Total Syntheses and Biological Evaluation of (±)-Botryosphaeridione, (±)-Pleodendione, 4-*epi*-Periconianone B, and Analogues

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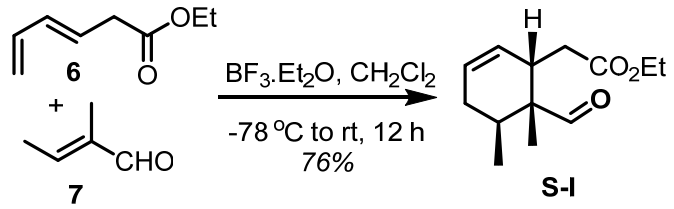
Supporting Information

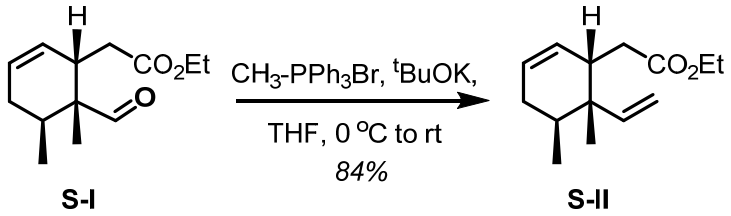
General:

All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa. All reagents, starting materials and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *para*-anisaldehyde, 2,4-DNP, $KMnO_4$ solution or Iodine adsorbed on silica gel followed by heating with a heat gun for ~15 sec. Column chromatography was performed on silica gel (100-200 or 230-400 mesh size). Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 400 MHz or 500 MHz spectrometer. Coupling constants were measured in Hertz. Chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. HRMS (ESI) were recorded on ORBITRAP mass analyser (Thermo Scientific, QExactive). Mass spectra were measured with ESI ionization in MSQ LCMS mass spectrometer. Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film. Chemical nomenclature was generated using Chem Bio Draw Ultra 13.0. Melting points of solids were measured in Buchi B-545 melting point apparatus.

Experimental Section:

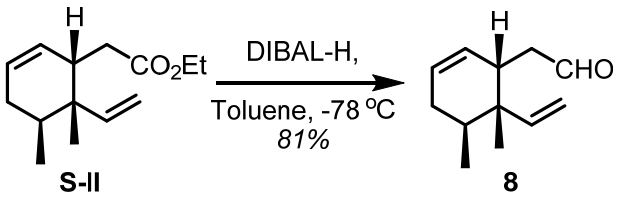


Ethyl 2-((1*R*,5*R*,6*S*)-6-formyl-5,6-dimethylcyclohex-2-en-1-yl) acetate (S-I): To a solution of diene **6** (6.0 g, 0.042 mol) and (*E*)-2-methylbut-2-enal **7** (10.3 mL, 0.107 mol) in dry CH_2Cl_2 (200 mL) was added $BF_3 \cdot OEt_2$ (10.6 mL, 0.085 mol) dropwise at –78 °C. The mixture was allowed to warm to room temperature and was stirred for 12 h at same temperature. The CH_2Cl_2 layer was washed with saturated $NaHCO_3$ (3 X 50 mL) followed by H_2O (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material obtained after the removal of solvent was purified by column chromatography (silica gel 100–200, 1.0:9.0 ethyl acetate: petroleum ether) to afford **S-I** (7.3 g, 76%) as light yellow oil. IRυ_{max}(film): 2978, 1732, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 5.71–5.66 (m, 1H), 5.64–5.57 (m, 1H), 4.13 (q, J = 7.2 Hz, 2H), 2.65–2.59 (m, 1H), 2.45 (dd, J = 15.8, 5.4 Hz, 1H), 2.37–2.30 (m, 1H), 2.25–2.18 (m, 1H), 2.17–2.05 (m, 1H), 1.79–1.72 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.08 (s, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 172.6, 127.4, 126.1, 60.4, 49.6, 37.6, 35.6, 30.6, 29.5, 15.7, 15.6, 13.9.

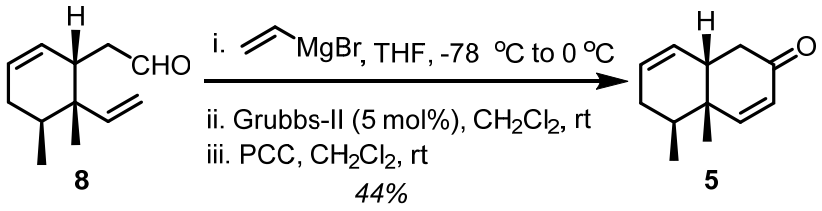


Ethyl 2-((1*R*,5*R*,6*S*)-5,6-dimethyl-6-vinylcyclohex-2-en-1-yl) acetate (S-II): To a suspension of methyl triphenylphosphonium bromide (26.8 g, 0.075 mol) in dry THF (100 mL) was added potassium *tert*-butoxide (7.6 g, 0.068 mol) at 0 °C. After 30 minutes, the solution became canary yellow color, to that aldehyde **S-I** (5.1 g, 0.022 mol) in THF (50 mL) was added and allowed to stir at 0 °C for 1 h. The reaction was quenched with brine (30 mL) and extracted with ethyl acetate (3 X 100 mL). Combined organic layer was washed with

water (40 mL), brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 0.5:9.5 ethyl acetate: petroleum ether) afforded **S-II** (4.2 g, 84%) as light brown oil. IRυ_{max}(film): 1725, 1521, 1417, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (dd, J = 18.3, 11.0 Hz, 1H), 5.65–5.53 (m, 2H), 5.06–5.05 (m, 1H), 5.03–5.02 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.48–2.39 (m, 2H), 2.23–2.18 (m, 1H), 2.12–2.07 (m, 1H), 1.73–1.62 (m, 2H), 1.25 (t, J = 7.3 Hz, 3H), 1.02 (s, 3H), 0.87 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 145.2, 128.6, 126.2, 113.3, 60.4, 41.2, 40.5, 36.7, 34.4, 31.5, 18.8, 16.4, 14.4; HRMS (ESI) calcd for $C_{14}H_{22}O_2[M+Na]^+$ 245.1512, found 245.1508.

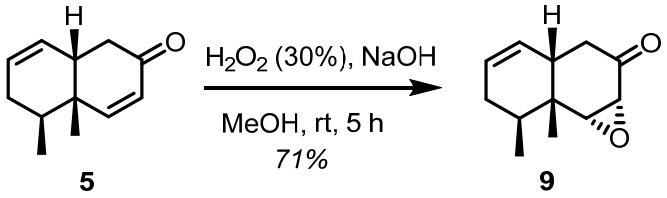


2-((1*S*,5*S*,6*R*)-5,6-Dimethyl-6-vinylcyclohex-2-en-1-yl) acetaldehyde (8) : To a solution of ester **S-II** (0.5 g, 2.25 mmol) in dry distilled toluene (15 mL) was added DIBAL-H (1.0 M in toluene, 1.36 mL, 1.36 mmol) at –78 °C dropwise. Stirred at this temperature for 10 min and then added DIBAL-H (1.0 M in toluene, 1.13 mL, 1.13 mmol) at –78 °C dropwise. After stirring at the same temperature for 0.5 h, the reaction was quenched with methanol (3 mL), diluted with Et_2O (20 mL) and saturated Na/K tartrate (15 mL). The solution was stirred at room temperature for 2 h. Extracted the solution with ethyl acetate (3 X 20 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4. The crude mixture was passed through small bed of silica gel and eluted with 20% ethyl acetate: petroleum ether. The eluent was concentrated *in vacuo* to give the aldehyde **8** (0.33 g, 81%) as a colorless oil which was immediately used for next step. IRυ_{max}(film): 2978, 1734, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 5.86–5.79 (m, 1H), 5.67–5.63 (m, 1H), 5.54–5.50 (m, 1H), 5.08–5.04 (m, 2H), 2.59–2.47 (m, 2H), 2.31–2.18 (m, 2H), 1.75–1.63 (m, 2H), 1.01 (s, 3H), 0.85 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 145.4, 128.6, 126.4, 113.8, 46.2, 40.4, 39.4, 34.1, 31.3, 18.7, 16.3; HRMS (ESI) calcd for $C_{12}H_{19}O[M+H]^+$ 179.1430, found 179.1431.



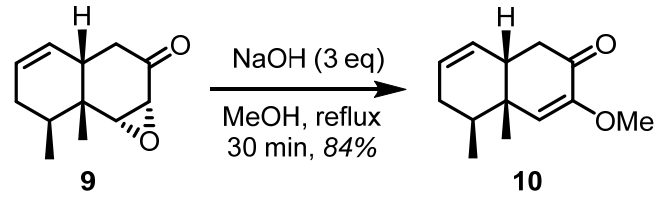
(4a*S*,5*S*,8a*S*)-4a,5-Dimethyl-4a,5,6,8a-tetrahydronaphthalen-2(1H)-one (5) : To a stirred solution of **8** (0.80 g, 4.49 mmol) in dry THF (20 mL) was added a solution of vinylmagnesium bromide (1M in THF, 6.7 mL, 6.74 mmol) at –78 °C, and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with water (15 mL), brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 1.5:8.5 ethyl acetate: petroleum ether as eluent) afforded alcohol as a mixture of diastereomers (0.70 g, 76%). This colorless oil was dissolved in dry CH_2Cl_2 (40 mL) and treated with Grubbs' second-generation catalyst (144 mg, 5 mol %) at room temperature. After stirring for 24 h, reaction mixture was filtered through celite pad and filtrate was concentrated *in vacuo*. The crude material obtained after the removal of solvent was purified by column chromatography (silica gel 100–200, 1.5:8.5 ethyl acetate: petroleum ether as eluent) to afford allylic alcohol as a mixture of diastereomers (435 mg, 72%).

To a solution of above allylic alcohols (435 mg, 2.44 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC was added PCC (788 mg, 3.66 mmol) portionwise. The resulting mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with diethyl ether (30 mL), filtered through a celite bed, and washed with diethyl ether (2 X 10 mL). The filtrate was concentrated in *vacuo*. Purification by column chromatography (silica gel 100–200, 1.0:9.0 ethyl acetate: petroleum ether as eluent) afforded **5** (344 mg, 80%) as colorless oil. IRυ_{max}(film): 2964, 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, J = 10.3 Hz, 1H), 5.86 (d, J = 10.3 Hz, 1H), 5.64–5.47 (m, 2H), 2.54–2.49 (m, 1H), 2.38–2.37 (m, 1H), 2.31–2.25 (m, 1H), 2.11–2.06 (m, 1H), 1.90–1.83 (m, 2H), 1.05 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 159.1, 128.8, 127.1, 126.3, 40.8, 40.7, 37.6, 33.0, 31.7, 20.4, 14.9; HRMS (ESI) calcd for $C_{12}H_{17}O[M+H]^+$ 177.1274, found 177.1274.



5 **9**

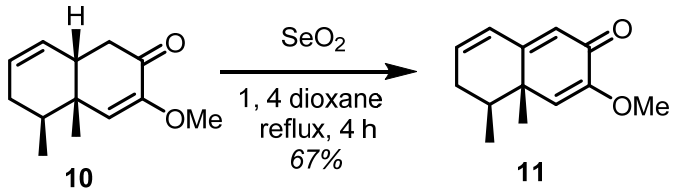
(1a*R*,3a*S*,7*S*,7a*R*,7b*R*)-7,7a-Dimethyl-3,3a,6,7,7a,7b-hexahydronaphtho[1,2-b] oxiren-2(1aH)-one (9) : To a solution of the *α,β*–unsaturated ketone **5** (3.0 g, 0.017 mol) in 30 mL of methanol was added 30% aqueous H_2O_2 (5.8 mL, 0.051 mol) and 6N NaOH (1.7 mL, 0.010 mol) at 0 °C. The reaction was stirred at room temperature for 5 h. The mixture was diluted with diethyl ether (80 mL), washed successively with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 1.0:9.0 ethyl acetate: petroleum ether as eluent) afforded epoxide **9** (2.3 g, 71%) as colorless oil. IRυ_{max}(film): 2968, 1714, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55–5.38 (m, 2H), 3.28 (d, J = 3.9 Hz, 1H), 3.16 (d, J = 3.9 Hz, 1H), 2.63–2.57 (m, 1H), 2.29–2.24 (m, 1H), 2.08–2.03 (m, 1H), 1.92–1.86 (m, 1H), 1.75–1.63 (m, 2H), 1.10 (s, 3H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 128.6, 125.7, 64.0, 56.1, 39.7, 36.8, 34.9, 31.1, 30.9, 18.1, 15.2; HRMS (ESI) calcd for $C_{12}H_{17}O_2[M+H]^+$ 193.1223, found 193.1227.



9 **10**

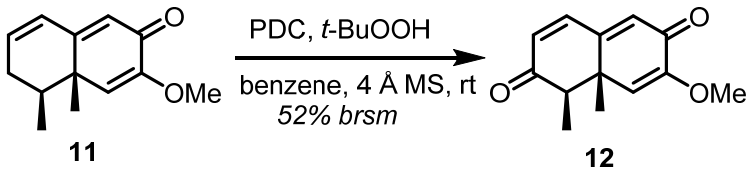
(4a*R*,5*S*,8a*S*)-3-Methoxy-4a,5-dimethyl-4a,5,6,8a-tetrahydronaphthalen-2(1H)-one (10) : To a solution of **9** (2.1 g, 0.010 mol) in MeOH (25 mL) was added NaOH (1.32 g, 0.033 mol) at room temperature. The resulting reaction mixture was heated to reflux for 30 min. The mixture was diluted with diethyl ether (60 mL), washed successively with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 2.0:8.0 ethyl acetate: petroleum ether as eluent) afforded **10** (1.9 g, 84%) as colorless oil. IRυ_{max}(film): 3018, 1687, 1215, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66–5.61 (m, 1H), 5.60 (s, 1H), 5.51–5.49 (m, 1H), 3.58 (s, 3H), 2.64–2.58 (m, 1H), 2.45–2.40 (m, 2H), 2.15–2.10 (m, 1H), 1.93–1.88 (m, 1H), 1.83–1.77 (m, 1H), 1.08 (s, 3H), 0.97 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

193.9, 149.3, 128.5, 126.6, 125.4, 54.9, 41.3, 40.7, 37.4, 33.4, 31.8, 21.8, 15.1; HRMS (ESI) calcd for $C_{13}H_{19}O_2[M+H]^+$ 207.1380, found 207.1379.



10 **11**

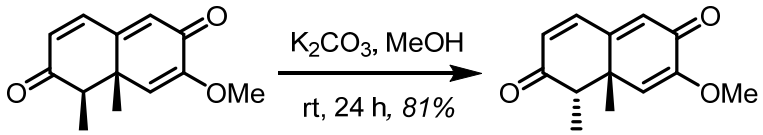
(4a*S*,5*S*)-3-Methoxy-4a,5-dimethyl-5,6-dihydronaphthalen-2(4aH)-one (11): To a stirred solution of **10** (1.7 g, 8.25 mmol) in 1, 4 dioxane (25 mL) at room temperature was added SeO_2 (2.7 g, 24.7 mmol) and the resulting mixture was refluxed for 4 h. After completion (by TLC), reaction mixture was allowed to cool at room temperature and diluted with EtOAc (60 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL), water (15 mL), brine (15 mL). The resulting organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the crude obtained was purified on column chromatography (silica gel 100–200, 4.0:6.0 ethyl acetate: petroleum ether) to afford **11** (1.1 g, 67%) as reddish oil. IRυ_{max}(film): 2927, 1665, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.25–6.23 (m, 1H), 6.14–6.10 (m, 1H), 6.03 (s, 1H), 5.90 (s, 1H), 3.66 (s, 3H), 2.29–2.22 (m, 1H), 2.08–2.01 (m, 1H), 1.89–1.81 (m, 1H), 1.11 (d, J = 7.0 Hz, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5, 162.6, 151.1, 136.1, 127.4, 123.4, 119.9, 54.9, 41.2, 36.4, 32.7, 20.6, 15.9; HRMS (ESI) calcd for $C_{13}H_{17}O_2[M+H]^+$ 205.1223, found 205.1222.



11 **12**

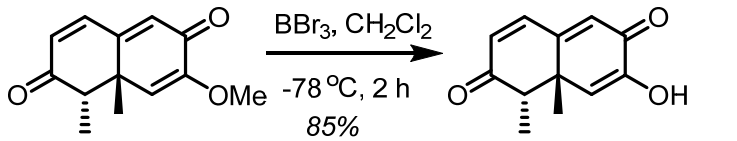
(1*R*,8a*R*)-7-Methoxy-1,8a-dimethyl-1,8a-dihydronaphthalene-2,6-dione (12) : To a stirred solution of **11** (1.1 g, 5.39 mmol) in benzene (60 mL) were added *t*-BuOOH (5M in decane), (5.4 mL, 26.9 mmol) and 4 Å MS (1 g) at room temperature. After 5 min, PDC (10.1 g, 26.9 mmol) was added and reaction mixture was stirred for 16 h. The reaction mixture was diluted with EtOAc (60 mL), filtered through a celite bed, and washed with EtOAc (2 X 20 mL). The filtrate was concentrated in *vacuo*. Purification by column chromatography (silica gel 100–200, 4.5:5.5 ethyl acetate: petroleum ether as eluent) afforded **12** (332 mg, 52% brsm, 29%) as light yellow solid. M.p.=110–112 °C IRυ_{max}(film): 2967, 1654, 1619, 1207 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$) δ 7.21 (d, J = 9.8 Hz, 1H), 6.45 (s, 1H), 6.28 (d, J = 9.8 Hz, 1H), 5.99 (s, 1H), 3.72 (s, 3H), 2.56 (q, J = 6.6 Hz, 1H), 1.34 (d, J = 6.8 Hz, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 180.4, 158.0, 151.5, 142.0, 131.5, 128.4, 121.0, 55.2, 51.0, 44.9, 23.8, 8.3; HRMS (ESI) calcd for $C_{13}H_{15}O_3[M+H]^+$ 219.1016, found 219.1014.



12 **13**

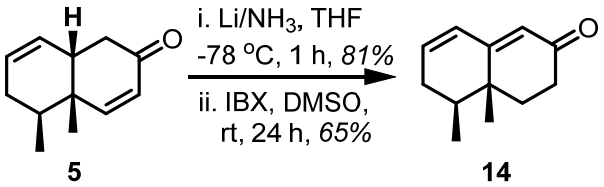
(1*S*,8a*R*)-7-Methoxy-1,8a-dimethyl-1,8a-dihydronaphthalene-2,6-dione (13): Compound **12** (60 mg, 0.275 mmol) was treated with K_2CO_3 (190 mg, 1.376 mmol) in MeOH (10 mL) at room temperature and stirred for 24 h. Solvent was removed under *vacuo* and crude residue was diluted with water (5 mL), and extracted with EtOAc (3 X 15 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 4.5:5.5 ethyl acetate: petroleum ether as eluent) afforded **13** (49 mg, 81%) as light yellow solid. M.p.=108–110 °C, IRυ_{max}(film): 2967, 1654, 1619, 1207 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 9.8 Hz, 1H), 6.55 (s, 1H), 6.17 (d, J = 9.8 Hz, 1H), 5.68 (s, 1H), 3.74 (s, 3H), 2.62 (q, J = 6.6 Hz, 1H), 1.39 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 180.9, 155.2, 152.5, 141.9, 130.5, 129.3, 121.9, 55.2, 53.4, 45.4, 29.7, 15.6; HRMS (ESI) calcd for $C_{13}H_{15}O_3[M+H]^+$ 219.1016, found 219.1015.



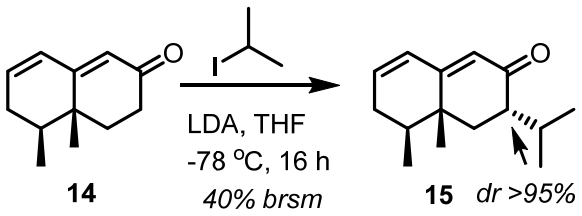
13 **(±)-botryosphaeridione (1)**

(1*S*,8a*R*)-7-Hydroxy-1,8a-dimethyl-1,8a-dihydronaphthalene-2,6-dione (1) : To a solution of **13** (20 mg, 0.092 mmol) in dry CH_2Cl_2 (5 mL) was added a solution of BBr_3 (1M in CH_2Cl_2, 0.18 mL, 0.183 mmol) dropwise at −78 °C. The reddish reaction mixture was stirred for 2 h at same temperature and was then quenched by adding saturated aqueous $NaHCO_3$ solution (3 mL). The cooling bath was removed and the mixture was stirred at room temperature for another 30 min. The mixture was diluted with CH_2Cl_2 (10 mL) and the

organic phase was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 3.0:7.0 ethyl acetate: petroleum ether as eluent) afforded (±)-botryosphaeridione **(1)** (16 mg, 85%) as pale yellow solid. M.p.=118–120 °C, IRυ_{max}(film): 2973, 1665, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 10.2 Hz, 1H), 6.63 (s, 1H), 6.42 (s, 1H), 6.20 (d, J = 10.2 Hz, 1H), 6.05 (s, 1H), 2.64 (q, J = 7.2 Hz, 1H), 1.38 (d, J = 7.2 Hz, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 181.4, 158.2, 148.2, 141.5, 129.7, 128.1, 123.8, 53.4, 45.7, 29.4, 15.6; HRMS (ESI) calcd for $C_{12}H_{13}O_3[M+H]^+$ 205.0859, found 205.0858.

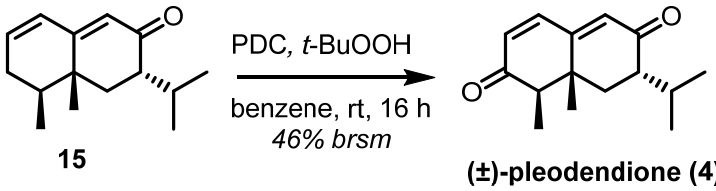


(4a*R*,5*S*)-4a,5-Dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3H)-one (14): A solution of α,β–unsaturated ketone **5** (4.4 g, 0.025 mol) in THF (60 mL) was added to liquid ammonia (120 mL) at −78 °C. Lithium (2.1 g, 0.30 mol) was added in small pieces and reaction mixture was stirred at −78 °C for 1 h. After consumption of starting material (by TLC), solid NH_4Cl (3.0 g) was added and ammonia was allowed to evaporate at room temperature. Water (30 mL) was added and reaction mixture was extracted with EtOAc (2 X 60 mL). Combined organic layer was washed with water (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford ketone (3.6 g, 81%) which was treated with IBX (17 g, 0.060 mmol) in DMSO (80 mL) at room temperature and stirred for 24 h. After the completion (by TLC), the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (25 mL). The aqueous layer was extracted with EtOAc (3 X 60 mL) and combined organic layer was washed with water (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 1.0:9.0 ethyl acetate: petroleum ether as eluent) afforded **14** (2.3 g, 65%) as colorless oil. IRυ_{max}(film): 2978, 1671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.23–6.11 (m, 2H), 5.68 (s, 1H), 2.61–2.40 (m, 2H), 2.25–2.18 (m, 1H), 2.12–2.01 (m, 2H), 1.76–1.68 (m, 2H), 1.03 (s, 3H), 0.95 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 163.7, 138.3, 128.3, 123.8, 38.2, 36.2, 34.2, 34.1, 32.7, 15.1, 14.5; HRMS (ESI) calcd for $C_{12}H_{17}O[M+H]^+$ 177.1274, found 177.1274.



(3*S*,4a*R*,5*S*)-3-Isopropyl-4a,5-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3H)-one (14) :

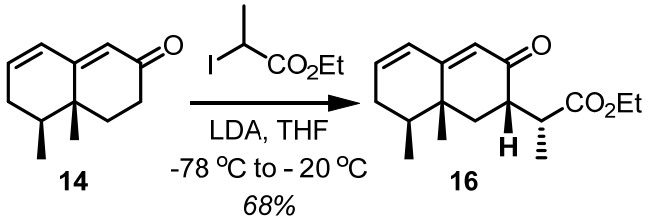
To a solution of diisopropylamine (0.72 mL, 5.11 mmol) in dry THF (10 mL) was added a solution of *n*-butyllithium in hexane (1.6M, 3.2 mL, 5.11 mmol) at –78 °C. The reaction was stirred for 30 min at –78 °C and **14** (300 mg, 1.70 mmol) in THF (5 mL) was added dropwise via syringe. After stirring for 30 min, HMPA (0.9 mL, 5.11 mmol) was added. After stirring for a further 20 min, isopropyl iodide (1.7 mL, 17.0 mmol) was added slowly. After stirring for 2 h at –78 ºC the mixture was warmed to room temperature and then stirred for a further 16 h. The reaction was quenched with 1N aqueous HCl (5 mL) extracted with EtOAc (3 X 10 mL) and combined organic layer was washed with water (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 0.5:9.5 ethyl acetate: petroleum ether as eluent) afforded **15** (115 mg, 40% brsm, 31%) as colorless oil. IRυ_{max}(film): 2973, 1671, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21–6.17 (m, 1H), 6.12–6.09 (m, 1H), 5.66 (s, 1H), 2.65–2.57 (m, 1H), 2.44–2.38 (m, 1H), 2.25–2.17 (m, 1H), 2.11–2.04 (m, 1H), 1.94–1.89 (m, 1H), 1.74–1.68 (m, 1H), 1.52–1.45 (m, 1H), 1.02 (s, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 162.4, 137.9, 128.0, 124.4, 47.8, 38.4, 36.4, 33.6, 32.6, 26.2, 20.4, 17.7, 15.6, 14.6; HRMS (ESI) calcd for $C_{15}H_{23}O[M+H]^+$ 219.1743, found 219.1743.



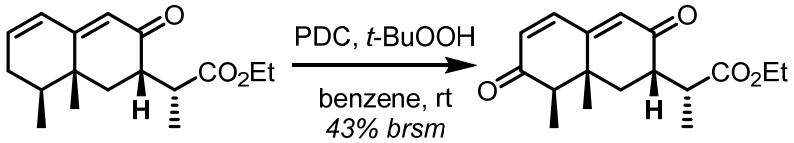
(1*R*,7*S*,8a*R*)-7-Isopropyl-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (4):

To a stirred solution of **15** (20 mg, 0.092 mmol) in benzene (6 mL) were added *t*-BuOOH (5M in decane), (0.09 mL, 0.458 mmol), 4 Å MS (20 mg) at room temperature. After 5 min, PDC (172 mg, 0.458 mmol) and reaction mixture was stirred for 16 h. The reaction mixture was diluted ethyl acetate (5 mL), filtered through a celite bed, and washed with ethyl acetate

(2 X 5 mL). The filtrate was concentrated in *vacuo*. Purification by column chromatography (silica gel 100–200, 2.0:8.0 ethyl acetate: petroleum ether as eluent) afforded pleodendione (**4**) (6 mg, 46% brsm, 28%) as yellow solid. M.p.=103–105 °C,IRυ_{max}(film): 2963, 1671, 1595, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J = 9.8 Hz, 1H), 6.19 (d, J = 9.8 Hz, 1H), 6.00 (s, 1H), 2.63–2.54 (m, 1H), 2.56 (q, J = 6.8 Hz, 1H), 2.36–2.31 (m, 1H), 1.97 (dd, J = 12.9, 4.7 Hz, 1H), 1.74 (t, J = 13.8 Hz, 1H), 1.14 (d, J = 6.8 Hz, 3H), 1.12 (s, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 200.1, 158.3, 142.3, 132.1, 129.7, 52.5, 47.4, 40.3, 34.4, 26.0, 20.3, 18.6, 17.7, 7.2; HRMS (ESI) calcd for $C_{15}H_{21}O_2[M+H]^+$ 233.1536, found 233.1534.

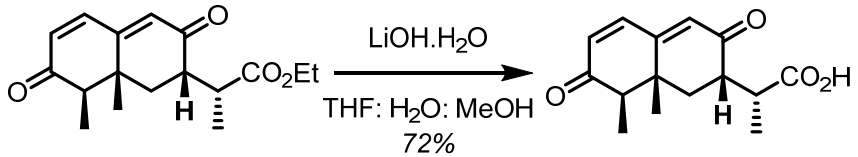


Ethyl(S)-2-((2*S*,8*S*,8a*R*)-8,8a-dimethyl-3-oxo-1,2,3,7,8,8a-hexahydronaphthalen-2-yl) propanoate (16) : To a solution of diisopropylamine (2.0 mL, 14.2 mmol) in dry THF (15 mL) was added a solution of *n*-butyllithium in hexane (1.6 M, 9.0 mL, 14.2 mmol) at –78 °C. The reaction was stirred for 30 min at –78 °C and **14** (500 mg, 2.84 mmol) in THF (10 mL) was added dropwise via syringe. After stirring for 30 min, HMPA (2.5 mL, 14.2 mmol) was added. After stirring for a further 20 min, ethyl-2-iodopropanoate (3.2 g, 14.2 mmol) was added slowly. The resulting mixture was maintained at –20 °C for 2 h. After the completion (by TLC), reaction was quenched with saturated NH_4Cl (5 mL) and extracted with EtOAc (3 X 15 mL) and combined organic layer was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 0.5:9.5 ethyl acetate: petroleum ether as eluent) afforded **16** (533 mg, 68%) as colorless oil. IRυ_{max}(film): 1725, 1661 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22–6.17 (m, 1H), 6.12–6.09 (m, 1H), 5.67 (s, 1H), 4.22–4.11 (m, 2H), 3.19–3.12 (m, 1H), 3.08 (ddd, J = 14.1, 4.7, 4.7 Hz, 1H), 2.24–2.17 (m, 1H), 2.11–2.03 (m, 1H), 1.94–1.90 (m, 1H), 1.73–1.67 (m, 1H), 1.58–1.52 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.08 (d, J = 8.0 Hz, 3H), 1.07 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 176.2, 162.9, 138.3, 127.9, 123.5, 60.5, 44.9, 38.5, 38.4, 36.8, 36.0, 32.6, 15.4, 14.5, 14.4, 12.7; HRMS (ESI) calcd for $C_{17}H_{25}O_3[M+H]^+$ 277.1798, found 277.1796.



16 18

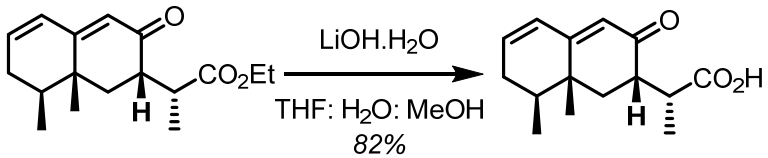
Ethyl (S)-2-((2*S*,8*R*,8a*R*)-8,8a-dimethyl-3,7-dioxo-1,2,3,7,8,8a-hexahydronaphthalen-2-yl)propanoate (18) : To a solution of **16** (300 mg, 1.08 mmol) in benzene (30 mL) were added *t*-BuOOH (5M in decane), (1.1 mL, 5.43 mmol), 4 Å MS (200 mg) at room temperature. After 5 min, PDC (2.0 g, 5.43 mmol) was added and reaction mixture was stirred for 16 h. The reaction mixture was diluted with EtOAc (20 mL), filtered through a celite bed, and washed with ethyl acetate (2 X 10 mL). The filtrate was concentrated in *vacuo*. Purification by column chromatography (silica gel 100–200, 2.0:8.0 ethyl acetate: petroleum ether as eluent) afforded **18** (87 mg, 43% brsm, 28%) as yellow solid. M.p.=121–123 °C, IRυ_{max}(film): 1730, 1668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 10.0 Hz, 1H), 6.22 (d, J = 10.0 Hz, 1H), 6.03 (s, 1H), 4.23–4.13 (m, 2H), 3.15–3.11 (m, 1H), 3.03 (ddd, J = 14.1, 4.7, 4.7 Hz, 1H), 2.57 (q, J = 6.8 Hz, 1H), 2.04–2.00 (m, 1H), 1.86–1.79 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.19 (s, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.11 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 198.5, 175.6, 158.8, 142.1, 132.3, 128.7, 60.8, 52.4, 44.4, 40.5, 38.1, 36.6, 18.5, 14.4, 13.0, 7.12; HRMS (ESI) calcd for $C_{17}H_{23}O_4[M+H]^+$ 291.1591, found 291.1588.



18 19

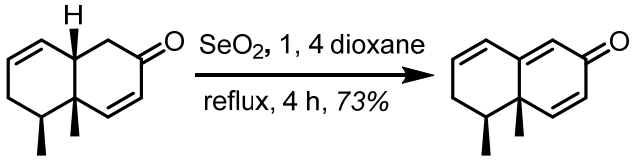
(S)-2-((2*S*,8*R*,8a*R*)-8,8a-Dimethyl-3,7-dioxo-1,2,3,7,8,8a-hexahydronaphthalen-2-yl) propanoic acid (19) : To a solution of **18** (50 mg, 0.172 mmol) in THF (3 mL) : MeOH (3 mL) was added LiOH.H_2O (36 mg, 0.862 mmol) in H_2O (3 mL) at 0 °C. The mixture was warmed up to room temperature and stirred for 12 h. The solvent was evaporated *in vacuo* and mixture was acidified to pH 2 with 1N HCl and extracted with EtOAc (3 X 10 mL). The combined organic layer was washed by brine (5 mL), dried over anhydrous Na_2SO_4, concentrated in *vacuo*. Purification by flash chromatography over silica gel (0.5:9.5; MeOH–DCM) afforded **19** (32 mg, 72%) as white solid. M.p.=135–138 °C, IRυ_{max}(film): 3023, 1717, 1655, 1620 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 9.8 Hz, 1H), 6.24 (d, J = 9.8 Hz,

1H), 6.06 (s, 1H), 3.23–3.19 (m, 1H), 3.04 (ddd, J = 14.4, 4.8, 4.8 Hz, 1H), 2.58 (q, J = 6.8 Hz, 1H), 2.08–2.05 (m, 1H), 1.89–1.84 (m, 1H), 1.22 (s, 3H), 1.18 (d, J = 7.2 Hz, 3H), 1.15 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 198.3, 181.2, 159.1, 142.1, 132.4, 128.6, 52.4, 44.3, 40.6, 38.1, 36.7, 18.6, 13.0, 7.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (d, J = 9.8 Hz, 1H), 6.23 (d, J = 9.8 Hz, 1H), 6.16 (s, 1H), 2.97–2.91 (m, 2H), 2.73 (q, J = 6.7 Hz, 1H), 1.91-1.89 (m, 2H), 1.10 (s, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 199.7, 198.5, 176.4, 158.8, 142.3, 131.7, 128.3, 51.3, 43.8, 37.6, 35.7, 18.0, 13.0, 6.9; HRMS (ESI) calcd for $C_{15}H_{18}O_4$[M+Na]$^+$ 285.1097, found 285.1096.



16 17

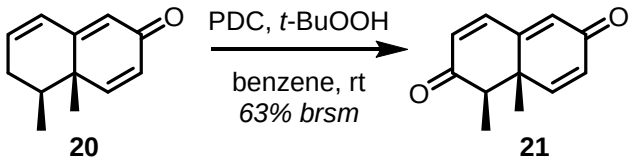
(S)-2-((2*S*,8*S*,8a*R*)-8,8a-Dimethyl-3-oxo-1,2,3,7,8,8a-hexahydronaphthalen-2-yl) propanoic acid (17) : Compound **17** was prepared using the similar experimental procedure as described above for preparation of **19**. M.p.=122–124 °C, IRυ_{max}(film): 1717, 1664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24–6.11 (m, 2H), 5.70 (s, 1H), 3.26–3.20 (m, 1H), 3.10 (ddd, J = 14.4, 4.8, 4.8 Hz, 1H), 2.26–2.19 (m, 1H), 2.13–2.05 (m, 1H), 2.00–1.96 (m, 1H), 1.76–1.69 (m, 1H), 1.62–1.55 (m, 1H), 1.13 (d, J = 7.1 Hz, 3H), 1.09 (s, 3H), 0.96 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 181.6, 163.4, 138.6, 127.9, 123.3, 44.7, 38.4, 36.8 (2C), 36.0, 32.6, 15.4, 14.5, 12.7; HRMS (ESI) calcd for $C_{15}H_{21}O_3$[M+H]$^+$ 249.1485, found 249.1483.



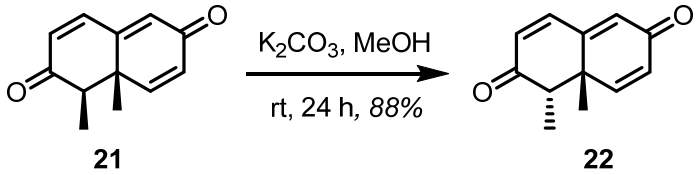
5 20

(4a*R*,5*R*)-4a,5-Dimethyl-5,6-dihydronaphthalen-2(4aH)-one (20) : Compound **20** was prepared using the similar experimental procedure as described above for preparation of **11**. IRυ_{max}(film): 2975, 1660 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 10.0 Hz, 1H), 6.26–6.23 (m, 2H), 6.13–6.10 (m, 1H), 6.00 (s, 1H), 2.31–2.23 (m, 1H), 2.13–2.04 (m, 1H),

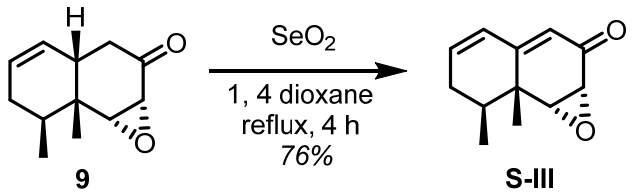
1.92–1.86 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 162.3, 153.2, 135.7, 128.3, 128.0, 123.8, 41.1, 35.2, 32.7, 19.3, 15.5; HRMS (ESI) calcd for $C_{12}H_{15}O[M+H]^+$ 175.1117, found 175.1116.



(1*S*,8a*S*)-1,8a-Dimethyl-1,8a-dihydronaphthalene-2,6-dione (21) : Compound **21** was prepared using the similar experimental procedure as described above for preparation of **12**. IRυ_{max}(film): 2975, 1661, 1626 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 10.0 Hz, 1H), 7.11 (d, J = 10.0 Hz, 1H), 6.41 (s, 1H), 6.37 (dd, J = 10.1, 1.8 Hz, 1H), 6.27 (d, J = 10.0 Hz, 1H), 2.60 (q, J = 6.8 Hz, 1H), 1.32 (d, J = 6.8 Hz, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 185.3, 157.7, 153.5, 142.6, 131.4, 129.1, 128.7, 49.7, 44.4, 22.4, 7.9; HRMS (ESI) calcd for $C_{12}H_{13}O_2[M+H]^+$ 189.0910, found 189.0910.

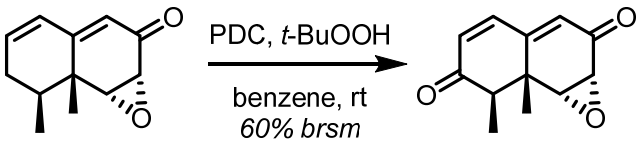


(1*R*,8a*S*)-1,8a-Dimethyl-1,8a-dihydronaphthalene-2,6-dione (22) : Compound **22** was prepared using the similar experimental procedure as described above for preparation of **13**. IRυ_{max}(film): 2975, 1661, 1626 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 9.8 Hz, 1H), 6.80 (d, J = 9.8 Hz, 1H), 6.52 (s, 1H), 6.42 (dd, J = 10.0, 1.7 Hz, 1H), 6.16 (d, J = 10.0 Hz, 1H), 2.63 (q, J = 7.2 Hz, 1H), 1.36 (s, 3H), 0.94 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 186.0, 155.0, 154.6, 142.7, 131.2, 129.8, 129.3, 52.4, 45.2, 28.2, 15.7; HRMS (ESI) calcd for $C_{12}H_{13}O_2[M+H]^+$ 189.0910, found 189.0910.



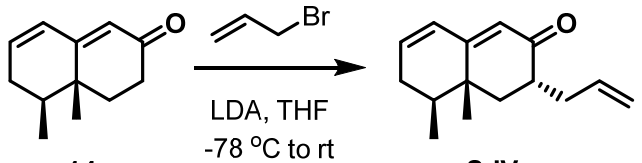
(1a*R*,7*R*,7a*S*,7b*R*)-7,7a-Dimethyl-6,7,7a,7b-tetrahydronaphtho[1,2-b]oxiren-2(1aH)-one (S-III) : Compound **S-III** was prepared using the similar experimental procedure as

described above for preparation of **11.** IRυ_{max}(film): 2968, 1665, 1210 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16–6.02 (m, 2H), 5.66 (s, 1H), 3.62 (d, J = 3.9 Hz, 1H), 3.37 (d, J = 3.9 Hz, 1H), 2.32–2.31 (m, 1H), 2.11–2.07 (m, 2H), 1.24 (s, 3H), 1.11 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 162.0, 136.0, 128.0, 120.3, 60.6, 54.5, 38.3, 34.4, 33.4, 16.1, 14.8; HRMS (ESI) calcd for $C_{12}H_{15}O_2[M+H]^+$ 191.1067, found 191.1066.



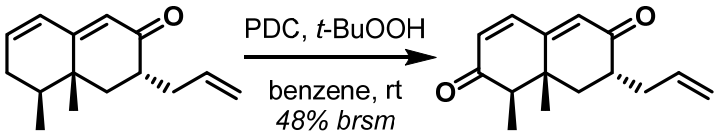
S-III **23**

(1a*R*,7*S*,7a*S*,7b*R*)-7,7a-Dimethyl-1a,7,7a,7b-tetrahydronaphtho[1,2-b]oxirene-2,6-dione (23) : Compound **23** was prepared using the similar experimental procedure as described above for preparation of **12**. IRυ_{max}(film): 2975, 1660, 1622 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 10.0 Hz, 1H), 6.20 (d, J = 10.0 Hz, 1H), 6.01 (s, 1H), 3.67 (d, J = 3.4 Hz, 1H), 3.48 (d, J = 3.4 Hz, 1H), 2.73 (q, J = 6.6 Hz, 1H), 1.35 (s, 3H), 1.34 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 191.6, 157.3, 142.8, 131.9, 124.6, 60.9, 54.4, 49.5, 41.0, 19.2, 7.8; HRMS (ESI) calcd for $C_{12}H_{13}O_3[M+H]^+$ 205.0859, found 205.0858.

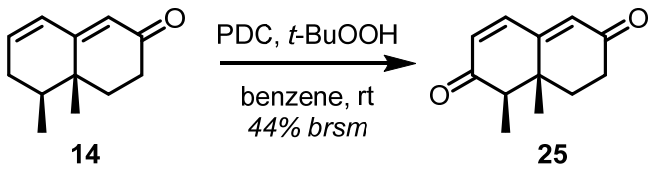


14 **S-IV**

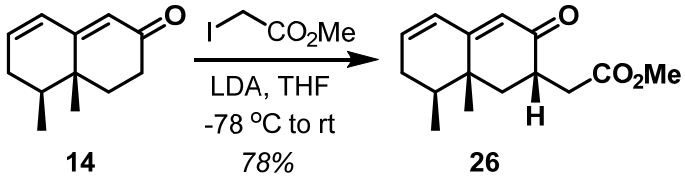
(3R,4aR,5S)-3-Allyl-4a,5-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3H)-one (S-IV) : Compound **S-IV** was prepared using the similar experimental procedure as described above for preparation of **15**. IRυ_{max}(film): 3019, 2864, 1673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21–6.10 (m, 2H), 5.83–5.73 (m, 1H), 5.67 (s, 1H), 5.08–5.02 (m, 2H), 2.77–2.71 (m, 1H), 2.57–2.49 (m, 1H), 2.23–2.03 (m, 4H), 1.70–1.65 (m, 1H), 1.45–1.38 (m, 1H), 1.04 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 163.0, 138.1, 136.6, 128.0, 123.6, 116.8, 42.0, 39.7, 38.3, 36.8, 34.3, 32.5, 15.6, 14.5; HRMS (ESI) calcd for $C_{15}H_{21}O[M+H]^+$217.1587, found 217.1586.



(1*R*,7*R*,8a*R*)-7-Allyl-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (24) : Compound **24** was prepared using the similar experimental procedure as described above for preparation of **12**. IRυ_{max}(film): 3020, 2929, 1673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 9.6 Hz, 1H), 6.22 (d, J = 9.6 Hz, 1H), 6.05 (s, 1H), 5.83–5.72 (m, 1H), 5.12–5.07 (m, 2H), 2.79–2.72 (m, 1H), 2.59–2.49 (m, 2H), 2.24–2.11 (m, 2H), 1.73–1.67 (m, 1H), 1.17 (s, 3H), 1.14 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 199.8, 158.8, 142.2, 135.7, 132.2, 129.0, 117.5. 52.3, 41.5, 40.6, 40.0, 33.7, 18.7, 7.1; HRMS (ESI) calcd for $C_{15}H_{19}O_2[M+H]^+$ 231.1380, found 231.1379.

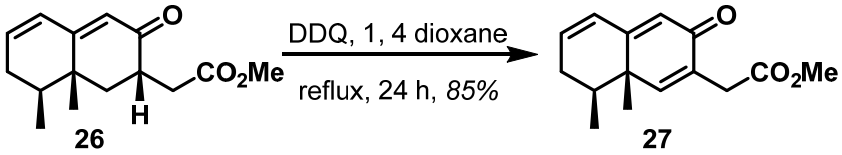


(1*R*,8a*R*)-1,8a-Dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (25) : Compound **25** was prepared using the similar experimental procedure as described above for preparation of **12**. IRυ_{max}(film): 3045, 1664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 9.8 Hz, 1H), 6.23 (d, J = 9.8 Hz, 1H), 6.05 (s, 1H), 2.61–2.52 (m, 3H), 2.16–2.11 (m, 1H), 2.04–1.96 (m, 1H), 1.16 (s, 3H), 1.15 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 198.8, 159.5, 142.4, 132.3, 129.2, 52.2, 40.0, 34.5, 33.5, 18.3, 7.1; HRMS (ESI) calcd for $C_{12}H_{15}O_2[M+H]^+$ 191.1067, found 191.1066.



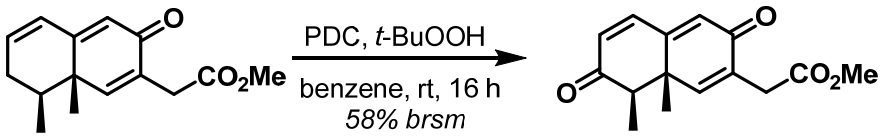
Methyl2-((2S,8S,8aR)-8,8a-dimethyl-3-oxo-1,2,3,7,8,8a-hexahydronaphthalen-2-yl)acetate (26) : Compound **26** was prepared using the similar experimental procedure as described above for preparation of **16**. IRυ_{max}(film): 1737, 1661, 1168 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22–6.10 (m, 2H), 5.68 (s, 1H), 3.70 (s, 3H), 3.09–3.01 (m, 1H), 2.96–2.91 (m, 1H), 2.34–2.28 (m, 1H), 2.24–2.17 (m, 1H), 2.11–2.03 (m, 2H), 1.74–1.68 (m, 1H), 1.59–

1.53 (m, 1H), 1.10 (s, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 173.3, 163.2, 138.3, 128.0, 123.0, 51.8, 40.7, 39.8, 38.2, 37.0, 34.9, 32.5, 15.5, 14.5; HRMS (ESI) calcd for $C_{15}H_{21}O_3[M+H]^+$ 249.1485, found 249.1485.



26 **27**

Methyl 2-((8*S*,8a*S*)-8,8a-dimethyl-3-oxo-3,7,8,8a-tetrahydronaphthalen-2-yl)acetate (27) : To a solution of **26** (150 mg, 0.604 mmol) in dry 1, 4 dioxane (10 mL) was added DDQ (412 mg, 1.81 mmol) at room temperature. The resulting mixture was refluxed for 24 h. After completion (by TLC), reaction mixture was allowed to cool at room temperature and diluted with CH_2Cl_2. The resulting mixture was filtered and filtrate was concentrated in *vacuo*. Purification by column chromatography (silica gel 100–200, 2.0:8.0 ethyl acetate: petroleum ether as eluent) afforded **27** (126 mg, 85%) as yellow solid. IRυ_{max}(film): 1739, 1619 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.26–6.23 (m, 1H), 6.13–6.08 (m, 1H), 6.01 (s, 1H), 3.67 (s, 3H), 3.35 (d, J = 16.5 Hz, 1H), 3.30 (d, J = 16.5 Hz, 1H), 2.30–2.23 (m, 1H), 2.12–2.04 (m, 1H), 1.96–1.89 (m, 1H), 1.11 (s, 3H), 1.10 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.3, 171.9, 162.1, 150.9, 135.7, 132.0, 127.7, 123.2, 52.1, 41.2, 35.2, 35.1, 32.7, 19.4, 15.6; HRMS (ESI) calcd for $C_{15}H_{19}O_3[M+H]^+$ 247.1329, found 247.1327.



27 **(±)-Hoaensieremodione 28**

Methyl 2-((8*R*,8a*R*)-8,8a-dimethyl-3,7-dioxo-3,7,8,8a-tetrahydronaphthalen-2-yl)acetate (28) : Compound **28** was prepared using the similar experimental procedure as described above for preparation of **12**. M.p.=123–125 °C, IRυ_{max}(film): 1739, 1661, 1619 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 9.8 Hz, 1H), 7.02 (s, 1H), 6.44 (s, 1H), 6.27 (d, J = 9.8 Hz, 1H), 3.71 (s, 3H), 3.41 (d, J = 16.5 Hz, 1H), 3.35 (d, J = 16.5 Hz, 1H), 2.63 (q, J = 6.8 Hz, 1H), 1.33 (d, J = 6.8 Hz, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 184.1, 171.1, 157.4, 151.3, 142.1, 132.6, 131.2, 128.3, 52.0, 49.5, 44.3, 34.7, 22.3, 7.8; HRMS (ESI) calcd for $C_{15}H_{17}O_4[M+H]^+$ 261.1121, found 261.1120.

Single X-ray Crystal Structure of 17 (KLH-Acid)

X-ray intensity data measurements of compound **17** (**KLH-Acid)** were carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 15 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX2 program (Bruker, 2006).[1] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[2] All the hydrogen atoms were placed in geometrically idealized position and constrained to ride on their parent atoms. An ORTEP view of both compounds were drawn with 30% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

Crystal data of **17** (**KLH-Acid)** $C_{15}H_{20}O_3$, M = 248.31, colorless plate, 0.36 x 0.26 x 0.20 mm^3, triclinic, space group *P*-1, a = 7.2066(3) Å, b = 9.6275(3)Å, c = 9.8499(3)Å, α=84.696(2)° β = 74.028(2)°, γ=81.042(2)°, V = 648.12(4) $Å^3$, Z = 2, T = 150(2)K, $2\theta_{max}$=50.0°, D_{calc} (g cm^{-3}) = 1.272, $F(000)$ = 268, μ (mm^{-1}) = 0.087, 8037 reflections collected, 2238 unique reflections (R_{int}= 0.0316), 1859 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.9693, T_{max} = 0.9828, 170 refined parameters, S = 1.071, $R1$ = 0.0513, $wR2$ = 0.1021 (all data R = 0.0659, $wR2$ = 0.1081), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.255, $\Delta\rho_{min}$= -0.176 ($eÅ^{-3}$).

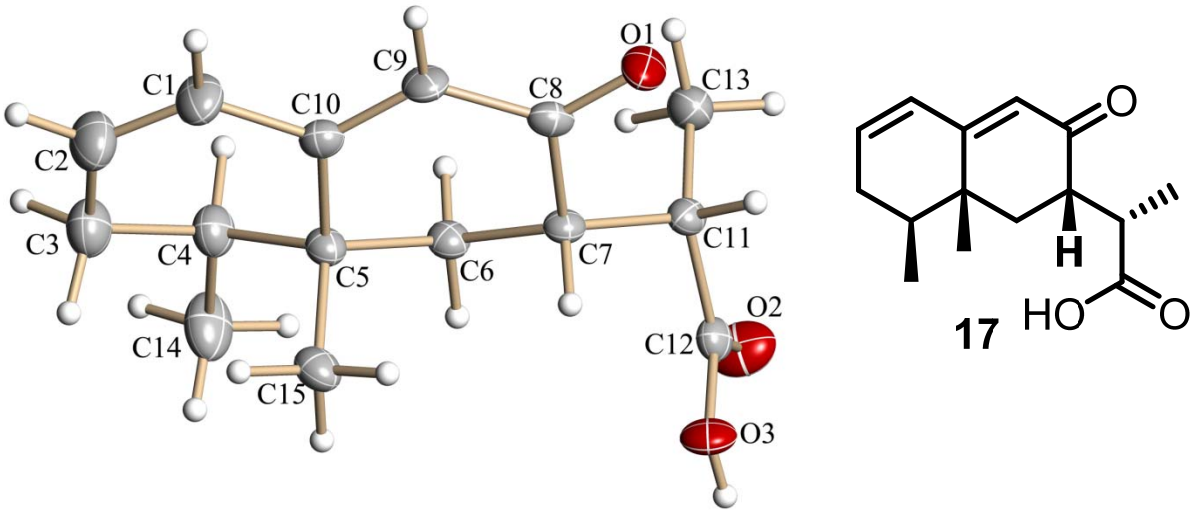


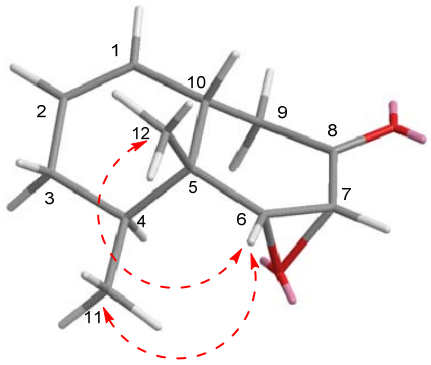
Figure 1. ORTEP of Compound **17** (KLH-Acid)

Crystallographic data for compound **17 (KLH-Acid)** deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1056739.

References

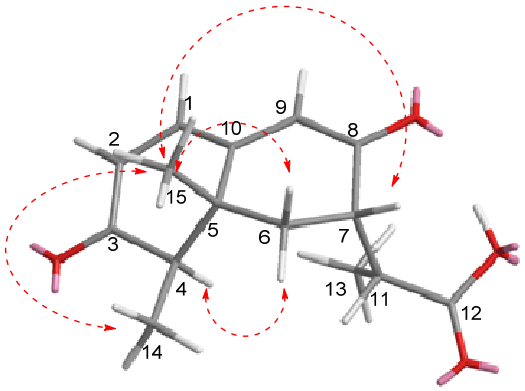
(1) Bruker (2006). *APEX2*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA. (2) Sheldrick, G. M. *Acta Crystallogr*., **2008**, *A64*, 112. (3) Farrugia, L. J. *J. Appl. Cryst.* **1997,** *30*, 565–565.

Key NOE correlation of Epoxide-9



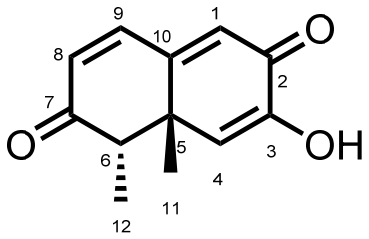
The ^{13}C NMR and DEPT spectra exhibited 12 carbon signals, corresponding to one carbonyl carbons, one quaternary carbons, two olefinic carbon, two oxygen attached carbon and two methyls. The ^{1}H-^{1}H COSY spectrum provided connectivities for H-6 and H-7. The stereochemistry of epoxide was deduced from NOESY experiments. H-6 having correlation with CH_3-12 and CH_3-11. This suggested that H-6, H-7, CH_3-12 and CH_3-11 are situated on same side making the epoxide in *α*-orientation

NOE correlation of compound 19



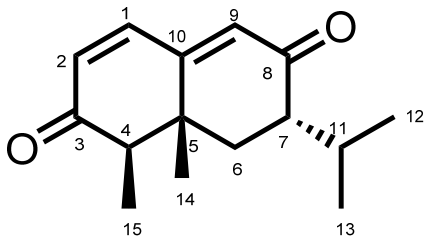
The stereochemistry of **19** was deduced from NOESY experiments. NOE correlations from CH_3-15 with CH_3-14, H-6*β* and H-7 indicated their *β*-orientations. There is strong NOE from H-4 to H-6*α* indicated their α-orientations.

Spectral Data Comparison of Natural Botryosphaeridione and Synthesized (±)-Botryosphaeridione



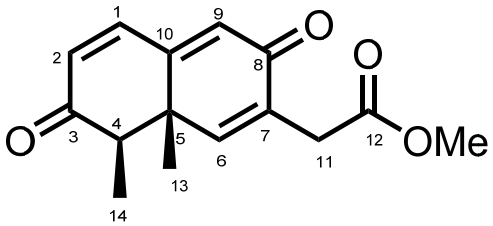
No	Natural Botryosphaeridione		Synthesized (±)-Botryosphaeridione	
	^{1}H-NMR	^{13}C-NMR	^{1}H-NMR	^{13}C-NMR
1	6.64 (s)	128.1	6.63 (s)	128.1
2	-	181.4	-	181.4
3-OH	6.41 (s)	148.2	6.42 (s)	148.2
4	6.06 (s)	123.7	6.05 (s)	123.8
5	-	45.7	-	45.7
6	2.64 (q, 7.2 Hz)	53.4	2.64 (q, 7.2 Hz)	53.4
7	-	201.0	-	201.5
8	6.20 (d, 10.2 Hz)	129.7	6.20 (d, 10.2 Hz)	129.7
9	7.22 (d, 10.2 Hz)	141.5	7.21 (d, 10.2 Hz)	141.5
10	-	158.2	-	158.2
11	1.39 (s)	29.4	1.38 (s)	29.4
12	0.91 (d, 7.2 Hz)	15.6	0.91 (d, 7.2 Hz)	15.6

Spectral Data Comparison of Natural Pleodendione and Synthesized (±)-Pleodendione



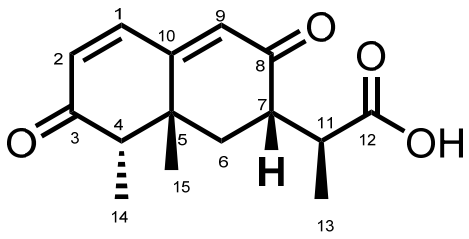
No	Natural Pleodendione		Synthesized (±)-Pleodendione	
	^{1}H-NMR	^{13}C-NMR	^{1}H-NMR	^{13}C-NMR
1	6.96 (d, 9.8 Hz)	142.3	6.96 (d, 9.8 Hz)	142.3
2	6.19 (d, 9.8 Hz)	132.2	6.19 (d, 9.8 Hz)	132.1
3	-	200.0 or 200.2	-	200.1 or 200.2
4	2.56 (q, 6.8 Hz)	52.6	2.56 (q, 6.8 Hz)	52.5
5	-	40.4	-	40.3
6	1.97 (dd, 12.9, 4.7 Hz) 1.74 (t, 14.0 Hz)	34.6	1.97 (dd, 12.9, 4.7 Hz) 1.74 (t, 13.8 Hz)	34.4
7	2.33 (ddd, 14.1, 4.6, 3.2 Hz)	47.5	2.36-2.31 (m)	47.4
8	-	200.0 or 200.2	-	200.1 or 200.2
9	6.00 (s)	129.8	6.00 (s)	129.7
10	-	158.4	-	158.3
11	2.63-2.55 (m)	26.2	2.63-2.54 (m)	26.0
12	0.82 (d, 7.0 Hz)	17.9 or 20.4	0.81 (d, 6.8 Hz)	17.7 or 20.3
13	0.97 (d, 7.0 Hz)	17.9 or 20.4	0.97 (d, 6.8 Hz)	17.7 or 20.3
14	1.12 (s)	18.6	1.12 (s)	18.6
15	1.14 (d, 7.0 Hz)	7.2	1.14 (d, 6.8 Hz)	7.2

Spectral Data Comparison of Natural Hoaensieremodione and Synthesized (±)-Hoaensieremodione

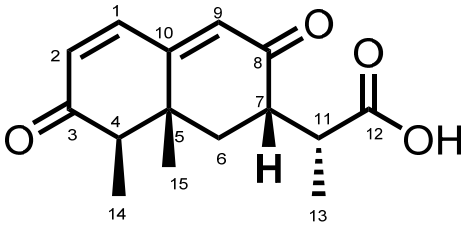


No	Natural Hoaensieremodione		Synthesized (±)-Hoaensieremodione	
	^{1}H-NMR	^{13}C-NMR	^{1}H-NMR	^{13}C-NMR
1	7.21 (d, 9.9 Hz)	142.1	7.20 (d, 9.8 Hz)	142.1
2	6.28 (d, 9.9 Hz)	131.3	6.27 (d, 9.8 Hz)	131.2
3	-	198.1	-	198.2
4	2.64 (q, 6.8 Hz)	49.6	2.63 (q, 6.8 Hz)	49.5
5	-	44.4	-	44.3
6	7.03 (s)	151.2	7.02 (s)	151.3
7	-	132.7	-	132.6
8	-	184.4	-	184.1
9	6.45 (s)	128.3	6.44 (s)	128.3
10	-	157.5	-	157.4
11	3.37 (d, 16.5 Hz) 3.42 (d, 16.5 Hz)	34.6	3.35 (d, 16.5 Hz) 3.41 (d, 16.5 Hz)	34.7
12	-	171.1	-	171.1
13	1.25 (s)	22.3	1.24 (s)	22.3
14	1.33 (d, 6.8 Hz)	7.8	1.33 (d, 6.8 Hz)	7.8
12-OMe	3.71 (s)	52.0	3.71 (s)	52.0

Spectral Data Comparison of Natural Periconianone B and Synthesized Periconianone B analogue



Natural Periconianone B



Synthesized Periconianone B analogue

NO	**Natural Periconianone B**		**Synthesized Periconianone B analogue**	
	^{1}H-NMR (600 MHz, DMSO-d_6)	**^{13}C-NMR** (150 MHz, DMSO-d_6)	**^{1}H-NMR** (400 MHz, DMSO-d_6)	**^{13}C-NMR** (100 MHz, DMSO-d_6)
1	7.28 (d, 9.6 Hz)	142.6	7.27 (d, 9.8 Hz)	142.3
2	6.12 (d, 9.6 Hz)	129.1	6.23 (d, 9.8 Hz)	128.3
3	-	202.5	-	199.7
4	2.37 (q, 7.2 Hz)	52.4	2.73 (q, 6.7 Hz)	51.3
5	-	39.2	-	Merged with DMSO-d_6
6	2.11 (dd, 14.4, 13.2 Hz, Hα) 1.52 (dd, 13.2, 4.8 Hz, Hβ)	32.5	1.91-1.89 (m, 2H)	35.7
7	3.04 (ddd, 14.4, 4.8, 4.8 Hz)	43.6	2.97-2.95 (m, 1H)	43.8
8	-	198.6	-	198.5
9	6.25 (s)	130.6	6.16 (s)	131.7
10	-	155.9	-	158.8
11	2.91 (dq, 4.8, 7.2 Hz)	37.6	2.93-2.91 (m, 1H)	37.6
12	-	176.4	-	176.4
13	1.02 (d, 7.2 Hz)	13.0	1.02 (d, 7.0 Hz)	13.0
14	0.96 (d, 7.2 Hz)	14.4	0.99 (d, 6.7 Hz)	6.94
15	1.28 (s)	24.6	1.10 (s)	18.0

Methodology

Cell culture

Mouse microglial cell line N9 was kindly gifted by Prof. Maria Pedroso de Lima, Center for Neuroscience and Cell Biology, University of Coimbra, Portugal and maintained in laboratory at 37°C in RPMI-1640media supplemented with 10% heat-in activated fetal bovine serum (FBS) and penicillin/streptomycin.

Cytotoxicity assay

Viability of cultured cells was determined by-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; Sigma) as described earlier (1).N9 was seeded in triplicate at a density of 2×10^4 cells per well on a 96-well plate. After 12 h, cells were treated with varying concentrations (0-100 μM) of all the compounds in a serum free condition for another 24 h. MTT solution (0.5 mg/ml) was then added to each well and incubate for 4 h at 37°C. At the end of the incubation period, the medium was removed and the resulting purple formazan was solubilised with acidic isopropanol (0.1 N HCl in absolute isopropanol), and the absorbance was read at 570 nm using Biorad Microplate reader (Biorad, USA).

Nitric oxide (NO) measurement

Nitrite, a stable oxidized product of NO, was measured in culture supernatant using Griess reagent (Sigma Aldrich) according to a previously reported method (2). After overnight seeding in 96-well plate (2×10^4 cells/well), N9 cell was treated with lipopolysachharide (LPS; Sigma) at a concentration of 1μg/ml along with different doses of compounds (as determined from cytotoxicity assay) and standard curcuminin serum-free culture for 24 h. Following treatment, media was collected and centrifuged at 2,000 rpm for 5 min to remove cellular debris. 50 μl of this media was then reacted with equal volume of Griess reagent for 15 min at room temperature in dark and absorbance was taken at 540 nm using Microplate reader (Biorad, USA). Nitrite concentrations were determined using standard solutions of sodium nitrite prepared in cell culture medium.

Assessment of reactive oxygen species (ROS)

Intracellular ROS generation is a significant marker of microglial inflammation. Here, the effects of compounds (21, 1, 22, 17 and 26) on LPS (1μg/ml) induced ROS level was assessed using the cell permeable, non-polar hydrogen peroxide-sensitive dye 5-(and-6)-chlromethyl-2', 7'- dichlorodihydrofluoresceindiacetate (CM-H_2DCFDA;Sigma Aldrich) as described previously (3). N9 cell was seeded in 6-well plate (2×10^5 cells/well) for overnight and then replaced with serum free media containing LPS and varying doses of compounds. After 24 h of treatment, the cells were washed with PBS and incubated with 5μMCM-H_2DCFDA for 30 min at 37°C in the dark. Following washing with PBS, cells were harvested and the mean fluorescent intensities (MFIs) were measured on the FL-1 channel on a fluorescence-activated cell sorting (FACS) Calibur flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA).

Cytokine bead array

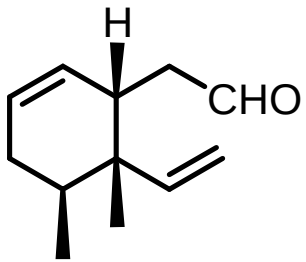
The cytokine bead array (CBA) kit (BD Biosciences, NJ, USA) was used to quantitatively measure cytokine levels in N9 cell lysates. After overnight seeding of cells in 6-well plate, they were treated with LPS along with compounds for 24 h and then cells were harvested for protein isolation. 30 µL of bead mix, containing a population of beads that have been coated with capture antibodies for cytokines, along with equal volume of PE-conjugated detection antibodies were incubated with 30 µg protein samples for 2 h at room temperature in dark and then the beads were acquired using Cell Quest Pro Software in FACS Calibur and analyzed using BD CBA software (Becton Dickinson, San Diego, CA) as indicated earlier (4).

References

1. D. Ghosh, M. K. Mishra, S. Das, D. K. Kaushik and A. Basu, *J Neurochem*., 2009, **110**, 1070.
2. D. K. Kaushik, M. Gupta, S. Das and A. Basu, *J Neuroinflammtion*, 2010, **7**, 68.
3. D. K. Kaushik, R. Mukhopadhyay, K. L. Kumawat, M. Gupta and A. Basu, *J Neuroinflammation,* 2012, **9**, 57.
4. A. Ghoshal, S. Das, S. Ghosh, M. K. Mishra, V. Sharma, P. Koli, E. Sen and A. Basu, *Glia*., 2007, **55**, 483.

^{1}H and ^{13}C Spectras

^{1}H NMR of Compound 8 ($CDCl_3$; 400 MHz)



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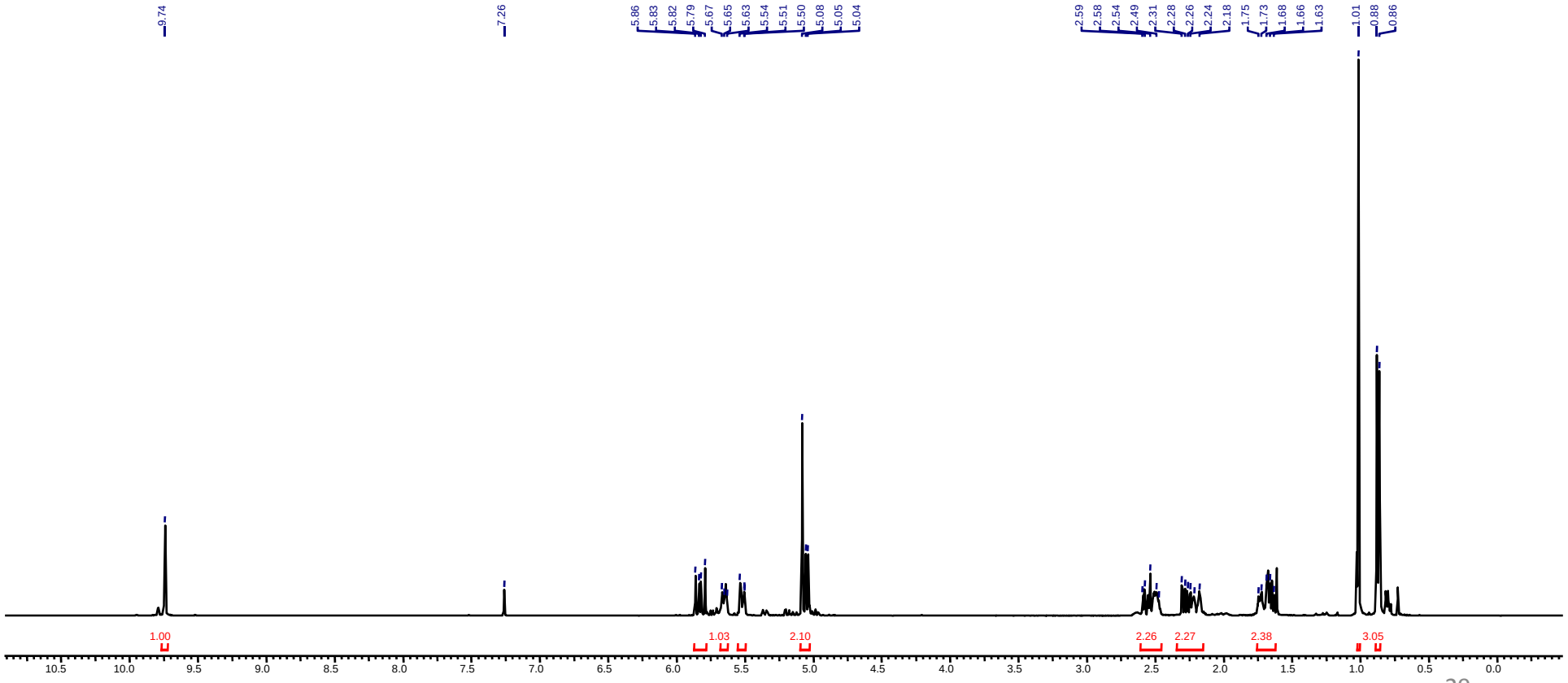
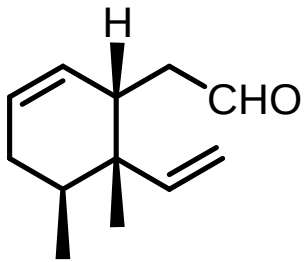


^{13}C NMR of Compound 8 ($CDCl_3$; 100 MHz)



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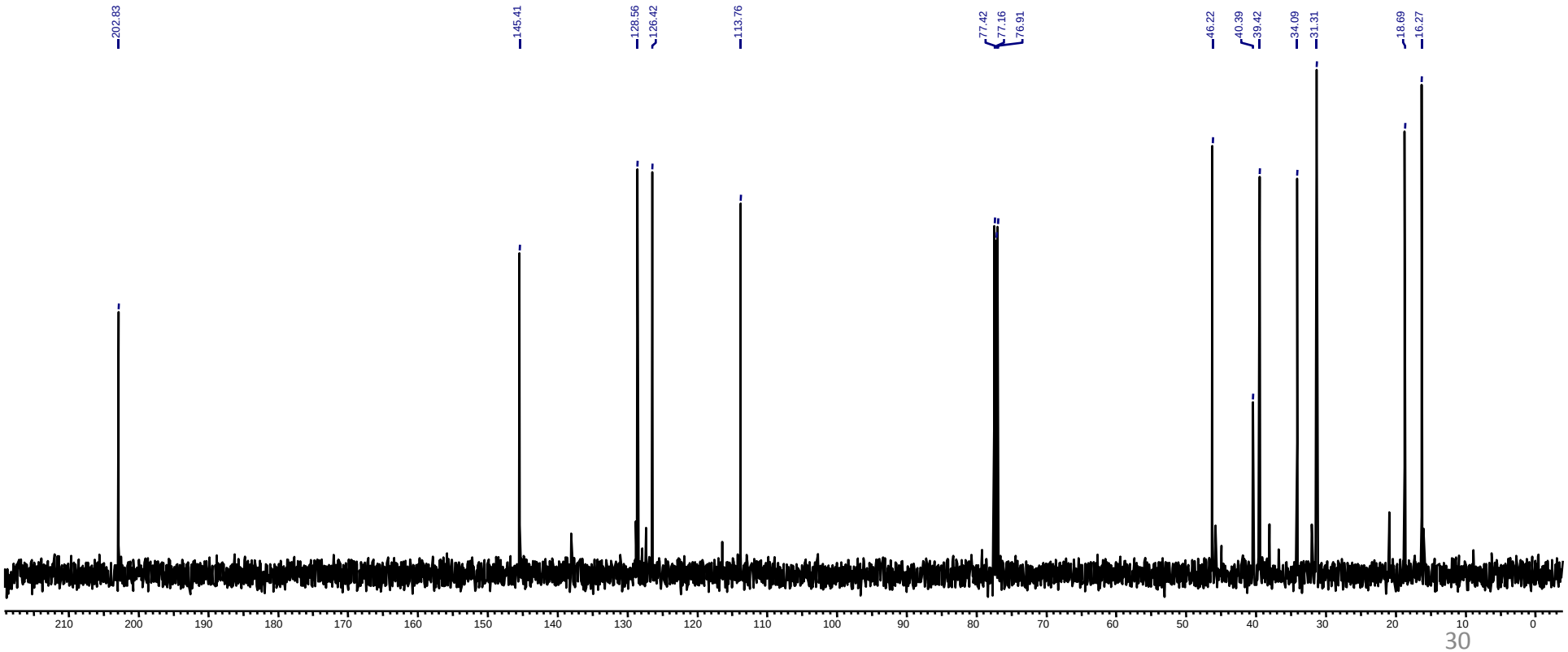
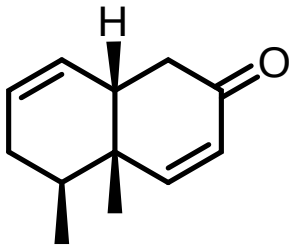


^{1} H NMR of Compound 5 ($CDCl_3$; 400 MHz)



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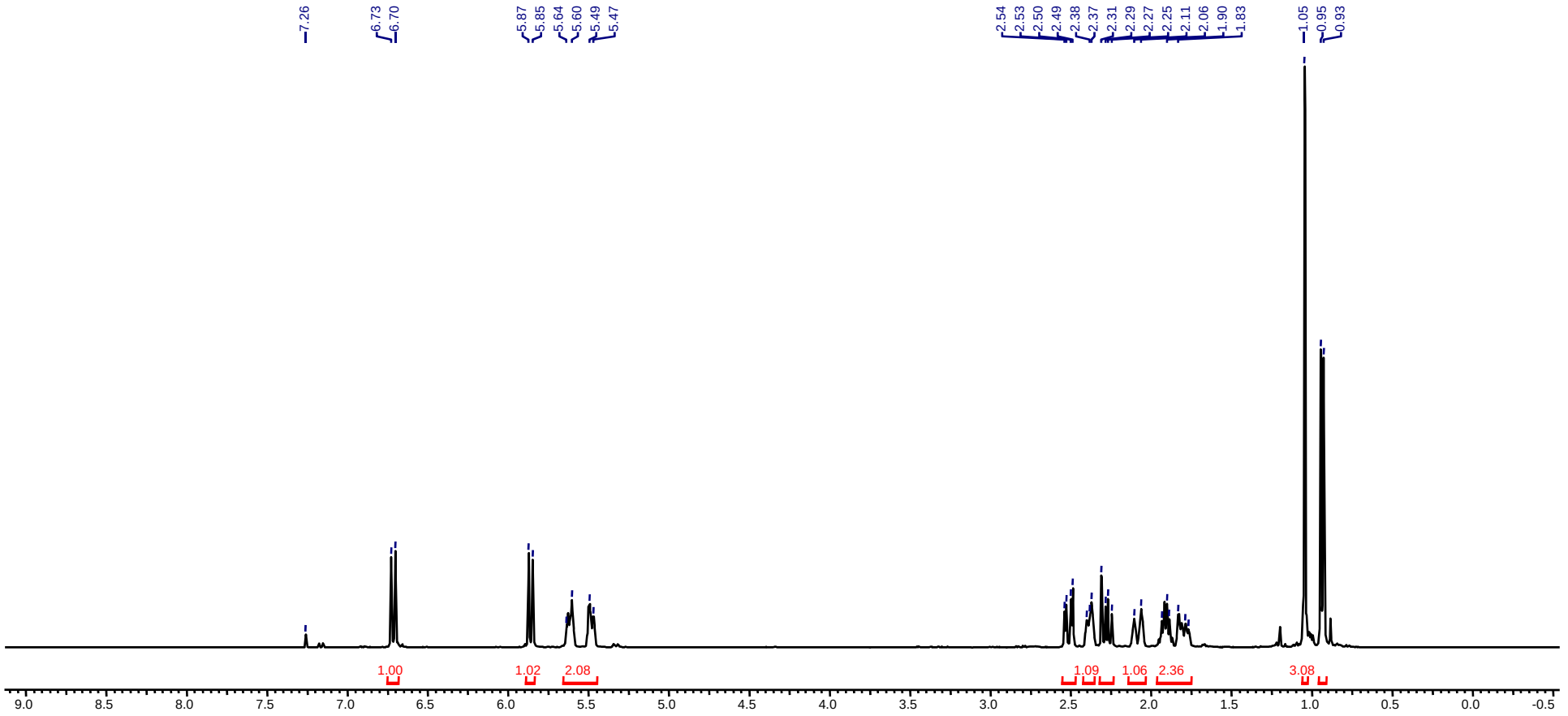
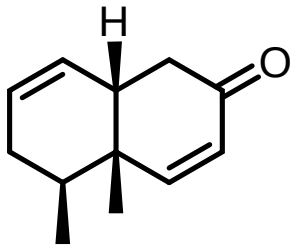


^{13}C NMR of Compound 5 ($CDCl_3$; 100 MHz)



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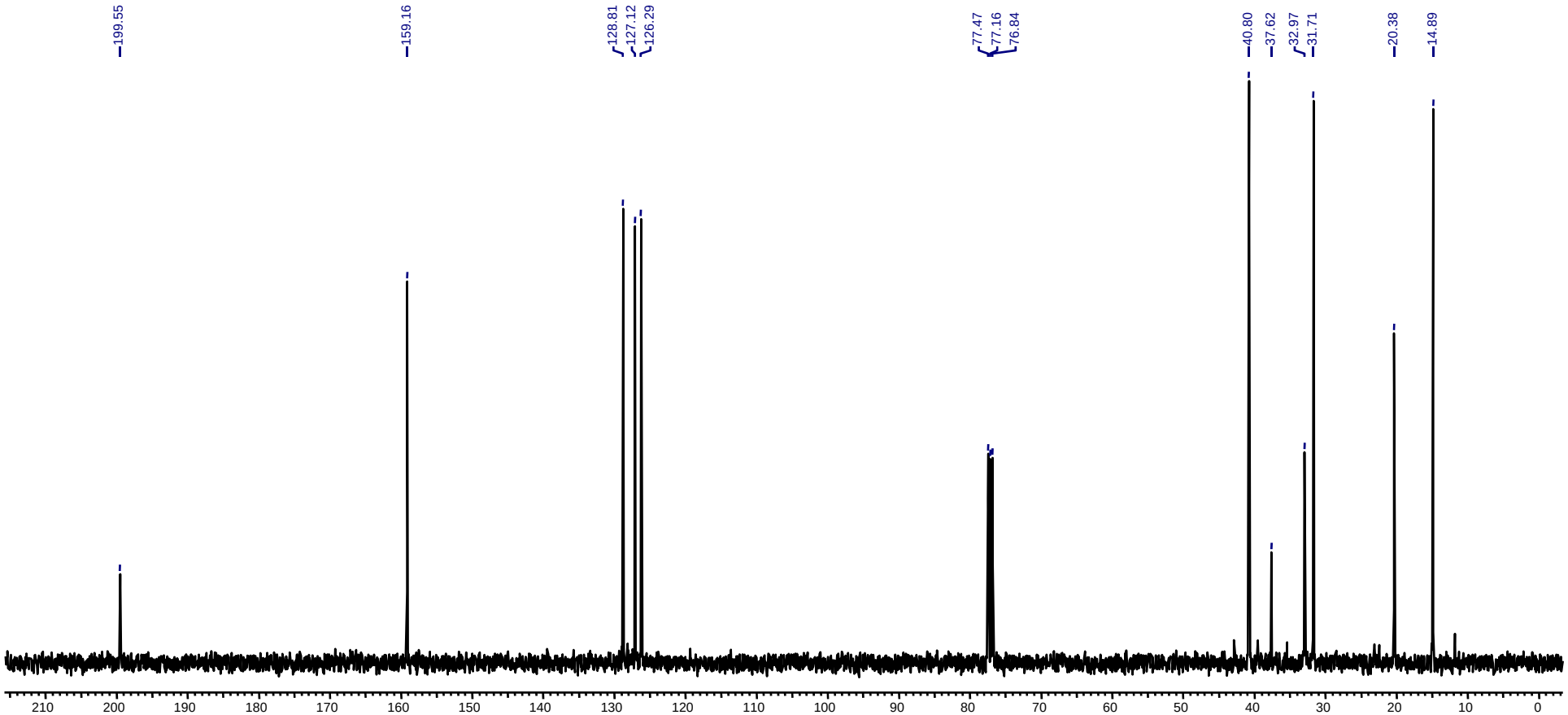
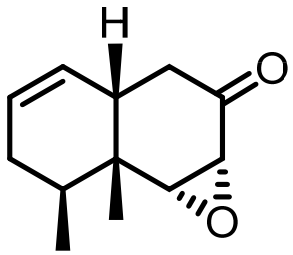


^{1} H NMR of Compound 9 ($CDCl_3$; 400 MHz)



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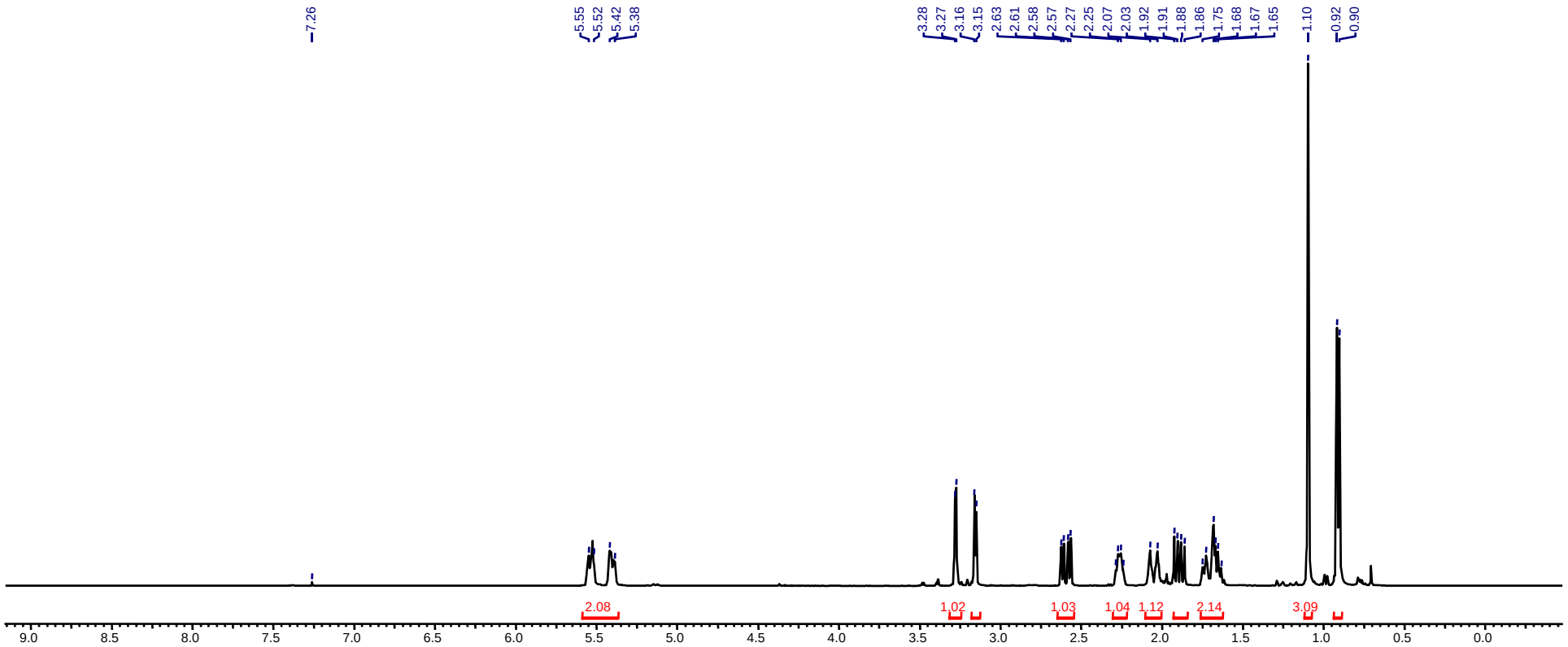
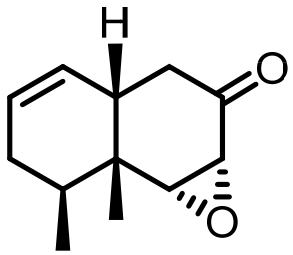


^{13}C NMR of Compound 9 ($CDCl_3$; 100 MHz)



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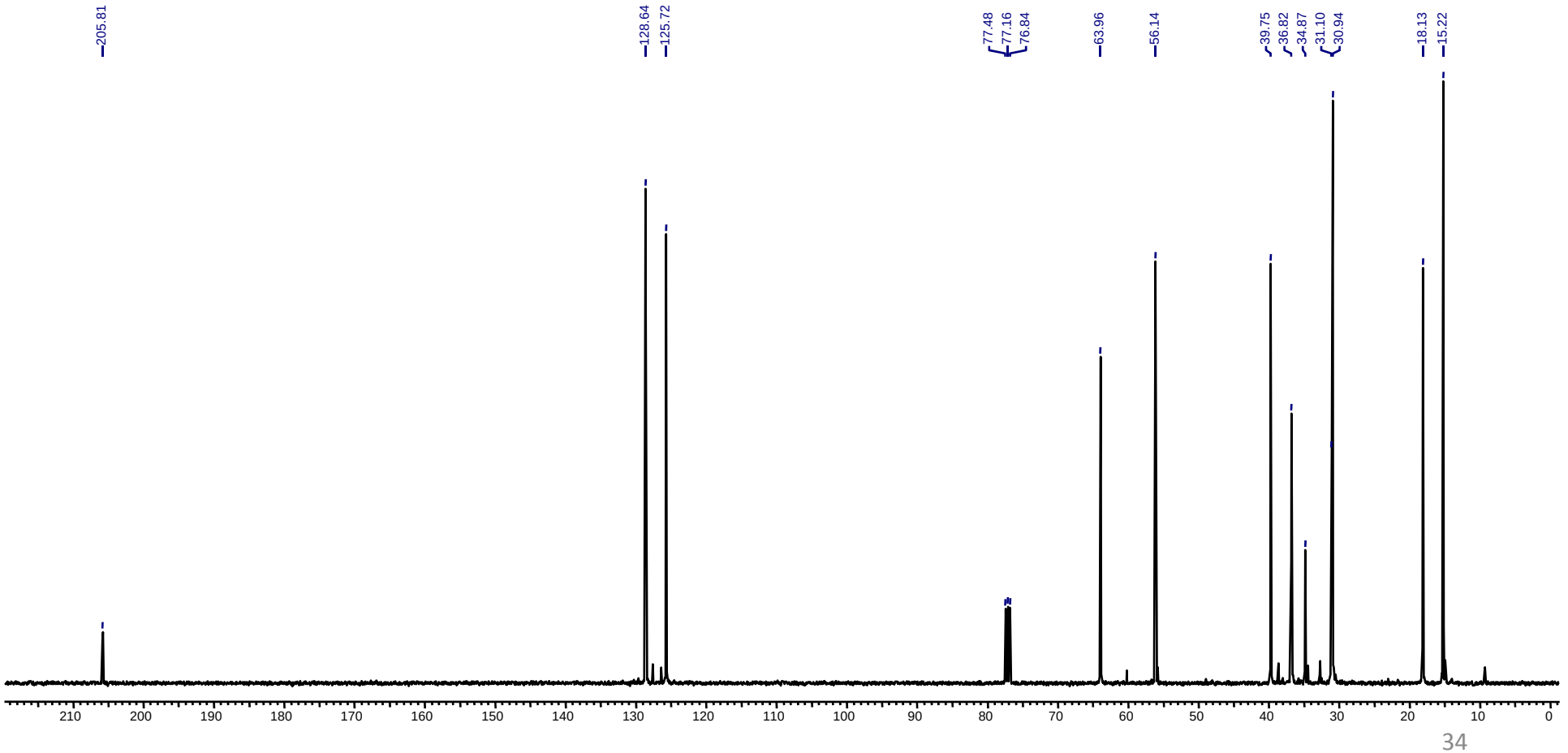
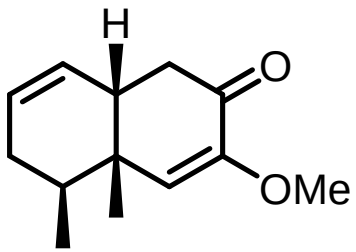


^{1} H NMR of Compound 10 ($CDCl_3$; 400 MHz)



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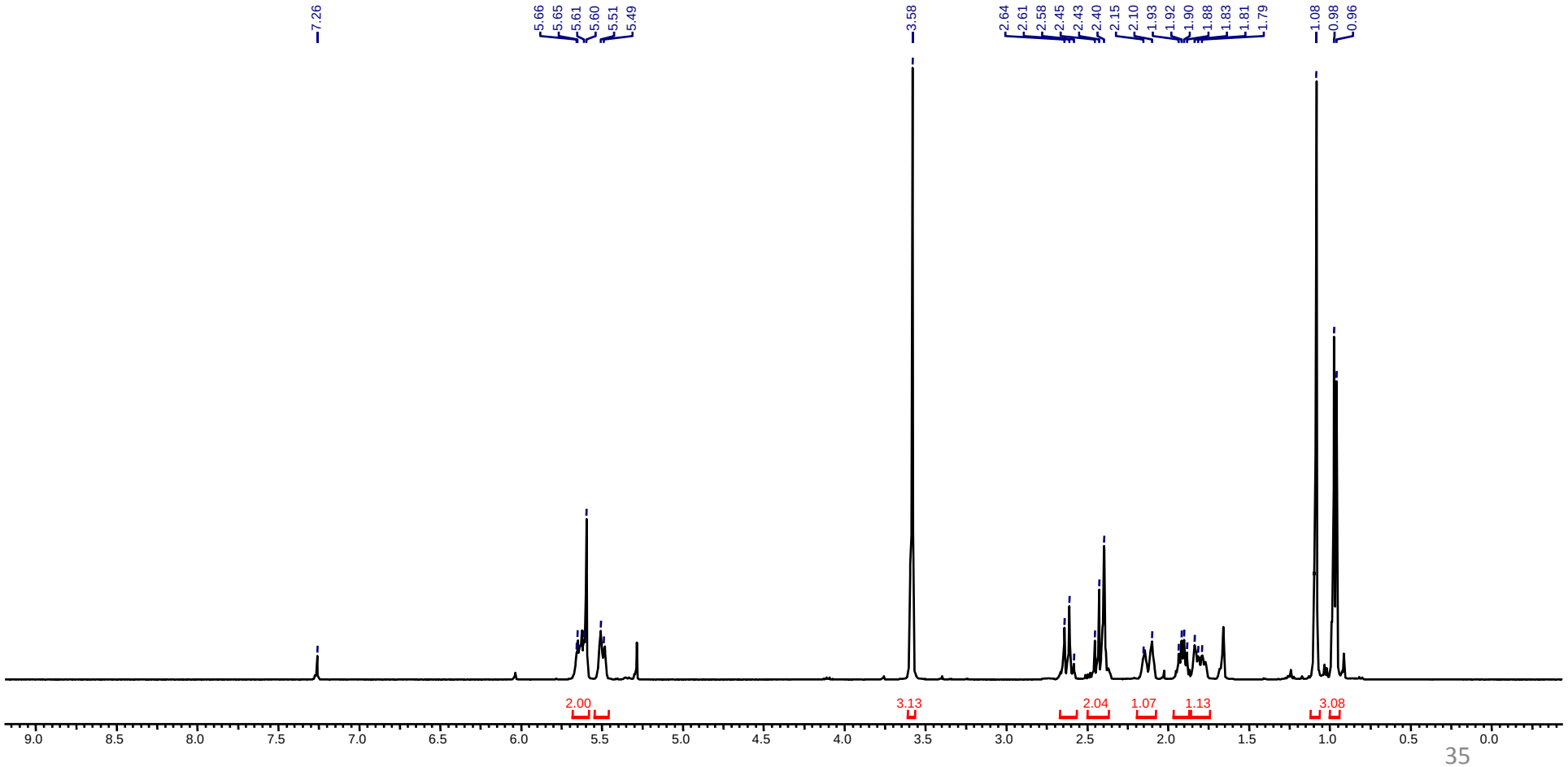
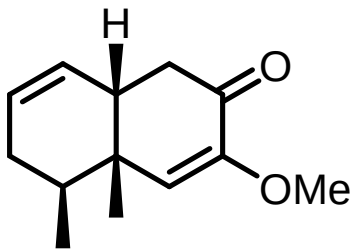


^{13}C NMR of Compound 10 ($CDCl_3$; 100 MHz)



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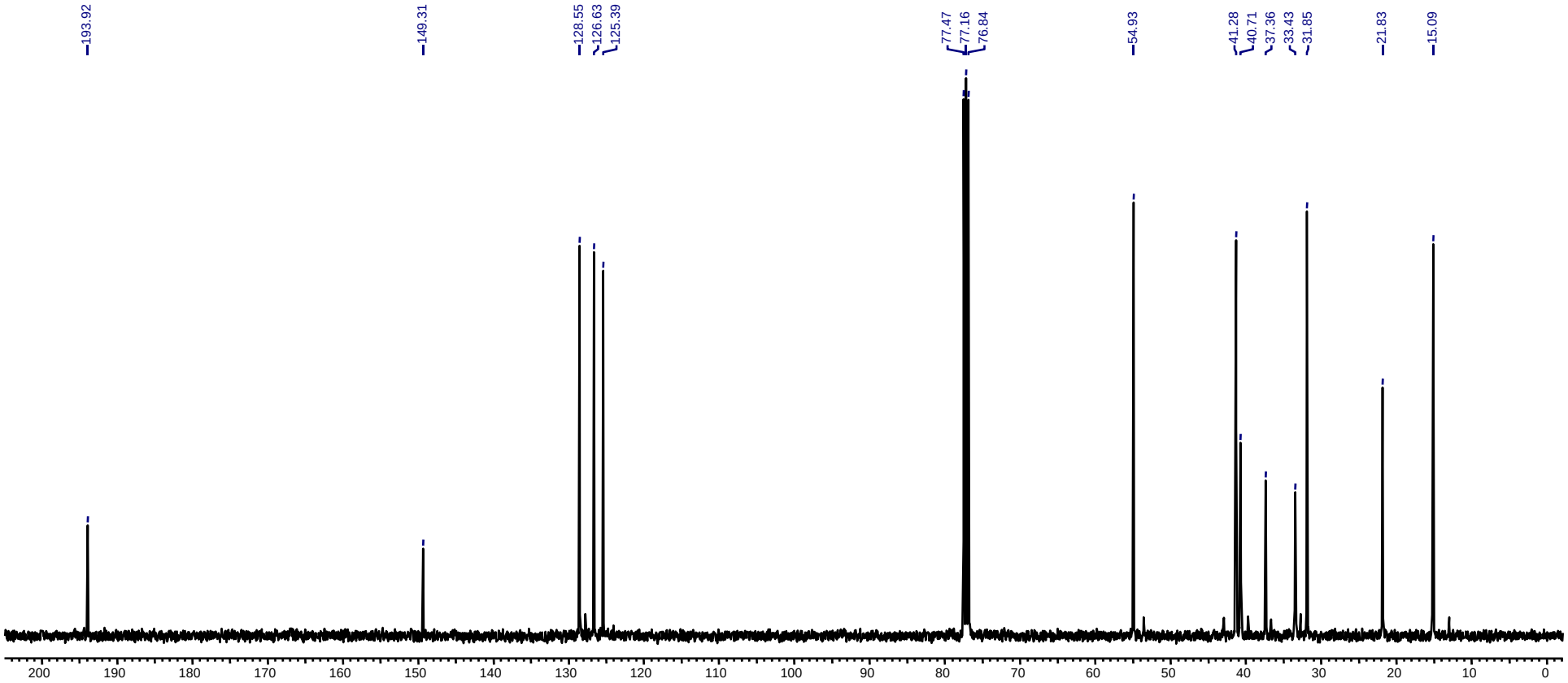
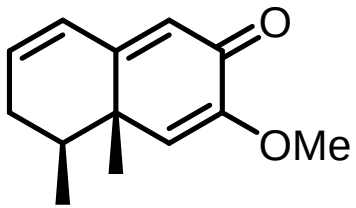


^{1} H NMR of Compound 11 ($CDCl_3$; 400 MHz)



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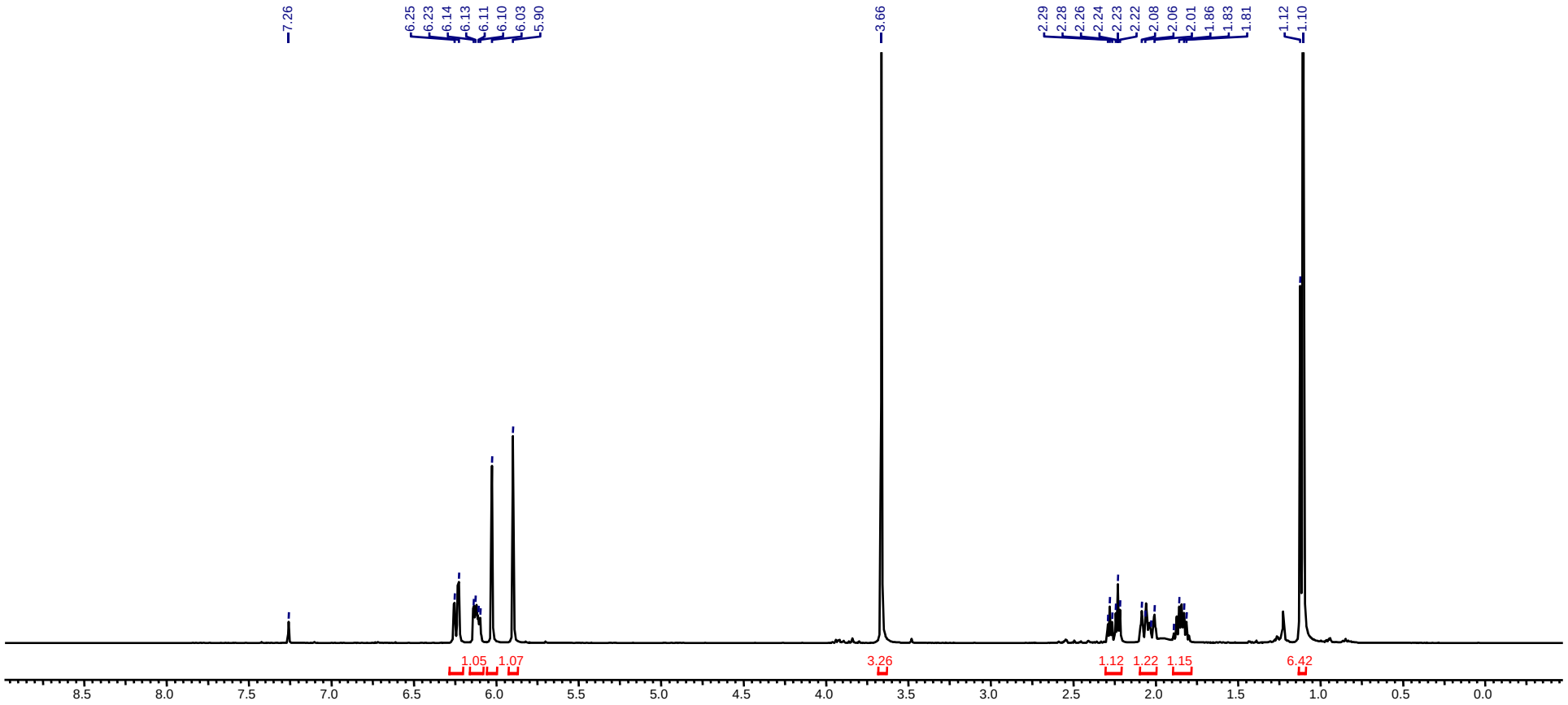
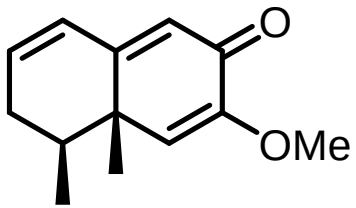


^{13}C NMR of Compound 11 ($CDCl_3$; 100 MHz)



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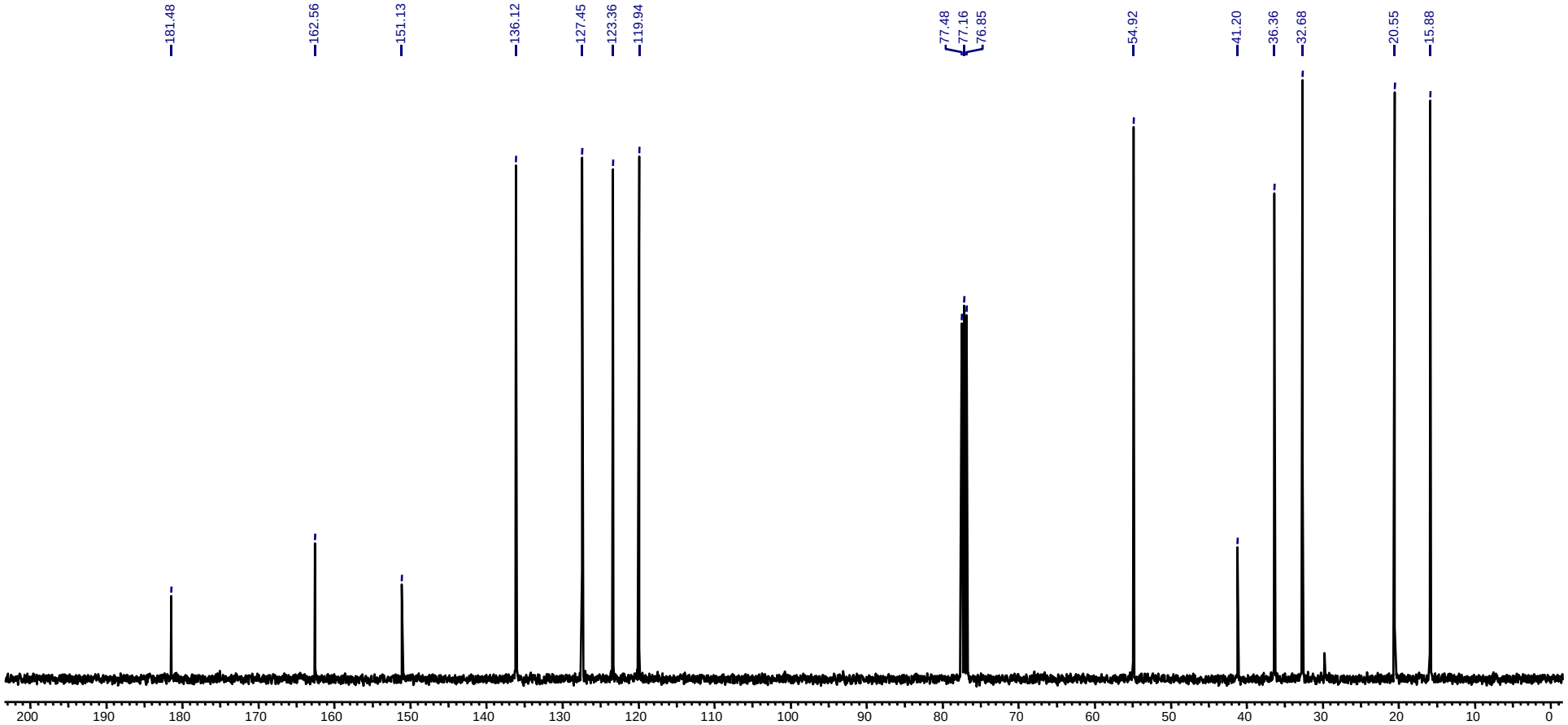
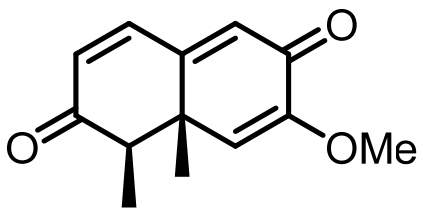


^{1} H NMR of Compound 12 ($CDCl_3$; 400 MHz)



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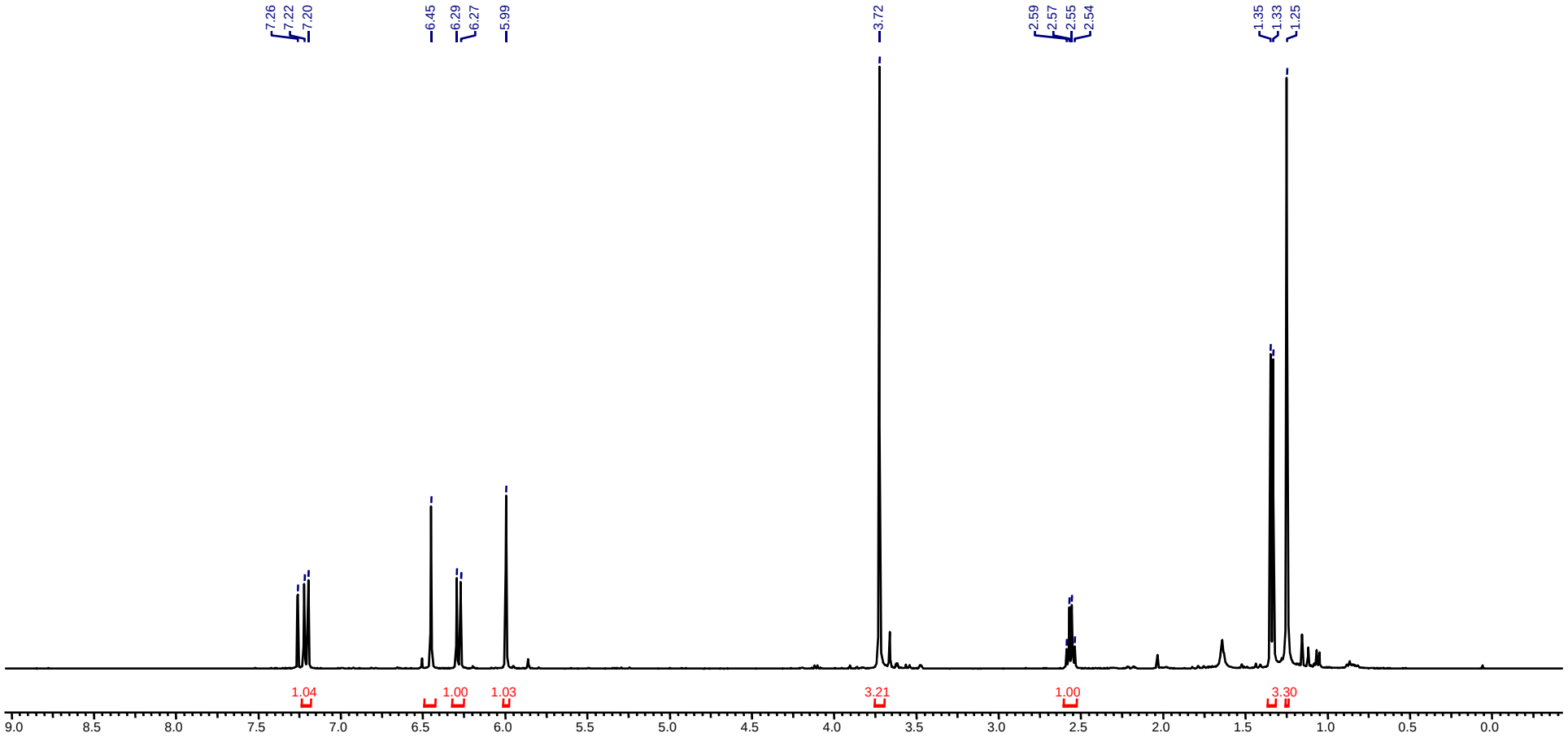
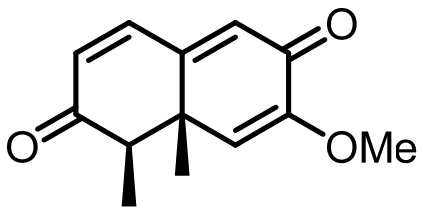


^{13}C NMR of Compound 12 ($CDCl_3$; 100 MHz)



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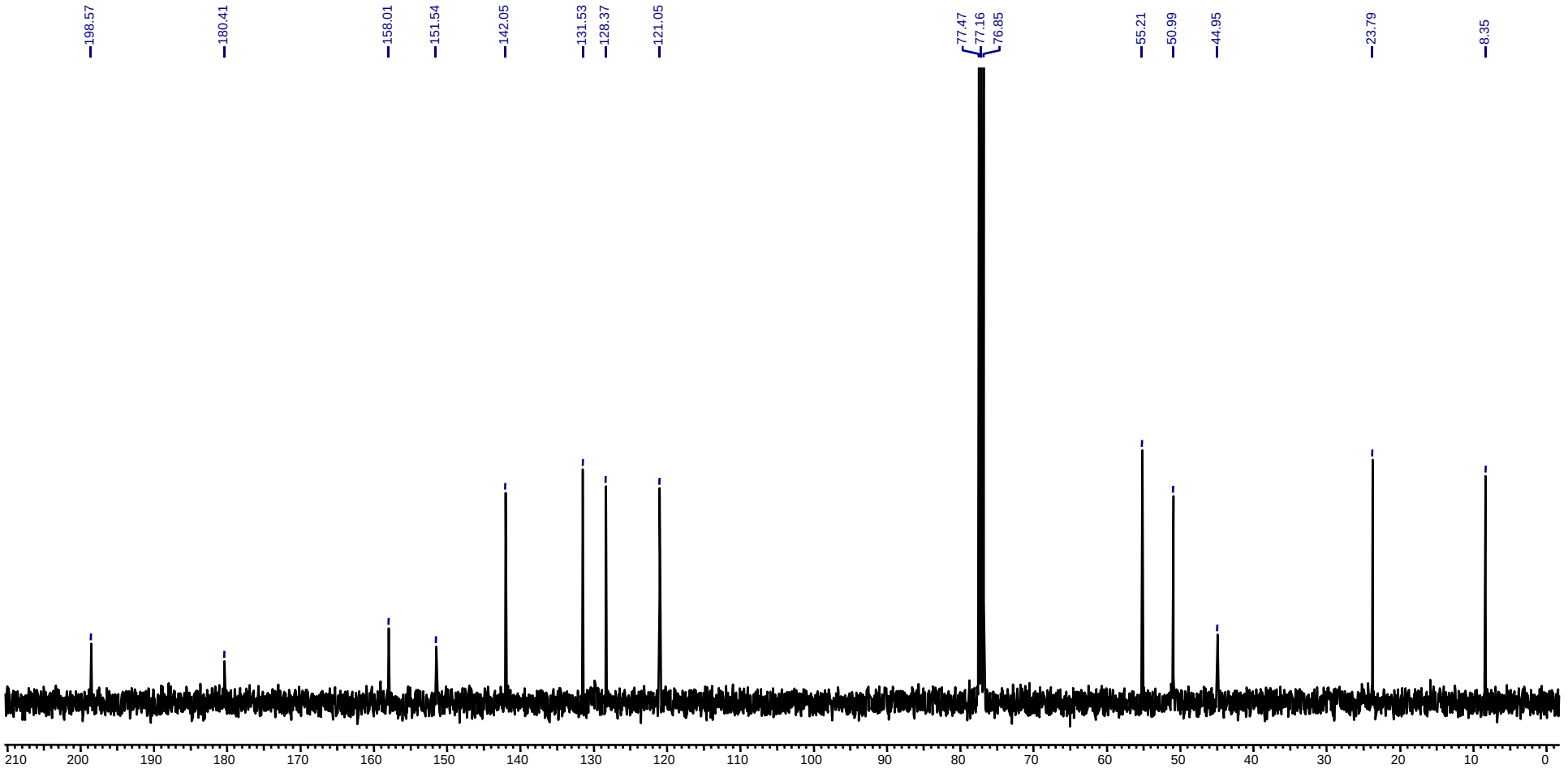
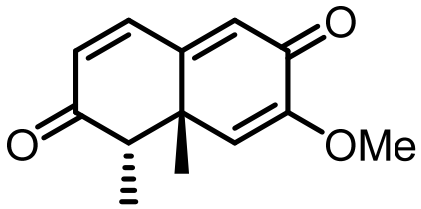


^{1} H NMR of Compound 13 ($CDCl_3$; 400 MHz)



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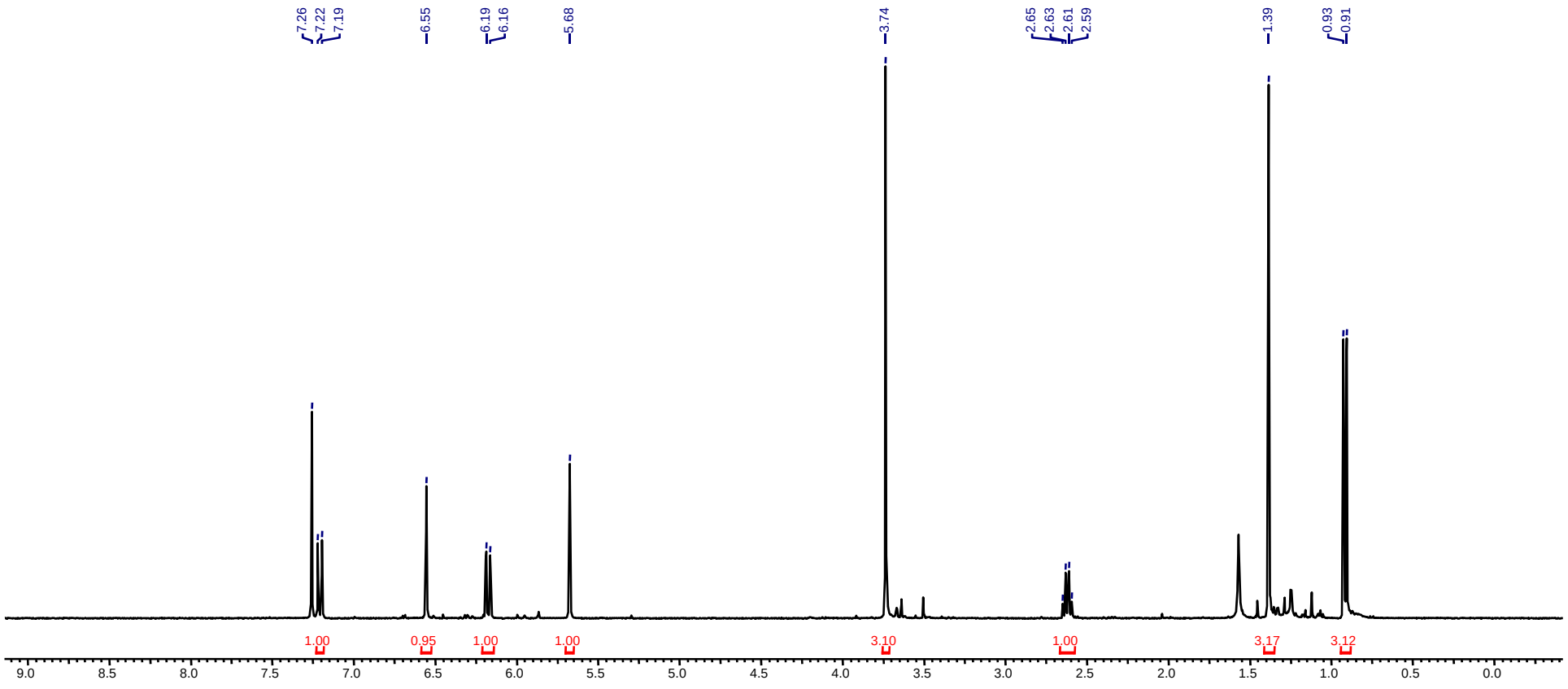
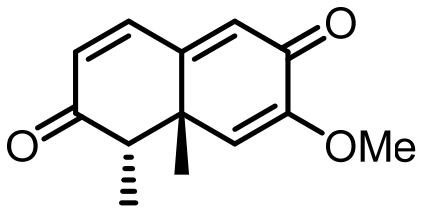


^{13}C NMR of Compound 13 ($CDCl_3$; 100 MHz)



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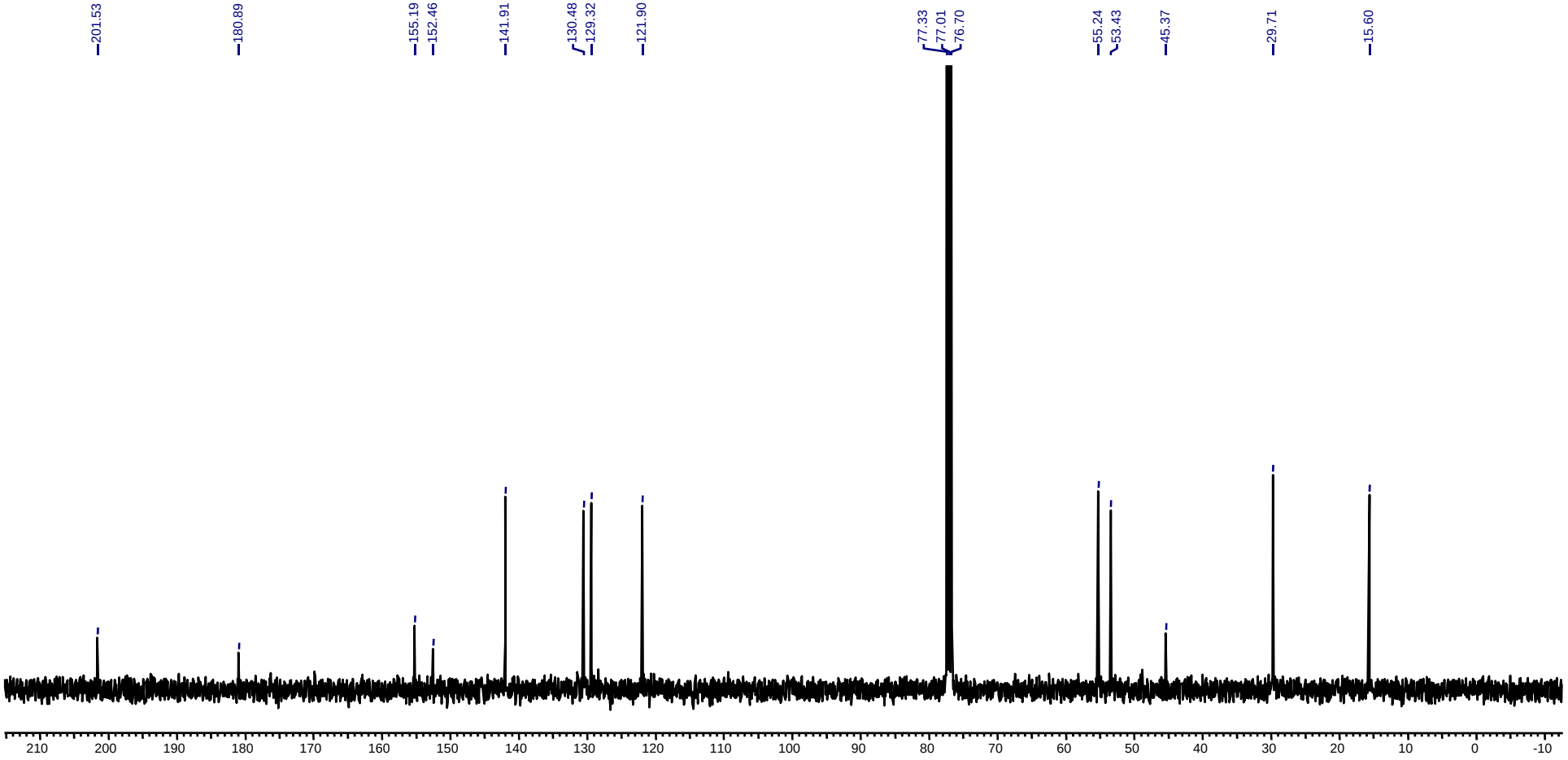
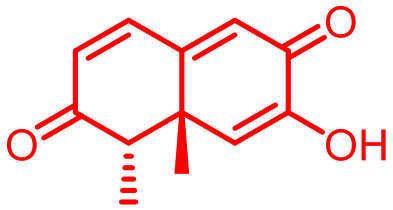
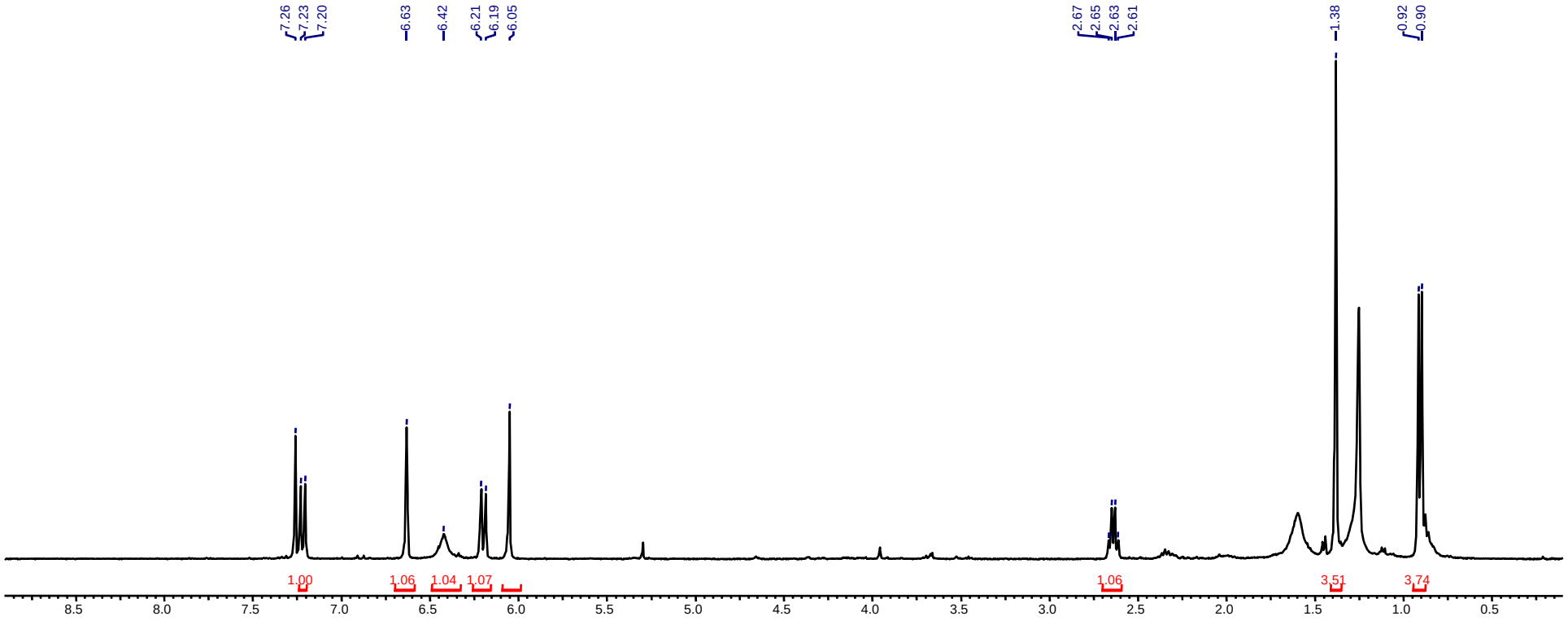


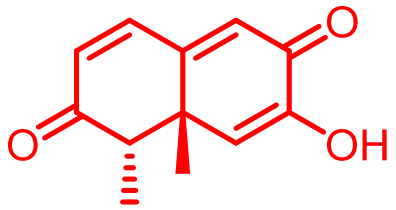
^{1} H NMR of Compound 1 ($CDCl_3$; 400 MHz)



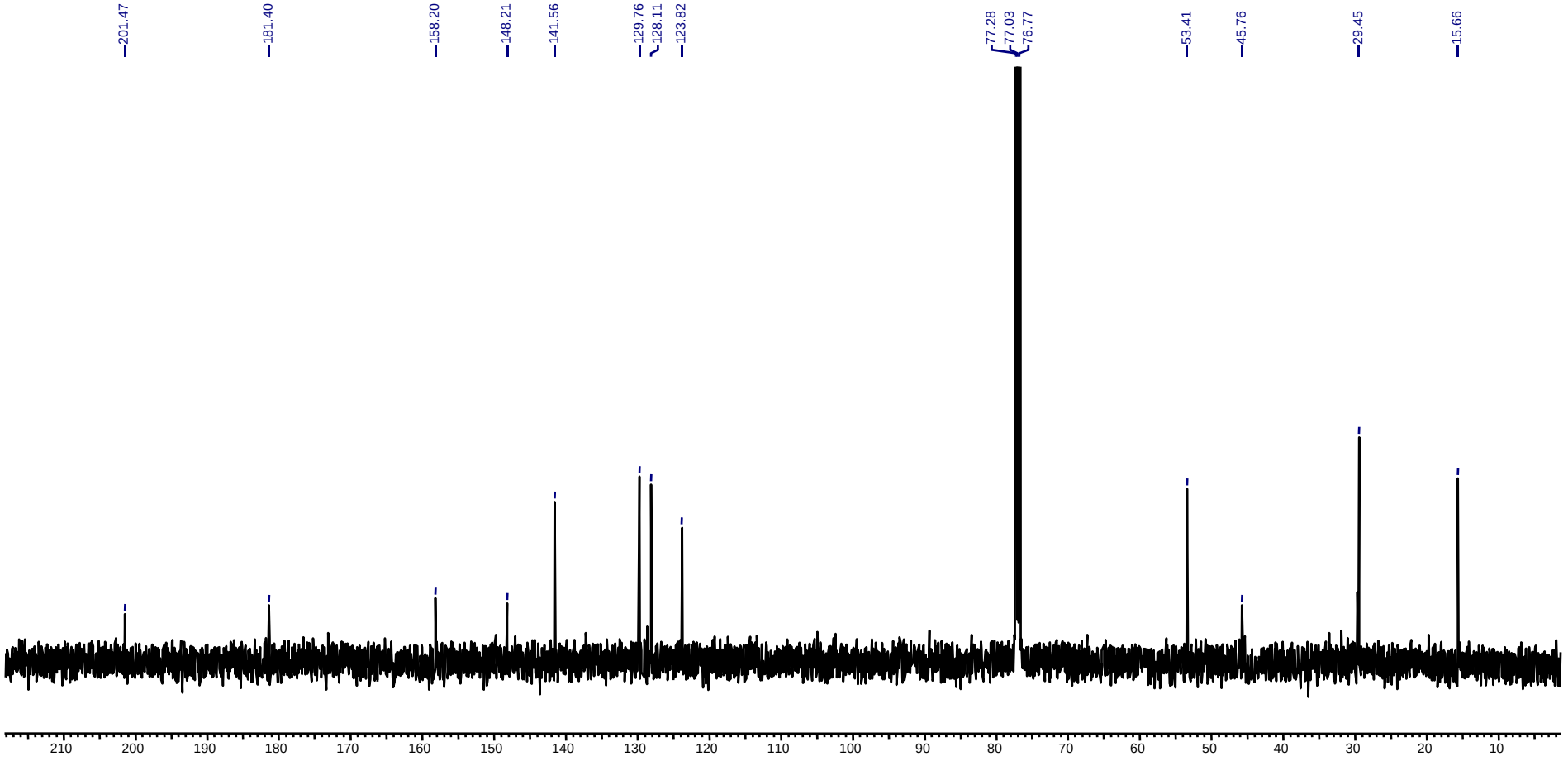
(±)-botryosphaeridione (1)

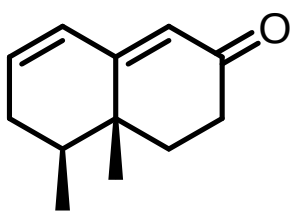


^{13}C NMR of Compound 1 ($CDCl_3$; 100 MHz)



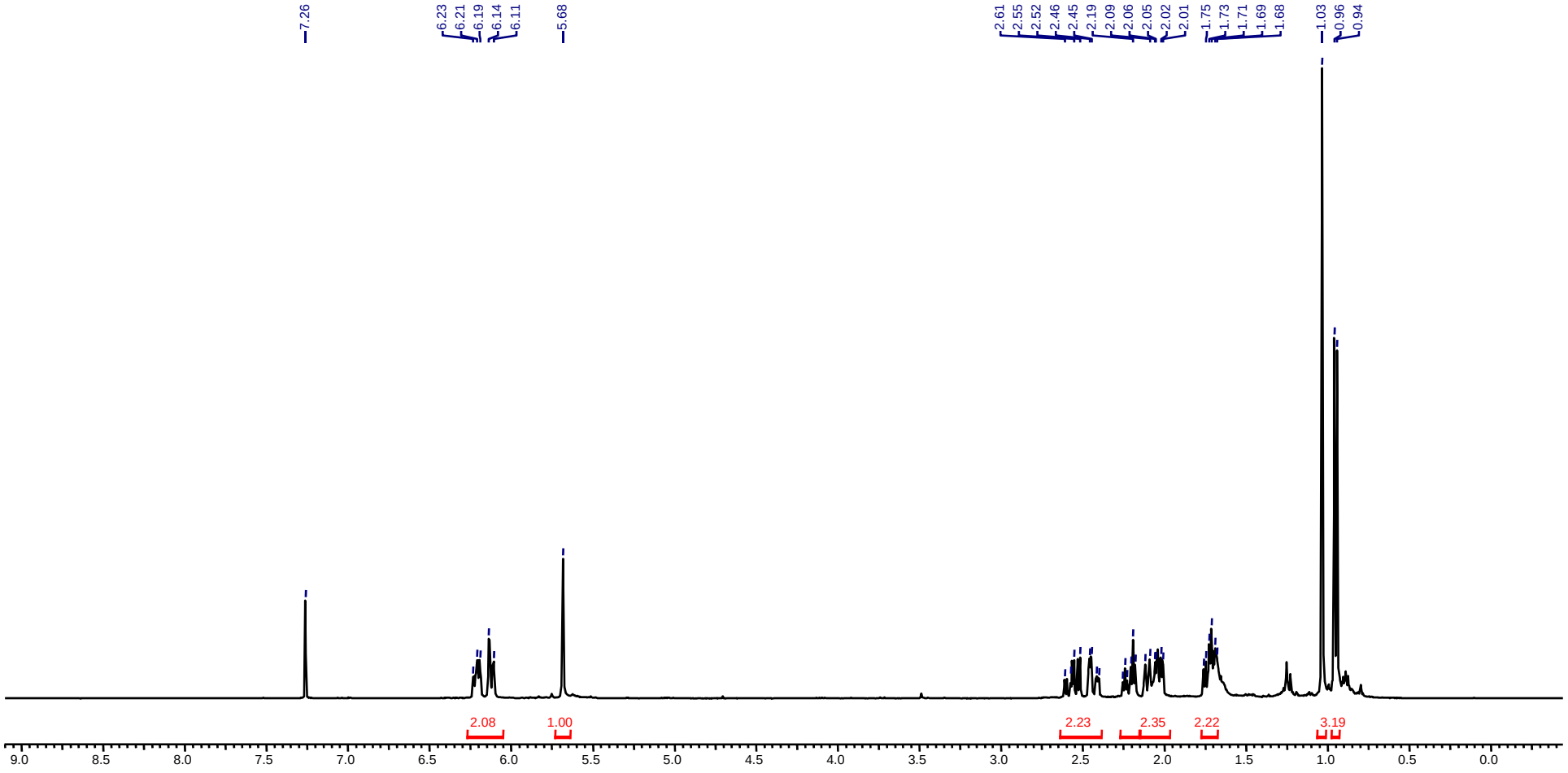
(±)-botryosphaeridione (1)

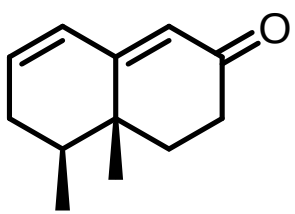




14

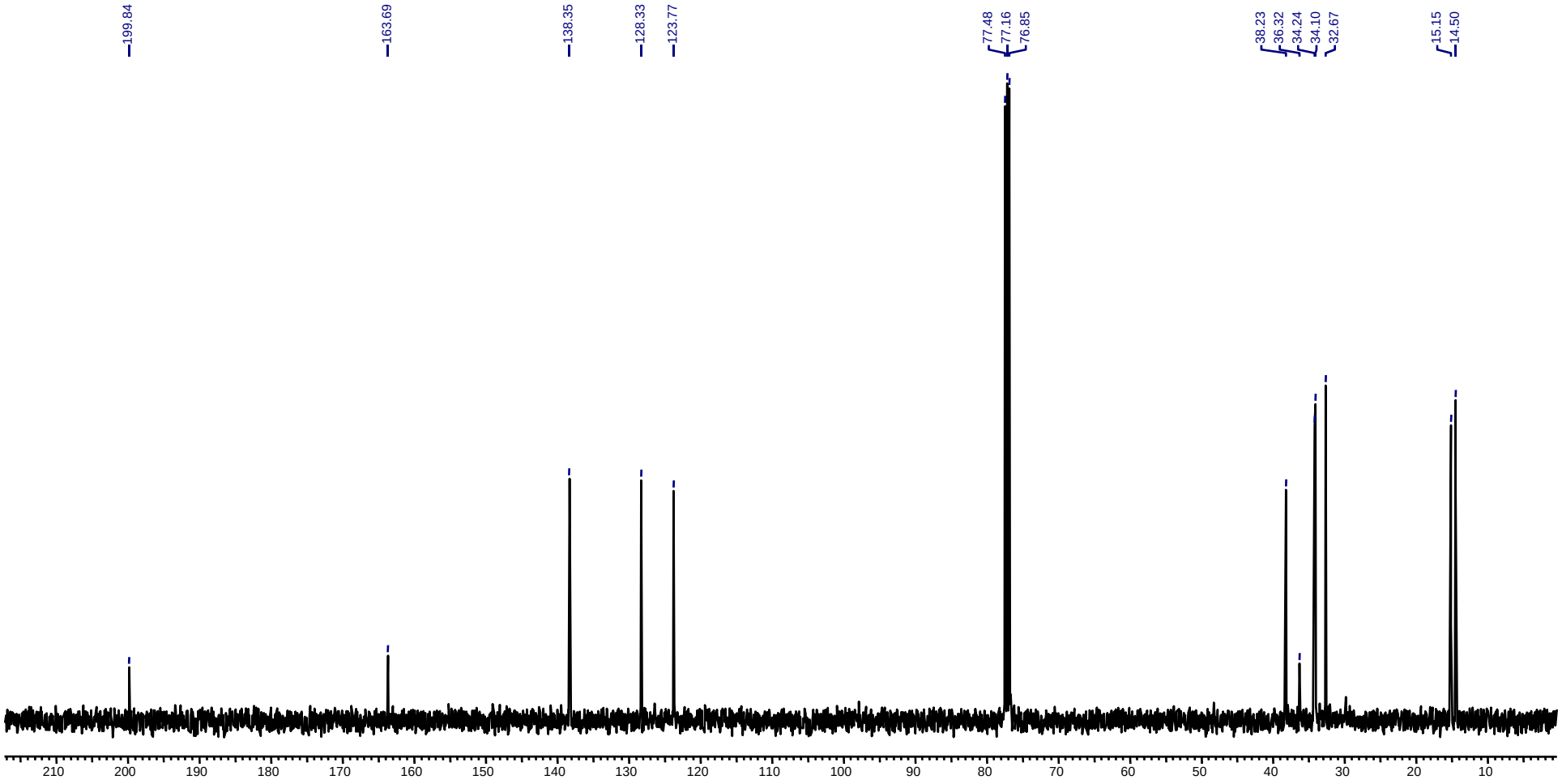
^{1} H NMR of Compound 14 ($CDCl_3$; 400MHz)

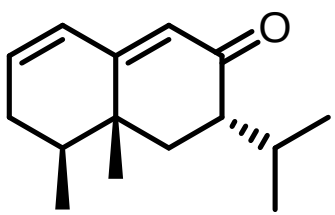




14

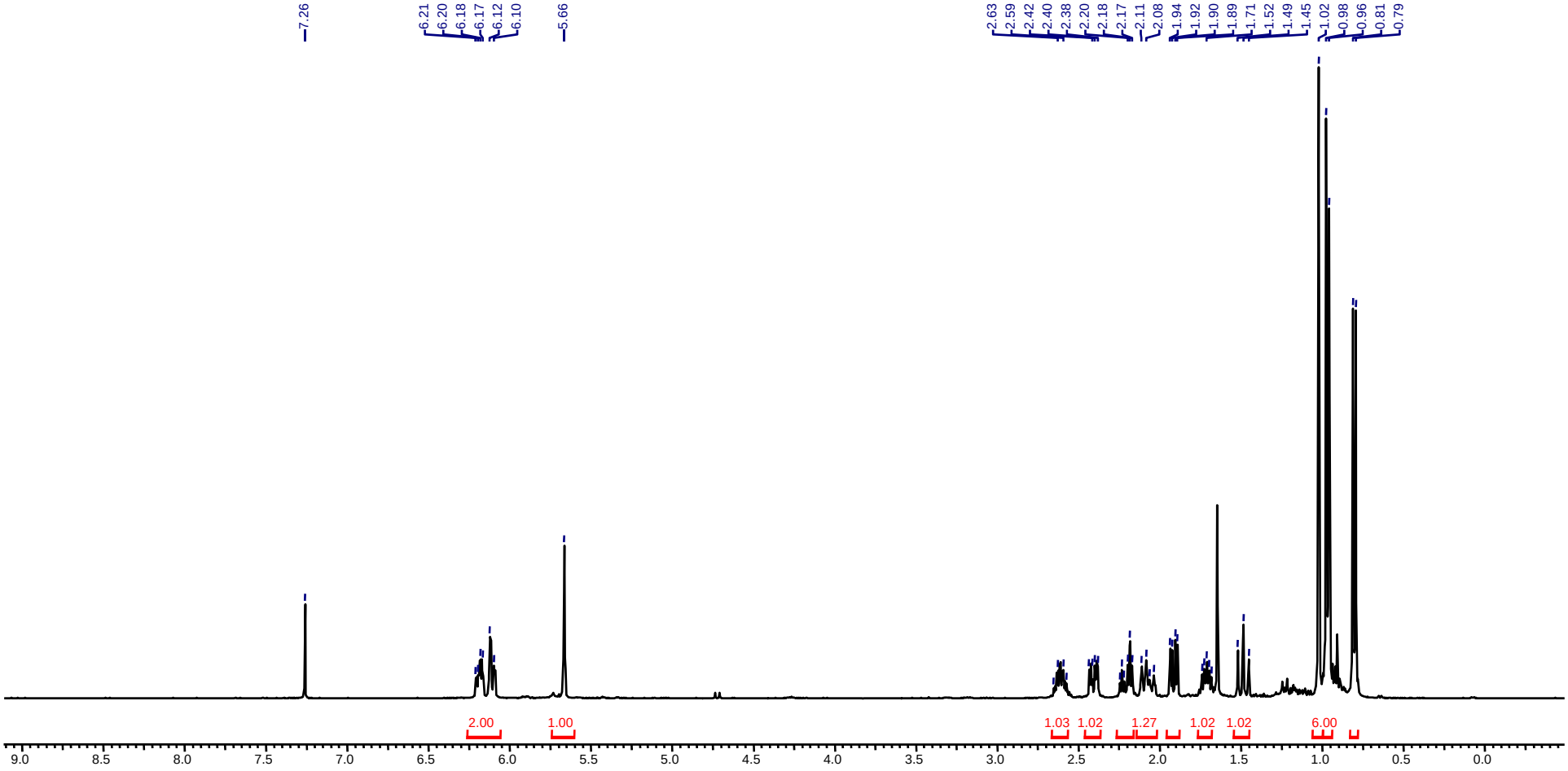
^{13}C NMR of Compound 14 ($CDCl_3$; 100 MHz)

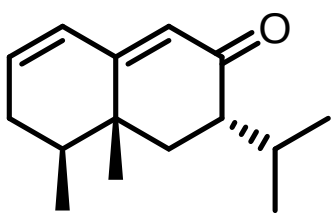




15

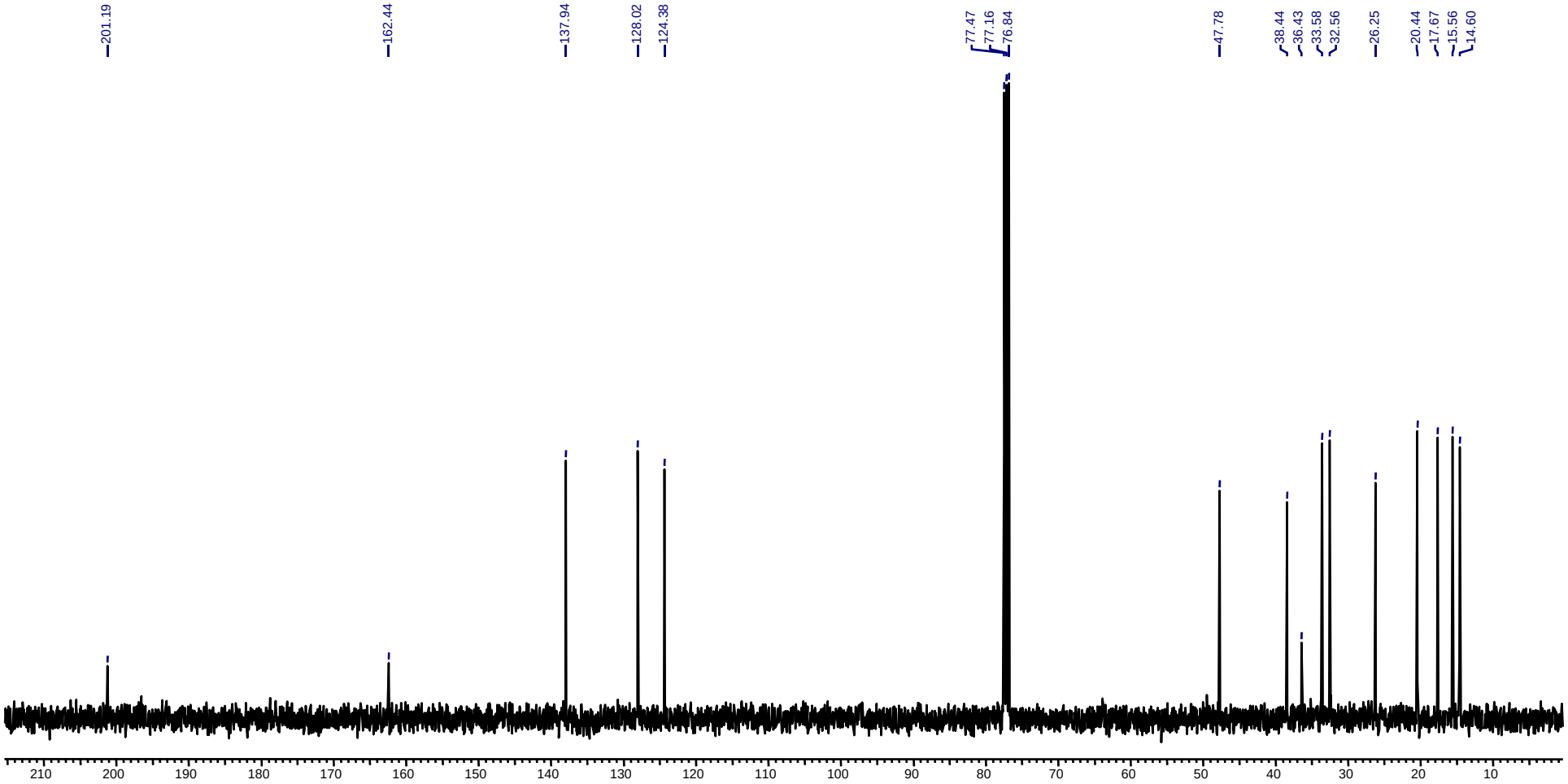
^{1}H NMR of Compound 15 ($CDCl_3$; 400 MHz)

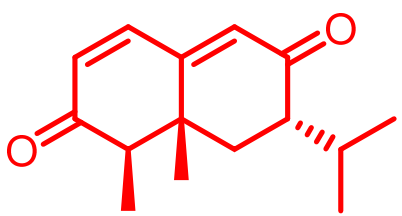




15

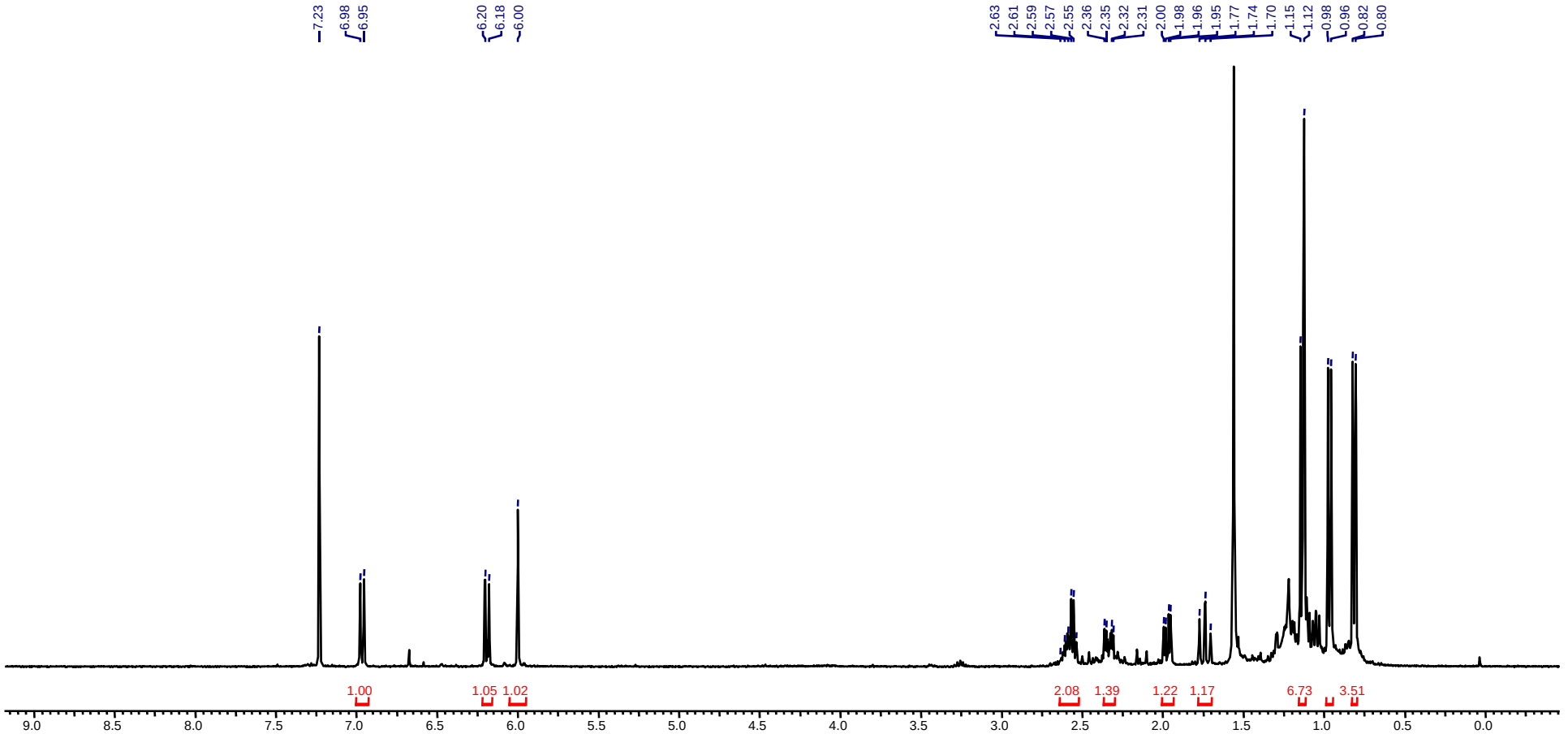
^{13}C NMR of Compound 15 ($CDCl_3$; 100 MHz)

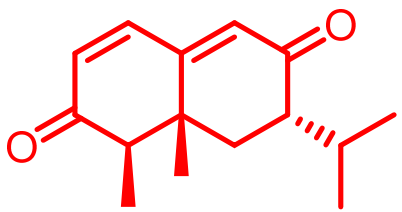




(±)-pleodendione (4)

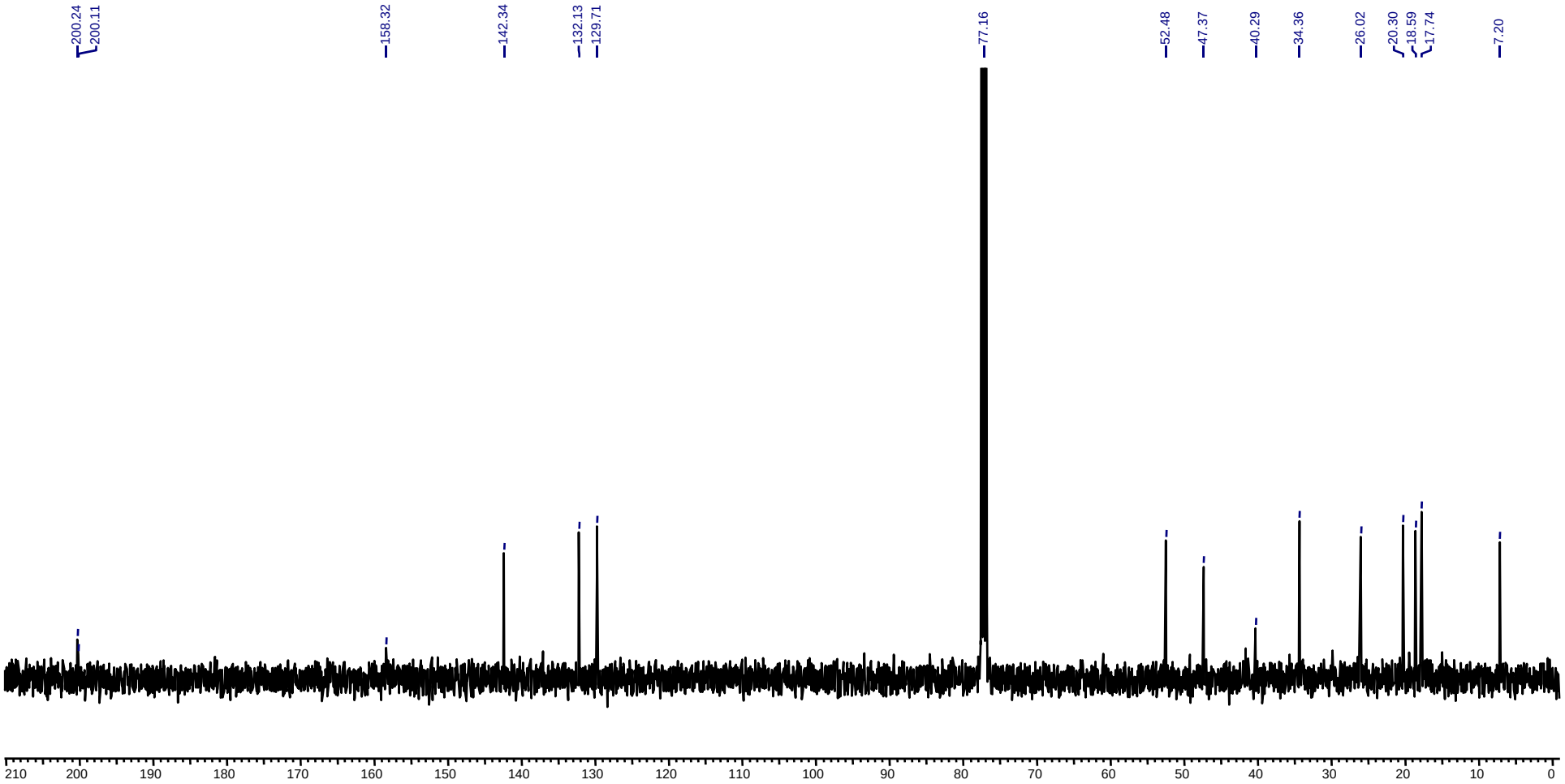
^{1} H NMR of Compound 4 ($CDCl_3$; 400 MHz)



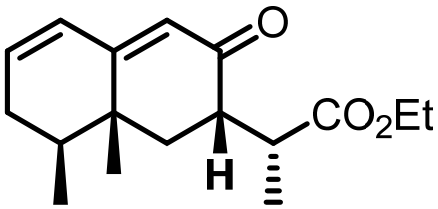


^{13}C NMR of Compound 4 ($CDCl_3$; 100 MHz)

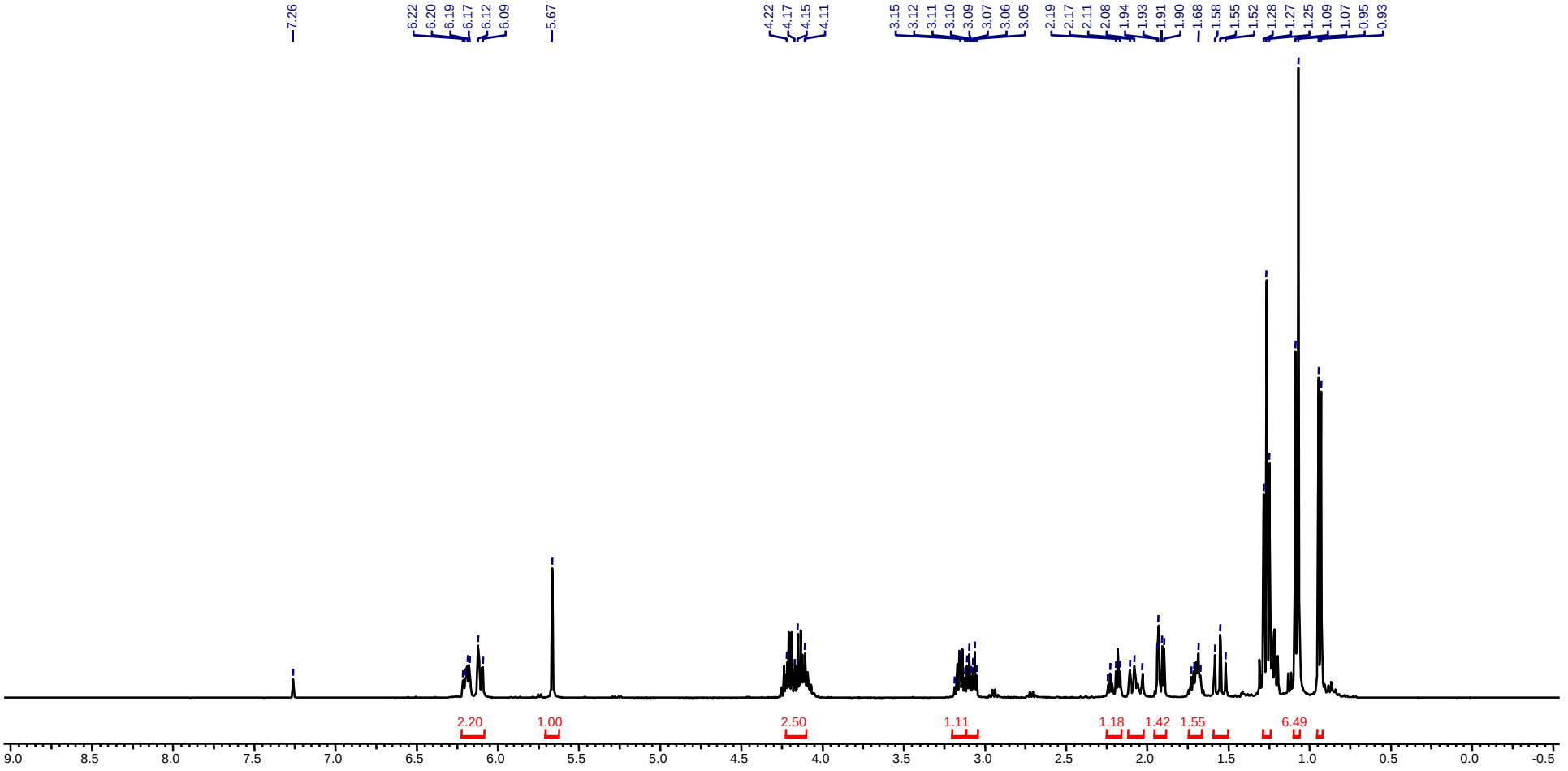
(±)-pleodendione (4)



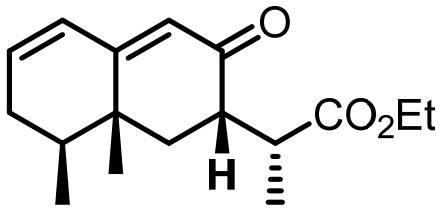
^{1} H NMR of Compound 16 ($CDCl_3$; 400 MHz)



16



^{13}C NMR of Compound 16 ($CDCl_3$; 100 MHz)



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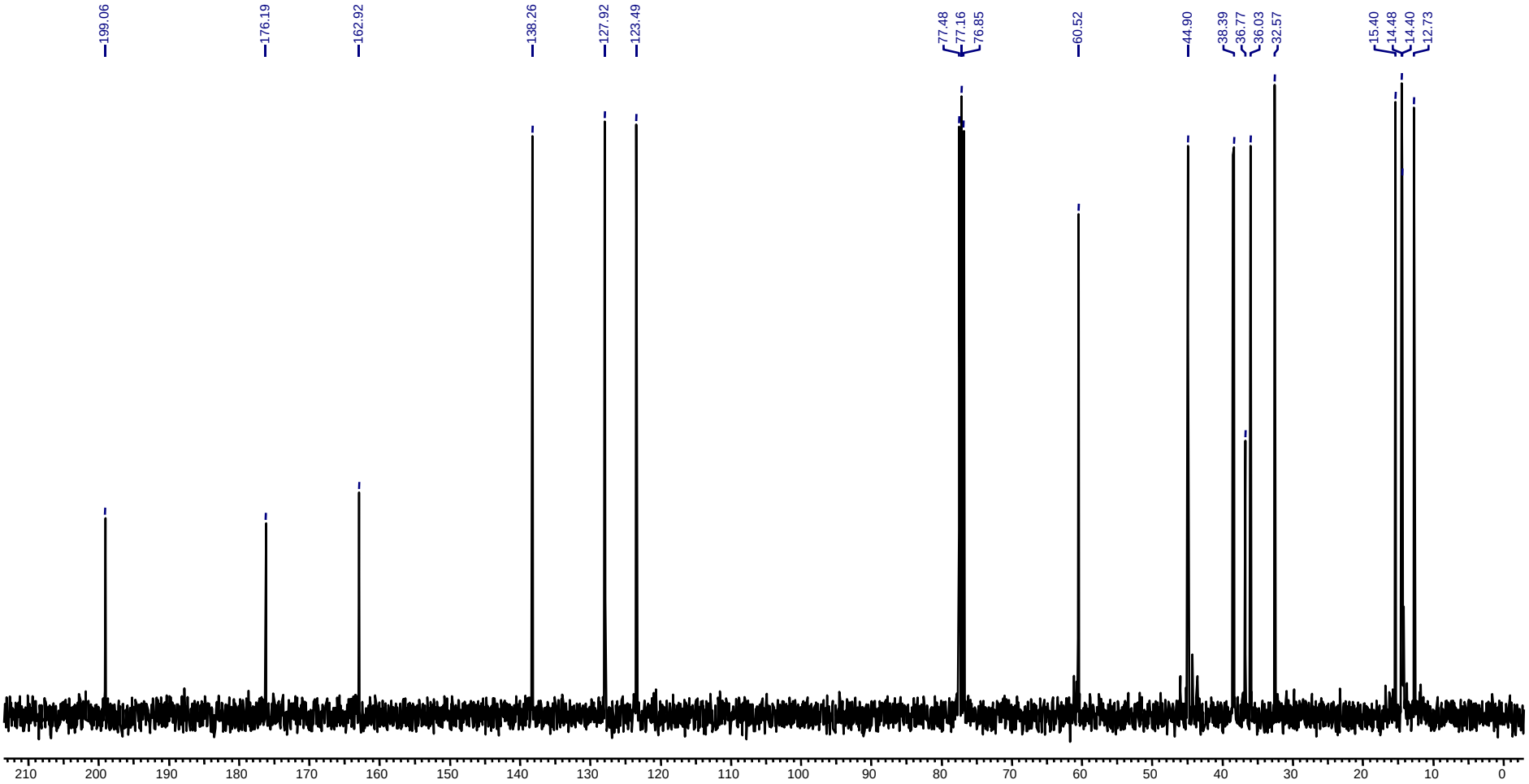
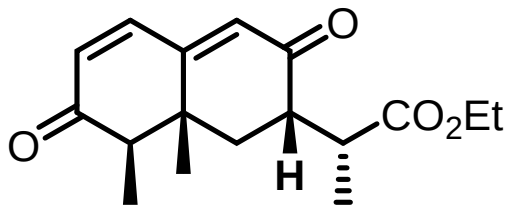


^{1} H NMR of Compound 18 ($CDCl_3$; 400 MHz)



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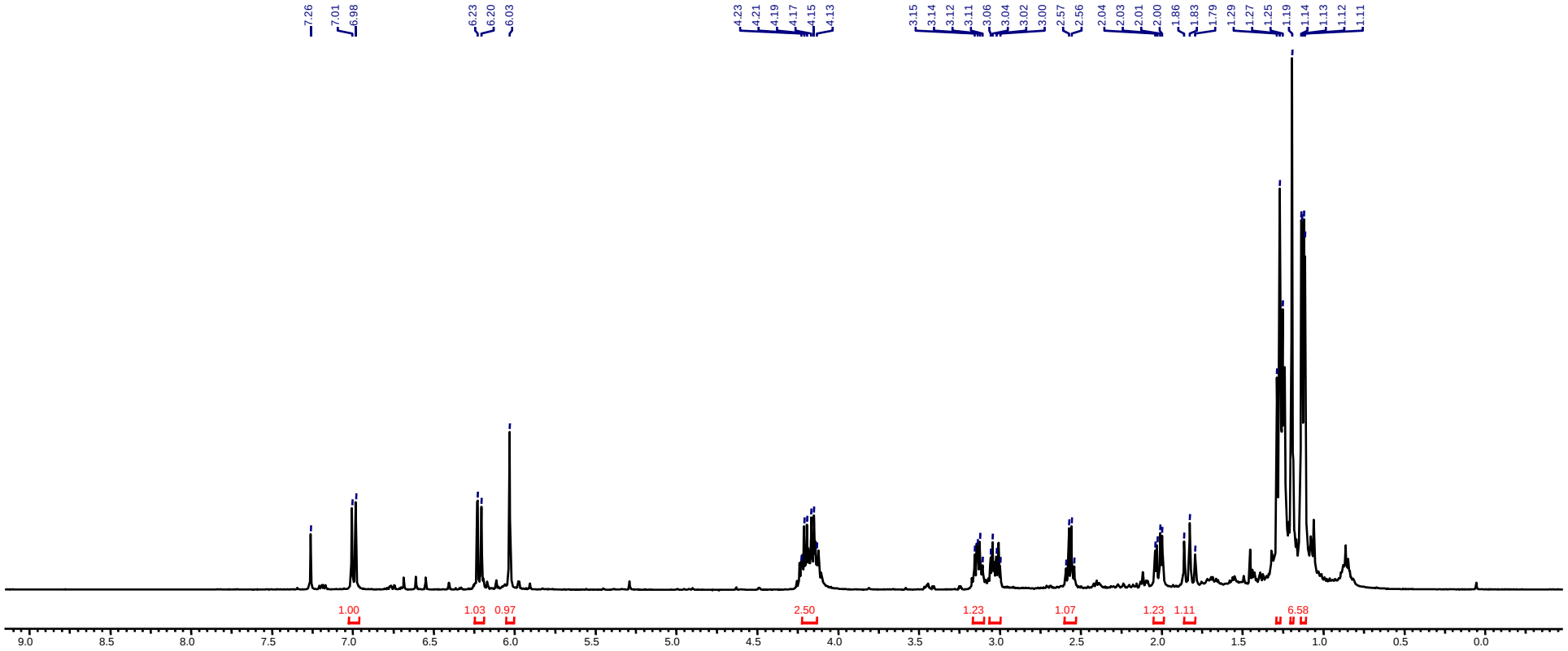
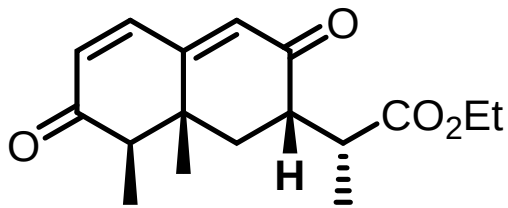


^{13}C NMR of Compound 18 ($CDCl_3$; 100 MHz)



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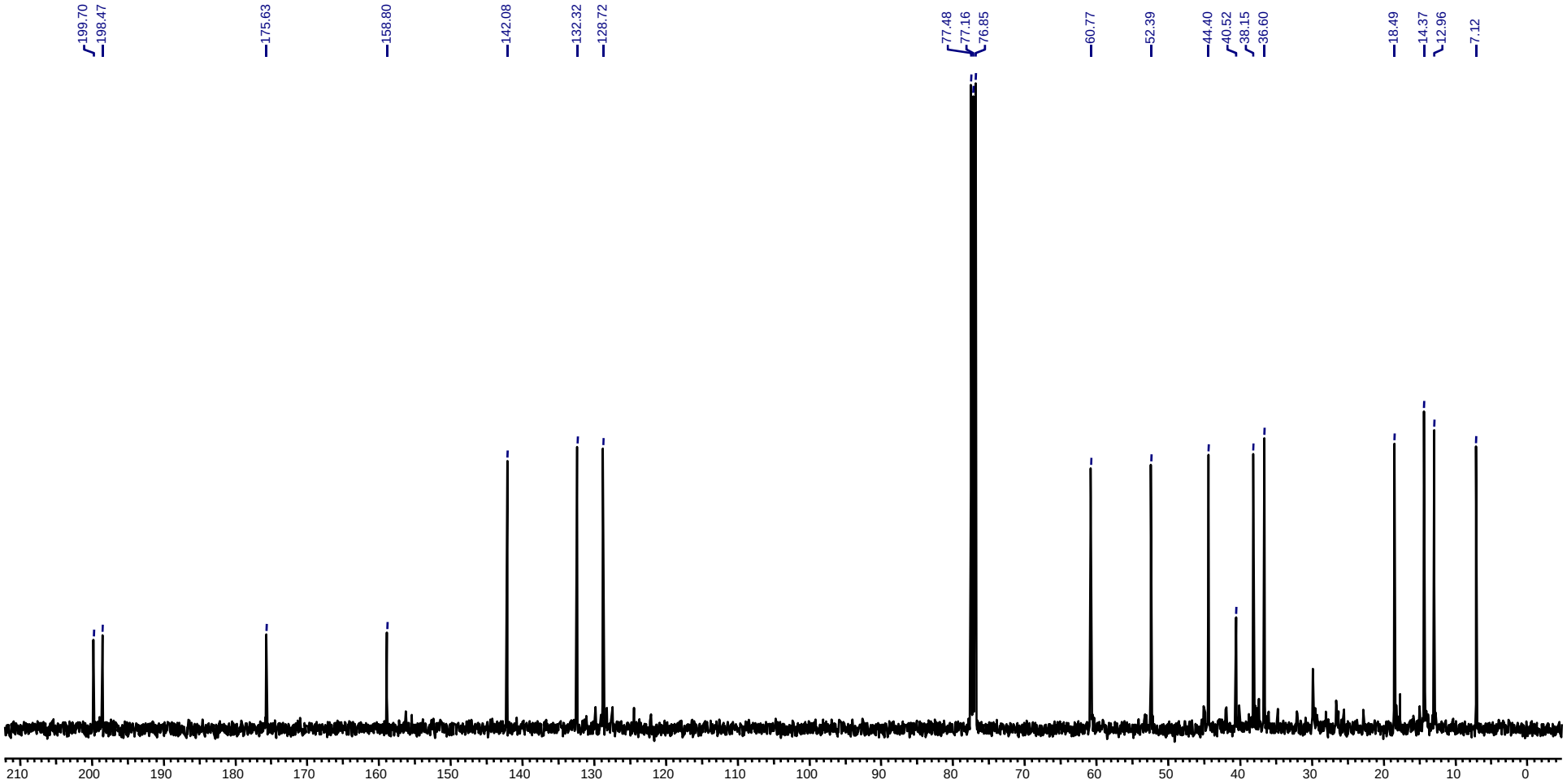
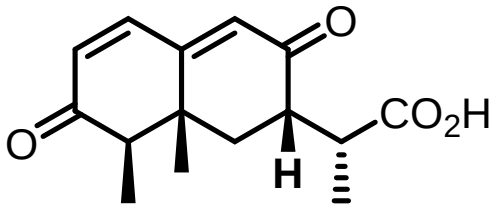
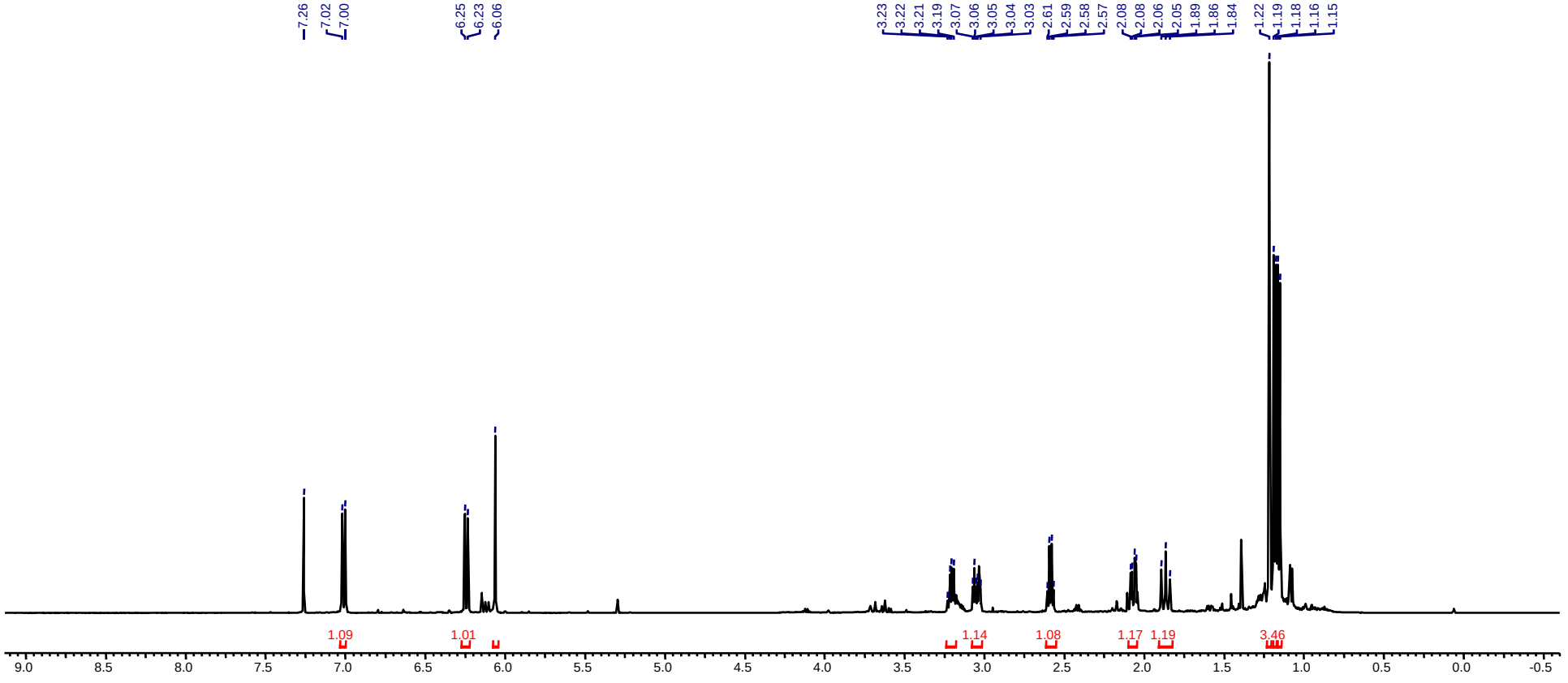


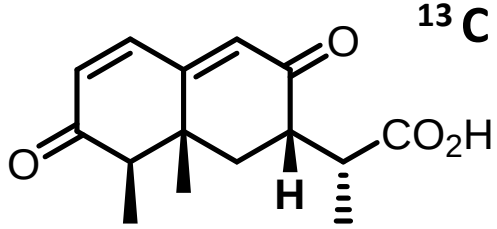
^{1} H NMR of Compound 19 ($CDCl_3$; 400 MHz)



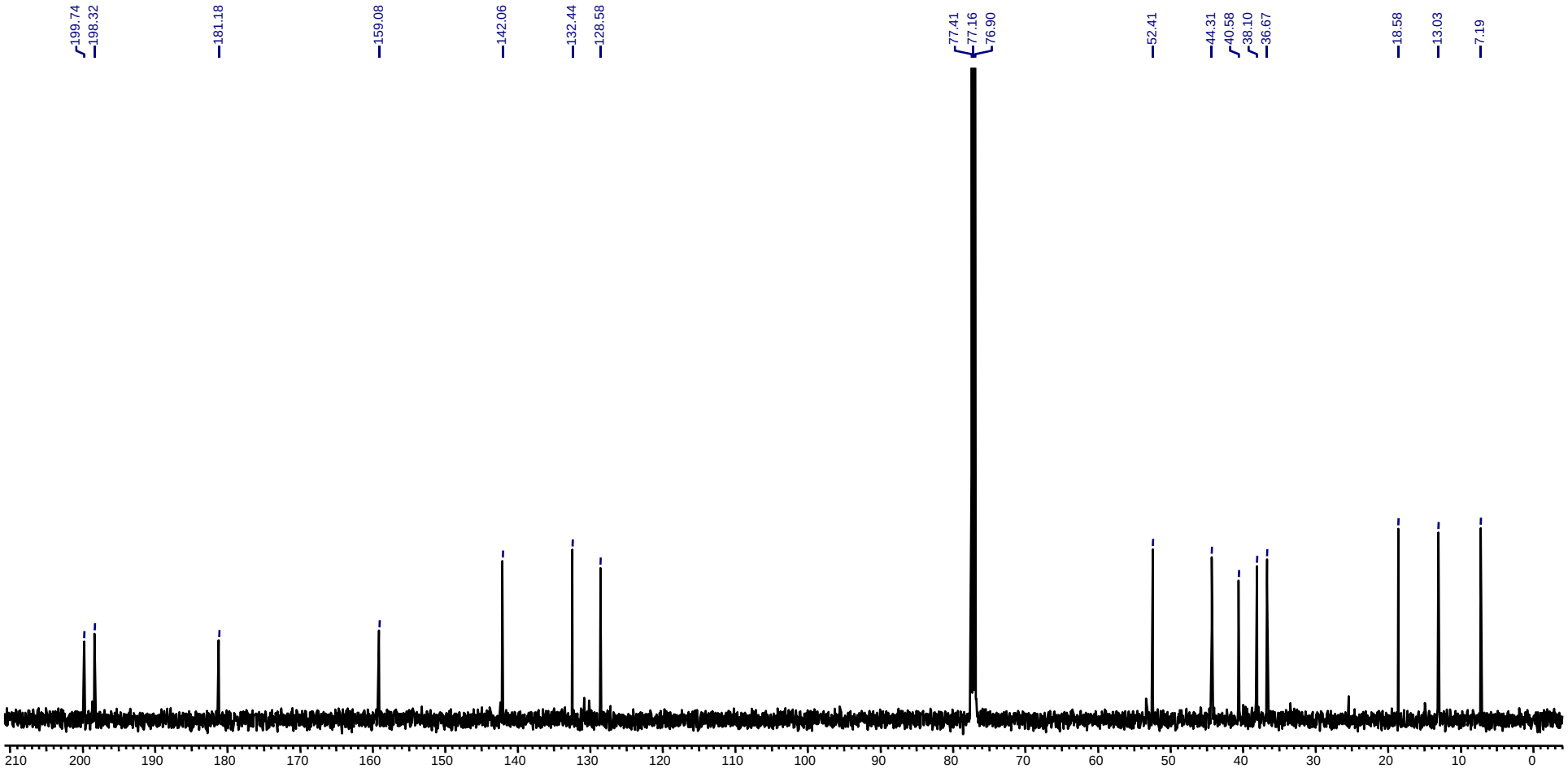
19



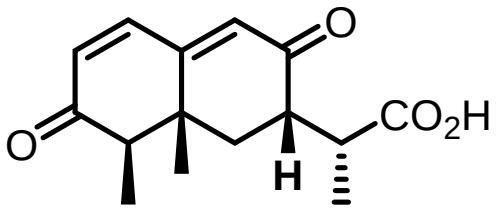
^{13}C NMR of Compound 19 ($CDCl_3$; 100 MHz)



19



^{1} H NMR of Compound 19 (DMSO-d_6; 400 MHz)



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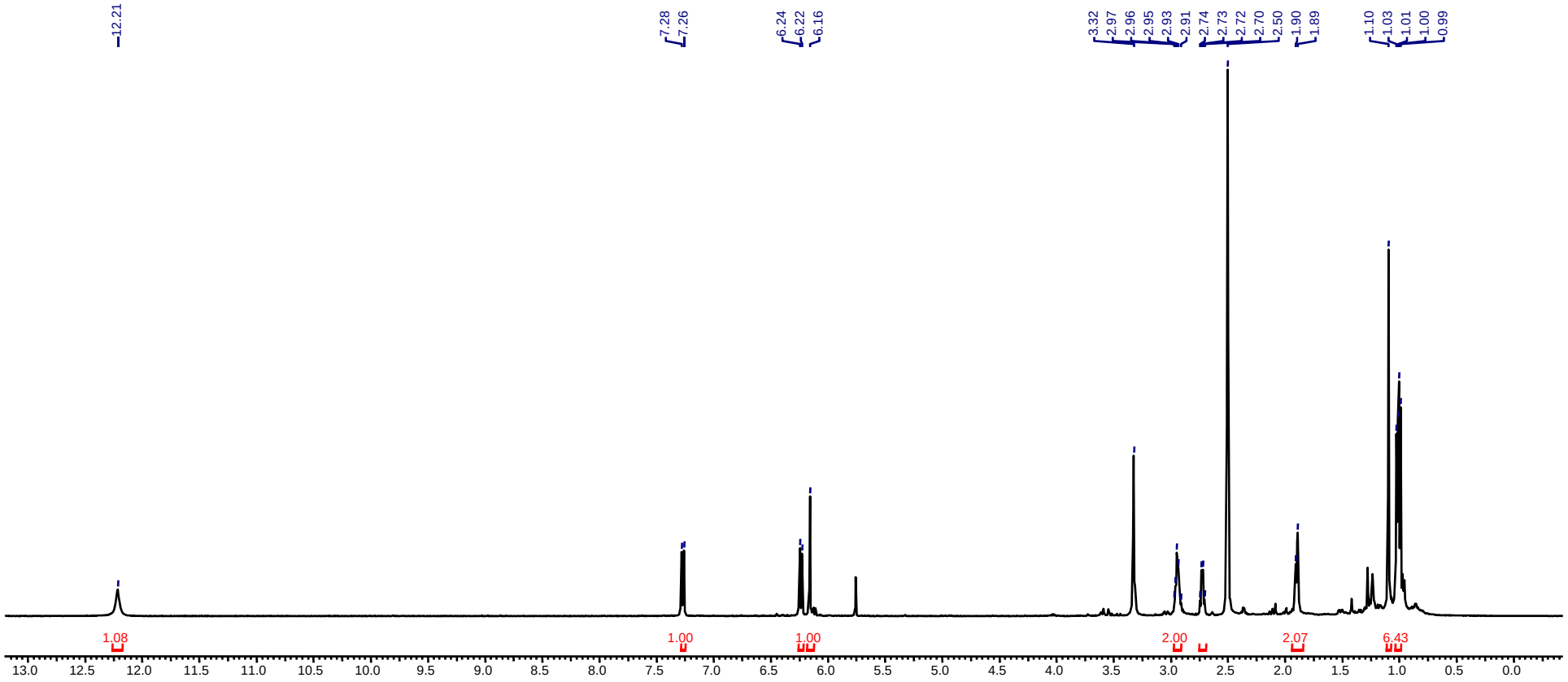
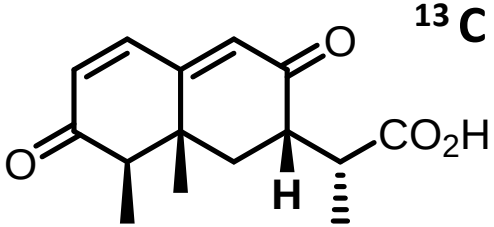


^{13}C NMR of Compound 19 (DMSO-d_6; 100 MHz)



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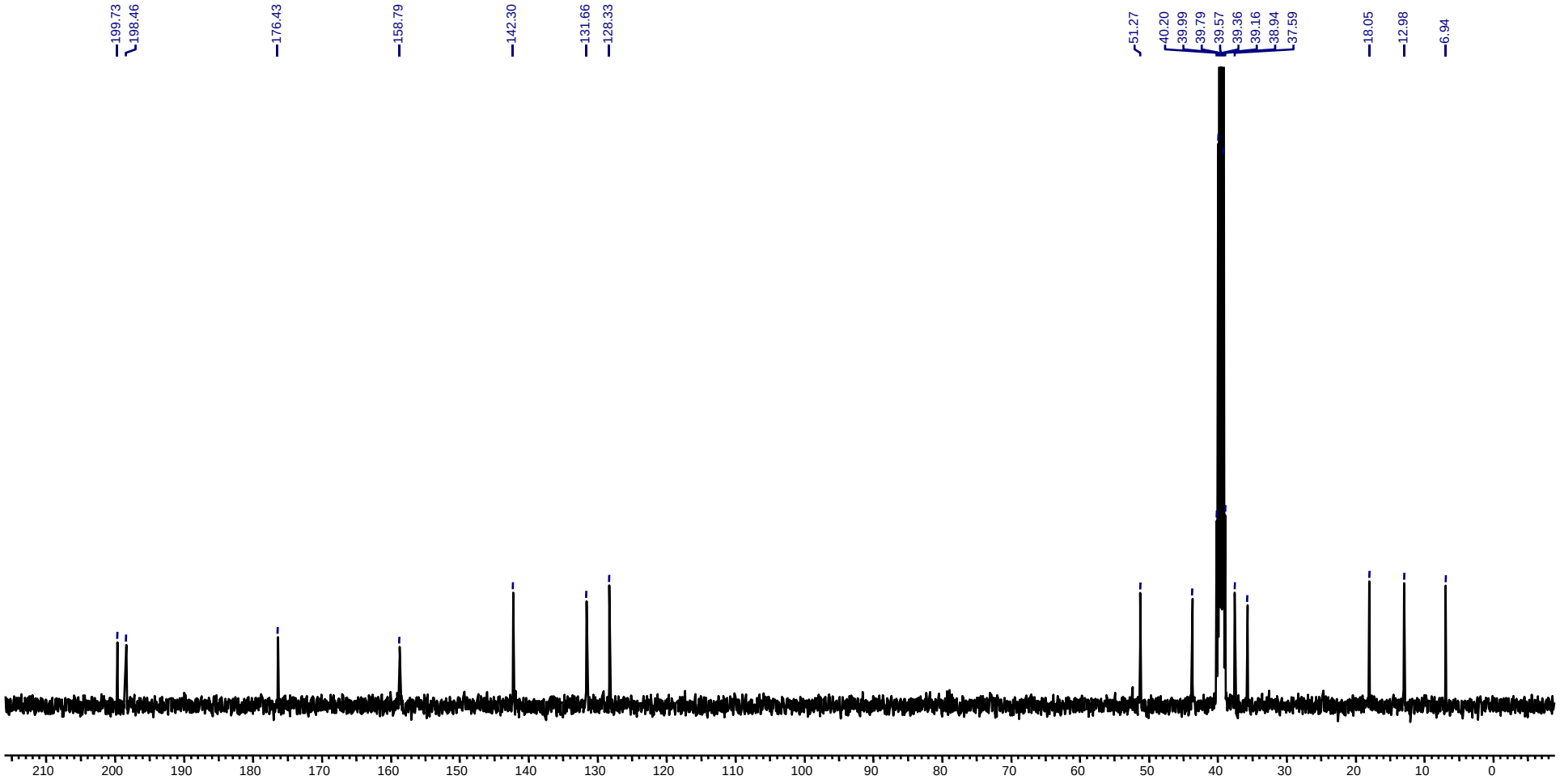
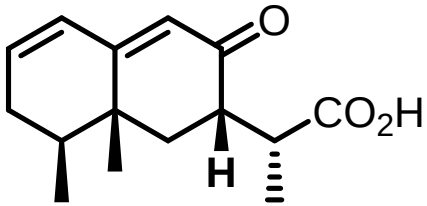
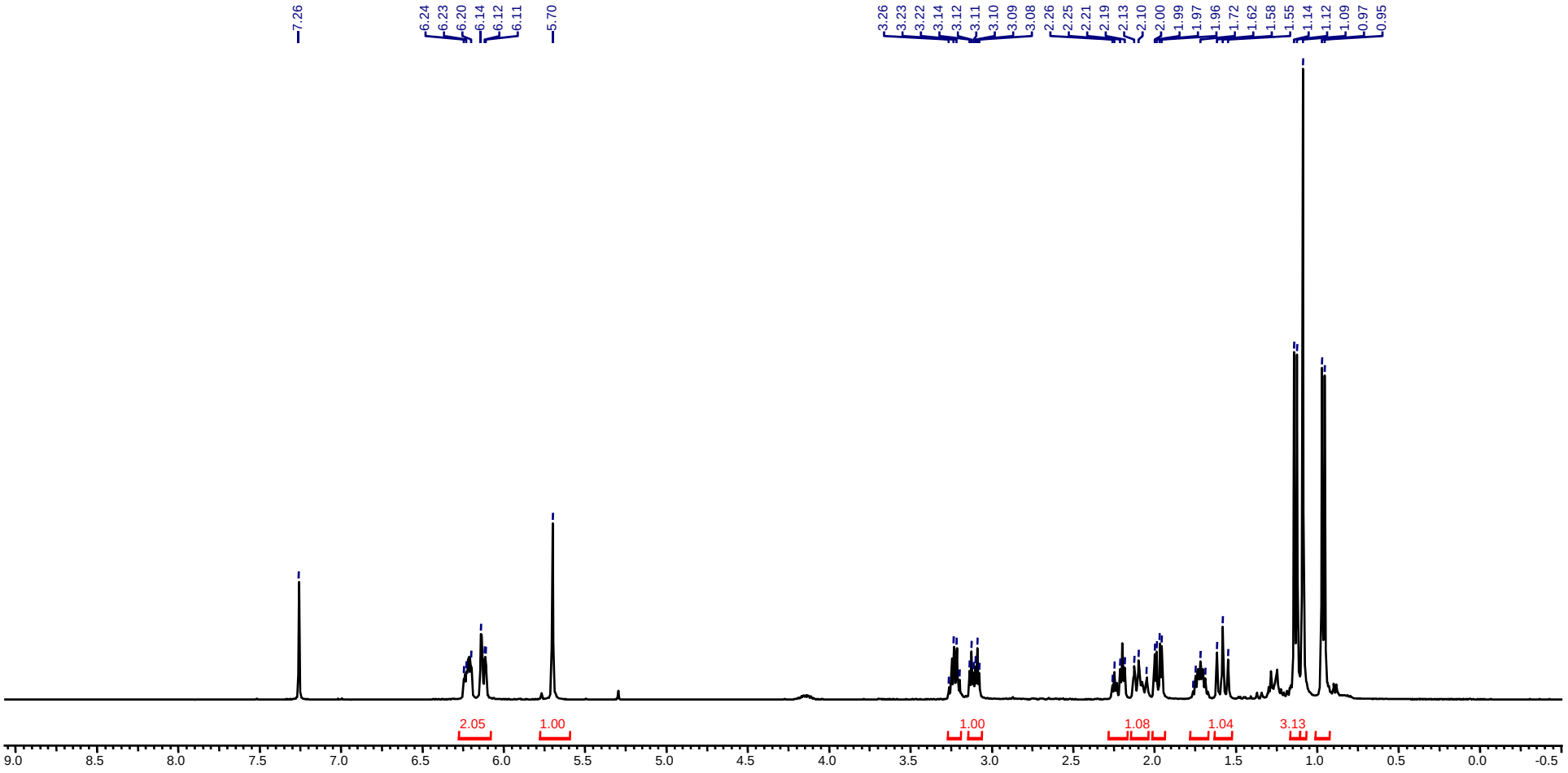
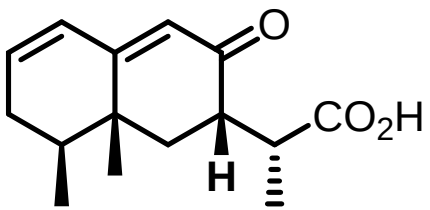




17

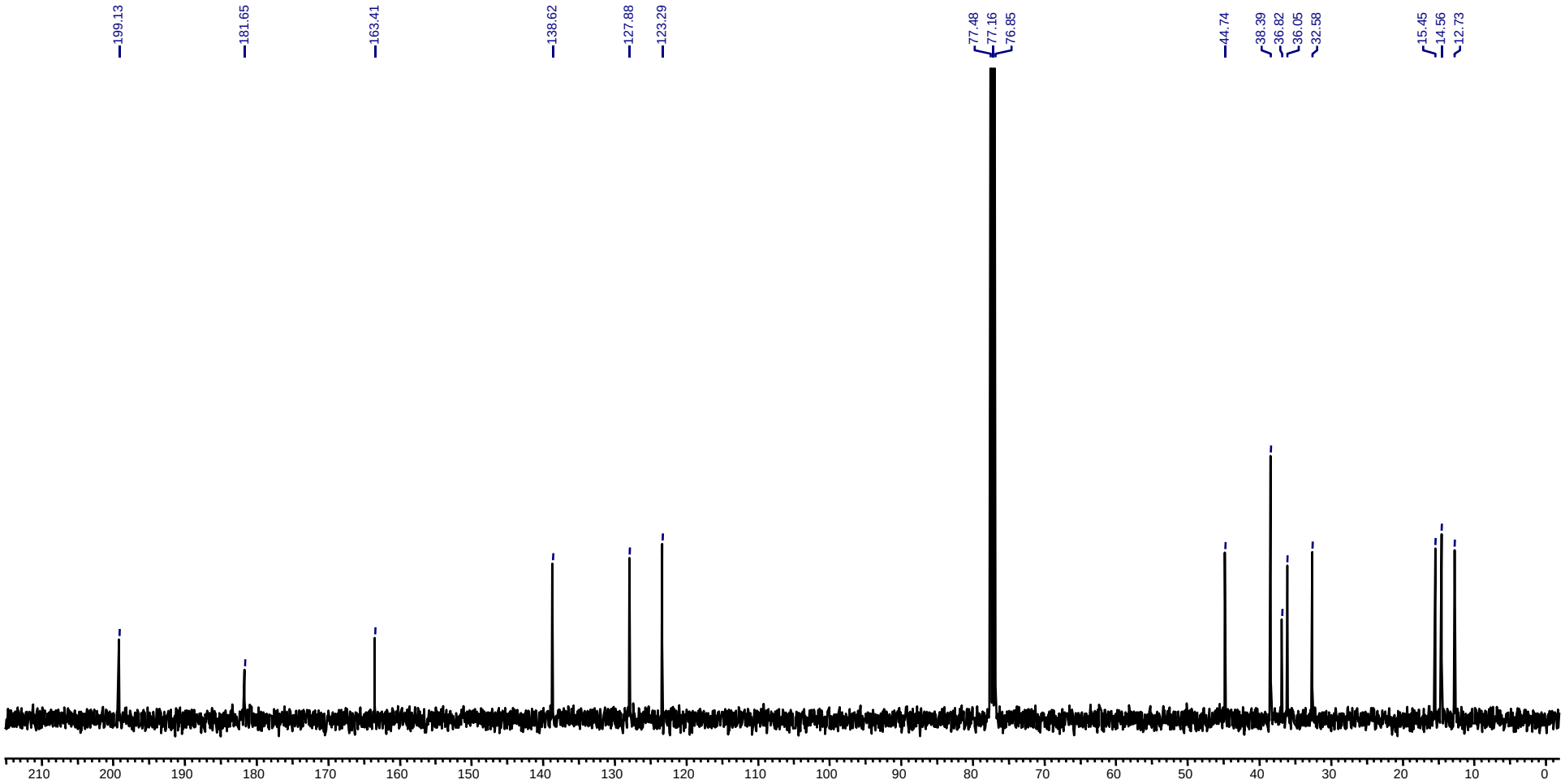
^{1}H NMR of Compound 17 ($CDCl_3$; 400 MHz)

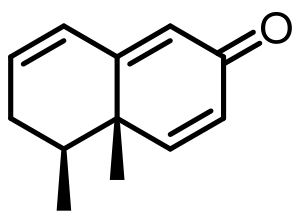




17

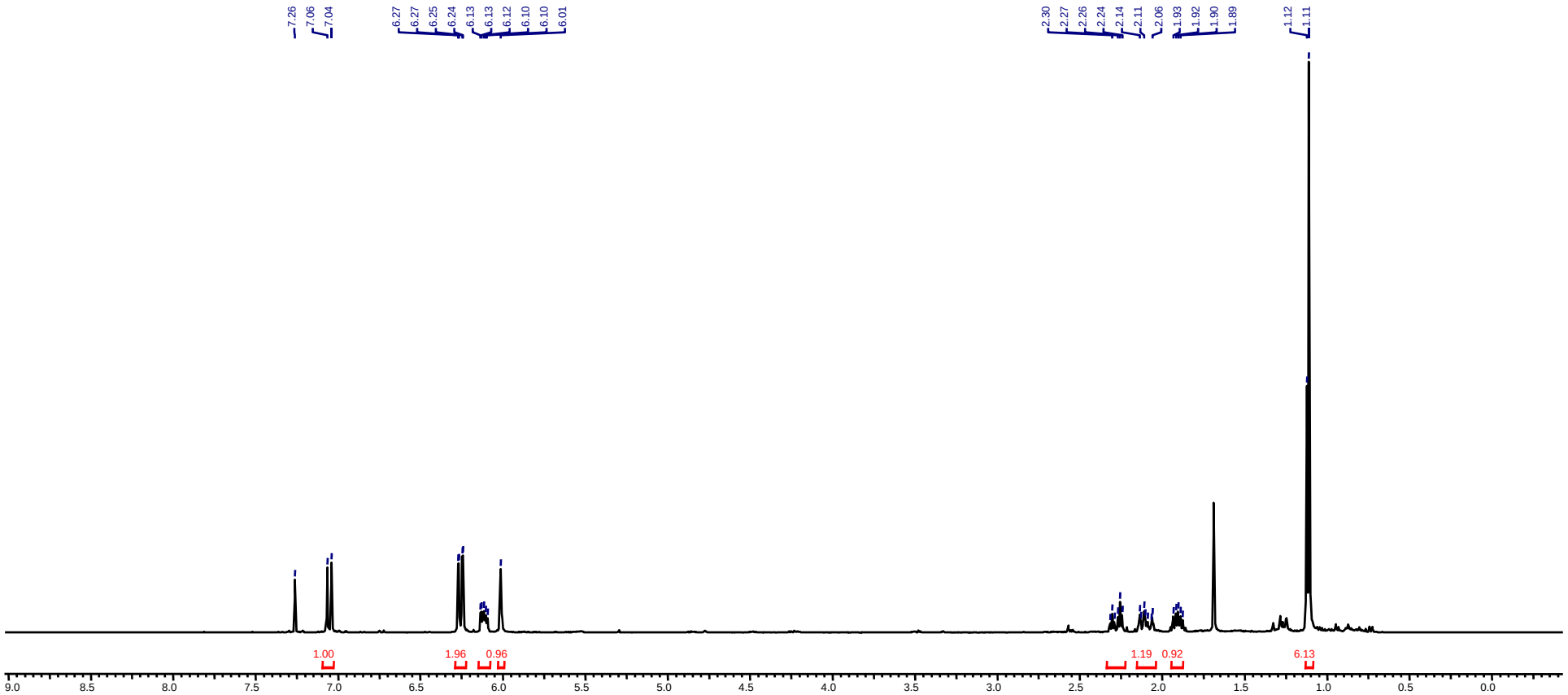
^{13}C NMR of Compound 17 ($CDCl_3$; 100 MHz)

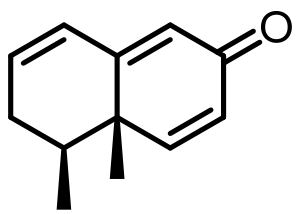




20

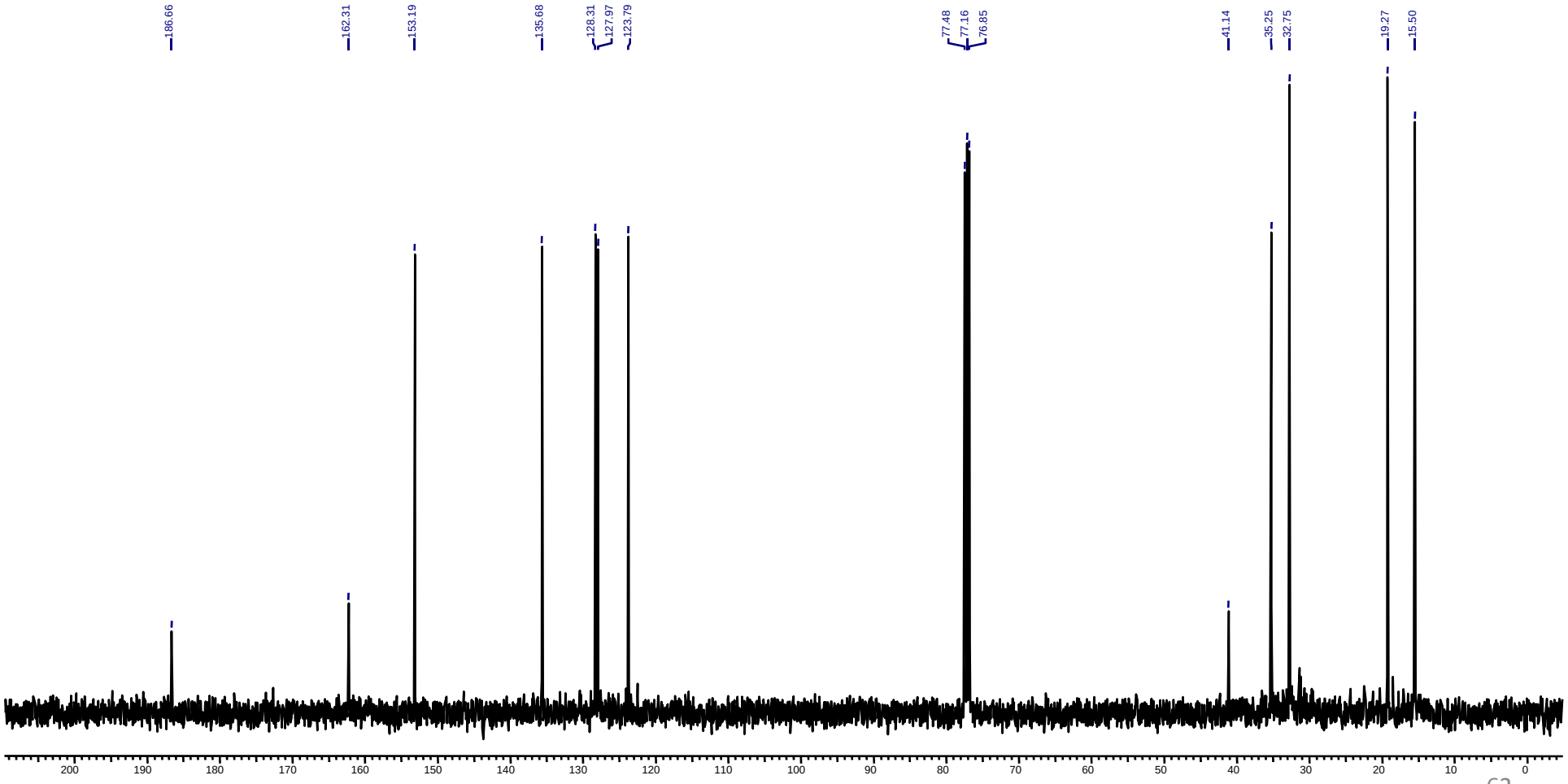
^{1}H NMR of Compound 20 ($CDCl_3$; 400 MHz)

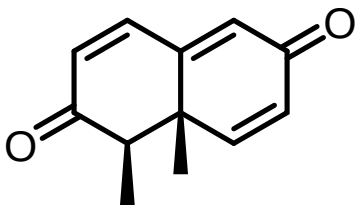




20

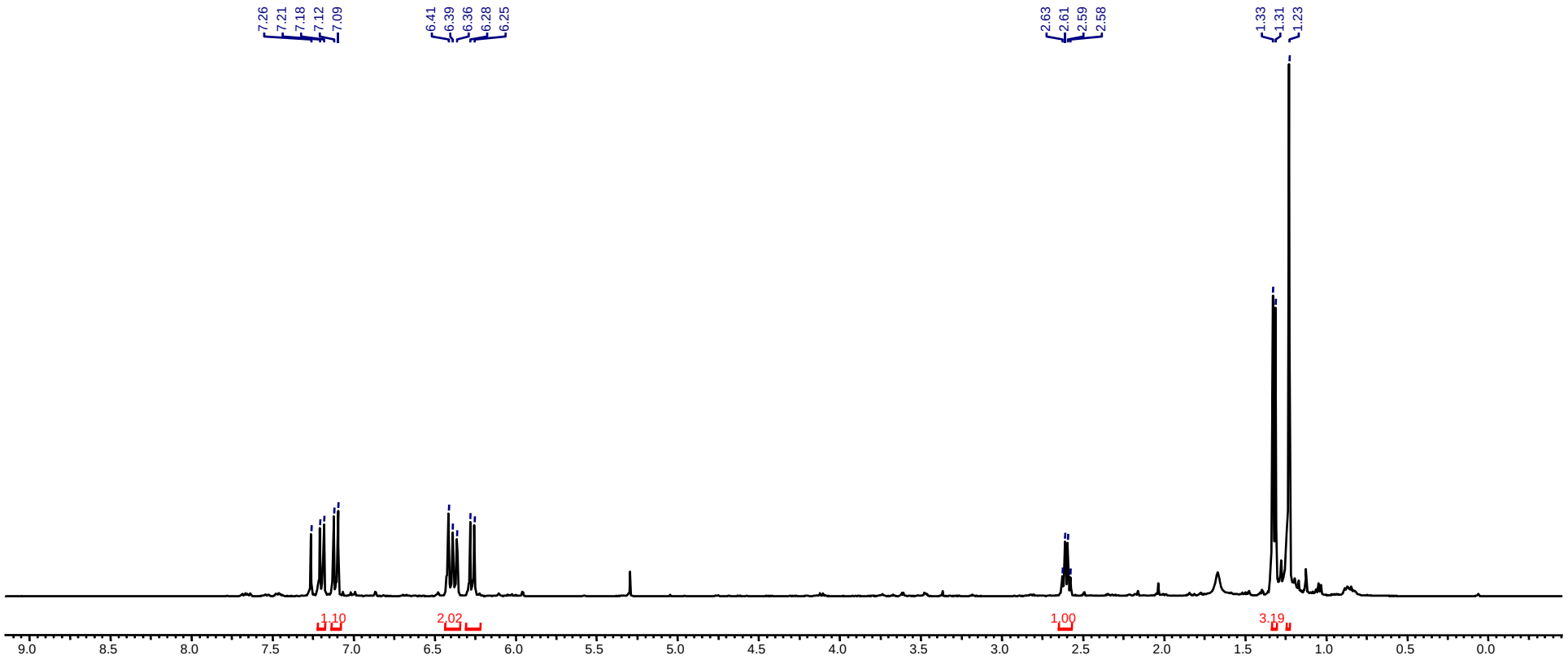
^{13}C NMR of Compound 20 ($CDCl_3$; 100 MHz)

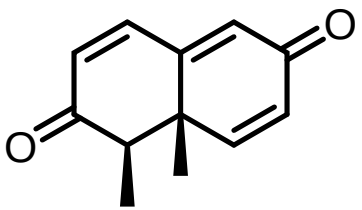




21

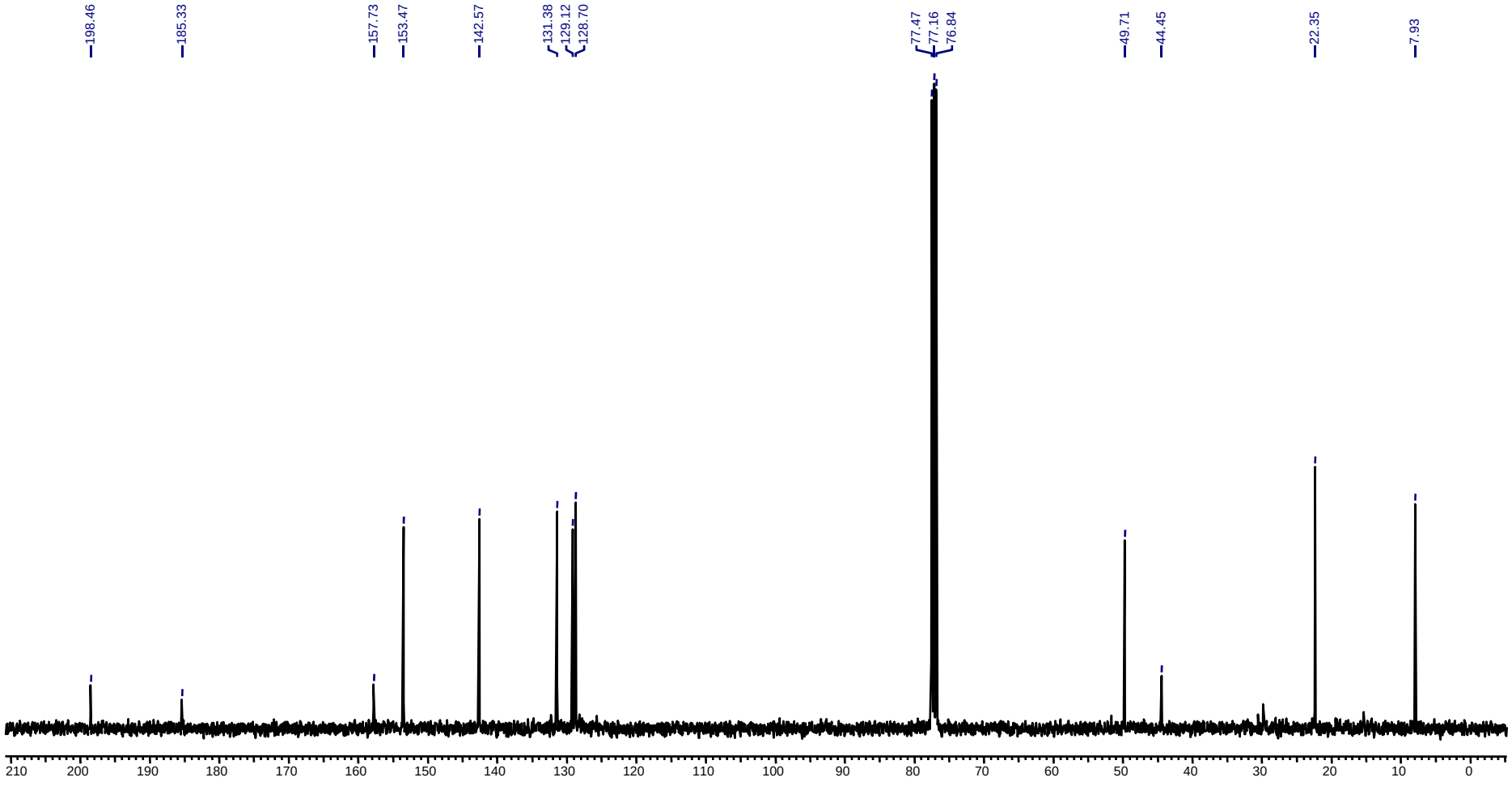
^{1} H NMR of Compound 21 ($CDCl_3$; 400 MHz)

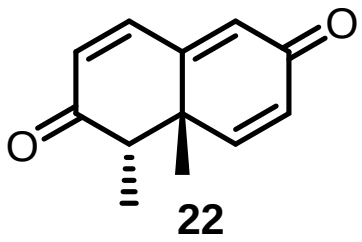




21

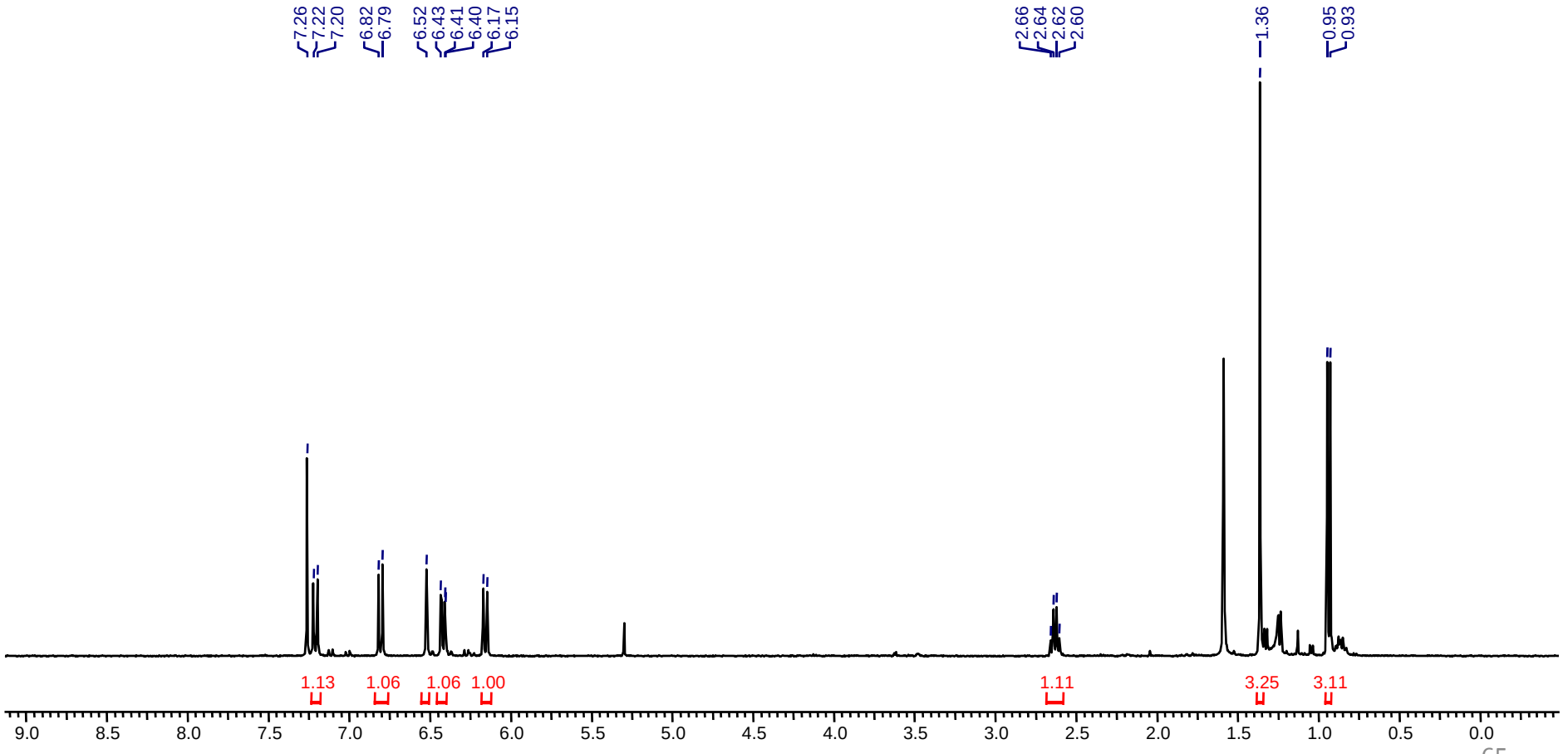
^{13}C NMR of Compound 21 ($CDCl_3$; 100 MHz)

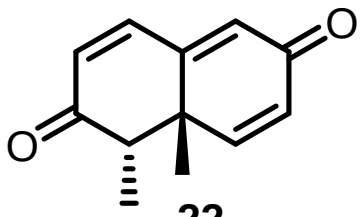




22

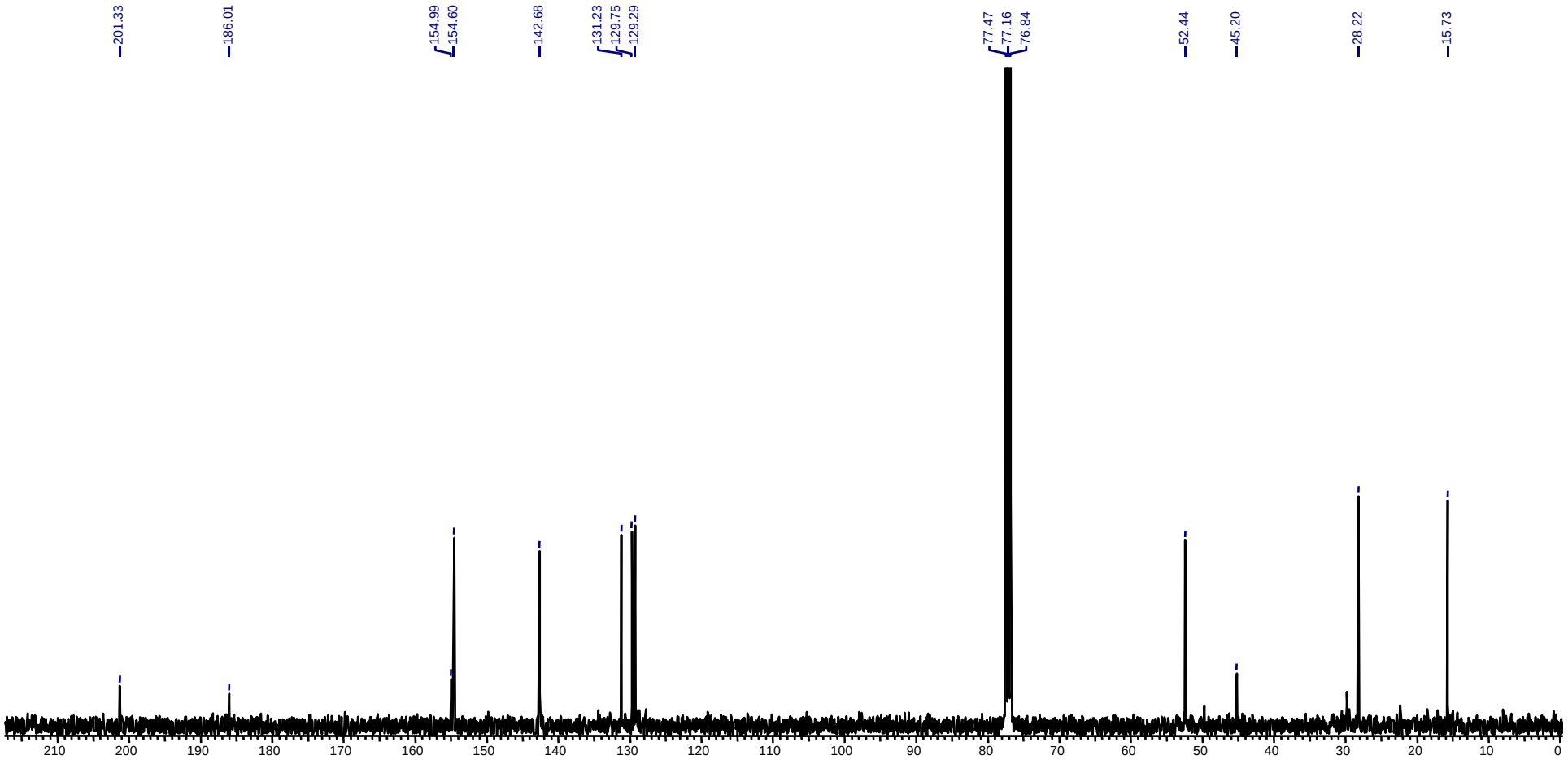
^{1}H NMR of Compound 22 ($CDCl_3$; 400 MHz)

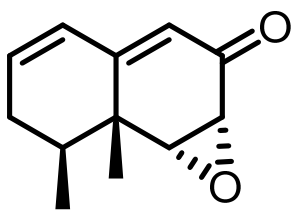




22

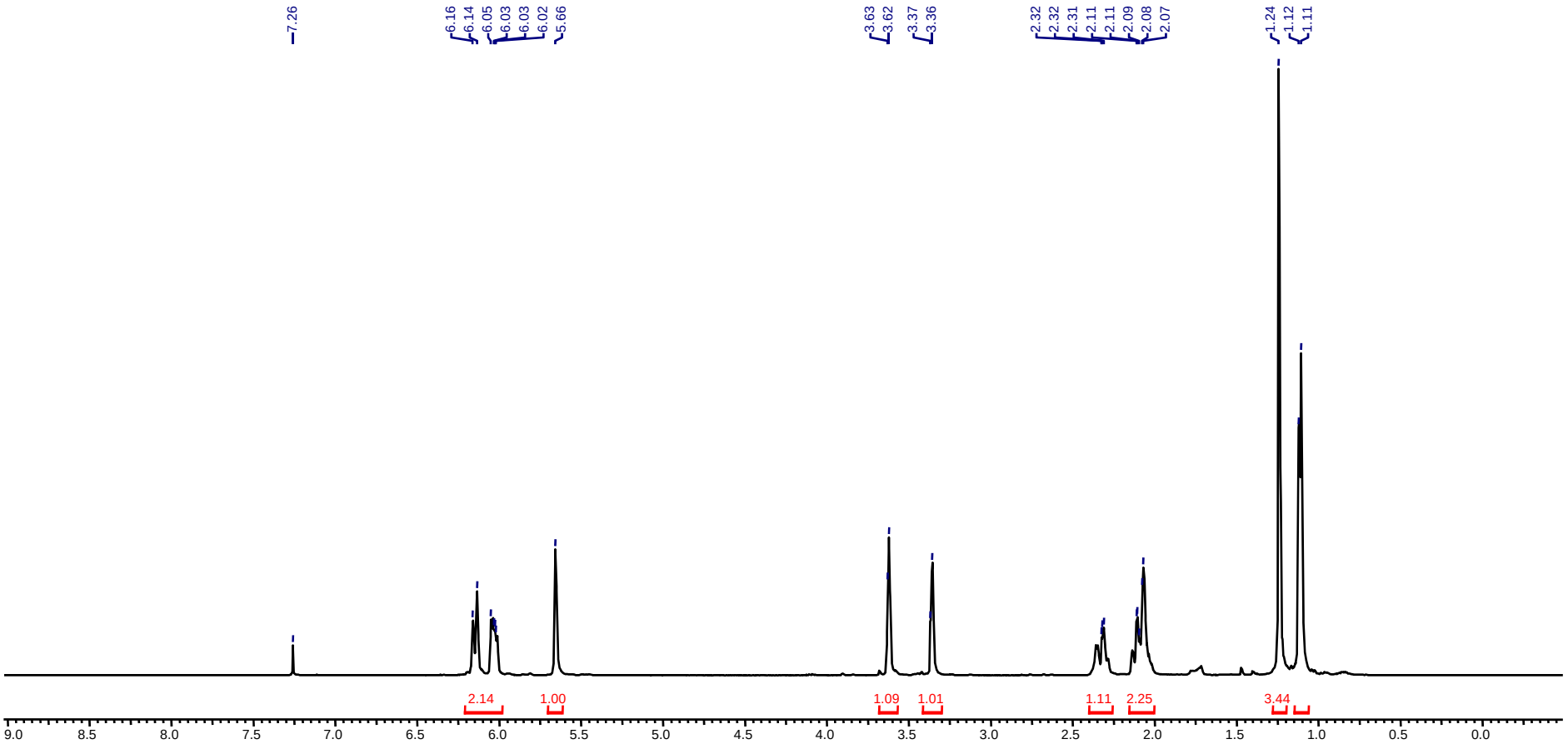
^{13}C NMR of Compound 22 ($CDCl_3$; 100 MHz)

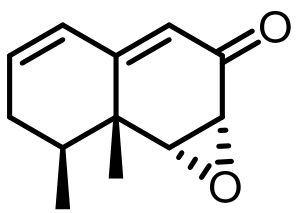




S-III

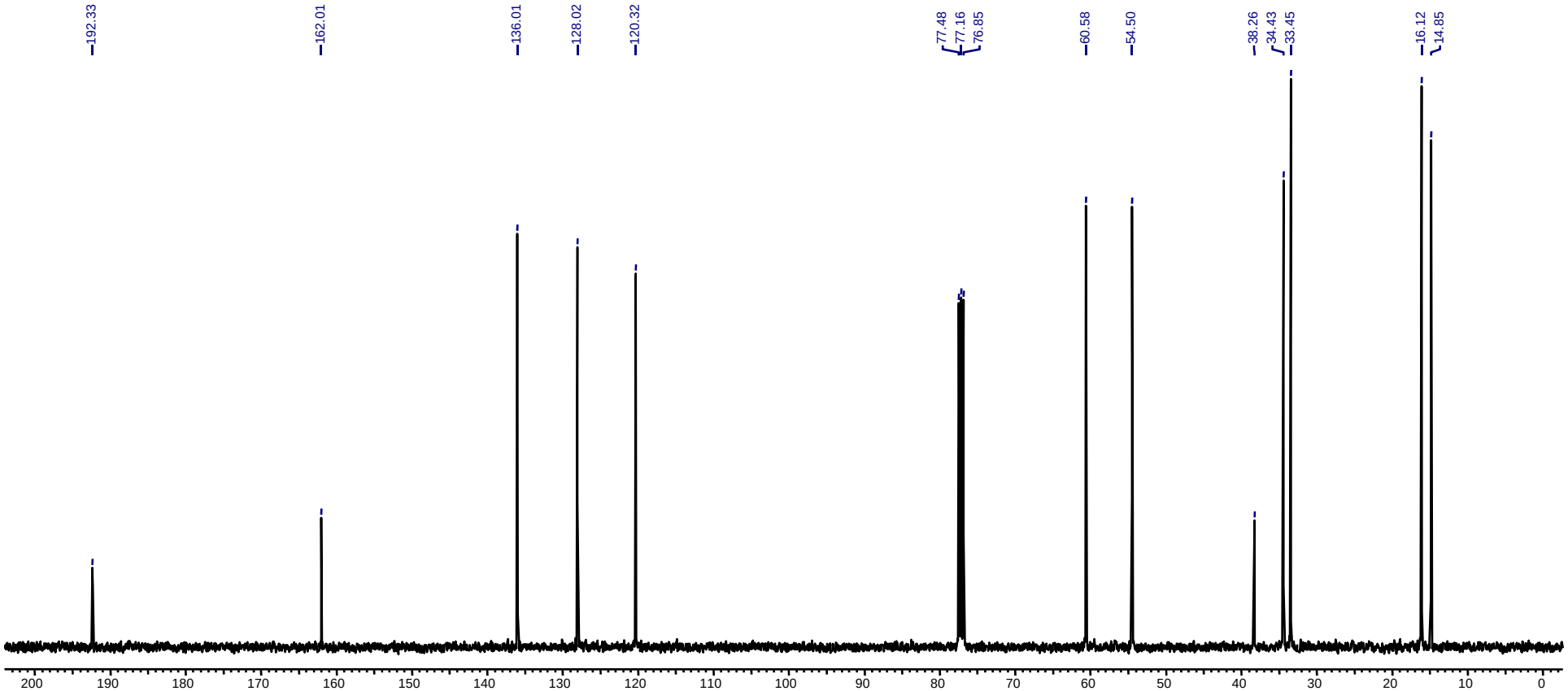
^{1}H NMR of Compound S-III ($CDCl_3$; 400 MHz)

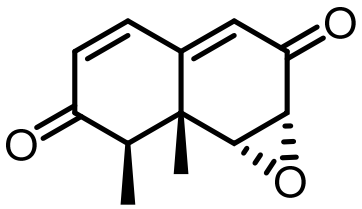




S-III

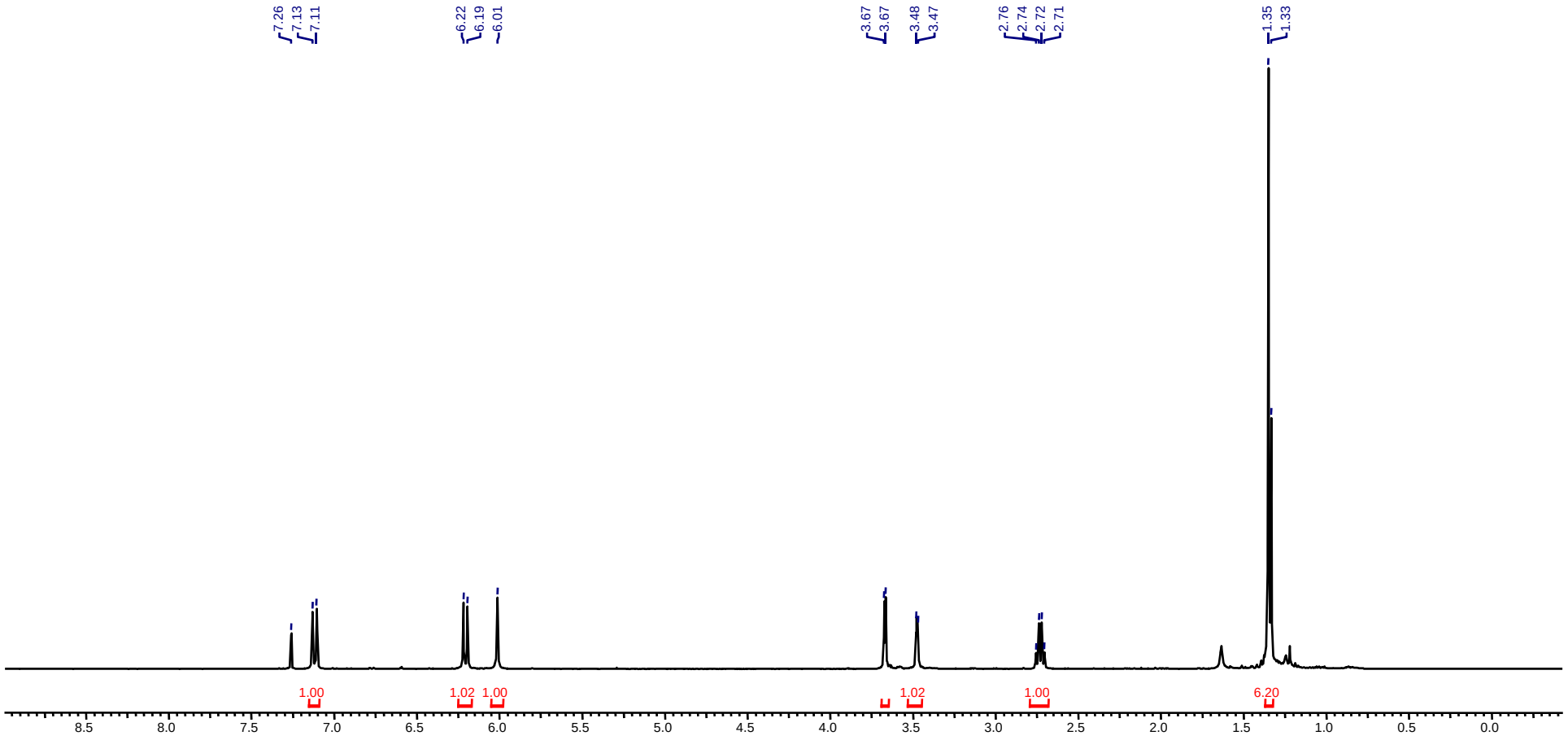
^{13}C NMR of Compound S-III ($CDCl_3$; 100 MHz)

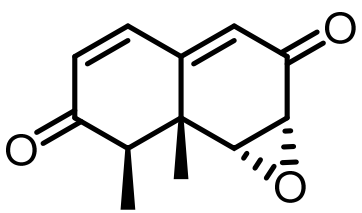




23

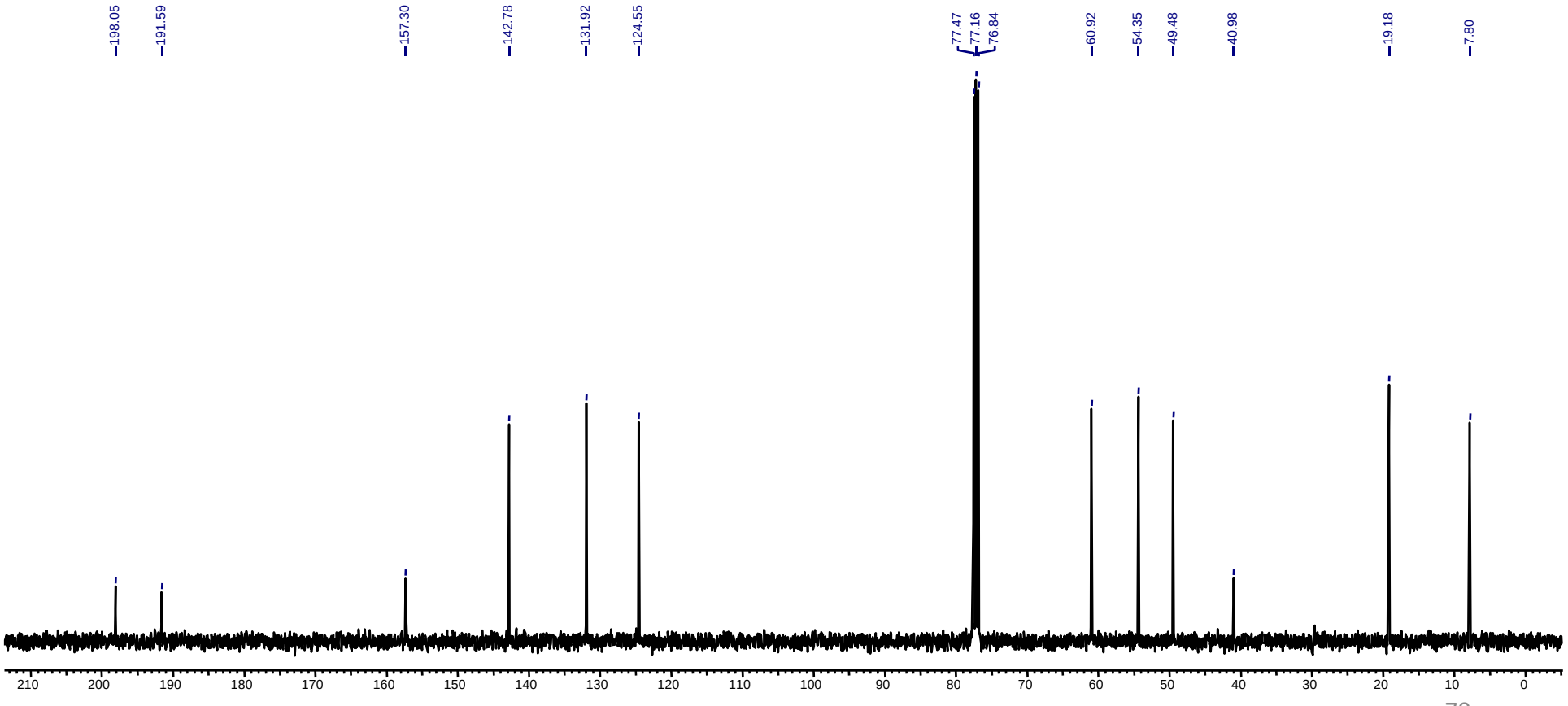
^{1} H NMR of Compound 23 ($CDCl_3$; 400 MHz)



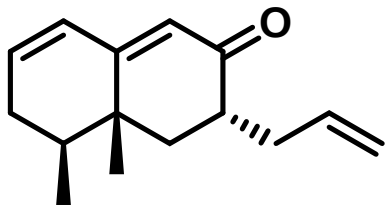


23

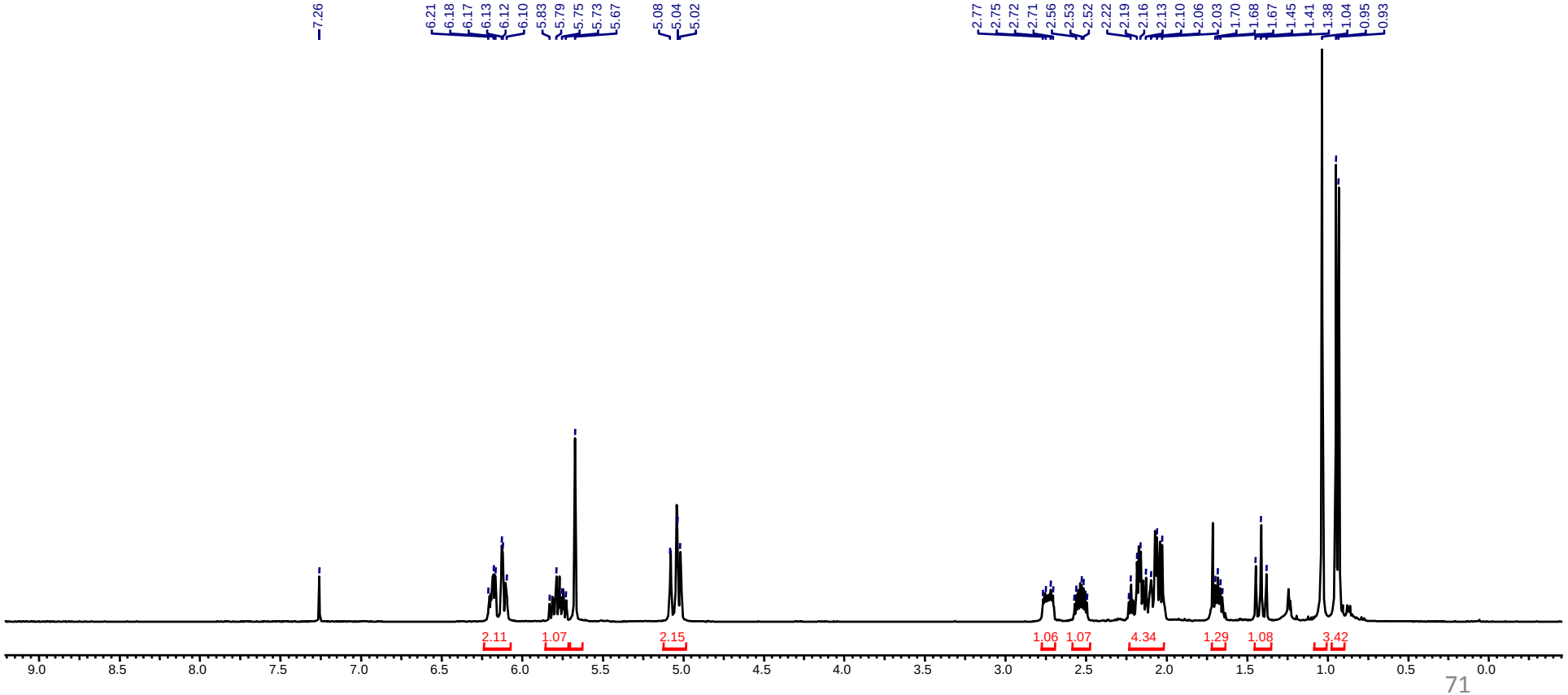
^{13}C NMR of Compound 23 ($CDCl_3$; 100 MHz)



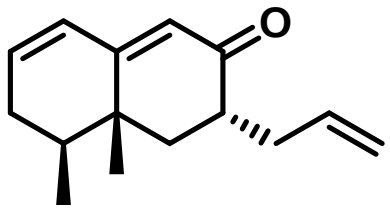
^{1} H NMR of Compound S-IV ($CDCl_3$; 400 MHz)



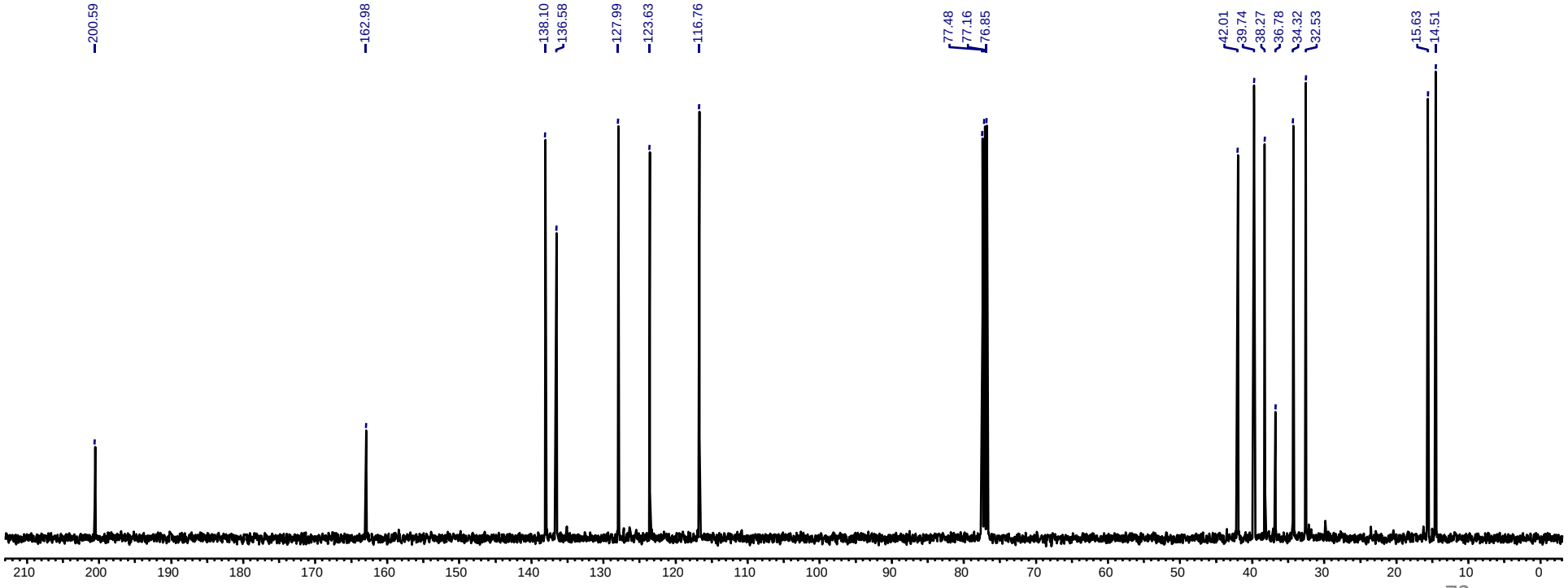
S-IV

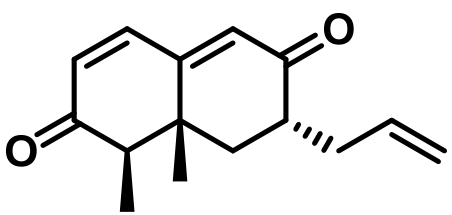


^{13}C NMR of Compound S-IV ($CDCl_3$; 100 MHz)



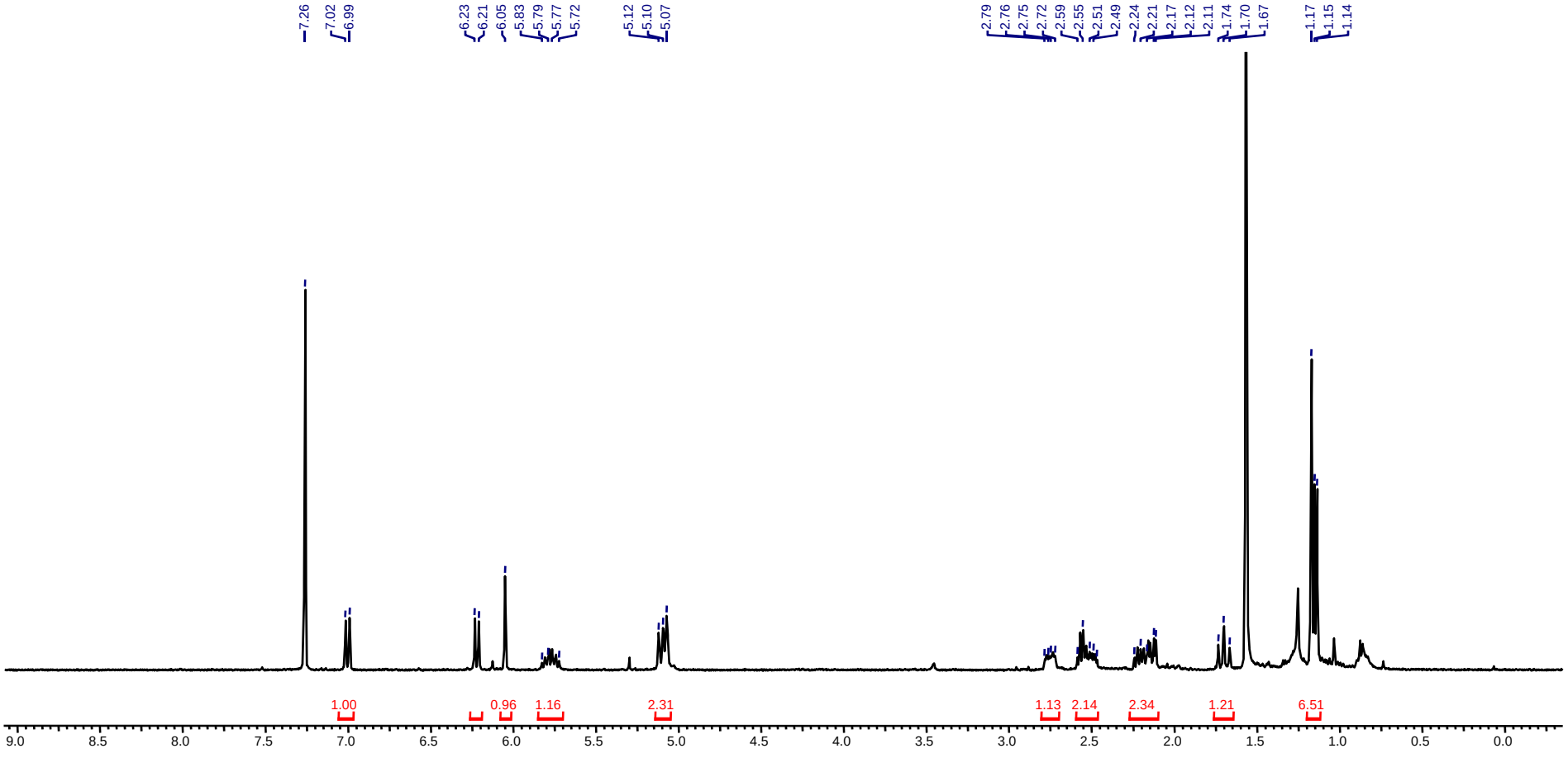
S-IV

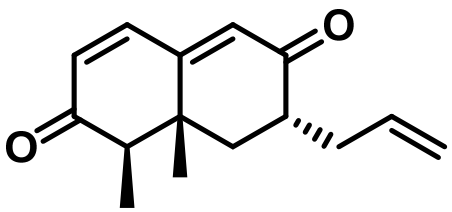




24

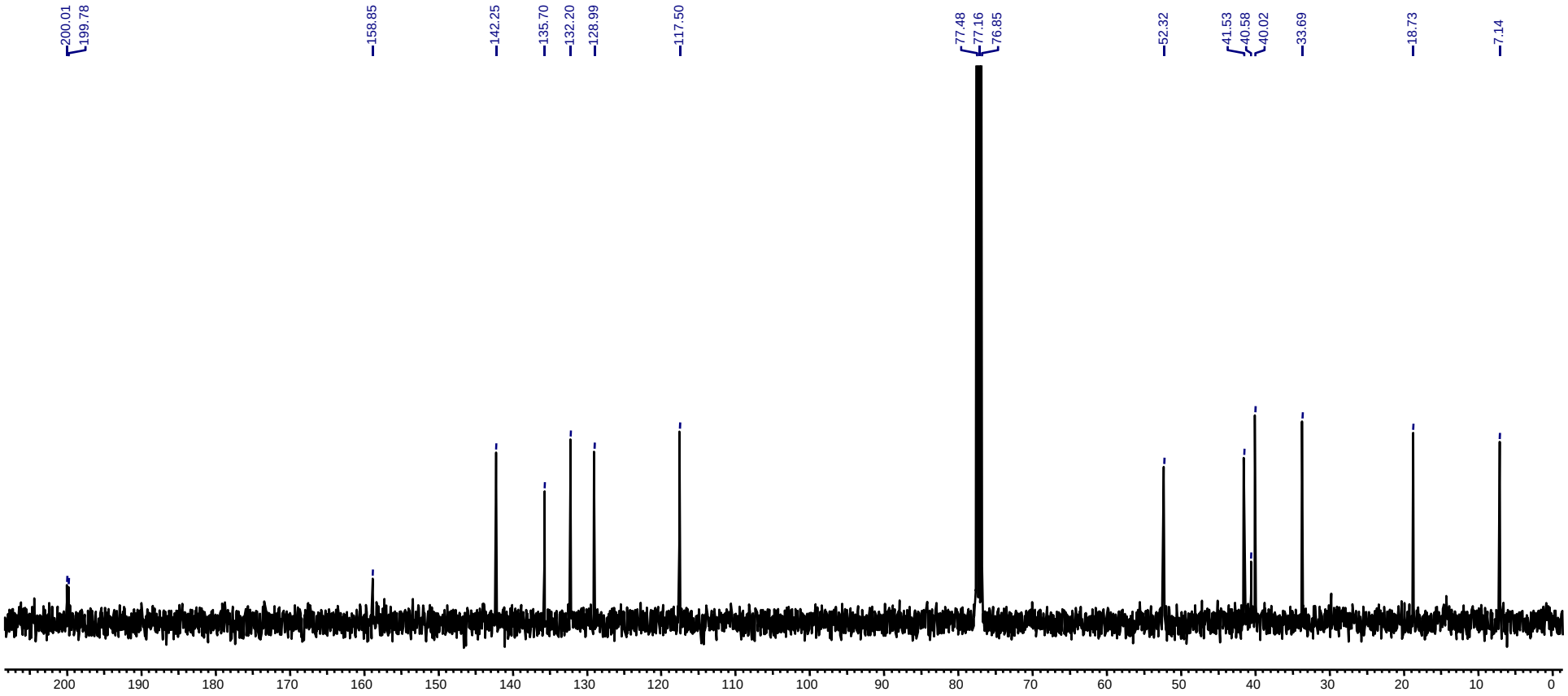
^{1} H NMR of Compound 24 ($CDCl_3$; 400 MHz)

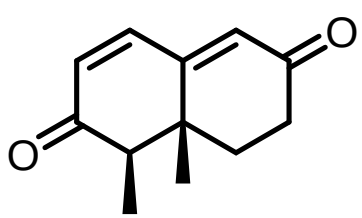




24

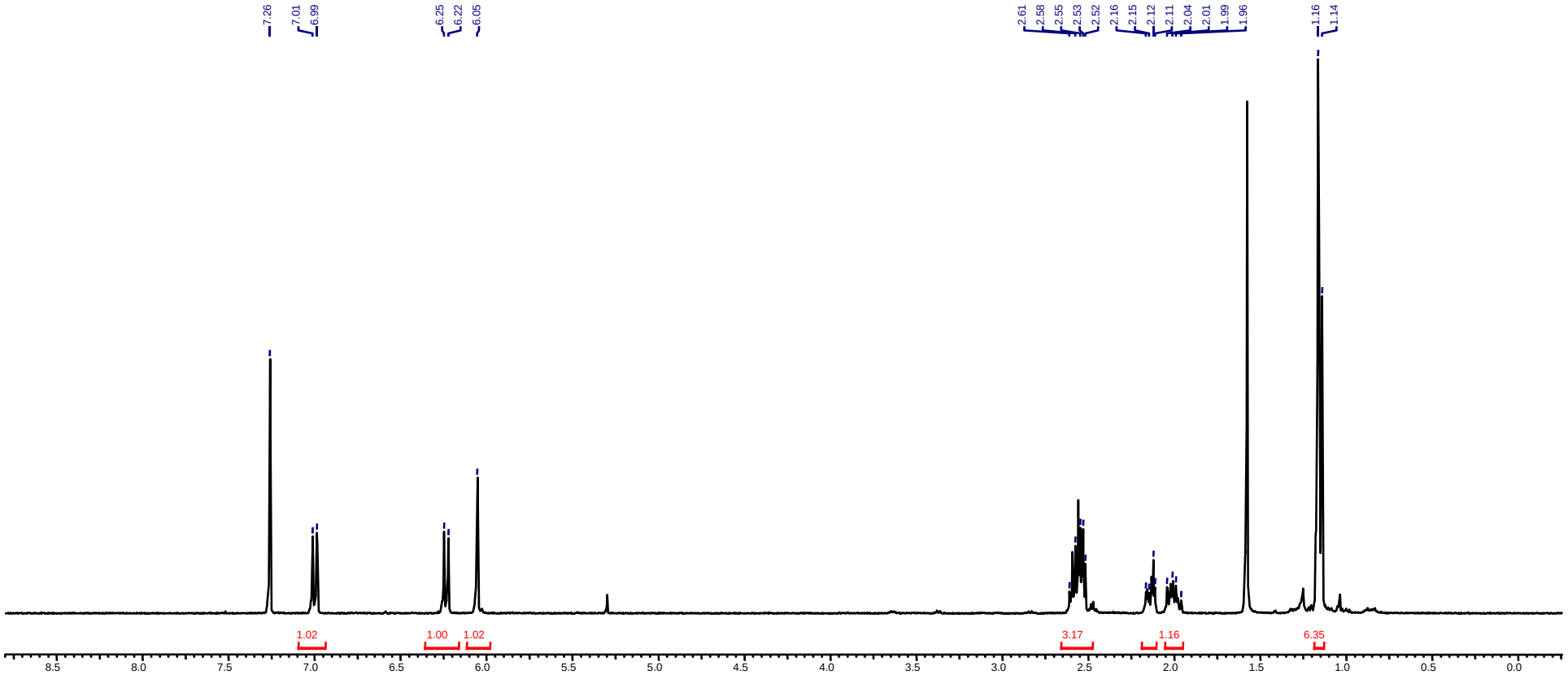
^{13}C NMR of Compound 24 ($CDCl_3$; 100 MHz)

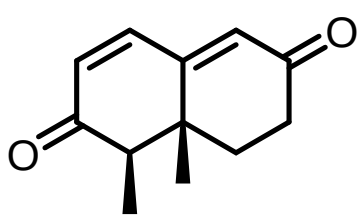




25

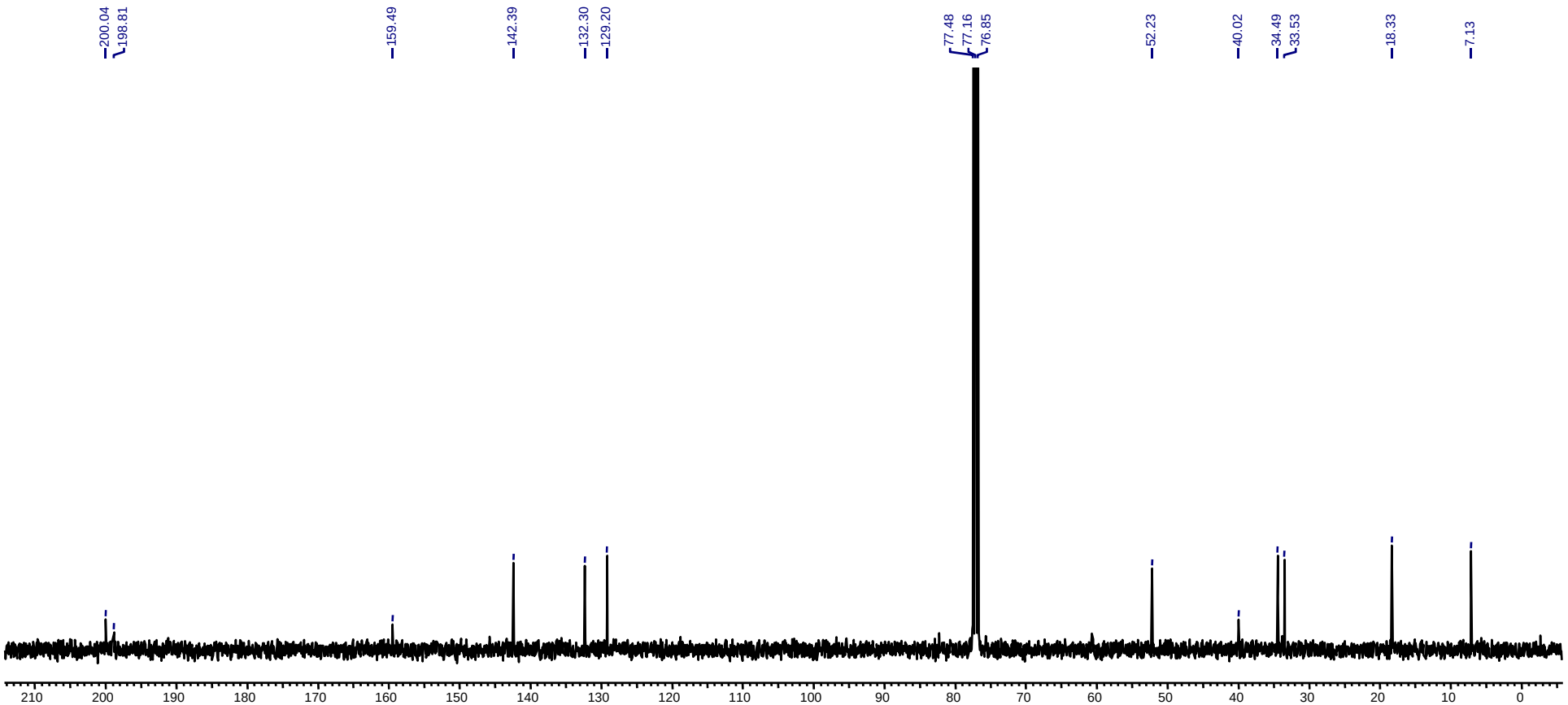
^{1} H NMR of Compound 25 ($CDCl_3$; 400 MHz)

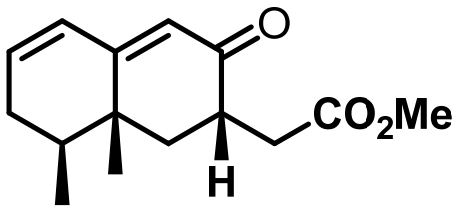




25

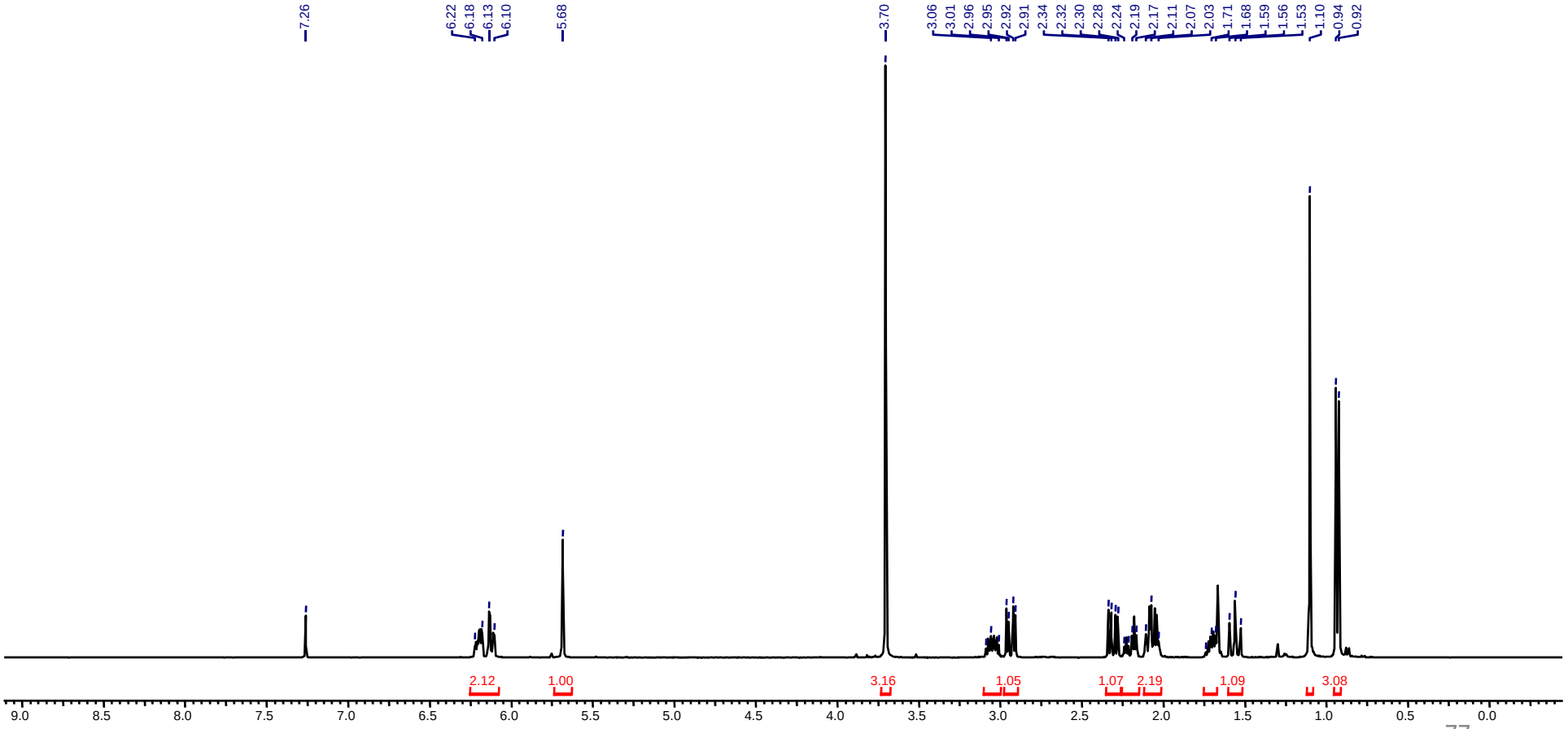
^{13}C NMR of Compound 25 ($CDCl_3$; 100 MHz)



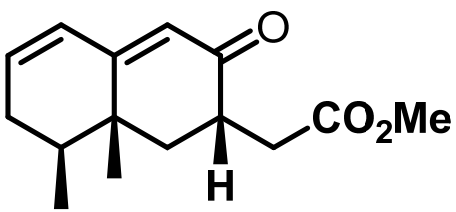


26

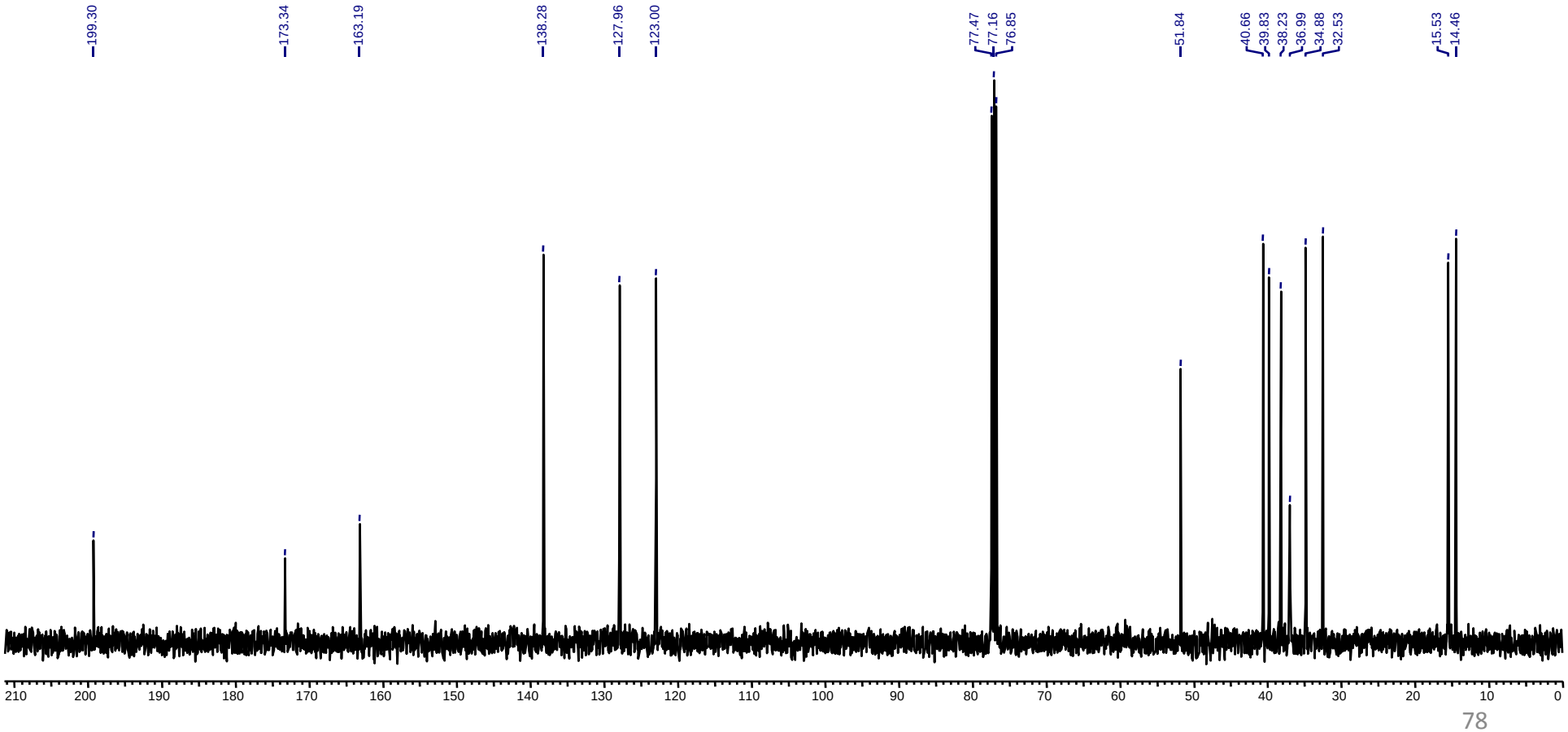
^{1} H NMR of Compound 26 ($CDCl_3$; 400 MHz)

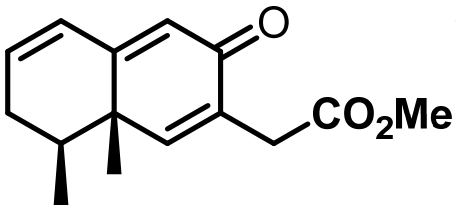


^{13}C NMR of Compound 26 ($CDCl_3$; 100 MHz)



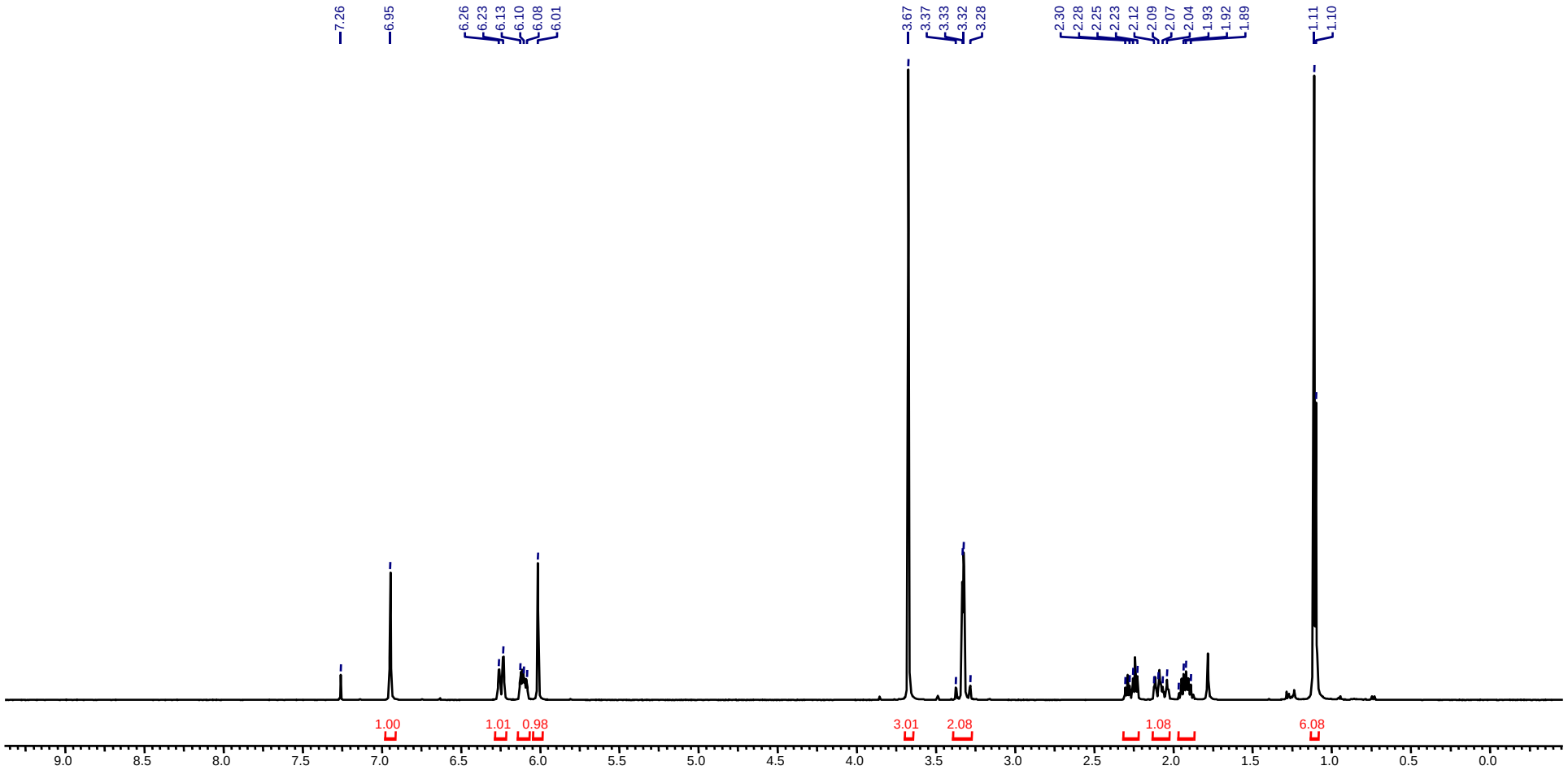
26

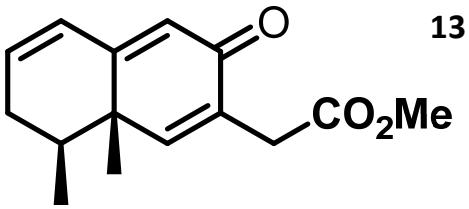




27

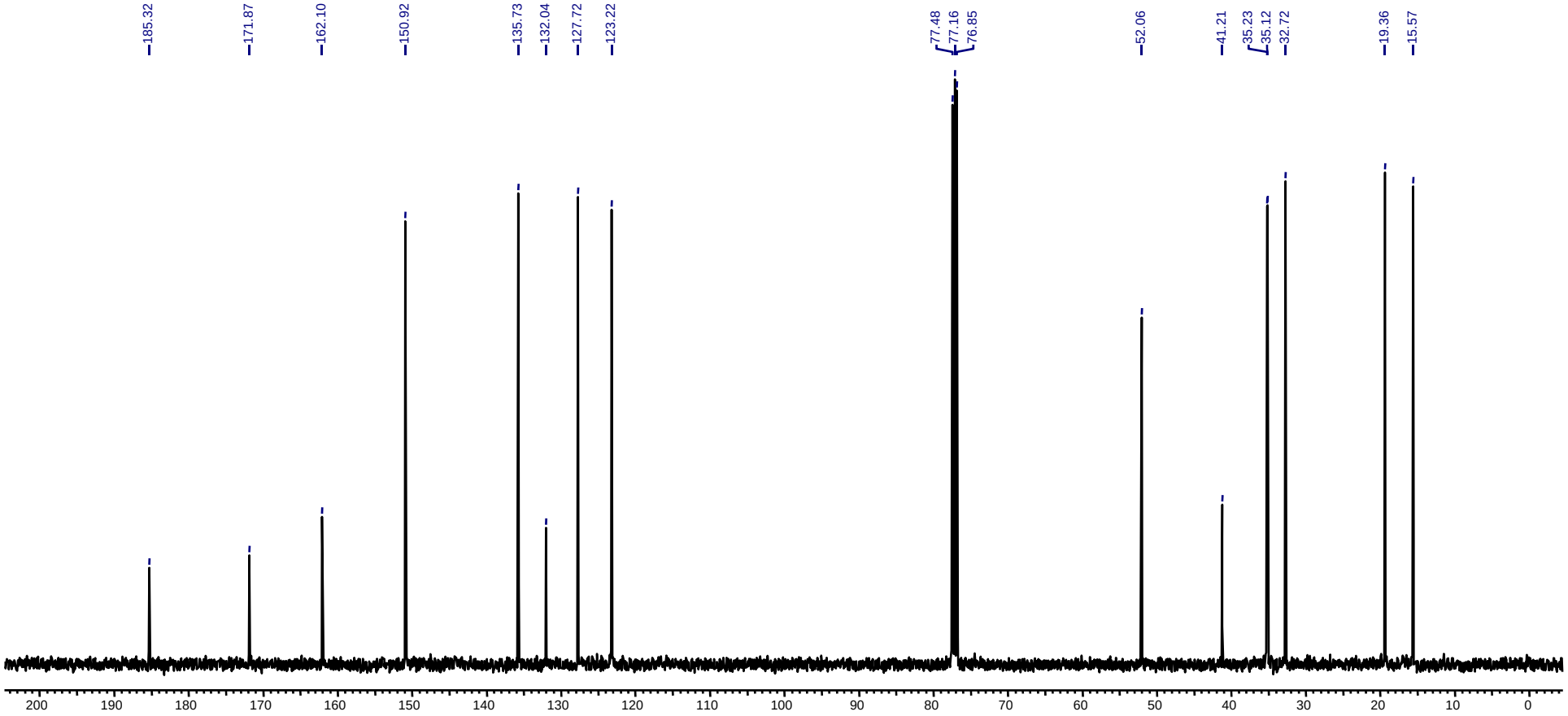
^{1}H NMR of Compound 27 ($CDCl_3$; 400 MHz)



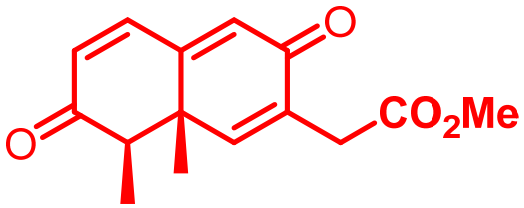


27

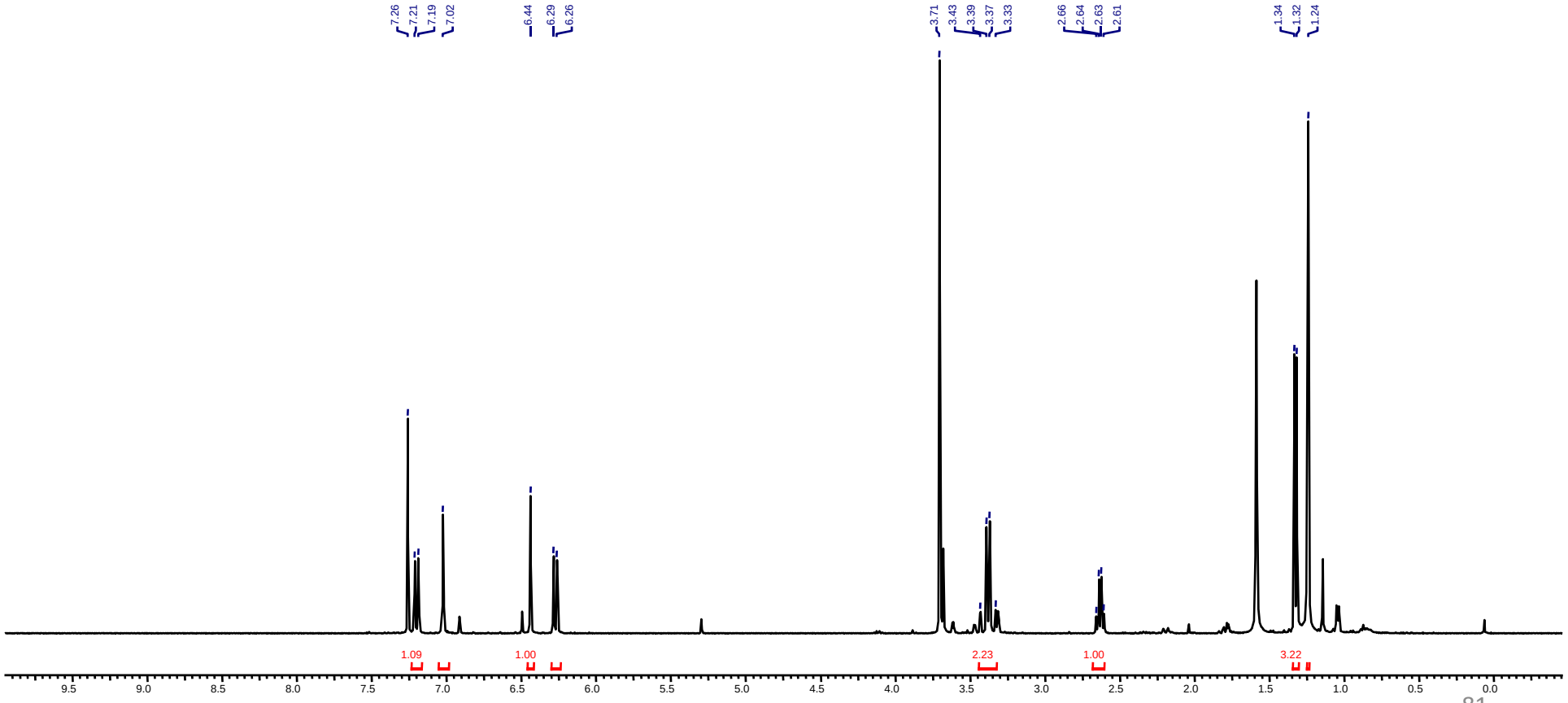
^{13}C NMR of Compound 27 ($CDCl_3$; 100 MHz)



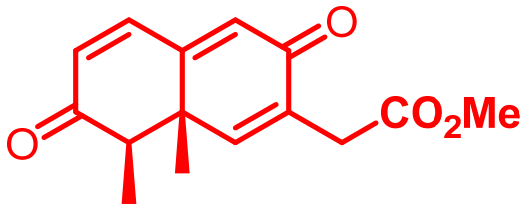
^{1} H NMR of Compound 28 ($CDCl_3$; 400 MHz)



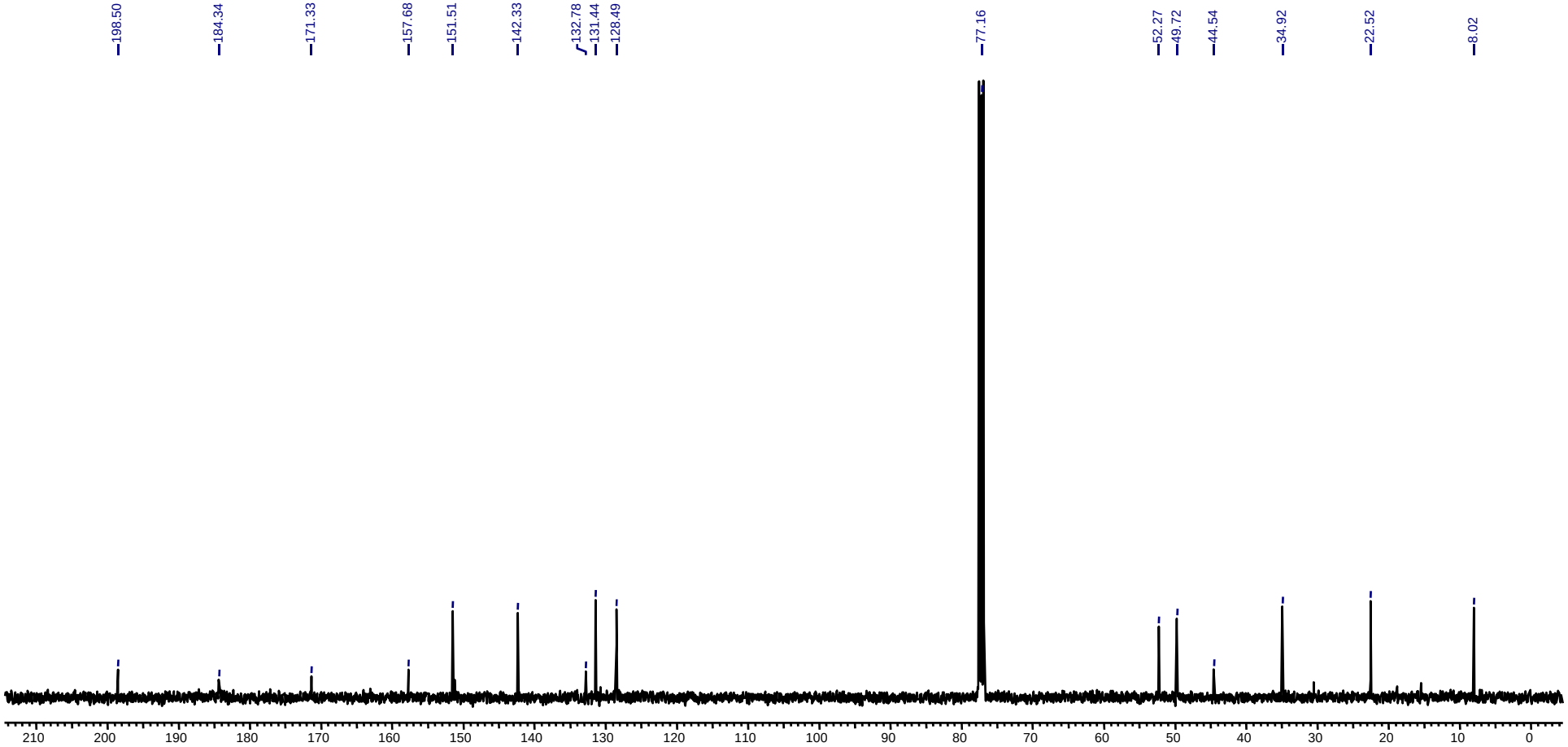
(±) hoaensieremodione 28



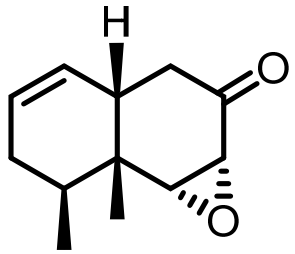
^{13}C NMR of Compound 28 ($CDCl_3$; 100 MHz)



(±) hoaensieremodione 28

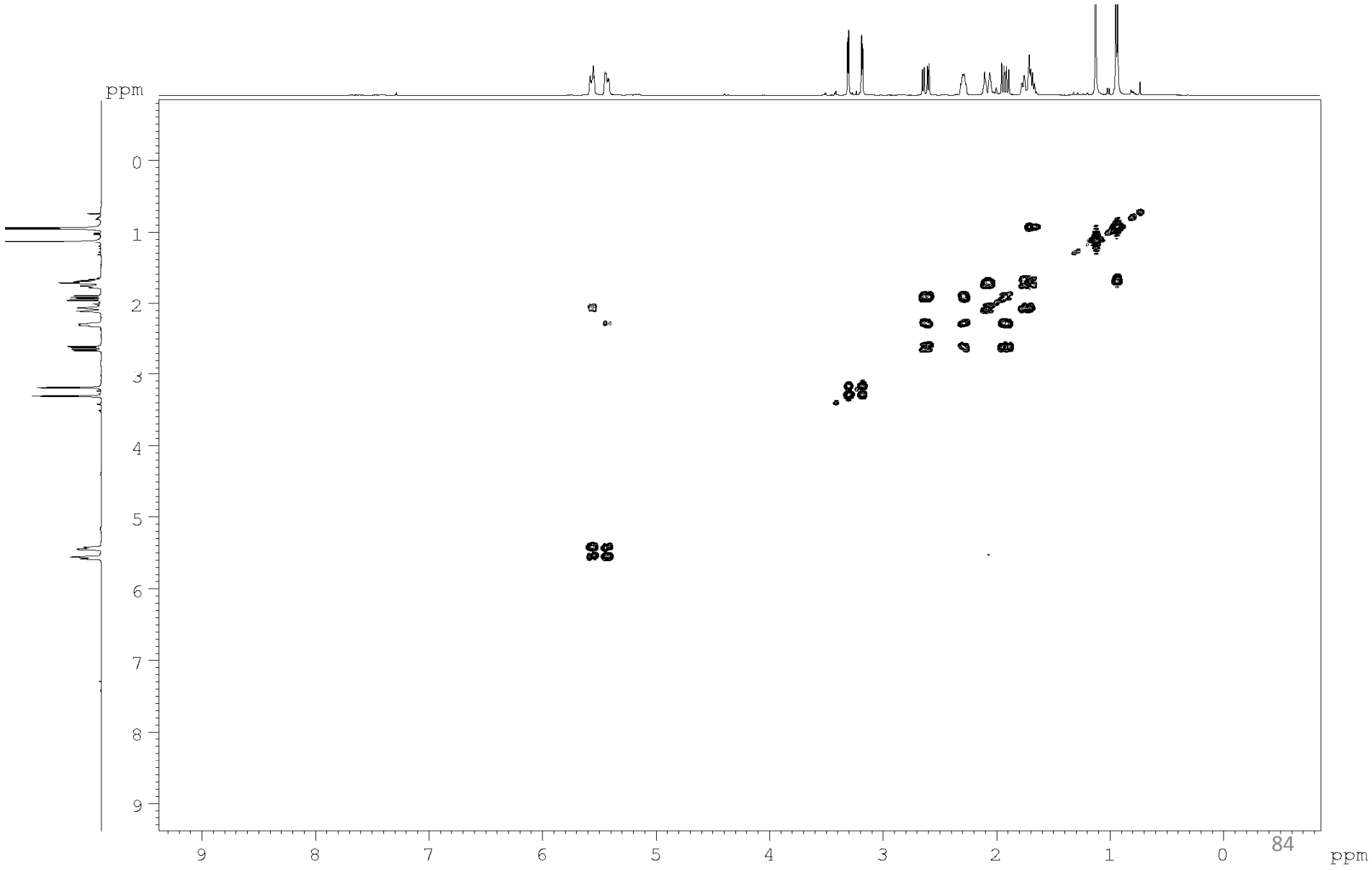


2D NMR Spectra for 9

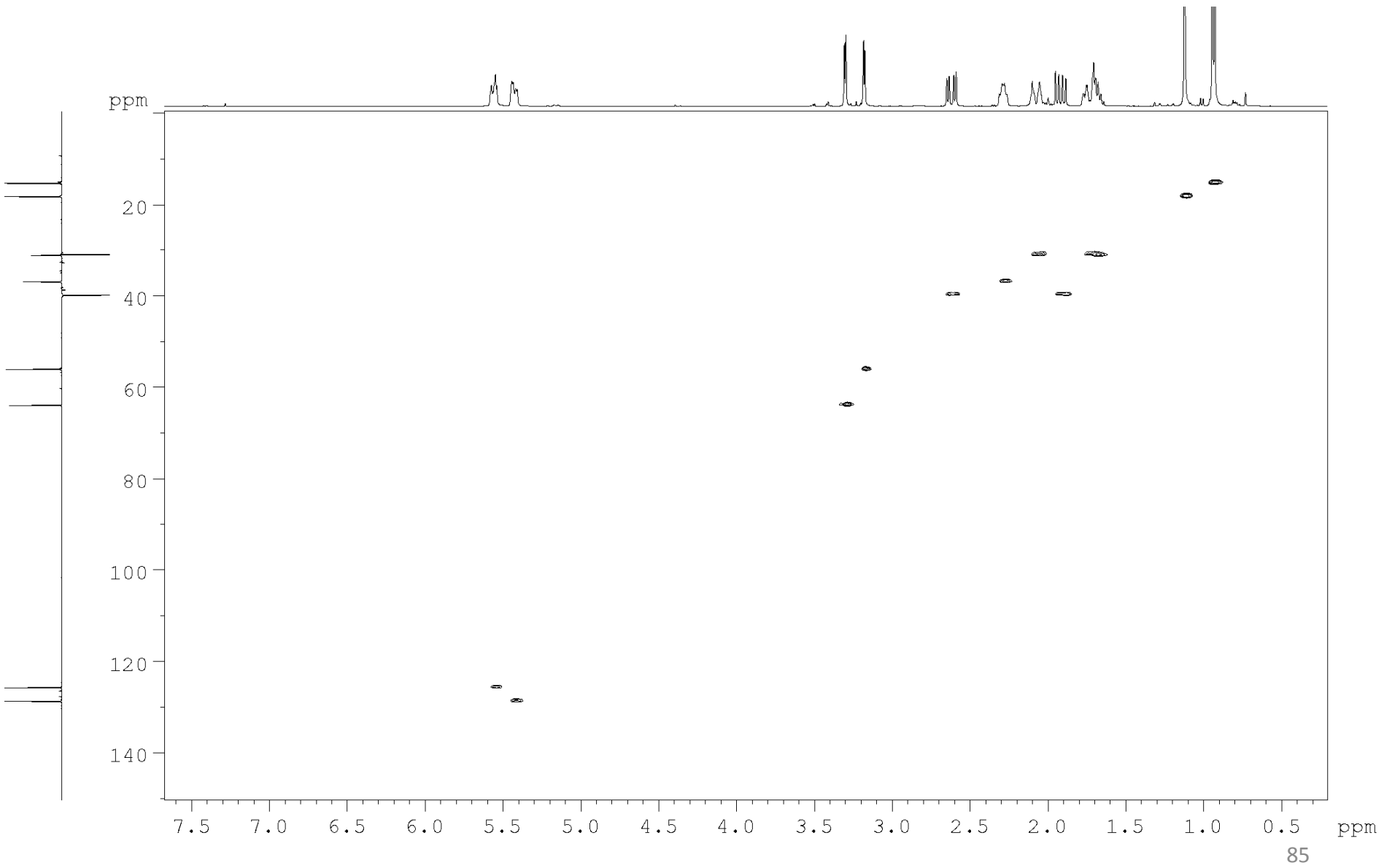


9

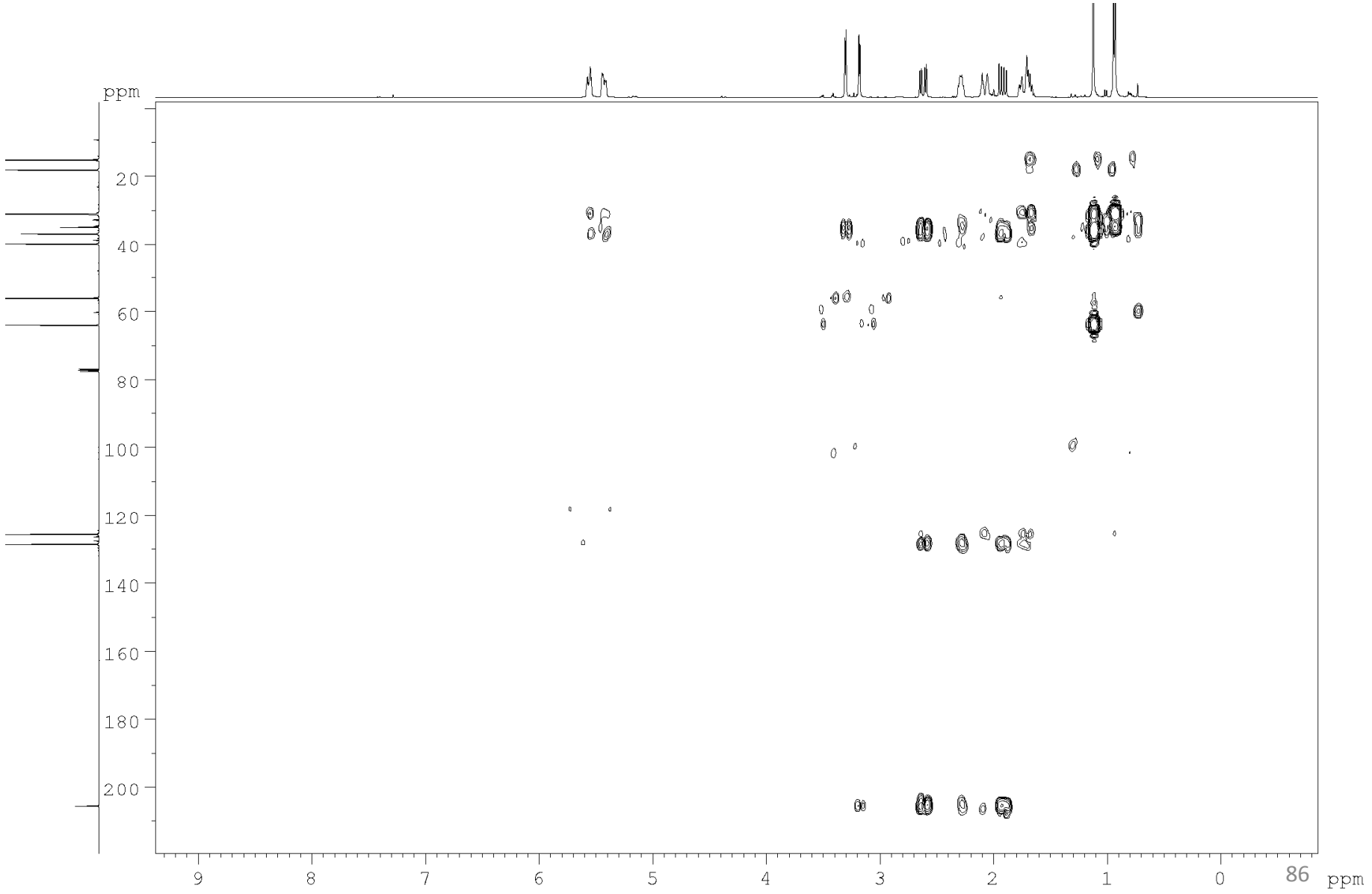
^{1}H-^{1}H COSY spectrum of 9 ($CDCl_3$; 400 MHz)



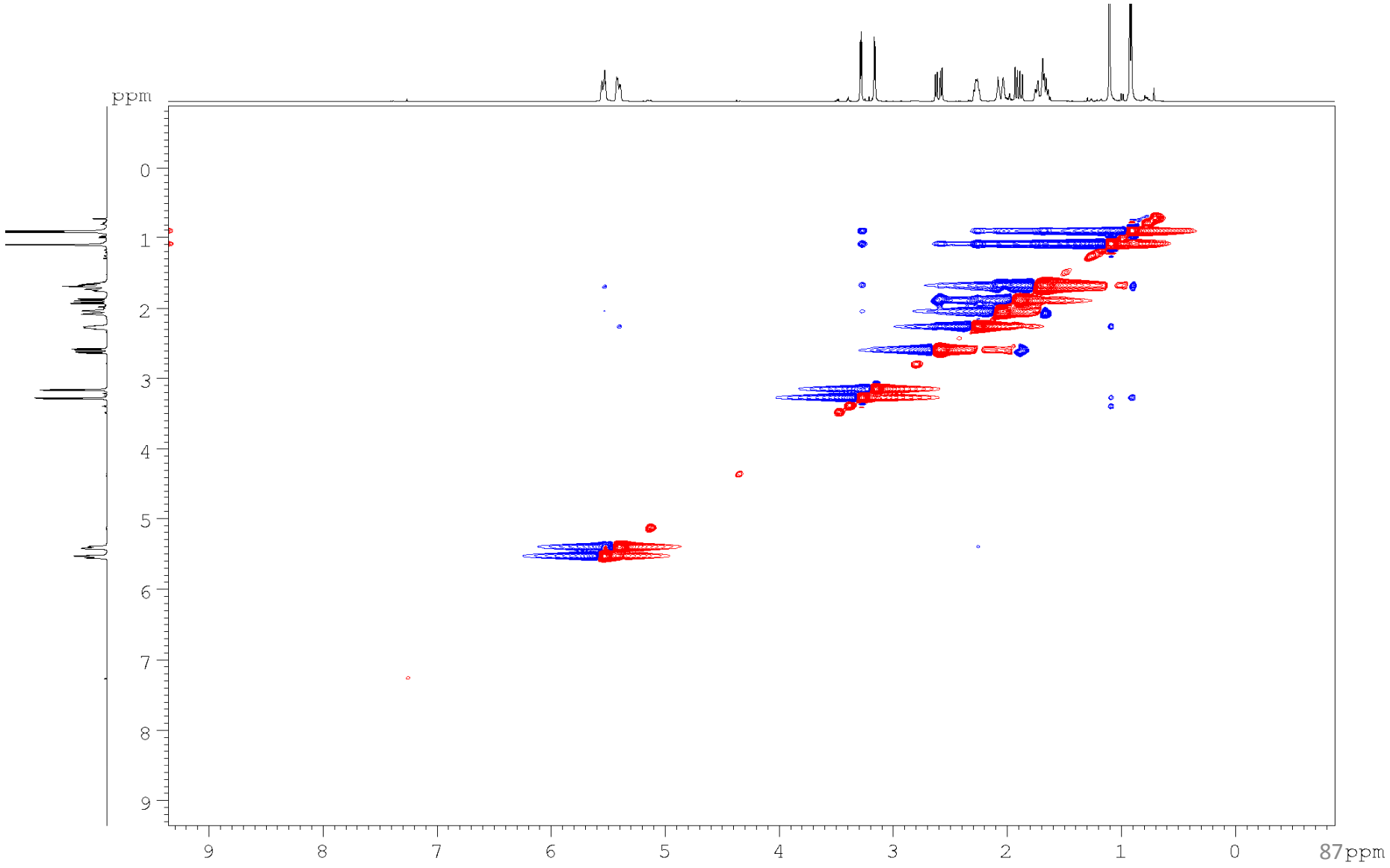
HSQC Spectrum of 9 ($CDCl_3$; 400 MHz)

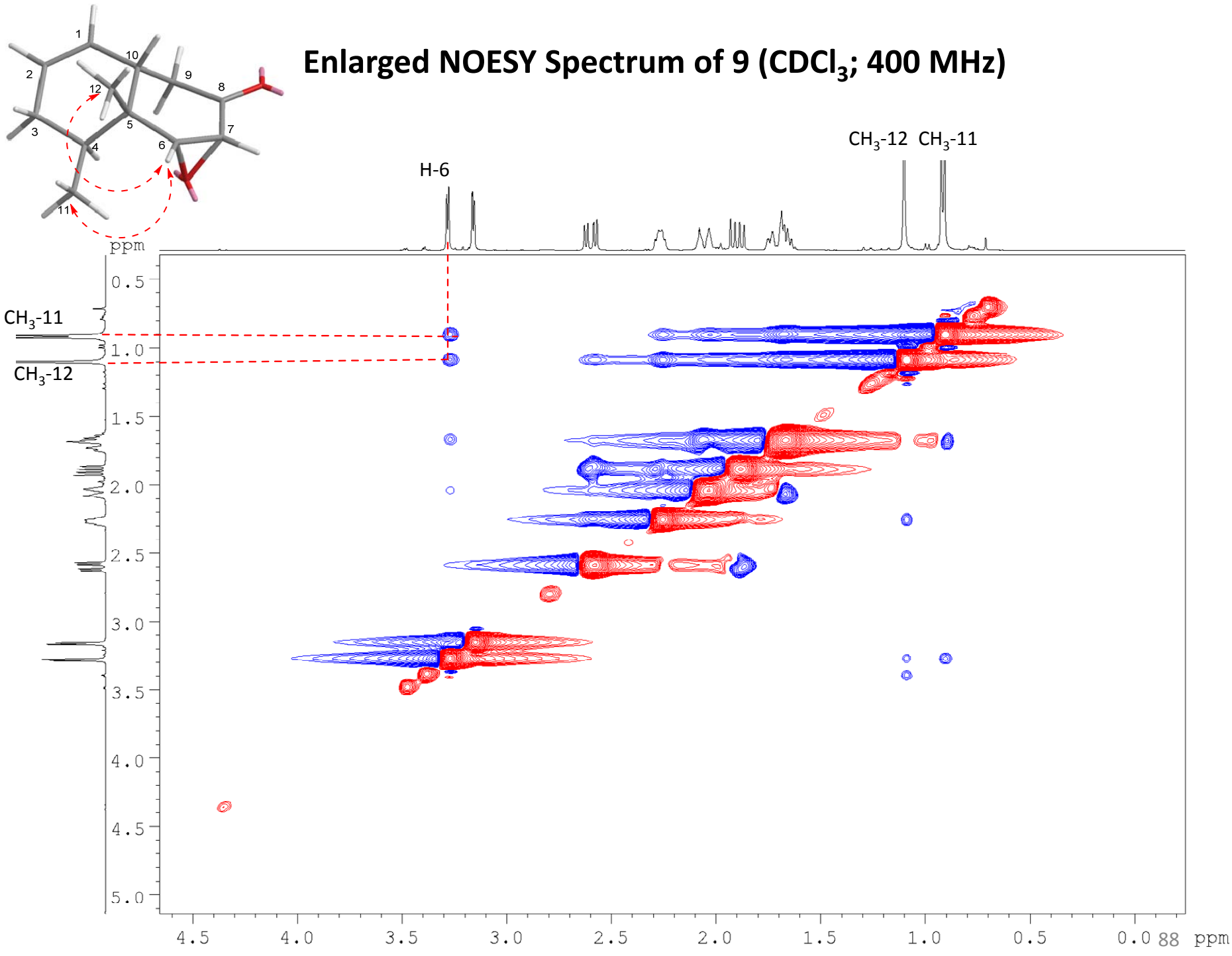


HMBC Spectrum of 9 ($CDCl_3$; 400 MHz)

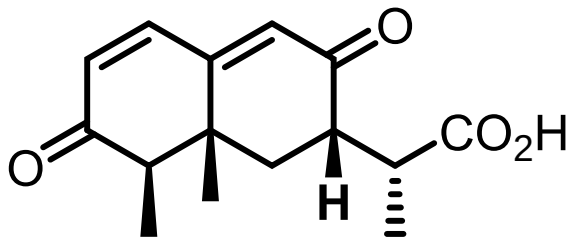


NOESY Spectrum of 9 ($CDCl_3$; 400 MHz)



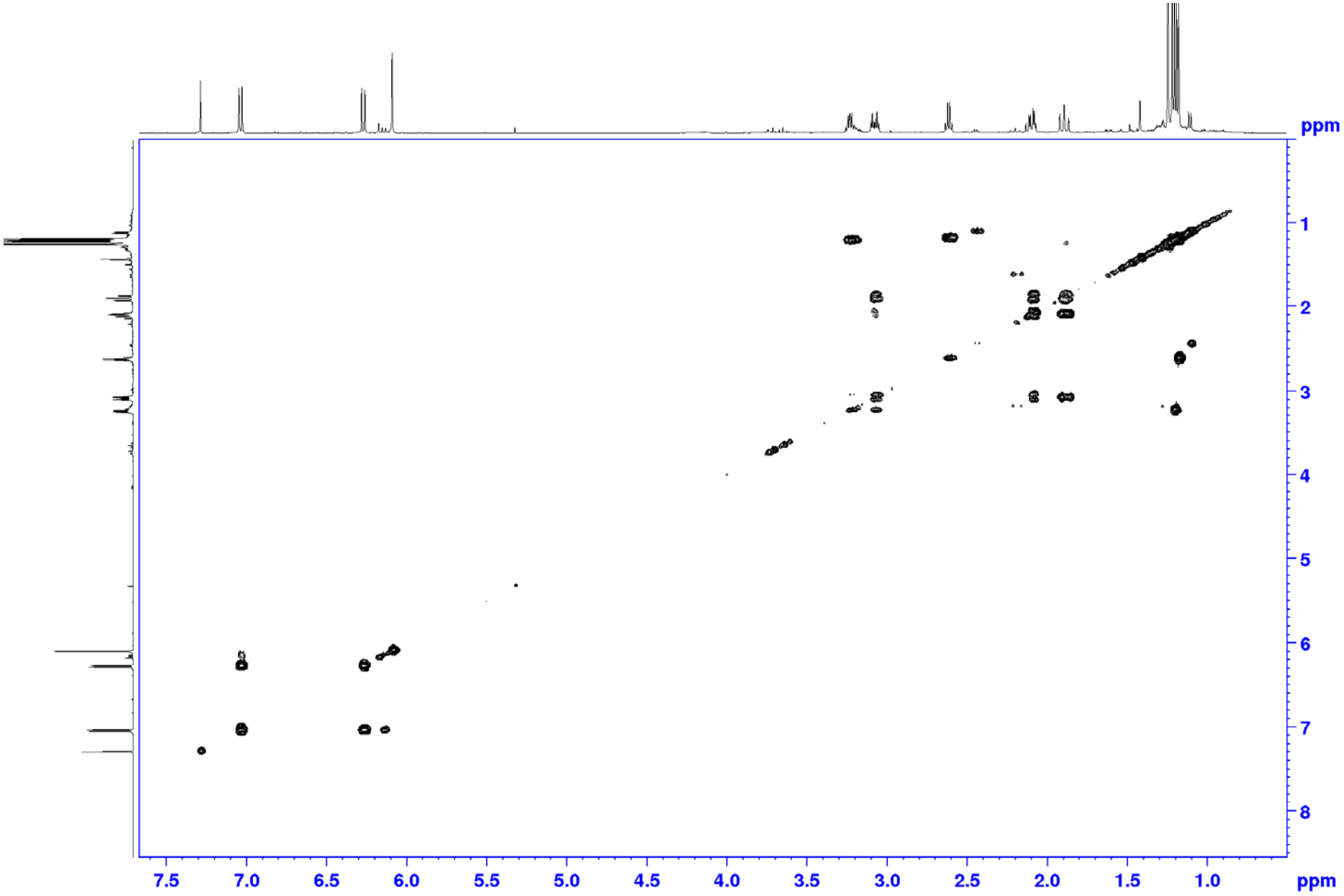

Enlarged NOESY Spectrum of 9 (CDCl3; 400 MHz)
1
2
3
4
5
6
7
8
9
10
11
12
H-6
CH3-12 CH3-11
CH3-11
CH3-12
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

2D NMR Spectra for 19

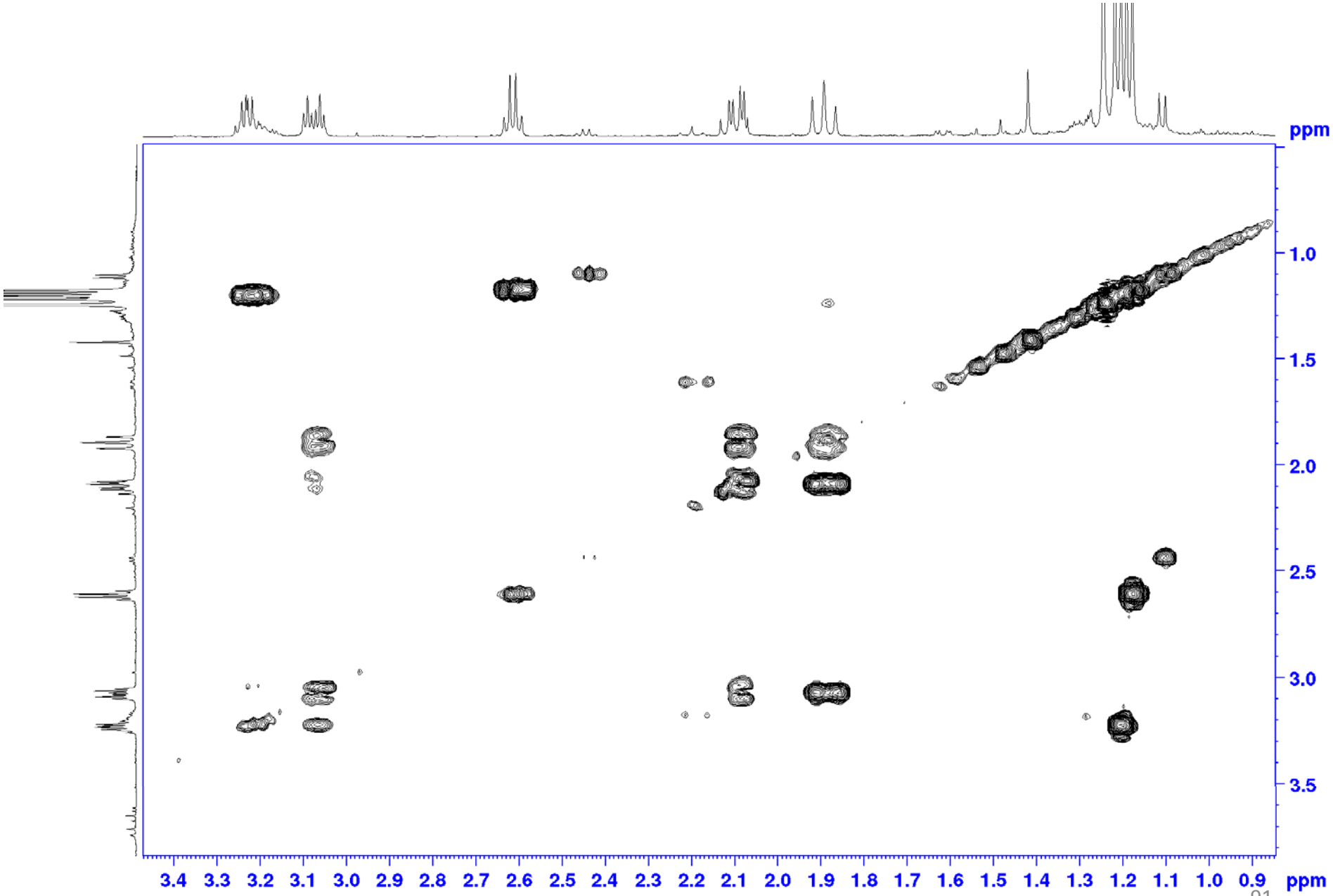


19

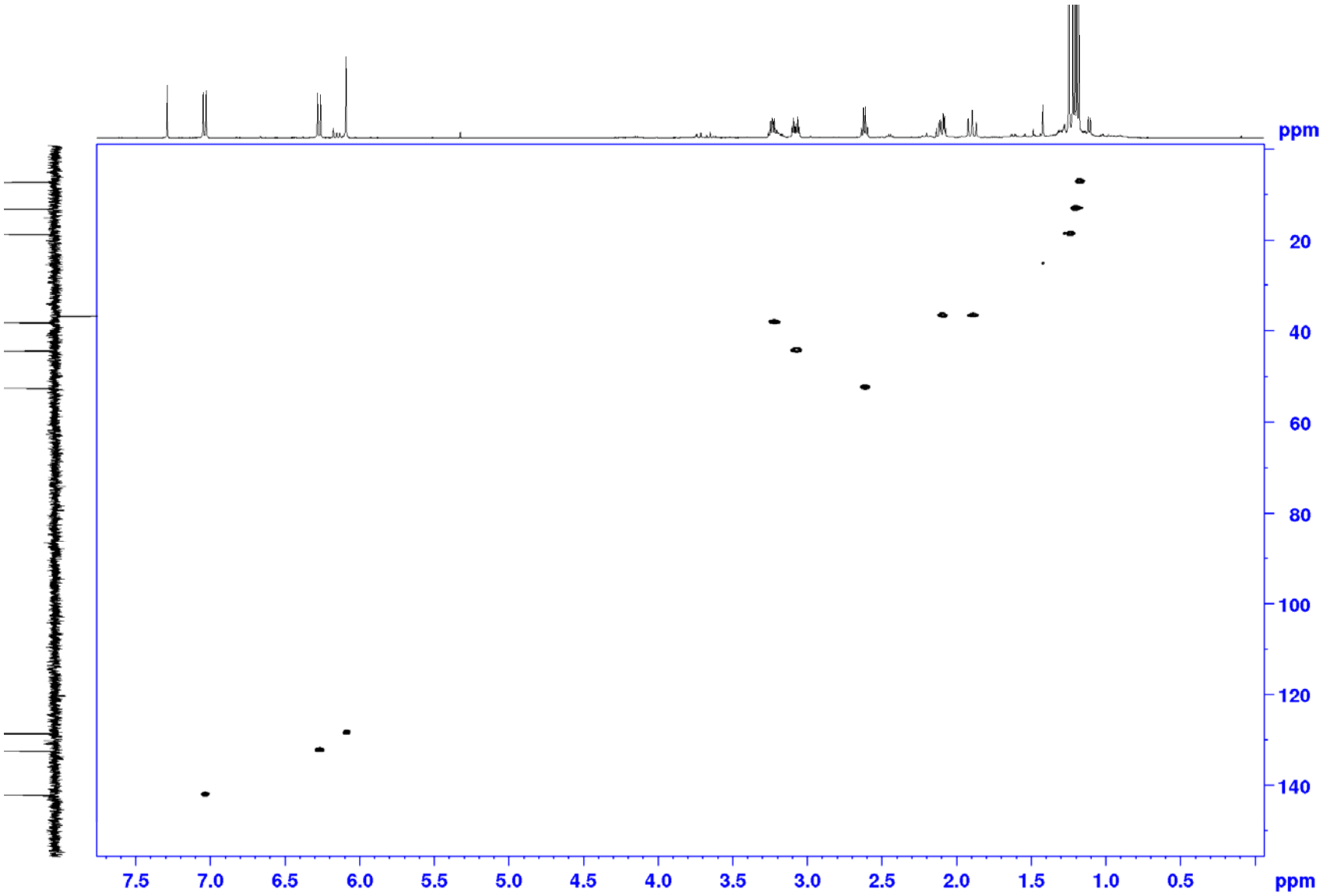
^{1}H-^{1}H COSY spectrum of 19 ($CDCl_3$; 400 MHz)



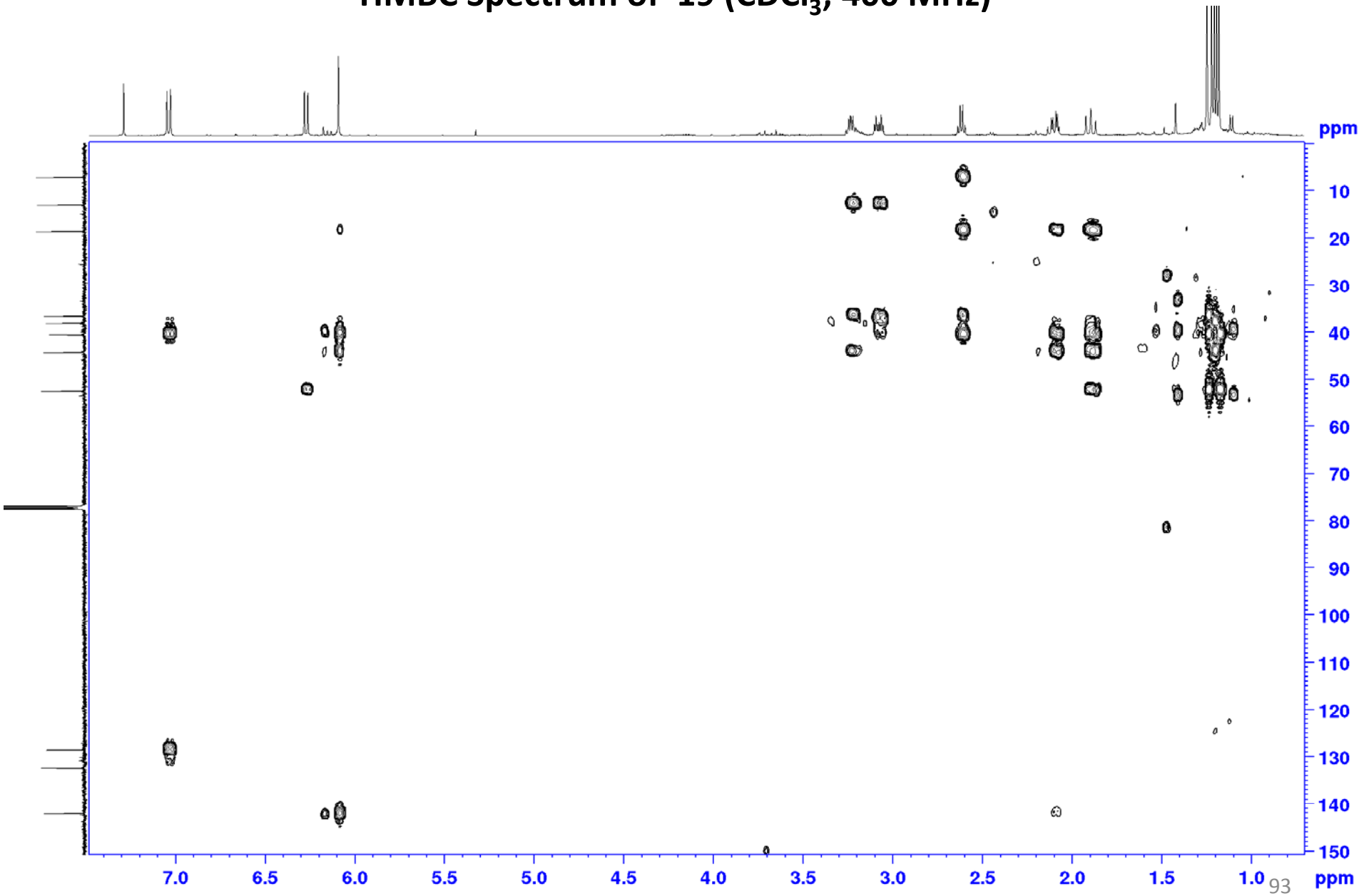
Enlarged ^{1}H-^{1}H COSY spectrum of 19 ($CDCl_3$; 400 MHz)



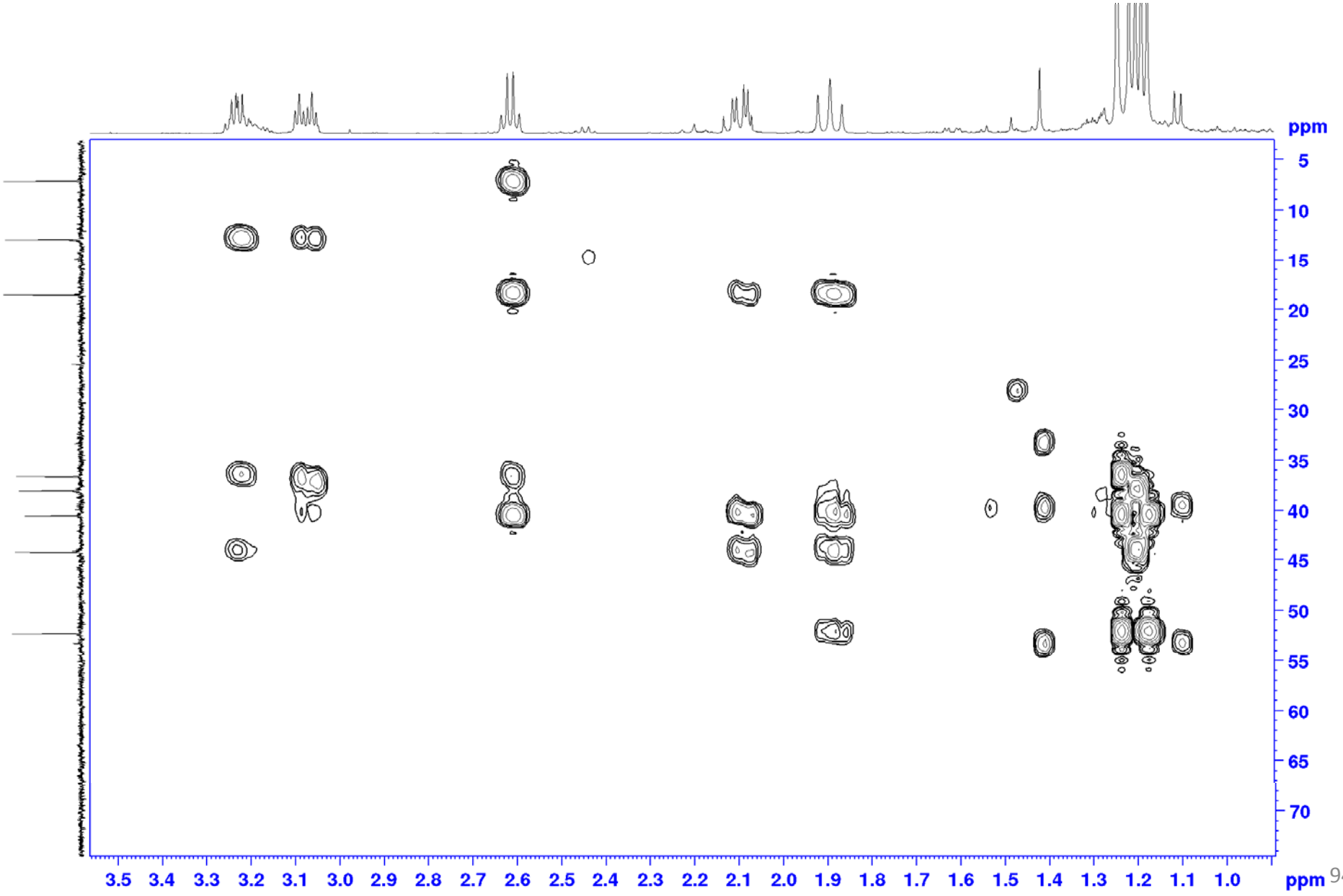
HSQC Spectrum of 19 ($CDCl_3$; 400 MHz)



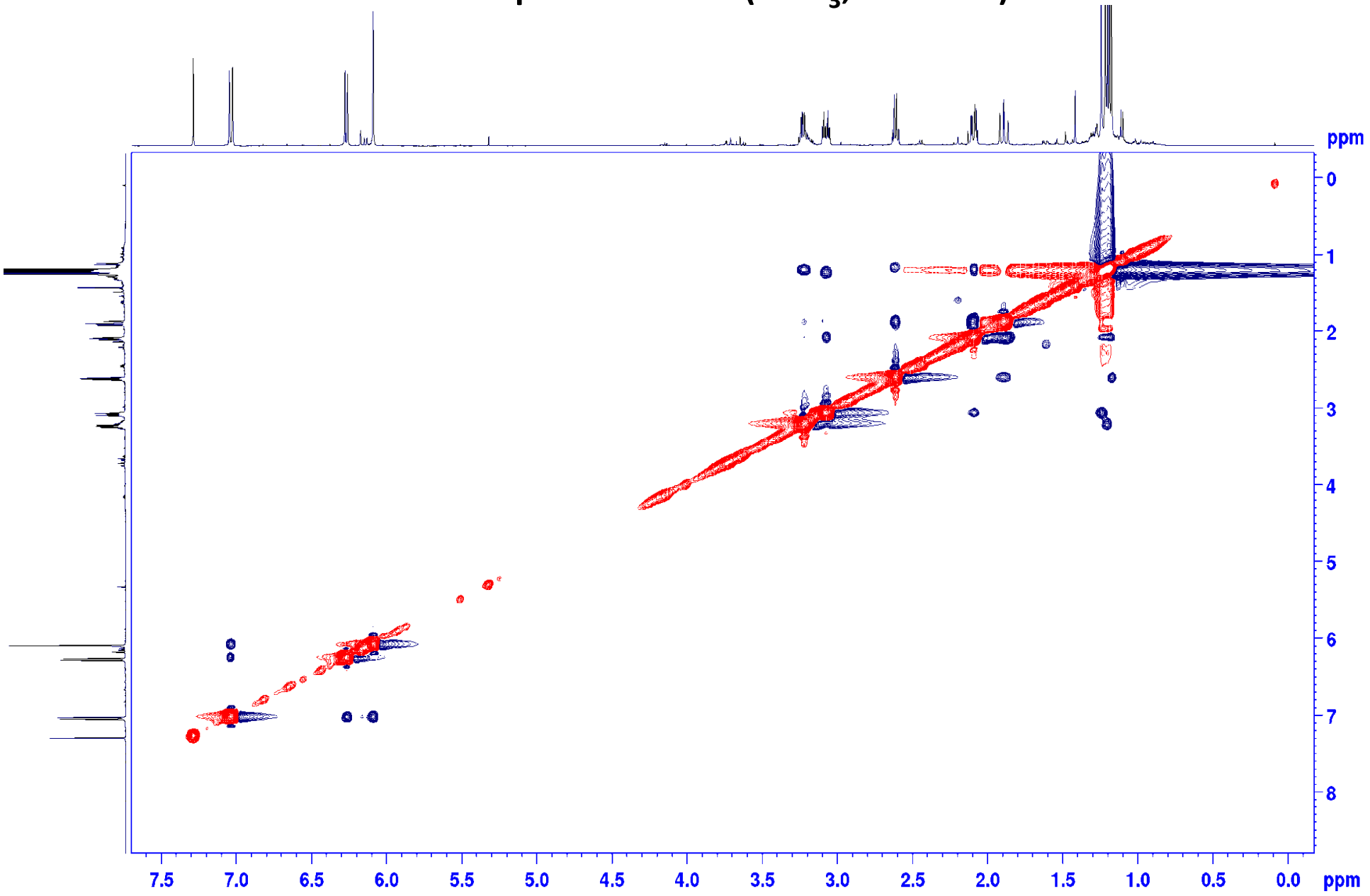
HMBC Spectrum of 19 ($CDCl_3$; 400 MHz)



Enlarged HMBC Spectrum of 19 ($CDCl_3$; 400 MHz)



NOESY Spectrum of 19 ($CDCl_3$; 400 MHz)



Enlarged NOESY Spectrum of 19 ($CDCl_3$; 400 MHz)