

CHEMISTRY

A **European** Journal

Supporting Information

A Two-Component Alkyne Metathesis Catalyst System with an Improved Substrate Scope and Functional Group Tolerance: Development and Applications to Natural Product Synthesis

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General. Unless stated otherwise, all reactions were carried out under Argon in flame-dried glassware. The solvents were purified by distillation over the indicated drying agents and were transferred under Argon: THF, Et₂O (Mg/anthracene), CH₂Cl₂, (CH₂Cl)₂, EtOAc, MeCN (CaH₂), hexane, pentane, toluene (Na/K), MeOH, EtOH (Mg), DMF (MS 4Å), DMSO (distilled over CaH₂, stored over MS 4Å). Flash chromatography: Merck silica gel 60 (40-63 μm) or Merck silica gel 60 (15-40 μm). NMR: Spectra were recorded on Bruker DPX 300, AV 400, AV 500 or AVIII 600 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale (CDCl₃: δ_H ≡ 7.26 ppm, δ_C ≡ 77.2 ppm; CD₂Cl₂: δ_H ≡ 5.32 ppm, δ_C ≡ 53.8 ppm; C₆D₆: δ_H ≡ 7.16 ppm, δ_C ≡ 128.0 ppm; [D₆]-DMSO: δ_H ≡ 2.50 ppm, δ_C ≡ 39.5 ppm). In cases in which assignments are reported, they are based upon 1D and 2D spectra recorded using the following pulse sequences from the Bruker standard pulse program library: DEPT; COSY (*cosygpaqf* and *cosydaqtp*); HSQC (*hsqcedetgpsisp2.2*) optimized for ¹*J*_{C,H} = 145 Hz; HMBC (*hmbcetgpl3nd*) for correlations via ^{*n*}*J*_{C,H}; HSQC-TOCSY (*invietgsmf*) using an MLEV17 mixing time of 120 ms; NOESY (*noesygpqh*). IR: Spectrum One (Perkin-Elmer) spectrometer, wavenumbers (ν̃) in cm⁻¹. MS (EI): Finnigan MAT 8200 (70 eV), ESI MS: ESQ3000 (Bruker), accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or Mat 95 (Finnigan). Unless stated otherwise, all commercially available compounds (ABCR, Acros, Aldrich, Alfa Aesar, TCI) were used as received.

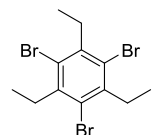
Synthesis of the Tridentate Ligands

Phenyltrivinylsilane (S1). Trichloromethylsilane (2.12 g, 10.0 mmol) was added dropwise at room temperature over 60 min to a solution of vinylmagnesium bromide (1 M in THF, 31.0 mL, 31.0 mmol) in THF (20 mL). After stirring for 16 h, the mixture was cooled to 0 °C and sat. aq. NH₄Cl (30 mL) was slowly introduced. Stirring was continued for 10 min at room temperature before the aqueous layer was extracted with ethyl acetate (2 × 50 mL) and the combined organic layers were dried over MgSO₄. Evaporation of the solvent and purification of the residue by flash chromatography (SiO₂, hexanes) afforded the title compound as a colorless oil (1.23 g, 66%). ¹H NMR (400 MHz, CDCl₃): δ = 7.54–7.59 (m, 2H), 7.35–7.42 (m, 3H), 6.35 (dd, *J* = 19.9, 14.6 Hz, 3H), 6.21 (dd, *J* = 14.6, 4.0 Hz, 3H), 5.84 ppm (dd, *J* = 19.9, 4.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 136.1, 135.2, 134.6, 133.9, 129.6, 128.0 ppm; IR (film): ν̃ = 3051, 3007, 2969, 2944, 1590, 1428, 1400, 1266, 1110, 1006, 956, 809, 699, 619, 549, 471 cm⁻¹; HRMS (EI (FE)): *m/z*: calcd. for [C₁₂H₁₄Si]⁺: 186.0864, found: 186.0865. The analytical and spectroscopic data are in agreement with those reported in the literature.¹

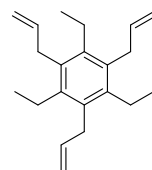
1,3,5-Triallylbenzene (10a). A solution of 1,3,5-tribromobenzene **9a** (1.67 g, 5.32 mmol), allyltributylstannane (5.87 g, 17.7 mmol) and (Ph₃P)₄Pd (1.54 g, 1.33 mmol, 25 mol%) in toluene (8 mL) was stirred for 18 h at 120 °C in a closed JYoung tube. After cooling to room temperature, the reaction was quenched with sat. aq. KF (20 mL). The mixture was diluted with *tert*-butyl methyl ether (20 mL) and stirred for 15 min before water (30 mL) and aq. sat. Na/K-tartrate (10 mL) were added. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), the combined extracts were dried over MgSO₄ and the solvent was evaporated. The crude product was purified by distillation (10⁻³ mbar, 65 °C) to give the title compound as a colorless oil (801 mg, 76%). ¹H NMR (400 MHz, CDCl₃): δ = 6.87 (s, 3H), 5.96 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 3H), 5.04–5.12 (m, 6H), 3.35 ppm (d, *J* = 6.8 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ = 140.5, 137.7,

126.8, 115.8, 40.3 ppm; HRMS (EI): m/z : calcd. for $[C_{15}H_{18}]$: 198.1410, found: 198.1409. The analytical and spectroscopic data are in agreement with those reported in the literature.²

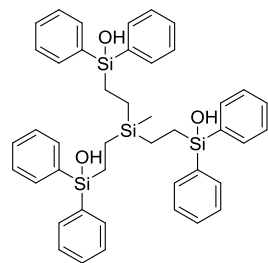
1,3,5-Tribromo-2,4,6-triethylbenzene (9b). 1,3,5-Triethylbenzene (3.86 g, 23.8 mmol) was added over 15 min to a mixture of bromine (20 mL) and iron powder (400 mg, 7.16 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 16 h before it was slowly poured into a solution of KOH (30 g) in aq. sat. $Na_2S_2O_3$. After extraction of the aqueous phase with CH_2Cl_2 (3 × 200 mL), the combined organic layers were dried over $MgSO_4$. The solvent was removed and the residue recrystallized from ethanol to give 1,3,5-tribromo-2,4,6-triethylbenzene as a colorless crystalline solid (7.20 g, 76%). mp = 103–105 °C; 1H NMR (400 MHz, $CDCl_3$): δ = 3.14 (q, J = 7.7 Hz, 6H), 1.17 ppm (t, J = 7.7 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6, 124.4, 32.8, 12.4 ppm; IR (film): $\tilde{\nu}$ = 2971, 2935, 2870, 1534, 1461, 1360, 1313, 1240, 1075, 1054, 1003, 893, 784, 663, 620 cm^{-1} ; HRMS (EI(DE)): m/z : calcd. for $[C_{12}H_{15}Br_3]^+$: 395.8723, found: 395.8724. The analytical and spectroscopic data are in agreement with those reported in the literature.³



1,3,5-Triallyl-2,4,6-triethylbenzene (10b). Allyltributylstannane (8.54 g, 25.8 mmol) was added to a solution of compound **9b** (2.57 g, 6.45 mmol), tetrakis(triphenylphosphine)palladium (1.16 g, 1.00 mmol, 16 mol%) and CsF (3.04 g, 20.0 mmol) in DMF (15 mL). The mixture was stirred for 3.5 h at 135 °C in a closed JYoung tube. After cooling to room temperature, methyl *tert*-butyl ether (200 mL) and aq. sat. KF (100 mL) were added and stirring was continued for 10 min. Water (100 mL) and aq. sat. Na/K-tartrate (100 mL) were added and the aqueous layer was extracted with methyl *tert*-butyl ether (3 × 150 mL). The combined extracts were dried over $MgSO_4$, the solvent was evaporated, and the crude product was purified by flash chromatography (SiO_2 , hexanes) to give the title compound as a colorless solid (1.10 g, 60%). mp = 57–58 °C; 1H NMR (400 MHz, $CDCl_3$): δ = 6.03 (ddt, J = 17.1, 10.1, 5.0 Hz, 3H), 4.86–4.83 (m, 3H), 4.72 (dq, J = 17.1, 1.9 Hz, 3H), 3.42 (dt, J = 5.0, 1.9 Hz, 6H), 2.54 (q, J = 7.5 Hz, 6H), 1.17 ppm (t, J = 7.5 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.3, 137.9, 133.0, 114.8, 33.0, 22.9, 15.5 ppm; IR (film): $\tilde{\nu}$ = 3080, 3001, 2962, 2927, 2897, 2869, 1817, 1636, 1485, 1448, 1422, 1403, 1376, 1291, 1227, 1198, 1117, 1059, 995, 927, 905, 823, 769, 629, 555 cm^{-1} ; HRMS (EI(DE)): m/z : calcd. for $[C_{21}H_{30}]$: 282.2345, found: 282.2348.

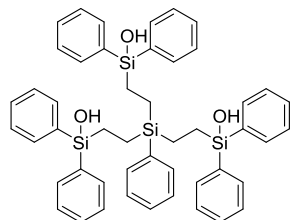


((Methylsilanetriyl)tris(ethane-2,1-diyl))tris(diphenylsilanol) (8a). Trivinylmethylsilane (746 mg, 6.00 mmol) was dissolved in toluene (50 mL) in a flame-dried Schlenk flask. After addition of Karstedt's catalyst (0.3 mL, 0.1 M in poly(dimethylsiloxane)) the mixture was heated to 60 °C and diphenylchlorosilane (4.05 g, 18.5 mmol) was added dropwise and stirring continued for 20 h at this temperature. The mixture was then allowed to reach ambient temperature before H_2O (10 mL) and triethylamine (0.5 mL) were added and the mixture stirred for 20 min; aq. sat. NH_4Cl (5 mL) was introduced and stirring continued for another 10 min. The aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the combined organic layers were dried over $MgSO_4$. The crude product was purified by flash chromatography (SiO_2 , hexanes/ethyl acetate, 4/1 to 3/1). The material was dissolved in CH_2Cl_2 (20 mL) and MS 3 Å (2 g) was added. After gentle stirring of the suspension for 2 h at room temperature, the MS was filtered off and the filtrate was evaporated. The product was dried for 4 h in high vacuum to afford the title compound as a colorless hygroscopic solid



(2.43 g, 56%). ^1H NMR (400 MHz, CD_3OD): δ = 7.54–7.48 (m, 12H), 7.35–7.26 (m, 18H), 0.90–0.79 (m, 6H), 0.56–0.47 (m, 6H), –0.11 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 138.2, 135.3, 130.6, 128.8, 8.2, 4.7, –6.4 ppm; IR (film): $\tilde{\nu}$ = 3258, 3068, 3047, 3012, 2908, 2879, 1589, 1427, 1249, 1111, 1053, 1027, 997, 818, 695, 664, 636, 499, 479, 445 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{43}\text{H}_{48}\text{O}_3\text{Si}_4+\text{Na}]^+$: 747.2569, found: 747.2573.

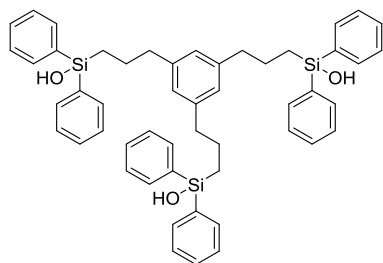
((Phenylsilanetriyl)tris(ethane-2,1-diyl))tris(diphenylsilanol) (8b). Diphenylchlorosilane (3.91 g, 17.9



mmol) was added dropwise to a solution of phenyltrivinylmethylsilane **51** (950 mg, 5.10 mmol) and Karstedt's catalyst (0.4 mL, 0.1 M in poly(dimethylsiloxane)) in toluene (20 mL) at 50 °C. The mixture was stirred for 16 h at this temperature before a second portion of Karstedt's catalyst (0.1 mL, 0.1 M in poly(dimethylsiloxane)) was added and stirring continued for another 2 h at 65 °C. The mixture was allowed to reach room temperature

before H_2O (20 mL) and triethylamine (0.5 mL) were added. After stirring for 20 min, aq. sat. $\text{NH}_4\text{Cl}_{\text{aq}}$ (5 mL) was introduced and stirring continued for 10 min. The water layer was extracted with ethyl acetate (3×100 mL) and the combined extracts were dried over MgSO_4 . Evaporation of the solvent and flash chromatography of the residue (SiO_2 , hexanes/ethyl acetate, 4/1 to 2/1) gave the crude product which was dried by stirring of a solution in CH_2Cl_2 (20 mL) in the presence of MS 3Å (2 g) for 2 h. The MS was filtered off, the solvent was evaporated and the resulting product dried for 4 h in high vacuum to afford the title compound as a colorless hygroscopic solid (2.31 g, 58%). mp = 56–60 °C; ^1H NMR (400 MHz, CDCl_3): δ = 7.51–7.55 (m, 12H), 7.30–7.42 (m, 23H), 2.38–2.41 (m, 3H), 0.84–1.00 ppm (m, 12H); ^{13}C NMR (100 MHz, CDCl_3): δ = 136.3, 136.0, 134.5, 134.3, 130.0, 129.2, 128.0, 127.9, 7.0, 2.3 ppm; IR (film): $\tilde{\nu}$ = 3298, 3067, 3046, 2910, 1705, 1589, 1486, 1427, 1304, 1262, 1110, 1049, 997, 828, 694, 665, 643, 501, 471, 445 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{48}\text{H}_{50}\text{O}_3\text{Si}_4+\text{Na}]^+$: 809.2729, found: 809.2729.

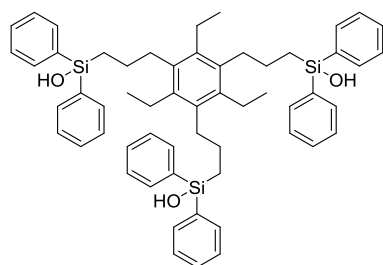
(Benzene-1,3,5-triyltris(propane-3,1-diyl))tris(diphenylsilanol) (11a). Prepared analogously at 50°C



reaction temperature from compound **10a** as a colorless hygroscopic solid (756 mg, 47%). mp = 57–65 °C; ^1H NMR (400 MHz, CDCl_3): δ = 7.52–7.56 (m, 12H), 7.30–7.41 (m, 18H), 6.71 (s, 3H), 2.56 (t, J = 7.4 Hz, 6H), 2.32–2.38 (m, 3H), 1.70–1.80 (m, 6H), 1.12–1.17 ppm (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ = 142.1, 136.3, 134.3, 130.0, 128.0, 126.5, 39.3, 24.9, 14.8 ppm; IR (film): $\tilde{\nu}$ = 3241, 3067, 3046, 2999, 2923, 2857, 1590, 1427, 1112, 1067, 1045, 1027, 997, 823, 734, 695,

504, 480, 448 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{51}\text{H}_{54}\text{O}_3\text{Si}_3+\text{Na}]^+$: 821.3274, found: 821.3273.

((2,4,6-Triethylbenzene-1,3,5-triyl)tris(propane-3,1-diyl))tris (diphenylsilanol) (11b). Prepared



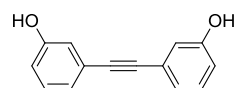
analogously from compound **10b** at 70°C reaction temperature; colorless hygroscopic solid (560 mg, 0.63 mmol, 54%). mp = 66–75 °C; ^1H NMR (400 MHz, CDCl_3): δ = 7.59 (d, J = 7.0 Hz, 12H), 7.32–7.44 (m, 18H), 2.50–2.59 (m, 6H), 2.38 (q, J = 7.2 Hz, 6H), 2.06–2.13 (m, 3H), 1.55–1.66 (m, 6H), 1.29 (t, J = 7.9 Hz, 6H), 1.06 ppm (t, J = 7.2 Hz, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ = 138.4, 136.4, 136.3, 134.3, 130.0, 128.1, 33.6, 25.0, 22.6, 16.5, 15.8 ppm; IR (film): $\tilde{\nu}$ = 3299, 3068, 3047,

2958, 2927, 2869, 1589, 1486, 1462, 1427, 1373, 1305, 1262, 1169, 1112, 1066, 1026, 997, 965, 944, 824, 762, 736, 696, 640, 504, 479, 449 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{57}\text{H}_{66}\text{O}_3\text{Si}_3+\text{Na}]^+$: 905.4212, found: 905.4212.

Homo-Metathesis Reactions

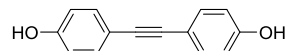
Representative Alkyne Metathesis Reaction using the Two-Component Catalyst System. Preparation of

3,3'-(Ethyne-1,2-diyl)diphenol. MS 5Å (200 mg) was added to a solution of 3-(prop-1-yn-1-yl)phenol (33.0 mg, 0.25 mmol) in toluene (2 mL) and the resulting suspension was stirred at room temperature for 1 h. A freshly prepared solution of the tris-silanol **11b** (22.1 mg, 25.0 μmol , 10 mol%) and $[\text{Mo}(\equiv\text{CEt})(\text{NAr}^t\text{Bu})_3]$ (16.6 mg, 25.0 μmol , 10 mol%), which had been stirred in toluene (1 mL) for 5 min, was added. The mixture was stirred for 14 h at room temperature before the molecular sieves were filtered off through a pad of Celite®, which was rinsed with ethyl acetate (20 mL). The combined filtrates were evaporated and the residue purified by flash chromatography (SiO_2 , hexanes/EtOAc, 4/1 to 2/1) to afford the title compound as a colorless solid (21.0 mg, 80%). ^1H NMR (400 MHz, CDCl_3): δ = 7.17 (t, J = 8.0 Hz, 2H), 6.96 (ddd, J = 7.6, 1.5, 1.0 Hz, 2H), 6.90 (dd, J = 2.6, 1.5 Hz, 2H), 6.78 ppm (ddd, J = 8.0, 2.5, 1.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ = 158.5, 130.6, 125.5, 123.9, 119.0, 116.9, 89.6 ppm; IR (film): $\tilde{\nu}$ = 3236, 3059, 2992, 2613, 1574, 1497, 1451, 1322, 1309, 1252, 1182, 1159, 1085, 970, 873, 752, 682 cm^{-1} ; HRMS (EI): m/z : calcd. for $[\text{C}_{14}\text{H}_{10}\text{O}_2]^+$: 210.0679, found: 210.0681. The analytical and spectroscopic data are in agreement with those reported in the literature.⁴

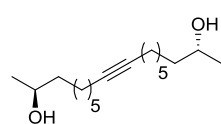


The following compounds were prepared analogously:

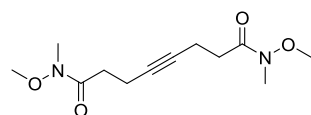
4,4'-(Ethyne-1,2-diyl)diphenol. Colorless solid. ^1H NMR (400 MHz, CD_3CN): δ = 7.35 (d, J = 8.6 Hz, 4H), 7.22 (s, 2H), 6.81 ppm (d, J = 8.6 Hz, 4H); ^{13}C NMR (100 MHz, CD_3CN): δ = 158.0, 133.8, 116.5, 115.6, 88.4 ppm; IR (film): $\tilde{\nu}$ = 3304, 1607, 1591, 1510, 1438, 1371, 1350, 1231, 1171, 1100, 766 cm^{-1} ; HRMS (EI): m/z : calcd. for $[\text{C}_{14}\text{H}_{10}\text{O}_2]^+$: 210.0680, found: 210.0681. The analytical and spectroscopic data are in agreement with those reported in the literature.⁵



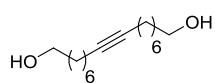
(2R,17R)-Octadec-9-yn-2,17-diol. Colorless solid; mp: 56–57 °C; ^1H NMR (400 MHz, CDCl_3): δ = 3.74–3.82 (m, 2H), 2.14 (t, J = 6.9 Hz, 4H), 1.27–1.51 (m, 22H), 1.18 ppm (d, J = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ = 80.4, 68.3, 39.4, 29.3, 29.2, 28.9, 25.9, 23.7, 18.8 ppm; IR (film): $\tilde{\nu}$ = 3325, 3243, 2960, 2940, 2849, 1496, 1466, 1373, 1354, 1294, 1127, 1107, 1046, 1010, 926, 836, 720, 673 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{18}\text{H}_{34}\text{O}_2+\text{Na}]^+$: 305.2448, found: 305.2451.



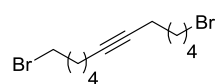
N^1, N^8 -Dimethoxy- N^1, N^8 -dimethyloct-4-ynediarnide. Colorless oil. ^1H NMR (400 MHz, CDCl_3): δ = 3.69 (s, 6H), 3.18 (s, 6H), 2.59–2.66 (m, 4H), 2.41 ppm (t, J = 8.4 Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ = 173.0, 79.6, 61.4, 32.3, 31.7, 14.4 ppm; IR (film): $\tilde{\nu}$ = 2937, 2247, 1736, 1656, 1420, 1386, 1336, 1242, 1177, 1107, 1044, 988, 917, 776, 728, 646, 606, 565, 509, 487, 437 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_4+\text{Na}]^+$: 279.1310, found: 279.1315.



Hexadec-8-yne-1,16-diol. Colorless solid; mp: 39–40 °C; ^1H NMR (400 MHz, CDCl_3): δ = 3.63 (t, J = 6.6 Hz, 4H), 2.19–2.09 (m, 4H), 1.62–1.29 ppm (m, 22H); ^{13}C NMR (100 MHz, CDCl_3): δ = 80.4, 63.1, 32.9, 29.1, 29.1, 28.9, 25.8, 18.8 ppm; IR (film): $\tilde{\nu}$ = 3348, 3265, 2931, 2851, 1457, 1423, 1381, 1361, 1297, 1249, 1211, 1133, 1109, 1094, 1055, 1040, 1014, 1005, 970, 896, 815, 756, 725, 650, 548, 478, 452, 432, 416 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{16}\text{H}_{30}\text{O}_2 + \text{Na}]^+$: 277.2140, found: 277.2138.



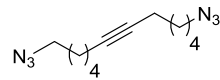
Representative Alkyne Metathesis Reaction using $[\text{Mo}(\equiv\text{CC}_6\text{H}_4\text{OMe})(\text{OSiPh}_3)_3]$ as the catalyst.



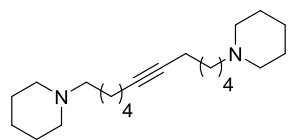
Preparation of 1,12-Dibromododec-6-yne. MS 5 Å (1.25 g) were added to a solution of 1-bromo-6-octyne (250 mg, 1.32 mmol) in toluene (6 mL) and the resulting suspension was gently stirred for 30 min before complex **1** (15 mg, 14.4 μmol , 1 mol%) was added. Stirring was continued for 90 min, and the mixture was filtered through a pad of Celite, which was carefully rinsed with ethyl acetate. The combined filtrates were evaporated and the residue purified by flash chromatography (pentanes) to give the title compound as a colorless oil (212 mg, 91%). ^1H NMR (400 MHz, CDCl_3): δ = 3.41 (t, J = 6.9 Hz, 4H), 2.16 (t, J = 6.5 Hz, 4H), 1.87 (dt, J = 6.9, 6.9 Hz, 4H), 1.58–1.45 ppm (m, 8H); ^{13}C NMR (100 MHz, CDCl_3): δ = 80.2, 33.9, 32.5, 28.3, 27.5, 18.8 ppm; IR (film): $\tilde{\nu}$ = 3302, 2936, 2860, 2213, 1904, 1732, 1671, 1431, 1349, 1230, 1199, 1023, 732, 642 cm^{-1} ; HRMS (EI): m/z : calcd. for $[\text{C}_{12}\text{H}_{20}\text{Br}_2]^+$: 321.9928, found: 321.9932.

The following compounds were prepared analogously:

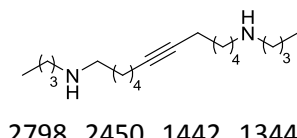
1,12-Diazidododec-6-yne. Colorless oil. ^1H NMR (400 MHz, CDCl_3): δ = 3.27 (t, J = 6.9 Hz, 4H), 2.19–2.14 (m, 4H), 1.66–1.57 (m, 4H), 1.55–1.42 ppm (m, 8H); ^{13}C NMR (100 MHz, CDCl_3): δ = 80.2, 51.5, 28.7, 28.6, 26.1, 18.8 ppm; IR (film): $\tilde{\nu}$ = 2936, 2861, 2087, 1456, 1349, 1333, 1257, 1097, 1026, 896, 839, 733, 668, 637, 557 cm^{-1} ; HRMS (CI(DE), *i*-butane): m/z : calcd. for $[\text{C}_{12}\text{H}_{21}\text{N}_6]^+$: 249.1826, found: 249.1828.



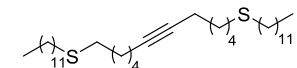
1,12-Di(piperidin-1-yl)dodec-6-yne. Colorless oil. ^1H NMR (400 MHz, CDCl_3): δ = 2.42–2.30 (b, 8H), 2.30–2.24 (m, 4H), 2.13 (t, J = 7.0 Hz, 4H), 1.61–1.54 (m, 8H), 1.53–1.31 ppm (m, 16H); ^{13}C NMR (100 MHz, CDCl_3): δ = 80.3, 59.7, 54.8, 29.3, 27.2, 26.7, 26.2, 24.7, 18.9 ppm; IR (film): $\tilde{\nu}$ = 3392, 2931, 2856, 2799, 2762, 2517, 1655, 1442, 1376, 1350, 1307, 1269, 1153, 1121, 1039, 962, 907, 860, 779, 731, 640, 514 cm^{-1} ; HRMS (ESI $^+$): m/z : calcd. for $[\text{C}_{22}\text{H}_{41}\text{N}_2 + \text{H}]^+$: 333.3264, found: 333.3264.



$\text{N}^1, \text{N}^{12}$ -Dibutyldodec-6-yne-1,12-diamine. Colorless solid; mp = 228–230 °C (decomp.); ^1H NMR (400 MHz, CDCl_3): δ = 3.68 (s, 2H), 2.71 – 2.61 (m, 8H), 2.20 – 2.10 (m, 4H), 1.64 – 1.30 (m, 20H), 0.91 ppm (t, J = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ = 80.3, 49.7, 49.5, 31.5, 28.9, 26.6, 20.6, 18.8, 14.1 ppm; IR (film): $\tilde{\nu}$ = 2953, 2867, 2798, 2450, 1442, 1344, 1042, 888, 790, 758 cm^{-1} ; HRMS (ESI $^+$): m/z : calcd. for $[\text{C}_{20}\text{H}_{41}\text{N}_2]^+$: 309.3264, found: 309.3264.



1,12-Bis(tridecylthio)dodec-6-yne. Colorless solid; mp = 55–56 °C, ^1H NMR (400 MHz, CDCl_3): δ = 2.53–2.47 (m, 8H), 2.17–2.12 (m, 4H), 1.64–1.53 (m, 8H), 1.51–1.45 (m, 8H), 1.42–1.21 (m, 36H), 0.88 ppm (t, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ =



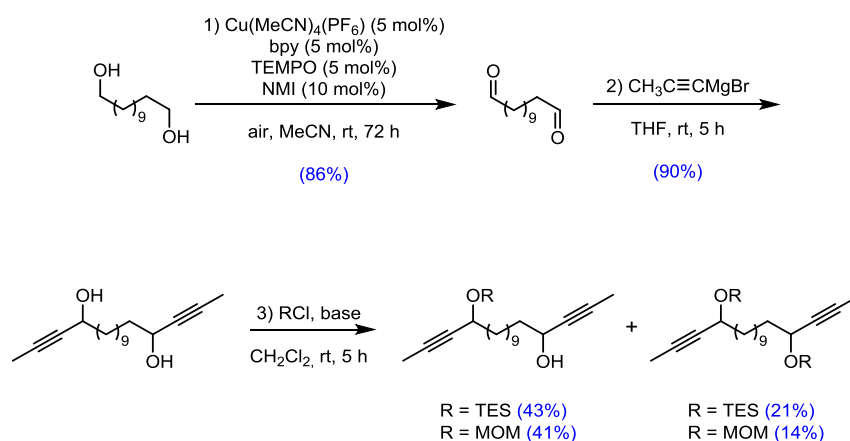
80.3, 32.4, 32.2, 32.1, 29.9, 29.82, 29.79, 29.77, 29.71, 29.51, 29.46, 29.44, 29.1, 28.9, 28.3, 22.8, 18.8, 14.3 ppm; IR (film): $\tilde{\nu}$ = 2953, 2917, 2847, 1459, 1426, 1370, 1297, 1250, 1199, 1186, 1026, 813, 762, 725, 512 cm^{-1} ; HRMS (EI): m/z : calcd. for $[\text{C}_{36}\text{H}_{70}\text{S}_2]^+$: 566.4917, found: 566.4919.

1,12-Bis(tridecylsulfinyl)dodec-6-yne. Colorless solid; mp = 108–110 °C, ^1H NMR (400 MHz, CDCl_3): δ = 2.73–2.56 (m, 8H), 2.20–2.13 (m, 4H), 1.83–1.68 (m, 8H), 1.61–1.38 (m, 12H), 1.36–1.20 (m, 32H), 0.87 ppm (t, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ = 80.2, 52.7, 52.5, 32.0, 29.74, 29.68, 29.51, 29.47, 29.4, 29.1, 28.8, 28.2, 22.82, 22.77, 22.4, 18.7, 14.3 ppm; IR (film): $\tilde{\nu}$ = 2912, 2848, 1466, 1081, 1015, 723, 463 cm^{-1} ; HRMS (ESI⁺): m/z : calcd. for $[\text{C}_{36}\text{H}_{70}\text{NaO}_2\text{S}_2]^+$: 621.4711, found: 621.4709.

1,24-Diiodotetracos-11-yne. Colorless solid; mp = 54–54.5 °C, ^1H NMR (400 MHz, CDCl_3): δ = 3.18 (t, J = 7.1 Hz, 4H), 2.12 (t, J = 7.1 Hz, 4H), 1.85–1.77 (m, 4H), 1.49–1.42 (m, 4H), 1.40–1.24 ppm (m, 28H); ^{13}C NMR (100 MHz, CDCl_3): δ = 80.4, 33.7, 30.7, 29.7, 29.6, 29.32, 29.30, 29.0, 28.7, 18.9, 7.4 ppm; IR (film): $\tilde{\nu}$ = 2953, 2917, 2846, 1457, 1422, 1336, 1314, 1289, 1259, 1229, 1197, 1163, 1097, 1050, 1035, 982, 802, 724, 602, 527, 456 cm^{-1} ; HRMS (EI): m/z : calcd. for $[\text{C}_{24}\text{H}_{44}\text{I}_2]^+$: 586.1528, found: 586.1532.

4,4'-(Ethyne-1,2-diyl)dianiline. Orange solid; ^1H NMR (400 MHz, CD_3OD): δ = 7.17 (d, J = 8.3 Hz, 4H), 6.65 (d, J = 8.3 Hz, 4H), 4.83 ppm (s, 6H); ^{13}C NMR (100 MHz, CD_3CD): δ = 149.1, 133.3, 115.9, 114.0, 88.4 ppm; IR (film): $\tilde{\nu}$ = 3418, 3371, 2594, 2525, 2490, 2446, 1604, 1516, 1325, 1274, 1172, 1148, 1107, 822, 521 cm^{-1} ; HRMS (ESI⁺): m/z : calcd. for $[\text{C}_{14}\text{H}_{12}\text{N}_2+\text{H}]^+$: 209.1072, found: 209.1073. The compound is literature known, spectra are reported in different solvents.⁶

Syntheses of the Diyne Model Substrates



Dodecan-1,12-dial (S2). $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ (622 mg, 1.98 mmol, 0.04 equiv), 2,2'-bipyridine (309 mg, 1.98 mmol, 0.04 equiv), TEMPO (309 mg, 1.98 mmol, 0.04 equiv) and N -methyl-imidazole (406 mg, 4.94 mmol, 0.1 equiv) were added sequentially to a solution of dodecan-1,12-diol (10 g, 49.4 mmol) in CH_3CN (50 mL) in an open flask. The resulting dark red mixture was

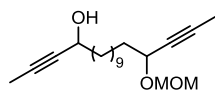
vigorously stirred open to air for 72 h, after which time the solution had turned blue. The mixture was diluted with CH₂Cl₂/hexane (1:1, 250 mL) and filtered through a plug of silica. Removal of the solvent furnished the title compound as a white solid, which was pure enough for further use (8.40 g, 86%). mp = 49–51 °C; ¹H NMR (400 MHz, CDCl₃): δ = 9.77 (t, 1.9 Hz, 2H), 2.42 (td, *J* = 7.3, 1.9 Hz, 4H), 1.63 (quint, *J* = 7.1 Hz, 4H), 1.29 ppm (brs, 12H); ¹³C NMR (100 MHz, CDCl₃): δ = 203.1 (2C), 44.0 (2C), 29.4 (4C), 29.2 (2C), 22.2 ppm (2C); IR (film): $\tilde{\nu}$ = 2924, 2853, 1721, 1464, 1391, 723, 521 cm⁻¹; HRMS (CI): *m/z*: calcd. for [C₁₂H₂₃O₂]⁺: 199.1698, found: 199.1696. The analytical and spectroscopic data are in agreement with those reported in the literature.⁷

Octadeca-2,16-diyne-4,15-diol (S3). A solution of 1-propynylmagnesium bromide (0.5 M in THF, 41.9 mL, 20.9 mmol) was added to a solution of dial **S2** (1.66 g, 8.37 mmol) in THF (15 mL) and the resulting mixture was stirred at ambient temperature for 5 h. The reaction was quenched with aq. sat. NH₄Cl (20 mL) and the aqueous layer extracted with methyl *tert*-butyl ether (3 × 30 mL). The combined extracts were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (hexane/methyl *tert*-butyl ether 6:1 to 3:1) to afford the title compound as a white solid (2.10 g, 90%). ¹H NMR (400 MHz, CDCl₃): δ = 4.25 (tq, *J* = 6.3, 2.0 Hz, 2H), 1.78 (d, *J* = 2.1 Hz, 6H), 1.63–1.55 (m, 4H), 1.65 (quint, *J* = 7.3 Hz, 4H), 1.22 ppm (brs, 12H); ¹³C NMR (100 MHz, CDCl₃): δ = 81.1 (2C), 80.6 (2C), 62.9 (2C), 38.3 (2C), 29.7 (4C), 29.4 (2C), 25.3 (2C), 3.7 ppm (2C); IR (film): $\tilde{\nu}$ = 3364, 2923, 2854, 1453, 1023 cm⁻¹; HRMS (ESI(pos)): *m/z*: calcd. for [C₁₈H₃₀O₂+Na]⁺: 301.2138, found: 301.2138.

Silyl ethers S4 and S5. Imidazole (91.7 mg, 1.35 mmol) and DMAP (11.0 mg, 0.09 mmol, 0.1 equiv) were added to a solution of diol **S3** (250 mg, 0.90 mmol) in CH₂Cl₂ (90 mL) at 0 °C, followed by TESCl (0.15 mL, 0.90 mmol). The resulting mixture was stirred at ambient temperature for 16 h. The reaction was quenched with aq. sat. NH₄Cl (40 mL) and the aqueous layer extracted with CH₂Cl₂ (3 × 40 mL). The combined extracts were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (hexane) to afford the mono-silyl ether **S4** (150 mg, 0.38 mmol, 43%) and the bis-silyl ether **S5** (97.3 mg, 0.19 mmol, 21%) as colorless oil each. Analytical data for **S4**: ¹H NMR (400 MHz, CDCl₃): δ = 4.35–4.26 (m, 2H), 1.85 (d, *J* = 2.1 Hz, 3H), 1.82 (d, *J* = 2.1 Hz, 3H), 1.68–1.58 (m, 4H), 1.46–1.35 (m, 4H), 1.27 (brs, 12H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.64 ppm (qd, *J* = 7.9, 3.5 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ = 81.2, 81.1, 80.6, 79.9, 63.1, 62.9, 39.2, 38.3, 29.7 (4C), 29.5, 29.4, 25.4, 25.3, 7.0 (3C), 4.9 (3C), 3.7 ppm (2C); IR (film): $\tilde{\nu}$ = 3360, 2921, 2854, 1459, 1238, 1078, 1004, 726 cm⁻¹; HRMS (ESI(pos)): *m/z*: calcd. for [C₂₄H₄₄O₂Si+Na]⁺: 415.3003, found: 415.3002.

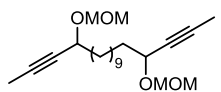
Analytical data for **S5**: ¹H NMR (400 MHz, CDCl₃): δ = 4.29 (tq, *J* = 6.5, 2.1 Hz, 2H), 1.82 (d, *J* = 2.1 Hz, 6H), 1.65–1.58 (m, 4H), 1.42–1.36 (m, 4H), 1.26 (brs, 12H), 0.97 (t, *J* = 7.9 Hz, 18H), 0.64 ppm (qd, *J* = 7.9, 3.5 Hz, 12H); ¹³C NMR (100 MHz, CDCl₃): δ = 81.2 (2C), 79.9 (2C), 63.1 (2C), 39.2 (2C), 29.7 (4C), 29.5 (2C), 25.4 (2C), 7.0 (6C), 4.9 (6C), 3.7 ppm (2C); IR (film): $\tilde{\nu}$ = 2922, 2876, 2855, 1460, 1340, 1239, 1084, 1005, 743 cm⁻¹; HRMS (ESI(pos)): *m/z*: calcd. for [C₃₀H₅₈O₂Si₂+Na]⁺: 529.3868, found: 529.3874.

Methoxymethyl ethers **S6 and **S7**.** Hünig's base (0.17 mL, 1.0 mmol) and DMAP (11.0 mg, 0.09 mmol,

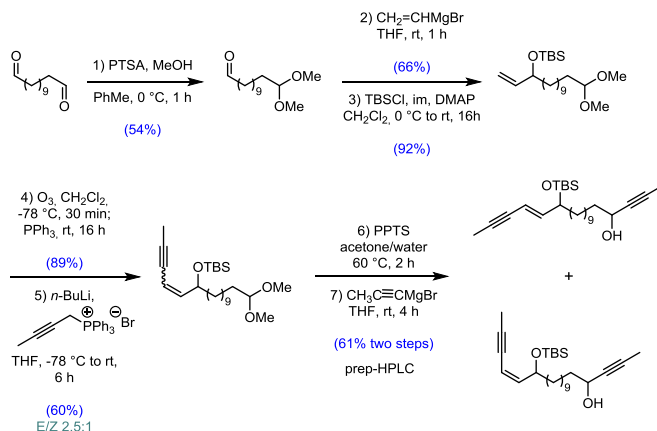


0.1 equiv) were added to a solution of diol **S3** (250 mg, 0.90 mmol) in CH₂Cl₂ (9 mL) at 0 °C, followed by MOMCl (68.2 μL, 0.90 mmol). The resulting mixture was stirred at ambient temperature for 16 h. The reaction was quenched with aq. sat. NH₄Cl

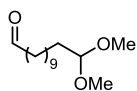
(8 mL) and the aqueous layer extracted with CH₂Cl₂ (3 × 10 mL). The combined extracts were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (hexane/methyl *tert*-butyl ether 9:1) to afford the mono-MOM derivative **S6** (119 mg, 41%) and the bis-MOM protected compound **S7** (44.8 mg, 0.12 mmol, 14%) as colorless oil each. Analytical data for **S6**: ¹H NMR (400 MHz, CDCl₃): δ = 4.94 (d, *J* = 6.7 Hz, 1H), 4.56 (d, *J* = 6.7 Hz, 1H), 4.29 (dtq, *J* = 17.3, 6.5, 2.1 Hz, 2H), 3.36 (s, 3H), 1.84 (d, *J* = 2.1 Hz, 6H), 1.71–1.60 (m, 4H), 1.47–1.37 (m, 4H), 1.27 ppm (brs, 12H); ¹³C NMR (100 MHz, CDCl₃): δ = 93.9, 81.6, 81.0, 80.7, 78.0, 66.0, 62.9, 55.7, 38.3, 36.1, 29.7 (4C), 29.5, 29.4, 25.5, 25.3, 3.71, 3.69 ppm; IR (film): $\tilde{\nu}$ = 3457, 2922, 2854, 1465, 1343, 1148, 1097, 1033, 921, 723 cm⁻¹; HRMS (ESI(pos)): *m/z*: calcd. for [C₂₀H₃₄O₃+Na]⁺: 345.2400, found: 345.2403.



Analytical data for **S7**: ¹H NMR (400 MHz, CDCl₃): δ = 4.95 (d, *J* = 6.8 Hz, 2H), 4.57 (d, *J* = 6.6 Hz, 2H), 4.27 (tq, *J* = 6.5, 2.1 Hz, 2H), 3.37 (s, 6H), 1.84 (d, *J* = 2.1 Hz, 6H), 1.74–1.62 (m, 4H), 1.48–1.39 (m, 4H), 1.28 (brs, 12H); ¹³C NMR (100 MHz, CDCl₃): δ = 94.0 (2C), 81.7 (2C), 78.0 (2C), 66.0 (2C), 55.7 (2C), 36.2 (2C), 29.71 (2C), 29.69 (2C), 29.5 (2C), 25.5 (2C), 3.7 ppm (2C); IR (film): $\tilde{\nu}$ = 2923, 2854, 1466, 1344, 1148, 1097, 1034, 920 cm⁻¹; HRMS (ESI(pos)): *m/z*: calcd. for [C₂₂H₃₈O₄+Na]⁺: 389.2662, found: 389.2660.



12,12-Dimethoxydodecanal (S8**).** *p*-TsOH·H₂O (288 mg, 1.51 mmol, 0.1 equiv) was added to a solution of

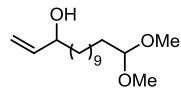


dodecan-1,12-dial (**S2**) (3.00 g, 15.1 mmol) and MeOH (1.29 mL, 31.8 mmol) in toluene (100 mL) at 0 °C. The solution was stirred for 1 h before it was poured into aq. sat. NaHCO₃ (60 mL). The aqueous layer was extracted with EtOAc (3 × 60 mL), and the combined

extracts were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 40:1) to furnish the title compound as a colorless oil (2.01 g, 54%). ¹H NMR (400 MHz, CDCl₃): δ = 9.75 (t, *J* = 1.6 Hz, 1H), 4.35 (t, *J* = 5.7 Hz, 1H), 3.30 (s, 6H), 2.41 (td, *J* = 7.3, 1.6 Hz, 2H), 1.65–1.55 (m, 4H), 1.26 ppm (brs, 14H); ¹³C NMR (100 MHz, CDCl₃): δ = 203.1, 104.7, 52.7

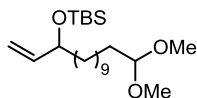
(2C), 44.1, 32.6, 29.7, 29.6, 29.5, 29.4, 29.28, 29.26, 24.7, 22.2 ppm; IR (film): $\tilde{\nu}$ = 2925, 2854, 1726, 1464, 1387, 1191, 1128, 1055, 953, 723 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{14}\text{H}_{28}\text{O}_3+\text{Na}]^+$: 267.1931, found: 267.1931. The analytical and spectroscopic data are in agreement with those reported in the literature.⁸

14,14-Dimethoxytetradec-1-en-3-ol (S9). A solution of vinylmagnesium bromide (1.0 M in THF, 6.87 mL, 6.87 mmol) was added to a solution of aldehyde **S8** (1.40 g, 5.73 mmol) in THF (50 mL).



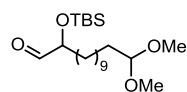
The resulting mixture was stirred at ambient temperature for 1 h. The reaction was quenched with aq. sat. NH_4Cl (20 mL) and the aqueous layer was extracted with methyl *tert*-butyl ether (3×25 mL). The combined extracts were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (hexane/methyl *tert*-butyl ether 12:1 to 3:1) to afford the title compound as a colorless oil (1.03 g, 66%). ^1H NMR (400 MHz, CDCl_3): δ = 5.86 (ddd, J = 16.9, 10.4, 6.3 Hz, 1H), 5.21 (dt, J = 17.2, 1.4 Hz, 1H), 5.09 (dt, J = 10.4, 1.3 Hz, 1H), 4.35 (t, J = 5.8 Hz, 1H), 4.08 (q, J = 6.5 Hz, 1H), 3.30 (s, 6H), 1.70 (brs, 1H), 1.61–1.48 (m, 4H), 1.26 ppm (brs, 16H); ^{13}C NMR (100 MHz, CDCl_3): δ = 141.5, 114.6, 104.7, 73.4, 52.7 (2C), 37.2, 32.6, 29.7 (4C), 29.64, 29.59, 25.5, 24.7 ppm; IR (film): $\tilde{\nu}$ = 3445, 2925, 2854, 1464, 1386, 1192, 1126, 1054, 991, 919 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{16}\text{H}_{32}\text{O}_3+\text{Na}]^+$: 295.2244, found: 295.2243. The analytical and spectroscopic data are in agreement with those reported in the literature.⁸

Silyl ether S10. Imidazole (250 mg, 3.67 mmol), DMAP (22.4 mg, 0.18 mmol, 0.1 equiv) and TBSCl (415 mg, 2.75 mmol) were successively added to a solution of alcohol **S9** (500 mg, 1.84 mmol) in CH_2Cl_2 (18 mL) at 0 °C. The resulting mixture was allowed to warm to ambient temperature and stirred for 16 h. The reaction was quenched with aq. sat. NaHCO_3 (10 mL) and the aqueous layer extracted with CH_2Cl_2 (3×15 mL). The



combined extracts were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (hexane/methyl *tert*-butyl ether 50:1) to afford the title compound as a colorless oil (653 mg, 92%). ^1H NMR (400 MHz, CDCl_3): δ = 5.79 (ddd, J = 17.1, 10.4, 6.0 Hz, 1H), 5.12 (ddd, J = 17.1, 1.9, 1.3 Hz, 1H), 5.00 (ddd, J = 10.4, 1.9, 1.2 Hz, 1H), 4.36 (t, J = 5.7 Hz, 1H), 4.06 (dtt, J = 7.2, 6.0, 1.3 Hz, 1H), 3.31 (s, 6H), 1.62–1.55 (m, 2H), 1.50–1.39 (m, 2H), 1.26 (brs, 16H), 0.89 (s, 9H), 0.05 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 142.1, 113.5, 104.7, 74.0, 52.7 (2C), 38.3, 32.6, 29.77, 29.75, 29.72, 29.70, 29.69, 29.6, 26.0 (3C), 25.4, 24.8, 18.4, -4.2, -4.7 ppm; IR (film): $\tilde{\nu}$ = 2926, 2855, 1463, 1361, 1252, 1126, 1076, 920, 835, 775 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{22}\text{H}_{46}\text{O}_3\text{Si}+\text{Na}]^+$: 409.3108, found: 409.3108.

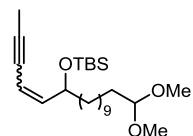
Aldehyde S11. Silyl ether **S10** (650 mg, 1.68 mmol) was dissolved in anhydrous CH_2Cl_2 (17 mL) and cooled to -78 °C. Ozone was bubbled through the solution until the blue color persisted (ca. 30 min). After purging the mixture with O_2 and Ar, PPh_3 (573 mg, 2.19 mmol) was added in one portion, the cooling bath was removed and the colorless solution stirred at



ambient temperature for 6 h. The mixture was concentrated and the residue purified by flash chromatography (hexane/methyl *tert*-butyl ether 40:1 to 20:1) to yield the title aldehyde as a colorless oil (582 mg, 89%). ^1H NMR (400 MHz, CDCl_3): δ = 9.59 (d, J = 1.7 Hz, 1H), 4.35 (t, J = 5.8 Hz, 1H), 3.95 (ddd, J = 7.1, 5.5, 1.8 Hz, 1H), 3.31 (s, 6H), 1.64–1.54 (m, 4H), 1.26 (brs, 16H), 0.92 (s, 9H), 0.08 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 204.7, 104.7, 77.8, 52.7 (2C), 32.8, 32.6, 29.7, 29.64 (2C), 29.62, 29.58, 29.55, 25.9 (3C), 24.7 (2C), 18.4, -4.5, -4.8 ppm; IR (film): $\tilde{\nu}$ = 2927, 2855, 1736, 1464,

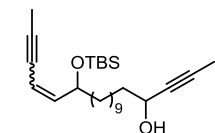
1362, 1253, 1123, 1076, 838, 778 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{21}\text{H}_{44}\text{O}_4\text{Si}+\text{Na}]^+$: 411.2901, found: 411.2903.

Enyne S12. *n*-BuLi (1.6 M in hexane, 1.37 mL, 2.20 mmol) was added to a solution of 2-butyntriphenylphosphonium bromide (869 mg, 2.20 mmol) in THF (10 mL) at 0 °C.



The resulting orange mixture was stirred at ambient temperature for 30 min before it was cooled to -78 °C. A solution of aldehyde **S11** (428 mg, 1.10 mmol) in THF (2 mL) was added and the resulting mixture stirred for 12 h at ambient temperature. The reaction was quenched with H_2O (10 mL) and the aqueous layer extracted with EtOAc (3×15 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (hexane/methyl *tert*-butyl ether 100:0 to 50:1) to afford an inseparable 1.7:1 mixture of (*E*)- and (*Z*)-enyne **S12** (279 mg, 60%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): (*E*)-enyne: δ = 6.01 (ddd, J = 15.8, 5.7, 0.8 Hz, 1H), 5.58 (dq, J = 15.8, 2.3, 1.4 Hz, 1H), 4.36 (t, J = 5.8 Hz, 1H), 4.10 (tdd, J = 6.3, 5.7, 1.4 Hz, 1H), 3.31 (s, 6H), 1.94 (d, J = 2.3 Hz, 3H), 1.62–1.57 (m, 2H), 1.49–1.42 (m, 2H), 1.25 (brs, 16H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 ppm (s, 3H); (*Z*)-enyne: δ = 5.73 (ddd, J = 10.7, 8.7, 0.8 Hz, 1H), 5.38 (dq, J = 10.7, 2.4, 0.9 Hz, 1H), 4.59 (dtd, J = 8.7, 6.3, 0.9 Hz, 1H), 4.36 (t, J = 5.8 Hz, 1H), 3.31 (s, 6H), 1.97 (d, J = 2.4 Hz, 3H), 1.62–1.57 (m, 2H), 1.49–1.42 (m, 2H), 1.25 (brs, 16H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): (*E*)-enyne: δ = 145.4, 109.0, 104.7, 86.0, 78.1, 72.8, 52.7 (2C), 38.1, 32.6, 29.8, 29.72 (2C), 29.70, 29.69, 29.6, 26.0 (3C), 25.2, 24.8, 18.4, 4.5, -4.3 , -4.7 ppm; (*Z*)-enyne: δ = 145.7, 108.6, 104.7, 90.7, 76.2, 70.8, 52.7 (2C), 37.8, 32.6, 29.8, 29.72 (2C), 29.70, 29.69, 29.6, 26.1 (3C), 25.3, 24.8, 18.4, 4.5, -4.2 , -4.8 ppm; IR (film): $\tilde{\nu}$ = 2926, 2855, 1463, 1361, 1253, 1126, 1074, 836, 776 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{25}\text{H}_{48}\text{O}_3\text{Si}+\text{Na}]^+$: 447.3265, found: 447.3269.

Enynes S13 and S14. Pyridinium *p*-toluenesulfonate (40.5 mg, 0.16 mmol, 0.3 equiv) was added to a solution of *E,Z*-**S12** (228 mg, 0.54 mmol) in acetone (50 mL) and water (1.4 mL), and the resulting mixture was stirred at 60 °C for 4 h. After cooling to ambient temperature, the mixture was concentrated, the residue partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL), and the aqueous layer extracted with CH_2Cl_2 (2×5 mL). The combined extracts were dried over Na_2SO_4 , filtered and concentrated to furnish the crude aldehyde, which was used in the next step without further purification.



A solution of 1-propynylmagnesium bromide in THF (0.5 M, 1.62 mL, 0.81 mmol) was added to a solution of the crude aldehyde in THF (5 mL) and the resulting reaction mixture stirred at ambient temperature for 4 h. The reaction was quenched with aq. sat. NH_4Cl (5 mL) and the aqueous layer was extracted with methyl *tert*-butyl ether (3×10 mL). The combined extracts were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 15:1) to afford a mixture of (*E*)- and (*Z*)-enynes **S13** and **S14**. The diastereoisomers were separated by preparative HPLC (Kromasil C18, 5 μm , 150 \times 30 mm, MeCN/ H_2O = 95:5, 35 °C, 25 bar, 35 mL/min, t_R (*E*) = 11.6 min, t_R (*Z*) = 13.4 min) to yield (*E*)-enyne **S13** (87.9 mg, 38% over two steps) and (*Z*)-enyne **S14** (50.2 mg, 23% over two steps) as a yellow oil each.

(*E*)-enyne **S13**: ^1H NMR (400 MHz, CDCl_3): δ = 6.00 (ddd, J = 15.8, 5.7, 0.8 Hz, 1H), 5.57 (dq, J = 15.8, 2.3, 1.4 Hz, 1H), 4.31 (tq, J = 6.6, 2.1 Hz, 1H), 4.10 (tdd, J = 6.3, 5.7, 1.5 Hz, 1H), 1.93 (d, J = 2.3 Hz, 3H), 1.84 (d, J = 2.1 Hz, 3H), 1.69–1.59 (m, 2H), 1.49–1.36 (m, 4H), 1.24 (brs, 14H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 145.4, 109.0, 86.0, 81.0, 80.7, 78.1, 72.8, 62.9, 38.3, 38.1, 29.74, 29.70 (2C), 29.67 (2C), 29.4, 26.0 (3C), 25.3, 25.1, 18.4, 4.4, 3.7, –4.3, –4.7 ppm; IR (film): $\tilde{\nu}$ = 3361, 2925, 2854, 1463, 1361, 1254, 1085, 955, 835, 775 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{26}\text{H}_{46}\text{O}_2\text{Si}+\text{Na}]^+$: 441.3159, found: 441.3159.

(*Z*)-enyne **S14**: ^1H NMR (400 MHz, CDCl_3): δ = 5.73 (dd, J = 10.6, 8.9 Hz, 1H), 5.38 (dq, J = 10.8, 2.4, 0.9 Hz, 1H), 4.59 (dtd, J = 8.9, 7.1, 0.9 Hz, 1H), 4.32 (tq, J = 6.5, 2.1 Hz, 1H), 1.97 (d, J = 2.4 Hz, 3H), 1.84 (d, J = 2.1 Hz, 3H), 1.69–1.60 (m, 2H), 1.47–1.36 (m, 4H), 1.27 (brs, 14H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 145.7, 108.7, 90.7, 81.0, 80.7, 76.2, 70.8, 62.9, 38.3, 37.8, 29.77, 29.75, 29.72, 29.71, 29.70, 29.5, 26.1 (3C), 25.4, 25.3, 18.3, 4.5, 3.7, –4.2, –4.8 ppm.

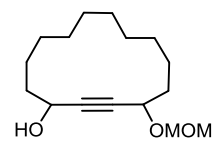
RCAM Reactions

Representative Procedure for Ring Closing Alkyne Metathesis Reactions using the Two-Component Catalyst System. Preparation of 3,14-Bis(methoxymethoxy)cyclotetradec-1-yne.

MS 5Å (200 mg) was added to a solution of diyne **S7** (36.7 mg, 100 μmol) in toluene (50 mL) at room temperature for 1 h. The mixture was then heated to 110 $^\circ\text{C}$ before a freshly prepared solution of trisilanol **11b** (19.4 mg, 22.0 μmol , 22 mol%) and complex **3** (13.3 mg, 20 mol%) in toluene (1 mL) was added, which had been stirred for 5 min prior to use. Stirring was continued at 110 $^\circ\text{C}$ for 0.5 h. The mixture was cooled to ambient temperature, the molecular sieves were filtered off through a pad of Celite, which was carefully rinsed with EtOAc, and the combined filtrates were evaporated. Purification of the residue by flash chromatography (SiO_2 , hexanes/EtOAc, 20/1 to 4/1) afforded the title compound as colorless oil (22 mg, 70%, mixture of diastereomers). ^1H NMR (400 MHz, CDCl_3): δ = 4.91 (dd, J = 6.8, 3.4 Hz, 2H), 4.59 (dd, J = 6.8, 3.0 Hz, 2H), 4.49–4.39 (m, 2H), 3.37 (s, 6H), 1.81–1.62 (m, 4H), 1.55–1.21 ppm (m, 16H); ^{13}C NMR (100 MHz, CDCl_3): δ = 94.3, 84.8, 84.6, 66.3, 66.2, 55.7, 35.1, 34.9, 26.6, 26.5, 25.9, 25.8, 23.82, 23.79, 22.44, 22.38 ppm; IR (film): $\tilde{\nu}$ = 2929, 2860, 2822, 2776, 1459, 1400, 1338, 1213, 1148, 1097, 1026, 919, 848, 792, 724, 704, 554, 441, 415 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{18}\text{H}_{32}\text{O}_4+\text{Na}]^+$: 355.2189, found: 335.2193.

The following compounds were prepared analogously:

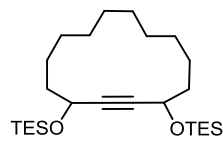
4-(Methoxymethoxy)cyclotetradec-2-yn-1-ol. Colorless oil (18 mg, 67%, mixture of diastereomers). ^1H



NMR (400 MHz, CDCl_3) δ = 4.92 (dd, J = 6.8, 5.5 Hz, 1H), 4.60 (dd, J = 6.8, 1.8 Hz, 1H), 4.56–4.40 (m, 2H), 3.38 (s, 3H), 1.89–1.82 (m, 1H), 1.78–1.63 (m, 4H), 1.56–1.22 ppm (m, 16H); ^{13}C NMR (100 MHz, CDCl_3): δ = 94.3, 87.11, 87.06, 84.1, 83.9, 66.3, 66.1, 63.0, 55.8, 37.2, 37.1, 35.0, 34.9, 26.6, 26.50, 25.9, 25.81, 25.77, 25.7, 23.9, 23.8,

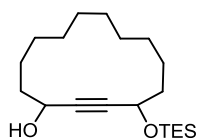
22.5, 22.4, 22.32, 22.30 ppm; IR (film): $\tilde{\nu}$ = 3400, 2928, 2859, 1459, 1429, 1338, 1260, 1213, 1150, 1097, 1026, 918, 865, 801, 731, 700, 509 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{16}\text{H}_{28}\text{O}_2+\text{Na}]^+$: 291.1928, found: 291.1931.

3,14-Bis((triethylsilyl)oxy)cyclotetradec-1-yne. Colorless oil (32 mg, 71%, mixture of diastereomers). ^1H



NMR (400 MHz, CDCl_3) δ = 4.51–4.39 (m, 2H), 1.73–1.21 (m, 20H), 0.97 (t, J = 7.9 Hz, 18H), 0.71–0.56 ppm (m, 12H); ^{13}C NMR (100 MHz, CDCl_3): δ = 85.9, 85.6, 63.4, 63.2, 38.7, 38.4, 26.7, 26.4, 26.1, 25.8, 24.0, 23.8, 22.4, 22.3, 7.0, 4.94, 4.88 ppm; IR (film): $\tilde{\nu}$ = 2949, 2935, 2875, 1732, 1459, 1414, 1378, 1348, 1334, 1260, 1239, 1074, 1006, 975, 843, 803, 726, 675, 533, 458 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{26}\text{H}_{52}\text{O}_2\text{Si}_2+\text{Na}]^+$: 475.3404, found: 475.3398.

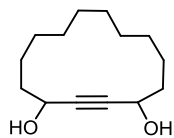
4-((Triethylsilyl)oxy)cyclotetradec-2-yn-1-ol. Colorless oil (21.8 mg, 64%, mixture of diastereomers). ^1H



NMR (400 MHz, CDCl_3) δ = 4.53–4.41 (m, 2H), 1.74–1.60 (m, 5H), 1.49–1.25 (m, 16H), 0.98 (t, J = 7.9 Hz, 9H), 0.70–0.59 ppm (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ = 87.1, 86.9, 85.4, 85.1, 63.3, 63.2, 63.1, 63.0, 38.4, 38.3, 37.2, 26.60, 26.56, 26.53, 26.47, 25.84, 25.82, 25.78, 25.7, 23.89, 23.85, 23.8, 22.4, 22.3, 7.0, 4.92, 4.90 ppm; IR (film): $\tilde{\nu}$

= 3359, 2931, 2874, 2859, 1458, 1413, 1378, 1334, 1259, 1239, 1151, 1072, 1006, 802, 726, 549, 427 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{20}\text{H}_{38}\text{O}_2\text{Si}+\text{Na}]^+$: 361.2521, found: 361.2533.

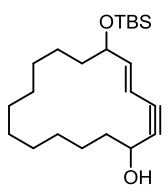
Cyclotetradec-2-yne-1,4-diol. Colorless solid (11.8 mg, 53%, mixture of diastereomers). mp = 110–111



^1H NMR (400 MHz, CDCl_3): δ = 4.58–4.44 (m, 2H), 1.98–1.89 (m, 2H), 1.79–1.62 (m, 4H), 1.52–1.26 ppm (m, 16H); ^{13}C NMR (100 MHz, CDCl_3): δ = 86.5, 86.2, 63.04, 62.96, 37.2, 37.1, 26.53, 26.50, 25.74, 25.71, 23.8, 22.4, 22.3 ppm; IR (film): $\tilde{\nu}$ = 3273, 2923, 2856, 1729, 1457, 1443, 1341, 1297, 1146, 1107, 1020, 945, 723, 702, 590, 533, 512, 440

cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{14}\text{H}_{24}\text{O}_2+\text{Na}]^+$: 247.1667, found: 247.1668.

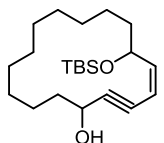
Macrocycle S15. Colorless oil (19.8 mg, 76%, *syn/anti*-mixture). ^1H NMR (400 MHz, CDCl_3): δ = 6.15 (dd,



J = 15.8, 5.2 Hz, 1H), 6.14 (dd, J = 15.8, 5.2 Hz, 1H), 5.72–5.62 (m, 2H), 4.55–4.48 (m, 2H), 4.28–4.23 (m, 2H), 1.84–1.65 (m, 8H), 1.48–1.38 (m, 8H), 1.35–1.19 (m, 24H), 0.89 (s, 18H), 0.04 (s, 6H), 0.03 ppm (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ = 148.1, 147.8, 108.1, 108.0, 90.59, 90.55, 84.53, 84.45, 72.33, 72.27, 63.43, 63.37, 37.3, 37.2, 36.1 (2C), 28.41, 28.38, 27.9 (4C), 27.8 (2C), 27.62 (2C), 27.57, 27.5, 26.0 (6C), 23.7, 23.5, 21.92, 21.86,

18.4 (2C), –4.6 (2C), –4.8 (2C) ppm; IR (film): $\tilde{\nu}$ = 3348, 2926, 2855, 1462, 1361, 1255, 1073, 956, 836, 776 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{22}\text{H}_{40}\text{O}_2\text{Si}+\text{Na}]^+$: 387.2690, found: 387.2691.

Macrocycle S16. Colorless oil (22.3 mg, 90%); the diastereomers could be separated by flash chromatography on silica gel (hexane/methyl *tert*-butyl ether 20:1). Faster eluting



diastereomer: ^1H NMR (300 MHz, CDCl_3): δ = 5.84 (dd, J = 10.9, 8.8 Hz, 1H), 5.48 (ddd, J = 10.8, 2.1, 0.8 Hz, 1H), 4.63 (td, J = 8.2, 4.9 Hz, 1H), 4.55 (ddd, J = 7.8, 5.1, 2.0 Hz, 1H), 1.79–1.66 (m, 2H), 1.53 (brs, 1H), 1.44–1.28 (m, 18H), 0.89 (s, 9H), 0.10 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ = 147.6, 107.7, 95.2, 81.5, 71.2, 63.6, 37.9, 36.9, 27.1

(2C), 26.9, 26.7, 26.1 (3C), 25.63, 25.60, 23.74, 23.71, 18.4, –4.1, –4.6 ppm; slower eluting diastereomer: ^1H NMR (300 MHz, CDCl_3): δ = 5.82 (dd, J = 10.9, 8.9 Hz, 1H), 5.48 (d, J = 10.9 Hz, 1H), 4.66–4.52 (m, 2H),

1.89–1.65 (m, 4H), 1.47–1.28 (m, 17H), 0.89 (s, 9H), 0.08 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ = 147.1, 107.7, 95.0, 81.8, 71.2, 63.2, 37.7, 36.7, 27.3, 27.1, 26.72, 26.71, 26.1, 26.0 (3C), 25.7, 23.8, 23.7, 18.3, –4.1, –4.7 ppm; IR (film): $\tilde{\nu}$ = 3432, 2927, 2856, 1461, 1361, 1071, 1018, 907, 835, 776, 732 cm^{-1} ; HRMS (ESI(pos)): m/z : calcd. for $[\text{C}_{22}\text{H}_{40}\text{O}_2\text{Si}+\text{Na}]^+$: 387.2690, found: 387.2692.

Total Synthesis of (±)-Manshurolide

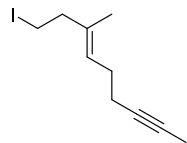
Vinyl iodide 14.⁹ AlMe_3 (2.0 M in hexane, 46.4 mL, 92.9 mmol) was slowly added to a solution of Cp_2ZrCl_2 (1.93 g, 6.59 mmol) in CH_2Cl_2 (130 mL) at -25°C . The mixture was stirred for 10 min before H_2O (0.85 mL, 47 mmol) was carefully added. After stirring for additional 10 min at -25°C , the solution was warmed to 0°C and a solution of 3-butyne-1-ol (2.27 mL, 30.0 mmol) and AlMe_3 (4.49 mL, 8.99 mmol) in CH_2Cl_2 (25 mL) was introduced. The mixture was stirred for 15 h at ambient temperature before it was cooled to -25°C and a solution of I_2 (11.4 g, 44.9 mmol) in Et_2O (50 mL) was added. After stirring for 2 h at ambient temperature, sat. aq. Rochelle salt solution was added causing the formation of a white precipitate. The solid was filtered off, the aqueous phase was extracted with *tert*-butyl methyl ether (3 x 40 mL), the combined extracts were washed with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (SiO_2 , pentane/*tert*-butyl methyl ether, 5/1) to give the title compound (admixed with remaining starting material) (4.13 g, 65%). ^1H NMR (400 MHz, CDCl_3): δ = 6.01 (1H, tq, J = 1.1, 1.1 Hz), 3.71 (2H, t, J = 6.3 Hz), 2.47 (2H, td, J = 6.3, 1.1 Hz), 1.86 ppm (3H, d, J = 1.1 Hz); ^{13}C NMR (150 MHz, CDCl_3): δ = 144.6, 77.1, 60.2, 42.5, 24.2 ppm; IR (film): $\tilde{\nu}$ = 3317, 2936, 2910, 2882, 1430, 1376, 1271, 1177, 1038, 1000, 948, 858, 764, 665, 558, 544, 462, 436 cm^{-1} ; MS (EI): m/z (%) 212 (25), 182 (5), 181 (10), 127 (5), 85 (100), 67 (36), 57 (18), 55 (42), 54 (25), 53 (36); HRMS (EI): m/z : calcd. for $\text{C}_5\text{H}_9\text{OI}$ [M^+]: 211.9698, found 211.9700.

Diiodide 17. A solution of vinyl iodide **14** (950 mg, 4.48 mmol) in $\text{Et}_2\text{O}/\text{MeCN}$ (45 mL, 2/1) was treated with PPh_3 (1.41 g, 5.38 mmol), imidazole (366 mg, 5.38 mmol) and I_2 (1.40 g, 5.52 mmol). The mixture was warmed to ambient temperature and stirred for 1 h. Pentane (40 mL) was added, the precipitate was filtered off, and the residue was washed with pentane/ Et_2O (30 mL, 30/1). The combined filtrates were concentrated and the residue purified by flash chromatography (SiO_2 , pentane/*tert*-butyl methyl ether, 50/1) to yield diiodide **17** as a colorless oil (1.04 g, 72%). ^1H NMR (300 MHz, CDCl_3): δ = 6.07 (d, 1H, J = 1.1 Hz), 3.23 (t, 2H, J = 7.5 Hz), 2.76 (td, 2H, J = 7.5, 1.1 Hz), 1.85 ppm (d, 3H, J = 1.1 Hz). ^{13}C NMR (75 MHz, CDCl_3): δ = 146.1, 78.0, 43.4, 23.2, 2.6 ppm; IR (film): $\tilde{\nu}$ = 3052, 2960, 2908, 1477, 1422, 1375, 1324, 1303, 1277, 1253, 1233, 1171, 1139, 1120, 1105, 897, 853, 834, 769, 754, 743, 696, 666, 610, 496, 478 cm^{-1} ; MS (EI): m/z (%) 322 (19), 209 (5), 196 (6), 195 (100), 167 (5), 155 (5), 127 (10), 81 (5), 68 (58), 67 (55), 53 (14); HRMS (EI): m/z : calcd. for $\text{C}_5\text{H}_8\text{I}_2$ [$M+\text{Na}^+$]: 321.8715, found 321.8712.

Iodide 18. A solution of 3-pentyn-1-ol (2.50 g, 29.7 mmol) in $\text{Et}_2\text{O}/\text{MeCN}$ (300 mL, 2/1) was treated with PPh_3 (9.51 g, 36.3 mmol), imidazole (2.47 g, 36.3 mmol) and I_2 (9.20 g, 36.3 mmol) at 0°C . The mixture was stirred for 1 h at ambient temperature. Pentane (70 mL) was added, the resulting suspension was filtered, the filter cake washed with pentane/ Et_2O (30 mL, 30/1), and the combined filtrates were carefully evaporated. The crude material was purified by flash chromatography

(SiO₂, pentane/Et₂O, 50/1) to give the highly volatile title compound as a colorless oil (3.44 g, 60%). ¹H NMR (300 MHz, CDCl₃): δ = 3.19 (t, 2H, *J* = 7.4 Hz), 2.71 (tq, 2H, *J* = 7.4, 2.3 Hz), 1.77 ppm (t, 3H, *J* = 2.3 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 78.0, 77.9, 24.3, 3.7, 2.8 ppm; IR (film): $\tilde{\nu}$ = 2916, 1434, 1333, 1248, 1170, 1151, 1028, 904, 840, 728, 595, 485 cm⁻¹; MS (EI): *m/z* (%) 194 (7), 141 (1), 127 (6), 67 (100), 66 (6), 65 (13), 63 (3), 51 (3); HRMS (EI): *m/z*: calcd. for C₅H₇I [*M*⁺]: 193.9592, found 193.9593.

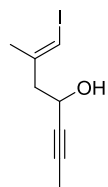
Iodide 19. *t*-BuLi (1.7 M in pentane, 3.87 mL, 6.59 mmol,) was added dropwise to a solution of iodide **18** (1.21 g, 6.21 mmol) in Et₂O (6.0 mL) at -78 °C. After stirring for further 30 min at this



temperature, a solution of ZnBr₂ in THF (0.5 M, 12.4 mL, 6.21 mmol,) was introduced. The mixture was allowed to warm to 0 °C and stirring continued for 40 min. In a second flask, a solution of alkenyl iodide **17** (1.00 g, 3.11 mmol) in THF (6.0 mL) was treated with Pd(dppf)Cl₂ (101 mg, 2 mol%) at ambient temperature before the solution of the

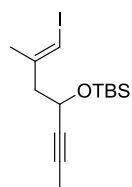
organozinc reagent was added. After stirring for 4.5 h, the reaction was quenched at 0 °C with H₂O (10 mL), the aqueous phase was extracted with *tert*-butyl methyl ether (4 x 8 mL), and the extracts were dried over Na₂SO₄ and evaporated. The residue was purified by flash chromatography (SiO₂, hexanes/toluene, 15/1) to yield the title compound as a colorless oil (652 mg, 80%). ¹H NMR (400 MHz, CDCl₃): δ = 5.27 – 5.23 (1H, m), 3.22 (2H, t, *J* = 7.7 Hz), 2.54 (2H, t, *J* = 7.7 Hz), 2.19 – 2.15 (4H, m), 1.78 (3H, t, *J* = 2.6 Hz), 1.62 ppm (3H, br s); ¹³C NMR (100 MHz, CDCl₃): δ = 134.9, 126.1, 79.0, 75.8, 43.9, 27.9, 19.1, 15.6, 5.0, 3.7 ppm; IR (film): $\tilde{\nu}$ = 2962, 2915, 2854, 1433, 1384, 1329, 1304, 1243, 1169, 1131, 1013, 903, 845, 734, 621, 552, 497, 474 cm⁻¹; GC-MS: *t*_R (70_20) = 11.3 min; MS (EI) *m/z* (%): 262 (4), 234 (11), 209 (15), 167 (13), 135 (14), 107 (65), 93 (82), 81 (100), 67 (44 (55 (49); HRMS (EI): *m/z*: calcd. for C₁₀H₁₅I [*M*⁺]: 262.0218, found 262.0216.

Compound 15. A solution of Dess-Martin periodinane (7.70 g, 18.2 mmol) in CH₂Cl₂ (57 mL) was added to a solution of alcohol **14** (3.50 g, 16.5 mmol) in CH₂Cl₂ (30 mL) at 0 °C. The mixture was stirred for 1.5 h at ambient temperature before it was diluted with Et₂O (175 mL) and poured into a mixture of sat. aq. NaHCO₃/Na₂S₂O₂ (1:1, 130 mL). The biphasic mixture was vigorously stirred for 10 min before the aqueous phase was extracted with Et₂O (3 x 175 mL). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. The crude aldehyde was very volatile and used to the next step without further purification (3.12 g, 90%).

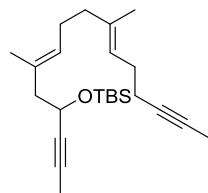


1-Propynylmagnesium bromide (0.5 M in THF, 60.9 mL, 30.5 mmol) was added to a solution of the crude aldehyde (3.12 g, 14.9 mmol) in THF (70 mL) at 0 °C. The mixture was stirred for 16 h at ambient temperature. For work up, sat. aq. NH₄Cl was added at 0 °C, the aqueous phase was extracted with EtOAc (3 x 100 mL), and the combined extracts were dried over Na₂SO₄ and concentrated. The crude material was purified by flash chromatography (SiO₂, hexanes/EtOAc, 8/1) to give the title compound as a colorless oil (3.32 g, 82%). ¹H NMR (400 MHz, CDCl₃): δ = 6.08 (1H, q, *J* = 1.1 Hz), 4.48 – 4.43 (1H, m), 2.59 – 2.56 (2H, m), 1.90 (3H, d, *J* = 1.1 Hz), 1.84 (3H, d; *J* = 2.2 Hz), 1.82 ppm (1H, br s); ¹³C NMR (100 MHz, CDCl₃): δ = 143.6, 82.1, 79.5, 78.6, 60.7, 47.7, 24.4, 3.7 ppm; IR (film): $\tilde{\nu}$ = 3353, 2916, 2852, 2230, 1663, 1617, 1434, 1376, 1339, 1274, 1141, 1041, 1010, 978, 762, 669, 522 cm⁻¹; MS (EI): *m/z* (%) 250 (1), 183 (3), 182 (67), 127 (2), 124 (2), 123 (21), 105 (12), 95 (18), 79 (4), 70 (4), 69 (100), 55 (23), 53 (15); HRMS (ESI): *m/z*: calcd. for C₈H₁₁OINa [*M*+Na⁺]: 272.9747, found 272.9746.

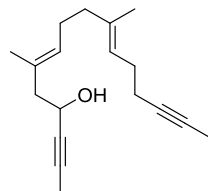
Compound 16. Imidazole (726 mg, 10.7 mmol) and TBSCl (842 mg, 5.59 mmol) were added to a solution of alcohol **15** (1.27 g, 5.08 mmol) in DMF (5.0 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C before *tert*-butyl methyl ether (60 mL) was added. The solution was washed with H₂O (3 x 40 mL) and brine, the organic phase was dried over Na₂SO₄ and evaporated. The residue was purified by flash chromatography (SiO₂, hexanes/*tert*-butyl methyl ether, 40/1) to afford the title compound as a colorless oil (1.61 g, 87%). ¹H NMR (400 MHz, CDCl₃): δ = 6.00 – 5.98 (1H, m), 4.39 (1H, qt, *J* = 9.0, 2.1 Hz), 2.58 (2H, qdd, *J* = 13.5, 9.0, 0.9 Hz), 1.86 (3H, d, *J* = 1.1 Hz), 1.81 (3H, d, *J* = 2.1 Hz), 0.88 (9H, s), 0.10 (3H, s), 0.07 ppm (3H, s); ¹³C NMR (100 MHz, CDCl₃): δ = 143.9, 81.0, 80.3, 78.4, 61.6, 48.6, 25.9 (3C), 24.5, 18.3, 3.7, –4.5, –5.0 ppm; IR (film): $\tilde{\nu}$ = 2954, 2928, 2895, 2856, 1471, 1462, 1436, 1389, 1361, 1342, 1277, 1251, 1142, 1078, 1005, 933, 829, 812, 775, 670, 531 cm^{–1}; MS (EI): *m/z* (%) 349 (1), 307 (40), 239 (2), 211 (2), 185 (16), 184 (16), 183 (100), 180 (53), 179 (20), 165 (19), 140 (6), 127 (13), 115 (11), 111 (21), 105 (16), 97 (77), 91(15), 83 (9), 77 (10), 75 (53), 73 (76), 57 (22); HRMS (ESI): *m/z*: calcd. for C₁₄H₂₅OISiNa [*M*+Na⁺]: 387.0612, found 387.0612.



Compound S17. *t*-BuLi (1.7 M in hexanes, 8.07 mL, 13.7 mmol,) was added to a solution of alkyl iodide **19** (1.62 g, 6.18 mmol) in Et₂O (20 mL) at –78 °C. After 5 min, a solution of 9-MeO-9-BBN (1.0 M, 16.5 mL, 16.5 mmol) in THF (15.6 mL) was introduced and the resulting mixture was stirred for 10 min at –78 °C before the solution was allowed to warm to ambient temperature. After 1 h, a solution of aqueous K₃PO₄ (3.0 M, 2.66 mL, 7.99 mmol), alkenyl iodide **16** (1.00 g, 2.74 mmol) and Pd(dppf)Cl₂ (202 mg, 10 mol%) in DMF (27 mL) was introduced and the mixture was stirred for 2 h at 50 °C. The reaction was quenched with sat. aq. NH₄Cl, the aqueous phase was extracted with *tert*-butyl methyl ether (4 x 5 mL), the combined organic layers were washed with H₂O (4 x 2 mL) and brine, dried over Na₂SO₄, and the solvent was evaporated. The crude material was purified by flash chromatography (SiO₂, hexanes/EtOAc, 100/1) to give the title compound as a colorless oil (615 mg, 60%). ¹H NMR (400 MHz, CDCl₃): δ = 5.22 – 5.14 (2H, m), 4.35 (1H, tq, *J* = 2.1 Hz), 2.28 (2H, t, *J* = 6.7 Hz), 2.20 – 2.05 (6H, m), 2.01 – 1.97 (2H, m), 1.81 (3H, d, *J* = 2.1 Hz), 1.78 (3H, t, *J* = 2.4 Hz), 1.62 (3H, br s), 1.61 (3H, br s), 0.88 (9H, s), 0.10 (3H, s), 0.07 ppm (3H, s); ¹³C NMR (100 MHz, CDCl₃): δ = 136.4, 131.1, 128.0, 123.1, 81.2, 80.2, 79.4, 75.6, 62.6, 49.2, 39.6, 27.9, 26.8, 26.0 (3C), 19.3, 18.5, 16.7, 16.2, 3.7(2), 3.6(9), –4.5, –4.9 ppm; IR (film): $\tilde{\nu}$ = 2927, 2856, 1472, 1462, 1443, 1386, 1361, 1343, 1253, 1142, 1084, 1005, 937, 906, 836, 777, 732, 650, 535 cm^{–1}; MS (EI): *m/z* (%) 249 (3), 193 (3), 185 (5), 184 (15), 183 (100), 127 (11), 121 (3), 105 (4), 74 (3), 73 (36), 69 (2); HRMS (ESI): *m/z*: calcd. for C₂₄H₄₀OISiNa [*M*+Na⁺]: 395.2741, found 395.2741.

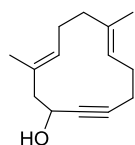


Diyne 20. CSA (12 mg, 54 μmol) was added to a solution of the TBS-ether **S17** (100 mg, 0.27 mmol) in MeOH (2.5 mL) at 0 °C. The mixture was stirred for 2.5 h, before it was diluted with CH₂Cl₂ (15 mL) and the reaction was quenched with sat. aq. NaHCO₃. The aqueous phase was extracted with CH₂Cl₂ (3 x 10 mL), the combined organic layers were dried over Na₂SO₄ and evaporated. The residue was purified by flash chromatography (SiO₂, hexanes/EtOAc, 15/1) to yield the title compound as a colorless oil (58 mg, 84%). ¹H NMR (400 MHz, CDCl₃): δ = 5.25 (1H, tq, *J* = 6.9, 1.1 Hz), 5.16 (1H, tq, *J* = 6.8, 1.2 Hz), 4.40 – 4.34 (1H, m), 2.40 – 2.29 (2H, m), 2.19 – 2.11 (6H, m), 2.05 – 2.01 (2H, m), 1.92 (1H, br d, *J* = 4.5 Hz), 1.84 (3H, d, *J* = 2.2 Hz), 1.78 (3H, t, *J* = 2.4 Hz), 1.66 (3H, br s), 1.60 ppm (3H, br s); ¹³C NMR



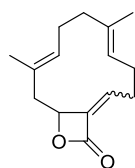
(100 MHz, CDCl₃): δ = 136.1, 130.7, 129.6, 123.6, 80.9, 80.1, 79.3, 75.6, 60.1, 48.5, 39.5, 27.8, 26.5, 19.3, 16.3, 16.1, 3.8, 3.7 ppm; IR (film): $\tilde{\nu}$ = 2918, 2856, 1438, 1383, 1023, 903, 723, 650 cm⁻¹; MS (EI): m/z (%) 243 (2), 225 (6), 189 (9), 187 (5), 176 (4), 175 (10), 161 (10), 147 (15), 133 (12), 121 (12), 109 (10), 107 (26), 105 (24), 93 (26), 91 (18), 81 (17), 79 (16), 77 (12), 69 (100), 68 (18), 67 (18); HRMS (ESI): m/z : calcd. for C₁₈H₂₆ONa [M +Na⁺]: 281.1876, found 281.1875.

Cycloalkyne 21. MS 5 Å (3.50 g) were dispersed in freshly distilled toluene (150 mL), trisilanlol **11b** (12.9 mg, 19.3 μ mol) was added, and the suspension was stirred for 1 h. Next, a solution of complex **3** (15.2 mg, 19.3 μ mol) in toluene (1 mL) was added and stirring continued for 30 min.



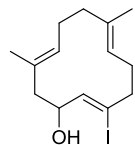
A second flask was charged with diyne **20** (50.0 mg, 194 μ mol), MS 5 Å (3.00 g) and toluene (235 mL) and the mixture was stirred for 1 h before the solution of the catalyst was introduced. The resulting mixture was stirred at reflux temperature for 1.5 h before it was allowed to cool. All insoluble materials were filtered off through a pad of Celite and the filtrate was concentrated. The residue was purified by flash chromatography (SiO₂, hexanes/EtOAc, 8/1) to give the title compound as a colorless solid (32.5 mg, 82%). ¹H NMR (400 MHz, CDCl₃): δ = 5.07 – 5.04 (1H, m), 4.99 – 4.95 (1H, m), 4.50 – 4.45 (1H, m), 2.46 – 2.41 (1H, m), 2.36 – 2.19 (6H, m), 2.13 (1H, br d, J = 4.3 Hz), 2.11 – 2.03 (3H, m), 1.59 (3H, br s), 1.49 ppm (3H, br s); ¹³C NMR (100 MHz, CDCl₃): δ = 135.3, 129.6, 129.1, 124.7, 86.1, 81.2, 62.3, 49.5, 39.3, 26.5, 25.0, 19.1, 16.1, 15.0 ppm; IR (film): $\tilde{\nu}$ = 3360, 2981, 2910, 2848, 1435, 1384, 1328, 1260, 1228, 1136, 1101, 1079, 1036, 1019, 998, 978, 903, 833, 811, 727, 650, 564, 550 cm⁻¹; MS (EI): m/z (%) 203 (1), 190 (4), 189 (27), 172 (7), 171 (47), 161 (12), 133 (8), 121 (9), 117 (9), 107 (11), 105 (13), 93 (17), 91 (26), 81 (12), 79 (15), 77 (11), 69 (100), 68 (68), 67 (17); HRMS (ESI): m/z : calcd. for C₁₄H₂₀ONa [M +Na⁺]: 227.1406, found 227.1406.

β -Lactone 22. A solution of alkynol **21** (25 mg, 0.12 mmol), Pd₂(dba)₃·CHCl₃ (4.1 mg, 4 mol%) and dppb (4.2 mg, 8 mol%) in CH₂Cl₂ (2.0 mL) was prepared and transferred to an autoclave. The autoclave was filled with CO (41 bar) and H₂ (14 bar) and the mixture was stirred at 95 °C for 24 h. The autoclave was allowed to reach ambient temperature before the pressure was released. The brown solution was filtered through a pad of Florisil and the filtrate was concentrated. The residue was purified by flash chromatography (SiO₂, hexanes/EtOAc, 20/1) to give the the title lactone as the main product (5.0 mg, 17%).

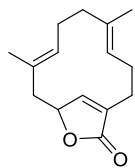


¹H NMR (400 MHz, CDCl₃): δ = 6.31 (1H, ddd, J = 12.6, 4.0, 1.6 Hz), 5.17 (1H, ddt, J = 9.4, 4.5, 1.6 Hz), 5.09 – 5.03 (2H, m), 2.87 – 2.84 (1H, m), 2.49 (1H, dd, J = 13.7, 9.4 Hz), 2.46 – 2.42 (1H, m), 2.41 – 2.37 (1H, m), 2.24 – 2.18 (1H, m), 2.12 – 2.09 (1H, m), 2.08 – 2.02 (1H, m), 2.01 – 1.95 (2H, m), 1.80 – 1.73 (1H, m), 1.62 (3H, br s), 1.56 ppm (3H, d, J = 1.4 Hz); ¹³C NMR (100 MHz, CDCl₃): δ = 164.9, 137.2, 135.6, 134.5, 130.7, 128.9, 125.6, 78.1, 45.7, 38.3, 32.2, 25.9, 25.4, 16.0, 15.4 ppm; MS (EI): m/z (%) 232 (2), 189 (7), 188 (25), 175 (4), 173 (28), 162 (11), 161 (11), 159 (11), 149 (11), 147 (25), 146 (11), 145 (17), 133 (18), 131 (27), 123 (13), 119 (18), 107 (17), 106 (11), 105 (10), 96 (39), 94 (10), 93 (15), 92 (16), 91 (46), 81 (11), 79 (31), 77 (24), 68 (100), 67 (48), 65 (14); HRMS (ESI): m/z : calcd. for C₁₅H₂₀O₂Na [M +Na⁺]: 255.1355, found 255.1355.

Compound 23. A solution of compound **21** (50 mg, 0.24 mmol) in Et₂O (1.8 mL) was dried over MS 3 Å. The solution was transferred to another flask via canula and a solution of Red-Al (0.12 mL, 0.61 mmol) in Et₂O (6.0 mL) was added dropwise at 0 °C. The ice bath was removed and the solution stirred at ambient temperature overnight. The solution was cooled to –25 °C before a solution of I₂ (186 mg, 0.73 mmol) in Et₂O (10 mL) was introduced. Stirring was continued for another 45 min before sat. aq. Na₂S₂O₃ was introduced. The aqueous phase was extracted with Et₂O (3 x 25 mL), and the combined extracts were dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (SiO₂, hexanes/EtOAc, 3/1) to yield the title compound as a colorless oil (77 mg, 97%). ¹H NMR (400 MHz, CDCl₃): δ = 5.19 (1H, d, *J* = 8.7 Hz), 4.86 – 4.83 (1H, m), 4.73 – 4.70 (1H, m), 4.52 – 4.47 (1H, m), 2.62 – 2.59 (1H, m), 2.52 – 2.48 (2H, m), 2.43 – 2.39 (1H, m), 2.36 – 2.30 (1H, m), 2.19 (1H, t, *J* = 11.5 Hz), 2.19 (1H, dd, *J* = 12.6, 3.3 Hz), 1.99 (1H, td, *J* = 12.9, 3.6 Hz), 1.96 – 1.91 (2H, m), 1.63 (3H, br s), 1.63 (1H, br d, *J* = 3.3 Hz), 1.57 ppm (3H, br s); ¹³C NMR (100 MHz, CDCl₃): δ = 138.9, 135.9, 130.6, 129.3, 124.2, 110.6, 75.4, 47.7, 45.9, 40.1, 26.3, 25.2, 17.3, 16.1 ppm; IR (film): $\tilde{\nu}$ = 2984, 2941, 1737, 1447, 1372, 1300, 1233, 1098, 1043, 938, 918, 847, 786, 634, 608 cm⁻¹; MS (EI): *m/z* (%) 333 (25), 332 (23), 317 (64), 291 (11), 258 (41), 245 (34), 228 (30), 222 (12), 122 (41), 121 (19), 106 (21), 97 (18), 95 (52), 81 (39), 70 (10), 69 (26), 68 (100); HRMS (ESI): *m/z*: calcd. for C₁₄H₂₁ONa [*M*+Na⁺]: 355.0529, found 355.0530.



(±)-Manshurolide (12). A solution of alkenyl iodide **23** (60 mg, 0.18 mmol) in MeCN (1.2 mL) was added to a stirred solution of Pd(OCOCF₃)₂ (9.0 mg, 15 mol%) and DPE-Phos (14.5 mg, 15 mol%) in MeCN (1.2 mL). Then, MeOH (0.6 mL) and *i*-Pr₂EtN (92 μL, 0.54 mmol) were added. The resulting solution was saturated with CO and was stirred under CO atmosphere for 48 h. The reaction was quenched by addition of sat. aq. NH₄Cl, the aqueous phase was extracted with EtOAc, the combined organic layers were dried over Na₂SO₄ and the solvent was evaporated. The residue was purified by flash chromatography (SiO₂, hexanes/EtOAc, 4/1) to give the title compound as colorless solid (40 mg, 95%). m.p. = 130–132 °C; for the NMR data, see Tables S-2 and S-3; IR (film): $\tilde{\nu}$ = 3078, 2955, 2918, 2850, 1743, 1433, 1355, 1327, 1259, 1203, 1110, 1086, 1068, 1036, 933, 896, 844, 834, 783 cm⁻¹; MS (EI): *m/z* (%) 233 (11), 232 (55), 187 (6), 164 (42), 149 (14), 137 (9), 136 (56), 135 (44), 122 (11), 121 (57), 107 (25), 105 (13), 97 (12), 96 (20), 95 (13), 94 (28), 93 (35), 91 (22), 81 (23), 80 (11), 79 (22), 77 (16), 70 (11), 69 (36), 68 (100), 67 (43); HRMS (ESI): *m/z*: calcd. for C₁₅H₂₀O₂Na [*M*+Na⁺]: 255.1355, found 255.1354.



The isolation paper reports an $[\alpha]_D^{24} = +56^\circ$ (EtOH, *c* = 0.79),¹⁰ whereas the two enantiomers obtained by separation of the racemic synthetic sample showed the following rotatory power (in the order, in which the enantiomers were eluting from the column): $[\alpha]_D^{20} = +519.8^\circ$ (*c* = 0.5, EtOH); $[\alpha]_D^{20} = -508.1^\circ$ (*c* = 0.53, EtOH). The separation of the enantiomers was performed with a Shimadzu LC-10A micro-preparative HPLC (Chiracel OD-H 09/13, 250 mm, Ø 7.6 mm) eluting with n-heptane/2-propanol (98:2, v/v; 2.8 mL/min, 4.1 MPa, 298K).

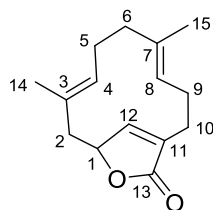


Table S-1: ^1H and ^{13}C data of manshurolide (in this case, the solvent peak for residual CHCl_3 was calibrated to $\delta_{\text{H}} \equiv 7.24$ ppm); numbering scheme as shown in the Insert.

^1H NMR (CDCl_3 , 600 MHz)						^{13}C NMR (CDCl_3 , 150 MHz)	
No.	δ (ppm)	Integral	Splitting	COSY	J (Hz)	δ (ppm)	HMBC
1	5.10	1H	dq	2a, 2b, 10b, 12	5.9, 2.0	80.9	1, 2a, 2b, 4, 12, 14
2a	2.64	1H	ddd	1, 2b, 5a	14.1, 5.8, 1.1	40.6	1, 2a, 2b, 4, 12, 14
2b	2.41	1H	ddt	1, 2a	14.1, 1.9, 0.7		
3	-	-	-	-	-	128.6	1, 2a, 2b, 4, 5a, 5b, 14
4	4.73	1H	dm	2b, 5a, 5b, 14	11.5	130.2	2a, 2b, 4, 5a, 5b, 6a, 6b, 14
5a	1.92	1H	m	2a, 4, 5b, 6a, 6b, 14	-	25.1	4, 5a, 5b, 6a, 6b, 14, 15
5b	2.31	1H	m	4, 5a, 6a, 6b	-		
6a	1.91	1H	m	5a, 5b, 6b	-	39.0	4, 5a, 5b, 6a, 6b, 8, 15
6b	2.15	1H	m	5a, 5b, 6a, 15	-		
7	-	-	-	-	-	135.6	5a, 6a, 6b, 9a, 9b, 15
8	4.70	1H	ddqi	10.9, 3.2, 1.4	9a, 9b, 10b, 15	125.0	6a, 6b, 8, 9a, 9b, 10a, 10b, 15
9a	2.06	1H	m	8, 9b, 10a, 10b, 15	-	24.4	8, 9b, 10a, 10b, 12, 15
9b	2.54	1H	m	8, 9a, 10a, 10b	-		
10a	2.24	1H	m	9a, 9b, 10b	-	25.6	8, 9a, 9b, 10a, 10b, 12, 15
10b	2.53	1H	m	1, 8, 9a, 9b, 10a, 12	-		
11	-	-	-	-	-	133.0	1, 9a, 9b, 10a, 10b, 12
12	6.80	1H	t	1, 10b	1.5	150.7	1, 2a, 2b, 10a, 10b, 12
13	-	-	-	-	-	173.9	1, 10a, 10b, 12
14	1.56	3H	t	4, 5a	1.4	18.9	2a, 2b, 4, 14
15	1.41	3H	dt	6b, 8, 9a	0.7, 1.4	14.9	5b, 6a, 8, 15

Table S-2. Comparison of the spectral data of synthetic manshurolide (**12**) (600 MHz, 298 K) with those of the natural product reported in the literature; (in this case, the solvent peak for residual CHCl₃ was calibrated to $\delta_{\text{H}} \equiv 7.24$ ppm)

# (lit.)	# (reassigned)	natural 12 (CDCl ₃)*		synthetic 12 (CDCl ₃)		Δ (δ (synth.)- δ (lit.))	
		¹ H	¹³ C	¹ H	¹³ C	Δ ¹ H	Δ ¹³ C
1	1	5.10	80.1	5.10	80.9	0.00	0.8
2	2	2.42	40.9	2.64	40.6	0.20	-0.3
				2.41		-0.01	
11	3	-	128.6	-	128.6	-	0.0
4	4	4.76	130.2	4.73	130.2	-0.03	0.0
5	5	1.93	25.4	1.92	25.1	-0.01	-0.3
		2.32		2.31		-0.01	
6	6	1.94	39.2	1.91	39.0	-0.03	-0.2
		2.15		2.15		0.00	
7	7	-	135.5	-	135.6	-	0.1
8	8	4.72	125.1	4.70	125.0	-0.02	-0.1
9	9	2.08	24.6	2.06	24.4	-0.02	-0.2
		2.56		2.54		-0.02	
10	10	2.28	25.8	2.24	25.6	-0.04	-0.3
		2.53		2.53		0.00	
3	11	-	133.1	-	133.0	-	-0.1
12	12	6.81	150.5	6.80	150.7	-0.01	0.2
13	13	-	173.6	-	173.9	-	0.3
14	14	1.57	19.1	1.56	18.9	-0.01	-0.2
15	15	1.43	15.1	1.41	14.9	-0.02	-0.2

¹) ¹H and ¹³C NMR shifts were reassigned according to 2D experiments.

²) Source of data: G. Rücker, C. W. Ming, R. Mayer, G. Will, A. Güllmann, *Phytochemistry* **1990**, 29, 983.

Total Synthesis of Ivorenolide A

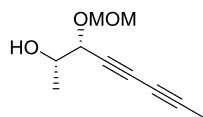
(S)-2-((4-Methoxybenzyl)oxy)propanal (38**)**. DIBAL-H (1.0 M in CH₂Cl₂, 5.64 mL, 5.64 mmol) was slowly added over the course of 1 h to a solution of methyl (S)-2-((4-methoxybenzyl)oxy)propanoate (1.15 g, 5.12 mmol)¹¹ in CH₂Cl₂ (25 mL) at –78 °C. The reaction was left to proceed at –78 °C for 20 min before it was quenched by slow addition of cold MeOH (3 mL) followed by sat. aq. Na/K-tartrate (25 mL). The suspension was stirred for 1 h at ambient temperature until clear phase separation was observed. The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL). The combined extracts were dried over MgSO₄ and the solvent was carefully evaporated. The crude material was purified by flash chromatography (SiO₂, 15% Et₂O in pentanes) yielding the desired aldehyde as a colorless liquid (0.88 g, 89%). [α]₂₀^D = –20.2 (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 9.63 (d, *J* = 1.8 Hz, 1H), 7.30 – 7.27 (m, 2H), 6.91 – 6.87 (m, 2H), 4.56 (d, *J* = 3.7 Hz, 2H), 3.91 – 3.83 (m, 1H), 3.81 (s, 3H), 1.31 ppm (d, *J* = 6.9 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 203.8, 159.6, 129.8, 114.1, 79.3, 71.9, 55.4, 15.5 ppm; IR (film): $\tilde{\nu}$ = 2837, 1732, 1612, 1513, 1302, 1246, 1174, 1090, 1032, 820; HRMS (ESI): *m/z*: calcd. for C₁₁H₁₄O₃Na 217.08357, found 217.08351.

(2S,3R)-2-((4-Methoxybenzyl)oxy)octa-4,6-diyn-3-ol (39**)**. A 25 mL Schlenk flask equipped with a cooling mantle was charged with (*R,R*)-ProPhenol (**41**) (83.2 mg, 0.13 mmol, 10 mol%), Ph₃P=O (72.5 mg, 0.26 mmol, 20 mol%) and toluene (5 mL). The solution was stirred for 10 min before ZnMe₂ (3.2 mL, 3.86 mmol) was added, followed by dropwise addition of diyne **29** (0.25 g, 3.86 mmol). Stirring was continued for 45 min. The solution was cooled to 0 °C, aldehyde **38** (0.25 g, 1.28 mmol) was added, and stirring was continued for 16 h at 0 °C. The reaction was quenched with sat. aq. NH₄Cl (15 mL), the aqueous layer was extracted with Et₂O (2 x 15 mL), and the combined organic layers were dried over MgSO₄. The solvent was carefully removed under reduced pressure and the crude product was purified by flash chromatography (20% Et₂O in pentanes) to yield the desired product as an colorless oil (205 mg, 61%). [α]₂₀^D = –11.2 (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.52 (dd, *J* = 56.9, 11.5 Hz, 2H), 3.81 (s, 3H), 3.65 (qd, *J* = 6.4, 3.7 Hz, 1H), 1.93 (s, 3H), 1.27 ppm (d, *J* = 6.9 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 130.1, 129.6, 114.0, 76.5, 71.2, 70.9, 65.8, 55.4, 15.0, 4.5, 1.2 ppm; IR (film): $\tilde{\nu}$ = 2932, 1612, 1513, 1302, 1248, 1175, 1083, 822; HRMS (ESI): *m/z*: calcd. for C₁₆H₁₈O₃Na 281.11486, found 281.11481.

1-Methoxy-4-(((2S,3R)-3-(methoxymethoxy)octa-4,6-diyn-2-yl)oxy)methyl)benzene (S18**)**. A 25 mL Schlenk flask was charged with alcohol **39** (120.0 mg, 0.46 mmol), CH₂Cl₂ (5 mL) and Hünig's base (0.174 mL, 1.0 mmol). The solution was cooled to 0 °C before MOM-Cl (0.061 mL, 0.81 mmol) was added. The cooling bath was removed and the mixture stirred for 16 h before the reaction was quenched with water (10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 x 10 mL), the combined organic layers were dried over MgSO₄ and the solvent was carefully removed under reduced pressure. The crude product was purified by flash chromatography (10% Et₂O in pentanes) to give the desired product as a colorless oil (118 mg, 85%). [α]₂₀^D = –43.0 (*c* = 0.5, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 7.30 – 7.26 (m, 2H), 6.89 – 6.85 (m, 2H), 4.91 (d, *J* = 6.7 Hz, 1H), 4.65 – 4.52 (m, 3H), 4.45 (dd, *J* = 4.2, 1.1 Hz, 1H), 3.80 (s, 3H), 3.67 (qd, *J* = 6.4, 4.2 Hz, 1H), 3.38 (s, 2H), 1.94 (d, *J* = 1.0 Hz, 3H), 1.27 ppm (d, *J* = 6.4 Hz, 3H); ¹³C NMR (101 MHz,

CDCl₃): δ = 159.3, 130.5, 129.5, 113.9, 94.6, 76.3, 72.0, 71.6, 71.3, 68.8, 64.0, 55.9, 55.4, 16.0, 4.5 ppm; IR (film): $\tilde{\nu}$ = 2932, 1513, 1247, 1148, 1097, 1023, 808; HRMS (ESI): m/z : calcd. for C₁₈H₂₂O₄Na 325.14096, found 325.14103.

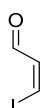
(2S,3R)-3-(Methoxymethoxy)octa-4,6-diyn-2-ol (40). DDQ (163 mg, 0.72 mmol) was added in one



portion to a solution of compound **S18** (110 mg, 0.36 mmol) in CH₂Cl₂ (4.5 mL) and pH ~7 buffer (0.5 mL) at 0 °C. The mixture was stirred for 3 h at this temperature before the reaction was quenched with sat. aq. NH₄Cl (5 mL). The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined extracts were dried over MgSO₄.

The solvent was removed under reduced pressure and the residue was purified by flash chromatography (20% Et₂O in pentanes) to give the title compound as a yellow oil (48 mg, 72%). $[\alpha]_{20}^D = -59.1$ ($c = 0.5$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 4.92 (d, $J = 6.8$ Hz, 1H), 4.66 (dd, $J = 6.8, 0.5$ Hz, 1H), 4.38 – 4.30 (m, 1H), 4.00 – 3.91 (m, 1H), 3.39 (s, 3H), 2.32 (d, $J = 5.6$ Hz, 1H), 1.94 (d, $J = 1.0$ Hz, 3H), 1.28 ppm (d, $J = 6.4$ Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 94.6, 77.2, 72.6, 71.5, 70.5, 69.5, 63.7, 56.0, 18.3, 4.4 ppm; IR (film): $\tilde{\nu}$ = 3441, 2892, 2258, 1098, 1026; HRMS (ESI): m/z : calcd. for C₁₀H₁₄O₃Na 205.08373, found 205.08351.

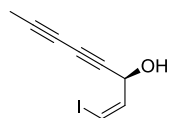
(Z)-3-Iodoacrylaldehyde (28). A 50 mL 3-necked round bottom flask equipped with a thermometer, a gas



inlet and a rubber septum was charged with ethyl-(Z)-iodoacrylate (5.0 mmol, 0.64 mL) and CH₂Cl₂ (10 mL). The solution was cooled to –80 °C (*n*-butanol/N₂(liq.) bath) before DIBAL-H (1 M in CH₂Cl₂, 5.1 mmol, 5.1 mL) was added very carefully at such a rate as to maintain the internal temperature between –76 °C and –82 °C. After complete addition, the reaction was stirred at –78 °C until GC/MS indicated complete consumption of the starting material. The reaction was carefully quenched at this temperature with anhydrous MeOH (2.5 mL) followed by sat. aq. Rochelle salt solution (12.5 mL). Stirring was continued at ambient temperature for 30 min before the mixture was filtered through a short pad of Celite. The solvent was carefully removed under reduced pressure, keeping the temperature of the water bath around 0 °C.

The crude aldehyde (810 mg, 86%) was not purified any further due to its instability; it was immediately transferred to a 25 mL Schlenk flask and dissolved in toluene (8.1 mL). The solution can be stored under argon at –20 °C for ca. 3- 4 weeks, without significant decomposition or isomerization of the double bond being observed.

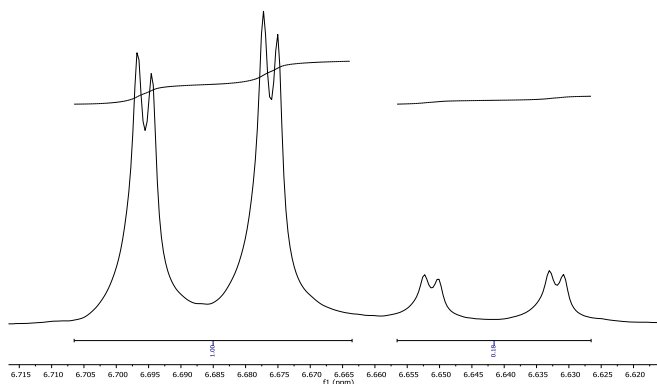
(S,Z)-1-Iodoocta-1-en-4,6-diyn-3-ol (30). A 25 mL Schlenk flask equipped with a cooling mantle was



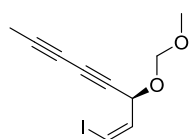
charged with Ph₃P=O (0.042 g, 0.15 mmol, 20 mol%), (*R,R*)-ProPhenol (**41**) (0.048 g, 0.076 mmol, 10 mol%) and toluene (3 mL). The solution was stirred for 5 min before diyne **29** (0.16 g, 2.5 mmol) was introduced, followed by the dropwise addition of ZnMe₂ (1.2 M in toluene, 1.62 mL, 1.95 mmol). The solution was stirred for 1 h at room temperature before it was cooled to 0 °C. A solution of aldehyde **28** (0.14 g, 0.76 mmol) in toluene (1.4 mL) was added dropwise at this temperature and the reaction was allowed to proceed overnight. For work up, the reaction was quenched with sat. aq. NH₄Cl (5 mL) and the resulting suspension was stirred for 1 h at room temperature until a clear separation of the layers was observed. The aqueous phase was extracted with Et₂O (3 x 10 mL), the combined extracts were dried over MgSO₄ and the solvent was evaporated.

Purification of the crude material yielded the desired product as a colorless oil which turns yellow on standing (0.18 g, 86%, 70% ee). $[\alpha]_{20}^D = +275.9$ ($c = 1.0$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): $\delta = 6.53$ (dd, $J = 7.7, 1.1$ Hz, 1H), 6.38 (t, $J = 7.7$ Hz, 1H), 5.16 (ddt, $J = 6.7, 4.0, 1.1$ Hz, 1H), 2.11 (d, $J = 5.0$ Hz, 1H), 1.94 ppm (d, $J = 1.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 139.1, 84.9, 78.6, 72.4, 71.2, 65.9, 63.6, 4.5$ ppm; IR (film): $\tilde{\nu} = 3333, 2257, 1607, 1427, 1261, 1029, 1008, 933, 735, 594$; HRMS (ESI): m/z : calcd. for $\text{C}_8\text{H}_7\text{IO}_2\text{Na}$ 268.94355, found 268.94338.

The ee (70%) was determined by formation of the (*R*)-MTPA-Ester and (*S*)-MTPA-esters according to the standard procedure.¹²



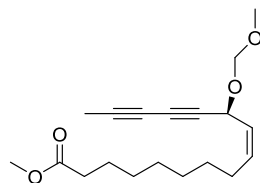
(*S,Z*)-1-iodo-3-(methoxymethoxy)octa-1-en-4,6-diyne (31). Hünig's base (0.87 mL, 5.0 mmol) and MOM-



Cl (0.26 mL, 3.5 mmol) were added successively to a solution of alcohol **30** (180 mg, 0.73 mmol, 1.0 eq.) in CH_2Cl_2 (4 mL) at 0 °C. The cooling bath was removed and the mixture stirred at room temperature until complete consumption of the starting material was observed. The reaction was quenched by addition of H_2O (5 mL) and the

aqueous layer was extracted with Et_2O (3 x 10 mL). The combined extracts were dried over MgSO_4 and the solvent evaporated under reduced pressure. Purification of the residue via flash chromatography (5% Et_2O in pentanes) yielded the title compound as pale yellow oil (181 mg, 85%). $[\alpha]_{20}^D = +172.2$ ($c = 1.0$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): $\delta = 6.53$ (dd, $J = 7.7, 1.1$ Hz, 1H), 6.38 (t, $J = 7.7$ Hz, 1H), 5.16 (ddt, $J = 6.7, 4.0, 1.1$ Hz, 1H), 4.87 (d, $J = 6.8$ Hz, 1H), 4.64 (d, $J = 6.9$ Hz, 1H), 3.41 (s, 3H), 1.94 ppm (d, $J = 1.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 137.5, 93.9, 85.6, 78.0, 71.7, 70.7, 68.8, 63.7, 56.1, 4.5$ ppm; IR (film): $\tilde{\nu} = 2887, 2256, 1262, 1147, 1094, 1053, 1008, 964, 926, 735$; HRMS (ESI): m/z : calcd. for $\text{C}_{10}\text{H}_{11}\text{IO}_2\text{Na}$ 312.97036, found 312.96960.

Methyl (*S,Z*)-11-(methoxymethoxy)hexadeca-9-en-12,14-diynoate (34). A 10 mL Schlenk flask was



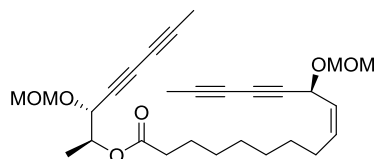
charged with Zn dust (56.1 mg, 0.86 mmol) and anhydrous LiCl (28.0 mg, 0.66 mmol). The mixture was dried in vacuum for 5 min at 150 °C (heat-gun). Once the flask had reached ambient temperature and was flushed with Ar, THF (0.3 mL) was introduced and the suspension was stirred at 60 °C before 1,2-dibromoethane (0.01 mL) was added. After stirring for 5 min, TMSCl (0.01 mL)

was introduced, followed by a solution of methyl 8-iodooctanoate (187 mg, 0.66 mmol) in THF (0.3 mL). The suspension was vigorously stirred for 5 h at 45 °C and then at room temperature overnight. GC/MS revealed ~90% conversion (prolonged stirring did not further increase the conversion) of the starting material. Stirring was stopped and the remaining Zn-dust was allowed to settle (~ 1 h.) giving a ~1 M solution of the organozinc compound **33**.

A second Schlenk flask was charged with Pd(PPh₃)₂Cl₂ (3.4 mg, 0.005 mmol, 4 mol%), alkenyl iodide **31** (40.0 mg, 0.13 mmol), THF (0.5 mL) and TMEDA (0.025 mL, 0.17 mmol). The resulting light yellow solution was stirred for 10 min at room temperature before it was warmed to 50 °C. At this temperature, an aliquot of the freshly prepared organozinc solution (1.5 equiv.) was added dropwise, resulting in a change of color from light yellow to deep orange. The mixture was stirred for another 1 h at 50 °C before it was allowed to cool to room temperature. The reaction was quenched with sat. aq. NH₄Cl (5 mL) and the mixture diluted with Et₂O (10 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 10 mL), the combined extracts were dried over MgSO₄ and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (EtOAc/hexanes 5% to 10%) to give the title compound as colorless oil (32.8 mg, 75%). [α]₂₀^D = +45.1 (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 5.67 – 5.58 (m, 1H), 5.50 – 5.42 (m, 1H), 5.14 (dt, *J* = 8.7, 1.1 Hz, 1H), 4.83 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 3.66 (s, 3H), 3.37 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.15 – 2.06 (m, 2H), 1.93 (d, *J* = 0.9 Hz, 3H), 1.66 – 1.58 (m, 2H), 1.38 (t, *J* = 6.6 Hz, 2H), 1.34 – 1.25 ppm (m, 6H); ¹³C NMR (101 MHz, CDCl₃): δ = 174.1, 134.5, 125.8, 93.2, 72.7, 70.3, 63.6, 61.1, 55.5, 51.3, 33.9, 29.0, 28.9, 28.8, 27.4, 24.7, 22.2, 13.9, 4.1 ppm; IR (film): $\tilde{\nu}$ = 2929, 2856, 1737, 1436, 1150, 1094, 1025, 923; HRMS (ESI): *m/z*: calcd. for C₁₉H₂₈O₄Na 343.18793, found 343.18798.

(5,Z)-11-(Methoxymethoxy)hexadeca-9-en-12,14-diynoic acid (S19). A solution of LiOH (0.5 M in water, 23.9 mg, 1.0 mmol) was added to a solution of ester **34** (34.0 mg, 0.11 mmol, 1.0 eq.) in THF/MeOH (2/1, 4 mL). The mixture was stirred at room temperature for 4 h before it was carefully acidified (pH = 2-3) with HCl (3 M) and diluted with Et₂O (10 mL). The aqueous phase was extracted with Et₂O (3 x 5 mL), the combined organic layers were dried over MgSO₄ and the solvent was evaporated under reduced pressure yielding the desired acid as pale yellow oil which was used without further purification (30 mg, 89%). [α]₂₀^D = +33.6 (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 5.63 (dtd, *J* = 10.7, 7.5, 1.1 Hz, 1H), 5.47 (ddt, *J* = 10.4, 8.6, 1.5 Hz, 1H), 5.14 (dt, *J* = 8.6, 1.1 Hz, 1H), 4.83 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 1H), 3.38 (s, 3H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.14 – 2.06 (m, 2H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.68 – 1.59 (m, 2H), 1.42 – 1.27 ppm (m, 7H); ¹³C NMR (101 MHz, CDCl₃): δ = 179.0, 134.7, 126.0, 93.4, 72.8, 70.5, 63.8, 61.3, 55.6, 33.8, 29.1, 29.0, 28.9, 27.5, 24.6, 4.3 ppm; IR (film): $\tilde{\nu}$ = 2928, 2855, 1707, 1150, 1093, 1025, 922; HRMS (ESI): *m/z*: calcd. for C₁₈H₂₅O₄ 305.17603, found 305.17584.

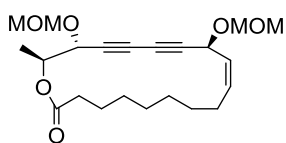
(2S,3R)-3-(Methoxymethoxy)octa-4,6-diyn-2-yl



(S,Z)-11-(methoxymethoxy)hexadeca-9-en-12,14-diynoate (35). Et₃N (0.02 mL, 0.14 mmol) and Yamaguchi-reagent (29.4 mg, 0.12 mmol) were successively added at 0 °C to a solution of acid **S19** (29.0 mg, 0.095 mmol) in toluene (1 mL). The mixture was stirred at this temperature until TLC indicates complete conversion of the

starting material. A solution of alcohol **40** (17.1 mg, 0.094 mmol) and DMAP (5.7 mg, 0.047 mmol) in toluene (1 mL) was added and stirring continued at ambient temperature for 2 h. The reaction was quenched at 0 °C with HCl (1 M, 5 mL) and the mixture was diluted with EtOAc (10 mL). The aqueous phase was extracted EtOAc (2 x 10 mL), the combined extracts were washed with brine, dried over MgSO₄, and the solvent was evaporated. The crude material was purified by flash chromatography (10% → 20% Et₂O in hexanes) to give the title compound as a colorless syrup (34 mg, 79 %). $[\alpha]_{20}^D = -6.5$ ($c = 0.5$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): $\delta = 5.63$ (dtd, $J = 10.7, 7.5, 1.1$ Hz, 1H), 5.46 (ddt, $J = 10.3, 8.7, 1.5$ Hz, 1H), 5.14 (dt, $J = 8.7, 1.1$ Hz, 1H), 5.07 (qd, $J = 6.5, 4.0$ Hz, 1H), 4.89 (d, $J = 6.8$ Hz, 1H), 4.83 (d, $J = 6.9$ Hz, 1H), 4.60 (d, $J = 6.9, 0.6$ Hz, 2H), 4.44 (dd, $J = 4.0, 1.1$ Hz, 1H), 3.37 (d, $J = 2.0$ Hz, 6H), 2.32 (t, $J = 7.5$ Hz, 2H), 2.14 – 2.06 (m, 2H), 1.94 (d, $J = 1.0$ Hz, 3H), 1.93 (d, $J = 0.9$ Hz, 3H), 1.65 – 1.58 (m, 2H), 1.37 (t, $J = 6.4$ Hz, 2H), 1.35 – 1.26 ppm (m, 9H); ¹³C NMR (101 MHz, CDCl₃): $\delta = 173.1, 134.9, 126.1, 94.4, 93.5, 72.9, 71.9, 70.6, 70.5, 68.1, 63.9, 63.7, 61.3, 55.8, 55.8, 34.5, 29.4, 29.2, 29.1, 29.1, 27.7, 25.0, 15.4, 4.4, 4.4, 1.2$ ppm; IR (film): $\tilde{\nu} = 2928, 2855, 1707, 1150, 1093, 1025, 922$; HRMS (ESI): m/z : calcd. for C₂₈H₃₈O₆Na 493.25662, found 493.25606.

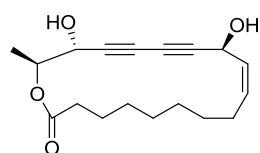
(12S,17R,18S,Z)-12,17-Bis(methoxymethoxy)-18-methyloxacyclooctadeca-10-en-13,15-diyn-2-one (36).



A solution of tris-silanol **11b** (9.7 mg, 0.011 mmol) and complex **3** (6.5 mg, 0.01 mmol) in toluene (1 mL) was vigorously stirred for 10 min to give a clear brown stock solution of the catalyst (0.01 mmol/mL) which has to be used within ca 30-40 min before it turns dark.

A 25 mL Schlenk flask was charged with 5 Å MS (2 mg/μmol substrate) under argon, the flask was evacuated and the molecular sieves were dried for 3 – 5 min at ca. 350°C (heat gun). The flask was backfilled with argon and a solution of compound **35** (15.0 mg, 0.031 mmol) in toluene (3.4 mL) was introduced. After stirring for 1 h, the flask was immersed into an oil bath at 60 °C and an aliquot of the catalyst stock solution (0.62 mL, 0.0062 mmol, 20 mol%) was added. The mixture was stirred at 60 °C for 45 min before it was cooled to room temperature and filtrated through a pad of silica, which was rinsed with EtOAc (30 mL). The combined filtrates were evaporated and the crude product was purified by flash chromatography (10% EtOAc in hexanes) to give the title compound as pale yellow oil (9.7 mg, 78%). $[\alpha]_{20}^D = -61.9$ (0.7, CHCl₃). ¹H NMR (400 MHz, CDCl₃): $\delta = 5.59$ (tdd, $J = 10.1, 5.8, 1.1$ Hz, 1H), 5.53 – 5.44 (m, 1H), 5.19 (d, $J = 8.0$ Hz, 1H), 5.07 – 5.00 (m, 1H), 4.90 (d, $J = 6.9$ Hz, 1H), 4.80 (d, $J = 6.8$ Hz, 1H), 4.61 (dd, $J = 6.9, 5.6$ Hz, 2H), 4.28 (dd, $J = 7.2, 0.9$ Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 2.39 – 2.23 (m, 2H), 2.20 – 2.08 (m, 2H), 1.75 – 1.65 (m, 1H), 1.63 – 1.56 (m, 1H), 1.55 – 1.46 (m, 1H), 1.41 – 1.28 (m, 9H); ¹³C NMR (101 MHz, CDCl₃): $\delta = 173.0, 134.6, 126.5, 94.5, 93.7, 75.8, 70.7, 70.5, 69.6, 69.1, 61.7, 56.1, 55.8, 35.5, 29.7, 29.6, 28.8, 28.7, 28.1, 25.5, 17.6$; IR (film): $\tilde{\nu} = 2932, 2857, 1738, 1151, 1098, 1027$; HRMS (ESI): m/z : calcd. for C₂₂H₃₂O₆Na 415.20942, found 415.20911.

(12S,17R,18S,Z)-12,17-Dihydroxy-18-methyloxacyclooctadeca-10-en-13,15-diyn-2-one (37).

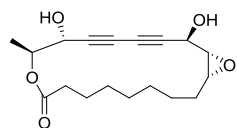


of compound **36** (9.0 mg, 0.023 mmol) in EtOH (1 mL) and HCl (3 M, 0.04 mL) was stirred at 70°C for 4 h. Since TLC revealed incomplete conversion, additional HCl (3 M, 0.04 mL) was added and stirring was continued for another 6 h at 70°C. The mixture was allowed to cool before it was neutralized with sat. aq. NaHCO₃. The

aqueous layer was extracted with *tert*-butyl methyl ether, the extracts were dried over MgSO₄ and

evaporated, and the residue was purified by flash chromatography (40% → 50% Et₂O in pentanes) to give the title compound as a colorless oil (4.4 mg, 64%). Small amounts of unreacted starting material was recovered and resubjected to MOM-cleavage under the same conditions. $[\alpha]_{20}^D = +61.2$ (0.5, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 5.59 – 5.46 (m, 2H), 5.27 (dd, *J* = 6.9, 3.4 Hz, 1H), 4.92 (qd, *J* = 6.5, 4.6 Hz, 1H), 4.39 – 4.29 (m, 1H), 3.17 (d, *J* = 8.1 Hz, 1H), 2.34 (t, *J* = 7.1 Hz, 2H), 2.16 – 2.10 (m, 1H), 1.75 – 1.56 (m, 2H), 1.41 – 1.18 (m, 11H); ¹³C NMR (101 MHz, CDCl₃): δ = 174.6, 133.6, 128.6, 79.0, 77.3, 74.2, 70.3, 69.1, 67.0, 59.1, 35.5, 29.7, 29.6, 28.8(2C), 28.2, 25.6, 17.5; IR (film): $\tilde{\nu}$ = 3383, 2929, 2856, 1713, 1262, 1046; HRMS (ESI): *m/z*: calcd. for C₁₈H₂₄O₄Na 327.15659, found 327.15668.

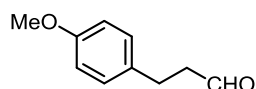
Ivorenolide A (24). *m*-CPBA (8.6 mg, 0.055 mmol) was added in one portion to a solution of compound **37** (3.4 mg, 0.011 mmol) in CH₂Cl₂ (1 mL) at 0°C. The mixture was stirred for 30 min at 0°C and for an additional 6 h at room temperature before the reaction was quenched with sat. aq. NaHCO₃ (5 mL). The aqueous layer was extracted with *tert*-butyl methyl ether (3 x 10 mL) and the combined organic layers were dried over MgSO₄. The solvent was evaporated and the residue purified by flash chromatography (30% → 40% → 50%



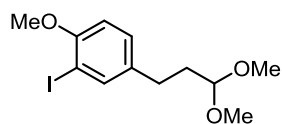
tert-butyl methyl ether in pentanes) to give the title compound as white crystals (2.5 mg, 74%). $[\alpha]_{20}^D = +39.2$ (0.2, MeOH). ¹H NMR (600 MHz, C₅D₅N): δ = 8.27 (s, (br) 2H, OH), 5.44 (dq, *J* = 8.4, 6.2 Hz, 1H), 4.79 – 4.67 (m, 2H), 3.51 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.09 (ddd, *J* = 10.1, 4.3, 3.0 Hz, 1H), 2.47 – 2.37 (m, 2H), 2.01 – 1.95 (m, 1H), 1.85 – 1.76 (m, 1H), 1.56 – 1.50 (m, 1H), 1.48 – 1.37 (m, 3H), 1.37 – 1.20 (m, 6H); ¹³C NMR (151 MHz, C₅D₅N): δ = 172.9, 81.3, 78.5, 72.8, 70.3, 68.7, 65.5, 62.2, 61.1, 57.0, 35.0, 30.0, 29.8, 29.1, 28.6, 26.2, 25.6, 17.7; IR (film): $\tilde{\nu}$ = 3394, 2928, 2856, 1735, 1458, 1260, 1046, 797; HRMS (ESI): *m/z*: calcd. for C₁₈H₂₄O₅Na 343.15156, found 343.15159.

Studies towards Lythrancepin I

3-(4-Methoxyphenyl)propanal (S20). A Schlenk tube was charged with NaHCO₃ (7.18 g, 85.5 mmol), Bu₄NCl (11.9 g, 42.7 mmol) and Pd(OAc)₂ (95.9 mg, 0.43 mmol) and the vessel was then evacuated and backfilled with Argon three times. A solution of 1-iodo-4-methoxybenzene (**43**, X = I) (10.0 g, 42.7 mmol) in DMF (43 mL) and allyl alcohol (4.36 mL, 64.1 mmol) were successively added and the mixture was stirred for 14 h at 50°C. The suspension was filtered through a plug of Celite, eluting with EtOAc (400 mL). The combined filtrates were washed with H₂O (2 x 100 mL) and brine (100 mL), and then dried over MgSO₄. The solvent was evaporated and the residue purified by flash chromatography (hexanes/EtOAc, 20:1 → 5:1) to afford the product as a yellow liquid (5.69 g, 81%). ¹H NMR (400 MHz, CDCl₃): δ = 9.80 (t, *J* = 1.4 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.76–2.72 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 201.7, 158.1, 132.3, 129.2 (2C), 114.0 (2C), 55.2, 45.5, 27.2 ppm; IR (film): $\tilde{\nu}$ = 2936, 2835, 2724, 1720, 1611, 1584, 1501, 1464, 1443, 1389, 1300, 1246, 1178, 1111, 1033, 860, 812, 769, 542, 519 cm⁻¹; MS (EI): *m/z* (%): 164 (41), 121 (100), 108 (27), 91 (16), 78 (11), 77 (19); HRMS (ESI): *m/z*: calcd. for C₁₀H₁₂O₂Na [M+Na]⁺: 187.07295, found 187.07299.



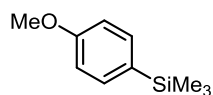
4-(3,3-Dimethoxypropyl)-2-iodo-1-methoxybenzene (44). Ag₂SO₄ (11.3 g, 36.4 mmol) and I₂ (9.23 g, 36.4



mmol) were added to a solution of 3-(4-methoxyphenyl)propanal (**S20**) (5.69 g, 34.7 mmol) in MeOH (347 mL). The initially dark brown suspension was vigorously stirred for 1 h, while turning bright yellow. The reaction was quenched with aq. sat. Na₂S₂O₃ (50 mL) and H₂O (150 mL) and the mixture

filtered through a plug of Celite, eluting with EtOAc (100 mL). Brine (500 mL) was added to the combined filtrates and the aqueous layer was extracted with EtOAc (3 x 500 mL). The combined extracts were dried (MgSO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 6:1) yielded the title compound as a yellow liquid (10.2 g, 87%). ¹H NMR (400 MHz, CDCl₃): δ = 7.61 (d, *J* = 2.1 Hz, 1H), 7.12 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 4.34 (t, *J* = 5.7 Hz, 1H), 3.85 (s, 3H), 3.33 (s, 6H), 2.60-2.56 (m, 2H), 1.89-1.84 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 156.3, 139.2, 135.8, 129.3, 110.8, 103.5, 85.9, 56.3 (2C), 52.7, 34.1, 29.4 ppm; IR (film): $\tilde{\nu}$ = 2950, 2939, 2830, 1490, 1459, 1440, 1384, 1278, 1252, 1181, 1124, 1077, 1053, 1019, 892, 812 cm⁻¹; MS (EI): *m/z* (%): 336 (22), 305 (14), 304 (100), 247 (67), 177 (21), 146 (13), 90 (11), 75 (48); HRMS (ESI): *m/z*: calcd. for C₁₂H₁₇O₃INa [M+Na]⁺: 359.01146, found 359.01138.

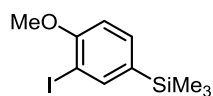
(4-Methoxyphenyl)trimethylsilane (45). *n*BuLi (1.6 M in hexanes, 65.2 mL, 104 mmol) was added within



45 min to a solution of 1-bromo-4-methoxybenzene (**43**, X = Br) (10.0 mL, 80.2 mmol) in THF (159 mL) at -78 °C. After stirring for 30 min at this temperature, TMSCl (15.3 mL, 120 mmol) was added dropwise. The suspension was stirred for 17 h at room

temperature before the reaction was quenched with H₂O (250 mL). The aqueous layer was extracted with EtOAc (3 x 250 mL), the combined extracts were dried (MgSO₄) and the solvent was evaporated to afford the product as a yellow liquid (14.3 g, 99%). ¹H NMR (400 MHz, CDCl₃): δ = 7.46 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 3.82 (s, 3H), 0.26 ppm (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 160.2, 134.7 (2C), 131.3, 113.5 (2C), 55.0, -0.9 (3C) ppm; IR (film): $\tilde{\nu}$ = 2954, 2899, 2836, 1595, 1565, 1503, 1464, 1277, 1246, 1182, 1111, 1033, 838, 756, 595, 522 cm⁻¹; MS (EI): *m/z* (%): 180 (16), 166 (14), 165 (100); HRMS (EI): *m/z*: calcd. for C₁₀H₁₆OSi [M]⁺: 180.09704, found 180.09701.

(3-Iodo-4-methoxyphenyl)trimethylsilane (46). A 2 L 2-necked round bottom flask equipped with a



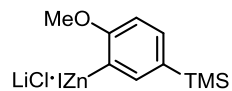
dropping funnel was charged with TMEDA (26.2 mL, 175 mmol) and Et₂O (300 mL).

*n*BuLi (1.6 M in hexanes, 198 mL, 317 mmol) was added dropwise to this solution at room temperature. The dropping funnel was rinsed with Et₂O (37.5 mL) and the

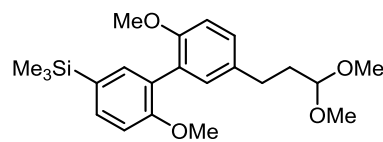
mixture was stirred for 30 min at room temperature. A solution of silane **45** (14.3 g, 79.4 mmol) in Et₂O (37.5 mL) was added within 10 min and the resulting suspension was stirred for 2.5 h at room temperature. Next, it was cooled to -78 °C and a solution of I₂ (68.5 g, 270 mmol) in THF (375 mL) was added within 1 h at this temperature. The slurry was allowed to reach room temperature within 14 h before the reaction was quenched with aq. sat. Na₂S₂O₃ (750 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 500 mL). The combined extracts were dried (MgSO₄) and the solvent was evaporated. The residue was purified by flash chromatography (hexanes/EtOAc, 40:1) to afford the product as a yellow liquid (19.9 g, 82%). ¹H NMR (300 MHz, CDCl₃): δ = 7.88 (d, *J* = 1.5 Hz, 1H), 7.43 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 3.89 (s, 3H), 0.25 ppm (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ = 158.5, 144.3, 134.7, 134.6, 110.9, 86.9, 56.1, -1.0 (3C) ppm; IR (film): $\tilde{\nu}$ = 3005, 2953, 2895,

2837, 1577, 1483, 1459, 1438, 1360, 1283, 1267, 1246, 1157, 1110, 1046, 1018, 833, 806, 753, 692, 667, 645, 607, 559, 520, 424 cm^{-1} ; MS (EI): m/z (%): 306 (41), 292 (14), 291 (100); HRMS (EI): m/z : calcd. for $\text{C}_{10}\text{H}_{15}\text{OISi} [\text{M}]^+$: 305.99369, found 305.99340.

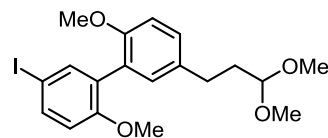
Arylzinc iodide lithium chloride adduct 47. A Schlenk tube was charged with pre-dried LiCl (1.66 g, 39.2 mmol) and then heated under vacuum (heatgun). Zinc powder (5.13 g, 78.4 mmol) was added and the solids were again heated under vacuum (heatgun). After the vessel had reached room temperature, THF (26 mL) was added and the suspension was stirred at 80 °C. 1,2-Dibromoethane (113 μL , 1.31 mmol) and TMSI (33 μL , 0.26 mmol) were added at this temperature before (3-iodo-4-methoxyphenyl)trimethylsilane (**46**) (8.00 g, 26.1 mmol) was introduced, followed by a second portion of 1,2-dibromoethane (113 μL , 1.31 mmol). The sealed tube was stirred for 24 h at 80 °C, after which the suspension was allowed to settle. Titration of the supernatant against I_2 showed a molarity of 0.75 M.



Biaryl 48. $\text{Pd}(\text{OAc})_2$ (85.7 mg, 0.382 mmol), SPhos (314 mg, 0.764 mmol) and an aliquot of the solution of the arylzinc iodide lithium chloride adduct **47** (0.75 M in THF, 28.0 mL, 21.0 mmol) were added to a solution of 4-(3,3-dimethoxypropyl)-2-iodo-1-methoxybenzene (**44**) (6.42 g, 19.1 mmol) in THF (28.5 mL) at room temperature. The resulting mixture was stirred for 2 h before it was filtered through a plug of silica, eluting with EtOAc (50 mL). The solvent of the combined filtrates was evaporated and the residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether, 4:1) to yield the product as a brown liquid (6.90 g, 93%). ^1H NMR (400 MHz, CDCl_3): δ = 7.52 (dd, J = 8.1, 1.7 Hz, 1H), 7.40 (d, J = 1.7 Hz, 1H), 7.19 (dd, J = 8.4, 2.3 Hz, 1H), 7.13 (d, J = 2.3 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 4.45 (t, J = 5.8 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.37 (s, 6H), 2.71-2.67 (m, 2H), 2.00-1.94 (m, 2H), 0.29 ppm (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ = 157.6, 155.3, 136.5, 134.0, 133.2, 131.4, 130.7, 128.2, 127.8, 127.1, 111.0, 110.3, 103.7, 55.7, 55.4, 52.6 (2C), 34.1, 29.9, -0.9 (3C) ppm; IR (film): $\tilde{\nu}$ = 2950, 2901, 2832, 1588, 1500, 1462, 1383, 1369, 1274, 1242, 1177, 1150, 1122, 1109, 1078, 1054, 1028, 912, 895, 836, 810, 754, 610 cm^{-1} ; MS (EI): m/z (%): 389 (23), 388 (80), 356 (20), 342 (11), 341 (35), 326 (13), 325 (46), 324 (100), 315 (21), 310 (16), 309 (41), 300 (10), 299 (30), 285 (14), 269 (14), 253 (13), 142 (24), 89 (19), 75 (39), 73 (33); HRMS (ESI): m/z : calcd. for $\text{C}_{22}\text{H}_{32}\text{O}_4\text{SiNa} [\text{M}+\text{Na}]^+$: 411.19621, found 411.19617.



Iodide 49. NIS (8.79 g, 39.1 mmol) was added to a solution of biaryl **48** (6.90 g, 17.8 mmol) in MeCN (178 mL) at room temperature. After stirring for 2.5 h, the solvent was evaporated and the residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether, 3:1 \rightarrow 2:1) to afford the title compound as white solid (5.75 g, 73%). ^1H NMR (400 MHz, CDCl_3): δ = 7.59 (dd, J = 8.7, 2.3 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H), 7.16 (dd, J = 8.4, 2.3 Hz, 1H), 7.04 (d, J = 2.3 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 8.7 Hz, 1H), 4.41 (t, J = 5.7 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.34 (s, 6H), 2.66-2.62 (m, 2H), 1.95-1.90 ppm (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ = 156.9, 155.0, 139.6, 137.1, 133.3, 131.1, 130.3, 128.8, 126.0, 113.2, 110.9, 103.6, 82.6, 55.7 (2C), 52.6 (2C), 34.1, 29.9 ppm; IR (film): $\tilde{\nu}$ = 2930, 2831, 1502, 1483, 1461, 1439, 1415, 1382, 1281, 1261, 1241, 1176, 1123, 1076, 1055, 1028, 961, 888,



808, 610, 588 cm^{-1} ; MS (EI): m/z (%): 443 (11), 442 (56), 410 (27), 379 (34), 378 (100), 353 (38), 252 (19), 75 (44); HRMS (ESI): m/z : calcd. for $\text{C}_{19}\text{H}_{23}\text{O}_4\text{I}\text{Na}$ $[\text{M}+\text{Na}]^+$: 465.05333, found 465.5333.

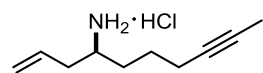
Aldehyde S21. PPTS (1.59 g, 6.33 mmol) was added to a solution of acetal **49** (5.60 g, 12.7 mmol) in acetone/ H_2O (110 mL, 10:1) and the resulting solution was stirred for 14 h at 50 °C. The organic solvent was evaporated before H_2O (100 mL) was added. The aqueous layer was extracted with EtOAc (3 x 100 mL), the combined extracts were dried (MgSO_4) and the solvent was evaporated to afford the product as a colorless foam (5.01 g, quant.). ^1H NMR (400 MHz, CDCl_3): δ = 9.83 (s, 1H), 7.60 (dd, J = 8.7, 2.2 Hz, 1H), 7.50 (d, J = 1.8 Hz, 1H), 7.16 (dd, J = 8.4, 2.0 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 8.7 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 2.93 (t, J = 7.5 Hz, 2H), 2.79 ppm (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ = 201.9, 156.9, 155.3, 139.6, 137.2, 131.9, 131.0, 130.1, 128.8, 126.2, 113.2, 111.1, 82.6, 55.8, 55.7, 45.4, 27.1 ppm; IR (film): $\tilde{\nu}$ = 2998, 2935, 2834, 2721, 1722, 1608, 1581, 1502, 1484, 1462, 1439, 1415, 1383, 1263, 1243, 1178, 1135, 1028, 887, 809, 610, 587 cm^{-1} ; MS (EI): m/z (%): 397 (17), 396 (100), 353 (46), 340 (20); HRMS (ESI): m/z : calcd. for $\text{C}_{17}\text{H}_{17}\text{O}_3\text{I}\text{Na}$ $[\text{M}+\text{Na}]^+$: 419.01146, found 419.01123.

Propargylic alcohol 50. Aldehyde **S21** (5.01 g, 12.6 mmol) was dissolved in a solution of $\text{LaCl}_3 \cdot 2 \text{LiCl}$ (0.6 M in THF, 21.5 mL, 12.9 mmol) and the mixture was stirred for 1 h at room temperature. The solution was cooled to 0 °C and propynyllithium (1.45 g, 31.6 mmol) was added in portions within 15 min at this temperature. After stirring for 2 h at 0 °C, the reaction was quenched with aq. sat. NH_4Cl (100 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash chromatography (hexanes/EtOAc, 3:1) to yield the title compound as a colorless foam (4.80 g, 87%). ^1H NMR (400 MHz, CDCl_3): δ = 7.60 (dd, J = 8.6, 2.3 Hz, 1H), 7.53 (d, J = 2.3 Hz, 1H), 7.18 (dd, J = 8.4, 2.2 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 8.6 Hz, 1H), 4.37 (t, J = 7.1 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 2.76 (t, J = 7.9 Hz, 2H), 2.06-1.94 (m, 3H), 1.87 ppm (d, J = 2.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 156.9, 155.0, 139.5, 137.1, 133.1, 131.1, 130.3, 128.8, 126.0, 113.2, 111.0, 82.5, 81.3, 80.1, 61.9, 55.7 (2C), 39.5, 30.4, 3.6 ppm; IR (film): $\tilde{\nu}$ = 3389, 2935, 2835, 1501, 1482, 1461, 1438, 1414, 1381, 1261, 1240, 1177, 1134, 1024, 907, 806, 728, 648, 610, 586, 501 cm^{-1} ; MS (EI): m/z (%): 437 (22), 436 (100), 354 (22), 353 (25), 340 (10); HRMS (ESI): m/z : calcd. for $\text{C}_{20}\text{H}_{21}\text{O}_3\text{I}\text{Na}$ $[\text{M}+\text{Na}]^+$: 459.04276, found 459.04271.

Hept-5-yn-1-al (52). A 500 mL 2-necked round bottom flask equipped with a reflux condenser was charged with hept-5-yn-1-ol (**51**) (3.81 g, 34.0 mmol) and MeCN (140 mL). $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (535 mg, 1.70 mmol), 2,2'-bipyridine (266 mg, 1.70 mmol), TEMPO (266 mg, 1.70 mmol), and NMI (0.27 mL, 3.4 mmol) were successively added, the joint was rinsed with MeCN (30 mL), closed with a rubber seal, and connected to an air-containing balloon. After stirring for 8 h at room temperature, H_2O (200 mL) and pentanes (200 mL) were added. The layers were separated, the aqueous layer was extracted with pentanes (3 x 200 mL, 4 x 100 mL) and the combined organic extracts were dried over Na_2SO_4 . Careful evaporation of the solvent yielded the product as a yellow liquid (3.41 g, 91%). ^1H NMR (400 MHz, CDCl_3): δ = 9.80 (t, J = 1.5 Hz, 1H), 2.56 (dt, J = 7.2, 1.5 Hz, 2H),

2.23-2.18 (tq, $J = 7.2$, 2.5 Hz, 2H), 1.80 (quint, $J = 7.2$ Hz, 2H), 1.77 ppm (t, $J = 2.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 202.1$, 77.9, 76.7, 42.8, 21.5, 18.2, 3.4 ppm; IR (film): $\tilde{\nu} = 2921$, 2844, 2724, 1721, 1437, 1411, 1390, 1364, 1335, 1243, 1177, 1071, 1032, 925, 866, 795, 689 cm^{-1} ; MS (EI): m/z (%): 82 (25), 68 (100), 67 (12), 66 (65), 65 (20), 55 (17), 53 (42), 51 (14), 41 (30), 39 (32), 29 (11), 27 (28); HRMS (EI): m/z : calcd. for $\text{C}_7\text{H}_{10}\text{O}$ $[\text{M}]^+$: 110.07317, found 110.07307.

(S)-Dec-1-en-8-yn-4-amine hydrochloride (53). *Preparation of the catalyst solution:* A Schlenk tube was

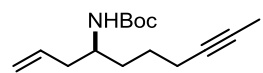


charged with (S)-VANOL (507 mg, 1.16 mmol), 2,4,6-trimethylphenol (315 mg, 2.31 mmol) and toluene (23.1 mL). $\text{BH}_3\text{-SMe}_2$ (310 μL , 3.47 mmol) and H_2O (62.5 μL , 3.47 mmol) were added and the solution was stirred for 1 h at 100 °C. The

solvent was carefully evaporated by vacuum distillation at 100 °C and the residue was dried under vacuum for 30 min at this temperature. After the vessel had reached room temperature, the residue was dissolved in *m*-xylene (23.1 mL).

Aza-Cope rearrangement: A suspension containing amine **58** (6.45 g, 23.1 mmol),¹³ activated molecular sieves (5Å, powder, 11.3 g), the freshly prepared catalyst stock solution (0.05 M in *m*-xylene, 23.1 mL, 1.16 mmol) and *m*-xylene (80 mL) was stirred for 30 min at 60 °C. Next, hept-5-yn-1-al (**52**) (2.64 g, 24.0 mmol) and benzoic acid (0.1 M in *m*-xylene, 11.5 mL, 1.15 mmol) were added and the mixture was stirred for 15 h at this temperature. The suspension was filtered through a plug of Celite, eluting with EtOAc (250 mL). The solvent of the combined filtrates was evaporated (high vacuum) and the residue was dissolved in THF (275 mL). HCl (1 M, 70.0 mL, 70.0 mmol) was added and the solution was stirred for 4 h at room temperature. H_2O (100 mL) was added to the reaction and the aqueous layer was washed with EtOAc (4 x 100 mL). The combined organic extracts were washed with HCl (1 M, 50 mL) and the aqueous extract was washed with EtOAc (50 mL). The solvent of the combined aqueous extracts was evaporated to yield the title compound as a yellow solid (3.95 g, 91%). $[\alpha]_{20}^D = +4.5^\circ$ ($c = 1.00$, MeCN/ H_2O , 1:1); ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{SO}$): $\delta = 8.13$ (br s, 3H), 5.80 (ddt, $J = 17.1$, 10.1, 7.0 Hz, 1H), 5.19-5.12 (m, 2H), 3.13 (quint, $J = 6.2$ Hz, 1H), 2.41-2.27 (m, 2H), 2.13-2.09 (m, 2H), 1.72 (t, $J = 2.5$ Hz, 3H), 1.61-1.55 (m, 2H), 1.53-1.44 ppm (m, 2H); ^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{SO}$): $\delta = 133.0$, 119.0, 78.8, 76.2, 49.7, 36.3, 30.9, 24.1, 17.9, 3.2 ppm; IR (film): $\tilde{\nu} = 2916$, 2893, 1601, 1511, 1461, 1446, 1434, 1392, 992, 918, 463, 411 cm^{-1} ; MS (EI): m/z (%): 110 (29), 94 (15), 93 (100), 91 (43), 77 (30), 70 (34), 65 (11), 56 (59), 53 (11), 43 (16), 42 (11), 41 (21), 39 (17); HRMS (ESI): m/z : calcd. for $\text{C}_{10}\text{H}_{18}\text{N}$ $[\text{M}-\text{Cl}]^+$: 152.14337, found 152.14344.

***tert*-Butyl (S)-dec-1-en-8-yn-4-ylcarbamate (S22).** Boc_2O (5.32 mL, 23.1 mmol) and NEt_3 (5.87 mL, 42.1

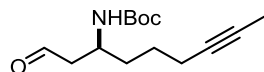


mmol) were added to a solution of (S)-dec-1-en-8-yn-4-amine hydrochloride (**53**) (3.95 g, 21.0 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The suspension was stirred for 3.5

h at room temperature before the organic solvent was evaporated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether, 10:1 \rightarrow 5:1) to afford the product as a colorless liquid which was kept at 50 °C under high vacuum overnight to remove any remaining volatile materials (4.71 g, 89%, 98% ee; determined by chiral GC-analysis: column: 25.0 m IVADEX 1/PS086 G 549, t_R (major enantiomer) = 72.92 min, t_R (minor enantiomer) = 73.60 min). $[\alpha]_{20}^D = -19.0^\circ$ ($c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): $\delta = 5.82$ -5.72 (m, 1H), 5.09-5.05 (m, 2H), 4.33 (d, $J = 7.4$ Hz, 1H), 3.63 (br s, 1H), 2.28-2.12 (m, 4H), 1.77 (t, $J = 2.5$ Hz, 3H), 1.63-1.47 (m, 4H), 1.43 ppm (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 155.5$, 134.4, 117.6, 79.0, 78.8, 75.8, 49.7, 39.6, 33.8, 28.4 (3C), 25.4, 18.6,

3.4 ppm; IR (film): $\tilde{\nu}$ = 3342, 2977, 2921, 2862, 1688, 1642, 1508, 1440, 1390, 1365, 1248, 1170, 1058, 993, 915, 778 cm^{-1} ; MS (EI): m/z (%): 154 (100), 110 (13), 93 (31), 57 (70); HRMS (ESI): m/z : calcd. for $\text{C}_{15}\text{H}_{25}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 274.17775, found 274.17750.

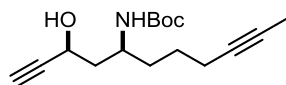
Amino aldehyde 54. A solution of *tert*-butyl (*S*)-dec-1-en-8-yn-4-ylcarbamate (**S22**) (4.71 g, 18.7 mmol)



and *N*-methylmorpholine-*N*-oxide (6.59 g, 56.2 mmol) in CH_2Cl_2 (187 mL) was treated with ozone at 0 °C until TLC showed full consumption of the starting material. The solution was purged with Argon for 5 min and the solvent was

evaporated after the addition of silica. The residue was purified by flash chromatography (hexanes/EtOAc, 3:1) to yield the title compound as a colorless liquid (3.63 g, 76%). $[\alpha]_{20}^D = -16.2^\circ$ ($c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ = 9.73 (t, $J = 1.9$ Hz, 1H), 4.69 (d, $J = 8.2$ Hz, 1H), 4.03-3.96 (m, 1H), 2.64-2.52 (m, 2H), 2.15-2.11 (m, 2H), 1.74 (t, $J = 2.5$ Hz, 3H), 1.63-1.45 (m, 4H), 1.39 ppm (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ = 201.1, 155.3, 79.5, 78.4, 76.1, 49.2, 46.1, 34.1, 28.3 (3C), 25.4, 18.4, 3.4 ppm; IR (film): $\tilde{\nu}$ = 3341, 2977, 2922, 1686, 1513, 1455, 1391, 1366, 1294, 1248, 1165, 1068, 864, 781 cm^{-1} ; MS (EI): m/z (%): 110 (13), 93 (11), 72 (16), 59 (14), 57 (100), 41 (16); HRMS (ESI): m/z : calcd. for $\text{C}_{14}\text{H}_{23}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 276.15701, found 276.15720.

β -Amino alcohol 56. *Procedure A:* Ethynylmagnesium bromide (0.5 M in THF, 143 mL, 71.6 mmol) was

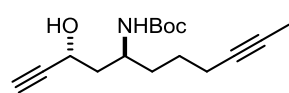


added within 15 min to a solution of amino aldehyde **54** (3.63 g, 14.3 mmol) in Et_2O (63 mL) at -78°C . After stirring for 2 h at -78°C and for 1 h at room temperature the reaction was quenched with aq. sat. Rochelle salt (300 mL).

The mixture was extracted with EtOAc (3 x 300 mL), the combined organic extracts were washed with H_2O (100 mL) and brine (100 mL) and dried over Na_2SO_4 . The solvent was evaporated and the residue was purified by flash chromatography (hexanes/ CH_2Cl_2 /acetone, 10:10:1 \rightarrow 5:5:1) to yield the β -amino alcohol **55** and separately the title compound as colorless foam (1.56 g, 39%).

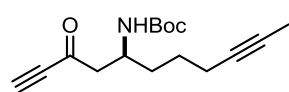
Procedure B: A Schlenk tube was charged with pre-dried LiCl (1.74 g, 41.1 mmol) and then heated under vacuum (heatgun). After the vessel had reached room temperature, a solution of β -amino ketone **S23** (1.14 g, 4.11 mmol) in Et_2O (200 mL) was introduced and the mixture was sonicated in an ultrasonic bath for 15 min. The resulting suspension was cooled to 0 °C before $\text{LiAlH}(\text{OtBu})_3$ (1 M in THF, 12.3 mL, 12.3 mmol) was added at this temperature. Stirring was continued for 2 h at 0 °C before the reaction was quenched with aq. sat. Rochelle salt (300 mL). The aqueous layer was extracted with EtOAc (3 x 300 mL), the combined extracts were washed with H_2O (100 mL) and brine (100 mL), dried (Na_2SO_4) and the solvent was evaporated. Purification of the crude material by flash chromatography (hexanes/ CH_2Cl_2 /acetone, 5:5:1) furnished the title compound as colorless foam (1.06 g, 92%). $[\alpha]_{20}^D = -19.6^\circ$ ($c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ = 4.57-4.52 (m, 1H), 4.45 (d, $J = 8.9$ Hz, 1H), 3.85-3.78 (m, 1H), 3.71 (d, $J = 8.2$ Hz, 1H), 2.41 (d, $J = 1.6$ Hz, 1H), 2.18-2.13 (m, 2H), 1.98 (ddd, $J = 13.9, 6.4, 3.7$ Hz, 1H), 1.78 (t, $J = 2.5$ Hz, 3H), 1.75-1.70 (m, 1H), 1.63-1.48 (m, 4H), 1.45 ppm (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ = 156.5, 85.2, 79.8, 78.5, 76.0, 72.2, 59.5, 47.2, 43.2, 34.8, 28.5 (3C), 25.3, 18.5, 3.4 ppm; IR (film): $\tilde{\nu}$ = 3343, 3296, 2975, 2922, 1686, 1511, 1455, 1442, 1392, 1366, 1290, 1248, 1166, 1070, 1049, 1028, 862, 803, 780, 733, 647 cm^{-1} ; MS (EI): m/z (%): 142 (16), 110 (14), 98 (32), 94 (81), 93 (19), 91 (13), 80 (12), 79 (14), 59 (22), 57 (100), 56 (17), 55 (15), 53 (17), 44 (21), 41 (29), 39 (11); HRMS (ESI): m/z : calcd. for $\text{C}_{16}\text{H}_{25}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 302.17266, found 302.17284

β -Amino alcohol 55. This compound was isolated as the minor product from the previous reaction



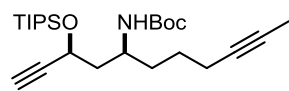
(*procedure A*, colorless foam, 1.32 g, 33%). $[\alpha]_{20}^D = +1.0^\circ$ ($c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): $\delta = 4.49$ (d, $J = 8.8$ Hz, 1H), 4.40 (ddt, $J = 10.3, 4.8, 2.4$ Hz, 1H), 4.33 (d, $J = 4.6$ Hz, 1H), 3.80-3.73 (m, 1H), 2.41 (d, $J = 2.0$ Hz, 1H), 2.15-2.12 (m, 2H), 1.93 (ddd, $J = 13.8, 10.6, 2.9$ Hz, 1H), 1.76 (t, $J = 2.5$ Hz, 3H), 1.61-1.47 (m, 5H), 1.42 ppm (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 157.3, 84.4, 80.2, 78.4, 76.2, 72.2, 58.6, 47.0, 45.0, 34.4, 28.3$ (3C), 25.5, 18.5, 3.4 ppm; IR (film): $\tilde{\nu} = 3298, 2976, 2921, 1679, 1509, 1455, 1439, 1392, 1366, 1293, 1247, 1164, 1074, 1051, 1030, 864, 782, 651\text{ cm}^{-1}$; MS (EI): m/z (%): 178 (11) 154 (17), 142 (20), 124 (10), 111 (13), 110 (19), 108 (12), 98 (34), 93 (16), 57 (100), 41 (17); HRMS (ESI): m/z : calcd. for $\text{C}_{16}\text{H}_{25}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 302.17266, found 302.17268.

β -Amino ketone S23. DMP (3.00 g, 7.09 mmol) was added to a solution of β -amino alcohol **55** (1.32 g,



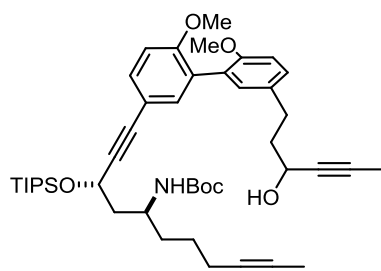
4.72 mmol) in CH_2Cl_2 (50 mL) at 0°C and the solution was stirred for 1.5 h at room temperature. The reaction was quenched with aq. sat. NaHCO_3 (50 mL) and aq. sat. $\text{Na}_2\text{S}_2\text{O}_3$ (50 mL), the mixture was stirred for another 15 min at room temperature and then extracted with EtOAc (3 x 100 mL). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as colorless foam (1.14 g, 87%). $[\alpha]_{20}^D = -3.9^\circ$ ($c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): $\delta = 4.73$ (d, $J = 8.9$ Hz, 1H), 4.06-3.98 (m, 1H), 3.27 (s, 1H), 2.88-2.77 (m, 2H), 2.15 (ddt, $J = 6.6$ Hz, 4.1 Hz, 2.5 Hz, 2H), 1.77 (t, $J = 2.5$ Hz, 3H), 1.62-1.45 (m, 4H), 1.42 ppm (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 185.4, 155.2, 81.3, 79.4, 79.2, 78.56, 76.1, 50.1, 47.1, 33.6, 28.3$ (3C), 25.5, 18.4, 3.5 ppm; IR (film): $\tilde{\nu} = 3353, 3263, 2977, 2922, 2864, 2092, 1682, 1506, 1455, 1392, 1366, 1295, 1249, 1167, 1106, 1054, 863\text{ cm}^{-1}$; MS (EI): m/z (%): 122 (11), 110 (15), 96 (20), 57 (100), 41 (24); HRMS (ESI): m/z : calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 300.15701, found 300.15700.

β -Amino alcohol 57. Imidazole (1.91 g, 28.1 mmol), DMAP (229 mg, 1.88 mmol) and TIPSCl (6.02 mL,



28.1 mmol) were added to a solution of β -amino alcohol **57** (2.62 g, 9.38 mmol) in CH_2Cl_2 (47 mL) at 0°C . The mixture was stirred for 16 h at room temperature before the reaction was quenched with aq. sat. NH_4Cl (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by flash chromatography (hexanes/*tert*-butyl methyl ether, 20:1) to obtain the product as a colorless foam which was kept at 50°C under high vacuum overnight to remove any remaining volatile materials (3.43 g, 84%). $[\alpha]_{20}^D = -3.9^\circ$ ($c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): $\delta = 4.58$ -4.54 (m, 2H), 3.78-3.71 (m, 1H), 2.44 (d, $J = 1.6$ Hz, 1H), 2.17-2.12 (m, 2H), 1.96-1.80 (m, 2H), 1.76 (t, $J = 2.5$ Hz, 3H), 1.67-1.50 (m, 4H), 1.42 (s, 9H), 1.16-1.10 (m, 3H), 1.07 ppm (t, $J = 6.0$ Hz, 18H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 155.3, 85.1, 78.8$ (2C), 75.8, 72.9, 61.1, 48.0, 44.4, 34.8, 28.4 (3C), 25.4, 18.6, 18.2 (6C), 12.2 (3C), 3.5 ppm; IR (film): $\tilde{\nu} = 3311, 2943, 2866, 1702, 1502, 1460, 1389, 1365, 1246, 1170, 1095, 1062, 882, 780, 682, 656\text{ cm}^{-1}$; MS (EI): m/z (%): 142(16), 110 (14), 98 (32), 94 (11), 93 (19), 91 (13), 80 (12), 79 (14), 59 (22), 57 (100), 56 (17), 55 (15), 53 (17), 44 (21), 41 (29), 39 (11); HRMS (ESI): m/z : calcd. for $\text{C}_{25}\text{H}_{45}\text{NO}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 458.30609, found 458.30594.

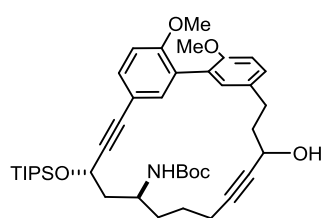
Triyne 59. NEt₃ (degassed, 5.49 mL, 39.4 mmol) was added to a Schlenk tube charged with (PPh₃)₂PdCl₂



(276 mg, 0.394 mmol), CuI (150 mg, 0.787 mmol) and a solution of iodide **50** (3.78 g, 8.66 mmol) and alkyne **57** (3.43 g, 7.87 mmol) in DMF (degassed, 50 mL). The resulting red solution was stirred for 2 h at room temperature before the reaction was quenched with H₂O (250 mL). The mixture was extracted with EtOAc (3 x 350 mL), the combined organic extracts were washed with H₂O (3 x 100 mL) and brine (100 mL) and dried over Na₂SO₄. The solvent was evaporated and the

residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether, 1:1) to afford the product as a yellow foam (4.02 g, 69%). $[\alpha]_{20}^D = -6.7^\circ$ (c = 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 7.39 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 7.16 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.06 (d, *J* = 2.2 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.86 (d, *J* = 7.6 Hz, 1H), 4.80 (t, *J* = 5.5 Hz, 1H), 4.39-4.34 (m, 1H), 3.82-3.76 (m, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 2.75 (t, *J* = 7.8 Hz, 2H), 2.16-2.13 (m, 2H), 2.04-1.88 (m, 4H), 1.85 (d, *J* = 2.1 Hz, 3H), 1.74 (t, *J* = 2.4 Hz, 3H), 1.68-1.51 (m, 4H), 1.40 (s, 9H), 1.23-1.15 (m, 3H), 1.11 ppm (t, *J* = 8.2 Hz, 18H), OH not detected; ¹³C NMR (100 MHz, CDCl₃): δ = 157.1, 155.3 (2C), 134.5, 133.1, 132.1, 131.4, 128.6, 128.0, 126.7, 114.8, 111.1, 110.8, 89.2, 84.8, 81.2, 80.2, 78.9, 78.7, 75.7, 62.0, 61.6, 55.8, 55.7, 48.4, 43.6, 39.7, 34.5, 30.5, 28.3 (3C), 25.4, 18.7, 18.1 (6C), 12.3 (3C), 3.5, 3.4 ppm; IR (film): $\tilde{\nu}$ = 3421, 2942, 2865, 1697, 1499, 1461, 1390, 1365, 1285, 1243, 1168, 1052, 1026, 910, 883, 812, 732, 682, 649, 505 cm⁻¹; MS (EI): *m/z* (%): 644 (32), 643 (80), 642 (100), 627 (10), 626 (29), 534 (14), 533 (19), 519 (11), 518 (10), 453 (10), 452 (22), 381 (15), 279 (24), 277 (11), 266 (14), 154 (14), 131 (15), 110 (14), 103 (15), 93 (16), 75 (11), 59 (15), 57 (14); HRMS (ESI): *m/z*: calcd. for C₄₅H₆₅NO₆SiNa [M+Na]⁺: 766.44734, found 766.44719.

Cyclodiyne 60. A suspension of ligand **11b** (312 mg, 0.353 mmol) and activated molecular sieves (5Å,

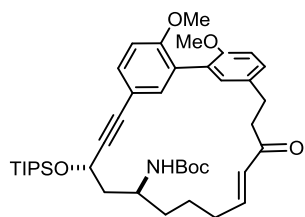


powder, 1.5 g) in toluene (15 mL) was stirred for 30 min before a solution of the molybdenum complex **3** (235 mg, 0.353 mmol) in toluene (15 mL) was added. The suspension was stirred for 30 min before it was added to a suspension of triyne **59** (1.75 g, 2.35 mmol) and activated molecular sieves (5Å, powder, 2.35 g) in toluene (1.18 L) at 120 °C. After stirring for 15 min at this temperature the mixture was allowed to cool to room temperature and

was subsequently filtered through a plug of silica, eluting with EtOAc (1 L). The solvent of the combined filtrates was evaporated and the residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether, 3:2) to yield the title compound as a white solid (1.06 g, 65%). The ¹H and ¹³C NMR spectra show 4 sets of signals, indicating that two diastereomers exist in solution, as two conformers each. $[\alpha]_{20}^D = -30.4^\circ$ (c = 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃):¹⁴ *Mixture of conformers*: δ = 7.31-7.22 (m, 2H), 7.16-6.99 (m, 2H), 6.84-6.79 (m, 2H), 5.08 (d, *J* = 8.9 Hz, 0.3H), 4.80 (dd, *J* = 8.8, 2.5 Hz, 0.3H), 4.66 (dd, *J* = 10.3, 3.2 Hz, 0.7H), 4.47 (d, *J* = 9.1 Hz, 0.7H), 4.02-3.97 (m, 0.7H), 3.86-3.82 (m, 0.3H), 3.75 (s, 3H), 3.73-3.65 (m, 1H), 3.71 (s, 3H), 2.83-2.61 (m, 2H), 2.33-2.23 (m, 1H), 2.17-2.11 (m, 1H), 2.07-1.96 (m, 2H), 1.94-1.83 (m, 2H), 1.75-1.67 (m, 2H), 1.65-1.55 (m, 2H), 1.35-1.33 (m, 9H), 1.19-1.12 (m, 3H), 1.09-1.00 ppm (m, 18H), OH not detected; ¹³C NMR (100 MHz, CDCl₃):¹⁵ *Mixture of conformers*: δ = 157.3, 157.2, 155.5 (2C), 155.4 (2C), 135.6 (2C), 133.3, 132.6, 132.5 (2C), 131.9, 130.7, 128.9 (2C), 128.5, 128.3, 128.2,

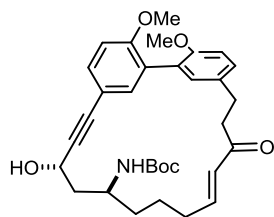
126.7, 115.1, 115.0, 111.4, 111.3, 110.7, 110.6, 89.5, 89.1, 86.3 (2C), 85.0, 84.7, 81.4, 80.4, 79.0 (2C), 63.1, 62.2, 62.0, 61.9, 61.5 (2C), 55.9, 55.8, 55.7 (2C), 48.7, 48.0, 45.0, 41.0, 37.8, 37.3, 34.9, 33.3, 30.6, 30.5, 28.4 (3C), 28.3 (3C), 25.9, 25.1, 18.0 (12C), 12.1 (6C) ppm; IR (film): $\tilde{\nu}$ = 3402, 2942, 2865, 1696, 1603, 1502, 1461, 1391, 1366, 1285, 1265, 1246, 1169, 1130, 1060, 1030, 910, 883, 813, 732, 685, 648 cm^{-1} ; MS (EI): m/z (%): 632 (12), 590 (25), 589 (57), 588 (100), 571 (13), HRMS (ESI): m/z : calcd. for $\text{C}_{41}\text{H}_{59}\text{NO}_6\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 712.40039, found 712.39998.

Enone 61. A solution of $[\text{CpRu}(\text{MeCN})_3]\text{PF}_6$ (1.0 mg, 2.3 μmol) and PCy_3 (0.65 mg, 2.3 μmol) in THF (0.5 mL) was added to a solution of propargylic alcohol **60** (13.0 mg, 18.8 μmol) and NH_4PF_6 (0.38 mg, 2.3 μmol) in THF (0.5 mL) at 80 °C. After stirring for 1 h at this temperature, the mixture was filtered through a plug of silica, rinsing with EtOAc (5 mL). The solvent of the combined filtrates was evaporated and the crude product purified by flash chromatography (hexanes/EtOAc, 3:1) to afford the title compound as a white-yellow solid (9.5 mg, 74%, 1:1 mixture of conformers).



$[\alpha]_{20}^D = -14.4^\circ$ ($c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CDCl_3):¹⁴ *Mixture of conformers*: $\delta = 7.36\text{--}7.32$ (m, 1H), 7.14 (dd, $J = 8.3, 2.1$ Hz, 0.5H), 7.11 (dd, $J = 8.3, 2.1$ Hz, 0.5H), 7.00 (d, $J = 2.1$ Hz, 0.5H), 6.99 (d, $J = 2.1$ Hz, 0.5H), 6.89–6.72 (m, 4H), 6.11 (d, $J = 15.8$ Hz, 0.5H), 6.01 (d, $J = 15.8$ Hz, 0.5H), 5.03 (d, $J = 9.1$ Hz, 0.5H), 4.84 (dd, $J = 9.1, 2.8$ Hz, 0.5H), 4.81–4.77 (m, 1H), 3.80–3.70 (m, 1H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.73 (s, 1.5H), 3.72 (s, 1.5H), 3.09–2.95 (m, 3H), 2.68–2.62 (m, 0.5H), 2.60–2.54 (m, 0.5H), 2.34–2.25 (m, 1H), 2.20–2.06 (m, 2H), 1.91–1.77 (m, 1H), 1.71–1.52 (m, 4H), 1.42 (s, 4.5H), 1.40 (s, 4.5H), 1.24–1.08 ppm (m, 21H); ^{13}C NMR (100 MHz, CDCl_3):¹⁵ *Mixture of conformers*: $\delta = 201.5, 201.2, 157.3, 157.2, 155.5$ (2C), 155.4, 155.3, 147.9, 147.6, 134.6, 134.5, 132.3, 132.2 (2C), 131.6, 131.5, 130.8, 130.2, 130.0, 129.6, 129.3, 128.6, 128.5, 127.1, 126.9, 114.9, 114.8, 111.1, 110.8, 110.6 (2C), 89.5, 89.4, 84.6, 84.5, 79.0, 78.9, 62.1, 62.0, 55.8 (2C), 55.7 (2C), 48.7, 48.1, 43.5, 42.5, 40.0, 39.6, 35.1, 34.9, 32.1 (2C), 30.7, 30.4, 28.4 (3C), 28.3 (3C), 25.5, 25.4, 18.0 (12C), 12.1 (6C) ppm; IR (film): $\tilde{\nu}$ = 3349, 2941, 2865, 1702, 1666, 1623, 1502, 1462, 1390, 1365, 1287, 1265, 1246, 1172, 1132, 1086, 1054, 1036, 883, 813, 733, 684 cm^{-1} ; MS (EI): m/z (%): 633 (10), 632 (14), 591 (12), 590 (39), 589 (89), 588 (100), 574 (12), 573 (18), 572 (42), 571 (14), 547 (11), 546 (22), 502 (19), 416 (19), 295 (11), 279 (28), 277 (39), 252 (13), 251 (43), 174 (14), 115 (11), 87 (11), 75 (14), 73 (12), 59 (18), 57 (31); HRMS (ESI): m/z : calcd. for $\text{C}_{41}\text{H}_{59}\text{NO}_6\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 712.40039, found 712.39987.

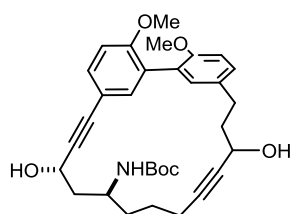
Enone 62. AcOH (3.11 μL , 54.3 μmol) and TBAF (1 M in THF, 54.3 μL , 54.3 μmol) were added to a solution of compound **61** (35.7 mg, 51.7 μmol) in THF (2 mL) at 0 °C. The solution was stirred for 15 h at room temperature. For work up, silica was added and the solvent was evaporated. Purification of the residue by flash chromatography (hexanes/EtOAc, 2:1) yielded the title compound as a white solid (27.9 mg, 99%, 1:1 mixture of conformers).



$[\alpha]_{20}^D = +7.8^\circ$ ($c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CDCl_3):¹⁴ *Mixture of conformers*: $\delta = 7.39\text{--}7.35$ (m, 1H), 7.16 (dd, $J = 8.4, 2.1$ Hz, 0.5H), 7.12 (dd, $J = 8.3, 2.1$ Hz, 0.5H), 7.05 (d, $J = 2.1$ Hz, 0.5H), 7.01 (d, $J = 2.1$ Hz, 0.5H), 6.91–6.71 (m, 4H), 6.16 (d, $J = 15.8$ Hz, 0.5H), 5.99 (d, $J = 15.8$ Hz, 0.5H), 4.70–4.65 (m, 1H), 4.62–4.60 (d, $J = 8.9$ Hz, 0.5H), 4.54 (d, $J = 8.6$ Hz, 0.5H), 3.80–3.71 (m, 1H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.73 (s, 1.5H), 3.72 (s, 1.5H), 3.13–2.94 (m, 3H), 2.69–2.60 (m, 1H), 2.37–2.12 (m, 2H), 2.06–1.95 (m, 1H), 1.84–1.75 (m, 1H), 1.64–

1.52 (m, 4H), 1.41 (s, 4.5H), 1.39 ppm (s, 4.5H), OH not detected; ^{13}C NMR (100 MHz, CDCl_3):¹⁵ *Mixture of conformers*: δ = 201.4, 200.6, 157.6, 157.5, 155.5 (4C), 147.3 (2C), 135.2, 135.0, 132.5, 132.3, 132.2, 131.7, 131.6, 130.6, 130.0, 129.8, 129.7, 129.4, 128.8, 128.7, 127.2, 127.0, 114.3 (2C), 111.2, 110.8, 110.6 (2C), 88.8, 88.7, 85.4 (2C), 79.4, 79.3, 61.2 (2C), 55.8, 55.7 (3C), 48.2, 47.9, 43.4, 43.2, 40.1, 40.0, 35.1, 35.0, 31.9, 31.8, 30.7, 29.6, 28.3 (6C), 25.2, 25.1 ppm; IR (film): $\tilde{\nu}$ = 3367, 3008, 2934, 2860, 1690, 1621, 1503, 1458, 1440, 1392, 1366, 1286, 1266, 1246, 1170, 1132, 1028, 816, 755 cm^{-1} ; MS (EI): m/z (%): 434 (26), 433 (100), 432 (92), 418 (10), 416 (25), 390 (17), 350 (14), 294 (13), 293 (27), 279 (24), 277 (13), 251 (25), 182 (20), 138 (12), 137 (11), 96 (11), 57 (36), 56 (10), 41 (10); HRMS (ESI): m/z : calcd. for $\text{C}_{32}\text{H}_{39}\text{NO}_6\text{Na}$ $[\text{M}+\text{Na}]^+$: 556.26696, found 556.26719.

Macrocycle 63 – Diastereomer A. AcOH (92.3 μL , 1.61 mmol) and TBAF (1 M in THF, 1.61 mL, 1.61 mmol) were added to a solution of compound **61** (1.06 g, 1.53 mmol) in THF (45 mL) at 0 °C. The solution was stirred for 13 h at room temperature. For work up, silica was added and the solvent was evaporated. Purification of the residue by flash chromatography (hexanes/EtOAc, 1:2) yielded the title compound as a white solid (808 mg, 99%).

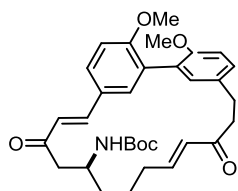


For analytical purposes the diastereomeric mixture was partly separated by flash chromatography (hexanes/EtOAc, 2:3), affording diastereomer A (as a 3:1 mixture of conformers) and diastereomer B; a finite assignment of the stereochemistry has not been made. $[\alpha]_{20}^D = +98.2^\circ$ ($c = 1.00$, CHCl_3); ^1H NMR (600 MHz, CDCl_3): *Mixture of conformers*: δ = 7.38-7.33 (m, 2H), 7.24-7.15 (m, 2H), 6.89-6.86 (m, 2H), 4.75-4.69 (m, 1H), 4.65 (d, $J = 8.9$ Hz, 0.75 Hz), 4.55-4.52 (m, 0.5H), 4.16 (t, $J = 7.4$ Hz, 0.75H), 3.94-3.89 (m, 0.75H), 3.83 (s, 3H), 3.80-3.75 (m, 0.25H), 3.79 (s, 2.25H), 3.77 (s, 0.75H), 3.61 (br s, 0.5H), 3.28 (d, $J = 6.5$ Hz, 0.75H), 3.23 (d, $J = 1.9$ Hz, 0.75H), 2.69-2.74 (m, 2H), 2.41-2.35 (m, 0.75H), 2.33-2.20 (m, 1.25H), 2.06-1.96 (m, 3H), 1.92-1.87 (m, 1H), 1.82-1.51 (m, 6H), 1.33 (s, 6.75H), 1.25 ppm (s, 2.25H); ^{13}C NMR (150 MHz, CDCl_3): *Major conformer*: δ = 157.2, 156.1, 155.3, 136.6, 132.6, 132.3, 130.5, 128.9, 128.2, 126.7, 114.7, 111.2, 110.6, 88.9, 85.3, 85.1, 82.5, 79.8, 60.9, 60.4, 55.8, 55.7, 47.7, 41.9, 37.4, 32.7, 30.2, 28.3 (3C), 24.0, 17.4 ppm; *Minor conformer*: δ = 157.3, 156.4, 155.5, 137.4, 133.7, 132.5, 131.5, 128.9, 128.5, 127.3, 114.5, 111.2, 110.6, 89.6, 85.7, 84.5, 81.5, 80.0, 62.5, 60.2, 55.8, 55.7, 47.5, 43.3, 39.6, 34.4, 30.5, 28.0 (3C), 25.2, 18.5 ppm; IR (film): $\tilde{\nu}$ = 3368, 2935, 2861, 1686, 1602, 1502, 1456, 1440, 1393, 1366, 1265, 1245, 1168, 1130, 1065, 1027, 898, 815, 736 cm^{-1} ; MS (EI): m/z (%): 434 (26), 433 (95), 432 (63), 416 (35), 415 (74), 414 (100), 400 (21), 398 (20), 384 (13), 371 (19), 367 (11), 306 (13), 294 (14), 293 (24), 279 (21), 277 (12), 252 (14), 251 (26), 57 (20); HRMS (ESI): m/z : calcd. for $\text{C}_{32}\text{H}_{39}\text{NO}_6\text{Na}$ $[\text{M}+\text{Na}]^+$: 556.26696, found 556.26718.

Macrocycle 63 – Diastereomer B. This compound was isolated as a 4.5:1 mixture of conformers. $[\alpha]_{20}^D = -87.5^\circ$ ($c = 0.88$, CHCl_3); ^1H NMR (600 MHz, CDCl_3): *Major conformer*: δ = 7.39 (dd, $J = 8.4$, 1.9 Hz, 1H), 7.30 (d, $J = 1.9$ Hz, 1H), 7.18 (dd, $J = 8.5$, 2.0 Hz, 1H), 7.07 (d, $J = 2.0$ Hz, 1H), 6.88 (d, $J = 7.7$ Hz, 1H), 6.87 (d, $J = 7.7$ Hz, 1H), 4.67 (dd, $J = 10.1$, 2.6 Hz, 1H), 4.54 (d, $J = 8.9$ Hz, 1H), 4.07 (t, $J = 7.4$ Hz, 1H), 3.81 (s, 3H), 3.79-3.74 (m, 1H), 3.77 (s, 3H), 2.87-2.80 (m, 1H), 2.79-2.71 (m, 1H), 2.34-2.23 (m, 2H), 2.14-2.06 (m, 2H), 2.03-1.92 (m, 4H), 1.83-1.79 (m, 1H), 1.73-1.56 (m, 3H), 1.24 ppm (s, 9H); ^{13}C NMR (150 MHz, CDCl_3): *Major conformer*: δ = 157.4, 155.9, 155.4, 136.4, 132.4, 132.0, 131.8, 128.5 (2C), 126.8, 114.4, 111.3, 110.5, 89.1, 86.0, 85.0, 80.9, 79.6, 61.1, 60.7, 55.9, 55.7, 47.6, 44.0, 38.0, 34.5, 30.2, 28.1 (3C), 25.3, 18.4

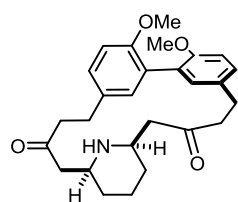
ppm; IR (film): $\tilde{\nu}$ = 3350, 2930, 2859, 1686, 1603, 1502, 1456, 1440, 1392, 1366, 1265, 1245, 1168, 1130, 1067, 1027, 896, 815, 735 cm^{-1} ; MS (pos. ESI): m/z (%): 1089.5 (38), 556.3 (100); HRMS (ESI): m/z : calcd. for $\text{C}_{32}\text{H}_{39}\text{NO}_6\text{Na}$ $[\text{M}+\text{Na}]^+$: 556.26696, found 556.26748.

Dienone 64. *Single redox isomerization:* A solution of $[\text{CpRu}(\text{MeCN})_3]\text{PF}_6$ (10.5 mg, 24.3 μmol) and phosphine **S24** (7.34 mg, 24.3 μmol) in THF (1 mL) was added to a solution of propargylic alcohol **62** (86.4 mg, 0.162 mmol) and NH_4PF_6 (3.99 mg, 24.3 μmol) in THF (2.2 mL) at 80 $^\circ\text{C}$. After stirring for 1 h at this temperature, silica was added and the solvent was evaporated. The crude material was purified by flash chromatography (hexanes/EtOAc, 1:1) to afford the title compound as a pale yellow foam (43.9 mg, 51%, 55% brsm, 2:1 mixture of conformers).



Double redox isomerization: A solution of compound **63** (460 mg, 0.862 mmol) and NH_4PF_6 (56.2 mg, 0.345 mmol) in THF (2.6 mL) were added within 1 h to a solution of $[\text{CpRu}(\text{MeCN})_3]\text{PF}_6$ (74.9 mg, 0.172 mmol) and phosphine **S24** (52.1 mg, 0.172 mmol) in THF (3 mL) at 80 $^\circ\text{C}$. After stirring for 9 h at this temperature, silica was added and the solvent was evaporated. The crude material was purified by flash chromatography (hexanes/*tert*-butyl methyl ether, 2:3, Merck silica gel 60 (15-40 μm)) to afford the title compound as a white-brown foam (218 mg, 47%, 2:1 mixture of conformers). $[\alpha]_{20}^D = +5.9^\circ$ ($c = 1.00$, CHCl_3); ^1H NMR (600 MHz, $\text{C}_6\text{D}_5\text{CD}_3$):¹⁶ *Major conformer:* $\delta = 7.45$ (d, $J = 15.8$ Hz, 1H), 7.13 (d, $J = 2.1$ Hz, 1H), 7.03 (m, 1H), 7.02 (m, 1H), 6.83 (d, $J = 2.1$ Hz, 1H), 6.59 (m, 1H), 6.59 (d, $J = 8.5$ Hz, 1H), 6.43 (d, $J = 8.5$ Hz, 1H), 6.32 (d, $J = 15.8$ Hz, 1H), 5.82 (dt, $J = 15.8, 1.4$ Hz, 1H), 5.63 (d, $J = 8.7$ Hz, 1H), 3.93-3.90 (m, 1H), 3.39 (s, 3H), 3.30 (s, 3H), 3.06 (ddd, $J = 15.2, 10.0, 3.7$ Hz, 1H), 2.88 (m, 1H), 2.69 (ddd, $J = 16.3, 10.0, 3.6$ Hz, 1H), 2.56 (dd, $J = 13.5, 4.8$ Hz, 1H), 2.35 (ddd, $J = 16.3, 7.3, 3.7$ Hz, 1H), 2.22 (dd, $J = 13.5, 4.3$ Hz, 1H), 1.82-1.77 (m, 1H), 1.58-1.53 (m, 1H), 1.47 (s, 9H), 1.43 (m, 1H), 1.14 (m, 1H), 1.09 (m, 1H), 1.04 ppm (m, 1H); *Minor conformer:* $\delta = 7.41$ (d, $J = 16.1$ Hz, 1H), 7.21 (br s, 1H), 7.07 (m, 2H), 6.96 (m, 1H), 6.60 (m, 1H), 6.58 (d, $J = 8.3$ Hz, 1H), 6.49 (d, $J = 16.1$ Hz, 1H), 6.47 (d, $J = 8.5$ Hz, 1H), 5.88 (dt, $J = 15.8, 1.5$ Hz, 1H), 4.27 (d, $J = 8.4$ Hz, 1H), 4.01-3.97 (m, 1H), 3.37 (s, 3H), 3.34 (s, 3H), 3.11 (m, 1H), 2.85 (m, 1H), 2.84 (m, 1H), 2.52-2.48 (m, 2H), 2.11 (m, 1H), 1.91-1.86 (m, 1H), 1.74-1.68 (m, 1H), 1.39 (s, 9H), 1.23 (m, 1H), 1.12 ppm (m, 3H); ^{13}C NMR (150 MHz, $\text{C}_6\text{D}_5\text{CD}_3$): *Major conformer:* $\delta = 199.3, 197.6, 160.1, 156.1, 155.3, 146.3, 143.4, 133.2, 131.2, 130.6$ (2C), 130.3, 129.9, 129.7, 128.1, 127.3, 125.2, 111.1, 110.9, 78.6, 55.2 (2C), 49.3, 42.5, 39.4, 34.7, 32.3, 28.6, 28.5 (3C), 25.7 ppm; *Minor conformer:* $\delta = 198.0, 196.9, 159.9, 156.1, 155.1, 146.0, 142.7, 133.2, 132.2, 131.0, 130.4, 130.2, 129.8, 129.7, 128.3, 127.4, 124.2, 111.1, 111.0, 78.8, 55.2$ (2C), 48.8, 46.2, 39.5, 35.2, 32.1, 28.9, 28.4 (3C), 24.4 ppm; IR (film): $\tilde{\nu}$ = 3359, 2930, 2859, 1697, 1624, 1591, 1501, 1461, 1440, 1365, 1270, 1249, 1169, 1131, 1086, 1029, 981, 910, 811, 731 cm^{-1} ; MS (EI): m/z (%): 534 (17), 533 (47), 479 (12), 478 (25), 477 (73), 476 (30), 461 (11), 460 (28), 459 (36), 434 (30), 433 (80), 432 (53), 418 (14), 417 (23), 416 (65), 415 (14), 405 (24), 391 (12), 390 (38), 388 (14), 374 (11), 321 (10), 309 (17), 308 (21), 307 (14), 297 (14), 296 (11), 295 (34), 294 (25), 293 (54), 281 (18), 280 (25), 279 (94), 278 (33), 277 (67), 276 (19), 275 (10), 267 (20), 266 (18), 265 (21), 263 (17), 262 (25), 261 (20), 255 (10), 254 (17), 253 (59), 251 (21), 249 (11), 240 (11), 239 (10), 237 (14), 235 (12), 233 (11), 201 (10), 199 (14), 183 (22), 152 (15), 149 (14), 138 (23), 124 (25), 111 (17), 110 (19), 109 (10), 98 (13), 97 (26), 96 (53), 95 (15), 85 (11), 83 (13), 82 (13), 81 (17), 71 (15), 70 (15), 69 (11), 59 (23), 57 (100), 56 (24); HRMS (ESI): m/z : calcd. for $\text{C}_{32}\text{H}_{39}\text{NO}_6\text{Na}$ $[\text{M}+\text{Na}]^+$: 556.26696, found 556.26728.

Piperidine 65. TFA (0.286 mL, 3.74 mmol) was added to a solution of dienone **64** (50.0 mg, 93.7 μ mol) in CH_2Cl_2 (1.67 mL) at 0 °C and the solution was stirred for 1.5 h at this temperature.



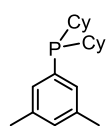
After removal of the solvent at 0 °C and coevaporation with Et_2O (5 mL), the resulting yellow foam was dried in vacuum for 30 min. Next, the residue was dissolved in CH_2Cl_2 (2 mL) and a solution of DBU (21.0 μ L, 0.14 mmol) in CH_2Cl_2 (2 mL) was added at –78 °C. The reaction was stirred for 2 h at this temperature and quenched with phosphate buffer (pH=7, 0.1 M aq. solution, 5 mL). The aqueous

layer was extracted with EtOAc (3 x 5 mL), the combined extracts were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash chromatography (hexanes/ EtOAc , 2:5 + 1 vol.% NEt_3) to yield the title compound as a white solid (29.7 mg, 73%, 1.1:1 mixture of conformers) and separately **9-epi-65**. $[\alpha]_{20}^D = -51.4^\circ$ ($c = 0.34$, CHCl_3); ^1H NMR (600 MHz, C_6D_6):¹⁶ *Major conformer*: $\delta = 7.66$ (d, $J = 15.6$ Hz, 1H), 7.60 (m, 1H), 7.44 (d, $J = 15.6$ Hz, 1H), 7.22 (d, $J = 2.3$ Hz, 1H), 7.05 (m, 1H), 6.90 (dd, $J = 8.4$, 2.3 Hz, 1H), 6.62 (d, $J = 8.4$ Hz, 1H), 6.50 (d, $J = 8.4$ Hz, 1H), 3.45 (s, 3H), 3.41 (s, 3H), 3.03 (ddd, $J = 13.8$, 10.8, 2.5 Hz, 1H), 2.85 (m, 1H), 2.66 (m, 1H), 2.40 (ddd, $J = 14.0$, 7.4, 2.1 Hz, 1H), 2.29 (dd, $J = 13.7$, 2.1 Hz, 1H), 2.26-2.21 (m, 2H), 2.19 (m, 1H), 2.02 (dd, $J = 18.7$, 4.5 Hz, 1H), 1.96 (dd, $J = 18.7$, 6.7 Hz, 1H), 1.49 (m, 1H), 1.29 (m, 1H), 1.21 (m, 1H), 1.15 (m, 1H), 0.83 (m, 1H), 0.68-0.61 ppm (m, 1H), NH not detected; *Minor conformer*: $\delta = 7.59$ (m, 1H), 7.58 (d, $J = 15.6$ Hz, 1H), 7.18 (d, $J = 15.6$ Hz, 1H), 7.06 (m, 1H), 6.97 (dd, $J = 8.4$, 2.3 Hz, 1H), 6.93 (d, $J = 2.3$ Hz, 1H), 6.64 (d, $J = 8.4$ Hz, 1H), 6.52 (d, $J = 8.4$ Hz, 1H), 3.44 (s, 6H), 2.91-2.87 (m, 1H), 2.62 (m, 2H), 2.60 (m, 1H), 2.47 (ddd, $J = 17.1$, 9.5, 2.7 Hz, 1H), 2.37 (dd, $J = 14.9$, 3.0 Hz, 1H), 2.17 (m, 1H), 2.16 (m, 1H), 2.14-2.11 (m, 1H), 2.09-2.06 (m, 1H), 1.53 (m, 1H), 1.34 (m, 1H), 1.29 (m, 1H), 1.15 (m, 1H), 1.00-0.93 (m, 1H), 0.74-0.68 ppm (m, 1H), NH not detected; ^{13}C NMR (150 MHz, C_6D_6): *Major conformer*: $\delta = 209.1$, 198.9, 159.4, 156.2, 139.9, 134.3, 133.0, 131.6, 130.9, 129.9, 128.9, 128.8, 128.5, 125.7, 111.4, 110.9, 55.6, 55.5, 55.2, 52.3, 52.1, 52.0, 44.5, 33.8, 32.7, 29.6, 25.0 ppm; *Minor conformer*: $\delta = 209.0$, 198.9, 159.4, 156.0, 138.4, 132.6, 131.8, 131.3, 130.5, 130.1, 129.3, 128.5, 128.3, 125.5, 111.8, 111.0, 55.7, 55.6, 54.6, 52.8, 51.0, 49.9, 42.6, 32.6, 32.3, 28.0, 24.9 ppm; IR (film): $\tilde{\nu} = 2926$, 2849, 1709, 1677, 1592, 1501, 1461, 1439, 1336, 1269, 1249, 1166, 1131, 1030, 812, 734 cm^{-1} ; MS (pos. ESI): m/z (%): 434 (30), 433 (100), 432 (10), 405 (20), 375 (20), 374 (68), 279 (12), 111 (17), 110 (15), 96 (33), 82 (28); HRMS (ESI): m/z : calcd. for $\text{C}_{27}\text{H}_{31}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 456.21453, found 456.21493.

Piperidine 9-epi-65. This compound was isolated from the previous reaction as a white solid (3.2 mg, 8%, 2:1 mixture of conformers). $[\alpha]_{20}^D = +8.9^\circ$ ($c = 0.62$, CHCl_3); ^1H NMR (600 MHz, CDCl_3):¹⁶ *Major conformer*: $\delta = 7.57$ (d, $J = 15.7$ Hz, 1H), 7.51 (d, $J = 2.3$ Hz, 1H), 7.37 (dd, $J = 8.5$, 2.3 Hz, 1H), 7.21 (m, 1H), 6.97 (d, $J = 15.7$ Hz, 1H), 6.92 (d, $J = 8.5$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 6.75 (d, $J = 2.1$ Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.65 (tt, $J = 9.5$, 2.7 Hz, 1H), 3.43 (ddt, $J = 12.0$, 4.0, 3.0 Hz, 1H), 3.28 (m, 2H), 3.18 (ddd, $J = 17.0$, 12.4, 2.9 Hz, 1H), 2.89-2.85 (m, 1H), 2.78 (dd, $J = 19.1$, 10.0 Hz, 1H), 2.61 (m, 1H), 2.53 (ddd, $J = 17.0$, 4.7, 3.1 Hz, 1H), 2.11 (dd, $J = 12.4$, 2.7 Hz, 1H), 1.92-1.89 (m, 1H), 1.71 (m, 1H), 1.65 (m, 2H), 1.47 (m, 1H), 1.03 ppm (m, 1H), NH not detected; *Minor conformer*: $\delta = 7.61$ (d, $J = 15.4$ Hz, 1H), 7.40 (d, $J = 2.2$ Hz, 1H), 7.33 (dd, $J = 8.4$, 2.2 Hz, 1H), 7.21 (m, 1H), 7.09 (dd, $J = 8.4$, 2.2 Hz, 1H), 6.98 (d, $J = 15.4$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 6.85 (m, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.72 (m, 1H), 3.40 (m, 1H), 3.33 (m, 1H), 3.27 (m, 1H), 2.69 (m, 1H), 2.66 (m, 1H), 2.61 (m, 2H), 2.41 (dd, $J = 18.5$, 4.4 Hz, 1H), 2.17 (dd, $J =$

13.2, 2.2 Hz, 1H), 1.74 (m, 1H), 1.65 (m, 1H), 1.63 (m, 2H), 1.47 (m, 1H), 1.08 ppm (m, 1H), NH not detected; ^{13}C NMR (150 MHz, CDCl_3): *Major conformer*: δ = 207.3, 200.9, 159.4, 155.3, 140.5, 132.6, 131.8, 129.9, 129.8, 129.4, 128.7, 127.2, 127.1, 123.2, 111.9, 110.9, 55.9, 55.8, 52.3, 51.1, 46.0, 45.1, 39.8, 32.1, 31.9, 26.7, 19.8 ppm; *Minor conformer*: δ = 209.4, 200.5, 159.2, 155.6, 140.7, 134.6, 132.1, 131.2, 130.6, 129.1, 128.9, 128.0 (2C), 125.0, 111.3, 110.8, 55.8 (2C), 52.1, 51.0, 46.6, 45.1, 44.9, 32.7, 32.5, 29.3, 19.7 ppm; IR (film): $\tilde{\nu}$ = 2927, 2854, 1712, 1676, 1591, 1501, 1461, 1439, 1336, 1270, 1132, 1029, 812, 753 cm^{-1} ; MS (pos. ESI): m/z (%): 434 (31), 433 (100), 432 (11), 405 (22), 377 (12), 375 (21), 374 (72), 279 (17), 253 (10), 251 (10), 152 (11), 138 (18), 111 (31), 110 (28), 97 (25), 96 (75), 95 (12), 94 (14), 84 (12), 83 (18), 82 (80), 81 (13), 80 (10); HRMS (ESI): m/z : calcd. for $\text{C}_{27}\text{H}_{32}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 434.23258, found 434.23280.

Phosphine S24.¹⁷ A Schlenk tube was charged with $\text{Pd}(\text{OAc})_2$ (113 mg, 0.504 mmol), di-*iso*-propylphosphinoferrocene (253 mg, 0.605 mmol) and NaOtBu (2.91 g, 30.3 mmol) and the vessel was evacuated and backfilled with Argon three times. Toluene (25 mL) was added and the mixture was stirred for 30 min at room temperature before 1-bromo-3,5-dimethylbenzene (4.67 g, 25.2 mmol) and dicyclohexylphosphine (5.10 mL, 25.2 mmol) were added. The solution was stirred for 15 h at 80 °C and was subsequently filtered through a plug of Celite, eluting with Et_2O (50 mL). The solvent of the combined filtrates was evaporated and the residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether, 20:1) to afford a mixture of the title compound and the corresponding phosphine oxide. This mixture was dissolved in toluene (50 mL). NEt_3 (17.2 mL, 123 mmol) followed by Cl_3SiH (3.79 mL, 37.6 mmol) were added and stirring continued for 15 h at 110 °C. The black solution was allowed to reach room temperature before Et_2O (degassed, 200 mL) and NaOH (degassed, 2 N, 200 mL) were added. The aqueous layer was extracted with Et_2O (3 x 200 mL), the combined extracts were washed with aq. sat. NaHCO_3 (degassed, 200 mL), H_2O (degassed, 200 mL) and brine (degassed, 200 mL). After drying (MgSO_4), the solvent was removed to afford the product as a white solid (4.72 g, 62%). ^1H NMR (400 MHz, CDCl_3): δ = 7.06 (s, 1H), 7.05 (s, 1H), 6.97 (s, 1H), 2.32 (s, 6H), 1.91-1.75 (m, 6H), 1.69-1.57 (m, 6H), 1.37-0.98 ppm (m, 10H); ^{13}C NMR (100 MHz, CDCl_3): δ = 137.0 (d, J = 7.4 Hz, 2C), 134.1 (d, J = 16.4 Hz), 132.4 (d, J = 19.2 Hz, 2C), 130.5, 32.5 (d, J = 12.1 Hz, 2C), 30.0 (d, J = 16.1 Hz, 2C), 28.9 (d, J = 7.5 Hz, 2C), 27.2 (d, J = 12.4 Hz, 2C), 27.0 (d, J = 7.3 Hz, 2C), 26.4 (2C), 21.4 ppm (2C); ^{31}P NMR (162 MHz, CDCl_3): δ = 3.0 ppm; IR (film): $\tilde{\nu}$ = 2922, 2849, 1447, 848, 694 cm^{-1} ; MS (EI): m/z (%): 302 (39), 247 (14), 221 (19), 220 (100), 139 (14), 138 (46), 137 (17); HRMS (EI): m/z : calcd. for $\text{C}_{20}\text{H}_{31}\text{P}$ $[\text{M}]^+$: 302.21634, found 302.21648.



Crystallographic Information

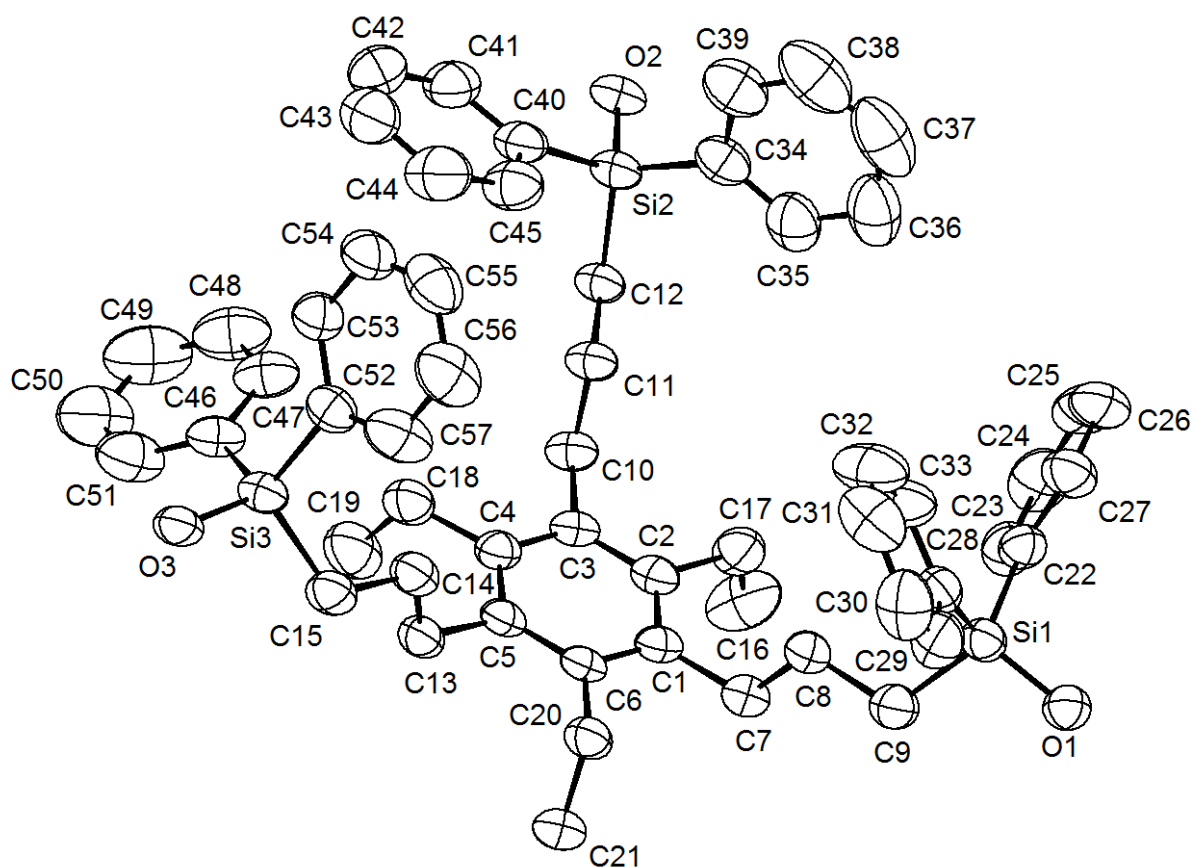


Figure S-1. Structure of compound **11b** in the solid state (CCDC deposition number 1469817)

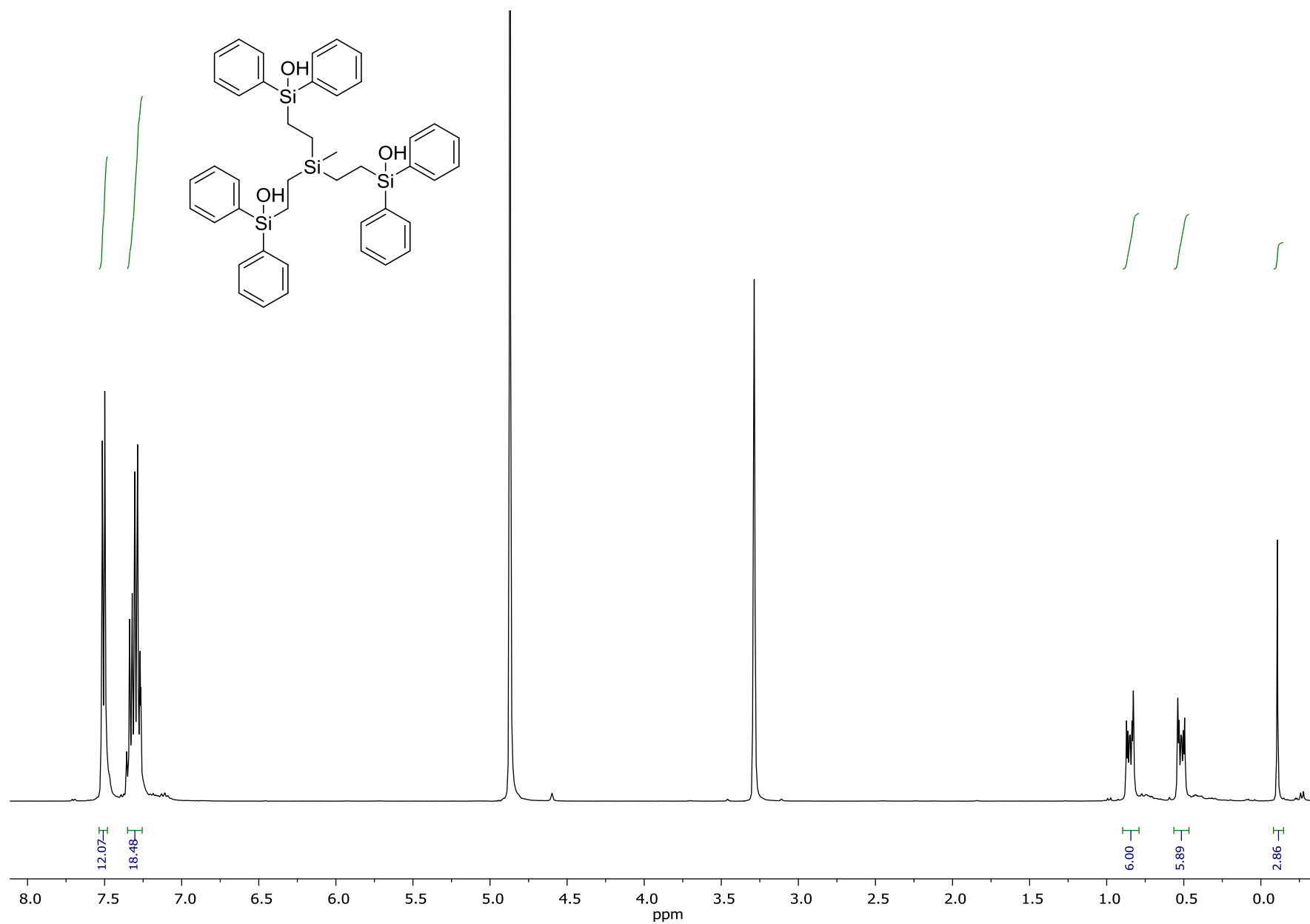
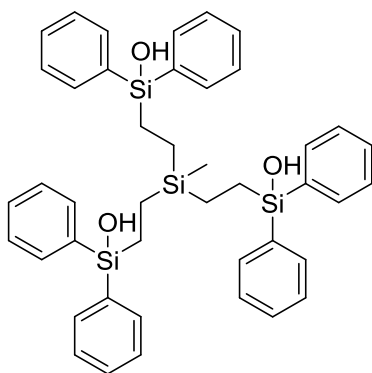
Table S-3. Crystal data and structure refinement.

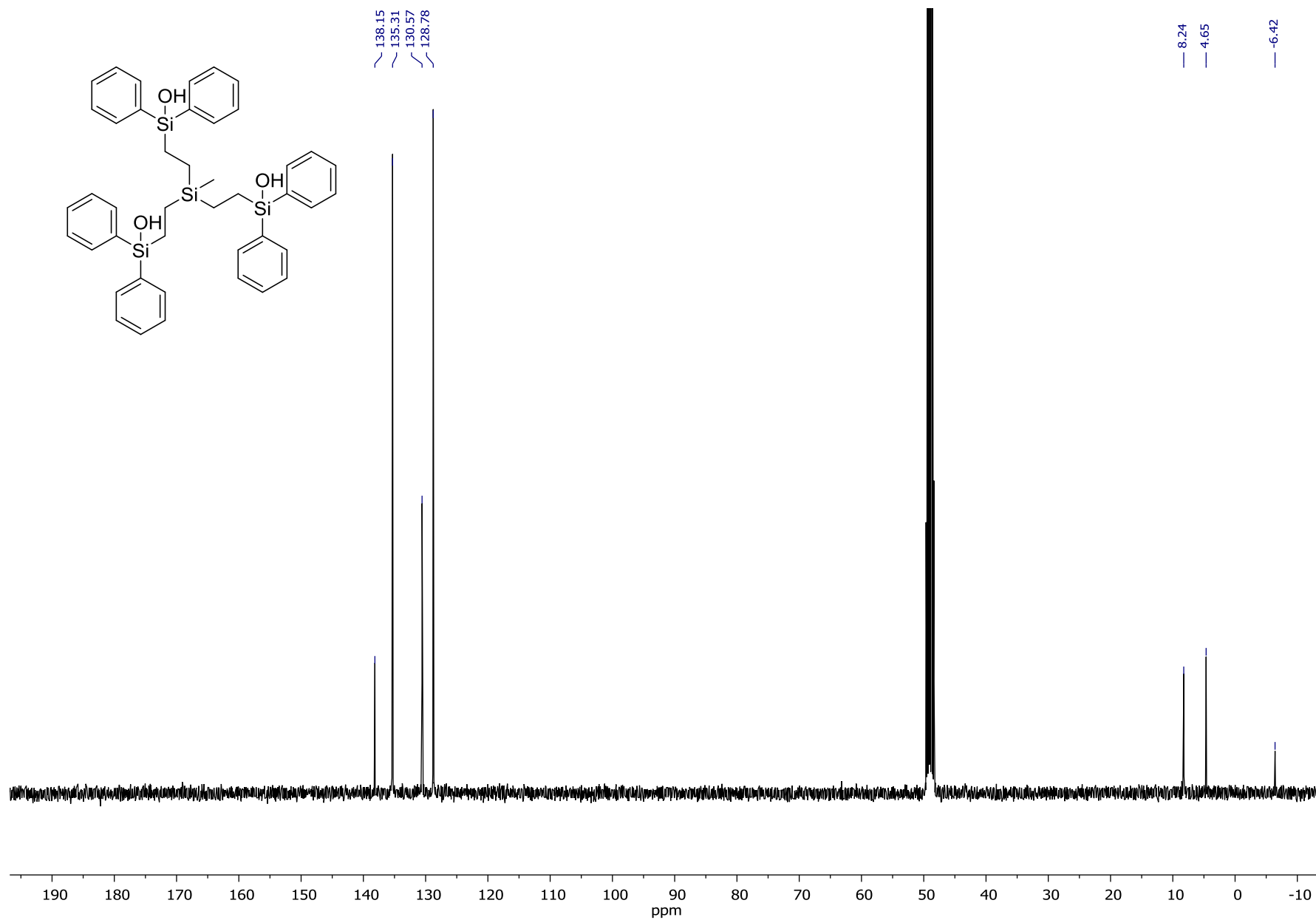
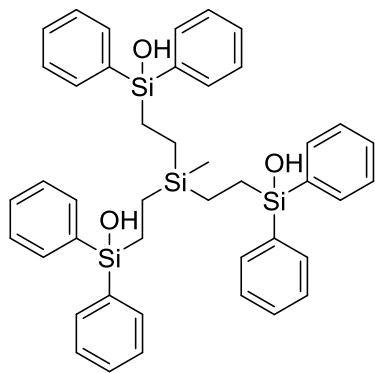
Empirical formula	$C_{57}H_{66}O_3Si_3$	
Color	colourless	
Formula weight	883.36 g·mol ⁻¹	
Temperature	180 K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	$P 2_1/n$, (no. 14)	
Unit cell dimensions	$a = 15.175(4)$ Å	$\alpha = 90^\circ$.
	$b = 19.071(5)$ Å	$\beta = 95.910(5)^\circ$.
	$c = 22.799(6)$ Å	$\gamma = 90^\circ$.

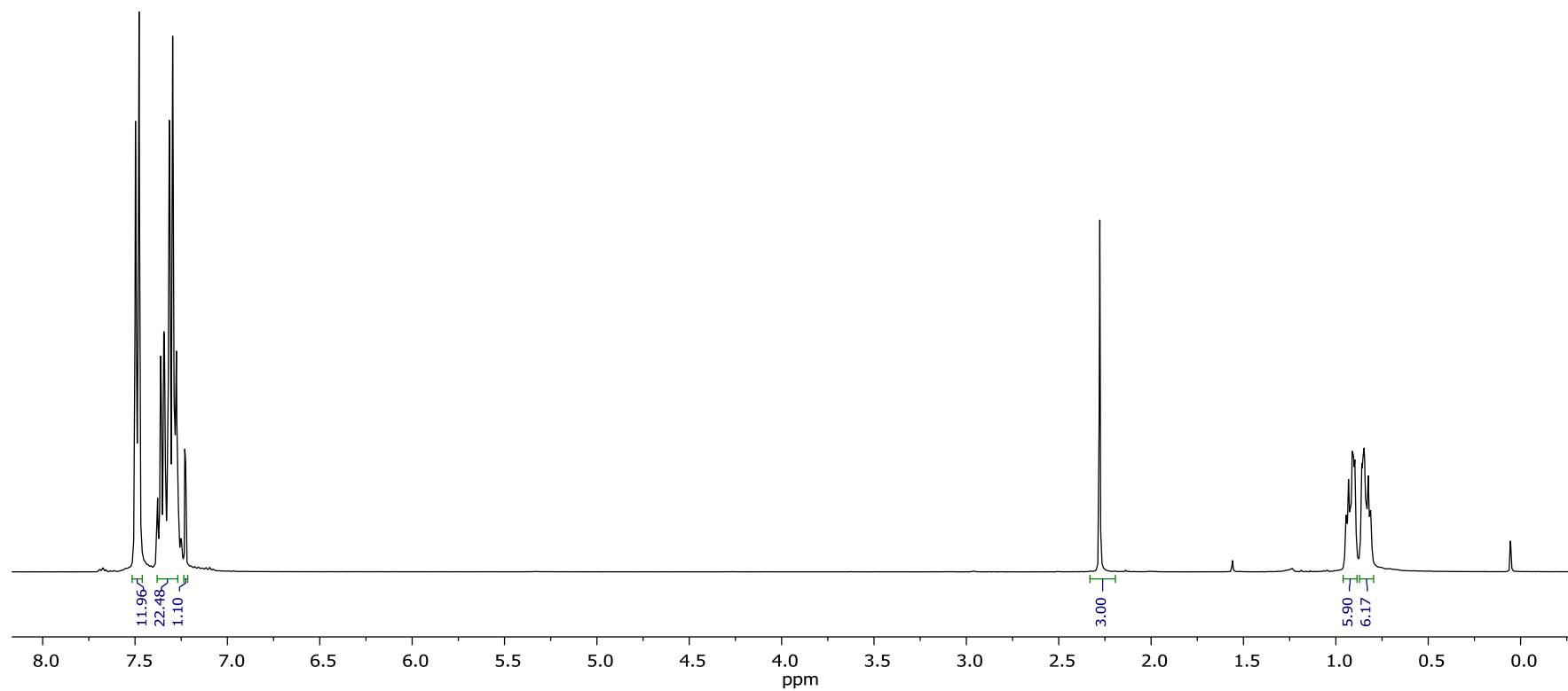
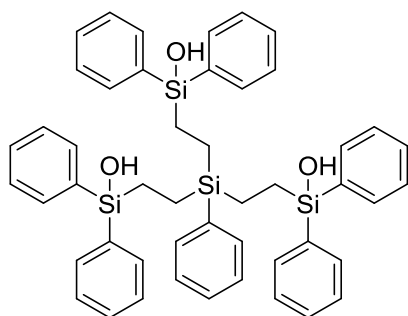
Volume	6563(3) Å ³	
Z	4	
Density (calculated)	0.894 Mg·m ⁻³	
Absorption coefficient	0.105 mm ⁻¹	
F(000)	1896 e	
Crystal size	0.187 x 0.110 x 0.067 mm ³	
θ range for data collection	2.728 to 26.372°.	
Index ranges	-18 ≤ h ≤ 18, -23 ≤ k ≤ 23, -28 ≤ l ≤ 28	
Reflections collected	133780	
Independent reflections	13393 [R _{int} = 0.1537]	
Reflections with I > 2σ(I)	6269	
Completeness to θ = 25.242°	99.9 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.98508 and 0.96520	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	13393 / 0 / 574	
Goodness-of-fit on F ²	0.999	
Final R indices [I > 2σ(I)]	R ₁ = 0.0599	wR ² = 0.1462
R indices (all data)	R ₁ = 0.1475	wR ² = 0.1947
Extinction coefficient	0	
Largest diff. peak and hole	0.344 and -0.270 e·Å ⁻³	
PLATON squeeze void / electrons	2049 Å ³ / 639 e (probe rad. 1.2 Å, ca. grid 0.3 Å)	

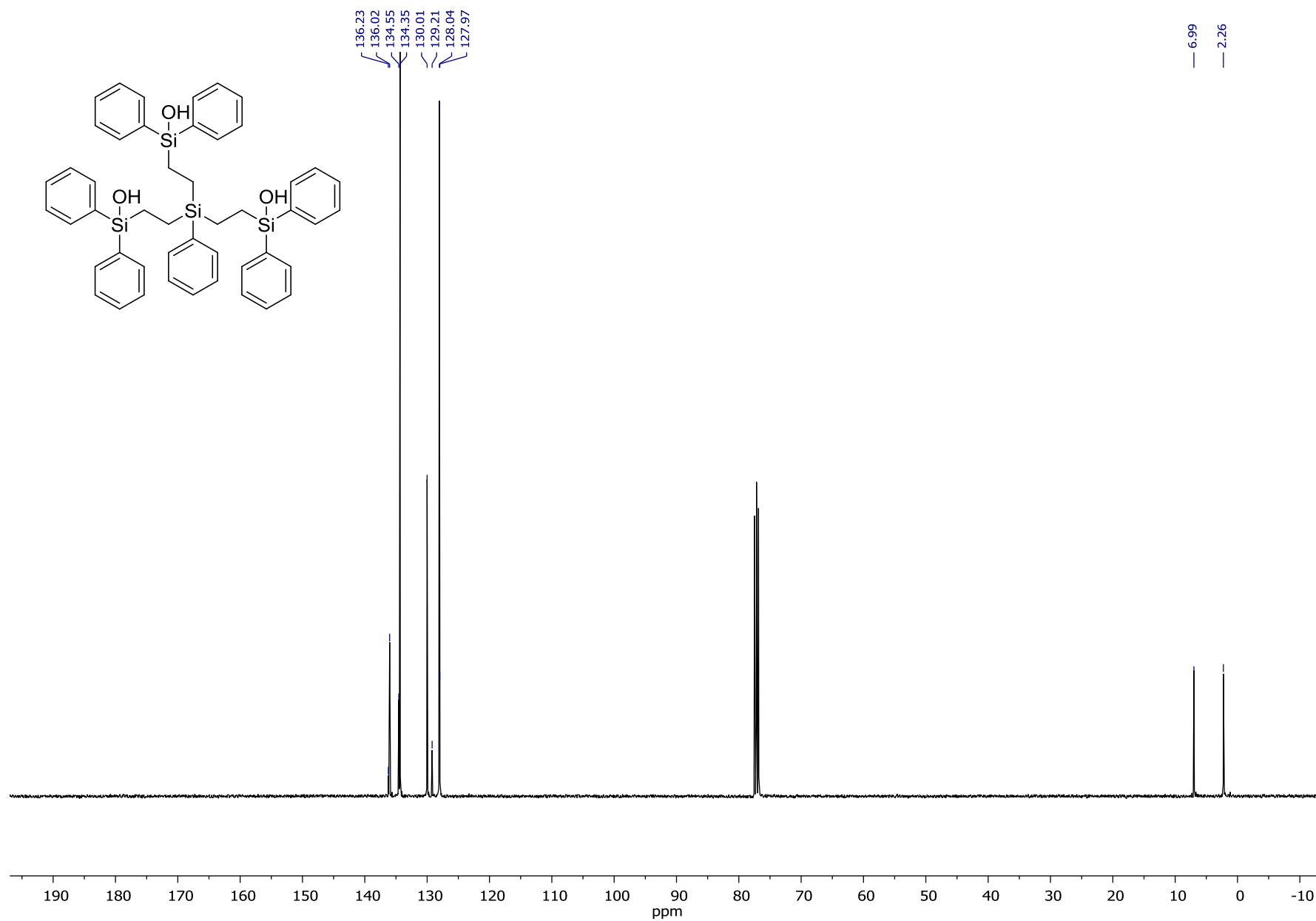
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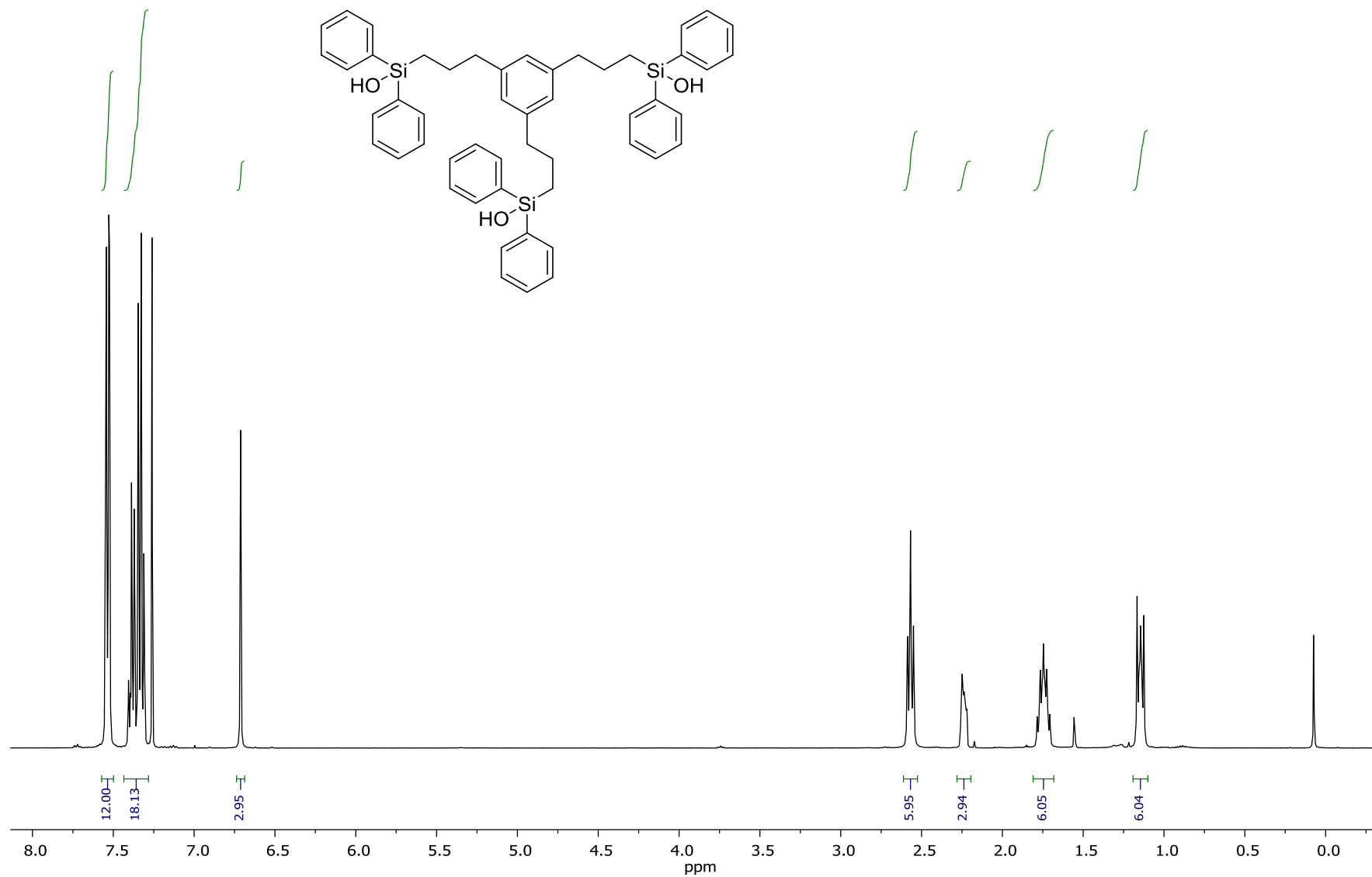
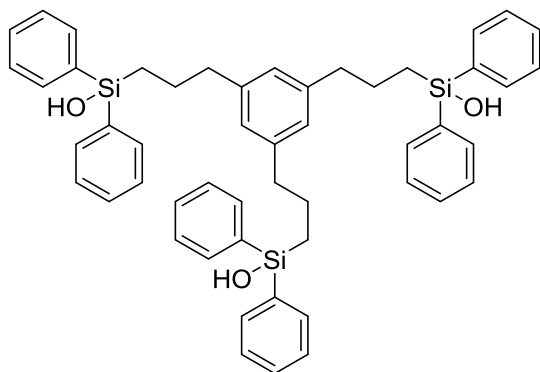
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- ¹⁵ All visible signals are listed.
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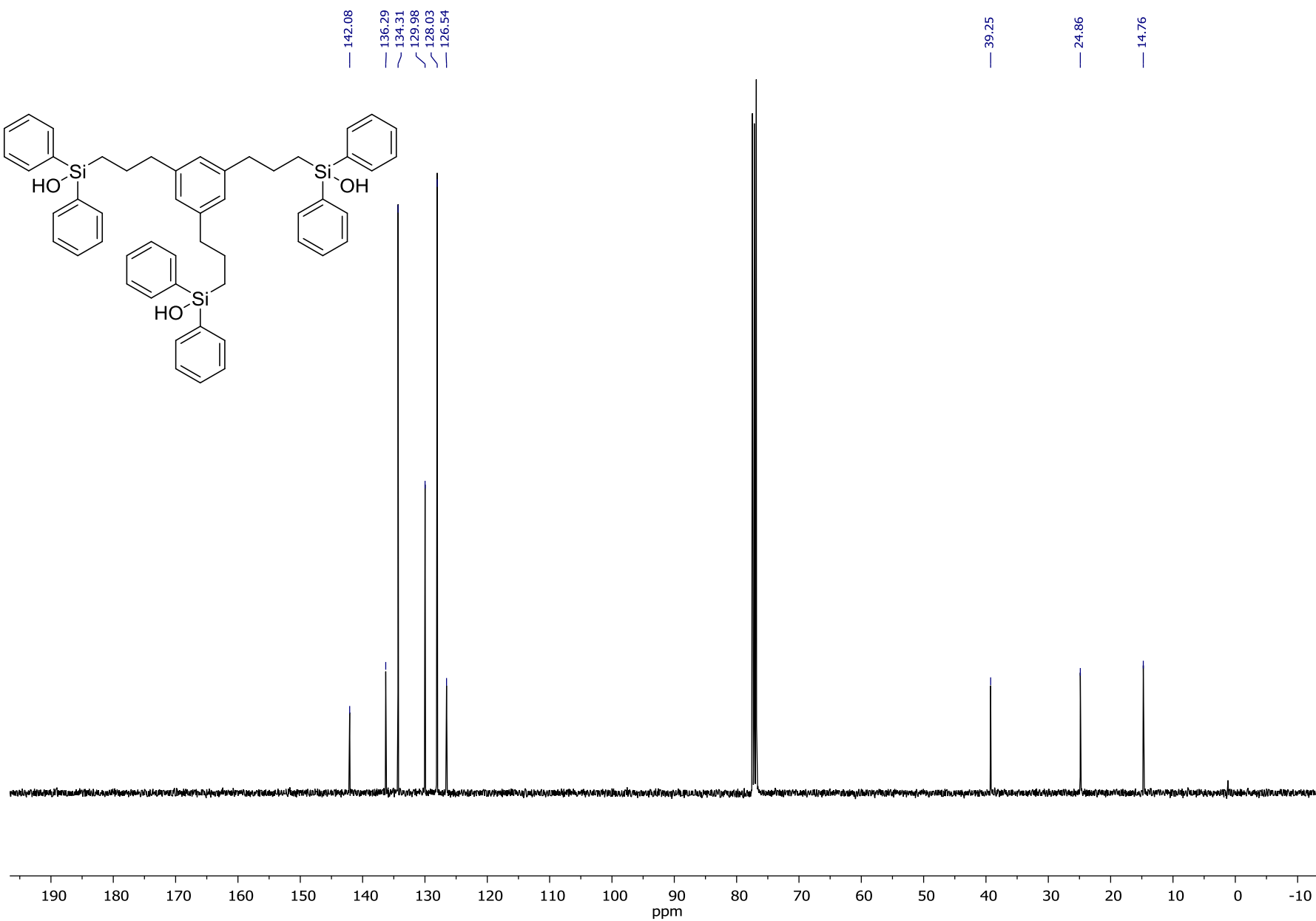
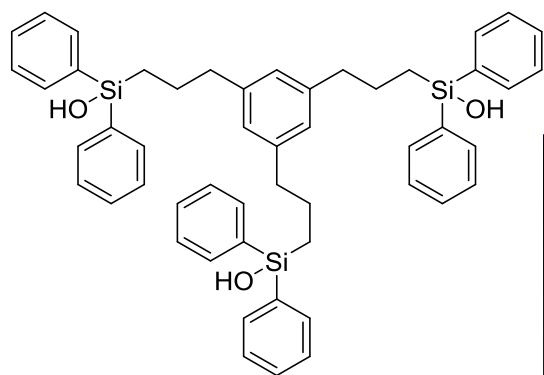


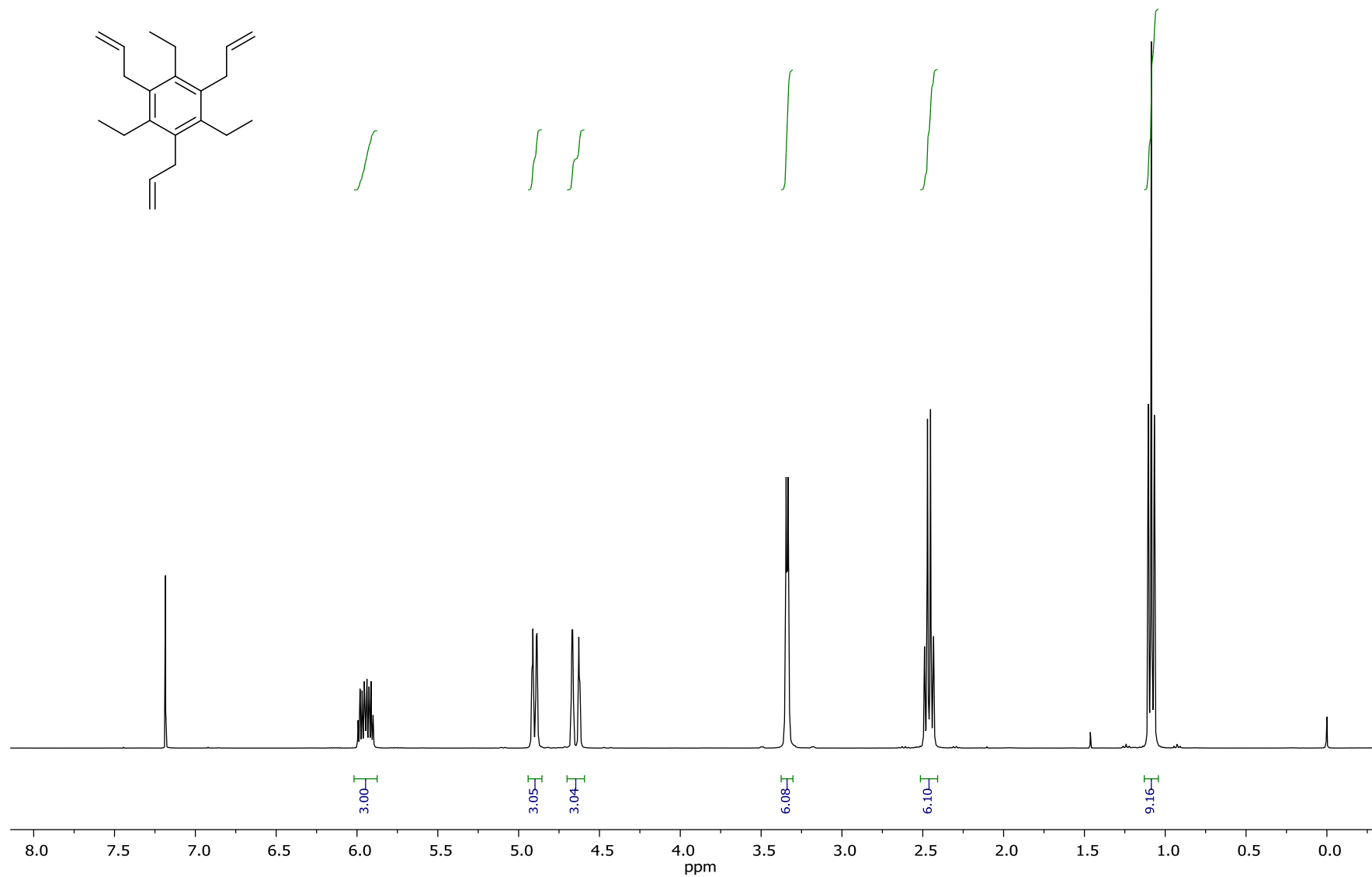
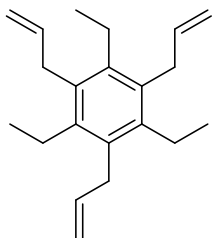


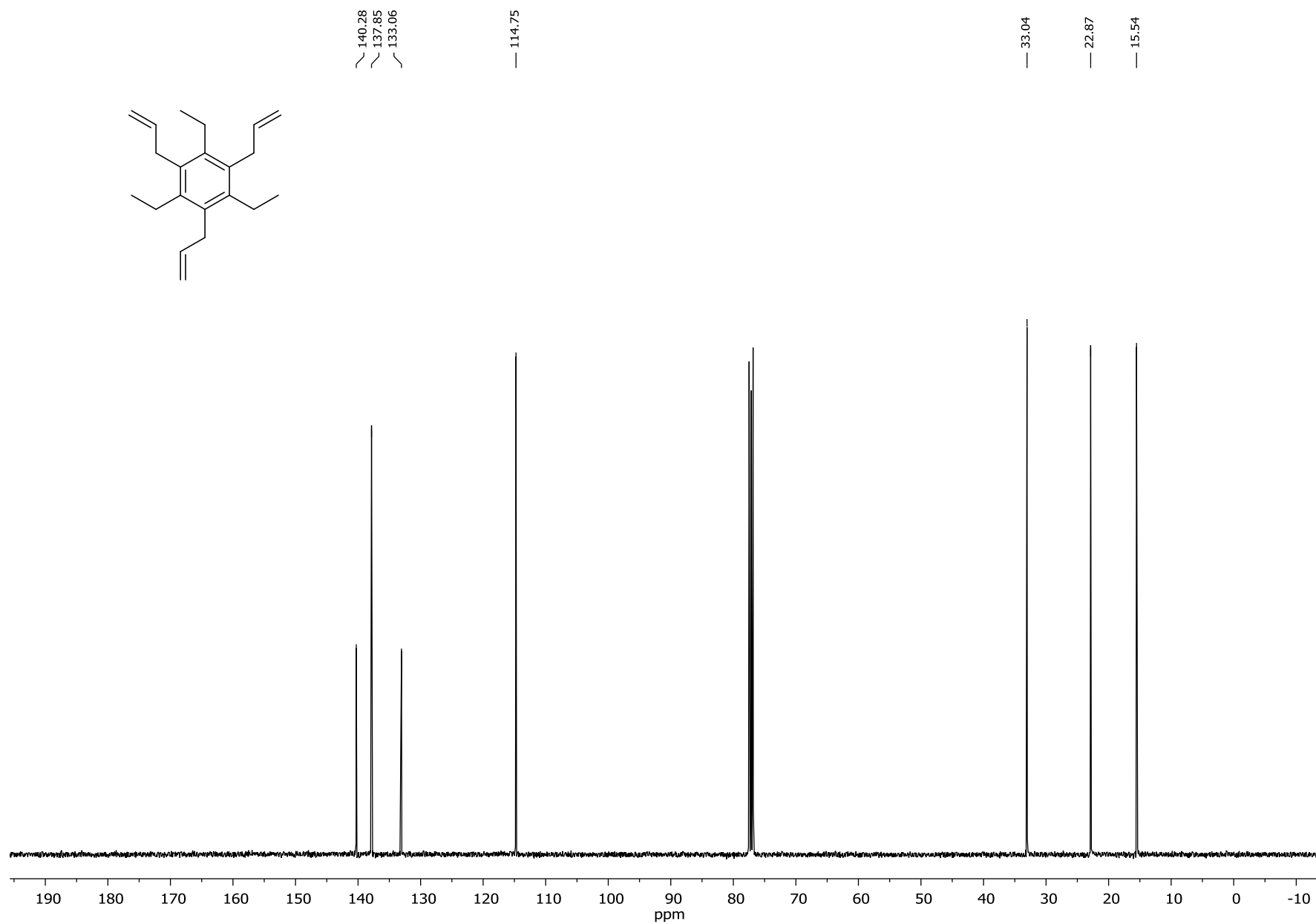
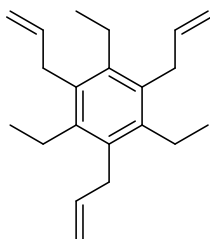


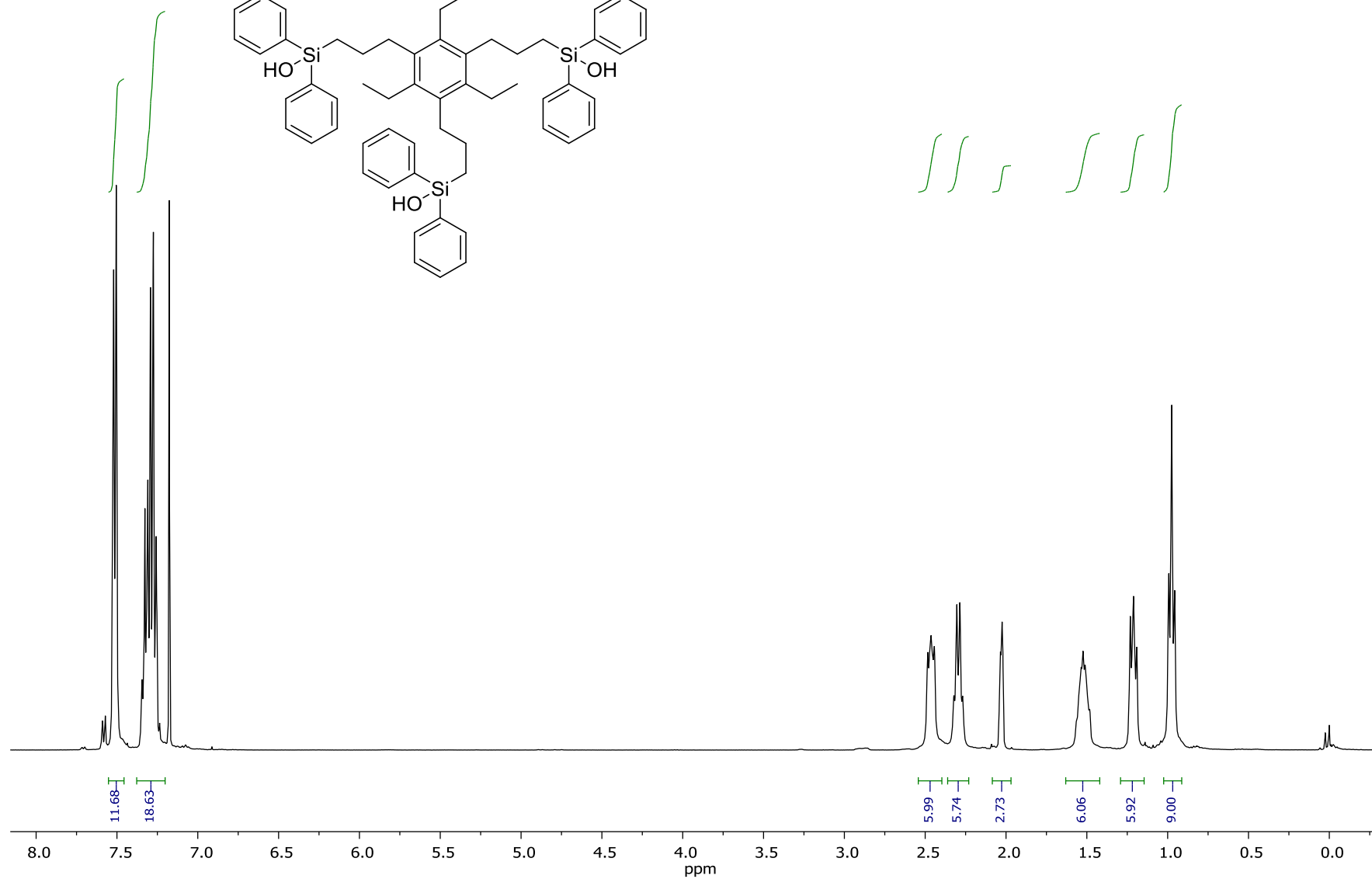
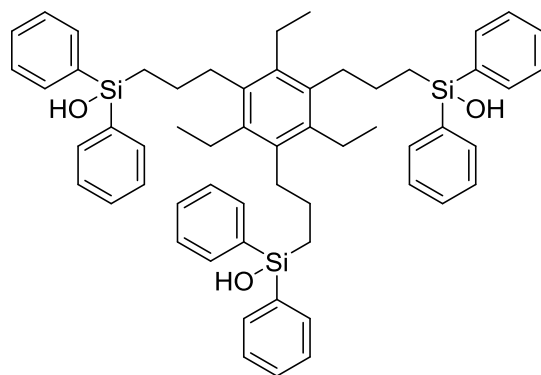


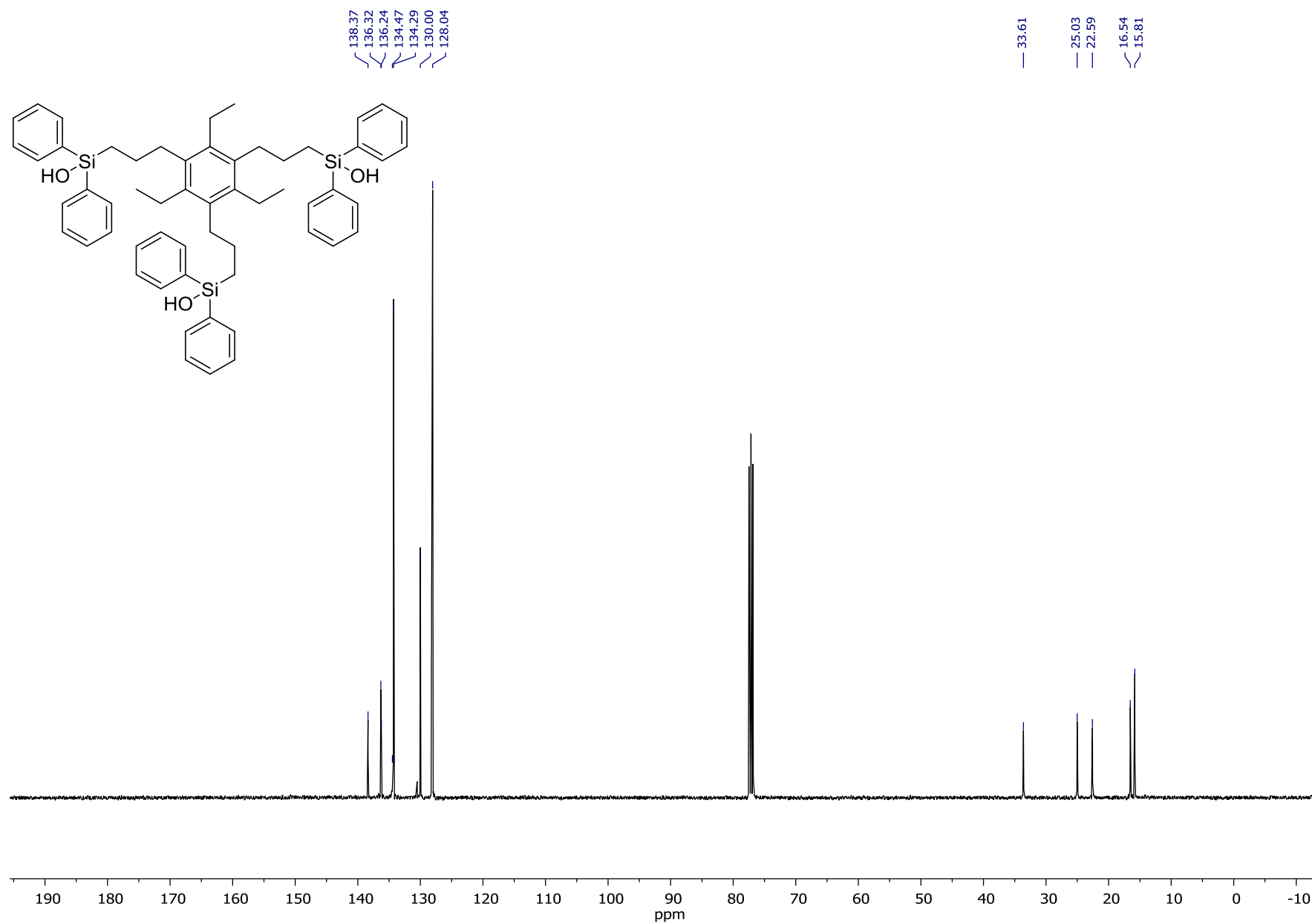
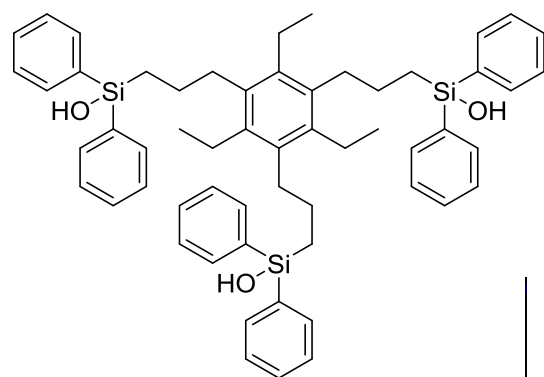


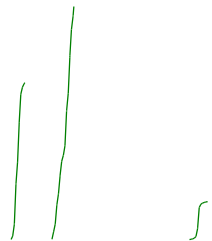


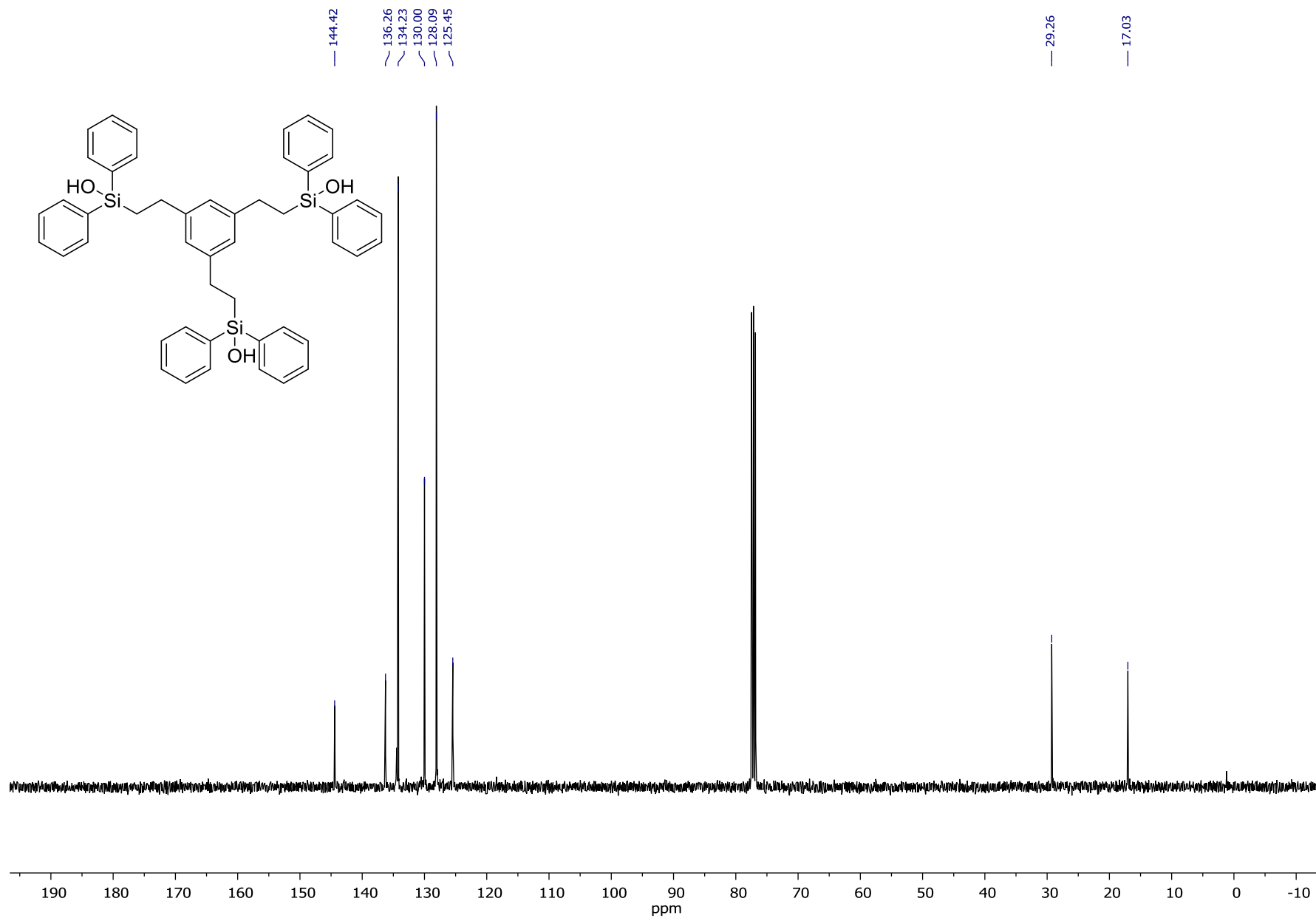
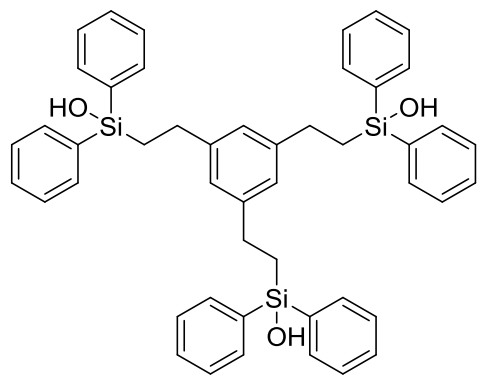


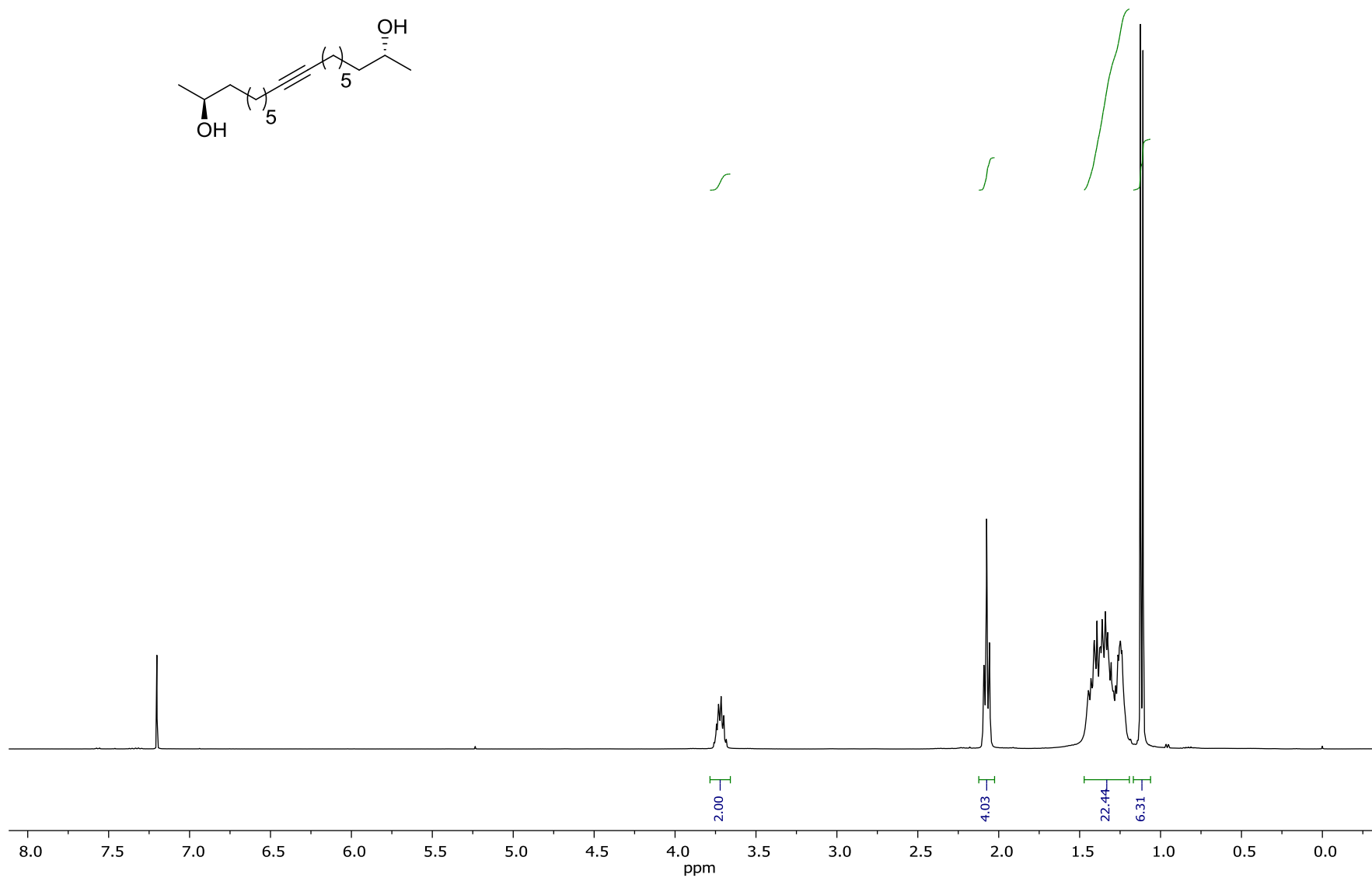
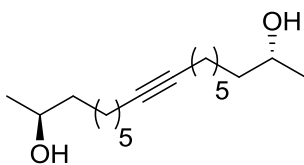


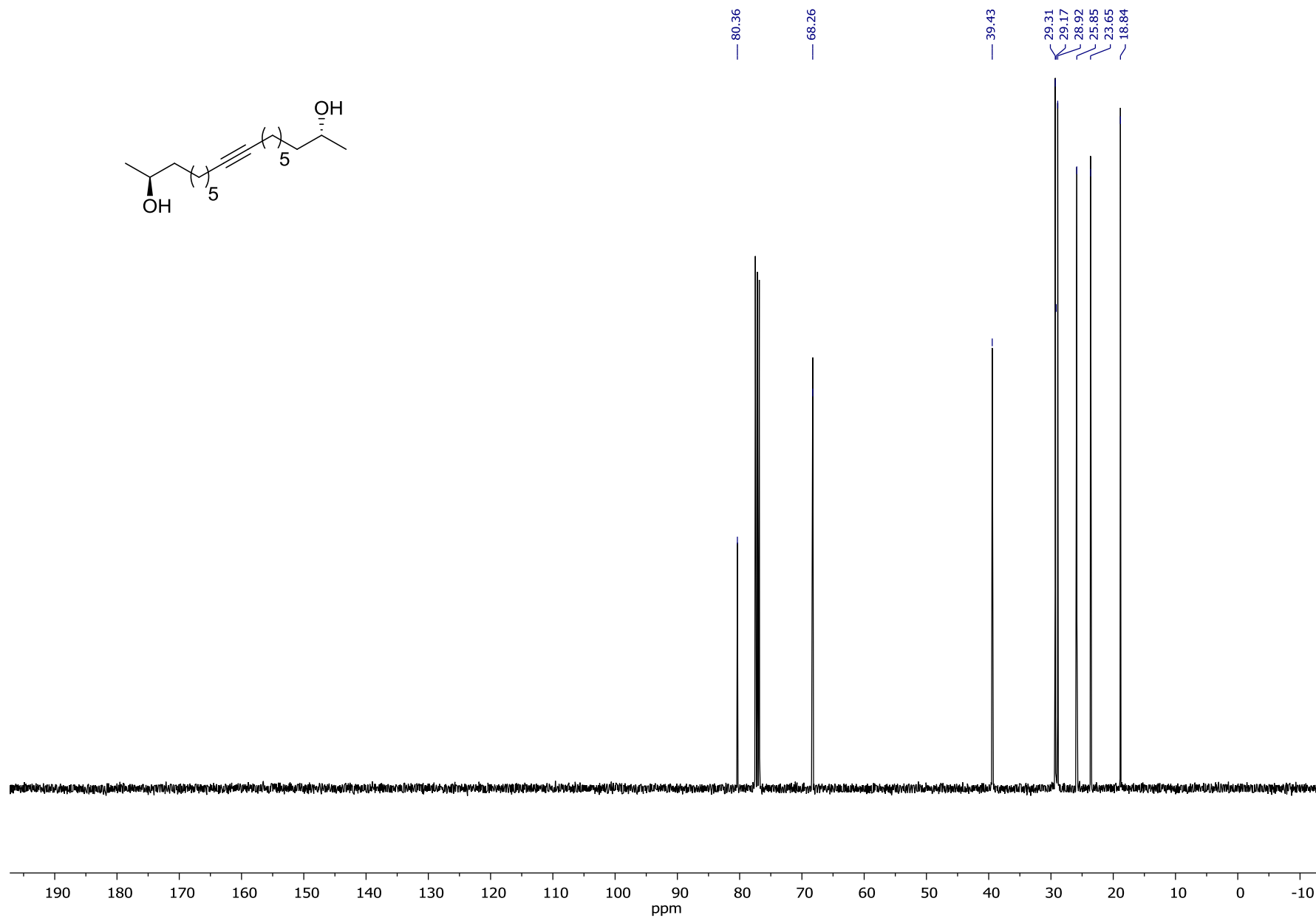
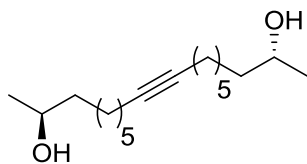


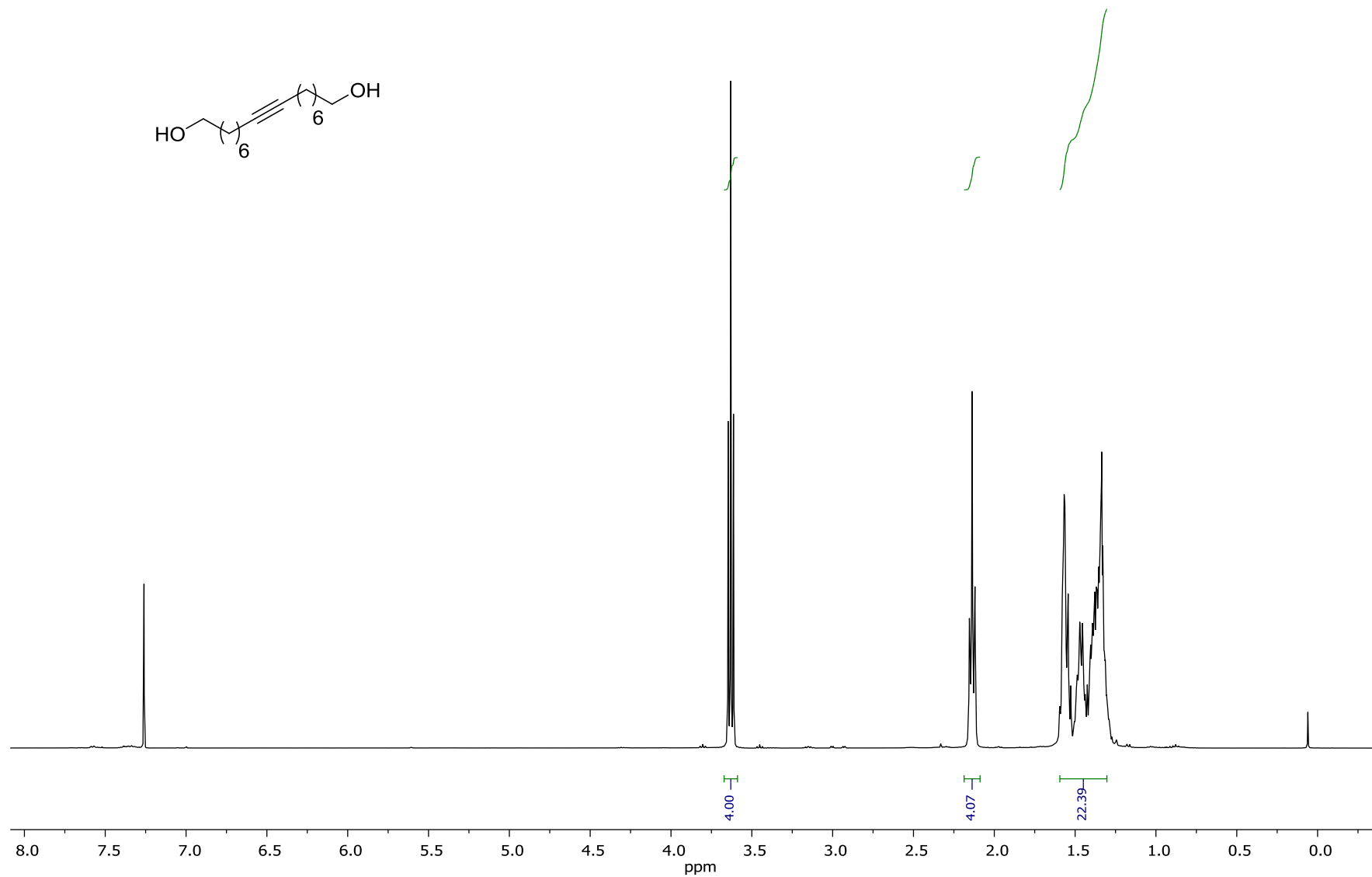
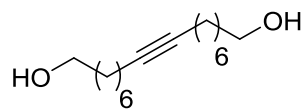


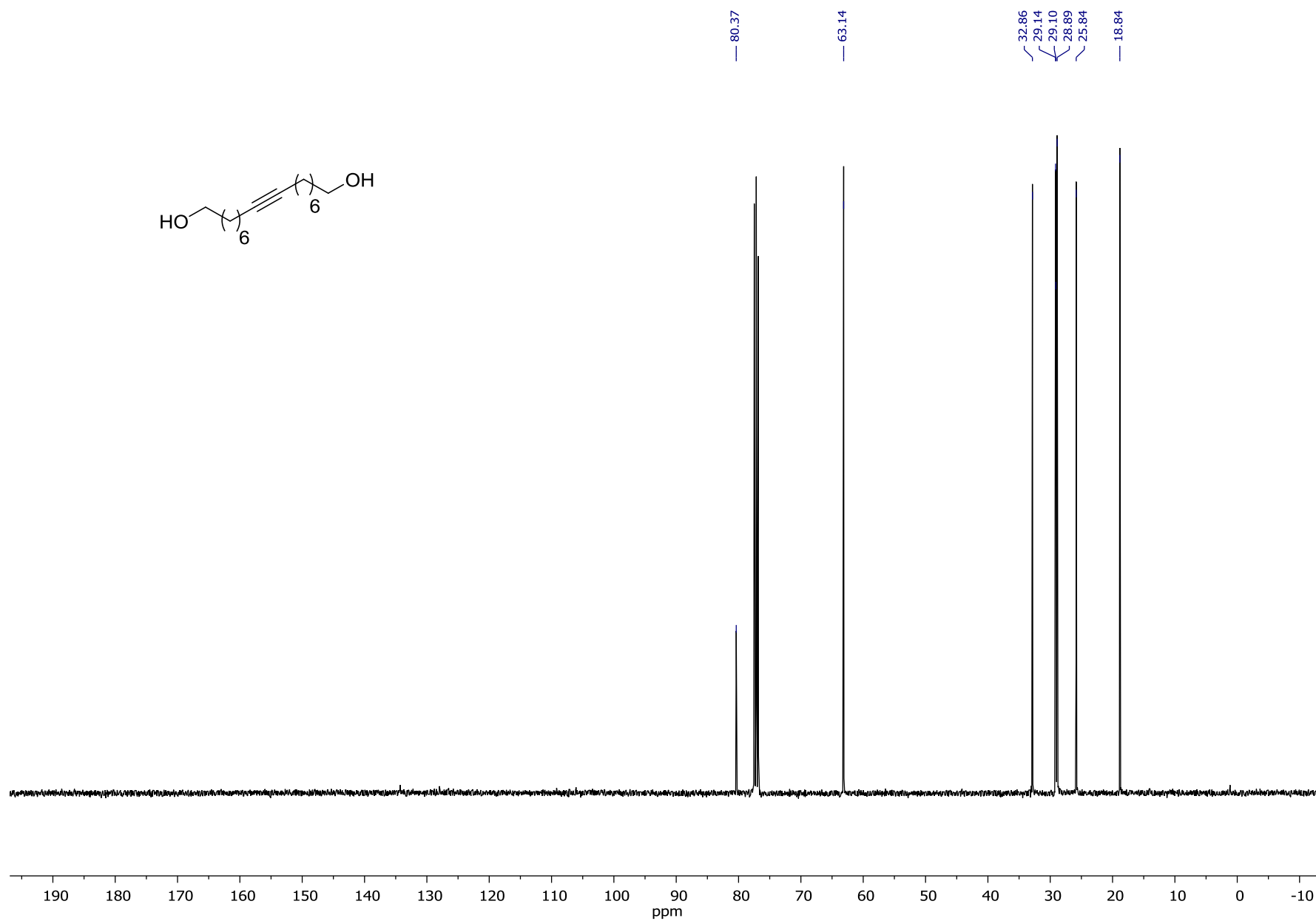
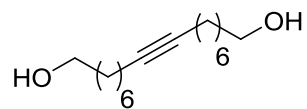


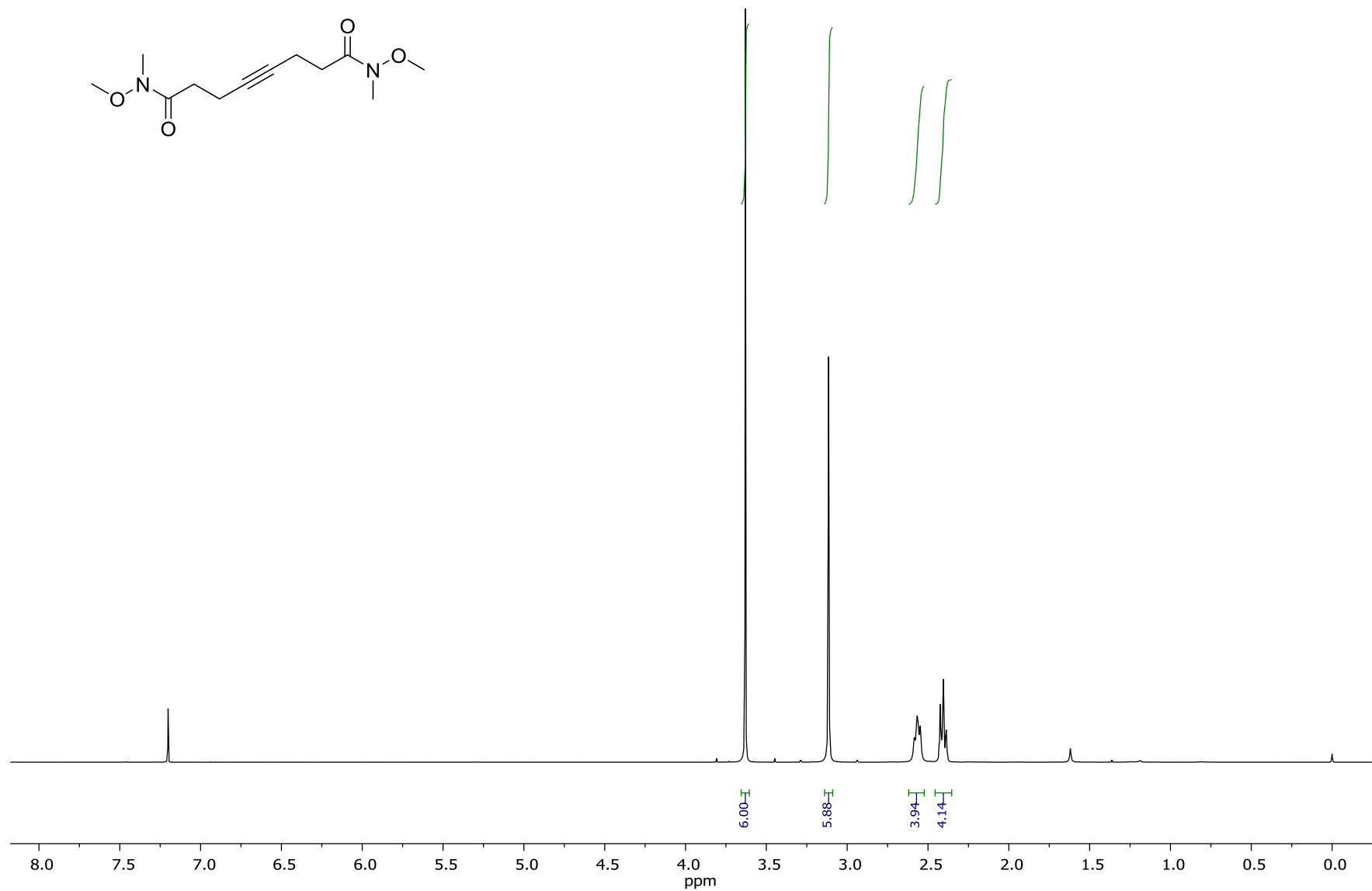
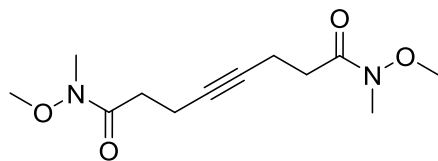


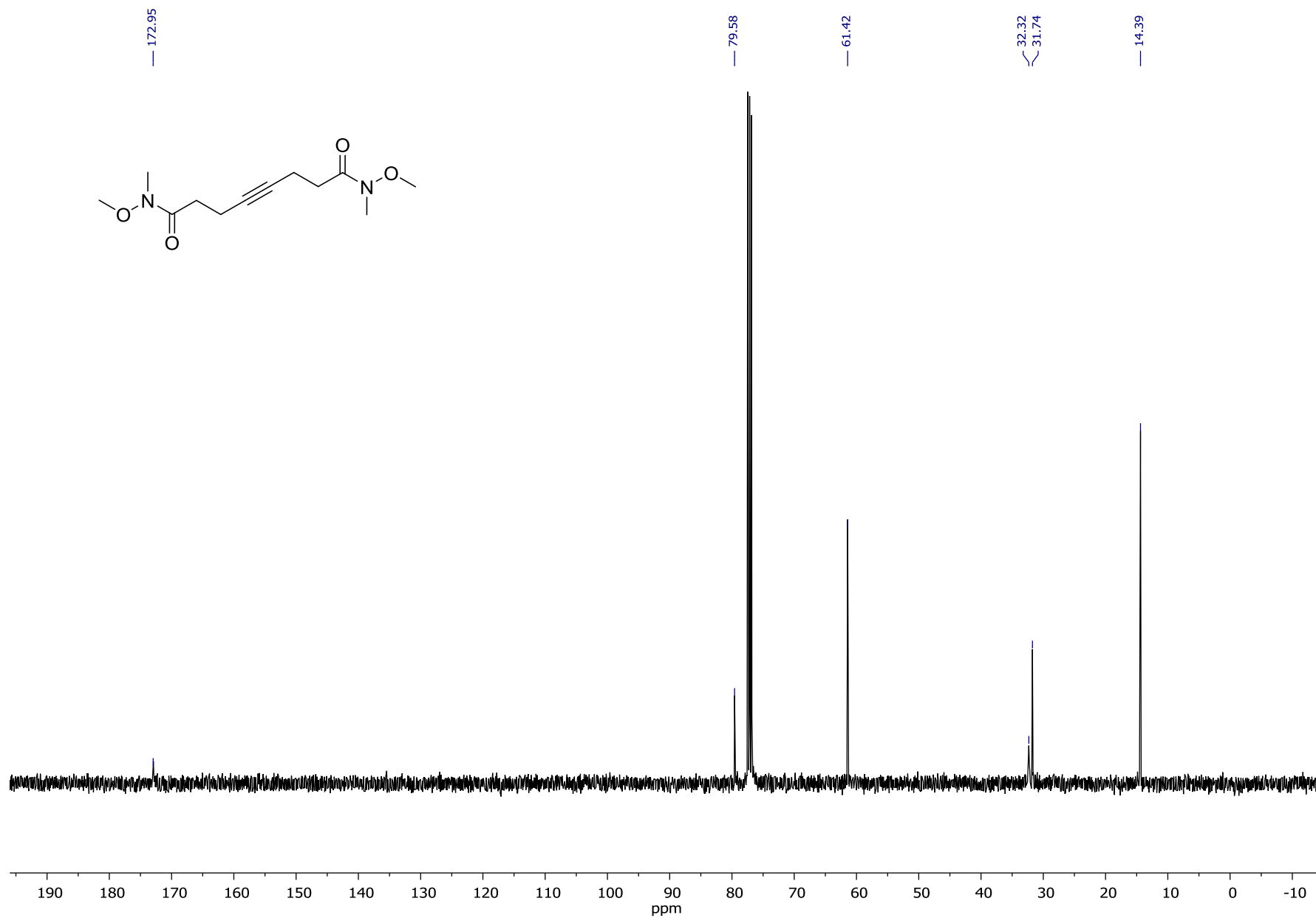
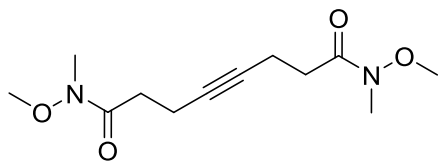


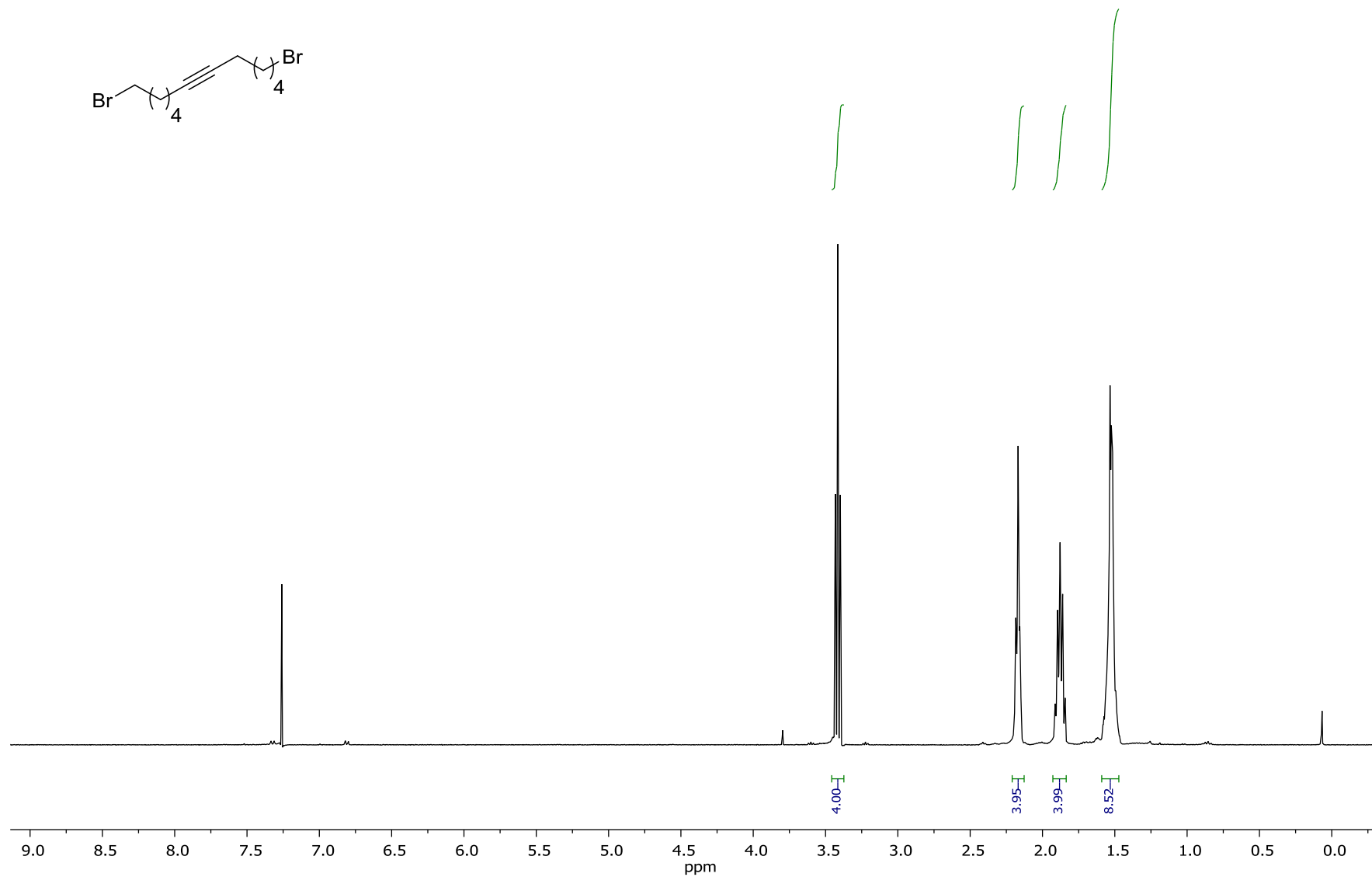
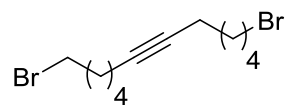


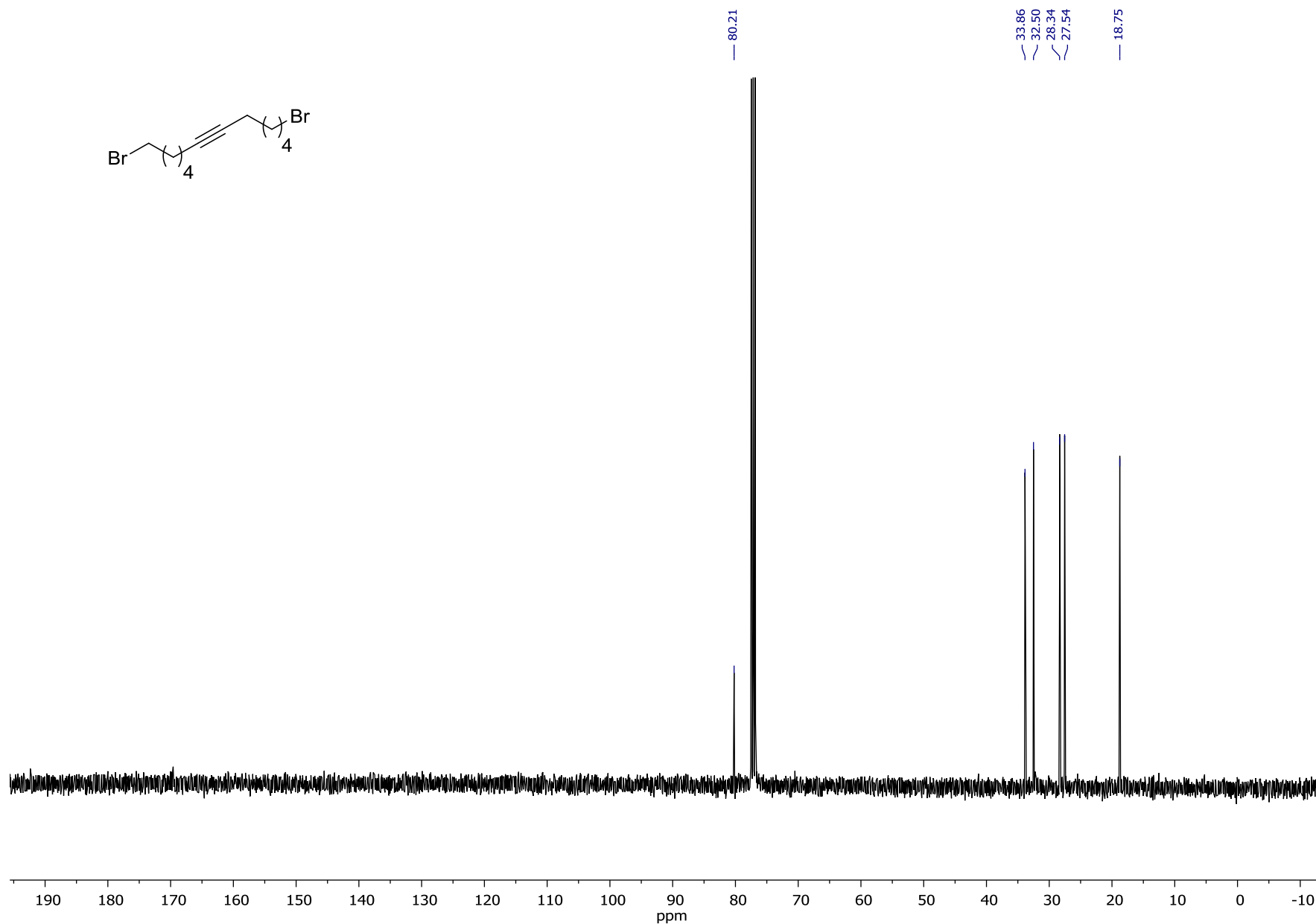
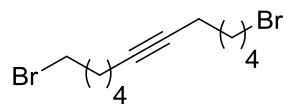


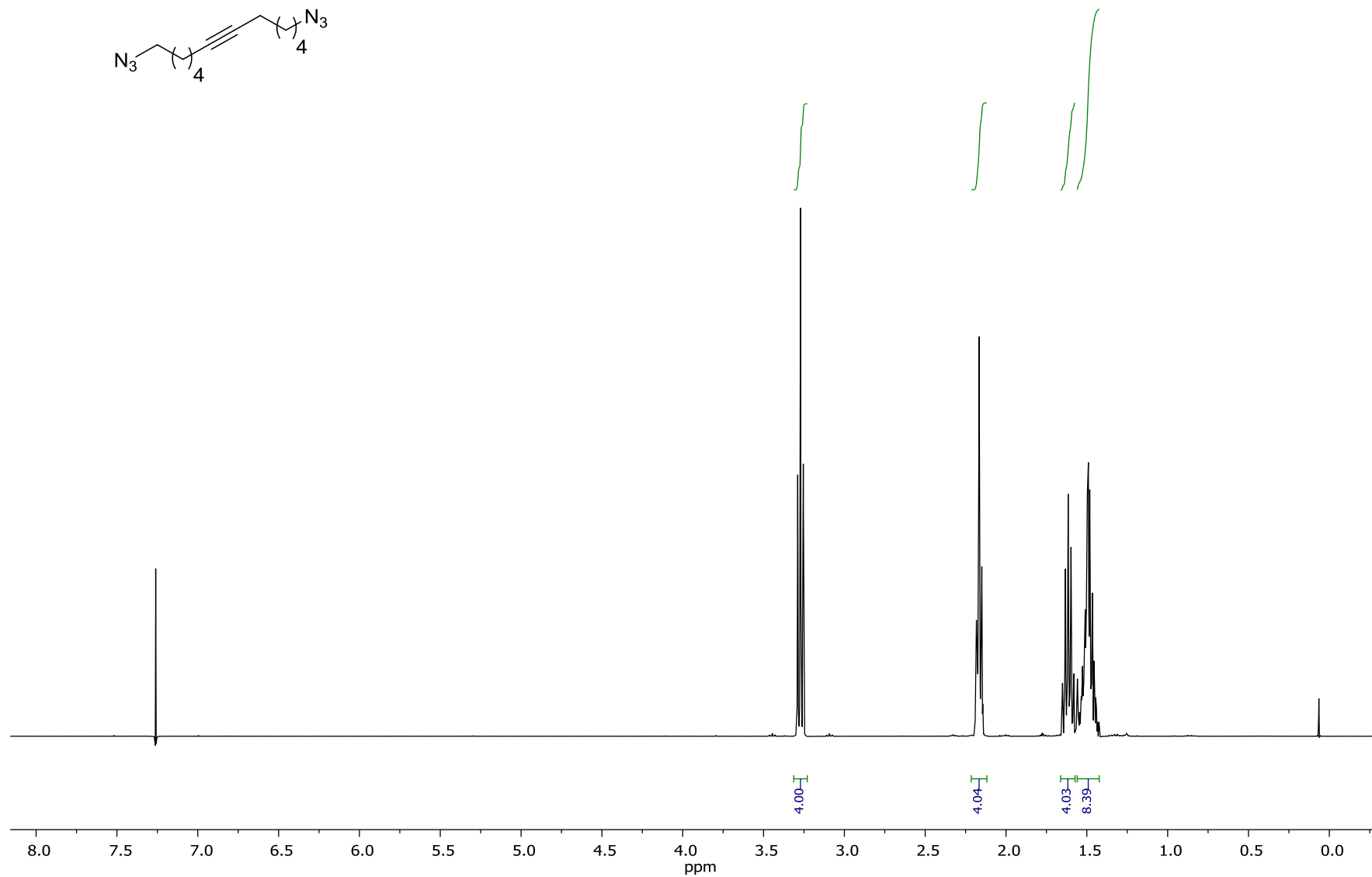
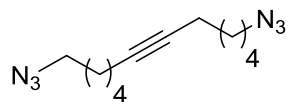


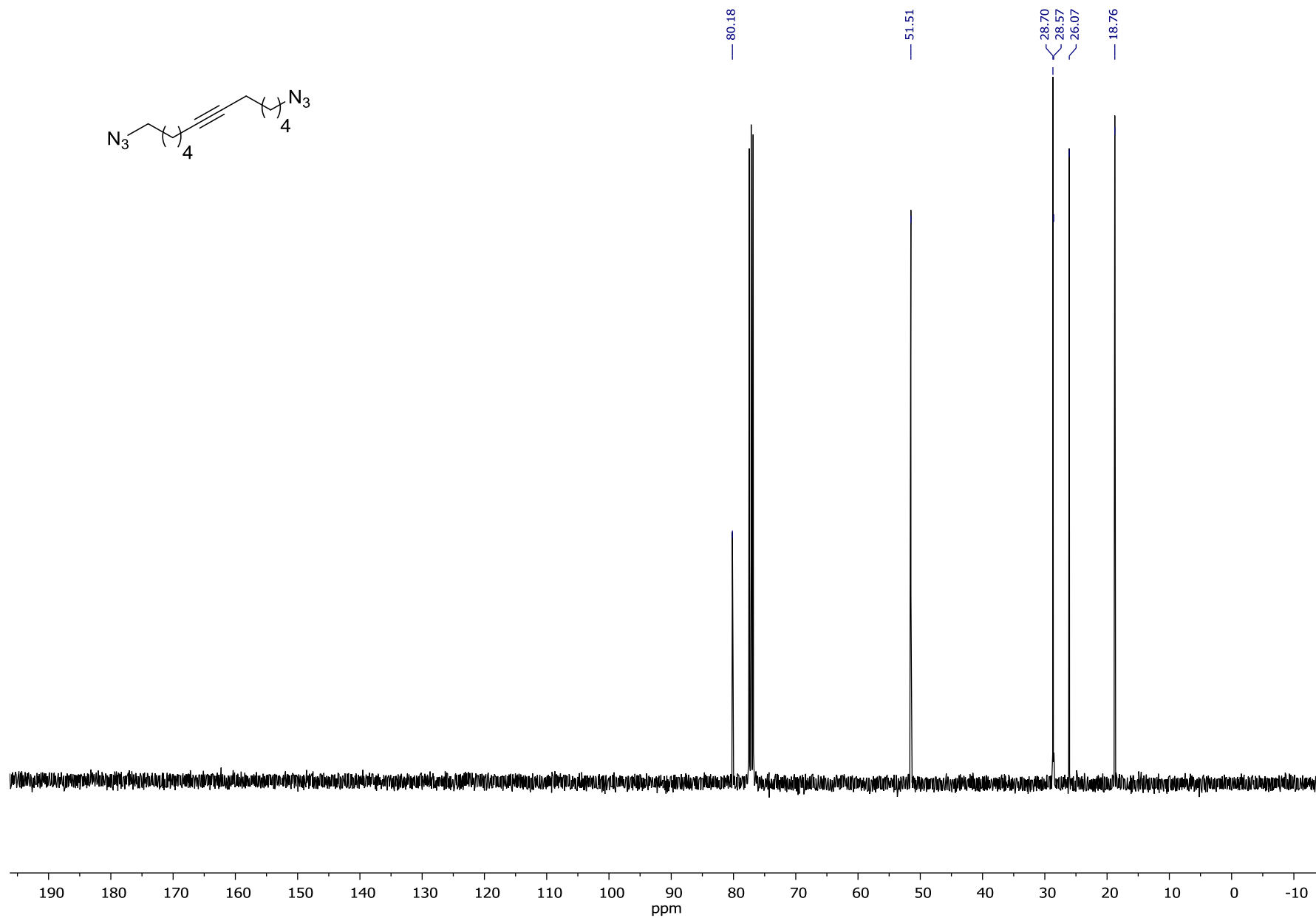


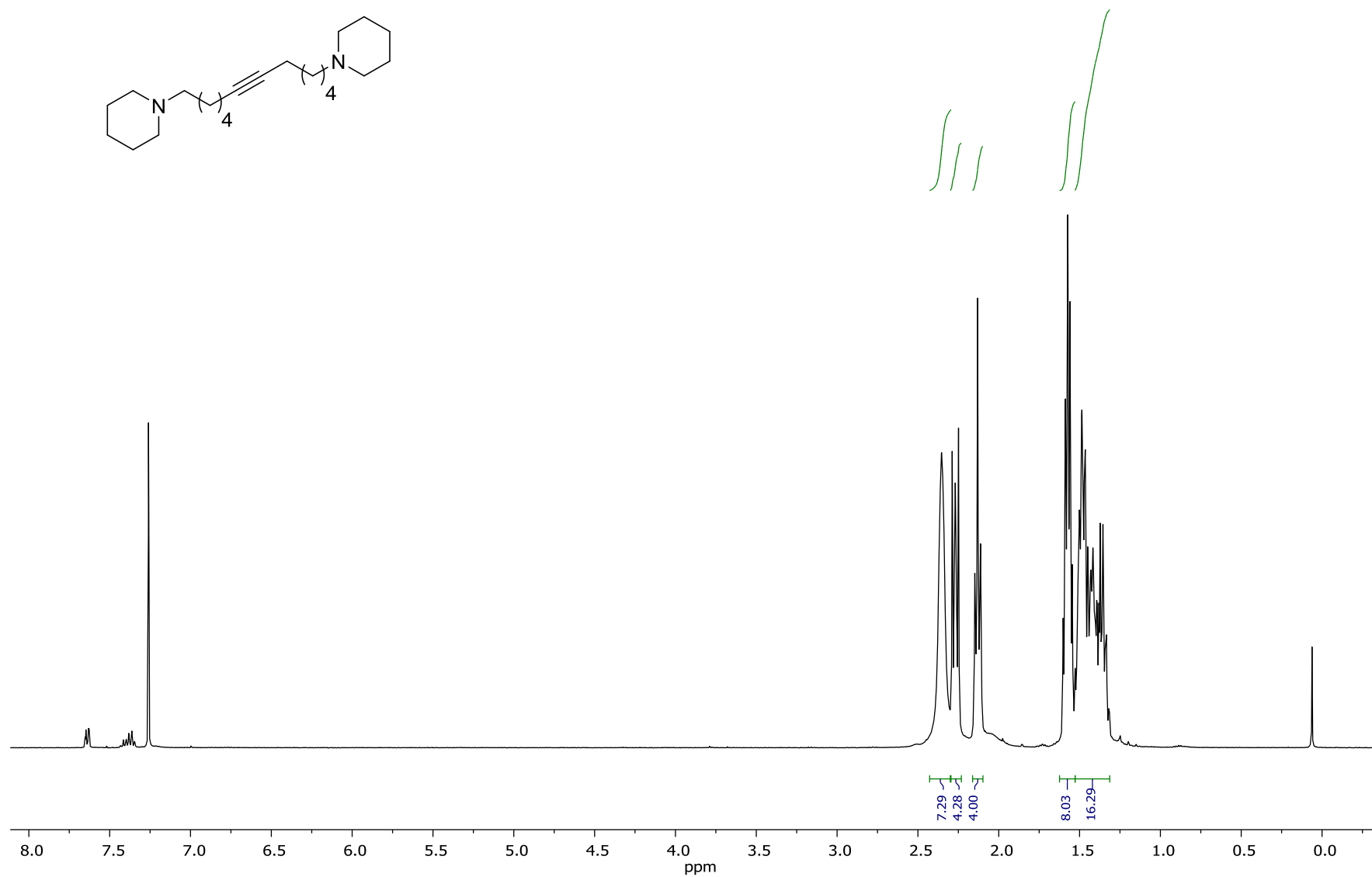
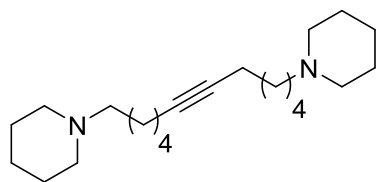


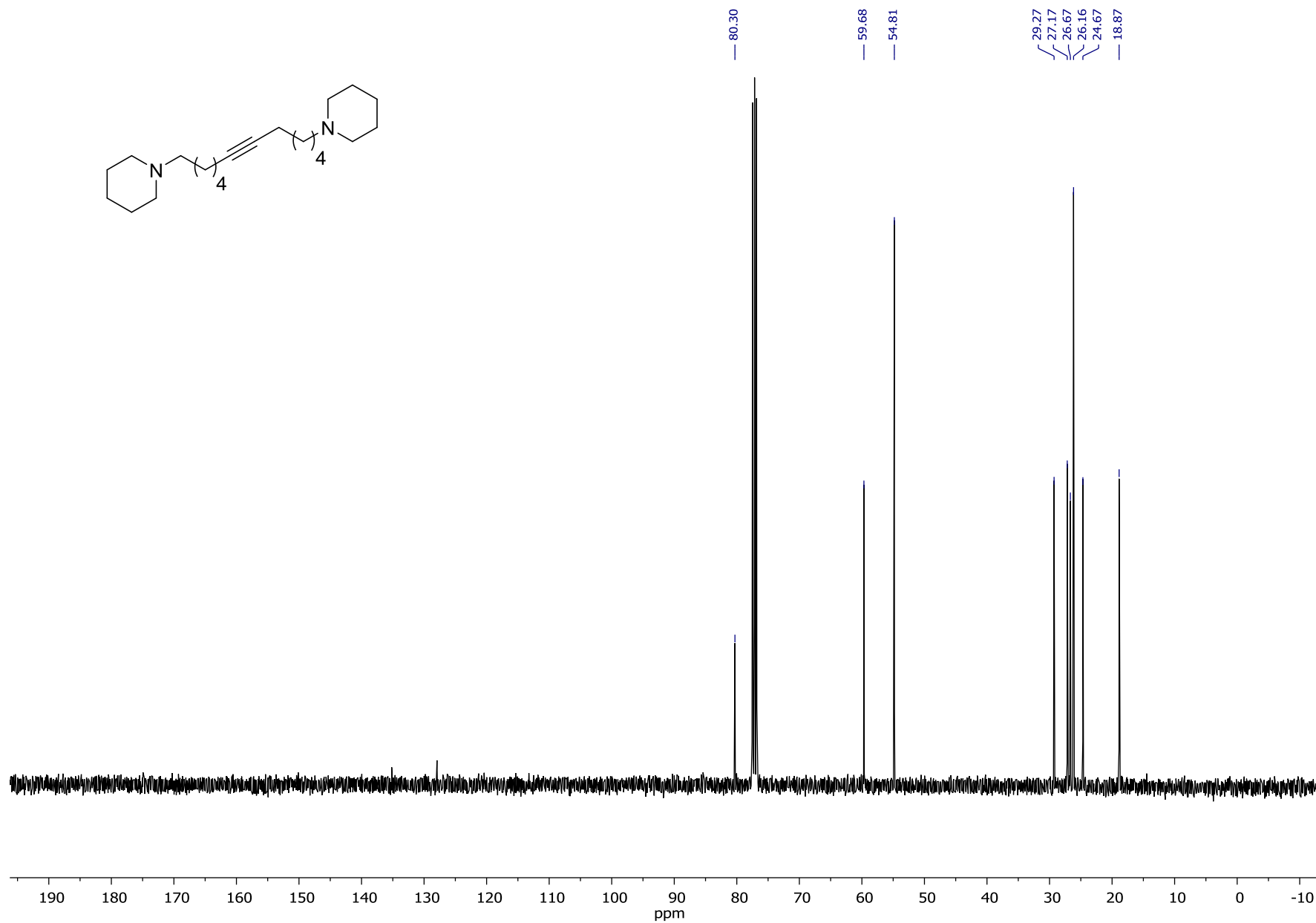
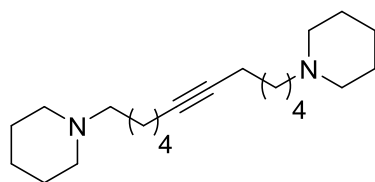


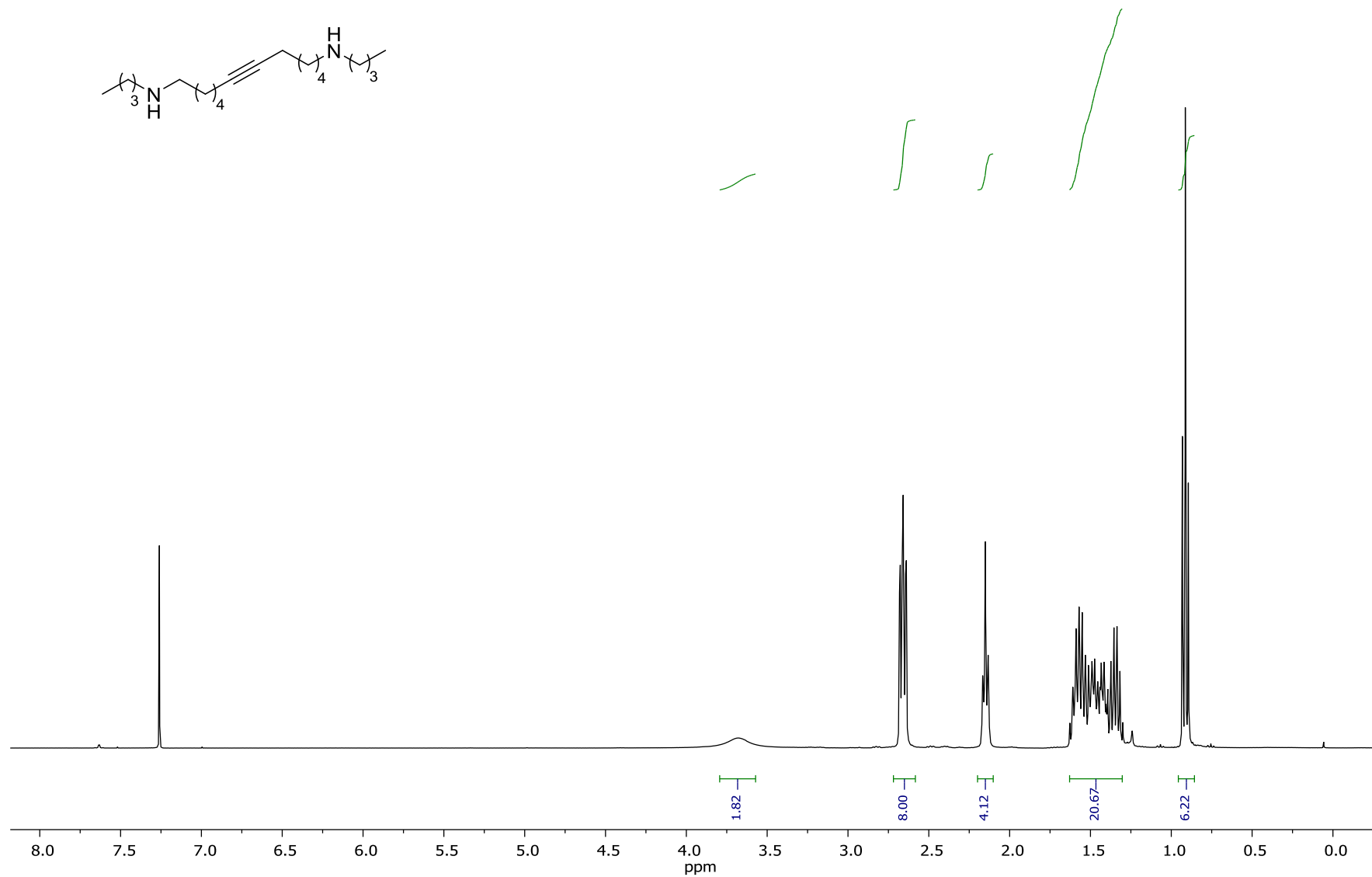
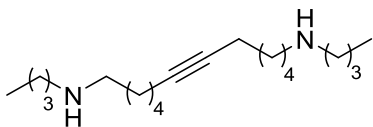


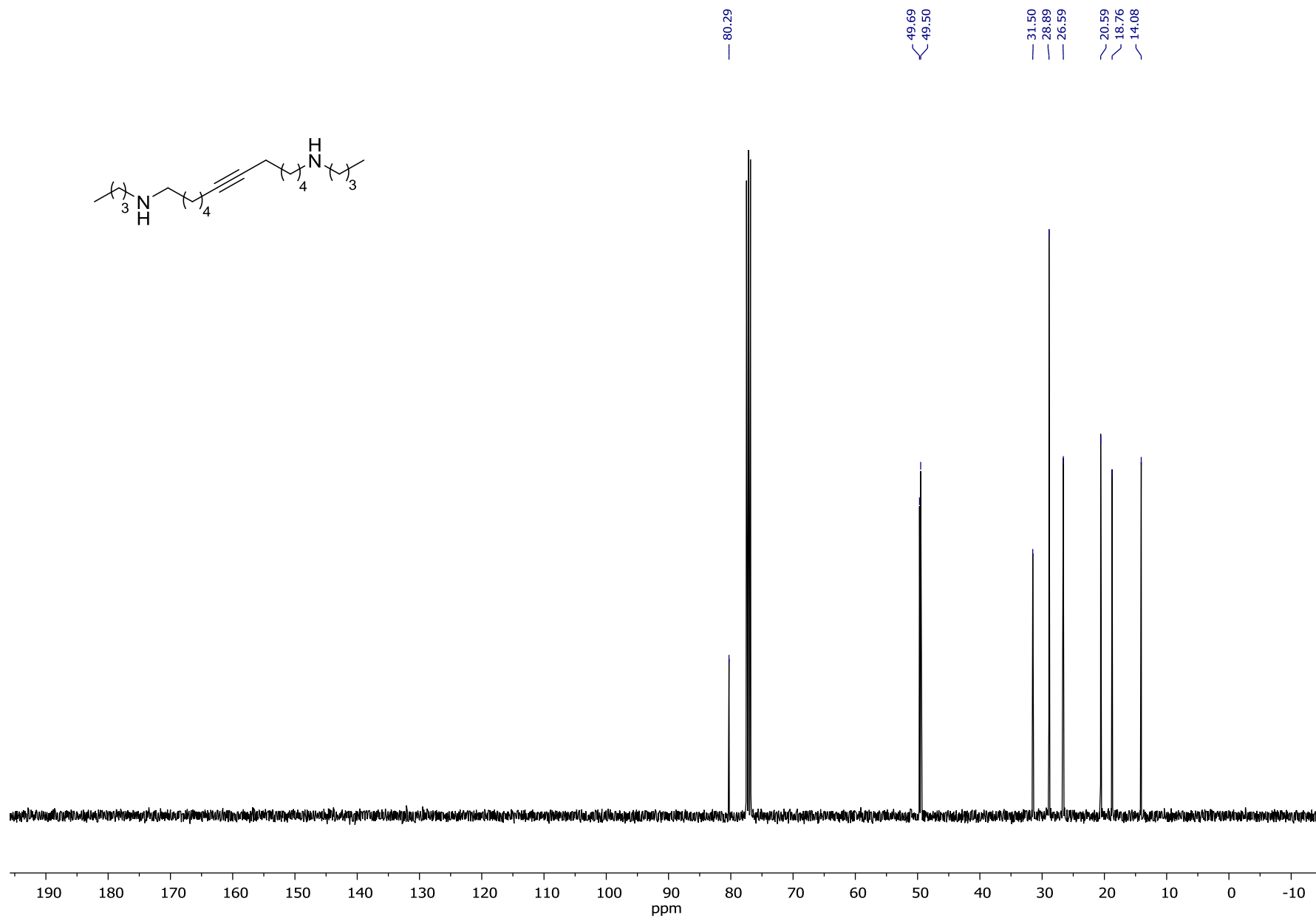
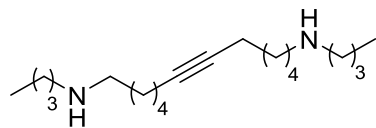


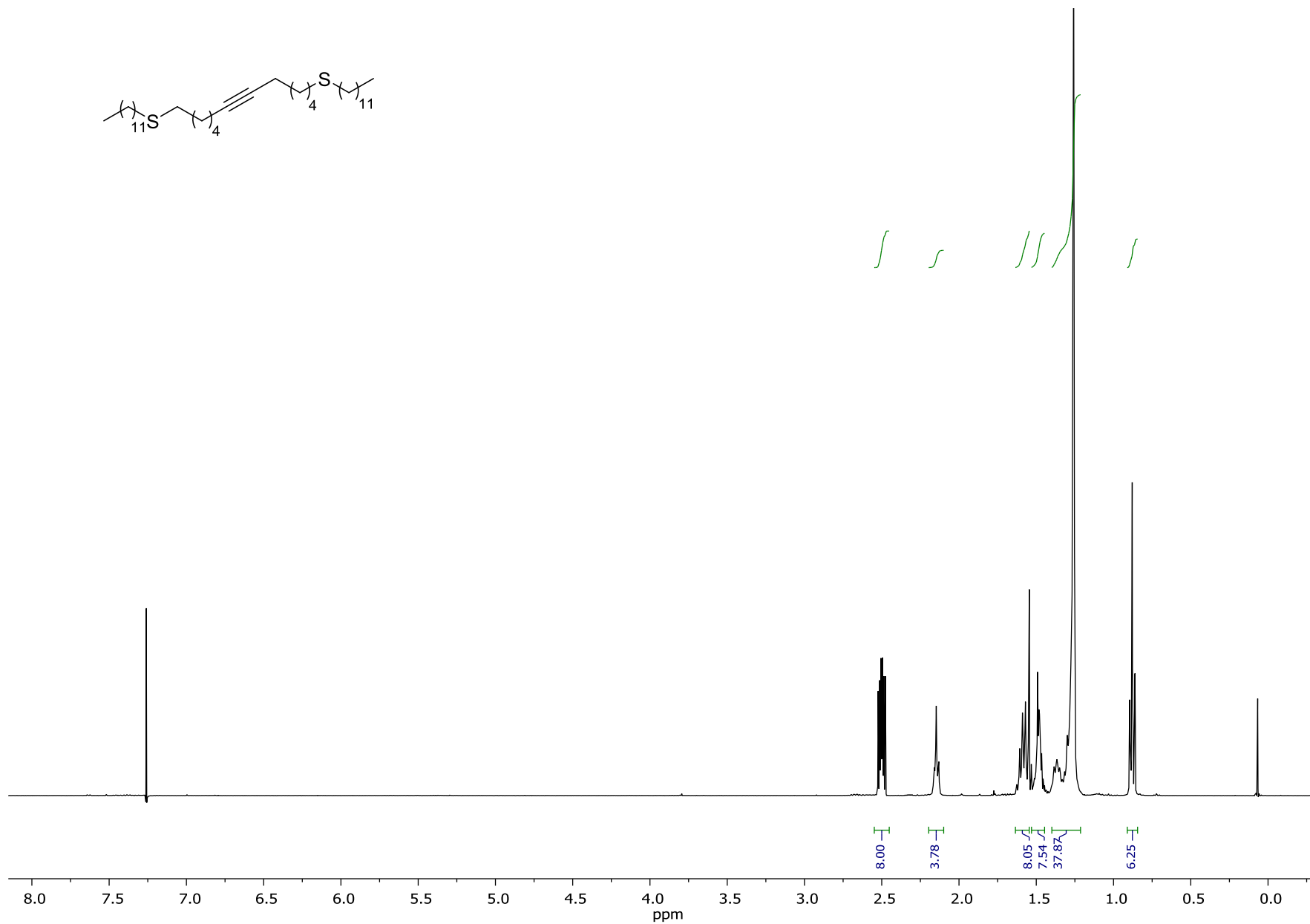
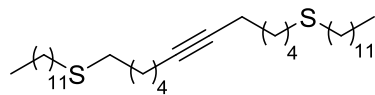


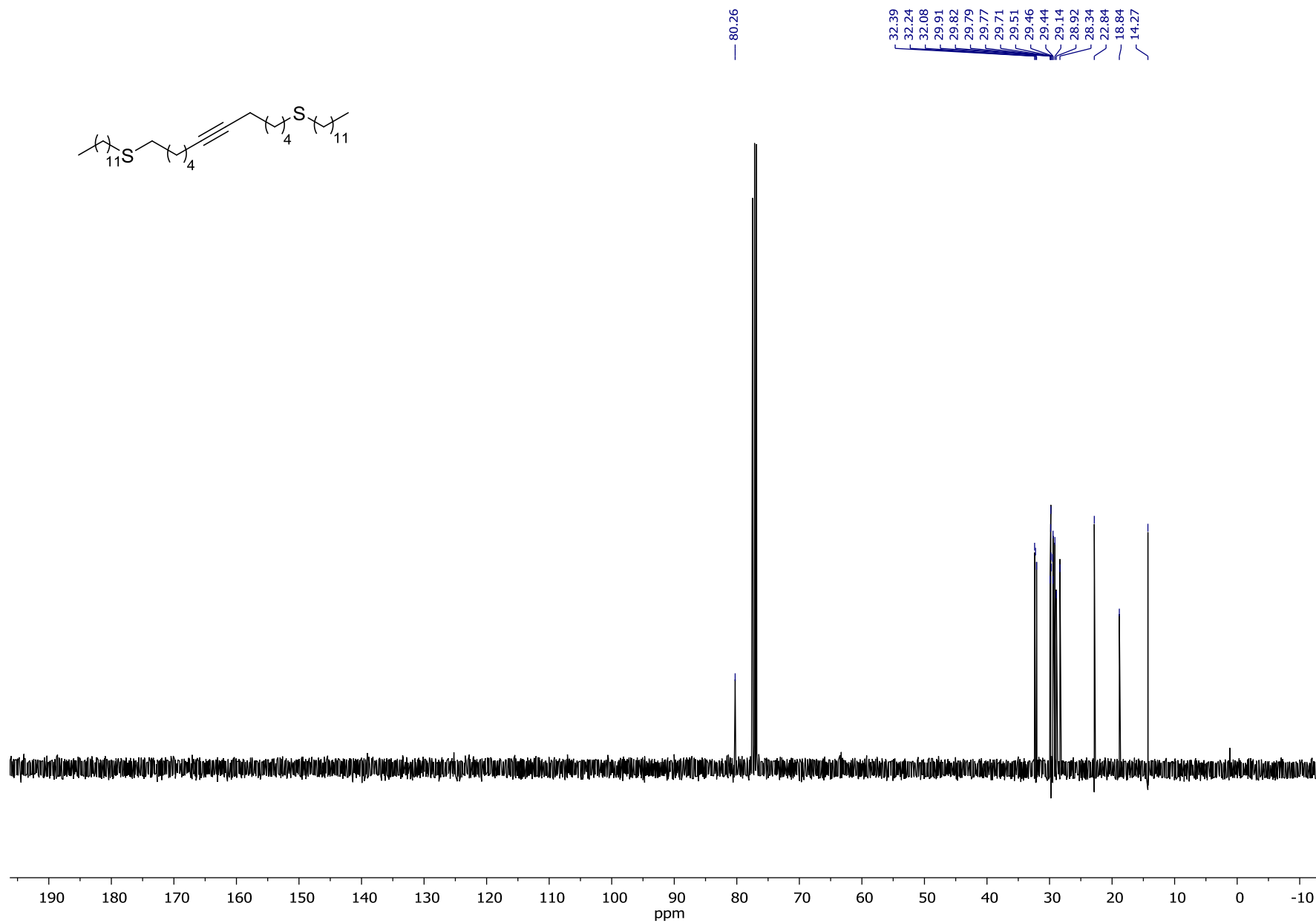
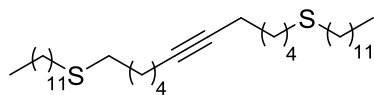


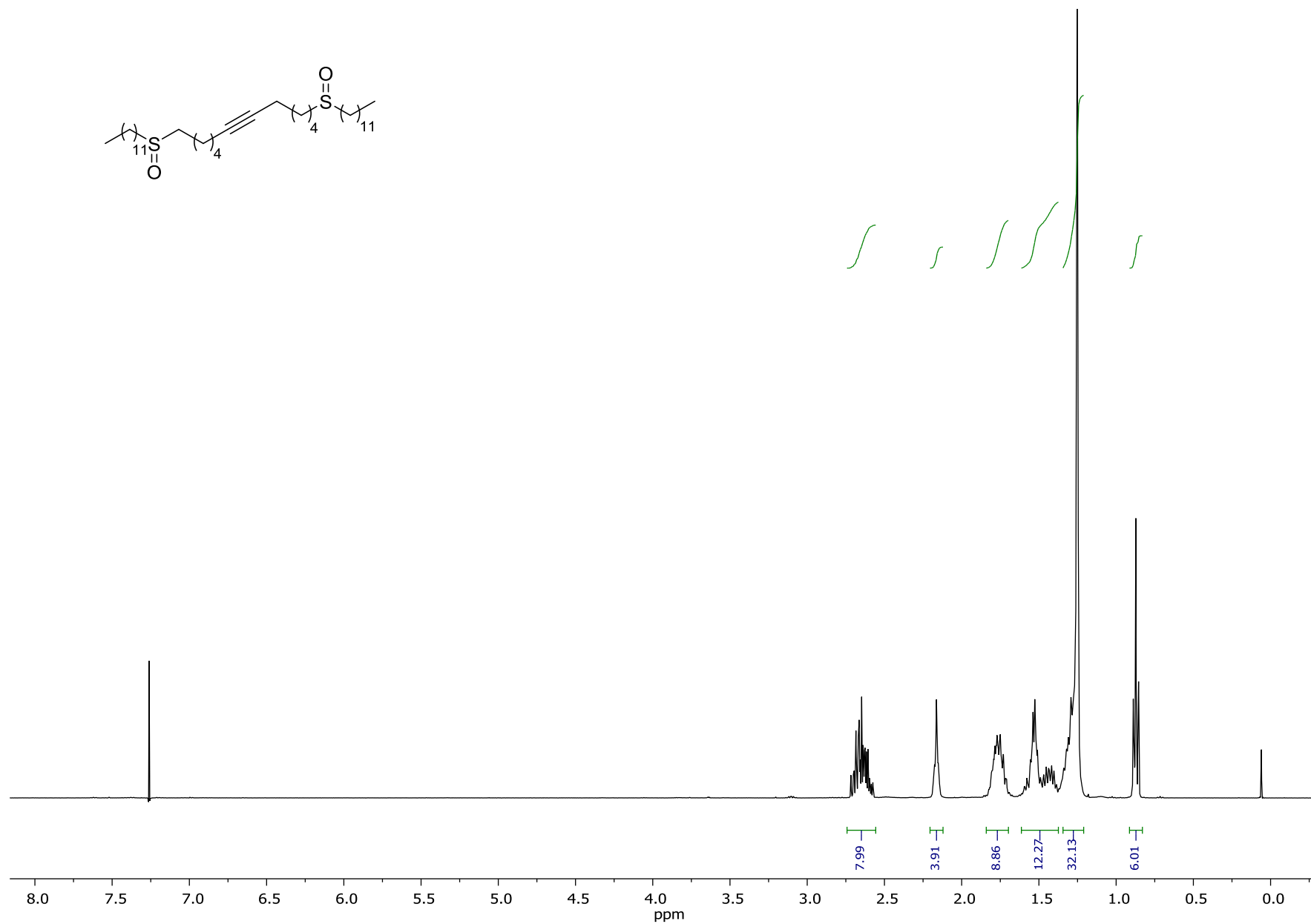
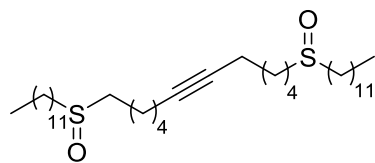


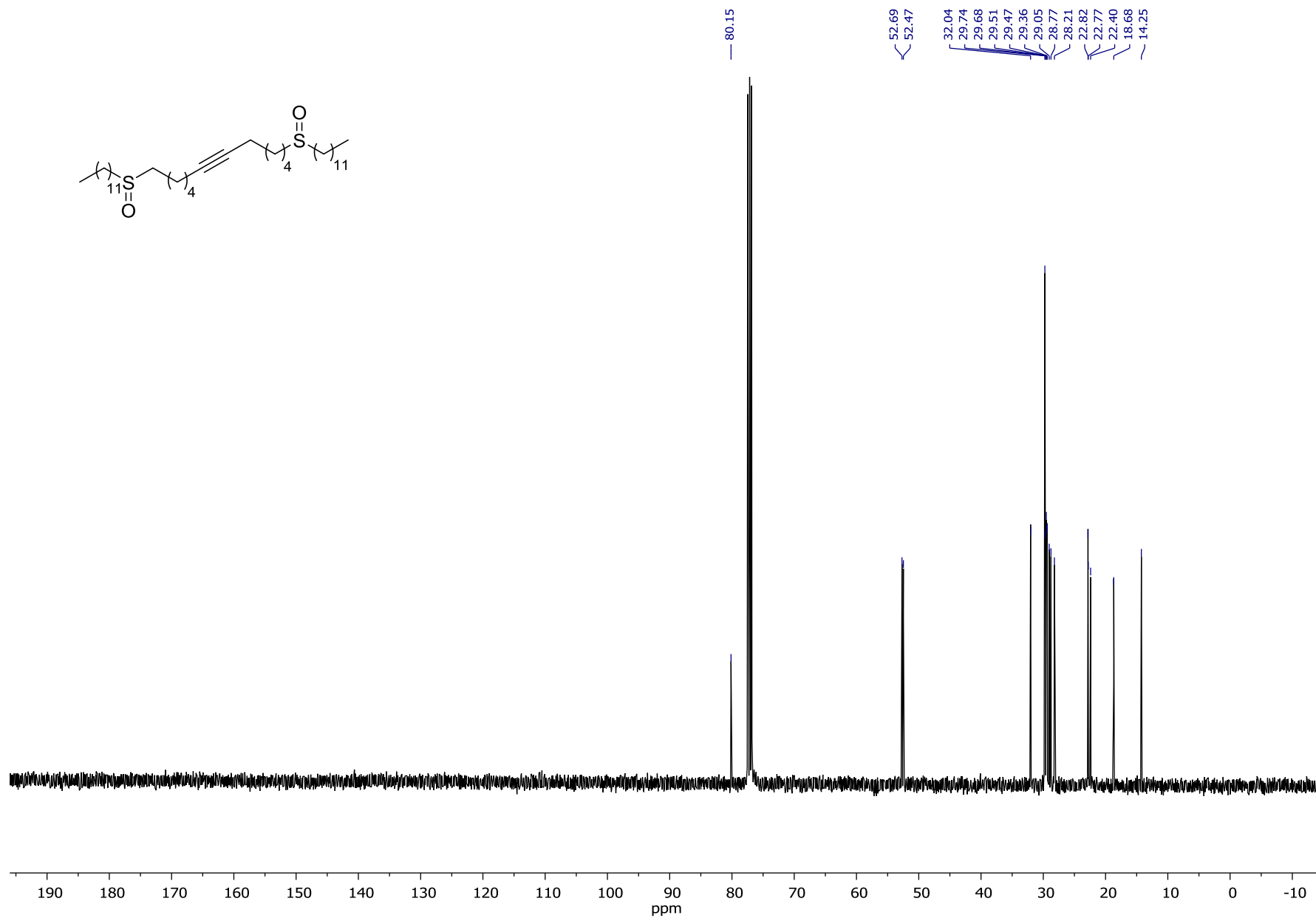
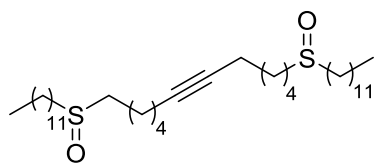


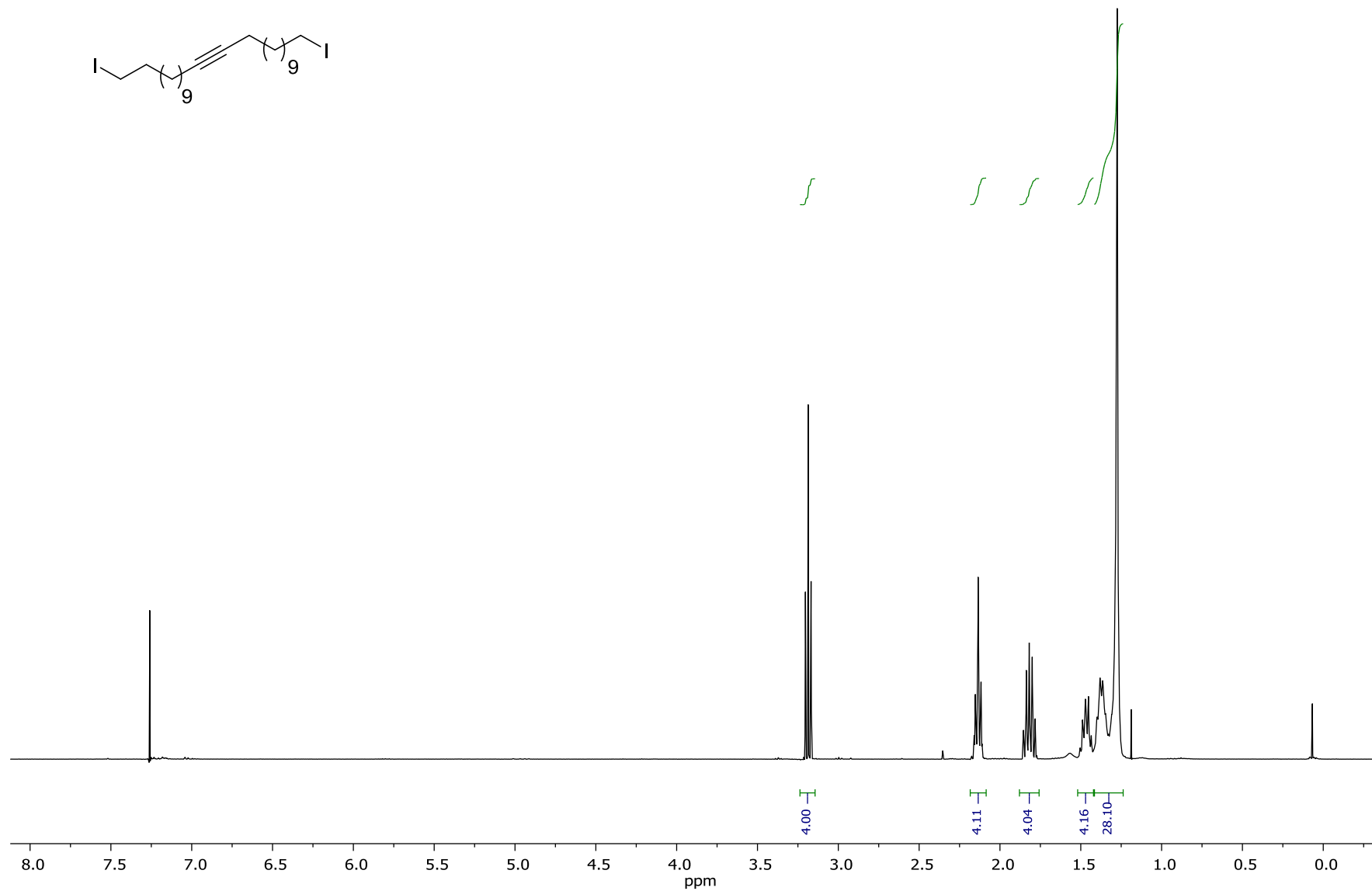
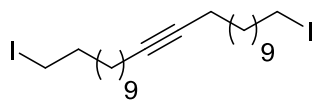


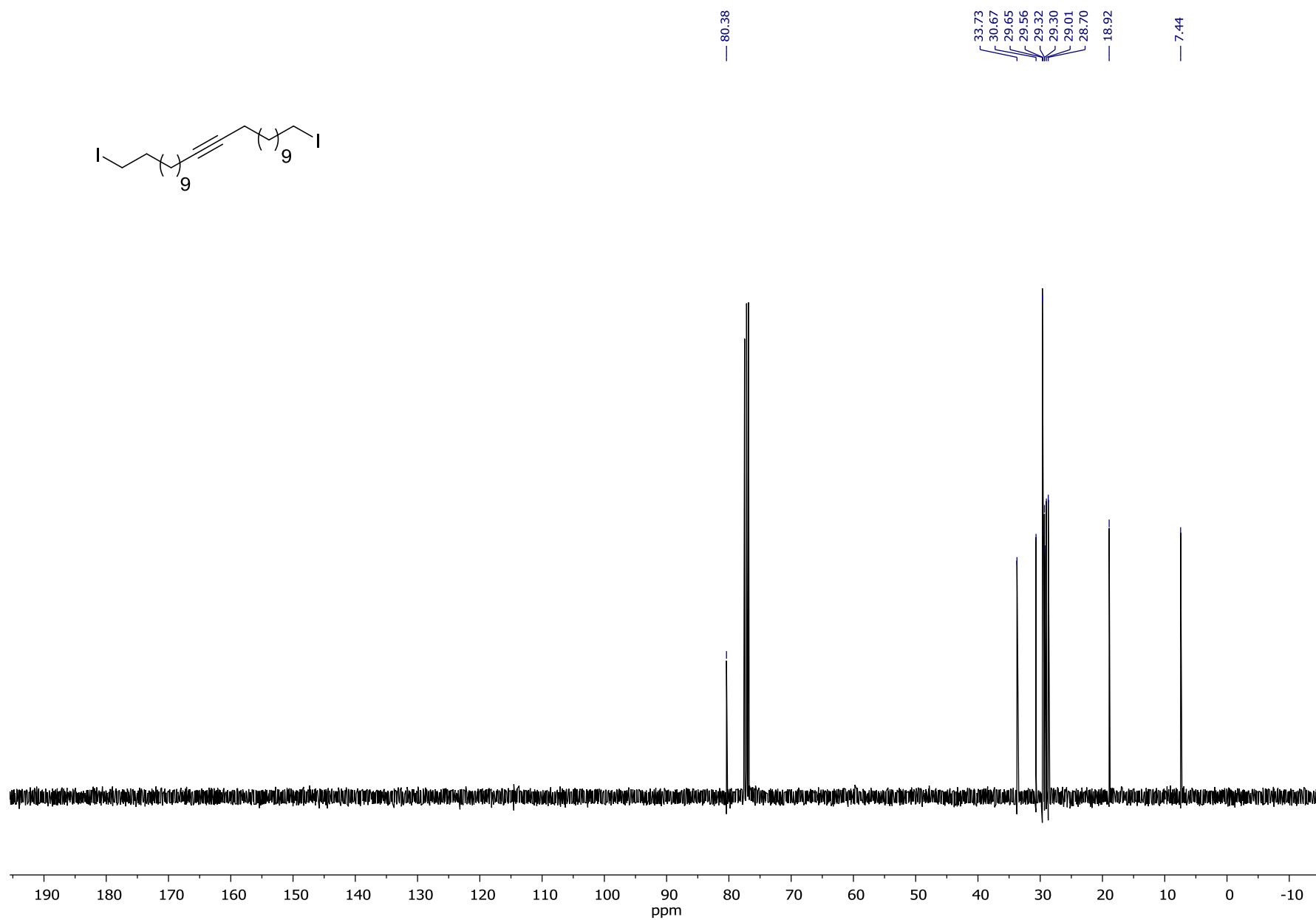
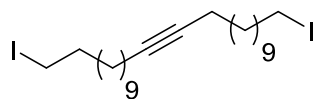


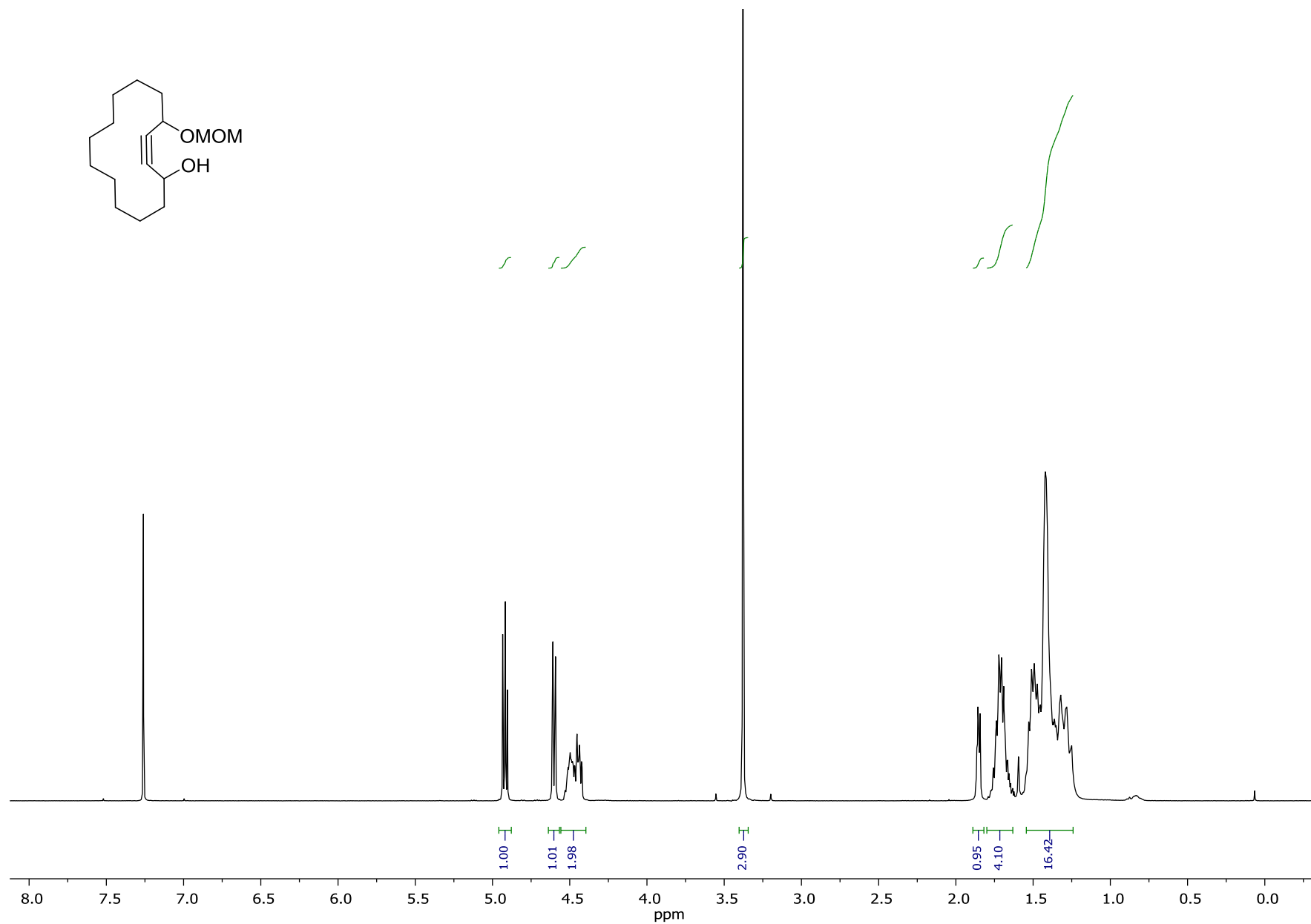
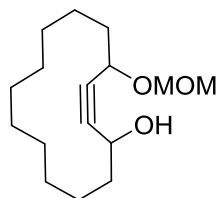


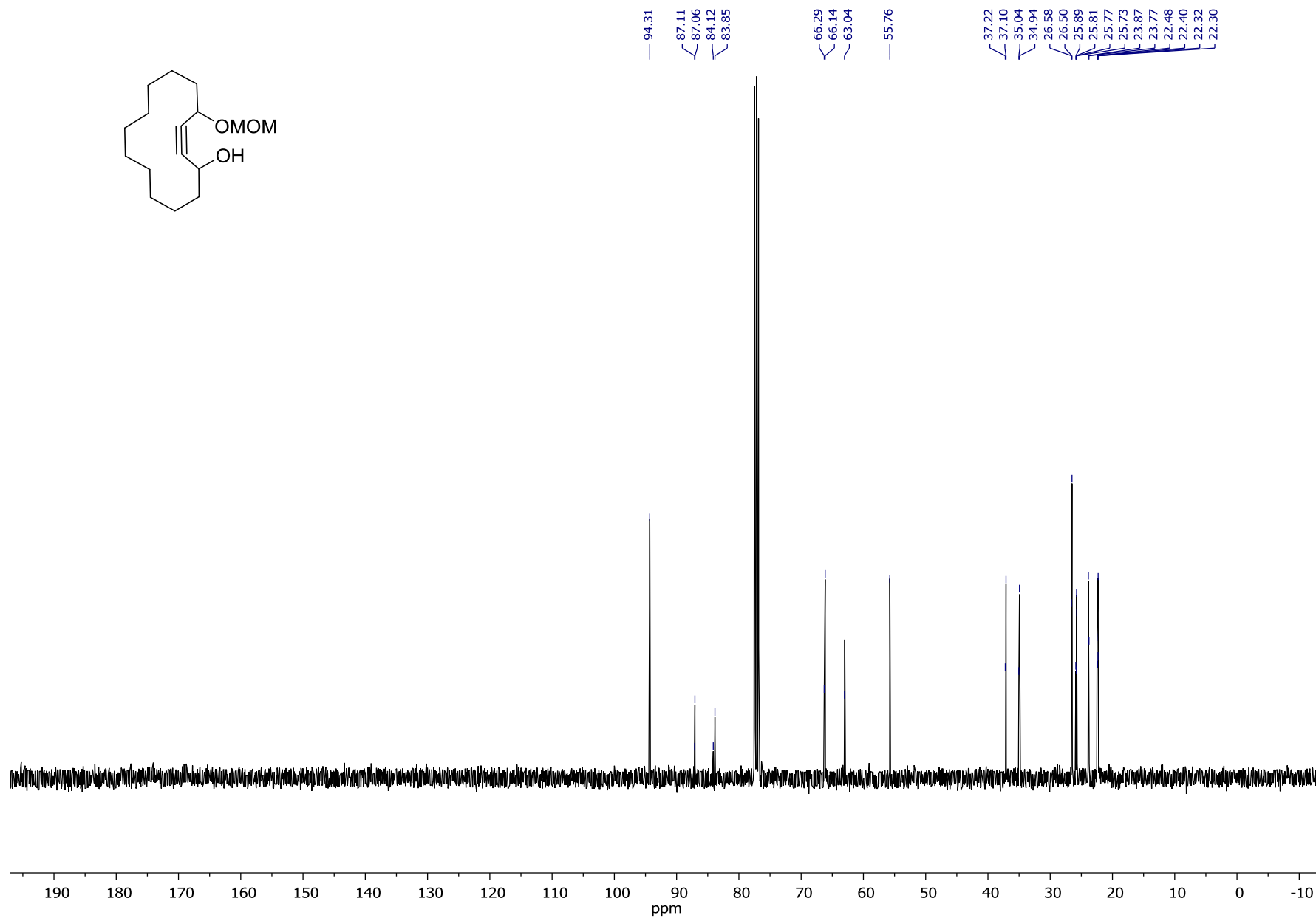
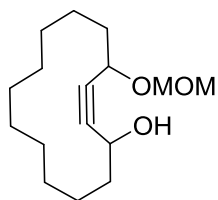


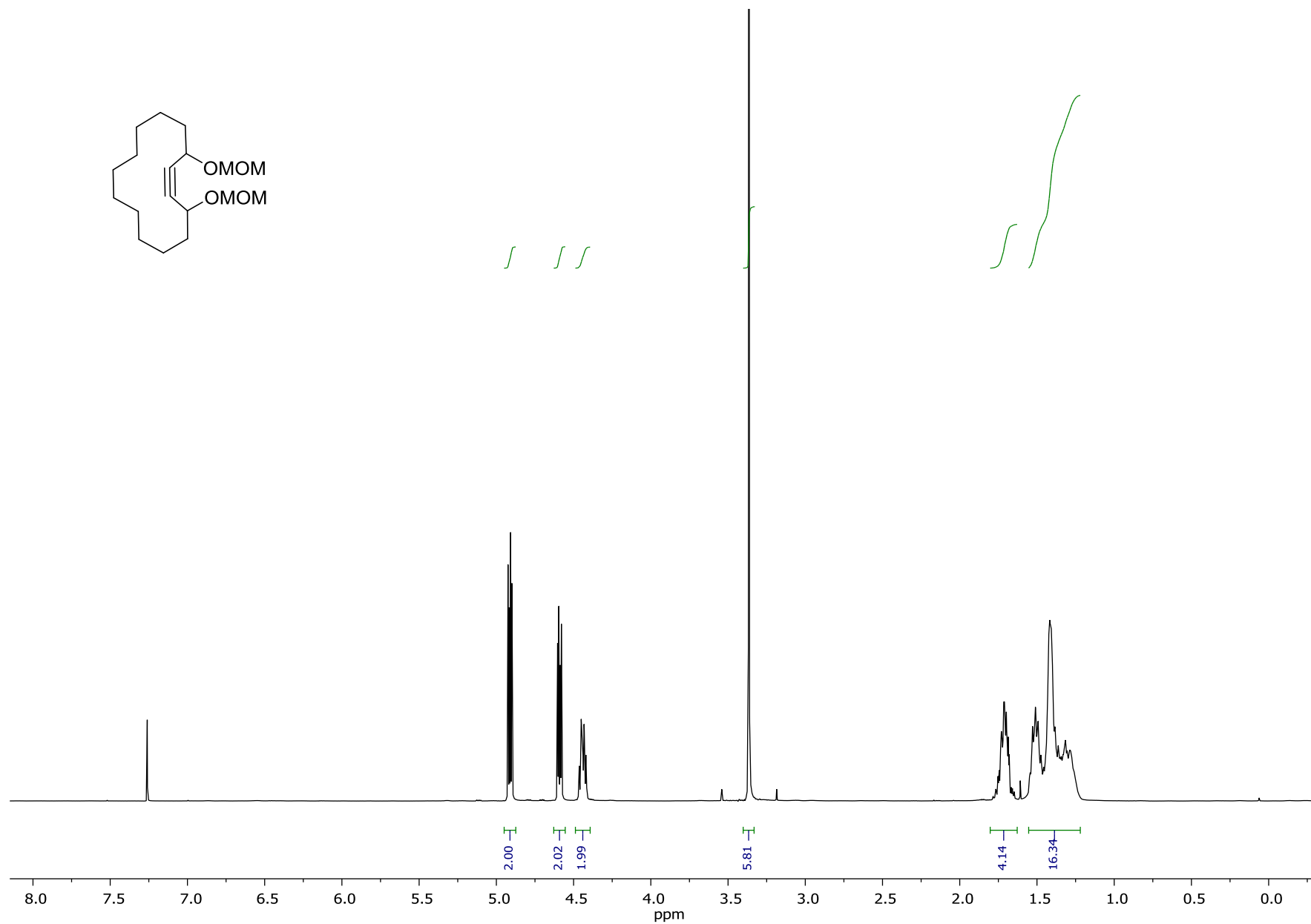
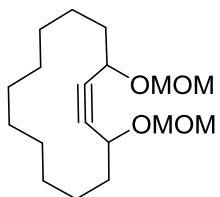


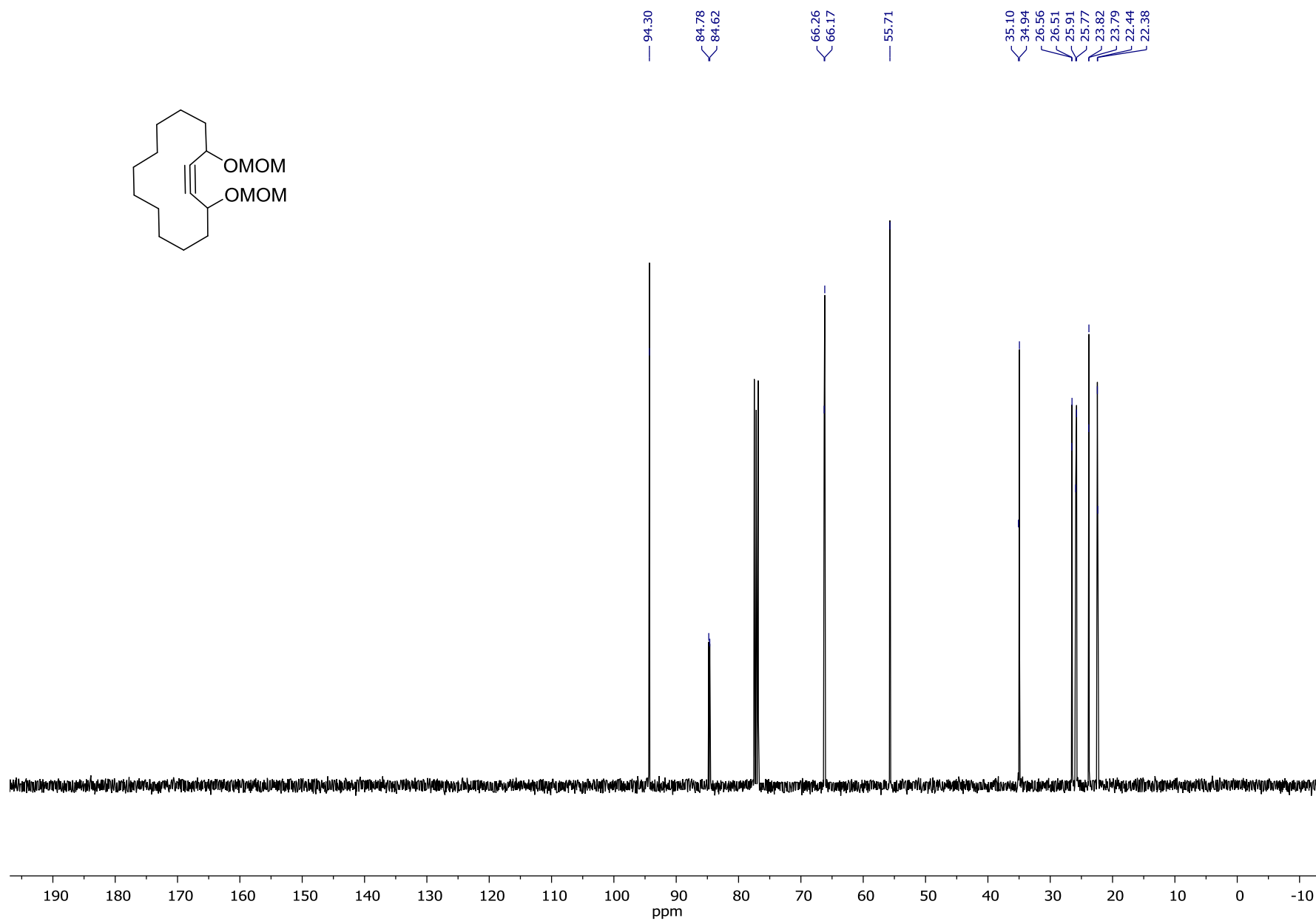
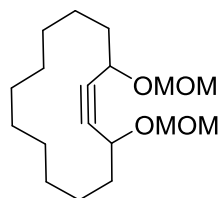


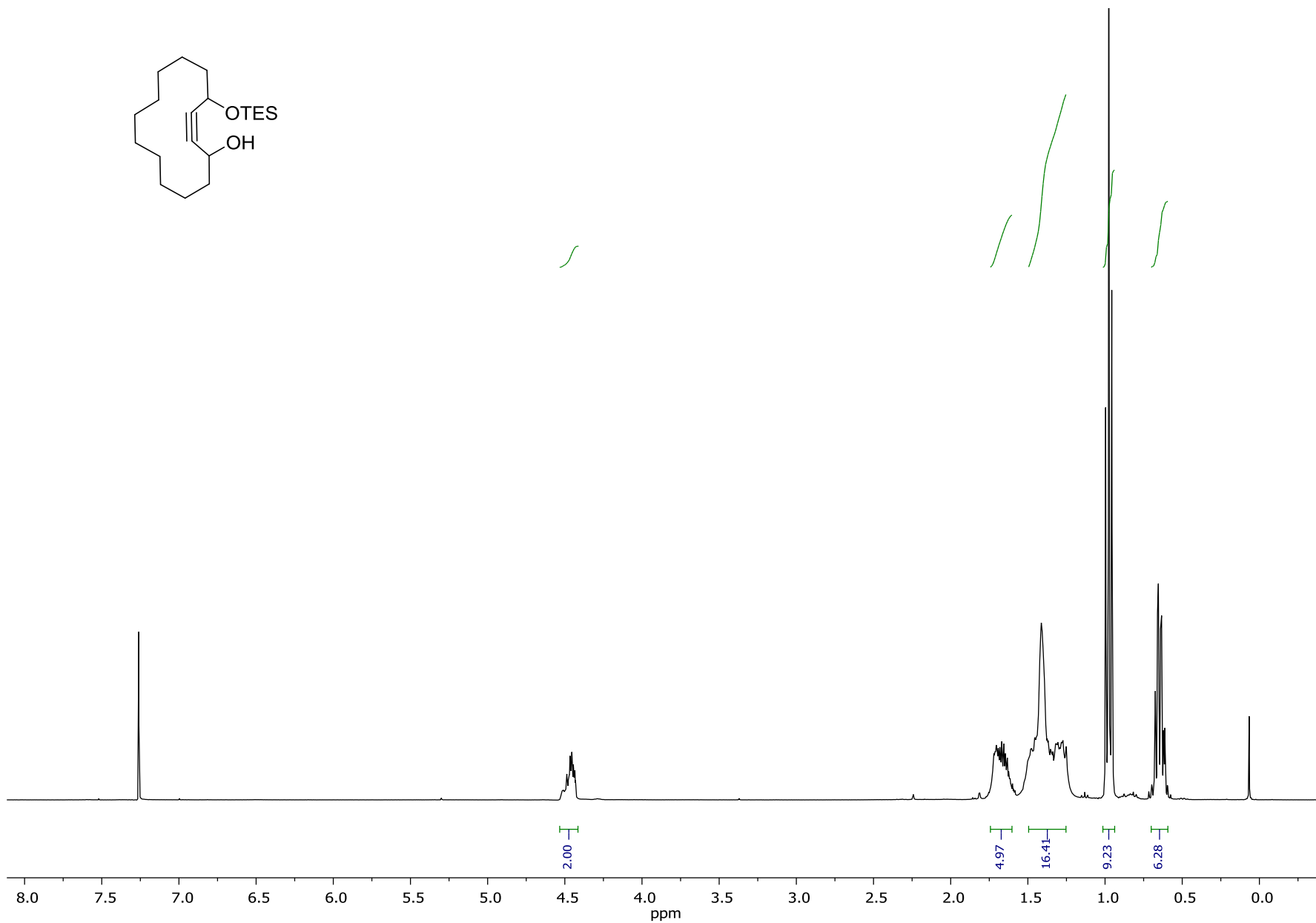


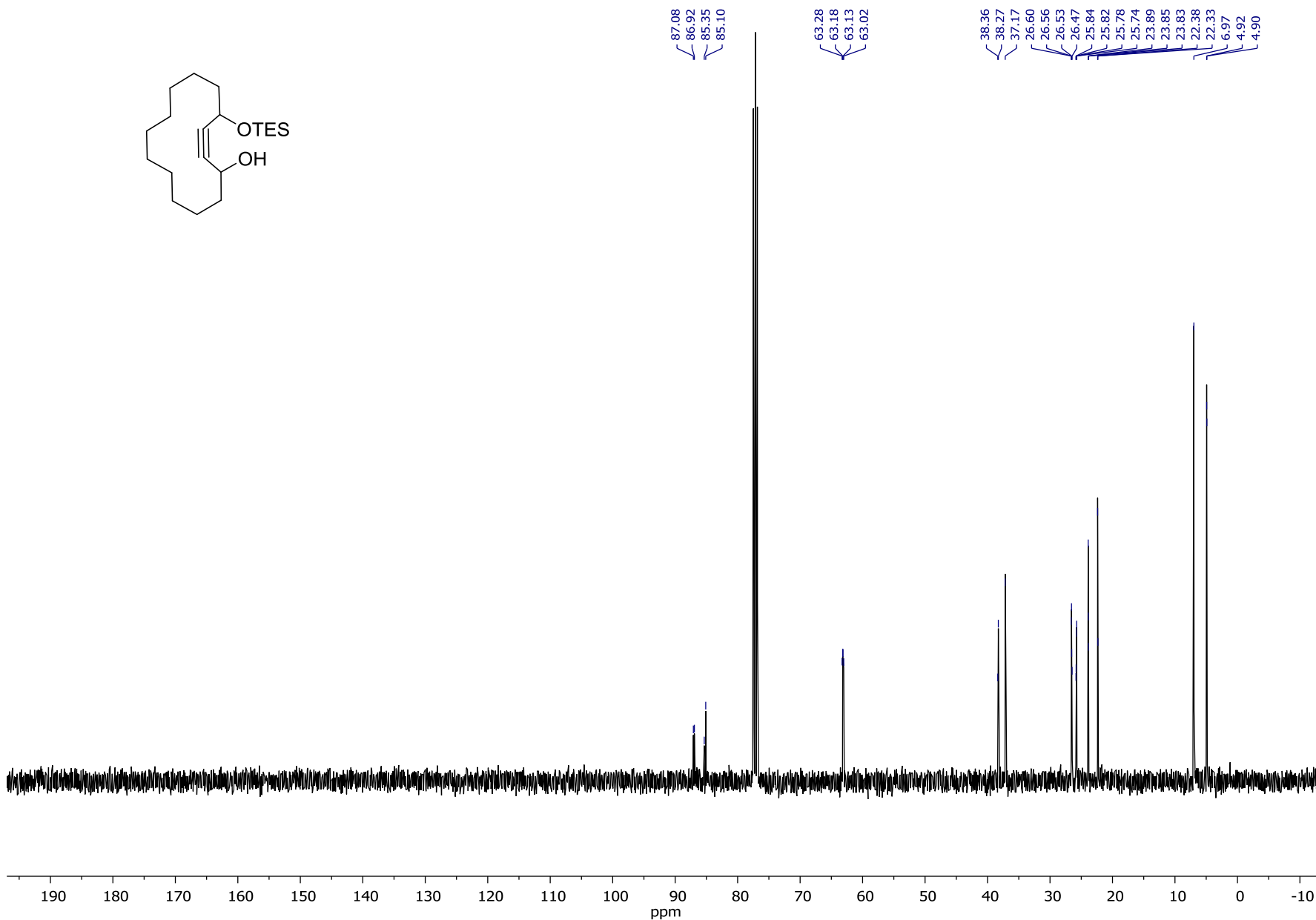


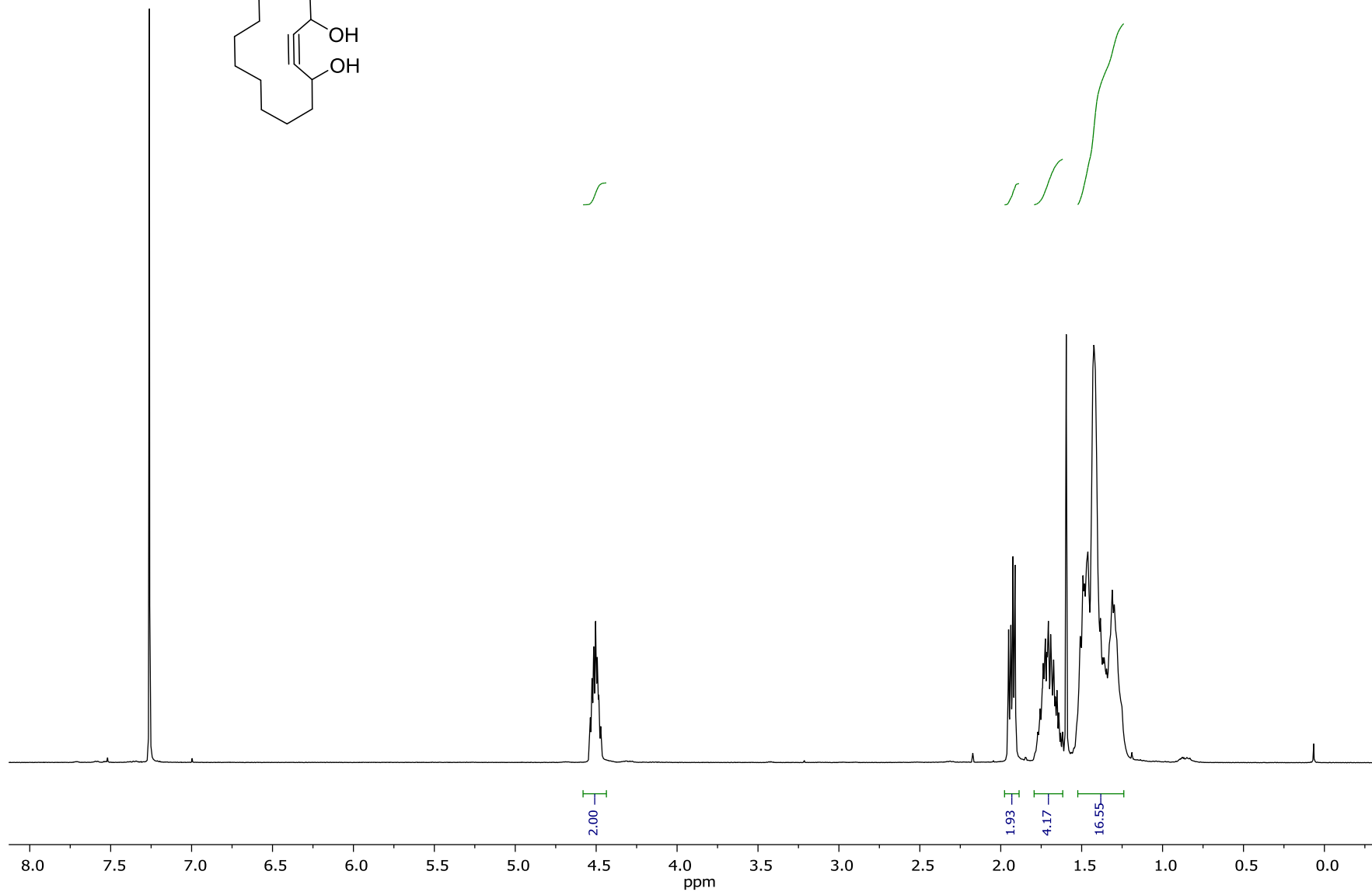
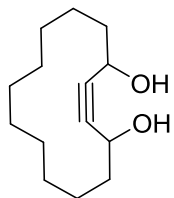


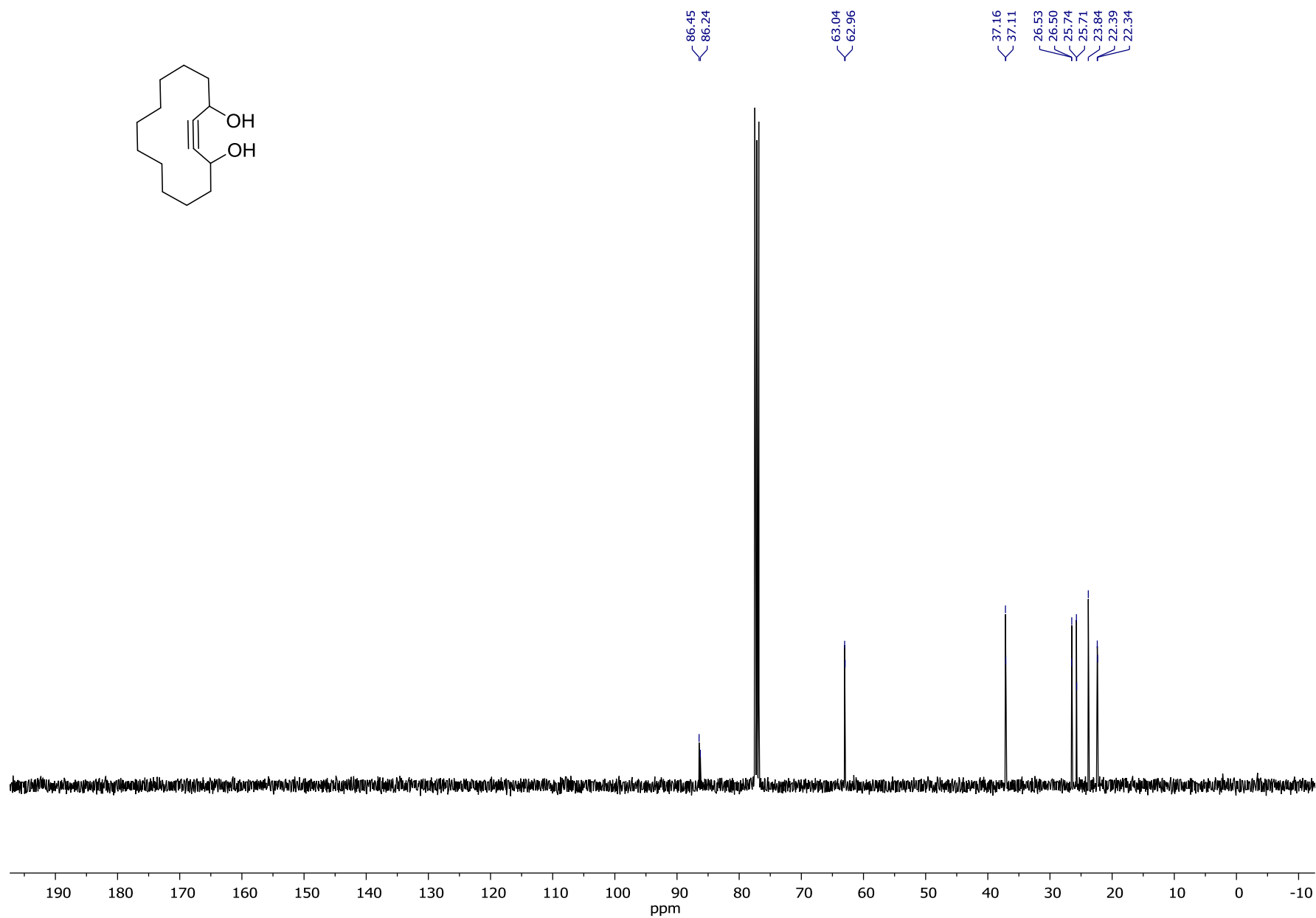
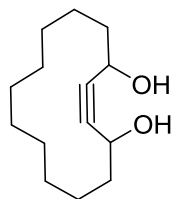


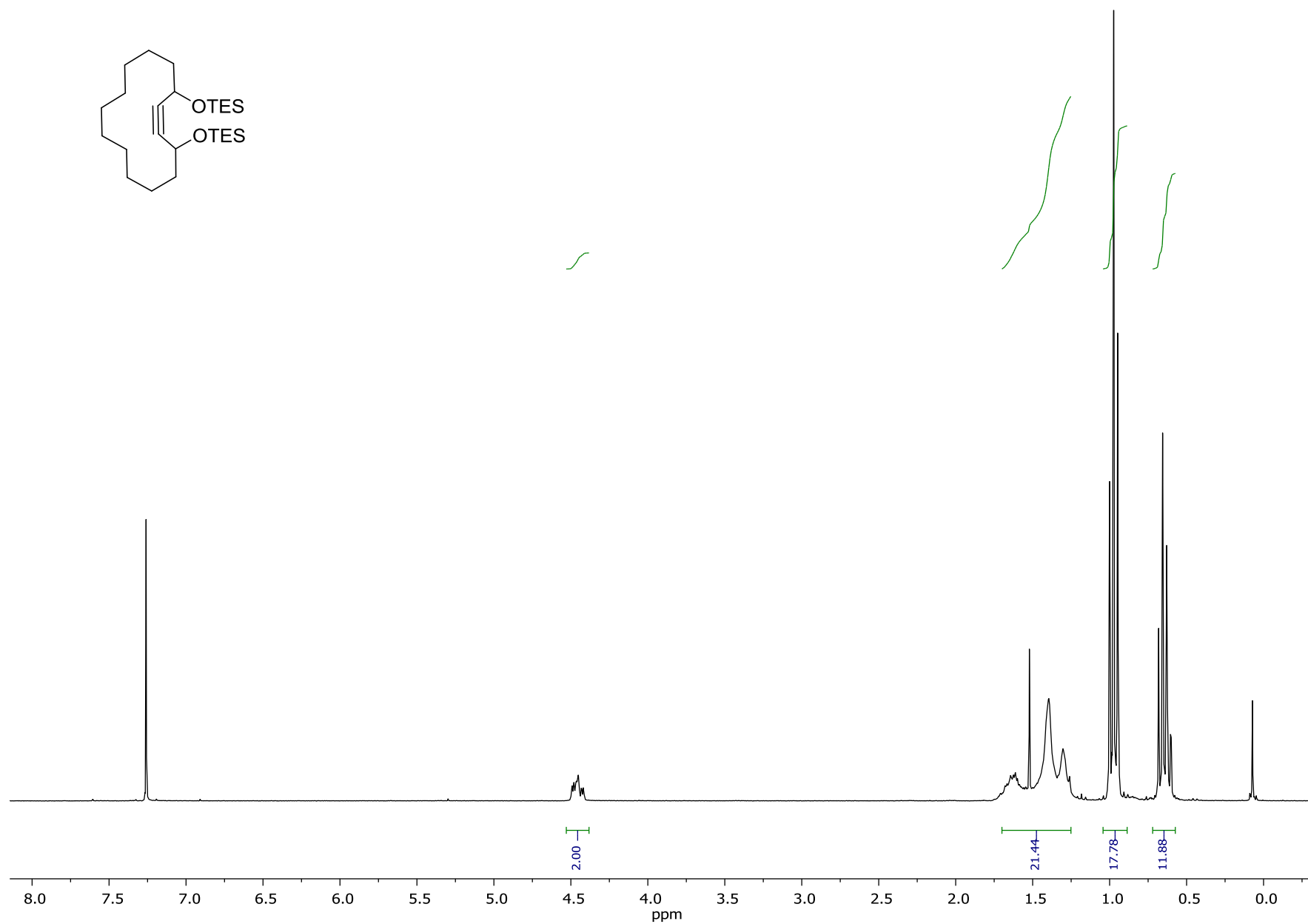
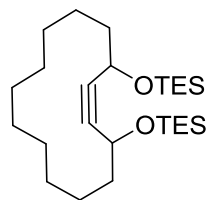


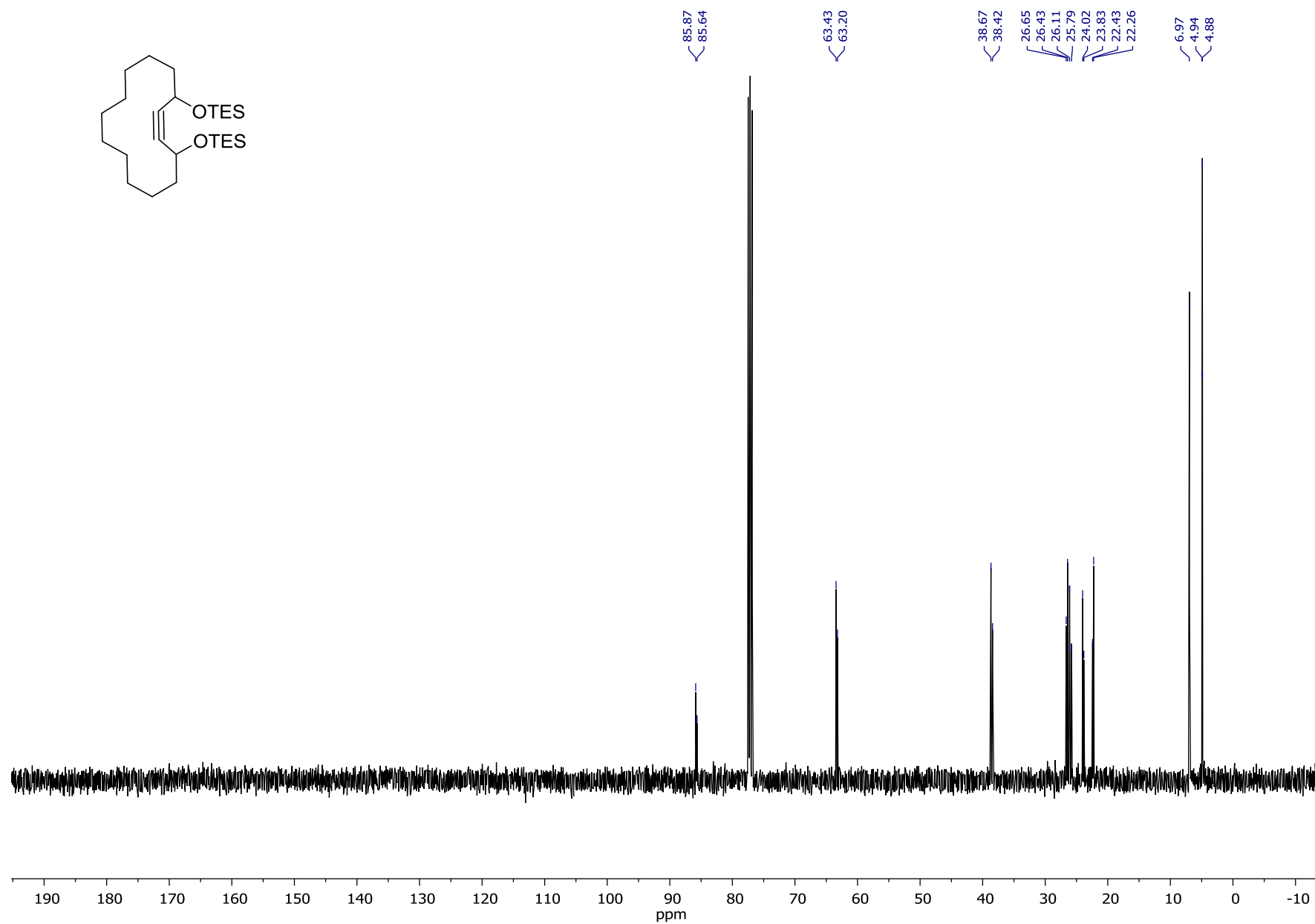
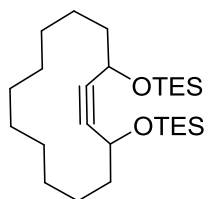


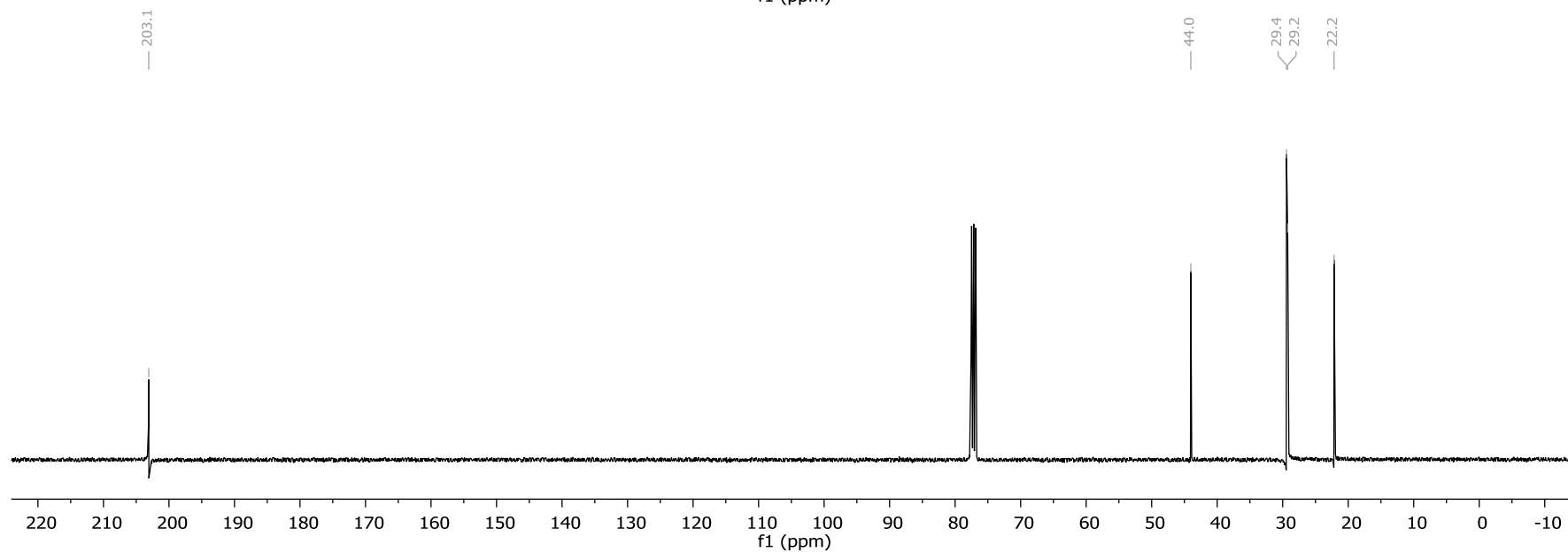
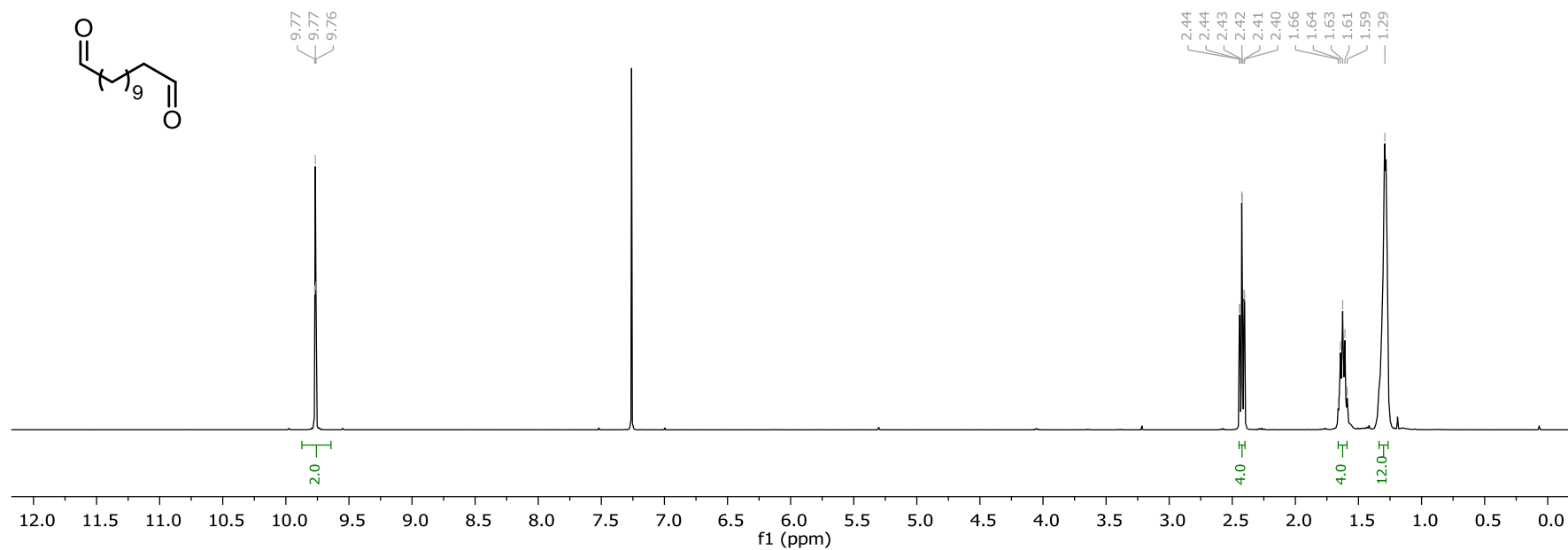
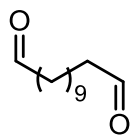


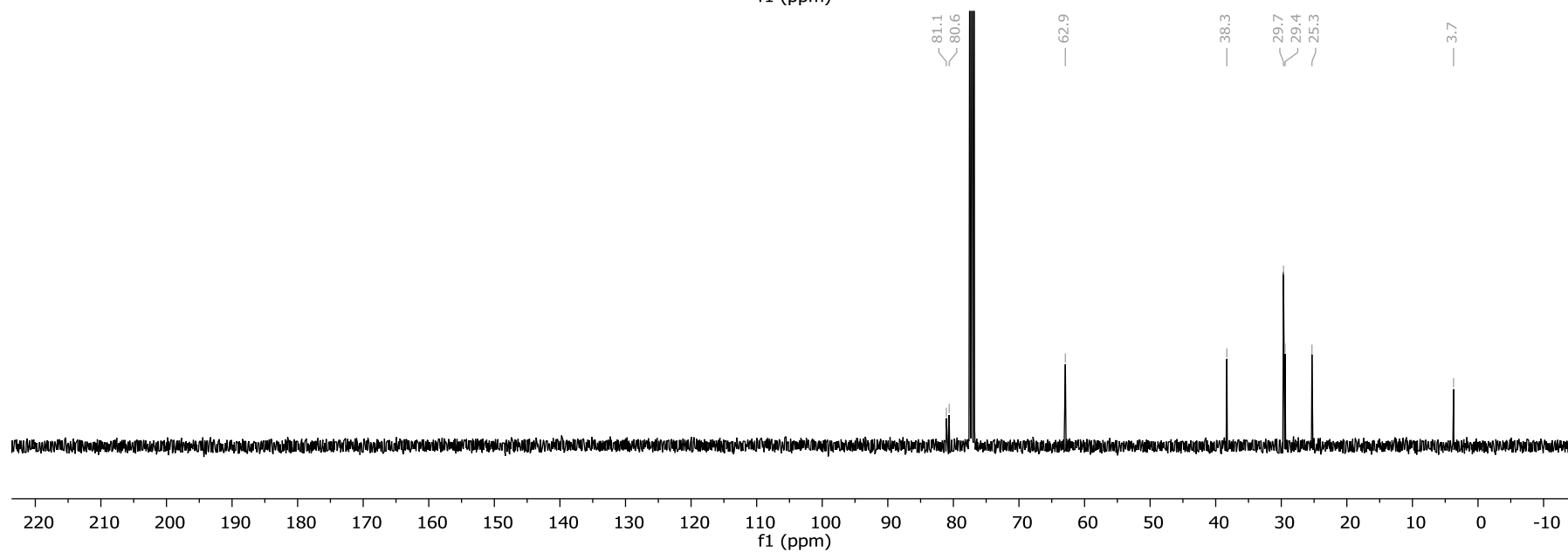
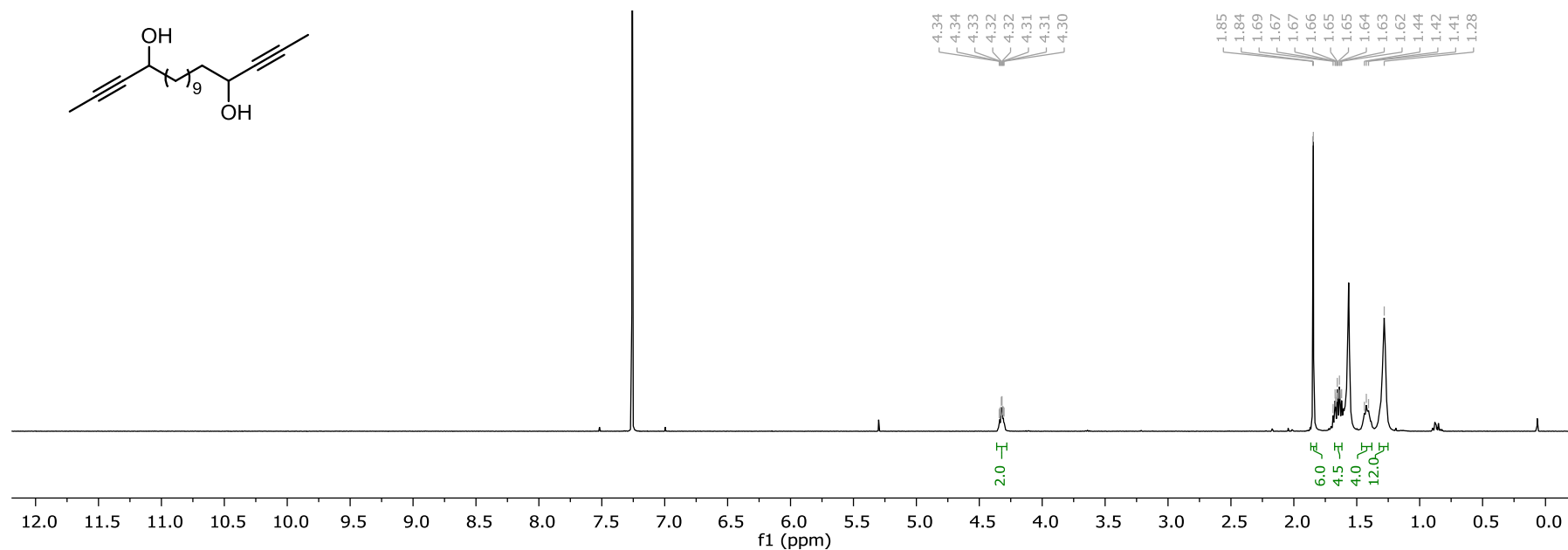
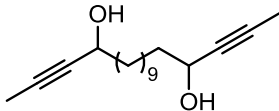


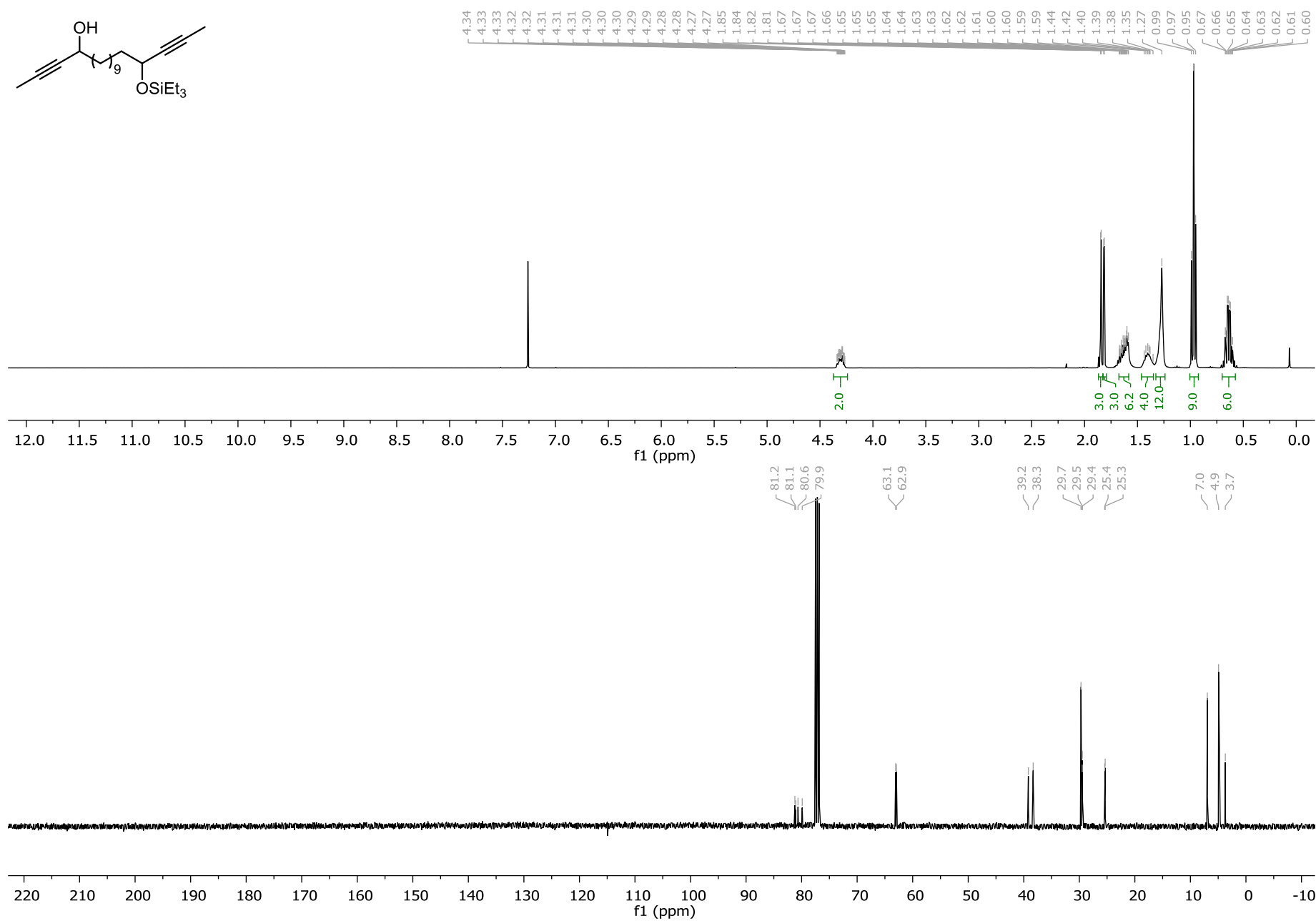
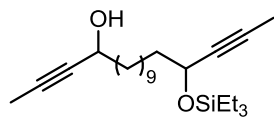


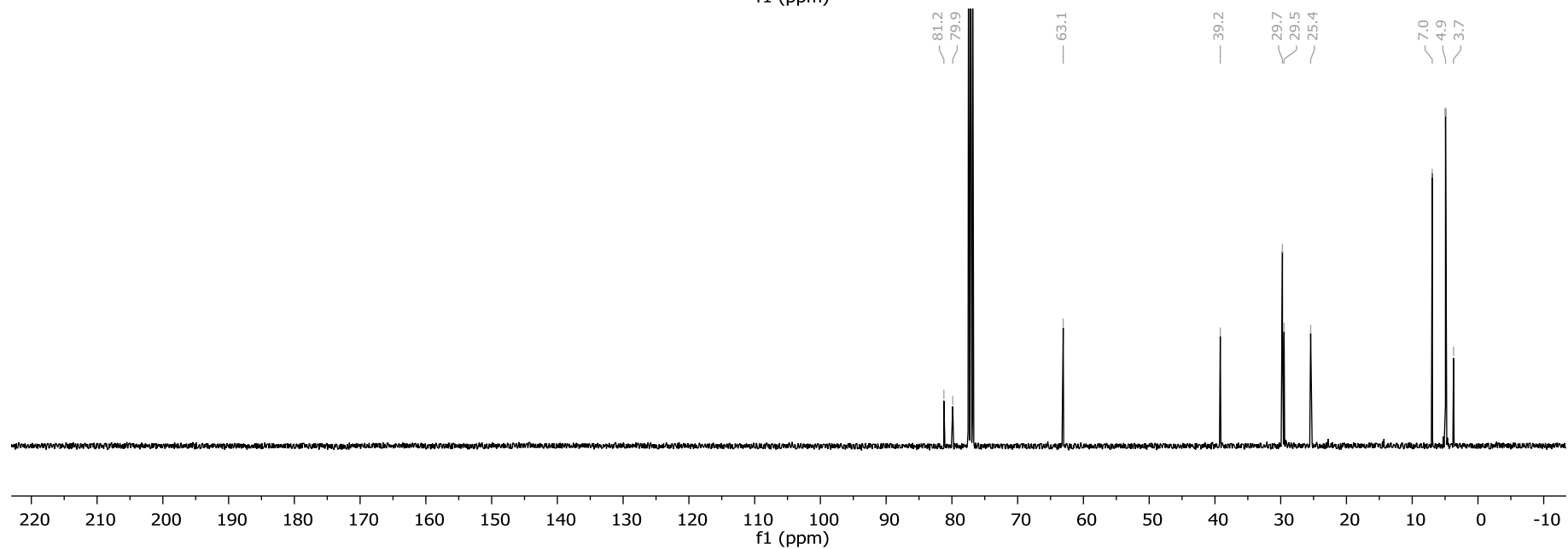
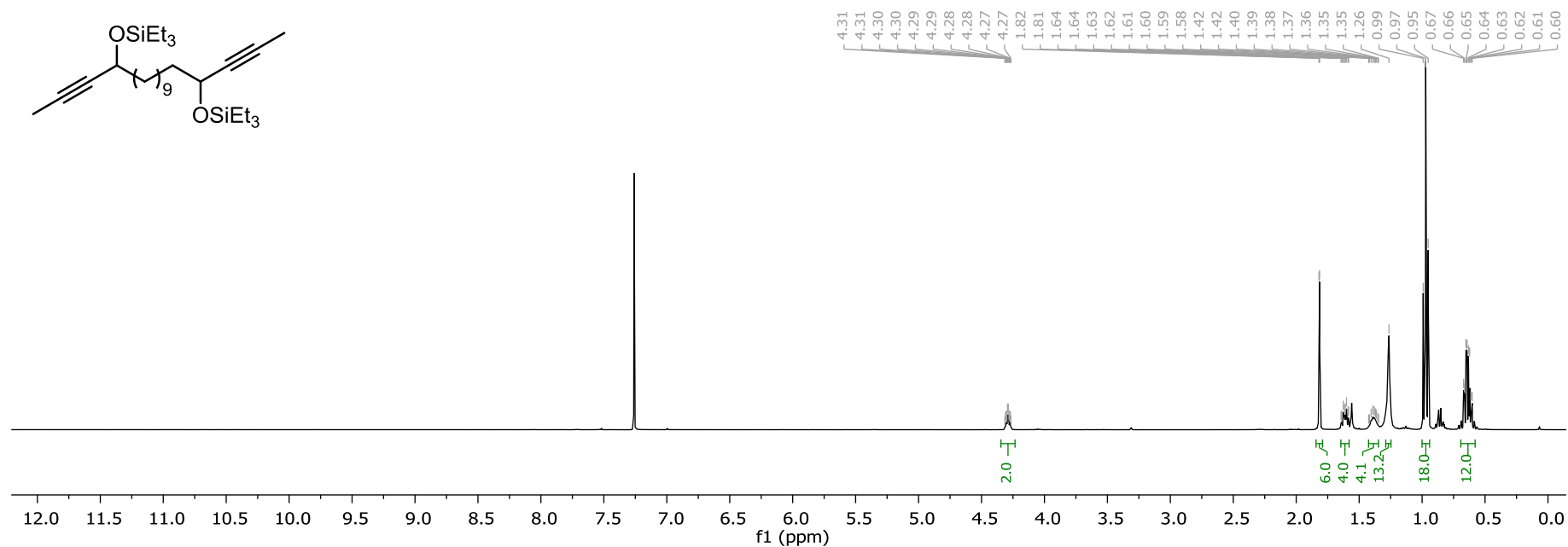
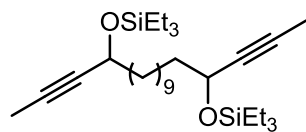


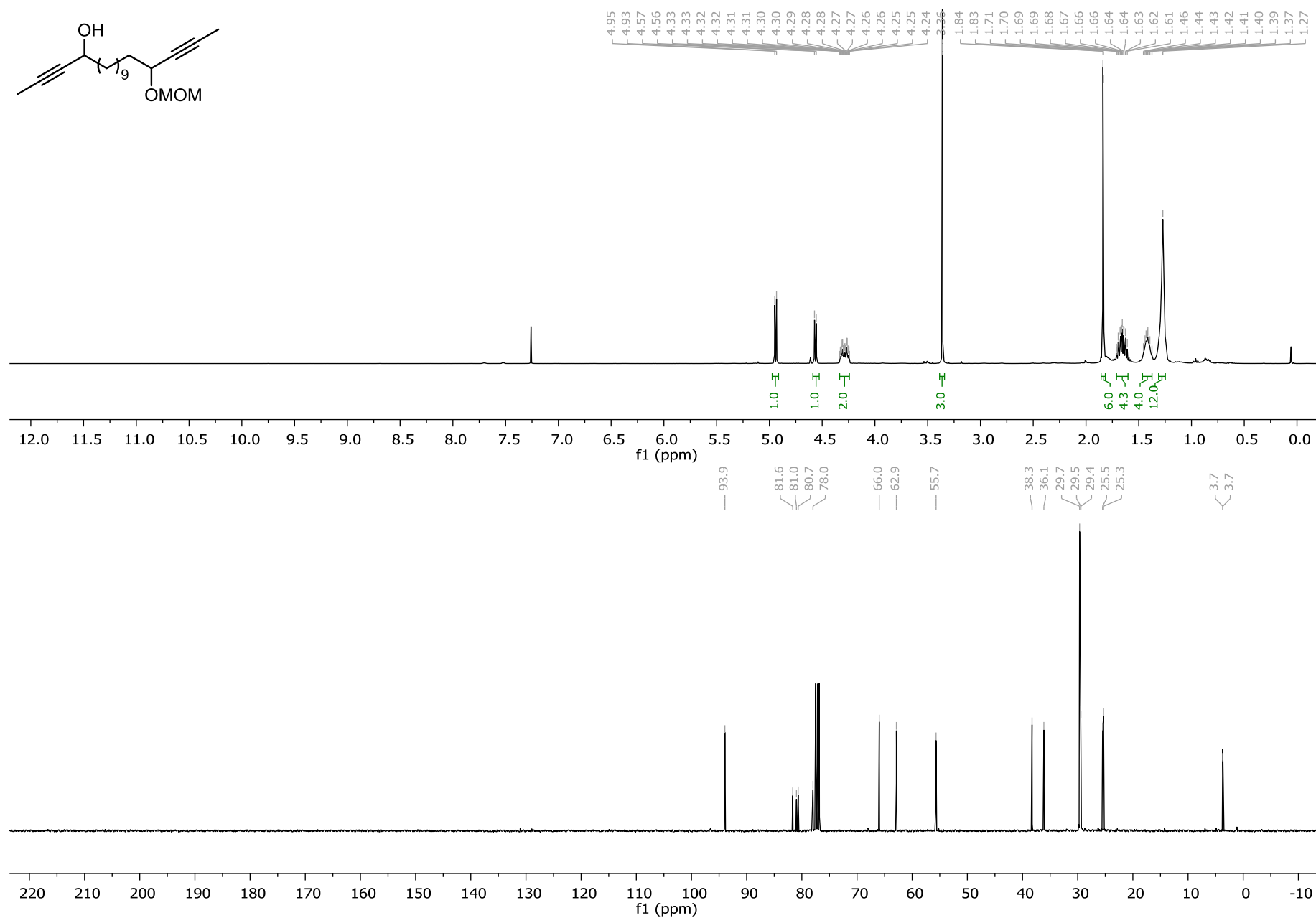
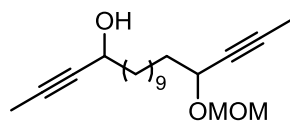


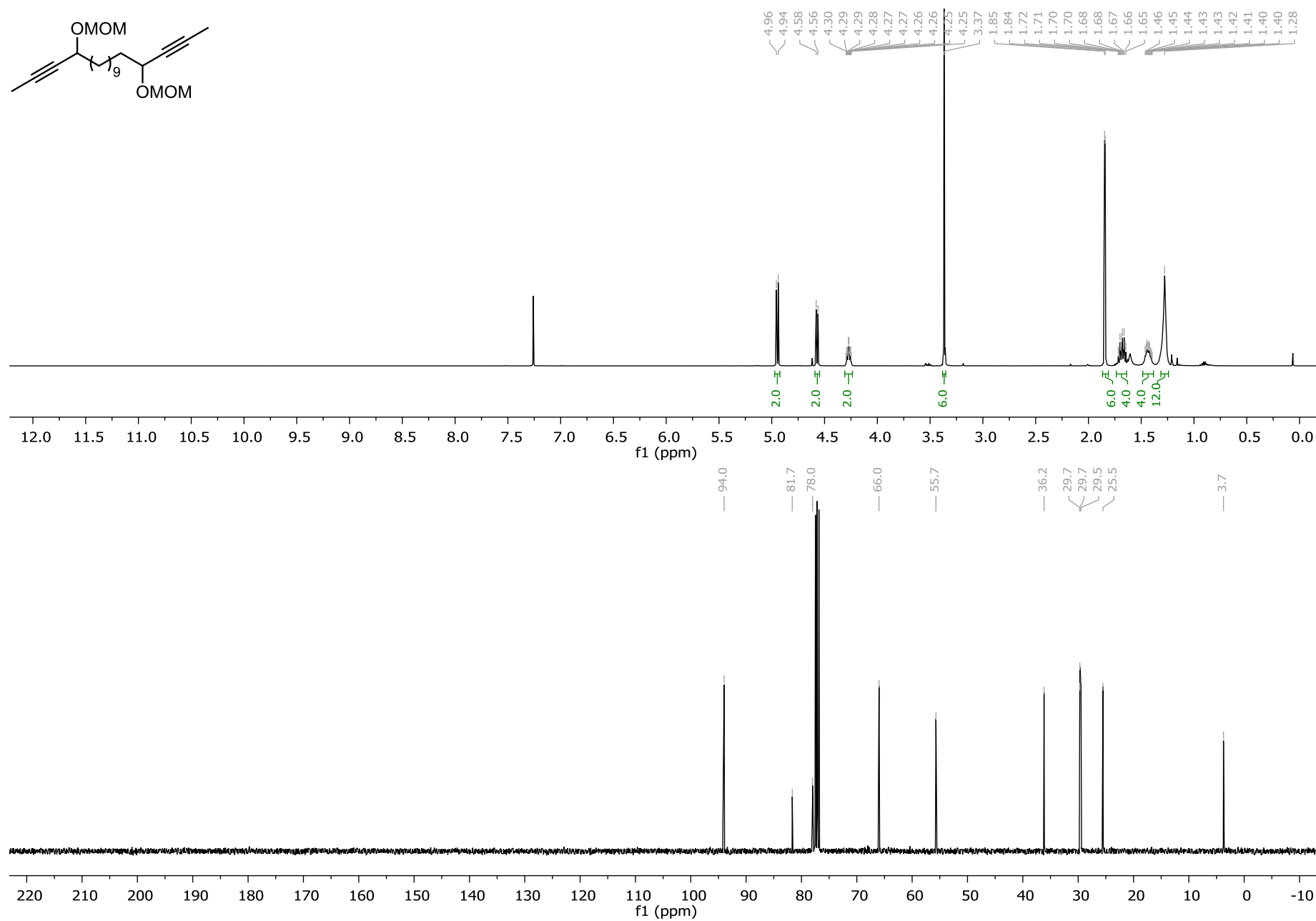
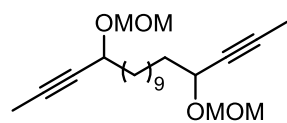


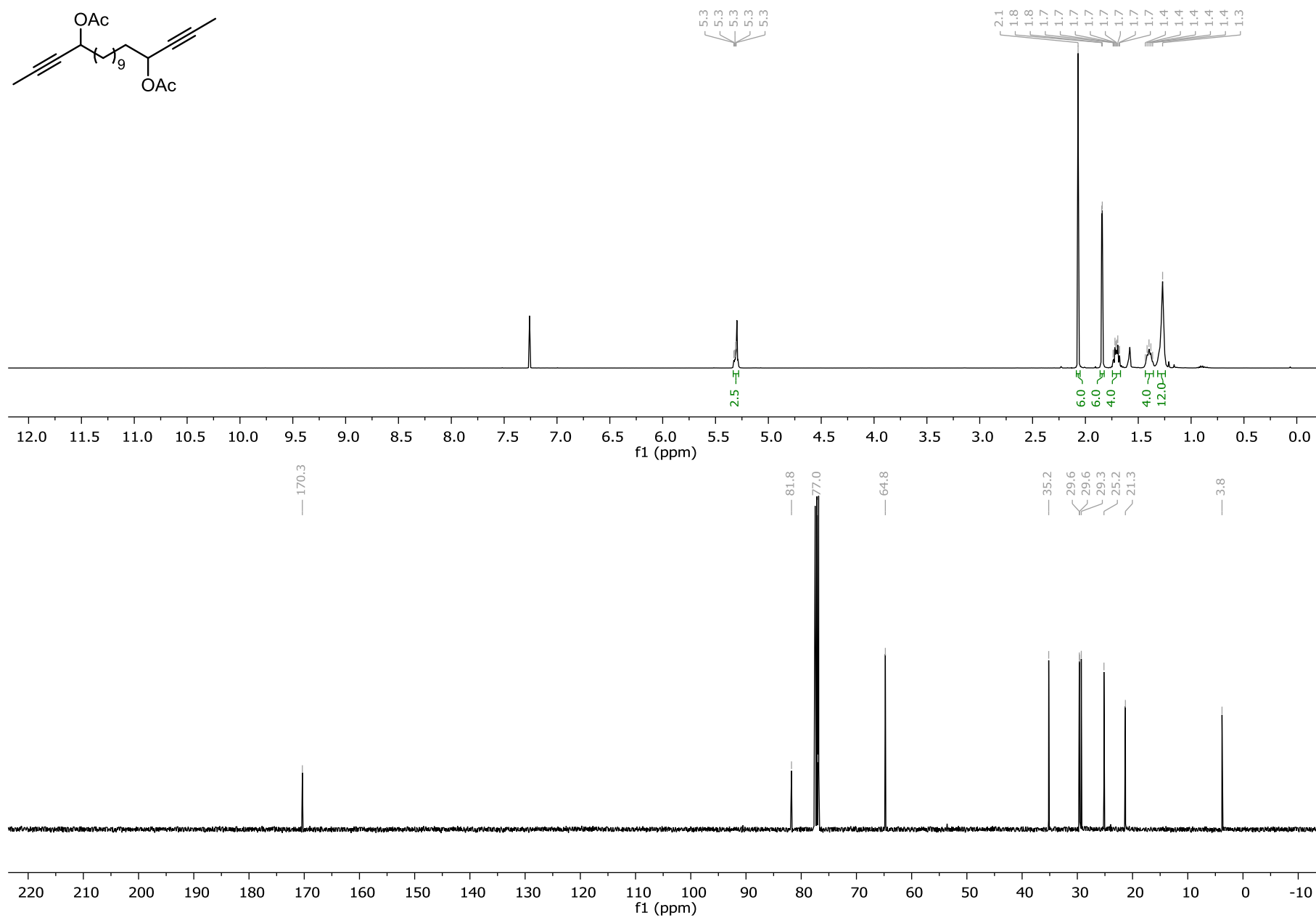
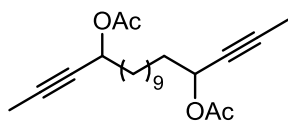


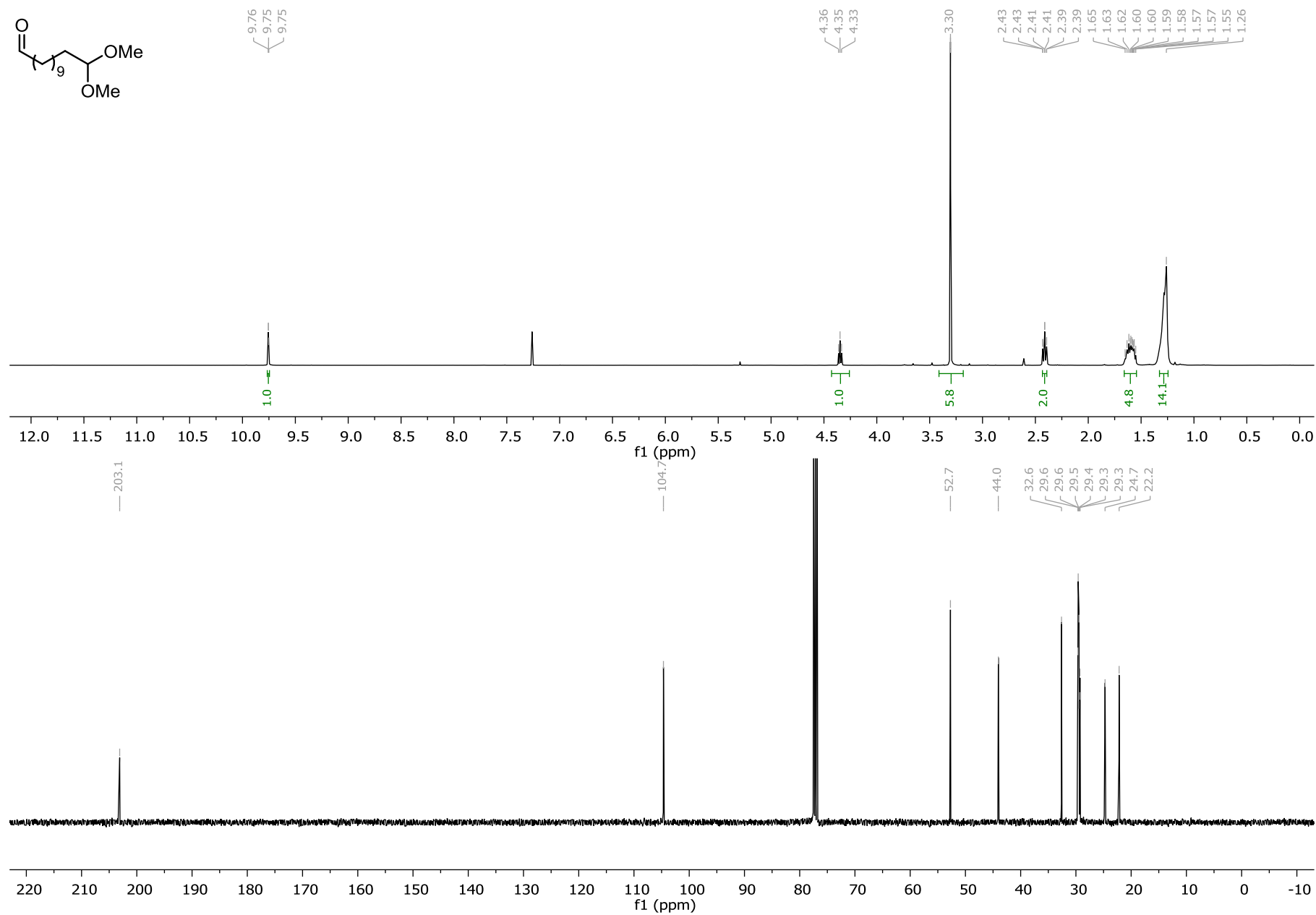
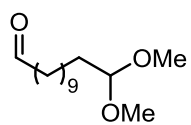


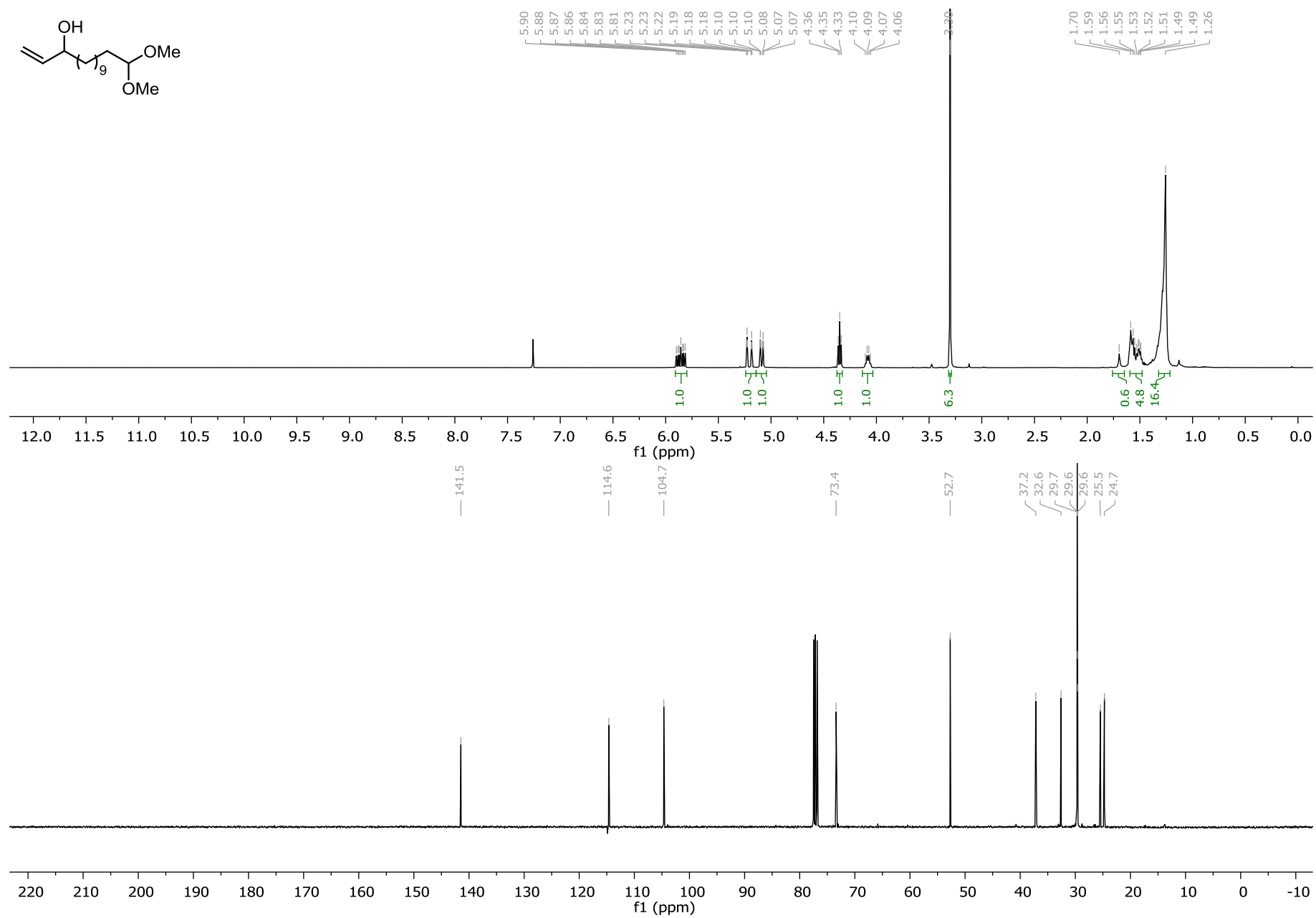
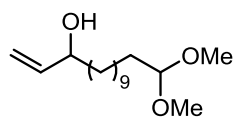


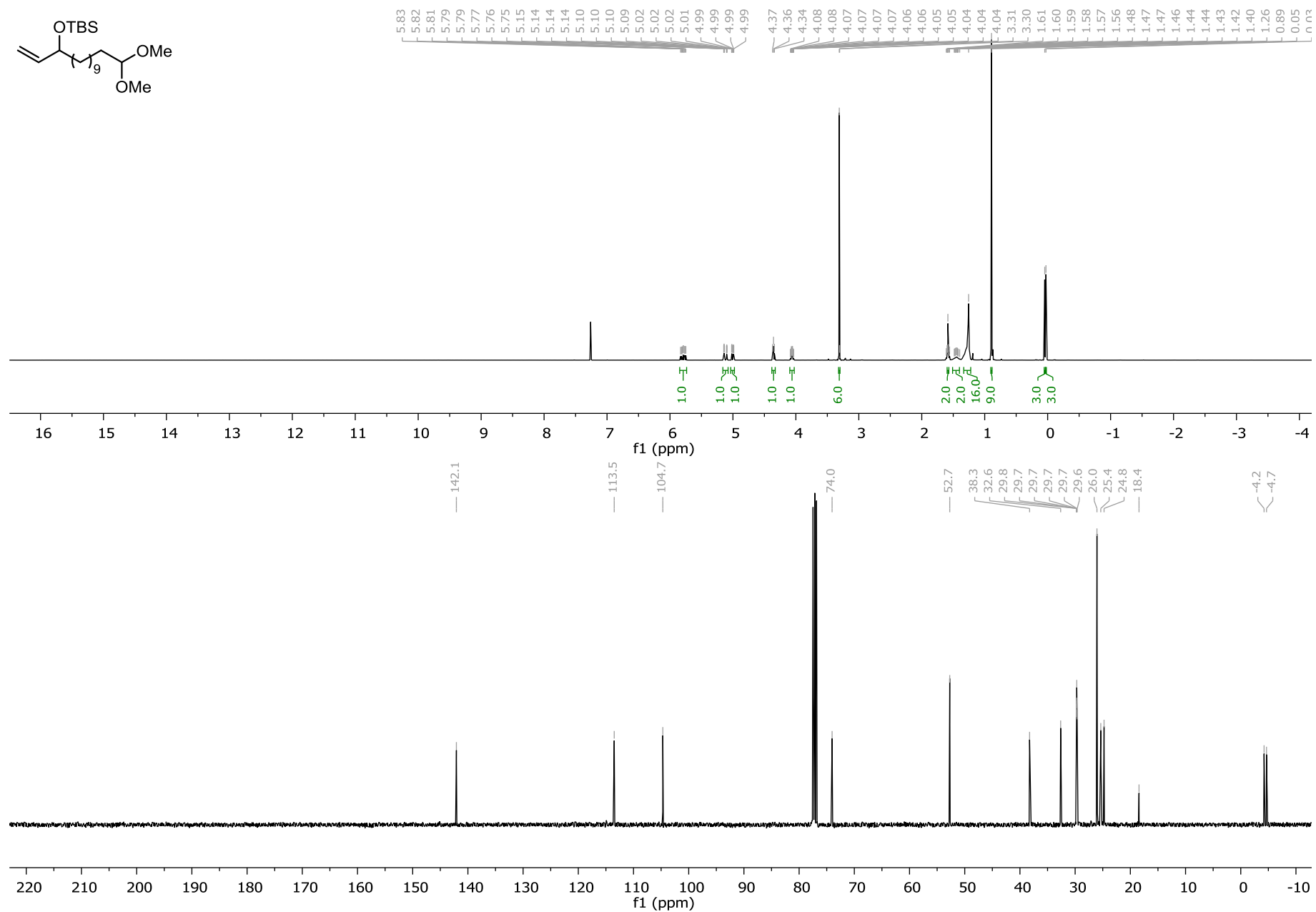
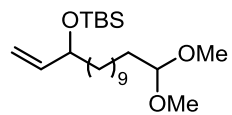


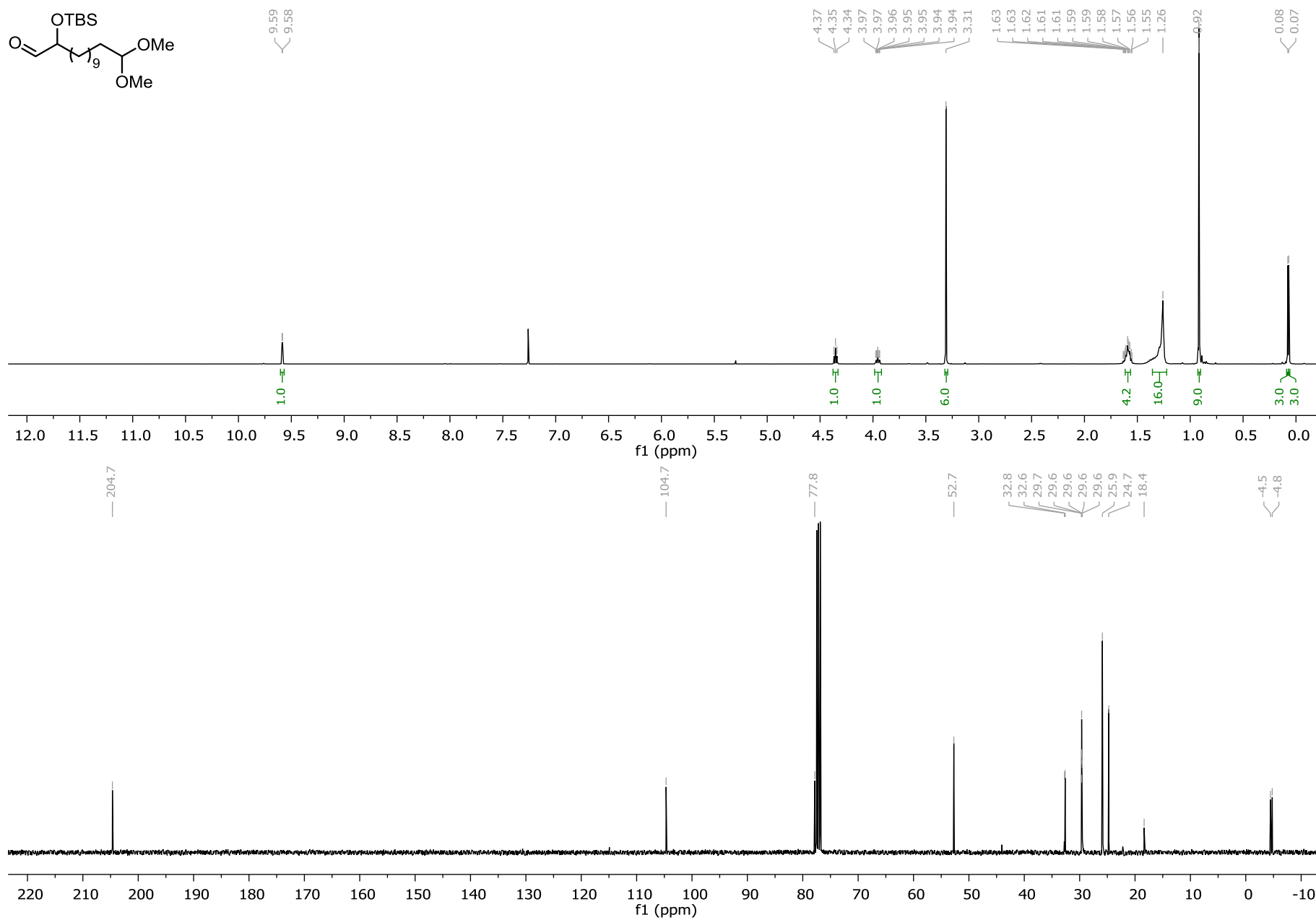
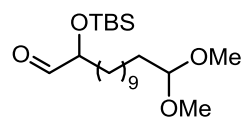


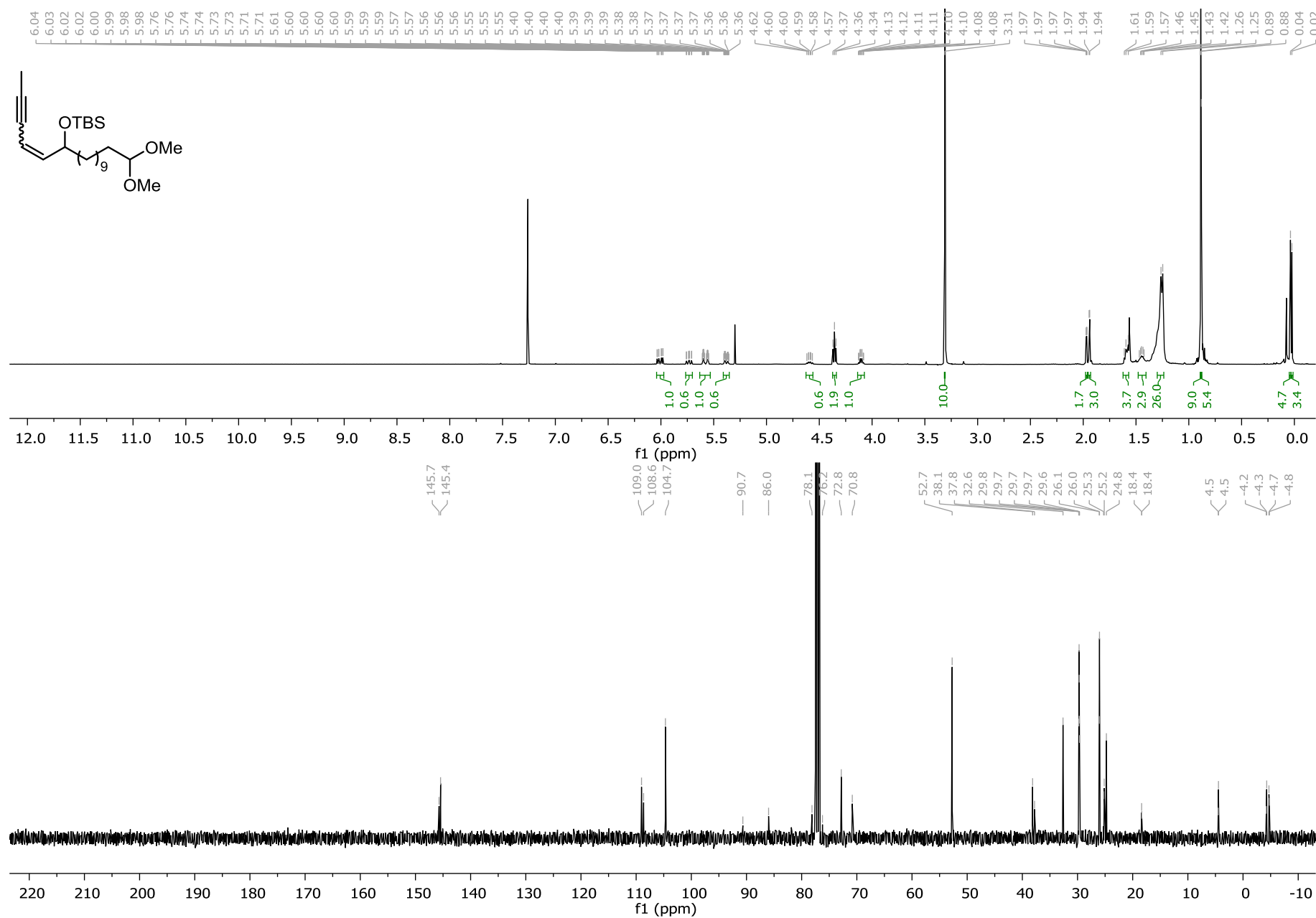


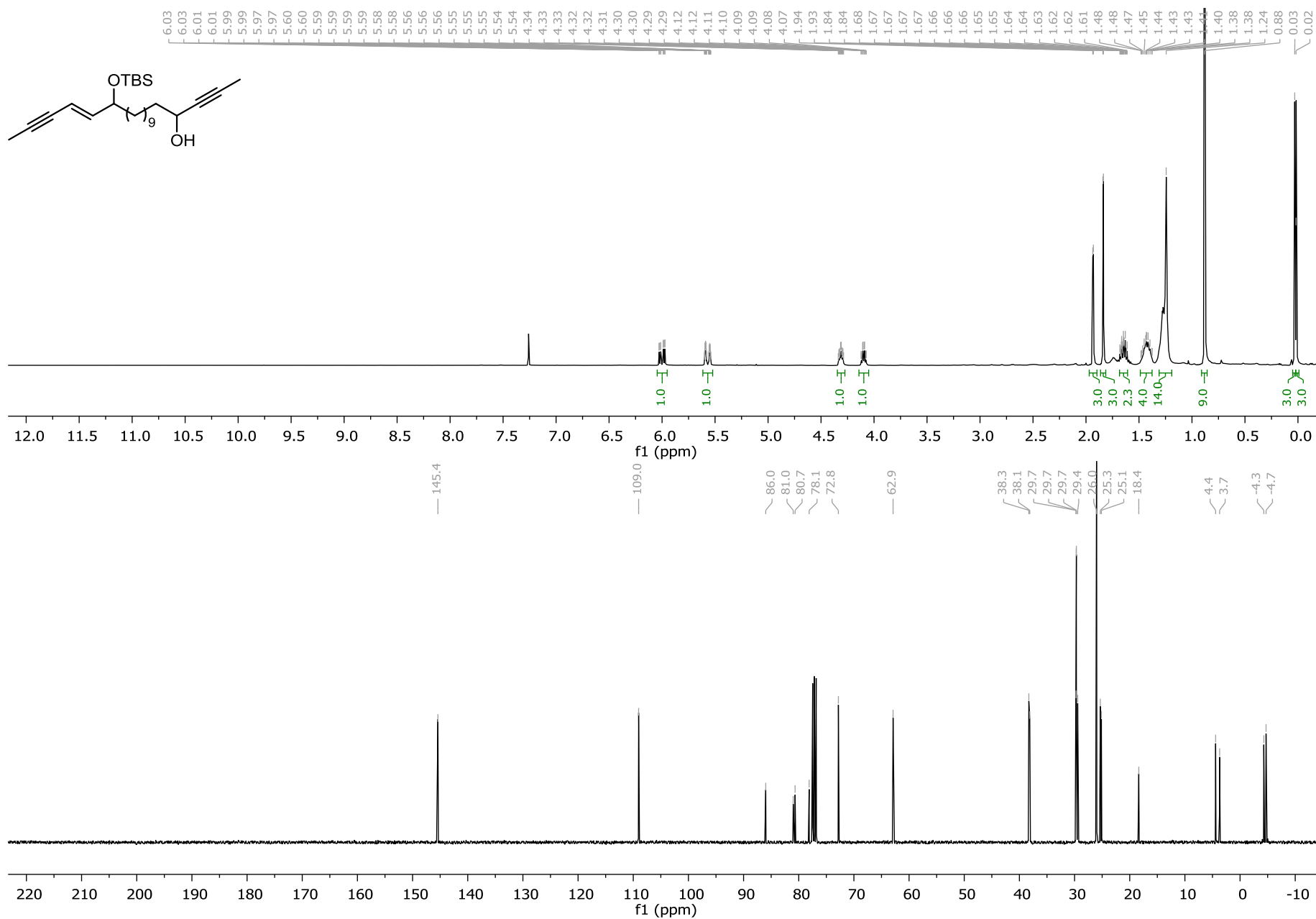


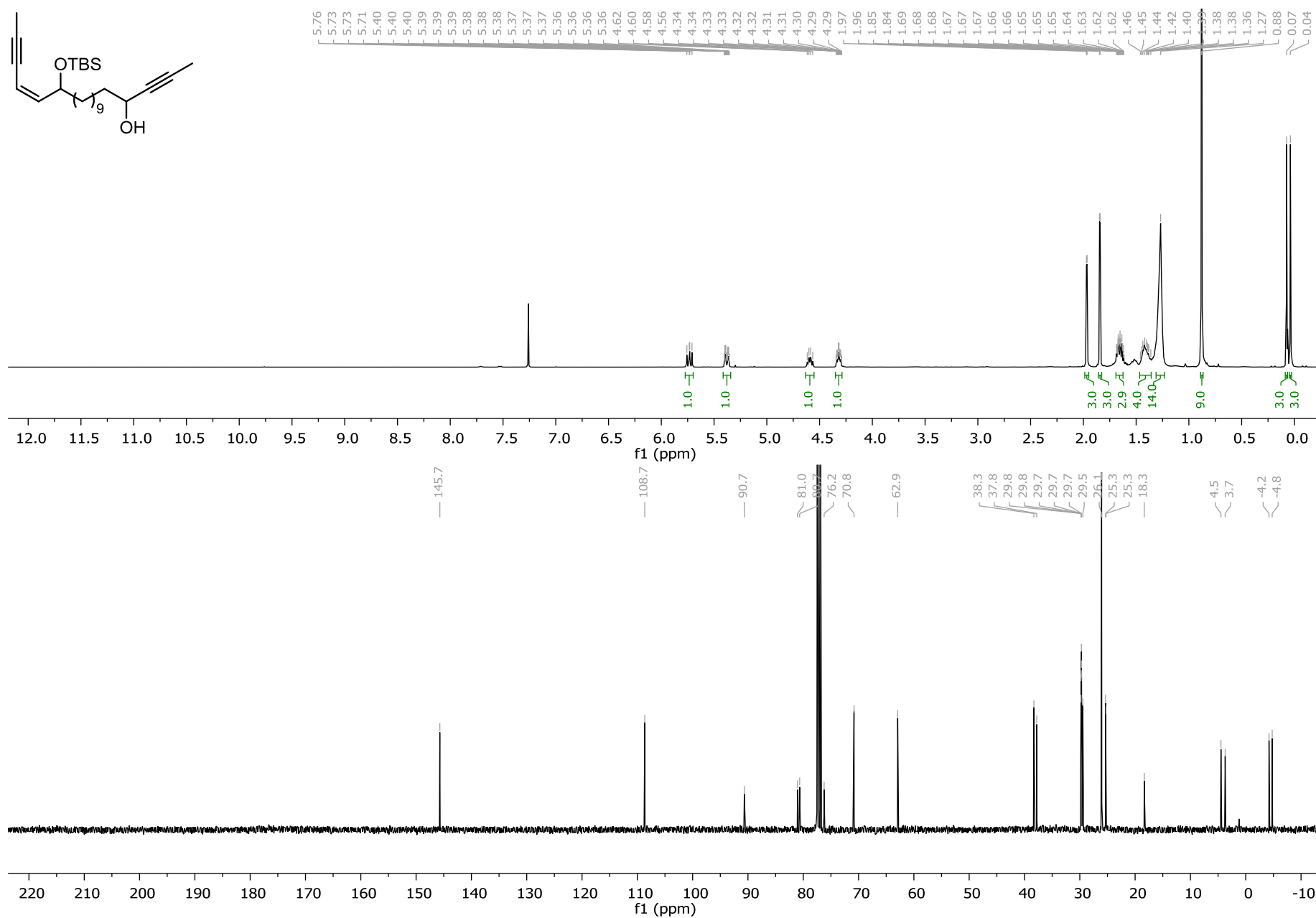
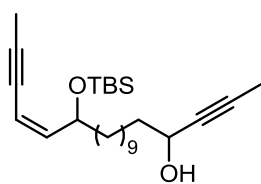


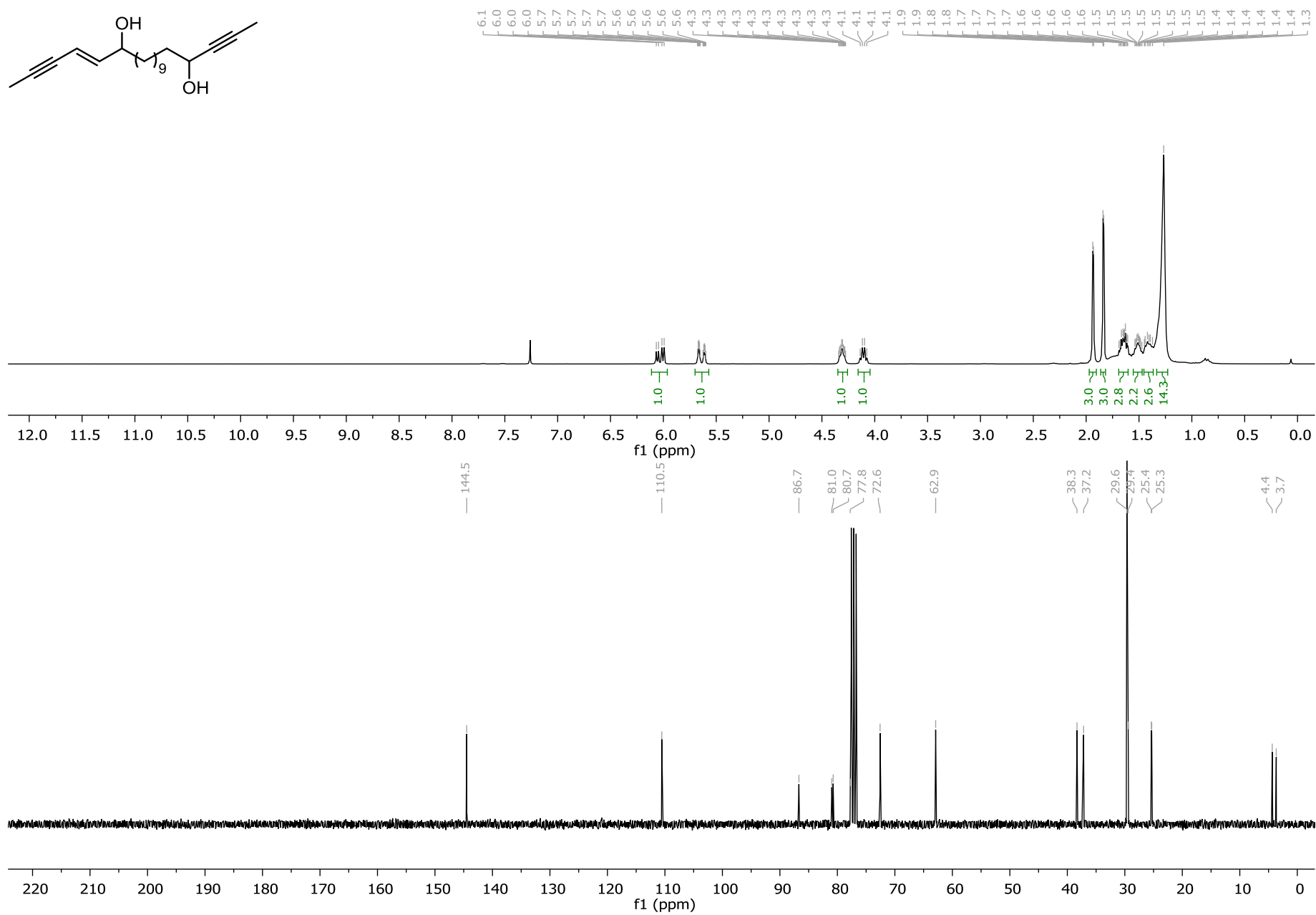
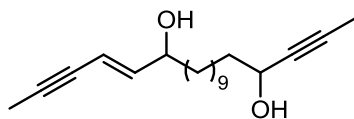


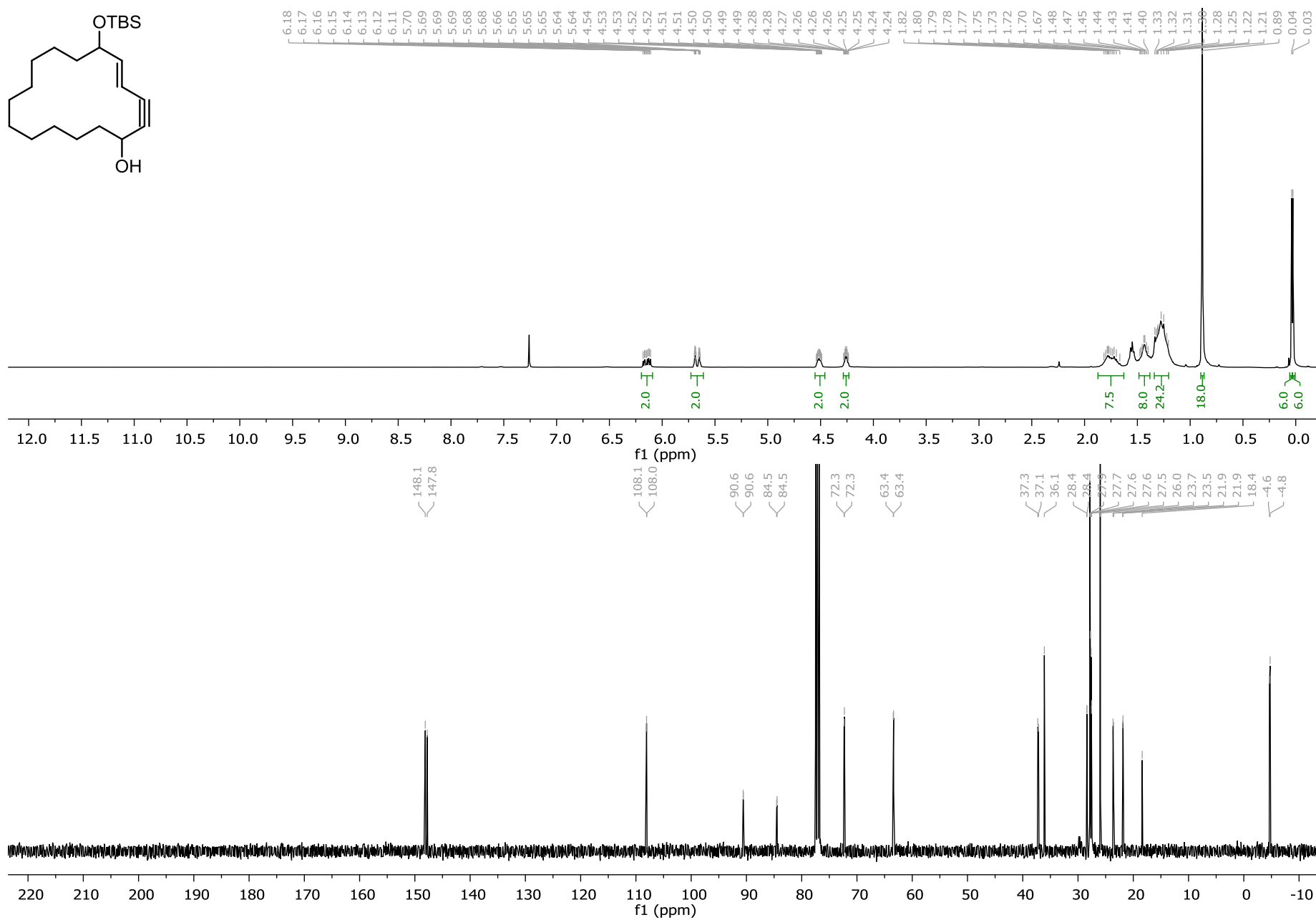
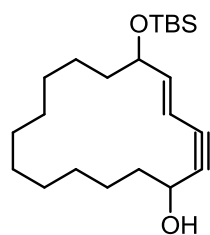


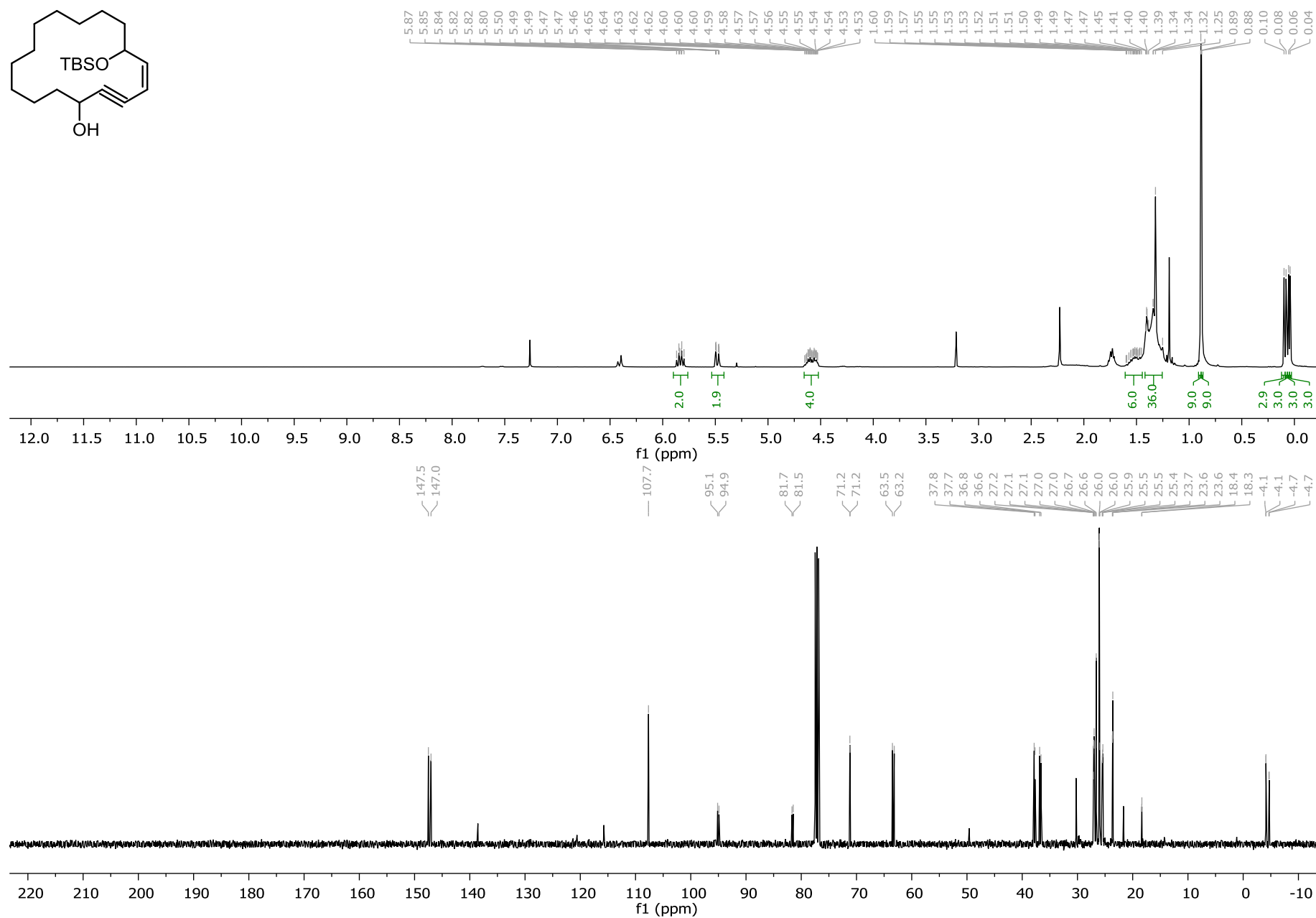
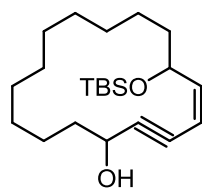


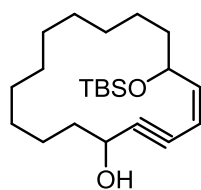




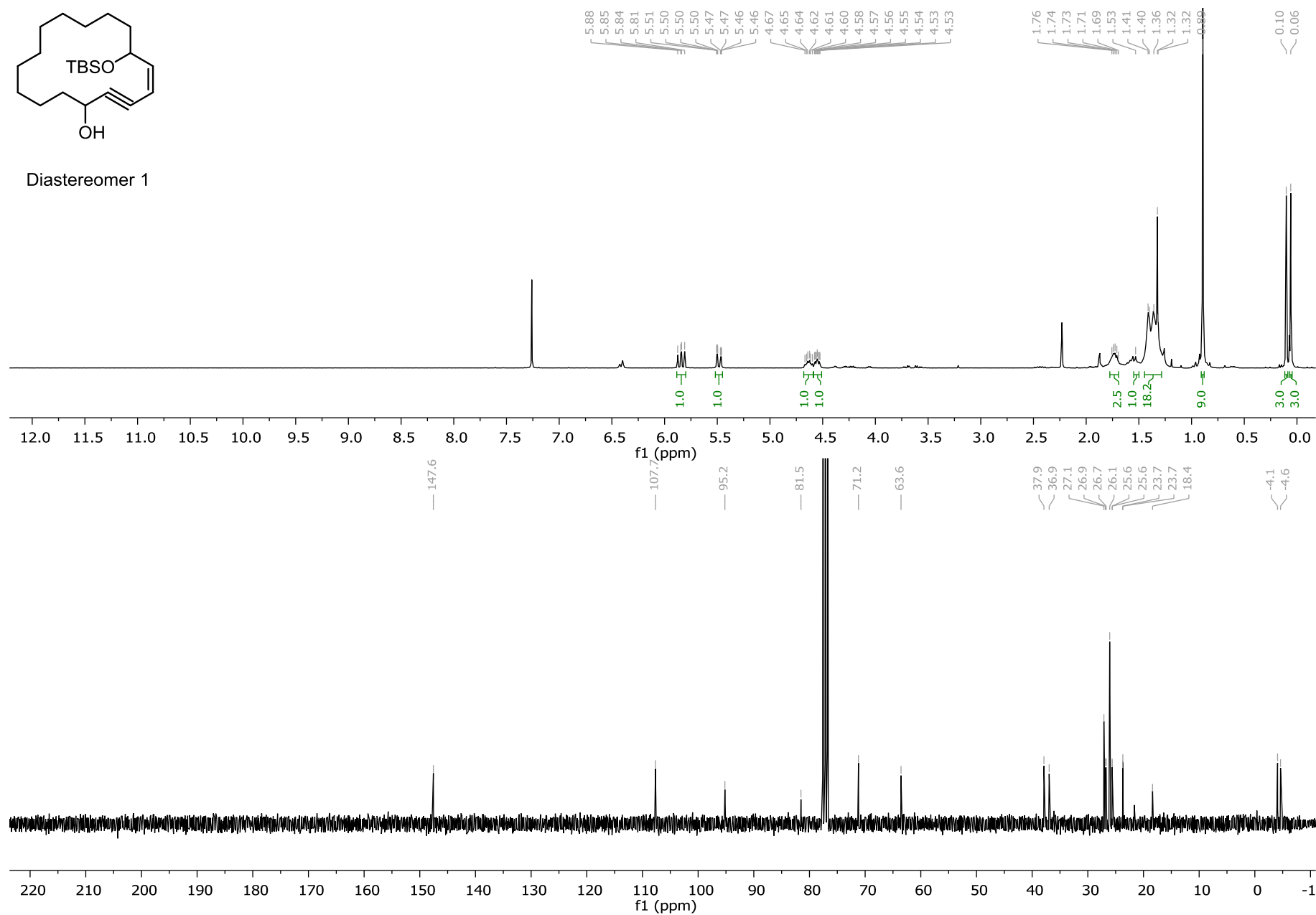


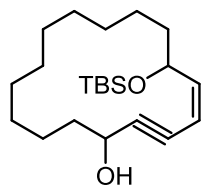




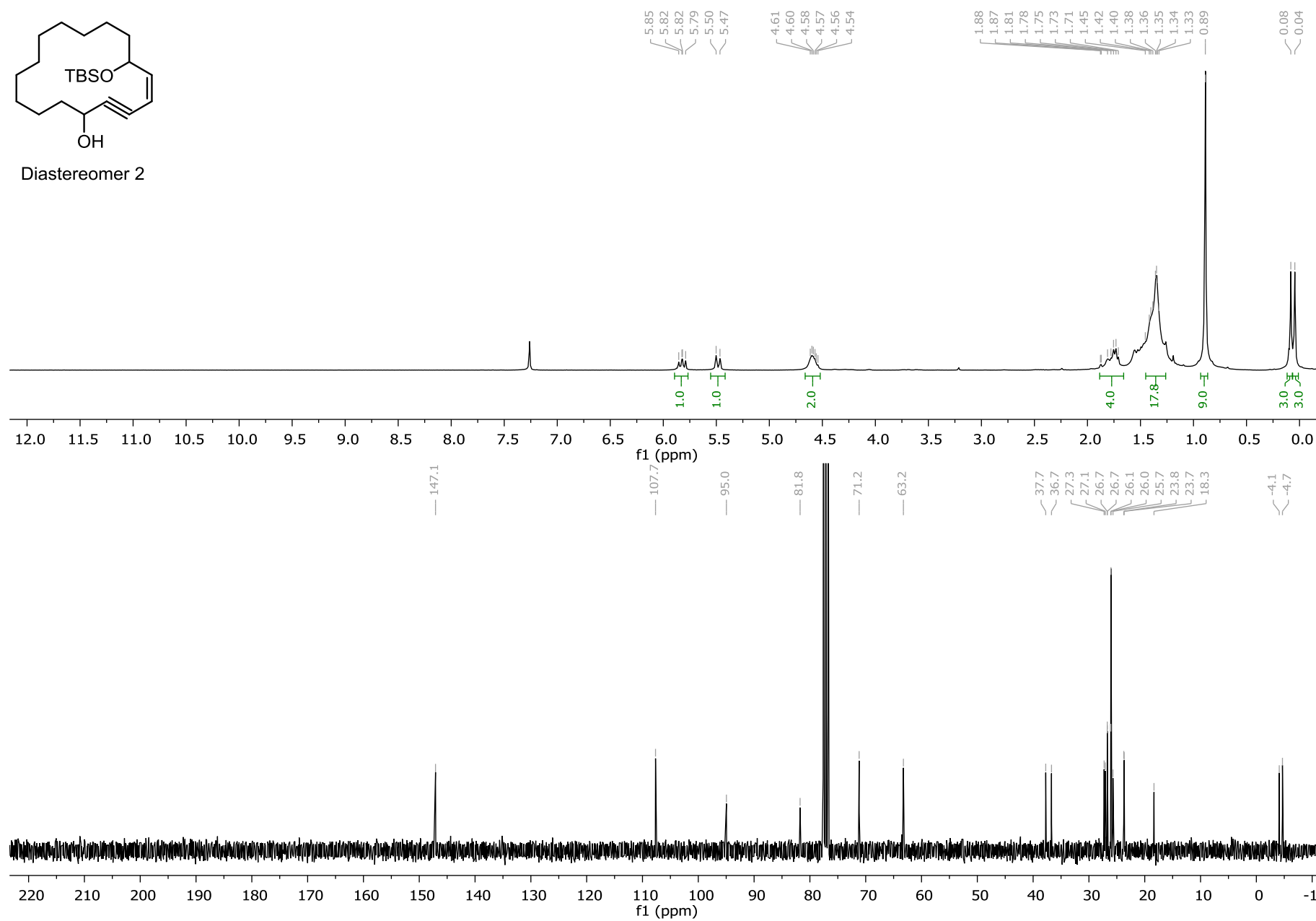


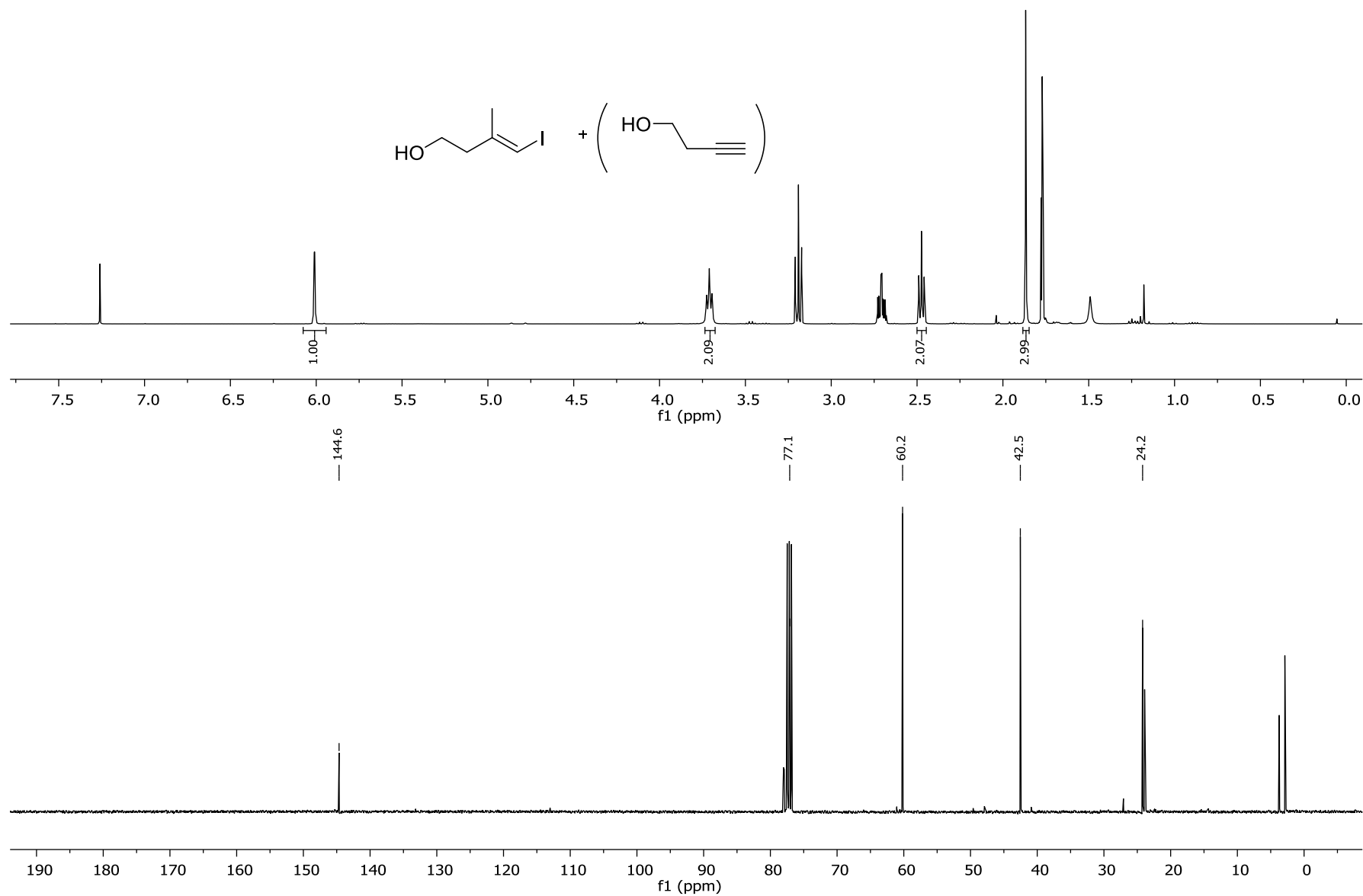
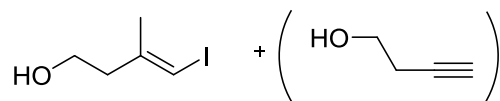
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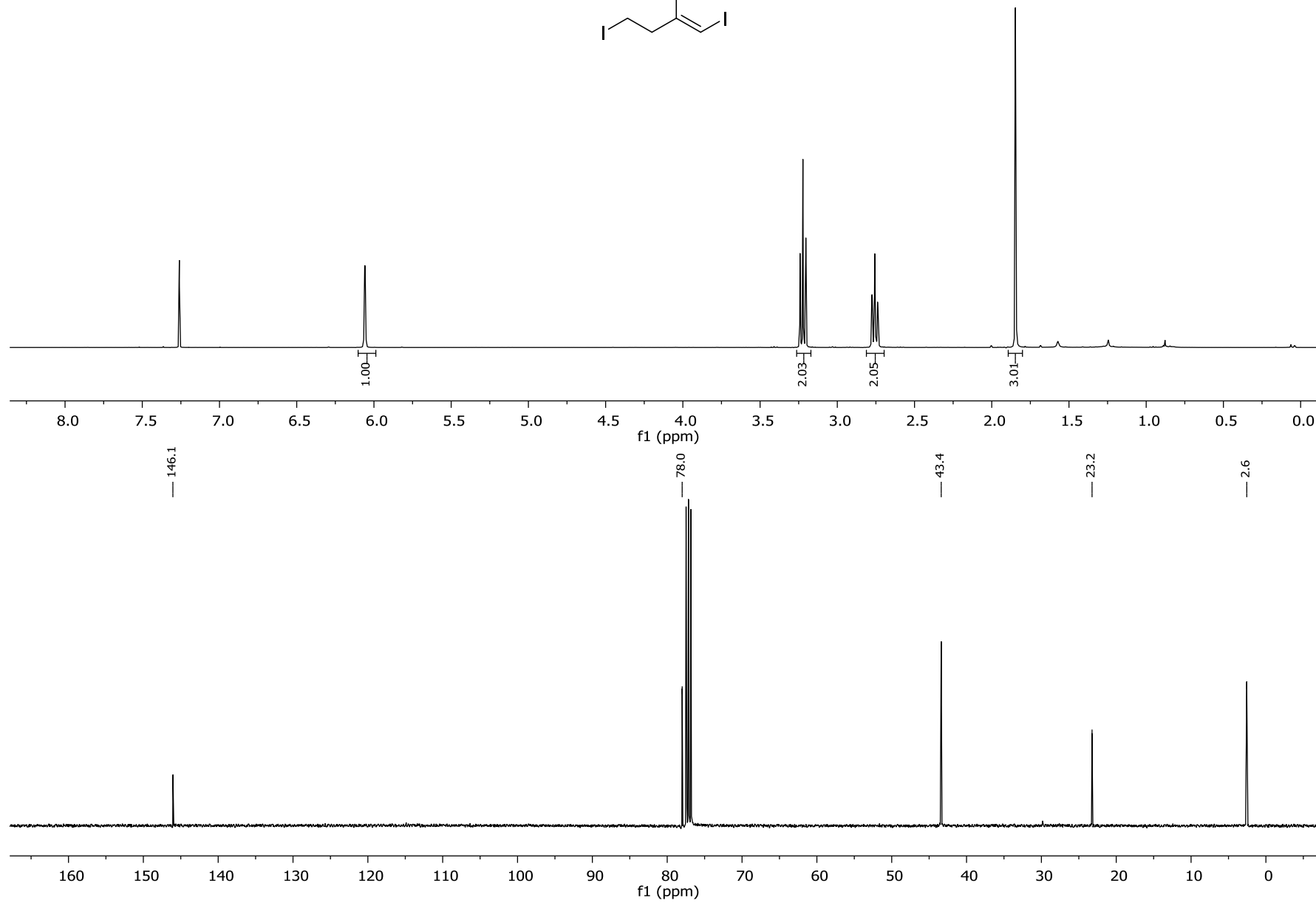
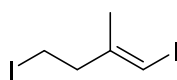


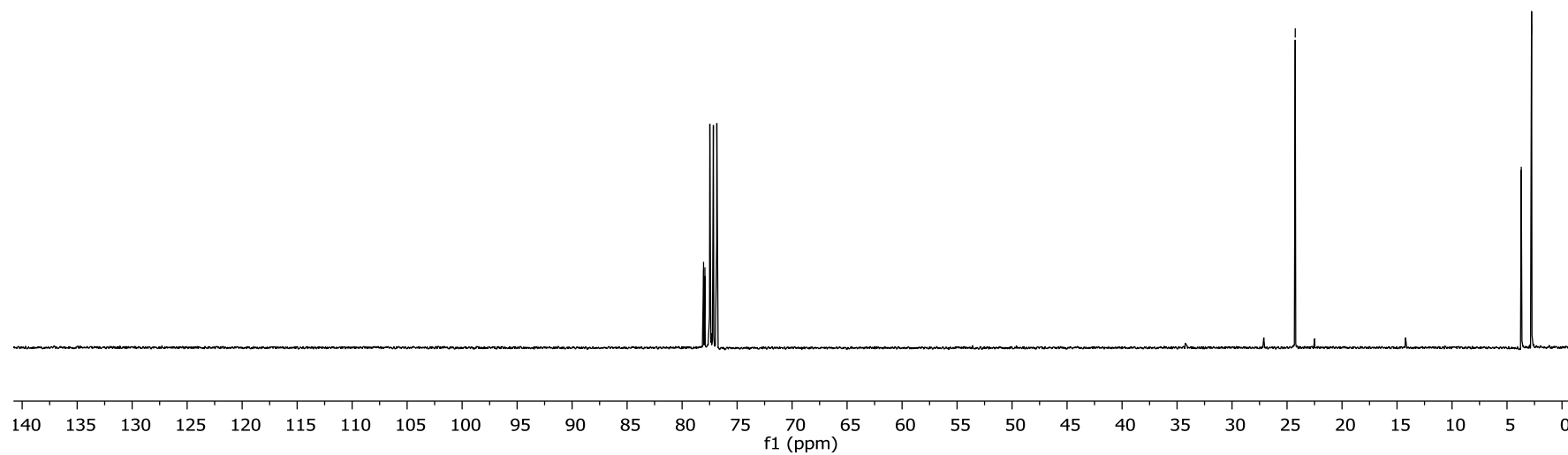
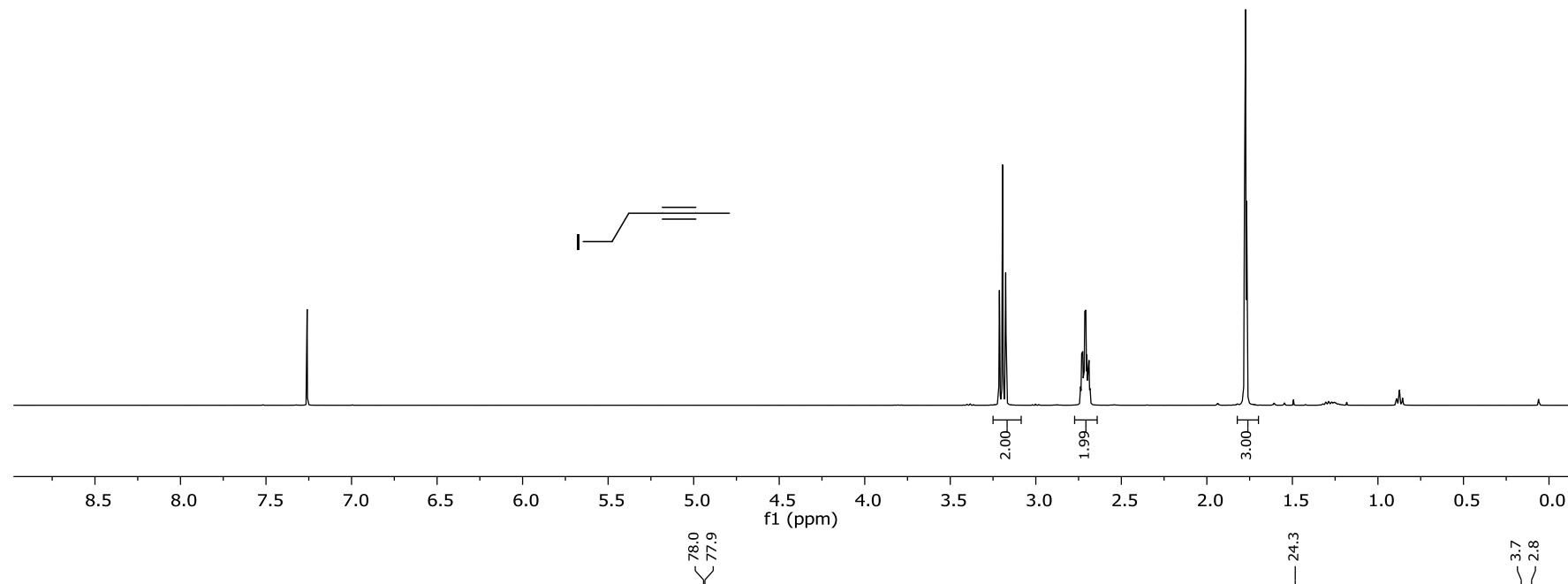


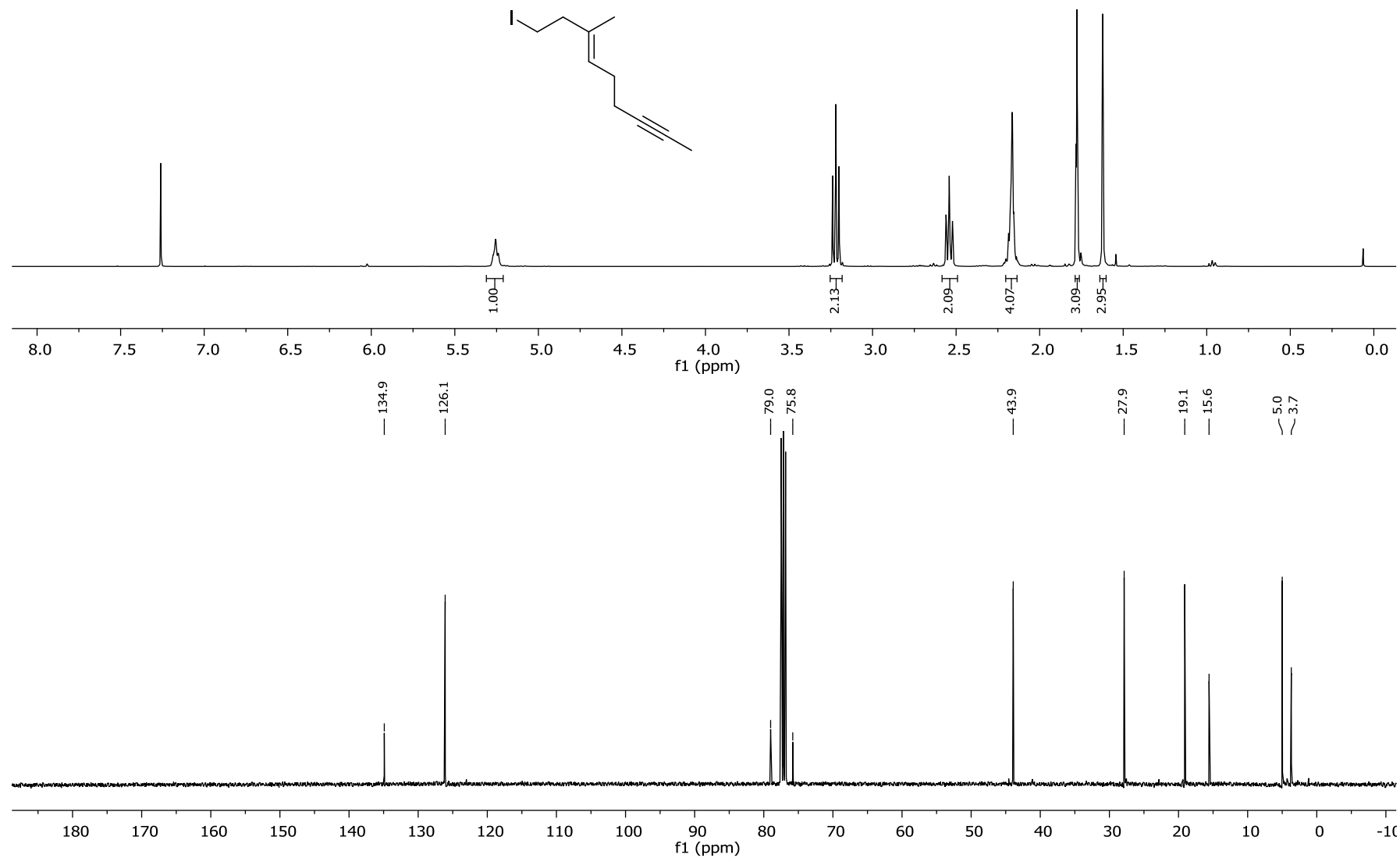
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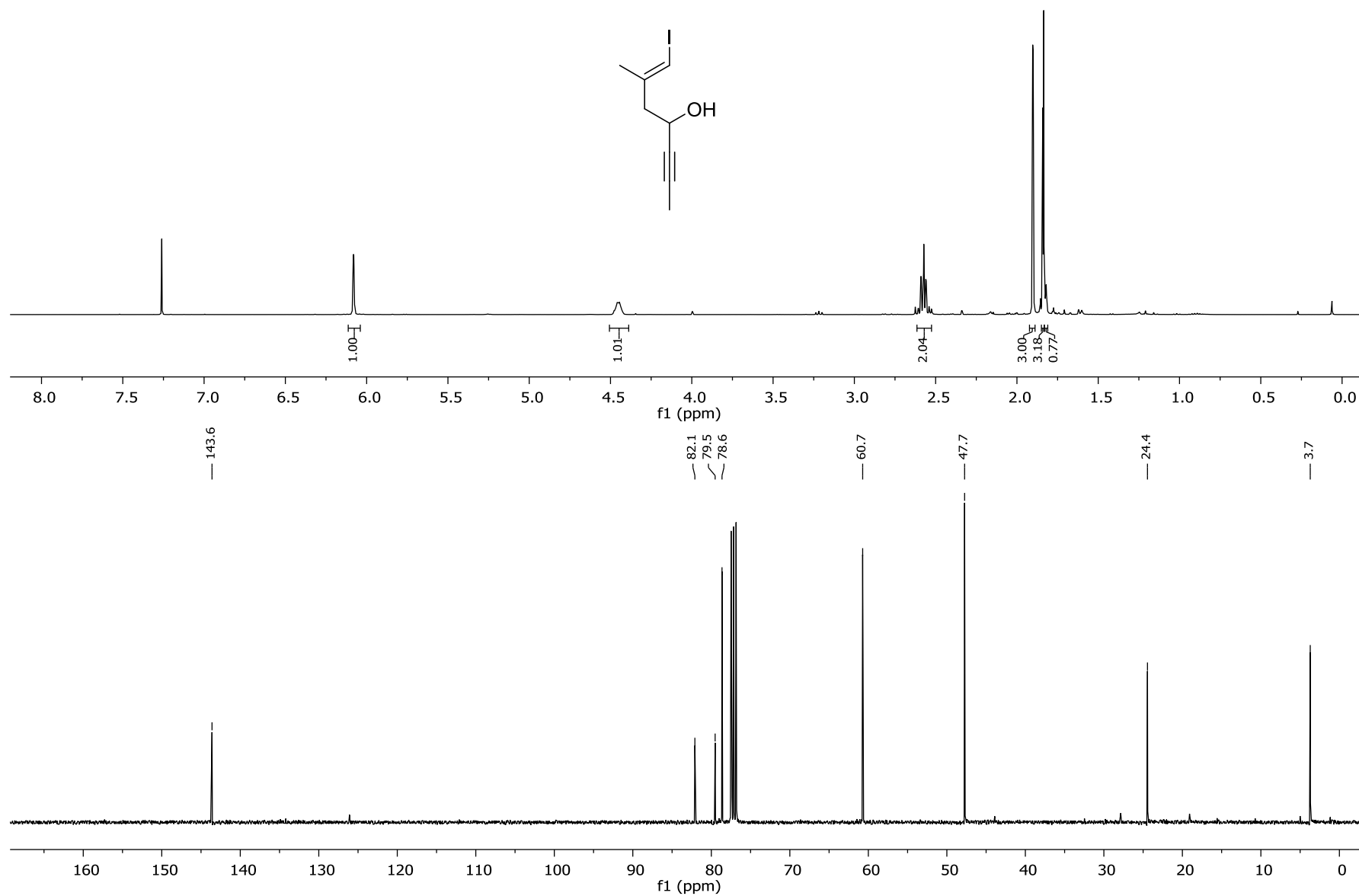
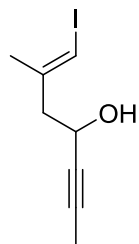


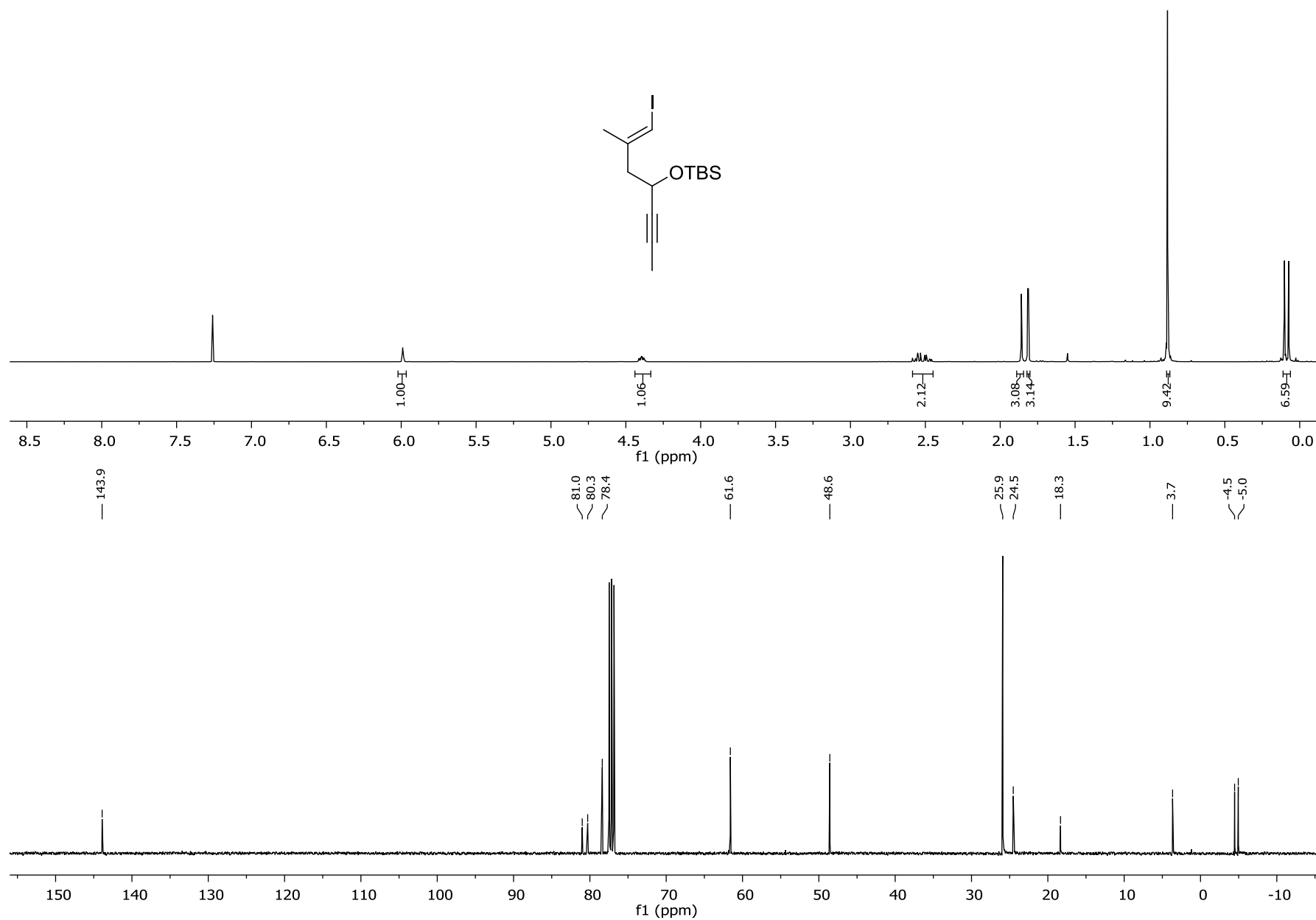
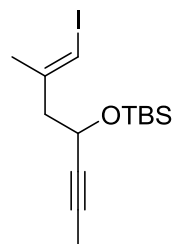


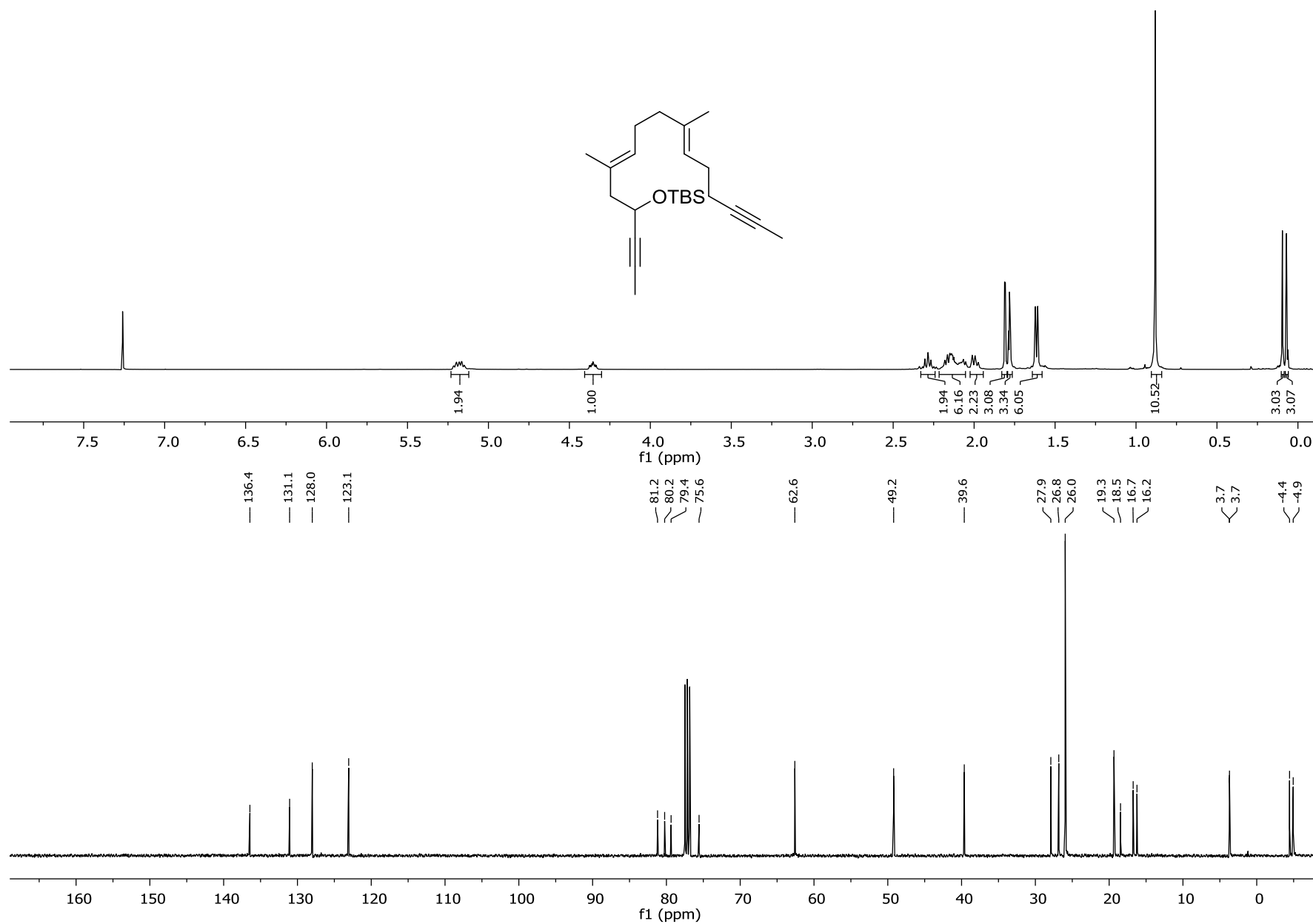
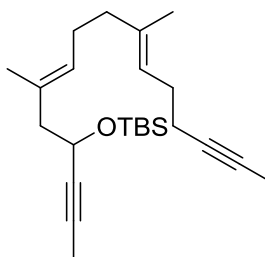


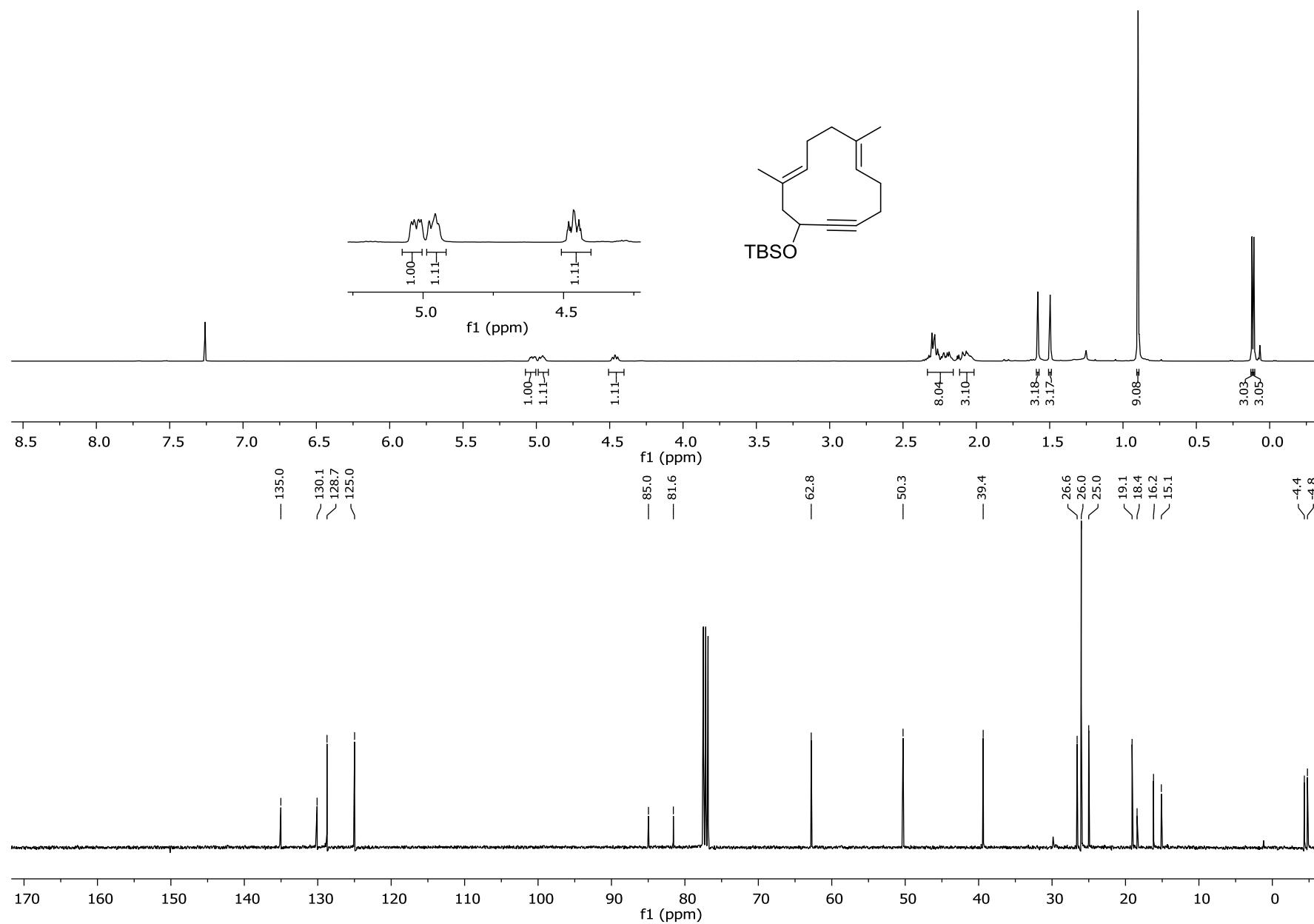


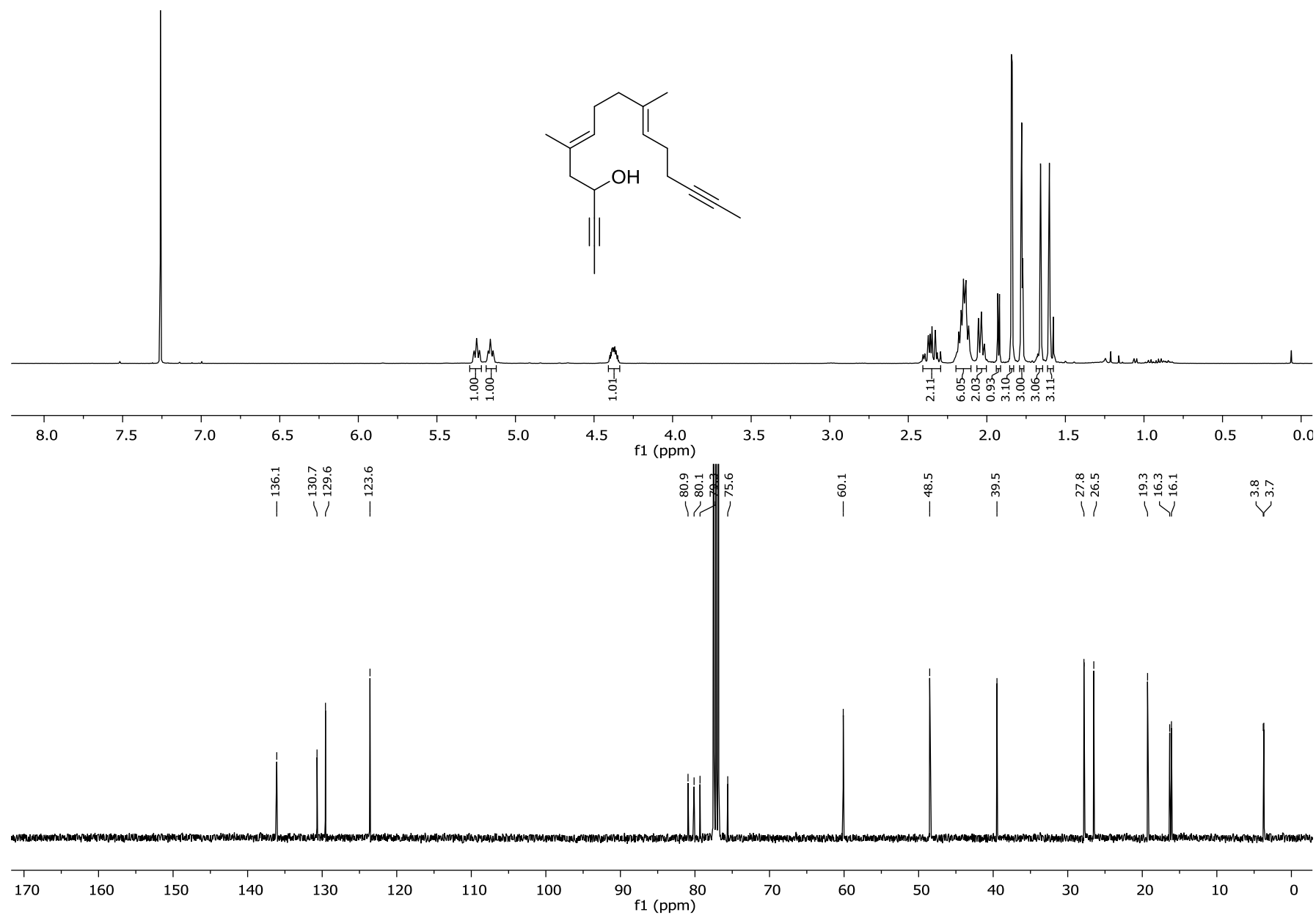


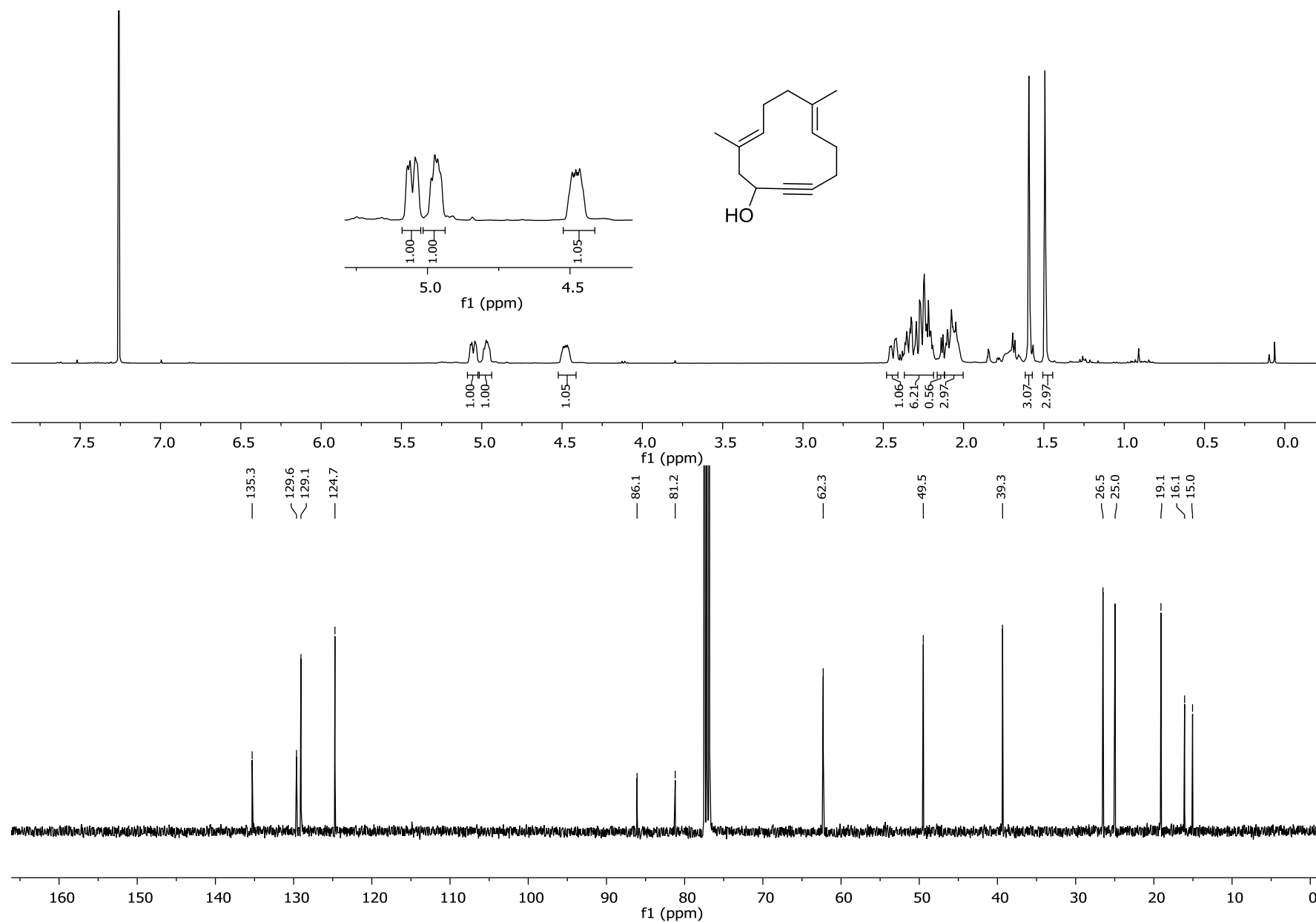


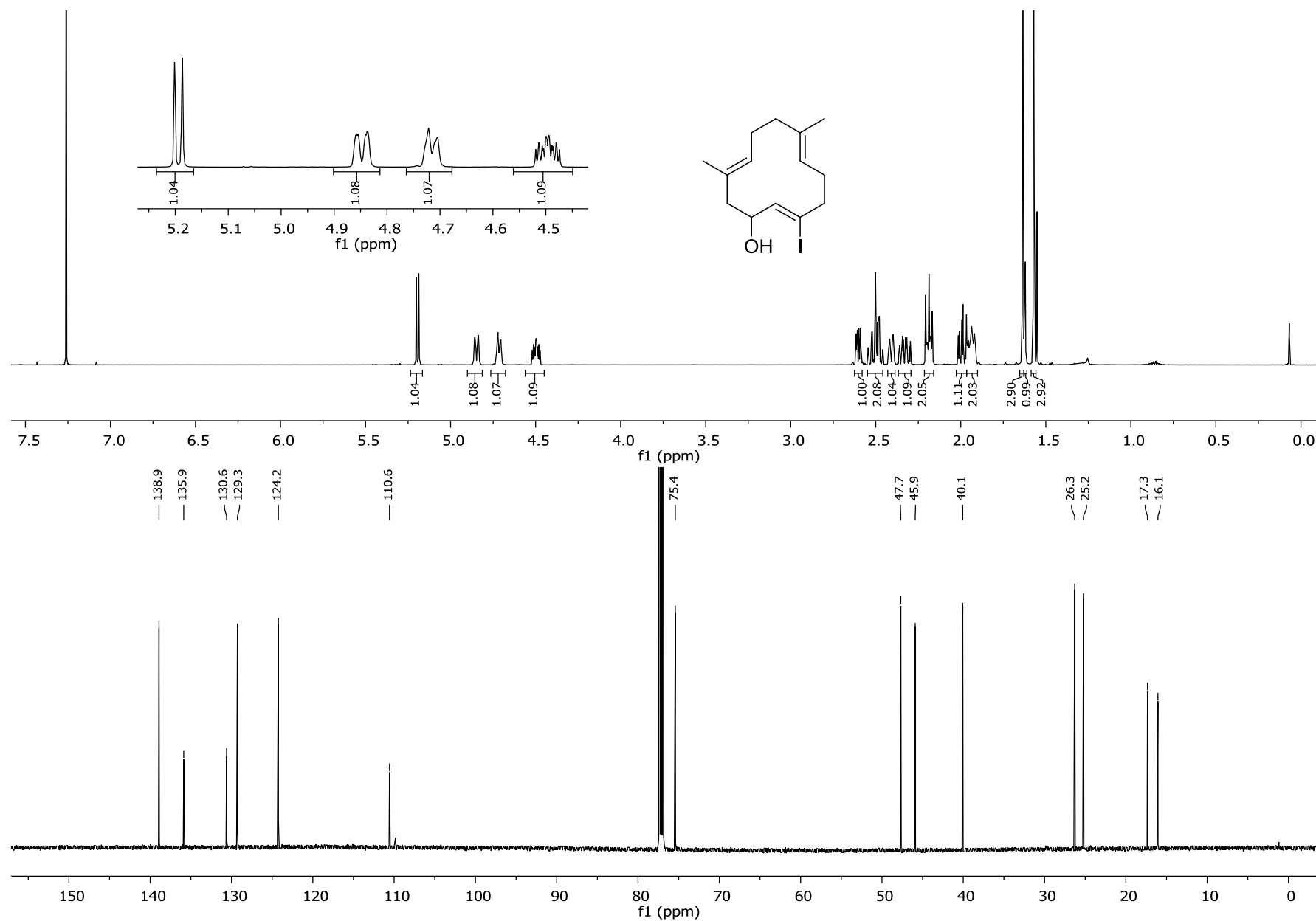


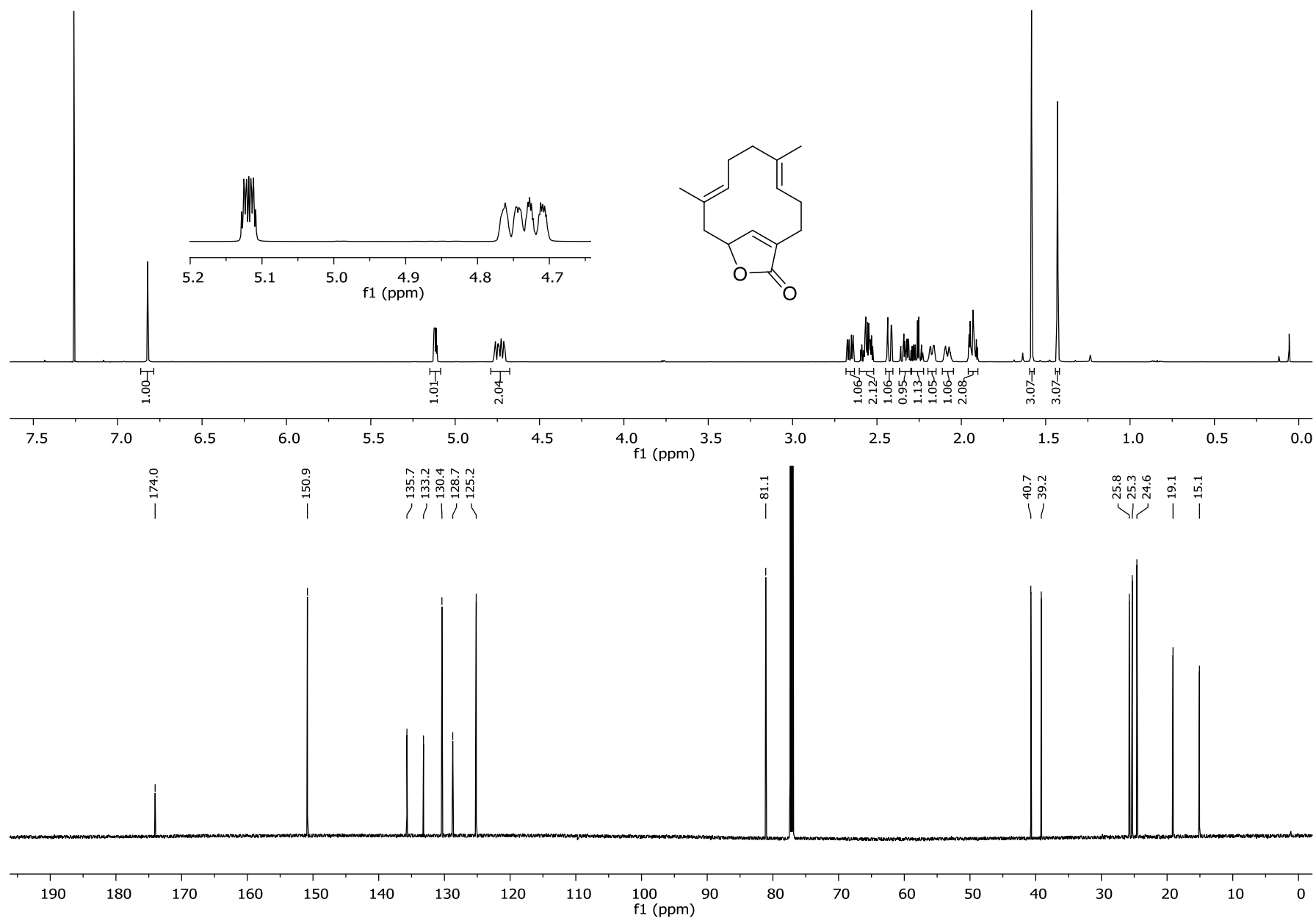


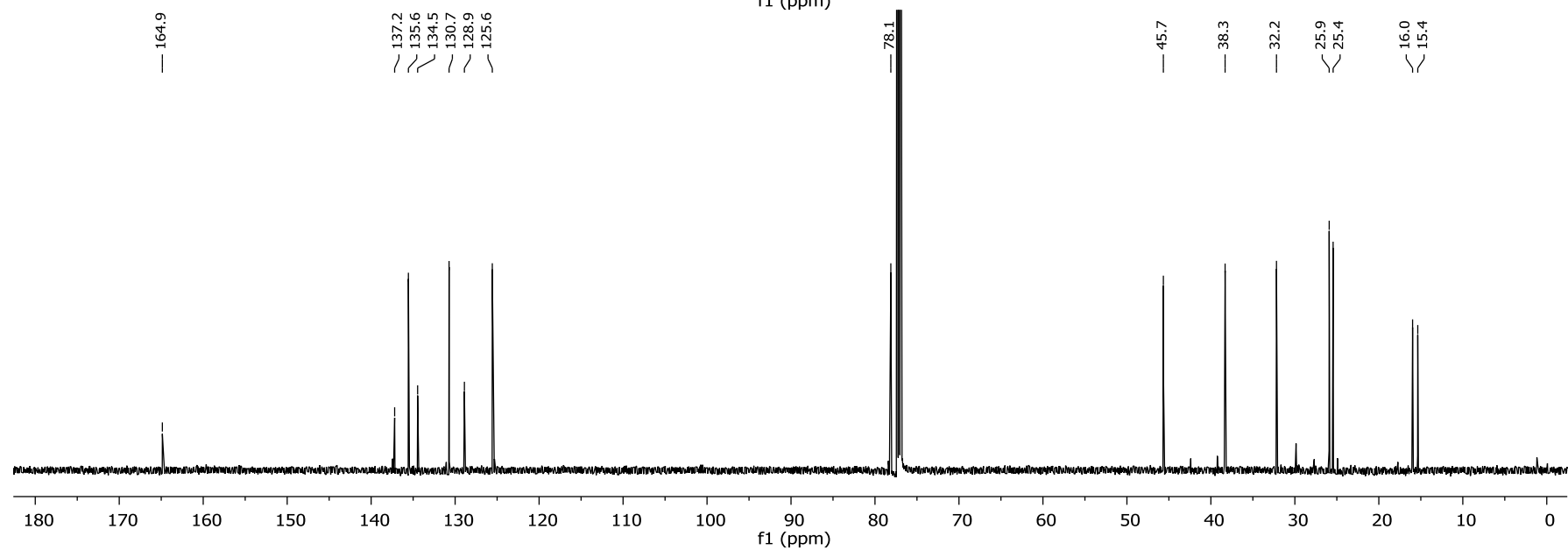
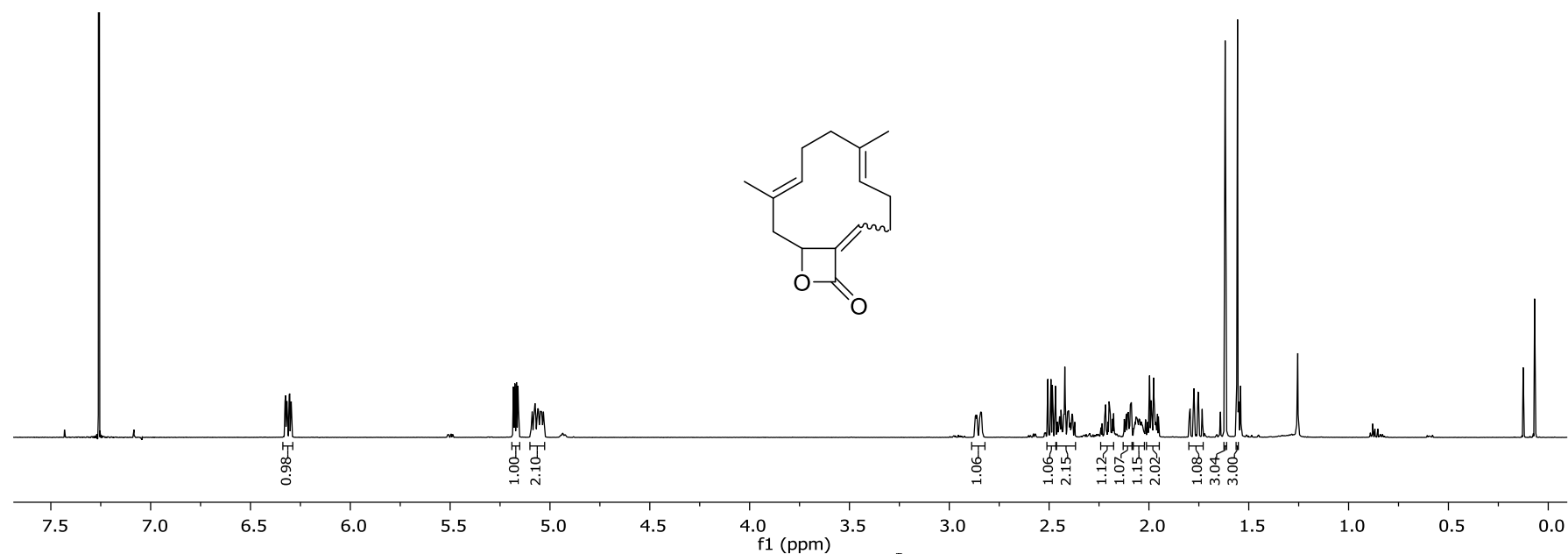


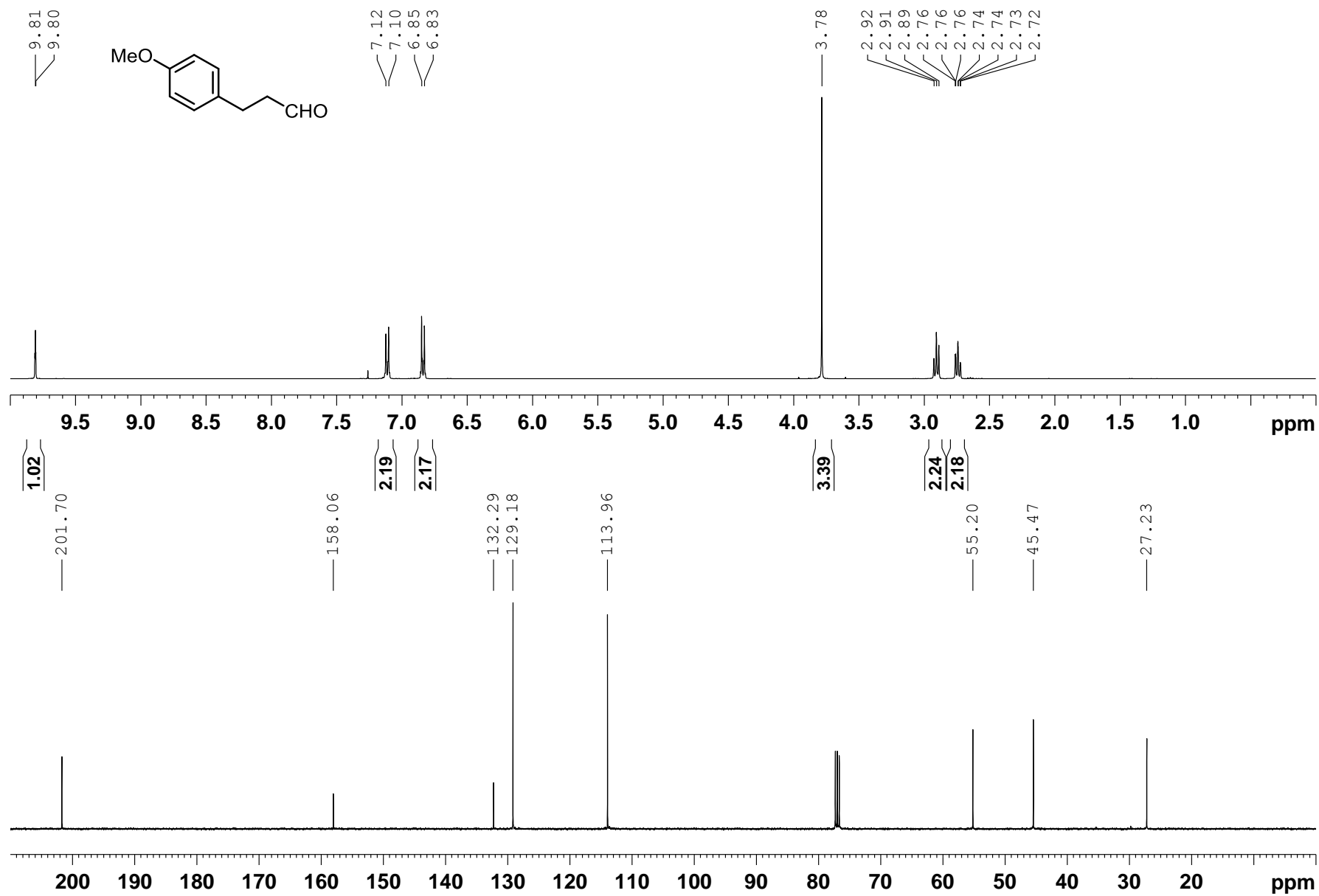


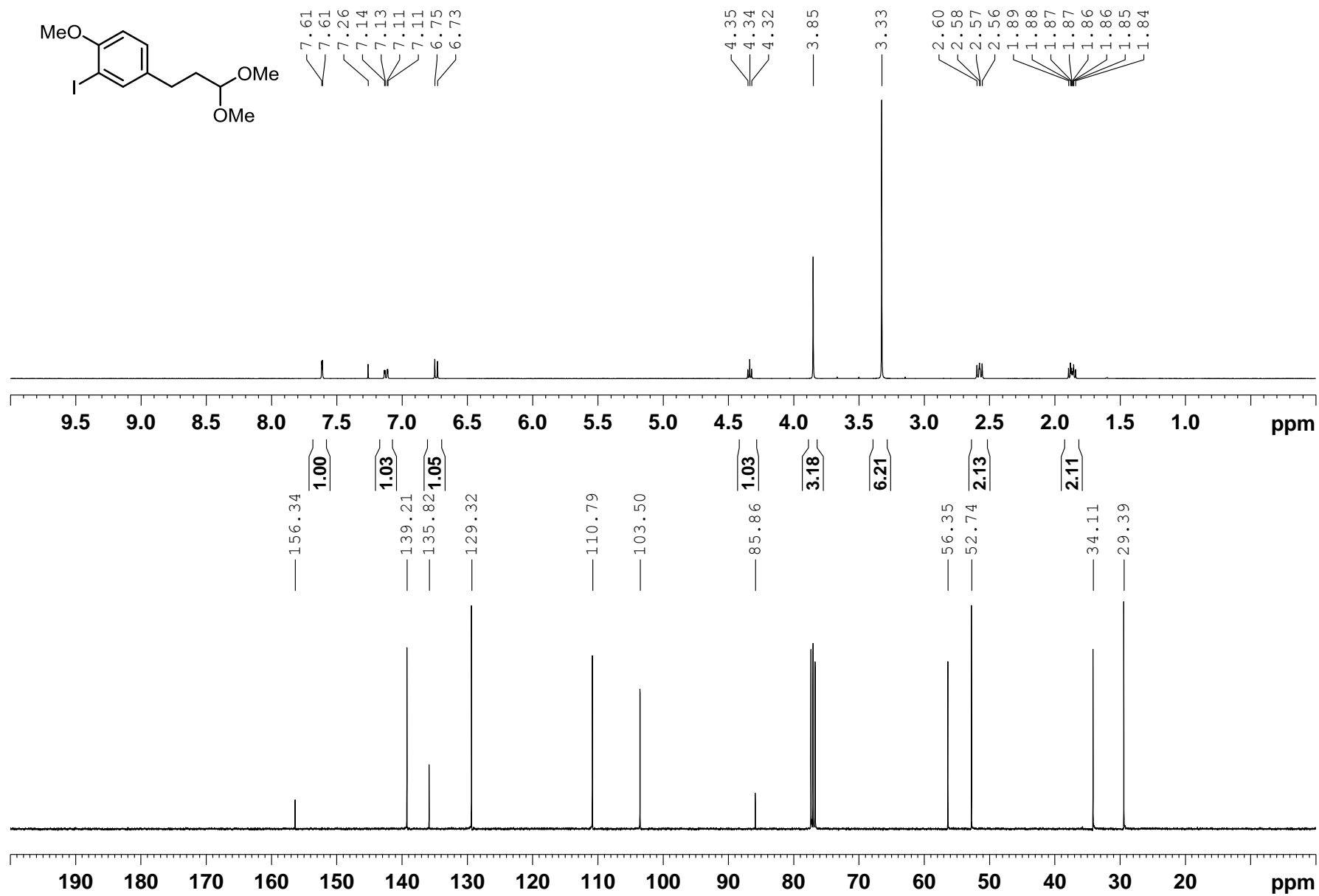


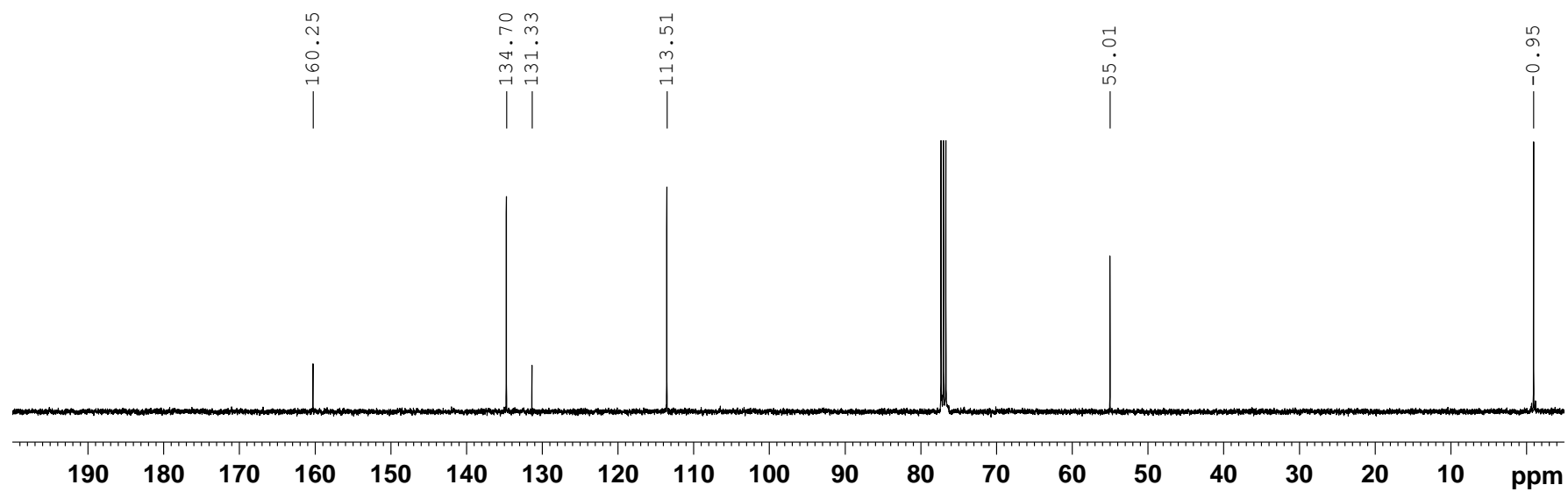
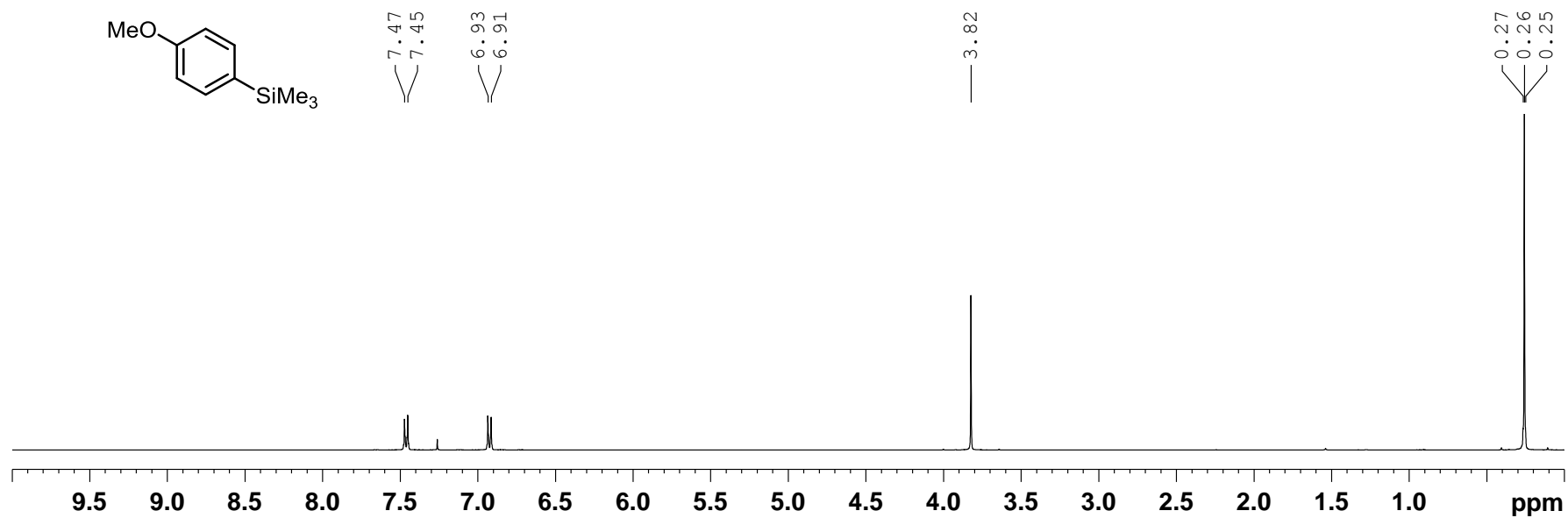
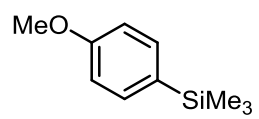


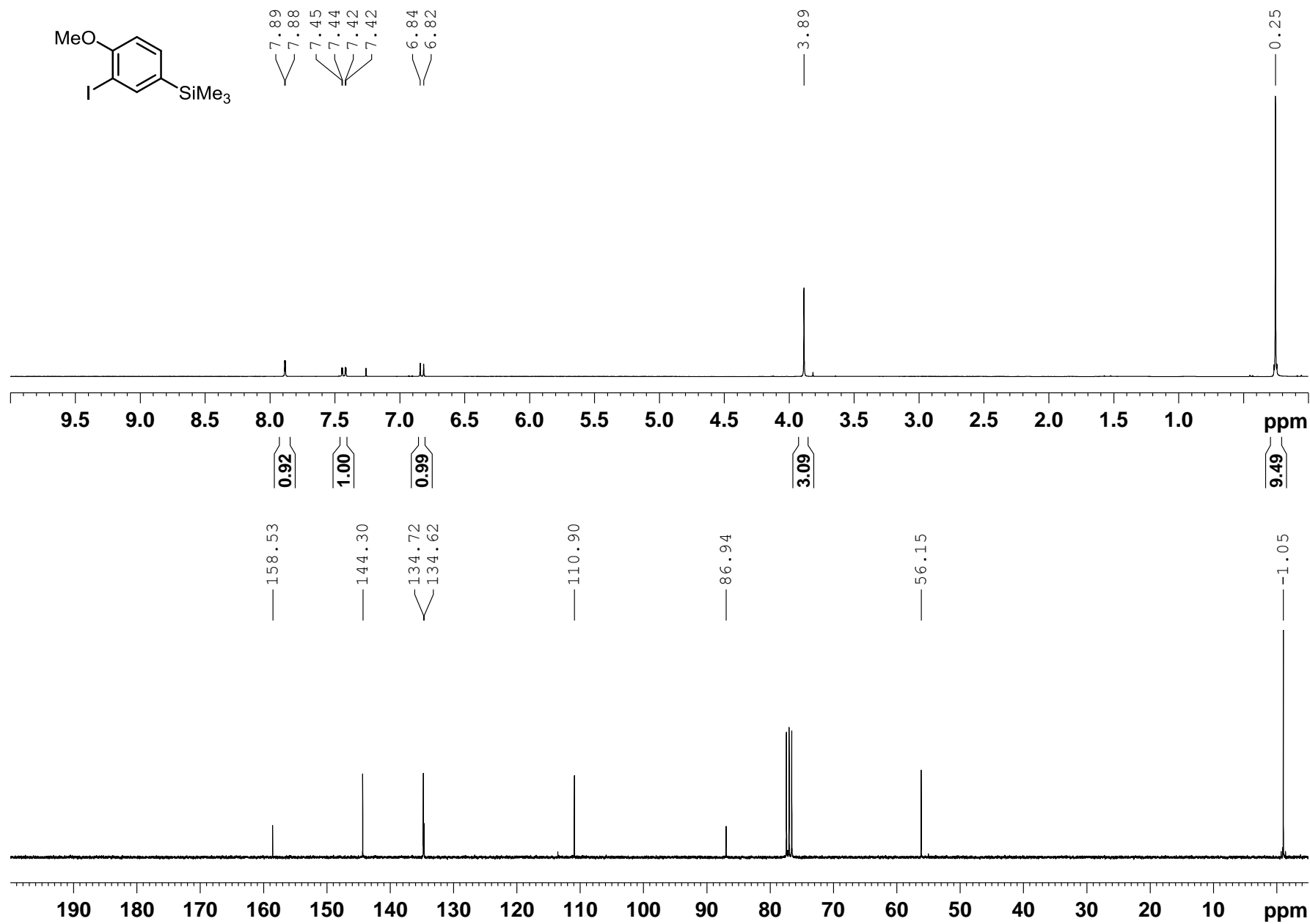
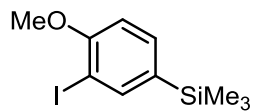


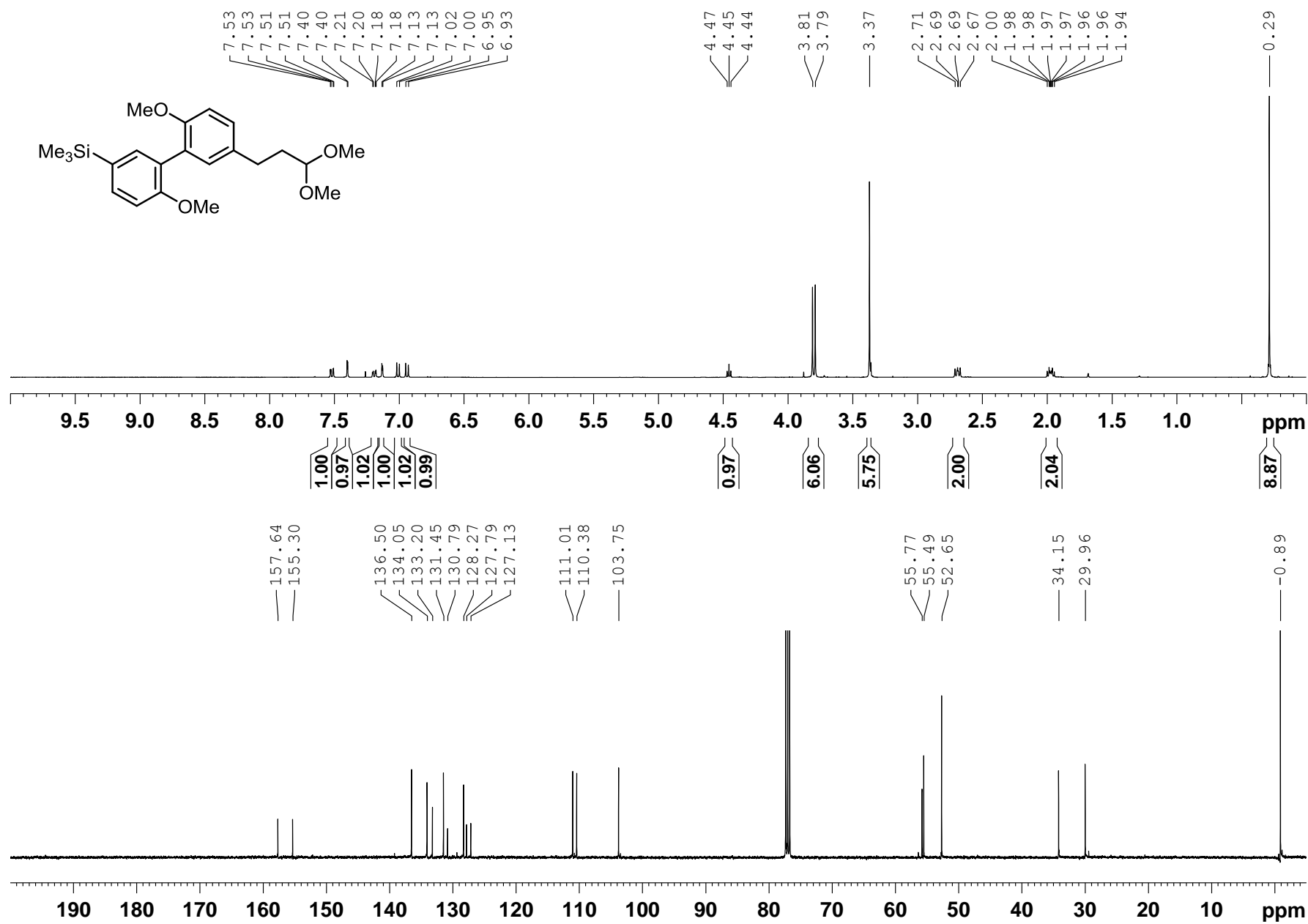


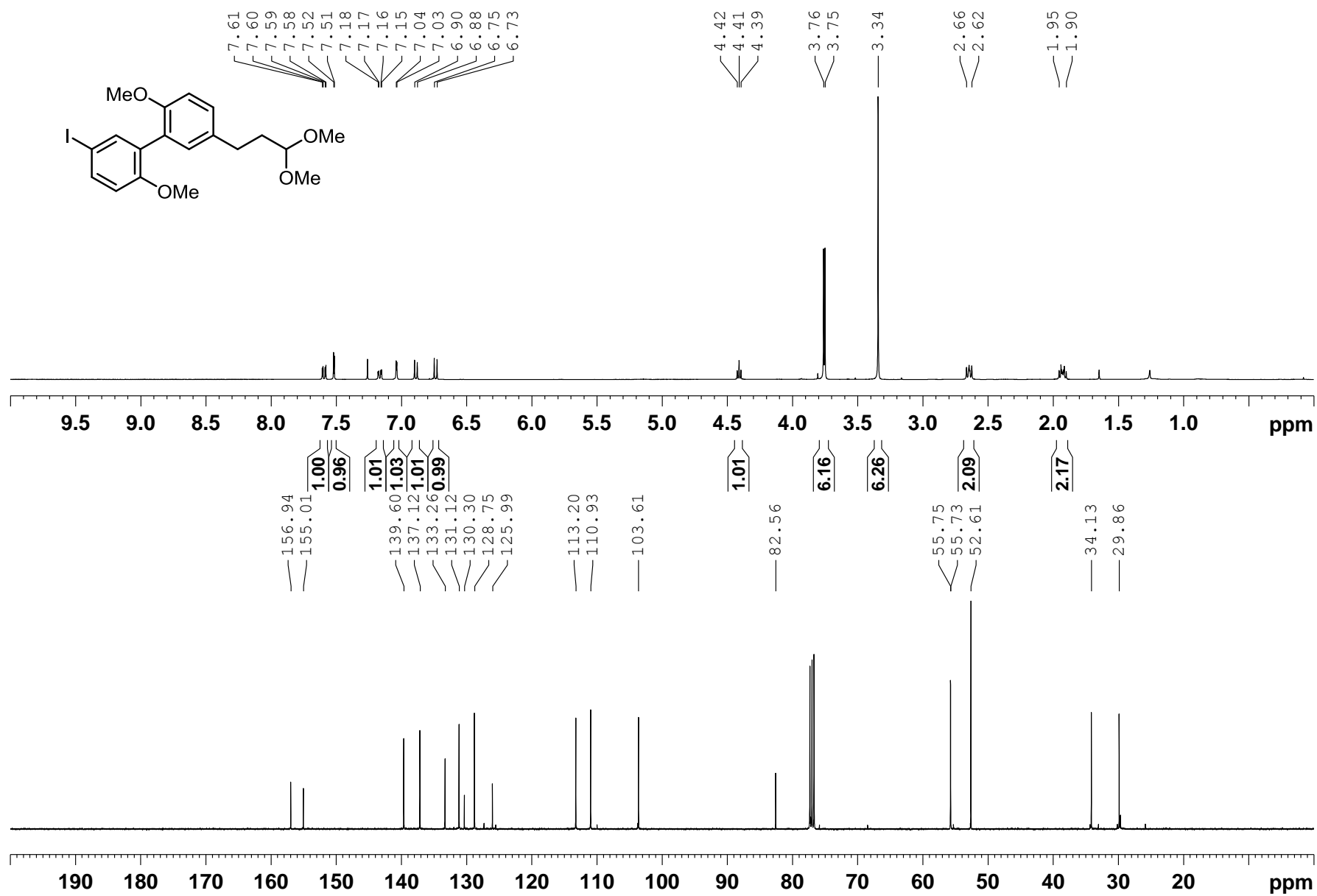


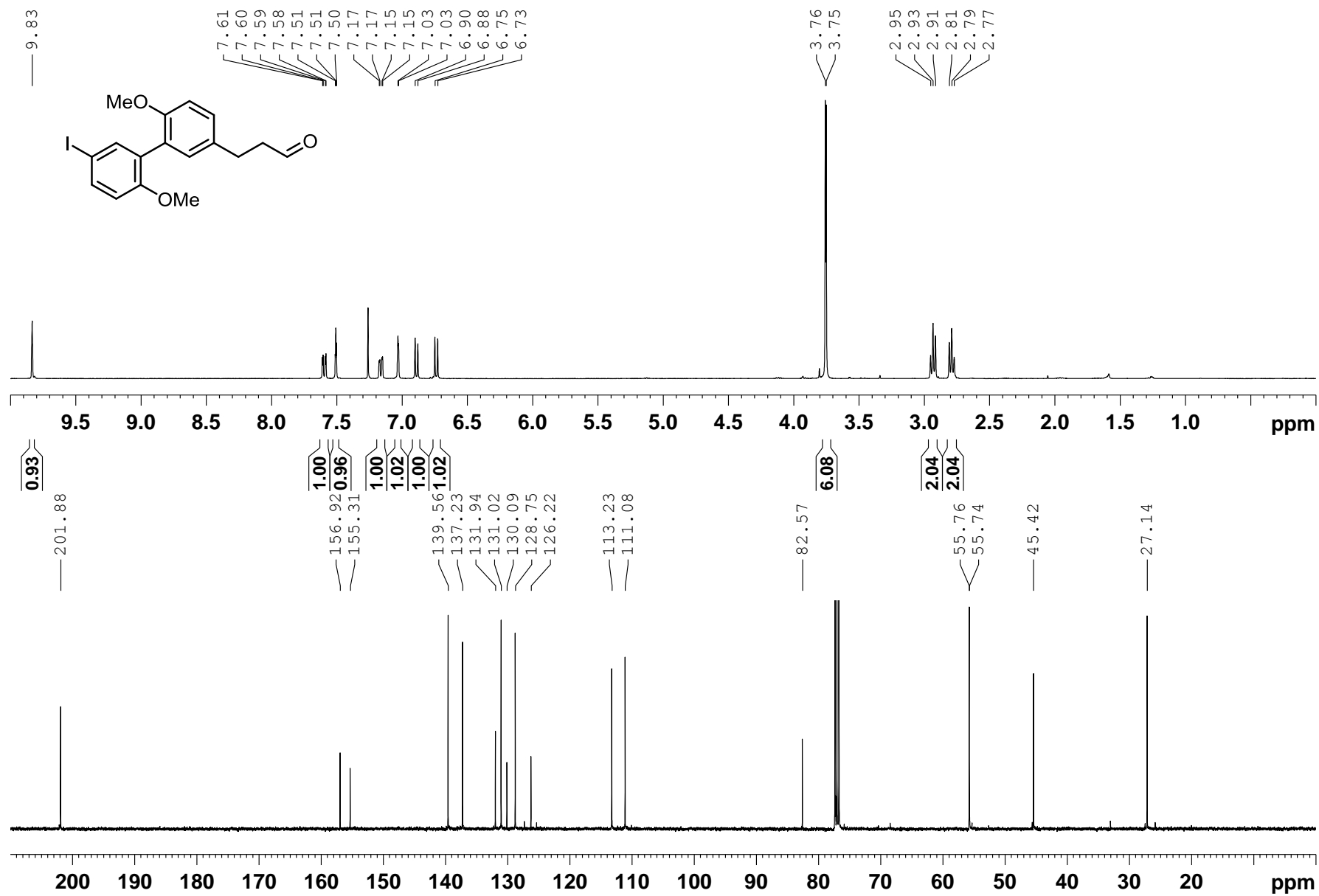


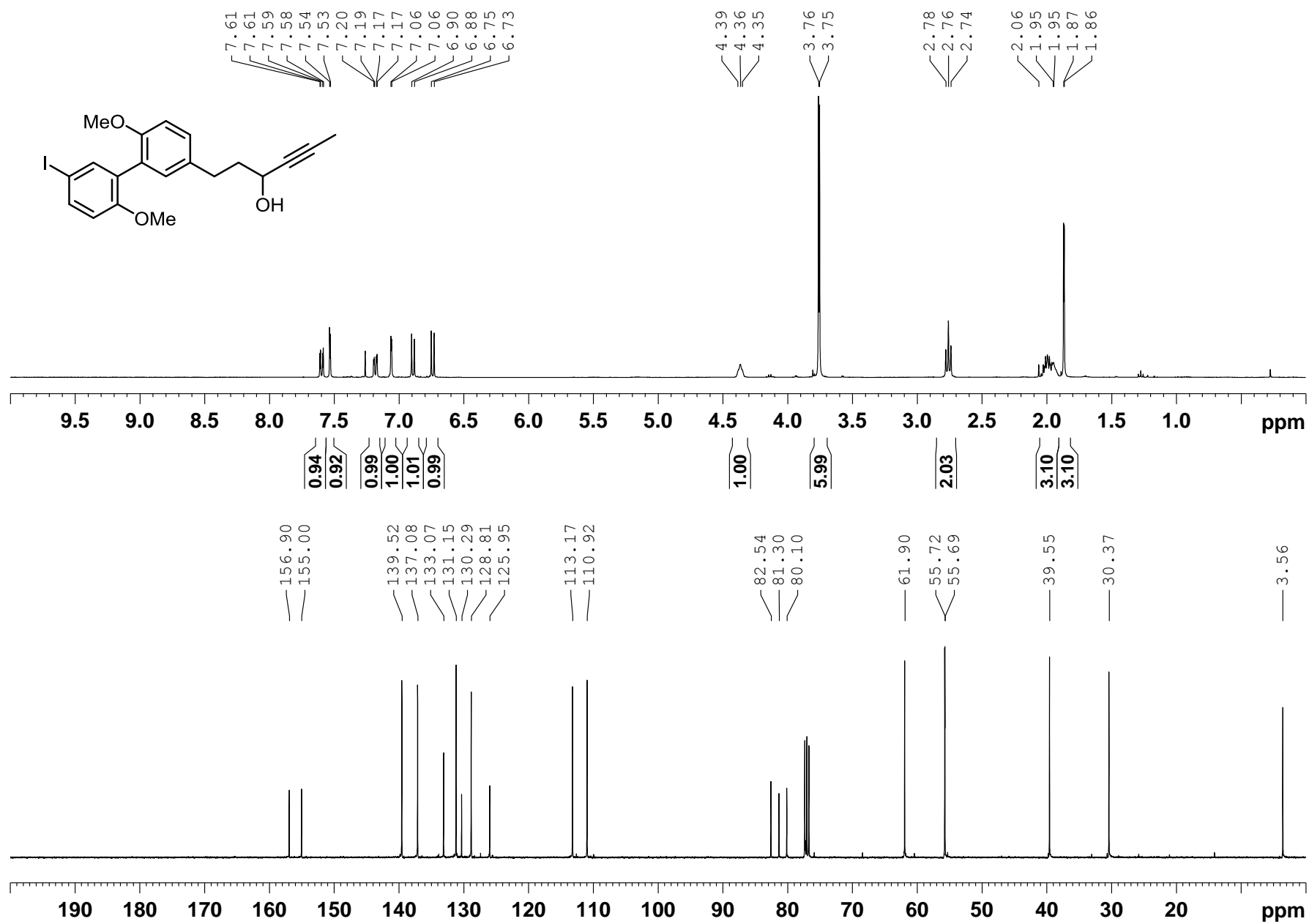


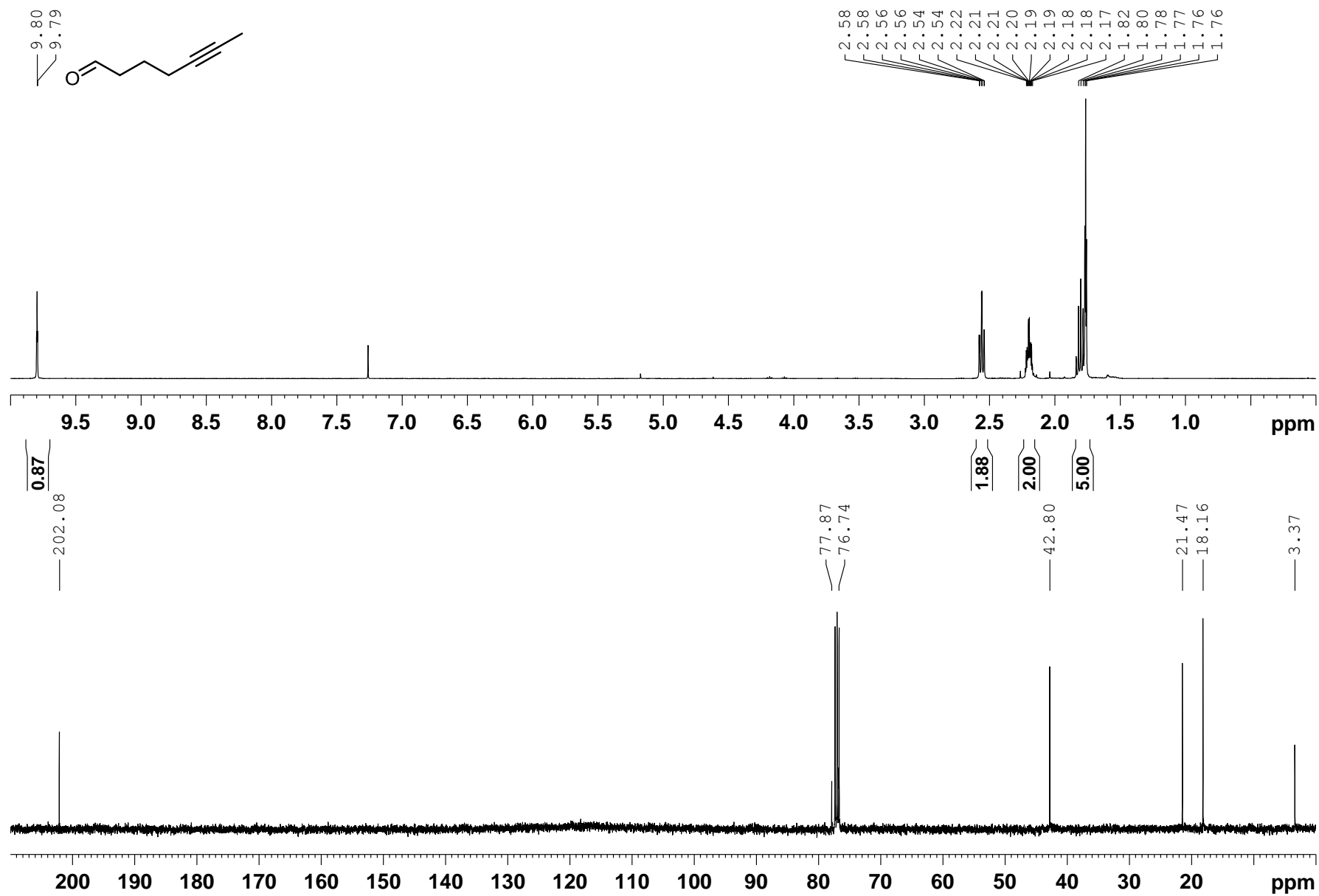


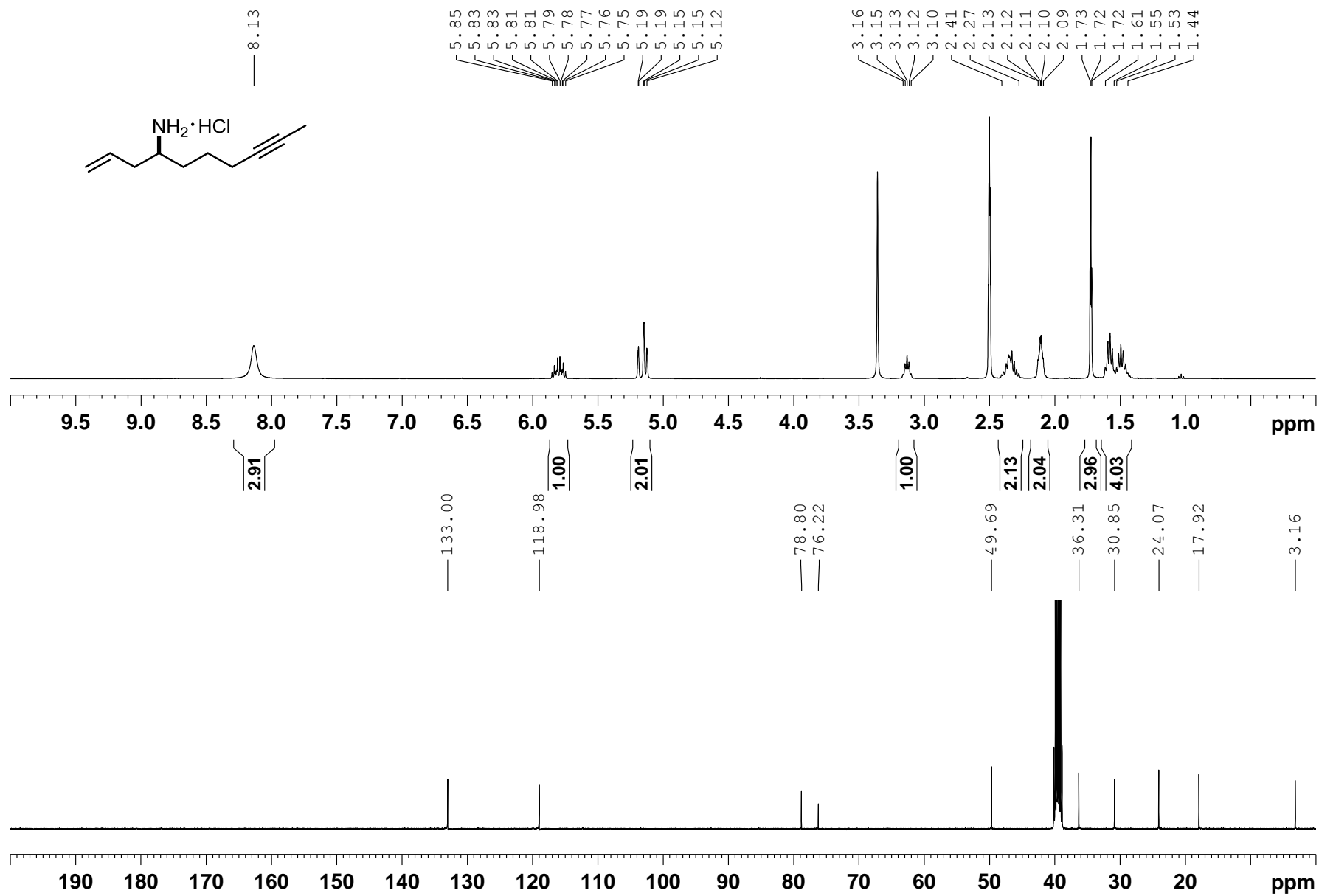


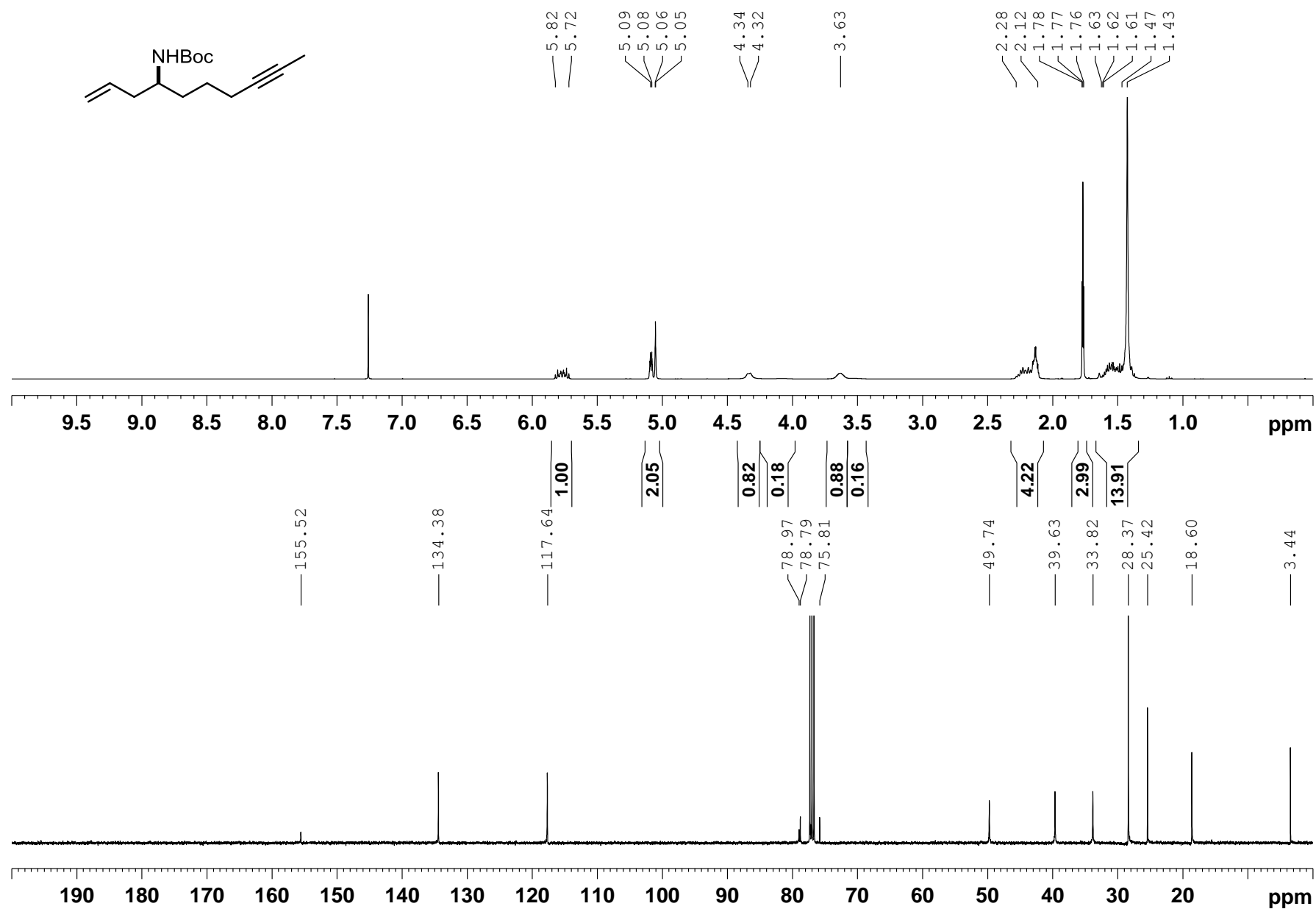


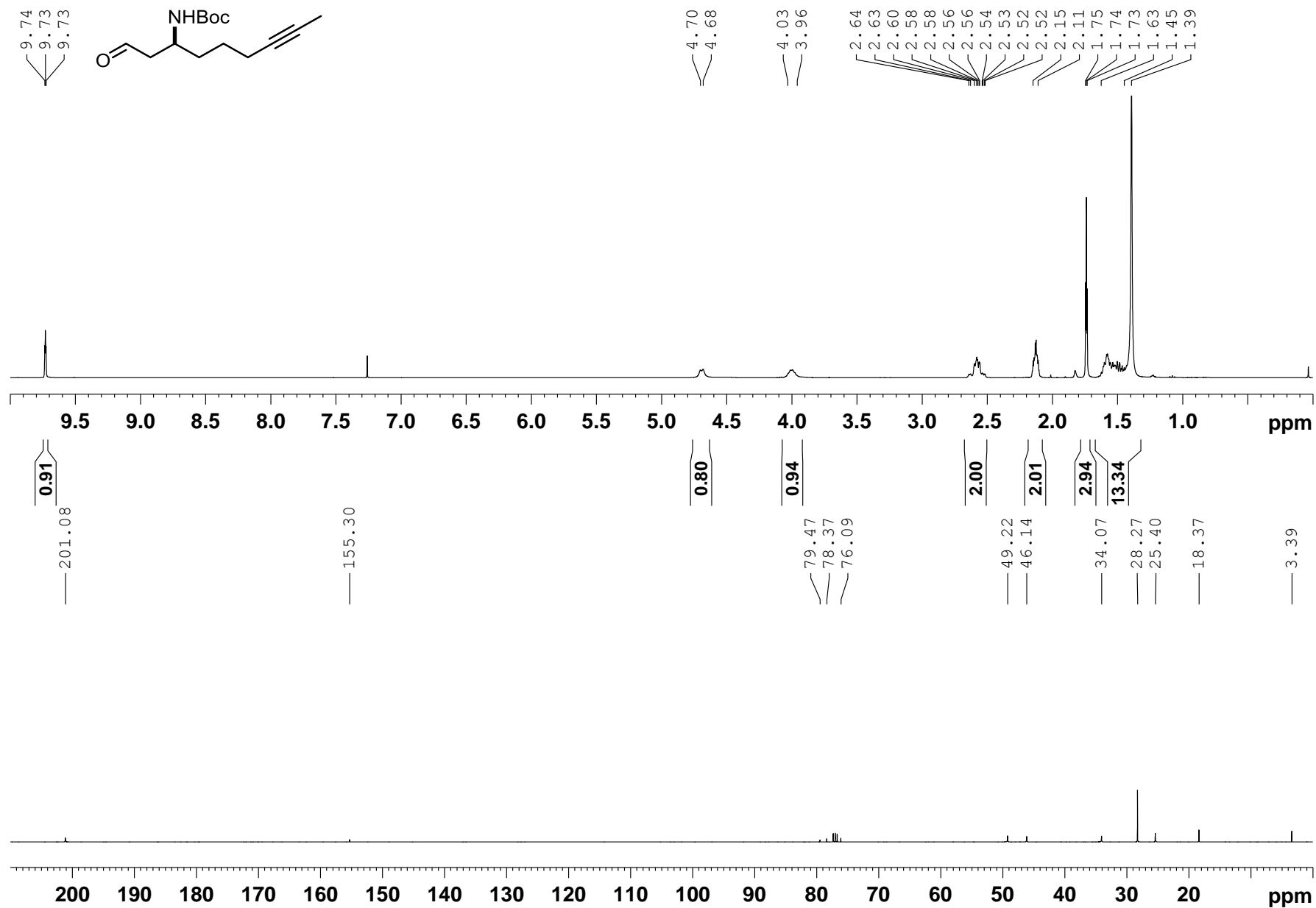


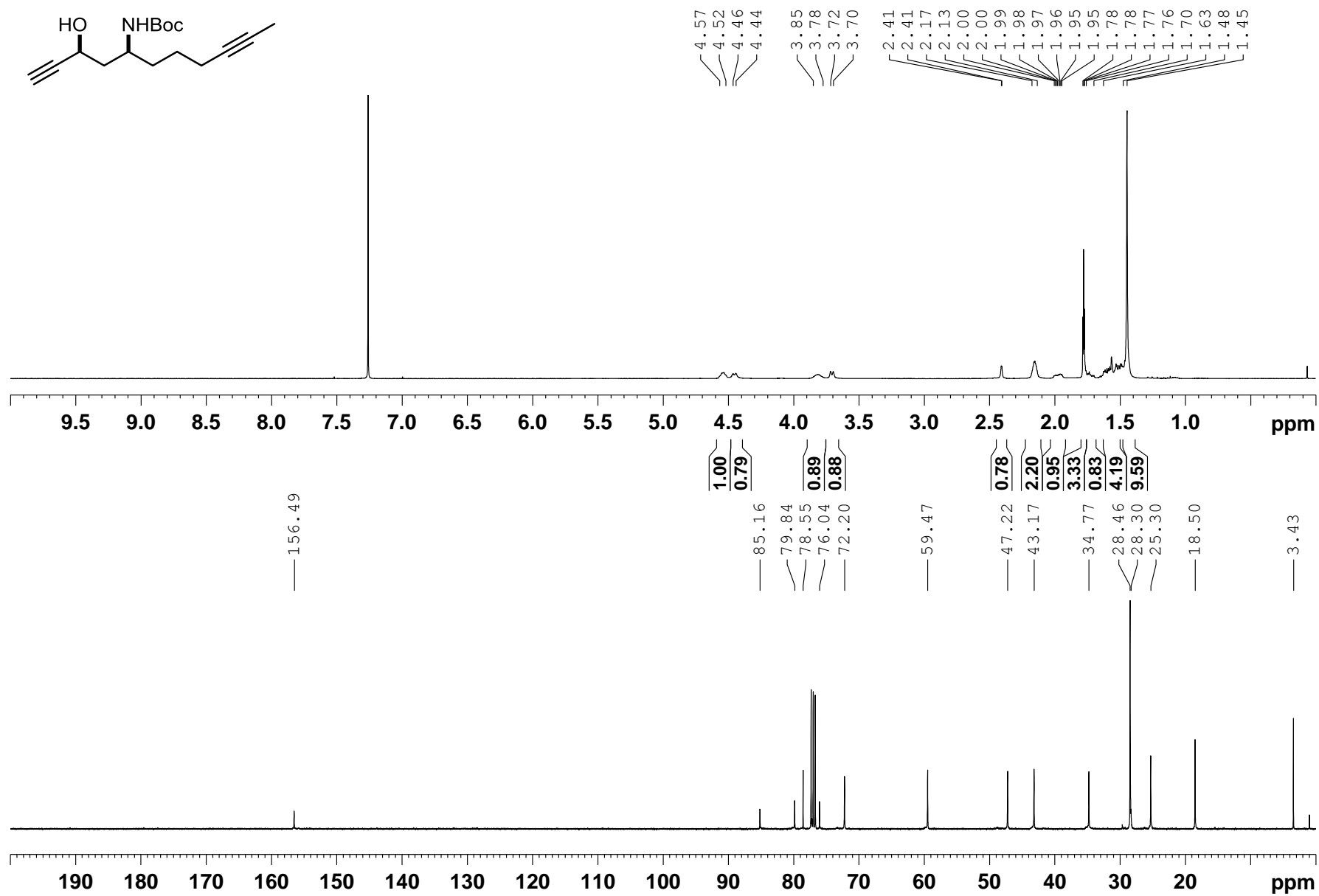


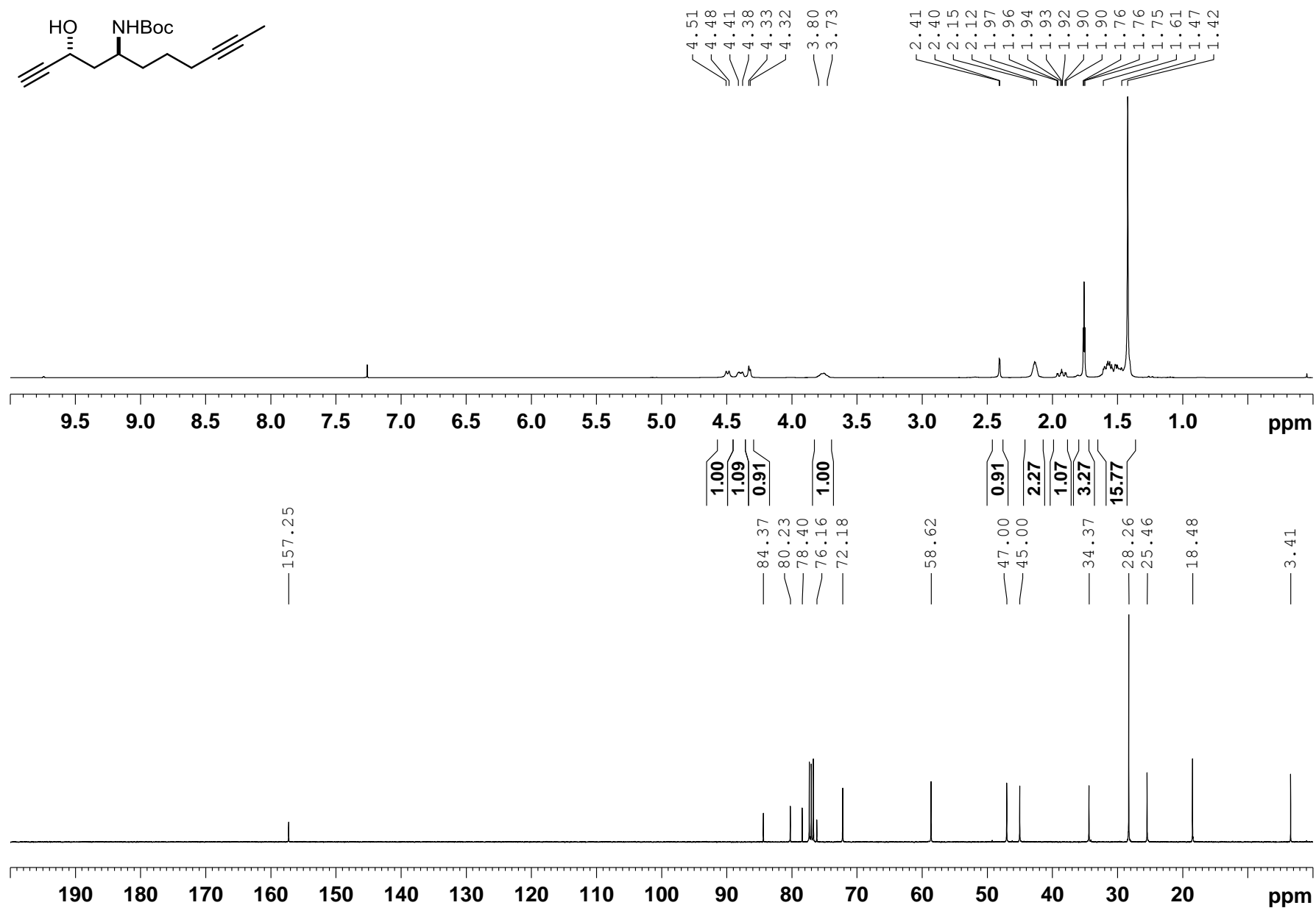


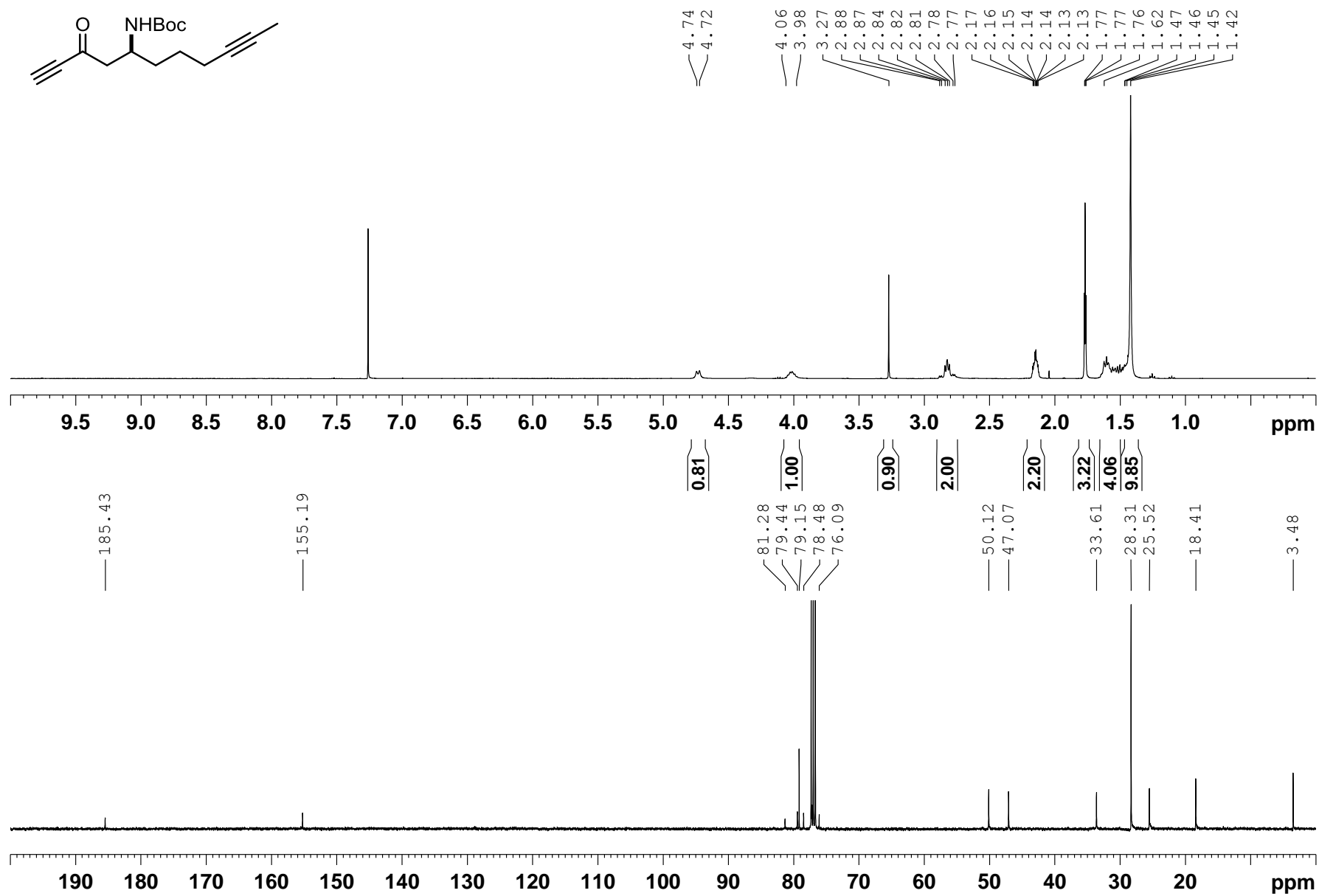


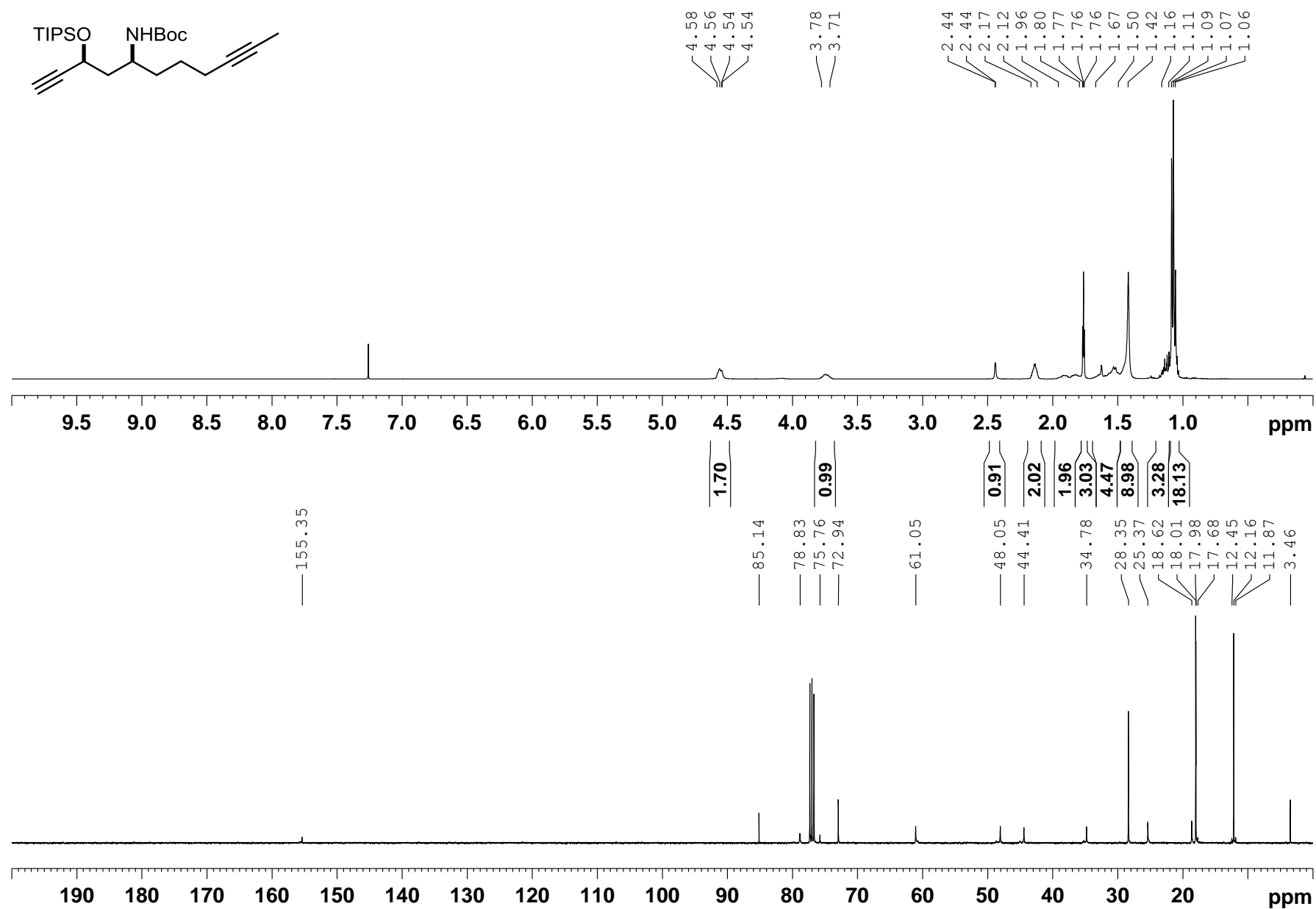


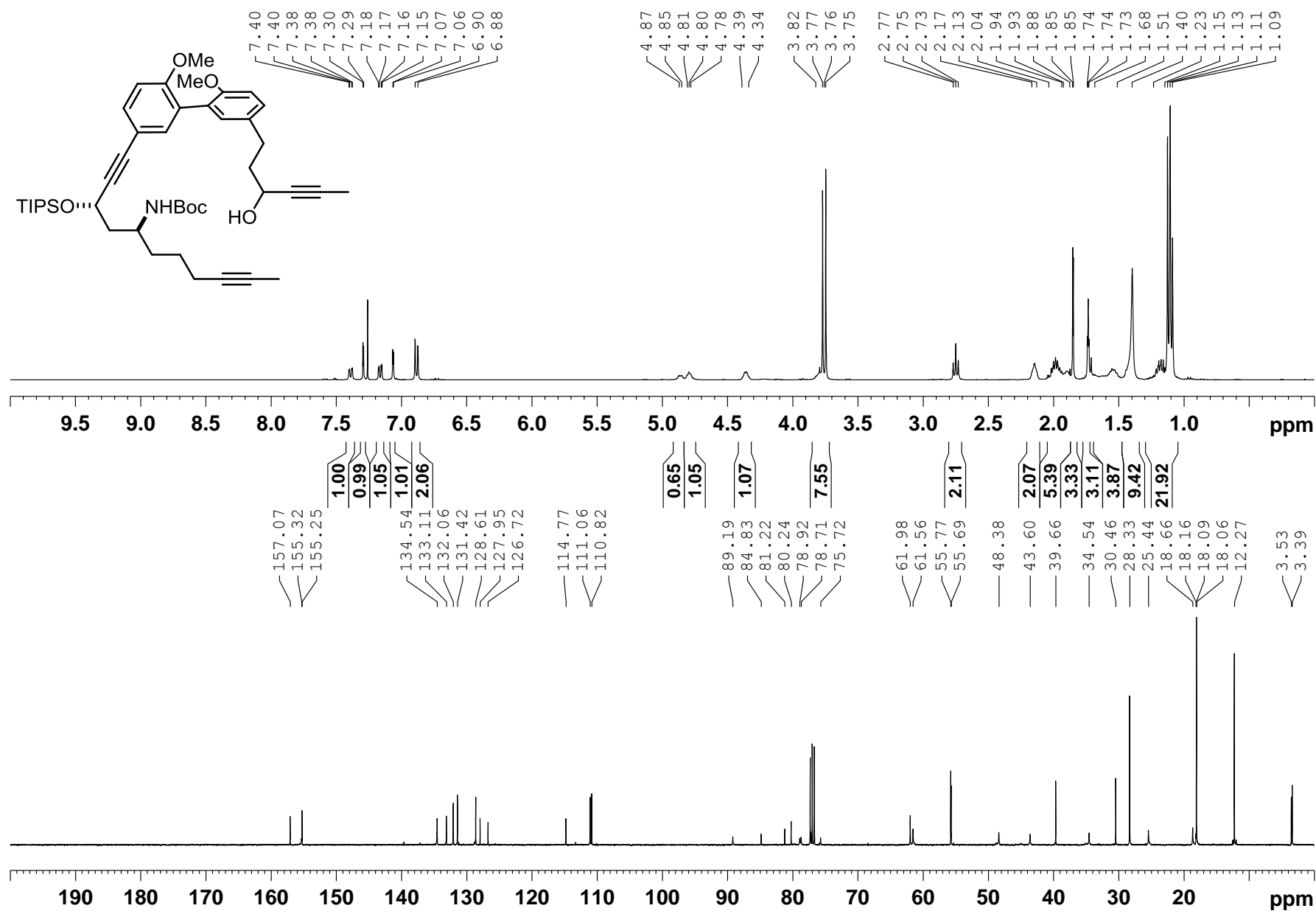


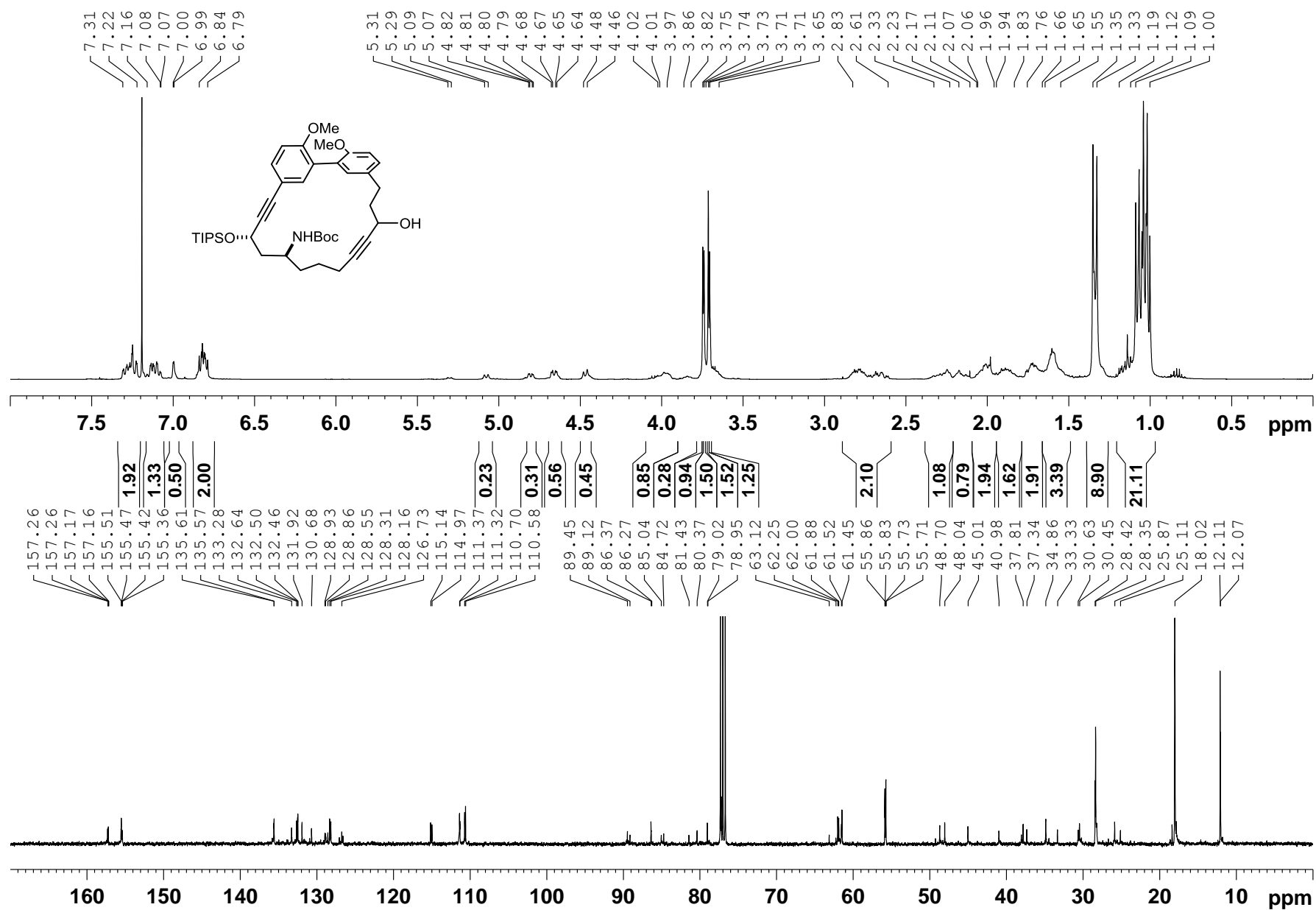


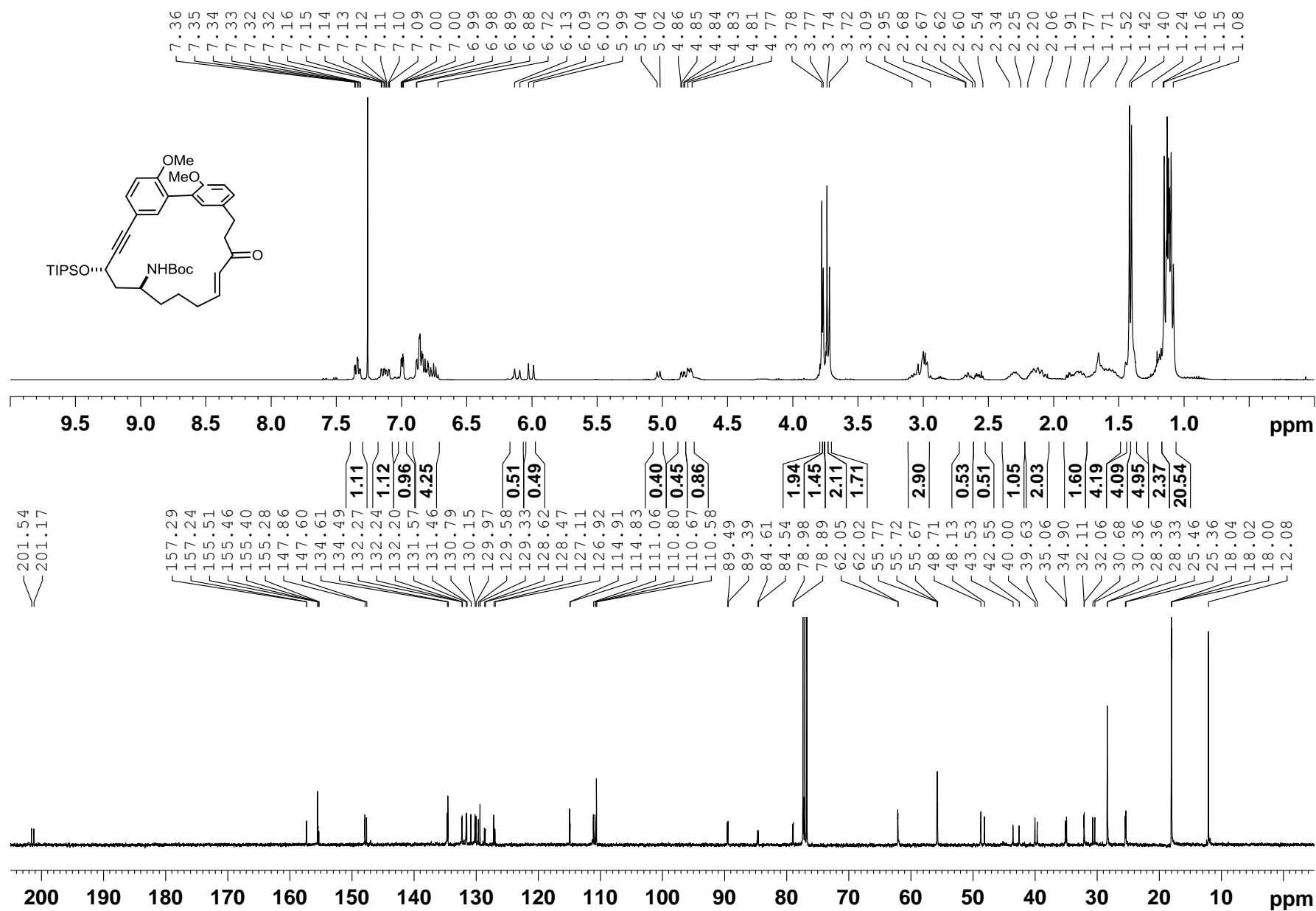


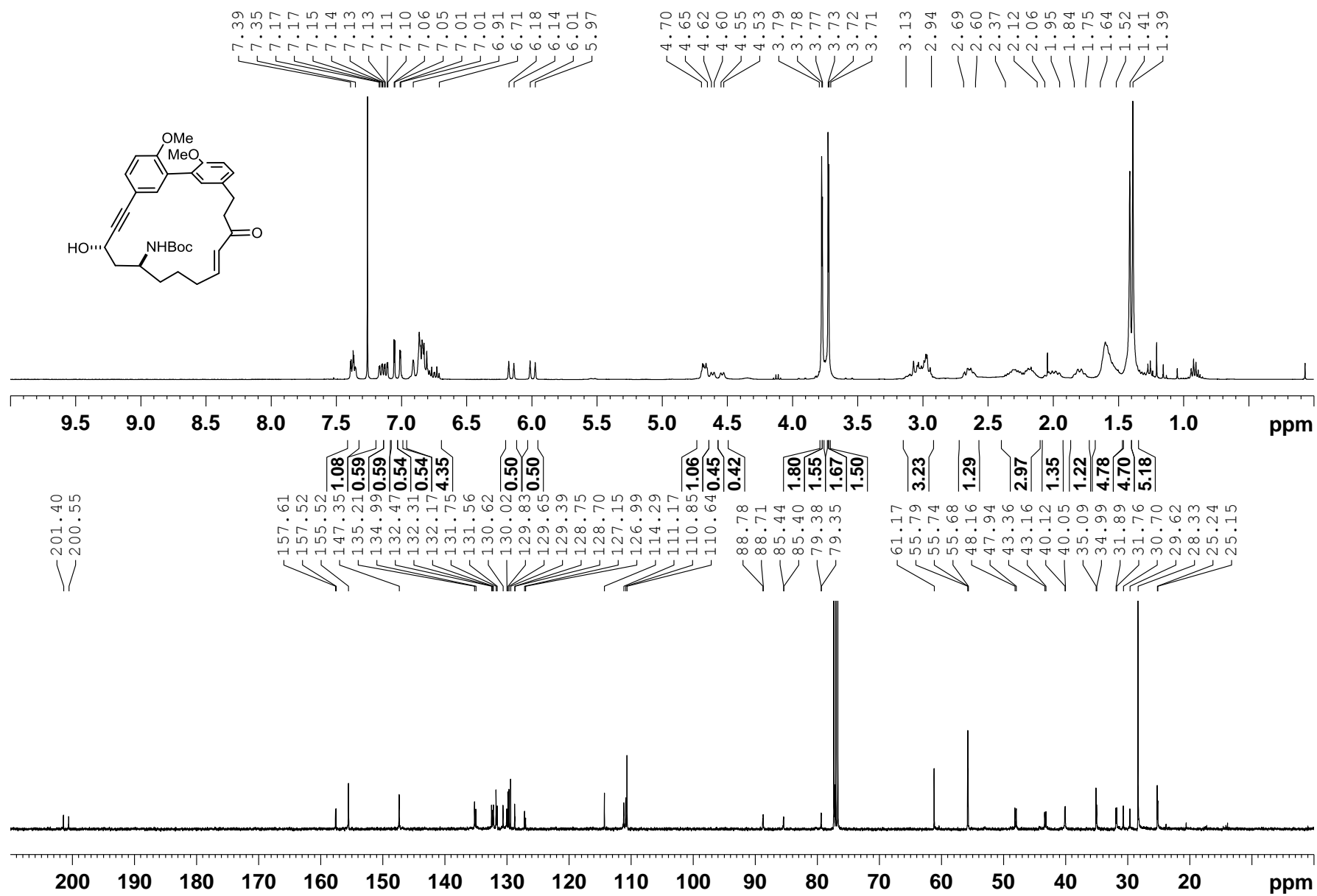


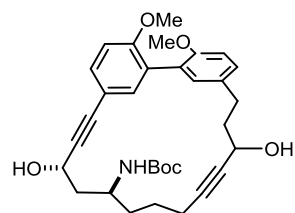




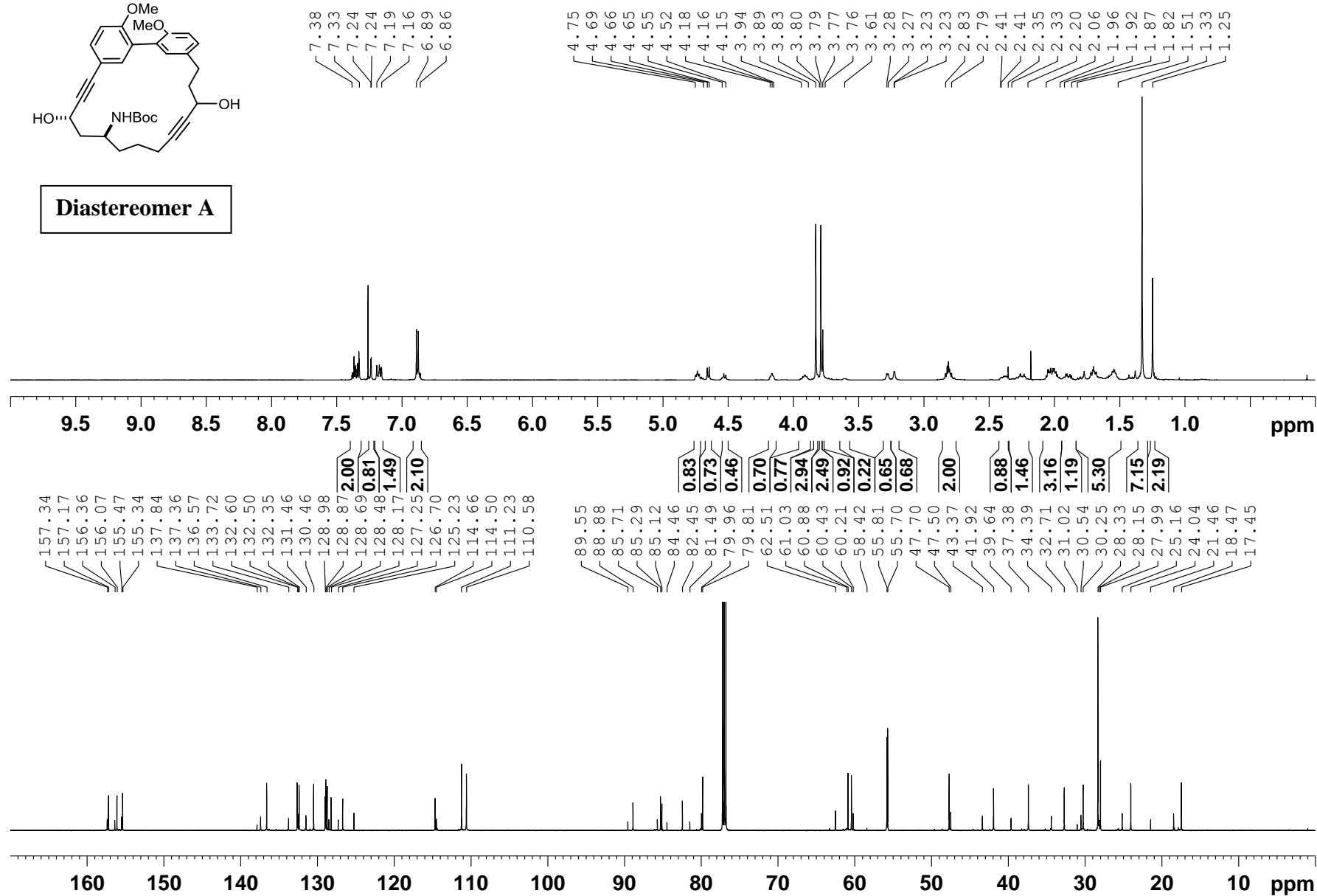


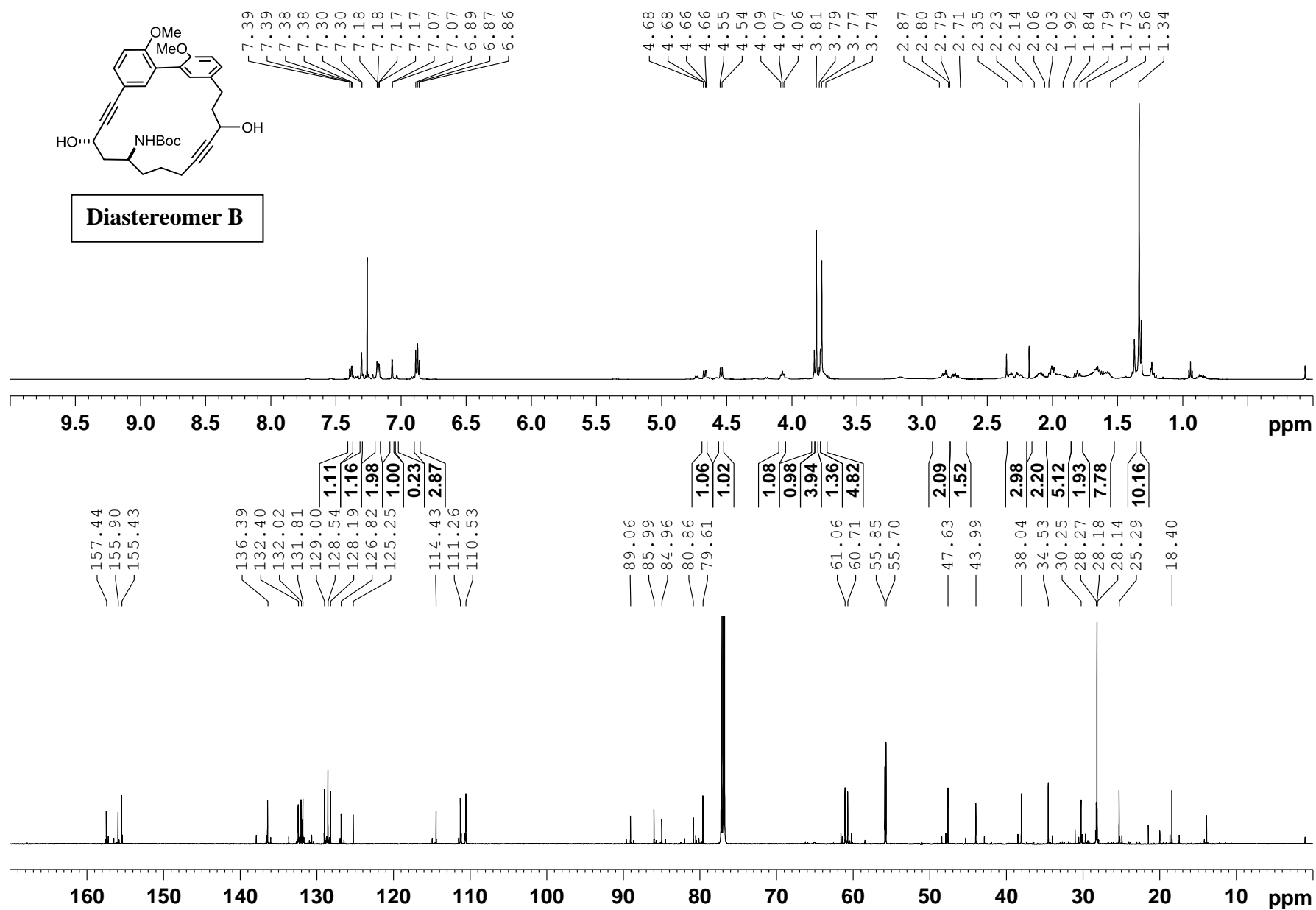


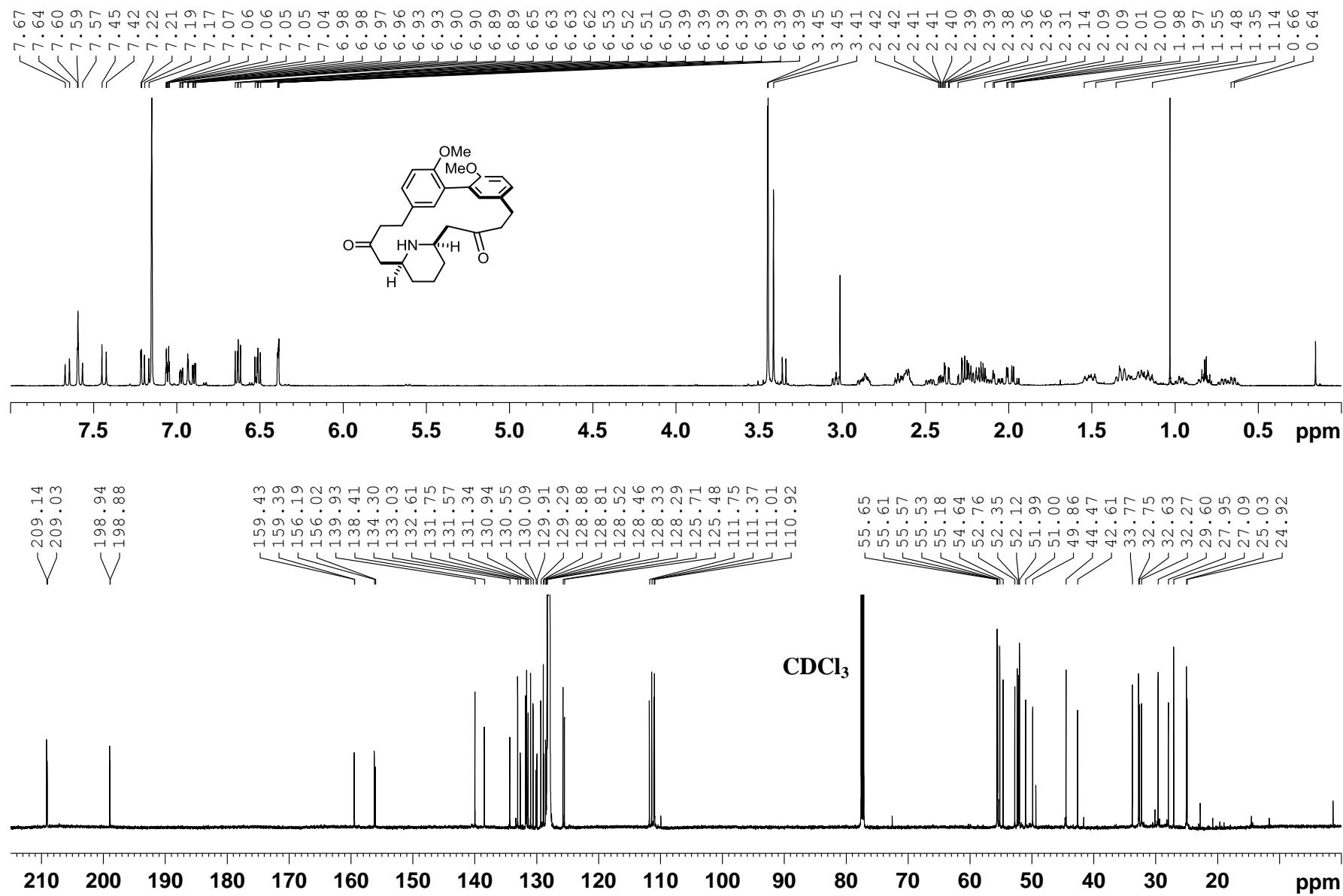


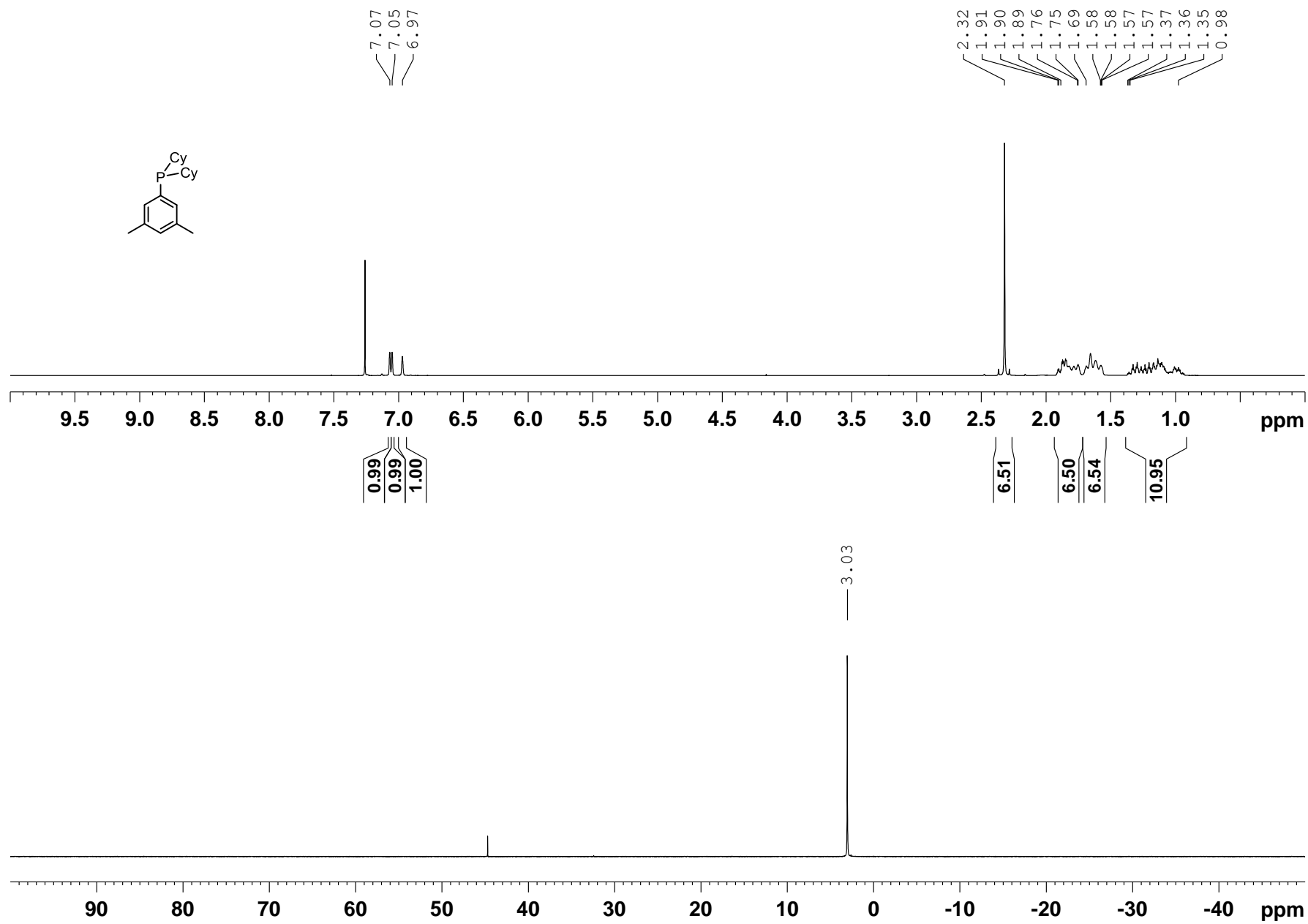


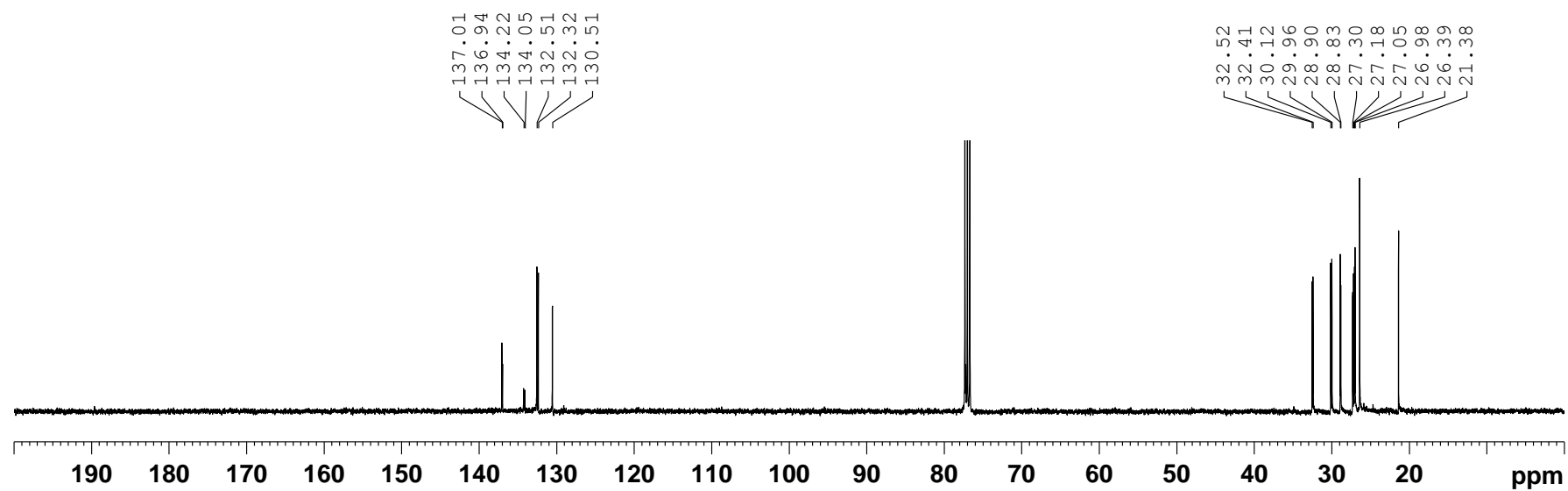
Diastereomer A

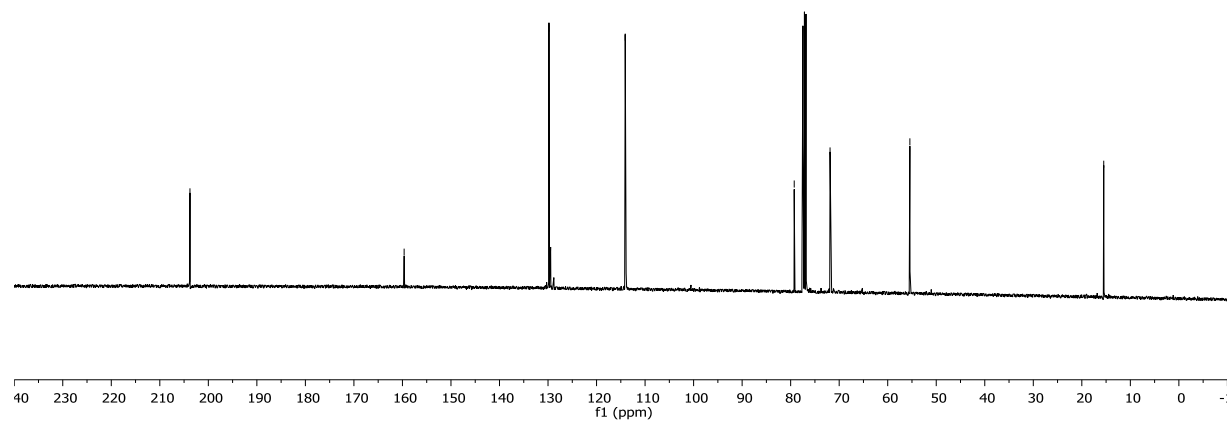
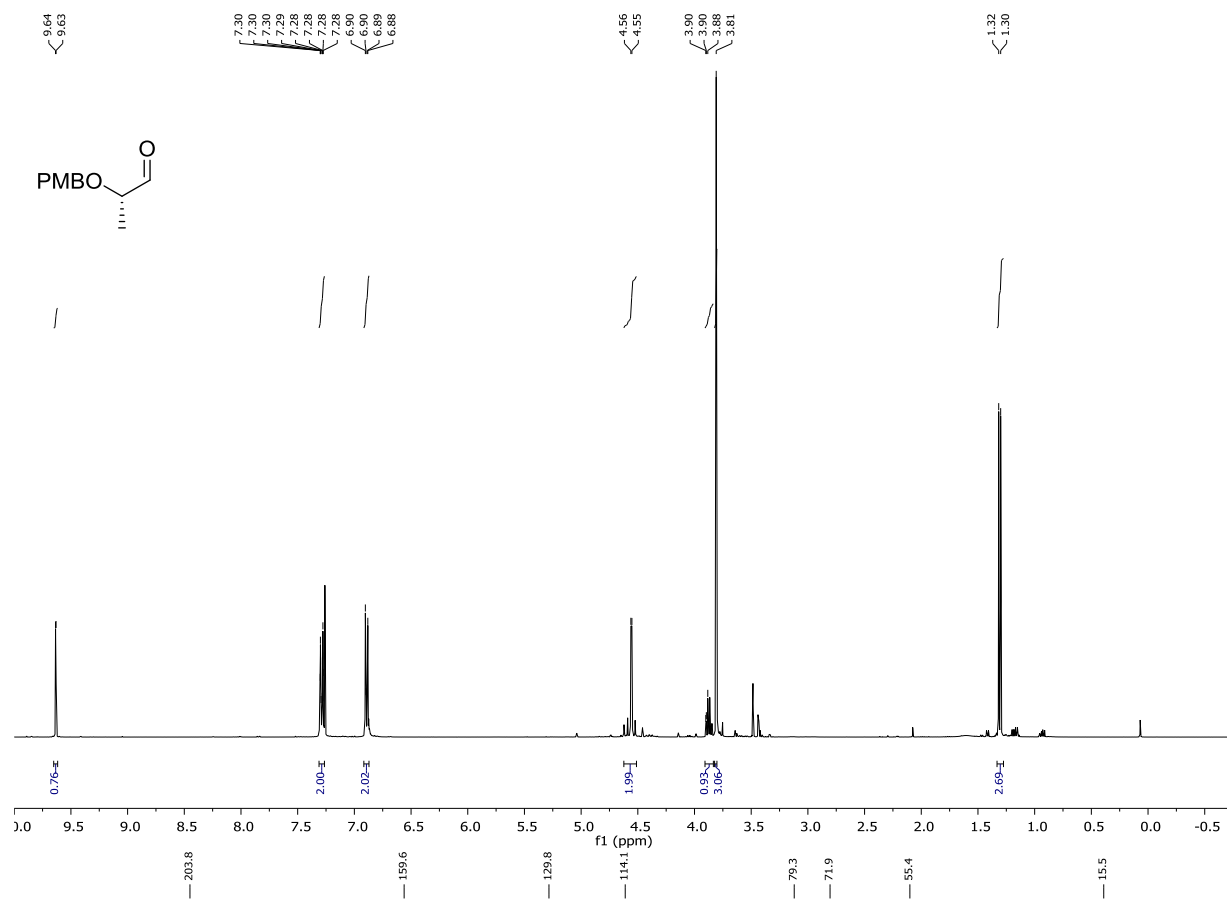


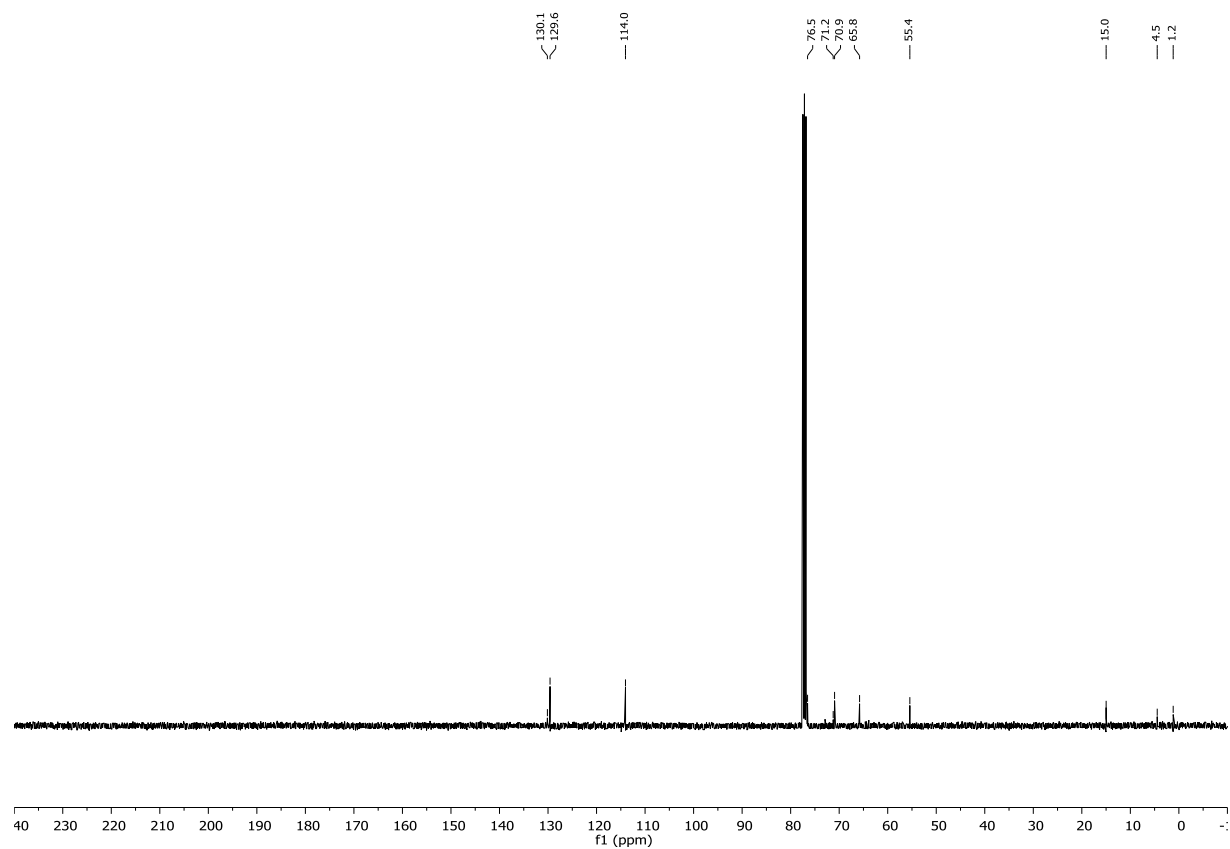




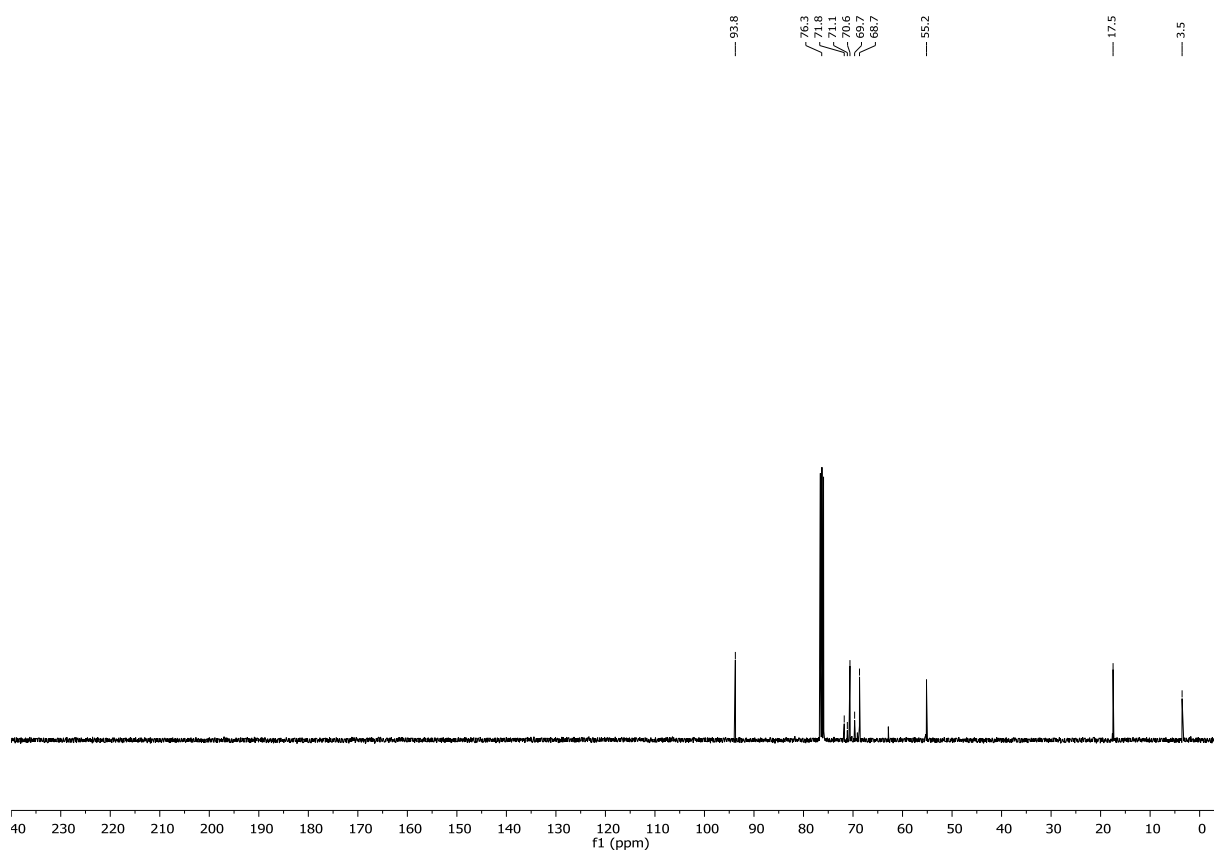
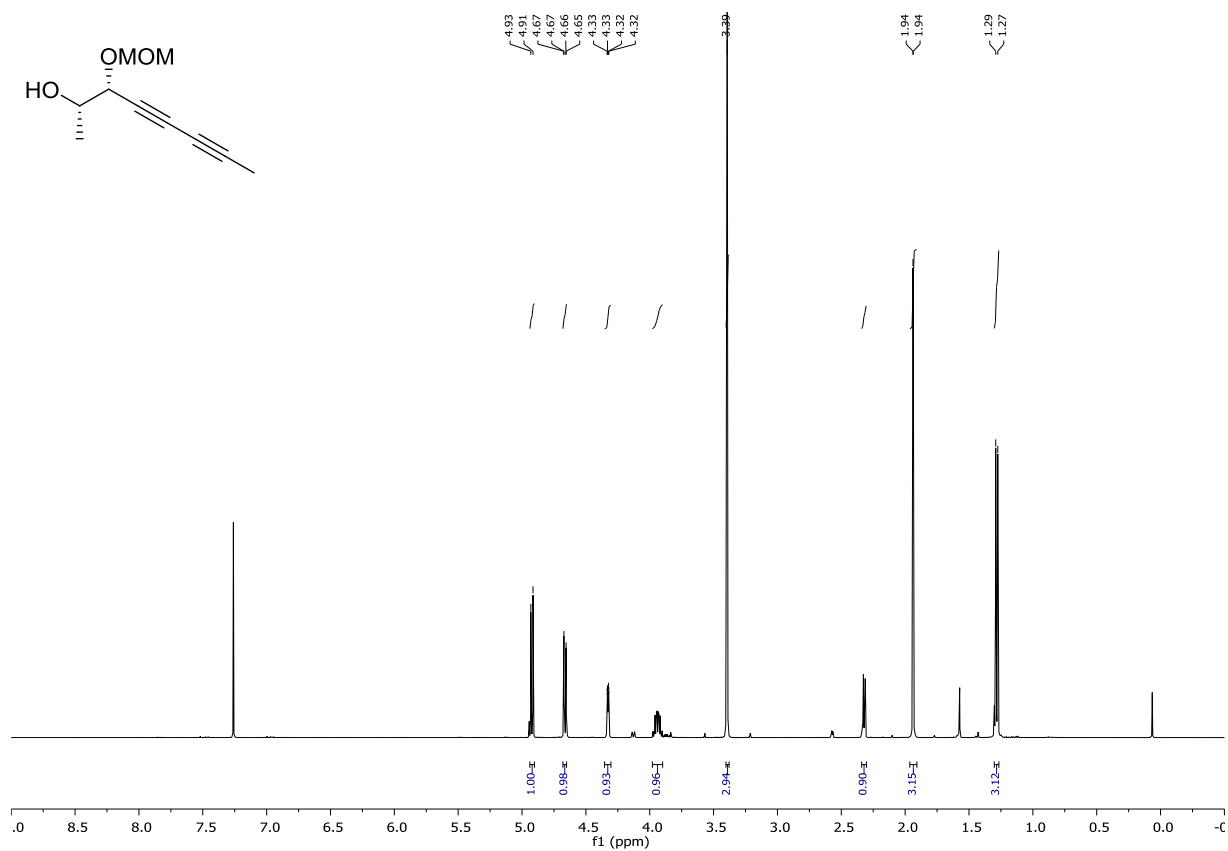


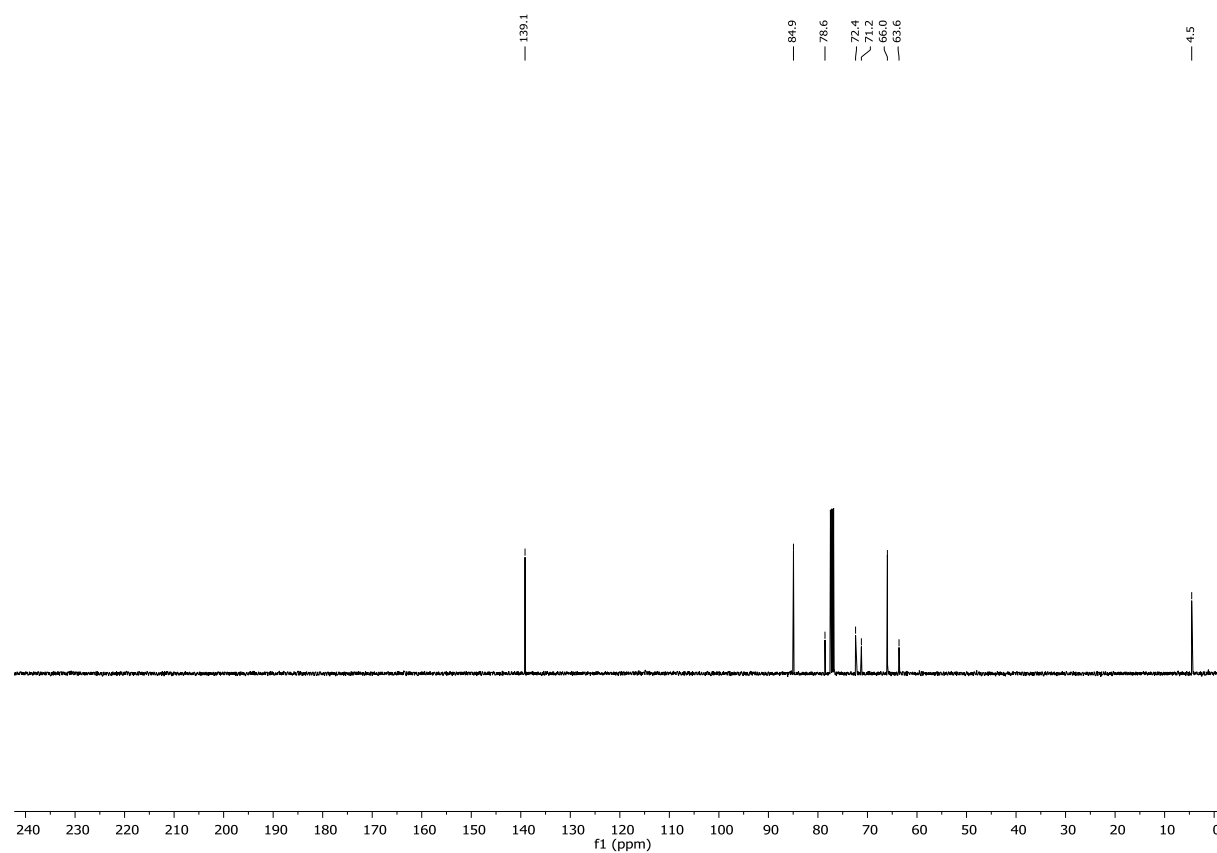
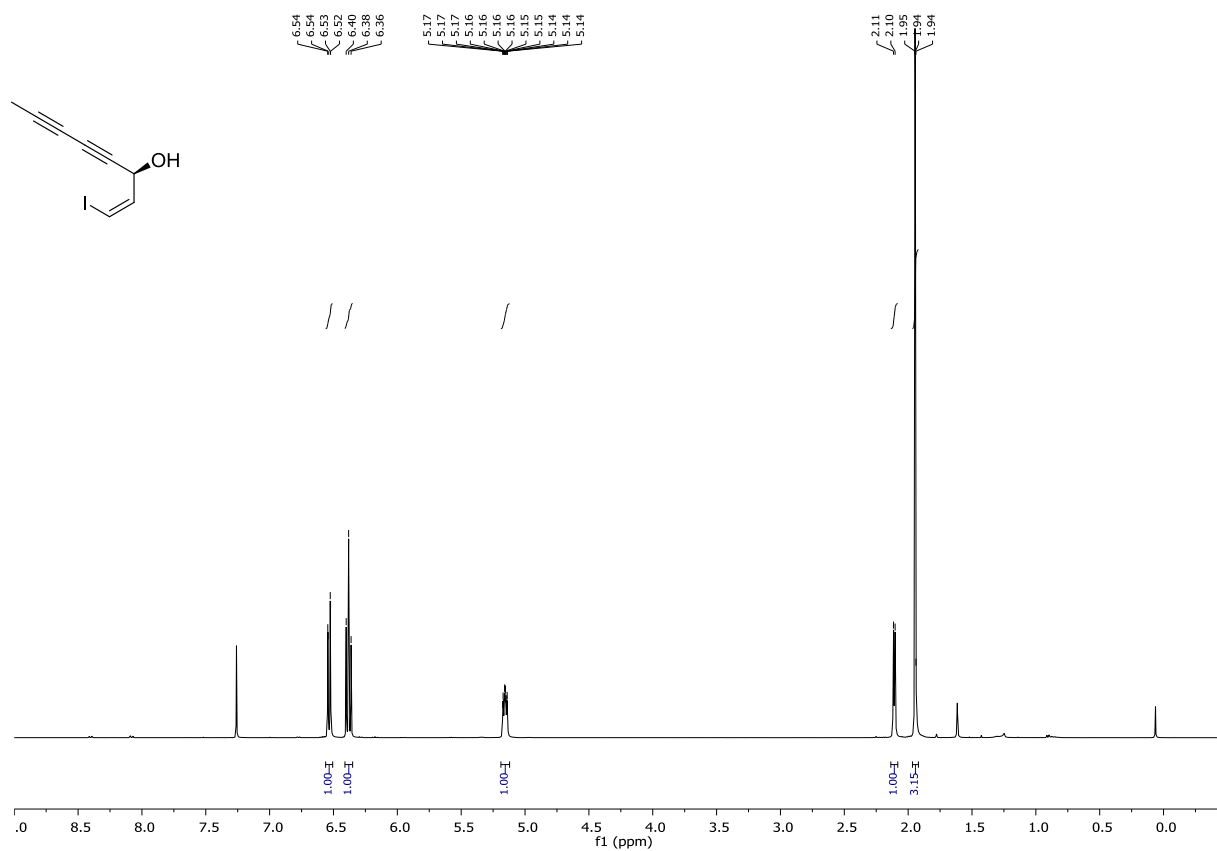


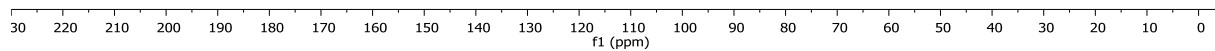


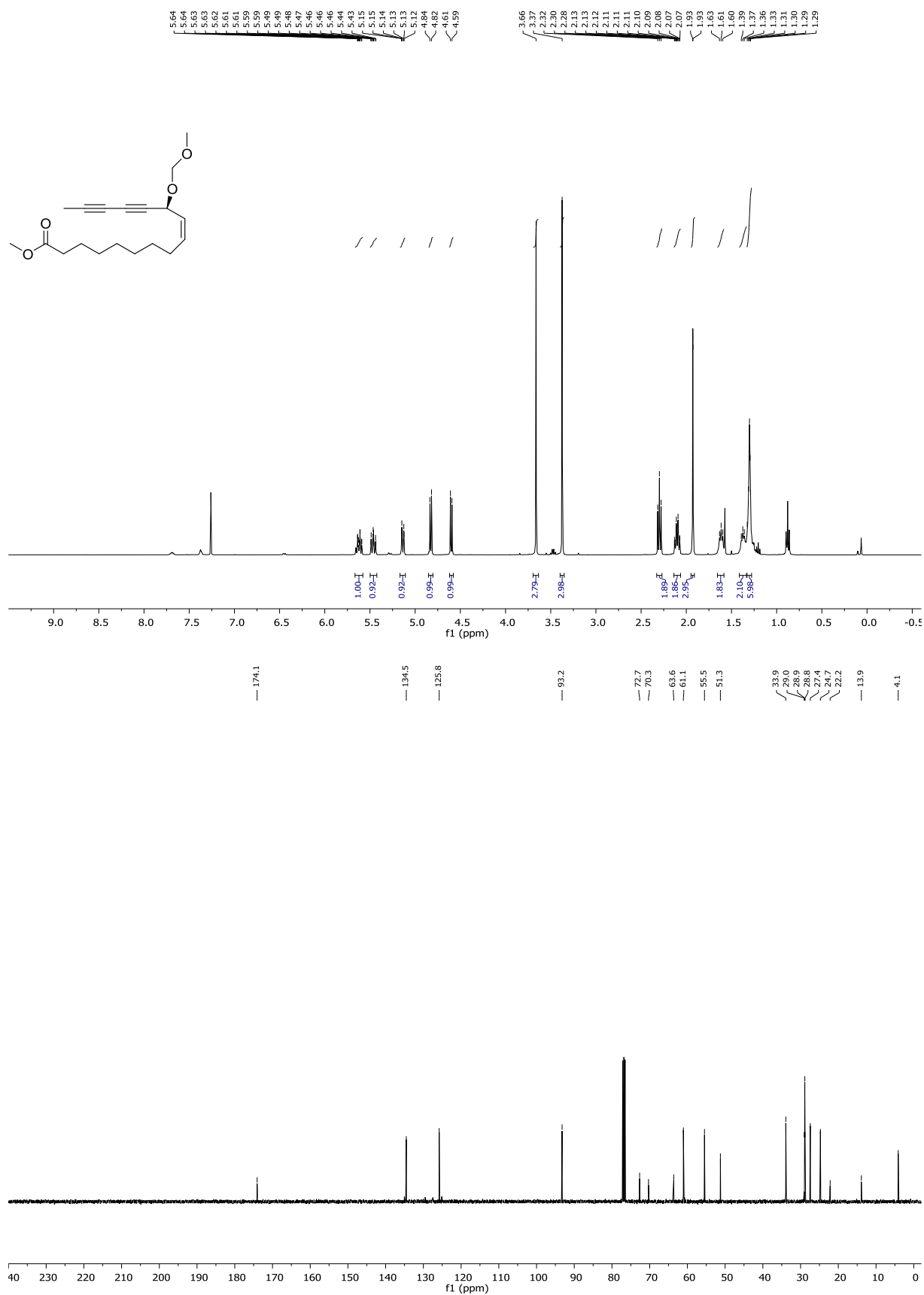


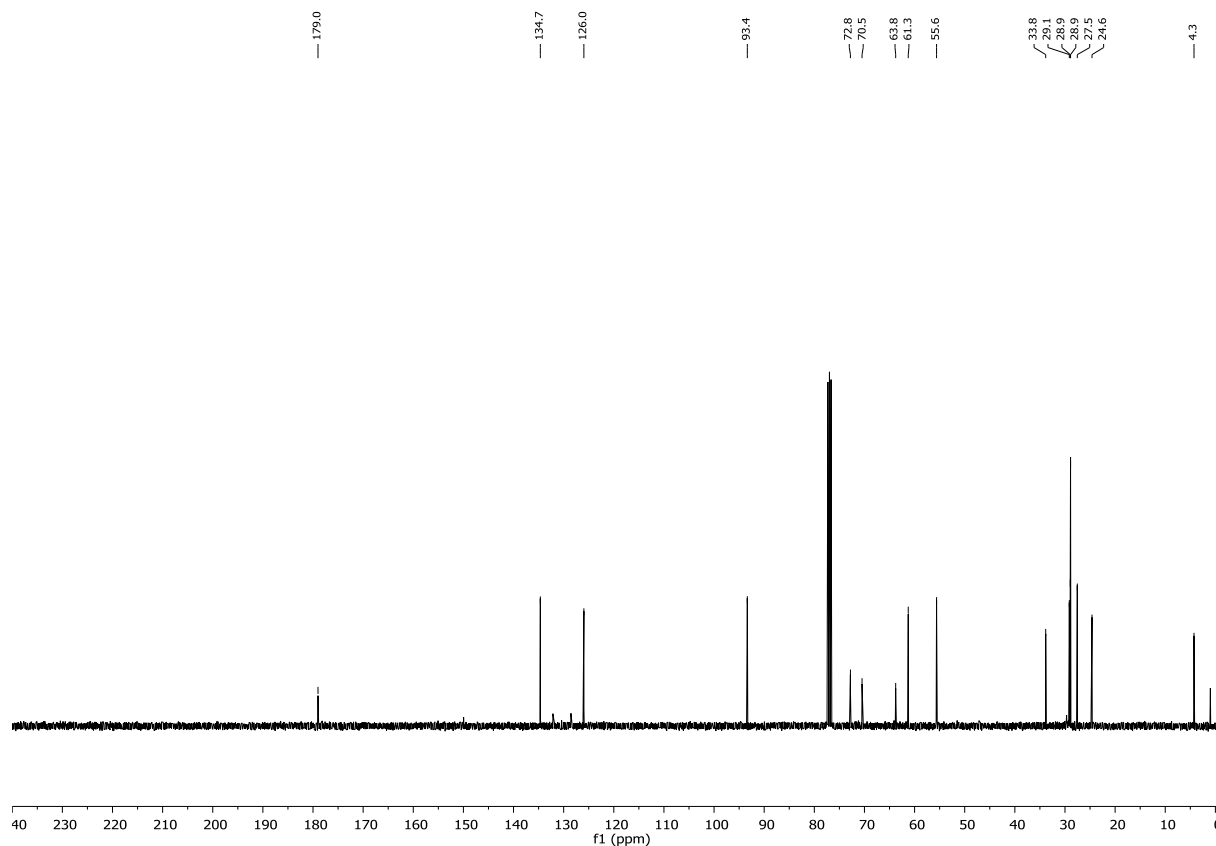
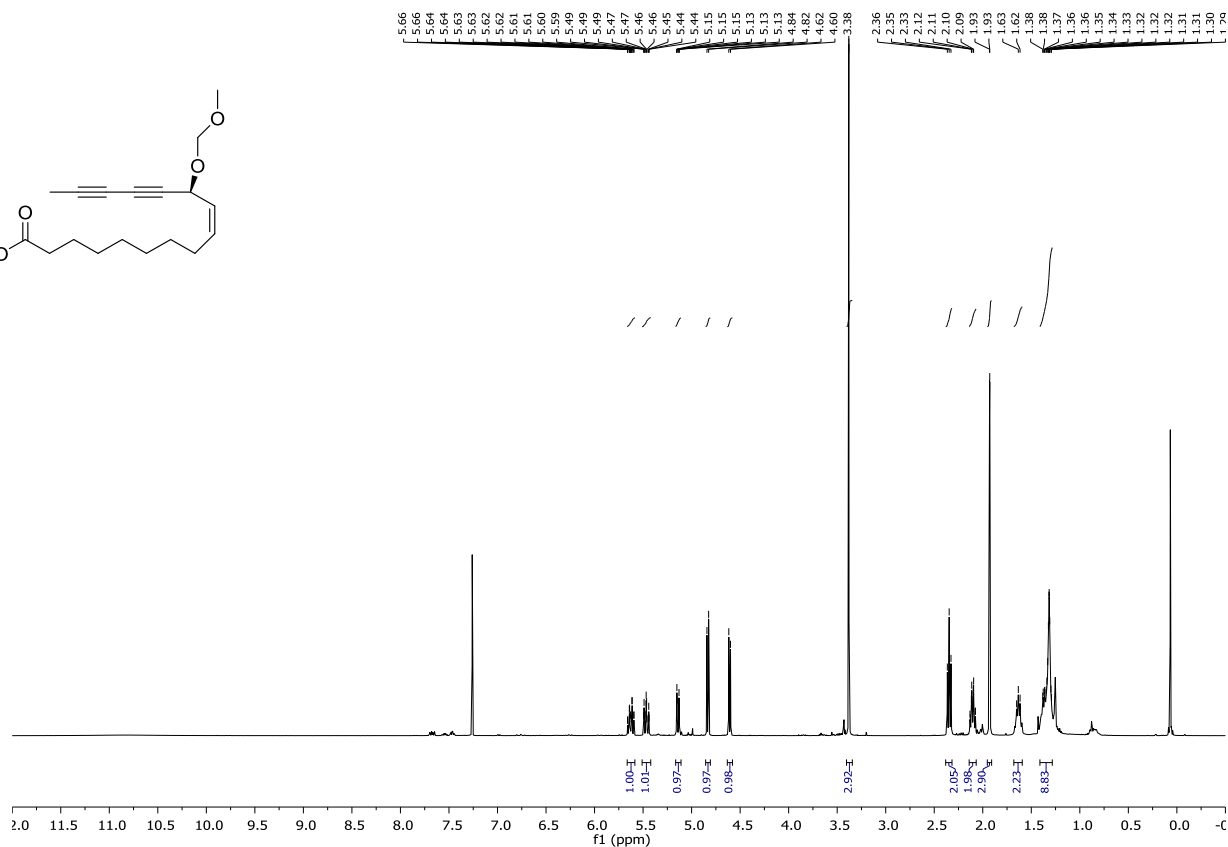
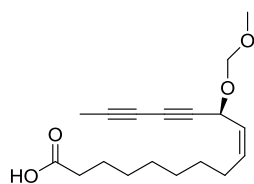


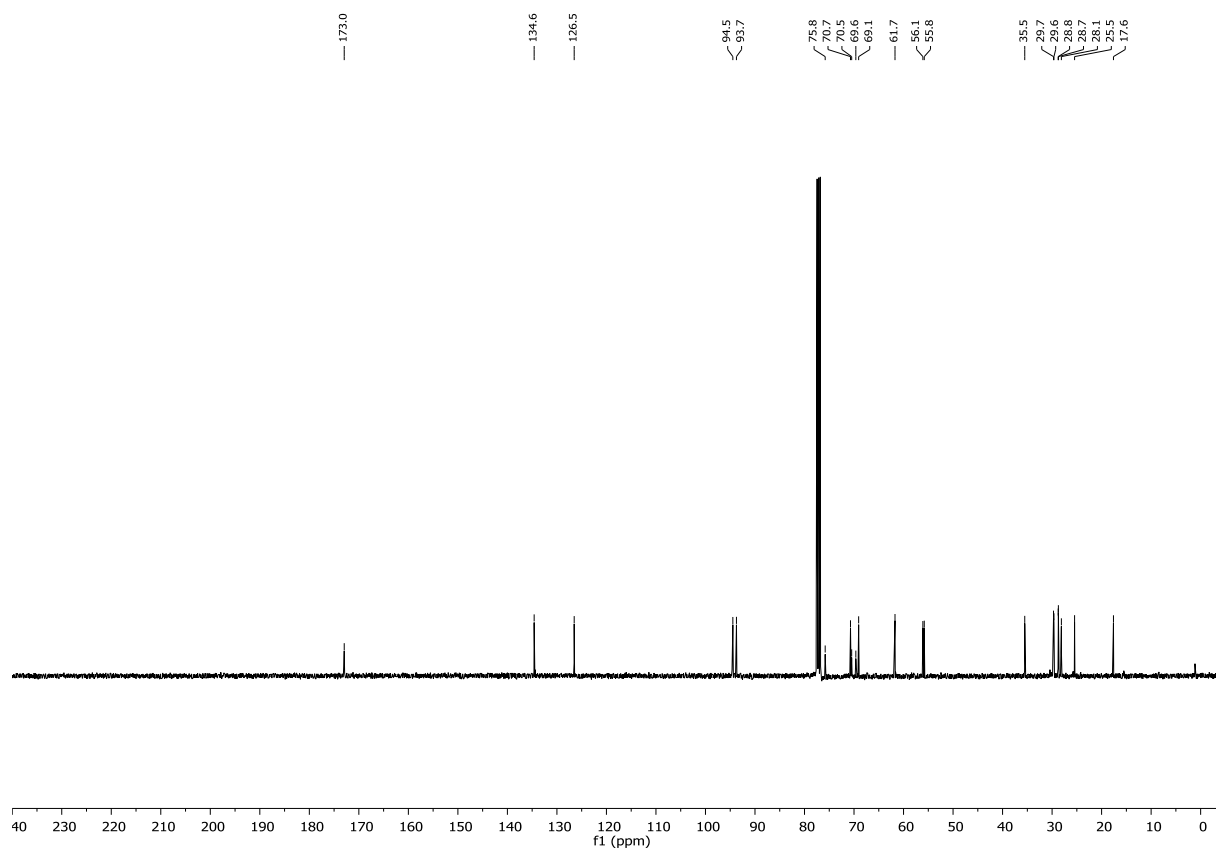
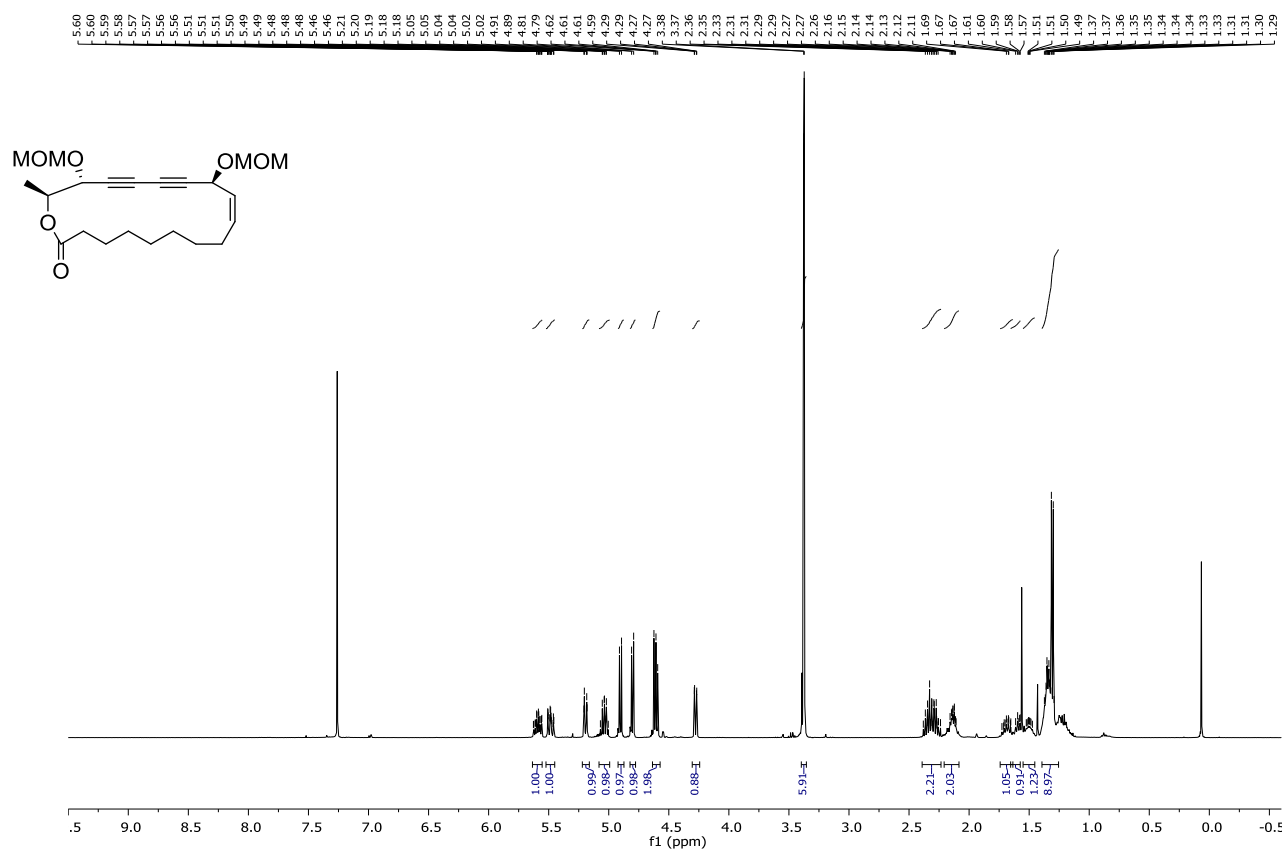


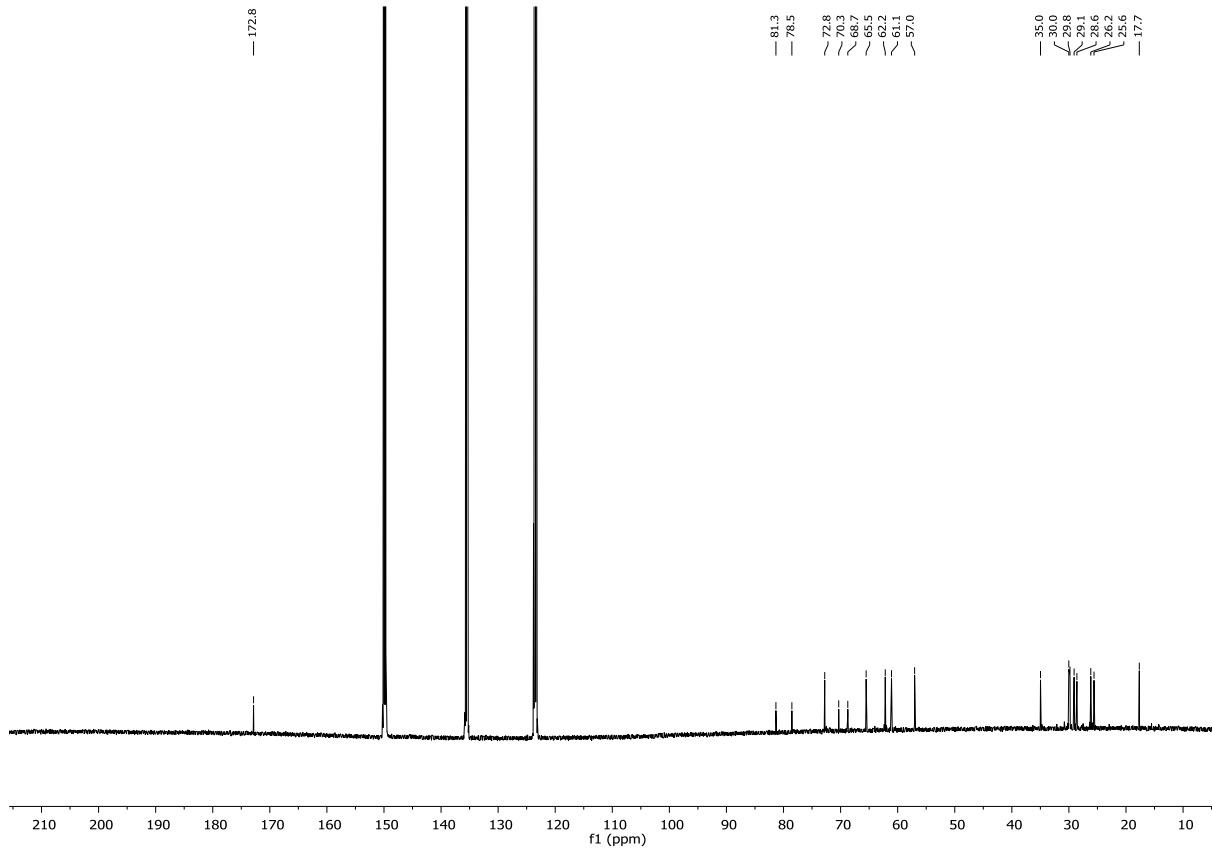
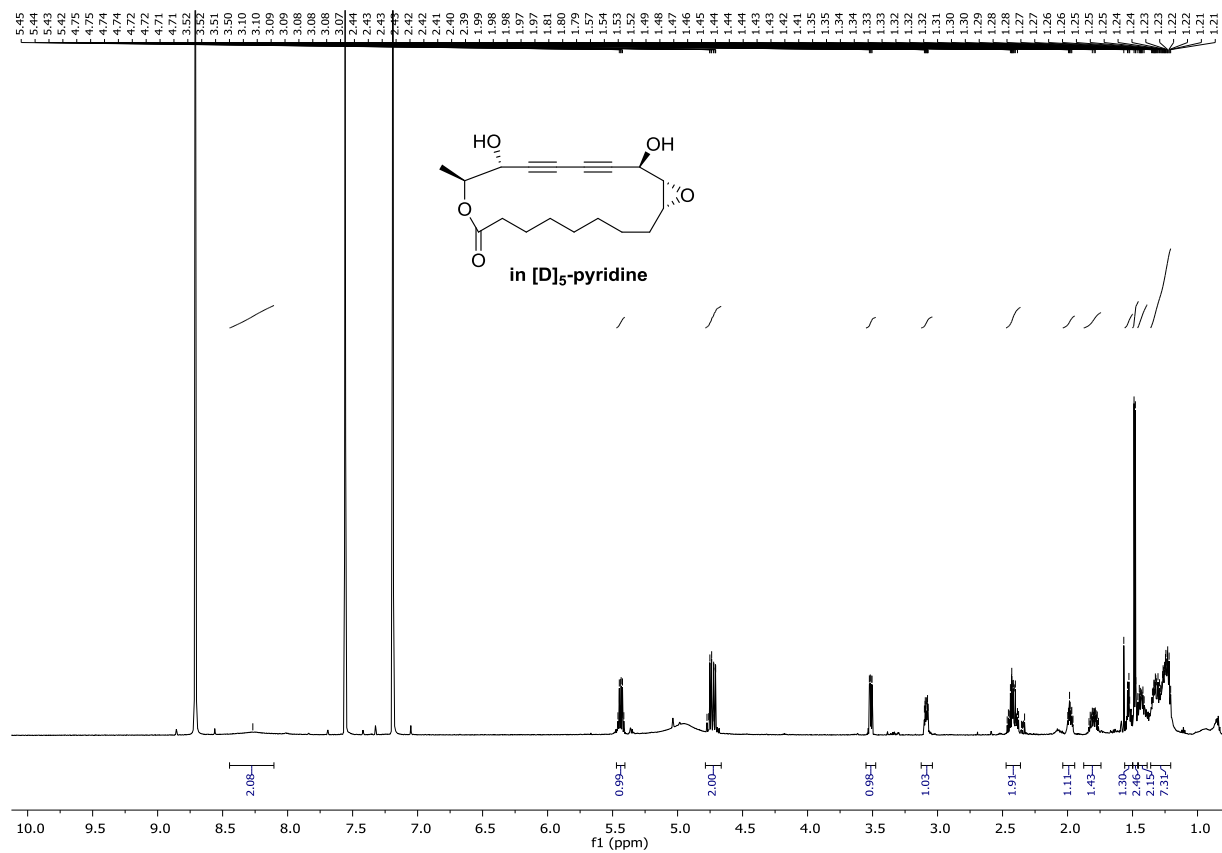




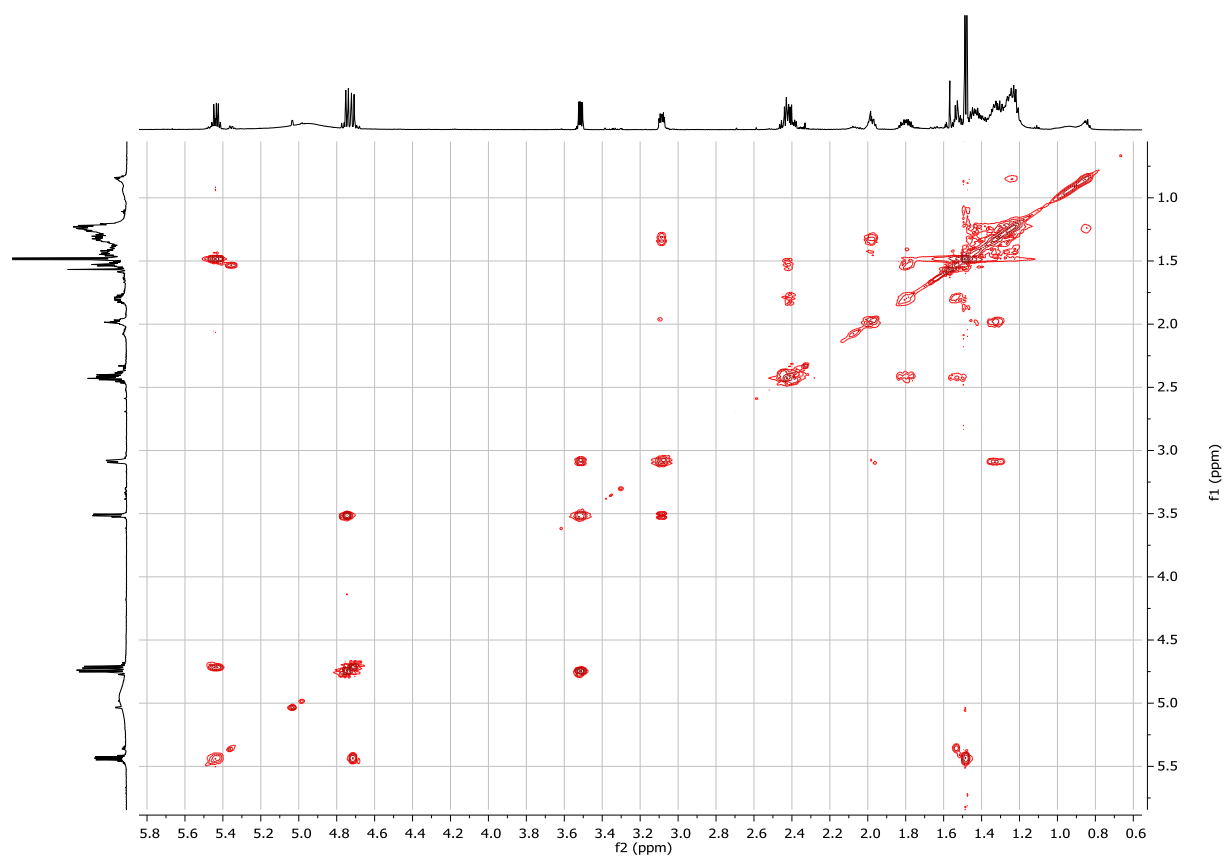








COSY-spectrum of Ivorenolide A in pyridine- d_5



^{13}C - ^1H -HSQC, ^{13}C - ^1H -HMBC spectra of Ivorenolide A in pyridine- d_5

