Supporting Information

Short Synthesis of Berkeleyamide D and Determination of the Absolute Configuration by the Vibrational Circular Dichroism Exciton Chirality Method

Kenta Komori,[†] Tohru Taniguchi,[‡] Shoma Mizutani,[†] Kenji Monde,[‡]
Kouji Kuramochi,[†,] and Kazunori Tsubaki[†]*

† Graduate School for Life and Environmental Sciences, Kyoto Prefectural University, 1-5 Shimogamo Hangi-cho, Sakyo-ku, Kyoto 606-8522,

‡ Faculty of Advanced Life Science, Frontier Research Center for Post-Genome Science and Technology, Hokkaido University, Kita 21 Nishi 11, Sapporo 001-0021, Japan

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1. General Information.

^{1}H and ^{13}C NMR spectra were recorded on a JEOL EX-270W spectrometer (270 and 67.8 MHz, respectively) or a Bruker Biospin Avance 400 (400 and 100 MHz, respectively) using $CDCl_3$ or CD_3OD as the solvent. Chemical shift values are expressed in δ (ppm) relative to tetramethylsilane or the residual solvent resonance ($CDCl_3$: δ 77.0 for ^{13}C NMR; CD_3OD: δ 3.30 for ^{1}H NMR; CD_3OD: δ 49.0 for ^{13}C NMR). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, br = broad, m = multiplet), coupling constants (*J*; Hz), and integration. Melting point (mp) data were determined with a Yanaco MP-3S instrument and were uncorrected. IR spectra for characterization were recorded on a Horiba FT210 spectrometer, using NaCl (neat) or KBr pellets (solid). MS spectra were obtained on a JEOL mass spectrometer (JMS-700 MStaion) using electron impact ionization (EI), or a Fourier transformation-ion cyclotron resonance-mass spectrometer, Bruker solariX (FT-ICR-MS) by using ESI and laser desorption ionization (LDI) techniques. Optical rotations were recorded in MeOH on a JASCO digital polarimeter (P-1010), and were recorded as $[\alpha]_D$ values (concentration in g/100 mL). VCD and IR spectra for determination of the absolute configuration of **1** were measured in $CDCl_3$ on a BioTools Chiralir spectrometer equipped with a second photoelastic modulator. Analytical TLC was performed on silica gel 60 F_{254} plates (0.5 mm, Merck). Flash column chromatography was performed on a SiliaFlash F60 column (230–400 mesh, Silicycle).

All solvents were reagent grade and were dried and distilled prior to use, if necessary. THF was dried over molecular sieves 4A (MS4A) prior to use. Acetonitrile was distilled over calcium hydride.

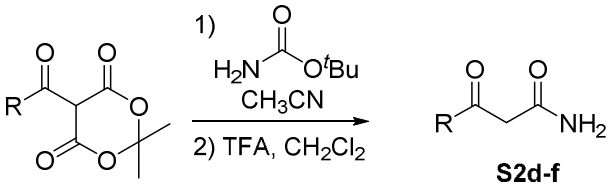
2. Detailed Experimental Procedures.

General Procedure for the Formation of α,β-epoxy-γ-lactam 8b (Table 1). Base (0.12 mmol) was added to a solution of **6b**[S1] (30 mg, 0.12 mmol) and methylglyoxal (40% aqueous solution, 45 mg, 0.25 mmol) in the indicated solvent (3.3 mL). The mixture was stirred at rt until no further TLC changes were observed. The reaction was quenched by the addition of water, and the mixture was diluted with EtOAc. After the layers were separated, the aqueous layer was extracted with EtOAc (×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (EtOAc/hexane = 1/1, v/v) to give **8b** as white solid. The ^1H and ^{13}C NMR spectra of **8b** were identical to those of our optically active form previously reported in the literature.[S2]

Entry 3: The reaction of **6b** and methylglyoxal in THF/H_2O (10:1) for 10 h gave **8b** (20 mg 69%).

Preparation of β-ketoamides S2d-f. β-Ketoamides **S2d-f** were prepared from known acylated Meldrum's acids **S1d-f** according to the procedure reported by Chhabra and co-workers (Scheme S1).[S3]

Scheme S1. Preparation of β-ketoamides S2d-f



S1d-f

S2d-f

d: *n*-$C_{17}H_{35}$
e: *n*-$C_{11}H_{23}$
f: *n*-C_5H_{11}

General Procedure for Preparation of β-ketoamides S2d-f. A solution of acylated Meldrum's acid (1 equiv) and *tert*-butyl carbonate (1.1~1.25 equiv) in acetonitrile was stirred under reflux until no further TLC changes were observed. After the mixture was concentrated, a solution of the reside in CH_2Cl_2 and trifluoroacetic acid (TFA) was stirred at rt. The residue was purified by column chromatography.

3-Oxoicosanamide (S2d). A solution of **S1d**[S3] (20 g, 48.7 mmol) and *tert*-butyl carbonate (6.3 g, 53.6 mmol) in acetonitrile (300 mL) was stirred under reflux for 30 min. Removal of *t*-butoxycarbonyl (Boc) group in CH_2Cl_2 (300 mL) and TFA (25 mL) gave the crude product. The crude product was purified by silica gel column chromatography ($CHCl_3$) to give **S2d** (8.0 g, 51% in two steps) as a white solid. Mp = 120−121°C; IR (KBr) ν_{max} = 3381, 3186, 2956, 2918, 2870, 2848, 1707, 1660, 1626, 1468, 1442, 1383, 1188, 1084, 723, 569 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (brs, 1H), 5.57 (brs, 1H), 3.43 (s, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 1.59 (brm, 2H), 1.25 (brs, 28H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 167.7, 48.2, 44.1, 31.9, 29.7 (6C), 29.6 (2C), 29.4 (2C), 29.3, 29.0, 23.4, 22.7, 14.2; HRMS (ESI-LDI) *m/z* calcd for $C_{20}H_{39}NO_2Na$ ($[M+Na]^+$) 348.2873, found 348.2872.

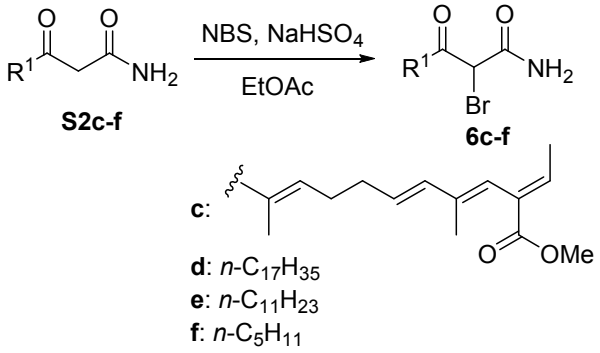
3-Oxotetradecanamide (S2e).[S2] A solution of **S1e**[S3] (15.2 g, 46.5 mmol) and *tert*-butyl carbonate (6.5 g, 55.8 mmol) in acetonitrile (300 mL) was stirred under reflux for 45 min. Removal of *t*-butoxycarbonyl (Boc) group in CH_2Cl_2 (120 mL) and TFA (12 mL) gave the crude product. The crude product was purified by silica gel column chromatography (hexanes/EtOAc = 1/1~1/2, v/v) to give **S2e** (5.7 g, 51% in two steps)

as a white solid. The ^{1}H and ^{13}C NMR spectra of **S2e** were identical to those previously reported in the literature.[S2]

3-Oxooctanamide (S2f). A solution of **S1f**[S3] (9.80 g, 40.4 mmol) and *tert*-butyl carbonate (5.91 g, 50.5 mmol) in acetonitrile (300 mL) was stirred under reflux for 1.5 h. Removal of *t*-butoxycarbonyl (Boc) group in CH_2Cl_2 (100 mL) and TFA (15 mL) gave the crude product. The crude product was purified by silica gel column chromatography (hexanes/EtOAc = 1/1~1/2, v/v) to give **S2f** (3.2 g, 50% in two steps) as a white solid. Mp = 97 °C; IR (KBr) ν_{max} = 3384, 3184, 2958, 2929, 2866, 2777, 1709, 1657, 1622, 1442, 1381, 1323, 1296, 1238, 1209, 1180, 1128, 1076, 1039, 1003, 910, 877, 806, 671, 600, 565, 472, 436 cm^{-1}; Because compound **S2f** was observed as a 17:1 keto-enol mixture in $CDCl_3$, NMR peaks derived from the keto isomer indicated: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (brs, 1H, NH), 5.93 (brs, 1H, NH), 3.42 (s, 2H), 2.54 (t, J = 7.2 Hz, 2H), 1.60 (quin, J = 7.2 Hz, 2H), 1.35−1,24 (brm, 4H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 168.1, 48.5, 43.9, 31.1, 23.0, 22.3, 13.9; HRMS (ESI-LDI) *m/z* calcd for $C_8H_{15}NO_2Na$ ($[M+Na]^+$) 180.0995, found 180.0998.

Preparation of α-bromo-β-ketoamides 6c-f. α,β-Bromo-β-ketoamides **6c-f** were prepared from **S2c-f** according to the procedure reported by Alexander and co-workers (Scheme S2).[S4]

Scheme S2. Preparation of α-bromo-β-ketoamides 6c-f



General Procedure for Preparation of α-bromo-β-ketoamides 6c-f. *N*-Bromosuccinimide (NBS, 0.8 or 1.0 equiv) was added in several portions to a solution of **S2c-f** (1 equiv) and $NaHSO_4$ (0.25 equiv) in THF at 0 °C. The mixture was stirred at 0 °C until no further TLC changes were observed. The reaction was quenched by the addition of water, and the mixture was diluted with EtOAc. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography. For preparation of **6d**, chloroform instead of EtOAc was used for solvent extraction.

Methyl (2*E*,3*E*,5*E*,9*E*)-13-amino-12-bromo-2-ethylidene-4,10-dimethyl-11,13-dioxo-3,5,9-tridecatrienate 6c. Following the general procedure, the reaction of **S2c**[S5] (64.2 mg, 0.20 mmol) with NBS (36 mg, 0.20 mmol) in the presence of $NaHSO_4$ (6.0 mg, 0.05 mmol) for 35 min gave the crude product. The crude product was purified by silica gel column chromatography (hexanes/EtOAc = 2/1, v/v) to give **6c** (72.4 mg, 91%) as a white solid. Mp = 102−104 °C; IR (KBr) ν_{max} = 3390, 3211, 3016, 2989, 2914, 2852, 1674, 1618, 1437, 1375, 1274, 1194, 1136, 1059, 1018, 972, 837, 727, 636 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.96 (dq, *J* = 0.8, 7.2 Hz, 1H), 6.82 (dt, *J* =0.8, 7.2 Hz, 1H), 6.71 (brs, 1H) 6.26 (d, *J* = 15.6 Hz, 1H), 6.04 (brs, 1H), 5.97 (s, 1H), 5.70 (td, *J* = 6.8, 15.6 Hz, 1H), 5.35 (s, 1H), 3.73 (s, 3H), 2.48−2.42 (m, 2H), 2.39−2.32 (m, 2H), 1.87 (s, 3H) 1.73 (dd, *J* = 1.2, 7.2 Hz, 3H), 1.63 (d, *J* =0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 167.9, 167.1, 146.5, 139.9, 137.7, 135.5, 134.9, 130.3, 127.0, 123.1, 51.9, 43.1, 31.4,

29.2, 15.9, 14.3, 11.9; HRMS (ESI-LDI) *m/z* calcd for $C_{18}H_{24}NO_4{}^{79}BrNa$ ($[M+Na]^+$) 420.0781, found 420.0775.

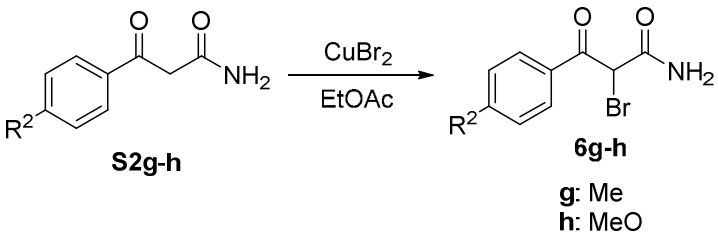
2-Bromo-3-oxoicosanamide 6d. Following the general procedure, the reaction of **S2d** (50 mg, 0.15 mmol) with NBS (21.9 mg, 0.12 mmol) in the presence of $NaHSO_4$ (4.6 mg, 0.04 mmol) in THF (3 mL) for 1 h gave the crude product. The crude product was purified by silica gel column chromatography ($CHCl_3$~$CHCl_3$/MeOH 40/1, v/v) to give **6d** (48.7 mg, 98%[a]) as a white solid. Mp = 117−118°C; IR (KBr) ν_{max} = 3388, 3192, 2956, 2918, 2850, 1724, 1672, 1471, 1396, 1192, 1076, 1045, 1016, 771, 719, 638, 584 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (brs, 1H, NH), 5.75 (brs, 1H, NH), 4.74 (s, 1H), 2.75 (t, *J* = 7.6 Hz, 2H), 1.63 (brm, 2H), 1,25 (brs, 28H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 166.1, 48.2, 40.3, 31.9, 29.7 (7C), 29.6, 29.4 (2C), 29.3, 28.8, 23.6, 22.7, 14.1; HRMS (ESI-LDI) *m/z* calcd for $C_{20}H_{38}NO_2{}^{79}BrNa$ ($[M+Na]^+$) 426.1978, found 426.1976. [a]Yield was calculated from NBS.

2-Bromo-3-oxotetradecanamide 6e. Following the general procedure, the reaction of **S2e** (30 mg, 0.12 mmol) with NBS (22.1 mg, 0.12 mmol) in the presence of $NaHSO_4$ (3.7 mg, 0.03 mmol) in THF (3 mL) for 1 h gave the crude product. The crude product was purified by silica gel column chromatography (hexanes/EtOAc = 6/1~4/1, v/v) to give **6e** (26.5 mg, 67%) as a white solid. Mp = 111−112°C; IR (KBr) ν_{max} = 3180, 2956, 2920, 2850, 1726, 1668, 1466, 1398, 1192, 1090, 1051, 769, 719, 644 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.63 (brs, 1H, NH), 5.97 (brs, 1H, NH), 4.74 (s, 1H), 2.75 (t, *J* = 7.0 Hz, 2H), 1.63 (brm, 2H), 1,26 (brs, 16H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 200.4, 166.3, 48.3, 40.2, 31.9, 29.6 (2C), 29.4, 29.3 (2C), 28.8, 23.6, 22.7, 14.1; HRMS (EI) *m/z* calcd for $C_{14}H_{26}O_2N^{79}Br$ ($[M]^+$) 319.1147, found 319.1150.

2-Bromo-3-oxooctanamide 6f. Following the general procedure, the reaction of **S2f** (650 mg, 4.13 mmol) with NBS (735 mg, 4.13 mmol) in the presence of $NaHSO_4$ (124 mg, 1.03 mmol) in THF (40 mL) for 3 h gave the crude product. The crude product was purified by silica gel column chromatography (hexanes/EtOAc = 4/1, v/v) to give **6f** (756 mg, 78%) as a white solid. Mp = 89−90 °C; IR (KBr) ν_{max} = 3180, 2956, 2933, 2866, 1726, 1670, 1558, 1541, 1512, 1398, 1190, 777, 669 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.72 (brs, 1H, NH), 6.56 (brs, 1H, NH), 4.77 (s, 1H), 2.76 (t, *J* = 7.6 Hz, 2H), 1.63 (quin, *J* = 7.6 Hz, 2H), 1.33-1.27 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 200.4, 166.6, 48.5, 40.0, 30.9, 23.2, 22.3, 13.8; HRMS (EI) *m/z* calcd for $C_8H_{14}O_2N^{79}Br$ ($[M]^+$) 235.0208, found 235.0209.

Preparation of α-bromo-β-ketoamides 6g and 6h. α,β-Bromo-β-ketoamides **6g** and **6h** were prepared from known β-ketoamides **S2g**[S6] and **S2h**[S6], respectively, according to the procedure reported by Herschhorn and co-workers (Scheme S3).[S1]

Scheme S3. Preparation of α-bromo-β-ketoamides 6g and 6h



General Procedure for Preparation of α-bromo-β-ketoamides 6c-f. $CuBr_2$ (1.0 or 1.2 equiv) was added to a solution of **S2g-h** (1 equiv) in EtOAc. The mixture was stirred at 50 °C until no further TLC changes were observed. The mixture was filtrated through Celite. The filtrate was diluted with EtOAc and H_2O. After the layers were separated, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (EtOAc/hexane = 2/1~1/1).

2-Bromo-3-(4-methylphenyl)-3-oxopropanamide (6g). The reaction of **S2g**[S6] (63.7 mg, 0.36 mmol) with $CuBr_2$ (80.3 mg, 0.36 mmol) for 13 h gave **6g** (68.2 mg, 74%) as a white solid. Mp = 141−142°C; IR (KBr) ν_{max} = 3334, 3159, 2989, 2974, 2812, 1685, 1606, 1562, 1541, 1512, 1456, 1390, 1286, 1188, 1005, 777 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.89 (brs, 1H, NH), 5.97 (brs, 1H, NH), 5.56 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 190.4, 167.1, 145.9, 131.0, 129.7 (2C), 129.4 (2C), 43.0, 21.8; HRMS (EI) *m/z* calcd for $C_{10}H_{10}O_2N^{79}Br$ ($[M]^+$) 254.9895, found 254.9897.

2-Bromo-3-(4-methoxyphenyl)-3-oxopropanamide (6h). The reaction of **S2h**[S6] (85.3 mg, 0.44 mmol) with $CuBr_2$ (118.0 mg, 0.53 mmol) for 14.5 h gave **6g** (81.5 mg, 68%) as a white solid. Mp = 133−135°C; IR (KBr) ν_{max} = 3398, 3188, 3008, 2970, 2935, 2844, 1682, 1599, 1512, 1462, 1394, 1271, 1173, 1026, 833, 777 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.9 Hz, 2H), 6.97 (d , *J* = 8.9 Hz, 2H), 6.93 (brs, 1H, NH), 5.95 (brs, 1H, NH), 5.55 (s, 1H), 3.90 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 189.3, 167.1, 164.8, 131.8 (2C), 126.4, 114.3 (2C), 55.6, 42.9; HRMS (EI) *m/z* calcd for $C_{10}H_{10}O_3N^{79}Br$ ($[M]^+$) 270.9844, found 270.9843.

Application of Darzens Reaction for Synthesis of Epolactaene (8c) and Its Derivatives 8d-h (Scheme 3). Triethylamine (23 μL, 0.17 mmol) was added to a solution of **6** (0.15 mmol) and methylglyoxal (40% aqueous solution, 54 mg, 0.30 mmol) in a 10:1 mixture of THF and H_2O (4.5 mL). The mixture was stirred at rt until no further TLC changes were observed. The reaction was quenched by the addition of water, and the mixture was diluted with EtOAc. After the layers were separated, the aqueous layer was extracted with EtOAc (×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography.

(±)-Epolactaene (8c). Following the general procedure, the reaction of **6c** (60 mg, 0.15 mmol) and methylglyoxal with triethylamine for 24 h gave the crude product. The crude product was purified by silica gel column chromatography (hexanes/EtOAc = 5/2~2/1, v/v) to give **8c** (40.4 mg, 69%) as a 4.7:1 diastereomeric mixture as an amorphous solid and the recovered **6c** (6.5 mg, 11%). The ^{1}H and ^{13}C NMR spectra of **8c** were identical to those reported for both natural epolactaene[S7] and our synthetic one[S8].

(1*RS*,5*RS*)-4-Hydroxy-4-methyl-1-octadecanoyl-6-oxa-3-azabicyclo[3.1.0]hexan-2-one (8d). Following the general procedure, the reaction of **6d** (60.6 mg, 0.15 mmol) and methylglyoxal with triethylamine for 4 h gave the crude product. The crude product was purified by silica gel column chromatography ($CHCl_3$/MeOH = 50/1, v/v) to give **8d** (39.0 mg, 66%) as a single diastereomer as colorless oil. The ^{1}H and ^{13}C NMR spectra of **8d** were identical to those of our optically active form previously reported in the literature.[S8]

(1*RS*,5*RS*)-1-Dodecanoyl-4-hydroxy-4-methyl-6-oxa-3-azabicyclo[3.1.0]hexan-2-one (8e). Following the general procedure, the reaction of **6e** (48.0 mg, 0.15 mmol) and methylglyoxal with triethylamine for 3.5 h gave the crude product. The crude product was purified by silica gel column chromatography ($CHCl_3$/MeOH = 50/1, v/v) to give **8e** (37.0 mg, 79%) as a single diastereomer as colorless oil. The ^{1}H and ^{13}C NMR spectra of **8e** were identical to those of the major isomer of our optically active form previously reported in the literature.[S8]

(1*RS*,5*RS*)-1-Hexanoyl-4-hydroxy-4-methyl-6-oxa-3-azabicyclo[3.1.0]hexan-2-one (8f). Following the general procedure, the reaction of **6f** (35.4 mg, 0.15 mmol) and methylglyoxal with triethylamine for 3.5 h gave the crude product. The crude product

was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100/1~40/1, v/v) to give **8f** (27.8 mg, 82%) as a single diastereomer as colorless oil. The ^1H and ^{13}C NMR spectra of **8f** were identical to those of the major isomer of our optically active form previously reported in the literature.[S8]

(1*RS*,5*RS*)-4-Hydroxy-4-methyl-1-(4-methylbenzoyl)-6-oxa-3-azabicyclo[3.1.0]hexan-2-one (8g). Following the general procedure, the reaction of **6g** (38.4 mg, 0.15 mmol) and methylglyoxal with triethylamine for 8.5 h gave the crude product. The crude product was purified by silica gel column chromatography (hexanes/EtOAc = 1/1, v/v) to give **8g** (22.9 mg, 62%) as a 7:1 diastereomeric mixture as colorless oil. IR (neat) ν_{max} = 3327, 2991, 2885, 2823, 1712, 1685, 1604, 1570, 1512, 1415, 1317, 1271, 1234, 1184, 1157, 1122, 1045, 941, 879, 854, 827, 760, 617, 488, 451, 428 cm^{-1}; Because compound **8g** was observed as a 7:1 diastereomeric mixture in CD_3OD, NMR peaks derived from the major isomer were indicated: ^1H NMR (400 MHz, CD_3OD) δ 8.00 (d, *J* = 8.0, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 4.17 (s, 1H), 2.46 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 190.7, 171.9, 147.1, 133.8, 130.5 (2C), 130.4 (2C), 84.8, 66.2, 64.4, 22.2, 21.8. HRMS (EI) *m/z* calcd for $C_{13}H_{13}O_4N$ ($[M]^+$) 247.0845, found 247.0848.

(1*RS*,5*RS*)-4-Hydroxy-4-methyl-1-(4-methoxylbenzoyl)-6-oxa-3-azabicyclo[3.1.0]hexan-2-one (8h). Following the general procedure, the reaction of **6h** (40.6 mg, 0.15 mmol) and methylglyoxal with triethylamine for 8.5 h gave the crude product. The crude product was purified by silica gel column chromatography (hexanes/EtOAc = 1/1, v/v) to give **8h** (21.3 mg, 54%) as a 7:1 diastereomeric mixture as colorless oil. IR (neat) ν_{max} = 3332, 3016, 2981, 2939, 2843, 1712, 1703, 1682, 1599, 1574, 1512, 1423, 1315, 1263, 1176, 1024, 941, 843, 756 cm^{-1}; Because compound **8h** was observed as a 7:1 diastereomeric mixture in CD_3OD, NMR peaks derived from the major isomer indicated. ^1H NMR (400 MHz, CD_3OD) δ 8.07 (dd, *J* = 7.0 Hz, 2.0 Hz, 2H), 7.05 (dd, *J* = 7.0 Hz, 2.0 Hz, 2H), 4.13 (s, 1H), 3.89 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 189.5, 172.0, 166.4, 132.8 (2C), 129.1, 115.2 (2C), 84.8, 66.0, 64.3, 56.2, 22.2. HRMS (EI) *m/z* calcd for $C_{13}H_{13}O_5N$ ($[M]^+$) 263.0794, found 263.0798.

Synthesis of (±)-Berkeleyamide D (1) (Scheme 4)

(1*RS*,5*RS*)-1-Acetyl-4-hydroxy-4-isobutyl-6-oxa-3-azabicyclo[3.1.0]hexan-2-one (5). Triethylamine (38 μL, 0.28 mmol) was added to a solution of **6a**[S4] (50 mg, 0.28 mmol) and isobutylglyoxal[S9] (35 mg, 0.31 mmol) in 2-propanol (5.0 mL). The mixture was stirred at rt for 5.5 h. The reaction was quenched by the addition of water, and the mixture was diluted with EtOAc. After the layers were separated, the aqueous layer was extracted with EtOAc (×2). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography. (hexanes/EtOAc = 3/1~2/1, v/v) to give **5** (40.5 mg, 68%) as a single diastereomer as a white solid. Mp = 115−117 °C; IR (KBr) ν_{max} = 3388, 2956, 2868, 1734, 1687, 1437, 1360, 1161, 1109, 947, 910, 876, 766, 710, 525, 471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (brs, 1H, NH), 4.97 (brs, 1H, OH), 4.24 (d, *J* = 2.4 Hz, 1H), 2.13 (s, 3H), 2.03 (m, 3H), 1.80−1.75 (m, 1H), 1.71−1.65 (m, 1H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 168.5, 85.4, 65.2 61.2, 43.5, 26.1, 24.2, 24.0, 23.6; HRMS (ESI-LDI) *m/z* calcd for $C_{10}H_{15}NO_4Na$ ($[M+Na]^+$) 236.0893, found 236.0901.

(1*RS*,4*SR*,5*RS*)-1-Acetyl-4-isobutyl-4-isoporopoxy-6-oxa-3-azabicyclo[3.1.0]hexan-2-one (9). A solution of **5** (50 mg, 0.23 mmol), 10-camphorsulfonic acid (26.7 mg, 0.12 mmol) and triisopropyl orthoformate (51 μL, 0.23 mmol) in 2-propanol (2.5 mL) was stirred rt for 4.5 h. The reaction was quenched by the addition of $NaHCO_3$ (9.6 mg, 0.12 mmol), and the mixture was diluted with EtOAc and H_2O. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography. (hexanes/EtOAc = 5/1, v/v) to give **9** (50.7 mg, 86%) as a single diastereomer as a white solid. Mp = 73−74°C; IR (KBr) ν_{max} = 3273, 2979, 2958, 2873, 1734, 1695, 1425, 1286, 1155, 1105, 1041, 947, 769, 577, 459 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.51 (brs, 1H, NH), 3.95 (d, *J* = 2.4 Hz, 1H), 3.83 (septet, *J* = 6.0 Hz, 1H), 2.30 (s, 3H), 1.94 (m, 1H), 1.68 (m, 2H), 1.14 (d, *J* = 6.0 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 168.3, 88.7, 65.2, 63.8, 61.8, 43.7, 27.2, 24.4 (2C), 24.1, 23.9, 23.4; HRMS (ESI-LDI) *m/z* calcd for $C_{13}H_{21}NO_4Na$ ($[M+Na]^+$) 278.1363, found 278.1361.

(5*SR*,8*SR*,9*RS*)-2-Benzyl-9-hydroxy-8-isobutyl-8-isopropoxy-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (10). A 1.6 M solution of *n*-BuLi (1.86 mL, 8.88 mmol) was added

to a solution of hexamethyldisilazane (1.86 mL, 8.88 mmol) in THF (100 mL) at −78 ˚C, and the mixture was stirred at −78 ˚C for 30 min. A solution of **9** (1.0 g, 4.03 mol) in THF (20 mL) was added to the solution of LHMDS at −78 ˚C and the mixture was stirred at −78 ˚C for 10 min. Phenylacetyl chloride (0.53 mL, 4.03 mmol) was added to the mixture, and the mixture was stirred at −78 ˚C for 40 min. The reaction was quenched by the addition of 1M aqueous HCl solution, and the mixture was diluted with EtOAc and H_2O. After the layers were separated, the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography. (hexanes/EtOAc = 6/1~2/1, v/v) to give **10** (0.28 g, 19%) as a colorless oil and **11** (0.17 g, 17%) as an amorphous solid. **10**: IR (neat) ν_{max} = 3411, 3213, 3018, 2970, 2871, 1724, 1701, 1595, 1496, 1458, 1412, 1365, 1277, 1149, 1109, 1024, 1003, 962, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.29 (m, 5H), 7.01 (brs, 1H, NH), 5.33 (s, 1H), 4.53 (d, *J* = 9.6 Hz, 1H), 3.96 (d, *J* = 17.2 Hz, 1H), 3.94 (d, *J* = 17.2 Hz, 1H), 3.82 (m, 1H), 3.41 (d, *J* = 9.6 Hz, 1H), 1.98 (dd, *J* = 13.2 Hz, 4.8 Hz, 1H), 1.94−1.88 (m, 1H), 1.83 (dd, *J* = 13.2 Hz, 6.4 Hz, 1H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 3.6 Hz, 3H), 1.00 (d, *J* = 3.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 195.6, 165.2, 133.5, 129.2 (2C), 128.9 (2C), 127.6, 105.0, 92.4, 92.2, 77.2, 64.7, 42.3, 37.2, 24.5, 24.4, 24.3, 23.9, 23.5; HRMS (ESI-LDI) *m/z* calcd for $C_{21}H_{27}NO_5Na$ ($[M+Na]^+$) 396.1781, found 396.1771.

Dimer 11: IR (neat) ν_{max} = 3238, 3109, 3018, 2974, 2962, 2933, 2873, 1734, 1712, 1464, 1387, 1371, 1271, 1155, 1109, 1074, 1039, 1009, 955, 930, 891, 831, 584, 515, 480, 451, 422 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.44 (brs, 1H, NH), 6.21 (brs, 1H, NH), 4.20 (d, *J* = 2.0 Hz, 1H), 4.00 (s, 1H), 3.91-3.83 (m, 2H), 3.89 (brs, 1H, OH), 3.33 (d, *J* = 15.6 Hz, 1H), 2.77 (d, *J* = 15.6 Hz, 1H), 1.98-1.90 (m, 2H), 1.67 (d, *J* = 6.0 Hz, 2H), 1.64 (d, *J* = 6.0 Hz, 2H), 1.52 (s, 3H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.14 (d, *J* = 6.4 Hz, 6H), 1.02 (d, *J* = 6.4 Hz, 6H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 171.4, 168.2, 88.7, 88.4, 69.7, 65.3, 65.0, 64.6, 64.2, 62.2, 61.5, 44.6, 43.8, 43.7, 24.5, 24.4 (2C), 24.3, 24.1 (2C), 24.0, 23.5 (2C); HRMS (ESI-LDI) *m/z* calcd for $C_{26}H_{42}N_2O_8Na$ ($[M+Na]^+$) 533.2833, found 533.2838.

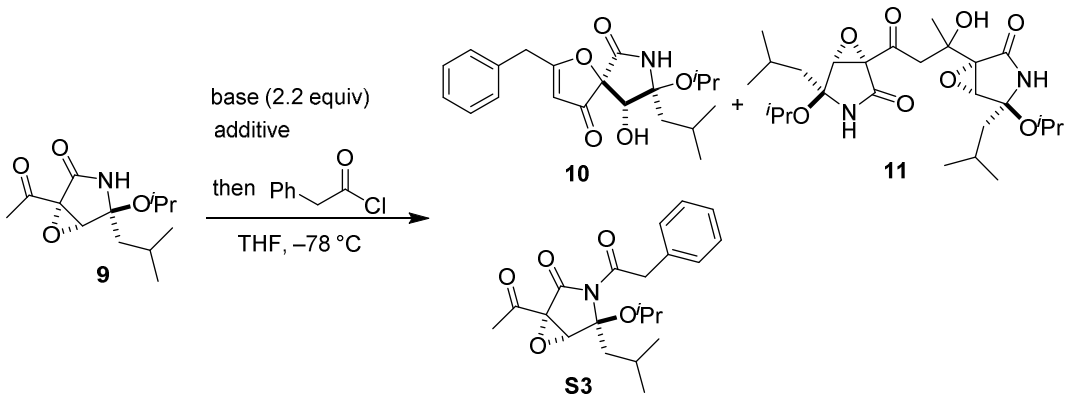
(±)-Berkeleyamide D (1). A solution of **10** (200 mg, 0.54 mmol) and *p*-toluenesulfonic acid monohydrate (20.4 mg, 0.11 mmol) in THF (4 mL) and H_2O (1 mL) was stirred rt for 16 h. The reaction was quenched by the addition of H_2O, and the mixture was diluted with EtOAc. After the layers were separated, the aqueous layer was extracted

with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography. (hexanes/EtOAc = 4/1~2/1, v/v) to give **(±)-1** (125.8 mg, 71%) as a white solid. Mp = 145 °C; IR (KBr) ν_{max} = 3388, 3213, 2949, 2868, 1732, 1670, 1574, 1452, 1389, 1277, 1151, 962, 758, 698, 598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5H), 6.60 (brs, 1H, NH), 5.51 (brs, 1H, OH), 5.37 (brs, 1H), 4.43 (d, *J* = 10.4 Hz, 1H), 4.03 (d, *J* = 17.2 Hz, 1H), 3.96 (d, *J* = 17.2 Hz, 1H), 3.00 (d, *J* = 10.4 Hz, 1H), 1.95 (m, 1H), 1.90 (m, 1H), 1.61 (m, 1H), 1.03 (d, *J* = 6.4 Hz, 3H) 1.01 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 197.8, 164.1, 133.2, 129.2 (2C), 129.0 (2C), 127.7, 104.4, 95.3, 84.9, 75.1, 45.5, 37.4, 24.0, 23.9, 23.8; HRMS (ESI-LDI) *m/z* calcd for $C_{18}H_{21}NO_5Na$ ($[M+Na]^+$) 354.1312, found 354.1305.

Conditions for Optical Resolution of (±)-Berkeleyamide D (1). CHIRALPAK IC (4.6 × 250 mm), hexane/2-propanol = 4:1, 2 mL/min, UV 254 nm, rt, t_R = 15.5 min for (−)-(5*S*)-isomer, 23.7 min for (+)-(5*R*)-isomer. (+)-(5*R*)-**1**: $[\alpha]^{17}_D$ = +84.6 (*c* 0.25, MeOH), (−)-(5*S*)-**1**: $[\alpha]^{17}_D$ = −85.7 (*c* 0.25, MeOH).

Comparison of Stability between 1 and 8-*epi*-1 by DFT Calculations. Conformational analyses were performed using the conformational search algorithm implemented in version 1.4.2 of the BARISTA software (Conflex Corp., Tokyo, Japan).[S10] The lower energy conformers of each compound, which differed from the most stable confer by less than 2 kcal/mol, were optimized using DFT calculations at the B3LYP/6-311+G(d,p) level, that were implemented in the Gaussian 09 program package (Gaussian, Inc., Wallingford, CT, USA).[S11] The lowest energy conformations were determined by comparing the energies of each conformer after zero point energy corrections.

Table S-1. Screening of Conditions for Formation of 10[a]



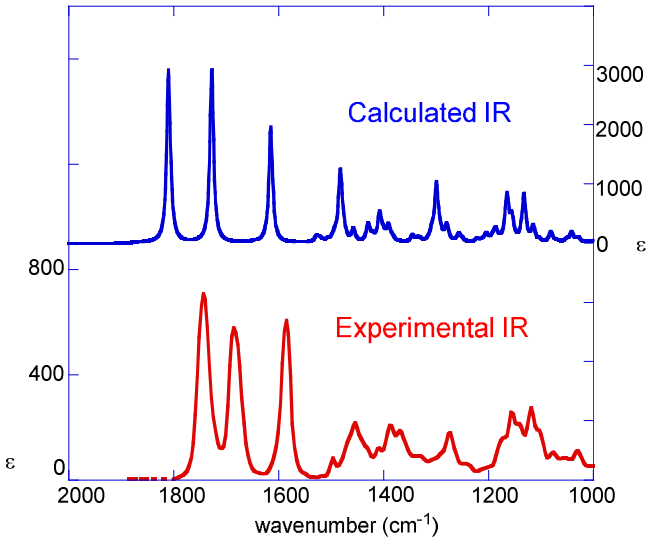
entry	base	additive (equiv)	yield (%)[b]			
			10	**11**	**S3**	recovered **9**
1	LHMDS	–	16	6	–	16
2	LHMDS	LiCl (2.2)	8	26	–	15
3	LHMDS	LiCl (6.6)	5	25	–	18
4	LHMDS	HMPA	4	19	–	27
5	^{n}BuLi	–	10	3	–	12
6	LDA	–	–	24	–	34
7	LTMP	–	8	26	–	16
8	NaHMDS	–	–	–	–	49
9	^{t}BuMgBr	–	–	–	34[c]	trace

[a]Reaction conditions: **9** (0.12 mmol), base (0.26 mmol), solvent (6 mL). [b]Yields were determined by ^{1}H NMR using 2,5-dimethylfuran as an internal standaed. [c]Isolated yield.

(1*RS*,4*SR*,5*RS*)-1-Acetyl-4-(2-methylpropyl)-6-oxa-3-(phenylacetyl)-4-(propan-2-yl oxy)-3-azabicyclo[3.1.0]hexan-2-one (S3). Yellow oil; IR (neat) ν_{max} = 3064, 3032, 2976, 2931, 2873, 1759, 1710, 1603, 1496, 1460, 1421, 1339, 1363, 1323, 1273, 1173, 1111, 1068, 1036, 947, 914, 717, 760, 607, 579, 561, 484, 438 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5H), 4.17 (s, 2H), 4.04 (s, 1H), 3.85 (septet, *J* = 6.4 Hz, 1H), 2.48 (dd, *J* = 14.4 Hz, 8.4 Hz, 1H), 2.33 (s, 3H), 1.98 (m, 1H), 1.67 (dd, *J* = 14.4 Hz, 4.8 Hz, 1H), 1.14 (d, *J* = 6.0 Hz, 3H), 1.05 (d, *J* = 6.4 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H),

0.96 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 172.4, 167.3, 133.2, 129.7 (2C), 128.5 (2C), 127.2, 94.0, 66.9, 62.4, 61.5, 44.8, 42.8, 27.2, 24.6, 24.4, 24.3, 23.6, 23.3; HRMS (ESI-LDI) *m/z* calcd for $C_{21}H_{27}NO_5Na$ ($[M+Na]^+$) 396.1781, found 396.1771.

(A) Calculated (blue) and Experimental (red) IR Spectra of (−)-**1**



(B) Calculated (blue) and Experimental (red) VCD Spectra of (−)-**1**

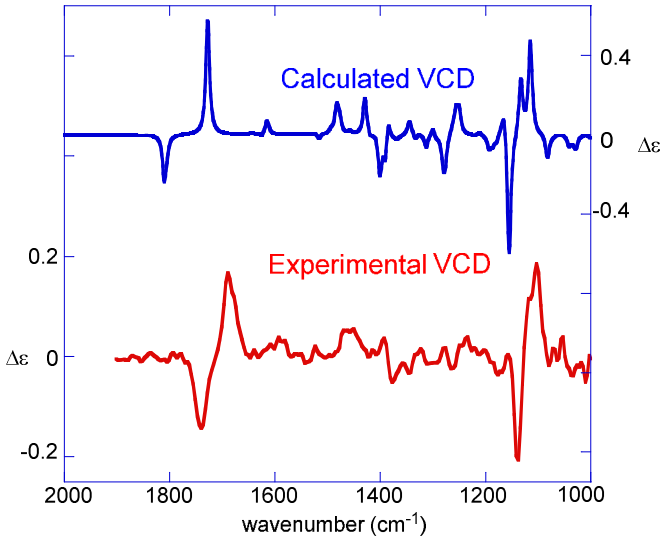
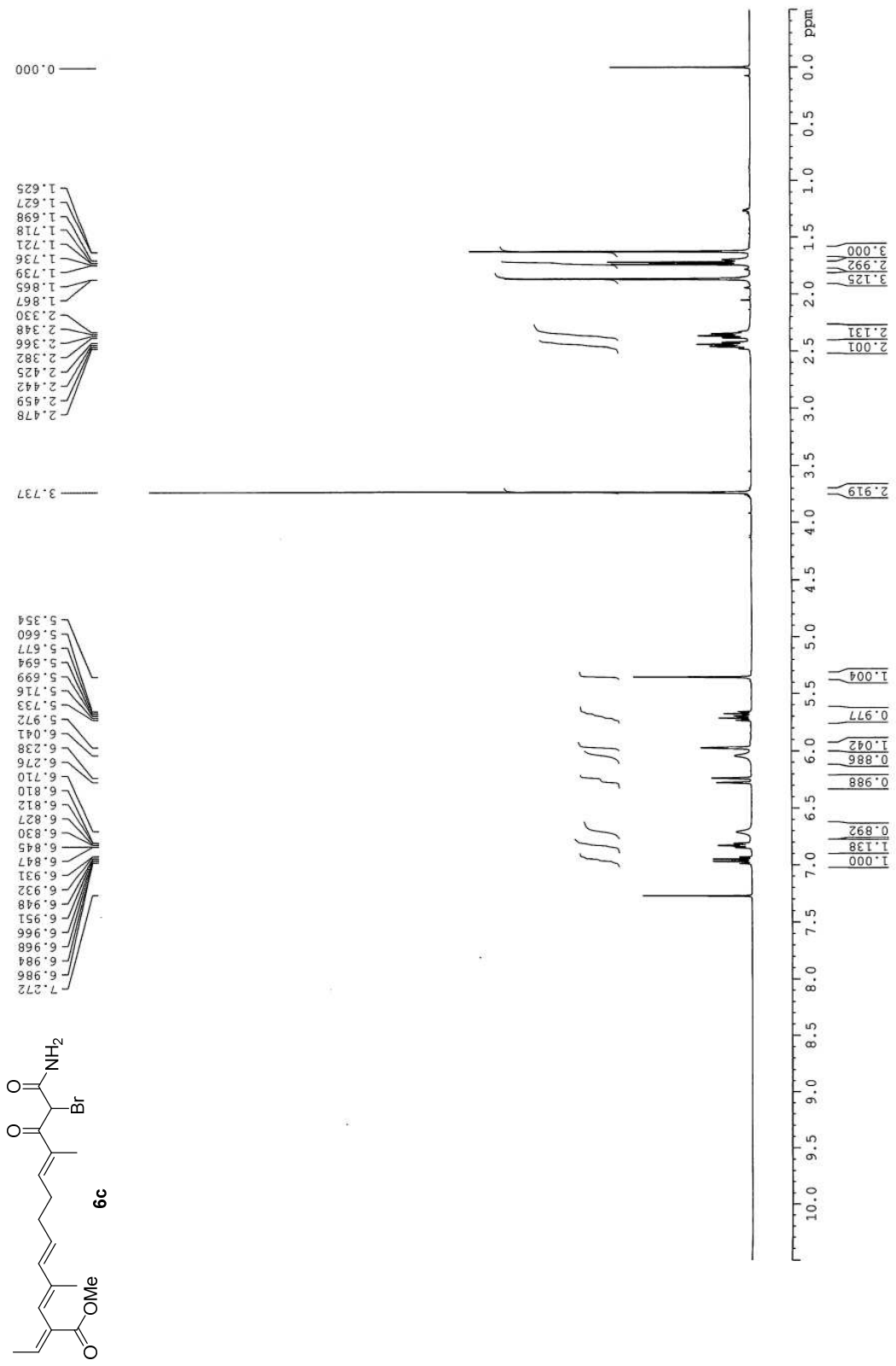


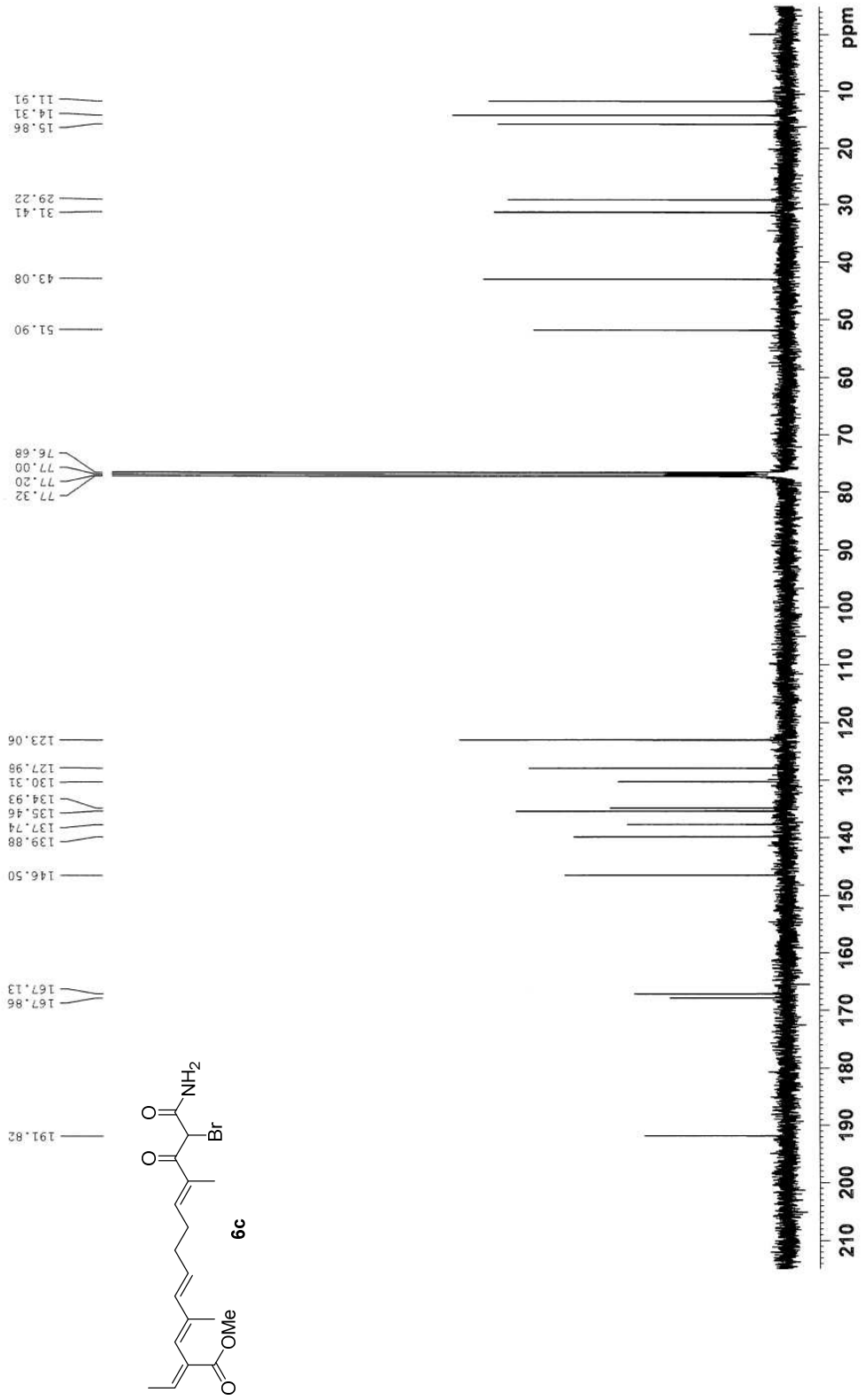
Figure S-1. Comparison of DFT-B3LYP/6-311+G(d,p)-calculated IR and VCD Spectra[a] of (−)-1 with Experimental Spectra

[a]Conformational analysis was performed using the MMFF94S conformer research algorithm implemented in BARISTA software (BARISTA, version. 1.4.2; CONFLEX Co.).[S10] The minimum geometries were optimized using DFT calculations at the B3LYP/6-311+G(d,p) level, implemented in the Gaussian 09 program package.[S11] Thirteen conformers of (−)-**1** within 3.0 kcal/mol from the most stable conformer were taken into account for the IR and VCD calculations at the same level of theory, and the resultant spectra of each conformer were averaged based on the Boltzmann populations.

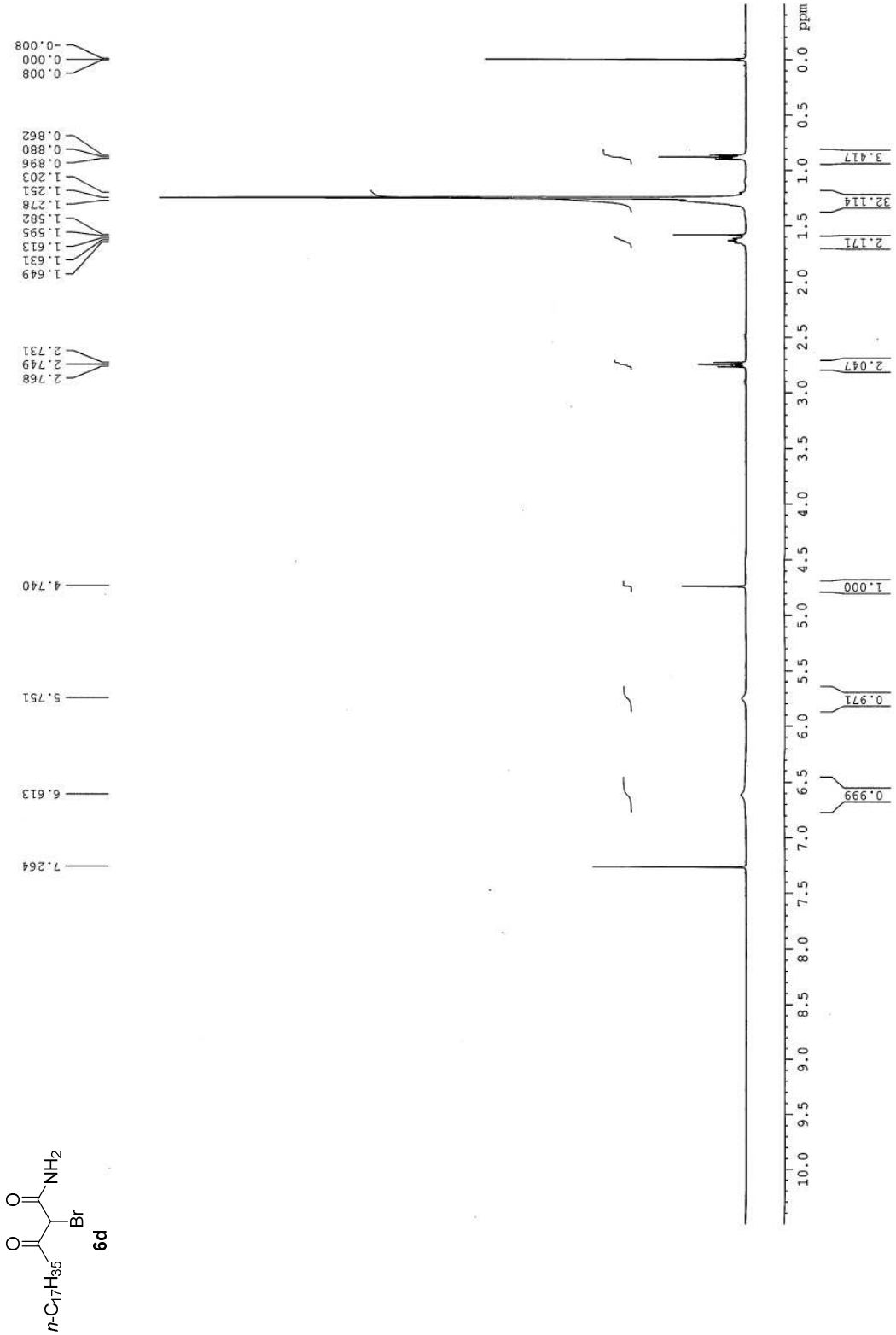
^{1}H NMR Spectrum of Compound **6c**



^{13}C NMR Spectrum of Compound **6c**

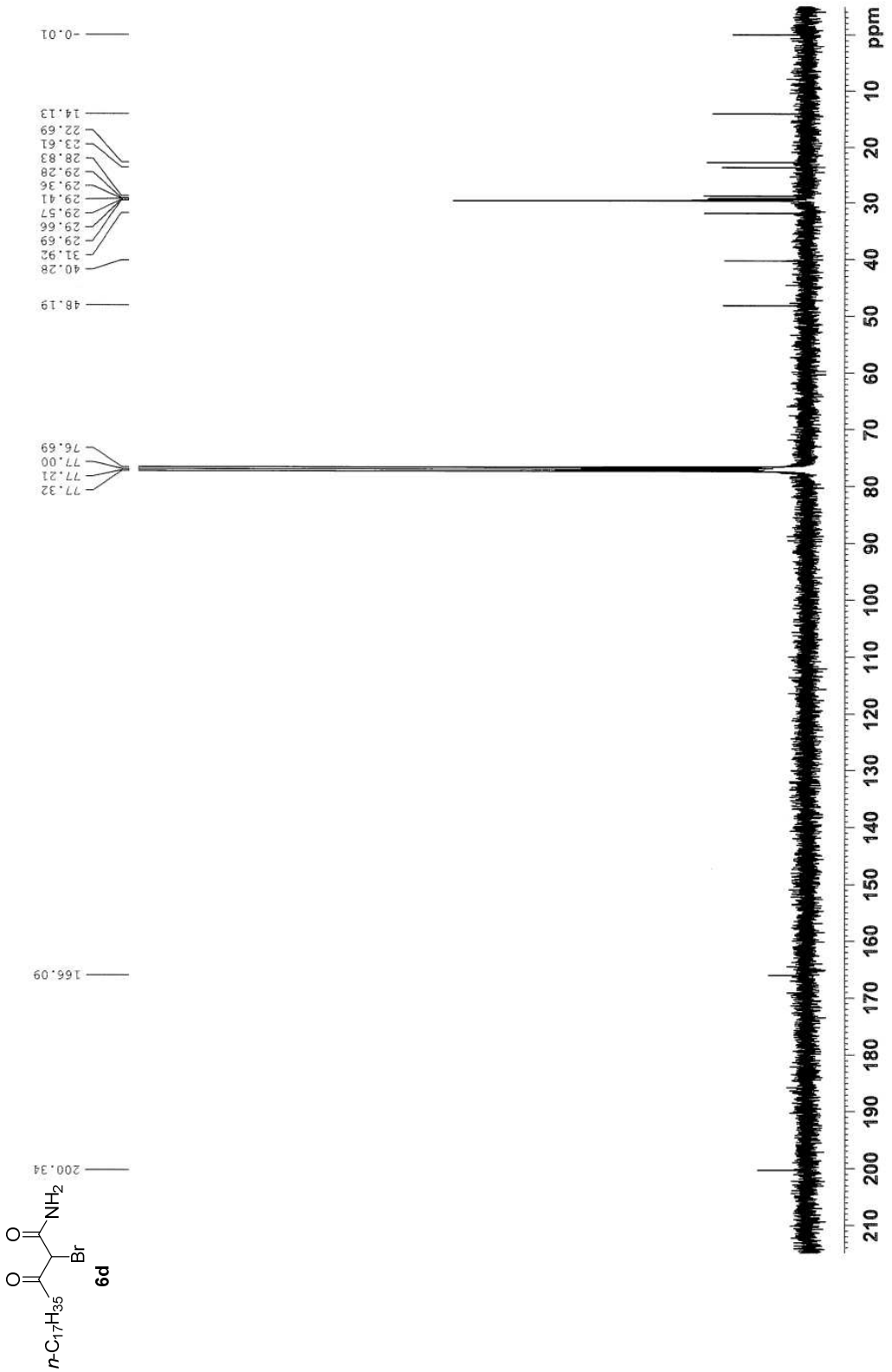


^{1}H NMR Spectrum of Compound **6d**

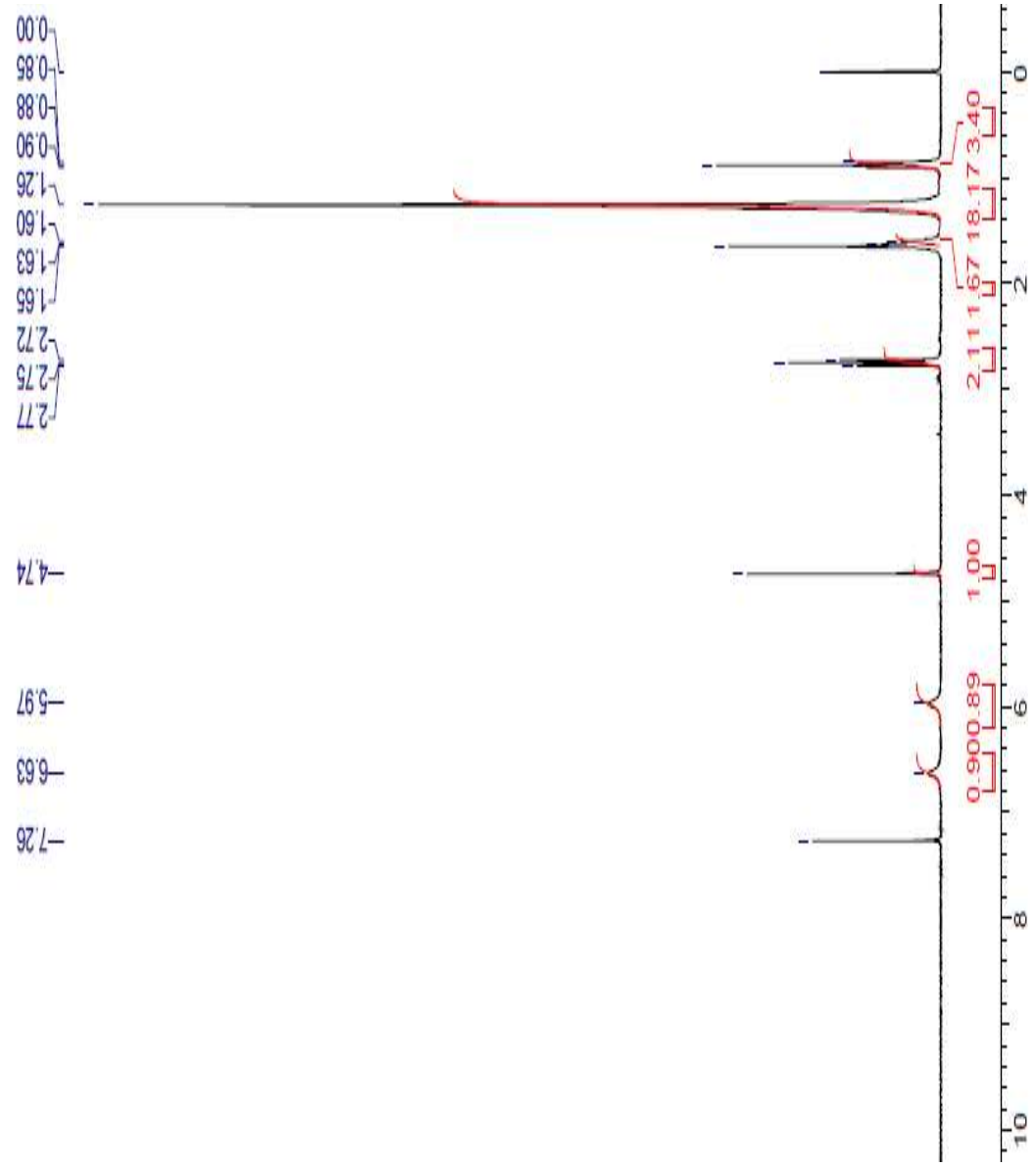


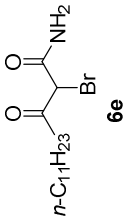
6d

^{13}C NMR Spectrum of Compound **6d**



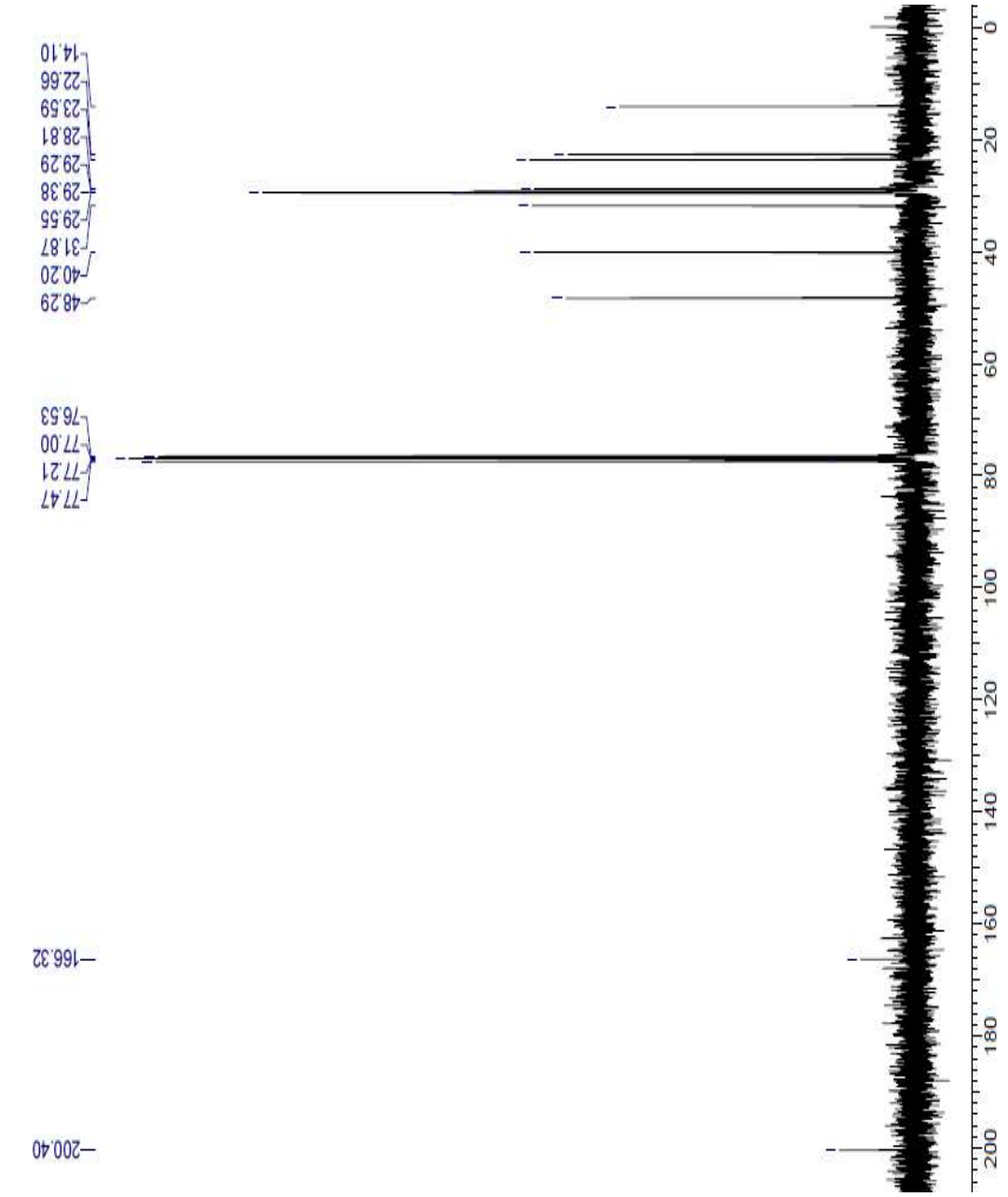
^{1}H NMR Spectrum of Compound **6e**

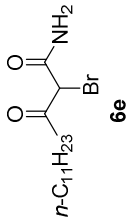




6e

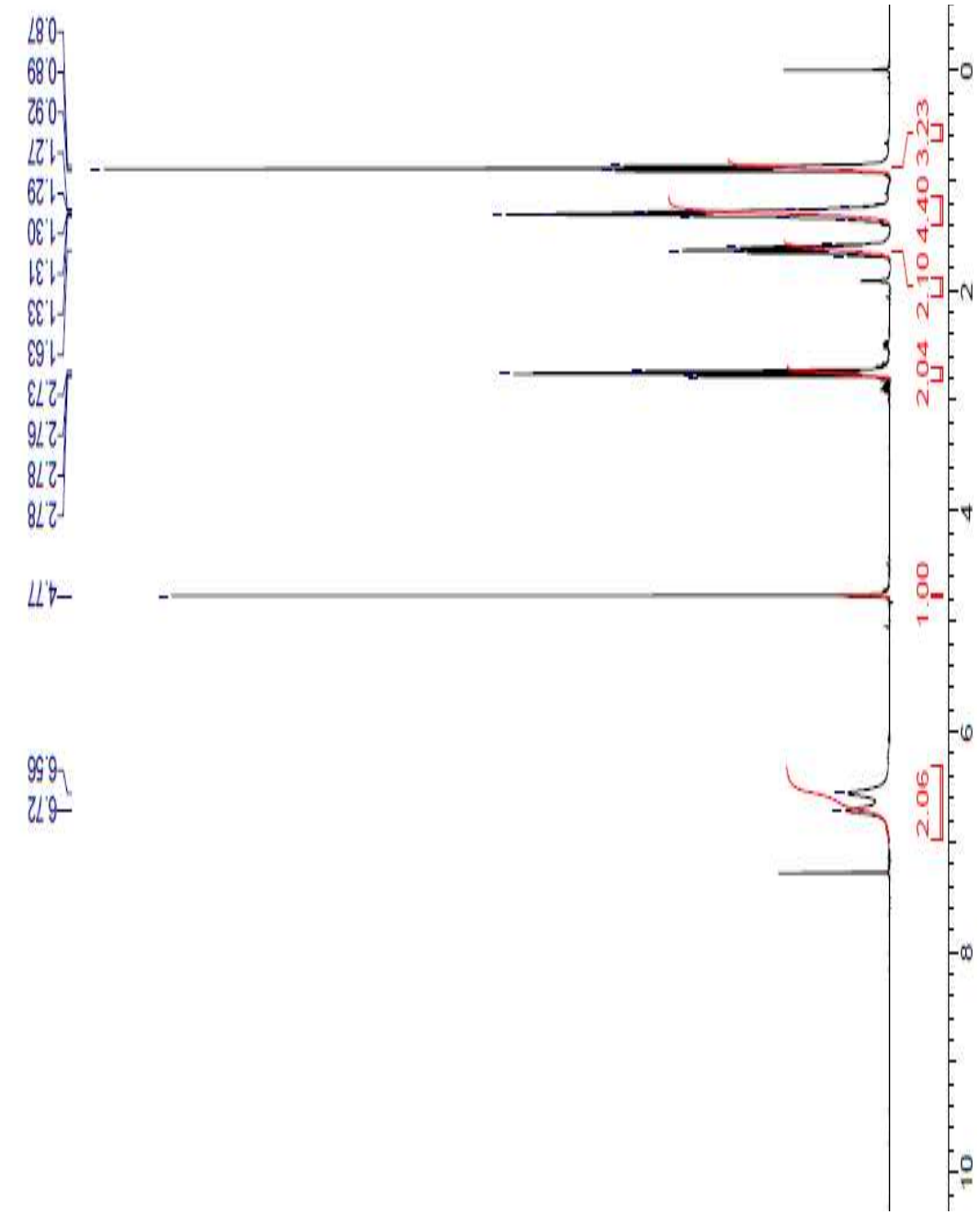
^{13}C NMR Spectrum of Compound **6e**

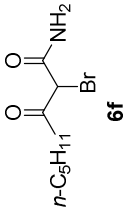




6e

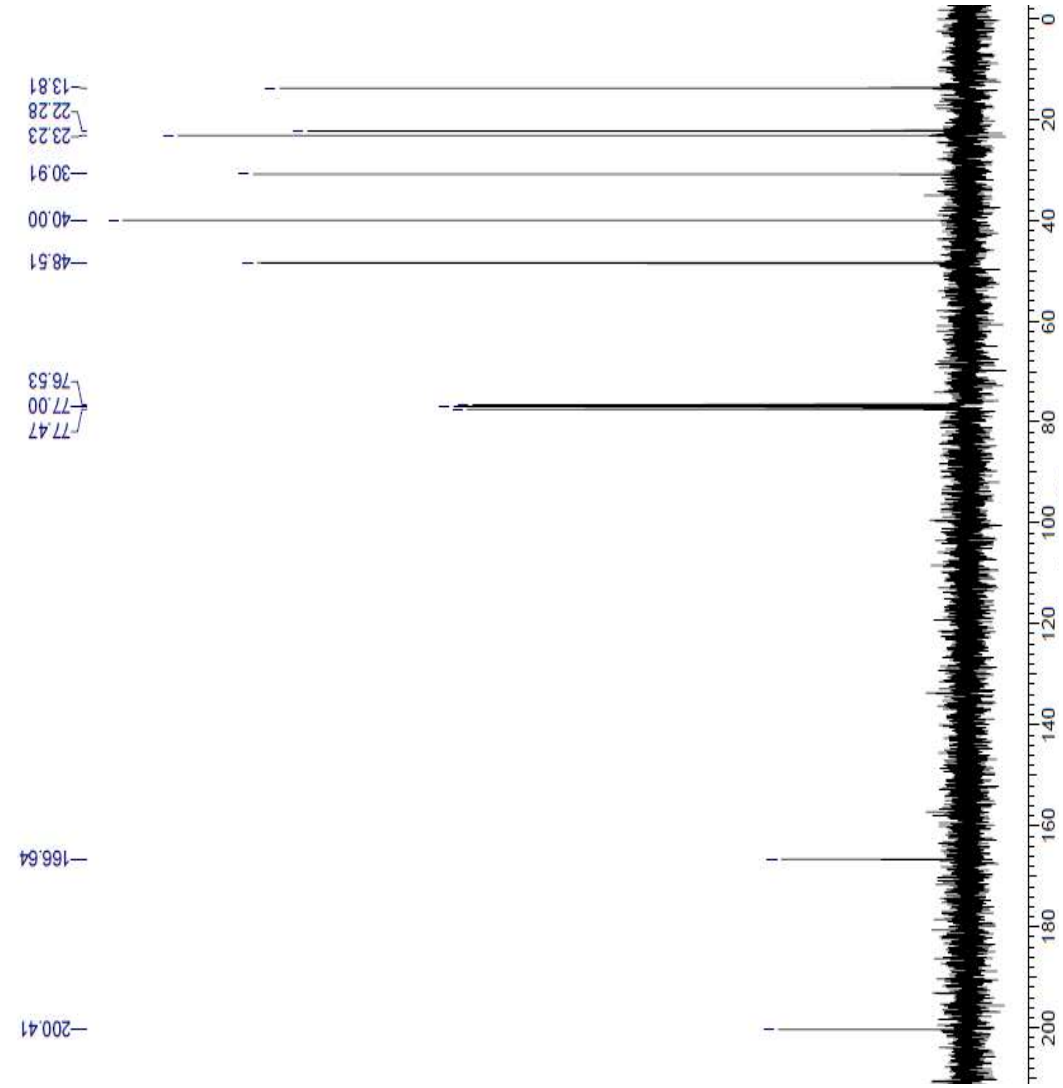
^{1}H NMR Spectrum of Compound **6f**

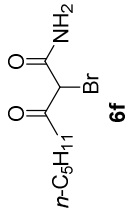




6f

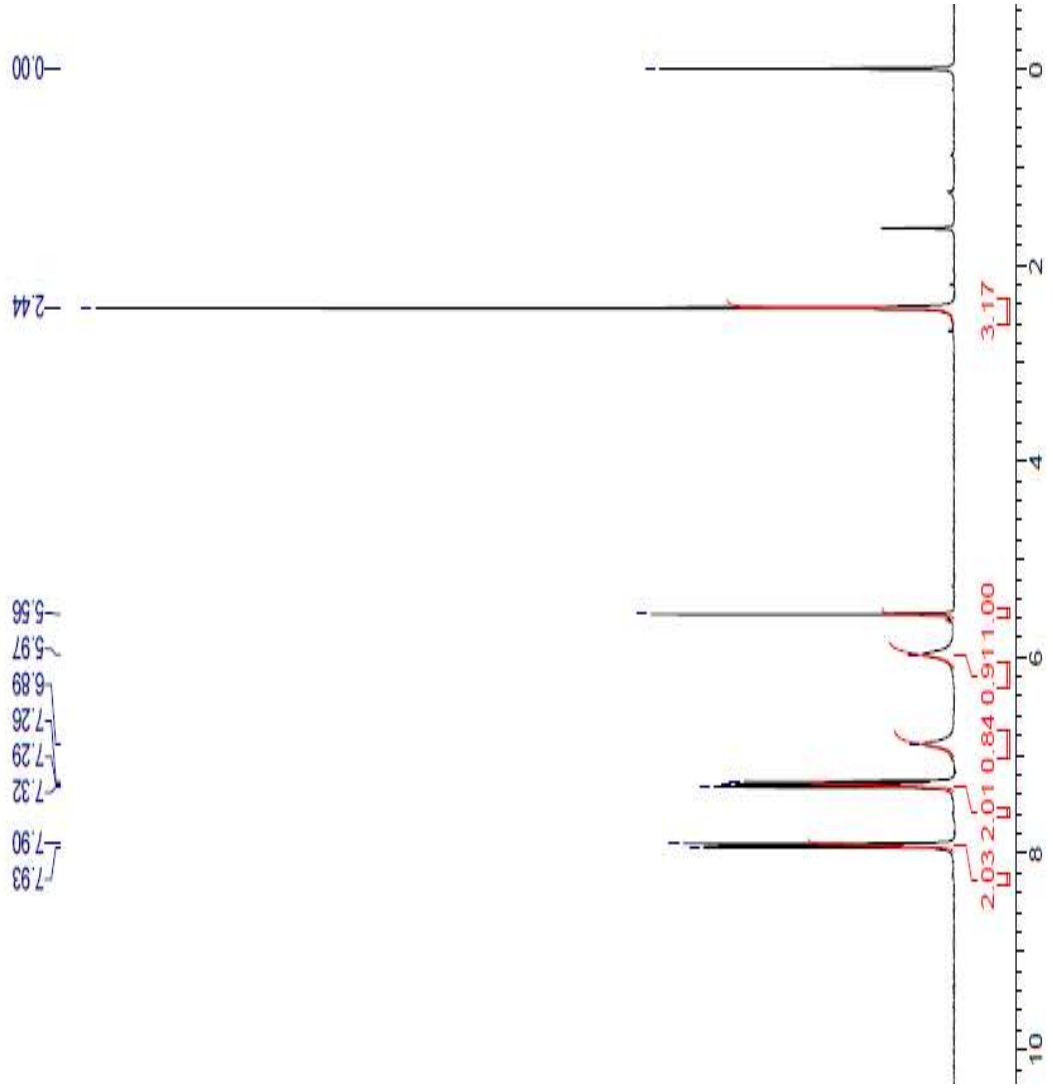
^{13}C NMR Spectrum of Compound **6f**

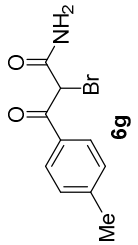




6f

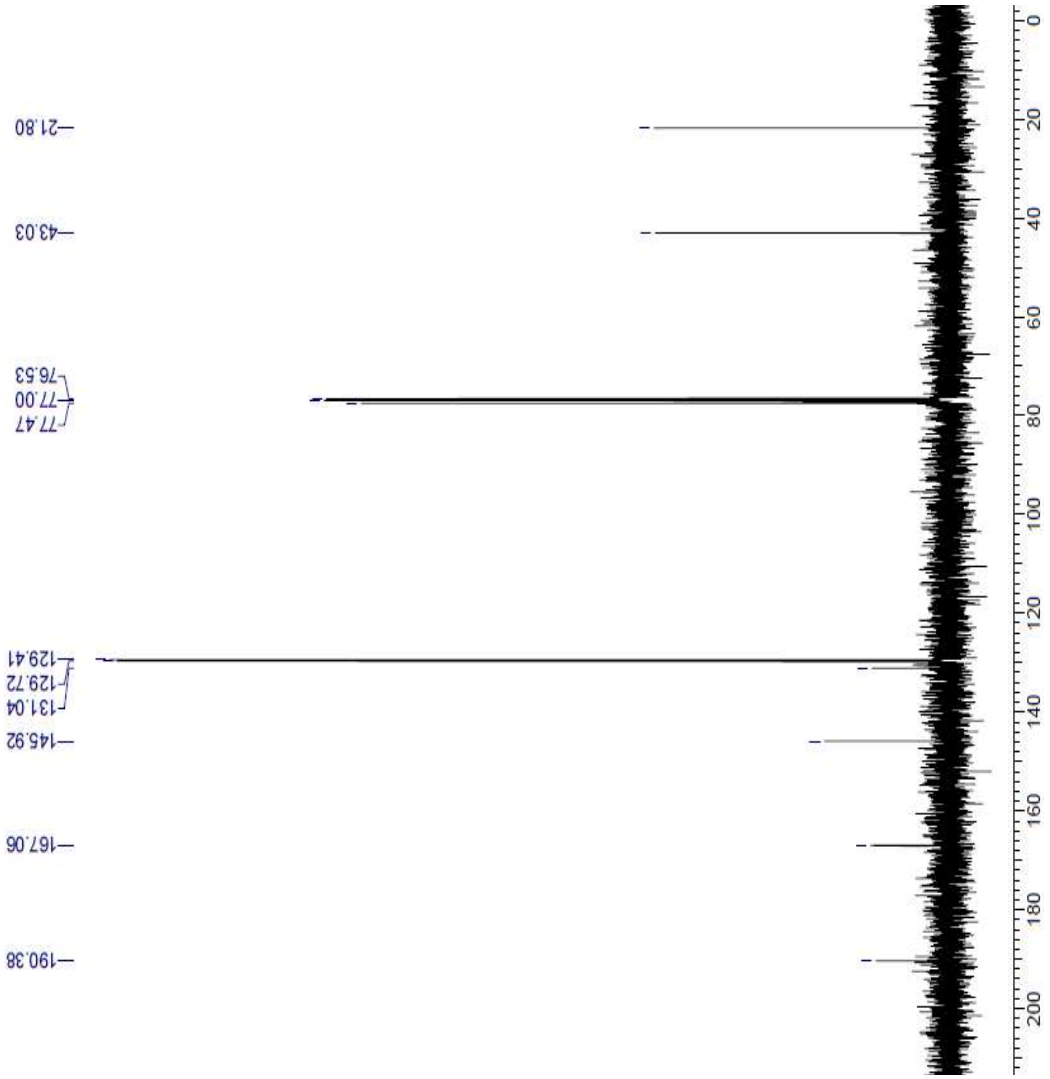
^{1}H NMR Spectrum of Compound **6g**

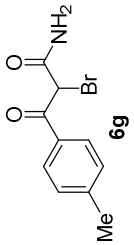




6g

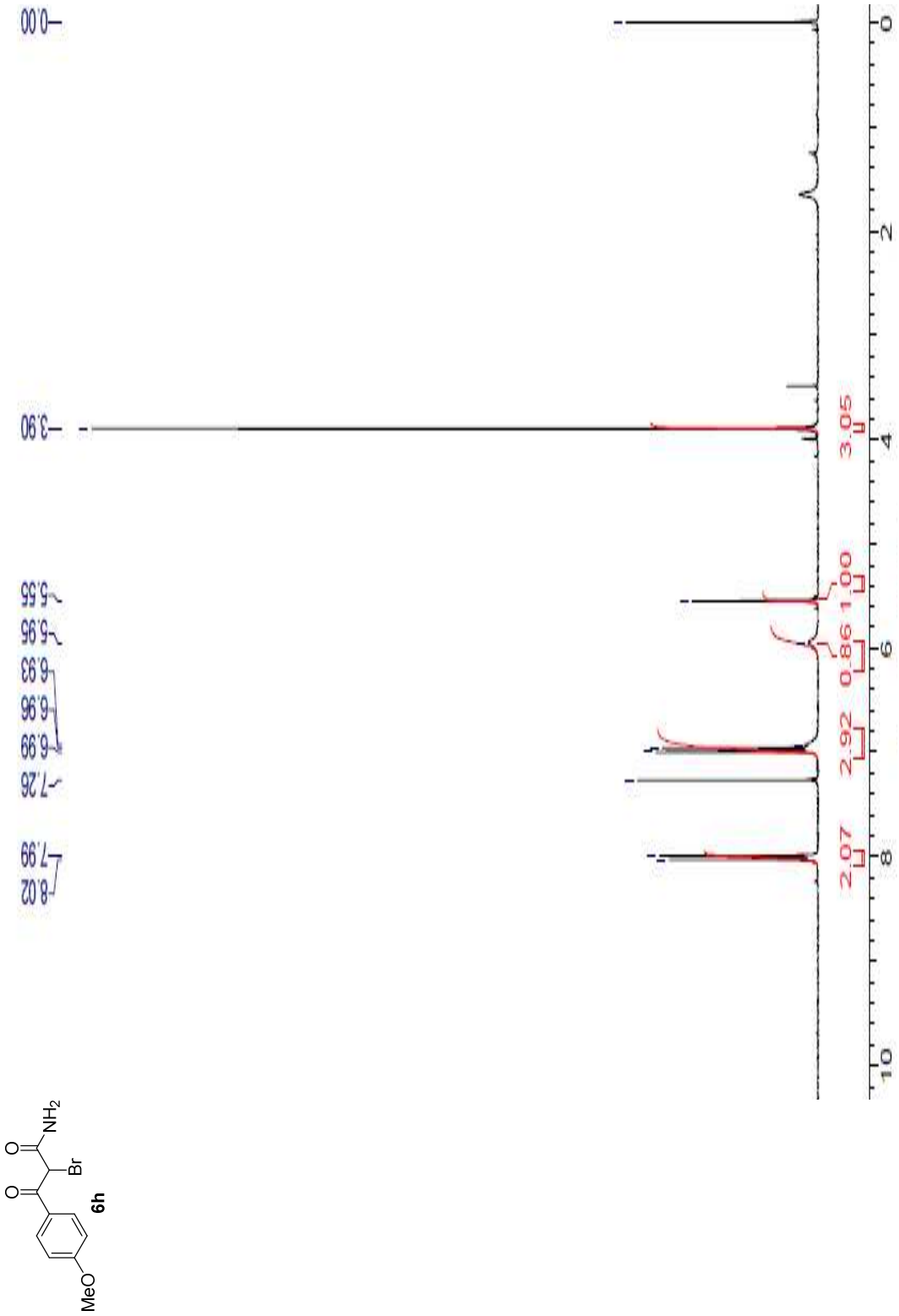
^{13}C NMR Spectrum of Compound **6g**





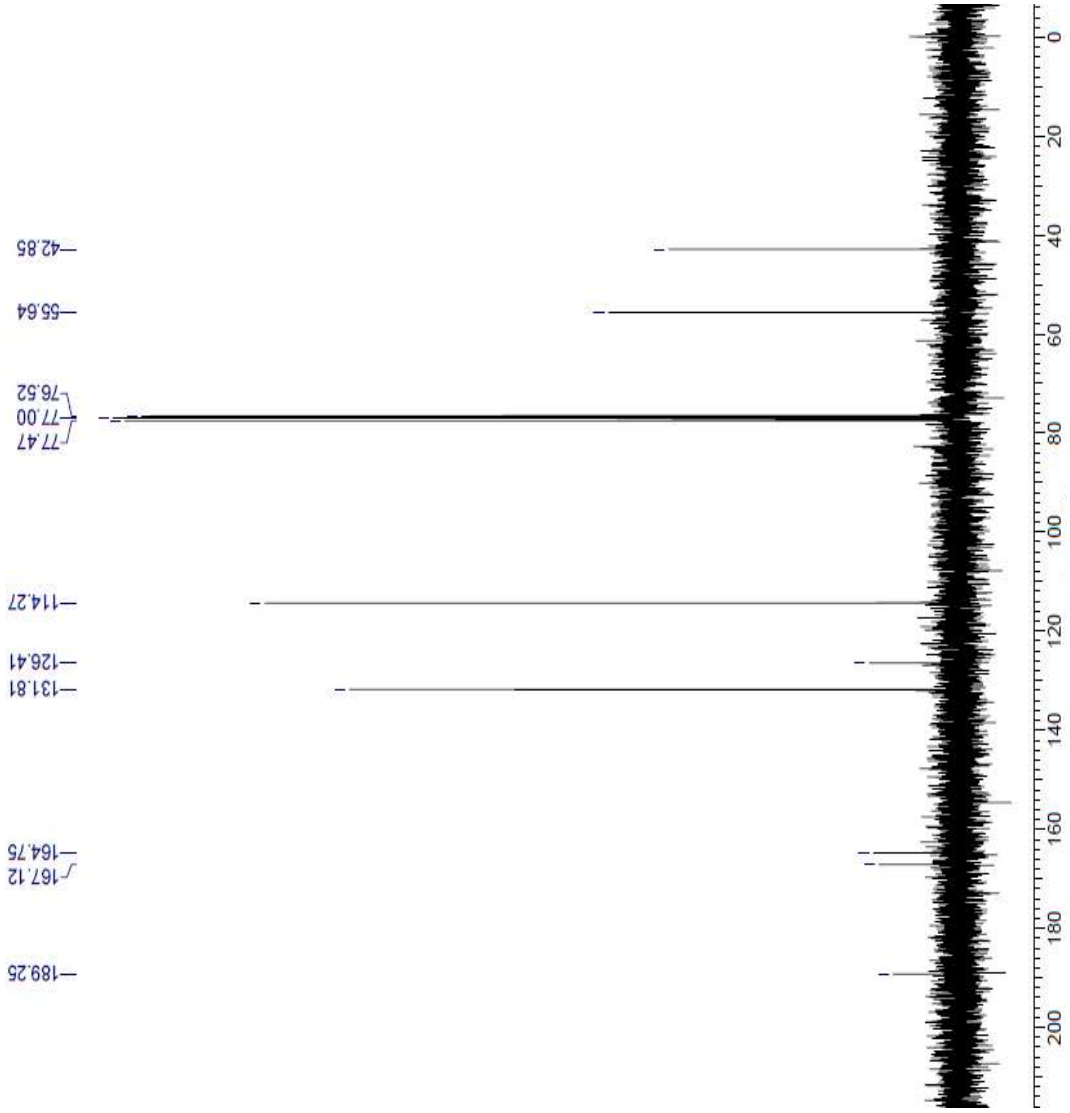
6g

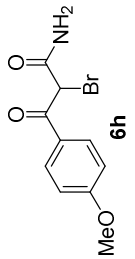
^{1}H NMR Spectrum of Compound **6h**



6h

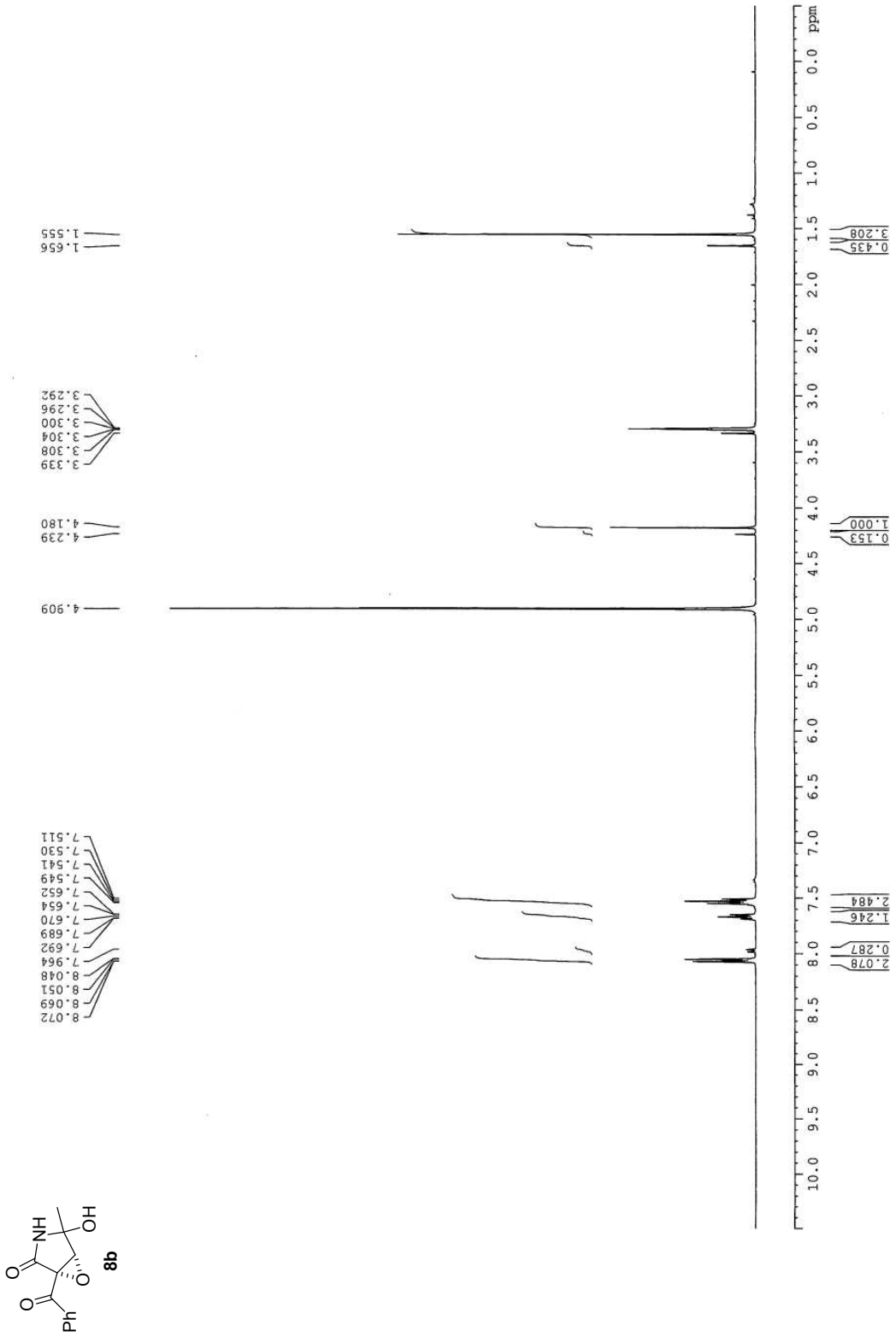
^{13}C NMR Spectrum of Compound **6h**



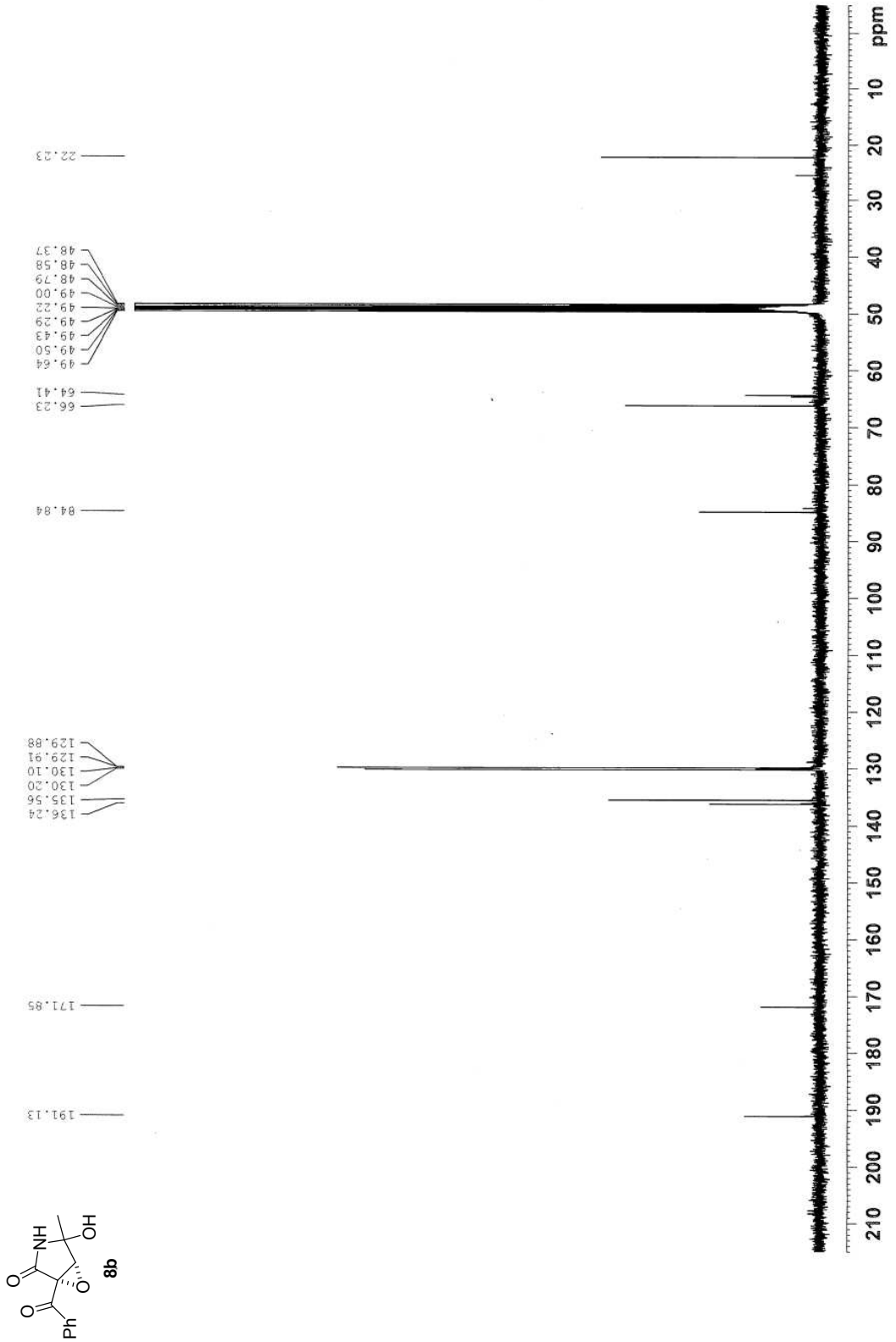


6h

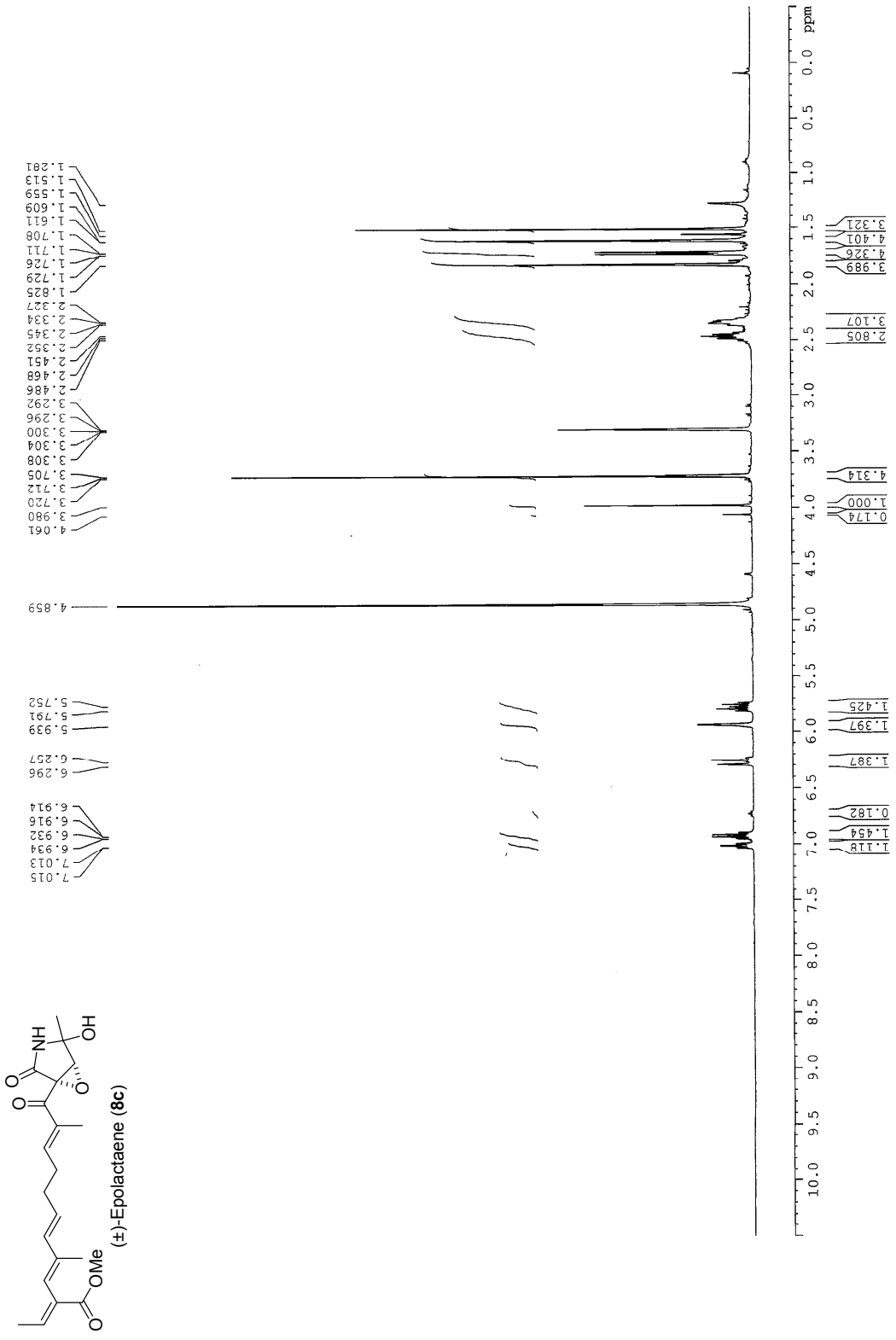
^{1}H NMR Spectrum of Compound **8b**



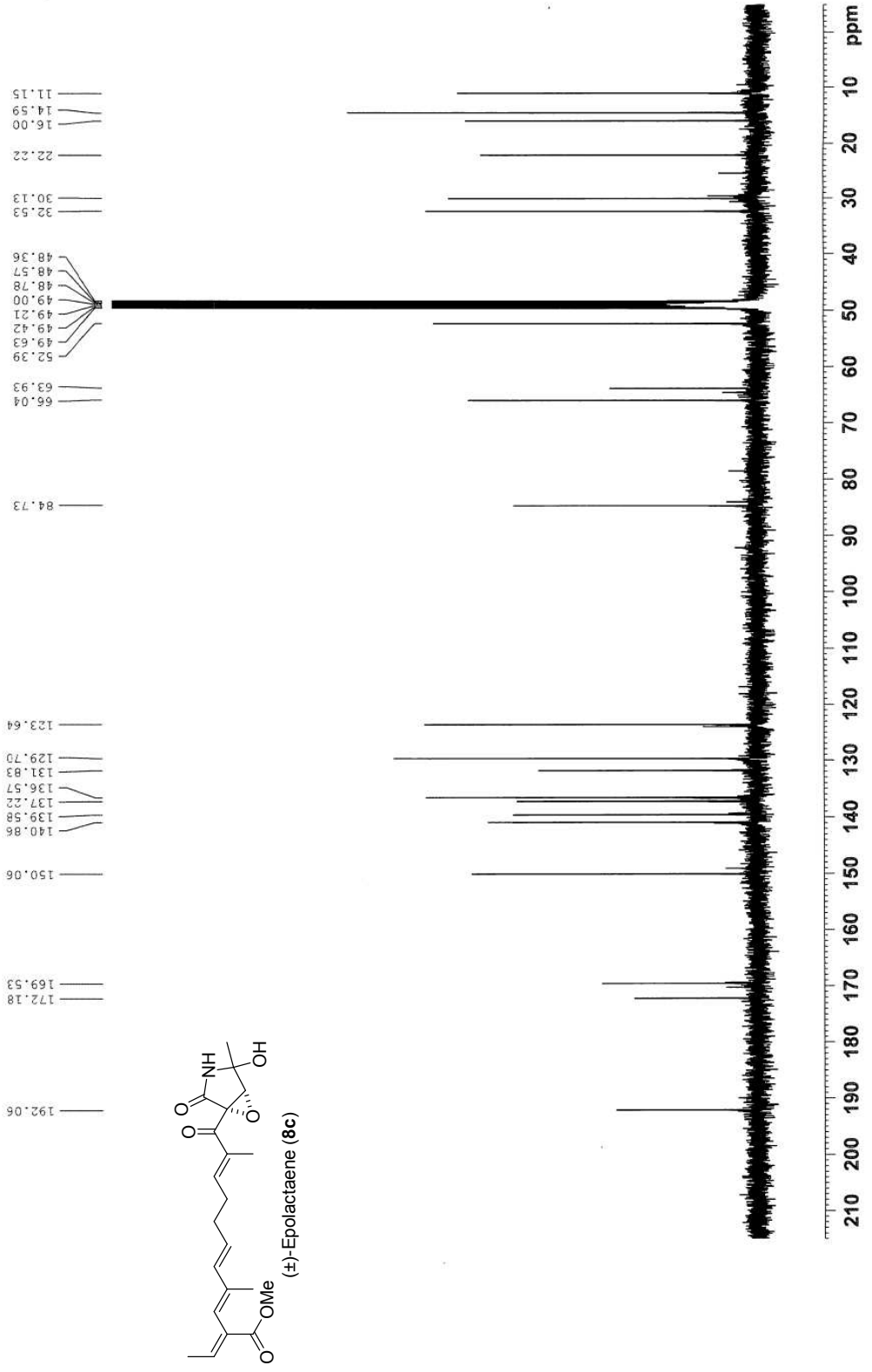
^{13}C NMR Spectrum of Compound **8b**



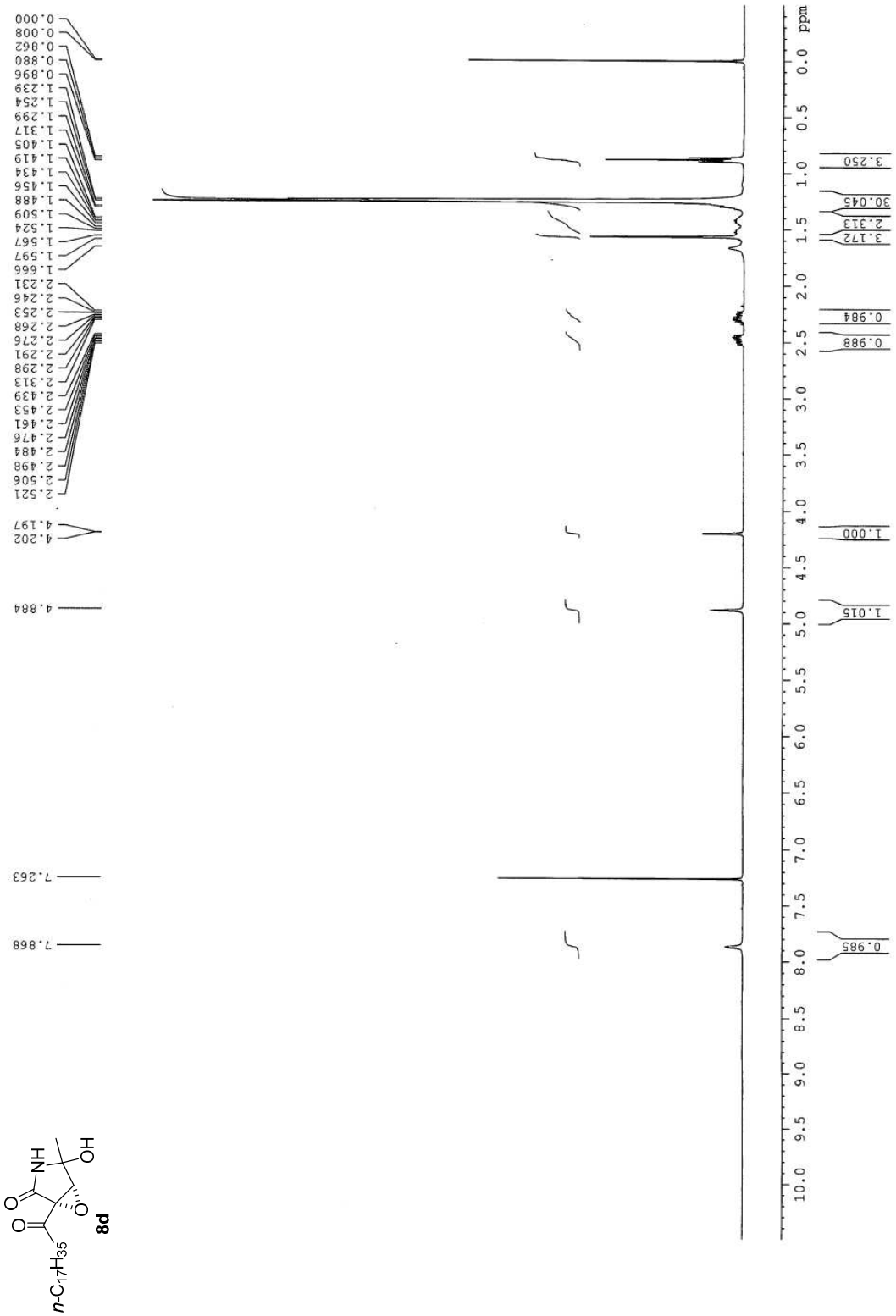
^{1}H NMR Spectrum of Compound **8c**



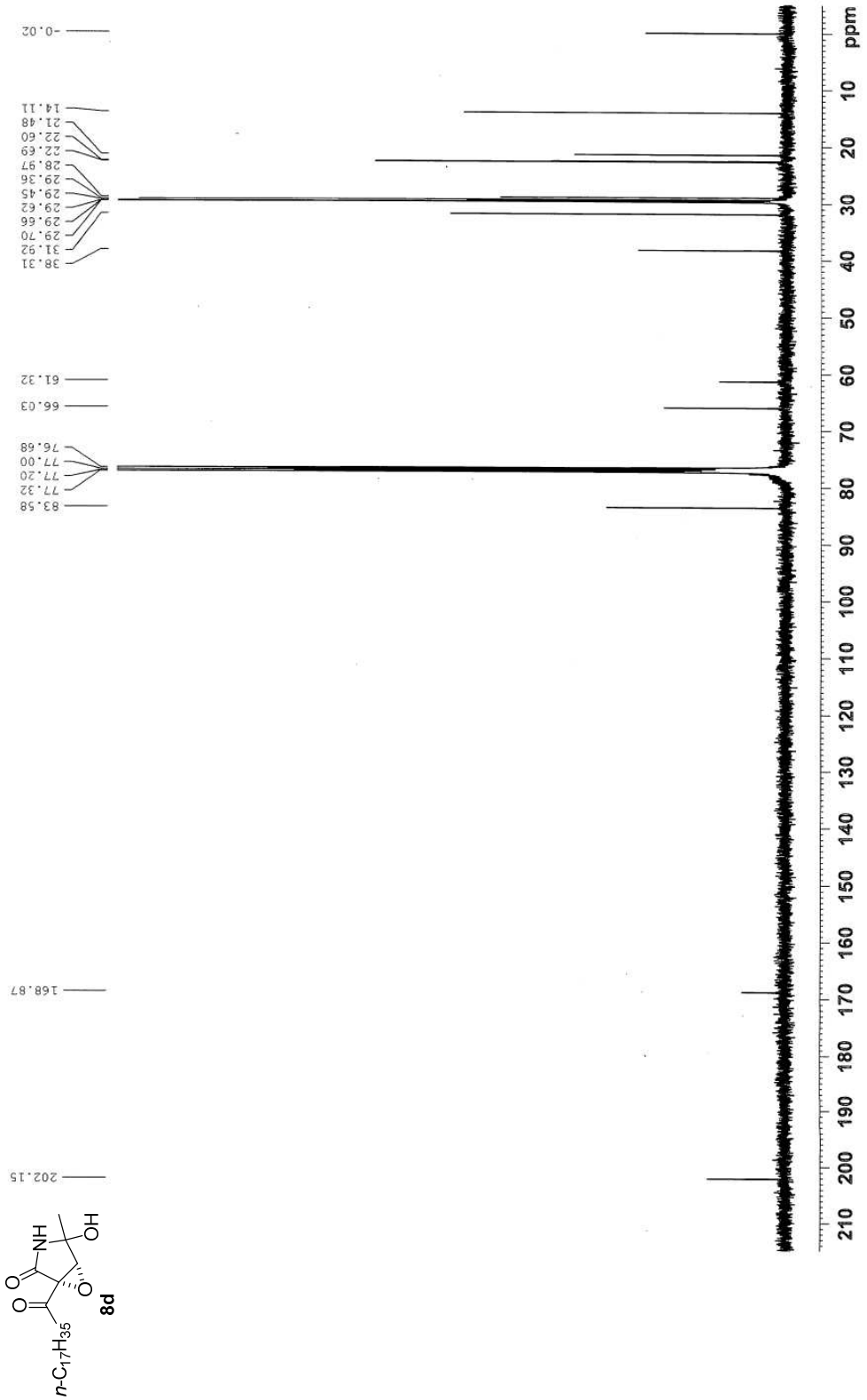
^{13}C NMR Spectrum of Compound **8c**



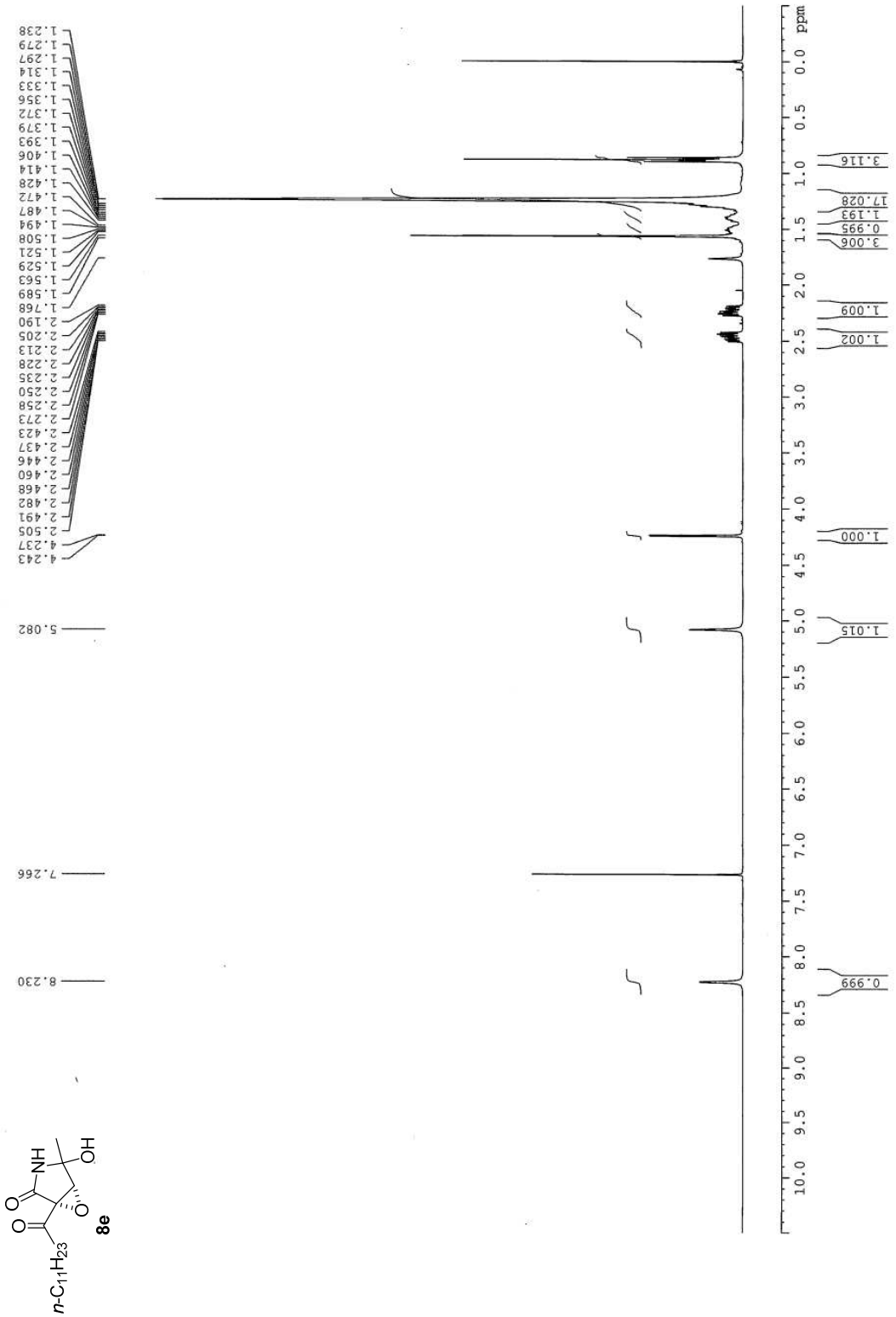
^{1}H NMR Spectrum of Compound **8d**



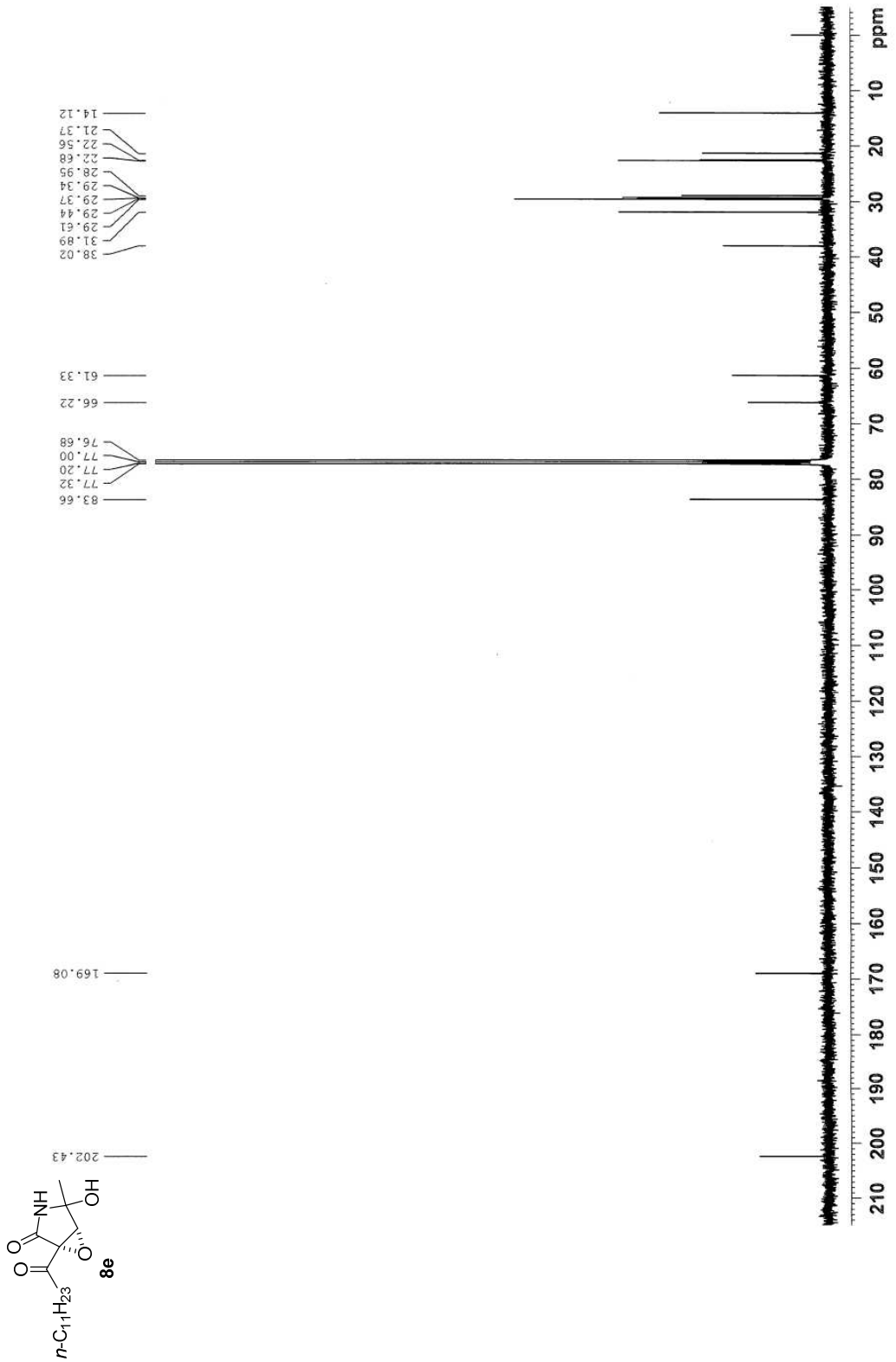
^{13}C NMR Spectrum of Compound **8d**



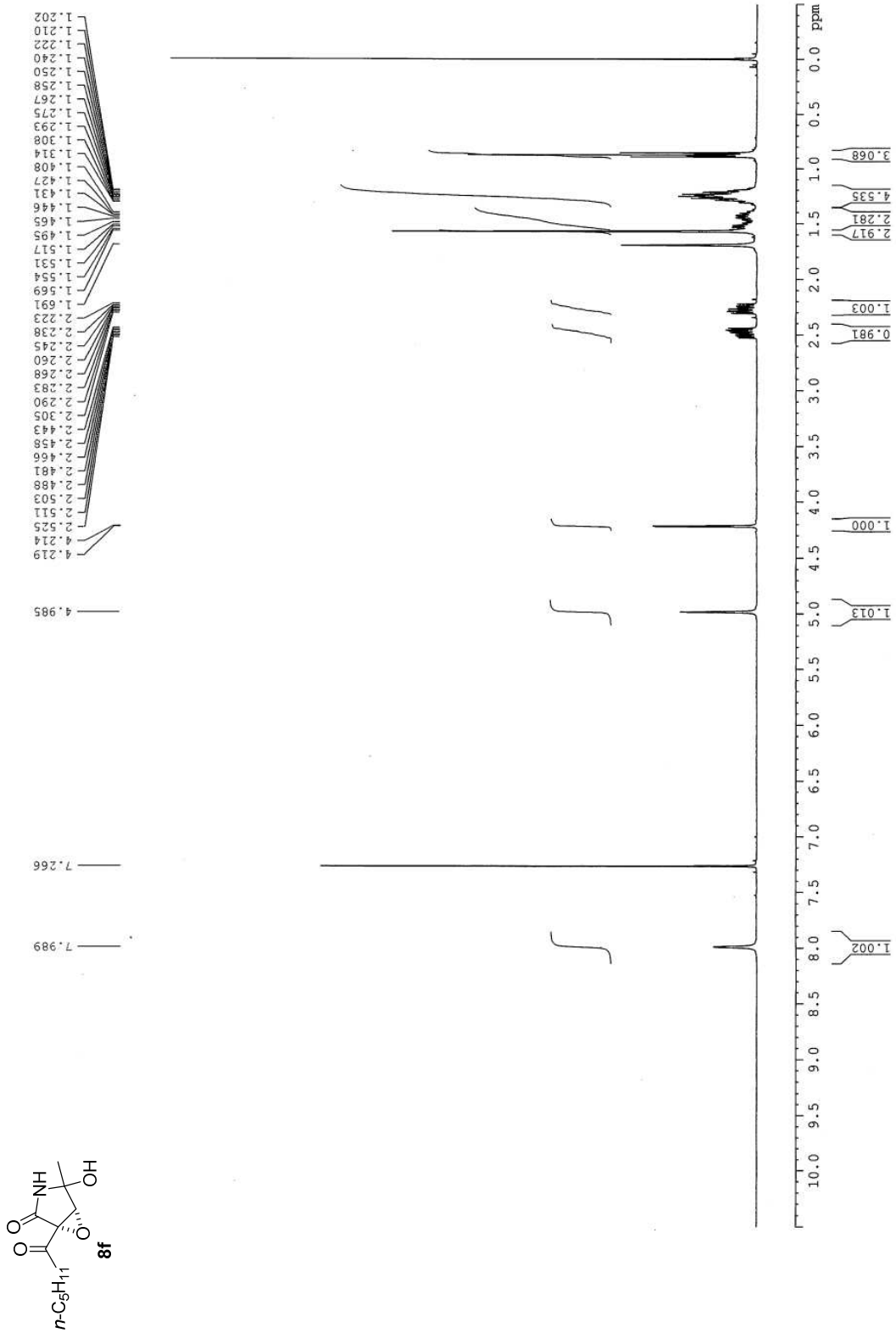
^{1}H NMR Spectrum of Compound **8e**



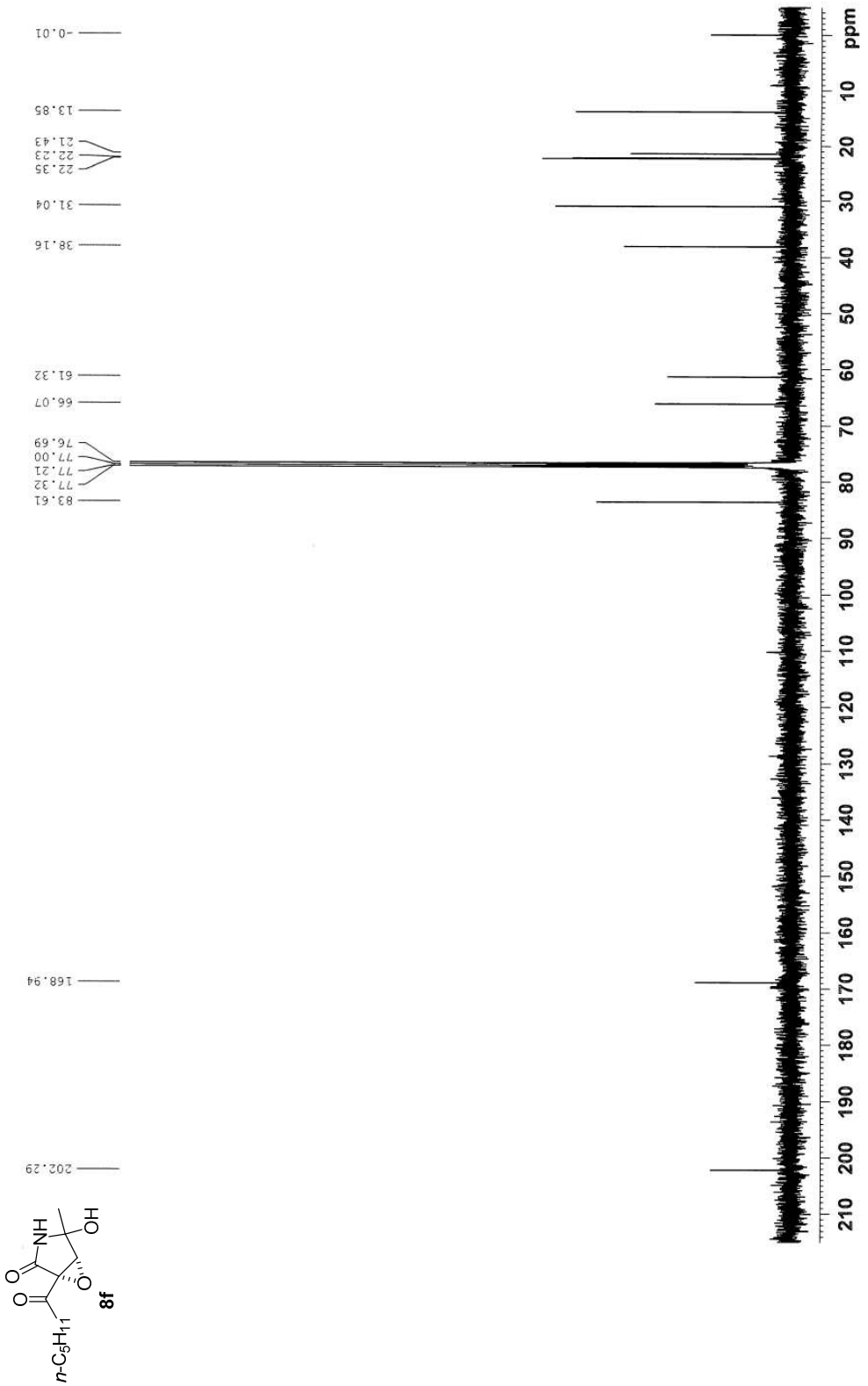
^{13}C NMR Spectrum of Compound **8e**



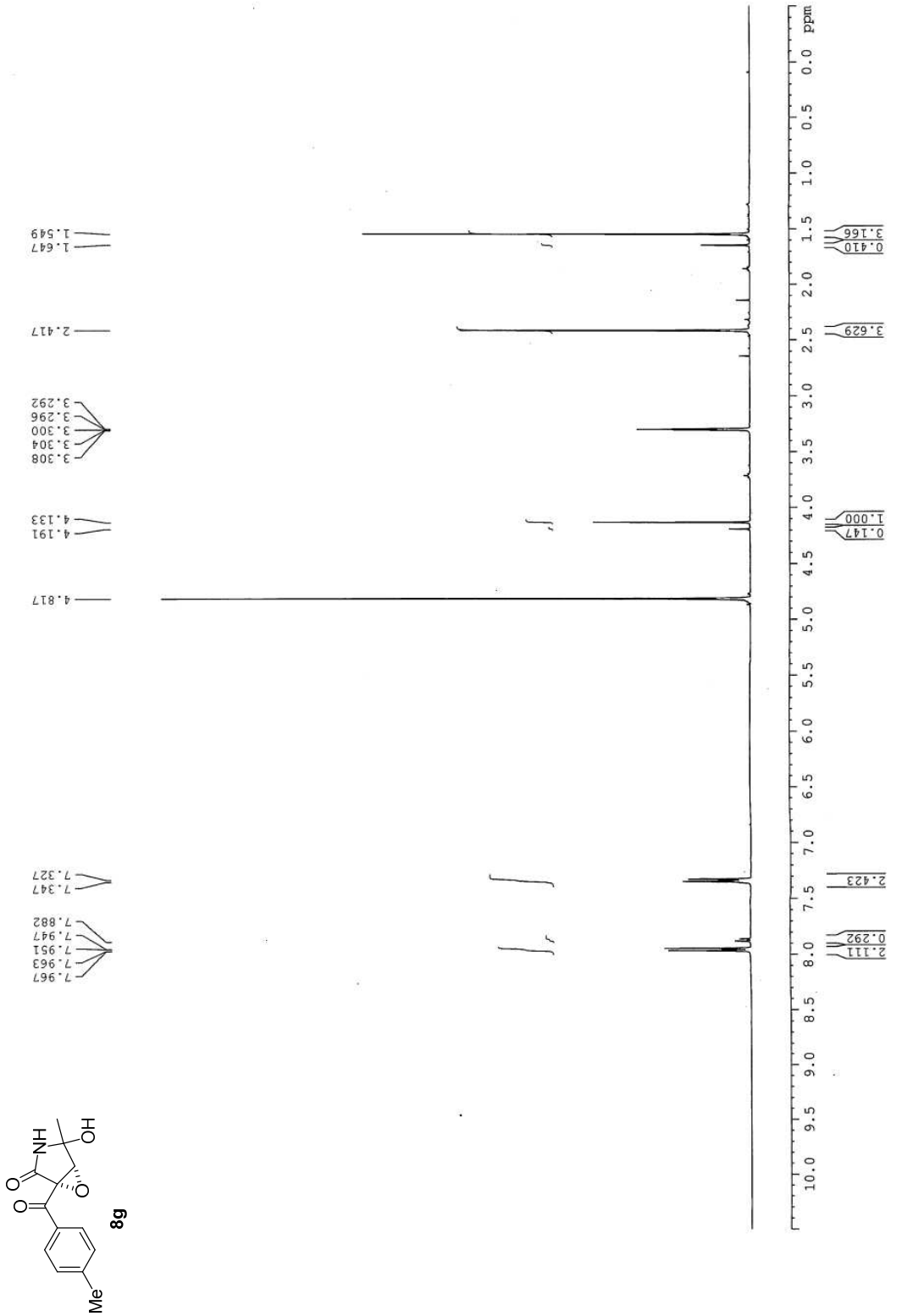
^{1}H NMR Spectrum of Compound **8f**



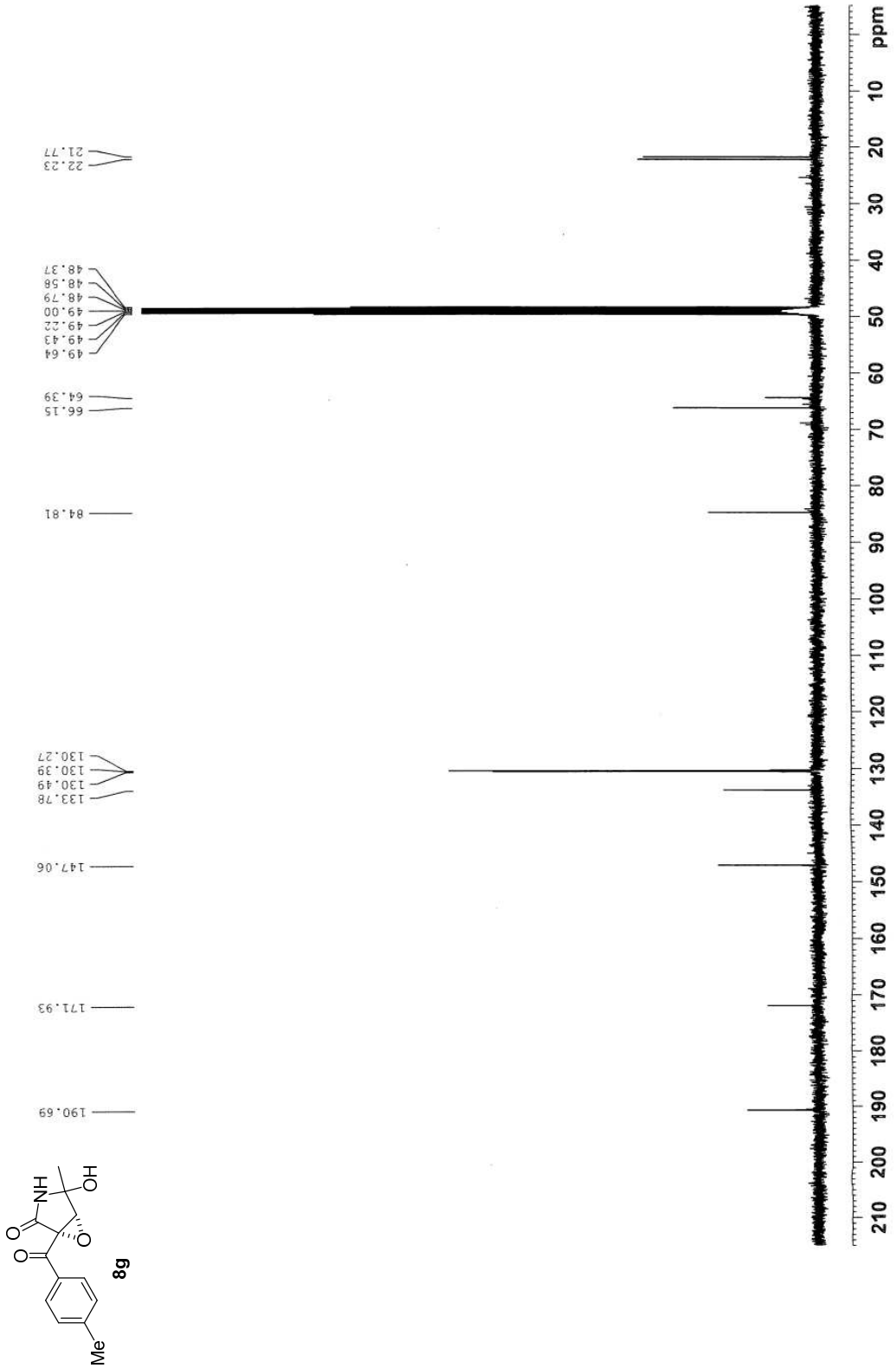
^{13}C NMR Spectrum of Compound **8f**



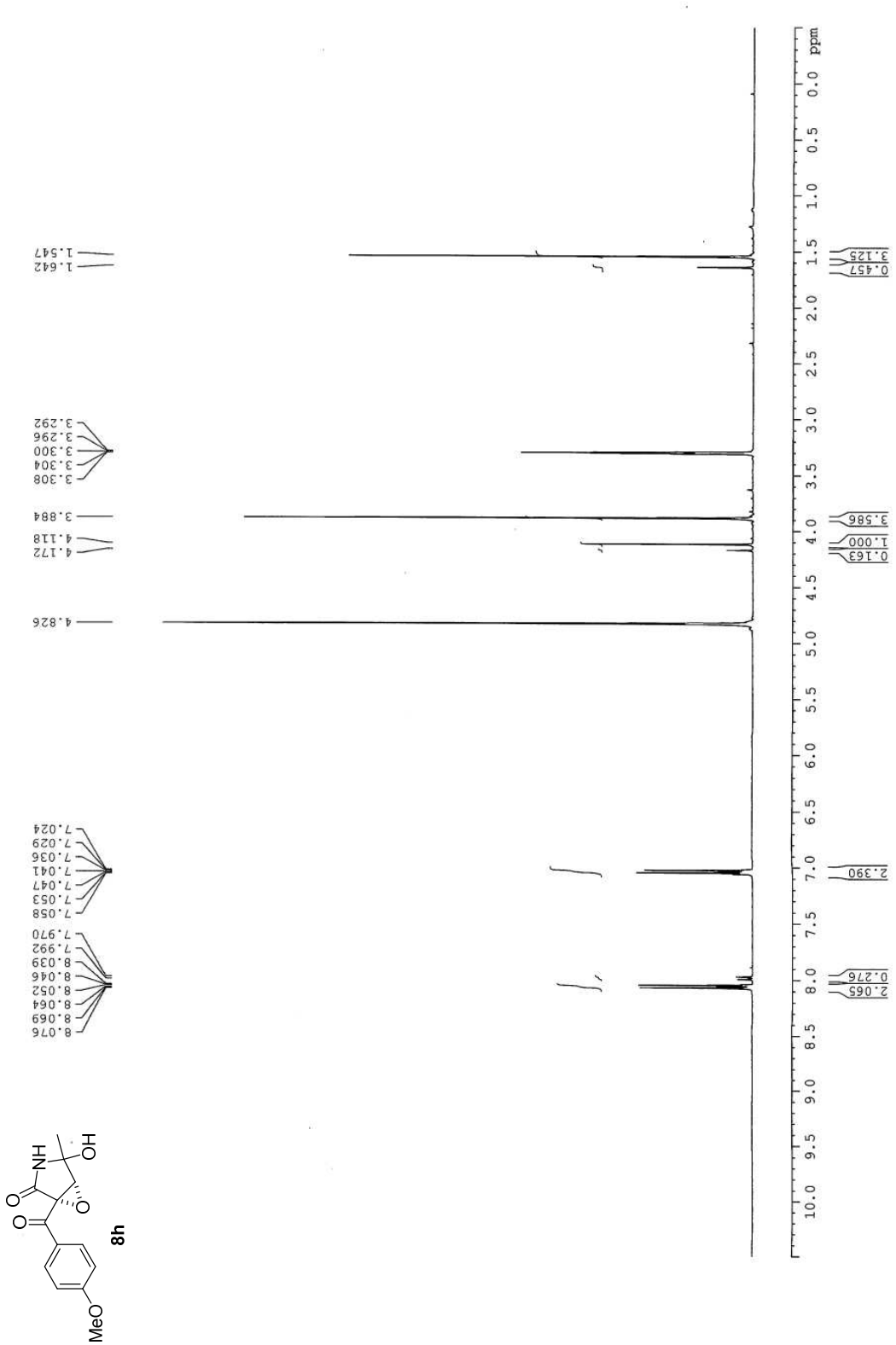
^{1}H NMR Spectrum of Compound **8g**



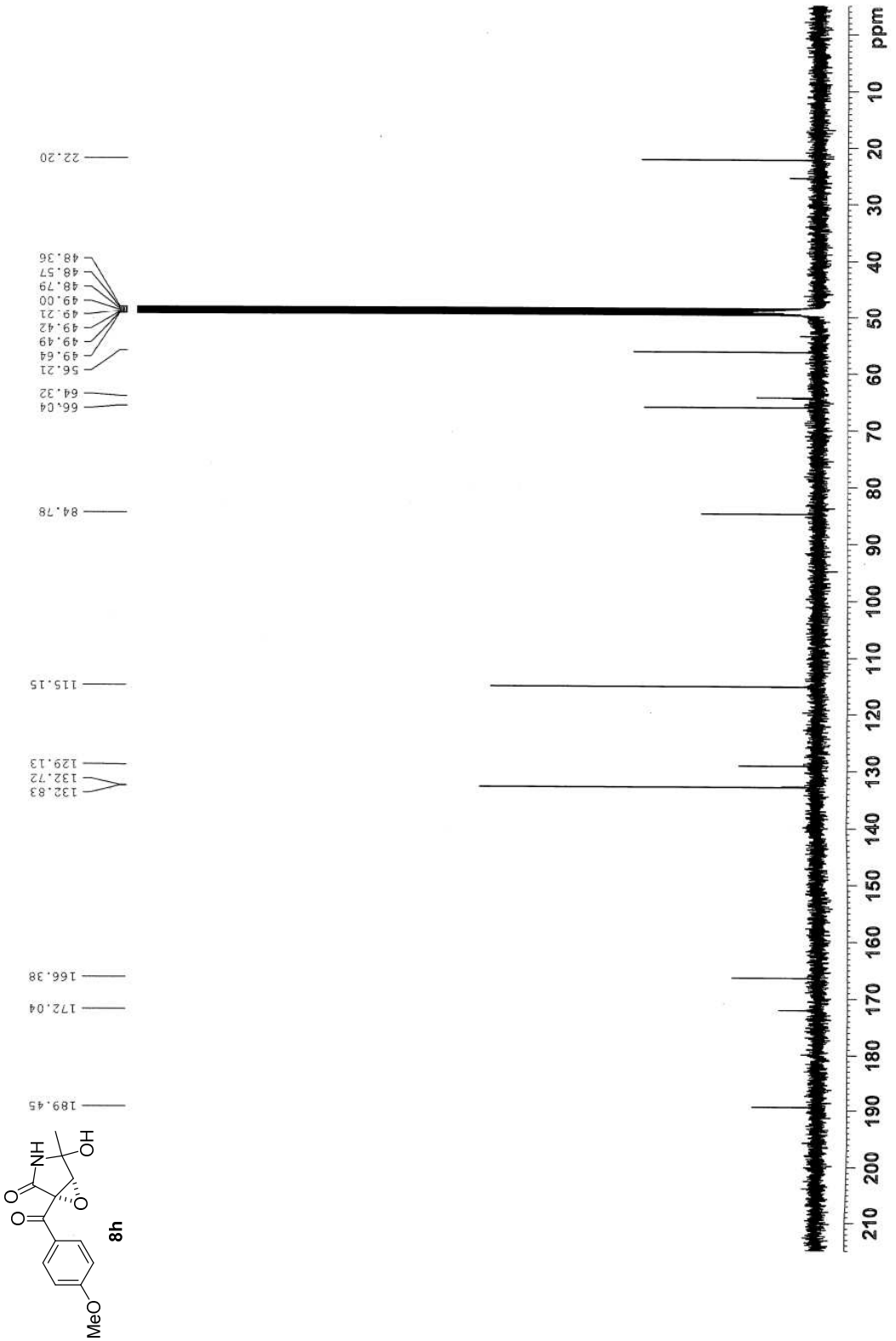
^{13}C NMR Spectrum of Compound **8g**



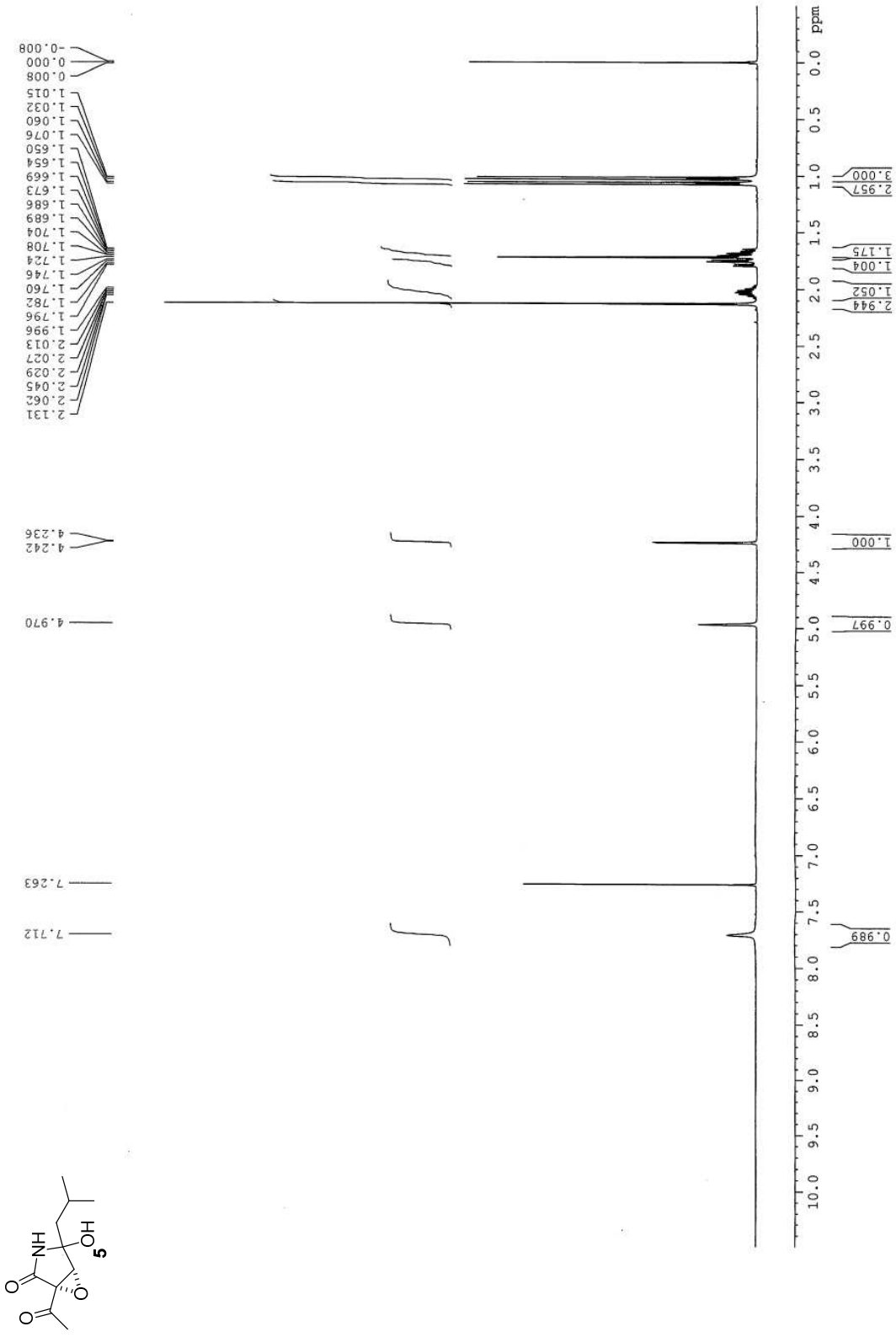
^{1}H NMR Spectrum of Compound **8h**



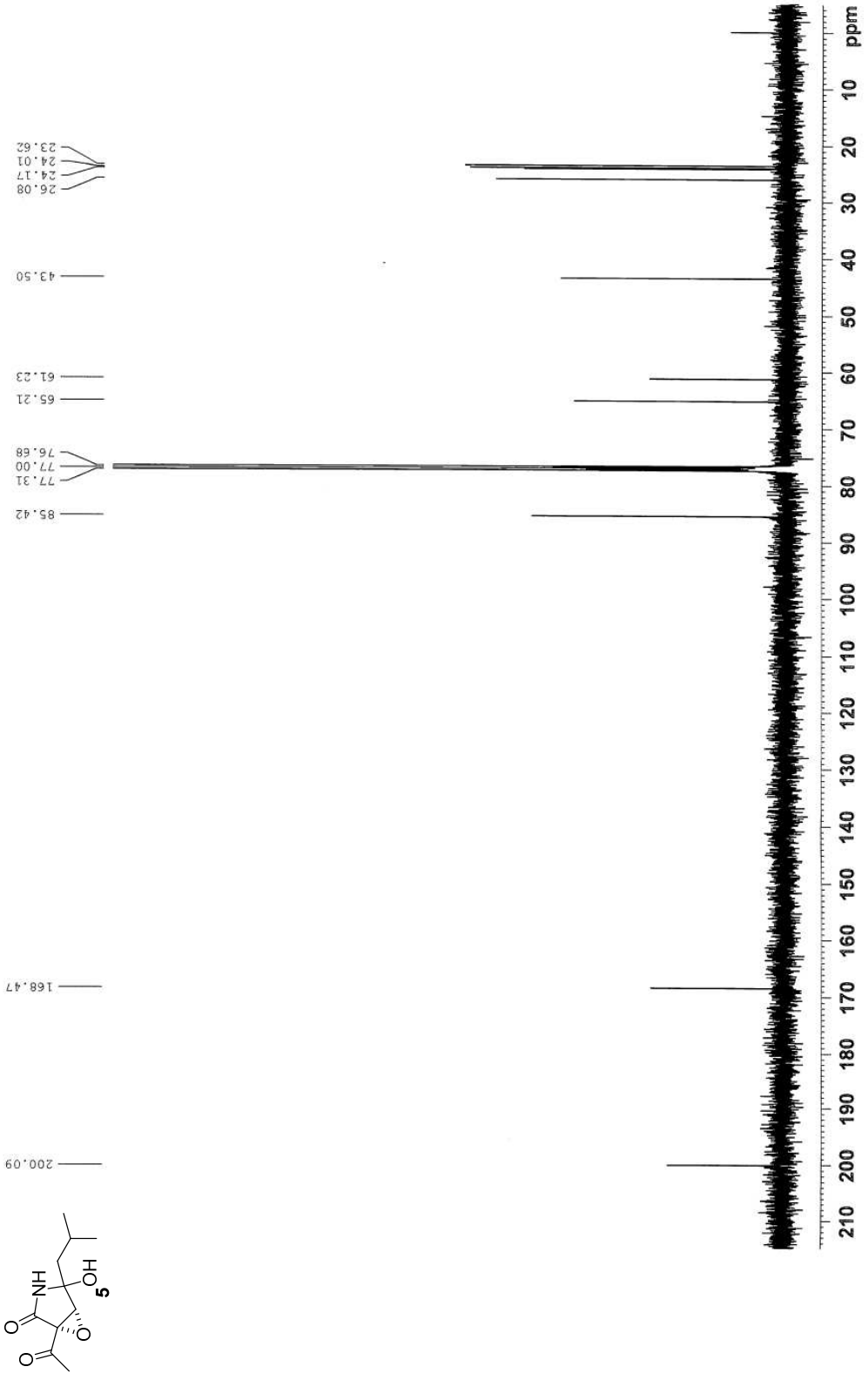
^{13}C NMR Spectrum of Compound **8h**



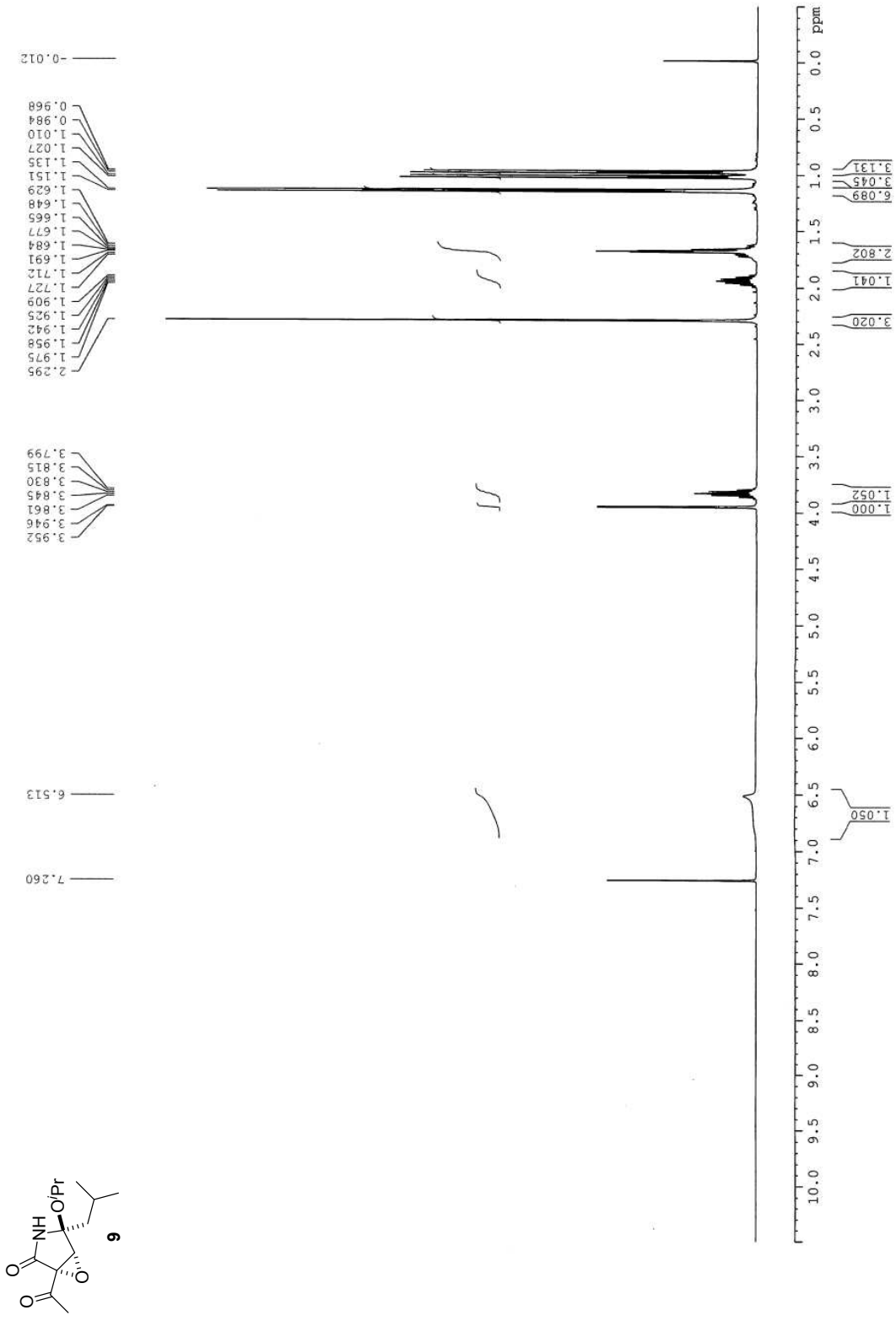
^{1}H NMR Spectrum of Compound **5**



^{13}C NMR Spectrum of Compound **5**

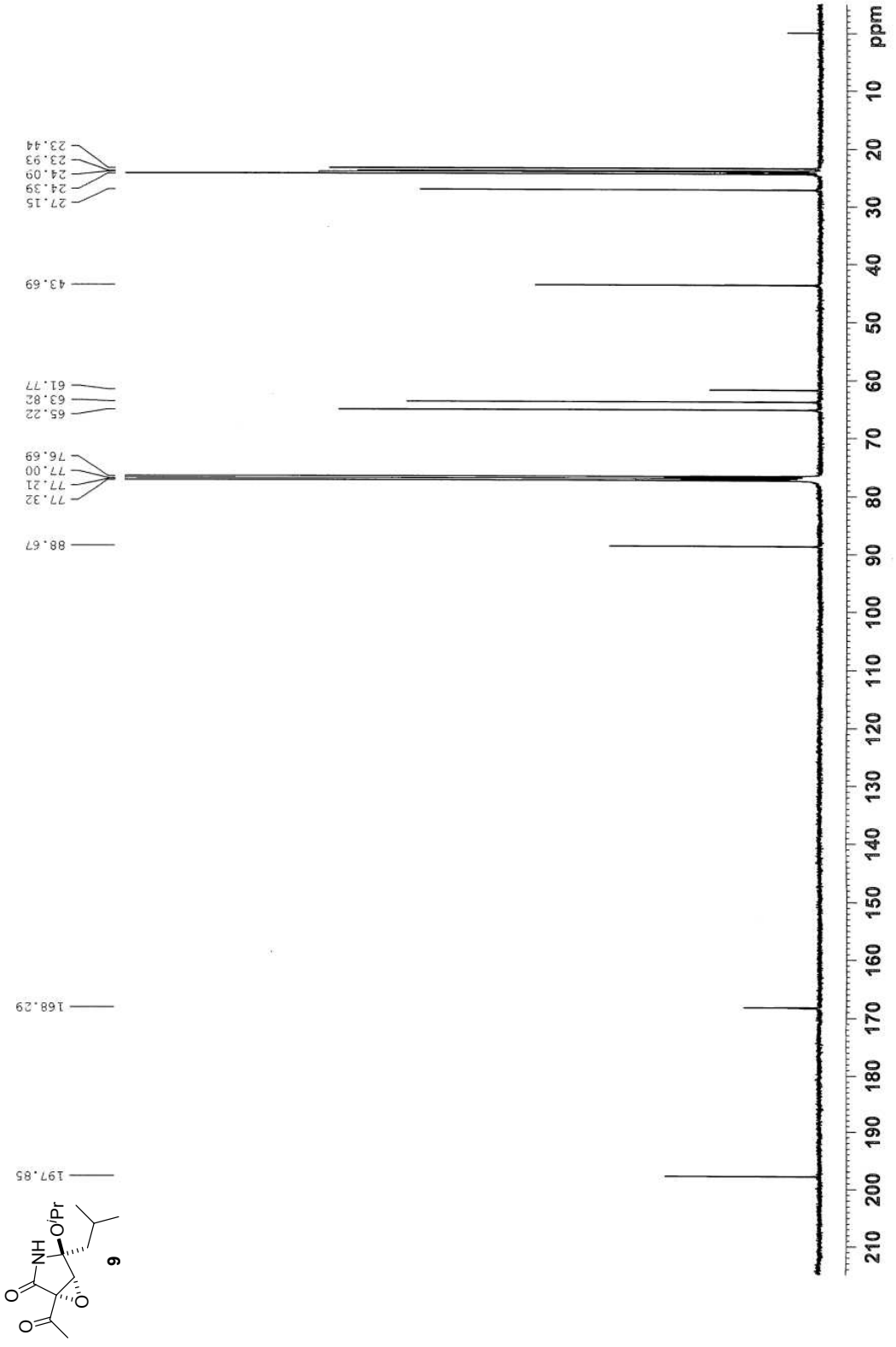


^{1}H NMR Spectrum of Compound **9**

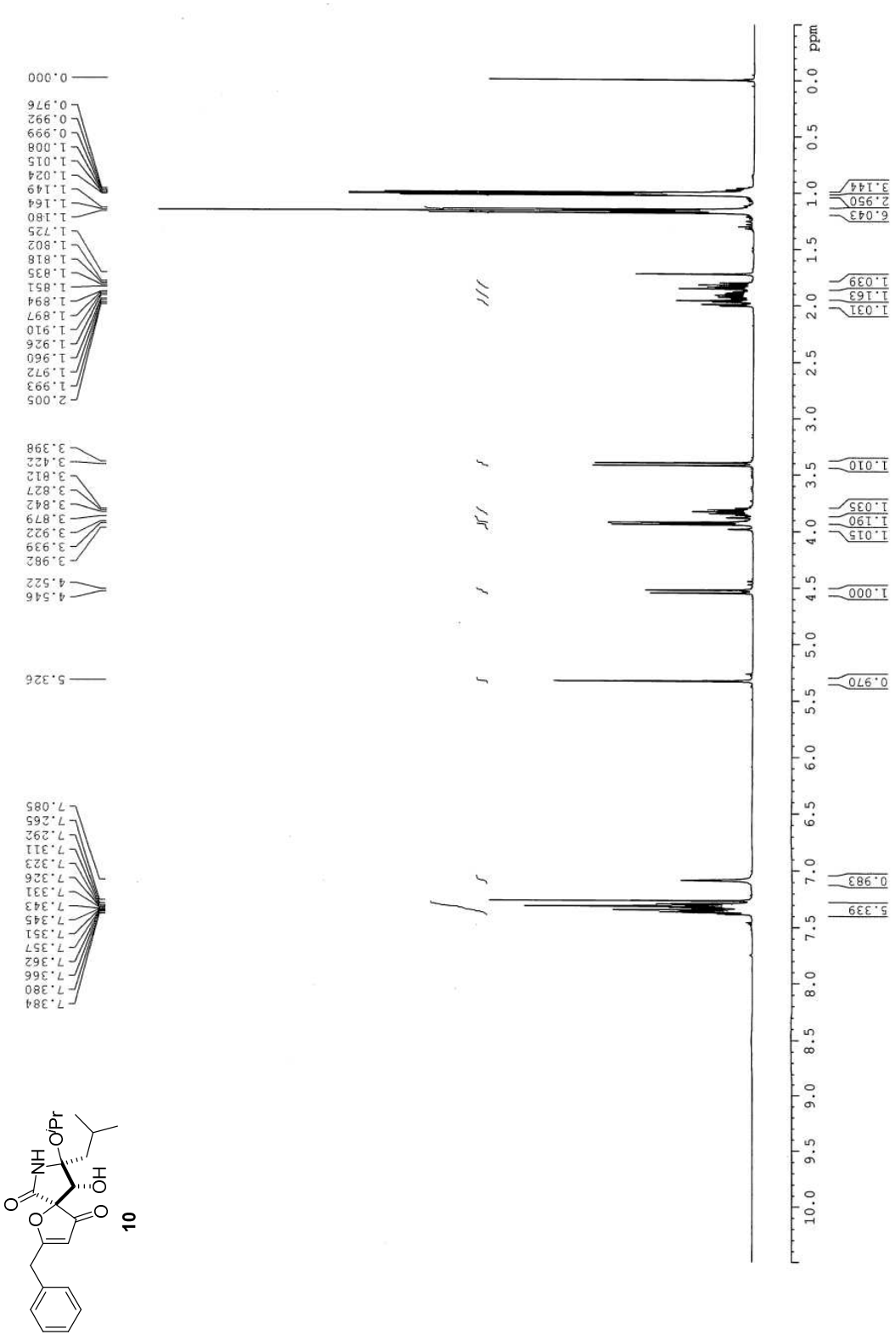


9

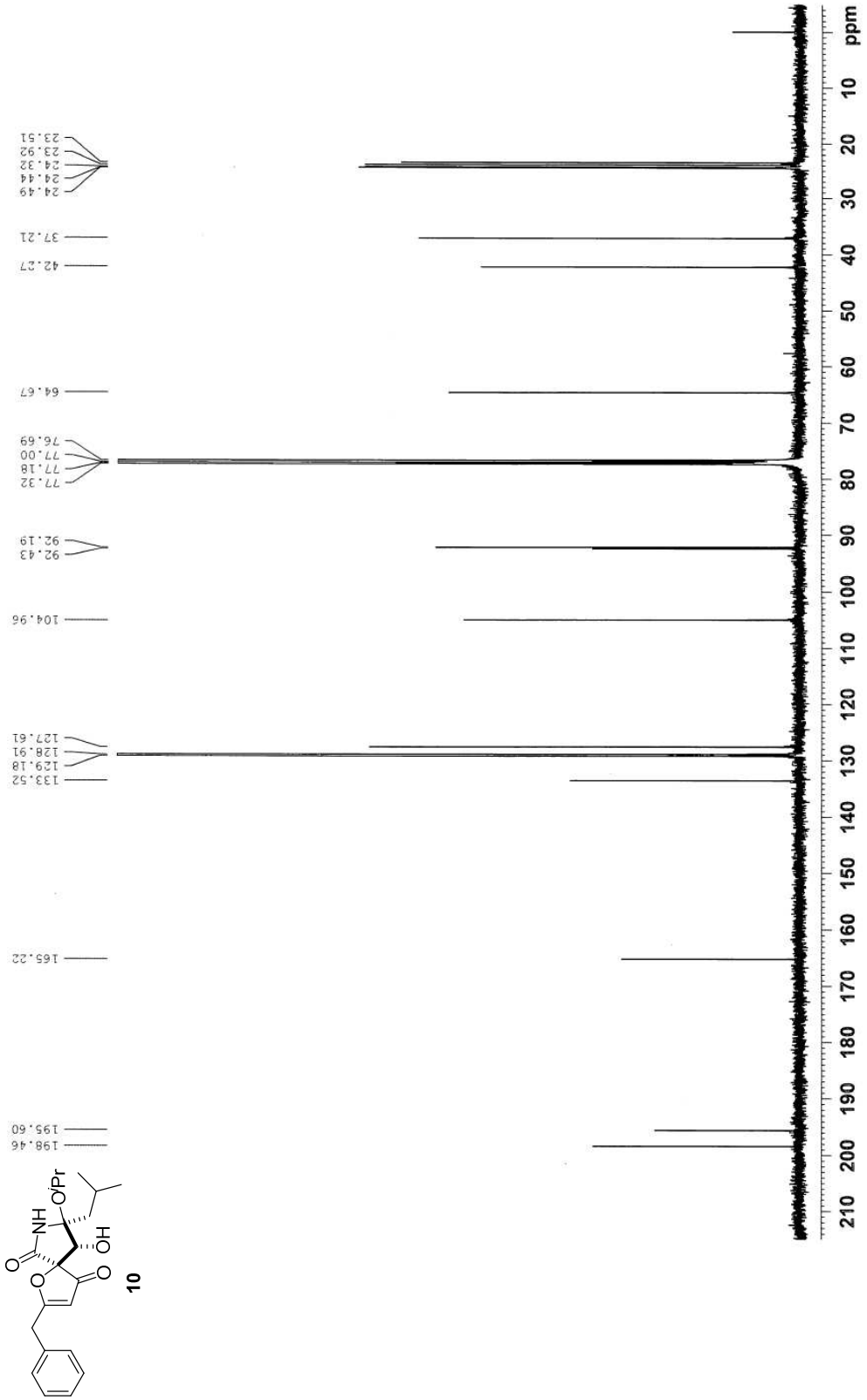
^{13}C NMR Spectrum of Compound **9**



^{1}H NMR Spectrum of Compound **10**

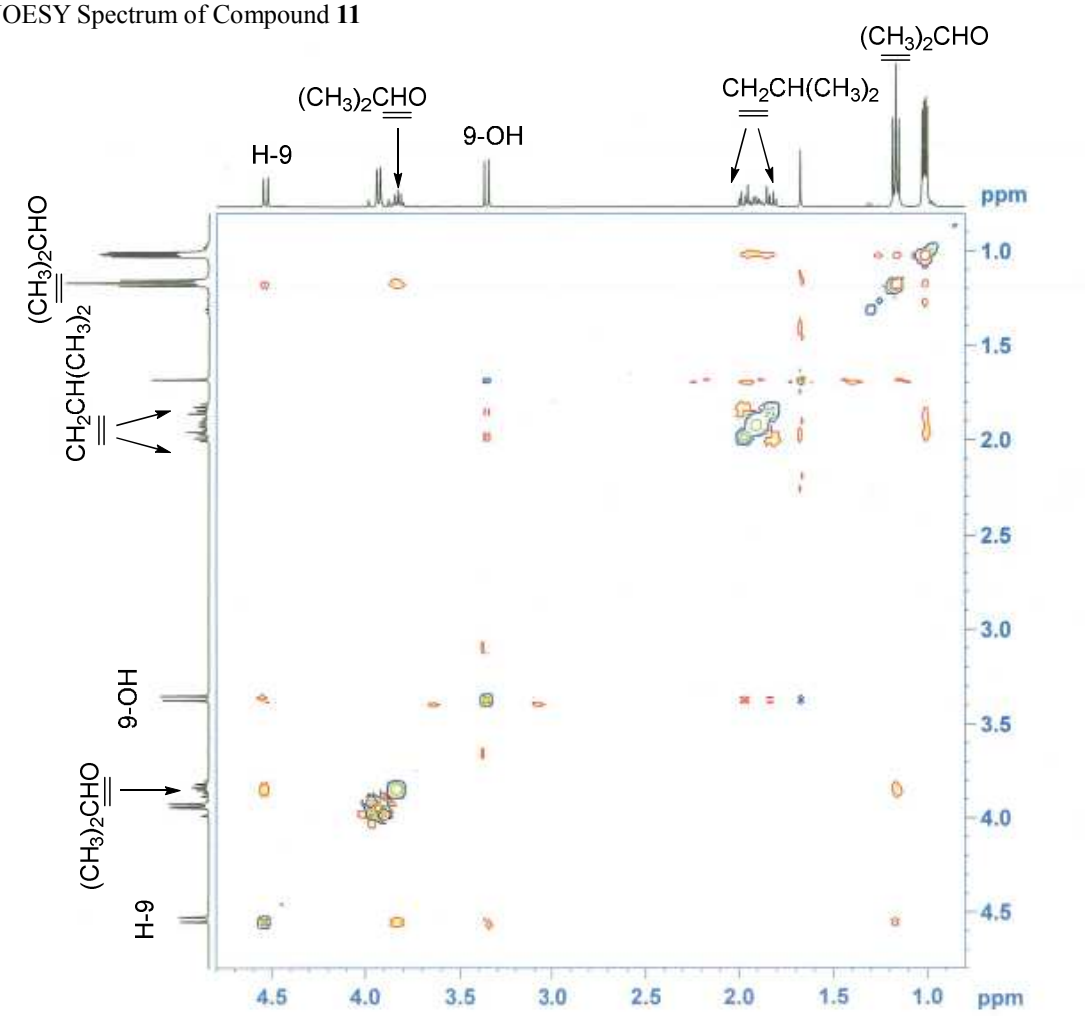


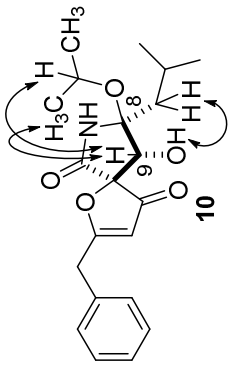
^{13}C NMR Spectrum of Compound **10**



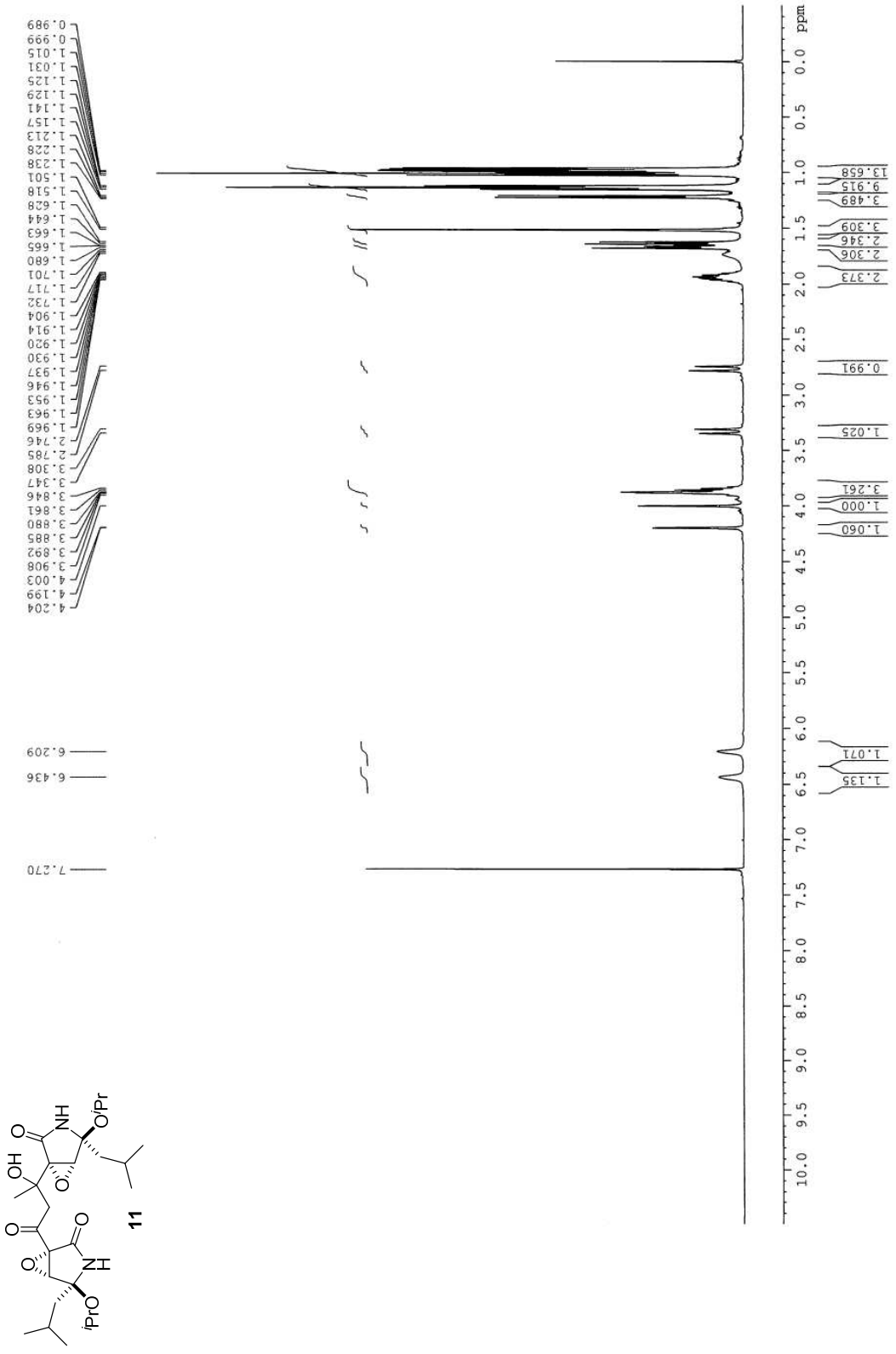
10

NOESY Spectrum of Compound **11**



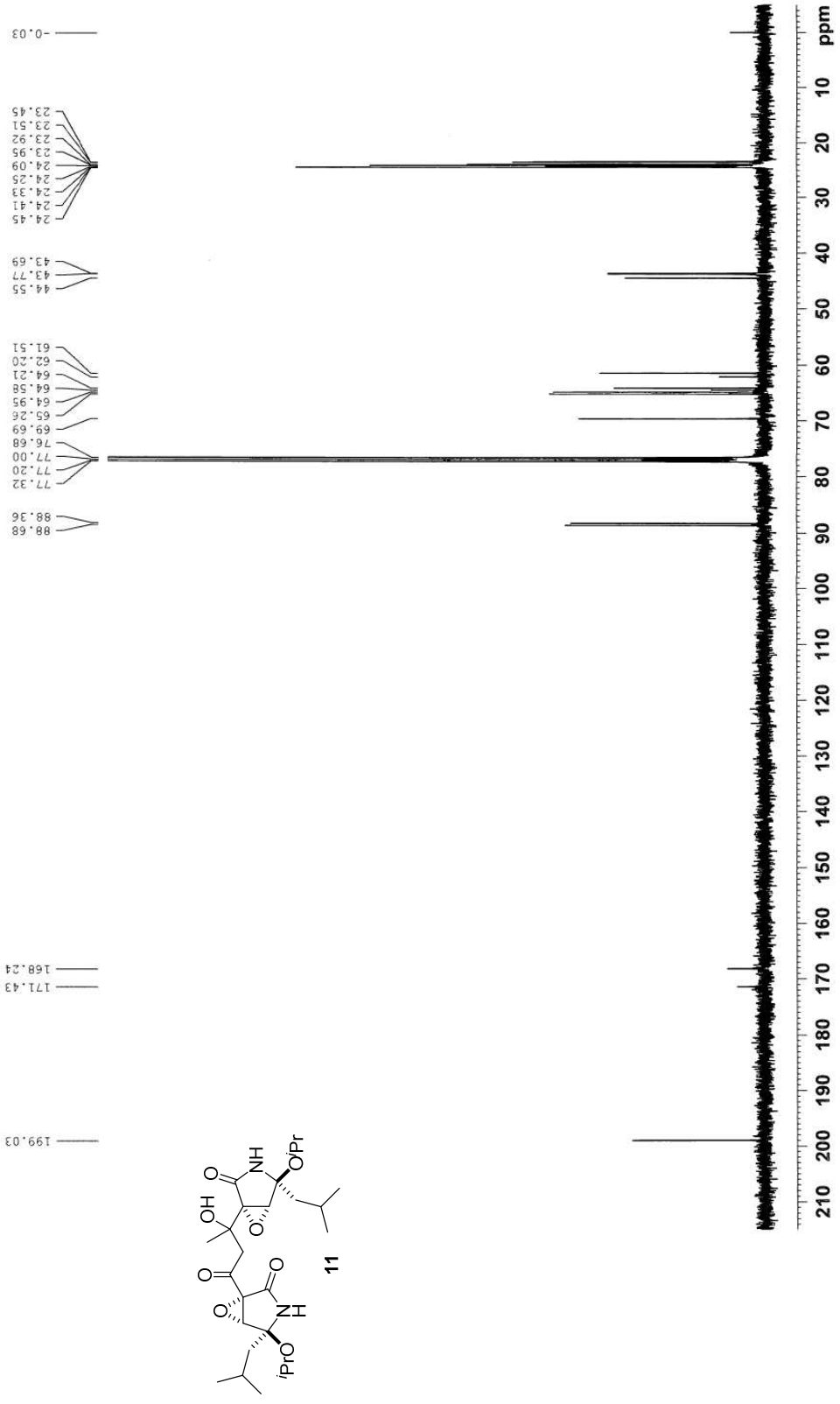


^{1}H NMR Spectrum of Compound **11**



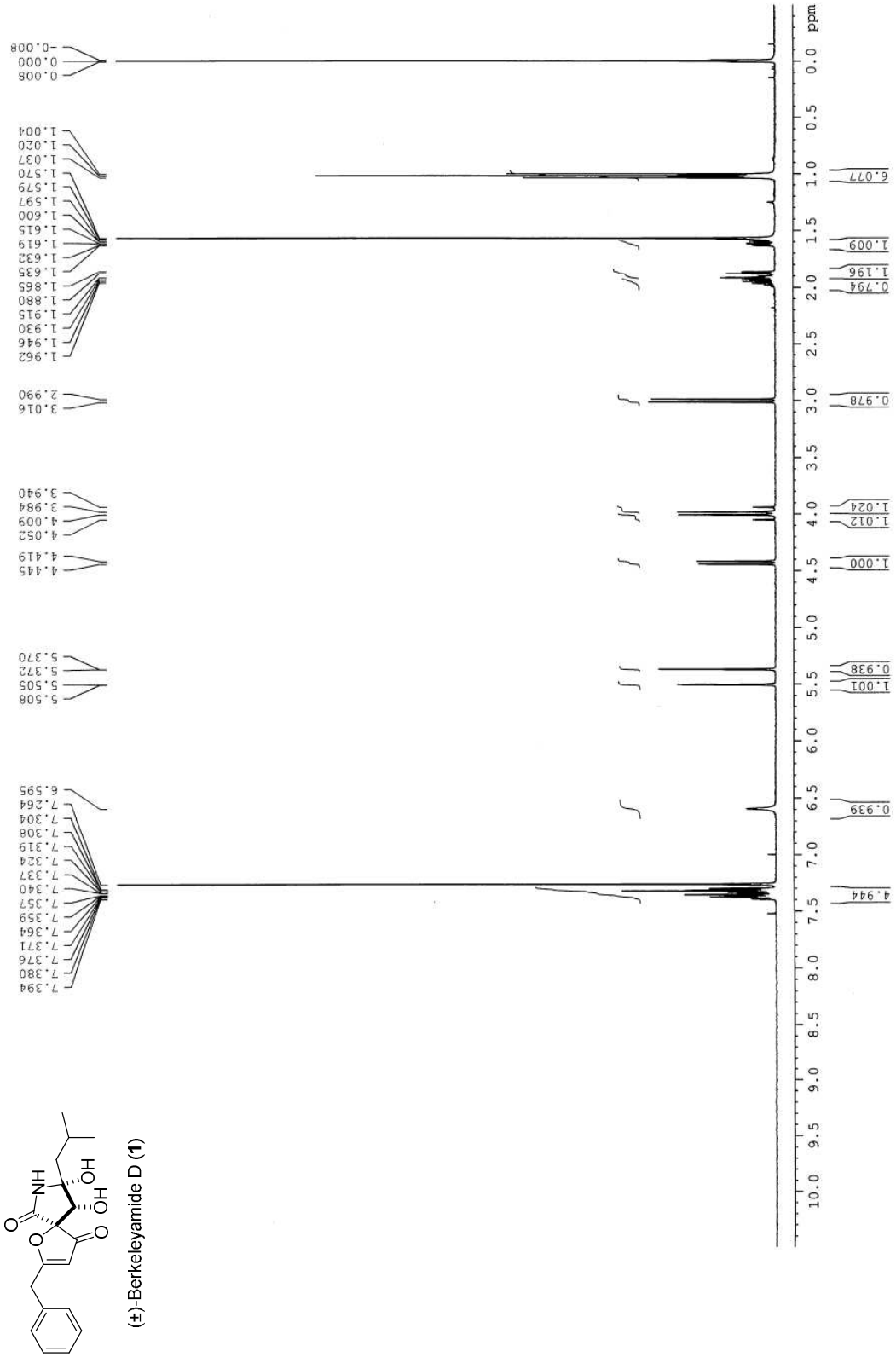
11

^{13}C NMR Spectrum of Compound **11**

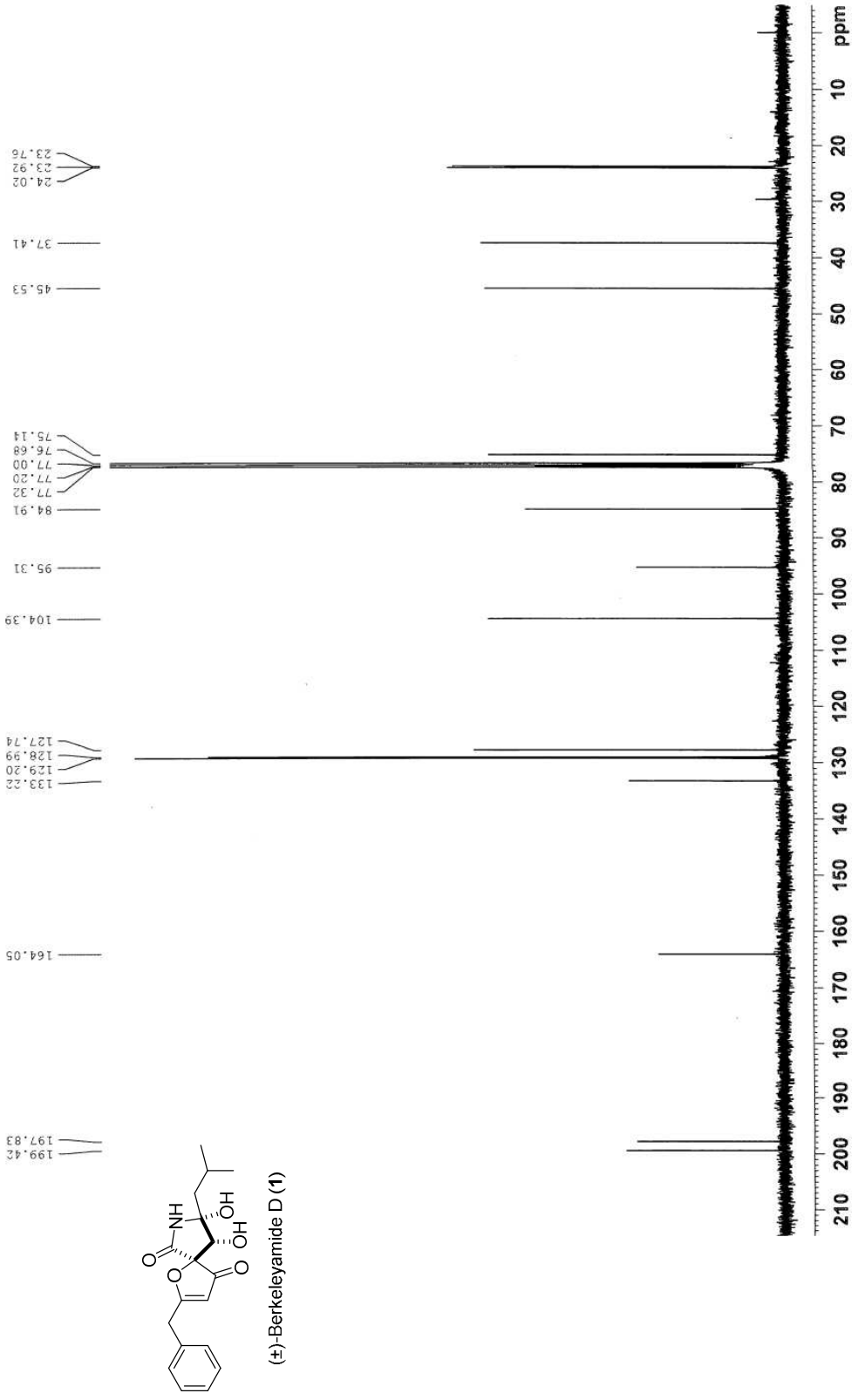


11

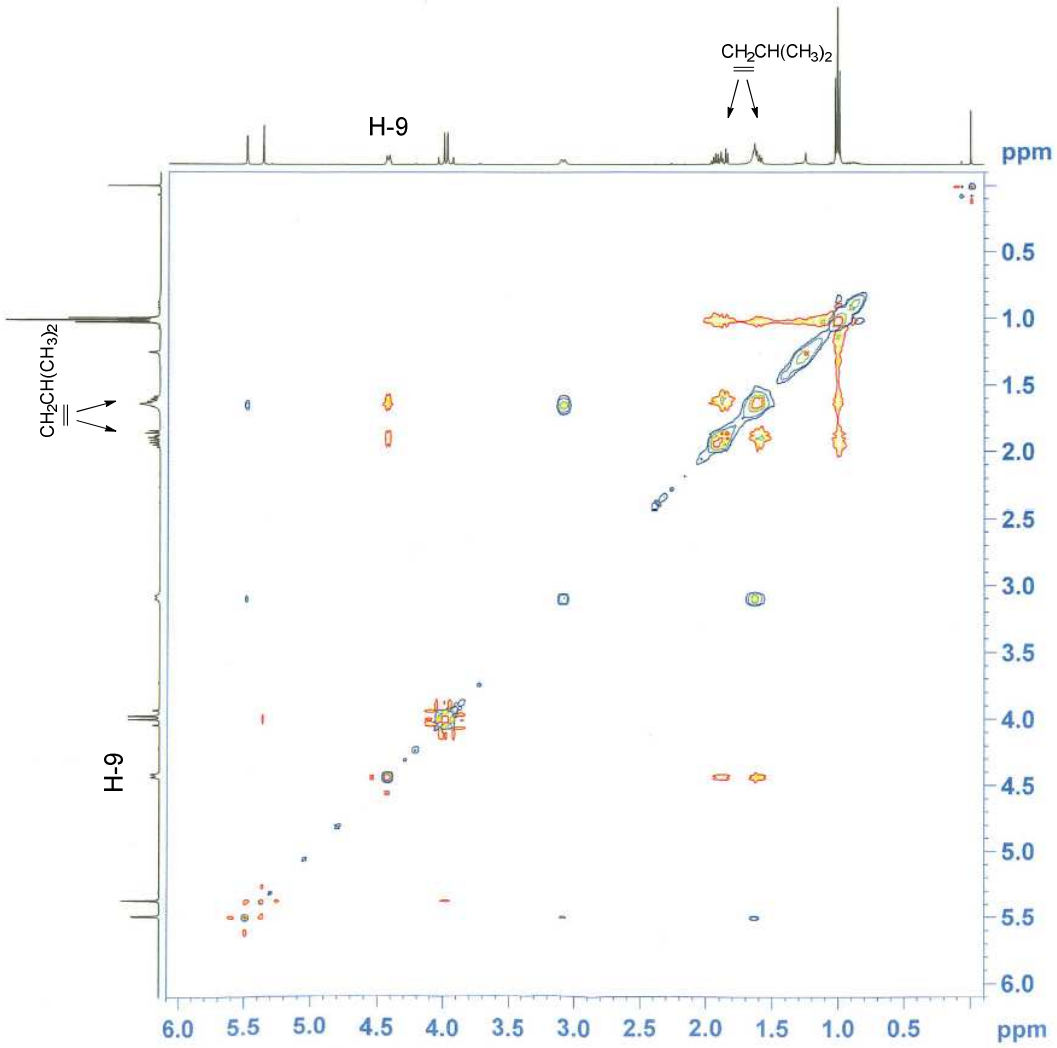
^{1}H NMR Spectrum of Compound (±)-**1**

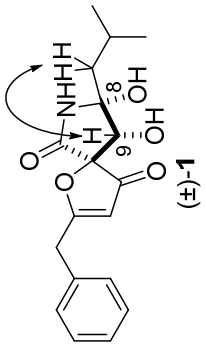


^{13}C NMR Spectrum of Compound (±)-**1**

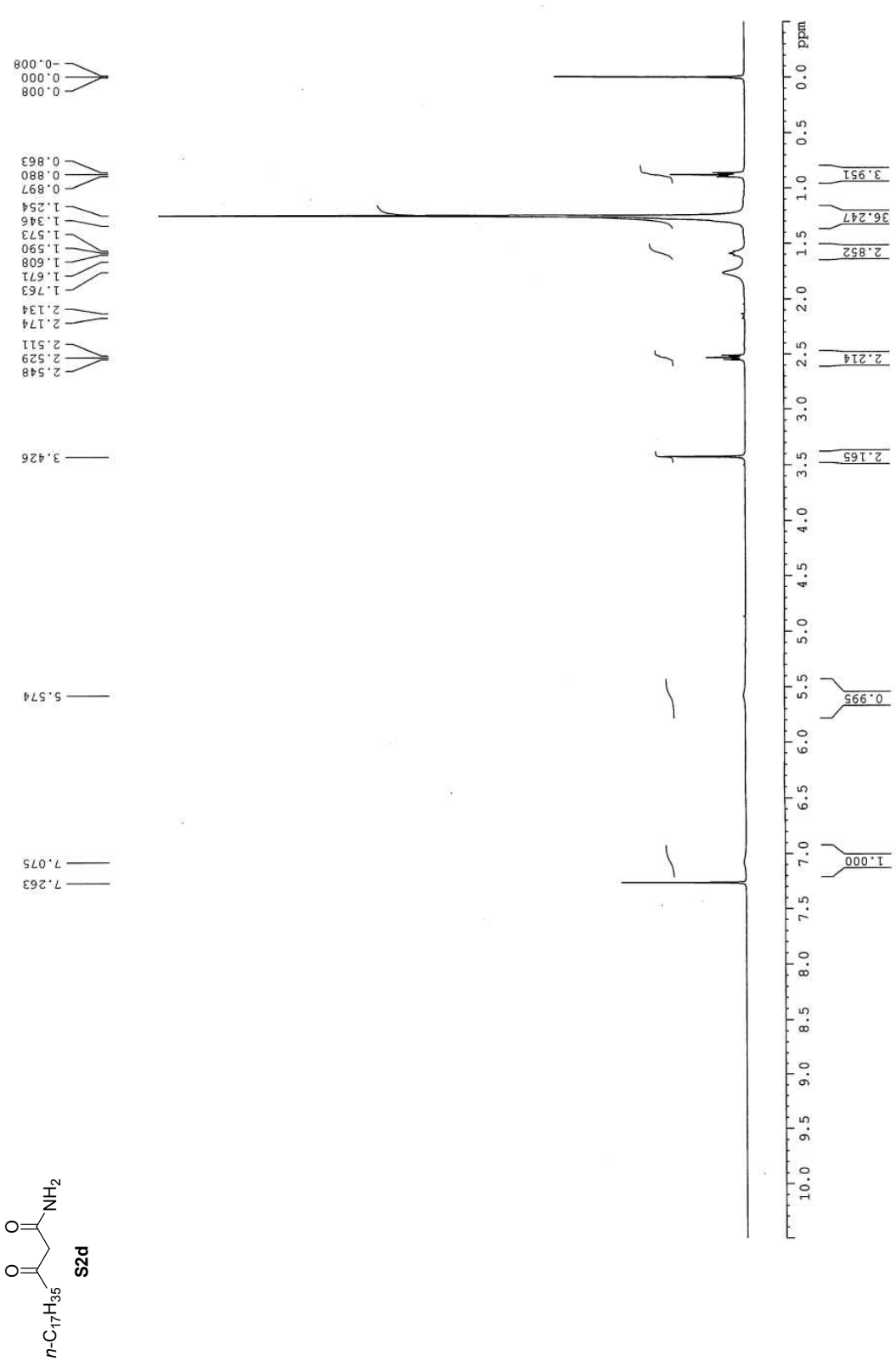


NOESY Spectrum of Compound (±)-**1**

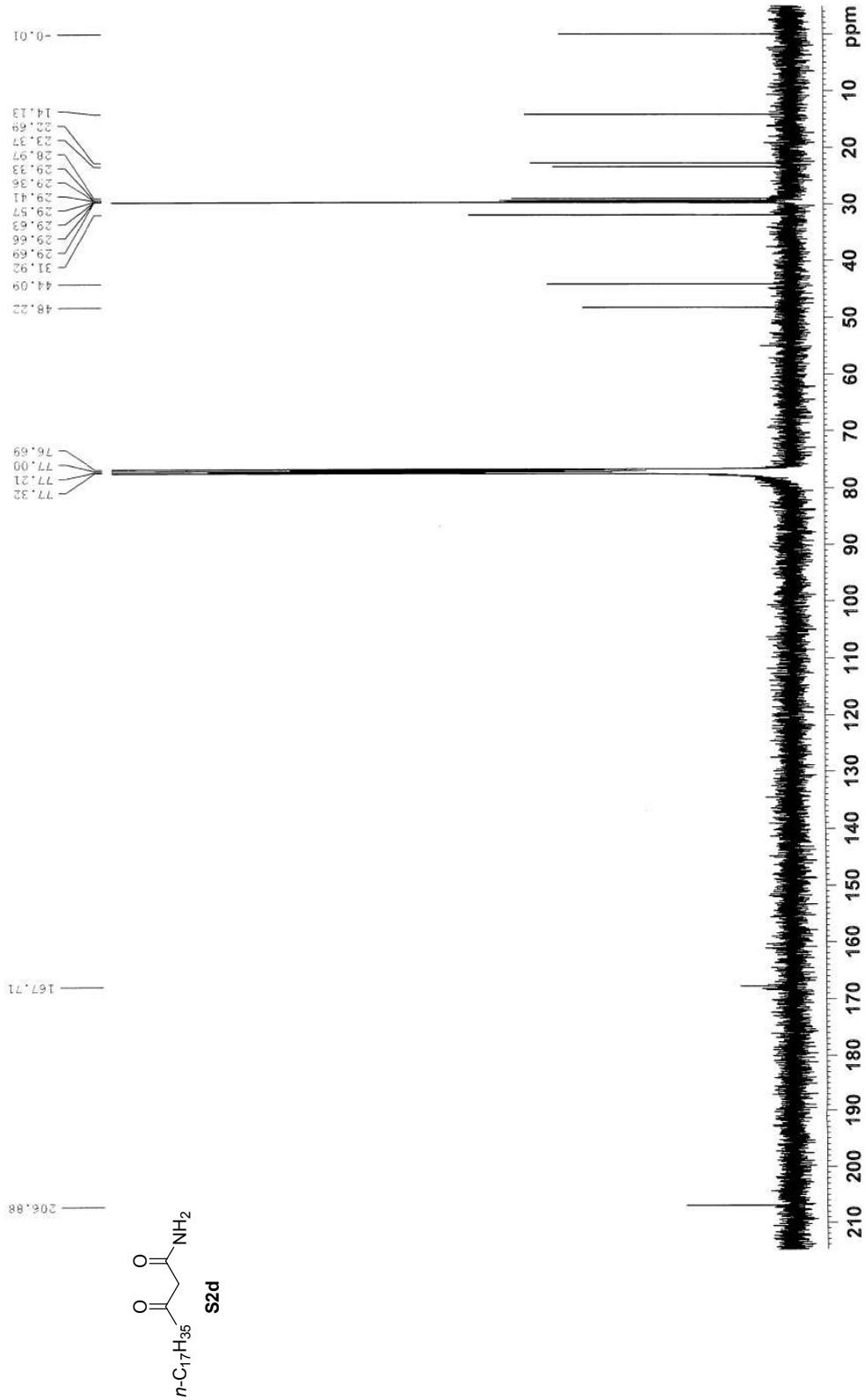




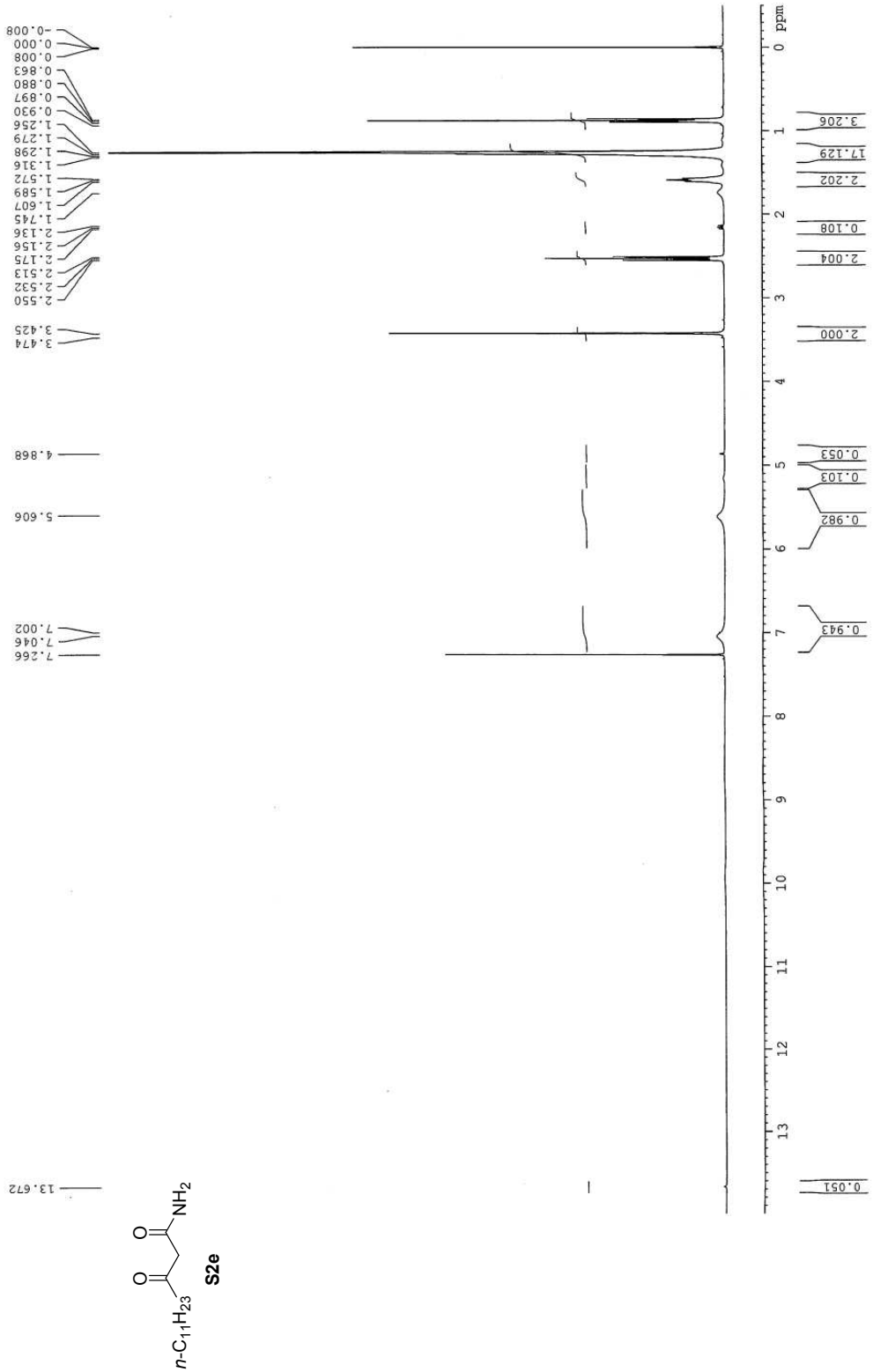
^{1}H NMR Spectrum of Compound **S2d**



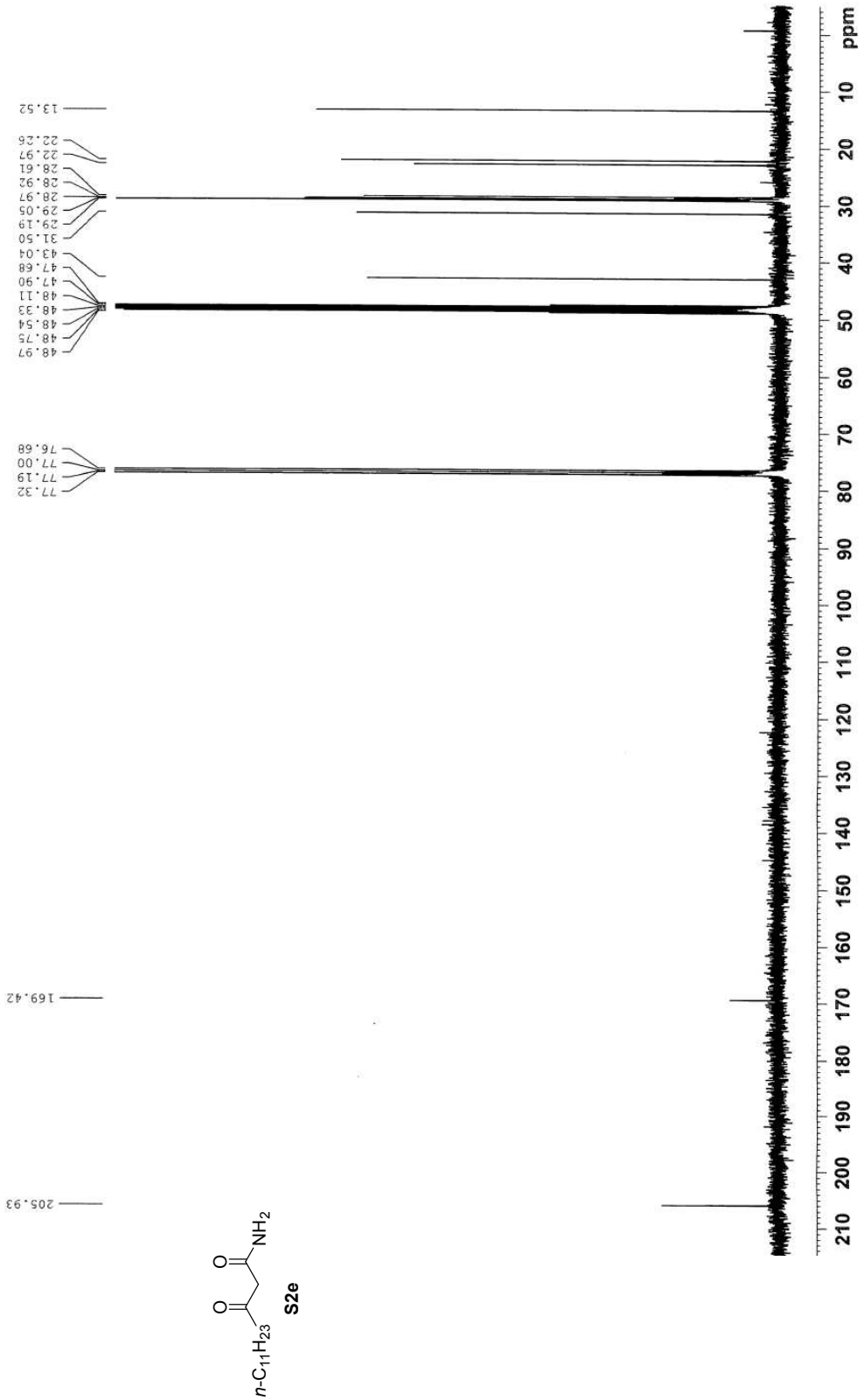
^{13}C NMR Spectrum of Compound **S2d**



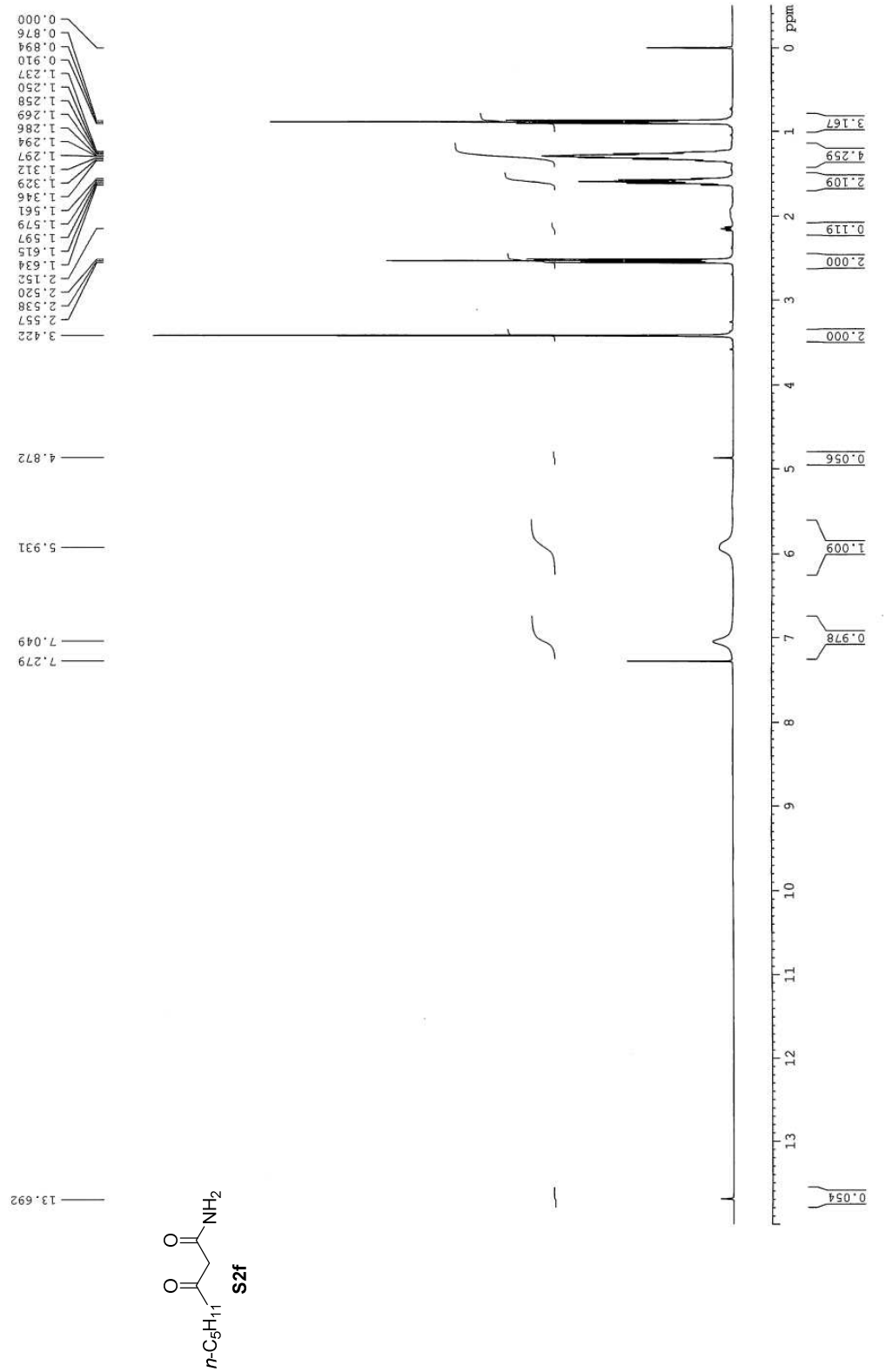
^{1}H NMR Spectrum of Compound **S2e**



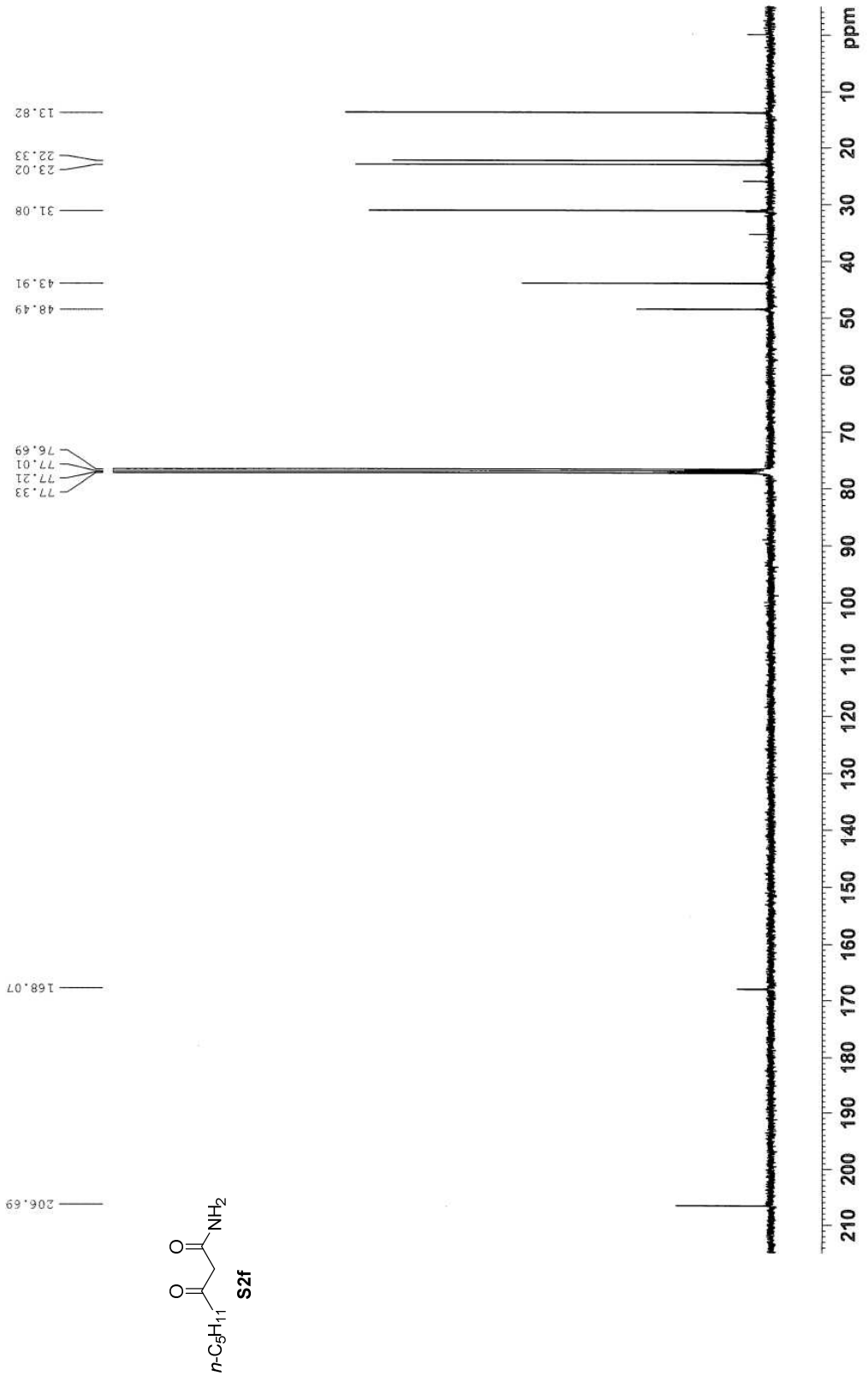
^{13}C NMR Spectrum of Compound **S2e**



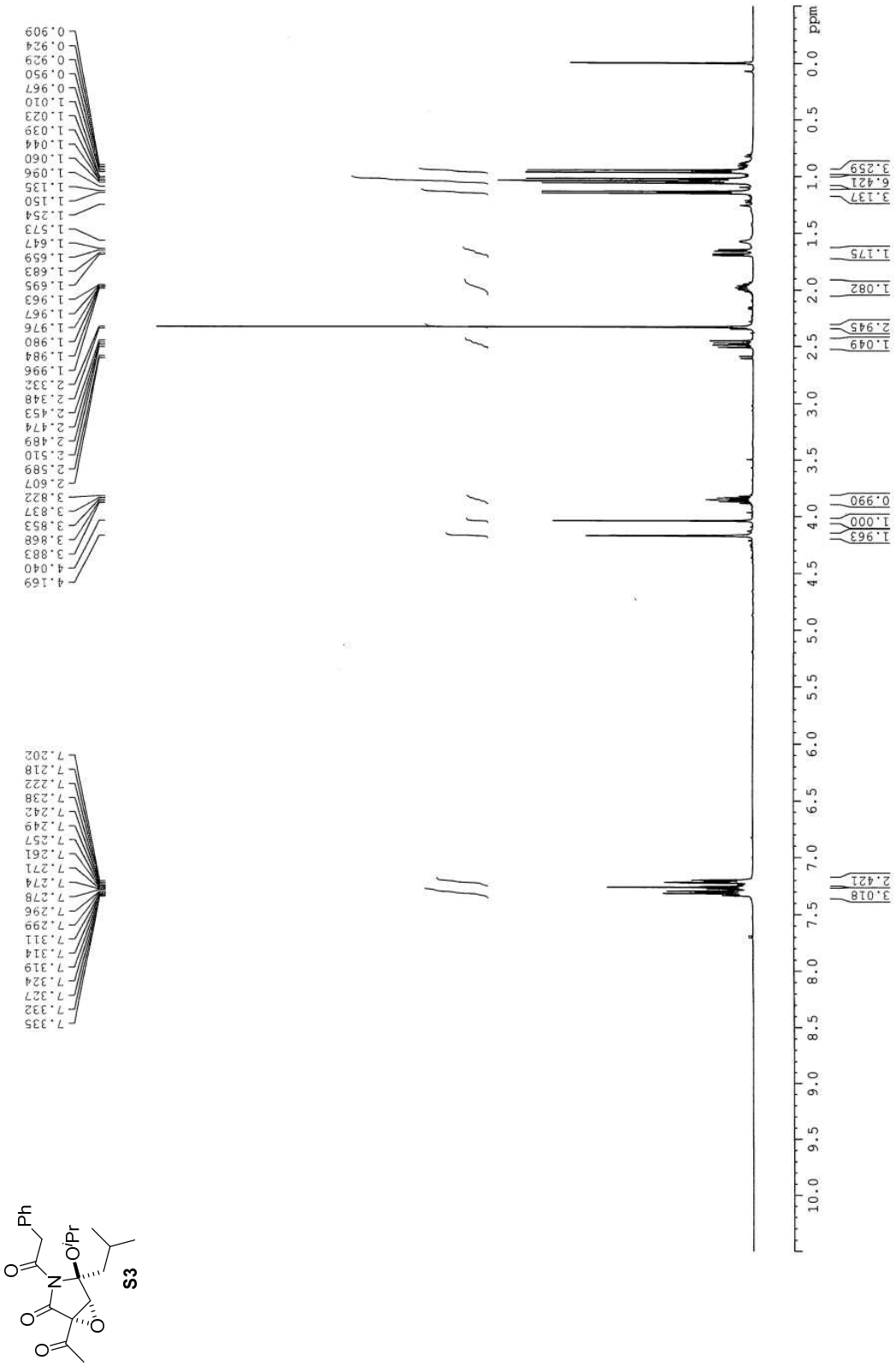
^{1}H NMR Spectrum of Compound **S2f**



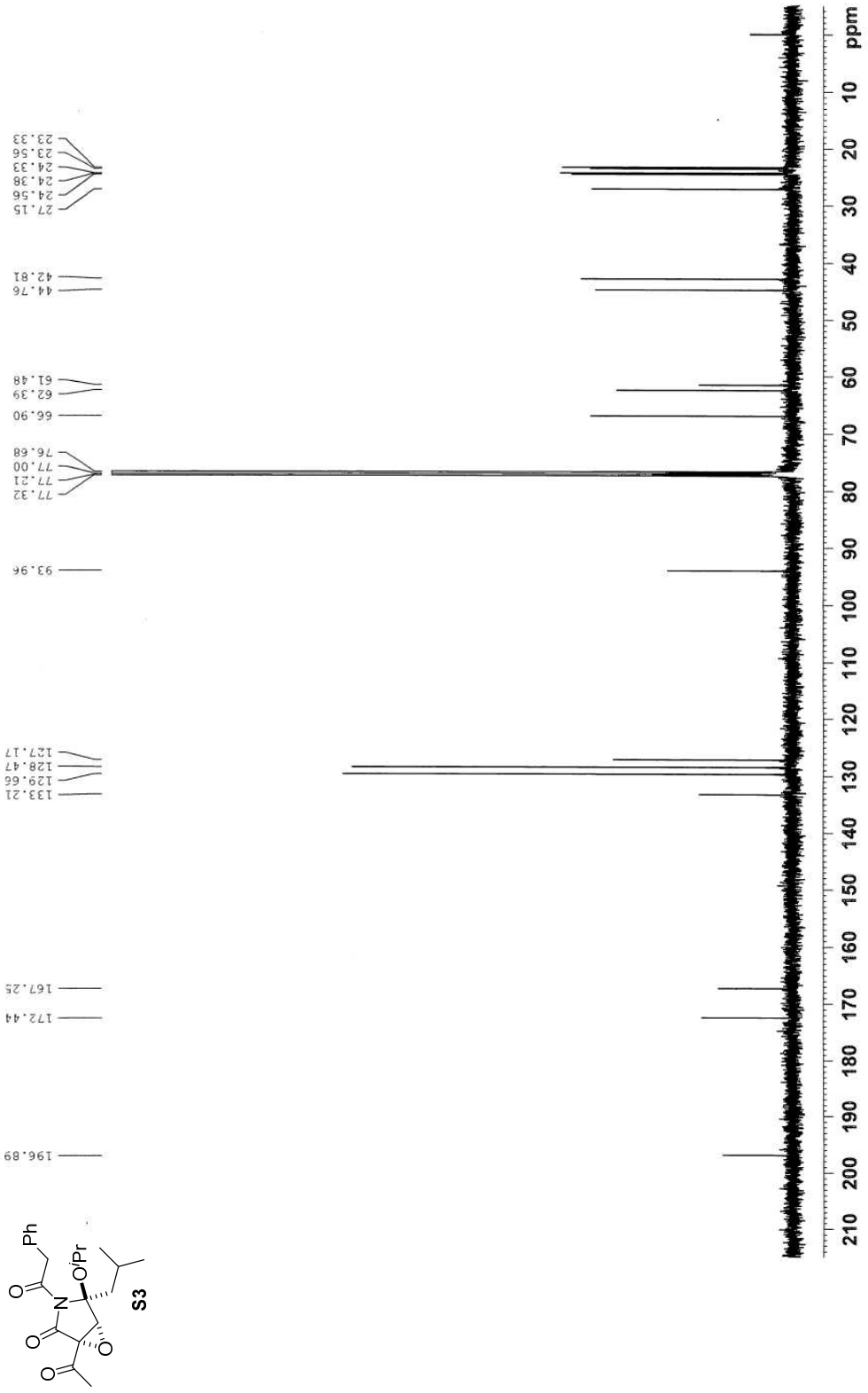
^{13}C NMR Spectrum of Compound **S2f**



^{1}H NMR Spectrum of Compound **S3**



^{13}C NMR Spectrum of Compound **S3**



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