Efforts toward Rapid Construction of the Cortistatin A Carbocyclic Core via Enyne-ene Metathesis

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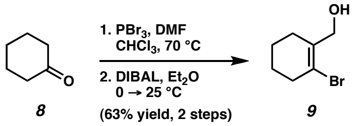
Materials and Methods

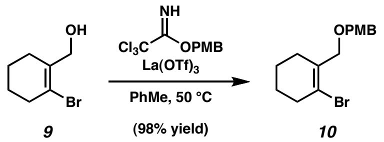
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre coated plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Analytical chiral HPLC was performed on a Chiralcel OD-H column (250 mm x 4.6 mm, 5 μm particle size, 0.8 mL/min flow rate) obtained from Daicel Chemical Industries, Ltd. ^1H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a Varian Inova 500 (at 500 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using 100 mm or 50 mm path-length cell. High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

Experimental Procedures and Spectroscopic Data

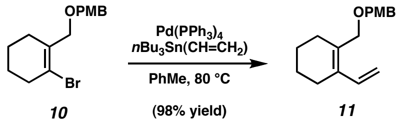


(2-Bromocyclohex-1-enyl)methanol (9).[1, 2] The allylic alcohol was synthesized according to a similar procedure.[3] To a solution of DMF (7.4 mL, 95.0 mmol, 3.0 equiv) in $CHCl_3$ (25 mL) was added PBr_3 (8.1 mL, 86.0 mmol, 2.7 equiv) dropwise at 0 °C. The mixture was stirred at 70 °C for 30 min, then cyclohexanone (**8**) (3.3 mL, 32.0 mmol, 1.0 equiv) was added dropwise over 30 min. After the resulting dark red solution was stirred at 70 °C for 1.5 h, it was poured into 4 M aq NaOAc (40 mL). Solid NaOH was added to the mixture to adjust the pH to 7.0 and the aqueous layer was extracted with hexanes. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated and the crude product was used in the next step without further purification. R_f = 0.80 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 2.77-2.72 (m, 2H), 2.30-2.25 (m, 2H), 1.80-1.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 143.9, 128.6, 39.1, 25.2, 24.5, 21.3; IR (Neat Film NaCl) 2937, 1681, 1619, 1449, 1340, 1208, 972 cm^{-1}.

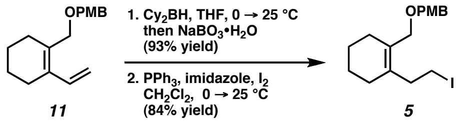
The crude product was dissolved in Et_2O (60 mL) and the solution was cooled to 0 °C. DIBAL (5.7 mL, 32.0 mmol, 1.0 equiv) was added slowly, and the mixture was stirred at 25 °C for 12 h. The reaction was quenched with H_2O (1.5 mL), 3 M aq NaOH (1.5 mL) and H_2O (3.0 mL), and stirred vigorously for 20 min. Na_2SO_4 (ca. 20 g) was added and the mixture was stirred for an additional 1 h. The white solid was removed by filtration and the filtrate was concentrated to afford a yellow oil, which was purified by flash chromatography (4:1 hexanes/EtOAc) to give **9** as a clear oil (3.85 g, 63% yield). R_f = 0.30 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (s, 2H), 2.52-2.50 (m, 2H), 2.28-2.24 (m, 2H), 1.69 (quintet, J = 3.0 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 121.0, 66.1, 36.9, 29.0, 24.9, 22.5.



1-(((2-Bromocyclohex-1-enyl)methoxy)methyl)-4-methoxybenzene (10). To a solution of **9** (1.01 g, 5.29 mmol, 1.0 equiv) in toluene (21 mL) was added 4-methoxybenzyl 2,2,2-trichloroacetimidate[4] (2.24 g, 7.93 mmol, 1.5 equiv) and $La(OTf)_3$ (164 mg, 0.28 mmol, 0.053 equiv). The mixture was stirred at 50 °C for 12 h. The reaction mixture was concentrated, and the crude residue was purified by flash chromatography (hexanes → 99:1 → 98:2 hexanes/EtOAc) to give **10** as a colorless oil (1.60 g, 98% yield). R_f = 0.40 (99:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 6.90-6.84 (m, 2H), 4.41 (s, 2H), 4.15 (s, 2H), 3.80 (s, 3H), 2.52-2.49 (m, 2H), 2.24-2.20 (m, 2H), 1.71-1.64 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 133.5, 130.8, 129.6, 122.3, 114.0, 73.2, 72.0, 55.5, 37.1, 29.2, 25.0, 22.5; IR (Neat Film NaCl) 2934, 2858, 2836, 1613, 1586, 1513, 1464, 1332, 1302, 1246, 1173, 1112, 1077, 1037, 972, 820 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{15}H_{19}BrO_2$ $[M]^+$: 310.0568, found 310.0563.



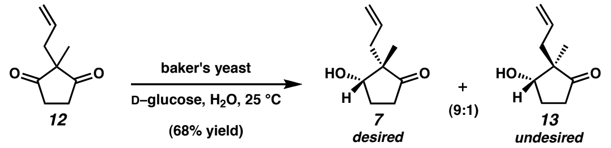
1-Methoxy-4-(((2-vinylcyclohex-1-enyl)methoxy)methyl)benzene (11). A Schlenk flask was charged with $Pd(PPh_3)_4$ (281 mg, 0.24 mmol, 0.1 equiv), evacuated and refilled with Ar. **10** (755 mg, 2.44 mmol, 1.0 equiv) in toluene (10 mL) and tributyl(vinyl)tin (1.0 mL, 3.41 mmol, 1.4 equiv) were added. The mixture was stirred at 80 °C for 2 d. The reaction mixture was concentrated, and the crude residue was purified by flash chromatography (hexanes → 99:1 → 98:2 hexanes/EtOAc) to give **11** as a colorless oil (618 mg, 98% yield). R_f = 0.50 (99:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 6.90-6.88 (m, 2H), 6.83 (dd, *J* = 17.1, 10.8 Hz, 1H), 5.20 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.01 (d, *J* = 10.8 Hz, 1H), 4.42 (s, 2H), 4.09 (s, 2H), 3.81 (s, 3H), 2.23-2.21 (m, 4H), 1.68-1.62 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 134.4, 133.9, 133.1, 130.9, 129.6, 114.0, 112.3, 71.9, 69.1, 55.5, 29.3, 25.3, 22.8, 22.7; IR (Neat Film NaCl) 3088, 2999, 2930, 2857, 2835, 1698, 1637, 1613, 1586, 1514, 1464, 1357, 1302, 1248, 1173, 1136, 1064, 1037, 986, 896, 820 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{22}O_2$ $[M]^+$: 258.1620, found 258.1623.



1-(((2-(2-Iodoethyl)cyclohex-1-enyl)methoxy)methyl)-4-methoxybenzene (5). A round bottom flask was cooled to 0 °C and charged with BH_3•THF (3.6 mL, 1 M in THF, 3.54 mmol, 1.5 equiv). Cyclohexene (0.73 mL, 7.20 mmol, 3.05 equiv) was added and the mixture was allowed to warm to 25 °C over 30 min. Then **11** (610 mg, 2.36 mmol, 1.0 equiv) in THF (5 mL) was added at 0 °C, and the mixture was allowed to warm to 25 °C over 5 h. The reaction was quenched with $NaBO_3$•H_2O (4.48 g, 44.9 mmol, 19 equiv) in H_2O (20 mL), and the mixture was stirred at 25 °C for 12 h. The aqueous layer was extracted with EtOAc and the combined organic phases were dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (9:1 → 7:1 → 5:1 hexanes/EtOAc) to give 2-(2-((4-Methoxybenzyloxy)methyl)cyclohex-1-enyl)ethanol as a colorless oil (608 mg, 93% yield). R_f = 0.20 (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.26 (m, 2H), 6.88-6.86 (m, 2H), 4.43 (s, 2H), 3.88 (s, 2H), 3.79 (s, 3H), 3.61 (t, *J* = 6.0 Hz, 2H), 2.66

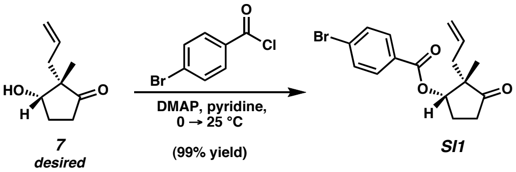
(br s, 1H), 2.31 (t, *J* = 6.0 Hz, 2H), 2.10 (br s, 2H), 2.01 (br s, 2H), 1.61-1.58 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 133.9, 130.9, 130.3, 129.9, 114.0, 72.6, 70.2, 60.5, 55.5, 36.8, 29.8, 29.5, 23.2, 23.1; IR (Neat Film NaCl) 3401, 2998, 2929, 2858, 2835, 1664, 1613, 1586, 1514, 1464, 1442, 1365, 1352, 1302, 1249, 1174, 1138, 1110, 1038, 821 cm^{-1}; HRMS (FAB+) *m*/*z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1804, found 277.1811.

To a solution of PPh_3 (527 mg, 2.01 mmol, 1.5 equiv) and imidazole (273 mg, 4.02 mmol, 3.0 equiv) in CH_2Cl_2 (8 mL) was added I_2 (544 mg, 2.14 mmol, 1.6 equiv) at 0 °C. The mixture was stirred at 0 °C for 30 min. Then 2-(2-((4-methoxybenzyloxy)methyl)cyclohex-1-enyl)ethanol (370 mg, 1.34 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added and the mixture was allowed to warm to 25 °C over 2 h and stirred at 25 °C for 16 h. After addition of 5% aq $Na_2S_2O_3$, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the crude residue was purified by flash chromatography (99:1 → 95:5 → 9:1 hexanes/EtOAc) to give **5** as a pale yellow oil (436 mg, 84% yield). $R_f = 0.50$ (99:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.26 (m, 2H), 6.89-6.87 (m, 2H), 4.41 (s, 2H), 3.89 (s, 2H), 3.80 (s, 3H), 3.12 (t, *J* = 8.5 Hz, 2H), 2.60 (t, *J* = 8.5 Hz, 2H), 2.07 (br s, 2H), 2.01 (br s, 2H), 1.60-1.58 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 135.1, 131.0, 130.7, 129.6, 114.0, 72.2, 69.8, 55.5, 38.2, 29.5, 28.5, 23.0, 22.9, 4.6; IR (Neat Film NaCl) 2998, 2927, 2855, 2833, 1612, 1586, 1513, 1463, 1354, 1302, 1248, 1172, 1134, 1068, 1037, 820 cm^{-1}; HRMS (FAB+) *m*/*z* calc'd for $C_{17}H_{23}IO_2$ $[M]^+$: 386.0743, found 386.0733.



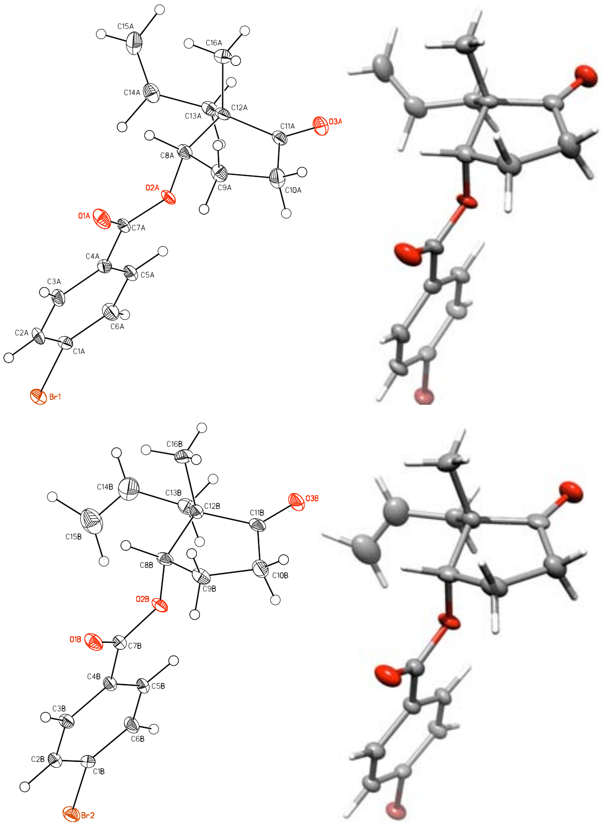
(2*S*, 3*S*)-2-allyl-3-hydroxy-2-methylcyclopentanone (**7**).[5] To a solution of D-Glucose (30.0 g) in H_2O (200 mL) was added dry active baker's yeast (20.0 g) at 35 °C. The suspension was stirred open to the air at 33 °C for 45 min. Dione **12** (1.71 g, 11.2 mmol, 1.0 equiv) was added dropwise, and the mixture was vigorously stirred at 25 °C for 5 d. The mixture was filtered over Celite, and the Celite was washed with H_2O and CH_2Cl_2. The filtrate was diluted with H_2O and extracted with CH_2Cl_2 in a continuous extractor for 48 h. The organic phase was concentrated and the crude residue was purified by flash chromatography (9:1 → 7:1 →

3:1 hexanes/EtOAc) to afford separated diastereoisomers **7** and **13** (1.16 g, 68% yield, 9 : 1 dr). **7** was isolated as a colorless oil. R_f = 0.27 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.17-5.10 (m, 2H), 4.13-4.10 (m, 1H), 2.51-2.43 (m, 1H), 2.37-2.16 (m, 4H), 1.97 (dddd, *J* = 13.0, 9.5, 9.5, 3.5 Hz, 1H), 1.90 (s, 1H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.9, 134.6, 118.4, 77.7, 53.4, 35.7, 34.3, 28.0 20.0; HRMS (EI+) *m/z* calc'd for $C_9H_{14}O_2$ $[M]^+$: 154.0994, found 154.0993; $[\alpha]_D^{24.6}$ +98.4° (*c* 1.01, $CHCl_3$, >99% ee). Analytical chiral HPLC assay with the benzoate of **7**: Chiralcel OD-H column, 1:9 2-propanol:hexanes, 0.8 mL/min, λ = 254 nm, isocratic method. **7-benzoate**: t_{fast} = 13.93 min (**(+)-7-benzoate**), t_{slow} = 15.51 min (**(–)-7-benzoate**). Enantioenriched **7-benzoate**: t_{fast} = 13.93 min (**(+)-7-benzoate**, >99%) (the trace corresponding to **(–)-7-benzoate** was below the threshold of detection).



(1*S*, 2*S*)-2-allyl-2-methyl-3-oxocyclopentyl 4-bromobenzoate (**SI1**). To a suspension of alcohol **7** (150 mg, 0.97 mmol, 1 equiv) and DMAP (11.9 mg, 0.097 mmol, 0.1 equiv) in pyridine (9 mL) cooled to 0 °C, *p*-bromobenzoylchloride (320 mg, 1.46 mmol, 1.5 equiv) was added. The reaction was allowed to gradually warm to 25 °C and quenched with water after 18 hours. The reaction mixture was extracted with CH_2Cl_2, the combined organic phases were dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the crude residue was purified by flash chromatography (hexanes → 90:10 hexanes/EtOAc) to afford **SI1** (335 mg, 99% yield) as a white solid. M. P.: 55-57 °C from 1:5 hexanes/EtOAc; R_f = 0.52 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 2H), 5.72 (dddd, J = 17.0, 10.5, 7.5, 7.5 Hz, 1H), 5.37 (m, 1H), 5.04-4.99 (m, 2H), 2.49-2.33 (comp. m, 5H), 2.20 (m, 1H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.0, 165.0, 133.1, 132.1, 131.2, 128.9, 128.6, 118.8, 79.9, 52.4, 35.9, 34.1, 25.9, 20.1; IR (Neat Film NaCl) 3076, 2976, 1742, 1721, 1590, 1484, 1398, 1271, 1113, 1102, 1012, 756 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{17}O_3Br$ $[M^+]$: 336.0361, found 336.0350; $[\alpha]_D^{25.0}$ +162.2° (*c* 0.61, $CHCl_3$).

The bromobenzoate was recrystallized from 1:5 hexanes/EtOAc to provide crystals suitable for x-ray analysis.



SYM10[6]

Note: Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 748731.

Table 1. Crystal data and structure refinement for SYM10 (CCDC 748731).

Empirical formula	$C_{16}H_{17}O_3Br$
Formula weight	337.21
Crystallization Solvent	Ethylacetate/hexanes
Crystal Habit	Block
Crystal size	0.20 x 0.19 x 0.12 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker KAPPA APEX II
Wavelength	0.71073 Å MoKα
Data Collection Temperature	100(2) K

θ range for 9810 reflections used in lattice determination	2.57 to 32.19°	
Unit cell dimensions	a = 5.7803(2) Å	
	b = 24.8200(11) Å	β= 91.528(2)°
	c = 10.2688(4) Å	
Volume	1472.71(10) Å^3	
Z	4	
Crystal system	Monoclinic	
Space group	P2$_1$	
Density (calculated)	1.521 Mg/m^3	
F(000)	688	
Data collection program	Bruker APEX2 v2009.7-0	
θ range for data collection	1.64 to 33.46°	
Completeness to θ = 33.46°	99.5 %	
Index ranges	$-8 \le h \le 8$, $-38 \le k \le 38$, $-15 \le l \le 15$	
Data collection scan type	ω scans; 24 settings	
Data reduction program	Bruker SAINT-Plus v7.66A	
Reflections collected	50019	
Independent reflections	11399 [R_{int}= 0.0523]	
Absorption coefficient	2.795 mm^{-1}	
Absorption correction	None	
Max. and min. transmission	0.7303 and 0.6048	

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	11399 / 1 / 497
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.549
Final R indices [I>2σ(I), 10256 reflections]	R1 = 0.0342, *w*R2 = 0.0548
R indices (all data)	R1 = 0.0391, *w*R2 = 0.0551
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.002

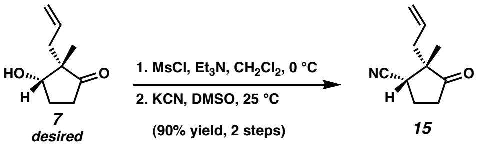
Average shift/error	0.000
Absolute structure determination	Anomalous differences
Absolute structure parameter	-0.002(4)
Largest diff. peak and hole	1.491 and -0.868 e.Å^{-3}

Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

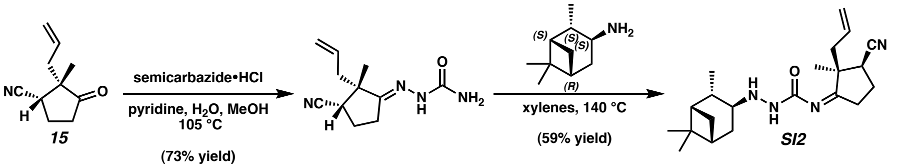
Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.



(1*S*, 2*S*)-2-allyl-2-methyl-3-oxocyclopentanecarbonitrile (**15**). To a solution of **7** (805 mg, 5.22 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added MsCl (0.8 mL, 10.4 mmol, 2.0 equiv) and Et_3N (1.5 mL, 10.4 mmol, 2.0 equiv) at 0 °C. The mixture was stirred at 0 °C for 1 h. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the crude mesylate was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (dddd, *J* = 11.4, 8.7, 7.2, 7.2 Hz, 1H), 5.16-5.10 (m, 2H), 5.02 (m, 1H), 3.05 (s, 3H), 2.45-2.28 (m, 6H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.0, 132.5, 119.2, 85.9, 52.4, 38.8, 35.4, 33.7, 26.4, 19.7; HRMS (FAB+) *m*/*z* calc'd for $C_{10}H_{17}SO_4$ $[M]^+$: 233.0848, found 233.0844.

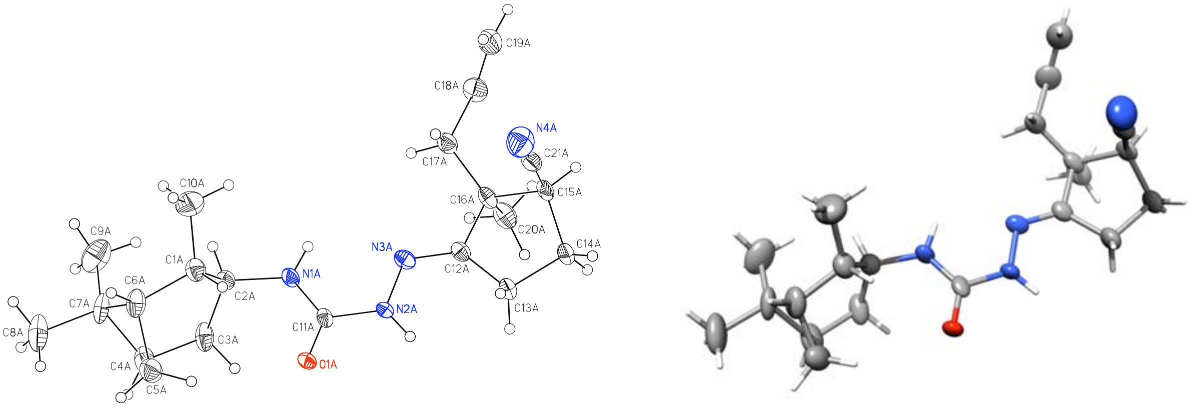
The resulting yellow oil was dissolved in DMSO (16 mL), KCN (680 mg, 10.4 mmol, 2.0 equiv) was added, and the mixture was stirred at 25 °C for 5 d. After addition of brine, the aqueous layer was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (8:1 → 6:1 hexanes/EtOAc) to give **15** (765 mg, 90% yield) as a yellow oil. R_f = 0.33 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dddd, *J* = 17.5, 10.0, 7.5, 7.5 Hz, 1H), 5.21-5.15 (m, 2H), 2.94-2.90 (m, 1H), 2.52-2.21 (m, 6H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.3, 131.8, 120.4, 119.4, 51.2, 39.1, 38.4, 35.5, 23.5, 21.2; IR (Neat Film NaCl) 3079, 2978, 2917, 2848, 2240, 1743, 1640, 1457, 1406, 1378, 1298, 1268, 1196, 1148, 1111, 1049, 994, 923 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{10}H_{13}NO$ $[M]^+$: 163.0997, found 163.0997; $[\alpha]_D^{24.3}$ +46.8° (*c* 0.80, $CHCl_3$).



(Isopinocampheylamine)-semicarbazone (SI2). Semicarbazide•HCl (51.2 mg, 0.46 mmol, 1.5 equiv) was added to a solution of ketone **15** (50 mg, 0.31 mmol, 1 equiv) in pyridine (2.7 mL), water (1.3 mL), and MeOH (0.4 mL). The reaction mixture was heated to 105 °C for 1 h and then cooled to 25 °C. After addition of water, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (CH_2Cl_2 → 9:1 CH_2Cl_2/MeOH) to afford the semicarbazone (49.7 mg, 73% yield) as a white solid. $R_f = 0.53$ (10:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, MeOD) δ 5.87 (dddd, *J* = 17.5, 10.0, 7.5, 7.5 Hz, 1H), 5.19-5.12 (m, 2H), 3.00 (m, 1H), 2.57-2.36 (m, 4H), 2.31 (m, 1H), 2.17 (m, 1H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 158.8, 133.2, 119.5, 117.8, 40.7, 39.1, 25.4, 24.9, 22.1; IR (Neat Film NaCl) 3215, 1691, 1490 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{11}H_{17}N_4O$ $[M+H]^+$: 221.1402, found 221.1408; $[\alpha]_D^{25.0}$ +60.5° (*c* 0.615, MeOH).

To a solution of the semicarbazone (30 mg, 0.136 mmol, 1 equiv) in xylenes (1.3 mL) was added (1*S*, 2*S*, 3*S*, 5*R*)-(+)-isopinocampheylamine (27.5 uL, 0.163 mmol, 1.2 equiv). The reaction mixture was refluxed for 18 hours. Upon cooling, the reaction mixture was concentrated and purified by column chromatography (100:1 → 1:100 hexanes/EtOAc) to give **SI2** as a light brown solid (28.5 mg, 59% yield). M. P.: 230-232 °C from $CDCl_3$; R_f = 0.67 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 5.92 (d, *J* = 9.0 Hz, 1H), 5.80 (dddd, *J* = 17.5, 15.0, 7.5, 7.5 Hz, 1H), 5.21-5.14 (m, 2H), 4.17 (m, 1H), 2.74 (dd, *J* = 7.0, 7.0 Hz, 1H), 2.63-2.52 (m, 2H), 2.45-2.40 (m, 4H), 2.30-2.17 (m, 2H), 1.97 (m, 1H), 1.86-1.83 (m, 2H), 1.60 (ddd, *J* = 13.5, 6.0, 2.5 Hz, 1H), 1.24 (s, 3H), 1.23 (s, 3H), 1.13 (d, *J* = 7.5 Hz, 3H), 1.05 (s, 3H), 0.92 (d, *J* = 10 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 156.1, 132.8, 119.5, 119.5, 48.4, 48.4, 48.0, 46.7, 41.8, 41.0, 40.0, 38.5, 37.9, 35.4, 28.2, 25.9, 25.4, 23.5, 23.5, 20.9; IR (Neat Film NaCl) 3414, 3192, 3080, 2911, 1669, 1659, 1534 cm $^{-1}$; HRMS (EI+) *m/z* calc'd for $C_{21}H_{32}ON_4$ [M^+]: 356.2576, found 356.2584; $[\alpha]_D^{25.0}$ +96.3 (c 1.09, $CHCl_3$).

The semicarbazone was recrystallized from $CDCl_3$ to provide crystals suitable for x-ray analysis.



SYM11[6, 7]

Note: Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 749151.

Table 2. Crystal data and structure refinement for SYM11 (CCDC 749151).

Empirical formula	$C_{21}H_{32}N_4O$
Formula weight	356.51
Crystallization Solvent	Methanol or $CDCl_3$
Crystal Habit	Blade
Crystal size	0.23 x 0.19 x 0.07 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker KAPPA APEX II	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 9942 reflections used in lattice determination	2.40 to 18.72°	
Unit cell dimensions	a = 17.5462(8) Å b = 11.0229(5) Å c = 32.8065(15) Å	β= 103.274(3)°
Volume	6175.6(5) Å^3	

Z	12
Crystal system	Monoclinic
Space group	$P2_1$
Density (calculated)	1.150 Mg/m^3
F(000)	2328
Data collection program	Bruker APEX2 v2009.7-0
θ range for data collection	1.19 to 26.40°
Completeness to θ = 26.40°	99.7 %
Index ranges	$-21 \le h \le 21, -13 \le k \le 13, -34 \le l \le 41$
Data collection scan type	ω scans; 9 settings
Data reduction program	Bruker SAINT-Plus v7.66A
Reflections collected	80862
Independent reflections	25063 [R_{int}= 0.0604]
Absorption coefficient	0.072 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9950 and 0.9836

Structure solution and Refinement

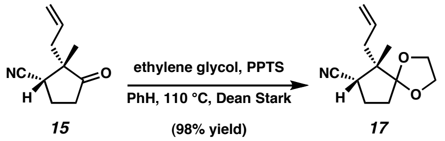
Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	25063 / 1 / 1429
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.387
Final R indices [$I>2\sigma(I)$, 16797 reflections]	R1 = 0.0574, *w*R2 = 0.0734
R indices (all data)	R1 = 0.0950, *w*R2 = 0.0768
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Absolute structure determination	Known stereo center
Absolute structure parameter	-1.1(8)
Largest diff. peak and hole	0.397 and -0.495 e.Å^{-3}

Special Refinement Details

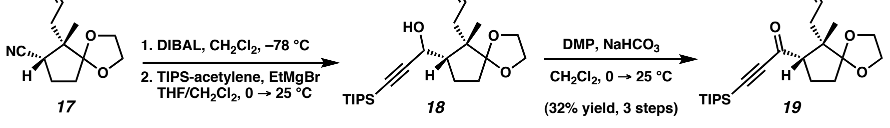
Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.



Nitrile (**17**). To a solution of **15** (800 mg, 4.90 mmol, 1.0 equiv) in benzene (49 mL) was added PPTS (308 mg, 1.23 mmol, 0.25 equiv) and ethylene glycol (1.9 mL, 34.3 mmol, 7.0 equiv). The flask was fitted with a Dean-Stark trap, and the mixture was refluxed at 110 °C for 2 d. The volatiles were removed, and the crude residue was purified by flash chromatography (95:5 → 9:1 hexanes/EtOAc) to give **17** (997 mg, 98% yield) as a pale yellow oil. $R_f = 0.42$ (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (dddd, *J* = 17.5, 10.0, 7.5, 7.5 Hz, 1H), 5.19-5.14 (m, 1H), 5.11-5.08 (m, 1H), 4.00-3.94 (m, 2H), 3.93-3.88 (m, 2H), 2.75-2.72 (m, 1H), 2.47 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.28 (ddt, *J* = 14.0, 7.0, 1.5 Hz, 1H), 2.17-2.08 (m, 1H), 2.04-1.96 (m, 2H), 1.93-1.86 (m, 1H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.5, 121.5, 118.6, 118.0, 65.7, 65.1, 49.1, 37.8, 37.3, 32.7, 23.8, 19.9; IR (Neat Film NaCl) 3077, 2979, 2916, 2888, 2849, 2237, 1639, 1462, 1439, 1380, 1310, 1290, 1202, 1173, 1148, 1132, 1043, 1005, 950, 928 cm^{-1}; HRMS (FAB+) *m*/*z* calc'd for $C_{12}H_{18}NO_2$ $[M+H]^+$: 208.1338, found 208.1331; $[\alpha]_D^{26.4}$ +78.0° (*c* 0.85, $CHCl_3$).

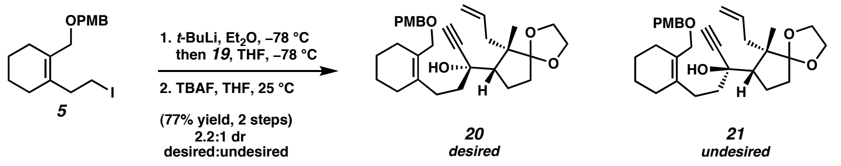


(**19**). To a solution of **17** (500 mg, 2.41 mmol, 1.0 equiv) in CH_2Cl_2 (23 mL) was added DIBAL (3.6 mL, 1 M in CH_2Cl_2, 3.62 mmol, 1.5 equiv) at –78 °C. The mixture was stirred at –78 °C for 1 h. Rochelle's salt (7.5 mL) was added and the mixture was stirred at 25 °C for

40 min. The phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the crude product was used in the next step without further purification.

The resulting colorless oil was dissolved in CH_2Cl_2 (12 mL) and added to a solution of TIPS-acetylene (3.2 mL, 14.5 mmol, 6.0 equiv) and ethylmagnesium bromide (3.2 mL, 3.0 M in Et_2O, 9.64 mmol, 4.0 equiv) in THF (29 mL) at 0 °C. The mixture was allowed to warm to 25 °C slowly and stirred at 25 °C for 24 h. After addition of saturated aq NH_4Cl, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (98:2 → 9:1 hexanes/EtOAc) to give **18** as a mixture of two diastereomers.

To a solution of **18** in CH_2Cl_2 (10 mL), DMP (601 mg, 1.43 mmol, 1.0 equiv) and $NaHCO_3$ (132 mg, 1.57 mmol, 1.1 equiv) were added at 0 °C. The mixture was allowed to warm to 25 °C over 2 h and stirred at 25 °C for 10 h. After addition of saturated aq $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (98:2 hexanes/EtOAc) to give **19** as a colorless oil (298 mg, 32% yield over 3 steps). $R_f = 0.60$ (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92-5.83 (m, 1H), 4.99-4.95 (m, 2H), 3.95-3.88 (m, 4H), 3.00 (t, J = 9.0 Hz, 1H), 2.38-2.26 (m, 2H), 2.11 (dd, J = 14.5, 8.0 Hz, 1H), 1.96-1.89 (m, 1H), 1.79-1.70 (m, 2H), 1.22 (s, 3H), 1.17-1.05 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.0, 135.7, 119.7, 117.6, 105.9, 96.7, 66.0, 64.5, 60.7, 50.6, 37.8, 32.0, 20.4, 19.6, 18.8, 11.4; IR (Neat Film NaCl) 3075, 2945, 2867, 2146, 1665, 1463, 1384, 1346, 1307, 1201, 1126, 1074, 1044, 998, 950, 917, 883 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{38}O_3Si$ $[M]^+$: 390.2590, found 390.2585; $[\alpha]_D^{19.1}$ +44.5° (*c* 1.03, $CHCl_3$).



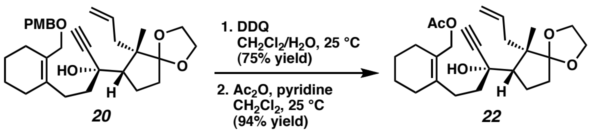
(**20**) and (**21**). To a solution of **5** (159 mg, 0.41 mmol, 1.5 equiv) in Et_2O (4.2 mL), *t*-BuLi (0.63 mL 0.88 mmol, 3.2 equiv) was added dropwise at –78 °C. The mixture was stirred at –78 °C for 30 min. A solution of **19** (107 mg, 0.27 mmol, 1.0 equiv) in THF (2.7 mL) was added, and the mixture was stirred at –78 °C for 1 h. After addition of saturated aq NH_4Cl, the aqueous layer was extracted with Et_2O. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (9:1 hexanes/EtOAc) to give the tertiary alcohol as a mixture of two diastereomers.

To a solution of this alcohol (147 mg, 0.23 mmol, 1.0 equiv) in THF (2.3 mL), TBAF (0.27 mL, 1 M in THF, 1.2 equiv) was added at 25 °C. The mixture was stirred at 25 °C for 1 h. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (8:1 → 1:1 hexanes/EtOAc) to give separated diastereomers **20** and **21** as colorless oils (104 mg, 77% yield, 2.2:1 dr).

20: R_f = 0.31 (7:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.27 (m, 2H), 6.87-6.85 (m, 2H), 6.14 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.04 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.01-4.98 (m, 1H), 4.40 (ABq, *J* = 11.5 Hz, 2H), 4.00-3.87 (m, 6H), 3.80 (s, 3H), 3.35 (s, 1H), 2.63 (dd, *J* = 14.5, 7.5 Hz, 1H), 2.55-2.50 (m, 1H), 2.49 (s, 1H), 2.30 (ddd, *J* = 12.5, 12.5, 5.0 Hz, 1H), 2.22 (ddd, *J* = 12.5, 12.5, 5.0 Hz, 1H), 2.08-2.01 (m, 5H), 1.85-1.54 (m, 10H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 138.4, 136.1, 131.2, 129.7, 128.3, 119.8, 115.8, 114.0, 87.6, 74.8, 71.9, 71.3, 70.0, 65.4, 64.5, 55.5, 54.0, 49.1, 41.5, 37.8, 31.3, 30.1, 28.3, 28.3, 23.3, 23.2, 22.7, 19.9; IR (Neat Film NaCl) 3436, 3294, 3065, 2929, 2879, 2836, 1997, 1633, 1612, 1584, 1514, 1462, 1302, 1248, 1173, 1140, 1070, 1036, 1006, 949, 907, 821 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{31}H_{43}O_5$ $[M+H]^+$: 495.3110, found 495.3133; $[\alpha]_D^{23.7}$ +6.4° (*c* 1.02, $CHCl_3$).

21: R_f = 0.39 (7:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 6.88-6.86 (m, 2H), 6.16 (dddd, *J* = 17.0, 10.0, 7.5, 6.5 Hz, 1H), 5.05 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.99 (dd, *J* = 10.0, 1.0 Hz, 1H), 4.41 (ABq, *J* = 11.5 Hz, 2H), 4.00-3.87 (m, 6H), 3.82 (s, 3H), 2.68 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.52 (s, 1H), 2.52-2.48 (m, 1H), 2.45 (s, 1H), 2.34-2.25 (m, 2H), 2.12-1.96 (m, 5H), 1.90-1.85 (m, 1H), 1.80-1.57 (m, 9H), 1.06 (s, 3H); ^{13}C NMR (125

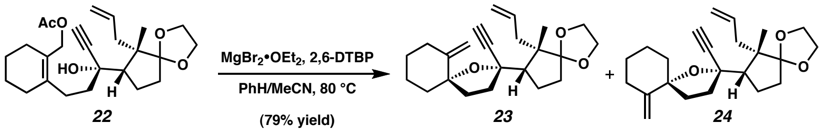
MHz, $CDCl_3$) δ 159.4, 138.4, 136.4, 131.0, 129.7, 128.4, 119.9, 116.1, 114.0, 86.4, 75.6, 74.4, 72.0, 70.1, 65.8, 64.2, 55.5, 55.3, 49.6, 42.5, 37.4, 31.8, 30.0, 28.6, 27.6, 23.3, 23.2, 23.0, 21.7; IR (Neat Film NaCl) 3436, 3302, 2930, 2884, 2832, 1995, 1638, 1613, 1514, 1458, 1302, 1248, 1174, 1141, 1068, 1037, 1003, 951, 907 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{31}H_{43}O_5$ $[M+H]^+$: 495.3110, found 495.3124; $[\alpha]_D^{23.5}$ +32.3° (*c* 0.98, $CHCl_3$).



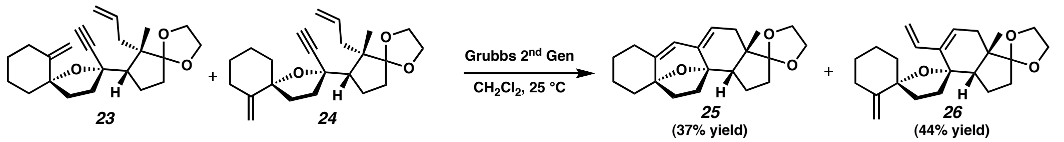
(**22**). To a solution of **20** (65 mg, 0.13 mmol, 1.0 equiv) in CH_2Cl_2 (13 mL) and H_2O (1.3 mL) was added DDQ (45 mg, 0.20 mmol, 1.5 equiv). The mixture was stirred at 25 °C for 1 h. After addition of saturated aq $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (3:1 hexanes/EtOAc) to give the allylic alcohol as a colorless oil (37 mg, 75% yield). R_f = 0.11 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.05-4.98 (m, 2H), 4.11 (ABq, *J* = 11.5 Hz, 2H), 3.97-3.86 (m, 4H), 3.47 (br s, 1H), 2.62 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.58 (s, 1H), 2.52 (dd, *J* = 15.0, 6.5 Hz, 1H), 2.36 (ddd, *J* = 12.5, 12.5, 5.0 Hz, 1H), 2.24 (ddd, *J* = 12.0, 12.0, 5.5 Hz, 1H), 2.14-1.99 (m, 5H), 1.88-1.54 (m, 11H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 135.3, 130.7, 119.8, 115.9, 87.4, 75.0, 71.4, 65.4, 64.5, 63.1, 54.0, 49.2, 41.4, 37.7, 31.2, 29.9, 28.1, 28.1, 23.3, 23.3, 22.6, 19.9; IR (Neat Film NaCl) 3401, 3304, 3070, 2919, 2884, 1995, 1724, 1636, 1459, 1434, 1377, 1318, 1274, 1246, 1217, 1176, 1138, 1070, 1038, 1003, 982, 937, 758 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{35}O_4$ $[M+H]^+$: 375.2535, found 375.2546; $[\alpha]_D^{26.2}$ +12.5° (*c* 0.67, $CHCl_3$).

To a solution of the allylic alcohol (44 mg, 0.12 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL), pyridine (39 μL, 0.48 mmol, 4.0 equiv) and Ac_2O (45 μL, 0.48 mmol, 4.0 equiv) were added. The mixture was stirred at 25 °C for 24 h. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with 10% aq HCl, saturated aq $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (8:1 hexanes/EtOAc) to give **22** as a colorless oil (46 mg, 94% yield). R_f = 0.28 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz,

$CDCl_3$) δ 6.14 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.06-4.98 (m, 2H), 4.59 (ABq, *J* = 11.5 Hz, 2H), 3.98-3.88 (m, 4H), 3.35 (s, 1H), 2.66-2.62 (m, 1H), 2.57 (s, 1H), 2.56-2.52 (m, 1H), 2.36-2.23 (m, 2H), 2.10-2.03 (m, 4H), 2.06 (s, 3H), 1.89-1.71 (m, 6H), 1.62-1.55 (m, 5H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 138.3, 137.9, 126.1, 119.8, 115.9, 87.3, 75.0, 71.2, 65.4, 65.0, 64.5, 54.0, 49.2, 41.5, 37.7, 31.3, 30.1, 28.4, 28.1, 23.1, 23.0, 22.7, 21.4, 19.9; IR (Neat Film NaCl) 3468, 3272, 3069, 2930, 2884, 1735, 1636, 1455, 1436, 1378, 1239, 1176, 1144, 1073, 1023, 952 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{33}O_3$ [M-OAc]$^+$: 357.2430, found 357.2440; $[\alpha]_D^{28.0}$ +4.0° (*c* 0.62, $CHCl_3$).



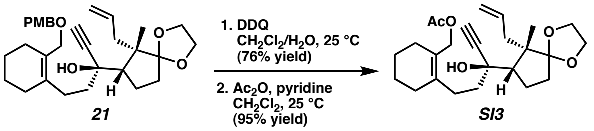
(**23**) and (**24**). To a solution of **22** (43 mg, 0.10 mmol, 1.0 equiv) in benzene (5 mL), 2,6-DTBP (0.14 mL 0.62 mmol, 6.0 equiv), $MgBr_2$•OEt_2 (107 mg, 0.41 mmol, 4.0 equiv) and MeCN (1.0 mL) were added, and the mixture was stirred at 80 °C for 2 d. After addition of brine, the aqueous layer was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (hexanes → 199:1 → 99:1 hexanes/EtOAc) to give **23** and **24** as a mixture of two diastereomers as a colorless oil (29 mg, 79% yield). R_f = 0.45 (99:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23-6.13 (m, 1H), 5.19 (d, *J* = 2.5 Hz, 0.5H), 5.02-4.92 (m, 2H), 4.88 (d, *J* = 2.0 Hz, 0.5H), 4.67 (s, 1H), 3.97-3.86 (m, 4H), 2.56-2.34 (m, 4H), 2.24-1.23 (m, 16H), 1.11 (s, 1.5H), 1.04 (s, 1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 152.2, 138.6, 138.5, 120.5, 120.3, 115.5, 115.5, 106.2, 105.4, 88.0, 87.5, 87.3, 86.7, 80.7, 80.1, 74.5, 74.4, 65.9, 65.8, 64.1, 64.1, 55.3, 54.7, 48.8, 48.6, 42.0, 39.9, 38.7, 38.4, 38.4, 38.2, 35.0, 34.9, 34.9, 33.7, 31.7, 31.4, 28.1, 28.0, 25.2, 24.7, 22.0, 21.2, 20.9, 20.7; IR (Neat Film NaCl) 3304, 3071, 2972, 2934, 2879, 2853, 1735, 1649, 1636, 1460, 1446, 1396, 1376, 1315, 1300, 1274, 1217, 1202, 1173, 1145, 1120, 1068, 1046, 1011, 947, 899 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{33}O_3$ [M+H]$^+$: 357.2430, found 357.2439.



(**25**) and (**26**). To a solution of **23** and **24** (24 mg, 0.067 mmol, 1.0 equiv) in CH_2Cl_2 (6.5 mL), Grubbs 2nd generation catalyst (8.6 mg, 0.010 mmol, 15 mol%) was added. The mixture was stirred at 25 °C for 2 d. The solvent was concentrated, and the residue was purified by flash chromatography (99:1 → 98:2 → 9:1 hexanes/EtOAc) to give **25** as a beige solid (8.2 mg, 37% yield) and **26** as a colorless oil (10.5 mg, 44% yield).

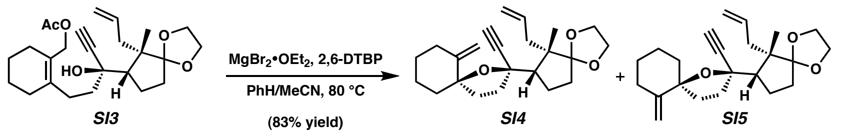
25: R_f = 0.47 (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (d, *J* = 2.0 Hz, 1H), 5.20 (t, *J* = 4.0 Hz, 1H), 3.95-3.88 (m, 4H), 2.32-2.28 (m, 2H), 2.24-2.12 (m, 3H), 2.05-1.78 (m, 10H), 1.74-1.60 (m, 4H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 137.3, 120.3, 120.1, 117.2, 81.4, 80.7, 65.6, 64.6, 51.0, 46.4, 39.8, 38.9, 35.5, 34.0, 31.7, 31.3, 26.1, 24.4, 23.1, 19.9; IR (Neat Film NaCl) 2919, 2858, 1995, 1727, 1465, 1451, 1427, 1375, 1310, 1279, 1259, 1202, 1175, 1158, 1098, 1070, 1024, 942, 912, 871 cm^{-1}; HRMS (FAB+) *m*/*z* calc'd for $C_{21}H_{29}O_3$ $[M+H]^+$: 329.2117, found 329.2122; $[\alpha]_D^{21.3}$ +176.8° (*c* 0.97, $CHCl_3$).

26: R_f = 0.42 (99:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.85 (t, *J* = 4.0 Hz, 1H), 5.35 (dd, *J* = 17.0, 2.0 Hz, 1H), 4.98 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.94 (d, *J* = 2.0 Hz, 1H), 4.67 (s, 1H), 3.92-3.87 (m, 4H), 2.43-2.38 (m, 1H), 2.34-2.24 (m, 2H), 2.16-2.05 (m, 3H), 2.02-1.60 (m, 11H), 1.54-1.48 (m, 2H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 139.8, 136.7, 122.5, 120.5, 113.8, 105.3, 85.4, 84.4, 65.6, 64.6, 51.5, 46.3, 40.4, 36.4, 35.0, 34.0, 33.2, 31.2, 28.6, 24.4, 23.9, 20.9; IR (Neat Film NaCl) 2930, 2853, 1995, 1736, 1648, 1460, 1442, 1372, 1311, 1261, 1200, 1151, 1137, 1078, 1030, 1009, 946, 894 cm^{-1}; HRMS (FAB+) *m*/*z* calc'd for $C_{23}H_{33}O_3$ $[M+H]^+$: 357.2430, found 357.2445.

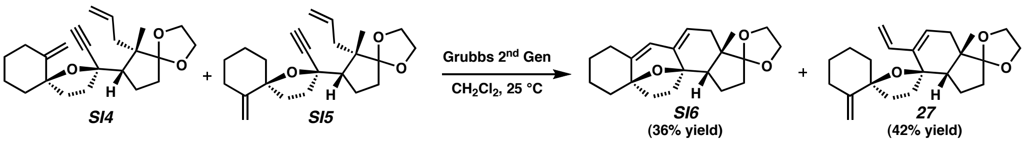


(**SI3**). To a solution of **21** (33 mg, 0.07 mmol, 1.0 equiv) in CH_2Cl_2 (7.0 mL) and H_2O (0.7 mL), DDQ (23 mg, 0.10 mmol, 1.5 equiv) was added. The mixture was stirred at 25 °C for 1 h. After addition of saturated aq $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (4:1 hexanes/EtOAc) to give the allylic alcohol as a colorless oil (19 mg, 76% yield). R_f = 0.20 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.16 (dddd, *J* = 17.0, 10.0, 8.0, 6.5 Hz, 1H), 5.09-5.04 (m, 1H), 5.01-4.98 (m, 1H), 4.13 (ABq, *J* = 11.5 Hz, 2H), 3.95-3.86 (m, 4H), 2.68 (dd, *J* = 14.5, 8.5 Hz, 1H), 2.59 (s, 1H), 2.52-2.47 (m, 1H), 2.42-2.32 (m, 1H), 2.31-2.14 (m, 1H), 2.13-1.91 (m, 5H), 1.90-1.55 (m, 12H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 135.5, 130.8, 119.8, 116.4, 86.4, 75.7, 74.5, 65.8, 64.2, 63.2, 55.3, 49.6, 42.5, 37.3, 31.8, 29.9, 28.3, 27.5, 23.3, 23.2, 23.0, 21.6; IR (Neat Film NaCl) 3402, 3305, 3072, 2919, 2884, 1718, 1635, 1459, 1436, 1377, 1320, 1276, 1246, 1216, 1176, 1138, 1070, 1039, 1002, 981, 952, 758 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{35}O_4$ $[M+H]^+$: 375.2535, found 375.2544; $[\alpha]_D^{26.1}$ +38.6° (*c* 0.62, $CHCl_3$).

To a solution of the allylic alcohol (18 mg, 0.05 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), pyridine (15 μL, 0.19 mmol, 4.0 equiv) and Ac_2O (18 μL, 0.19 mmol, 4.0 equiv) were added. The mixture was stirred at 25 °C for 21 h. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with 10% aq HCl, saturated aq $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (8:1 hexanes/EtOAc) to give **SI3** as a colorless oil (19 mg, 95% yield). R_f = 0.34 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17 (dddd, *J* = 18.0, 10.0, 8.0, 6.5 Hz, 1H), 5.08-5.04 (m, 1H), 5.01-4.99 (m, 1H), 4.60 (ABq, *J* = 12.0 Hz, 2H), 3.96-3.87 (m, 4H), 2.69 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.58 (s, 1H), 2.54-2.49 (m, 1H), 2.41 (s, 1H), 2.34 (t, *J* = 8.0 Hz, 2H), 2.12 (t, *J* = 9.0 Hz, 1H), 2.06 (s, 3H), 2.05-2.02 (m, 4H), 1.92-1.68 (m, 6H), 1.68-1.57 (m, 4H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 138.3, 138.0, 126.2, 119.8, 116.3, 86.1, 75.8, 74.4, 65.8, 65.0, 64.2, 55.2, 49.6, 42.6, 37.4, 31.8, 30.1, 28.3, 27.7, 23.1, 22.7, 22.7, 21.6, 21.4; IR (Neat Film NaCl) 3481, 3303, 3071, 2924, 2856, 1736, 1636, 1461, 1436, 1378, 1318, 1239, 1177, 1143, 1075, 1024, 953 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M-OAc]^+$: 357.2430, found 357.2426; $[\alpha]_D^{27.9}$ +44.6° (*c* 0.42, $CHCl_3$).



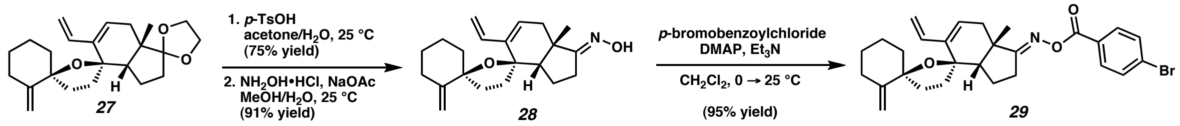
(**SI4**) and (**SI5**). To a solution of **SI3** (31 mg, 0.08 mmol, 1.0 equiv) in benzene (4 mL), 2,6-DTBP (0.10 mL, 0.45 mmol, 6.0 equiv), $MgBr_2$•OEt_2 (77 mg, 0.30 mmol, 4.0 equiv) and MeCN (0.6 mL) were added, and the mixture was stirred at 80 °C for 2 d. After addition of brine, the aqueous layer was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (99:1 hexanes/EtOAc) to give **SI4** and **SI5** as a mixture of two diastereomers as a colorless oil (22 mg, 83% yield). R_f = 0.46 (99:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.23 (d, *J* = 2.5 Hz, 0.4H), 5.02-4.91 (m, 2.6H), 4.71 (s, 0.4H), 4.65 (s, 0.6H), 3.97-3.86 (m, 4H), 2.75-2.71 (m, 1H), 2.60-2.54 (m, 1H), 2.47 (s, 0.4H), 2.47 (s, 0.6H), 2.42-2.36 (m, 1H), 2.21-1.29 (m, 16H), 1.12 (s, 1.2H), 1.07 (s, 1.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 152.4, 138.9, 138.8, 120.0, 119.9, 115.1, 115.1, 106.6, 106.0, 87.9, 87.7, 87.5, 87.1, 81.5, 81.5, 74.7, 74.6, 65.7, 65.7, 64.3, 64.2, 57.2, 56.4, 49.3, 49.3, 42.1, 41.9, 41.6, 40.6, 37.8, 37.5, 34.9, 34.8, 34.5, 33.8, 32.4, 32.4, 28.1, 27.9, 25.2, 24.6, 23.0, 22.9, 22.0, 21.9; IR (Neat Film NaCl) 3302, 3070, 2972, 2935, 2879, 2858, 1649, 1636, 1459, 1446, 1396, 1375, 1298, 1243, 1174, 1137, 1105, 1075, 1050, 1002, 950, 899 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M+H]^+$: 357.2430, found 357.2426.



(**SI6**) and (**27**). To a solution of **SI4** and **SI5** (20 mg, 0.056 mmol, 1.0 equiv) in CH_2Cl_2 (2.8 mL), Grubbs 2nd generation catalyst (7 mg, 0.008 mmol, 15 mol%) was added. The mixture was stirred at 25 °C for 2 d. The solvent was concentrated, and the residue was purified by flash chromatography (99:1 → 98:2 → 9:1 hexanes/EtOAc) to give **SI6** as a white solid (6.7 mg, 36% yield) and **27** as a colorless oil (8.3 mg, 42% yield).

SI6: R_f = 0.42 (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (s, 1H), 5.34 (d, *J* = 5.5 Hz, 1H), 3.91-3.88 (m, 4H), 2.31-2.25 (m, 2H), 2.18-2.05 (m, 4H), 1.96-1.70 (m, 10H), 1.61-1.48 (m, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 139.8, 120.1, 119.7, 118.2, 83.4, 79.5, 65.6, 64.6, 49.5, 46.1, 37.4, 35.5, 34.3, 34.0, 31.7, 30.1, 26.2, 24.4, 24.2, 19.5; IR (Neat Film NaCl) 2924, 2853, 1995, 1726, 1623, 1461, 1377, 1310, 1259, 1153, 1072, 1055, 946, 907 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{28}O_3$ $[M]^+$: 328.2039, found 328.2038; $[\alpha]_D^{24.3}$ –159.9° (*c* 0.90, $CHCl_3$).

27: R_f = 0.42 (99:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (ddd, *J* = 17.0, 11.0, 1.0 Hz, 1H), 5.92 (dd, *J* = 5.5, 2.0 Hz, 1H), 5.35 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.04 (d, *J* = 2.0 Hz, 1H), 5.00 (dd, *J* = 11.0, 2.0 Hz, 1H), 4.69 (s, 1H), 3.96-3.85 (m, 4H), 2.44-2.39 (m, 1H), 2.26 (dd, *J* = 12.0, 8.0 Hz, 1H), 2.15-2.01 (m, 3H), 1.97-1.82 (m, 4H), 1.80-1.73 (m, 2H), 1.70-1.65 (m, 2H), 1.61-1.52 (m, 2H), 1.50-1.43 (m, 2H), 1.31-1.25 (m, 2H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 138.0, 137.0, 124.4, 120.4, 114.2, 105.5, 85.7, 83.0, 65.6, 64.8, 50.2, 44.7, 40.8, 34.9, 34.3, 33.9, 33.2, 31.0, 28.5, 24.7, 23.8, 19.4; IR (Neat Film NaCl) 3079, 2932, 2876, 2858, 1736, 1648, 1619, 1460, 1446, 1374, 1317, 1305, 1263, 1200, 1152, 1087, 1068, 1055, 1021, 1009, 950, 893, 755 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M+H]^+$: 357.2430, found 357.2429; $[\alpha]_D^{24.2}$ +3.1° (*c* 0.93, $CHCl_3$).

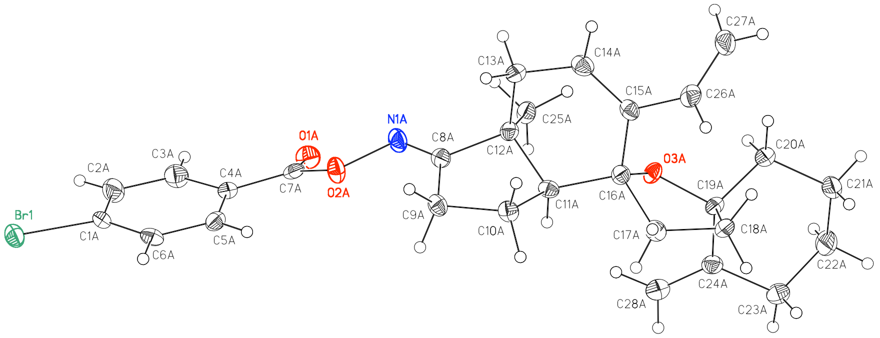


(**29**). To a solution of **27** (31 mg, 0.09 mmol, 1.0 equiv) in acetone (0.9 mL) was added H_2O (2.4 μL, 0.13 mmol, 1.5 equiv) and *p*-TsOH (3.3 mg, 0.02 mmol, 0.2 equiv) at 25 °C. The mixture was stirred at 25°C for 15 h, and the solvent was concentrated. After addition of EtOAc, the organic phase was washed with saturated aq $NaHCO_3$, H_2O and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the crude residue was purified by flash chromatography (99:1 → 98:2 hexanes/EtOAc) to afford the desired product that was used directly in the next step.

To the resulting ketone (15 mg, 0.05 mmol, 1.0 equiv) dissolved in MeOH/H_2O (3 mL, 5:1) was added NaOAc (38 mg, 0.45 mmol, 10 equiv) and $NH_2OH•H_2O$ (34 mg, 0.49 mmol, 11 equiv) at 25 °C. The mixture was stirred at 25°C for 14 h, and the solvent was concentrated. After addition of H_2O, the aqueous layer was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (5:1 hexanes/EtOAc) to give **28**.

To a solution of oxime **28** (14 mg, 0.04 mmol, 1.0 equiv) in CH_2Cl_2 (0.4 mL), *p*-bromobenzoylchloride (11 mg, 0.05 mmol, 1.2 equiv), DMAP (1 mg, 0.01 mmol, 0.2 equiv), and Et_3N (12 μL, 0.08 mmol, 2.0 equiv) were added at 0 °C. The mixture was stirred at 0 °C for 2 h. After addition of saturated aq NH_4Cl, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (99:1 → 98:2 → 95:5 hexanes/EtOAc) to give **29** as a white solid (20 mg, 95% yield). M.P.: 91-93 °C from ethyl acetate/heptane; R_f = 0.38 (95:5 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91-7.88 (m, 2H), 7.60-7.57 (m, 2H), 6.43 (ddd, *J* = 17.0, 10.5, 1.0 Hz, 1H), 5.89 (dd, *J* = 5.5, 2.0 Hz, 1H), 5.37 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.06 (dd, *J* = 11.0, 2.0 Hz, 1H), 4.95 (d, *J* = 2.0 Hz, 1H), 4.66 (s, 1H), 2.83 (dd, *J* = 19.5, 8.5 Hz, 1H), 2.67-2.60 (m, 1H), 2.43-2.38 (m, 1H), 2.25 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.20 (d, *J* = 19.0 Hz, 1H), 2.13-2.01 (m, 4H), 1.96-1.75 (m, 4H), 1.71-1.61 (m, 2H), 1.58 (s, 3H), 1.54-1.41 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7, 163.5, 154.1, 138.8, 136.4, 132.1, 131.3, 128.6, 128.5, 122.4, 115.0, 105.4, 85.9, 81.8, 53.3, 44.3, 40.8, 34.8, 34.4, 33.9, 32.5, 28.5, 27.4, 24.5, 24.5, 22.4; IR (Neat Film NaCl) 3079, 2932, 2855, 1746, 1648, 1590, 1483, 1447, 1398, 1379, 1320, 1254, 1174, 1069, 1011, 906, 875, 750, 732 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{28}H_{33}BrO_3N$ $[M+H]^+$: 510.1644, found 510.1644; $[\alpha]_D^{22.9}$ +30.4° (*c* 0.90, $CHCl_3$).

The compound was recrystallized from ethyl acetate/heptane to provide crystals suitable for x-ray analysis.



CCB02[6]

Note: Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 751261.

Table 3. Crystal data and structure refinement for CCB02 (751261).

Empirical formula	$C_{28}H_{32}NO_3Br$
Formula weight	510.46
Crystallization Solvent	Ethyl acetate/heptane
Crystal Habit	Plate
Crystal size	0.43 x 0.29 x 0.06 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker KAPPA APEX II	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 9936 reflections used in lattice determination	2.45 to 29.34°	
Unit cell dimensions	a = 11.4503(6) Å b = 6.5371(3) Å c = 33.2116(16) Å	 β= 92.180(3)°
Volume	2484.1(2) Å^3	
Z	4	
Crystal system	Monoclinic	
Space group	$P2_1$	
Density (calculated)	1.365 Mg/m^3	
F(000)	1064	
Data collection program	Bruker APEX2 v2.1-0	
θ range for data collection	1.78 to 29.74°	
Completeness to θ = 29.74°	92.7 %	
Index ranges	$-15 \le h \le 15$, $-9 \le k \le 8$, $-45 \le l \le 45$	
Data collection scan type	ω scans; 12 settings	
Data reduction program	Bruker SAINT-Plus v7.34A	
Reflections collected	36895	
Independent reflections	12339 [R_{int}= 0.0299]	
Absorption coefficient	1.684 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7459 and 0.6043	

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods

Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	12339 / 1 / 851
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.004
Final R indices [$I>2\sigma(I)$, 10737 reflections]	R1 = 0.0294, *w*R2 = 0.0515
R indices (all data)	R1 = 0.0387, *w*R2 = 0.0534
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.004
Average shift/error	0.000
Absolute structure determination	Anomalous differences
Absolute structure parameter	0.010(3)
Largest diff. peak and hole	0.567 and -0.323 e.Å^{-3}

Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Experimental Spectra

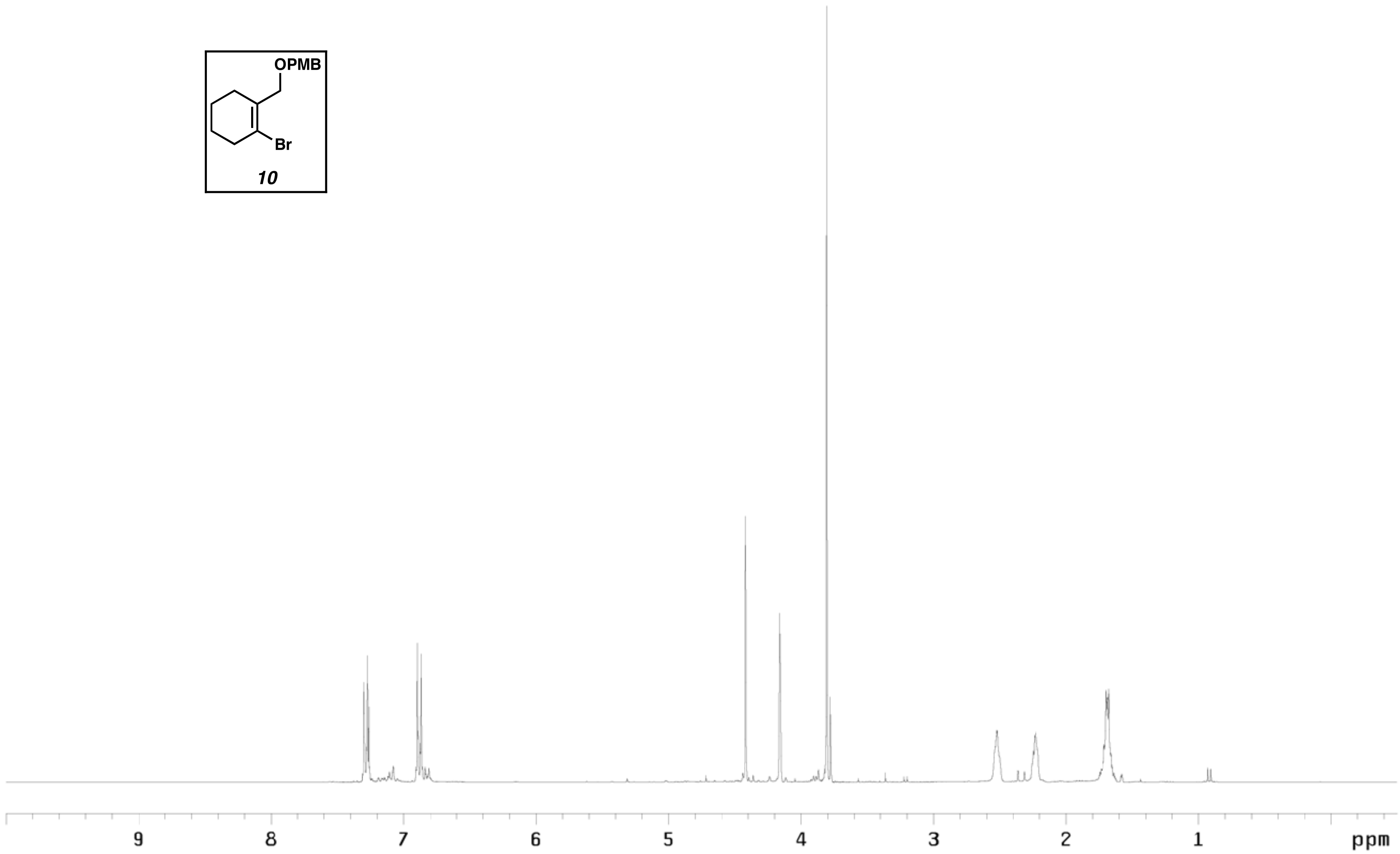


Figure 1.1 ^{1}H NMR (300 MHz, $CDCl_3$) of bromide **10**.

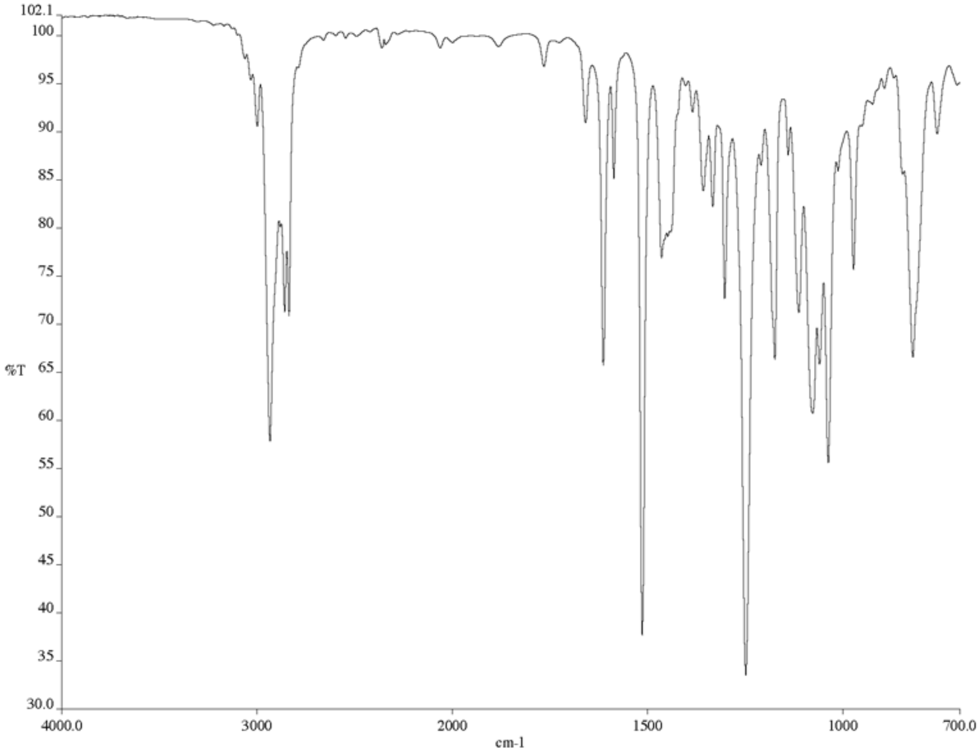


Figure 1.2 Infrared spectrum (Neat Film NaCl) of bromide **10**.

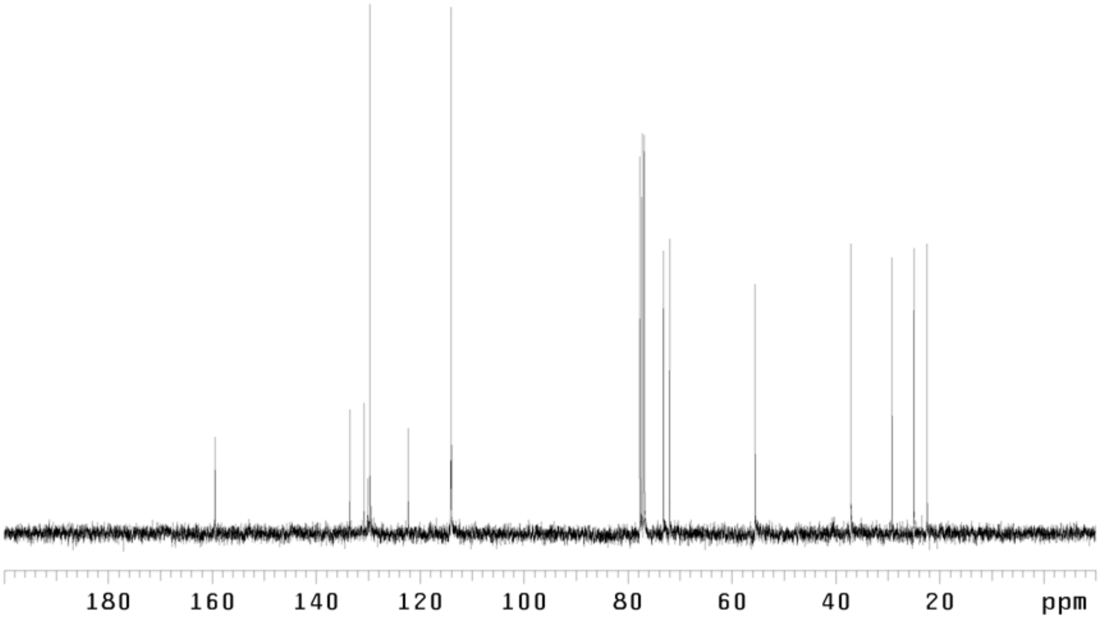


Figure 1.3 ^{13}C NMR (75 MHz, $CDCl_3$) of bromide **10**.

Figure 2.1 ^{1}H NMR (300 MHz, $CDCl_3$) of diene **11**.

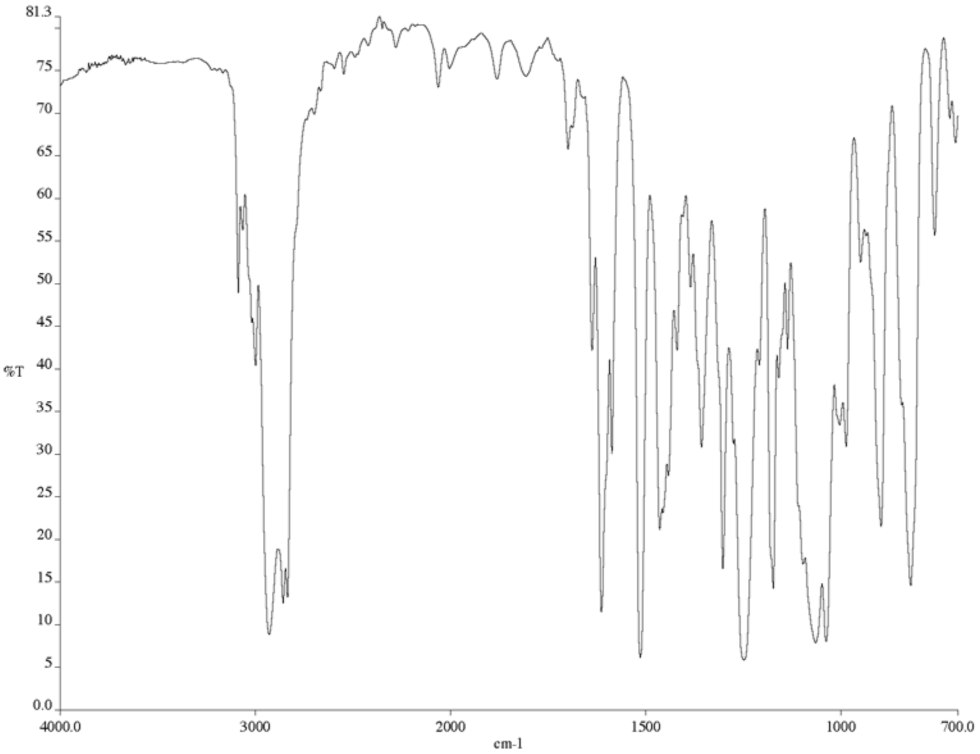


Figure 2.2 Infrared spectrum (Neat Film NaCl) of diene **11**.

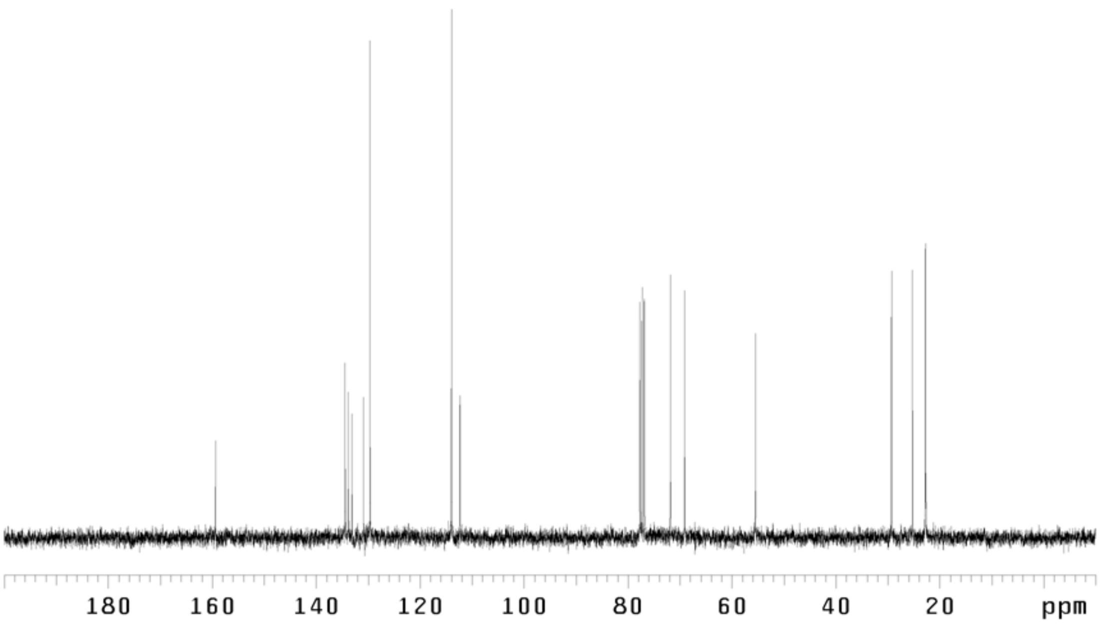


Figure 2.3 ^{13}C NMR (75 MHz, CDCl$_3$) of diene **11**.

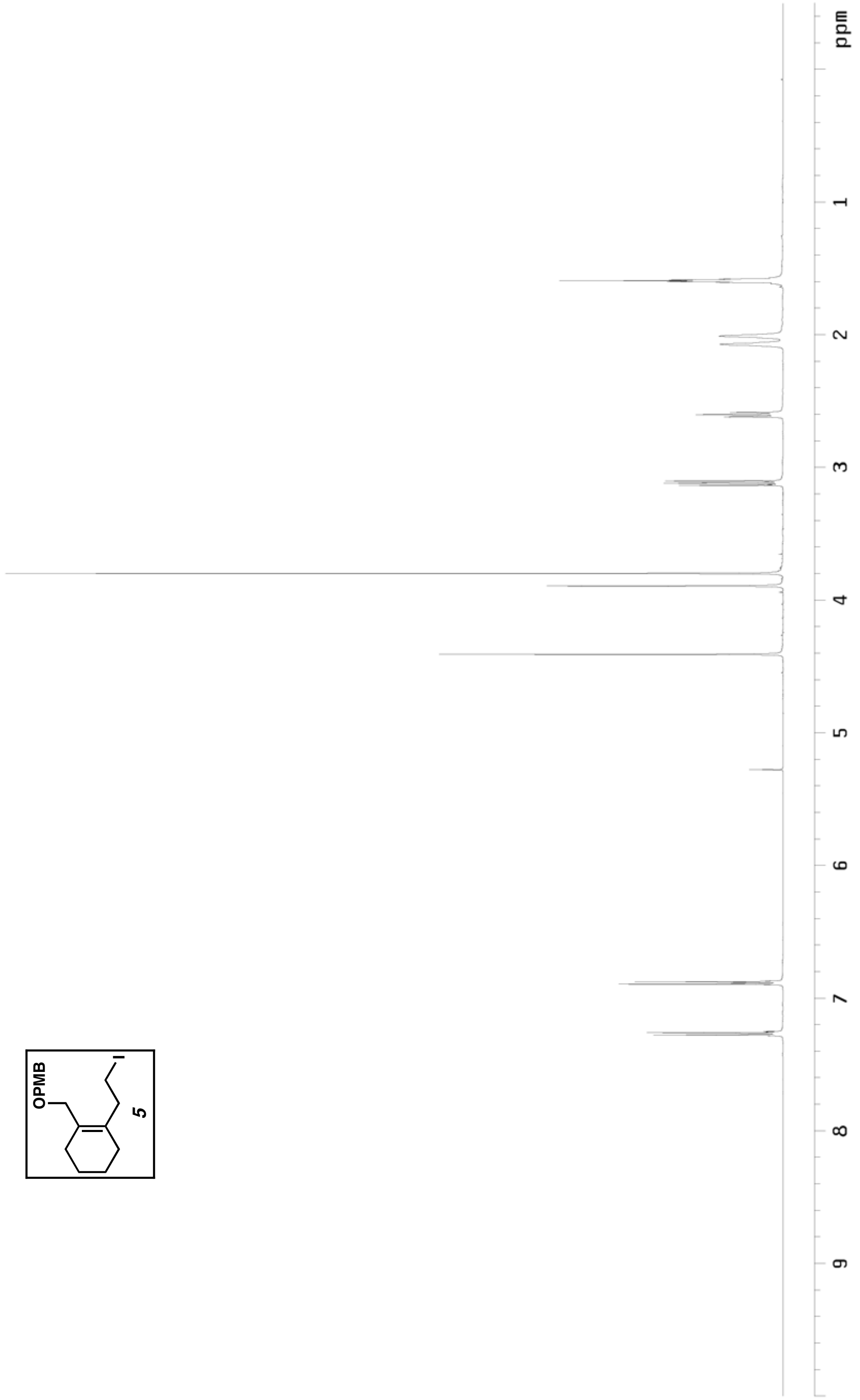


Figure 3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of iodide **5**.

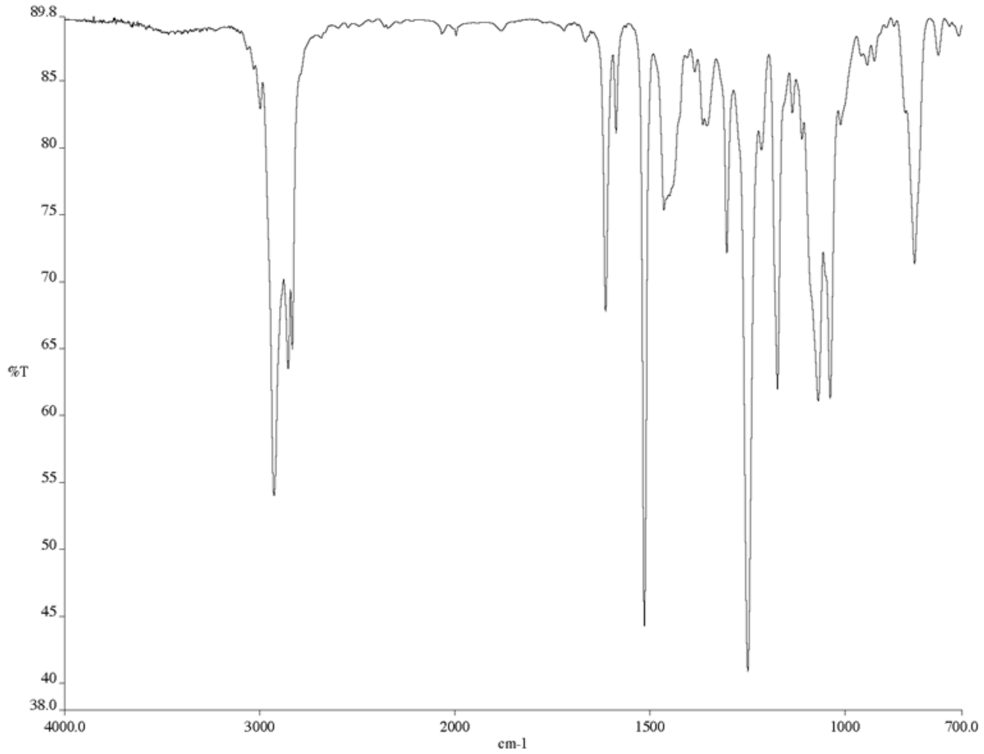


Figure 3.2 Infrared spectrum (Neat Film NaCl) of iodide **5**.

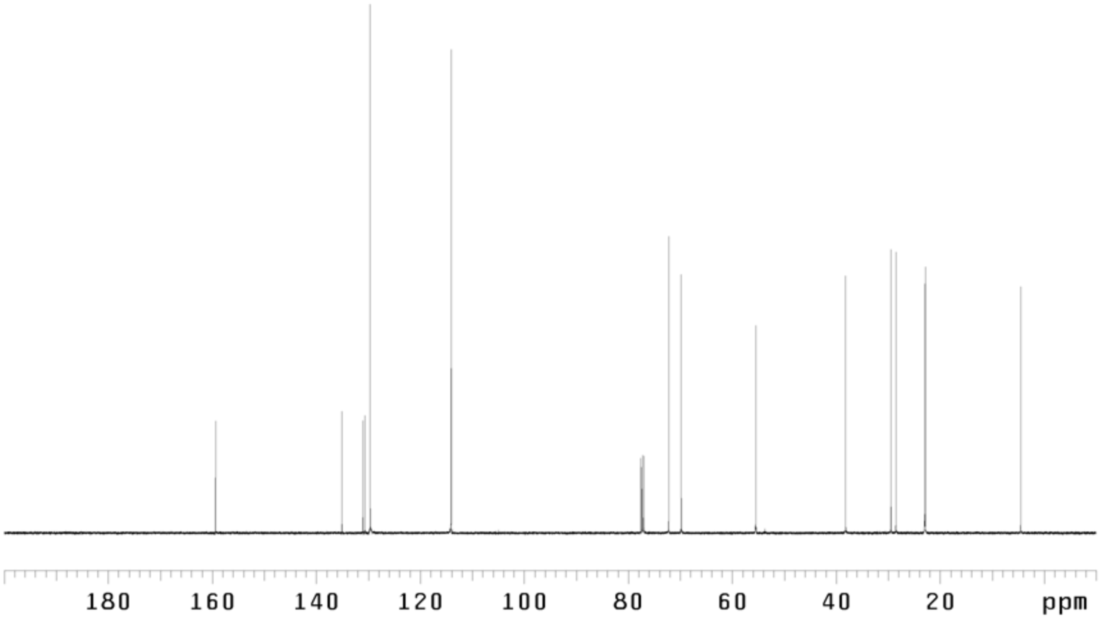


Figure 3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of iodide **5**.

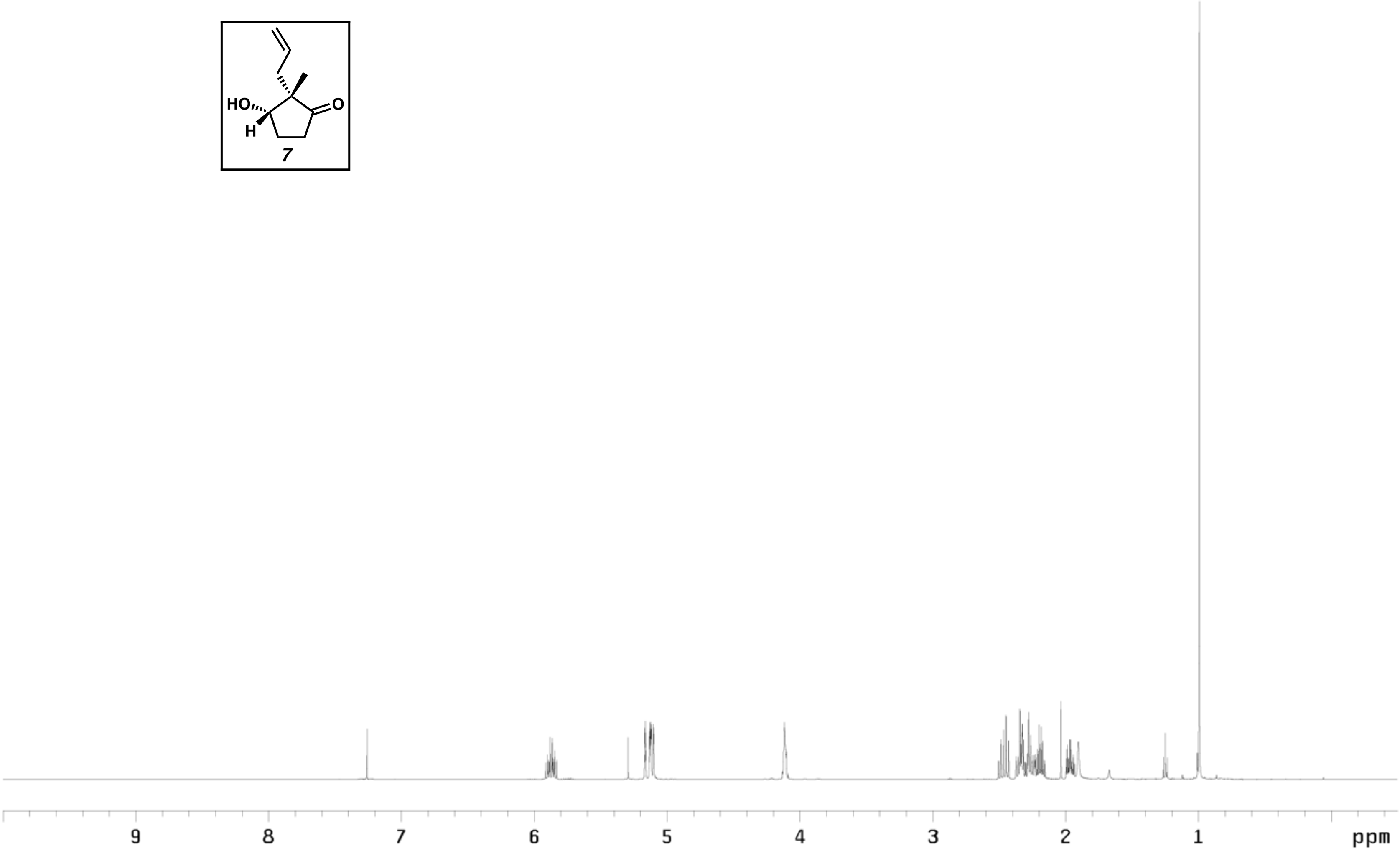


Figure 4.1 ^{1}H NMR (500 MHz, CDCl$_3$) of alcohol **7**.

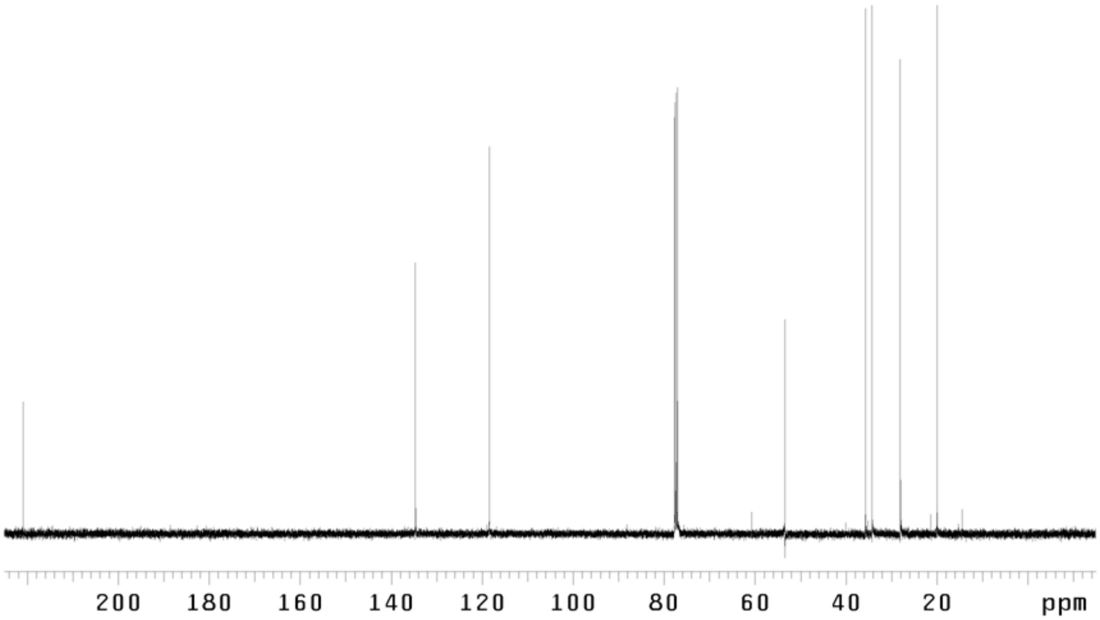


Figure 4.2 ^{13}C NMR (125 MHz, CDCl$_3$) of alcohol **7**.

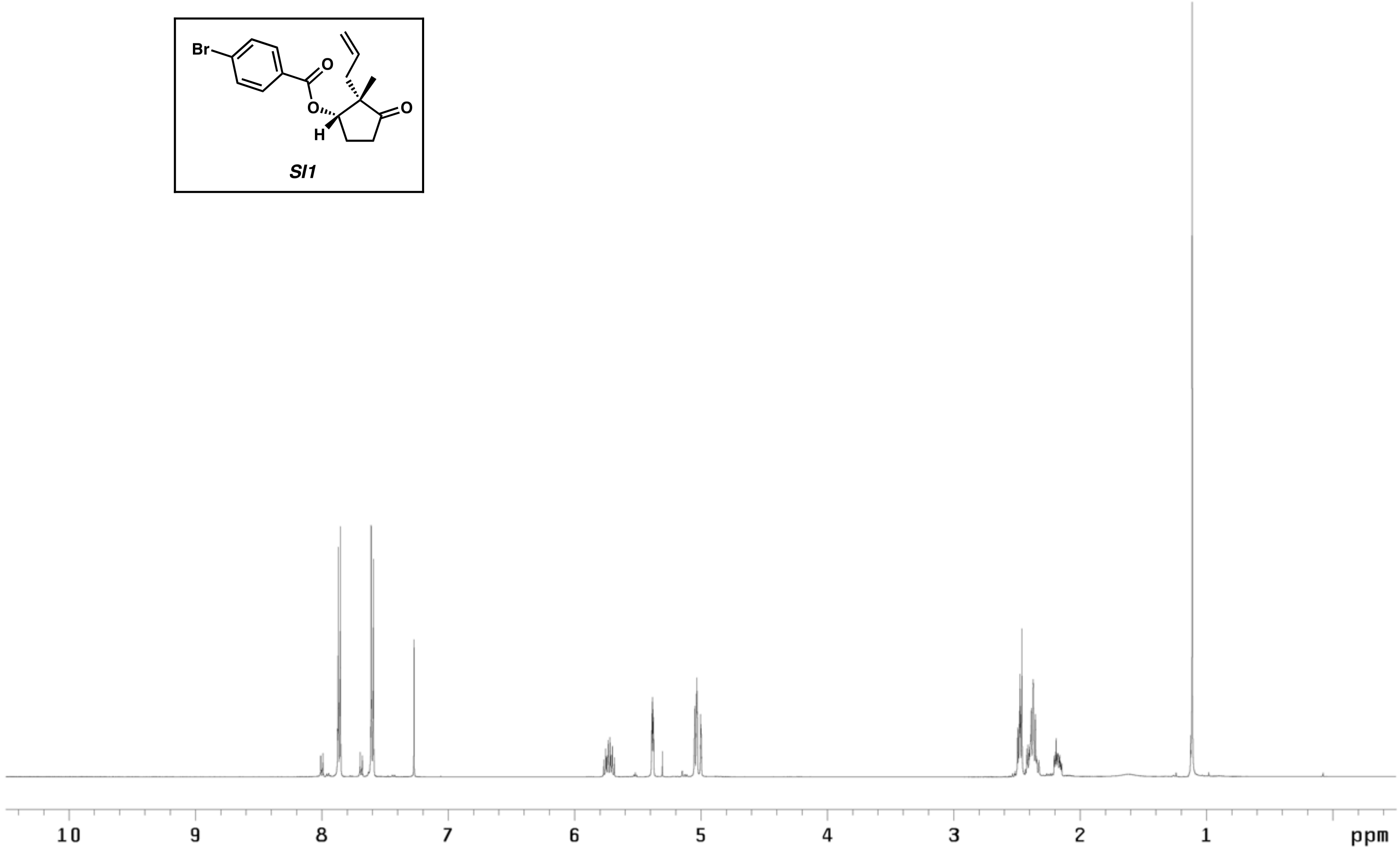


Figure 5.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI1**.

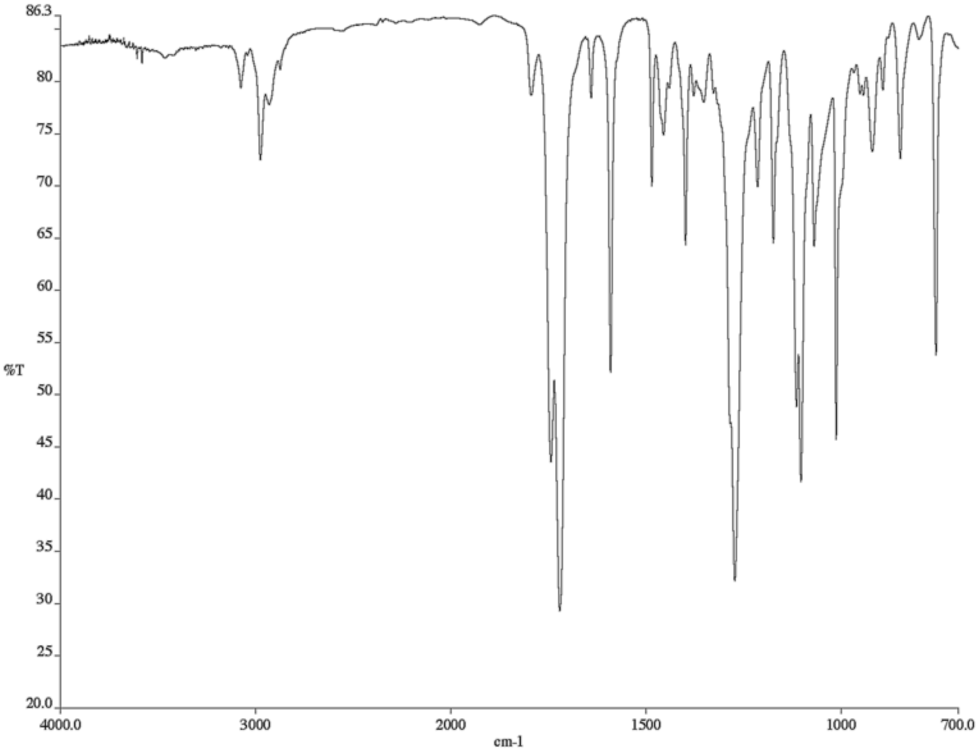


Figure 5.2 Infrared spectrum (thin film/NaCl) of compound **SI1**

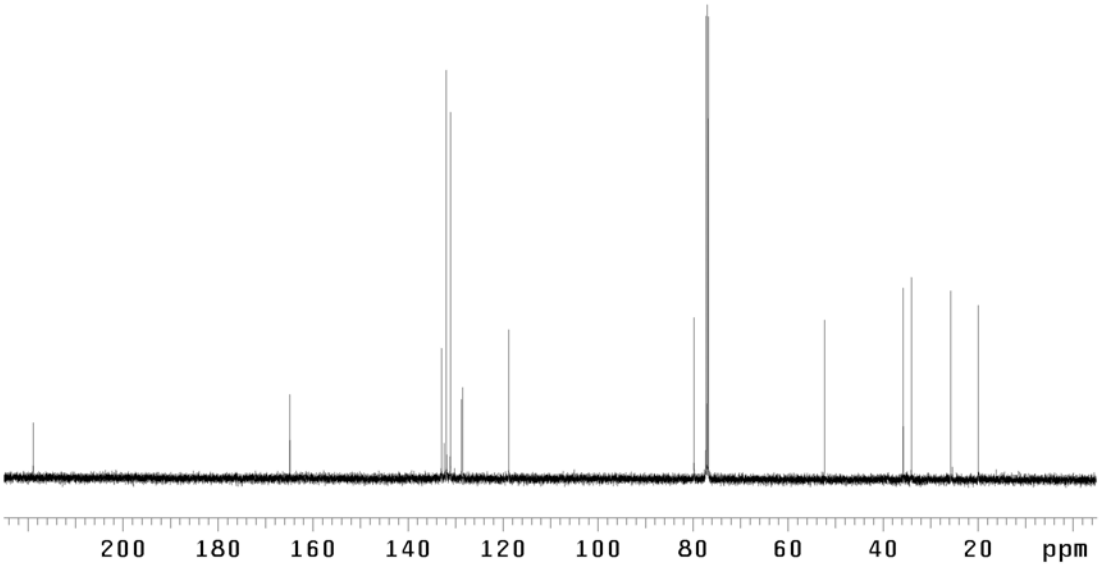


Figure 5.3 ^{13}C NMR (125 MHz, CDCl$_3$) of compound **SI1**.

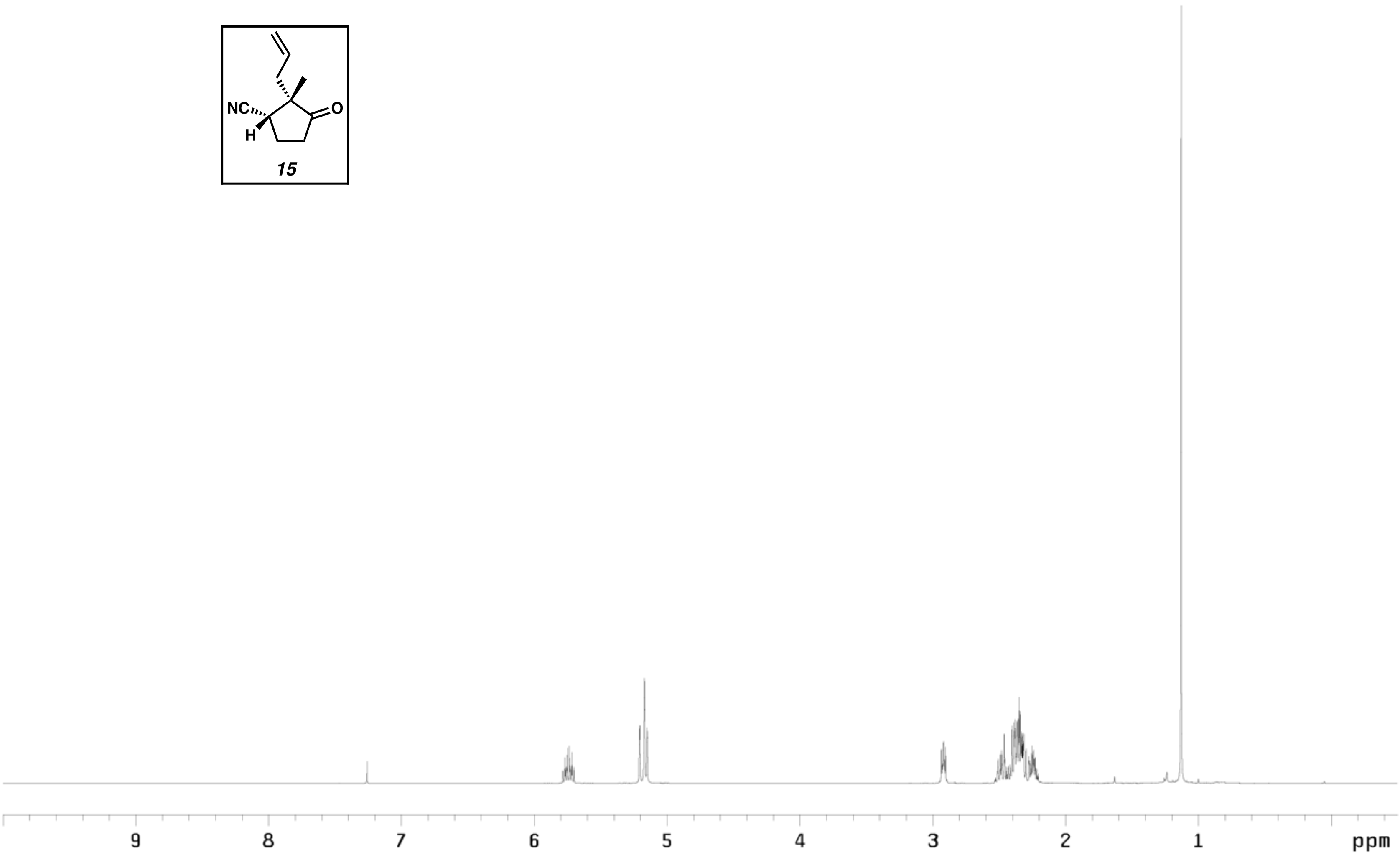


Figure 6.1 ^{1}H NMR (500 MHz, $CDCl_3$) of nitrile **15**.

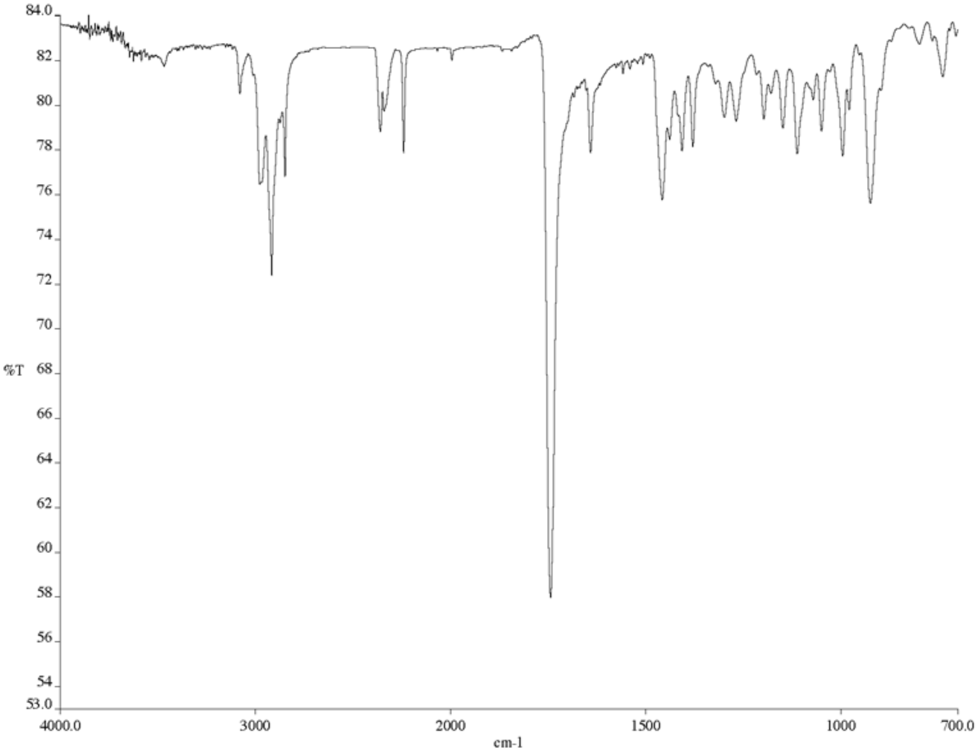


Figure 6.2 Infrared spectrum (Neat Film NaCl) of nitrile **15**.

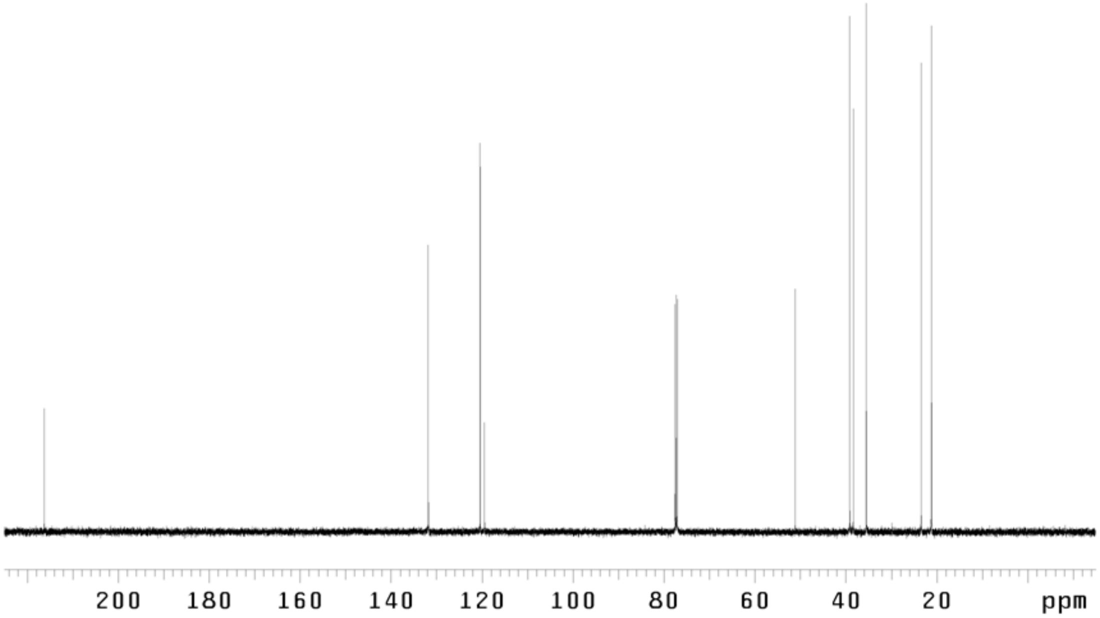


Figure 6.3 ^{13}C NMR (125 MHz, CDCl$_3$) of nitrile **15**.

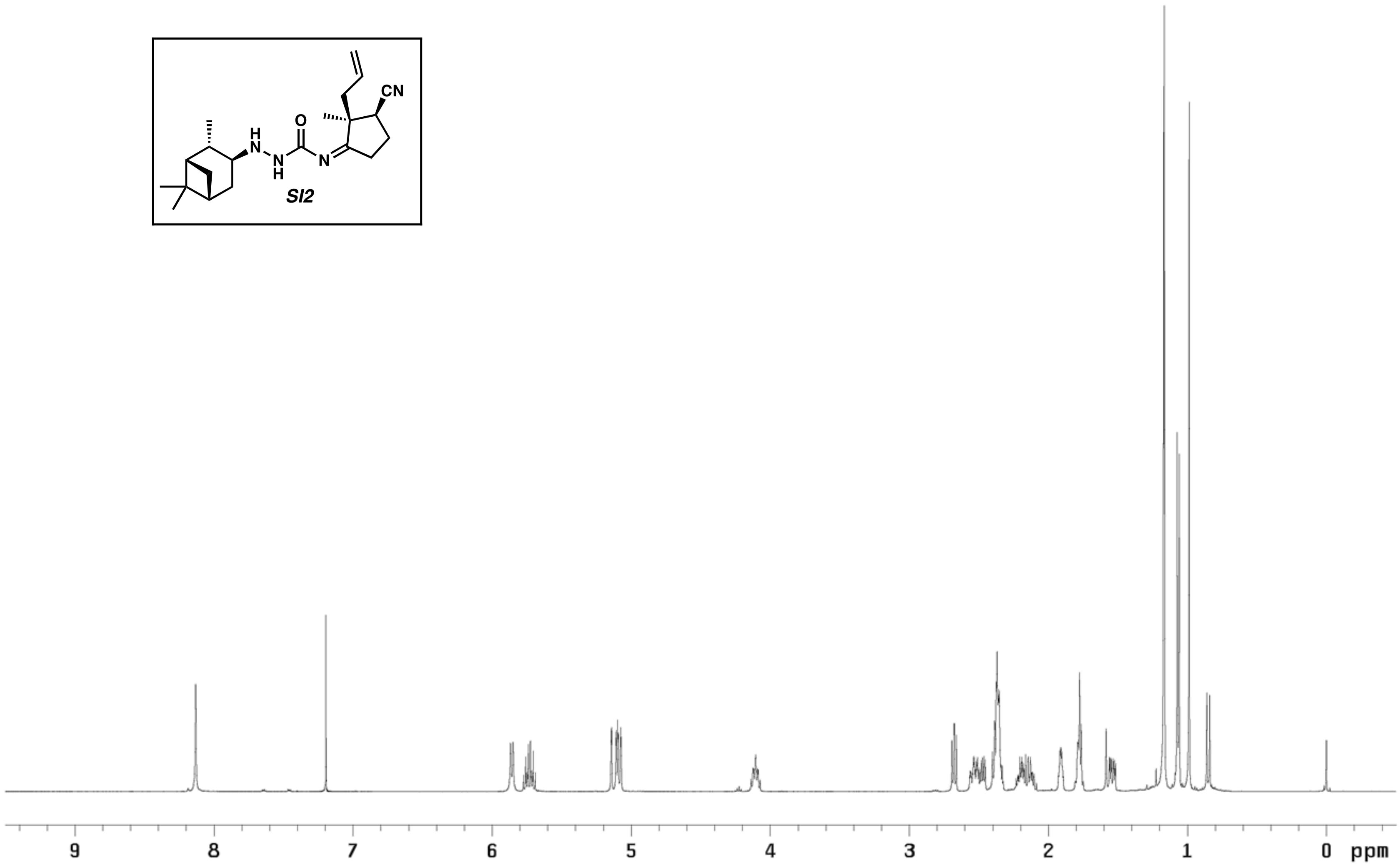


Figure 7.1 ^{1}H NMR (500 MHz, CDCl$_3$) of compound **SI2**.

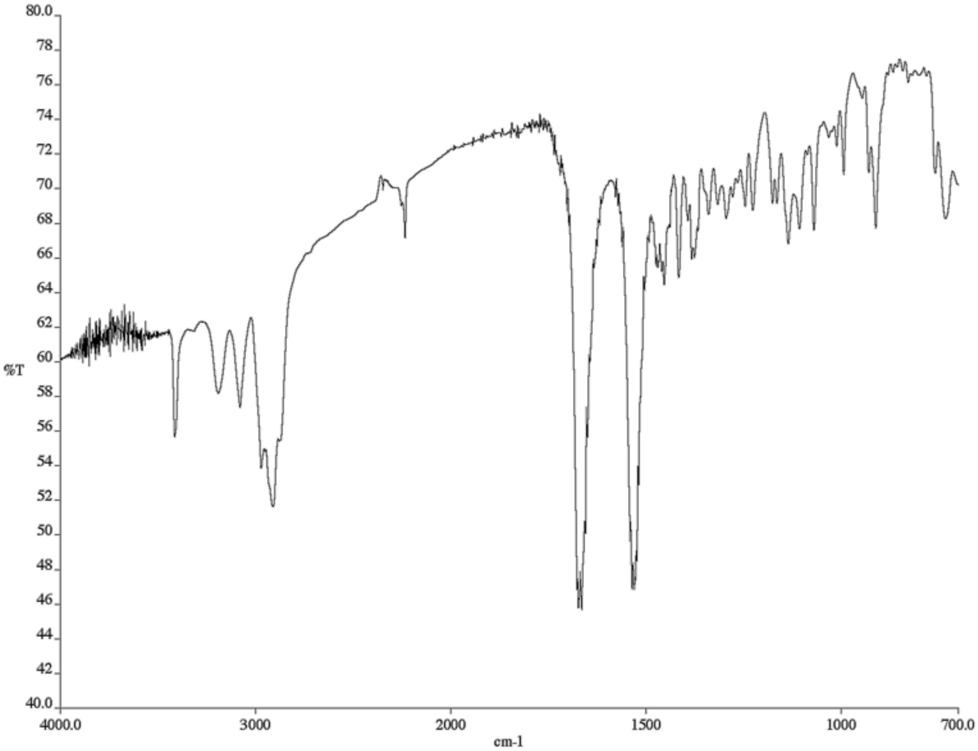


Figure 7.2 Infrared spectrum (thin film/NaCl) of compound **SI2**.

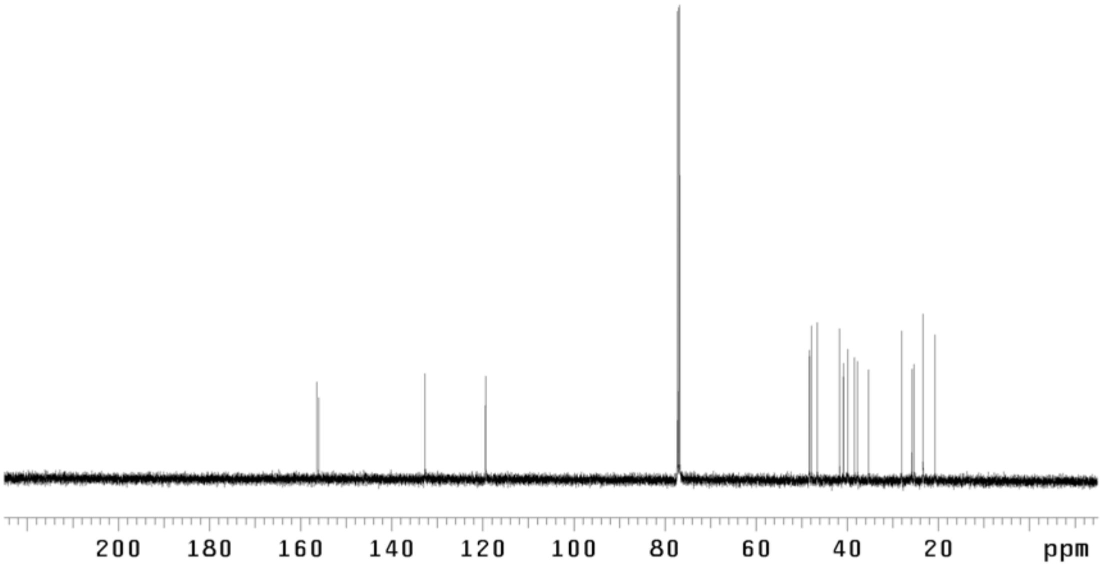


Figure 7.3 ^{13}C NMR (125 MHz, CDCl$_3$) of compound **SI2**.

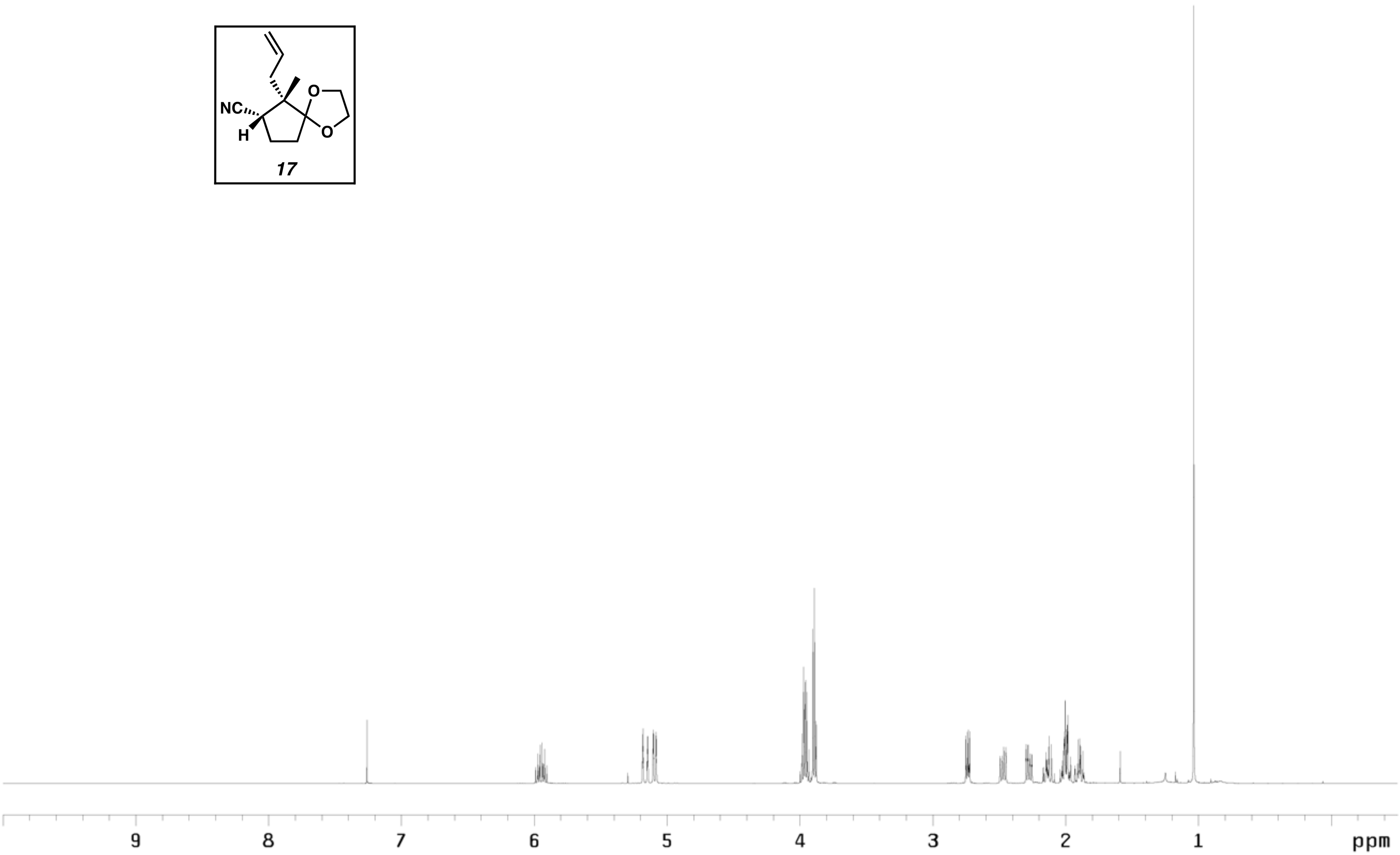


Figure 8.1 ^{1}H NMR (500 MHz, CDCl$_3$) of ketal **17**.

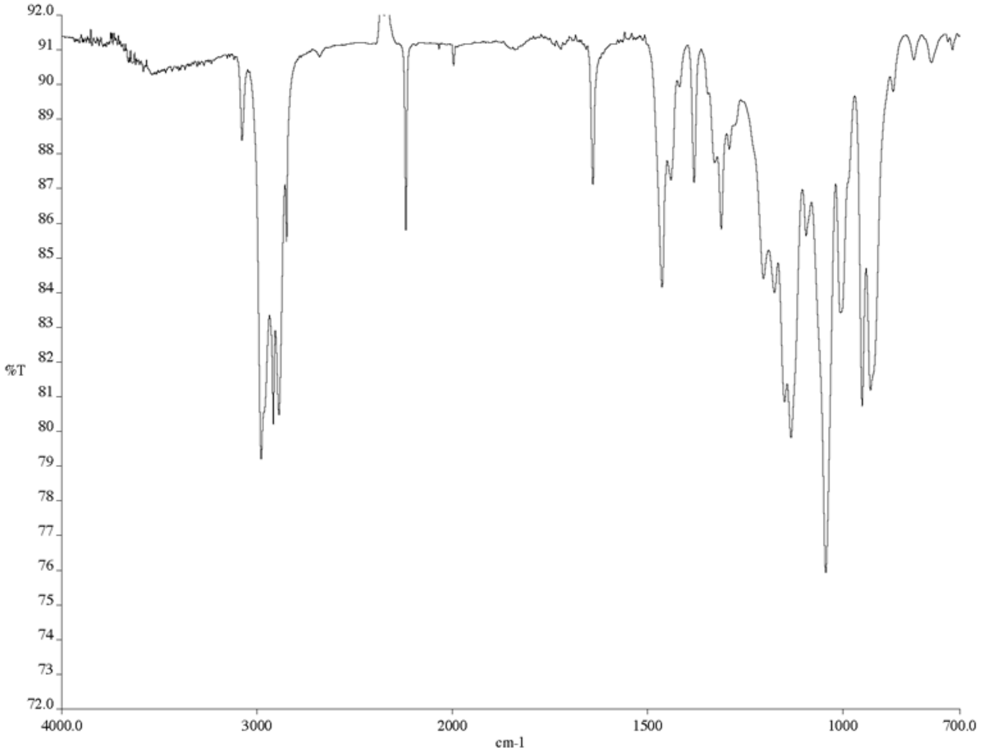


Figure 8.2 Infrared spectrum (Neat Film NaCl) of ketal **17**.

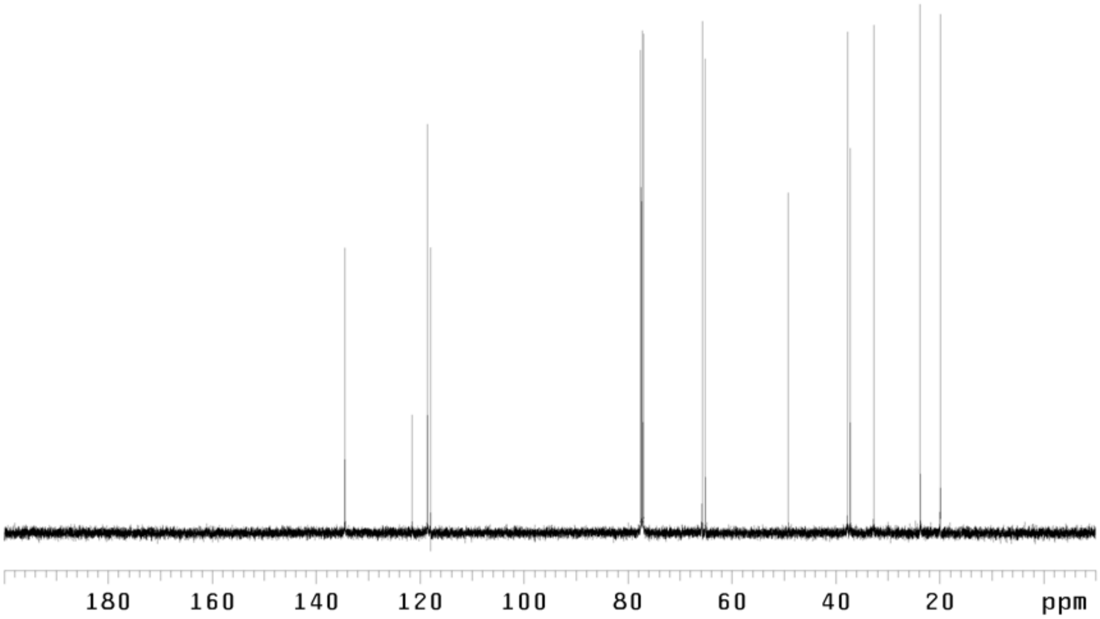


Figure 8.3 ^{13}C NMR (125 MHz, CDCl$_3$) of ketal **17**.

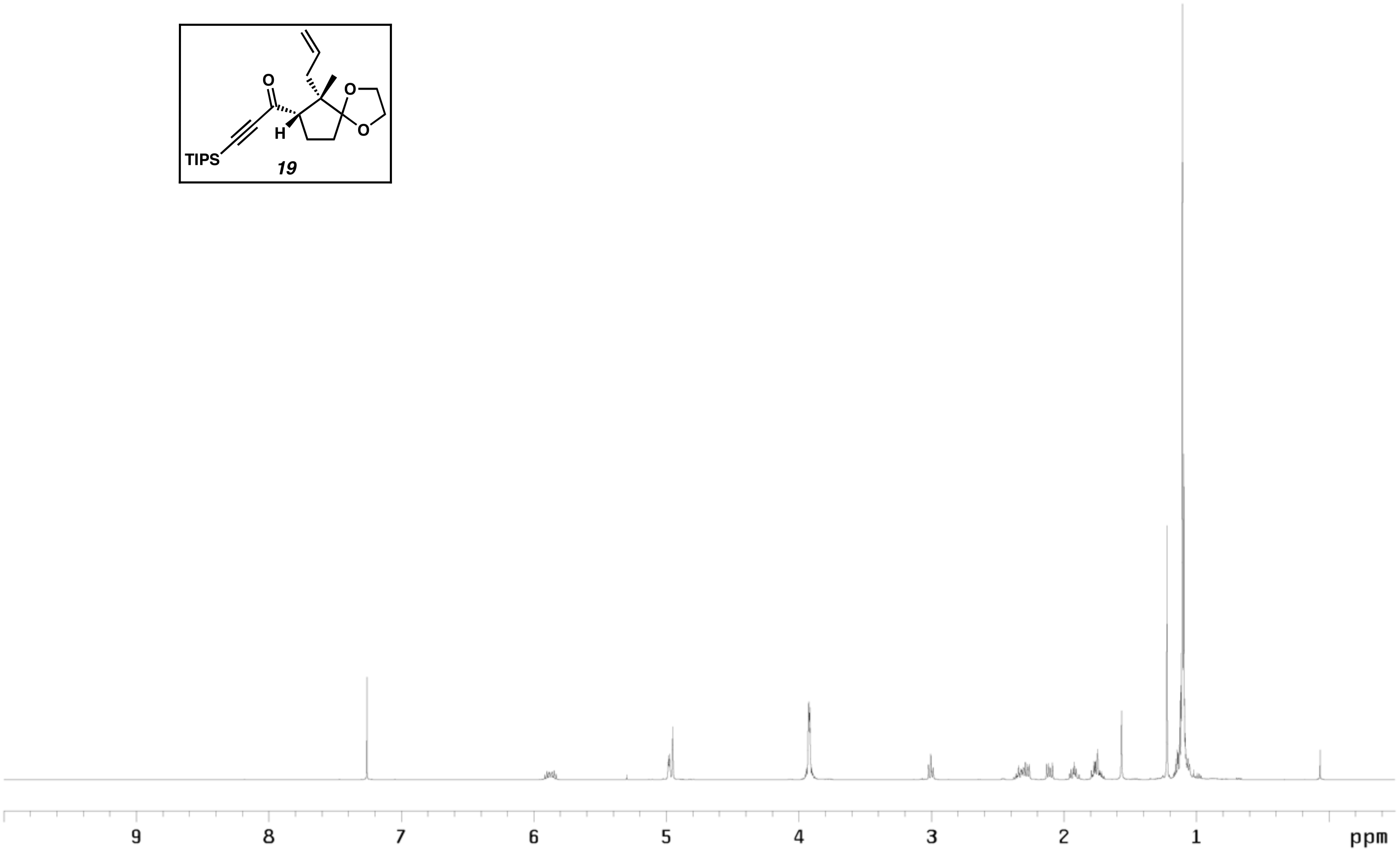


Figure 9.1 ^{1}H NMR (500 MHz, CDCl$_3$) of ynone **19**.

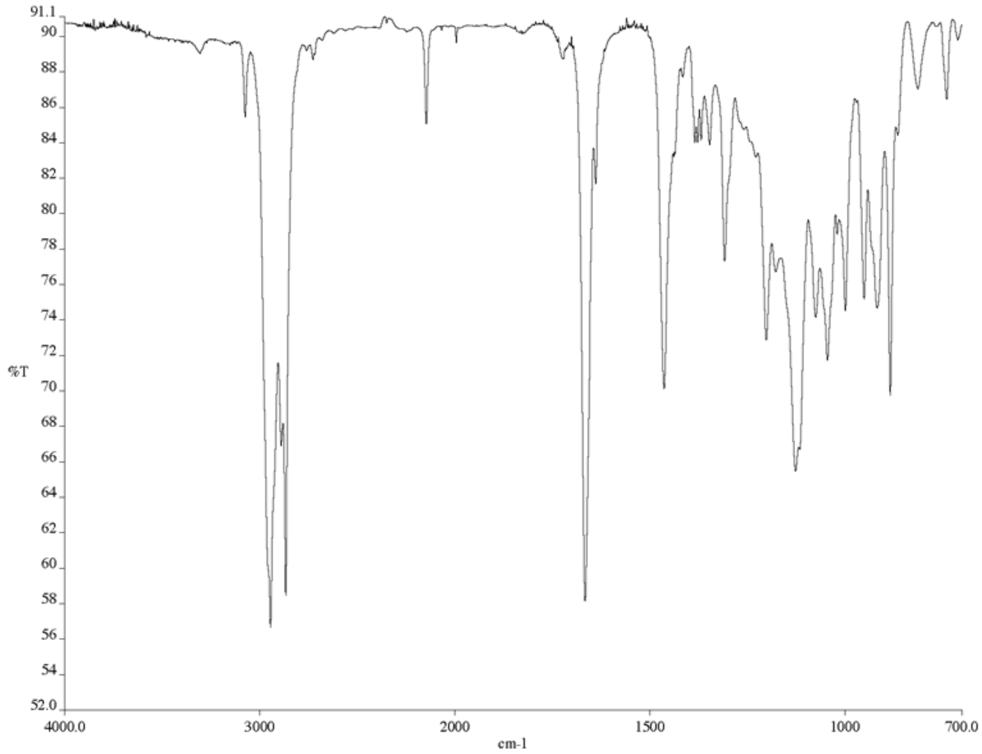


Figure 9.2 Infrared spectrum (Neat Film NaCl) of ynone **19**.

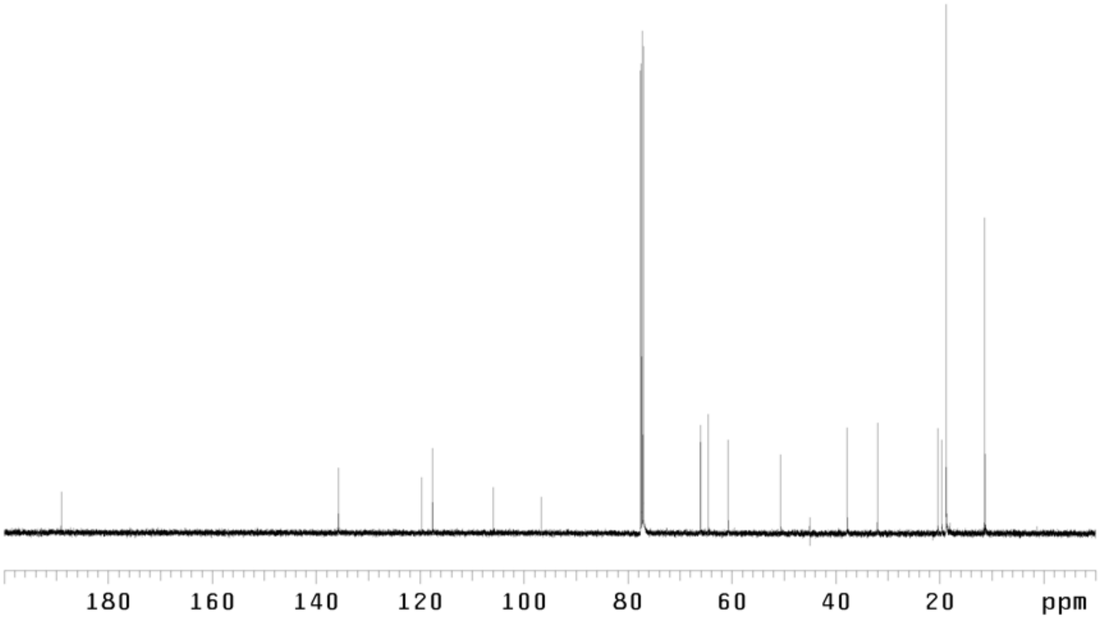


Figure 9.3 ^{13}C NMR (125 MHz, CDCl$_3$) of ynone **19**.

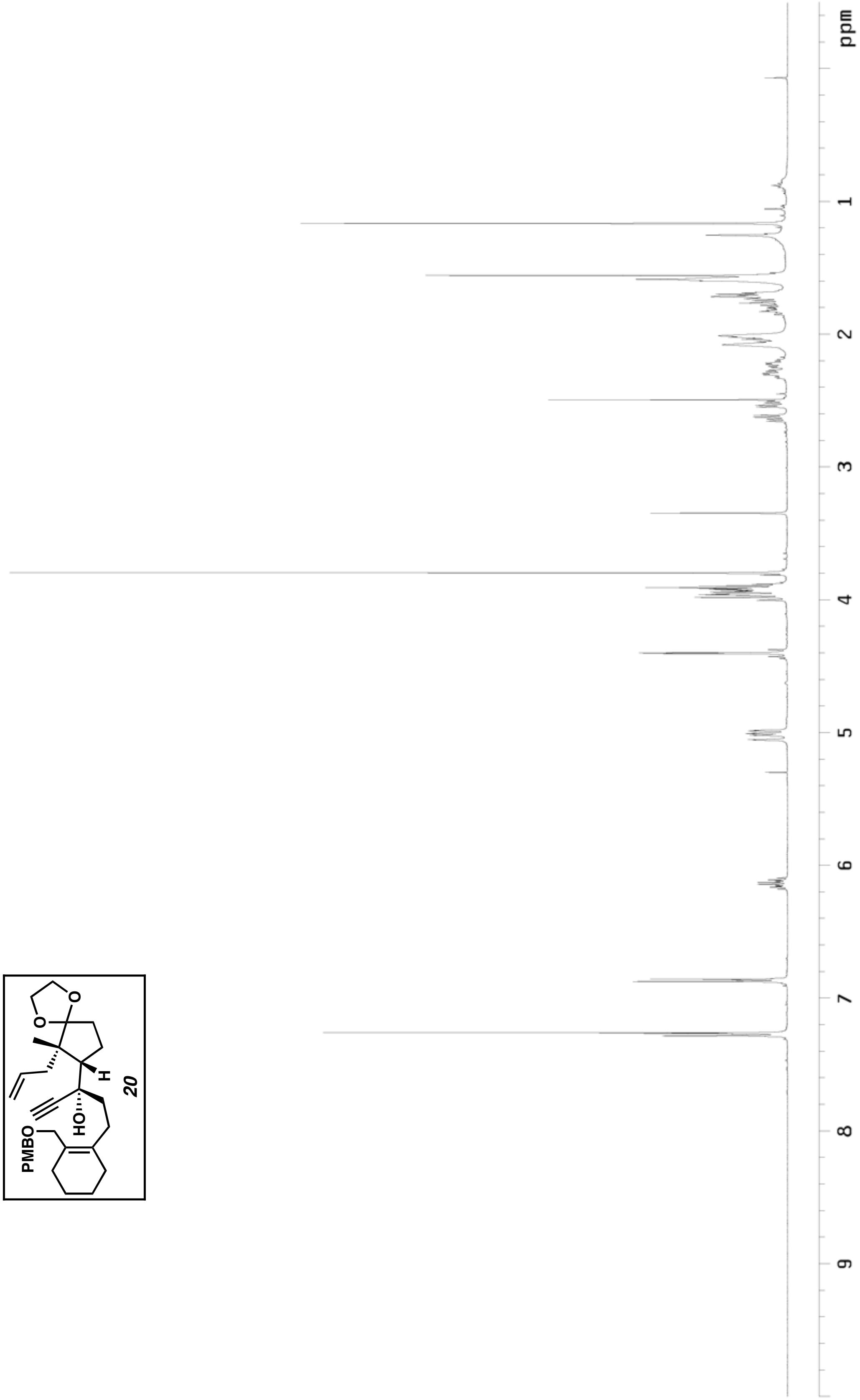


Figure 10.1 ^{1}H NMR (500 MHz, CDCl$_3$) of compound **20**.

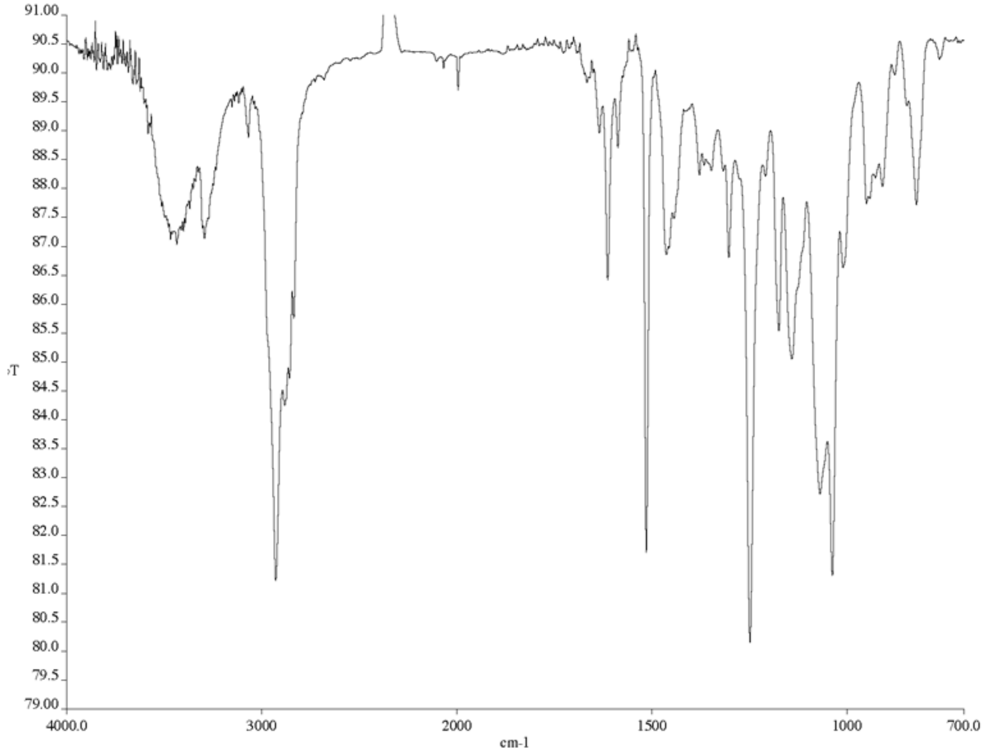


Figure 10.2 Infrared spectrum (Neat Film NaCl) of compound **20**.

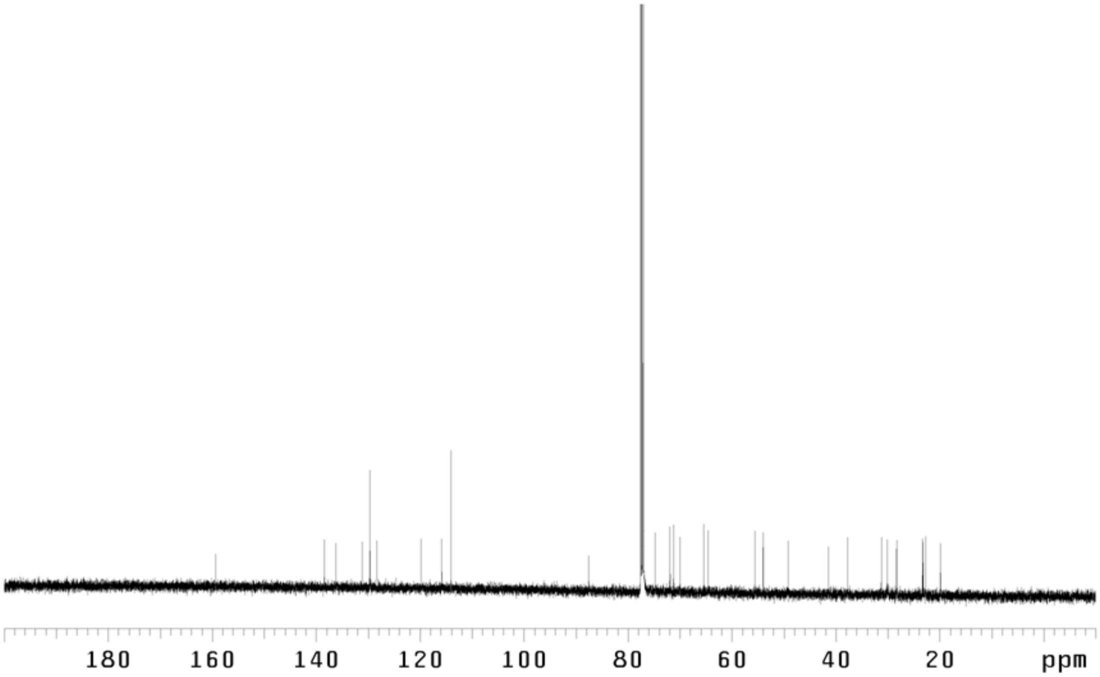


Figure 10.3 ^{13}C NMR (125 MHz, CDCl$_3$) of compound **20**.

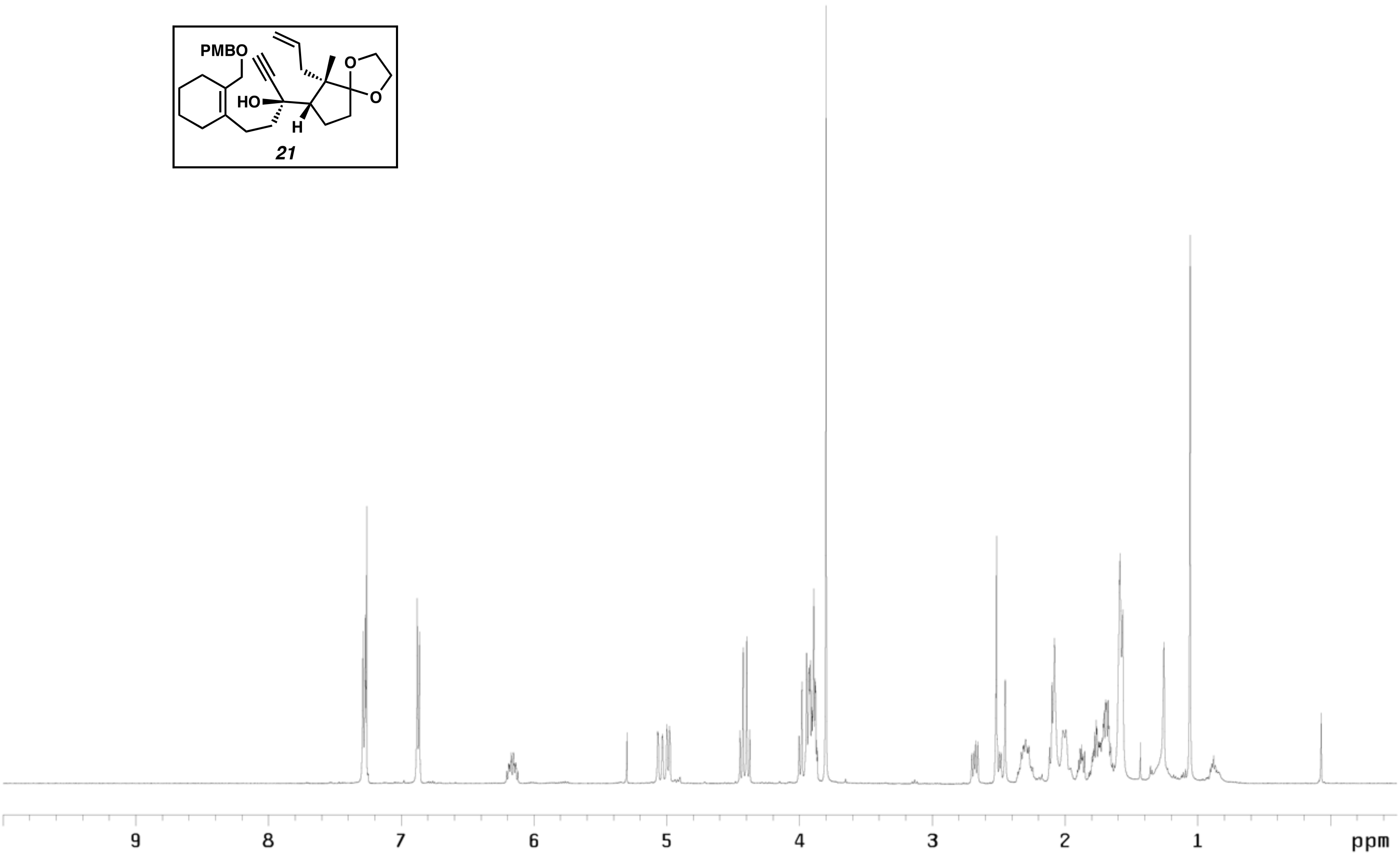


Figure 11.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **21**.

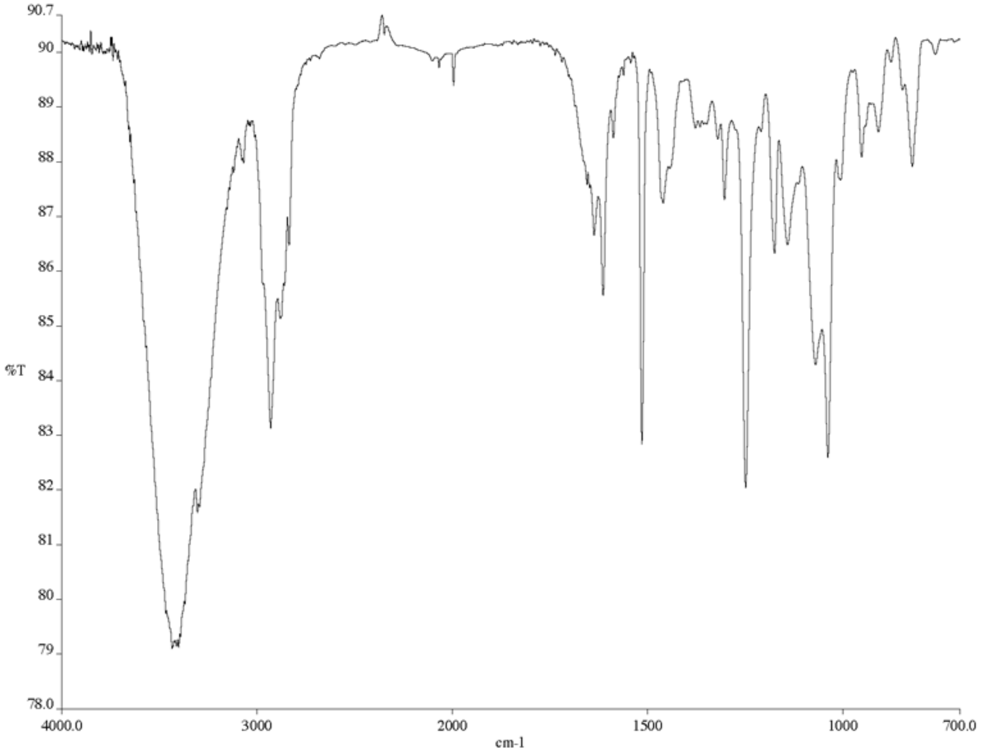


Figure 11.2 Infrared spectrum (Neat Film NaCl) of compound **21**.

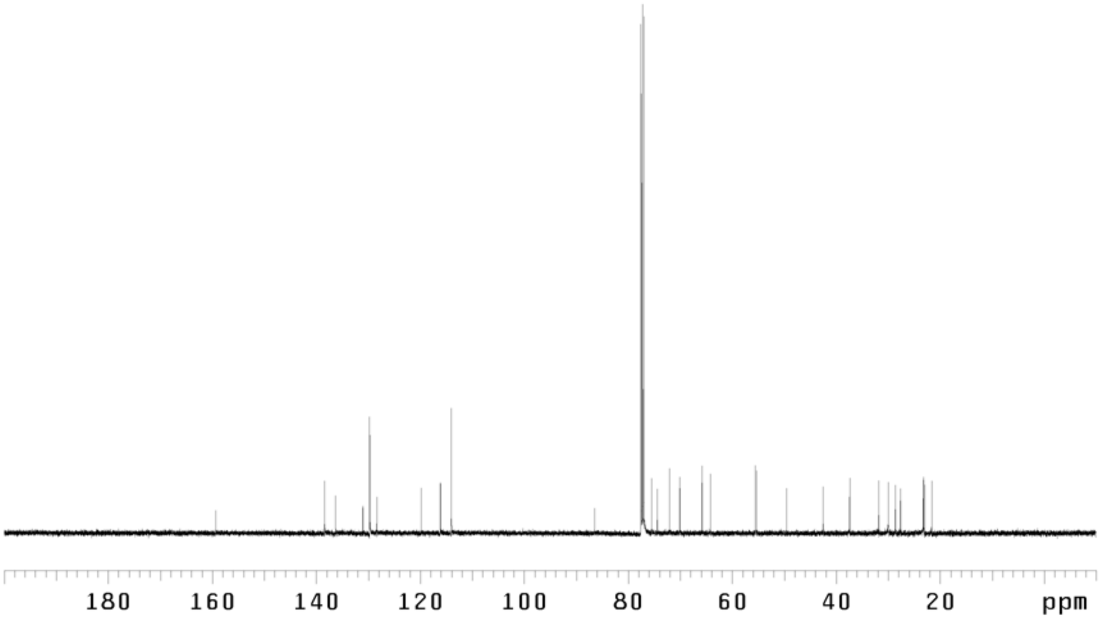


Figure 11.3 ^{13}C NMR (125 MHz, CDCl$_3$) of compound **21**.

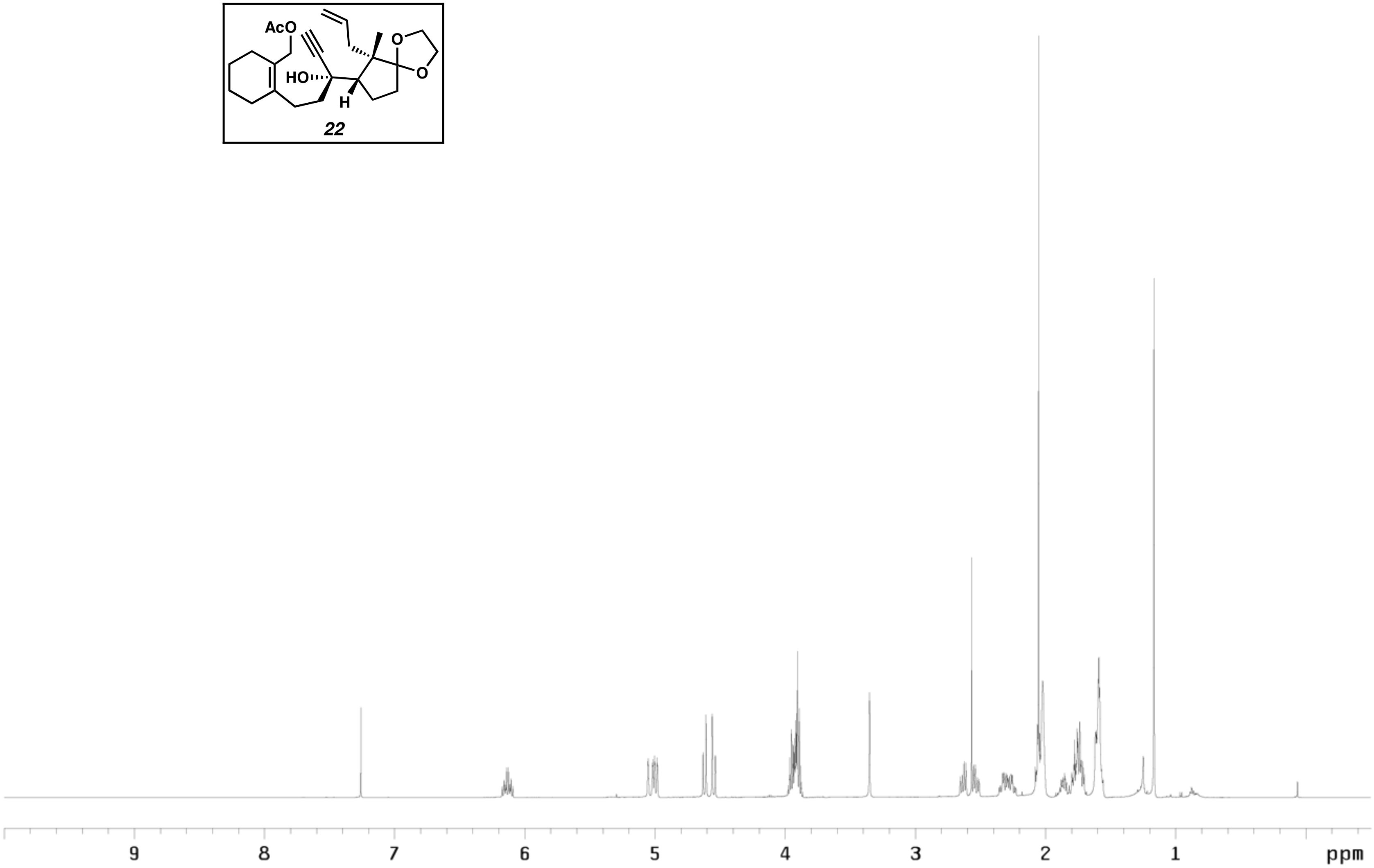


Figure 12.1 ^{1}H NMR (500 MHz, CDCl$_3$) of compound **22**.

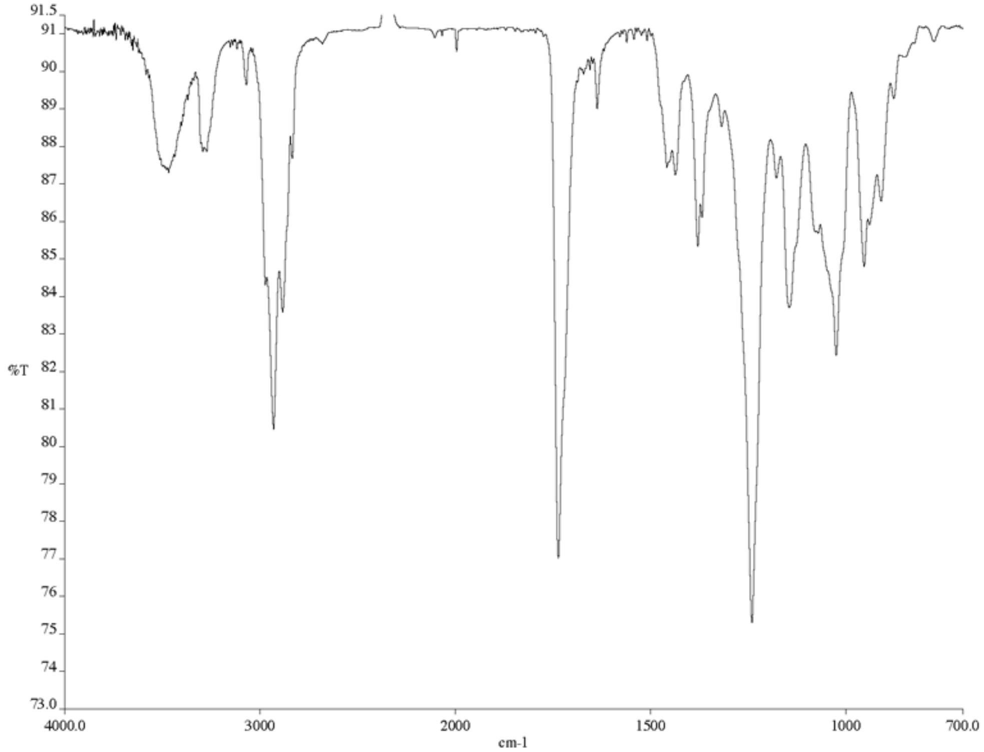


Figure 12.2 Infrared spectrum (Neat Film NaCl) of compound **22**.

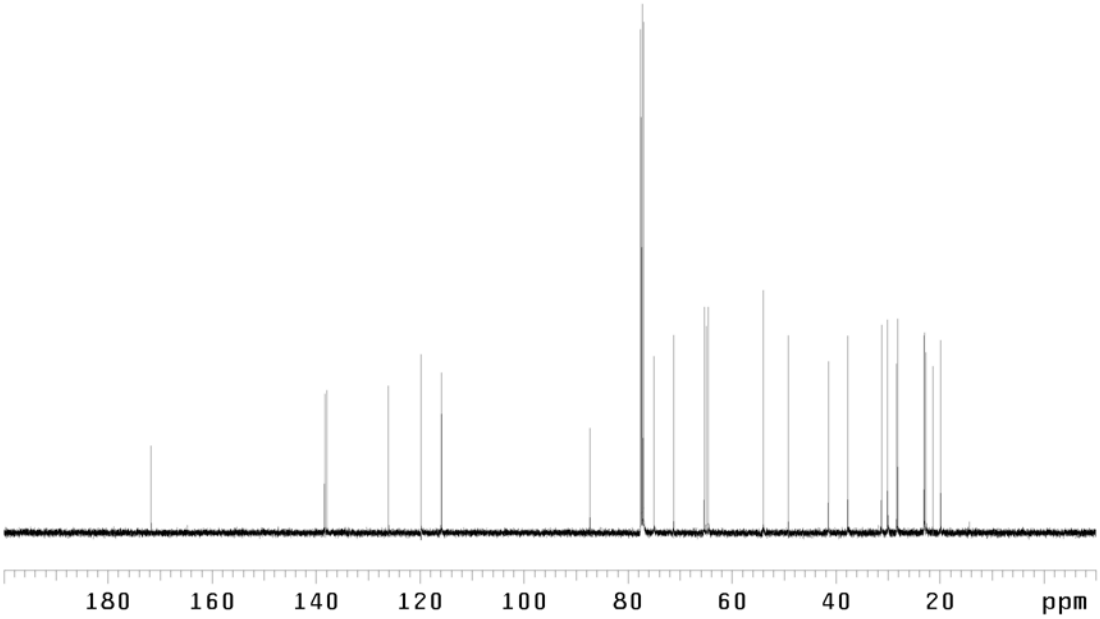


Figure 12.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **22**.

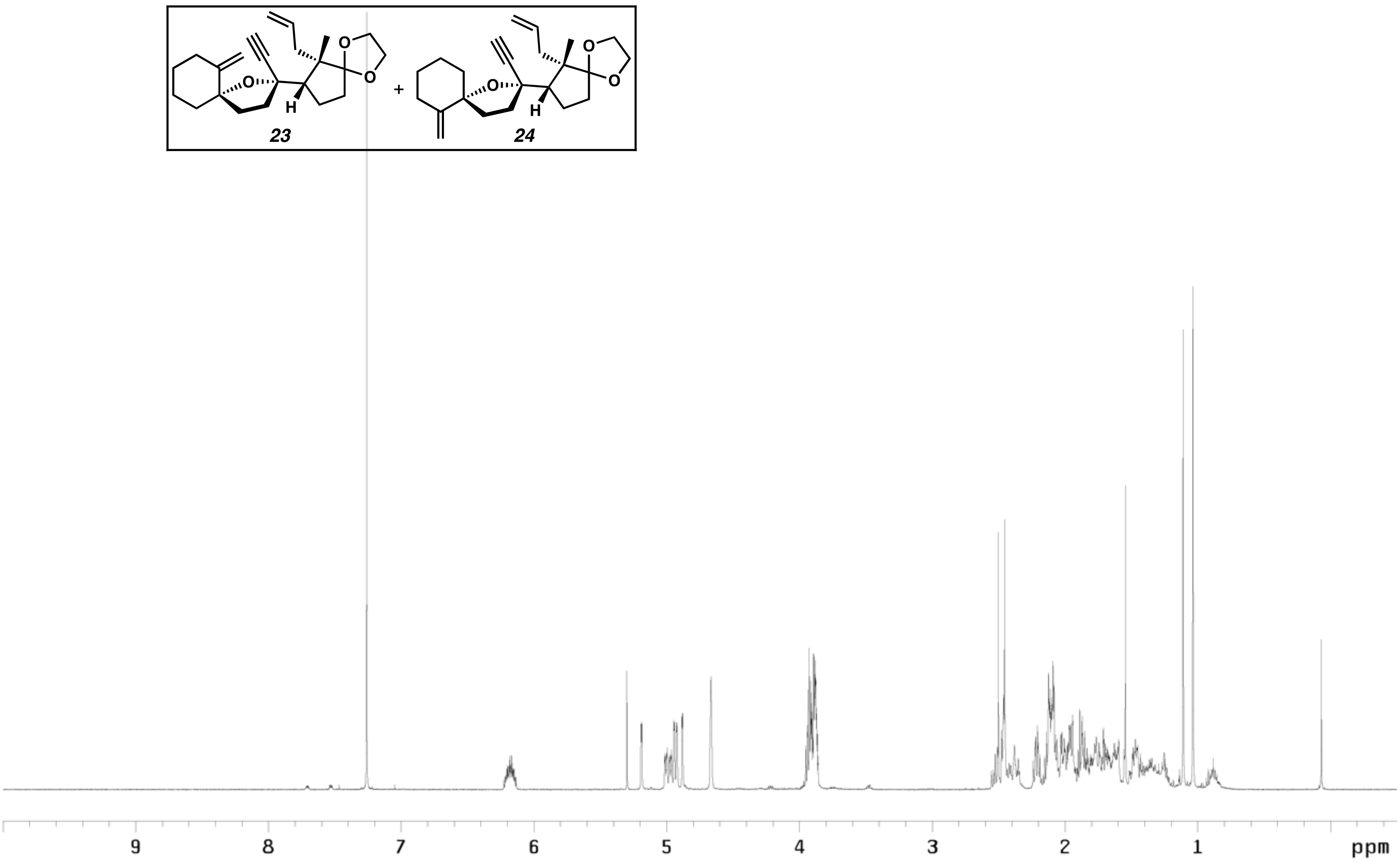


Figure 13.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **23** and **24**.

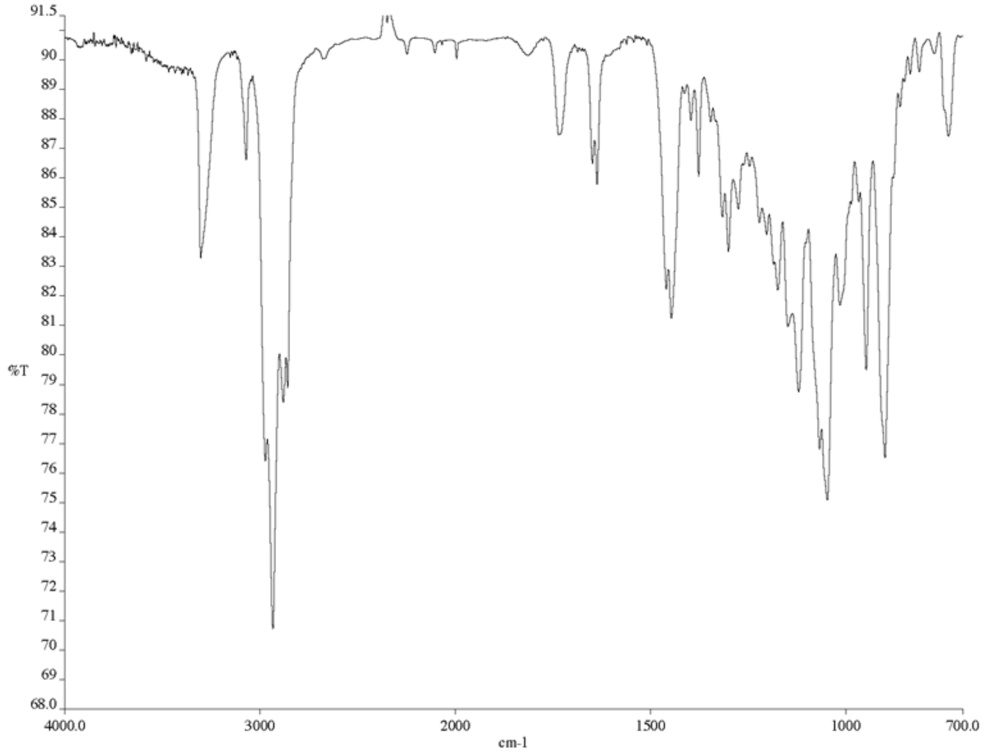


Figure 13.2 Infrared spectrum (Neat Film NaCl) of compounds **23** and **24**.

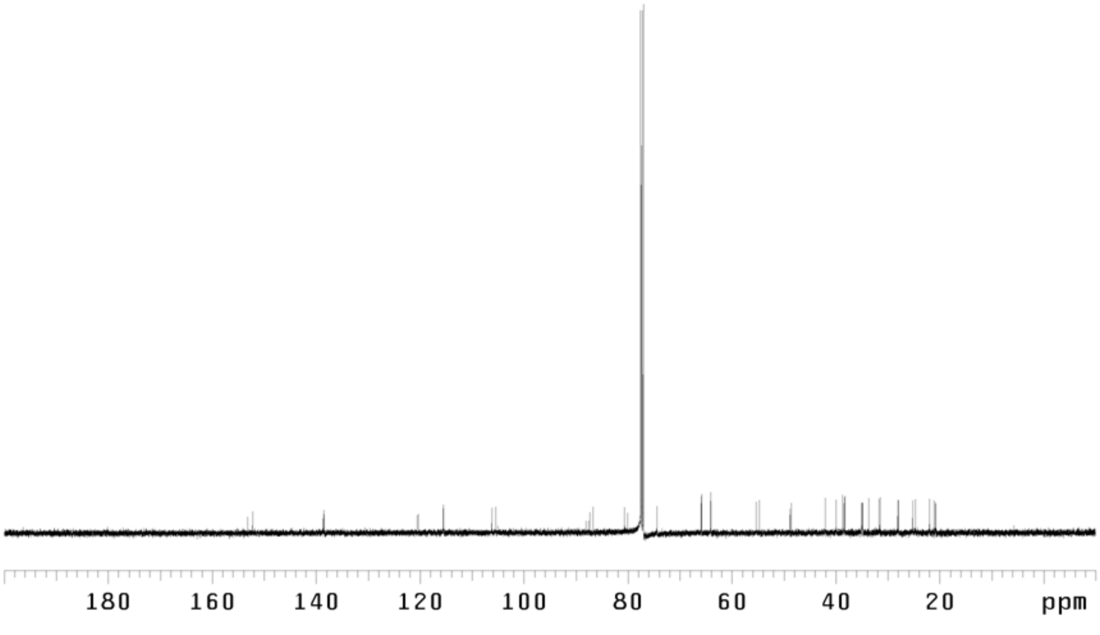


Figure 13.3 ^{13}C NMR (125 MHz, CDCl$_3$) of compounds **23** and **24**.

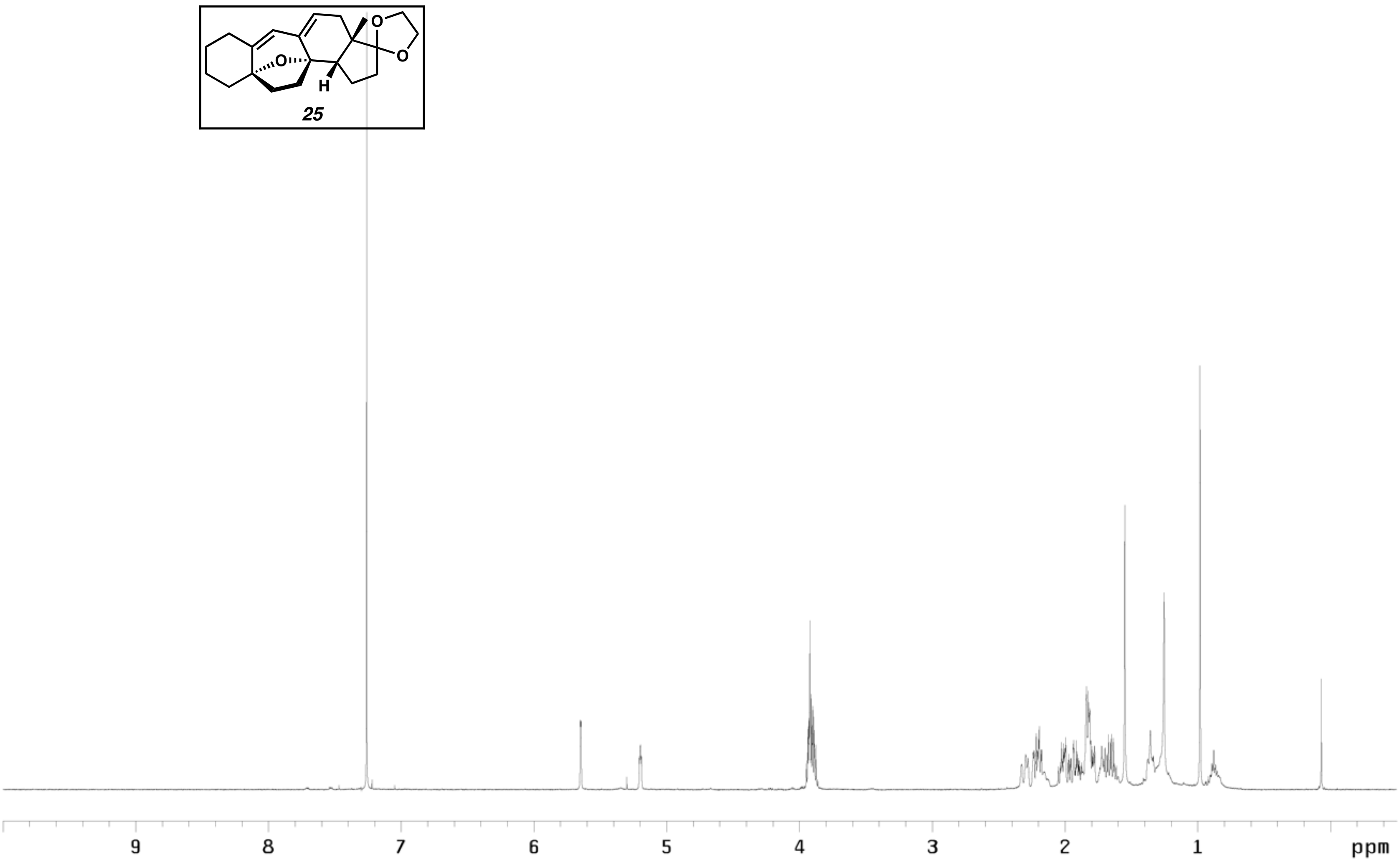


Figure 14.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **25**.

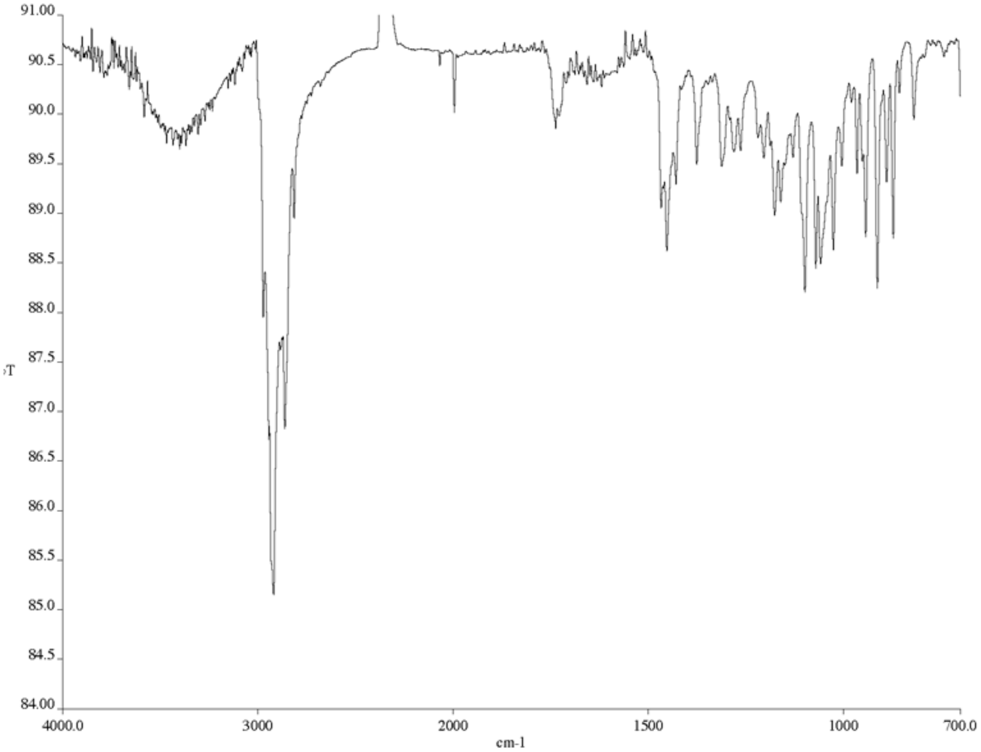


Figure 14.2 Infrared spectrum (Neat Film NaCl) of compound **25**.

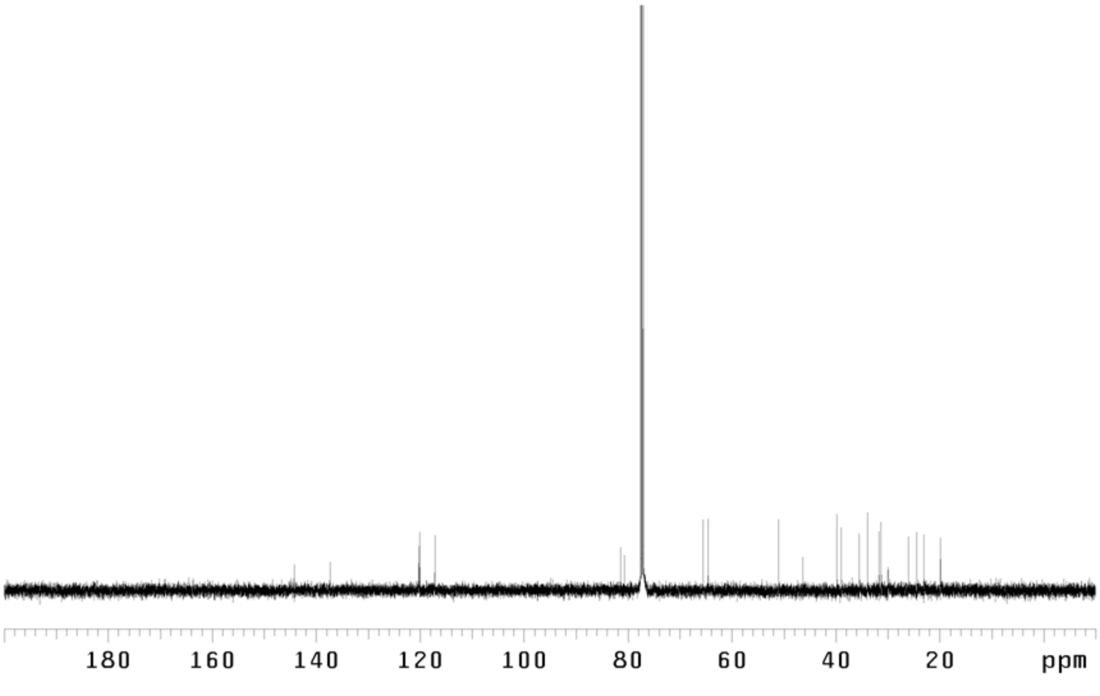


Figure 14.3 ^{13}C NMR (125 MHz, CDCl$_3$) of compound **25**.

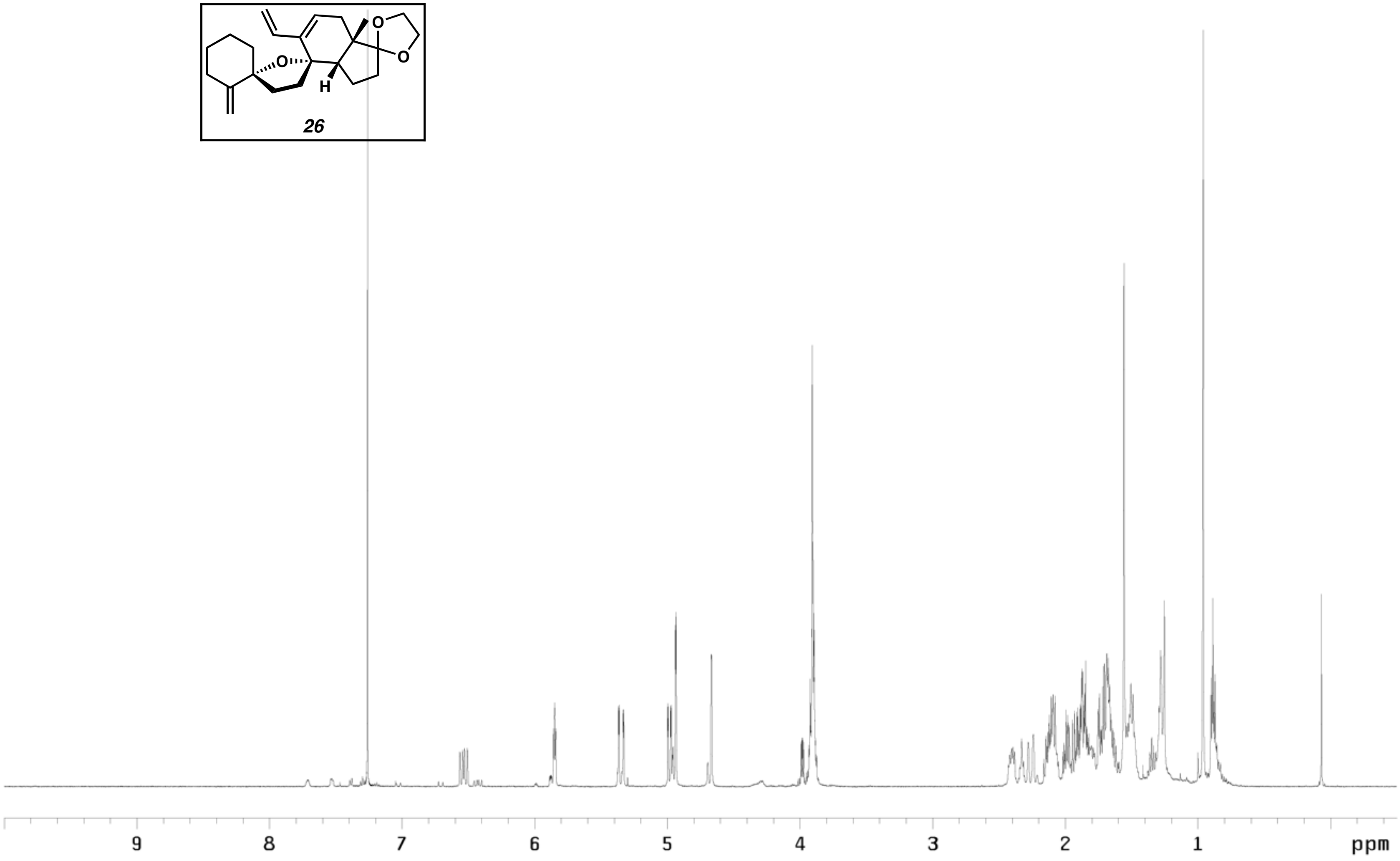


Figure 15.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26**.

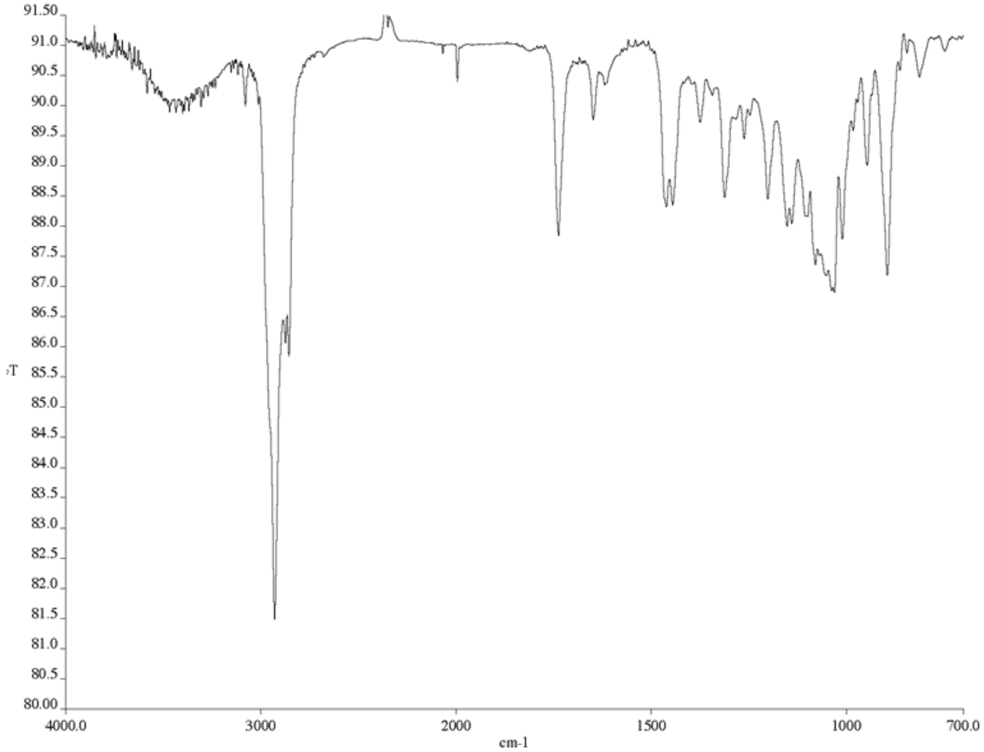


Figure 15.2 Infrared spectrum (Neat Film NaCl) of compound **26**.

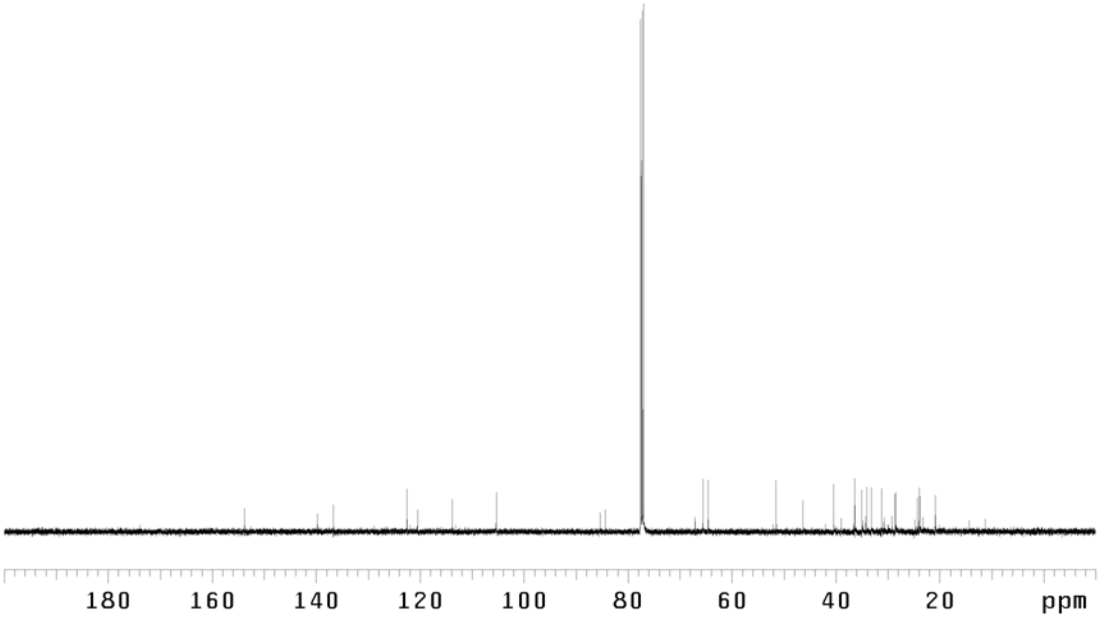


Figure 15.3 ^{13}C NMR (125 MHz, CDCl$_3$) of compound **26**.

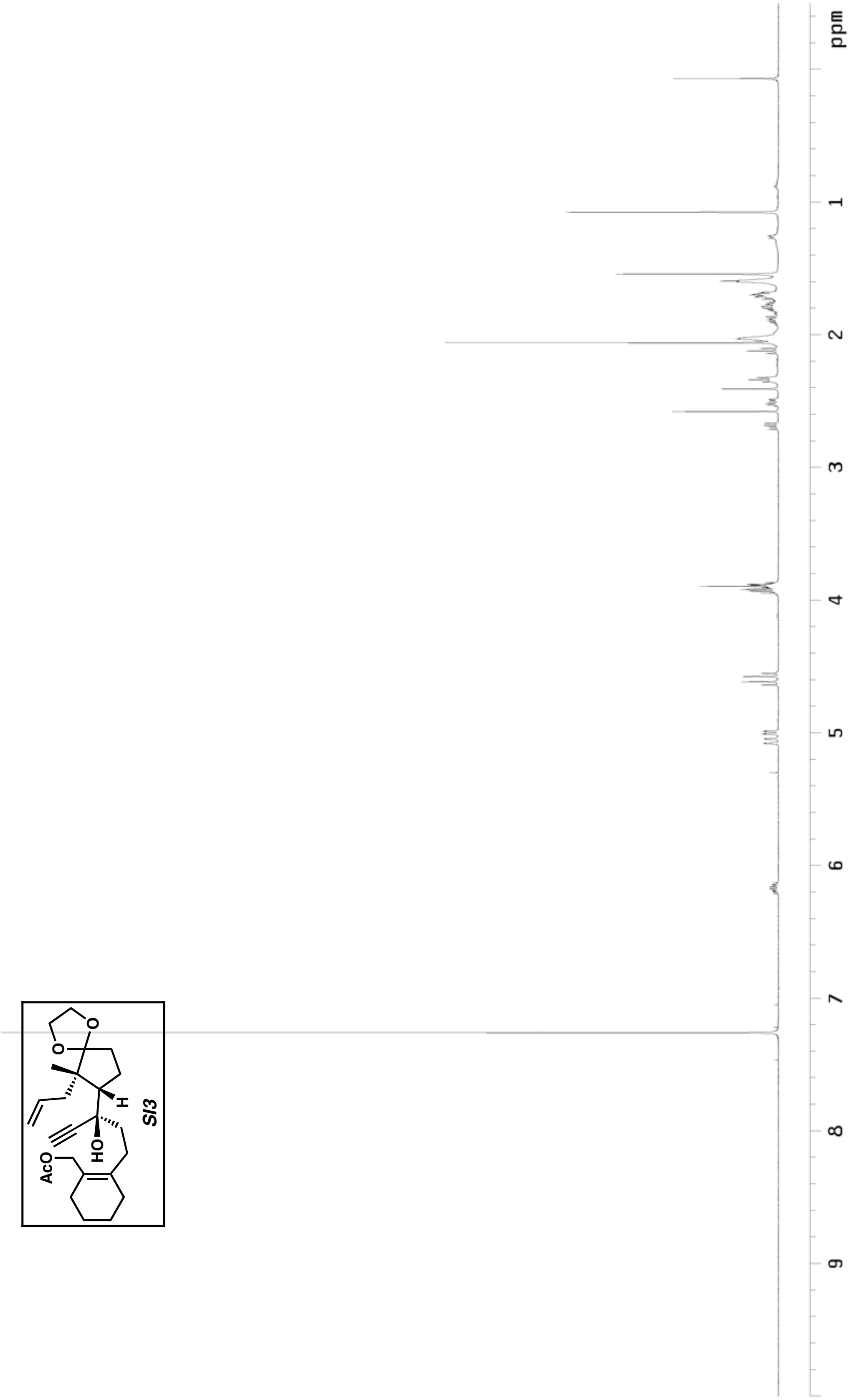


Figure 16.1 ^{1}H NMR (500 MHz, CDCl$_3$) of compound **SI3**.

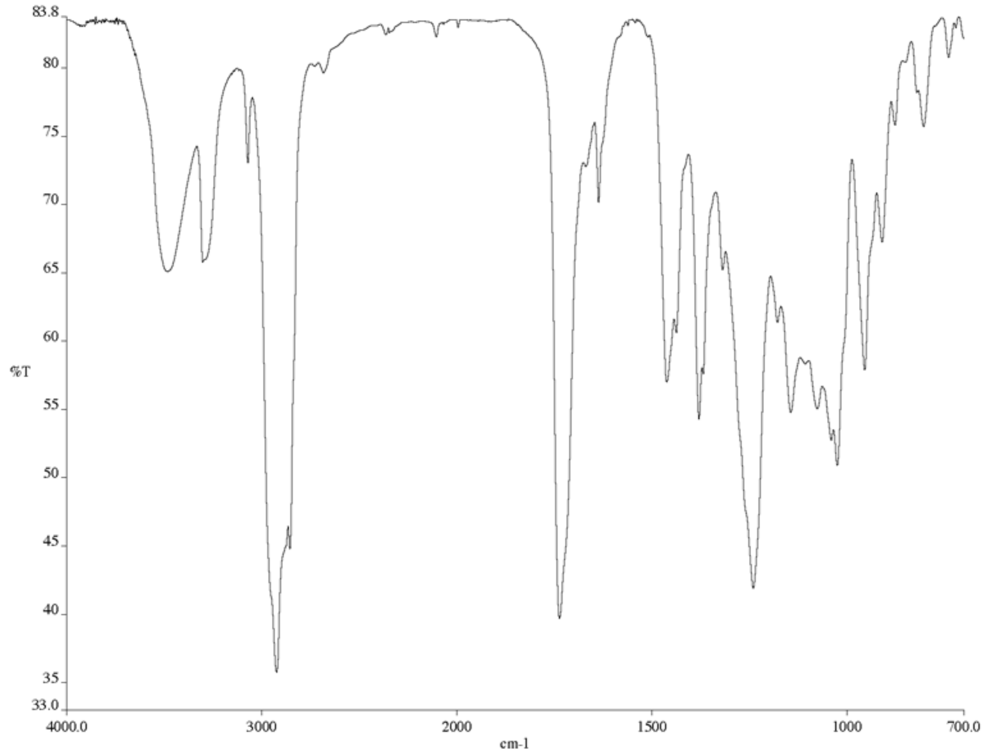


Figure 16.2 Infrared spectrum (Neat Film NaCl) of compound **SI3**.

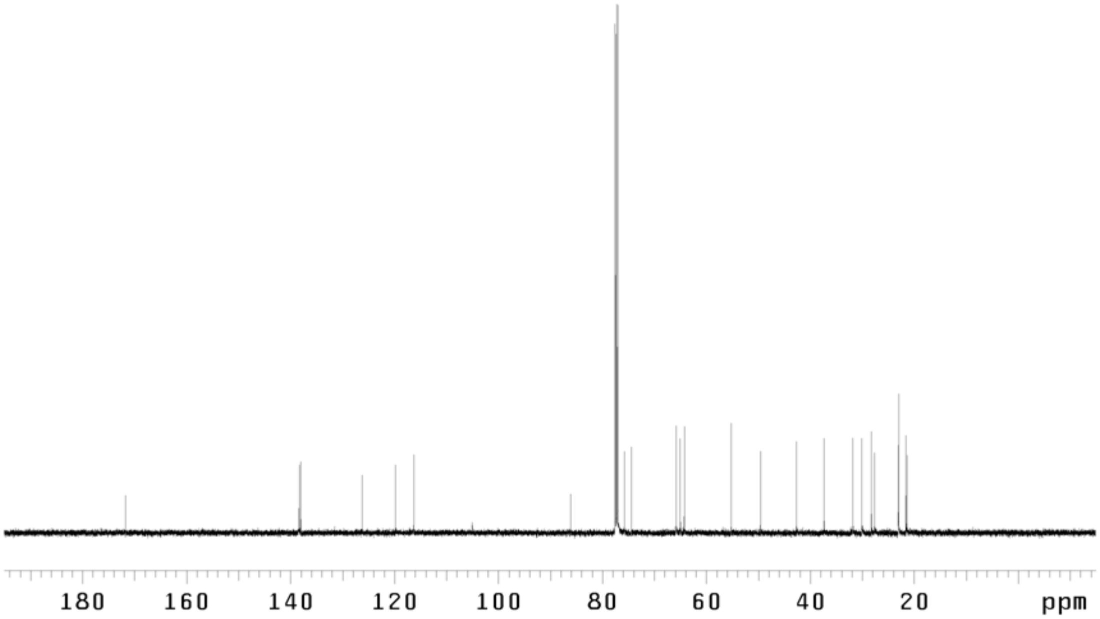


Figure 16.3 ^{13}C NMR (125 MHz, CDCl$_3$) of compound **SI3**.

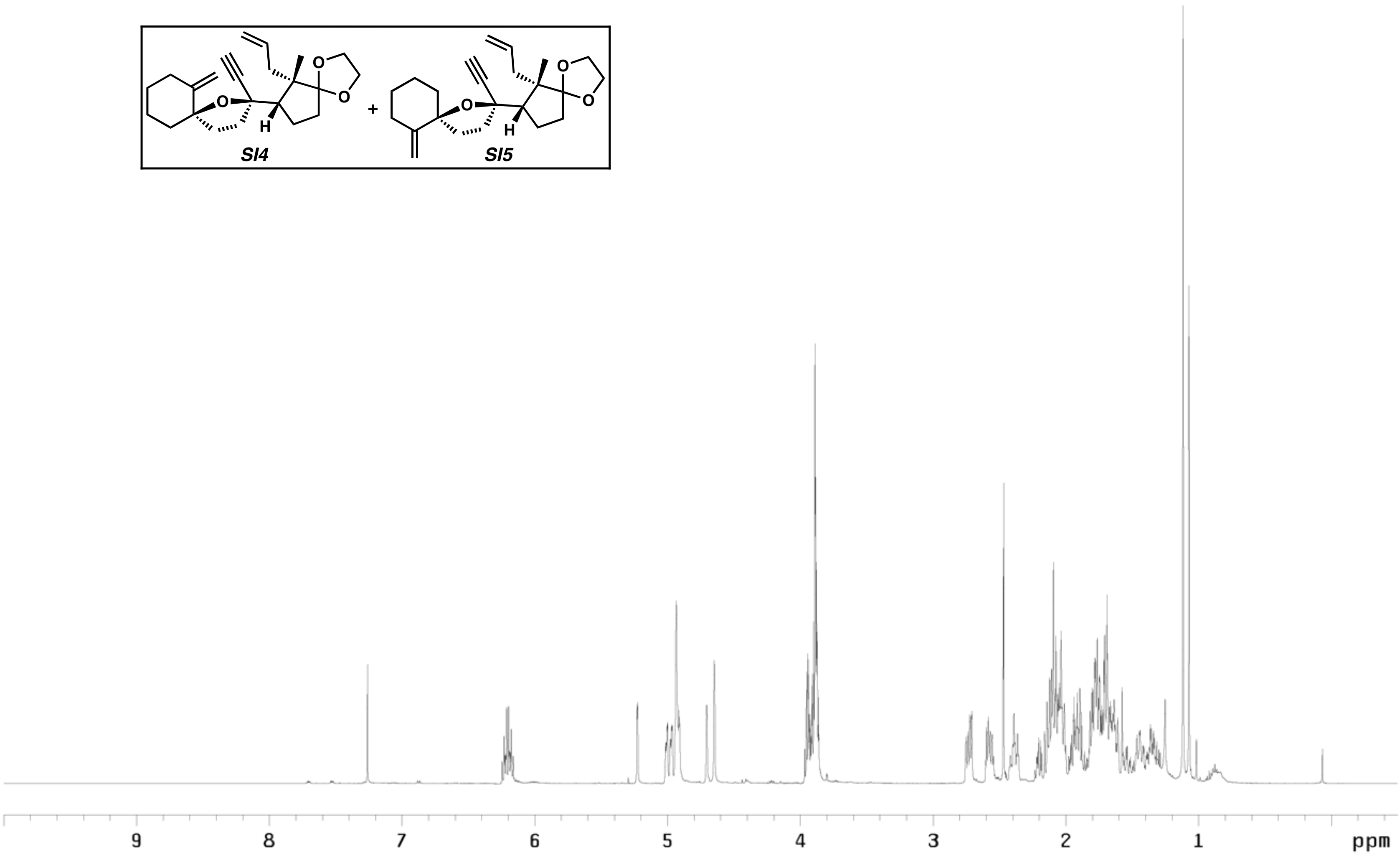


Figure 17.1 ^{1}H NMR (500 MHz, CDCl$_3$) of compounds **SI4** and **SI5**.

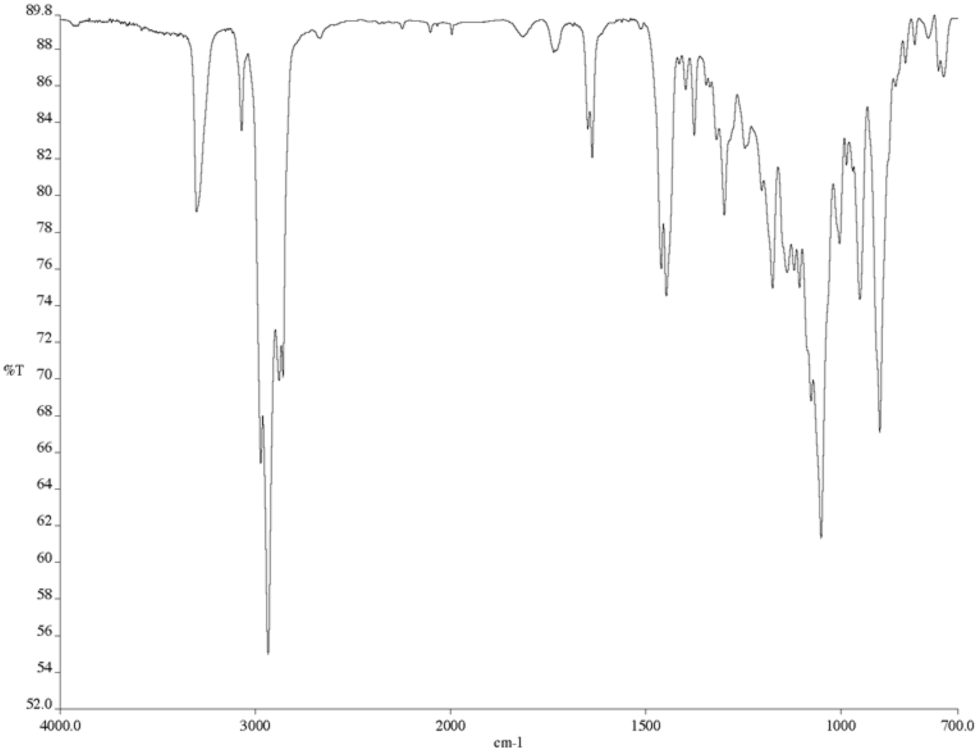


Figure 17.2 Infrared spectrum (Neat Film NaCl) of compounds **SI4** and **SI5**.

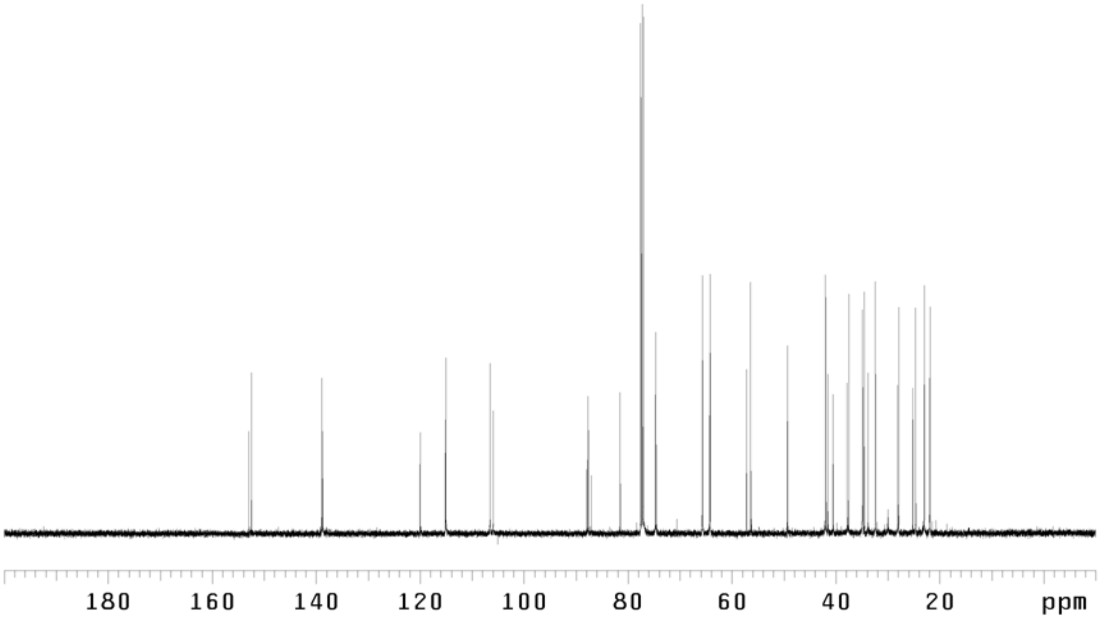


Figure 17.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **SI4** and **SI5**.

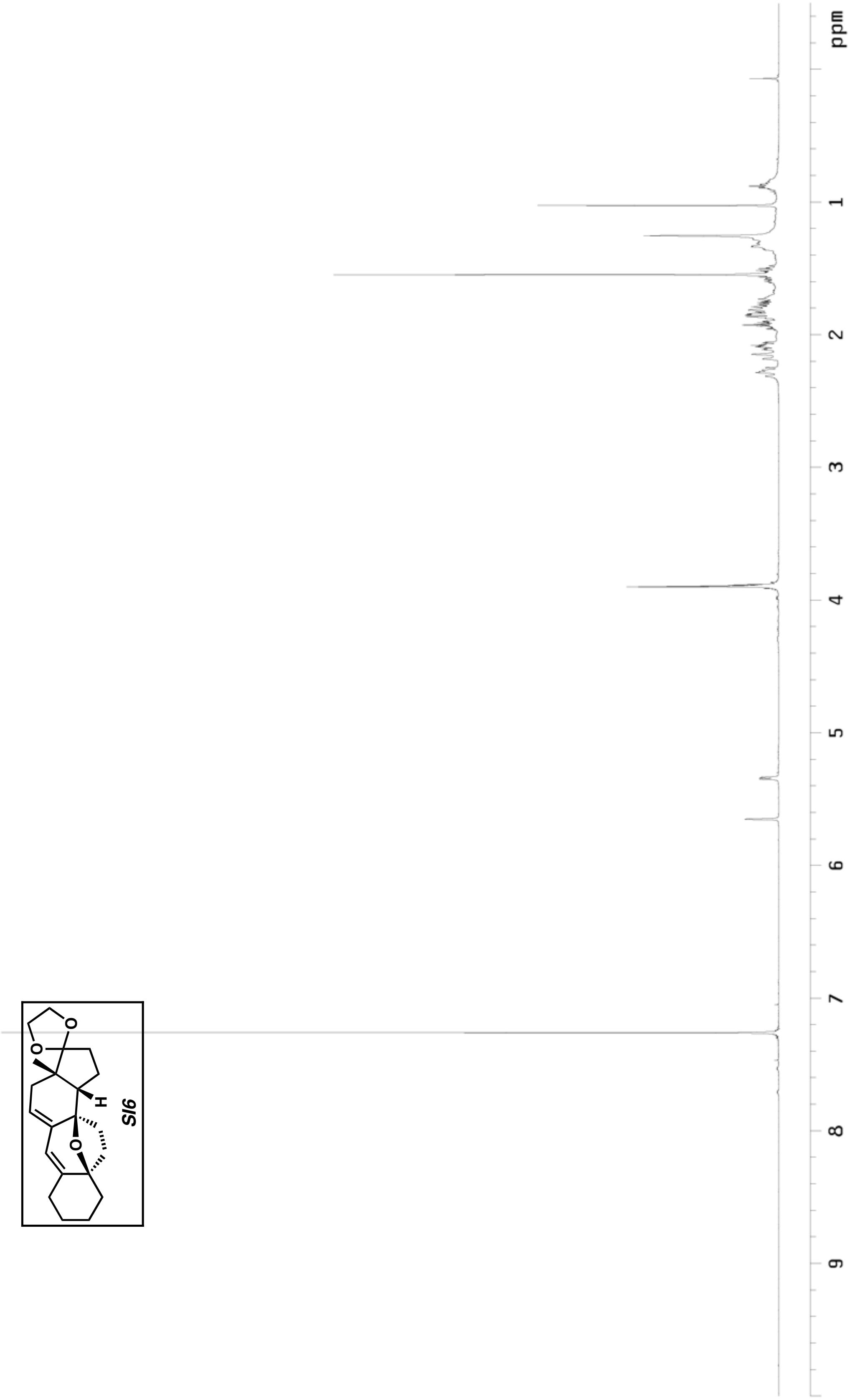


Figure 18.1 ^{1}H NMR (500 MHz, CDCl$_3$) of compound **SI6**.

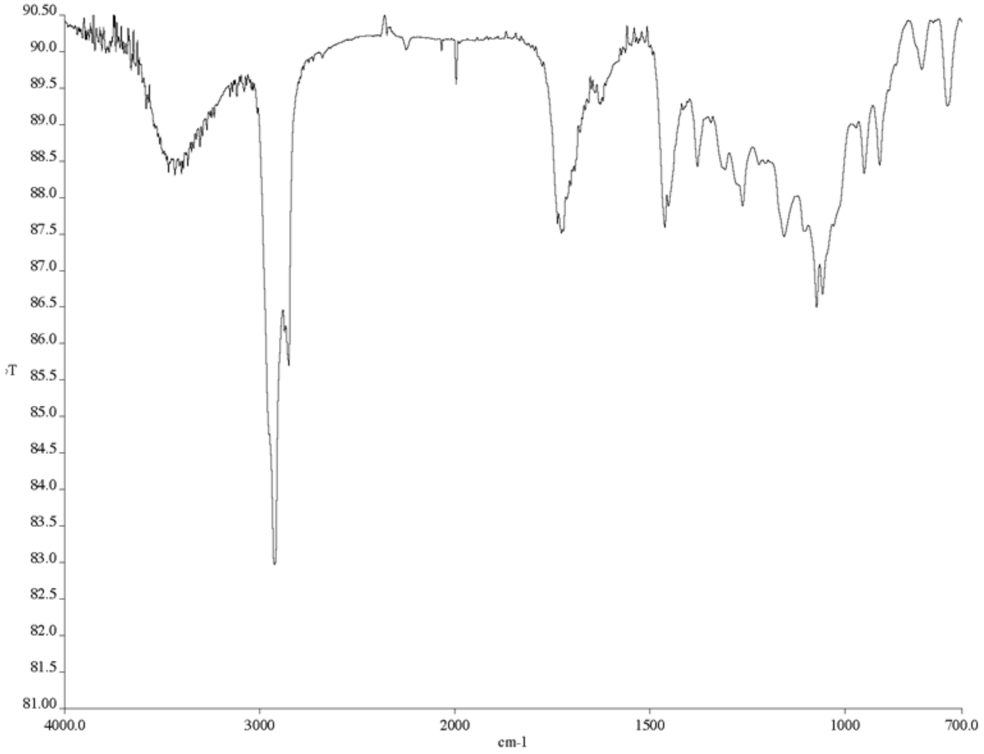


Figure 18.2 Infrared spectrum (Neat Film NaCl) of compound **SI6**.

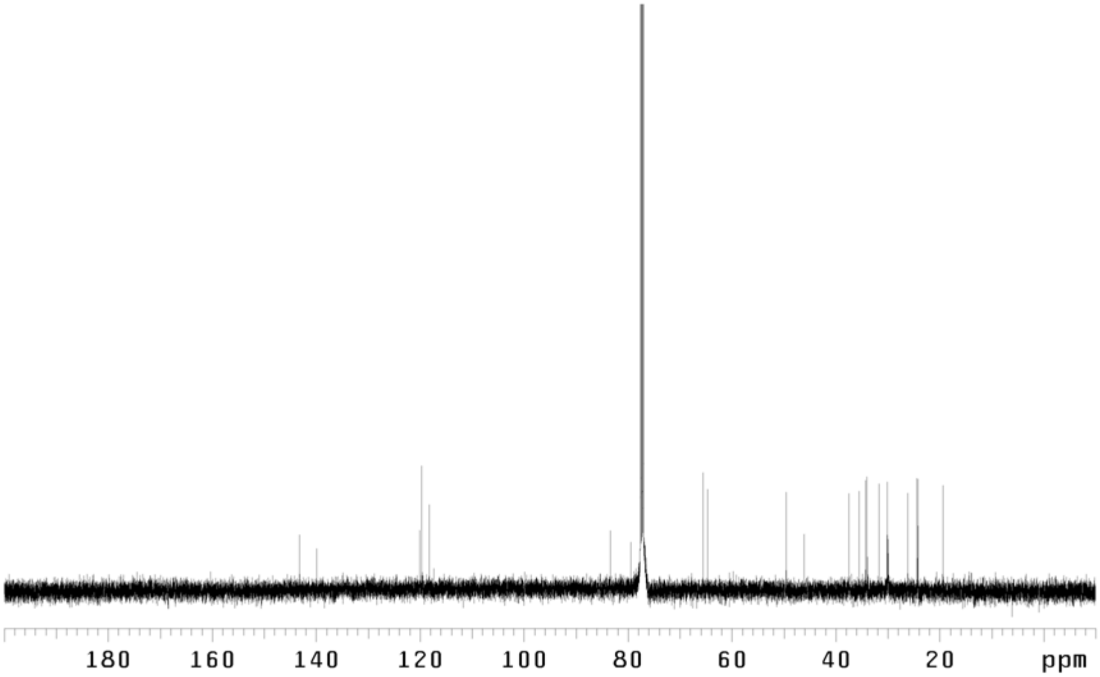


Figure 18.3 ^{13}C NMR (125 MHz, CDCl$_3$) of compound **SI6**.

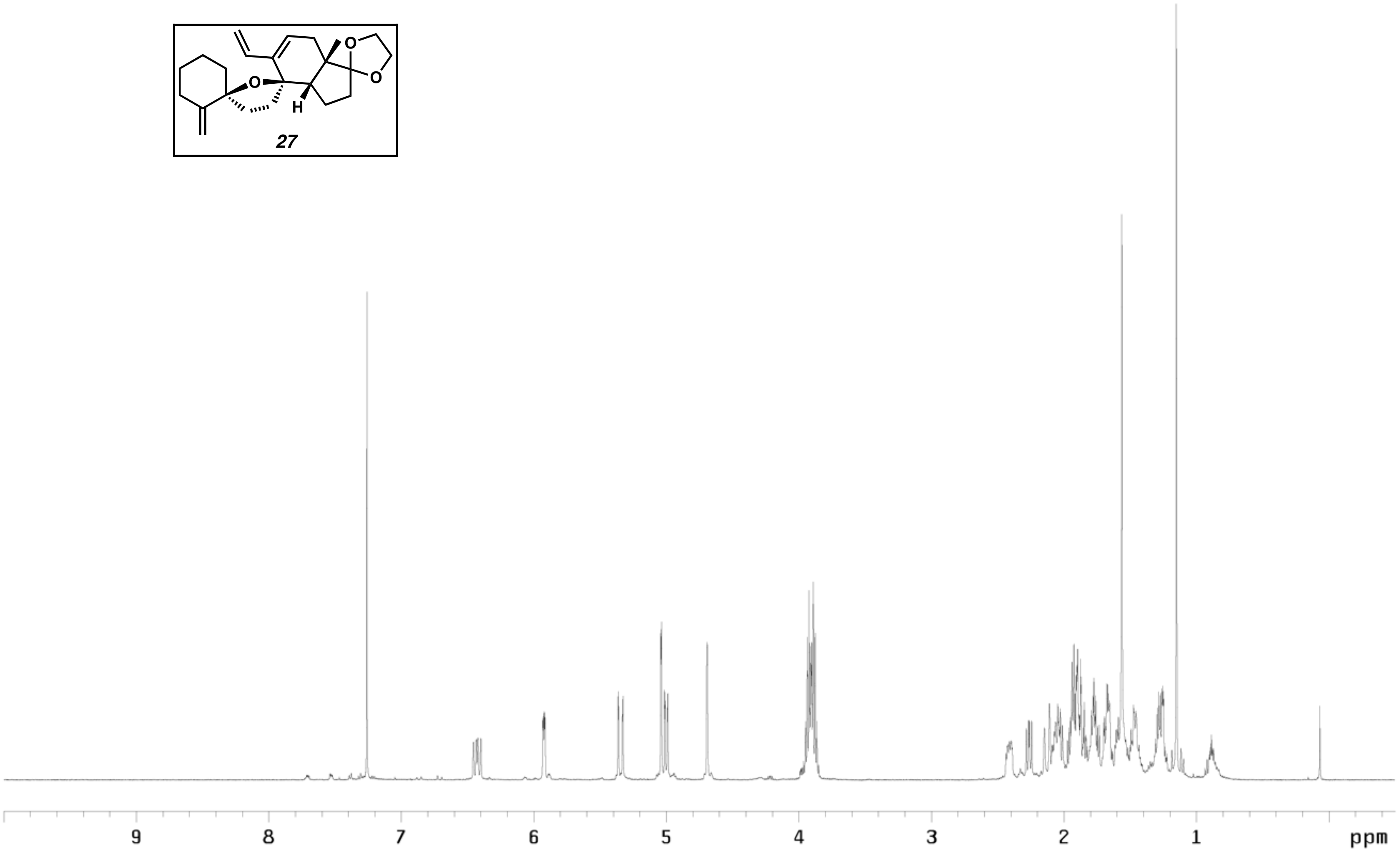


Figure 19.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **27**.

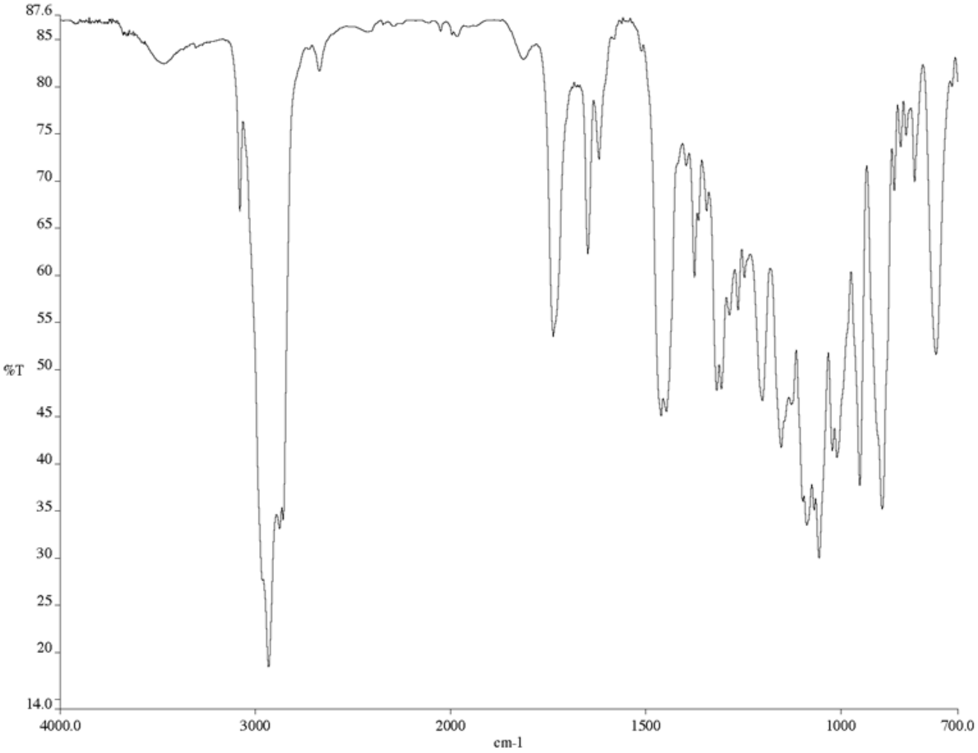


Figure 19.2 Infrared spectrum (Neat Film NaCl) of compound **27**.

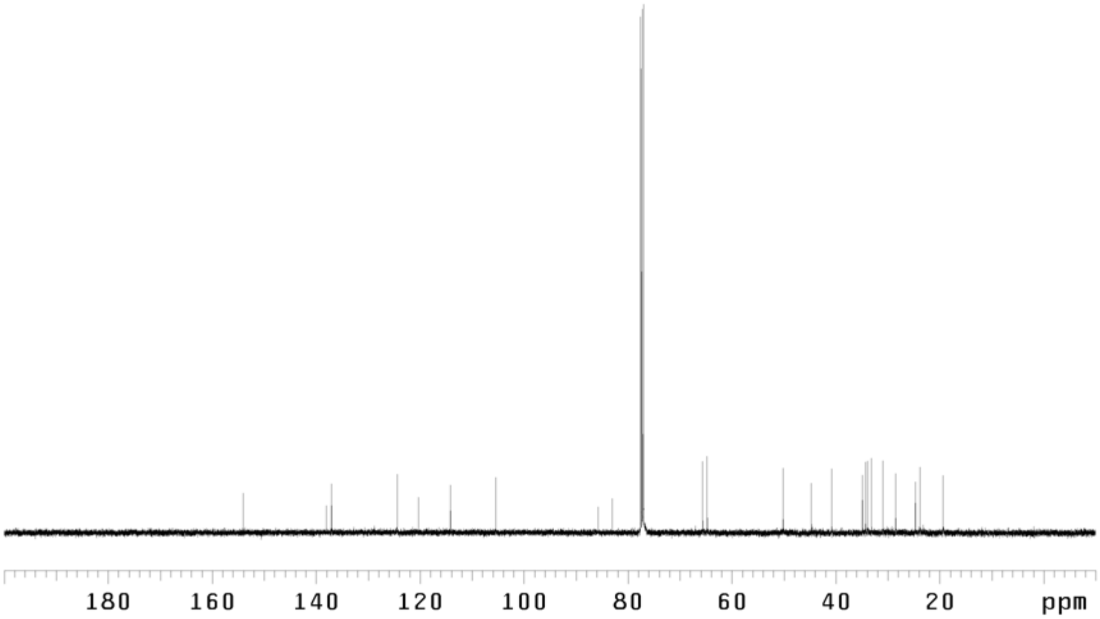


Figure 19.3 ^{13}C NMR (125 MHz, CDCl$_3$) of compound **27**.

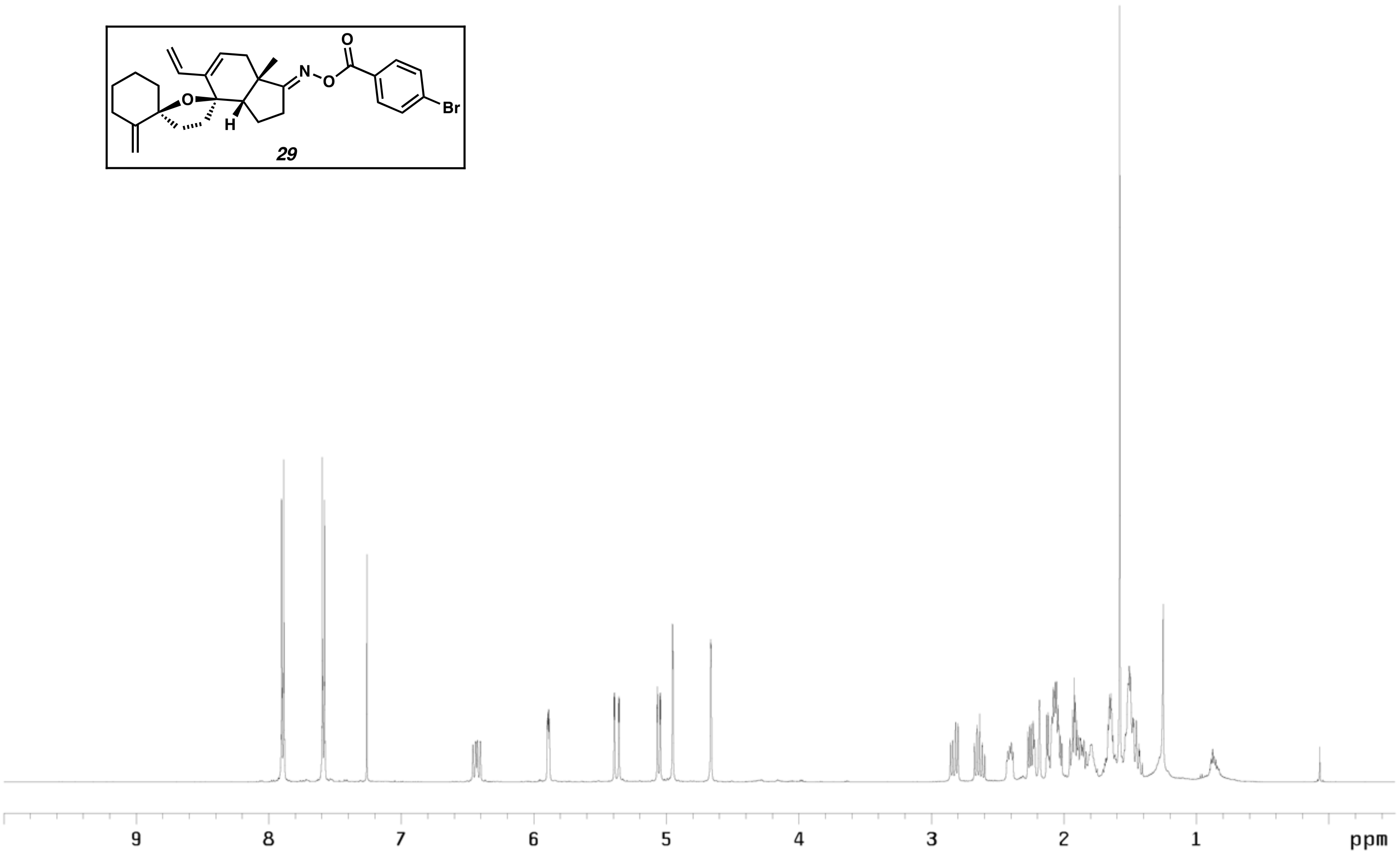


Figure 20.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **29**.

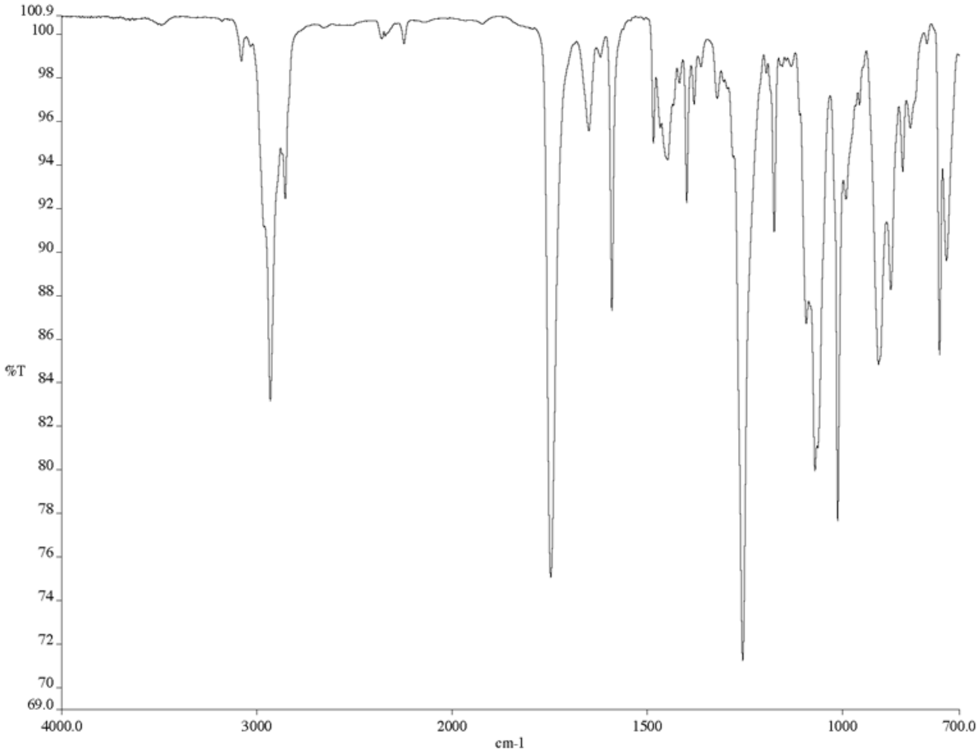


Figure 20.2 Infrared spectrum (Neat Film NaCl) of compound **29**.

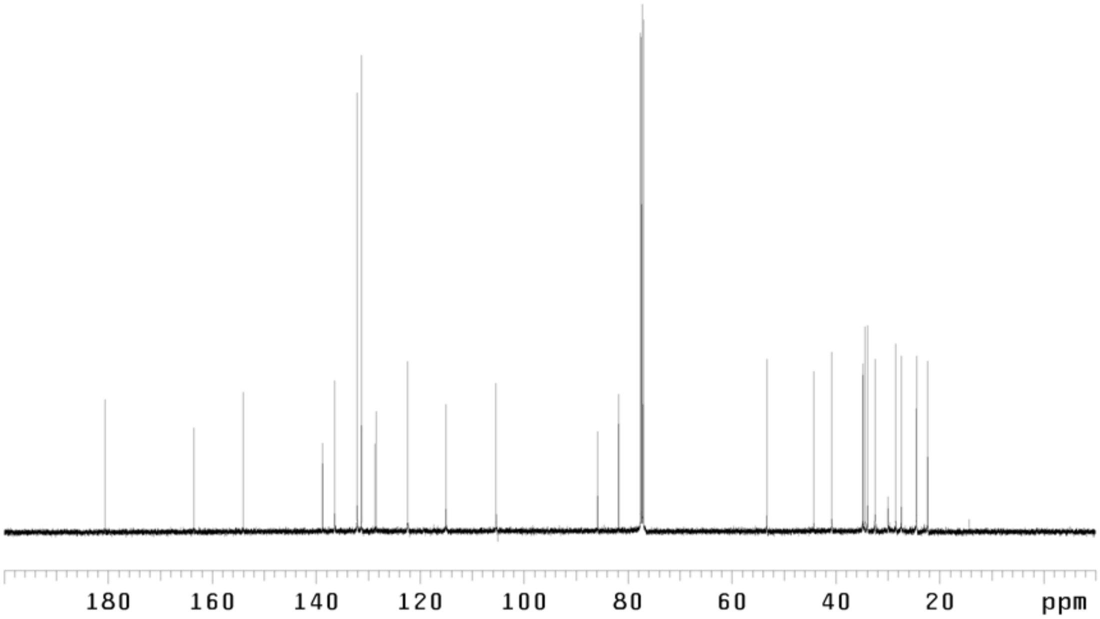


Figure 20.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **29**.

References

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[5] D. W. Brooks, H. Mazdiyasni, P. G. Grothaus, *J. Org. Chem.*, 1987, **52**, 3223–3232
[6] The percentage probability chosen for the ellipsoids is 50%.
[7] Although there are six independent molecules in the asymmetric unit, only one of these is shown (in two views).