A rapid and convergent synthesis of the integrastatin core

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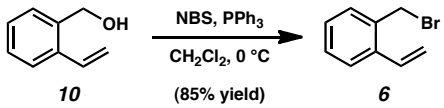
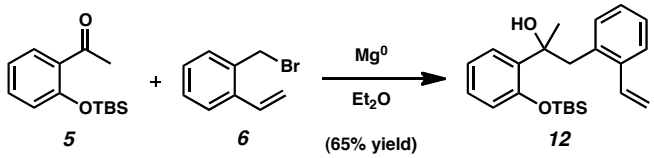
Materials and Methods. Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Stryene **8** was prepared according to the method of Seijas, et al.[1] Benzylic alcohol **10** was prepared according to the method of Bonnaud, et al.[2] Ketone **5** was prepared according to the method of Murata, et al.[3] Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or CAM staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired either using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode or from the Caltech Mass Spectral Facility.

Spectroscopic Data



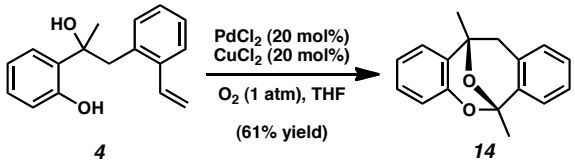
Benzylic bromide 6. R_f 0.56 (10:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.51 (m, 1H), 7.35–7.29 (m, 2H), 7.28–7.23 (m, 1H), 7.11 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.76 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.45 (dd, *J* = 11.0, 1.2 Hz, 1H), 4.58 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.25, 134.56, 133.36, 130.23, 129.13, 128.11, 126.43, 117.08, 31.63; IR (NaCl/film) 3066, 1847, 1627, 1569, 1486, 1453, 1416, 1223, 1210, 1184, 987, 917, 772, 758 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_9H_9{}^{79}Br$ $[M]^+$: 195.9888, found 195.9897.



Tertiary alcohol 12. R_f 0.38 (10:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.18–7.11 (m, 2H), 7.08–7.00 (m, 2H), 6.93 (dd, *J* = 17.3, 10.9 Hz, 1H), 6.88–6.81 (m, 2H), 6.78 (dd, *J* = 7.7, 1.1 Hz, 1H), 5.51 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.13 (dd, *J* = 10.9, 1.4 Hz, 1H), 4.42 (s, 1H), 3.37 (d, *J* = 13.4 Hz, 1H), 3.31 (d, *J* = 13.4 Hz, 1H), 1.56 (s, 3H), 1.08 (s, 9H), 0.42 (s, 3H), 0.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.22, 138.25, 135.68, 135.53, 135.46, 132.02, 128.16, 127.97, 127.22, 126.77, 125.89, 121.24, 118.46, 115.23, 76.45, 44.79, 27.07, 26.30, 18.70, –3.36, –3.64; IR (NaCl/film) 3532, 2931, 2859, 1598, 1577, 1485, 1445, 1255, 1234, 1052, 906, 838,

781, 753 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{33}O_2Si$ $[M+H]^+$: 369.2250, found 369.2260.

Diol 4. R_f 0.22 (10:1 hexanes:ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.55 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.33–7.25 (m, 1H), 7.25–7.14 (m, 2H), 7.12–6.96 (m, 3H), 6.89 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.87–6.79 (m, 1H), 5.63 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.29 (dd, *J* = 10.9, 1.3 Hz, 1H), 3.36 (d, *J* = 13.9 Hz, 1H), 3.20 (d, *J* = 13.9 Hz, 1H), 2.51 (s, 1H), 1.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.81, 138.43, 135.12, 133.51, 132.13, 129.72, 129.09, 127.53, 127.46, 126.37, 126.12, 119.54, 117.76, 116.21, 79.13, 44.54, 28.12; IR (NaCl/film) 3306, 1618, 1582, 1491, 1453, 1374, 1293, 1237, 1154, 1095, 1036, 989, 914, 865, 752 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{17}O$ $[M+H]^+–H_2O$: 237.1279, found 237.1268.



Tetracycle 14. R_f 0.41 (10:1 hexanes:ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.23–7.12 (m, 2H), 7.11–7.02 (m, 2H), 7.02–6.97 (m, 1H), 6.85 (td, *J* = 7.5, 1.2 Hz, 1H), 6.71 (dd, *J* = 8.2, 1.1 Hz, 1H), 3.29 (d, *J* = 16.0 Hz, 1H), 2.95 (d, *J* = 16.1 Hz, 1H), 1.98 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.06, 135.87, 133.19, 128.20, 128.18, 128.06, 127.42, 126.75, 125.72, 124.58, 120.71, 116.81,

97.66, 73.08, 43.09, 27.62, 26.67; IR (NaCl/film) 2994, 2932, 1607, 1585, 1484, 1452, 1382, 1299, 1275, 1249, 1115, 1081, 978, 899, 879, 760 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{17}O_2$ $[M+H]^+$: 253.1223, found 253.1211.

References

(1) Seijas, J. A.; Pilar Vázquez-Tato, M.; Entenza, C.; Montserrat Martínez, M.; Gabriela Ónega, M.; Veiga, S. *Tetrahedron Lett*. **1998**, *39*, 5073–5076.
(2) Bonnaud, B.; Funes, P.; Jubault, N.; Vacher, B. *Eur. J. Org. Chem*. **2005**, 3360–3369.
(3) Murata, T.; Sasaki, S.; Takashi, Y.; Ikegami, Y.; Masuda, T.; Shimada, M.; Shintani, T.; Shimazaki, M.; Lowinger, T. B.; Ziegelbauer, K. B.; Fuchikami, K.; Umeda, M.; Komura, H.; Yoshida, N. U.S. Patent US2004/97563 A1, 2004.

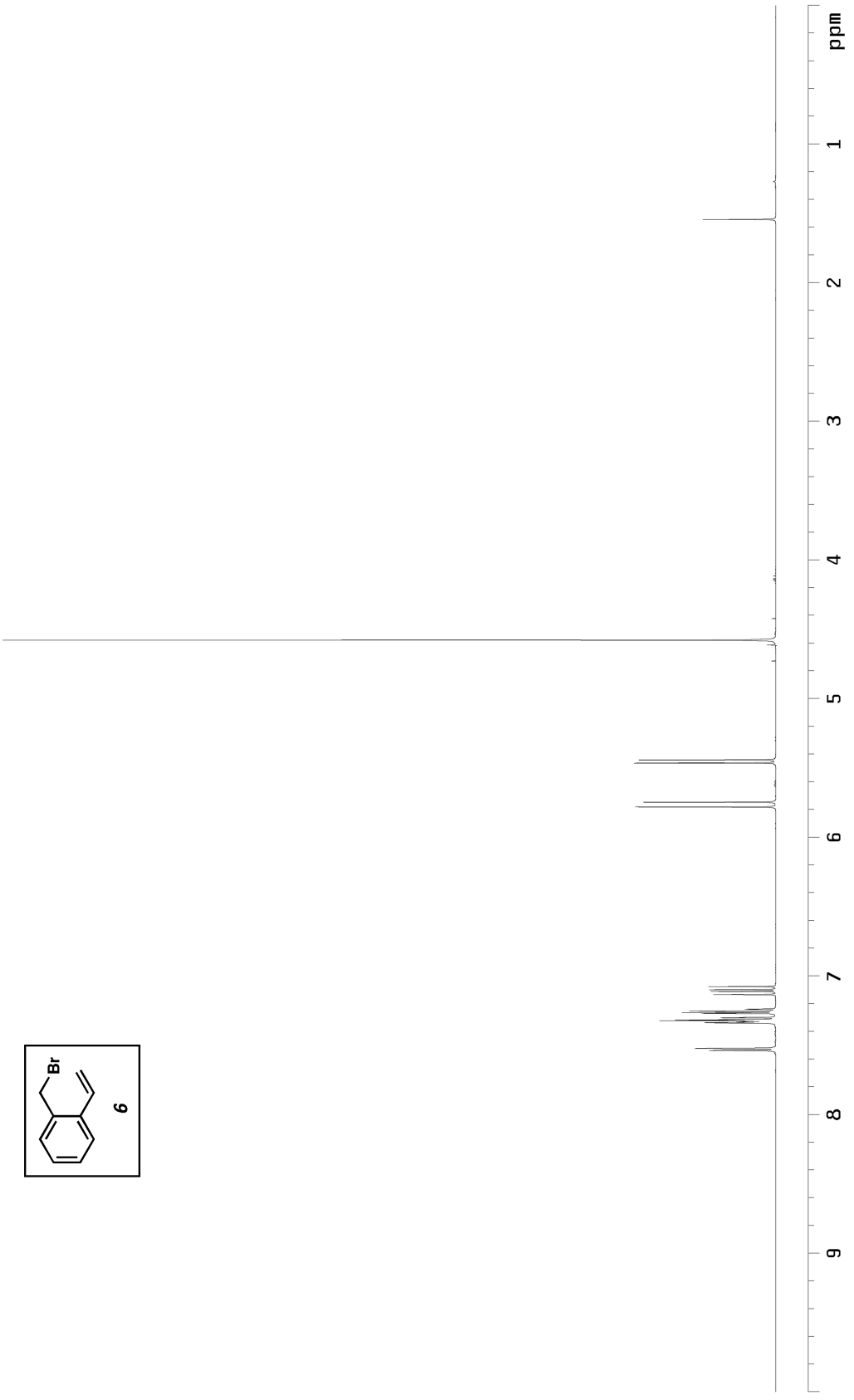


Figure 1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6**.

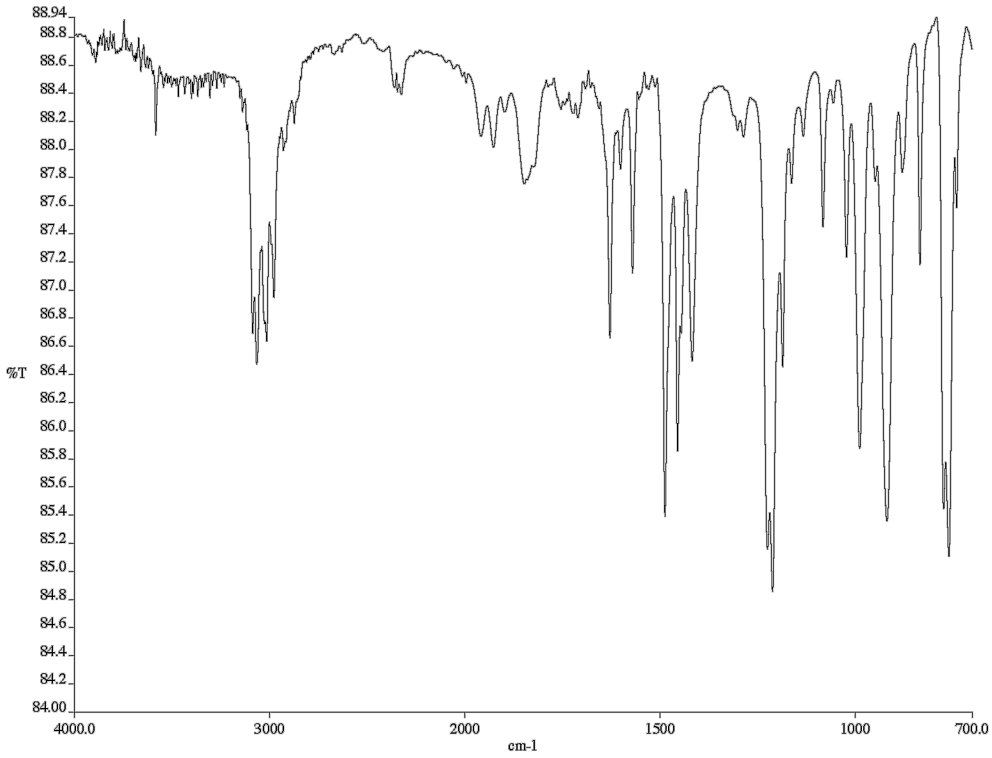


Figure 1.2 Infrared spectrum (thin film/NaCl) of compound **6**.

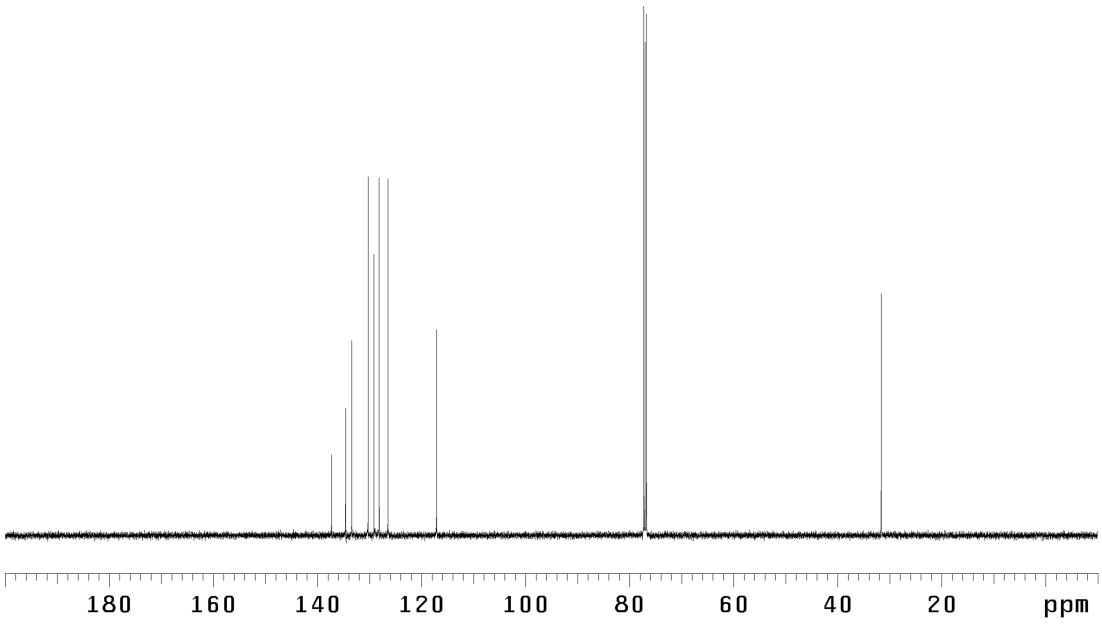


Figure 1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6**.

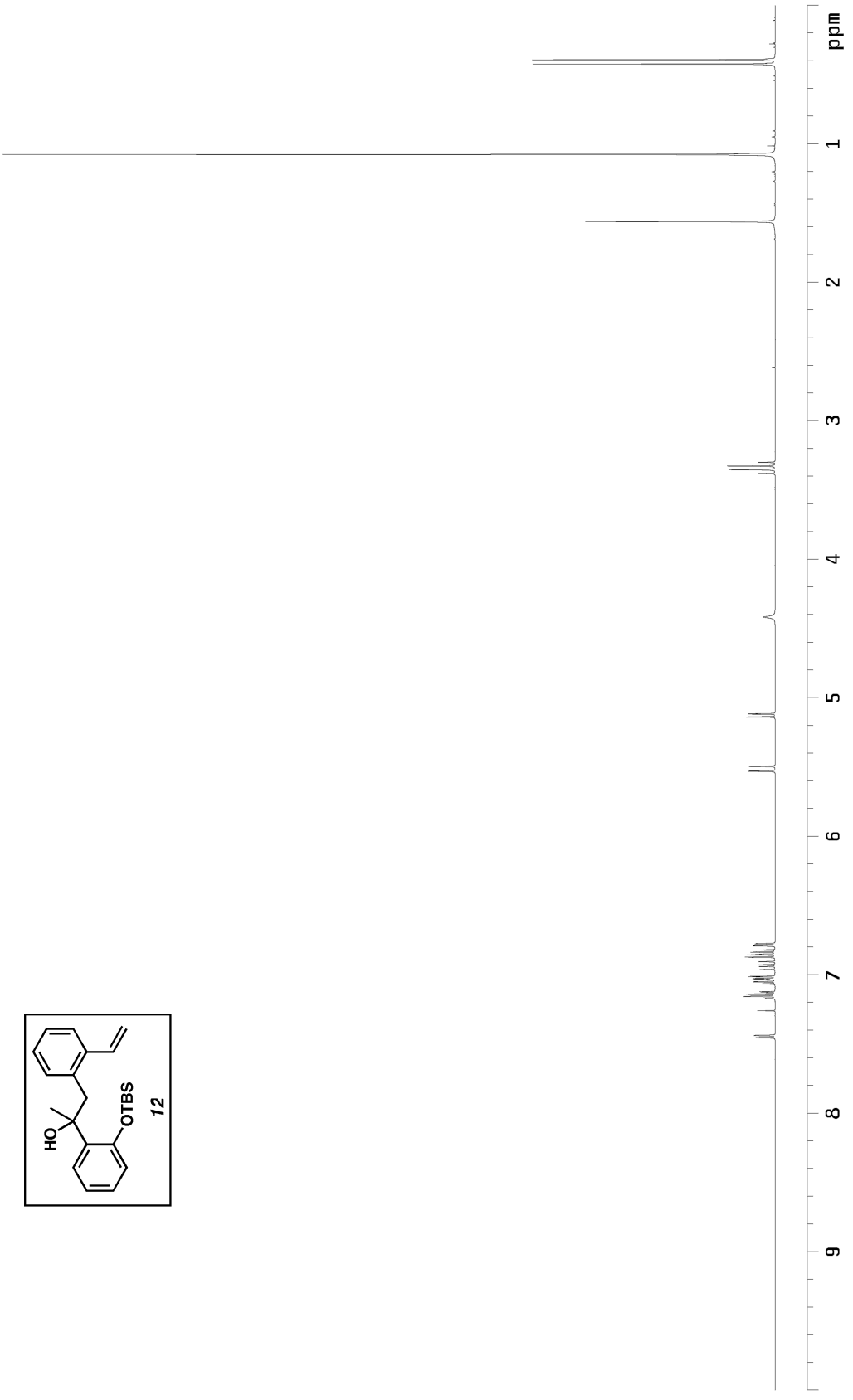


Figure 2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **12**.

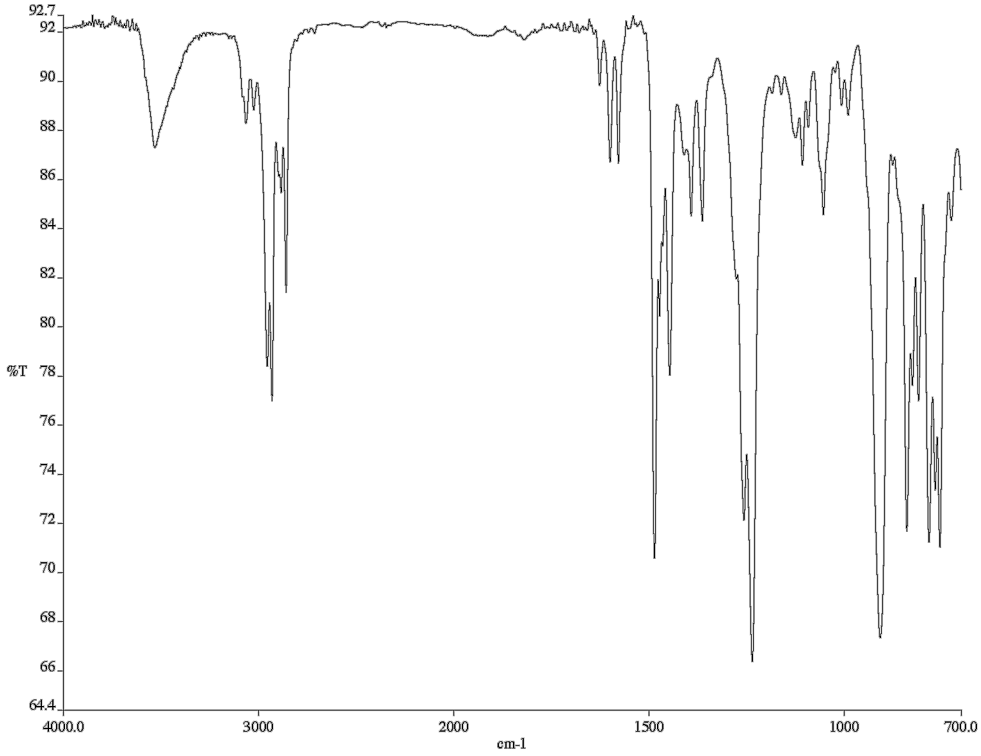


Figure 2.2 Infrared spectrum (thin film/NaCl) of compound **12**.

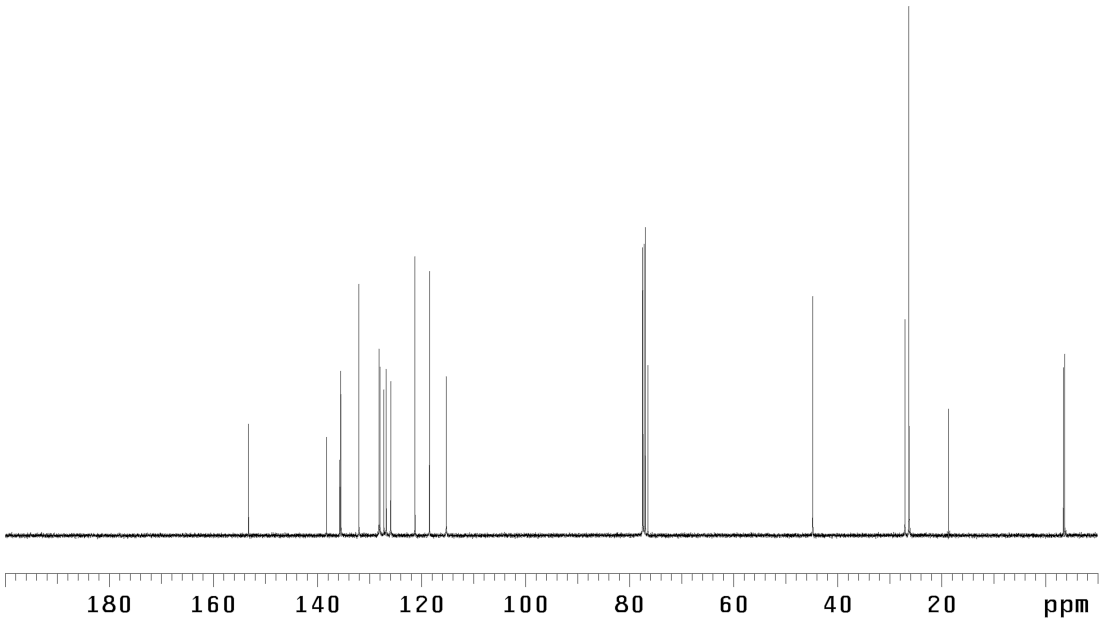


Figure 2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **12**.

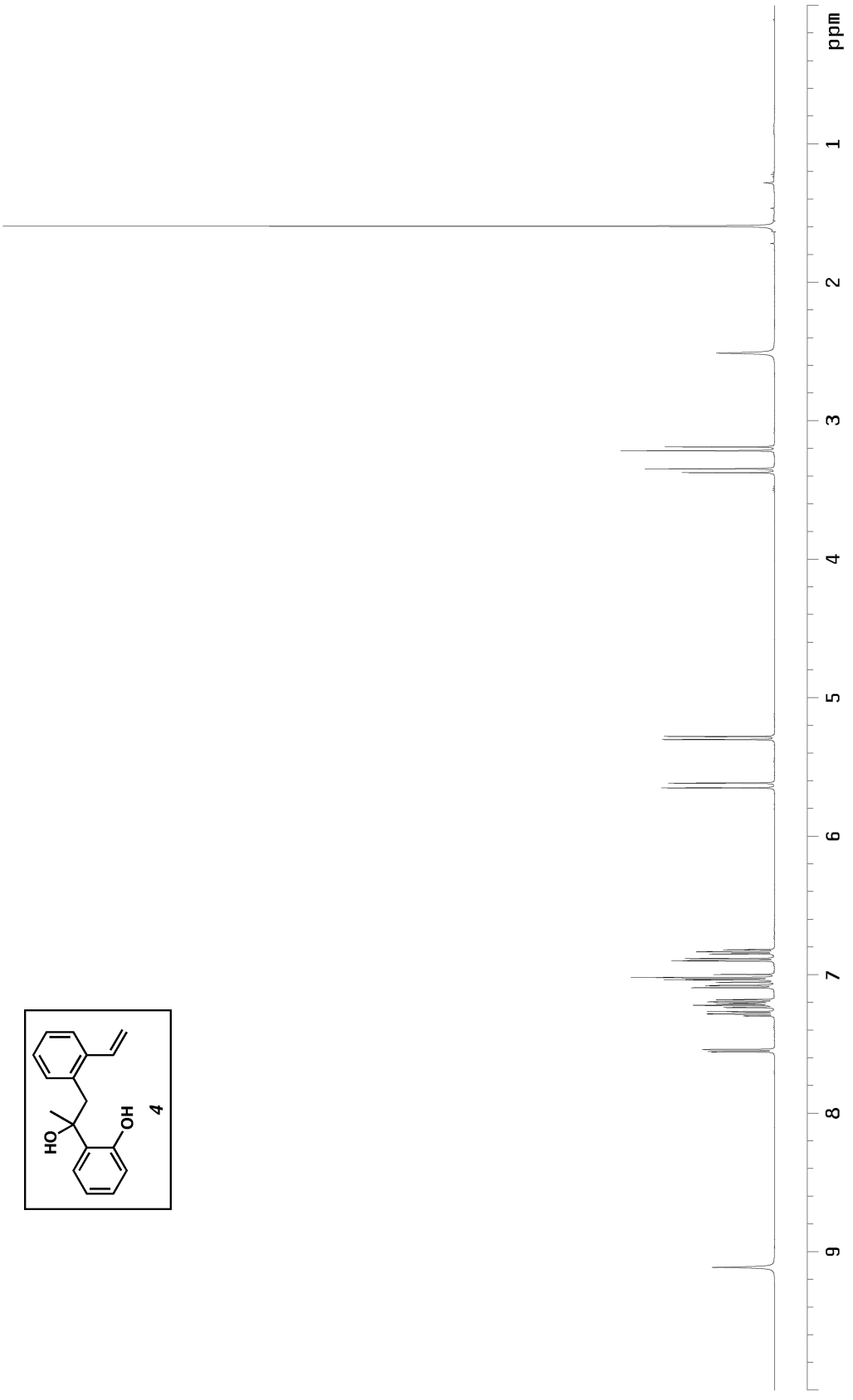


Figure 3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4**.

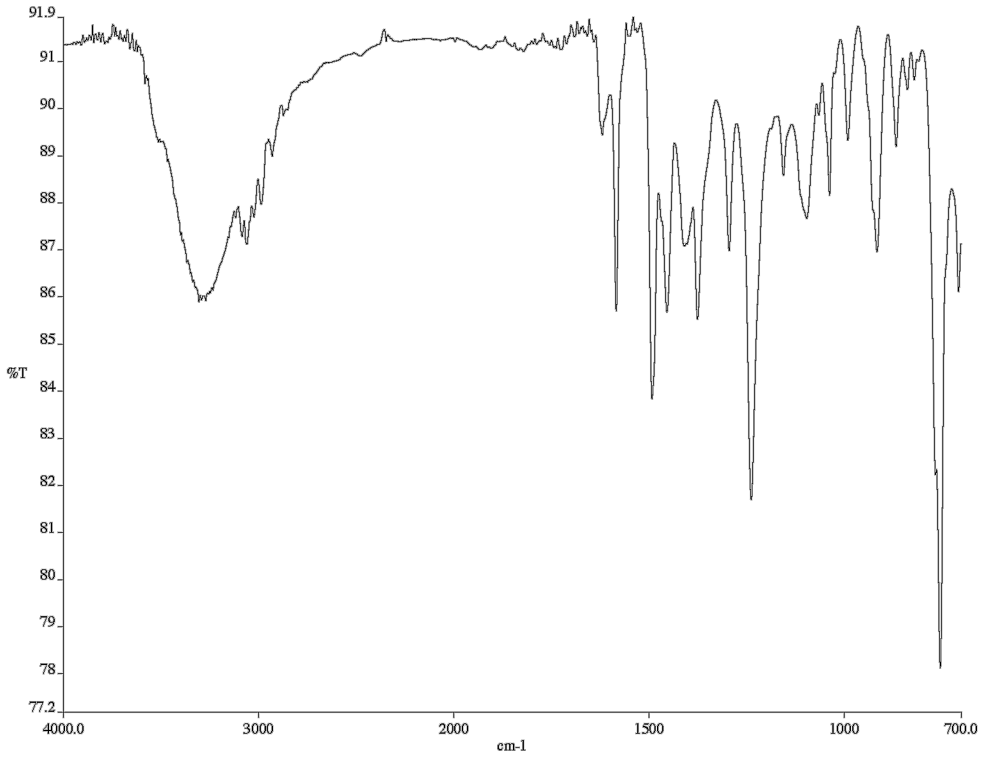


Figure 3.2 Infrared spectrum (thin film/NaCl) of compound **4**.

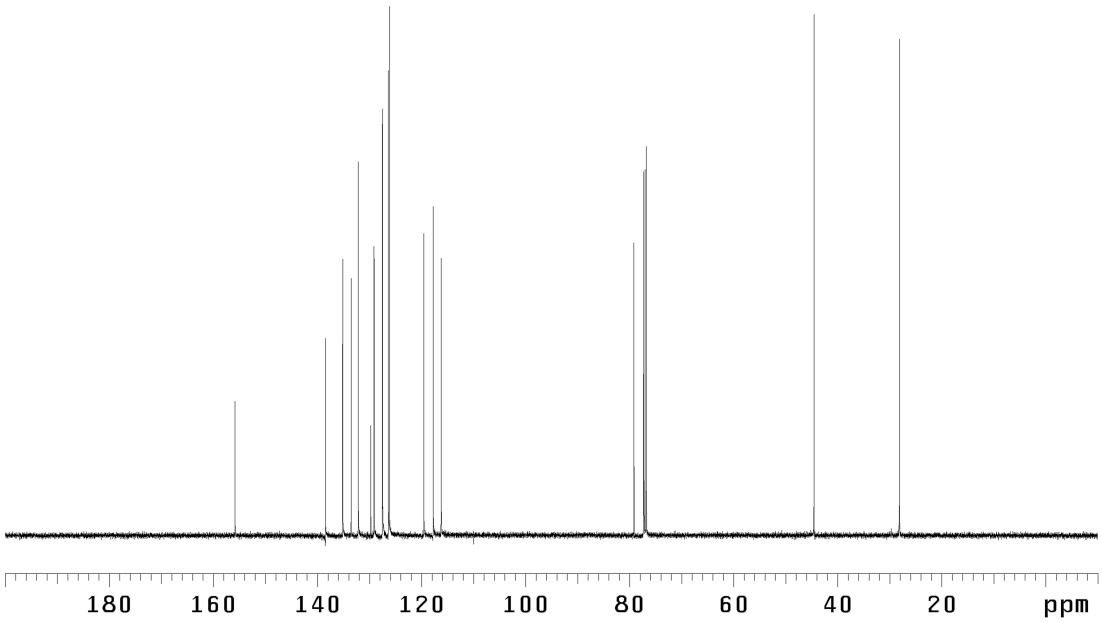


Figure 3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4**.

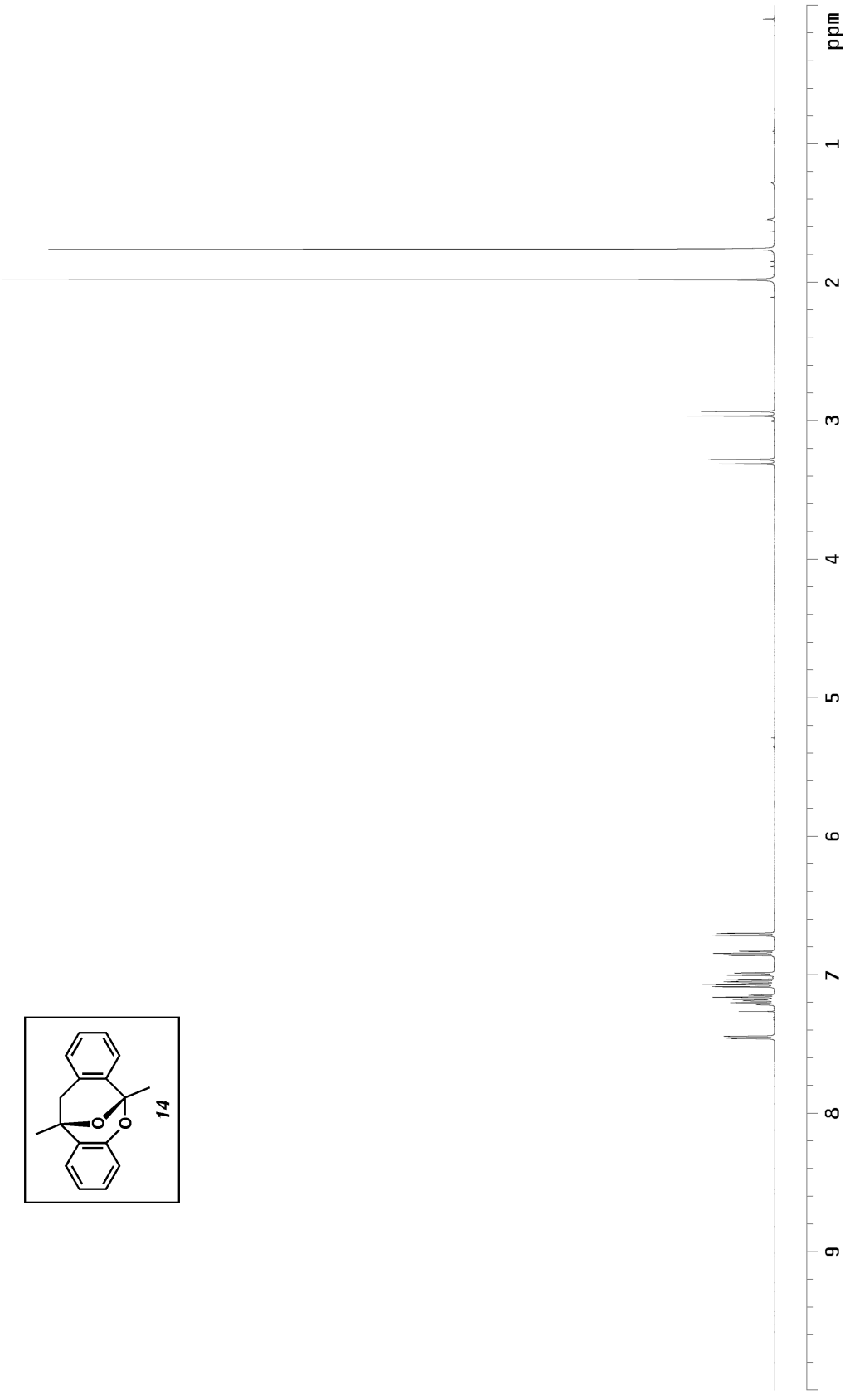


Figure 4.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **14**.

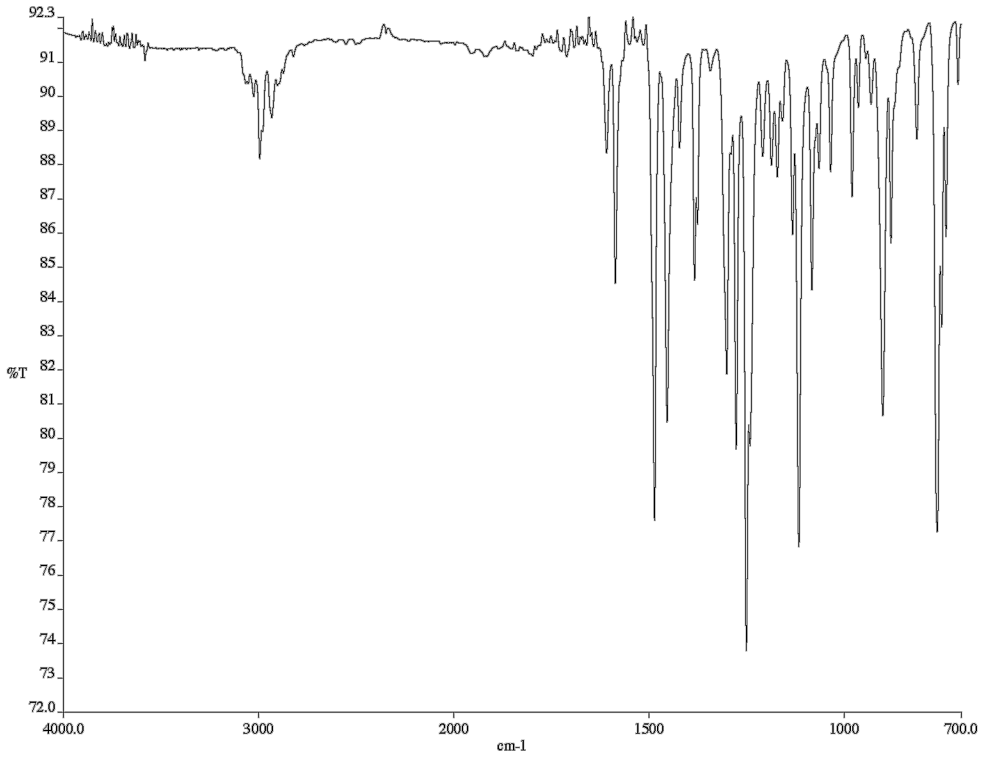


Figure 4.2 Infrared spectrum (thin film/NaCl) of compound **14**.

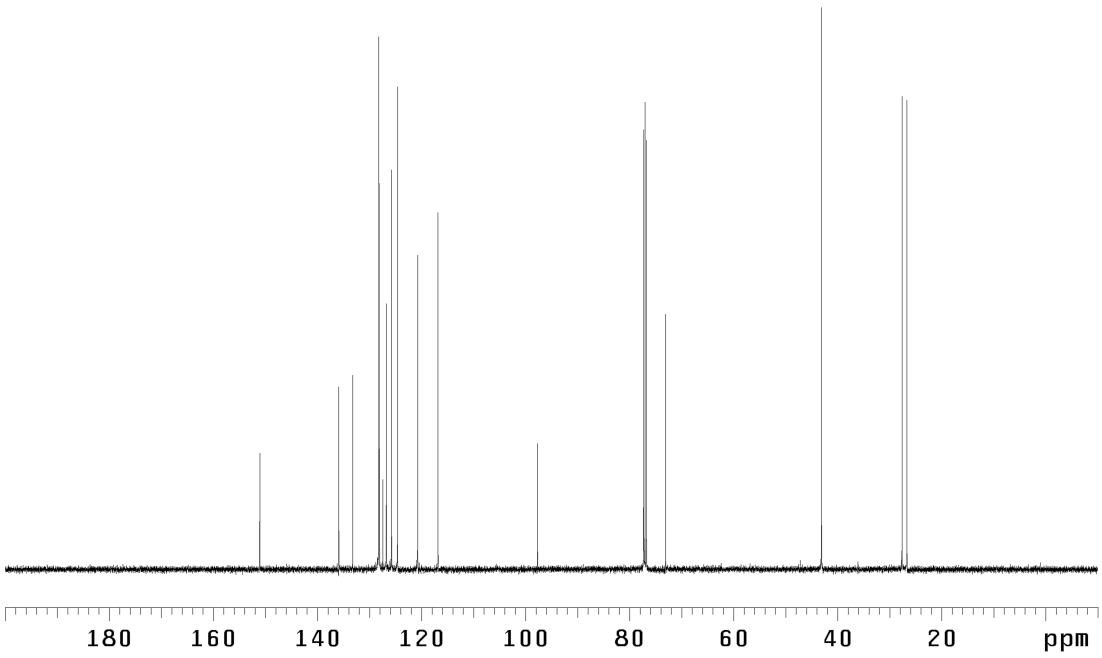


Figure 4.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **14**.