Total Synthesis of (–)-Hennoxazole

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Supporting Information

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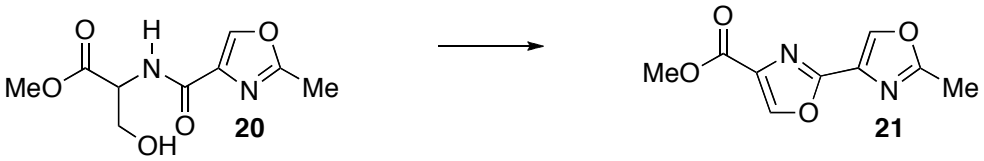
General Information. Oxygen- or moisture-sensitive reactions were carried out in flame-dried or oven-dried glassware sealed with rubber septa under a positive pressure of dry nitrogen. Similarly sensitive liquids and solutions were transferred by gas-tight syringe or cannula. Unless indicated otherwise, reagents and solvents were purchased and used without purification. Ether, THF, and CH_2Cl_2, were purified by passage through a bed of activated alumina.[1] Analytical TLC was performed with 0.25 mm silica gel 60 plates with 254 nm fluorescent indicator from SiliCycle. Plates were visualized under UV light and treatment with either acidic *p*-anisaldehyde stain or aqueous ceric ammonium molybdate (CAM) solution followed by gentle heating. The term flash chromatography refers to preparative silica gel column chromatography as described by Still and co-workers.[2] Silica gel 60, 230–240 mesh, was purchased from SiliCycle (R10030B). ^{1}H NMR spectra are reported in ppm using tetramethylsilane (0.00 ppm) or solvent ($CDCl_3$: 7.24 ppm; acetone-d_6: 2.04 ppm) as an internal standard. Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded at 125 MHz and are reported in ppm using solvent as an internal standard ($CDCl_3$: 77.00 ppm, acetone-d_6: 206.00 ppm). Unless noted otherwise on the spectra, NMR spectra are recorded in $CDCl_3$. Infrared spectra were recorded as thin films on NaCl plates on a Fourier transform spectrometer (FTIR). Melting points are uncorrected. Optical rotations were measured using a sodium (589, D line) lamp and are reported as follows: $[\alpha]_{\lambda}^{T\,^{\circ}C}$ (c = g/100 mL, solvent).

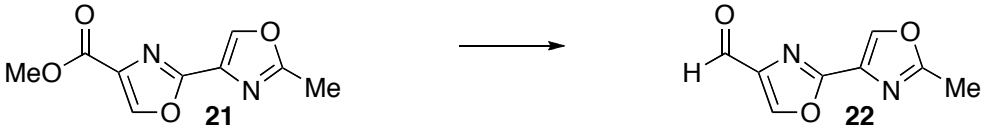
(1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, 1518.
(2) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem* **1978**, *43*, 2923.

Bisoxazole Methyl Ester 21.[3]



Following Wipf & Williams' method,[4] a solution of serine amide **20** (1.000 g, 4.38 mmol, 1 equiv) in CH_2Cl_2 (40 mL) was cooled to –20 °C and Deoxo-Fluor (0.89 mL, 4.82 mmol, 1.1 equiv) was added dropwise. After 15 min, TLC showed complete consumption of starting material. Subsequent addition of $BrCCl_3$ (1.56 mL, 15.8 mmol, 3.6 equiv) followed by DBU (2.35 mL, 15.8 mmol, 3.6 equiv) led to an immediate darkening of color. The reaction mixture was allowed to warm to 0 °C and was stirred at that temp for 3 h. The reaction was quenched by the addition of sat $NaHCO_3$ (40 mL) at 0 °C, and the resulting suspension was extracted with EtOAc (3 × 50 mL). The combined organics were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to provide the crude product as a light brown solid. Silica gel chromatography (60% EtOAc/hexanes; TLC: R_f = 0.57 in 100% EtOAc, CAM stain) gave bisoxazole methyl ester **21** (752 mg, 82%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.28 (s, 1H), 3.95 (s, 3H), 2.56 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 161.3, 155.8, 143.5, 139.2, 134.2, 129.6, 52.2, 13.7 ppm.

Preparation of Bisoxazole Aldehyde 22.[5]



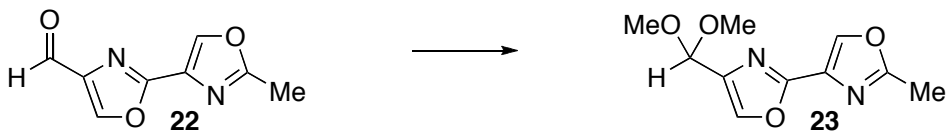
To a solution of bisoxazole ester **21** (328 mg, 1.58 mmol, 1 equiv) in CH_2Cl_2 (50 mL) at –78 °C was added DIBAL-H (3.94 mL of a 1.0 M solution in CH_2Cl_2, 3.94 mmol, 2.5 mmol) dropwise. The reaction mixture was stirred at –78 °C for 20 min and was then quenched by the addition of methanol (10 mL) and half-saturated aq Rochelle's salt. The resulting suspension was allowed to warm to rt and was stirred for 5 h until two distinct layers formed. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined organics were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to provide bisoxazole aldehyde **22** (287 mg, 100%) as a yellow solid, which was used without further purification (TLC: R_f = 0.42 in 40% Et_2O/CH_2Cl_2, UV, CAM stain). Mp 175.5–175.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.32 (s, 1H), 8.24 (s, 1H), 2.57 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.1, 163.1, 156.3, 143.5, 141.5, 139.3, 129.5, 13.7 ppm; IR (film) 3124, 1686, 1295, 1206 cm^{-1}; HRMS (EI): Exact mass calcd for $C_8H_6N_2O_3$ $[M]^+$: 178.0378; Found: 178.0387. Elemental analysis calcd for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.73; Found: C, 54.08; H, 3.45; N, 15.70.

(3) Chattopadhyay, S. K.; Kempson, J.; McNeil, A.; Pattenden, G.; Reader, M.; Rippon, D. E.; Waite, D. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2415–2428.

(4) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168.

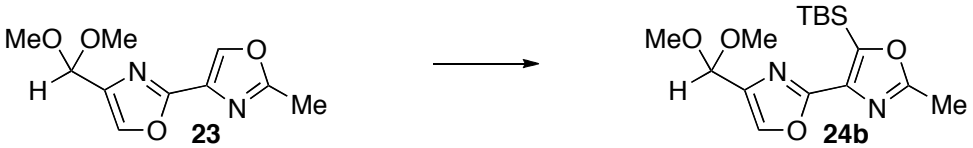
(5) Williams, D. R.; Brooks, D. A.; Moore, J. L.; A. Stewart, A. O. *Tetrahedron Lett.* **1996**, *37*, 983–986.

Bisoxazole Dimethylacetal 23.



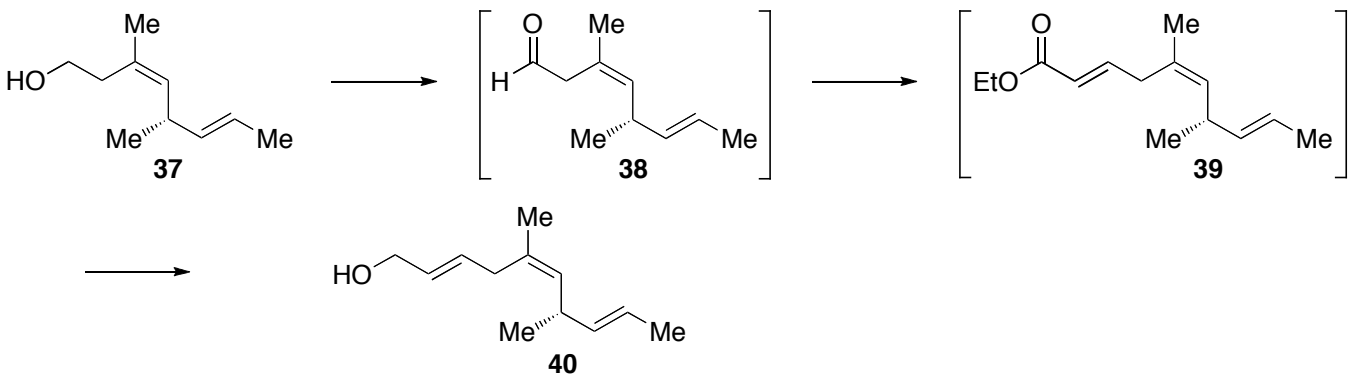
To a solution of bisoxazole aldehyde **22** (502 mg, 2.82 mmol, 1 equiv) in $CHCl_3$ (20 mL, it is essential to select a grade that is *not* stabilized with ethanol) at –30 °C was added TMSOMe (1.16 mL, 8.45 mmol, 3.0 equiv) followed by TMSOTf (153 μL, 0.845 mmol, 0.3 equiv) and the mixture turned slightly cloudy and took on a deeper orange color. After 14 h at –30 °C, an additional 1.0 equiv of TMSOMe and 0.1 equiv TMSOTf were added and the reaction was stirred for another 24 h before quenching with pyridine (1 mL). The mixture was warmed to rt and was poured into sat aq $NaHCO_3$ (40 mL) and was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were dried over a 1:1 mixture of K_2CO_3 and Na_2SO_4, filtered, and concentrated *in vacuo* to yield a white solid. Purification by silica gel chromatography (Et_3N-deactivated silica gel, 1:1:1 Et_2O/CH_2Cl_2/hexanes; TLC: R_f = 0.71, 100% Et_2O, UV) provided bisoxazole dimethylacetal **23** (609 mg, 96%) as a white solid. Mp 63.5–64.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.72 (s, 1H), 5.48 (s, 1H), 3.39 (s, 6H), 2.54 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 155.5, 139.5, 138.2, 136.8, 130.3, 98.3, 52.8, 13.7 ppm; IR (film) 3119, 1636, 1530, 1305, 1106, 1058, 984 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{12}N_2O_4$ $[M]^+$: 224.0797; Found: 224.0794. Elemental analysis calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49; Found: C, 53.68; H, 5.41; N, 12.41.

TBS-Protected Bisoxazole Dimethylacetal 24b.



To bisoxazole dimethylacetal **23** (649 mg, 2.89 mmol, 1 equiv) in dry THF (29 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 1.27 mL, 3.18 mmol, 1.1 equiv). The reaction mixture gradually took on a bright yellow color. After stirring at –78 °C for 30 min, TBSOTf (0.696 mL, 3.03 mmol, 1.05 equiv) was added dropwise. The reaction mixture was stirred at –78 °C and the color slowly faded from yellow to almost colorless. After 40 min, TLC indicated some unreacted SM. An additional amount of TBSOTf (0.100 mL, 0.435 mmol, 0.15 equiv) was added. After 20 minutes, TLC showed complete consumption of SM. The reaction was quenched by the addition of sat aq $NaHCO_3$ (30 mL) and the resulting suspension was warmed to rt and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over a 1:1 mixture of K_2CO_3 and Na_2SO_4, filtered, and concentrated *in vacuo* to yield a colorless solid. Purification by silica gel chromatography (15→55% Et_2O/hexanes; TLC: R_f= 0.74, 80% ether/ hexanes, UV) provided TBS-protected bisoxazole dimethylacetal **24b** (860 mg, 88%) as a colorless, crystalline solid. Mp 89.2–90.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 5.47 (s, 1H), 3.38 (s, 6H), 2.54 (s, 3H), 0.95 (s, 9H), 0.38 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 156.6, 154.8, 139.6, 136.5, 98.6, 52.7, 26.4, 17.6, 13.7, –5.9 ppm; IR (film) 2929, 1611, 1114, 1101, 1061 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{23}N_2O_3Si$ $[M - OCH_3]^+$: 307.1478; Found: 307.1492. Elemental analysis calcd for $C_{16}H_{26}N_2O_4Si$: C, 56.78; H, 7.74; N, 8.28; Found: C, 56.98; H, 7.67; N, 8.29.

Trienyl Alcohol 40.

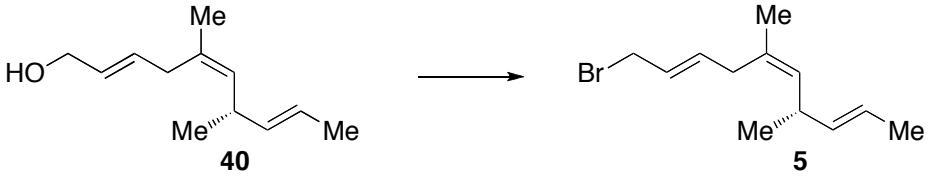


(a) Oxidation. A 25 mL concentration flask containing alcohol **37** (92.9 mg, 0.602 mmol, 1 equiv) in dry CH_2Cl_2 (6 mL) was cooled to 0 °C. Dess-Martin periodinane (DMP) (0.332 g, 0.783 mmol, 1.3 equiv) was added, and the solution became a cloudy white. After 5 min, the solution was warmed to rt. After 1 h, a 1:1 mixture of sat aq $Na_2S_2O_4$ and sat aq $NaHCO_3$ (12 mL) was added to the crude mixture which was then stirred vigorously for 15 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 12 mL). The combined organics were washed with sat aq $NaHCO_3$ (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a light yellow oil with a white precipitate. The residue was suspended in 20% Et_2O/pentane (5 mL) and filtered through a small plug of Celite (additional 5 mL rinse). The solvent was removed *in vacuo* to aldehyde **38** (116 mg, with DMP contaminants) as a light yellow oil (TLC: R_f = 0.82, 15% EtOAc/hexanes, anisaldehyde stain) which was carried on without further purification. Due to the volatility of aldehyde **38**, it should not be exposed to pressures lower than 5 mm Hg: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (t, *J* = 2.4 Hz, 1H), 5.42-5.34 (m, 2H), 5.32 (d, *J* = 10.2 Hz, 1H), 3.12 (d, *J* = 2.4 Hz, 2H), 2.95 (ddq, *J* = 10.2, 9.1, 6.8 Hz, 1H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.64 (d, *J* = 5.6 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 135.3, 134.8, 124.7, 123.3, 47.5, 35.8, 24.4, 21.4, 17.8 ppm; IR (film) 3022, 2966, 2927, 2870, 2717, 1726, 1450, 1379, 1238, 1170, 1120, 1048, 1017, 970, 857 cm^{-1}.

(b) Horner–Wadsworth-Emmons Olefination. To a 10 mL concentration flask was added NaH (48 mg of a 60% dispersion in oil, 1.2 mmol, 2.0 equiv). The white solid was washed in dry pentanes (3 × 1 mL) and suspended in dry THF (0.4 mL). To this suspension was added triethylphosphonoacetate (0.251 mL, 1.26 mmol, 2.1 equiv) dropwise *via* syringe, and the solid dissolved to give a light yellow solution. After 1 h, the solution was cooled to 0 °C, and unpurified aldehyde **38** (theoretical from above, 0.602 mmol, 1 equiv) was added *via* cannula in dry THF (0.5 mL), producing a bright yellow/orange solution. After 30 min, the solution was warmed to rt and after an additional 30 min, sat aq NH_4Cl (20 mL) was added along with Et_2O (20 mL), and the layers were separated. The aqueous layer was further extracted with Et_2O (2 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield ethyl ester **39** (270 mg, with phosphate contaminants) as a clear, yellow oil (TLC: R_f = 0.80 in 20% EtOAc/hexanes, anisaldehyde stain) which was carried on without further purification. Due to the volatility of ester **39**, it should not be exposed to pressures lower than 5 mm Hg: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.82 (dt, *J* = 15.6, 1.4 Hz, 1H), 5.41-5.31 (m, 2H), 5.12 (d, *J* = 9.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.95 (dd, *J* = 6.7, 2.0 Hz, 2H), 2.90 (m, 1H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.63 (d, *J* = 5.0 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 146.4, 135.7, 132.3, 129.7, 123.0, 122.0, 60.2, 35.6, 35.0, 23.5, 21.4, 17.9, 14.3 ppm; IR (film) 3022, 2966, 2927, 2870, 2717, 1725, 1450, 1379, 1048, 970, 857 cm^{-1}.

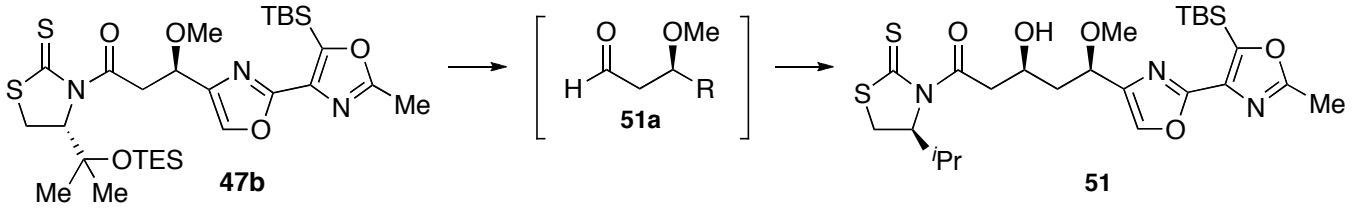
(c) Reduction. To a 50 mL concentration flask containing ethyl ester **39** as an unpurified mixture (theoretical from above, 0.602 mmol, 1 equiv) in dry CH_2Cl_2 (8.6 mL) at 0 °C was added DIBAL-H (1.99 mL of a 1.0 *M* solution in CH_2Cl_2, 1.99 mmol, 3.3 equiv) dropwise *via* syringe. Some gas evolution was evident. After 1 h, half-saturated Rochelle's salt (20 mL) and Et_2O (20 mL) was added and the mixture stirred vigorously overnight and allowed to warm to rt. The layers were separated and the aqueous layer was further extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a clear, yellow oil. The product was purified *via* automated silica column chromatography (0→15% EtOAc/hexanes, 10 g column; TLC: R_f = 0.28 in 20% EtOAc/hexanes, CAM stain) to provide alcohol **40** (82.7 g, 76% yield for three steps) as a clear, colorless oil. Due to the volatility of alcohol **40**, it should not be exposed to pressures lower than 5 mm Hg for more than several hours. When left overnight at 0.5 mm Hg for characterization purposes, partial product loss was observed: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70-5.60 (m, 2H), 5.42-5.33 (m, 2H), 5.04 (d, *J* = 9.4 Hz, 1H), 4.13-4.07 (m, 2H), 3.05-2.97 (m, 1H), 2.82-2.69 (m, 2H), 1.67 (d, *J* = 1.4 Hz, 3H), 1.64 (d, *J* = 3.9 Hz, 3H), 1.33 (br s, 1H), 1.01 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 131.6, 130.9, 130.5, 129.9, 122.7, 63.7, 35.4, 35.0, 23.4, 21.5, 17.9 ppm; IR (film) 3325, 2963, 2870, 1449, 1377, 1042, 968, 868 cm^{-1}; $[\alpha]_D^{24}$ = –80.6° (*c* = 1.00, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{12}H_{20}O$ $[M]^+$: 180.1514; Found: 180.1514; Anal calcd for $C_{12}H_{20}O$: C, 79.94%, H, 11.18%; Found: C, 79.72%, H, 11.35%.

Side Chain Allylic Bromide Coupling Fragment 5.



To a 25 mL concentration flask containing alcohol **40** (81.8 mg, 0.454 mmol, 1 equiv) in dry THF (2 mL) was added Et_3N (0.253 mL, 1.82 mmol, 4 equiv). The solution was cooled to –40 °C and MsCl (0.105 mL, 1.36 mmol, 3 equiv) was added dropwise. A white precipitate formed immediately. After 50 min at 40 °C, the suspension was warmed to 0 °C. After 30 min, a solution of LiBr (0.394 g, 4.54 mmol, 10 equiv) in THF (4 mL) was added dropwise *via* cannula. After 30 min, the flask was warmed to rt and stirred for an additional 30 min. The reaction was quenched with ice-cold sat aq $NaHCO_3$ (15 mL) and diluted with pentane (5 mL). The layers were separated and the aqueous layer was further extracted with pentane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a clear, yellow oil. The product was purified *via* automated silica column chromatography (pentane, 4 g column; TLC: R_f = 0.89 in 20% EtOAc/hexanes, anisaldehyde stain) to provide bromide **5** (95.8 g, 87% yield) as a clear, colorless oil. Due to the volatility of bromide **5**, it should not be exposed to pressures lower than 5 mm Hg for extended periods: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75-5.67 (m, 2H), 5.42-5.32 (m, 2H), 5.06 (d, *J* = 8.9 Hz, 1H), 4.00-3.92 (m, 2H), 3.03-2.95 (m, 1H), 2.82-2.74 (m, 2H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.64 (d, *J* = 4.5 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 133.8, 131.4, 131.0, 127.2, 122.8, 35.4, 34.9, 33.3, 23.5, 21.5, 18.0 ppm; IR (film) 2964, 2927, 2868, 156, 1438, 1377, 1203, 965, 854, 580 cm^{-1}; $[\alpha]_D^{24}$ = –69.3° (*c* = 1.00, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{12}H_{19}Br$ $[M]^+$: 242.0670; Found: 242.0663.

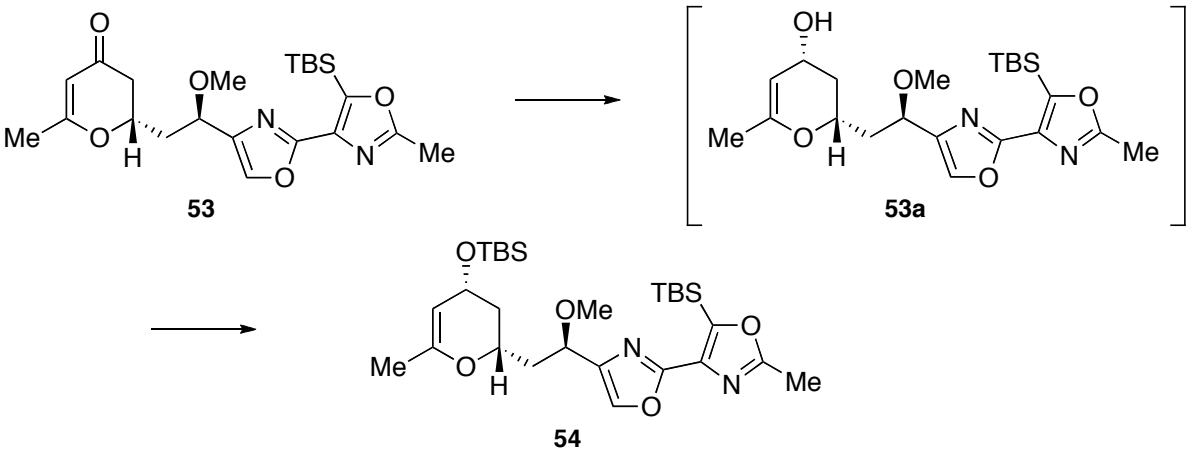
Thiazolidinethione Alcohol 51.



(a) Reduction. To a 10 mL flask containing bisoxazole methyl ether **47b** (248 mg, 0.388 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL) under N_2 at –78 °C was added DIBAL-H (0.581 mL of a 1.0 M solution in CH_2Cl_2, 1.5 equiv) dropwise *via* syringe. After stirring for 1 h, the reaction was quenched by the addition of MeOH (7.5 mL). Rochelle's salt (10 mL of a 7:5 mixture of saturated solution and water) was added and the biphasic mixture was warmed to rt and stirred rapidly for 45 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. This material was quickly subjected to flash chromatography (CH_2Cl_2 until the auxiliary was eluted then 30% Et_2O/CH_2Cl_2; TLC: R_f = 0.09 in 70% Et_2O/hexanes) to provide (*R*)-3-(2-(5-(*tert*-butyldimethylsilyl)-2-methyloxazol-4-yl) oxazol-4-yl)-3-methoxypropanal (**51a**) as a relatively unstable clear oil that was used immediately in the next step: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.67 (s, 1H), 4.81 (d, *J* = 7.6, 4.7 Hz, 1H), 3.38 (s, 3H), 3.03 (dd, *J* = 16.9, 7.7 Hz, 1H), 2.94 (dd, *J* = 16.9, 4.6 Hz, 1H), 2.55 (s, 3H), 0.96 (s, 9H), 0.34 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 165.1, 156.8, 154.8, 140.8, 138.7, 135.2, 71.3, 56.9, 48.0, 26.3, 17.4, 13.6, –6.0 ppm.

(b) Aldol Reaction. To a 10 mL flask was added $Sn(OTf)_2$ (0.353 g, 0.847 mmol, 2.3 equiv) in a glove box. This tin compound was dissolved in CH_2Cl_2 (3.5 mL), the flask was cooled to –50 °C, *N*-ethyl piperidine (0.121 mL, 0.884 mmol, 2.4 equiv) was added dropwise *via* syringe, followed by (*S*)-*N*-acetyl-4-*i*Pr-thiazolidinethione (***ent*-44a**, 0.122 g, 0.552 mmol, 1.5 equiv). The solution was stirred at –50 °C for 4.5 h to form the tin enolate and then was cooled to –110 °C in a liquid nitrogen/hexanes slurry before aldehyde **51a** (theoretical from above, 0.388 mmol, 1 equiv) was added *via* cannula in CH_2Cl_2 (1.5 mL). The solution was kept between –90 and –100 °C for 2 h and was then warmed to –78 °C over 30 min and allowed to stir for an additional 30 min at –78 °C. The reaction was quenched with pH 7 buffer and filtered with CH_2Cl_2 (25 mL) through a plug of Celite into a separatory funnel containing sat aq $NaHCO_3$ (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give a clear yellow oil. ^{1}H NMR integration of the unpurified product indicated a 3:1 diastereomer ratio. This material was purified *via* automated silica column chromatography (40→70% EtOAc/hexanes, 110 g column; TLC: R_f = 0.28 in 70% EtOAc/hexanes) to provide diastereomerically pure alcohol **51** (214.2 mg, 46% yield over two steps) as a clear, yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 5.15 (dd, *J* = 7.0, 6.8 Hz, 1H), 4.53 (dd, *J* = 7.2, 6.3 Hz, 1H), 4.33-4.26 (m, 1H), 3.57-3.47 (m, 3H), 3.39-3.30 (m, 1H), 3.34 (s, 3H), 3.03 (d, *J* = 11.1 Hz, 1H), 2.54 (s, 3H), 2.42-2.31 (m, 1H), 2.20-2.12 (m, 1H), 2.11-2.03 (m, 1H). 1.06 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 7.3 Hz, 3H), 0.95 (s, 9H), 0.38 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.8, 172.2, 165.0, 156.7, 154.7, 141.3, 138.9, 135.3, 75.1, 71.3, 66.4, 56.6, 45.4, 40.9, 30.7, 30.5, 26.5, 19.0, 17.7, 17.5, 13.7, –5.9 ppm; IR (film) 3420, 2958, 2930, 2855, 1696, 1616, 1583, 1469, 1363, 1314, 1157, 1094, 1036, 930, 844, 781, 730, 668 cm^{-1}; $[\alpha]_D^{25}$ = +212.1° (*c* = 1.03, $CHCl_3$); HRMS (CI): Exact mass calcd for $C_{25}H_{40}N_3O_5S_2Si$ $[M + H]^+$: 554.2179; Found: 554.2181.

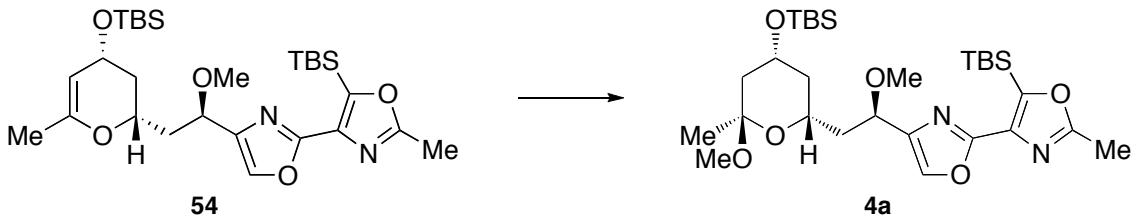
Glycal 54.



(a) Luche Reduction. To a 10 mL flask containing dihydropyranone **53** (218.7 mg, 0.5056 mmol, 1 equiv) under an Ar atmosphere was added a solution of $CeCl_3 \bullet 7H_2O$ (207 mg, 0.556 mmol, 1.1 equiv) in a 1:1 mixture of THF/MeOH (7.2 mL). The suspension was cooled to –78 °C and $NaBH_4$ (38.3 mg, 1.01 mmol, 2 equiv) was added as a solid in one portion. After 15 min, the flask was allowed to warm to –40 °C over 1 h.After an additional 45 min at –40 °C, the flask was recooled to –78 °C and the reaction mixture was poured into pH 7 buffer (150 mL) and was diluted with Et_2O (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (4 x 50 mL) The combined organic layers were filtered through a plug of silica gel and concentrated *in vacuo* to give the corresponding allylic alcohol (**53a**) which was carried on immediately without any further purification: TLC: $R_f = 0.36$ in 80% EtOAc/hexanes.

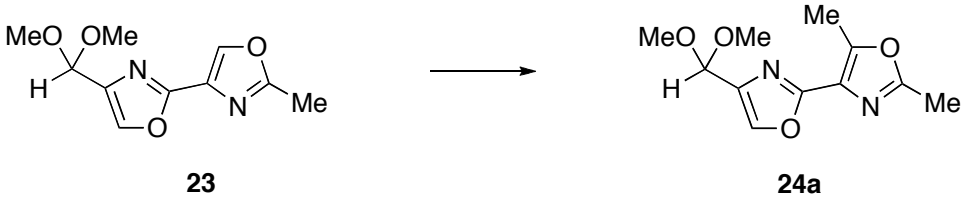
(b) TBS Protection. To a 5 mL flask containing allylic alcohol **53a** (theoretical from above, 0.5056 mmol, 1 equiv) under an Ar atmosphere was added imidazole (103 mg, 1.52 mmol, 3 equiv) a catalytic amount of DMAP, and anhydrous DMF (2.0 mL). TBS-Cl (167.6 mg, 1.11 mmol, 2.2 equiv) was added and the reaction was stirred for 4 h. The solution was diluted with brine (50 mL) and EtOAc (50 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organics were washed with water (2 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. This material was purified *via* flash chromatography (5→9% Et_2O/CH_2Cl_2, TLC: $R_f = 0.31$ in 10% Et_2O/CH_2Cl_2) to provide allylic TBS ether **54** (177.0 mg, 61% yield over two steps) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 1H), 4.46 (dd, *J* = 8.0, 6.0 Hz, 1H), 4.42 (s, 1H), 4.35 (dd, *J* = 8.3, 7.0 Hz, 1H), 3.86-3.78 (m, 1H), 3.29 (s, 3H), 2.54 (s, 3H), 2.26 (ddd, *J* = 14.3, 8.7, 5.9 Hz, 1H), 2.15 (ddd, *J* = 12.7, 8.2, 4.3 Hz, 1H), 1.95 (dd, *J* = 13.0, 6.6 Hz, 1H), 1.69 (s, 3H), 1.68-1.59 (m, 1H), 0.95 (s, 9H), 0.88 (s, 9H), 0.39 (s, 3H), 0.38 (s, 3H), 0.06 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 156.6, 154.7, 152.0, 141.2, 139.1, 135.9, 101.3, 72.6, 71.5, 64.3, 56.3, 39.5, 37.6, 26.5, 25.9, 19.8, 18.2, 17.6, 13.8, –4.7, –5.9 ppm; IR (film) 2928, 2857, 1675, 1586, 1463, 1383, 1252, 1062, 837, 837, 780, 495 cm^{-1}; $[\alpha]_D^{25}$ = +18.5° (*c* = 1.00, $CHCl_3$); HRMS (CI): Exact mass calcd for $C_{28}H_{48}N_2O_5Si_2Li$ $[M + Li]^+$: 555.3262; Found: 555.3267.

Preparation of Pyran/Bisoxazole Coupling Fragment 4a (R = TBS).



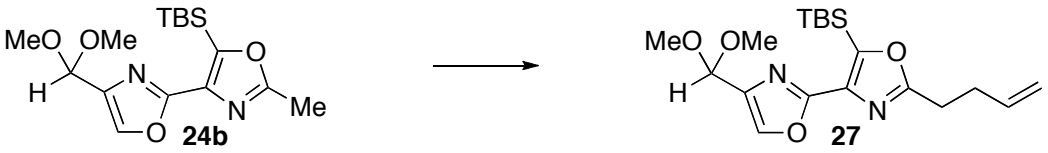
To a 5 mL flask containing TBS ether **54** (170.0 mg, 0.3097 mmol, 1 equiv) in benzene (10 mL) under an argon atmosphere was added MeOH (0.376 mL, 30 equiv) and trimethyl orthoformate (0.170 mL, 5 equiv). A spatula tip of PPTS was added in one portion and the reaction was stirred for 90 min. The reaction was quenched with sat aq $NaHCO_3$ (50 mL) and diluted with EtOAc (40 mL). The layers were separated and the aqueous phase was further extracted with EtOAc (3 × 20 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. This material was purified *via* flash chromatography (0→40% EtOAc/hexanes, TLC: R_f = 0.57 in 40% EtOAc/hexanes) to provide mixed methyl acetal **4a** (R = TBS, 144.4 mg, 80% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 4.45 (dd, *J* = 7.7, 6.4 Hz, 1H), 4.02-3.93 (m, 1H), 3.51-3.42 (m, 1H), 3.29 (s, 3H), 3.00 (s, 3H), 2.54 (s, 3H), 2.18-2.06 (m, 2H), 1.95 (dd, *J* = 12.8, 4.5 Hz, 1H), 1.79 (d, *J* = 10.3 Hz, 1H), 1.31 (dd, *J* = 23.7, 11.6 Hz, 1H), 1.30 (s, 3H), 1.22 (dd, *J* = 23.6, 11.8 Hz, 1H), 0.95 (s, 9H), 0.87 (s, 9H), 0.39 (s, 3H), 0.38 (s, 3H), 0.04 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 156.6, 154.8, 141.4, 139.1, 135.9, 99.6, 72.7, 65.8, 65.1, 56.3, 47.6, 45.3, 41.0, 40.3, 26.5, 25.8, 23.7, 18.0, 17.6, 13.8, –4.6, –5.9 ppm; IR (film) 2929, 2857, 1612, 1586, 1463, 1377, 1319, 1251, 1192, 1084, 1034, 930, 914, 870, 837, 779, 670, 580, 490 cm^{-1}; $[\alpha]_D^{25}$ = –20.1° (*c* = 1.01, $CHCl_3$); HRMS (CI): Exact mass calcd for $C_{29}H_{52}N_2O_6Si_2Li$ $[M + Li]^+$: 587.3479; Found: 587.3523.

Methylated Bisoxazole Dimethylacetal 24a



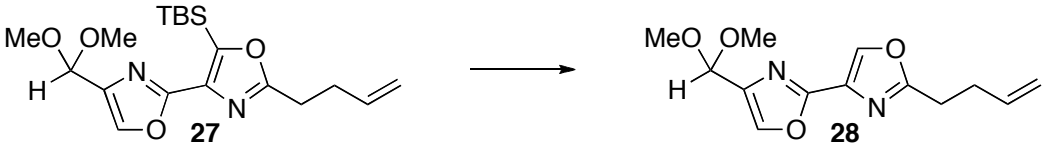
To bisoxazole dimethylacetal **23** (78.8 mg, 0.351 mmol, 1 equiv) in dry THF (2.0 mL) at –78 °C was added *n*-BuLi (2.72 M in hexanes, 129 μL, 0.351 mmol, 1 equiv). The reaction mixture gradually took on a bright yellow color. After stirring at –78 °C for 30 min, MeI (24 μL, 0.386 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 30 min and the color slowly faded from yellow to colorless. The reaction was quenched by the addition of sat. aq $NaHCO_3$ (2.5 mL) and the resulting suspension was warmed to rt and extracted with EtOAc. The combined organic layers were dried over a 1:1 mixture of K_2CO_3 and Na_2SO_4, filtered. and concentrated *in vacuo* to yield a colorless solid. Purification by silica gel chromatography (0→40% EtOAc/hexanes; TLC: R_f= 0.60, 100% ether UV) provided methylated bisoxazole dimethylacetal **24a** (65.5 mg, 78%) as a colorless, crystalline solid. Mp 97.0–98.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 5.47 (s, 1H), 3.39 (s, 6H), 2.64 (s, 3H), 2.47 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 156.5, 149.6, 139.3, 136.2, 124.9, 98.5, 52.8, 13.6, 11.5 ppm; IR (film) 2937, 1593, 1197, 1097, 1055, 980 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{14}N_2O_4$ $[M]^+$: 238.0954; Found: 238.0950; Anal calcd for $C_{11}H_{14}N_2O_4$: C, 55.46%, H, 5.92, N, 11.76%; Found: C, 55.57%, H, 5.97%, N, 11.66%.

Allylated Bisoxazole Dimethylacetal 27



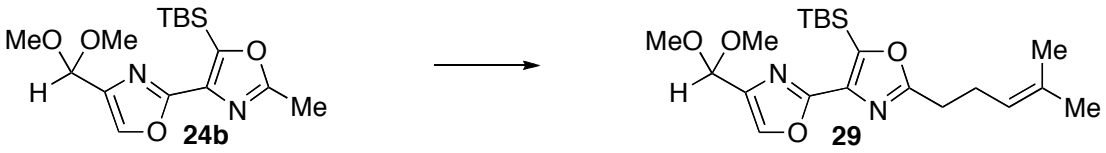
To as solution of diethylamine (22.0 μL, 0.213 mmol, 1.5 equiv) in THF (1 mL) at –78 °C was added *n*-BuLi (133 μL of a 1.5 M solution in hexanes, 0.199 mmol, 1.4 equiv). After stirring for 5 min, warming to 0 °C for 10 min, and then recooling to –78 °C, this solution was added *via* cannula to protected bisoxazole dimethyl acetal **24b** (48.0 mg, 0.142 mmol, 1 equiv) in dry THF (1 mL) at –78 °C. The reaction mixture immediately took on a bright red color and was stirred at –78 °C for 30 min. Allyl iodide (14.3 μL, 0.156 mmol, 1.1 equiv) was added dropwise, which caused a color change to light orange. After stirring at –78 °C for 15 min, sat aq $NaHCO_3$ (2 mL) was added and the reaction was warmed to rt. The resulting suspension was partitioned between CH_2Cl_2 (10 mL) and sat aq $NaHCO_3$ (10 ml) and The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over a 1:1 mixture of K_2CO_3 and Na_2SO_4, filtered, and concentrated *in vacuo* to yield a colorless liquid. Purification by silica gel chromatography (20% Et_2O/hexanes; TLC: R_f= 0.77, 70% Et_2O/hexanes UV) provided allylated bisoxazole **27** (47.0 mg, 88%) as a clear colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 5.86 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1H), 5.47 (s, 1H), 5.08 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.01 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.37 (s, 6H), 2.96 (t, *J* = 7.9 Hz, 2H), 2.57 (dt, *J* = 7.9, 6.7 Hz, 2H), 0.94 (s, 9H), 0.38 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 156.6, 154.8, 139.6, 138.9, 136.5, 136.3, 115.9, 98.6, 52.8, 30.9, 27.5, 26.4, 17.6, −5.9 ppm; IR (film) 2931, 2858, 1612, 1580, 1470, 1251, 1391, 1193, 1103, 1062 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{18}H_{27}N_2O_3Si$ [M–OCH_3]$^+$: 347.1791; Found: 347.1795; Anal calcd for $C_{19}H_{30}N_2O_4Si$: C, 60.29%, H, 7.99%, N, 7.40%; Found: C, 60.59%, H, 8.02%, N, 7.37%.

Deprotected Allylated Bisoxazole 28



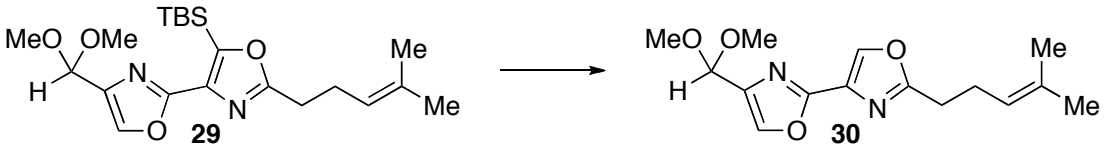
To alylated TBS-protected bisoxazle **27** (16 mg, 0.042 mmol, 1 equiv) in dry THF (425 μL) at 0 °C was added tetrabutylammoium fluoride (TBAF) (51 μL of a 1.0 M solution in THF, 0.051 mmol, 1.2 equiv). After stirring at 0 °C for 10 min, the reaction was quenched by the addition of sat aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (1 mL). The mixture was partitioned between CH_2Cl_2 (5 mL) and sat aq $NaHCO_3$ (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) The combined organic layers were dried over a 1:1 mixture of K_2CO_3 and Na_2SO_4, filtered, and concentrated *in vacuo* to yield a colorless liquid. Purification by silica gel chromatography (1:1:1 CH_2Cl_2/Et_2O/hexanes; TLC: R_f= 0.53, 70% Et_2O/ hexanes, UV) provided deptotected allylated bisoxazole **28** (10.0 mg, 90%) as a clear colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.72 (s, 1H), 5.86 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1H), 5.48 (s, 1H), 5.09 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.03 (dd, *J* = 10.2, 1.4 Hz, 1H), 3.39 (s, 6H), 2.95 (t, *J* = 7.4 Hz, 2H), 2.58 (dt, *J* = 7.4, 6.7 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 155.6, 139.5, 138.3, 136.8, 136.1, 130.3, 116.1, 98.3, 52.8, 30.7, 27.5 ppm; IR (film) 2939, 1103, 1059, 984, 916 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{16}N_2O_4$ [M]$^+$: 264.1110; Found: 264.1114; Anal calcd for $C_{13}H_{16}N_2O_4$: C, 59.08%, H, 6.10%, N, 10.60%; Found: C, 58.94%, H, 6.16%, N, 10.46%.

Prenylated Bisoxazole 29



A 0.5 M solution of $LiNEt_2$ was prepared by addition of *n*-BuLi (1.00 mL of a 2.72 *M* solution in hexanes, 2.72 mmol) to diethylamine (0.310 mL, 3.00 mmol) in THF (4.13 mL) at –78 °C under an atmosphere of argon. After 5 min, the flask was warmed to 0 °C. In a separate flask, TBS-protected bisoxazole dimethylacetal **24b** (100.8 mg, 0.298 mmol, 1 equiv) in THF (2.0 mL) was cooled to –78 °C under an atmosphere of argon and the $LiNEt_2$ solution prepared above was added dropwise until a yellow color persisted (to remove any adventitious acid source—about 4 drops). After this zero point, $LiNEt_2$ (0.893 mL of a 0.5 M solution in THF, 0.447 mmol, 1.5 equiv) was added dropwise via gastight syringe. The reaction took on an bright orange/red color. After stirring at –78 °C for 30 min, prenyl bromide (39 μL, 0.327 mmol, 1.1 equiv) was added dropwise causing the reaction to fade to light orange-yellow almost immediately. After 15 min, the reaction was quenched with sat aq $NaHCO_3$ (5 mL) and the color turned a very light yellow. The mixture was diluted with EtOAc (5 mL) and warmed to rt. The layers were separated and the aqueous phase was further extracted with EtOAc (3 × 5 mL). The combined organics were dried over a 1:1 mixture of anhydrous K_2CO_3 and Na_2SO_4, filtered, and concentrated *in vacuo*. This material was purified *via* automated silica column chromatography (0→15% EtOAc/hexanes, TLC: R_f = 0.81 in 70% Et_2O/hexanes) to provide prenylated bisoazole **29** (103.1 mg, 91% yield) as a clear colorless oil ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 1.0 Hz, 1H) 5.47 (d, *J* = 0.8 Hz, 1H), 5.15 (tt, *J* = 7.2, 1.3 Hz, 1H), 3.37 (s, 6H), 2.87 (t, *J* = 7.4 Hz, 2H), 2.48 (dt, *J* = 7.6, 7.4 Hz, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 0.95, (s, 9H), 0.38 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 156.7, 154.6, 139.6, 138.9, 136.5, 133.4, 122.2, 98.6, 52.8, 28.3, 26.4, 25.7, 25.6, 17.62, 17.58, –5.9 ppm; IR (film) 2954, 2930, 1469, 1251, 1104, 1062, 843, 124 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{21}H_{34}N_2O_4Si$ $[M]^+$: 406.2288; Found: 406.2273; Anal calcd for $C_{21}H_{34}N_2O_4Si$: C, 62.03%, H, 8.43%, N, 6.89%; Found: C, 62.17%, H, 8.56%, N, 6.94%.

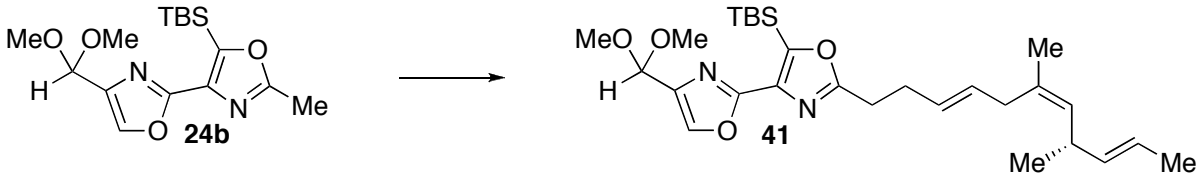
Deprotected Prenylated Bisoxazole 30



To prenylated TBS-protected bisoxazole **29** (44.9 mg, 0.110 mmol, 1 equiv) in dry THF (2.0 mL) at 0 °C was added tetrabutylammoium fluoride (TBAF) (132 μL of a 1.0 M solution in THF, 0.133 mmol, 1.2 equiv). After stirring at 0 °C for 10 min, the reaction was quenched by the addition of sat aq $NaHCO_3$ (2 mL) and CH_2Cl_2 (2 mL). The mixture was partitioned between CH_2Cl_2 (10 mL) and sat aq $NaHCO_3$ (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) The combined organic layers were dried over a 1:1 mixture of K_2CO_3 and Na_2SO_4, filtered, and concentrated *in vacuo* to yield a colorless liquid. Purification by silica gel chromatography (1:1:2 CH_2Cl_2/Et_2O/hexanes; TLC: R_f= 0.66, 70% Et_2O/hexanes, UV) provided deprotected prenylated bisoxazole **30** (31.8 mg, 99%) as a clear colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.72 (d, *J* = 1.0 Hz, 1H), 5.48 (s, 1H), 5.14 (tt, *J* =7.2, 1.3 Hz, 1H), 3.39 (s, 6H), 2.86 (t, *J* = 7.4 Hz, 2H), 2.50 (dt, *J* = 7.7, 7.4 Hz, 2H), 1.68 (s, 3H), 1.60 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 155.6, 139.5, 138.2, 136.8, 133.7, 130.2, 121.8, 98.3,

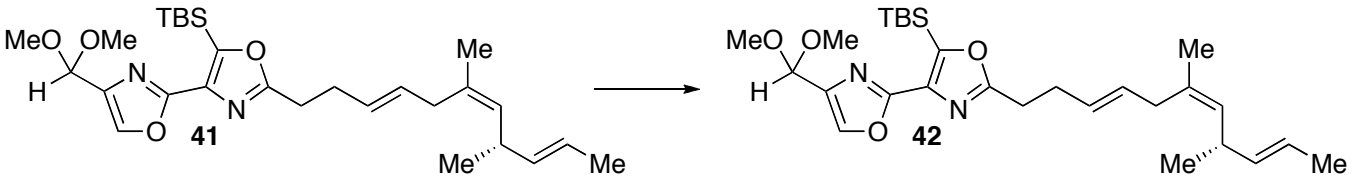
52.8, 28.3, 25.6, 25.5, 17.6 ppm; IR (film) 2933, 1103, 1059, 984 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{20}N_2O_4$ $[M]^+$: 292.1423; Found: 292.1392; Anal calcd for $C_{15}H_{20}N_2O_4$: C, 61.63%, H, 6.90%, N, 9.58%; Found: C, 61.38%, H, 7.06%, N, 9.36%.

Trienyl Bisozaxole 41



To as solution of diethylamine (59 μL, 0.568 mmol, 2.1 equiv) in THF (1.5 mL) at –78 °C was added *n*-BuLi (340 μL of a 1.59 M solution in hexanes, 0.541 mmol, 2.0 equiv). After stirring for 5 min, warming to 0 °C for 10 min, and then recooling to –78 °C, this solution was added *via* cannula to protected bisoxazole dimethyl acetal **24b** (93.1 mg, 0.271 mmol, 1 equiv) in dry THF (1.5 mL) at –78 ° C. The reaction mixture immediately took on a bright red color and was stirred at –78 °C for 30 min. Side chain allylic bromide **7** (106 mg, 0.436 mmol, 1.5 equiv) in THF (1 mL) was added dropwise *via* cannula, which caused a color change to light orange. After stirring at –78 °C for 15 min, sat aq $NaHCO_3$ (4 mL) was added and the reaction was warmed to rt. The resulting suspension was partitioned between CH_2Cl_2 (15 mL) and sat aq $NaHCO_3$ (15 ml) and The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a clear yellow liquid. Purification by silica gel chromatography (25% Et_2O/hexanes; TLC: R_f= 0.81, 70% Et_2O/hexanes UV) provided trienyl bisoxazole **41** (106.7 mg, 79%) as a clear colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 0.8 Hz, 1H), 5.50-5.39 (m, 2H), 5.47 (s, 1H), 5.35-5.33 (m, 2H), 4.99 (d, *J* = 9.2 Hz, 1H), 3.37 (s, 6H), 3.03-2.95 (m, 1H), 2.91 (t, *J* = 7.4 Hz, 2H), 2.71 (dd, *J* = 14.4, 6.2 Hz, 1H), 2.65 (dd, *J* = 14.4, 6.2 Hz, 1H), 2.51 (dt, *J* = 7.4, 7.4 Hz, 2H), 1.63 (d, *J* = 4.7 Hz, 3H), 1.60 (d, *J* = 1.2 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.95 (s, 9H), 0.38 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 156.6, 154.7, 139.6, 138.9, 136.5, 136.2, 132.1, 130.4, 129.5, 128.8, 122.5, 98.6, 52.8, 35.3, 35.2, 29.9, 28.2, 26.5, 23.3, 21.4, 17.9, 17.6, –5.9 ppm; IR (film) 2957, 2930, 2858, 1612, 1579, 1464, 1448, 1376, 1318, 1251, 1193, 1161, 1104, 1063, 1005, 970, 929, 910, 843, 824, 812, 782, 748, 688, 582, 456 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{28}H_{44}N_2O_4Si$ $[M]^+$: 500.3070; Found: 500.3080; Anal calcd for $C_{28}H_{44}N_2O_4Si$: C, 67.16%, H, 8.86%, N, 5.59%; Found: C, 67.43%, H, 8.94%, N, 5.40%.

Deprotected Trienyl Bisoxazole 42



To TBS-protected trienyl bisoxazole **41** (54.4 mg, 0.109 mmol, 1 equiv) in dry THF (2.2 mL) at 0 °C was added tetrabutylammoium fluoride (TBAF) (130 μL of a 1.0 M solution in THF, 0.130 mmol, 1.2 equiv). After stirring at 0 °C for 10 min, the reaction was quenched by the addition of sat aq $NaHCO_3$ (2 mL). The mixture was partitioned between CH_2Cl_2 (10 mL) and sat aq $NaHCO_3$ (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield an orange liquid. Purification by silica gel

chromatography (1:1:2 CH_2Cl_2/Et_2O/hexanes; TLC: R_f= 0.66, 70% Et_2O/hexanes, UV) provided deprotected trienyl bisoxazole **42** (39.8 mg, 95%) as a clear colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.71 (d, *J* = 1.0 Hz, 1H), 5.49-5.41 (m, 2H), 5.47 (s, 1H), 5.37-5.30 (m, 2H), 4.98 (d, *J* = 9.2 Hz, 1H), 3.40 (s, 3H), 3.02-2.93 (m, 1H), 2.89 (t, *J* = 7.4,Hz, 2H), 2.70 (dd, *J* = 14.6, 6.2 Hz, 1H), 2.65 (dd, *J* = 14.6, 6.2 Hz, 1H), 2.51 (dt, *J* = 7.4, 7.4 Hz, 2H), 1.62 (d, *J* = 4.9 Hz, 3H), 1.60 (d, *J* = 1.2 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H) ppm; IR (film) 3135, 2962, 2832, 2730, 1635, 1579, 1829, 1501, 1448, 1377, 1310, 1266, 1193, 1158, 1102, 1061, 969, 917, 854, 781, 734, 653 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{22}H_{30}N_2O_4$ $[M]^+$: 386.2206; Found: 386.2190; Anal calcd for $C_{22}H_{30}N_2O_4$: C, 68.37%, H, 7.82%, N, 7.25%; Found: C, 68.52%, H, 8.04%, N, 7.24%.

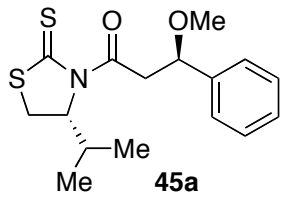
General procedure for $TiCl_4$/Hünig's base aldol-type reactions with acetals

To the *N*-acetyl-thiazolidinethione (1.3 equiv) in CH_2Cl_2 (0.2 M) under argon atmosphere at 0 °C was added $TiCl_4$ (1.3 equiv) dropwise *via* syringe. After 10 min, the orange solution was cooled to –78 °C and (*i*-Pr)$_2$NEt (1.3 equiv) was added *via* syringe and the solution turned a characteristic blood-red color. After stirring for 30 min, the solution was warmed to –50 °C and stirred for 2 h. The dimethyl acetal (1 equiv) was added dropwise *via* cannula in CH_2Cl_2 (approx 0.3 M) followed by the dropwise addition of BF_3•OEt_2 (1.3 equiv). The solution was stirred at –78 °C for 2 h. The reaction was quenched by pouring into a rapidly stirring 1:1 mixture of CH_2Cl_2 and half-sat NH_4Cl. The layers were separated and the aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. ^1H NMR integration of the unpurified product was used to determine the diastereomer ratio. Silica column chromatography provided diastereomerically pure methyl ether.

General procedure for $PhBCl_2$/sparteine aldol-type reactions with acetals

To the *N*-acetyl-thiazolidinethione (1.3 equiv) in CH_2Cl_2 (0.2 M) under argon atmosphere at 0 °C was added $PhBCl_2$ (1.3 equiv) dropwise *via* syringe. After 10 min, sparteine (2.6 equiv) was added *via* syringe and the resulting solution was warmed to rt and stirred for 30 min. The solution was cooled to –78 °C and the dimethyl acetal (1 equiv) was added dropwise *via* cannula in CH_2Cl_2 (approx 0.3 M) followed by the dropwise addition of BF_3•OEt_2 (1.1 equiv). The solution was stirred at –78 °C for 1.5 h and then was warmed to rt over 2 h. After stirring at rt an additional 1 h, the reaction was quenched with sat aq NH_4Cl. The contents of the flask were transferred to a separatory funnel containing a 4:1 mixture of hexanes:CH_2Cl_2. The layers were separated and the aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. ^1H NMR integration of the unpurified product was used to determine the diastereomer ratio. Silica column chromatography provided diastereomerically pure methyl ether.

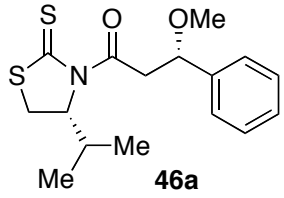
Methyl Ether 45a



45a

Yellow crystals. Mp 92.3–92.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.33 (m, 4H), 7.32-7.26 (m, 1H), 5.00 (ddd, *J* = 7.7, 6.0, 1.5 Hz, 1H), 4.71 (dd, *J* = 7.6, 5.7 Hz, 1H), 3.86 (dd, *J* = 16.6, 7.6 Hz, 1H), 3.69 (dd, *J* = 16.6, 5.7 Hz, 1H), 3.30 (dd, *J* = 11.4, 8.1 Hz, 1H), 3.21 (s, 3H), 2.96 (dd, *J* = 11.4, 1.5 Hz, 1H), 2.40-2.31 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 7.1, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 171.0, 140.4, 128.4, 127.9, 126.9, 79.9, 71.7, 56.5, 46.1, 30.5, 30.2, 19.0, 17.4 ppm; IR (film) 2964, 2933, 2891, 2821, 1698, 1467, 1364, 1306, 1255, 1207, 1156, 1096, 1038, 1006, 987, 895, 701 cm^{-1}; $[\alpha]_D^{24}$ = –214.2° (*c* = 1.00, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{16}H_{21}NO_2S_2$ $[M]^+$: 323.1014; Found: 323.0997.

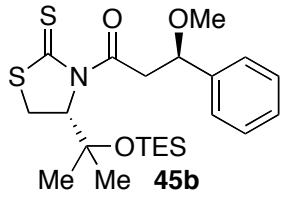
Methyl Ether 46a



46a

Clear yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.33 (m, 4H), 7.33-7.28 (m, 1H), 5.16 (dd, *J* = 6.9, 6.9 Hz, 1H), 4.81 (dd, *J* = 9.7, 3.0 Hz, 1H), 3.76 (dd, *J* = 17.1, 9.7 Hz, 1H), 3.53 (dd, *J* = 11.4, 8.1 Hz, 1H), 3.46 (dd, *J* = 17.1, 3.1 Hz, 1H), 3.22 (s, 3H), 3.03 (d, *J* = 11.4, 1H), 2.41-2.25 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.9, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.8, 171.0, 140.5, 128.5, 128.0, 126.7, 79.5, 71.7, 56.7, 46.6, 30.8, 30.7, 19.0, 17.7 ppm; IR (film) 3029, 2961, 2930, 2822, 1678, 1455, 1365, 1313, 1275, 1161, 1096, 1039, 762, 701 cm^{-1}; $[\alpha]_D^{24}$ = –266.0° (*c* = 1.34, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{16}H_{21}NO_2S_2$ $[M]^+$: 323.1014; Found: 323.1053.

Methyl Ether 45b

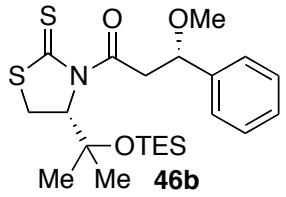


45b

Clear yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.33 (m, 4H), 7.32-7.27 (m, 1H), 5.19 (dd, *J* = 8.1, 1.0 Hz, 1H), 4.72 (dd, *J* = 7.8, 5.5 Hz, 1H), 3.90 (dd, *J* = 16.7, 7.8 Hz, 1H), 3.65 (dd, *J* = 16.7, 5.5 Hz, 1H), 3.35 (dd, *J* = 11.4, 1.1 Hz, 1H), 3.30 (dd, *J* = 11.4, 8.2 Hz, 1H), 3.21 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H), 0.95 (t, *J* = 7.9 Hz, 6H), 0.61 (q, *J* = 7.9 Hz, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 170.5, 140.6, 128.4, 127.9, 127.0, 79.9 76.7, 72.6, 56.6, 45.8, 30.1, 28.1, 26.1, 7.0, 6.5 ppm; IR (film) 2955, 2937, 2876, 2823, 1736, 1700, 1456, 1369, 1312, 1272, 1242, 1169, 1150, 1102, 1036, 745, 724,

701 cm^{-1}; $[\alpha]_D^{24}$ = –74.5° (*c* = 1.00, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{22}H_{35}NO_3S_2Si$ $[M]^+$: 453.1828; Found: 453.1829.

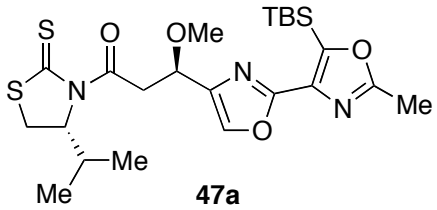
Methyl Ether 46b



46b

Clear yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.33 (m, 4H), 7.33-7.28 (m, 1H), 5.30 (d, *J* = 8.1, 1H), 4.82 (dd, *J* = 9.5, 3.3 Hz, 1H), 3.75 (dd, *J* = 17.0, 9.6 Hz, 1H), 3.49 (dd, *J* = 16.8, 3.6 Hz, 1H), 3.48 (dd, *J* = 8.1, 3.3 Hz, 1H), 3.42 (d, *J* = 11.3 Hz, 1H), 3.21 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H), 0.94 (t, *J* = 7.9 Hz, 6H), 0.60 (q, *J* = 7.9 Hz, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 170.3, 140.5, 128.5, 128.0, 126.8, 79.6 76.7, 72.6, 56.6, 46.0, 30.3, 28.1, 26.2, 7.1, 6.6 ppm; IR (film) 2955, 2910, 2876, 2822, 1736, 1700, 1456, 1368, 1312, 1242, 1148, 1102, 1036, 971, 934, 745, 724, 701 cm^{-1}; $[\alpha]_D^{24}$ = –68.2° (*c* = 0.84, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{22}H_{35}NO_3S_2Si$ $[M]^+$: 453.1828; Found: 453.1855.

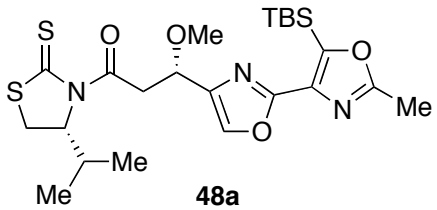
Methyl Ether 47a



47a

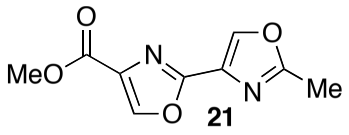
Clear yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 5.11 (dd, *J* = 7.4, 6.6 Hz, 1H), 4.84 (dd, *J* = 6.6, 6.0 Hz, 1H), 4.02 (dd, *J* = 17.8, 7.1 Hz, 1H), 3.80 (dd, *J* = 17.8, 5.5 Hz, 1H), 3.49 (dd, *J* = 11.4, 8.1 Hz, 1H), 3.37 (s, 3H), 3.02 (d, *J* = 11.4 Hz, 1H), 2.54 (s, 3H), 2.42-2.34 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.95 (s, 9H), 0.39 (s, 3H), 0.38 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 170.9, 164.9, 156.5, 154.7, 140.8, 138.8, 135.4, 72.2, 71.4, 56.8, 43.5, 30.6, 30.1, 26.3, 18.9, 17.5, 17.4, 13.7, –5.99, –6.01 ppm; IR (film) 2957, 2930, 2895, 2857, 1698, 1613, 1585, 1469, 1364, 1314, 1252, 1163, 1103, 1039, 930, 842, 782 cm^{-1}; $[\alpha]_D^{24}$ = –238.7° (*c* = 1.00, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{23}H_{35}N_3O_4S_2Si$ $[M]^+$: 509.1838; Found: 509.1840.

Methyl Ether 48a



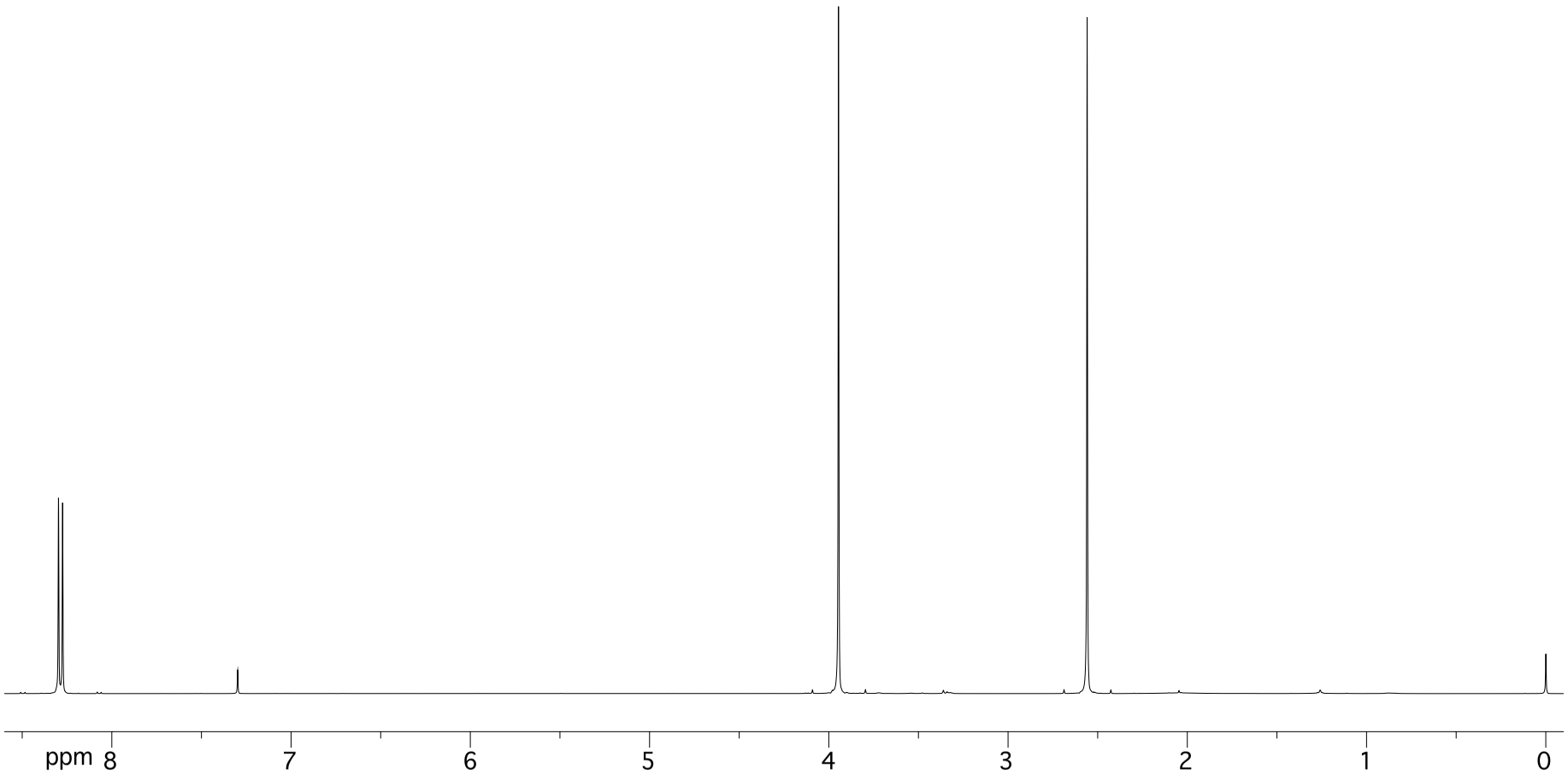
48a

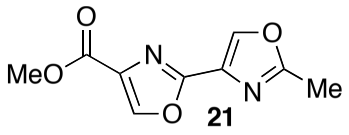
Clear yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 5.17 (dd, *J* = 6.9, 6.9 Hz, 1H), 4.89 (dd, *J* = 9.4, 2.9 Hz, 1H), 3.87 (dd, *J* = 17.9, 9.5 Hz, 1H), 3.65 (dd, *J* = 17.9, 2.9 Hz, 1H), 3.56 (dd, *J* = 11.4, 7.9 Hz, 1H), 3.38 (s, 3H), 3.04 (d, *J* = 11.7 Hz, 1H), 2.54 (s, 3H), 2.42-2.35 (m, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.96 (s, 9H), 0.40 (s, 3H), 0.39 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 170.7, 165.0, 156.7, 154.9, 141.0, 138.9, 135.1, 72.2, 71.5, 57.3 43.9, 30.8, 30.7, 26.5, 19.0, 17.8, 17.6, 13.8, –5.8 ppm; IR (film) 2956, 2929, 2857, 1698, 1466, 1364, 1315, 1250, 1165, 1104, 1040, 930, 841, 823, 811, 781, 680 cm^{-1}; $[\alpha]_D^{24}$ = –111.3° (*c* = 1.02, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{23}H_{35}N_3O_4S_2Si$ $[M]^+$: 509.1838; Found: 509.1847.



21

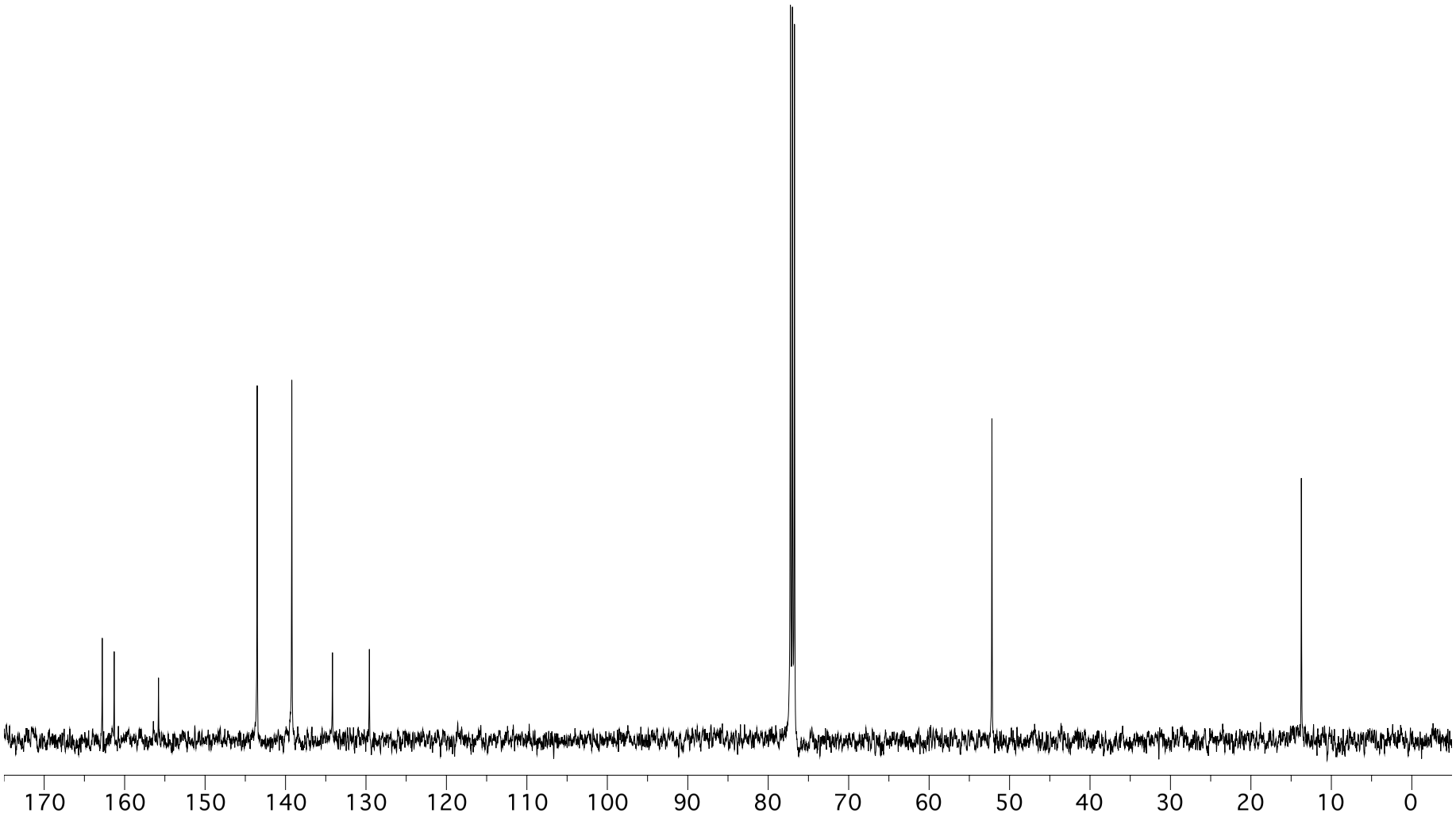
^{1}HNMR: 500 MHz in $CDCl_3$

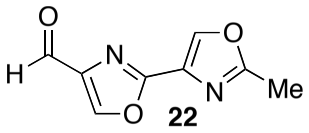




21

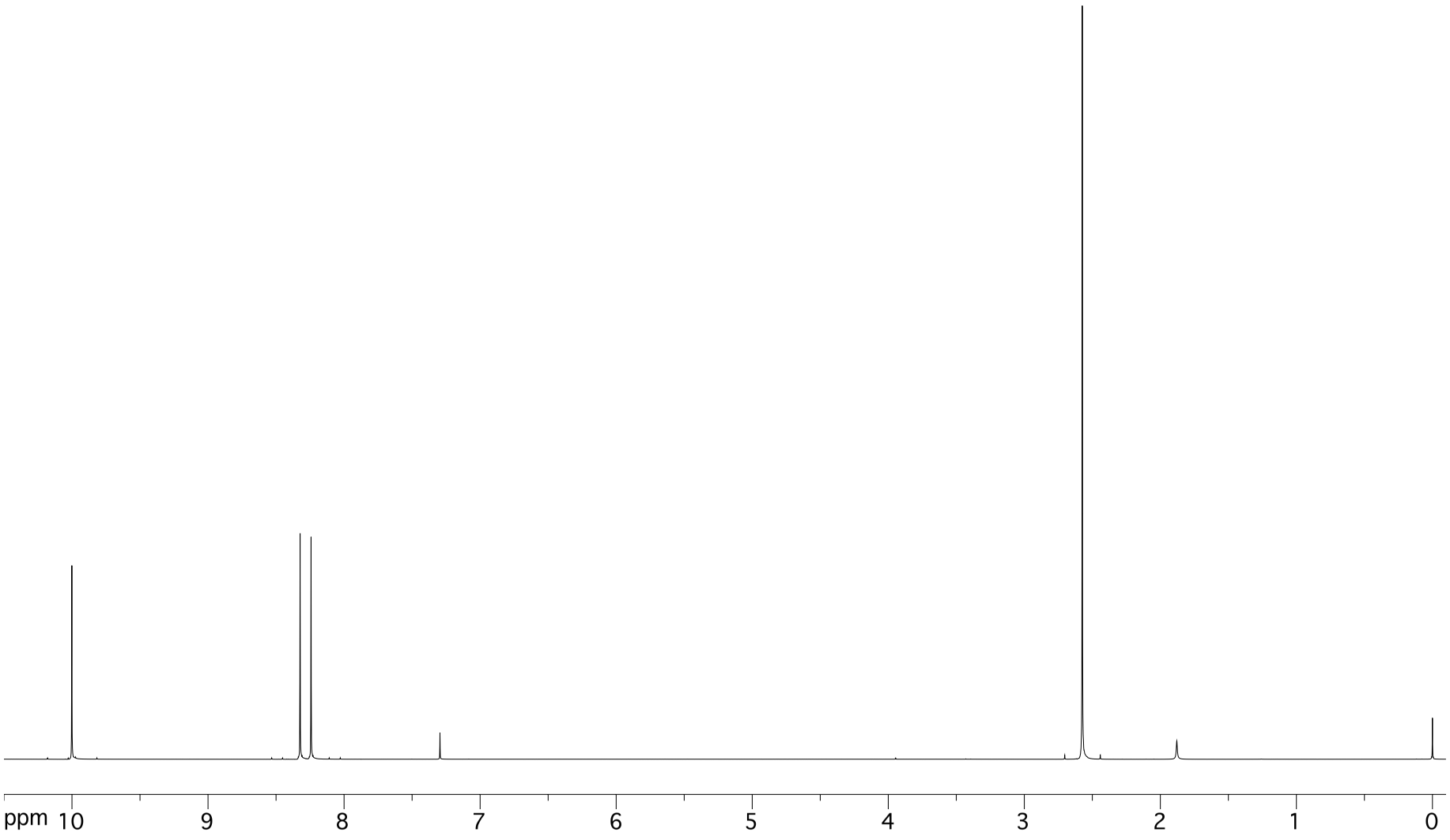
^{13}CNMR: 125 MHz in $CDCl_3$

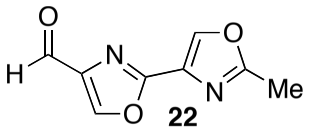




22

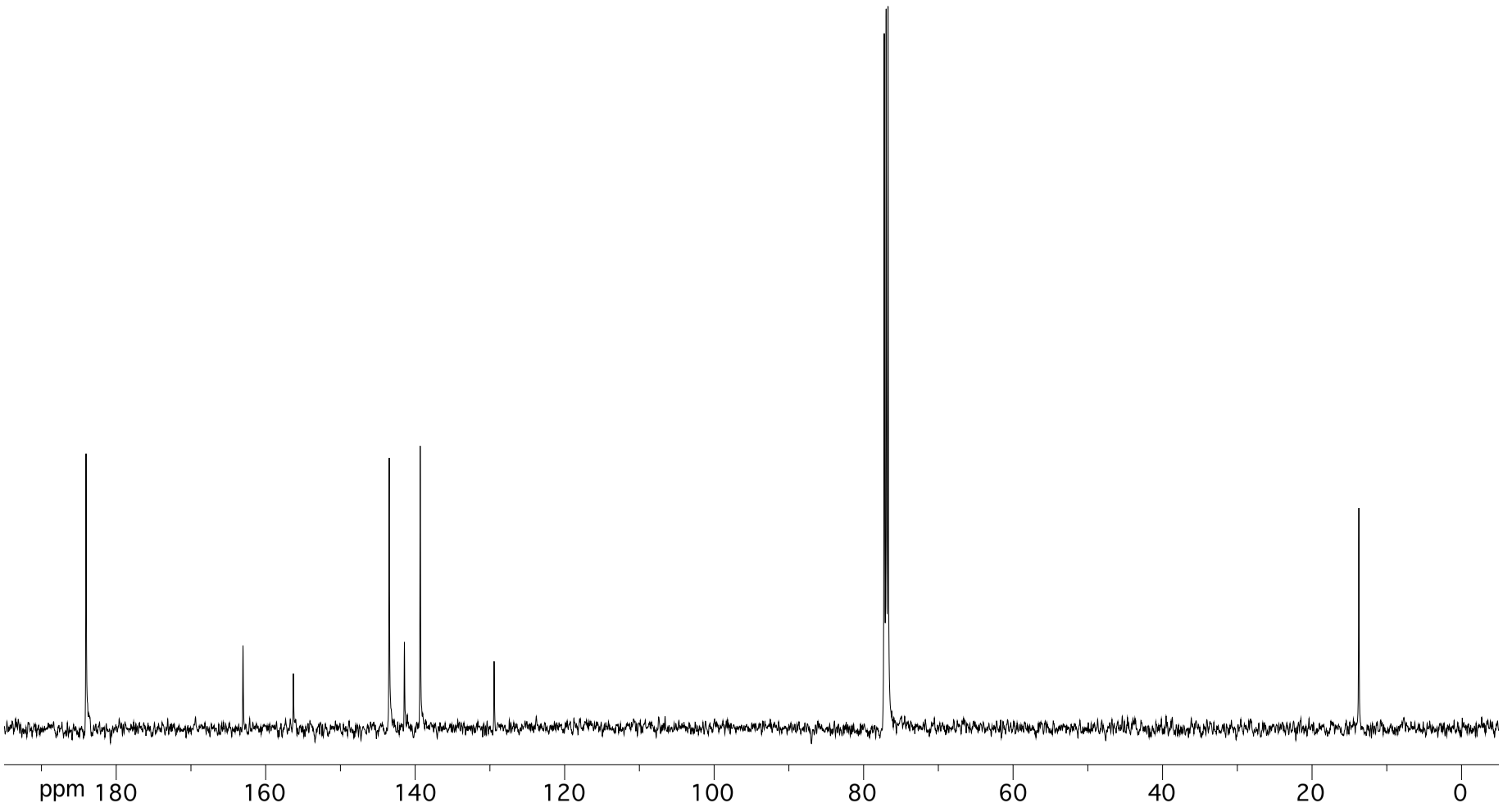
^{1}HNMR: 500 MHz in $CDCl_3$

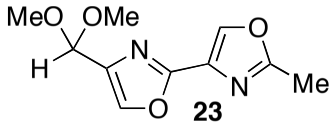




22

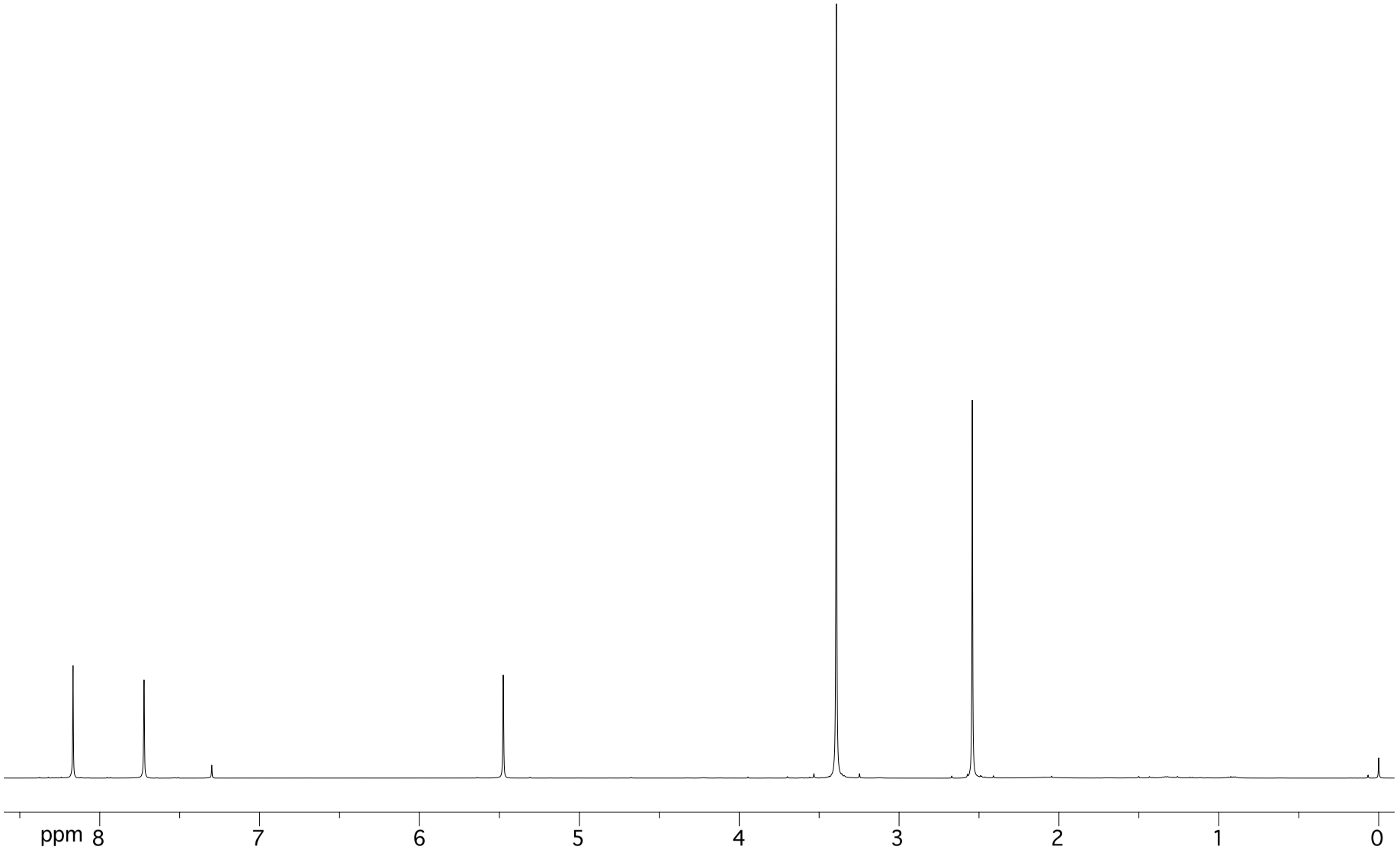
^{13}CNMR: 125 MHz in $CDCl_3$

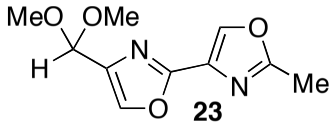




23

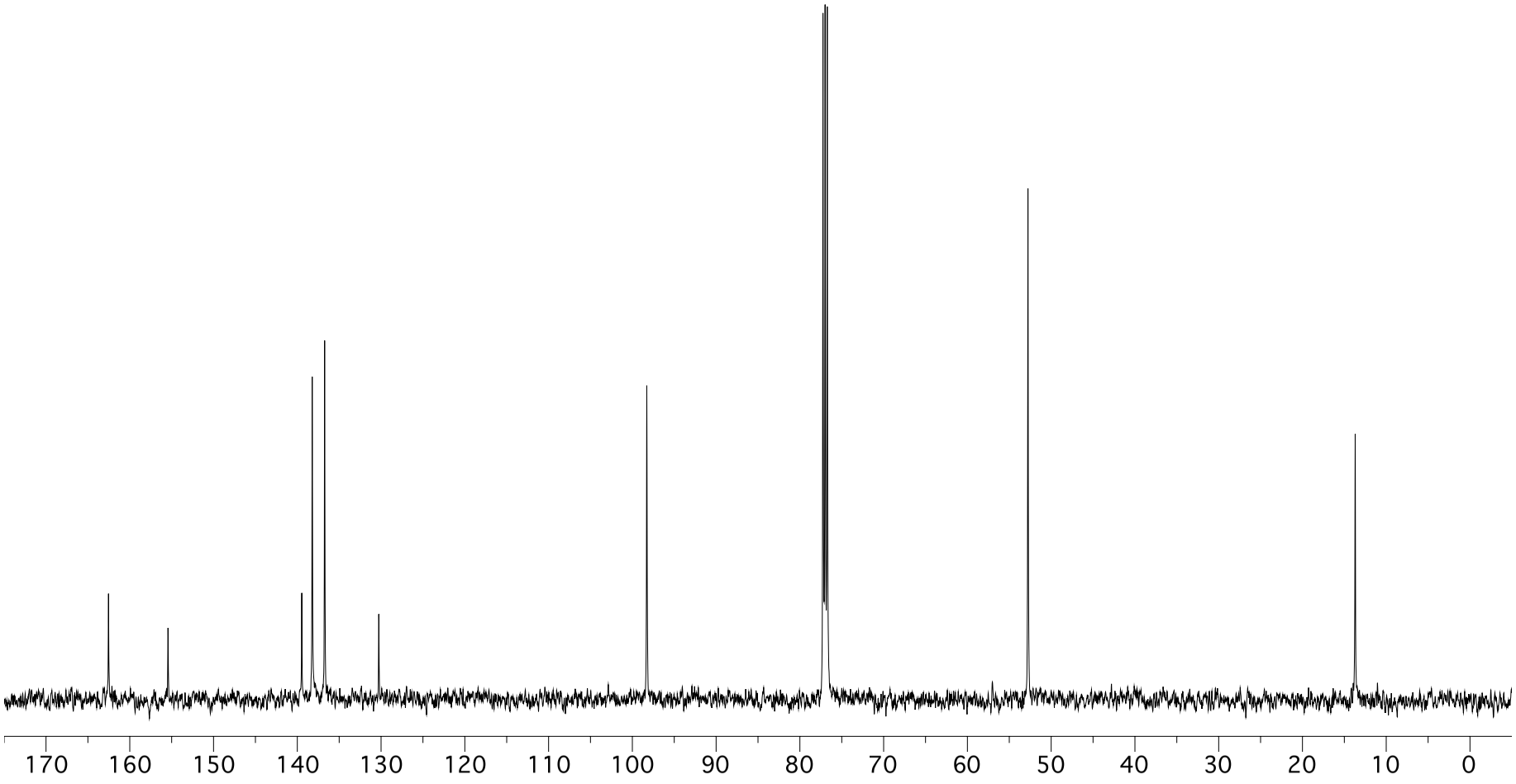
^{1}HNMR: 500 MHz in $CDCl_3$

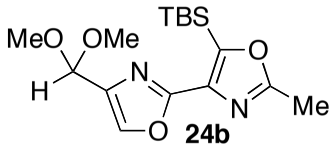




23

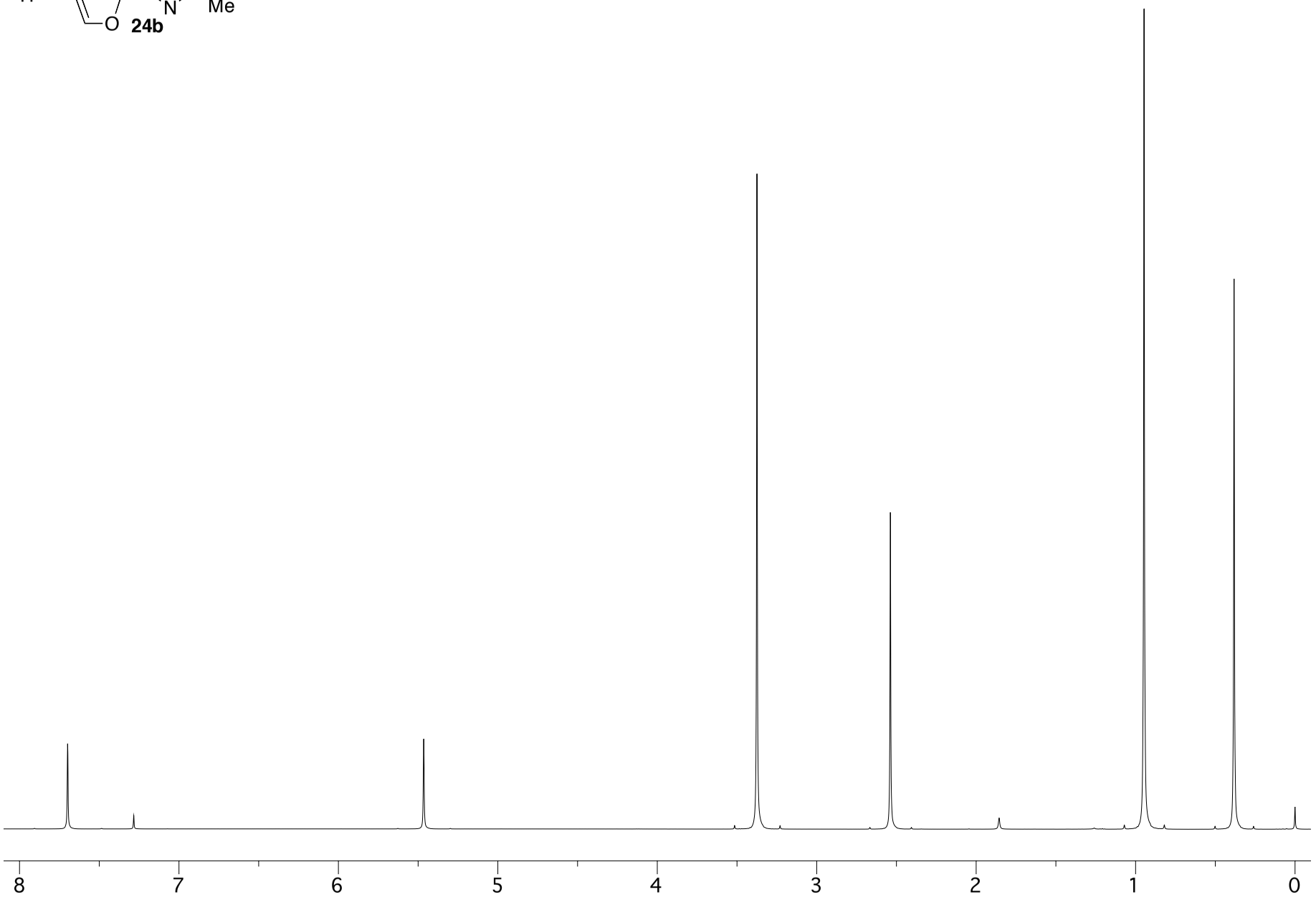
^{13}CNMR: 125 MHz in $CDCl_3$

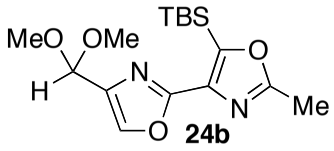




24b

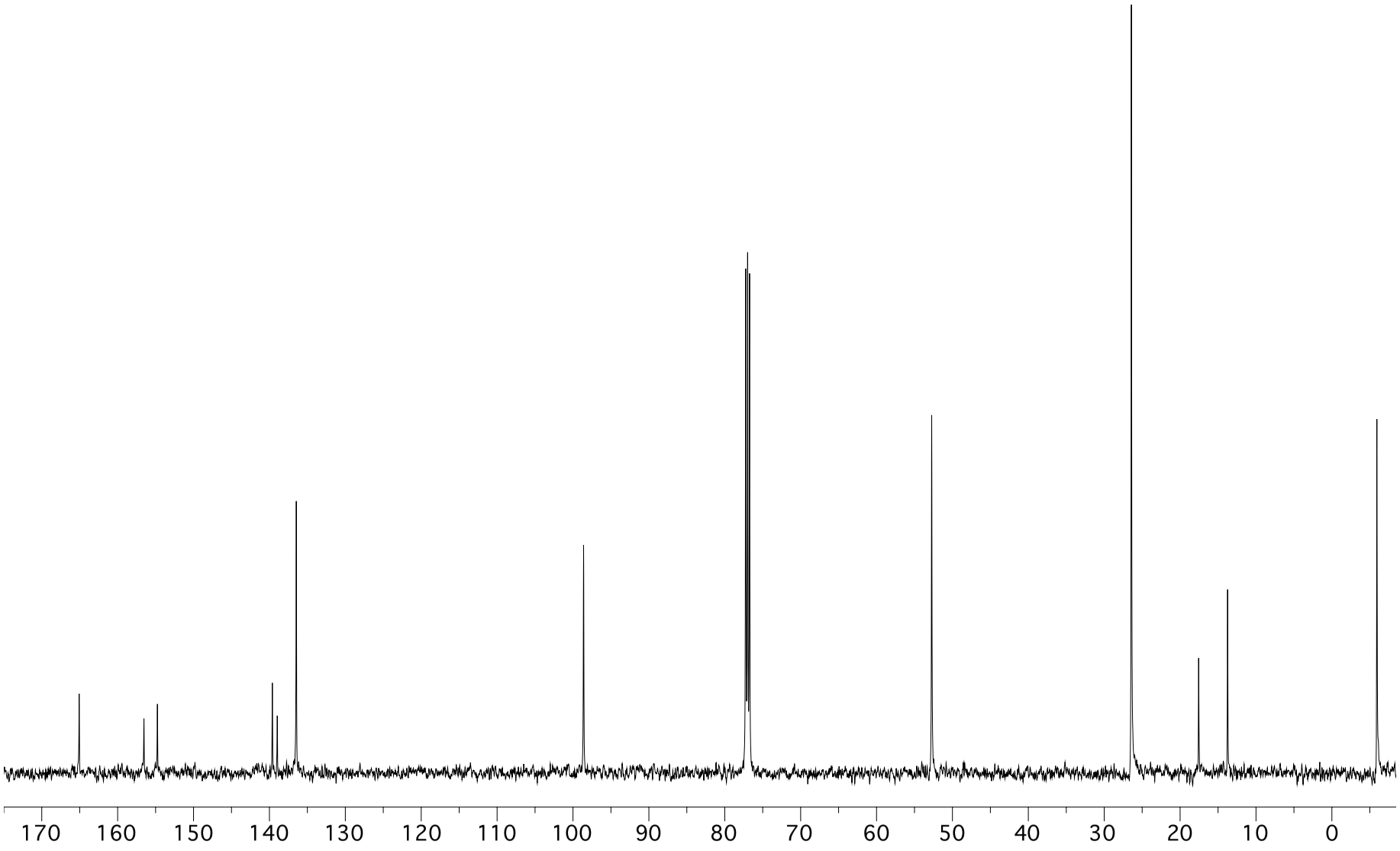
^{1}HNMR: 500 MHz in $CDCl_3$

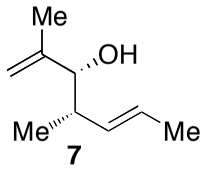




24b

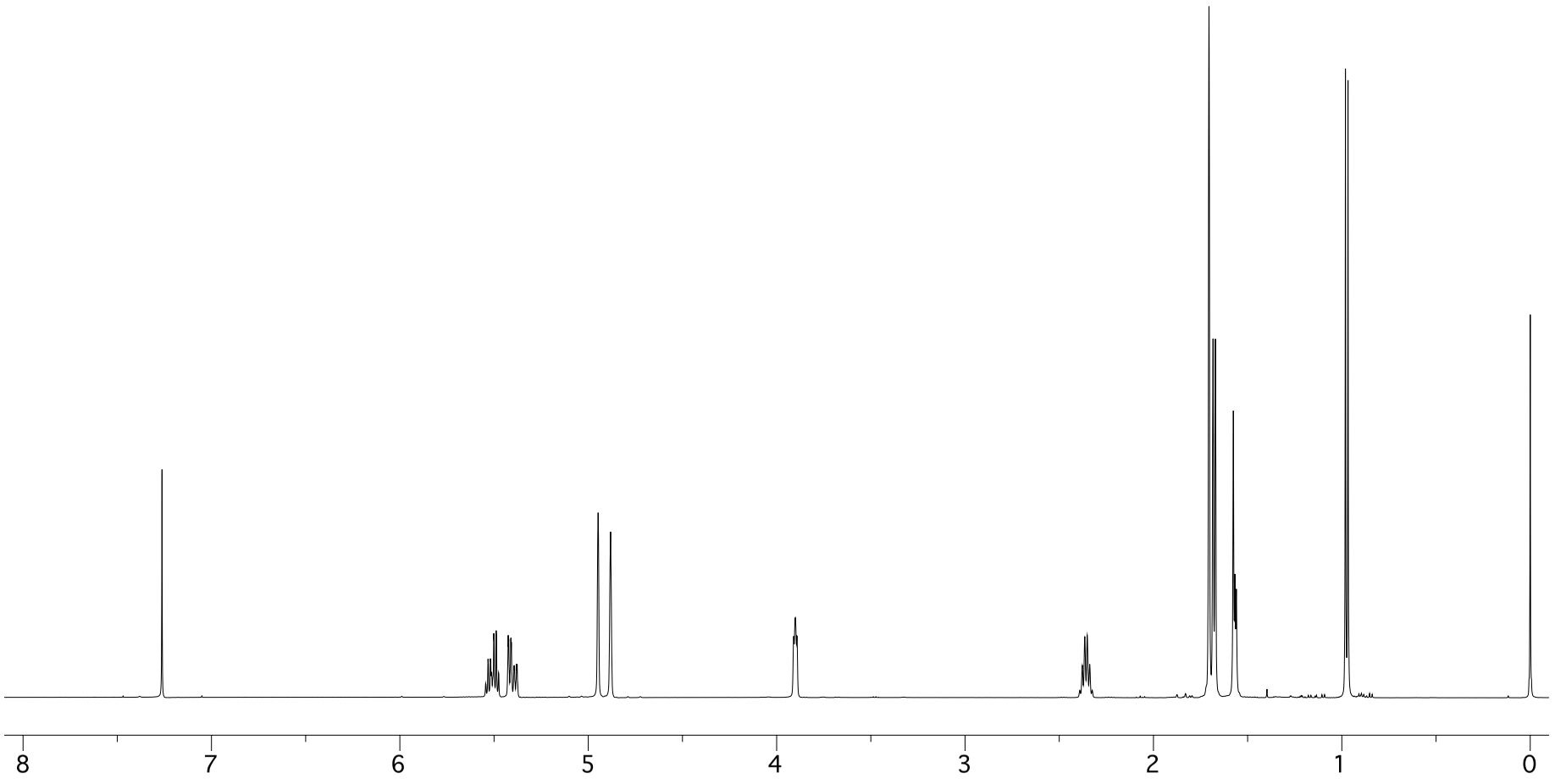
^{13}CNMR: 125 MHz in $CDCl_3$

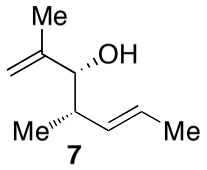




7

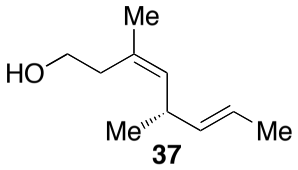
^{1}HNMR: 500 MHz in $CDCl_3$





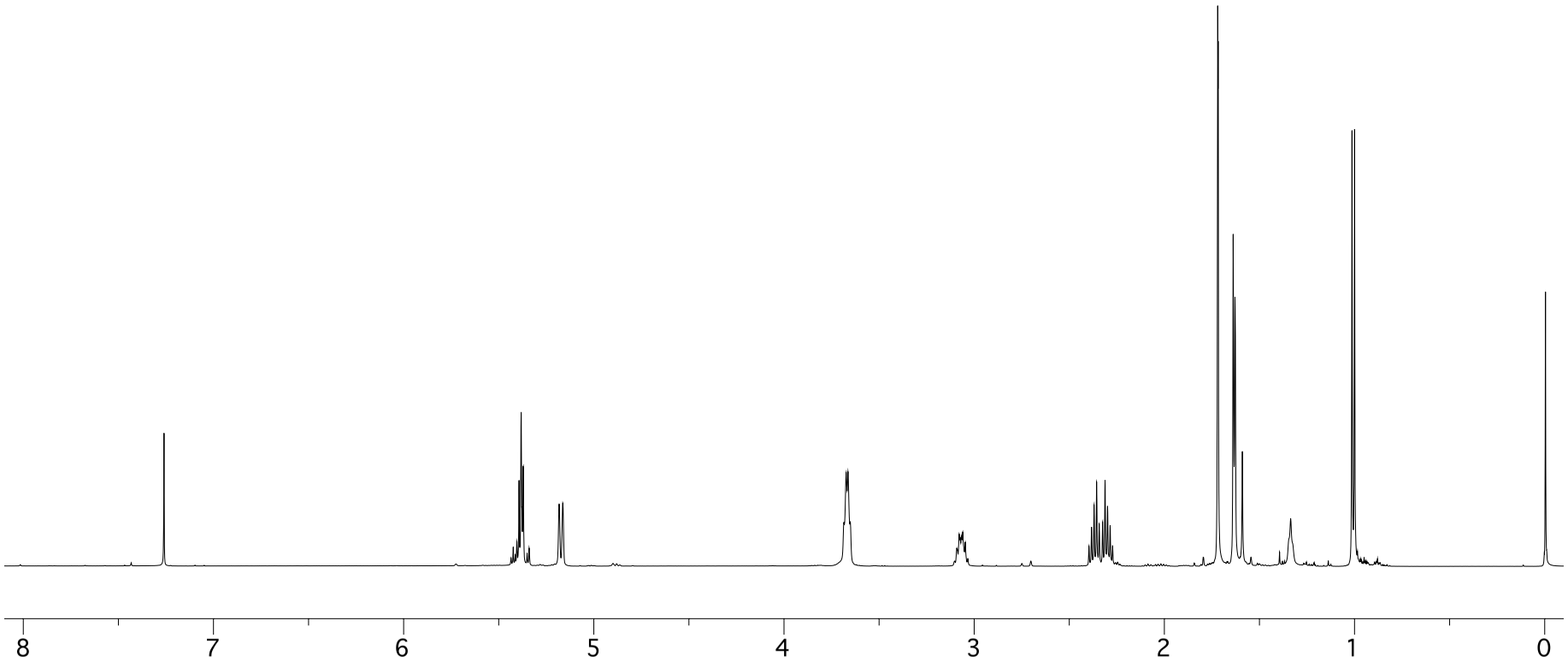
7

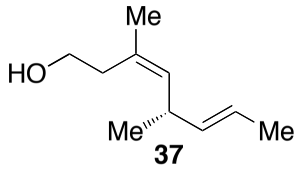
^{13}CNMR: 125 MHz in $CDCl_3$



37

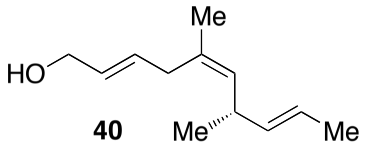
^{1}HNMR: 500 MHz in $CDCl_3$





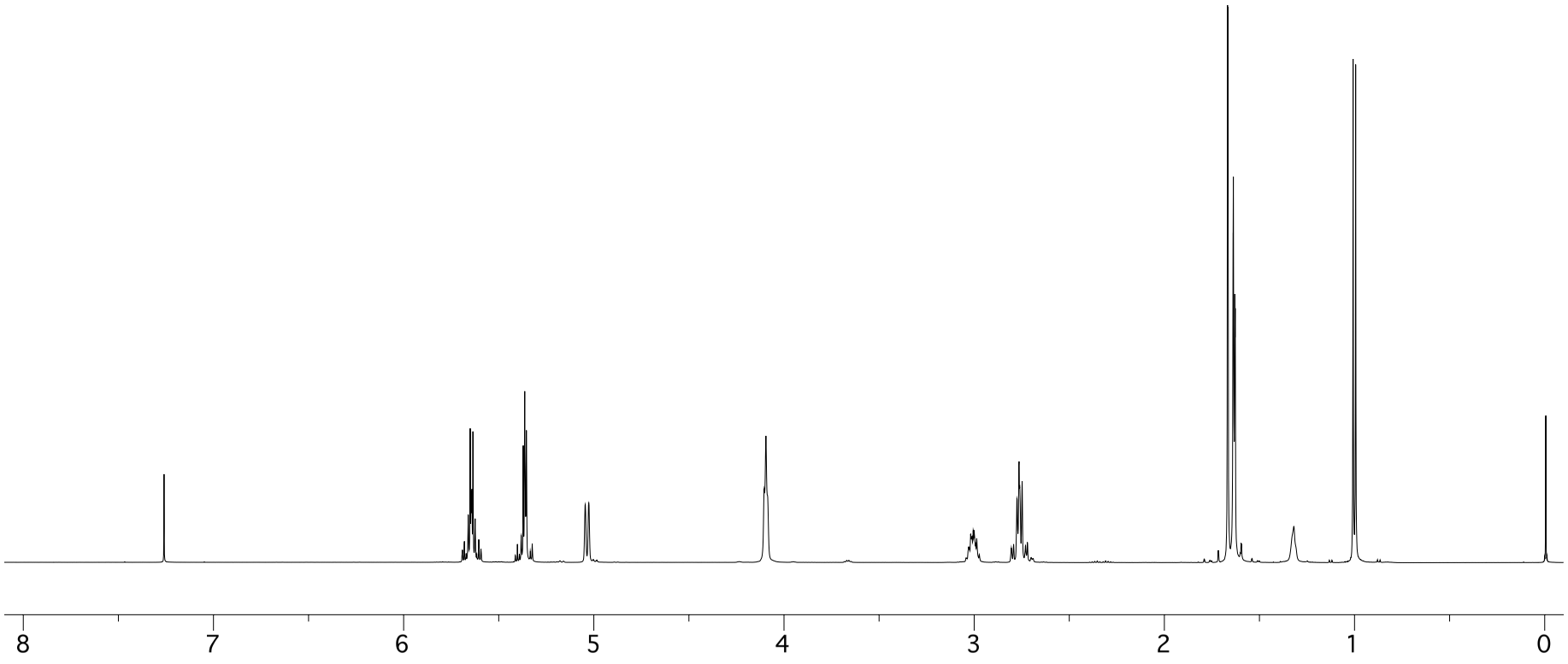
37

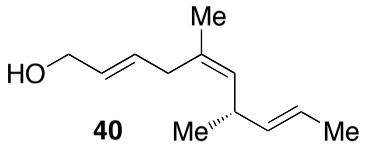
^{13}CNMR: 125 MHz in $CDCl_3$



40

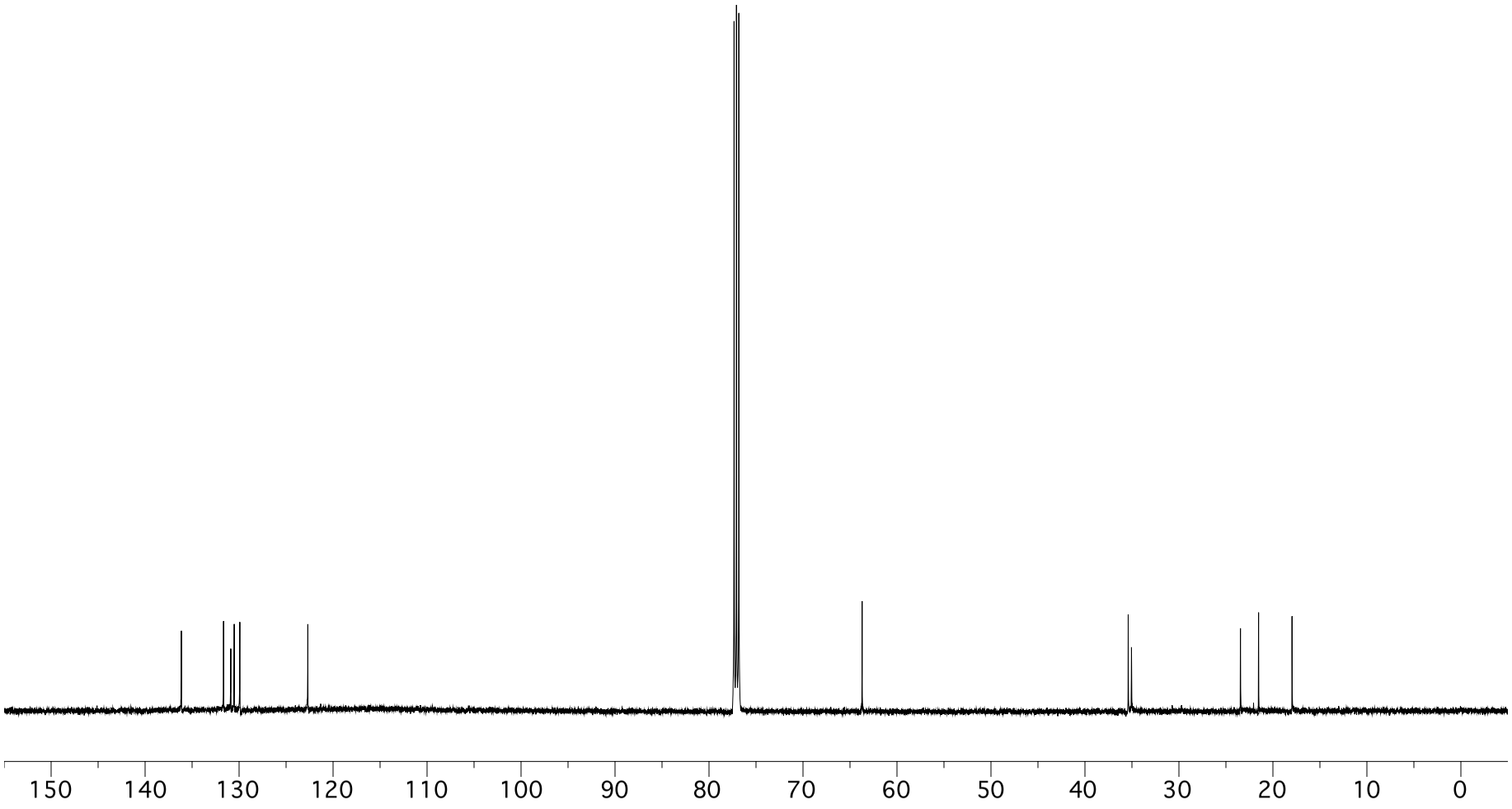
^{1}HNMR: 500 MHz in $CDCl_3$

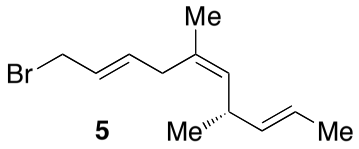




40

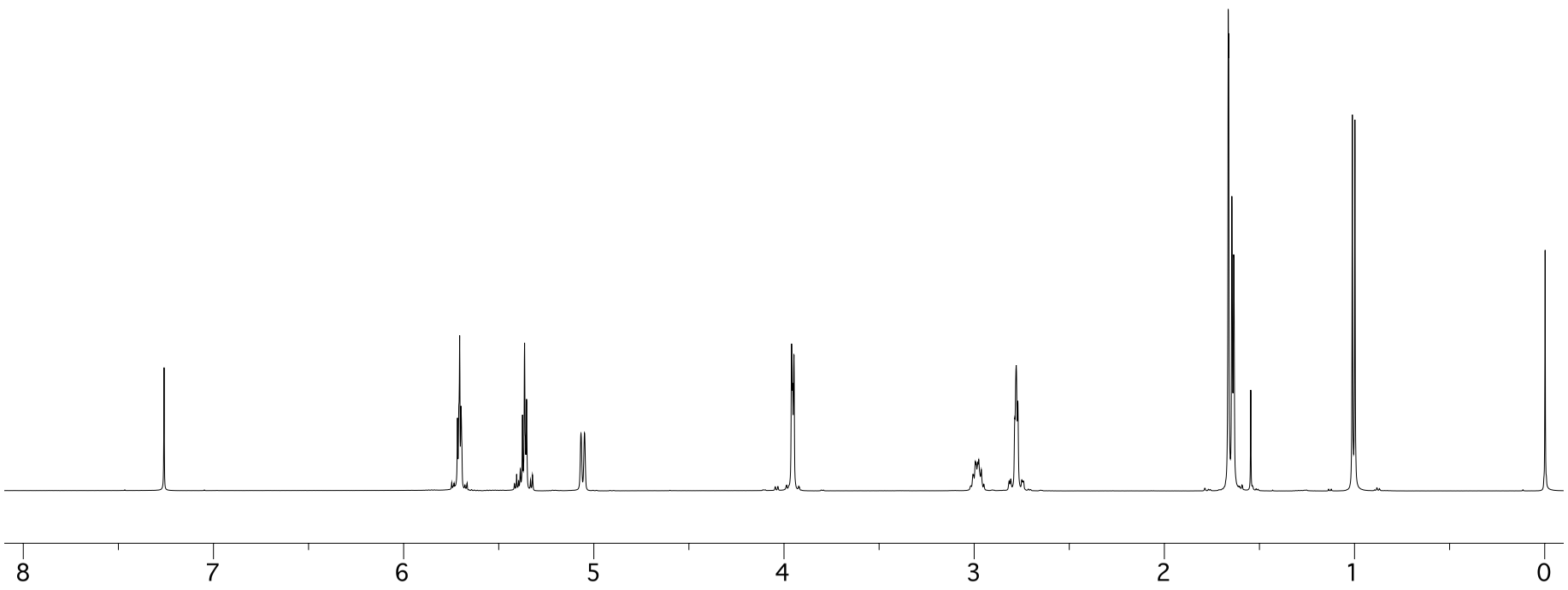
^{13}CNMR: 125 MHz in $CDCl_3$

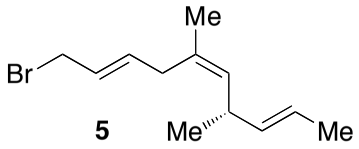




5

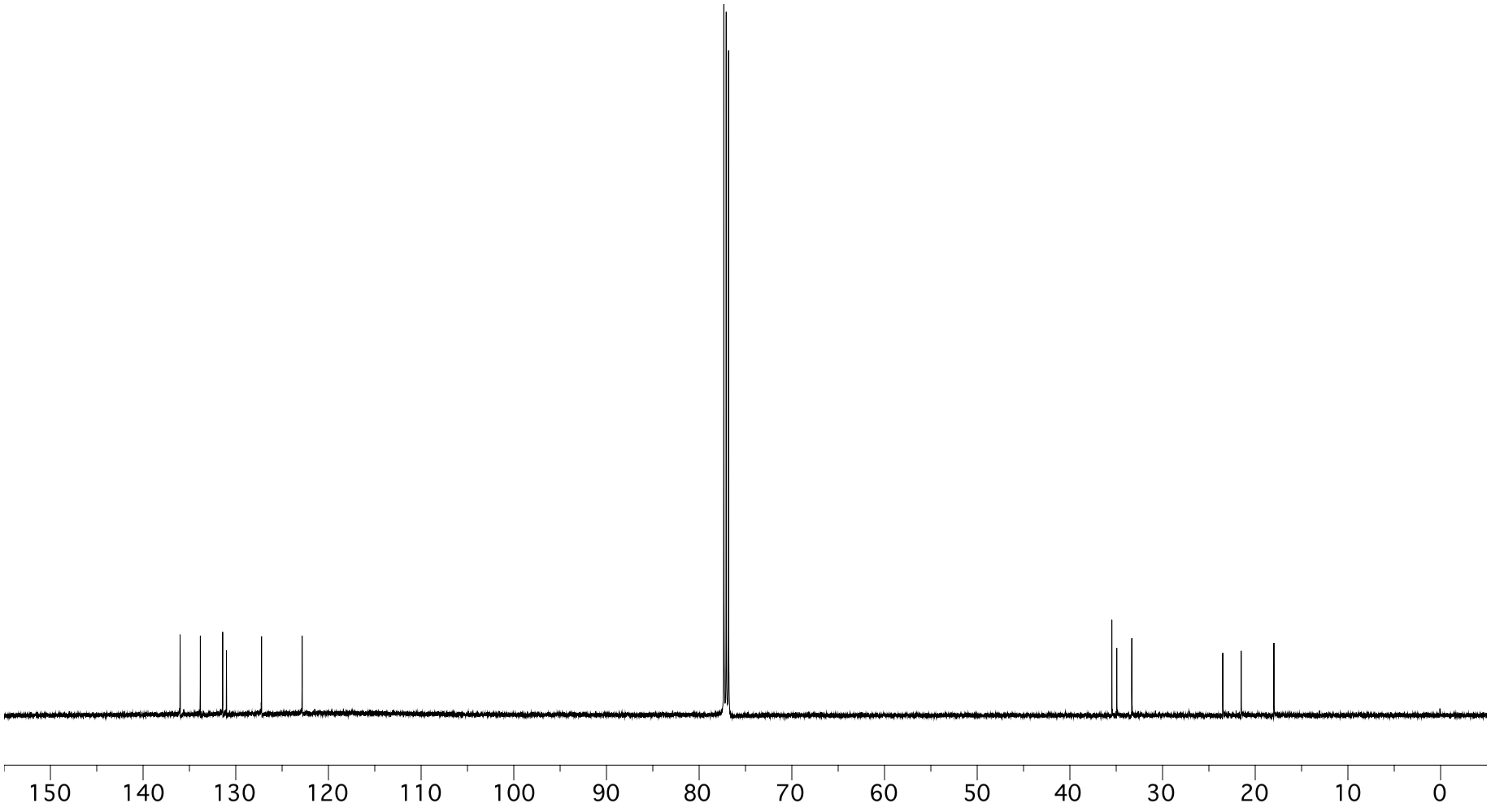
^{1}HNMR: 500 MHz in $CDCl_3$

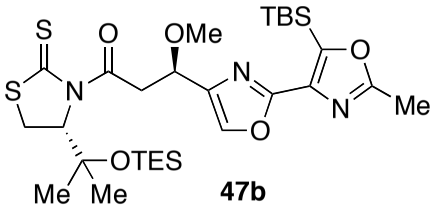




5

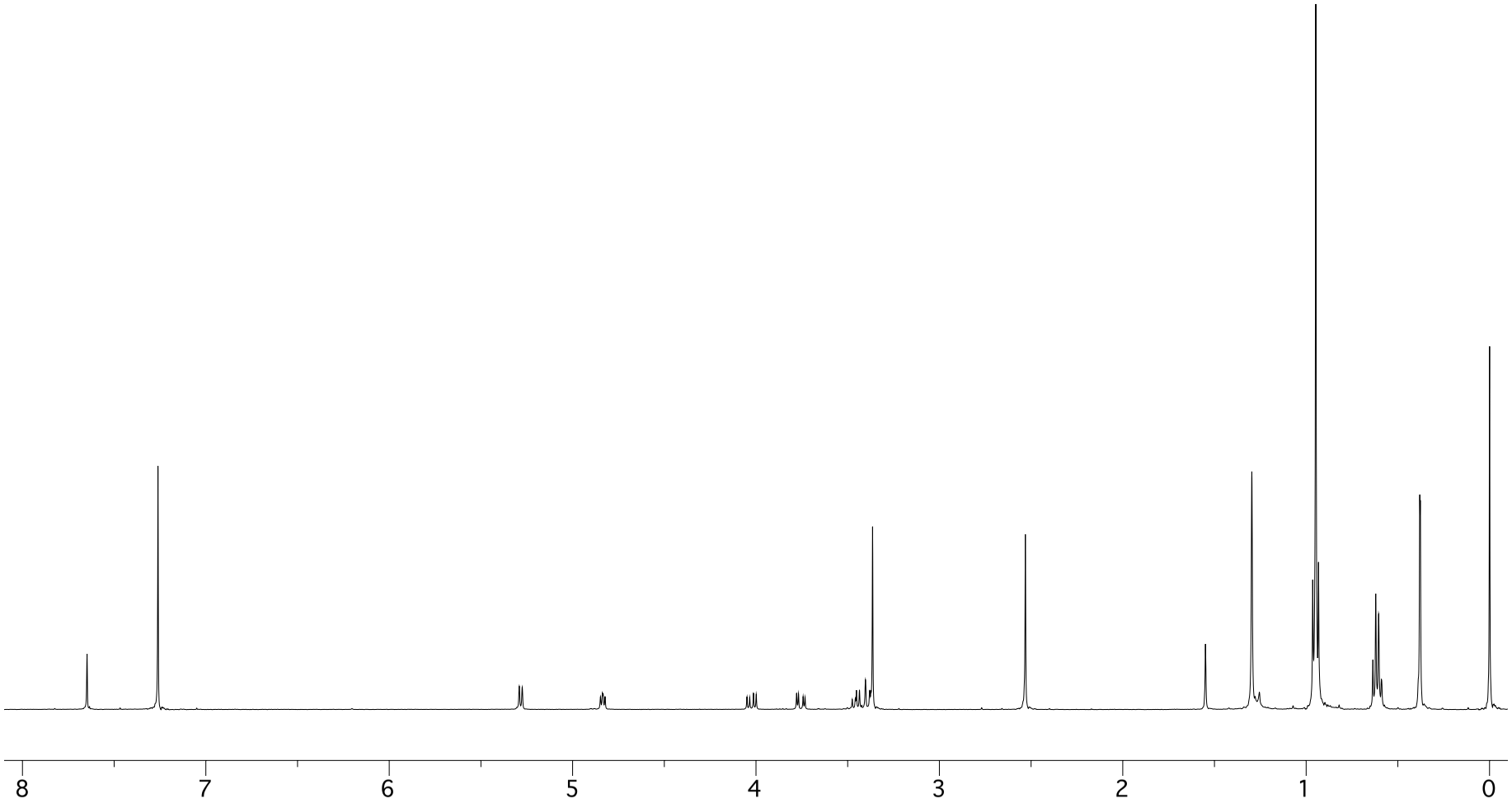
^{13}CNMR: 125 MHz in $CDCl_3$

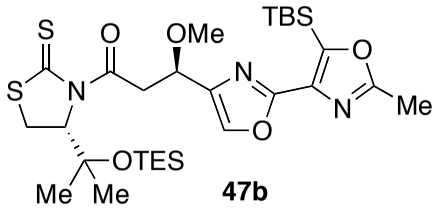




47b

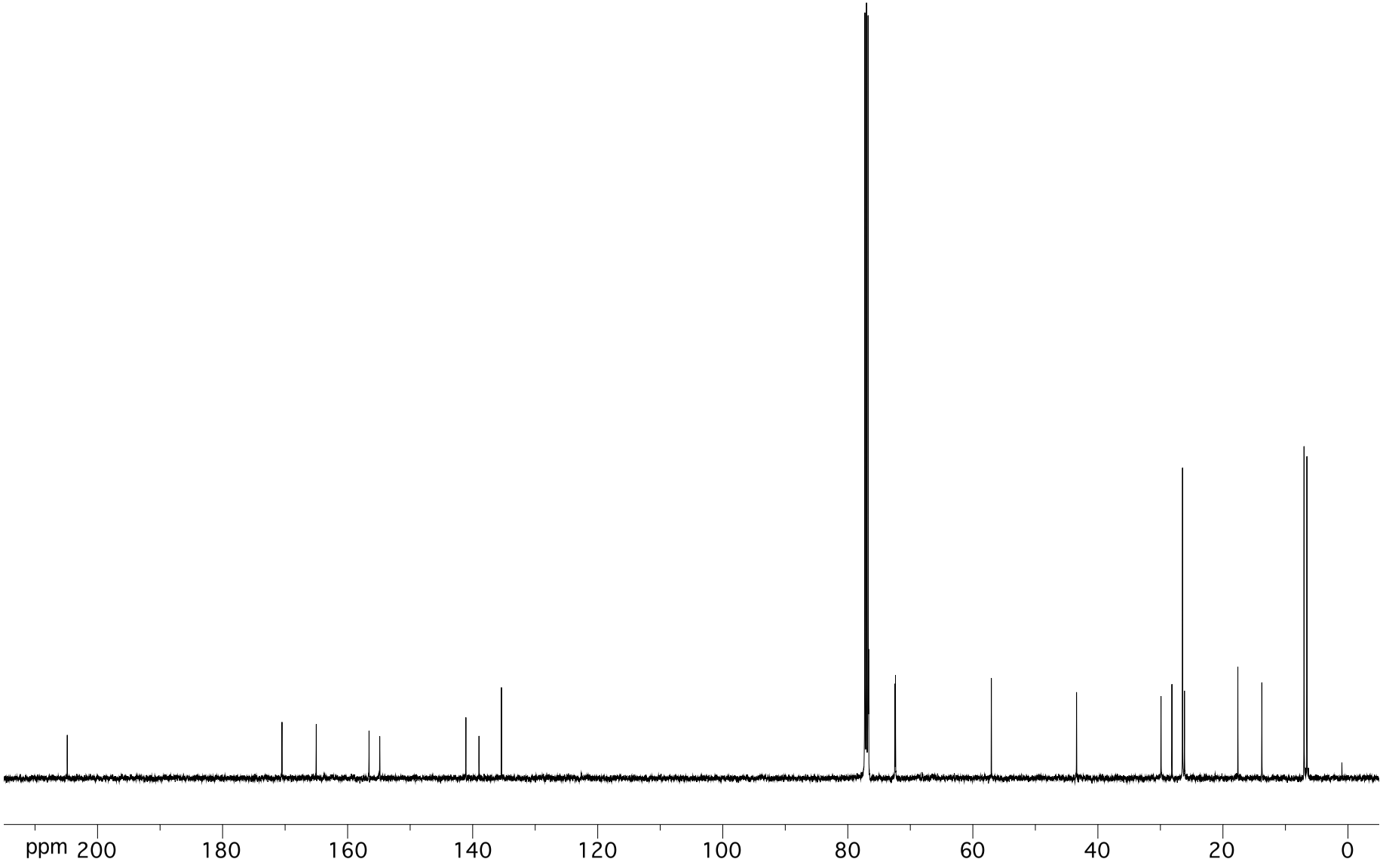
^{1}HNMR: 500 MHz in $CDCl_3$

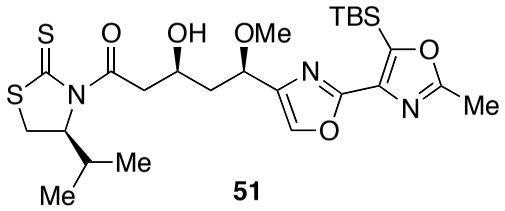




47b

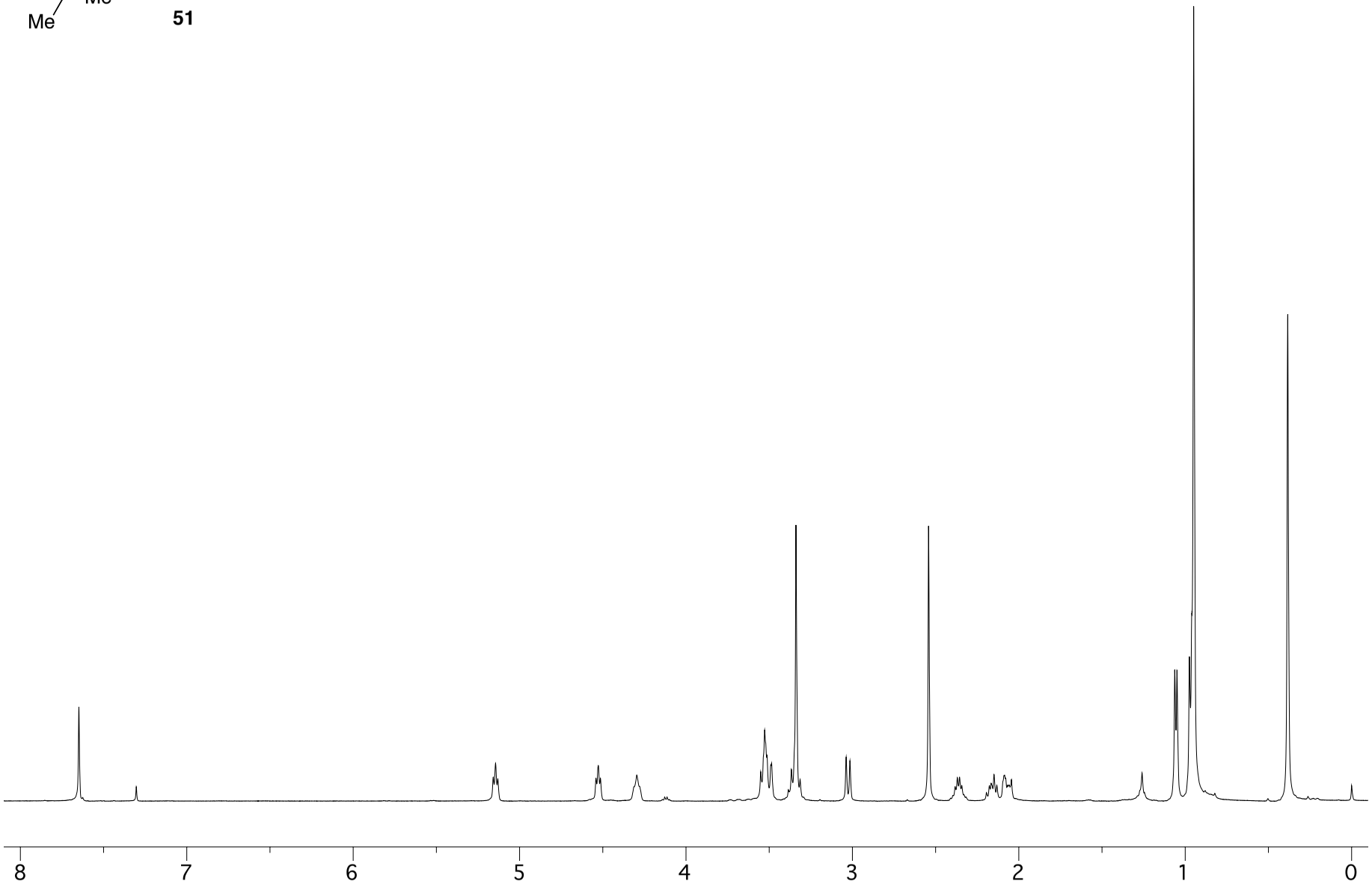
^{13}CNMR: 125 MHz in $CDCl_3$

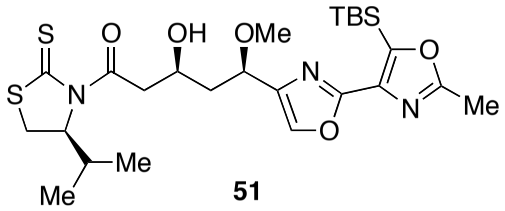




51

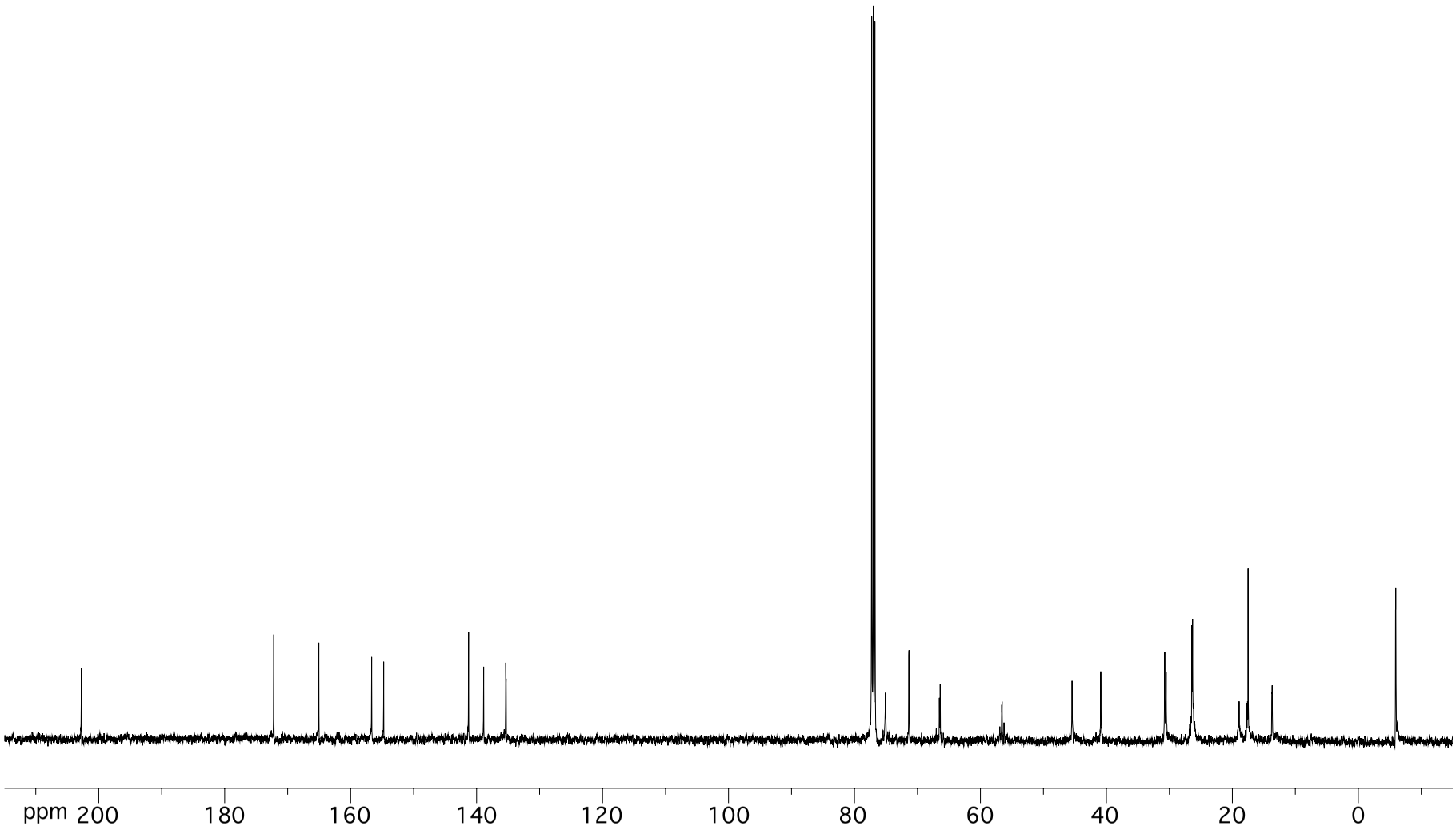
^{1}HNMR: 500 MHz in $CDCl_3$

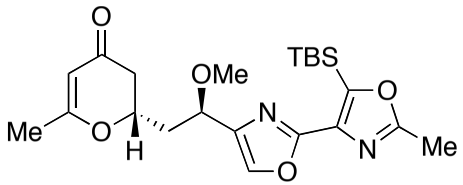




51

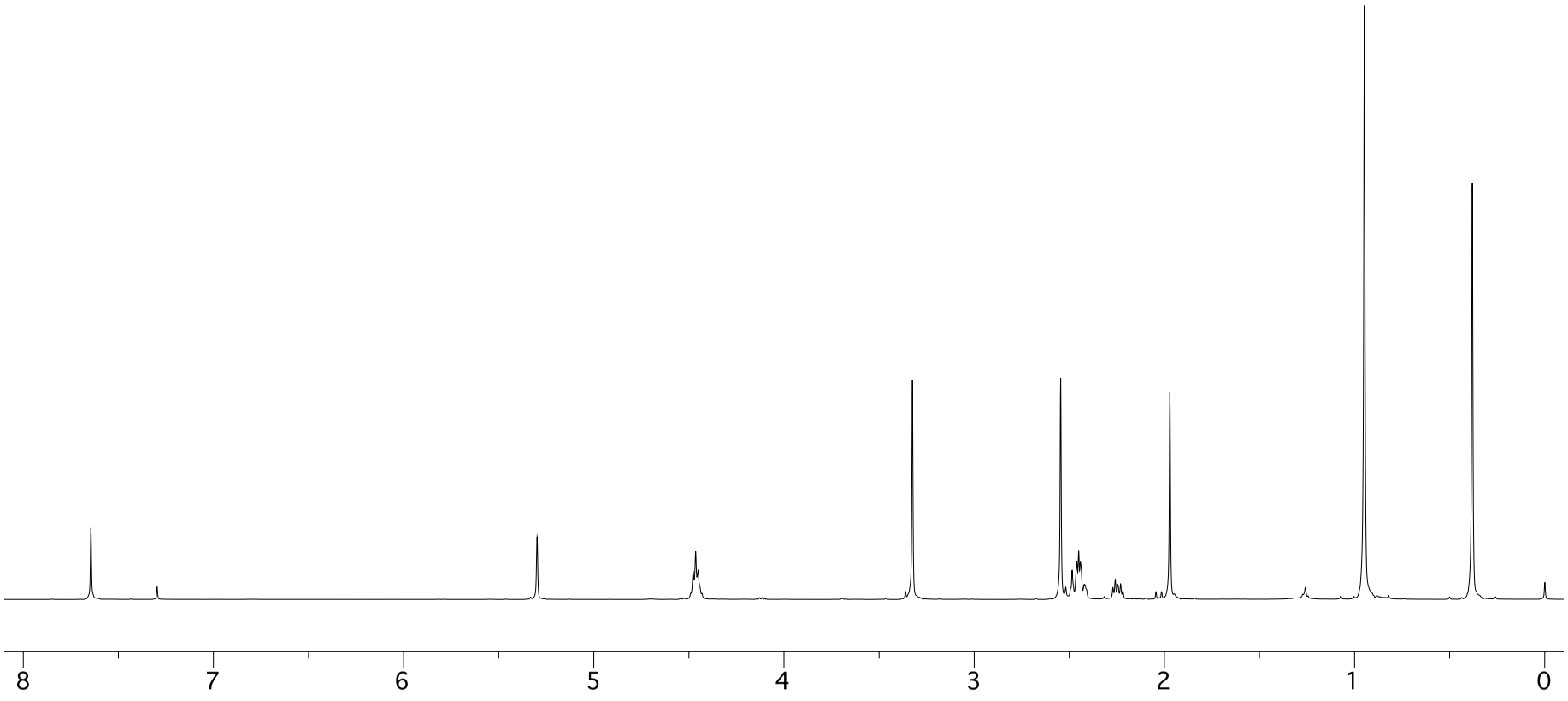
^{13}CNMR: 125 MHz in $CDCl_3$

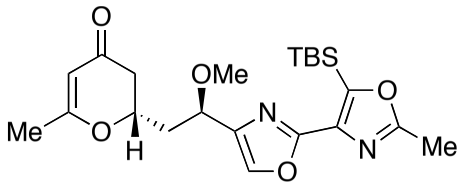




53

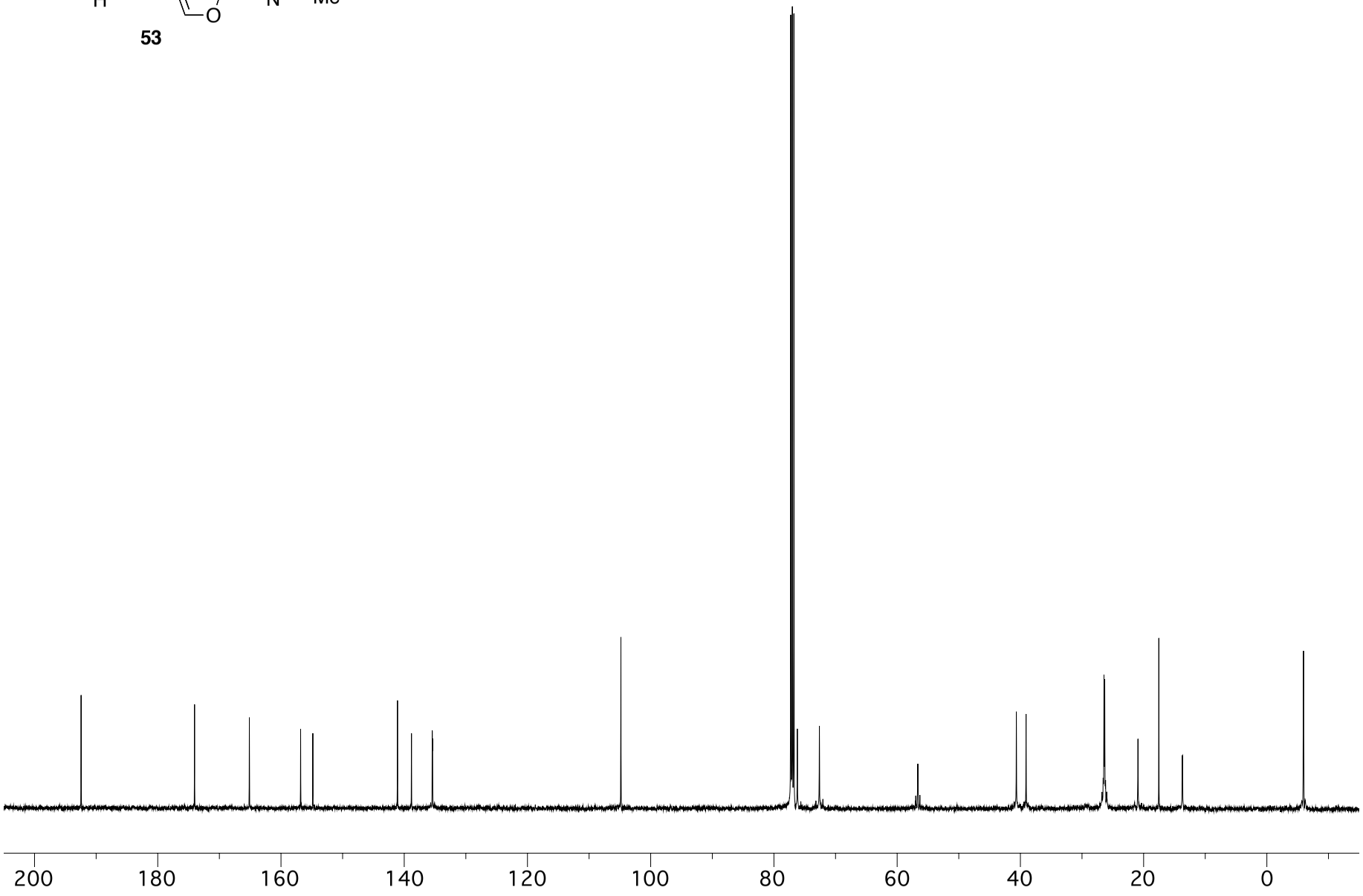
^{1}HNMR: 500 MHz in $CDCl_3$

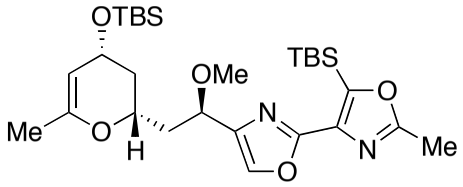




53

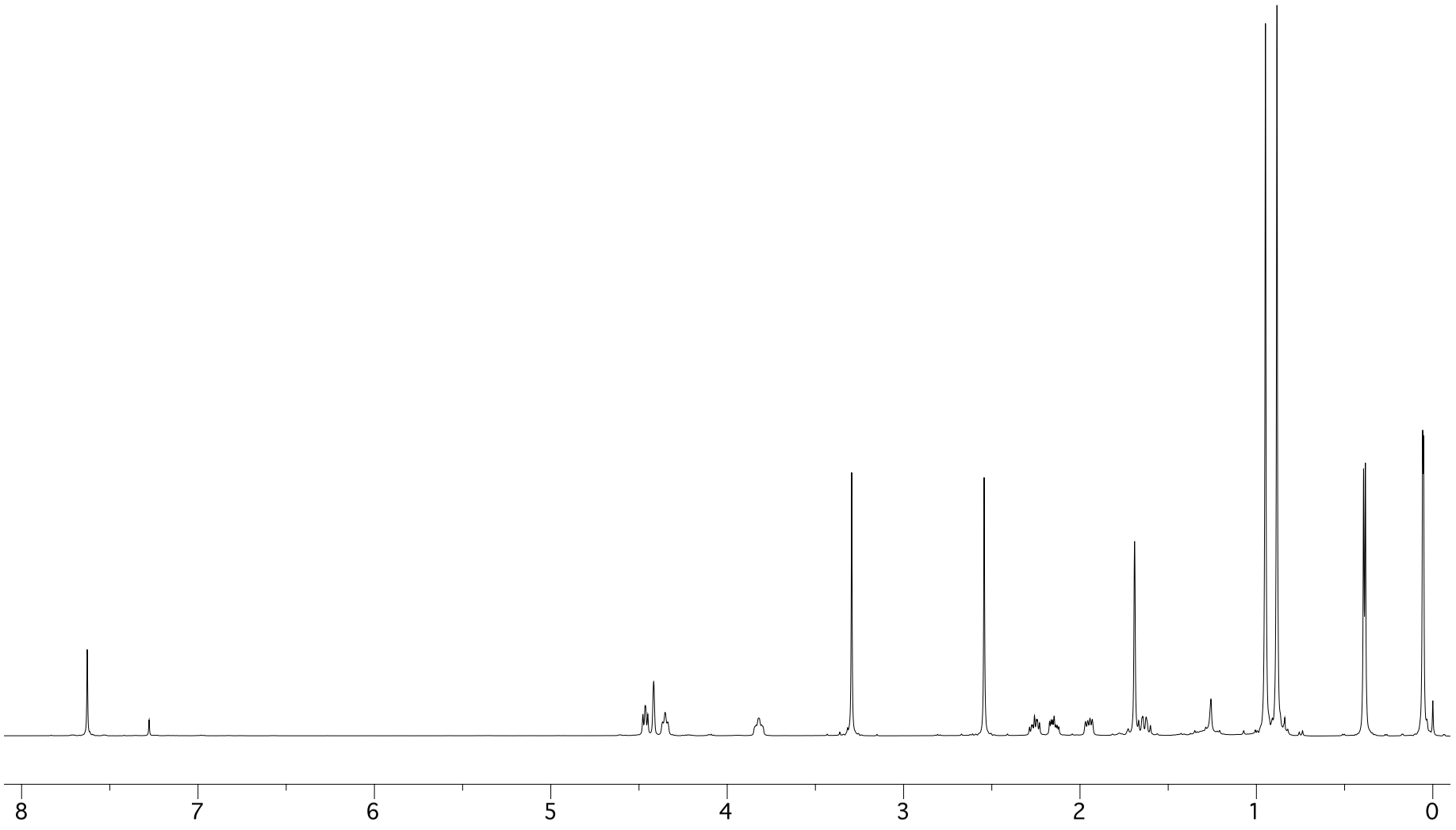
^{13}CNMR: 125 MHz in $CDCl_3$

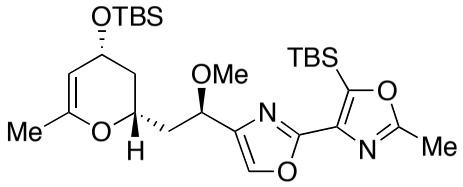




54

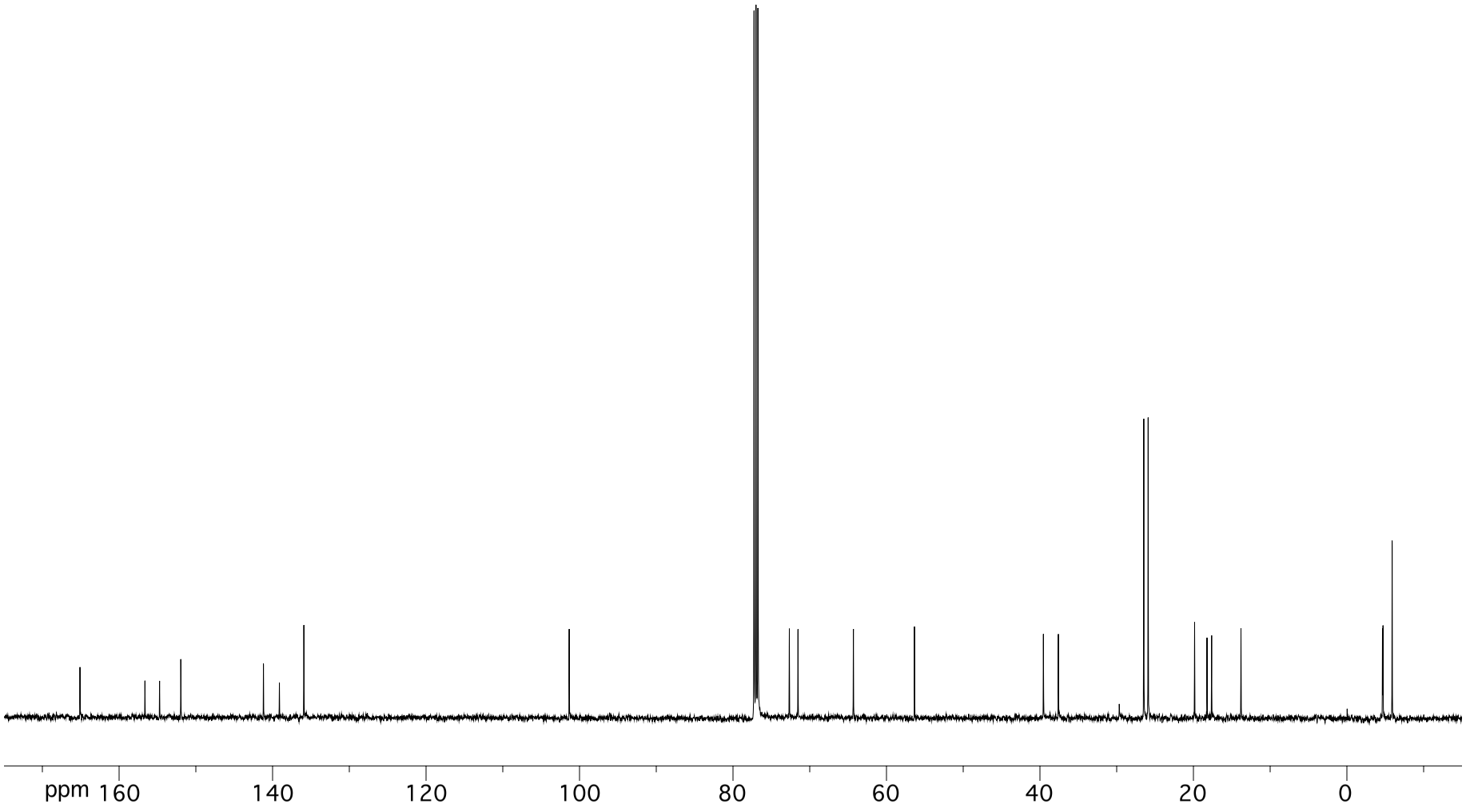
^{1}HNMR: 500 MHz in $CDCl_3$

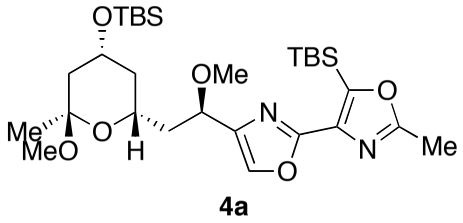




54

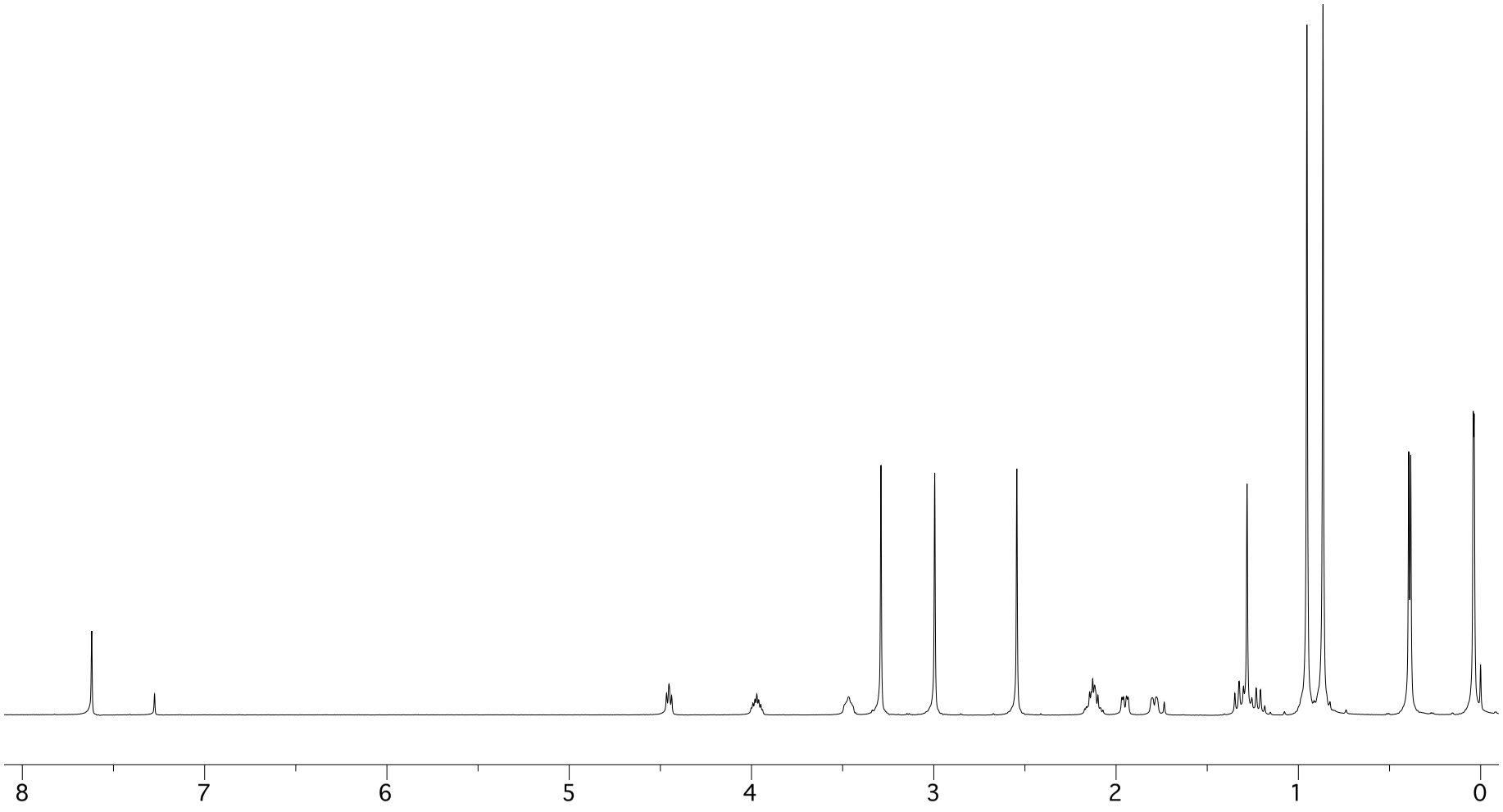
^{13}CNMR: 125 MHz in $CDCl_3$

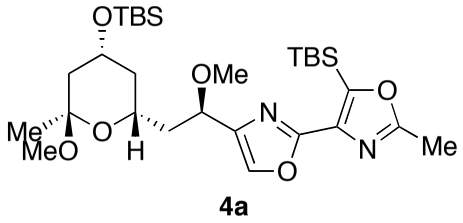




4a

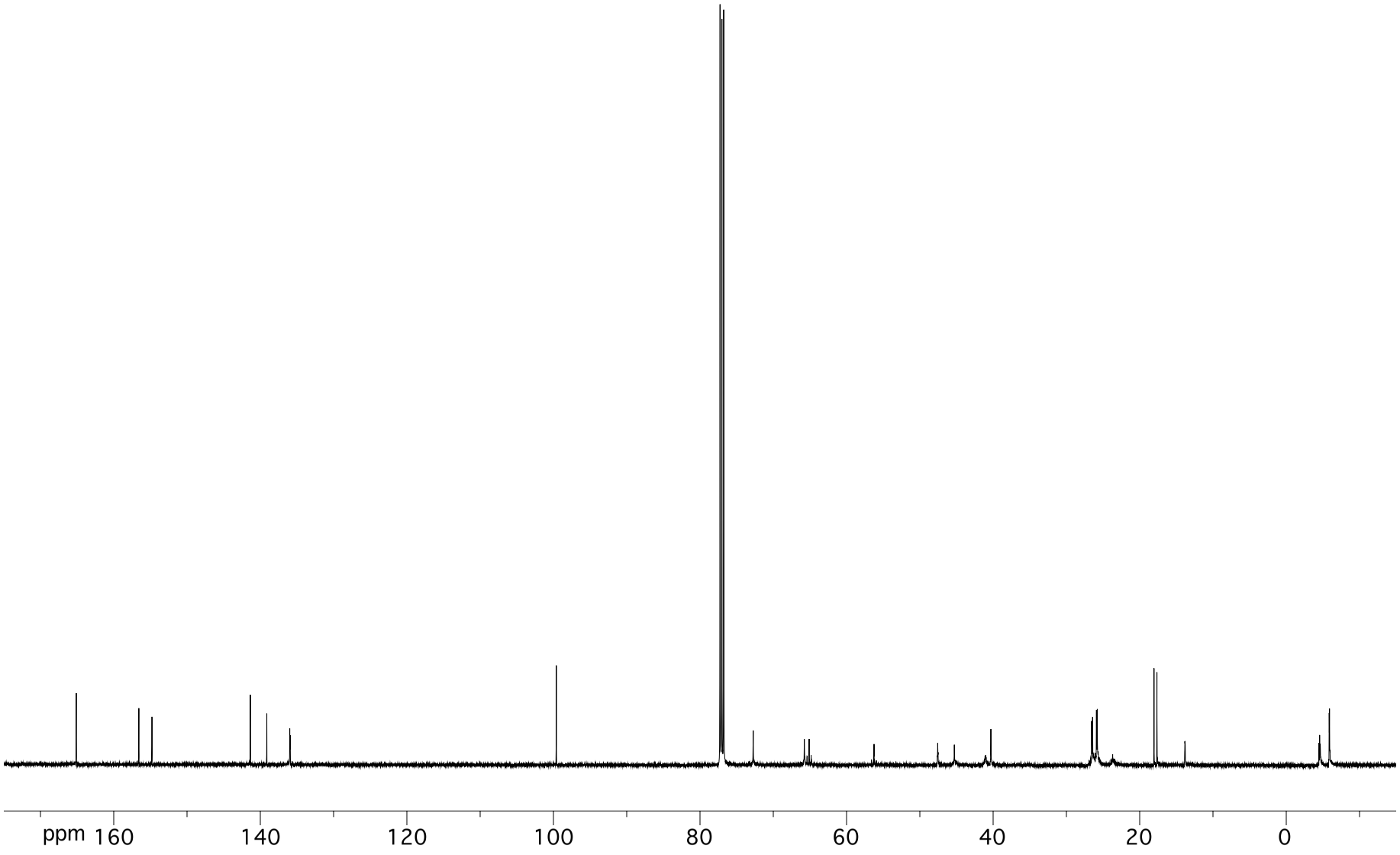
^{1}HNMR: 500 MHz in $CDCl_3$

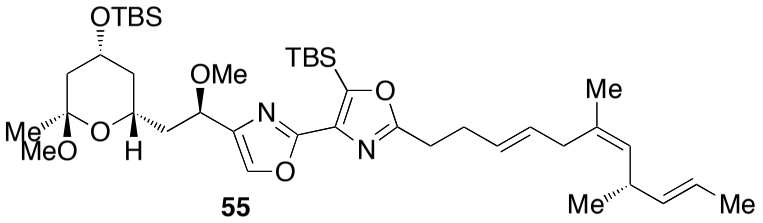




4a

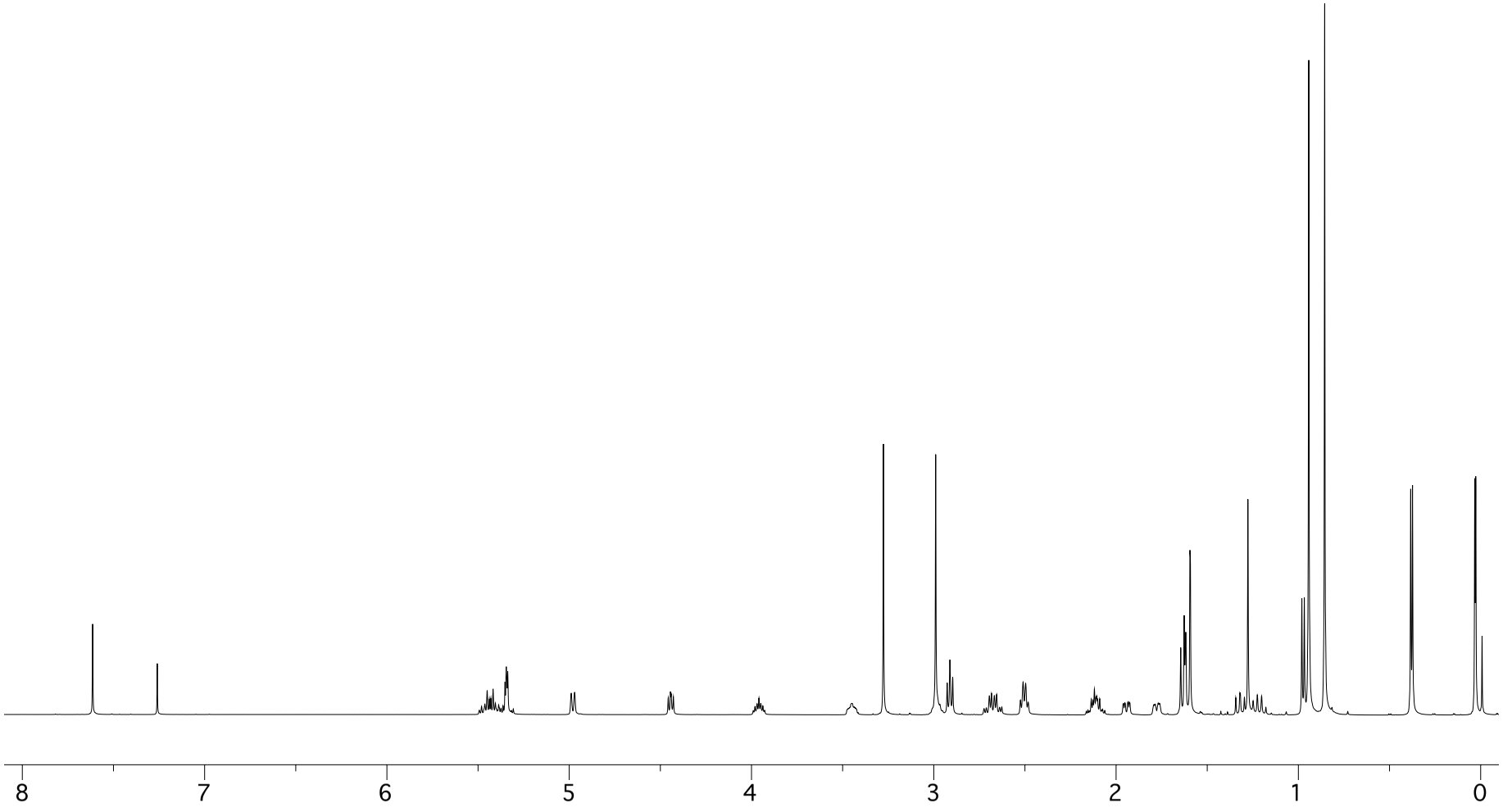
^{13}CNMR: 125 MHz in $CDCl_3$

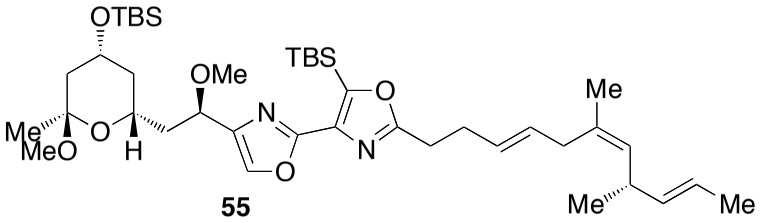




55

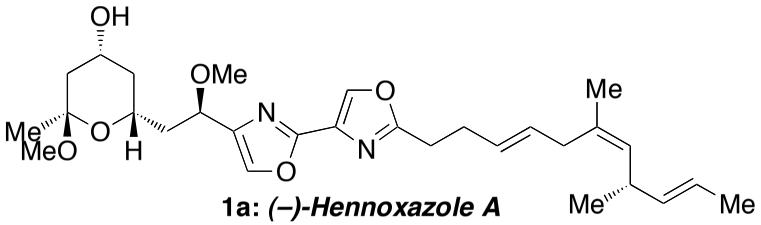
^{1}HNMR: 500 MHz in $CDCl_3$





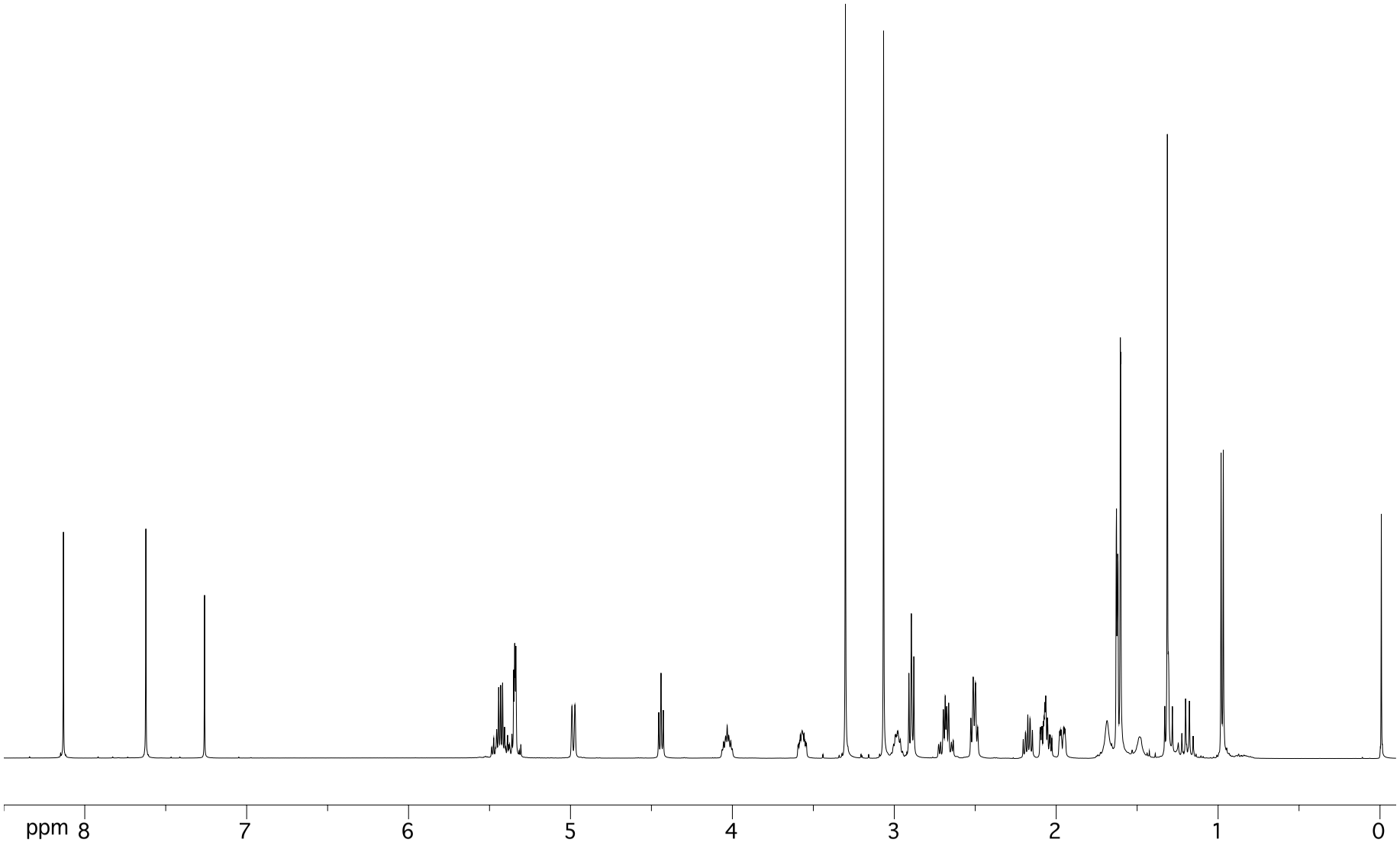
55

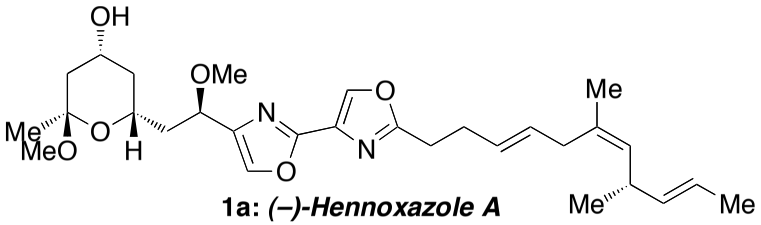
^{13}CNMR: 125 MHz in $CDCl_3$



1a: *(–)-Hennoxazole A*

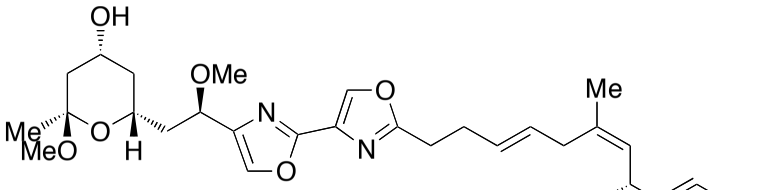
^{1}HNMR: 500 MHz in $CDCl_3$





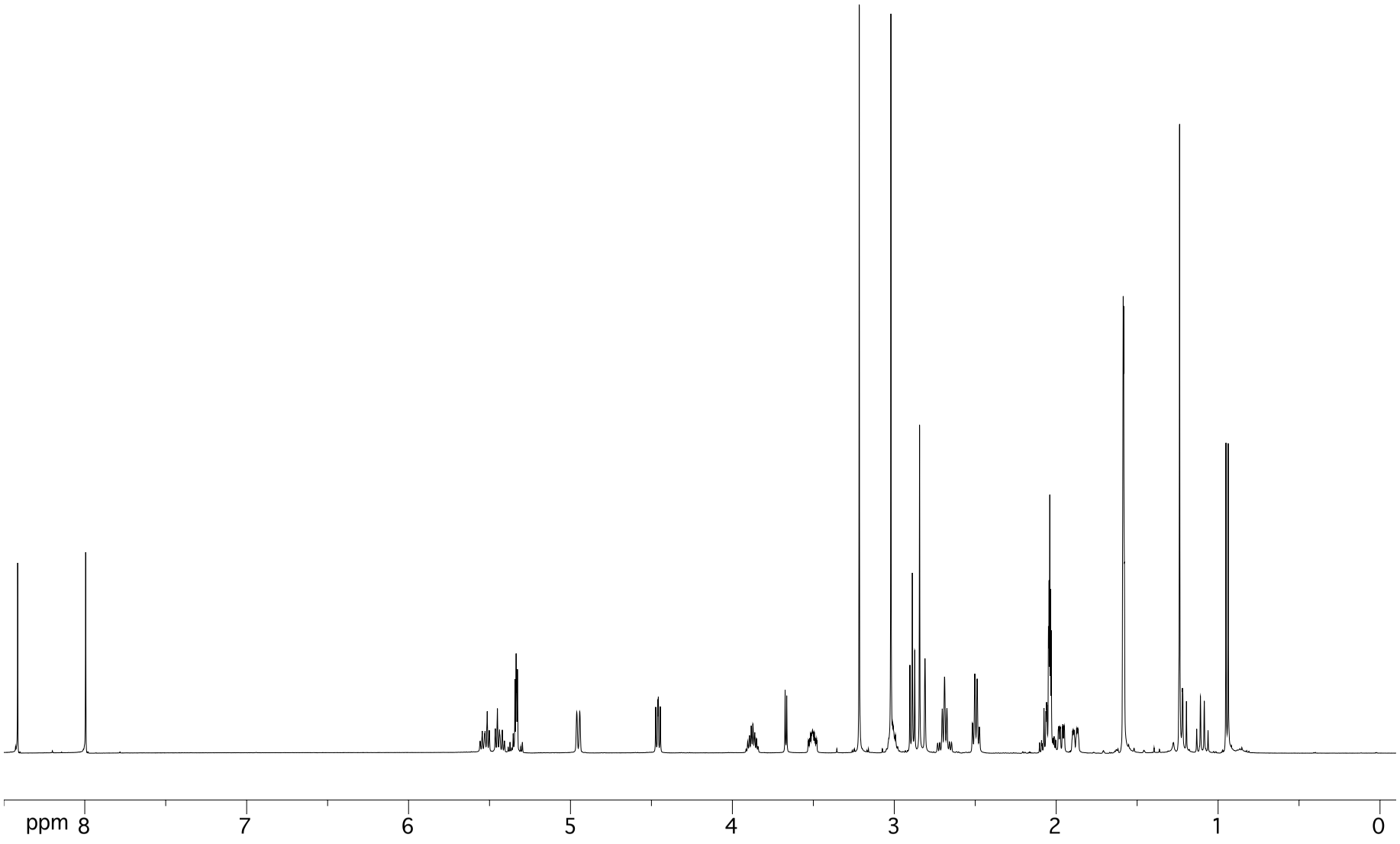
1a: *(–)-Hennoxazole A*

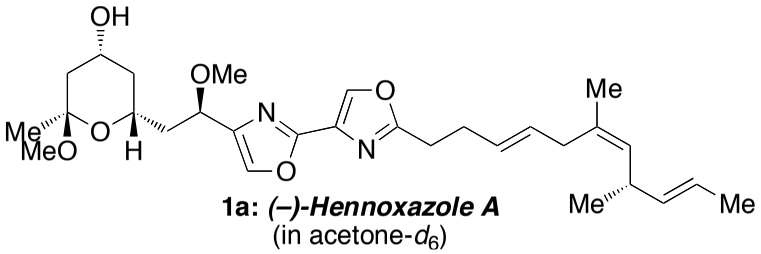
^{13}CNMR: 125 MHz in $CDCl_3$



1a: *(–)-Hennoxazole A*
(in acetone-d_6)

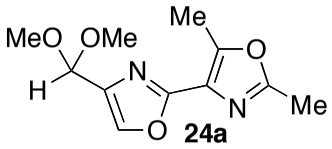
^{1}HNMR: 500 MHz in acetone-d_6





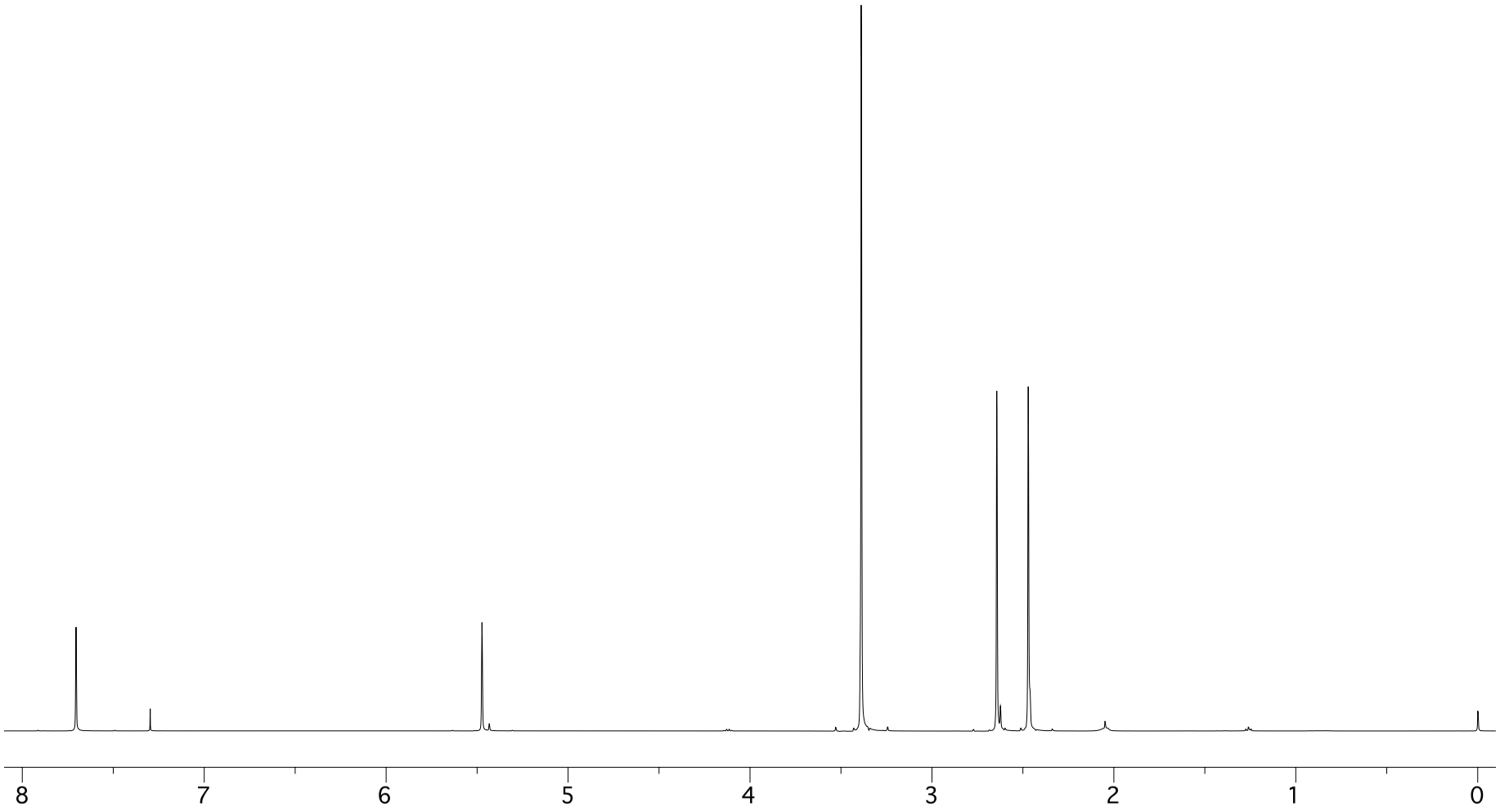
1a: *(–)-Hennoxazole A*
(in acetone-d_6)

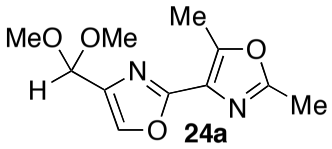
^{13}C NMR: 125 MHz in acetone-d_6



24a

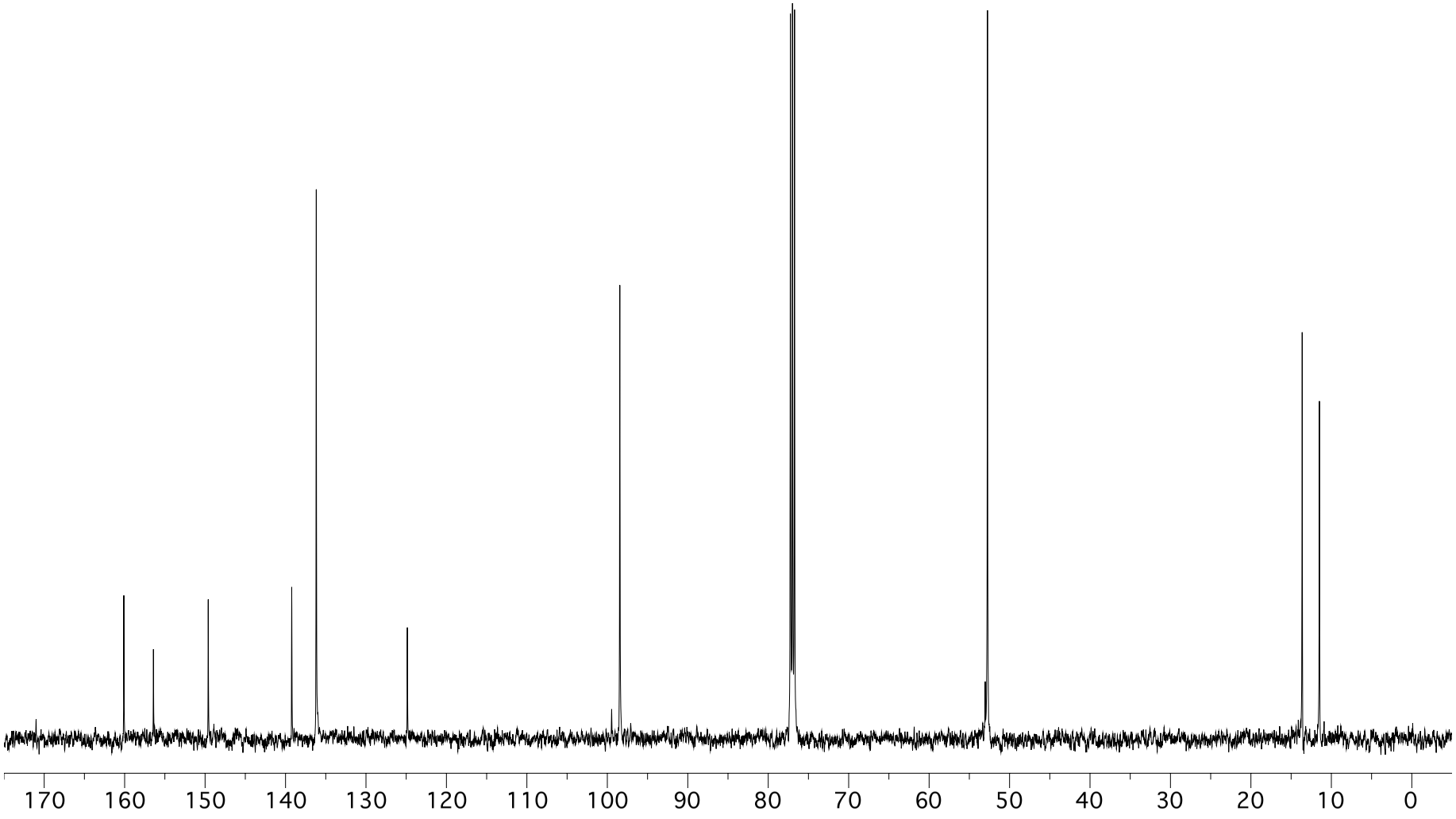
^{1}HNMR: 500 MHz in $CDCl_3$

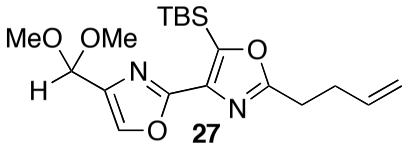




24a

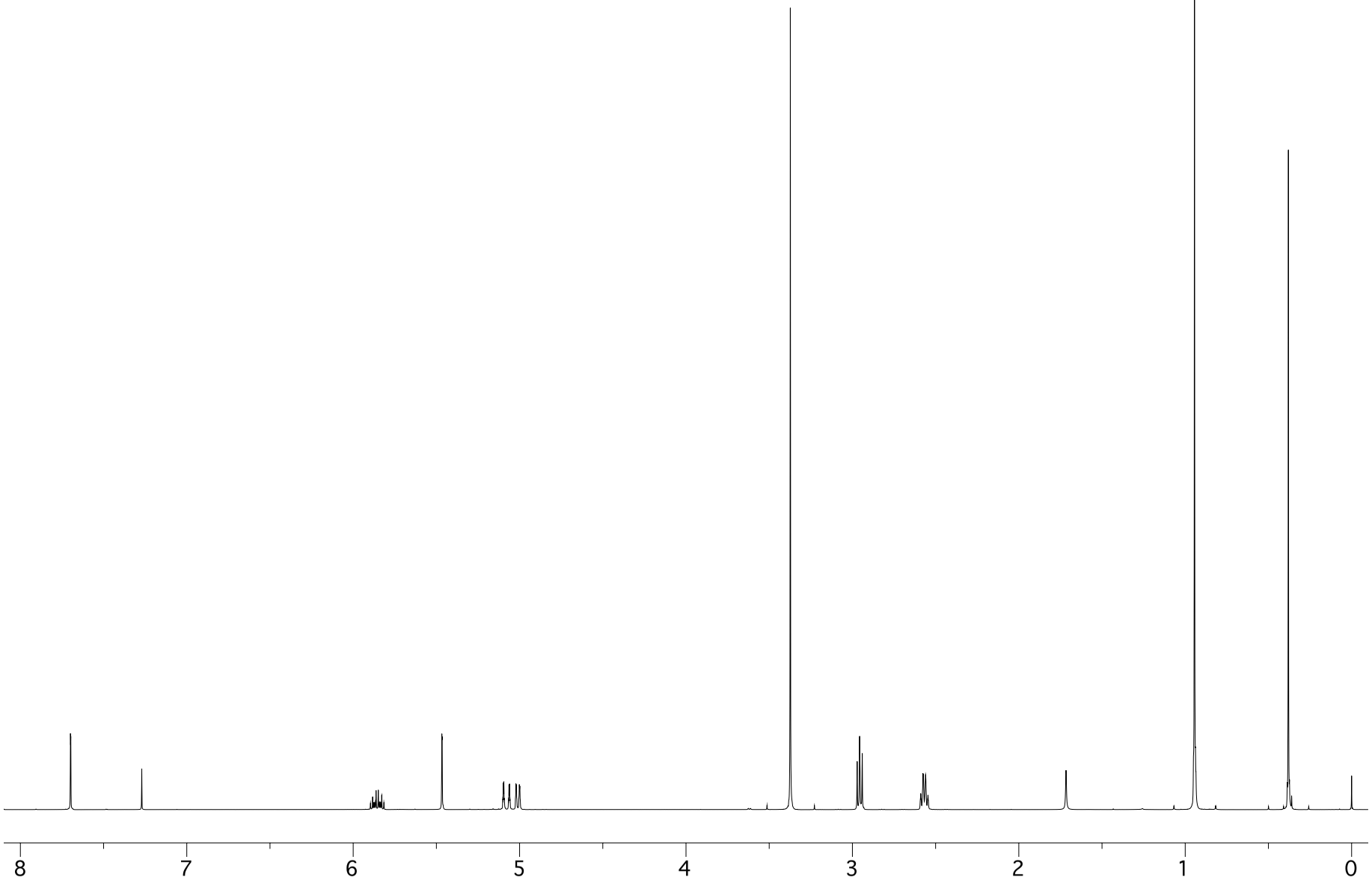
^{13}CNMR: 125 MHz in $CDCl_3$

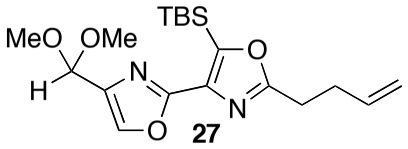




27

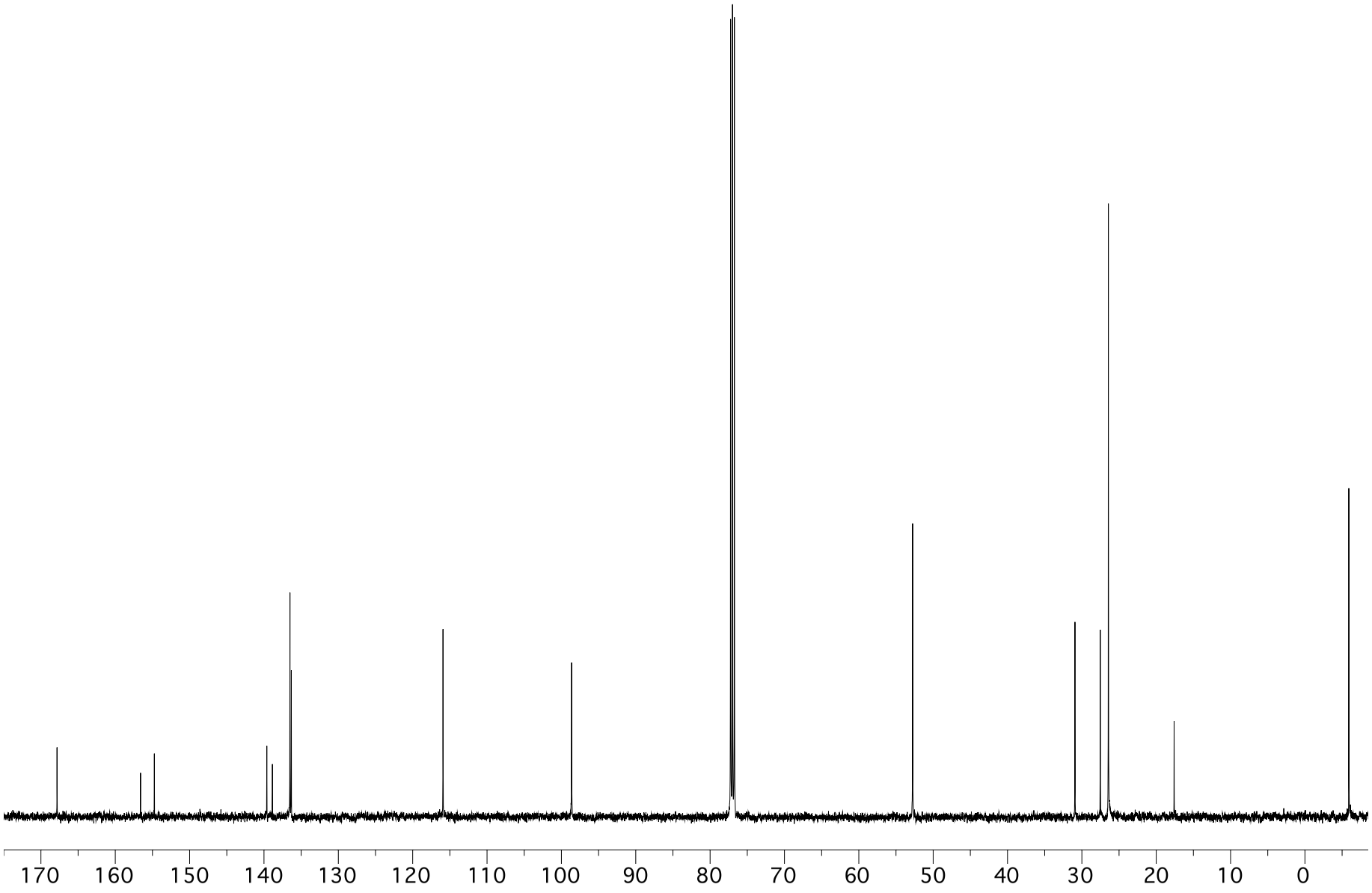
^{1}HNMR: 500 MHz in $CDCl_3$

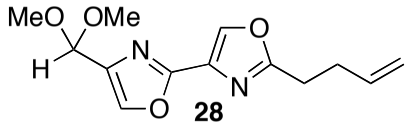




27

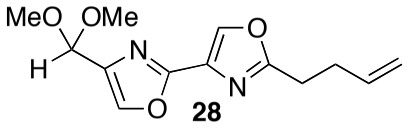
^{13}CNMR: 125 MHz in $CDCl_3$





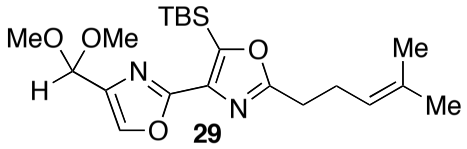
28

^{1}HNMR: 500 MHz in $CDCl_3$



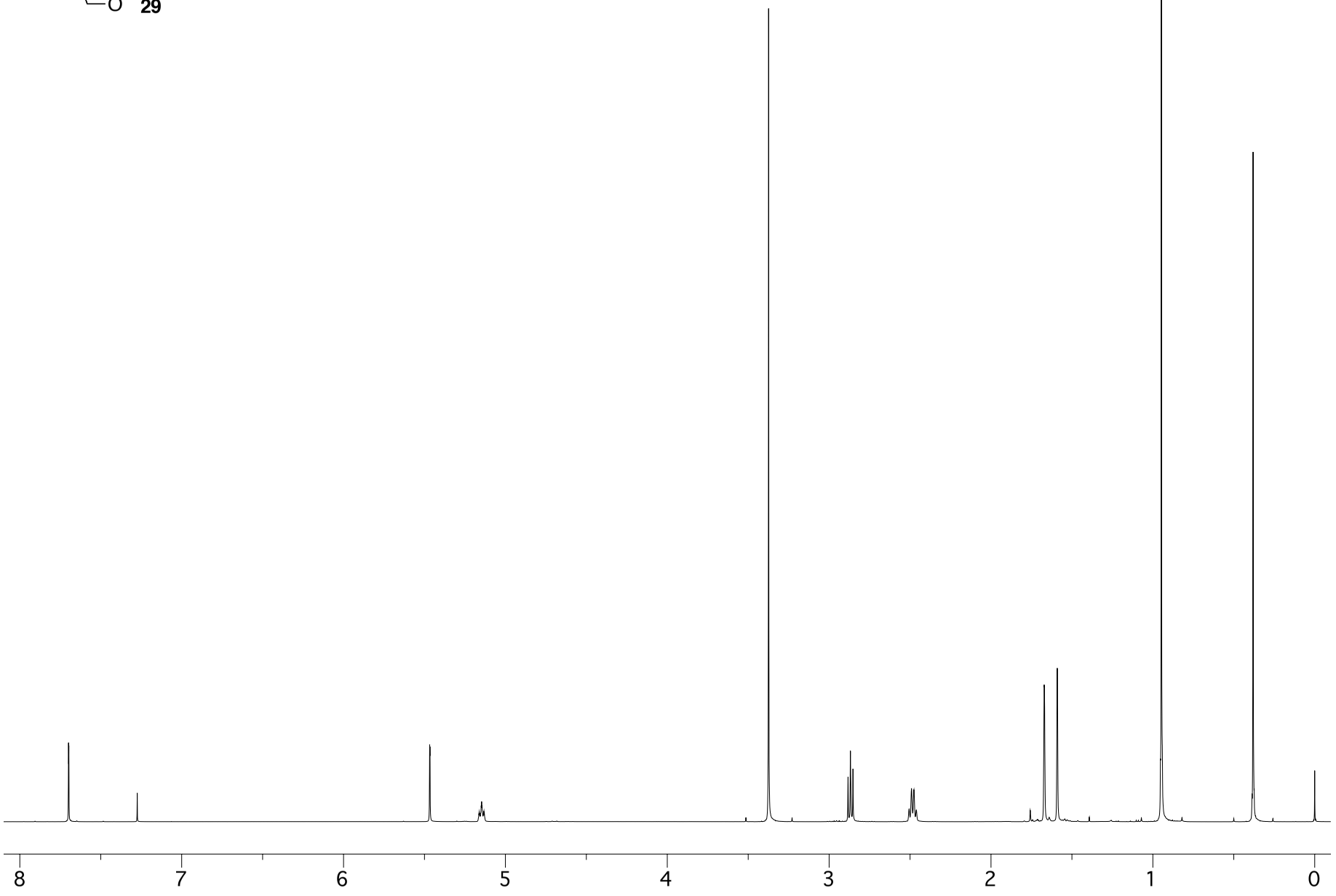
28

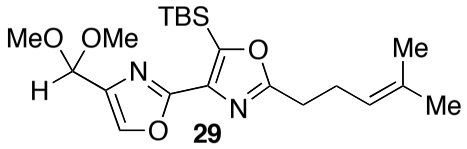
^{13}CNMR: 125 MHz in $CDCl_3$



29

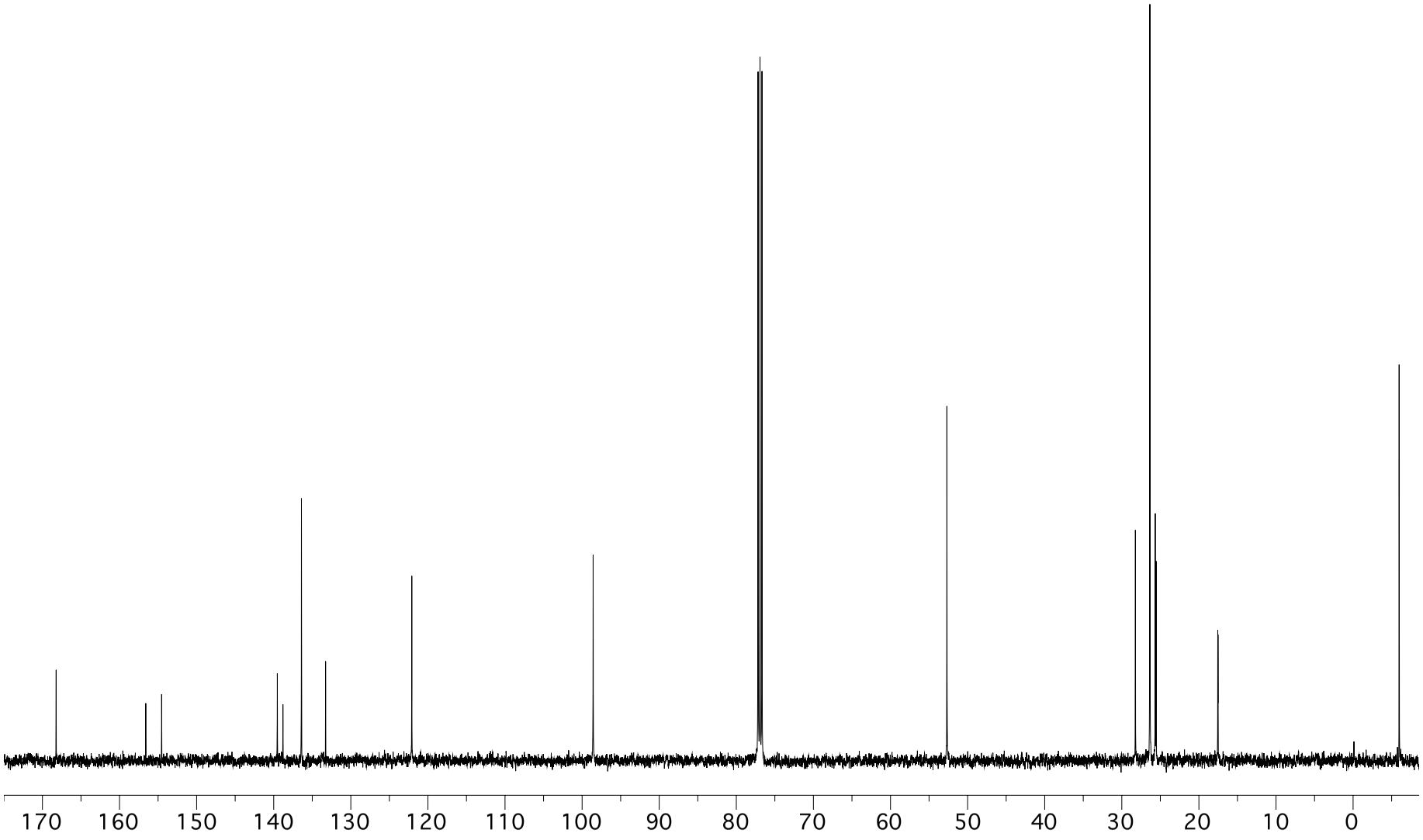
^{1}HNMR: 500 MHz in $CDCl_3$

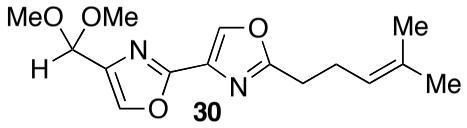




29

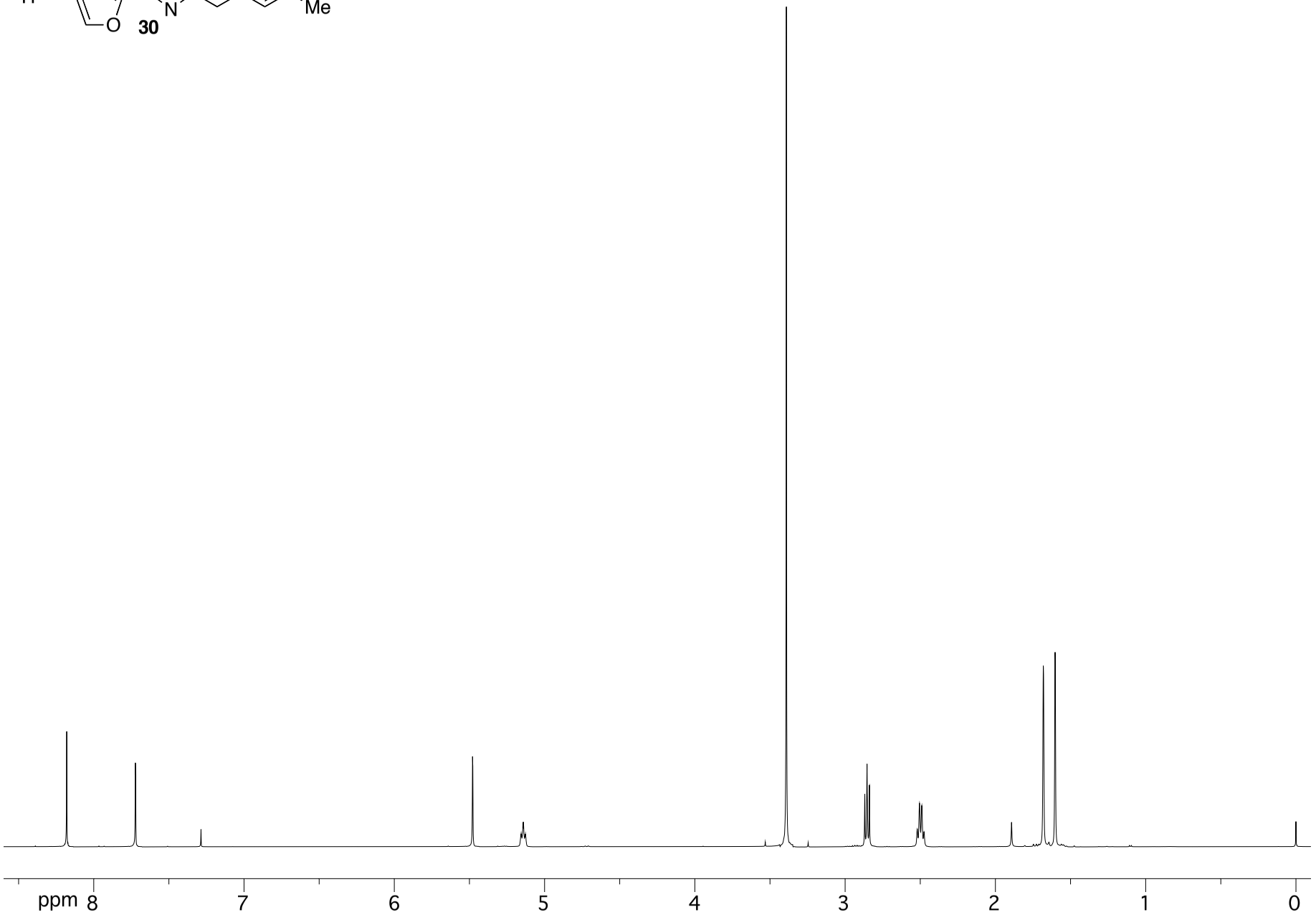
^{13}CNMR: 125 MHz in $CDCl_3$

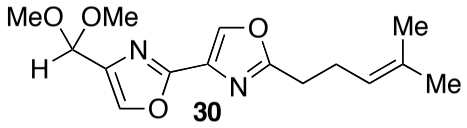




30

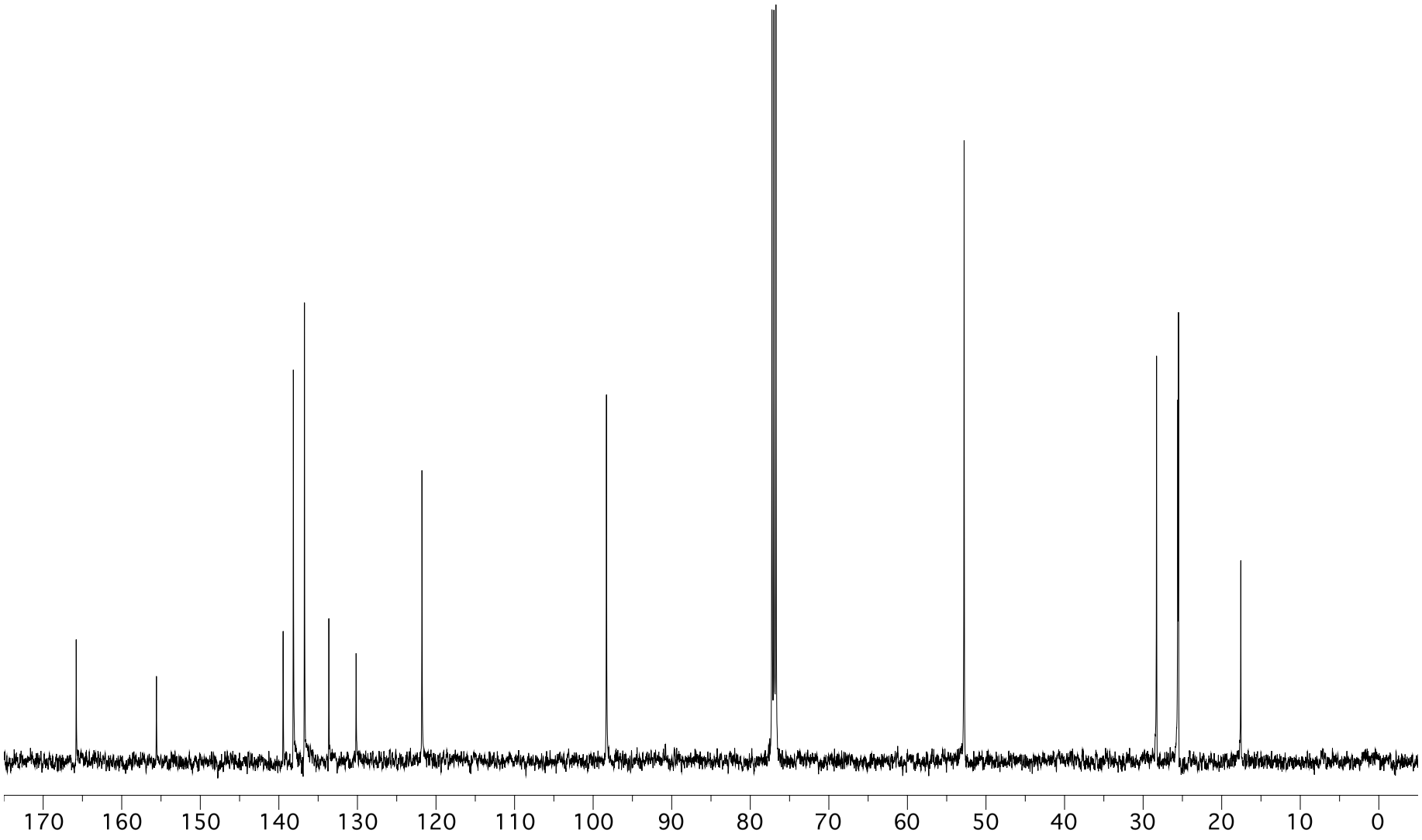
^{1}HNMR: 500 MHz in $CDCl_3$

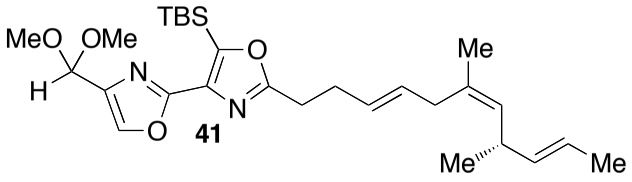




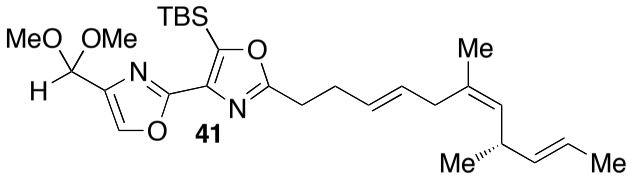
30

^{13}CNMR: 125 MHz in $CDCl_3$

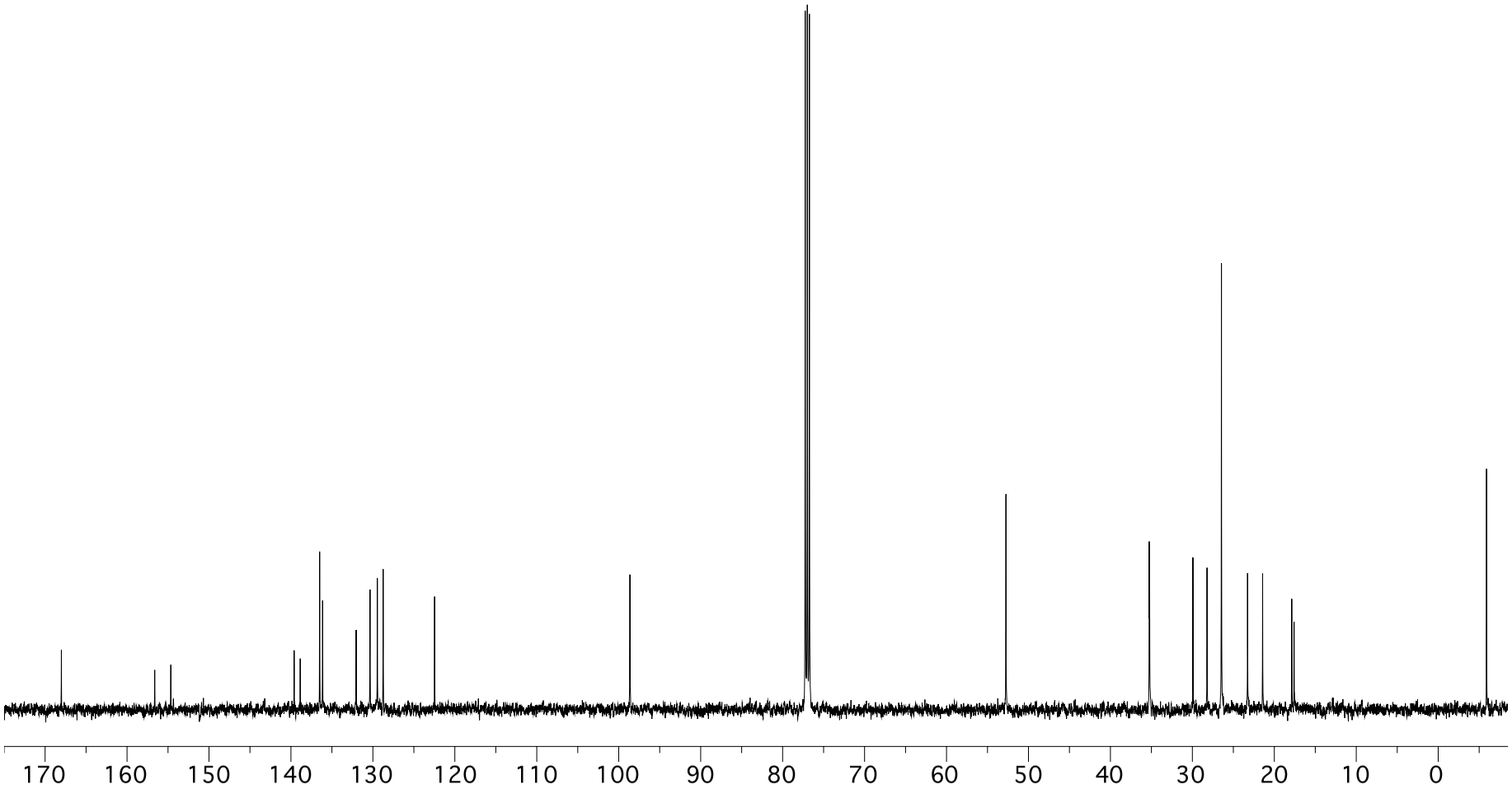


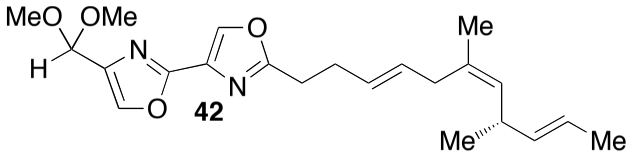


^{1}HNMR: 500 MHz in $CDCl_3$



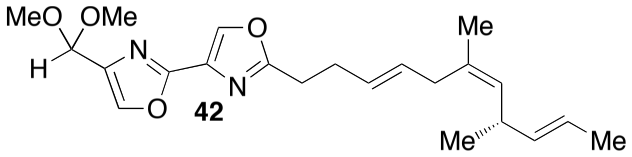
^{13}CNMR: 125 MHz in $CDCl_3$





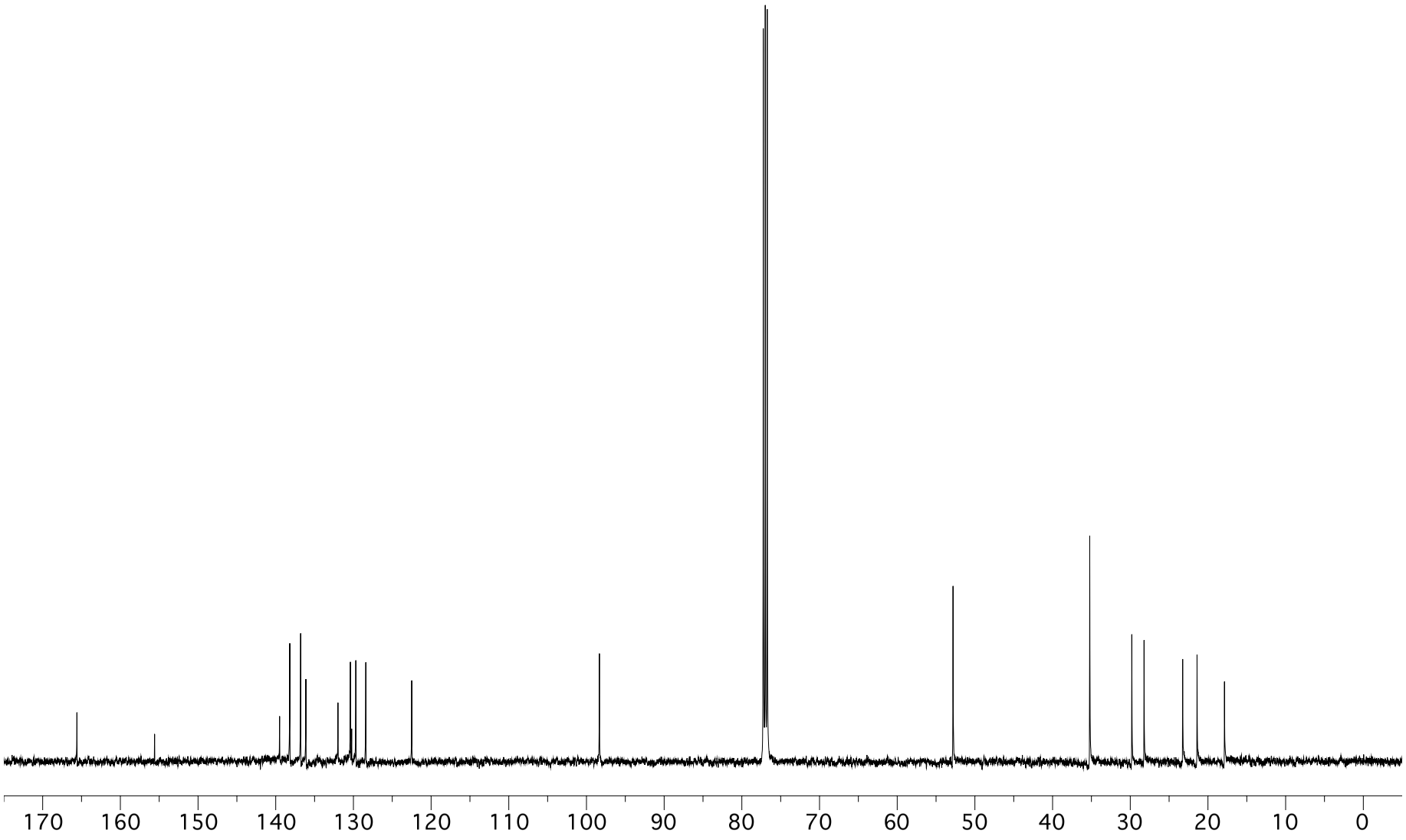
42

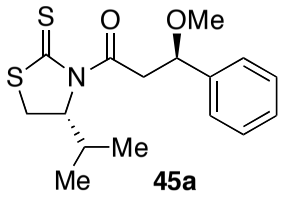
^{1}HNMR: 500 MHz in $CDCl_3$



42

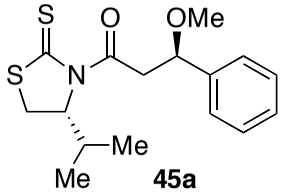
^{13}CNMR: 125 MHz in $CDCl_3$





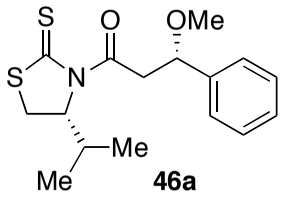
45a

^{1}HNMR: 500 MHz in $CDCl_3$



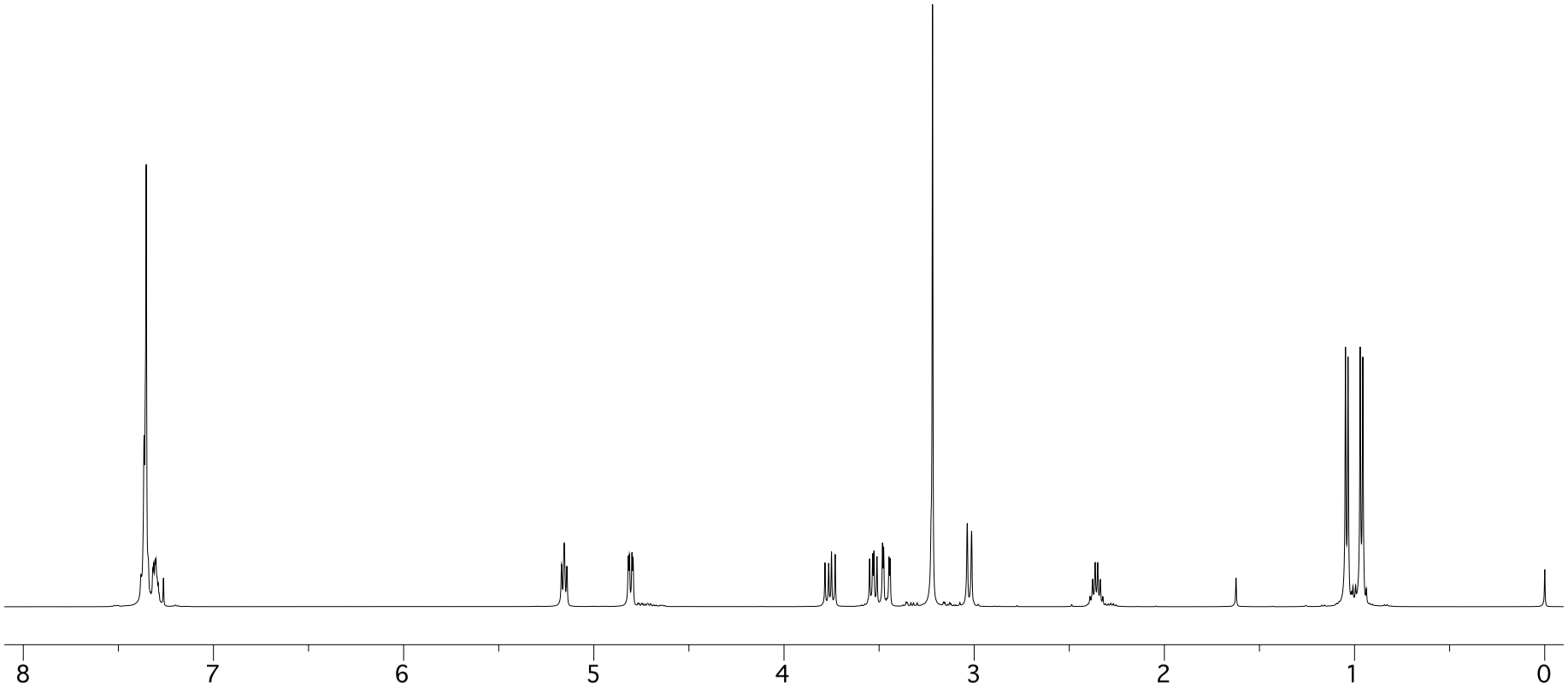
45a

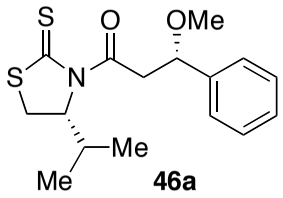
^{13}CNMR: 125 MHz in $CDCl_3$



46a

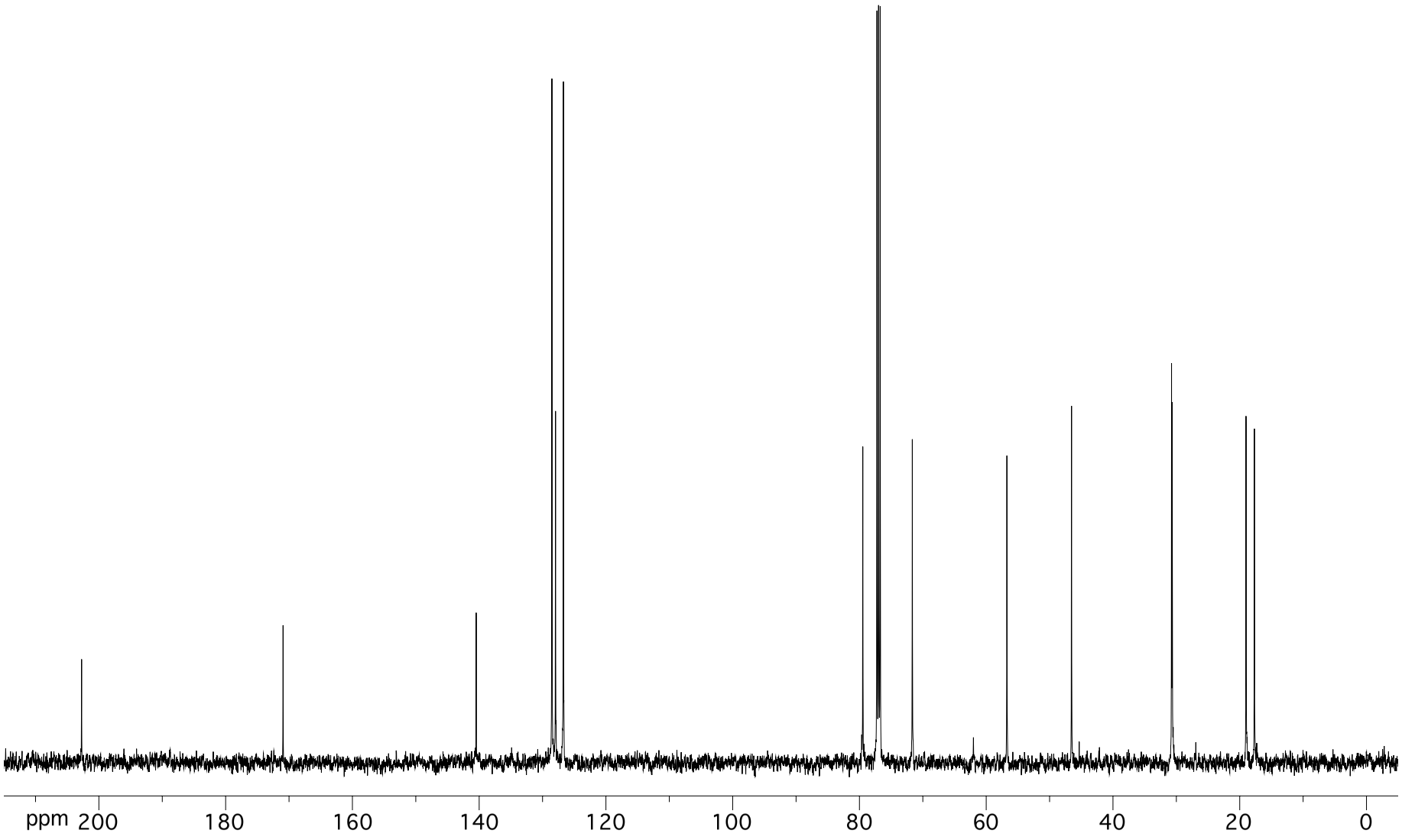
^{1}HNMR: 500 MHz in $CDCl_3$

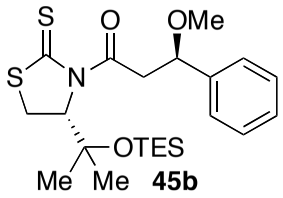




46a

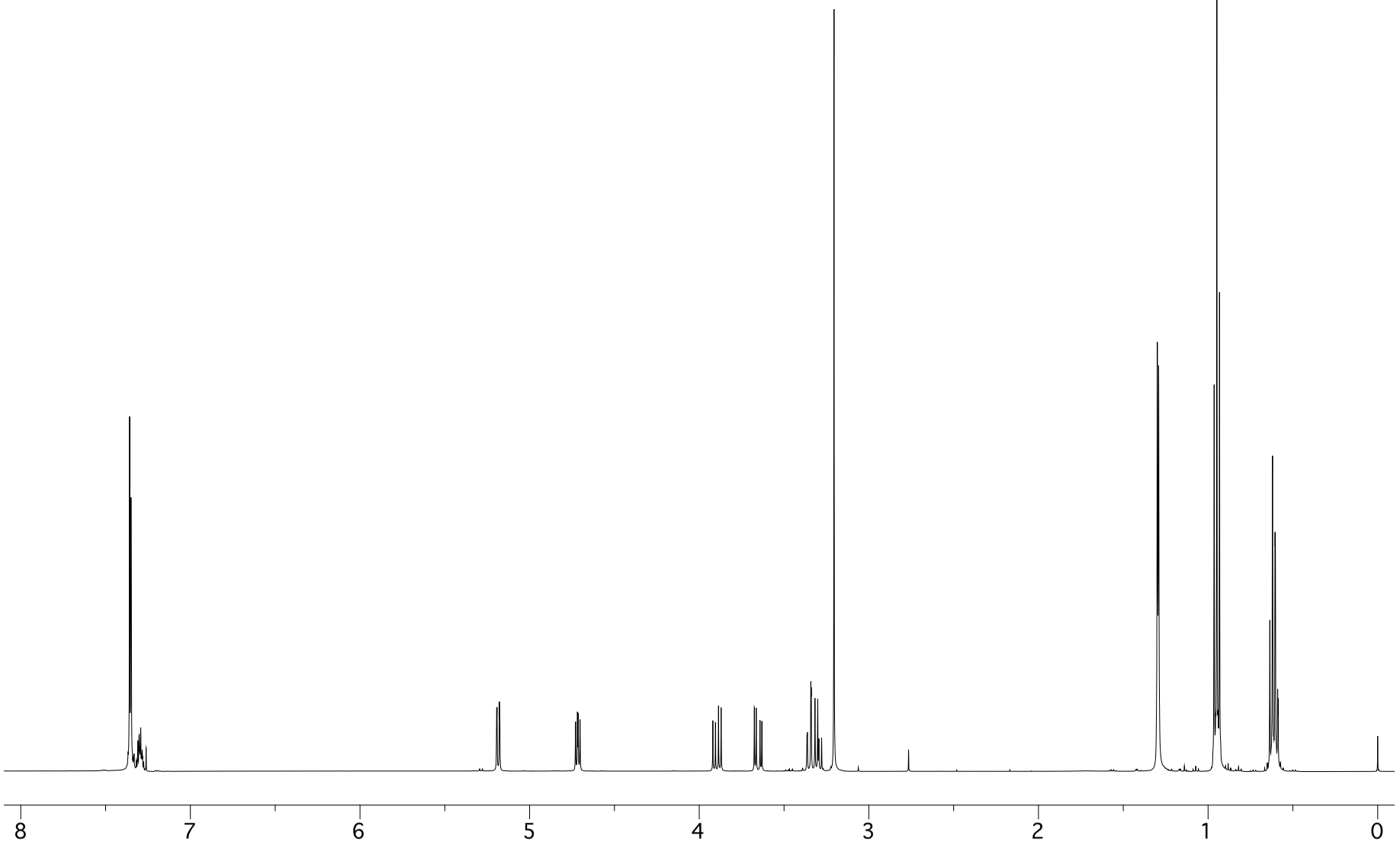
^{13}CNMR: 125 MHz in $CDCl_3$

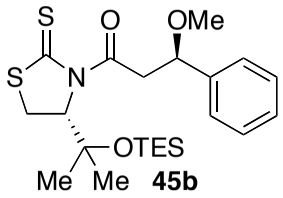




45b

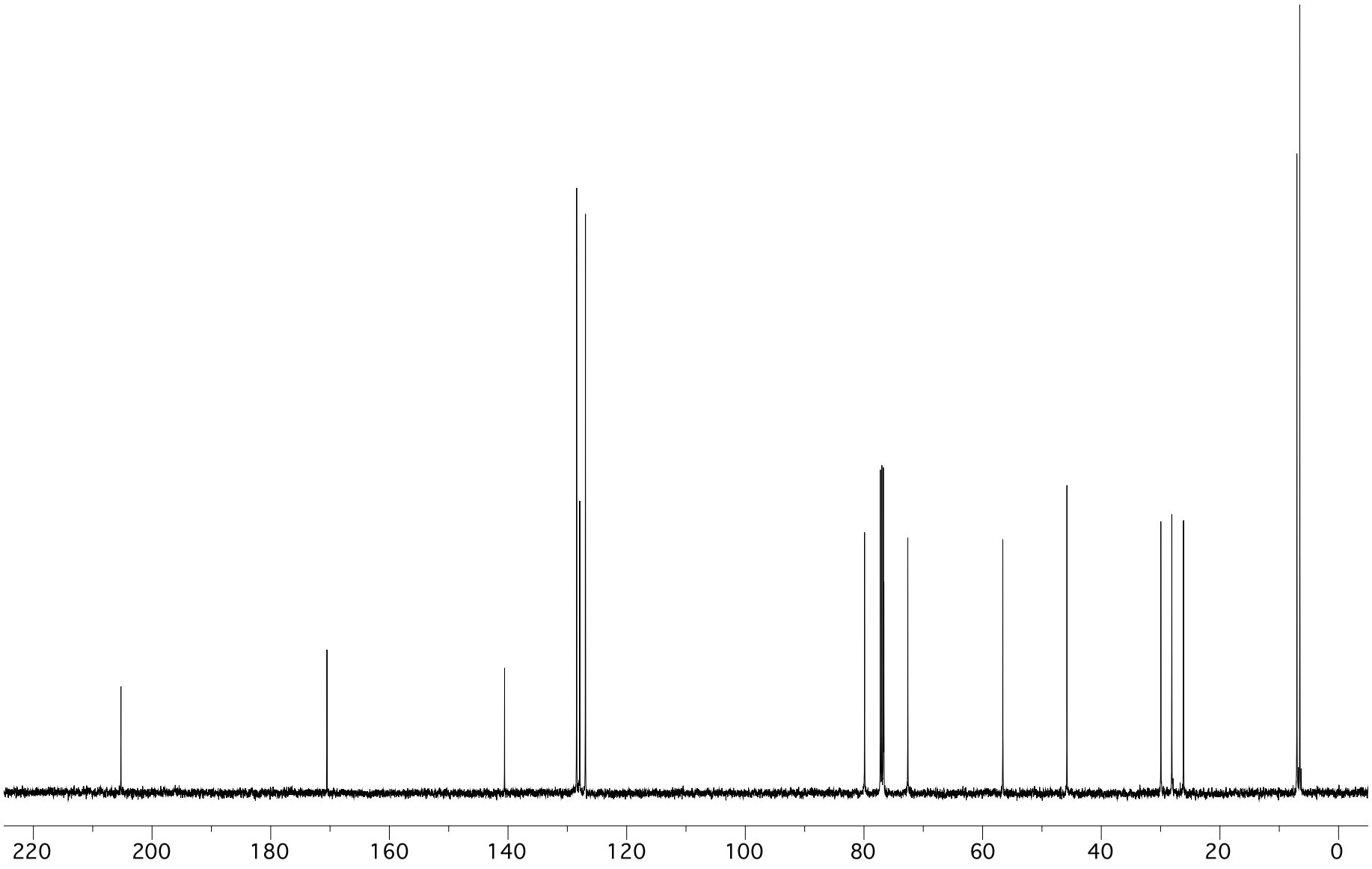
^{1}HNMR: 500 MHz in $CDCl_3$

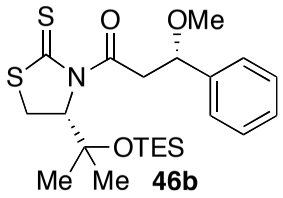




45b

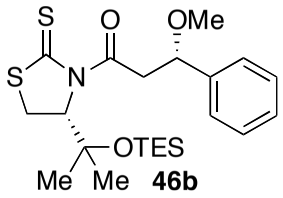
^{13}CNMR: 125 MHz in $CDCl_3$





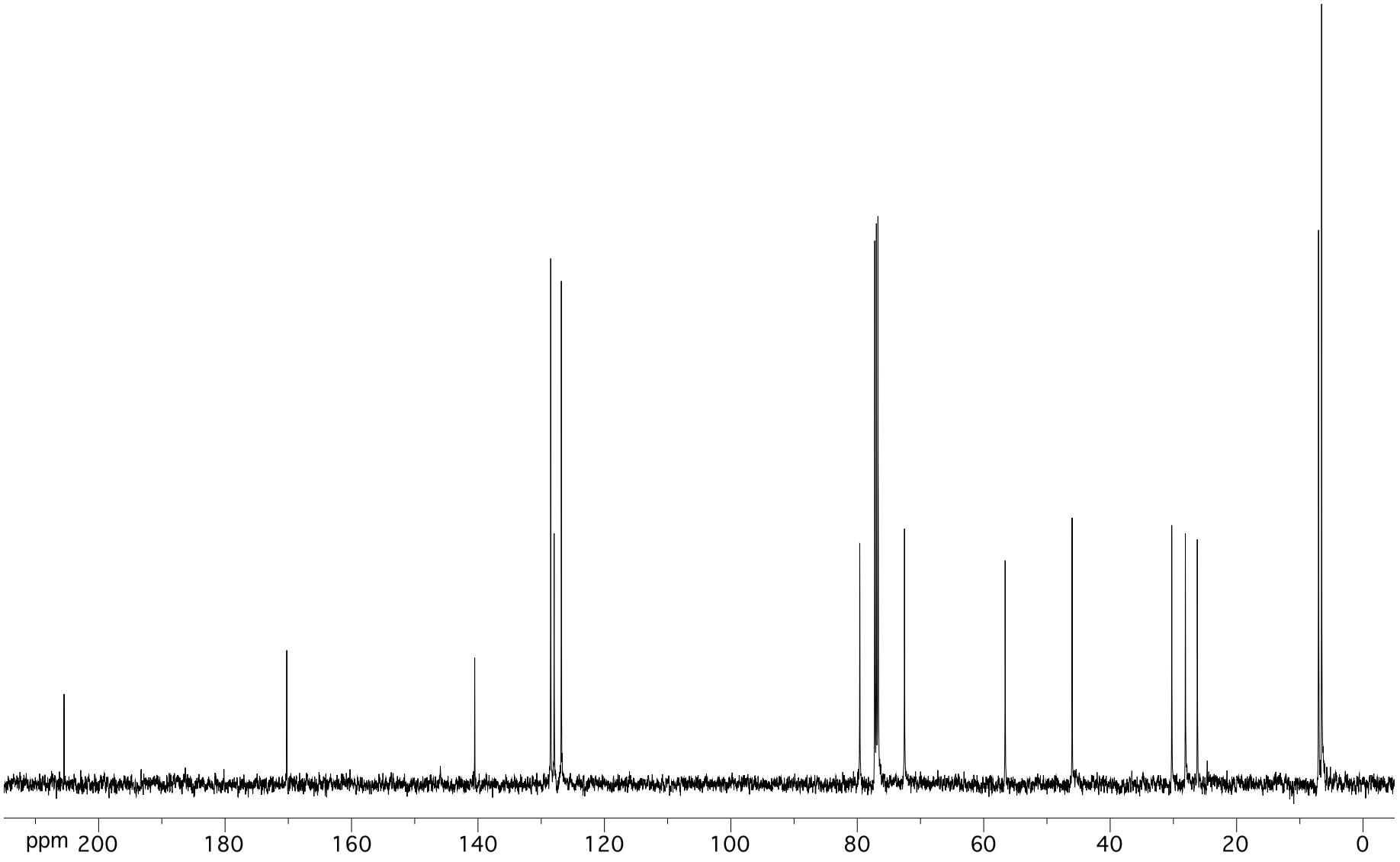
46b

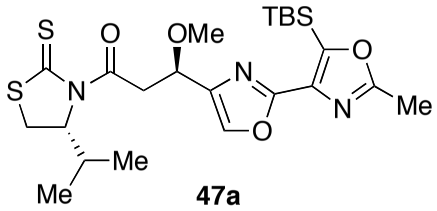
^{1}HNMR: 500 MHz in $CDCl_3$



46b

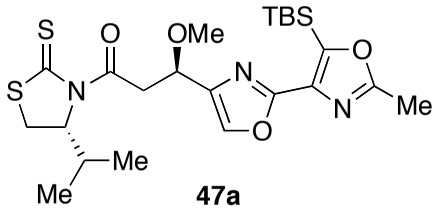
^{13}CNMR: 125 MHz in $CDCl_3$





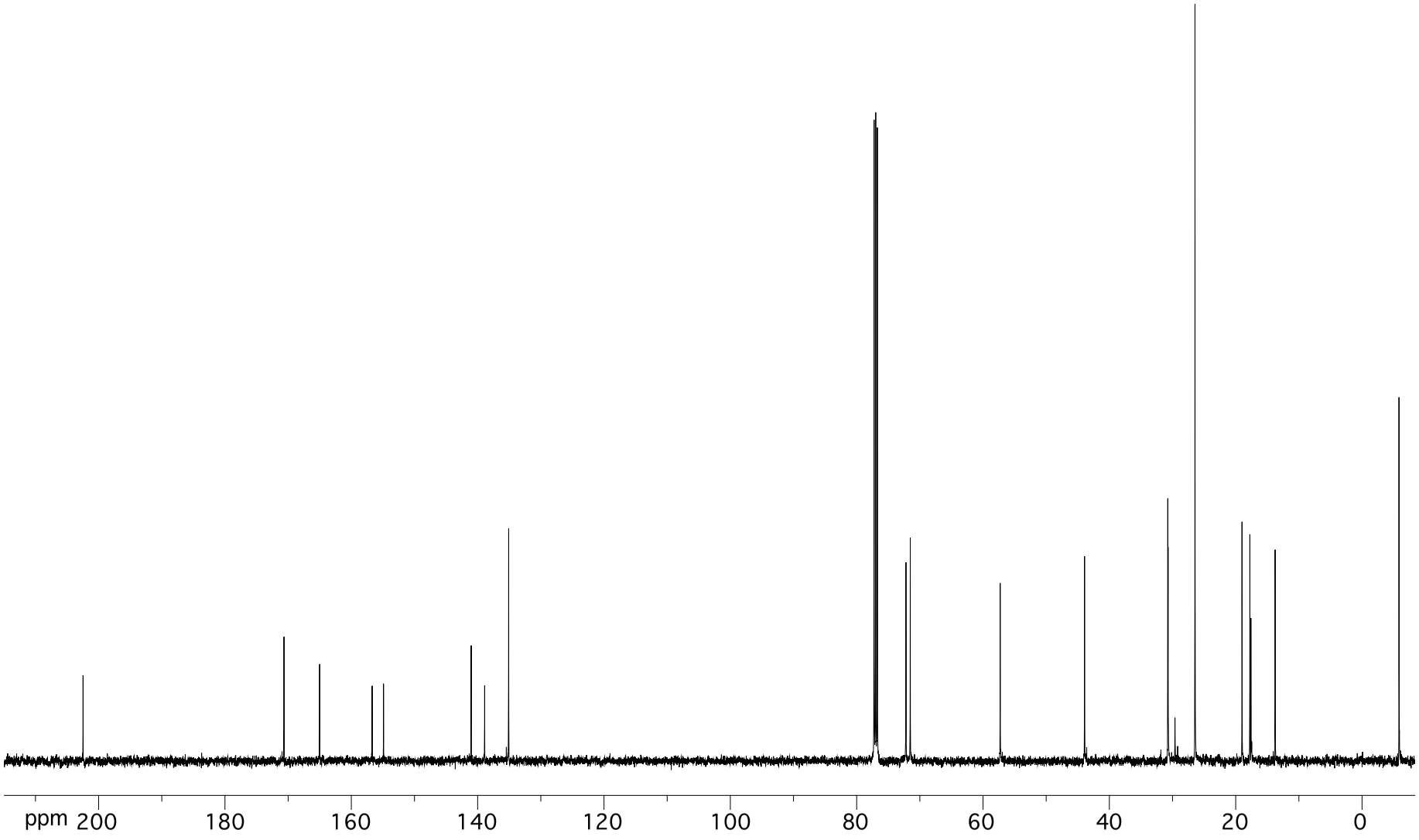
47a

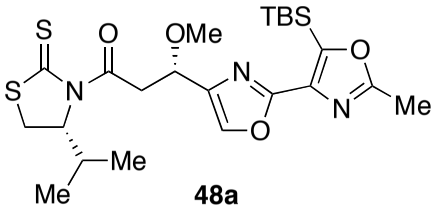
^{1}HNMR: 500 MHz in $CDCl_3$



47a

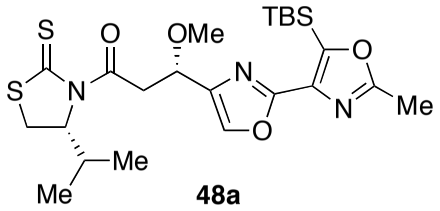
^{13}CNMR: 125 MHz in $CDCl_3$





48a

^{1}HNMR: 500 MHz in $CDCl_3$



48a

^{13}CNMR: 125 MHz in $CDCl_3$