Supporting Information

A Carbohydrate-Derived Splice Modulator

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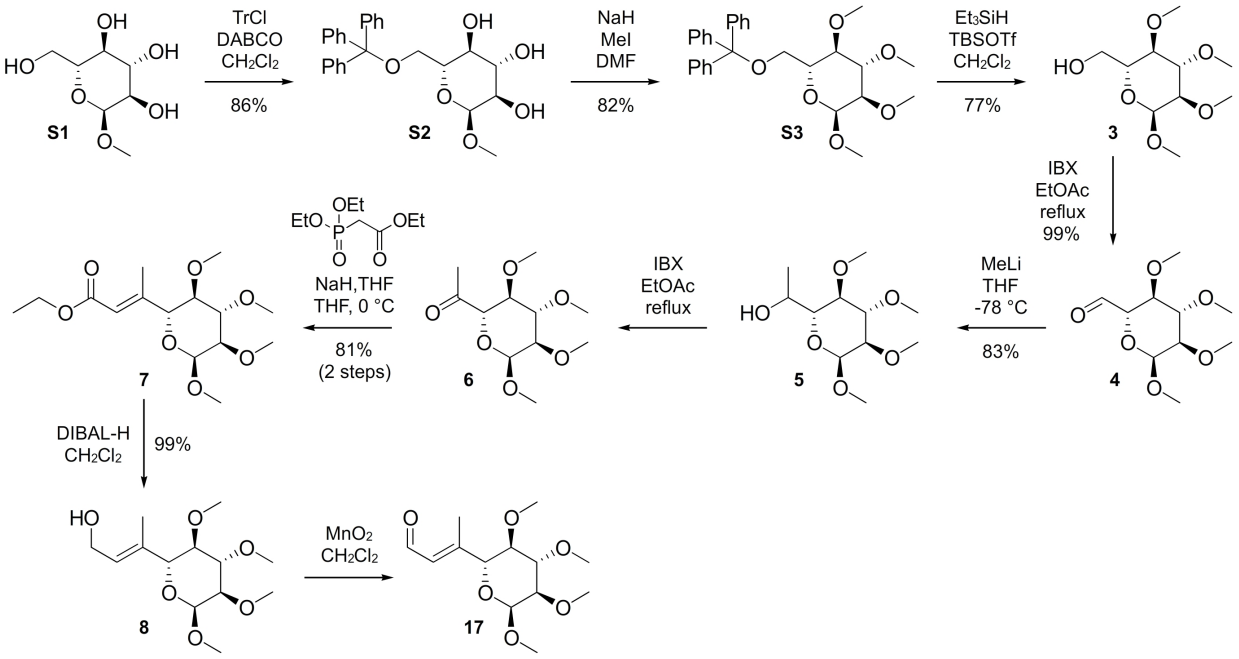
A. General experimental methods: Chemical reagents were purchased from Acros, Fluka, Sigma-Aldrich, or TCI. Deuterated NMR solvents were purchased from Cambridge Isotope Laboratories. All reactions were conducted with rigorously dried anhydrous solvents that were obtained by passing through a solvent column composed of activated A1 alumina. Anhydrous *N*,*N*-dimethylformamide was obtained by passage over activated molecular sieves and a subsequent NaOCN column to remove traces of dimethylamine. Triethylamine (Et_3N) was dried over Na and freshly distilled. Ethyl-*N,N*-diisopropylamine ($EtNiPr_2$) was distilled from ninhydrin, then from potassium hydroxide. Anhydrous CH_3CN was obtained by distillation from CaH_2. All reactions were performed under positive pressure of Ar in oven-dried glassware sealed with septa, with stirring from a Teflon coated stir bars using an IKAMAG RCT-basic mechanical stirrer (IKA GmbH). Solutions were heated using either a sand or silicon oil bath. Analytical Thin Layer Chromatography (TLC) was performed on Silica Gel 60 F254 precoated glass plates (EM Sciences). Preparative TLC (pTLC) was conducted on Silica Gel 60 plates (EM Sciences). Visualization was achieved with UV light and/or an appropriate stain (I_2 on SiO_2, $KMnO_4$, bromocresol green, dinitrophenylhydrazine, ninhydrin, and ceric ammonium molybdate). Flash chromatography was carried out Geduran Silica Gel 60 (40-63 mesh) from EM Biosciences. Yields and characterization data correspond to isolated, chromatographically and spectroscopically homogeneous materials. ^{1}H NMR spectra were recorded on Varian Mercury 300, Varian Mercury 400 spectrometers, Varian Mercury Plus 400, a JEOL ECA500, or a Varian VX500 spectrometer. A majority of the ^{13}C NMR spectra were recorded at 125 MHz on a Varian VX500 spectrometer equipped with an Xsens Cold probe. The remaining spectra were either collected at 125 MHz on a JEOL ECA 500, 100 MHz on a Varian Mercury 400 or 100 MHz on a Varian Mercury Plus 400 spectrometer. Chemical shifts for ^{1}H NMR and ^{13}C NMR analyses were referenced to the reported values of Gottlieb,[1] using the signal from the residual solvent for ^{1}H spectra, or to the ^{13}C signal from the deuterated solvent. Chemical shift δ values for ^{1}H and ^{13}C spectra are reported in parts per million (ppm) relative to these referenced values, and multiplicities are abbreviated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All ^{13}C NMR spectra were recorded with complete proton decoupling. FID files were processed using MestraNova 6.0.2. (MestreLab Research). Electrospray (ESI) mass spectrometric analyses were performed using a ThermoFinnigan LCQ Deca spectrometer, and high-resolution analyses were conducted using a ThermoFinnigan MAT900XL mass spectrometer with electron impact (EI) ionization. A Thermo Scientific LTQ Orbitrap XL mass spectrometer was used for high-resolution electrospray ionization mass spectrometry analysis (HR-ESI-MS). FTIR spectra were obtained on a Nicolet magna 550 series II spectrometer as thin films on either KBr or NaCl discs, and peaks are reported in wavenumbers (cm^{-1}). Optical rotations $[\alpha]_D$ were measured using a Perkin-Elmer Model 241 polarimeter with the specified solvent and concentration and are quoted in units of deg cm^2 g^{-1}. Spectral data and procedures are provided for all new compounds and copies of select spectra have been provided.

B. Synthesis of core chain component 8. Component **8** was prepared in 8 steps in 36% overall yield from α-methyl-D-glucopyranoside (**S1**) as shown in Scheme 1 (in the manuscript) and Scheme S1 (below). Preparation of 6-trityl-α-methyl-α-D-glucopyranoside **S2** was achieved by modification of methods developed by Crich,[S1] as described below. The following section provides a complete description of the synthetic procedures and spectroscopic properties of intermediated **S2**-**S3**, **3**-**8** and **17**.



Scheme S1. Synthesis of core component **8**. Preparation of **8** required three chromatographic purifications as the crude products of **S2**, **3**, **4**, and **6** could be used without additional purification. Flash chromatography was required to purify intermediates **S3**, **5**, and **7**. The final materials were stored at **8**, aldehyde **17** was prepared immediately before the component coupling process as described in Scheme 3 and Scheme S3.

(2*S*,3*R*,4*S*,5*R*,6*R*)-2,3,4,5-tetramethoxy-6-((trityloxy)methyl)tetrahydro-2H-pyran (S3). Trityl ether **S2** (10.1 g, 23.2 mmol), prepared from α-methyl-D-glucopyranoside (**S1**) according to the DABCO method of Gadakh,[S1] was suspended in DMF (110 mL), placed under a strict Ar atmosphere and cooled to 0 °C. NaH (4.82 g, 120.4 mmol) was added in four portions over the period of 15 min. After stirring at 0 °C for 1.5 h, MeI (11.53 mL, 185.2 mmol) was added in a drop wise fashion. The reaction was then slowly warmed to rt and stirred at rt for 12 h. In order to optimize yield, the mixture was retreated prior to work up by cooling the flask to 0 °C and adding an additional aliquot of NaH (2.41, 60.2 mmol). After 30 min, a second aliquot of MeI (5.7 mL, 92.6 mmol) was added and the mixture was warmed to rt. After 7 h at rt, satd. NH_4Cl (200 mL) was added in a drop wise fashion. The mixture was extracted with EtOAc (3 × 200 mL), washed with H_2O (200 mL) and satd. NH_4Cl (200 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure **S3** (9.13 g, 82%) was obtained by flash chromatography eluting with a gradient of hexanes to EtOAc.

Intermediate **S3**: TLC (1:1 hexanes/EtOAc): R_f = 0.67; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49 (m, 6H), 7.29 (m, 6H), 7.24 (m, 3H), 4.92 (d, *J* = 3.6 Hz, 1H), 3.62 (s, 3H), 3.60 (m, 1H), 3.56 (s, 3H), 3.48 (t, *J* = 9.2 Hz, 1H), 3.44 (s, 3H). 3.39 (dd, *J* = 2.0, 10.0 Hz, 1H), 3.30 (m, 2H), 3.27 (s, 3H), 3.11 (dd, *J* = 4.3, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.1, 128.9, 127.9, 127.1, 97.4, 86.3, 83.8, 82.0, 80.0, 70.2, 62.5, 61.1, 60.6, 59.2, 55.1; HR-ESI-MS *m/z* calcd. for $C_{29}H_{34}O_6$ $[M+Na]^+$: 501.2248, found 501.2249.

(2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)methanol (3). Intermediate **S3** (8.78 g, 18.4 mmol) was dissolved in CH_2Cl_2 (180 mL). Et_3SiH (5.86 mL, 36.7 mmol) was added neat followed by the addition of TBSOTf (0.04 mL, 0.2 mmol). An immediate yellow color appeared. If the CH_2Cl_2 is not sufficiently dry additional amounts of TBSOTf will be required. After 2 h, the yellow color disappeared and TLC analysis indicated that the reaction was

complete. Satd. $NaHCO_3$ solution (0.1 mL) was added and the mixture was dried with Na_2SO_4 and concentrated on a rotary evaporator. Pure **S3** (9.13 g, 83%) was obtained by extraction between hexanes and CH_3CN. Briefly, the crude product was dissolved in CH_3CN (100 mL) and washed with hexanes (3 × 200 mL). The CH_3CN was collected and dried via rotary evaporation to afford pure **3** (4.34 g, 77%) as a white solid.

Alcohol **3**: TLC (1:1 hexanes/EtOAc): R_f = 0.13; ^{1}H NMR (CD_3OD, 500 MHz) δ 4.83 (d, *J* = 3.6 Hz, 1H), 3.74 (dd, *J* = 2.2, 11.9 Hz, 1H), 3.65 (dd, *J* = 4.6, 11.9 Hz, 1H), 3.58 (s, 3H), 3.53 (s, 3H), 3.47 (s, 3H), 3.45 (m, 2H), 3.38 (s, 3H), 3.18 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.12 (dd, *J* = 8.9, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 98.4, 84.7, 83.0, 80.6, 72.5, 61.9, 61.0, 60.8. 58.8, 55.4; HR-ESI-MS *m/z* calcd. for $C_{10}H_{20}O_6$ $[M+Na]^+$: 259.1152, found 259.1155.

1-((2*S*,3*S*,4*S*,5*R*,6*S*)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)ethan-1-one (5). Alcohol **5** was prepared through a back-to-back two-step procedure without purification of intermediate aldehyde **4**. Alcohol **3** (2.21 g, 9.4 mmol) was dissolved in EtOAc (120 mL). IBX (5.57 g, 20.6 mmol) was added as a solid and the mixture was brought to reflux with vigorous stirring. After 4 h, the mixture was cooled to 0 °C and flushed through a pad SiO_2 (200 g) washing with EtOAc (400 mL). The combined fractions were dried and submitted immediately for the next step. Aldehyde **4** (2.19 g, 9.4 mmol) was dried by azeotropic removal of toluene (3 × 200 mL). The resulting wax was dissolved in THF (100 mL) and cooled to -80 °C. A 1.6 M solution of MeLi in ether (23.4 mL, 37.4 mmol) was added slowly to this solution. After 15 min at -80 °C, the mixture was warmed to rt over 2 h and stirred at rt for an additional 1 h. Satd. NH_4Cl (100 mL) was added slowly. The mixture was extracted with EtOAc (3 × 50 mL), washed with brine (200 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure **5** (1.95 g, 83%) was obtained as a ~2:1 mixtures of isomers by flash chromatography eluting with a gradient of hexanes to EtOAc.

Alcohol **5**: TLC (1:1 hexanes/EtOAc): Rf = 0.16; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.82 (d, *J* = 3.6 Hz, 1H, minor), 4.78 (d, *J* = 3.6 Hz, 1H, major), 3.98 (m, 1H, both), 3.62 (s, 3H, minor), 3.61 (s, 3H, major), 3.58 (s, 3H, both), 3.55 (m, 1H, both), 3.51 (s, 3H, minor), 3.51 (s, 3H, major), 3.46 (m, 2H, both), 3.40 (s, 3H, major), 3.38 (s, 3H, minor), 3.30 (dd, *J* = 1.6, 9.9 Hz, 1H, minor), 3.24 (dd, *J* = 8.6, 9.2 Hz 1H, minor), 3.16 (dd, *J* = 3.6, 9.6 Hz, 1H, both), 3.09 (dd, *J* = 8.8, 9.9 Hz, 1H, major), 2.75 (d, *J* = 4.7 Hz, OH, 1H, major), 1.77 (d, *J* = 9.7 Hz, OH, 1H, minor), 1.29 (d, *J* = 6.6 Hz, 3H, minor), 1.23 (d, *J* = 6.5 Hz, 3H, major);^{13}C NMR ($CDCl_3$, 125 MHz) δ 97.6, 97.3, 83.9, 83.9, 82.5, 82.2, 82.0, 79.9, 72.9, 72.1, 68.8, 65.5, 61.0, 60.9, 60.8, 60.4, 59.2, 59.1, 55.2, 55.2, 20.4, 18.3; HR-ESI-MS *m/z* calcd. for $C_{11}H_{22}O_6$ $[M+Na]^+$: 273.1309, found 273.1308.

1-((2*S*,3*S*,4*S*,5*R*,6*S*)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)ethan-1-one (6). Alcohol **5** (1.0 g, 4.0 mmol) was dissolved in EtOAc (50 mL). IBX (3.36 g, 12.0 mmol) was added as a solid and the mixture was brought to reflux with vigorous stirring. After 4 h, a second aliquot of IBX (3.36 g, 12.0 mmol) was added and the mixture was continued to stir at reflux for an additional 4 h. The mixture was cooled to 0 °C and flushed through a pad SiO_2 (200 g) washing with EtOAc (400 mL). The combined fractions were dried and used immediately as a crude product **6** (992.3 mg, 99%). Samples of pure ketone were obtained by flash chromatography eluting with a gradient of hexanes to EtOAc.

Ketone **6**: TLC (1:1 hexanes/EtOAc): R_f = 0.40; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.85 (d, *J* = 3.5 Hz, 1H), 4.00 (d, *J* = 10 Hz, 1H), 3.61 (s, 3H), 3.53 (t, *J* = 9.2 Hz, 1H), 3.51 (s, 3H), 3.49 (s, 3H), 3.43 (s, 3H), 3.22 (t, *J* = 9.8 Hz, 1H), 3.20 (dd, *J* = 3.6, 9.7 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.0, 98.0, 83.5, 81.4, 80.8, 74.1, 61.2, 60.6, 59.3, 55.8, 28.3; HR-ESI-MS *m/z* calcd. for $C_{11}H_{20}O_6$ $[M+Na]^+$: 271.1152, found 271.1149.

Ethyl (E)-3-((2R,3R,4S,5R,6S)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)but-2-enoate (7). NaH (400 mg, 60% w/w in oil, 10.0 mmol) was suspended in THF (30 mL) and cooled to 0

°C. Triethyl phosphonoacetate (2.51 g, 11.2 mmol) was added in a drop wise fashion to the suspension of NaH. After stirring for 1.5 h, crude ketone **5** (992.0 mg, 4.0 mmol) dissolved in THF (10 mL) was added. The mixture was warmed to rt. TLC analysis indicated that the reaction was complete after 3 h. Satd. NH_4Cl (50 mL) was added slowly. The mixture was extracted with EtOAc (3 × 100 mL), washed with brine (200 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure **7** (0.982 g, 81%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/EtOAc.

Ester **7**: TLC (1:1 hexanes/EtOAc): R_f = 0.59; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.94 (dd, *J* = 0.7, 1.5 Hz, 1H), 4.80 (d, *J* = 3.6 Hz, 1H), 4.16 (dq, *J* = 1.2, 7.2 Hz, 1H), 3.89 (d, *J* = 9.8 Hz, 1H), 3.61 (s, 3H), 3.52 (s, 3H), 3.50 (dd, *J* = 8.8, 9.6 Hz, 1H), 3.42 (s, 3H), 3.38 (s, 3H), 3.20 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.04, (dd, *J* = 8.7, 9.8 Hz, 1H), 2.20 (d, *J* = 2.2 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.3, 153.9, 119.7, 97.6, 83.2, 82.5, 81.5, 75.1, 61.1, 60.5, 59.9, 59.1, 55.3, 15.0, 14.3; HR-ESI-MS *m/z* calcd. for $C_{15}H_{26}O_7$ $[M+Na]^+$: 341.1574, found 341.1571.

Ethyl (E)-3-((2R,3R,4S,5R,6S)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)but-2-enoate (8). Ester **7** (981.0 mg, 3.1 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to -78 °C. A 1.0 M solution of DIBAL-H in toluene (9.3 mL, 9.3 mmol) was added drop wise. After 20 min, the reaction mixture was slowly warmed to rt over 2 h and then stirred at rt for 1 h. The mixture was recooled to -78 °C and EtOAc (5 mL) was added, followed by a satd. Solution of Rochelle's salt (100 mL). The mixture was warmed to rt and stirred at rt for 5 h until the mixture provided two clear phases. The crude product was recovered by extraction EtOAc (3 × 100 mL), washed with brine (100 mL), drying over Na_2SO_4 and concentration on a rotary evaporator. Pure **8** (0.845 g, 99%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:2 hexanes/EtOAc.

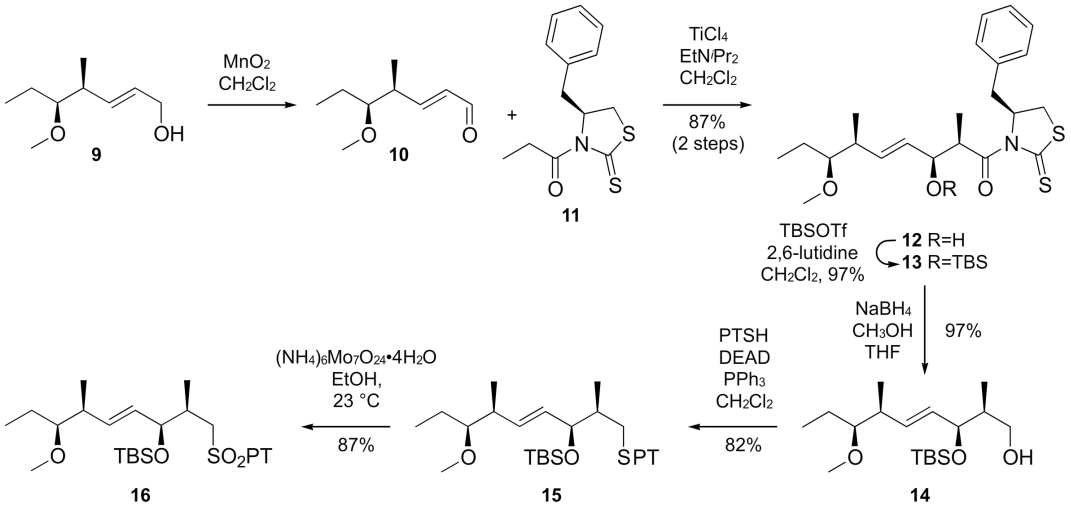
Allylic alcohol **8**: TLC (1:1 hexanes/EtOAc): Rf = 0.09; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.76 (dt, *J* = 2.1, 6.8 Hz, 1H), 4.79 (d *J* = 3.6 Hz, 1H), 4.25 (dq, *J* = 6.3, 13.1 Hz, 1H), 3.86 (d, *J* = 9.8 Hz, 1H), 3.62 (s, 3H), 3.52 (s, 3H), 3.50 (m, 1H), 3.44 (s, 3H), 3.39 (s, 3H), 3.19 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.05 (dd, *J* = 8.8, 9.8 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.9, 130.0, 97.6, 83.3, 81.8, 81.6, 75.6, 61.2, 60.3, 59.4, 59.2, 55.4, 12.5; HR-ESI-MS *m/z* calcd. for $C_{13}H_{24}O_6$ $[M+Na]^+$: 299.1465, found 299.1463.

C. Synthesis of side chain component 16. Sulfone **16** was prepared in 6 steps in 58% overall yield from allylic alcohol **9**, as shown in Scheme 2 (in the manuscript) and Scheme S2 (below). Gram scaled preparation of allylic alcohol **9** was accomplished in 11 steps and 27% overall yield from L-Phe.[S1] The bulk of the effort in preparing **9** arose from the preparation of auxiliary **11**, which was readily recycled.[S1] The following section provides a complete description of the synthetic procedures and spectroscopic properties of intermediated **10**, **12**, **13**, and **14**-**16**.

(2*R*,3*S*,6*S*,7*S*,*E*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-7-methoxy-2,6-dimethylnon-4-en-1-one (12). Allylic alcohol **9**[S2] (1.12 g, 7.1 mmol) was dissolved in CH_2Cl_2 (50 mL) and MnO_2 (9.31 g, 107.2 mmol) was added as a powder. The slurry was vigorously stirred at rt until TLC indicated complete conversion, typically 24-36 h. The mixture was applied to a DCVC column containing 150 g SiO_2. The column was washed with EtOAc (3 × 100 mL) and dried via rotary evaporation. The resulting product, aldehyde **10** (1.12 g, 99% yield) was further dried via toluene azeotrope (3 × 10 mL) and used immediately without further purification. Crimmins auxiliary **11** (2.28 g, 8.6 mmol) was dissolved in CH_2Cl_2 (70 mL) and cooled 0 °C. $TiCl_4$ (0.99 mL, 9.0 mmol) was added in a drop wise fashion. After 5 min at 0 °C, EtN^iPr_2 (1.64 mL, 9.4 mmol) was added in a drop wise fashion. The mixture was stirred at 0 °C for 30 min and then cooled to -78 °C. Aldehyde **10** (1.12, 7.2 mmol) was dissolved in CH_2Cl_2 (25 mL) and added in a drop wise fashion. The mixture was stirred at -78 °C for 2.5 h then slowly warmed

over 1.5 h to 0 °C. After 15 min at 0 °C, satd. NH_4Cl (50 mL) was added. The mixture was extracted with EtOAc (3 × 100 mL), washed with brine (50 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure adduct **12** (2.65 g, 87%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/EtOAc.

Adduct **12**: TLC (3:1 hexanes/EtOAc): R_f = 0.39; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (m, 2H), 7.28 (m, 3H), 5.73 (ddd, *J* = 1.3, 7.8, 15.6 Hz, 1H), 5.51 (ddd, *J* = 1.1, 5.8, 15.6 Hz, 1H), 5.38 (ddd, *J* = 4.0, 7.3, 11.3 Hz, 1H), 4.79 (dq, *J* = 3.2, 7.0 Hz, 1H), 4.60 (m, 1H), 3.38 (dd, *J* = 4.6, 11.8 Hz, 1H), 3.35 (s, 3H), 3.24 (dd, *J* = 4.0, 13.2 Hz, 1H), 3.04 (dd, *J* = 10.4, 13.2 Hz, 1H), 2.92 (m, 1H), 2.89 (d, *J* = 11.6 Hz, 1H), 2.42 (td, *J* = 6.8, 12.1 Hz, 1H), 1.59 (s, OH, 1H), 1.53 (dqd, *J* = 4.3, 7.5, 14.9 Hz, 1H), 1.41 (td, *J* = 7.1, 14.1 Hz, 1H), 1.18 (d, *J* = 7.0 Hz, 1H), 1.03 (d, *J* = 6.8 Hz, 1H), 0.89 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.8, 177.7, 136.5, 135.4, 129.6, 129.1, 128.7, 127.4, 86.3, 72.2, 69.1, 57.8, 43.4, 39.5, 37.1, 31.9, 23.8, 16.2, 11.4, 9.8; HR-ESI-MS *m/z* calcd. for $C_{22}H_{31}NO_3S_2$ $[M+Na]^+$: 444.1638, found 444.1639.



Scheme S2. Synthesis of side chain component **16**. Preparation of **16** required four chromatographic purifications as the crude products of **10** and **13** could be used without additional purification. Flash chromatography was required to purify intermediates **12**, **14**,**15** and **16**. The materials was stored at **16**, and used as described in Scheme 3 and Scheme S3.

(2*R*,3*S*,6*S*,7*S*,*E*)-1-((S)-4-benzyl-2-thioxothiazolidin-3-yl)-3-((tert-butyldimethylsilyl)oxy)-7-methoxy-2,6-dimethylnon-4-en-1-one (13). Adduct **12** (3.22 g, 7.64 mmol) and 2,6-lutidine (2.65 mL, 22.9 mmol) were dissolved in CH_2Cl_2 (125 mL) and cooled 0 °C. TBSOTf (3.50 mL, 15.3 mmol) was added in a drop wise fashion. After 15 min at 0 °C, the mixture was warmed to 10 °C over 2 h. After 15 min at 10 °C, satd. $NaHCO_3$ (0.5 mL) was added and the mixture was stirred at rt for 30 min. The mixture was applied to a DCVC column containing 200 g SiO_2. The column was washed with EtOAc (3 × 200 mL) and dried via rotary evaporation. The resulting product **10** (3.98 g, 97% yield) was further dried via toluene azeotrope (3 × 50 mL) and used as is. Pure samples of **13** were obtained for spectroscopic analyses via flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/EtOAc.

Adduct **13**: TLC (3:1 hexanes/EtOAc): R_f = 0.75; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (m, 2H), 7.28 (m, 3H), 5.59 (d, *J* = 6.9 Hz, 1H), 5.57 (d, *J* = 6.1 Hz, 1H), 5.33 (dddd, *J* = 1.2, 3.5, 7.4, 10.8 Hz, 1H), 4.80 (t, *J* = 6.6 Hz, 1H), 4.51 (t, *J* = 6.5 Hz, 1H), 3.35 (m, 1H), 3.31 (m, 1H), 3.30 (s, 3H), 3.17 (dd, *J* = 3.4, 13.1 Hz, 1H), 2.99 (dd, *J* = 11.0, 13.2 Hz, 1H), 2.87 (dd, *J* = 4.3, 6.7 Hz, 1H), 2.84 (d, *J* = 11.6 Hz, 1H), 2.33 (h, *J* = 6.7, 1H), 1.67 (m, 1H), 1.50 (ttd, *J* = 3.6, 7.5, 14.8 Hz, 1H), 1.38 (pq, 7.1, 14.1 Hz, 1H), 1.26 (dd, *J* = 6.5, 4.27 Hz, 1H), 1.21 (d, *J* = 6.8 Hz,

3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.84 (t, *J* = 7.5 Hz, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.2, 176.3, 136.8, 135.1, 131.1, 129.5, 129.1, 127.3, 86.2, 75.2, 69.3, 57.6, 45.2, 39.4, 37.2, 31.6, 26.1, 25.9, 23.8, 18.4, 16.0, 14.2, 9.7, -3.7, -4.2; HR-ESI-MS *m/z* calcd. for $C_{28}H_{45}NO_3S_2Si$ $[M+Na]^+$: 558.2502, found 558.2503.

(2*S*,3*S*,6*S*,7*S*,*E*)-3-((tert-butyldimethylsilyl)oxy)-7-methoxy-2,6-dimethylnon-4-en-1-ol (14). Adduct **13** (1.33 g, 2.5 mmol) was dissolved in a mixture of THF (53 mL) and CH_3OH (13 mL) and cooled to 0 °C. $NaBH_4$ (159.0 mg, 19.9 mmol) was added in 3 portions over 5 min. The mixture was stirred at 0 °C for 1.5 h. If not complete via TLC analysis additional $NaBH_4$ could be added to complete the reaction. If complete, satd. NH_4Cl (25 mL) was added. The resulting mixture was extracted with EtOAc (3 × 100 mL), washed with brine (50 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure alcohol **14** (802.0 mg, 97%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/EtOAc.

Alcohol **14**: TLC (3:1 hexanes/EtOAc): R_f = 0.55; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.51 (m, 2H), 4.13 (m, 2H), 3.62 (ddd, *J* = 2.8, 8.6, 11.2 Hz, 1H), 3.46 (ddd, 4.2, 7.4, 11.2 Hz, 1H), 3.34 (s, 3H), 3.03 (bs, 1H), 2.89 (ddd, *J* = 4.1, 6.1, 7.4 Hz, 1H), 2.41 (m, 1H), 1.95 (m, 1H), 1.76 (bs, 1H), 1.53 (dtd, *J* = 4.3, 7.5, 14.8 Hz, 1H), 1.38 (ddt, *J* = 6.7, 7.7, 13.5 Hz, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.78 (dd, *J* = 7.1 Hz, 3H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.9, 129.9, 86.4, 78.2, 65.9, 57.6, 41.5, 39.4, 25.9, 23.5, 18.2, 16.2, 13.0, 9.8, -4.0, -4.9; HR-ESI-MS *m/z* calcd. for $C_{18}H_{38}NO_3Si$ $[M+Na]^+$: 353.2482, found 353.2485.

5-(((2*R*,3*S*,6*S*,7*S*,*E*)-3-((tert-butyldimethylsilyl)oxy)-7-methoxy-2,6-dimethylnon-4-en-1-yl)thio)-1-phenyl-1H-tetrazole (15). Alcohol **14** (1.01 g, 3.1 mmol), 1-phenyl-1H-tetrazole-5-thiol (817.5 mg, 4.6 mmol) and PPh_3 (1.20 g, 4.6 mmol) were dissolved in THF (50 mL). The solution was cooled to 0 °C. DEAD (720.0 µL, 4.6 mmol) was added in a drop wise fashion until a yellow color persists. Additional DEAD up to 1.2 mmol could be added if needed if the color does not persist. After 30 min, the solution was allowed to warm to rt over 30 min. After 4 h at rt, H_2O (20 mL) was added. The resulting mixture was extracted with EtOAc (3 × 50 mL), washed with brine (25 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure sulfide **15** (1.24 g, 82%) was obtained by flash chromatography eluting with a gradient of hexanes to 2:1 hexanes/EtOAc.

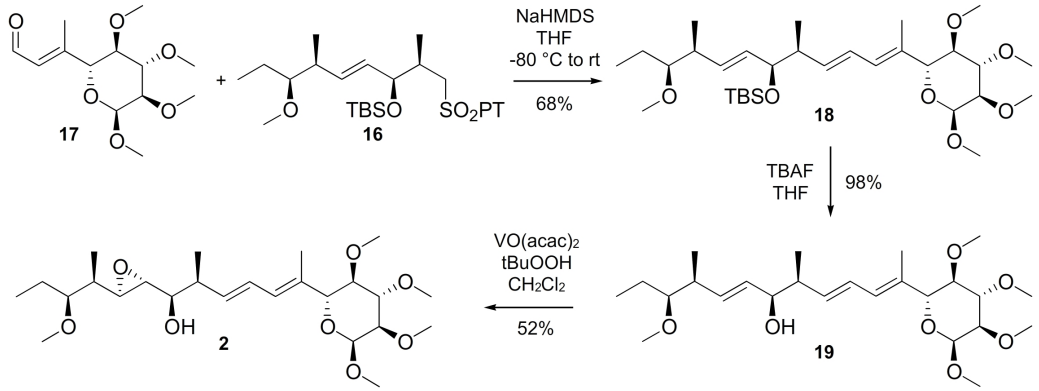
Sulfide **15**: TLC (3:1 hexanes/EtOAc): R_f = 0.70; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (m, 5H), 5.55 (ddd, *J* = 0.8, 7.7, 15.5 Hz, 1H), 5.43 (ddd, *J* = 1.0, 7.7, 15.5 Hz, 1H), 4.13 (dd, *J* = 0.9, 4.1, 6.9 Hz, 1H), 3.51 (dd, *J* = 6.5, 12.7 Hz, 1H), 3.33 (s, 3H), 3.25 (dd, *J* = 7.3, 12.7 Hz, 1H), 2.89 (ddd, *J* = 4.3, 6.1, 7.0 Hz, 1H), 2.38 (h, *J* = 6.9 Hz, 1H), 2.03 (dh, *J* = 4.1, 6.8 Hz, 1H), 1.51 (dqd, *J* = 4.3, 7.5, 14.9 Hz, 1H), 1.38 (pd, *J* = 7.3, 14.4 Hz, 1H), 1.01 (d, *J* = 6.9 Hz, 1H), 1.00 (d, *J* = 6.8 Hz, 1H), 0.88 (s, 9H), 0.88 (t, *J* = 7.4 Hz, 1H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.0, 135.0, 133.9, 130.4, 130.1, 129.9, 124.0, 86.3, 76.1, 57.7, 40.1, 39.3, 36.8, 26.0, 23.7, 18.3, 15.9, 14.6, 9.7, -3.8, -4.7; HR-ESI-MS *m/z* calcd. for $C_{25}H_{42}N_4O_2SSi$ $[M+Na]^+$: 513.2690, found 513.2693.

5-(((2*R*,3*S*,6*S*,7*S*,*E*)-3-((tert-Butyldimethylsilyl)oxy)-7-methoxy-2,6-dimethylnon-4-en-1-yl)sulfonyl)-1-phenyl-1H-tetrazole (16). Sulfide **15** (1.95 g, 4.0 mmol) was dissolved in EtOH (40 mL) and cooled to 0 °C. In a vial, a 30% v/v solution of H_2O_2 (3.6 mL) was added to solid $(NH_4)_6Mo_7O_{24}•4H_2O$ (2.45 g, 20.0 mmol) and shaken until the bubbling ceased (~ 5 min). This solution was then added to the cooled solution of **15** in EtOH via glass pipette. After 20 min, the mixture was warmed to rt and stirred overnight. The resulting mixture was diluted with H_2O (50 mL), extracted with EtOAc (3 × 50 mL), washed with brine (25 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure sulfone **16** (1.82 g, 87%) was obtained by flash chromatography eluting with a gradient of hexanes to 2:1 hexanes/EtOAc. The remainder of the

material was either the sulfide **15** (R_f higher than **16**), the corresponding sulfoxide (R_f higher than **16**) or a mixture of both. These materials were readily resubmitted to the oxidation procedure to provide additional samples of **16**.

Sulfone **16**: TLC (3:1 hexanes/EtOAc): R_f = 0.66; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (m, 2H), 7.61 (m, 3H), 5.61 (ddd, *J* = 1.1, 7.9, 15.6 Hz, 1H), 5.36 (ddd, *J* = 1.1, 7.0, 15.6 Hz, 1H), 4.18 (dd, *J* = 4.3, 6.7 Hz, 1H), 4.07 (dd, *J* = 3.4, 14.4 Hz, 1H), 3.46 (dd, *J* = 9.1, 14.4 Hz, 1H), 3.34 (s, 3H), 2.90 (ddd, *J* = 4.4, 6.0, 7.0 Hz, 1H), 2.43 (m, 1H), 2.40 (tt, *J* = 6.5, 13.6 Hz, 1H), 1.51 (m, 1H), 1.39 (pq, *J* = 7.3, 14.4 Hz, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.89 (t, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.2, 136.2, 133.3, 131.6, 129.8, 128.9, 125.3, 86.2, 75.8. 58.5, 57.7, 39.3, 35.3, 26.0, 23.7, 18.3, 15.9, 15.3, 9.8, -4.0, -4.8; HR-ESI-MS *m/z* calcd. for $C_{25}H_{42}N_4\ O_4SSi$ $[M+Na]^+$: 545.2588, found 545.2587.

D. Procedures for the component coupling to alkene 19. A two-step procedure was used to prepare alkene **18** from side chain component **16** and core component **9**, as shown in Scheme 3 (in the manuscript) and Scheme S3 (below). The following section provides a complete description of the synthetic procedures and spectroscopic properties of intermediates **17**-**18**.



Scheme S3. Synthesis of epoxide **2**. Preparation of **16** required 3 chromatographic purifications as the crude product **17** as shown in Scheme S1 could be used without additional purification.

(*E*)-3-((2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5,6-Tetramethoxytetrahydro-2H-pyran-2-yl)but-2-enal (17). Allylic alcohol **8** (468.2 mg, 1.7 mmol) was dissolved in CH_2Cl_2 (20 mL) and MnO_2 (2.21 g, 25.4 mmol) was added as a powder. The slurry was vigorously stirred at rt until TLC indicated complete conversion, typically 20-24 h. The mixture was applied to a DCVC column containing 80 g SiO_2. The column was washed with EtOAc (3 × 50 mL) and dried via rotary evaporation. The resulting product, aldehyde **17** (459.2 mg, 99% yield) was further dried via toluene azeotrope (3 × 10 mL) and used as is.

Aldehyde **17**: TLC (1:1 hexanes/EtOAc): R_f = 0.38; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.11 (d, *J* = 7.8 Hz, 1H), 6.12 (d, *J* = 7.1 Hz, 1H), 4.83 (d, *J* = 3.6 Hz, 1H), 4.00 (d, *J* = 9.8 Hz, 1H), 3.64 (s, 3H), 3.54 (s, 3H), 3.53 (m, 1H), 3.45 (s, 3H), 3.41 (s, 3H), 3.22 (dd, *J* = 3.6, 9.7 Hz, 1H), 3.06 (dd, *J* = 8.8, 9.8 Hz, 1H); 2.23 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.2, 157.9, 129.5, 97.9, 83.5, 82.8, 81.8, 74.5, 61.2, 60.7, 59.3, 55.6, 14.3; HR-ESI-MS *m/z* calcd. for $C_{13}H_{22}O_6$ $[M+Ma]^+$: 297.1309, found 297.1306.

tert-Butyl(((2*E*,4*E*,6*S*,7*S*,8*E*,10*S*,11*S*)-11-methoxy-6,10-dimethyl-2-((2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)trideca-2,4,8-trien-7-yl)oxy)dimethylsilane (18). Highly dry THF for this procedure was required and was distilled fresh from Na

benzophenone ketyl prior to use. Sulfone **16** (568.4 mg, 1.09 mmol) was dissolved in freshly distilled THF (30 mL) and cooled to -78 °C. A 2 M solution of NaHMDS in THF (572.0 mL, 1.14 mmol) was added in a drop wise fashion. After 1 h at -78°C, freshly prepared and dried aldehyde **17** (328.2 mg, 1.19 mmol) was added in THF (15 mL). The solution was warmed to rt over 1.5 h and stirred overnight. The resulting mixture was diluted with satd. NH_4Cl (50 mL), extracted with EtOAc (3 × 200 mL), washed with brine (25 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure alkene **18** (423.1 mg, 68%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/EtOAc. This was accompanied by ~11% of the chromatographically isolable *cis*-C8,C9 isomer of **18** indicating that the reaction occurred with ~6:1 ratio of *trans* : *cis*.

Alkene **18**: TLC (1:1 hexanes/EtOAc): R_f = 0.62; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.22 (ddd, *J* = 1.2, 10.8, 15.8 Hz, 1H), 6.08 (dd, *J* = 1.5, 10.7 Hz, 1H), 5.69 (dd, *J* = 7.6, 15.2 Hz, 1H), 5.38 (m, 2H), 4.79 (d, *J* = 3.6 Hz, 1H), 3.90 (dd, *J* = 5.5, 6.4 Hz, 1H), 3.85 (d, *J* = 9.8 Hz, 1H), 3.62 (s, 3H), 3.52 (s, 3H), 3.49 (m, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 3.33 (s, 3H), 3.19 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.07 (dd, *J* = 8.8, 9.8 Hz, 1H), 2.86 (dt, *J* = 4.3, 6.7 Hz, 1H), 2.31 (m, 2H), 1.79 (d, *J* = 1.3 Hz, 3H), 1.52 (m, 1H), 1.38 (pd, *J* = 7.4, 14.2 Hz, 1H), 1.00 (d, *J* = 6.8 Hz, 6H), 0.88 (s, 9H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.02 (s, 3H), -0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.7, 134.1, 131.8, 131.3, 130.5, 125.4, 97.6, 86.3, 83.4, 82.0, 81.9, 77.8, 76.2, 61.2, 60.2, 59.2, 57.7, 55.2, 44.2, 39.7, 26.0, 23.7, 18.4, 16.4, 15.5, 12.7, 9.4, -3.9, -4.6; HR-ESI-MS *m/z* calcd. for $C_{31}H_{58}O_7Si$ $[M+Na]^+$: 593.3844, found 593.3846.

E. Procedures for synthesis of epoxides 2 and 20. A two-step procedure was used to convert alkene **17** to the targeted epoxide **2** or **20**. The following section provides a complete description of the synthetic procedures and spectroscopic properties of intermediates **19** and epoxide **2**, and the corresponding epoxide isomer **20**.

(2*E*,4*E*,6*S*,7*S*,8*E*,10*S*,11*S*)-11-methoxy-6,10-dimethyl-2-((2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)trideca-2,4,8-trien-7-ol (19). Alkene **18** (79.2 mg, 0.14 mmol) was dissolved in wet THF (8 mL) in an Oakridge 15 mL Teflon tube (Nalgene). Solid TBAF (108.8 mg, 0.41 mmol) was added and the mixture was stirred at rt until TLC analysis showed complete conversion (typically 5-6 h). NH_4Cl (5 mL) was added and the resulting mixture was extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure alkene **19** (54.2 mg, 86%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/EtOAc.

Alcohol **19**: TLC (1:1 hexanes/EtOAc): R_f = 0.41; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.33 (ddd, *J* = 1.1, 10.9, 15.2 Hz, 1H), 6.10 (dd, *J* = 1.6, 10.7 Hz, 1H), 5.64 (dd, *J* = 8.2, 15.2 Hz, 1H), 5.58 (dd, *J* = 7.9, 15.5 Hz, 1H), 5.45 (dd, *J* = 6.9, 15.5 Hz, 1H), 4.79 (d, *J* = 3.6 Hz, 1H), 3.97 (m, 2H), 3.85 (d, *J* = 9.8 Hz, 1H), 3.62 (s, 3H), 3.52 (s, 3H), 3.49 (m, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 3.34 (s, 3H), 3.19 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.08 (dd, *J* = 8.8, 9.8 Hz, 1H), 2.89 (dt, *J* = 4.1, 6.6 Hz, 1H), 2.43 (m, 1H), 2.37 (m, 1H), 1.80 (d, *J* = 1.3 Hz, 1H), 1.52 (dqd, *J* = 4.1, 7.4, 14.8 Hz, 1H), 1.38 (pd, *J* = 7.3, 14.4 Hz, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.9, 135.4, 132.5, 130.2, 130.0, 127.0, 97.6, 86.3, 83.4, 82.0, 81.9, 76.4, 76.1, 61.1, 60.3, 59.2, 57.7, 55.3, 43.5, 39.5, 23.7, 16.3, 15.8, 12.8, 9.6; HR-ESI-MS *m/z* calcd. for $C_{25}H_{44}O_7$ $[M+Na]^+$: 479.2979, found 479.2981.

(1*R*,2*S*,3*E*,5*E*)-1-((2*R*,3*R*)-3-((2*R*,3*S*)-3-methoxypentan-2-yl)oxiran-2-yl)-2-methyl-6-((2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)hepta-3,5-dien-1-ol (2). Alkene **18** (42.1 mg, 73.8 μmol) was dissolved in CH_2Cl_2 (2 mL) in a 2 dram vial equipped with a Teflon cap. Solid $VO(acac)_2$ (58.7 mg, 221.4 μmol) was added and the mixture was cooled to -

78 °C. A solution of 5.5 M solution t-BuOOH in hexanes (58.7 µL, 332.0 µmol) was added and the mixture was warmed for 2 h over -20 °C. The flask was then stored at -20 °C for 6 h at which point dimethylsulfide (100 µL) was added. After 15 min at -20 °C, the mixture was warmed to rt and stirred for an additional 30 min. The resulting contents were flushed through a pad of SiO_2 (10 g) flushing with EtOAc (20 mL), and concentrated on a rotary evaporator. Epoxide **2** (22.8 mg, 52%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/EtOAc, followed by pTLC in a tank containing 2:1 hexanes/EtOAc.

Epoxide **2**: TLC (1:1 hexanes/EtOAc): R_f = 0.39; ^{1}H NMR (C_6D_6, 500 MHz) δ 6.45 (ddd, *J* = 1.1, 10.9, 15.1 Hz, 1H), 6.30 (dd, *J* = 1.1, 11.0 Hz, 1H), 5.66 (dd, *J* = 8.5, 15.1 Hz, 1H), 4.68 (d, *J* = 3.6 Hz, 1H), 4.16 (d, *J* = 9.7 Hz, 1H), 3.84 (dd, *J* = 8.7, 9.6 Hz, 1H), 3.62 (s, 3H), 3.36 (s, 3H), 3.26 (s, 3H), 3.21 (m, 3H), 3.15 (s, 3H), 3.11 (s, 3H), 2.89 (dd, *J* = 2.3, 6.8 Hz, 1H), 2.85 (dd, *J* = 2.3, 4.6 Hz, 1H), 2.82 (td, J = 4.8, 7.4 Hz, 1H), 2.42 (h, *J* = 7.6 Hz 1H), 1.85 (d, *J* = 1.3 Hz, 3H), 1.74 (bs, 1H), 1.55 (dt, *J* = 4.3, 6.9 Hz, 1H), 1.48 (qd, *J* = 7.3, 14.6 Hz, 1H), 1.36 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (C_6D_6,125 MHz) δ 136.3, 133.2, 129.4, 126.6, 97.7, 83.5, 83.4, 82.2, 82.2, 76.2, 71.7, 60.6, 59.7, 58.8, 57.7, 57.2, 56.7, 54.6, 41.7, 38.7, 23.5, 16.2, 12.4, 10.4, 9.6; HR-ESI-MS *m/z* calcd. for $C_{25}H_{44}O_8$ $[M+Na]^+$: 495.2928, found 495.2926.

F. Biological Assays and Screens.

Primary chronic lymphocytic leukemia (CLL) cells sampling and cell culture: Peripheral blood mononuclear cells (PBMC) from CLL patients were obtained from the CLL Research Consortium (CRC) tissue bank. This protocol was approved by the institutional review board (IRB) of the University of California, San Diego. Blood samples were taken from two CLL patients after written informed consent for blood sample collection and confirmation of diagnosis for CLL diseases, The PBMCs were separated from heparinized venous blood by density gradient centrifugation using Ficoll-Hypaque media (GE Healthcare). The samples with >95% positivity for leukemic B cells was confirmed by staining for CD5 and CD19 followed by assessment using flow cytometry. B cells were maintained in RPMI 1640 medium supplemented with 10% FBS, 2 mM L-glutamine, and 100 U/mL of penicillin and 100 µg/mL of streptomycin at 37 °C in an atmosphere containing 5% CO_2.

***In vitro* cytotoxicity analyses:** The CLL-B cells (3×10^5 cells) were treated for 48 h with 10, 100, 300, and 1000 nM of **1a**, **1b**, **2** or **19** at 37 °C in an atmosphere containing 5% CO_2. Fludarabine (F-ara-A) dosed at 10 µM was used as a control. The cells were centrifuged and labeled with CD19/CD5/DiOC6 and subjected to flow cytometry. The data was analyzed using FlowJo software. In order to discriminate the compound specific-induced apoptosis *versus* background spontaneous cell death from in vitro culture conditions, we calculated the percentage of specific induced apoptosis (SIA) using the following formula: % SIA = [(compound induced apoptosis − media only spontaneous apoptosis) / (100 − media only spontaneous apoptosis)] × 100. The dose-response curves were plotted to determine IC_{50} values using the GraphPad Prism version 6.0c software.

Reverse transcriptase PCR (RT-PCR) analyses: CLL-B (5×10^6 cells/well) were treated with a given dose of compound from a DMSO stock solution over 4 h. RNA isolation and cDNA preparation, PCR reaction was performed in 20 µL of reaction volume as described previously.[S3] PCR conditions give by incubation at 94 °C for 3 min; 35 cycles of 94 °C for 30 s, 55-60 °C (annealing temperature: 55 °C for *GAPDH*, 53.6 °C for *RNU6A*, 58 °C for *DNAJB1*, 54 °C for *SF3A1*, 55 °C for *PRPF4*, 55 °C for *ARF4*, and 55 °C for *U2AF2*) for 30 s, and 72 °C for 1 min; followed by 72 °C for 5 min. PCR products were separated on a 2% agarose gel and stained with ethidium bromide. Details of the primers used for RT-PCR are provided in Table S1.

Quantitative reverse transcription-PCR (qRT-PCR): cDNA was prepared using identical methods as used for RT-PCR analysis. The amount of unspliced RNA for different genes was determined using Power SYBR Green PCR master mix (Applied Biosystems) by qRT-PCR using specific primers designed for detection of the intron of each gene (Supplementary Table S2). The qPCR was performed using 5 pM of each primer on 20 ng of the obtained cDNA. PCR conditions were as follows: one cycle of 50 °C for 2 min (UDG Incubation), one cycle of 95 °C for 10 min (UDG Inactivation), followed by 95 °C for 15 sec; 60 °C for 30 s for 40 cycles and adding a step for dissociation using a 7900 HT Fast Real Time PCR System (Applied Biosystems). Unspliced RNA levels were calculated using 2-ΔΔCT method.[S4] *GAPDH* was used as a control for normalization.

G. Additional References.

(S1) Noel, A.; Delpech, B.; Crich, D. *Org. Lett.* **2012**, *14*, 4138.

(S2) Villa, R.; Mandel, A. L.; Jones, B. D.; La Clair, J. J.; Burkart, M. D. *Org. Lett.* 2012, *14*, 5396.

(S3) Kashyap, M. K.; Kumar, D.; Villa, R.; La Clair, J. J.; Benner, C.; Sasik, R.; Jones, H.; Ghia, E. M.; Rassenti, L. Z.; Kipps, T. J.; Burkart, M. D.; Castro, J. E. *Haematologica*. **2015**, *100*, 945

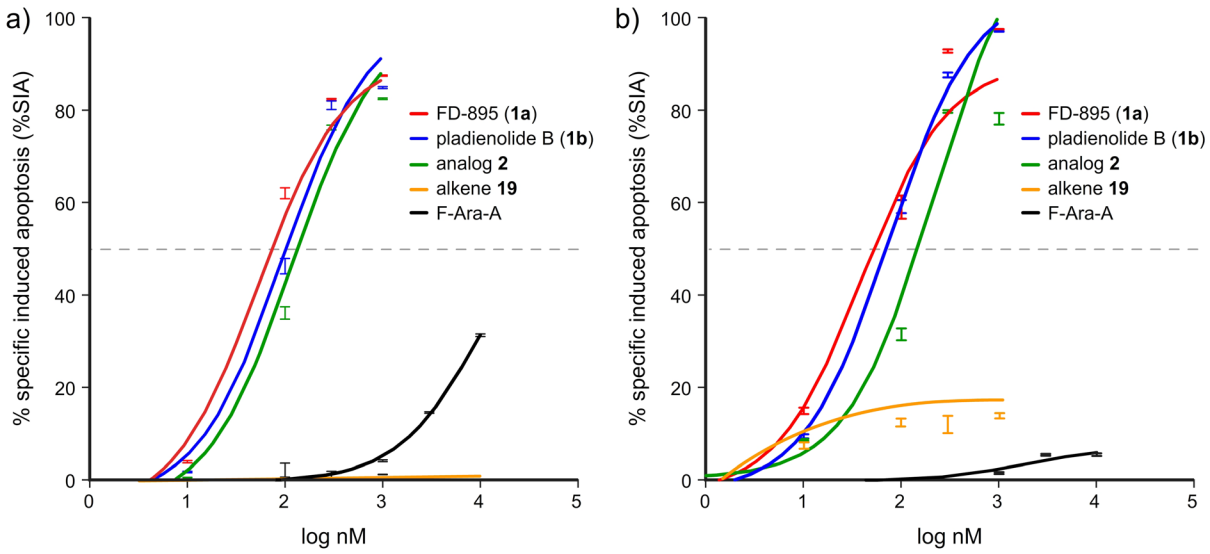
(S4) Livak, K.J., Schmittgen, T.D. *Methods*. **2001,** *25*,402.

Table S1. RT-PCR forward (FP) and reverse (FP) primers as defined by the exon, sequence and annealing temperature (Ta).

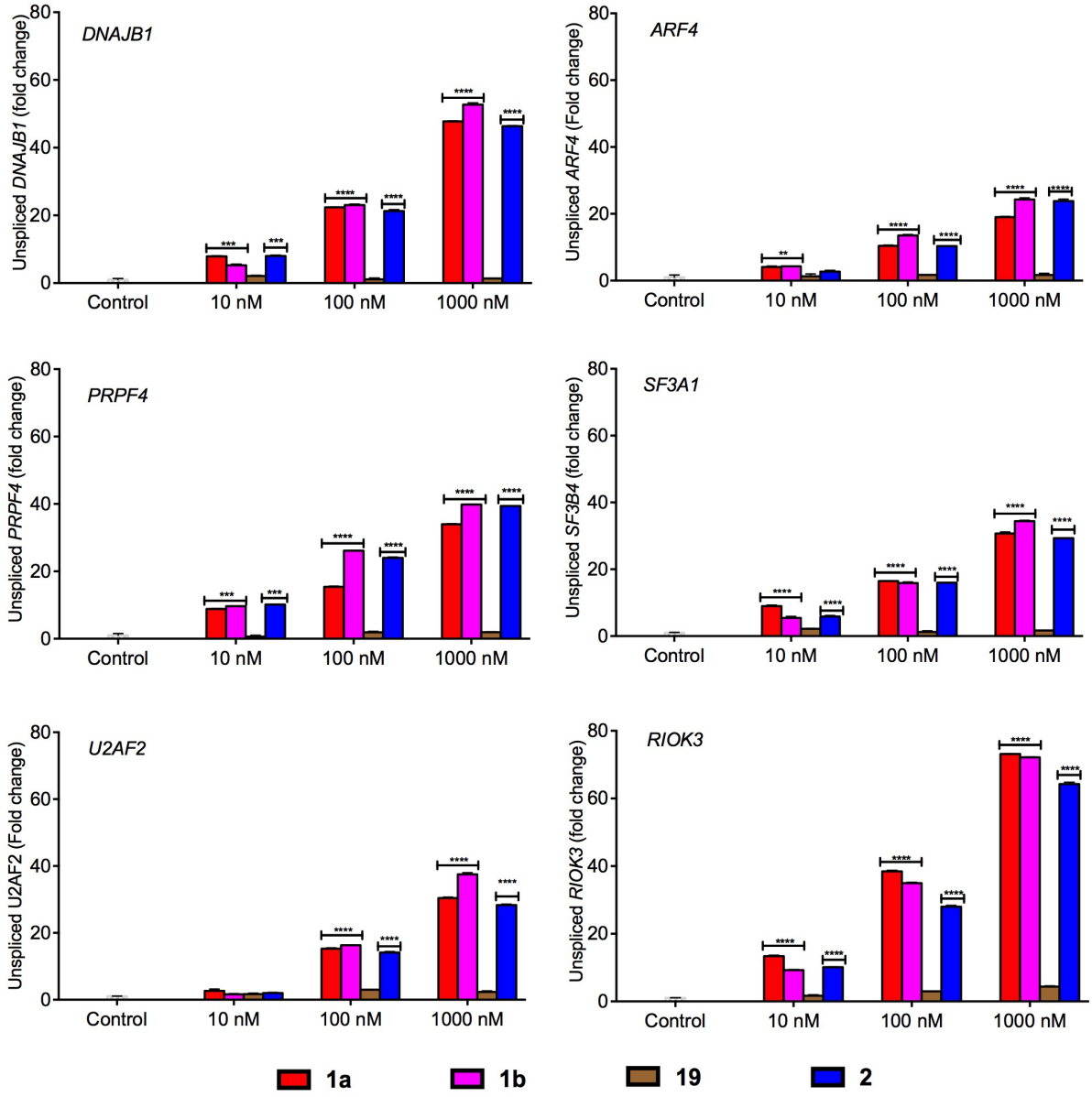
Primer	Direction	Exon	5' Sequence 3'	Ta
DNAJB1	FP	Exon 2	GAACCAAAATCACTTTCCCCAAGGAAGG	58
	RP	Exon 3	AATGAGGTCCCCACGTTTCTCGGGTGT	
SF3A1	FP	Exon 6	GGCCTATGCTCAGATCGACT	54
	RP	Exon 7	ATCAGACTCGACCTCCATC	
PRPF4	FP	Exon 8	GAGTGGGCTTTGCAAGCTCT	55
	RP	Exon 9	CTGTCGAGACTCCAAAGCTT	
ARF4	FP	Exon 2	GATTGGATGCTGCTGGCAA	55
	RP	Exon 3	CACCAACATCCCATACTGTG	
U2AF2	FP	Exon 4	AGGTCCGTAAATACTGGGAC	55
	RP	Exon 5	CTCAGTGATGCCAAAGGGGA	
GAPDH	FP	Exon 3	TGGTCACCAGGGCTGCTT	55
	RP	Exon 4	AGCTTCCCGTTCTCAGCCTT	
RNU6A	FP	Intronless	CGCTTCGGCAGCACATATAC	53.6
	RP	Intronless	GAATTTGCGTGTCATCCTT	
H2A	FP	Intronless	ATGGCTGCGGTCCTCGAGTAT	61.0
	RP	Intronless	TCAGTTCCTCGTTGCGGAT	

Table S2. Sequences of the qRT-PCR primers used in this study.

qRT-PCR primers		
Primer	**Location**	**5' Sequence 3'**
DNAJB1-FP	Intron 2	GGCCTGATGGGTCTTATCTATGG
DNAJB1-RP	Intron 2	TTAGATGGAAGCTGGCTCAAGAG
RIOK3 -FP	Intron 3	CCTTATTGTGACAACTTCATTGAG
RIOK3-RP	Intron 3	TGAAGATTTACTTAGGAGCACA
SF3A1-FP	Intron 6	GGTGTTCCCAGAGAGCAGTAG
SF3A1-RP	Intron 6	GCTGGGGCCATGTCTGTTTT
PRPF4-FP	Intron 8	TGCTTGACACTCAGACCCCA
PRPF4-RP	Intron 8	AAAATGCCAGAGTGTGACTGC
ARF4-FP	Intron 2	GTAAGAAAGTTTACAGATGACTT
ARF4-RP	Intron 2	AGATAATCAACATGCTTAACAAA
U2AF2-FP	Intron 4	TCTCCGTCAGTCATTCCCCT
U2AF2-RP	Intron 4	TCATTCCCCTGTCAACCACG
GAPDH-FP	Exon 3	TGGTCACCAGGGCTGCTT
GAPDH-RP	Exon 4	AGCTTCCCGTTCTCAGCCTT
FP: forward primer; RP reverse primer		

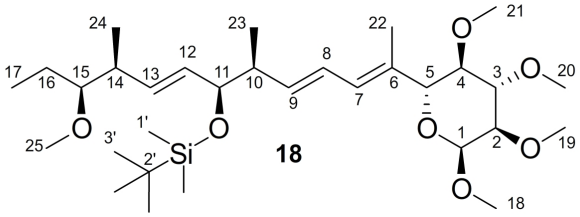


Supplementary Figure S1. CLL-B cells cultured either alone or with stromal cell support were treated with **1a**, **1b**, **2**, **19**, or F-ara-A for 48 h at 37 °C followed by flow cytometric analysis and determination of the % SIA, as described in the experimental procedures above. . Analyses were derived from two CLL patients as indicated in the plots a) and b).



Supplementary Figure S2. qRT-PCR data associated with the RT-PCR data from selected genes depicted in Fig. 5 of the manuscript. The statistical differences for the mean values were compared with control are indicated as follows: ***, and **** denote means $p<0.001$; and $p<0.0001$, respectively. GAPDH was used as a control for normalization.

Table S3. NMR data (^{1}H 500 MHz, ^{13}C 100 MHz, $CDCl_3$) for alkene **18**



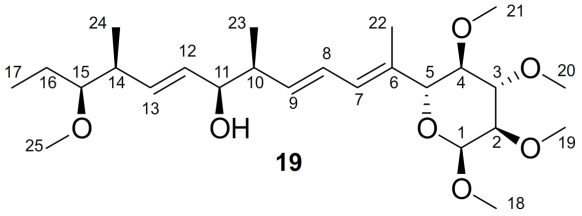
No.	δ_H (J in Hz)	δC, type	gCOSY	HMBC
1	4.79 d (3.6)	97.6, CH	2	2,5,18
2	3.19 dd (3.6, 9.6)	81.9, CH	1,3	3,19
3	3.49 m	83.4, CH	2,4	2,4,20
4	3.07 dd (8.8, 9.8)	82.0, CH	3,5	3,5,6,21
5	3.85 d (9.8)	76.2, CH	4	4,6,22
6		131.3, C		
7	6.08 dd (1.5, 10.7)	130.5, CH	8,22	5,8,9,22
8	6.22 ddd (1.2, 10.8, 15.2)	125.4, CH	7,9	7,10
9	5.69 dd (7.6, 15.2)	138.7, CH	8,10	7,10,11,23
10	2.31 m	44.2, CH	9,11,23	8,9,11,23
11	3.90 (5.5, 6.4)	77.8, CH	10,12	9,10,12,13,23
12	5.38 m	131.8, CH	11,13	11,14
13	5.38 m	134.1, CH	12,14	11,14,24
14	2.31 m	39.7, CH	13,15,24	12,13,15,16,24
15	2.86 dt (4.3, 6.7)	86.3, CH	14,16	13,17,24,25
16a	1.52 m	23.7, CH_2	15,16b,17	14,17
16b	1.38 pd (7.4, 14.2)		15,16a,17	14,15,17
17	0.87 t (7.4)	9.4, CH_3	16a,16b	15,16
18[a]	3.39 s	55.2, CH_3		1
19[a]	3.41 s	60.2, CH_3		2
20[a]	3.62 s	61.2, CH_3		3
21[b]	3.52 s	59.2, CH_3		4
22	1.79 d (1.3)	12.7, CH_3	7	5,6,7,8
23	1.00 d (6.8)	15.5, CH_3	10	9,10,11
24	1.00 d (6.8)	16.4, CH_3	14	13,14,15
25[c]	3.33 s	57.7, CH_3		15
1a'	0.02 s	-4.6, CH_3		
1b'	-0.01 s	-3.9, CH_3		
2'		18.4, C		
3'	0.88 s	26.0, CH_3		

[a] Protons and carbons at 18 and 20 were assigned by ^{1}H,^{13}C HMBC data.

[b] Protons and carbons at 19 and 21 were assigned by ^{1}H,^{13}C HMBC data. However, they could not be unambiguously established due to the close proximity of C2 and C4.

[b] The assignment of the protons and carbons at 25 was further confirmed by the fact that the chemical shifts of protons and carbons at 18, 19, 20 and 21 were comparable to that in precursors such as allylic alcohol **8**.

Table S4. NMR data (^{1}H 500 MHz, ^{13}C 100 MHz, $CDCl_3$) for alcohol **19**



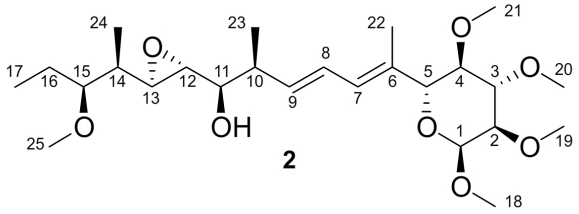
19

No.	δ_H (J in Hz)	δC, type	gCOSY	HMBC
1	4.79 d (3.6)	97.6, CH	2	2,5,18
2	3.19 dd (3.6, 9.6)	81.9, CH	1,3	3,19
3	3.49 m	83.4, CH	2,4	2,4,20
4	3.08 dd (8.6, 9.8)	82.0, CH	3,5	3,5,6,21
5	3.85 d (9.8)	76.1, CH	4	4,6,7,22
6		130.2, C		
7	6.10 dd (1.6, 10.7)	130.0, CH	8,22	5,8,9,22
8	6.33 ddd (1.1, 10.9, 15.2)	127.0, CH	7,9	7,10
9	5.64 dd (8.2, 15.2)	136.9, CH	8,10	7,10,11,23
10	2.43 m	43.5, CH	9,11,23	8,9,11,23
11	3.97 m	76.4, CH	10,12	9
11-OH	3.97 m			11
12	5.45 dd (6.9, 15.5)	132.5, CH	11,13	11,13,14
13	5.58 dt (7.9, 15.5)	135.4, CH	12,14	11,12,14,24
14	2.37 m	39.5, CH	13,15,24	12,13,15,16,24
15	2.89 dt (4.1, 6.6)	86.3, CH	14,16	13,17,24,25
16a	1.52 dqd (4.2, 7.4, 14.8)	23.7, CH_2	15,16b,17	17
16b	1.39 pd (7.3, 14.4)		15,16a,17	14,15,17
17	0.88 t (7.4)	9.6, CH_3	16a,16b	15,16
18[a]	3.38 s	57.7, CH_3		1
19[a]	3.41 s	60.3, CH_3		2
20[a]	3.62 s	61.1, CH_3		3
21[a]	3.52 s	59.2, CH_3		4
22	1.80 d (1.3)	12.8, CH_3	7	5,6,7,8
23	1.03 d (6.8)	16.3, CH_3	10	9,10,11
24	1.01 d (6.8)	15.8, CH_3	14	13,14,15
25[b]	3.34 s	55.3, CH_3		15

[a] Protons at carbons at 18, 19, 20 and 21 were assigned by ^{1}H,^{13}C HMBC data.

[b] The assignment of the protons and carbons at 25 was further confirmed by the fact that the chemical shifts of protons and carbons at 18, 19, 20 and 21 were comparable to that in precursors such as allylic alcohol **8**.

Table S5. NMR data (^{1}H 500 MHz, ^{13}C 100 MHz, C_6D_6) for epoxide **2**



2

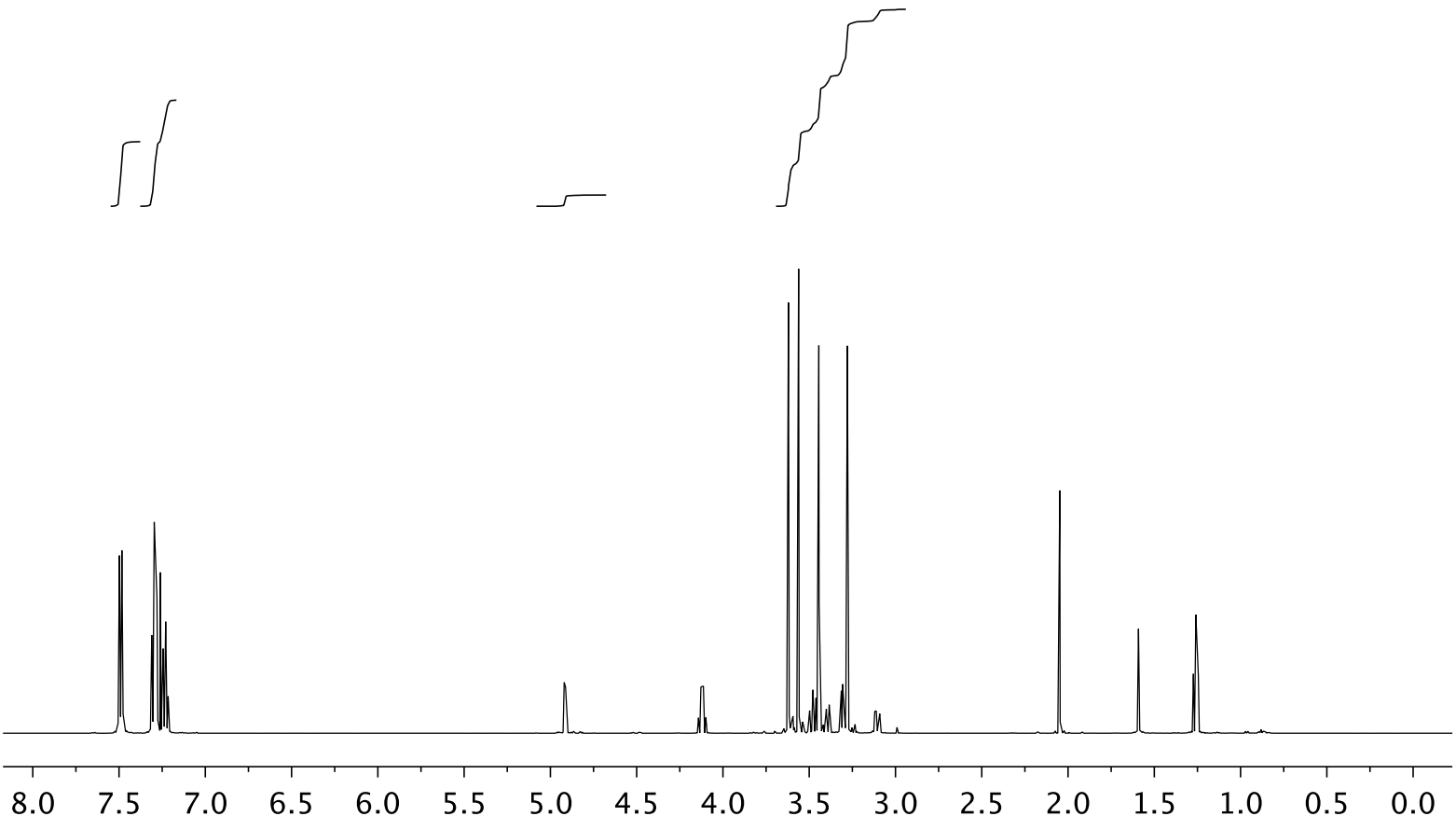
No.	δ_H (*J* in Hz)	δC, type	gCOSY	HMBC
1	4.68 d (3.6)	97.7, CH	2	2,5,18
2	3.21 m	82.2, CH[b]	1,3	3,19
3	3.84 dd (8.7, 9.6)	83.4, CH	2,4	2,4,20
4	3.21 m	82.2, CH[b]	3,5	3,5,6,21
5	4.16 d (9.7)	76.2, CH	4	4,6,7,22
6		133.2, C		
7	6.30 dd (1.1, 11.0)	129.4, CH	8,22	5,8,9,22
8	6.45 ddd (1.1, 10.9, 15.1)	126.6, CH	7,9	6,7,10
9	5.66 dd (8.5, 15.1)	136.3, CH	8,10	7,10,11,23
10	2.42 h (7.6)	41.7, CH	9,11,23	8,9,11,12,23
11	3.21 m	71.7, CH	10,12	9
11-OH	1.74 m			9,11
12	2.85 dd (2.3, 4.6)	58.8, CH	11[c]	11
13	2.89 dd (2.3, 6.8)	57.7, CH	14[c]	12,24
14	1.55 dt (4.3, 6.9)	38.7, CH	13,15,24	13, 24
15	2.82 td (4.8, 7.4)	83.5, CH	14,16	13,17,24,25
16a	1.48 qd (7.3, 14.6)	23.5, CH_2	15,16b,17	14,15,17
16b	1.36 m		15,16a,17	15,17
17	0.84 t (7.4)	9.6, CH_3	16a,16b	15,16
18[a]	3.15 s	54.6, CH_3		1
19[a]	3.26 s	57.2, CH_3		2
20[a]	3.62 s	60.6, CH_3		3
21[a]	3.36 s	59.7, CH_3		4
22	1.85 d (1.3)	12.4, CH_3	7	5,6,7
23	1.14 d (6.9)	16.2, CH_3	10	9,10,11
24	1.00 d (6.8)	10.4, CH_3	14	13,14,15
25[b]	3.11 s	56.7, CH_3		15

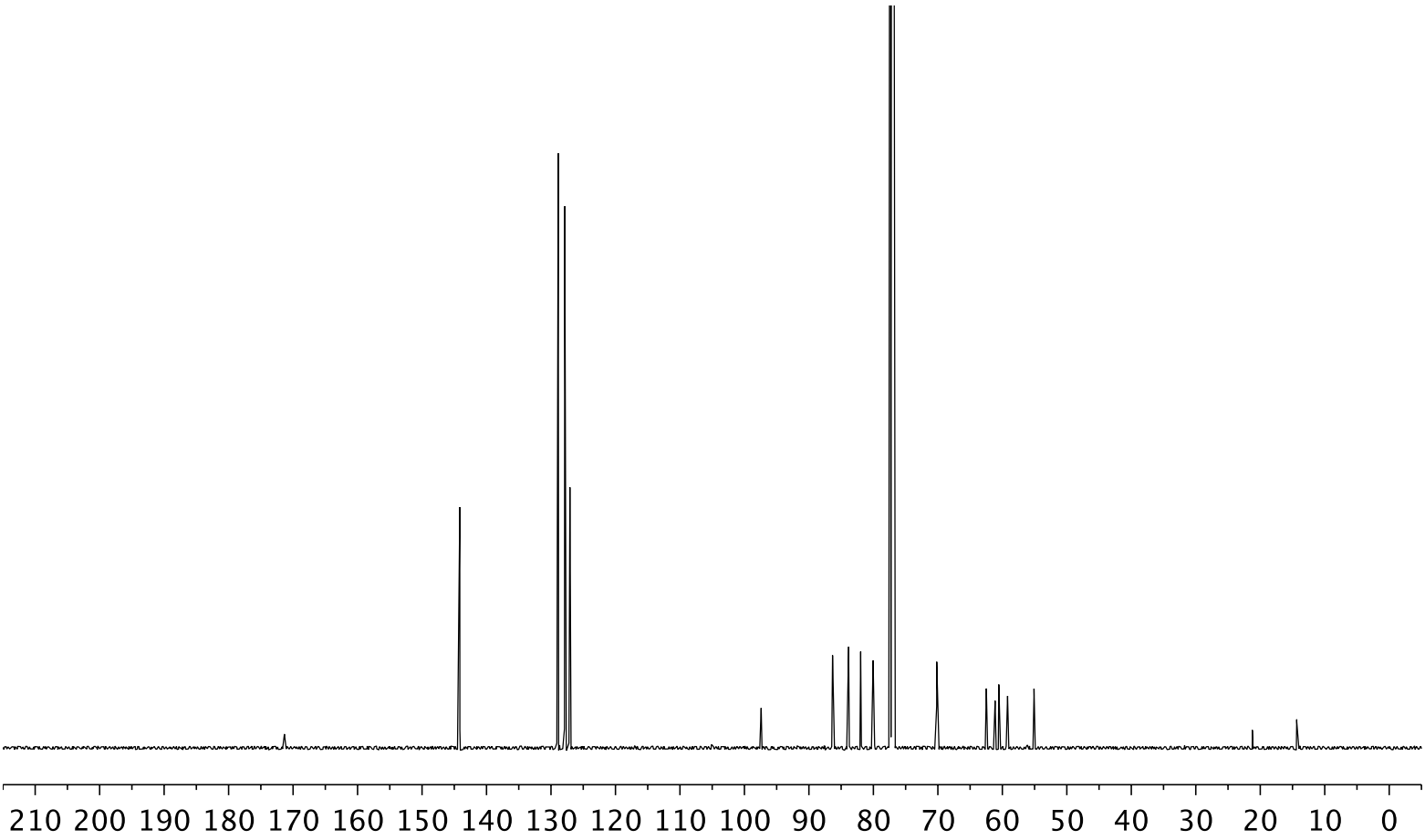
[a] Protons at carbons at 18, 19, 20 and 21 were assigned by ^{1}H,^{13}C HMBC data.

[b] Protons at carbons 2 and 4 were assigned by ^{1}H,^{13}C HMBC data.

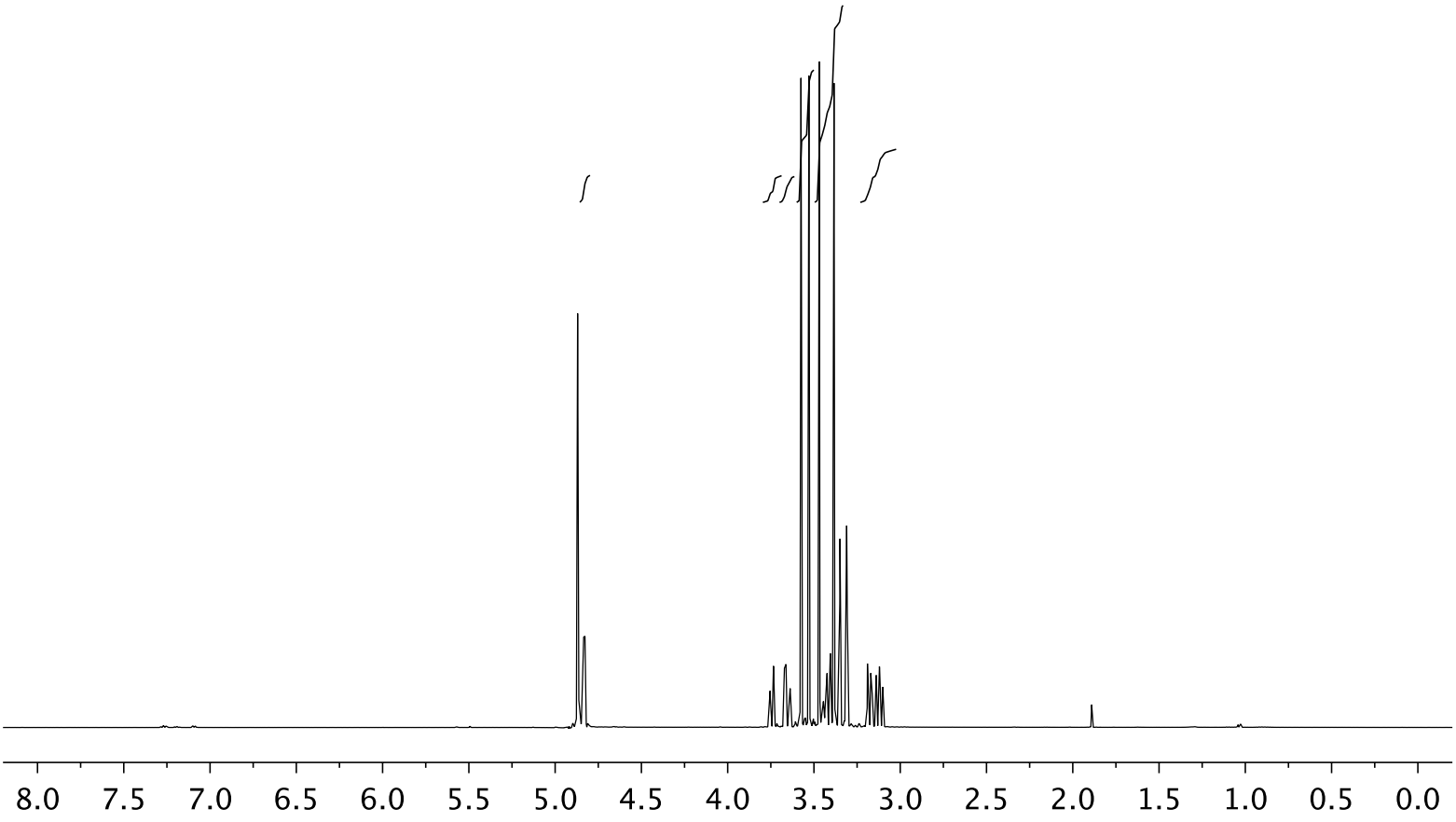
[c] The gCOSY peak for 12,13 was not identified due to the proximity of protons at C12 and C13

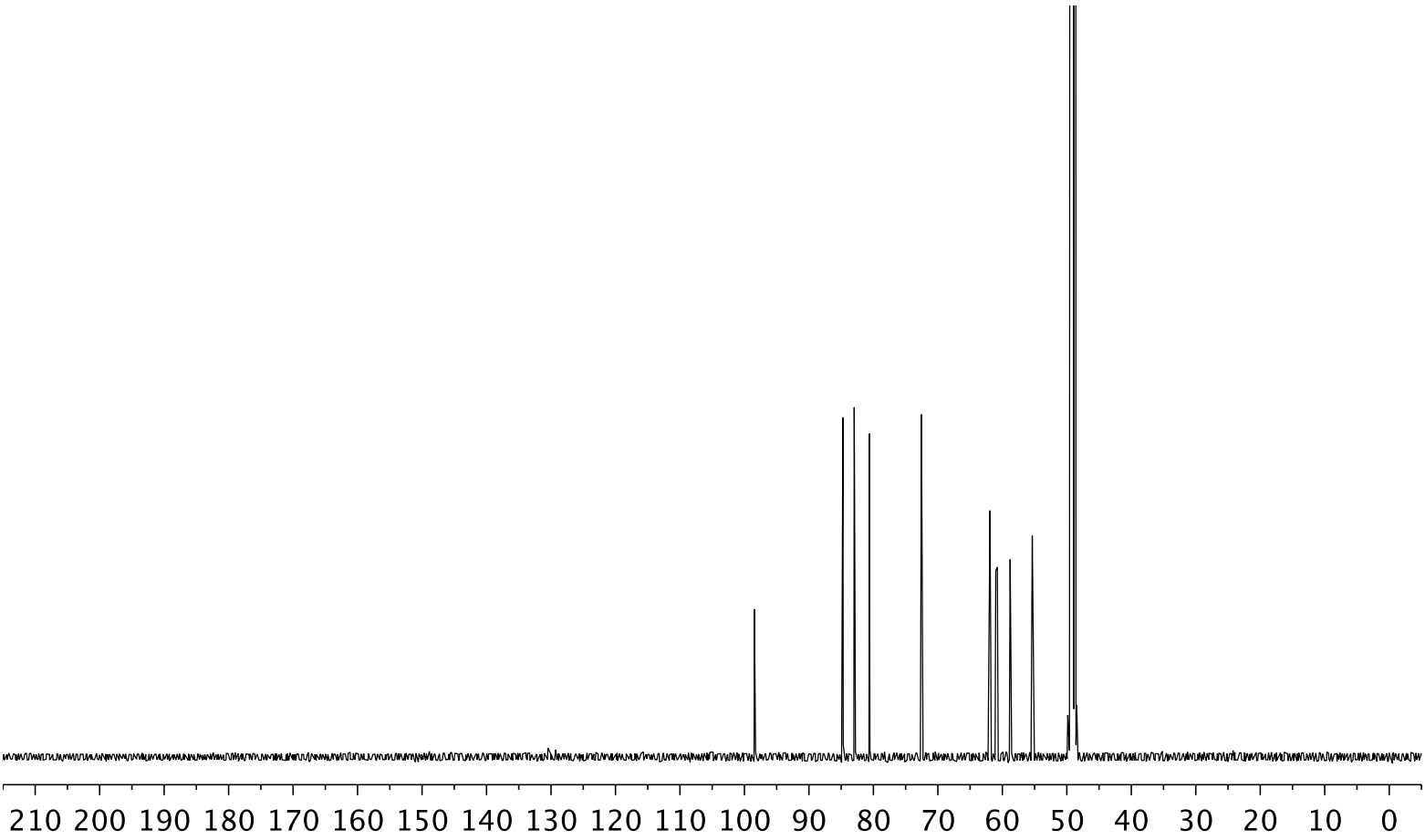
^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of tritylether **S3** in $CDCl_3$



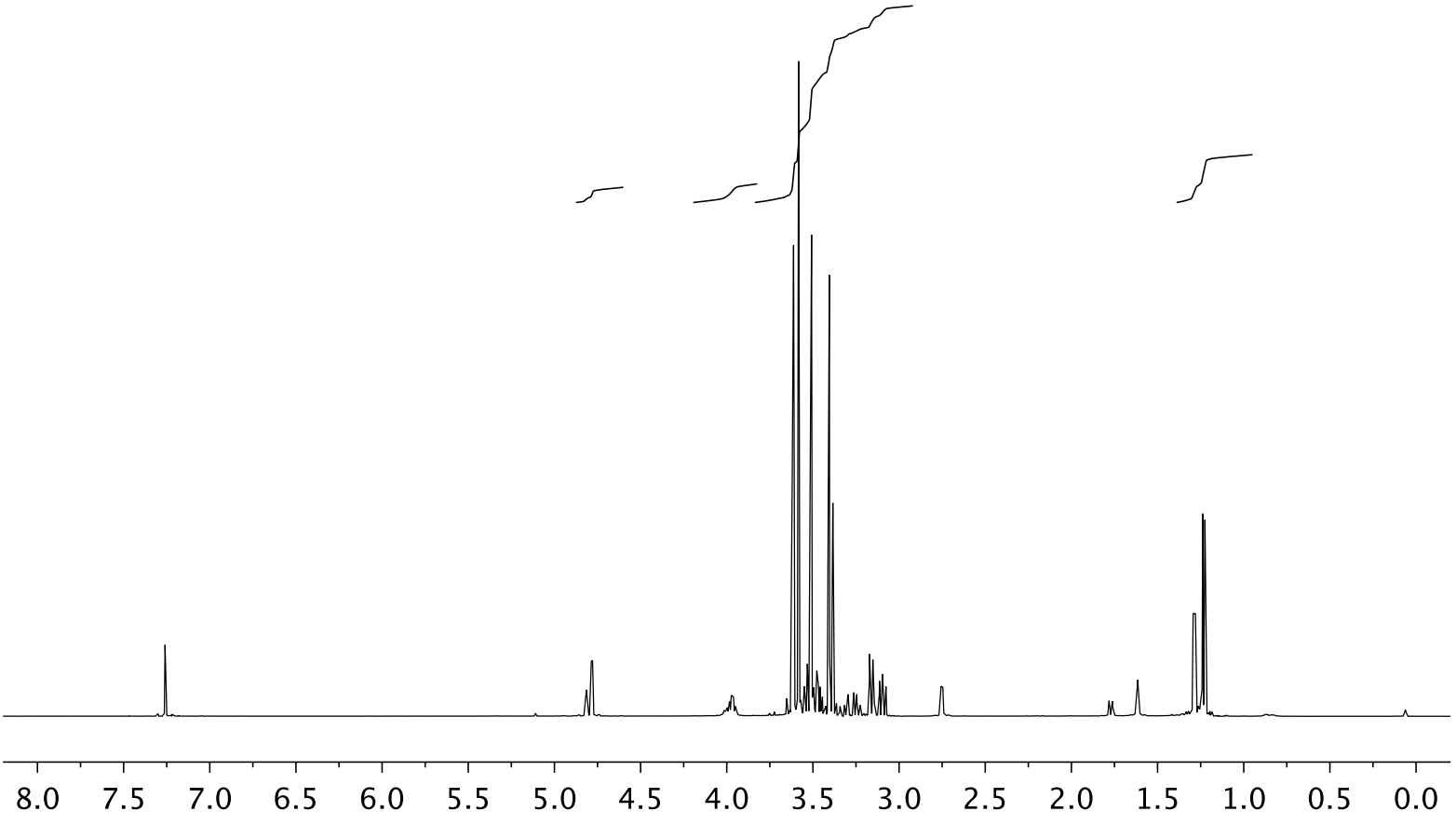


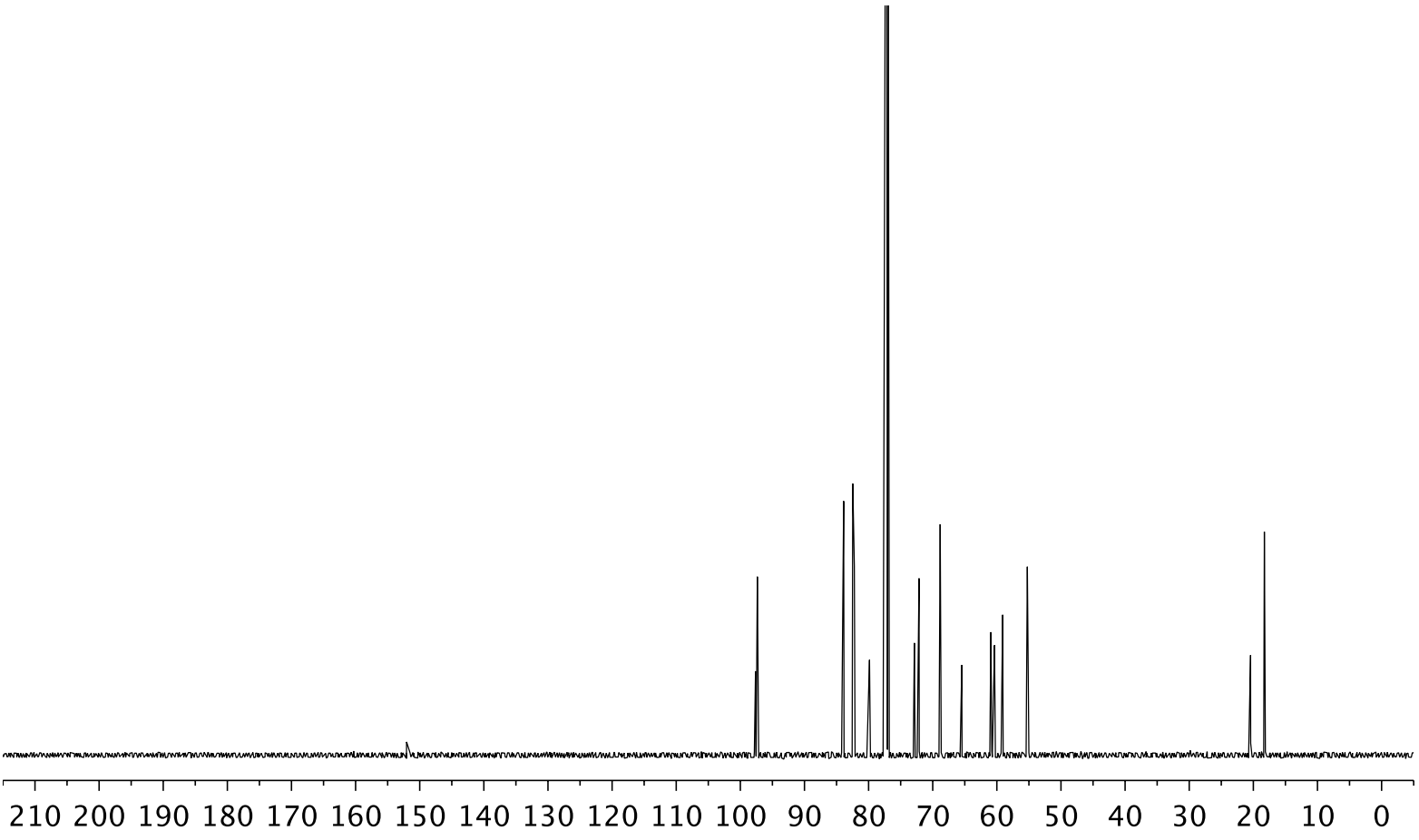
^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of alcohol **3** in CD_3OD



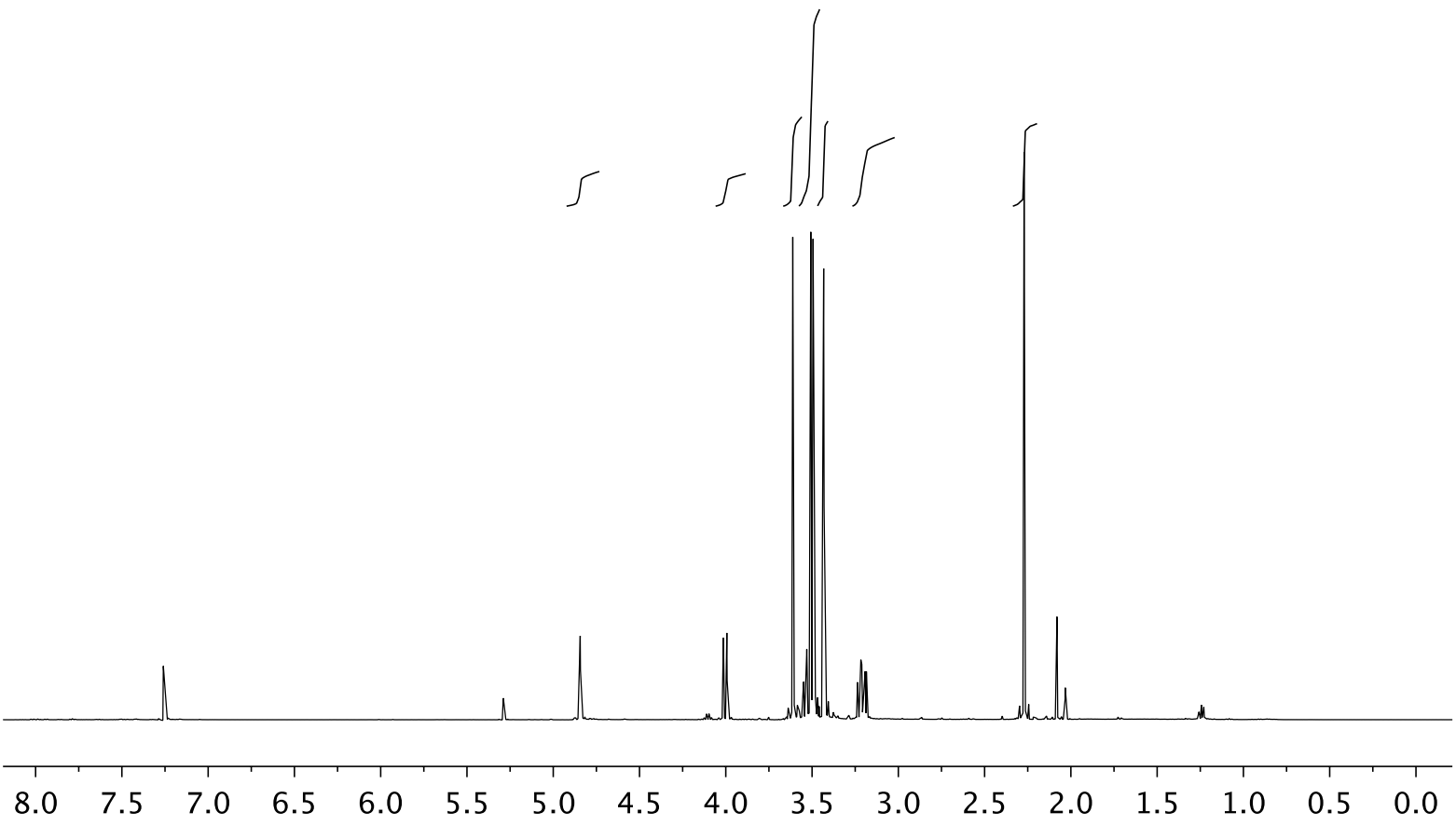


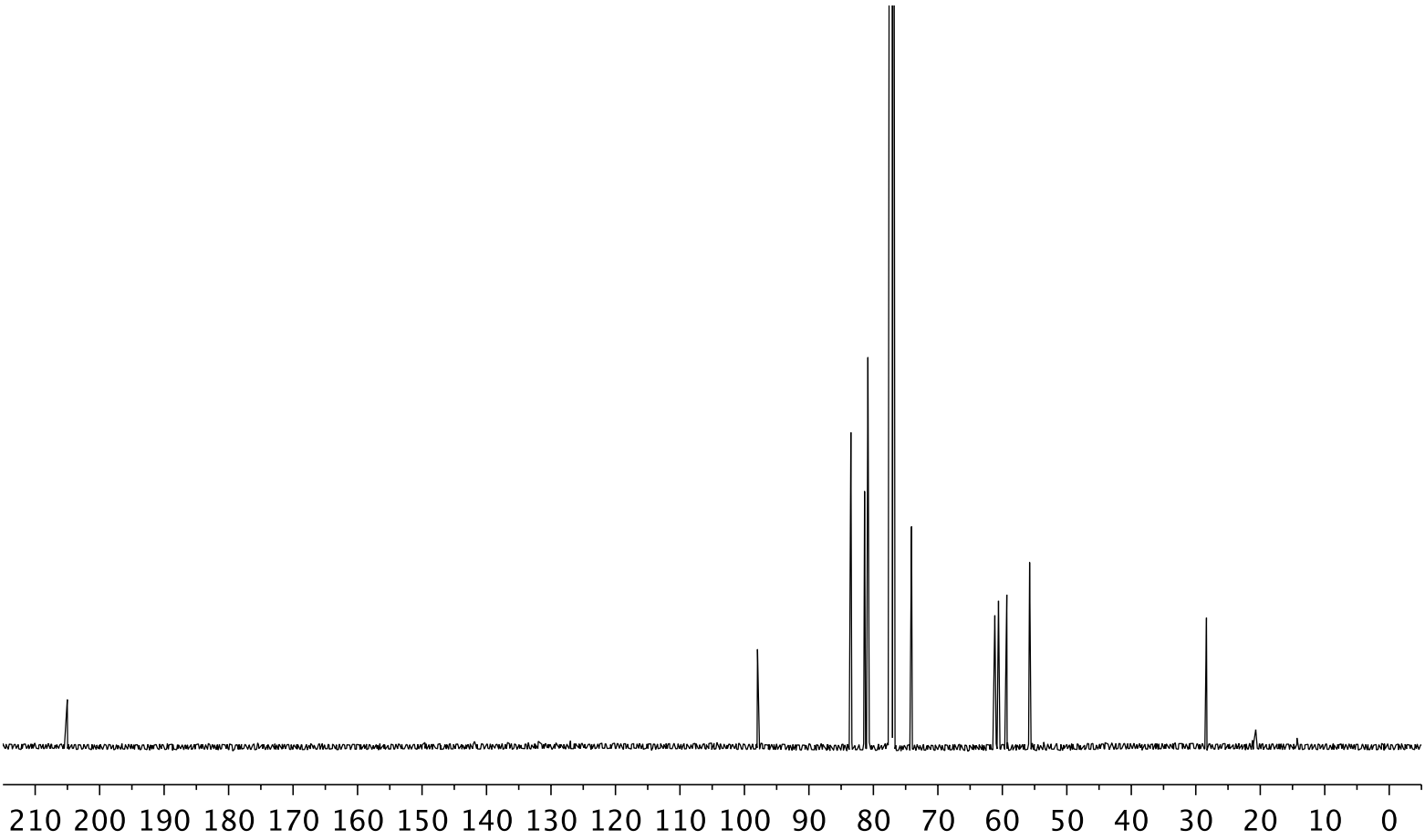
^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of alcohol **5** in $CDCl_3$



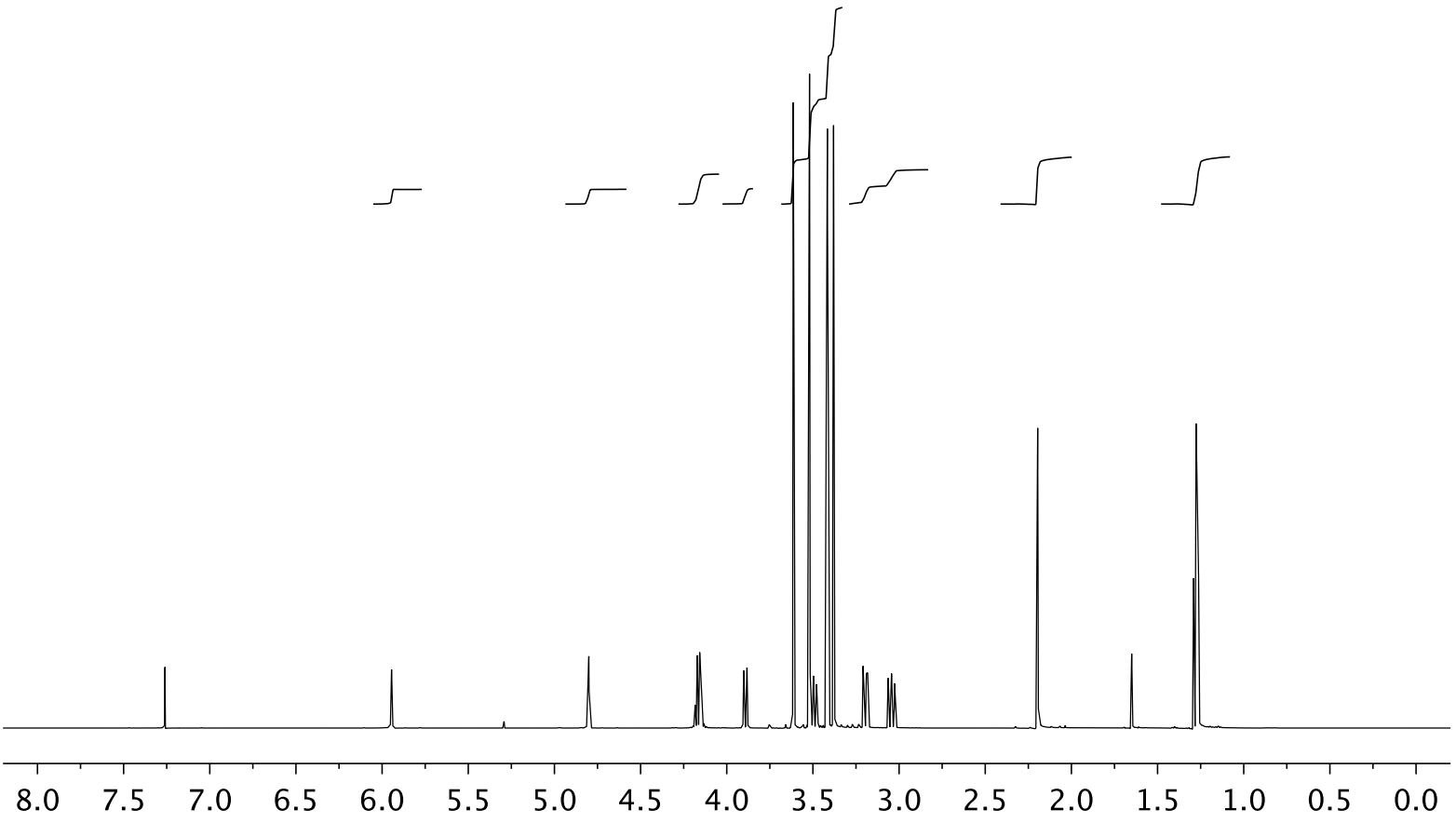


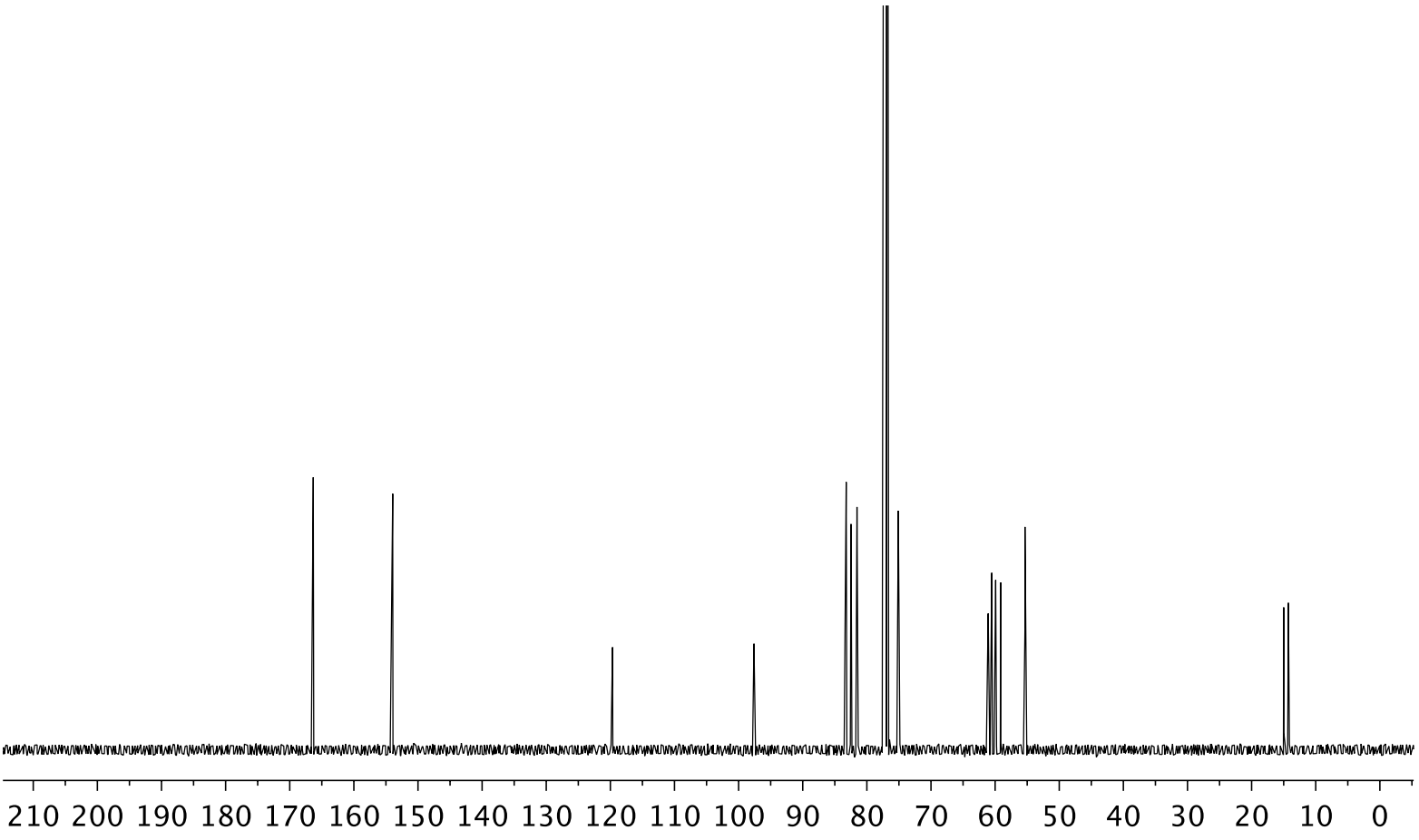
^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of ketone **6** in $CDCl_3$



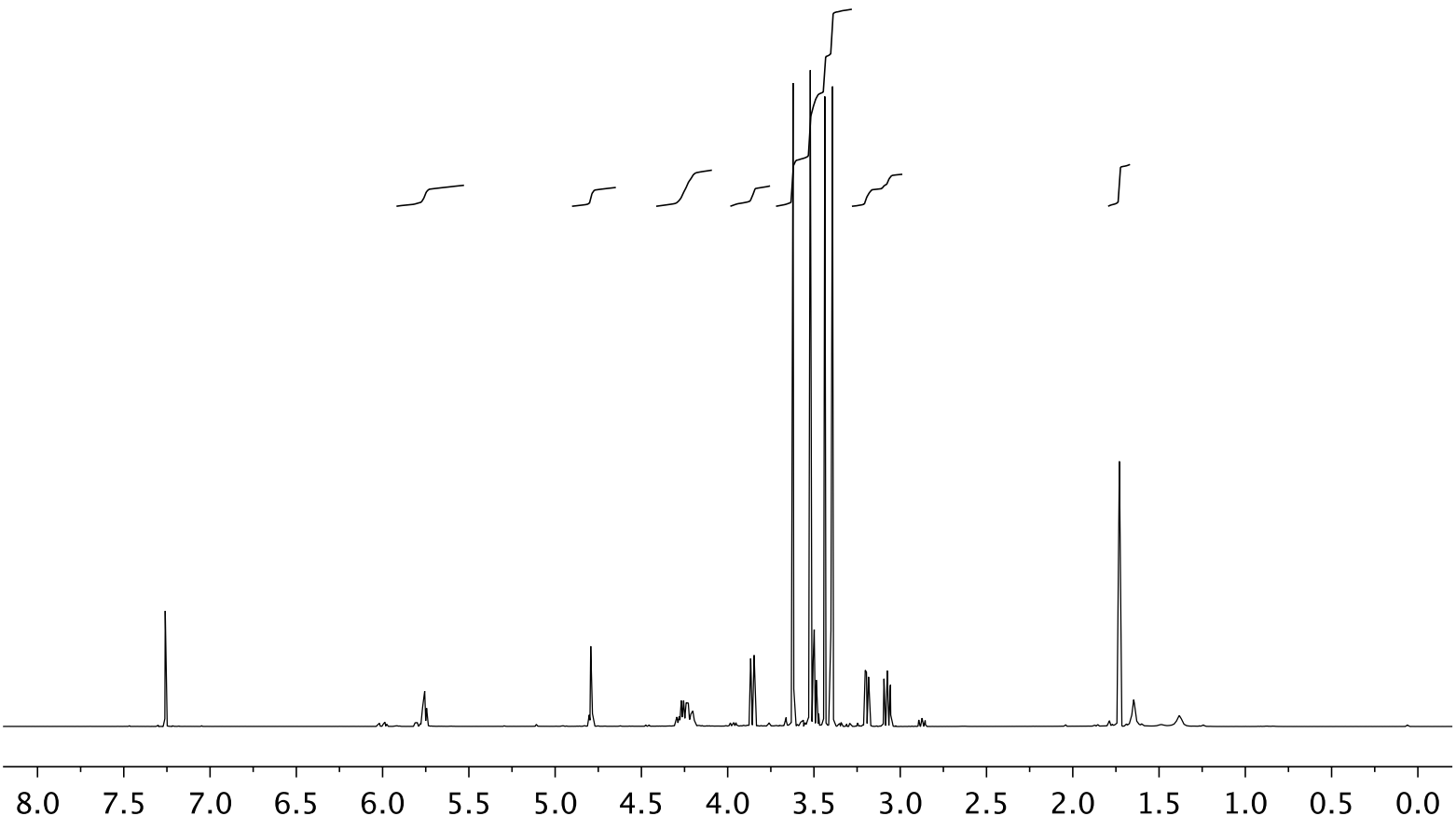


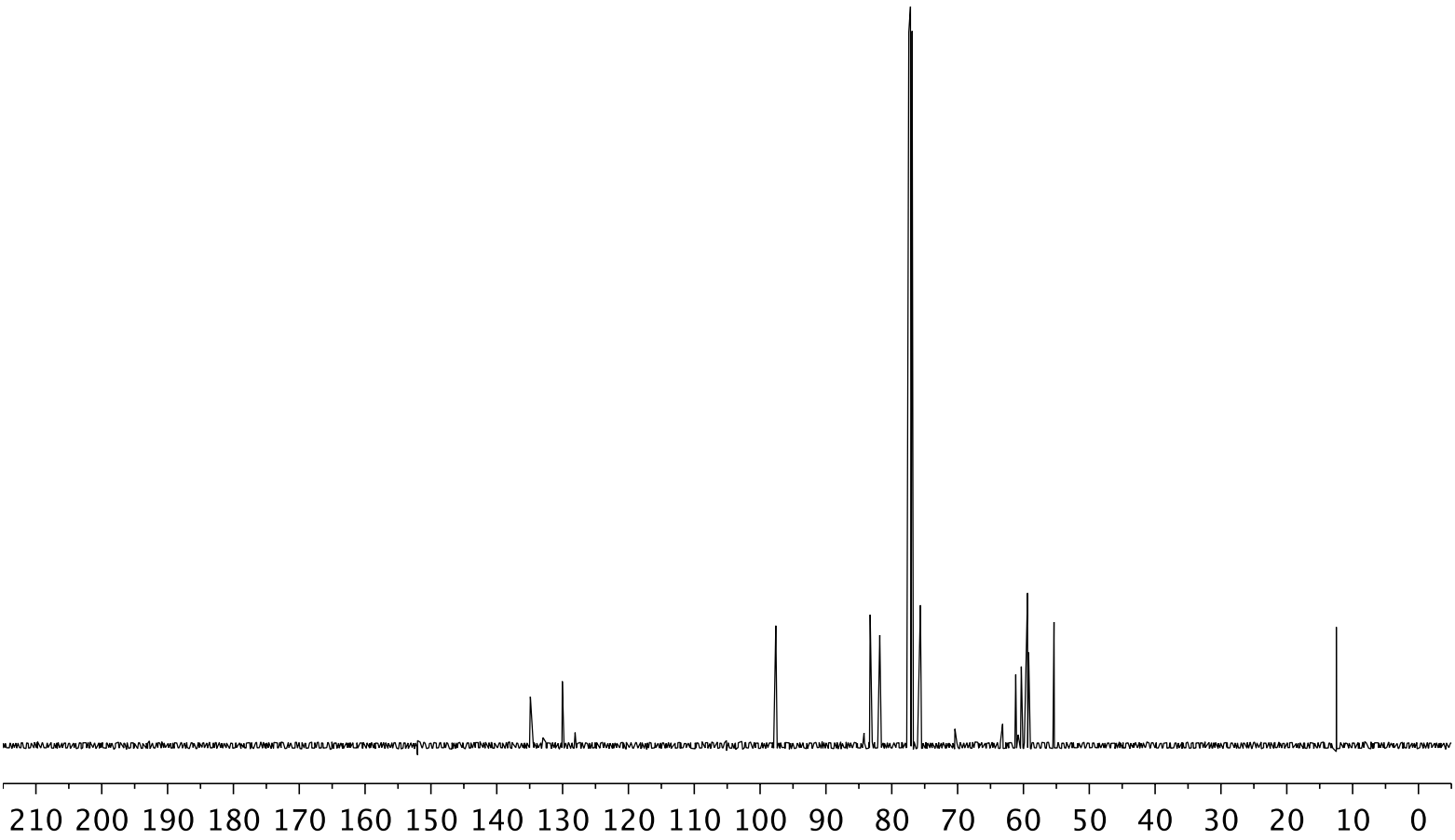
^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of enone **7** in $CDCl_3$



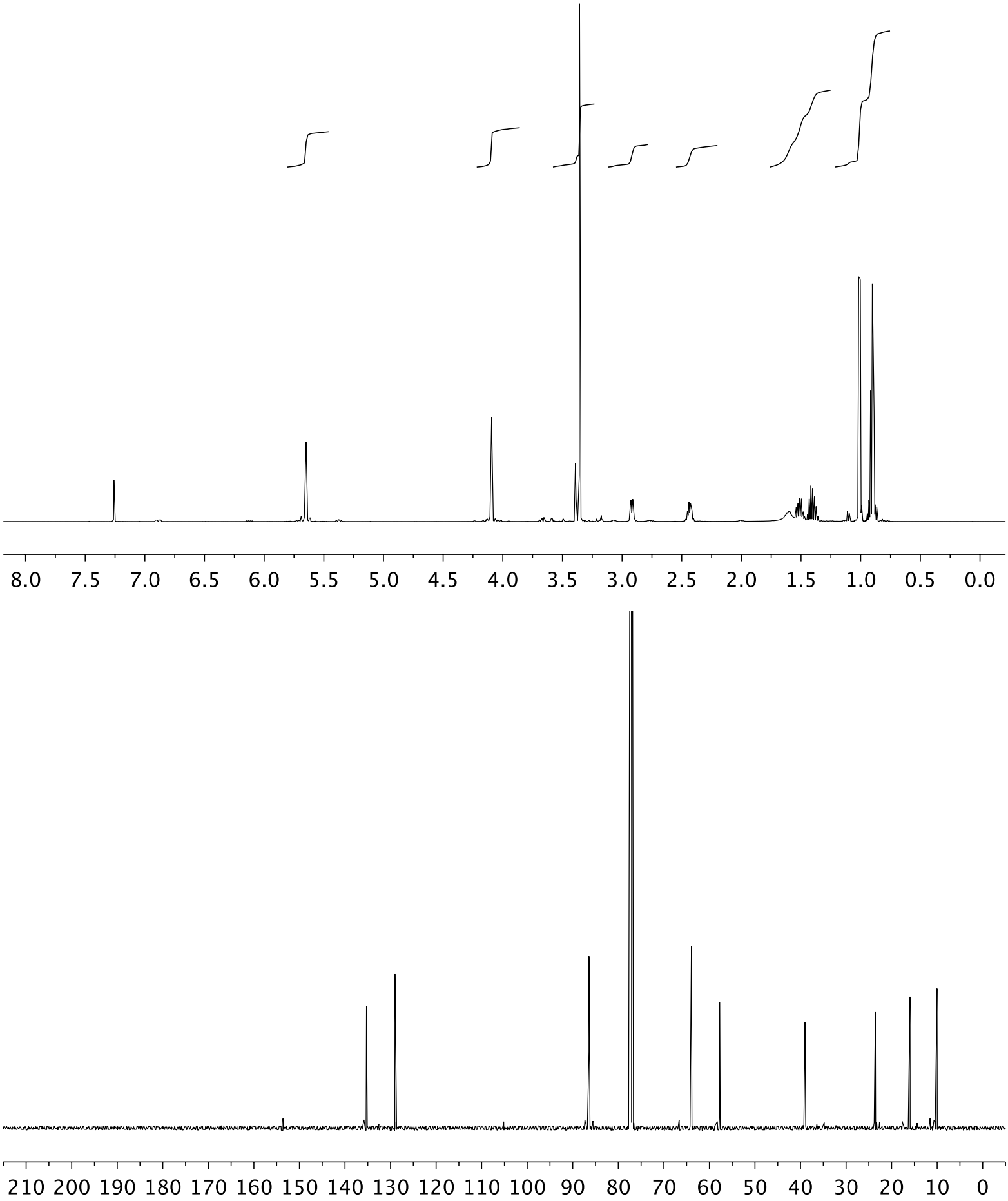


^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of allylic alcohol **8** in $CDCl_3$

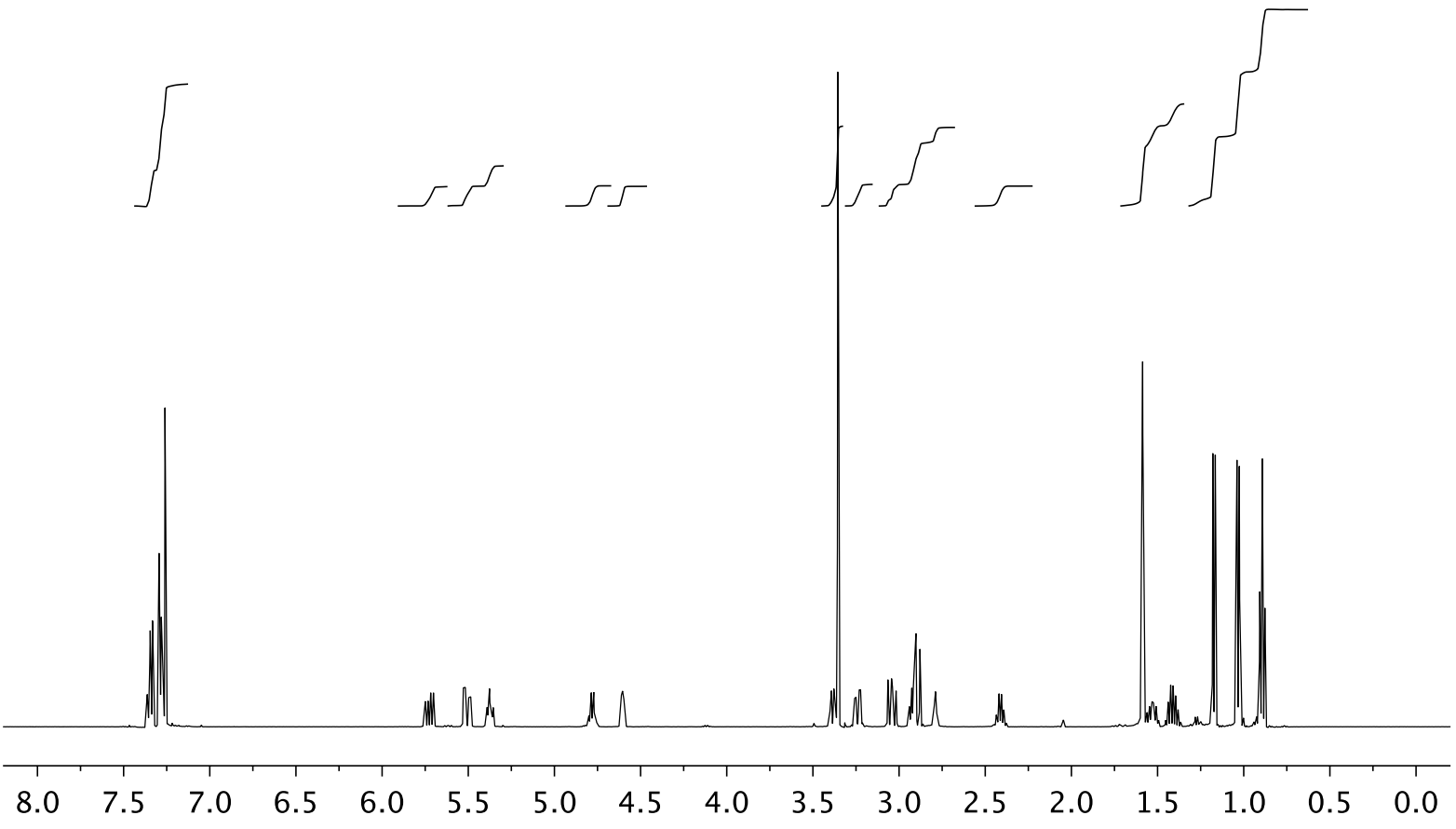


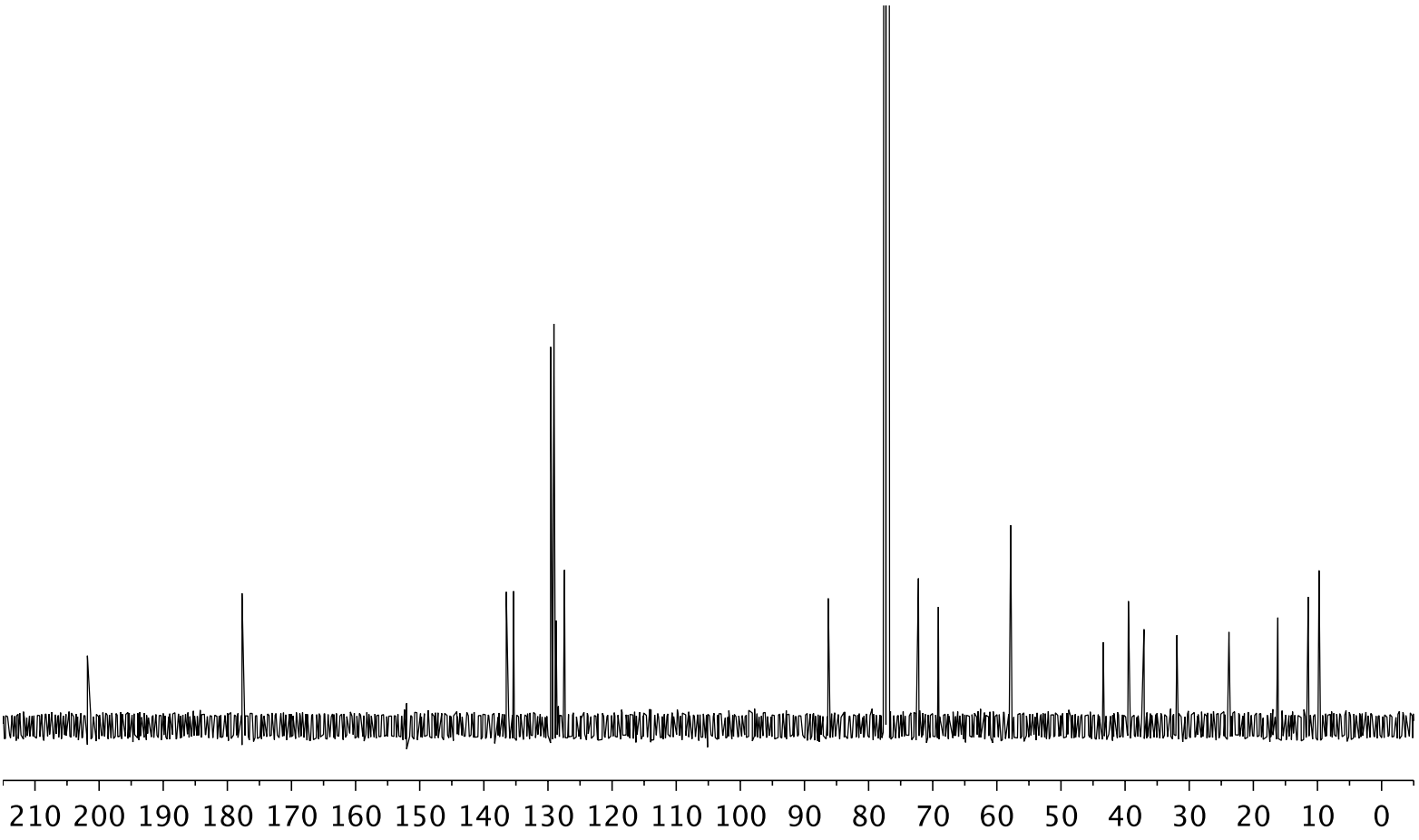


^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of alcohol **9** in $CDCl_3$

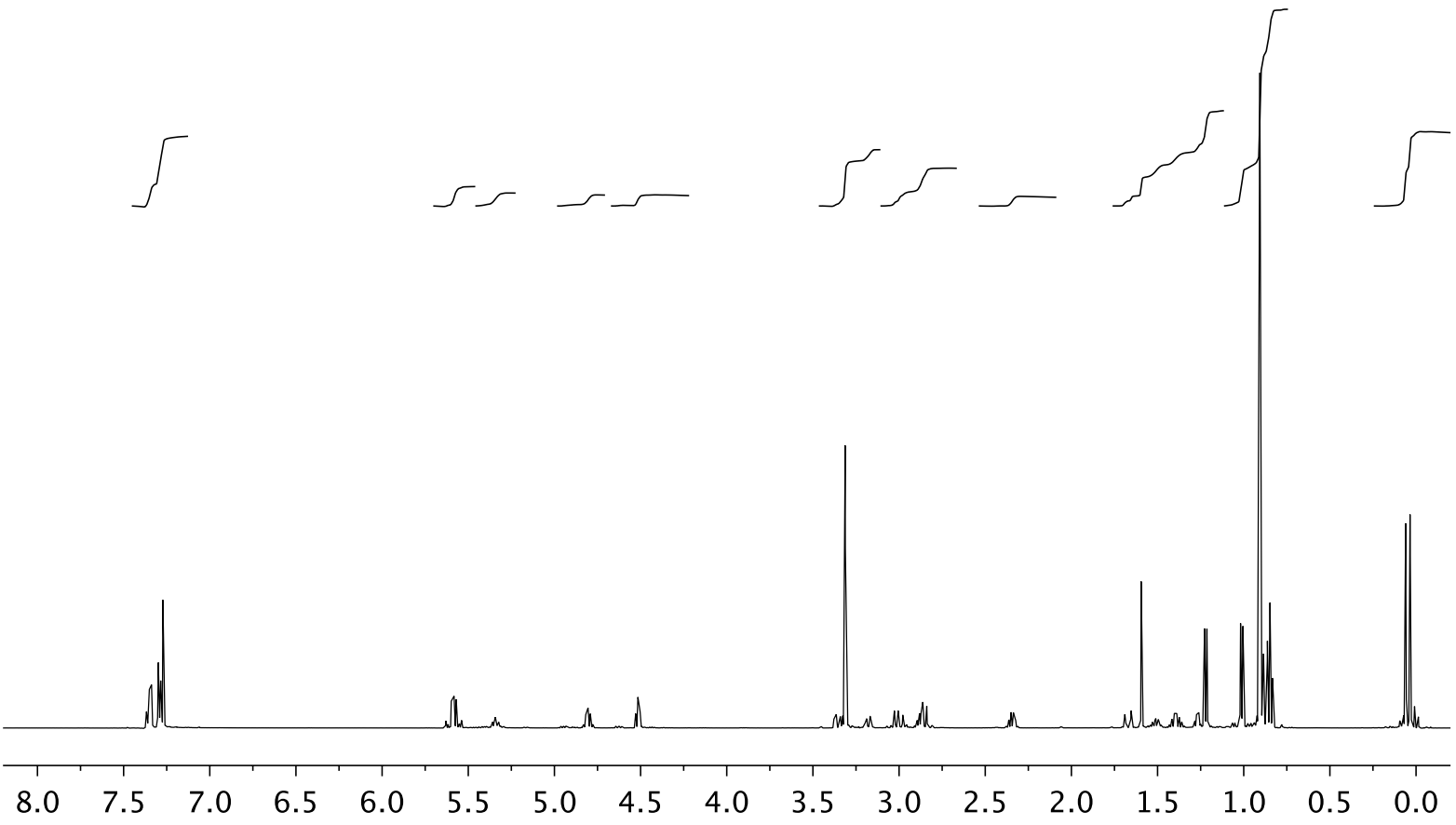


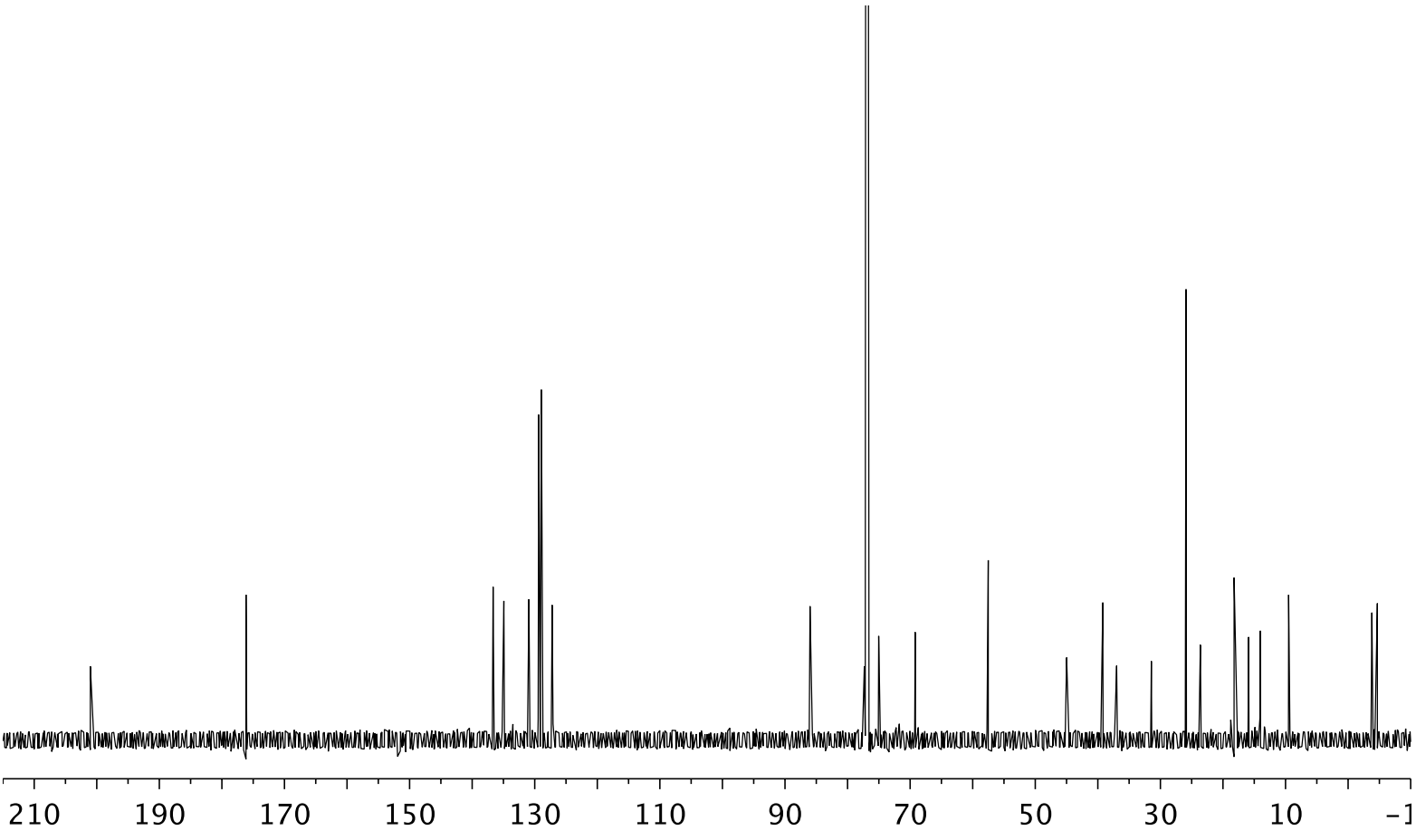
^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of adduct **12** in $CDCl_3$



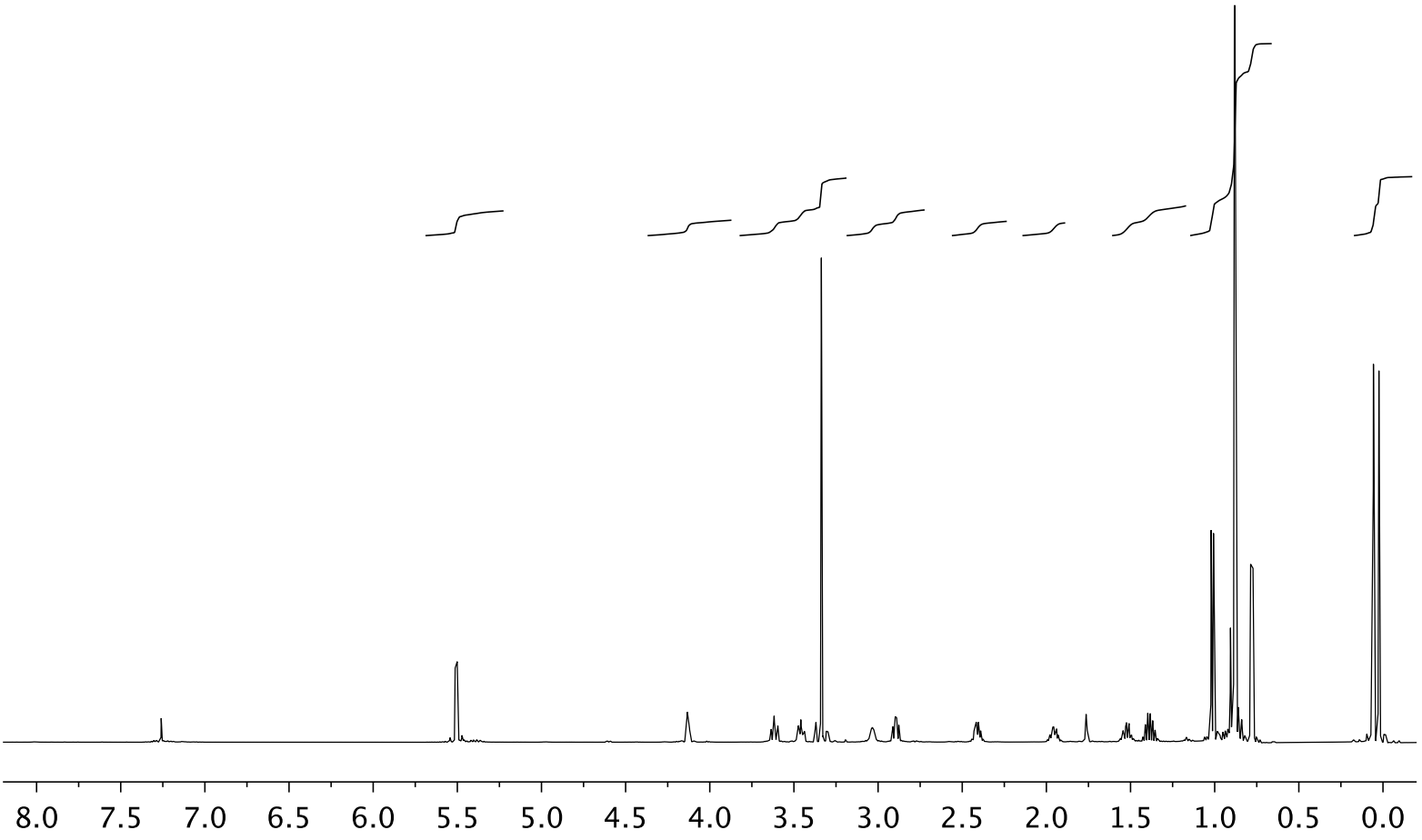


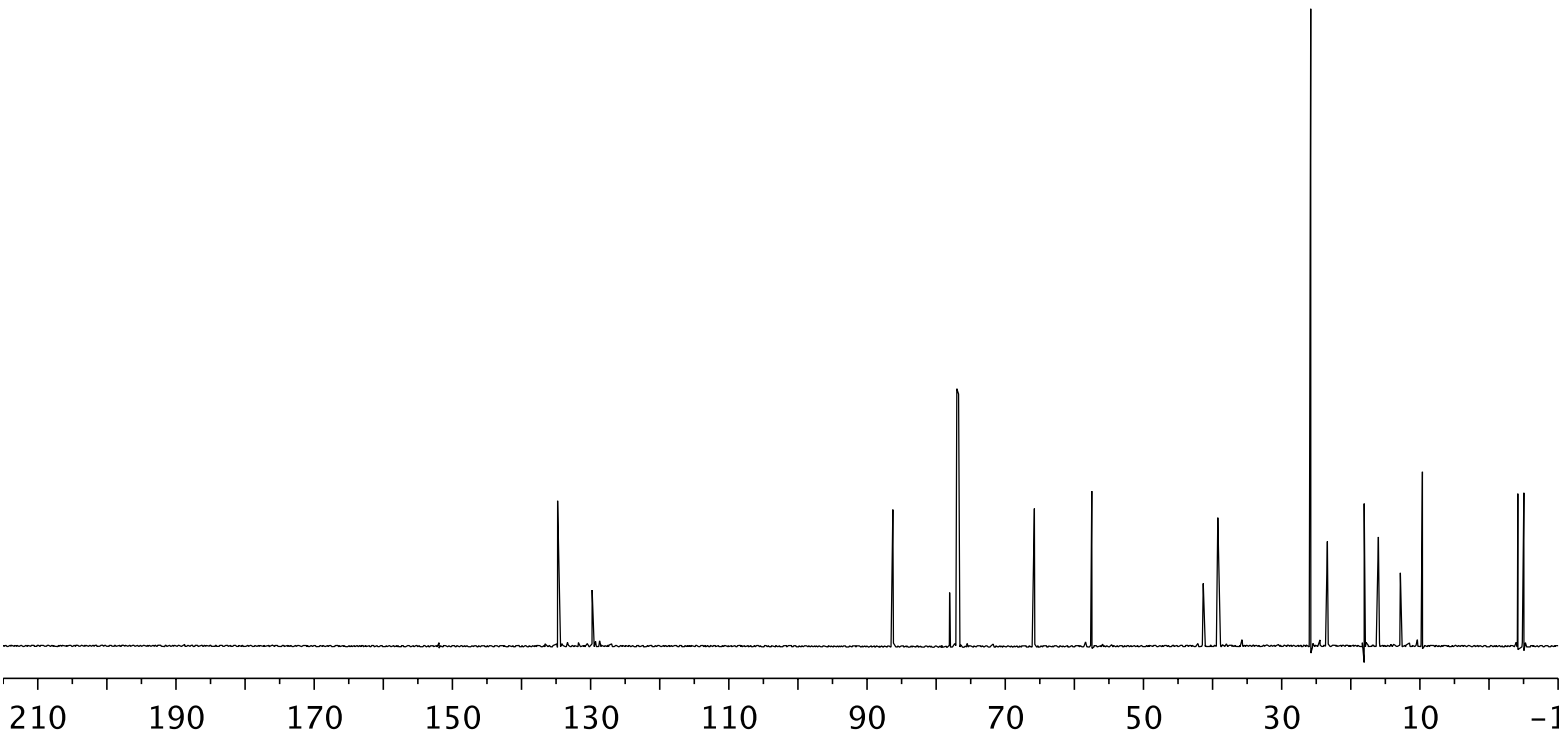
^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of adduct **13** in $CDCl_3$



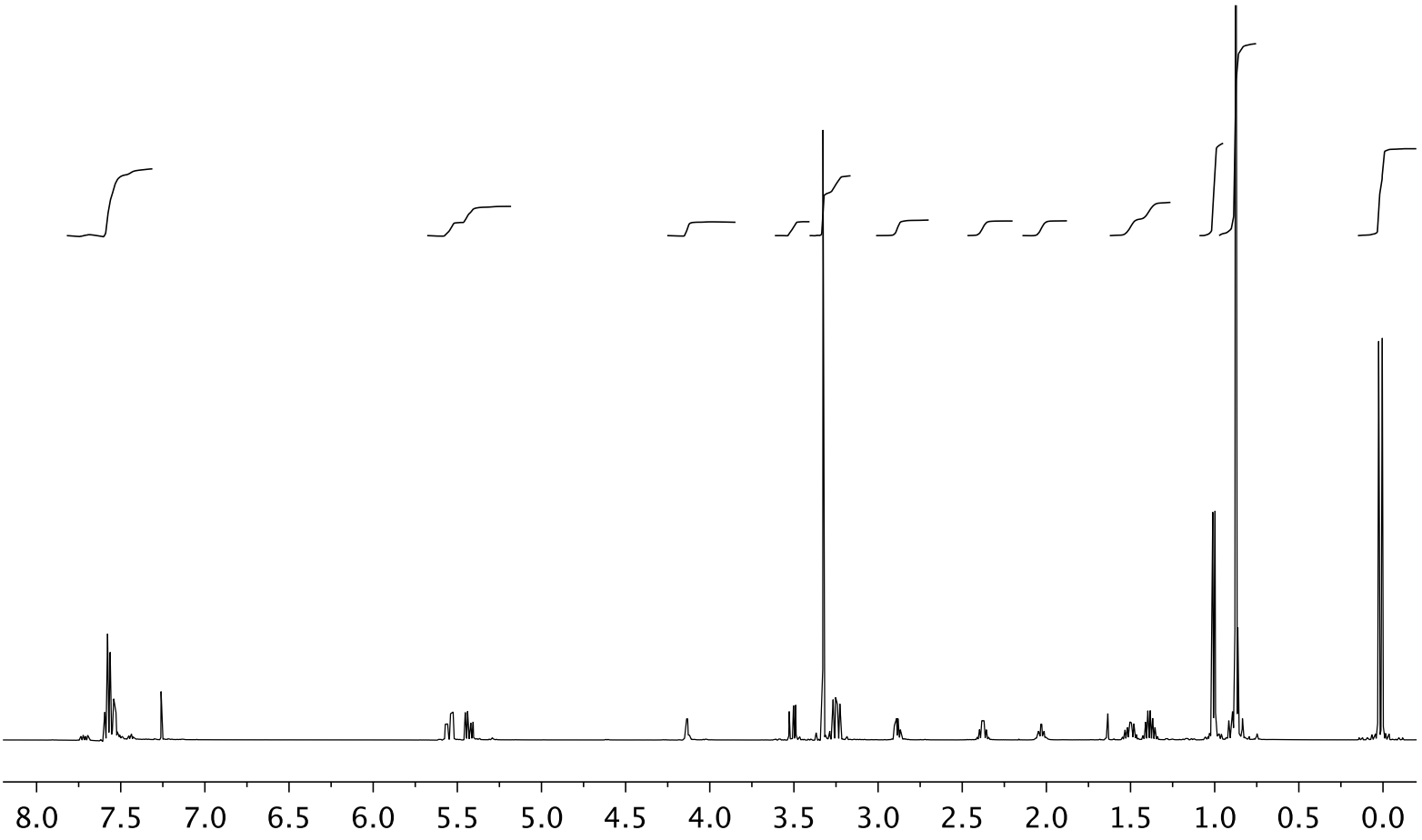


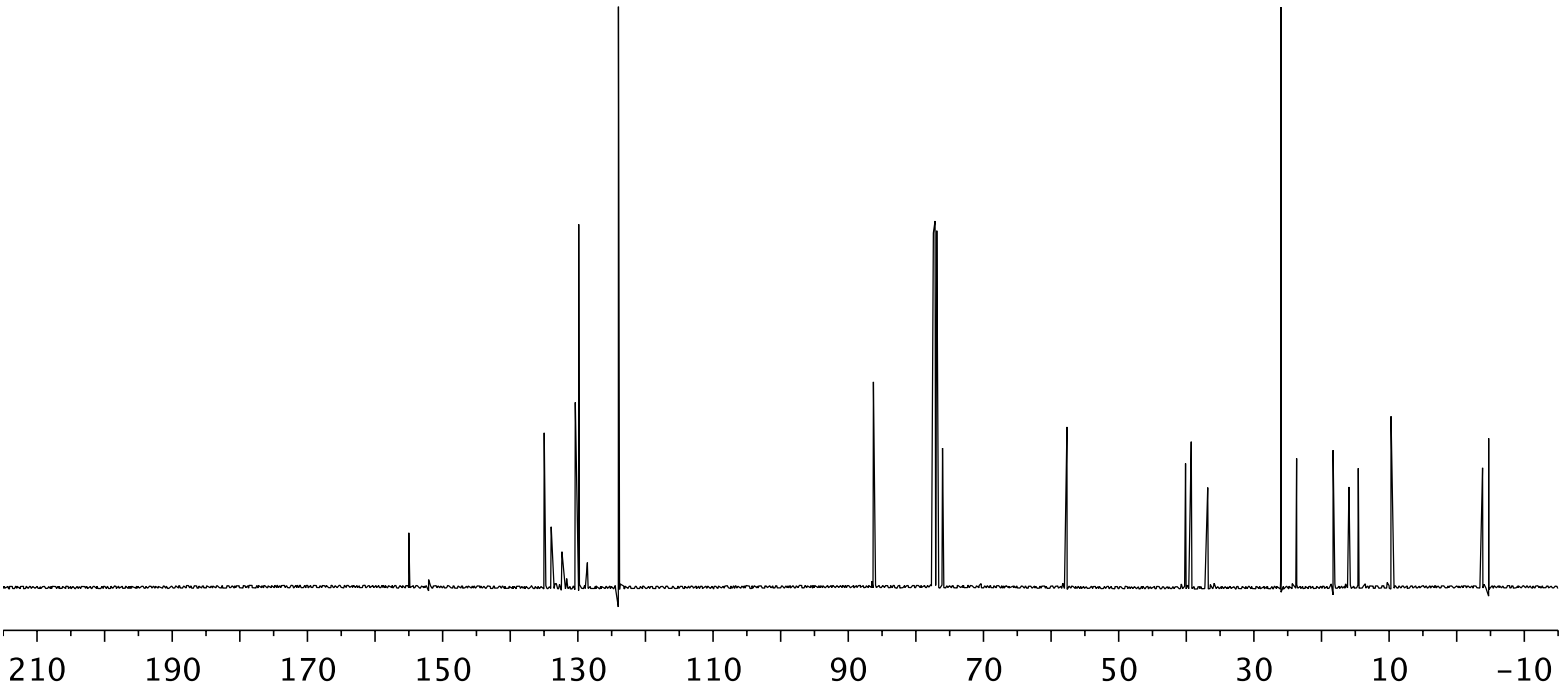
^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of alcohol **14** in $CDCl_3$



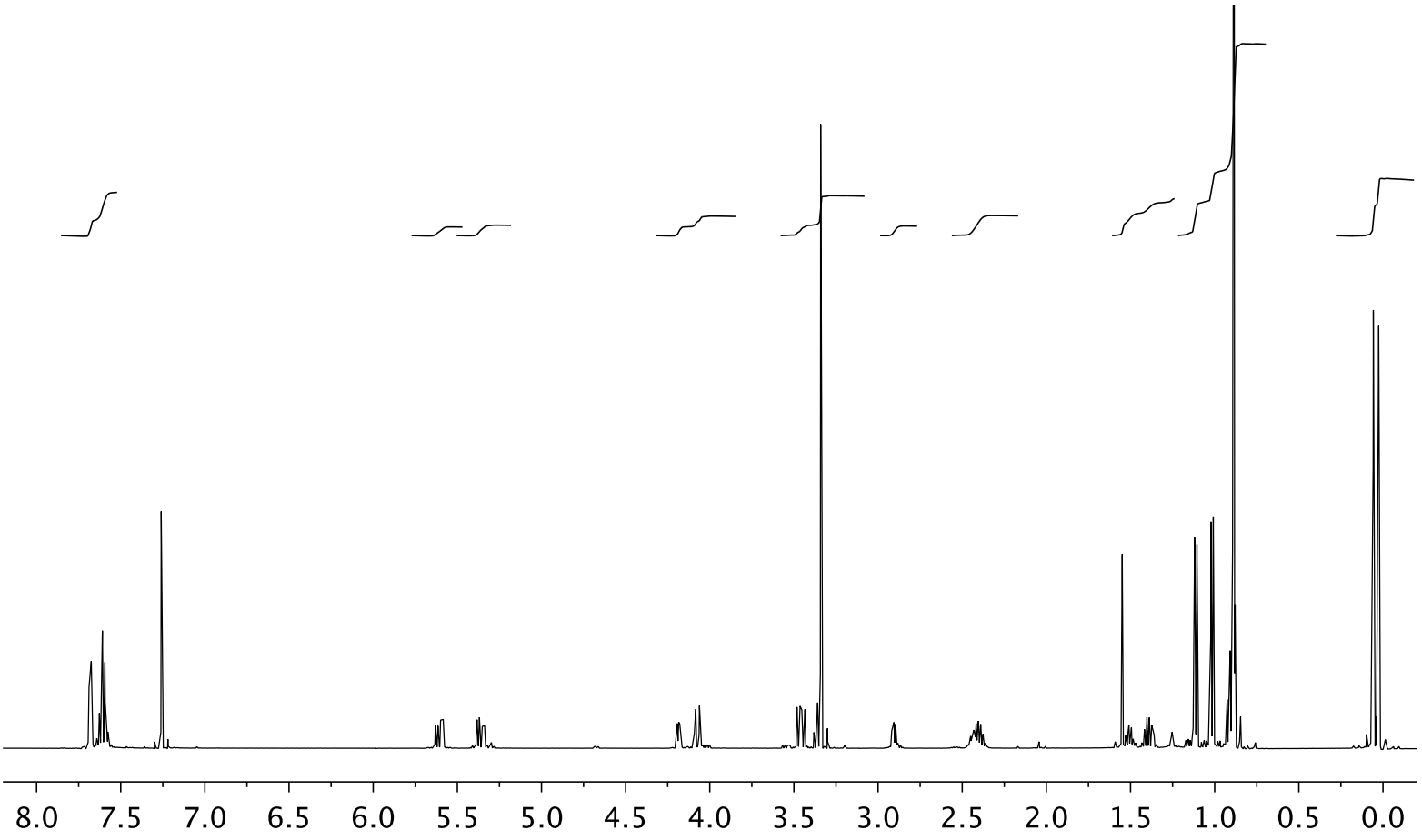


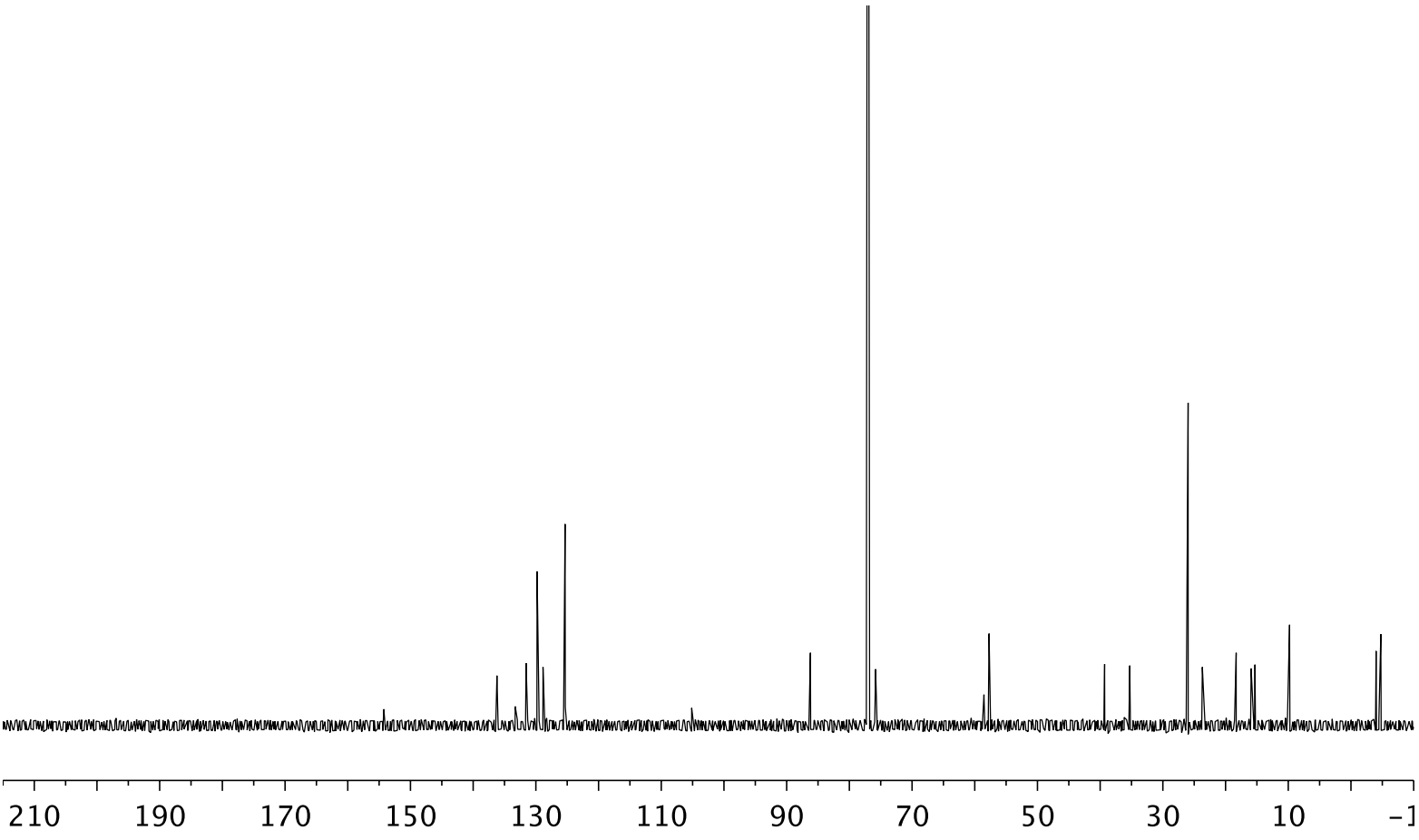
^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of sulfide **15** in $CDCl_3$



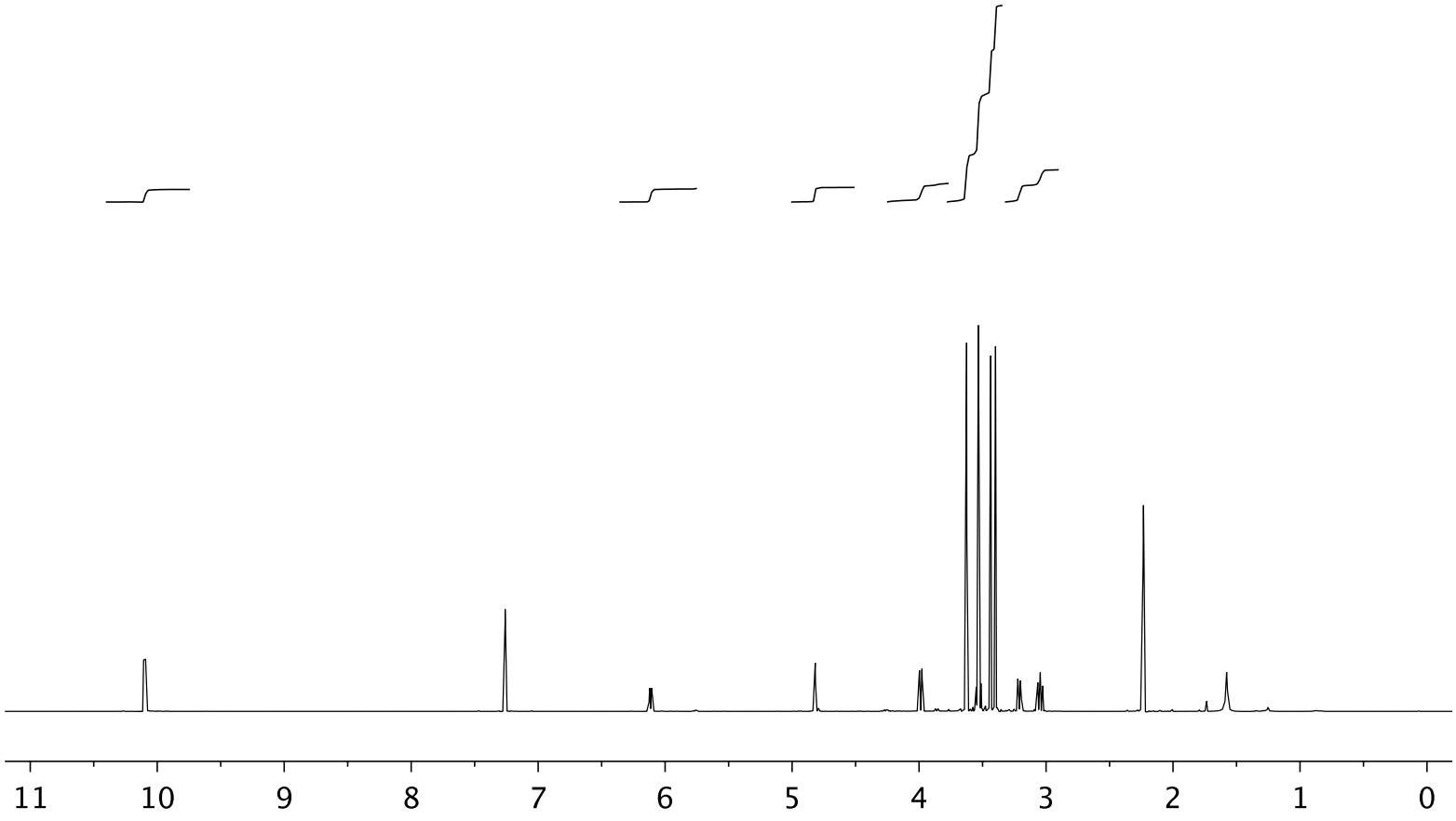


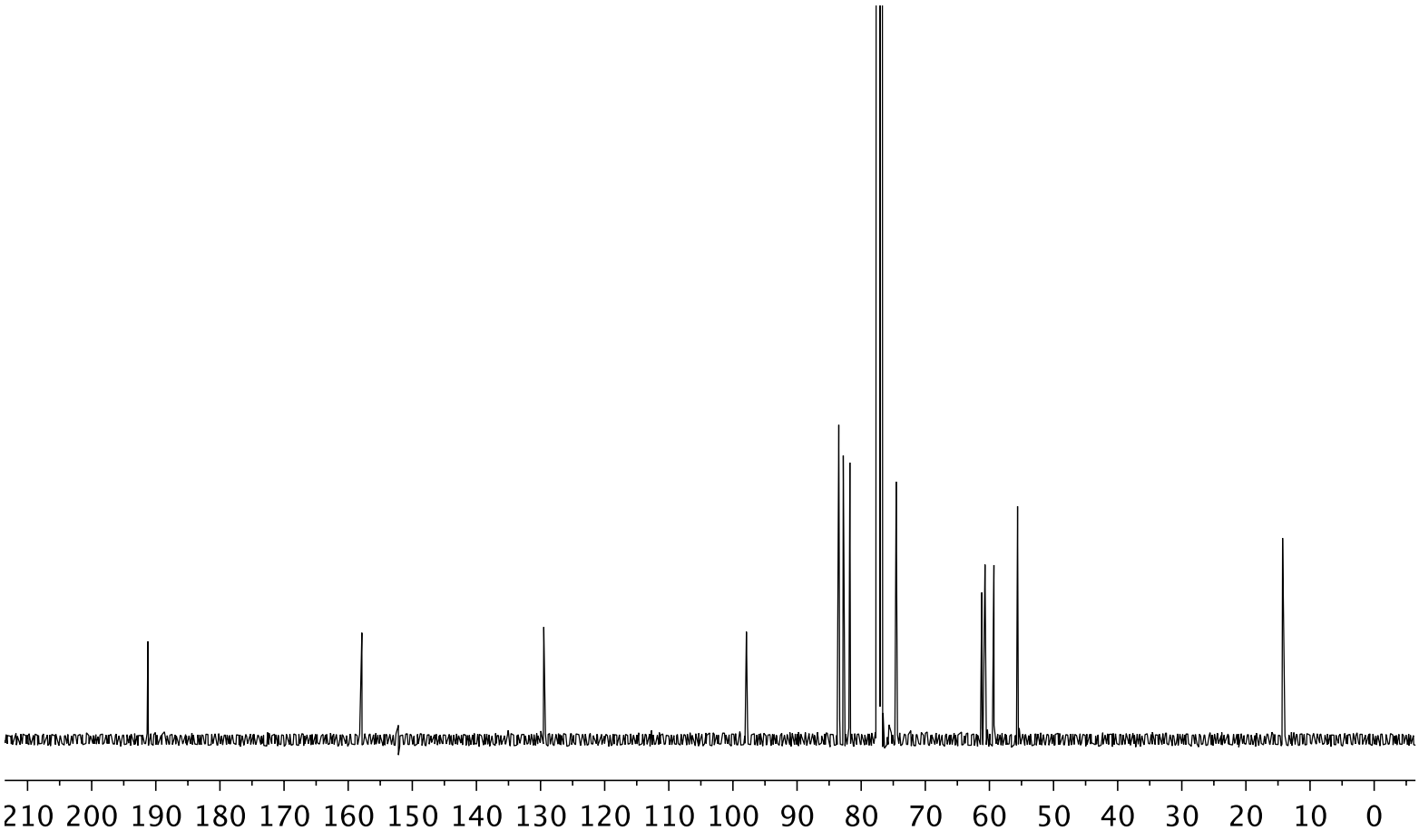
^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of sulfone **16** in $CDCl_3$



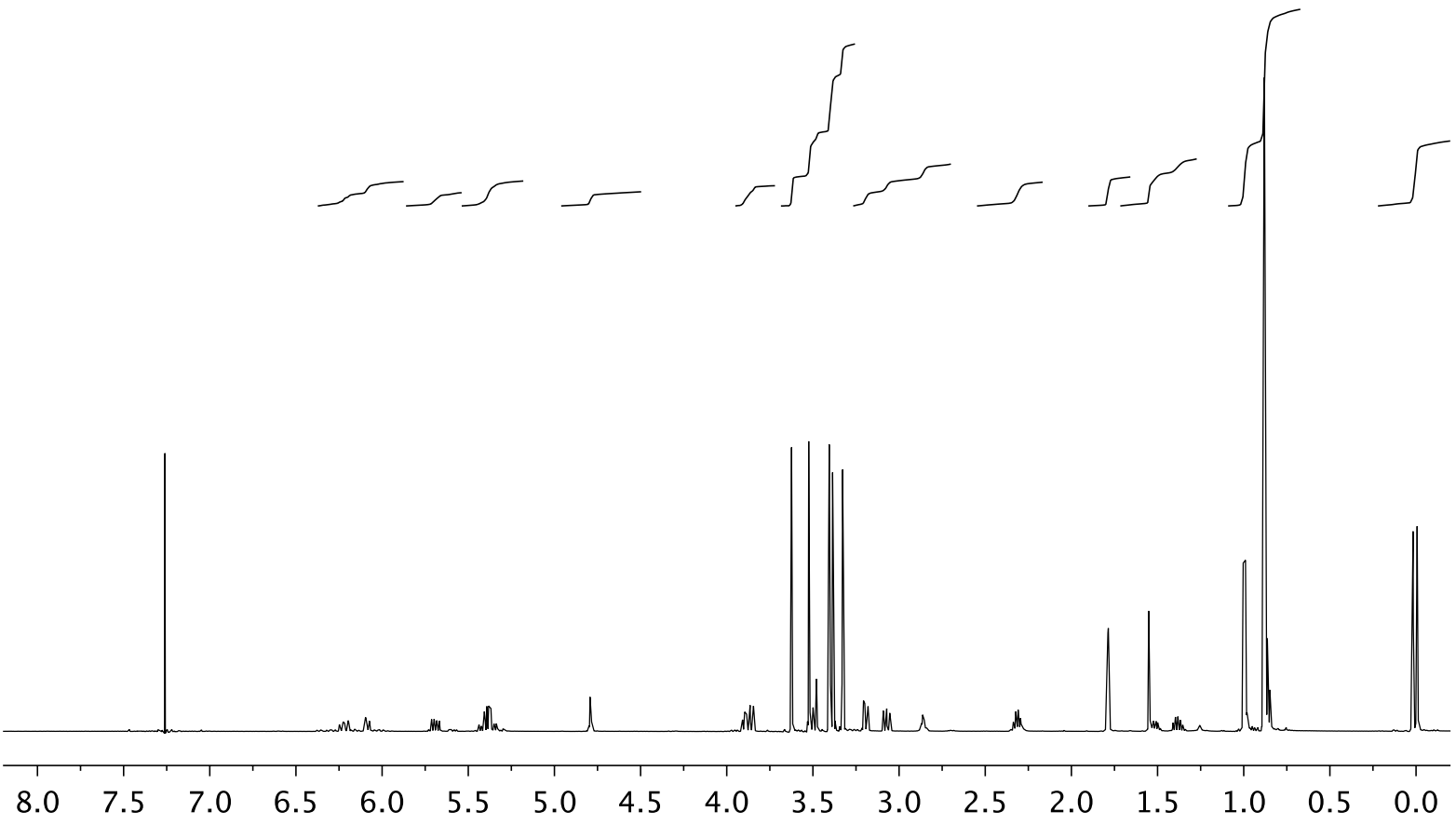


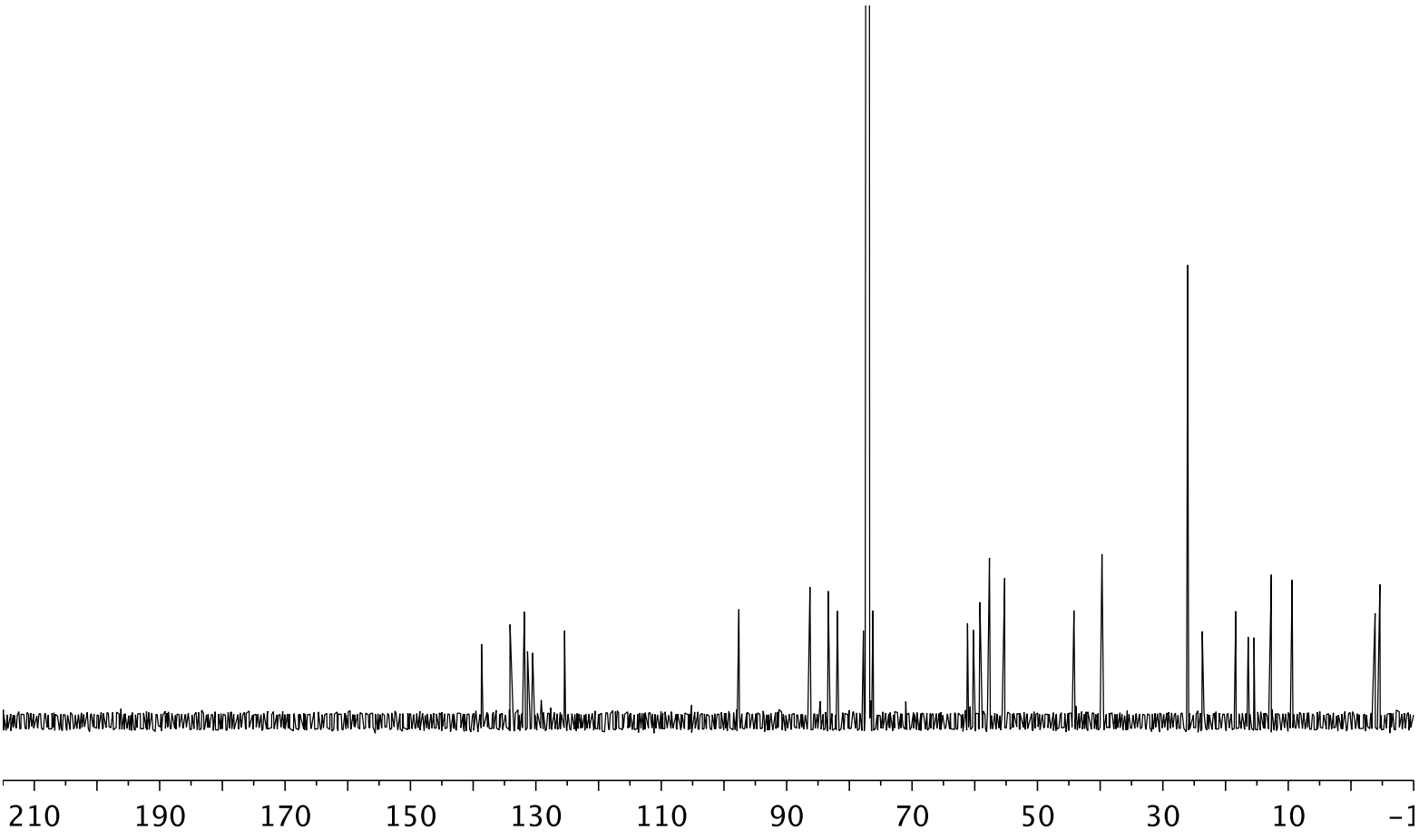
^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of aldehyde **17** in $CDCl_3$



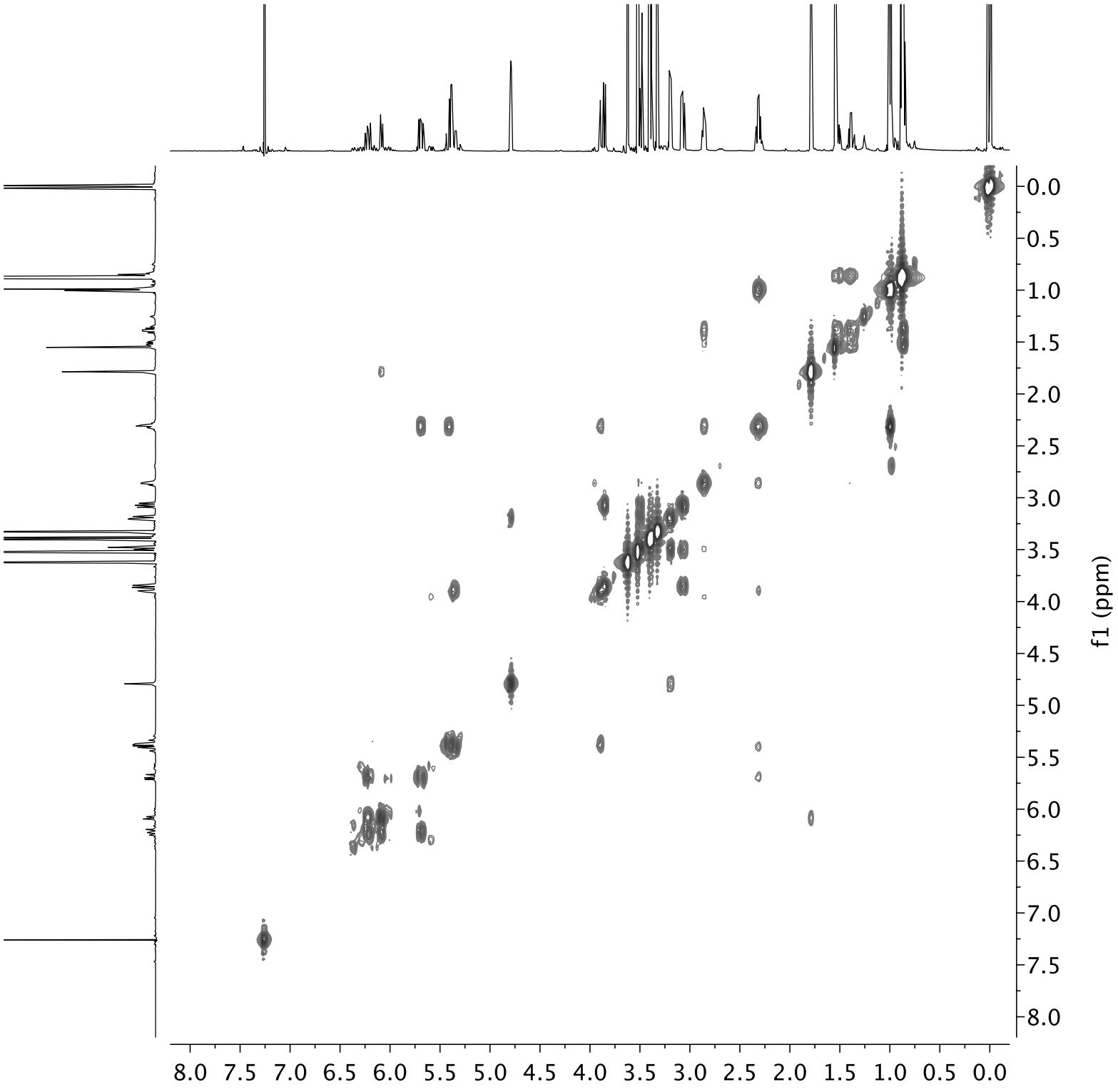


^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of alkene **18** in $CDCl_3$

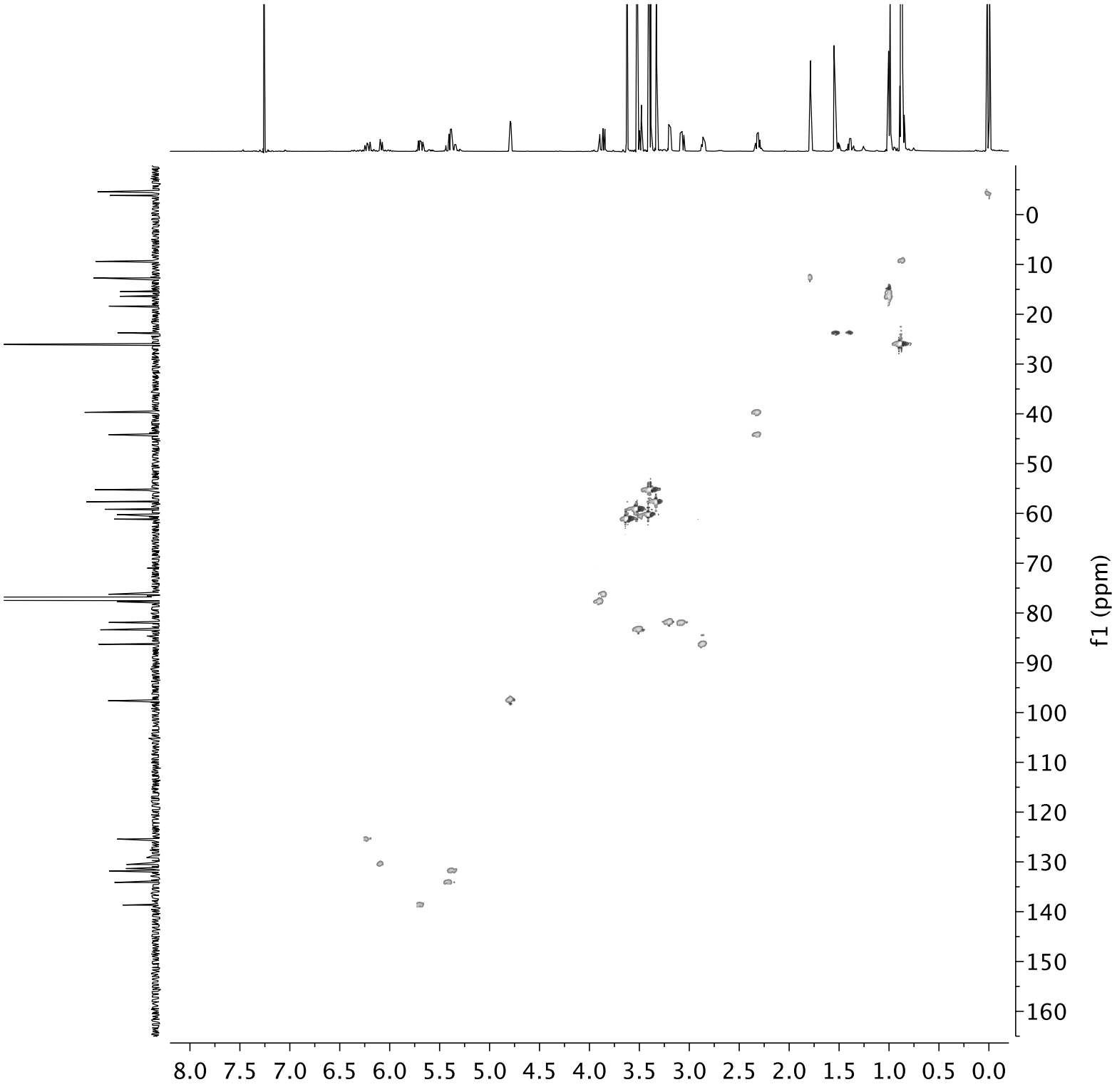




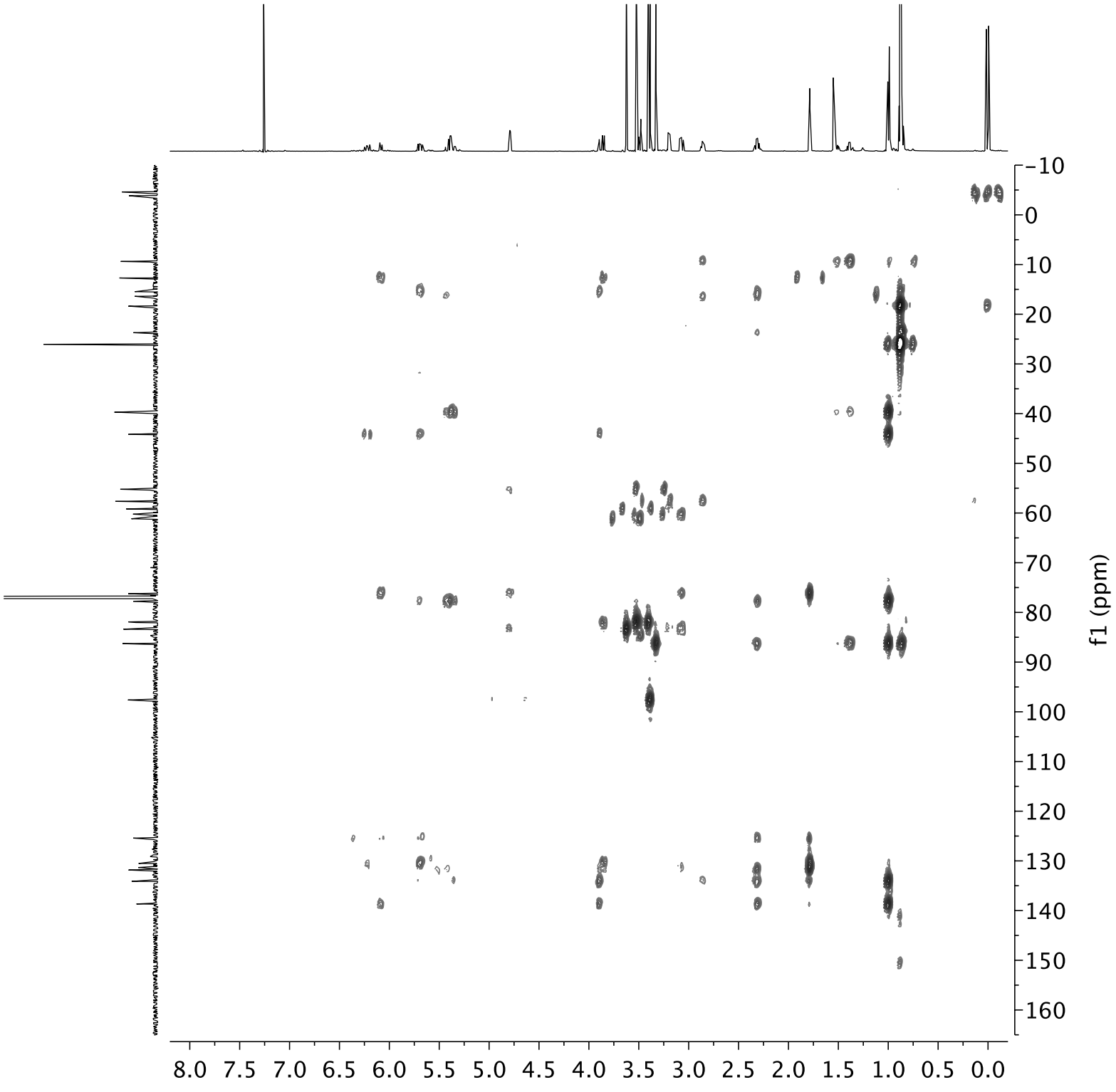
$^{1}H,^{1}H$-gCOSY NMR (500 MHz) spectra of alkene **18** in $CDCl_3$



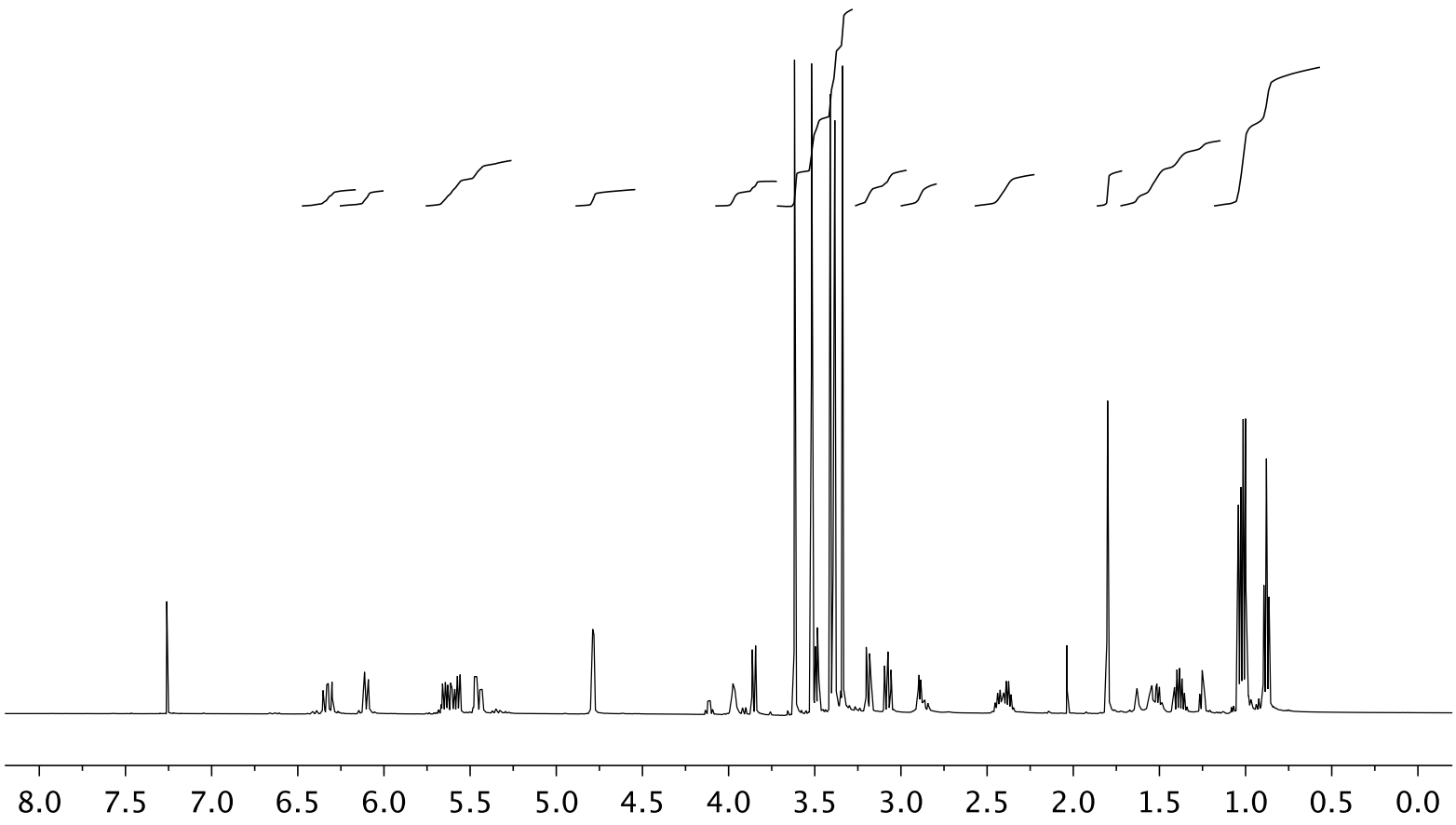
$^{1}H,^{13}C$-gHSQC NMR (500 MHz) spectra of alkene **18** in $CDCl_3$

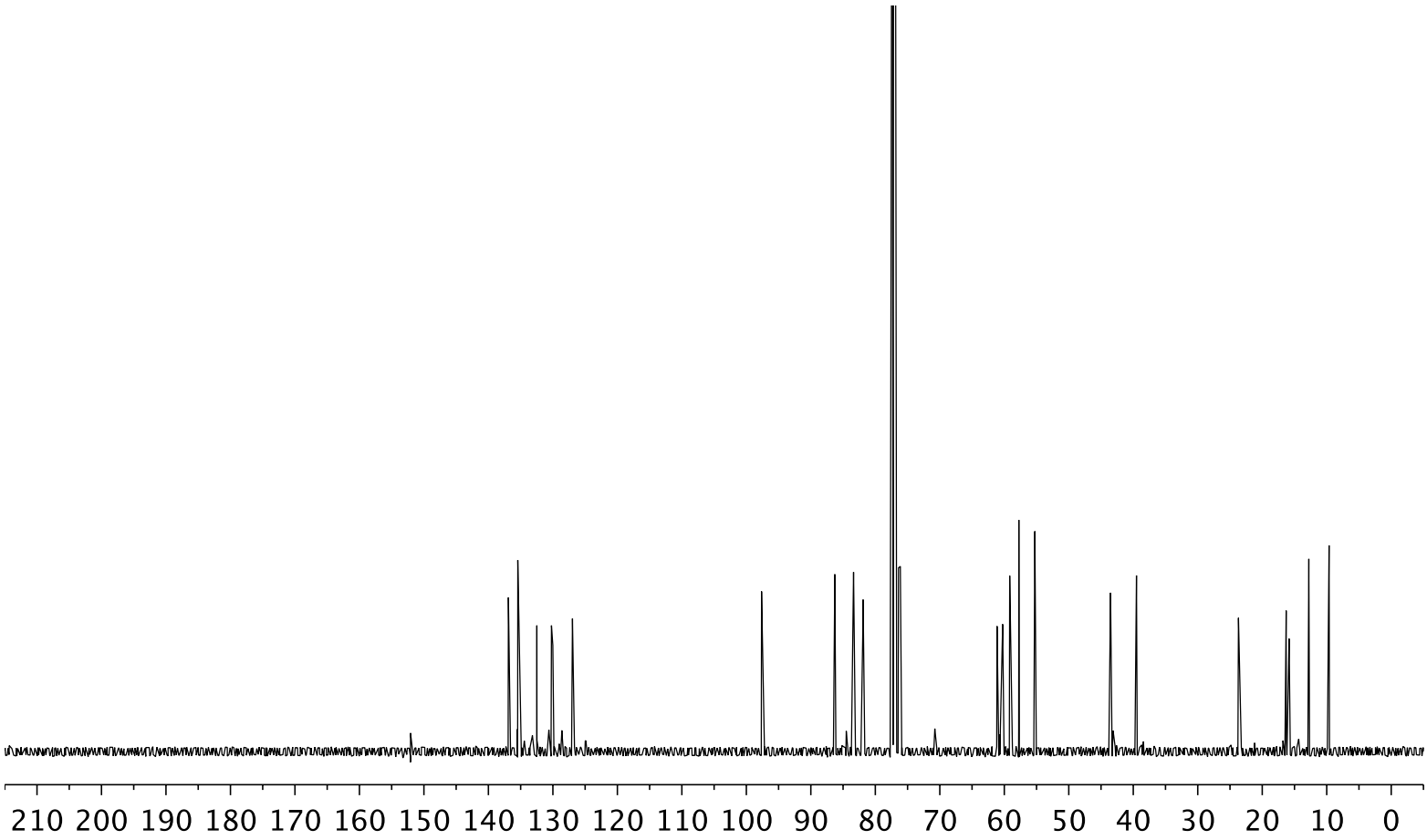


$^{1}H,^{13}C$-gHMBC NMR (500 MHz) spectra of alkene **18** in $CDCl_3$

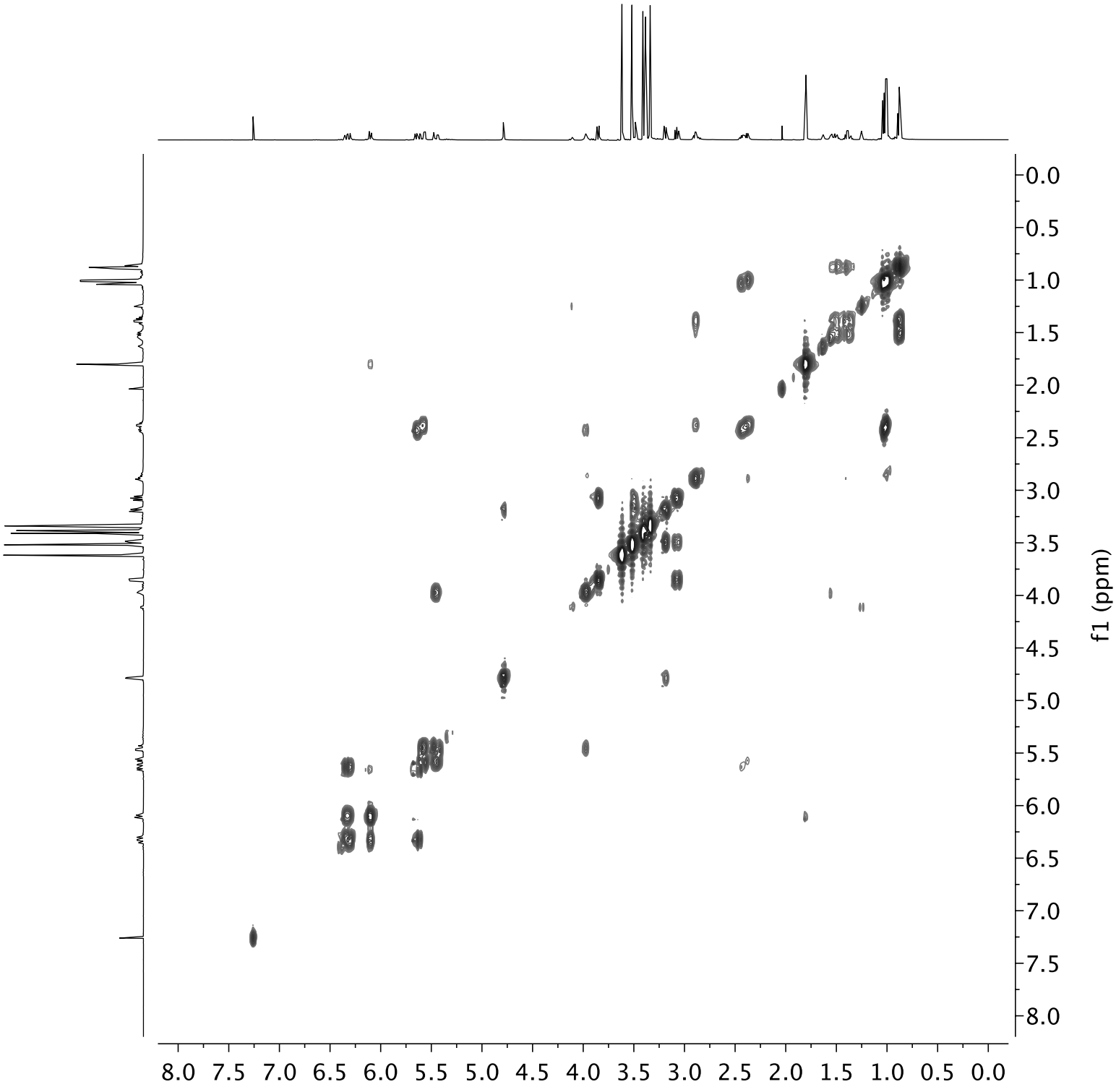


^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of alcohol **19** in $CDCl_3$

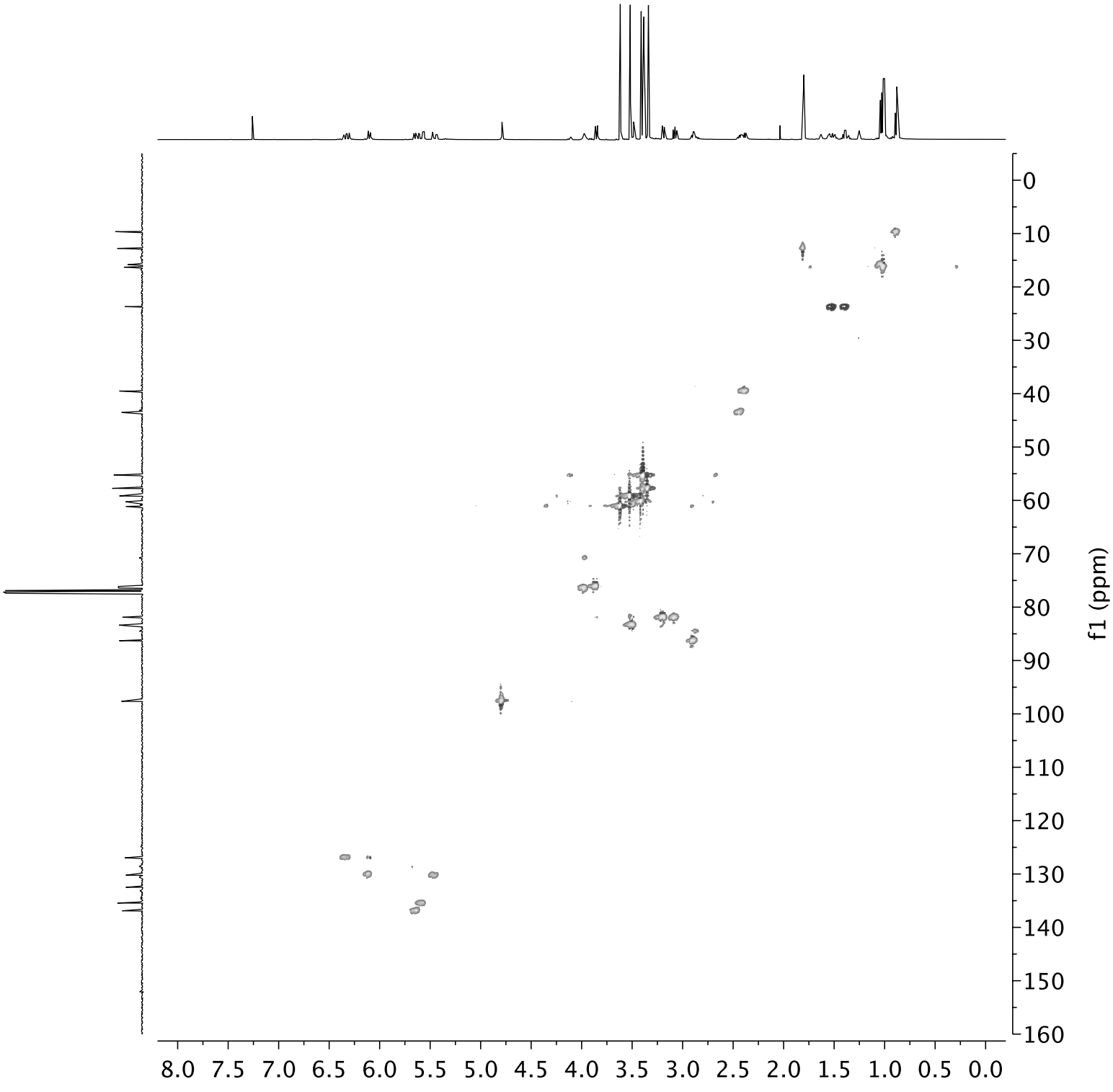




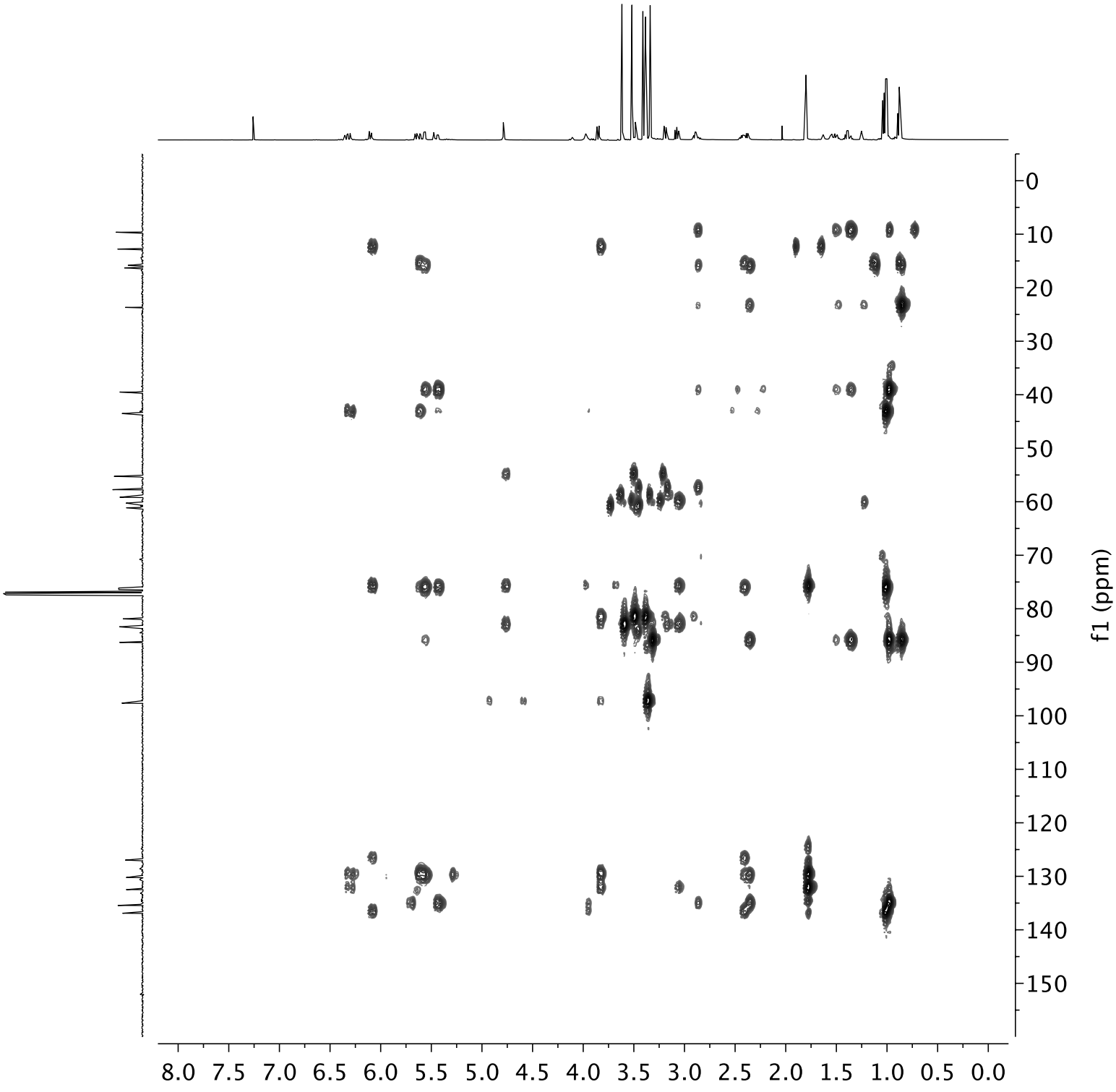
$^{1}H,^{1}H$-gCOSY NMR (500 MHz) spectra of alcohol **19** in $CDCl_3$



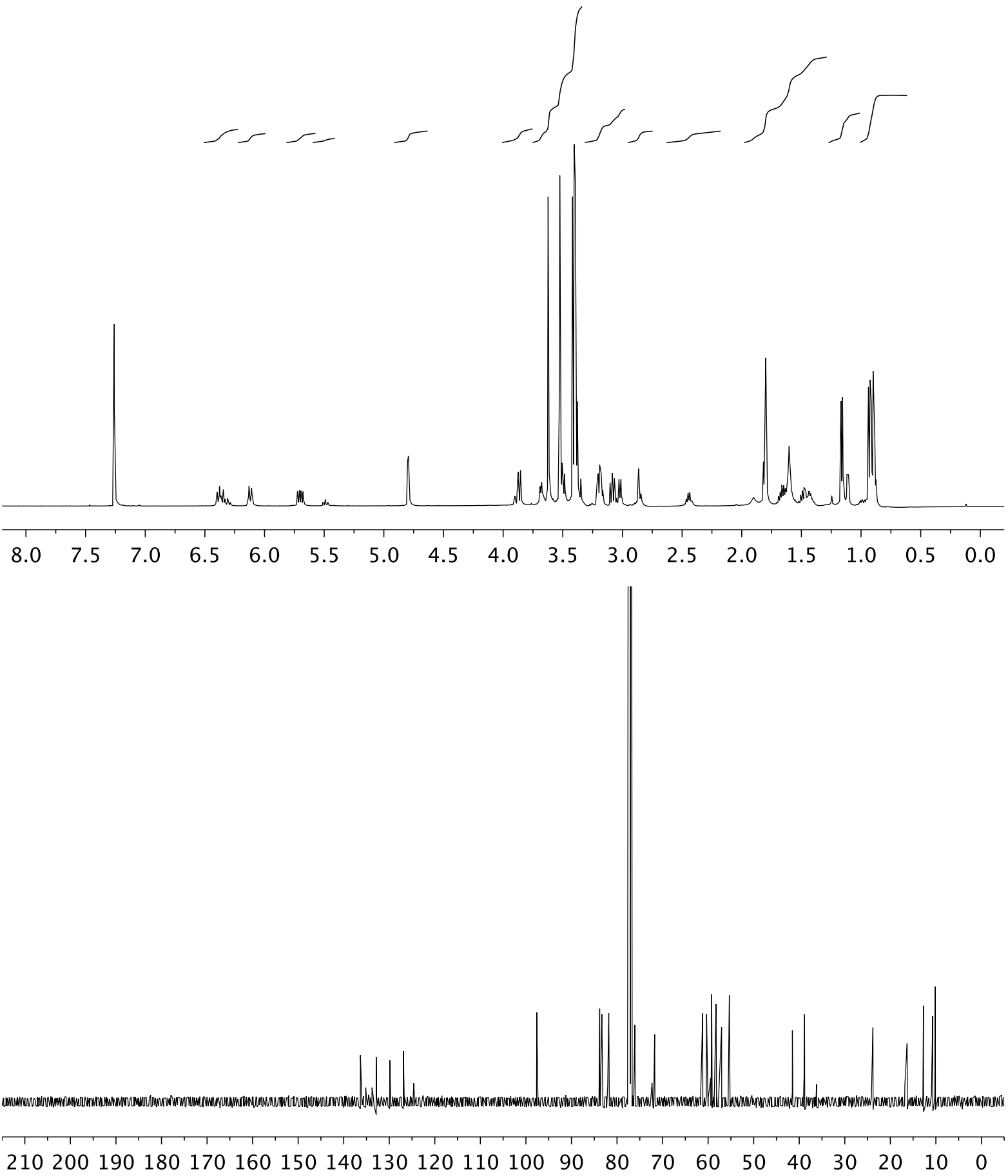
$^{1}H,^{13}C$-gHSQC NMR (500 MHz) spectra of alcohol **19** in $CDCl_3$



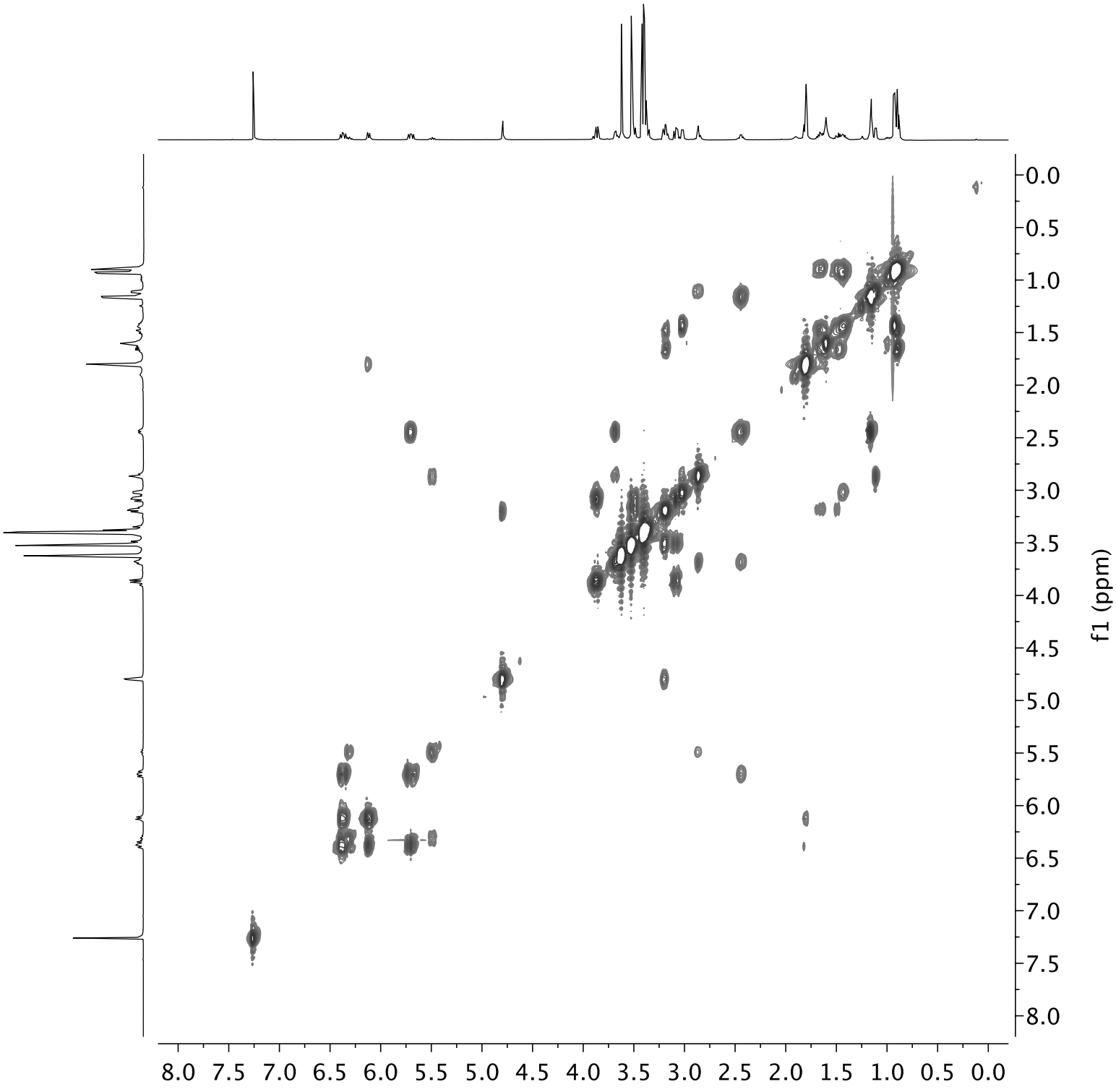
$^{1}H,^{13}C$-gHMBC NMR (500 MHz) spectra of alcohol **19** in $CDCl_3$



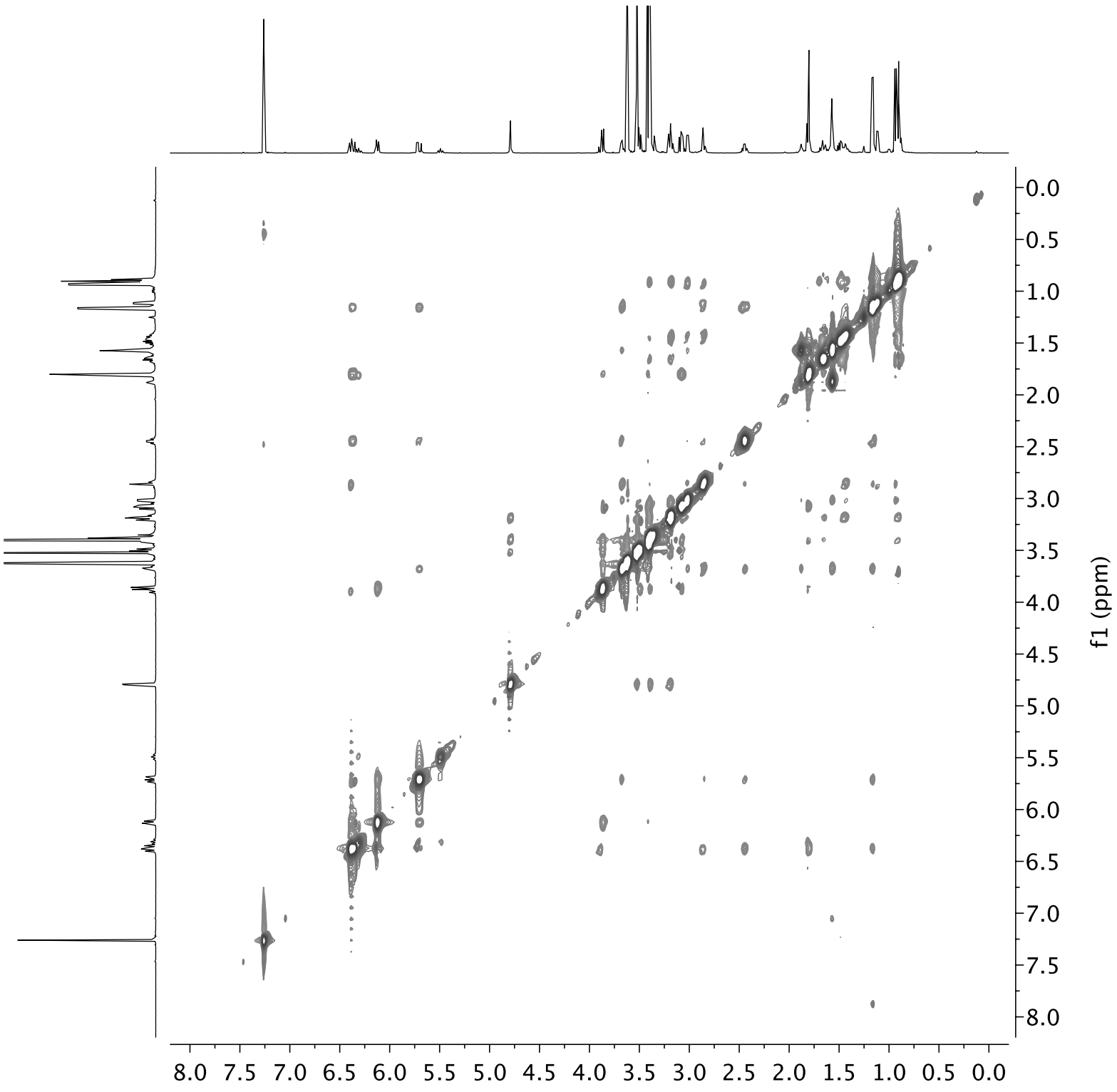
^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of epoxide **2** in $CDCl_3$



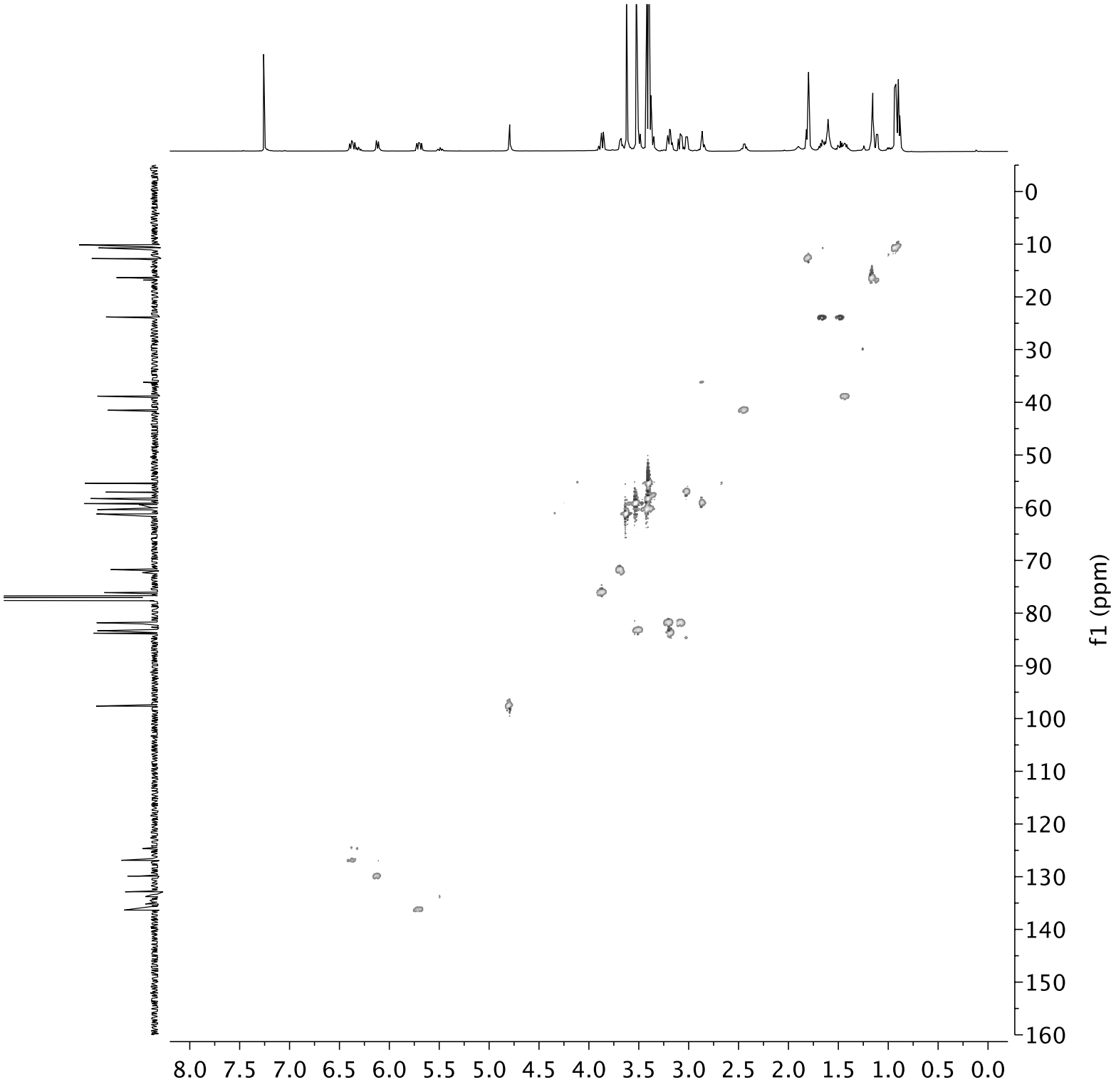
$^{1}H,^{1}H$-gCOSY NMR (500 MHz) spectra of epoxide **2** in $CDCl_3$



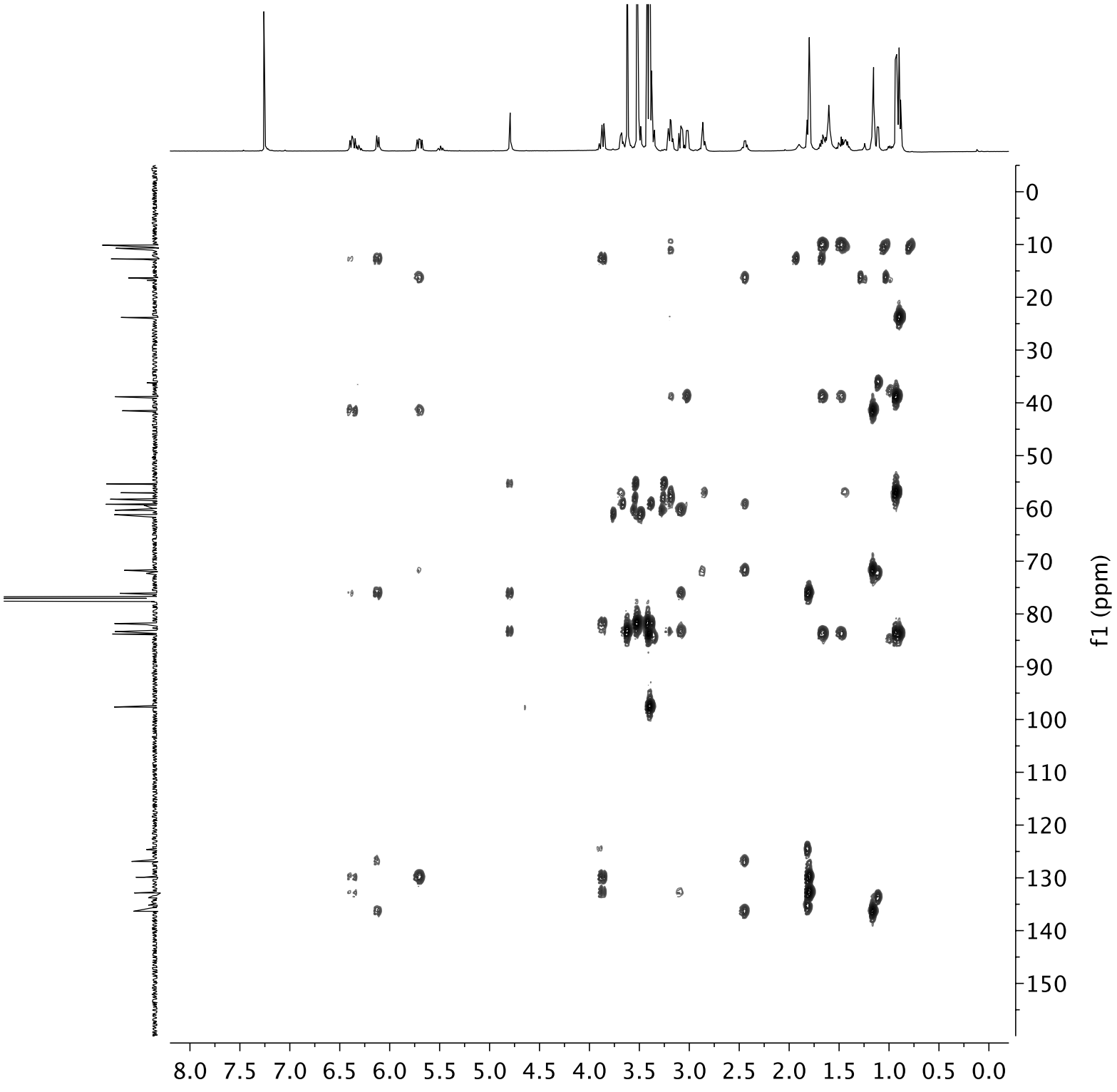
$^{1}H,^{1}H$-NOESY NMR (500 MHz) spectra of epoxide **2** in $CDCl_3$



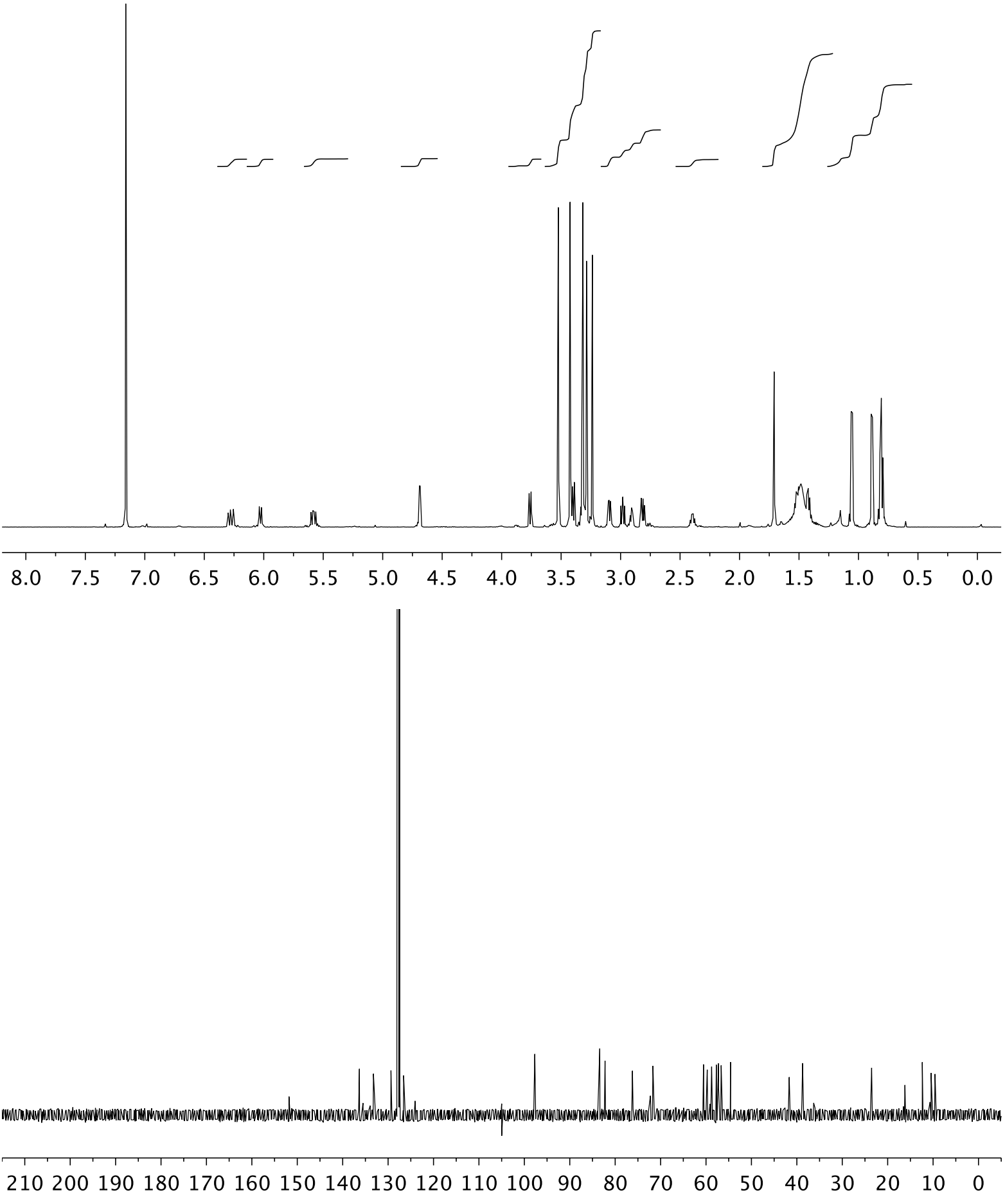
$^{1}H,^{13}C$-gHSQC NMR (500 MHz) spectra of epoxide **2** in $CDCl_3$



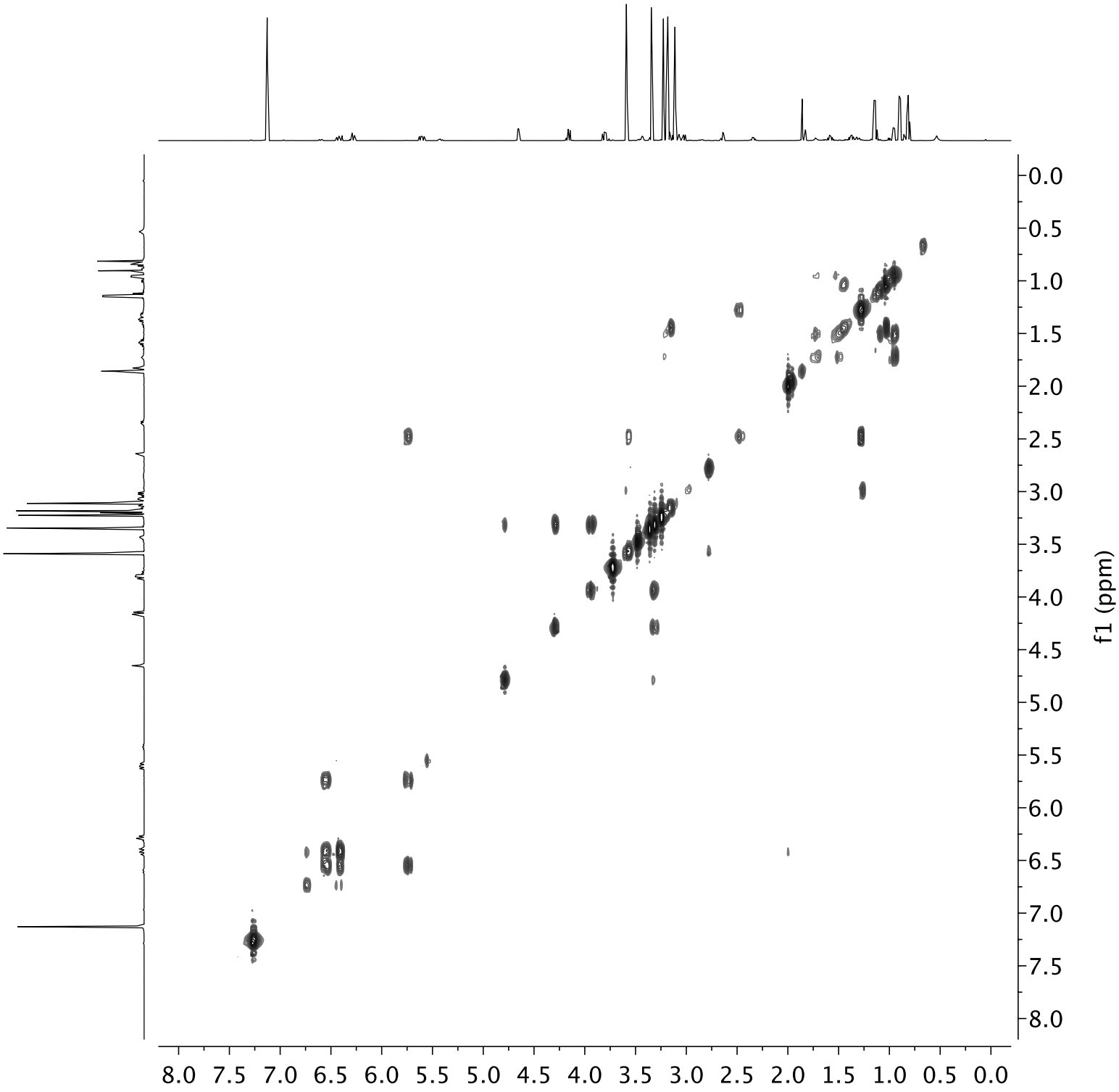
$^{1}H,^{13}C$-gHMBC NMR (500 MHz) spectra of epoxide **2** in $CDCl_3$



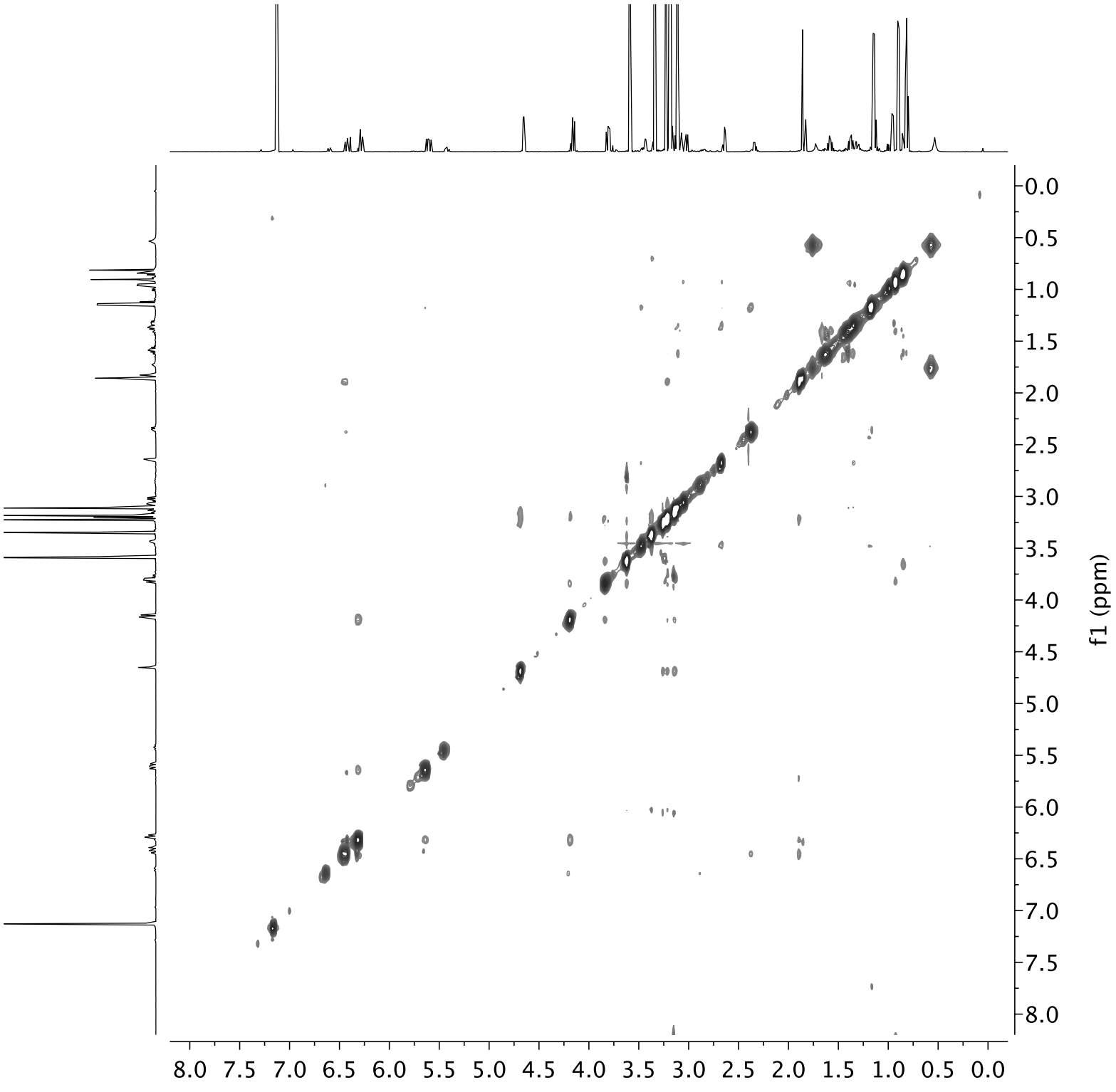
^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra of epoxide **2** in d_6-benzene



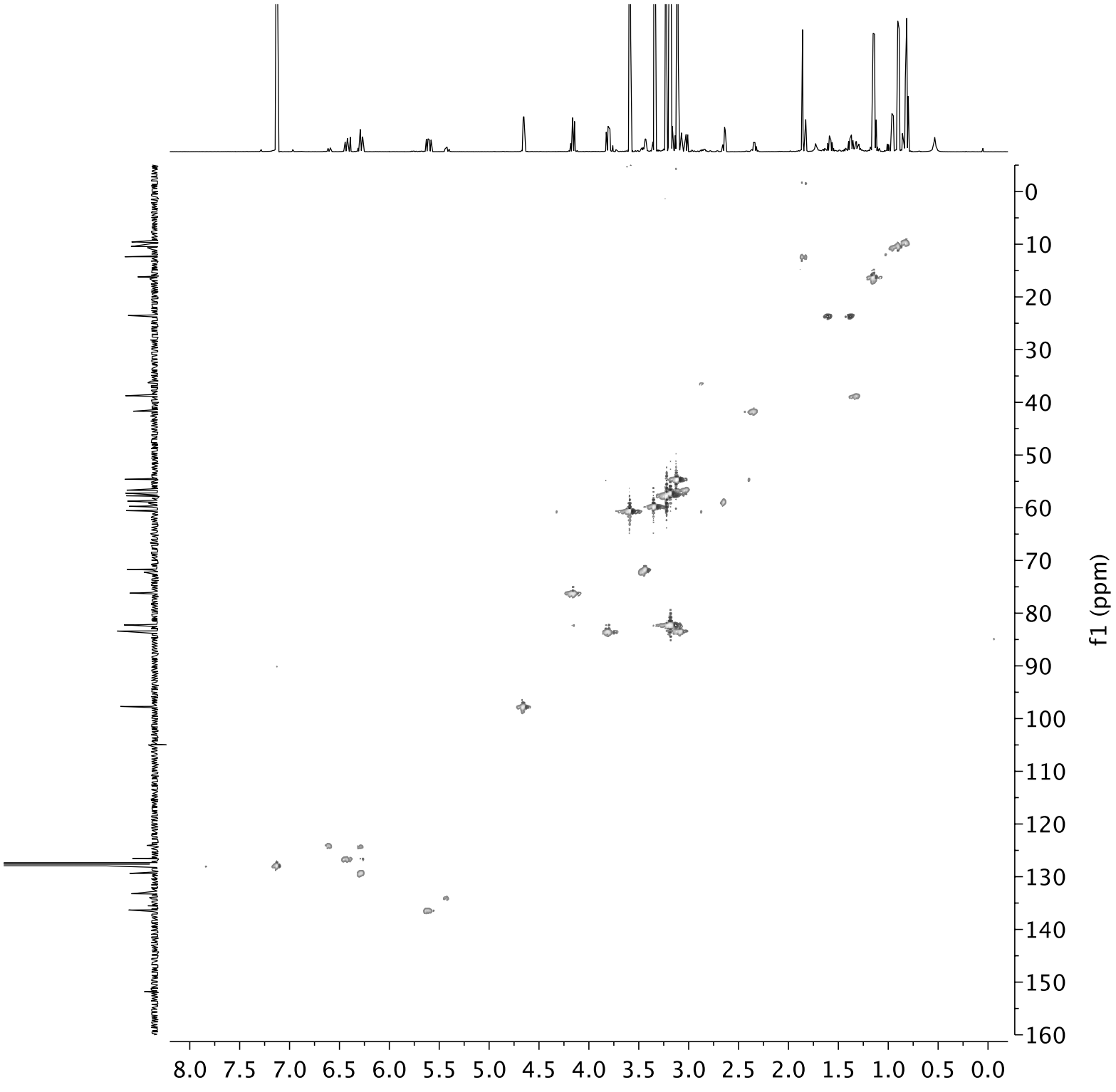
^{1}H,^{1}H-gCOSY NMR (500 MHz) spectra of epoxide **2** in d_6-benzene



^{1}H,^{1}H–NOESY NMR (500 MHz) spectra of epoxide **2** in d_6–benzene



$^{1}H,^{13}C$-gHSQC NMR (500 MHz) spectra of epoxide **2** in d_6-benzene



$^{1}H,^{13}C$-gHMBC NMR (500 MHz) spectra of epoxide **2** in d_6-benzene