Total Synthesis of the Spirocyclic Imine Marine Toxin (–)-Gymnodimine and an Unnatural C4-Epimer

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Supporting Information

Experimental procedures and characterization data (including ^{1}H, ^{13}C NMR spectra) for selected intermediates as outlined below.

CCDC-801790, CCDC-801791, and CCDC-655682 contain the supplementary crystallographic data for *anti*-aldol adduct **13**, *N*-Ts lactam (+)-**7a**, and **83**, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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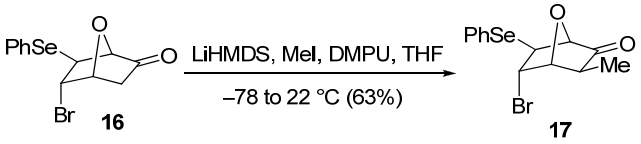
General Procedure

All non aqueous reactions were carried out under nitrogen atmosphere in oven-dried (120 ºC) glassware. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified by Mbraun solvent purification system or were distilled immediately prior to use from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), benzene, and toluene were purified by Mbraun solvent purification system or were distilled from calcium hydride immediately prior to use. *N*,*N*-Dimethylformamide was purified by Mbraun solvent purification system or was distilled from calcium hydride and stored over 4Å molecular sieves. Methanol (MeOH) was distilled from magnesium prior to use. Triethylamine (Et_3N), 2,6-lutidine and pyridine (py.) were distilled from calcium hydride immediately prior to use. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride and stored over 4Å molecular sieves. Acetone and hexanes were used as received. The molarities indicated for organolithium reagents were established according to literature procedure.[1] All other commercially obtained reagents were used as received. Brine refers to saturated aqueous solution of sodium chloride. Rochelle's salt solution refers to 2 M aqueous sodium potassium tartrate.

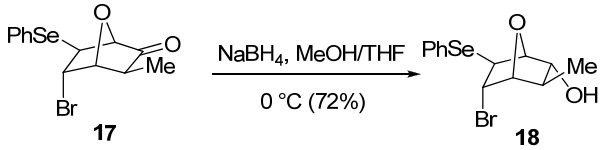
Flash column chromatography was performed using 60Å Silica Gel (Baker, 230-400 mesh) as a stationary phase. Thin layer chromatography (TLC) was performed using glass-backed silica gel 60F254 (Merck, 250 μm thickness). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity-500, VXR-300, or XL-200E spectrometer. ^{1}H NMR chemical shifts are reported as δ values in ppm relative to deuterochloroform ($CDCl_3$, 7.27 ppm). ^{1}H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), sep (septet), m (multiplet), br s (broad singlet), dd (doublet of doublet), dt (doublet of triplet), dq (doublet of quartet), tt (triplet of triplet), ddd (doublet of doublet of doublet). $CDCl_3$ served as an internal standard (77.0 ppm) for all ^{13}C spectra. Mass spectra were obtained on a VG analytical 70S high resolution, double focusing, sectored (EB) mass spectrometer at the center for Chemical Characterization and Analysis (Texas A&M). Thin layer chromatography (TLC) was performed using glass-backed silica gel 60F254 (Merck, 250 μm thickness). Infrared spectra were recorded with a Nicolet Impact 410 FTIR spectromer. Optical rotations were measured with a

(1) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509-510.

JASCO DIP-360 digital polarimeter. Combustion analyses were performed by Atlantic Microlabs (Norcross, GA).

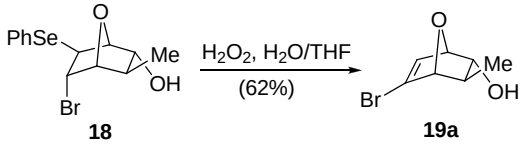


Methyl ketone 17. To a solution of hexamethyldisilazine (1.46 mL, 6.93 mmol) in THF (70 mL) was added *n*-BuLi (2.14 M in THF, 4.05 mL, 8.67 mmol) dropwise. This solution was stirred at 0 °C for 1 h and was cooled to –78 °C. After 10 min, methyl iodide (3.60 mL, 57.8 mmol) was added at –78 °C. At the same time, a solution of **16** (2.00 g, 5.78 mmol) and DMPU (5 mL) in THF (50 mL) (pre-cooled at –78 °C) was added to the reaction mixture dropwise via a cannula over 2 h. The reaction mixture was stirred at –78 °C for 10 h, gradually warmed up to 22 °C and stirred for an additional 10 h. The reaction mixture was diluted with Et_2O and neutralized to pH 7 with 1 N HCl. The organic layer was washed with H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/hexanes) to provide 1.32 g (63% yield) of the desired product **17** as a colorless oil: R_f = 0.43 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.60 (m, 2H), 7.29-7.34 (m, 3H), 4.47 (dd, *J* = 0.9 Hz, 4.5 Hz, 1H), 4.28 (s, 1H), 4.23 (d, *J* = 4.5 Hz, 1H), 3.39 (d, *J* = 4.5 Hz, 1H), 2.92 (q, *J* = 7.5 Hz, 1H), 1.23 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 135.0, 129.5, 128.7, 127.6, 85.9, 85.2, 50.6, 46.8, 43.2, 13.6; IR (thin film) 2967, 1767, 1585, 1476 cm^{-1}.



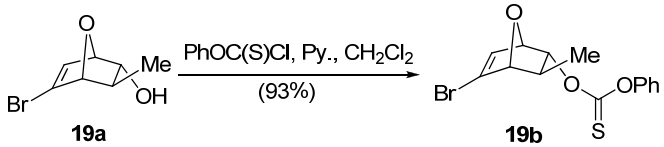
Alcohol 18. To a solution of methyl ketone **17** (0.56 g, 1.55 mmol) in THF/MeOH (1:1, 46 mL) was added $NaBH_4$ at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (4 X 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/hexanes) to provide 391 mg (72% yield) of the desired product **18** as a pale yellow oil, along with 126 mg (21% yield) of the undesired epimer as a white solid. Selected data for **18**: R_f = 0.36 (30% EtOAc/hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50-7.60 (m, 2H), 7.29-7.34 (m, 3H), 4.38 (d, *J* = 4.8 Hz, 1H), 4.15 (t, *J* = 4.8 Hz, 1H), 4.05 (d, *J*

= 4.8 Hz, 1H), 4.01 (d, *J* = 4.8 Hz, 1H), 3.84 (dd, *J* = 3.2 Hz, 4.8 Hz, 1H), 2.40 (dq, *J* = 3.2 Hz, 7.2 Hz, 1H), 1.82 (br s, 1H), 1.13 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.0, 129.2, 127.8, 87.3, 86.8, 80.1, 53.2, 44.2, 40.1, 18.6.



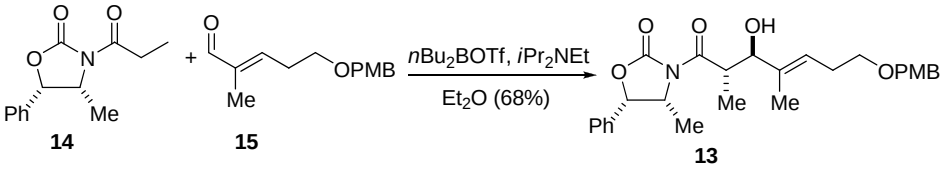
18 **19a**

Vinyl Bromide 19a. A solution of 30% H_2O_2 (1.15 mL, 10.8 mmol) was added slowly to a stirred solution of **18** (391 mg, 1.08 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at 22 °C for 3 h. The reaction was quenched by diluting with H_2O (5 mL) and then extracting with CH_2Cl_2 (3 X 10 mL). The combined organic layers were washed with saturated Na_2CO_3 solution (5 mL), H_2O (5 mL), brine (5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (20% EtOAc/hexanes) to provide 137 mg (62% yield) of the desired product **19a** as a colorless oil: R_f = 0.26 (30% EtOAc/hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.39 (d, *J* = 1.8 Hz, 1H), 4.75 (ddd, *J* = 0.9 Hz, 1.8 Hz, 4.4 Hz, 1H), 4.28 (s, 1H), 3.89 (dd, *J* = 2.2 Hz, 4.4 Hz, 1H), 2.18 (s, 1H), 1.47 (dq, *J* = 2.2 Hz, 6.4 Hz, 1H), 1.22 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 131.3, 128.6, 89.9, 82.2, 78.8, 43.1, 17.8; IR (thin film) 3382, 2924, 1644, 1309 cm^{-1}.



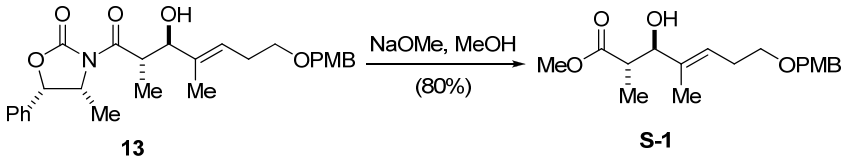
19a **19b**

Thiocarbonate 19b. To a solution of alcohol **19a** (52.7 mg, 0.257 mmol) in CH_2Cl_2 (2.5 mL) was added pyridine (76.5 µl, 0.951 mmol) and phenoxylthiocarbonyl chloride (39.2 µl, 0.283 mmol) at 22 °C. The reaction was stirred for 2 h, the solvent was evaporated, and the residue was partitioned between ethyl acetate and water. The organic layer was successively washed with cold 1N HCl (5 mL), H_2O (5 mL), saturated $NaHCO_3$ solution (5 mL) and brine (5 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (5% EtOAc/hexanes) to provide 79 mg (93% yield) of the desired product as a yellow oil: R_f = 0.55 (30% EtOAc/hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.05-7.50 (m, 5H), 6.38 (d, *J* = 1.2 Hz, 1H), 5.15-5.28 (m, 1H), 5.21 (s, 1H), 4.42 (s, 1H), 1.95 (dq, *J* = 2.2 Hz, 6.4 Hz, 1H), 1.45 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.6, 153.3, 131.2, 129.6, 128.3, 126.7, 121.8, 89.7, 87.6, 80.1, 40.7, 18.4.



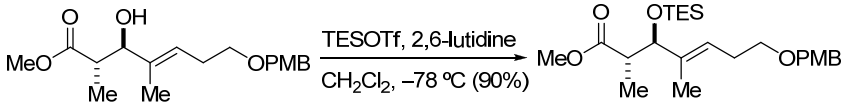
14 **15** **13**

***anti*-Aldol Product 13**. To a cooled (0 °C) solution of imide **14** (4.88 g, 21.0 mmol) in Et_2O (63 mL) was added nBu$_2$BOTf solution (1.0 M in Et_2O, 42 mL, 42 mmol) followed by iPr$_2$NEt (4.19 mL, 24.0 mmol). The resulting yellow slurry was stirred for 45 min and was cooled to –78 °C. A pre-cooled (–78 °C) solution of aldehyde **15** (6.12 g, 26 mmol) in Et_2O (30 mL) was added over 30 min. The solution was stirred at –78 °C for 6 h and was diluted with Et_2O (30 mL). The reaction was quenched at –78 °C with 1 M tartaric acid (60 mL), warmed to 22 °C, and was stirred for 2 h. The reaction mixture was partitioned between Et_2O and H_2O. The aqueous layer was extracted with Et_2O (2 X 50 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (2 X 50 mL). The combined organic layers were then cooled to 0 °C and a 3:1 MeOH/30 % H_2O_2 solution (60 mL) was added. After stirring at 22 °C for 30 min, the solution was washed with saturated $NaHCO_3$ solution (40 mL), brine (40 mL), dried (Mg_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/hexanes → 30% EtOAc/hexanes) to provide 5.12 g (68% yield) of the desired product as a viscous, colorless oil. Upon standing at 22 °C, the product crystallized to provide colorless needle-like crystals suitable for X-ray analysis. R_f = 0.19 (30% EtOAc/hexanes); $[\alpha]_D^{23}$ +18.5° (*c* 1.22, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.40 (m, 7H), 6.85 (dt, *J* = 8.7 Hz, 2.1 Hz, 2H), 5.64 (d, *J* = 7.2 Hz, 1H), 5.45 (dq, *J* = 7.2 Hz, 1.2 Hz, 1H), 4.76 (d, *J* = 6.6 Hz, 1H), 4.41 (s, 2H), 4.11 (m, 2H), 3.78 (s, 3H), 3.43 (t, *J* = 6.6 Hz, 2H), 2.34 (q, *J* = 6.6 Hz, 3H), 1.67 (d, *J* = 1.2 Hz, 3H), 1.04 (d, *J* = 2.1, 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 159.1, 153.4, 136.3, 133.3, 130.5, 129.1, 128.7, 125.6, 125.5, 113.7, 81.1, 78.9, 77.2, 72.5, 69.2, 55.2, 40.6, 28.4, 14.8, 14.3, 11.0; IR (thin film) 3489, 2929, 1783, 1696, 1509 cm^{-1}; HRMS (FAB) Calcd for $C_{27}H_{33}NNaO_6$[M+Na]: 490.2206. Found: 490.2227; Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 2.99; Found: C, 69.30; H, 7.17; N, 2.92.



13 **S-1**

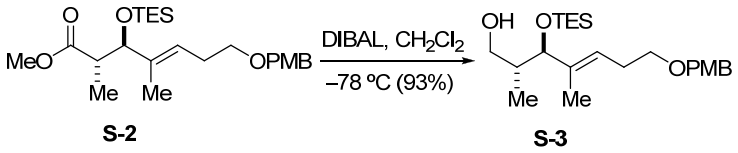
β-Hydroxy Methylester S-1. To a solution of imide **13** (1.79 g, 3.83 mmol) in methanol (38 mL) at –78 °C was added sodium methoxide (0.802 mL, 4.21 mmol, 30 wt% in methanol). The solution was stirred until the cooling bath (–78 °C) had gradually warmed to –10 °C. Saturated NH_4Cl solution (5 mL) was added. The resulting mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3 X 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (30% EtOAc/hexanes → 50% EtOAc/hexanes) to provide 0.98 g (80% yield) of the desired ester as a colorless oil, along with recovered chiral oxazolidinone as a white crystalline solid. R_f = 0.39 (50% EtOAc/hexanes); $[\alpha]_D^{23}$ –9.59 (*c* 2.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (dt, *J* = 8.7 Hz, 2.7 Hz, 2H), 6.84 (dt, *J* = 8.7 Hz, 2.7 Hz, 2H), 5.43 (dt, *J* = 1.2 Hz, 7.2 Hz, 1H), 4.40 (s, 2H), 4.07 (d, *J* = 9.0 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.43 (t, *J* = 6.9 Hz, 2H), 2.62 (dq, *J* = 6.9 Hz, 9.0 Hz, 1H), 2.33 (q, *J* = 7.2 Hz, 2H), 1.58 (d, *J* = 1.2 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 159.2, 136.0, 130.5, 129.2, 125.7, 113.8, 79.9, 72.6, 69.2, 55.2, 51.8, 43.2, 28.3, 14.4, 10.9; IR (thin film) 3460, 2952, 1744 cm^{-1}; HRMS (FAB) Calcd for $C_{18}H_{26}NaO_5$[M+Na]: 345.1678. Found: 345.1689; Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13; Found: C, 66.76; H, 7.96.



S-1 **S-2**

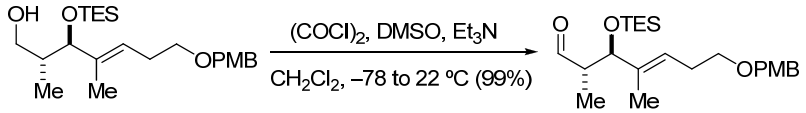
Silyl ether S-2. To a solution of β-hydroxy methylester **S-1** (876 mg, 2.72 mmol) in CH_2Cl_2 (27 mL) at –78 °C was added 2,6-lutidine (0.95 mL, 8.16 mmol) followed by triethylsilyl triflate (0.675 mL, 2.99 mmol). After stirring at –78 °C for 10 min, the reaction was quenched by addition of saturated $NaHCO_3$ solution (20 mL). The mixture was extracted with Et_2O (2 X 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography (5% EtOAc/hexanes) to provide 1.07 g (90% yield) of the desired silyl ether as a colorless oil. R_f = 0.33 (10% EtOAc/hexanes); $[\alpha]_D^{23}$ –10.3 (*c* 2.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 6.87 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 5.40 (dt, *J* = 1.2 Hz, 6.9 Hz, 1H), 4.43 (s, 2H), 4.10 (d, *J* = 9.9 Hz, 1H), 3.80 (s, 3H), 3.67 (s, 3H),), 3.45 (dt, *J* = 6.9 Hz, 0.9 Hz, 2H), 2.60 (dq, *J* = 9.6 Hz, 6.9 Hz, 1H), 2.34 (q, *J* = 6.9 Hz, 2H), 1.56 (d, *J* = 1.2 Hz, 3H), 0.89 (d, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.8 Hz, 9H), 0.52 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 159.1, 136.5, 130.5, 129.2, 125.5, 113.7,

81.4, 72.6, 69.3, 55.2, 51.4, 44.7, 28.3, 14.2, 10.3, 6.7, 4.7; IR (thin film) 2953, 1738, 1513, 1062 cm^{-1}.



S-2 **S-3**

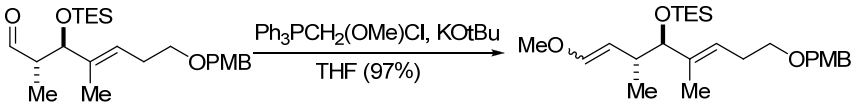
Alcohol S-3. To a solution of ester **S-2** (6.57 g, 15.05 mmol) in CH_2Cl_2 (150 mL) at –78 °C was added 1 M solution of DIBAl-H in CH_2Cl_2 (33.11 mmol, 33.11 mL) slowly. The reaction was stirred at –78 °C for 30 min, and was slowly quenched with 1M tartaric acid (34 mL). The reaction mixture was separated and the organic layer was washed with H_2O (2 X 50 mL). The aqueous phase was extracted with Et_2O (3 X 30 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes) to provide 5.74 g (93% yield) of the desired alcohol **S-3** as a colorless oil. R_f = 0.45 (30% EtOAc/hexanes); $[\alpha]_D^{23}$ +3.16 (*c* 3.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dt, *J* = 6.9, 3 Hz, 2H), 6.88 (dt, *J* = 6.9 Hz, 3 Hz, 2H), 5.40 (t, *J* = 6.9 Hz, 1H), 4.46 (s, 2H), 3.87 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 3H), 3.64 (d, *J* = 5.4 Hz, 2H), 3.49 (t, *J* = 6.9 Hz, 2H), 3.24 (s, 1H), 2.37 (q, *J* = 6.9 Hz, 2H), 1.81-1.94 (m, 1H), 1.62 (s, 3H), 0.96 (t, *J* = 7.8 Hz, 9H), 0.75 (d, *J* = 6.9 Hz, 3H), 0.62 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 137.6, 130.5, 129.1, 124.1, 113.7, 85.3, 72.5, 69.3, 67.5, 55.2, 38.1, 28.2, 14.1, 11.3, 6.7, 4.7; IR (thin film) 3466, 2957, 1612, 1509, 1092 cm^{-1}; HRMS (FAB) Calcd for $C_{23}H_{40}NaO_4Si$[M+Na]: 431.2594. Found: 431.2589; Anal. Calcd for $C_{23}H_{40}O_4Si$: C, 67.60; H, 9.86; Found: C, 67.51; H, 9.89.



S-3 **S-4**

Aldehyde S-4. To a solution of oxalyl chloride (266 µl, 3.04 mmol) in CH_2Cl_2 (30 mL) at –78 °C was added DMSO (432 µl, 6.09 mmol). After stirring for 10 min, a solution of alcohol **S-3** (828.4 mg, 2.03 mmol) and Et_3N (1.42 mL, 10.15 mmol) in CH_2Cl_2 (20 mL) was added. The reaction mixture was stirred at –78 °C for 30 min, and was allowed to warm to 0 °C slowly. The reaction mixture was diluted with saturated $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (20 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$,

and concentrated *in vacuo.* The residue was purified by flash chromatography (10% EtOAc/hexanes) to provide 796 mg (97% yield) of the desired aldehyde **S-4** as a colorless oil. R_f = 0.44 (25% EtOAc/hexanes); $[\alpha]_D^{22}$ +18.2 (*c* 2.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (d, *J* = 3.0 Hz, 1H), 7.28 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 6.90 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 5.45 (t, *J* = 6.9 Hz, 1H), 4.47 (s, 2H), 4.12 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 3H), 3.49 (t, *J* = 6.9 Hz, 2H), 2.52-2.63 (m, 1H), 2.38 (q, *J* = 6.9 Hz, 2H), 1.64 (s, 3H), 0.86-0.97 (m, 12H), 0.58 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 159.1, 136.5, 130.5, 129.2, 125.0, 113.7, 80.3, 72.6, 69.3, 55.2, 50.0, 28.3, 10.9, 6.7, 4.7; IR (thin film) 2957, 2876, 1726, 1612, 1512 cm^{-1}.



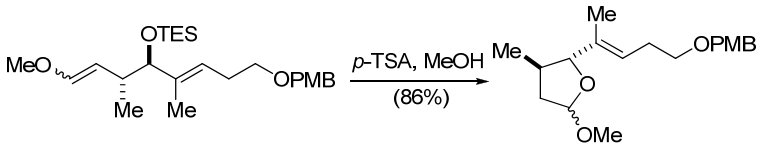
S-4 **21**

Methoxy Olefin 21. To a slurry of (methoxymethyl)triphenylphosphonium chloride (1.25 g, 3.55 mmol) in THF (35 mL) at 0 °C was slowly added KO^{t}Bu (1.0 M in *t*-BuOH, 3.61 mL, 3.61 mmol). After stirring at 0 °C for 20 min, the slurry turned into an orange-reddish solution. To this solution was added a solution of the aldehyde **S-4** (462 mg, 1.14 mmol) in THF (12 mL). The reaction was allowed to warm to 22 °C and was then stirred for another 2 h. The reaction mixture was then poured into water (20 mL) and extracted with Et_2O (2 X 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (5% EtOAc/hexanes) to provide 481 mg (97% yield) of a mixture of methoxy olefins (*cis*:*trans*=1:3) as a colorless oil. R_f = 0.44 (10% EtOAc/hexanes); IR (thin film) 3060, 2957, 1656, 1612, 1512 cm^{-1}; HRMS (FAB) Calcd for $C_{25}H_{42}NaO_4Si$[M+Na]: 457.2745. Found: 457.2750.

Major isomer (*trans*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 6.90 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 6.29 (d, *J* = 12.6 Hz, 1H), 5.34 (t, *J* = 6.9 Hz, 1H), 4.73 (dd, *J* = 8.4 Hz, 12.6 Hz, 1H), 4.48 (s, 2H), 3.83 (s, 3H), 3.64 (d, *J* = 7.8 Hz, 1H), 3.52 (s, 3H), 3.48 (t, *J* = 6.9 Hz, 2H), 2.37 (q, *J* = 6.9 Hz, 2H), 2.19 (sext, *J* = 7.8 Hz, 1H), 1.61 (s, 3H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.58 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 145.8, 138.6, 130.7, 129.2, 122.0, 113.7, 110.5, 82.4, 72.5, 69.7, 59.3, 55.2, 33.8, 28.2, 18.0, 11.9, 6.9, 4.9.

Minor isomer (*cis*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 6.90 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 5.87 (dd, *J* = 0.9 Hz, 6.3 Hz, 1H), 5.34 (t, *J* = 6.9 Hz, 1H), 4.48 (s, 2H), 4.31 (dd, *J* = 6.3 Hz, 9.3 Hz, 1H), 3.83 (s, 3H), 3.75 (d, *J* = 6.6 Hz, 1H), 3.56 (s, 3H), 3.48 (t, *J* =

6.9 Hz, 2H), 2.79 (sext, *J* = 7.2 Hz, 1H), 2.37 (q, *J* = 6.9 Hz, 2H), 1.63 (s, 3H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.58 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 146.8, 138.6, 130.7, 129.1, 122.9, 113.7, 106.4, 83.4, 72.5, 69.6, 59.3, 55.6, 37.2, 28.2, 18.0, 11.4, 6.9, 4.9.

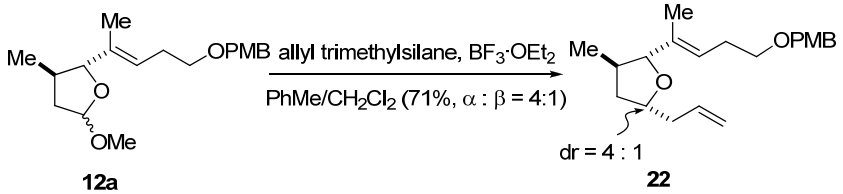


21 **12a**

Methoxy Furanose **12a**. To a solution of methoxy olefin **21** (846 mg, 1.95 mmol) in CH_3OH (20 mL) at 0 °C was added *p*-TsOH (37.1 mg, 0.19 mmol). The reaction mixture was stirred at 22 °C for 30 min. The reaction was carefully poured into saturated $NaHCO_3$ solution (40 mL). The pH was adjusted to neutral by addition of solid $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 (3 X 45 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/hexanes) to provide 583 mg (86% yield) of furanose as a colorless oil and as a mixture (1.5:1) of diastereomers. R_f = 0.35 (25% EtOAc/hexanes); IR (thin film) 2953, 1612, 1512, 1454, 1249 cm^{-1}; LRMS (FAB) Cacld for $C_{19}H_{28}NaO_4$[M+Na]: 343. Found: 343.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 6.90 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 5.45 (dt, *J* = 6.8 Hz, 1.2 Hz, 1H), 4.94 (d, *J* = 4.8 Hz, 1H), 4.48 (s, 2H), 3.85 (d, *J* = 8.7 Hz, 1H), 3.83 (s, 3H), 3.50 (dt, *J* = 1.2 Hz, 6.9 Hz, 2H), 3.39 (s, 3H), 2.42 (q, *J* = 6.9 Hz, 2H), 2.19-2.31 (m, 1H), 2.09 (dd, *J* = 6.6 Hz, 12.6 Hz, 1H), 1.61-1.71 (m, 1H), 1.67 (d, *J* = 1.2 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.5, 130.6, 129.2, 125.0, 113.7, 104.3, 93.6, 72.5, 69.4, 55.3, 54.5, 41.7, 34.1, 28.7, 15.7, 10.8.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 6.90 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 5.50 (dt, *J* = 6.8 Hz, 1.2 Hz, 1H), 5.06 (dd, *J* = 3.0 Hz, 5.4 Hz, 1H), 4.48 (s, 2H), 3.93 (d, *J* = 8.7 Hz, 1H), 3.84 (s, 3H), 3.50 (dt, *J* = 1.2 Hz, 6.9 Hz, 2H), 3.40 (s, 3H), 2.42 (q, *J* = 6.9 Hz, 2H), 2.34-2.45 (m, 1H), 1.90-2.08 (m, 1H), 1.64 (d, *J* = 1.2 Hz, 3H), 1.49-1.58 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H).

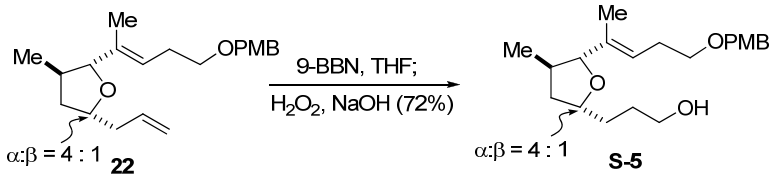


12a **22**

Allylated Furan 22. To a solution of methoxy furanose **12a** (171.9 mg, 0.537 mmol) and allyltrimethyl silane (256 µl, 1.61 mmol) in toluene/CH_2Cl_2 (5 mL, 1 : 1) at –78 °C was added $BF_3{\cdot}OEt_2$ (74.7 µl, 0.591 mmol) dropwise. The reaction mixture was stirred at –78 °C for 6 h, and quenched with saturated $NaHCO_3$ solution (2 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/hexanes) to provide 168 mg (71% yield) of the desired product as a colorless oil and as an inseparable mixture of diastereomers (α : β = 4:1). R_f = 0.26 (10% EtOAc/hexanes); IR (thin film) 3075, 2957, 1612, 1512, 1037 cm^{-1}; HRMS (FAB) Cacld for $C_{21}H_{30}NaO_3$[M+Na]: 353.2093. Found: 353.2077.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 6.90 (dt, *J* = 8.7 Hz, 3 Hz, 2H), 5.77-5.93 (m, 1H), 5.46 (t, *J* = 6.9 Hz, 1H), 5.06-5.14 (m, 2H), 4.47 (s, 2H), 4.02-4.14 (m, 1H), 3.83 (s, 3H), 3.69 (d, *J* = 8.1 Hz, 1H), 3.48 (dt, *J* = 1.2 Hz, 7.5 Hz, 2H), 2.40 (q, *J* = 7.5 Hz, 2H), 1.96-2.44 (m, 4H), 1.81-1.89 (m, 1H), 1.60-1.73 (m, 1H), 1.67 (s, 3H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.7, 134.9, 130.6, 129.2, 123.9, 116.7, 113.7, 92.3, 77.0, 72.5, 69.5, 55.2, 40.8, 39.0, 35.9, 28.5, 16.9, 11.3.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 6.90 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 5.77-5.93 (m, 1H), 5.42 (t, *J* = 6.9 Hz, 1H), 5.06-5.14 (m, 2H), 4.47 (s, 2H), 4.02-4.14 (m, 1H), 3.83 (s, 3H), 3.78 (d, *J* = 9.0 Hz, 1H), 3.48 (dt, *J* = 1.2 Hz, 7.5 Hz, 2H), 2.40 (q, *J* = 7.5 Hz, 2H), 1.96-2.44 (m, 4H), 1.81-1.89 (m, 1H), 1.60-1.73 (m, 1H), 1.65 (s, 3H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.7, 135.1, 130.6, 129.2, 123.9, 116.7, 113.7, 91.5, 78.5, 72.5, 69.5, 55.2, 40.9, 40.6, 37.8, 28.5, 16.1, 11.1.

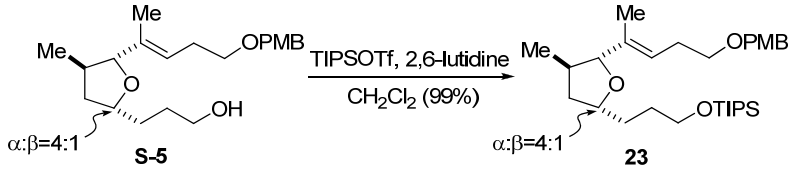


Alcohol S-5. To a solution of the alkene **22** (54.7 mg, 0.166 mmol, α:β = 4 : 1) in THF (2 mL) at 0 °C was added 9-BBN (0.5 M solution in THF, 398 µl, 0.2 mmol). The reaction was stirred at 0 °C for 5 h, and an additional 1.2 equivalent of 9-BBN was added. The reaction was stirred at 22 °C overnight, cooled to 0 °C and was quenched with 3 M NaOH solution (400 µl) and H_2O_2 (136

µl, 30 wt% aqueous solution). After vigorously stirring at 0 °C for 30 min, the reaction mixture was diluted with Et_2O (1 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 X 5 mL). The combined organic layers were washed with brine (2 X 5 mL), dried (Na_2SO_4), and concentrated in *vacuo*. The residue was purified by flash chromatography (40% EtOAc/hexanes) to provide 41.8 mg (72% yield) of the desired product as a colorless oil and as an inseparable mixture of diastereomers (α : β = 4:1). R_f = 0.21 (50% EtOAc/hexanes); IR (thin film) 3425, 2935, 1612, 1509, 1096 cm^{-1}; HRMS (FAB) Calcd for $C_{21}H_{32}NaO_4$[M+Na]: 371.2198. Found: 371.2185.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 6.90 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 5.45 (t, *J* = 7.2 Hz, 1H), 4.46 (s, 2H), 3.96-4.07 (m, 1H), 3.83 (s, 3H), 3.71 (d, *J* = 8.4 Hz, 1H), 3.67 (q, *J* = 4.5 Hz, 2H), 3.47 (dt, *J* = 1.2 Hz, 7.2 Hz, 2H), 2.53 (br s, 1H), 2.39 (q, *J* = 7.2 Hz, 2H), 1.96-2.13 (m, 1H), 1.66-1.84 (m, 6H), 1.64 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.4, 130.5, 129.2, 124.0, 113.7, 92.5, 77.8, 72.5, 69.4, 62.9, 55.2, 40.0, 36.0, 33.5, 29.9, 28.4, 17.1, 11.4.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 6.90 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 5.40 (m, *J* = 6.6 Hz, 1H), 4.46 (s, 2H), 3.96-4.07 (m, 1H), 3.83 (s, 3H), 3.80 (d, *J* = 9.6 Hz, 1H), 3.67 (q, *J* = 4.5 Hz, 2H), 3.47 (dt, *J* = 1.2 Hz, 7.2 Hz, 2H), 2.39 (q, *J* = 7.2 Hz, 2H), 2.14-2.23 (m, 1H), 1.66-1.84 (m, 6H), 1.64 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.4, 130.5, 129.2, 123.9, 113.7, 91.4, 79.4, 72.5, 69.4, 62.9, 55.2, 41.6, 37.8, 33.5, 29.9, 28.4, 16.1, 11.4.

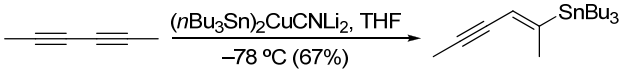


TIPS Ether 23. To a solution of alcohol **S-5** (33.8 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) at –78 °C was added 2,6-lutidine (34 µl, 0.29 mmol) followed by TIPSOTf (28.7 µl, 0.11 mmol). The reaction was stirred at –78 °C for 40 min and then quenched with saturated $NaHCO_3$ solution (1 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 X 5 mL). The combined organic layers were washed with H_2O (2 mL) and brine (2 mL), dried over $MgSO_4$, and concentrated in *vacuo*. The residue was purified by flash chromatography (10% EtOAc/hexanes) to provide 48 mg (99% yield) of the desired product as a colorless oil and as an inseparable mixture of

diastereomers (α : β = 4:1). R_f = 0.33 (10% EtOAc/hexanes); IR (thin film) 2938, 1505, 1098, 1033 cm^{-1}; HRMS (FAB) Calcd for $C_{30}H_{53}O_4Si$[M+H]: 505.3713. Found 505.3700.

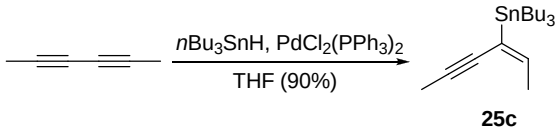
Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 6.90 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 5.45 (t, *J* = 7.2 Hz, 1H), 4.47 (s, 2H), 3.96-4.07 (m, 1H), 3.83 (s, 3H), 3.73 (t, *J* = 6.0 Hz, 2H), 3.69 (d, *J* = 8.4 Hz, 1H), 3.48 (dt, *J* = 1.2 Hz, 7.5 Hz, 2H), 2.40 (q, *J* = 7.5 Hz, 2H), 1.96-2.12 (m, 1H), 1.50-1.85 (m, 6H), 1.64 (s, 3H), 1.08 (s, 21H), 0.97 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.9, 130.6, 129.2, 123.7, 113.7, 92.2, 77.6, 72.5, 69.5, 63.4, 55.2, 39.8, 36.0, 32.7, 29.4, 28.5, 18.0, 17.1, 12.0, 11.3.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 6.90 (dt, *J* = 8.7 Hz, 3.0 Hz, 2H), 5.41 (t, *J* = 7.2 Hz, 1H), 4.47 (s, 2H), 3.96-4.07 (m, 1H), 3.83 (s, 3H), 3.80 (d, *J* = 9.6 Hz, 1H), 3.73 (t, *J* = 6.0 Hz, 2H), 3.48 (dt, *J* = 1.2 Hz, 7.5 Hz, 2H), 2.40 (q, *J* = 7.5 Hz, 2H), 2.12-2.24 (m, 1H), 1.50-1.85 (m, 6H), 1.64 (s, 3H), 1.08 (s, 21H), 0.98 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.9, 130.6, 129.2, 123.7, 113.7, 91.3, 79.3, 72.5, 69.5, 63.4, 55.2, 41.5, 37.8, 32.7, 29.5, 28.5, 17.7, 16.2, 12.4, 11.2.



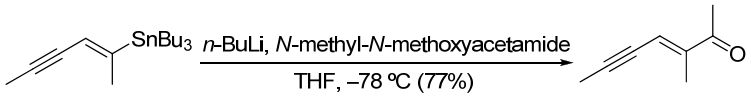
25a

Vinyl stannane 25a: To a slurry of CuCN (6.9 g, 76.8 mmol) in THF (300 mL) at –35 ºC was added *n*-BuLi (2.3 M in hexanes, 67 mL, 154 mmol). The resulting yellow homogenous solution was stirred at –35 ºC for 30 min, cooled to –78 ºC and *n*Bu_3SnH (41 mL, 154 mmol) was added. The yellow-greenish solution was stirried at –78 ºC for 30 min and a solution of 2,4-hexadiyne (3 g, 38.4 mmol) in THF (20 mL) was added down the side of the flask. The reaction mixture was stirred at –78 ºC for 3 h, and was quenched by slow addition of MeOH (45 mL) followed by saturated NH_4Cl solution (45 mL). The mixture was warmed to room temperature, extracted with Et_2O, washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash chromatography (hexanes) to afford 9.5 g (67% yield) of the desired vinyl stannane as a colorless oil as mixture of isomers (7:1). Major isomer: R_f = 0.65 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (m, 1H), 2.09 (d, *J* = 2.0 Hz, 3H), 2.02 (d, *J* = 2.0 Hz, 3H), 1.49 (m, 6H), 1.31 (qt, *J* = 7.5 Hz, 7.5 Hz, 6H), 0.91 (q, *J* = 8.0 Hz, 6H), 0.89 (q, *J* = 7.5 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 118.7 (d, *J* = 15 Hz), 89.7, 77.2, 29.3, 27.6, 22.9, 13.9, 9.5, 4.6; LRMS calcd for for $C_{18}H_{34}LiSn$ [M+Li]: 377. Found: 377.



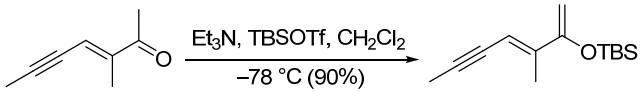
25c

Vinyl stannane 25c: To a solution of 2,4-hexadiyne (52 mg, 0.666 mmol) in THF (2 mL) was added $PdCl_2(PPh_3)_2$ (23 mg, 0.0333 mmol). *n*-BuSnH (200 µl, 0.732 mmol) was then added over a period of 30 min. The reaction mixture was stirred at room temperature for 30 min, concentrated *in vacuo*, and purified by flash chromatography (pentane) to afford 220 mg (90% yield) of the desired product as a slightly yellow oil. R_f = 0.68 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (q, *J* = 6.5 Hz, 1H), 2.04 (s, 3H), 1.95 (d, *J* = 6.5 Hz, 3H), 1.53 (m, 6H), 1.33 (qt, *J* = 7.5 Hz, 7.5 Hz, 6H), 0.95 (t, *J* = 8.0 Hz, 6H), 0.90 (t, *J* = 7.5 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7, 124.9, 94.5, 81.1, 29.2, 27.6, 18.7, 13.7, 10.2, 5.1; LRMS calcd for $C_{18}H_{34}LiSn$ [M+Li]: 377. Found: 377.



25a **S-6**

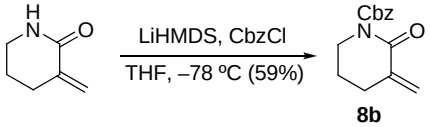
Ketone S-6: To a solution of vinyl stannane **25a** (7.08 g, 19.2 mmol) in THF (150 mL) at –78 ºC was added *n*-BuLi (2.0 M in hexanes, 12.0 mL, 24.0 mmol). After stirring at –78 ºC for 20 min, *N*-methoxy-*N*-methyl acetamide (2.4 g, 23.0 mmol) in THF (15 mL) was added dropwise. The resulting light yellow solution was stirred at –78 ºC for 1 h, warmed to room temperature and was quenched by 1 N HCl solution (about 40 mL) until the mixture was slightly acidic. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Mg_2SO_4), concentrated *in vacuo* and purified by flash chromatography (5% Et_2O/pentane →10% Et_2O/pentane) to afford 1.8 g (77% yield) of the desired product as a yellow oil. R_f = 0.43 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (m, 1H), 2.31 (d, *J* = 1.0 Hz, 3H), 2.10 (dq, *J* = 2.5 Hz, 0.5 Hz, 3H), 1.97 (q, *J* = 0.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 146.3, 121.0, 101.3, 76.7, 25.5, 14.1, 4.9; IR (thin film): 2220, 1668 cm^{-1}; LRMS Calcd. for $C_8H_{11}O$ [M+H]: 123. Found: 123.



S-6 (*E*)-**24**

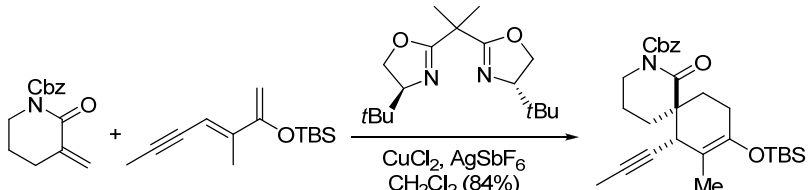
Silyl enol ether (*E*)-24: To a solution of ketone **S-6** (643 mg, 5.25 mmol) in CH_2Cl_2 (30 mL) at –78 ºC was added Et_3N (1.47 mL, 10.5 mmol) and TBSOTf (1.31 mL, 5.79 mmol). The

reaction mixture was stirred at –78 ºC for 10 min and quenched by pH 7 buffer. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography on basic Al_2O_3 (pentane) to afford 1.12 g (90% yield) of the desired product as a colorless oil. R_f = 0.57 (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (m, 1H), 4.54 (d, *J* = 1.5 Hz, 1H), 4.36 (br s, 1H), 2.05 (d, *J* = 2.4 Hz, 3H), 2.01 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 142.6, 107.7, 93.5, 93.3, 78.1, 25.8, 18.2, 15.8, 4.7, –4.7; IR (thin film): 2220 cm^{-1}; LRMS (ESI) Calcd. for $C_{14}H_{25}OSi$ [M+H]: 237. Found: 237.



8b

***N*-Cbz lactam 8b**: To a solution of α-methylene δ-lactam (400 mg, 3.60 mmol) in THF (36 mL) at –78 ºC was added LiHMDS (1.0 M in THF, 4.32 mL, 4.32 mmol). After stirring at –78 ºC for 20 min, benzyl chloroformate (617 µl, 4.32 mmol) was added. The reaction mixture was stirred at –78 ºC for 30 min and quenched by pH 7 buffer. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (10% → 30% → 50% Et_2O/hexanes) to afford 523 mg (59% yield) of the desired product as a slightly yellowish oil which solidifies upon standing in refrigerator overnight. m.p.51–53 ºC; R_f = 0.45 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.31 (m, 5H), 6.36 (dd, *J* = 0.9 Hz, 0.9 Hz, 1H), 5.45 (dd, *J* = 0.9 Hz, 0.9 Hz, 1H), 5.31 (s, 2H), 3.81 (app q, *J* = 3.9 Hz, 2H), 2.60 (tt, *J* = 0.9 Hz, 3.9 Hz, 2H), 1.90 (tt, *J* = 3.9 Hz, 3.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 154.4, 138.2, 135.4, 128.5, 128.2, 128.0, 125.6, 68.5, 47.0, 29.1, 22.4; IR (thin film): 1697 cm^{-1}; LRMS (ESI) Calcd. for $C_{14}H_{16}NO_3$ [M+H]: 246. Found: 246.

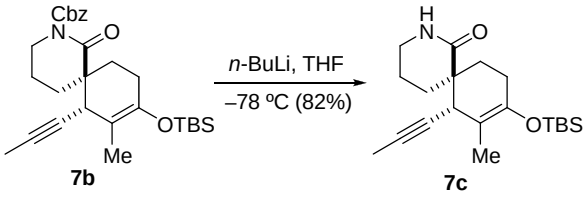


8b (*E*)-**24** **7b**

***N*-Cbz spirolactam 7b**: A flask wrapped with aluminum foil was charged with $CuCl_2$ (69.4 mg, 0.516 mmo) and (*S*, *S*)-*tert*-butyl-bis(oxazoline) (167 mg, 0.568 mmol) in a glove box. The flask was removed from the glove box and CH_2Cl_2 (3 mL) was added. The greenish homogeneous

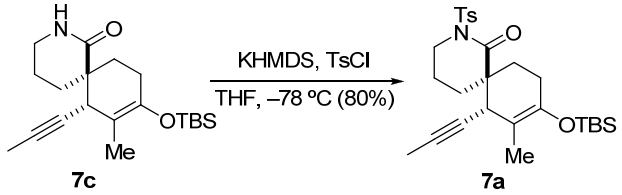
solution was stirred at room temperature in dark for 3.5 h, then a solution of $AgSbF_6$ (354.7 mg, 1.03 mmol, weighed in a glove box) in CH_2Cl_2 (3 mL) was added. White precipitate formed immediately. After stirring at room temperature for 2 h, the dark green mixture was filtered through a pad of oven-dried Celite, rinsed with CH_2Cl_2 (3 mL) and the resulting blue catalyst solution was used in the reaction.

To this catalyst solution was added a solution of Cbz lactam **8b** (1.27 g, 5.16 mmol) in CH_2Cl_2 (6 mL) followed by a solution of TBS enol ether (*E*)-**24** (1.83 g, 7.74 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature in dark for 11 h, concentrated *in vacuo* and purified by flash chromatography (5%→7.5%→10% → 20% EtOAc/hexanes) to provide 2.1 g (84%) of the desired product as a slightly yellow oil. R_f = 0.48 (20% EtOAc/hexanes); $[\alpha]_D^{21}$ + 87.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.32 (m, 5H), 5.27 (dd, AB system, *J* =12.0 Hz, 2H), 3.82 (m, 1H), 3.77 (m, 1H), 3.69 (m, 1H), 2.14-2.07 (m, 3H), 1.98-1.91 (m, 2H), 1.85-1.78 (m, 3H), 1.75 (d, *J* = 2.5 Hz, 3H), 1.71 (q, *J* = 1.5 Hz, 3H), 0.94 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 154.9, 141.8, 135.7, 128.5, 128.1, 128.0, 110.2, 79.3, 77.7, 68.3, 48.0, 47.6, 40.8, 30.3, 21.2, 26.7, 25.8, 20.1, 18.1, 14.8, 3.6, –3.9; IR (thin film): 1772, 1721 cm^{-1}; LRMS calcd for $C_{28}H_{40}NO_4Si$ [M+H]: 482. Found: 482. CAUTION: The product is readily oxidized to an α,β-unsaturated ketone when exposed to air and should be immediately (within one hour) used in the following deprotection step after purification.



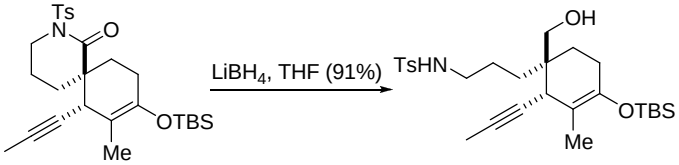
Spirolactam 7c: To a solution of the lactam **7b** (500 mg, 1.04 mmol) in THF (30 mL, degassed through freeze-thaw processes) at –78 ºC was added *n*-BuLi (2.0 M in hexanes, 675 µl, 1.35 mmol). After stirring for 15 min, another 600 µl of *n*-BuLi (2.0 M in hexanes) was added. The reaction mixture was stirred for 15 min and was quenched by pH 7 buffer. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography (50% → 70% EtOAc/hexanes) to provide 296 mg (82% yield) of the desired lactam as a white powder. R_f = 0.40 (50% EtOAc/hexanes); $[\alpha]_D^{21}$ +105.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (br s, 1H, NH), 3.97 (br s, 1H), 3.40-3.24 (m, 2H), 2.18-1.88 (m, 8H), 1.79 (d, *J* = 2.5 Hz, 3H), 1.71 (app d, *J* = 1.5 Hz, 3H), 0.94 (s, 9H), 0.12 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 141.5, 109.9, 79.1, 78.1, 44.3, 42.4, 39.6, 30.1, 26.3, 25.8, 24.6, 19.6, 18.1, 14.7, 3.6, –3.8, –3.9; IR (thin film): 3192, 1655 cm^{-1}; LRMS calcd for $C_{20}H_{34}NO_2Si$ [M+H]: 348. Found: 348. A mixture of spirolactam **7c** (3 mg, 0.00863 mmol) and (+)-Eu(hfc)$_3$ (10 mg, 0.00863 mmol) was dissolved in $CDCl_3$. ^{1}H NMR showed separated peaks for two enantiomers and integration gave 83% ee.



7c **7a**

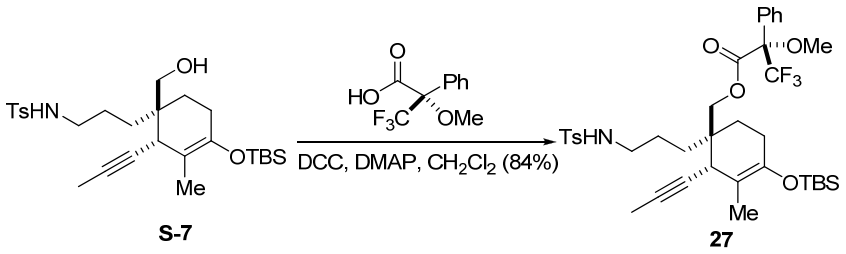
***N*-Tosyl spirolactam 7a**: To a solution of the lactam **7c** (270 mg, 0.777 mmol) in THF (20 mL) at –78 ºC was added KHMDS (0.5 M in toluene, 2.33 mL, 1.17 mmol). After stirring at –78 ºC for 20 min, TsCl (recrystallized from ether, 250 mg, 1.17 mmol) was added. The reaction mixture was stirred at –78 ºC for 1 h, warmed to room temperature over a period of 1 h, and quenched with pH 7 buffer. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (10%→20% Et_2O/hexanes) to afford 311 mg (80% yield) of product as a white solid. NMR matched with previously reported. $[\alpha]_D^{21}$ +125.7 (*c* 1.0, $CHCl_3$). Recrystallization from heptane provided white crystals suitable for X-ray analysis.



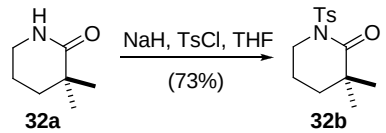
7a **S-7**

Amino alcohol S-7: To a solution of tosyl lactam **7a** (7.0 mg, 0.0140 mmol) in THF (1 mL) at 0 ºC was added $LiBH_4$ (2M in THF, 70 µl, 0.140 mmol). The reaction mixture was stirred at 25 ºC for 4 h and then quenched by pH 7 buffer. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried (Na_2SO_4), concentrated and purified by flash chromatography (60% EtOAc/Hexanes) to afford 6.4 mg (91% yield) of the desired product as a white foam. R_f = 0.15 (30% EtOAc/hexanes); $[\alpha]_D^{21}$ +42.4 (*c* 0.42, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 4.54 (t, *J* = 5.5 Hz, 1 H), 3.49 (d, *J* = 11.0 Hz, 1H), 3.36 (d, *J* = 11.0 Hz, 1H), 2.96 (dt, *J* = 6.0 Hz, 5.5 Hz, 2H), 2.64 (br s, 1H), 2.43 (s, 3H), 1.98 (m, 2H), 1.81 (d, *J* = 2.5 Hz, 3H), 1.66 (app q, *J* = 1.5 Hz, 3H), 1.56 (m, 3H), 1.48 (m, 3H), 0.94 (s, 9H), 0.12

(3H, s), 0.09 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 143.1, 136.9, 130.0, 127.2, 110.3, 78.7, 78.5, 64.8, 43.9, 39.2, 39.0, 30.1, 27.1, 27.0, 25.8, 23.2, 21.5, 18.2, 15.4, 3.6, –3.6, –3.9; IR (thin film): 3478, 3278 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{43}LiNO_4SSi$ [M+Li]: 512.2842. Found: 512.2844.

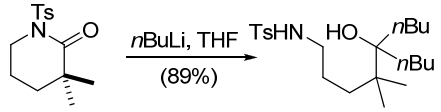


Mosher ester 27: To a solution of (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (5 mg, 0.0198 mmol) in CH_2Cl_2 (1 mL) was added DCC (3 mg, 0.0149 mmol), a solution of amino alcohol **S-7** (5 mg, 0.00990 mmol) in CH_2Cl_2 (1 mL) and a crystal of DMAP successively. The reaction mixture was stirred at room temperature for 12 h and concentrated *in vacuo*. ^{19}F NMR integration of the crude reaction mixture showed ratio of 97.6 : 2.4 of the two diastereomers corresponding to 95% ee. The crude mixture was purified by flash chromatography (30% EtOAc/hexanes) to provide 6 mg (84% yield) of the desired product as a colorless oil. ^{19}F NMR integration of the pure product gave the same ratio. R_f = 0.50 (30% EtOAc/hexanes); $[\alpha]_D^{21}$ +26.0 (*c* 0.63, $CHCl_3$); ^{19}F NMR (300 MHz, $CFCl_3$) δ –71.25 (minor diastereomer), –71.29 (major diastereomer); ^{1}H NMR (500 MHz, C_6D_6) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.09 (m, 2H), 7.04 (m, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 4.04 (s, 2H), 3.93 (t, *J* = 6.0 Hz, 1H), 3.38 (s, 3H), 2.64 (dt, *J* = 6.5 Hz, 6.5 Hz, 2H), 2.54 (br s, 1H), 1.98 (m, 2H), 1.89 (s, 3H), 1.83 (s, 3H), 1.63 (m, 1H), 1.54 (d, *J* = 2.5 Hz, 3H), 1.40 (m, 1H), 1.34 (m, 1H), 1.25 (m, 1H), 1.10 (m, 2H), 0.95 (s, 9H), 0.074 (s, 3H), 0.068 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 166.5, 143.5, 142.7, 138.6, 132.9, 130.0, 129.6, 128.7, 128.3, 127.7, 127.5, 125.4 (q, CF_3, *J* = 287 Hz), 123.1, 110.5, 85.2, 78.9, 78.1, 67.0, 55.4, 43.8, 38.6, 38.2, 32.3, 27.5, 27.4, 25.9, 23.7, 21.1, 18.3, 15.9, 3.3, –3.6, –3.7; IR (thin film): 3283, 1752 cm^{-1}; LRMS (ESI) calcd for $C_{37}H_{50}F_3LiNO_6SSi$ [M+Li]: 728. Found: 728.



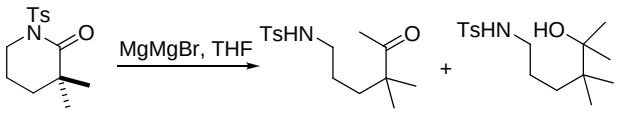
***N*-Ts lactam 32b**. A solution of 3,3-dimethylpiperidin-2-one (**32a**) (0.52 g, 4.1 mmol) in THF (15 mL) was treated with NaH (80% in mineral oil, 280 mg, 9.3 mmol). After stirring for 48

min, TsCl (780 mg, 4.1 mmol) was added and the mixture was stirred for 17 h. Saturated NH_4Cl solution was then added and the mixture was extracted with one portion of ethyl acetate and washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (with 5% → 10% EtOAc/hexanes) to afford 838 mg (73% yield) of the product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 3.93 (t, *J* = 6.0 Hz, 2H), 2.43 (s, 3H), 2.00-1.90 (m, 2H), 1.72-1.62 (m, 2H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 144.3, 136.0, 129.2, 128.3, 47.7, 40.9, 35.6, 26.9, 21.5, 20.1; HRMS (ESI) Calcd for $C_{14}H_{19}LiNO_3S$ [M+Li]: 288.1246. Found 288.1257.



32b **38a**

Alcohol 38a. A solution of *N*-Ts lactam **32b** (34.2 mg, 0.12 mmol) in THF (3 mL) at –78 °C was treated with *n*-BuLi (2.5 M in hexanes, 97 μL, 0.24 mmol). The suspension was warmed to room temperature and stirred for 13 h. The solvent was concentrated *in vacuo* and the residue was purified by flash chromatography (5% → 10% EtOAc/hexanes) to provide 42.4 mg (89% yield) of the product as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J*= 8.1 Hz, 2H), 7.31 (d, *J*= 8.7 Hz, 2H), 4.50 (br s, 1H, NH), 3.0-2.9 (m, 2H), 2.43 (s, 3H), 1.58-1.40 (m, 7H), 1.39-1.20 (m, 10H), 0.91 (t, *J* = 6.8 Hz, 2H), 0.81(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 136.8, 129.6, 127.1, 77.7, 44.3, 40.9, 35.0, 33.8, 27.0, 25.0, 23.7, 21.8, 21.5, 14.1; IR (thin film) 3533, 3274 cm^{-1}; HRMS Calcd for $C_{22}H_{39}LiNO_3S$ [M+Li]: 404.2811. Found 404.2815.



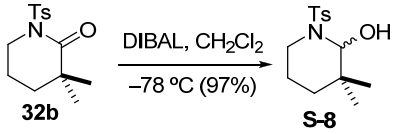
32b **37b** (69%) **38b** (21%)

Ketone 37b and alcohol 38b: A solution of *N*-Ts lactam **32b** (23 mg, 0.083 mmol) in THF (3 mL) at –78 °C was treated with MeMgBr (3.0 M in ether, 100 μL, 0.30 mmol) over 1.5 h. The suspension was warmed to room temperature and stirred for 12 h. The solvent was concentrated *in vacuo* and the residue was purified by flash chromatography (30% EtOAc/hexanes) to provide 17 mg (69% yield) of the ketone **37b** as a colorless oil, along with 5 mg (21% yield) of the alcohol **38b** as a colorless oil.

Ketone 37b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.73 (m, 2H), 7.33-7.30 (m, 2H), 4.59 (t, *J* = 6.3 Hz, 1H, NH), 2.90 (q, *J* = 6.6 Hz, 2H), 2.43 (s, 3H), 2.08 (s, 3H), 1.50-1.28 (m, 4H), 1.07 (s,

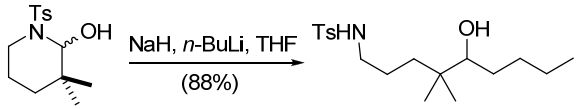
6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 143.4, 136.9, 129.7, 127.1, 47.3, 43.5, 36.3, 25.0, 24.9, 24.3, 21.5; IR (thin film) 3286, 1700 cm^{-1}.

Alcohol 38b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.74 (m, 2H), 7.33-7.30 (m, 2H), 4.55 (t, *J* = 5.7 Hz, 1H, NH), 2.94 (q, *J* = 6.6 Hz, 2H), 2.43 (s, 3H), 1.48-1.40 (m, 2H), 1.29-1.20 (m, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 0.81 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 137.0, 129.7, 127.1, 75.5, 44.2, 39.5, 33.6, 25.3, 25.1, 21.5, 21.3; IR (thin film) 3513, 3283 cm^{-1}; HRMS Calcd for $C_{16}H_{27}LiNO_3S$ [M+Li]: 320.1872. Found 320.1873.



32b **S-8**

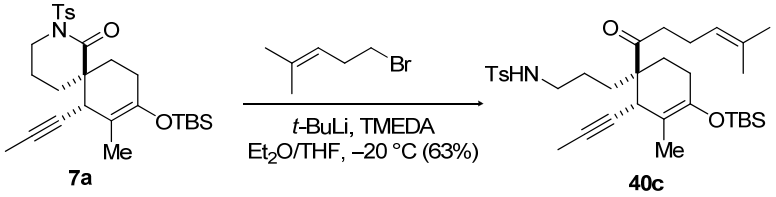
Carbinol amine S-8. To a solution of *N*-Ts lactam **32b** (1.47 g, 5.22 mmol) in CH_2Cl_2 (16 mL) at –78 °C was added DIBAL-H (4.836 mL). The reaction was stirred at –78 °C for 2 h, diluted with CH_2Cl_2 (26 mL) and quenched with methanol. Rochelle's salt solution (26 mL) was added and the mixture was stirred for an additional 12 h. The layers were separated and the organic phase was washed with brine and filtered through a plug of silica gel. The solvent was concentrated *in vacuo* and the residue was purified by flash chromatography (9% EtOAc/hexanes) to provide 1.43 g (97% yield) of the product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.74 (m, 2H), 7.35-7.29 (m, 2H), 4.96 (d, *J* = 3.9 Hz, 1H), 3.59 (dd, *J* = 12.0 Hz, 3.9 Hz, 1H), 3.04 (td, *J* = 12.0 Hz, 3.0 Hz, 1H), 2.45 (s, 3H), 2.13 (d, *J* = 4.2 Hz, 1H), 1.80-1.55 (m, 4H), 0.98 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 137.1, 130.0, 127.6, 84.0, 39.4, 35.2, 30.7, 27.4, 24.1, 21.8, 21.3; IR (thin film) 3517 cm^{-1}; HRMS Calcd for $C_{14}H_{22}LiNO_3S$ [M+Li]: 290.1402. Found 290.1401.



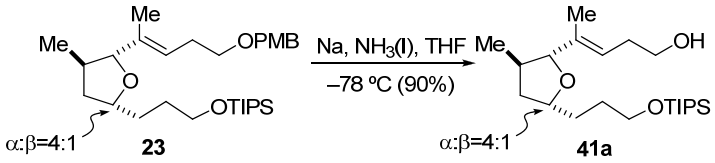
S-8 **39**

Amino alcohol 39. To a solution of carbinol amine **S-8** (80 mg, 0.28 mmol) in THF (9mL) at 0 °C was added NaH (80% in mineral oil, 8.5 mg, 0.28 mmol). The suspension was stirred for 15 min, cooled to –78 °C, and was treated with *n*-BuLi (2.44 M in hexanes, 120 μL, 0.283 mmol). The reaction was stirred for at –78 °C for 15 min, concentrated *in vacuo* and the residue was purified by flash chromatography (30% EtOAc/hexanes) to provide 85 mg (88% yield) of the desired product as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.31 (m, 2H), 7.33-7.27 (m, 2H), 4.45 (t, *J* = 5.9 Hz, 1H, NH), 3.19 (d, *J* = 9.6 Hz, 1H, OH), 2.92 (q, *J* = 6.5 Hz, 2H), 2.44 (s, 3H), 1.52-1.07 (m,

11H), 0.92 (t, J = 6.9 Hz, 3H), 0.80 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 137.2, 130.0, 127.4, 78.7, 44.4, 37.3, 35.8, 31.2, 30.0, 29.6, 24.4, 23.3, 23.0, 22.9, 21.8, 14.4.

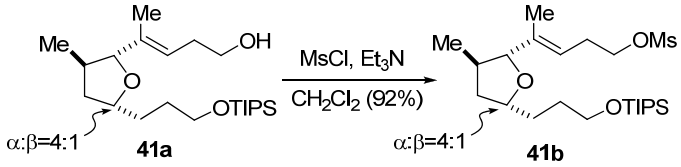


Amino ketone 40c: To a solution of 5-bromo-2-methyl-2-pentene (9.3 mg, 0.0571 mmol) in Et_2O (1 mL) at –78 ºC was added *t*-BuLi (1.2 M in pentane, 0.095 mL, 0.114 mmol) dropwise. After stirring for 5 min, freshly distilled TMEDA (0.034 mL, 0.228 mmol) was added followed by a solution of **7a** (26 mg, 0.0519 mmol) in THF (1 mL). The reaction mixture was stirred at –20 ºC for 4 h, warmed to room temperature and stirred for 10 h. The reaction was quenched by pH 7 buffer. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash chromatography (10% → 20% EtOAc/hexanes) to afford 19 mg (63% yield) of product as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 5.03 (triplet of septet, J = 7.5 Hz, 1.5 Hz, 1H,), 4.27 (t, J = 6.5 Hz, 1H), 3.24 (br s, 1H), 2.90 (dt, J = 6.5 Hz, 6.5 Hz, 2H), 2.44 (s, 3H), 2.38 (t, J = 7.5 Hz, 2H), 2.18 (tt, J = 7.5 Hz, 7.5 Hz, 2H), 2.00-1.85 (m, 4H), 1.83 (d, J = 2.5 Hz, 3H), 1.70 (br s, 3H), 1.66 (s, 3H), 1.60 (s, 3H), 1.73 (m, 1H), 1.53 (m, 1H), 1.30 (m, 1H), 1.16 (m, 1H), 0.90 (s, 9H), 0.03 (d, J = 1.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 143.7, 143.5, 137.1, 133.0, 130.0, 127.4, 123.3, 112.8, 78.9, 78.7, 53.6, 43.6, 37.2, 37.0, 34.5, 28.3, 28.2, 26.03, 25.96, 24.1, 22.5, 21.8, 18.4, 17.9, 16.0, 3.9, –3.5, –3.7. IR (thin film, cm^{-1}): 3283, 1701. HRMS calcd for $C_{33}H_{51}LiNO_4SSi$ [M+Li]:592.3468. Found: 592.3478.

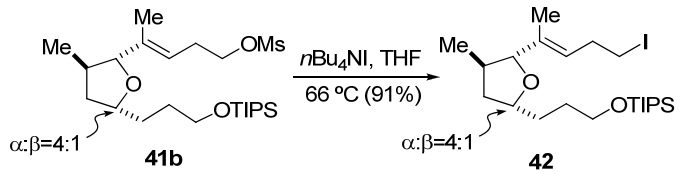


Alcohol 41a: To a three-necked flask immersed in acetone/dry ice bath (–78 ºC) equipped with a cold finger was condensed about 40 mL of liquid ammonia. Sodium (376 mg, 16.4 mmol, cut in small pieces) was added and the resulting blue mixture was stirred for 10 min. Then a solution of PMB ether **23** (826 mg, 1.64 mmol) in THF (25 mL) was added. The reaction mixture was stirred at –78 ºC for 45 min and quenched by slow addition of MeOH (10 mL). The solution was warmed to room temperature, stirred in open air for 1 h and then water (10 mL) and Et_2O (10 mL) were added.

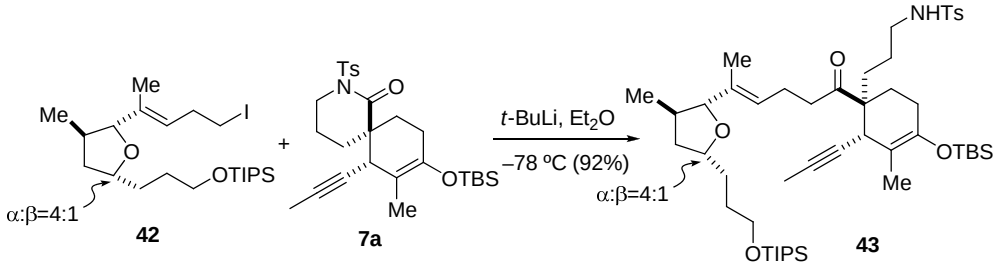
The aqueous layer was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (30% EtOAc/hexanes) to provide 566 mg (90% yield) of the desired product as a colorless oil as a mixture of two diastereomers (4:1). Major diastereomer: R_f = 0.37 (30% EtOAc/hexanes); $[\alpha]_D^{21}$ – 17.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (t, *J* = 7.0 Hz, 1H), 3.99 (m, 1H), 3.71 (m, 2H), 3.69 (d, *J* = 8.0 Hz, 1H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.35 (m, 2H), 2.01 (m, 1H), 1.78 (ddd, *J* = 5.5 Hz, 8.5 Hz, 12.5 Hz, 1H), 1.68 (m, 2H), 1.65 (s, 3H), 1.55 (m, 3H), 1.06 (m, 21H), 0.96 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 123.2, 92.2, 77.8, 63.4, 62.3, 39.8, 36.1, 32.8, 31.4, 29.5, 18.0, 17.1, 11.9, 11.4.; IR (thin film): 3401 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{44}LiO_3Si$ [M+Li]:391.3220. Found: 391.3219.



Mesylate 41b: To a solution of the alcohol **41a** (450 mg, 1.17 mmol) in CH_2Cl_2 (20 mL) at –78 ºC was added Et_3N (815 µl, 5.85 mmol) and methanesulfonyl chloride (136 µl, 1.75 mmol). The reaction mixture was stirred at –78 ºC for 10 min and quenched with pH7 buffer. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography on Et_3N deactivated SiO_2 (30% EtOAc/hexanes) to afford 498 mg (92% yield) of the desired product as a colorless oil as a mixture of diastereomers (4:1). Major diastereomer: R_f = 0.47 (30% EtOAc/hexanes); $[\alpha]_D^{21}$ –12.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (t, *J* = 7.0 Hz, 1H), 4.22 (dt, *J* = 2.5 Hz, 6.5 Hz, 2H), 4.00 (m, 1H), 3.71 (t, *J* = 6.0 Hz, 2H), 3.68 (d, *J* = 8.0 Hz, 1H), 3.01 (s, 3H), 2.53 (dt, *J* = 7.0 Hz, 7.0 Hz, 2H), 2.00 (m, 1H), 1.78 (ddd, *J* = 5.5 Hz, 8.5 Hz, 12.5 Hz, 1H), 1.68-1.52 (m, 5H), 1.65 (s, 3H), 1.05 (m, 21H), 0.96 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 120.5, 91.8, 77.9, 69.1, 63.3, 39.7, 37.5, 36.3, 32.7, 29.5, 27.8, 18.0, 17.1, 12.0, 11.6; LRMS (ESI) Calcd. for $C_{23}H_{46}LiO_5SSi$ [M+Li]: 469. Found: 469.

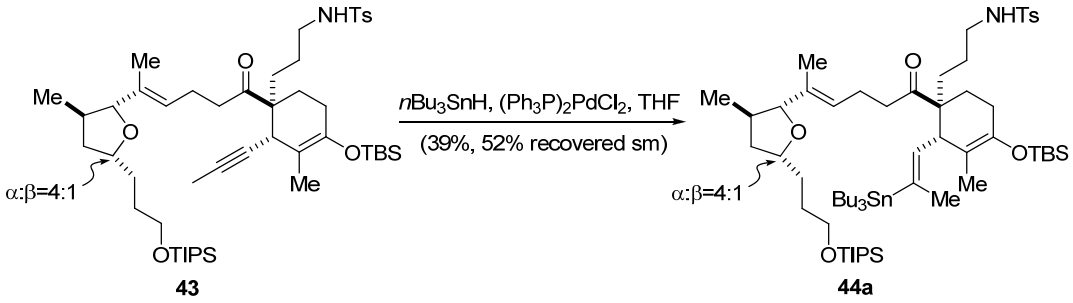


Alkyl iodide 42: To a solution of mesylate **41b** (180 mg, 0.389 mmol) in THF (10 mL) was added tetrabutylammonium iodide (287 mg, 0.778 mmol). The mixture was refluxed for 4 h, concentrated *in vacuo* and purified by flash chromatography (5% EtOAc/hexanes) to afford 176 mg (91% yield) of the desired product as a colorless oil as a mixture of two diastereomers (4:1). Major diastereomer: R_f = 0.53 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (t, *J* = 7.0 Hz, 1H), 4.01 (m, 1H), 3.71 (t, *J* = 5.5 Hz, 2H), 3.68 (d, *J* = 8.0 Hz, 1H), 3.13 (dt, *J* = 2.0 Hz, 7.5 Hz, 2H), 2.69-2.61 (m, 2H), 2.05-1.98 (m, 1H), 1.79 (ddd, *J* = 5.5 Hz, 8.5 Hz, 12.5 Hz, 1H), 1.62 (s, 3H), 1.70-1.52 (m, 5H), 1.06 (m, 21H), 0.94 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 125.9, 91.9, 77.9, 63.3, 39.7, 36.2, 32.8, 32.0, 29.5, 18.0, 17.1, 12.0, 11.6, 5.4; IR (thin film): 2945, 2868, 1107 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{43}LiIO_2Si$ [M+Li]: 501.2237. Found: 501.2234.



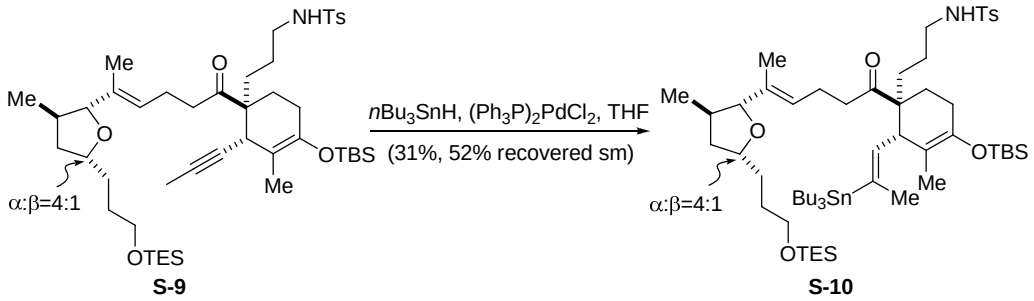
Amino ketone 43: Alkyl iodide **42** (83 mg, 0.168 mmol) and *N*-Ts spirolactam **7a** (67 mg, 0.134 mmol) were placed in a flask and azeotropically dried with toluene. The mixture was dissolved in Et_2O (15 mL) and the resulting solution was cooled to –78 ºC. *t*-BuLi (1.5 M in pentane, 246 µl, 0.369 mmol) was then added dropwise. The reaction mixture was stirred at –78 ºC for 2 h and quenched by pH 7 buffer. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (5%→10%→15% EtOAc/hexanes) to afford 107 mg (92% yield) of the desired product as a colorless oil as a mixture of two diastereomers (4:1). Major diastereomer: R_f = 0.50 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ +62.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.51 (t, *J* = 6.0 Hz, 1H, -NH), 5.31 (t, *J* = 7.0 Hz, 1H), 4.03 (m, 1H), 3.67 (m, 2H), 3.62 (d, *J* = 8.0 Hz, 1H), 3.17 (br s, 1H), 2.85 (m, 2H), 2.47 (m, 1H), 2.43 (s, 3H), 2.38-2.32 (m, 2H), 2.15 (m, 1H), 2.04-1.90 (m, 5H), 1.80 (d, *J* = 2.5 Hz, 3H), 1.78 (m, 2H), 1.68 (s, 3H), 1.65 (m, 1H), 1.62 (s, 3H), 1.62-1.45 (m, 7H), 1.05 (m, 21H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 143.6, 142.9, 137.6, 135.3, 129.5, 126.9, 126.4, 112.4, 92.1, 78.4, 78.2, 77.9, 63.3, 53.3, 43.4, 39.5, 37.2, 36.1, 35.9,

34.0, 32.7, 29.4, 27.8, 26.8, 25.7, 23.9, 21.5, 21.4, 18.04, 17.96, 16.9, 15.7, 11.9, 11.1, 3.6, –3.8, –4.2; IR (thin film): 3437, 3298, 1701 cm^{-1}; HRMS (ESI) Calcd. for $C_{49}H_{83}LiNO_6SSi_2$ [M+Li]: 876.5640. Found: 876.5641.



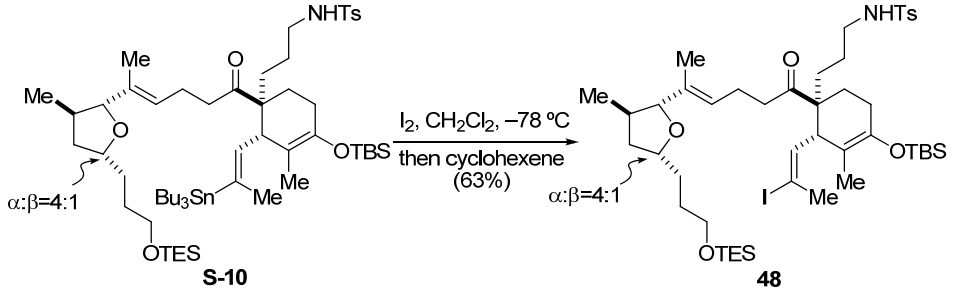
43 **44a**

Vinyl stannane 44a: To a solution of alkyne **43** (235 mg, 0.270 mmol) in THF (8 mL) at room temperature was added $PdCl_2(PPh_3)_2$ (45 mg, 0.0641 mmol) and tributyltin hydride (545 µl, 2.03 mmol) in five portions, with 12 h between every portion. The resulting dark reaction mixture was concentrated *in vacuo* and purified by flash chromatography (5%→10%→15% EtOAc/hexanes) to provide 122 mg (39% yield) of the desired product as a colorless oil as a mixture of two diastereomers (4:1), along with 122 mg (52%) of the recovered starting material. Major diastereomer: R_f = 0.63 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.82 (t, *J* = 6.5 Hz, 1H, -NH), 5.31 (t, *J* = 7.5 Hz, 1H), 5.18 (dq, *J* = 9.5 Hz, 2.0 Hz, 1H), 4.07 (m, 1H), 3.67 (m, 2H), 3.63 (d, *J* = 8.0 Hz, 1H), 3.46 (d, *J* = 9.5 Hz, 1H), 2.78-2.46 (m, 4H), 2.41 (s, 3H), 2.37 (m, 1H), 2.20-1.94 (m, 5H), 1.92 (d, *J* = 2.0 Hz, 3H), 1.79 (m, 1H), 1.65 (s, 3H), 1.62-1.56 (m, 3H), 1.49 (m, 12H), 1.30 (m, 8H), 1.08 (m, 2H), 1.04 (m, 21H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.88 (m, 24H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8, 143.7, 142.7, 140.1, 139.5, 137.9, 135.2, 129.4, 126.89, 126.85, 113.9, 92.3, 78.0, 63.3, 53.2, 43.5, 42.2, 39.5, 36.0, 35.9, 33.4, 32.8, 29.4, 29.2, 27.7, 27.3, 25.9, 25.0, 24.1, 21.5, 21.4, 19.8, 18.2, 18.0, 16.9, 15.3, 13.7, 12.0, 11.2, 9.2, –3.9, –4.2; IR (thin film): 3280, 3186, 1703 cm^{-1}.



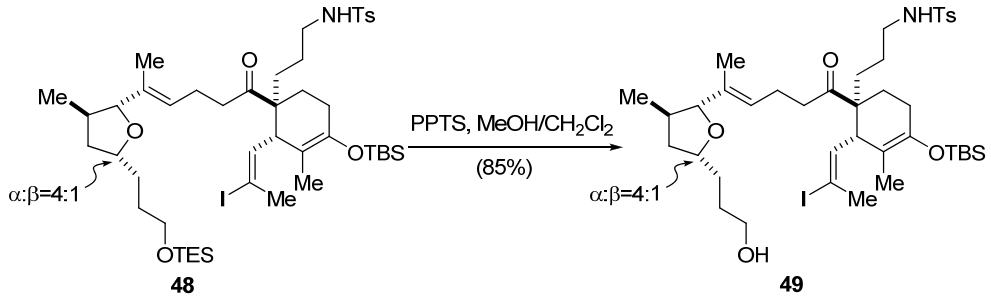
S-9 **S-10**

Vinyl stannanne S-10: To a solution of the alkyne **S-9** (62 mg, 0.0748 mmol) in THF (4 mL) at room temperature was added $PdCl_2(PPh_3)_2$ (3 mg, 0.00374 mmol) followed by a solution of tributyltin hydride (20 µl, 0.0748 mmol) in hexanes (0.5 mL) over 10 h via a syringe pump. The same addition procedure was repeated for four times. The resulting dark reaction mixture was concentrated *in vacuo* and purified by flash chromatography (hexanes→10%→15% EtOAc/hexanes) to afford 26 mg (31% yield) of the vinyl stannane intermediate as a colorless oil as a mixture of two diastereomers (4:1), along with 32 mg (52%) of the recovered starting material. Major diastereomer: R_f = 0.63 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ + 116.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.86 (t, *J* = 6.5 Hz, 1H, -NH), 5.30 (t, *J* = 7.5 Hz, 1H), 5.17 (dq, *J* = 9.5 Hz, 1.5 Hz, 1H), 4.07 (m, 1H), 3.62 (m, 3H), 3.45 (d, *J* = 9.5 Hz, 1H), 2.78-2.52 (m, 4H), 2.41 (s, 3H), 2.34 (m, 1H), 2.18-1.94 (m, 5H), 1.91 (d, *J* = 1.5 Hz, 3H), 1.79 (m, 1H), 1.64 (s, 3H), 1.62-1.54 (m, 3H), 1.48 (m, 12H), 1.29 (m, 8H), 1.10 (m, 2H), 0.98-0.84 (m, 36H), 0.58 (q, *J* = 8.0 Hz, 6H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8, 143.7, 142.8, 140.1, 139.4, 137.8, 135.2, 129.4, 126.9, 126.8, 113.9, 92.3, 77.9, 62.8, 53.2, 43.5, 42.2, 39.4, 35.9, 35.8, 33.3, 32.8, 29.24, 29.17, 27.6, 27.3, 25.8, 24.9, 24.1, 21.5, 21.4, 19.8, 18.2, 16.9, 15.3, 13.7, 11.1, 9.1, 6.8, 4.3, –3.9, –4.2; IR (thin film): 3280, 3185, 1701, 1684 cm^{-1}; LRMS Calcd. for $C_{58}H_{106}INO_6SSi_2Sn$ [M+H]: 1120. Found: 1120.



Vinyl iodide 48: To a solution of the vinyl stannanne **S-10** (24 mg, 0.0223 mmol) in CH_2Cl_2 (2 mL) at –78 ºC was added a solution of iodine (10 mg) in CH_2Cl_2 (1 mL) until the reaction went to *ca*. 90% completion as monitored by TLC (*ca*. 0.5 mL of the iodine solution was added). The reaction mixture was quenched by cyclohexene (100 µl), warmed to room temperature and stirred for 30 min. The mixture was concentrated *in vacuo* and purified by flash chromatography (5%→10%→15% EtOAc/hexanes) to afford 13 mg (63%) of the desired product as a colorless oil as a mixture of two diastereomers (4:1), along with 2 mg (8%) of the recovered starting material. Major diastereomer: R_f = 0.47 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ + 120.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500

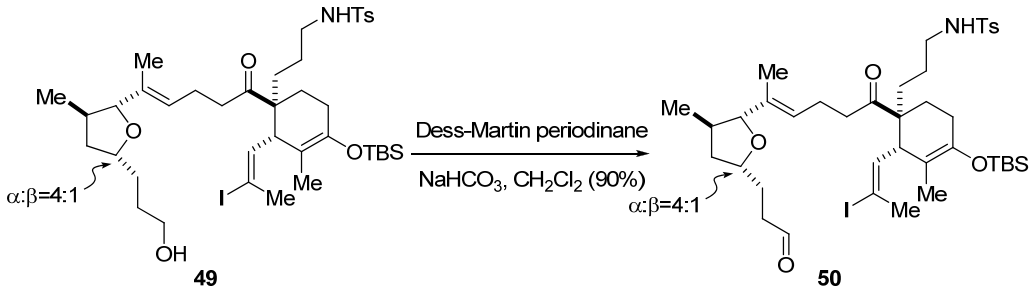
MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.87 (dq, *J* = 11.0 Hz, 1.5 Hz, 1H), 5.79 (t, *J* = 6.0 Hz, 1H, -NH), 5.33 (t, *J* = 7.0 Hz, 1H), 4.04 (m, 1H), 3.64 (d, *J* = 8.0 Hz, 1H), 3.59 (m, 2H), 3.21 (d, *J* = 11.0 Hz, 1H), 2.75 (m, 2H), 2.56 (m, 1H), 2.51 (m, 1H), 2.47 (d, *J* = 1.5 Hz, 3H), 2.43 (s, 3H), 2.37 (m, 1H), 2.14 (m, 1H), 2.01 (m, 4H), 1.78 (m, 1H), 1.68 (m, 1H), 1.65 (s, 3H), 1.58 (m, 2H), 1.52 (s, 3H), 1.48 (m, 3H), 1.33 (m, 2H), 1.12 (m, 1H), 1.01 (m, 1H), 0.95 (m, 12H), 0.90 (s, 9H), 0.59 (q, *J* = 8.0 Hz, 6H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 144.3, 142.9, 140.3, 137.7, 135.3, 129.6, 126.9, 126.6, 112.3, 95.0, 92.2, 77.9, 62.8, 53.1, 45.5, 43.3, 39.4, 35.91, 35.86, 33.4, 32.7, 29.3, 28.1, 27.5, 25.8, 25.3, 24.1, 21.5, 21.4, 18.1, 16.9, 15.2, 11.2, 6.8, 4.4, –3.8, –4.2; IR (thin film): 3280, 3181, 1703, 1684 cm^{-1}; LRMS (ESI) Calcd. for $C_{46}H_{79}INO_6SSi_2$ [M+H]: 956. Found: 956.



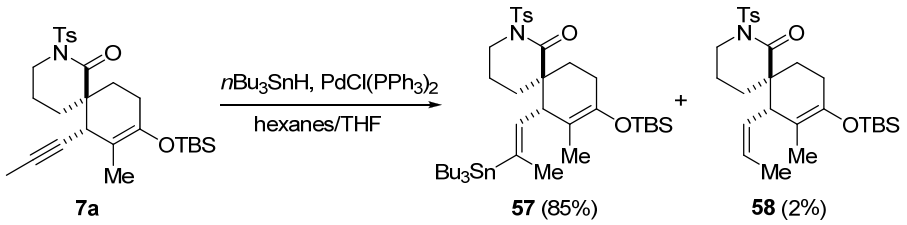
48 **49**

Alcohol 49: To a solution of the silyl ether **48** (16 mg, 0.0167 mmol) in CH_2Cl_2/MeOH (1:1, 2 mL) at 0 ºC was added pyridinium *p*-toluenesulfonate (4 mg, 0.0167 mmol). After stirring at 0 ºC for 20 min, the reaction mixture was quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (5%→10%→15% EtOAc/hexanes) to afford 12 mg (85%) of the desired alcohol as a colorless oil as a mixture of two diastereomers (4:1). Major diastereomer: R_f = 0.13 (30% EtOAc/hexanes); $[\alpha]^{20}_D$ + 118.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.01 ((t, *J* = 6.0 Hz, 1H, -NH), 5.86 (dq, *J* = 11.0 Hz, 1.5 Hz, 1H), 5.35 (t, *J* = 7.0 Hz, 1H), 4.07 (m, 1H), 3.65 (d, *J* = 8.0 Hz, 1H), 3.62 (m, 2H), 3.21 (d, *J* = 11.0 Hz, 1H), 2.75 (m, 2H), 2.61-2.53 (m, 2H including -OH), 2.48 (m, 1H), 2.45 (d, *J* = 1.5 Hz, 3H), 2.43 (s, 3H), 2.38 (m, 1H), 2.14 (m, 1H), 2.06-1.92 (m, 5H), 1.78 (m, 1H), 1.68 (m, 5H), 1.64 (s, 3H), 1.51 (s, 3H), 1.30 (m, 2H), 1.10 (m, 1H), 1.01 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 144.3, 143.0, 140.3, 137.5, 135.1, 129.6, 127.0, 126.7, 112.3, 94.9, 92.4, 78.0, 62.7, 53.0, 45.4, 43.4, 39.7, 36.03, 35.98, 33.7, 33.2, 29.6, 28.1, 27.5, 25.8, 25.5, 24.0, 21.5, 21.3, 18.1, 17.1, 15.2, 11.3, –3.8, –

4.1; IR (thin film): 3498, 3292, 3168, 1701, 1686 cm^{-1}; LRMS (ESI) Calcd. for $C_{40}H_{65}INO_6SSi_2$ [M+H]: 842. Found: 842.



Aldehyde 50: A solution of the alcohol **49** (3.0 mg, 0.00356 mmol, azeotropically dried with toluene) in CH_2Cl_2 (1 mL) containing anhydrous $NaHCO_3$ powder (4 mg) at 0 ºC was treated with Dess–Martin periodinane (3 mg, 0.00713 mmol). The reaction mixture was stirred at room temperature for 1.5 h, diluted with Et_2O and filtered through a pad of Celite. The solution was concentrated *in vacuo* and the residue was purified by flash chromatography (20%→30% EtOAc/hexanes) to afford 2.7 mg (90%) of the desired product as a colorless oil as a mixture of two diastereomers (4:1). Major diastereomer: R_f = 0.45 (30% EtOAc/hexanes); $[\alpha]^{20}_D$ + 154.4 (*c* 0.73, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.5 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.87 (dq, *J* = 10.5 Hz, 1.5 Hz, 1H), 5.66 (t, *J* = 6.5 Hz, 1H, -NH), 5.32 (t, *J* = 7.5 Hz, 1H), 4.12 (m, 1H), 3.64 (d, *J* = 8.5 Hz, 1H), 3.21 (d, *J* = 10.5 Hz, 1H), 2.79 (m, 1H), 2.70 (m, 1H), 2.61-2.49 (m, 4H), 2.46 (d, *J* = 1.5 Hz, 3H), 2.44 (s, 3H), 2.38 (m, 1H), 2.13 (m, 1H), 2.06-1.92 (m, 4H), 1.81 (m, 3H), 1.71 (m, 1H), 1.63 (s, 3H), 1.51 (s, 3H), 1.48 (m, 1H), 1.30 (m, 2H), 1.14 (m, 1H), 1.00 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 202.3, 144.4, 143.1, 140.3, 137.4, 135.0, 129.7, 127.06, 126.96, 112.2, 95.0, 92.6, 77.2, 53.0, 45.5, 43.4, 40.5, 39.5, 35.9, 35.8, 33.5, 28.7, 28.1, 27.5, 25.8, 25.3, 24.1, 21.51, 21.45, 18.1, 16.7, 15.2, 11.2, –3.8, –4.1; IR (thin film): 3274, 3192, 1723, 1703, 1689 cm^{-1}; LRMS (ESI) Calcd. for $C_{40}H_{63}INO_6SSi_2$ [M+H]: 840. Found: 840.

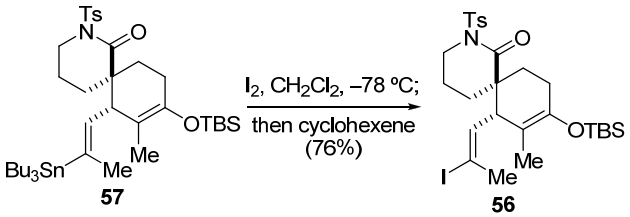


Vinyl stannane 57 and alkene 58. To a solution of alkyne **7a** (231 mg, 0.461 mmol) in a mixed solvent of THF/hexanes (1:7, total 10.4 mL, hexanes were dried over powdered 4Å

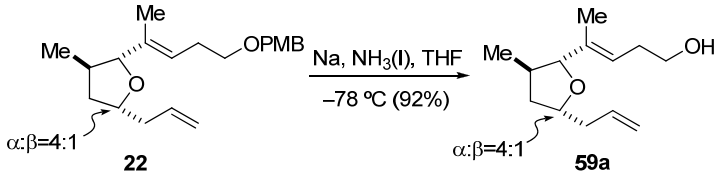
molecular sieves) containing $PdCl_2(PPh_3)_2$ (16 mg, 0.0231 mmol) at room temperature was added a solution of tributyltin hydride (124 μl, 0.461 mmol) in hexanes (1 mL) over 12 h via a syringe pump. After finishing the addition, another 16 mg of $PdCl_2(PPh_3)_2$ was added followed by syringe pump addition of a solution of tributyltin hydride (124 μl) in hexanes (1 mL) over 12 h. The dark reaction mixture was concentrated *in vacuo* and purified by flash chromatography (hexanes→5%→10% EtOAc/hexanes) to afford 310 mg (85%) of the desired product **57** as a colorless oil, 5 mg (2%) of hydrogenated product **58** as a white solid, and 14 mg (6%) of the recovered starting material.

Vinyl stannane 57: R_f = 0.72 (20% EtOAc/hexanes); $[\alpha]_D^{21}$ +128.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.16 (dq, *J* = 10.5 Hz, 1.5 Hz, 1H), 3.92 (ddd, *J* = 6.0 Hz, 6.0 Hz, 12.0 Hz, 1H), 3.82 (ddd, *J* = 6.0 Hz, 6.0 Hz, 12.0 Hz, 1H), 3.64 (d, *J* = 10.5 Hz, 1H), 2.43 (s, 3H), 2.24 (m, 2H), 1.96-1.84 (m, 4H), 1.68-1.60 (m, 2H), 1.57 (d, *J* = 1.5 Hz, 3H), 1.45 (m, 6H), 1.40 (s, 3H), 1.30 (m, 6H), 0.93 (s, 9H), 0.89 (t, *J* = 7.0 Hz, 9H), 0.83 (t, *J* = 8.0 Hz, 6H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 144.1, 142.3, 141.0, 139.1, 136.5, 129.1, 128.6, 112.0, 47.2, 46.6, 43.3, 31.4, 29.2, 28.2, 27.4, 26.9, 25.8, 21.6, 20.6, 19.2, 18.1, 14.4, 13.7, 9.1, -3.9, -4.1; IR (thin film): 1688 cm^{-1}; LRMS (ESI) Calcd. for $C_{39}H_{67}LiNO_4SSiSn$ [M+Li]: 800. Found: 800.

Alkene 58: m.p.122-126 ºC; R_f = 0.57 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 2H), 5.42 (dq, *J* = 11.0 Hz, 7.0 Hz, 1H), 5.06 (ddq, *J* = 11.0 Hz, 11.0 Hz, 1.5 Hz, 1H), 3.95 (ddd, *J* = 6.0 Hz, 6.0 Hz, 12.0 Hz, 1H), 3.83 (m, 1H), 3.60 (d, *J* = 11.0 Hz, 1H), 2.44 (s, 3H), 2.04 (m, 2H), 1.96-1.88 (m, 3H), 1.86-1.80 (m, 1H), 1.70 (ddd, *J* = 5.0 Hz, 5.0 Hz, 13.0 Hz, 1H), 1.67-1.61 (m, 1H), 1.41 (s, 3H), 1.28 (dd, *J* = 7.0 Hz, 1.5 Hz, 3H), 0.94 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 144.2, 142.1, 136.6, 129.1, 128.9, 128.5, 127.0, 111.9, 47.3, 46.9, 42.8, 31.5, 26.9, 26.8, 25.8, 21.6, 20.7, 18.1, 14.1, 12.7, –3.9, –4.0; IR (thin film): 1686 cm^{-1}; LRMS (ESI) Calcd. for $C_{27}H_{41}LiNO_4SSi$ [M+Li]: 510. Found: 510.

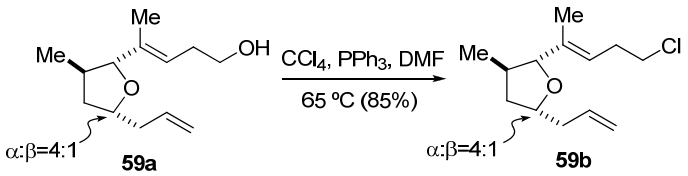


Vinyl iodide 56: To a solution of the vinyl stannane **57** (268 mg, 0.338 mmol) in CH_2Cl_2 (15 mL) at –78 ºC was added a solution of iodine (79 mg, 0.321 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at –78 ºC for 10 min and quenched by cyclohexene (1 mL). The yellowish mixture was warmed to room temperature and stirred until the solution turned to colorless (*ca*. 1 h). The solvent was evaporated and the residue was purified by flash chromatography (hexanes→5%→10% EtOAc/hexanes) to afford 161 mg (76%) of the desired product as a white solid and 21 mg (8%) of the recovered starting material. m.p.180-183 ºC; R_f = 0.52 (20% EtOAc/hexanes); $[\alpha]_D^{21}$ +126.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 5.82 (dq, *J* = 11.5, 1.5 Hz, 1H), 3.96 (m, 1H), 3.89 (m, 1H), 3.53 (d, *J* = 11.5 Hz, 1H), 2.45 (s, 3H), 2.12-2.00 (m, 2H), 1.98-1.88 (m, 3H), 1.87 (d, *J* = 1.5 Hz, 3H), 1.83-1.77 (m, 1H), 1.75-1.70 (m, 1H), 1.69-1.64 (m, 1H), 1.41 (app d, *J* = 1.5 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 144.4, 142.7, 140.1, 136.6, 129.4, 128.4, 110.4, 97.6, 47.4, 46.9, 46.8, 31.9, 27.5, 26.5, 26.3, 25.8, 21.6, 20.8, 18.1, 14.1, –3.87, –3.91; IR (thin film): 1675 cm^{-1}; LRMS (ESI) Calcd. for $C_{27}H_{40}LiINO_4SSi$ [M+Li]: 636. Found: 636.

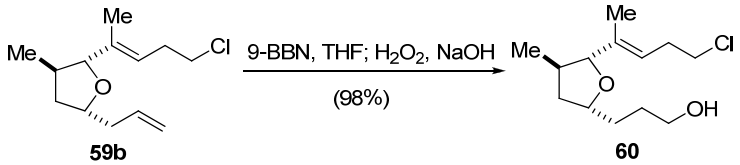


Alcohol 59a: In a three-necked flask immersed in acetone/dry ice bath (–78 ºC) equipped with a cold finger was condensed about 40 mL of liquid ammonia. Sodium (1.04 g, 45.0 mmol, cut in small pieces) was added and the resulting blue mixture was stirred at -78 ºC for 10 min. Then a solution of the PMB ether **22** (1.86 g, 5.63 mmol) in THF (30 mL) was added. The reaction mixture was stirred at –78 ºC for 30 min and quenched by slow addition of MeOH (15 mL). The solution was warmed to room temperature, stirred in open air for 1 h and saturated NH_4Cl solution (20 mL) was added. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and concentrated *in vacuo*. The residue was purified by flash chromatography (40% EtOAc/hexanes) to afford 1.09 g (92%) of the desired product as a colorless oil as a mixture of two diastereomers (4:1). Major diastereomer: R_f = 0.27 (30% EtOAc/hexanes); $[\alpha]_D^{21}$ –26.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.41 (t, *J* = 7.5 Hz, 1H), 5.05 (m, 2H), 4.02 (m, 1H), 3.66 (d, *J* = 8.0 Hz, 1H), 3.61 (t, *J* = 7.0 Hz, 2H), 2.33 (m, 2H), 2.28 (m, 1H), 2.24 (m, 1H), 1.99 (m, 1H), 1.81 (ddd, *J* = 5.5 Hz, 8.5 Hz, 12.5 Hz, 1H), 1.62 (s, 3H), 1.60 (m, 1H), 0.93 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 134.9, 123.7, 116.8, 92.3, 77.2, 62.1, 40.7,

39.0, 35.9, 31.3, 16.9, 11.4; IR (thin film): 3395 cm^{-1}; HRMS (ESI) Calcd. for $C_{13}H_{22}LiO_2$ [M+Li]: 217.1780. Found: 217.1777.

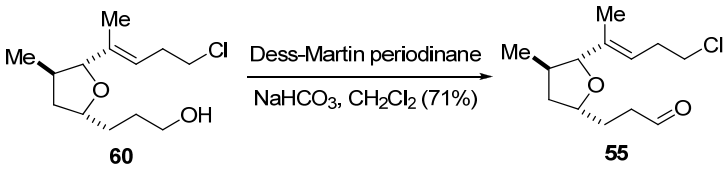


Chloride 59b: To a solution of the alcohol **59a** (500 mg, 2.38 mmol) in DMF (20 mL) were added carbon tetrachloride (1.38 mL, 14.3 mmol) and triphenylphosphine (1.87 g, 7.13 mmol). The reaction mixture was stirred at 65 ºC for 1 h, cooled to room temperature, and quenched by water. The mixture was extracted with Et_2O and the combined organic layers were washed with water, brine, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes→5% EtOAc/hexanes) to afford 461 mg (85%) of the desired product as a colorless oil as a mixture of two diastereomers (4:1). Major diastereomer: R_f = 0.34 (5% EtOAc/hexanes); $[\alpha]_D^{21}$ –24.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.43 (t, *J* = 7.5 Hz, 1H), 5.06 (m, 2H), 4.04 (m, 1H), 3.69 (d, *J* = 8.5 Hz, 1H), 3.50 (m, 2H), 2.53 (m, 2H), 2.36 (m, 1H), 2.25 (m, 1H), 1.99 (m, 1H), 1.83 (ddd, *J* = 5.5 Hz, 8.5 Hz, 12.5 Hz, 1H), 1.64 (m, 1H), 1.63 (s, 3H), 0.96 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 134.9, 123.1, 116.8, 92.0, 77.1, 44.0, 40.7, 38.9, 36.1, 31.2, 16.9, 11.5; IR (thin film): 1641 cm^{-1}; HRMS (ESI) Calcd. for $C_{13}H_{22}ClO$ [M+H]: 229.1359. Found: 229.1365.



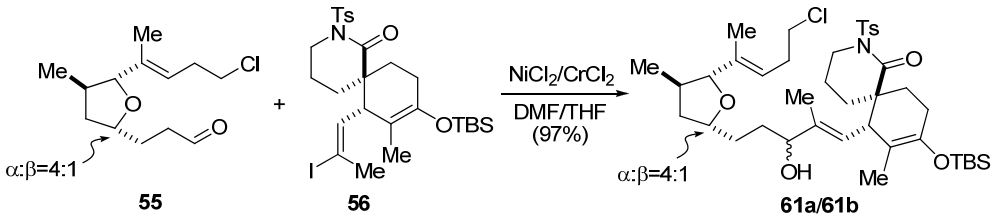
Alcohol 60: To a solution of the alkene **59b** (745 mg, 3.26 mmol) in THF (35 mL) at 0 ºC was added 9-BBN (0.5 M in THF, 9.1 mL, 4.56 mmol). The reaction mixture was stirred at room temperature for 12 h, cooled to 0 ºC and quenched by 2 N NaOH solution (10 mL) and H_2O_2 solution (35 wt% in H_2O, 10 mL). The mixture was stirred at 0 ºC for 30 min. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (20% → 40 % EtOAc/hexanes) to afford 791 mg (98%) of the desired alcohol as a colorless oil as a mixture of two diastereomers (4:1). Major diastereomer: R_f = 0.19 (30% EtOAc/hexanes); $[\alpha]_D^{21}$ –16.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (t, *J* = 7.0 Hz, 1H), 4.00 (m, 1H), 3.71 (d, *J* = 8.0 Hz,

1H), 3.66 (m, 2H), 3.52 (m, 2H), 2.52 (m, 2H), 2.44 (brs, 1H, -OH), 2.02 (m, 1H), 1.78 (ddd, *J* = 5.5 Hz, 8.5 Hz, 12.5 Hz, 1H), 1.68 (m, 5H), 1.63 (s, 3H), 0.97 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 123.2, 92.1, 77.9, 62.9, 44.0, 39.9, 36.2, 33.4, 31.1, 29.8, 17.1, 11.6; IR (thin film): 3378 cm^{-1}; LRMS (APCI) Calcd. for $C_{13}H_{24}ClO_2$ [M+H]: 247. Found: 247.



60 **55**

Aldehyde 55: To a solution of alcohol **60** (161 mg, 0.652 mmol) in CH_2Cl_2 (10 mL) containing anhydrous $NaHCO_3$ powder (329 mg, 3.91 mmol) at 0 ºC was added Dess–Martin periodinane (553 mg, 1.30 mmol). The reaction mixture was stirred at room temperature for 80 min, diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (10%→20%→30% EtOAc/hexanes) to afford 113 mg (71%) of the desired aldehyde as a colorless oil as a mixture of two diastereomers (4:1). Major diastereomer: R_f = 0.52 (30% EtOAc/hexanes); $[\alpha]^{20}_D$ –16.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.5 Hz, 1H), 5.43 (t, *J* = 7.0 Hz, 1H), 4.00 (m, 1H), 3.69 (d, *J* = 8.0 Hz, 1H), 3.53 (m, 2H), 2.54 (m, 4H), 2.01 (m, 1H), 1.90-1.75 (m, 3H), 1.69 (ddd, *J* = 8.0 Hz, 8.0 Hz, 12.0 Hz, 1H), 1.62 (s, 3H), 0.97 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 137.0, 123.3, 92.1, 76.7, 44.0, 40.6, 40.0, 36.1, 31.1, 28.6, 16.8, 11.5; IR (thin film): 1724 cm^{-1}; LRMS (ESI) Calcd. for $C_{13}H_{21}ClLiO_2$ [M+Li]: 251. Found: 251.



55 **56** **61a/61b**

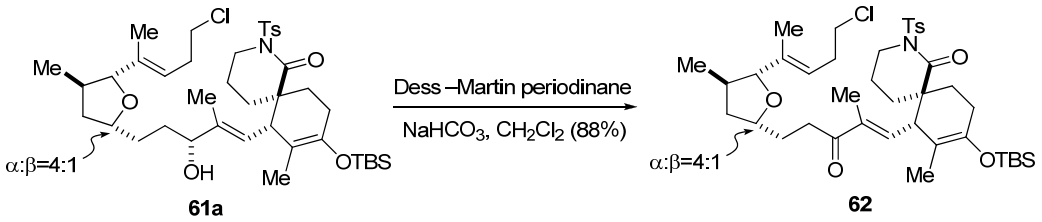
Alcohols 61a and 61b: Anhydrous DMF used in this experiment was degassed through freeze-thaw processes (three times) and further dried over activated powdered 4Å molecular sieves. THF was degassed through freeze-thaw processes (three times).

In a glove box, anhydrous $CrCl_2$ (5 g, 40.7 mmol) and anhydrous $NiCl_2$ (26 mg, 0.201 mmol) were thoroughly mixed. A flask was charged with 995 mg (8.10 mmol) of this mixture. The flask was taken out of the glove box and DMF (4 mL) was added. The resulting green mixture was stirred at room temperature for 30 min. In a separate flask the aldehyde **55** (198 mg, 0.810 mmol) and the

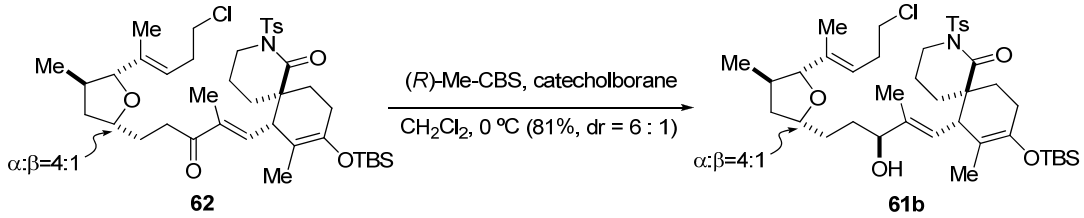
vinyl iodide **56** (1.02 g, 1.62 mmol) were azeotropically dried with toluene (2 mL × 2) and dissolved in THF (4 mL). The substrate solution was added to the $NiCl_2/CrCl_2$ solution plus 8 mL of THF/DMF (1:1) rinse. The reaction mixture was stirred at room temperature for 18 h and quenched by water (10 mL). The solution was extracted with Et_2O (20 mL × 3), the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (20%→30%→40% EtOAc/hexanes) to afford 327 mg (54%) of the desired diastereomer **61b** as a white foam as a mixture of two diastereomers (4:1), and 260 mg (43%) of the epimeric diastereomer **61a** as a white foam as a mixture of two diastereomers (4:1).

Diastereomer 61b: R_f = 0.42 (40% EtOAc/hexanes); $[\alpha]_D^{21}$ +83.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.43 (t, *J* = 7.0 Hz, 1H), 5.14 (d, *J* = 11.5 Hz, 1H), 3.97-3.85 (m, 3H), 3.81 (m, 1H), 3.69 (d, *J* = 8.0 Hz, 1H), 3.53 (m, 3H), 2.52 (m, 3H), 2.42 (s, 3H), 2.00 (m, 4H), 1.94-1.84 (m, 3H), 1.80-1.66 (m, 2H), 1.62 (s, 3H), 1.60-1.46 (m, 6H), 1.38 (s, 3H), 1.33 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 144.1, 142.1, 140.1, 137.1, 136.5, 129.1, 128.6, 123.8, 123.2, 111.9, 92.0, 77.8, 76.7, 47.2, 47.0, 44.0, 43.6, 39.8, 36.2, 32.1, 31.8, 31.4, 31.1, 27.0, 26.7, 25.8, 21.6, 20.7, 18.1, 17.1, 14.3, 12.5, 11.5, –3.9, –4.0; IR (thin film): 3538, 3426, 1682 cm^{-1}; LRMS (ESI) Calcd. for $C_{40}H_{63}ClNO_6SSi$ [M+H]: 748. Found: 748.

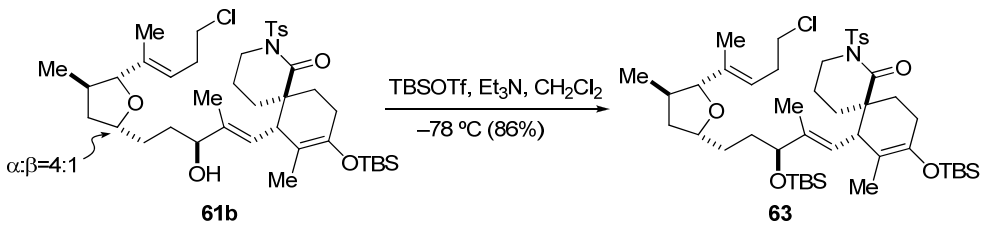
Diastereomer 61a: R_f = 0.27 (40% EtOAc/hexanes); $[\alpha]_D^{21}$ + 93.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 5.43 (t, *J* = 6.5 Hz, 1H), 5.17 (d, *J* = 11.0 Hz, 1H), 4.01-3.88 (m, 3H), 3.81 (m, 1H), 3.70 (d, *J* = 8.0 Hz, 1H), 3.53 (m, 3H), 2.53 (dt, *J* = 6.5 Hz, 6.5 Hz, 2H), 2.43 (s, 3H), 2.40 (br s, OH, 1H), 1.62 (s, 3H),1.46 (s, 3H), 1.39 (s, 3H), 2.06-1.64 (m, 11H), 1.59-1.48 (m, 4H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 144.4, 142.1, 140.5, 137.2, 136.5, 129.2, 128.6, 124.4, 123.1, 111.9, 92.1, 78.2, 78.0, 47.4, 47.2, 40.03, 40.01, 39.8, 36.3, 33.0, 32.0, 31.1, 31.0, 26.83, 26.76, 25.8, 21.6, 20.7, 18.1, 17.1, 14.4, 11.7, 11.5, –3.88, –3.94; IR (thin film): 3537, 3424, 1682 cm^{-1}.



Ketone 62: To a solution of the alcohol **61a** (178 mg, 0.238 mmol) in CH_2Cl_2 (10 mL) containing anhydrous $NaHCO_3$ powder (200 mg, 2.38 mmol) at 0 ºC was added Dess–Martin periodinane (202 mg, 0.476 mmol). The reaction mixture was stirred at room temperature for 80 min, diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (20%→30% EtOAc/hexanes) to afford 156 mg (88%) of the desired ketone as a colorless oil. R_f = 0.59 (30% EtOAc/hexanes); $[\alpha]^{20}_D$ + 103.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.28 (d, *J* = 11.5 Hz, 1H), 5.44 (t, *J* = 7.0 Hz, 1H), 3.97 (m, 2H), 3.77 (m, 1H), 3.69 (d, *J* = 8.5 Hz, 1H), 3.65 (d, *J* = 11.5 Hz, 1H), 3.52 (m, 2H), 2.76 (ddd, *J* = 5.5 Hz, 9.5 Hz, 16.5 Hz, 1H), 2.63 (m, 1H), 2.54 (m, 2H), 2.44 (s, 3H), 2.06 (m, 2H), 2.02-1.92 (m, 3H), 1.87-1.68 (m, 8H), 1.62 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.93 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 174.6, 144.6, 143.2, 139.9, 138.7, 137.1, 136.1, 129.2, 128.4, 123.5, 110.2, 92.2, 77.2, 47.1, 46.8, 45.0, 44.0, 40.0, 36.1, 34.3, 31.3, 31.2, 31.1, 27.5, 26.8, 25.8, 21.6, 20.6, 18.1, 16.8, 14.2, 11.6, 11.4, –3.8, –3.9; IR (thin film): 1672 cm^{-1}; LRMS (ESI) Calcd. for $C_{40}H_{61}ClLiNO_6SSi$ [M+H]: 746. Found: 746.

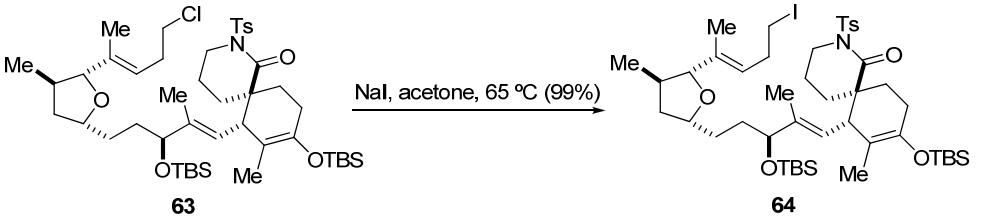


Alcohol 61b from the reduction of ketone 62: Ketone **62** (250 mg, 0.335 mmol) was azeotropically dried with toluene (2 mL), dissolved in CH_2Cl_2 (20 mL) and cooled to 0 ºC. A solution of (*R*)-Me-CBS oxazaborolidine (1.0 M in PhMe, 335 µl, 0.335 mmol) was added followed by catecholborane (107 µl, 1.00 mmol). The mixture was stirred at 0 ºC for 3 h and then quenched by water (2 mL). 2N NaOH solution (8 mL) was added and the black mixture was vigorously stirred at room temperature for 20 min. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, and concentrated *in vacuo*. The residue was purified by flash chromatography (10%→20%→30%→40% EtOAc/hexanes) to afford 173 mg (69%) of the desired product **61b** and 29 mg (12%) of the epimer **61a**.



61b **63**

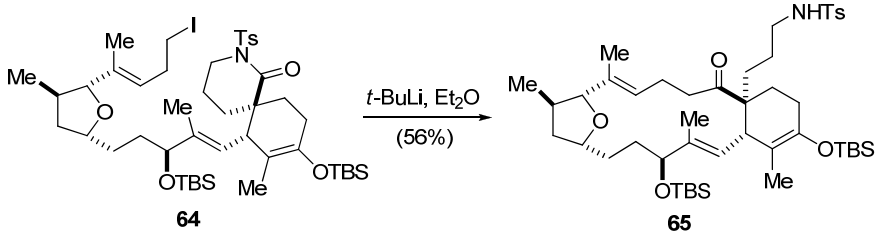
TBS ether 63: To a solution of the alcohol **61b** (237 mg, 0.317 mmol) in CH_2Cl_2 (20 mL) at –78 ºC were added Et_3N (220 µl, 1.58 mmol) and TBSOTf (179 µl, 0.792 mmol). The reaction mixture was stirred at –78 ºC for 10 min and was quenched by pH 7 buffer. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (5%→10%→15% EtOAc/hexanes) to afford 236 mg (86%) of the desired TBS ether as a white foam. R_f = 0.15 (10% EtOAc/hexanes); $[\alpha]^{20}_D$ = +74.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 5.43 (t, *J* = 7.0 Hz, 1H), 5.00 (d, *J* = 11.5 Hz, 1H), 3.93 (m, 3H), 3.76 (m, 1H), 3.67 (d, *J* = 8.5 Hz, 1H), 3.51 (m, 3H), 2.53 (m, 2H), 2.42 (s, 3H), 2.02 (m, 3H), 1.86 (m, 3H), 1.74 (m, 3H), 1.66 (m, 4H), 1.62 (s, 3H), 1.52 (m, 2H), 1.40 (s, 3H), 1.35 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 9H), 0.86 (s, 9H), 0.081 (s, 3H), 0.076 (s, 3H), 0.009 (s, 3H), –0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 144.1, 142.0, 140.2, 137.4, 136.4, 129.1, 128.7, 123.9, 122.9, 112.3, 91.8, 77.91, 77.90, 47.1, 47.0, 44.0, 43.3, 39.6, 36.2, 32.8, 32.3, 31.5, 31.2, 27.5, 26.8, 25.82, 25.76, 21.6, 20.4, 18.11, 18.07, 17.0, 14.7, 11.8, 11.5, –3.9, –4.0, –4.7, –4.9; IR (thin film): 1684 cm^{-1}; LRMS (ESI) Calcd. for $C_{46}H_{77}ClNO_6SSi_2$ [M+H]: 862 Found: 862.



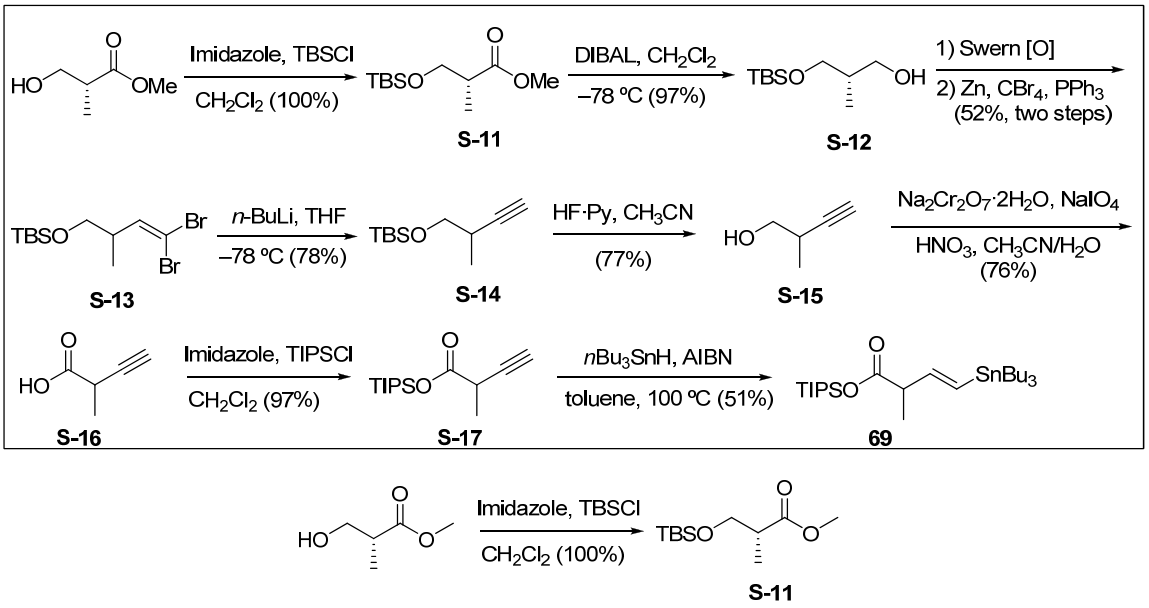
63 **64**

Iodide 64. A solution of TBS ether **63** (236 mg, 0.274 mmol) in acetone (20 mL) containing NaI (410 mg, 2.74 mmol) was heated at 65 ºC for 4 d. The reaction mixture was directly concentrated *in vacuo* and purified by flash chromatography (5%→10% EtOAc/hexanes) to afford 262 mg (99%) of the desired product as a slightly yellow oil. R_f = 0.15 (10% EtOAc/hexanes); $[\alpha]^{20}_D$ = + 67.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 5.37 (t, *J* = 6.5 Hz, 1H), 5.01 (d, *J* = 11.5 Hz, 1H), 3.92 (m, 3H), 3.75 (m, 1H), 3.67 (d, *J* = 8.5 Hz, 1H), 3.49 (d, *J* = 11.5 Hz, 1H), 3.15 (m, 2H), 2.65 (m, 2H), 2.43 (s, 3H), 2.01 (m, 3H),

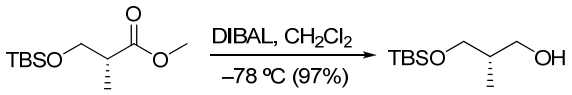
1.86 (m, 3H), 1.74 (m, 3H), 1.64 (m, 4H), 1.60 (s, 3H), 1.52 (m, 2H), 1.40 (s, 3H), 1.35 (s, 3H), 0.98 (d, J = 6.5 Hz, 3H), 0.93 (s, 9H), 0.86 (s, 9H), 0.082 (s, 3H), 0.077 (s, 3H), 0.01 (s, 3H), –0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 144.1, 142.0, 140.2, 136.9, 136.4, 129.1, 128.7, 125.8, 123.9, 112.3, 91.8, 77.96, 77.92, 47.1, 47.0, 43.3, 39.6, 36.2, 32.8, 32.3, 31.9, 31.2, 27.5, 26.8, 25.83, 25.77, 21.6, 20.4, 18.12, 18.08, 17.0, 14.7, 11.8, 11.5, 5.4, –3.9, –4.0, –4.6, –4.9; IR (thin film): 1686 cm^{-1}; LRMS (ESI) Calcd. for $C_{46}H_{77}INO_6SSi_2$ [M+H]: 954. Found: 954.



***N*-Tosyl amine 65**: Alkyl iodide **64** (96 mg, 0.101 mmol) was azeotropically dried with PhMe (1 mL) and dissolved in Et_2O (15 mL). *t*-BuLi (1.6 M in pentane, 140 µl) was then added dropwise at room temperature. The resulting slightly yellow solution was stirred at room temperature for 15 min and quenched by pH 7 buffer (5 mL). The aqueous layer was extracted with Et_2O and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography (5%→10%→15%→20% EtOAc/hexanes) to afford 47 mg (56%) of the desired product as a white foam. R_f = 0.30 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ + 20.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 5.01 (br t, J = 5.0 Hz, 1H), 4.94 (dd, J = 11.5 Hz, 1.5 Hz, 1H), 4.86 (t, J = 5.5 Hz, 1H, NH), 4.09 (m, 1H), 3.99 (br s, 1H), 3.84 (dd, J = 3.5 Hz, 11.5 Hz, 1H), 3.68 (d, J = 11.5 Hz, 1H), 2.94 (m, 2H), 2.74 (ddd, J = 3.0 Hz, 12.5 Hz, 19.0 Hz, 1H), 2.61 (ddd, J = 3.0 Hz, 3.0 Hz, 19.0 Hz, 1H), 2.44 (s, 3H), 2.21 (m, 2H), 2.10-1.96 (m, 5H), 1.82 (m, 1H), 1.73 (m, 2H), 1.69 (d, J = 1.5 Hz, 3H), 1.66-1.56 (m, 2H), 1.53 (s, 3H), 1.50 (m, 3H), 1.46 (s, 3H), 1.41 (m, 2H), 1.11 (d, J = 7.0 Hz, 3H), 0.96 (s, 9H), 0.86 (s, 9H), 0.142 (s, 3H), 0.135 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 143.1, 143.0, 140.5, 136.8, 135.5, 129.5, 127.2, 123.8, 122.6, 111.9, 89.1, 79.4, 78.1, 53.3, 45.4, 43.7, 37.6, 36.9, 34.6, 32.9, 32.1, 28.8, 27.3, 25.8, 25.6, 24.6, 23.4, 21.5, 20.6, 20.0, 18.1, 18.0, 14.2, 13.8, 10.7, -3.6, -3.8, –4.76, –4.82; IR (thin film): 3281, 1701, 1683 cm^{-1}; HRMS Calcd. for $C_{46}H_{77}LiNO_6SSi_2$ [M+Li]: 834.5170. Found: 834.5163.



TBS ether S-11. To a solution of (*R*)-3-hydroxy-2-methylpopionic acid methyl ester (32.66 g, 27.65 mmol) and imidazole (19.586 g, 28.77 mmol) in CH_2Cl_2 (500 mL) at 0 °C was added TBSCl (42.912 g, 28.47 mmol) in several portions over 5 min. The ice bath was removed and the cloudy mixture was stirred vigorously at room temperature for 4 h. Filtration through sintered-glass funnel followed by removal of the solvent *in vacuo* gave 64.23 g (100%) of the crude product as a colorless oil. The crude product was clean by ^{1}H NMR and no further purification was required. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.68 (s, 3H), 3.89 (dd, *J* = 9.5, 5.8 Hz, 1H), 2.69-2.60 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H); 0.042 (s, 3H), 0.038 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 65.3, 51.4, 42.5, 25.8, 18.2, 13.4, –5.5.



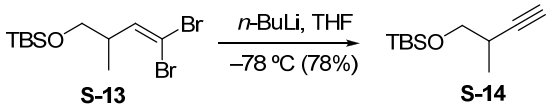
Alcohol S-12. To a solution of (*R*)-methyl-3-(tert-butyldimethylsilyloxy)-2-methylpropanoate (**S-11**) (64.23 g, 276.4 mmol) in CH_2Cl_2 (500 mL) at –78 °C was added DIBAL-H (103.0 mL, 577.8 mmol) over 1 h. The mixture was stirred for another 5 h, and water (60 mL) was added slowly, followed by CH_2Cl_2 (500 mL) and Rochell's solution (500 mL). The mixture was left stirring for 21 h at room temperature. The organic layer was separated, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (15% EtOAc/hexanes) to afford 56.1 g (99%) of the product as a colorless oil. Spectra data of **S-12** matched with that of

previously reported.[2] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.59-3.55 (m, 2H), 3.51 (dd, *J* = 9.5, 7.5 Hz, 1H), 2.98 (broad s, 1H, OH), 1.92-1.85 (m, 1H), 0.86 (s, 9H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.032 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.2, 67.6, 37.1, 25.7, 18.1, 13.0, –5.7 (two signals).

S-12 **S-13**

Dibromide S-13. To a solution of oxalyl chloride (65.48 mL, 738.3 mmol) in CH_2Cl_2 (2 L) at –78 °C was slowly added DMSO (105.1 mL, 1.475 mol). After 35 min, a solution of Et_3N (259.8 mL, 1.852 mol) and (*S*)-3-(tert-butyldimethylsilyloxy)-2-methylpropan-1-ol (**S-12**) (56.1 g, 274.5 mmol) in CH_2Cl_2 (100 mL) was added. The mixture was stirred for 4 h, diluted with water and the organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 62.3 g of crude aldehyde (ca. 90% pure). The yellow oil is unstable to silica gel chromatography and was used without further purification.

To a slurry of activated Zn dust (101.68 g, 1.55 mol) and triphenylphosphine (258.0 g, 0.985 mol) in CH_2Cl_2 (2 L) at 0 °C was added carbon tetrabromide (354.77 g, 1.07 mol) in portions. After stirring for 19 h, a solution of (*R*)-3-(tert-butyldimethylsilyloxy)-2-methylpropanal (62.3 g, crude) in CH_2Cl_2 (100 mL) was added and the reaction mixture stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was filtered in portions through a plug of silica gel and purified by flash chromatography (15% EtOAc/hexanes) to afford 51.0 g (52% for two steps) of the product as a colorless oil. Spectra data of **S-13** matched with that of previously reported.[3] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (d, *J* = 9.0 Hz, 1H), 3.54 (d, *J* = 6.6 Hz, 2H), 2.73-2.59 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 9H), 0.083 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 92.3, 88.5, 65.9, 41.0, 25.9, 18.3, 15.5, –5.4 (two singlets).

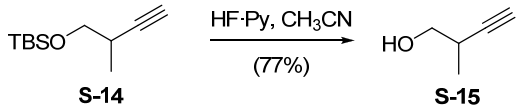


S-13 **S-14**

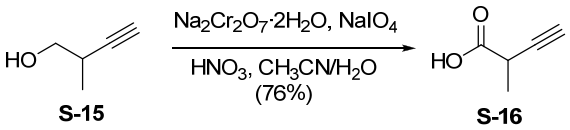
Alkyne S-14. A solution of the dibromide **S-13** (51.0 g, 142 mmol) in THF (500 mL) at –78 °C was treated with *n*-BuLi (2.50 M in hexane, 220 mL, 550 mmol). After stirring for 110 min, the reaction was quenched by the addition of water (50 mL) and allowed to warm to room temperature. Ether (1000 mL) was added and the organic layer was separated and washed with water (2 x 500

[2] Marshall, J. A.; Grote, J.; Audia, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1186–1194.
[3] Yan, J.; Zhu, J.; Matasi, J. J.; Herndon, J. W. *J. Org. Chem.* **1999**, *64*, 1291–1301.

mL), brine (2 x 500 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes) to afford 22.05 g (78%) of the product as colorless oil. Spectra data of **S-14** matched with that of previously reported.[3] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.48 (dd, *J* = 9.5, 7.5 Hz, 1H), 2.62-2.55 (m, 1H), 2.04 (d, *J* = 2.5 Hz, 1H), 1.19 (d, *J* = 7 Hz, 3H), 0.91 (s, 9H), 0.080 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 86.5, 69.0, 67.0, 28.9, 25.9, 18.3, 17.2, –5.4, –5.3;

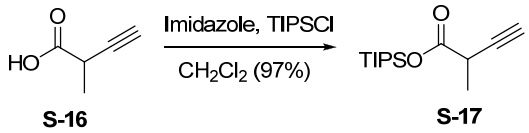


Alcohol S-15. To a solution of (S)-3-tert-butyl dimethyl(2-methylbut-3-ynyloxyl)silane (**S-14**) (22.0 g, 110.9 mmol) in acetonitrile (400 mL) was added HF·pyridine complex (70%, 20 mL,). The mixture was stirred for 14 h and quenched with saturated $NaHCO_3$ solution. Ether (800 mL) was added and the organic layer was washed with brine (2 x 500 mL), water (2 x 500 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford 7.20 g (77%) of the desired product as a yellow oil. The crude alcohol was used directly without further purification due to its instability to silica chromatography and distillation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66-3.65 (m, 2H), 2.77-2.64 (m, 1H), 2.45 (br s, 1H), 2.15 (d, *J* = 2.4 Hz, 1H), 1.22 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.9, 69.8, 66.3, 28.8, 16.7.



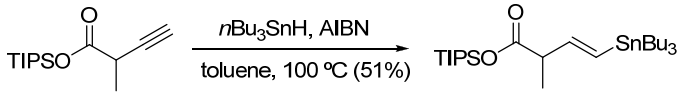
Carboxylic acid S-16. To a vigorously stirred solution consisting of aq. HNO_3 (69-71%, 355 mg), $Na_2Cr_2O_7·2H_2O$ (355 mg), and water (200 mL) at 0 °C was added $NaIO_4$ (56.96 g). Subsequently, a solution of the alcohol **S-15** (7.2 g) in acetonitrile (70 mL) was added in one portion. The ice bath was removed and the mixture was vigorously stirred for 24 h. The aqueous phase was extracted with EtOAc (2 X 200 mL). The combined organic phases was dried (Na_2SO_4) and concentrated *in vacuo* to provide 6.425 g (76%) of the desired product as a pale yellow oil which was used directly without further purification. Spectra data of **S-16** matched with that of previously reported.[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (qd, *J* = 7.5, 2.7 Hz, 1H), 2.32 (d, *J* = 2.7 Hz, 1H), 1.54 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 81.2, 71.5, 32.2, 18.1.

[4] Kim, C.-H.; An, H.-J.; Shin, W.-K.; Yu, W.; Woo, S.-K.; Jung, S.-K.; Lee. E. *Chem. Asian J.* **2008**, *3*, 1523–1534.



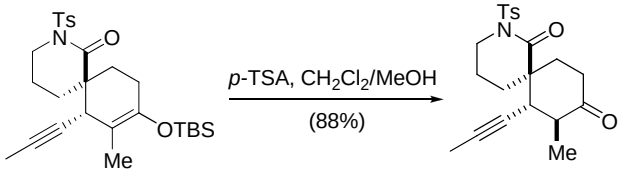
S-16 **S-17**

TIPS ester S-17. To a solution of 2-methylbut-3-ynoic acid (**S-16**) (1.00 g, 10.2 mmol) and TIPSCl (2.14 mL, 9.99 mmol) in CH_2Cl_2 (26 mL) was added imidazole (611 mg, 10.0 mmol). The mixture was stirred at room temperature for 1 h and was then diluted with H_2O and CH_2Cl_2. The layers were separated, and the organic layer was washed with water, brine (170 mL), dried (Na_2SO_4), and concentrated to afford 2.52 g (97%) of the TIPS ester as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (qd, *J* = 7.2, 2.7 Hz, 1H), 2.22 (d, *J* = 2.7 Hz, 1H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.40-1.24 (m, 3H), 1.08 (d, *J* = 7.2 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 82.0, 70.6, 33.6, 18.1, 17.6, 12.2; HRMS Calcd for $C_{14}H_{26}O_2Si$ [M+Li]: 261.1862. Found 261.1865.



S-17 **69**

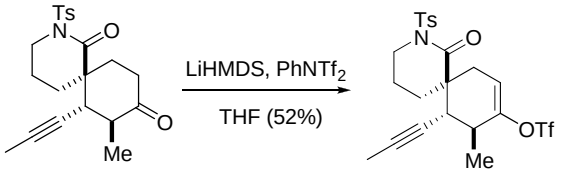
Vinyl stannane 69. A solution of triisopropylsilyl 2-methylbut-3-ynoate (**S-17**) (2.358 g, 9.267 mmol) and tributyltin hydride (2.709 g, 2.467 mL, 9.307 mmol) in toluene (124 mL) was immersed in a preheated oil bath (90 °C) for 5 min before AIBN (76.4 mg, 0.465 mmol) was added in one portion. The solution was then heated at 100 °C for 80 min. The mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was purified on floricil (50-100 mesh) (eluted with 4.8 % EtOAc/hexanes) to afford 2.591 g (51%) of the product as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14-6.09 (m, 2H), 3.26-3.16 (m, 1H), 1.72-1.25 (m, 18H), 1.10 (d, *J* = 7.2 Hz, 18H), 1.00-0.85 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.4, 146.6, 129.5, 48.9, 29.0, 27.2, 17.7, 16.6, 13.6, 11.9**;** LRMS Calcd for $C_{26}H_{54}O_2SiSn$ [M+H]: 547. Found 547.



7a **74**

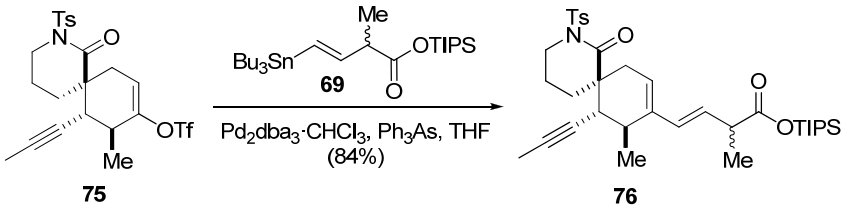
Ketone 74. To a solution of the *N*-tosyl lactam **7a** (140 mg, 0.279 mmol) in CH_2Cl_2/MeOH (1:1, 10 mL) at 0 ºC was added *p*-TSA·H_2O (200 mg). The reaction was stirred at room temperature for 12 h and quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash

chromatography (30% → 50% EtOAc/hexanes) to afford 95 mg (88%) of the desired product as a white power. R_f = 0.12 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.25 (m, 1H), 3.68 (ddt, *J* = 3.5 Hz, 12.0 Hz, 12.0 Hz, 1H), 2.97 (dq, *J* = 2.5 Hz, 13.0 Hz, 1H), 2.42 (s, 3H), 2.35 (m, 2H), 2.25 (dq, *J* = 6.5 Hz, 13.0 Hz, 1H), 2.14 (m, 2H), 2.04-1.88 (m, 4H), 1.65 (d, *J* = 2.5 Hz, 3H), 1.09 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 144.5, 135.8, 129.0, 128.4, 126.3, 80.8, 76.7, 48.8, 46.7, 45.0, 44.3, 35.9, 32.2, 24.6, 21.5, 20.5, 12.3, 3.3; IR (thin film): 1703, 1676 cm^{-1}; LRMS (ESI) calcd for $C_{21}H_{25}LiNO_4S$ [M+Li]: 394. Found: 394.



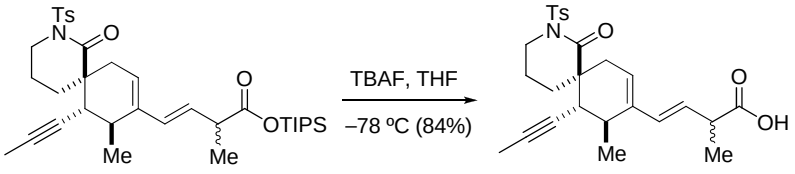
74 **75**

Vinyl triflate 75. To a solution of the ketone **74** (213.5 mg, 0.551 mmol) in THF (21.4 mL) was added LiHMDS (20% solution in THF, 2.476 mL, 2.618 mmol). After stirring at room temperature for 1 h, the green reaction mixture was treated with a solution of $PhNTf_2$ (0.854 g, 2.39 mmol) in THF (10.7 mL). After 15 min, ether (60 mL) was added, resulting in a dark red homogeneous mixture. The organic layer was washed with brine (2 x 60 mL), water (60 mL), dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (9% EtOAc/hexanes) to afford 149 mg (52%) of the product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 5.63-5.59 (m, 1H), 4.32-4.24 (m, 1H), 3.59 (td, *J* = 12, 3.5 Hz, 1H), 2.81-2.76 (m, 1H), 2.61-2.54 (m, 1H), 2.44 (s, 3H), 2.41-2.32 (m, 1H), 2.19 (ddd, *J* = 18, 6.5, 1.5 Hz, 1H), 2.11-1.95 (m, 2H), 1.88-1.78 (m, 2H), 1.63 (d, *J* = 2.0 Hz, 3H), 1.27 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 149.6, 144.6, 136.0, 129.2, 128.7, 118.4 (q, J_{C-F} = 318.1 Hz), 115.6, 80.1, 76.4, 47.6, 47.0, 43.2, 35.4, 32.5, 25.5, 21.6, 20.5, 15.2, 3.3; IR (thin film): 1681, 1599 cm^{-1}; LRMS (ESI) Calcd for $C_{22}H_{24}LiNO_6S_2F_3$ [M+Li]: 526. Found: 526.



75 **76**

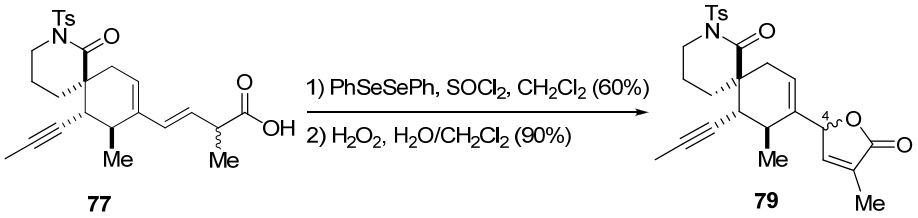
Diene 76. A stock solution of palladium was prepared as follows: To a RBF purged with nitrogen and charged with $Pd_2dba_3 \cdot CHCl_3$ (17 mg, 0.016 mmol) and triphenylarsine (21.5 mg, 0.0068 mmol) was added THF (degassed through freeze-pump-thaw process, five cycles, 2 mL). The heterogeneous mixture was placed in a water bath at 40 °C and stirred for 5-10 min until it became dark yellow. To a solution of triflate **75** (30 mg, 0.058 mmol) and stannane **69** (248 mg, 0.46 mmol) in THF (degassed, 2.25 mL) was added this Pd catalyst solution (0.93 mL). The resulting solution was stirred at room temperature for 21 h and then concentrated *in vacuo*. The residue was purified by flash chromatography (5% EtOAc/hexanes) to afford 30.3 mg (84%) of the product as a colorless oil. The product consisted of a mixture of *E*/*Z* isomers (*E* being major) and each isomer consisted of two epimers epimeric at the methyl position. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.96 (d, *J* = 16.5 Hz, 1H), 5.86 (d, *J* = 10.5 Hz, 1H, minor Z), 5.80 (d, *J* = 11 Hz, 1H, minor E epimer), 5.66-5.58 (m, 1H), 5.54-5.48 (m, 1H), 5.39-5.35 (m, 1H, minor), 4.30-4.20 (m, 1H), 3.66-3.56 (m, 1H), 3.50-3.40 (m,1H, minor Z), 3.15 (app q, *J* = 7.1 Hz, 1H), 2.72-2.66 (m, 1H), 2.44 (s, 3H), 2.24-2.15 (m, 1H), 2.11 (dd, *J* = 17.8, 5.8 Hz, 1H), 2.10-1.66 (m, 5H), 1.63 (d, *J* = 1.0 Hz, 3H, Z isomer or other epimer), 1.60 (d, *J* = 1.0 Hz, 3H, major diastereomer), 1.34-1.24 (m, 3H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.16 (d, *J* = 6.5 Hz, 3H), 1.06 (d, *J* = 7.5 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 175.4, 175.1, 174.8 (two signals), 144.6 (two signals), 139.1 (two signals), 137.1, 136.6 (two signals), 131.6, 131.5, 130.8, 130.3, 129.4, 128.9 (two signals), 128.8, 128.4 (two signals), 122.6, 122.4, 121.8, 79.1 (two signals), 78.9 (two signals), 78.6, 48.0 (two signals), 47.9 (two signals), 47.4 (two signals), 47.3, 45.1, 44.8, 43.4 (two signals), 42.8, 40.9, 35.8, 34.7, 34.3 (two signals), 34.2, 25.9, 25.4 (two signals), 21.9, 20.9 (two signals), 19.2, 19.1 (two signals), 18.0, 17.8, 17.6, 12.1 (four signals), 3.7; IR (film) 2871, 1716, 1683 cm^{-1}; HRMS (ESI) Calcd for $C_{35}H_{51}LiNO_3SiS$ [M+Li]: 632.3417. Found 632.3423.



76 **77**

Carboxylic acid 77. To a solution of **76** (15.6 mg, 0.025 mmol) in THF (2 mL) at –78 °C was added TBAF (1.0 M in THF, 25 μL, 0.025 mmol). The reaction was stirred –78 °C for 10 min and was quenched with pH 7 buffer (5 mL). The reaction was extracted with ethyl acetate (15 mL) and the combined organics were concentrated *in vacuo*. The residue was purified by flash

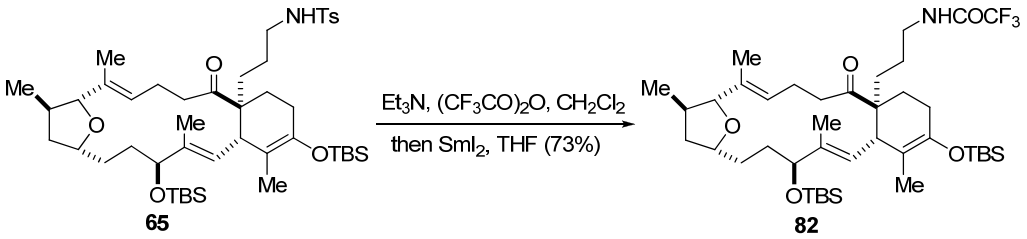
chromatography (EtOAc→5% MeOH/EtOAc) to afford 9.8 mg (84%) of the product as a white foam. The product consisted of a mixture of *E*/*Z* isomers (*E* being major) and each isomer consisted of two epimers epimeric at the methyl position. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.96 (dd, *J* = 16.0, 3.5 Hz, 1H), 5.89 (d, *J* = 11.5 Hz, 1H, minor Z), 5.84 (d, *J* = 10.5 Hz, 1H, minor epimer), 5.60 (dd, *J* = 16.0, 8 Hz, 1H), 5.53 (d, *J* = 5.5 Hz, 1H), 5.49 (dd, *J* = 11, 10.5 Hz, 1H, minor Z), 5.43 (d, *J* = 12.5 Hz, 1H, minor epimer), 5.38-5.34 (m, 1H, minor Z), 4.29-4.20 (m, 1H), 3.64-3.56 (m, 1H), 3.55-3.46 (m,1H, minor Z), 3.22-3.13 (m, 1H), 2.71-2.65 (m, 1H), 2.46 2.44 (s, 3H, minor), 2.43 (s, 3H), 2.25-2.15 (m, 1H), 2.11 (dd, *J* = 18.0, 6.5 Hz, 1H), 2.06-1.67 (m, 5H (another 3 overlapping protons attributable to other isomers, total 8), 1.62 (d, *J* = 2.5 Hz, 3H, major diastereomer, another 1.36 overlapping protons attributable to other isomers, total 4.36), 1.31 (d, *J* = 7.0 Hz, 3H), 1.29 (d, *J* = 7.0 Hz, 3H, other major diastereomer), 1.26 (d, *J* = 7.0 Hz, 3H, minor Z), 1.16 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 1H, minor epimer), 1.07 (d, *J* = 7.0 Hz, 3H, minor Z), 1.00 (d, *J* = 7.0 Hz, 1H, minor epimer); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6 (two signals), 175.4, 175.3, 144.6 (two signals), 138.8, 137.1, 136.6, 136.5, 132.1, 132.0, 131.4, 129.5, 129.4, 128.9, 127.2 (two signals), 123.2, 123.0, 122.0, 79.0 (three signals), 78.8, 78.7, 48.0, 47.9 (two signals), 47.4, 47.3, 43.4 (two signals), 43.0, 42.8, 38.8, 35.7, 34.7, 34.3 (two signals), 34.2, 26.0, 25.5 (two signals), 21.9, 20.9, 20.8, 19.1, 19.0, 18.6, 17.8, 17.5, 17.4, 3.7; IR (film) 2871, 1716, 1683 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{31}LiNO_5S$ [M+Li]: 476.2083. Found 476.2085.



Phenylselenide 78. A stock solution of PhSeCl was prepared as follows: A solution of diphenyl diselenide (113 mg, 0.36 mmol) in CH_2Cl_2 (5 mL) at 0 °C was treated with sulfuryl chloride (28.9 μL, 0.36 mmol) and the red homogeneous solution was stirred for 15 min. To a solution of acid **77** (2 mg, 0.0043 mmol) in CH_2Cl_2 (1 mL) at –78 °C was added the PhSeCl solution (29.6 μL, 0.0041 mmol). The mixture was warmed to –40 °C over 40 minutes and was then concentrated *in vacuo*. The residue was purified by flash chromatography (50% EtOAc/hexanes) to

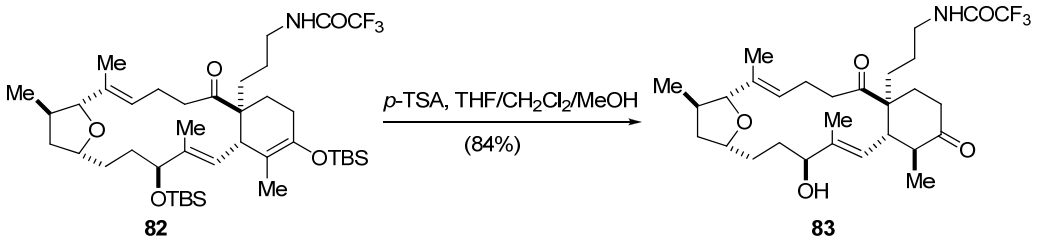
afford 1.7 mg (60%) of the product as a colorless oil. HRMS (ESI) Calcd for $C_{32}H_{35}LiNO_5SSe$ [M+Li]: 632.1561 Found 632.1566.

To a solution of the selenolactone **78** (1 mg, 1.6 μmol) in CH_2Cl_2 (1 mL) at 0 °C was added H_2O_2 (35% in H_2O, 20 μL). After stirring for 5 min, another 20 μL of H_2O_2 solution was added. The reaction mixture was stirred for another 40 minutes and then concentrated *in vacuo*. The residue was purified by flash chromatography (50% EtOAc/hexanes) to afford 0.7 mg (90%) of the product as a colorless oil. HRMS (ESI) Calcd for $C_{26}H_{29}LiNO_5S$ [M+Li]: 474.1926. Found 474.1924.



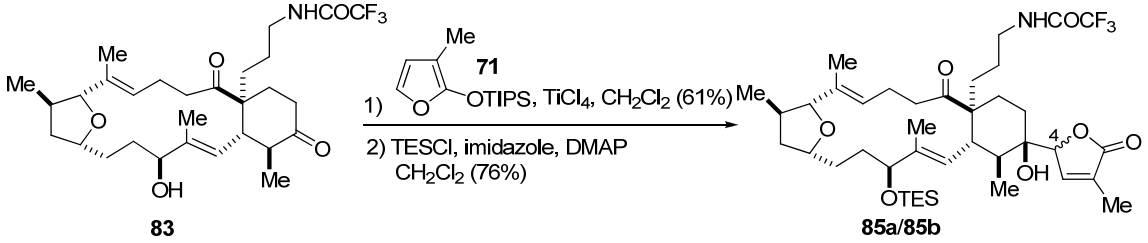
65 **82**

Trifluoroacetamide 82: To a solution of the tosylamine **65** (37 mg, 0.447 mmol) in CH_2Cl_2 (4 mL) at 0 ºC was added triethylamine (62 μl, 0.447 mmol) and trifluoroacetic anhydride (38 μl, 0.268 mmL). After stirring at 0 ºC for 15 min, SmI_2 (0.1 M in THF) was added until the intermediate disappeared as monitored by TLC (*ca*. 0.5 mL of SmI_2 solution was added). The reaction mixture was stirred for additional 10 min and quenched by half saturated $Na_2S_2O_3$ solution (2 mL). The aqueous layer was extracted with Et_2O and the organic layers were concentrated *in vacuo* and purified by flash chromatography (5%→10%→15% EtOAc/hexanes) to afford 25 mg (73%) of the desired product as a white foam. R_f = 0.65 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ + 1.26 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (br s, 1H), 5.00 (br t, *J* = 5.0 Hz, 1H), 4.96 (d, *J* = 11.5 Hz, 1H), 4.06 (m, 1H), 3.97 (br s, 1H), 3.81 (dd, *J* = 3.5 Hz, 11.5 Hz, 1H), 3.73 (d, *J* = 11.5 Hz, 1H), 3.35 (m, 2H), 2.81 (m, 1H), 2.65 (m, 1H), 2.28 (m, 1H), 2.18 (m, 1H), 2.09 (m, 4H), 1.98 (m, 1H), 1.86 (m, 1H), 1.77 (m, 1H), 1.69 (s, 3H), 1.64 (m, 2H), 1.56 (m, 1H), 1.49 (s, 3H), 1.47 (s, 3H), 1.43 (m, 3H), 1.38-1.28 (m, 2H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.96 (s, 9H), 0.86 (s, 9H), 0.142 (s, 3H), 0.135 (s, 3H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3, 157.6 (*C*OCF_3, q, *J* = 37 Hz), 143.2, 140.8, 135.7, 123.6, 122.4, 115.9 (CF_3, q, *J* = 286 Hz), 112.0, 89.1, 79.4, 78.1, 53.8, 45.5, 40.6, 37.6, 36.6, 34.7, 32.9, 31.9, 28.8, 27.6, 25.8, 25.7, 23.4, 23.2, 20.5, 19.9, 18.2, 18.0, 14.2, 13.9, 10.8, –3.6, –3.8, –4.77, –4.85; IR (thin film): 3319, 1722, 1709 cm^{-1}; LRMS (ESI) Calcd. for $C_{41}H_{70}F_3NNaO_5Si_2$ [M+Na]: 792. Found: 792.



82 **83**

Ketone 83: To a solution of the silyl ether **82** (17 mg, 0.0221 mmol) in THF/CH_2Cl_2/MeOH (1:1:1, 1.8 mL) at room temperature was added *p*-toluenesulfonic acid monohydrate (17 mg, 0.0883 mmL). The reaction mixture was stirred at room temperature for 2.5 h and quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography (40%→70%→100% EtOAc/hexanes) to afford 10 mg (84%) of the desired product as a white foam. R_f = 0.42 (70% EtOAc/hexanes); $[\alpha]^{20}_D$ –84.4 (*c* 0.473, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (d, *J* = 11.0 Hz, 1H), 4.97 (br t, *J* = 5.0 Hz, 1H), 4.09 (m, 1H), 3.98 (br s, 1H), 3.91 (dd, *J* = 11.5 Hz, 2.5 Hz, 1H), 3.43 (m, 2H), 3.00 (dd, *J* = 11.5 Hz, 11.5 Hz, 1H), 2.69 (m, 2H), 2.52 (m, 1H), 2.46-2.38 (m, 2H), 2.29 (m, 1H), 2.24-2.14 (m, 3H), 2.12-1.96 (m, 4H), 1.85 (m, 1H), 1.72-1.62 (m, 3H), 1.69 (s, 3H), 1.52 (s, 3H), 1.47 (m, 1H), 1.36 (m, 1H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.06 (m, 1H), 1.03 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.4, 209.6, 157.6 (*C*OCF_3, q, *J* =36 Hz), 140.7, 136.1, 124.6, 121.8, 98.2, 78.8, 78.0, 115.9 (CF_3, q, *J* = 286 Hz), 55.0, 50.5, 45.9, 40.2, 37.7, 37.5, 36.7, 34.8, 31.9, 31.3, 31.1, 23.3, 22.8, 20.5, 19.9, 14.2, 11.9, 11.2; IR (thin film): 3483, 3320, 1706, 1558 cm^{-1}; LRMS (ESI) Calcd. for $C_{29}H_{42}F_3NNaO_5$ [M+Na]: 564. Found: 564. Recrystallization from EtOAc provided colorless crystals suitable for X-ray analysis.



83 **85a/85b**

Alcohols 85a/85b: A mixture of the ketone **83** (8.4 mg, 0.0155 mmol) and silyloxyfuran **71** (39 mg, 0.155 mmol) was azeotropically dried with PhMe and dissolved in CH_2Cl_2 (0.8 mL). At room temperature to this vigorously stirred solution was added $TiCl_4$ (1.0 M in CH_2Cl_2, 39 µl) dropwise over 30 s. The cloudy yellow reaction mixture was stirred at room temperature for 30 s and quenched by saturated NH_4Cl solution. The mixture was extracted with Et_2O and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography

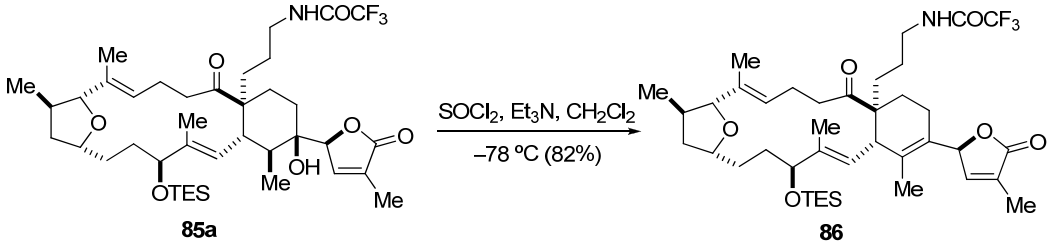
(40%→70%→100% EtOAc/hexanes) to afford 6.1 mg (61%) of the addition product **84** as a white solid as a mixture of two diastereomers (epimeric at C4 position, dr = 1.1:1). R_f = 0.16 (70% EtOAc/hexanes).

A mixture of **84** (10.0 mg, 0.0156 mmol, used as a mixture of two diastereomers), imidazole (21 mg, 0.313 mmol) and one crystal of DMAP was azeotropically dried with PhMe. The mixture was dissolved in CH_2Cl_2 (1 mL) and at room temperature was treated with TESCl (26 µl, 0.156 mmol). White precipitate formed immediately. The reaction mixture was stirred at room temperature for 5 min and quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined organic layers were concentrated and purified by flash chromatography (30%→40%→50% EtOAc/hexanes) to afford 4.1 mg (34%) of the desired product **85a** and 5.0 mg (42%) the C-4 epimer **85b**, respectively. The initial assignment of the stereochemistry of the two diastereomers **85a** and **85b** was based on the comparison of their ^{13}C NMR with that of model compounds, see Table S-1 for details.

85a: R_f = 0.65 (70% EtOAc/hexanes); $[\alpha]^{20}_D$ –48.8 (*c* 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (br s, 1H, -NH), 7.22 (dq, *J* = 1.5 Hz, 1.5 Hz, 1H), 5.00 (br s, 1H), 4.97 (dq, *J* = 1.5 Hz, 1.5 Hz, 1H), 4.89 (d, *J* = 11.0 Hz, 1H), 4.07 (m, 1H), 3.97 (br s, 1H), 3.78 (dd, *J* = 3.0 Hz, 11.5 Hz, 1H), 3.34 (m, 2H), 2.96 (dd, *J* = 11.0 Hz, 11.0 Hz, 1H), 2.76 (m, 2H), 2.21 (m, 3H), 2.02 (m, 5H), 1.97 (dd, *J* = 1.5 Hz, 1.5 Hz, 3H), 1.85 (m, 2H), 1.68 (s, 3H), 1.62 (m, 3H), 1.51 (s, 3H), 1.48 (m, 3H), 1.33 (m, 2H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.55 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9, 173.9, 157.5 (*C*OCF_3, q, *J* = 36 Hz), 147.0, 141.2, 135.8, 131.1, 123.7, 122.4, 115.9 (CF_3, q, *J* = 286 Hz), 89.1, 83.0, 79.6, 78.0, 73.8, 54.9, 43.3, 40.4, 37.5, 36.73, 36.68, 34.7, 32.9, 32.3, 26.4, 25.2, 22.9, 22.4, 20.6, 19.9, 14.2, 11.3, 10.9, 10.8, 6.9, 4.9; IR (thin film): 3468, 3326, 1754, 1721, 1711 cm^{-1}; LRMS (ESI) Calcd. for $C_{40}H_{62}F_3LiNO_7$ [M+Li]: 760. Found: 760.

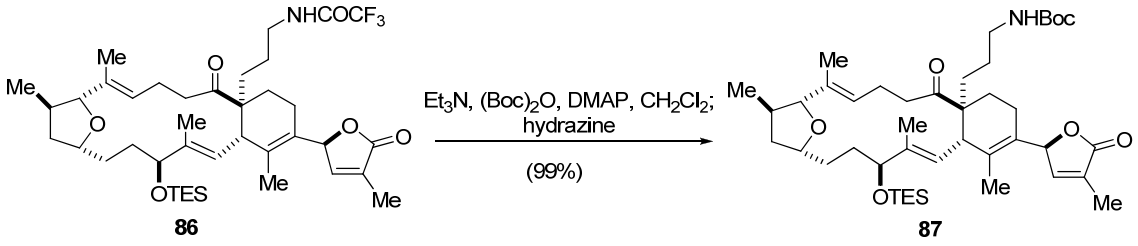
85b: R_f = 0.81 (70% EtOAc/hexanes); $[\alpha]^{20}_D$ –14.1 (*c* 0.778, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (br s, 1H, -NH), 7.05 (dq, *J* = 1.5 Hz, 1.5 Hz, 1H), 5.15 (dq, *J* = 1.5 Hz, 1.5 Hz, 1H), 5.00 (br s, 1H), 4.83 (d, *J* = 11.0 Hz, 1H), 4.06 (m, 1H), 3.97 (br s, 1H), 3.77 (dd, *J* = 3.5 Hz, 11.5 Hz, 1H), 3.35 (m, 2H), 3.12 (dd, *J* = 11.0 Hz, 11.0 Hz, 1H), 2.79 (m, 2H), 2.23 (m, 3H), 2.03 (m, 4H), 1.99 (dd, *J* = 1.5 Hz, 1.5 Hz, 3H), 1.87 (m, 2H), 1.69 (s, 3H), 1.62 (m, 3H), 1.51 (s, 3H), 1.46 (m, 4H), 1.30 (m, 2H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.55 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1, 173.5, 157.8 (*C*OCF_3, q, *J* = 36 Hz), 144.0,

141.9, 135.6, 132.1, 123.3, 122.5, 117.1 (CF_3, q, J = 286 Hz), 89.1, 86.1, 79.7, 78.0, 73.9, 54.7, 42.8, 40.3, 37.6, 37.5, 36.8, 34.7, 32.9, 32.3, 26.8, 25.1, 23.1, 22.5, 20.6, 20.0, 14.2, 11.4, 11.3, 11.0, 6.9, 4.9; IR (thin film): 3447, 3328, 1757, 1716 cm^{-1}.



85a **86**

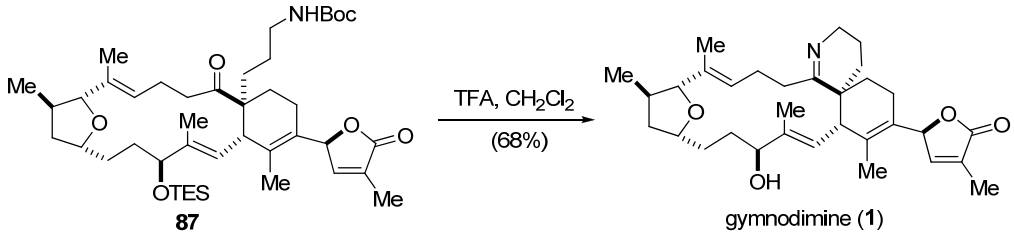
Olefin 86: To a solution of the alcohol **85a** (2 mg, 0.00265 mmol, azeotropically dried with PhMe) in CH_2Cl_2 (1 mL) at –78 ºC was added Et_3N (three drops) and 48 µl of a solution of $SOCl_2$ (20 µl) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at –78 ºC for 1 h and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography (40% EtOAc/hexanes) to afford 1.6 mg (82%) of the desired olefin **86** and its regioisomer ($\Delta^{5,6}$: $\Delta^{5,24}$ = 3:1). R_f = 0.58 (40% EtOAc/hexanes); $[\alpha]^{20}_D$ –67.7 (*c* 0.268, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (br s, 1H, -NH), 6.92 (br s, 1H), 5.84 (br s, 1H), 4.97 (m, 2H), 4.07 (m, 1H), 3.98 (br s, 1H), 3.85 (dd, J = 3.0 Hz, 11.5 Hz, 1H), 3.63 (d, J = 11.5 Hz, 1H), 3.33 (m, 2H), 2.70 (m, 3H), 2.28 (m, 1H), 2.18 (m, 1H), 2.13 (m, 2H), 1.98 (s, 3H), 1.92 (m, 2H), 1.83 (m, 4H), 1.73 (s, 3H), 1.68 (s, 3H), 1.64 (m, 2H), 1.52 (s, 3H), 1.45 (m, 2H), 1.32 (m, 2H), 1.11 (d, J = 7.0 Hz, 3H), 0.93 (t, J = 8.0 Hz, 9H), 0.56 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6, 174.6, 157.6 (*C*OCF_3, q, J = 36 Hz), 146.6, 142.6, 135.9, 132.6, 130.4, 125.2, 122.31, 122.28, 116.0 (CF_3, q, J = 286 Hz), 89.1, 80.3, 79.2, 78.1, 53.6, 46.7, 40.4, 37.6, 36.5, 34.6, 32.9, 31.9, 28.2, 23.3, 23.0, 20.5, 19.9, 19.6, 16.3, 14.2, 11.0, 10.7, 6.9, 4.9; IR (thin film): 3502, 3328, 1761, 1721, 1707 cm^{-1}; LRMS (MALDI) Calcd. for $C_{40}H_{60}F_3NNaO_6$ [M+Na]: 758. Found: 758.



86 **87**

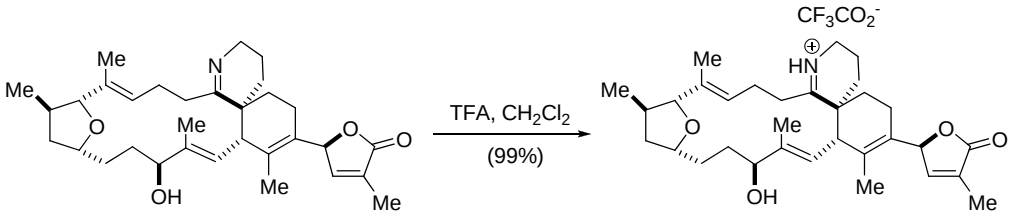
Boc amine 87: To a solution of the trifluoroacetamide **86** (4.0 mg, 0.00534 mmol, azeotropically dried with PhMe, R_f = 0.33 in 40% EtOAc/hexanes) in CH_2Cl_2 (1.2 mL) at room

temperature was added Et_3N (50 µl), DMAP (5 mg) and a solution of $(Boc)_2O$ (36 mg, 0.163 mmo) in CH_2Cl_2 (1.2 mL). After 25 min, TLC indicated the starting material was completely converted to a new intermediate (R_f = 0.48, 40% EtOAc/hexanes). Hydrazine hydrate (20 µl) was added and the cloudy reaction mixture was stirred at room temperature for 5 min (TLC indicated the complete hydrolysis of this intermediate). The mixture was then quenched with saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc, the combined organic layers were concentrated *in vacuo* and purified by flash chromatography (20%→25%→30%→35% EtOAc/hexanes) to provide 4.0 mg (99% yield) of the desired Boc amine **87** as a white solid. R_f = 0.33 (40% EtOAc/hexanes); $[\alpha]^{22}_D$ –51.2 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (br s, 1H), 5.82 (br s, 1H), 5.06~5.01 (m, 2H), 4.70 (br s, 1H, NH), 4.09 (m, 1H), 3.98 (br s, 1H), 3.88 (dd, *J* = 2.4 Hz, 11.2 Hz, 1H), 3.59 (d, *J* = 10.8 Hz, 1H), 3.24~3.04 (m, 2H), 2.63 (m, 2H), 2.20 (m, 2H), 2.11~2.00 (m, 3H), 1.97 (s, 3H), 1.91 (m, 1H), 1.80 (m, 2H), 1.74 (m, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 1.61 (m, 1H), 1.52 (s, 3H), 1.46 (s, 9H), 1.53~1.42 (m, 3H), 1.35 (m, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.04 (m, 1H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.56 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 174.7, 156.1, 146.7, 142.1, 135.6, 132.4, 130.3, 125.0, 123.0, 122.6, 89.2, 80.4, 79.3, 78.8, 78.2, 53.0, 46.7, 41.1, 37.5, 37.0, 34.7, 33.1, 32.3, 28.4, 28.3, 25.0, 24.1, 20.6, 20.0, 19.5, 16.3, 14.2, 10.9, 10.6, 6.9, 4.9; IR (thin film): 3334, 1760, 1702 cm^{-1}; LRMS (ESI) Calcd. for $C_{43}H_{69}NNaO_7Si$ [M+Na]: 762. Found: 762.



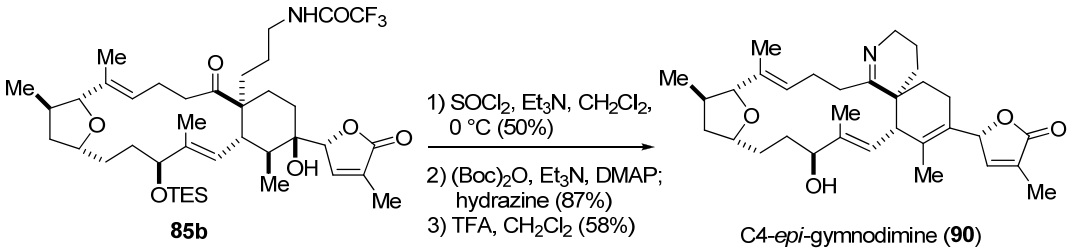
Gymnodimine (**1**): To a solution of the Boc amine **87** (4.0 mg) in CH_2Cl_2 (0.8 mL) was added trifluoroacetic acid (200 µl). After 30 min, the reaction was quenched by careful addition of solid $NaHCO_3$ (320 mg). After stirring for 5 min, saturated $NaHCO_3$ (1 mL) was added. The mixture was extracted with EtOAc/CH_2Cl_2 (5:1, 1.5 mL) for 6 times. The combined organic layers were concentrated *in vacuo* and purified by flash chromatography (basic Al_2O_3, CH_2Cl_2→5%→10%→15%→20% MeOH/CH_2Cl_2) to provide a primary amine (R_f = 0.24, 15% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3). Upon standing under high vacuum for 10 h, this amine cyclized to provide 1.9 mg (68% yield) of gymnodimine as a white solid. R_f = 0.43 (10%

MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); $[\alpha]^{22}_D$ –43.9 (*c* 0.33, $CHCl_3$); Key ^{1}H NMR signals (400 MHz, $CDCl_3$(passed through basic Al_2O_3)) δ 6.91 (br s, 1H, H3), 5.83 (br s, 1H, H4), 5.29 (d, *J* = 11.6 Hz, 1H, H8), 5.05 (br s, 1H, H18), 4.09 (m, 1H, H13), 4.01 (dd, *J* = 3.2 Hz, 11.6 Hz, 1H, H10), 3.98 (br s, 1H, H16), 3.65 (m, 1H, H7), 3.57 (m, 1H, H32a), 3.41 (m, 1H, H32b), 2.48 (m, 3H, H19a, H20), 1.97 (s, 3H, H25), 1.82 (s, 3H, H27), 1.69 (s, 3H, H26), 1.53 (s, 3H, H29), 1.09 (d, *J* = 7.2 Hz, 3H, H28); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 171.7, 147.0, 139.5, 134.5, 132.7, 130.2, 127.0, 124.8, 124.4, 89.5, 80.5, 79.3, 77.7, 49.8, 46.0, 41.3, 37.5, 37.2, 33.5, 32.4, 31.6, 30.8, 26.3, 21.8, 20.6, 20.1, 19.1, 16.7, 14.5, 11.1, 10.6; HRMS (ESI) Calcd. for $C_{32}H_{46}NO_4$ [M+H]: 508.3427. Found: 508.3430.



gymnodimine (**1**)

Gymnodimine•TFA salt. (Note: The TFA salt was prepared for comparison to the only reported optical rotation data for this salt of gymnodimine.) To a solution of gymnodimine (0.6 mg) at 22 °C was added trifluoroacetic acid (10 μl). The solvent was then evaporated and the residue was dried under high vacuum for 10 h to provide gymnodimine•TFA salt as a white solid (0.6 mg, 99% yield). $[\alpha]^{22}_D$ –14.1 (*c* 0.06, MeOH); lit $[\alpha]^{25}_D$ –10.4 (*c* 0.13, MeOH).[5] ^{1}H NMR of synthetic gymnodimine•TFA matched with that of previously reported data.[5]



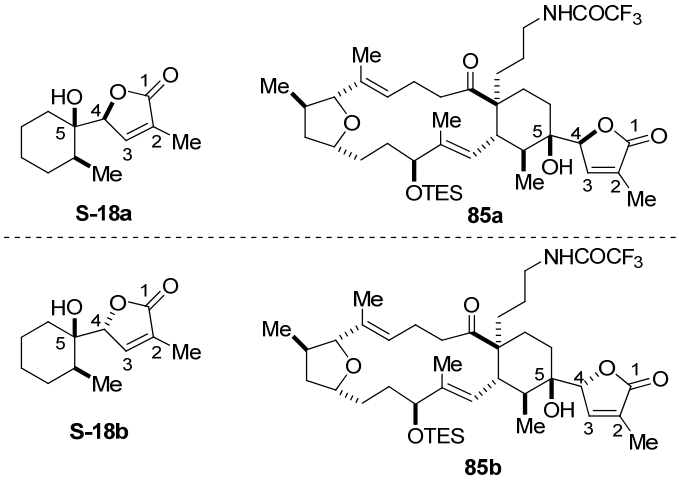
85b C4-*epi*-gymnodimine (**90**)

C4-*epi*-Gymnodimine (90). This C4-epimer of gymnodimine was prepared from diastereomeric trifluoroacetamide **85b** in a similar three-step sequence as described for gymnodimine (1) above to give C4-*epi*-gymnodimine (C4-*epi*-1) as a white solid. R_f = 0.43 (10% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); $[\alpha]^{22}_D$ +55.8 (*c* 0.12, $CHCl_3$); Key ^{1}H NMR signals (400 MHz, $CDCl_3$(passed through basic Al_2O_3)) δ 6.87 (br s, 1H, H3), 5.85 (br s, 1H, H4),

(5) Seki, T.; Sataki, M.; Mackenzie, L.; Kaspar, T. F.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093.

5.28 (d, J = 11.2 Hz, 1H, H8), 5.05 (br s, 1H, H18), 4.09 (m, 1H, H13), 3.99 (m, 1H, H10), 3.98 (br s, 1H, H16), 3.70 (m, 1H, H7), 3.58 (m, 1H, H32a), 3.40 (m, 1H, H32b), 2.49 (m, 3H, H19a, H20), 1.97 (s, 3H, H25), 1.84 (s, 3H, H27), 1.76 (s, 3H, H26), 1.54 (s, 3H, H29), 1.09 (d, J = 7.2 Hz, 3H, H28); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 171.8, 147.5, 139.5, 135.0, 134.4, 130.7, 127.3, 124.6, 124.4, 89.5, 79.7, 79.5, 77.7, 49.7, 46.2, 41.0, 37.5, 37.2, 33.5, 32.4, 31.7, 30.9, 26.5, 21.8, 20.6, 20.1, 19.9, 17.3, 14.5, 11.1, 10.7; HRMS (ESI) Calcd. for $C_{32}H_{46}NO_4$ [M+H]: 508.3427. Found: 508.3430.

Table S-1. Comparison of ^{13}C NMR chemical shifts of model hydroxyl ketones **S-18a**/**S-18b** with **85a**/**85b**

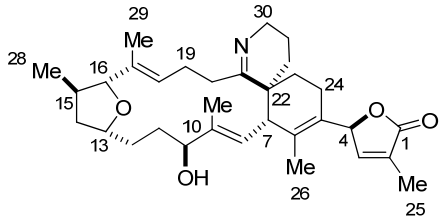


C#	**S-18a** (300 MHz, $CDCl_3$)[a]	**85a** (500 MHz, $CDCl_3$)	$\Delta_1 = \Delta_{\mathbf{85a}} - \delta_{\mathbf{S\text{-}18a}}$	**S-18b** (300 MHz, $CDCl_3$)[a]	**85b** (500 MHz, $CDCl_3$)	$\Delta_2 = \Delta_{\mathbf{85b}} - \delta_{\mathbf{S\text{-}18b}}$
1	174.3	173.9	-0.4	174.1	173.5	-0.6
2	130.6	131.1	+0.5	131.1	132.1	+1.0
3	147.8	147.0	-0.8	145.1	144.0	-1.1
4	83.1	83.0	-0.1	86.3	86.1	-0.2
5	74.4	73.8	-0.6	74.5	73.9	-0.6

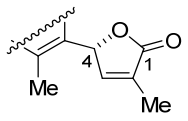
[a] Data taken ref 6.

[6] Kong, K.; Romo, D. *Org. Lett*. **2006**, *8*, 2909–2912.

Table S-2. Comparison of assigned ^{1}H NMR chemical shifts[a] of natural gymnodimine (**1**) with synthetic gymnodimine and C4-*epi*-gymnodimine (**90**)



Gymnodimine (**1**)



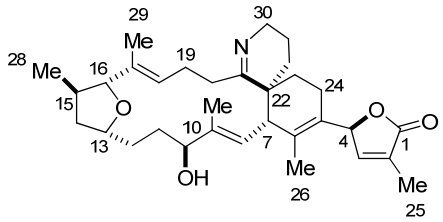
C4-*epi*-gymnodimine (**90**)

C#	**Natural Gymnodimine** (300 MHz, $CDCl_3$)[a]	**No. H**	**Synthetic gymnodimine** (400 MHz, $CDCl_3$)	**C4-*epi*-Gymnodimine** (400 MHz, $CDCl_3$)
3	6.89	1	6.91	6.87
4	5.80	1	5.83	5.85
7	3.63	1	3.65	3.70
8	5.26	1	5.29	5.28
10	4.00	1	4.01	3.99
13	4.08	1	4.09	4.09
16	3.95	1	3.98	3.98
18	5.00	1	5.05	5.05
19a,20	2.49	3	2.48	2.49
25	1.94	3	1.97	1.97
26	1.67	3	1.69	1.76
27	1.80	3	1.82	1.84
28	1.07	3	1.09	1.09
29	1.51	3	1.53	1.54
32	3.55	1	3.57	3.58
	3.40	1	3.41	3.40

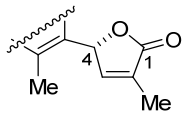
[a] Data taken ref. 7.

(7) Stewart, M.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T.; Hannah, D. J. *Tetrahedron Lett.* **1997**, *38*, 4889.

Table S-3. Comparison of assigned ^{13}C NMR chemical shifts[a] of natural gymnodimine (**1**) with synthetic gymnodimine and C4-*epi*-gymnodimine (**90**)



Gymnodimine (**1**)

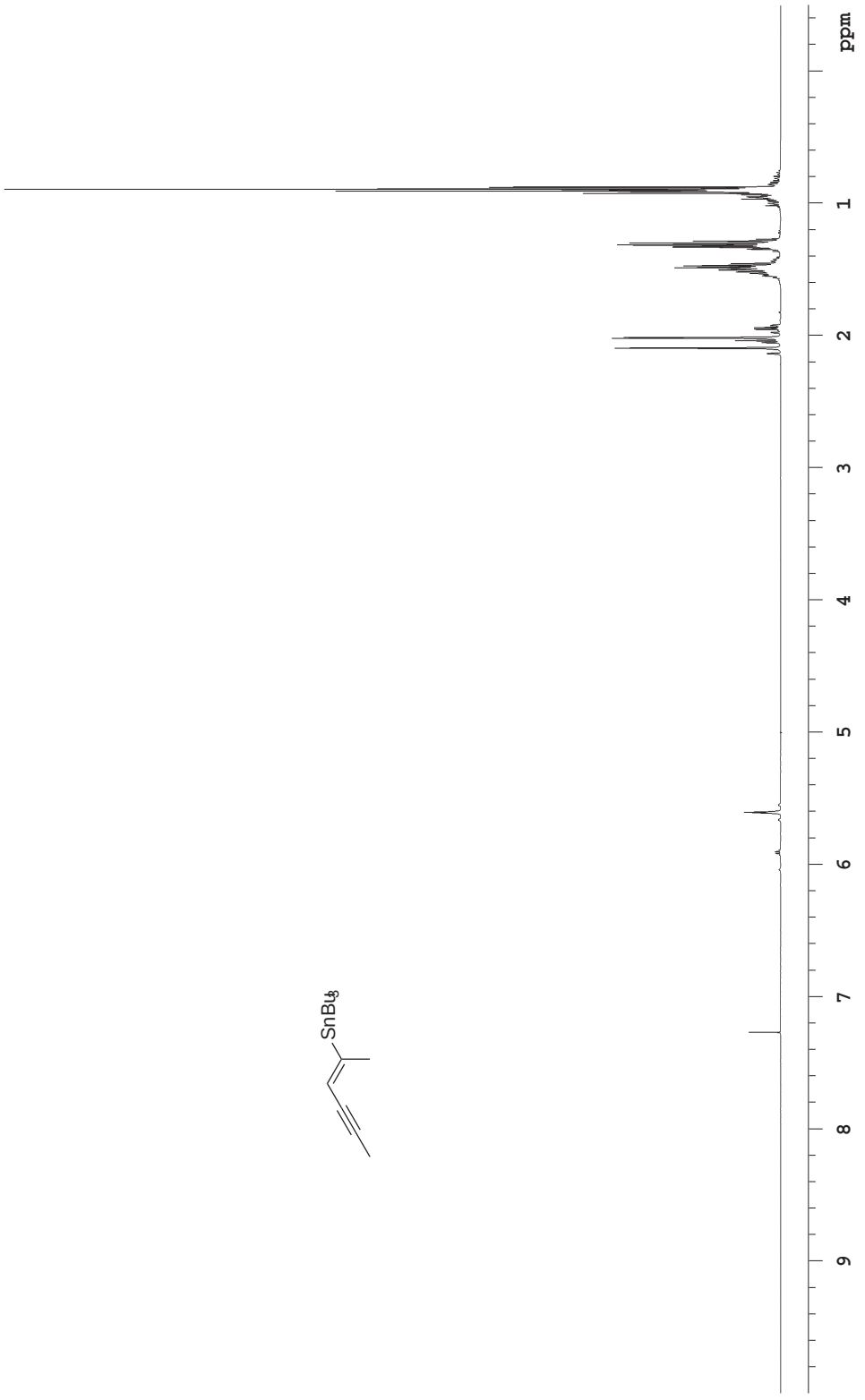


C4-*epi*-gymnodimine (**90**)

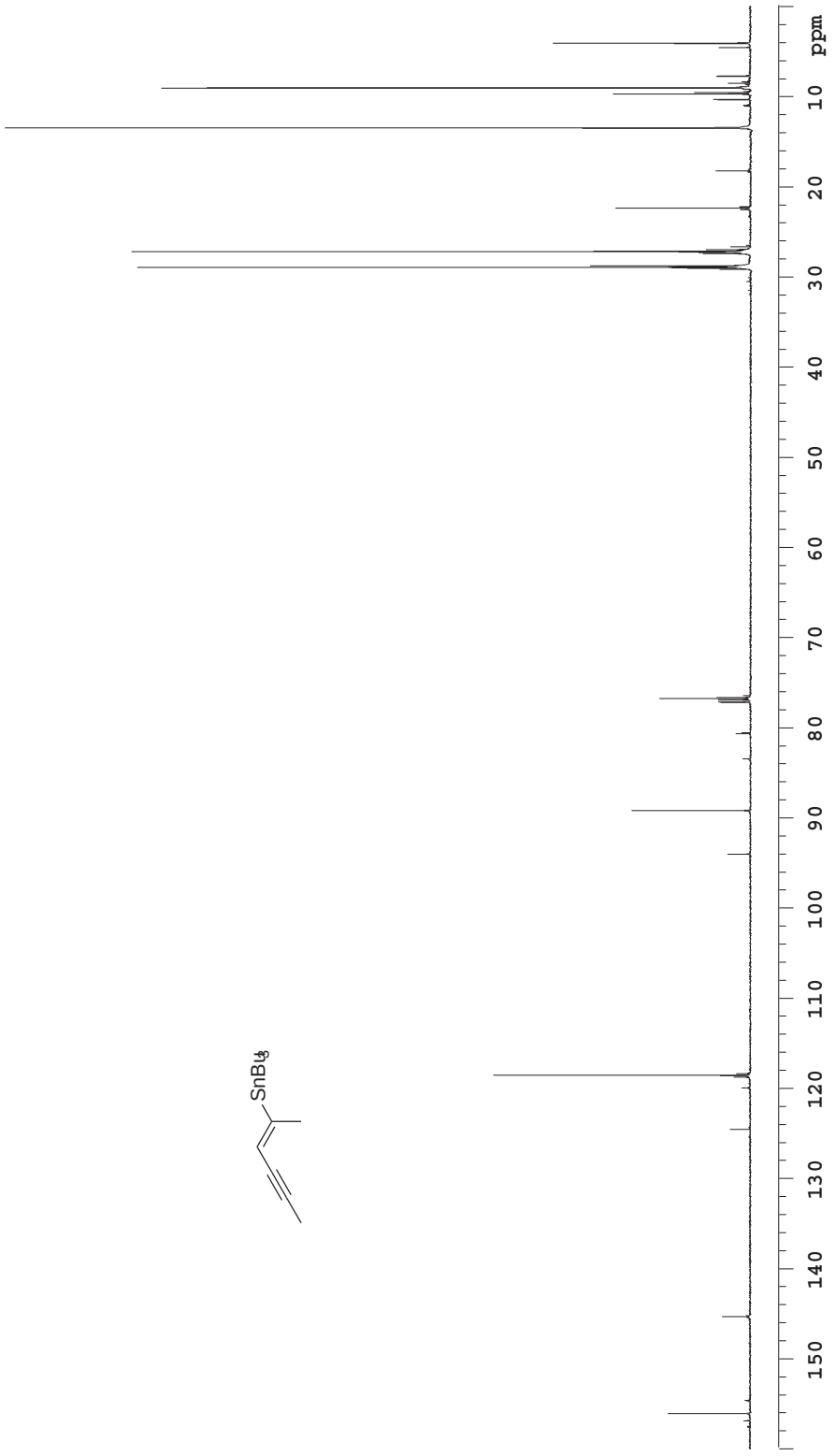
C#	**Natural Gymnodimine** (75 MHz, $CDCl_3$)[a]	**Synthetic Gymnodimine** (100 MHz, $CDCl_3$)	**C4-*epi*-Gymnodimine** (100 MHz, $CDCl_3$)	$\Delta_1 = \delta_{\text{syn. gymno}} - \delta_{\text{nat. gymno.}}$	$\Delta_2 = \delta_{\text{C4-epi-gymno}} - \delta_{\text{nat. gymno}}$
1	174.5	174.7	174.5	+0.2	0.0
2	130.2	130.2	130.7	0.0	+0.5
3	146.8	147.0	147.5	+0.2	+0.7
4	80.4	80.5	79.7	+0.1	–0.7
5	124.7	124.8	124.6	+0.1	–0.1
6	132.5	132.7	135.0	+0.2	+2.5
7	46.1	46.0	46.2	–0.1	+0.1
8	126.7	127.0	127.3	+0.3	+0.6
9	139.6	139.5	139.5	–0.1	–0.1
10	79.2	79.3	79.5	+0.1	+0.3
11	31.7	31.6	31.7	–0.1	0.0
12	32.5	32.4	32.4	–0.1	–0.1
13	77.8	77.7	77.7	–0.1	–0.1
14	37.3	37.2	37.5	–0.1	+0.2
15	37.6	37.5	37.2	–0.1	–0.4
16	89.5	89.5	89.5	0.0	0.0
17	134.9	134.5	134.4	–0.4	–0.5
18	123.6	124.4	124.4	+0.8	+0.8
19	21.8	21.8	21.8	0.0	0.0
20	31.0	30.8	30.9	–0.2	–0.1
21	174.0[b]/171.4[c]	171.7	171.8	–2.3	–2.2
22	41.6	41.3	41.0	–0.3	–0.6

23	33.6	33.5	33.5	–0.1	–0.1
24	19.2	19.1	19.9	–0.1	+0.7
25	10.7	10.6	10.7	–0.1	0.0
26	16.8	16.7	17.3	–0.1	+0.5
27	11.2	11.1	11.1	–0.1	–0.1
28	20.2	20.1	20.1	–0.1	–0.1
29	14.6	14.5	14.5	–0.1	–0.1
30	26.2	26.3	26.5	+0.1	+0.3
31	20.4	20.6	20.6	+0.2	+0.2
32	49.6	49.8	49.7	+0.2	+0.1

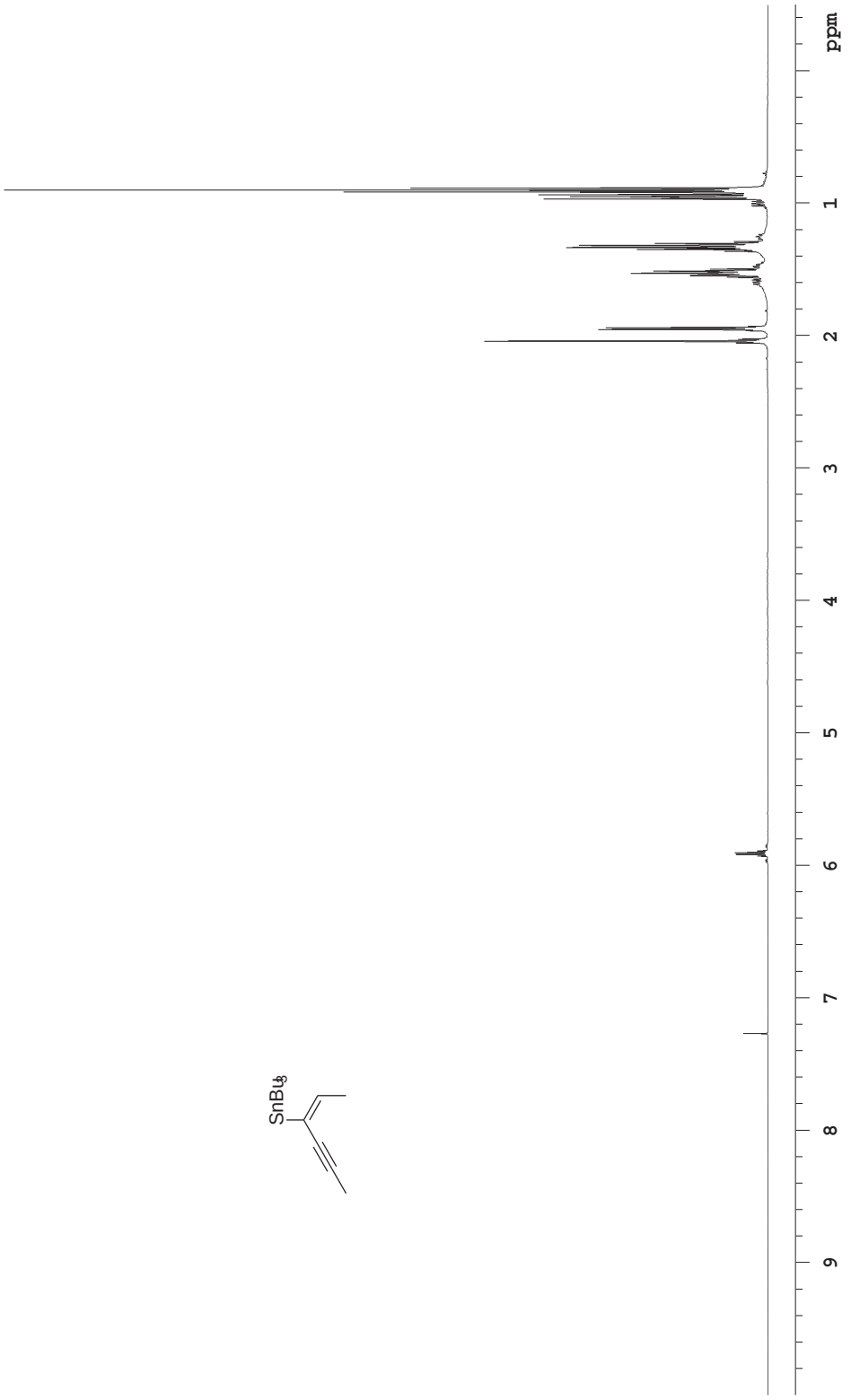
[a] Data taken from ref. 7. [b] In ref. 7, carbon signals in the region of δ 180-100 were not directly detected due to low peak intensity but were instead deduced from 2D NMR experiments (HMQC and HMBC). [c] Data taken from ref. 5. The 2.6 ppm reported discrepancy for the imine carbon (C21) by the isolation reports (refs. 5 and 7) is likely due to different protonation state of the N atom, but as expected the chemical shift for the free base of our synthetic gymnodimine is most consistent with Yasumoto's data for gymnodimine taken in C_5D_5N.



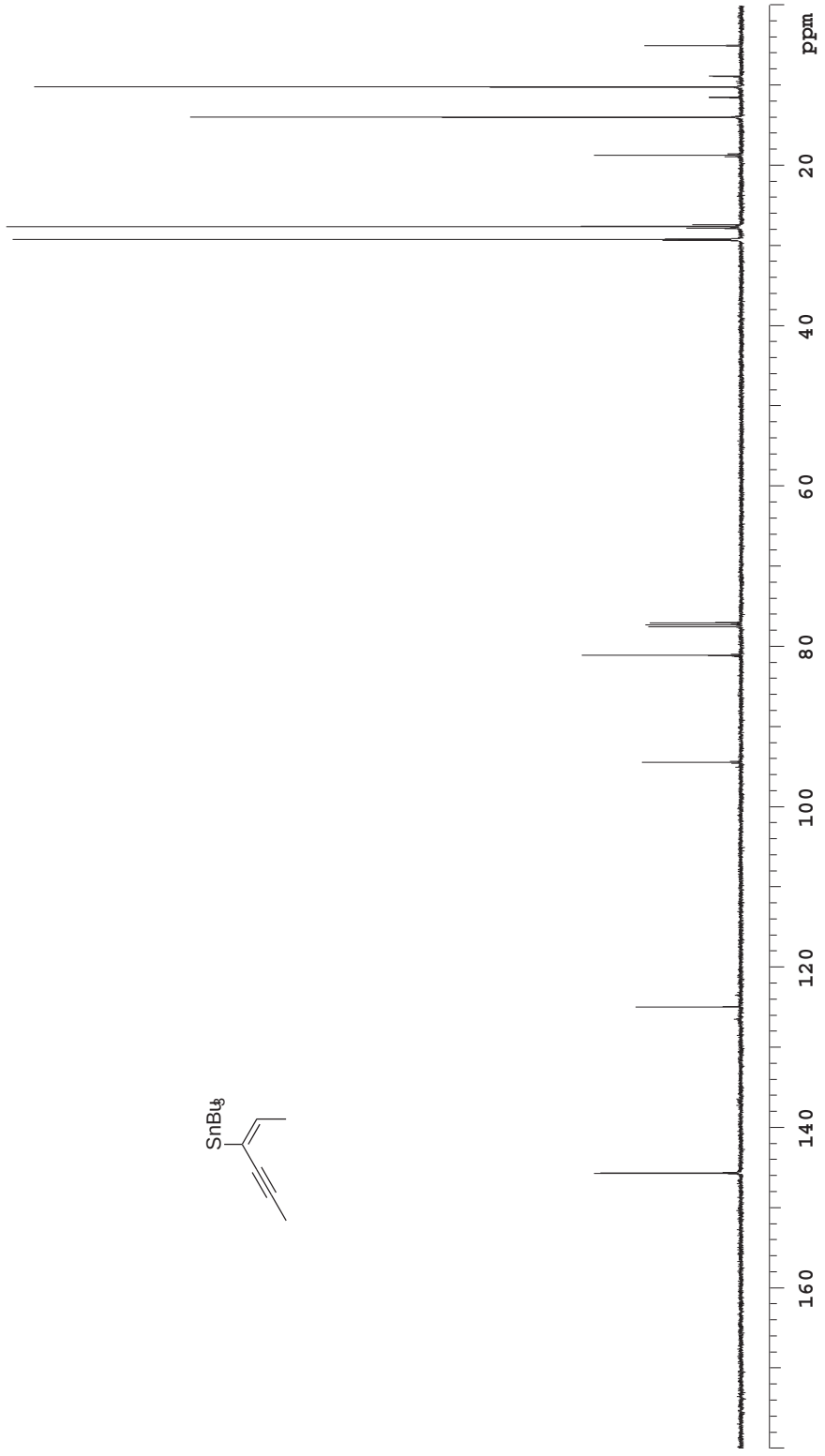
^{1}H NMR spectrum of vinyl stannane **25a**



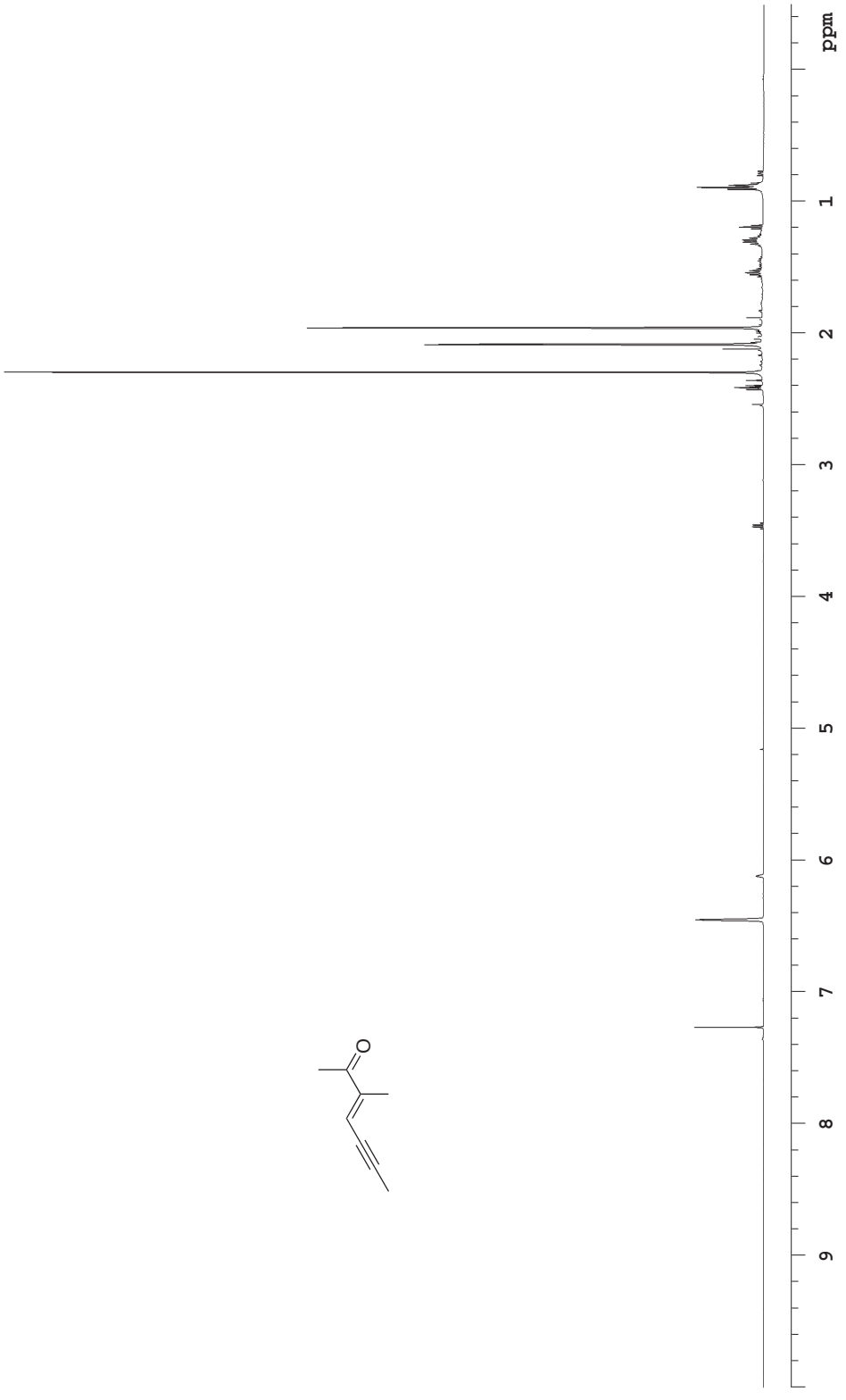
^{13}C NMR spectrum of vinyl stannane **25a**



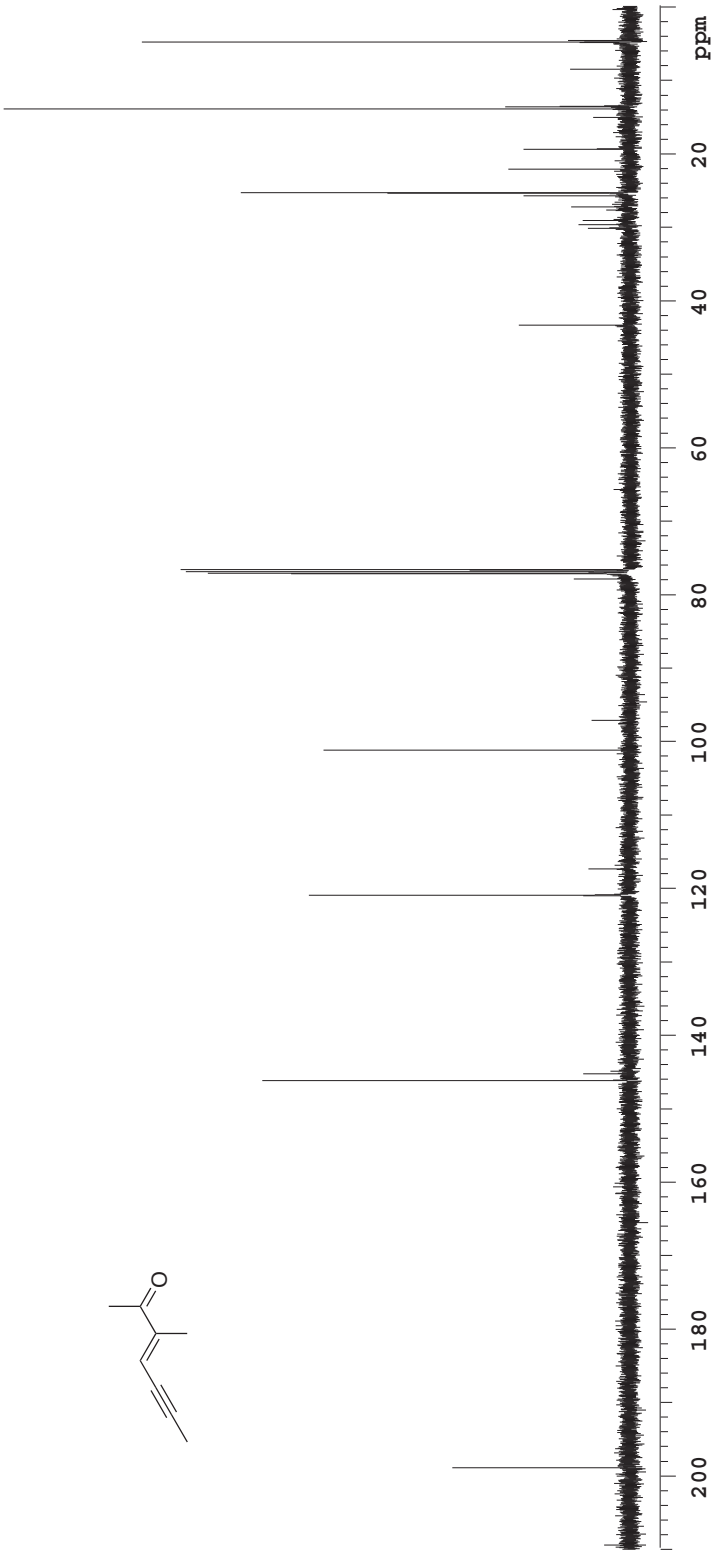
^{1}H NMR spectrum of vinyl stannane **25c**



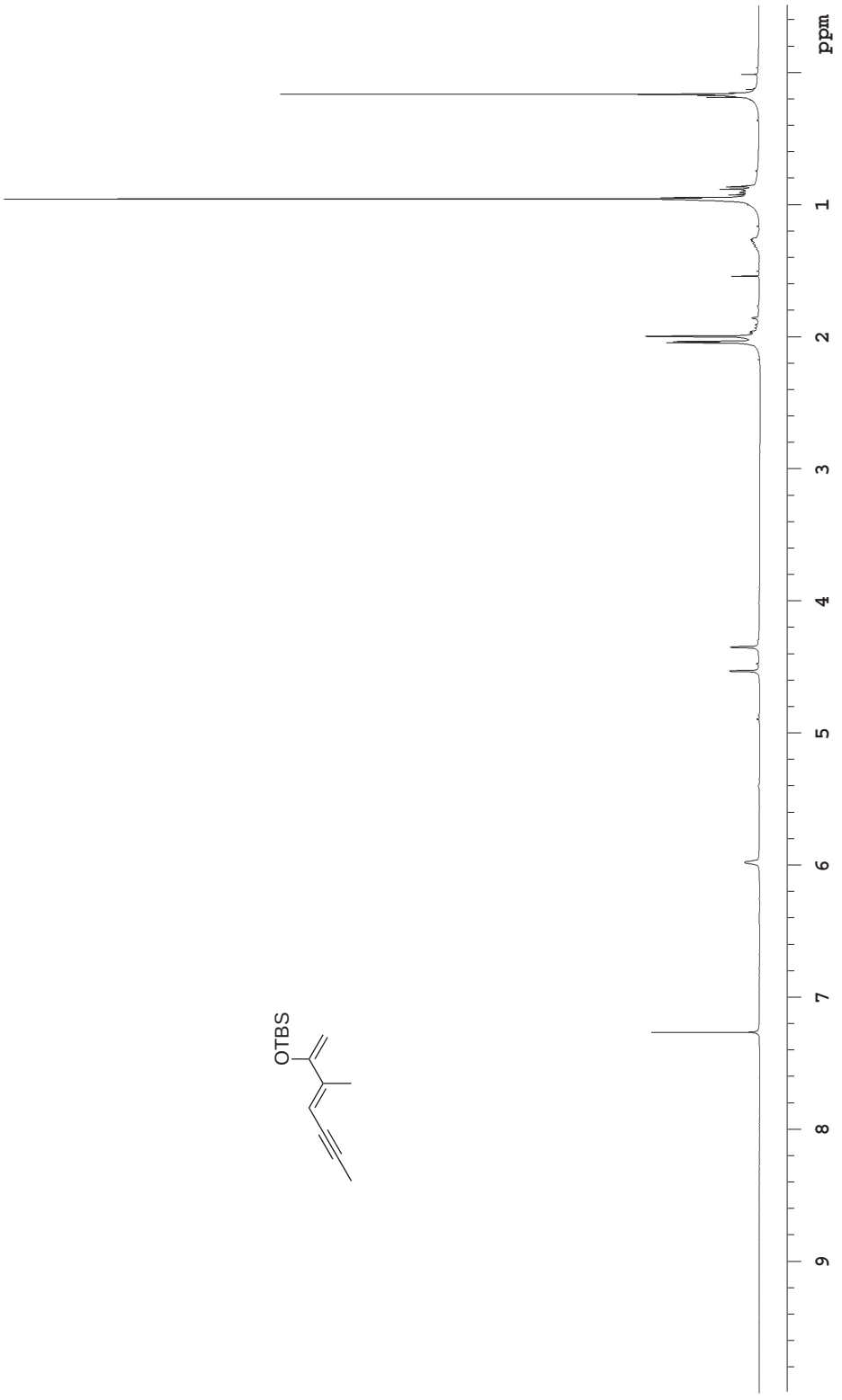
^{13}C NMR spectrum of vinyl stannane **25c**



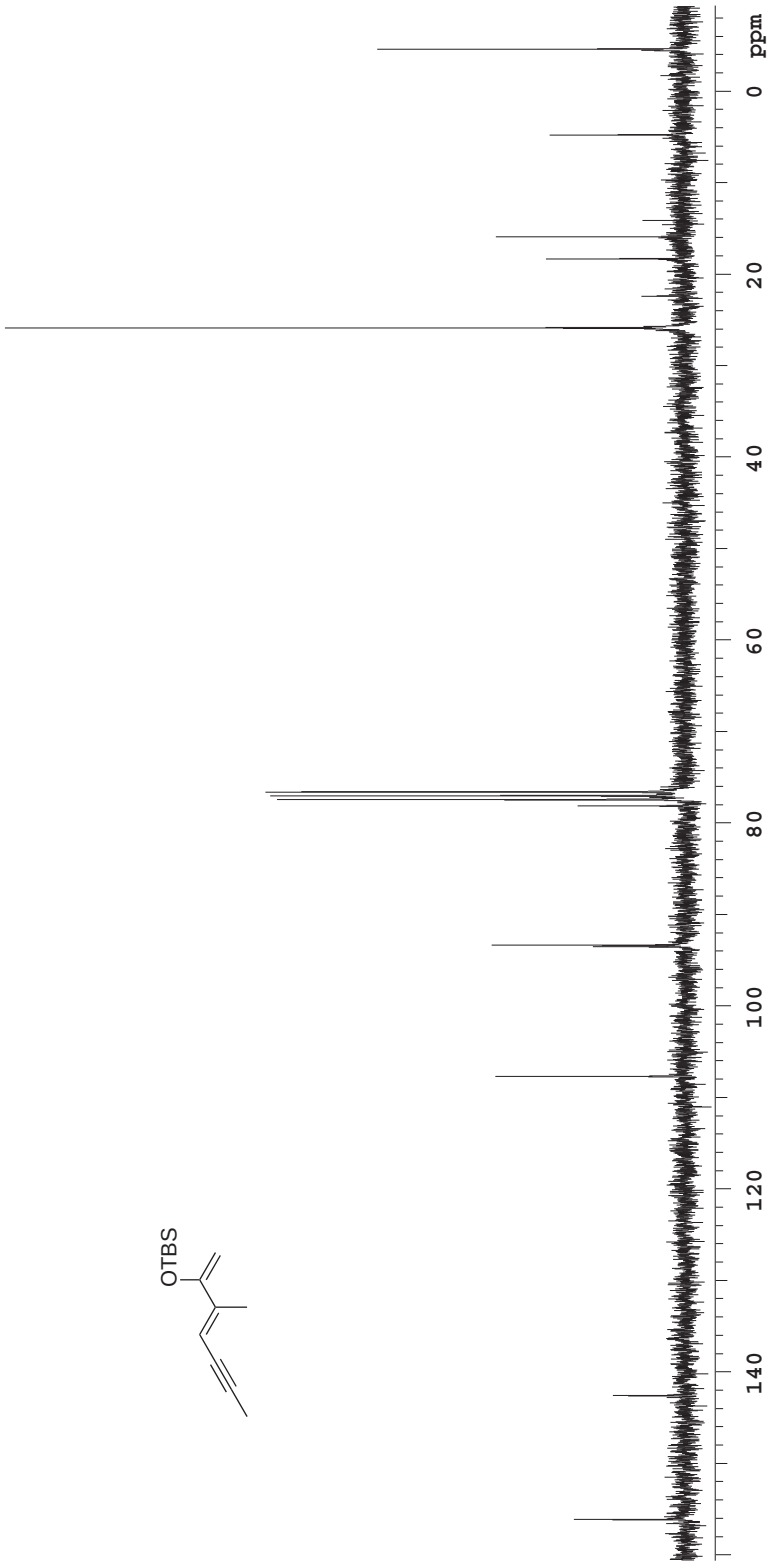
^{1}H NMR spectrum of ketone **S-6**



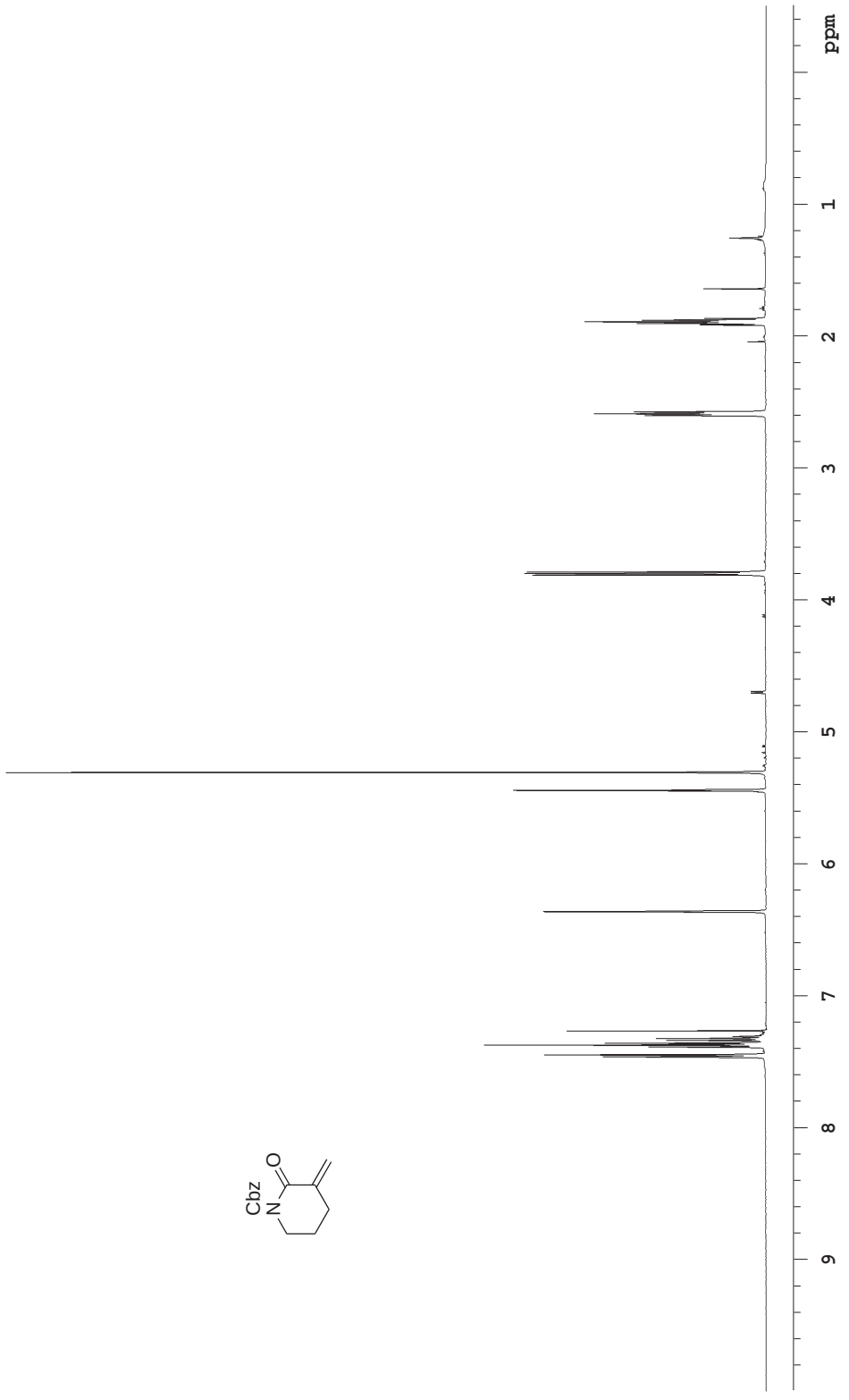
^{13}C NMR spectrum of ketone **S-6**



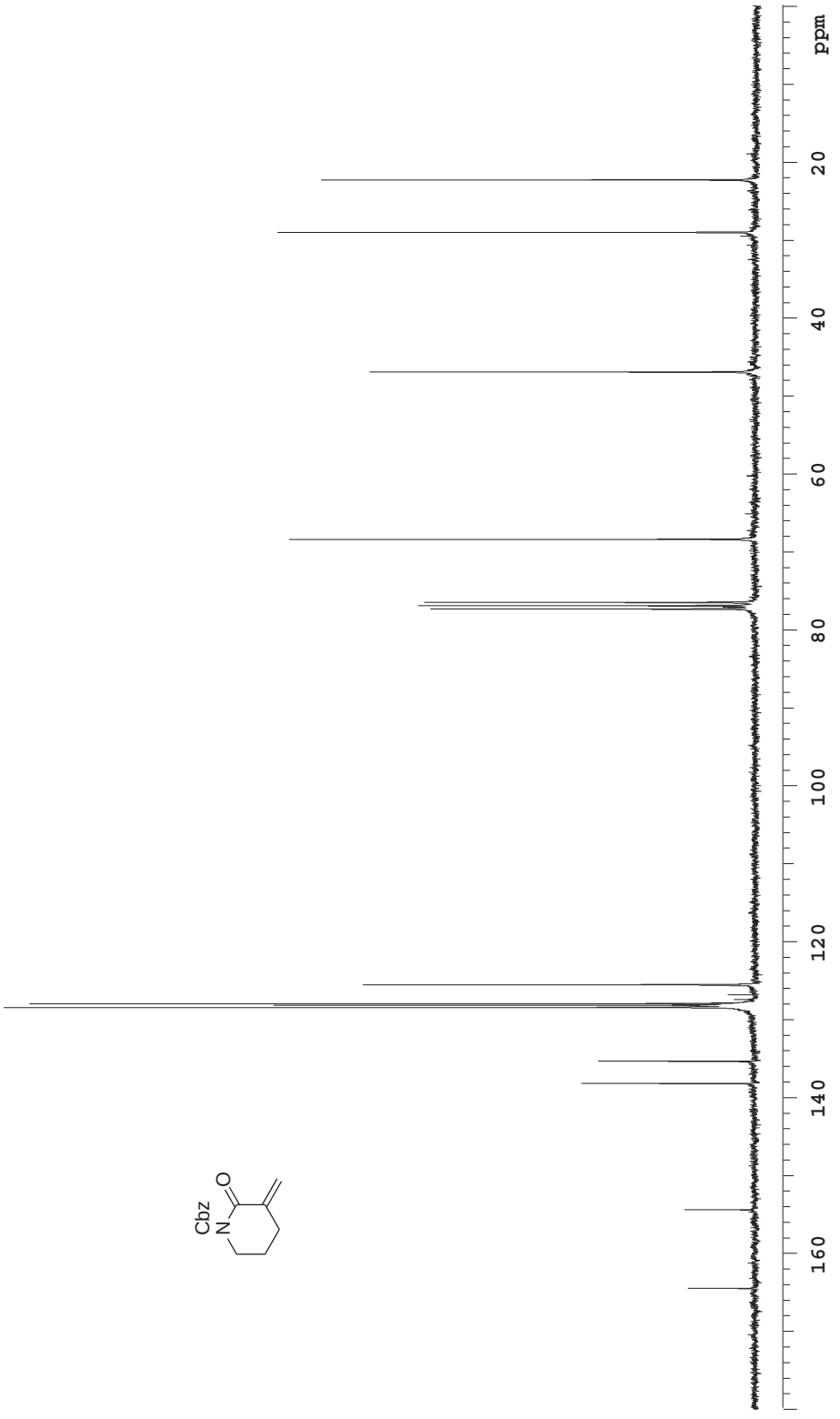
^{1}H NMR spectrum of silylenol ether (*E*)-**24**



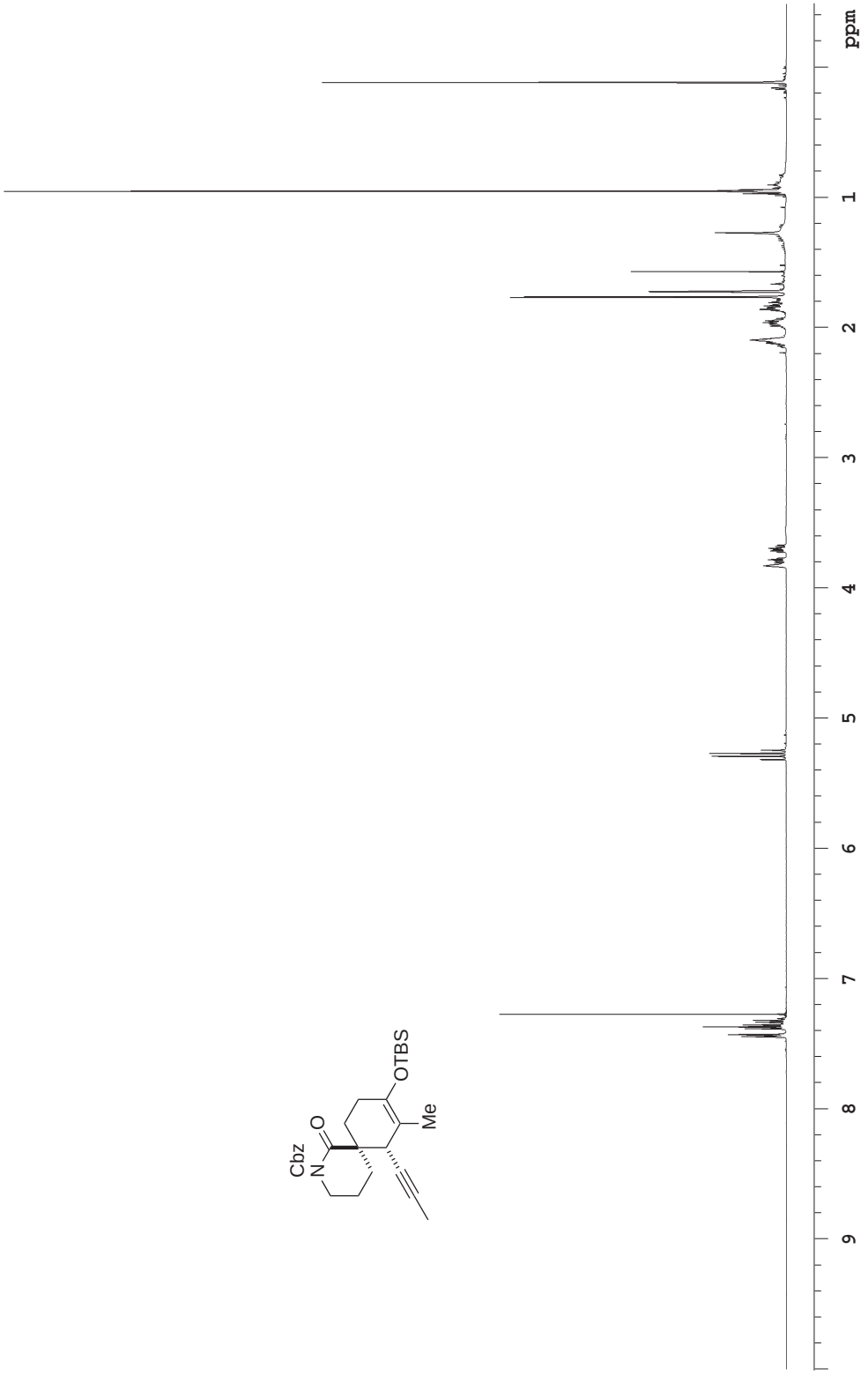
^{13}C NMR spectrum of silylenol ether (*E*)-**24**



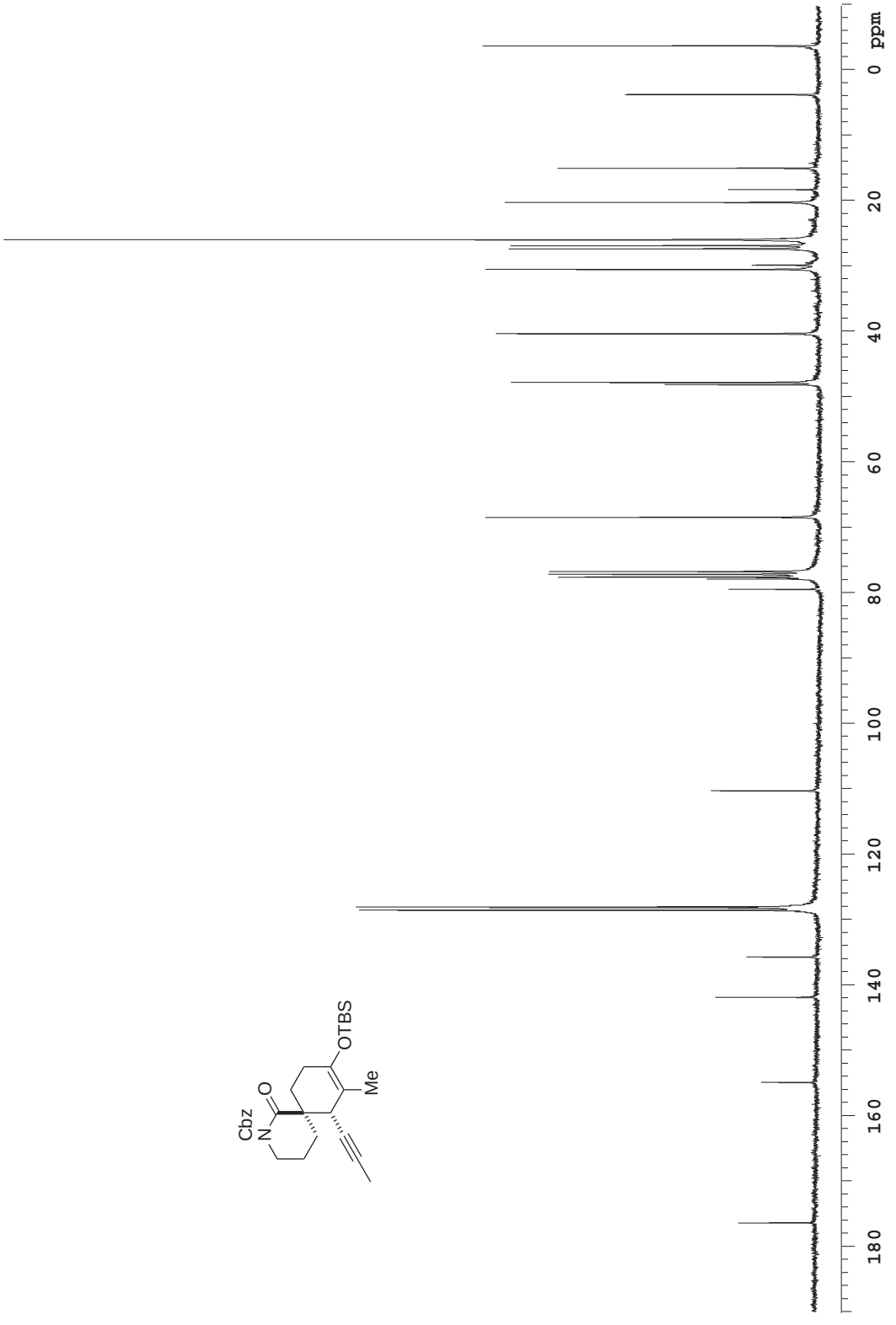
^{1}H NMR spectrum of *N*-Cbz lactam **8b**



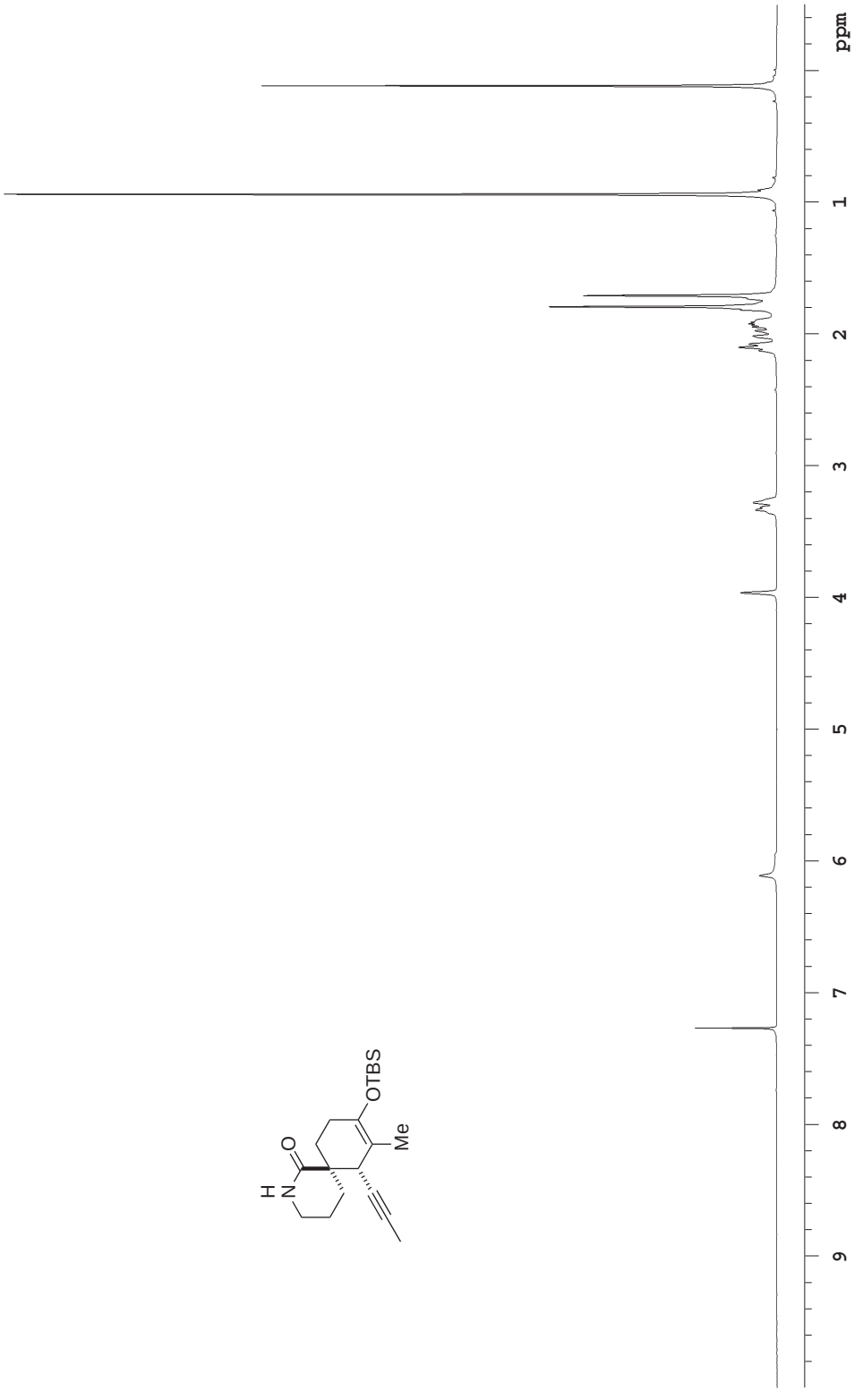
^{13}C NMR spectrum of *N*-Cbz lactam **8b**



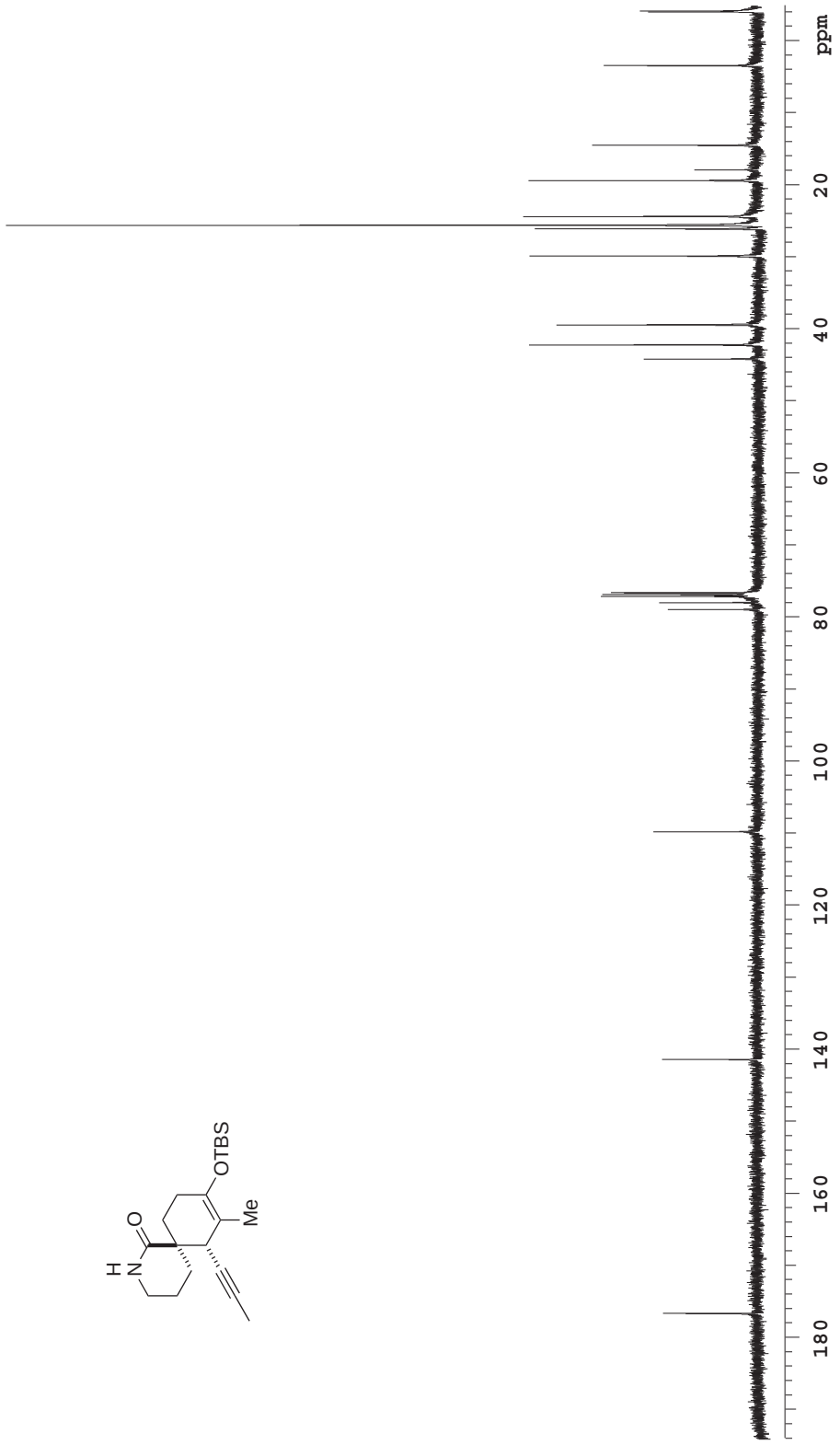
^{1}H NMR spectrum of *N*-Cbz spirolactam **7b**



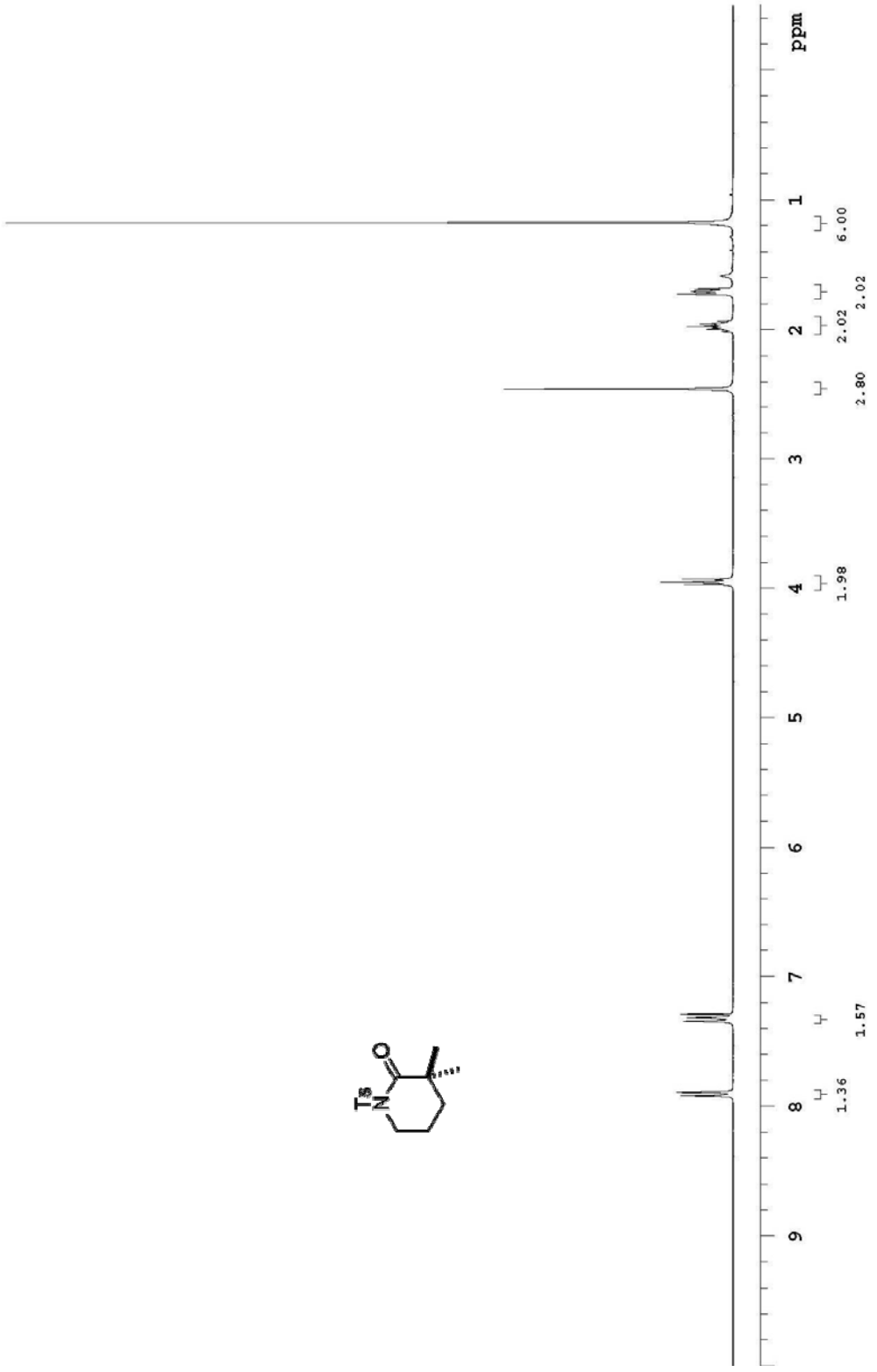
^{13}C NMR spectrum of *N*-Cbz spirolactam **7b**



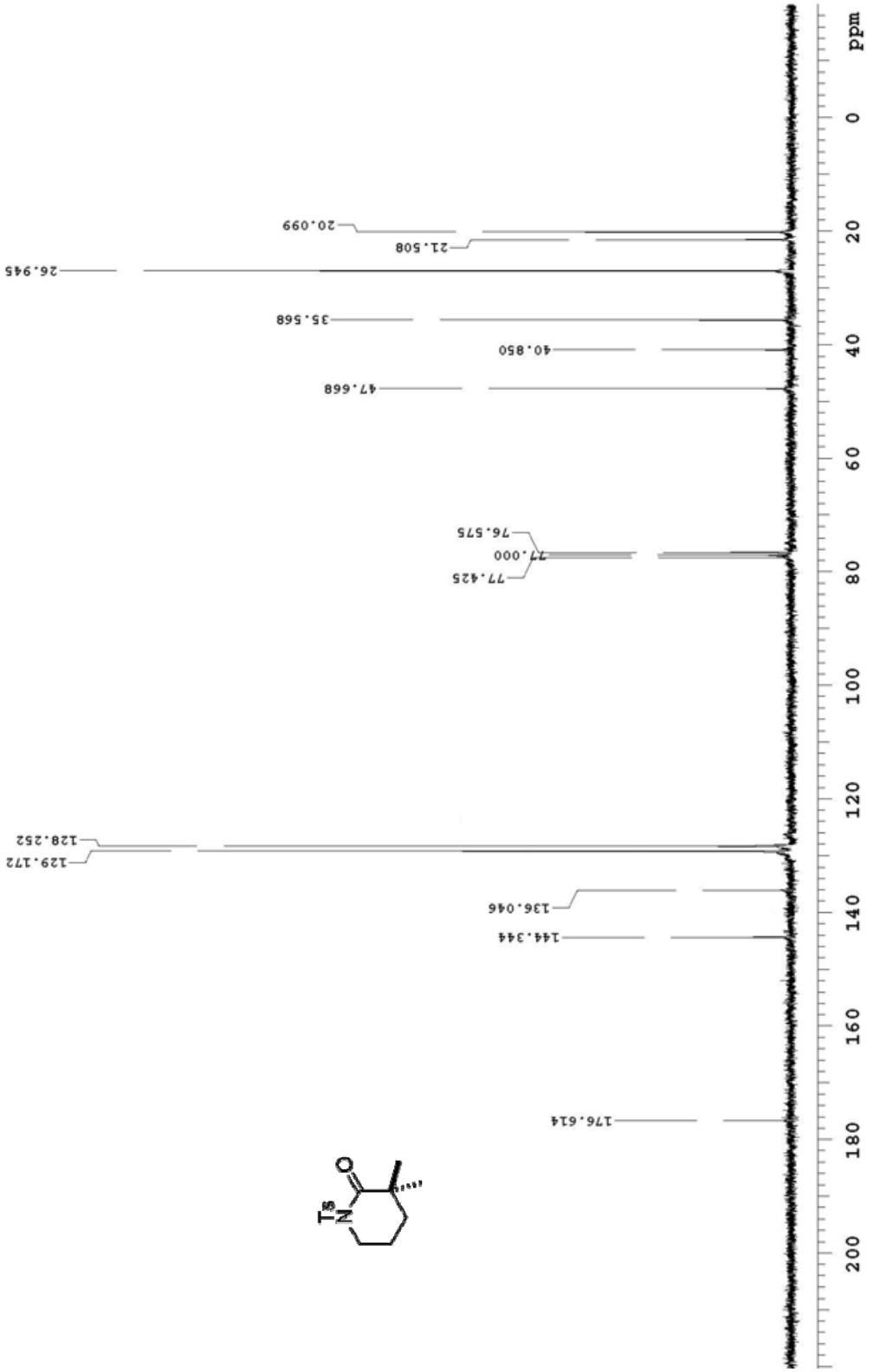
^{1}H NMR spectrum of spirolactam **7c**



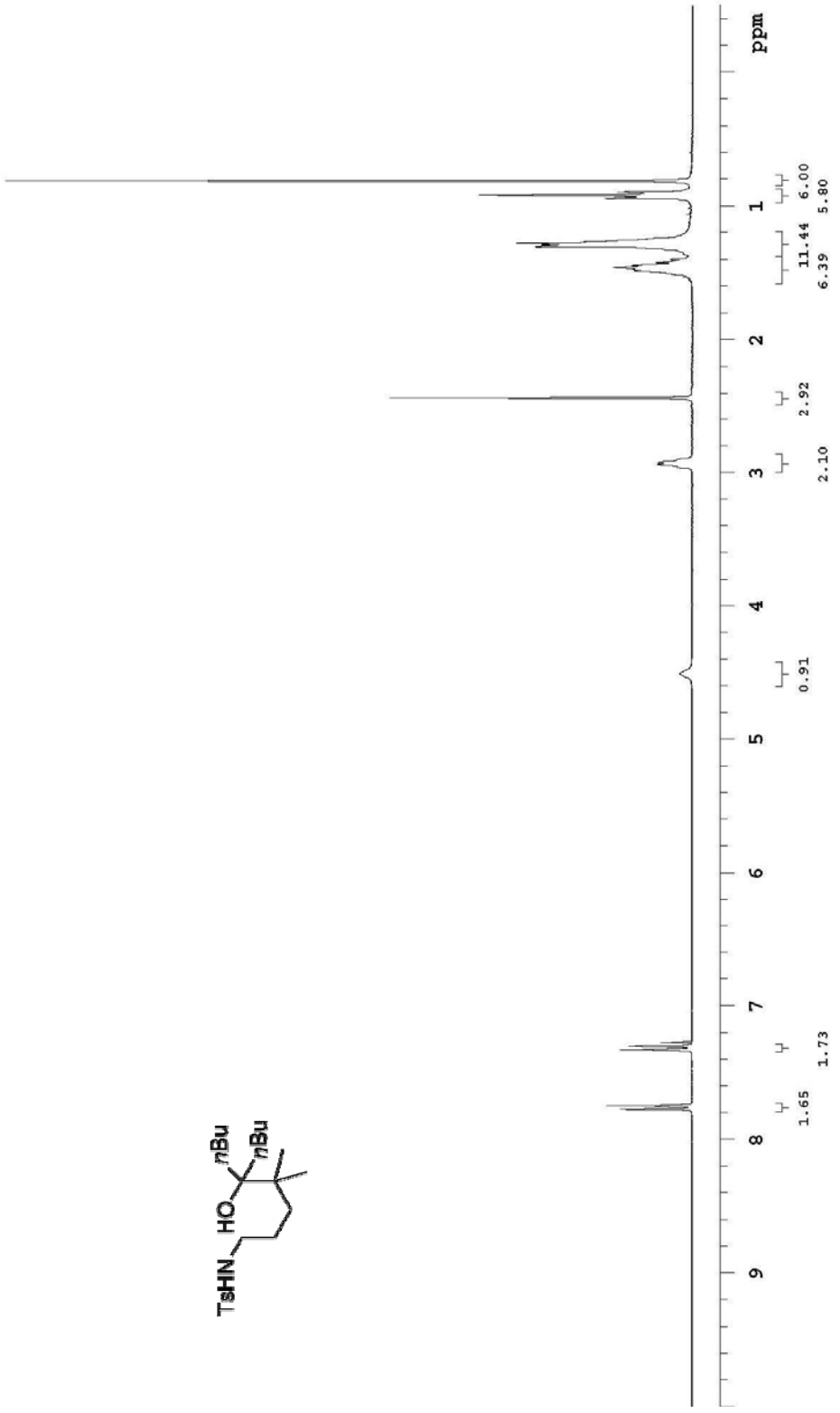
^{13}C NMR spectrum of spirolactam **7c**



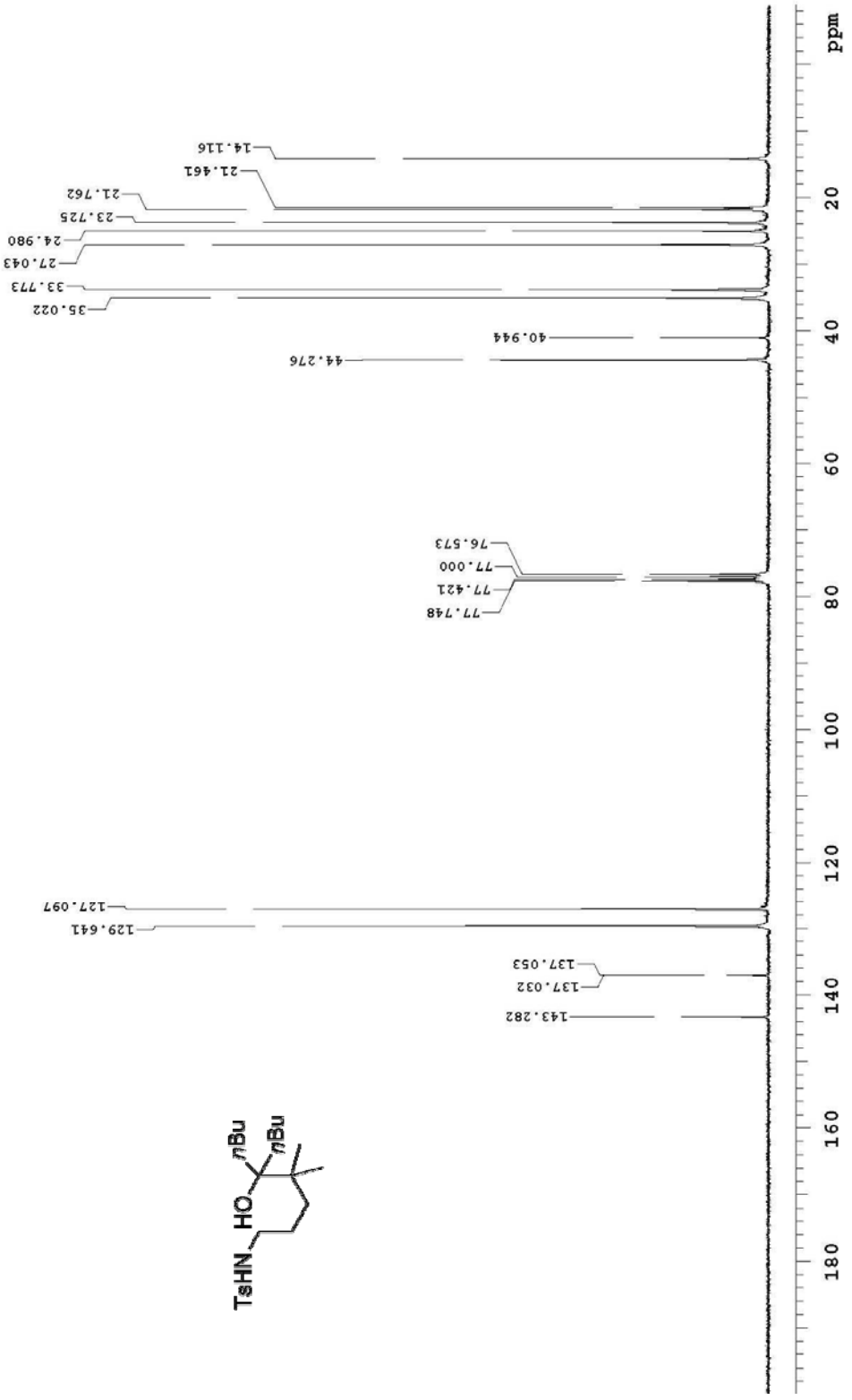
^{1}H NMR spectrum of *N*-Ts lactam **32b**



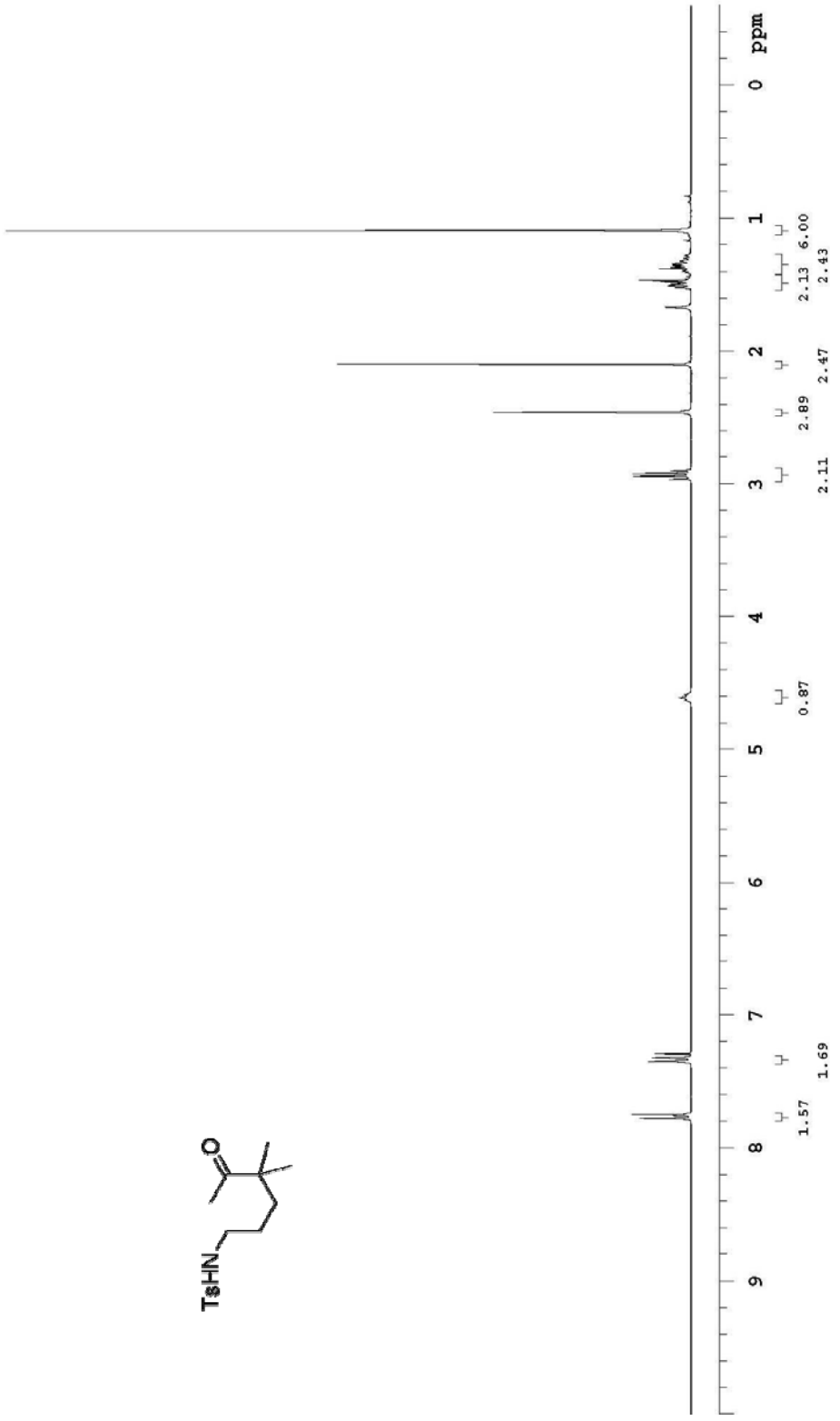
^{13}C NMR spectrum of *N*-Ts lactam **32b**



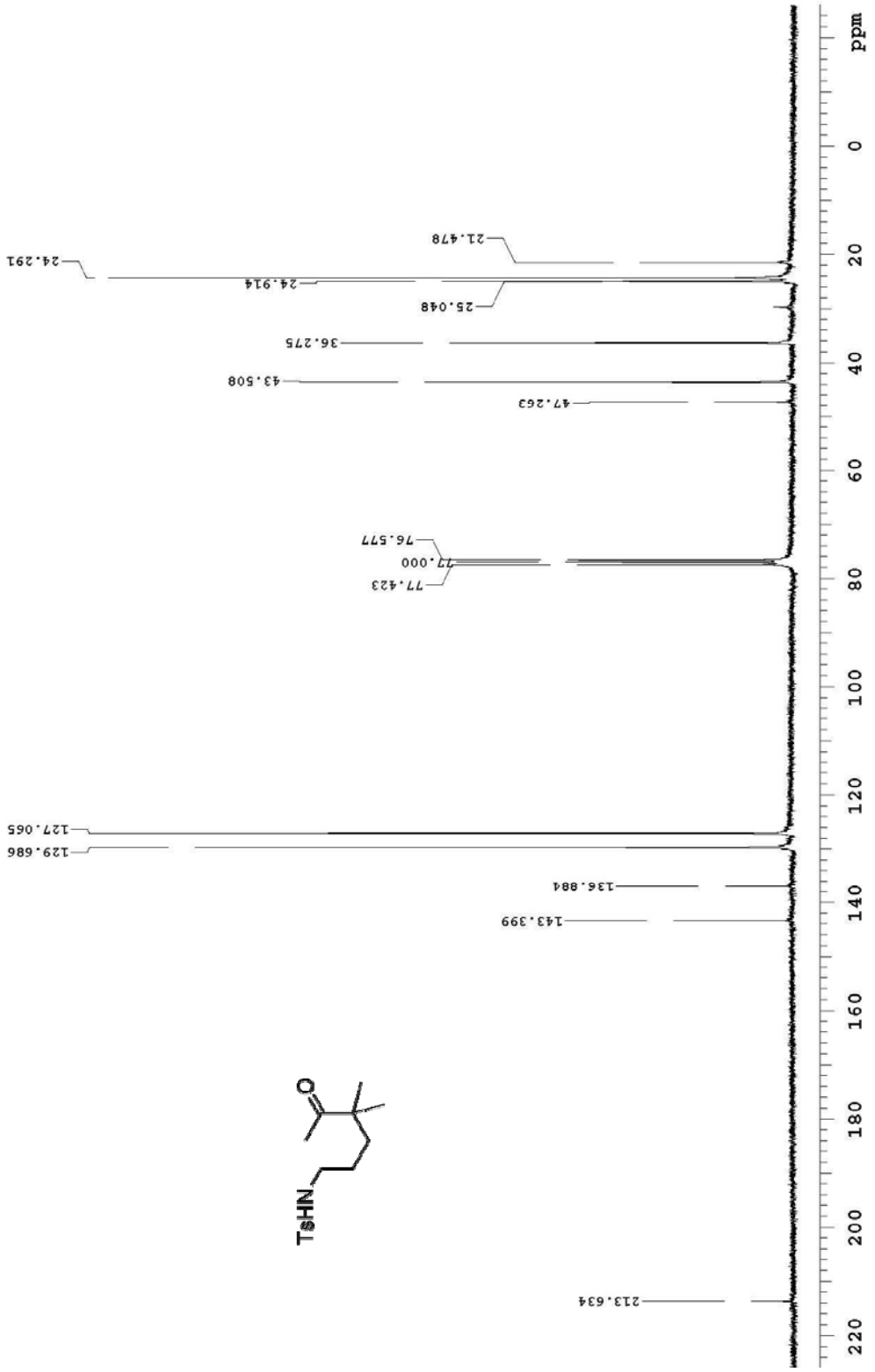
^{1}H NMR spectrum of *N*-Ts alcohol **38a**



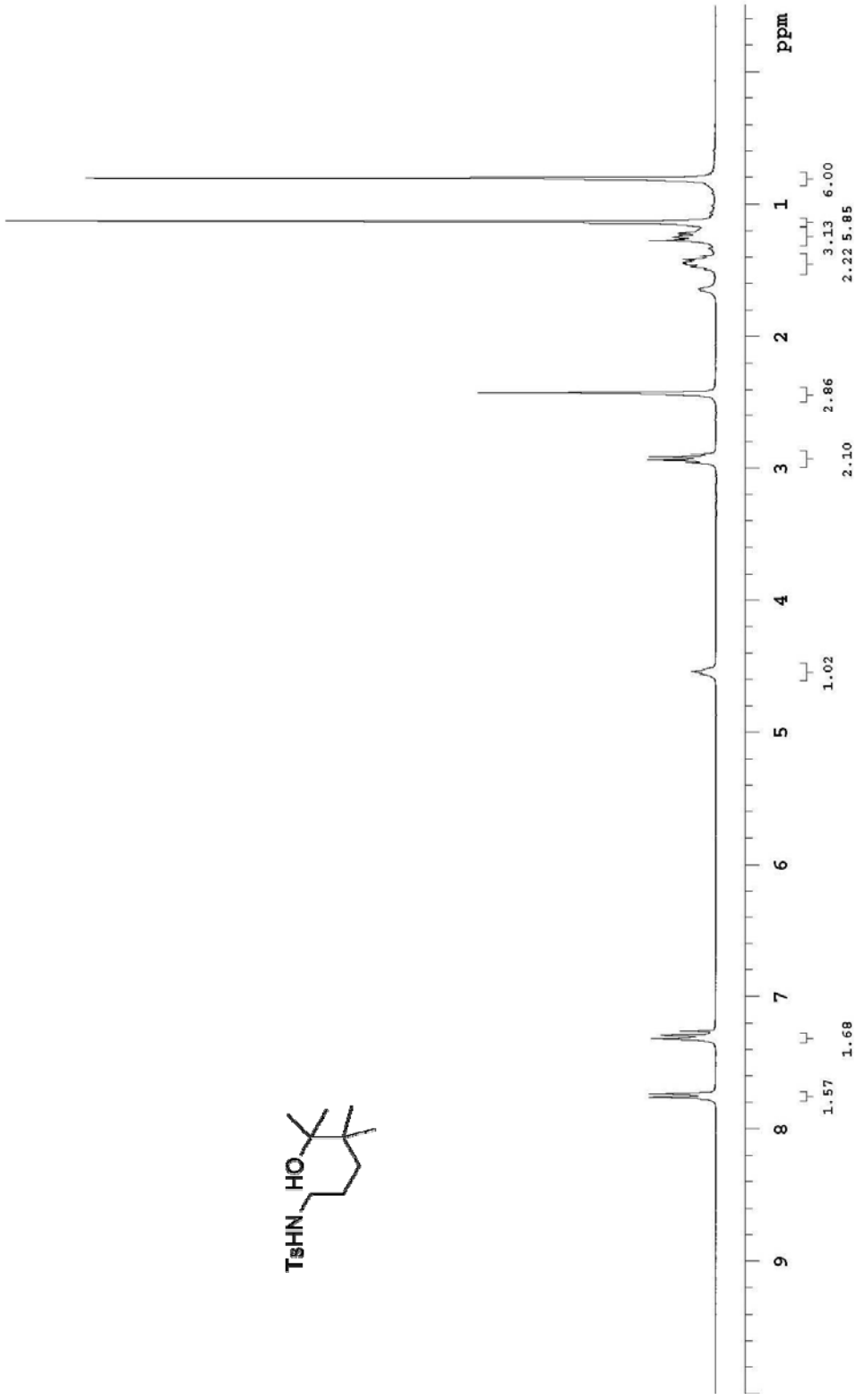
^{13}C NMR spectrum of *N*-Ts alcohol **38a**



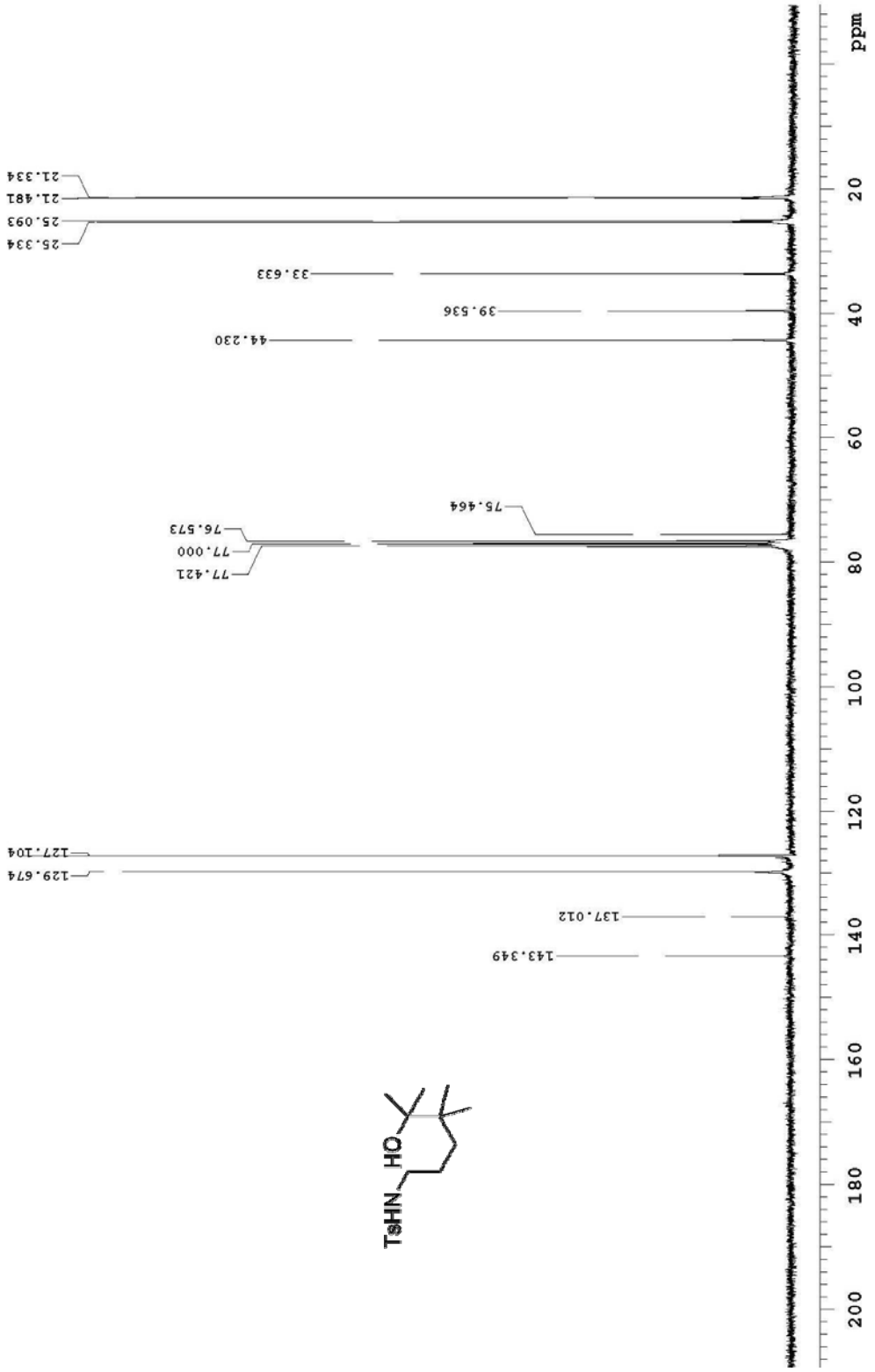
^{1}H NMR spectrum of ketone **37b**



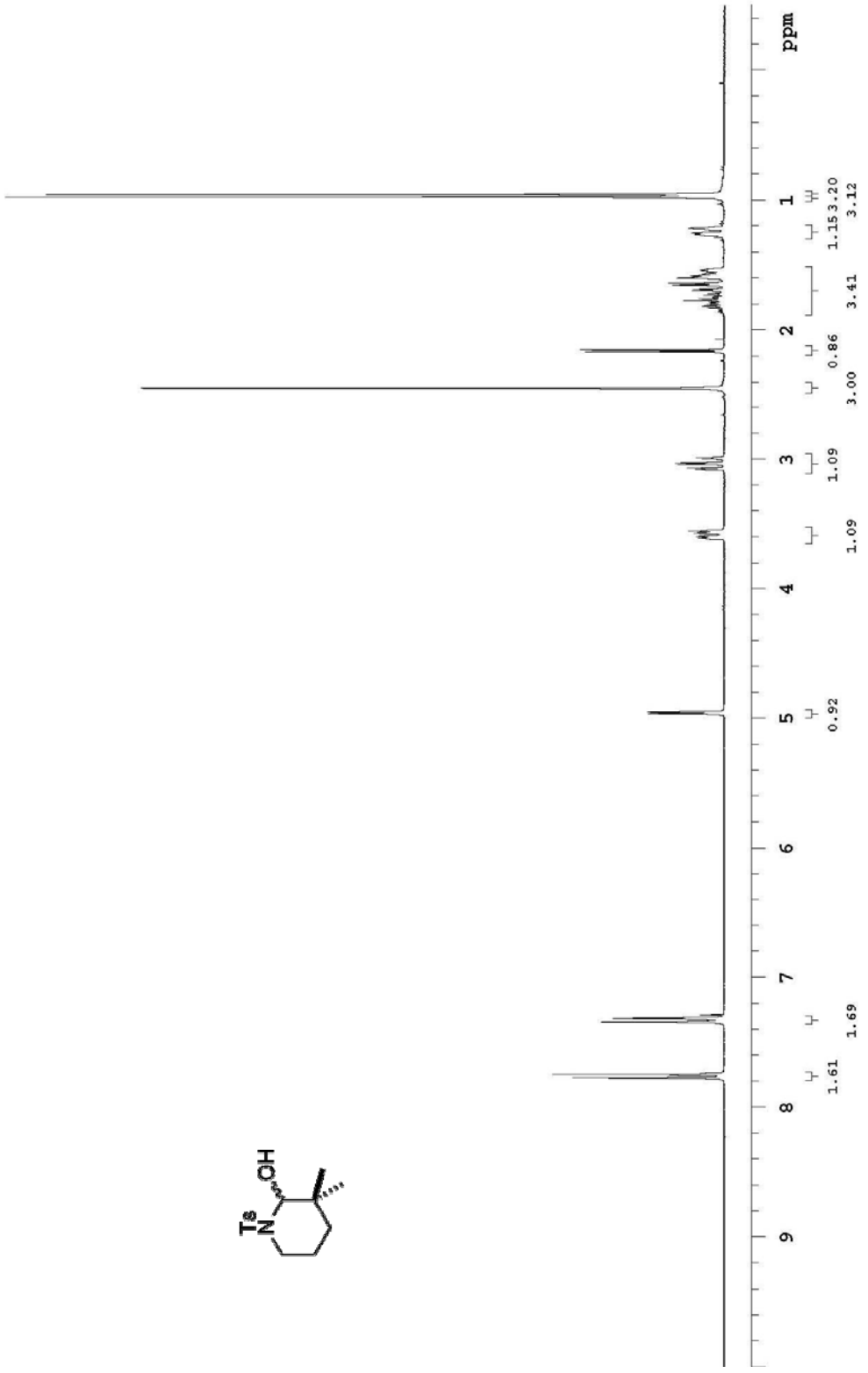
^{13}C NMR spectrum of ketone **37b**



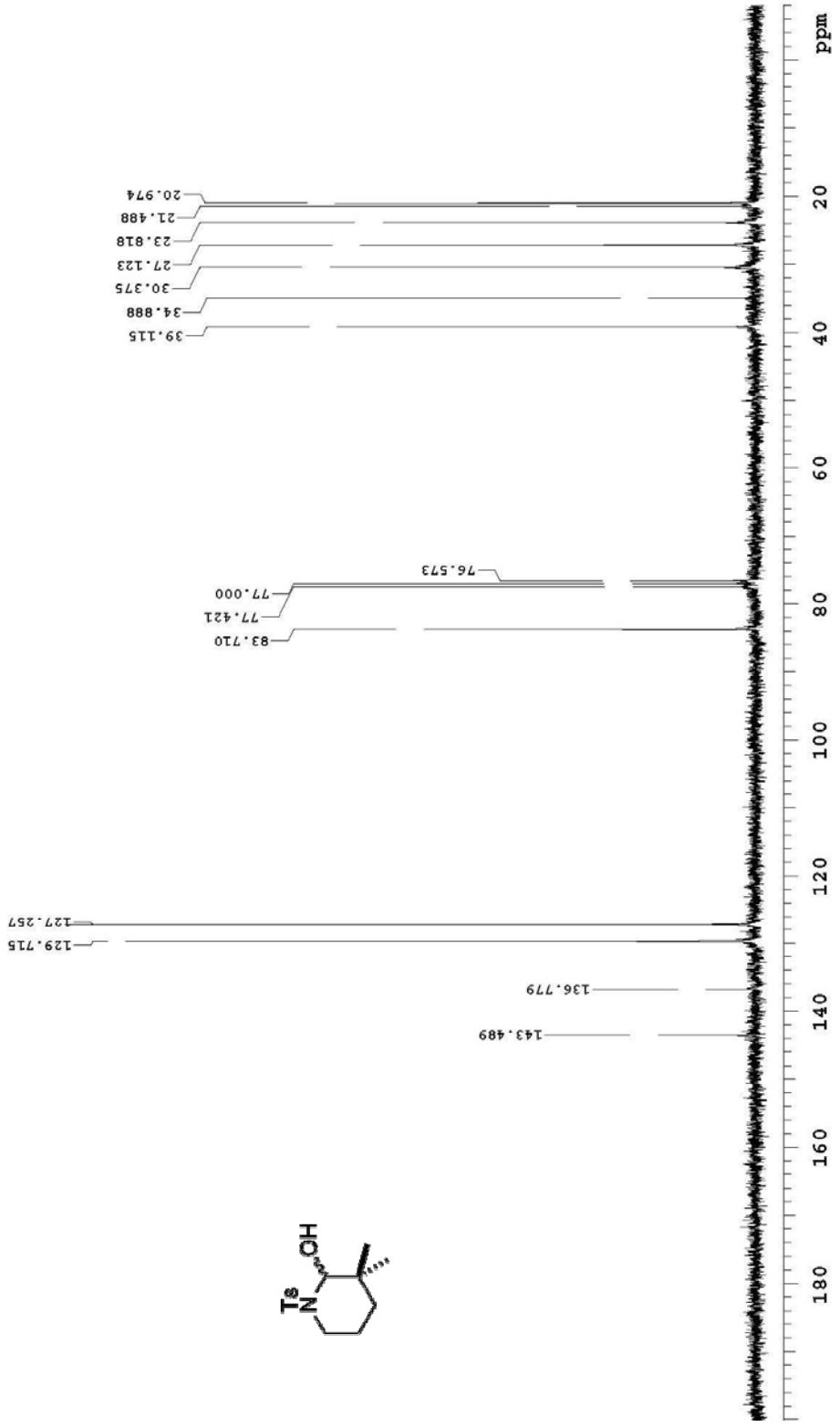
^{1}H NMR spectrum of alcohol **38b**



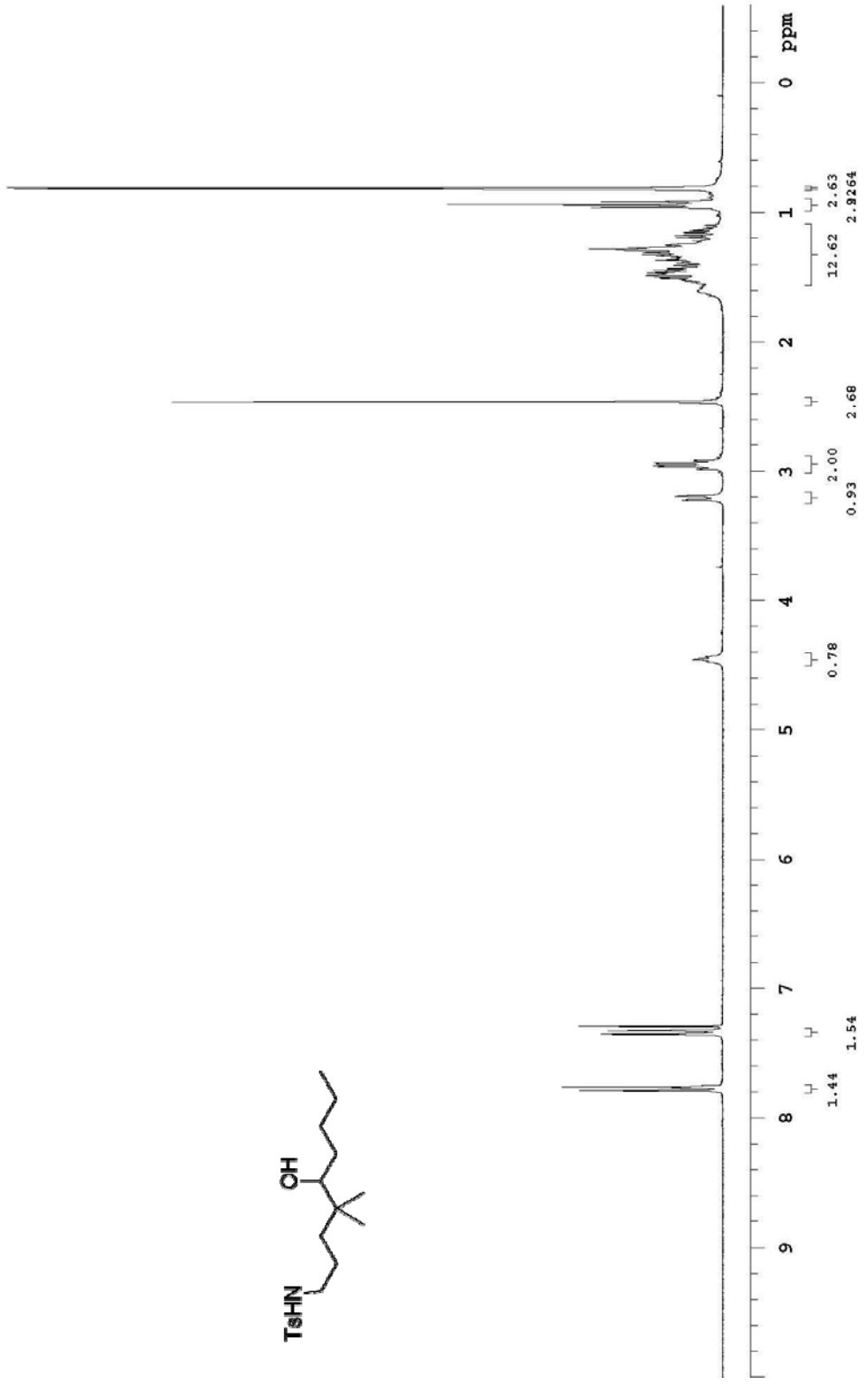
^{13}C NMR spectrum of alcohol **38b**



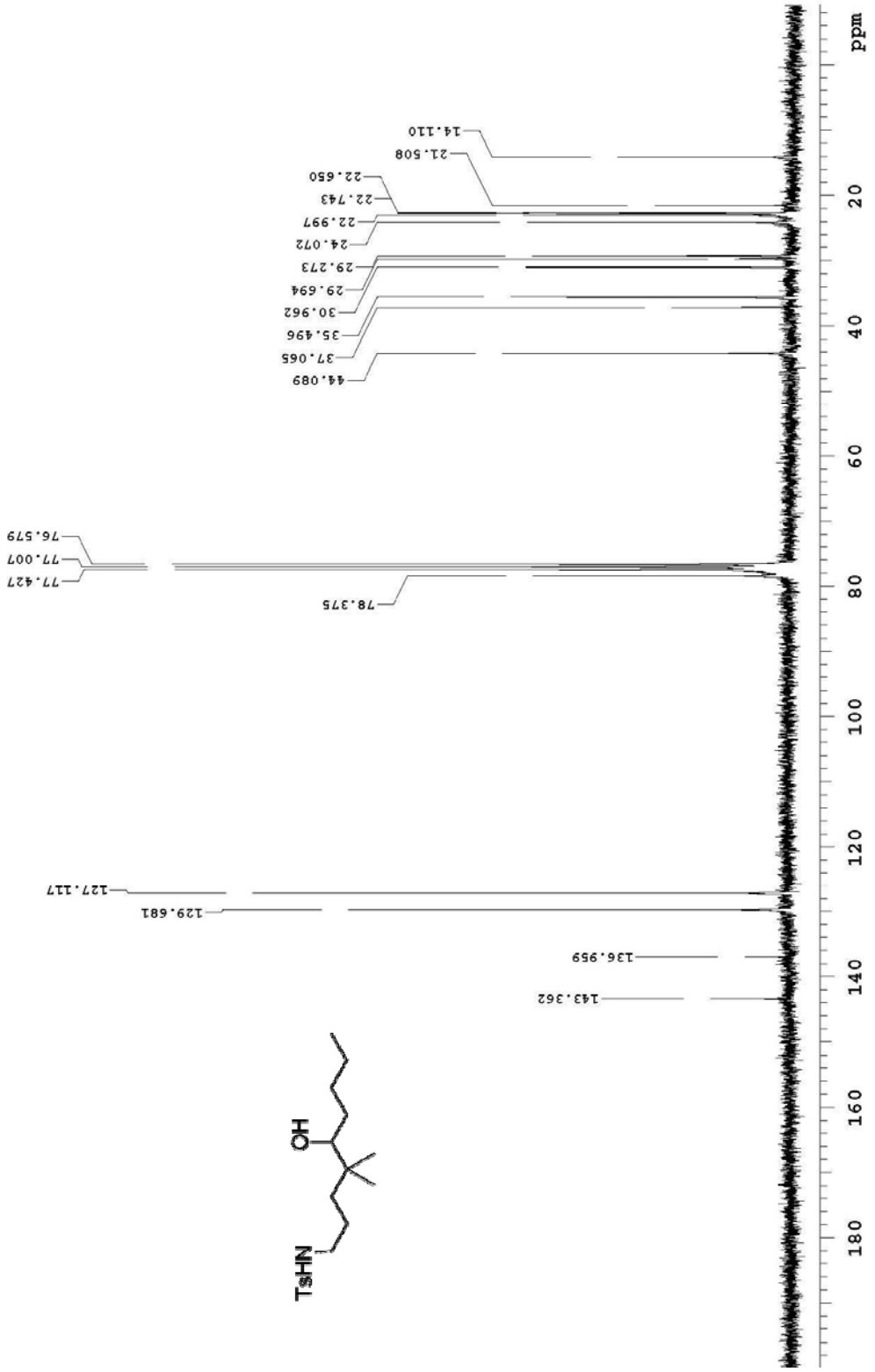
^{1}H NMR spectrum of carbinol amine **S-8**



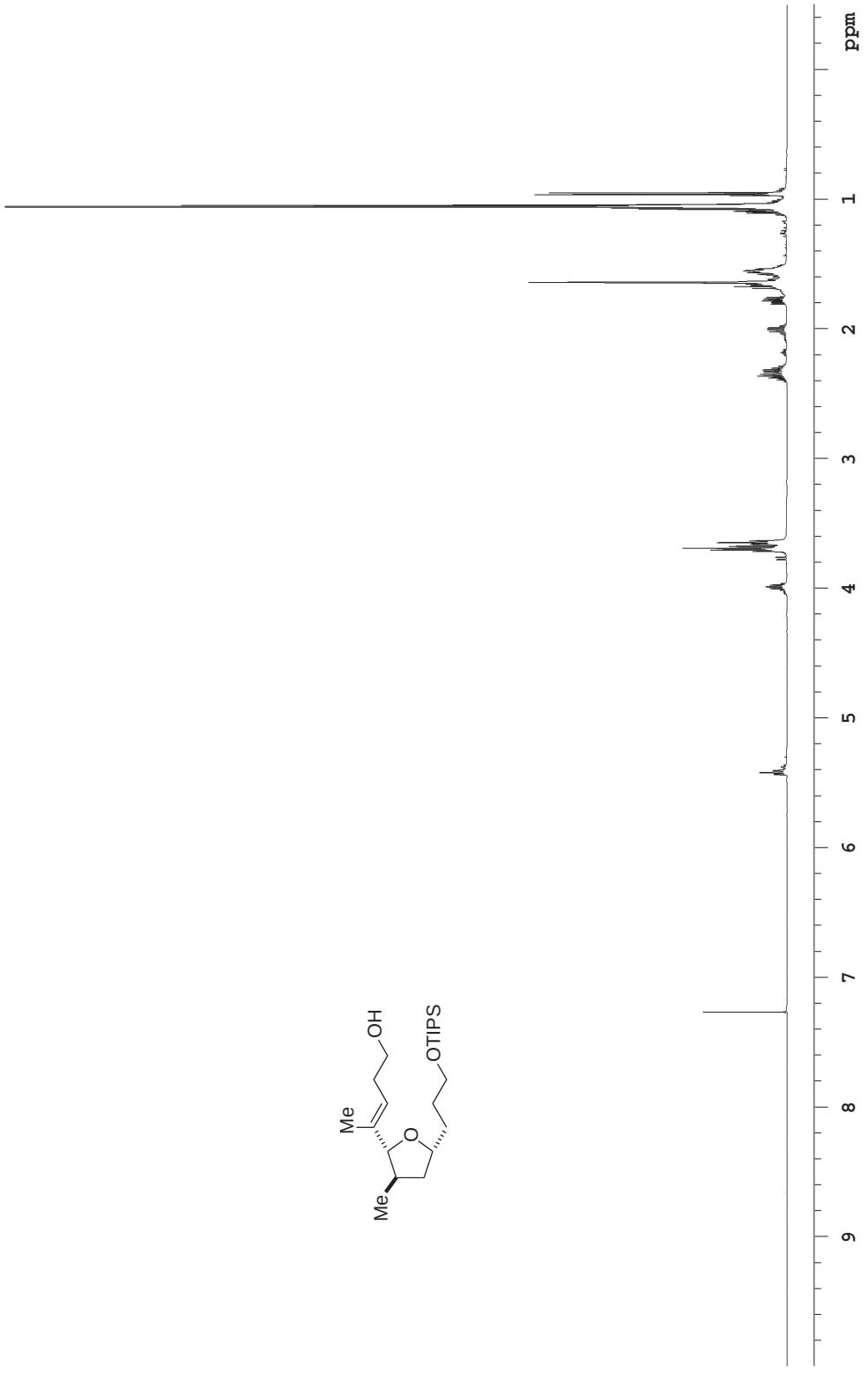
^{13}C NMR spectrum of carbinol amine **S-8**



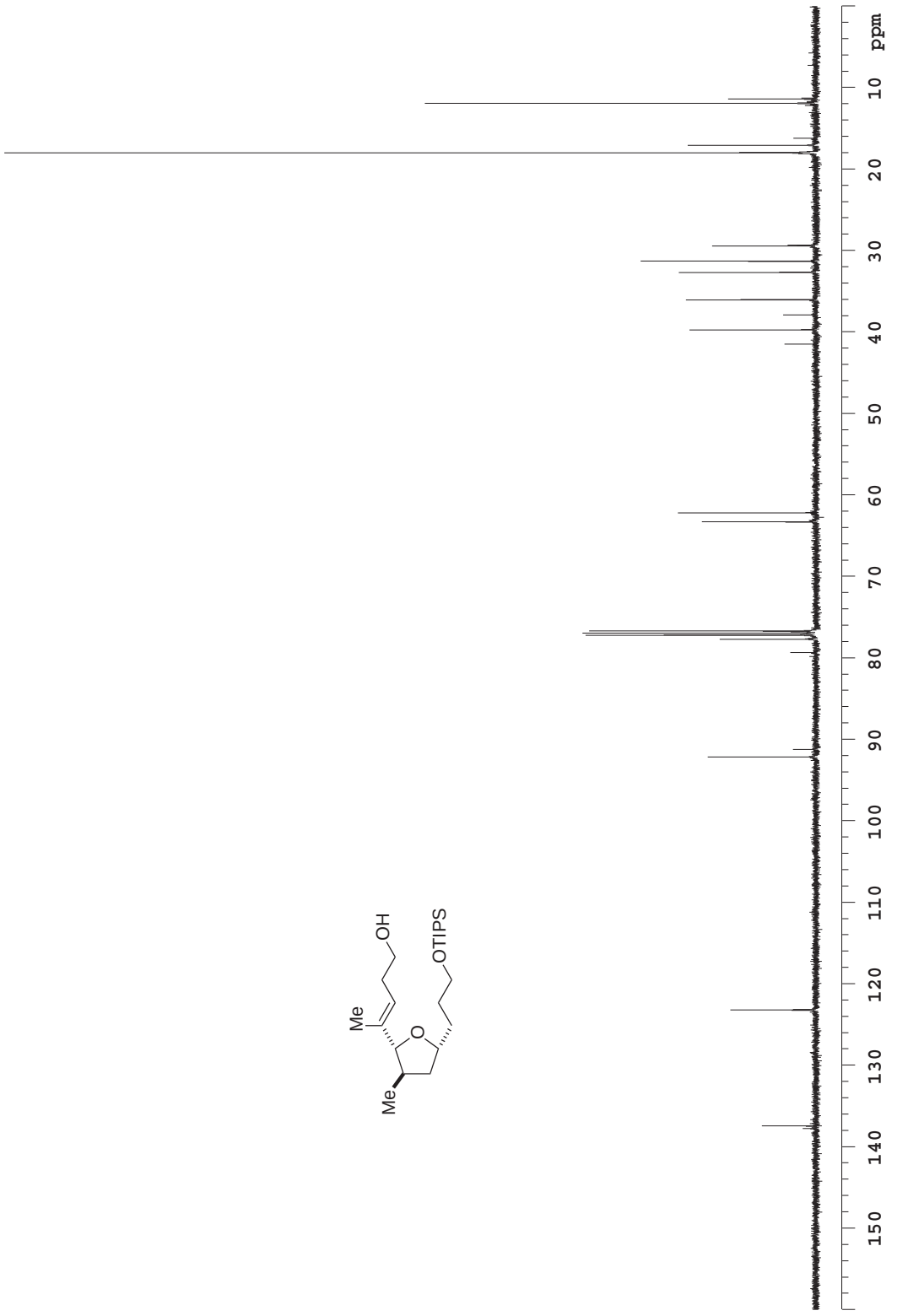
^{1}H NMR spectrum of alcohol **39**



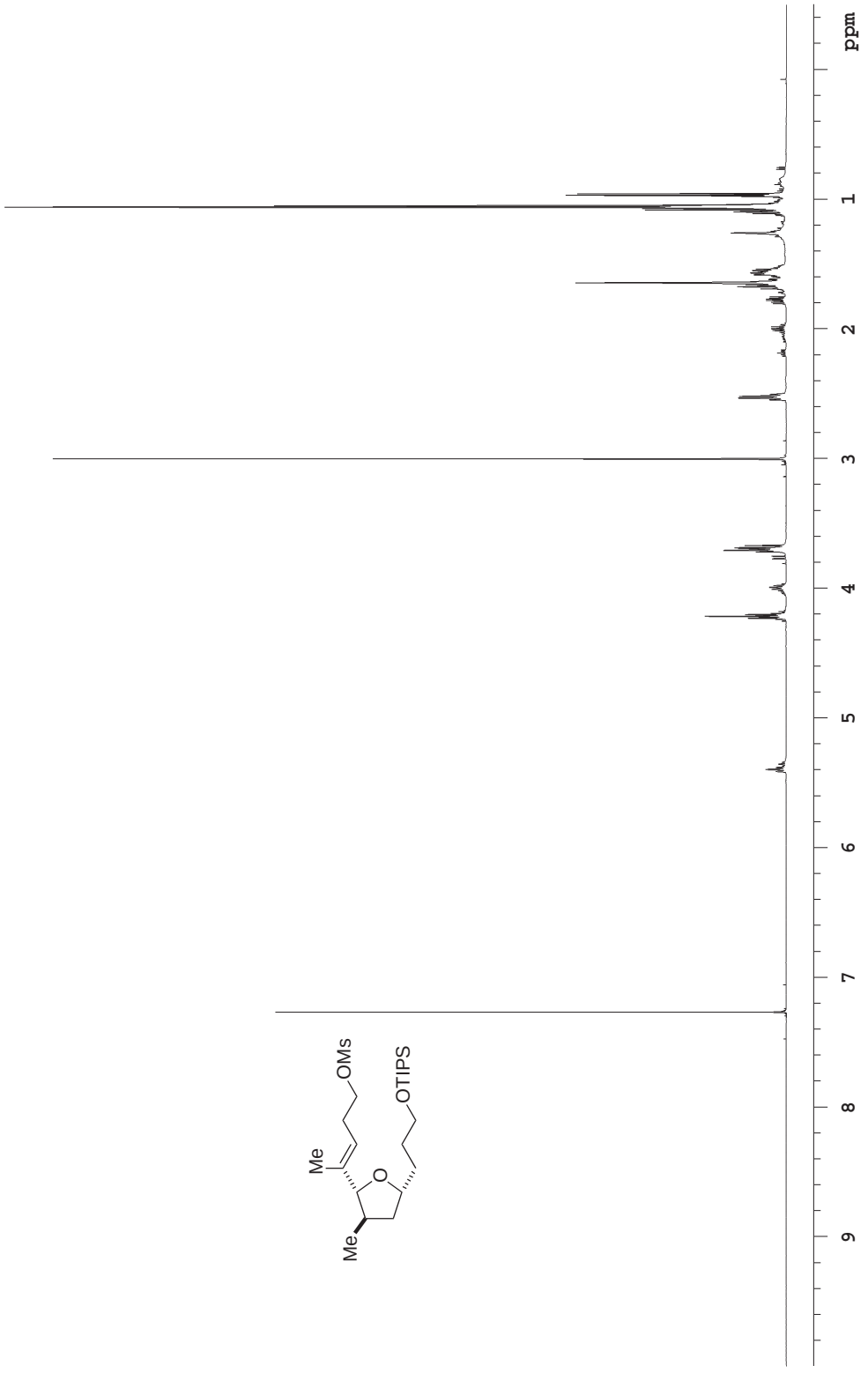
^{13}C NMR spectrum of alcohol **39**



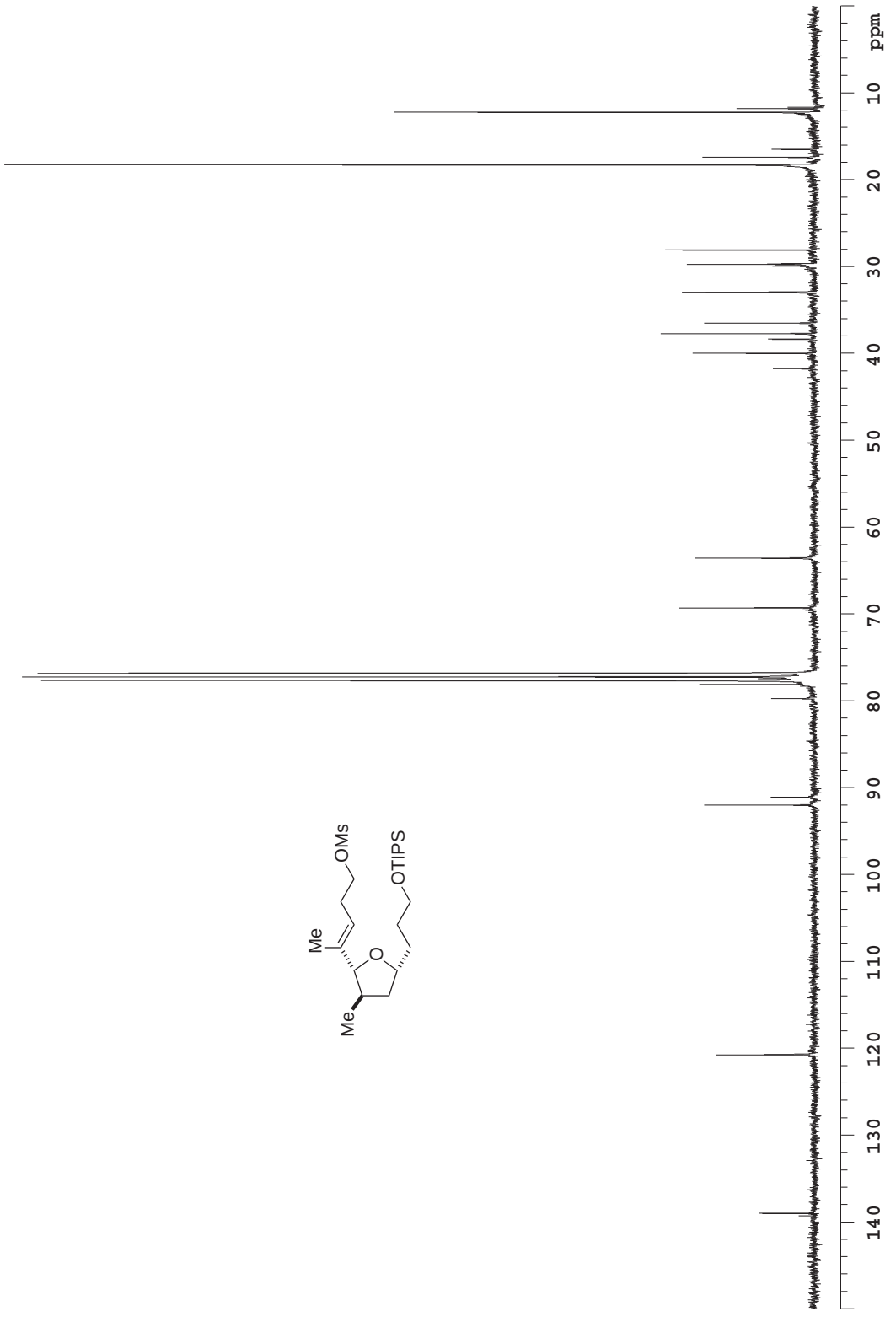
^{1}H NMR spectrum of alcohol **41a**



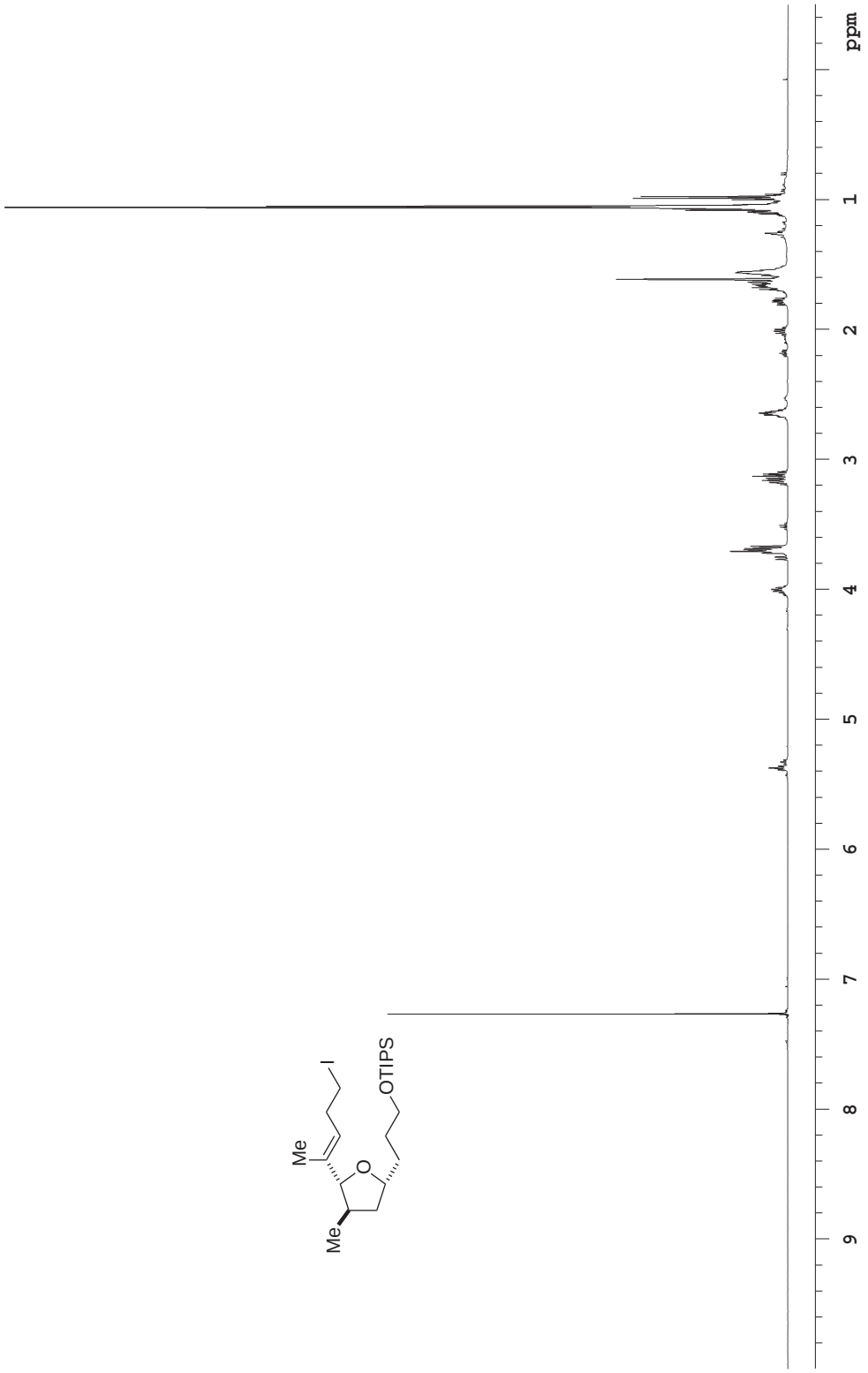
^{13}C NMR spectrum of alcohol **41a**



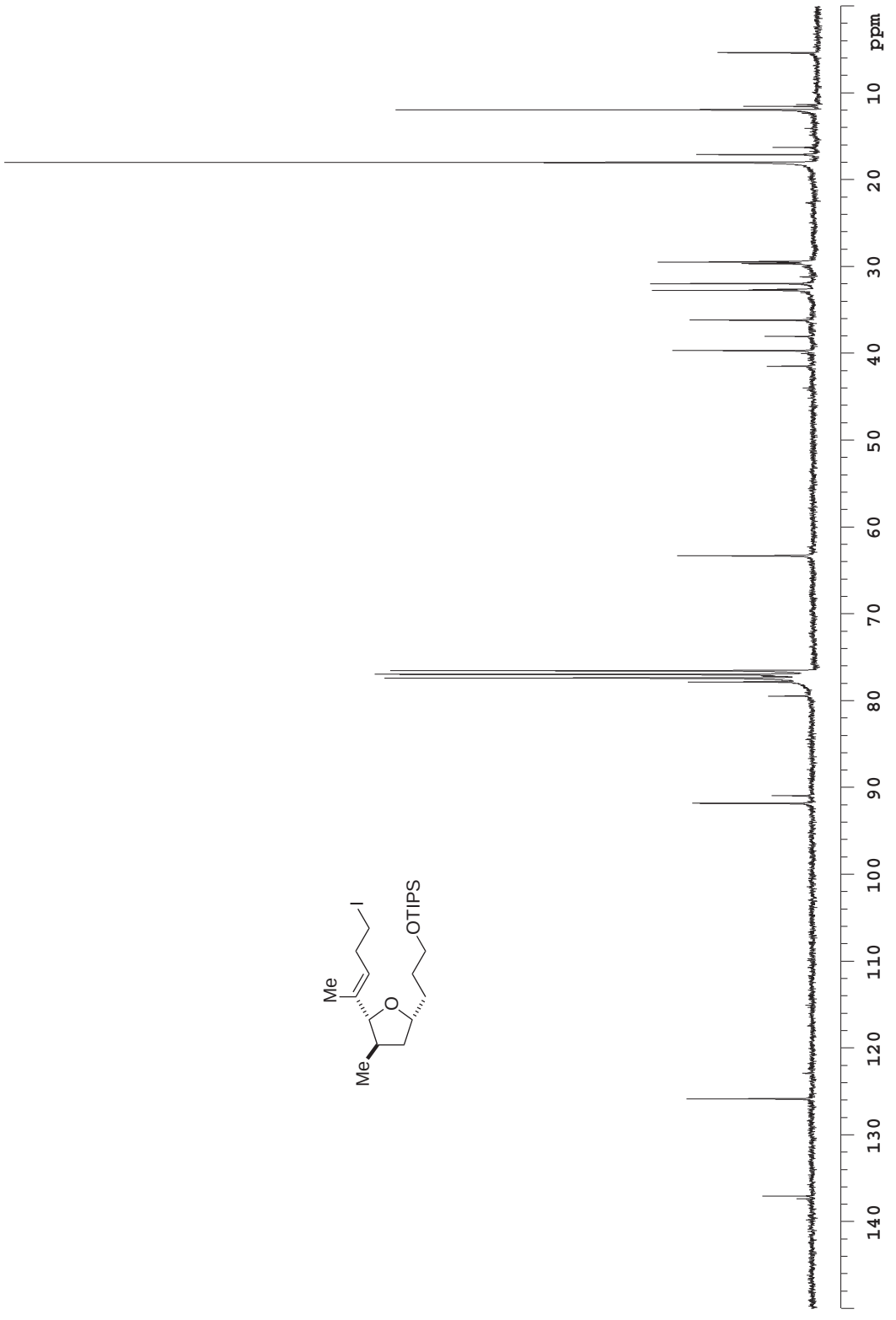
^{1}H NMR spectrum of mesylate **41b**



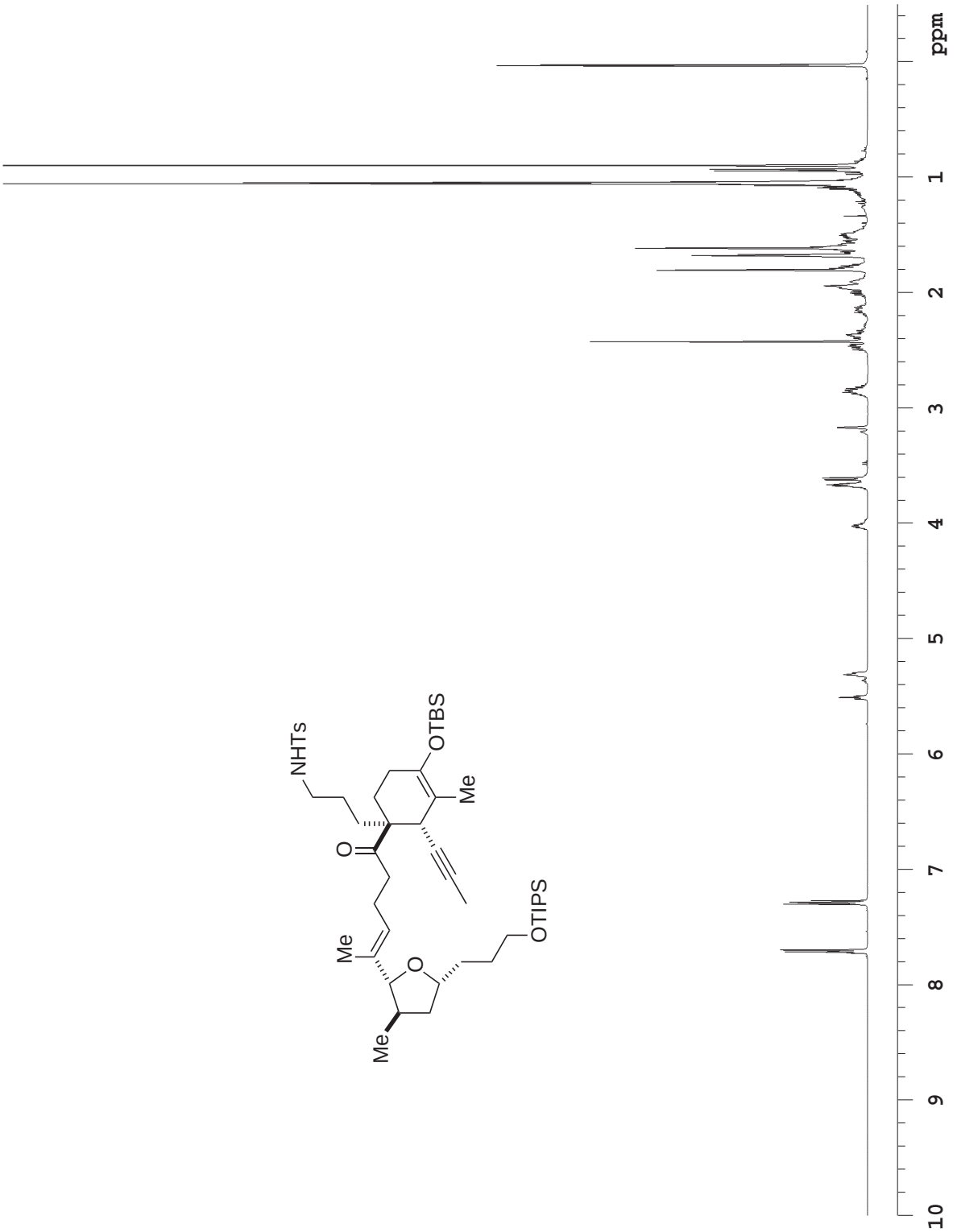
^{13}C NMR spectrum of mesylate **41b**



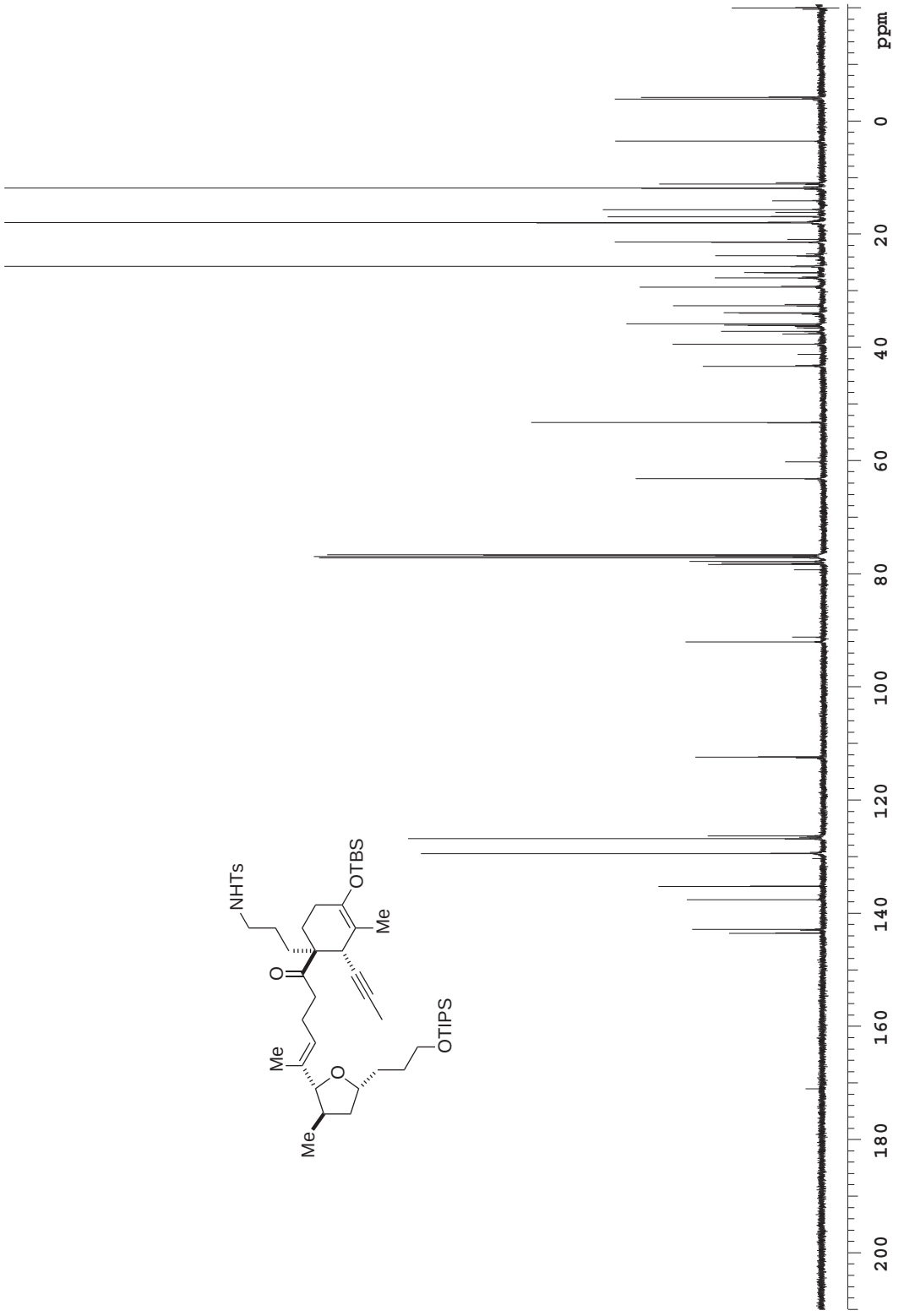
^{1}H NMR spectrum of alkyl iodide **42**



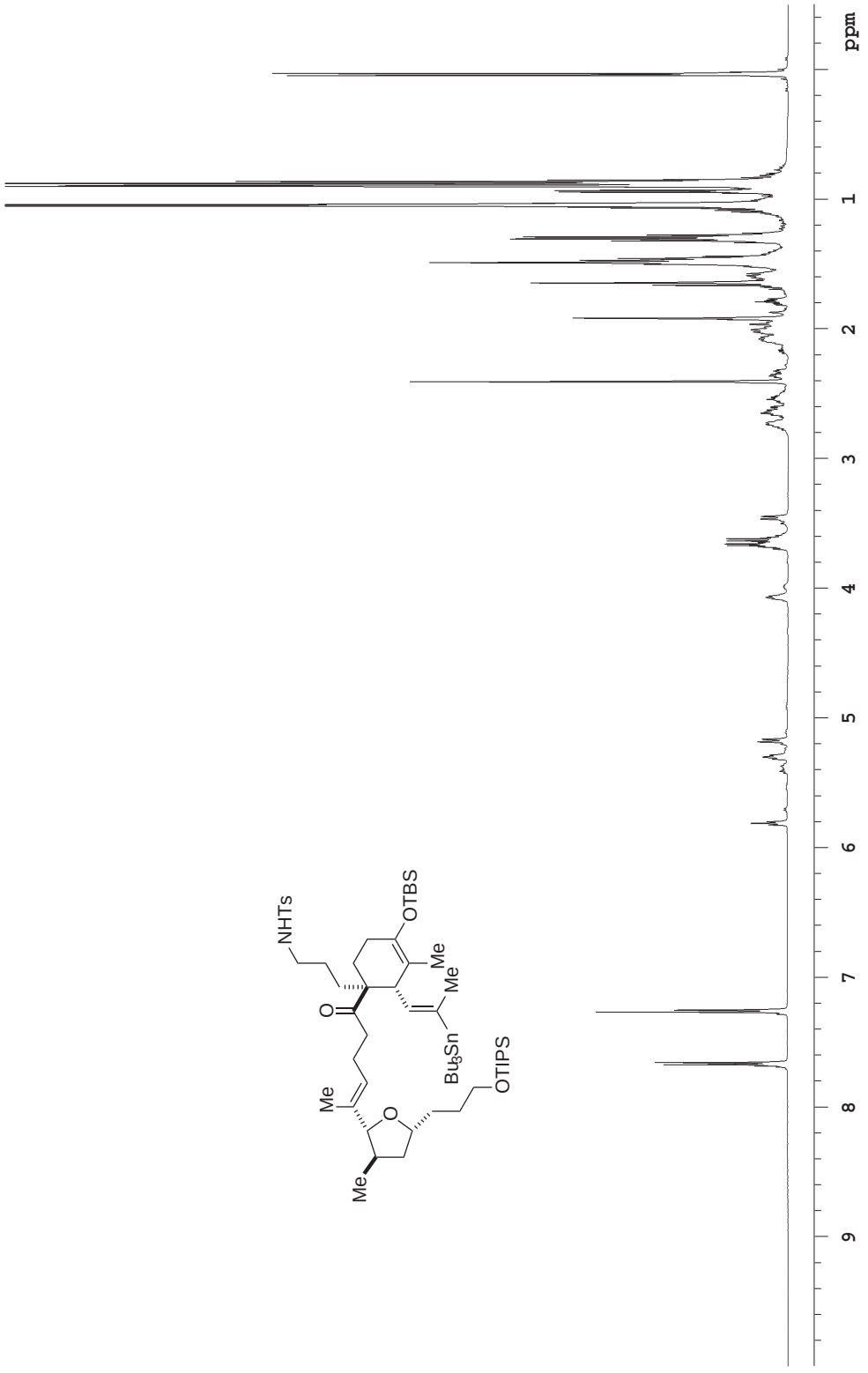
^{13}C NMR spectrum of alkyl iodide **42**



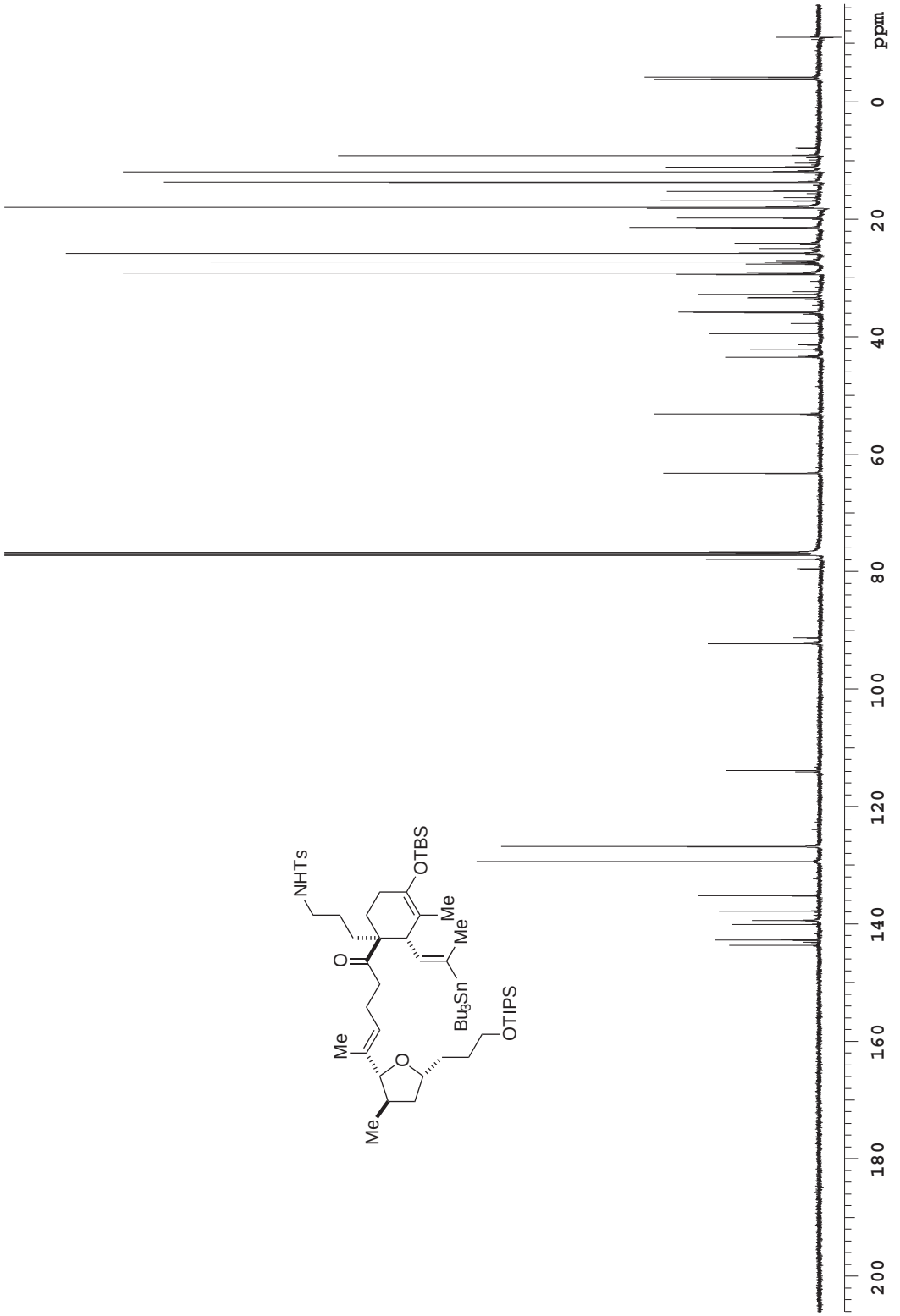
^{1}H NMR spectrum of amino ketone **43**



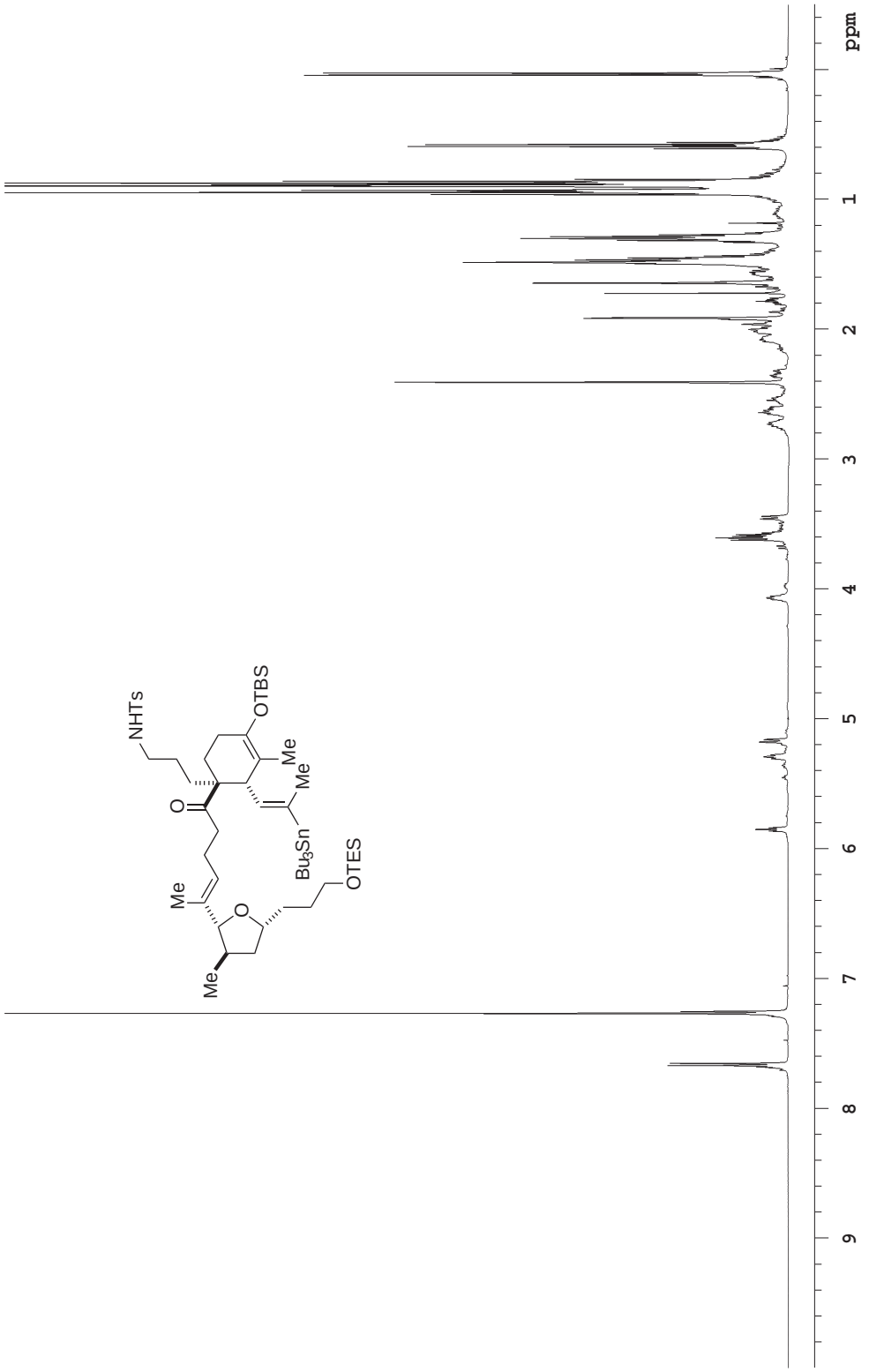
^{13}C NMR spectrum of amino ketone **43**



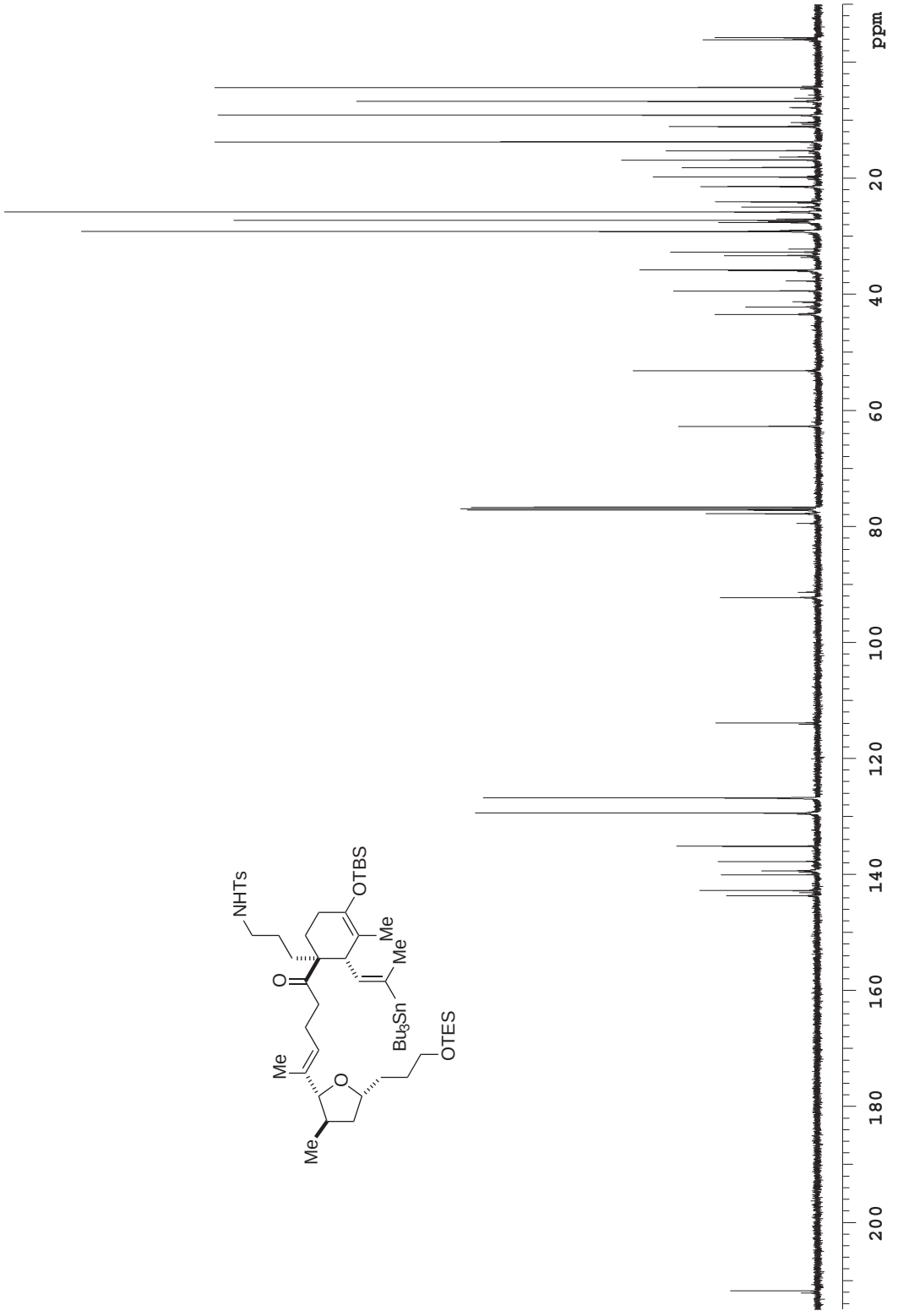
^{1}H NMR spectrum of vinyl stannane **44a**



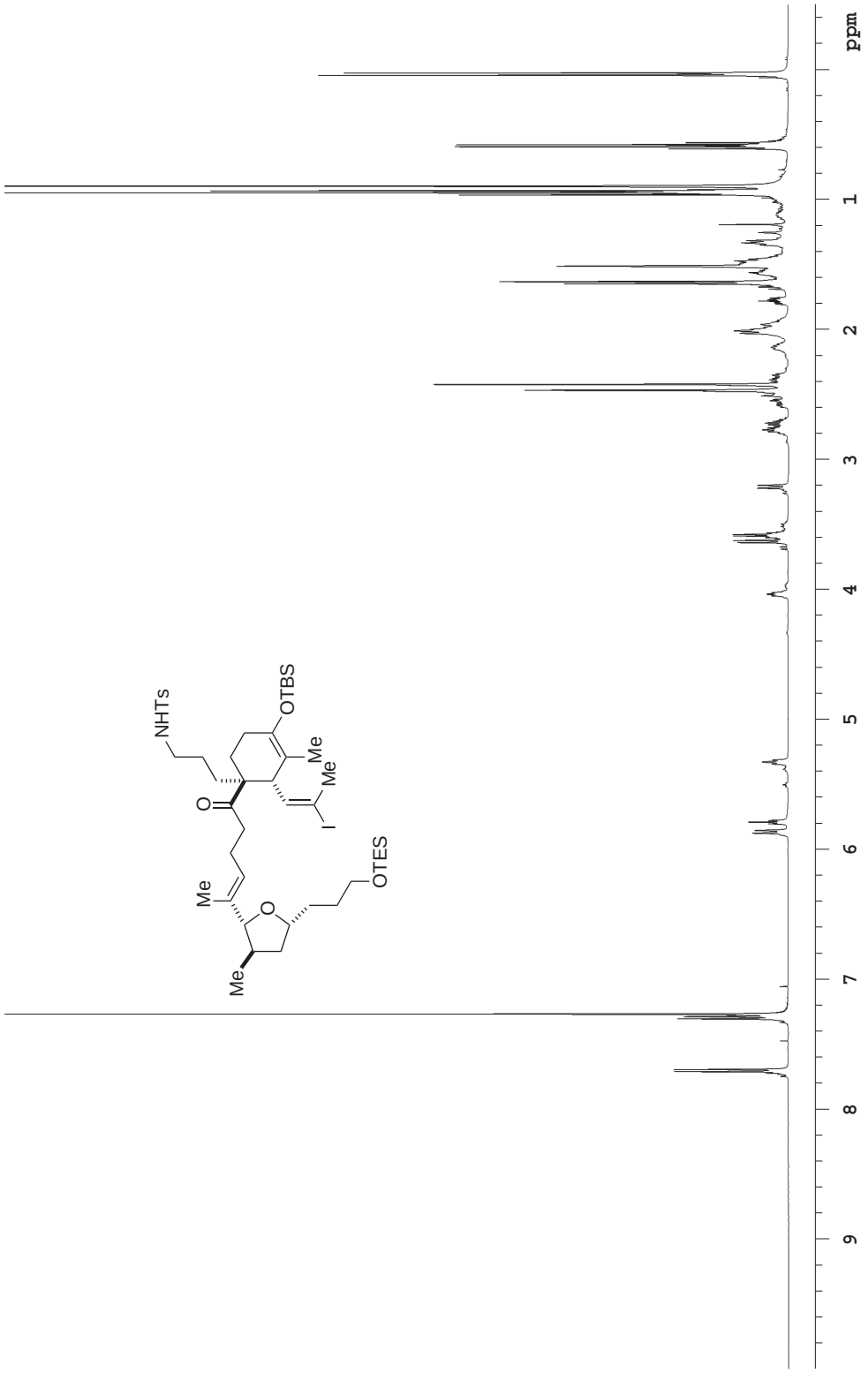
^{13}C NMR spectrum of vinyl stannane **44a**



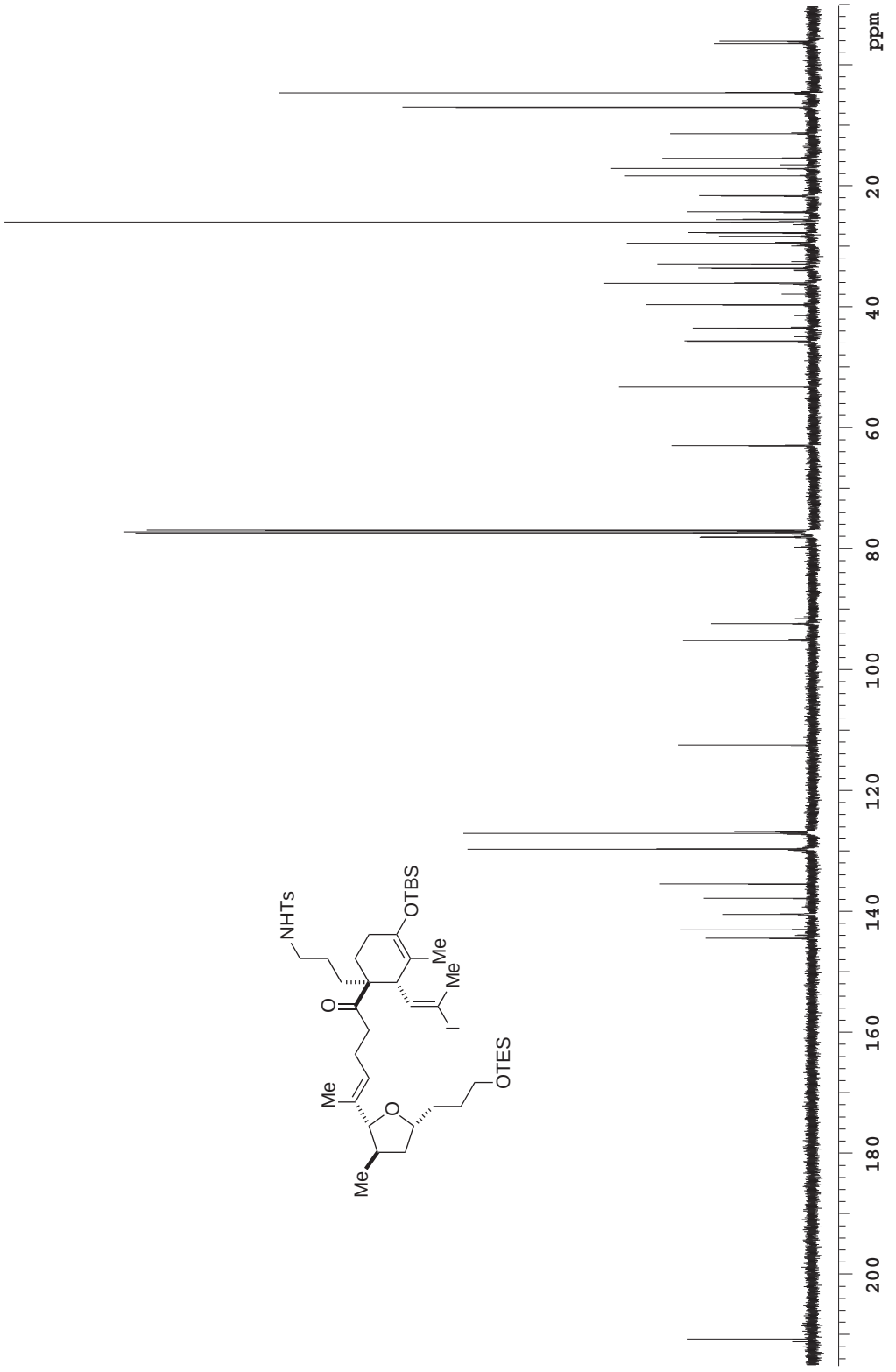
^{1}H NMR spectrum of vinyl stannanne **S-10**



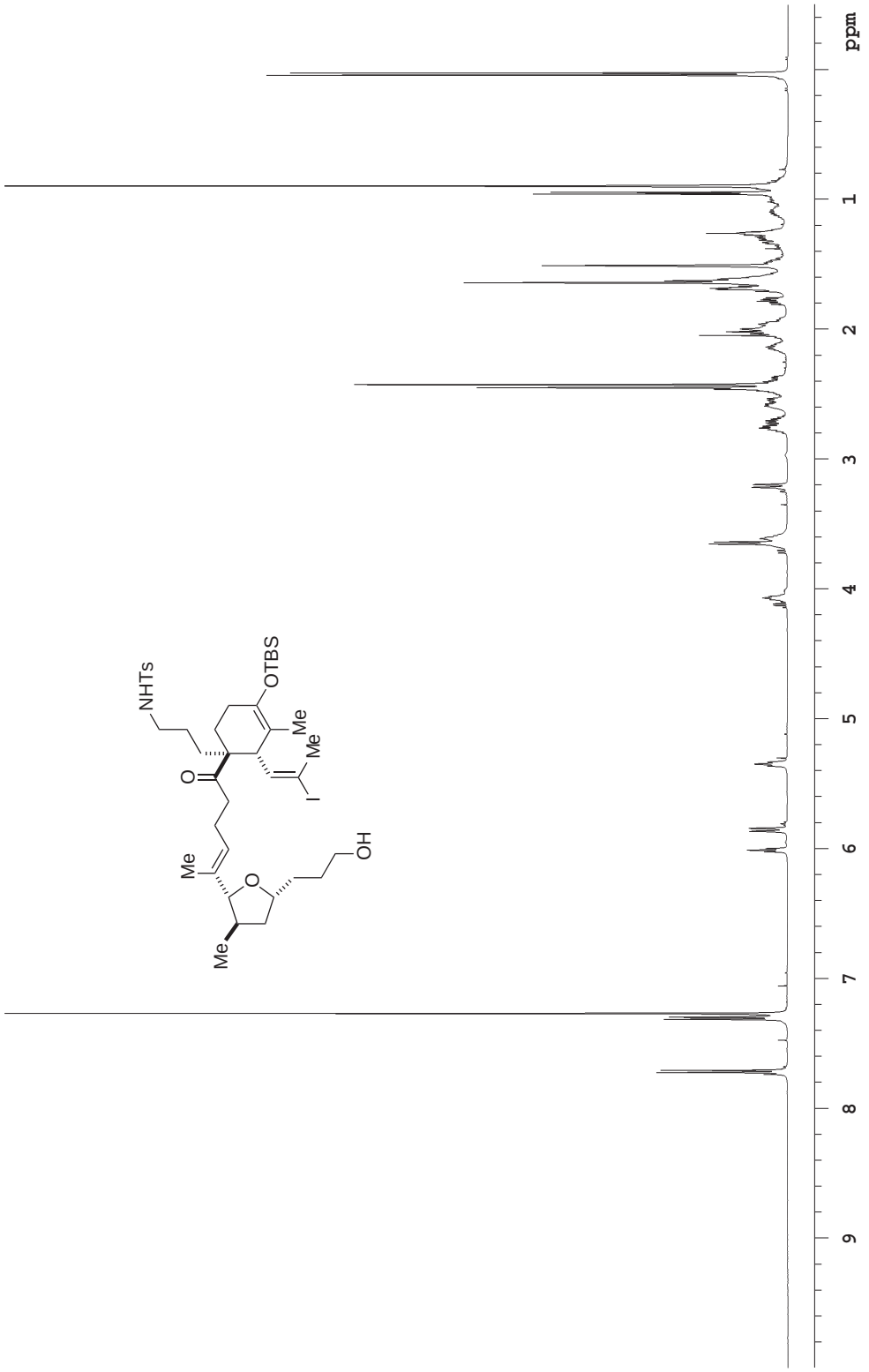
^{13}C NMR spectrum of vinyl stannane **S-10**



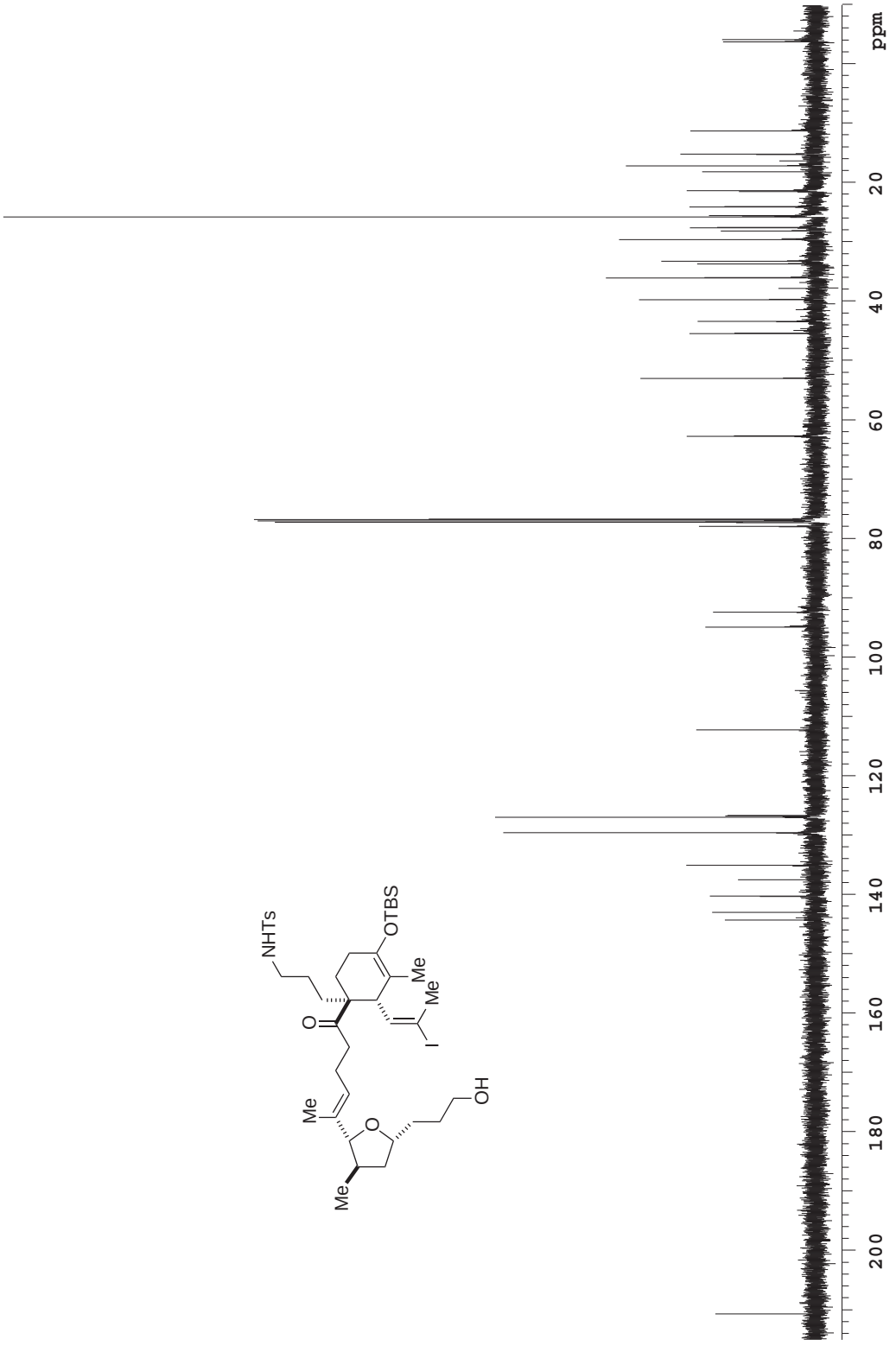
^{1}H NMR spectrum of vinyl iodide **48**



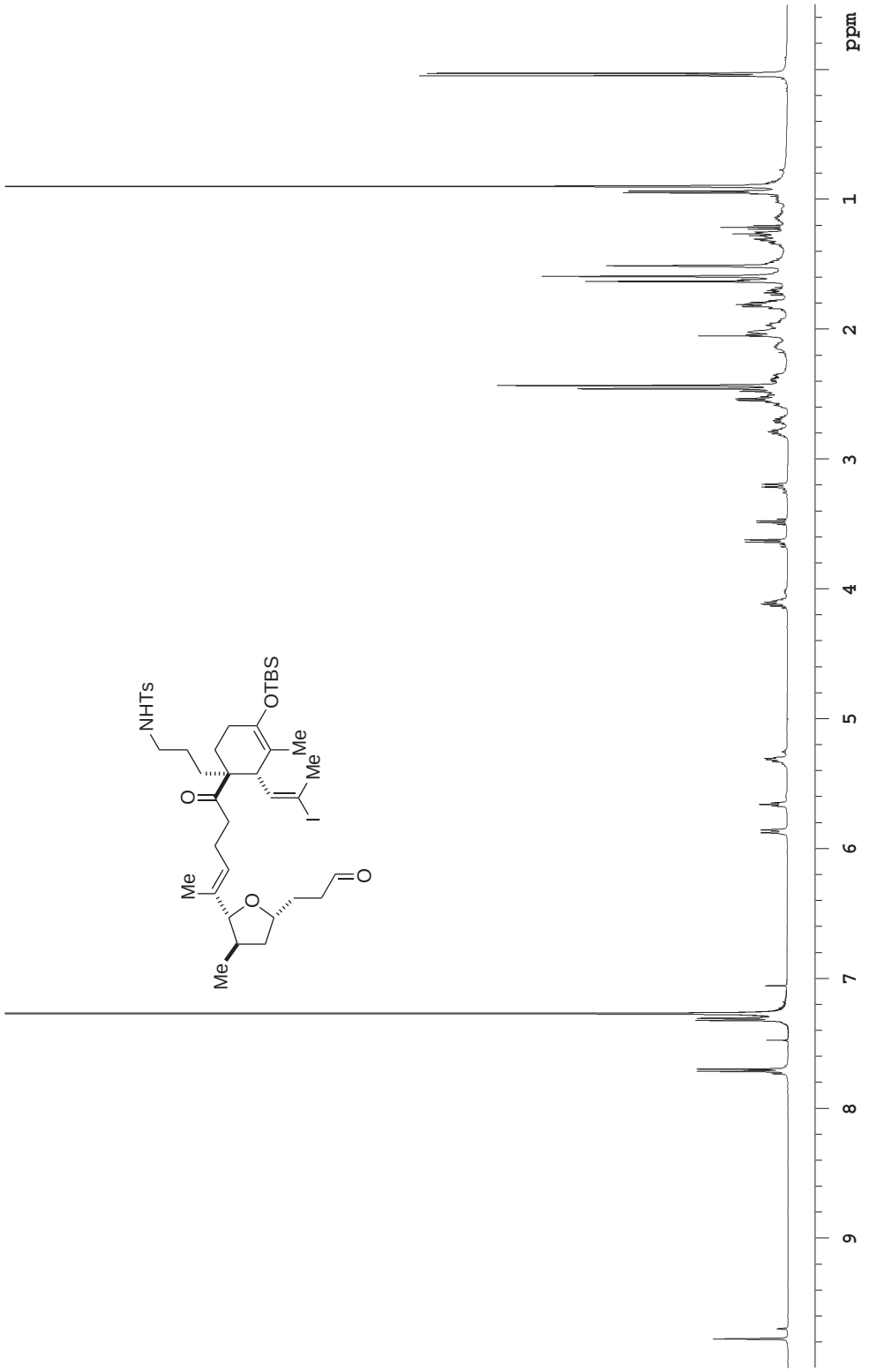
^{13}C NMR spectrum of vinyl iodide **48**



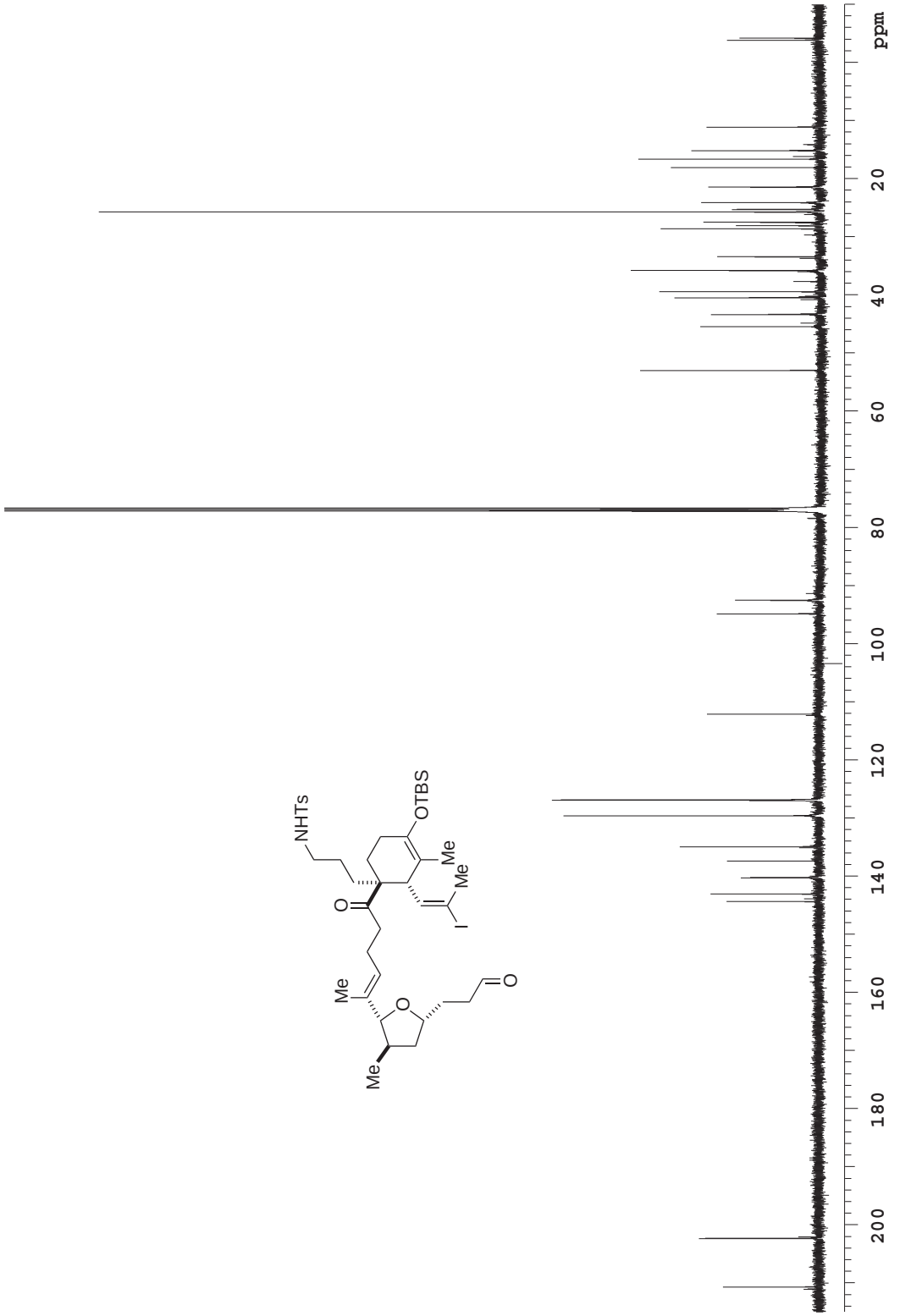
^{1}H NMR spectrum of alcohol **49**



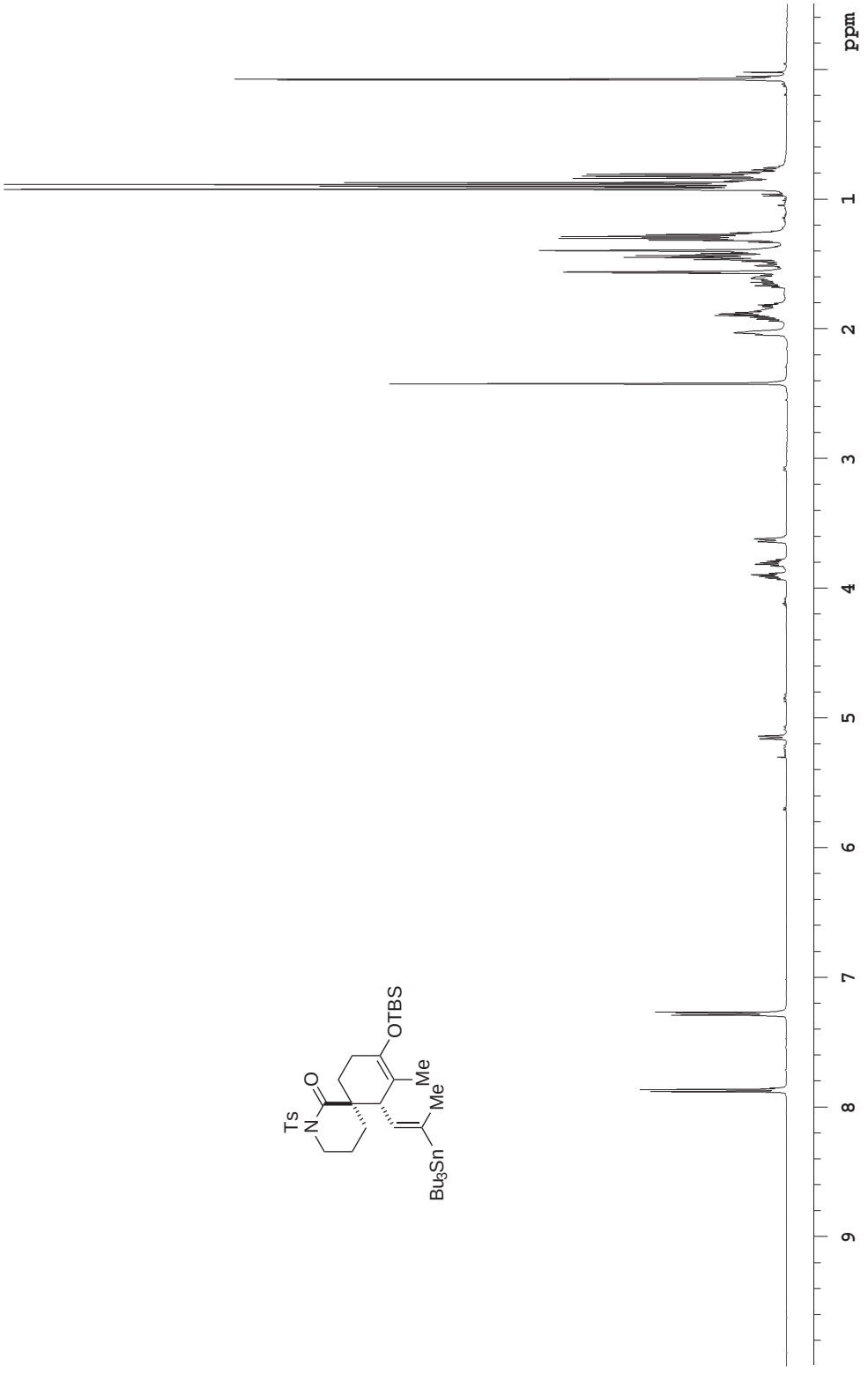
^{13}C NMR spectrum of alcohol **49**



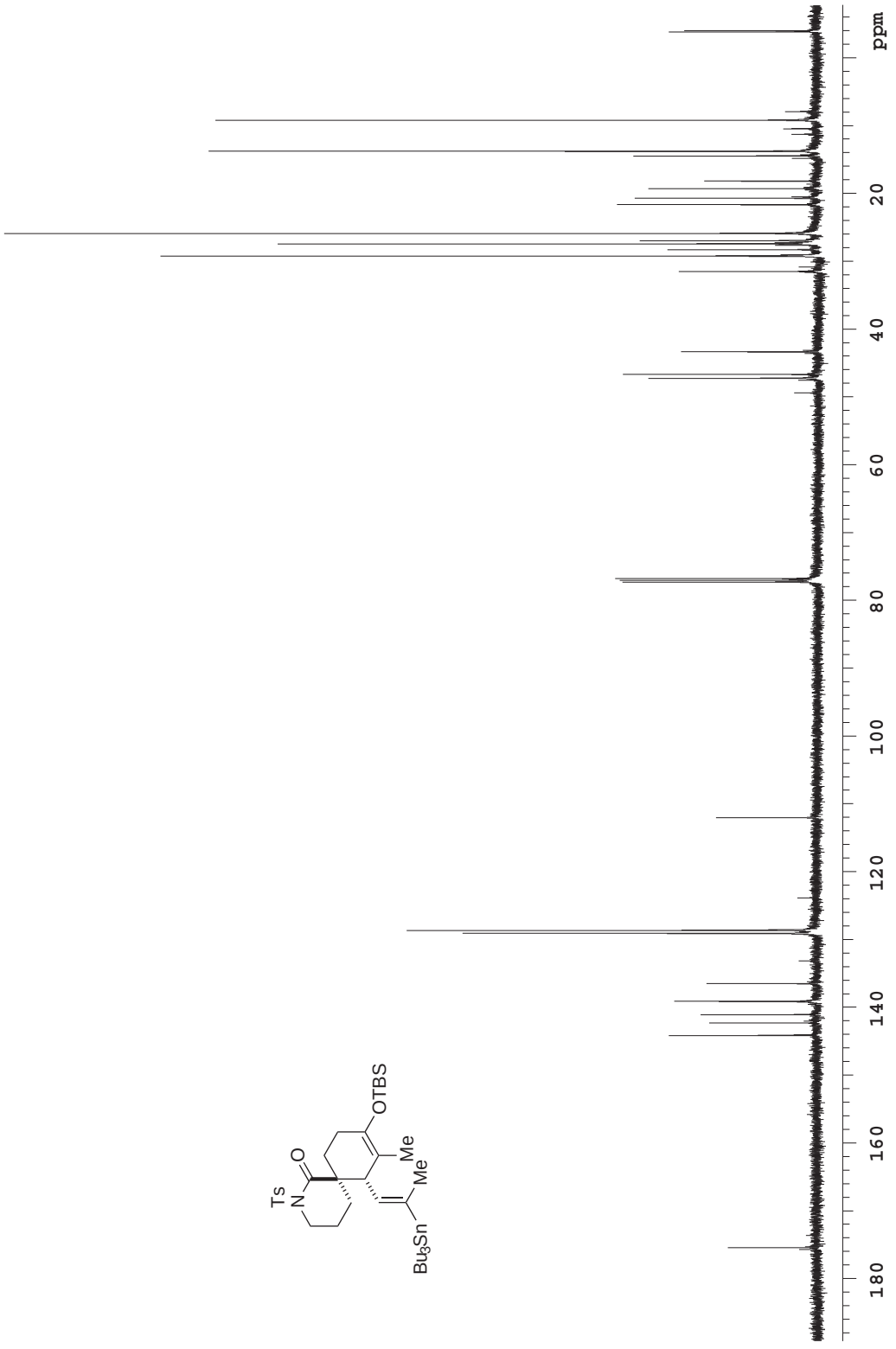
^{1}H NMR spectrum of aldehyde **50**



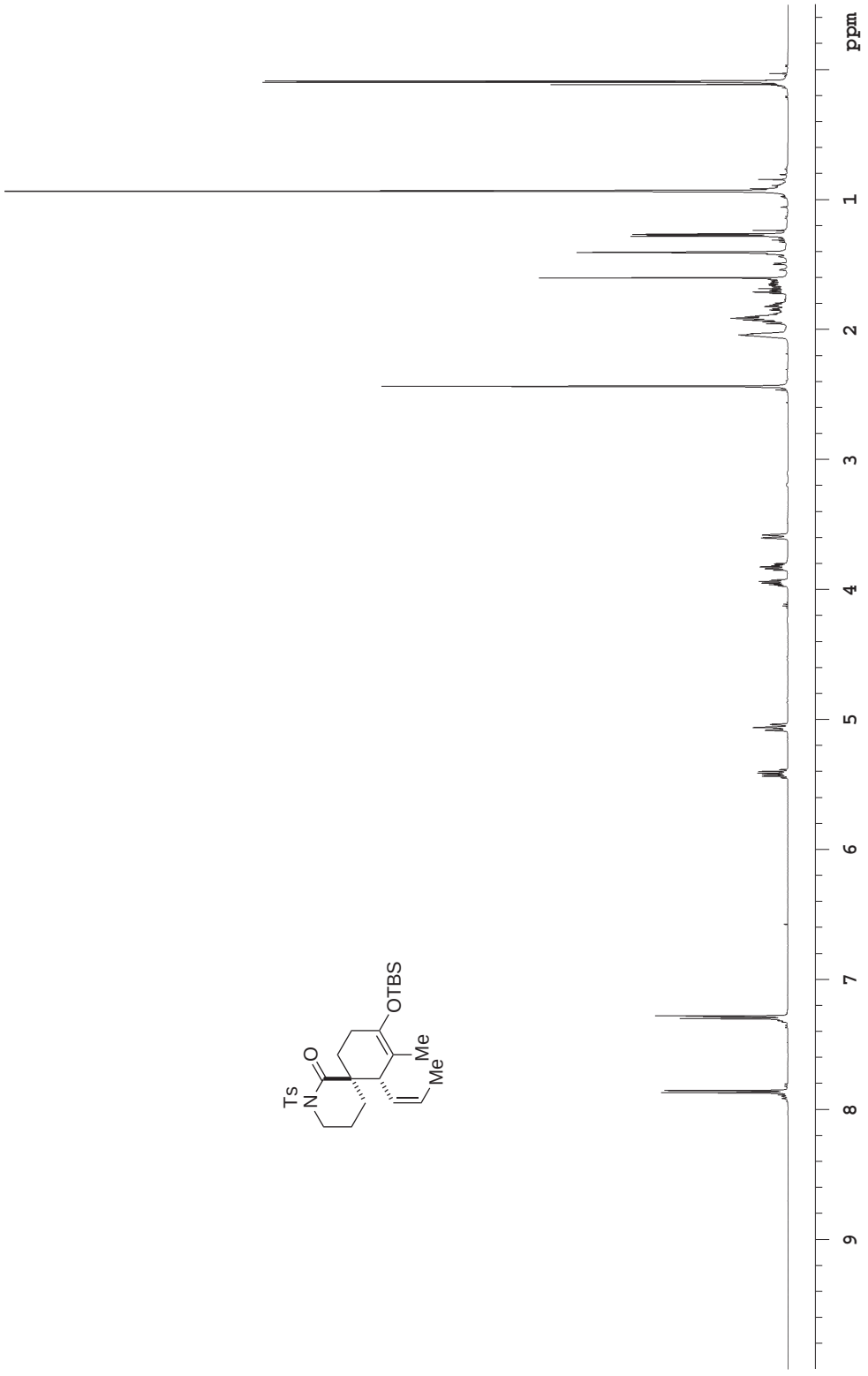
^{13}C NMR spectrum of aldehyde **50**



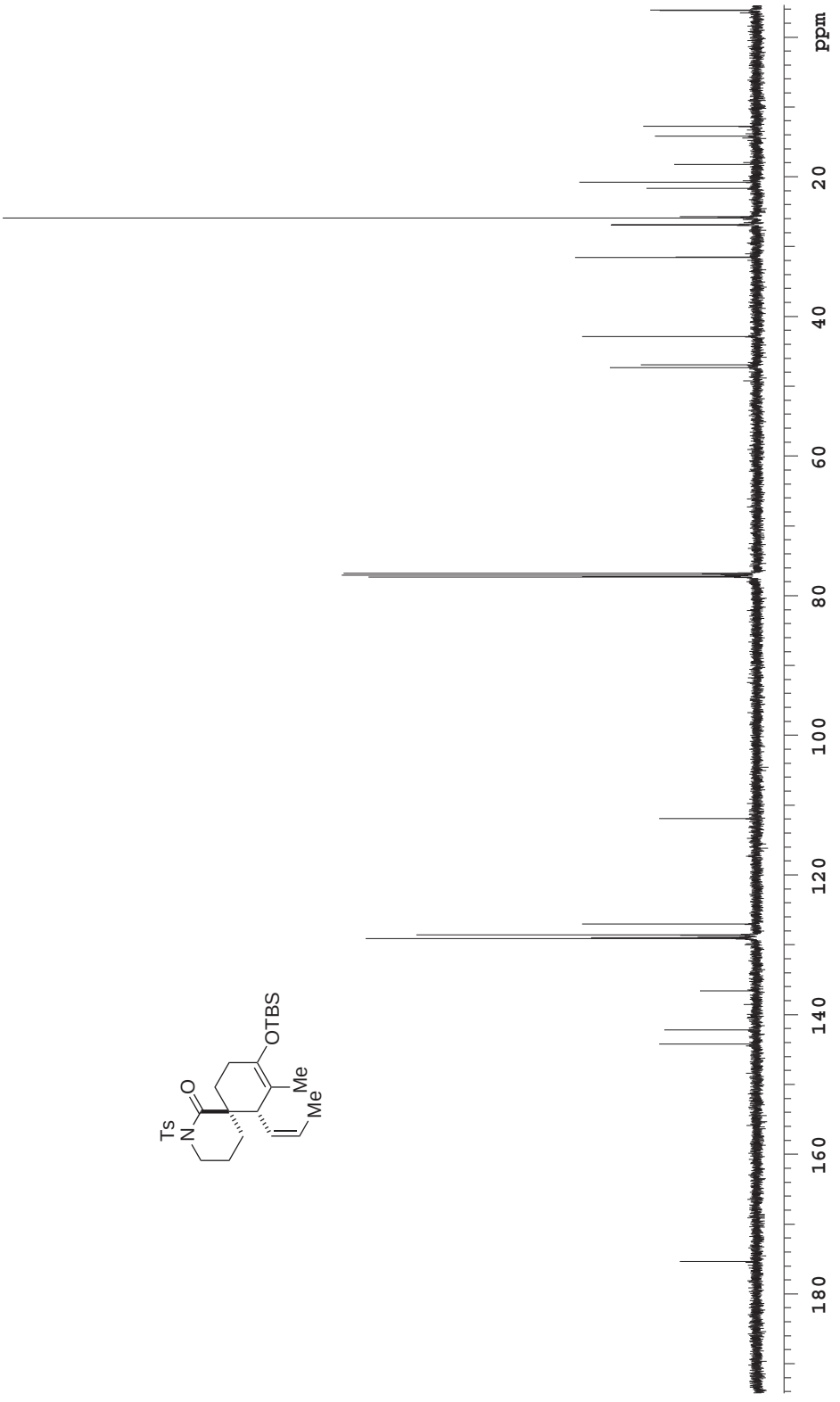
^{1}H NMR spectrum of vinyl stannane **57**



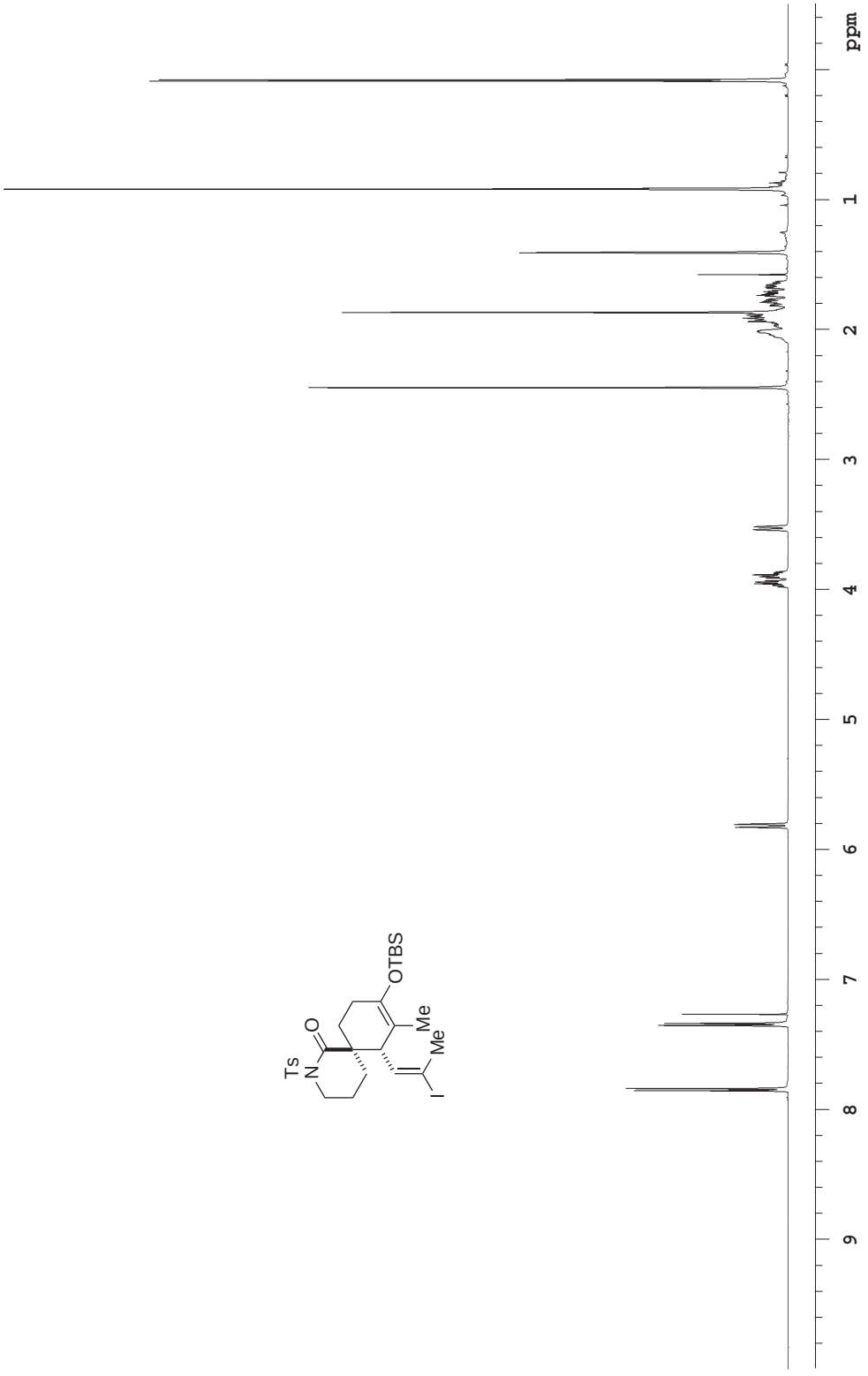
^{13}C NMR spectrum of vinyl stannane **57**



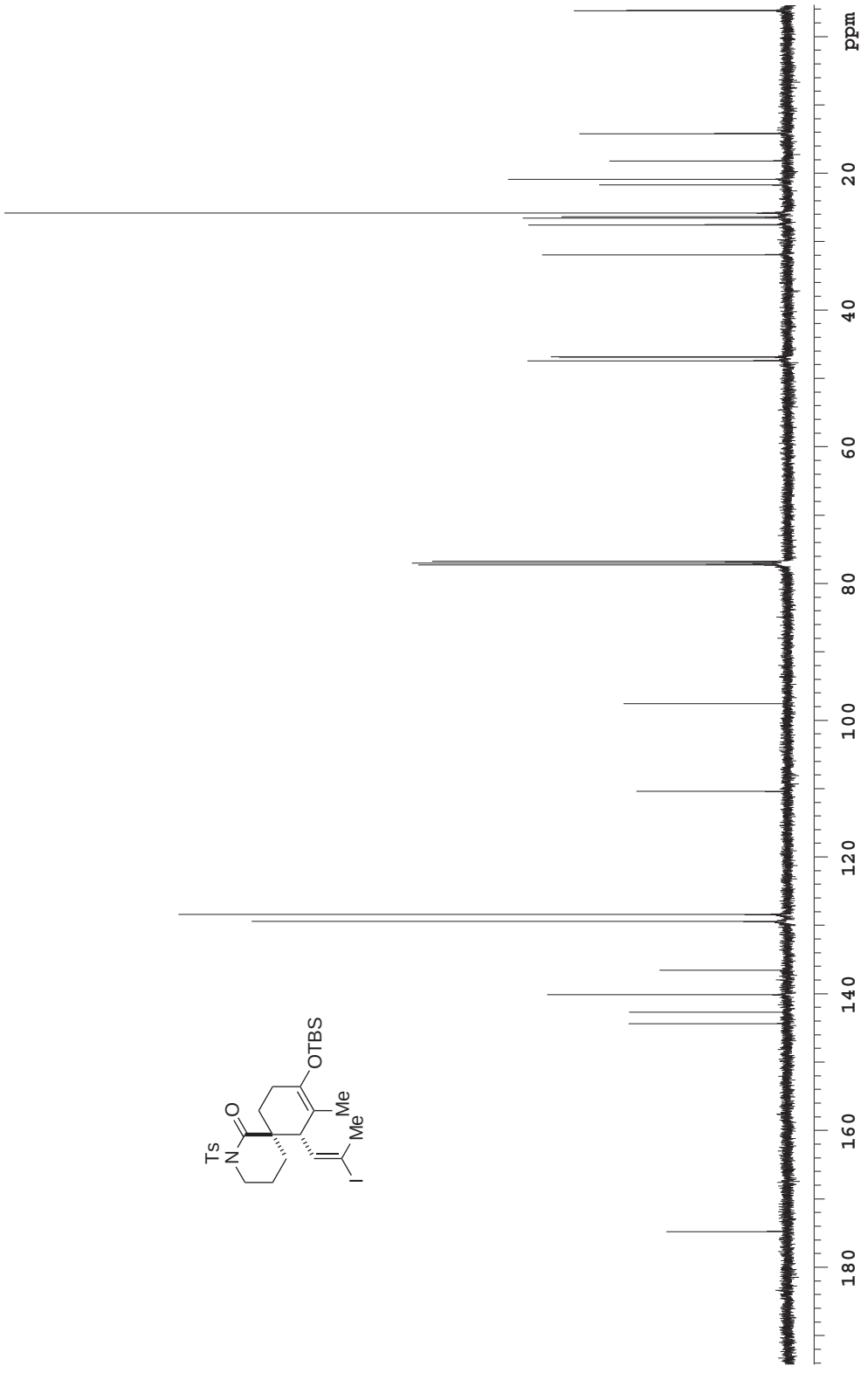
^{1}H NMR spectrum of hydrogenated product **58**



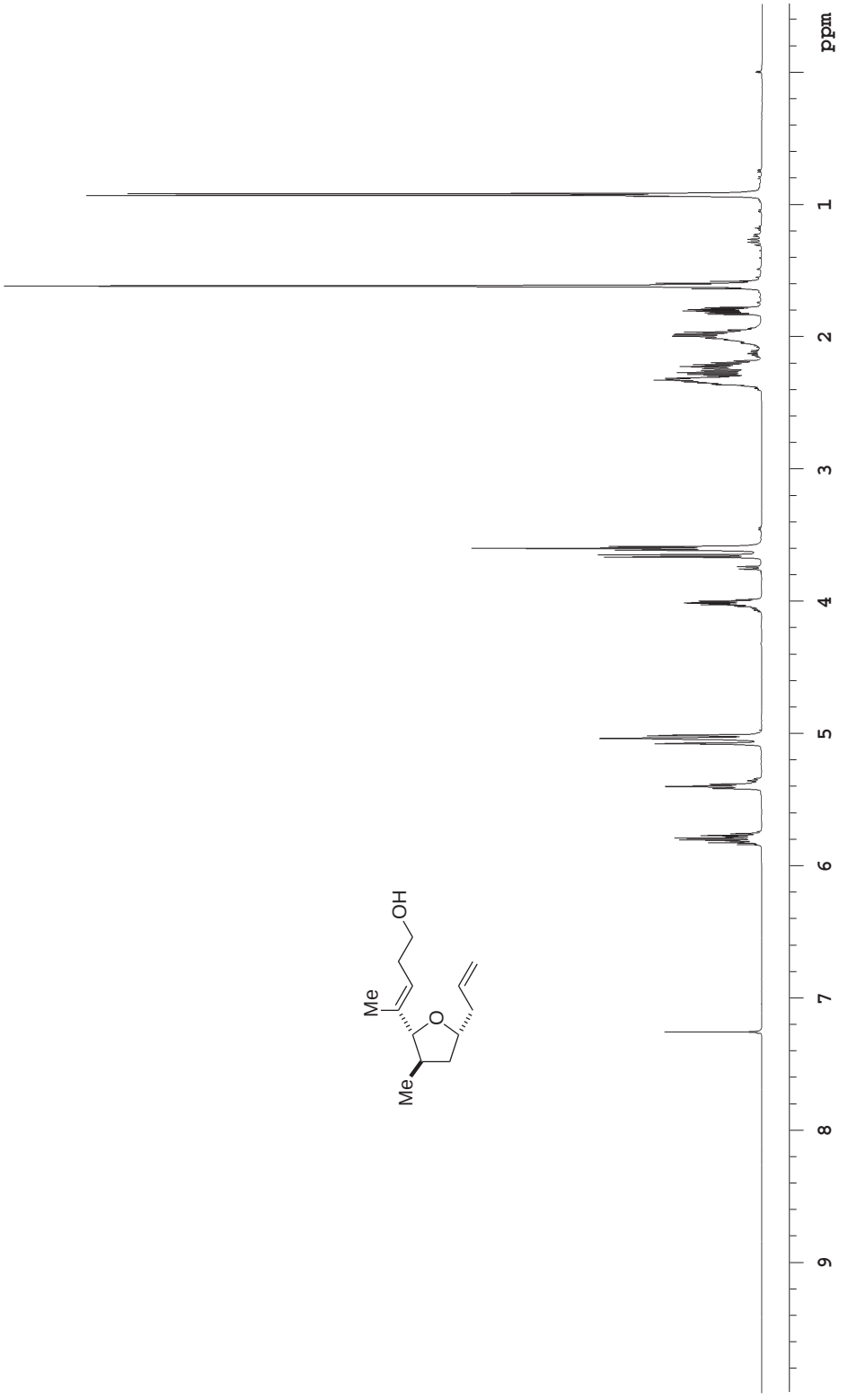
^{13}C NMR spectrum of hydrogenated product **58**



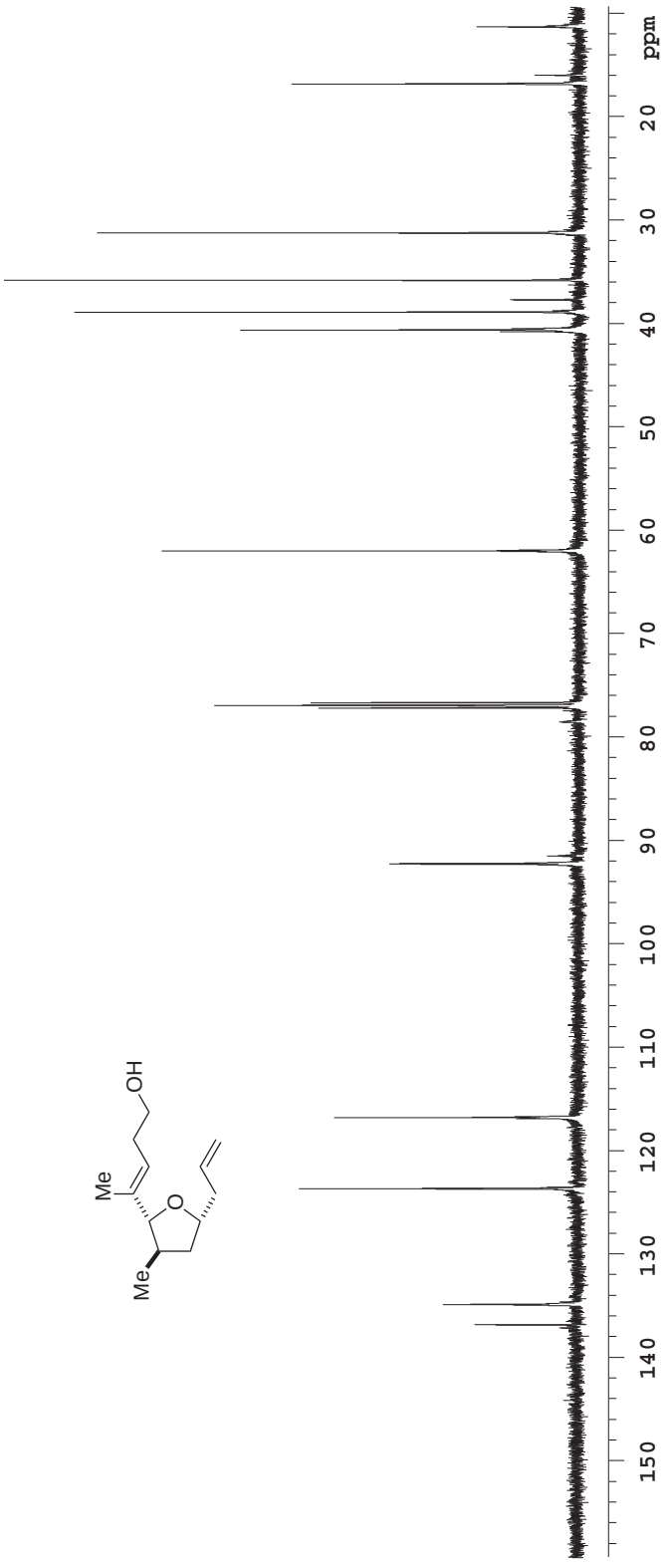
^{1}H NMR spectrum of vinyl iodide **56**



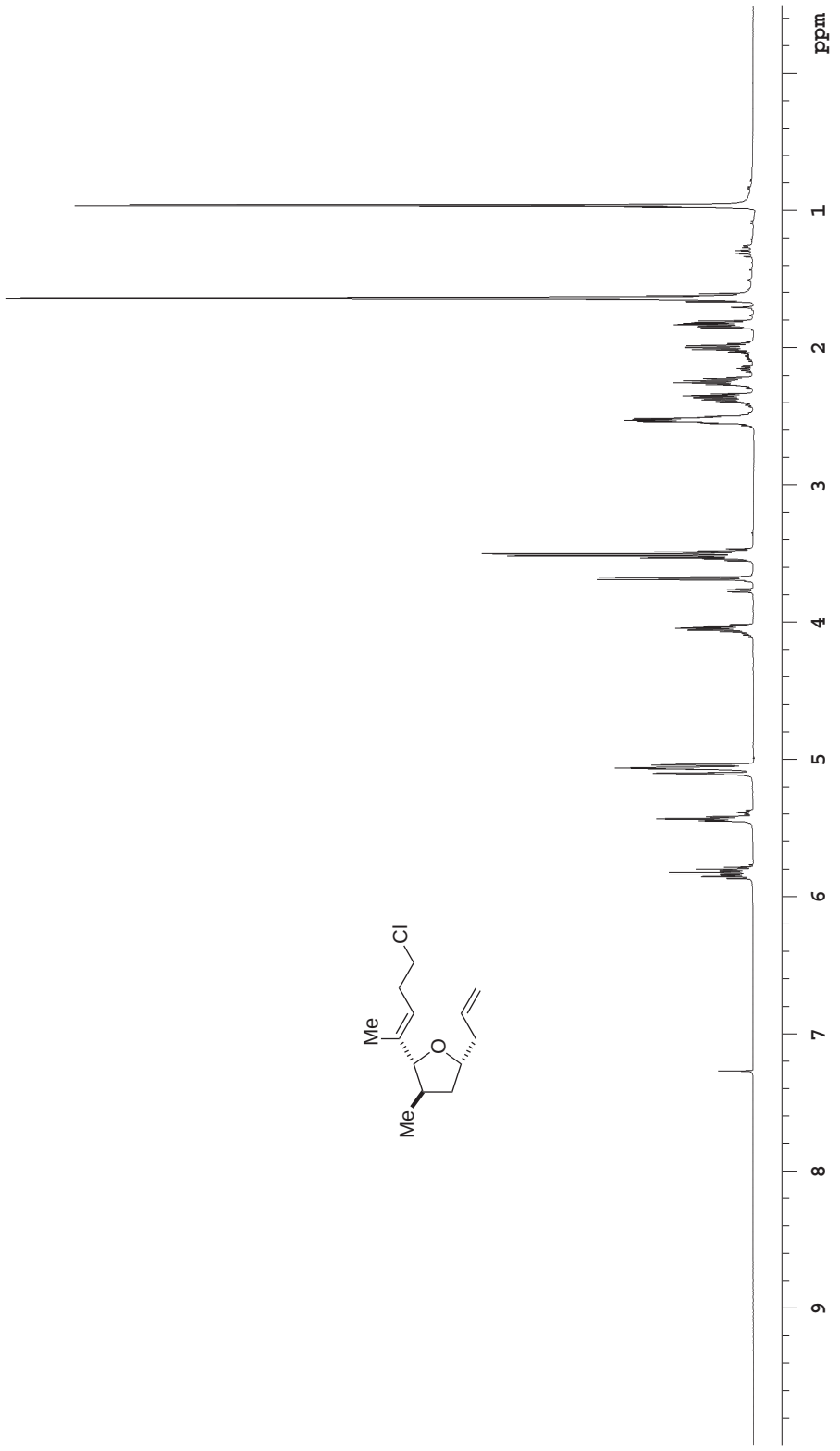
^{13}C NMR spectrum of vinyl iodide **56**



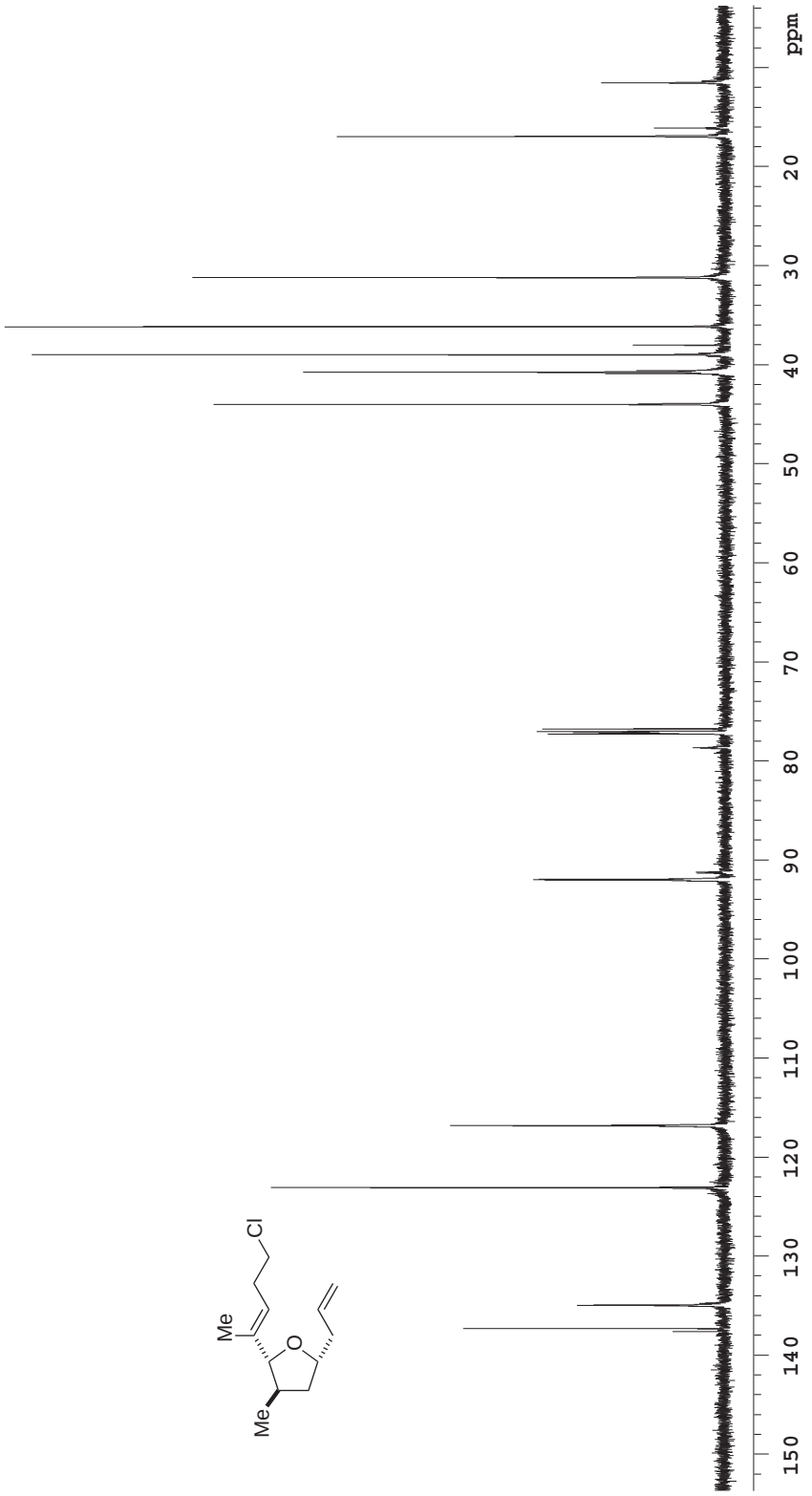
^{1}H NMR spectrum of alcohol **59a**



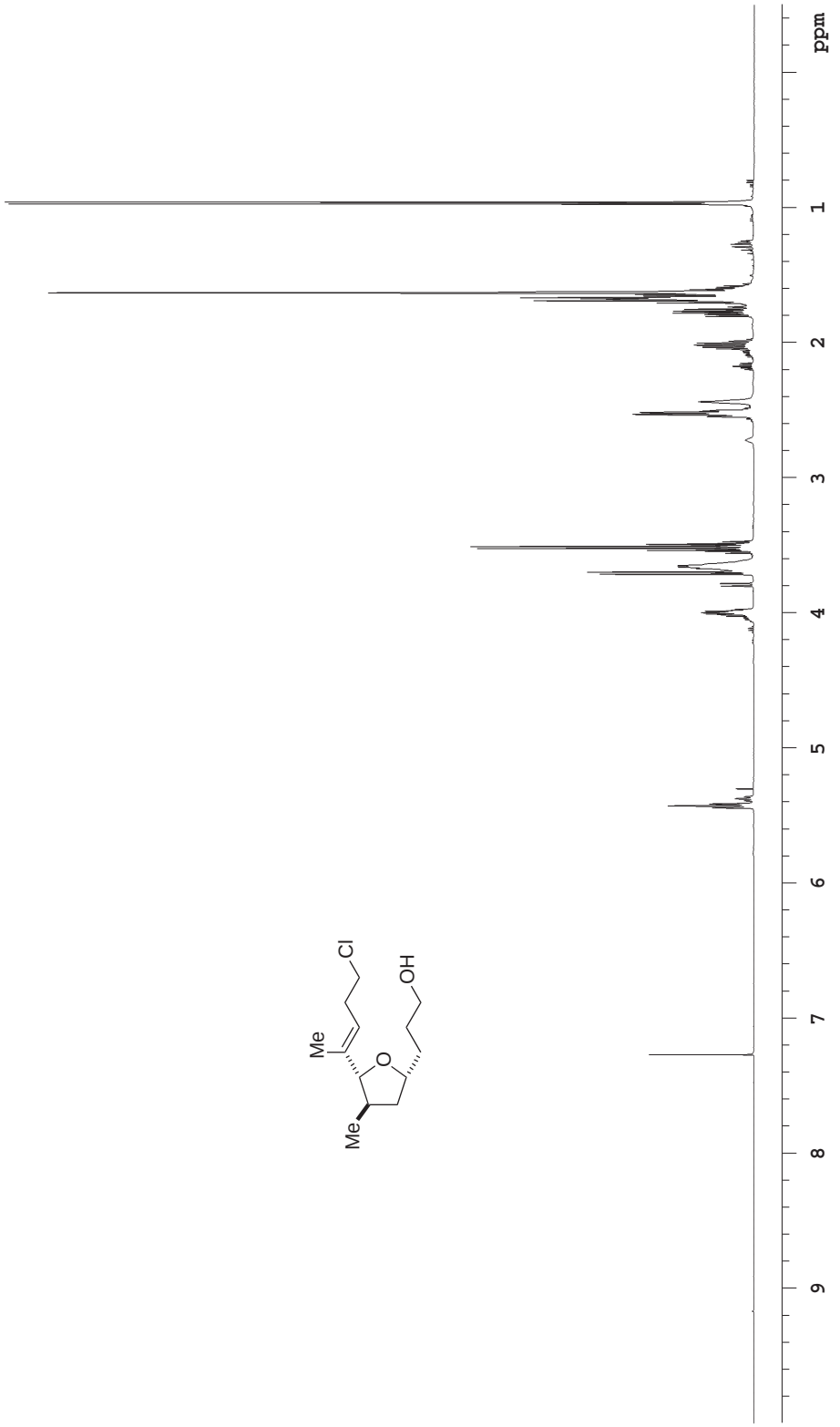
^{13}C NMR spectrum of alcohol **59a**



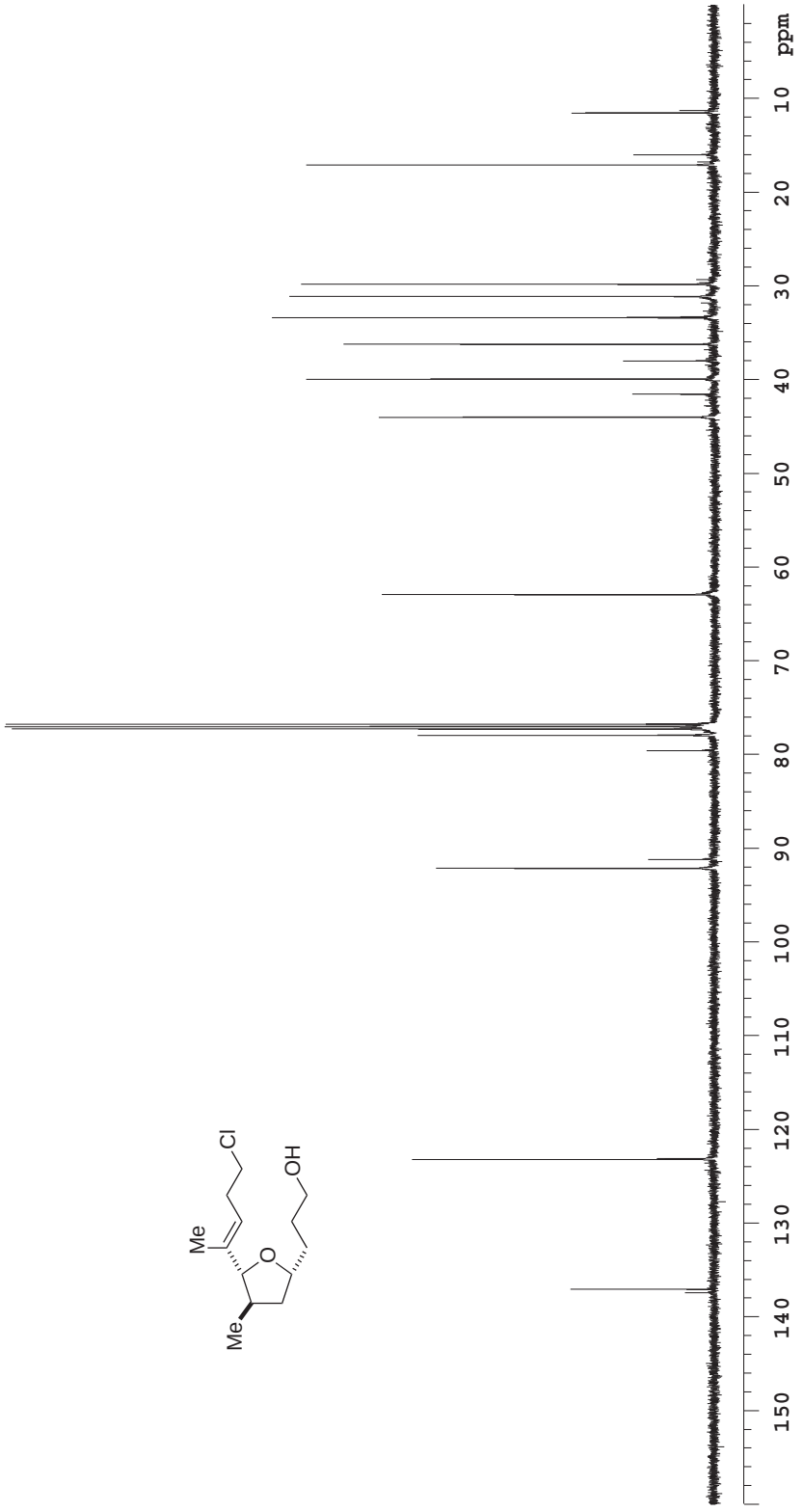
^{1}H NMR spectrum of chloride **59b**



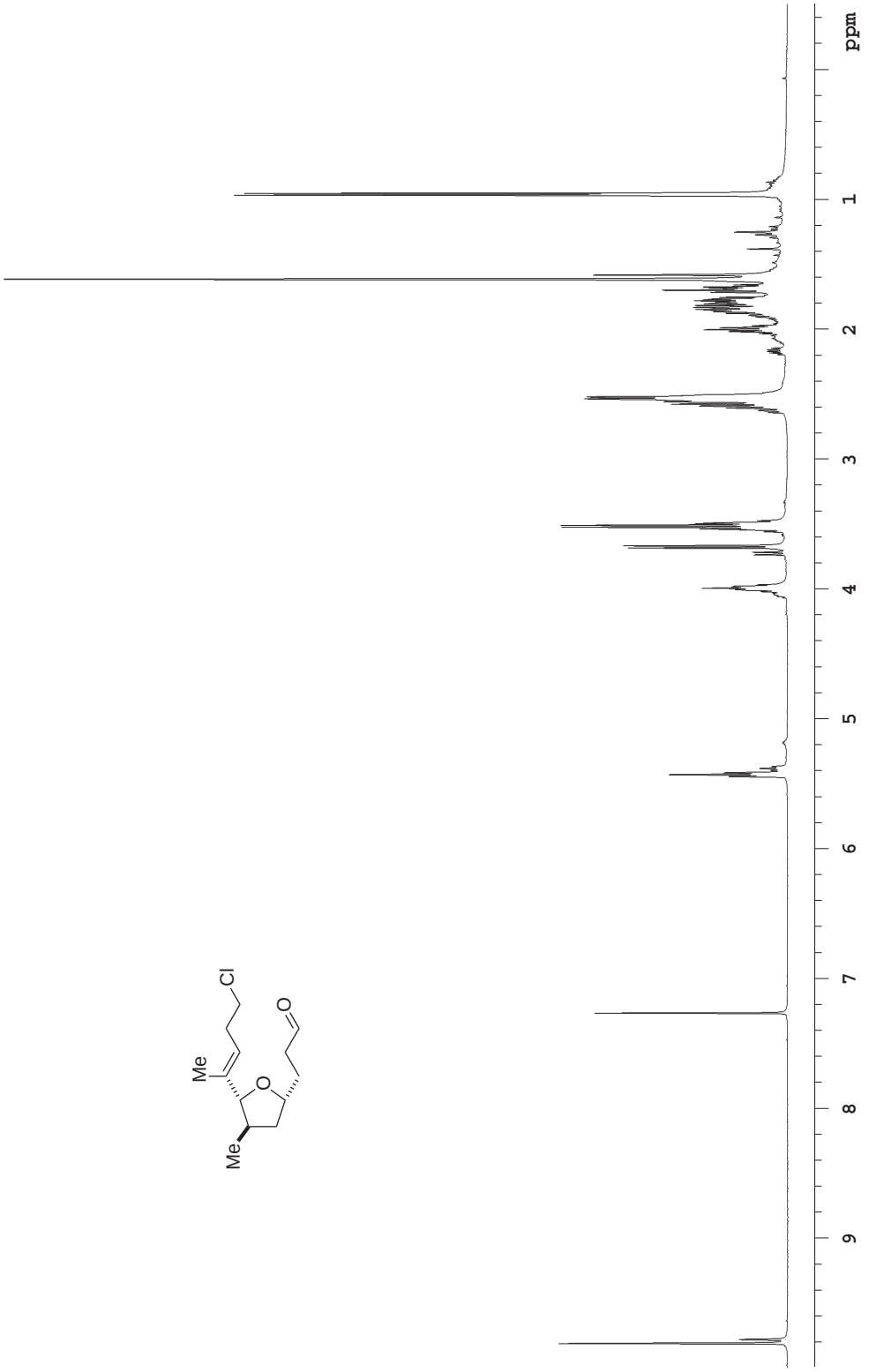
^{13}C NMR spectrum of chloride **59b**



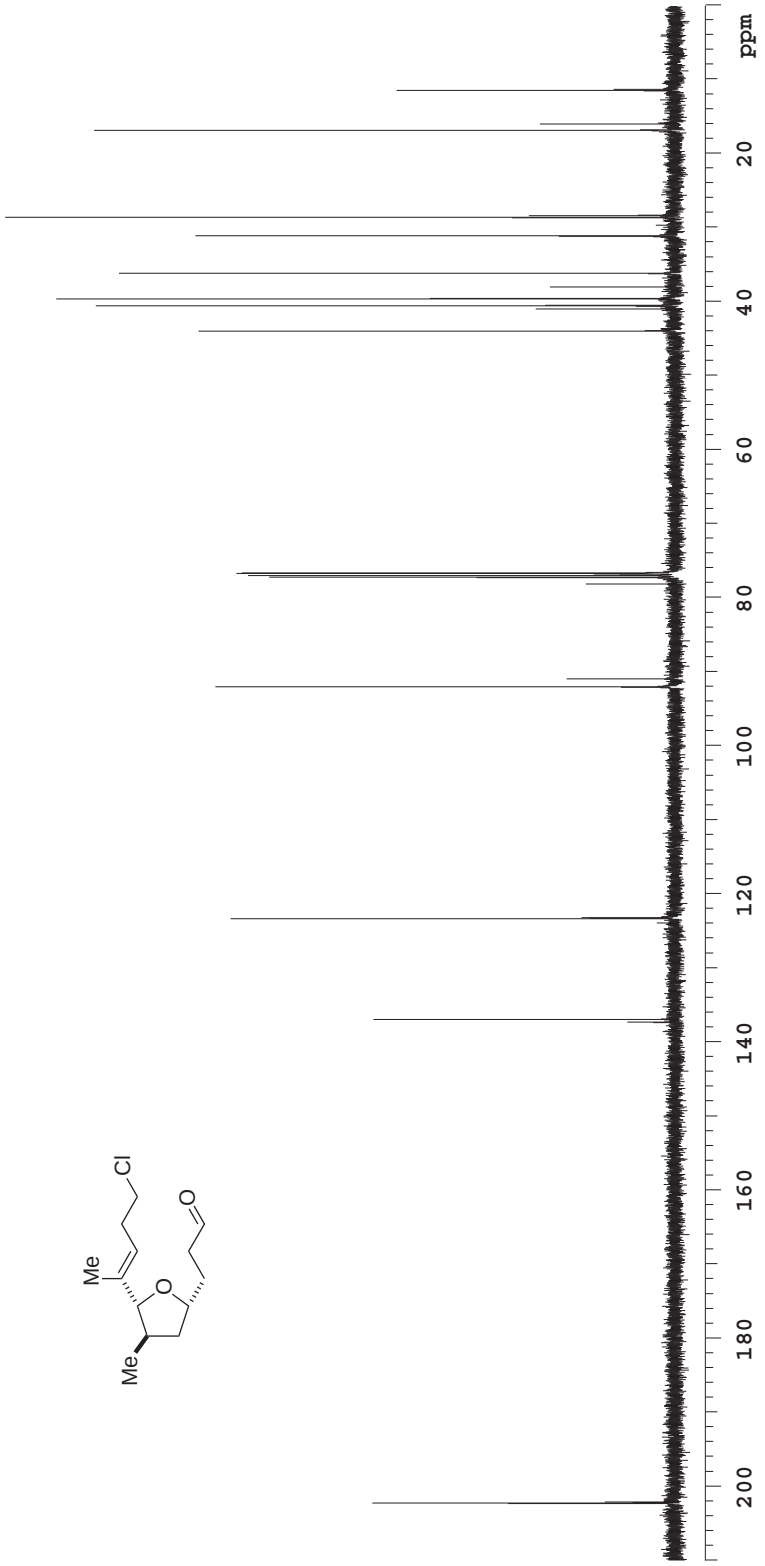
^{1}H NMR spectrum of alcohol **60**



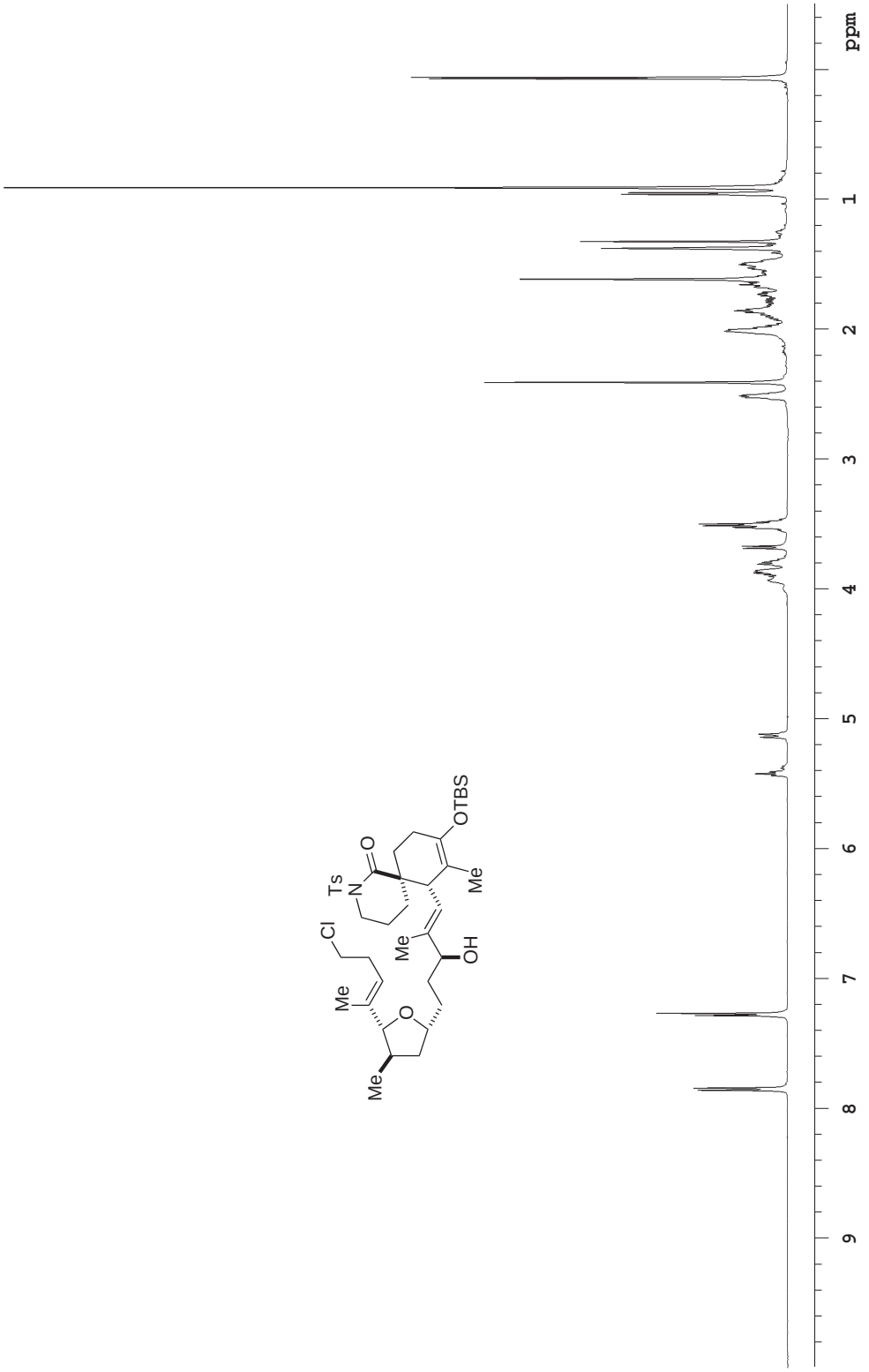
^{13}C NMR spectrum of alcohol **60**



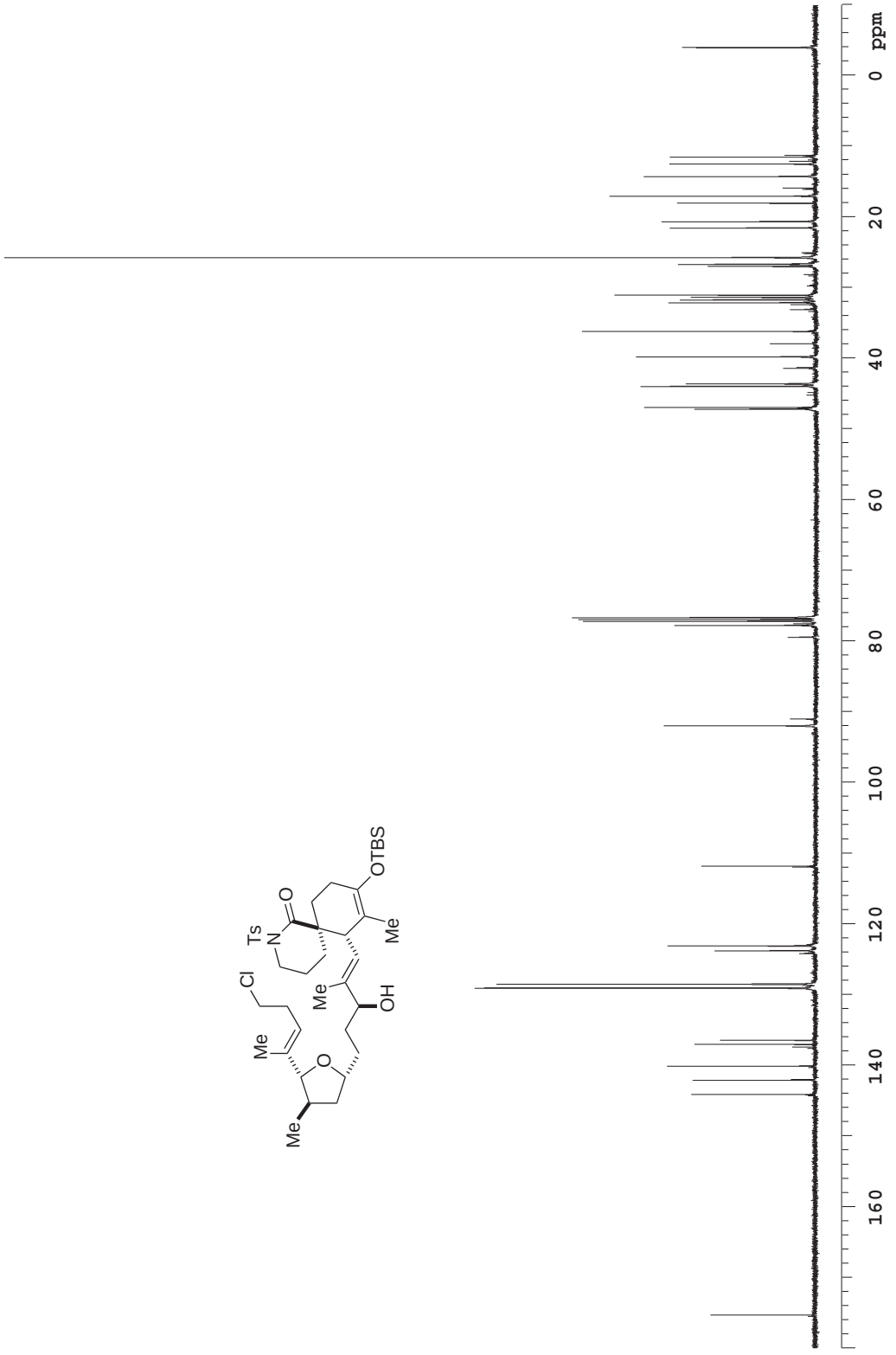
^{1}H NMR spectrum of aldehyde **55**



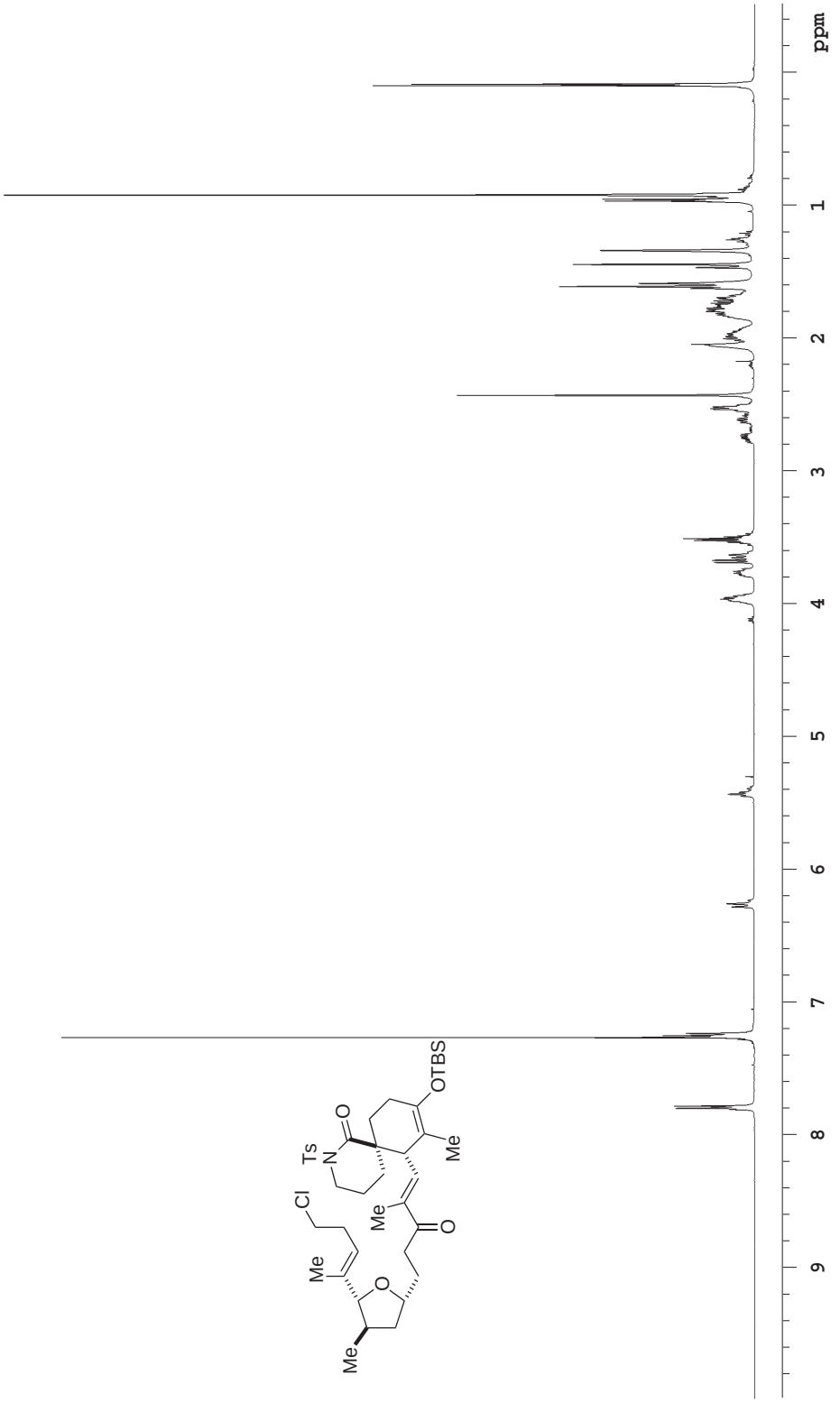
^{13}C NMR spectrum of aldehyde **55**



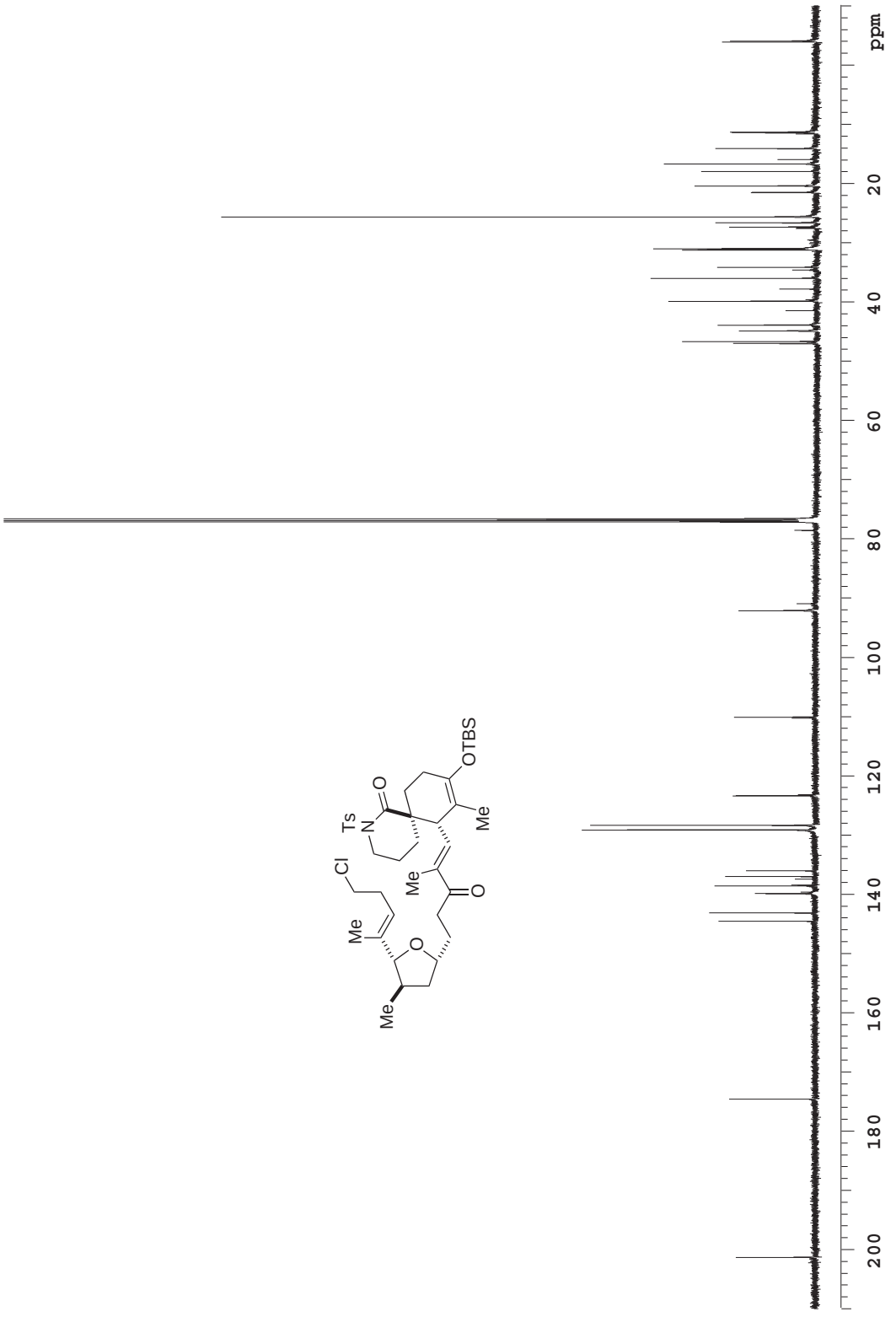
^{1}H NMR spectrum of alcohol **61b**



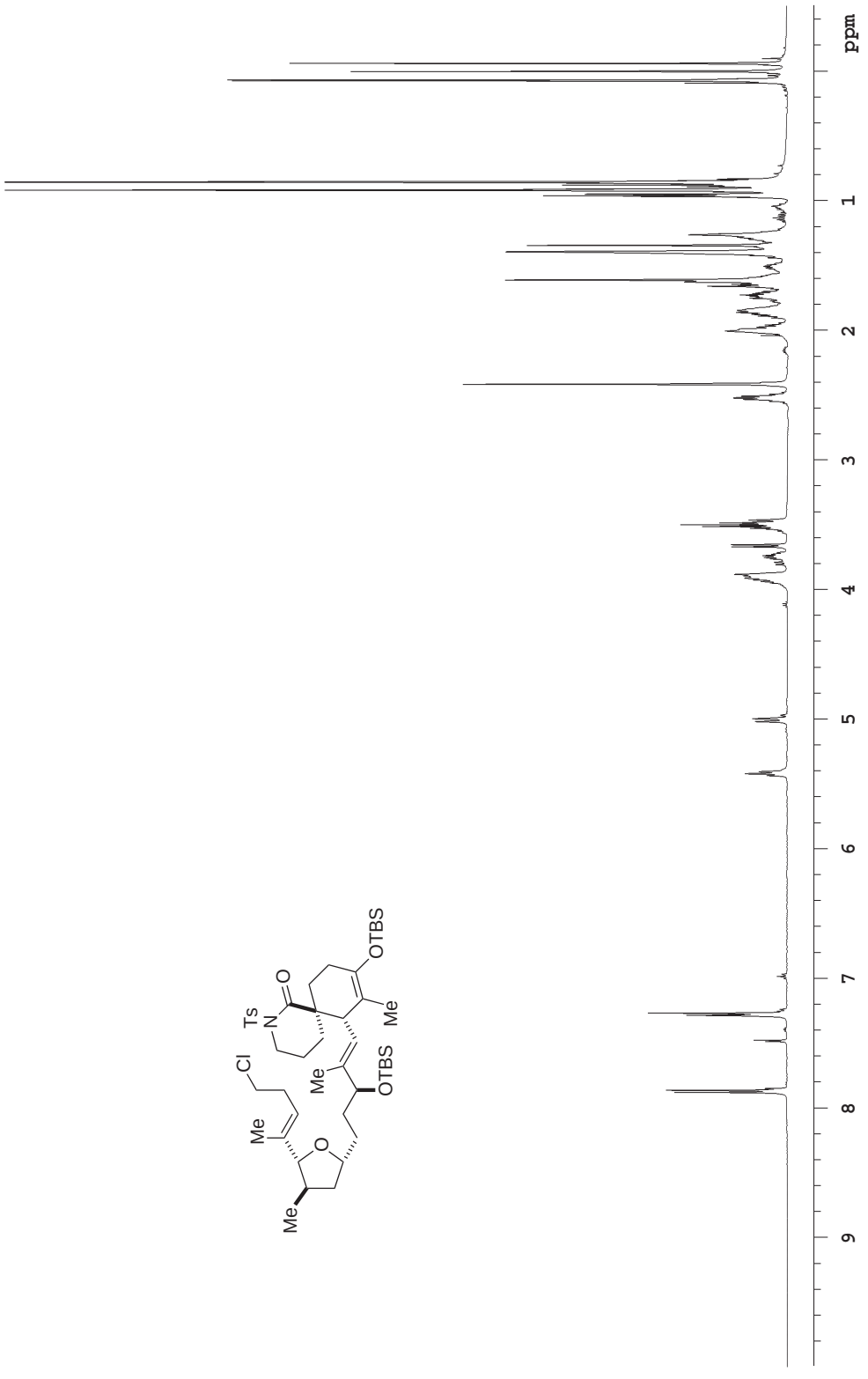
^{13}C NMR spectrum of alcohol **61b**



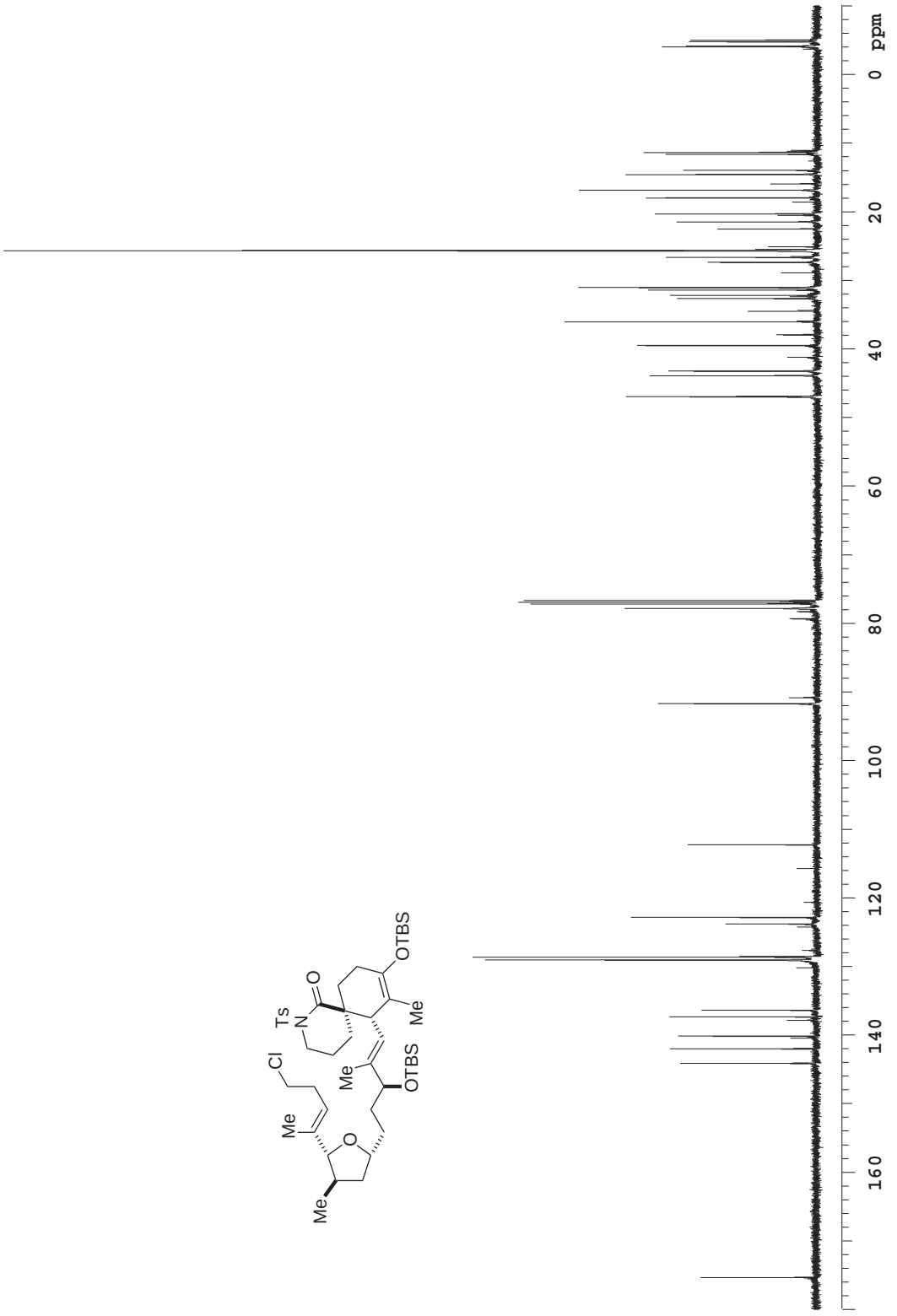
^{1}H NMR spectrum of ketone **62**



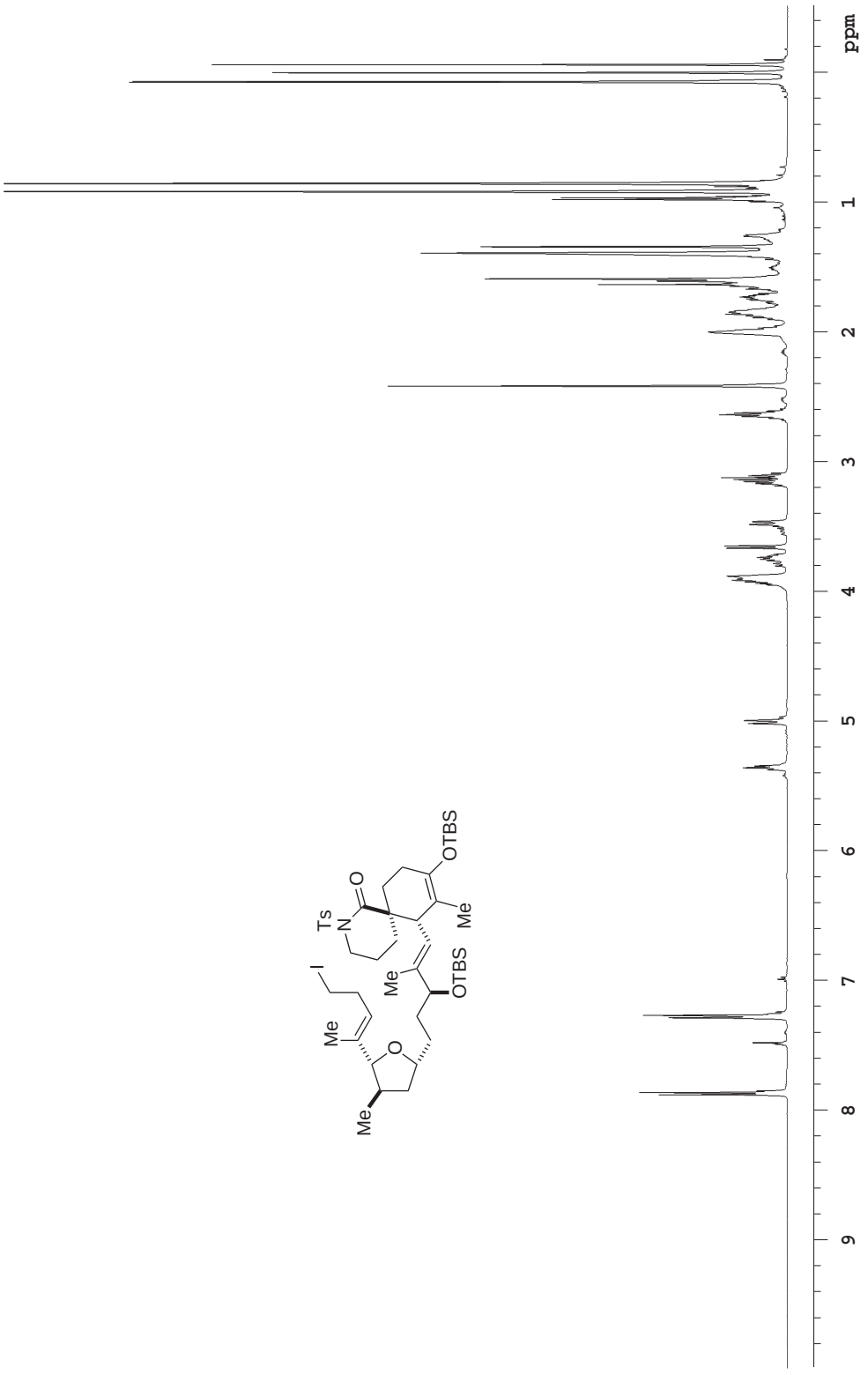
^{13}C NMR spectrum of ketone **62**



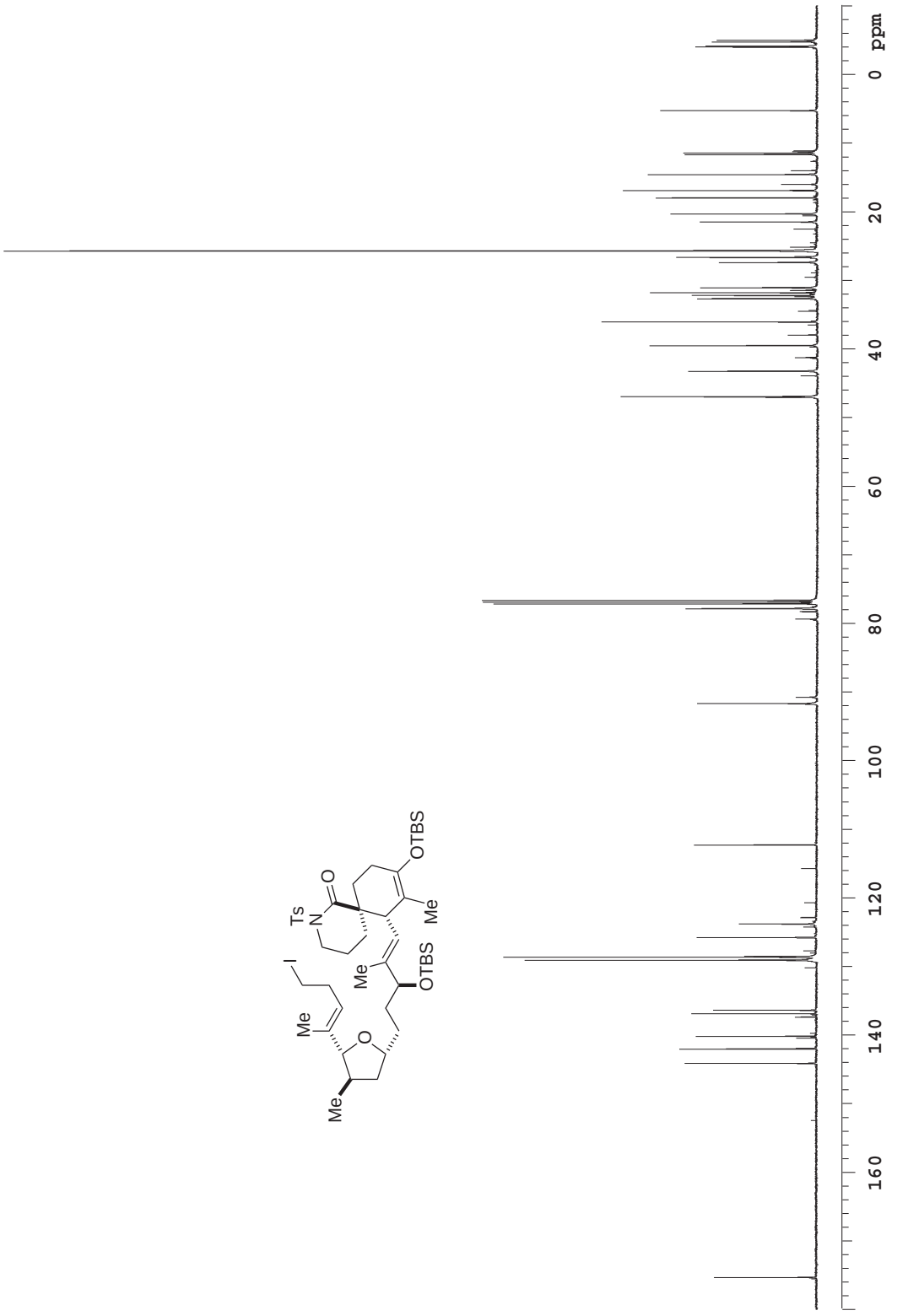
^{1}H NMR spectrum of chloride **63**



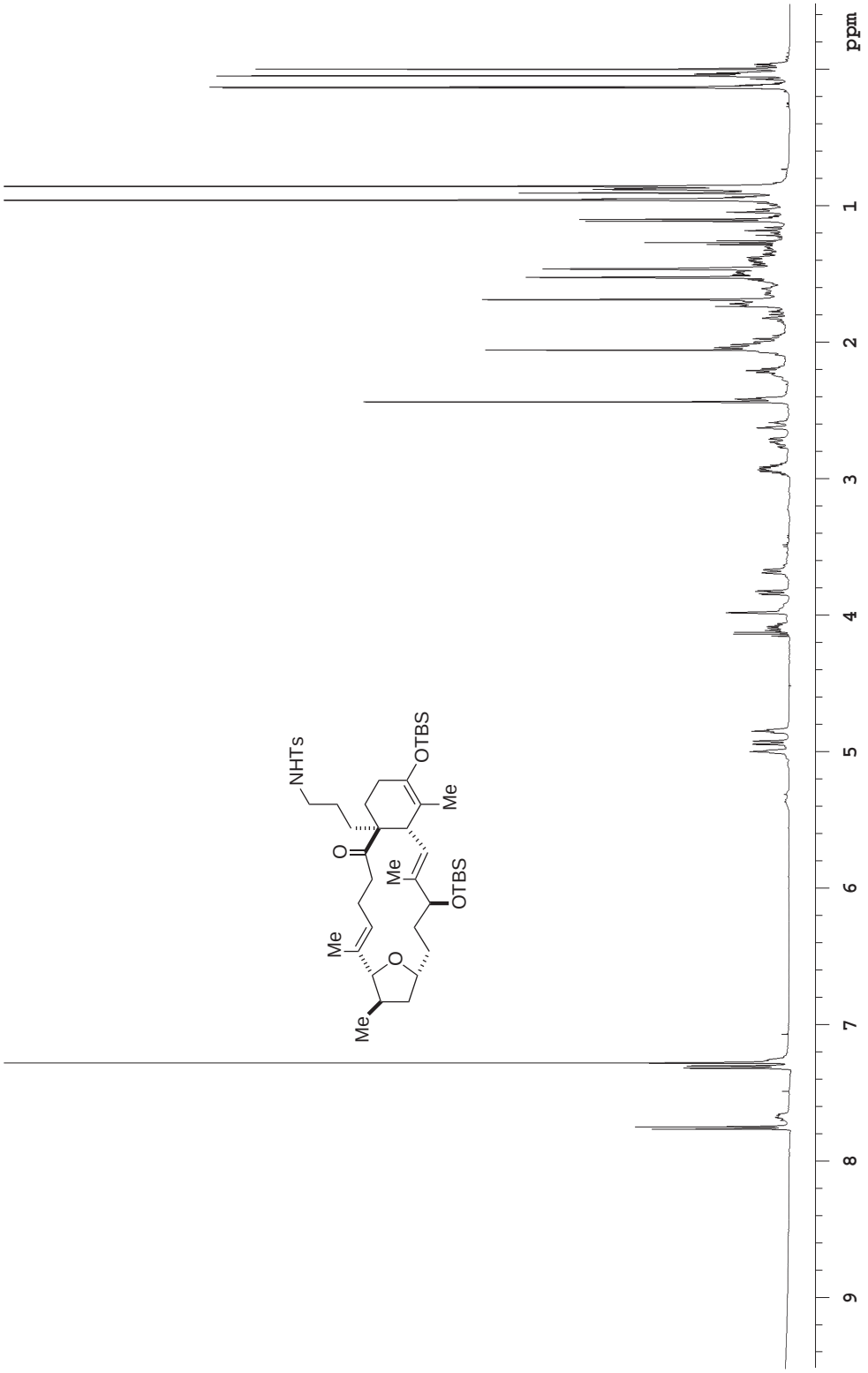
^{13}C NMR spectrum of chloride **63**



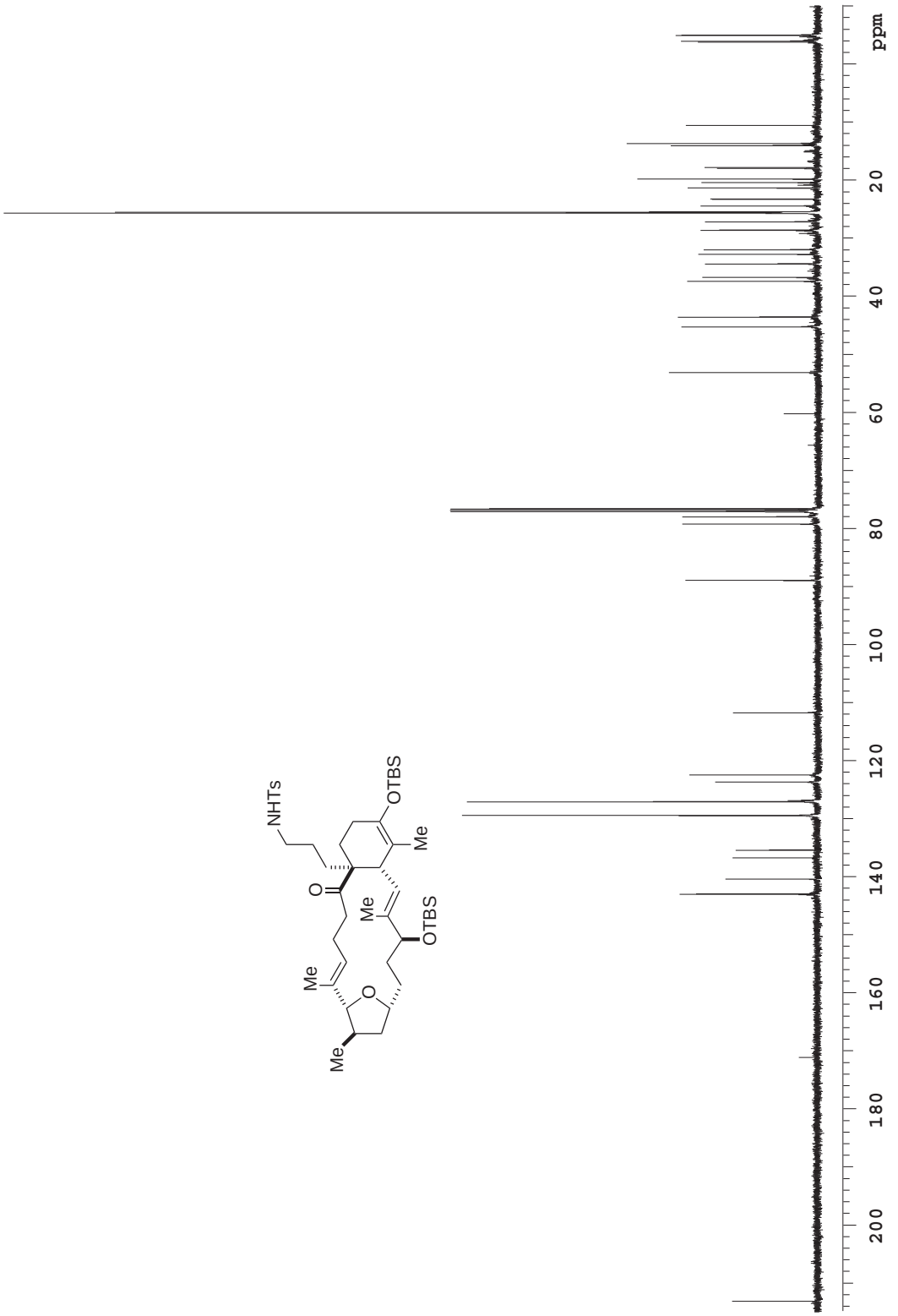
^{1}H NMR spectrum of iodide **64**



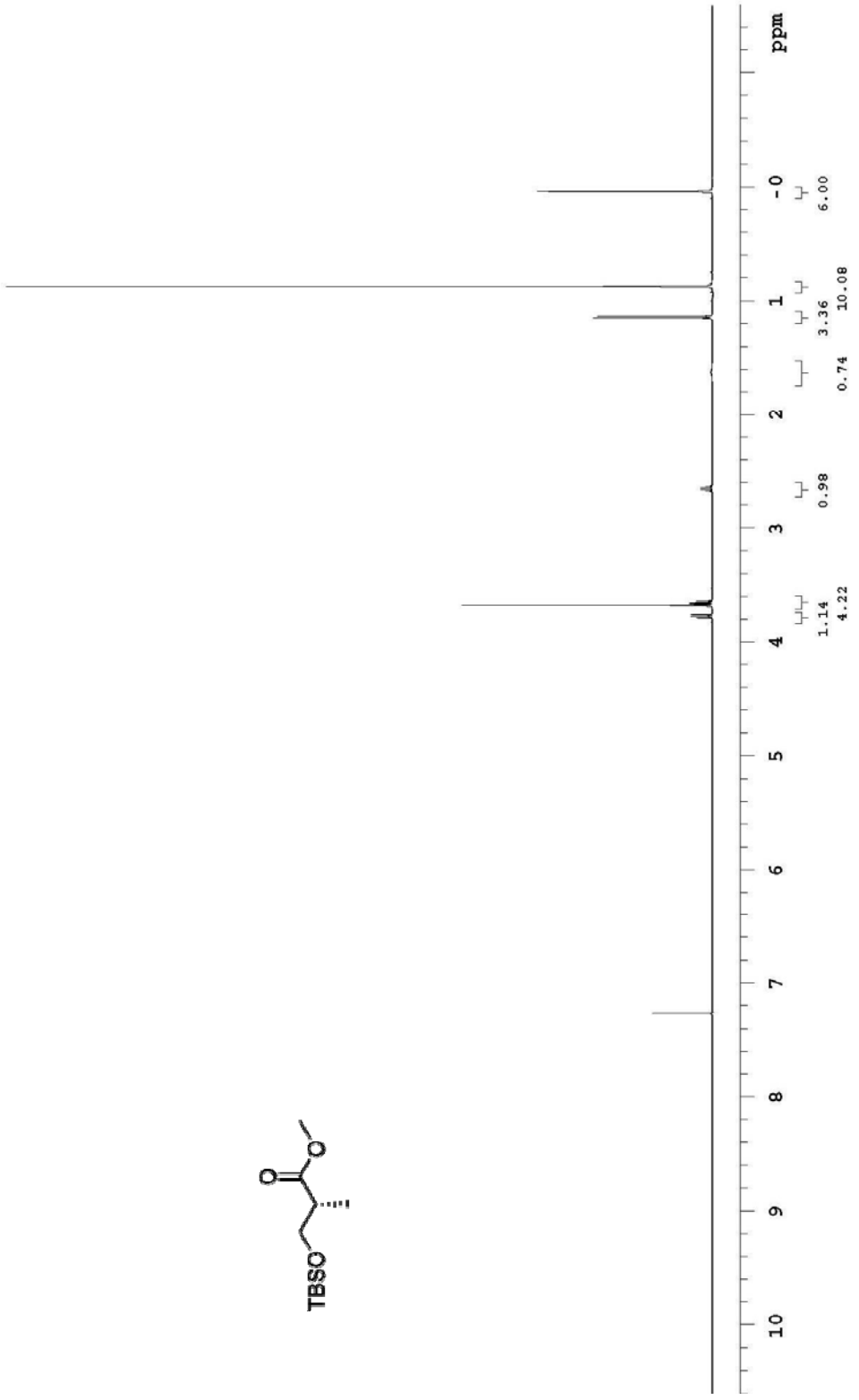
^{13}C NMR spectrum of iodide **64**



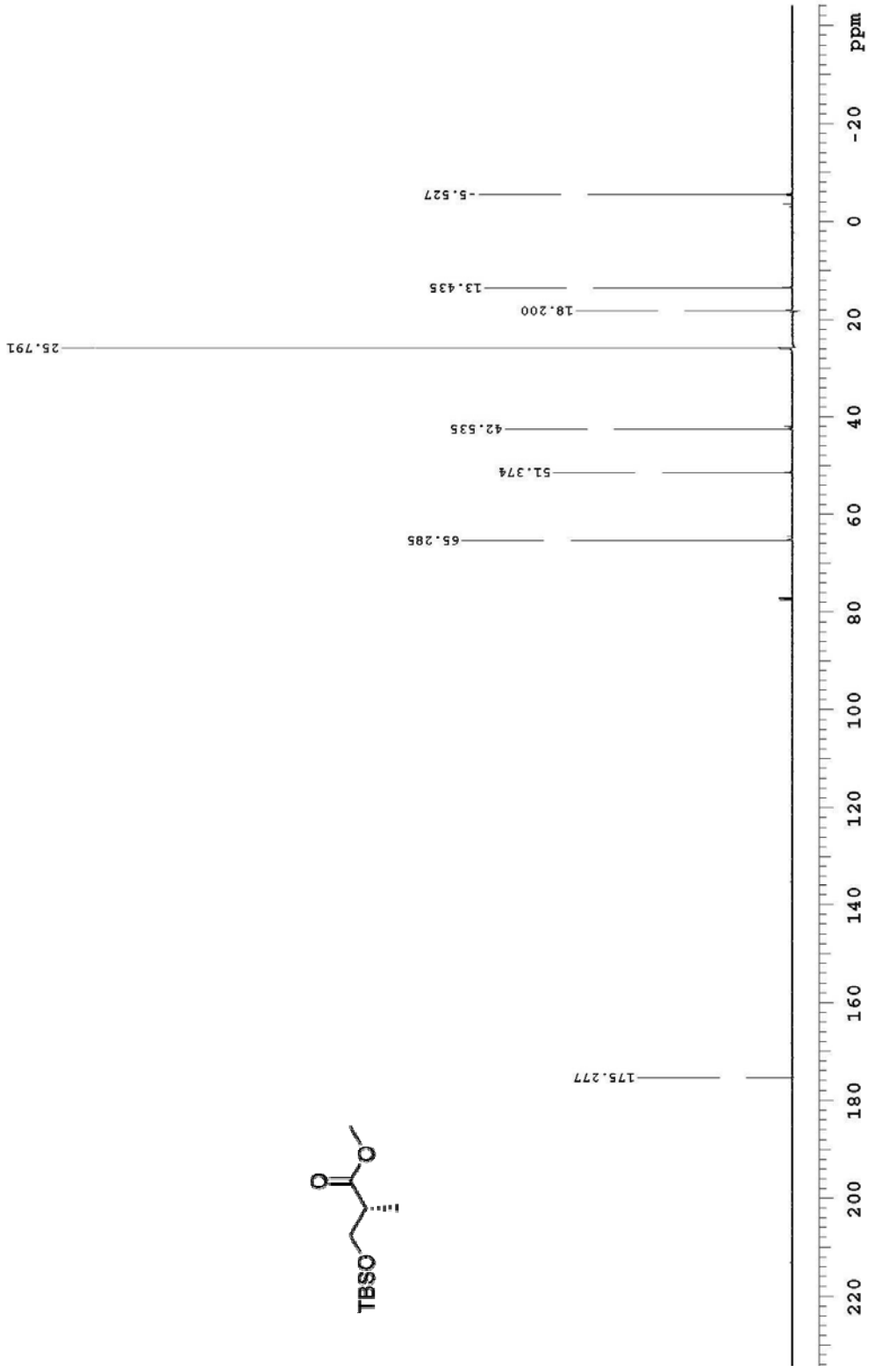
^{1}H NMR spectrum of *N*-tosyl amine **65**



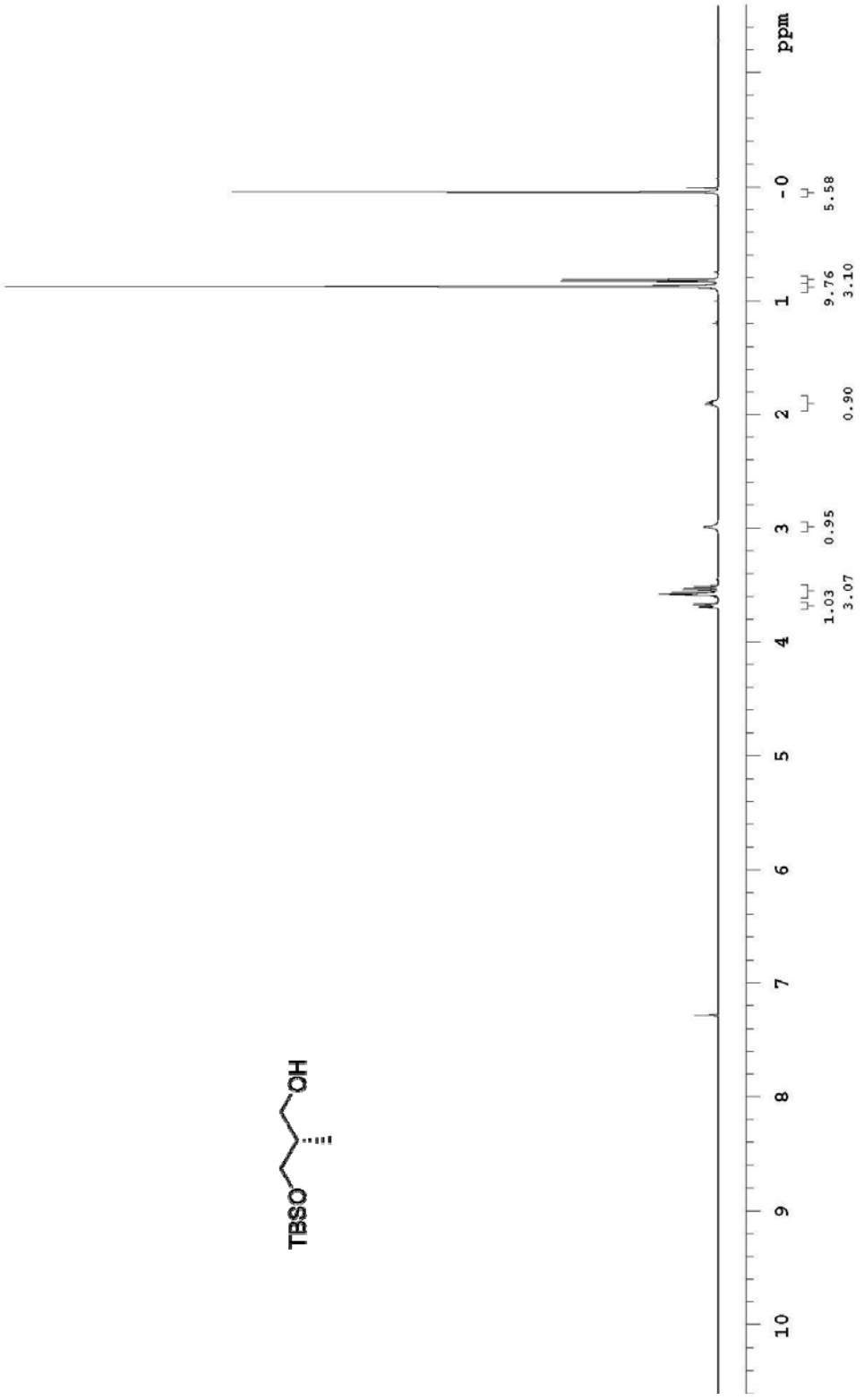
^{13}C NMR spectrum of *N*-tosyl amine **65**



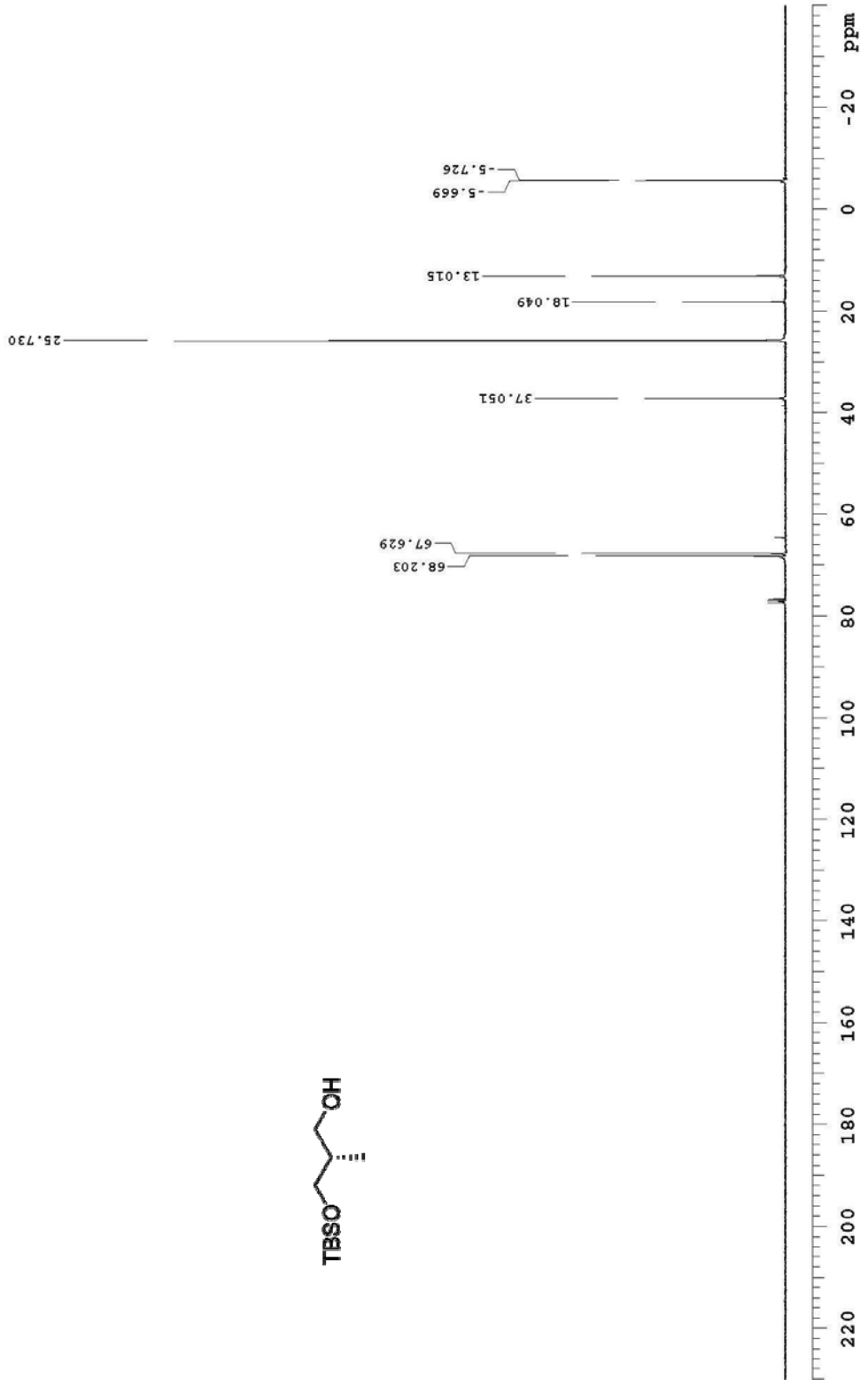
^{1}H NMR spectrum of ester **S-11**



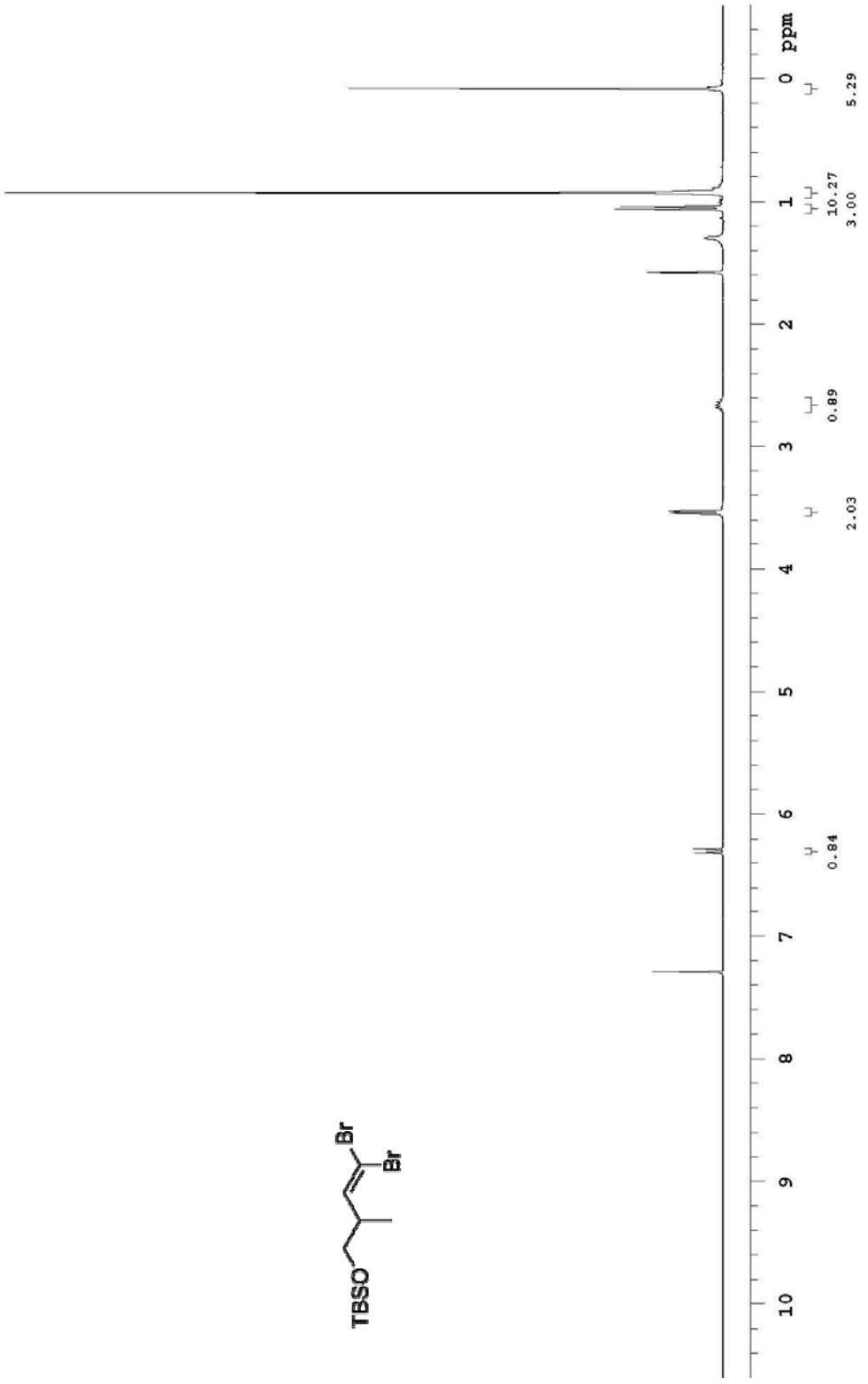
^{13}C NMR spectrum of ester **S-11**



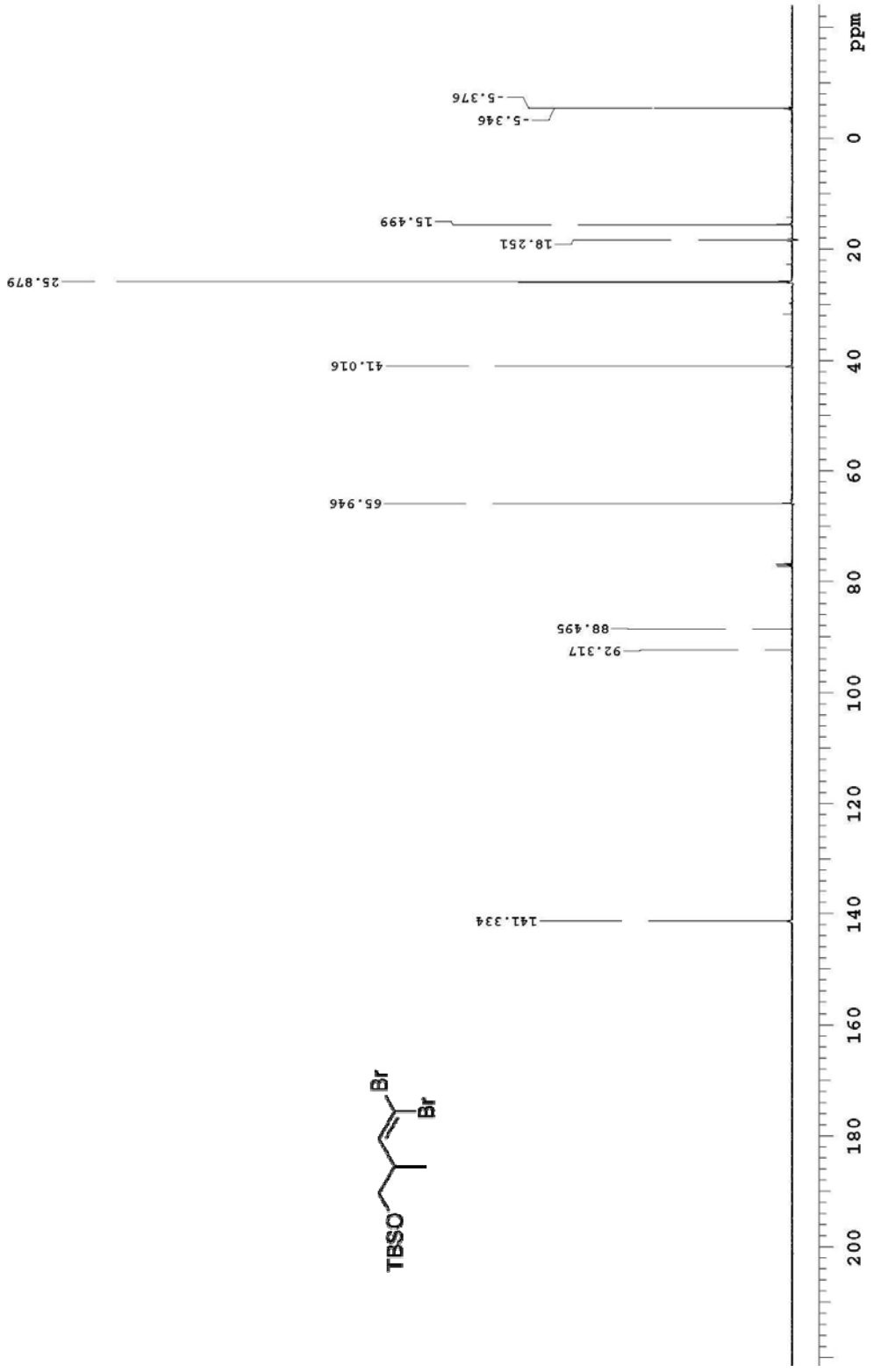
^{1}H NMR spectrum of TBS alcohol **S-12**



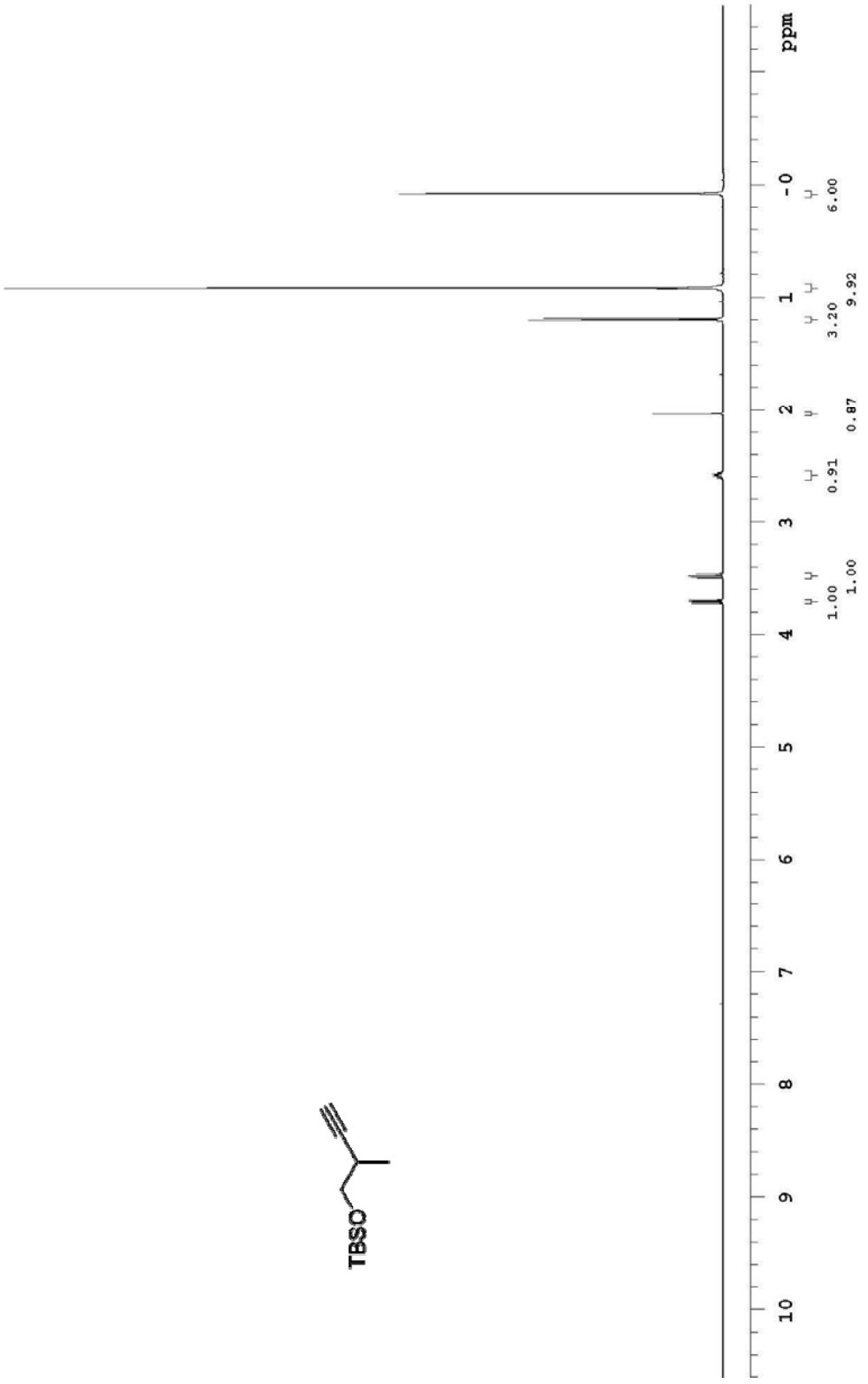
^{13}C NMR spectrum of TBS alcohol **S-12**



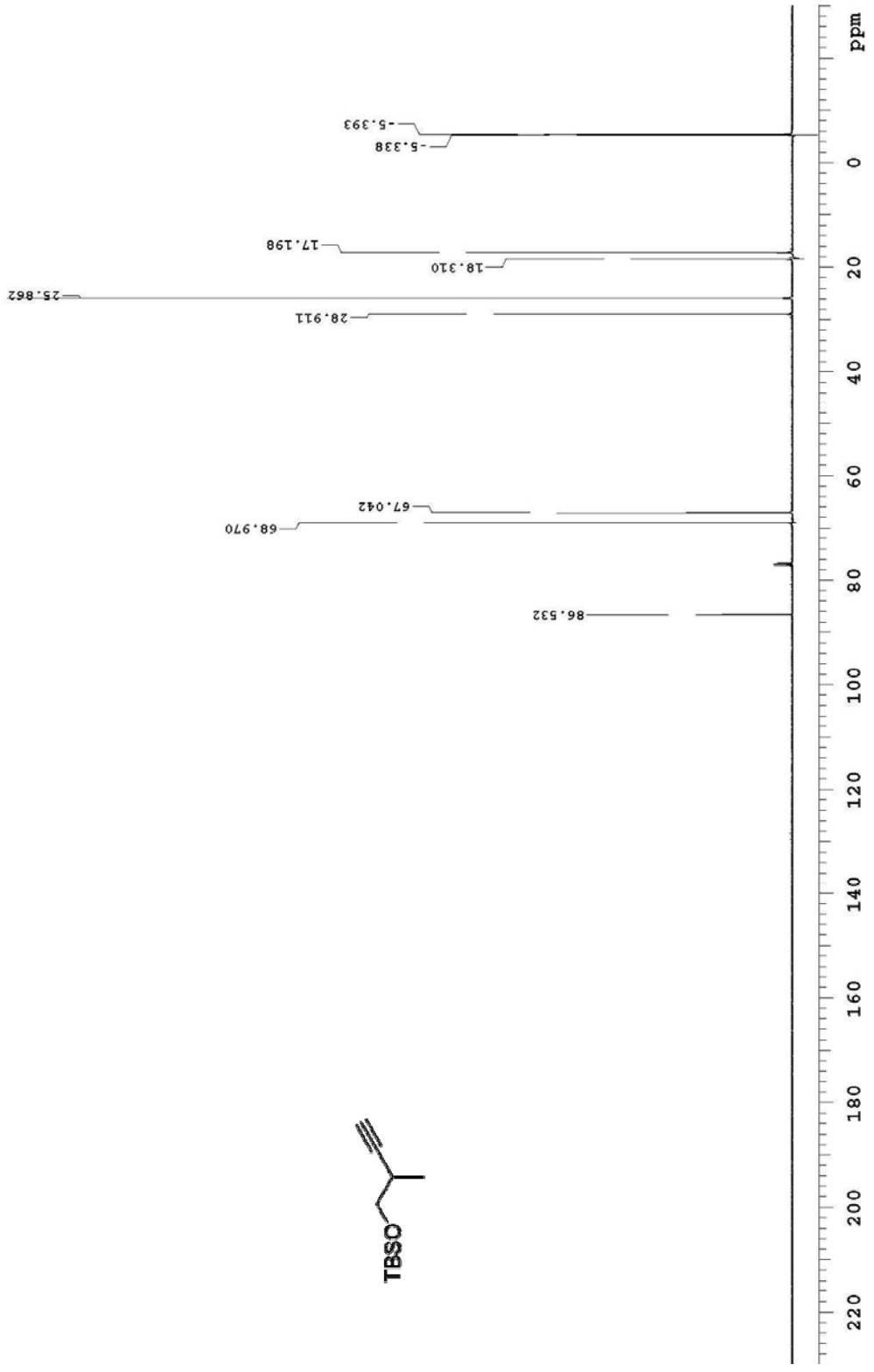
^{1}H NMR spectrum of dibromide **S-13**



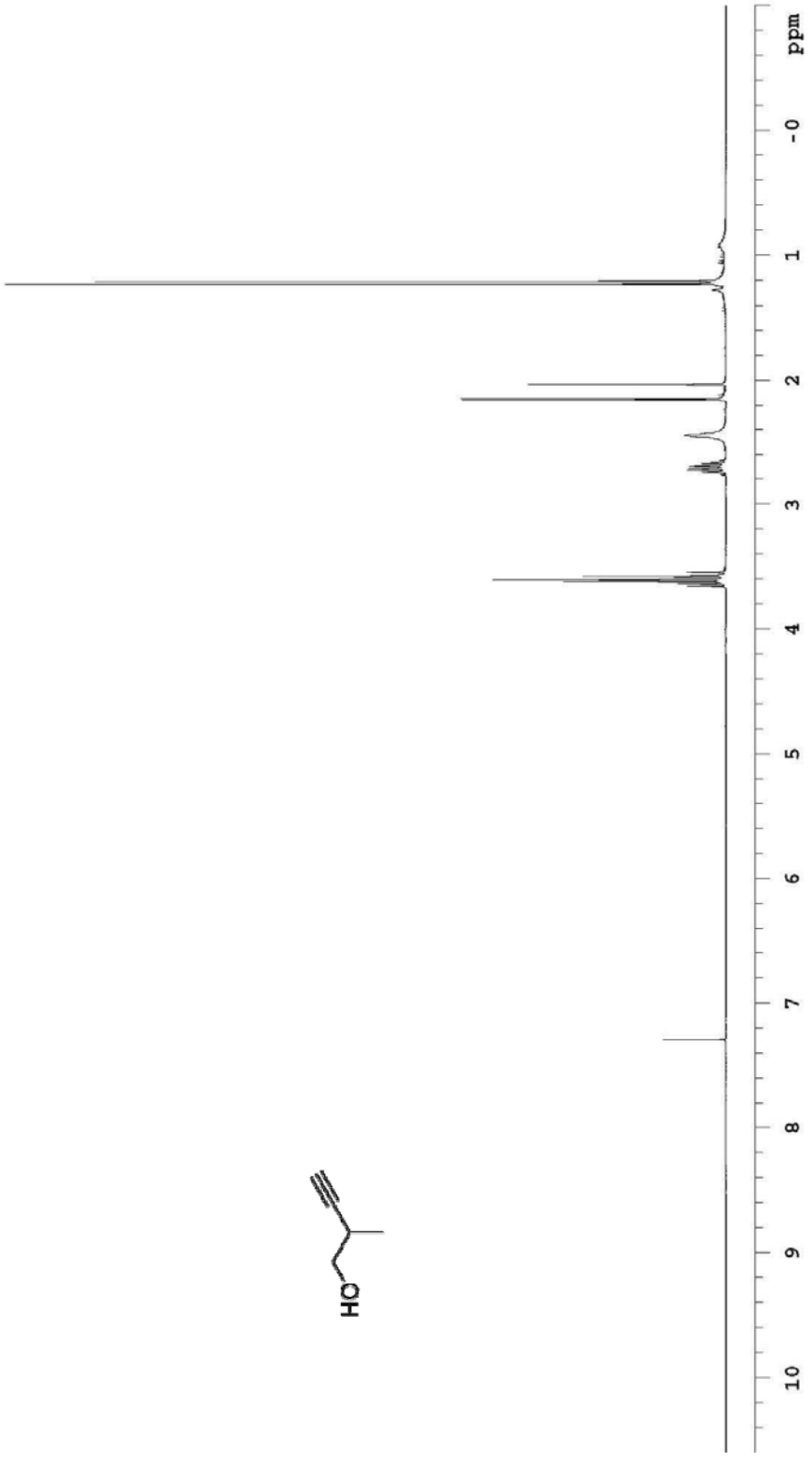
^{13}C NMR spectrum of dibromide **S-13**



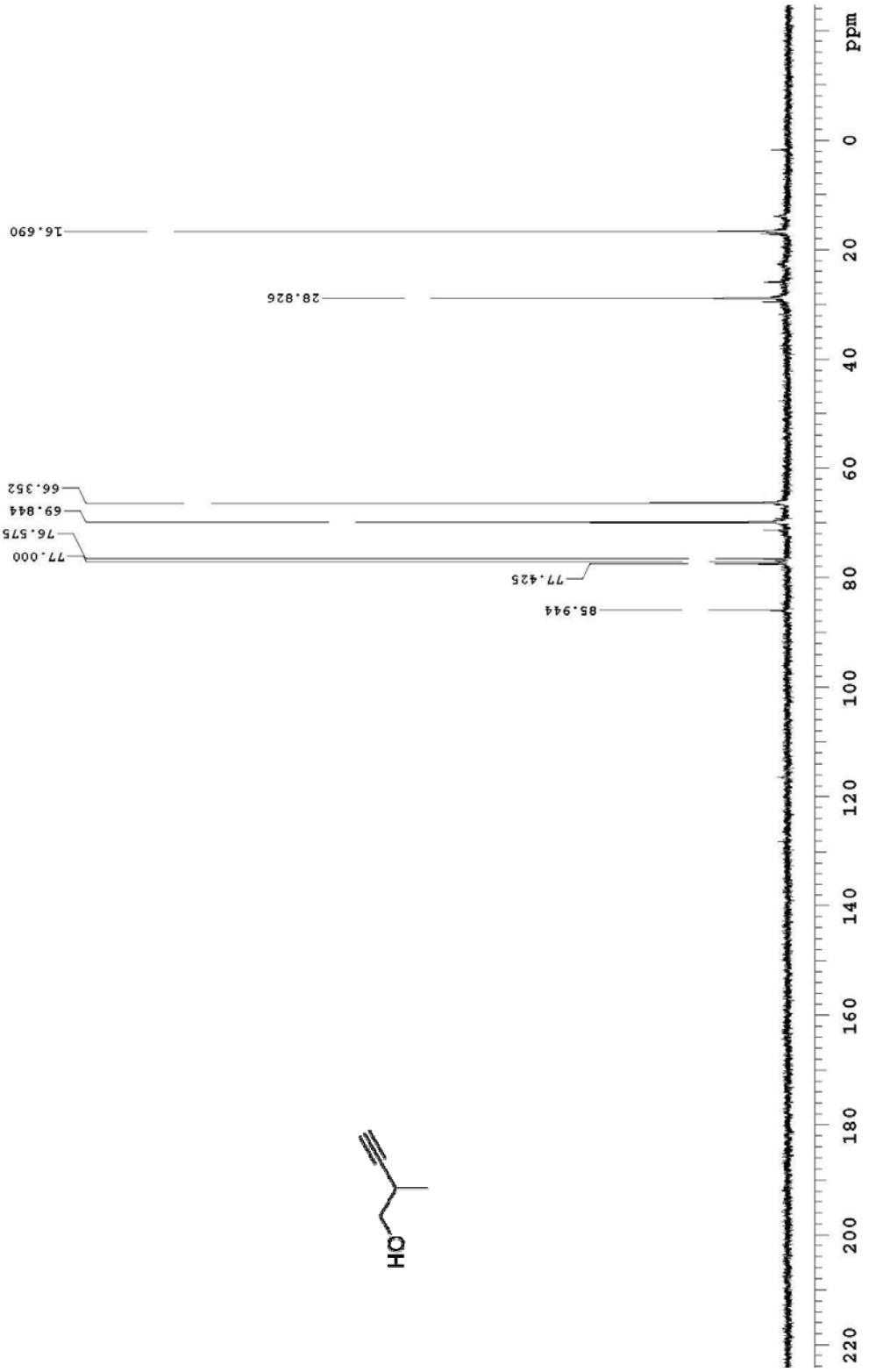
^{1}H NMR spectrum of alkyne **S-14**



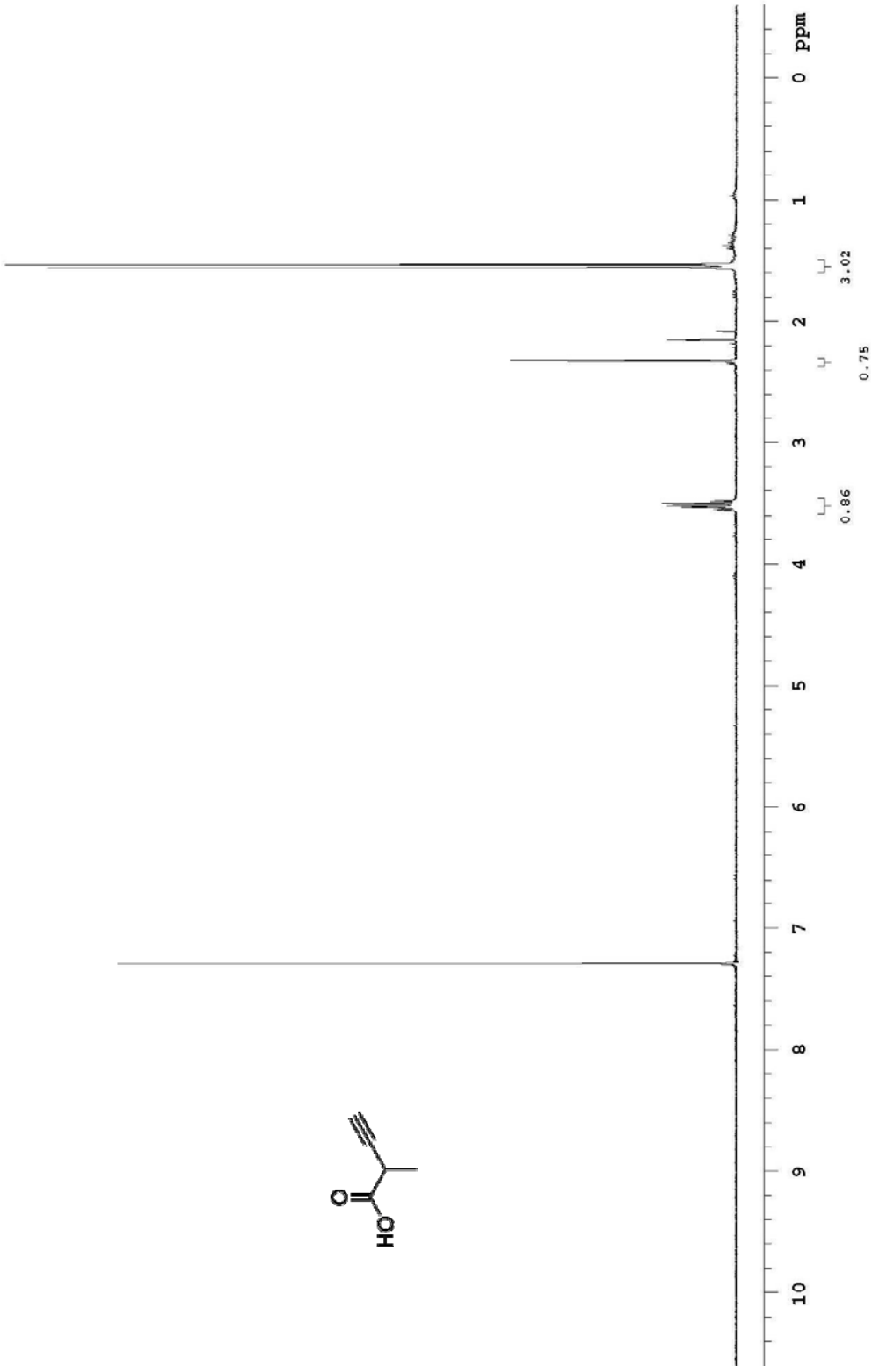
^{13}C NMR spectrum of alkyne **S-14**



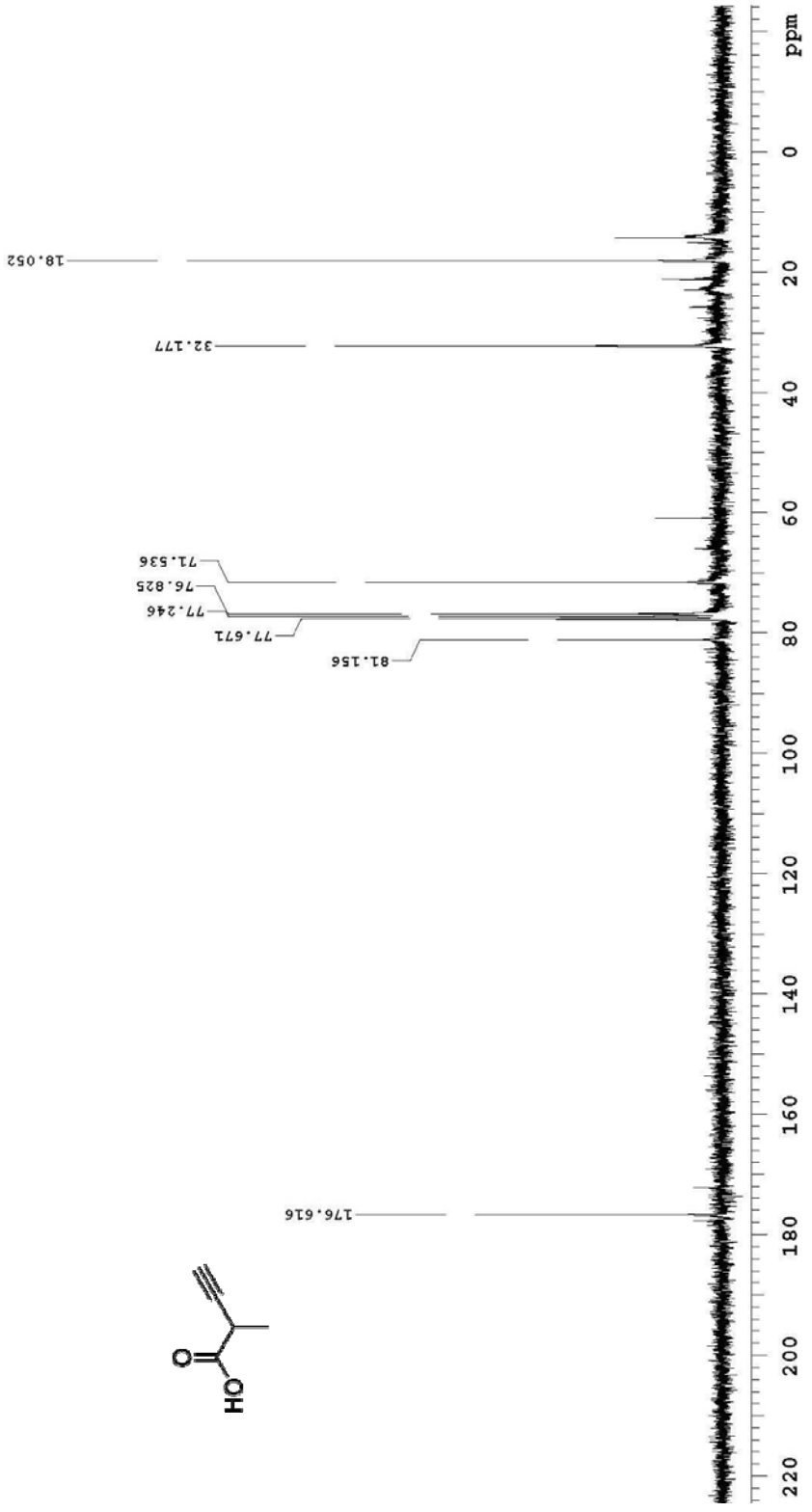
^{1}H NMR spectrum of alcohol **S-15**



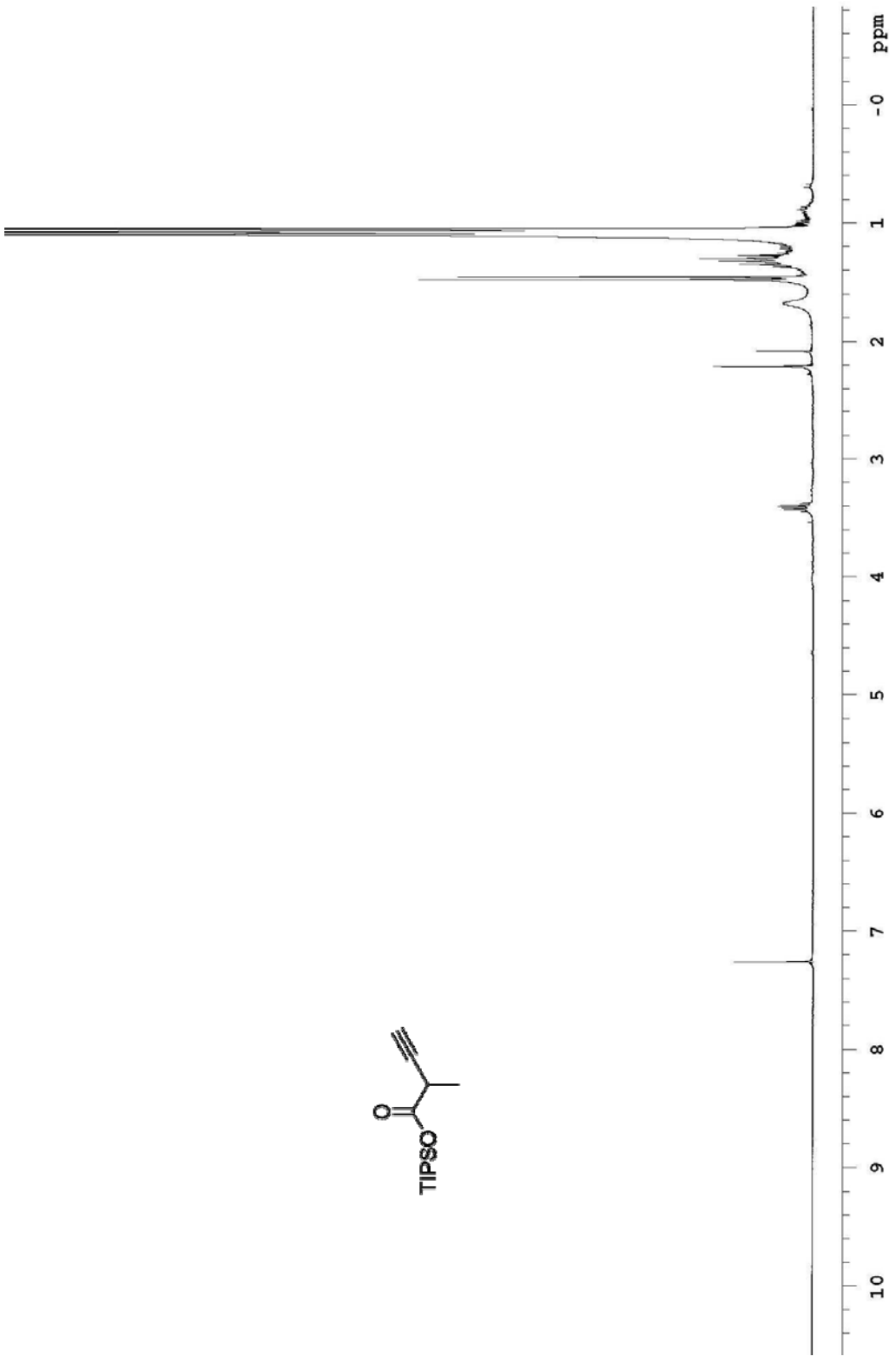
^{13}C NMR spectrum of alcohol **S-15**



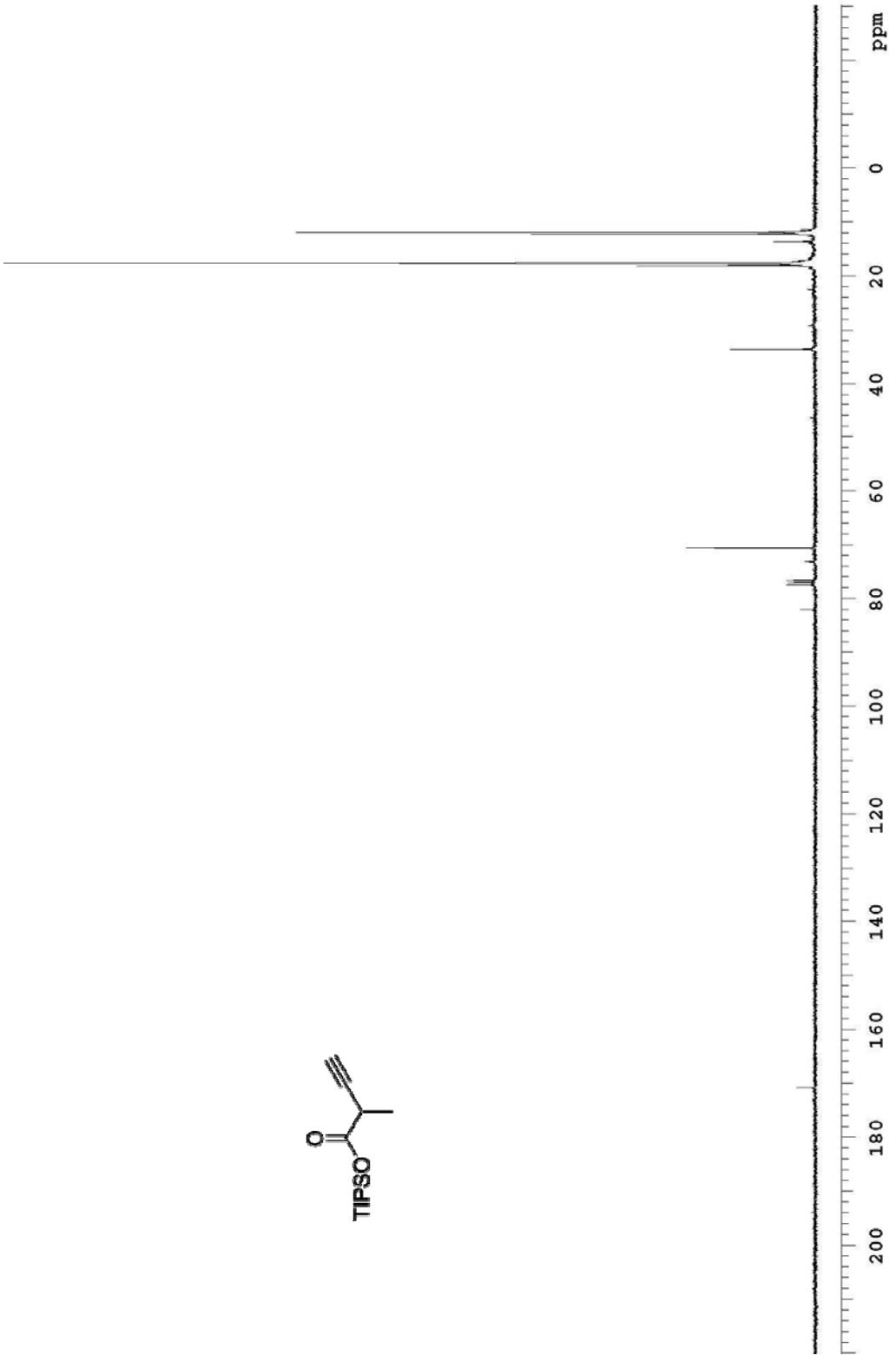
^{1}H NMR spectrum of carboxylic acid **S-16**



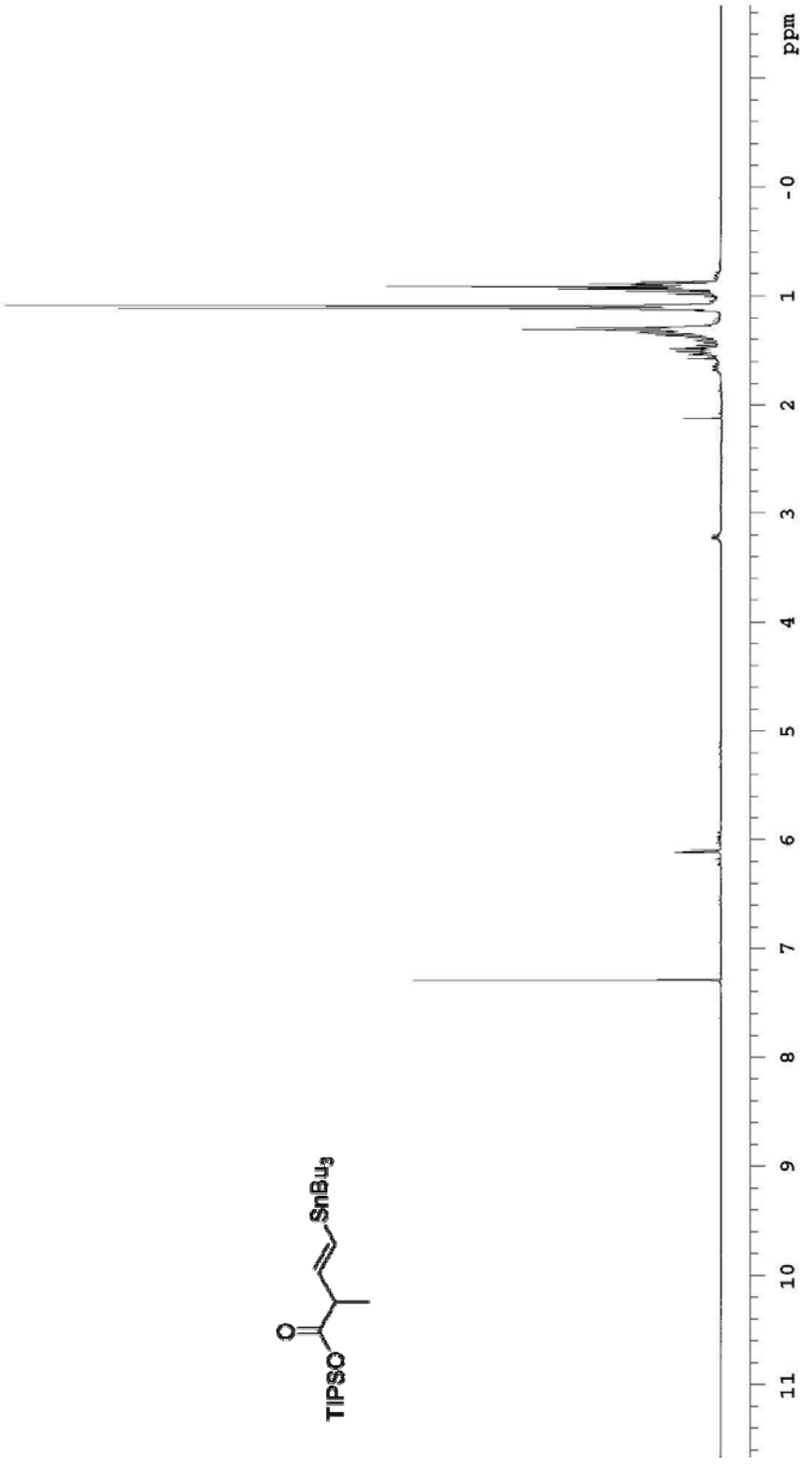
^{13}C NMR spectrum of carboxylic acid **S-16**



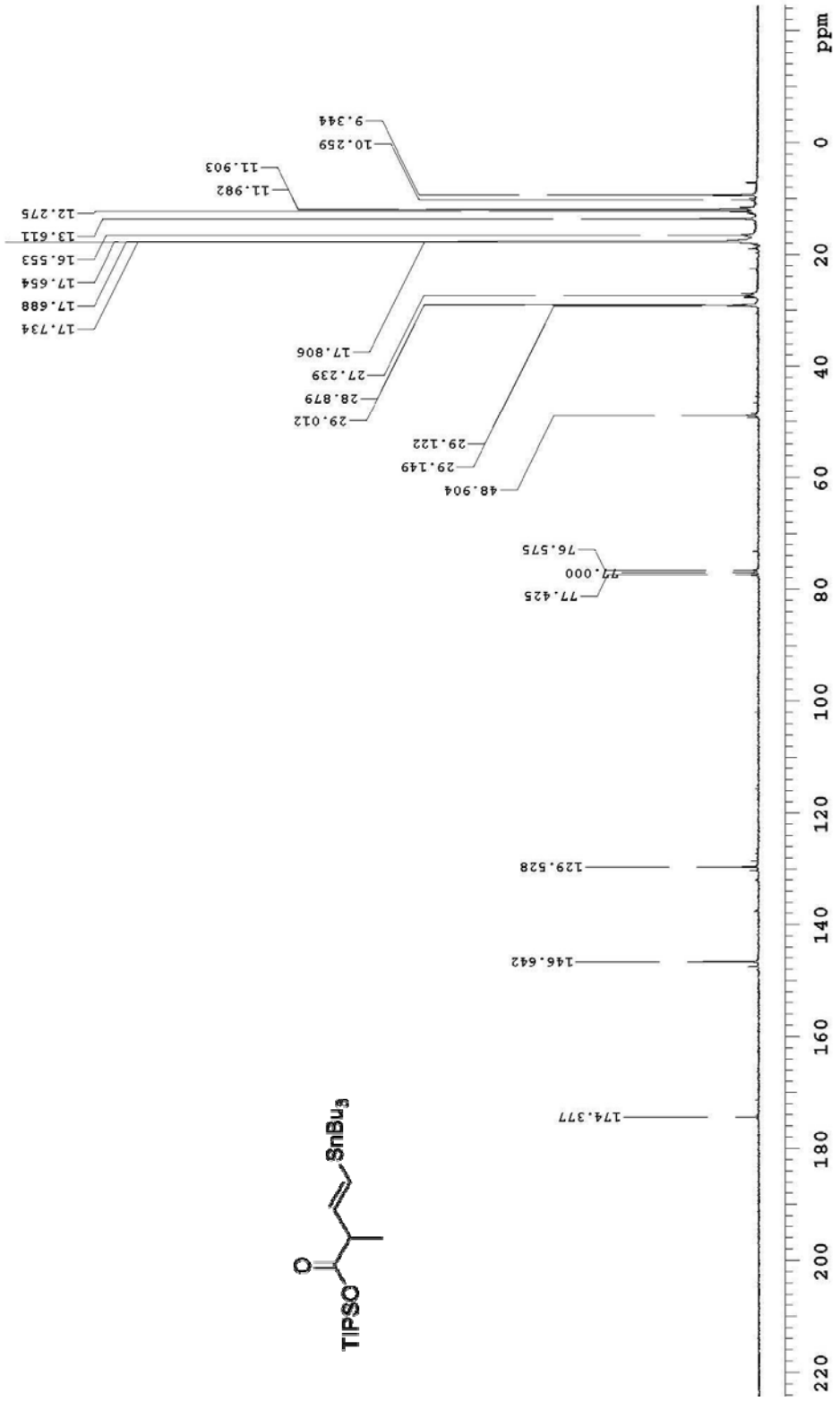
^{1}H NMR spectrum of TIPS ester **S-17**



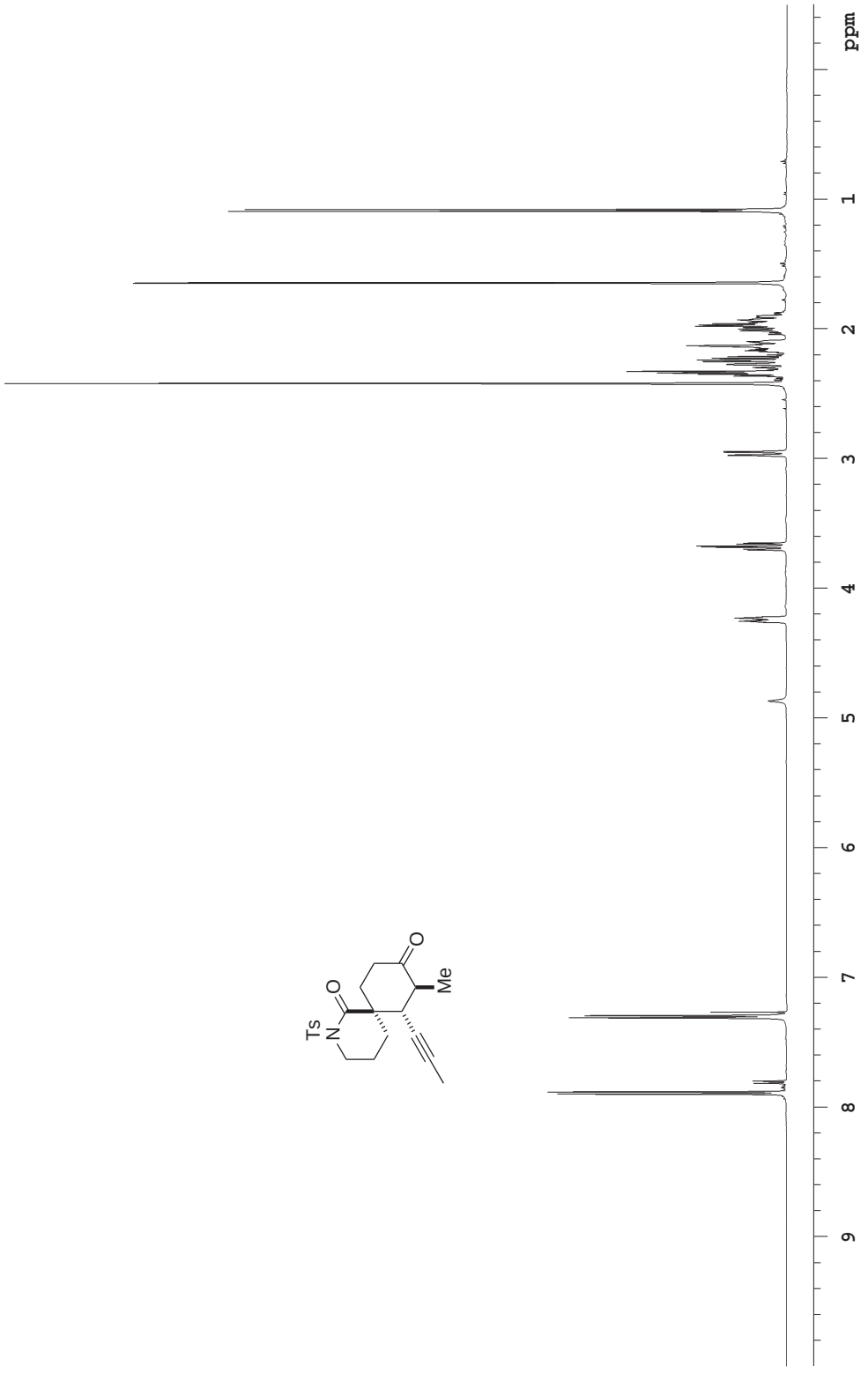
^{13}C NMR spectrum of TIPS ester **S-17**



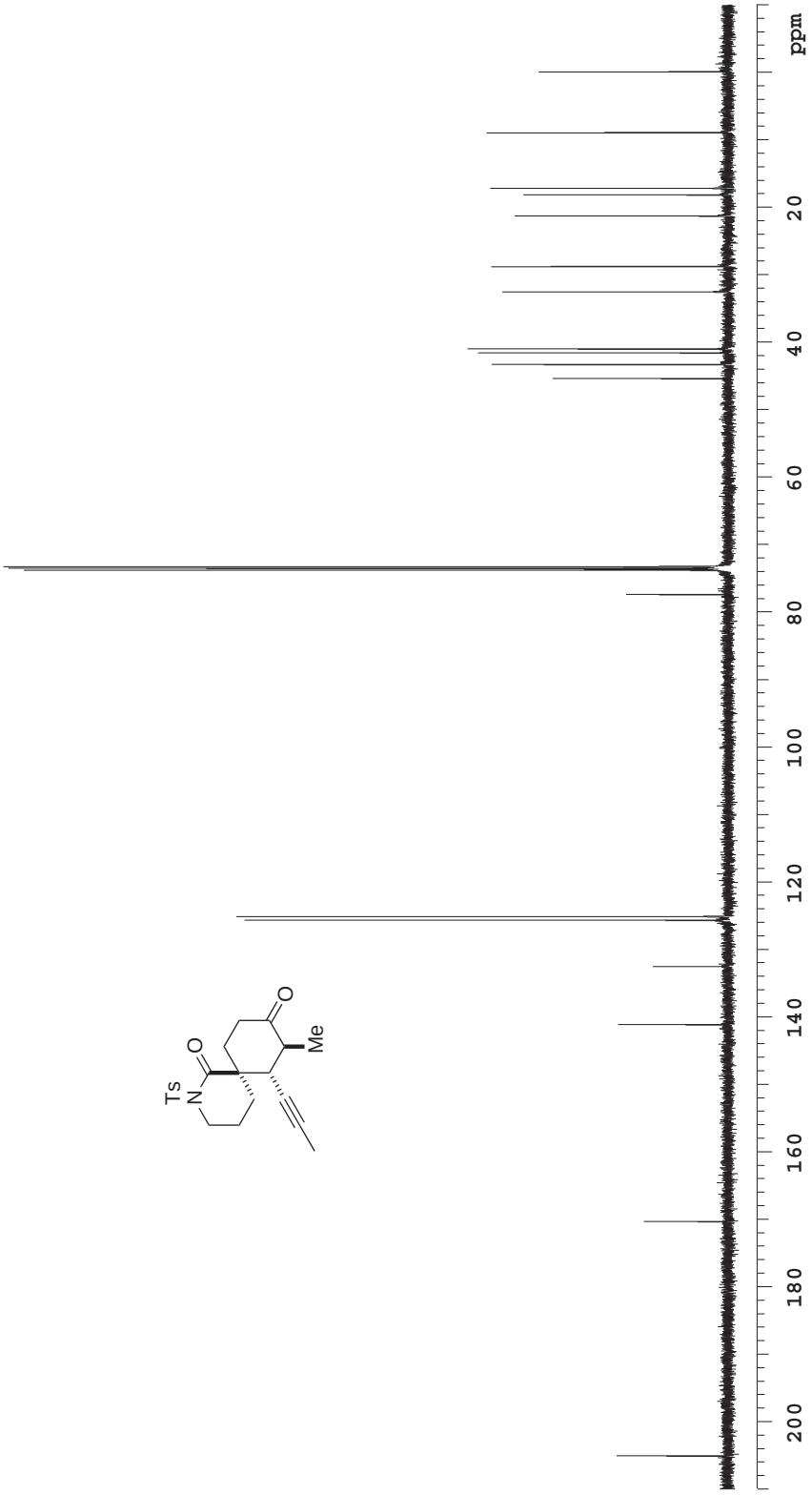
^{1}H NMR spectrum of vinyl stannane **69**



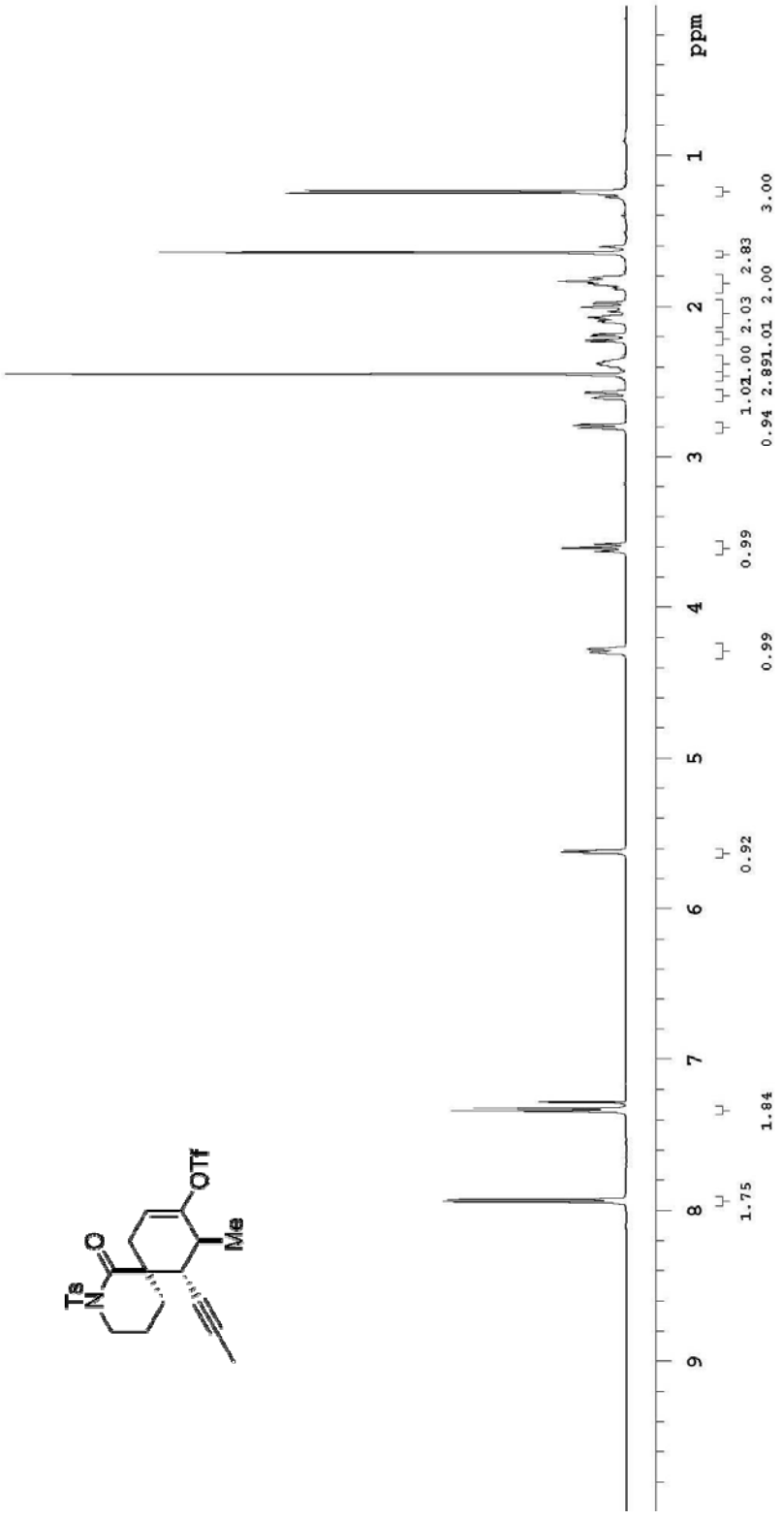
^{13}C NMR spectrum of vinyl stannane **69**



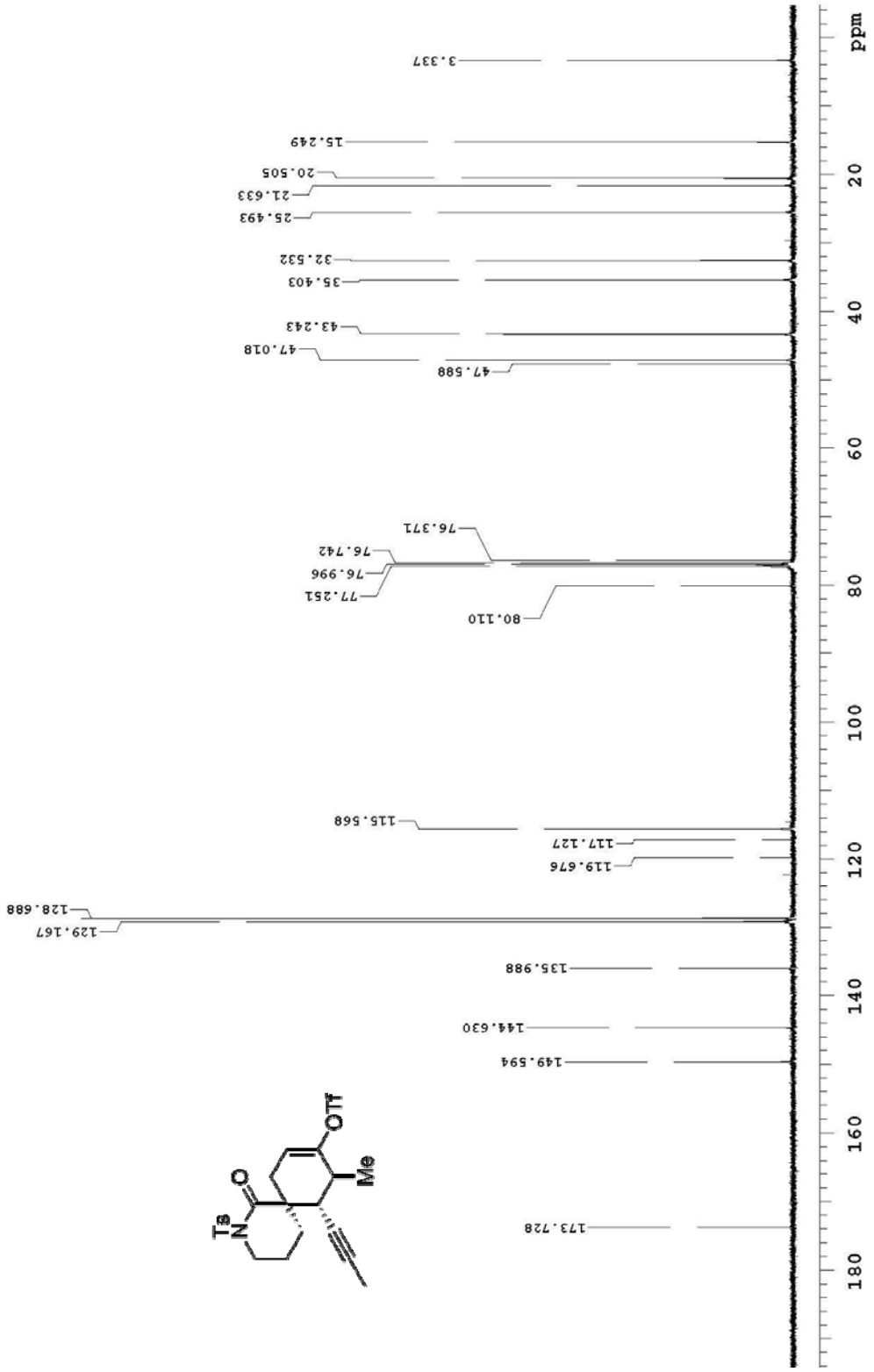
^{1}H NMR spectrum of ketone **74**



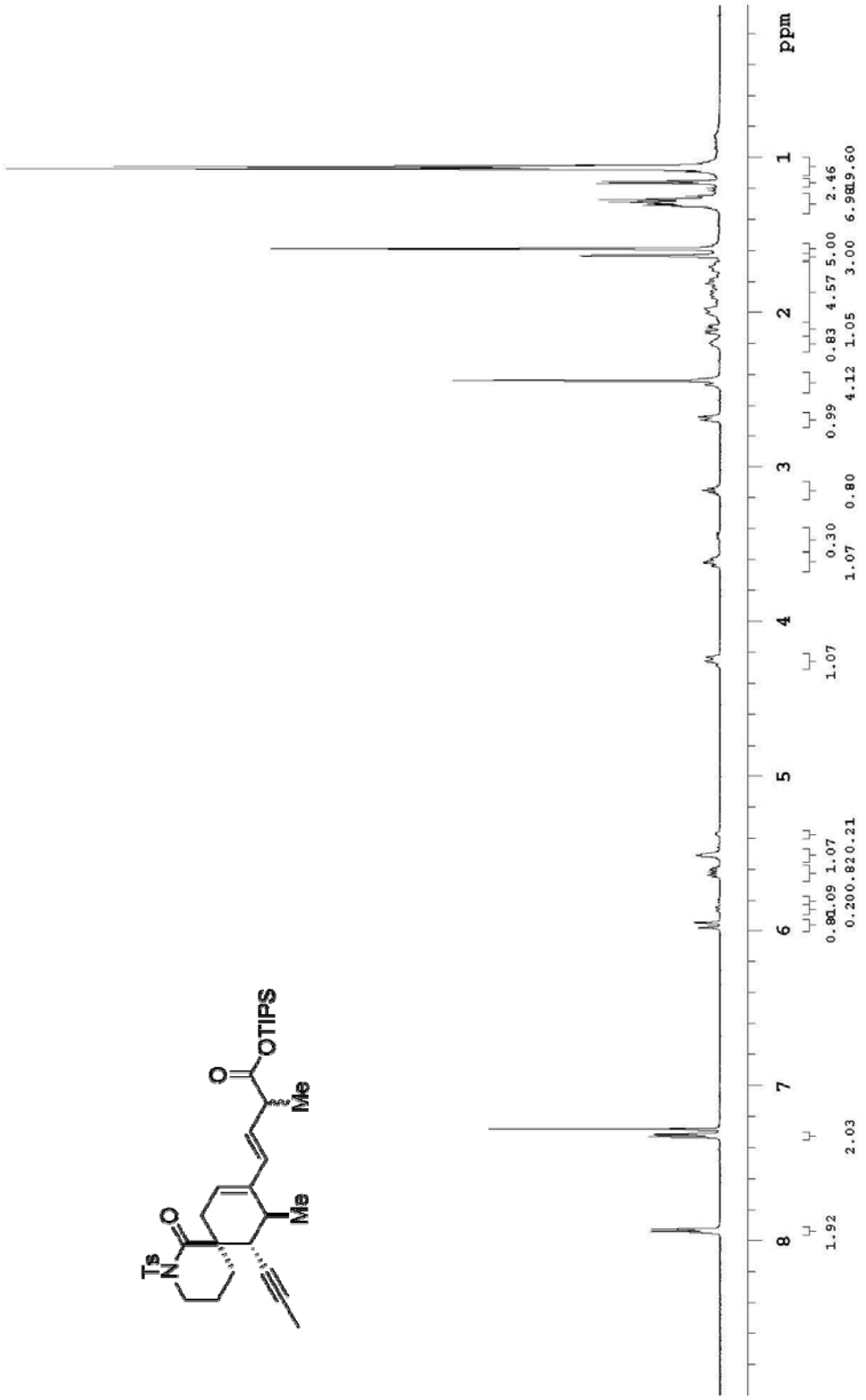
^{13}C NMR spectrum of ketone **74**



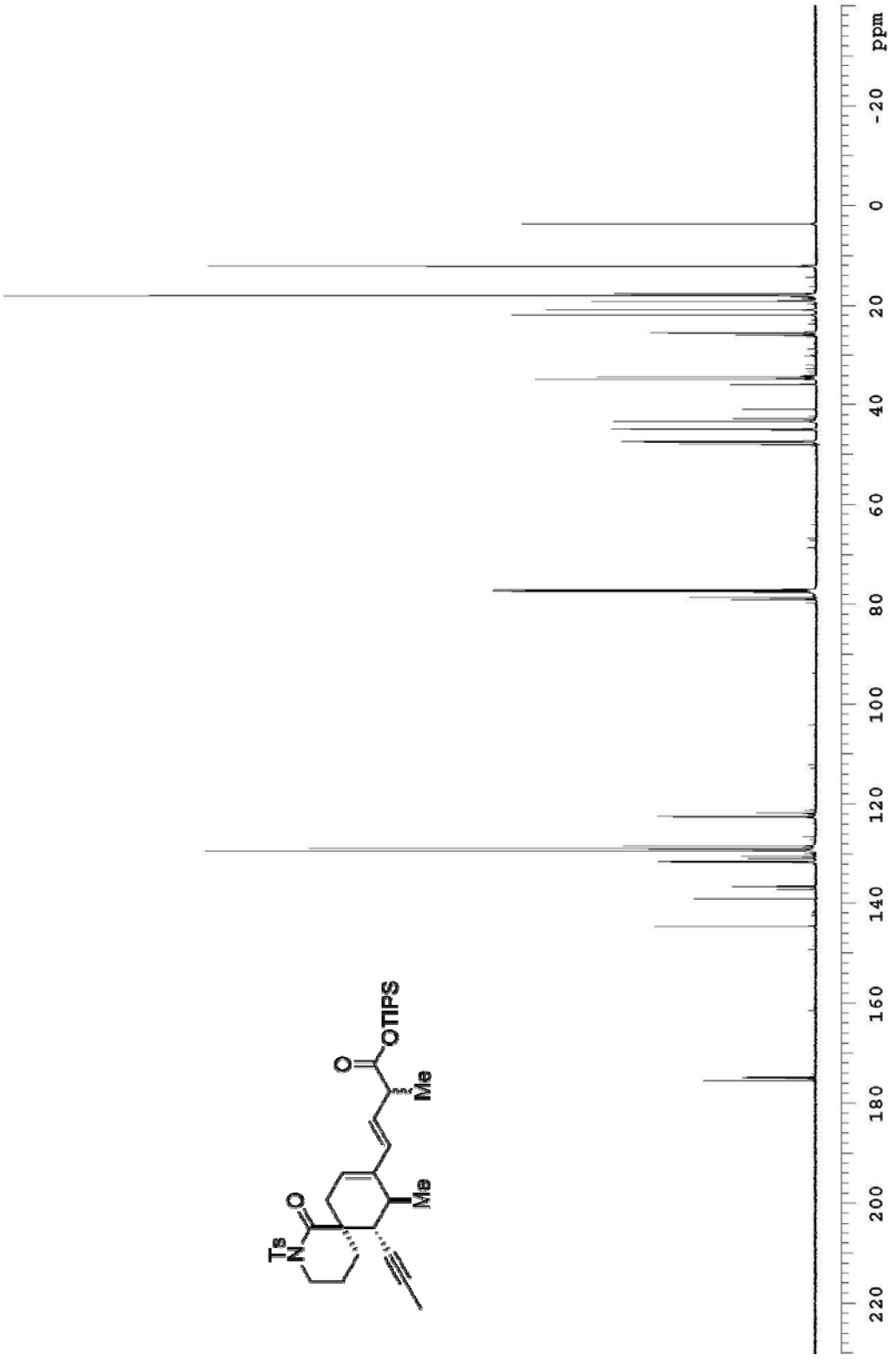
^{1}H NMR spectrum of vinyl triflate **75**



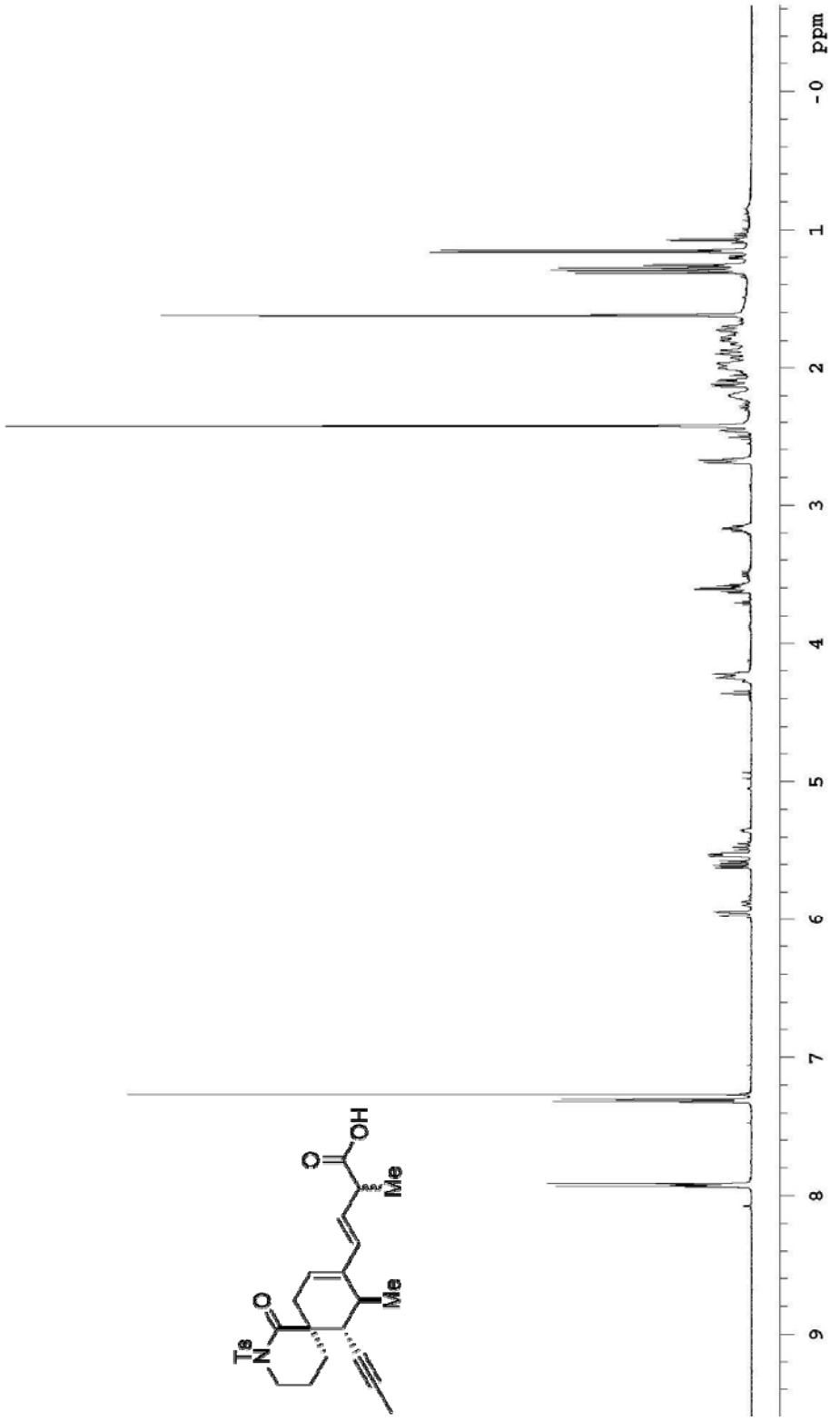
^{13}C NMR spectrum of vinyl triflate **75**



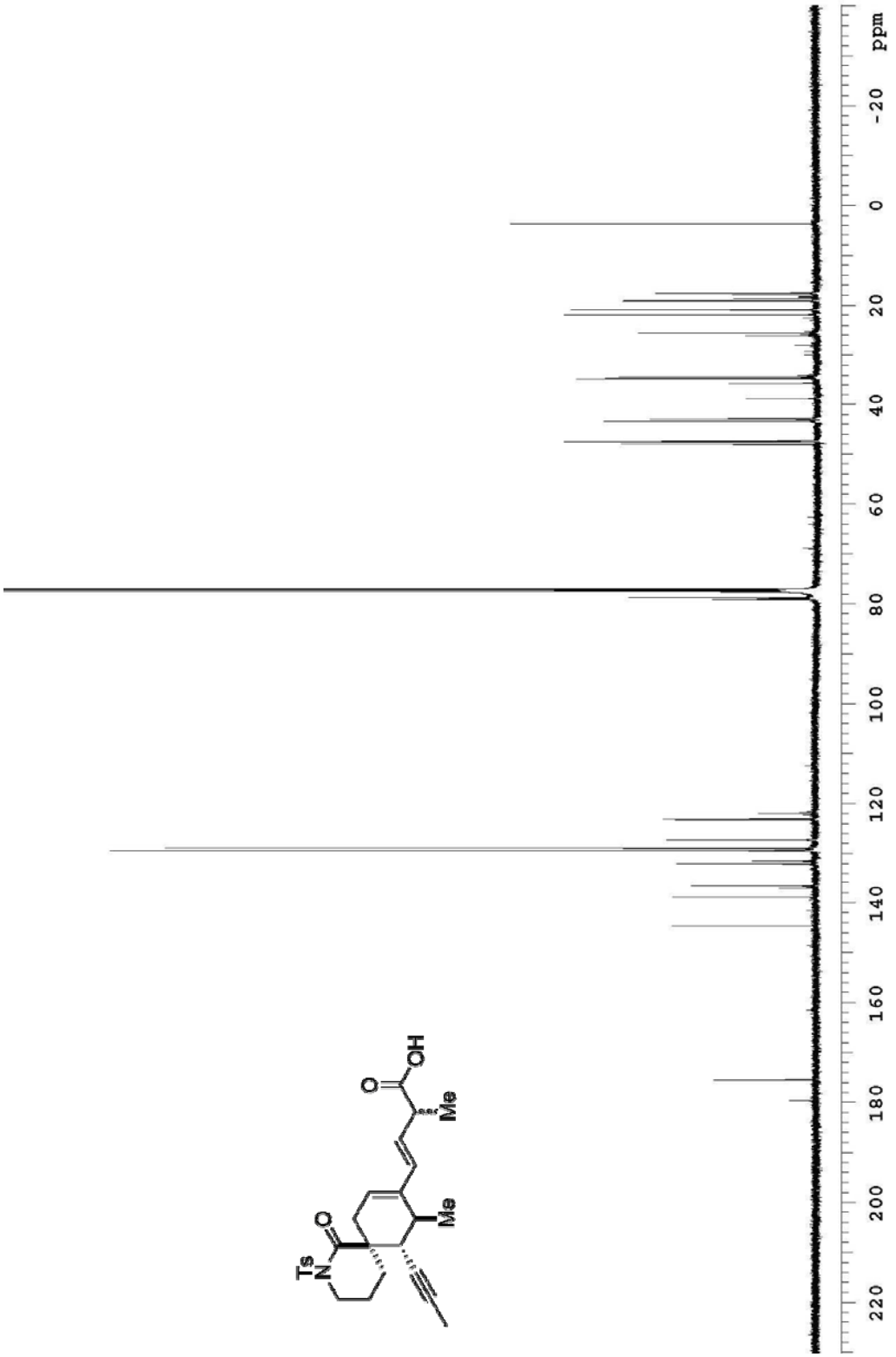
^{1}H NMR spectrum of diene **76**



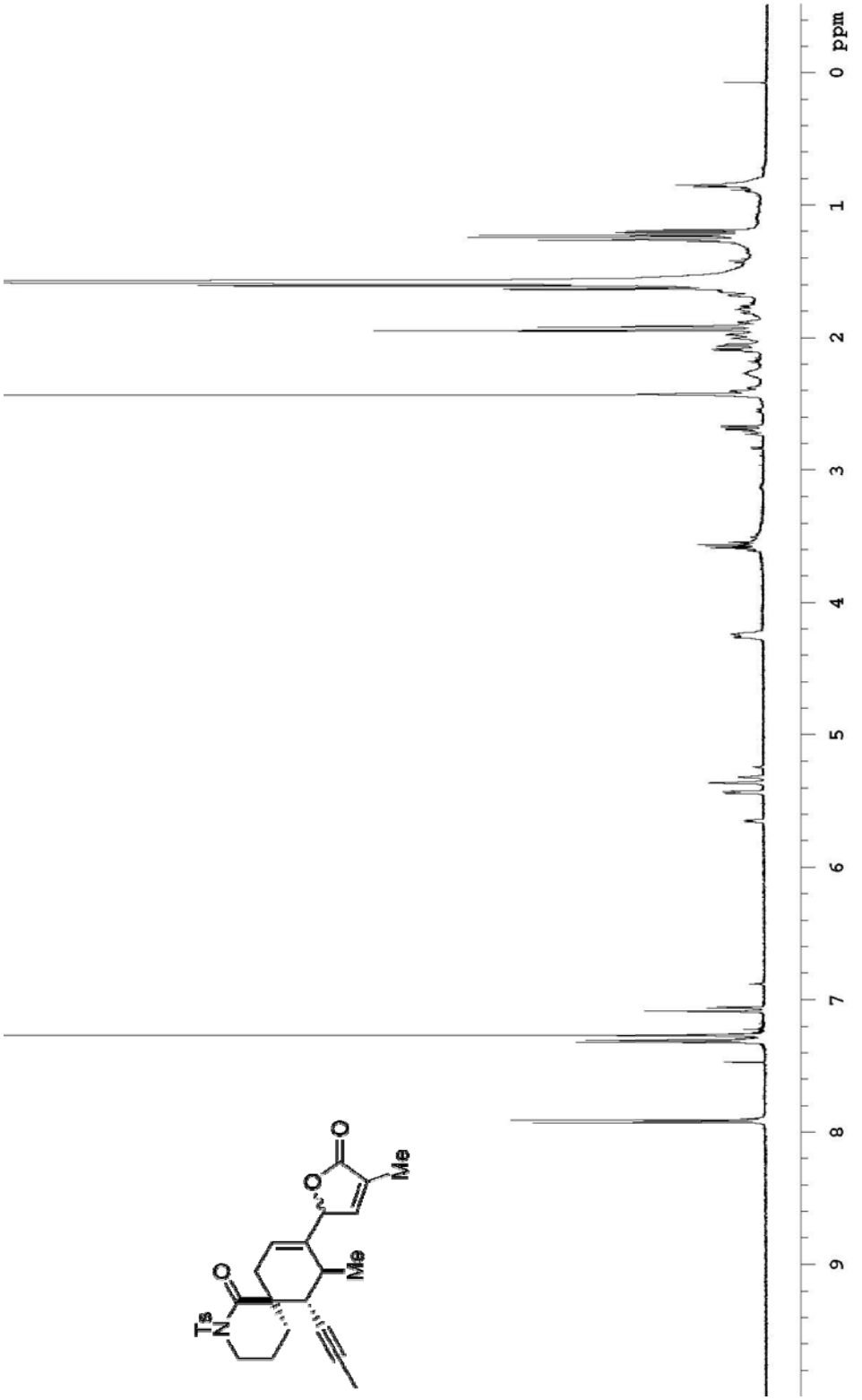
^{13}C NMR spectrum of diene **76**



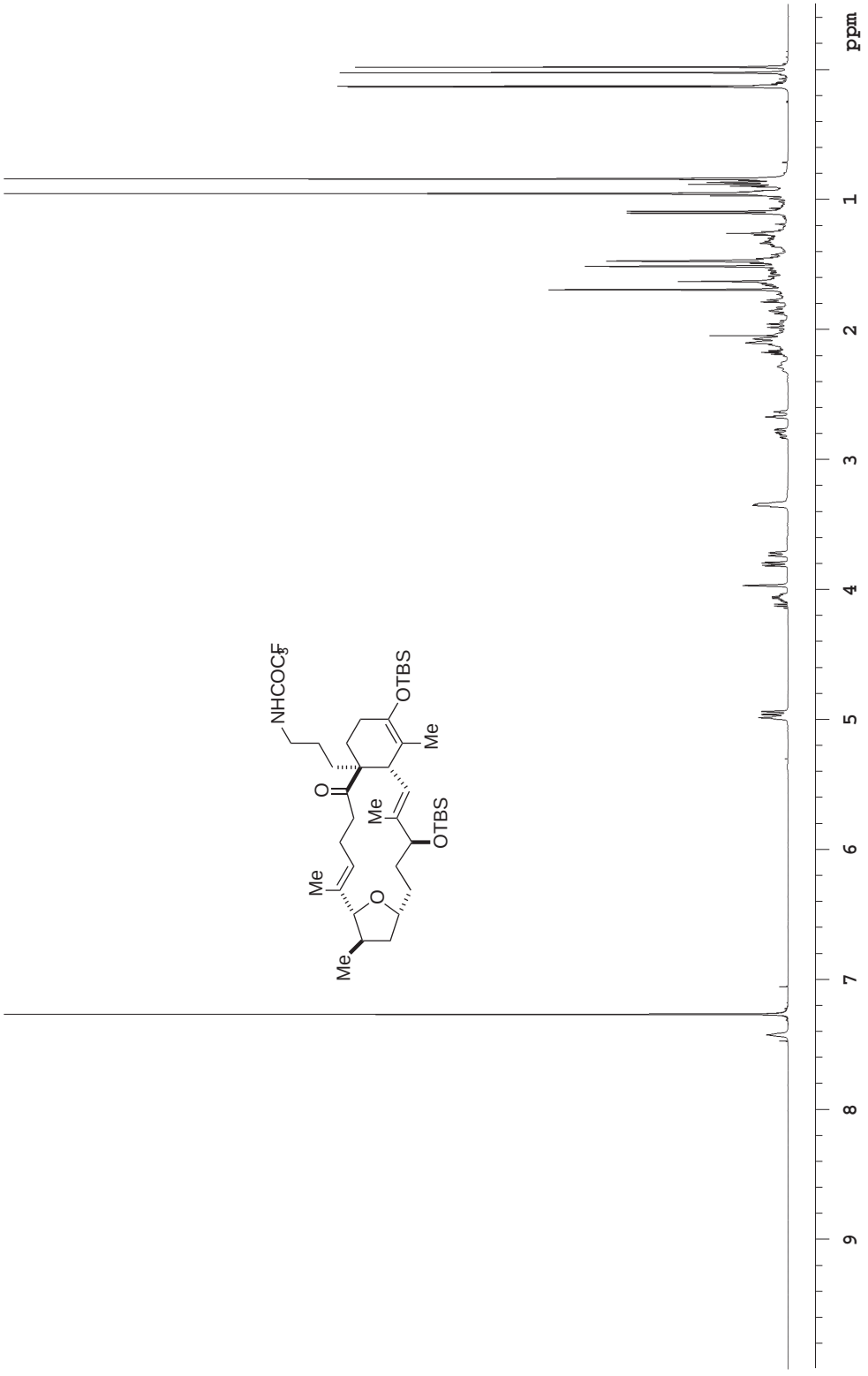
^{1}H NMR spectrum of carboxylic acid **77**



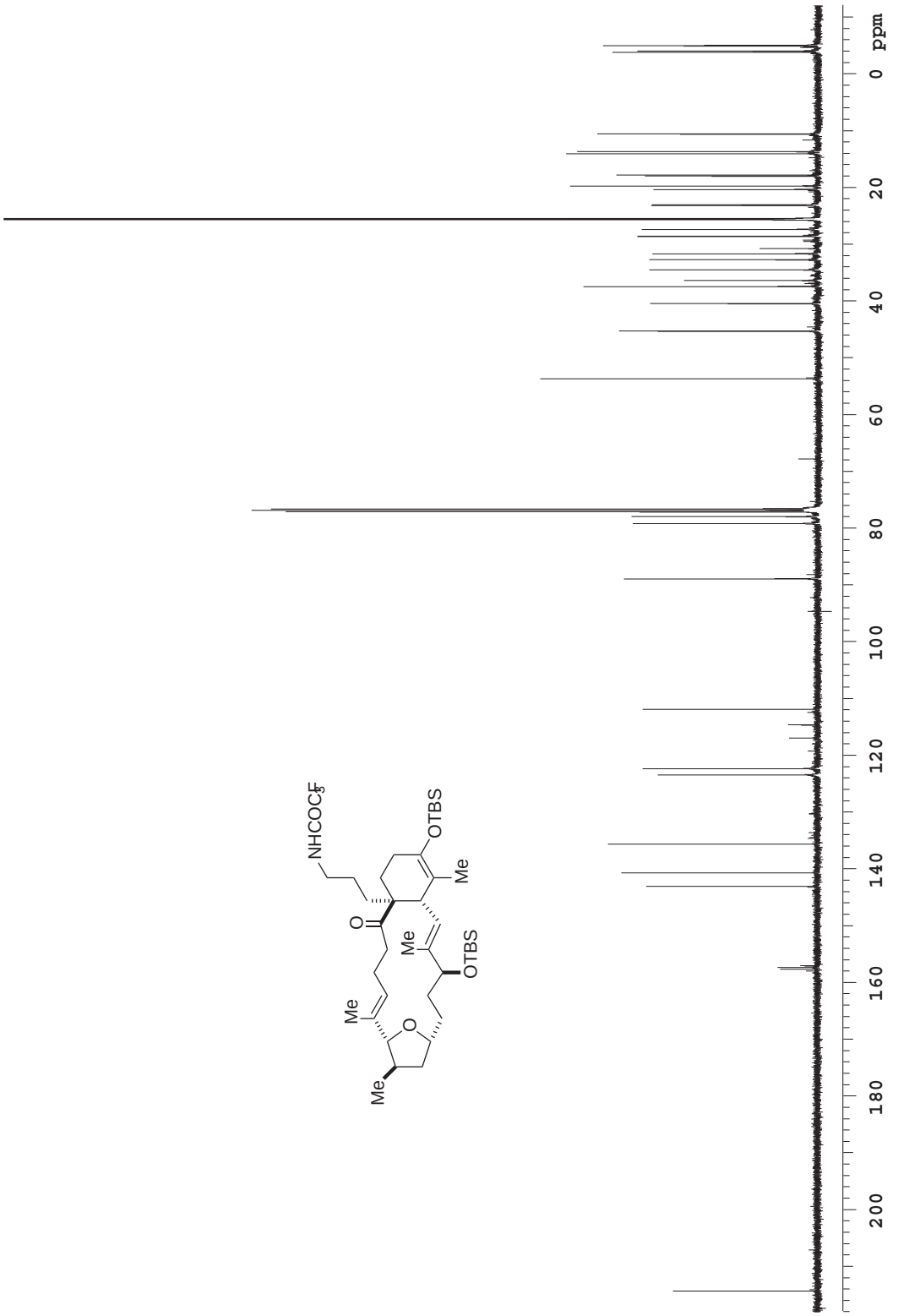
^{13}C NMR spectrum of carboxylic acid **77**



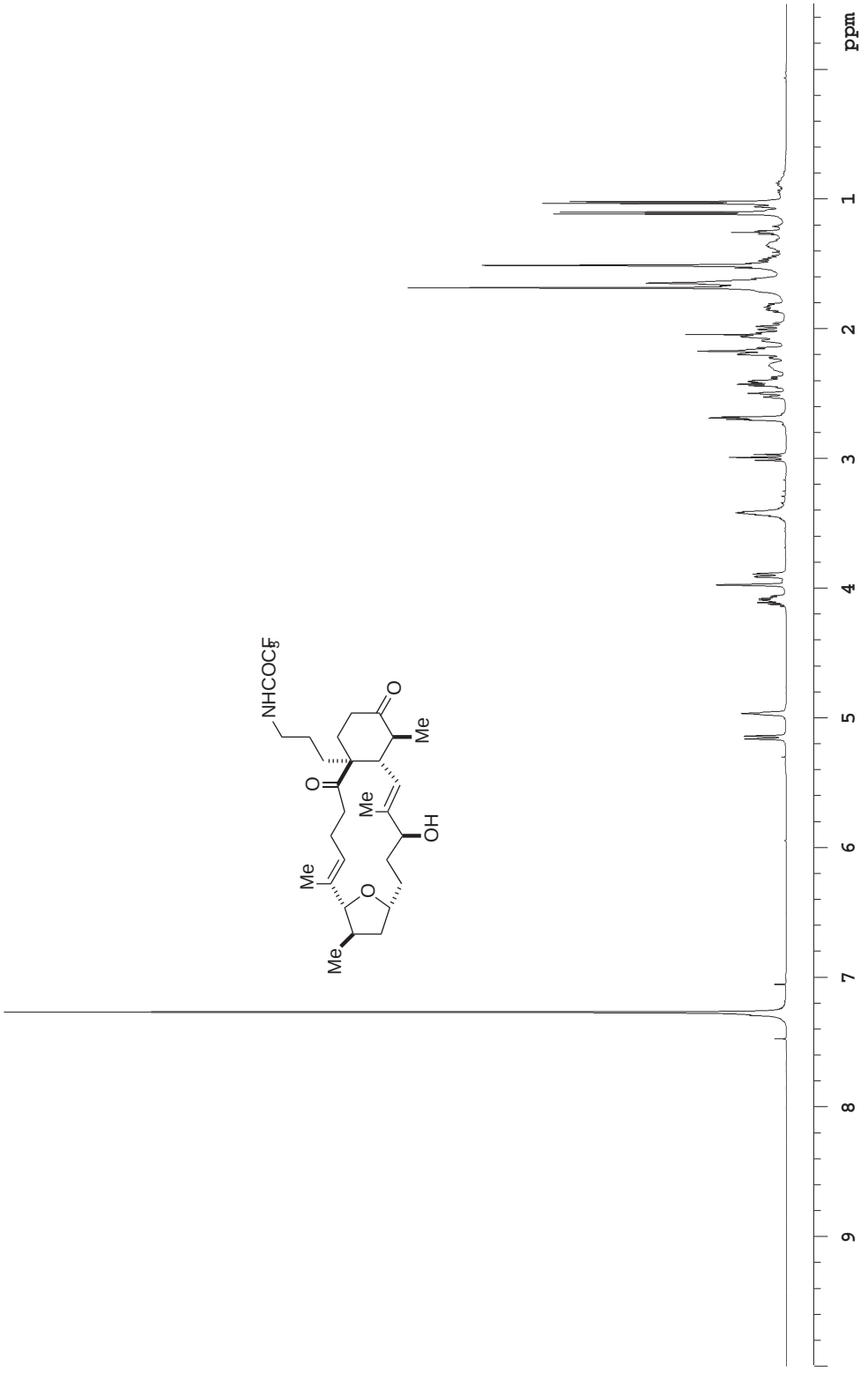
^{1}H NMR spectrum of butenolide **79**



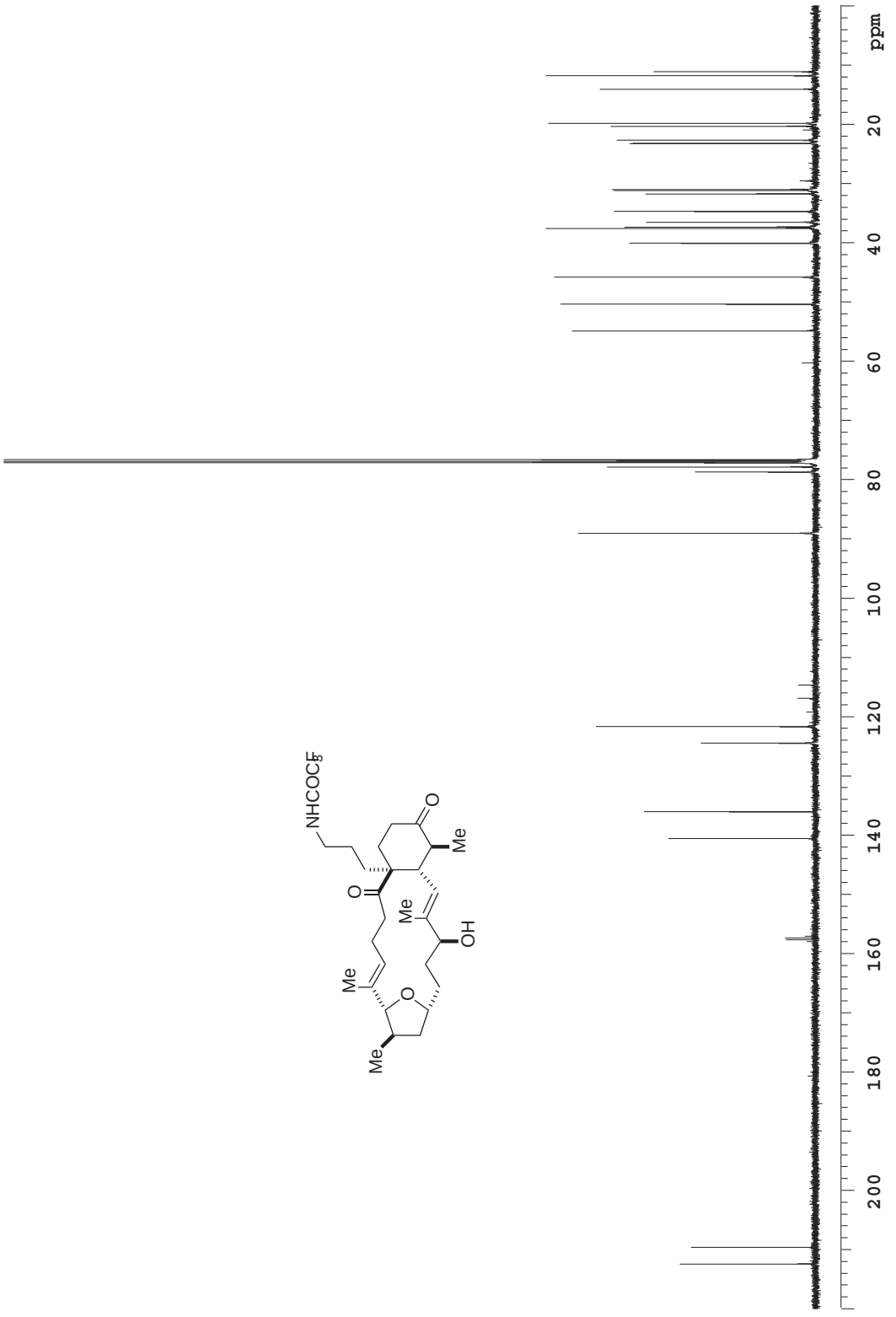
^{1}H NMR spectrum of trifluoroacetamide **82**



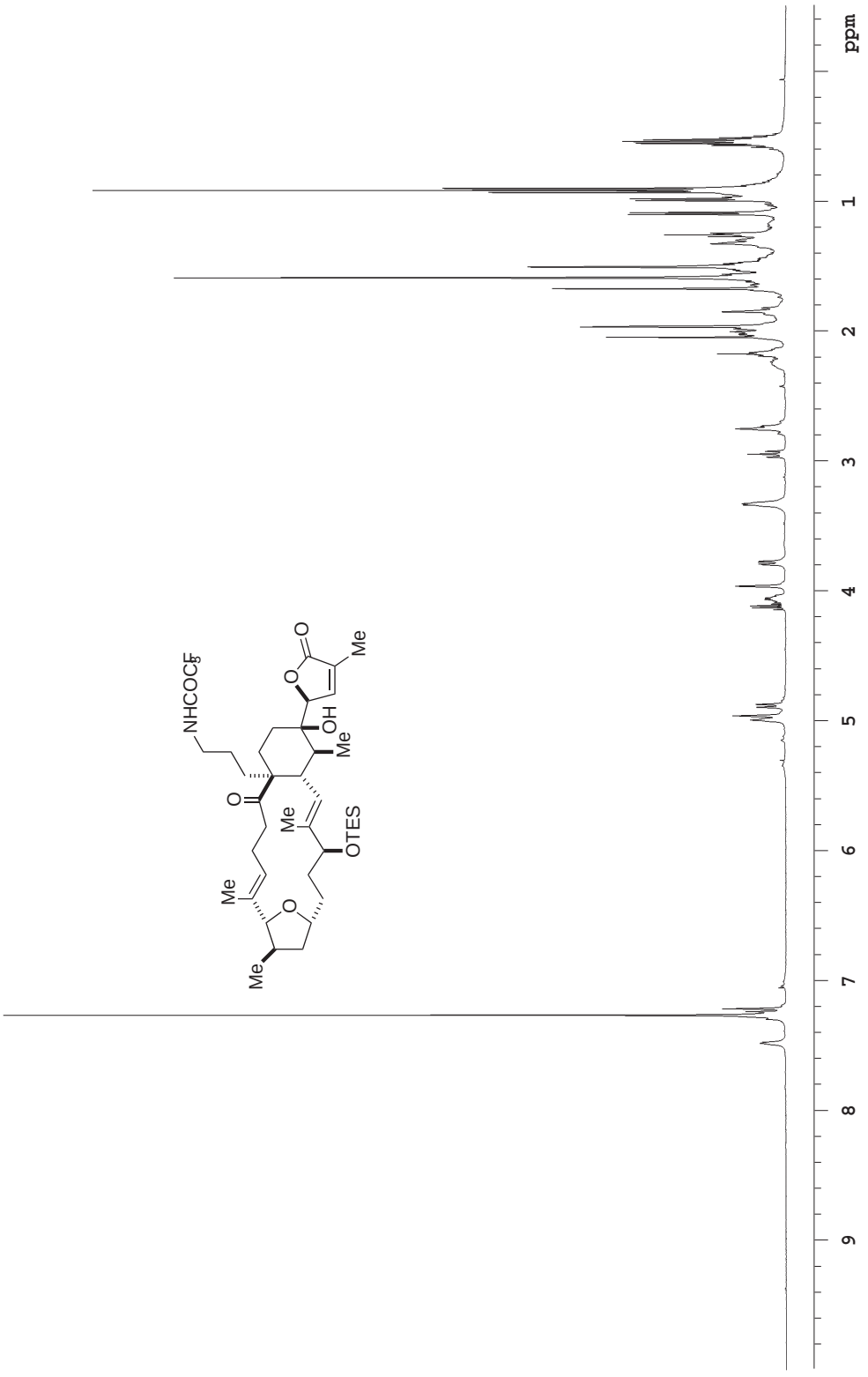
^{13}C NMR spectrum of trifluoroacetamide **82**



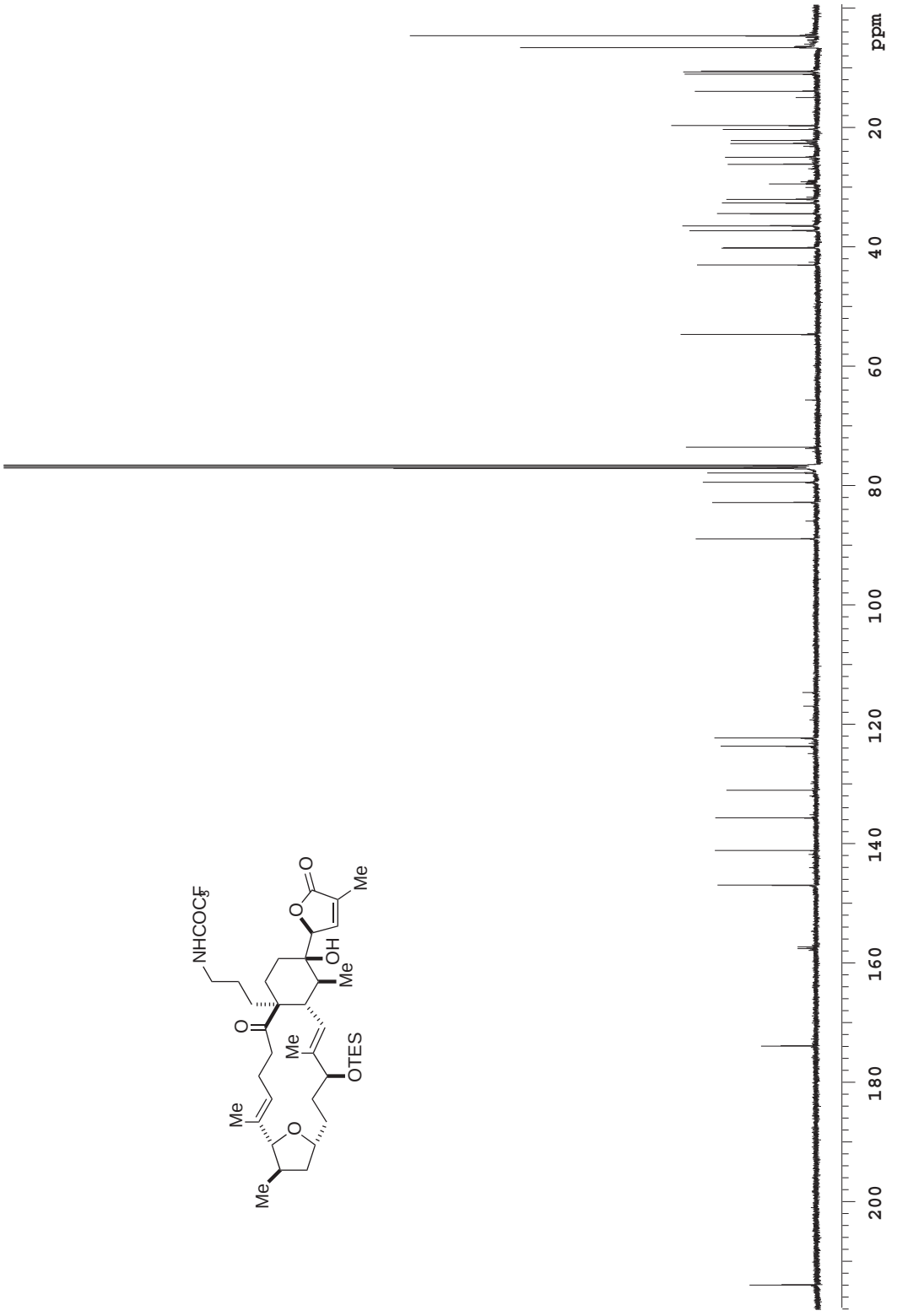
^{1}H NMR spectrum of ketone **83**



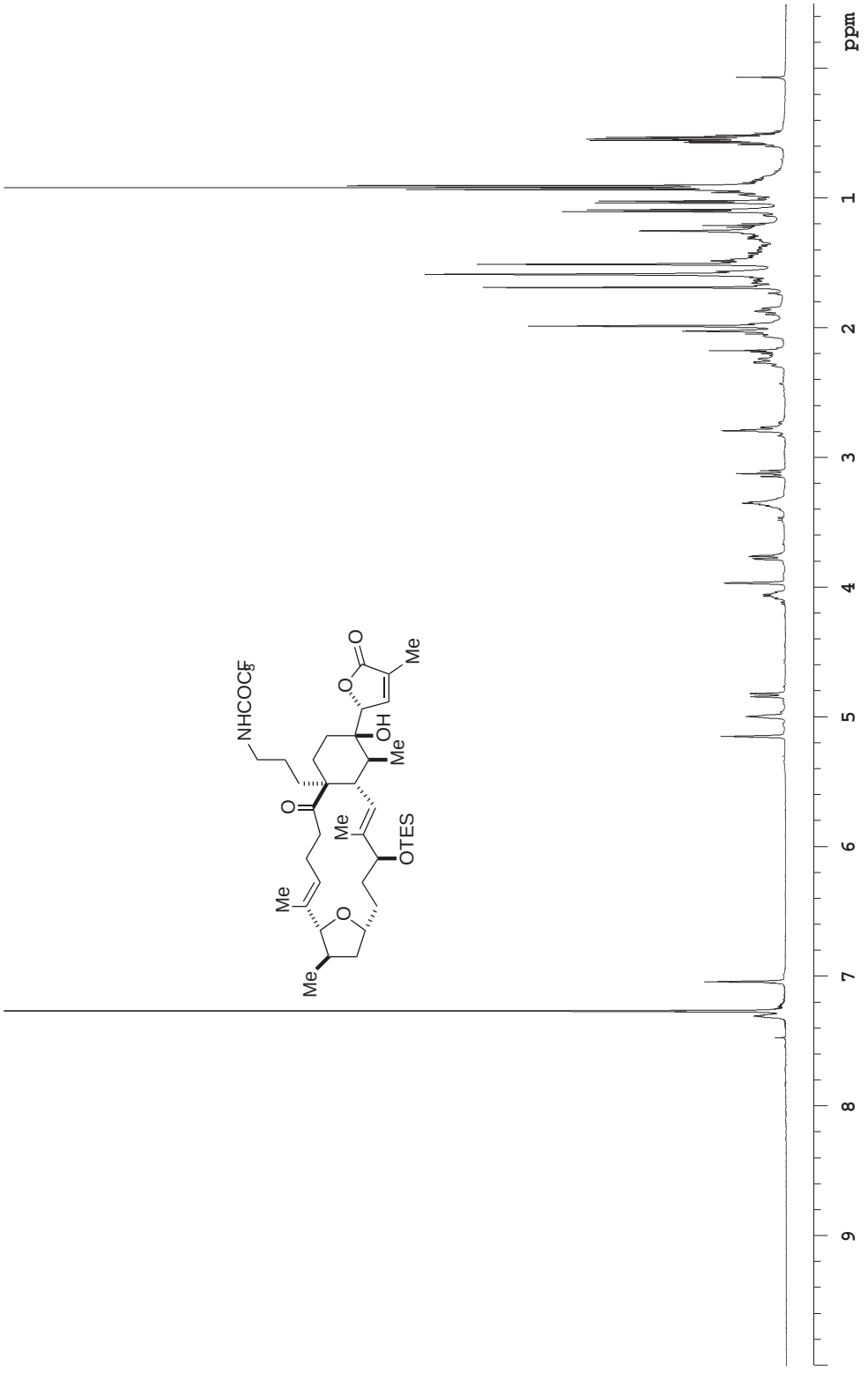
^{13}C NMR spectrum of ketone **83**



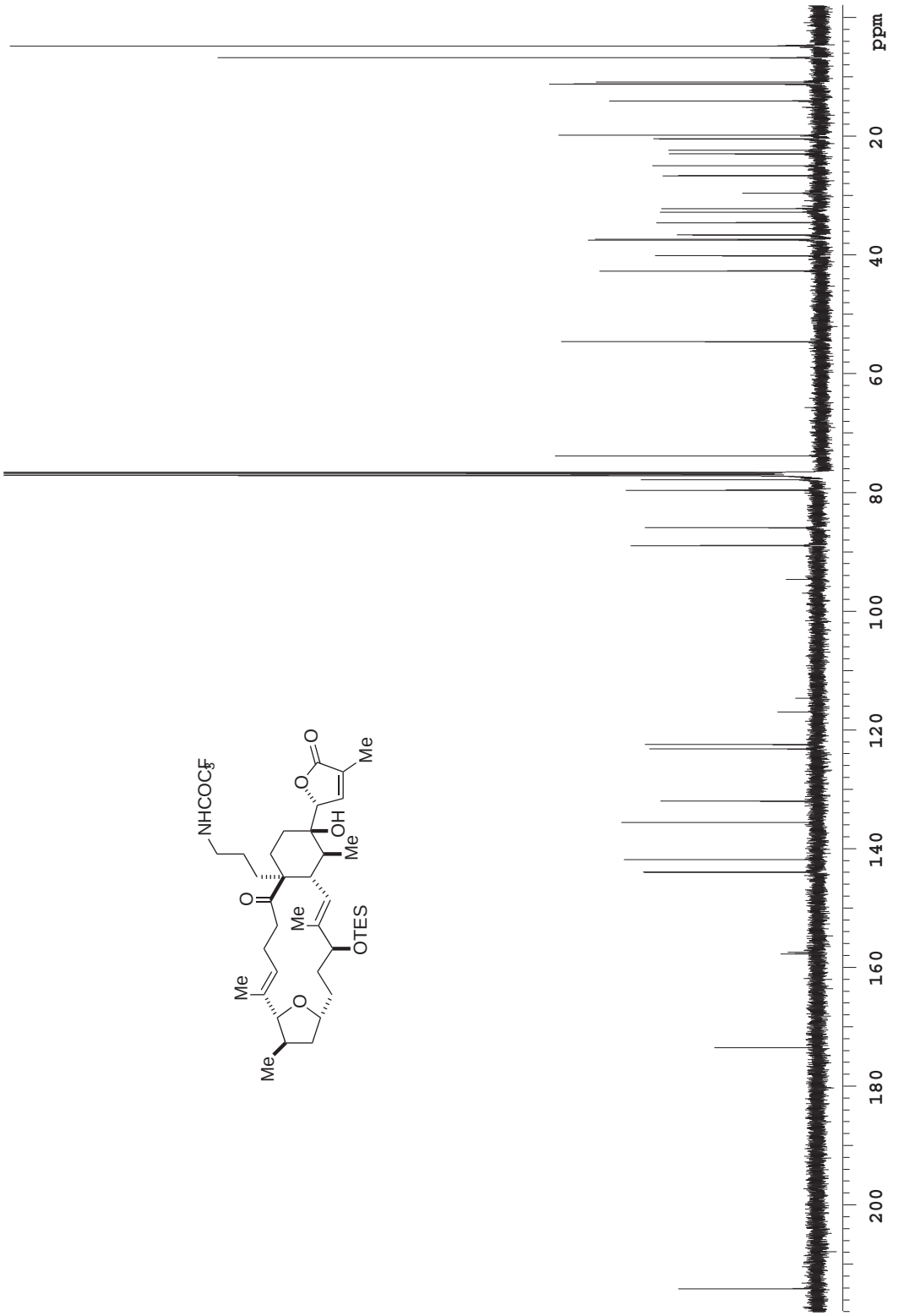
^{1}H NMR spectrum of alcohol **85a**



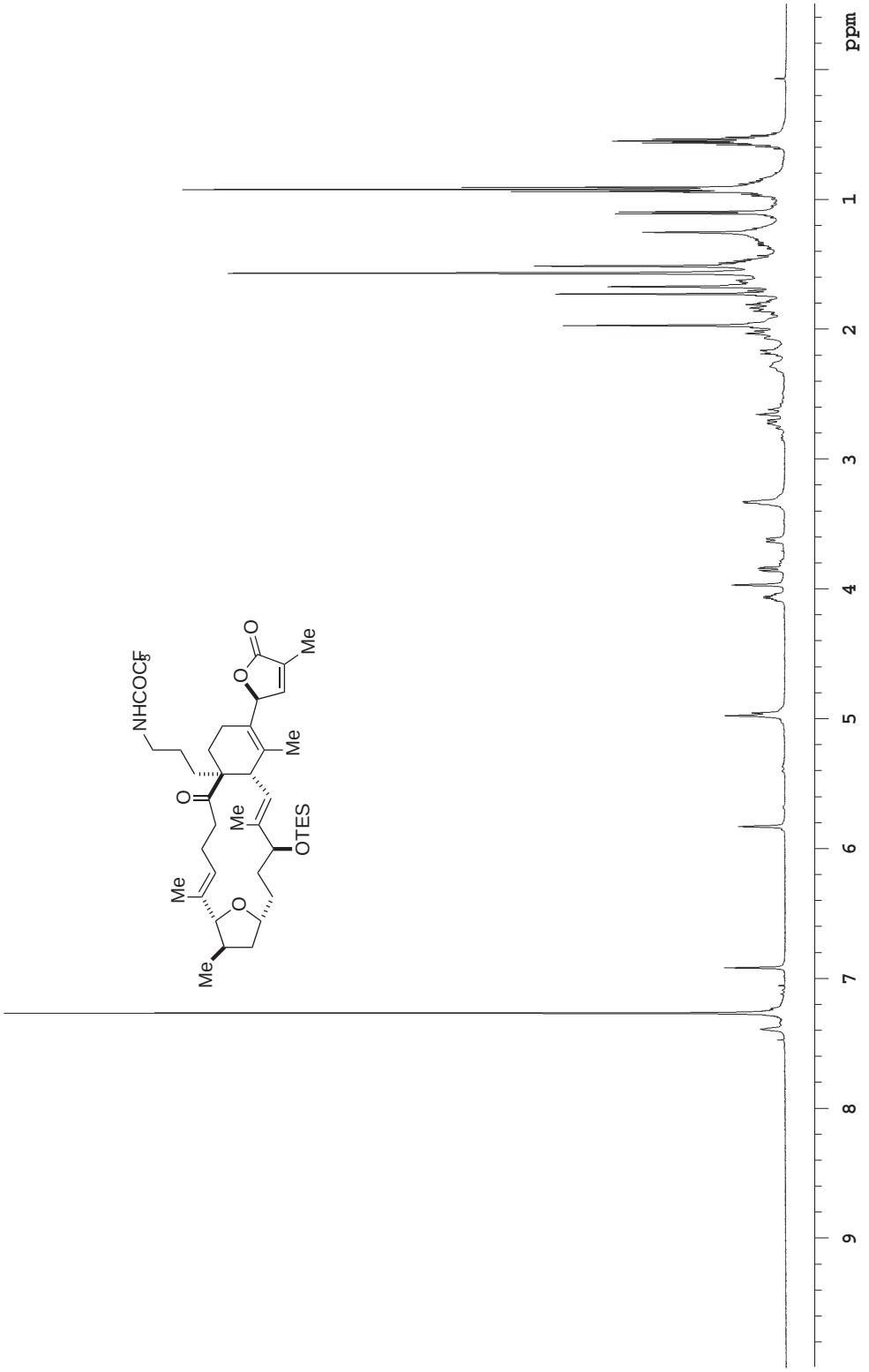
^{13}C NMR spectrum of alcohol **85a**



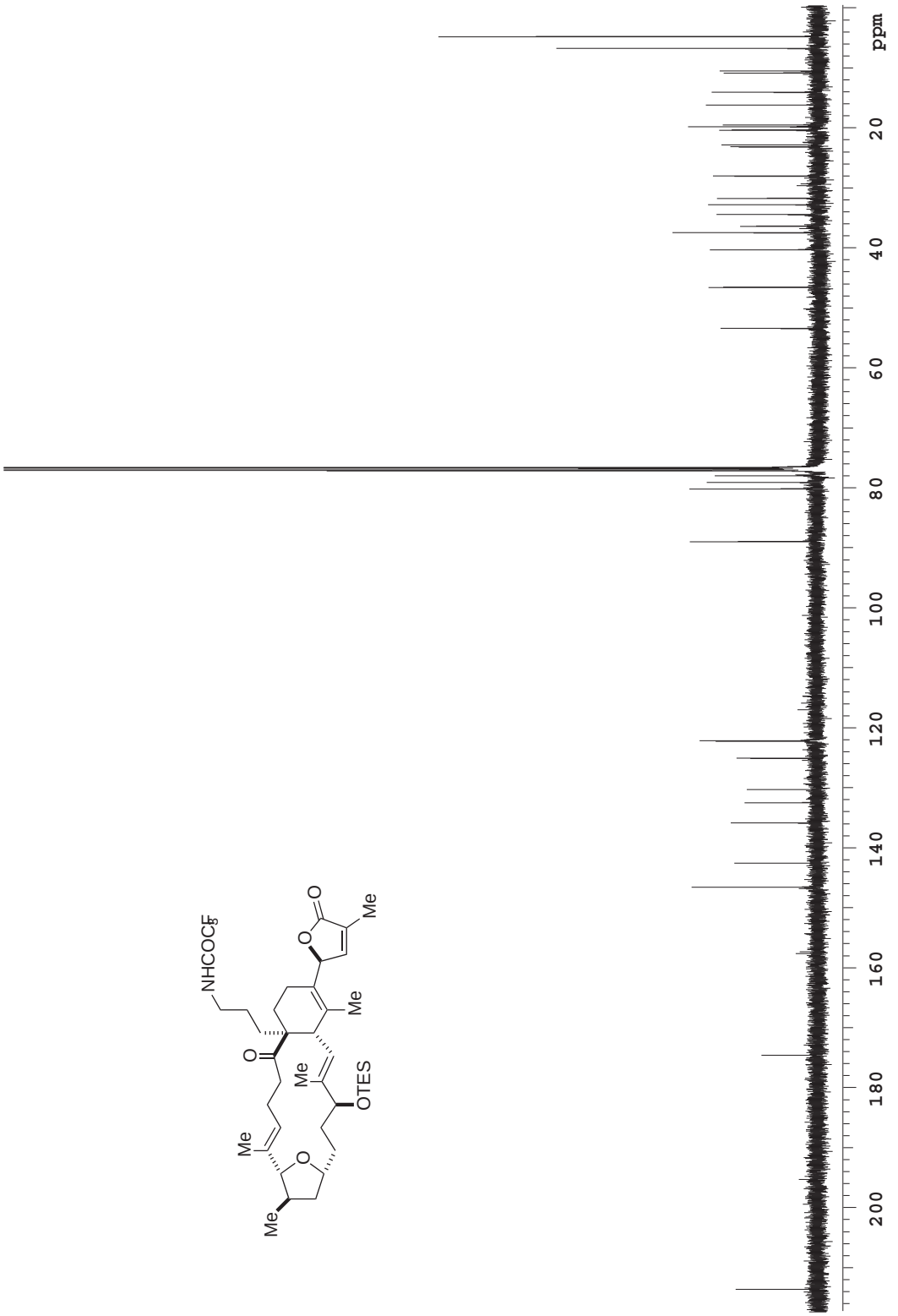
^{1}H NMR spectrum of alcohol **85b**



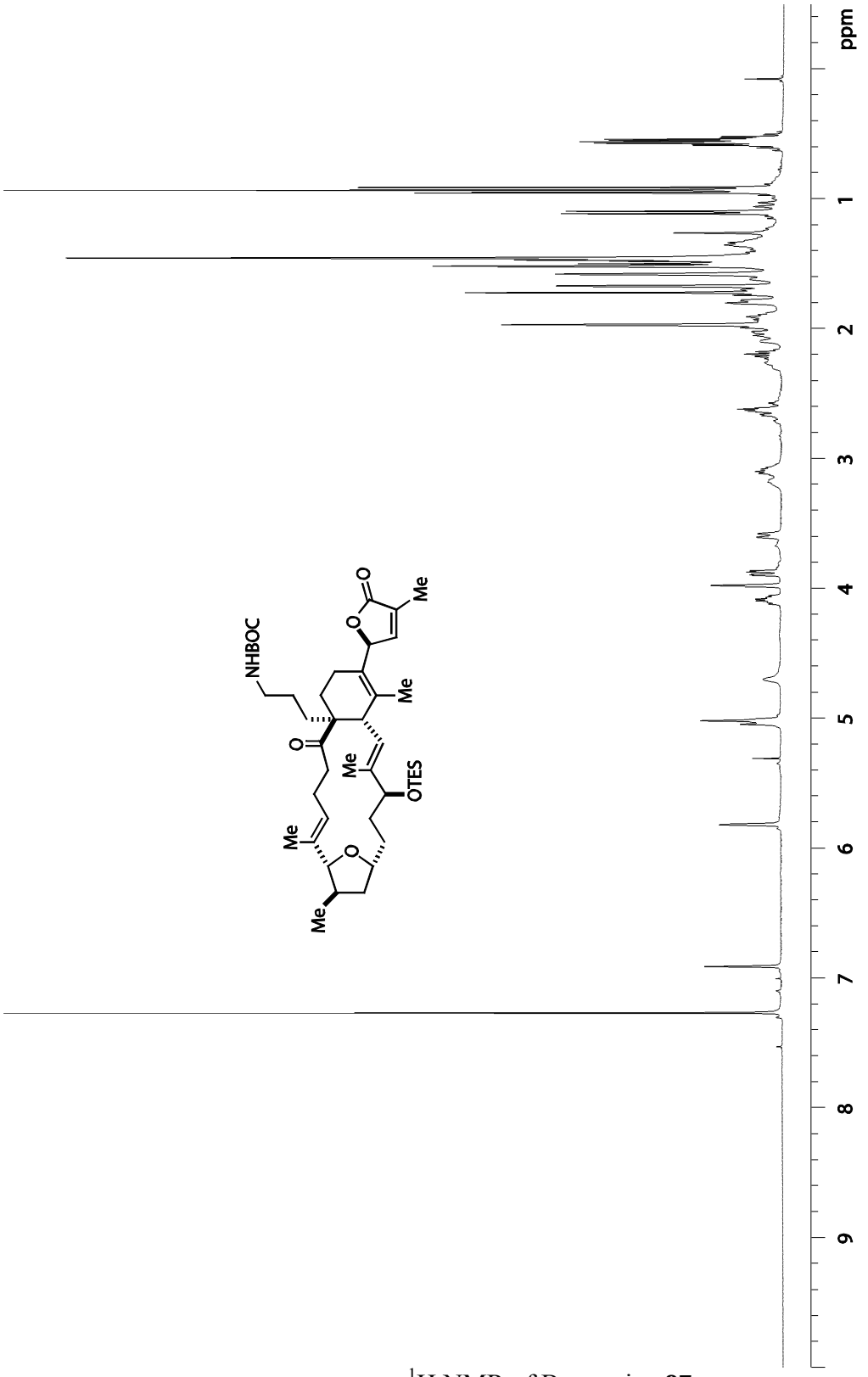
^{13}C NMR spectrum of alcohol **85b**



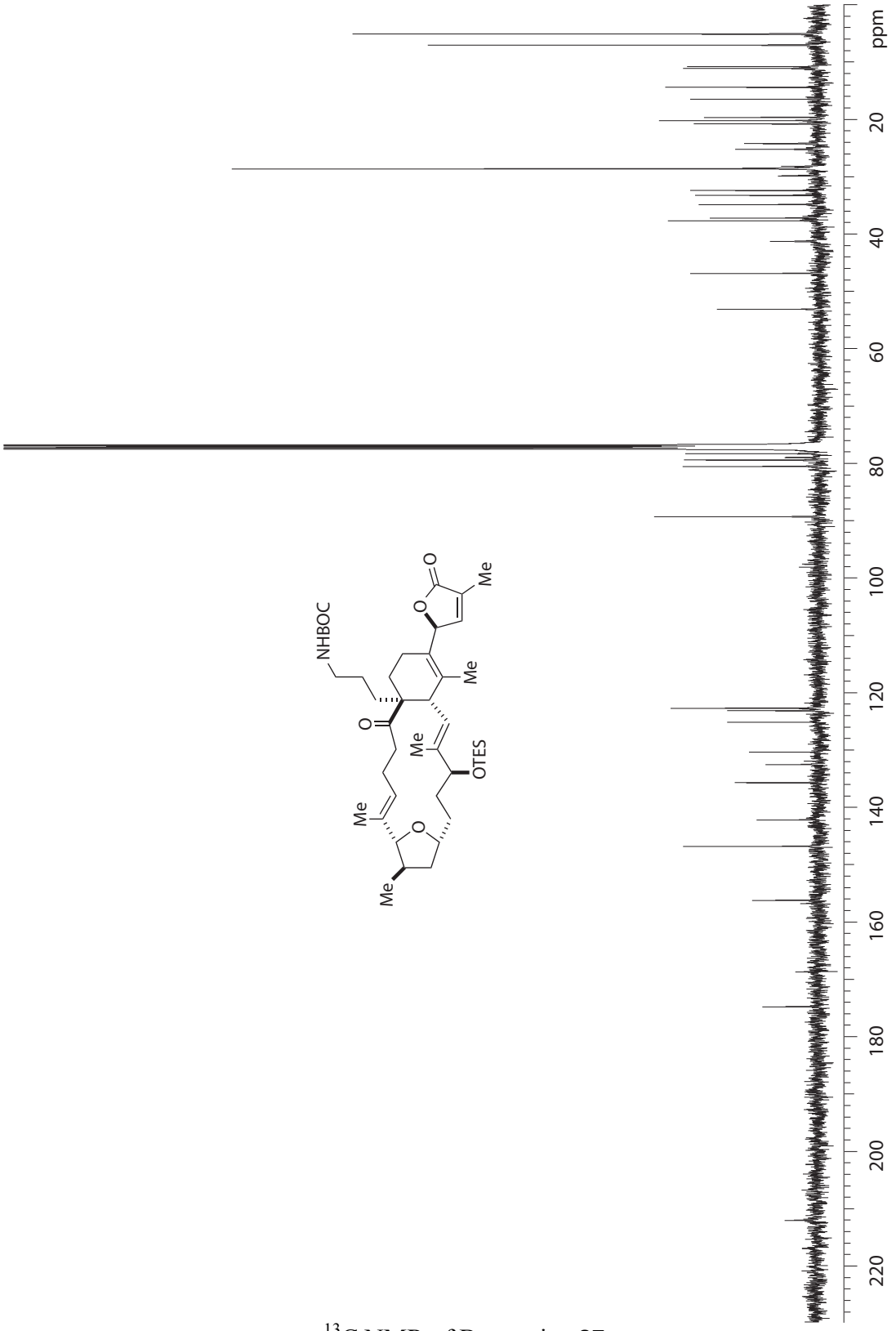
^{1}H NMR spectrum of olefin **86**



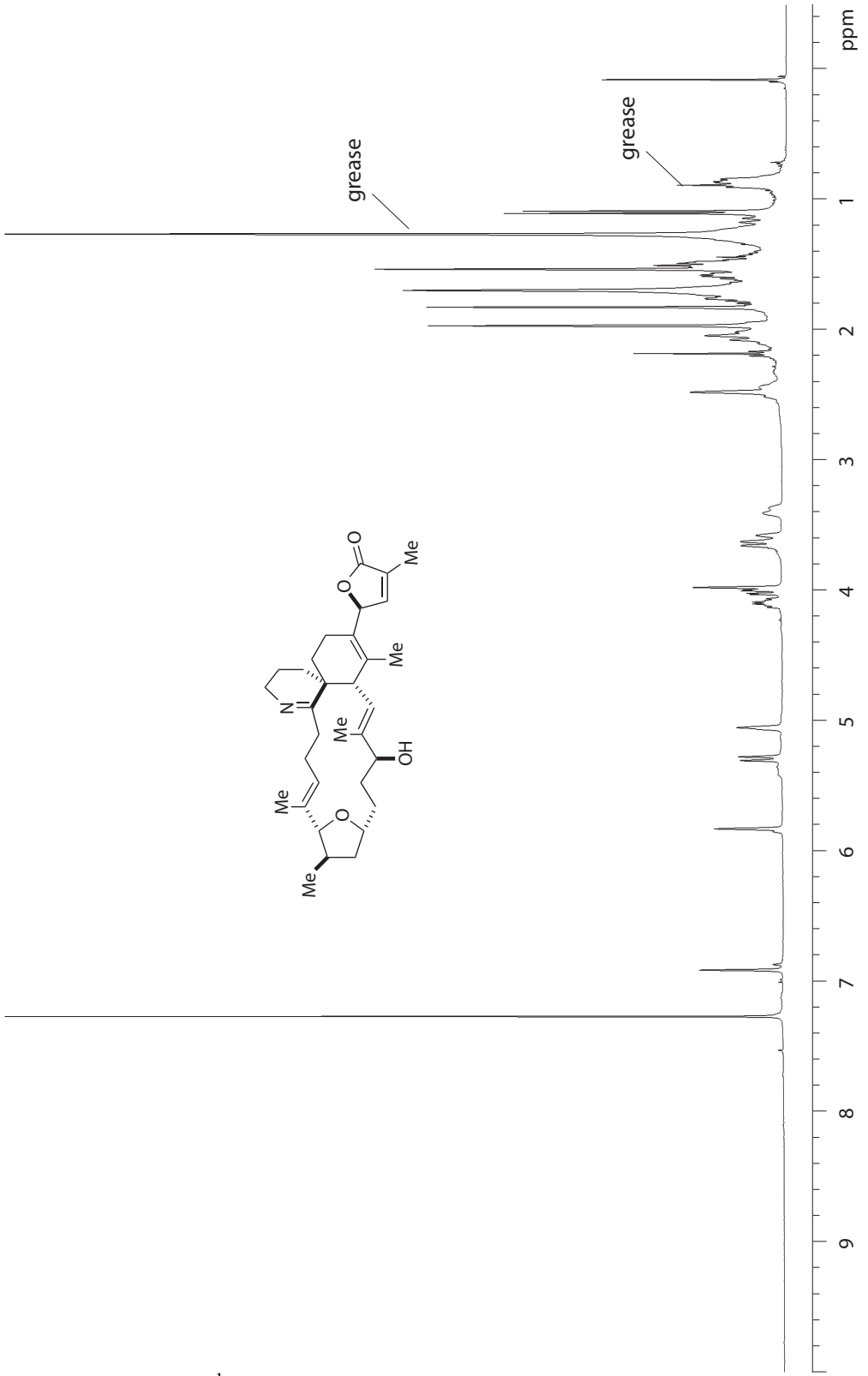
^{13}C NMR spectrum of olefin **86**



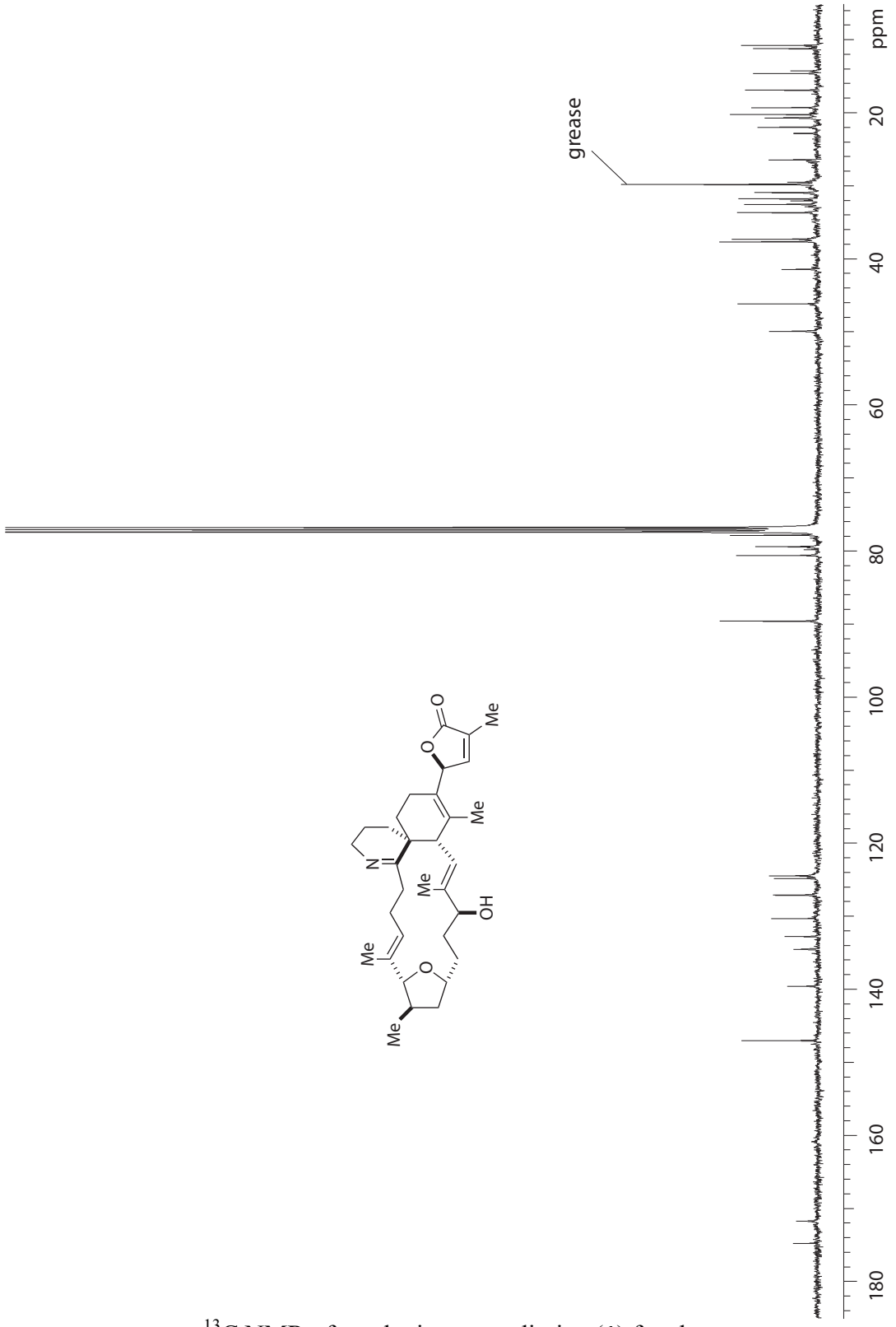
^{1}H NMR of Boc amine **87**



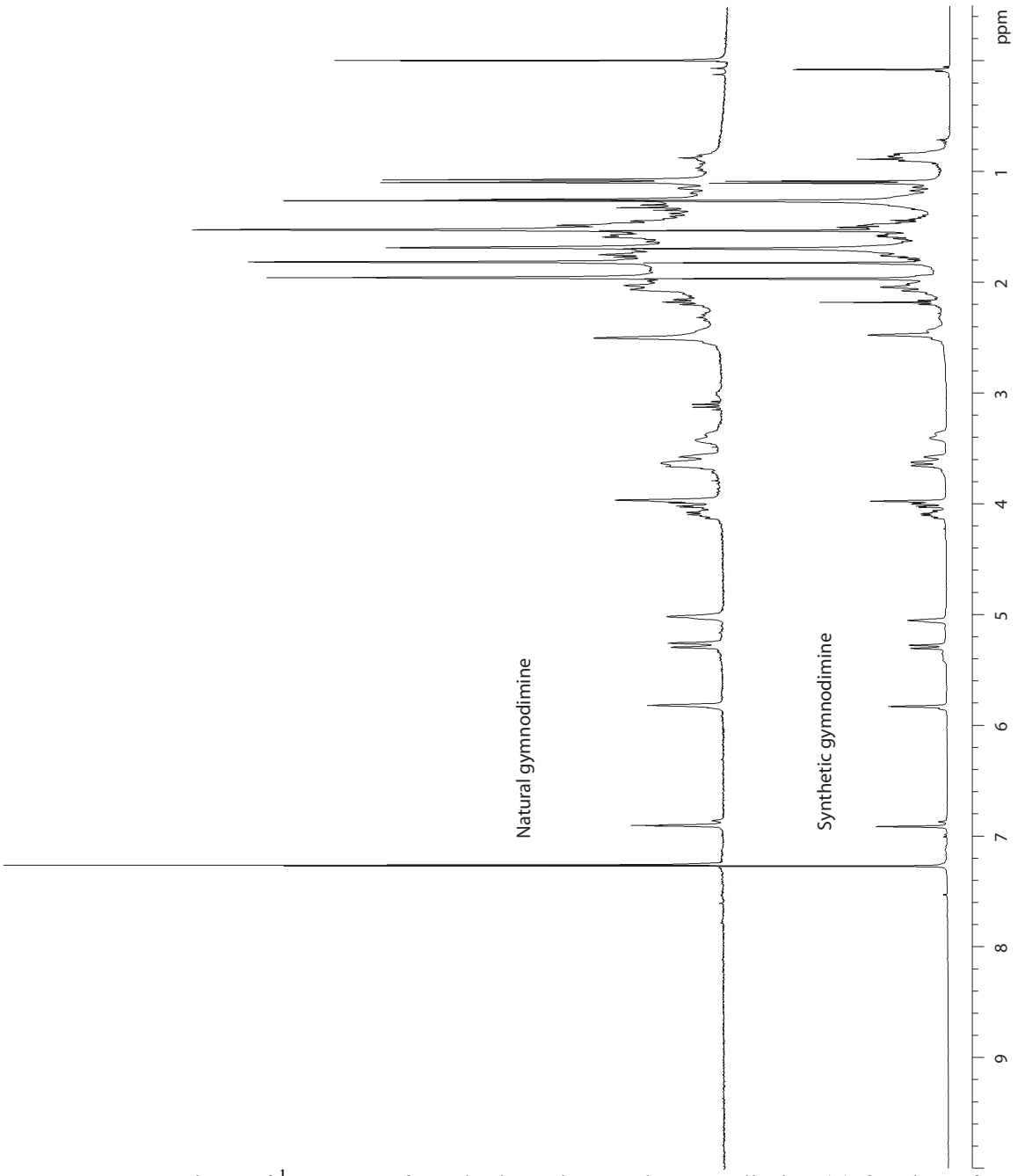
^{13}C NMR of Boc amine **87**



^{1}H NMR of synthetic gymnodimine (**1**) free base

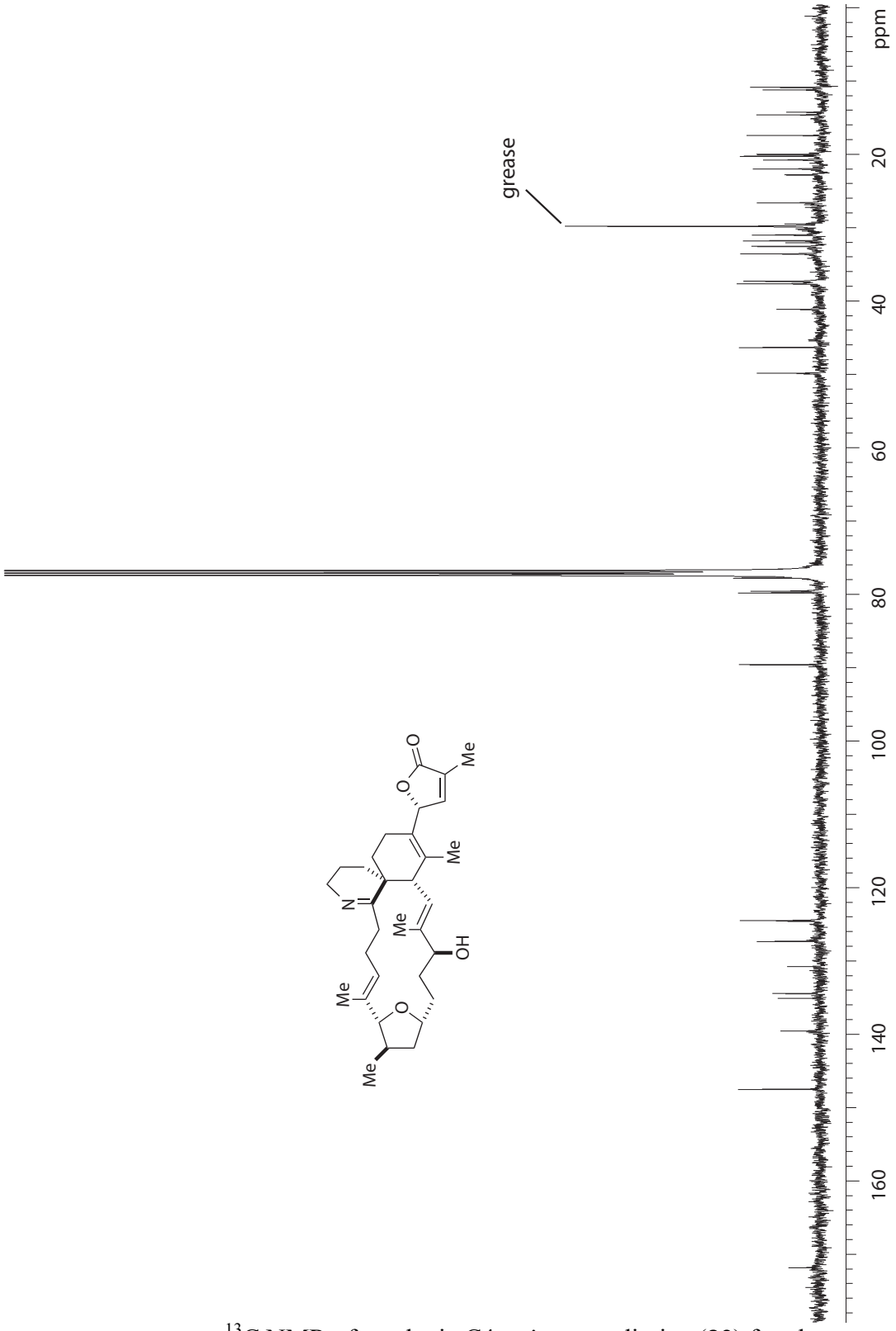


^{13}C NMR of synthetic gymnodimine (**1**) free base



Comparison of ^{1}H NMR of synthetic and natural gymnodimine (**1**) free base forms

^{1}H NMR of synthetic C4-*epi*-gymnodimine (**90**) free-base



^{13}C NMR of synthetic C4-*epi*-gymnodimine (**90**) free-base