Total Synthesis and Stereochemical Reassignment of Citrafungin A.

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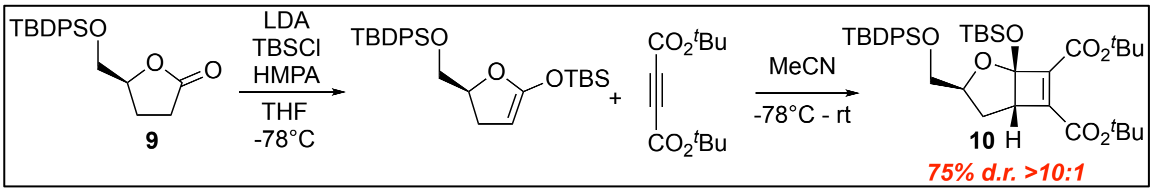
Supporting Information

Experimental Section

General

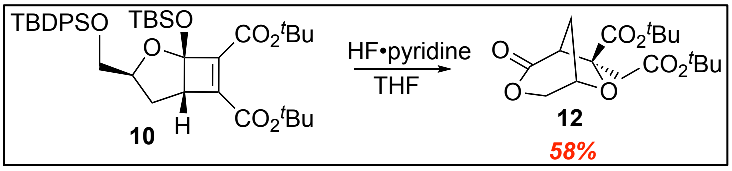
All reactions were performed under an inert argon or nitrogen atmosphere in flame-dried or oven-dried (150 °C) glassware. Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O) and dichloromethane (DCM) were obtained from a solvent dispensing system where solvents were dried by passage through two packed columns of neutral alumina under argon. Dry methanol (MeOH) was distilled from magnesium methoxide or $CaSO_4$ and stored over 4 Å molecular sieves. Dry triethylamine (NEt_3) and acetonitrile (MeCN) were freshly distilled from calcium hydride under nitrogen atmosphere. Diisopropylamine (DIPA) was distilled from NaOH under nitrogen or argon atmosphere immediately prior to use. Hexamethylphosphoramide (HMPA) and *N,N*-dimethylformamide (DMF) were dried by storage over 4 Å molecule sieves. All other commercial reagents were used as received. Brine refers to a saturated aqueous solution of NaCl and petrol refers to petroleum spirits of the fraction boiling between 40 and 60 °C. Flash chromatography was carried out using silica gel 60. Analytical thin layer chromatography (TLC) was conducted on aluminium backed plates (2 mm silica gel 60 F_{254}) and chromatograms were visualised under UV light (365 nm) and with solutions of 20% w/w phosphomolybdic acid in ethanol (PMA), 20% w/w potassium permanganate in water (PP) or 5% w/v cerium (IV) ammonium molybdate and 1% w/v ceric sulphate in dilute sulphuric acid (CAM). Melting points were obtained in open capillaries and are uncorrected. Optical rotations were recorded at 22 °C in a 10.0 cm microcell and units are deg.cm^2g^{-1}. Infrared (IR) spectra were recorded using an attenuated total reflectance (ATR) attachment. High-resolution mass spectra (HRMS) were obtained using electrospray ionisation (ESI). Nuclear magnetic resonance (NMR) spectra were recorded at 400, 500 or 600 MHz and chemical sifts (δ) were internally referenced to the residual proton resonance $CDCl_3$ (δ 7.26 ppm), CD_3CN and CD_3OD (δ 3.31 ppm).

Cyclobutene diester 10



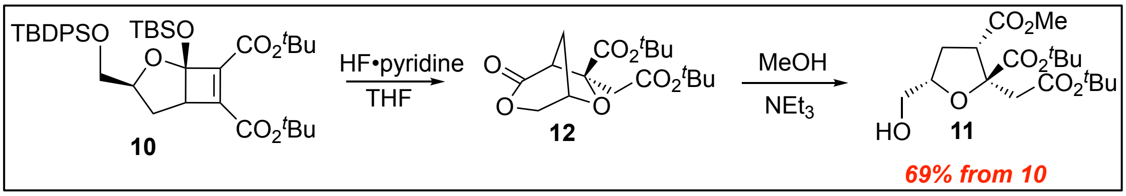
To a solution of diisopropylamine (4.2 mL, 30.2 mmol) in THF (8 mL) at -78 °C was added ^{n}BuLi (2.5 M in hexanes, 11.3 mL, 28.2 mmol) and the resultant solution was warmed to 0 °C for 10 minutes. The solution was cooled again to -78 °C and a solution of lactone **9** (5 g, 14.1 mmol) in THF (10 mL) was added dropwise (1.0 mL/min) and the resultant mixture stirred at -78 °C for 1.5 hours. A solution of TBSCl (2.76 g, 18.3 mmol) and HMPA (2 mL) in THF (10 mL) was then added dropwise (1.0 mL/min) and the reaction mixture stirred for an additional 30 mins at -78 °C then 1 h at rt. The mixture was then cooled to 0 °C, diluted with hexane (25 mL), quenched with water (25 mL) and the organic layer was washed with water, brine then dried over Na_2SO_4 and concentrated to afford the crude silyl ketene acetal, which was immediately dissolved in CH_2Cl_2 (20 mL) and cooled to -78 °C. Di-*tert*-butyl but-2-ynedioate (3.19g, 14.1 mmol) was added and the solution allowed to warm to rt and stirred overnight. The solvent was removed under reduced pressure and purification by flash chromatography with 5% EtOAc/petrol as eluent to afford the cyclobutene **10** (7.35 g, 75%), as a yellow oil. $[\alpha]_D = -12.8$ (*c* 1.15, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.19 (s, 3H), 0.90 (s, 9H), 1.06 (s, 9H), 1.51 (s, 9H), 1.52 (s, 9H), 1.72 (m, 1H), 1.91 (dd, J = 12.9, 5.1 Hz, 1H), 3.21 (d, J = 7.6 Hz, 1H), 3.91 - 3.80 (m, 2H), 4.03 (dq, J = 9.6, 4.7 Hz, 1H), 7.47 - 7.33 (m, 6H), 7.69 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -3.3, -2.9, 17.9, 19.4, 25.8, 27.0, 28.0, 28.2, 28.2, 28.3, 55.1, 65.0, 78.8, 81.9, 82.3, 106.1, 127.8, 127.8, 129.8, 129.8, 133.5, 133.6, 135.7, 135.8, 140.3, 143.0, 159.8, 161.6. IR (thin film): 702, 838, 1112, 1255, 1275, 1713, 2858, 2931, 2959 cm^{-1}. HRMS (ESI) calc. for $C_{39}H_{59}O_7Si_2$: $(M + H)^+$, 695.3800, found: $(M + H)^+$, 695.3799.

Lactone 12



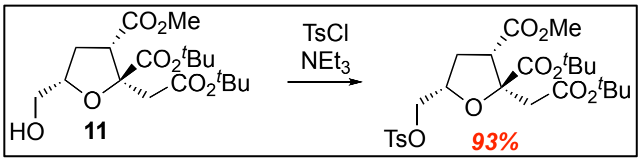
To a solution of cyclobutene **10** (3 g, 4.32 mmol) in THF (25 mL) was added HF•pyridine (70%, 1.1 mL, 43.2 mmol) and the resultant solution stirred at rt for 24 hours. The mixture was diluted with EtOAc (25 mL), quenched with solid $NaHCO_3$ (5 g) and the result suspension was filtered through a pad of celite and the filter cake was washed with EtOAc. The solvent was concentrated under reduced pressure. Purification by flash chromatography with 50% EtOAc/Petrol as eluent afforded lactone **12** (857 mg, 58%) as a yellow solid. m.p. 107.3-111.0°C. $[\alpha]_D = +39.5$ (*c* 1.15, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.47 (s, 9H), 2.10 (d, *J* = 12.2, 1H), 2.54 (dddd, *J* = 12.1, 5.9, 4.2, 1.8 Hz, 1H), 2.69 (d, *J* = 17.2 Hz, 2H), 3.01 (d, *J* = 17.2 Hz, 1H), 3.31 (dt, *J* = 4.0, 0.8 Hz, 1H), 4.20 (dd, *J* = 11.7, 1.8 Hz, 1H), 4.33 (dt, *J* = 11.7, 1.0 Hz, 2H), 4.67 (br d, *J* = 5.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 27.9, 28.2, 28.8, 29.8, 41.6, 49.2, 74.0, 75.6, 81.7, 82.6, 84.3, 168.6, 168.9, 169.6. IR (film): 1058, 1094, 1148, 1223, 1363, 1725, 1751, 2953, 2981 cm^{-1}. HRMS (ESI): calc. for $C_{17}H_{26}O_7Na$: $(M + Na)^+$, 365.1577, found: $(M + Na)^+$, 365.1572.

Alcohol 11



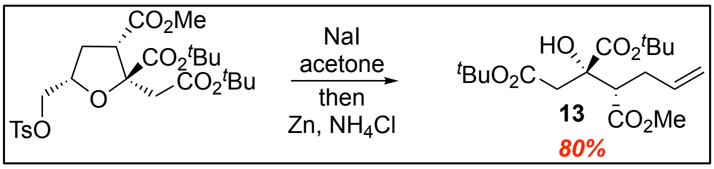
To a solution of cyclobutene **10** (3 g, 4.3 mmol) in THF (25 mL) was added HF•pyridine (70%, 1.1 mL, 43.2 mmol) and the resultant solution stirred at r.t. for 24 hours. The mixture was diluted with EtOAc (25 mL), quenched with solid $NaHCO_3$ (5 g) and the resultant suspension was filtered through a pad of Celite and the fliter cake was washed with EtOAc. The solvent was concentrated under reduced pressure. The crude lactone **12** was dissolved in MeOH (25 mL) and NEt_3 (3.0 mL, 21.6 mmol) was added and the resultant solution stirred at rt. for 16 h. Concentration of the reation mixture under reduced pressure and purification of the crude product by flash chromatography (50% EtOAc/Petrol) afforded alcohol **11** (1.11 g, 69%, over 2 steps) as a yellow oil. $[\alpha]_D = +47.1$ (*c* 1.12, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.48 (s, 9H), 2.19 (ddd, *J* = 12.7, 7.6, 7.0 Hz, 1H), 2.43 (dt, *J* = 12.7, 9.2 Hz, 1H), 2.80 (ABq, *J* = 15.0 Hz, 2H), 3.36 (dd, *J* = 9.1, 7.9 Hz, 1H), 3.53 (dd, *J* = 12.4, 3.1 Hz, 1H), 3.70 (s, 3H), 3.90 (dd, *J* = 12.4, 2.6 Hz, 1H), 4.33 (ddt, *J* = 6.3, 6.0, 3.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.0, 28.1, 30.0, 41.1, 50.8, 52.2, 63.0, 80.7, 81.8, 82.3, 84.7, 169.7, 170.3, 172.2. IR (film): 845, 1060, 1147, 1367, 1730, 2934, 2979, 3466 cm^{-1}. HRMS (ESI) calc. for $C_{18}H_{30}O_8Na$: $(M + Na)^+$, 397.1839, found: $(M + Na)^+$, 397.1835.

Tosylate



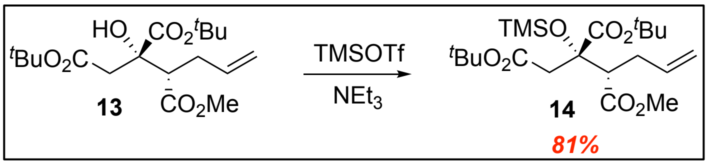
To a solution of alcohol **11** (2 g, 5.34 mmol) in dry CH_2Cl_2 (26 mL) at 0°C was added TsCl (1.52 g, 8.01 mmol), NEt_3 (2.2 mL, 16.02 mmol) and DMAP (65 mg, 0.53 mmol) and after stirring for 30 min, the reaction was warmed to rt over 2h. The resulting deep purple solution was diluted with EtOAc and H_2O and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with 1 M aqueous HCl, sat.aqueous $NaHCO_3$, H_2O and brine then dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography with 20% EtOAc/petrol as eluent to give tosylate (2.62 g, 93%) as a yellow oil. $[\alpha]_D = +35.7$ (*c* 1.2, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.45 (s, 9H), 2.09 (dt, *J* = 13.2, 6.6 Hz, 1H), 2.31 (dt, *J* = 13.1, 7.8 Hz, 1H), 2.43 (s, 3H), 2.68 (ABq, *J* = 16.9 Hz, 2H), 3.36 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.67 (s, 3H), 4.13 (d, *J* = 5.5 Hz, 2H), 4.39 (m, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.8, 27.9, 28.1, 31.8, 40.4, 49.8, 52.2, 70.7, 76.8, 81.3, 82.3, 85.7, 128.2, 129.9, 132.9, 144.9, 168.8, 170.4, 172.2. IR (thin film): 664, 814, 836, 958, 984, 1146, 1174, 1365, 1732, 2979 cm^{-1}. HRMS (ESI) calc. for $C_{25}H_{36}O_{10}SNa$: $(M + Na)^+$, 551.1927, found: $(M + Na)^+$, 551.1924.

Alkene 13



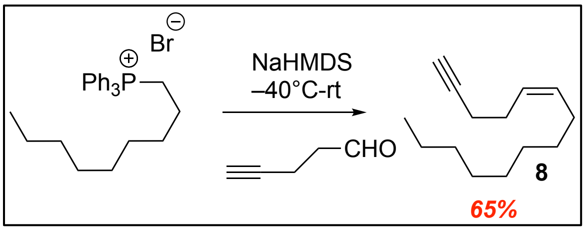
A solution of the tosylate (2.51 g, 4.7 mmol) and sodium iodide (11.98 g, 47.3 mmol) in acetone (30 mL) was heated to reflux for 12 h then cooled and filtered through a pad of celite. The filtrate was concentrated and the residue was dissolved in EtOH (95%, 50 mL) and activated zinc power (3.09 g, 47.3 mmol) and NH_4Cl (1.26 g, 23.6 mmol) were added and the mixture was stirred at rt for 3 h. The mixture was diluted with Et_2O (50 mL), filtered through a pad of celite. The filtrate was concentrated and the residue was purified by flash chromatography with 10% EtOAc/petrol as eluent to afford the alkene **13** (2.02 g, 80%) as a clear oil. $[\alpha]_D$= +10.6 (*c* 0.67, CH_2Cl_2).^1H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.49 (s, 9H), 2.30 (m, 1H), 2.51 (m, 1H), 2.62 (d, *J* = 16.7 Hz, 1H) 2.73 (dd, *J* = 11.9, 3.1 Hz, 1H), 2.98 (d, *J* = 16.7 Hz, 2H), 3.69 (s, 3H), 3.96 (s, 1H), 5.00 (d, *J* = 9.8 Hz, 1H), 5.05 (dd, *J* = 17.1 Hz, 1H), 5.67 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) 27.9, 28.2, 31.6, 41.8, 51.9, 53.7, 75.2, 81.6, 83.4, 117.3, 135.0, 170.0, 172.2, 172.8. IR (film): 8451 1149, 1249, 1368, 1730, 2935, 2980, 3484 cm^{-1}. HRMS (ESI) calc. for $C_{18}H_{30}O_7Na$: $(M + Na)^+$, 381.1890, found: $(M + Na)^+$, 381.1887.

Silyl ether 14



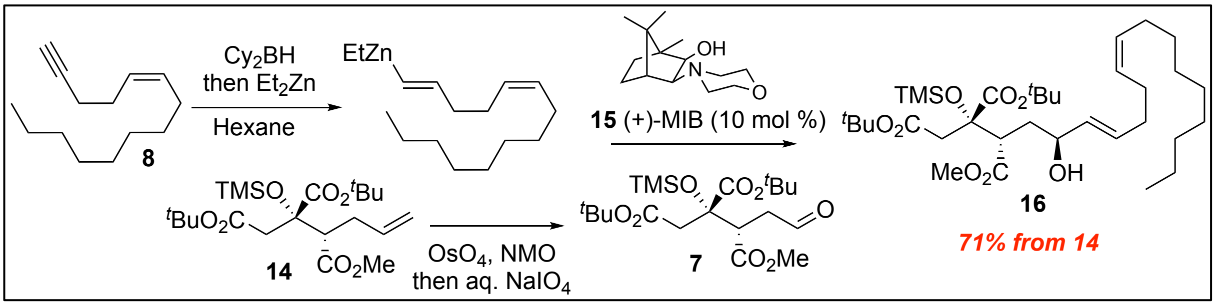
To a solution of Et_3N (300 µl, 2.1mmol) and triester **13** (500mg, 1.4 mmol) in anhydrous CH_2Cl_2 (10ml) at 0 °C was added TMSOTf (370, 1.7 mmol) and the solution was stirred for 2h. The mixture was warmed to rt and stirred for 1h the cooled to 0 °C, diluted with petroleum ether and quenched with H_2O. The aqueous phase was extracted with petroleum ether and the combined organic layers were washed with brine then dried over Na_2SO_4 and concentrated. Purification by flash chromatography with 5% EtOAc/petrol as eluent afforded silyl ether **14** (488 mg, 81%) as a clear oil. $[\alpha]_D$= +5.6 (*c* 2.0, CH_2Cl_2). ^1H NMR (600 MHz, $CDCl_3$) δ 0.16 (s, 9H), 1.43 (s, 9H), 1.46 (s, 9H), 2.50 - 2.37 (m, 2H), 2.62 (d, *J* = 16.0 Hz, 1H), 2.78 (dd, *J* = 11.5, 3.4 Hz, 1H), 2.96 (d, *J* = 16.0 Hz, 1H), 3.65 (s, 3H), 5.00 (dd, *J* = 10.1, 0.7 Hz, 1H), 5.05 (dq, *J* = 17.6, 1.5 Hz, 2H), 5.68 (dddd, *J* = 17.0, 10.1, 7.1, 6.6, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 2.6, 28.0, 28.3, 32.2, 42.7, 51.6, 54.8, 78.7, 80.6, 82.2, 117.0, 135.4, 169.1, 171.5, 172.5. IR (film): 840, 1145, 1247, 1368, 1738, 2954, 2980 cm^{-1}. HRMS (ESI) calc. for $C_{21}H_{38}O_7SiNa$: $(M + Na)^+$, 453.2285, found: $(M + Na)^+$, 453.2278.

Alkyne 8 (Procedure reported by Barrett *et al.*)[1]



To a solution of (1-nonyl)triphenylphosphonium bromide (5.4 g, 11.5 mmol) in anhydrous THF (50 ml) was added LiHMDS in THF (1 M; 10.6 mL, 10.6 mmol) dropwise at -40 ºC. The resulting red-orange solution was warmed to 0 ºC for 1h and cooled back to -40 ºC. 4-Pentynal (788 mg, 9.6 mmol) in THF (5 mL) was added dropwise and the mixture was warmed to 0 ºC for 3h. The resulting yellow solution was diluted with Et_2O (50 mL) and quenched with sat. NH_4Cl. The organic layer was washed with brine, dried $MgSO_4$ and concentrated. Purification of the residue by flash chromatography with petrol as eluent afforded alkyne **8** (1.2 g, 65%) as a colourless oil. ^1H NMR (600 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.9, 3H), 1.38 - 1.20 (m, 12H), 1.94 (t, *J* = 2.4 Hz, 1H), 2.04 (q, *J* = 7.2 Hz, 2H), 2.31 - 2.19 (m, 4H), 5.37-5.47 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.3, 19.0, 22.8, 26.5, 27.5, 29.5, 29.7, 29.8, 32.0, 68.4, 84.4, 127.5, 131.9. IR (film): 722, 1465, 2854, 2924, 2956, 3314 cm^{-1}.

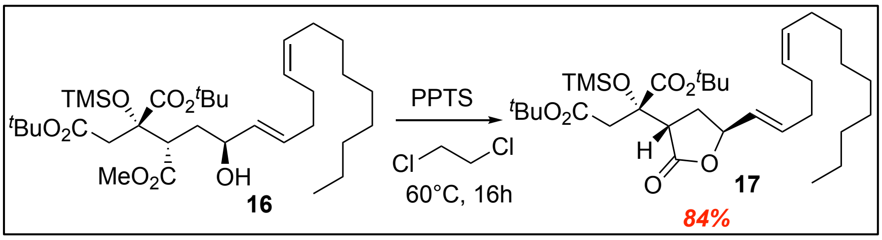
Allylic alcohol 16



To a solution of NMO (140 mg, 1.15 mmol) and alkene **14** (100 mg, 0.23 mmol) in THF/H_2O (3:1, 4 ml) was added OsO_4 (59 µl, 0.39M in benzene, 0.023 mmol) and the resultant mixture was stirred for 4h. $NaIO_4$ (197 mg, 0.92 mmol) was then added and the mixture was stirred for a further 16h. The reaction mixture was diluted with Et_2O and quenched with sat. aqueous $Na_2S_2O_3$. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with H_2O, brine then dried over Na_2SO_4 and concentrated. The crude aldehyde **7** (99.4 mg, 0.23 mmol, 100%) was used directly next reaction without further purification.

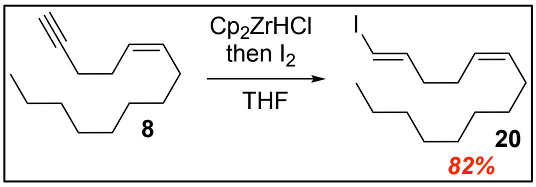
To a suspension of freshly prepared Cy_2BH (110 mg, 0.62 mmol) in anhydrous hexane (1 ml) at 0 °C was added a solution of alkyne **8** (133 mg, 0.69 mmol) in hexane (1 ml) dropwise. The suspension was warmed to rt and stirred for 1h until a clear solution was obtained. This solution was cooled to -78 °C and a solution of $ZnEt_2$ (1 M in hexanes, 620 μL, 0.62 mmol) was added followed by and a solution of (+)-MIB^2 (11 mg, 0.046 mmol) in hexane (1 ml) dropwise. The reaction mixture was warmed to -20 °C for 1h to form a grey suspension and a solution of crude aldehyde in hexane (1 ml) was added dropwise. The suspension was stirred under 0 °C for 2h and quenched with H_2O. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine then dried over Na_2SO_4 and concentrated. Purification by flash chromatography with 10% EtOAc/petrol as eluent afforded allylic alcohol **16** (102 mg, 71% over 2 steps) as a clear oil. $[\alpha]_D = -3.6$ (*c* 1.3, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 9H) 0.88 (t, *J* = 6.8 Hz, 3H), 1.22-133 (m, 12H), 1.43 (s, 9H), 1.47 (s, 9H), 1.61 (m, 1H), 1.81 (ddd, *J* = 13.8, 8.6, 2.2 Hz, 1H), 1.98 – 2.11 (m, 6H), 2.60 (d, *J* = 16.0 Hz, 1H), 2.93 (d, *J* = 16.0 Hz, 1H), 3.03 (dd, *J* = 11.6, 1.8 Hz, 1H), 3.68 (s, 3H), 3.98 (br s, 1H), 5.32 - 5.39 (m, 2H), 5.47 (dd, *J* = 15.4, 6.8 Hz, 1H), 5.66 (dt, *J* = 15.4, 6.1 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 2.6, 14.3, 22.81, 22.83, 27.0, 27.4, 28.0, 28.3, 29.5, 29.5, 29.7, 29.9, 31.7, 32.0, 32.5, 35.6, 42.8, 50.9, 51.8, 71.0, 78.8, 80.7, 82.2, 128.8, 130.8, 131.8, 132.7, 169.3, 171.5, 173.3. IR (film): 844, 1151, 1247, 1368, 1740, 2856, 2927, 2955, 3491 cm^{-1}. HRMS (ESI) calc. for $C_{34}H_{62}O_8SiNa$: $(M + Na)^+$, 649.4112, found: $(M + Na)^+$, 649.4109.

Lactone 17



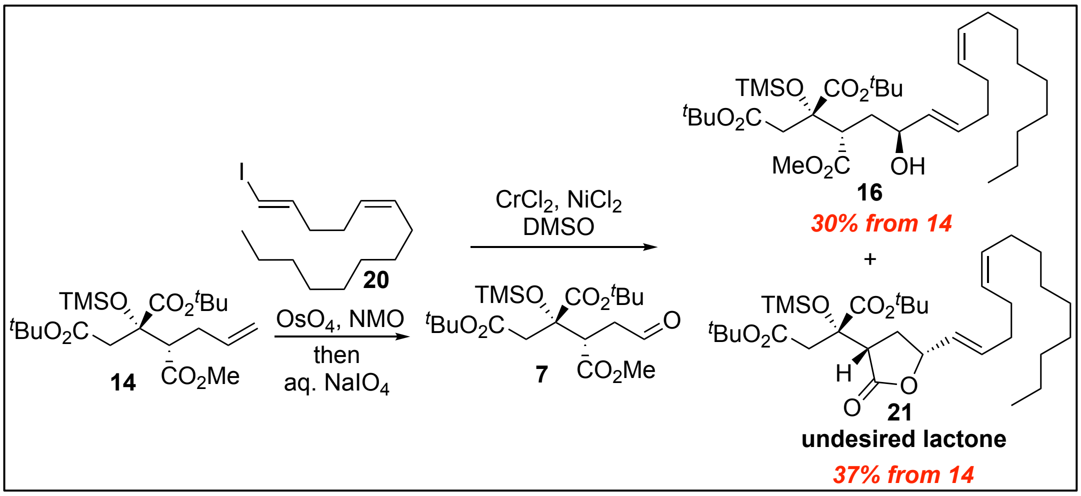
To a solution of the alcohol **16** (80 mg, 0.13 mmol) in 1,2-dichloroethane (10 mL) at 0°C was added PPTS (6.4 mg, 0.025mmol). The solution was stirred at 60°C for 16h and then concentrated. Purification by flash chromatography with 5% EtOAc/petrol as eluent afforded the lactone **17** (65 mg, 84%) as clear oil. $[\alpha]_D = -11.6$ (*c* 1.5, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.17 (s, 9H), 0.87 (t, *J* = 6.9 Hz, 3H), 1.27-1.33 (m, 12H), 1.45 (s, 9H), 1.47 (s, 9H), 1.99-2.03 (m, 3H), 2.10 - 2.13 (m, 4H), 2.48 (ddd, *J* = 13.2, 7.7, 5.4 Hz, 1H), 3.10 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.15 (s, 3H), 4.88 (q, *J* = 7.2 Hz, 1H), 5.30-5.42 (m, 2H), 5.45 (dd, *J* = 15.3, 7.3 Hz, 1H), 5.76 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 2.3, 14.3, 22.8, 26.6, 27.4, 28.0, 28.2, 29.45, 29.46, 29.6, 29.8, 31.3, 32.0, 32.3, 43.0, 48.1, 79.0, 79.8, 80.9, 82.2, 128.4, 128.7, 131.0, 134.7, 169.3, 170.7, 175.9. IR (thin film): 756, 842, 1106, 1149, 1249, 1368, 1734, 1748, 1770, 2856, 2926, 2956 cm^{-1}. HRMS (ESI) calc. for $C_{33}H_{58}O_7SiNa$: $(M + Na)^+$, 617.3850, found: $(M + Na)^+$, 617.3845.

Vinyl iodide 20 (alternative proceedure to that reported)[3]



A solution of alkyne **4** (400 mg, 2.1 mmol) in THF (10 ml) in a foil wrapped flask was treated with Schwartz's reagent (567 mg, 2.2 mmol) at -20 °C and stirred in the dark for 1h. The reaction mixture was added a solution of I_2 (304 mg, 1.2 mmol) in THF (3mL) and stirred for a further 30 min. Sat. aqueous $Na_2S_2O_3$ was then added to quench reaction. The aqueous phase was extracted with hexane and the combined organic layers were washed with brine then dried over Na_2SO_4 and concentrated. Purification by flash chromatography with 100% petrol as eluent afforded vinyl iodide **20** (551 mg, 82%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.26 - 1.30 (m, 12H), 2.00 (q, *J* = 7.0 Hz, 2H), 2.15 - 2.07 (m, 4H), 5.31 (m, 1H), 5.41 (m, 1H), 6.01 (dt, *J* = 14.3, 1.3 Hz, 1H), 6.52 (dt, *J* = 14.3, 7.0 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.3, 22.8, 26.3, 27.4, 29.5, 29.5, 29.7, 29.8, 32.1, 36.2, 74.9, 127.9, 131.4, 146.2.

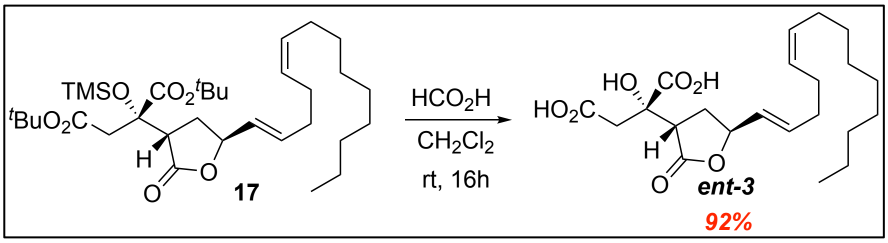
Kishi-Nozaki coupling: Undesired *cis*-Lactone 21



A solution of NMO (162 mg, 1.38 mmol) and silyl ester **14** (119 mg, 0.28 mmol) in THF/H_2O (3:1, 4 ml) was added OsO_4 (71 µl, 0.39 M in benzene, 0.028 mmol) and stirred for 4h. The resulting solution was added $NaIO_4$ (238 mg, 1.11 mmol) and kept stirred further 16h. The reaction mixture was quenched by $Na_2S_2O_3$ (sat.). The aqueous phase was extracted with EtOAc and the combined organic layers were washed with H_2O, brine then dried over Na_2SO_4 and concentrated to give the crude aldehyde which was used directly next reaction without further purification. A mixture of $NiCl_2$ (3.6 mg, 0.028 mmol) and $CrCl_2$ (206 mg, 1.68 mmol) in anhydrous DMSO (degassed, 3 ml) was stirred for 30 min. A mixture of aldehyde (120 mg, 0.28 mmol) and vinyl iodide[3] (445 mg, 1.39 mmol) in anhydrous DMSO (degassed, 3 ml) were added to the mixture at rt and the resulting mixture was stirred at 50 °C for 24 h. The reaction mixture was diluted with water and extracted with Et_2O, washed with brine, dried, concentrated, and chromatographed with 5% EtOAc/petrol as eluent to give the undesired lactone **21** (49 mg, 30%). $[\alpha]_D = -36.6$ (*c* 0.76, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.16 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H), 1.35 - 1.22 (m, 12H), 1.44 (s, 9H), 1.46 (s, 9H), 2.00 (q, *J* = 7.0 Hz, 2H), 2.12 - 2.19 (m, 5H), 2.29 (ddd, *J* = 12.7, 8.8, 6.4 Hz, 1H), 3.21 (dd, *J* = 11.5, 8.9 Hz, 1H), 3.25 (ABq, *J* = 16.6 Hz, 2H), 4.67 (dt, *J* = 10.2, 7.0 Hz, 1H), 5.33 (m, 1H), 5.39 (m, 1H), 5.47 (dd, *J* = 15.3, 7.6 Hz, 1H), 5.80 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 2.4, 14.3, 22.8, 26.7, 27.4, 28.0, 28.3, 29.4, 29.5, 29.7, 29.8, 31.3, 32.0, 32.4, 42.5, 48.5, 77.6, 78.5, 80.9, 82.2, 128.2, 128.4, 131.0, 135.6, 169.5, 170.9, 175.0. IR (thin firm): 842, 1150, 1248, 1368, 1733, 1749, 1772, 2855, 2926, 2956 cm^{-1}. HRMS (ESI) calc. for $C_{33}H_{58}O_7SiNa$: $(M + Na)^+$, 617.3850, found: $(M + Na)^+$, 617.3846.

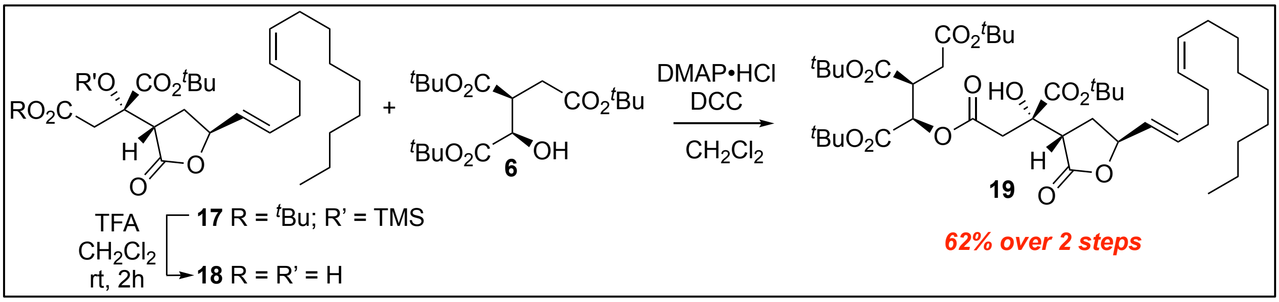
Further elution with 10% EtOAc/Petrol gave the desired alcohol **16** (65 mg, 37%).

Diacid *ent*-3



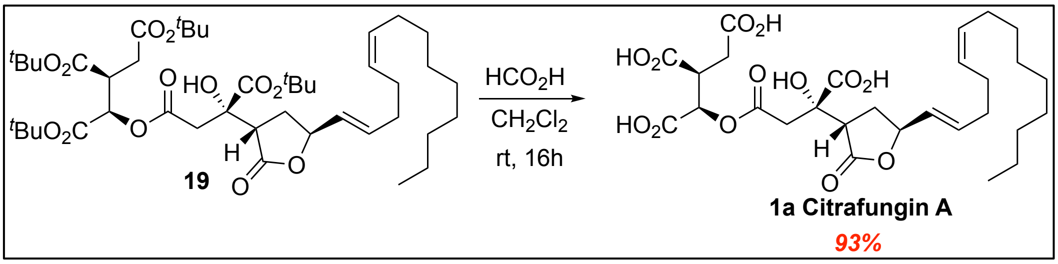
To a solution of the lactone **17** (20 mg, 0.034 mmol) in CH_2Cl_2 (1 ml) at 0°C was added formic acid (1 ml). The solution was stirred at rt. for 16h and toluene (2 ml) was added. The mixture was concentrated to give crude diacid and purification by flash chromatography with 5% MeCN/ CH_2Cl_2 as eluent afforded the diacid ***ent*-3** (13 mg, 92%) as a white gum. $[\alpha]_D = +10.5$ (*c* 1.1, MeOH); Lit. $[\alpha]_D = +9.4$ (*c* 10.85, MeOH) ^{1}H NMR (600 MHz, d_6-acetone) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.29-1.35 (m, 12H), 2.04 - 2.06 (m, 2H), 2.08 - 2.16 (m, 5H), 2.41 (m, 1H), 2.61 (s, 1H), 3.02 (dd, *J* = 10.0, 6.2 Hz, 1H), 3.03 (d, *J* = 16.6 Hz, 2H), 3.53 (d, *J* = 16.6 Hz, 2H), 4.99 (q, *J* = 7.1 Hz, 1H), 5.35-5.42 (m, 2H), 5.58 (dd, *J* = 15.5, 7.3 Hz, 1H), 5.81 (dt, *J* = 15.4, 6.5 Hz, 1H). ^{13}C NMR (151 MHz, CD_3CN) δ 14.4, 23.4, 27.2, 27.9, 30.0, 30.03, 30.2, 30.4, 31.1, 32.6, 32.8, 40.8, 46.8, 76.0, 80.3, 129.3, 129.5, 131.5, 135.6, 172.3, 174.4, 176.1. ^{13}C NMR (151 MHz, d_6-acetone) δ 14.4, 23.3, 27.3, 27.8, 30.0, 30.04, 30.4, 31.5, 32.6, 32.9, 41.4, 46.8, 75.9, 80.0, 129.4, 130.0, 131.2, 134.8, 172.3, 175.1, 175.7. IR (thin film): 968, 1187, 1729, 2854, 2924, 2956, 3256 cm^{-1}. HRMS (ESI) calc. for $C_{22}H_{35}O_7$: $(M + H)^+$, 411.2383, found: $(M + H)^+$, 411.2380.

Citrafungin A tetra-*t*-butyl-ester (19)

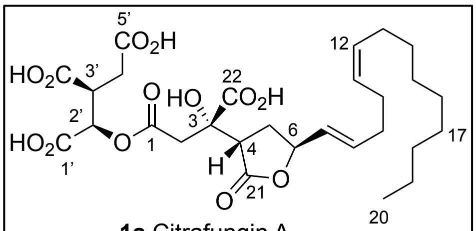


To a solution of the lactone **17** (48 mg, 0.08 mmol) in CH_2Cl_2 (4 mL) at 0°C was added TFA (300μL). The solution was stirred at 0°C for 1 h then at rt for 2 h before toluene (2 mL) was added. The mixture was concentrated to give the crude mono acid **18** which was used directly to next reaction without further purification. To a solution of crude acid **18** and alcohol **6** (57 mg, 0.16 mmol) in CH_2Cl_2 (500μL) was added DMAP•HCl (12 mg, 0.08 mmol) at 0°C. The reaction mixture was stirred for 10 min before DCC (33 mg, 0.16 mmol) was added, and the resulting solution was stirred at rt for 18 h. The reaction mixture was concentrated and purification of the residue by flash chromatography using 10% EtOAc/petrol as the eluent to afforded citrafungin A tetra-*t*-butyl ester (**19**) (40 mg, 62%) as a yellow oil. $[\alpha]_D = +20.5$ (*c* 0.46, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.9 Hz, 3H), 1.26 (m, 12H), 1.44 (s, 18H), 1.46 (s, 9H), 1.48 (s, 9H), 1.96 – 2.02 (m, 2H), 2.14 - 2.05 (m, 4H), 2.37 - 2.30 (m, 1H), 2.38 (dd, *J* = 16.9, 5.0 Hz, 1H), 2.64 (dd, *J* = 16.8, 9.6 Hz, 1H), 2.88 (m, 1H), 2.91 (d, *J* = 15.4 Hz, 2H), 3.51 (ddd, *J* = 9.2, 5.1, 3.8 Hz, 1H), 3.62 (d, *J* = 15.4 Hz, 2H), 4.40 (d, *J* = 1.1 Hz, 1H), 5.01 (q, *J* = 7.3 Hz, 1H), 5.21 (d, *J* = 3.2 Hz, 1H), 5.30 - 5.39 (m, 2H), 5.43 (dd, *J* = 15.4, 7.5 Hz, 1H), 5.78 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.3, 22.8, 26.6, 27.4, 27.9, 28.10, 28.13, 28.2, 29.4, 29.5, 29.6, 29.8, 31.2, 32.0, 32.3, 33.5, 41.0, 43.7, 46.7, 72.5, 76.5, 80.2, 81.1, 82.3, 83.6, 83.7, 128.2, 128.4, 131.0, 135.3, 166.9, 169.0, 169.9, 170.6, 171.5, 175.3. IR (thin film): 844, 1148, 1252, 1369, 1733, 2856, 2928, 2979, 3455 cm^{-1}. HRMS (ESI) calc. for $C_{44}H_{72}O_{13}Na$: (M + Na)$^+$, 831.4871, found: (M + Na)$^+$, 831.4862.

Citrafungin A (1a)



To a solution of the tetra-*t*-butyl ester **19** (30 mg, 0.037 mmol) in CH_2Cl_2 (0.5 ml) at 0°C was added formic acid (0.5 ml). The solution was stirred at rt for 16h and toluene (2 ml) was then added. The mixture was concentrated to give citrafungin A **1a** (20 mg, 93%). $[\alpha]_D$ = +24.3 (*c* 0.75, MeOH). ^{1}H NMR (500 MHz, d_6-acetone) δ 0.88 (t, *J*=7.0 Hz, 3H), 1.29-1.35 (m, 12H), 2.05 (q, 6.5, 1H), 2.11 (m, 2H), 2.13 (m, 2H), 2.40 (ddd, *J* = 13.2, 7.5, 5.8 Hz, 1H), 2.62 (dd, *J* =17.3, 5.0 Hz, 1H), 2.82 (dd, *J* =17.3, 9.3 Hz, 1H), 3.08 (dd, *J* =9.7, 6.0 Hz, 1H), 3.15 (d, *J* =16.4 Hz, 1H), 3.58 (ddd, *J* =9.0, 5.0, 3.6 Hz, 1H), 3.69 (d, *J* =16.4 Hz, 1H), 5.00 (q, *J* =7.0 Hz, 1H), 5.34 (m, 1H), 5.37 (m, 1H), 5.49 (d, *J* = 3.6 Hz, 1H), 5.59 (dd, *J* =15.4, 7.4 Hz, 1H), 5.82 (m, 1H). ^{13}C NMR (151 MHz, d_6-acetone, highest peak set to 175.0 ppm) δ 13.8, 22.8, 26.7, 27.3, 29.4, 29.5, 29.7, 29.9, 30.9, 31.7, 32.1, 32.3, 40.9, 42.7, 46.4, 72.0, 75.6, 79.5, 128.8, 129.3, 130.7, 134.4, 168.7, 169.5, 170.9, 172.2, 173.6, 175.0. ^{3}C NMR (151 MHz, d_6-acetone set to 29.8 ppm) 14.4, 23.3, 27.3, 27.8, 29.98, 30.02, 30.2, 30.4, 31.5, 32.3, 32.6, 32.9, 41.4, 43.3, 46.9, 72.5, 76.2, 80.1, 129.4, 129.8, 131.2, 135.0, 169.2, 170.1, 171.5, 172.8, 174.2, 175.5. IR (thin film): 966, 1179, 1721, 2854, 2924, 3451 cm^{-1}. HRMS (ESI) calc. for $C_{28}H_{41}O_{13}$: (M + H)$^+$, 585.2548, found: (M + H)$^+$, 585.2545.



1a Citrafungin A

H atom	Nat.^{4} δ, m, *J* Hz	Syn. 1a δ, m, *J* Hz	Syn. 1^1 δ, m, *J* Hz
H2$_a$	3.66, d, 16	3.68, d, 16.4	3.70, d, 16.3
H2$_b$	3.13, d, 16.5	3.15. d, 16.4	3.16, d, 16.3
H4	3.07, dd, 10, 6	3.08, dd, 9.7, 6.0	3.05, dd, 9.7, 5.8
H5$_a$	2.39, ddd, 13, 7.5, 6.0	2.40, ddd, 13.4, 7.6, 6.0	2.39, ddd, 13.2, 7.4, 6.0
H5$_b$	2.11, m	2.13, m	2.16-2.03, m
H6	4.99, q, 7	5.00, q, 7.0	4.99, q, 7.1
H7	5.57, dd, 15, 7.5	5.59, dd, 15.4, 7.4	5.58, dd, 15.4, 7.4
H8	5.81, dt, 15.5, 7	5.82, dt, 15.3, 6.2	5.82, dt, 14.9, 6.3
H9$_{ab}$	2.11, m	2.11, m	2.16-2.03
H10$_{ab}$	2.13, m	2.13, m	2.16-2.03
H11	5.34, m	5.34, m	5.41-5.33, m
H12	5.37, m	5.37, m	5.41-5.33, m
H13$_{ab}$	2.04, q, 6.5	2.05, q, 6.5	2.16-2.03, m
H14-19	1.28, m	1.29-1.35, m	1.28, m
H20	0.86, t, 7	0.88, t, 7.0	0.87, t, 6.9
H2'	5.47, d, 3.5	5.49, d, 3.6 Hz	5.49, d, 3.4
H3'	3.56, ddd, 8.5, 5.0, 3.5	3.58, ddd, 9.0, 5.0, 3.6	3.56, ddd, 8.8, 4.8, 5.7
H4'$_a$	2.80, dd, 17.5, 9.5	2.82, dd, 17.3, 9.3	2.81, dd, 17.2, 9.4
H4'$_b$	2.60, dd, 17, 4.5	2.62, dd, 17.3, 5.0	2.61, dd, 17.2, 4.9

Table 1: Comparison of ^{1}H spectral data for natural^4 (600 MHz, d_6-acetone) and synthetic citrafungin A (**1a**) (500 MHz, d_6-acetone) and synthetic **1**^{1} (600 MHz, d_6-acetone).

Carbon	**Nat.[4]**	**Syn. 1a**	**Syn. 1[1]**	**Nat. - 1a**	**Nat. - 1**
1	169.4	169.5	169	-0.1	0.4
2	40.7	40.9	40.8	-0.2	-0.1
3	75.5	75.6	75.6	-0.1	-0.1
4	46.3	46.4	46.3	-0.1	0
5	30.8	30.9	30.9	-0.1	-0.1
6	79.4	79.5	79.5	-0.1	-0.1
7	129.1	129.3	129.2	-0.2	-0.1
8	134.4	134.4	134.4	0	0
9	32.2	32.3	32.3	-0.1	-0.1
10	26.6	26.7	26.7	-0.1	-0.1
11	128.7	128.8	128.8	-0.1	-0.1
12	130.6	130.7	130.6	-0.1	0
13	27.2	27.3	27.2	-0.1	0
14	29.7	29.9	30.3	-0.2	-0.6
15	29.6	29.7	-	-0.1	-
16	29.5	29.5	-	0	-
17*	28.8*	29.4	-	-0.6*	-
18	31.9	31.7	31.8	0.2	0.1
19	22.7	22.8	22.7	-0.1	0
20	13.8	13.8	13.8	0	0
21	175	175	175	0	0
22	173.6	173.6	173.8	0	-0.2
1'	168.7	168.7	169.2	0	-0.5
2'	71.9	72	71.9	-0.1	0
3'	42.6	42.7	42.7	-0.1	-0.1
4'	31.6	31.7	31.8	-0.1	-0.2
5'	172.3	172.2	172.3	0.1	0
6'	170.9	170.9	171.1	0	-0.2

Table 2: ^{13}C NMR chemical shift data and shift differences for natural[4] citrafungin A (150 MHz, *d*$_6$-acetone) and synthetic **1a** (126 MHz, *d*$_6$-acetone) and synthetic **1**[1] (75 MHz, *d*$_6$-acetone). *Misassigned in isolation paper[4]

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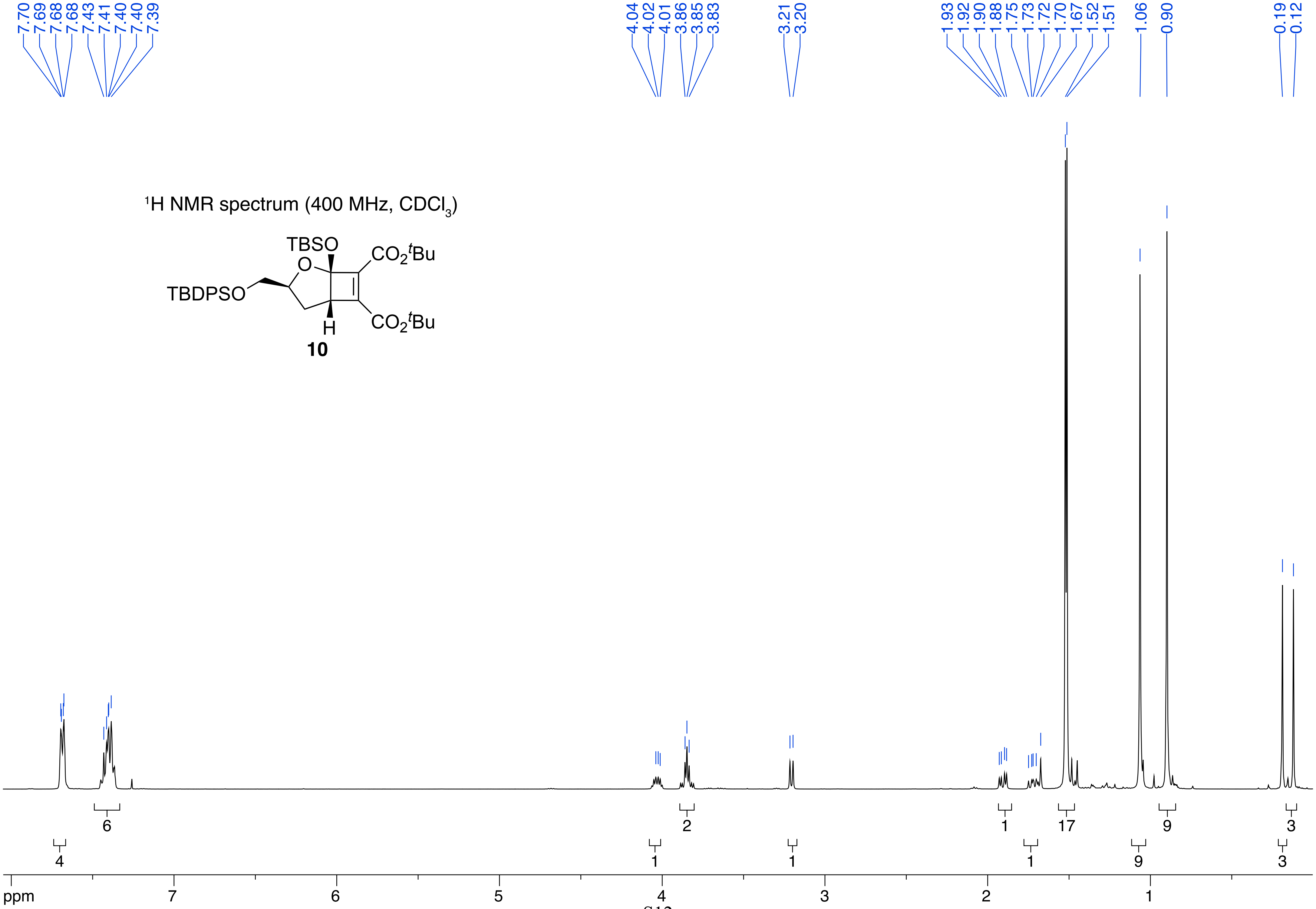
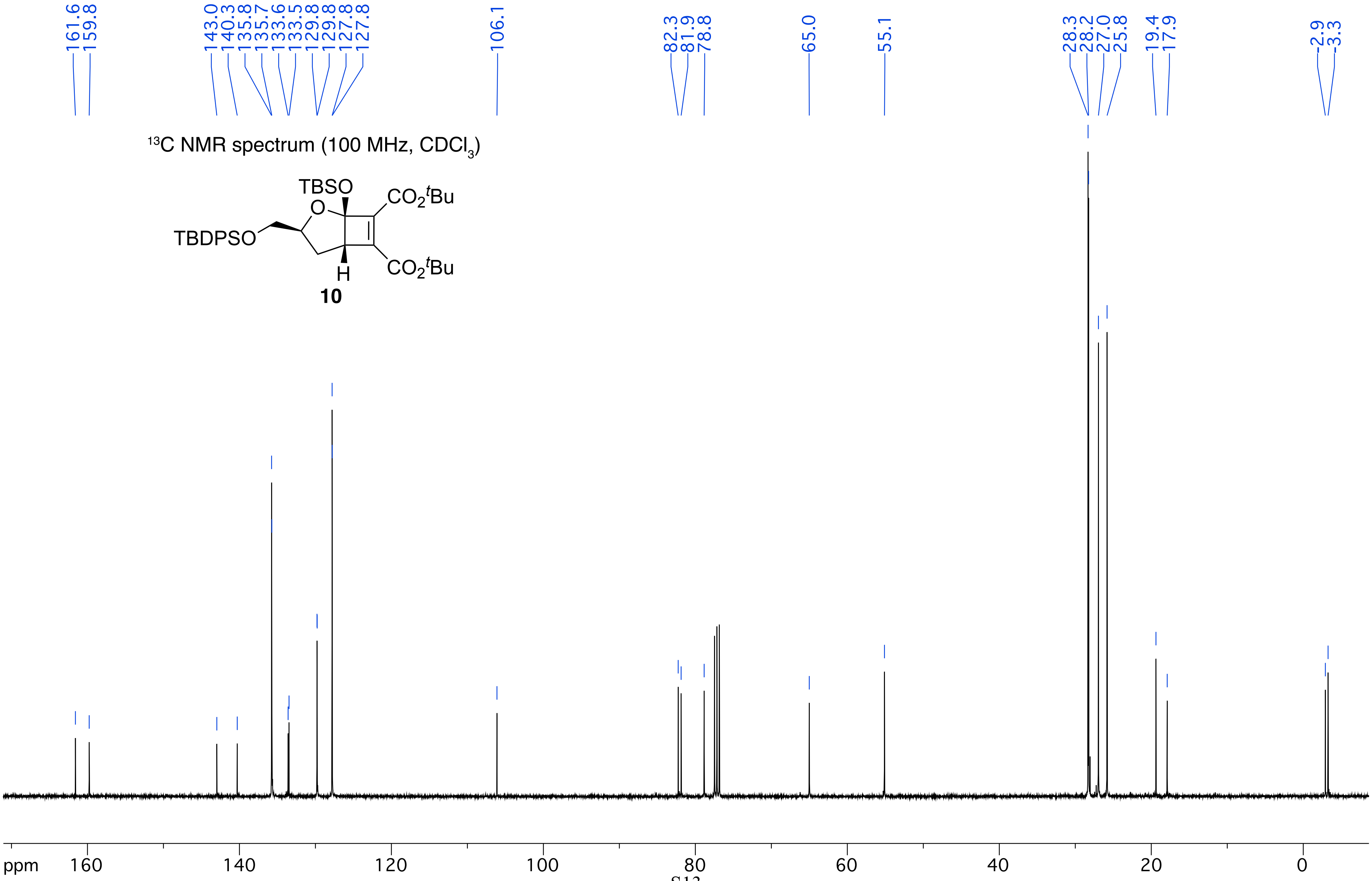


^{1}H NMR spectrum (400 MHz, $CDCl_3$)

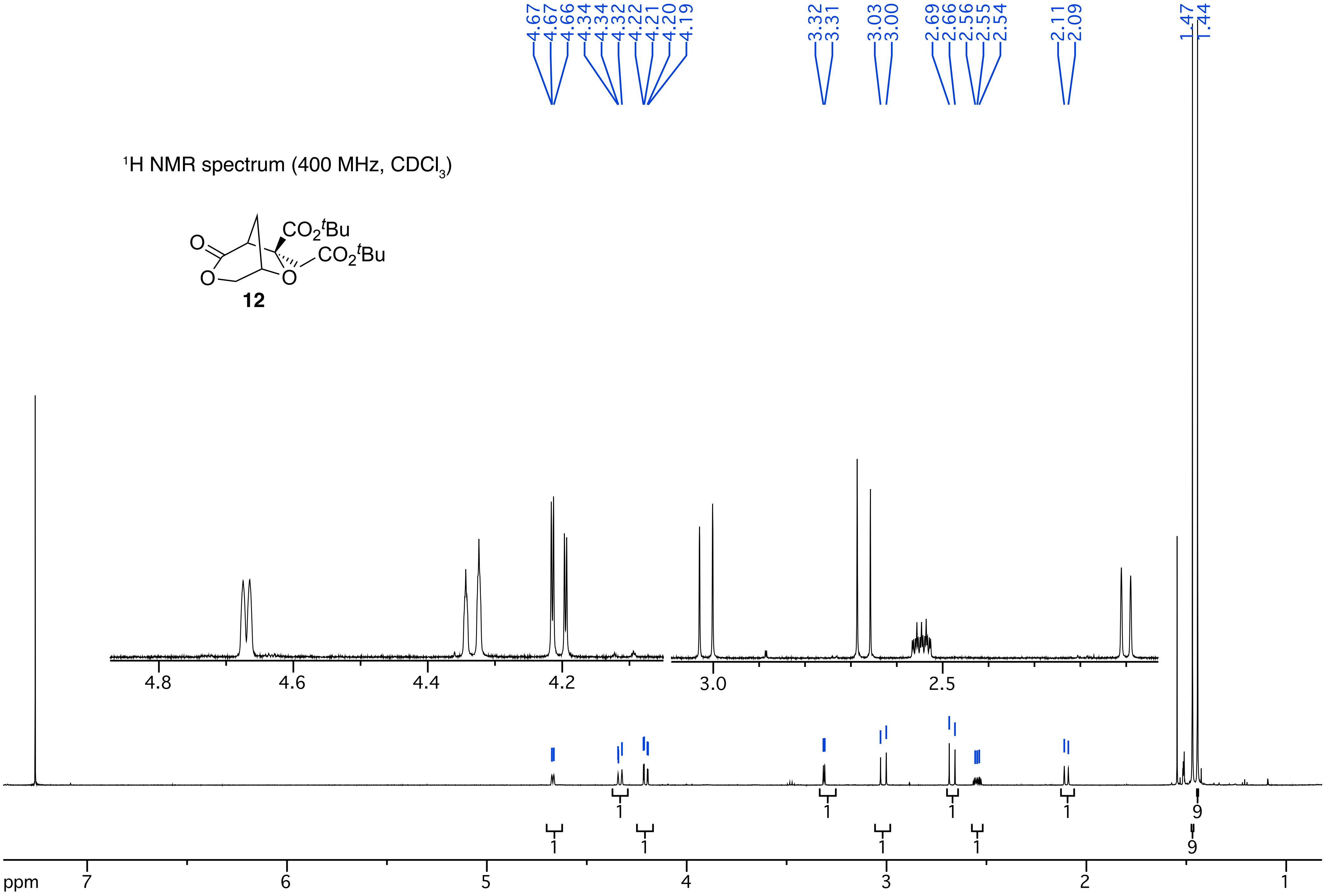
10



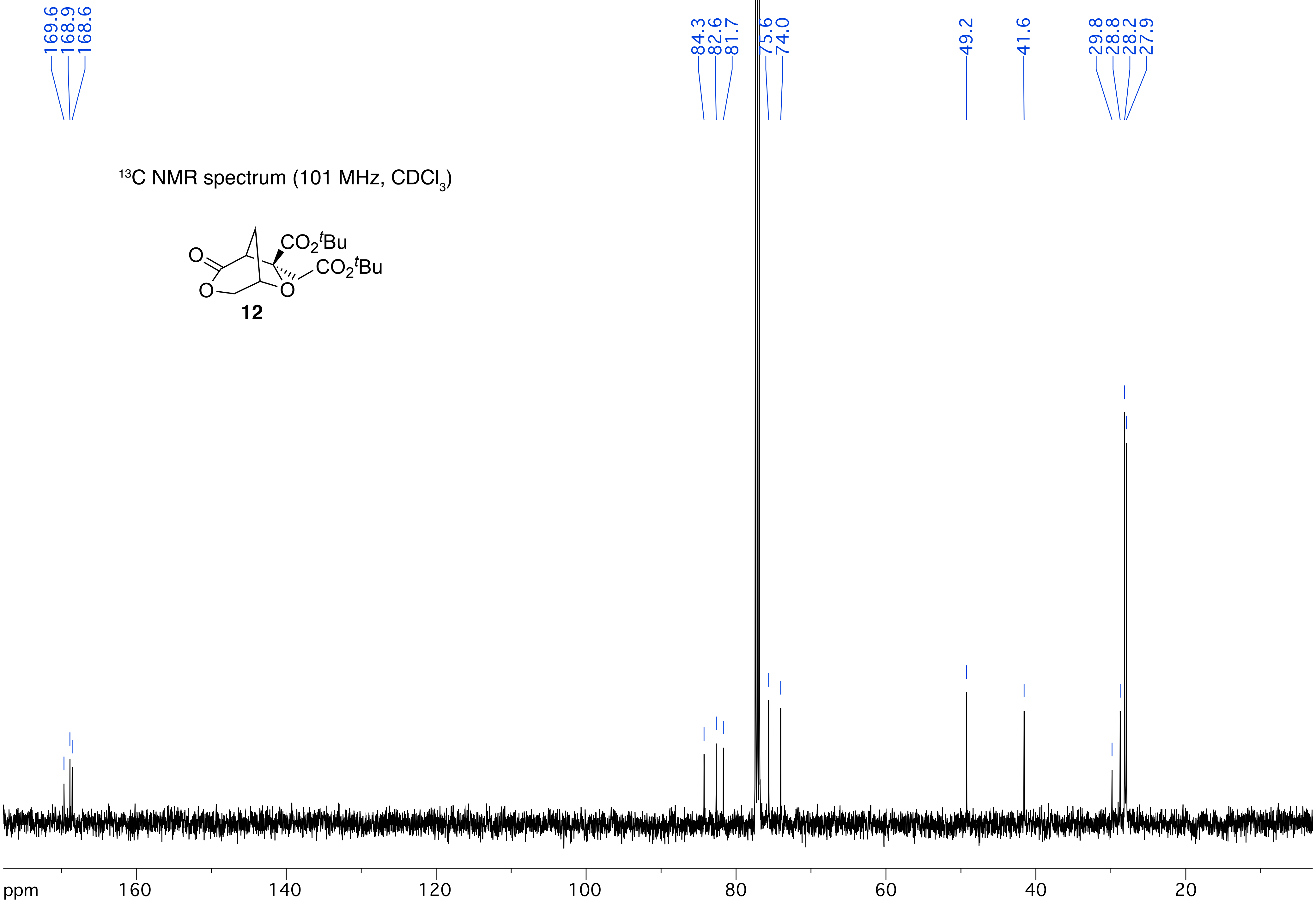
^{13}C NMR spectrum (100 MHz, CDCl$_3$)

10

^{1}H NMR spectrum (400 MHz, $CDCl_3$)

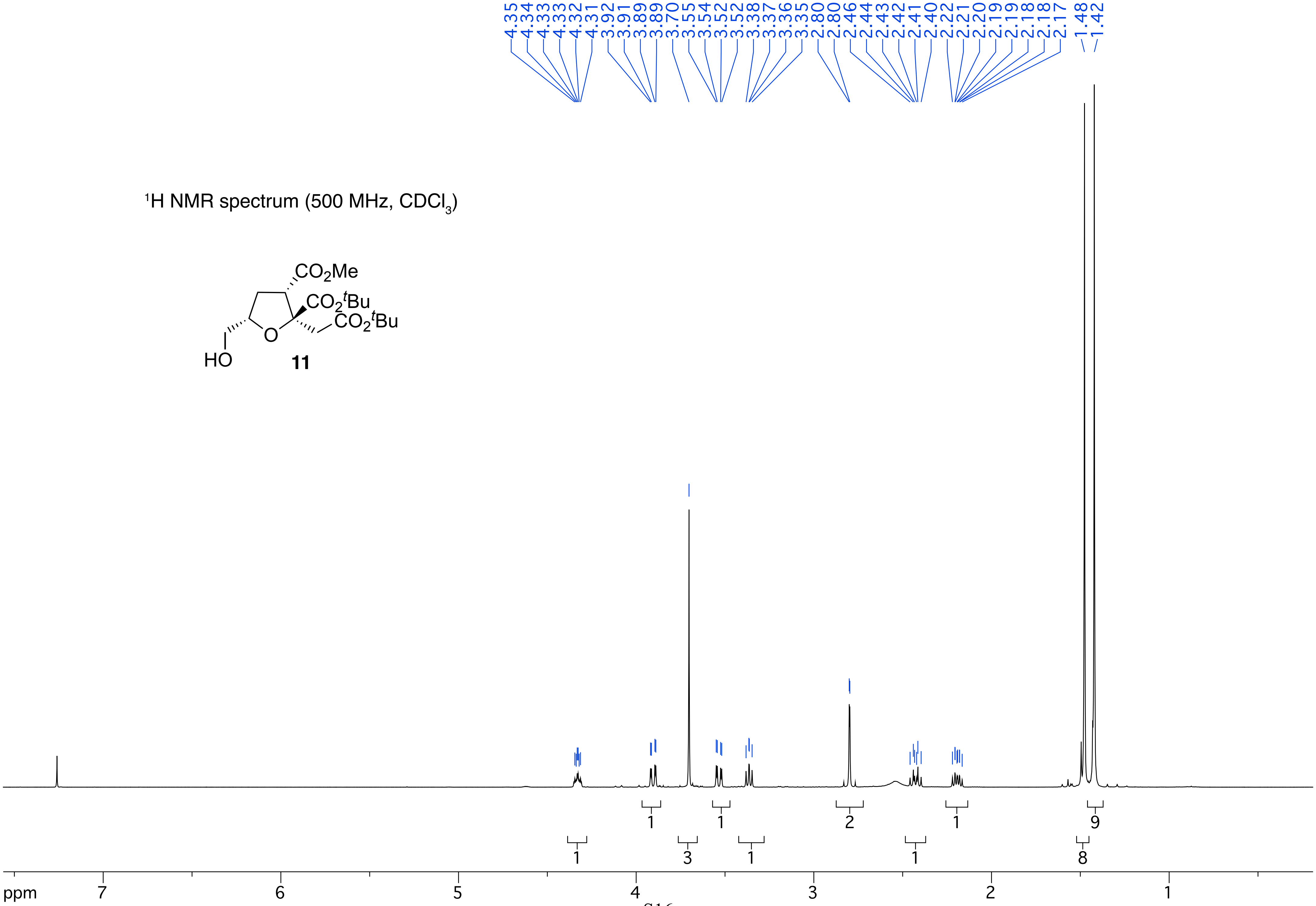


12



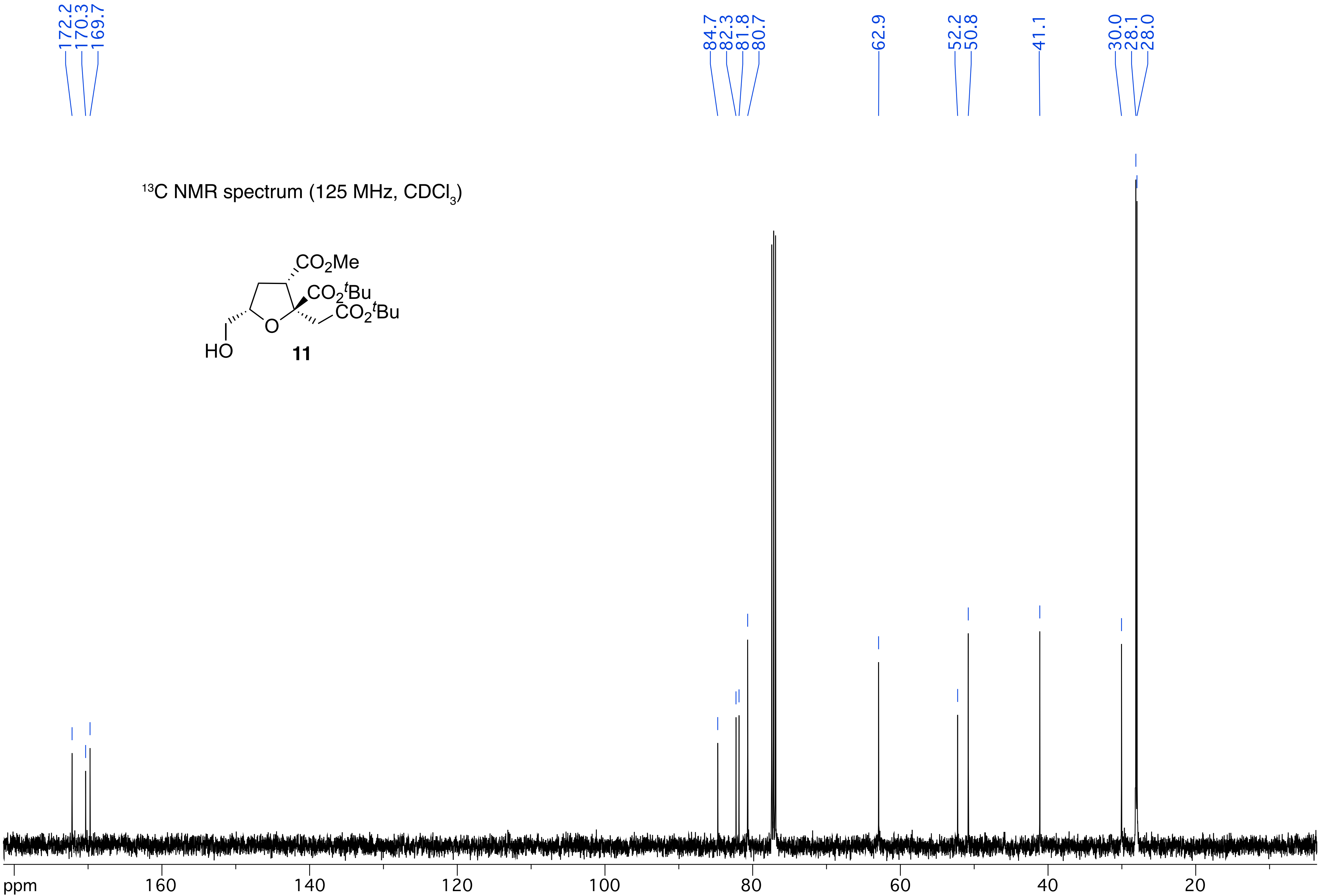
^{13}C NMR spectrum (101 MHz, $CDCl_3$)

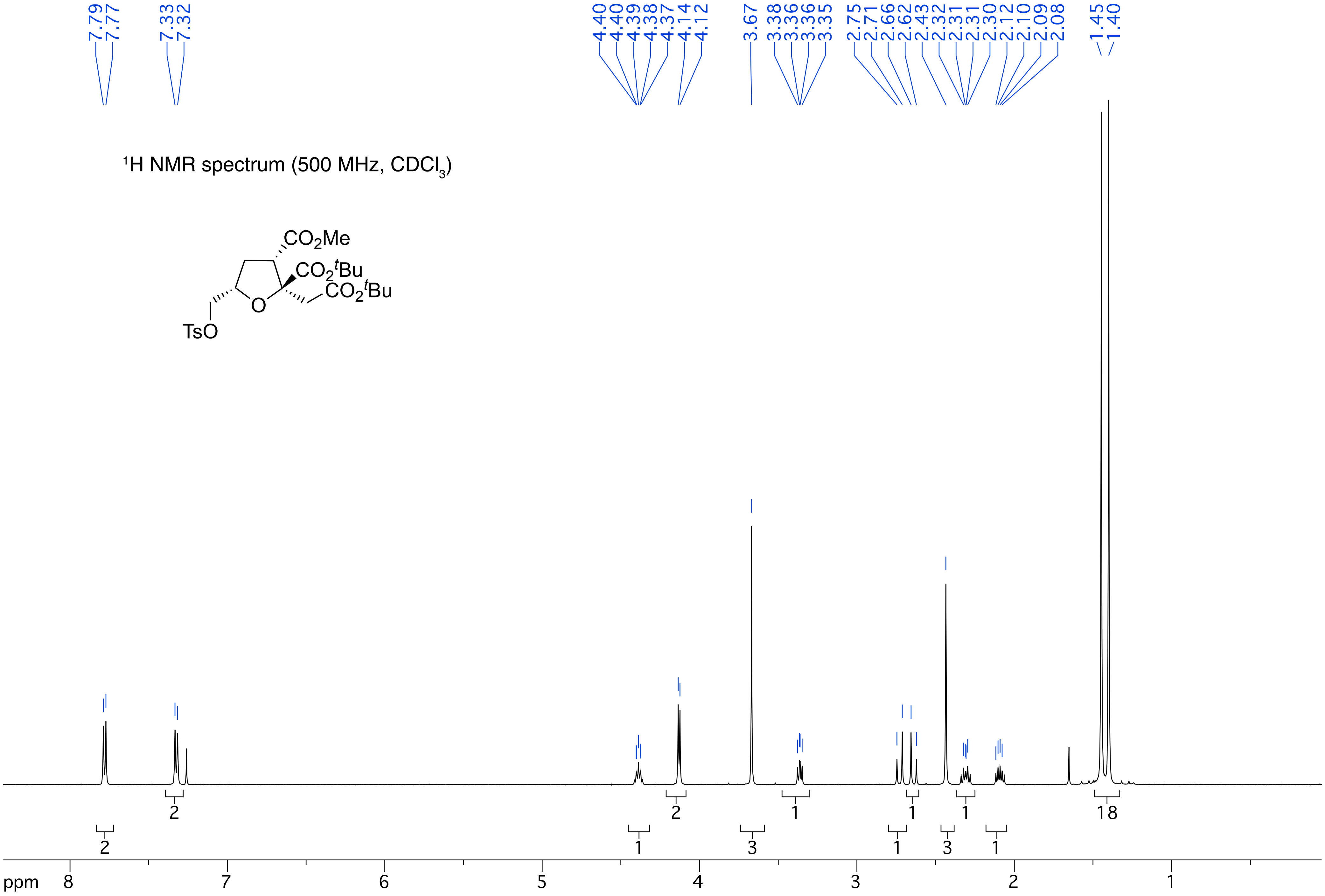
12

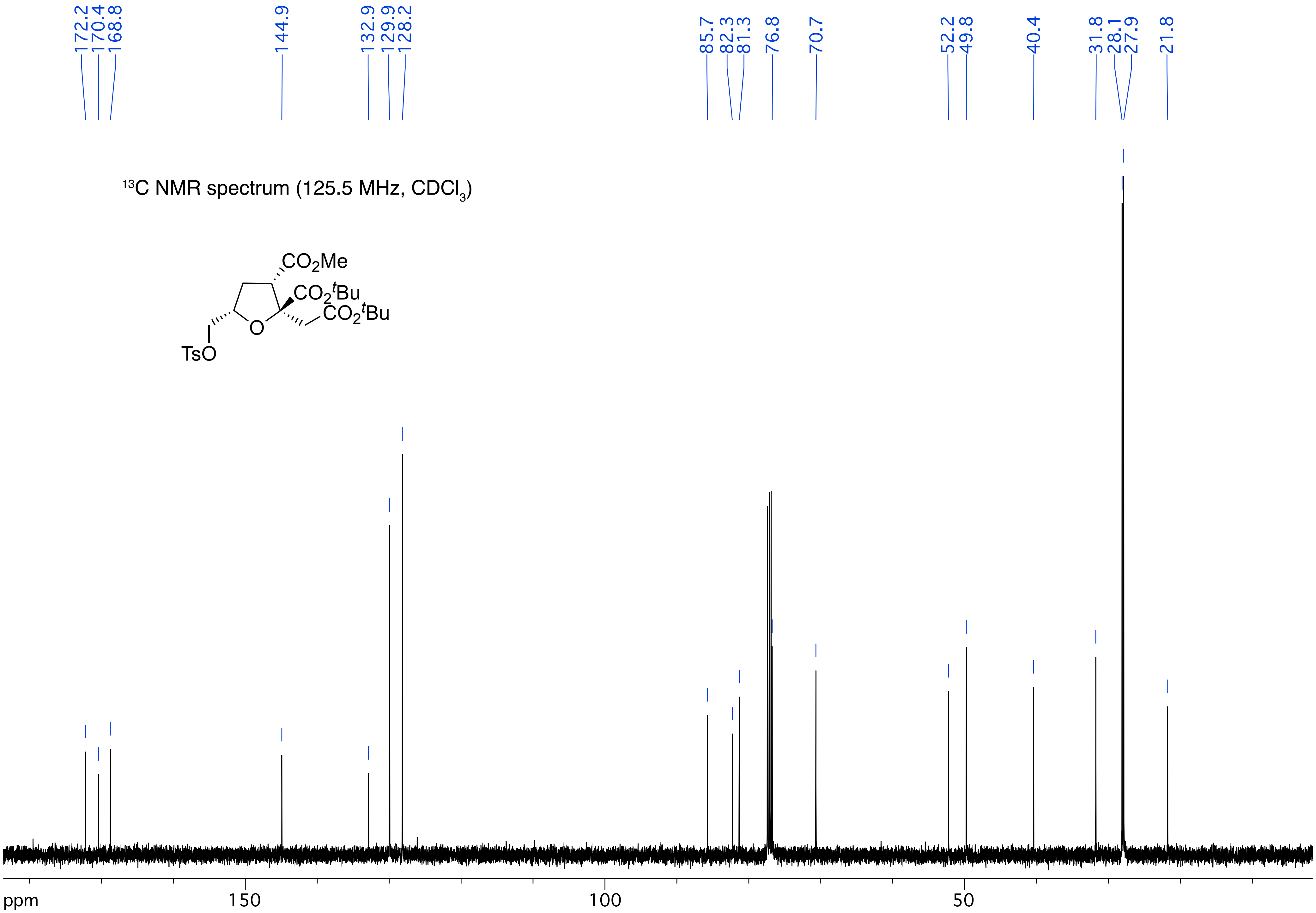


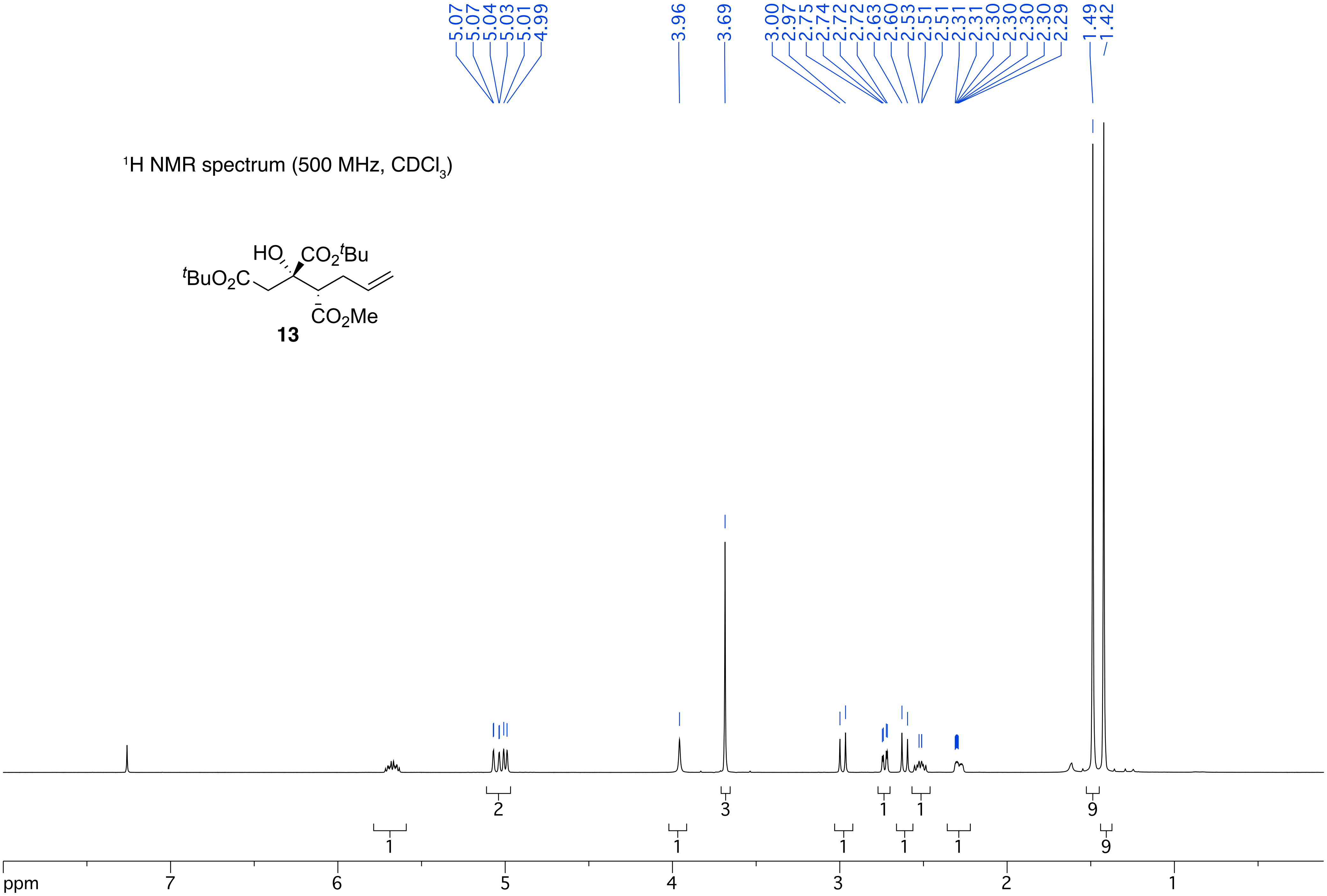
^{1}H NMR spectrum (500 MHz, $CDCl_3$)

11


^{13}C NMR spectrum (125 MHz, CDCl$_3$)

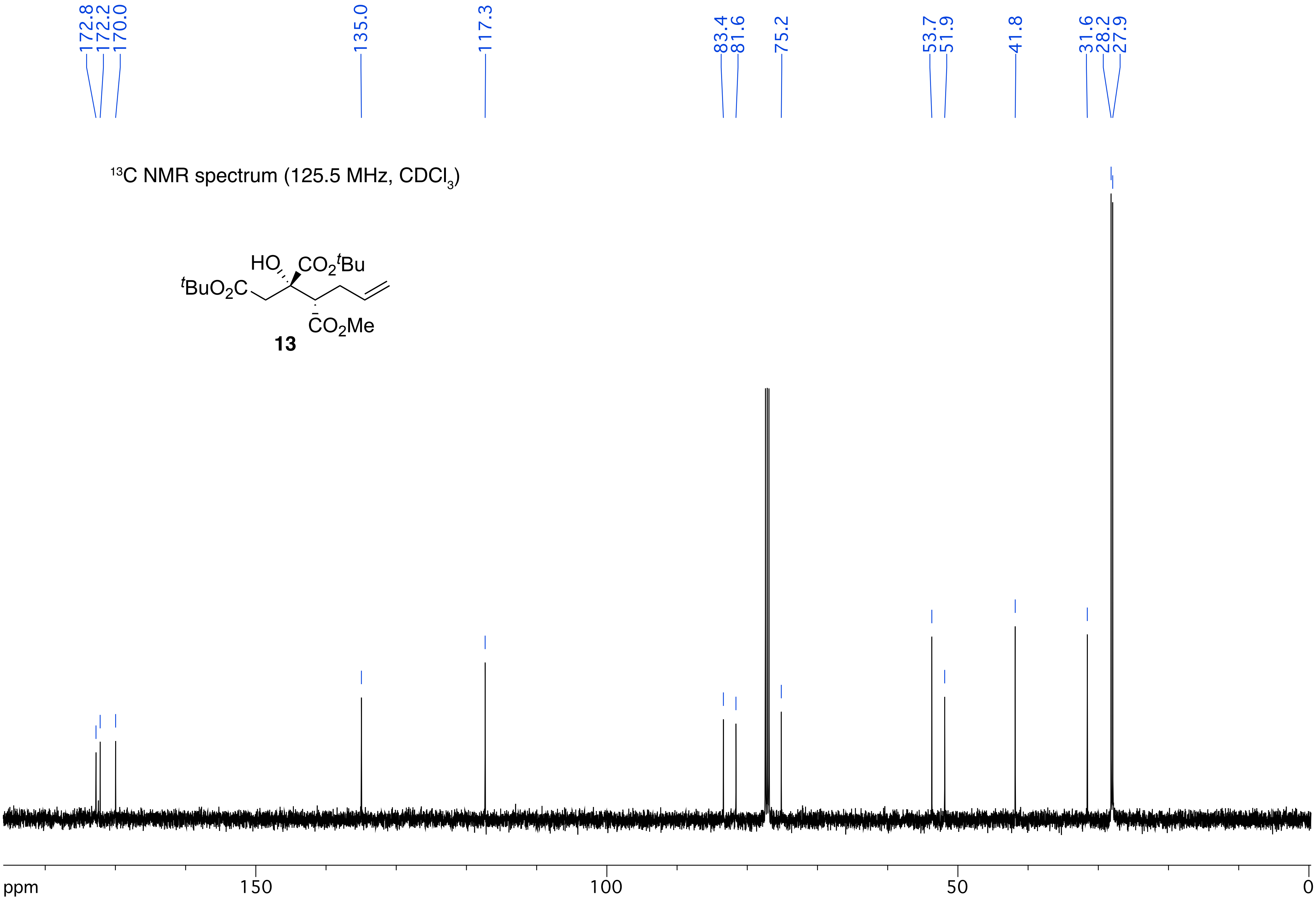

7.79
7.77
7.33
7.32
4.40
4.40
4.39
4.38
4.37
4.14
4.12
3.67
3.38
3.36
3.36
3.35
2.75
2.71
2.66
2.62
2.43
2.32
2.31
2.31
2.30
2.12
2.10
2.09
2.08
1.45
1.40
^{1}H NMR spectrum (500 MHz, $CDCl_3$)
CO_2Me
$CO_2{}^tBu$
$CO_2{}^tBu$
O
TsO
2
2
1
2
3
1
1
1
3
1
1
18
ppm
8
7
6
5
4
3
2
1


172.2
170.4
168.8
144.9
132.9
129.9
128.2
85.7
82.3
81.3
76.8
70.7
52.2
49.8
40.4
31.8
28.1
27.9
21.8
^{13}C NMR spectrum (125.5 MHz, $CDCl_3$)
CO_2Me
$CO_2{}^tBu$
$CO_2{}^tBu$
O
TsO
ppm
150
100
50



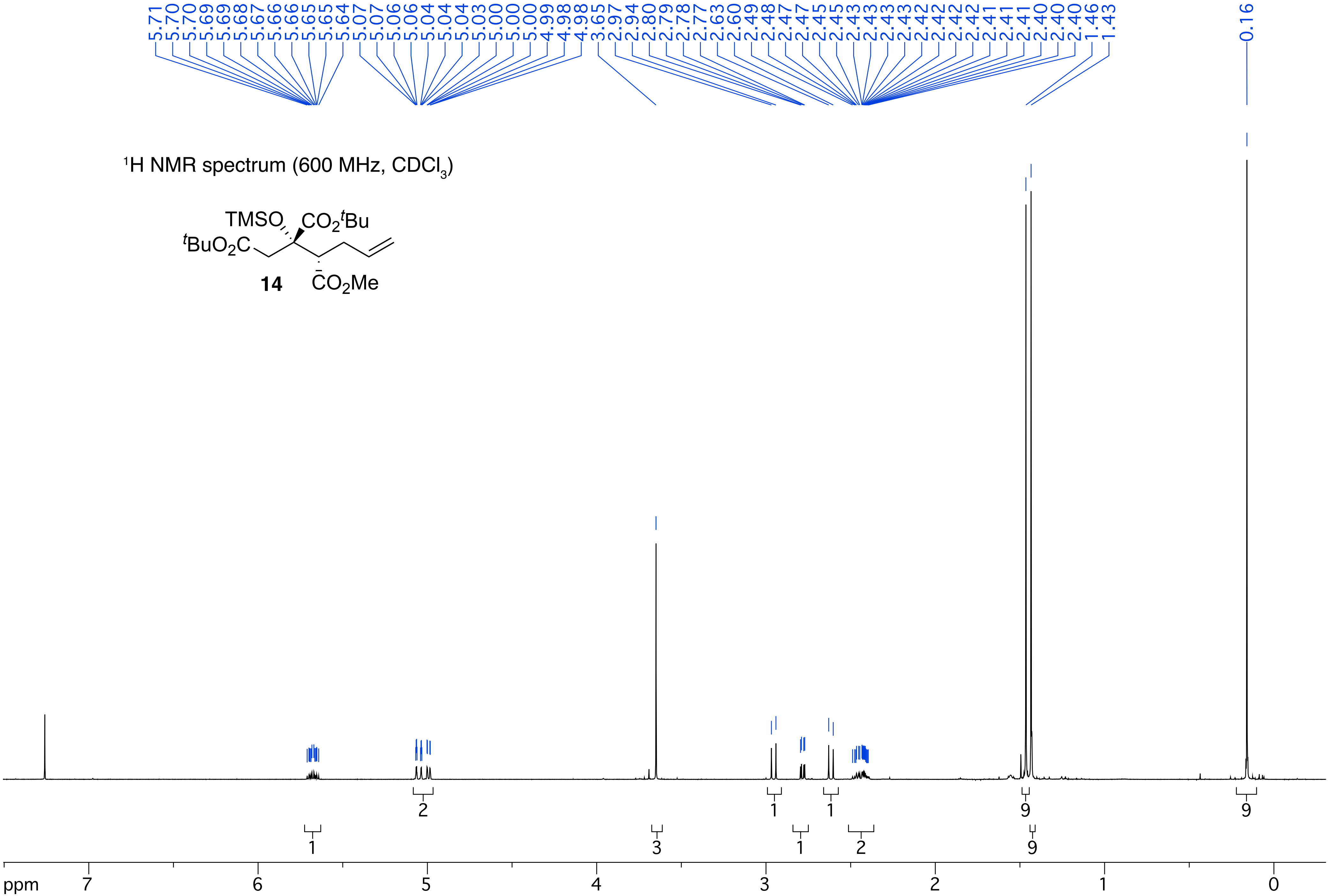
^{1}H NMR spectrum (500 MHz, $CDCl_3$)

13



^{13}C NMR spectrum (125.5 MHz, $CDCl_3$)

13


1H NMR spectrum (600 MHz, CDCl3)
TMSO
CO2tBu
tBuO2C
CO2Me
14
5.71
5.70
5.70
5.69
5.69
5.68
5.67
5.66
5.66
5.65
5.65
5.64
5.07
5.07
5.06
5.06
5.04
5.04
5.04
5.03
5.00
5.00
5.00
4.99
4.98
4.98
3.65
2.97
2.94
2.80
2.79
2.78
2.77
2.63
2.60
2.49
2.48
2.47
2.47
2.45
2.45
2.43
2.43
2.43
2.43
2.42
2.42
2.42
2.42
2.41
2.41
2.41
2.40
2.40
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1.43
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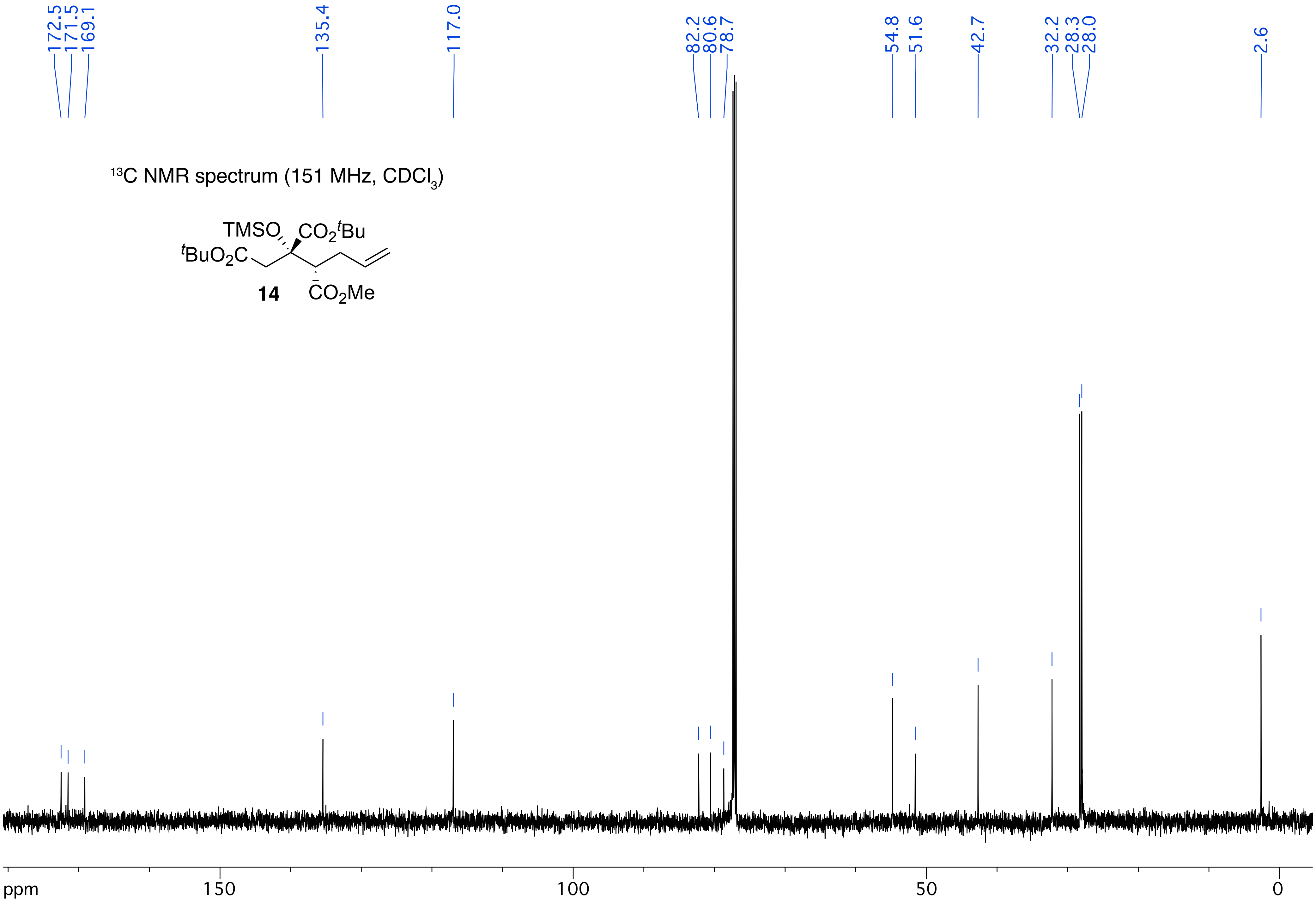
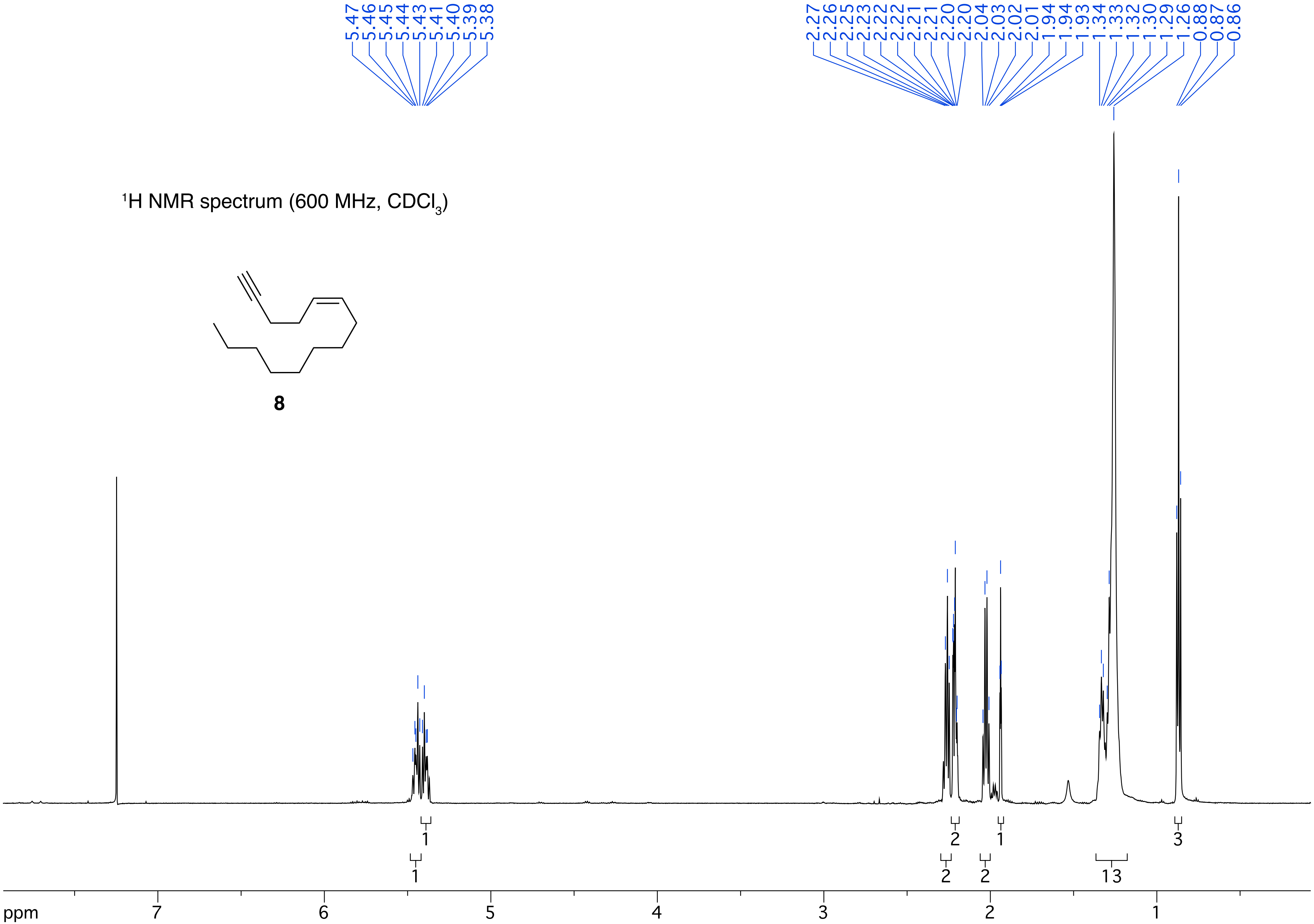


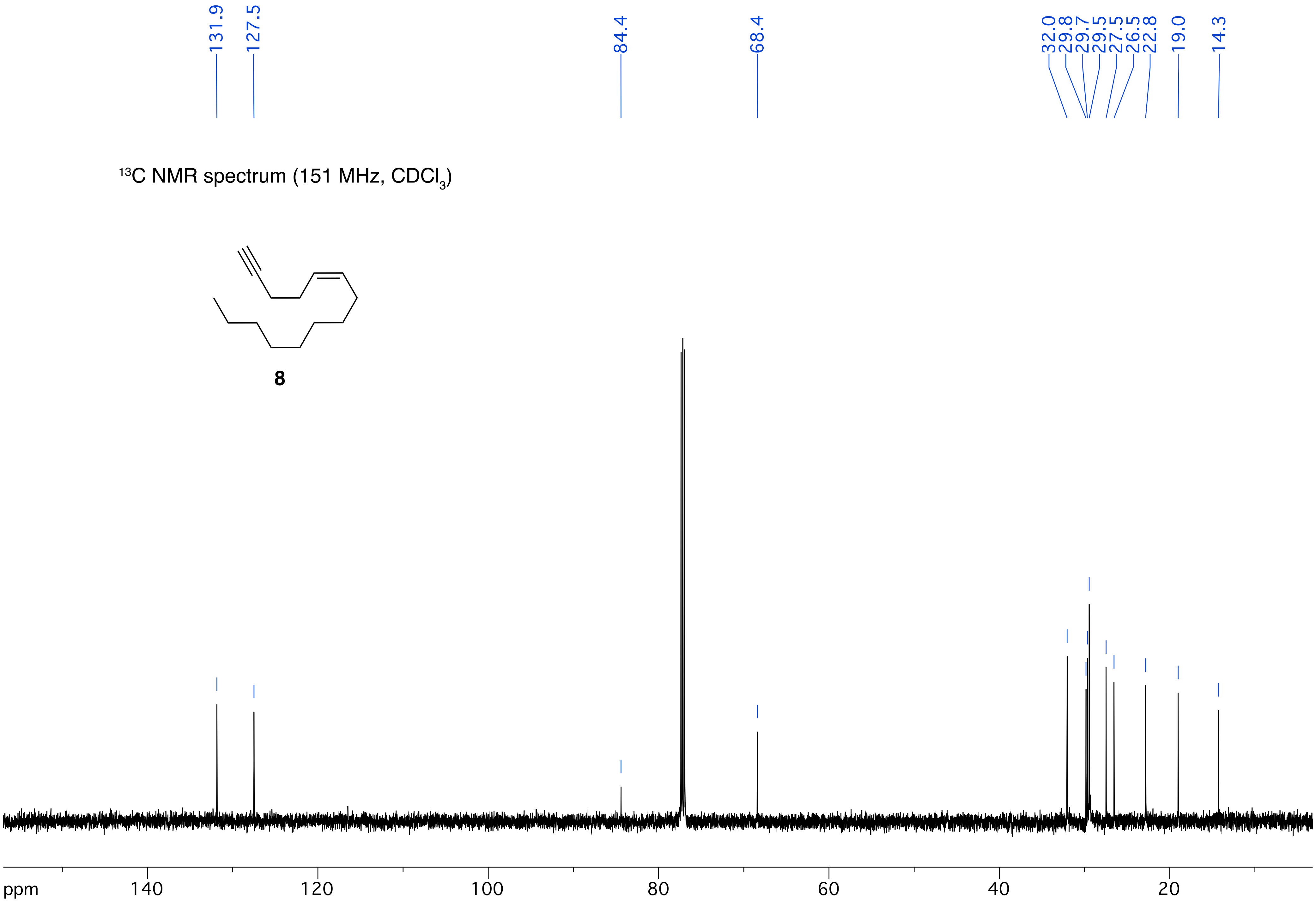
^{13}C NMR spectrum (151 MHz, CDCl$_3$)

14



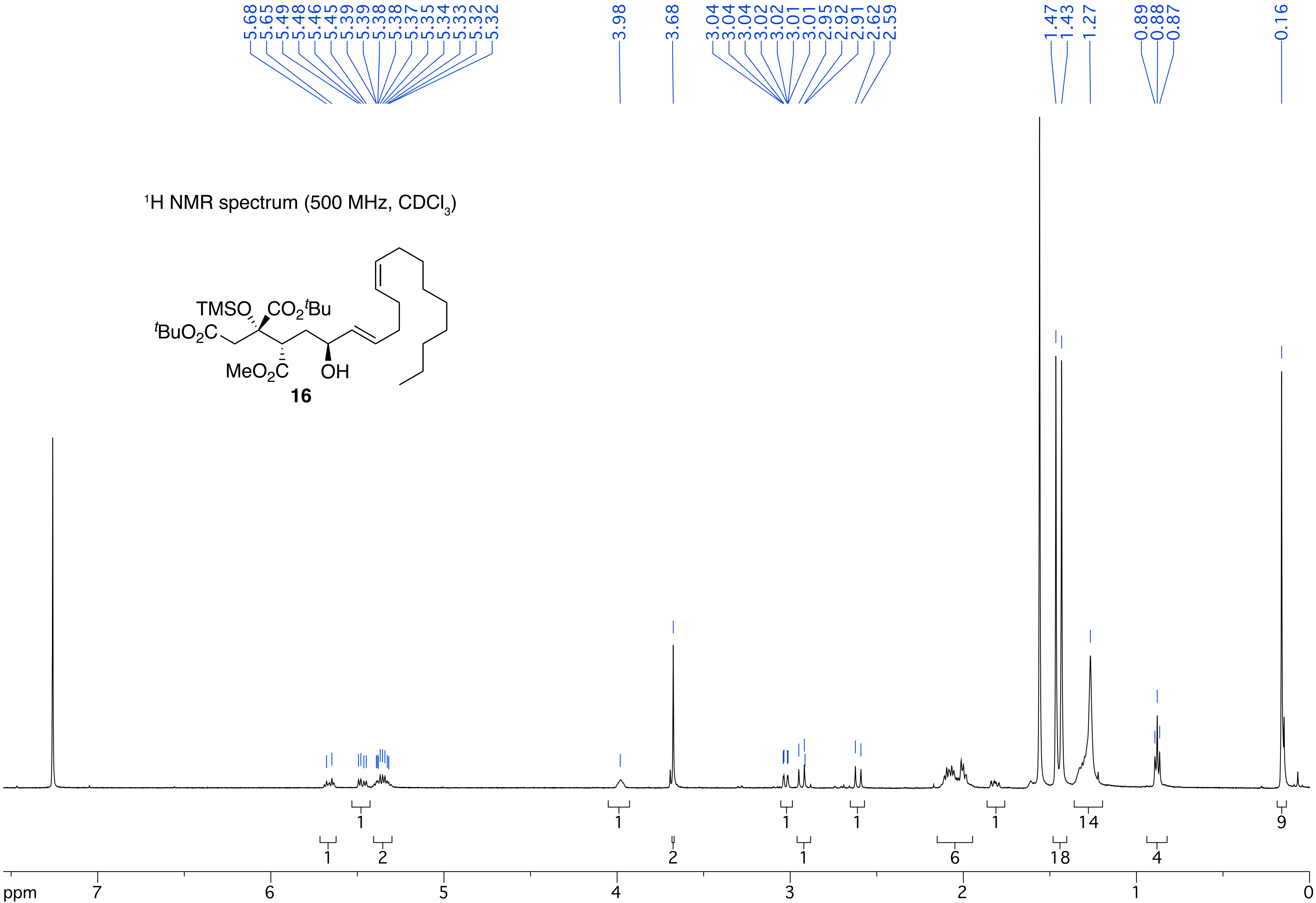
^{1}H NMR spectrum (600 MHz, $CDCl_3$)

8

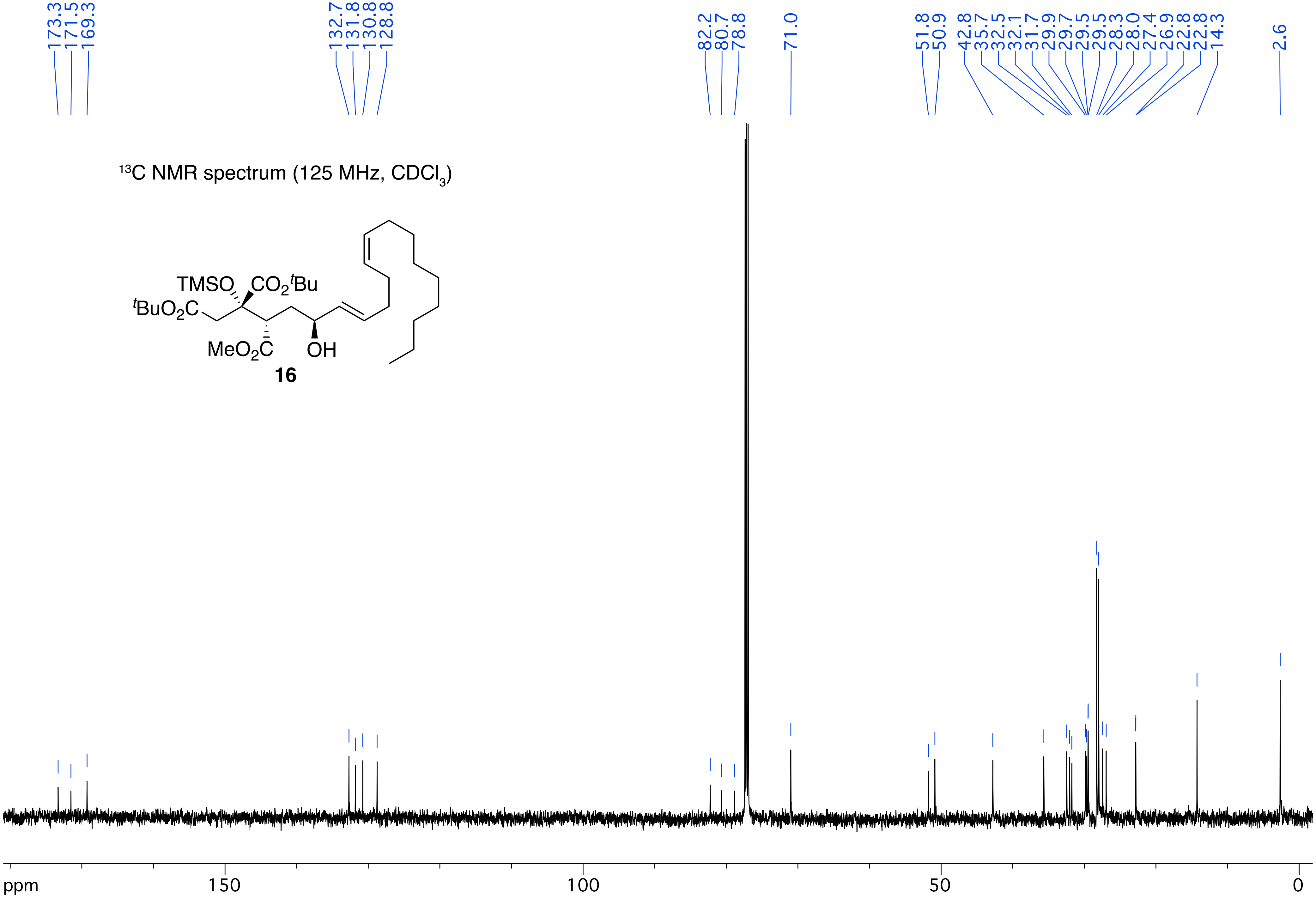


^{13}C NMR spectrum (151 MHz, CDCl$_3$)

8

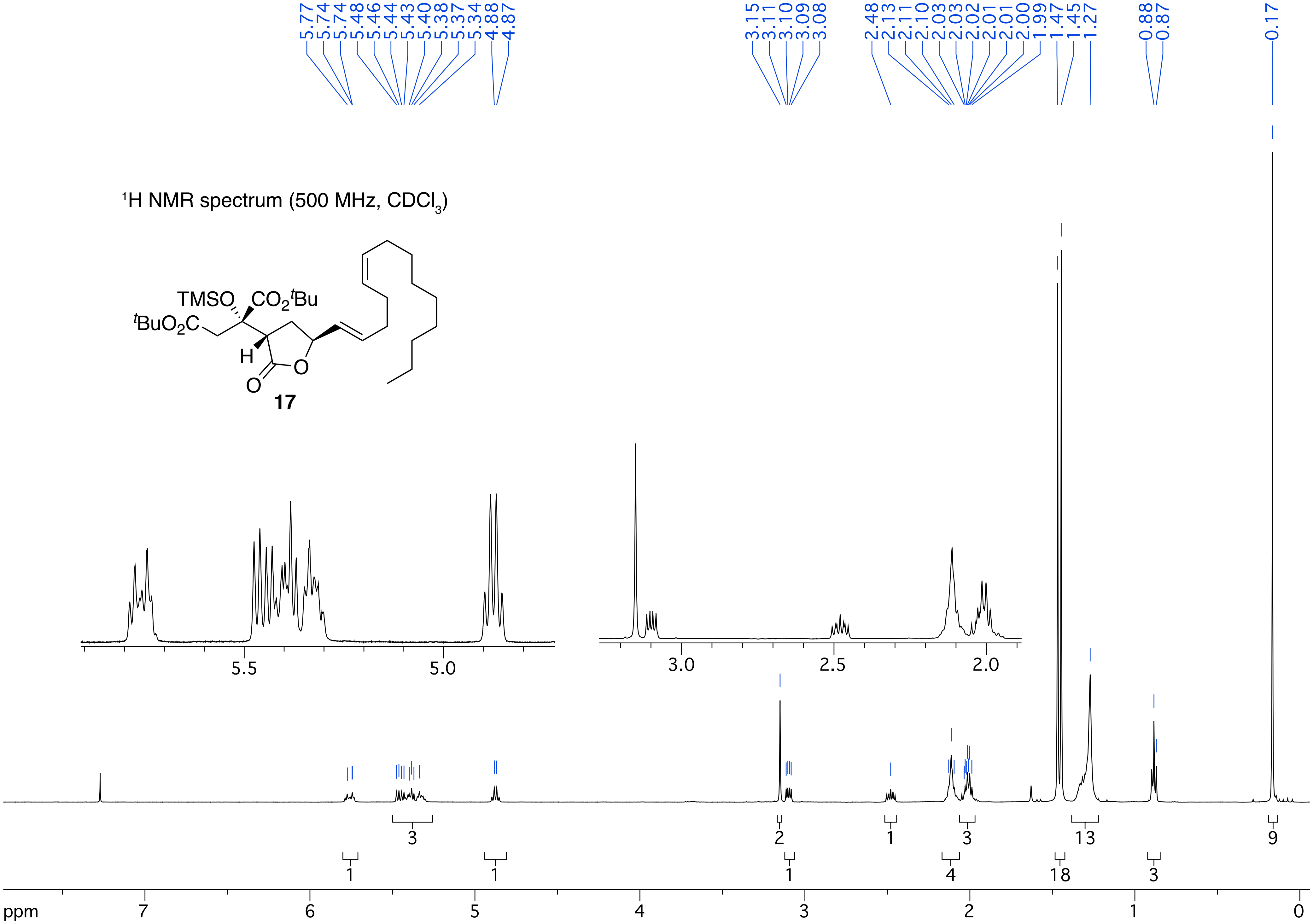

^1H NMR spectrum (500 MHz, $CDCl_3$)

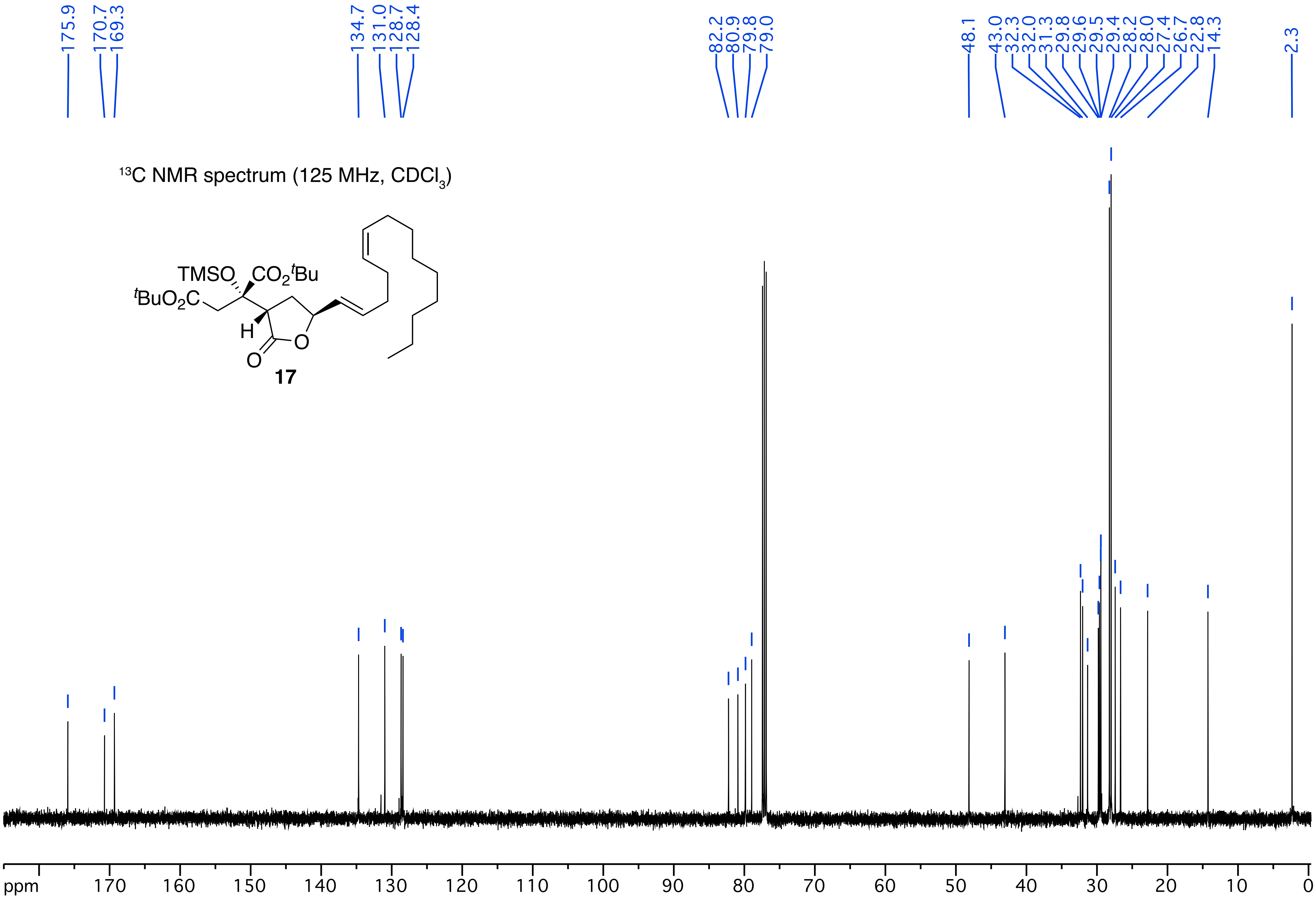
16



^{13}C NMR spectrum (125 MHz, $CDCl_3$)

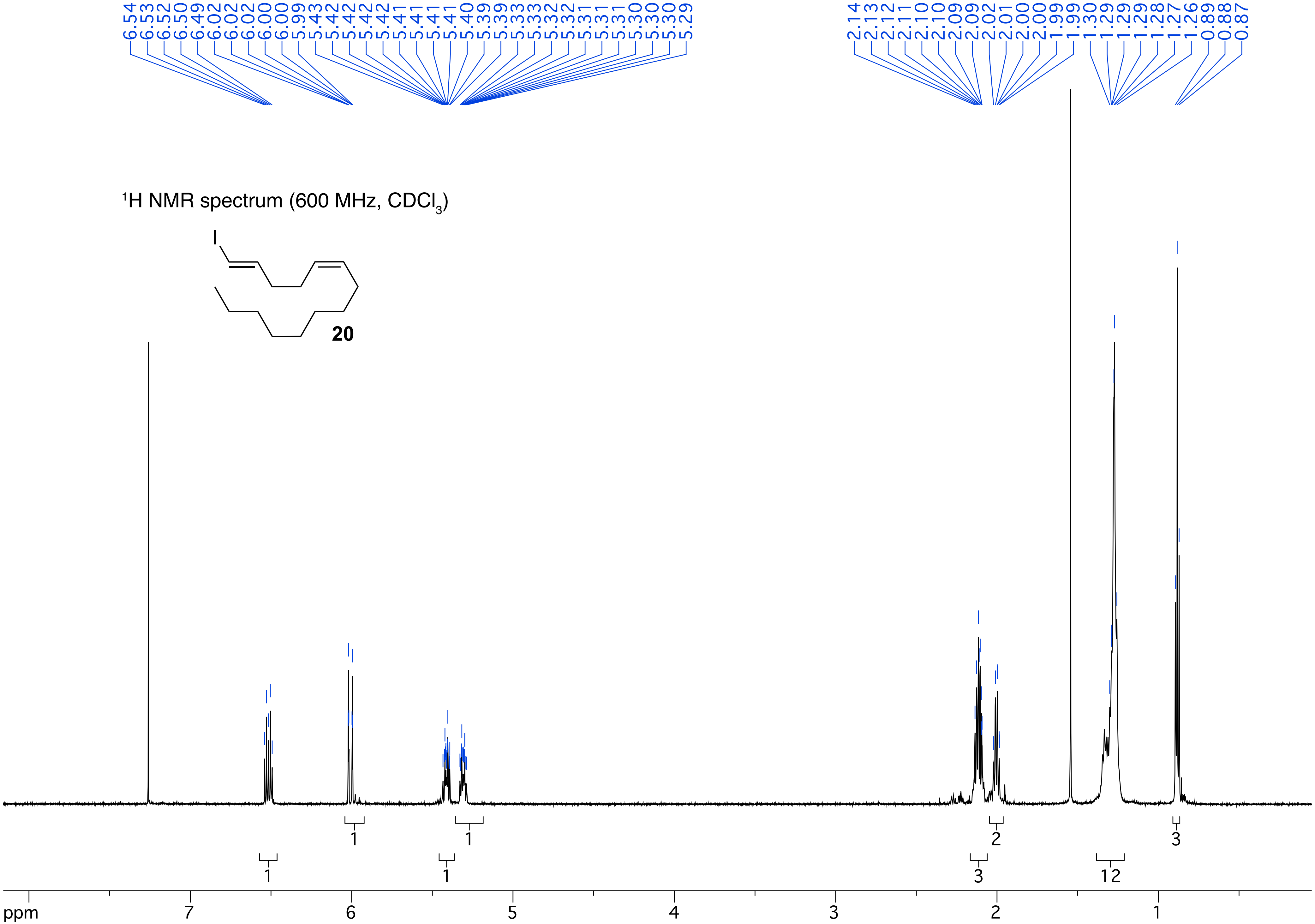
16


5.77
5.74
5.74
5.48
5.46
5.44
5.43
5.40
5.38
5.37
5.34
4.88
4.87
3.15
3.11
3.10
3.09
3.08
2.48
2.13
2.11
2.10
2.03
2.03
2.02
2.01
2.01
2.00
1.99
1.47
1.45
1.27
0.88
0.87
0.17
^{1}H NMR spectrum (500 MHz, CDCl$_3$)
TMSO
CO$_2$^{t}Bu
^{t}BuO$_2$C
H
O
O
17
5.5
5.0
3.0
2.5
2.0
3
2
1
3
13
9
1
1
1
4
18
3
ppm
7
6
5
4
3
2
1
0



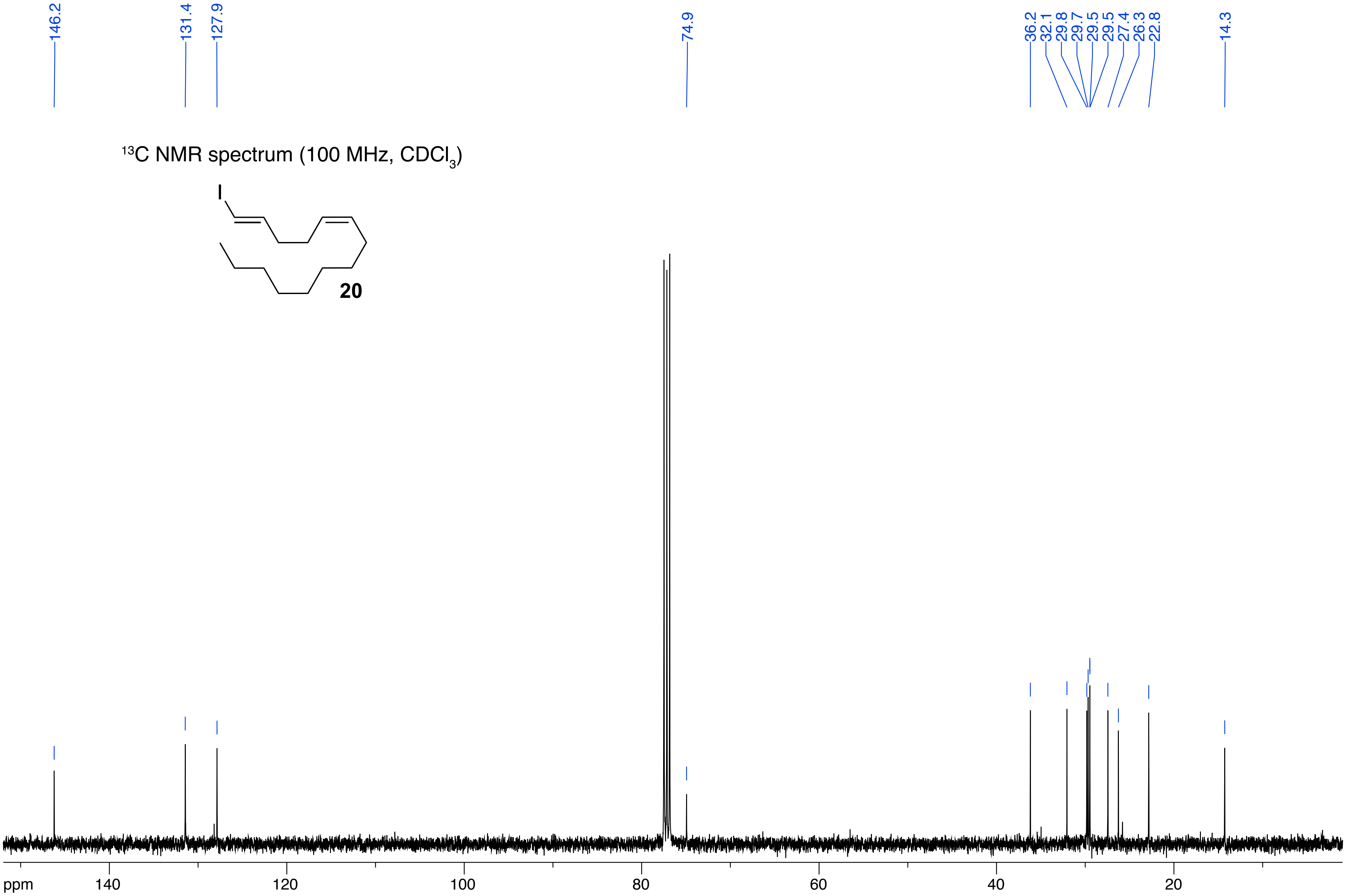
^{13}C NMR spectrum (125 MHz, $CDCl_3$)

17

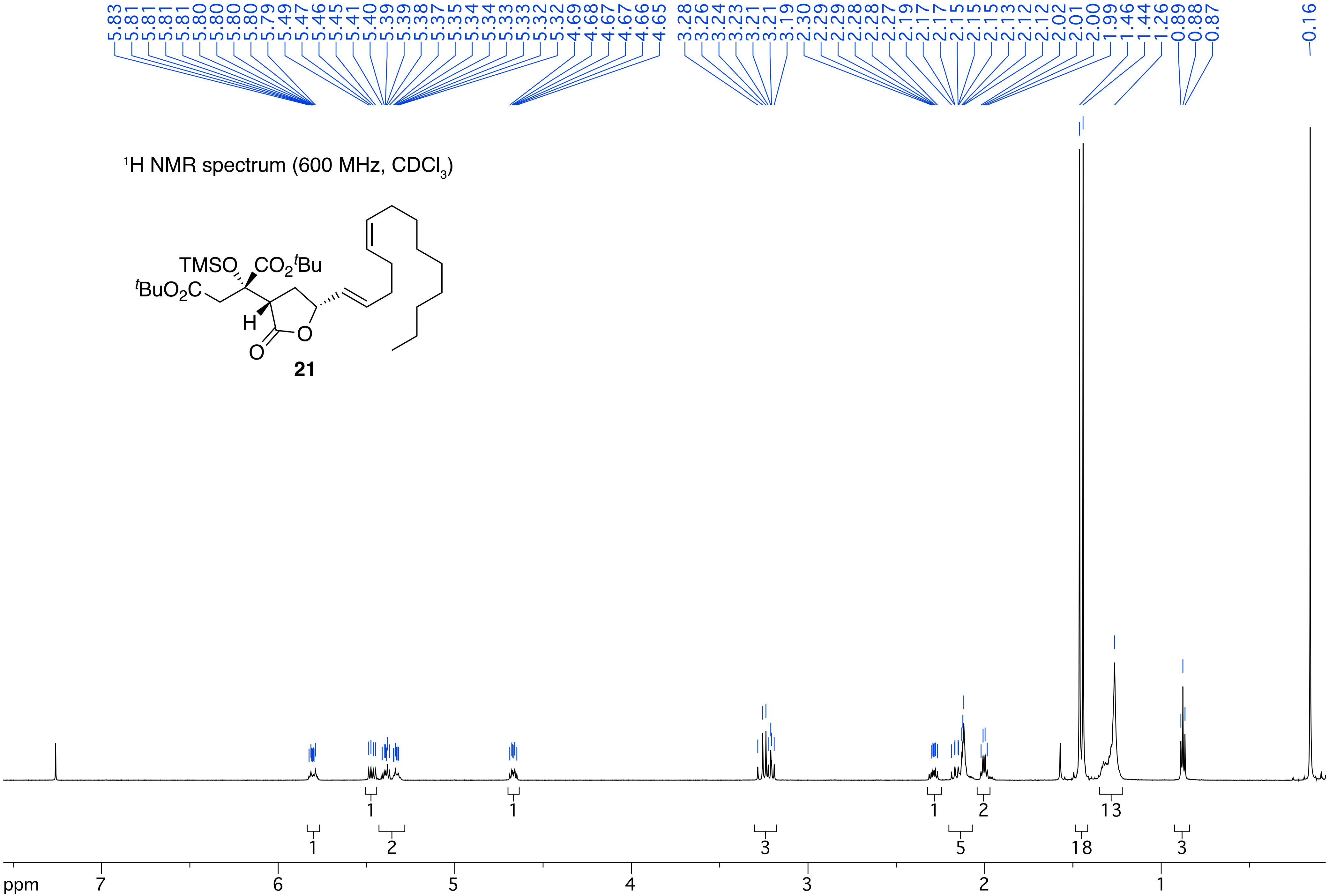


^{1}H NMR spectrum (600 MHz, $CDCl_3$)

20

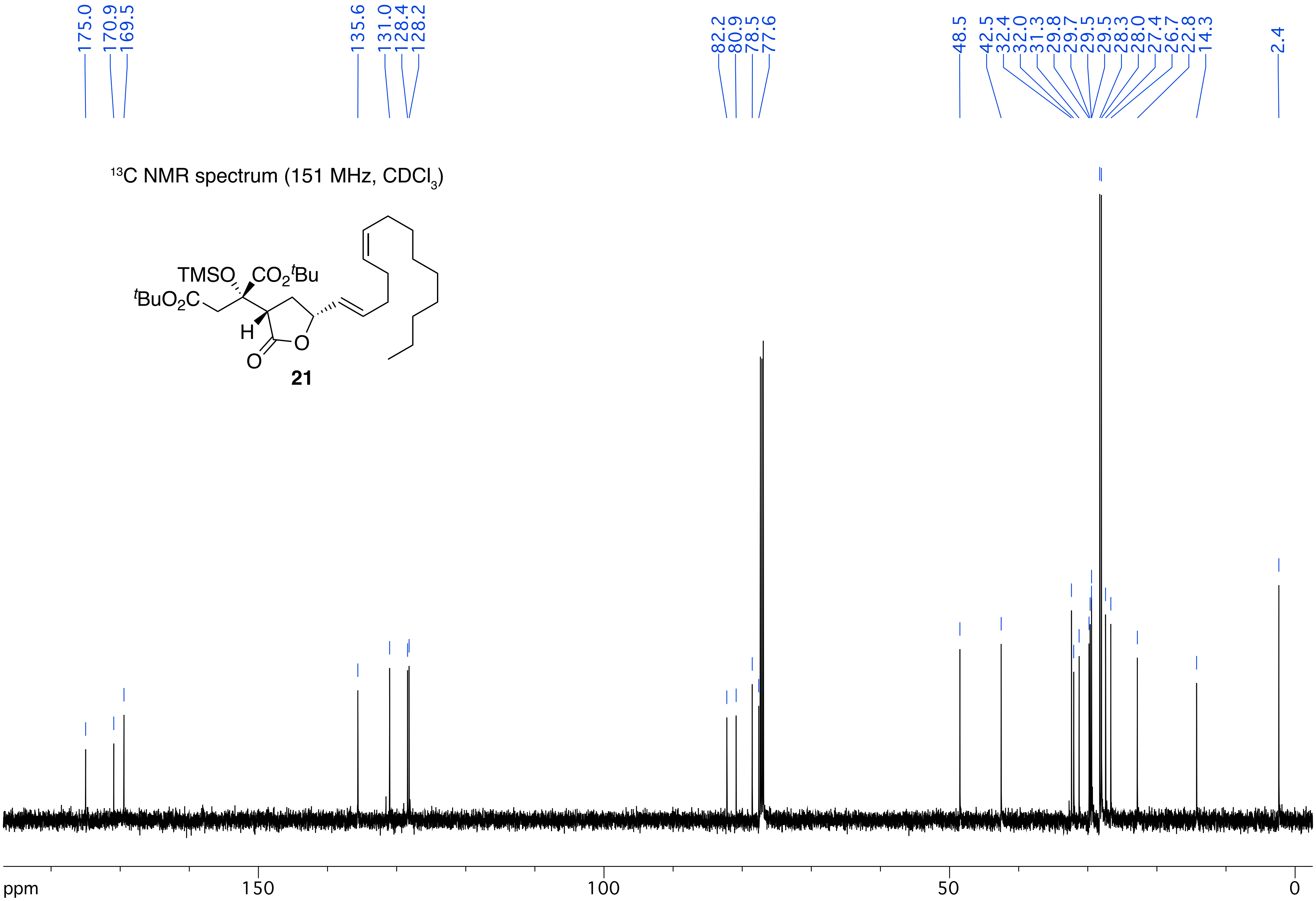

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

20

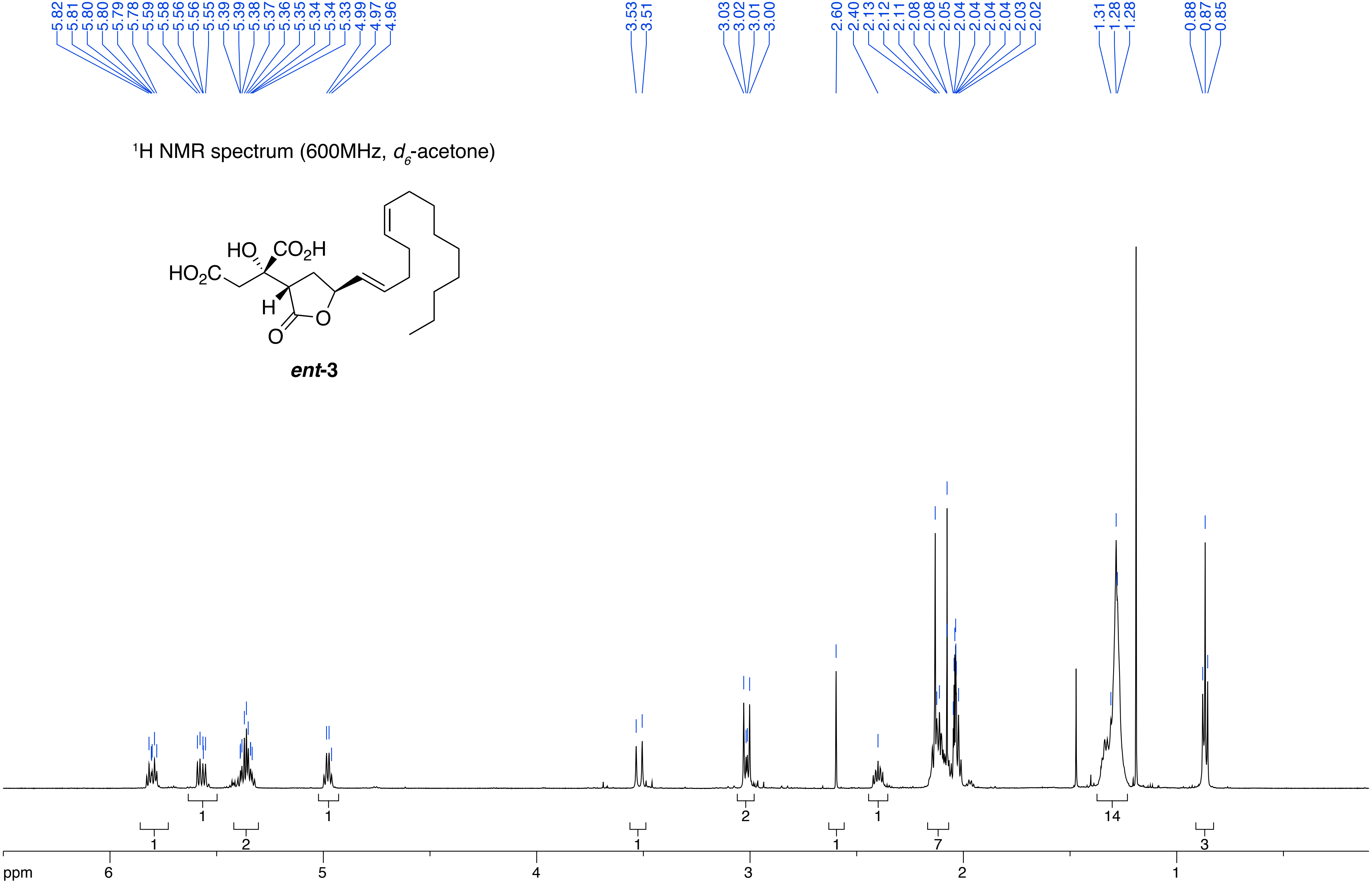


^{1}H NMR spectrum (600 MHz, $CDCl_3$)

21

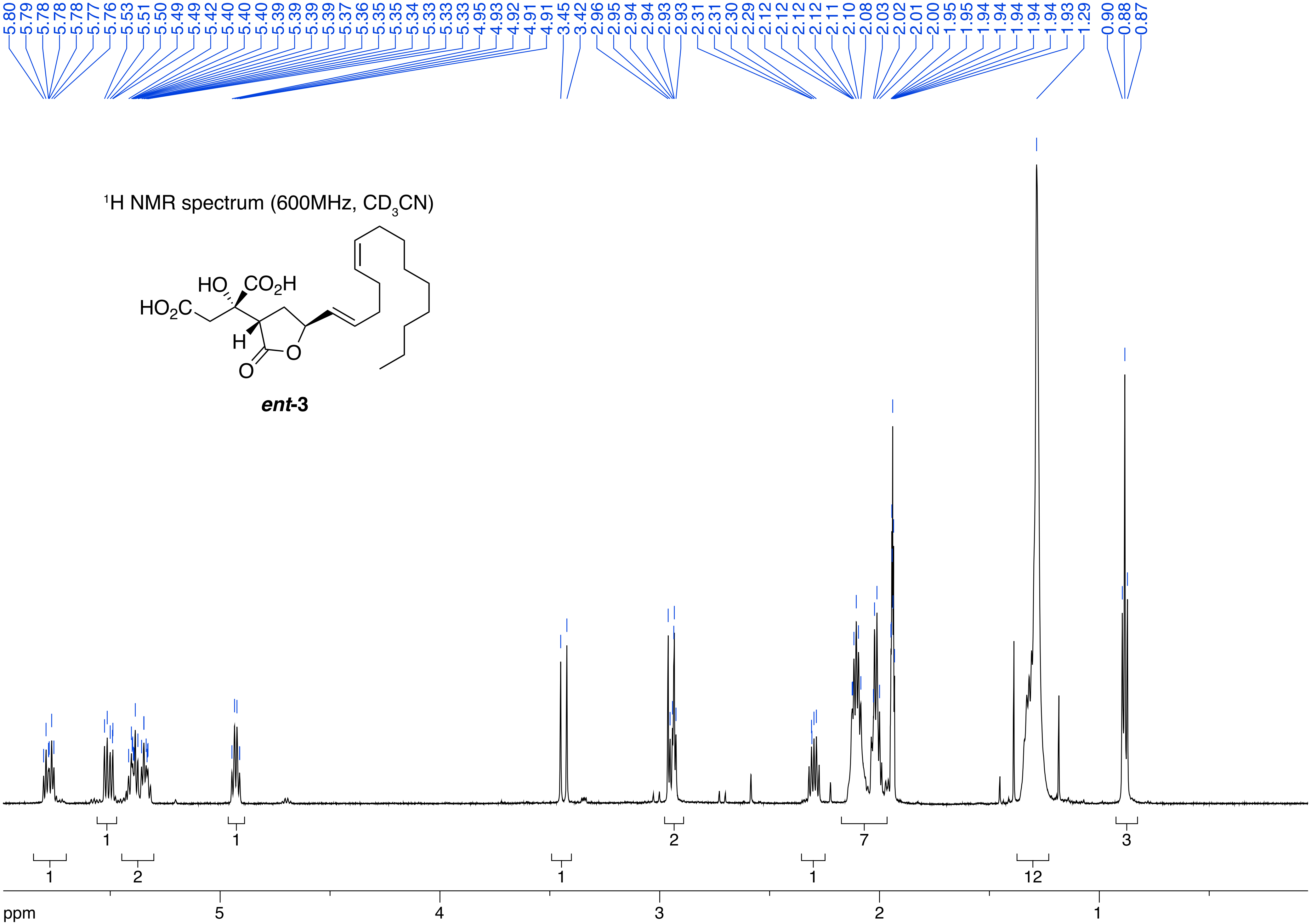

175.0
170.9
169.5
135.6
131.0
128.4
128.2
82.2
80.9
78.5
77.6
48.5
42.5
32.4
32.0
31.3
29.8
29.7
29.5
29.5
28.3
28.0
27.4
26.7
22.8
14.3
2.4
^{13}C NMR spectrum (151 MHz, CDCl$_3$)
TMSO
CO$_2$^{t}Bu
^{t}BuO$_2$C
H
O
O
ppm
150
100
50
0

21

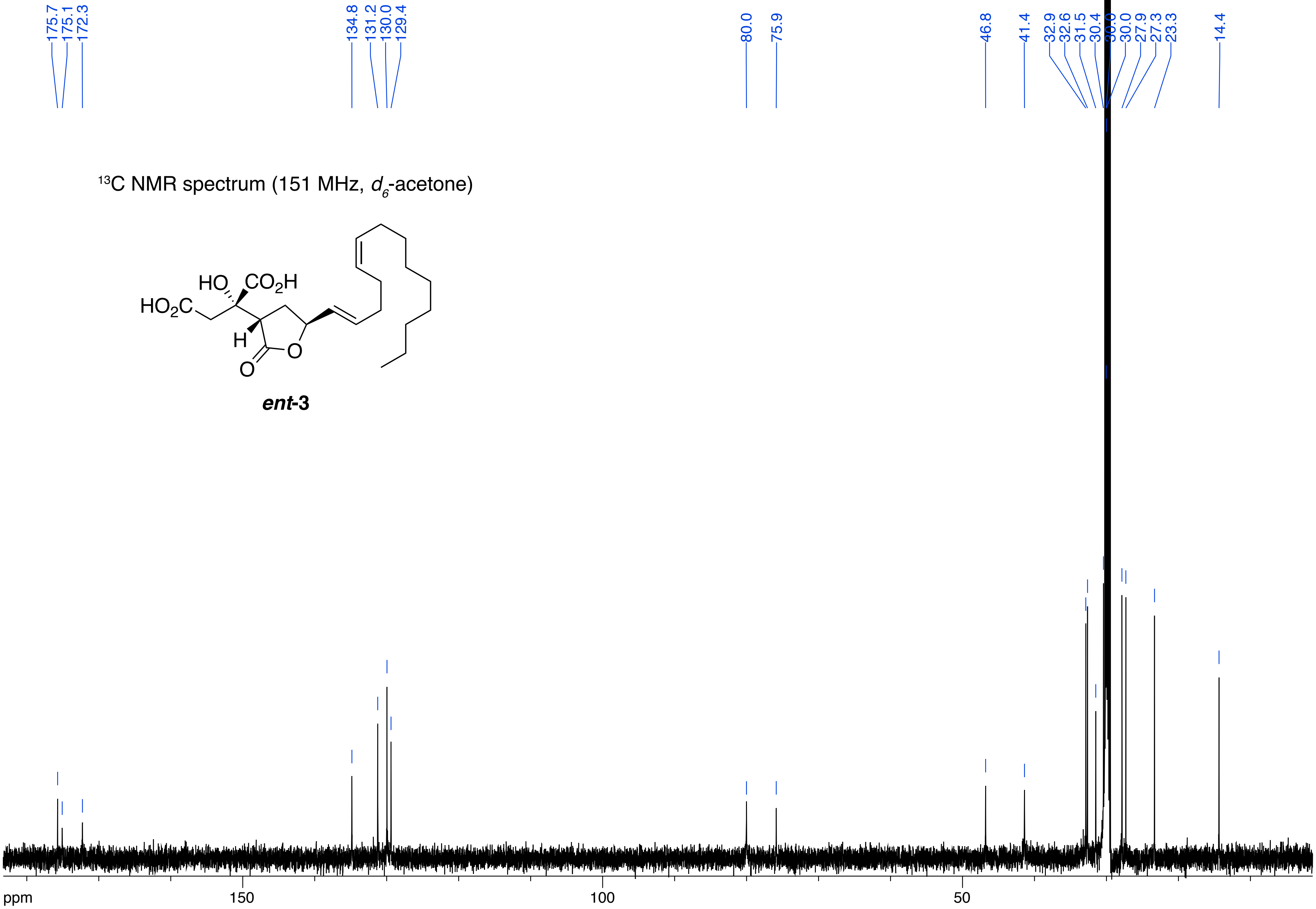


^{1}H NMR spectrum (600MHz, d_6-acetone)

***ent*-3**

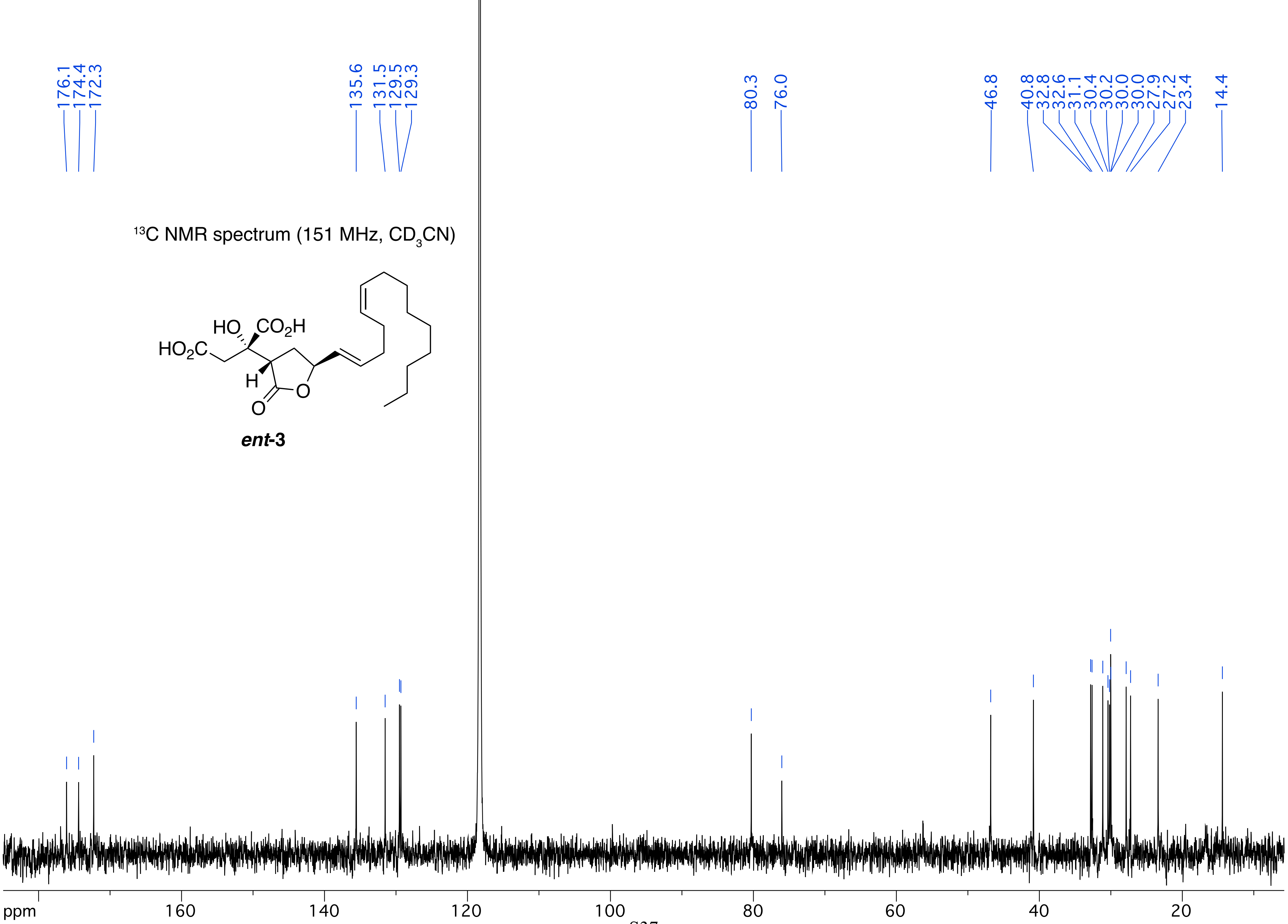

¹H NMR spectrum (600MHz, CD$_3$CN)
HO
CO$_2$H
HO$_2$C
H
O
O
5.80
5.79
5.78
5.78
5.78
5.77
5.76
5.53
5.51
5.50
5.49
5.49
5.42
5.40
5.40
5.40
5.39
5.39
5.39
5.39
5.37
5.36
5.35
5.35
5.34
5.33
5.33
5.33
4.95
4.93
4.92
4.91
4.91
3.45
3.42
2.96
2.95
2.94
2.94
2.93
2.93
2.31
2.31
2.30
2.29
2.12
2.12
2.12
2.12
2.11
2.10
2.08
2.03
2.02
2.01
2.00
1.95
1.95
1.94
1.94
1.94
1.94
1.94
1.93
1.29
0.90
0.88
0.87
1
1
2
7
3
1
2
1
1
12
ppm
5
4
3
2
1

***ent*-3**



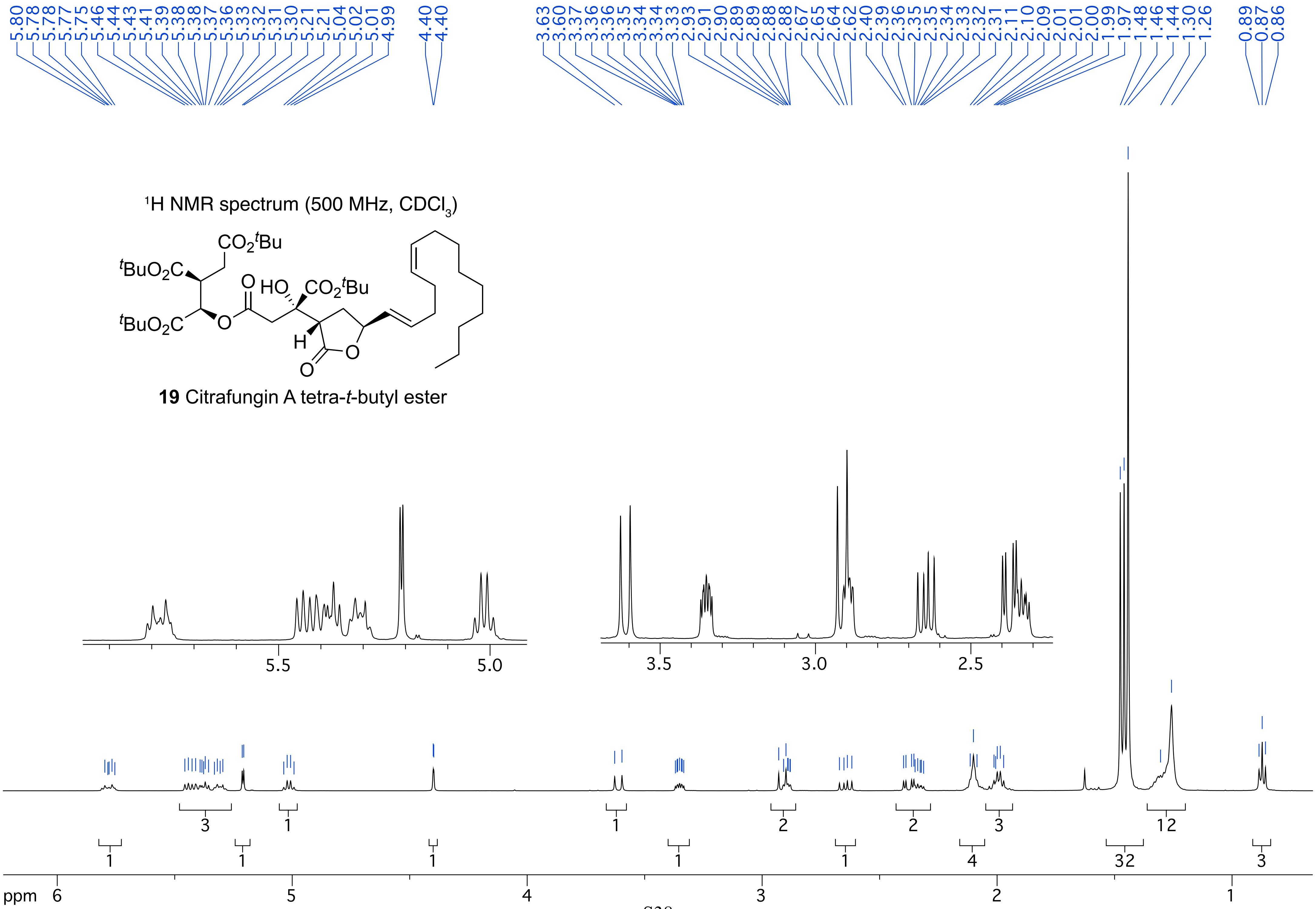
^{13}C NMR spectrum (151 MHz, d_6-acetone)

***ent*-3**



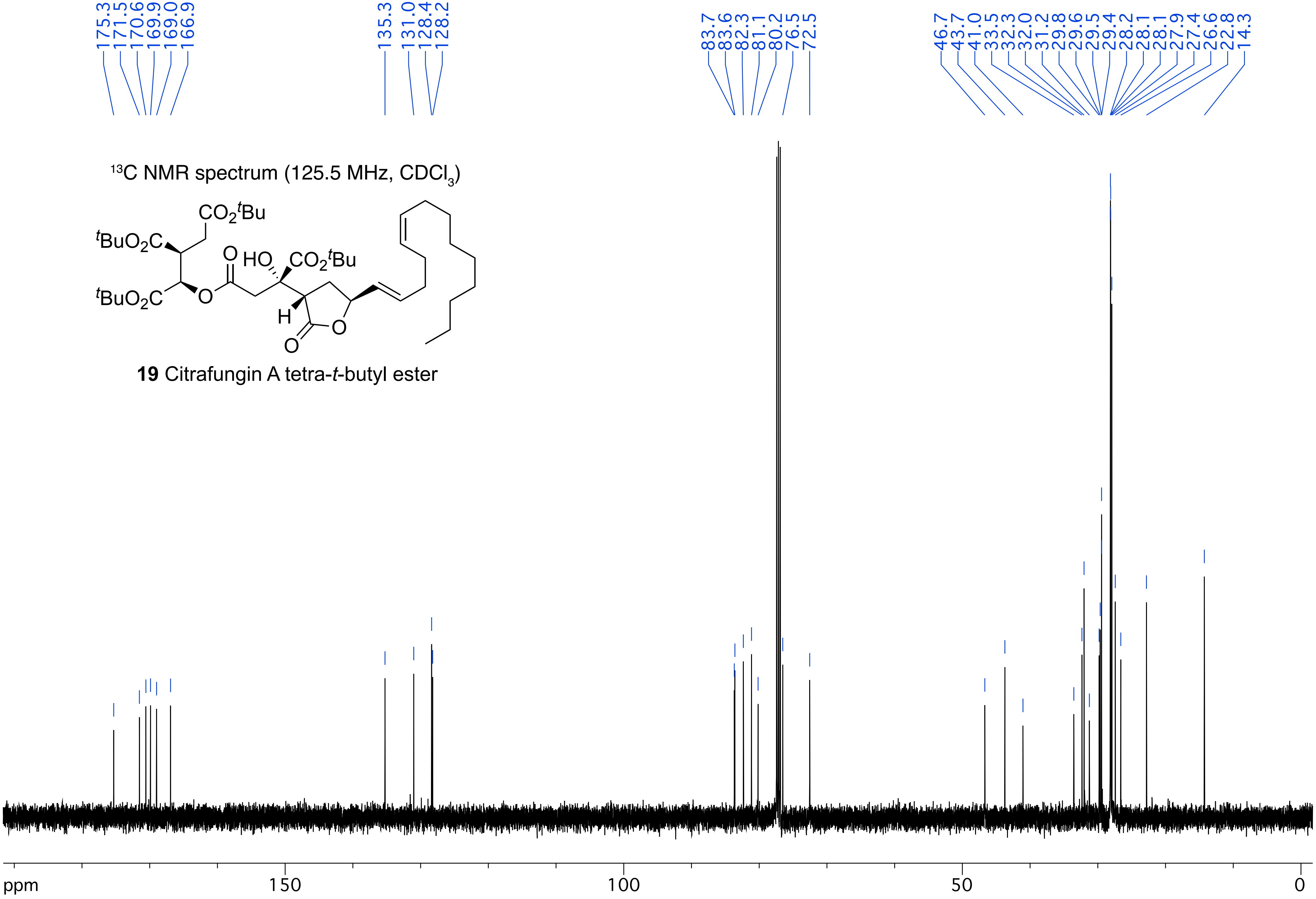
^{13}C NMR spectrum (151 MHz, CD_3CN)

***ent*-3**



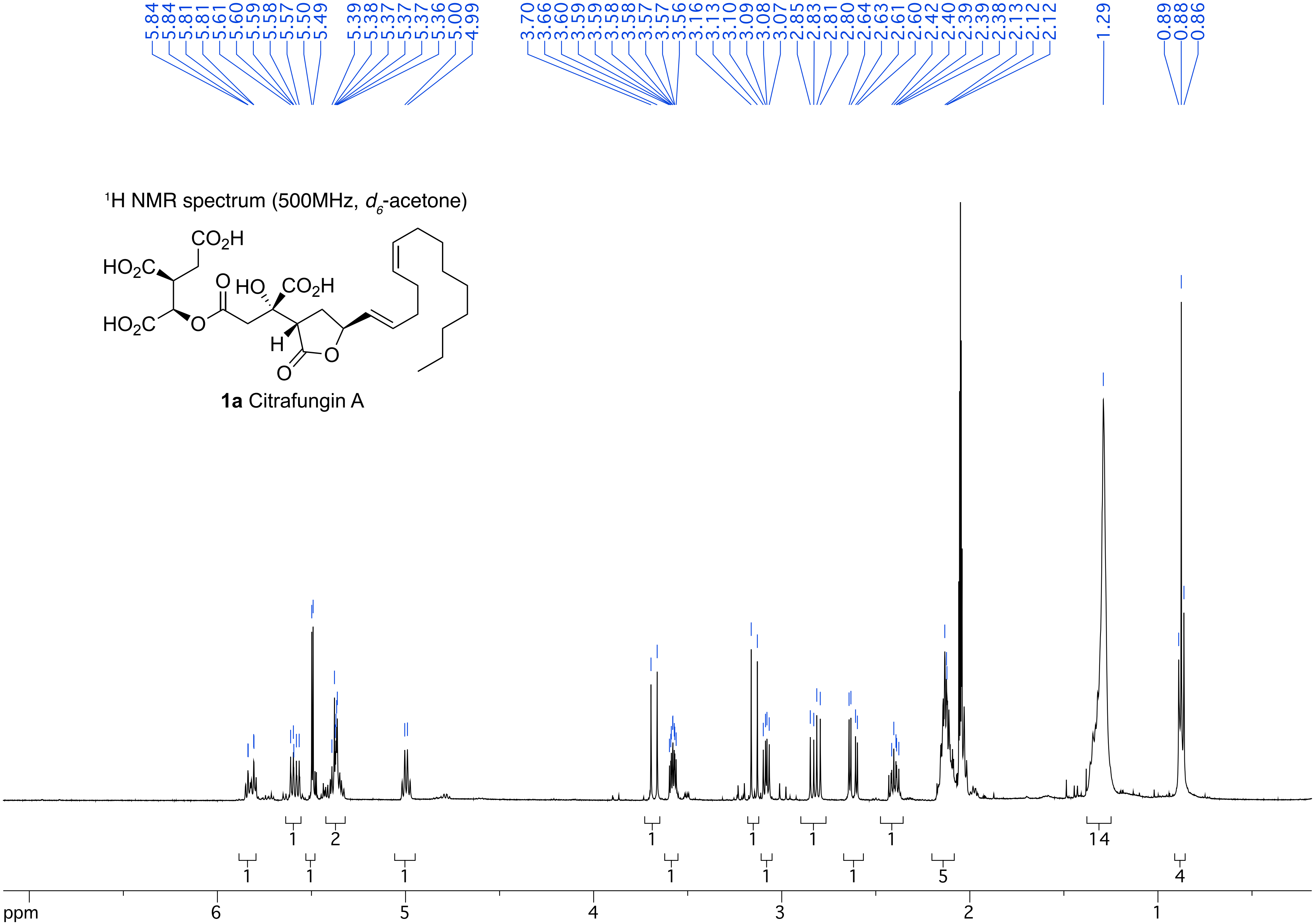
^{1}H NMR spectrum (500 MHz, $CDCl_3$)

19 Citrafungin A tetra-*t*-butyl ester



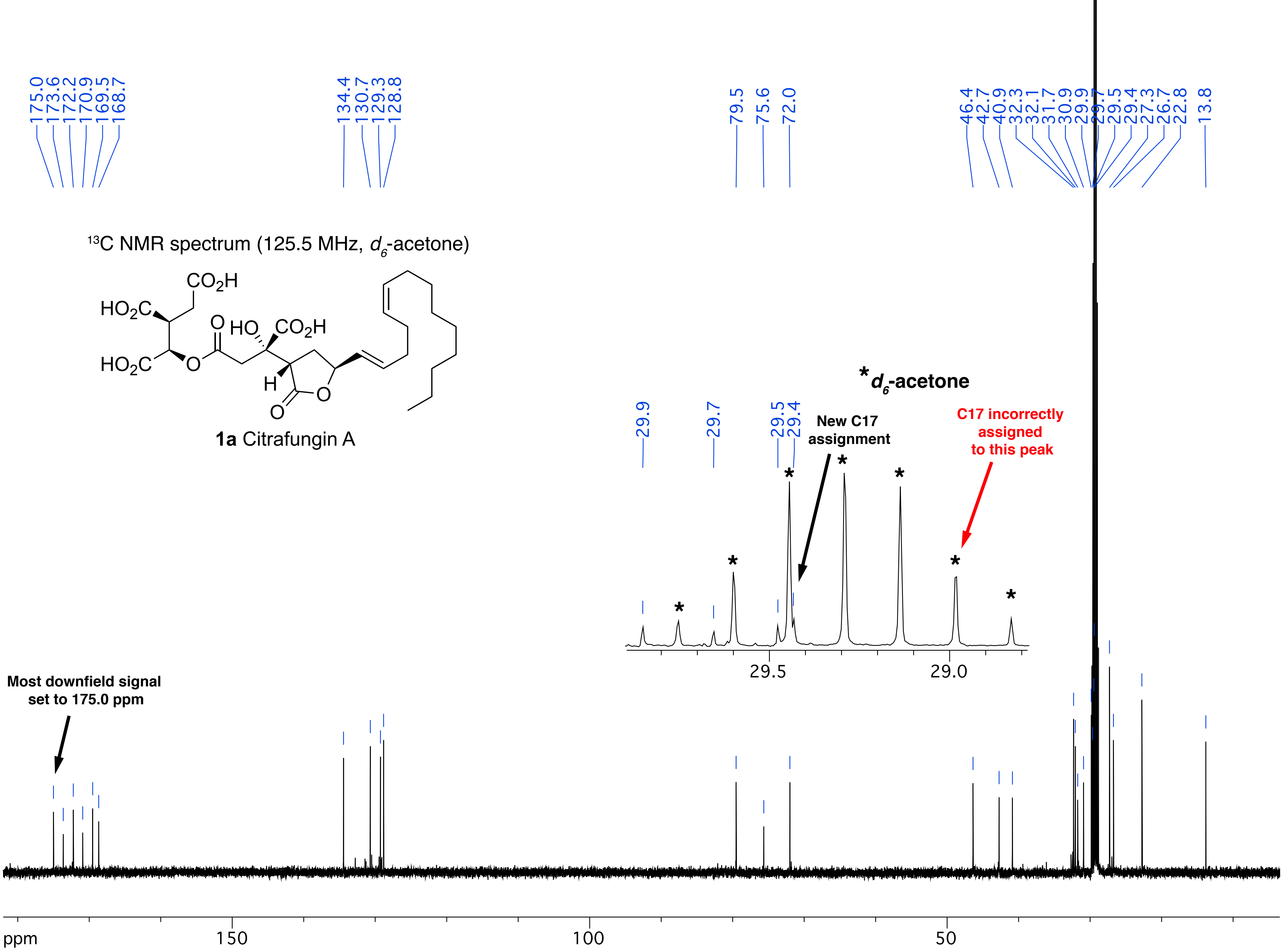
^{13}C NMR spectrum (125.5 MHz, $CDCl_3$)

19 Citrafungin A tetra-*t*-butyl ester

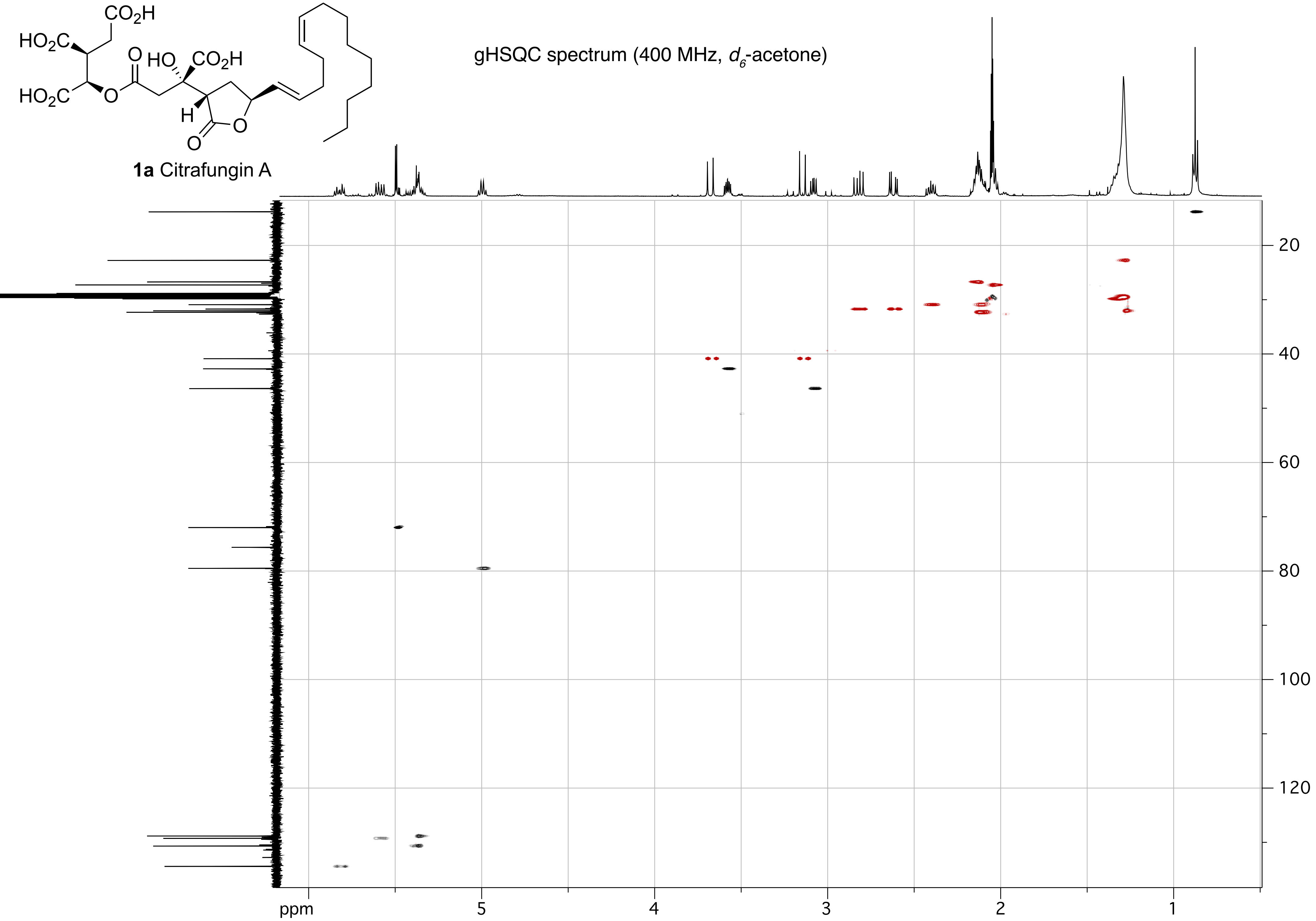


^{1}H NMR spectrum (500MHz, *d*$_6$-acetone)

1a Citrafungin A

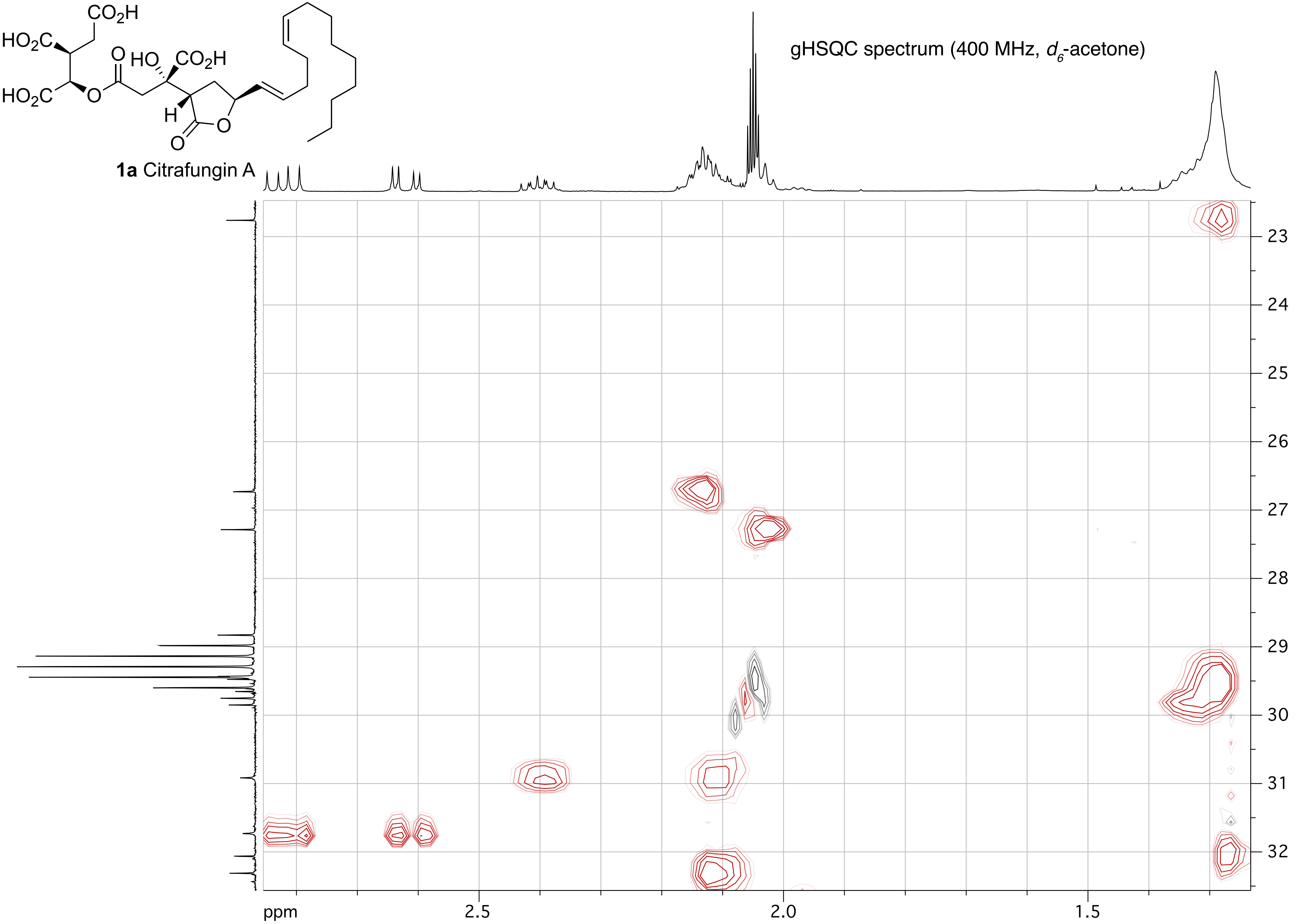

^{13}C NMR spectrum (125.5 MHz, d_6-acetone)

1a Citrafungin A



1a Citrafungin A

gHSQC spectrum (400 MHz, d_6-acetone)



1a Citrafungin A

gHSQC spectrum (400 MHz, d_6-acetone)