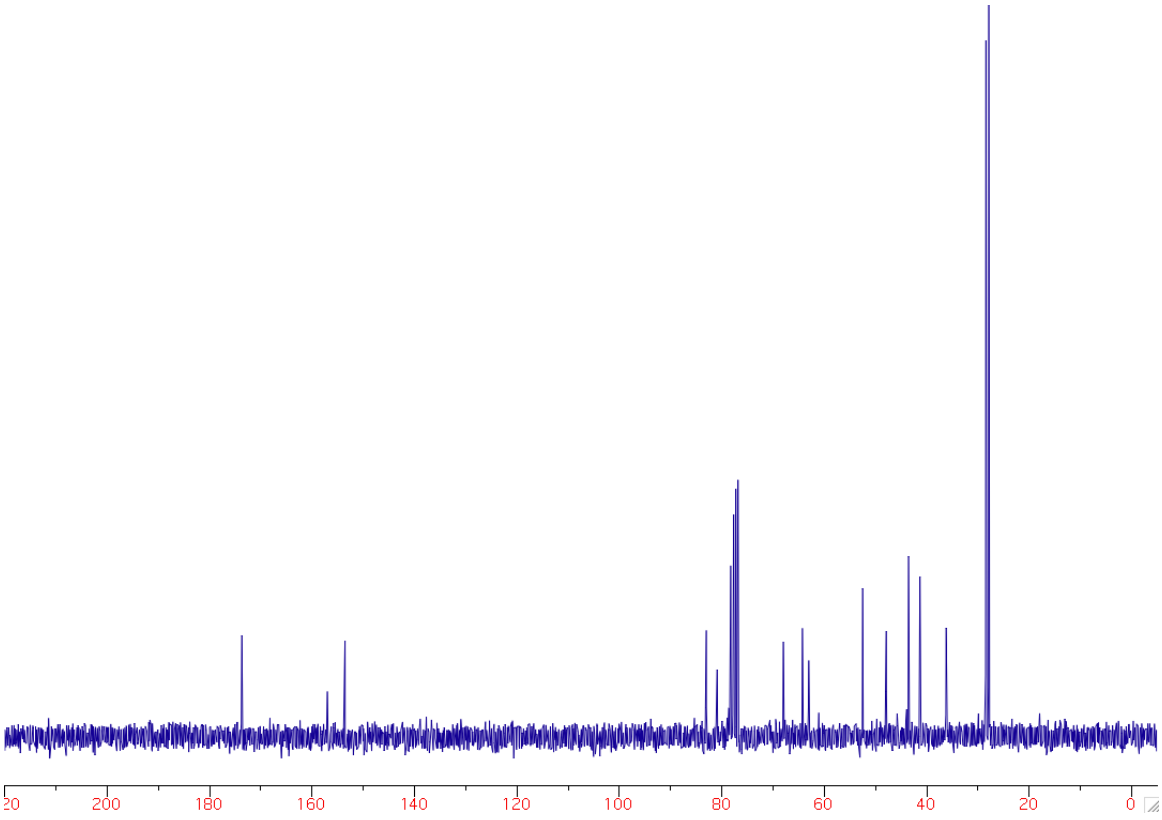

^{13}C NMR (75 MHz, $CDCl_3$)