A Simple and Efficient Pathway for the Total Synthesis of Marine Natural Products: Bengamide E and 5-*epi*-Bengamide E

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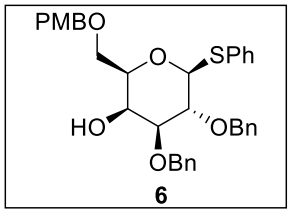
1. General Information

All the reactions were carried out under nitrogen or argon atmosphere and monitored by thin layer chromatography (TLC) using silica gel GF_{254} plates with detection by charring with 5% (v/v) H_2SO_4 in methanol or by phosphomolybdic acid (PMA) stain or by ultraviolet (UV) detection. All the chemicals were purchased from local suppliers and Sigma-Aldrich Chemicals Company. Solvents used in the reactions were distilled over dehydrating agents. Silica-gel (100-200 mesh) was used for column chromatography. IR spectra were recorded on JASCO FT/IR-5300. ^{1}H, ^{13}C, DEPT, COSY spectra were recorded on Bruker 400 MHz and 500 MHz NMR spectrometer in deuterated solvents ($CDCl_3$ / DMSO-d_6). ^{1}H NMR chemical shifts were reported in ppm (δ) with TMS as internal standard (δ 0.00) and ^{13}C NMR were reported in chemical shifts with solvent reference ($CDCl_3$, δ 77.00). High-resolution mass spectra (HRMS) were recorded on Bruker maXis ESI-TOF spectrometer.

2. Experimental Section

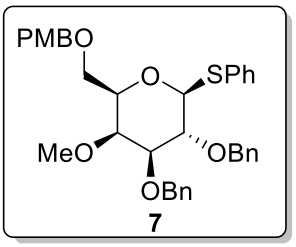
(2*R*,3*S*,4*S*,5*R*,6*S*)-4,5-bis(benzyloxy)-2-(((4-methoxybenzyl)oxy)methyl)-6(phenylthio)tetrahydro-2*H*-pyran-3-ol (6):



6

A solution of compound **5** (14.0 g, 24.5 mmol) in anhydrous DMF (100 mL) was cooled to 0 °C. Solid $NaCNBH_3$ (7.7 g, 122.7 mmol) was added portion-wise for 15 min. The mixture was stirred under a nitrogen atmosphere for 30 min. A solution of TFA (18.8 mL, 245.6 mmol) in dry DMF (50 mL) was added dropwise to the reaction mixture. The resulting suspension was stirred for 2 h at 0 °C and then overnight at room temperature. Solid $NaHCO_3$ was added to neutralize the reaction mixture. DMF was evaporated and the residue was diluted with ethyl acetate (300 mL) and the organic phase was washed with water (2 x100 mL) and brine (100 mL) solution. The organic phase was collected, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography to afford pure compound **6** as a white solid (12.9 g, 92 %). R_f = 0.62 (30 % AcOEt/hexane). $[\alpha]_D^{25}$=+0.5 (c = 1.5, CH_2Cl_2). mp = 95-97 °C
IR (neat): 3433, 2902, 2857, 1616, 1587 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58-7.56 (m, 2H), 7.41-7.39 (m, 2H), 7.35-7.23 (m, 13H), 6.88-6.85 (m, 2H), 4.82 (d, 1H, *J* = 10.5 Hz), 4.75-4.68 (m, 3H), 4.63 (d, 1H, *J* = 10.0 Hz), 4.49 (s, 2H), 4.09-4.08 (m, 1H), 3.79 (s, 3H), 3.78-3.71 (m, 3H), 3.58-3.55 (m, 2H) 2.54 (d, 1H, *J* = 1.8 Hz).
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ 159.2, 138.1, 137.6, 133.9, 131.7 (3), 130.0, 129.3 (2), 128.8 (2), 128.4 (2), 128.3 (2), 128.2 (2), 127.9 (2), 127.7 (2), 127.2, 113.8, 87.6, 82.5, 77.2, 76.9, 75.6, 73.3, 72.0, 69.1, 66.8, 55.2.
HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{34}H_{36}NaO_6S$ 595.2125, found 595.2128

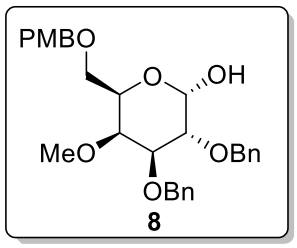
(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4-bis(benzyloxy)-5-methoxy-6-(((4-methoxybenzyl)oxy)methyl)-2-(phenylthio)tetrahydro-2*H*-pyran (7):



7

A suspension of **6** (10.0 g, 17.4 mmol) in anhydrous DMF (60 mL) and NaH (1.38 g, 60% in oil, 34.8 mmol) was stirred at 0 °C. After stirring for 15 min, methyl iodide (2.70 mL, 34.8 mmol) was added and stirring was continued for 2 h. After completion of the reaction (by TLC) the reaction mixture was cooled again to 0 °C prior to the addition of methanol (10 mL) and water. The resulting mixture was then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (100 mL), brine (100 mL) and dried over anhydrous sodium sulphate. After filtration and concentration of the filtrate to dryness under vacuum, a residue was obtained that was purified by column chromatography over silica gel to afford pure compound **7** as white solid (9.73 g, 95 %) R_f = 0.40 (20% AcOEt /hexane). mp = 88-90 °C
IR (neat): 3033, 2923, 2855, 1616,1513,1087 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58-7.56 (m, 2H), 7.43-7.38 (m, 2H), 7.36-7.23 (m, 13H), 6.91-6.89 (m, 2H), 4.86 (d, 1H, *J* = 10.0 Hz), 4.81 (d, 1H, *J* = 10.0 Hz), 4.76 (d, 2H, *J* = 10.0 Hz), 4.66 (d, 1H, *J* = 10.0 Hz), 4.50 (q, 2H, *J* = 11.5 Hz), 3.86-3.82 (m, 4H), 3.74-3.71 (m, 2H), 3.66 (dd, 1H, *J* = 6.0 Hz, *J* = 9.5 Hz), 3.60 (s, 3H), 3.59-3.56 (m, 2H).
^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 159.3, 138.3, 138.1, 134.4, 131.6 (2), 130.0, 129.6 (2), 128.8 (2), 128.4 (2), 128.3 (4), 127.7 (3), 127.5, 127.1, 113.8 (2), 88.2, 83.8, 77.8, 77.1, 75.8, 75.8, 73.3, 72.6, 68.2, 61.3, 55.3.
HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{35}H_{38}NaO_6S$ 609.2281, found 609.2289.

(3*R*,4*S*,5*S*,6*R*)-3,4-bis(benzyloxy)-5-methoxy-6-(((4-methoxybenzyl)oxy)methyl)tetrahydro-2*H*-pyran-2-ol (8):

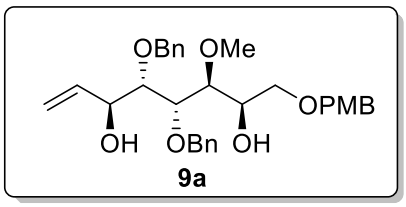


8

N-Bromo succinimide (3.64 g, 20.4 mmol) was added to a solution of **7** (10.0 g, 17.0 mmol) in acetone/H_2O (100 mL; 9/1, v/v) at 0 °C. After 30 min, 20 mL of a saturated aqueous sodium bicarbonate solution was added. The reaction mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed once with water (100 mL), brine (100 mL) and dried over anhydrous sodium sulphate. After filtration and concentration, the crude product was purified by column chromatography to give compound **8** as an anomeric mixture as a white solid (7.8 g, 93 %). The compound was used as an anomeric mixture for next step. R_f = 0.52 (40% AcOEt/hexane). mp = 90-92 °C
IR (neat): 3353, 2934, 2865, 1614, 1514, 1157, 1076, 734 cm^{-1}.
Selective data for major anomer (8α): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.25 (m, 10H), 7.23 (bd, 2H), 6.88-6.86 (m, 2H), 5.24 (d, 1H, *J* = 3.5 Hz), 4.83-4.80 (m, 1H), 4.75 (d, 2H, *J* = 10.0 Hz), 4.68 (d, 1H, *J* = 11.5 Hz), 4.51 (d, 1H, *J* = 11.5 Hz), 4.43 (dd, 1H, *J* = 4.0 Hz, *J* = 11.5 Hz), 4.14

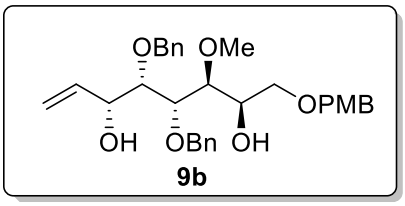
(t, 1H, *J* = 6.5 Hz), 3.93 (dd, 1H, *J* = 3.5 Hz, *J* = 10.0 Hz), 3.85 (dd, 1H, *J* = 3.0 Hz, *J* = 10.0 Hz), 3.80 (s, 3H), 3.71 (bd, 1H, *J* = 2.0 Hz), 3.64-3.58 (m, 2H), 3.54 (s, 3H), 3.17 (bs, 1H).
$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): 159.4, 138.5, 138.3, 130.0, 129.6 (2), 128.4 (3), 128.3, 128.1, 127.9 (2), 127.8, 127.7, 127.6 (2), 113.9, 91.9, 78.5, 77.0, 76.7, 73.7, 73.2, 72.8, 69.3, 68.3, 61.4, 55.3.
HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{29}H_{34}NaO_7$ 517.2197, found 517.2199.

(2*R*,3*S*,4*S*,5*S*,6*S*)-4,5-bis(benzyloxy)-3-methoxy-1-((4-methoxybenzyl)oxy)oct-7-ene-2,6-diol (9a) and (2*R*,3*S*,4*S*,5*S*,6*R*)-4,5-bis(benzyloxy)-3-methoxy-1-((4-methoxybenzyl)oxy)oct-7-ene-2,6-diol (9b):



9a

To a stirred solution of the hemiacetal **8** (2.5 g, 5.0 mmol) in anhydrous THF (20.0 mL) at 0 °C under nitrogen, vinyl magnesium bromide (1 M in THF) (50.0 mL, 50.0 mmol) was added dropwise in three portions. The reaction mixture was stirred at 0 °C for 4 h and then 12 h at room temperature. After the complete consumption of starting material (monitored by TLC), the reaction was quenched by the careful addition of aqueous NH_4Cl solution. The phases were separated between ethyl acetate (3 x 100 mL) and water (100 mL). The combined organic layer was washed once with water (100 mL), brine (100 mL) and dried over anhydrous sodium sulphate. After filtration and concentration, the crude product containing the mixture of two diastereomers was purified by column chromatography over silica gel (Hexane/AcOEt; 7:3), affording compound **9a** (1.79 g, 68 %) and **9b** (580 mg, 22 %), total (2.37 g, 90 %; **9a**:**9b** = 3:1).
Compound **9b** was synthesized from hemiacetal **8** (2.0 g, 4.0 mmol) and vinyl magnesium bromide (1 M in THF) (48.0 mL, 48.0 mmol) at -78 °C using the above procedure. **9a** (660 mg, 31 %) and **9b** (1.33 g, 63 %), total (1.99 g, 94 %; **9a**:**9b** = 1:2).
9a; colorless oil. R_f = 0.44 (40 % AcOEt in hexanes).
Diastereomer 9a: IR (neat): 3440, 2926, 2856 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.26 (m, 12H), 6.88 (d, 1H, *J* = 9.0 Hz), 6.03 (ddd, 1H, *J* = 6.0 Hz, *J* = 10.5 Hz, *J* = 17.0 Hz), 5.45 (d, 1H, *J* = 17.0 Hz), 5.30 (d, 1H, *J* = 10.5 Hz), 4.78-4.73 (m, 3H), 4.67 (d, 1H, *J* = 11.5 Hz), 4.53 (m, 3H), 4.11-4.10 (m, 1H), 3.96 (dd, 1H, *J* = 4.5 Hz, *J* = 6.0 Hz), 3.81 (s, 3H), 3.68 (t, 1H, *J* = 4.5 Hz), 3.60-3.55 (m, 3H), 3.36 (s, 3H), 2.96 (bs, 2H).
$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ 159.3, 138.1, 137.9, 137.4, 130.1, 129.4 (2), 128.4 (4), 128.1 (2), 127.9 (2), 127.8, 127.7, 116.7, 113.8 (2), 80.6, 79.5, 78.9, 74.2, 72.9, 72.8, 72.2, 70.8, 69.4, 59.8, 55.2.
HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{31}H_{38}NaO_7$ 545.2510, found 545.2508**.**

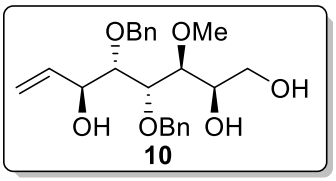


9b

9b; colorless oil. R_f = 0.46 (40 % AcOEt in hexanes).

Diastereomer 9b: IR (neat): 3442, 2928, 2860 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.30 (m, 10H), 7.28-7.26 (m, 2H), 6.89 (d, 2H, *J* = 8.5 Hz), 5.97 (ddd, 1H, *J* = 5.0 Hz, *J* = 10.5 Hz, *J* = 17.0 Hz), 5.36 (dt, 1H, *J* = 1.5 Hz, *J* = 17.5 Hz), 5.22 (dt, 1H, *J* = 1.5 Hz, *J* = 10.5 Hz), 4.78-4.66 (m, 5H), 4.50 (d, 2H, *J* = 5.0 Hz), 4.35 (bs, 1H), 4.06-4.04 (m, 1H). 3.93 (dd, 1H, *J* = 4.0 Hz, *J* = 6.0 Hz), 3.82 (s, 3H), 3.66-3.62 (m, 2H), 3.59 (d, 2H *J* = 6.0 Hz), 3.42 (s, 3H).
^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 159.3, 138.5, 138.1, 138.0, 130.1, 129.5 (2), 128.4 (4), 128.0 (2), 127.9 (2), 127.8, 127.7, 115.9, 113.8 (2), 81.5, 80.1 (2), 74.6 (2), 73.1, 71.8, 70.6, 70.0, 59.7, 55.3.
HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{31}H_{38}NaO_7$ 545.2510, found 545.2509**.**

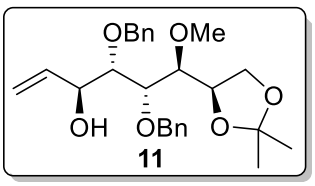
(2*R*,3*S*,4*S*,5*S*,6*S*)-4,5-bis(benzyloxy)-3-methoxyoct-7-ene-1,2,6-triol (10):



10

Compound **9a** (1.7 g, 3.3 mmol) was dissolved in a mixture of acetonitrile/water (40 mL, 9:1 v/v) and the reaction mixture was stirred for 15 min at room temperature. Then Ceric ammonium nitrate (5.4 g, 9.9 mmol) was added at room temperature and the reaction mixture was stirred for 1 h. After completion of the reaction as confirmed by TLC, the solvent was removed completely, and the crude product was directly loaded on the column for purification to afford pure compound **10** as colorless oil (1.2 g, 90 %). R_f = 0.25 (5% MeOH/$CHCl_3$).
IR (neat): 3402, 2926, 2852, 1458 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.29 (m, 10H), 6.06 (ddd, 1H, *J* = 5.5 Hz, *J* = 10.5 Hz, *J* = 16.5 Hz), 5.51 (d, 1H, *J* = 15.5 Hz), 5.31 (d, 1H, *J* = 10.5 Hz), 4.79 (dd, 2H, *J* = 2.5 Hz, *J* = 11.0 Hz), 4.73 (d, 1H, *J* = 11.0 Hz), 4.68 (d, 1H, *J* = 11.5 Hz), 4.48 (t, 1H, *J* = 5.0 Hz), 3.99-3.93 (m, 2H), 3.73 (dd, 1H, *J* = 7.0 Hz, *J* = 11.0 Hz), 3.68-3.64 (m, 2H), 3.50 (dd, 1H, *J* = 2.0 Hz, *J* = 5.5 Hz), 3.39 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 137.9, 137.7, 137.3, 128.5 (4), 128.2 (2), 128.0, 127.9 (2), 127.8, 116.8, 80.8, 80.3, 79.1, 74.4, 73.1, 72.3, 71.2, 64.1, 59.6.
HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{30}NaO_6$ 425.1935, found 425.1939.

(3*S*,4*S*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-methoxyhex-1-en-3-ol (11):



11

Compound **10** (1.0 g, 2.5 mmol) was dissolved in anhydrous acetonitrile (40 mL) and stirred for 10 min at room temperature. To the resulting solution, 2,2-dimethoxypropane (0.27 mL, 3.2 mmol) and camphor sulphonic acid (0.06 g, 0.24 mmol) were added. After stirring the reaction mixture for 3 h at room temperature, the reaction mixture was quenched with triethylamine and concentrated in vacuo to form a yellow solid. The crude product was subsequently purified by flash column chromatography to afford pure pale-yellow oil **11** (1.01 g, 92 %). R_f = 0.48 (30 % AcOEt/hexane).

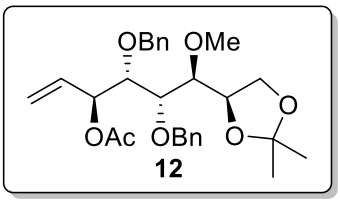
IR (neat): 3456, 2985, 2934, 1452, 1072, cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.27 (m, 10H), 6.01 (ddd, 1H, *J* = 5.5 Hz, *J* = 10.5 Hz, *J* = 17.5 Hz), 5.46 (dt, 1H, *J* = 1.5 Hz, *J* = 17.0 Hz), 5.31 (dt, 1H, *J* = 2.0 Hz, *J* = 10.5 Hz), 4.73 (d, 2H, *J* = 11.5 Hz,), 4.62-4.53 (m, 3H), 4.32-4.29 (m, 1H), 3.98 (dd, 1H, *J* = 6.5 Hz, *J* = 8.5 Hz), 3.79-3.75 (m, 2H), 3.65 (dd, 1H, *J* = 3.0 Hz, *J* = 6.0 Hz), 3.45-3.42 (m, 4H), 3.08 (d, 1H *J* = 5.5 Hz), 1.45 (s, 3H), 1.34 (s, 3H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ 138.0, 137.9, 137.8, 128.5 (2), 128.4 (2), 128.0 (4), 127.9, 127.8, 116.4, 108.8, 81.4, 80.4, 79.2, 76.6, 73.7, 72.5, 72.1, 66.3, 60.6, 26.5, 25.6.

HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{26}H_{34}NaO_6$ 465.2248, found 465.2256.

(3*R*,4*S*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-methoxyhex-1-en-3-yl acetate (12):



12

Compound **11** (0.90 g, 2.0 mmol) was dissolved in pyridine (4.0 mL) and the reaction mixture was stirred for 15 min at 0 °C. Acetic anhydride (0.37 mL, 4.0 mmol) was added very slowly at 0 °C and the reaction mixture was allowed to come to room temperature and stirred for 3 h. After complete consumption of starting material, solvent was evaporated under reduced pressure and directly loaded on the column for purification. The Purified compound was obtained as colorless oil **12** (0.92 g, 93%). R_f = 0.60 (30% AcOEt /hexane).

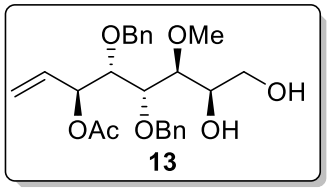
IR (neat): 2929, 1731, 1067 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.29 (m, 10H), 6.10 (ddd, 1H, *J* = 6.0 Hz, *J* = 10.5 Hz, *J* = 17.0 Hz), 5.64 (dd, 1H, *J* = 5.0 Hz, *J* = 6.0 Hz), 5.43 (dd, 1H, *J* = 1.5 Hz, *J* = 17.5 Hz), 5.35 (d, 1H, *J* = 10.5 Hz), 4.80 (d, 1H, *J* = 11.5 Hz), 4.70-4.59 (m, 3H), 4.29 (dd, 1H, *J* =7.5 Hz, *J* =13.5 Hz), 3.99-3.96 (m, 1H), 3.83-3.78 (m, 2H), 3.68 (dd, 1H, *J* = 4.5 Hz, *J* = 7.5 Hz), 3.46 (m, 3H), 3.39 (dd, 1H, *J* = 5.5 Hz, *J* = 7.5 Hz), 2.07(s, 3H), 1.45 (s, 3H), 1.37 (s, 3H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ 169.9, 138.2, 137.9, 133.3, 128.3 (4), 127.9 (4), 127.7, 127.6, 118.7, 108.6, 81.3, 80.3, 79.4, 76.9, 74.7, 74.5, 73.4, 66.4, 60.2, 26.4, 25.5, 21.2.

HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{28}H_{37}O_7$ 485.2534, found 485.2530.

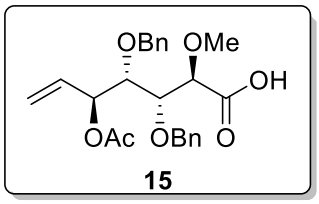
(3*S*,4*S*,5*S*,6*S*,7*R*)-4,5-bis(benzyloxy)-7,8-dihydroxy-6-methoxyoct-1-en-3-yl acetate (13):



13

The compound **12** (800 mg, 1.6 mmol) was dissolved in methanol (15 mL) and treated with *p*-toluene sulphonic acid (28 mg, 0.16 mmol) at 25 °C. The reaction mixture was stirred for 1 h. After removal of solvent the crude product was purified by column chromatography to give compound **13** as colorless oil (690 mg, 94 %). R_f = 0.30 (30% AcOEt /hexane).
IR (neat): 3430, 2927, 1732 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.18 (m, 10H), 6.01 (ddd, 1H, *J* = 7.0 Hz, *J* = 10.5 Hz, *J* = 17.5 Hz), 5.42 (bd, 1H, *J* = 7.0 Hz), 5.34-5.28 (m, 2H), 4.70 (d, 1H, *J* = 11.0 Hz), 4.66 (d, 1H, *J* = 11.0 Hz), 4.61 (d, 1H, *J* = 3.5 Hz), 4.60 (d, 1H, *J* = 3.5 Hz), 3.89 (bs, 1H), 3.75-3.74 (m, 2H), 3.64 (dd, 1H, *J* = 6.5 Hz, *J* = 11.0 Hz), 3.57 (dd, 1H, *J* = 5.0 Hz, *J* = 11.0 Hz), 3.36-3.34 (m, 1H), 3.28 (s, 3H), 3.06 (bs, 1H), 1.95 (s, 3H).
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ 170.0, 138.2, 137.8, 132.6, 128.4 (4), 128.1 (2), 128.0 (2), 127.9, 127.7, 119.7, 80.5, 79.8, 79.3, 75.4, 75.1, 74.2, 71.3, 64.0, 59.1, 21.2.
HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{33}O_7$ 445.2221, found 445.2223.

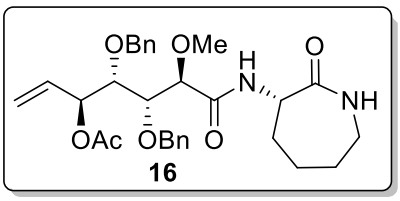
(2*R*,3*R*,4*S*,5*S*)-5-acetoxy-3,4-bis(benzyloxy)-2-methoxyhept-6-enoic acid (15):



15

To a solution of compound **13** (0.65 g, 1.4 mmol) in THF and water (24.0 mL, 5:1 v/v), sodium periodate (0.32 g, 2.1 mmol) and sodium hydrogen carbonate (135 mg, 1.6 mmol) were added sequentially. After stirring for 1 h at room temperature, the suspension was filtered through a plug of celite and the filtrate was concentrated under reduced pressure. NaH_2PO_4 (0.90 g, 7.5 mmol) and aqueous $NaClO_2$ (0.40 g, 4.5 mmol) were added to a vigorously stirred suspension of crude aldehyde **14** (0.60 g, 1.5 mmol) in 2-methyl-2-butene (1.2 g, 17.0 mmol) and ^{t}BuOH (1.0 mL) at room temperature and continued stirring for 40 min. After the complete disappearance of starting material, the solvent was removed and the resulting solid residue was dissolved in methanol and filtered through celite; the filtrate was concentrated in vacuo to obtain the acid derivative **15,** which is used for the next step without further purification. R_f = 0.25 (5% MeOH/$CHCl_3$).

(3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-methoxy-7-oxo-7-(((*S*)-2-oxoazepan-3-yl)amino)hept-1-en-3-yl acetate (16):

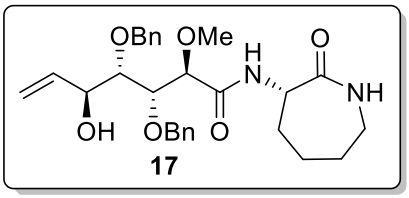


16

To a stirred solution of the crude acid **15** (200 mg, 0.46 mmol) in dry DMF was added Hunig's base (131 mg, 1.02 mmol). After 30 min, L-(-)-α-amino-caprolactam (90 mg, 0.70 mmol) was added. When the solution was homogenous benzotriazol-1-yloxytris (dimethyl amino) phosphonium hexafluorophosphate (BOP) (243 mg, 0.55 mmol) was added in one portion and

the mixture was stirred at room temperature 12 h. The reaction mixture was quenched with ammonium chloride and extracted with ether. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude product was purified by silica gel column chromatography to afford compound **16** as a white foam (218 mg, 87 %). R_f = 0.40 (100 % AcOEt). $[\alpha]_D^{25}$=+32.58 (c = 0.5, $CHCl_3$).
IR (neat): 3395, 2931, 2851, 1660, 1740 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87(d, 1H, *J* = 6.0 Hz), 7.35-7.22 (m, 10H), 6.03 (ddd, 1H, *J* = 7.0 Hz, *J* = 10.5 Hz, *J* = 17.0 Hz), 5.95 (dd, 1H, *J* = 7.0 Hz, *J* = 6.5 Hz), 5.50 (dd, 1H, *J* = 4.5 Hz, *J* = 7.5 Hz), 5.37 (dt, 1H, *J* = 1.6 Hz, *J* = 17.2 Hz), 5.33 (m, 1H), 4.72-4.61 (m, 4H), 4.51 (ddd, 1H, *J* = 1.5 Hz, *J* = 6.0 Hz, *J* =11.0 Hz), 4.00 (dd, 1H, *J* = 3.5 Hz, *J* = 6.5 Hz), 3.78 (d, 1H, *J* = 3.5 Hz), 3.88 (dd, 1H, *J* = 4.0 Hz, *J* = 7.0 Hz), 3.36 (s, 3H), 3.31-3.18 (m, 2H), 2.09-2.06 (m, 1H), 2.01 (s, 3H), 1.98-1.95 (m, 1H), 1.88-1.80 (m, 2H), 1.50-1.37(m, 2H).
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ 175.0, 169.8, 168.9, 138.7, 138.3, 132.9, 128.2 (2), 128.1 (4), 128.0 (2), 127.5, 127.4, 119.4, 82.0, 80.5, 80.1, 74.9 (2), 74.8, 58.4, 51.9, 42.1, 31.4, 28.9, 27.9, 21.2.
HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{30}H_{39}N_2O_7$;539.2752, found 539.2757.

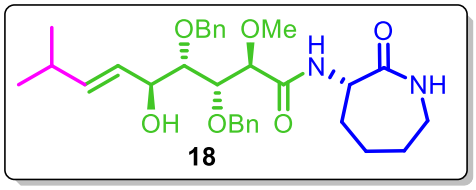
(2*R*,3*R*,4*S*,5*S*)-3,4-bis(benzyloxy)-5-hydroxy-2-methoxy-*N*-((*S*)-2-oxoazepan-3-yl)hept-6-enamide (17):



17

Compound **16** (200 mg, 0.37 mmol) was dissolved in anhydrous methanol (5.0 mL) and potassium carbonate (5 mg, 0.037 mmol) was added and the reaction mixture was stirred for 1 h. After completion of the reaction, methanol was evaporated under a vacuum, and the crude compound was stirred in hexane and decanted to yield **17** as a white foam (180 mg, 98%). R_f = 0.50 (30% AcOEt /hexane). $[\alpha]_D^{25}$=+39.34 (c = 0.5, $CHCl_3$).
IR (neat): 3392, 2928, 1648 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$+DMSO): δ 7.21-7.14 (m, 10H), 5.92 (ddd, 2H, *J* = 6.0 Hz, *J* = 10.5 Hz, *J* = 17.0 Hz), 5.28 (d, 1H, *J* = 17.0 Hz), 5.13 (d, 1H, *J* = 10.5 Hz), 4.56-4.48 (m, 4H), 4.31 (d, 1H, *J* = 10.5 Hz), 4.25 (t, 1H, *J* = 6.0 Hz), 3.91-3.87 (m, 2H), 3.58 (dd, 1H, *J* = 4.5, *J* = 6.0), 3.26 (s, 3H), 3.11-303 (m, 2H), 1.87-1.82 (m, 2H), 1.72-1.62 (m, 2H), 1.38-1.21 (m, 2H).
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$+DMSO): δ 175.0, 169.7, 130.0, 137.8, 137.5, 128.0 (4), 127.8 (4), 127.4 (2), 116.2, 81.6, 81.1, 80.1, 74.3, 74.0, 72.3, 58.1, 51.6, 41.5, 30.9, 28.4, 27.5.
HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{28}H_{37}N_2O_6$ 497.2646, found 497.2650.

(2*R*,3*R*,4*S*,5*S*,*E*)-3,4-bis(benzyloxy)-5-hydroxy-2-methoxy-8-methyl-*N*-((*S*)-2-oxoazepan-3-yl)non-6-enamide (18):



18

To a stirred solution of **17** (100 mg, 0.20 mmol) and 3-methyl-1-butene/CH_2Cl_2 (16 mL, 5:1 v/v) in a sealed tube, was added second-generation Grubb's catalyst (51 mg, 0.06 mmol) at 0 °C, and the resulting solution was allowed to come at room temperature. The reaction mixture was stirred at 40 °C for 8 h. After completion of the reaction (indicated by TLC), the solvent was evaporated under vacuum, and the resulting crude reaction mixture was purified by silica gel column chromatography to yield **18** as a brown foam (103 mg, 95.0 %). R_f = 0.35 (6 % Acetone/hexane). $[\alpha]_D^{25}$=+50.19 (c = 0.5, $CHCl_3$).

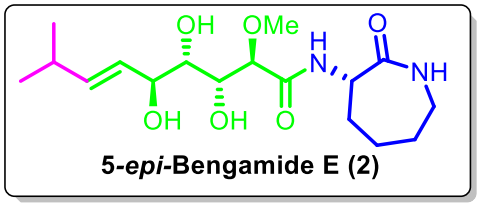
IR (neat): 3382, 2956, 2937, 1657 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, 1H, *J* = 6.0 Hz), 7.35-7.25 (m, 10H), 6.25 (t, 1H, *J* = 6.0 Hz), 5.77 (ddd, 1H, *J* = 1.0 Hz, *J* = 6.5 Hz, *J* = 15.5 Hz), 5.57 (ddd, 1H, *J* = 1.0 Hz, *J* = 7.0 Hz, *J* = 15.5 Hz), 4.75 (d, 1H, *J* = 11.0 Hz), 4.68 (d, 2H, *J* = 4.0 Hz), 4.62 (d, 1H, *J* = 11.0 Hz), 4.47 (ddd, 1H, *J* = 1.5 Hz, *J* = 6.0 Hz, *J* = 11.0 Hz), 4.33 (t, 1H, *J* = 6.5 Hz), 4.06 (d, 1H, *J* = 3.0 Hz), 3.99 (dd, 1H, *J* = 3.0 Hz, *J* = 6.0 Hz), 3.74 (t, 1H, *J* = 6.0 Hz), 3.40 (s, 3H), 3.21-3.18 (m, 2H), 2.37-2.30 (m, 1H), 2.10 (bd, 1H, *J* = 12.0 Hz), 2.00-1.97 (m, 1H), 1.85-1.76 (m, 2H), 1.53-1.48 (m, 1H), 1.43-1.35 (m, 1H), 1.00 (d, 6H, *J* = 2.5 Hz).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ 175.0, 169.5, 140.6, 138.5, 138.2, 128.3 (2), 128.2 (4), 127.9 (2), 127.6 (2), 126.4, 82.2, 81.8, 81.0, 74.6, 74.3, 72.7, 58.6, 52.0, 42.0, 31.4, 30.9, 28.9, 27.9, 22.3 (2).

HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{31}H_{43}N_2O_6$ 539.3116, found 539.3123.

(2*R*,3*R*,4*S*,5*S*,*E*)-3,4,5-trihydroxy-2-methoxy-8-methyl-*N*-((*S*)-2-oxoazepan-3-yl)non-6-enamide (2):



5-*epi*-Bengamide E (2)

To a solution of **18** (50 mg, 0.09 mmol) in a mixture of THF (3 mL) and liquid ammonia (15 mL) at -78 °C was added sodium metal until the blue color persisted. After 1 h, the starting material was completely consumed (monitored by TLC), the reaction mixture was allowed to come at room temperature and NH_3 (g) was evaporated very slowly. The residue was then partitioned between ethyl acetate (2 x 25 mL) and water (25 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude was purified by flash chromatography on silica gel (10:1 ethyl acetate/methanol) to give **2** as an off-white foam (20 mg, 62%). R_f = 0.30 (10 % MeOH/AcOEt).

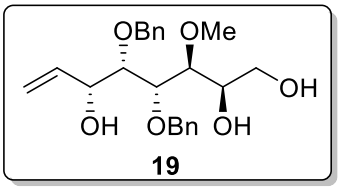
IR (neat): 3332, 1650 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 8.05 (bd, 1H, *J* = 6.5 Hz), 6.24 (bs, 1H), 5.79 (dd, 1H, *J* = 6.0 Hz, *J* = 15.5 Hz), 5.51 (dd, 1H, *J* = 6.0 Hz, *J* = 15.0 Hz), 4.56 (dd, 1H, *J* = 6.5 Hz, *J* = 11.0 Hz), 4.45 (bs, 1H), 4.30 (d, 1H, *J* = 6.5 Hz), 4.02 (d, 1H, *J* = 6.5 Hz), 3.82 (d, 1H, *J* = 7.0 Hz), 3.66 (d, 1H, *J* = 3.5 Hz), 3.56 (s, 3H), 3.32-3.29 (m, 2H), 2.36-2.32 (m, 1H), 2.10-2.04 (m, 2H), 1.90-1.83 (m, 2H), 1.62-1.55 (m, 1H), 1.48-1.43 (m, 1H), 1.02 (d, J = 6.5 Hz, 6H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ 174.7, 172.2, 140.4, 125.7, 80.6, 75.0, 71.9, 71.4, 60.0, 52.0, 42.1, 31.1, 30.7, 28.8, 27.9, 22.2 (2).

HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{30}N_2O_6Na$ 381.1996, found 381.1994.

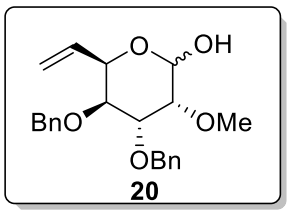
(2*R*,3*S*,4*S*,5*S*,6*R*)-4,5-bis(benzyloxy)-3-methoxyoct-7-ene-1,2,6-triol (19):



19

Compound **9b** (320 mg, 0.61 mmol) was dissolved in a mixture of acetonitrile/water (9:1 v/v, 8.0 mL) and the reaction mixture was stirred for 10 min at room temperature. Then Ceric ammonium nitrate (1.0 g, 1.83 mmol) was added at room temperature and the reaction mixture was stirred for 1 h. After the reaction was confirmed by TLC, solvent was removed completely, and the crude product **19** obtained was directly used for the next step without purification. R_f = 0.30 (5% MeOH/$CHCl_3$).

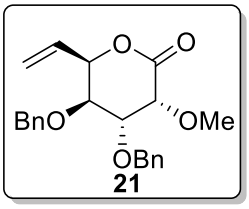
(3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-3-methoxy-6-vinyltetrahydro-2*H*-pyran-2-ol (20):



20

Sodium meta periodate (331 mg, 1.55 mmol) was dissolved in water (1.0 mL) and added to compound **19** (~0.61 mmol) in methanol (8.0 mL) at room temperature, a slightly exothermic reaction was observed. The reaction mixture was stirred 12 h at room temperature. After the starting material was consumed, the precipitate was filtered and washed with methanol. The solution was concentrated and provided the crude hemiacetal **20,** which was utilized for the next step without further purification. R_f = 0.42 (30 % AcOEt/hexane).

(3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-3-methoxy-6-vinyltetrahydro-2*H*-pyran-2-one 21:



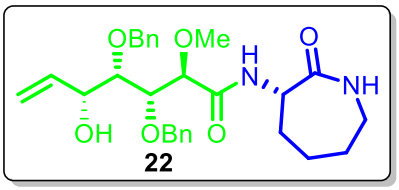
21

A solution of compound **20** (~0.61 mmol) in dichloromethane (15.0 mL) was cooled to 0 °C and sodium bicarbonate (282 mg, 3.35 mmol) was added slowly. After 10 min, Dess-Martin periodinane (DMP) (852 mg, 2.01 mmol) was added portion-wise to the reaction mixture and stirred at the same temperature for 3 h. After completion of the reaction (monitored by TLC), the precipitate was filtered and washed with dichloromethane (3 x 10 mL). The obtained solution was washed with saturated $NaHCO_3$ solution (20 mL), water (20 mL) and brine solution (20 mL). The organic layer was dried over Na_2SO_4 and filtered. Evaporation of the solvent under reduced pressure afforded the crude product which was purified by flash column chromatography to give **21** as a colorless oil (203 mg, 90% over three steps). R_f = 0.48 (30 % AcOEt/ hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): 7.40-7.33 (m, 6H), 7.30-7.28 (m, 2H), 7.26-7.25 (m, 2H), 5.96 (ddd, 1H, *J* = 6.5 Hz, *J* = 10.5 Hz, *J* = 17.0 Hz), 5.41 (dd, 1H, *J* = 1.0 Hz *J* = 17.0 Hz), 5.32 (d, 1H,

J = 10.5 Hz), 5.12 (dt, 1H, *J* = 1.0 Hz *J* = 7.0 Hz), 4.89 (d, 1H, *J* = 7.0 Hz), 4.61 (t, 2H, *J* = 11.5 Hz), 4.53 (d, 1H, *J* = 12.0 Hz), 4.22 (d, 1H, *J* = 3.0 Hz), 4.10 (dd, 1H, *J* = 3.0 Hz, *J* = 4.5 Hz), 3.68 (dd, 1H, *J* = 3.0 Hz, *J* = 4.5 Hz), 3.63 (s, 3H).
$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ 170.4, 137.7, 137.0, 132.4, 128.6 (2), 128.5 (2), 128.3, 128.0, 127.9 (4), 118.7, 80.3, 77.2, 76.8, 75.7, 73.6, 73.5, 60.0.
HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{25}O_5$; 369.1697, found 369.1699.

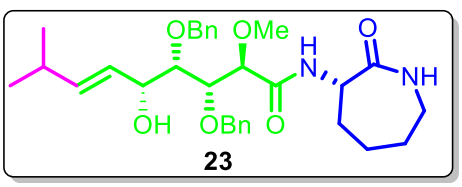
(2*R*,3*R*,4*S*,5*R*)-3,4-bis(benzyloxy)-5-hydroxy-2-methoxy-*N*-((*S*)-2-oxoazepan-3-yl)hept-6-enamide (22):



22

Lactone **21** (100 mg, 0.27 mmol) was dissolved in 9:1 mixture of THF-dioxane (4.0 mL) and stirred at room temperature. After 15 min L-(-)-α-amino-caprolactam (75 mg, 0.59 mmol) and triethylamine (0.08 mL, 0.54 mmol) were added to the reaction mixture and stirred at 60 °C 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated and the residue was purified by column chromatography to give **22** as a pale-yellow oil (129 mg, 96 %): R_f = 0.30 (5 % MeOH/ $CHCl_3$).
IR (neat): 3390, 2928, 1647 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, 1H, *J* = 6.0 Hz), 7.34-7.25 (m, 10H), 6.25 (bs, 1H), 6.05 (ddd, 1H, *J* = 4.0 Hz, *J* = 10.5 Hz, *J* = 17.0 Hz), 5.46 (dt, 1H, *J* = 1.5 Hz *J* = 17.5 Hz), 5.25 (dt, 1H, *J* = 1.5 Hz *J* = 10.5 Hz), 4.81 (d, 1H, *J* = 11.0 Hz), 4.71 (d, 1H, *J* = 11.0 Hz,), 4.66 (d, 1H, *J* = 11.5 Hz), 4.61 (d, 1H, *J* = 11.0Hz), 4.53(dd, 1H, *J* = 6.0 Hz, *J* = 9.5 Hz),4.48 (bd, 1H, *J* = 1.5 Hz), 4.25 (d, 1H, *J* = 2.0 Hz), 4.01 (dd, 1H, *J* = 2.0 Hz, *J* = 7.5 Hz), 3.80 (dd, 1H, *J* = 3.0 Hz, *J* = 8.0 Hz), 3.44 (s, 3H), 3.27-321 (m, 2H), 2.13 (bd, 1H, *J* = 12.5 Hz), 2.04-1.97 (m, 1H), 1.88-1.83 (m, 2H), 1.59-1.51 (m, 1H), 1.45-1.37 (m, 1H).
$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ 174.9, 170.1, 138.5, 138.4, 137.9, 128.3 (2), 128.2 (2), 128.1 (2), 128.0 (2), 127.6, 127.4, 115.1, 81.9 (2), 80.8, 75.1, 74.6, 71.0, 58.6, 52.0, 42.0, 31.4, 28.9, 27.9.
HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{28}H_{37}N_2O_6$ 497.2646, found 497.2649.

(2*R*,3*R*,4*S*,5*R*,*E*)-3,4-bis(benzyloxy)-5-hydroxy-2-methoxy-8-methyl-*N*-((*S*)-2-oxoazepan-3-yl) non-6-enamide (23):

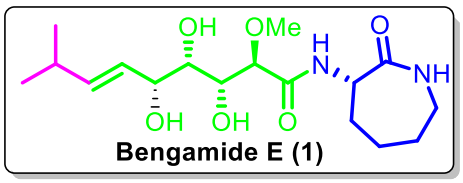


23

Compound **23** was synthesized from **22** (100 mg, 0.20 mmol), 3-methyl-1-butene/CH_2Cl_2 (16mL, 5:1 v/v) and second-generation Grubbs catalyst (51 mg, 0.06mmol) by following the procedure reported for the preparation of **18** from **17**. Brown foam (103 mg, 95.0 %). R_f = 0.35 (6 % Acetone/hexane).
IR (neat): 3383, 2955, 2937, 1658 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, 1H, *J* = 6.0 Hz), 7.33-7.25 (m, 10H), 6.18 (bs, 1H), 5.81 (ddd, 1H, *J* = 1.5 Hz, *J* = 6.5 Hz, *J* = 15.5 Hz), 5.61 (ddd, 1H, *J* = 1.0 Hz, *J* = 5.0 Hz, *J* = 15.5 Hz), 4.81 (d, 1H, *J* = 11.0 Hz), 4.72 (d, 1H, *J* = 11.5 Hz), 4.66 (d, 1H, *J* = 11.0 Hz), 4.60 (d, 1H, *J* = 11.5 Hz), 4.55-4.51 (m, 1H), 4.43 (bs, 1H), 4.22 (d, 1H, *J* = 2.0 Hz), 4.01 (dd, 1H, *J* = 2.0 Hz, *J* = 8.0 Hz), 3.87 (d, 1H, *J* = 5.0 Hz), 3.78 (dd, 1H, *J* = 3.0 Hz, *J* = 8.0 Hz), 3.44 (s, 3H), 3.26-3.22 (m, 2H), 2.36-2.29 (m, 1H), 2.13 (bd, 1H, *J* = 12.5 Hz), 2.04-2.01 (m, 1H),1.87-1.83 (m, 2H), 1.58-1.50 (m, 1H), 1.45-1.37 (m, 1H), 1.02 (dd, 6H, *J* = 1.5 Hz, *J* = 7.0 Hz).
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ 174.9, 170.0, 138.7, 138.6, 138.5, 128.3 (2), 128.2 (2), 128.1 (2), 128.0 (3), 127.4, 126.5, 82.4, 82.0, 80.9, 75.1, 74.8, 70.9, 58.5, 52.0, 42.0, 31.4, 30.8, 28.9, 27.9, 22.4, 22.3.
HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{31}H_{43}N_2O_6$ 539.3116, found 539.3117.

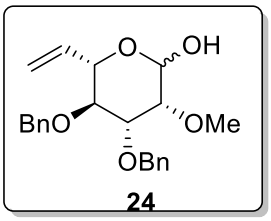
(2*R*,3*R*,4*S*,5*R*,E)-3,4,5-trihydroxy-2-methoxy-8-methyl-*N*-((*S*)-2-oxoazepan-3-yl)non-6-enamide (1)[20]:



Bengamide E (1)

Bengamide-E **1** was synthesized from compound **23** (50 mg, 0.093 mmol) by following the procedure reported for the preparation of **2** from **18**. Colorless syrup (21 mg, 63%). R_f = 0.48 (10 % MeOH/AcOEt). $[\alpha]_D^{25}$=+ 34.19 (c = 0.23, $CHCl_3$), ([α]lit +32 (*c* 0.2, $CHCl_3$).[17]
IR (neat): 3332, 1660, 1650 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): 7.98 (bd, 1H, *J* = 5.5 Hz), 6.07 (bs, 1H), 5.78 (dd, 1H, *J* = 6.5 Hz, *J* = 15.5 Hz), 5.45 (dd, 1H, *J* = 6.0 Hz, *J* = 14.5 Hz), 4.54 (dd, 1H, *J* = 6.5 Hz, *J* = 10.0 Hz), 4.23 (bt, 1H, *J* = 6.0 Hz), 3.82 (bd, 1H, *J* = 7.0 Hz), 3.78 (d, 1H, *J* = 7.0 Hz), 3.60 (bs, 1H), 3.54 (s, 3H), 3.34-3.28 (m, 2H), 2.33-2.29 (m, 1H), 2.08-2.00 (m, 3H), 1.89-1.81 (m, 1H), 1.47-1.28 (m, 1H), 1.33-1.30 (m, 1H), 1.01 (d, 3H, *J* = 2.5 Hz), 0.99 (d, 3H, J=2.5 Hz).
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ 174.7, 172.2, 141.9, 125.3, 80.9, 74.3, 72.8, 72.3, 59.9, 52.0, 42.1, 31.0, 30.8, 28.8, 27.9, 22.2, 22.1.
HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{30}N_2O_6Na$ 381.1996, found 381.1995.

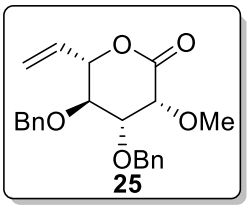
(3*R*,4*R*,5*S*,6*S*)-4,5-bis(benzyloxy)-3-methoxy-6-vinyltetrahydro-2*H*-pyran-2-ol (24):



24

Sodium meta periodate (330 mg, 1.55 mmol) was dissolved in water (1.0 mL) and added to compound **10** (250 mg, 0.62 mmol) in methanol (8.0 mL) at room temperature. A slightly exothermic reaction was observed. The reaction mixture was stirred 12 h at room temperature. After the starting material was consumed, the precipitate was filtered and the filter cake was washed with methanol. The filtrate was evaporated to dryness to yield the crude hemiacetal **24**, which was utilized in the next step without further purification. R_f = 0.50 (30 % AcOEt/hexane).

(3*R*,4*R*,5*S*,6*S*)-4,5-bis(benzyloxy)-3-methoxy-6-vinyltetrahydro-2*H*-pyran-2-one (25):



25

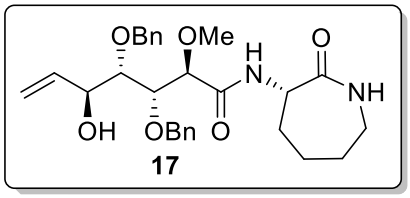
A solution of compound **24** (~0.60 mmol) in anhydrous dichloromethane (15 mL) was cooled to 0 °C and sodium bicarbonate (0.19 g, 3.40 mmol) was added slowly. After 10 min, Dess-Martin periodinane (DMP) (0.86 g, 2.04 mmol) was added portion-wise to the reaction mixture and stirred at 0 °C for 3 h. After completion of the reaction (monitored by TLC), the precipitate was filtered and washed with dichloromethane (2 x 10 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (15 mL), water (15 mL) and brine solution (15 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography of crude product provided lactone **25** as a colorless oil (205 mg, 90 % over two steps). R_f = 0.55 (30 % AcOEt/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): 7.38-7.32 (m, 8H), 7.23-7.22 (m, 2H), 5.90 (ddd, 1H, *J* = 6.0 Hz, *J* = 10.5 Hz, *J* = 17.0 Hz), 5.45 (dt, 1H, *J* = 1.0 Hz, *J* = 17.0 Hz), 5.31 (dt, 1H, *J* = 1.5 Hz *J* = 12.0 Hz), 4.87 (d, 1H, *J* = 12.5 Hz), 4.65 (d, 1H, *J* = 12.5 Hz), 4.55 (dd, 1H, *J* = 6.5 Hz, *J* = 7.5 Hz), 4.40 (dd, 2H, *J* = 1.5 Hz, *J* = 12.0 Hz), 4.21 (d, 1H, *J* = 3.0 Hz), 4.12 (dd, 1H, *J* = 1.5 Hz, *J* = 3.0 Hz), 3.65 (dd, 1H, *J* = 1.5 Hz, *J* = 8.0 Hz), 3.62 (s, 3H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ 169.1, 137.7, 136.8, 133.4, 128.6 (2), 128.5 (2), 128.3, 128.2 (2), 128.0 (3), 118.6, 80.5, 78.9, 78.2, 76.6, 73.1, 72.3, 59.2.

HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{25}O_5$; 369.1697, found 369.1695.

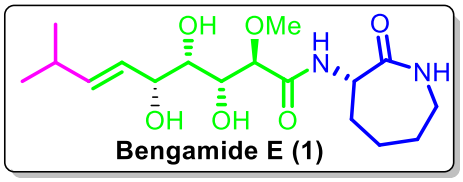
(2*R*,3*R*,4*S*,5*S*)-3,4-bis(benzyloxy)-5-hydroxy-2-methoxy-*N*-((*S*)-2-oxoazepan-3-yl)hept-6-enamide (17):



17

Lactone **25** (118 mg, 0.32 mmol) was dissolved in 9:1 mixture of THF-dioxane (8.0 mL) and stirred at room temperature. After 15 min L-(-)-α-amino-caprolactam (90 mg, 0.70 mmol) and triethylamine (0.090 mL, 0.64 mmol) was added to the reaction mixture and stirred at 60 °C for 12 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure and the obtained crude product was purified by column chromatography to give **17** as a colorless oil (150 mg, 95 %): R_f = 0.45 (5 % MeOH/ $CHCl_3$). The spectral data of compound was found to be the same as reported above.

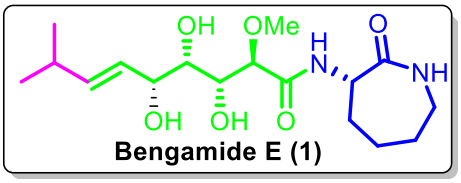
Table 1. Comparison of ^{1}H-NMR spectroscopic data of natural and synthetic bengamide E 1:



Bengamide E (1)

Natural bengamide E[1] (δ_1 = ppm, *J* in Hz) (300 MHz, $CDCl_3$)	Francisco Sarabia et al.[1] (δ_1 = ppm, *J* in Hz) (400 MHz, $CDCl_3$)	Our spectra (δ_2 = ppm, *J* in Hz) (500 MHz, $CDCl_3$)
7.92 (d, 1H, *J* =6.6 Hz)	7.97 (bd, 1H, *J* =6.5 Hz, N*H*)	7.98 (bd, 1H, *J* = 5.5 Hz, N*H*)
6.92 (bs, 1H)	6.12 (bs, 1H, N*H*)	6.07 (bs, 1H, N*H*)
5.73 (dd, 1H, *J* = 6.6, 15.6 Hz)	5.76 (dd, 1H, *J* = 6.5, 15.6 Hz, -C*H*=)	5.78 (dd, 1H, *J* = 6.5 Hz, *J* = 15.5 Hz, -C*H*=)
5.40 (dd, 1H, *J* = 7.2, 15.6 Hz,)	5.43 (dd, 1H, *J* = 6.91, 15.6 Hz, -C*H*=)	5.45 (dd, 1H, *J* = 6.0 Hz, *J* = 14.5 Hz, C*H*=)
4.53 (dd, 1H, *J* = 6.9, 10.5 Hz)	4.52 (dd, 1H, *J* = 6.5, 10.2 Hz, C*H*-CON)	4.53 (dd, 1H, *J* = 6.5 Hz, *J* = 10.0 Hz, C*H*-CON)
4.17 (dd, 1H, *J* =6.0 Hz, 6.3 Hz)	4.21 (bt, 1H, *J* = 5.9 Hz, C*H*-OH)	4.22 (bt, 1H, *J* = 6.0 Hz, C*H*-OH)
3.79(m, 2H)	3.81(bd, 1H, *J* = 7.5 Hz, C*H*-OH)	3.83(bd, 1H, *J* = 7.0 Hz, C*H*-OH)
-	3.76 (d, 1H, *J*= 7.5 Hz, C*H*-OMe)	3.78 (d, 1H, *J* = 7.0 Hz, C*H*-OMe)
3.59 (bd, 1H, *J* =5.4 Hz)	3.59 (m, 1H, C*H*-OH)	3.61 (brs, 1H, C*H*-OH)
3.46 (s, 3H)	3.52 (s, 3H, OMe)	3.54 (s, 3H, OMe)
3.25 (bm, 2H)	3.32-3.21 (m, 2H, -C*H*2-NH),	3.34-3.28 (m, 2H, -C*H*2-NH)
2.28 (m, 1H)	2.34-2.24 (m, 1H, C*H*(CH3)2)	2.35-2.28 (m, 1H, C*H*(CH3)2)
1.99 (m, 2H)	1.90-1.71 (m, 3H, -C*H*2-)	2.08-2.02 (m, 3H, -C*H*2)
1.80 (m, 2H, -C*H*2-)	1.62-1.50 (m, 1H, -C*H*2-)	1.89-1.81 (m, 1H, -C*H*2-)
1.57 (m, 1H, -C*H*2-)	1.47-1.33 (m, 2H, -C*H*2-)	1.46-1.39(m, 1H, -C*H*2-)
1.34 (m, 1H, -C*H*2-)		1.33-1.28(m, 1H, -C*H*2-)
0.94 (d, 6H, *J*= 6.6Hz, (C*H*3)2CH)	0.97 (d, 3H, *J*= 2.2 Hz, (C*H*3)2CH)	0.99 (dd, 6H, *J* = 2.5 Hz *J* = 7.0 Hz, (C*H*3)2CH)
	0.98 (d, 3H, *J*= 2.2 Hz, (C*H*3)2CH)	

Table 2. Comparison of ^{13}C-NMR spectroscopic data for natural and synthetic bengamide E 1:

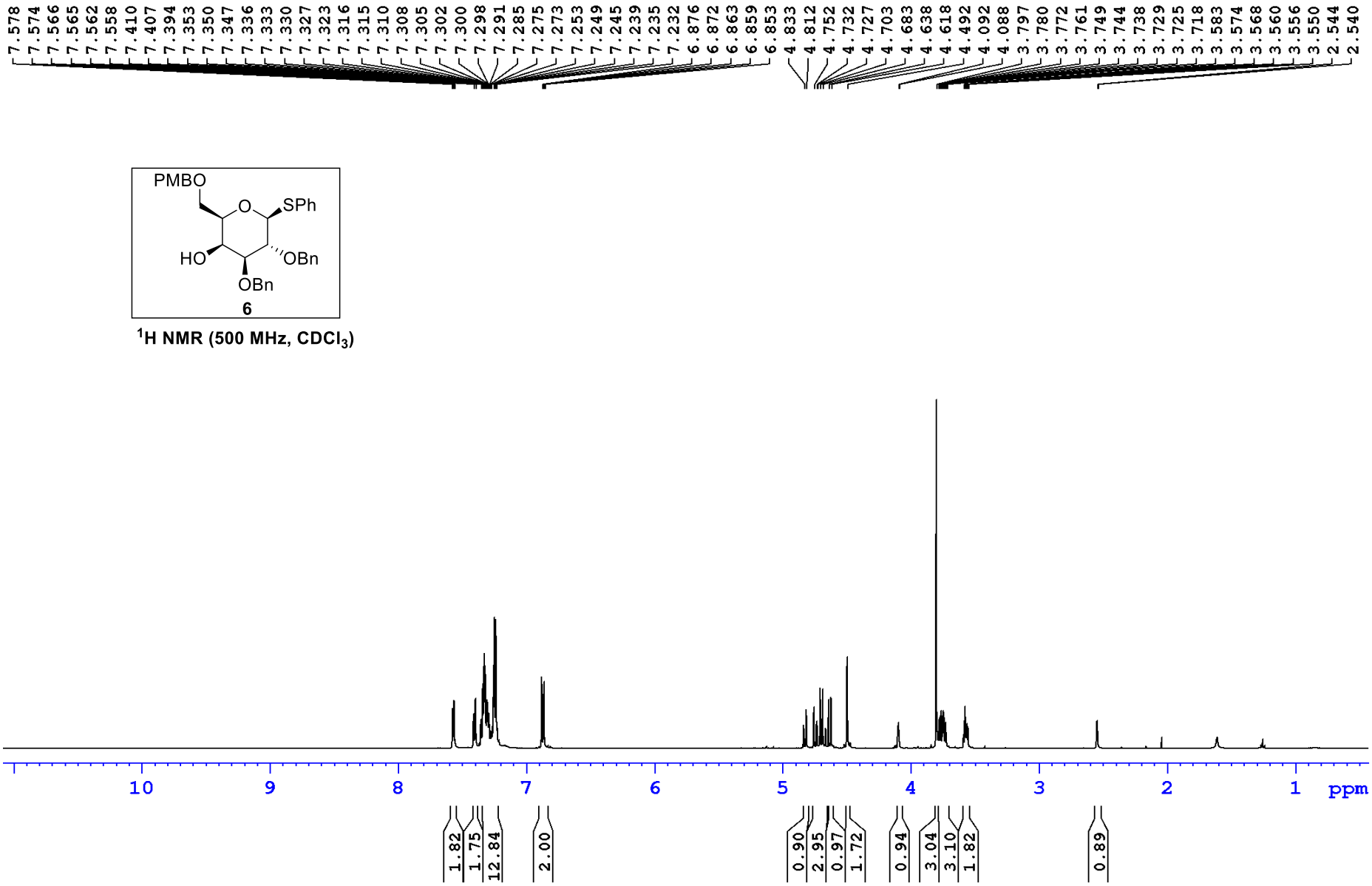


Bengamide E (1)

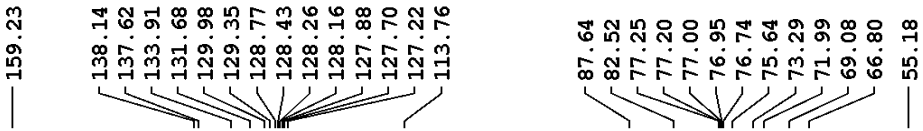
Natural bengamide E[1] (δ_1 =ppm)^{13}C NMR (75 MHz, $CDCl_3$)	Francisco Sarabia et al.[2] (δ_1 =ppm)^{13}C NMR (100 MHz, $CDCl_3$)	Our spectra (δ_2 =ppm)^{13}C NMR (125 MHz, $CDCl_3$)
22.1	22.1	22.1
22.2	22.2	22.2
28.0	27.9	27.9
28.7	28.8	28.8
30.8	30.8	30.8
31.0	31.0	31.0
42.0	42.1	42.1
52.0	51.9	52.0
59.9	59.9	59.9
72.4	72.3	72.4
72.7	72.8	72.8
74.1	74.3	74.3
81.7	80.8	80.9
125.5	125.3	125.4
141.6	141.9	141.9
171.7	172.4	172.2
175.2	174.7	174.7

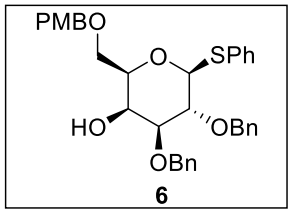
Reference

1. M. Adamczeski, E. Quiñoá, and P. Crews, *J. Am. Chem. Soc.* 1989, **111**, 647–654
2. Sarabia and A. Sánchez-Ruiz, *J. Org. Chem.*, 2005, **70**, 9514–9520.



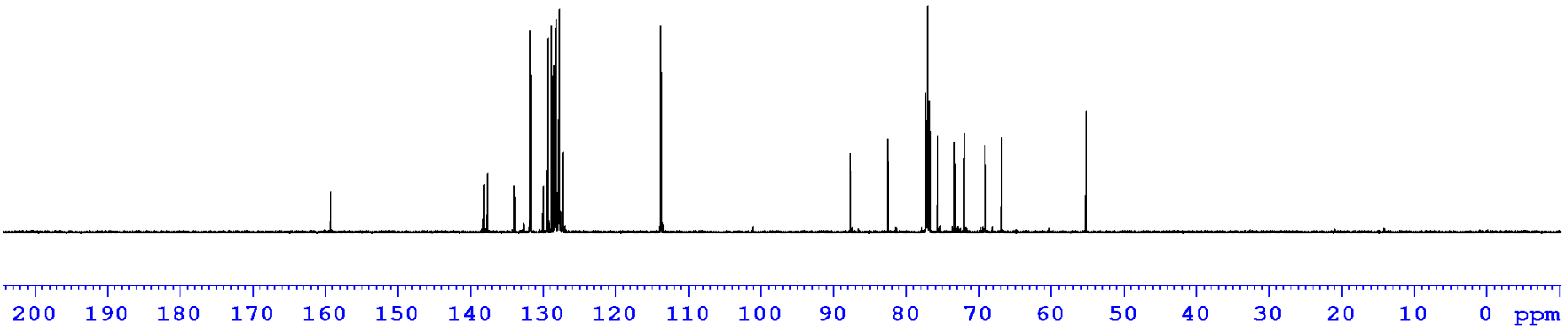
^{1}H NMR (500 MHz, $CDCl_3$)

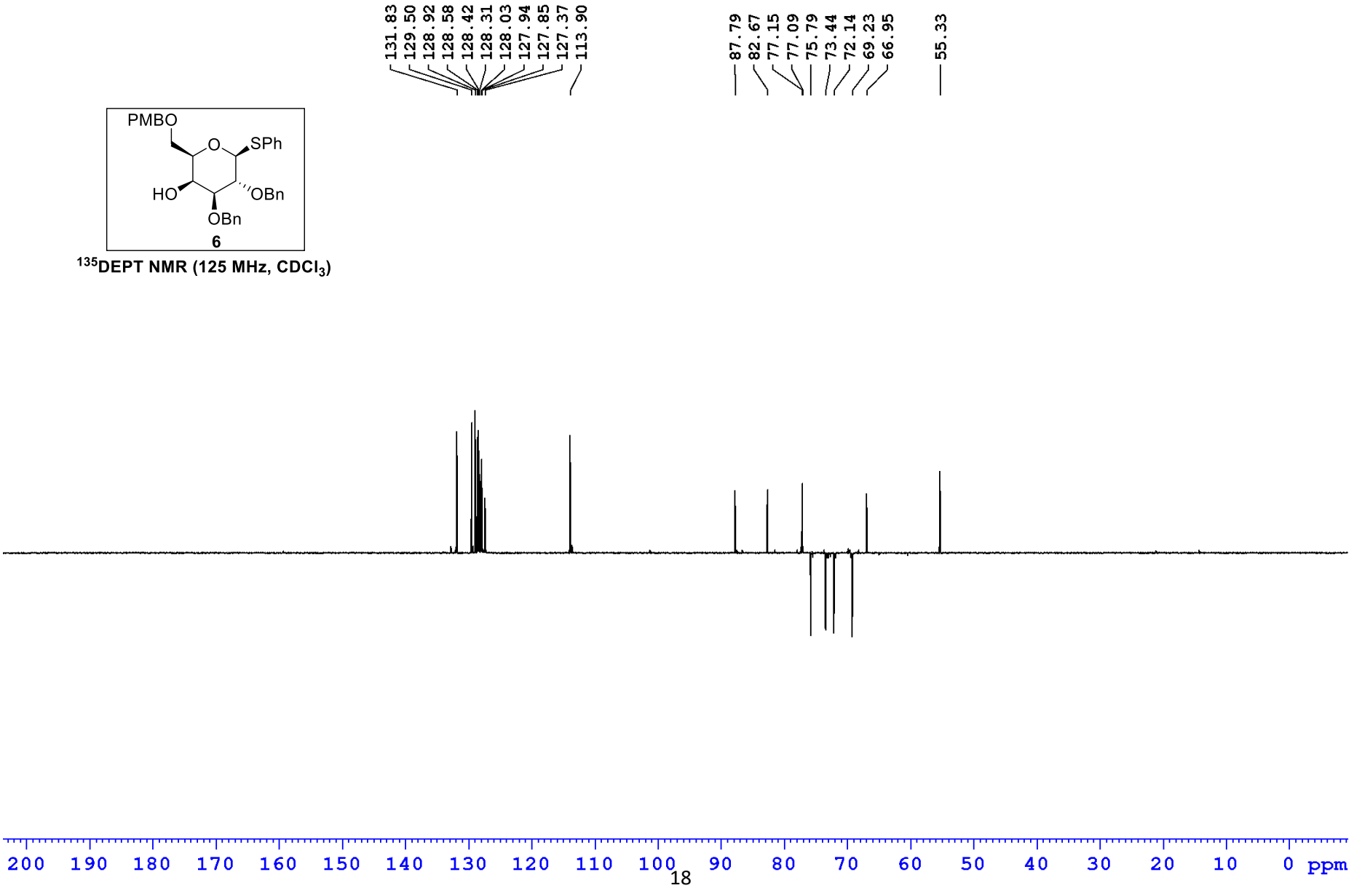




6

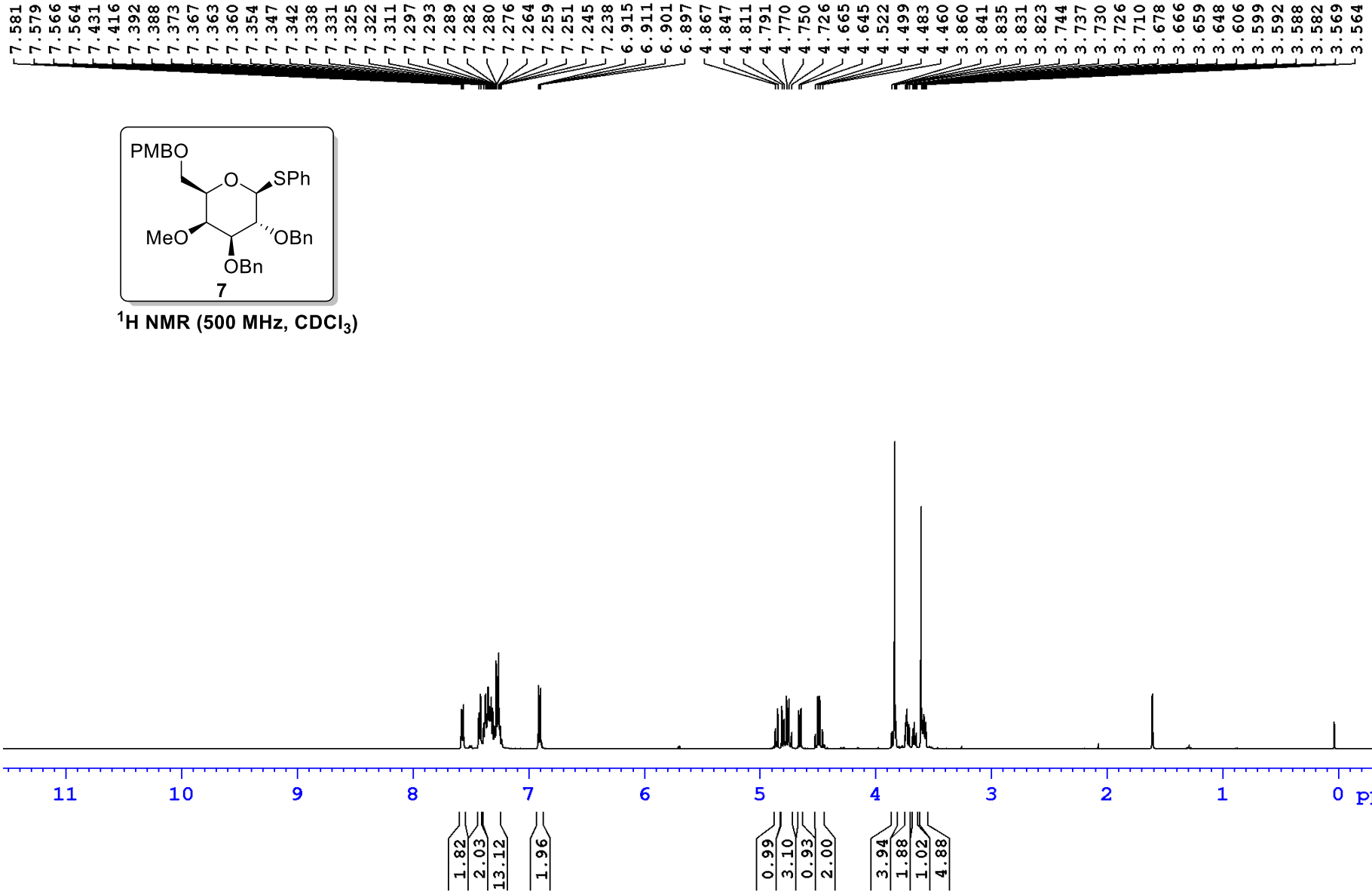
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



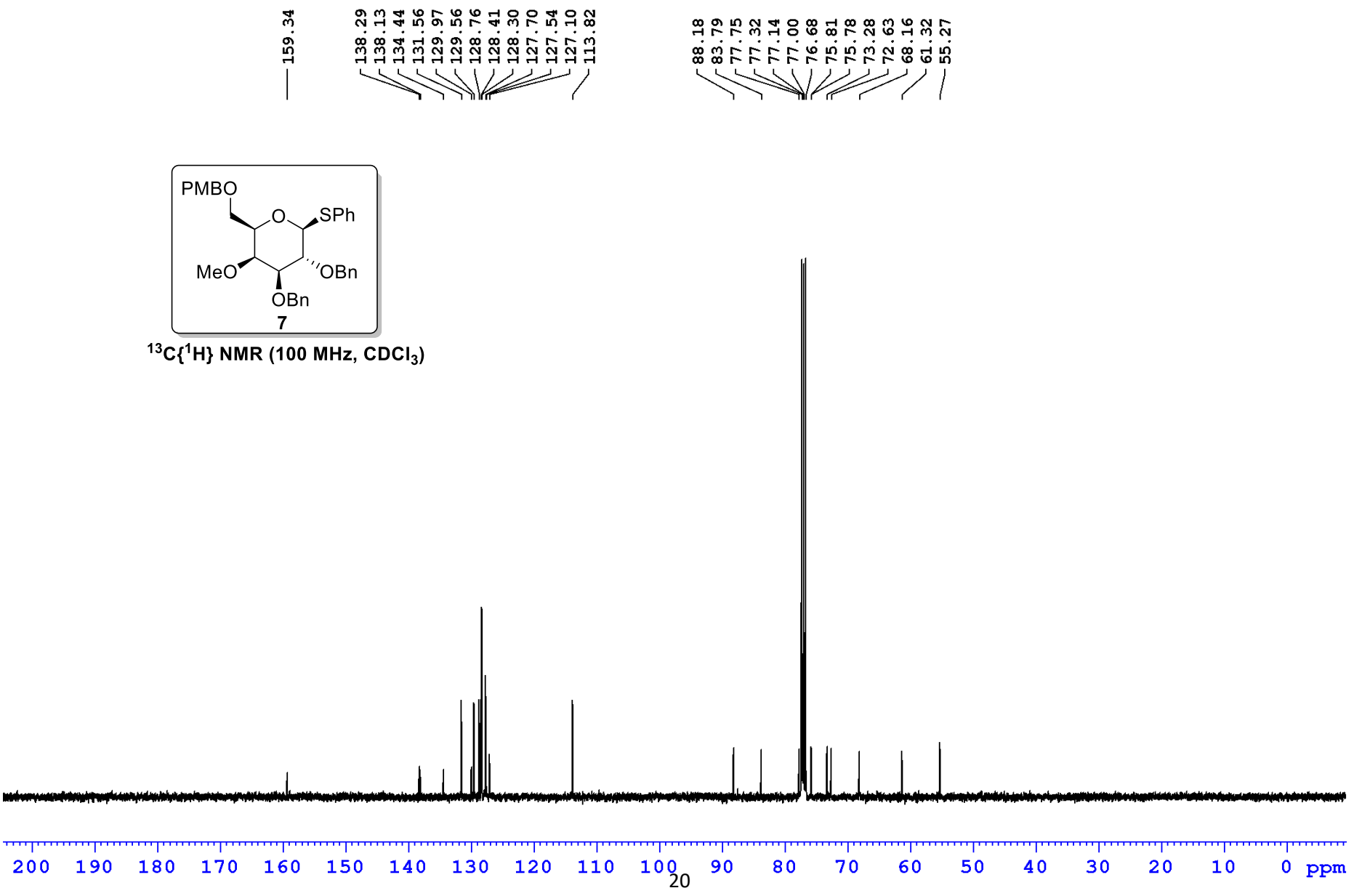


6

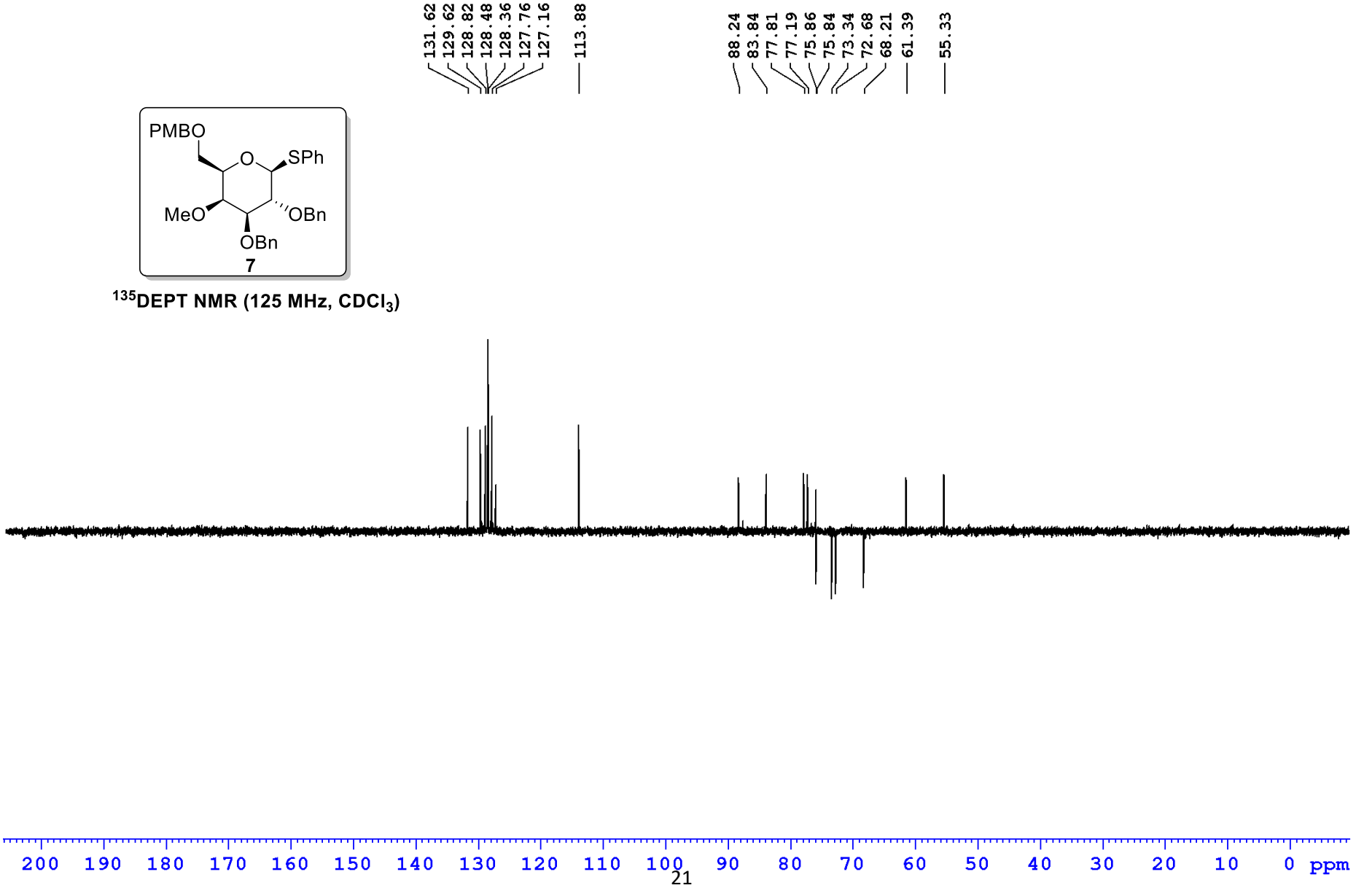
^{135}DEPT NMR (125 MHz, $CDCl_3$)



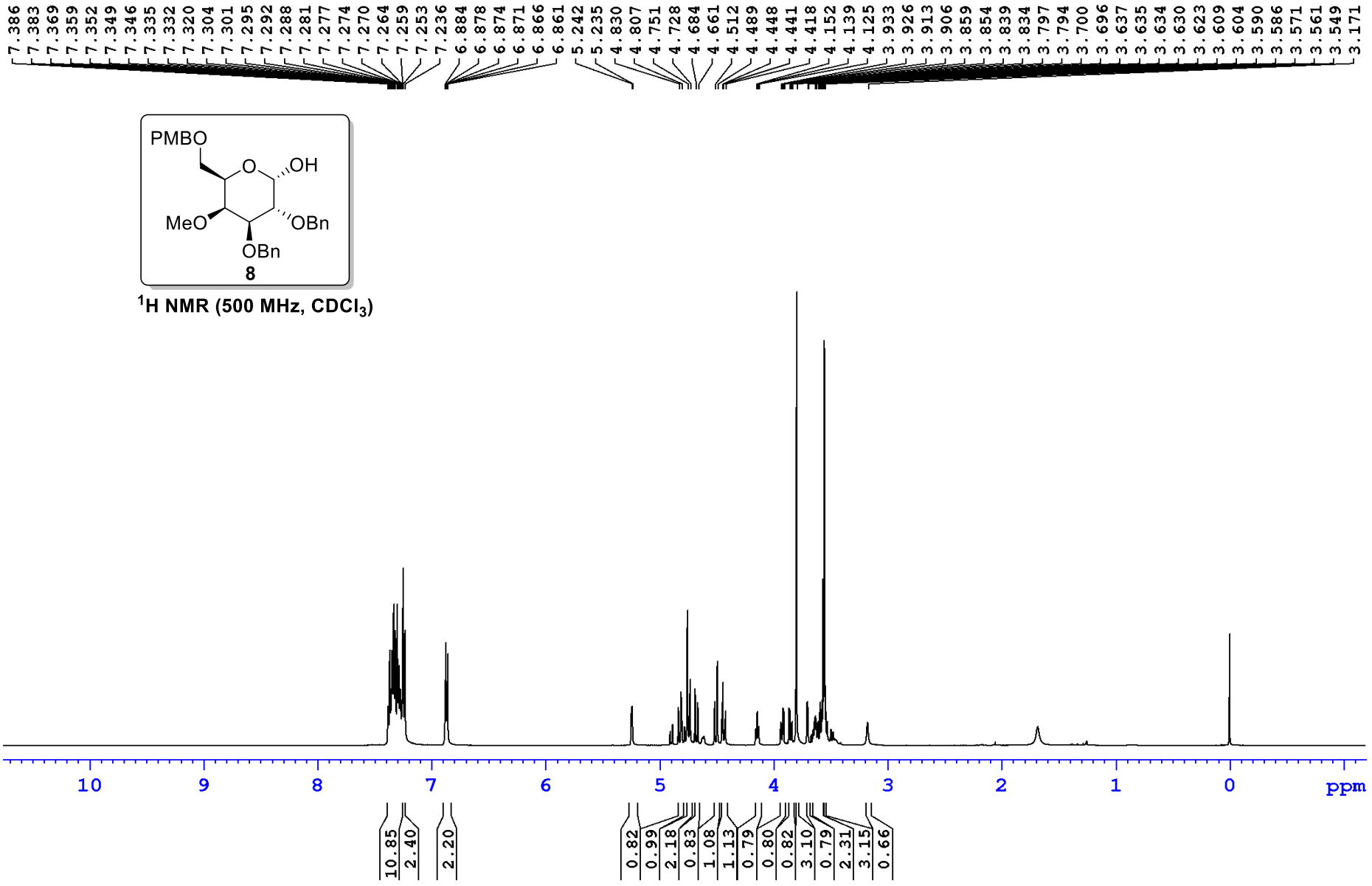
^{1}H NMR (500 MHz, $CDCl_3$)



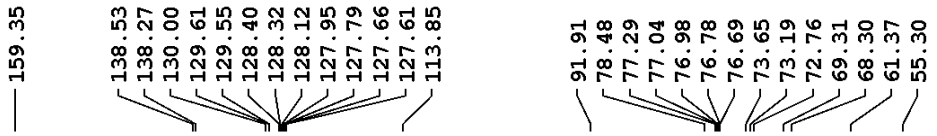
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)

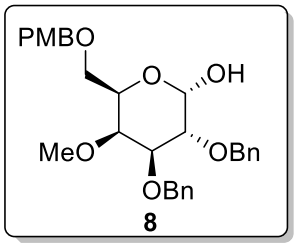


^{135}DEPT NMR (125 MHz, $CDCl_3$)



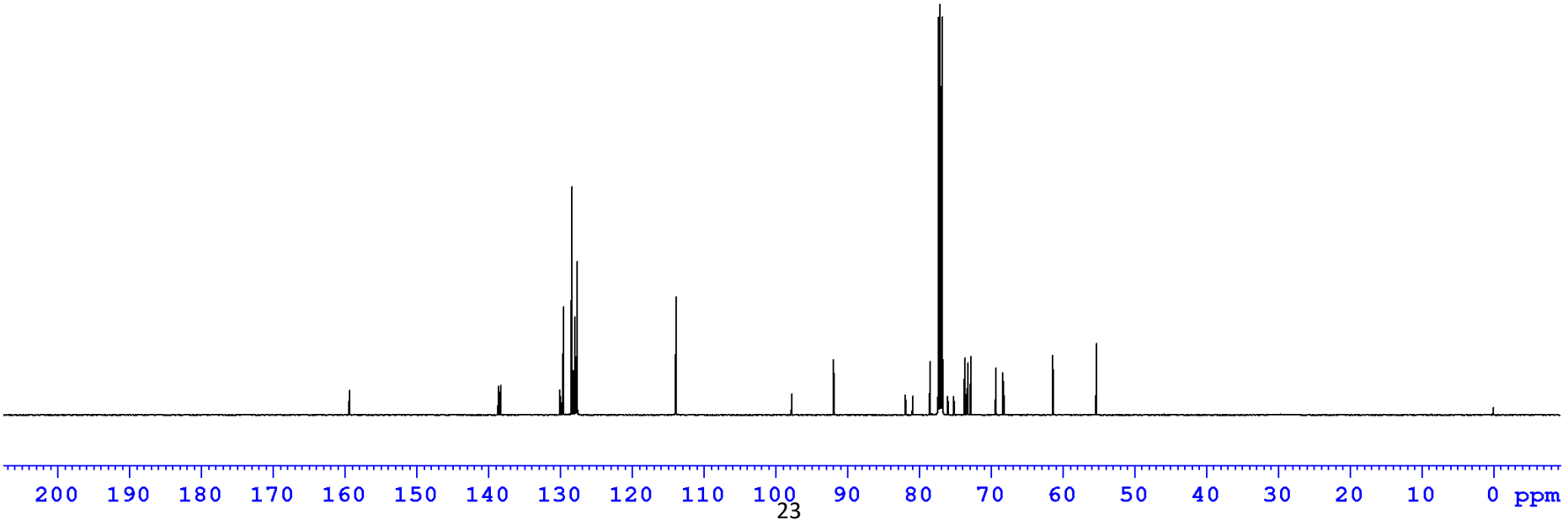
^{1}H NMR (500 MHz, $CDCl_3$)

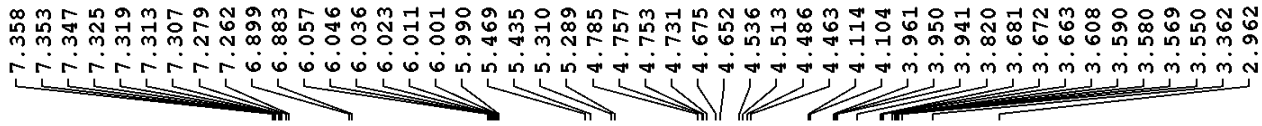


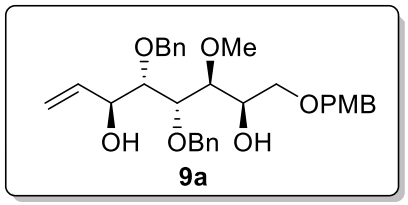


8

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)

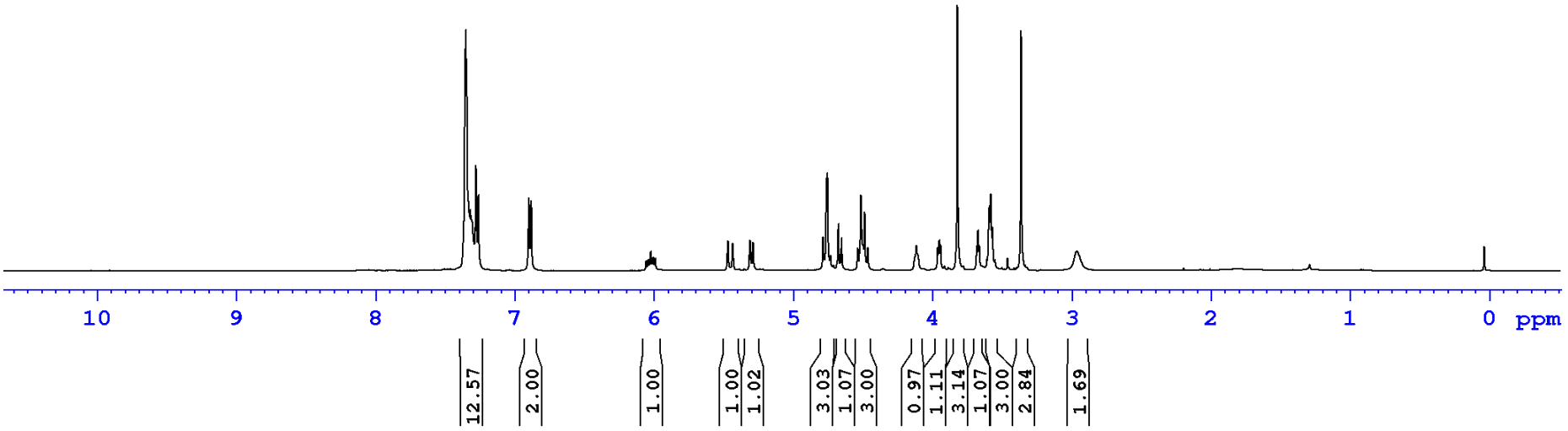


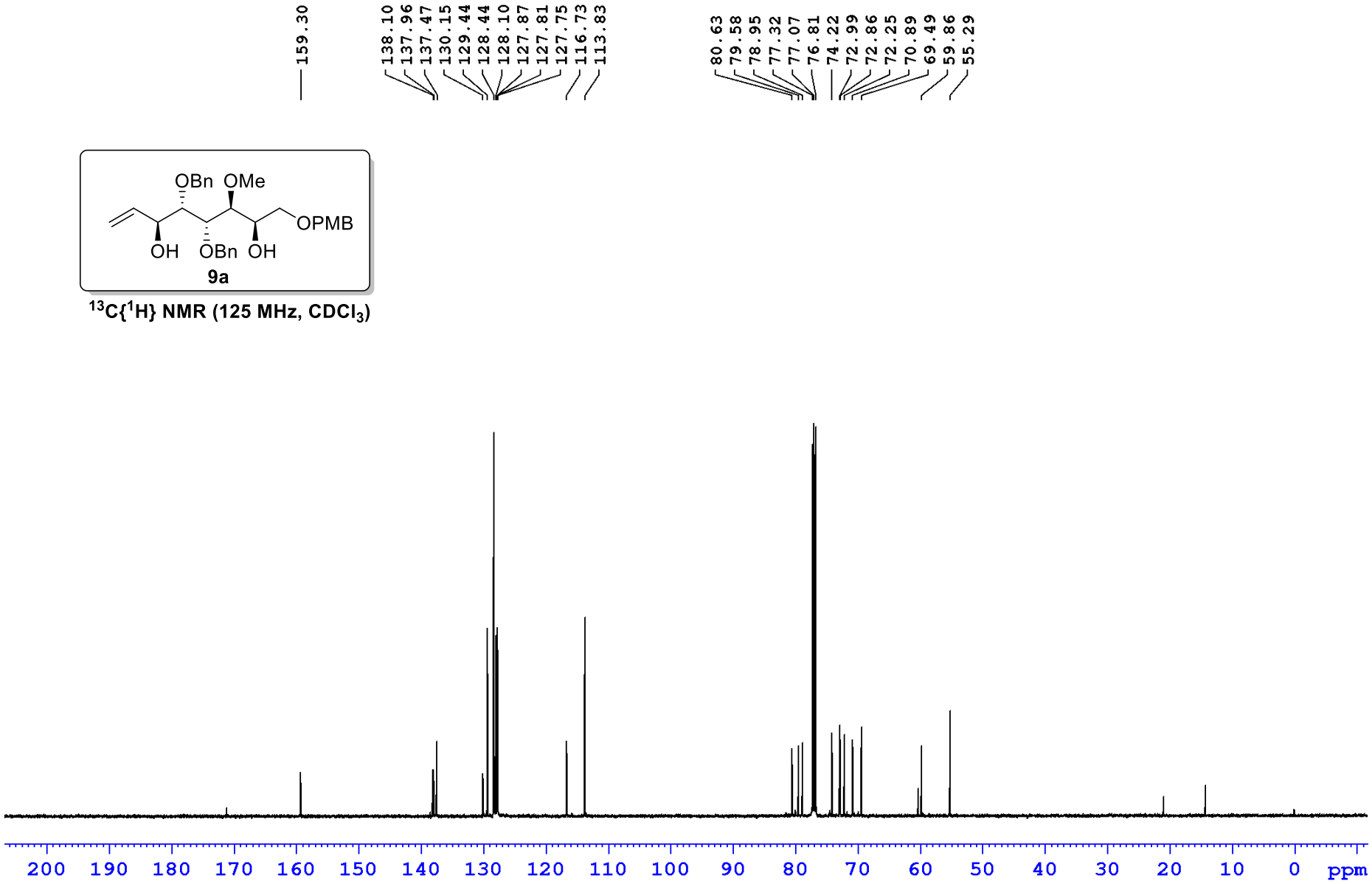




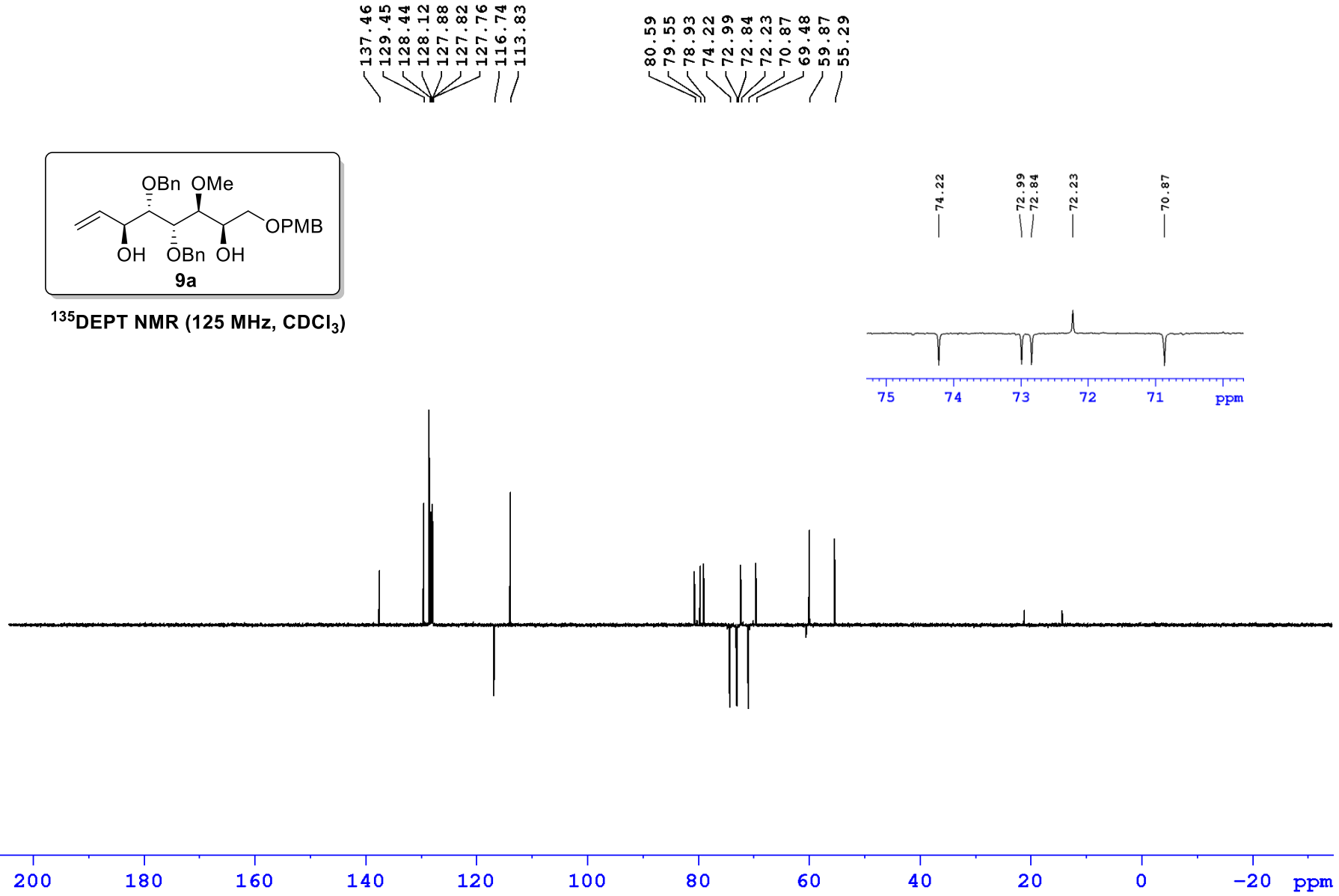
9a

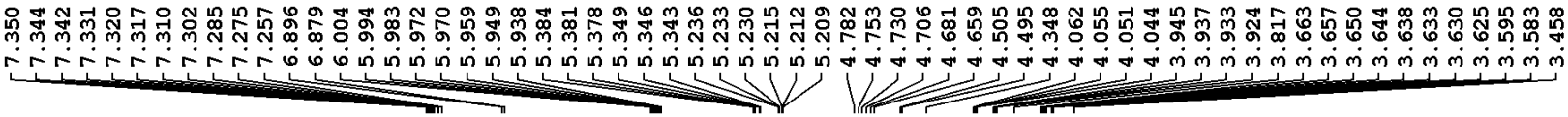
^{1}H NMR (500 MHz, $CDCl_3$)

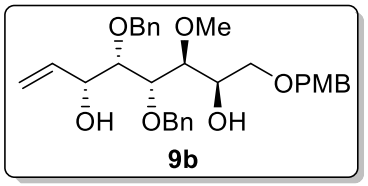




$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)

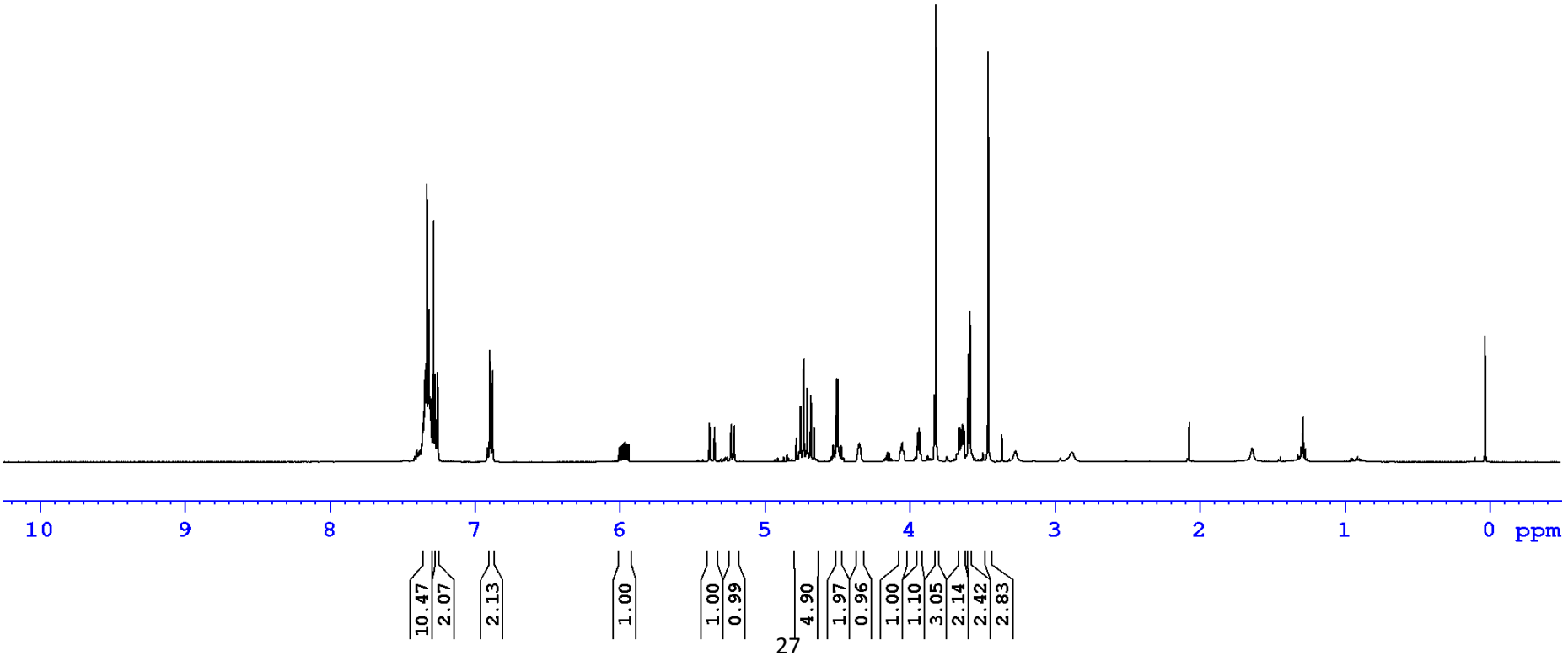

137.46
129.45
128.44
128.12
127.88
127.82
127.76
116.74
113.83
80.59
79.55
78.93
74.22
72.99
72.84
72.23
70.87
69.48
59.87
55.29
OBn OMe
OPMB
OH OBn OH
9a
135DEPT NMR (125 MHz, CDCl3)
74.22
72.99
72.84
72.23
70.87
75 74 73 72 71 ppm
200 180 160 140 120 100 80 60 40 20 0 -20 ppm

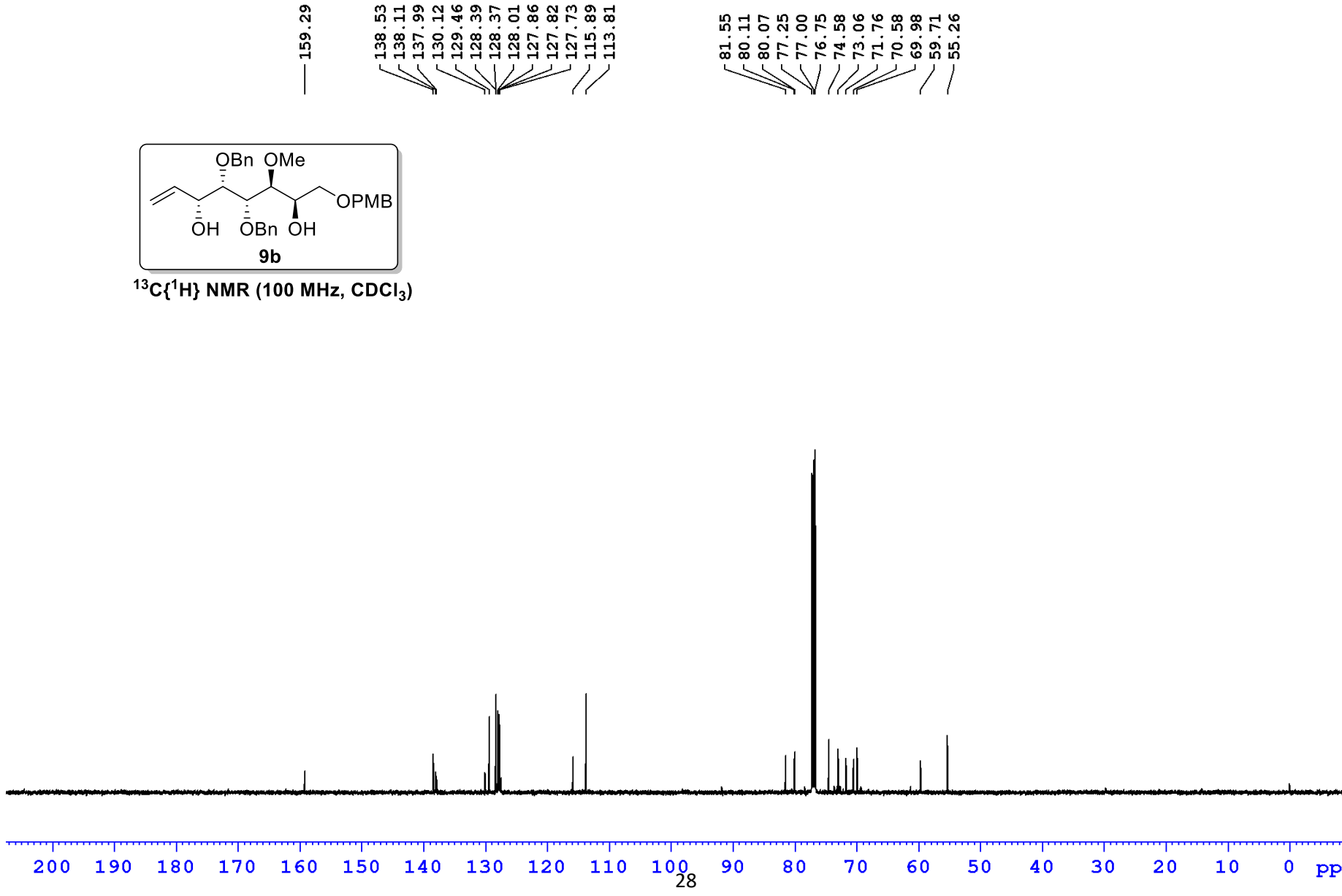




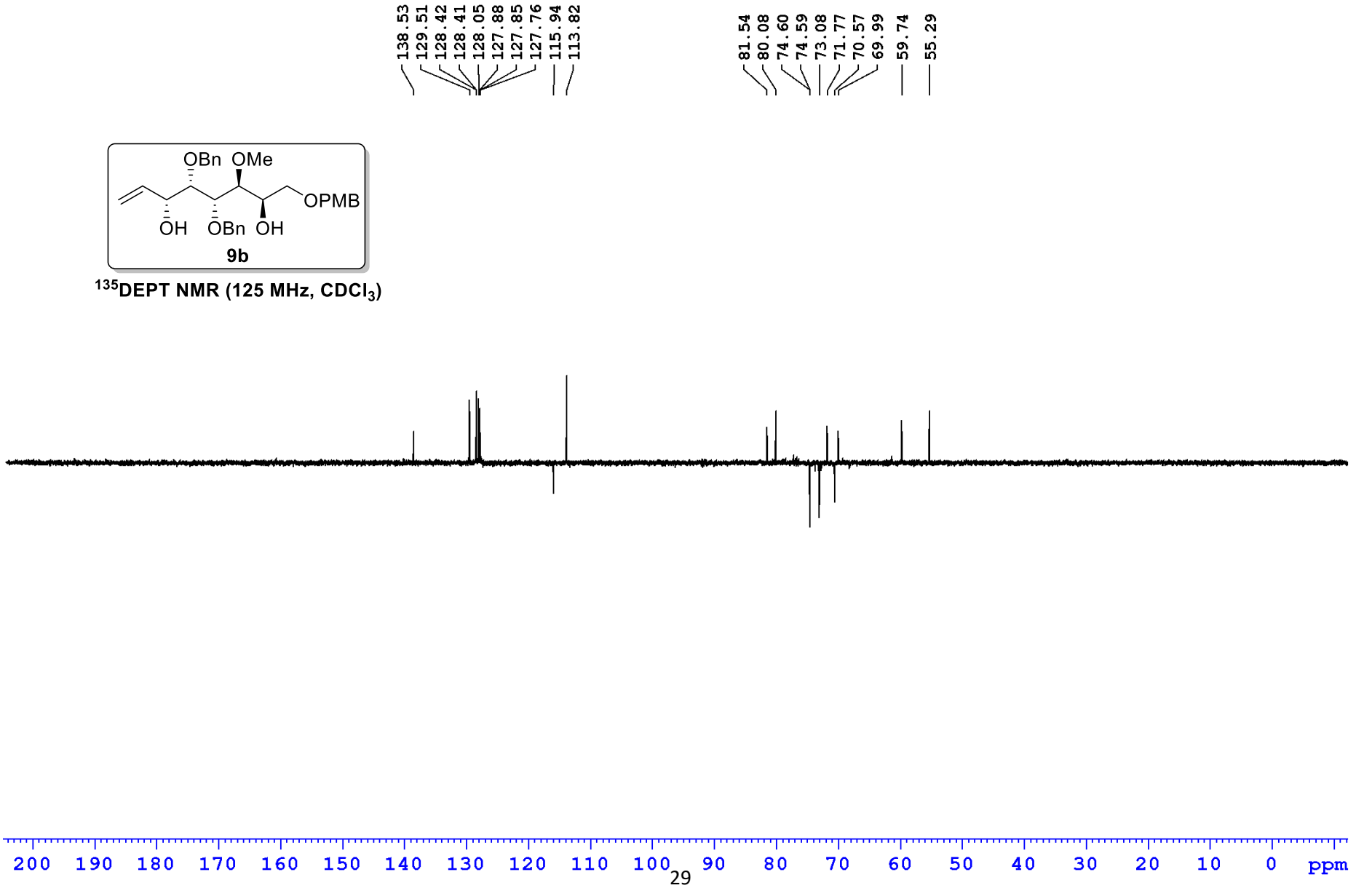
9b

^{1}H NMR (500 MHz, $CDCl_3$)

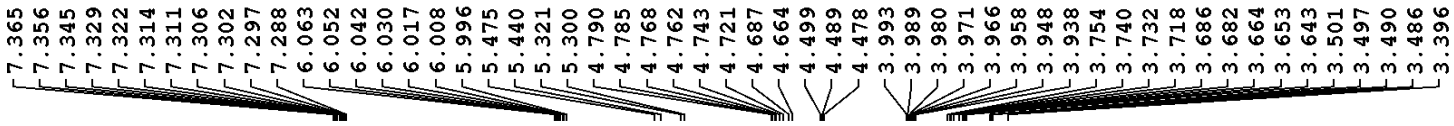


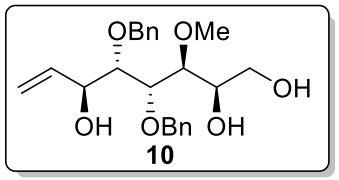


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



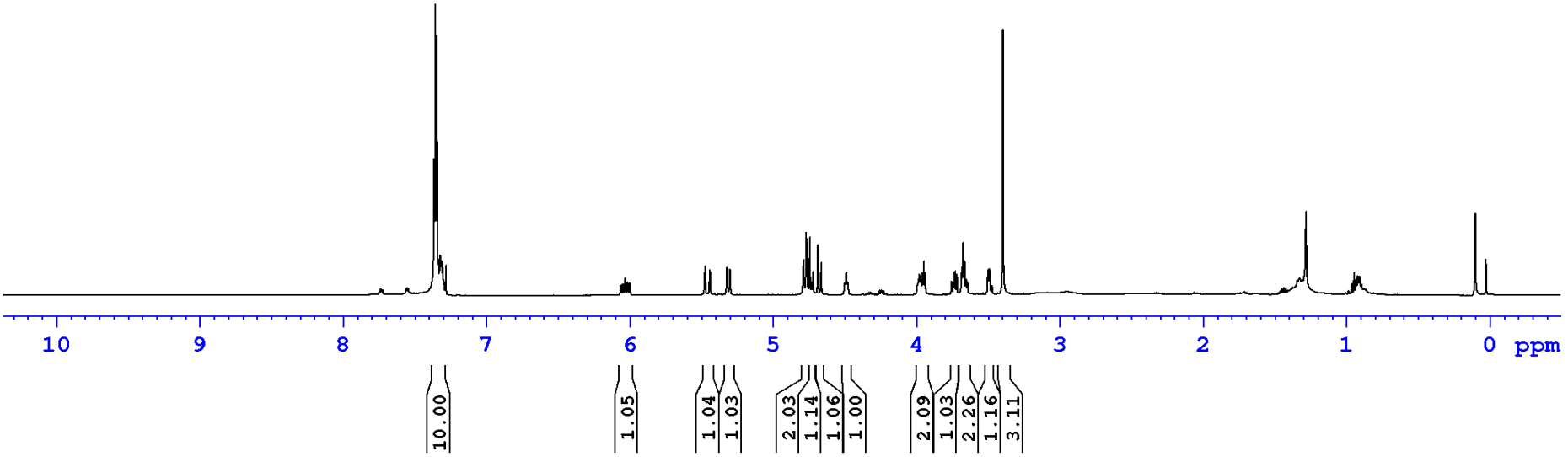
^{135}DEPT NMR (125 MHz, $CDCl_3$)

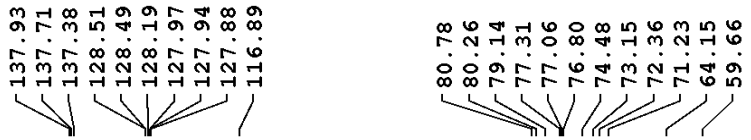


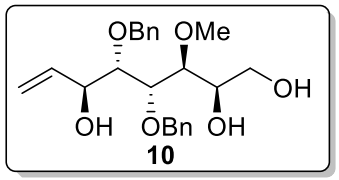


10

^{1}H NMR (500 MHz, $CDCl_3$)

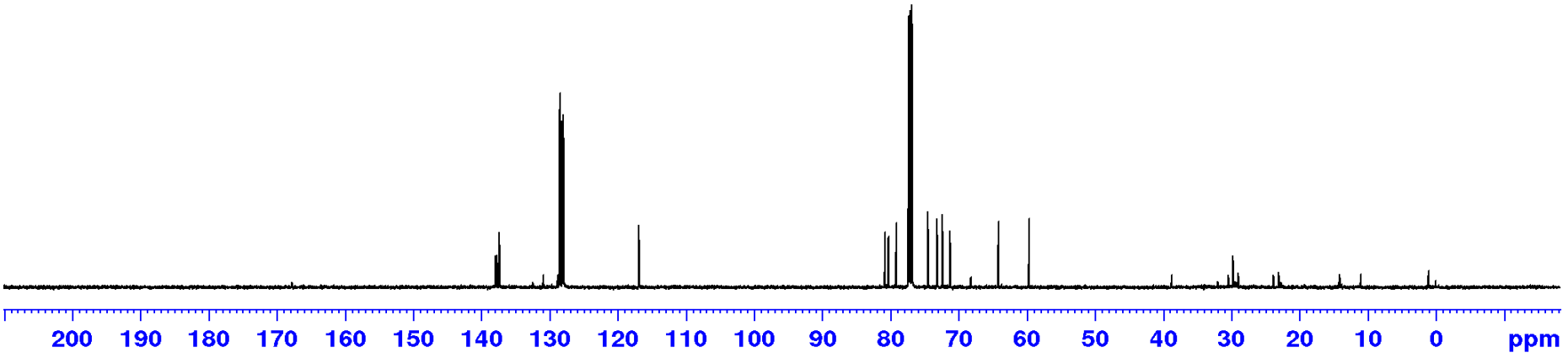


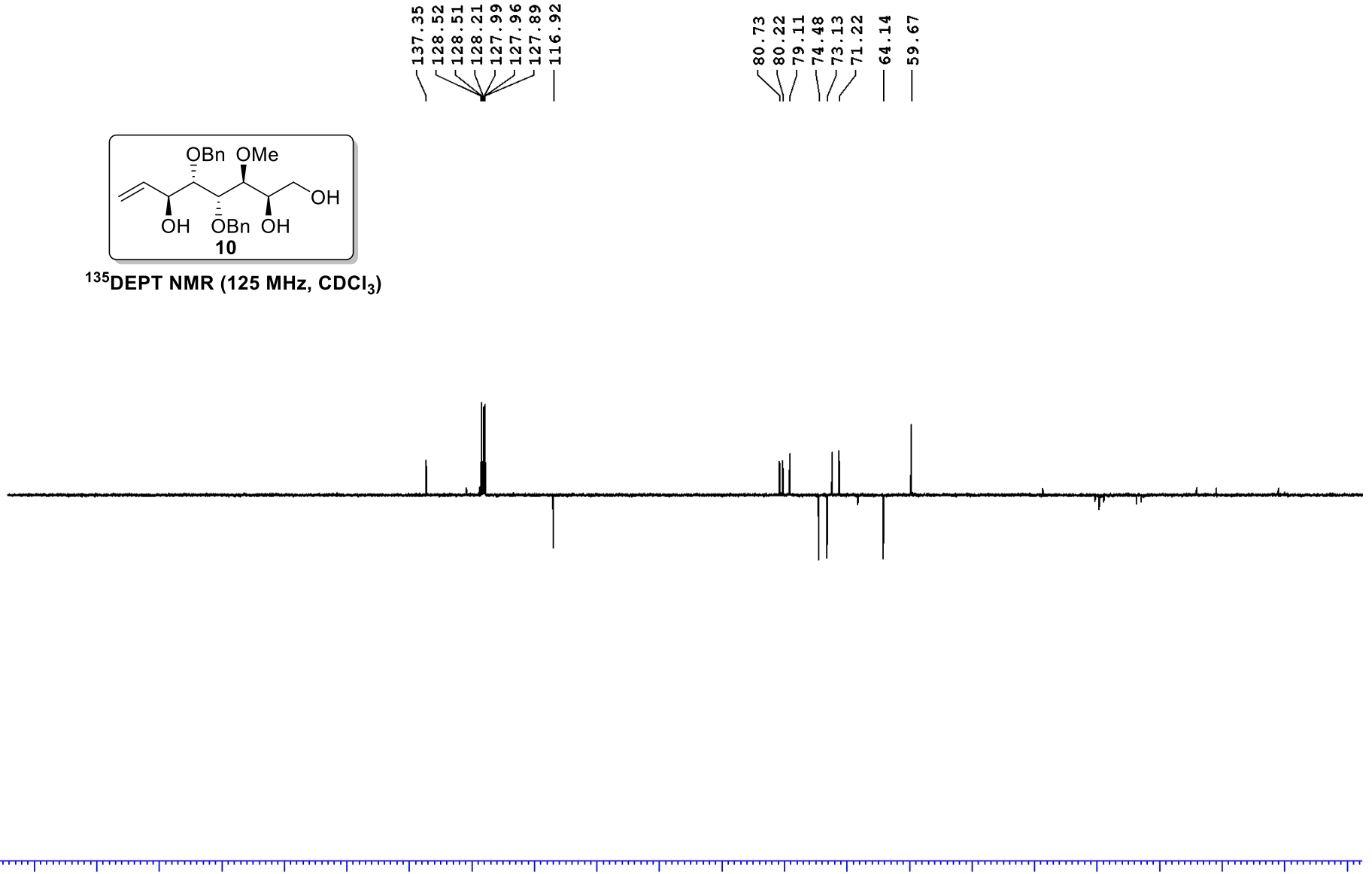




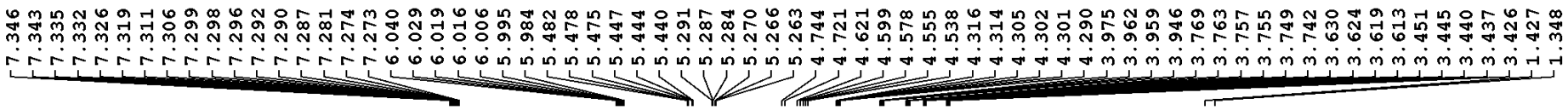
10

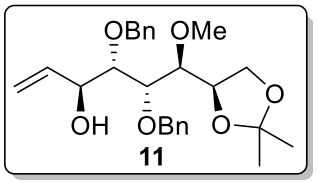
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)





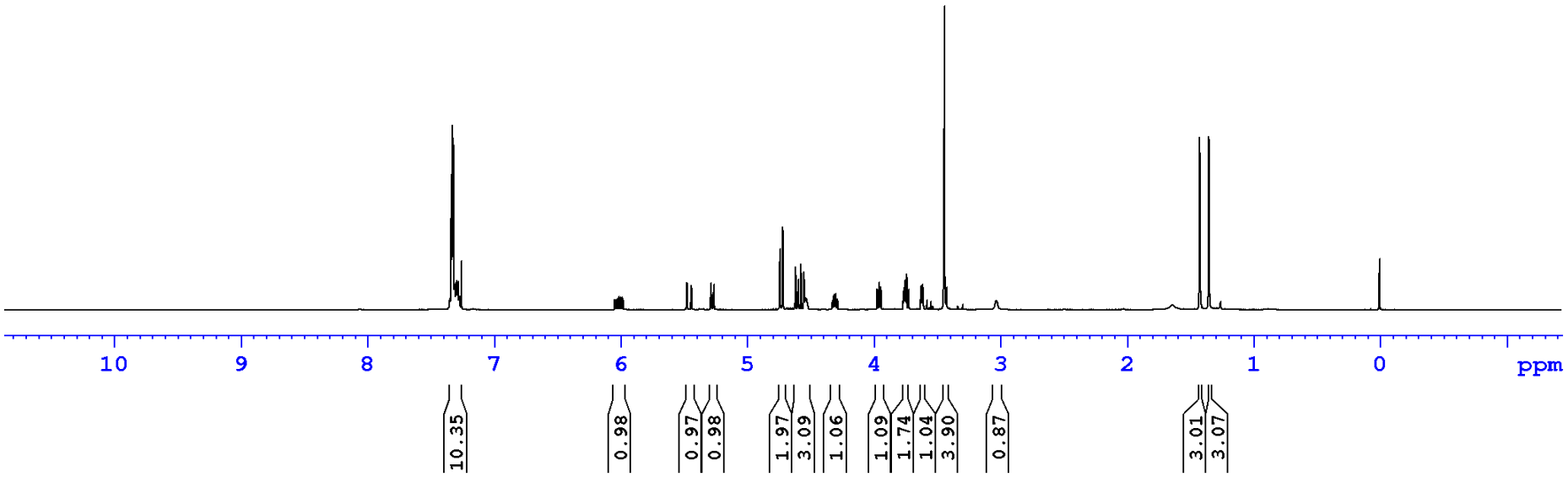
^{135}DEPT NMR (125 MHz, $CDCl_3$)

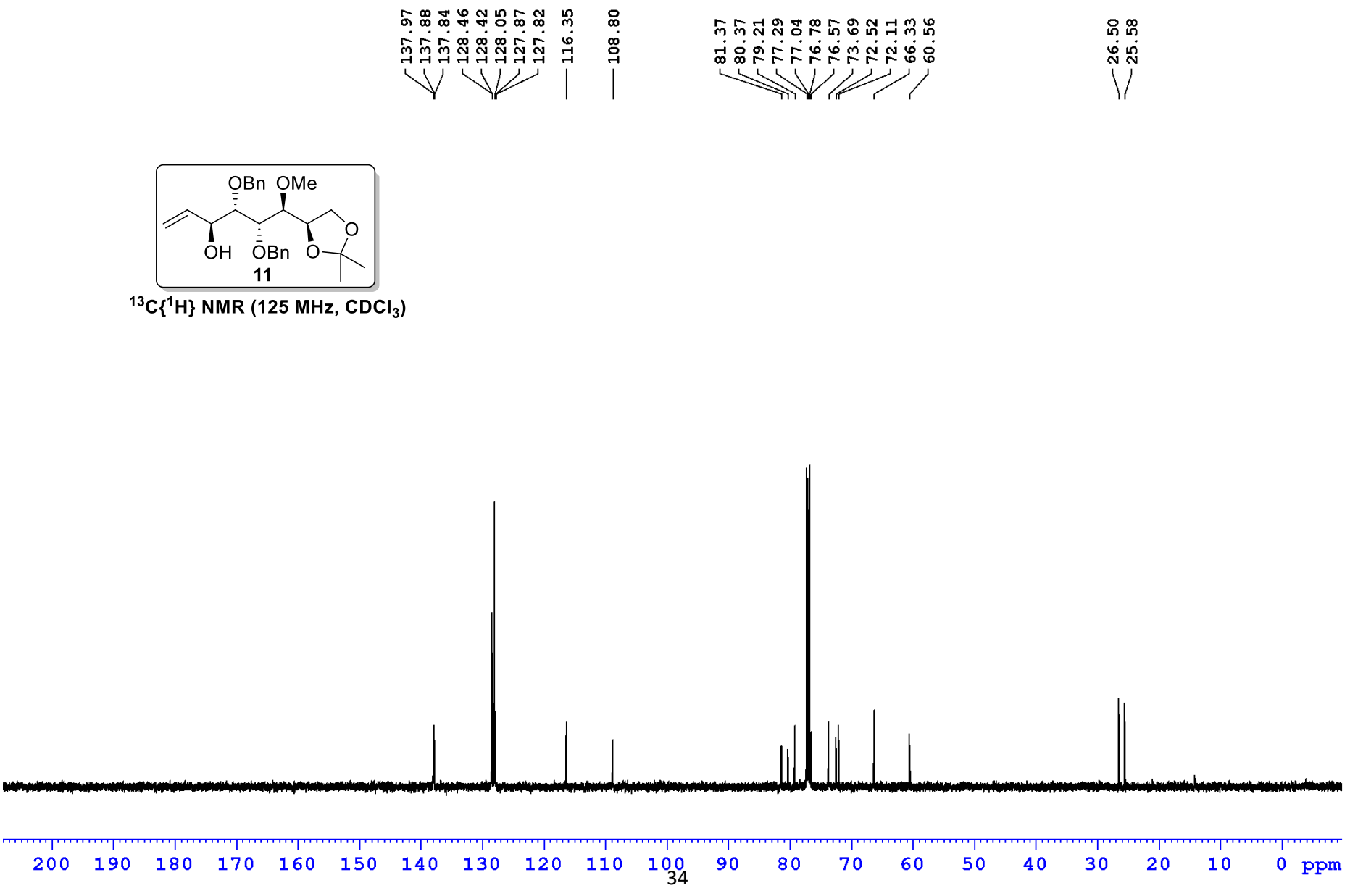




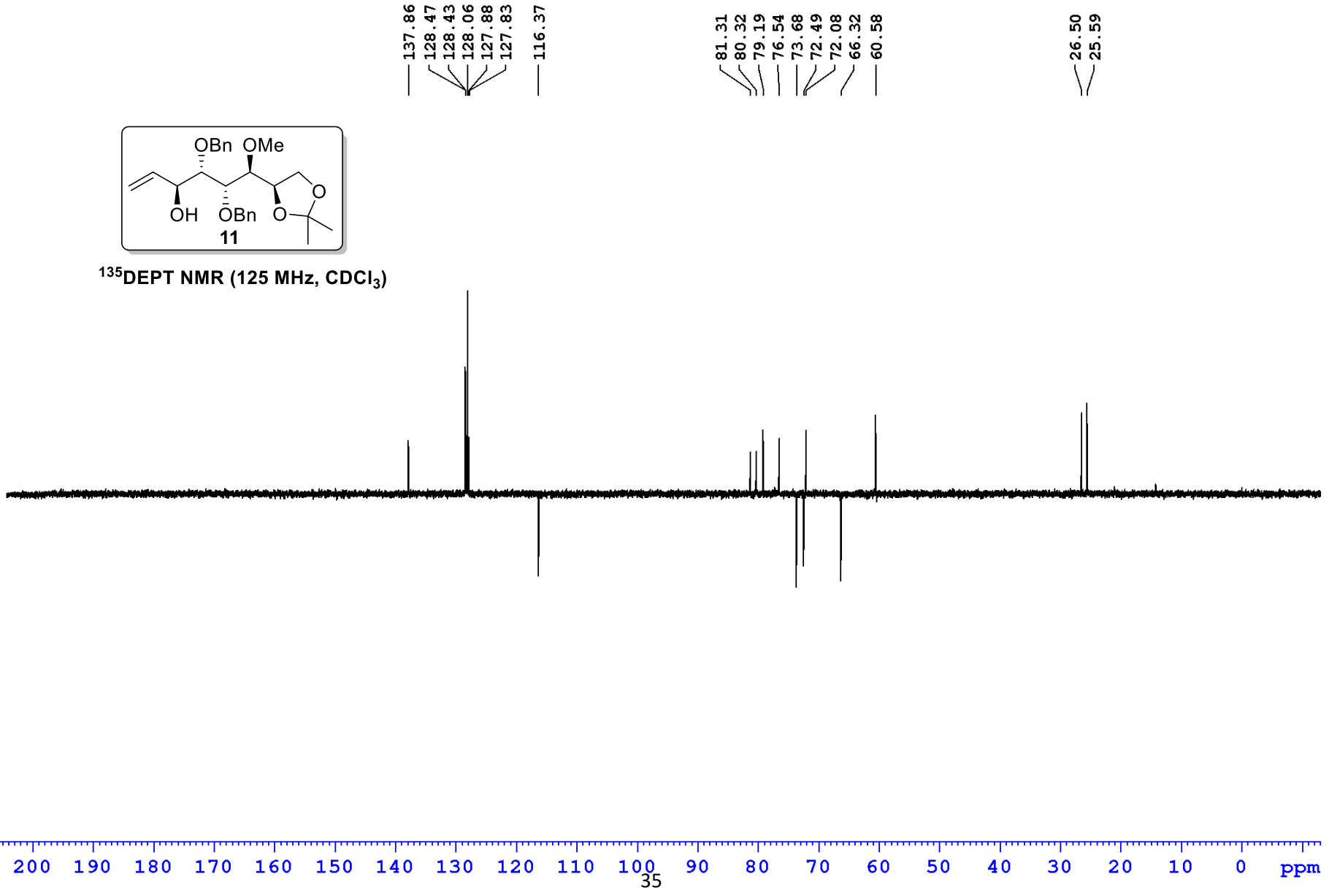
11

^{1}H NMR (500 MHz, $CDCl_3$)

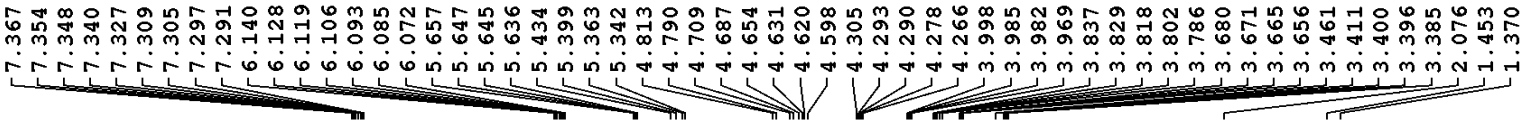


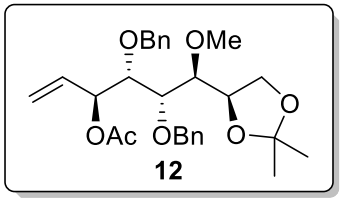


$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



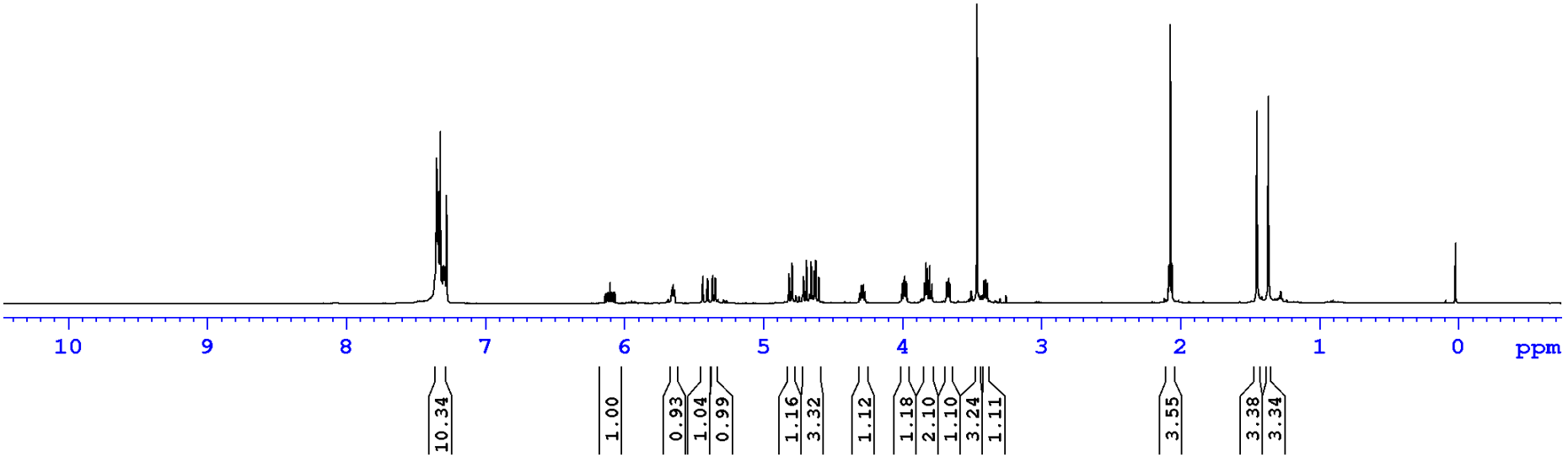
^{135}DEPT NMR (125 MHz, $CDCl_3$)

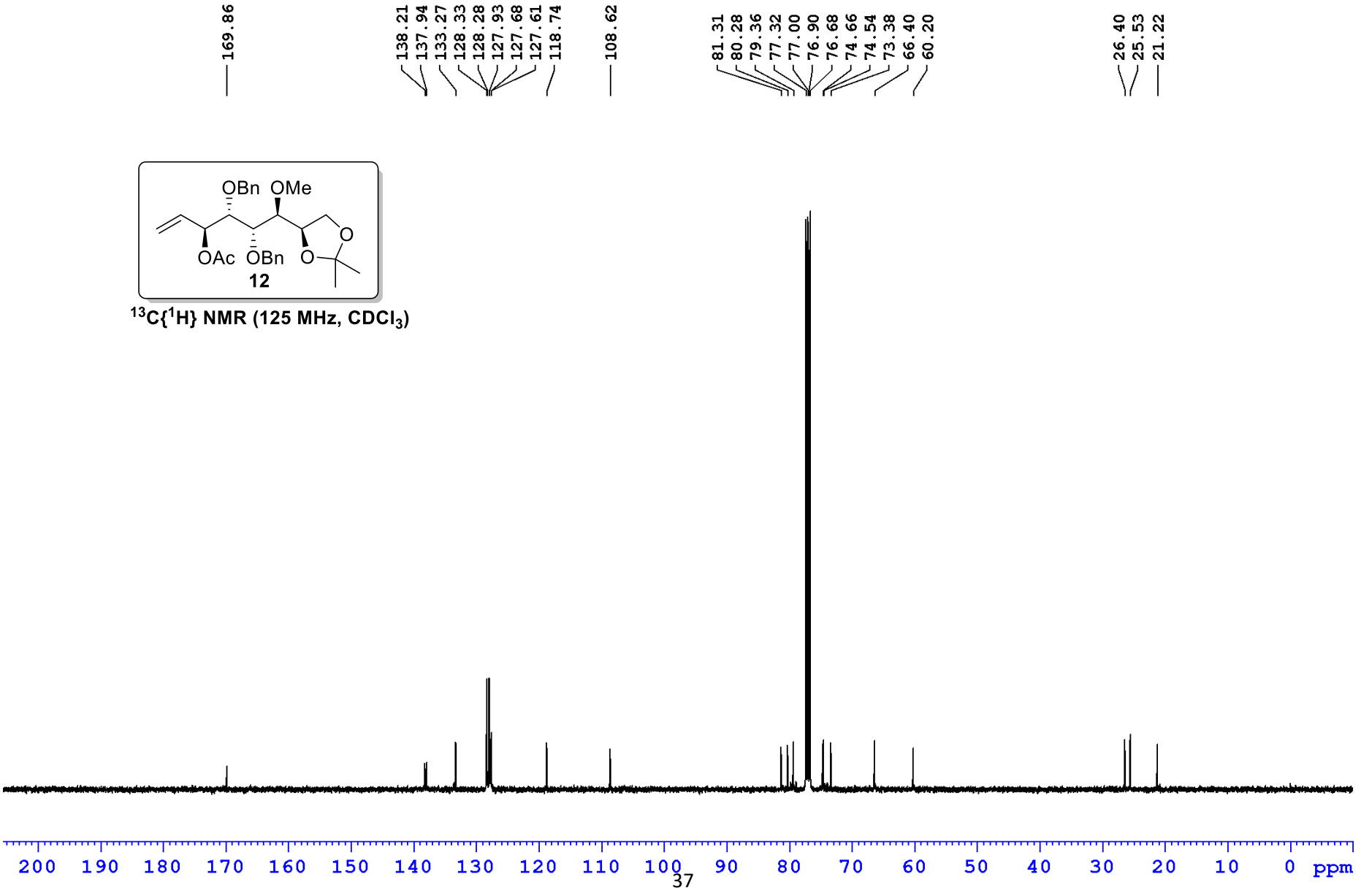




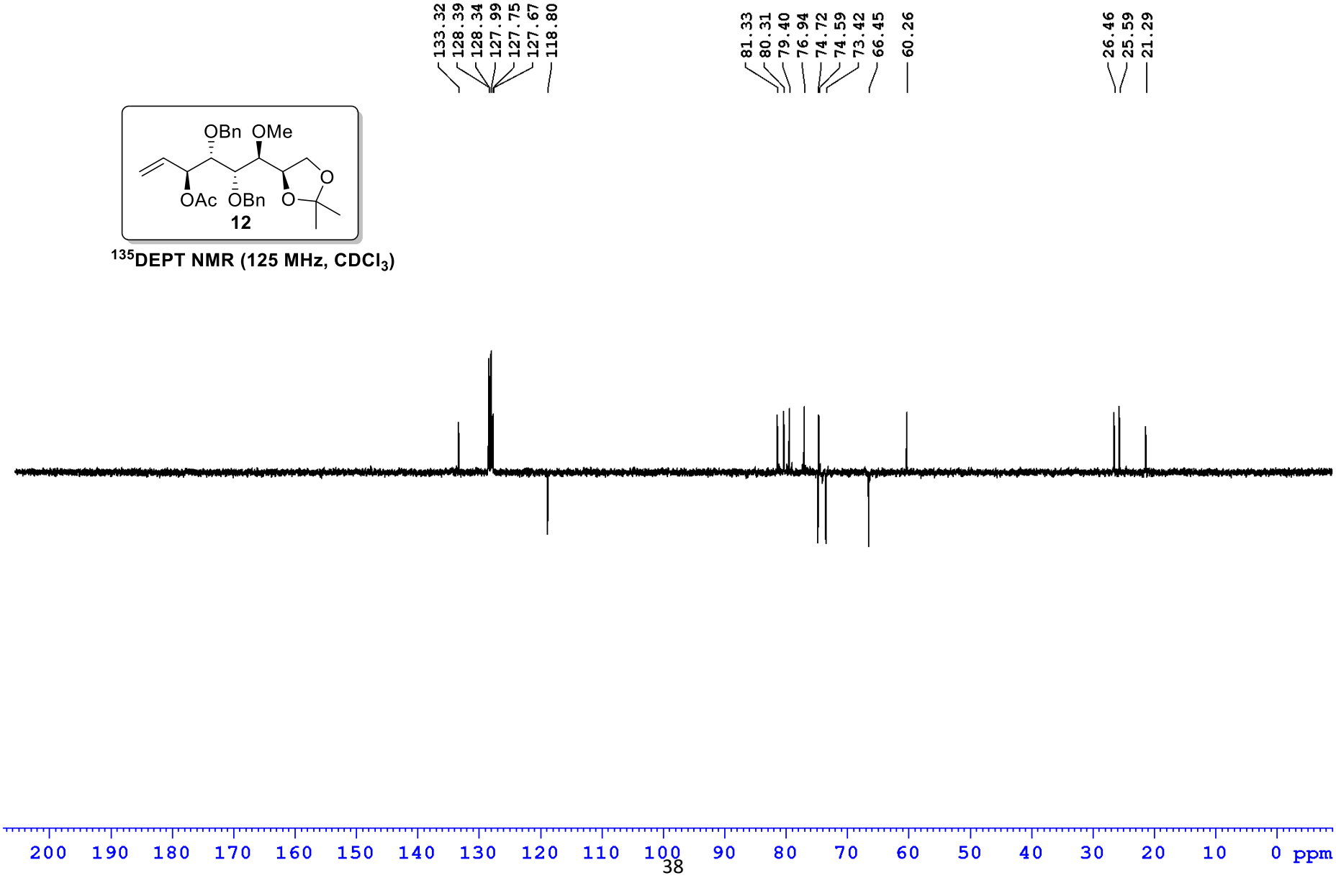
12

^{1}H NMR (500 MHz, $CDCl_3$)

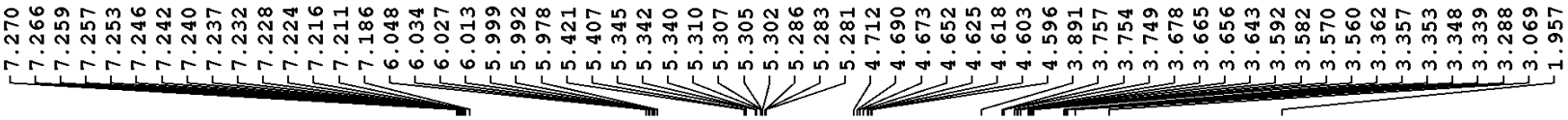


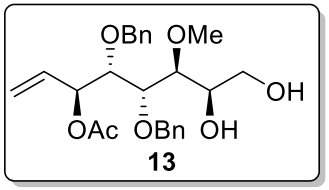


$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



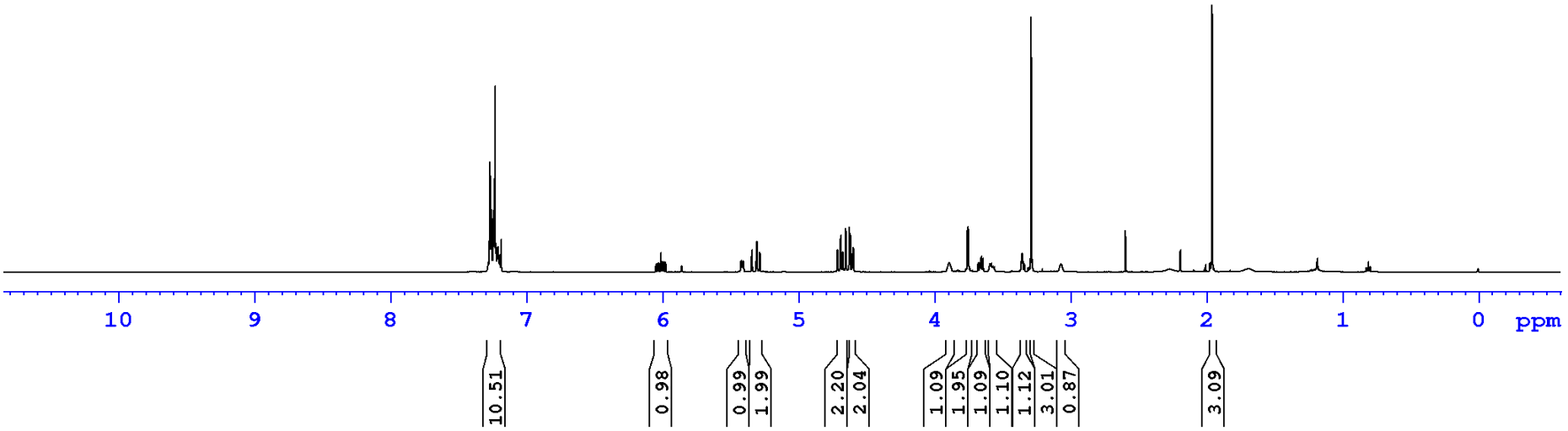
^{135}DEPT NMR (125 MHz, $CDCl_3$)

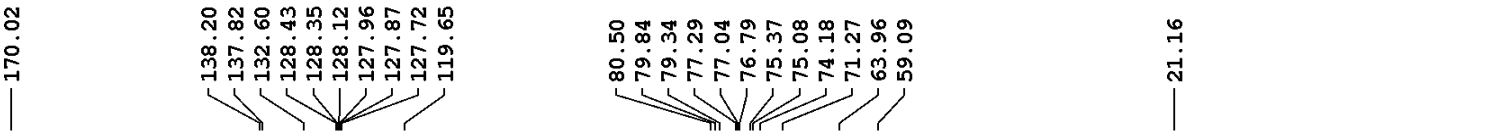


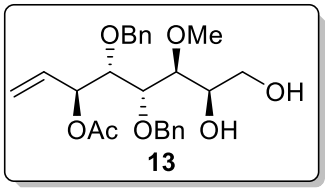


13

^{1}H NMR (500 MHz, $CDCl_3$)

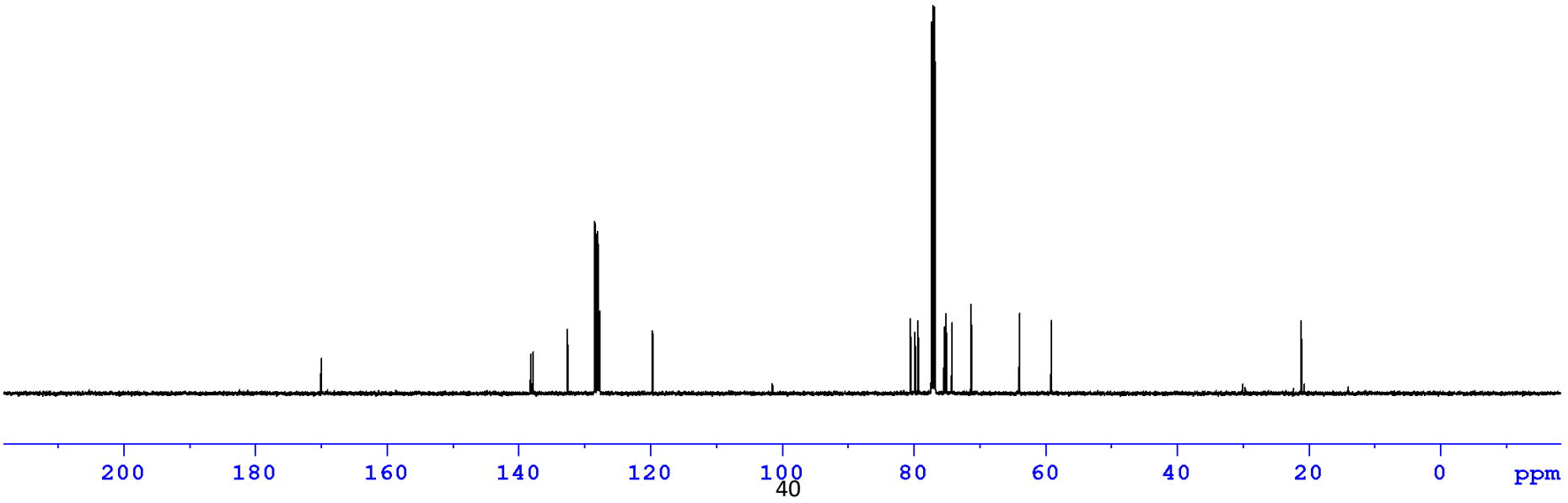


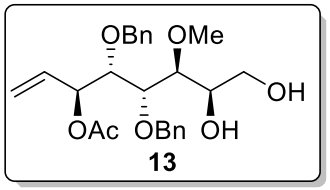




13

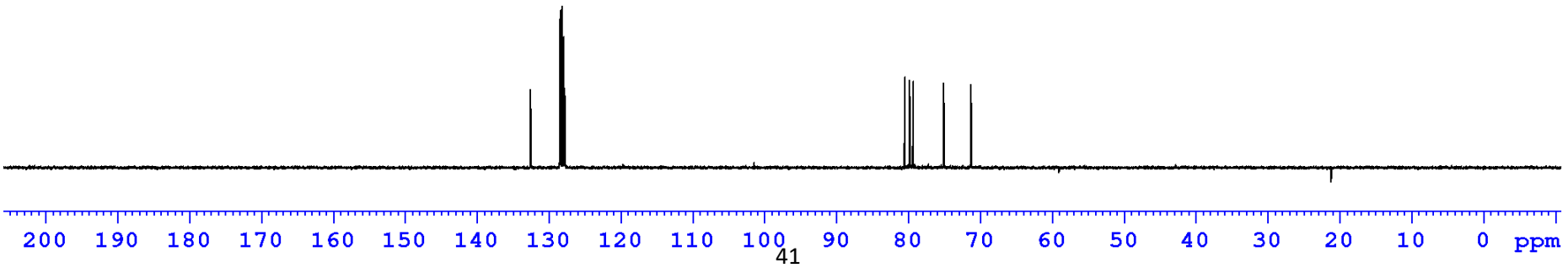
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)

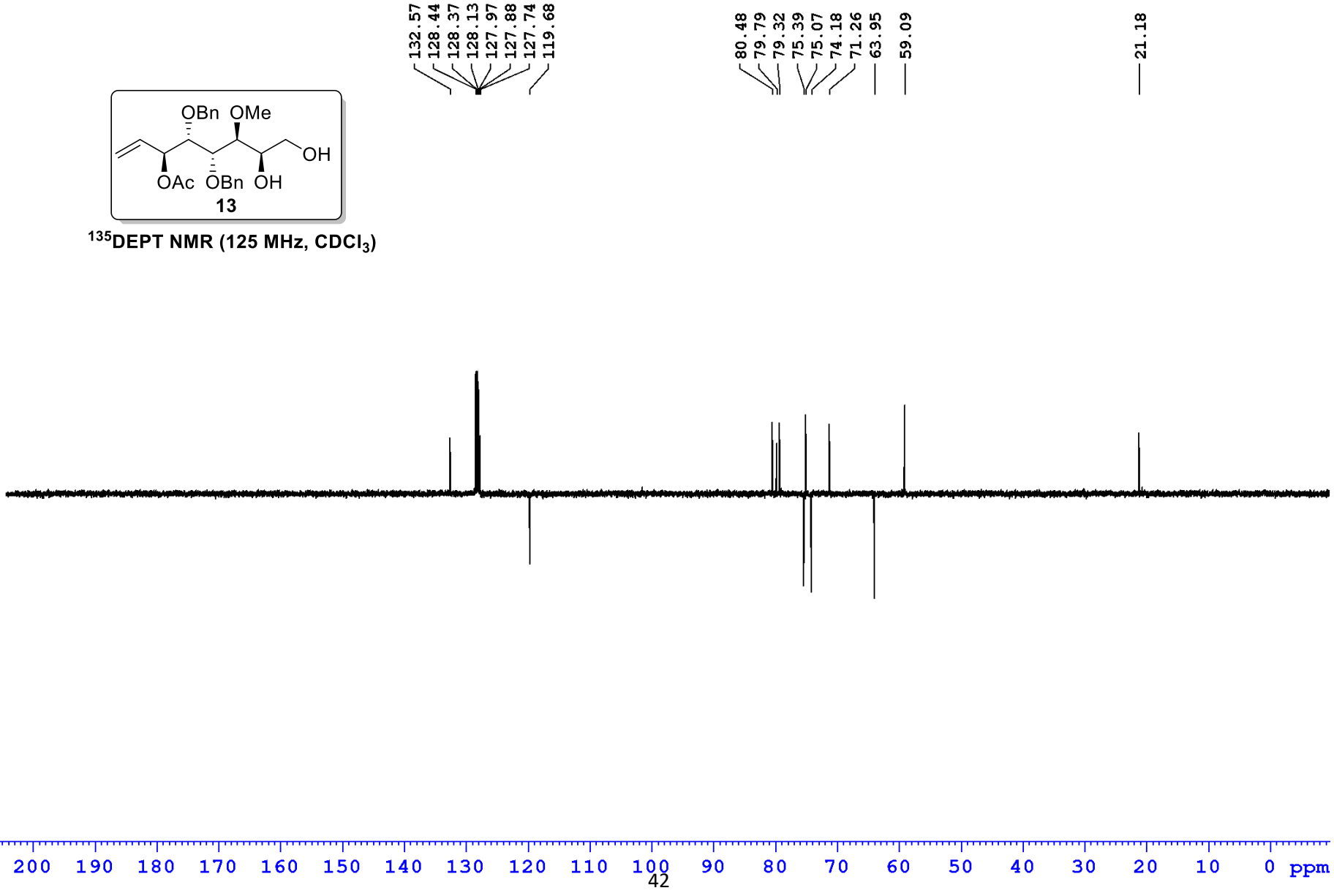




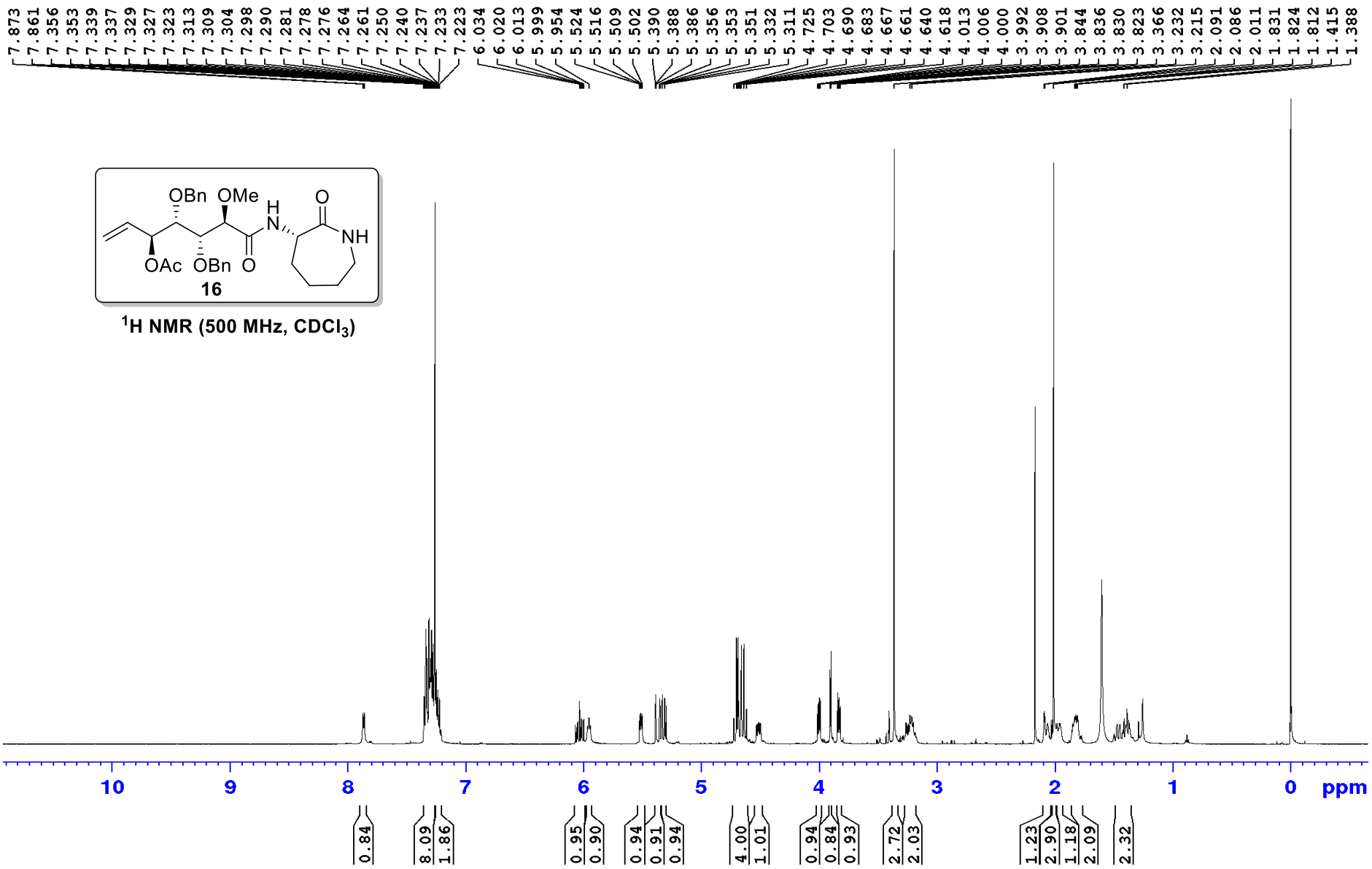
13

^{90}DEPT NMR (125 MHz, $CDCl_3$)

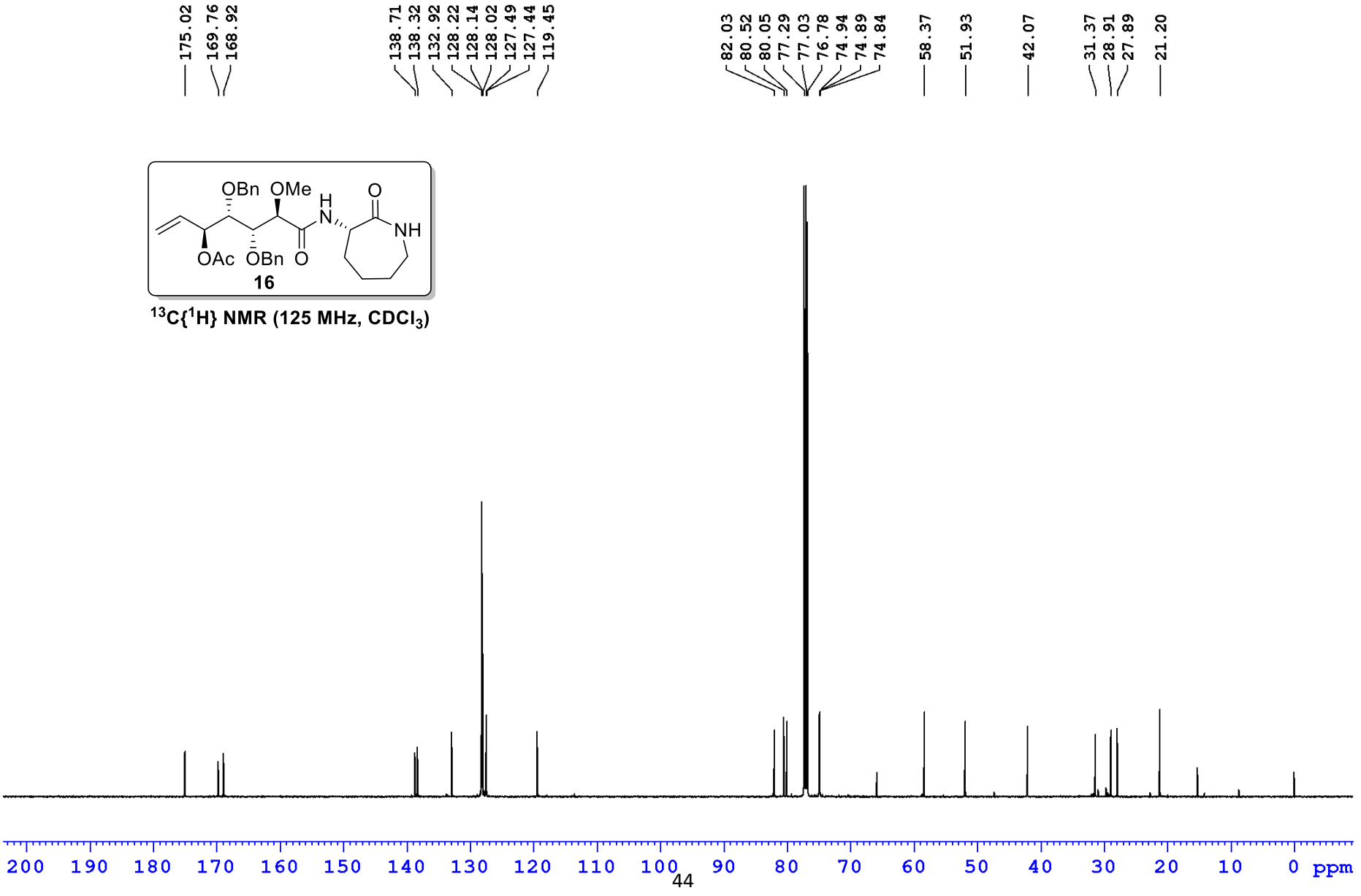




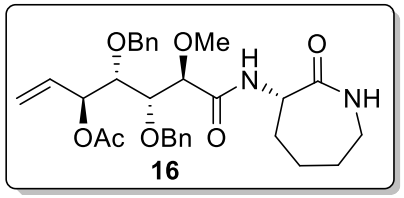
^{135}DEPT NMR (125 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



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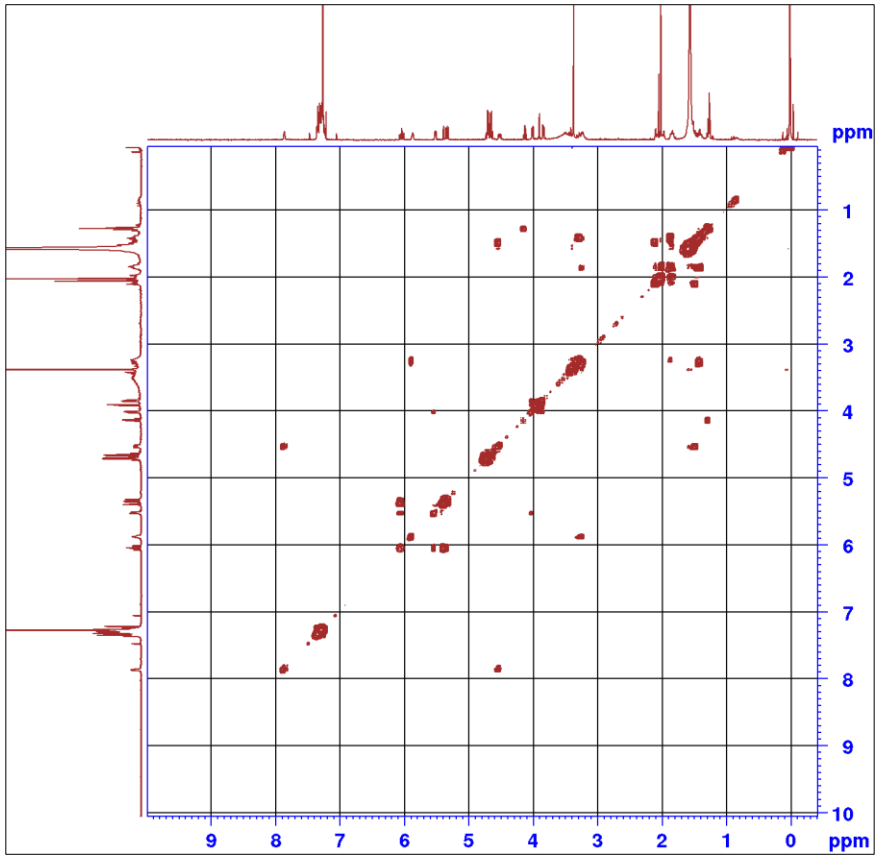
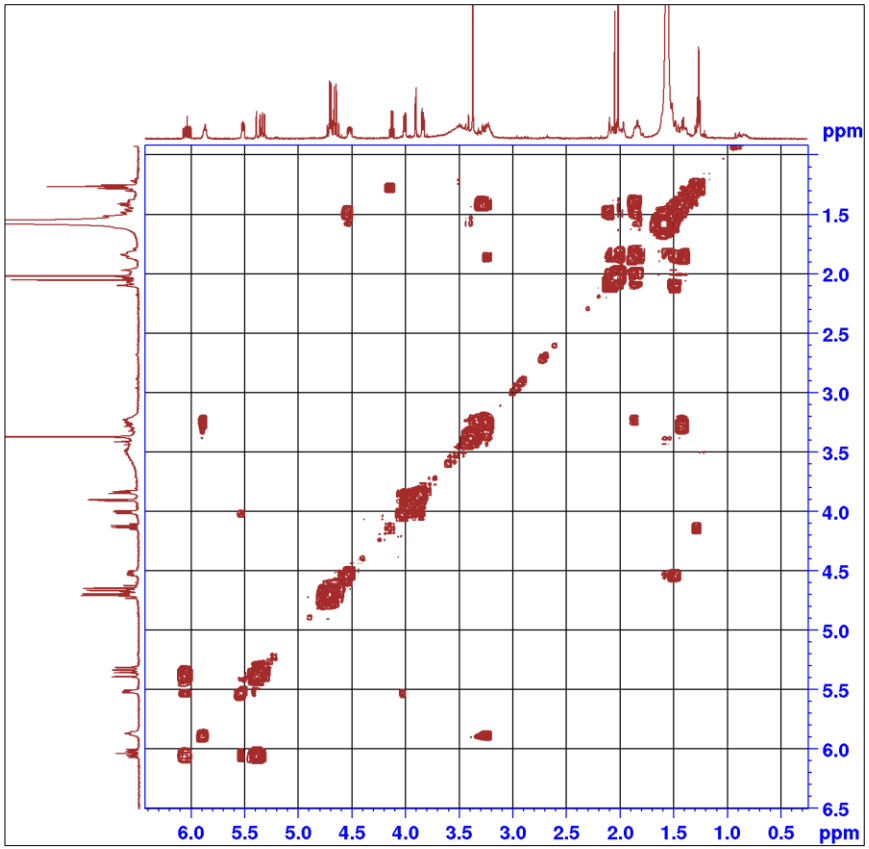
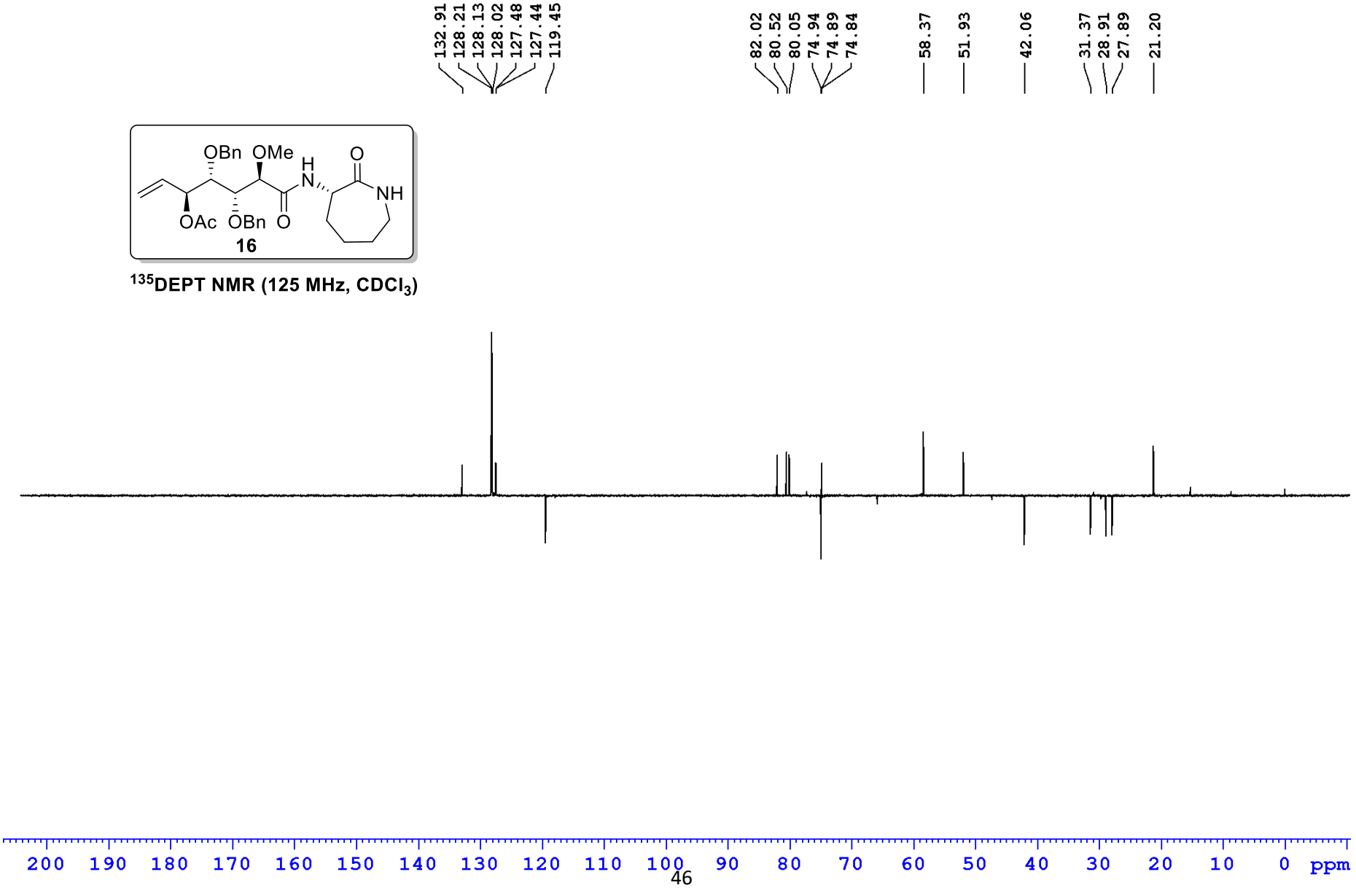
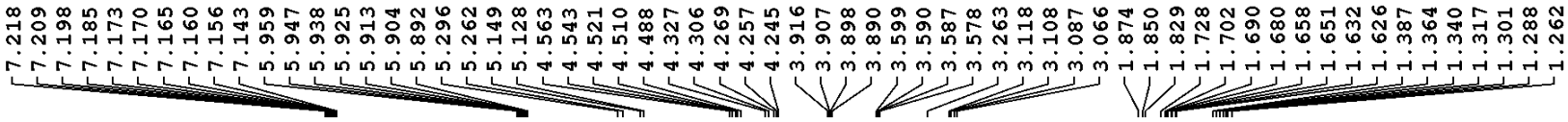
COSY Spectrum (500 MHz, $CDCl_3$)

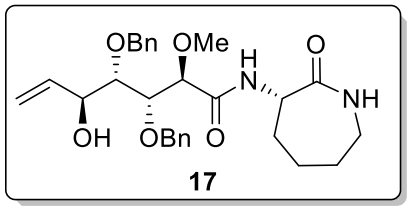






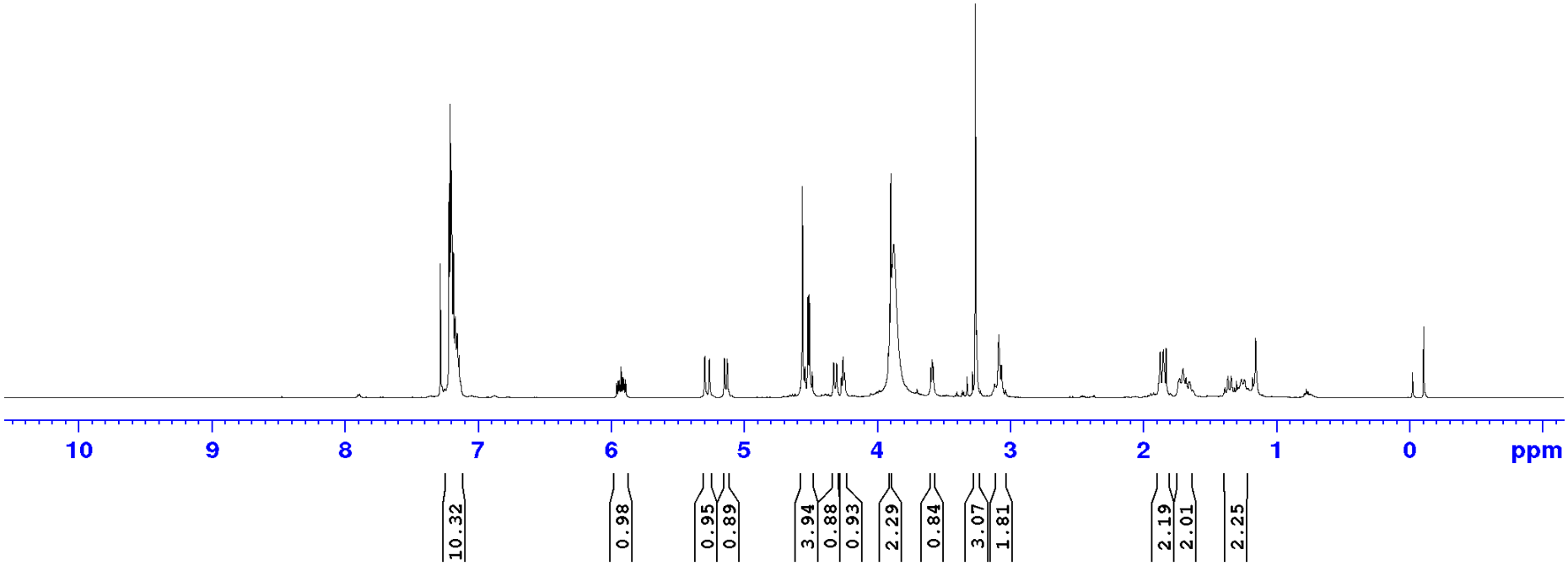
^{135}DEPT NMR (125 MHz, $CDCl_3$)

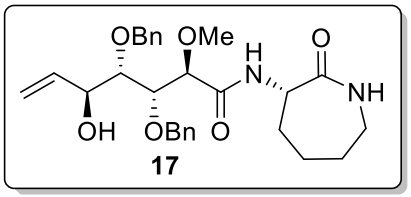




17

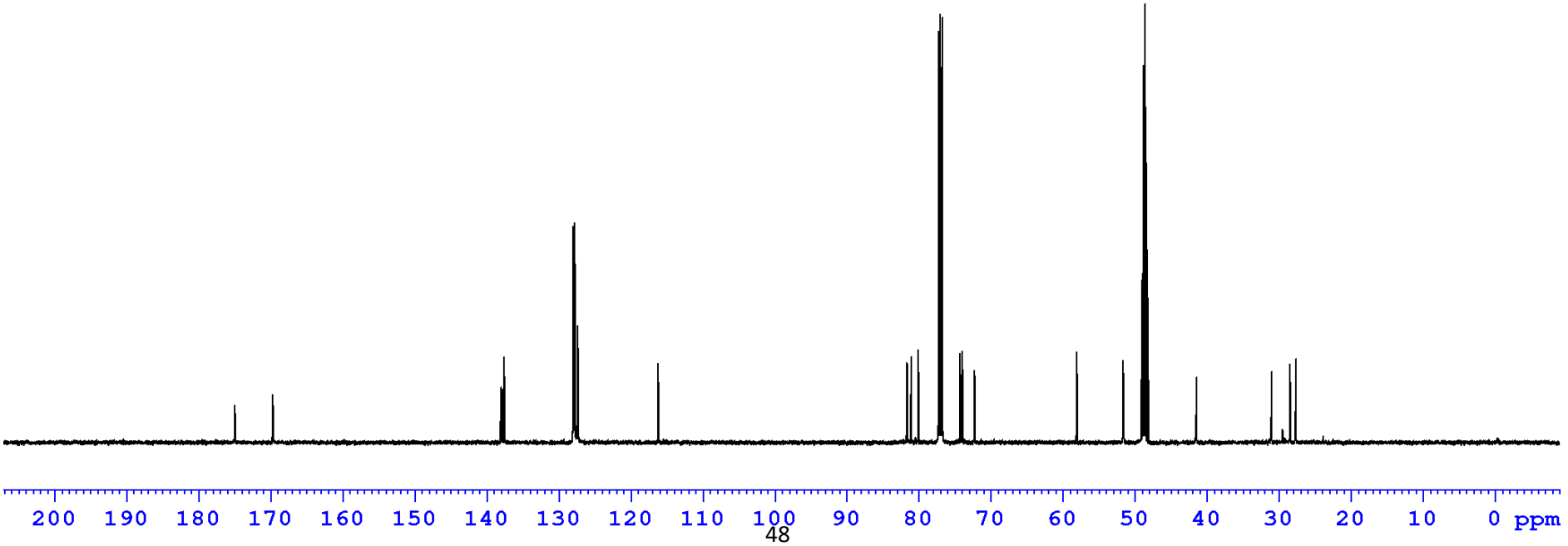
^{1}H NMR (500 MHz, $CDCl_3$ + DMSO)

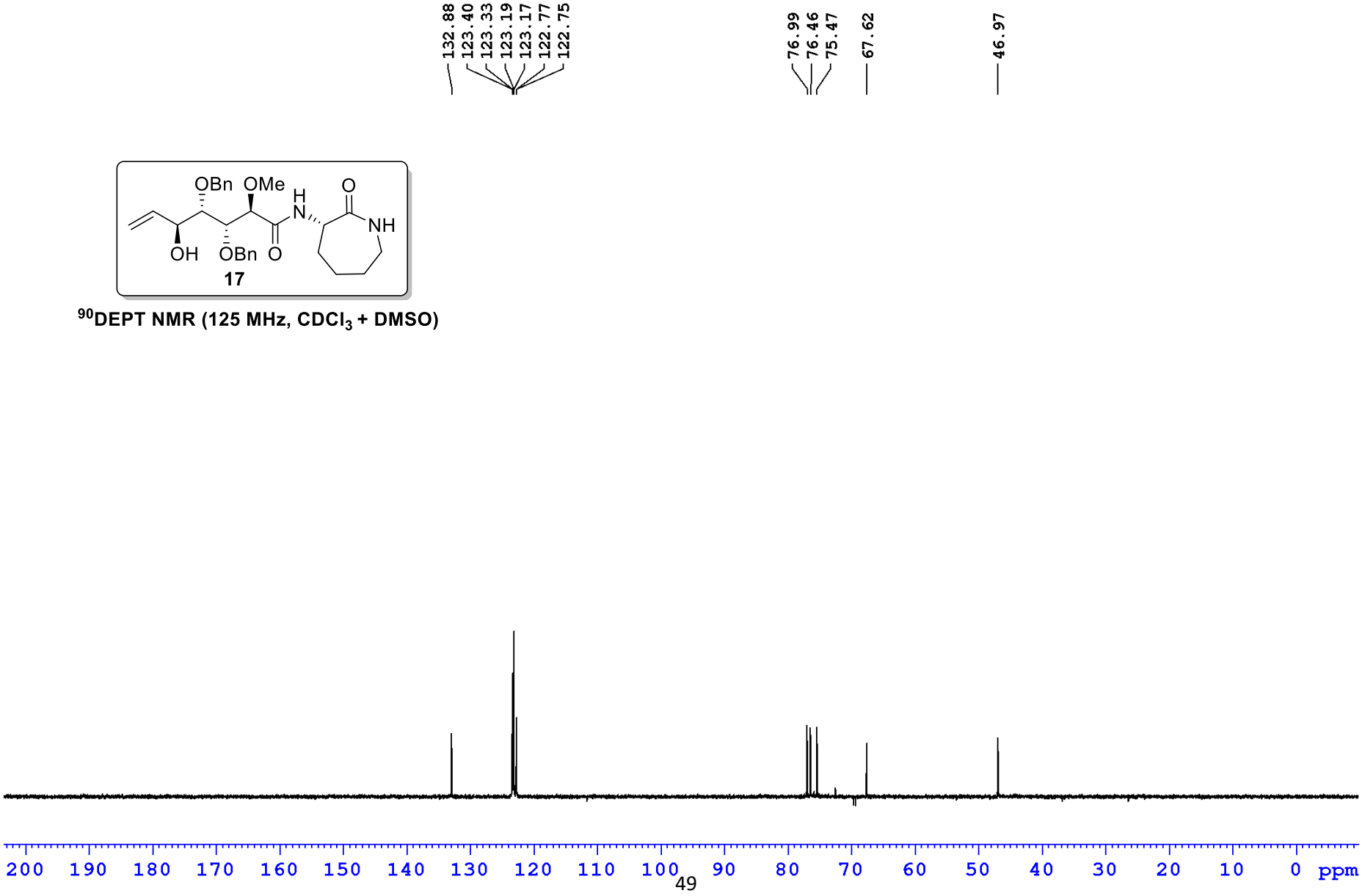




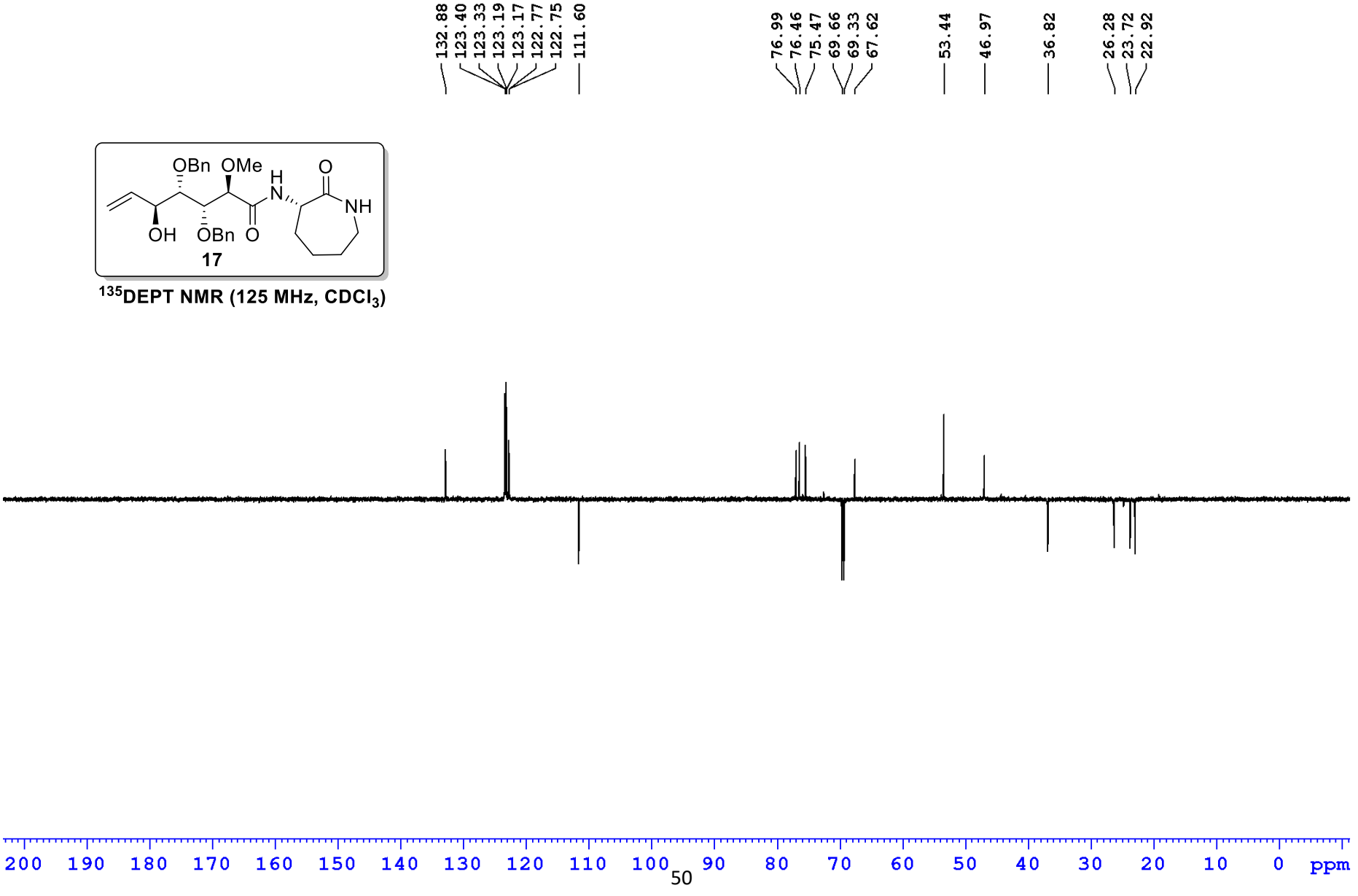
17

$^{13}C\{^{1}H\}$ NMR (125 MHz $CDCl_3$ + DMSO)

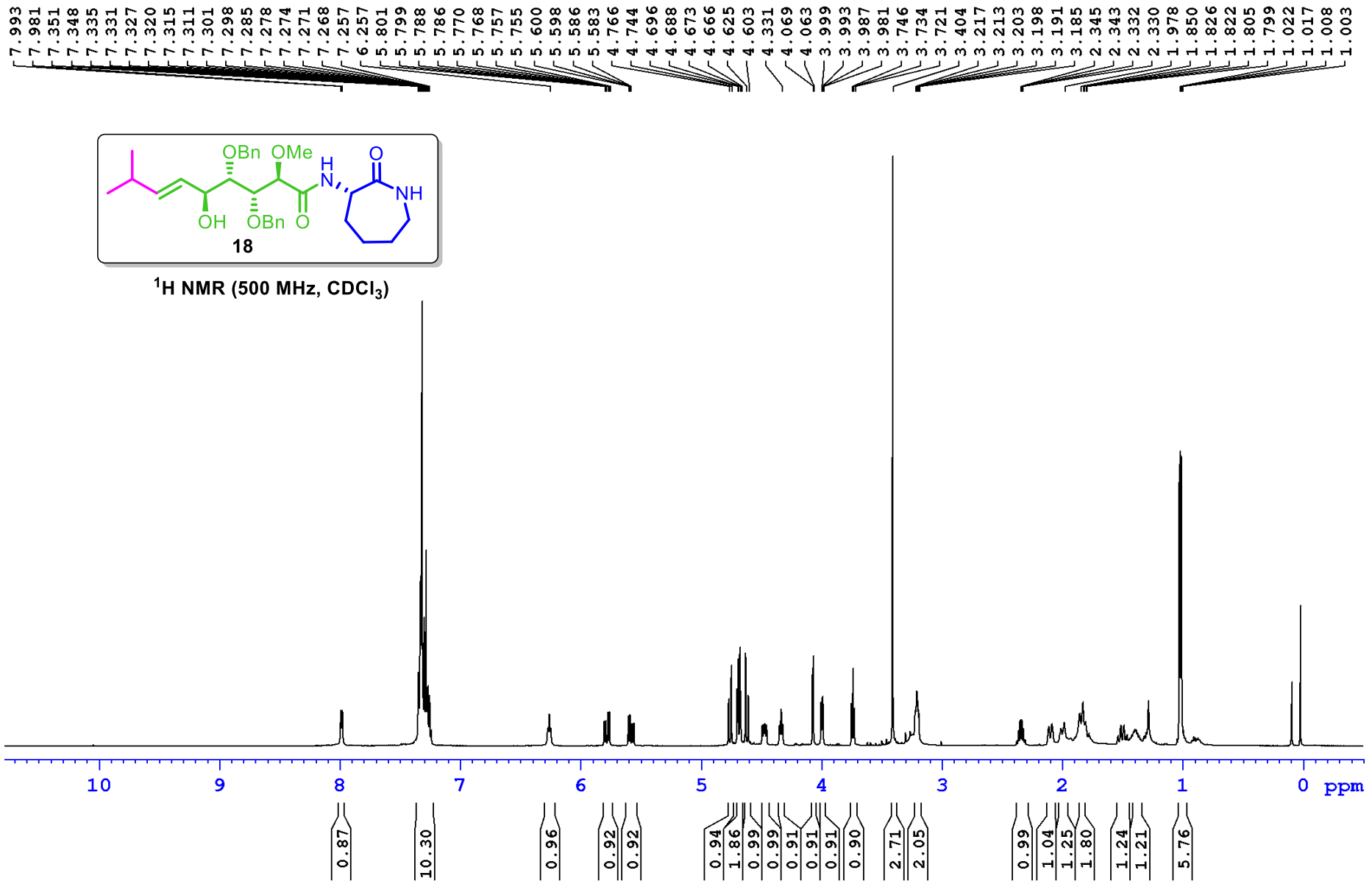


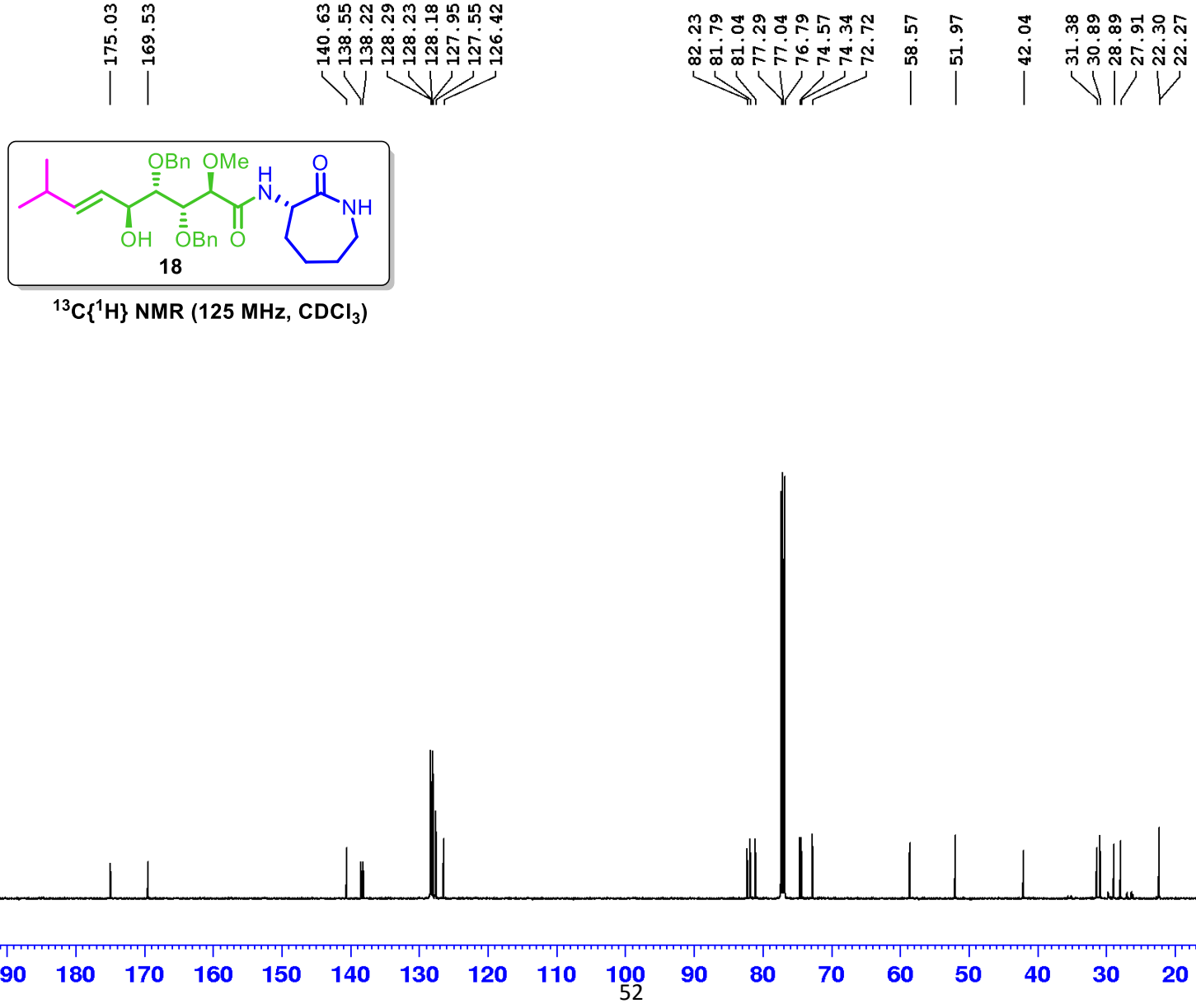


^{90}DEPT NMR (125 MHz, $CDCl_3$ + DMSO)

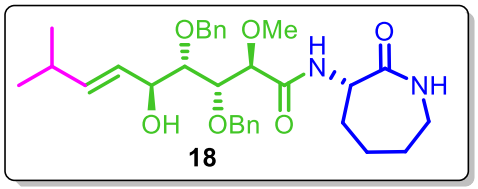


^{135}DEPT NMR (125 MHz, $CDCl_3$)


7.993 7.981 7.351 7.348 7.335 7.331 7.327 7.320 7.315 7.311 7.301 7.298 7.285 7.278 7.274 7.271 7.268 7.257 6.257 5.801 5.799 5.788 5.786 5.770 5.768 5.757 5.755 5.600 5.598 5.586 5.583 4.766 4.744 4.696 4.688 4.673 4.666 4.625 4.603 4.331 4.069 4.063 3.999 3.993 3.987 3.981 3.746 3.734 3.721 3.404 3.217 3.213 3.203 3.198 3.191 3.185 2.345 2.343 2.332 2.330 1.978 1.850 1.826 1.822 1.805 1.799 1.022 1.017 1.008 1.003
OBn OMe
H
N
O
NH
OH OBn O
18
^{1}H NMR (500 MHz, CDCl$_3$)
10 9 8 7 6 5 4 3 2 1 0 ppm
0.87 10.30 0.96 0.92 0.92 0.94 1.86 0.99 0.99 0.91 0.91 0.91 0.90 2.71 2.05 0.99 1.04 1.25 1.80 1.24 1.21 5.76

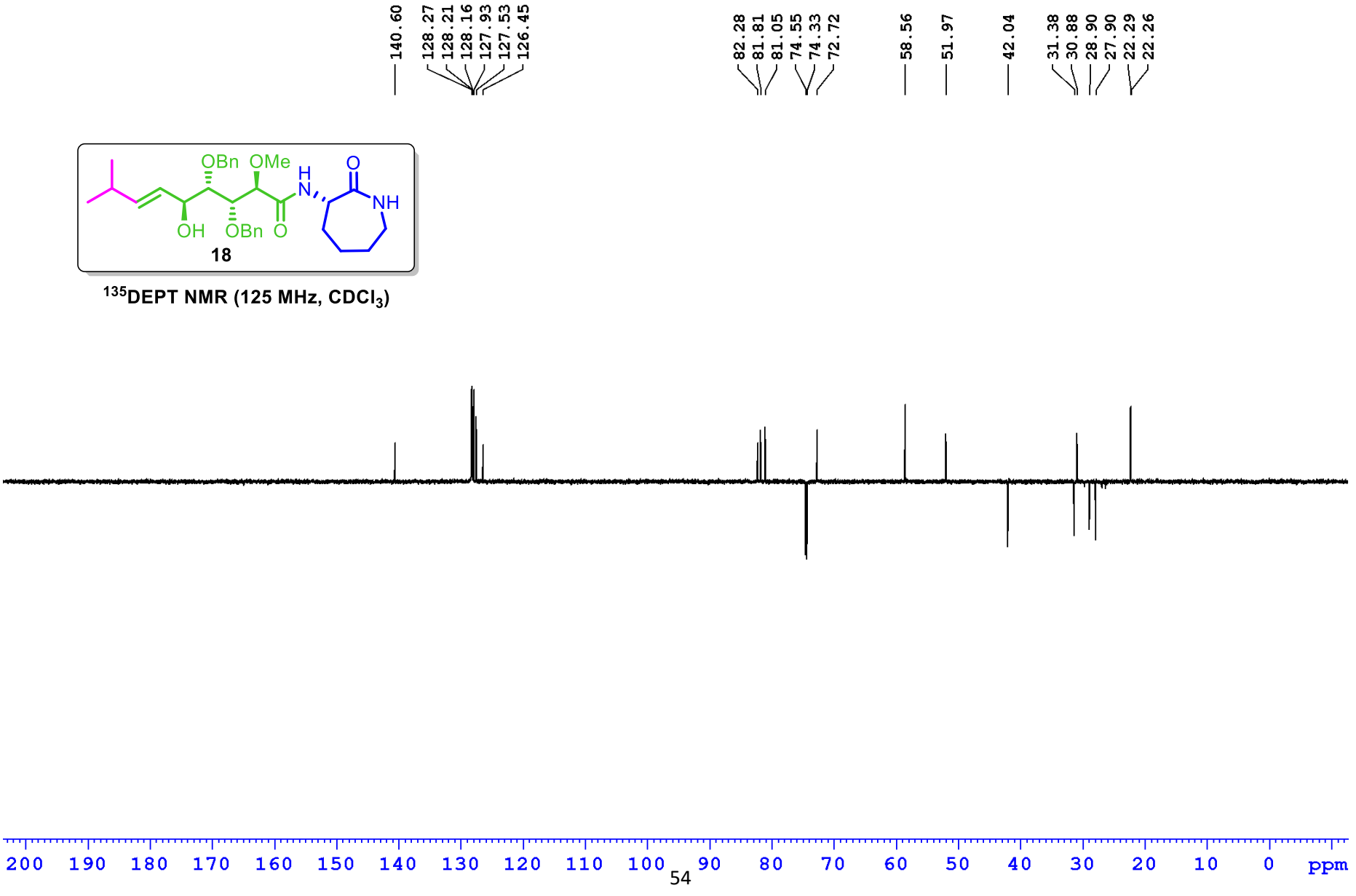


$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)

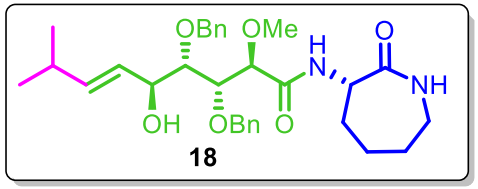


18

^{90}DEPT NMR (125 MHz, $CDCl_3$)

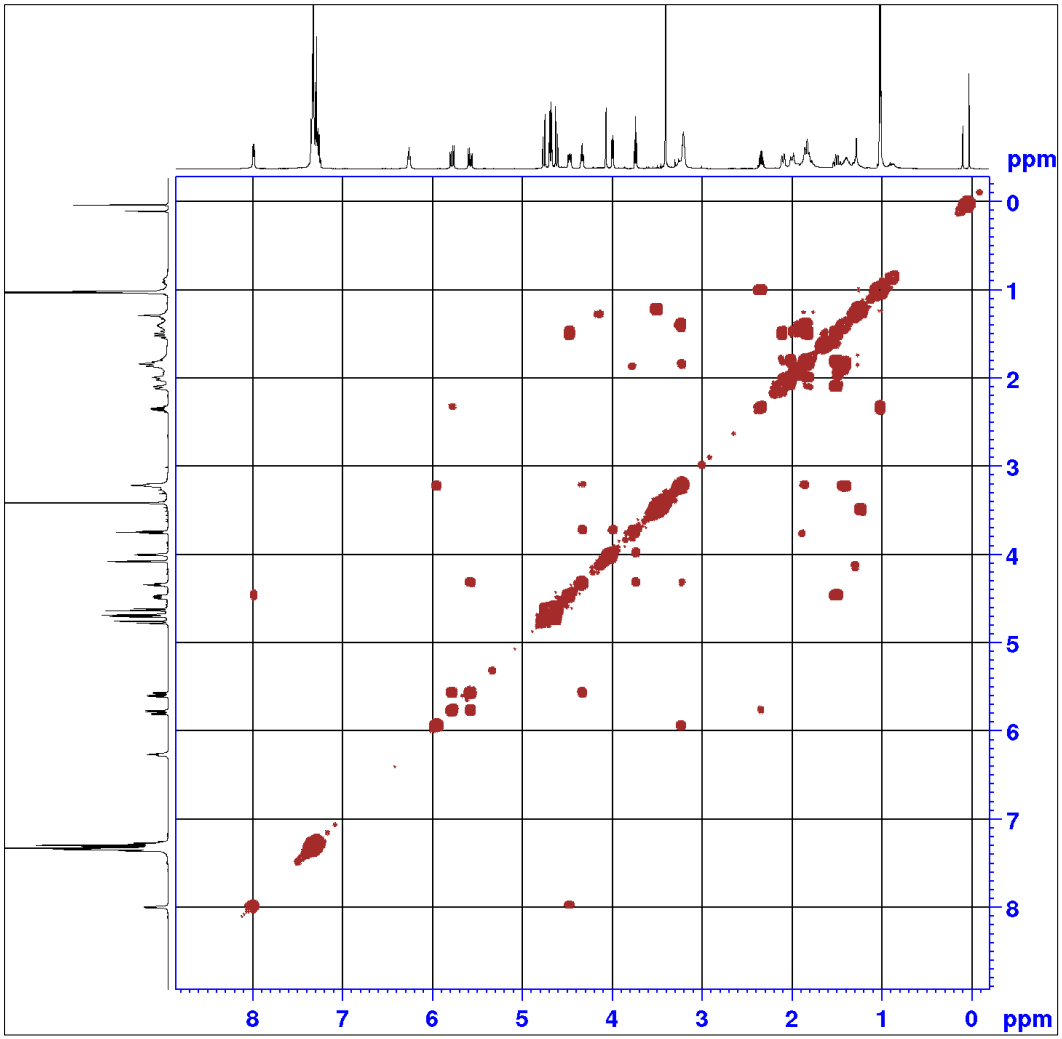


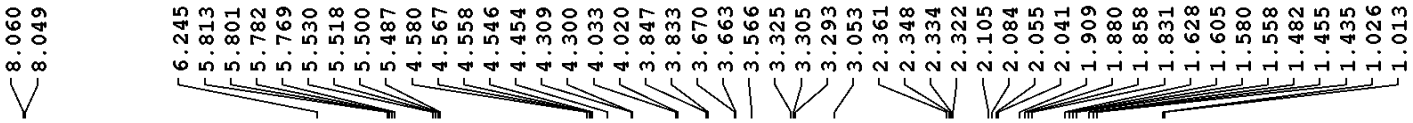
^{135}DEPT NMR (125 MHz, $CDCl_3$)

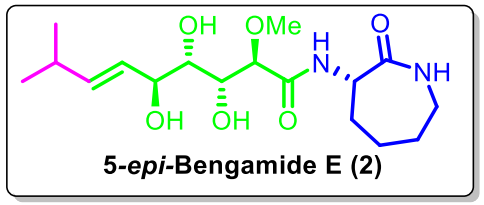


18

(COSY Spectrum, 500MHz, $CDCL_3$)

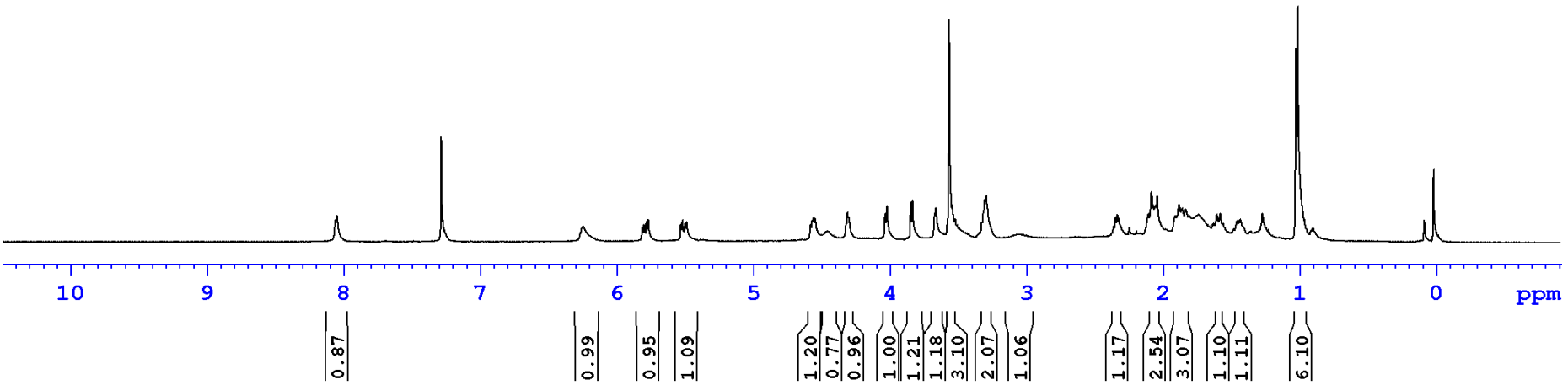


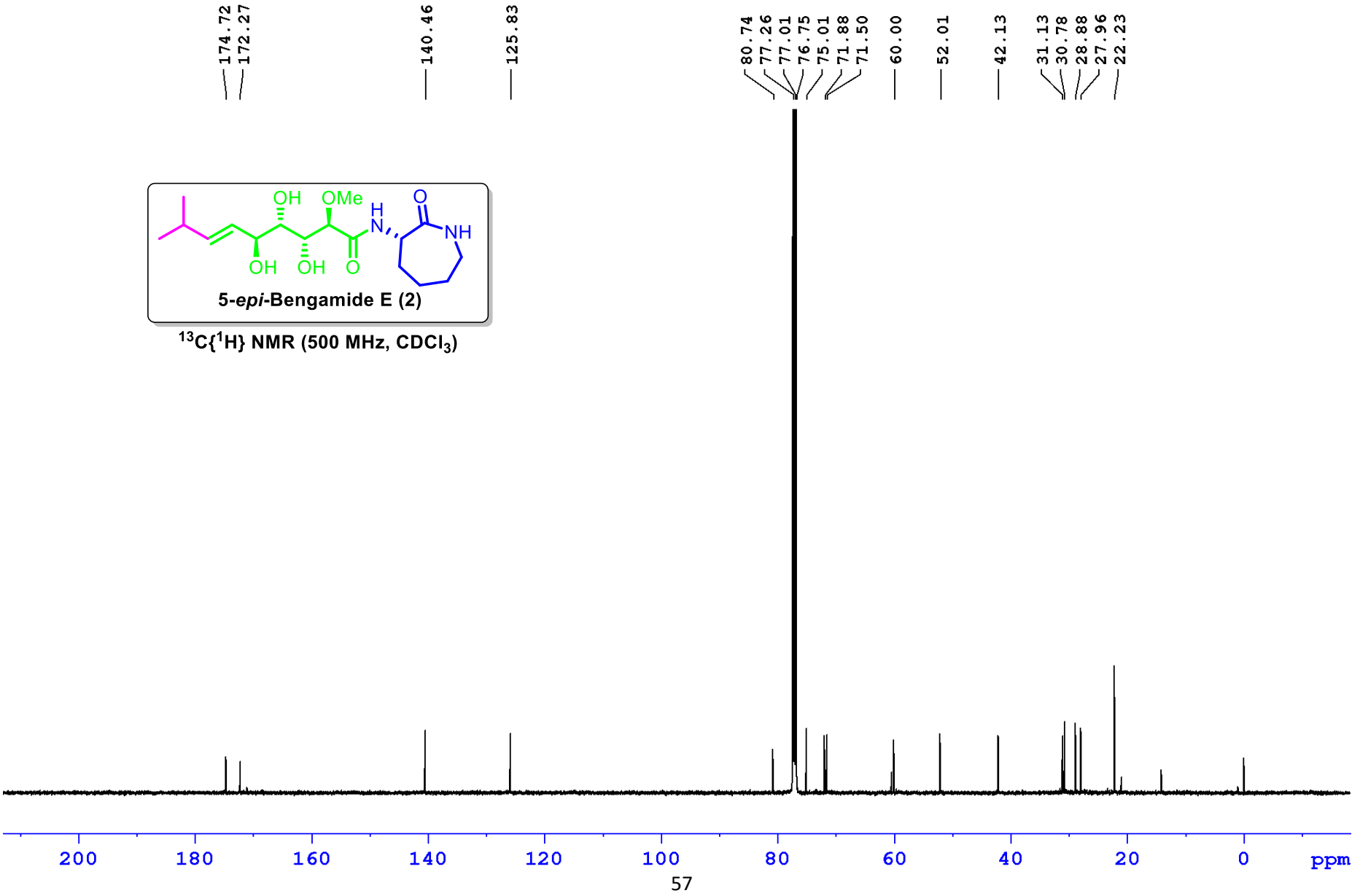




5-*epi*-Bengamide E (2)

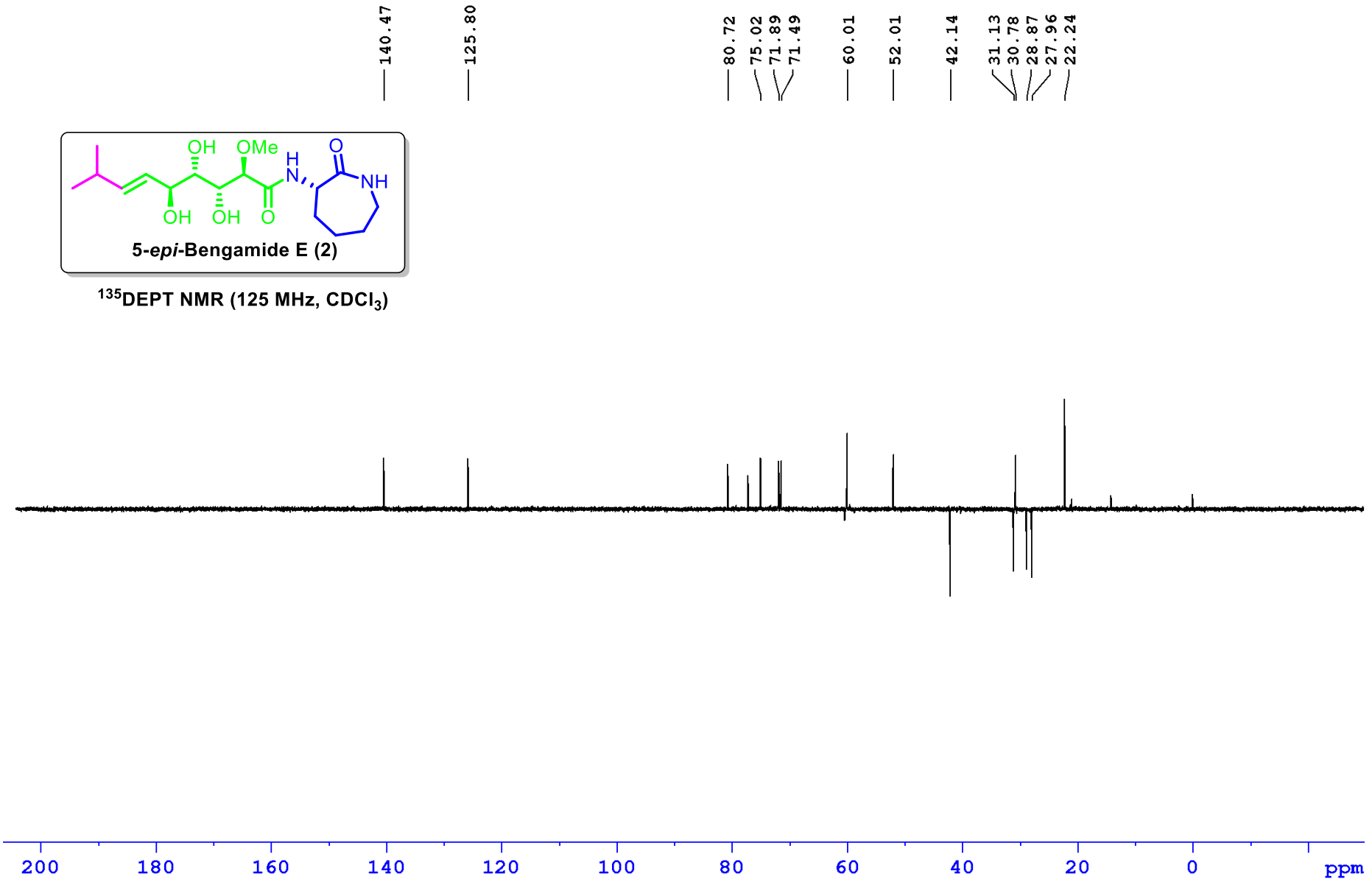
^{1}H NMR (500 MHz, $CDCl_3$)





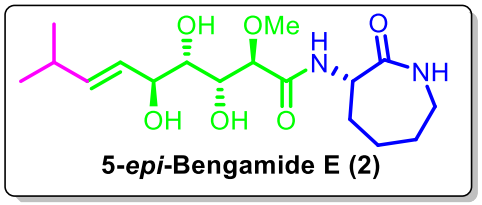
5-*epi*-Bengamide E (2)

$^{13}C\{^{1}H\}$ NMR (500 MHz, $CDCl_3$)



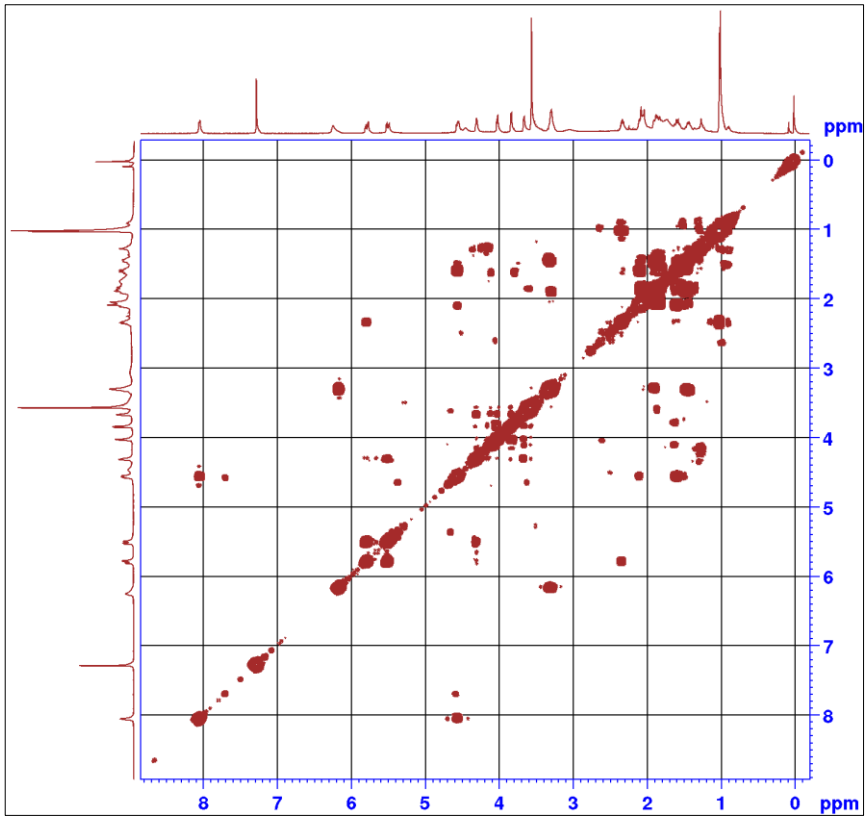
5-*epi*-Bengamide E (2)

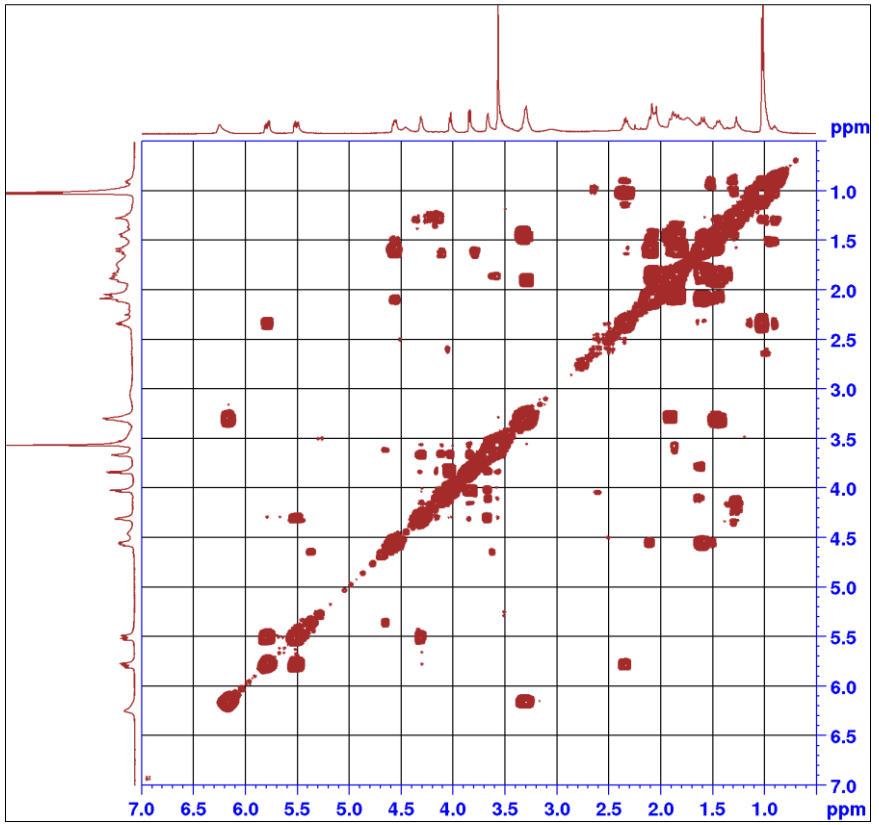
^{135}DEPT NMR (125 MHz, $CDCl_3$)

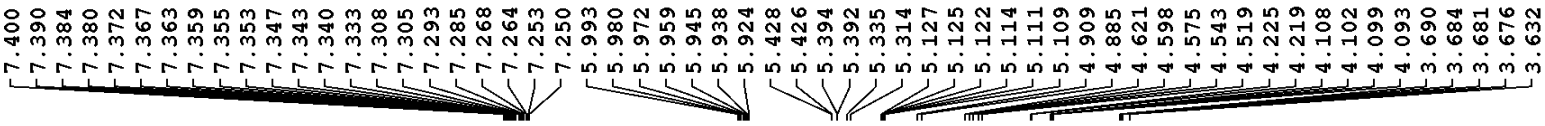


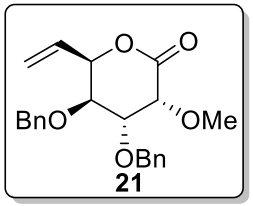
5-*epi*-Bengamide E (2)

(COSY Spectrum, 500MHz, $CDCL_3$)



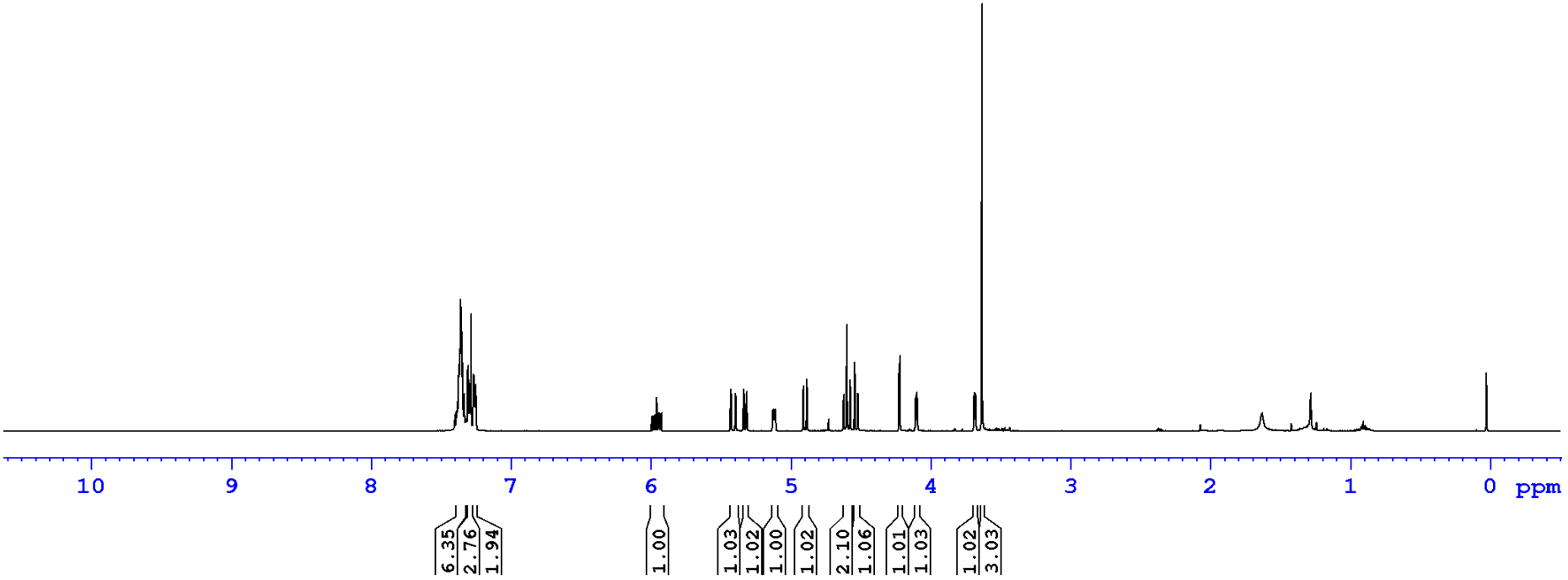


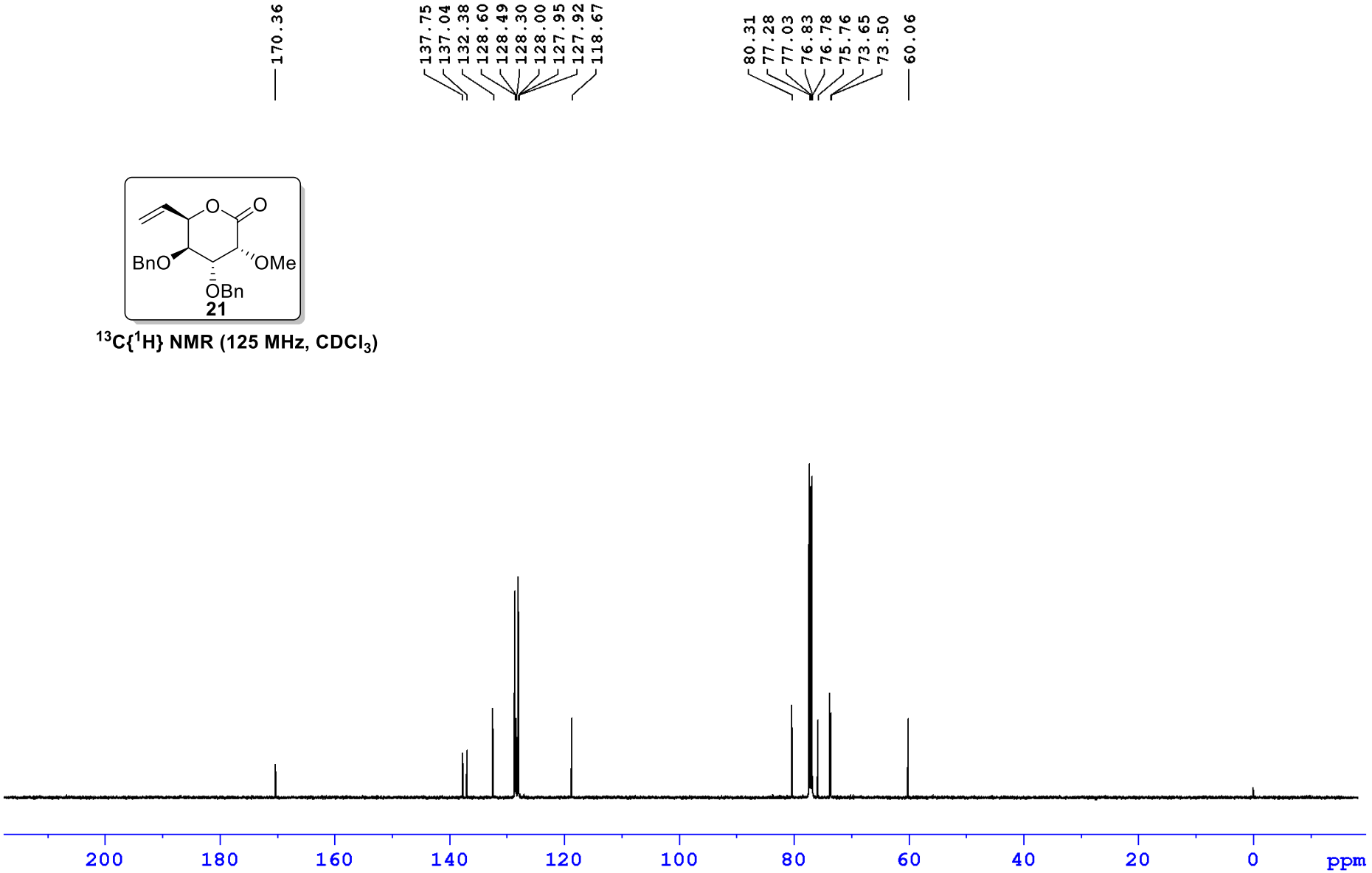




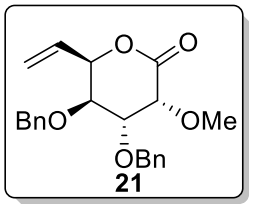
21

1H NMR (500 MHz, $CDCl_3$)





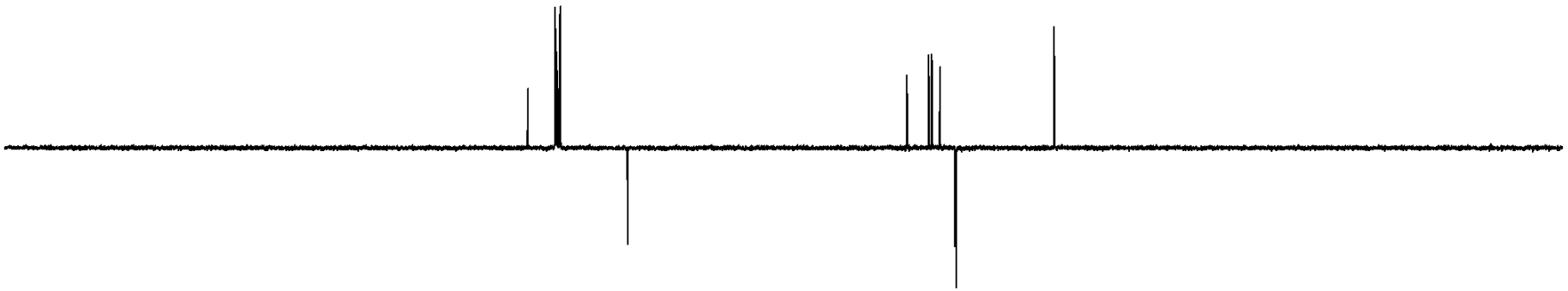
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)

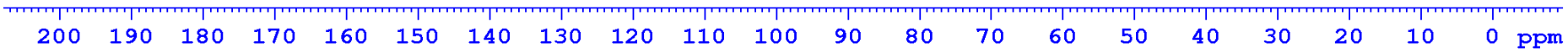


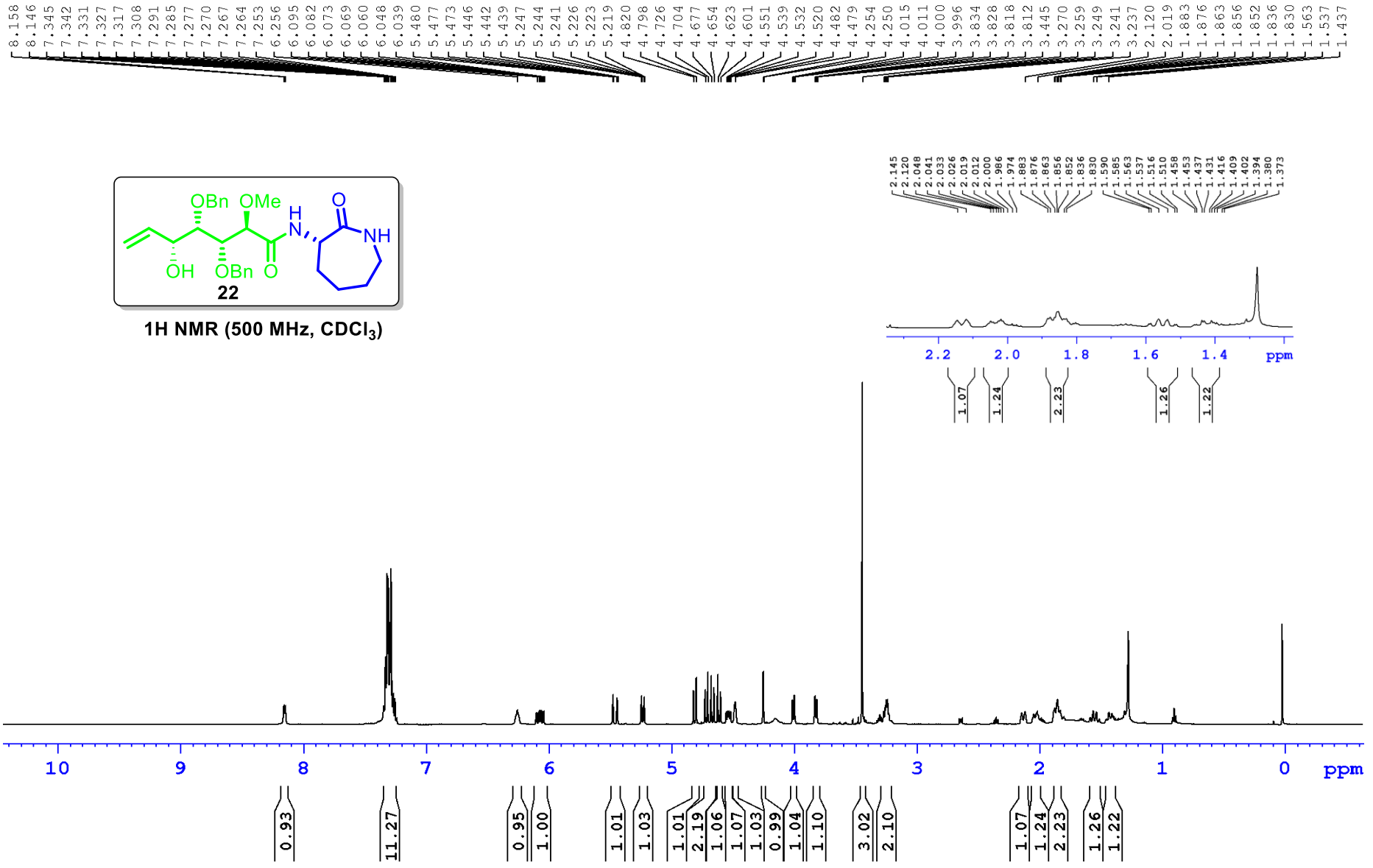
21

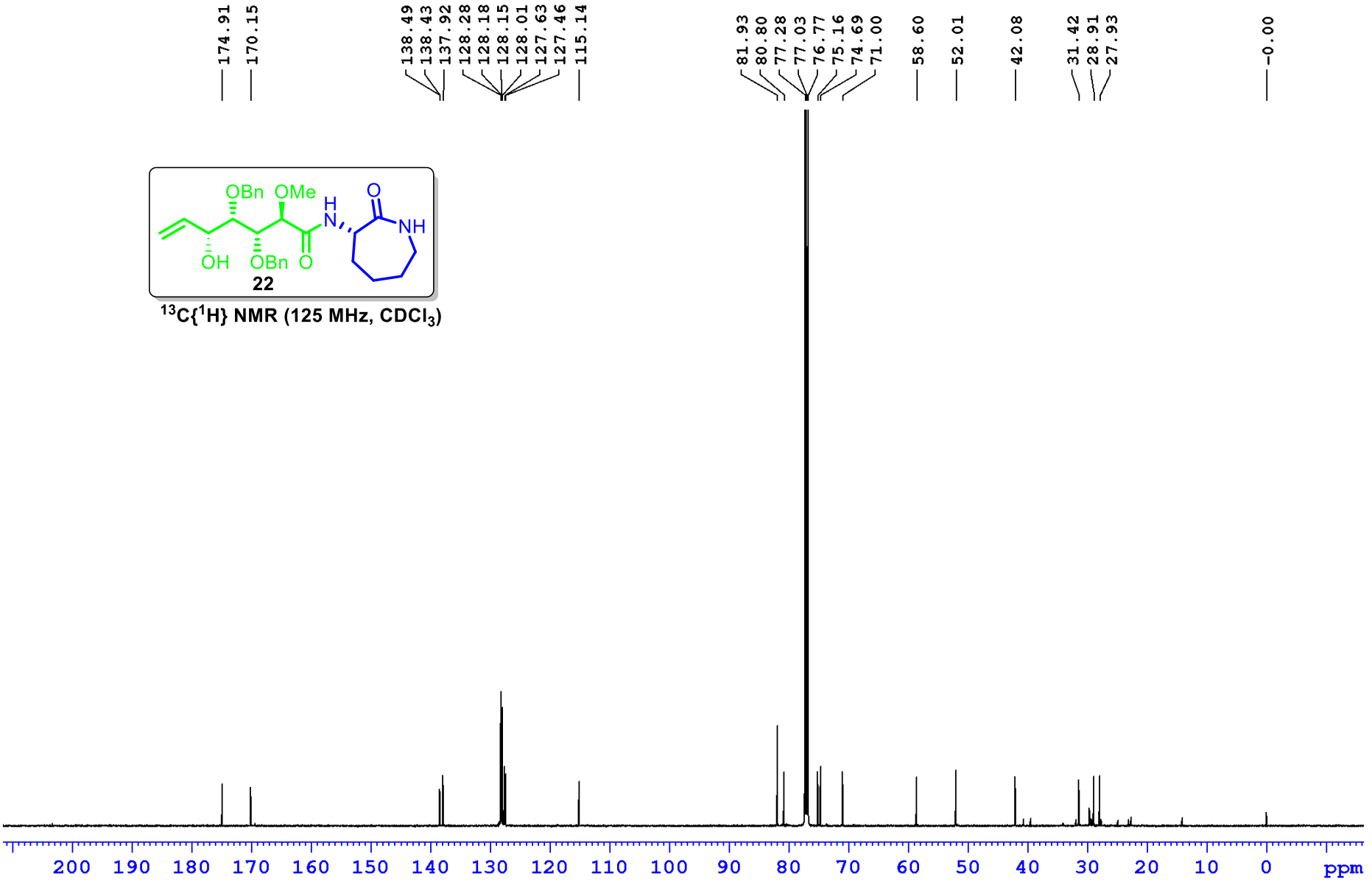
^{135}**DEPT NMR (125 MHz, $CDCl_3$)**

132.38
128.60
128.49
128.29
128.00
127.95
127.92
118.67
80.31
77.30
76.83
75.76
73.65
73.50
60.05

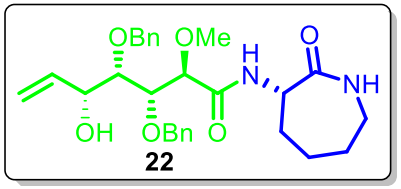





8.158 8.146 7.345 7.342 7.331 7.327 7.317 7.308 7.291 7.285 7.277 7.270 7.267 7.264 7.253 6.256 6.095 6.082 6.073 6.069 6.060 6.048 6.039 5.480 5.477 5.473 5.446 5.442 5.439 5.247 5.244 5.241 5.226 5.223 5.219 4.820 4.798 4.726 4.704 4.677 4.654 4.623 4.601 4.551 4.539 4.532 4.520 4.482 4.479 4.254 4.250 4.015 4.011 4.000 3.996 3.834 3.828 3.818 3.812 3.445 3.270 3.259 3.249 3.241 3.237 2.120 2.019 1.883 1.876 1.863 1.856 1.852 1.836 1.830 1.563 1.537 1.437
OBn OMe H N O NH OH OBn O
22
1H NMR (500 MHz, CDCl3)
2.145 2.120 2.048 2.041 2.033 2.026 2.019 2.012 2.000 1.986 1.974 1.883 1.876 1.863 1.856 1.852 1.836 1.830 1.590 1.585 1.563 1.537 1.516 1.510 1.458 1.453 1.437 1.431 1.416 1.409 1.402 1.394 1.380 1.373
2.2 2.0 1.8 1.6 1.4 ppm
1.07 1.24 2.23 1.26 1.22
10 9 8 7 6 5 4 3 2 1 0 ppm
0.93 11.27 0.95 1.00 1.01 1.03 1.01 2.19 1.06 1.07 1.03 0.99 1.04 1.10 3.02 2.10 1.07 1.24 2.23 1.26 1.22

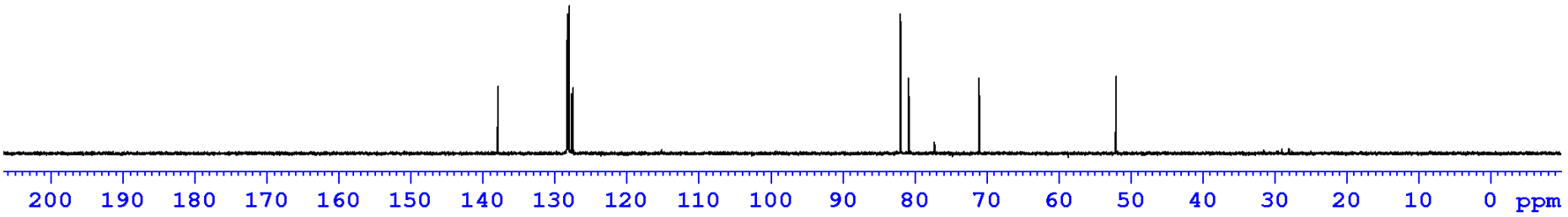


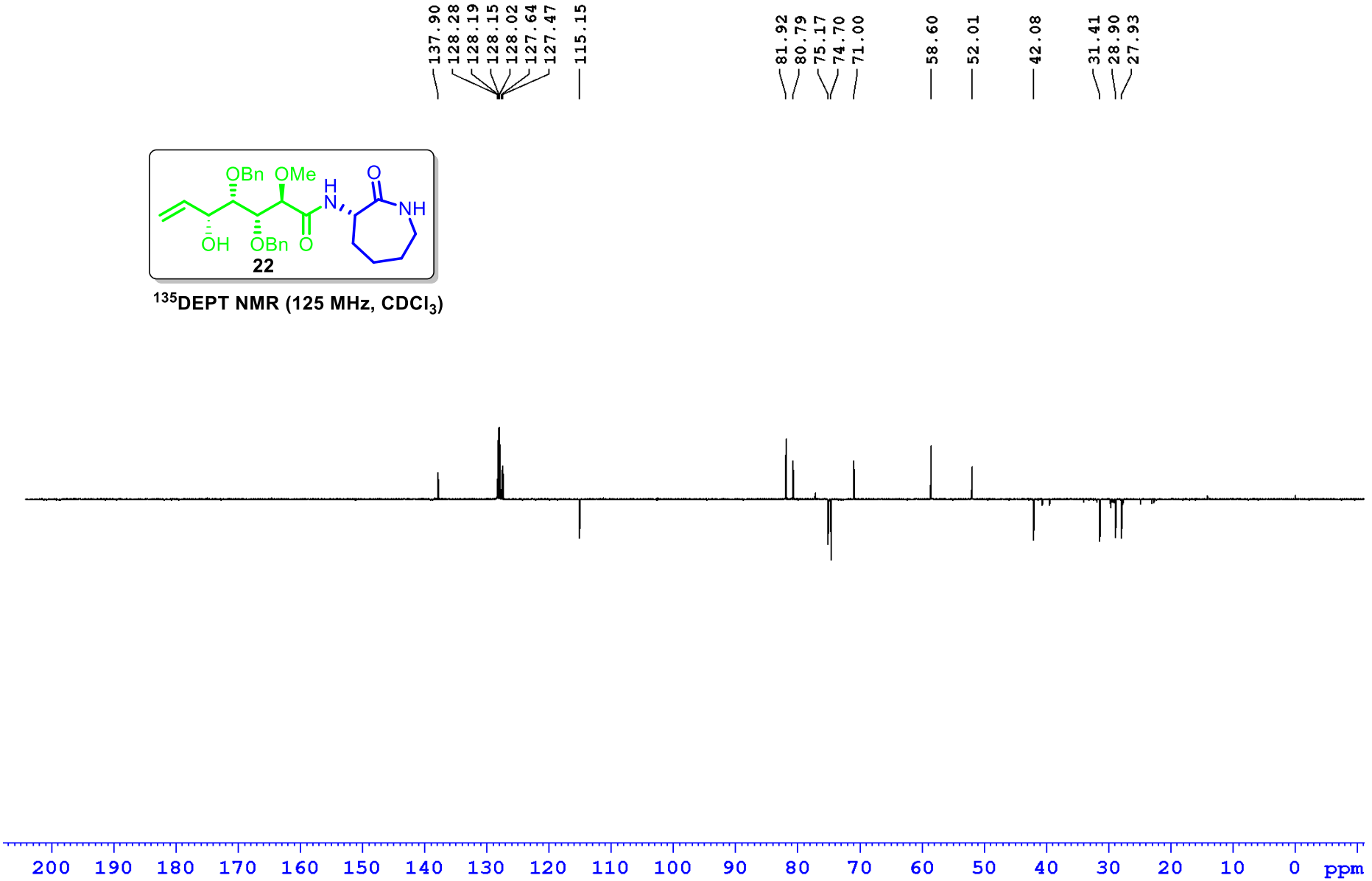
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



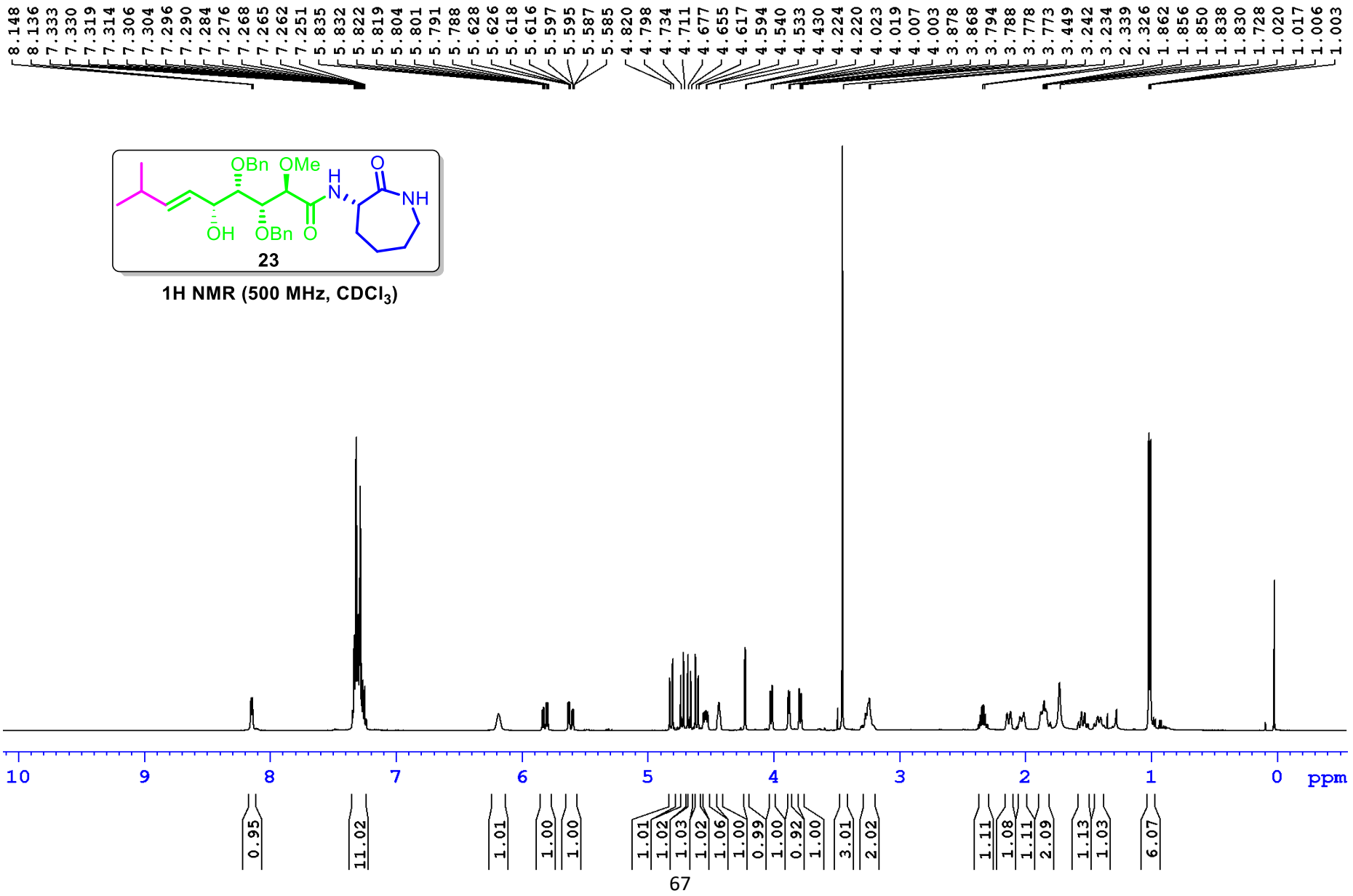
22

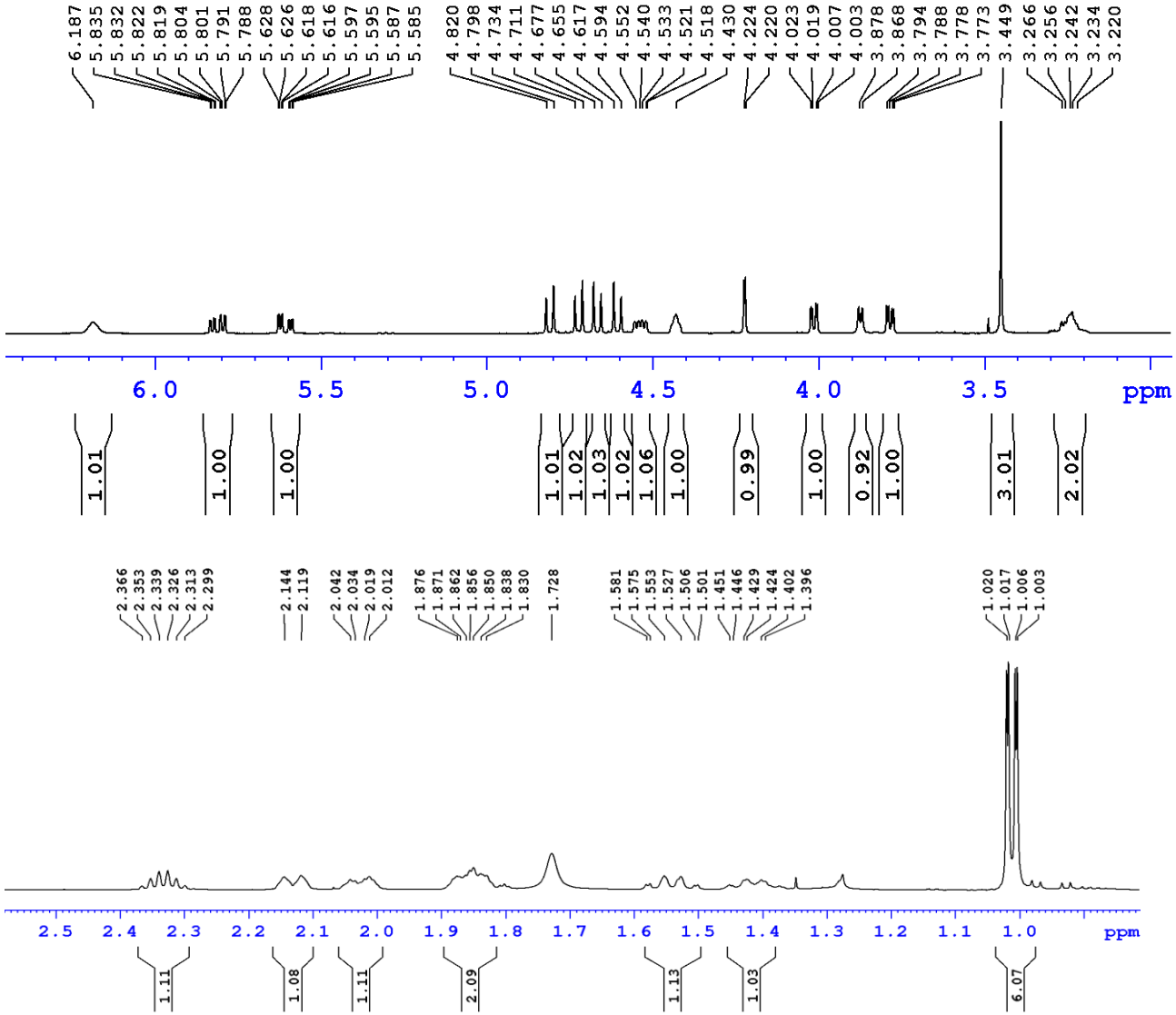
^{90}DEPT NMR (125 MHz, $CDCl_3$)

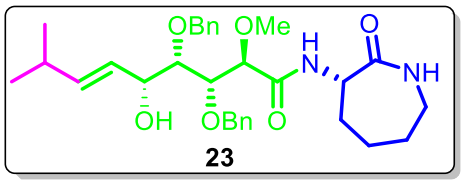




^{135}DEPT NMR (125 MHz, $CDCl_3$)

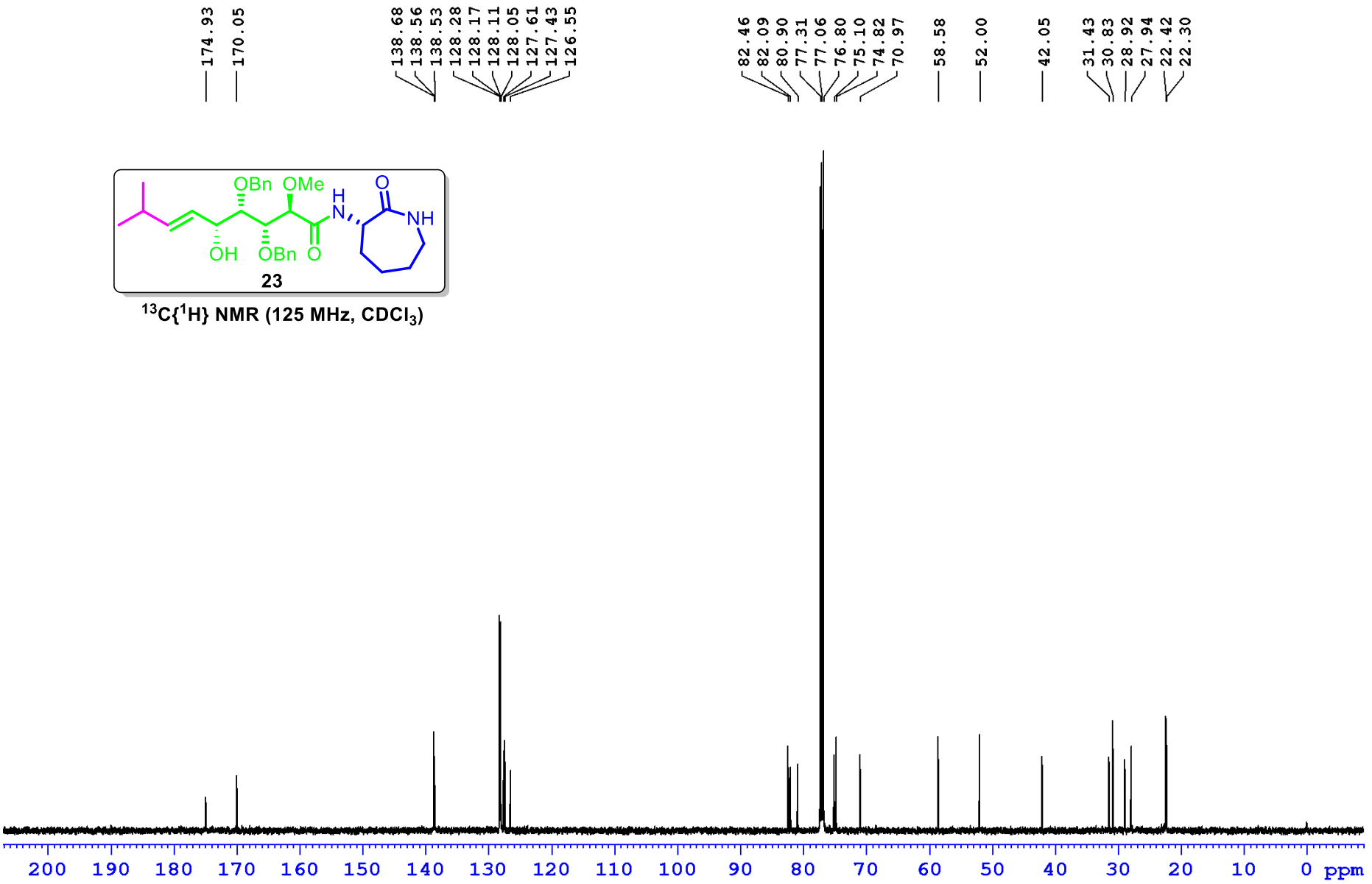

8.148 8.136 7.333 7.330 7.319 7.314 7.306 7.304 7.296 7.290 7.284 7.276 7.268 7.265 7.262 7.251 5.835 5.832 5.822 5.819 5.804 5.801 5.791 5.788 5.628 5.626 5.618 5.616 5.597 5.595 5.587 5.585 4.820 4.798 4.734 4.711 4.677 4.655 4.617 4.594 4.540 4.533 4.430 4.224 4.220 4.023 4.019 4.007 4.003 3.878 3.868 3.794 3.788 3.778 3.773 3.449 3.242 3.234 2.339 2.326 1.862 1.856 1.850 1.838 1.830 1.728 1.020 1.017 1.006 1.003
OBn OMe
H N
O
NH
OH OBn O
23
1H NMR (500 MHz, CDCl3)
10 9 8 7 6 5 4 3 2 1 0 ppm
0.95 11.02 1.01 1.00 1.00 1.01 1.02 1.03 1.02 1.06 1.00 0.99 1.00 0.92 1.00 3.01 2.02 1.11 1.08 1.11 2.09 1.13 1.03 6.07



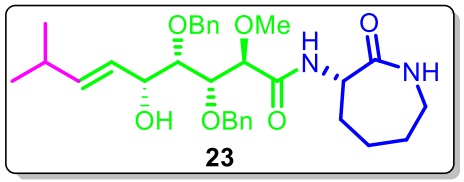


23

1H NMR expansion (500 MHz, $CDCl_3$)

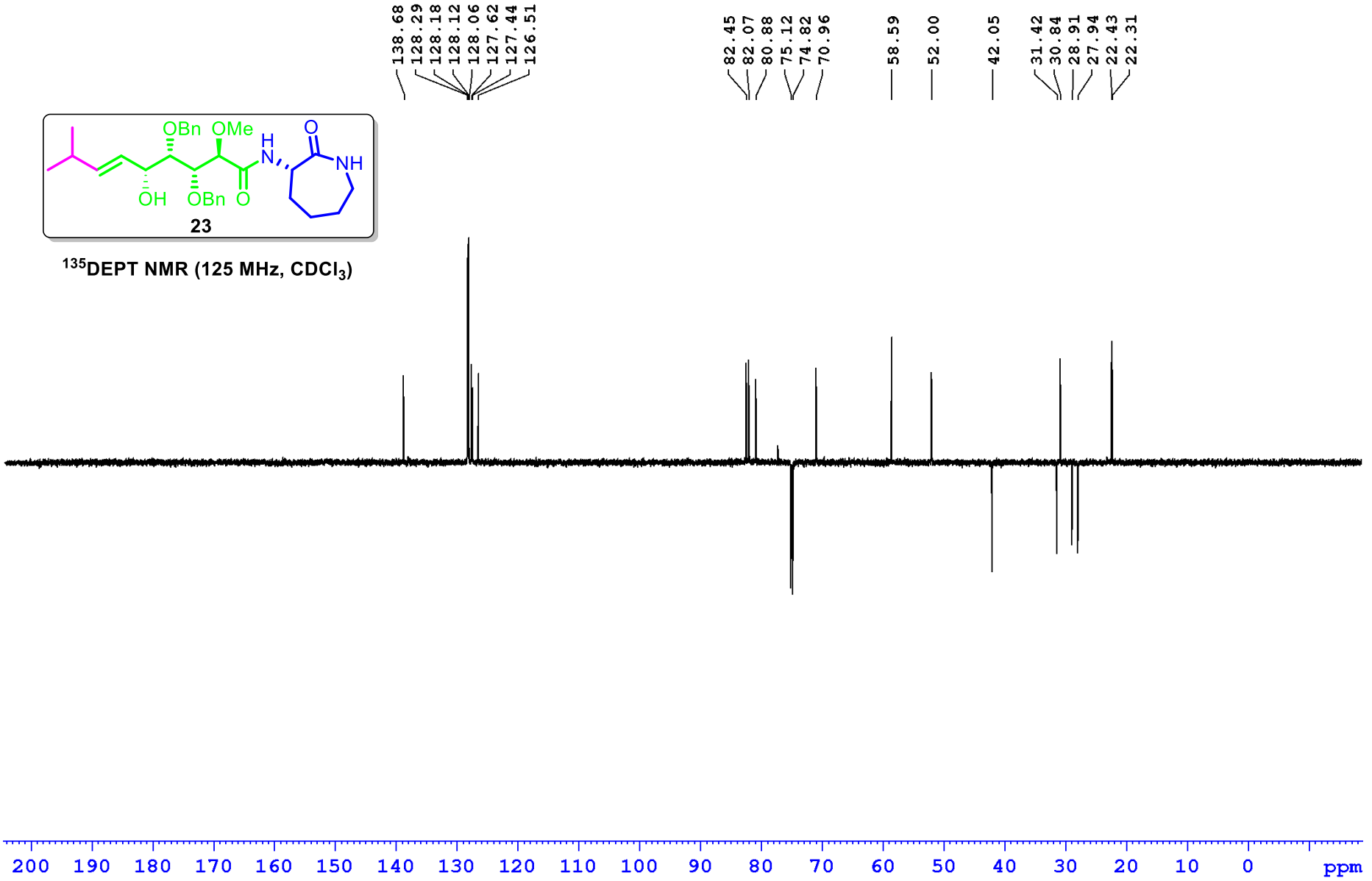


$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)

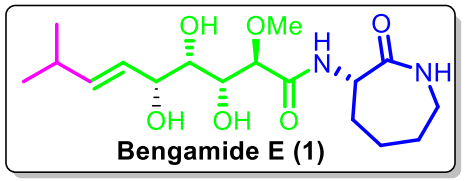


23

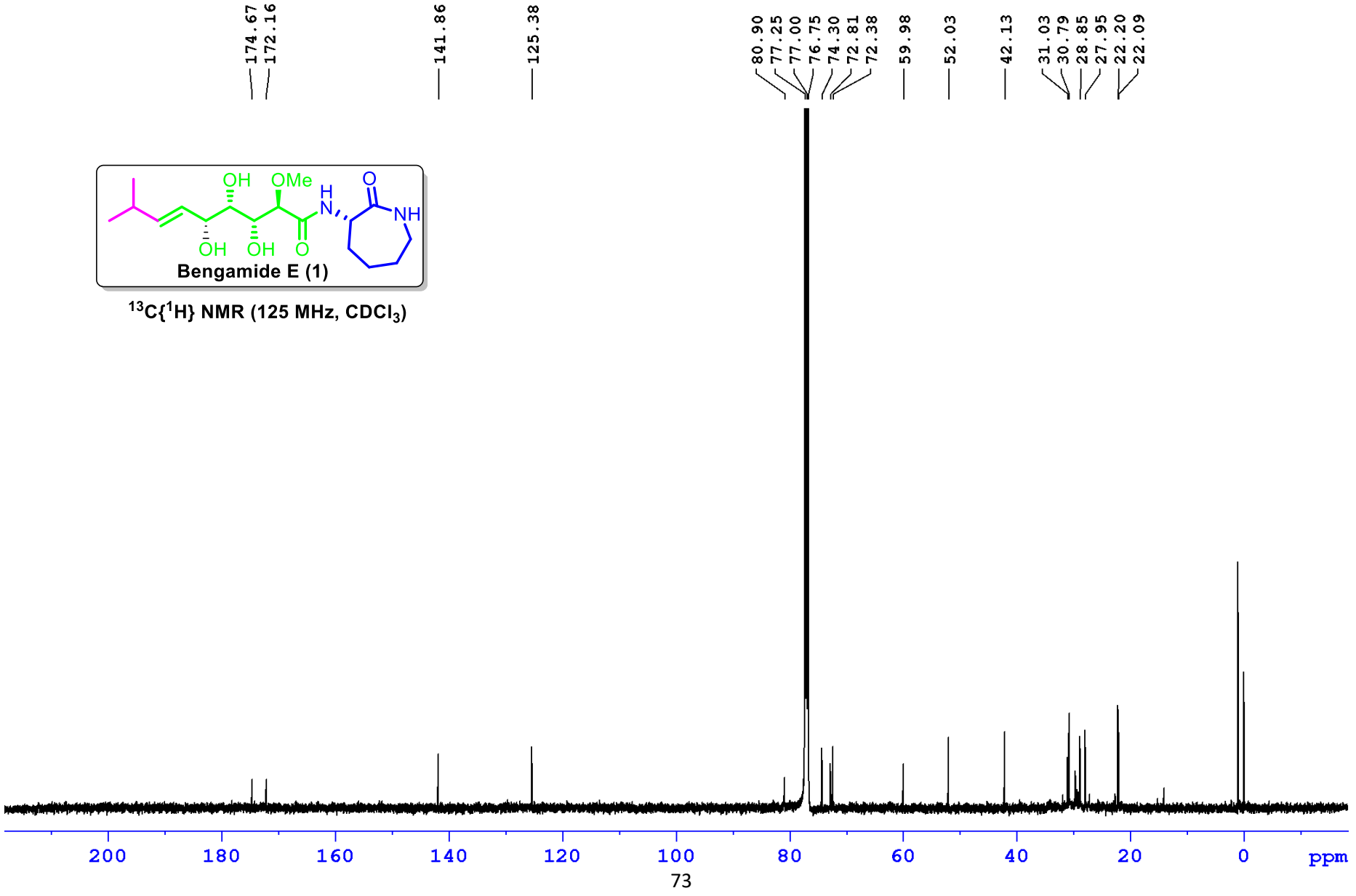
^{90}DEPT NMR (125 MHz, $CDCl_3$)



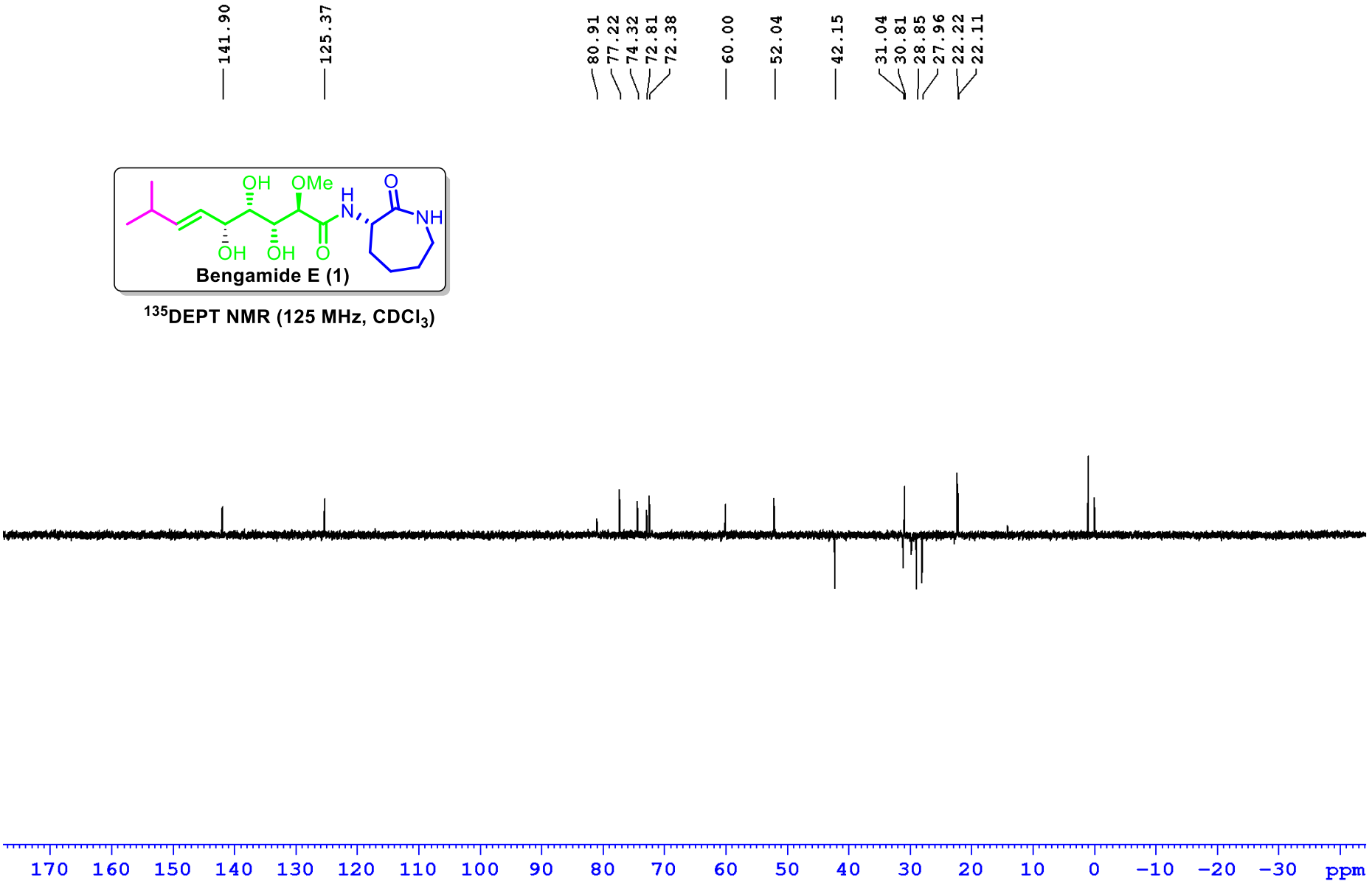
^{135}DEPT NMR (125 MHz, $CDCl_3$)



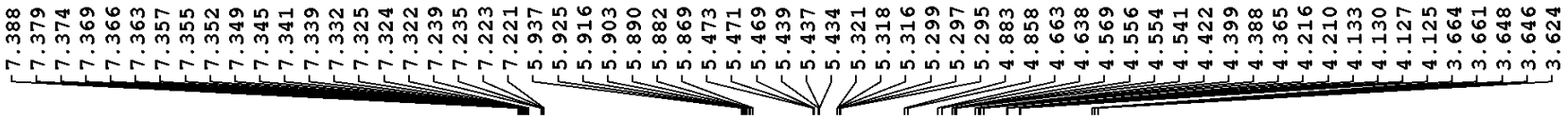
1H NMR (500 MHz, $CDCl_3$)

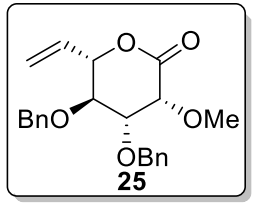


$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



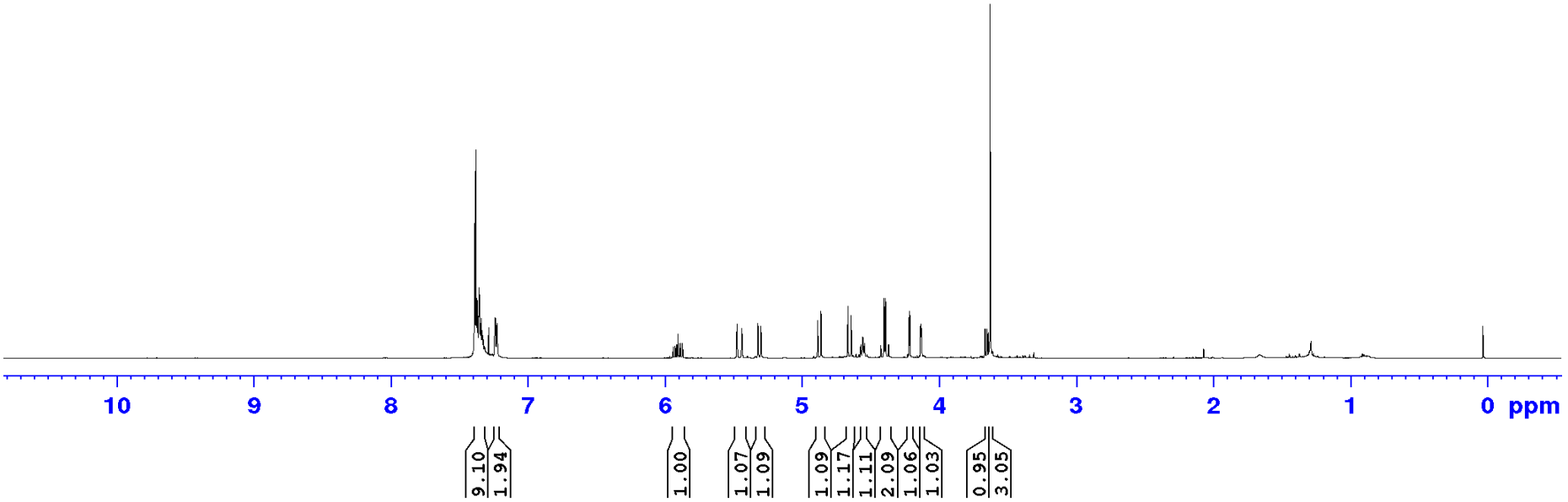
^{135}DEPT NMR (125 MHz, $CDCl_3$)

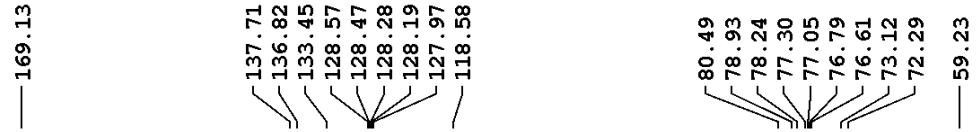


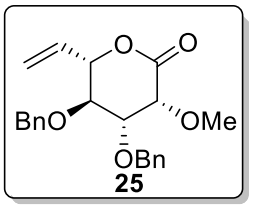


25

1H NMR (500 MHz, $CDCl_3$)

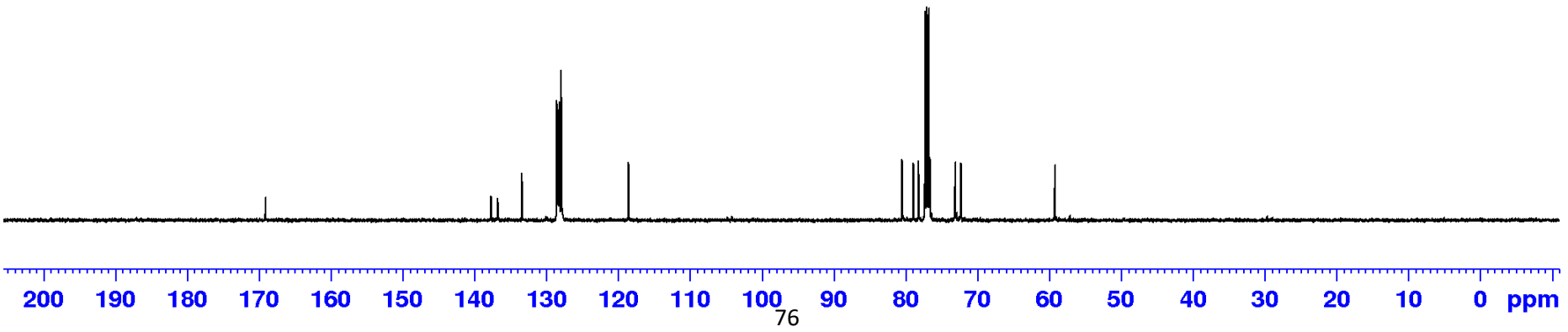


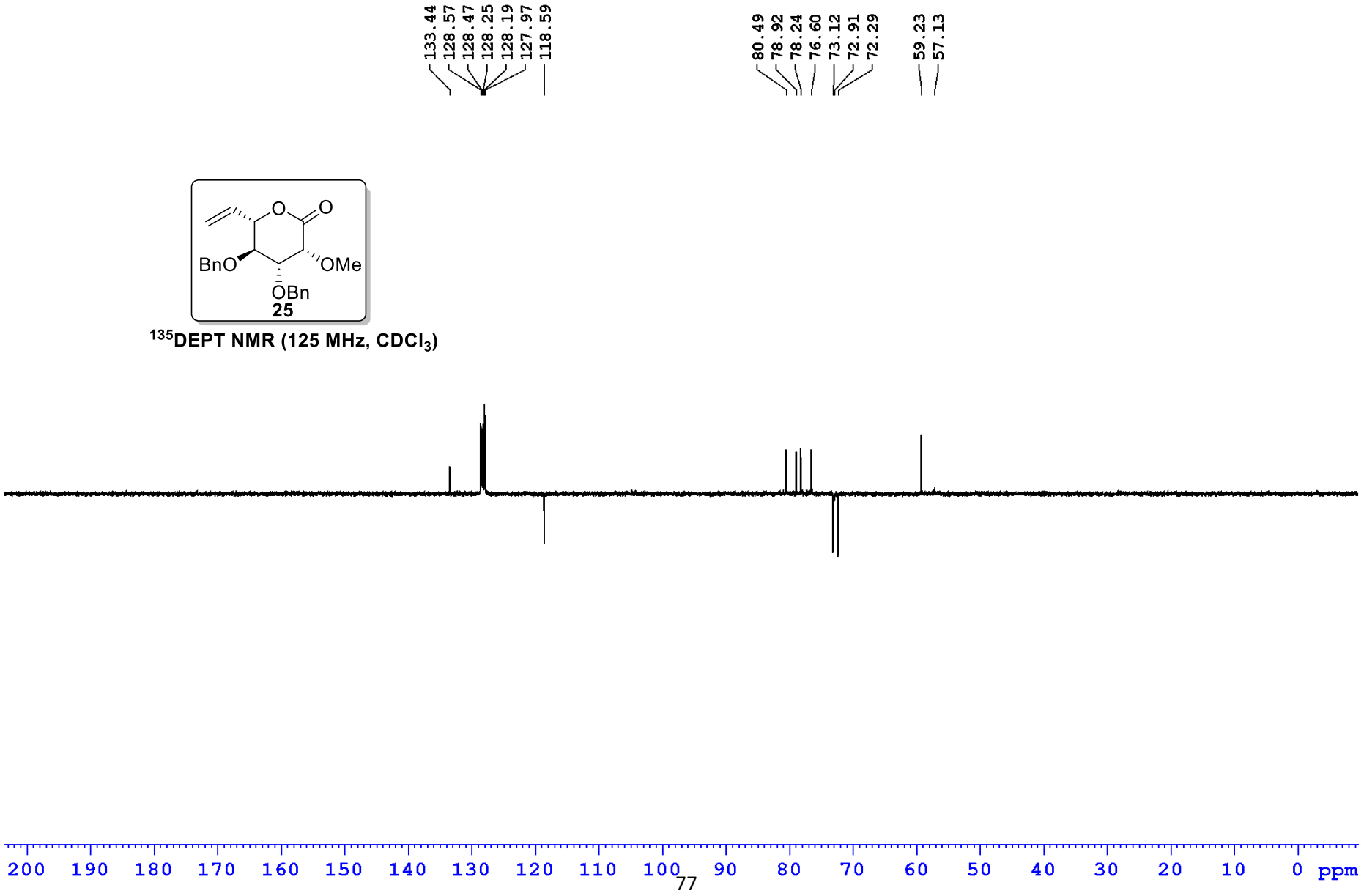




25

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)





^{135}DEPT NMR (125 MHz, $CDCl_3$)