Rapid Synthesis of Cyclic Oligomeric Depsipeptides with Positional, Stereochemical, and Macrocycle Size Distribution Control

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Spectral Data

Supplementary Experimental Results

*Details on MCO reaction profile from monomer **5***:

- The total isolated yield of macrocycles from the inaugural reaction (without salt additive) was 64% (18, 24, 30, and 36 ring atoms). The sizes of macrocycles reported in the main text are the only sizes that were isolated from the reaction (with or without salt additives). No other ring-sizes, such as 6- or 12- membered rings were detected by liquid chromatography/mass spectrometry (LCMS) analysis.

*Details on MCO reaction profile from monomer **13***:

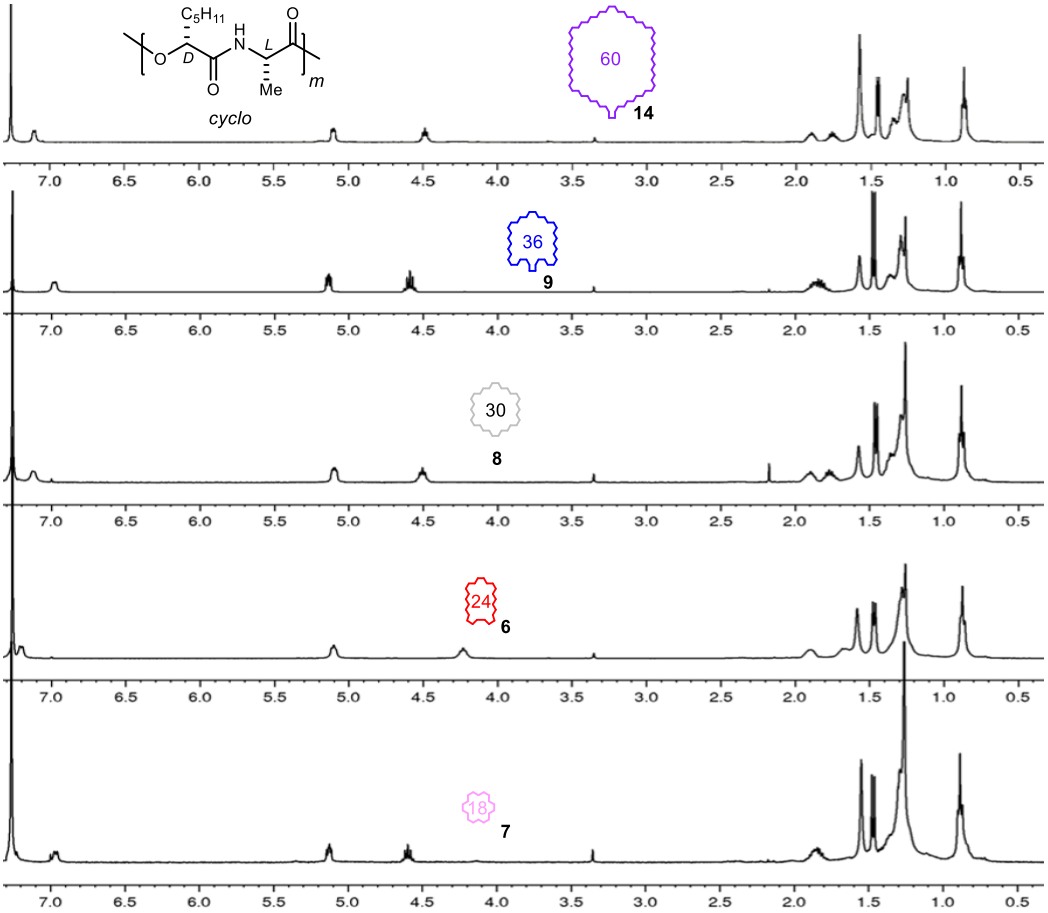
- The sizes of macrocycles reported in the main text are the only sizes that were isolated from the reaction (24, 36, and 60 ring atoms). Neither monocyclized (12-membered ring; $m = 2$) nor 48-membered rings ($m = 8$) were observed in conditions with or without salt additives.
- 12-membered ring formation without a Thorpe-Ingold-inducing functionality is known to be difficult, which may explain why this size was not observed.
- The 48-membered ring was not observed. The linear chain may reside in a conformation that is more favorable to couple in a linear fashion rather than cyclize. Linear acylated-DIAD by-products that correspond to a 48-membered chain have been observed in small amounts by LCMS.

*Further examination of salt effects in MCO with monomer **20***:

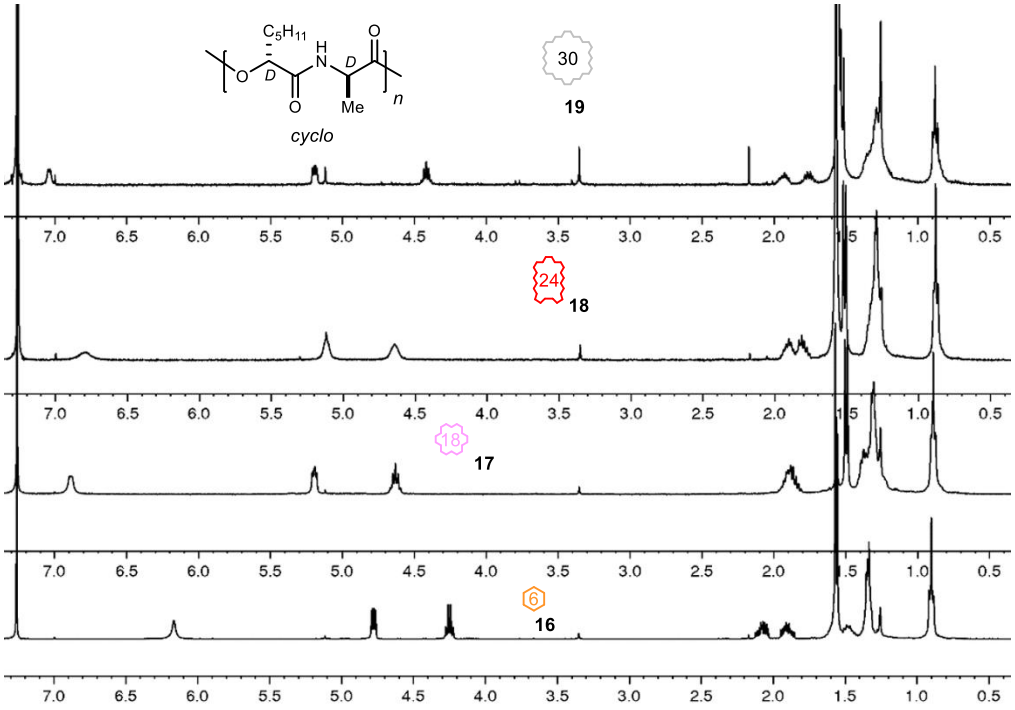
- Using 5 equiv of salt additive is key to achieving optimal yield in this MCO. Much less than 5 equiv did not have an effect, and much greater than 5 equiv seemed to inhibit the reaction.
- To test if these observations were due to a salt concentration effect, the reaction was run at twice the optimal concentration (10 mM) with 2.5 equiv salt additive. These conditions *did not* afford product even though they had the same overall salt concentration as optimal conditions (5 equiv salt at 5 mM, 31% yield).
- However, 5 equiv salt at twice the optimal concentration (10 mM) did afford product in 24% yield.

Supplementary Figures

Stacked NMR spectrum (400 MHz, $CDCl_3$) of D,L-Macrocycles ***6,7,8,9,14***



Stacked NMR spectrum (400 MHz, $CDCl_3$) of D,D-macrocycles ***16,17,18,19***



Experimental Section

Glassware was flame-dried under vacuum for all non-aqueous reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. Benzene and dichloromethane (CH_2Cl_2) were dried by passage through a column of activated alumina as described by Grubbs.[1] Blay[2,3] and IndaBOX[4 5]ligands were prepared according to literature procedures. Bromonitromethane (90% technical grade) was used as received. NIS was recrystallized from dioxane/CCl_4. Flash column chromatography were performed using Sorbent Technologies 230-400 mesh silica gel with solvent systems indicated. Analytical thin layer column chromatography was performed using Sorbent Technologies 250 µm glass-backed UV254 silica gel plates, and were visualized by fluorescence upon 250 nm radiation and/or the by use of ceric ammonium molybdate (CAM), phosphomolybdic acid (PMA), or potassium permanganate ($KMnO_4$). Solvent removal was effected by rotary evaporation under vacuum (~ 25-40 mm Hg). All extracts were dried with $MgSO_4$ unless otherwise noted.

Preparative HPLC was performed on an Agilent 1260 system (column: Zorbax Eclipse XDB-C18; 21.2 mm x 150 mm, 5 µm, flow rate 8 mL/min) with 210 nm monitoring wavelength and acetonitrile/water (+0.1% TFA) gradient as indicated.

Nuclear magnetic resonance spectra (NMR) were acquired on a Bruker AV-400 (400 MHz), Bruker DRX-500 (500 MHz), or Bruker AV II-600 (600 MHz) instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 ($CDCl_3$), and δ 2.50 and δ 39.5 (DMSO-d_6), unless otherwise specified. Ratios of diastereomers and isomeric products were measured directly from integration of ^{1}H NMR absorptions of protons common to the components. Reported chemical shifts and integrations for amides resulting from Umpolung Amide Synthesis (UmAS) correspond to only the major diastereomer. Mass spectra were recorded on a Thermo Electron Corporation MAT 95XP-Trap mass spectrometer by use of the ionization method noted by the Indiana University Mass Spectrometry Facility. IR spectra were recorded on a Nicolet Avatar 360 spectrophotometer and are reported in wavenumbers (cm^{-1}) as neat films on a NaCl plate (transmission). Melting points were measured on a Meltemp melting point apparatus and are not corrected. Optical rotations were measured on a Perkin Elmer-341 polarimeter.

General Procedures

Umpolung Amide Synthesis (UmAS): A round-bottom flask was charged with bromonitroalkane (1 equiv, 0.2 M), amine (1.2 equiv), 2-Me-THF, and H_2O (5 equiv). The mixture was cooled to 0 °C and treated with NIS (1 equiv) followed by K_2CO_3 (2 equiv) and an O_2 balloon. The heterogeneous solution was stirred for 2 days at 0 °C, and then treated at 0 °C with 1 N HCl and poured into CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with satd aq $Na_2S_2O_3$, dried, and concentrated. The crude residue was subjected to flash column chromatography to afford the amide.

One-Pot UmAS: A round-bottom flask was charged with nitroalkane (1 equiv, 0.2 M), amine (2.0 equiv), DME, and H_2O (5 equiv). The mixture was then treated with DBTCE (1.2 equiv) followed by NaI (0.1 equiv), K_2CO_3 (2 equiv) and an O_2 balloon. The heterogeneous solution was vigorously stirred for 1-2 days at ambient temperature, and then treated at 0 °C with 1 N HCl and poured into CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with satd aq $Na_2S_2O_3$, dried, and concentrated. The crude residue was subjected to flash column chromatography to afford the amide.

Global Deprotection: A flame-dried round-bottomed flask under inert atmosphere was charged with $AlCl_3$ (10 equiv), and toluene (0.05 M relative to amide) at 0 °C. Then MOM and benzyl-protected depsipeptide (1.0 equiv) were dissolved in a small amount of toluene and added dropwise to the stirring solution. The reaction was allowed to slowly warm to ambient temperature and stir until starting material was no longer present by TLC. The mixture was then cooled to 0 °C and quenched with satd aq Rochelle's salt. The heterogeneous solution was stirred at ambient temperature until two distinct layers were apparent, and then diluted with EtOAc and water. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried, and concentrated to a residue that was subjected to preparative HPLC. Preparative HPLC was performed on an Agilent 1260 system (column: Zorbax Eclipse XDB-C18; 21.2 mm x 150 mm, 5 µm, flow rate 8 mL/min) with 210 nm monitoring wavelength and gradient of 5 to 95% acetonitrile in water (+0.1% TFA) over 30 min. The desired fractions were then diluted with EtOAc, washed with water (three times), followed by brine, and then dried and concentrated.[6]

Didepsipeptide MCO: A flame-dried round-bottomed flask under inert atmosphere was charged with a salt additive (2.5 equiv), *seco*-acid (1 equiv), PPh_3 (6 equiv), and benzene to bring the final concentration of *seco*-acid to 0.02 M. DIAD (5.0 equiv) was then added to the stirred solution in 15 aliquots over 120 minutes. The reaction was allowed to stir at ambient temperature for 24 h, and then concentrated to afford a residue that was subjected to the MCO Purification Protocol.

Methoxymethylene ether (MOM) Deprotection: A flame-dried round-bottom flask under argon atmosphere was charged with MOM-protected amide (1 equiv, 0.05 M) in CH_2Cl_2. Thiophenol (5 equiv) was added to the solution, followed by $Et_2O{\bullet}BF_3$ (5 equiv). The reaction was allowed to stir for 1 h at room temperature and then poured into CH_2Cl_2. The organic solution was washed twice with satd aq $NaHCO_3$, followed by brine, and then dried and concentrated. The residue was subjected to flash column chromatography to furnish the alcohol.

Benzyl Deprotection: A round-bottom flask was charged with benzyl ester (1 equiv, 0.1 M) in MeOH. 10% Pd/C (1 mass equiv) was added to the stirring solution and a light vacuum (60 Torr) was applied, followed by backflush

using a hydrogen balloon. The reaction was allowed to stir for 1 h and then filtered through Celite and concentrated to furnish the carboxylic acid.

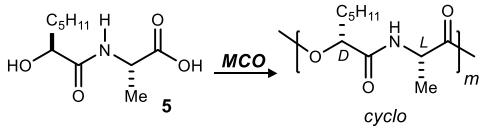
Mitsunobu: A flame-dried round-bottom flask under inert atmosphere was charged with PPh_3 (2 equiv), DIAD (2 equiv), and benzene, and was stirred at ambient temperature for 30 m. The alcohol (1 equiv, 0.05 M) was added to the solution, followed by the carboxylic acid (1.1 equiv). The reaction was stirred for 24 h, and then concentrated to afford a residue that was subjected to flash column chromatography.

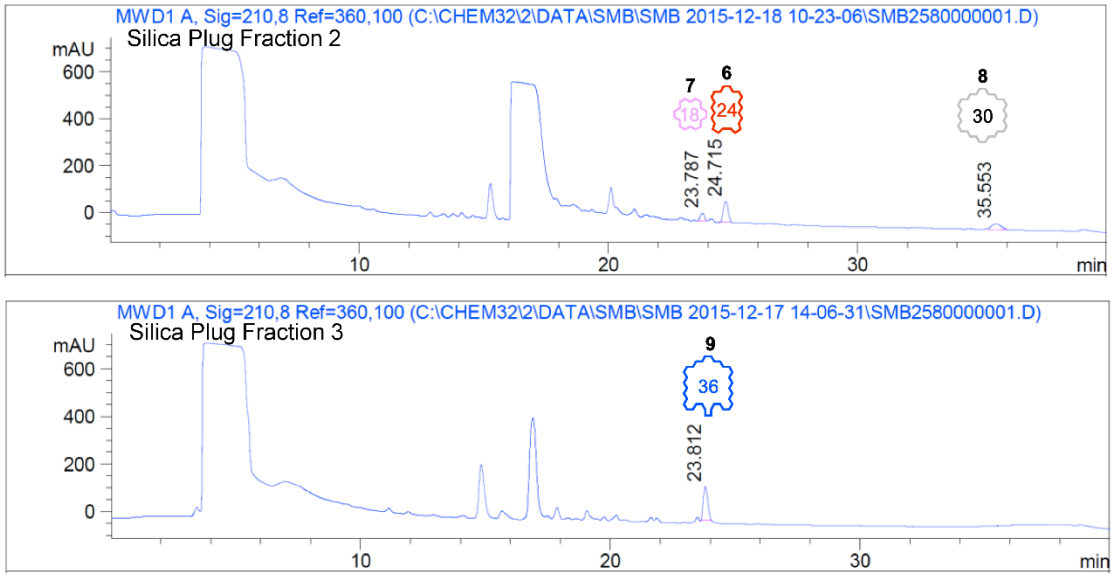
Tetradepsipeptide MCO: A flame-dried round-bottomed flask under inert atmosphere was charged with a salt additive (5 equiv), *seco*-acid (1 equiv in CH_2Cl_2, 0.38 M), PPh_3 (3 equiv), and benzene to bring the final concentration of *seco*-acid to 0.005 M. DIAD (2.5 equiv) was then added to the stirred solution in 5 aliquots over 40 minutes. The reaction was allowed to stir at ambient temperature for 24 h, and then concentrated to afford a residue that was subjected to the MCO purification protocol.

General MCO Purification Information

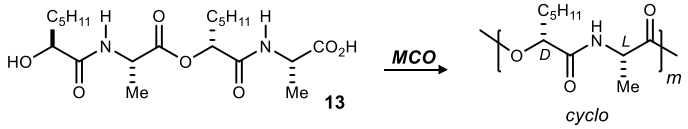
MCO Purification Protocol: The crude residue was filtered through a plug (1.9 cm x 8.2 cm) of silica gel to remove excess Mitsunobu reagents, and to roughly separate macrocyclic products into two fractions prior to separation using preparatory HPLC. [Some macrocycles exhibited similar R_f by prep-HPLC, but very different R_f when using normal phase silica gel; see figures below.] A stepwise MeOH/DCM gradient allowed the crude mixture to be separated into three fractions (Fraction 1: 0.5-1% MeOH/DCM; Fraction 2: 2-3% MeOH/DCM; Fraction 3: 20% MeOH DCM) prior to prep HPLC purification. The contents of Fraction 1 (Mitsunobu reagent byproducts only) were discarded, and Fractions 2 & 3 were dissolved (separately) in DMSO and subjected to prep HPLC purification. Preparative HPLC was performed on an Agilent 1260 system (column: Zorbax Eclipse XDB-C18; 21.2 mm x 150 mm, 5 µm, flow rate 8 mL/min) with 210 nm monitoring wavelength and gradient of 5 to 95% acetonitrile in water (+0.1% TFA) over 40 min. Fractions containing macrocyclic products were then diluted with EtOAc and washed twice with satd aq $NaHCO_3$, followed by brine, and then dried and concentrated.[6]

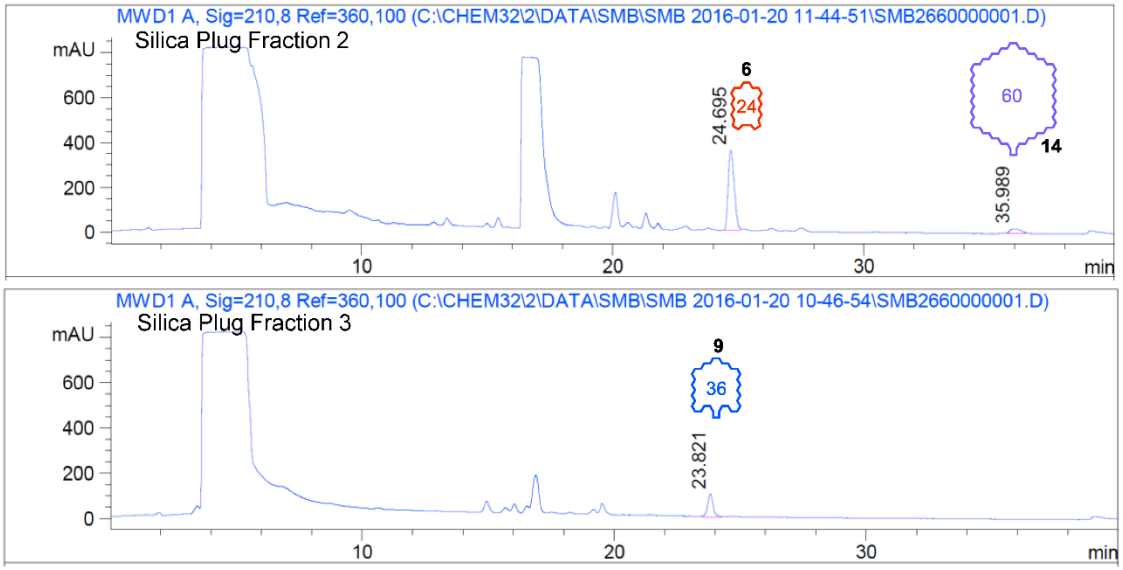
*Sample prep HPLC traces from MCO of didepsipeptide **5**:*



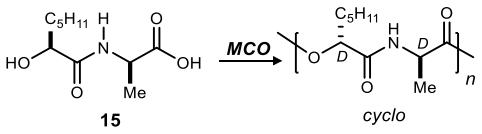


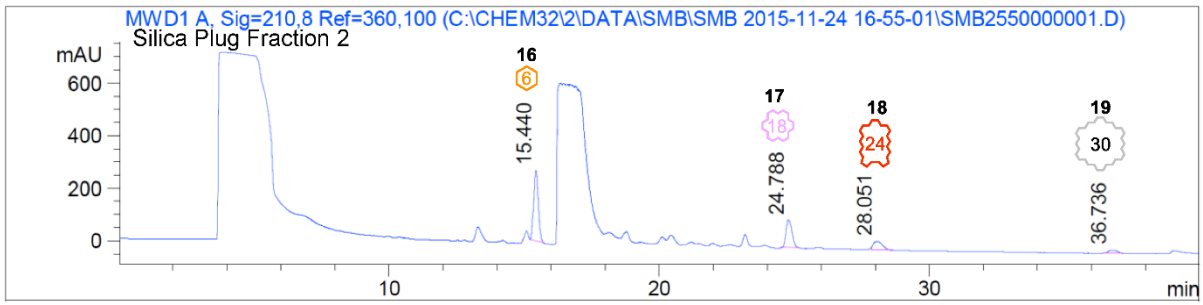
*Sample prep HPLC traces from MCO of tetradepsipeptide **13**:*



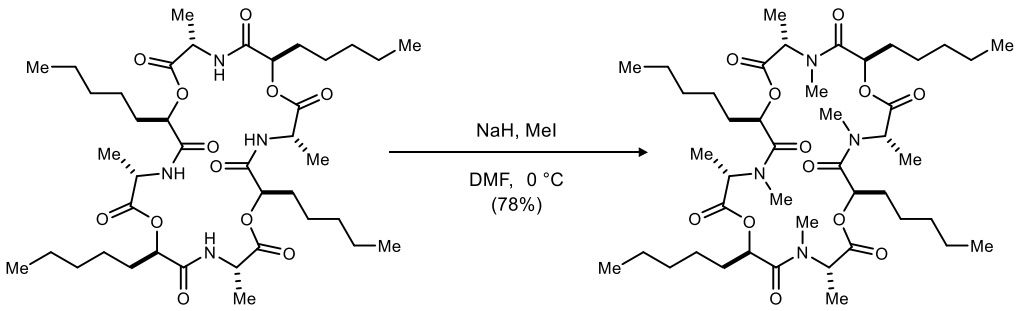


*Sample prep HPLC traces from MCO of didepsipeptide **15**:*





Experimental and Characterization Data for Reported Compounds



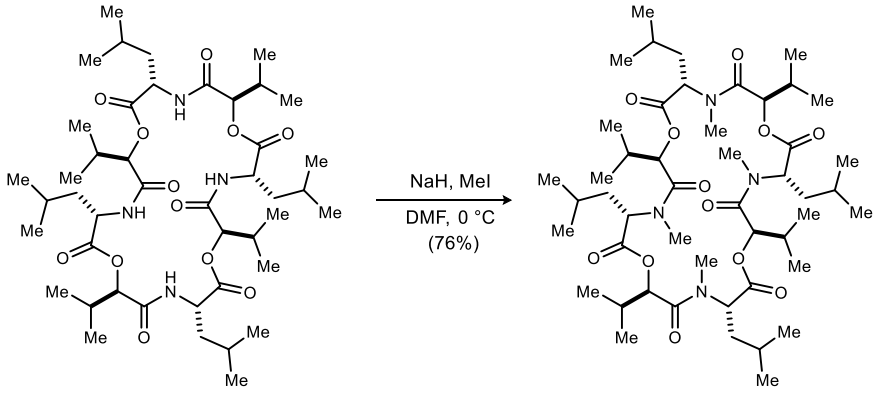
(–)-Verticilide (*nat*-1). A flame-dried round-bottom flask was charged with *N*-H depsipeptide **6** (20.0 mg, 25.1 μmol) and dry DMF (500 μL) at 0 °C. Methyl iodide (62.5 μL, 1.00 mmol) was then added to the reaction mixture, and NaH (6.0 mg, 251 μmol in DMF (250 μL)) was added slowly to the reaction mixture in 50 μL aliquots over 15 minutes. The reaction was allowed to stir at 0 °C for 25 m, and it was then quenched by the dropwise addition of satd aq NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with satd aq $NaHCO_3$, satd aq $Na_2S_2O_3$, water and brine, and then dried and concentrated to afford a residue that was subjected to flash column chromatography (SiO_2, 1-5% methanol in dichloromethane) to afford (-)-verticilide (16.7 mg, 78%) as a colorless oil. $[\alpha]_D^{20}$ -47 (*c* 0.21, MeOH)[7]; R_f = 0.21 (5% MeOH/DCM); IR (film) 2955, 2920, 2851, 1746, 1667, 1539, 1466, 1378, 1199, 1019 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{44}H_{76}N_4NaO_{12}$ $[M+Na]^+$ 875.5357, found 875.5341.

(+)-Verticilide (*ent*-1) was prepared following an identical procedure. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 25.2 m) afforded (+)-verticilide with spectroscopic data identical to its enantiomer, except $[\alpha]_D^{20}$ +48 (*c* 0.16, MeOH).

Comparison of prepared (-)-verticilide and literature values:[7]

^{1}H δ Literature	Mult, *J* values	^{1}H δ Synthesis	Mult, *J* values
0.88	m	0.82-0.89	br m
1.30	m	1.06-1.31	br m
1.31	m		
1.38	d, *J* = 7.2 Hz	1.38	d, *J* = 7.2 Hz
1.39	d, *J* = 7.4 Hz	1.39	d, *J* = 7.5 Hz
1.41	d, *J* = 7.4 Hz	1.41	d, *J* = 7.3 Hz
1.45	d, *J* = 7.3 Hz	1.45	d, *J* = 7.4 Hz
1.59	d, *J* = 7.3 Hz	1.59	d, *J* = 7.0 Hz
1.78	m	1.73-1.90	br m
2.89	s	2.89	s
2.91	s	2.91	s
2.96	s	2.96	s
3.01	s	3.01	s
3.18	s	3.18	s
4.56	q, *J* = 7.3 Hz	4.56	q, *J* = 7.3 Hz
5.11	dd, *J* = 10.6, 2.5 Hz	5.11	dd, *J* = 11.0, 2.4 Hz
5.30	q, *J* = 7.4 Hz	5.3	q, *J* = 7.3 Hz
5.32	dd, *J* = 10.1, 3.3 Hz	5.32	dd, *J* = 9.9, 3.3 Hz
5.36	dd, *J* = 9.0, 5.3 Hz	5.36	dd, *J* = 8.5, 5.0 Hz
5.40	q, *J* = 7.2 Hz	5.4	q, *J* = 7.2 Hz
5.42	m	5.42	m (overlapping)
5.45	dd, *J* = 8.4, 5.3 Hz	5.45	dd, *J* = 8.4, 5.4 Hz
5.53	q, *J* = 7.3 Hz	5.53	q, *J* = 7.3 Hz
5.54	q, *J* = 7.4 Hz	5.54	q, *J* = 7.5 Hz

^{13}C Literature values	^{13}C Synthesis values	Difference	^{13}C Literature values	^{13}C Synthesis values	Difference
13.88 (3C)	13.89	0.01	31.2	31.16	0.04
13.9	13.95	0.05	31.36 (2C)	31.32	0.04
13.93	14	0.07	31.4 (3C)	31.39	0.01
14	14.1	0.1	31.5	31.46	0.04
14.2	14.2	0	51.5	51.47	0.03
14.8	14.8	0	51.76	51.63	0.13
15	15	0	51.85	51.72	0.13
15.9	15.88	0.02	51.94	51.87	0.07
22.39 (3C)	22.39	0	54.4	54.4	0
22.42 (2C)	22.42	0	70.7	70.65	0.05
24.76 (2C)	24.74	0.02	70.8	70.72	0.08
24.82	24.82	0	71	70.91	0.09
24.83	24.96	0.13	71.3	71.22	0.08
25.1	25.07	0.03	71.6	71.5	0.1
29.4	29.45	0.05	169.2	169.2	0
30.66	30.65	0.01	169.3	169.26	0.04
30.73	30.71	0.02	169.8	169.79	0.01
30.92	30.83	0.09	169.9 (2C)	169.87	0.03
30.97	30.87	0.1	170	169.92	0.08
30.98	30.93	0.05	170.8 (2C)	170.71	0.09
31	30.97	0.03	171	171	0
31.1	31.09	0.01	171.2	171.3	0.1

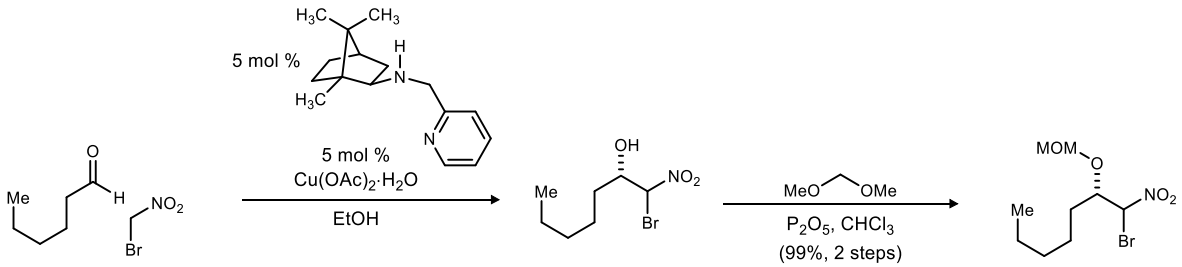


(–)-Bassianolide (*nat*-2). A flame-dried vial was charged with the *N*-H depsipeptide (7.0 mg, 8.2 μmol) and dry DMF (164 μL) at 0 °C. Methyl iodide (20.4 μL, 328 μmol) was added to the reaction mixture, and NaH (2.0 mg, 82 μmol in DMF (82 μL)) was then added dropwise. The reaction was allowed to stir at 0 °C for 25 m, and it was then quenched by the dropwise addition of satd aq NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with satd aq $NaHCO_3$, satd aq $Na_2S_2O_3$, water and brine, and then dried and concentrated to afford a residue that was subjected to preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 25.0 min) to afford (-)-bassianolide (5.7 mg, 76%) as an amorphous solid. $[\alpha]_D^{20}$ -60 (*c* 0.11, $CHCl_3$);[8] R_f = 0.23 (10% acetone/$CHCl_3$); IR (film) 2957, 2922, 2852, 1738, 1669, 1460, 1375, 1261, 1203, 1091, 1019 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{48}H_{84}N_4NaO_{12}$ $[M+Na]^+$ 931.5983, found 931.5953.

Comparison of prepared (-)-bassianolide and literature values: [9]

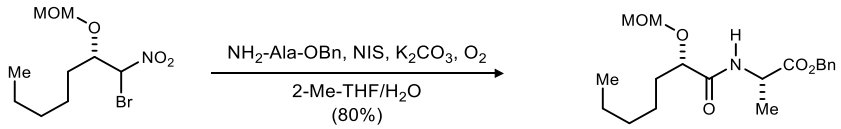
^{1}H δ Literature	Mult, *J* values	^{1}H δ Synthesis	Mult, *J* values
0.52	d, *J* = 7.0 Hz	0.55	d, *J* = 6.8 Hz
0.63	d, *J* = 7.0 Hz	0.67	d, *J* = 7.6 Hz
0.83-1.00	m	0.84-1.04	m
1.28	m	1.28-1.51	s of m
1.39	m		
1.51	m		
1.58	m	1.58	m
1.68-1.85	m	1.68-1.88	m
2.07	m	2.00-2.25	br m
2.15-2.22	m		
2.82	s	2.89	s
2.85	s	3.01	s
2.98	s	3.04	s
3.01	s	3.1	s
3.22	s	3.25	s
4.39	dd, *J* = 11.6, 4.0 Hz	4.43	dd, *J* = 10.6, 4.4 Hz
4.96	d, *J* = 2.3 Hz	4.99	d, *J* = 2.8 Hz
5.15	d, *J* = 7.7 Hz	5.16	br m
5.25	d, *J* = 6.9 Hz	5.28	d, *J* = 6.8 Hz
5.41	d, *J* = 7.9 Hz	5.45	d, *J* = 8.0 Hz
5.41	dd, J = 12.1, 4.2 Hz	5.45	dd, J = 11.8, 4.3 Hz
5.48	d, *J* = 2.2 Hz	5.5	d, *J* = 2.0 Hz
5.59	dd, J = 12.2, 4.6 Hz	5.62	dd, J = 12.3, 4.4 Hz
5.62	dd, *J* = 12.2, 4.3 Hz	5.65	dd, *J* = 12.3, 4.2 Hz

^{13}C Literature values	^{13}C Synthesis values	Difference	^{13}C Literature values	^{13}C Synthesis values	Difference
14.7	14.7	0	30.5	30.5	0
15.7	15.7	0	30.7	30.8	0.1
17.8	17.9	0.1	30.9	30.9	0
18.1	18	0.1	31	31.2	0.2
18.2	18.2	0	31.6	31.6	0
18.4	18.4	0	36.7	36.74	0.04
18.5	18.44	0.06	36.7	36.78	0.08
18.6	18.6	0	37.6	37.6	0
18.7	18.7	0	37.9	37.9	0
20.2	20.1	0.1	38.5	38.5	0
20.6	20.6	0	53.3	53.2	0.1
20.8	20.7	0.1	54.2	54.2	0
20.8	20.8	0	54.3	54.23	0.07
21	21	0	57.5	57.5	0
21.3	21.2	0.1	74.2	74.2	0
23.4	23.3	0.1	74.3	74.3	0
23.5	23.4	0.1	75.2	75.2	0
23.5	23.5	0	76.8	76.8	0
23.6	23.6	0	168.7	168.6	0.1
23.7	23.7	0	169.1	169.1	0
24.7	24.7	0	169.4	169.4	0
24.9	24.8	0.1	170.2	170.2	0
24.9	24.9	0	170.3	170.24	0.06
25.2	25.2	0	170.5	170.5	0
25.4	25.4	0	170.8	170.8	0
28.2	28.2	0	171	171	0
29.6	29.55	0.05	171.4	171.3	0.1
29.7	29.58	0.12	171.5	171.5	0
30.2	30.2	0			

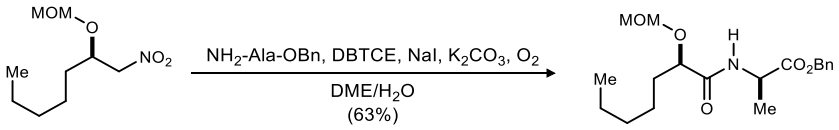


(2*S*)-1-Bromo-2-(methoxymethoxy)-1-nitroheptane (3). Following the Blay[3] enantioselective Henry procedure, Blay ligand (79.5 mg, 326 µmol) and $Cu(OAc)_2$•H_2O (65.0 mg, 326 µmol) stirred at ambient temperature in EtOH (26 mL) for 1 h. The royal blue solution was then cooled to -20 °C and hexanal (800 µL, 6.51 mmol) was added and allowed to stir for 10 m before bromonitromethane (4.54 mL, 65.1 mmol) addition. After stirring for 5 days at -20 °C, the reaction was quenched dropwise at -20 °C with pre-chilled 1 N HCl and the aqueous layer was extracted with CH_2Cl_2. Following drying and concentration under reduced pressure, the crude alcohol was dissolved in $CHCl_3$ (33 mL), treated with P_2O_5 (9.24 g, 65.1 mmol) and dimethoxymethane (11.5 mL, 76.1 mmol), and stirred at ambient temperature overnight. The reaction was cooled to 0 °C, quenched slowly with satd aq $NaHCO_3$, and then poured into CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The organic layers were dried and concentrated to an oil that was subjected to flash column chromatography (SiO_2, 0.5-5% diethyl ether in hexanes) to afford the title compound in 2:1 d.r. as a pale yellow oil (1.84 g, 99%, 2 steps).

The diastereomers were determined to be 84% ee by chiral HPLC analysis (Chiralcel OZ-H, 2% ^{i}PrOH /hexanes, 0.4 mL/min, $t_r(d_1e_1$, minor) = 11.3 min, $t_r(d_1e_2$, major) = 12.3 min, $t_r(d_2e_1$, minor) = 13.2 min, $t_r(d_2e_2$, major) = 13.8 min). R_f = 0.52 (10% EtOAc/hexanes); IR (film) 2956, 2929, 2863, 1575, 1462, 1328, 1156, 1104, 1010, 923 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.12 (d, *J* = 3.4 Hz, 1H), 5.92 (d, *J* = 8.2 Hz, 1H), 4.70 (d, *J* = 7.1 Hz, 1H), 4.67 (d, *J* = 7.1 Hz, 1H), 4.65 (d, *J* = 7.0 Hz, 1H), 4.63 (d, *J* = 7.0 Hz, 1H), 4.25 (ddd, *J* = 8.2, 5.6, 4.0 Hz, 1H), 4.16 (ddd, *J* = 7.6, 5.4, 3.4 Hz, 1H), 3.39 (s, 3H), 3.36 (s, 3H), 1.82-1.66 (series of m, 4H), 1.48-1.26 (series of m, 12H), 0.91-0.88 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 97.3, 97.0, 84.0, 80.8, 79.3, 79.2, 56.4 (2C), 31.6, 31.43, 31.39, 30.2, 24.8, 23.1, 22.4 (2C), 13.92, 13.91; HRMS (CI): Exact mass calcd for $C_9H_{17}BrNO_4$ $[M-H]^+$ 282.0335, found 282.0331.

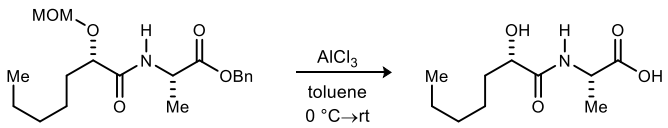


Benzyl ((*S*)-2-(methoxymethoxy)heptanoyl)-*L*-alaninate (4). Following the UmAS general procedure, bromonitroalkane (1400 mg, 4.927 mmol) and amine (1060 mg, 5.912 mmol) afforded a mahogany colored oil. The residue was subjected to flash column chromatography (SiO_2, 10-20% ethyl acetate in hexanes) to afford the major diastereomer as a waxy yellow solid (1380 mg, 80%). Mp = 44-47 °C; $[\alpha]_D^{20}$ -71 (*c* 0.13, $CHCl_3$); R_f = 0.41 (30% EtOAc/hexanes); IR (film) 3263, 2953, 1741, 1652, 1533, 1458, 1220, 1156, 1126, 1099, 1067, 1018, 753, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (m, 5H), 7.08 (br d, *J* = 7.6 Hz, 1H), 5.20 (d, *J* = 12.2 Hz, 1H), 5.15 (d, *J* = 12.2 Hz, 1H), 4.69 (dq, *J* = 7.3, 7.3 Hz, 1H), 4.67 (d, *J* = 6.7 Hz, 1H), 4.65 (d, *J* = 6.7 Hz, 1H), 4.07 (dd, *J* = 6.2, 4.9 Hz, 1H), 3.38 (s, 3H), 1.80-1.70 (m, 2H), 1.43 (d, *J* = 7.2 Hz, 3H), 1.41-1.26 (br m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.7, 172.1, 135.3, 128.6, 128.5, 128.2, 96.1, 77.4, 67.2, 56.2, 47.5, 32.8, 31.6, 24.3, 22.5, 18.6, 14.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{29}NNaO_5$ $[M+Na]^+$ 374.1943, found 374.1936.

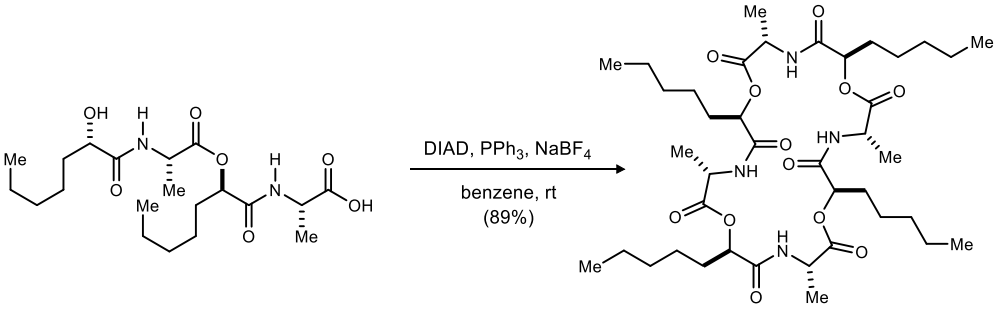


Benzyl ((*R*)-2-(methoxymethoxy)heptanoyl)-*D*-alaninate (*ent*-4). Following the One-Pot UmAS general procedure, nitroalkane (940 mg, 4.58 mmol) and amine (1.64 g, 9.16 mmol) afforded an orange oil. The residue was subjected to flash column chromatography (SiO_2, 10-30% ethyl acetate in hexanes) to afford the major

diastereomer as a waxy yellow solid (1.02 g, 63%), with spectroscopic data identical to its enantiomer, except $[\alpha]_D^{20}$ +70 (*c* 0.12, $CHCl_3$).

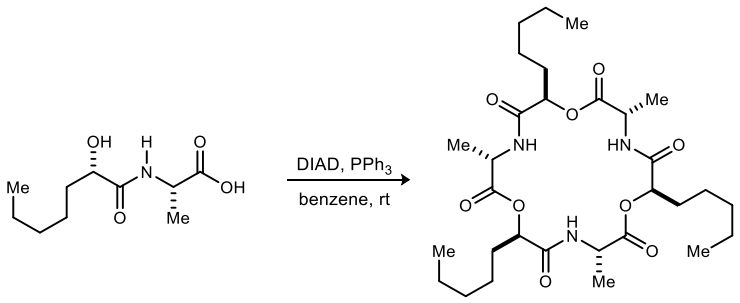


((*S*)-2-Hydroxyheptanoyl)-*L*-alanine (5). Following the Global Deprotection general procedure, the amide (215 mg, 699 μmol) stirred at ambient temperature for 25 m to afford a yellow residue. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 12.2 m) provided the *seco*-acid (114 mg, 75%) as a tan crystalline solid. Mp = 70-72 °C; $[\alpha]_D^{20}$ -14 (*c* 0.17, $CHCl_3$); R_f = 0.28 (20% MeOH/DCM); IR (film) 3386, 2925, 2855, 1729, 1649, 1535, 1459, 1378, 1300, 1220, 1154 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.76 (br d, *J* = 7.3 Hz, 1H), 5.45 (br s, 1H), 4.21 (br dq, *J* = 7.2, 7.2 Hz, 1H), 3.84 (dd, *J* = 7.3, 4.0 Hz, 1H), 1.65-1.57 (m, 1H), 1.49-1.40 (m, 1H), 1.36-1.30 (m, 2H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.25-1.19 (br m, 4H), 0.85 (t, *J* = 6.8 Hz, 3H), COO*H* not observed; ^{13}C NMR (100 MHz, DMSO-d_6) ppm 173.9, 173.5, 70.7, 47.1, 34.2, 31.1, 24.1, 22.0, 17.6, 13.9; HRMS (CI): Exact mass calcd for $C_{10}H_{18}NO_3$ [M-OH] 200.1281, found 200.1282.

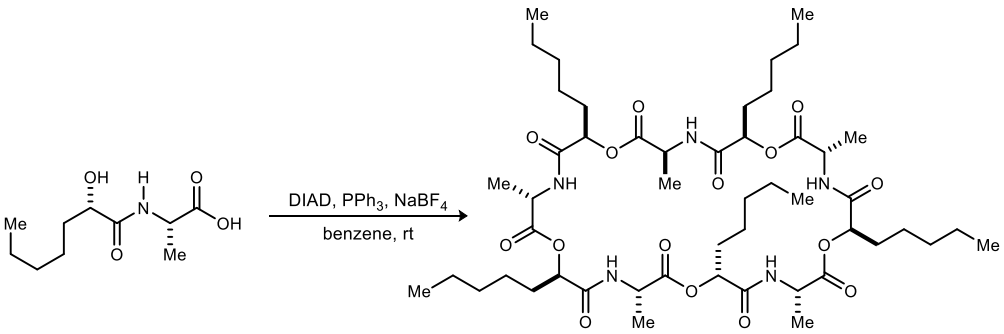


(3*S*,6*R*,9*S*,12*R*,15*S*,18*R*,21*S*,24*R*)-3,9,15,21-Tetramethyl-6,12,18,24-tetrapentyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (6). Following the Tetradepsipeptide MCO general procedure, the *seco*-acid (20.0 mg, 48.0 μmol) with $NaBF_4$ (26.4 mg, 240 μmol) were stirred at ambient temperature for 24 h to afford a pale yellow oil. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 24.8 m) provided the 24-membered macrocycle (17.0 mg, 89%) as a white solid. Mp = 205-207 °C; $[\alpha]_D^{20}$ -6.3 (*c* 0.13, $CHCl_3$); R_f = 0.21 (50% EtOAc/Hexanes); IR (film) 3275, 2956, 2929, 2860, 1746, 1657, 1458, 1377, 1247, 1159, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (br d, *J* = 7.2 Hz, 1H), 5.10 (dd, *J* = 7.4, 5.2 Hz, 1H), 4.23 (dq, *J* = 7.2, 7.0 Hz, 1H), 1.91-1.86 (m, 1H), 1.70-1.60 (m, 1H) 1.46 (d, *J* = 7.0 Hz, 3H), 1.36-1.25 (br m, 6H), 0.89-0.85 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.94, 170.87, 74.2, 48.5, 31.34, 31.27, 24.8, 22.4, 15.9, 13.8; HRMS (ESI): Exact mass calcd for $C_{40}H_{69}N_4O_{12}$ $[M+H]^+$ 797.4912, found 797.4877.

(3*R*,6*S*,9*R*,12*S*,15*R*,18*S*,21*R*,24*S*)-3,9,15,21-Tetramethyl-6,12,18,24-tetrapentyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (*ent*-6) was prepared following an identical procedure from ***ent*-13**. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 24.8 m) provided the 24-membered macrocycle with spectroscopic data identical to its enantiomer, except $[\alpha]_D^{20}$ +6.4 (*c* 0.25, $CHCl_3$).

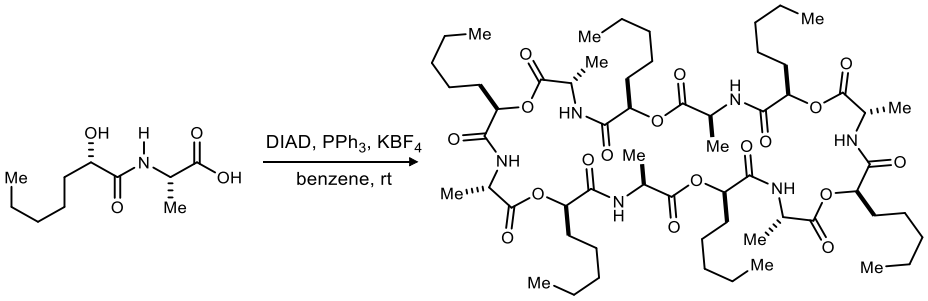


(3*S*,6*R*,9*S*,12*R*,15*S*,18*R*)-3,9,15-Trimethyl-6,12,18-tripentyl-1,7,13-trioxa-4,10,16-triazacyclooctadecane-2,5,8,11,14,17-hexaone (7). Following the Didepsipeptide MCO general procedure, the *seco*-acid (15.0 mg, 69.0 μmol) without a salt additive was stirred at ambient temperature for 24 h to afford a pale yellow oil. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 23.8 m) provided the 18-membered macrocycle (1.2 mg, 9%) as a colorless oil. $[\alpha]_D^{20}$ -23 (*c* 0.10, $CHCl_3$); R_f = 0.27 (4% MeOH/DCM); IR (film) 3209, 2922, 2853, 1756, 1696, 1556, 1457, 1380, 1260, 1211, 1171, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (br d, *J* = 8.4 Hz, 1H), 5.12 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.59 (dq, *J* = 7.4, 7.2 Hz, 1H), 1.91-1.77 (m, 2H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.37-1.29 (br m, 6H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.5, 169.5, 74.9, 48.5, 31.4, 31.3, 24.5, 22.4, 17.4, 14.0; HRMS (ESI): Exact mass calcd for $C_{30}H_{51}N_3NaO_9$ $[M+Na]^+$ 620.3523, found 620.3516.

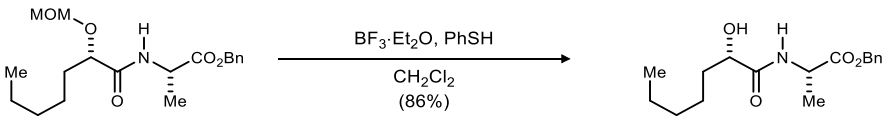


(3*S*,6*R*,9*S*,12*R*,15*S*,18*R*,21*S*,24*R*,27*S*,30*R*)-3,9,15,21,27-Pentamethyl-6,12,18,24,30-pentapentyl-1,7,13,19,25-pentaoxa-4,10,16,22,28-pentaazacyclotriacontane-2,5,8,11,14,17,20,23,26,29-decaone (8). Following the Didepsipeptide MCO general procedure, the *seco*-acid (15.0 mg, 69.0 μmol) with $NaBF_4$ (19.0 mg, 173 μmol) were stirred at ambient temperature for 24 h to afford a pale yellow oil. Preparative HPLC (5-95%

aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 35.5 m) provided the 30-membered macrocycle (2.60 mg, 19%) as a colorless oil. $[\alpha]_D^{20}$ +3.3 (*c* 0.30, $CHCl_3$); R_f = 0.25 (3% MeOH/DCM); IR (film) 3315, 2957, 2924, 2854, 1747, 1664, 1547, 1458, 1380, 1261, 1200, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (br d, *J* = 3.2 Hz, 1H), 5.09 (dd, *J* = 7.8, 4.4 Hz, 1H), 4.50 (dq, *J* = 7.2, 6.4 Hz, 1H), 1.91-1.86 (m, 1H), 1.80-1.71 (m, 1H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.39-1.28 (br m, 6H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.1, 170.2, 74.3, 48.5, 31.4, 31.3, 24.6, 22.4, 17.0, 13.9; HRMS (ESI): Exact mass calcd for $C_{50}H_{85}N_5NaO_{15}$ $[M+Na]^+$ 1018.5940, found 1018.5908.



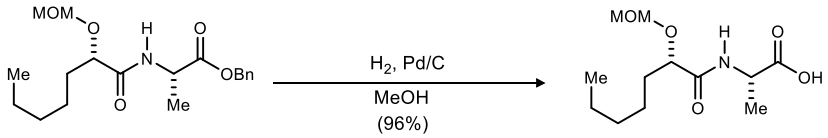
(3*S*,6*R*,9*S*,12*R*,15*S*,18*R*,21*S*,24*R*,27*S*,30*R*,33*S*,36*R*)-3,9,15,21,27,33-Hexamethyl-6,12,18,24,30,36-hexapentyl-1,7,13,19,25,31-hexaoxa-4,10,16,22,28,34-hexaazacyclohexatriacontan-2,5,8,11,14,17,20,23,26,29,32,35-dodecaone (9). Following the Didepsipeptide MCO general procedure, the *seco*-acid (15.0 mg, 69.0 μmol) with KBF_4 (21.8 mg, 173 μmol) were stirred at ambient temperature for 24 h to afford a pale yellow oil. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 23.8 m) provided the 36-membered macrocycle (6.0 mg, 44%) as an opaque film. $[\alpha]_D^{20}$ -12 (*c* 0.10, $CHCl_3$); R_f = 0.10 (4% MeOH/DCM); IR (film) 3286, 2955, 2925, 2856, 1748, 1656, 1542, 1454, 1376, 1260, 1189, 1158, 1115, 1062, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (br d, *J* = 7.8 Hz, 1H), 5.13 (dd, *J* = 7.6, 4.7 Hz, 1H), 4.59 (dq, *J* = 7.3, 7.3 Hz, 1H), 1.92-1.76 (m, 2H), 1.47 (d, *J* = 7.1 Hz, 3H), 1.40-1.25 (br m, 6H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 171.4, 169.4, 74.8, 48.4, 31.3, 31.2, 24.4, 22.4, 17.3, 13.9; HRMS (ESI): Exact mass calcd for $C_{60}H_{101}N_6Na_2O_{18}$ $[M-H+2Na]^+$ 1239.6968, found 1239.6981.



Benzyl ((*S*)-2-hydroxyheptanoyl)-*L*-alaninate (10). Following the general MOM deprotection procedure, the amide (434 mg, 1.23 mmol) afforded a crude pale yellow oil. Flash column chromatography (SiO_2, 20-40% ethyl

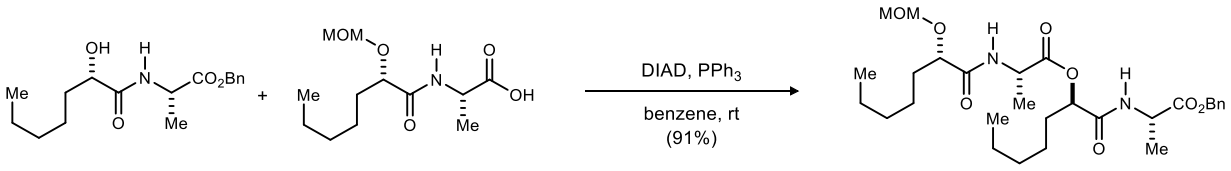
acetate in hexanes) afforded the alcohol (325 mg, 86%) as a pale yellow oil. $[\alpha]_D^{20}$ -23 (*c* 0.43, $CHCl_3$); R_f = 0.25 (30% EtOAc/hexanes); IR (film) 3393, 3034, 2955, 2929, 2859, 1743, 1655, 1524, 1455, 1386, 1307, 1200, 1155, 1083, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (m, 5H), 6.94 (br d, *J* = 7.1 Hz, 1H), 5.21 (d, *J* = 12.3 Hz, 1H), 5.16 (d, *J* = 12.3 Hz, 1H), 4.66 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.13 (ddd, *J* = 8.3, 4.7, 3.6 Hz, 1H), 2.56 (br d, *J* = 5.0 Hz, 1H), 1.86-1.77 (m, 1H), 1.67-1.57 (m, 1H), 1.44 (d, *J* = 7.2 Hz, 3H), 1.40-1.25 (br m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 173.4, 172.8, 135.3, 128.6, 128.5, 128.1, 72.1, 67.2, 47.8, 34.8, 31.5, 24.5, 22.5, 18.4, 14.0; HRMS (ESI): Exact mass calcd for $C_{17}H_{25}NNaO_4$ $[M+Na]^+$ 330.1681, found 330.1667.

Benzyl ((*R*)-2-hydroxyheptanoyl)-*D*-alaninate (*ent*-10) was prepared following an identical procedure from *ent*-4. Flash column chromatography (SiO_2, 20-40% ethyl acetate in hexanes) afforded the alcohol with spectroscopic data identical to its enantiomer, except $[\alpha]_D^{20}$ +31 (*c* 0.72, $CHCl_3$).



((*S*)-2-(Methoxymethoxy)heptanoyl)-*L*-alanine (11). Following the general benzyl-deprotection procedure, the amide (492 mg, 1.40 mmol) afforded the acid (351 mg, 96%) as an analytically pure orange oil. $[\alpha]_D^{20}$ -39 (*c* 0.26, $CHCl_3$); R_f = 0.28 (20% MeOH/DCM); IR (film) 3407, 2955, 2932, 2860, 1733, 1657, 1531, 1457, 1216, 1155, 1101, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (br d, *J* = 7.0 Hz, 1H), 4.71 (s, 2H), 4.60 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.10 (dd, *J* = 6.2, 4.8 Hz, 1H), 3.41 (s, 3H), 1.80-1.70 (m, 2H), 1.48 (d, *J* = 7.0 Hz, 3H), 1.42-1.26 (br m, 6H) 0.88 (t, *J* = 6.6 Hz, 3H), COO*H* not observed; ^{13}C NMR (125 MHz, $CDCl_3$) ppm 175.5, 173.2, 96.3, 77.5, 56.2, 47.8, 32.7, 31.5, 24.3, 22.5, 17.9, 14.0; HRMS (ESI): Exact mass calcd for $C_{12}H_{23}NNaO_5$ $[M+Na]^+$ 284.1474, found 284.1478.

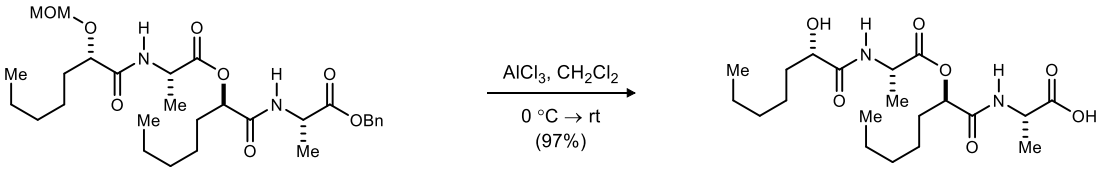
((*R*)-2-(Methoxymethoxy)heptanoyl)-*D*-alanine (*ent*-11) was prepared following an identical procedure from *ent*-4, affording the acid with spectroscopic data identical to its enantiomer, except $[\alpha]_D^{20}$ +41 (*c* 0.20, $CHCl_3$).



Benzyl ((*R*)-2-((((*S*)-2-(methoxymethoxy)heptanoyl)-*L*-alanyl)oxy)heptanoyl)-*L*-alaninate (12). Following the Mitsunobu general procedure, alcohol (340 mg, 1.11 mmol) and acid (310 mg, 1.19 mmol) were reacted at

ambient temperature for 24 h to afford a crude brown oil. Flash column chromatography (SiO_2, 15-35% ethyl acetate in hexanes) provided the tetradepsipeptide (550 mg, 91%) as a white solid. Mp = 114 °C; $[\alpha]_D^{25}$ -17 (*c* 0.27, $CHCl_3$); R_f = 0.22 (30% EtOAc/hexanes); IR (film) 3310, 2955, 2930, 2859, 1747, 1657, 1535, 1456, 1378, 1344, 1201, 1156, 1104, 1059, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 5H), 7.10 (br d, *J* = 7.2 Hz, 1H), 6.98 (br d, *J* = 6.8 Hz, 1H), 5.21 (d, *J* = 12.2 Hz, 1H), 5.19 (dd, *J* = 7.8, 4.1 Hz, 1H), 5.13 (d, *J* = 12.2 Hz, 1H), 4.68 (s, 2H), 4.59 (dq, *J* = 7.3, 7.2 Hz, 1H), 4.45 (dq, *J* = 7.0, 6.8 Hz, 1H), 4.03 (dd, *J* = 6.3, 4.8 Hz, 1H), 3.41 (s, 3H), 1.93-1.68 (series of m, 4H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.43 (d, *J* = 7.3 Hz 3H), 1.38-1.26 (br m, 12H), 0.89-0.85 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 173.0, 172.4, 172.2, 169.3, 135.6, 128.5, 128.3, 128.1, 96.3, 77.5, 74.7, 66.9, 56.3, 48.4, 48.0, 32.6, 31.6, 31.5, 31.2, 24.5, 24.3, 22.5, 22.4, 17.5, 17.3, 14.0, 13.9; HRMS (ESI): Exact mass calcd for $C_{29}H_{46}N_2NaO_8$ $[M+Na]^+$ 573.3152, found 573.3126.

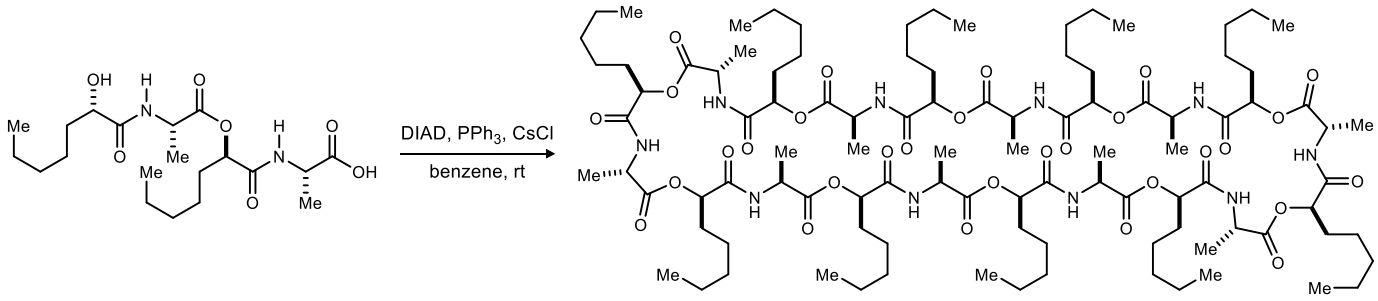
Benzyl ((*S*)-2-((((*R*)-2-(methoxymethoxy)heptanoyl)-*D*-alanyl)oxy)heptanoyl)-*D*-alaninate (*ent*-12) was prepared following an identical procedure, but using *ent*-10 and *ent*-11. Flash column chromatography (SiO_2, 15-35% ethyl acetate in hexanes) afforded the tetradepsipeptide with spectroscopic data identical to its enantiomer, except $[\alpha]_D^{20}$ +12 (*c* 0.10, $CHCl_3$).



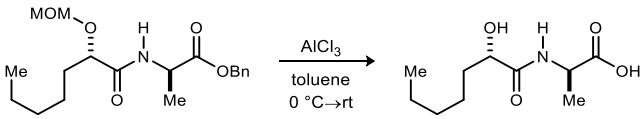
((*R*)-2-((((*S*)-2-Hydroxyheptanoyl)-*L*-alanyl)oxy)heptanoyl)-*L*-alanine (13). A flame-dried round-bottomed flask under inert atmosphere was charged with $AlCl_3$ (169 mg, 1.27 mmol) and CH_2Cl_2 (1.3 mL) at 0 °C. The MOM and benzyl-protected depsipeptide (70.0 mg, 127 μmol) was dissolved in CH_2Cl_2 (500 μL) and added dropwise to the stirring solution. The reaction was allowed to slowly warm to ambient temperature and stir for 15 m, and then poured into ice water. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water and brine, dried, and concentrated to a yellow residue that was subjected to preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 17.5 m) to afford the *seco*-acid (51.3 mg, 97%) as a colorless foam. $[\alpha]_D^{20}$ +6 (*c* 0.10, $CHCl_3$); R_f = 0.16 (10% MeOH/DCM); IR (film) 3316, 2956, 2929, 2859, 1746, 1655, 1537, 1457, 1379, 1304, 1210, 1155, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (br d, *J* = 6.0 Hz, 1H), 7.06 (br s, 1H), 5.21 (dd, *J* = 7.9, 4.0 Hz, 1H), 4.53 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.45 (br dq, *J* = 6.9, 6.9 Hz, 1H), 4.15 (dd, *J* = 7.8, 3.7 Hz, 1H), 1.97-1.77 (series of m, 3H), 1.68-1.58 (m, 1H), 1.49 (d, *J* = 7.2 Hz, 3H), 1.47 (d, *J* = 7.3 Hz, 3H), 1.42-1.15 (br m, 12H), 0.91-0.86 (m, 6H), COO*H* and O*H* not observed; ^{13}C NMR (125 MHz, $CDCl_3$) ppm 174.3, 173.8, 173.2, 172.3, 74.6, 72.0, 48.47, 48.42, 34.4, 31.4 (2C), 31.2, 24.5, 24.4,

22.5, 22.4, 17.0 (2C), 13.97, 13.92; HRMS (ESI): Exact mass calcd for $C_{20}H_{36}N_2NaO_7$ $[M+Na]^+$ 439.2420, found 439.2440.

((*S*)-2-((((*R*)-2-Hydroxyheptanoyl)-*D*-alanyl)oxy)heptanoyl)-*D*-alanine (*ent*-13) was prepared following an identical procedure, but from *ent*-12. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 17.5 m) afforded the *seco*-acid with spectroscopic data identical to its enantiomer, except $[\alpha]_D^{20}$ -7 (*c* 0.10, $CHCl_3$).

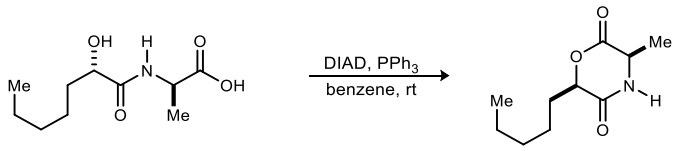


(3*S*,6*R*,9*S*,12*R*,15*S*,18*R*,21*S*,24*R*,27*S*,30*R*,33*S*,36*R*,39*S*,42*R*,45*S*,48*R*,51*S*,54*R*,57*S*,60*R*)-3,9,15,21,27,33,39,45,51,57-Decamethyl-6,12,18,24,30,36,42,48,54,60-decapentyl-1,7,13,19,25,31,37,43,49,55-decaoxa-4,10,16,22,28,34,40,46,52,58-decaazacyclohexacontan-2,5,8,11,14,17,20,23,26,29,32,35,38,41,44,47,50,53,56,59-icosaone (14). Following the Tetradepsipeptide MCO general procedure, the *seco*-acid (18.0 mg, 43.0 μmol) with CsCl (36.2 mg, 215 μmol) was stirred for 24 h at ambient temperature to afford a pale yellow oil. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 36.0 m) provided the 60-membered macrocycle (2.5 mg, 15%) as a colorless oil. $[\alpha]_D^{20}$ +33 (*c* 0.11, $CHCl_3$); R_f = 0.27 (4% MeOH/DCM); IR (film) 3312, 2957, 2925, 2855, 1750, 1658, 1545, 1456, 1381, 1261, 1195, 1157, 1064, 1020, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (br d, *J* = 6.8 Hz, 1H), 5.10 (dd, *J* = 8.4, 4.2 Hz, 1H), 4.49 (dq, *J* = 7.2, 7.2 Hz, 1H), 1.95-1.86 (m, 1H), 1.80-1.71 (m, 1H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.39-1.25 (br m, 6H), 0.88 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 171.9, 170.2, 74.2, 48.5, 31.3, 31.2, 24.5, 22.3, 16.9, 13.9; HRMS (ESI): Exact mass calcd for $C_{100}H_{170}N_{10}NaO_{30}$ $[M+Na]^+$ 2015.2014, found 2015.2047.

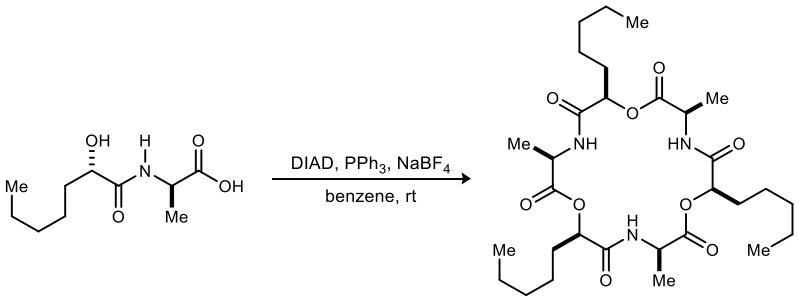


((*S*)-2-Hydroxyheptanoyl)-*D*-alanine (15). Following the global deprotection general procedure, the amide[10] (202 mg, 575 μmol) was stirred at ambient temperature for 25 m to afford a yellow residue. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 12.7 m) provided the *seco*-acid (93.7 mg, 75%) as a tan solid. Mp = 85-87 °C; $[\alpha]_D^{20}$ -25 (*c* 0.40, $CHCl_3$); R_f = 0.40 (20% MeOH/DCM); IR (film) 3315, 2923,

2854, 1732, 1626, 1537, 1457, 1292, 1258, 1210, 1158, 1128, 1080, 1020 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.75 (br d, *J* = 7.0 Hz, 1H), 5.46 (br s, 1H), 4.14 (br dq, *J* = 7.7, 6.6 Hz, 1H), 3.84 (dd, *J* = 7.3, 4.0 Hz, 1H), 1.64-1.56 (m, 1H), 1.49-1.40 (m, 1H), 1.36-1.30 (m, 2H), 1.27 (d, *J* = 7.1 Hz, 3H), 1.25-1.19 (br m, 4H), 0.85 (t, *J* = 6.9 Hz, 3H), COO*H* not observed; ^{13}C NMR (125 MHz, DMSO-d_6) ppm 173.9, 173.5, 70.8, 47.3, 34.2, 31.1, 24.1, 22.0, 17.7, 13.9; HRMS (ESI): Exact mass calcd for $C_{10}H_{18}NO_4$ $[M-H]^-$ 216.1236, found 216.1246.

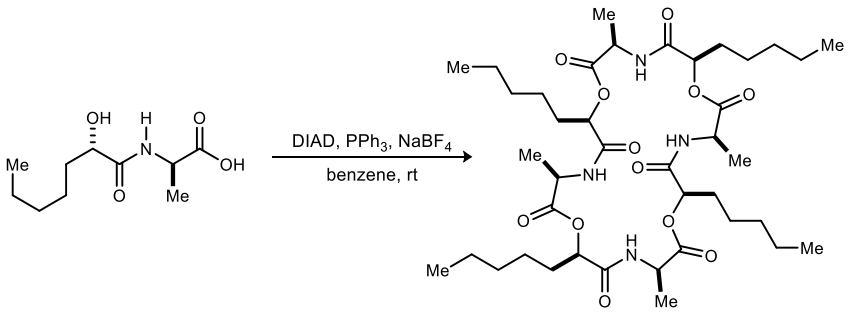


(3*R*,6*R*)-3-Methyl-6-pentylmorpholine-2,5-dione (16). Following the Didepsipeptide MCO general procedure, the *seco*-acid (20.0 mg, 92.0 μmol) without a salt additive was stirred at ambient temperature for 24 h to afford a pale yellow oil. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 15.5 min) provided the 6-membered macrocycle (6.1 mg, 33%) as a viscous oil. $[\alpha]_D^{20}$ +6.1 (*c* 0.28, $CHCl_3$); R_f = 0.17 (2% MeOH/DCM); IR (film) 3376, 2923, 2855, 1730, 1651, 1531, 1458, 1260, 1153, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.17 (br s, 1H), 4.78 (dd, *J* = 7.9, 4.0 Hz, 1H), 4.25 (q, *J* = 6.8 Hz, 1H), 2.12-2.03 (m, 1H), 1.94-1.85 (m, 1H), 1.49 (d, *J* = 6.7 Hz, 3H), 1.61-1.53 (m, 1H), 1.50-1.43 (m, 1H), 1.37-1.32 (br m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 168.4, 168.1, 78.2, 49.3, 31.3, 30.3, 24.2, 22.3, 17.5, 13.9; HRMS (CI): Exact mass calcd for $C_{10}H_{18}NNaO_3$ $[M+H]^+$ 200.1281, found 200.1279.

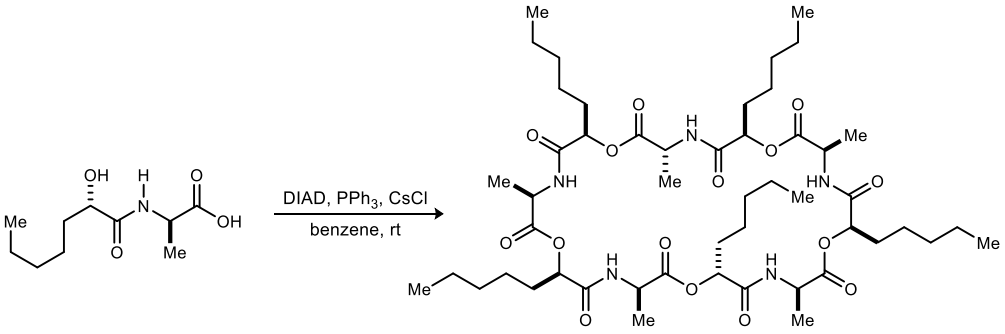


(3*R*,6*R*,9*R*,12*R*,15*R*,18*R*)-3,9,15-Trimethyl-6,12,18-tripentyl-1,7,13-trioxa-4,10,16-triazacyclooctadecane-2,5,8,11,14,17-hexaone (17). Following the Didepsipeptide MCO general procedure, the *seco*-acid (20.0 mg, 92.0 μmol) with $NaBF_4$ (25.1 mg, 230 μmol) were stirred at ambient temperature for 24 h to afford a pale yellow oil. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 24.8 min) provided the 18-membered macrocycle (5.3 mg, 29%) as an opaque film. $[\alpha]_D^{20}$ +26 (*c* 0.25, $CHCl_3$); R_f = 0.30 (3% MeOH/DCM); IR (film) 3277, 2952, 2853, 1753, 1663, 1542, 1456, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

6.89 (br d, *J* = 5.2 Hz, 1H), 5.19 (dd, *J* = 5.5, 4.6 Hz, 1H), 4.63 (dq, *J* = 7.1, 7.1 Hz, 1H), 1.96-1.81 (m, 2H), 1.49 (d, *J* = 7.1 Hz, 3H), 1.39-1.26 (br m, 6H), 0.89 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.8, 169.6, 74.3, 48.9, 31.6, 31.3, 24.6, 22.4, 17.5, 13.9; HRMS (ESI): Exact mass calcd for $C_{30}H_{51}N_3NaO_9$ $[M+Na]^+$ 620.3523, found 620.3547.

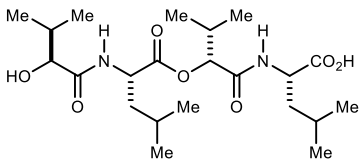


(3*R*,6*R*,9*R*,12*R*,15*R*,18*R*,21*R*,24*R*)-3,9,15,21-Tetramethyl-6,12,18,24-tetrapentyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (18). Following the Didepsipeptide MCO general procedure, the *seco*-acid (20.0 mg, 92.0 μmol) and $NaBF_4$ (25.1 mg, 230 μmol) were stirred at ambient temperature for 24 h to afford a pale yellow oil. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 28.2 min) provided the 24-membered macrocycle as a white solid (5.0 mg, 27%). Mp = 173-175 °C; $[\alpha]_D^{20}$ +32 (*c* 0.13 $CHCl_3$); R_f = 0.26 (3% MeOH/DCM); IR (film) 3281, 2924, 2854, 1750, 1655, 1543, 1458, 1260, 1060 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.79 (br m, 1H), 5.13 (br dd, *J* = 6.5, 5.5 Hz, 1H), 4.66 (br dq, *J* = 6.9, 6.7 Hz, 1H), 1.94-1.88 (m, 1H), 1.83-1.77 (m, 1H), 1.51 (d, *J* = 7.2 Hz, 3H), 1.35-1.25 (br m, 6H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.7, 169.6, 74.9, 48.4, 31.3, 31.1, 24.4, 22.4, 17.5, 13.9; HRMS (ESI): Exact mass calcd for $C_{40}H_{68}N_4NaO_{12}$ $[M+Na]^+$ 819.4731, found 819.4739.

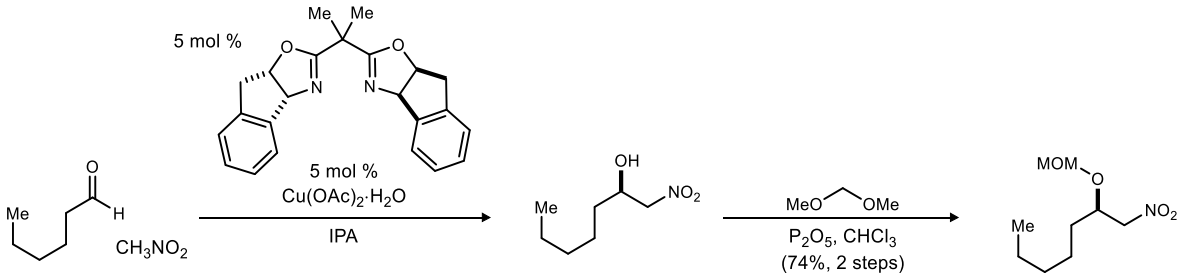


(3*R*,6*R*,9*R*,12*R*,15*R*,18*R*,21*R*,24*R*,27*R*,30*R*)-3,9,15,21,27-Pentamethyl-6,12,18,24,30-pentapentyl-1,7,13,19,25-pentaoxa-4,10,16,22,28-pentaazacyclotriacontane-2,5,8,11,14,17,20,23,26,29-decaone (19). Following the Didepsipeptide MCO general procedure, the *seco*-acid (15.0 mg, 69.0 μmol) with CsCl (29.1 mg, 173 μmol) were stirred at ambient temperature for 24 h to afford a pale yellow oil. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 36.8 min) provided the 30-membered macrocycle (3.7

mg, 27%) as an opaque film. $[\alpha]_D^{20}$ +6.0 (*c* 0.10, $CHCl_3$); R_f = 0.37 (3% MeOH/DCM); IR (film) 3298, 2924, 2853, 1749, 1656, 1544, 1458, 1378, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (br d, *J* = 6.8 Hz, 1H), 5.19 (dd, *J* = 8.4, 4.1 Hz, 1H), 4.42 (dq, *J* = 6.8, 6.7 Hz, 1H), 1.96-1.89 (m, 1H), 1.78-1.69 (m, 1H), 1.52 (d, *J* = 7.2 Hz, 3H), 1.39-1.28 (br m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.9, 170.3, 74.5, 49.0, 31.7, 31.3, 24.6, 22.4, 17.3, 13.9; HRMS (ESI): Exact mass calcd for $C_{50}H_{85}N_5NaO_{15}[M+Na]^+$ 1018.5940, found 1018.5942.

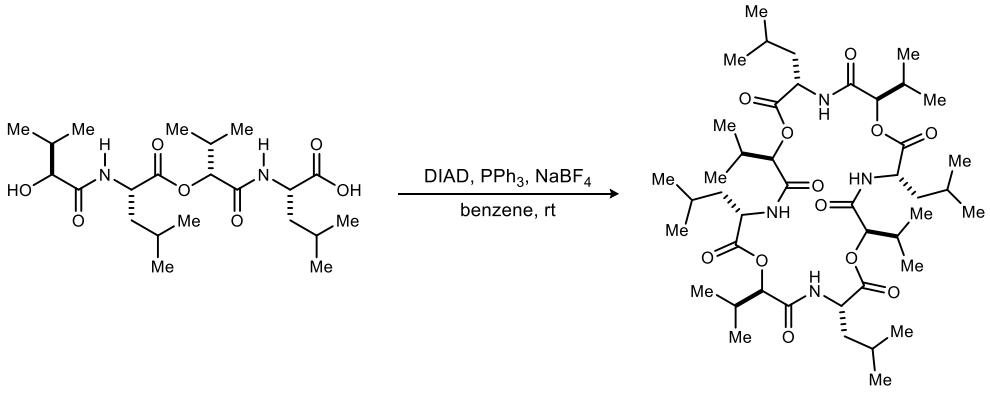


((*R*)-2-((((*S*)-2-Hydroxy-3-methylbutanoyl)-*L*-leucyl)oxy)-3-methylbutanoyl)-*L*-leucine (20). Compound **20** was prepared following an analogous 6-step sequence to **13**. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 18.3 min) provided the *seco*-acid (170 mg, 36%, 6 steps) as a pale yellow oil. $[\alpha]_D^{25}$ -30 (*c* 0.13, $CHCl_3$); R_f = 0.19 (10% MeOH/DCM); IR (film) 3314, 2961, 2931, 2874, 1740, 1656, 1545, 1469, 1369, 1237, 1155, 1022 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, *J* = 8.1 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 5.56 (br s, 1H), 4.76 (d, *J* = 4.0 Hz, 1H), 4.44 (ddd, *J* = 10.2, 8.0, 5.0 Hz, 1H), 4.28 (ddd, *J* = 11.0, 8.5, 4.1 Hz, 1H), 3.76 (d, *J* = 3.4 Hz, 1H), 2.14 (qqd, *J* = 6.8, 4.0 Hz, 1H), 2.02 (qqd, *J* = 6.8, 3.5 Hz, 1H), 1.80 (ddd, *J* = 13.0, 10.3, 4.7 Hz, 1H), 1.66-1.45 (m, 5H), 0.93-0.84 (m, 18H), 0.79 (d, *J* = 6.2 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H), COO*H* not observed; ^{13}C NMR (125 MHz, DMSO-d_6) ppm 173.8, 173.6, 171.9, 168.6, 77.9, 75.1, 50.1, 49.7, 39.7, 39.5, 31.2, 30.0, 24.2, 24.0, 22.9, 22.8, 21.2, 20.8, 19.1, 18.8, 16.5, 16.0; HRMS (ESI): Exact mass calcd for $C_{22}H_{40}N_2NaO_7$ $[M+Na]^+$ 467.2733, found 467.2714.



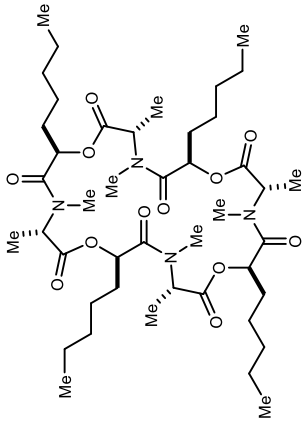
(*R*)-2-(Methoxymethoxy)-1-nitroheptane (S1). Following the Evans[11] enantioselective Henry procedure, IndaBOX (117 mg, 326 μmol) and $Cu(OAc)_2$•H_2O (65.0 mg, 326 μmol) stirred at ambient temperature in IPA (26 mL) for 1 h. The cerulean blue solution was then cooled to 0 °C and hexanal (800 μL, 6.51 mmol) was added and allowed to stir for 10 m before nitromethane (3.50 mL, 65.1 mmol) addition. After stirring for 4 days at 0 °C, the reaction was quenched dropwise at 0 °C with pre-chilled 1 N HCl and the aqueous layer was extracted with CH_2Cl_2. Following drying and concentration under reduced pressure, the crude alcohol was dissolved in $CHCl_3$ (32.6 mL), treated with P_2O_5 (9.24 g, 65.1 mmol) and dimethoxymethane (11.5 mL, 130 mmol), and stirred at

ambient temperature overnight. The reaction was cooled to 0 °C, quenched slowly with satd aq $NaHCO_3$, and then poured into CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The organic layers were dried and concentrated to an oil that was subjected to flash column chromatography (SiO_2, 3-6% diethyl ether in hexanes) to afford the title compound as a pale yellow oil (990 mg, 74%, 2 steps). The enantiopurity was determined to be 96% ee by chiral HPLC analysis (Chiralcel OD-H, 2% ^{i}PrOH /hexanes, 0.4 mL/min, t_r(e_1, major) = 16.4 min, t_r(e_2, minor) = 18.9 min). $[\alpha]_D^{20}$ -10 (c 0.60, $CHCl_3$); R_f = 0.16 (6% Et_2O/hexanes); IR (film) 2932, 2861, 1558, 1463, 1385, 1156, 1138, 1105, 1032, 919 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (d, J = 7.1 Hz, 1H), 4.65 (d, J = 7.1 Hz, 1H), 4.50 (dd, J = 12.4, 8.1 Hz, 1H), 4.42 (dd, J = 12.4, 3.9 Hz, 1H), 4.27 (dddd, J = 8.1, 6.1, 6.1, 3.9 Hz, 1H), 3.35 (s, 3H), 1.71-1.56 (m, 2H), 1.38-1.29 (br m, 6H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 96.2, 79.1, 74.9, 55.9, 32.3, 31.6, 24.5, 22.5, 13.9; HRMS (CI): Exact mass calcd for $C_9H_{19}N_1O_4Na$ $[M+Na]^+$ 228.1212, found 228.1207.



(3*S*,6*R*,9*S*,12*R*,15*S*,18*R*,21*S*,24*R*)-3,9,15,21-Tetraisobutyl-6,12,18,24-tetraisopropyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (S2). Following the Tetradepsipeptide MCO general procedure, the *seco*-acid (20.0 mg, 45.0 μmol) with $NaBF_4$ (24.7 mg, 225 μmol) was stirred for 18 h at ambient temperature to afford a chunky white solid. Preparative HPLC (5-95% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 26.2 m) provided the 24-membered macrocycle (6.0 mg, 31%) as a white powder. $[\alpha]_D^{20}$ -21 (c 0.11, MeOH); R_f = 0.1 (3% MeOH/DCM); IR (film) 3353, 2958, 2922, 2852, 1736, 1654, 1557, 1459, 1261, 1099, 1157, 1020, 800 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (d, J = 9.6 Hz, 1H), 4.69 (d, J = 5.6 Hz, 1H), 4.66 (ddd, J = 12.3, 9.6, 2.7 Hz, 1H), 2.31 (ddd, J = 12.7, 12.7, 2.6 Hz, 1H), 2.06 (br qqd, J = 6.7 Hz, 1H), 1.50-1.42 (br m, 1H), 1.39-1.36 (ddd, 12.7, 12.7, 2.6 Hz, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H), 0.77 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 171.9, 168.4, 79.4, 49.2, 40.7, 29.9, 23.10, 23.07, 20.2, 18.5, 18.2; HRMS (ESI): Exact mass calcd for $C_{44}H_{76}N_4NaO_{12}$ $[M+Na]^+$ 875.5357, found 875.5361.

Figure 1. ^{1}H NMR (400 MHz, $CDCl_3$) of (*nat*-1)



^{1}H δ Literature	Mult, J values	^{1}H δ Synthesis	Mult, J values
0.88	m	0.82-0.89	br m
1.30	m	1.06-1.31	br m
1.31	m		
1.38	d, J = 7.2 Hz	1.38	d, J = 7.2 Hz
1.39	d, J = 7.4 Hz	1.39	d, J = 7.5 Hz
1.41	d, J = 7.4 Hz	1.41	d, J = 7.3 Hz
1.45	d, J = 7.3 Hz	1.45	d, J = 7.4 Hz
1.59	d, J = 7.3 Hz	1.59	d, J = 7.0 Hz
1.78	m	1.73-1.90	br m
2.89	s	2.89	s
2.91	s	2.91	s
2.96	s	2.96	s
3.01	s	3.01	s
3.18	s	3.18	s
4.56	q, J = 7.3 Hz	4.56	q, J = 7.3 Hz
5.11	dd, J = 10.6, 2.5 Hz	5.11	dd, J = 11.0, 2.4 Hz
5.30	q, J = 7.4 Hz	5.3	q, J = 7.3 Hz
5.32	dd, J = 10.1, 3.3 Hz	5.32	dd, J = 9.9, 3.3 Hz
5.36	dd, J = 9.0, 5.3 Hz	5.36	dd, J = 8.5, 5.0 Hz
5.40	q, J = 7.2 Hz	5.4	q, J = 7.2 Hz
5.42	m	5.42	m (overlapping)
5.45	dd, J = 8.4, 5.3 Hz	5.45	dd, J = 8.4, 5.4 Hz
5.53	q, J = 7.3 Hz	5.53	q, J = 7.3 Hz
5.54	q, J = 7.4 Hz	5.54	q, J = 7.5 Hz

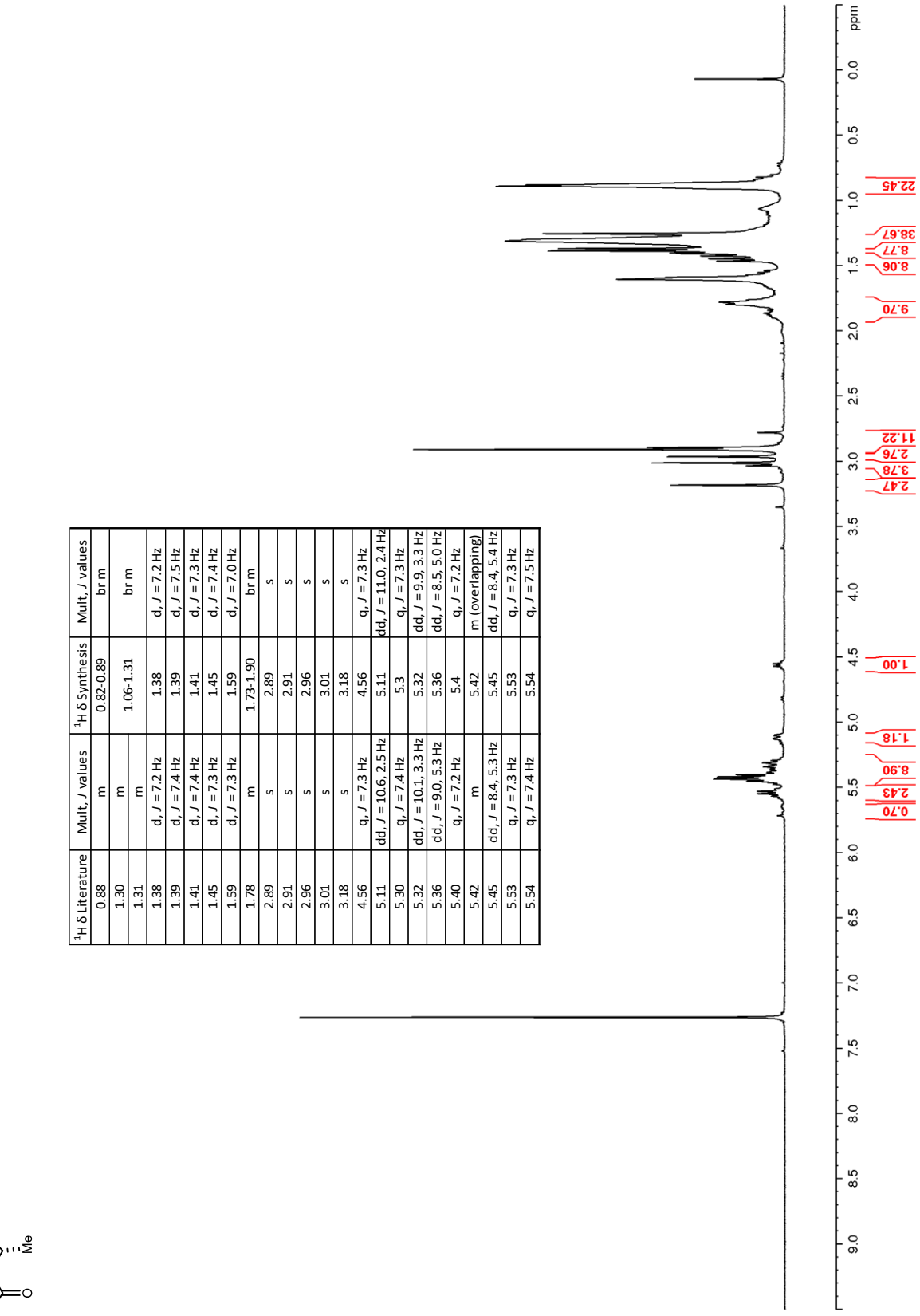
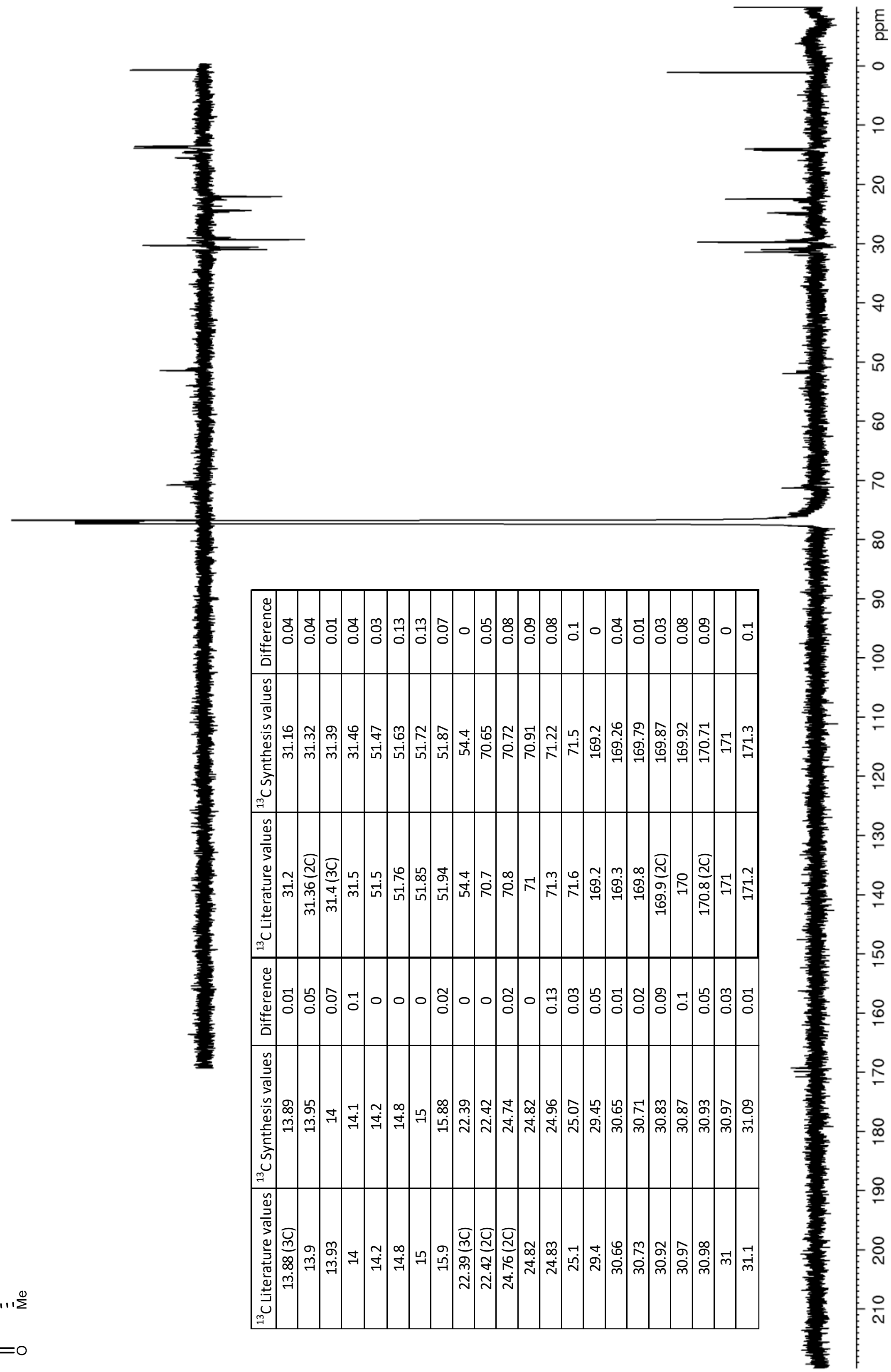


Figure 2. ^{13}C NMR (150 MHz, $CDCl_3$) of **(*nat*-1)**



^{13}C Literature values	^{13}C Synthesis values	Difference	^{13}C Literature values	^{13}C Synthesis values	Difference
13.88 (3C)	13.89	0.01	31.2	31.16	0.04
13.9	13.95	0.05	31.36 (2C)	31.32	0.04
13.93	14	0.07	31.4 (3C)	31.39	0.01
14	14.1	0.1	31.5	31.46	0.04
14.2	14.2	0	51.5	51.47	0.03
14.8	14.8	0	51.76	51.63	0.13
15	15	0	51.85	51.72	0.13
15.9	15.88	0.02	51.94	51.87	0.07
22.39 (3C)	22.39	0	54.4	54.4	0
22.42 (2C)	22.42	0	70.7	70.65	0.05
24.76 (2C)	24.74	0.02	70.8	70.72	0.08
24.82	24.82	0	71	70.91	0.09
24.83	24.96	0.13	71.3	71.22	0.08
25.1	25.07	0.03	71.6	71.5	0.1
29.4	29.45	0.05	169.2	169.2	0
30.66	30.65	0.01	169.3	169.26	0.04
30.73	30.71	0.02	169.8	169.79	0.01
30.92	30.83	0.09	169.9 (2C)	169.87	0.03
30.97	30.87	0.1	170	169.92	0.08
30.98	30.93	0.05	170.8 (2C)	170.71	0.09
31	30.97	0.03	171	171	0
31.1	31.09	0.01	171.2	171.3	0.1

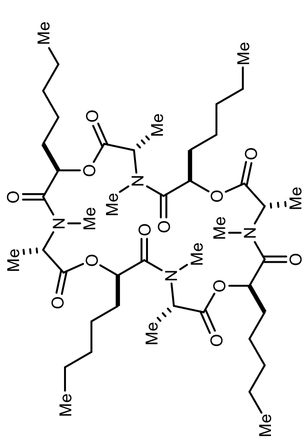
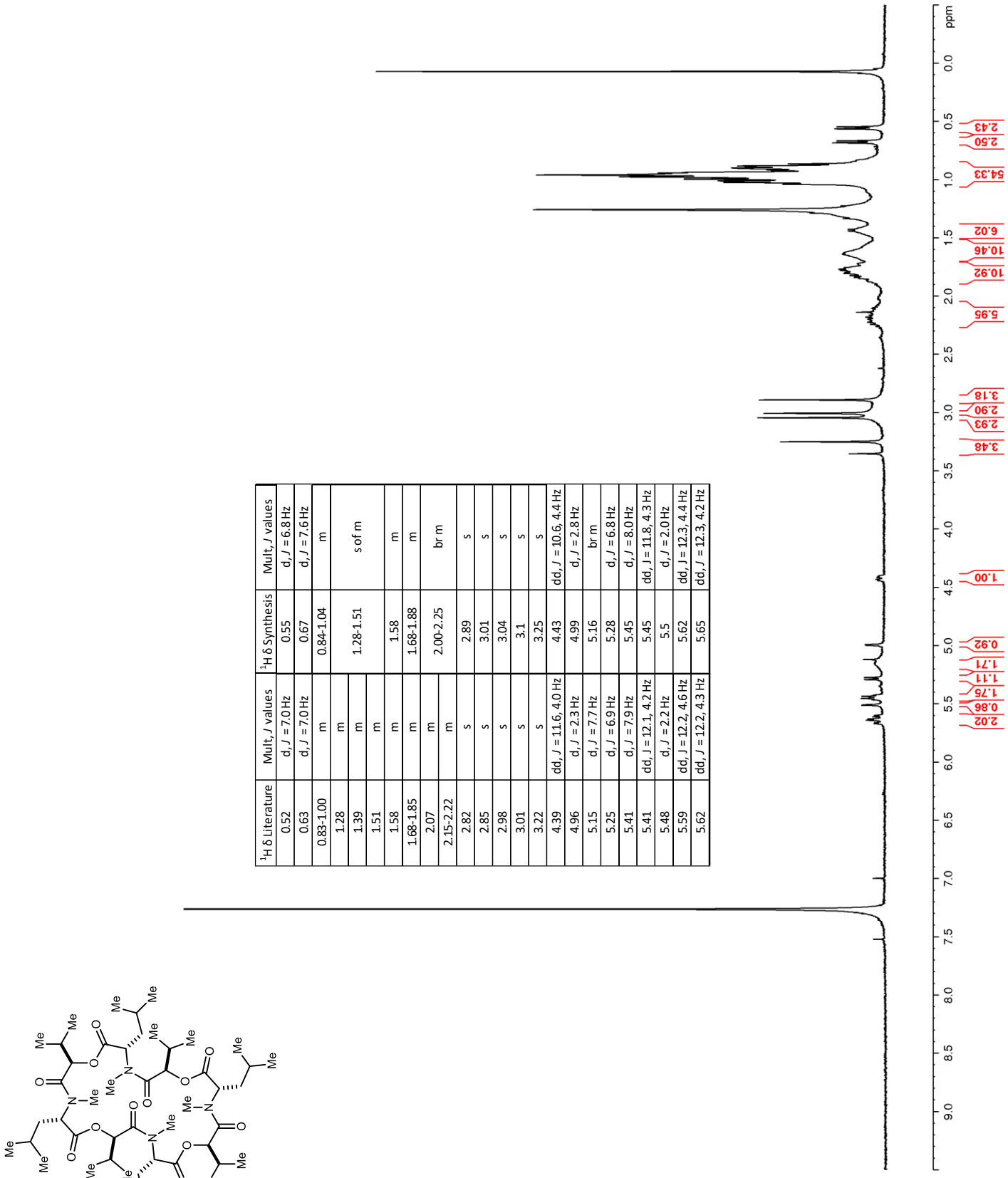
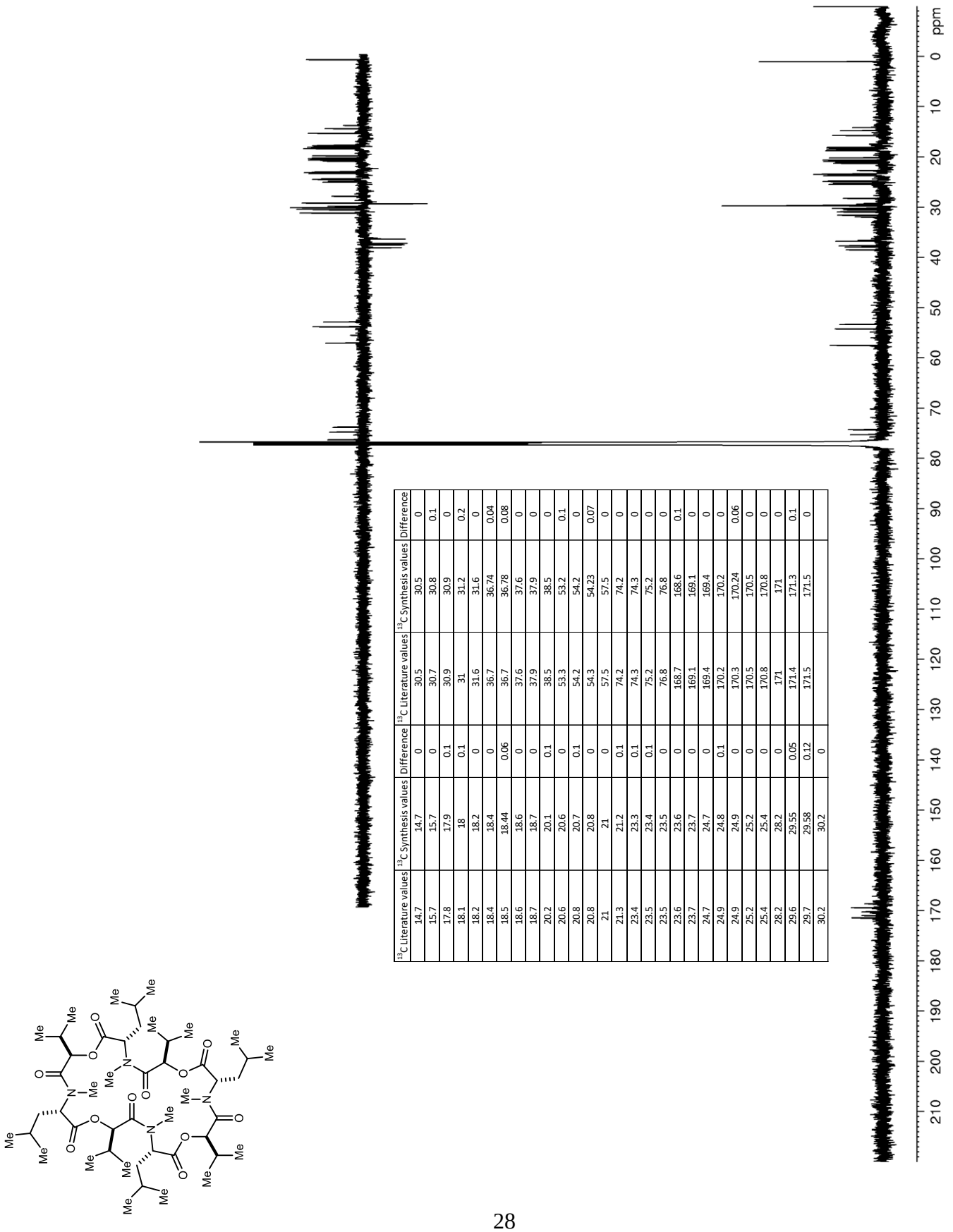


Figure 3. ^{1}H NMR (400 MHz, $CDCl_3$) of ***(nat*-2)**



^{1}H δ Literature	Mult, *J* values	^{1}H δ Synthesis	Mult, *J* values
0.52	d, *J* = 7.0 Hz	0.55	d, *J* = 6.8 Hz
0.63	d, *J* = 7.0 Hz	0.67	d, *J* = 7.6 Hz
0.83-1.00	m	0.84-1.04	m
1.28	m	1.28-1.51	s of m
1.39	m		
1.51	m		
1.58	m	1.58	m
1.68-1.85	m	1.68-1.88	m
2.07	m	2.00-2.25	br m
2.15-2.22	m		
2.82	s	2.89	s
2.85	s	3.01	s
2.98	s	3.04	s
3.01	s	3.1	s
3.22	s	3.25	s
4.39	dd, *J* = 11.6, 4.0 Hz	4.43	dd, *J* = 10.6, 4.4 Hz
4.96	d, *J* = 2.3 Hz	4.99	d, *J* = 2.8 Hz
5.15	d, *J* = 7.7 Hz	5.16	br m
5.25	d, *J* = 6.9 Hz	5.28	d, *J* = 6.8 Hz
5.41	d, *J* = 7.9 Hz	5.45	d, *J* = 8.0 Hz
5.41	dd, J = 12.1, 4.2 Hz	5.45	dd, J = 11.8, 4.3 Hz
5.48	d, *J* = 2.2 Hz	5.5	d, *J* = 2.0 Hz
5.59	dd, J = 12.2, 4.6 Hz	5.62	dd, J = 12.3, 4.4 Hz
5.62	dd, *J* = 12.2, 4.3 Hz	5.65	dd, *J* = 12.3, 4.2 Hz

Figure 4. ^{13}C NMR (150 MHz, $CDCl_3$) of **(*nat*-2)**



^{13}C Literature values	^{13}C Synthesis values	Difference	^{13}C Literature values	^{13}C Synthesis values	Difference
14.7	14.7	0	30.5	30.5	0
15.7	15.7	0	30.7	30.8	0.1
17.8	17.9	0.1	30.9	30.9	0
18.1	18	0.1	31	31.2	0.2
18.2	18.2	0	31.6	31.6	0
18.4	18.4	0	36.7	36.74	0.04
18.5	18.44	0.06	36.7	36.78	0.08
18.6	18.6	0	37.6	37.6	0
18.7	18.7	0	37.9	37.9	0
20.2	20.1	0.1	38.5	38.5	0
20.6	20.6	0	53.3	53.2	0.1
20.8	20.7	0.1	54.2	54.2	0
20.8	20.8	0	54.3	54.23	0.07
21	21	0	57.5	57.5	0
21.3	21.2	0.1	74.2	74.2	0
23.4	23.3	0.1	74.3	74.3	0
23.5	23.4	0.1	75.2	75.2	0
23.5	23.5	0	76.8	76.8	0
23.6	23.6	0	168.7	168.6	0.1
23.7	23.7	0	169.1	169.1	0
24.7	24.7	0	169.4	169.4	0
24.9	24.8	0.1	170.2	170.2	0
24.9	24.9	0	170.3	170.24	0.06
25.2	25.2	0	170.5	170.5	0
25.4	25.4	0	170.8	170.8	0
28.2	28.2	0	171	171	0
29.6	29.55	0.05	171.4	171.3	0.1
29.7	29.58	0.12	171.5	171.5	0
30.2	30.2	0			

Figure 5. ^{1}H NMR (600 MHz, $CDCl_3$) of **3**

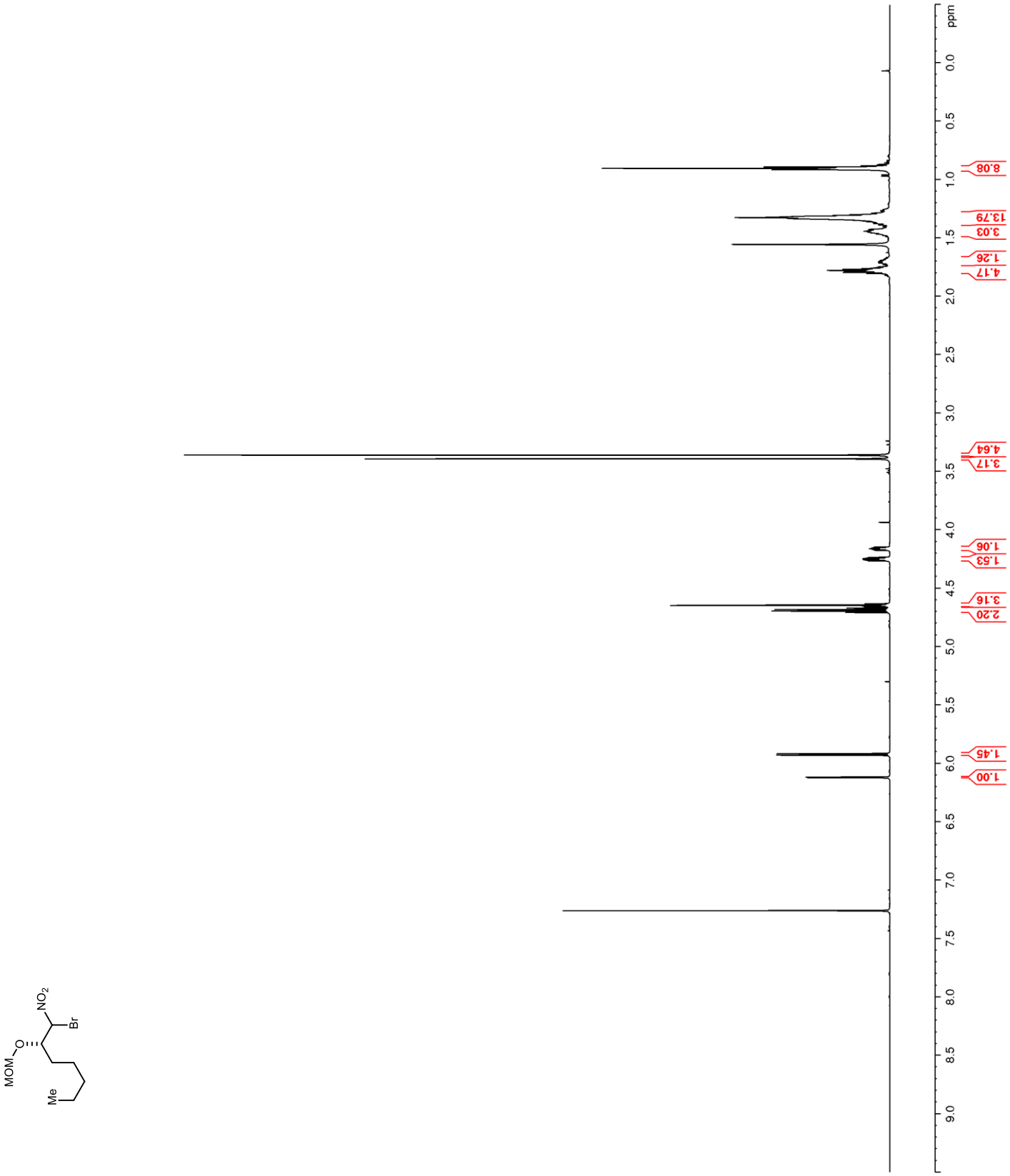


Figure 6. ^{13}C NMR (150 MHz, $CDCl_3$) of **3**

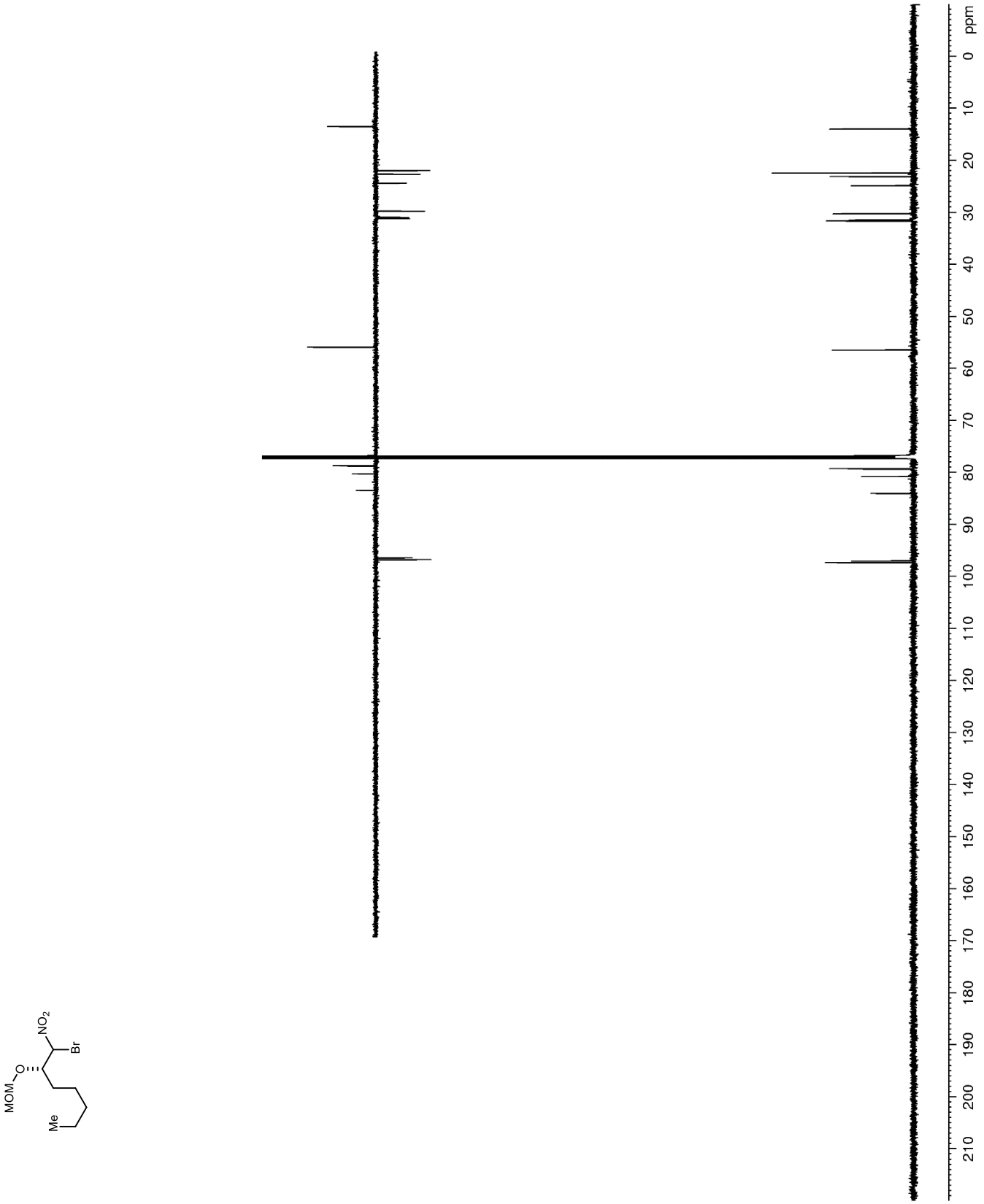


Figure 7. ^{1}H NMR (400 MHz, $CDCl_3$) of **4**

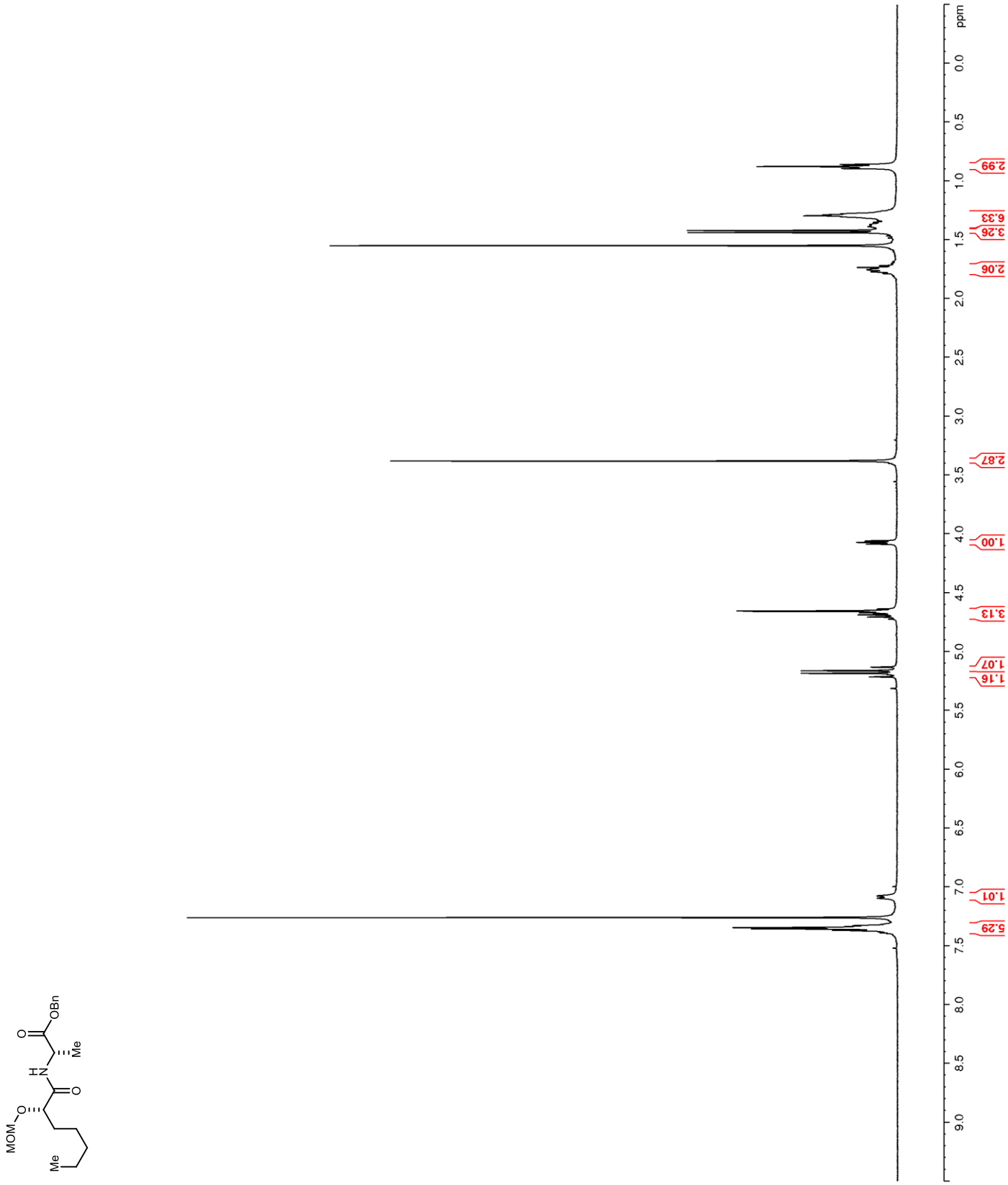


Figure 8. ^{13}C NMR (150 MHz, $CDCl_3$) of **4**

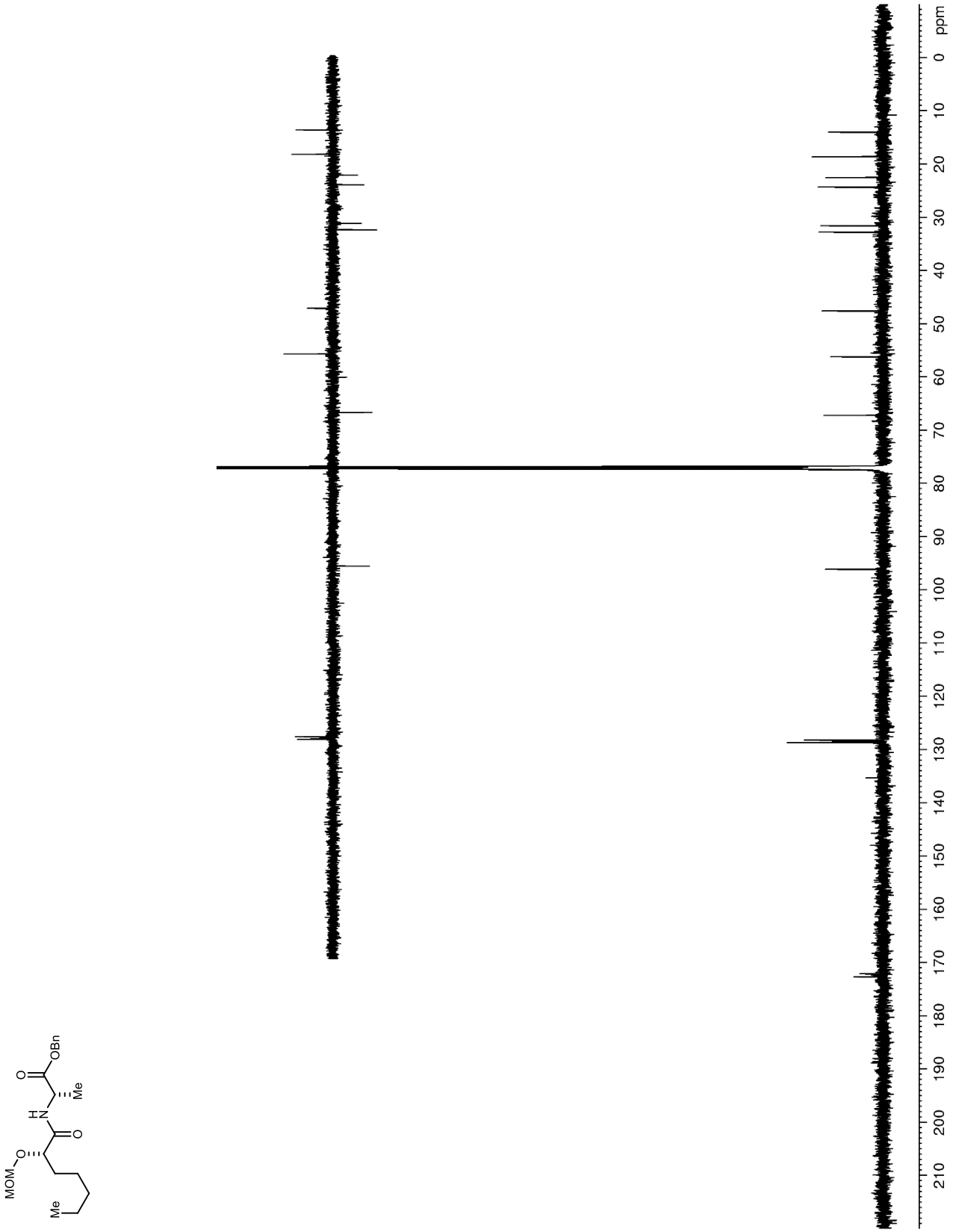


Figure 9. ^{1}H NMR (400 MHz, DMSO-d_6) of **5**

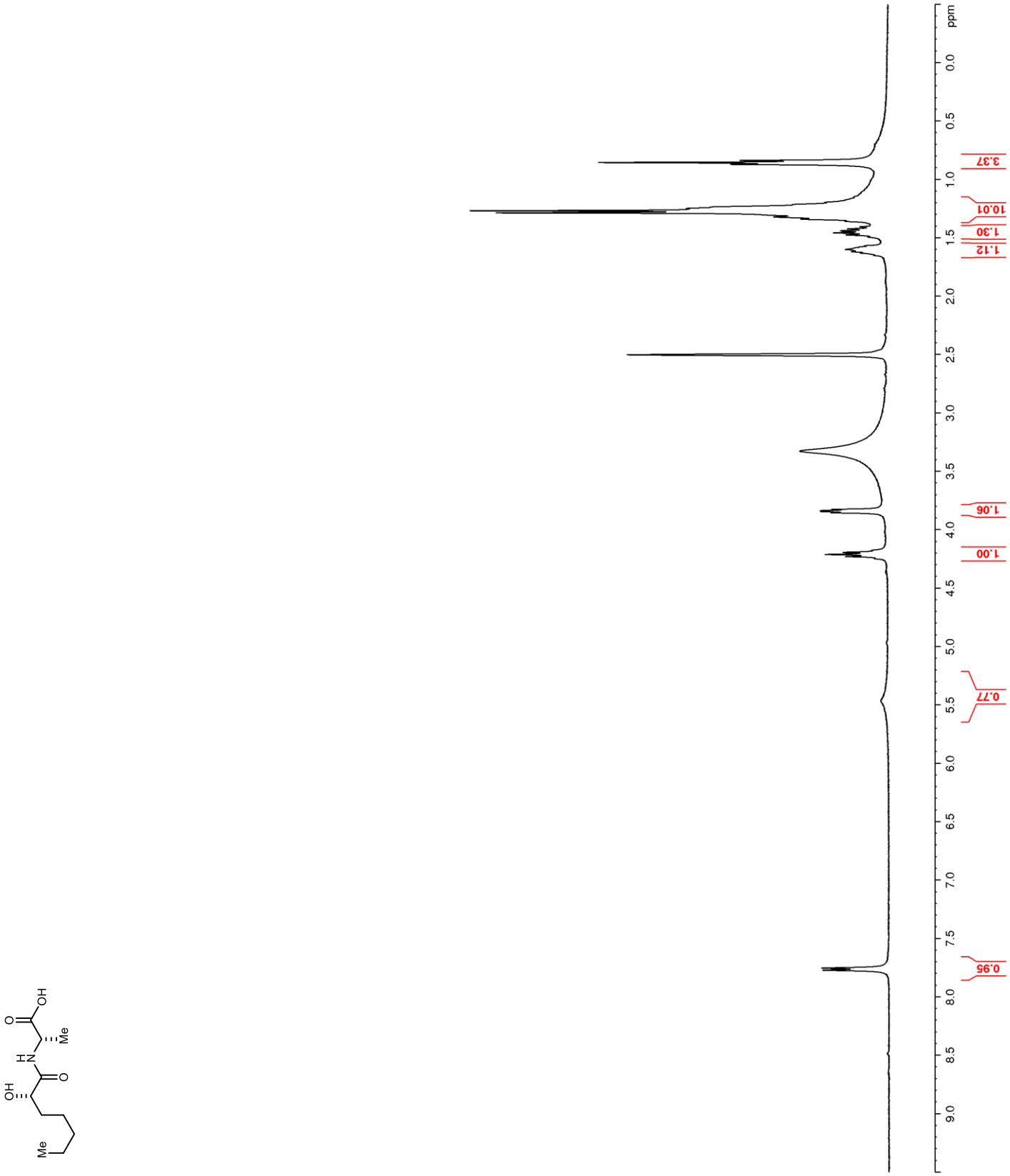


Figure 10. ^{13}C NMR (125 MHz, DMSO-d_6) of **5**

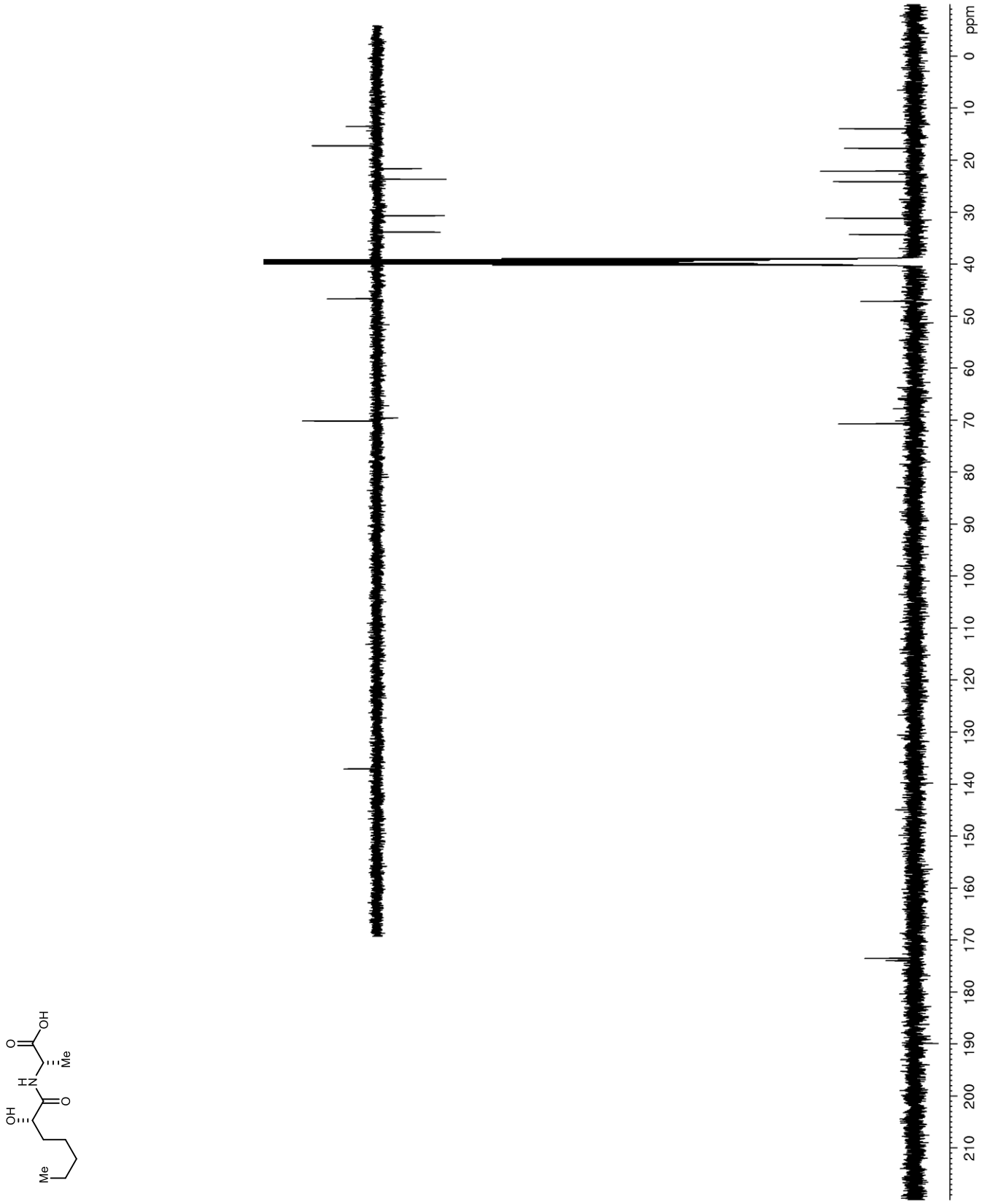


Figure 11. ^{1}H NMR (400 MHz, $CDCl_3$) of **6**

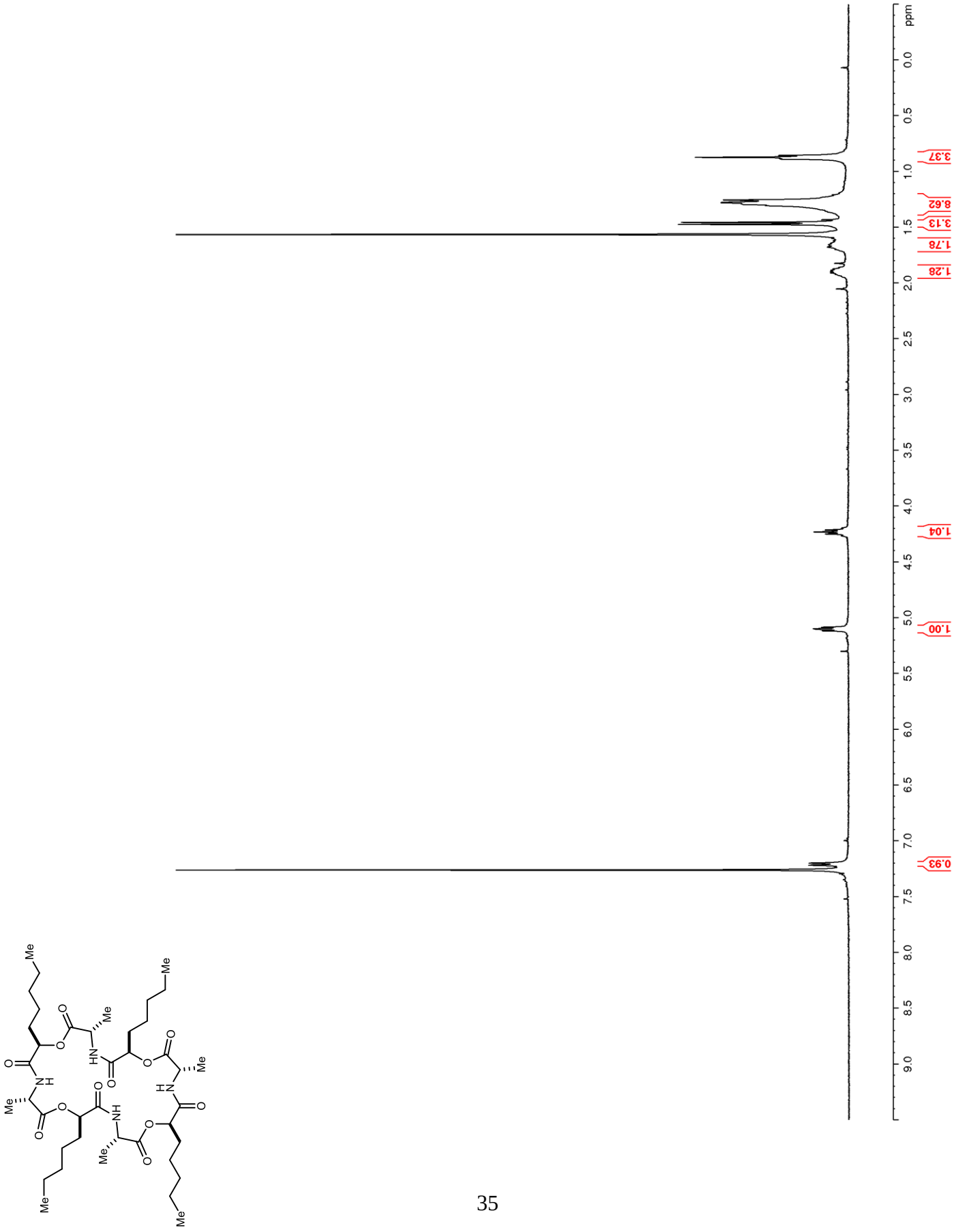
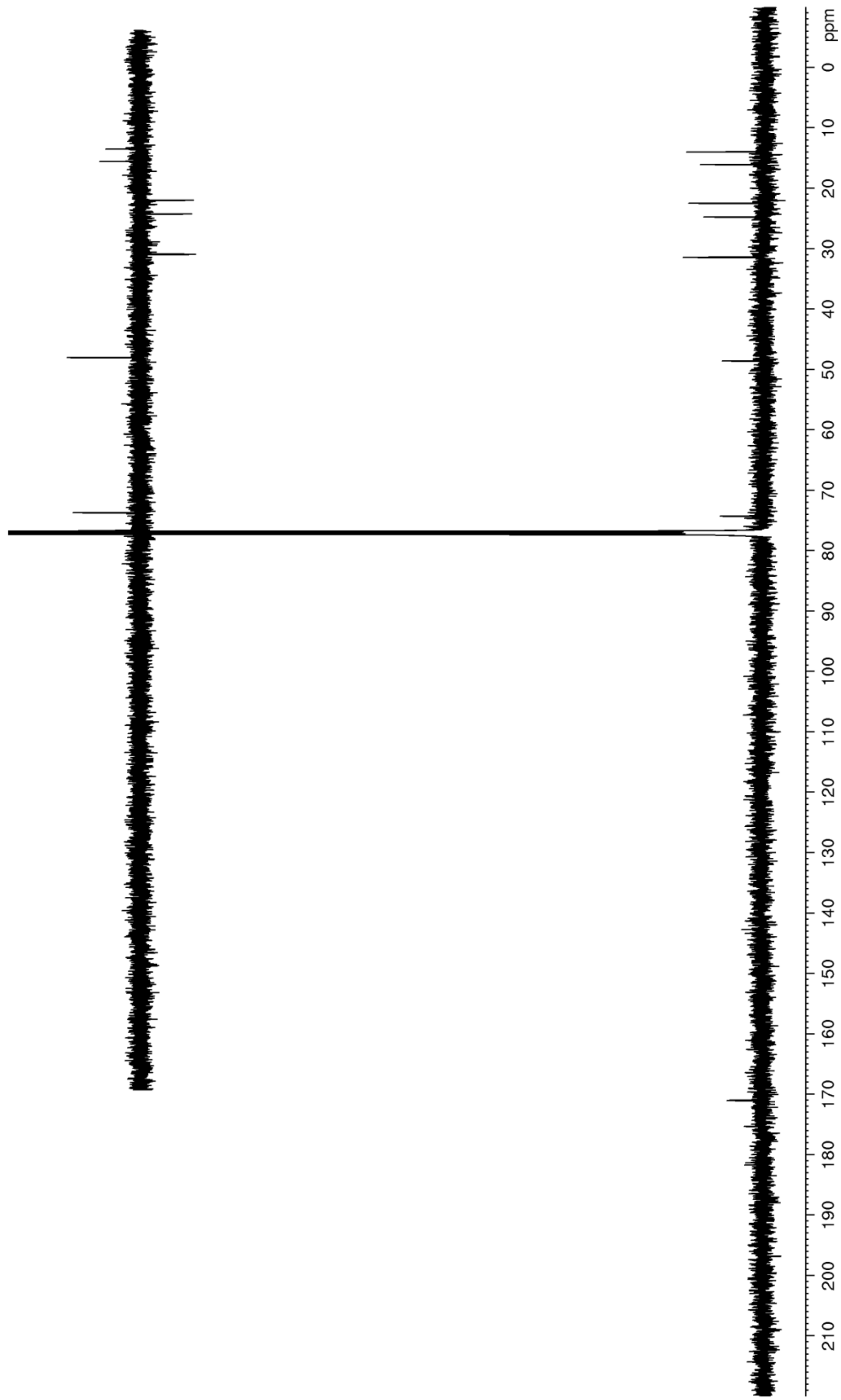


Figure 12. ^{13}C NMR (125 MHz, $CDCl_3$) of **6**



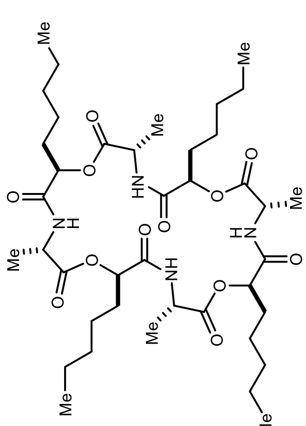


Figure 13. ^{1}H NMR (400 MHz, $CDCl_3$) of **7**

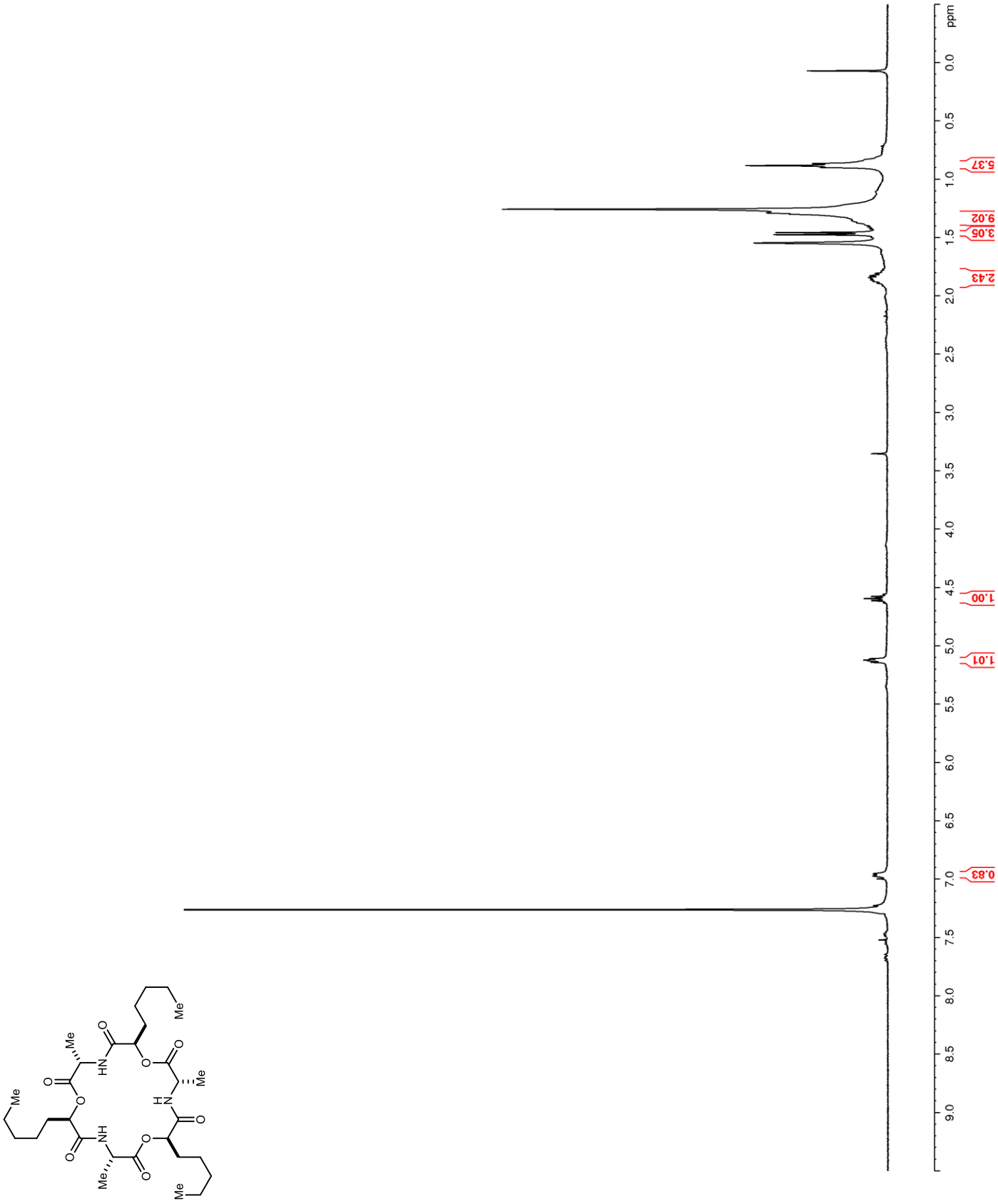


Figure 14. ^{13}C NMR (150 MHz, $CDCl_3$) of **7**

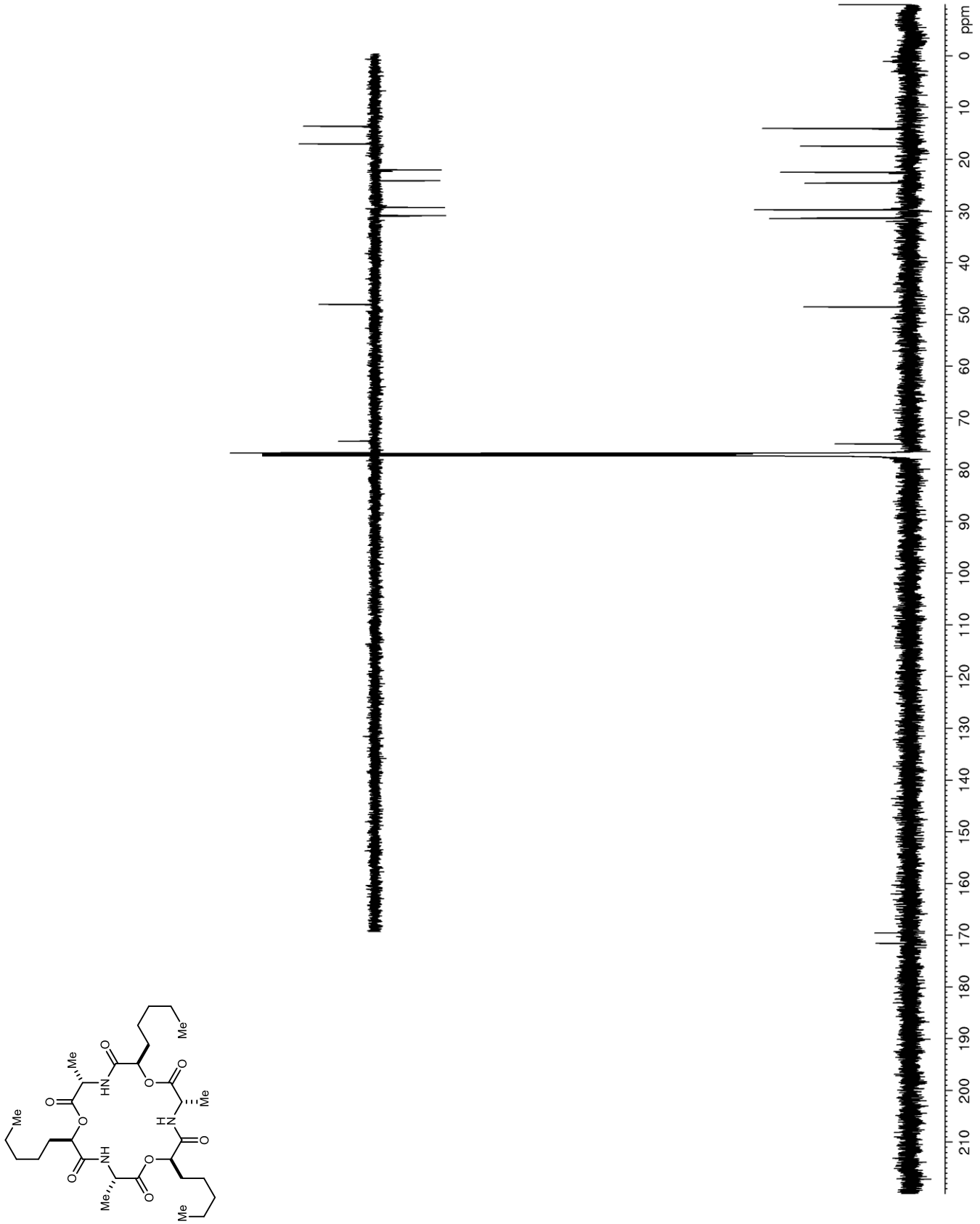


Figure 15. ^{1}H NMR (400 MHz, $CDCl_3$) of **8**

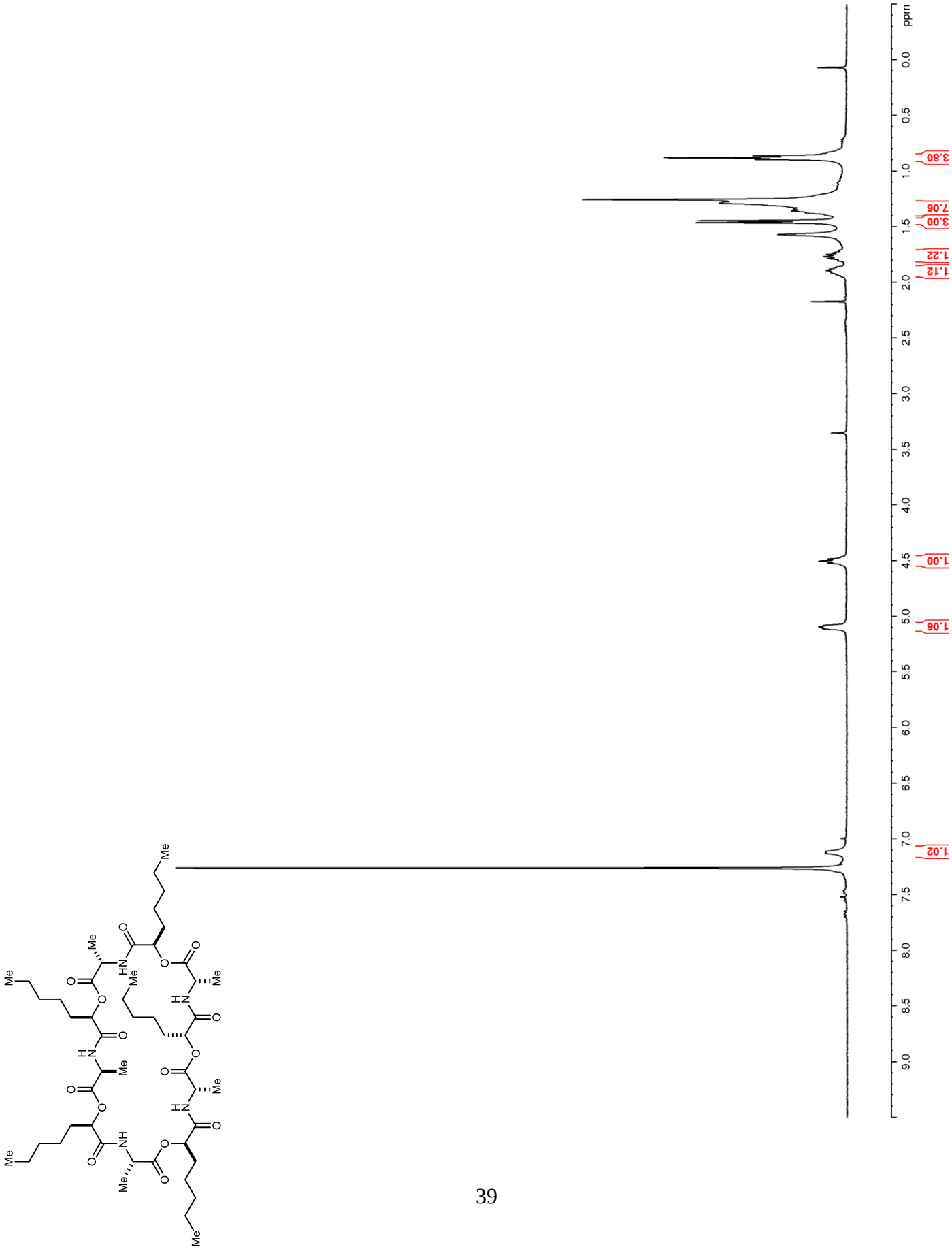


Figure 16. ^{13}C NMR (150 MHz, $CDCl_3$) of **8**

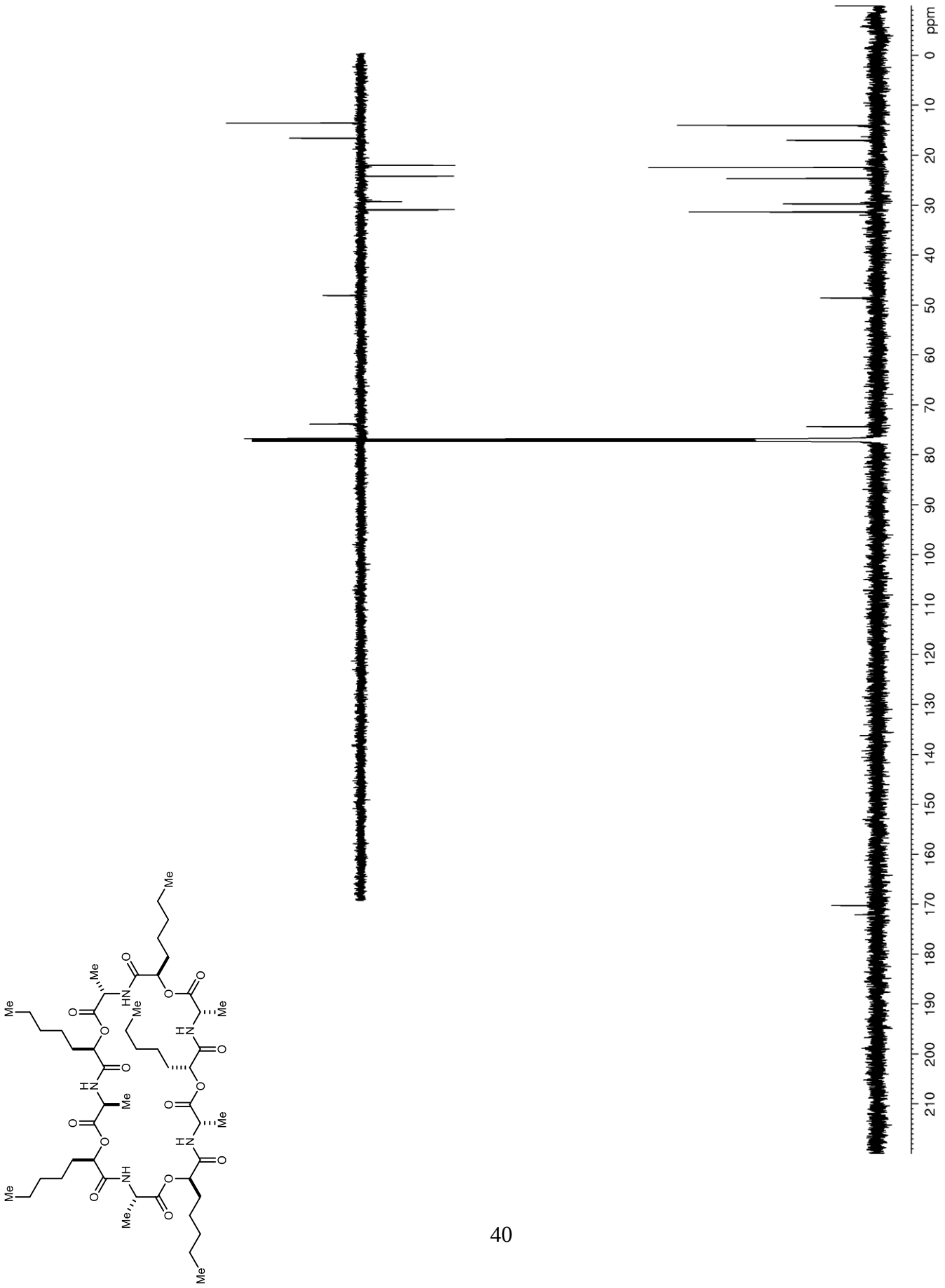


Figure 17. ^{1}H NMR (400 MHz, $CDCl_3$) of **9**

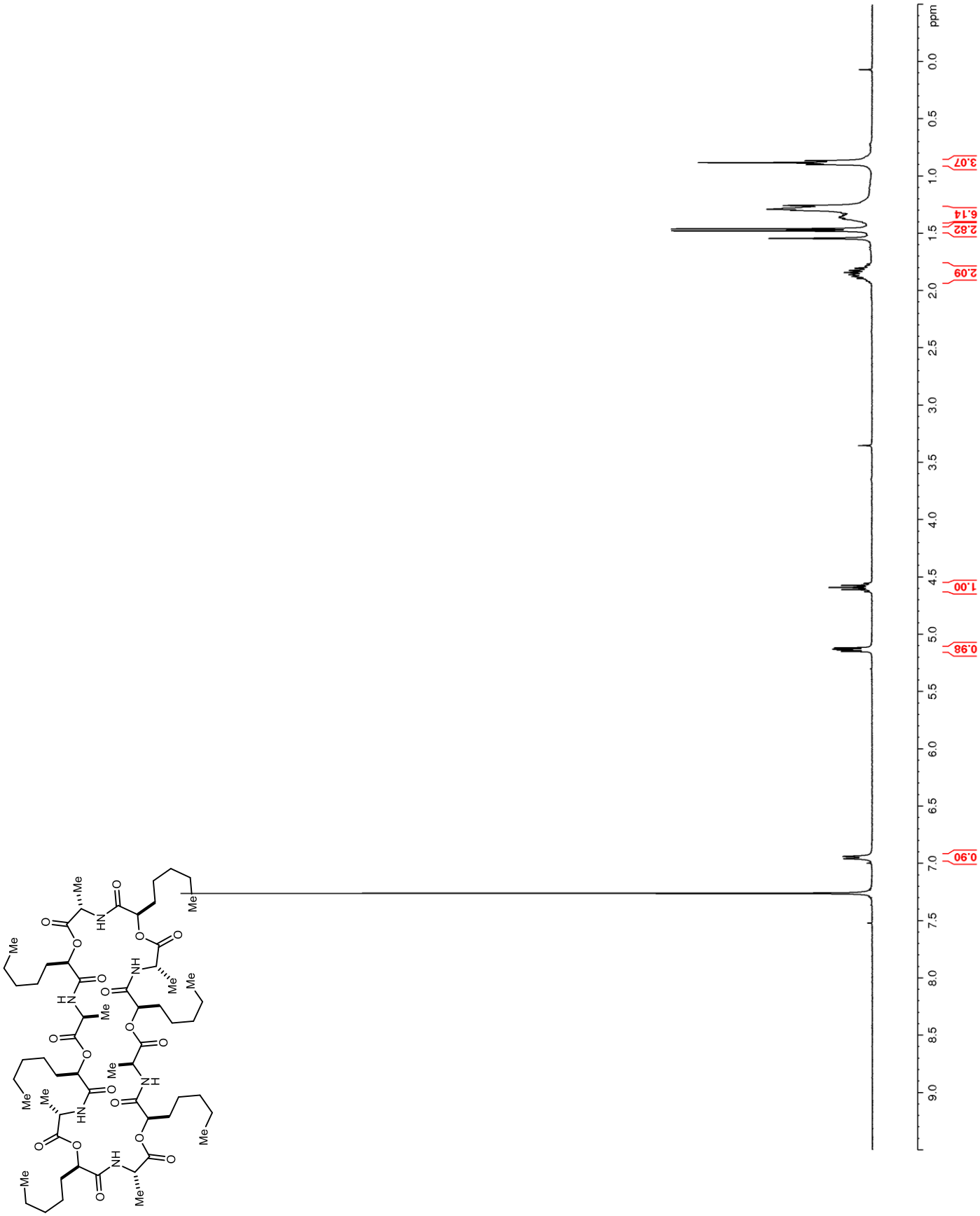


Figure 18. ^{13}C NMR (125 MHz, $CDCl_3$) of **9**

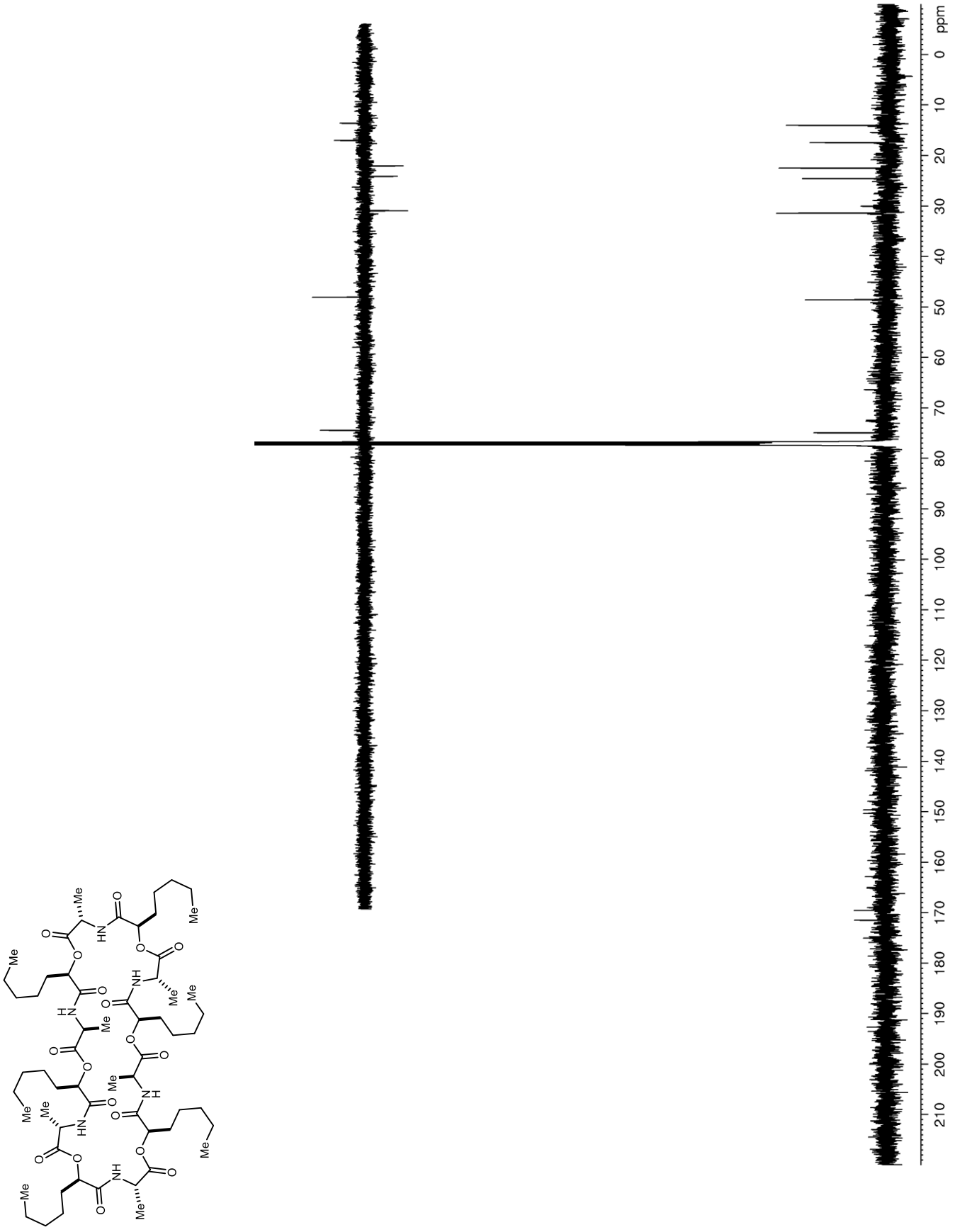


Figure 19. ^{1}H NMR (400 MHz, $CDCl_3$) of **10**

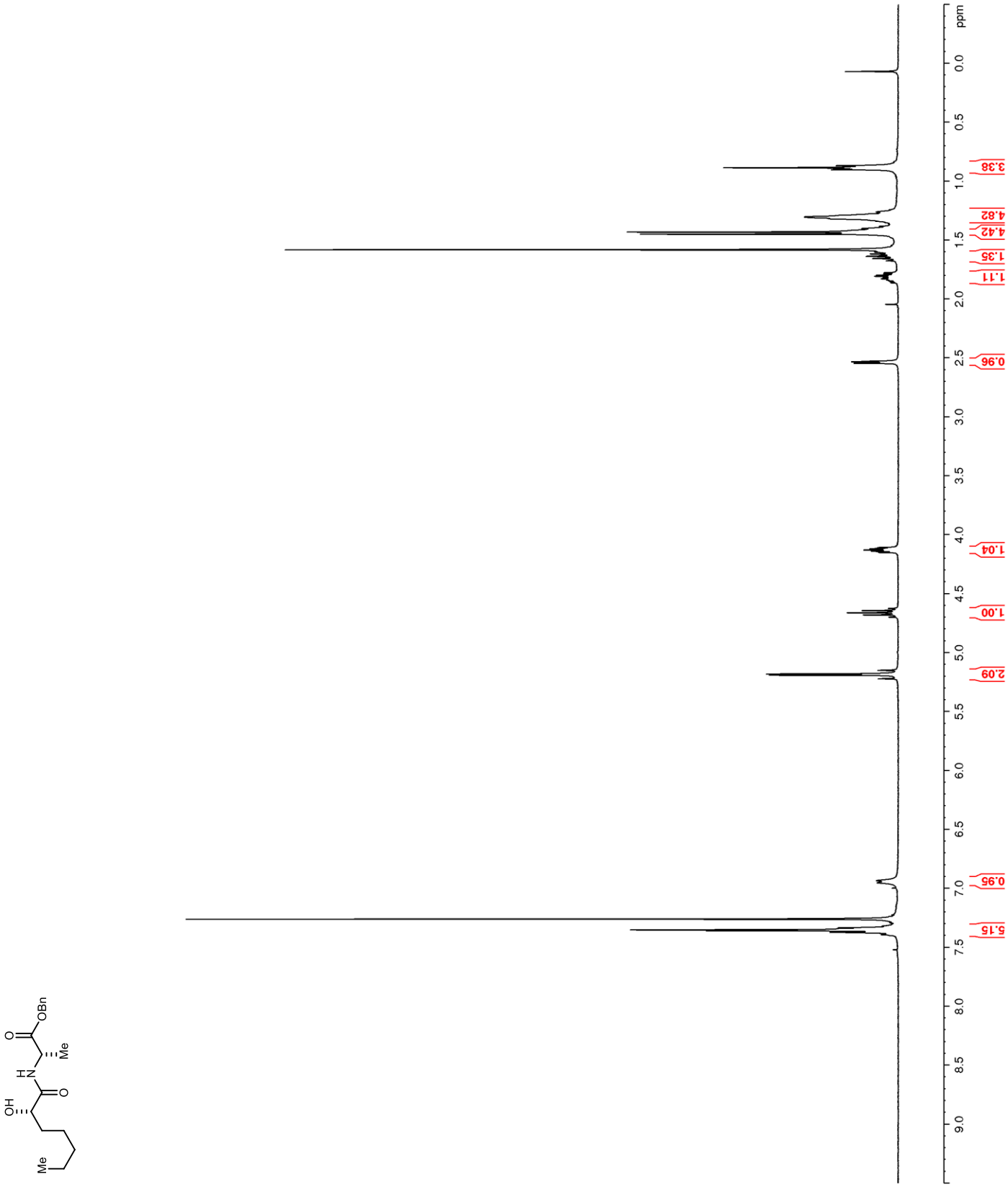


Figure 20. ^{13}C NMR (125 MHz, $CDCl_3$) of **10**

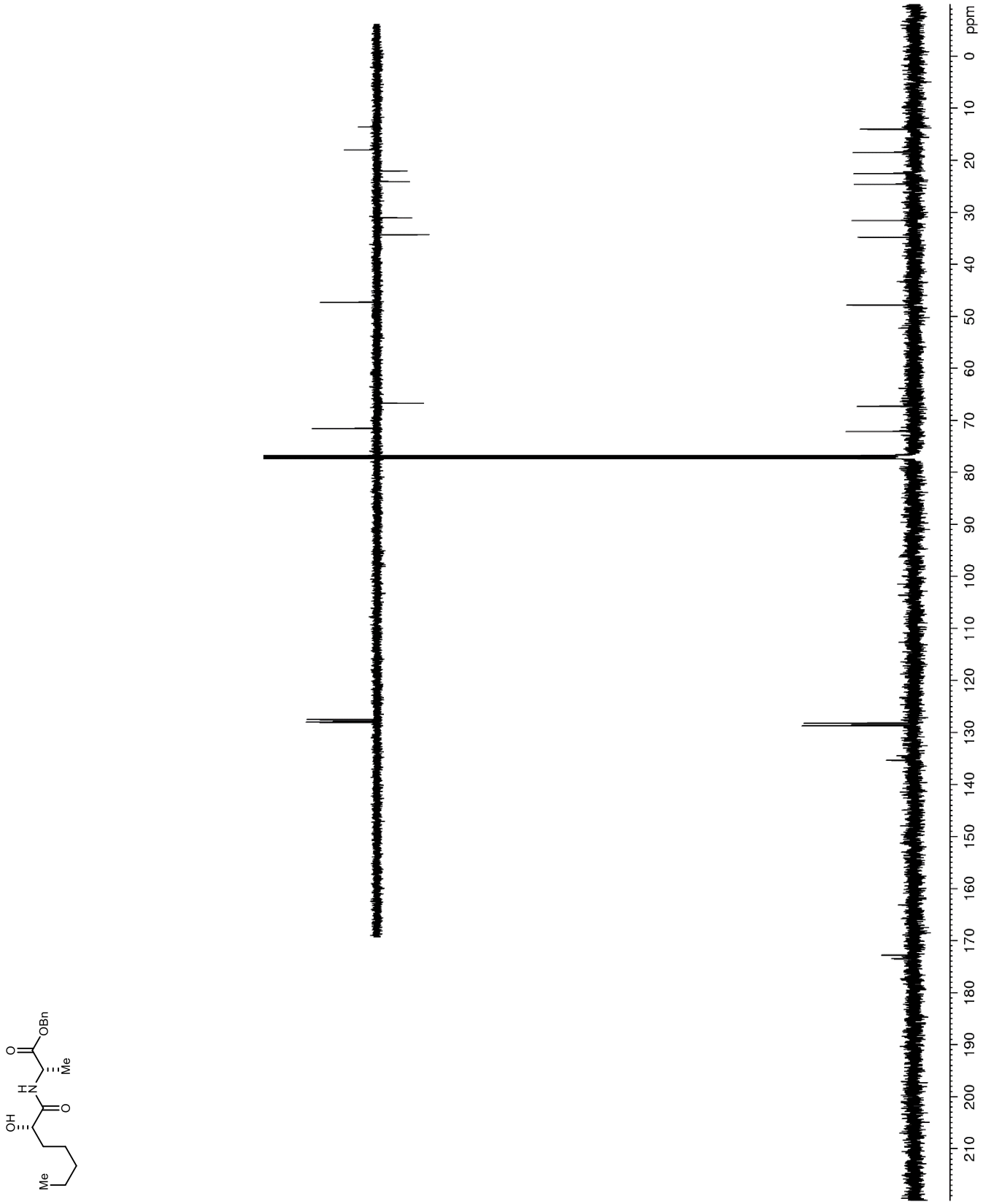


Figure 21. ^{1}H NMR (400 MHz, $CDCl_3$) of **11**

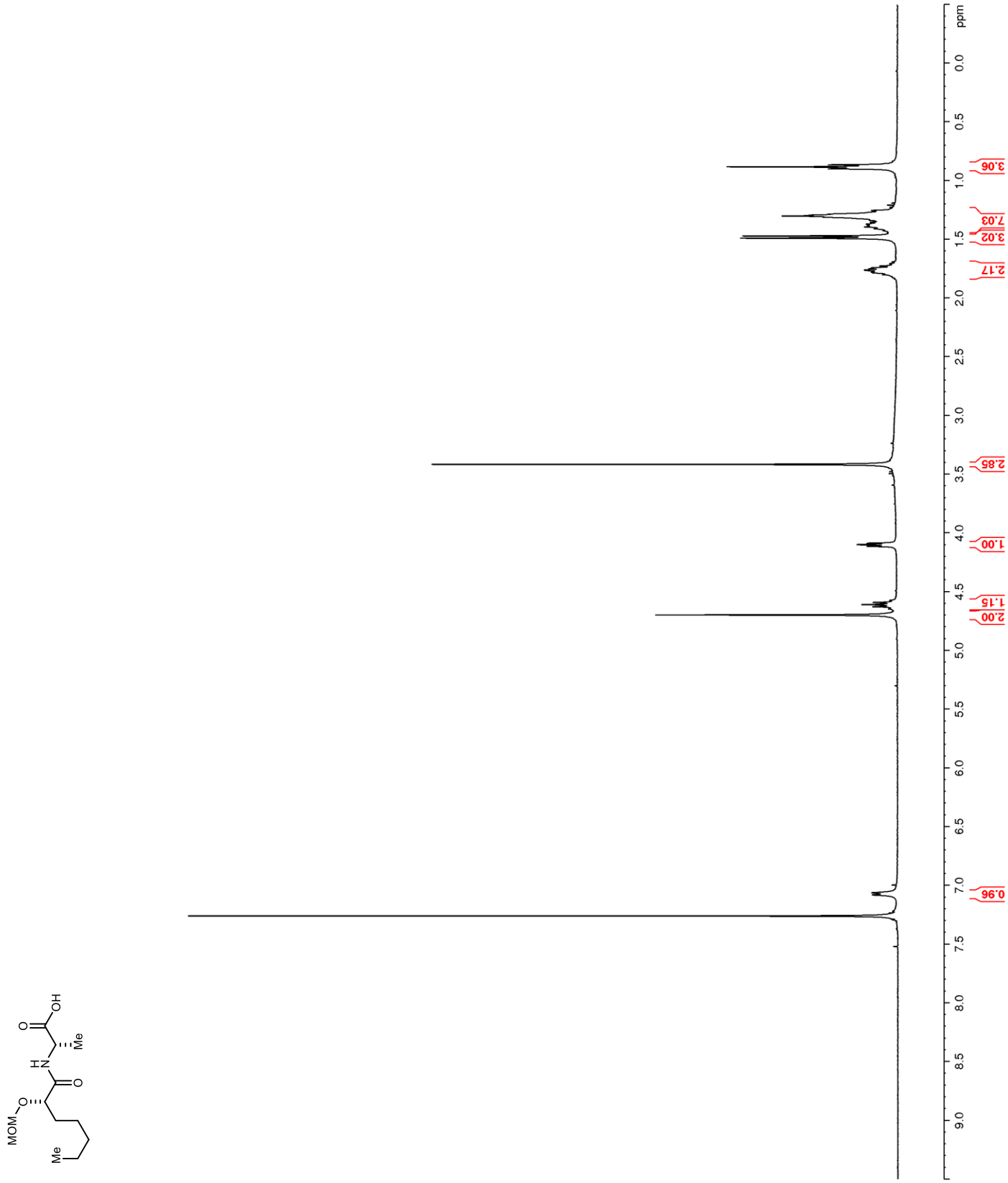


Figure 22. ^{13}C NMR (125 MHz, $CDCl_3$) of **11**

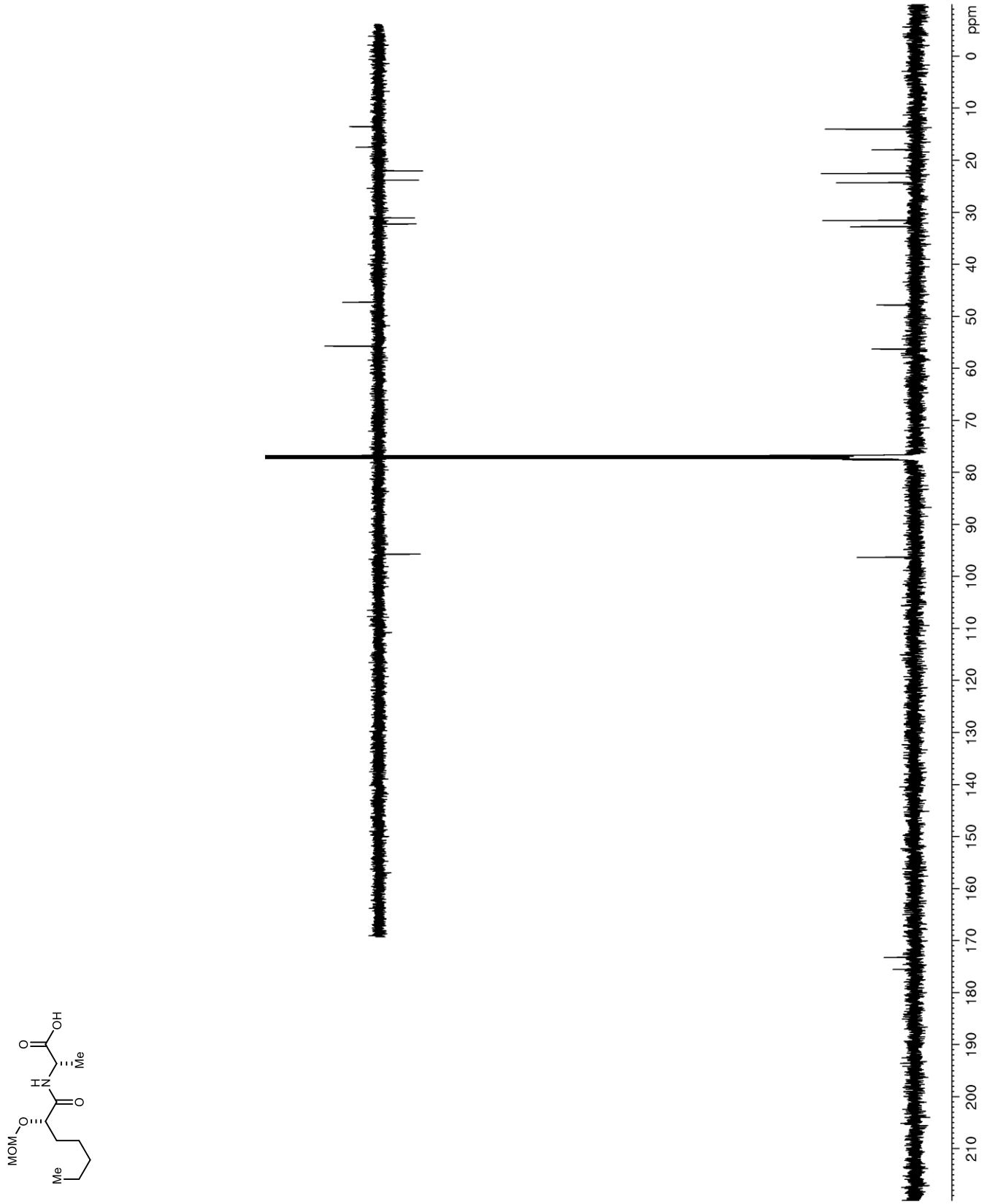


Figure 23. ^{1}H NMR (400 MHz, $CDCl_3$) of **12**

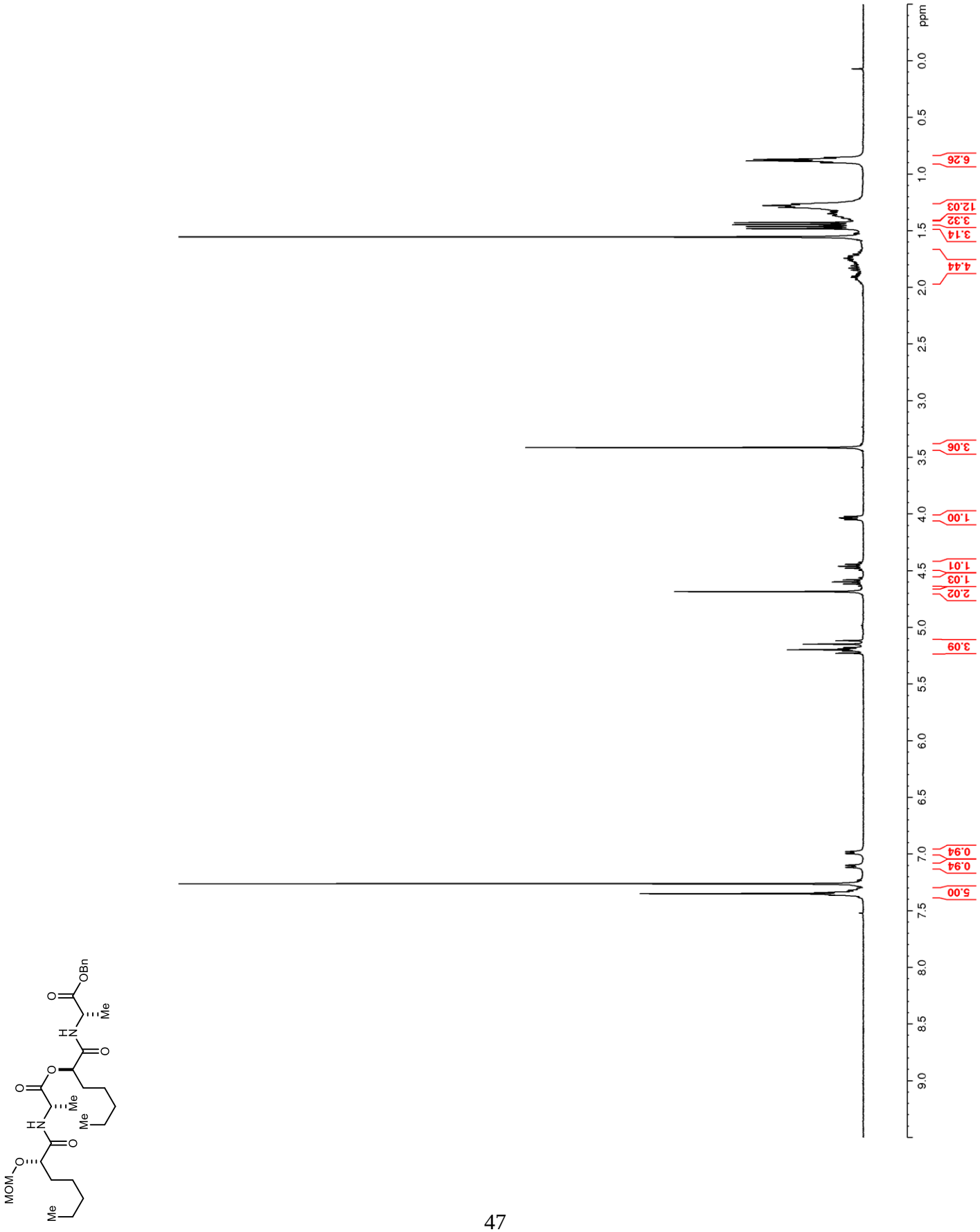


Figure 24. ^{13}C NMR (125 MHz, $CDCl_3$) of **12**

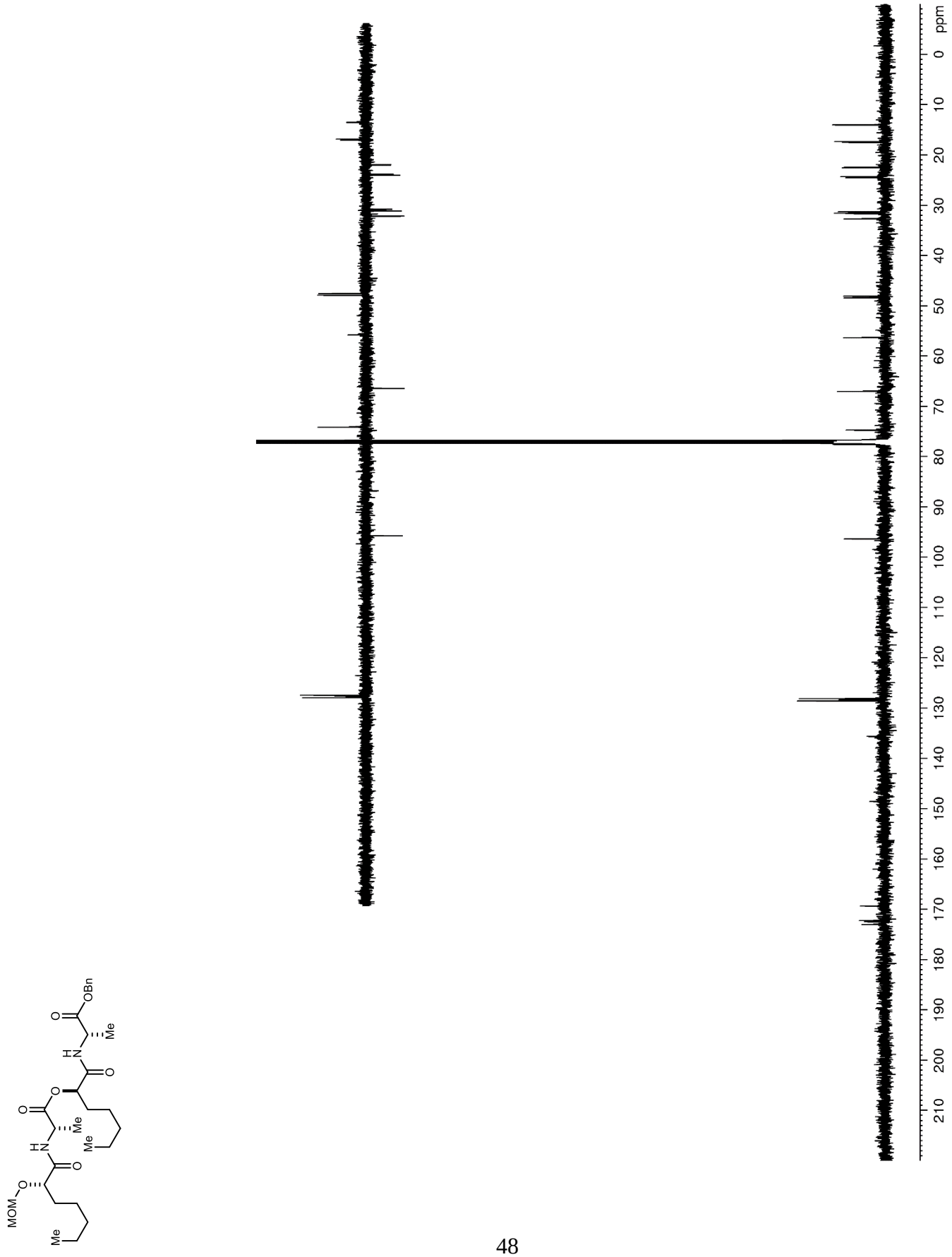


Figure 25. ^{1}H NMR (400 MHz, $CDCl_3$) of **13**

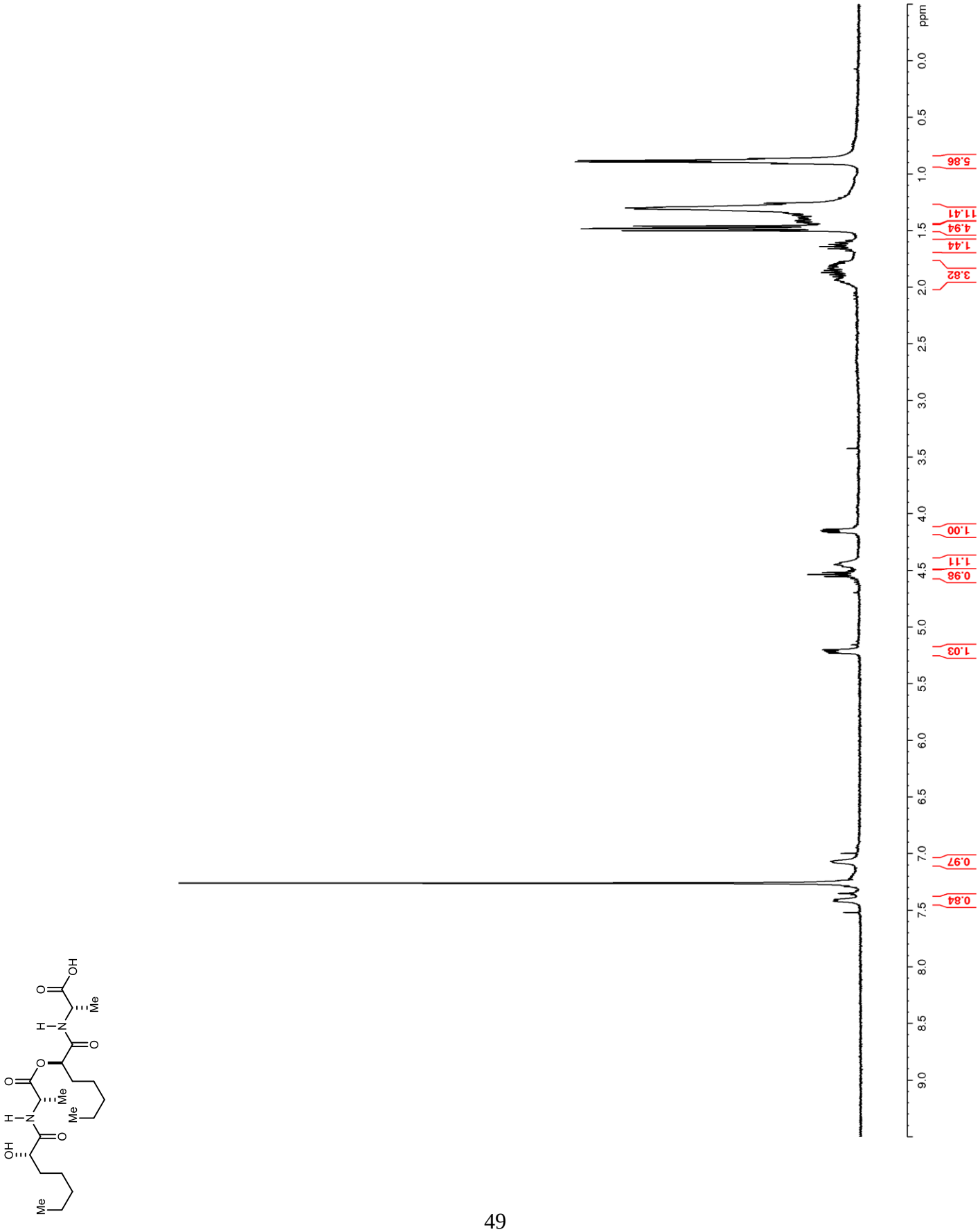
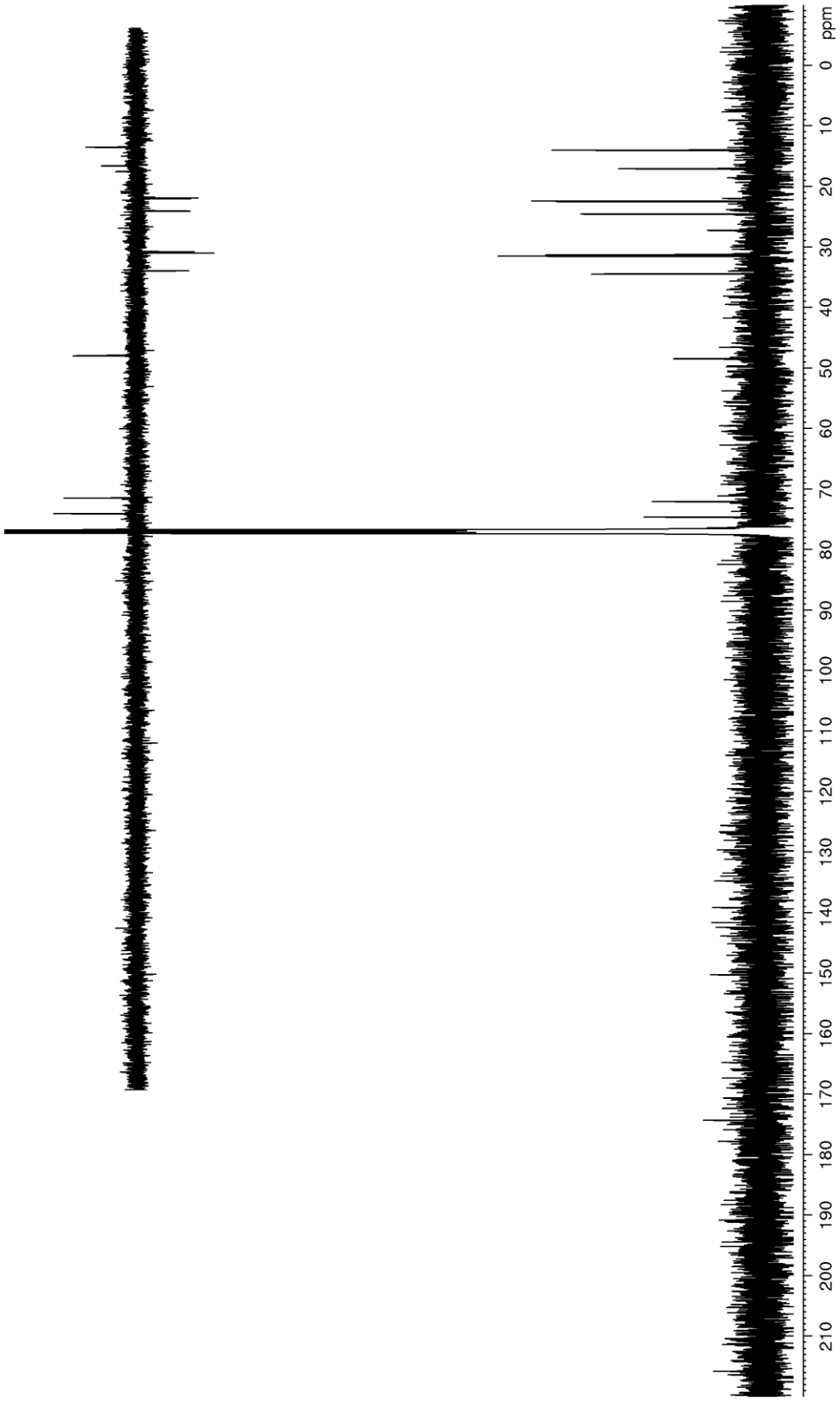


Figure 26. ^{13}C NMR (125 MHz, $CDCl_3$) of **13**



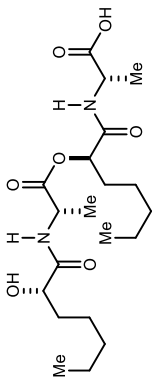


Figure 27. ^{1}H NMR (400 MHz, $CDCl_3$) of **14**

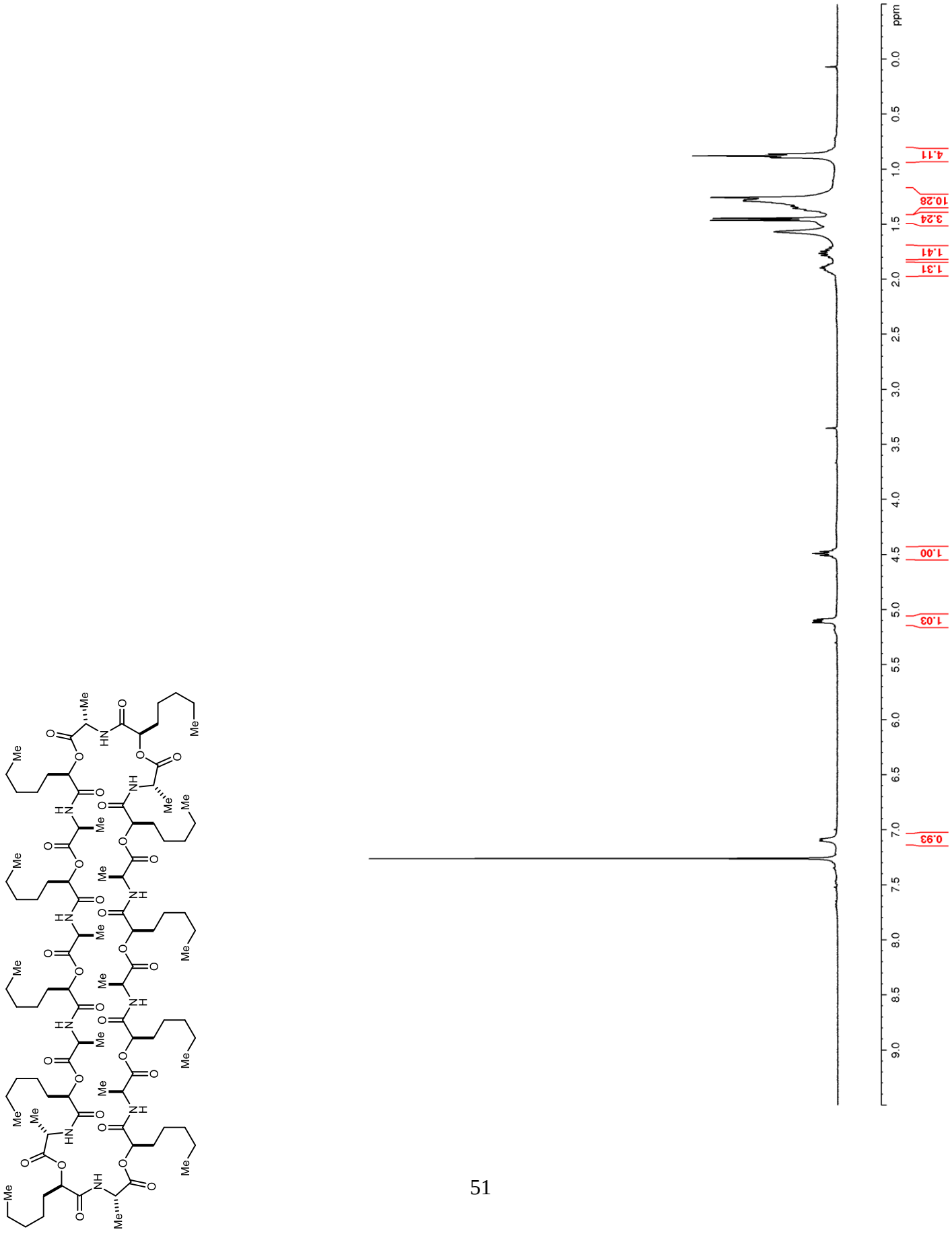


Figure 28. ^{13}C NMR (125 MHz, $CDCl_3$) of **14**

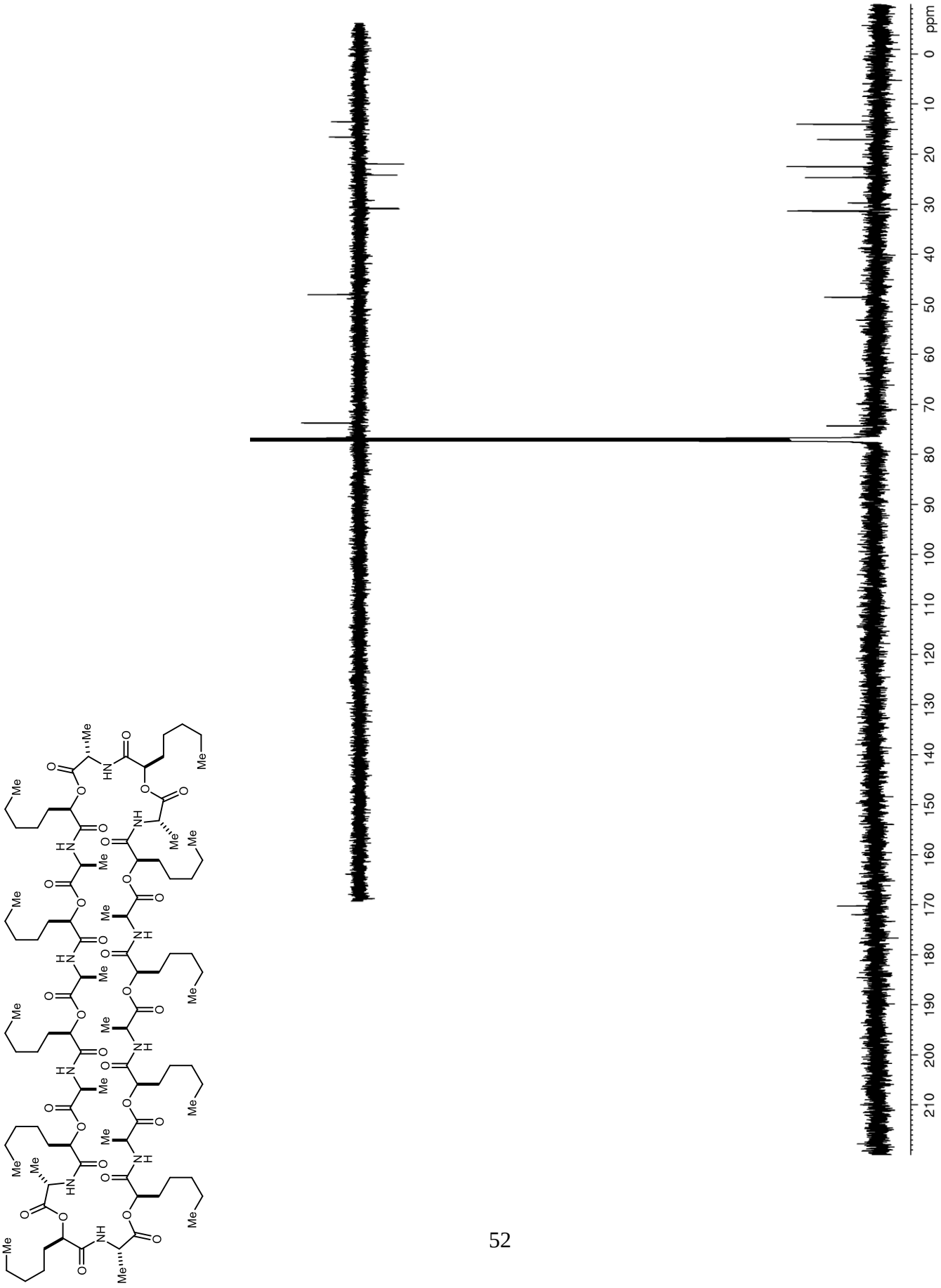


Figure 29. ^{1}H NMR (400 MHz, DMSO-d_6) of **15**

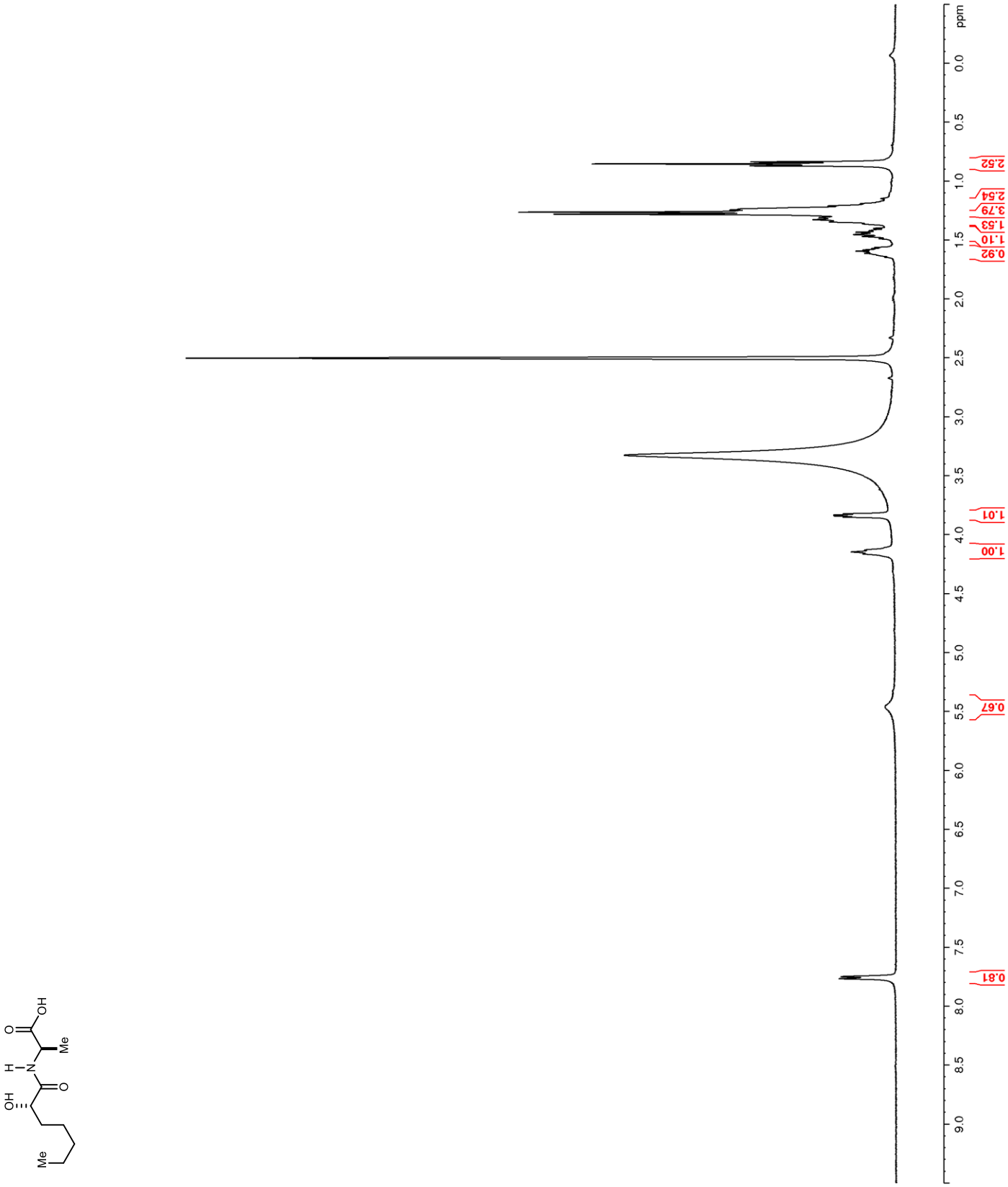
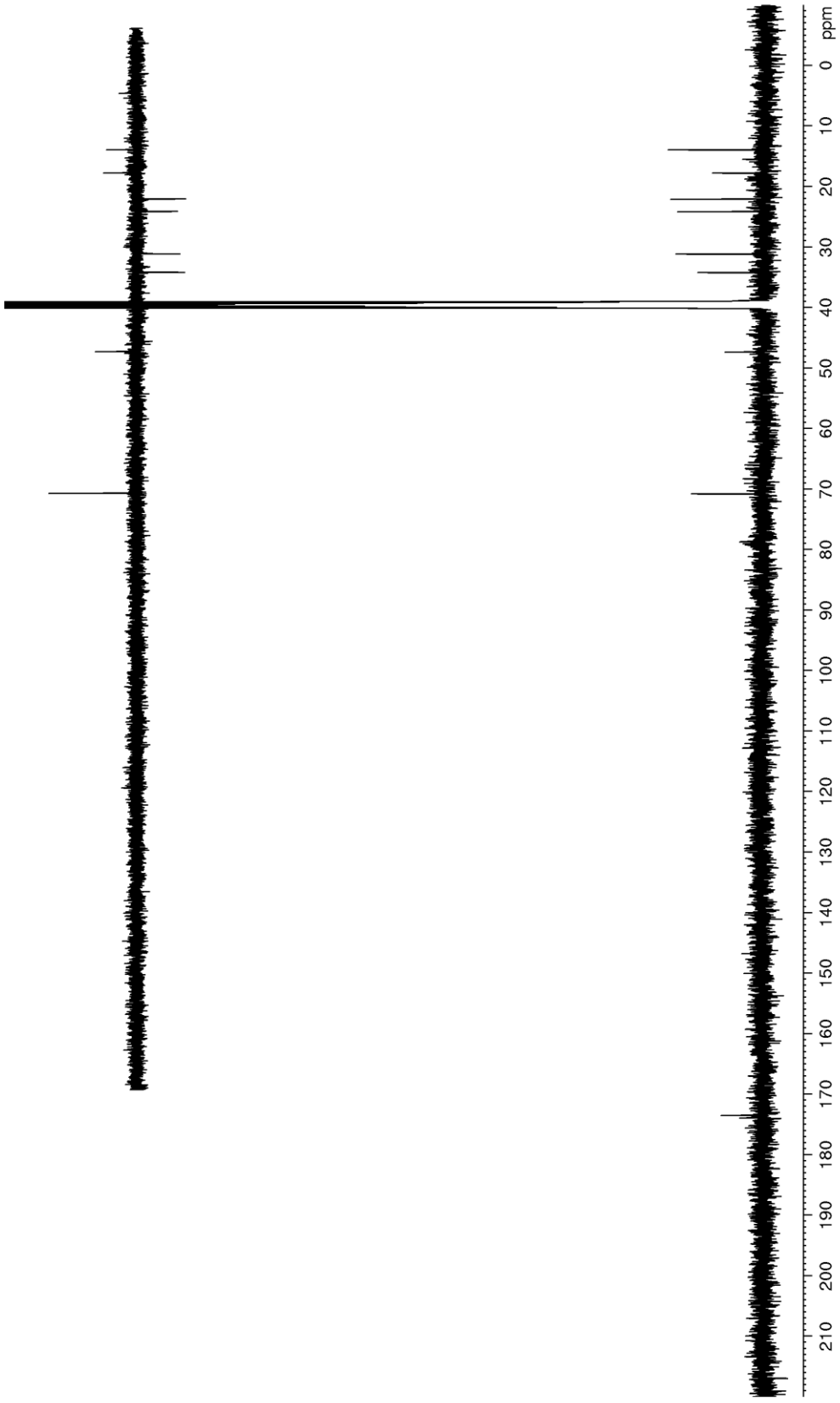


Figure 30. ^{13}C NMR (125 MHz, DMSO-d_6) of **15**



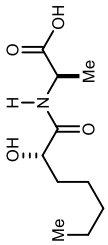


Figure 31. ^{1}H NMR (400 MHz, $CDCl_3$) of **16**

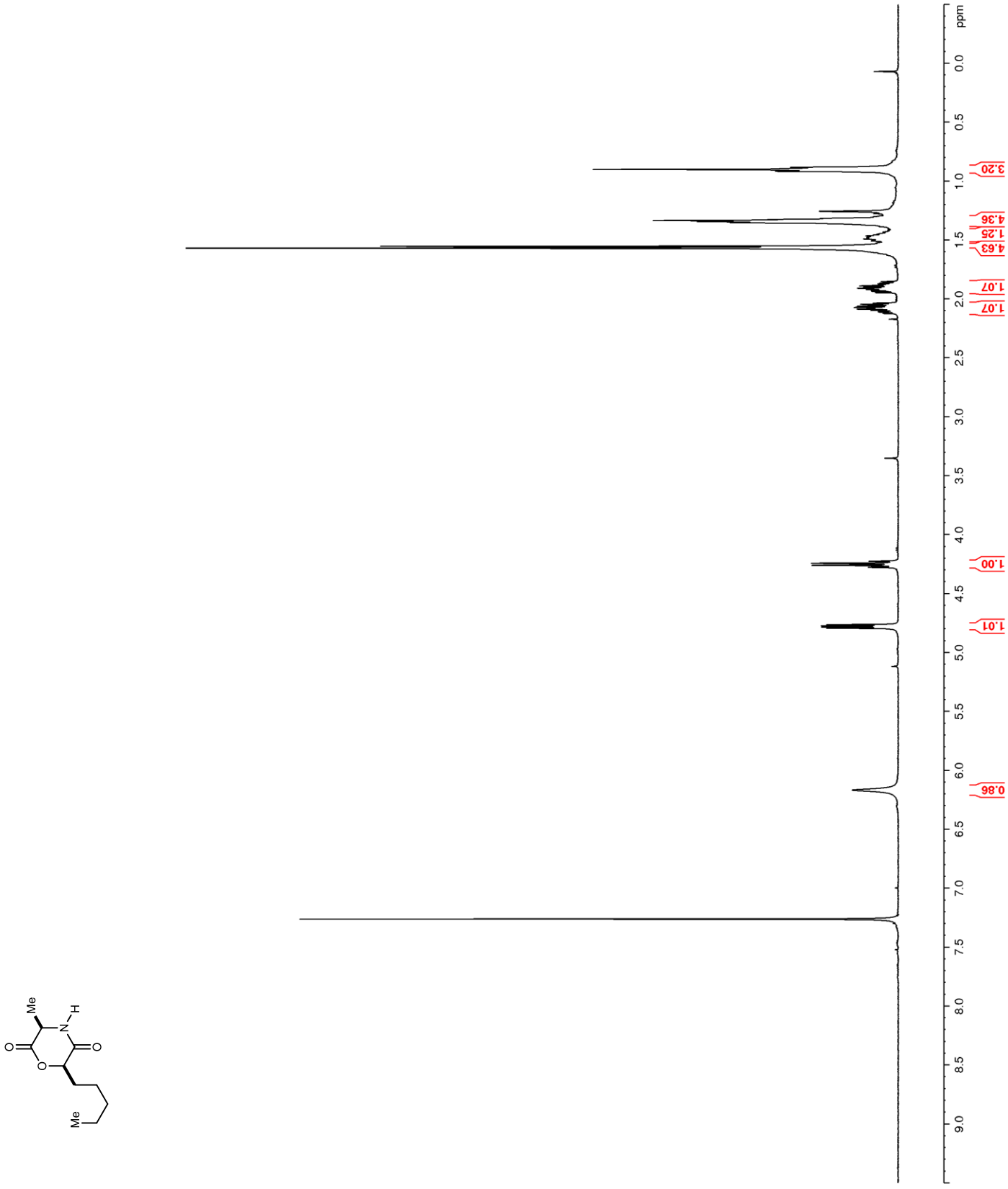
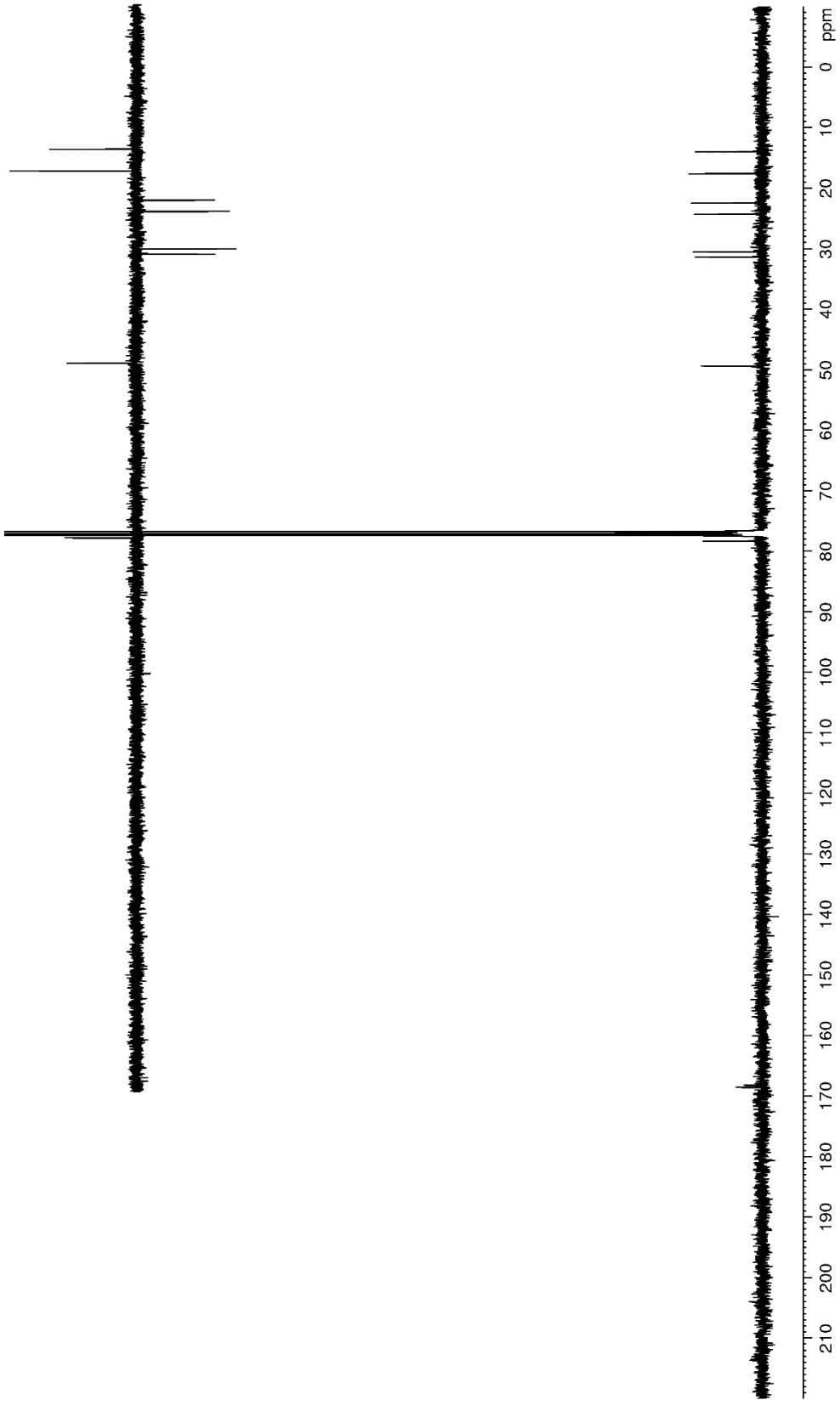


Figure 32. ^{13}C NMR (100 MHz, $CDCl_3$) of **16**



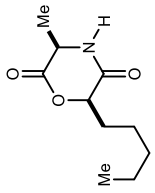


Figure 33. ^{1}H NMR (400 MHz, $CDCl_3$) of **17**

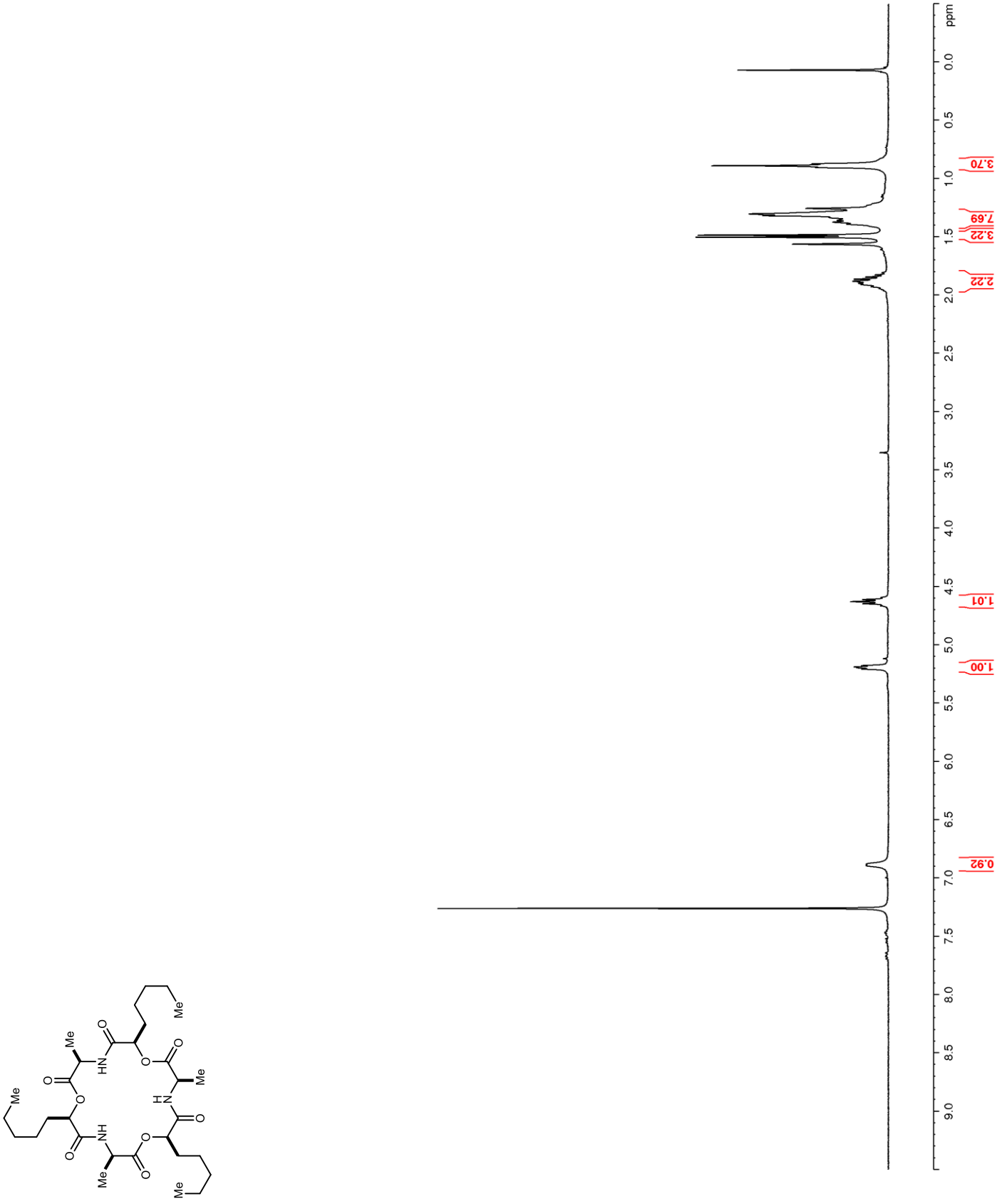


Figure 34. ^{13}C NMR (150 MHz, $CDCl_3$) of **17**

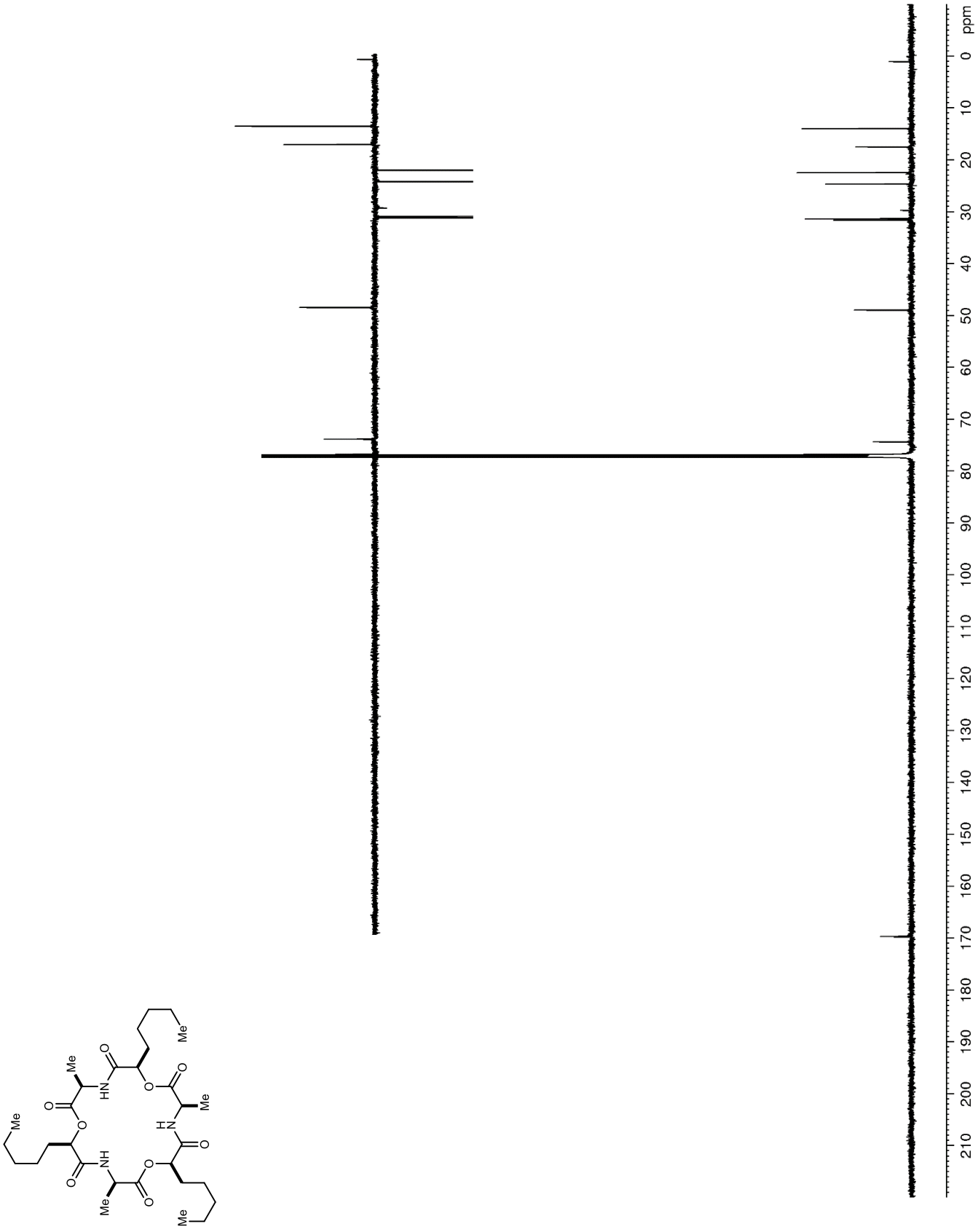
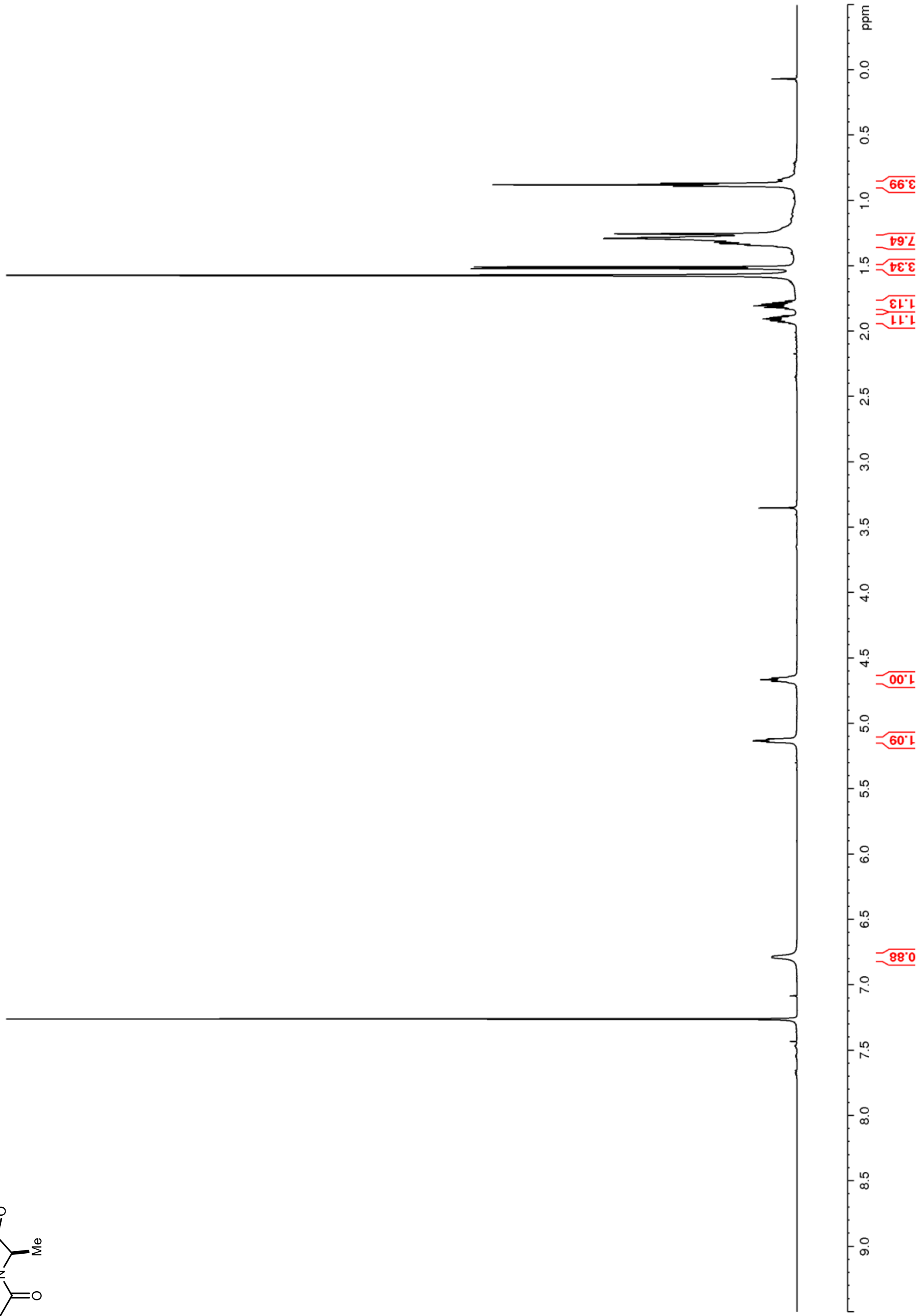


Figure 35. ^{1}H NMR (600 MHz, $CDCl_3$) of **18**



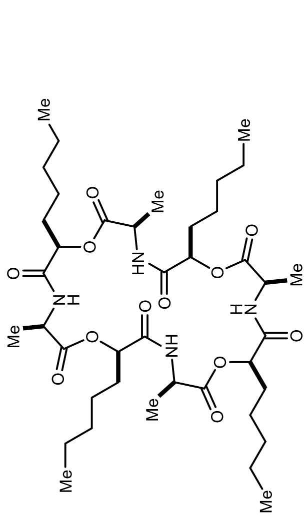


Figure 36. ^{13}C NMR (150 MHz, $CDCl_3$) of **18**

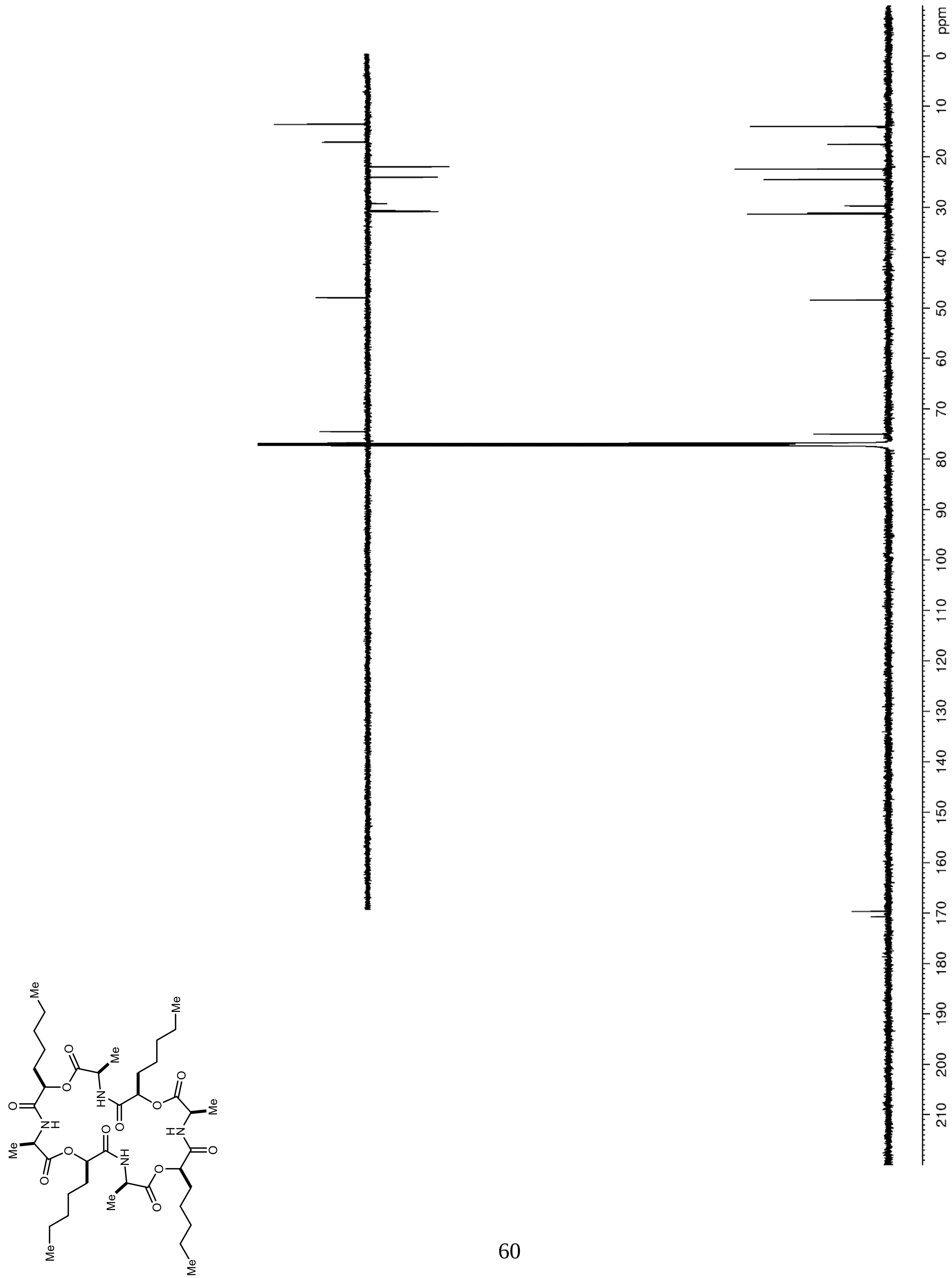


Figure 37. ^{1}H NMR (400 MHz, $CDCl_3$) of **19**

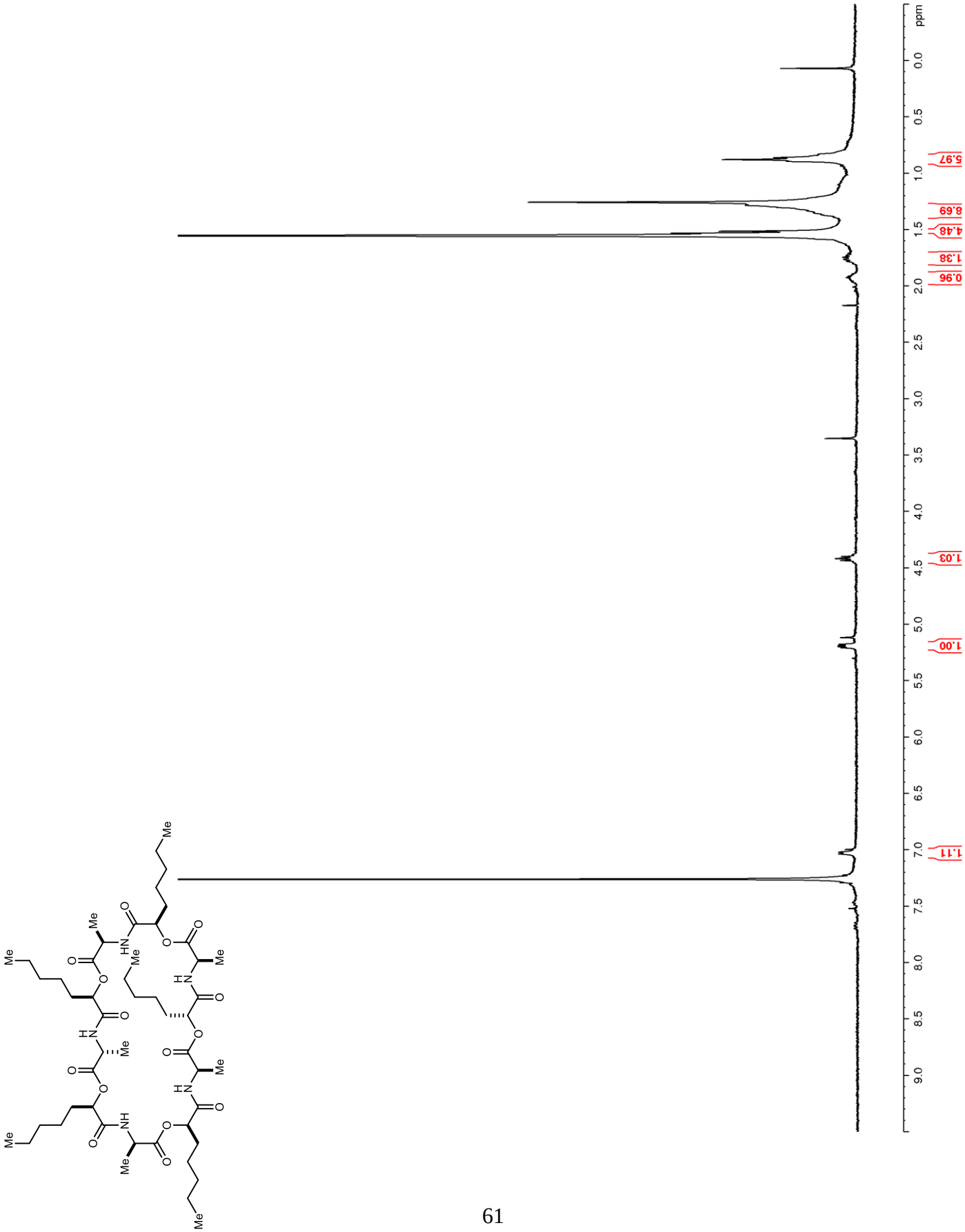


Figure 38. ^{13}C NMR (150 MHz, $CDCl_3$) of **19**

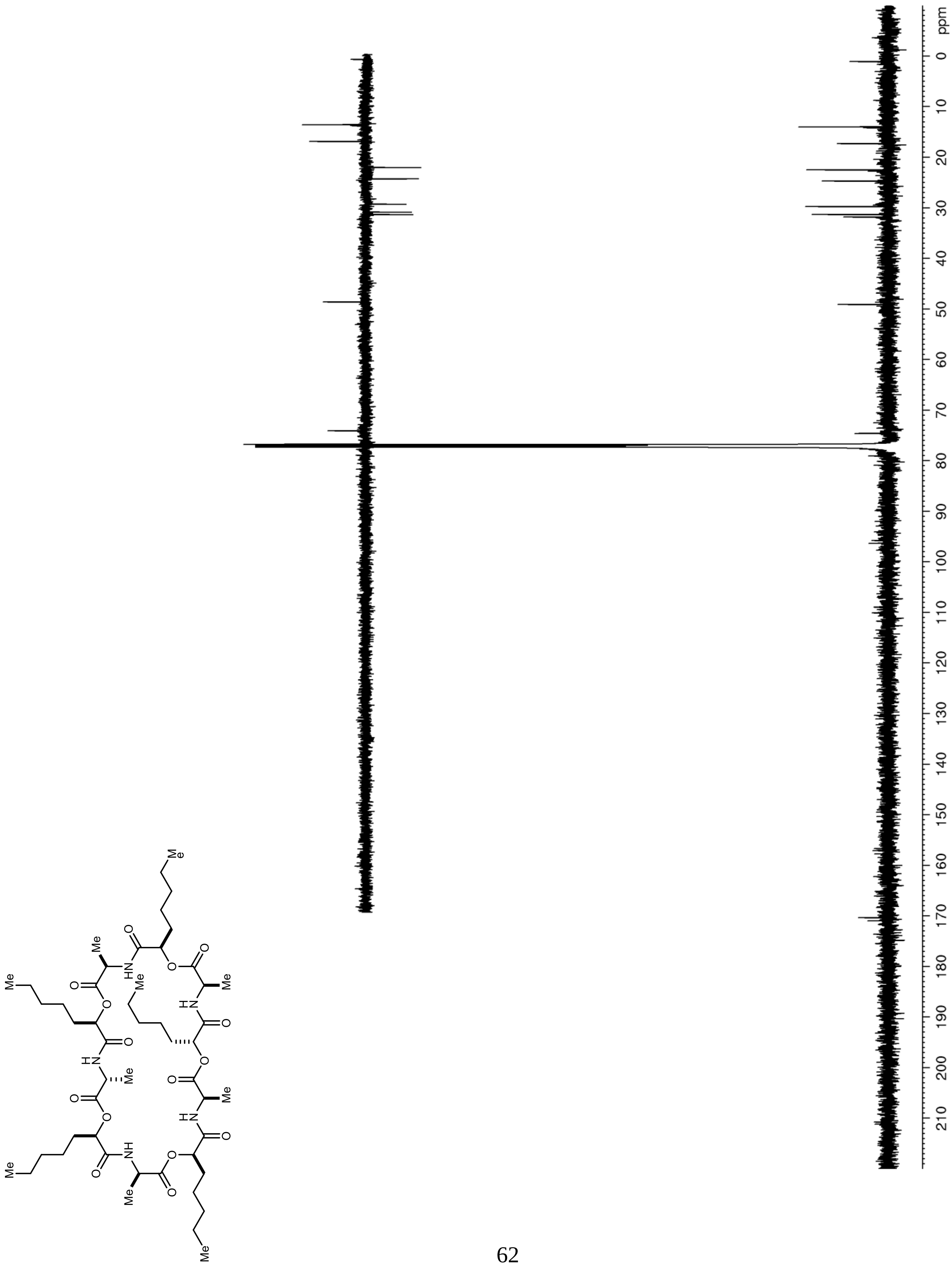


Figure 39. ^{1}H NMR (400 MHz, DMSO-d_6) of **20**

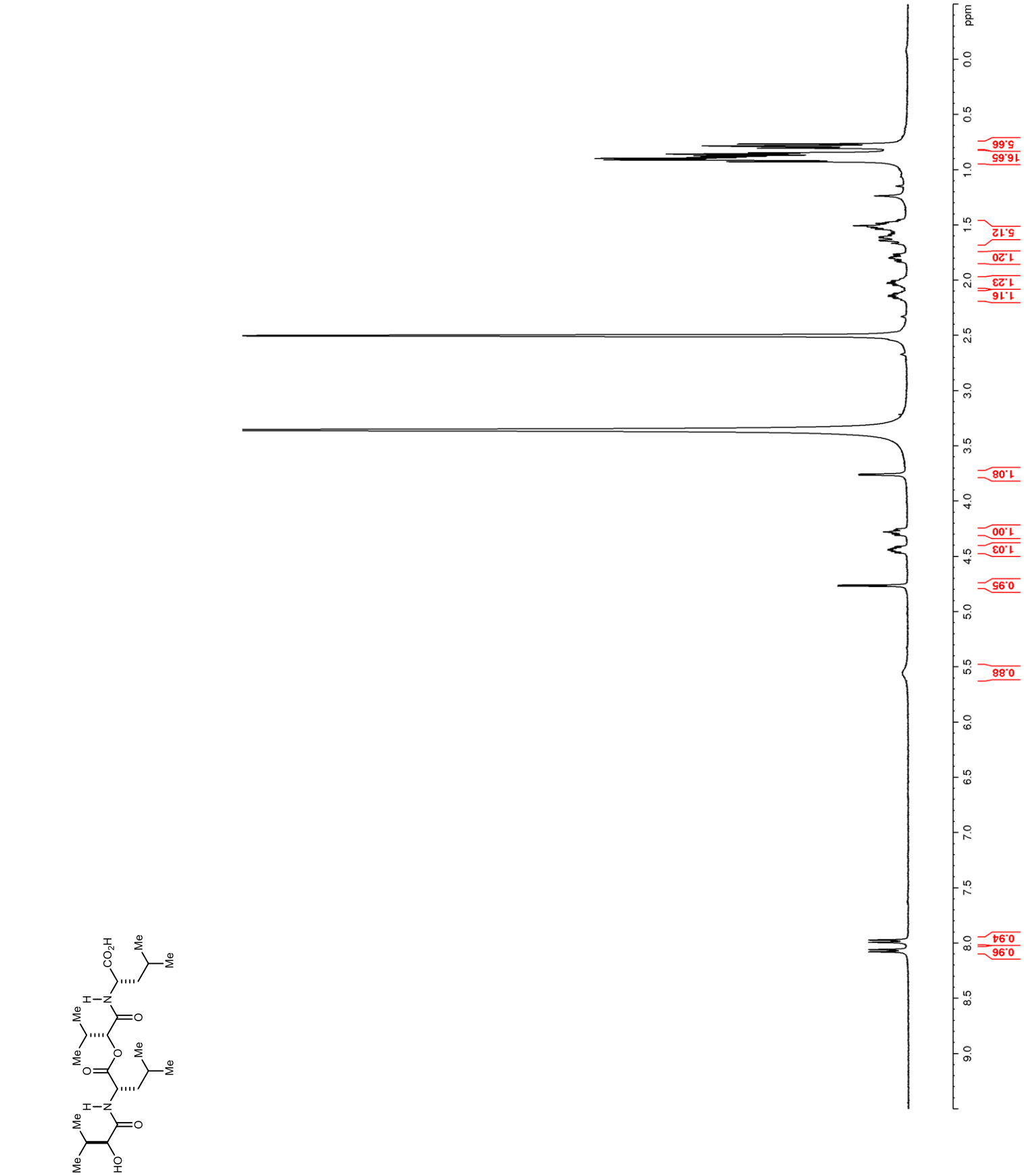


Figure 40. ^{13}C NMR (125 MHz, DMSO-d_6) of **20**

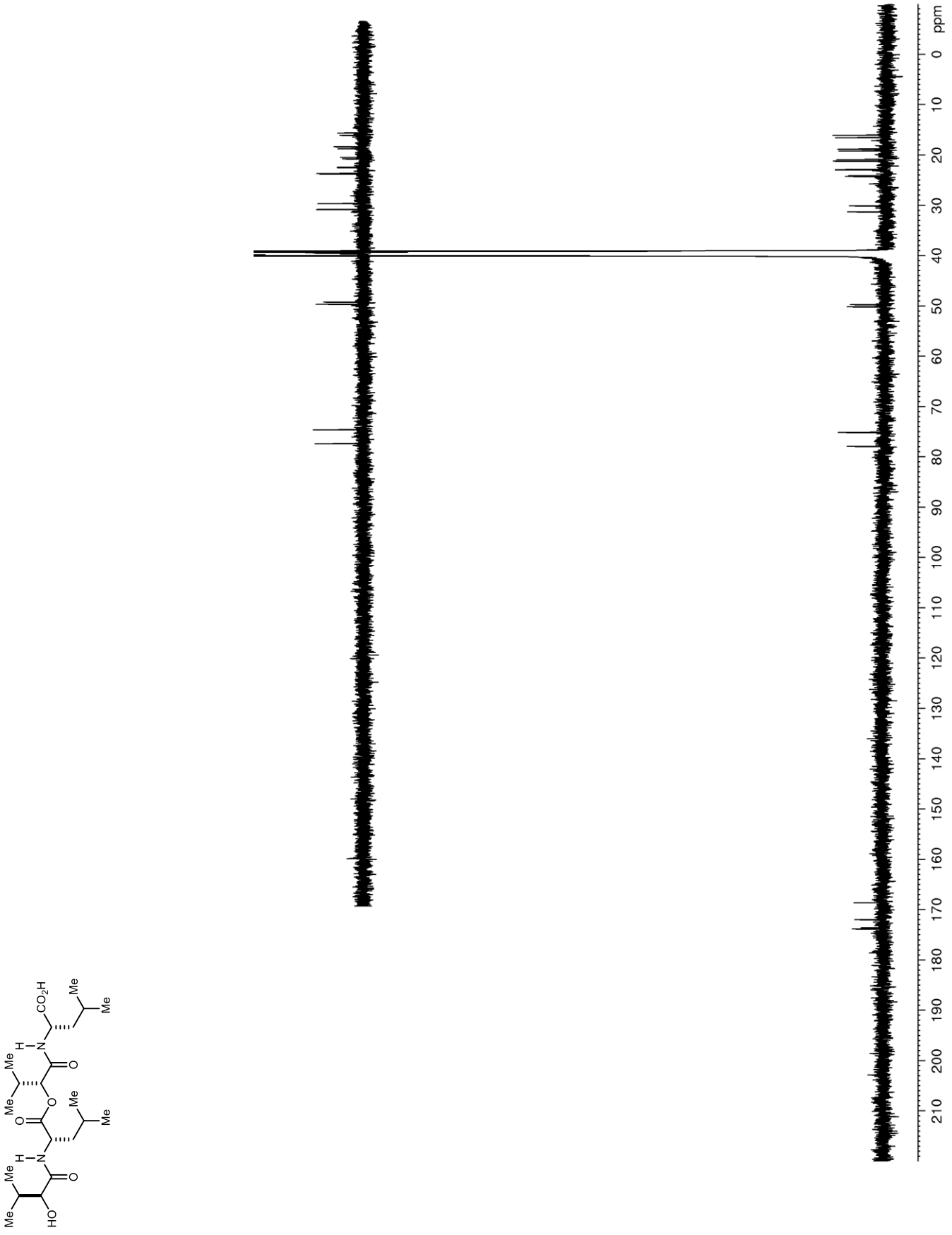


Figure 41. ^{1}H NMR (400 MHz, $CDCl_3$) of **S1**

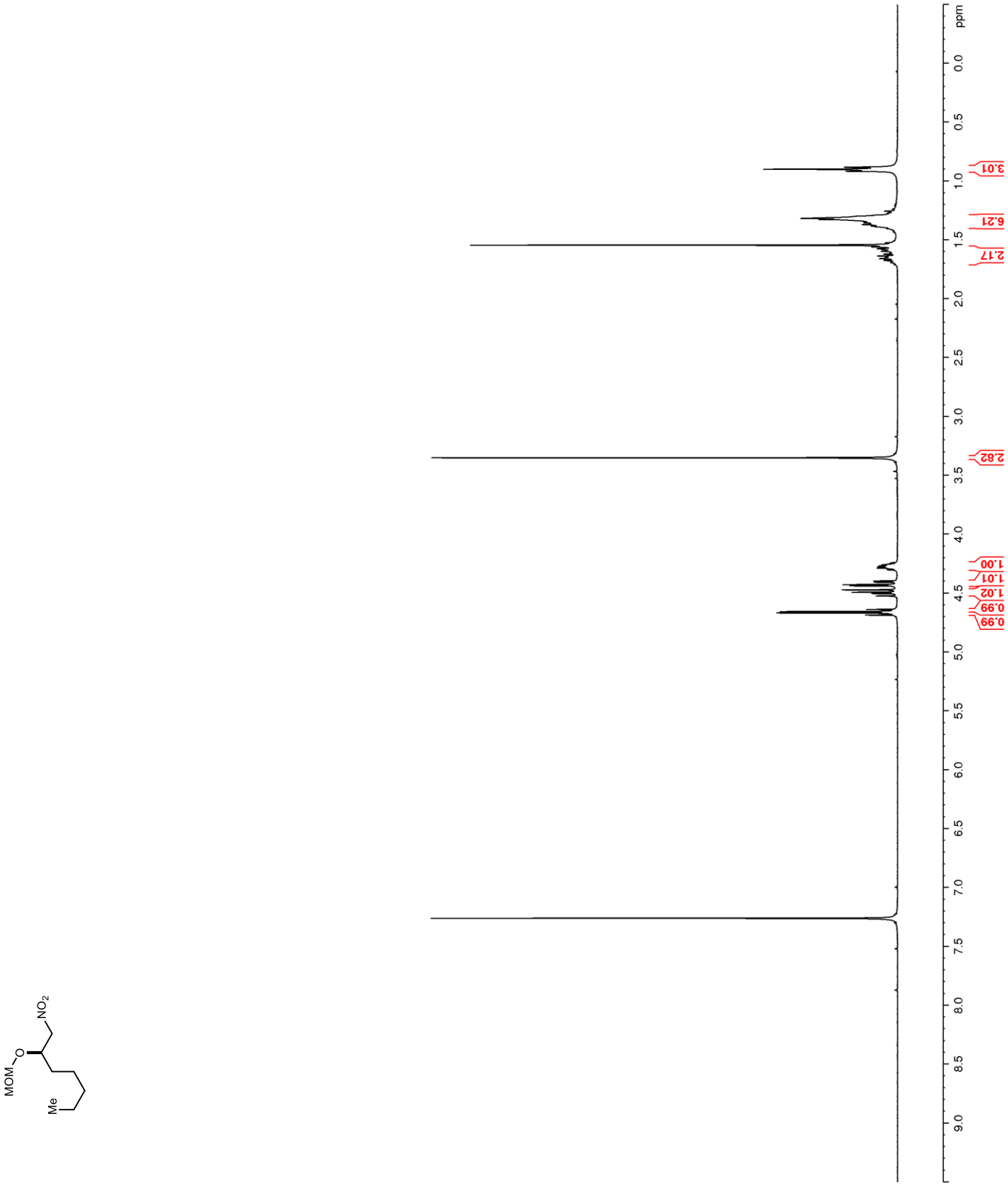


Figure 42. ^{13}C NMR (100 MHz, $CDCl_3$) of **S1**

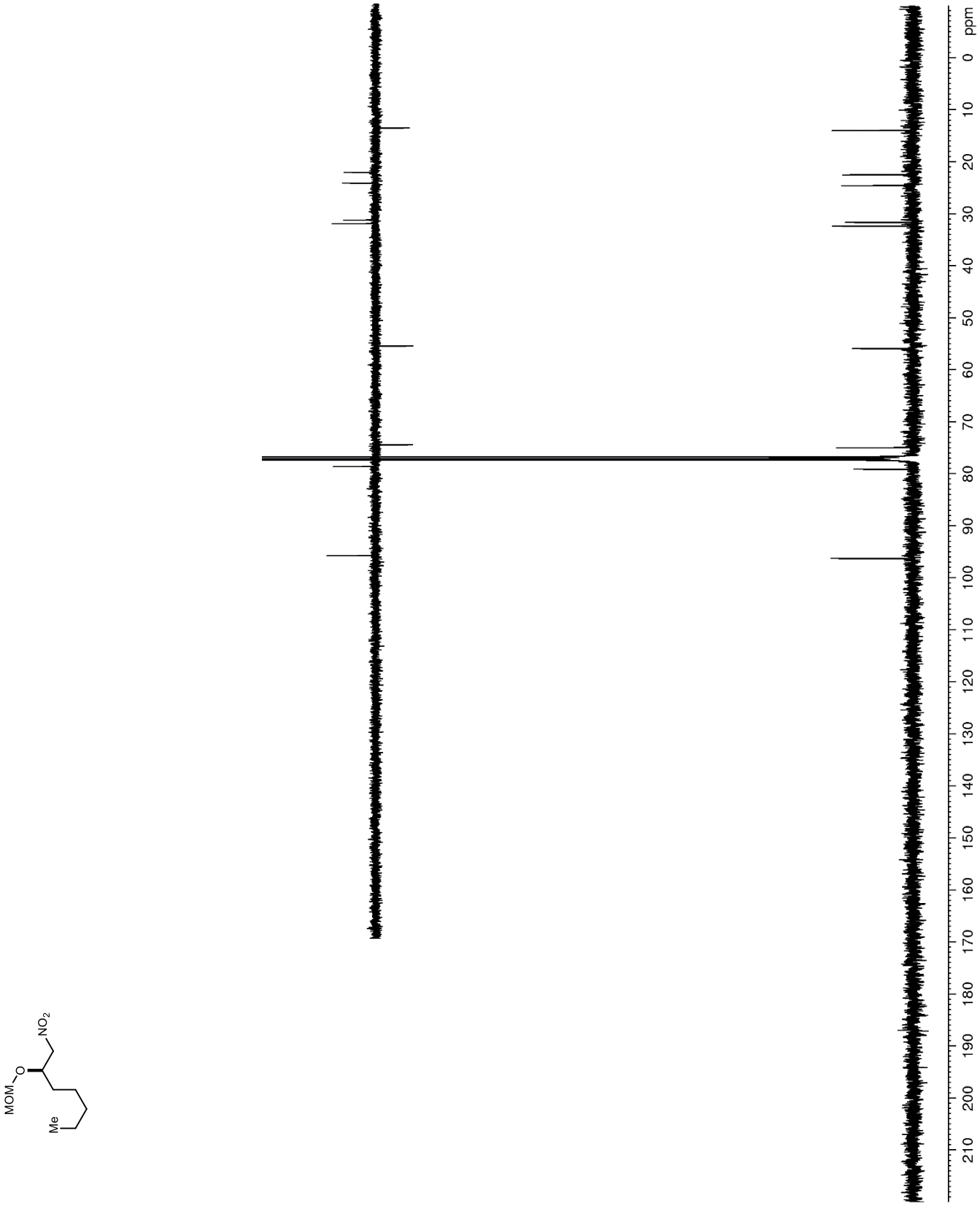


Figure 43. ^{1}H NMR (400 MHz, DMSO-d_6) of **S2**

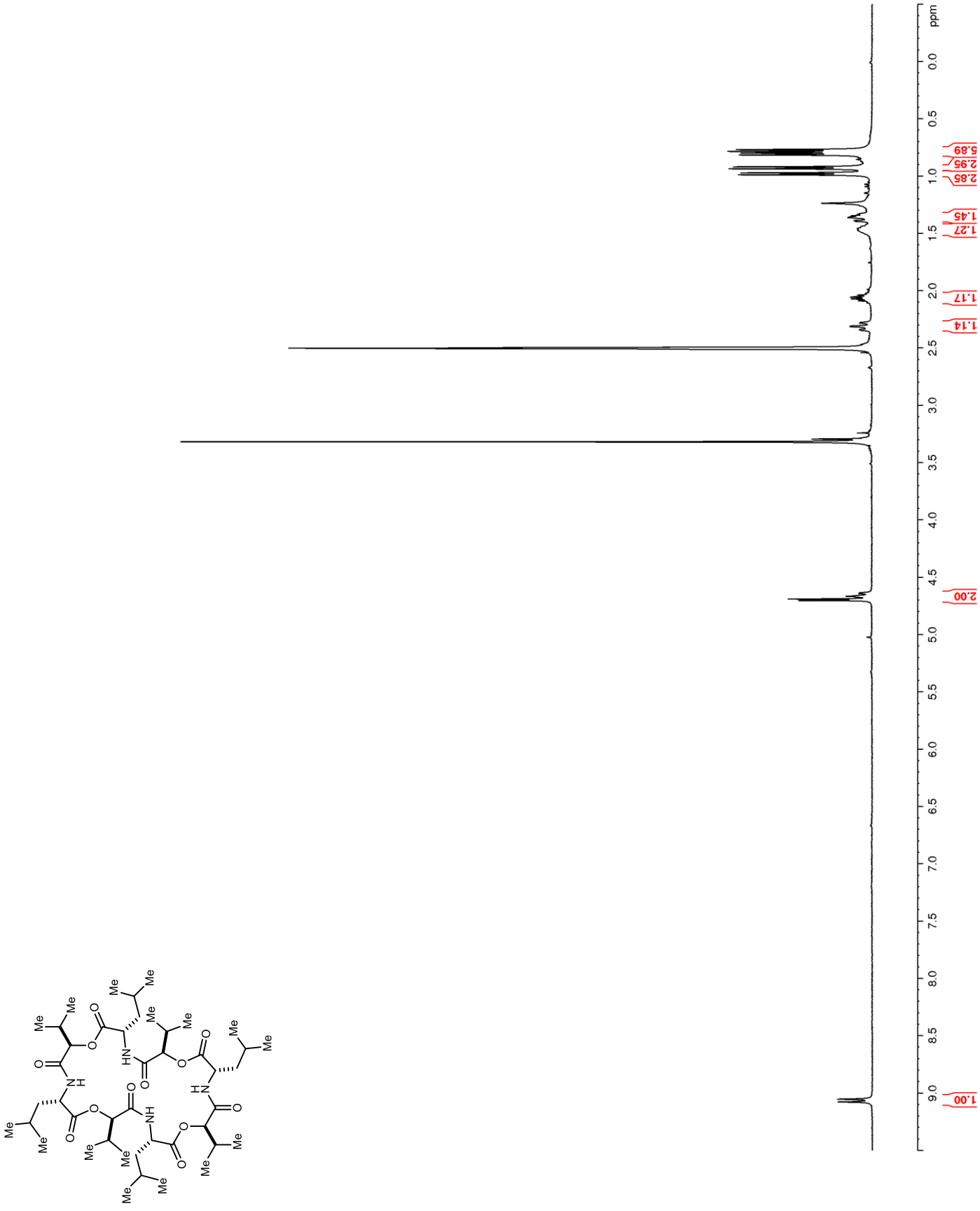
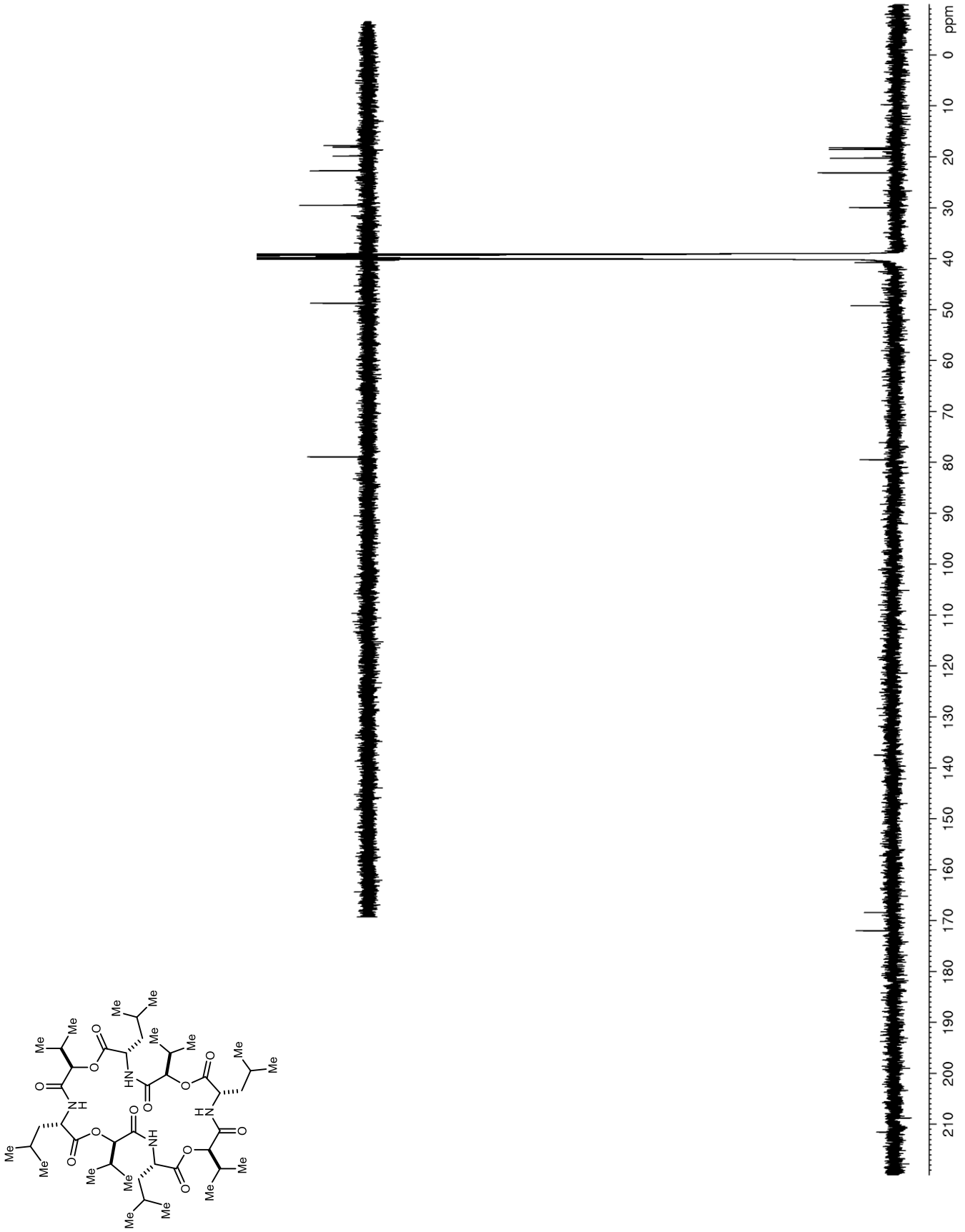


Figure 44. ^{13}C NMR (125 MHz, DMSO-d_6) of **S2**



[1] Pangborn AB, Giardello MA, Grubbs RH, Rosen RK, & Timmers FJ (1996) Safe and Convenient Procedure for Solvent Purification. *Organometallics* 15:1518-1520.

[2] Blay G, Climent E, Fernández I, Hernández-Olmos V, & Pedro JR (2007) Enantioselective Henry reaction catalyzed with copper(II)–iminopyridine complexes. *Tetrahedron: Asymmetry* 18:1603-1612.

[3] Blay G, Domingo LR, Hernández-Olmos V, & Pedro JR (2008) New Highly Asymmetric Henry Reaction Catalyzed by CuII and a C1-Symmetric Aminopyridine Ligand, and Its Application to the Synthesis of Miconazole. *Chem. Eur. J.* 14:4725-4730.

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[6] Unless otherwise specified, preparatory HPLC fractions containing depsipeptides (macrocyclic or linear) were subjected to extractive workup. These compounds are sensitive to cleavage under the high-heat conditions necessary to remove the acidic water-acetonitrile solvent system via rotary evaporation. Additionally, these compounds hold onto polar solvents & TFA, so the washes (water for acidic depsipeptides, satd aq $NaHCO_3$ for non-acidic depsipeptides) are necessary for full removal.

[7] Lit value: $[\alpha]_D^{25}$ -53 (*c* 0.20, MeOH). Shiomi K, *et al.* (2010) Verticilide, a new ryanodine-binding inhibitor, produced by Verticillium sp. FKI-1033. *J. Antibiot.* 63:77-82.

[8] Lit: $[\alpha]_D^{22}$ -73 (*c* 3.3, $CHCl_3$) Kanaoka M, *et al.* (1978) Bassianolide, a New Insecticidal Cyclodepsipeptide from Beauveria bassiana and Verticillium lecanii. *Agric. Biol. Chem.* 42:629-635.

[9] Kwon H-C, *et al.* (2000) Cytotoxic Cyclodepsipeptides of *Bombycis corpus* 101A. *J. Pharm. Soc. Korea* 44:115-118.

[10] Amide was prepared following an identical procedure to 4, except with *D*-alanine benzyl ester as the amine.

[11] Evans DA, *et al.* (2003) A new copper acetate-bis(oxazoline)-catalyzed, enantioselective Henry reaction. *J. Am. Chem. Soc.* 125:12692-12693.