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Concise Total Syntheses of Amphidinolides C and F

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SUPPORTING INFORMATION

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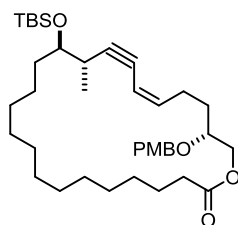
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General: All experiments involving air- and moisture-sensitive compounds were performed under an atmosphere of dry argon in flame-dried glassware. The solvents were purified by distillation over the drying agents indicated, and were transferred under argon: THF, Et₂O (Mg/anthracene), CH₂Cl₂ (P₄O₁₀), Et₃N (CaH₂), MeOH (Mg), DMF (Desmodur[®], dibutyltin dilaurate), toluene (Na/K). Thin layer chromatography (TLC): Macherey-Nagel precoated plates (POLYGRAM[®] SIL/UV254); flash chromatography: Merck silica gel 60N (Spherical, neutral, 230–400 mesh), unless stated otherwise. ¹H and ¹³C NMR spectra were recorded by using a DPX 300 (300 MHz), AV 400 (400 MHz), AV 500 (500 MHz), AV 600 (600 MHz) spectrometer in the solvent indicated; chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to tetramethylsilane scale (CDCl₃: δ_C = 77.16 ppm; residual CHCl₃ in CDCl₃: δ_H = 7.26 ppm; CD₂Cl₂: δ_C = 53.84 ppm; residual CHDCl₂ in CD₂Cl₂: δ_H = 5.32 ppm; C₆D₆: δ_C = 128.06 ppm; residual C₆H₆ in C₆D₆: δ_H = 7.16 ppm; (CD₃)₂CO: δ_C = 205.87 ppm; residual (CH₃)₂CO in (CD₃)₂CO: δ_H = 2.09 ppm). Multiplicities are described by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, pent. = pentet, m = multiplet, b = broad. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were recorded with a Perkin-Elmer Spectrum One FT-IR spectrometer equipped with Perkin-Elmer Universal ATR Sampling Accessory, wavenumbers ($\tilde{\nu}$) in cm⁻¹. Optical rotations ($[\alpha]_D^{20}$) were measured with a Perkin-Elmer Model 343 polarimeter. Low resolution mass spectra (MS) were obtained with a Finnigan MAT 8200 (70 eV, EI); high-resolution mass spectra (HRMS) were obtained with a Finnigan MAT 95 (ESI-MS) or a Bruker APEX III FT-ICR-MS (7 T magnet). Unless stated otherwise, all commercially available compounds (Aldrich, Strem, TCI, Alpha-Aesar, Acros) were used as received.

Where indicated, the signal assignments in the NMR spectra are unambiguous; the numbering scheme is arbitrary and shown in the inserts. The assignments are based upon 1D and 2D spectra recorded using the following pulse sequences from the Bruker standard pulse program library: DEPT; COSY (*cosygpqf* and *cosydqtp*); HSQC (*hsqcedetgpsisp2.2*) optimized for ¹J_{C,H} = 145 Hz; HMBC (*hmbcetgp13nd*) for correlations via ⁿJ_{C,H}; HSQC-TOCSY (*invietgsml*) using an MLEV17 mixing time of 120 ms; NOESY (*noesygpqh*).

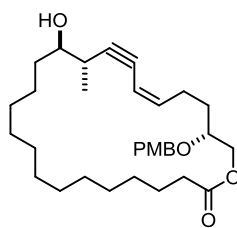
Model Studies.

Representative Procedure for the Preparation of Enyne 6. Freshly distilled CH₂Cl₂ (0.47 mL, 7.2 mmol) was added to a solution of complex **10** (158 mg, 0.29 mmol, 40 mol%) in toluene (10 mL). After 5 minutes, this solution was transferred via canula into a solution of diyne **5** (500 mg, 0.734 mmol) in toluene (290 mL) and the resulting mixture was stirred at 80 °C for 40 h. The mixture was filtered through a pad of silica and the filtrate was evaporated. The resulting oil was taken up in *tert*-butyl methyl ether and the resulting solution was washed with HCl (1 M, 3 x), NaHCO₃ sat. and brine, before it was dried (MgSO₄) and evaporated. Purification of the residue by flash chromatography (hexanes/EtOAc, 88:12) afforded the macrocyclic enyne **6** as a colorless oil (417 mg, 91%, *anti:syn* = 90:10). $[\alpha]_D^{20}$ = -15.4 ° (c = 1.08, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 7.27 (d, J = 8.1 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.77 (dt, J = 10.7, 7.2 Hz, 1H), 5.47 (dd, J =



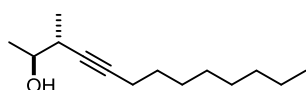
10.7, 1.9 Hz, 1H), 4.60 (dd, $J = 11.1$ Hz, 1H), 4.49 (d, $J = 11.1$ Hz, 1H), 4.25 (dd, $J = 11.6$, 4.1 Hz, 1H), 4.08 (dd, $J = 11.6$, 5.2 Hz, 1H), 3.80 (s, 3H), 3.71 (quint., $J = 4.0$ Hz, 1H), 3.58 (sext., $J = 4.4$ Hz, 1H), 2.71-2.79 (m, 1H), 2.42 (q, $J = 4.0$ Hz, 2H), 2.35 (t, $J = 7.0$ Hz, 2H), 1.57-1.80 (m, 5H), 1.20-1.47 (m, 19H), 1.16 (d, $J = 7.0$ Hz, 3H), 0.90 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 173.9$, 159.4, 141.5, 130.6, 129.5 (2C), 113.9 (2C), 110.2, 97.1, 78.8, 76.2, 74.5, 71.8, 65.6, 55.4, 34.3, 33.2, 33.0, 31.4, 29.4, 28.9, 28.8, 28.4, 28.2, 28.1 (2C), 27.8, 26.3, 26.0 (4C), 24.7, 18.2, 15.0, -4.3, -4.4 ppm; IR (film): $\nu = 2927$, 2855, 1736, 1613, 1513, 1462, 1247, 1088, 1036 cm^{-1} ; MS (EI) m/z (%): 569 (8), 505 (3), 121 (100); HRMS (ESI) calcd. for $\text{C}_{38}\text{H}_{62}\text{O}_5\text{SiNa}$ [$\text{M}+\text{Na}^+$] 649.4254, found 649.4259.

Enyne 7. TBAF (403 mg, 1.28 mmol) was added to a solution of compound **6** (200 mg, 0.319 mmol) in THF (3.2 mL) and the resulting mixture was stirred for 20 h at room temperature. The reaction was quenched with sat. aq. NH_4Cl and the aqueous phase was extracted with *tert*-butyl methyl ether (2 x). The combined extracts were washed with brine, dried (MgSO_4) and evaporated, and the residue was purified by flash chromatography (hexanes/ EtOAc , 85:15) to give the title alcohol as a colorless oil (121 mg, 74%, *anti:syn* = 90:10).

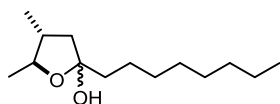


^1H NMR (400 MHz, CDCl_3): $\delta = 7.27$ (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 5.82 (ddd, $J = 10.6$, 7.3, 7.3 Hz, 1H), 5.48 (dd, $J = 10.7$, 1.6 Hz, 1H), 4.59 (d, $J = 11.2$ Hz, 1H), 4.48 (d, $J = 11.2$ Hz, 1H), 4.27 (dd, $J = 11.7$, 3.8 Hz, 1H), 4.09 (dd, $J = 11.7$, 5.7 Hz, 1H), 3.80 (s, 3H), 3.56-3.62 (m, 1H), 3.42-3.48 (m, 1H), 2.67-2.74 (m, 1H), 2.36-2.48 (m, 2H), 2.35 (t, $J = 7.1$ Hz, 2H), 1.49-1.80 (m, 7H), 1.19-1.35 (21H) ppm; ^{13}C NMR (100 MHz, CDCl_3): $\delta = 174.0$, 159.4, 142.1, 130.7, 129.5 (2C), 113.9 (2C), 110.0, 95.4, 79.8, 76.2, 74.6, 71.7, 65.8, 55.4, 35.4, 34.3, 33.7, 31.0, 29.0, 28.6, 28.2, 28.2, 28.0, 28.0, 27.9, 27.9, 26.4, 25.4, 24.7, 17.6 ppm; IR (film): $\nu = 3474$, 2925, 2854, 1733, 1612, 1513, 1456, 1246, 1172 cm^{-1} ; MS (EI) m/z (%): 391(2), 121 (100); HRMS (ESI) calcd. for $\text{C}_{32}\text{H}_{48}\text{O}_5\text{Na}$ [$\text{M}+\text{Na}^+$] 535.3389, found 535.3394.

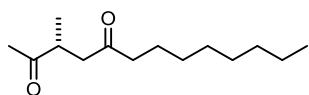
Compound 16. *n*BuLi (1.6 M in hexane, 12.6 mL, 20.22 mmol) was slowly added to a solution of 1-decyne (4.1 mL, 22.45 mmol) in THF (112 mL) at room temperature. After 15 min, the mixture was cooled to -70 °C before *cis*-2,3-dimethyloxirane (500 μL , 5.61 mmol) was added, followed by $\text{BF}_3\cdot\text{OEt}_2$ (3.2 mL, 25.24 mmol). The mixture was stirred for 12 h at this temperature. Sat. aq. NH_4Cl (50 mL) was added dropwise and the mixture was allowed to reach room temperature. The aqueous phase was extracted with Et_2O (3 x 50 mL), the combined organic layers were washed with H_2O (2 x 20 mL), dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (SiO_2 , pentane/ Et_2O 20/1) afforded the title compound as colorless oil (1.09 g, 92%).



Diketone 19. PdCl_2 (3.5 mg, 10 mol%) was added to a solution of compound **16** (40 mg, 0.20 mmol) in H_2O (10 μL) and acetonitrile (627 μL). The orange suspension was heated at 80 °C



for 1 h to give a yellow solution, which was cooled to room temperature and concentrated. The crude product was passed through a short pad of silica, eluting with pentane/Et₂O (6.5/1), to give compound **18** as a mixture of the hydroxy-ketone and the ketal forms (37 mg, 84%). IR (film): 3048, 2956, 2923, 2854, 1711, 1456, 1378, 1102, 1073, 987, 917; MS (EI): *m/z* (%): 228 (0.55), 141 (12), 115 (100), 97 (13), 86 (11), 73 (24), 70 (19), 55 (18), 43 (19); HRMS (ESIpos) calcd. for C₁₄H₂₈O₂Na [M + Na⁺] 251.1981, found 251.1980.

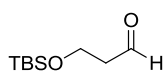


PDC (125 mg, 0.32 mmol) was added to a solution of this compound (12.4 mg, 0.054 mmol) in dichloromethane (418 μL). The resulting mixture was stirred for 12 h at room temperature before it was diluted with Et₂O (5 mL) and filtered through a pad of Celite. The filtrate was evaporated to give the title compound which was pure enough to confirm its identity (11.7 mg, 95%). ¹H NMR (400 MHz, C₆D₆): δ = 2.85-2.75 (m, 1H), 2.69 (dd, *J* = 9.2, 17.4 Hz, 1H), 2.13-1.95 (m, 2H), 1.87 (s, 3H), 1.80 (dd, *J* = 4.0, 17.4 Hz, 1H), 1.59-1.45 (m, 2H), 1.58-1.08 (m, 10H), 0.90 (t, *J* = 6.9 Hz, 3H), 0.74 (d, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, C₆D₆): δ = 209.4, 208.0, 45.6, 42.7, 41.6, 32.2, 29.8, 29.6 (x 2), 28.2, 24.1, 23.1, 16.5, 14.4; IR (film): 2921, 2852, 1462, 1377, 1259, 1012, 790.

Preparation of Fragment F

Compound S1. A flame-dried round-bottomed flask equipped with an argon inlet, a rubber septum and a magnetic stir-bar, was charged with 1,3-propanediol (28.7 mL, 400 mmol), CH₂Cl₂ (400 mL) and triethylamine (33.4 mL, 240 mmol) to give a clear solution. After cooling to 0 °C using an ice bath, a solution of TBSCl (30.1 g, 200 mmol) in CH₂Cl₂ (60 mL) was added via cannula and the resulting mixture was stirred at room temperature overnight (15 h). For work up, aq. sat. NaHCO₃ (100 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (40 mL), and the combined organic phases were washed with H₂O (100 mL) and brine (100 mL). The organic layer was then dried using MgSO₄, filtered and evaporated and the remaining yellow oil was purified by flash chromatography (SiO₂, hexanes/EtOAc, 30→50%) to afford **S1** as a colorless oil (32.7 g, 86%). ¹H NMR (400 MHz, CDCl₃): δ = 3.84 (t, *J* = 5.6 Hz, 2H), 3.80 (t, *J* = 5.6 Hz, 2H), 2.31 (bs, 1H), 1.78 (quint, *J* = 5.6 Hz, 2H), 0.90 (s, 9H), 0.08 ppm (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ = 63.1, 62.6, 34.4, 26.0 (3C), 18.3, -5.4 ppm (2C); IR (film): 3347, 2929, 2857, 1472, 1388, 1361, 1254, 1086, 1006, 961, 833, 773 cm⁻¹.

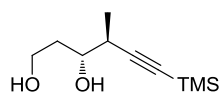
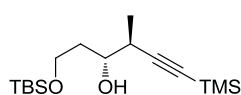
Compound 21. A round-bottomed flask, equipped with a magnetic stir-bar, was charged with alcohol **S1** (14.0 g, 73.6 mmol). CH₂Cl₂ (360 mL) and pH 8.6 carbonate buffer (365 mL) containing potassium bromide (876 mg, 7.36 mmol, 0.10 equiv) were added and the resulting biphasic mixture was cooled to 0 °C using an ice bath. Once this temperature was reached, 2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO, 115 mg, 0.736 mmol, 0.01 equiv) was introduced, causing a color change of the organic layer to bright orange. Next, an aqueous solution of sodium hypochlorite (~ 10%, 95 mL) was diluted with pH 8.6 carbonate buffer (365 mL) in an Erlenmeyer flask. This solution was also cooled to 0 °C before it was added to the biphasic mixture, which was then stirred at this temperature



until the reaction was complete, as judged by TLC analysis (ca. 1 h; note: when complete conversion is reached, a color change occurs from bright orange to light yellow). The reaction was quenched with aq. sat. $\text{Na}_2\text{S}_2\text{O}_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL) and the combined extracts were washed with H_2O (100 mL) and brine (100 mL) before being dried over Na_2SO_4 . The solvent was evaporated to give the volatile aldehyde **21** (11.9 g, 86%) as a colorless oil, which was used in the next step without further purification. ^1H NMR (300 MHz, C_6D_6): δ = 9.40 (t, J = 1.9 Hz, 1H), 3.57 (t, J = 6.0 Hz, 2H), 2.03 (dt, J = 1.9, 6.0 Hz, 2H), 0.90 (s, 9H), -0.02 ppm (s, 6H); ^{13}C NMR (100 MHz, C_6D_6): δ = 200.5, 58.0, 47.2, 26.6 (3C), 18.9, -4.8 ppm (2C); IR (film): 2955, 2930, 2886, 2858, 1727, 1472, 1464, 1389, 1361, 1254, 1212, 1094, 970, 820, 774 cm^{-1} ; MS (EI): m/z (%): 131 (M^+ -57, 68), 101 (100), 75 (51), 59 (27), 45(10); HRMS (CI, *i*-butane) calcd. for $\text{C}_9\text{H}_{21}\text{O}_2\text{Si}$ [$\text{M} + \text{H}^+$] 189.1311, found 189.1309.

Compound 23. A three-necked, jacketed Schlenk flask, equipped with a magnetic stir-bar, argon bubbler and two septa, was charged with $\text{Pd}(\text{OAc})_2$ (596 mg, 2.65 mmol, 0.05 equiv), THF (16 mL) and PPh_3 (696 mg, 2.65 mmol, 0.05 equiv). The resulting orange solution was cooled to -78 °C before a solution of (*R*)-**22** (17.5 g, 79.6 mmol) in THF (20 mL) was added. After stirring for 10 min, a solution of aldehyde **21** (10.0 g, 53.1 mmol) in THF (16 mL) was introduced before diethylzinc (1.0 M in hexane, 159 mL, 159 mmol) was added via cannula (care was taken to add the solution dropwise directly into the mixture). The reaction was stirred for 1 h at this temperature before it was allowed to gradually warm to -20 °C over 4 h and stirred at this temperature for 12 h. At this point, the gray mixture was diluted with *tert*-butyl methyl ether (80 mL) and the reaction was carefully quenched with aqueous sat. NH_4Cl (40 mL). The resulting emulsion was filtered through a pad of Celite that was carefully rinsed with *tert*-butyl methyl ether (160 mL). The aqueous layer was extracted with *tert*-butyl methyl ether (3 x 50 mL). The combined extracts were washed with aq. sat. NH_4Cl (70 mL), H_2O (100 mL) and brine (100 mL), dried over MgSO_4 , filtered and evaporated. The crude product was purified by flash chromatography (SiO_2 , hexanes/*tert*-butyl methyl ether gradient, 3→7%) to give the title compound as a mixture of diastereomers (14.5 g, 87%, *anti:syn* = 90:10). $[\alpha]_D^{20} = -6.2^\circ$ (c = 1.07, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ = 4.00-3.59 (m, 3H), 3.53 (bs, 1H, *syn*), 2.90 (bs, 1H, *anti*), 2.60 (dq, J = 4.5, 7.0 Hz, 1H, *anti*), 2.64-2.48 (m, 1H, *syn*), 1.83-1.61 (m, 2H), 1.21 (d, J = 6.6 Hz, 3H, *syn*), 1.20 (d, J = 7.1 Hz, 3H, *anti*), 0.90 (s, 9H), 0.14 (s, 9H, *anti*), 0.13 (s, 9H, *syn*), 0.08 (s, 6H, *syn*), 0.07 ppm (s, 6H, *anti*); ^{13}C NMR (75 MHz, CDCl_3 , only for major *anti*-isomer): δ = 108.3, 86.9, 73.3, 62.0, 36.3, 34.0, 26.0 (3C), 18.4, 16.6, 0.3 (3C), -5.3 ppm (2C); IR (film): 3509, 2956, 2930, 2858, 2167, 1472, 1388, 1361, 1249, 1081, 833, 774 cm^{-1} ; MS (EI): m/z (%): 261 (M^+ -53, 8), 189 (33), 147 (20), 131 (100), 126 (19), 101 (12), 89 (29), 75 (40), 73 (86), 59 (14); HRMS (ESI-pos) calcd. for $\text{C}_{16}\text{H}_{34}\text{O}_2\text{Si}_2\text{Na}$ [$\text{M} + \text{Na}^+$] 337.1989, found 337.1987.

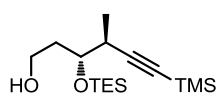
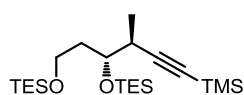
Compound S2. A round-bottomed flask, equipped with a magnetic stir-bar and a glass stopper was charged with alcohol **23** (10.0 g, 31.8 mmol) and HCl (1% in EtOH, *v/v*, 46 mL). The cloudy mixture was stirred at room temperature for 12 h. The resulting clear solution was slowly added to a separatory funnel containing aq. sat. NaHCO_3 (90 mL) and *tert*-butyl methyl ether (90 mL). The aqueous



layer was extracted with *tert*-butyl methyl ether (3 x 50 mL), the combined organic phases were washed with H₂O (50 mL) and brine (50 mL), dried over Na₂SO₄, filtered and evaporated. The crude product was triturated with hexane until a white solid had formed. The mother liquor was decanted and the solid recrystallized from hot hexane (~ 30 mL; the mixture was placed in the freezer overnight to induce crystallization). The small white needles were collected and dried under vacuum to afford diol **S2** (5.8 g, 91%). m.p. = 39-41°C (hexane); $[\alpha]_D^{20} = -9.6^\circ$ (c = 1.67, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 3.96-3.80 (m, 2H), 3.68 (ddd, *J* = 3.9, 5.5, 8.6 Hz, 1H), 2.58 (dq, *J* = 5.8, 7.0 Hz, 1H), 1.88 (bs, 2H), 1.84-1.70 (m, 2H), 1.20 (d, *J* = 7.0 Hz, 3H), 0.16 ppm (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 107.3, 88.1, 74.3, 61.5, 36.3, 34.8, 17.1, 0.3 ppm (3C); IR (film): 3343, 2958, 2165, 1408, 1248, 1055, 835, 758 cm⁻¹; MS (EI): *m/z* (%): 126 (M⁺-74, 34), 75 (17), 73 (100); HRMS (ESI-pos) calcd. for C₁₀H₂₀O₂SiNa [M + Na⁺] 223.1125, found 223.1126.

Compound S3. A Schlenk flask, equipped with a magnetic stir-bar and a glass stopper, was charged with diol **S2** (4.1 g, 27.0 mmol) and CH₂Cl₂ (100 mL). The resulting solution was cooled to 0 °C before 2,6-lutidine (7.1 mL, 62.1 mmol) and TESOTf (9.7 mL, 43.5 mmol) were successively added. The colorless mixture was stirred at this temperature for 1 h. Then a second portion of 2,6-lutidine (3.6 mL, 40.5 mmol) and TESOTf (4.9 mL, 28.3 mmol) were added and stirring continued for 30 min. The reaction was quenched with aq. sat. NH₄Cl (40 mL) and the aqueous layer extracted with *tert*-butyl methyl ether (3 x 30 mL). The combined organic phases were washed with brine (30 mL), dried over Na₂SO₄ and concentrated to a pale yellow oil, which was purified by flash chromatography (SiO₂, hexanes/*tert*-butyl methyl ether gradient, 0.5 → 2%) to give **S3** as a colorless oil (8.8 g, quant.). $[\alpha]_D^{20} = +1.2^\circ$ (c = 1.15, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 3.89 (quint, *J* = 4.1 Hz, 1H), 3.74-3.64 (m, 2H), 2.60 (dq, *J* = 4.4, 7.0 Hz, 1H), 1.89 (ddt, *J* = 3.6, 7.6, 13.5 Hz, 1H), 1.68-1.55 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.61 (q, *J* = 7.9 Hz, 6H), 0.60 (q, *J* = 7.9 Hz, 6H), 0.13 ppm (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 109.4, 85.8, 71.2, 60.1, 36.2, 33.7, 14.9, 7.0 (3C), 6.9 (3C), 5.2 (3C), 4.7 (3C), 0.3 ppm (3C); IR (film): 2955, 2877, 2163, 1458, 1414, 1375, 1248, 1088, 1003, 839, 724 cm⁻¹; MS (EI): *m/z* (%): 399 (M⁺-29, 14), 303 (91), 217 (24), 189 (22), 171 (12), 145 (17), 117 (100), 115 (18), 93 (17), 87 (21), 73 (17), 59 (12); HRMS (ESI-pos) calcd. for C₂₂H₄₈O₂Si₃Na [M + Na⁺] 451.2854, found 451.2854.

Compound S4. A three-necked, jacketed Schlenk flask equipped with a magnetic stir-bar, an argon bubbler and two septa was charged with compound **S3** (5.0 g, 11.7 mmol) and CH₂Cl₂ (115 mL). The solution was cooled to -50 °C before MeOH (110 mL) was added and the mixture stirred for 15 min. Next, a solution of PPTS (293 mg, 1.17 mmol, 0.10 equiv) in MeOH (5 mL) was slowly added via syringe and stirring continued at -50 °C for 15 h. The reaction was quenched with aq. sat. NaHCO₃ (100 mL) and the mixture allowed to reach ~ 5 °C. H₂O (100 mL) was added and the aqueous phase extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were washed with H₂O (100 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated to a colorless oil, which was purified by flash chromatography (SiO₂, hexanes/EtOAc gradient, 1 → 3%) to afford **S4** as a colorless oil (2.9 g, 80%). $[\alpha]_D^{20} = +0.7^\circ$ (c = 0.6, CHCl₃); ¹H NMR (400 MHz,



C₆D₆): δ = 4.03 (quint, J = 4.1 Hz, 1H), 3.66-3.54 (m, 2H), 2.71 (dq, J = 4.4, 7.1 Hz, 1H), 1.97 (dddd, J = 3.9, 5.6, 7.6, 14.0 Hz, 1H), 1.69 (dddd, J = 5.4, 5.7, 8.4, 14.0 Hz, 1H), 1.19 (d, J = 7.0 Hz, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.57 (q, J = 7.9 Hz, 6H), 0.20 ppm (s, 9H); ¹³C NMR (100 MHz, C₆D₆): δ = 109.7, 86.3, 72.6, 59.9, 36.0, 34.0, 15.2, 7.1 (3C), 5.4 (3C), 0.3 ppm (3C); IR (film): 3343, 2956, 2877, 2165, 1458, 1414, 1375, 1248, 1082, 1005, 837, 724 cm⁻¹; MS (EI): m/z (%): 285 (M⁺-29, 8), 189 (100), 159 (71), 145 (18), 131 (42), 117 (80), 115 (29), 103 (14), 87 (36), 75 (30), 59 (25); HRMS (ESI-pos) calcd. for C₁₆H₃₄O₂Si₂Na [M + Na⁺] 337.1990, found 337.1991.

Compound 24. A jacketed Schlenk flask, equipped with a magnetic stir-bar and a glass stopper, was charged with alcohol **S4** (2.0 g, 6.36 mmol) and CH₂Cl₂ (66 mL). The solution was cooled to -30 °C before diisopropylethylamine (4.2 mL, 24.2 mmol) was added, followed by DMSO (4.5 mL, 63.6 mmol).

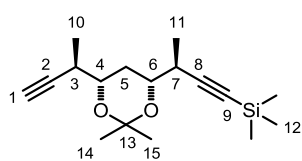
The mixture was stirred for 5 min before SO₃·pyridine (6.1 g, 38.1 mmol) was introduced in one portion. The mixture was stirred at -30 °C for 1 h before the reaction was quenched with aq. pH 7.0 buffer (95 mL). The mixture was warmed until two clear layers had formed. The aqueous phase was extracted with Et₂O (2 x 50 mL), the combined organic extracts were washed with brine (100 mL), dried over Na₂SO₄, filtered and evaporated. The resulting yellow oil was purified by flash chromatography (SiO₂, pentane/Et₂O gradient, 1 → 2%) to afford the title compound (1.8 g, 93%) as a pale yellow oil (88:12, *anti:syn*). [α]_D²⁰ = -7.1° (c = 1.21, CHCl₃); ¹H NMR (400 MHz, C₆D₆): δ = 9.59 (t, J = 1.9 Hz, 1H, *syn*), 9.55 (dd, J = 1.4, 2.4 Hz, 1H *anti*), 4.30 (dt, J = 4.2, 7.6 Hz, 1H, *anti*), 4.07 (ddd, J = 4.4, 6.0, 10.5 Hz, 1H, *syn*), 2.82-2.50 (m, 2H), 2.39 (dd of ABq, J = 2.4, 7.6, 16.4 Hz, 1H, *anti*), 2.30 (dd of ABq, J = 1.7, 4.3, 16.4 Hz, 1H, *syn*), 1.10 (d, J = 7.1 Hz, 3H, *anti*), 1.07 (d, J = 7.0 Hz, 3H, *syn*), 0.96 (t, J = 8.0 Hz, 9H, *syn*), 0.92 (t, J = 7.9 Hz, 9H, *anti*), 1.02-0.90 (m, 6H, *syn*), 0.51 (q, J = 7.7 Hz, 6H, *anti*), 0.20 (s, 9H, *syn*), 0.19 ppm (s, 9H, *anti*); ¹³C NMR (100 MHz, CDCl₃, chemical shifts of the major *anti-isomer*): δ = 201.7, 108.1, 87.4, 69.7, 47.5, 33.7, 14.6, 6.9 (3C), 5.1 (3C), 0.2 ppm (3C); IR (film): 2957, 2878, 2168, 1728, 1458, 1413, 1373, 1249, 1084, 1011, 839, 746 cm⁻¹; MS (EI): m/z (%): 283 (M⁺-29, 5), 187 (56), 157 (100), 147 (12), 131 (30), 115 (49), 107 (29), 101 (12), 87 (32), 73 (19), 59 (22); HRMS (ESI-pos) calcd. for C₁₆H₃₂O₂Si₂Na [M + Na⁺] 335.1833, found 335.1834.

Compound 26. A Schlenk flask, equipped with a magnetic stir-bar, and glass stopper was charged with aldehyde **24** (806 mg, 2.58 mmol), (*S*)-**25** (420 mg, 2.84 mmol), THF (8.3 mL) and HMPA (2.1 mL). PdCl₂(dppf)·CH₂Cl₂ (105 mg, 0.129 mmol, 0.05 equiv) was then added, immediately followed by indium(I) iodide (748 mg, 3.10 mmol). The suspension underwent various color changes from a dark red via orange to finally give a cloudy green mixture, which was stirred at room temperature for 2 h. The reaction was quenched with aq. sat. NH₄Cl (10 mL) and Et₂O (6 mL), and the resulting biphasic mixture was stirred for 15 min. The aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with H₂O (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and evaporated. The residue was purified without delay by flash chromatography (SiO₂, pentane/Et₂O gradient, 1 → 2%) to give the title compound as a colorless oil (691 mg, 73%, dr ≥ 92:Σ8,¹ GC/MS). [α]_D²⁰ = +11.7° (c =

¹ Refers to the sum (Σ) of all other isomers present at this stage.

1.40, CHCl₃); ¹H NMR (400 MHz, C₆D₆): δ = 4.13 (ddd, *J* = 4.0, 5.1, 7.8 Hz, 1H), 3.84-3.77 (m, 1H), 2.75 (dq, *J* = 4.0, 7.0 Hz, 1H), 2.27 (ddq, *J* = 2.5, 4.4, 7.0 Hz, 1H), 2.53 (d, *J* = 4.0 Hz, 1H), 2.27 (ddd, *J* = 2.8, 5.2, 14.0 Hz, 1H), 1.88 (d, *J* = 2.4 Hz, 1H), 1.88 (ddd, *J* = 7.8, 9.4, 14.1 Hz, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.53 (q, *J* = 7.7 Hz, 6H), 0.20 ppm (s, 9H); ¹³C NMR (100 MHz, C₆D₆): δ = 109.1, 86.7, 85.8, 74.1, 72.7, 71.0, 37.4, 33.6, 33.4, 16.4, 15.2, 7.1 (3C), 5.4 (3C), 0.3 ppm (3C); IR (film): 3533, 3312, 2957, 2878, 2168, 1457, 1412, 1375, 1248, 1086, 1066, 1006, 830, 725 cm⁻¹; MS (EI): *m/z* (%): 337 (M⁺-29, 10), 241 (61), 223 (37), 211 (32), 197 (47), 183 (49), 175 (11), 161 (19), 157 (15), 147 (12), 133 (17), 131 (14), 115 (88), 109 (100), 103 (39), 97 (13), 87 (67), 81 (28), 75 (49), 73 (54), 59 (39); HRMS (ESI-pos) calcd. for C₂₀H₃₈O₂Si₂Na [M + Na⁺] 389.2302, found 389.2306.

Compound 30. A Schlenk flask equipped with a magnetic stir-bar and septum was charged



with compound **26** (9.5 mg, 0.0260 mmol), CH₂Cl₂ (300 μL) and MeOH (300 μL). Camphorsulfonic acid (0.60 mg, 0.00260 mmol, 0.10 equiv) was added and the solution stirred for 30 h. For work up, aq. sat. NaHCO₃ (2 mL) was introduced and the mixture was extracted with CH₂Cl₂ (3 x 1 mL). The combined extracts were

washed with brine (1 mL), dried over MgSO₄ and evaporated. The resulting white solid was dissolved in CH₂Cl₂ (260 μL) and the solution cooled to 0°C before dimethoxypropane (32 μL, 0.260 mmol) and camphorsulfonic acid (0.60 mg, 0.00260 mmol, 0.1 equiv) were successively introduced. The mixture was gradually warmed to room temperature and stirred for 15 h. The reaction was quenched with aq. sat. NaHCO₃ (2 mL) and the mixture extracted with CH₂Cl₂ (3 x 1 mL). The combined organic phases were washed with brine (1 mL), dried over MgSO₄ and evaporated. The crude product was purified by flash chromatography (SiO₂, hexanes/EtOAc gradient, 20 → 30%) to afford acetone **30** (4.3 mg, 57% over both steps). ¹H NMR (600 MHz, CDCl₃): δ = 3.88 (ddd, *J* = 2.5, 4.8, 11.7 Hz, 1H, H-6), 3.86 (ddd, *J* = 2.5, 4.8, 11.7 Hz, 1H, H-4), 2.65 (dq, *J* = 4.8, 7.0 Hz, 1H, H-7), 2.62 (dq, *J* = 4.8, 7.1 Hz, 1H, H-3), 2.09 (d, *J* = 2.5 Hz, 1H, H-1), 1.61 (dt, *J* = 2.5, 12.6 Hz, 1H, H-5a), 1.48 (dt, *J* = 11.7, 12.6 Hz, 1H, H-5b), 1.43 (s, 3H, H-15), 1.41 (s, 3H, H-14), 1.20 (d, *J* = 7.1 Hz, 3H, H-10), 1.17 (d, *J* = 7.1 Hz, 3H, H-11), 0.14 ppm (s, 9H, H-12); ¹³C NMR (150 MHz, CDCl₃): δ = 108.3 (C, C-8), 98.8 (C, C-13), 85.9 (C, C-9), 85.6 (C, C-2), 71.0 (HC, C-4), 71.0 (HC, C-6), 69.7 (HC, C-1), 32.0 (HC, C-7), 31.1 (HC, C-3), 29.9 (H₃C, C-14), 27.9 (H₂C, C-5), 19.8 (H₃C, C-15), 15.3 (H₃C, C-10), 15.0 (H₃C, C-11), 0.1 ppm ((H₃C)₃Si, C-12); IR (film): 3312, 2990, 2879, 2169, 1456, 1380, 1275, 1259, 1200, 1171, 1103, 839, 758 cm⁻¹; MS (EI): *m/z* (%): 277 (M⁺-15, 41), 181 (19), 167 (71), 109 (44), 95 (72), 81 (40), 79 (17), 73 (100), 59 (45), 53 (14), 43 (26); HRMS (ESI-pos) calcd. for C₁₇H₂₈O₂SiNa [M + Na⁺] 315.1751, found 315.1751.

The relative stereochemistry was determined according to Rychnovsky and co-workers (Figure 1).¹ These authors demonstrated that *syn*-1,3 diol acetone exists in a defined chair conformation, in which the two alkyl substituents are equatorially disposed. The axial methyl group of the acetone has a characteristic ¹³C-chemical shift of ≈ 19 ppm, whereas the chemical shift of the equatorial methyl group is ≈ 30 ppm.

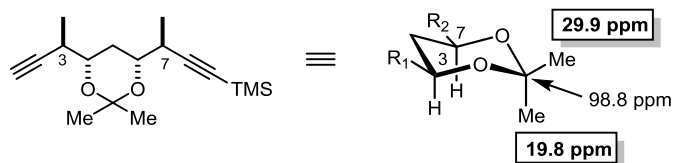


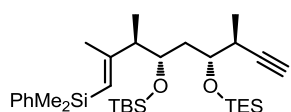
Figure S-1: Assignment of the relative stereochemistry of the 1,3-*syn*-hydroxyl groups in compound **30**

Compound S5. A Schlenk flask was charged with alcohol **26** (3.3 g, 8.92 mmol), and CH₂Cl₂ (31 mL). The resulting solution was cooled to 0 °C before 2,6-lutidine (2.1 mL, 17.8 mmol) was introduced. After ~ 5 min, TBSOTf (2.1 mL, 9.27 mmol) was added and the solution stirred at 0 °C for 1.5 h. For work up, the mixture was diluted with aq. sat. NH₄Cl (40 mL) and Et₂O (100 mL) and the aqueous layer extracted with Et₂O (3 x 30 mL). The combined extracts were washed with H₂O (30 mL) and brine (30 mL), dried over Na₂SO₄, filtered and evaporated, and the crude product was purified by flash chromatography (SiO₂, pentane) to afford the title compound as a colorless oil (4.1 g, 96%). $[\alpha]_D^{20} = +5.1^\circ$ (c = 0.95, CHCl₃); ¹H NMR (400 MHz, C₆D₆): δ = 4.01 (ddd, *J* = 3.6, 5.4, 7.4 Hz, 1H), 3.98 (dt, *J* = 3.5, 6.3 Hz, 1H), 2.82-2.71 (m, 2H), 2.54 (ddd, *J* = 5.5, 6.4, 13.8 Hz, 1H), 1.98 (d, *J* = 2.5 Hz, 1H), 1.90 (ddd, *J* = 6.2, 7.3, 13.7 Hz, 1H), 1.31 (d, *J* = 7.0 Hz, 3H), 1.31 (d, *J* = 7.0 Hz, 3H), 1.02-0.97 (m, 18H), 0.59 (q, *J* = 8.0 Hz, 6H), 0.24 (s, 9H), 0.09 (s, 3H), 0.06 ppm (s, 3H); ¹³C NMR (100 MHz, C₆D₆): δ = 108.9, 86.5, 85.8, 72.1, 72.0, 70.7, 38.6, 33.6, 32.3, 26.1 (3C), 18.3, 16.4, 15.8, 7.2 (3C), 5.6 (3C), 0.4 (3C), -4.0, -4.4 ppm; IR (film): 3315, 2957, 2879, 2168, 1462, 1374, 1249, 1063, 1006, 835, 774 cm⁻¹; MS (EI): *m/z* (%): 451 (M⁺-29, 7), 269 (44), 223 (11), 197 (100), 147 (12), 115 (20), 87 (18), 73 (55), 59 (11); HRMS (ESI-pos) calcd. for C₂₆H₅₂O₂Si₃Na [M + Na⁺] 503.3167, found 503.3165.

Compound 27. A precooled (0 °C) Schlenk flask was charged with a solution of phenyldimethylsilyl lithium (1.3 M in THF, 4.3 mL, 5.61 mmol) and THF (11 mL). CuCN (251 mg, 2.81 mmol) was then added in one portion (THF (6 mL) was used to rinse the CuCN-containing flask). The resulting blood red solution was stirred at 0 °C for 30 min, causing a color change to dark red/purple, before it was transferred via cannula into a solution of alkyne **S5** (900 mg, 1.87 mmol) in THF (15.2 mL) at 0°C. The mixture was stirred at this temperature for 1 h. Next, methyl iodide (1.2 mL, 18.7 mmol) was introduced and stirring continued at 0 °C for an additional 1 h. For work up, ammonium hydroxide (30% v/v in H₂O, 38 mL) and Et₂O (18 mL) were added under vigorous stirring. The biphasic mixture was transferred into a separatory funnel containing H₂O (80 mL) and Et₂O (40 mL), and the aqueous layer was extracted with Et₂O (3 x 40 mL). The combined organic phases were washed with H₂O (3 x 30 mL) and brine (30 mL), dried over Na₂SO₄, filtered and evaporated. The crude material was purified by flash chromatography (SiO₂, pentane/Et₂O gradient, 0 to 2%), affording the title compound as a colorless oil (782 mg, 77%). When performed on somewhat smaller scales, yields of up to 90% were reached. $[\alpha]_D^{20} = -3.6^\circ$ (c = 2.13, CHCl₃); ¹H NMR (400 MHz, C₆D₆): δ = 7.68-7.64 (m, 2H), 7.31-7.26 (m, 2H), 7.25-7.20 (m, 1H), 5.71 (s, 1H), 4.15-4.10 (m, 1H), 4.07 (dt, *J* = 3.8, 6.3 Hz, 1H),

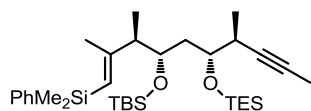
2.79 (dq, $J = 3.6, 7.0$ Hz, 1H), 2.54 (dq, $J = 4.5, 6.9$ Hz, 1H), 2.09 (ddd, $J = 5.5, 6.4, 11.9$ Hz, 1H), 1.93 (s, 3H), 1.91-1.82 (m, 1H), 1.32 (d, $J = 7.0$ Hz, 3H), 1.22 (d, $J = 7.0$ Hz, 3H), 1.05 (t, $J = 7.9$ Hz, 9H), 1.01 (s, 9H), 0.67 (q, $J = 7.8$ Hz, 6H), 0.48 (s, 3H), 0.47 (s, 3H), 0.21 (s, 9H), 0.17 (s, 3H), 0.12 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 159.0, 140.2, 134.2$ (2C), 129.1, 128.2 (2C), 122.7, 109.6, 86.5, 72.1, 71.9, 50.5, 38.5, 33.8, 26.2 (3C), 22.6, 18.3, 16.7, 14.7, 7.3 (3C), 5.7 (3C), 0.4 (3C), $-0.4, -0.5, -3.8, -4.2$ ppm; IR (film): 2956, 2878, 2167, 1610, 1461, 1427, 1374, 1248, 1111, 1043, 1005, 825, 772, 726 cm^{-1} ; MS (ESI-pos) [$\text{M} + \text{Na}^+$] 653 (100); HRMS (ESI-pos) calcd. for $\text{C}_{35}\text{H}_{66}\text{O}_2\text{Si}_4\text{Na}$ [$\text{M} + \text{Na}^+$] 653.4032, found 653.4033.

Compound S6. A round-bottomed flask, equipped with a reflux condenser and an argon inlet



on top of the reflux condenser, was charged with alkyne **27** (3.7 g, 5.86 mmol), MeOH (65 mL) and potassium carbonate (2.4 g, 17.6 mmol). The mixture was stirred at 40 °C for 3.5 h before it was allowed to cool. Et₂O (100 mL) and H₂O (60 mL) were added and the aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organic phases were washed with brine (30 mL), dried over Na₂SO₄, filtered and evaporated. The crude product was purified by flash chromatography (SiO₂, pentane/Et₂O gradient, 0 to 2%) to furnish the title compound as a pale yellow oil (2.7 g, 84%). $[\alpha]_D^{20} = -8.2^\circ$ ($c = 2.12, \text{CHCl}_3$); ^1H NMR (400 MHz, C_6D_6): $\delta = 7.66$ (dd, $J = 1.4, 7.9$ Hz, 2H), 7.29-7.24 (m, 2H), 7.23-7.17 (m, 1H), 5.72 (s, 1H), 4.07 (ddd, $J = 3.8, 5.1, 7.6$ Hz, 1H), 4.03 (dt, $J = 3.3, 6.7$ Hz, 1H), 2.71 (ddq, $J = 2.6, 3.8, 7.0$ Hz, 1H), 2.52 (dq, $J = 3.6, 7.0$ Hz, 1H), 2.16 (ddd, $J = 5.4, 6.7, 12.3$ Hz, 1H), 1.90 (s, 3H), 1.88-1.79 (m, 1H), 1.82 (d, $J = 2.4$ Hz, 1H), 1.31 (d, $J = 7.0$ Hz, 3H), 1.23 (d, $J = 7.0$ Hz, 3H), 1.02 (t, $J = 7.9$ Hz, 9H), 0.99 (s, 9H), 0.64 (dq, $J = 1.6, 8.4$ Hz, 6H), 0.45 (s, 3H), 0.44 (s, 3H), 0.10 (s, 3H), 0.09 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 158.6, 140.2, 134.3$ (2C), 129.1, 128.2 (2C), 123.0, 85.7, 72.0, 71.8, 71.0, 50.0, 37.6, 31.9, 26.2 (3C), 22.5, 18.3, 16.1, 14.1, 7.3 (3C), 5.6 (3C), $-0.5, -0.6, -4.1, -4.3$ ppm; IR (film): 3312, 2955, 2878, 1609, 1461, 1427, 1374, 1248, 1111, 1043, 1005, 835, 772 cm^{-1} ; MS (EI): m/z (%): 355 ($\text{M}^+ - 203, 5$), 223 (10), 197 (100), 135 (25), 115 (15), 73 (12); HRMS (ESI-pos) calcd. for $\text{C}_{32}\text{H}_{58}\text{O}_2\text{Si}_3\text{Na}$ [$\text{M} + \text{Na}^+$] 581.3637, found 581.3638.

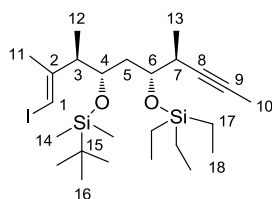
Compound 28. A Schlenk flask was charged with alkyne **S6** (2.8 g, 4.94 mmol) and THF (52



mL). The resulting solution was cooled to -78 °C before *n*-BuLi (1.6 M in hexane, 3.9 mL, 6.17 mmol) was added dropwise, causing a color change to light red. The solution was stirred at -78 °C for 1 h before methyl iodide (3.1 mL, 49.4 mmol) was introduced and the cooling bath removed. The mixture was allowed to reach room temperature over the course of 1 h. The reaction was quenched with aq. sat. NH₄Cl (50 mL), and the aqueous layer was extracted with Et₂O (3 x 30 mL). The combined extracts were washed with H₂O (30 mL) and brine (30 mL), dried over Na₂SO₄, filtered and evaporated, and the residue was purified by flash chromatography (SiO₂, pentane/Et₂O gradient, 0 → 2%) to afford the title compound as a colorless oil (2.7 g, 99%). $[\alpha]_D^{20} = -1.4^\circ$ ($c = 0.97, \text{CHCl}_3$); ^1H NMR (400 MHz, C_6D_6): $\delta = 7.69$ -7.66 (m, 2H), 7.30-7.25 (m, 2H), 7.24-7.18 (m, 1H), 5.75 (s, 1H), 4.17 (ddd, $J = 4.1, 5.2, 7.4$ Hz, 1H), 4.08 (dt, $J = 3.5, 6.5$ Hz, 1H), 2.83-2.74 (m, 1H), 2.54 (dq, $J = 3.9, 6.8$ Hz, 1H), 2.17 (ddd, $J = 5.4, 6.8, 13.8$ Hz, 1H), 1.92 (s, 3H), 1.85 (ddd, $J = 6.6, 7.3, 13.8$ Hz, 1H), 1.53

(d, $J = 2.4$ Hz, 3H), 1.36 (d, $J = 7.0$ Hz, 3H), 1.25 (d, $J = 7.0$ Hz, 3H), 1.05 (t, $J = 7.9$ Hz, 9H), 1.01 (s, 9H), 0.67 (dq, $J = 1.5, 8.0$ Hz, 6H), 0.46 (s, 3H), 0.45 (s, 3H), 0.15 (s, 3H), 0.11 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 159.0, 140.3, 134.2$ (2C), 129.1, 128.2 (2C), 122.5, 81.2, 77.7, 72.2, 72.1, 50.0, 37.6, 32.4, 26.2 (3C), 22.6, 18.3, 16.5, 14.3, 7.3 (3C), 5.6 (3C), 3.7, -0.5 (2 x 1C), $-4.1, -4.3$ ppm; IR (film): 2955, 2877, 1610, 1461, 1427, 1373, 1247, 1110, 1068, 1041, 1004, 834, 772 cm^{-1} ; MS (EI): m/z (%): 369 ($\text{M}^+ - 203$, 15), 237 (89), 211 (100), 135 (50), 115 (28), 87 (18), 73 (19); HRMS (ESI-pos) calcd. for $\text{C}_{33}\text{H}_{60}\text{O}_2\text{Si}_3\text{Na}$ [$\text{M} + \text{Na}^+$] 595.3793, found 595.3796.

Compound 29. Note: the product is light-sensitive and all manipulations were performed in the dark. A Schlenk flask was charged with vinyl silane **28** (691 mg,

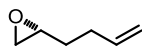


1.21 mmol), benzene (2.8 mL) and MeCN (6.9 mL). The resulting solution was cooled to 0 °C before a solution of NIS (1.4 g, 6.03 mmol) (the NIS must be white and crystalline) in MeCN (6.9 mL) was added dropwise (~ 5 min). The bright red mixture was kept at 0 °C for 4 h before the reaction was quenched with aq. sat. $\text{Na}_2\text{S}_2\text{O}_3$ (3.5 mL)

under vigorous stirring. The colorless solution was added to a separatory funnel containing Et_2O (80 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined extracts were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4 , filtered and evaporated (in the dark). The remaining pale yellow oil was quickly purified by flash chromatography (SiO_2 , pentane/ Et_2O gradient, 0 to 1%) to afford the title compound as a colorless oil (572 mg, 84%). $[\alpha]_D^{20} = +6.5^\circ$ ($c = 1.02, \text{C}_6\text{H}_6$); ^1H NMR (600 MHz, C_6D_6): $\delta = 6.10$ (s, 1H, H-1), 3.94 (ddd, $J = 3.8, 4.4, 8.4$ Hz, 1H, H-6), 3.89 (ddd, $J = 3.9, 5.2, 7.2$ Hz, 1H, H-4), 2.71 (m, 1H, H-7), 2.55 (m, 1H, H-3), 2.07 (ddd, $J = 4.5, 7.2, 13.8$ Hz, 1H, H-5a), 1.97 (d, $J = 1.1$ Hz, 3H, H-11), 1.72 (d, $J = 2.5$ Hz, 3H, H-10), 1.72 (ddd, $J = 5.2, 8.4, 13.8$ Hz, 1H, H-5b), 1.28 (d, $J = 7.0$ Hz, 3H, H-13), 1.05 (d, $J = 7.0$ Hz, 3H, H-12), 0.98 (t, $J = 8.0$ Hz, 9H, H-18), 0.96 (s, 9H, H-16), 0.58 (q, $J = 8.0$ Hz, 6H, H-17), 0.09 (s, 3H, H-14a), 0.06 ppm (s, 3H, H-14b); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 149.4$ (C, C-2), 80.8 (C, C-8), 78.2 (C, C-9), 78.1 (HC, C-1), 72.3 (HC, C-4), 71.9 (HC, C-6), 47.7 (HC, C-3), 37.5 (H_2C , C-5), 32.7 (HC, C-7), 26.1 ($(\text{H}_3\text{C})_3$, C-16), 23.6 (H_3C , C-11), 18.2 (CSi, C-15), 15.4 (H_3C , C-12), 15.2 (H_3C , C-13), 7.3 ($(\text{H}_3\text{C})_3$, C-18), 5.5 ($(\text{H}_2\text{C})_3\text{Si}$, C-17), 4.1 (H_3C , C-10), -4.1 (H_3CSi , C-14a), -4.5 ppm (H_3CSi , C-14b); IR (film): 2956, 2930, 2878, 2857, 1607, 1471, 1461, 1412, 1374, 1251, 1152, 1110, 1095, 1066, 1042, 1004, 950, 885, 832, 772 cm^{-1} ; MS (EI): m/z (%): 507 ($\text{M}^+ - 57$, 4), 369 (19), 365 (13), 339 (28), 237 (53), 211 (100), 115 (24), 97 (14), 87 (19), 73 (55), 59 (12); HRMS (ESI-pos) calcd. for $\text{C}_{25}\text{H}_{49}\text{O}_2\text{Si}_2\text{INa}$ [$\text{M} + \text{Na}^+$] 587.2208, found 587.2203.

Preparation of Fragment G

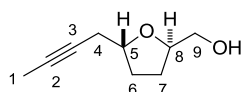
Compound 43. A Schlenk flask, equipped with a magnetic stir-bar and a glass stopper, was charged with (R,R) -(-)- N,N' -bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (1.3 g, 2.13 mmol, 0.01 equiv), toluene (8.0 mL) and acetic acid (183 μL , 3.20 mmol, 0.015 equiv). The resulting solution was stirred under air for 1 h. During this time the color changed from red to dark brown. The solvent was removed



under reduced pressure and the residue dried in high vacuum for 1 h, providing a dark brown solid.

This material was dissolved in (\pm)-1,2-epoxy-5-hexene (24.0 mL, 213 mmol) and the resulting mixture cooled to 0°C before H₂O (2.1 mL, 115 mmol, 0.54 equiv) was added dropwise. Stirring was continued for 30 min at 0°C and at room temperature for 24 h. For work up, the volatile material was isolated by vacuum transfer (50 to 15 mbar, 40°C) into a cooled (0°C) receiving flask. The resulting oil was filtered through a plug of silica to remove residual water to afford the title compound as a colorless liquid (7.5 g, 36%, > 99% ee). $[\alpha]_D^{20} = +6.6^\circ$ ($c = 0.39$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 5.85$ (ddt, $J = 6.6, 10.2, 17.1$ Hz, 1H), 5.07 (dq, $J = 1.7, 17.1$ Hz, 1H), 5.00 (ddt, $J = 1.3, 2.5, 10.1$ Hz, 1H), 2.94 (ddt, $J = 2.7, 4.0, 5.4$ Hz, 1H), 2.76 (dd, $J = 4.1, 4.9$ Hz, 1H), 2.49 (dd, $J = 2.7, 5.0$ Hz, 1H), 2.30-2.15 (m, 2H), 1.64 ppm (ddt, $J = 1.5, 5.3, 7.6$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 137.8, 115.3, 52.0, 47.3, 31.9, 30.3$ ppm; IR (film): 3048, 2980, 2923, 2848, 1641, 1483, 1442, 1410, 1261, 1210, 1132, 1084, 996, 910, 837, 733 cm⁻¹; MS (EI): m/z (%): 98 (M⁺, 0.5), 83 (11), 79 (11), 67 (77), 65 (10), 57 (32), 55 (52), 54 (77), 53 (33), 41 (100), 39 (89), 31 (72), 29 (77), 27 (64); HRMS (CI (FE), *i*-butane) calcd. for C₆H₁₁O [M + H⁺] 99.0810, found 99.0809. The enantiomeric excess was determined by GC using a chiral stationary phase (column. 30 M BGB 174 / BGB 1701 G 513, detector FID, temp. 220 / 50 iso / 320, gas, 0.6 bar H₂, sample 0.2 μ L in CH₂Cl₂, $t_R = 17.3$ min for (*R*)-**43**, 18.0 min for (*S*)-**43**).

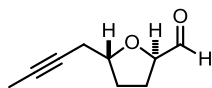
Compound 44. Propyne (~ 53 mL) was condensed at -78°C into a Schlenk flask, equipped with a magnetic stir-bar and a glass stopper. THF (51 mL) was then added prior to the dropwise addition of *n*-BuLi (1.6 M in hexane, 32.1 mL, 51.4 mmol). The resulting cloudy white mixture was stirred for 30 min at -78°C before BF₃•OEt₂ (6.8 mL, 53.4 mmol) was added dropwise. Stirring was continued for 30 min at this temperature before a solution of epoxide **43** (5.0 g, 50.9 mmol) in THF (50 mL) was slowly added via cannula. The turbid mixture was stirred for 1 h at -78°C before the reaction was quenched with aq. sat. NH₄Cl (20 mL). After reaching room temperature, the biphasic mixture was transferred to a separatory funnel containing Et₂O (20 mL) and H₂O (40 mL). The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organic layers were washed with H₂O (20 mL) and brine (20 mL), dried over Na₂SO₄ and evaporated. The crude material was purified by flash chromatography (SiO₂, pentane/Et₂O gradient, 0 \rightarrow 33%) to afford the title compound as a colorless oil (6.1 g, 87%). $[\alpha]_D^{20} = -5.8^\circ$ ($c = 0.37$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 5.81$ (ddt, $J = 6.6, 10.1, 17.2$ Hz, 1H), 5.03 (ddt, $J = 1.5, 3.2, 17.2$ Hz, 1H), 4.98-4.92 (m, 1H), 3.69 (dt, $J = 6.3, 11.3$ Hz, 1H), 2.36 (ddt, $J = 2.3, 4.8, 16.4$ Hz, 1H), 2.29-2.02 (m, 4H), 1.78 (t, $J = 2.3$ Hz, 3H), 1.63-1.55 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 138.2, 114.8, 78.4, 75.1, 69.6, 35.2, 29.9, 27.7, 3.5$ ppm; IR (film): 3379, 3078, 2977, 2920, 2856, 1641, 1435, 1341, 1211, 1118, 1077, 1024, 994, 910, 848 cm⁻¹; MS (EI): m/z (%): 138 (M⁺, 0.5), 123 (11), 109 (11), 105 (16), 97(11), 85 (50), 79 (11), 67 (78), 57 (43), 55 (77), 54 (85), 41 (100), 29 (64); HRMS (EI (FE)) calcd. for C₉H₁₄O 138.1045, found 138.1043.



Compound 45. A round-bottomed flask, equipped with a magnetic stir-bar and a rubber septum, was charged with alcohol **44** (4.0 g, 29.0 mmol), 2-propanol (250 mL) and Co(nmp)₂ (1.6 g, 2.90 mmol, 0.10

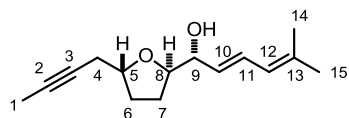
equiv).² The mixture were purged with O₂ (~ 10 min) before *tert*-butyl hydroperoxide (4.8 M in toluene, 604 μL, 2.90 mmol, 0.10 equiv) was added to the green solution. The mixture was stirred at 55 °C under O₂ (1 atm, balloon) for 17 h before it was cooled to room temperature and purged with argon. The green solution was concentrated to ~ 1/10 of the volume by rotary evaporation (water bath at room temperature, 75 mbar) and transferred into a separatory funnel containing Et₂O (50 mL) and HCl (1.0 M in H₂O, 70 mL). The aqueous layer was extracted with Et₂O (3 x 15 mL). The combined extracts were washed with H₂O (3 x 20 mL) and brine (30 mL), filtered, dried over Na₂SO₄, and evaporated. The crude product was purified by flash chromatography (SiO₂, pentane/acetone gradient, 0 → 30%) to give the title compound as a pale yellow oil (3.8 g, 84%). [α]_D²⁰ = -10.0 ° (c = 0.15, CHCl₃); ¹H NMR (500 MHz, C₆D₆): δ = 3.99-3.92 (m, 1H, H-5), 3.94-3.89 (m, 1H, H-8), 3.41 (ddd, *J* = 3.5, 6.9, 11.4 Hz, 1H, H-9a), 3.24 (dt *J* = 5.7, 11.4 Hz, 1H, H-9b), 2.38 (ddq, *J* = 2.6, 5.1, 16.3 Hz, 1H, H-4a), 2.24 (ddq, *J* = 2.6, 7.0, 16.3 Hz, 1H, H-4b), 1.81-1.77 (bm, 1H, HO), 1.77-1.72 (m, 1H, H-6a), 1.52 (t, *J* = 2.6 Hz, 3H, H-1), 1.54-1.49 (m, 1H, H-7a), 1.51-1.46 (m, 1H, H-6b), 1.39-1.32 ppm (m, 1H, H-7b); ¹³C NMR (125 MHz, C₆D₆): δ = 80.0 (HC, C-8), 78.1 (HC, C-5), 76.9 (C, C-2), 76.3 (C, C-3), 65.0 (H₂C, C-9), 31.6 (H₂C, C-6), 27.4 (H₂C, C-7), 26.1 (H₂C, C-4), 3.4 ppm (H₃C, C-1); IR (film): 3423, 2919, 2872, 1641, 1444, 1370, 1195, 1099, 1043, 973, 928, 882, 812 cm⁻¹; MS (ED): *m/z* (%): 154 (M⁺, 0.1), 101 (100), 95 (13), 83 (12), 79 (14), 57 (77), 55 (28), 53 (12), 43 (18), 41 (10), 39 (10), 27 (11); HRMS (CI (DE), ammonia gas) calcd. for C₉H₁₅O₂ [M + H⁺] 155.1072, found 155.1071.

Compound 46. Aldehyde **46** is fairly unstable and can be stored only for a few days at -18 °C under Ar. Moreover, it is quite volatile and care must be taken when removing the solvent to avoid material loss.



A Schlenk flask was charged with alcohol **45** (1.1 g, 7.26 mmol), CH₂Cl₂ (73 mL), diisopropylethylamine (8.9 mL, 50.8 mmol), and DMSO (2.6 mL, 36.3 mmol). The resulting mixture was cooled to 0 °C and stirred at this temperature for 5 min before SO₃·pyridine (3.5 g, 21.8 mmol) was introduced in one portion. The pale yellow solution was stirred for 1 h at 0 °C before the reaction was quenched with aq. HCl (1.0 M in H₂O, 100 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL), and the combined extracts were washed with H₂O (20 mL) and brine (20 mL). The crude product was purified by flash chromatography (SiO₂, pentane/Et₂O gradient, 70 to 85%) to afford aldehyde **46** (983 mg, 89%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 9.66 (d, *J* = 1.8 Hz, 1H), 4.39 (ddd, *J* = 1.7, 6.8, 8.3 Hz, 1H), 4.21 (quint, *J* = 6.3 Hz, 1H), 2.50-2.35 (m, 2H), 2.23 (dddd, *J* = 3.9, 7.4, 7.8, 12.8 Hz, 1H), 2.11-2.00 (m, 1H), 1.98 (ddt, *J* = 6.7, 7.9, 12.4 Hz, 1H), 1.84-1.74 (m, 1H), 1.79 ppm (t, *J* = 2.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 202.8, 83.4, 79.5, 77.4, 75.1, 30.4, 27.3, 25.5, 3.7 ppm; IR (film): 2920, 2805, 2714, 1730, 1445, 1372, 1293, 1190, 1069, 1002, 883 cm⁻¹; HRMS (CI (FE), *i*-butane) calcd. for C₉H₁₃O₂ [M + H⁺] 153.0916, found 153.0916.

Compound 47. The preparation of 1-bromo-4-methyl-1,3-pentadiene (**48**) is a modification of the procedure described by Charreau and co-workers:³



A Schlenk flask was charged with a solution of diisopropylamine (1.7 mL, 12.0 mmol) in Et₂O/THF (16.8 mL/24.0 mL). The solution was cooled to -78 °C before *n*-BuLi (1.6 M in hexane, 7.5 mL, 12.0 mmol) was

added dropwise. The resulting pale yellow LDA solution was allowed to reach room temperature and stirred for 30 min, before it was cooled to $-95\text{ }^{\circ}\text{C}$ using a pentane/ N_2 (liq.) bath. Once this temperature had been reached, a pre-cooled ($-78\text{ }^{\circ}\text{C}$) solution of dibromomethane (838 μL , 12.0 mmol) in THF (12.1 mL) was carefully added via cannula and the resulting yellow mixture stirred at $-95\text{ }^{\circ}\text{C}$ for 30 min. During this time a separate Schlenk flask was charged with phenyl prenyl sulfone (2.5 g, 12.0 mmol). The solid was dissolved in THF (19.3 mL) and the resulting solution cooled to $-78\text{ }^{\circ}\text{C}$ before $n\text{-BuLi}$ (1.6 M in hexane, 7.5 mL, 12.0 mmol) was added, causing a color change to bright orange. Once the addition was complete, the cooling bath was removed and the solution of the lithiated sulfone allowed to reach room temperature. After stirring for 30 min, the solution was cooled again to $-78\text{ }^{\circ}\text{C}$ and was then slowly added via cannula to the carbene solution stirred at $-95\text{ }^{\circ}\text{C}$. When the addition was complete, the resulting yellow/brown mixture was warmed over the course of 2.5 h to $-20\text{ }^{\circ}\text{C}$. The reaction was quenched with EtOH (1.2 mL) and aq. sat. NH_4Cl (24 mL). The contents were immediately transferred to a separatory funnel and diluted with H_2O until two clear layers were observed. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL), the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over MgSO_4 , filtered and evaporated. The remaining pale yellow oil was subjected, without delay, to flash chromatography (SiO_2 , pentane). The resulting 1-bromo-4-methyl-1,3-pentadiene **48** was immediately used in the next step. *This product is very sensitive to temperature and light and should be freshly prepared and manipulated within 1h; otherwise, isomerization may lead to futile mixtures.*

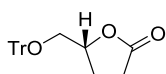
A Schlenk flask was charged with freshly prepared bromide **48** (1.7 g, 10.6 mmol). After immersing the flask into a dry ice/acetone bath, Et_2O (20.9 mL) was added at $-78\text{ }^{\circ}\text{C}$ followed by $t\text{-BuLi}$ (1.7 M in pentane, 13.7 mL, 23.3 mmol). The resulting yellow lithiodiene solution was stirred at this temperature for 1 h. A Schlenk flask was charged with freshly sublimed zinc bromide (3.6 g, 16.1 mmol) and Et_2O (26.4 mL), and the resulting mixture was stirred at room temperature until a colorless solution had formed. This solution was then cooled to $-35\text{ }^{\circ}\text{C}$ before the solution of the lithio-diene was added dropwise over 10 min. The mixture was warmed to $0\text{ }^{\circ}\text{C}$ and stirred for 1 h at this temperature before a solution of lithio ($-$)- N -methyl-ephedrine [prepared from ($-$)- N -methyl-ephedrine (1.9 g, 10.6 mmol) and $n\text{-BuLi}$ (1.6 M in hexane, 6.7 mL, 10.6 mmol) in toluene (17.4 mL) at $0\text{ }^{\circ}\text{C}$] was added and stirring continued at $0\text{ }^{\circ}\text{C}$ for 1 h. The mixture was then cooled to $-20\text{ }^{\circ}\text{C}$ before a solution of aldehyde **46** (253 mg, 1.66 mmol) in Et_2O (2.0 mL) was introduced. The resulting mixture was stirred at $-20\text{ }^{\circ}\text{C}$ for 18 h before the reaction was quenched with aq. sat. NH_4Cl (60 mL) and diluted with H_2O (50 mL). The aqueous phase was extracted with Et_2O (3 x 30 mL), and the combined extracts were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4 , filtered and evaporated. The remaining pale yellow oil was purified by flash chromatography (SiO_2 , pentane/ Et_2O gradient, 12.5 to 50%) to afford fragment **47** as a colorless oil (312 mg, 80%, dr ~ 88:12, $^1\text{H NMR}$). $[\alpha]_D^{20} = +19.3\text{ }^{\circ}$ ($c = 0.67$, CHCl_3); $^1\text{H NMR}$ (600 MHz, C_6D_6): $\delta = 6.71$ (ddd, $J = 1.2, 11.0, 15.1\text{ Hz}$, 1H, H-11), 5.87 (bd, $J = 11.0\text{ Hz}$, 1H, H-12), 5.58 (dd, $J = 6.2, 15.1\text{ Hz}$, 1H, H-10), 4.02-3.96 (m, 1H, H-5), 3.99-3.94 (m, 1H, H-9), 3.92-3.87 (m, 1H, H-8), 2.82 (bs, 1H, HO), 2.41 (ddq, $J = 2.6, 5.1, 16.3\text{ Hz}$, 1H, H-4a), 2.25 (ddq, $J = 2.6, 7.3, 16.3\text{ Hz}$, 1H, H-4b), 1.84-1.78 (m, 1H, H-6a), 1.66-1.61 (m, 1H, H-7a), 1.61 (s, 3H, H-14), 1.59 (s, 3H, H-15), 1.53 (t, $J = 2.6\text{ Hz}$, 3H, H-1), 1.55-1.49 (m, 1H, H-6b), 1.50-1.43 ppm (m,

¹H, H-7b); ¹³C NMR (150 MHz, C₆D₆): δ = 134.9 (C, C-13), 129.8 (HC, C-10), 128.5 (HC, C-11), 125.5 (HC, C-12), 83.2 (HC, C-8), 78.1 (HC, C-5), 77.0 (C, C-2), 76.2 (C, C-3), 75.4 (HC, C-9), 31.7 (H₂C, C-6), 28.0 (H₂C, C-7), 25.9 (H₂C, C-4 and H₃C, C-14), 18.2 (H₃C, C-15), 3.4 ppm (H₃C, C-1); IR (film): 3434, 2968, 2919, 1659, 1443, 1376, 1280, 1220, 1055, 986, 960, 871, 812 cm⁻¹; MS (EI): *m/z* (%): 234 (M⁺, 5), 123 (55), 111 (21), 105 (12), 95 (100), 93 (18), 81 (18), 79 (33), 77 (15), 67 (23), 55 (21), 53 (12), 43 (42), 41 (16); HRMS (EI (DE)) calcd. for C₁₅H₂₂O₂ 234.1620, found 234.1618.

Preparation of Fragment E

Compound 32.⁴ A round-bottomed flask, equipped with a magnetic stir-bar, an additional funnel and a gas outlet, was successively charged with D-glutamic acid (25.0 g, 170 mmol), H₂O (60 mL) and conc. HCl (25 mL). The resulting solution was cooled to 0 °C before a solution of NaNO₂ (15.2 g, 221 mmol) in H₂O (80 mL) was added dropwise (~ 40 min), causing a gentle evolution of N₂ gas. Once the addition was complete, the colorless solution was warmed to room temperature and stirred for 72 h. All volatile materials were then evaporated (bath temperature 50 °C, 75 mbar) to leave a white solid that was washed with EtOAc (100 mL) and filtered off. The filter cake was washed again with EtOAc (2 x 100 mL), the combined filtrates were dried with MgSO₄, and evaporated and the residue carefully dried at 2.3 x 10⁻² mbar. The remaining pale yellow solid (20.1 g, 91%) was used in the next step without further purification. Its spectral data matched those reported in the literature.^{4a-b}

This crude material (20.1 g, 154 mmol) was further dried by azeotropic distillation of toluene (50 mL) followed by drying in high vacuum, before it was dissolved in THF (320 mL). After cooling to 0 °C, borane dimethylsulfide complex (18.3 mL, 193 mmol) was added dropwise (~ 15 min). Once the addition was complete, the mixture was stirred at room temperature overnight (16 h). For work up, the mixture was cooled to 0 °C and the reaction carefully quenched with MeOH (81 mL). The solvents were evaporated (18 mbar) and the remaining yellow oil was passed through a silica gel plug (hexanes/EtOAc, 50%) to afford alcohol **31** as a pale yellow oil (11.8 g, 66%), the spectral data of which match those reported in the literature.^{4a-b}

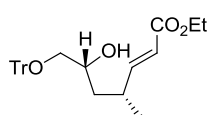


A round-bottomed flask, equipped with a large magnetic stir-bar, an argon adaptor and a glass stopper, was charged with alcohol **31** (11.8 g, 102 mmol). Pyridine (55 mL) was then added, followed by trityl chloride (28.9 g, 104 mmol), and the resulting yellow mixture was stirred overnight (~ 14 h), during which time a thick suspension was formed. The mixture was diluted with H₂O (500 mL) and extracted with EtOAc (3 x 100 mL). The combined extracts were washed with H₂O (100 mL) and brine (100 mL), dried over MgSO₄, and evaporated. The remaining orange syrup was purified by flash chromatography (SiO₂, hexanes/EtOAc, 10%) and the collected product recrystallised from hexane to afford compound **32** in the form of colorless needles (33.1 g, 91%). The spectral data matched those reported in the literature.^{4a} M.p. 148-150 °C; $[\alpha]_D^{20} = -7.9^\circ$ (c = 0.09, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 7.46-7.40 (m, 6H), 7.34-7.28 (m, 7H), 7.27-7.22 (m, 2H), 4.65 (dddd, *J* = 3.5, 4.3, 10.1, 11.6 Hz, 1H), 3.42 (dd, *J* = 3.5, 10.4 Hz, 1H), 3.16 (dd, *J* = 4.3, 10.4 Hz, 1H), 2.69 (ddd, *J* = 6.6, 10.1, 17.8 Hz, 1H), 2.51 (ddd, *J* = 7.0, 10.1,

17.8 Hz, 1H), 2.25 (dddd, $J = 6.6, 7.9, 10.1, 17.9$ Hz, 1H), 2.04 ppm (dddd, $J = 5.8, 6.8, 10.1, 17.6$ Hz, 1H); IR (film): 3062, 3001, 2961, 2919, 2872, 1771, 1594, 1488, 1449, 1342, 1218, 1183, 1082, 1043, 950, 751, 697 cm^{-1} ; MS (EI): m/z (%): 358 (M^+ , 26), 281 (24), 258 (21), 243 (100), 183 (11), 165 (55), 105 (25), 99 (17), 77 (11), 43 (13); HRMS (ESI-pos) calcd. for $\text{C}_{24}\text{H}_{22}\text{O}_3\text{Na}$ [$M + \text{Na}^+$] 381.1461, found 381.1460.

Compound S7. This compound was prepared by adapting a procedure of Nishida and co-workers:⁵ A round-bottomed flask, equipped with a magnetic stir-bar, an argon inlet and a septum, was charged with diisopropylamine (6.3 mL, 44.9 mmol) and THF (220 mL). The solution was cooled to -78 °C before *n*-BuLi (1.6 M in hexane, 24.1 mL, 38.5 mmol) was added dropwise to afford a light yellow solution, which was allowed to warm to 0 °C and stirred at this temperature for 15 min. Next, the mixture was cooled to -78 °C before a solution of lactone **32** (11.5 g, 32.1 mmol) in THF (80 mL) was slowly added. Stirring was continued for 15 min at this temperature before a solution of methyl iodide (2.4 mL, 38.5 mmol) in THF (40 mL) was introduced and the mixture gradually warmed to -30 °C over 4 h. The reaction was quenched with aq. sat. Na_2SO_4 (100 mL) and the mixture diluted with *tert*-butyl methyl ether (100 mL). The aqueous layer was extracted with *tert*-butyl methyl ether (3 x 50 mL), the combined extracts were washed with H_2O (100 mL) and brine (100 mL), dried over MgSO_4 and evaporated. The resulting material was used in the next step without further purification.

Another round-bottomed flask, equipped with a magnetic stir-bar, an argon inlet and a septum, was charged with diisopropylamine (6.3 mL, 44.9 mmol) and THF (200 mL). The solution was cooled to -78 °C before *n*-BuLi (1.6 M in hexane, 24.1 mL, 38.5 mmol) was slowly added. The resulting light yellow solution was warmed to 0 °C and stirred for 15 min before it was cooled back to -78 °C. A solution of the crude material of the previous step in THF (119 mL) was added over the course of ~ 25 min and stirring was continued at this temperature for 20 min. The reaction was quenched with aq. sat. Na_2SO_4 (100 mL) and the aqueous layer extracted with *tert*-butyl methyl ether (3 x 70 mL). The combined organic extracts were washed with H_2O (100 mL) and brine (100 mL), dried over MgSO_4 and evaporated. The residue was dried in high vacuum to afford lactone **S7** as a white solid (11.1 g, 93% over two steps). The crude material was of sufficient purity to be used in the next step. M.p. 111 - 113 °C (*tert*-butyl methyl ether); $[\alpha]_D^{20} = -6.0^\circ$ ($c = 0.025$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): $\delta = 7.48$ - 7.40 (m, 6H), 7.34 - 7.28 (m, 6H), 7.27 - 7.22 (m, 3H), 4.52 (dddd, $J = 4.0, 5.2, 6.0, 10.4$ Hz, 1H), 3.29 (dd, $J = 3.9, 10.4$ Hz, 1H), 3.26 (dd, $J = 5.3, 10.4$ Hz, 1H), 2.68 (ddq, $J = 7.1, 8.9, 11.7$ Hz, 1H), 2.37 (ddd, $J = 6.1, 8.9, 12.6$ Hz, 1H), 1.69 (ddd, $J = 10.3, 11.7, 12.5$ Hz, 1H), 1.28 ppm (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 179.5, 143.7$ (3C), 128.8 (6C), 128.1 (6C), 127.3 (3C), $86.9, 77.3, 65.2, 35.5, 33.2, 15.5$ ppm; IR (film): 3058, 2973, 2935, 2873, 1768, 1595, 1489, 1449, 1375, 1356, 1346, 1319, 1294, 1207, 1175, 1158, 1105, 1035, 1025, 996, 958, 930, 901, 785, 769, 748, 697 cm^{-1} ; MS (EI): m/z (%): 372 (M^+ , 18), 295 (24), 258 (26), 243 (100), 165 (31), 113 (13), 105 (14); HRMS (EI) calcd. for $\text{C}_{25}\text{H}_{24}\text{O}_3$ 372.1725, found 372.1722.

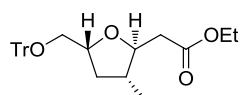


Compound 33. A round-bottomed flask was charged with lactone **S7** (10.3 g, 27.5 mmol) and CH_2Cl_2 (111 mL). The resulting solution was cooled to -78 °C before Dibal-H (1.0 M in hexane, 31.4 mL, 31.4 mmol) was added

dropwise over ~ 15 min. The mixture was stirred at this temperature for 1.25 h before the reaction was quenched by the dropwise addition of MeOH (21 mL). The mixture was transferred into an Erlenmeyer flask containing aq. sat. sodium potassium tartrate (Rochelle salt, 62 mL). The contents were vigorously stirred at ambient temperature for 11 h. The resulting biphasic mixture was diluted with H₂O (150 mL) and the aqueous layer extracted with CH₂Cl₂ (3 x 50 mL). The combined extracts were washed with H₂O (50 mL) and brine (50 mL), dried over MgSO₄ and evaporated to give a pale yellow oil.

The crude lactol was azeotropically dried with toluene before it was dissolved in toluene (138 mL). After addition of Ph₃P=CHCOOEt (14.4 g, 41.3 mmol), the mixture was stirred at 80 °C for 16 h. The solvent was evaporated and the remaining syrup purified by flash chromatography (SiO₂, hexanes/EtOAc gradient, 0 to 30%) to give alkene **33** as a pale yellow oil (9.9 g, 80% over two steps). $[\alpha]_D^{20} = -22.8^\circ$ (c = 0.87, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = 7.45-7.40 (m, 6H), 7.34-7.28 (m, 6H), 7.28-7.22 (m, 3H), 6.86 (dd, *J* = 7.7, 15.7 Hz, 1H), 5.69 (dd, *J* = 1.2, 15.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.85-3.77 (m, 1H), 3.19 (dd, *J* = 3.2, 9.4 Hz, 1H), 3.02 (dd, *J* = 7.4, 9.4 Hz, 1H), 2.49-2.38 (m, 1H), 1.58 (ddd, *J* = 6.5, 8.6, 13.9 Hz, 1H), 1.35-1.28 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.03 ppm (d, *J* = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 166.9, 154.2, 143.9 (3C), 128.8 (6C), 128.0 (6C), 127.3 (3C), 119.7, 86.9, 68.7, 67.8, 60.3, 39.3, 32.9, 19.0, 14.4 ppm; IR (film): 3479, 3059, 2931, 2872, 1775, 1716, 1651, 1597, 1490, 1448, 1368, 1277, 1181, 1074, 1034, 986, 900, 765, 747, 706 cm⁻¹; HRMS (ESI-pos) calcd. for C₂₉H₃₂O₄Na [M + Na⁺] 467.2193, found 467.2191.

Compound S8. A round-bottomed flask was charged with alkene **33** (9.9 g, 22.2 mmol) and THF (113 mL). After cooling to 0 °C, a solution of TBAF·3H₂O (1.0 M in THF, 33.3 mL, 33.3 mmol) was added and the mixture stirred at this temperature for 2.5 h. After the reaction was judged complete by TLC, the solvent was evaporated and the residue purified by flash chromatography (SiO₂, hexanes/EtOAc gradient, 3 to 5%) to afford the title compound as a white solid (8.1 g, 82%).



Crystals suitable for X-ray analysis were obtained from acetone.

M.p. 112-113 °C (acetone); $[\alpha]_D^{20} = -6.9^\circ$ (c = 3.05, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = 7.49-7.42 (m, 6H), 7.32-7.18 (m, 9H), 4.27-4.12 (m, 1H), 4.18 (dq, *J* = 1.8, 7.1 Hz, 2H), 3.90 (td, *J* = 4.2, 8.5 Hz, 1H), 3.16 (dd, *J* = 5.3, 9.4 Hz, 1H), 3.02 (dd, *J* = 4.8, 9.4 Hz, 1H), 2.57 (dd, *J* = 4.2, 14.8 Hz, 1H), 2.49 (dd, *J* = 8.1, 14.8 Hz, 1H), 2.23-2.15 (m, 1H), 2.00-1.87 (m, 1H), 1.43 (ddd, *J* = 8.9, 10.8, 12.3 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.03 ppm (d, *J* = 6.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 171.7, 144.3 (3C), 128.9 (6C), 127.9 (6C), 127.0 (3C), 86.5, 81.6, 77.4, 66.8, 60.6, 40.0, 39.5, 37.9, 16.3 14.4 ppm; IR (film): 3058, 3032, 2959, 2929, 2872, 1734, 1596, 1490, 1448, 1383, 1367, 1321, 1275, 1251, 1196, 1153, 1092, 1075, 1032, 992, 945, 899, 836, 776, 765, 747, 701 cm⁻¹; MS (EI): *m/z* (%): 444 (M⁺, 0.3), 243 (100); HRMS (ESI-pos) calcd. for C₂₉H₃₂O₄Na [M + Na⁺] 467.2193, found 467.2195.

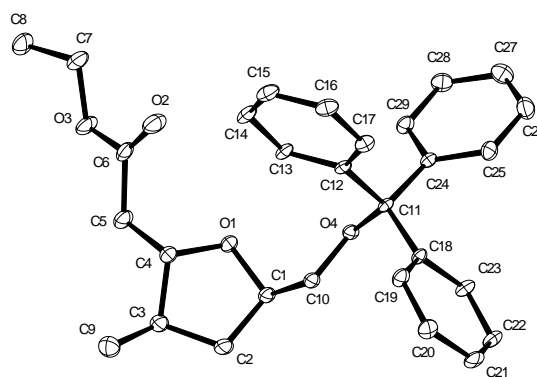
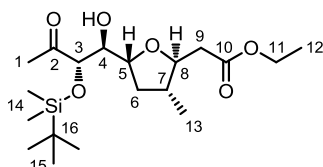


Figure S2. Structure of compound **S8** in the solid state; anisotropic displacement parameters are drawn at the 50% probability level, hydrogen atoms are omitted for clarity. **CCDC 815411** contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Compound 34. A round-bottomed flask was charged with compound **S8** (8.1 g, 18.2 mmol), CH_2Cl_2 (364 mL) and EtOH (20.5 mL). The mixture was cooled to 0 °C before trifluoroacetic acid (38.9 mL) was slowly added. The mixture was stirred at 0 °C for 1 h before the reaction was quenched at 0 °C by the slow addition of aq. sat. NaHCO_3 (Note: once the biphasic mixture has a pH ~ 7-8, it became colorless). The mixture was transferred to a separatory funnel and the aqueous layer extracted with EtOAc (3 x 80 mL). The combined extracts were washed with brine (80 mL) and the solvents evaporated. The remaining crude oil was dissolved in EtOAc (420 mL), aq. sat. K_2CO_3 (140 mL) was added, and the resulting mixture stirred for 15 min. The aqueous layer was extracted with EtOAc (80 mL), the combined organic phases were washed with H_2O (80 mL) and brine (80 mL), dried over MgSO_4 and concentrated. The residue was purified by flash chromatography (SiO_2 , hexanes/EtOAc gradient, 25 to 75%) to give the title compound as a pale yellow oil (3.4 g, 93%). $[\alpha]_D^{20} = -28.0^\circ$ ($c = 1.95$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): $\delta = 4.06$ (q, $J = 7.2$ Hz, 2H), 4.01 (ddt, $J = 3.5, 5.9, 9.5$ Hz, 1H), 3.76 (dt, $J = 4.4, 8.3$ Hz, 1H), 3.54 (dd, $J = 3.4, 11.7$ Hz, 1H), 3.42 (dd, $J = 5.6, 11.7$ Hz, 1H), 2.97 (bs, 1H), 2.45 (dd, $J = 4.5, 15.3$ Hz, 1H), 2.38 (dd, $J = 7.9, 15.3$ Hz, 1H), 2.01 (dt, $J = 6.4, 12.2$ Hz, 1H), 1.95-1.83 (m, 1H), 1.39-1.35 (ddd, $J = 9.5, 10.5, 12.0$ Hz, 1H), 1.17 (t, $J = 7.1$ Hz, 3H), 0.95 ppm (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3): $\delta = 171.5, 81.4, 78.9, 64.7, 60.5, 39.8, 39.2, 36.3, 16.2, 14.1$ ppm; IR (film): 3457, 2956, 2930, 2870, 1783, 1732, 1462, 1369, 1327, 1276, 1254, 1191, 1093, 1027, 939, 836, 779, 673, 662 cm^{-1} ; MS (EI): m/z (%): 171 ($\text{M}^+ - 31$, 100), 157 (10), 144 (17), 129 (11), 125 (82), 115 (48), 99 (34), 97 (69), 83 (31), 71 (27), 69 (76), 68 (12), 57 (29), 55 (39), 45 (15), 43 (54), 41 (56), 31 (20), 29 (72), 27 (31); HRMS (ESI-pos) calcd. for $\text{C}_{10}\text{H}_{18}\text{O}_4\text{Na}$ [$\text{M} + \text{Na}^+$] 225.1097, found 225.1097.

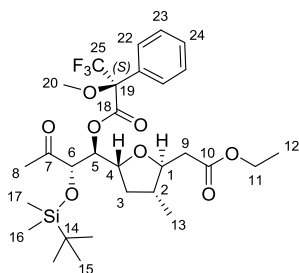
Compound 37. A Schlenk flask was charged with alcohol **34** (2.0 g, 9.74 mmol), which was azeotropically dried with benzene. CH_2Cl_2 (98 mL) was added and the resulting solution cooled to 0 °C before DMSO (3.5 mL, 48.7 mmol) and diisopropylethylamine (11.9 mL, 68.2 mmol) were successively introduced. The mixture was stirred at 0 °C for ~ 5



min prior to the addition of SO_3 -pyridine (4.6 g, 29.2 mmol) and stirring was continued at 0 °C for 1 h. The reaction was then quenched with aq. sat. NaHCO_3 (50 mL), the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), the combined organic phases were dried over MgSO_4 and evaporated to give crude aldehyde **35**, which was immediately used in the next. Its spectral data matched those reported in the literature.⁶

The crude aldehyde **35** (985 mg, 4.92 mmol) was azeotropically dried with benzene before it was dissolved in DMF (3.6 mL). 1-(*tert*-Butyldimethylsiloxy)-2-propanone (**36**) (21.1 mL, 0.108 mol) and L-proline (283 mg, 2.46 mmol) were added and the mixture was stirred for 18 h. For work up, the DMF was distilled off under reduced pressure and the residue purified by flash chromatography (SiO_2 , hexanes/EtOAc gradient, 8 to 12%) to afford product **37** as a colorless oil (1.2 g, 63% over 2 steps). $[\alpha]_D^{20} = -4.3^\circ$ ($c = 0.49$, CH_2Cl_2); ^1H NMR (600 MHz, CDCl_3): $\delta = 4.13$ (q, $J = 7.1$ Hz, 2H, H-11), 4.12-4.07 (m, 1H, H-5), 3.89 (d, $J = 7.1$ Hz, 1H, H-3), 3.85 (ddd, $J = 4.1, 8.1, 8.7$ Hz, 1H, H-8), 3.52 (ddd, $J = 3.4, 7.1, 8.1$ Hz, 1H, H-4), 2.49 (dd, $J = 4.1, 15.1$ Hz, 1H, H-9a), 2.41 (dd, $J = 8.1, 15.1$ Hz, 1H, H-9b), 2.34 (d, $J = 8.1$ Hz, 1H, HO), 2.19 (s, 3H, H-1), 2.07 (ddd, $J = 5.7, 6.8, 12.1$ Hz, 1H, H-6a), 2.02-1.96 (m, 1H, H-7), 1.58 (ddd, $J = 10.2, 11.0, 12.1$ Hz, 1H, H-6b), 1.24 (t, $J = 7.2$ Hz, 3H, H-12), 1.03 (d, $J = 6.5$ Hz, 3H, H-13), 0.88 (s, 9H, H-15), 0.05 (s, 3H, H-14a), 0.01 ppm (s, 3H, H-14b); ^{13}C NMR (150 MHz, CDCl_3): $\delta = 210.4$ (C, C-2), 171.3 (C, C-10), 82.1 (HC, C-8), 79.3 (HC, C-3), 76.4 (HC, C-5), 74.3 (HC, C-4), 60.5 (H_2C , C-11), 40.1 (HC, C-7), 39.5 (H_2C , C-9), 36.8 (H_2C , C-6), 25.7 (H_3C , C-1 and $(\text{H}_3\text{C})_3$, C-15), 18.0 (CSi, C-16), 16.1 (H_3C , C-13), 14.2 (H_3C , C-12), -5.1 (H_3CSi , C-14a), -5.2 ppm (H_3C , C-14b); IR (film): 3456, 2957, 2931, 2859, 1737, 1667, 1463, 1419, 1251, 1208, 1142, 1095, 1033, 945, 897, 836, 778, 713, 675 cm^{-1} ; MS (EI): m/z (%): 313 ($\text{M}^+ - 75$, 71), 201 (16), 188 (21), 171 (100), 143 (12), 131 (33), 129 (10), 125 (62), 113 (19), 109 (18), 97 (25), 83 (15), 75 (44), 73 (30), 69 (14), 55 (10), 43 (19), 29 (11); HRMS (ESI-pos) calcd. for $\text{C}_{19}\text{H}_{36}\text{O}_6\text{SiNa}$ [$\text{M} + \text{Na}^+$] 411.2173, found 411.2173.

Mosher Ester Analysis of Alcohol 37. To a solution of alcohol **37** (3.0 mg, 0.00772 mmol) in CH_2Cl_2 (150 μL) was added pyridine (3.9 μL , 0.0479 mmol) followed by (*R*)- α -methoxy- α -trifluoromethyl-phenylacetyl chloride ((*R*)-MTPA-Cl) (8.1 μL , 0.0432 mmol) and DMAP (19 mg, 0.154 mmol). The reaction was stirred overnight before a second portion of pyridine (9.7 μL , 0.120 mmol), (*R*)-MTPA-Cl (14 μL , 0.0726 mmol) and DMAP (50 mg, 0.406 mmol) was added. The reaction was stirred until TLC analysis showed complete consumption of the substrate. Standard aqueous workup followed by flash chromatography (SiO_2 , hexanes/EtOAc, 10%) gave the corresponding (*S*)-Mosher ester (**S**)-MTPA-**37**, which



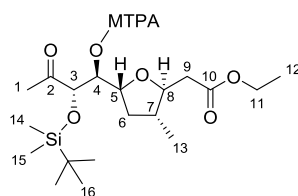
analyzed as follows: ^1H NMR (400 MHz, CDCl_3 , 300 K): $\delta = 7.61$ -7.55 (m, 2H, H-22), 7.39-7.35 (m, 3H, H-23, H-24), 5.21 (dd, $J = 4.6, 6.6$ Hz, 1H, H-5), 4.12-4.01 (m, 1H, H-4), 4.06 (d, $J = 4.6$ Hz, 1H, H-6), 4.05 (qd, $J = 7.2, 10.8$ Hz, 2H, H-11), 3.76 (ddd, $J = 4.4, 8.0, 9.2$ Hz, 1H, H-1), 3.52 (q, $^5J_{\text{HF}} = 1.2$ Hz, 3H, H-20), 2.44 (dd, $J = 4.4, 14.8$ Hz, 1H, H-9a), 2.34 (dd, $J = 8.0, 14.8$ Hz, 1H, H-9b), 2.18 (ddd, $J = 6.4, 7.3, 12.0$ Hz, 1H, H-3a), 2.15 (s, 3H, H-8), 1.91 (qdd, $J = 6.8, 9.2, 11.0$ Hz, 1H, H-2), 1.20 (t, $J = 7.0$ Hz, 3H, H-12), 1.15 (ddd, $J = 9.6, 11.0, 12.0$ Hz, 1H, H-3b), 0.89 (s, 9H, H-15), 0.89 (d, $J = 6.4$ Hz, 3H, H-13), 0.09 (s, 3H, H-16),

0.06 ppm (s, 3H, H-17); ^{13}C NMR NMR (100 MHz, CDCl_3 , 300 K): δ = 209.5 (C, C-7), 171.0 (C, C-10), 166.1 (C, C-18), 132.3 (C, C-21), 129.5 (HC, C-24), 128.2 (2 HC, C-23), 127.8 (2 HC, C-22), 81.3 (HC, C-1), 79.0 (HC, C-5), 77.5 (HC, C-6), 75.2 (HC, C-4), 60.4 (H_2C , C-11), 55.6 (H_3C , C-20), 39.9 (HC, C-2), 39.3 (H_2C , C-9), 37.2 (H_2C , C-3), 26.4 (H_3C , C-8), 25.6 (3 H_3C , C-15), 18.1 (C, C-14), 15.6 (H_3C , C-13), 14.1 (H_3C , C-12), -4.8 (H_3C , C-16), -5.2 ppm (H_3C , C-17) (signals for C-25 and C-19 could not be detected).

The same procedure was followed for the preparation of (*R*)-MTPA-37 ester, which analyzed as follows: ^1H NMR (400 MHz, CDCl_3 , 300 K): δ = 7.61-7.55 (m, 2H, H-22), 7.37-7.32 (m, 3H, H-23, H-24), 5.24 (dd, J = 3.4, 8.2 Hz, 1H, H-5), 4.09 (ddd, J = 6.0, 8.1, 9.5 Hz, 1H, H-4), 4.06 (qd, J = 7.2, 11.0 Hz, 2H, H-11), 3.95 (d, J = 3.4 Hz, 1H, H-6), 3.86 (ddd, J = 4.0, 8.0, 9.2 Hz, 1H, H-1), 3.57 (q, $^5J_{\text{HF}}$ = 1.4 Hz, 3H, H-20), 2.49 (dd, J = 4.0, 14.8 Hz, 1H, H-9a), 2.35 (dd, J = 8.0, 14.8 Hz, 1H, H-9b), 2.28 (dt, J = 6.4, 12.0 Hz, 1H, H-3a), 1.98 (qdd, J = 6.8, 9.0, 10.8 Hz, 1H, H-2), 1.76 (s, 3H, H-8), 1.25 (ddd, J = 9.7, 11.0, 12.1 Hz, 1H, H-3b), 1.21 (t, J = 7.1 Hz, 3H, H-12), 1.03 (d, J = 6.6 Hz, 3H, H-13), 0.88 (s, 9H, H-15), 0.05 (s, 3H, H-16), 0.00 ppm (s, 3H, H-17); ^{13}C NMR NMR (100 MHz, CDCl_3 , 300 K): δ = 209.9 (C, C-7), 170.9 (C, C-10), 166.0 (C, C-18), 132.7 (C, C-21), 129.4 (HC, C-24), 128.2 (2 HC, C-23), 127.4 (2 HC, C-22), 123.4 (q, $^1J_{\text{CF}}$ = 289 Hz, F_3C , C-25), 85.0 (C, C-19), 81.3 (HC, C-1), 79.5 (HC, C-5), 77.6 (HC, C-6), 75.5 (HC, C-4), 60.4 (H_2C , C-11), 55.9 (H_3C , C-20), 40.1 (HC, C-2), 39.4 (H_2C , C-9), 37.7 (H_2C , C-3), 26.4 (H_3C , C-8), 25.6 (3 H_3C , C-15), 18.1 (C, C-14), 15.9 (H_3C , C-13), 14.1 (H_3C , C-12), -5.1 (H_3C , C-16), -5.3 ppm (H_3C , C-17).

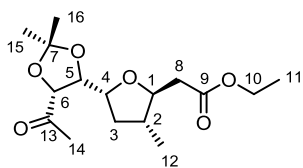
Both products were analyzed according to Hoyer and co-workers:⁷

Table S1. Mosher Ester Analysis for the Assignment of the C(4) Stereocenter (δ , ppm); arbitrary numbering as shown in the Insert



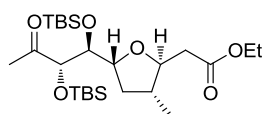
Assignment	$\delta(37)$	$\delta[(S)\text{-ester}]$	$\delta[(R)\text{-ester}]$	$\Delta\delta^{SR}(= \delta_S - \delta_R)$	
				ppm	Hz (400 MHz)
1	2.19	2.15	1.76	+0.39	+156
3	3.89	4.06	3.95	+0.11	+44
15	0.01	0.06	0.00	+0.06	+24
14	0.05	0.09	0.05	+0.04	+16
16	0.88	0.89	0.88	+0.01	+4
9b	2.49	2.34	2.35	-0.01	-4
11	4.13	4.05	4.06	-0.01	-4
12	1.24	1.20	1.21	-0.01	-4
4	3.52	5.21	5.24	-0.03	-12
5	4.09	4.06	4.09	-0.03	-12
9a	2.41	2.44	2.49	-0.05	-20
7	2.00	1.91	1.98	-0.07	-28
6a	2.07	2.18	2.28	-0.10	-40
6b	1.58	1.15	1.25	-0.10	-40
8	3.85	3.76	3.86	-0.10	-40
13	1.03	0.89	1.03	-0.14	-56

Compound 42. A Teflon screw-capped vial was charged with alcohol **37** (69 mg, 0.178 mmol) and THF (2.6 mL). The solution was cooled to 0 °C before pyridine (588 μ L, 7.30 mmol), HF·pyridine (401 μ L, 4.45 mmol) and EtOH (39 μ L, 0.676 mmol) were added. The vial was placed in the refrigerator for 48 h. Since TLC analysis showed that the reaction was incomplete, a second portion of HF·pyridine (99 μ L, 1.10 mmol) was added. After additional 7 h, the reaction was quenched with aq. sat. NaHCO₃ (3 mL) and the aqueous layer was extracted with EtOAc (3 x 2 mL). The combined extracts were dried over MgSO₄ and concentrated to give the desired diol **S9** (44 mg, 90%) as an oil, which was directly used in the next step.



The crude diol **S9** (13 mg, 0.0474 mmol) was dissolved in 2,2-dimethoxypropane (474 μ L, 3.87 mmol). TsOH (0.82 mg, 0.00474 mmol, 0.1 equiv) was added and the mixture stirred overnight. The reaction was quenched with aq. sat. NaHCO₃ (1 mL) and the aqueous layer extracted with EtOAc (3 x 1 mL). The combined extracts were dried over MgSO₄ and evaporated and the residue was purified by flash chromatography (SiO₂, hexanes/EtOAc, 50%) to afford acetal **42** (10 mg, 67% over two steps). It should be noted that this compound was found rather unstable on silica gel as well as upon storage in the freezer. ¹H NMR (400 MHz, [D₆]-acetone): δ = 4.40 (d, J = 8.6 Hz, 1H, H-6), 4.33 (dd, J = 1.6, 8.7 Hz, 1H, H-5), 4.05 (q, J = 7.0 Hz, 2H, H-10), 4.01 (ddd, J = 1.6, 6.9, 9.0 Hz, 1H, H-4), 3.86 (dt, J = 3.0, 9.4 Hz, 1H, H-1), 2.52 (dd, J = 3.0, 15.0 Hz, 1H, H-8a), 2.19 (dd, J = 9.4, 15.0 Hz, 1H, H-8b), 2.12 (s, 3H, H-14), 2.09 (dt, J = 7.0, 12.0 Hz, 1H, H-3a), 1.89-1.77 (m, 1H, H-2), 1.66 (ddd, J = 9.0, 11.0, 11.8 Hz, 1H, H-3b), 1.57-1.54 (m, 3H, H-15), 1.33-1.31 (m, 3H, H-16), 1.21 (t, J = 7.1 Hz, 3H, H-11), 1.00 ppm (d, J = 6.4 Hz, 3H, H-12); ¹³C NMR (100 MHz, [D₆]-acetone): δ = 210.1 (C, C-13), 171.7 (C, C-9), 110.3 (C, C-7), 83.5 (HC, C-1), 82.0 (HC, C-6), 81.3 (HC, C-5), 75.8 (HC, C-4), 60.6 (H₂C, C-10), 40.7 (HC, C-2), 39.8 (H₂C, C-8), 37.0 (H₂C, C-3), 27.9 (H₃C, C-14), 26.8 (H₃C, C-15), 24.9 (H₃C, C-16), 15.7 (H₃C, C-12), 14.5 ppm (H₃C, C-11).

Compound 38. A Schlenk flask was charged with alcohol **37** (4.2 g, 10.7 mmol) and CH₂Cl₂ (107 mL). The resulting solution was cooled to 0 °C before pyridine (4.3 mL, 53.4 mmol) and TBSOTf (9.8 mL, 42.7 mmol) were sequentially added. The mixture was stirred at room temperature until TLC analysis showed complete consumption of starting material (~ 2.5 to 3 h). For work up, aq. sat. NH₄Cl (100 mL) was added and stirring continued for 15 min. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL) and the combined extracts were washed with H₂O (30 mL) and brine (30 mL).

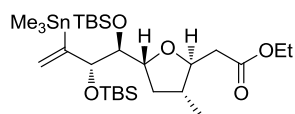
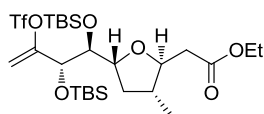


HCl (1% v/v in EtOH, 48 mL) was added and the resulting mixture stirred for 30 min to complete the hydrolysis of the silyl enol ether, which is a by-product of the reaction. A standard extractive work up with Et₂O (300 mL) and H₂O (100 mL) furnished a light yellow syrup which was purified by flash chromatography (SiO₂, hexanes/EtOAc gradient, 2 to 4%) to afford bis-TBS protected product **38** as a colorless oil (5.1 g, 95%). $[\alpha]_D^{20} = -14.4^\circ$ (c = 1.35, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = 4.11 (q, J = 7.1 Hz, 2H), 3.90 (d, J = 2.0 Hz, 1H), 3.87 (ddd, J = 5.8, 8.2, 10.2 Hz, 1H), 3.81 (dt, J = 3.8, 8.8 Hz, 1H), 3.67 (dd, J = 2.0,

8.1 Hz, 1H), 2.48 (dd, $J = 3.8, 14.9$ Hz, 1H), 2.39 (dd, $J = 8.6, 14.9$ Hz, 1H), 2.27-2.15 (m, 1H), 2.20 (s, 3H), 1.98-1.85 (m, 1H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.28-1.16 (m, 1H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.93 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 212.2, 171.8, 81.2, 80.5$ (2C), 79.4, 60.7, 40.3, 39.7, 38.2, 28.2, 26.2 (3C), 26.0 (3C), 18.6, 18.4, 16.1, 14.3, -4.5 (2C), $-4.7, -4.9$ ppm; IR (film): 2955, 2930, 2888, 2857, 1738, 1714, 1472, 1463, 1388, 1350, 1252, 1193, 1131, 1079, 1039, 963, 938, 856, 834, 806, 777, 679 cm^{-1} ; MS (EI): m/z (%): 445 ($\text{M}^+ - 57, 42$), 313 (71), 245 (36), 183 (18), 171 (100), 147 (10), 143 (13), 129 (21), 125 (36), 115 (14), 109 (34), 97 (12), 75 (21), 73 (79); HRMS (ESI-pos) calcd. for $\text{C}_{25}\text{H}_{50}\text{O}_6\text{Si}_2\text{Na}$ [$\text{M} + \text{Na}^+$] 525.3038, found 525.3033.

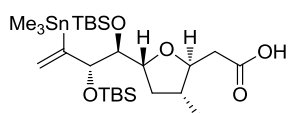
Compound 39. A Schlenk flask was charged with ketone **38** (1.34 g, 2.66 mmol), which was azeotropically dried with benzene. The compound was then dissolved in THF (13.4 mL) and the solution cooled to -78 °C. Next, a cold (-78 °C) solution of KHMDS (574 mg, 2.87 mmol) in THF (11.3 mL) was added dropwise via cannula. The resulting yellow solution was stirred for 1 h at -78 °C before a pre-cooled (-78 °C) solution of phenyl triflimide (2.4 g, 6.65 mmol, azeotropically dried with benzene prior to use) in THF (12.1 mL) was added (note that at -78 °C, the triflimide solution in THF becomes cloudy). The resulting pale yellow mixture was stirred at -78 °C for 3 h before the reaction was quenched at this temperature with aq. sat. NH_4Cl (50 mL). After reaching ambient temperature, the mixture was added to a separatory funnel containing *tert*-butyl methyl ether (100 mL) and H_2O (50 mL). The aqueous layer was extracted with *tert*-butyl methyl ether (3 x 30 mL). The combined extracts were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4 , filtered and evaporated. The residue was purified by flash chromatography (SiO_2 , hexanes/*tert*-butyl methyl ether gradient, 0 to 1%) to afford enol triflate **39** as a colorless oil (1.2 g, 71%). $[\alpha]_D^{20} = -8.3^\circ$ ($c = 1.35, \text{CH}_2\text{Cl}_2$); ^1H NMR (400 MHz, CDCl_3): $\delta = 5.30$ (dd, $J = 0.9, 3.4$ Hz, 1H), 5.25 (d, $J = 3.4$ Hz, 1H), 4.26 (d, $J = 2.9$ Hz, 1H), 4.12 (q, $J = 7.2$ Hz, 2H), 4.04 (dt, $J = 6.2, 10.2$ Hz, 1H), 3.80 (dt, $J = 4.1, 8.6$ Hz, 1H), 3.63 (dd, $J = 3.1, 6.7$ Hz, 1H), 2.50 (dd, $J = 4.0, 14.8$ Hz, 1H), 2.42 (dd, $J = 8.2, 14.8$ Hz, 1H), 2.06 (dt, $J = 6.2, 11.8$ Hz, 1H), 1.99-1.86 (m, 1H), 1.34 (q, $J = 11.1$ Hz, 1H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.02 (d, $J = 6.5$ Hz, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.6, 155.2, 120.2, 106.2, 81.1, 78.8, 77.6, 74.9, 60.6, 40.5, 39.7, 37.6, 26.2$ (3C), 25.9 (3C), 18.5, 18.3, 16.0, 14.3, $-4.2, -4.8$ ppm (3C); IR (film): 2957, 2931, 2888, 2859, 1737, 1668, 1473, 1463, 1419, 1325, 1251, 1208, 1142, 1096, 1032, 945, 897, 835, 813, 777, 713, 676, 665 cm^{-1} ; MS (EI): m/z (%): 577 ($\text{M}^+ - 57, 100$), 319 (30), 315 (41), 183 (30), 171 (64), 147 (14), 125 (26), 115 (18), 109 (34), 75 (13), 73 (56); HRMS (ESI-pos) calcd. for $\text{C}_{26}\text{H}_{49}\text{O}_8\text{Si}_2\text{SF}_3\text{Na}$ [$\text{M} + \text{Na}^+$] 657.2531, found 657.2532.

Compound 40. A Schlenk flask was charged with anhydrous LiCl (336 mg, 7.92 mmol) and triflate **39** (503 mg, 0.792 mmol). The contents were azeotropically dried with benzene before tris(2-furyl)-phosphine (110 mg, 0.475 mmol) was added, followed by THF (7.8 mL). The resulting solution was subjected to three freeze/pump/thaw degassing cycles. Once the contents reached room temperature, $\text{Pd}_2(\text{dba})_3$ (109 mg, 0.119 mmol) and hexamethylditin



(493 μL , 2.38 mmol) were added and the dark mixture was stirred for 1.5 h. At this time, a second portion of hexamethylditin (493 μL , 2.38 mmol) was introduced and stirring continued for 1.75 h before a third portion of hexamethylditin (493 μL , 2.38 mmol) was introduced. After an additional 1 h, the mixture was diluted with Et_2O (30 mL) and the suspension filtered through a pad of Celite, which was carefully rinsed with Et_2O (60 mL). The combined filtrates were evaporated and the residue was purified by flash chromatography (SiO_2 , hexanes/*tert*-butyl methyl ether gradient, 1 to 2%) to afford stannane **40** as a colorless oil (412 mg, 80%). $[\alpha]_D^{20} = -23.7^\circ$ ($c = 0.33$, CHCl_3); ^1H NMR (400 MHz, C_6D_6): $\delta = 5.98$ (dd, $J = 1.5, 2.7$ Hz, $J_{\text{Sn-H}} = 72.6$ Hz, 1H), 5.36 (dd, $J = 1.5, 2.7$ Hz, $J_{\text{Sn-H}} = 35.4$ Hz, 1H), 4.49-4.45 (m, $J_{\text{Sn-H}} = 24.3$ Hz, 1H), 4.10 (ddd, $J = 5.6, 7.2, 10.2$ Hz, 1H), 4.03 (dq, $J = 1.5, 7.2$ Hz, 2H), 3.89 (ddd, $J = 4.0, 8.1, 8.9$ Hz, 1H), 3.79 (dd, $J = 3.1, 7.3$ Hz, 1H), 2.36 (dd, $J = 8.0, 14.9$ Hz, 1H), 2.28 (dd, $J = 4.0, 14.9$ Hz, 1H), 1.97 (quint, $J = 6.1$ Hz, 1H), 1.67-1.54 (m, 1H), 1.29-1.18 (m, 1H), 1.12 (s, 9H), 1.03 (s, 9H), 1.06-1.01 (m, 3H), 0.75 (d, $J = 6.5$ Hz, 3H), 0.36 (s, 3H), 0.32 (s, 3H), 0.29 (s, $J_{\text{Sn-H}} = 26.0$ Hz, 9H), 0.22 (s, 3H), 0.13 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 170.9, 155.3, 126.4, 83.0, 81.1, 80.2, 80.1, 60.3, 40.4, 39.6, 38.8, 26.9$ (3C), 26.5 (3C), 19.1, 18.9, 16.1, 14.3, -3.3, -3.4, -3.9, -4.0, -7.7 ppm (3C); IR (film): 2954, 2929, 2888, 2856, 1739, 1472, 1462, 1388, 1361, 1326, 1250, 1194, 1131, 1068, 1038, 1004, 956, 928, 912, 890, 871, 830, 773, 716, 675 cm^{-1} ; MS (EI): m/z (%): 639 (12), 635 (68), 593 (13), 503 (14), 411 (51), 337 (16), 315 (36), 297 (12), 279 (22), 251 (11), 239 (22), 213 (24), 183 (60), 171 (71), 165 (61), 125 (35), 109 (100), 95 (28), 73 (96); HRMS (ESI-pos) calcd. for $\text{C}_{28}\text{H}_{58}\text{O}_5\text{Si}_2\text{SnNa}$ [$\text{M} + \text{Na}^+$] 673.2736, found 673.2742.

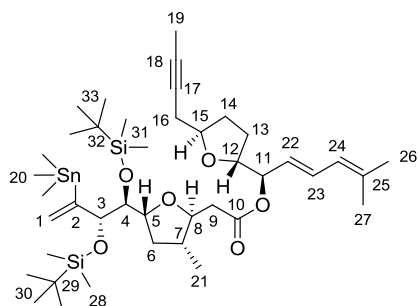
Compound 41. *This acid is labile and can be stored only for limited time at -18°C under Ar.*



A round-bottomed flask, equipped with a condenser, was charged with ester **40** (1.3 g, 2.25 mmol), THF (9.5 mL), EtOH (9.5 mL) and potassium hydroxyde (3 M in H_2O , 10.3 mL, 36.0 mmol). The mixture was stirred at 45°C for 5 h before it was cooled to room temperature. The reaction was quenched with HCl (1 M in H_2O) until a pH ~ 2 was reached and the aqueous phase extracted with Et_2O (5 x 25 mL). The combined organic layers were washed with H_2O (2 x 25 mL), dried over Na_2SO_4 , filtered and evaporated. The remaining colorless oil was azeotropically dried three times with benzene to give acid **41** as a colorless wax (1.2 g, quant.). $[\alpha]_D^{20} = -17.8^\circ$ ($c = 2.60$, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6): $\delta = 5.99$ (dd, $J = 1.5, 2.7$ Hz, $J_{\text{Sn-H}} = 72.6$ Hz, 1H), 5.36 (dd, $J = 1.5, 2.7$ Hz, $J_{\text{Sn-H}} = 35.4$ Hz, 1H), 4.50-4.46 (m, $J_{\text{Sn-H}} = 23.6$ Hz, 1H), 4.12 (ddd, $J = 5.8, 7.1, 10.2$ Hz, 1H), 3.81-3.73 (m, 2H), 2.33-2.22 (m, 2H), 1.92 (quint, $J = 6.1$ Hz, 1H), 1.59-1.46 (m, 1H), 1.29-1.18 (m, 1H), 1.13 (s, 9H), 1.04 (s, 9H), 0.70 (d, $J = 6.5$ Hz, 3H), 0.37 (s, 3H), 0.32 (s, 3H), 0.29 (s, $J_{\text{Sn-H}} = 26.5$ Hz, 9H), 0.23 (s, 3H), 0.14 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 177.1, 155.2, 126.4, 82.9, 80.6, 80.2, 79.9, 40.3, 39.1, 38.7, 26.8$ (3C), 26.4 (3C), 19.0, 18.8, 15.8, -3.3, -3.5, -3.9, -4.1, -7.8 ppm (3C); IR (film): 2978, 2667, 2589, 1781, 1712, 1465, 1435, 1420, 1351, 1328, 1294, 1270, 1236, 1210, 1147, 1061, 1012, 963, 854, 803, 777, 708 cm^{-1} ; MS (EI): m/z (%): 607 ($\text{M}^+ - 15$, 41), 345 (12), 335 (11), 325 (11), 287 (43), 239 (21), 209 (18), 185 (13), 171 (45), 165 (79), 163 (60), 155 (86), 143 (34), 125 (24), 109 (21), 95 (12), 75 (39), 73 (100); HRMS (ESI-neg) calcd. for $\text{C}_{26}\text{H}_{53}\text{O}_5\text{Si}_2\text{Sn}$ [$\text{M} - \text{H}$]: 621.2464, found 621.2465.

Fragment Coupling and Completion of the Total Synthesis

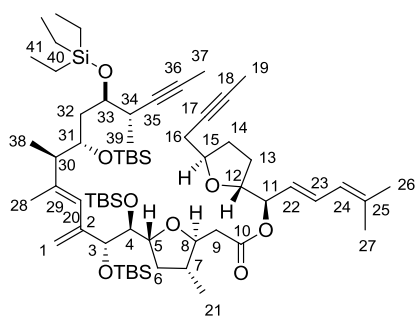
Compound 49. A Schlenk flask was charged with acid **41** (1.06 g, 1.699 mmol), which had been previously dried azeotropically from toluene (3 x). Toluene (25 mL) and triethylamine (2.1 mL, 14.95 mmol) were added to form a colorless solution. 2,4,6-Trichlorobenzoyl chloride (569 μ L, 3.568 mmol) was added and the mixture was stirred at room temperature under argon for 1 h. As the reaction progressed, the mixture became turbid and pale yellow.



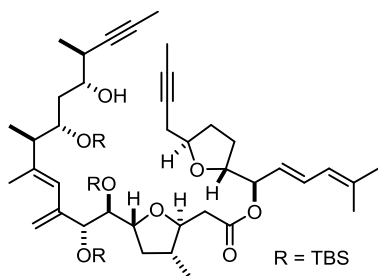
To a separate conical flask was added alcohol **47** (518 mg, 2.209 mmol) along with DMAP (706 mg, 5.776 mmol). Toluene (18 mL) was introduced and the contents were stirred until the DMAP was fully dissolved (~ 5 min). This solution was transferred via cannula into the Schlenk flask. The resulting mixture was stirred at room temperature for 3 h. Toluene (78 mL) was then added, followed by aq. sat. NaHCO_3 (47 mL). The aqueous layer was diluted with

H_2O (156 mL) and extracted with toluene (3 x 30 mL). The combined organic extracts were washed with H_2O (1 x 30 mL) and brine (1 x 30 mL) before they were dried (Na_2SO_4), filtered and concentrated to a yellow oil. The crude product was purified using flash chromatography (SiO_2 , hexanes/acetone gradient, 0 to 2%) to afford ester **49** (990 mg, 72%) as colorless oil. $[\alpha]_D^{20} = -13.6^\circ$ ($c = 0.63$, CH_2Cl_2); $^1\text{H NMR}$ (600 MHz, C_6D_6): $\delta = 6.71$ (dd, $J = 11.0, 14.9$ Hz, 1H, H-23), 5.97 (dd, $J = 1.4, 2.5$ Hz, $^3J_{\text{Sn,H}} = \sim 146$ Hz, 1H, H-1a), 5.83 (dm, $J = 11.2$ Hz, 1H, H-24), 5.64 (dd, $J = 8.4, 14.9$ Hz, 1H, H-22), 5.57 (dd, $J = 6.2, 8.4$ Hz, 1H, H-11), 5.35 (dd, $J = 1.3, 2.6$ Hz, $^3J_{119\text{Sn,H}} = 72.4$ Hz, $^3J_{117\text{Sn,H}} = 70.8$ Hz, 1H, H-1b), 4.47 (m, $^3J_{\text{Sn,H}} = \sim 50$ Hz, 1H, H-3), 4.19 (m, 2H, H-12 and H-15), 4.10 (ddd, $J = 5.9, 7.2, 12.9$ Hz, 1H, H-5), 3.93 (ddd, $J = 4.4, 7.4, 9.0$ Hz, 1H, H-8), 3.79 (dd, $J = 3.3, 7.2$ Hz, 1H, H-4), 2.50 (dd, $J = 4.4, 15.4$ Hz, 1H, H-9a), 2.50 (m, 1H, H-16a), 2.38 (dd, $J = 7.5, 15.4$ Hz, 1H, H-9b), 2.32 (m, 1H, H-16b), 1.92 (m, 1H, H-6a), 1.91 (m, 1H, H-14a), 1.72 (m, 1H, H-13a), 1.64 (m, 1H, H-7), 1.59 (m, 1H, H-14b), 1.57 (m, 1H, H-13b), 1.57 (s, 3H, H-26), 1.54 (s, 3H, H-27), 1.52 (t, $J = 2.5$ Hz, 3H, H-19), 1.24 (m, 1H, H-6b), 1.14 (s, 9H, H-33), 1.03 (s, 9H, H-30), 0.76 (d, $J = 6.5$ Hz, 3H, H-21), 0.39 (s, 3H, H-31a), 0.34 (s, 3H, H-31b), 0.30 (s, $^3J_{117\text{Sn,H}} = 51.6$ Hz, $^3J_{119\text{Sn,H}} = 54.1$ Hz, 9H, H-20), 0.22 (s, 3H, H-28a), 0.13 ppm (s, 3H, H-28b); $^{13}\text{C NMR}$ (150 MHz, C_6D_6): $\delta = 170.2$ (C, C-10), 155.3 ($^1J_{119\text{Sn,C}} = -440.3$ Hz, $^1J_{117\text{Sn,C}} = -421.8$ Hz, C, C-2), 136.8 (C, C-25), 131.7 (HC, C-23), 126.4 ($^2J_{119\text{Sn,C}} = -26.3$ Hz, $^2J_{117\text{Sn,C}} = -25.1$ Hz, H_2C , C-1), 125.9 (HC, C-22), 125.1 (HC, C-24), 82.9 ($^2J_{119\text{Sn,C}} = -50.4$ Hz, $^2J_{117\text{Sn,C}} = -49.0$ Hz, HC, C-3), 80.7 (HC, C-8), 80.5 (HC, C-12), 80.0 (HC, C-5), 79.9 (HC, C-4), 78.3 (HC, C-15), 77.2 (HC, C-11), 77.0 (C, C-18), 76.2 (C, C-17), 40.4 (HC, C-7), 40.0 (H_2C , C-9), 38.8 (H_2C , C-6), 31.4 (H_2C , C-14), 28.3 (H_2C , C-13), 26.9 ($(\text{H}_3\text{C})_3$, C-33), 26.4 ($(\text{H}_3\text{C})_3$, C-30), 26.0 (H_2C , C-16), 25.9 (H_3C , C-26), 19.0 (CSi, C-32), 18.8 (CSi, C-29), 18.2 (H_3C , C-27), 16.1 (H_3C , C-21), 3.4 (H_3C , C-19), -3.2 (H_3CSi , C-31a), -3.3 (H_3CSi , C-31b), -3.9 (H_3CSi , C-28a), -4.1 (H_3CSi , C-28b), -7.7 ppm ($^1J_{119\text{Sn,C}} = -347.5$ Hz, $^1J_{117\text{Sn,C}} = -332.1$ Hz, $(\text{H}_3\text{C})_3\text{Sn}$, C-20); IR (film): 2956, 2930, 2855, 1739, 1471, 1464, 1421, 1257, 1212, 1143, 1110, 1039, 1026, 950, 837, 779, 748, 703 cm^{-1} ; MS (EI): m/z (%): 607 ($\text{M}^+ - 231$, 34), 217 (100), 171 (15), 165 (32), 163 (31), 133 (58), 123 (14), 105 (11), 95 (74), 85 (13), 79 (20), 73 (27); HRMS (ESI-pos) calcd. for $\text{C}_{41}\text{H}_{74}\text{O}_6\text{Si}_2\text{SnNa}$ [$\text{M} + \text{Na}^+$] 861.3937, found 861.3934.

Compound 50. A Schlenk flask was charged with tetrabutylammonium diphenylphosphinate (327 mg, 0.712 mmol). The compound was first dried azeotropically with toluene (1 mL) and then dried in vacuo. Next, DMF (830 μ L) was added, followed by a solution of stannane **49** (149 mg, 0.178 mmol) in DMF (830 μ L). The flask containing the stannane was rinsed with DMF (830 μ L) and this washing was also added to the Schlenk flask. A solution of iodide **29** (131 mg, 0.231 mmol) in DMF (830 μ L) was then added and the flask rinsed with DMF (830 μ L), which was also added to the Schlenk flask. Finally, Pd(PPh₃)₄ (62 mg, 0.0534 mmol) and copper(I) thiophene-2-carboxylate (CuTC) (102 mg, 0.534 mmol) were quickly introduced in solid form each. The orange/brown mixture was stirred at room temperature for 2 h. For work up, the mixture was diluted with Et₂O (20 mL) and 2-(dimethylamino)ethanethiol hydrochloride (0.1 M in H₂O, 12.4 mL) was added. The aqueous phase was extracted with Et₂O (3 x 20 mL). The combined extracts were washed with H₂O (10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and evaporated. The remaining viscous orange oil was purified by flash chromatography (SiO₂, hexanes/acetone gradient, 3 to 10%) to afford bis-alkyne **50** as a colorless oil (119 mg, 56%).



The remaining viscous orange oil was purified by flash chromatography (SiO₂, hexanes/acetone gradient, 3 to 10%) to afford bis-alkyne **50** as a colorless oil (119 mg, 56%). $[\alpha]_D^{20} = -22.4^\circ$ (c = 1.40, CH₂Cl₂); ¹H NMR (600 MHz, C₆D₆): δ = 6.71 (dd, *J* = 11.0, 14.9 Hz, 1H, H-23), 6.08 (s, 1H, H-20), 5.83 (dm, *J* = 11.0 Hz, 1H, H-24), 5.64 (dd, *J* = 8.3, 14.9 Hz, 1H, H-22), 5.59 (dd, *J* = 6.1, 8.3 Hz, 1H, H-11), 5.55 (s, 1H, H-1a), 5.19 (s, 1H, H-1b), 4.36 (s, 1H, H-3), 4.22-4.14 (m, 3H, H-5, H-12, H-15), 4.13 (m, 1H, H-31), 4.05 (m, 1H, H-33), 3.97 (ddd, *J* = 4.2, 8.1, 8.9 Hz, 1H, H-8), 3.87 (dd, *J* = 2.2, 7.7 Hz, 1H, H-4), 2.77 (m, 1H, H-34), 2.60 (m, 1H, H-30), 2.56 (dd, *J* = 8.1, 15.5 Hz, 1H, H-9a), 2.49 (dm, *J* = 16.3 Hz, 1H, H-16a), 2.42 (dd, *J* = 4.2, 15.5 Hz, 1H, H-9b), 2.31 (dm, *J* = 16.3 Hz, 1H, H-16b), 2.15 (m, 1H, H-32a), 2.14 (m, 1H, H-6a), 2.08 (d, *J* = 1.1 Hz, 3H, H-28), 1.90 (m, 1H, H-14a), 1.84 (m, 1H, H-32b), 1.76 (m, 1H, H-7), 1.72 (m, 1H, H-13a), 1.68 (d, *J* = 2.4 Hz, 3H, H-37), 1.59 (m, 2H, H-13b and H-14b), 1.58 (s, 3H, H-26), 1.54 (s, 3H, H-27), 1.53 (m, 3H, H-19), 1.36-1.28 (m, 7H, H-38, H-39 and H-6b), 1.18 (s, 9H, TBS), 1.04 (s, 9H, TBS), 1.04 (m, 9H, TBS), 1.03 (s, 9H, TBS), 0.81 (d, *J* = 6.5 Hz, 3H, H-21), 0.65 (m, 6H, H-40), 0.40 (s, 3H, TBS), 0.39 (s, 3H, TBS), 0.25 (s, 3H, TBS), 0.17 (s, 3H, TBS), 0.16 (s, 3H, TBS), 0.16 ppm (s, 3H, TBS); ¹³C NMR (150 MHz, C₆D₆): δ = 170.3 (C, C-10), 146.0 (C, C-2), 141.3 (C, C-29), 136.7 (C, C-25), 131.7 (HC, C-23), 126.3 (HC, C-20), 126.0 (HC, C-22), 125.1 (HC, C-24), 115.1 (H₂C, C-1), 80.9 (C, C-35), 80.6 (HC, C-8), 80.5 (HC, C-12), 80.2 (HC, C-4), 80.0 (HC, C-5), 79.1 (HC, C-3), 78.3 (HC, C-15), 77.9 (C, C-36), 77.1 (HC, C-11), 76.9 (C, C-18), 76.2 (C, C-17), 72.9 (HC, C-31), 72.1 (HC, C-33), 47.8 (HC, C-30), 40.5 (HC, C-7), 40.0 (H₂C, C-9), 38.6 (H₂C, C-6), 38.0 (H₂C, C-32), 32.5 (HC, C-34), 31.4 (H₂C, C-14), 28.3 (H₂C, C-13), 26.6 ((H₃C)₃, TBS), 26.2 ((H₃C)₃, TBS), 26.2 ((H₃C)₃, TBS), 26.0 (H₂C, C-16), 25.9 (H₃C, C-26), 18.9 (CSi, TBS), 18.7 (CSi, TBS), 18.3 (CSi, TBS), 18.2 (H₃C, C-27), 17.9 (H₃C, C-28), 16.2 (H₃C, C-21), 15.8 (H₃C, C-39), 15.5 (H₃C, C-38), 7.3 (H₃CSi, C-41), 5.5 ((H₂C)₃Si, C-40), 3.8 (H₃C, C-37), 3.4 (H₃C, C-19), -3.7 (H₃CSi, TBS), -4.0 (H₃CSi, TBS), -4.2 (H₃CSi, TBS), -4.4 (H₃CSi, TBS), -4.4 (H₃CSi, TBS), -4.6 ppm (H₃CSi, TBS); IR (film): 2961, 2930, 2859, 2313, 1735, 1474, 1463, 1426, 1391, 1258, 1209, 1143, 1107, 1090, 1030, 836, 778, 767, 751, 702 cm⁻¹; MS (ESI-pos) [M + Na⁺] 1133 (100); HRMS (ESI-pos) calcd. for C₆₃H₁₄O₈Si₄Na

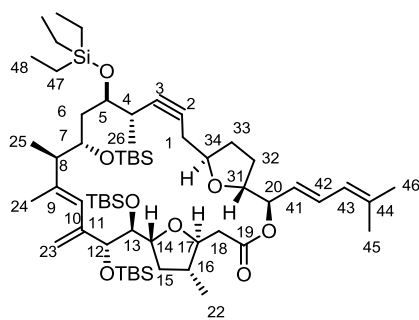


$[M + Na^+]$ 1133.7483, found 1133.7481.

Alcohol 52. A solution of pyridinium *p*-toluenesulfonate (PPTS) (0.026 M in $CH_2Cl_2/MeOH$ (9:1), 1.0 mL, 0.027 mmol) was added at 0 °C to a solution of compound **50** (19.8 mg, 0.018 mmol) in dichloromethane (1.7 mL) and MeOH (187 μ L). After stirring at this temperature for 8 h, a second portion of PPTS (0.026 M in $CH_2Cl_2/MeOH$ (9:1), 1.0 mL,

0.027 mmol) was added and the mixture was stirred for an additional 15 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined extracts were washed with sat. aq. $NaHCO_3$ (5 mL) and H_2O (2 x 3 mL), dried over Na_2SO_4 , filtered, and evaporated. Purification of the residue by flash chromatography (SiO_2 , hexanes/EtOAc, 10/1) afforded alcohol **52** as a colorless oil (15.7 mg, 89%). $[\alpha]_D^{20} = +14.3^\circ$ ($c = 1.00$, CH_2Cl_2); IR (film): 2955, 2928, 2856, 1739, 1462, 1387, 1252, 1072, 1005, 959, 835, 776; MS (ESIpos) $[M + Na^+]$ 1019 (100); HRMS (ESIpos) calcd. for $C_{57}H_{100}O_8Si_3Na$ $[M + Na^+]$ 1019.6618, found 1019.6622.

Compound 51. A Schlenk flask, equipped with a magnetic stir-bar and a glass stopper, was charged with diyne **50** (70 mg, 0.0629 mmol), which was dried azeotropically by evaporation of degassed toluene (3 x). The residue was then dissolved in degassed toluene (11 mL). After this the glass stopper was replaced with an argon bubbler.



In parallel, a stock solution of the catalyst was prepared as follows: a Schlenk flask equipped with a magnetic stir-bar and a glass stopper was charged with complex **10** (21 mg,

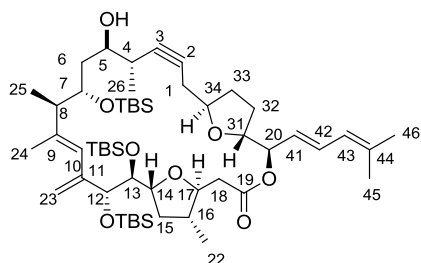
0.0336 mmol).⁸ Degassed toluene (2.1 mL) was added, followed by degassed CH_2Cl_2 (63 μ L), and the resulting mixture was stirred for 15 min to provide a 0.015 M stock solution of the activated catalyst.

An aliquot of the catalyst solution (812 μ L, 0.0126 mmol, 0.20 equiv) was added to the Schlenk flask containing the diyne to give a pale brown mixture. The flask was immersed into a preheated oil bath (60 °C) and the mixture stirred for 6 h before a second aliquot of the catalyst solution (406 μ L, 0.00629 mmol, 0.10 equiv) was introduced. The dark-brown mixture was stirred overnight (~ 14 h) before it was cooled to room temperature, diluted with Et_2O (8 mL) and washed with aq. sat. NH_4Cl (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over Na_2SO_4 , filtered and evaporated, and the remaining pale brown oil purified by flash chromatography (SiO_2 , hexanes/*tert*-butyl methyl ether gradient, 10 \rightarrow 15%) to give product **51** as a colorless syrup (49 mg, 73%). When performed with 259 mg of diyne **50** (0.233 mmol), the reaction afforded a lower yield of the product (124 mg, 50%).

$[\alpha]_D^{20} = +40.2^\circ$ ($c = 0.38$, CH_2Cl_2); 1H NMR (600 MHz, C_6D_6 , significant line broadening): $\delta = 6.65$ (dd, $J = \sim 11, \sim 15$ Hz, 1H, H-42), 6.48 (s, 1H, H-10), 5.77 (d, $J = \sim 11$ Hz, 1H, H-43), 5.48 (t, $J = 8.2$ Hz, 1H, H-20), 5.43 (dd, $J = 15.8$ Hz, 1H, H-41), 5.10 (s, 1H, H-23a), 5.04 (s, 1H, H-23b), 4.26 (bs, 1H, H-34), 4.15 (s, 1H, H-12), 4.12 (m, 1H, H-7), 4.10 (m, 1H, H-14), 4.03 (m, 1H, H-5), 4.00 (m, 1H, H-31), 3.80 (d, $J = \sim 7$ Hz, 1H, H-13), 3.58 (bs, 1H, H-17),

2.86 (d, $J = \sim 15$ Hz, 1H, H-1a), 2.82 (m, 1H, H-4), 2.73 (bs, 1H, H-8), 2.57 (dd, $J = \sim 4, \sim 13$ Hz, 1H, H-18a), 2.53 (m, 1H, H-16), 2.40 (dd, $J = 8.0, 13.5$ Hz, 1H, H-6a), 2.33 (d, $J = \sim 13$ Hz, 1H, H-18b), 2.18 (dd, $J = 9.0, 15.0$ Hz, 1H, H-1b), 2.13 (d, $J = 1.0$ Hz, 3H, H-24), 2.07 (m, 1H, H-33a), 2.06 (m, 1H, H-15a), 1.83 (ddd, $J = 3.2, 10.0, 13.6$ Hz, 1H, H-6b), 1.60 (m, 1H, H-32a), 1.57 (m, 1H, H-33b), 1.54 (s, 3H, H-45), 1.48 (s, 3H, H-46), 1.45 (m, 3H, H-25), 1.43 (m, 1H, H-32b), 1.34 (m, 3H, H-26), 1.29 (s, 9H, TBS), 1.13 (m, 1H, H-15b), 1.07 (t, $J = 8.0$ Hz, 9H, H-48), 1.05 (s, 9H, TBS), 1.01 (s, 9H, TBS), 0.82 (d, $J = \sim 6$ Hz, 3H, H-22), 0.70 (q, $J = \sim 8$ Hz, 6H, H-47), 0.49 (s, 3H, TBS), 0.43 (s, 3H, TBS), 0.25 (s, 3H, TBS), 0.22 (s, 3H, TBS), 0.13 (s, 3H, TBS), 0.12 ppm (s, 3H, TBS); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 169.1$ (C, C-19), 147.2 (C, C-11), 140.4 (C, C-9), 137.2 (C, C-44), 132.0 (HC, C-42), 129.4 (HC, C-10), 125.9 (HC, C-41), 124.9 (HC, C-43), 114.9 (H_2C , C-23), 83.7 (HC, C-13), 83.0 (C, C-2 or C-3), 81.2 (HC, C-17), 80.1 (HC, C-31), 79.8 (HC, C-14), 79.3 (C, C-2 or C-3), 77.7 (HC, C-34 and C-12), 76.2 (HC, C-20), 73.8 (HC, C-7), 72.4 (HC, C-5), 47.6 (HC, C-8), 38.7 (H_2C , C-6 and C-15), 37.7 (HC, C-16), 37.6 (H_2C , C-18), 32.9 (HC, C-4), 31.2 (H_2C , C-33), 27.8 (H_2C , C-32), 27.0 ($(\text{H}_3\text{C})_3$, TBS), 26.8 (H_2C , C-1), 26.2 (2 x $(\text{H}_3\text{C})_3$, TBS), 25.9 (H_3C , C-45), 19.2 (CSi, TBS), 18.6 (CSi, TBS), 18.3 (CSi, TBS), 18.2 (H_3C , C-46), 17.5 (H_3C , C-25), 16.3 (H_3C , C-24), 16.1 (H_3C , C-22), 14.4 (H_3C , C-26), 7.3 ($(\text{H}_3\text{C})_3$, C-48), 5.5 ($(\text{H}_2\text{C})_3\text{Si}$, C-47), -3.9 (H_3CSi , TBS), -4.1 (2 x H_3CSi , TBS), -4.4 (H_3CSi , TBS), -4.5 (H_3CSi , TBS), -4.8 ppm (H_3CSi , TBS); IR (film): 2953, 2929, 2859, 1740, 1473, 1463, 1428, 1391, 1380, 1361, 1257, 1211, 1141, 1093, 1067, 1043, 836, 778, 746, 702 cm^{-1} ; MS (ESI-pos) $[\text{M} + \text{Na}^+]$ 1079 (100); HRMS (ESI-pos) calcd. for $\text{C}_{59}\text{H}_{108}\text{O}_8\text{Si}_4\text{Na}$ $[\text{M} + \text{Na}^+]$ 1079.7014, found 1079.7013.

Compound 53. *Method A:* A Schlenk flask was charged with alkyne **51** (123.5 mg, 0.117 mmol), CH_2Cl_2 (11.2 mL) and MeOH (1.2 mL). The resulting solution was cooled to 0°C before a solution of pyridinium *p*-toluenesulfonate (PPTS, 0.026 M in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1), 299 μL , 0.0584 mmol) was added. The mixture was stirred at 0°C for 9 h before a second portion of PPTS (0.026 M in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1), 299 μL , 0.0584 mmol) was added. After stirring for additional 2.5 days, a third portion of PPTS (0.026 M in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1), 299 μL , 0.0584 mmol) was added. The reaction was quenched 12 h later with aq. sat. NaHCO_3 (10 mL), the mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were washed with aq. sat. NaHCO_3 (5 mL) and H_2O (2 x 5 mL), dried (Na_2SO_4), filtered, and evaporated. The resulting yellow oil was purified by flash chromatography (SiO_2 , hexanes/*tert*-butyl methyl ether gradient, 10 to 15%) to afford alcohol **53** as a pale yellow oil (101 mg, 92%).

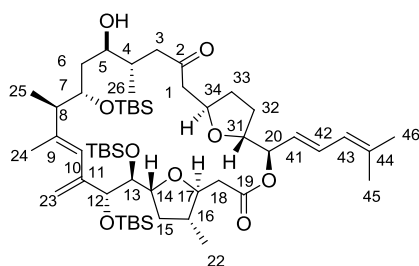


Method B: A solution of compound **52** (53.9 mg, 0.0540 mmol) in toluene (200 μL) was added to a suspension of molecular sieves (5\AA , 698 mg) in toluene (27 mL) and the resulting mixture was stirred for 30 min before it was warmed to 100°C . At this temperature, a solution of complex **9** (11.2 mg, 0.0108 mmol, 0.2 equiv)⁸ in toluene (200 μL) was introduced and the suspension stirred for 45 min. A second portion of catalyst **9** (2.8 mg, 0.00270 mmol, 0.05 equiv) was added and stirring was continued for 30 min. The mixture was then allowed

to reach ambient temperature before it was filtered through a pad of silica, which was carefully rinsed with EtOAc. The combined filtrates were evaporated and the residue purified by flash chromatography (SiO₂: 15 x 40 μm, hexanes/EtOAc, 10/1) to afford macrolactone **53** in the form of a colorless oil (30.5 mg, 60%).

$[\alpha]_D^{20} = +16.5^\circ$ ($c = 1.00$, CH₂Cl₂); ¹H NMR (500 MHz, CD₂Cl₂, 253 K): $\delta = 6.50$ (dd, $J = 11.2, 15.2$ Hz, 1H, H-42), 6.28 (s, 1H, H-10), 5.75 (d, $J = 11.2$ Hz, 1H, H-43), 5.32 (dd, $J = 8.0, 15.2$ Hz, 1H, H-41), 4.95 (s, 1H, H-23a), 4.90 (t, $J = 8.0$ Hz, 1H, H-20), 4.81 (s, 1H, H-23b), 4.06-3.99 (m, 2H, H-31 and H-34), 3.90 (dt, $J = 2.8, 10.4$ Hz, 1H, H-7), 3.87 (d, $J = 2.4$ Hz, 1H, H-12), 3.82 (ddd, $J = 1.6, 8.4, 10.0$ Hz, 1H, H-17), 3.59-3.51 (m, 2H, H-14 and H-13), 3.28 (t, $J = 9.2$ Hz, 1H, H-5), 2.49 (dd, $J = 1.6, 15.6$ Hz, 1H, H-18a), 2.43 (dq, $J = 2.4, 7.2$ Hz, 1H, H-8), 2.36 (d, $J > 16$ Hz, 1H, H-1a), 2.31 (dd, $J = 10.0, 15.6$ Hz, 1H, H-18b), 2.30-2.25 (m, 1H, H-4), 2.24 (ddd, $J = 2.4, 8.8, \sim 16$ Hz, 1H, H-1b), 2.05-1.96 (m, 2H, H-15a; H-33a), 1.96-1.88 (m, 1H, H-32a), 1.89-1.82 (m, 1H, H-16), 1.75 (s, 6H, H-45 and H-46), 1.72 (s, 3H, H-24), 1.67 (dd, $J = 10.4, 13.6$ Hz, 1H, H-6a), 1.61-1.52 (m, 1H, H-32b), 1.47-1.37 (m, 1H, H-33b), 1.30-1.22 (m, 1H, H-6b), 1.17-1.13 (m, 1H, H-15b), 1.04 (d, $J = 6.8$ Hz, 3H, H-25), 1.00 (d, $J = 6.4$ Hz, 3H, H-26), 0.99 (d, $J = 6.4$ Hz, 3H, H-22), 0.89 (s, 9H, TBS), 0.86 (s, 9H, TBS), 0.81 (s, 9H, TBS), 0.08 (s, 3H, TBS), 0.05 (s, 3H, TBS), 0.04 (s, 3H, TBS), 0.03 (s, 3H, TBS), -0.02 (s, 3H, TBS), -0.06 ppm (s, 3H, TBS); ¹³C NMR (125 MHz, CD₂Cl₂, 253 K): $\delta = 170.8$ (C, C-19), 145.9 (C, C-11), 140.4 (C, C-9), 137.9 (C, C-44), 131.1 (HC, C-42), 128.5 (HC, C-10), 125.0 (HC, C-41), 124.0 (HC, C-43), 114.7 (H₂C, C-23), 82.0 (HC, C-13), 81.5 (C, C-3), 81.2 (C, C-2), 80.3 (HC, C-17), 79.4 (HC, C-31), 79.1 (HC, C-14), 77.9 (HC, C-20), 77.6 (HC, C-12), 77.5 (HC, C-34), 73.0 (HC, C-7), 71.5 (HC, C-5), 46.4 (HC, C-8), 40.4 (H₂C, C-6), 40.1 (HC, C-16), 39.6 (H₂C, C-18), 38.5 (H₂C, C-15), 34.8 (HC, C-4), 32.1 (H₂C, C-33), 29.1 (H₂C, C-32), 26.33 ((H₃C)₃, TBS), 26.27 (H₂C, C-1), 26.0 (H₃C, C-45), 25.74 ((H₃C)₃, TBS), 25.66 ((H₃C)₃, TBS), 18.8 (CSi, TBS), 18.4 (CSi, TBS), 18.4 (H₃C, 46), 17.9 (CSi, TBS), 17.6 (H₃C, C-26), 16.1 (H₃C, C-22), 15.6 (H₃C, C-25), 15.4 (H₃C, C-24), -4.1 (H₃CSi, TBS), -4.7 (H₃CSi, TBS), -4.9 (H₃CSi, TBS), -5.0 (H₃CSi, TBS), -5.0 (H₃CSi, TBS), -5.5 ppm (H₃CSi, TBS); IR (film): 2955, 2928, 2856, 2892, 1740, 1470, 1462, 1387, 1361, 1252, 1192, 1145, 1123, 1082, 1073, 1036, 1005, 958, 902, 835, 776 cm⁻¹; MS (ESI-pos) [$M + Na^+$] 965 (100); HRMS (ESI-pos) calcd. for C₅₃H₉₄O₈Si₃Na [$M + Na^+$] 965.6149, found 965.6145.

Compound 55. A Schlenk flask was charged with alcohol **53** (231 mg, 0.245 mmol) (3 x



azeotropically dried with toluene) and degassed Et₂O (15 mL). A solution of [Cl₂Pt(CH₂=CH₂)₂] (0.00128 M in Et₂O, 382 μL, 0.490 μmol) was added and the resulting mixture stirred at room temperature for 20 min. The mixture was then filtered through a pad of Florisil and the filtrate evaporated to give a colorless oil (231 mg, quant.), which was used in the next step without purification.

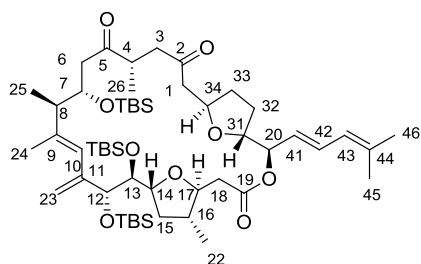
The resulting crude enol ether **54** (231 mg, 0.245 mmol) was dissolved in a solution of pyridinium *p*-toluenesulfonate (PPTS, 0.00477 M in wet benzene, 46 mL, 0.221 mmol) and the resulting mixture was stirred for 20 min at room temperature. Aq. sat. NaHCO₃ (30 mL) and H₂O (30 mL) were added and the aqueous layer extracted with EtOAc (3 x 20 mL). The

combined extracts were washed with aq. sat. NaHCO_3 (20 mL) and brine (20 mL), dried over Na_2SO_4 , filtered, and evaporated to give a colorless oil that was purified by flash chromatography (SiO_2 , hexanes/*tert*-butyl methyl ether gradient, 5 to 12%) to give **55** as a colorless oil (235 mg, 98%). As the product is a mixture of three compounds (hydroxyl-ketone and two hemi-ketals), full characterization was postponed until after the next step. IR (film): 3495, 2954, 2927, 2855, 1735, 1462, 1378, 1360, 1250, 1079, 1005, 984, 958, 902, 832, 774, 669 cm^{-1} ; MS (ESI-pos) $[\text{M} + \text{Na}^+]$ 983 (100); MS (ESI-neg) $[\text{M} - \text{H}^-]$ 959 (100); HRMS (ESI-pos) calcd. for $\text{C}_{53}\text{H}_{96}\text{O}_9\text{Si}_3\text{Na}$ $[\text{M} + \text{Na}^+]$ 983.6254, found 983.6260.

Compound 56. A Schlenk flask, equipped with a magnetic stir-bar and a glass stopper, was charged with compound **55** (9.0 mg, 0.00936 mmol). CH_2Cl_2 (488 μL) and tetra-propylammonium perruthenate (TPAP) (9.9 mg, 0.0281 mmol) were then introduced and the resulting solution was stirred at room temperature for 2 h. The mixture was filtered through a pad of silica which was carefully rinsed with CH_2Cl_2 (4 mL). The combined filtrates were evaporated and the remaining colorless oil was purified by thin-layer-chromatography (20 x 20 cm, TLC aluminium oxide 60 F_{254} basic, hexanes/ CH_2Cl_2 , 50%) to provide diketone **56** as a colorless oil (6.3 mg, 70%).

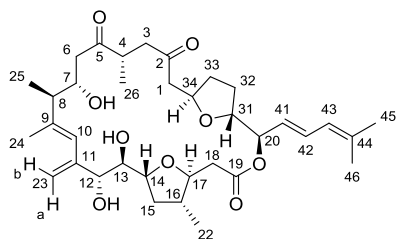
When the reaction was performed with a substantially larger amount of **55** (235 mg, 0.244 mmol), it was important to add the required TPAP (257 mg, 0.732 mmol) in portions at 0°C to avoid partial isomerization.

$[\alpha]_D^{23} = +9.2^\circ$ ($c = 0.55$, CHCl_3); ^1H NMR (500 MHz, CDCl_3 , 253 K, signals of the major conformer): $\delta = 6.50$ (dd, $J = 11.3, 14.7$ Hz, 1H, H-42), 5.99 (s, 1H, H-10), 5.71 (d, $J = 11.2$ Hz, 1H, H-43), 5.29 (dd, $J = 8.0, 15.0$ Hz, 1H, H-41), 4.99 (s, 1H, H-23a), 4.89 (t, $J = 8.3$ Hz, 1H, H-20), 4.84 (s, 1H, H-23b), 4.49 (ddt, $J = < 2, \sim 7, \sim 8$ Hz, 1H, H-34), 4.11 (m, 1H, H-7), 4.10 (q, $J = 7.5$ Hz, 1H, H-31), 3.84 (dt, $J = 3.2, 9.0$ Hz, 1H, H-17), 3.82 (bs, 1H, H-12), 3.55 (m, 1H, H-14), 3.44 (dd, $J = 2.5, 8.0$ Hz, 1H, H-13), 2.96 (m, 1H, H-4), 2.93 (dd, $J = 10.0, 19.0$ Hz, 1H, H-6a), 2.75 (m, 2H, H-3), 2.60 (dd, $J = 2.0, 14.3$ Hz, 1H, H-1a), 2.41 (dd, $J = 2.5, 16.0$ Hz, 1H, H-18a), 2.34 (m, 1H, H-1b), 2.32 (m, 1H, H-18b), 2.31 (m, 1H, H-8), 2.27 (m, 1H, H-6b), 2.15 (m, 1H, H-33a), 1.95 (m, 1H, H-32a), 1.82 (m, 1H, H-16), 1.70 (s, 9H, H-45, H-46 and H-24), 1.56 (m, 1H, H-32b), 1.51 (m, 1H, H-33b), 1.15 (m, 1H, H-15a), 1.05 (d, $J = 5.2$ Hz, 3H, H-26), 1.02 (d, $J = 7.0$ Hz, 3H, H-25), 0.99 (m, 1H, H-15b), 0.97 (d, $J = 6.4$ Hz, 3H, H-22), 0.84 (s, 9H, TBS), 0.83 (s, 9H, TBS), 0.78 (s, 9H, TBS), 0.02 (s, 3H, TBS), 0.00 (s, 3H, TBS), -0.02 (s, 3H, TBS), -0.06 (s, 3H, TBS), -0.07 (s, 3H, TBS), -0.10 ppm (s, 3H, H_3C , TBS); ^1H NMR (500 MHz, CDCl_3 , 253 K, characteristic signals for minor conformer): $\delta = 6.50$ -6.45 (m, 1H), 5.70-5.65 (m, 1H), 5.49 (s, 1H), 5.40 (s, 1H), 5.40 (dd, $J = \sim 9, \sim 15$ Hz, 1H), 5.15 (dd, $J = 4.8, 9.3$ Hz, 1H), 5.01-4.95 (m, 1H), 4.63-4.57 (m, 1H), 4.35-4.28 (m, 1H), 4.19 (s, 1H), 4.10-4.05 (m, 1H), 3.95-3.89 (m, 1H), 3.46-3.39 (m, 1H), 2.51-2.45 (m, 1H), 2.23-2.19 (m, 1H), 2.10-2.02 (m, 1H), 1.73-1.68 (m, 9H), 0.86 (s, 9H), 0.80 (m, 1H), 0.80 (s, 9H), 0.78 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.00-(-0.02) (m, 3H), -0.03 (s, 3H), -0.05 (m, 3H), -0.08 ppm (s, 3H); ^{13}C NMR (125 MHz, CDCl_3 , 253 K, signals of the major conformer): $\delta = 211.3$ (C, C-5), 208.0 (C, C-2), 170.7 (C, C-19), 145.9 (C, C-11), 140.2 (C, C-9), 138.3 (C, C-44), 131.4 (HC, C-42), 128.5 (HC, C-10), 124.4 (HC, C-41),



123.8 (HC, C-43), 114.5 (H₂C, C-23), 81.2 (HC, C-13), 79.6 (HC, C-17), 79.4 (HC, C-31), 78.4 (HC, C-14), 77.8 (HC, C-20), 76.9 (HC, C-12), 75.2 (HC, C-34), 71.1 (HC, C-7), 50.7 (H₂C, C-1), 46.2 (H₂C, C-6), 46.2 (HC, C-8), 42.0 (H₂C, C-3), 40.5 (HC, C-4 and C-16), 39.7 (H₂C, C-18), 37.2 (H₂C, C-15), 32.2 (H₂C, C-33), 28.6 (H₂C, C-32), 26.2 (H₃C, C-45), 26.2 ((H₃C)₃, TBS), 25.8 ((H₃C)₃, TBS), 25.7 ((H₃C)₃, TBS), 18.6 (H₃C, C-46), 18.6 (CSi, TBS), 18.4 (CSi, TBS), 17.9 (H₃C, C-26), 17.8 (CSi, TBS), 16.3 (H₃C, C-22), 15.9 (H₃C, C-25), 15.4 (H₃C, C-24), -4.2 (H₃CSi, TBS), -4.3 (H₃CSi, TBS), -4.7 (H₃CSi, TBS), -4.8 (H₃CSi, TBS), -5.1 (H₃CSi, TBS), -5.3 ppm (H₃CSi, TBS); ¹³C NMR (125 MHz, CDCl₃, 253 K, characteristic signals of the minor conformer): δ = 211.7, 208.6, 170.7, 144.5, 140.5, 138.3, 131.6, 124.8, 123.9, 113.5, 80.1, 79.6, 78.2, 77.7, 75.9, 49.6, 47.1, 43.0, 42.3, 41.2, 40.7, 32.6, 26.2, 25.9 (3C), 25.9 (3C), 25.7 (3C), 18.5, 18.3, 18.2, 15.9, -4.4, -4.9, -4.9 (2C), -5.0, -5.1 ppm; IR (film): 2955, 2927, 2856, 1739, 1707, 1462, 1361, 1251, 1087, 1038, 1004, 958, 836, 776 cm⁻¹; MS (EI): *m/z* (%): 958 (M⁺, 27), 433 (65), 375 (23), 255 (20), 239 (24), 163 (39), 147 (22), 95 (26), 75 (46), 73 (100); HRMS (ESI-pos) calcd. for C₅₃H₉₄O₉Si₃Na [M + Na⁺] 981.6098, found 981.6092.

Amphidinolide F (4). A Schlenk flask, equipped with a magnetic stir-bar and a glass stopper, was charged with diketone **56** (15.0 mg, 0.0156 mmol), acetonitrile (2.3 mL), Et₃N·3HF (1.84 mL) and triethylamine (1.6 mL). The resulting solution was stirred at 40°C for 3 d before it was allowed to reach ambient temperature. The mixture was diluted with EtOAc (3 mL) and aq. sat. NaHCO₃ (6 mL), and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic phases were washed with aq.



sat. NaHCO₃ (2 x 3 mL) and brine (3 mL), dried over Na₂SO₄, filtered, and evaporated. The remaining yellow oil was purified by thin-layer-chromatography (20 x 20 cm, TLC silicagel 60 F₂₅₄ basic, hexanes/acetone, 50%) to provide amphidinolide F (5.7 mg, 60%) as a colorless oil. The single largest batch, on which the deprotection was carried out, furnished 38.7 mg of amphidinolide F (**4**). [α]_D²³ = -49.0° (c = 0.10, CHCl₃); ¹H NMR (600 MHz, CDCl₃, 5.5 mg in 700 μL, 298 K): δ = 6.50 (dd, *J* = 11.0, 15.1 Hz, 1H, H-42), 5.98 (s, 1H, H-10), 5.74 (d, *J* = 11.1 Hz, 1H, H-43), 5.31 (dd, *J* = 8.6, 15.1 Hz, 1H, H-41), 5.18 (t, *J* = 8.2 Hz, 1H, H-20), 5.15 (d, *J* = 1.6 Hz, 1H, H-23a), 4.93 (t, *J* = 1.4 Hz, 1H, H-23b), 4.33 (ddt, *J* = 4.0, 6.0, 8.2 Hz, 1H, H-34), 4.12-4.08 (m, 1H, H-12), 4.06 (q, *J* = 7.7 Hz, 1H, H-31), 3.99 (bs, 1H, HO-7), 3.92 (dt, *J* = 1.7, 9.0 Hz, 1H, H-7), 3.79 (dt, *J* = 3.1, 9.3 Hz, 1H, H-14), 3.79 (dt, *J* = 3.1, 9.3 Hz, 1H, H-17), 3.53 (dd, *J* = 3.4, 6.0 Hz, 1H, H-13), 3.49 (bs, 1H, HO-12), 3.16-3.08 (m, 1H, H-12), 3.02 (dd, *J* = 9.0, 17.5 Hz, 1H, H-3a), 2.73 (dd, *J* = 9.4, 15.2 Hz, 1H, H-6), 2.69 (dd, *J* = 8.4, 16.1 Hz, 1H, H-1a), 2.51 (dd, *J* = 2.4, 15.4 Hz, 1H, H-6b), 2.51 (dd, *J* = 9.0, 15.8 Hz, 1H, H-18a), 2.48 (dd, *J* = 3.6, 15.7 Hz, 1H, H-18b), 2.46 (dd, *J* = 3.0, 15.8 Hz, 1H, H-1b), 2.30 (dd, *J* = 4.1, 17.5 Hz, 1H, H-3b), 2.25 (qd, *J* = 6.8, 9.0 Hz, 1H, H-8), 2.11-2.06 (m, 1H, H-15a), 2.09-2.03 (m, 1H, H-33a), 1.91 (dddd, *J* = 3.8, 7.2, 8.2, 12.8 Hz, 1H, H-32a), 1.83-1.75 (m, 1H, H-16), 1.74 (s, 3H, H-45), 1.73 (s, 3H, H-46), 1.69 (d, *J* = 1.3 Hz, 3H, H-24), 1.69 (bs, 1H, HO-13), 1.63-1.54 (m, 1H, H-32b), 1.51-1.46 (m, 1H, H-33b), 1.46-1.39 (m, 1H, H-15b), 1.07 (d, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.97 ppm (d, *J* = 6.6 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃, 5.5 mg in 700 μL, 298 K): δ = 213.8 (C, C-5), 207.9 (C, C-2), 171.2 (C, C-19), 144.4 (C, C-11), 140.0 (C, C-9), 138.3 (C, C-44), 132.0 (HC, C-42), 124.6 (HC, C-10), 124.2 (HC, C-41), 124.0 (HC, C-43), 116.1 (H₂C,

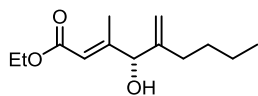
C-23), 81.5 (HC, C-17), 79.9 (HC, C-31), 78.8 (HC, C-14), 77.7 (HC, C-20), 77.0 (HC, C-12), 76.4 (HC, C-13), 75.0 (HC, C-34), 70.7 (HC, C-7), 49.3 (HC, C-8), 48.5 (H₂C, C-1), 46.1 (H₂C, C-3), 45.5 (H₂C, C-6), 42.7 (HC, C-4), 39.8 (HC, C-16), 38.7 (H₂C, C-18), 36.7 (H₂C, C-15), 32.0 (H₂C, C-33), 28.4 (H₂C, C-32), 26.1 (H₃C, C-45), 18.5 (H₃C, C-46), 16.2 (H₃C, C-26), 15.5 (H₃C, C-25), 15.4 (H₃C, C-22), 14.3 ppm (H₃C, C-24); IR (film): 2924, 1740, 1365, 1217 cm⁻¹; MS (ESI-pos) [M + Na⁺] 639 (100); HRMS (ESI-pos) calcd. for C₃₅H₅₂O₉Na [M + Na⁺] 639.3504, found 639.3503.

Total Synthesis of Amphidinolide C

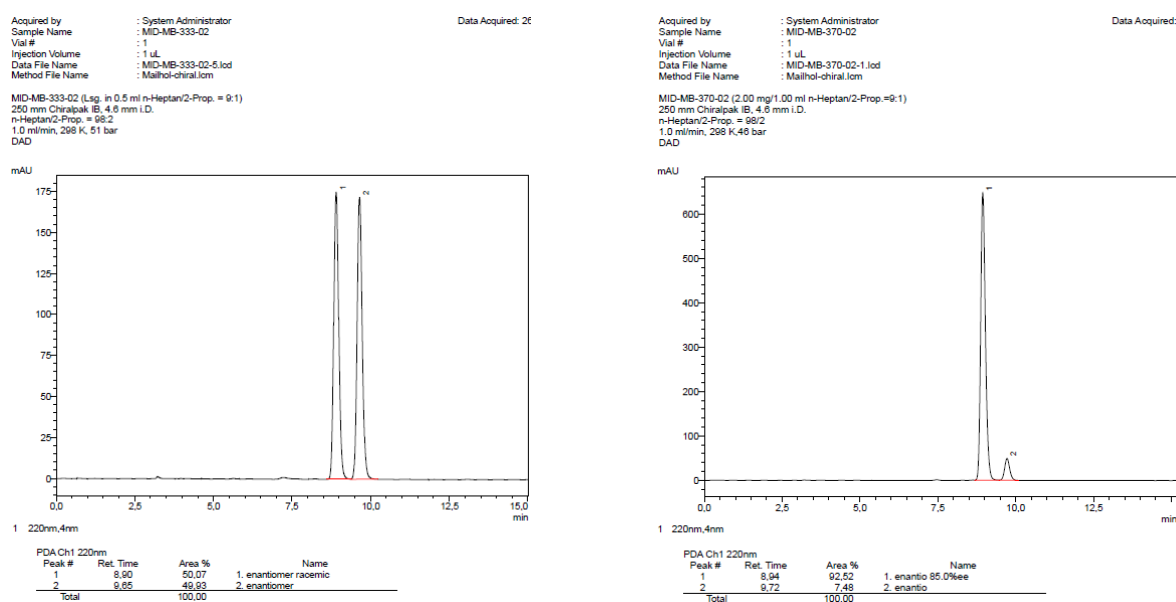
Iodide 57. 1-Hexyne (1.49 mL, 10.0 mmol) was added dropwise to a solution of I-9-BBN (1.0 M in hexane, 10.0 mL, 10.0 mmol) in pentane (70 mL) at -20 °C. The resulting brown mixture was stirred for 1 h at this temperature before glacial acetic acid (7.0 mL) was added. Stirring was continued for 1 h at 0 °C before aq. sodium hydroxide (3.0 M, 80 mL) and aq. hydrogen peroxide (30% w/w, 13 mL) were introduced. After stirring for an additional 30 min at room temperature, the aqueous phase was extracted with pentane (3 x 30 mL). The combined organic layers were successively washed with H₂O (30 mL), sat. aq. NaHCO₃ (30 mL) and H₂O (30 mL) before they were dried over Na₂SO₄ and concentrated in vacuo. The crude product was purified by flash chromatography (SiO₂, pentane) to afford the title compound as a colorless liquid (1.84 g, 88%). ¹H NMR (400 MHz, CDCl₃): δ = 6.00 (q, *J* = 1.4 Hz, 1H), 5.70-5.66 (m, 1H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.54-1.45 (m, 2H), 1.33 (sext, *J* = 7.3 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 125.3, 112.9, 45.2, 31.4, 21.5, 13.9; IR (film): 2957, 2929, 2871, 1616, 1464, 1211, 1150, 889; MS (EI): *m/z*: 210 (19), 168 (41), 83 (25), 55 (100), 53 (11), 43 (10), 41 (88), 39 (29), 29 (13), 27 (19); HRMS (ESIpos) calcd. for C₆H₁₁I [M⁺] 209.9905, found 209.9905. The analytical data match those reported in literature.⁹

Dialkenyl Zinc Derivative 58. *n*BuLi (1.6 M in hexane, 11.3 mL, 18.1 mmol) was added dropwise to a solution of alkenyl iodide **57** (3.80 g, 18.1 mmol) in Et₂O (10.0 mL) at -78 °C and the mixture was stirred for 1 h at this temperature. The solution was warmed to 0 °C before freshly sublimed ZnBr₂ (2.04 g, 9.05 mmol) was added. The mixture was stirred for 30 min at 0 °C and for 4 h at ambient temperature. Stirring was stopped, the heterogeneous mixture was allowed to settle and the supernatant liquid was carefully transferred into a two-neck flask equipped with a distillation head. The solvent was evaporated under a flow of argon before the resulting light-grey mixture was distilled at 60 °C under vacuum (2.10⁻² mbar) to afford the dialkenyl zinc derivative **58** as a colorless liquid (1.38 g, 66%). The compound was subsequently dissolved in toluene and the resulting stock solution was titrated by the method reported by Knochel *et al.*¹⁰ This solution was kept in a freezer for 14 days without noticeable loss of reactivity.

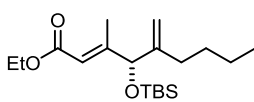
Compound S10. (-)-MIB (31.8 mg, 133 μmol)¹¹ was added to a solution of the dialkenyl zinc reagent **58** (0.225 M in toluene, 11.8 mL, 2.65 mmol) in toluene (41.0 mL) at -30 °C and the mixture was stirred for 1 h at this temperature. Aldehyde **59** (181 μL, 1.33 mmol) was then added over 10 min and stirring continued for 30 min at this temperature. The reaction was quenched with



sat. aq. NH_4Cl (40 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined extracts were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (SiO_2 , hexanes/*tert*-butyl methyl ether, 20/1 to 6/1) to afford the title compound as colorless liquid (290 mg, 97%, 85% ee). HPLC analysis: 250 mm Chiralpak IB, \varnothing 4.6 mm, *n*-heptane/2-propanol = 9/1, 1.0 mL/min, 298 K, 46 bar, DAD, 220 nm); $[\alpha]_D^{20} = +28.0^\circ$ ($c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): $\delta = 6.05$ (quint, $J = 1.2$ Hz, 1H), 5.14 (quint, $J = 1.0$ Hz, 1H), 5.01 (q, $J = 1.5$ Hz, 1H), 4.54 (d, $J = 3.6$ Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 2.03 (d, $J = 1.3$ Hz, 3H), 2.05 – 1.95 (m, 1H), 1.95 – 1.82 (m, 1H), 1.75 (d, $J = 3.8$ Hz, 1H), 1.49 – 1.37 (m, 2H), 1.37 – 1.29 (m, 2H), 1.29 (t, $J = 7.2$ Hz, 3H), 0.90 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 166.9$, 157.8, 148.4, 116.1, 112.4, 79.8, 59.9, 30.9, 30.0, 22.6, 15.0, 14.3, 14.1; IR (film): 3510, 2982, 2959, 2933, 2873, 1698, 1646, 1446, 1368, 1351, 1215, 1145, 1039; MS (EI): m/z : 153 (65), 139 (28), 137 (15), 123 (22), 115 (100), 112 (17), 11 (18), 110 (22), 109 (24), 99 (10), 98 (15), 97 (36), 95 (29), 93 (19), 87 (77), 81 (14), 79 (13), 71 (25), 69 (60), 67 (14), 55 (39), 43 (37), 41 (59), 39 (19), 29 (31), 27 (15); HRMS (ESIpos) calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_3\text{Na}$ [$\text{M} + \text{Na}^+$] 249.1461, found 249.1462.



Compound 60. TBSCl (290 mg, 1.92 mmol), imidazole (218 mg, 3.20 mmol) and DMAP (31.3 mg, 256 μmol) were successively added to a solution of alcohol **S10** (290 mg, 1.28 mmol) in CH_2Cl_2 (11.0 mL) at 0°C . The mixture was stirred at ambient temperature for 48 h before the reaction was quenched with sat. aq. NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined extracts were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (SiO_2 , pentane/*tert*-butyl methyl ether, 50/1) to afford the title compound as a colorless liquid (425 mg, 98%). $[\alpha]_D^{20} = +20.1^\circ$ ($c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): $\delta = 5.99$ (quint, $J = 1.3$ Hz, 1H), 5.15 – 5.06 (m, 1H), 4.91 (q, $J = 1.5$ Hz, 1H), 4.43 (s, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 1.98 (d, $J = 1.4$ Hz, 3H), 1.96 – 1.85 (m, 1H), 1.85 – 1.69 (m, 1H), 1.45 – 1.33 (m, 2H), 1.32 – 1.23 (m, 2H), 1.28 (t, $J = 7.1$ Hz, 3H), 0.89 (s, 9H), 0.89 – 0.85 (m, 3H), 0.02 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta =$

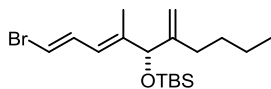


167.1, 158.7, 148.6, 115.7, 111.8, 81.0, 59.8, 30.0, 29.8, 25.9 (3C), 22.7, 18.4, 14.6, 14.4, 14.1, -4.9, -5.0; IR (film): 2956, 2930, 2858, 1718, 1646, 1464, 1832, 1365, 1316, 1253, 1210, 1144, 1092, 1045, 875; MS (EI): m/z (%): 295 (6), 284 (21), 283 (100), 255 (16), 237 (9), 103 (52), 93 (10), 75 (37), 73 (24); HRMS (ESIpos) calcd. for $C_{19}H_{36}O_3SiNa$ [$M + Na^+$] 363.2326, found 363.2327.

Compound 61. Dibal-H (1 M in CH_2Cl_2 , 2.43 mL, 2.43 mmol) was added at -78 °C to a solution of compound **60** (330 mg, 969 μ mol) in CH_2Cl_2 (1.5 mL). The mixture was stirred at this temperature for 30 min before the reaction was quenched with methanol (1 mL) followed by sat. aq. Rochelle's salt (4 mL) and *tert*-butyl methyl ether (10 mL). The mixture was stirred for 2 h until the layers would clearly separate. The aqueous layer was extracted with *tert*-butyl methyl ether (2 x 10 mL), and the organic phases were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography (SiO_2 , hexanes/EtOAc 9/1) to afford the title compound as a colorless liquid (275 mg, 95%). $[\alpha]_D^{20} = -22.9$ ° ($c = 1.00$, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$): $\delta = 5.67$ (tquint, $J = 6.8$, 1.3 Hz, 1H), 5.14 – 5.07 (m, 1H), 4.88 – 4.82 (m, 1H), 4.38 (s, 1H), 4.19 (d, $J = 6.6$ Hz, 2H), 1.90 (dt, $J = 15.7$, 7.8 Hz, 1H), 1.85 – 1.75 (m, 1H), 1.50 (s, 3H), 1.46 – 1.34 (m, 3H), 1.33 – 1.19 (m, 2H), 0.89 (s, 9H), 0.88 (t, $J = 7.2$ Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H), -0.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.4$, 139.5, 125.0, 110.0, 80.5, 59.5, 30.9, 30.2, 25.9 (3C), 22.7, 18.4, 14.2, 11.7, -4.8, -4.9; IR (film): 3312, 2956, 2929, 2857, 1647, 1463, 1338, 1361, 1251, 1071, 1005, 873, 834; MS (EI): m/z (%): 242 (13), 241 (65), 185 (20), 171 (16), 149 (18), 107 (29), 105 (11), 93 (34), 79 (9), 77 (7), 76 (7), 75 (100), 73 (39), 57 (19); HRMS (ESIpos) calcd. for $C_{17}H_{34}O_2SiNa$ [$M + Na^+$] 321.2220, found 321.2221. The analytical data match those reported in literature.¹²

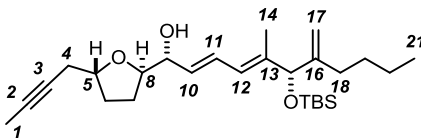
Compound 62. NBS (327 mg, 1.83 mmol) was added in portions over 15 min to a solution of alcohol **61** (365 mg, 1.22 mmol) and PPh_3 (481 mg, 1.83 mmol) in THF (6 mL) at -20 °C. The temperature was increased over 30 min to 0 °C. Sodium sulfinate (402 mg, 2.45 mmol) and TBAI (45.2 mg, 122 μ mol, 0.1 equiv) were then introduced in three portions over 10 min into the white suspension and the resulting mixture was stirred at room temperature for 5 h. For work up, the mixture was diluted with EtOAc (6 mL) and sat. aq. $Na_2S_2O_3$ (6 mL). The aqueous phase was extracted with EtOAc (3 x 4 mL), and the combined extracts were washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (SiO_2 , hexanes/*tert*-butyl methyl ether, 10/1) afforded the title compound as a colorless liquid (468 mg, 91%). $[\alpha]_D^{20} = -6.2$ ° ($c = 1.00$, CH_2Cl_3); 1H NMR (400 MHz, $CDCl_3$): $\delta = 7.89$ – 7.83 (m, 2H), 7.65 – 7.58 (m, 1H), 7.54 – 7.48 (m, 2H), 5.48 (tquint, $J = 8.1$, 1.5 Hz, 1H), 5.04 – 4.98 (m, 1H), 4.86 – 4.78 (m, 1H), 4.32 (s, 1H), 3.87 (d, $J = 7.8$ Hz, 2H), 1.90 – 1.77 (m, 1H), 1.74 – 1.61 (m, 1H), 1.40 – 1.23 (m, 4H), 1.27 (s, 3H), 0.89 (t, $J = 7.2$ Hz, 3H), 0.84 (s, 9H), -0.02 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.0$, 146.5, 139.0, 133.7, 129.2 (2C), 128.4 (2C), 111.2, 110.7, 80.3, 55.9, 30.2, 30.0, 25.8 (3C), 22.7, 18.3, 14.2, 12.1, -4.9, -5.0; IR (film): 2955, 2928, 2857, 1646, 1477, 1307, 1251, 1151, 1085, 1067, 873, 835, 775, 741, 688, 528; MS (EI): m/z (%): 365 (6), 339 (2), 281 (4), 200 (14), 199 (100), 149 (25), 135 (35), 73 (15); HRMS (ESIpos) calcd. for $C_{23}H_{38}O_3SSiNa$ [$M + Na^+$] 445.2203, found 445.2201.

Compound 63. *n*BuLi (1.6 M in hexane, 365 μ L, 584 μ mol) was added dropwise at -78 $^{\circ}$ C to a solution of freshly distilled diisopropylamine (82 μ L, 584 μ mol) in Et₂O (0.8 mL) and THF (1.1 mL). The resulting pale yellow mixture was allowed to warm to room temperature and stirred for 30 min before it was cooled to -95 $^{\circ}$ C using a pentane/N_{2(l)} bath. Next, a cold (-78 $^{\circ}$ C) solution of dibromomethane (41 μ L, 584 μ mol) in THF (0.6 mL) was slowly added *via* cannula to this cold LDA solution and the resulting yellow mixture was stirred at -95 $^{\circ}$ C for 30 min.



During this time *n*BuLi (1.6 M in hexane, 361 μ L, 556 μ mol) was added to a solution of sulfone **62** (235 mg, 556 μ mol) and THF (2.0 mL) at -78 $^{\circ}$ C, causing the appearance of a bright orange color. After stirring for 30 min at this temperature, the mixture was cooled to -100 $^{\circ}$ C and added *via* cannula to the cold (-95 $^{\circ}$ C) carbene solution. The yellow mixture was allowed to slowly warm to -78 $^{\circ}$ C and was kept at this temperature for 2 h. The reaction was quenched with EtOH (150 μ L) and sat. aq. NH₄Cl (3 mL). The contents were diluted with H₂O until two clear layers were observed. The aqueous layer was extracted with CH₂Cl₂ (3 x 4 mL), and the combined organic layers were washed with H₂O (5 mL) and brine (5 mL), dried with MgSO₄ and concentrated to a yellow oil. Purification by flash chromatography (SiO₂, pentane) afforded a mixture of *E* and *Z* isomers (106 mg, *E/Z* = 4/1) in addition to recovered sulfone **62** (80.0 mg, 34%). Purification of this mixture by HPLC (250 mm Nucleodur HTec-C18, 10 μ m, \varnothing 4.6 mm, methanol/ H₂O = 95/5, 1.0 mL/min, 308 K, 6.6 MPa, DAD, 250 nm) afforded *E*-**63** as a colorless oil (70.0 mg, 34%, 51% brsm). IR (film): 2955, 2929, 2857, 1643, 1577, 1463, 1251, 1074, 938, 834, 775; ¹H NMR (400 MHz, CD₂Cl₂): δ = 6.97 (dd, *J* = 11.3, 13.3 Hz, 1H), 6.30 (d, *J* = 13.3 Hz, 1H), 6.06 (d, *J* = 11.4 Hz, 1H), 5.12-5.10 (m, 1H), 4.89-4.87 (m, 1H), 4.41 (s, 1H), 1.91 (dt, *J* = 7.6, 15.5 Hz, 1H), 1.79 (dt, *J* = 7.4, 15.4 Hz, 1H), 1.58 (d, *J* = 1.3 Hz, 3H), 1.44-1.34 (m, 2H), 1.34-1.24 (m, 2H), 0.90 (s, 9H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ¹³C NMR (100 MHz, CD₂Cl₂): δ = 149.8, 141.1, 134.5, 123.0, 110.5, 108.3, 80.9, 30.9, 30.5, 26.0 (3C), 23.0, 18.6, 14.2, 12.6, -4.9 (2C); MS (EI): *m/z* (%): 374 (9), 329 (15), 317 (85), 293 (32), 233 (26), 161 (24), 151 (11), 139 (29), 119 (31), 106 (15), 105 (45), 95 (15), 75 (100), 57 (17), 41 (14); HRMS (ESIpos) calcd. for C₁₈H₃₃OBrSi [M⁺] 372.1484, found 372.1480.

Compound 65. *t*BuLi (1.7 M in pentane, 108 μ L, 182 μ mol) was added dropwise to a solution of dienyl bromide **63** (34.0 mg, 91.0 μ mol) in Et₂O (1.0 mL) and the resulting yellow mixture was stirred at this temperature for 1 h.

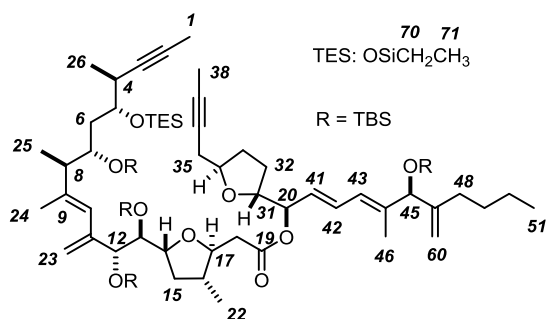


In parallel, a mixture of freshly sublimed zinc bromide (84.1 mg, 373 μ mol) and Et₂O (600 μ L) was stirred in a jacketed Schlenk flask until a colorless solution had formed (ca. 10 min). This solution was then stirred for 10 min at -35 $^{\circ}$ C before the solution of the lithiodiene was added dropwise. The mixture was warmed to 0 $^{\circ}$ C and stirred for 1 h at this temperature.

During this time, *n*BuLi (1.6 M in hexane, 63 μ L, 100 μ mol) was added to a solution of (–)-N-methylephedrine (18.0 mg, 100 μ mol) in toluene (200 μ L) at 0 $^{\circ}$ C and the mixture was stirred at this temperature for 30 min. This solution was then added *via* cannula to the Schlenk flask containing the organozinc reagent and the resulting light yellow solution was stirred at 0 $^{\circ}$ C for an additional 1 h. The mixture was then cooled to -20 $^{\circ}$ C and a solution of aldehyde **46**

(ddd, $J = 4.8, 7.2, 8.8$ Hz, 1H, H-17), 3.80 (dd, $J = 3.2, 7.4$ Hz, 1H, H-13), 2.53 (dd, $J = 7.2, 15.5$ Hz, 1H, H-18a), 2.47 (ddq, $J = 2.6, 5.1, 16.3$ Hz, 1H, H-35a), 2.36 (dd, $J = 4.2, 15.5$ Hz, 1H, H-18b), 2.28 (ddq, $J = 2.6, 7.6, 16.2$ Hz, 1H, H-35b), 2.50-1.50 (m, 1H, H-48a), 2.00-1.90 (m, 1H, H-15a), 1.95-1.85 (m, 2H, H-33a, H-48b), 1.72-1.66 (m, 1H, H-32a), 1.68 (s, 3H, H-46), 1.70-1.62 (m, 1H, H-16), 1.61-1.51 (m, 2H, H-32b, H-33b), 1.52 (t, $J = 2.5$ Hz, 3H, H-38), 1.45-1.37 (m, 2H, H-49), 1.30-1.20 (m, 3H, H-15b, H-50), 1.14 (s, 9H, *t*Bu-TBS), 1.07 (s, 9H, *t*Bu-TBS), 0.99 (s, 9H, *t*Bu-TBS), 0.85 (t, $J = 7.3$ Hz, 3H, H-51), 0.79 (d, $J = 6.4$ Hz, 3H, H-22), 0.39 (s, 3H, CH₃-TBS), 0.34 (s, 3H, CH₃-TBS), 0.29 (s, 9H, H-24), 0.21 (s, 3H, CH₃-TBS), 0.13 (s, 3H, CH₃-TBS), 0.09 (s, 3H, CH₃-TBS), 0.07 (s, 3H, CH₃-TBS); ¹³C NMR (125 MHz, C₆D₆): $\delta = 170.1$ (C, C-19), 155.3 (C, C-11), 149.8 (C, C-47), 140.6 (C, C-44), 130.7 (HC, C-42), 128.5 (HC, C-41), 126.4 (H₂C, C-23), 125.1 (HC, C-43), 110.4 (H₂C, C-60), 82.9 (HC, C-12), 81.2 (HC, C-45), 80.7 (HC, C-17), 80.4 (HC, C-31), 80.1 (HC, C-13), 80.0 (HC, C-14), 78.4 (HC, C-34), 76.9 (C, C-37), 76.6 (HC, C-20), 76.1 (C, C-36), 40.5 (HC, C-16), 39.9 (H₂C, C-18), 38.9 (H₂C, C-15), 31.4 (H₂C, C-33), 31.0 (H₂C, C-48), 30.4 (H₂C, C-49), 28.2 (H₂C, C-32), 26.9 ((H₃C)₃, *t*Bu-TBS), 26.4 ((H₃C)₃, *t*Bu-TBS), 26.0 ((H₃C)₃, *t*Bu-TBS, H₂C, C-35), 22.9 (H₂C, C-50), 19.1 (C, *t*Bu-TBS), 18.8 (C, *t*Bu-TBS), 18.5 (C, *t*Bu-TBS), 16.3 (H₃C, C-22), 14.2 (H₃C, C-51), 12.2 (H₃C, C-46), 3.4 (H₃C, C-38), -3.2 (H₃C-Si, TBS), -3.3 (H₃C-Si, TBS), -3.9 (H₃C-Si, TBS), -4.1 (H₃C-Si, TBS), -4.8 (H₃C-Si, TBS), -4.9 (H₃C-Si, TBS), -7.8 (3xH₃C, C-24); MS (ESIpos) [$M + Na^+$] 1073 (100); HRMS (ESIpos) calcd. for C₅₃H₉₈O₇Si₃SnNa [$M + Na^+$] 1073.5534, found 1073.5538.

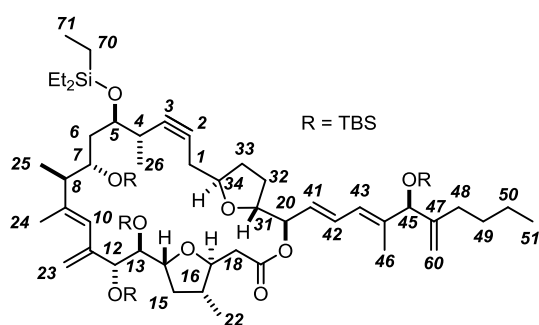
Compound 67. A Schlenk flask was charged with tetrabutylammonium diphenylphosphinate (268 mg, 0.58 mmol). This compound was aprotically dried with toluene (1 mL) before DMF (2 mL) was added, followed by a solution of stannane **66** (153 mg, 0.15 mmol) in DMF (1.5 mL). The flask containing the stannane was rinsed with DMF (2 x 500 μ L) and this washing was also added to the Schlenk flask. Next, a solution of iodide **29** (107 mg, 0.19 mmol) in DMF (2.5 mL) was added, followed by



(Pd(PPh₃)₄) (50 mg, 0.044 mmol, 0.3 equiv) and CuTC (83 mg, 0.44 mmol) as a solid each. The resulting orange/brown mixture was stirred at room temperature for 1 h before it was diluted with Et₂O (10 mL). 2-(Dimethylamino)ethanethiol hydrochloride (0.1 M in H₂O, 10 mL) was added and the aqueous phase extracted with Et₂O (3 x 3 mL). The combined extracts were washed with H₂O (3 mL) and brine (3 mL), dried over Na₂SO₄, filtered and evaporated. The crude material was purified by flash chromatography (SiO₂: 15-40 μ m, hexanes/EtOAc, 40/1 to 10/1) to afford the title compound as a yellow oil (148 mg, 77%). [α]_D²⁰ = +7.8° (c = 1.00, CH₂Cl₂); IR (film): 2955, 2929, 2857, 1742, 1462, 1387, 1252, 1072, 835, 776; ¹H NMR (500 MHz, C₆D₆): $\delta = 6.75$ (dd, $J = 11.1, 15.2$ Hz, 1H, H-42), 6.27 (d, $J = 11.1$ Hz, 1H, H-43), 6.06 (s, 1H, H-10), 5.82 (dd, $J = 7.8, 15.2$ Hz, 1H, H-41), 5.59 (dd, $J = 5.8, 7.6$ Hz, 1H, H-20), 5.54 (dd, $J = 1.3, 2.3$ Hz, 1H, H-23a), 5.27 (s, 1H, H-60a), 5.18 (s, 1H, H-23b), 4.94 (s, 1H, H-60b), 4.50 (s, 1H, H-45), 4.36 (s, 1H, H-12), 4.20-4.10 (m, 4H, H-34, H-14, H-31, H-7), 4.04 (ddd, $J = 3.9, 5.2, 8.1$ Hz, 1H, H-5), 3.96 (ddd, $J = 4.6, 7.8, 8.9$ Hz, 1H, H-17), 3.86 (dd, $J = 2.0, 7.8$ Hz, 1H, H-13), 2.79-2.73 (m, 1H, H-4), 2.62-2.55 (m, 1H, H-8), 2.57

(dd, $J = 7.5, 15.4$ Hz, 1H, H-18a), 2.46 (ddq, $J = 2.5, 5.0, 16.3$ Hz, H-35a), 2.38 (dd, $J = 4.5, 15.4$ Hz, 1H, H-18b), 2.27 (ddq, $J = 2.5, 7.6, 16.3$ Hz, 1H, H-35b), 2.19-2.11 (m, 2H, H-15a, H-6a), 2.07 (s, 3H, H-24), 2.04-1.96 (m, 1H, H-48a), 1.93-1.80 (m, 3H, H-33a, H-48b, H-6b), 1.80-1.74 (m, 1H, H-16), 1.72-1.66 (m, 1H, H-32a), 1.68 (s, 3H, H-46), 1.67 (m, 3H, H-1), 1.62-1.51 (m, 2H, H-33b, H-32b), 1.53 (t, $J = 2.6$ Hz, 3H, H-38), 1.45-1.36 (m, 2H, H-49), 1.37-1.27 (m, 1H, H-15b), 1.31 (d, $J = 7.1$ Hz, 3H, H-26), 1.31 (d, $J = 7.0$ Hz, 3H, H-25), 1.27-1.21 (m, 2H, H-50), 1.17 (s, 9H, *t*Bu-TBS), 1.04 (t, $J = 8.0$ Hz, 9H, H-71), 1.04 (s, 9H, *t*Bu-TBS), 1.02 (s, 9H, *t*Bu-TBS), 0.99 (s, 9H, *t*Bu-TBS), 0.85 (t, $J = 7.3$ Hz, 3H, H-51), 0.83 (d, $J = 6.6$ Hz, 3H, H-22), 0.66 (q, $J = 7.8$ Hz, 6H, H-70), 0.39 (s, 3H, CH₃-TBS), 0.38 (s, 3H, CH₃-TBS), 0.23 (s, 3H, CH₃-TBS), 0.17 (s, 3H, CH₃-TBS), 0.16 (s, 3H, CH₃-TBS), 0.15 (s, 3H, CH₃-TBS), 0.09 (s, 3H, CH₃-TBS), 0.06 (s, 3H, CH₃-TBS); ¹³C NMR (125 MHz, C₆D₆): $\delta = 170.2$ (C, C-19), 149.8 (C, C-47), 146.0 (C, C-11), 141.3 (C, C-9), 140.5 (C, C-44), 130.6 (HC, C-42), 128.5 (HC, C-41), 126.3 (HC, C-10), 125.2 (HC, C-43), 115.1 (H₂C, C-23), 110.3 (H₂C, C-60), 81.2 (HC, C-45), 81.0 (C, C-3), 80.6 (HC, C-17), 80.4 (HC, C-31), 80.2 (HC, C-13), 80.0 (HC, C-14), 79.2 (HC, C-12), 78.4 (HC, C-34), 77.9 (C, C-2), 76.9 (C, C-37), 76.5 (HC, C-20), 76.1 (C, C-36), 72.9 (HC, C-7), 72.2 (HC, C-5), 47.8 (HC, C-8), 40.6 (HC, C-16), 39.9 (H₂C, C-18), 38.7 (H₂C, C-15), 38.0 (H₂C, C-6), 32.6 (HC, C-4), 31.4 (H₂C, C-33), 31.1 (H₂C, C-48), 30.4 (H₂C, C-49), 28.1 (H₂C, C-32), 26.6 ((H₃C)₃, *t*Bu-TBS), 26.2 ((H₃C)₃, *t*Bu-TBS), 26.2 ((H₃C)₃, *t*Bu-TBS), 26.04 ((H₃C)₃, *t*Bu-TBS), 26.01 (H₂C, C-35), 22.9 (H₂C, C-50), 18.9 (C, *t*Bu-TBS), 18.7 (C, *t*Bu-TBS), 18.5 (C, *t*Bu-TBS), 18.3 (C, *t*Bu-TBS), 17.8 (H₃C, C-24), 16.3 (H₃C, C-22), 15.8 (H₃C, C-26), 15.4 (H₃C, C-25), 14.2 (H₃C, C-51), 12.4 (H₃C, C-46), 7.3 (3xH₃C, C-71), 5.6 (3xH₂C, C-70), 3.8 (H₃C, C-1), 3.4 (H₃C, C-38), -3.6 (H₃C-Si, TBS), -4.0 (H₃C-Si, TBS), -4.1 (H₃C-Si, TBS), -4.4 (H₃C-Si, TBS), -4.4 (H₃C-Si, TBS), -4.5 (H₃C-Si, TBS), -4.8 (H₃C-Si, TBS), -4.9 (H₃C-Si, TBS); MS (ESIpos) [$M + Na^+$] 1345 (100); HRMS (ESIpos) calcd. for C₇₅H₁₃₈O₉Si₅Na [$M + Na^+$] 1345.9079, found 1345.9080.

Macrolactone 68. A Schlenk flask was charged with diyne **67** (147 mg, 0.111 mmol) which

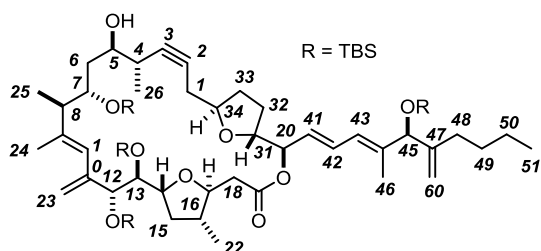


was azeotropically dried with toluene (3 x). Toluene (20 mL) was then added and the stopper was replaced by an argon bubbler. In a second Schlenk flask, a stock solution of the catalyst was prepared (0.015 M) by stirring a solution of complex **10** (21 mg, 0.0336 mmol)⁸ in degassed toluene (2.1 mL) and degassed CH₂Cl₂ (63 μ L) for 15 min at room temperature. An aliquot of this catalyst solution (1.43 mL, 0.0222 mmol, 0.2

equiv) was then added to the solution of the diyne substrate. The flask was immersed into a preheated (60 °C) oil bath and the mixture stirred at this temperature for 3 h 40 min before a second portion of the catalyst solution (714 μ L, 0.0111 mmol, 0.10 equiv) was introduced. After a total of 4 h reaction time, the mixture was allowed to cool before it was diluted with Et₂O. The light brown solution was washed with aq. sat. NH₄Cl (2 x 20 mL) and brine (2 x 10 mL) before being dried over Na₂SO₄, filtered and evaporated. The crude product was purified by flash chromatography (hexanes/EtOAc, 60/1) to provide macrolactone **68** as a pale yellow oil. (98 mg, 70%). [α]_D²⁰ = +32.2 ° (c = 1.00, CH₂Cl₂); IR (film): 2955, 2929, 2856, 1741,

1462, 1361, 1263, 1067, 835, 774; ^1H NMR (600 MHz, C_6D_6): δ = 6.70 (dd, J = 11.6, 14.8 Hz, 1H, H-42), 6.44 (bs, 1H, H-10), 6.26 (d, J = 10.9 Hz, 1H, H-43), 5.63 (dd, J = 8.0, 15.1 Hz, 1H, H-41), 5.48 (t, J = 8.0 Hz, 1H, H-20), 5.24 (s, 1H, H-60a), 5.11 (bs, 1H, H-23a), 5.03 (bs, 1H, H-23b), 4.93 (s, 1H, H-60b), 4.49 (s, 1H, H-45), 4.24 (bs, 1H, H-34), 4.15 (bs, 1H, H-12), 4.12-4.04 (m, 2H, H-7, H-14), 4.01 (dt, J = 3.4, 9.8 Hz, 1H, H-5), 3.96 (bs, 1H, H-31), 3.79 (d, J = 7.7 Hz, 1H, H-13), 3.54 (bs, 1H, H-17), 2.84-2.77 (m, 2H, H-1a, H-4), 2.73-2.67 (m, 1H, H-8), 2.52 (dd, J = 5.1, 13.6 Hz, 1H, H-18a), 2.53-2.45 (m, 1H, H-16), 2.37 (t, J = 11.2 Hz, 1H, H-6a), 2.30 (d, J = 13.4 Hz, 1H, H-18b), 2.19-2.11 (m, 1H, H-1b), 2.11 (s, 3H, H-24), 2.08-2.02 (m, 2H, H-15a, H-33a), 2.01-1.96 (m, 1H, H-48a), 1.90-1.86 (m, 1H, H-48b), 1.81 (ddd, J = 3.4, 9.8, 13.2 Hz, 1H, H-6b), 1.65 (s, 3H, H-46), 1.60-1.52 (m, 2H, H-32a, H-33b), 1.45-1.37 (m, 6H, H-25, H-32b, H-49), 1.33 (d, J = 6.8 Hz, 3H, H-26), 1.27 (s, 9H, *t*Bu-TBS), 1.26-1.19 (m, 2H, H-50), 1.18-1.10 (m, 1H, H-15b), 1.06 (t, J = 8.0 Hz, 9H, H-71), 1.04 (s, 9H, *t*Bu-TBS), 1.01 (s, 9H, *t*Bu-TBS), 0.98 (s, 9H, *t*Bu-TBS), 0.84 (t, J = 7.4 Hz, 3H, H-51), 0.86-0.80 (m, 3H, H-22), 0.70 (q, J = 7.9 Hz, 6H, H-70), 0.46 (s, 3H, CH_3 -TBS), 0.41 (s, 3H, CH_3 -TBS), 0.23 (s, 3H, CH_3 -TBS), 0.21 (s, 3H, CH_3 -TBS), 0.13 (s, 6H, 2 x CH_3 -TBS), 0.08 (s, 3H, CH_3 -TBS), 0.06 (s, 3H, CH_3 -TBS); ^{13}C NMR (150 MHz, C_6D_6): δ = 169.0 (C, C-19), 149.7 (C, C-47), 147.1 (C, C-11), 140.9 (C, C-9), 140.8 (C, C-44), 131.0 (HC, C-42), 129.3 (HC, C-10), 128.5 (HC, C-41), 124.9 (HC, C-43), 115.0 (H_2C , C-23), 110.5 (H_2C , C-60), 83.6 (HC, C-13), 83.1 (C, C-3), 81.2 (2 x HC, C-45, C-17), 80.1 (HC, C-31), 79.8 (HC, C-14), 79.3 (C, C-2), 77.8 (HC, C-34), 77.7 (HC, C-12), 75.8 (HC, C-20), 73.8 (HC, C-7), 72.4 (HC, C-5), 47.7 (HC, C-8), 38.8 (H_2C , C-6), 38.7 (H_2C , C-15), 37.8 (HC, C-16), 37.7 (H_2C , C-18), 32.9 (HC, C-4), 31.2 (H_2C , C-33), 30.9 (H_2C , C-48), 30.4 (H_2C , C-49), 27.8 (H_2C , C-32), 26.9 ($(\text{H}_3\text{C})_3$, *t*Bu-TBS), 26.8 (H_2C , C-1), 26.2 (2 x $(\text{H}_3\text{C})_3$, *t*Bu-TBS), 26.0 ($(\text{H}_3\text{C})_3$, *t*Bu-TBS), 22.9 (H_2C , C-50), 19.1 (C, *t*Bu-TBS), 18.6 (C, *t*Bu-TBS), 18.5 (C, *t*Bu-TBS), 18.3 (C, *t*Bu-TBS), 17.4 (H_3C , C-25), 16.3 (2 x H_3C , C-24, C-22), 14.4 (H_3C , C-26), 14.2 (H_3C , C-51), 12.5 (H_3C , C-46), 7.3 (3 x H_3C , C-71), 5.5 (3 x H_2C , C-70), -3.9 (H_3C -Si, TBS), -4.0 (2 x H_3C -Si, TBS), -4.4 (H_3C -Si, TBS), -4.4 (H_3C -Si, TBS), -4.7 (H_3C -Si, TBS), -4.8 (H_3C -Si, TBS), -4.9 (H_3C -Si, TBS); MS (ESIpos) [$\text{M} + \text{Na}^+$] 1291 (100); HRMS (ESIpos) calcd. for $\text{C}_{71}\text{H}_{132}\text{O}_9\text{Si}_5\text{Na}$ [$\text{M} + \text{Na}^+$] 1291.8610, found 1291.8614.

Alcohol S11. A solution of pyridinium *p*-toluenesulfonate (PPTS) (0.026 M in $\text{CH}_2\text{Cl}_2/\text{MeOH}$

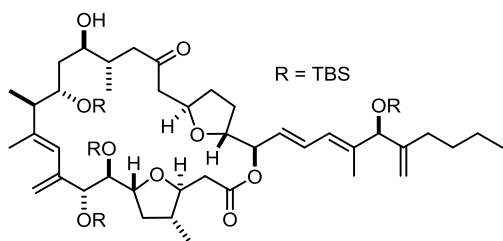


(9:1), 624 μL , 0.2 equiv) was added to a solution of macrolactone **68** (103 mg, 0.0811 mmol) in CH_2Cl_2 (7.6 mL) and MeOH (851 μL) at 0 °C. The mixture was stirred at this temperature for 24 h before the reaction was quenched with sat. aq. NaHCO_3 (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), and the

combined extracts were washed with sat. aq. NaHCO_3 (1 x 5 mL), H_2O (1 x 5 mL) and brine (1 x 5 mL), dried over Na_2SO_4 , filtered, and evaporated. The crude product was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 5/1) to afford alcohol **S11** as a colorless oil (83 mg, 88%). $[\alpha]_D^{20} = +4.5^\circ$ ($c = 1.00$, CH_2Cl_2); IR (film): 2955, 2928, 2857, 1737, 1472, 1388, 1252, 1075, 835, 776; ^1H NMR (600 MHz, C_6D_6 , 283 K, line broadening) (the NMR spectra contained traces of toluene): δ = 6.88-6.82 (m, 1H, H-42), 6.58 (bs, 1H, H-10), 6.33 (dd, J = 11.1, 5.4 Hz, 1H, H-43), 5.72-5.62 (m, 1H, H-41), 5.51-5.43 (m, 1H, H-20),

5.24 (s, 1H, H-60a), 5.02 (bs, 1H, H-23a), 4.95 (bs, 1H, H-23b), 4.93 (s, 1H, H-60b), 4.50 (s, 1H, H-45), 4.34 (bs, 1H, H-7), 4.13-4.02 (m, 2H, H-34, H-31), 4.03 (s, 1H, H-12), 3.98-3.92 (m, 1H, H-17), 3.79 (bs, 1H, H-13), 3.78-3.68 (m, 2H, H-14, H-5), 2.83 (bs, 1H, H-8), 2.60 (s, 1H, OH), 2.55 (bs, 1H, H-4), 2.41-2.33 (m, 1H, H-18a), 2.23 (d, $J = 16.0$ Hz, 1H, H-18b), 2.20-2.14 (m, 1H, H-1a), 2.06 (s, 3H, H-24), 2.04-1.97 (m, 2H, H-6a, H-48a), 1.97-1.91 (m, 1H, H-1b), 1.91-1.83 (m, 1H, H-48b), 1.79-1.75 (m, 1H, H-15a), 1.72-1.63 (m, 2H, H-6b, H-33a), 1.67 (s, 3H, H-46), 1.58-1.50 (m, 1H, H-32a), 1.48-1.42 (m, 1H, H-16), 1.42-1.34 (m, 3H, H-49, H-32b), 1.32 (bs, 3H, H-25), 1.26 (bs, 12H, H-26, *t*Bu-TBS), 1.23-1.13 (m, 2H, H-50), 1.10-0.98 (m, 2H, H-33b, H-15b), 1.03 (s, 9H, *t*Bu-TBS), 1.02 (s, 9H, *t*Bu-TBS), 0.99 (s, 9H, *t*Bu-TBS), 0.84 (t, $J = 7.2$ Hz, 3H, H-51), 0.63 (d, $J =$ Hz, 3H, H-22), 0.47 (bs, 6H, 2 x CH₃-TBS), 0.24 (s, 3H, CH₃-TBS), 0.15 (s, 3H, CH₃-TBS), 0.14 (s, 6H, 2 x CH₃-TBS), 0.09 (s, 3H, CH₃-TBS), 0.07 (s, 3H, CH₃-TBS); ¹³C NMR (150 MHz, C₆D₆, 283 K, line broadening) (the NMR spectra contained traces of toluene): $\delta = 170.2$ (C, C-19), 149.7 (C, C-47), 146.7 (C, C-11), 141.2 (C, C-9), 140.9 (C, C-44), 131.2 (HC, C-42), 128.8 (HC, C-10), 128.4 (HC, C-41), 124.8 (HC, C-43), 114.9 (H₂C, C-23), 110.5 (H₂C, C-60), 82.4 (HC, C-13), 82.2 (C, C-3), 81.5 (C, C-2), 81.2 (HC, C-45), 80.6 (HC, C-17), 79.7 (HC, C-31), 79.4 (HC, C-14), 78.1 (HC, C-12), 77.7 (HC, C-34), 77.1 (HC, C-20), 73.7 (HC, C-7), 72.0 (HC, C-5), 47.1 (HC, C-8), 40.8 (H₂C, C-6), 39.9 (HC, C-16), 39.7 (H₂C, C-18), 38.7 (H₂C, C-15), 35.4 (HC, C-4), 31.6 (H₂C, C-33), 30.8 (H₂C, C-48), 30.3 (H₂C, C-49), 28.8 (H₂C, C-32), 26.9 ((H₃C)₃, *t*Bu-TBS), 26.5 (H₂C, C-1), 26.2 ((H₃C)₃, *t*Bu-TBS), 26.2 ((H₃C)₃, *t*Bu-TBS), 26.0 ((H₃C)₃, *t*Bu-TBS), 22.9 (H₂C, C-50), 19.2 (C, *t*Bu-TBS), 18.8 (C, *t*Bu-TBS), 18.5 (C, *t*Bu-TBS), 18.3 (C, *t*Bu-TBS), 17.6 (H₃C, C-26), 16.3 (H₃C, C-22), 16.2 (H₃C, C-25), 16.1 (H₃C, C-24), 14.2 (H₃C, C-51), 12.6 (H₃C, C-46), -3.4 (H₃C-Si, TBS), -4.1 (H₃C-Si, TBS), -4.3 (H₃C-Si, TBS), -4.5 (H₃C-Si, TBS), -4.6 (2 x H₃C-Si, TBS), -4.9 (2 x H₃C-Si, TBS); MS (ESIpos) [$M + Na^+$] 1177 (100); HRMS (ESIpos) calcd. for C₆₅H₁₁₈O₉Si₄Na [$M + Na^+$] 1177.7745, found 1177.7752.

Compound 69 (equilibrium of hydroxyketone and hemiketal form). *The analysis was severely complicated by the hydroxyketone/hemiketal equilibrium and additional massive line broadening (copies of the spectra are shown below). Therefore full characterization was postponed to the stage of the natural product.*

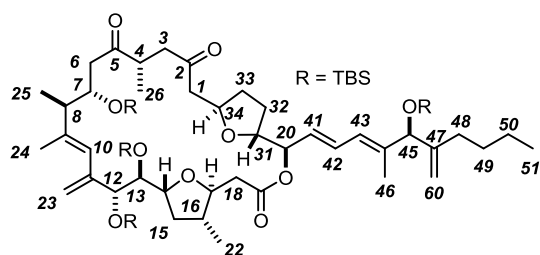


A Schlenk flask was charged with alcohol **S11** (83 mg, 71.8 μ mol) (azeotropically dried by evaporation of toluene, 3 x) and degassed Et₂O (4.5 mL). A solution of [Cl₂Pt(CH₂=CH₂)]₂ (0.00128 M in Et₂O, 112 μ L, 0.144 μ mol, 0.002 equiv) was added and the resulting solution was stirred at room temperature for 15 min. The mixture was then filtered through a pad of Florisil and the filtrate evaporated to give a colorless oil.

This crude enol ether (83 mg, 71.8 μ mol) was dissolved in a solution of pyridinium *p*-toluenesulfonate (PPTS, 0.00477 M in wet benzene, 13.5 mL, 64.6 μ mol) and the resulting mixture was stirred for 15 min at ambient temperature. Aq. sat. NaHCO₃ (15 mL) was added and the aqueous layer extracted with EtOAc (3 x 15 mL). The combined extracts were washed with aq. sat. NaHCO₃ (15 mL) and brine (15 mL), dried over Na₂SO₄, filtered, and evaporated

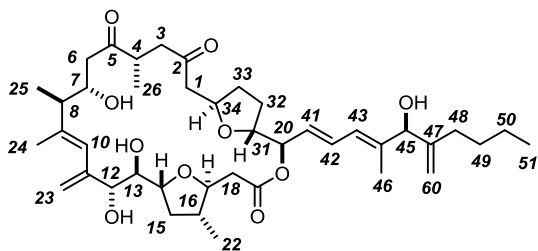
to give a colorless oil which was purified by flash chromatography (hexanes/EtOAc, 10/1) to give compound **69** as a colorless oil (79 mg, 91%). MS (ESIpos) $[M + Na^+]$ 1195 (100); HRMS (ESIpos) calcd. for $C_{65}H_{120}O_{10}Si_4Na$ $[M + Na^+]$ 1195.7850, found 1195.7845.

Amphidinolide C (1). A Schlenk flask was charged with hydroxyl ketone **69** (75 mg, 64.5



μmol) and CH_2Cl_2 (5.1 mL). A solution of tetrapropylammonium perruthenate (TPAP) (90 mg, 258 μmol) in CH_2Cl_2 (0.032 M) was slowly added at 0°C and the resulting mixture was stirred at ambient temperature for 2 h once the addition was complete. The mixture was filtered through a pad of silica that was carefully rinsed with

CH_2Cl_2 (40 mL) and EtOAc (20 mL). The combined filtrates were evaporated and the residue was purified by flash chromatography (neutral alumina, hexanes/ CH_2Cl_2 , 1/4) to provide the corresponding diketone as a colorless oil (50 mg, 65%). $[\alpha]_D^{20} = +2.0^\circ$ ($c = 0.45$, CHCl_3); IR (film): 2956, 2929, 2896, 2857, 1739, 1708, 1252, 1087, 834, 776; ^1H NMR (500 MHz, CDCl_3 , 253 K): $\delta = 6.46$ (dd, $J = 11.1, 15.0$ Hz, 1H, H-42), 5.99 (bs, 1H, H-10), 5.97 (d, $J = 11.4$ Hz, 1H, H-43), 5.42 (dd, $J = 7.7, 15.1$ Hz, 1H, H-41), 5.04 (s, 1H, H-60a), 5.00 (s, 1H, H-23a), 4.95 (t, $J = 8.3$ Hz, 1H, H-20), 4.85 (s, 1H, H-23b), 4.80 (s, 1H, H-60b), 4.54-4.46 (m, 1H, H-34), 4.31 (s, 1H, H-45), 4.13 (d, $J = 9.5$ Hz, 1H, H-7), 4.02 (q, $J = 7.2$ Hz, 1H, H-31), 3.87-3.81 (m, 1H, H-17), 3.83 (s, 1H, H-12), 3.61-3.55 (m, 1H, H-14), 3.45 (dd, $J = 3.0, 7.8$ Hz, 1H, H-13), 3.00-2.92 (m, 1H, H-4), 2.92 (dd, $J = 10.1, 18.5$ Hz, 1H, H-6a), 2.78 (dd, $J = 4.0, 18.9$ Hz, 1H, H-3a), 2.71 (dd, $J = 8.0, 19.3$ Hz, 1H, H-3b), 2.60 (d, $J = 14.2$ Hz, 1H, H-1a), 2.45 (d, $J = 15.7$ Hz, 1H, H-18a), 2.40-2.32 (m, 3H, H-18b, H-1b, H-8), 2.28 (d, $J = 18.4$ Hz, 1H, H-6b), 2.19-2.13 (m, 1H, H-33a), 2.02-1.92 (m, 2H, H-32a, H-15a), 1.87-1.78 (m, 2H, H-16, H-48a), 1.71 (s, 3H, H-24), 1.69-1.62 (m, 1H, H-48b), 1.62-1.57 (m, 1H, H-32b), 1.52 (s, 3H, H-46), 1.55-1.47 (m, 1H, H-33b), 1.36-1.27 (m, 2H, H-49), 1.27-1.14 (m, 3H, H-50, H-15b), 1.06 (d, $J = 7.3$ Hz, 3H, H-26), 1.02 (d, $J = 6.8$ Hz, 3H, H-25), 0.98 (d, $J = 6.3$ Hz, 3H, H-22), 0.88-0.81 (m, 30H, H-51, 3 x *t*Bu-TBS), 0.79 (s, 9H, *t*Bu-TBS), 0.03 (s, 3H, CH_3 -TBS), 0.01 (s, 3H, CH_3 -TBS), -0.01 (s, 3H, CH_3 -TBS), -0.05 (s, 3H, CH_3 -TBS), -0.05 (s, 9H, 3 x CH_3 -TBS), -0.09 (s, 3H, CH_3 -TBS); ^{13}C NMR (125 MHz, CDCl_3 , 253 K): $\delta = 211.2$ (C, C-5), 208.0 (C, C-2), 170.7 (C, C-19), 149.3 (C, C-47), 145.9 (C, C-11), 140.5 (C, C-44), 140.3 (C, C-9), 130.4 (HC, C-42), 128.5 (HC, C-10), 126.6 (HC, C-41), 123.6 (HC, C-43), 114.5 (H_2C , C-23), 109.8 (H_2C , C-60), 81.3 (HC, C-13), 80.3 (HC, C-45), 79.7 (HC, C-17), 79.5 (HC, C-31), 78.5 (HC, C-14), 77.5 (HC, C-20), 77.0 (HC, C-12), 75.3 (HC, C-34), 71.2 (HC, C-7), 50.7 (H_2C , C-1), 46.3 (HC, C-8), 46.2 (H_2C , C-6), 42.1 (H_2C , C-3), 40.6 (HC, C-4), 40.6 (HC, C-16), 39.6 (H_2C , C-18), 38.2 (H_2C , C-15), 32.3 (H_2C , C-33), 30.1 (H_2C , C-48), 29.6 (H_2C , C-49), 28.7 (H_2C , C-32), 26.2 ($(\text{H}_3\text{C})_3$, *t*Bu-TBS), 25.8 ($(\text{H}_3\text{C})_3$, *t*Bu-TBS), 25.7 ($(\text{H}_3\text{C})_3$, *t*Bu-TBS), 25.7 ($(\text{H}_3\text{C})_3$, *t*Bu-TBS), 22.5 (H_2C , C-50), 18.6 (C, *t*Bu-TBS), 18.4 (C, *t*Bu-TBS), 18.2 (C, *t*Bu-TBS), 17.9 (H_3C , C-26), 17.8 (C, *t*Bu-TBS), 16.3 (H_3C , C-22), 15.8 (H_3C , C-25), 15.4 (H_3C , C-24), 14.2 (H_3C , C-51), 12.4 (H_3C , C-46), -4.3 (H_3C -Si, TBS), -4.7 (H_3C -Si, TBS), -4.8 (H_3C -Si, TBS), -4.9 (H_3C -Si, TBS), -5.1 (H_3C -Si, TBS), -5.1 (H_3C -Si, TBS), -5.2 (H_3C -Si, TBS), -5.3 (H_3C -Si, TBS); MS (ESIpos) $[M + Na^+]$ 1193 (100); HRMS (ESIpos) calcd. for $C_{65}H_{118}O_{10}Si_4Na$ $[M + Na^+]$ 1193.7694, found 1193.7701.



Et₃N·3HF (1.3 mL) and Et₃N (1.1 mL) were successively added to a solution of this diketone (10 mg, 8.53 μmol) in CH₃CN (1.6 mL). The resulting mixture was stirred at 40 °C for 4 d. The mixture was then diluted with EtOAc (10 mL) and the reaction quenched with aq. sat. NaHCO₃ (15 mL). The aqueous layer was extracted with

EtOAc (3 x 10 mL), the combined organic phases were washed with aq. sat. NaHCO₃ (10 mL) and brine (10 mL) before they were dried over Na₂SO₄ and evaporated. The residue was purified by preparative thin layer chromatography (20 x 20 cm, TLC silicagel 60 F₂₅₄ basic, hexanes/acetone, 1/1) to afford amphidinolide C (**1**) as white amorphous solid (4.0 mg, 66%). $[\alpha]_D^{23} = -102^\circ$ ($c = 0.21$, CHCl₃); IR (film): 3437, 2959, 2925, 1708, 1458, 1379, 1260, 1023, 800, 754; ¹H NMR (600 MHz, C₆D₆): $\delta = 6.75$ (dd, $J = 11.1, 15.2$ Hz, 1H, H-42), 6.24 (bs, 1H, H-10), 6.23 (d, $J \sim 11$ Hz, 1H, H-43), 5.65 (dd, $J = 8.2, 15.1$ Hz, 1H, H-41), 5.43 (t, $J = 7.4$ Hz, 1H, H-20), 5.24 (bs, 1H, H-60a), 5.15 (d, $J = 1.5$ Hz, 1H, H-23a), 4.96 (bs, 1H, H-23b), 4.92 (s, 1H, H-60b), 4.35 (bs, 1H, H-45), 4.31-4.24 (m, 2H, H-12, H-34), 4.09-4.02 (m, 2H, H-7, H-14), 3.98 (q, $J = 7.1$ Hz, 1H, H-31), 3.83 (dt, $J = 2.5, 9.4$ Hz, 1H, H-17), 3.79 (bs, 1H, OH), 3.72 (bs, 1H, OH), 3.57 (bs, 1H, H-13), 3.53 (bs, 1H, OH), 3.10-3.04 (m, 1H, H-4), 2.97 (dd, $J = 8.5, 17.7$ Hz, 1H, H-3a), 2.70 (dd, $J = 9.0, 15.7$ Hz, 1H, H-6a), 2.53 (dd, $J = 9.6, 15.6$ Hz, 1H, H-18a), 2.41 (dd, $J = 8.5, 14.8$ Hz, 1H, H-1a), 2.38 (dd, $J = 2.5, 15.9$ Hz, 1H, H-6b), 2.32 (dd, $J = 2.6, 15.6$ Hz, 1H, H-18b), 2.23 (quint, $J = 7.1$ Hz, 1H, H-8), 2.10 (dd, $J = 4.8, 17.7$ Hz, 1H, H-3b), 2.09 (dd, $J = 4.3, 14.7$ Hz, 1H, H-1b), 1.95 (dt, $J = 7.5, 15.3$ Hz, 1H, H-48a), 1.88-1.83 (m, 1H, H-48b), 1.80 (dt, $J = 6.6, 11.7$ Hz, 1H, H-15a), 1.74 (d, $J = 1.2$ Hz, 3H, H-24), 1.76-1.69 (m, 1H, H-33a), 1.66 (d, $J = 1.0$ Hz, 3H, H-46), 1.59 (bs, 1H, OH), 1.57-1.51 (m, 1H, H-32a), 1.51-1.45 (m, 1H, H-16), 1.43-1.32 (m, 4H, H-15b, H-49, H-32b), 1.24-1.17 (m, 2H, H-50), 1.09-1.05 (m, 1H, H-33b), 0.94 (d, $J = 7.1$ Hz, 3H, H-26), 0.94 (d, $J = 6.9$ Hz, 3H, H-25), 0.83 (t, $J = 7.3$ Hz, 3H, H-51), 0.66 (d, $J = 6.5$ Hz, 3H, H-22); ¹³C NMR (150 MHz, C₆D₆): $\delta = 213.2$ (C, C-5), 207.5 (C, C-2), 171.2 (C, C-19), 149.4 (C, C-47), 145.9 (C, C-11), 141.0 (C, C-44), 140.5 (C, C-9), 131.2 (HC, C-42), 128.2 (HC, C-41), 125.5 (HC, C-43), 125.3 (HC, C-10), 115.3 (H₂C, C-23), 110.4 (H₂C, C-60), 81.7 (HC, C-17), 80.1 (HC, C-31), 79.9 (HC, C-45), 79.2 (HC, C-14), 77.6 (HC, C-12), 77.2 (HC, C-20), 76.6 (HC, C-13), 75.6 (HC, C-34), 71.1 (HC, C-7), 49.3 (HC, C-8), 48.7 (H₂C, C-1), 46.4 (H₂C, C-3), 45.9 (H₂C, C-6), 42.5 (HC, C-4), 40.2 (HC, C-16), 39.2 (H₂C, C-18), 37.0 (H₂C, C-15), 32.3 (H₂C, C-33), 31.7 (H₂C, C-48), 30.4 (H₂C, C-49), 28.4 (H₂C, C-32), 22.8 (H₂C, C-50), 16.2 (H₃C, C-26), 15.8 (H₃C, C-25), 15.3 (H₃C, C-22), 15.3 (H₃C, C-24), 14.2 (H₃C, C-51), 12.6 (H₃C, C-46); MS (ESIpos) $[M + Na]^+$ 737 (100); HRMS (ESIpos) calcd. for C₄₁H₆₂O₁₀Na $[M + Na]^+$ 737.4235, found 737.4230.

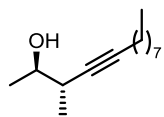
Table S2. Comparison of the ^{13}C NMR data (δ , ppm) of amphidinolide C (**1**).

Atom no.	Synthetic 1 (150 MHz, C_6D_6) this study	Natural 1 (125 MHz, C_6D_6) ¹³	$\Delta\delta$ (Synthetic–Natural)
1	171.2	171.1	0.1
2	39.2	39.2	0.0
3	81.7	81.8	–0.1
4	40.2	40.2	0.0
5	37.0	37.0	0.0
6	79.2	79.2	0.0
7	76.6	76.5	0.1
8	77.6	77.7	–0.1
9	145.9	146.0	–0.1
10	125.3	125.2	0.1
11	140.5	140.7	–0.2
12	49.3	49.3	0.0
13	71.1	71.1	0.0
14	45.9	45.9	0.0
15	213.2	213.3	–0.1
16	42.5	42.4	0.1
17	46.3	46.4	–0.1
18	207.5	207.5	0.0
19	48.7	48.7	0.0
20	75.6	75.7	–0.1
21	32.3	32.3	0.0
22	28.4	28.3	0.1
23	80.1	80.1	0.0
24	77.3	77.3	0.0
25	128.2	128.5	–0.3
26	131.2	131.1	0.1
27	125.5	125.5	0.0
28	141.0	140.9	0.1
29	79.9	79.9	0.0
30	149.4	149.4	0.0
31	31.7	31.7	0.0
32	30.4	30.4	0.0
33	22.8	22.8	0.0
34	14.2	14.2	0.0
35	15.3	15.4	–0.1
36	115.3	115.2	0.1
37	15.3	15.4	–0.1
38	15.8	15.8	0.0
39	16.2	16.2	0.0
40	12.6	12.6	0.0
41	110.4	110.4	0.0

References

- (1) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945-948. (b) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9-17.
- (2) (a) Palmer, C.; Morra, N. A.; Stevens, A. C.; Bajtos, B.; Machin, B. P.; Pagenkopf, B. L. *Org. Lett.* **2009**, *11*, 5614-5617.; (b) Morra, N. A.; Pagenkopf, B. L. *Org. Lett.* **2011**, *13*, 572-575.
- (3) Charreau, P.; Julia, M.; Verpeaux, J.-N. *J. Organomet. Chem.* **1989**, *379*, 201-210.
- (4) (a) Shiro, Y.; Kato, K.; Fuji, M.; Ida, Y.; Akita, H. *Tetrahedron* **2006**, *62*, 8687-8695. (b) Cai, X.; Chorghade, M. S.; Fura, A.; Grewal, G. S.; Jauregui, K. A.; Lounsbury, H. A.; Scannell, R. T.; Yeh, C. G.; Yong, M. A.; Yu, S. *Org. Proc. Res. Dev.* **1999**, *3*, 73-76.
- (5) Nishida, Y.; Konno, M.; Fukushima, Y.; Ohru, H.; Meguro, H. *Agric. Biol. Chem.* **1986**, *50*, 191-193.
- (6) Bates, R. H.; Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2008**, *10*, 4343-4346.
- (7) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols* **2007**, *2*, 2451-2458.
- (8) (a) Cummins, C. C. *Chem. Commun.* **1998**, 1777-1786. (b) Fürstner, A.; Mathes, C.; Lehmann, C. W. *Chem. Eur. J.* **2001**, *7*, 5299-5317.
- (9) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731-734.
- (10) Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890-891.
- (11) Chen, Y. K.; Jeon, S.-J.; Walsh, P. J.; Nugent, W. A. *Org. Synth.* **2005**, *82*, 87-92.
- (12) Mahapatra, S.; Carter, R. G. *J. Am. Chem. Soc.* **2013**, *135*, 10792-10803.
- (13) Kobayashi, J.; Ishibashi, M.; Wälchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Am. Chem. Soc.* **1988**, *110*, 490-494.

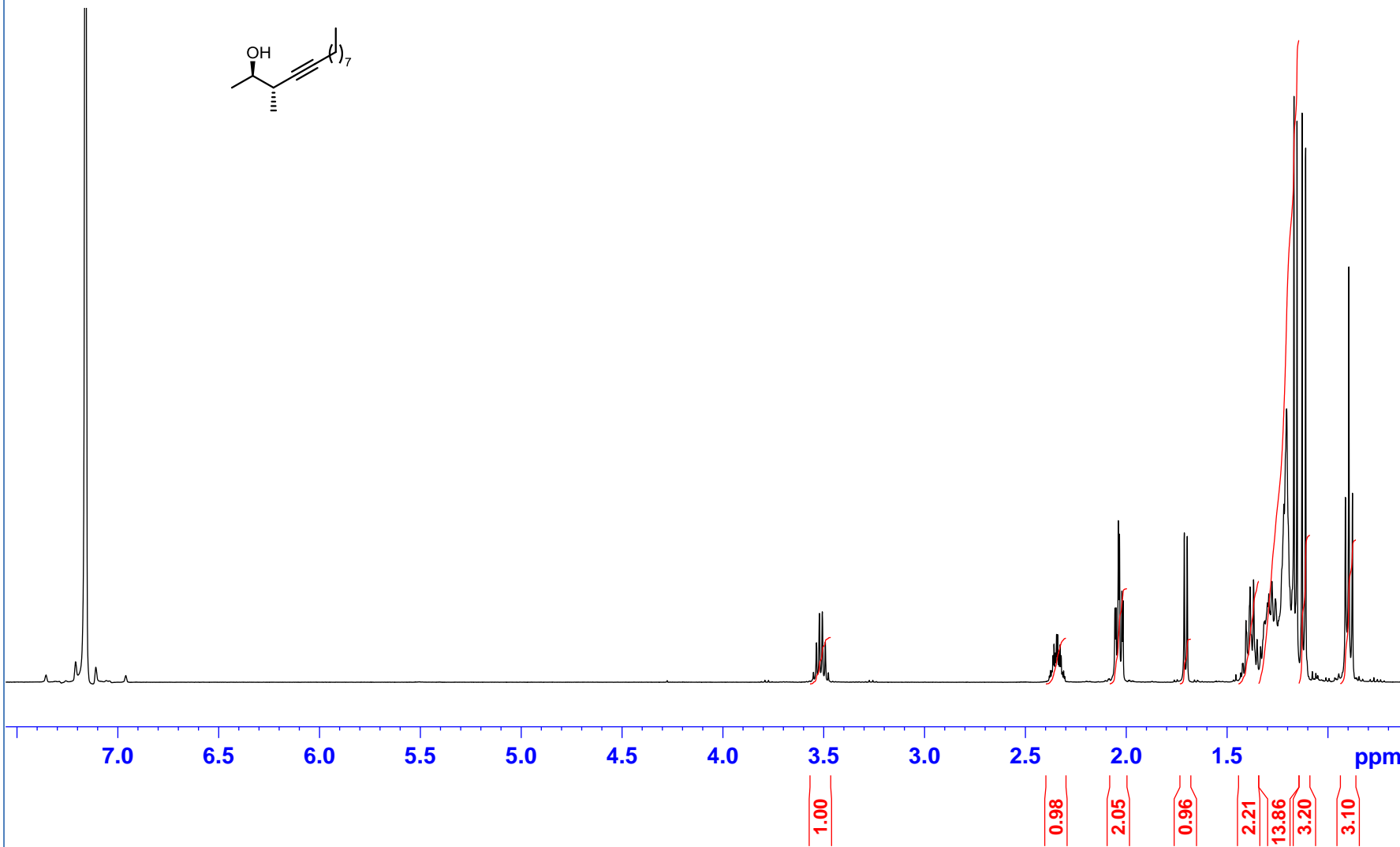
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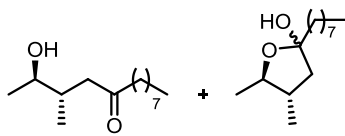
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1403.30
1397.33

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936.50
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813.74

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547.62
467.59
461.43
451.39
444.42
365.52
358.68
351.55



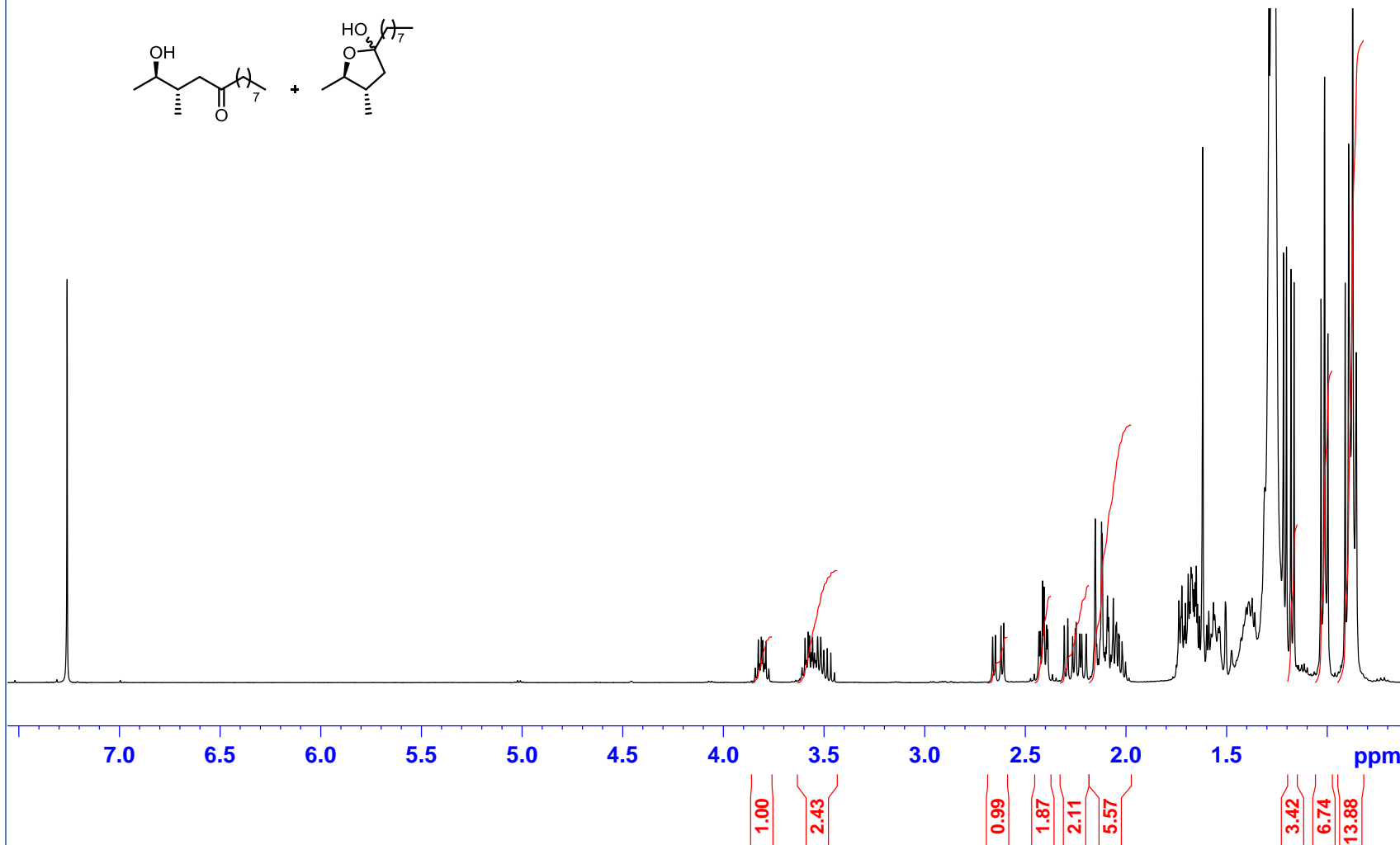
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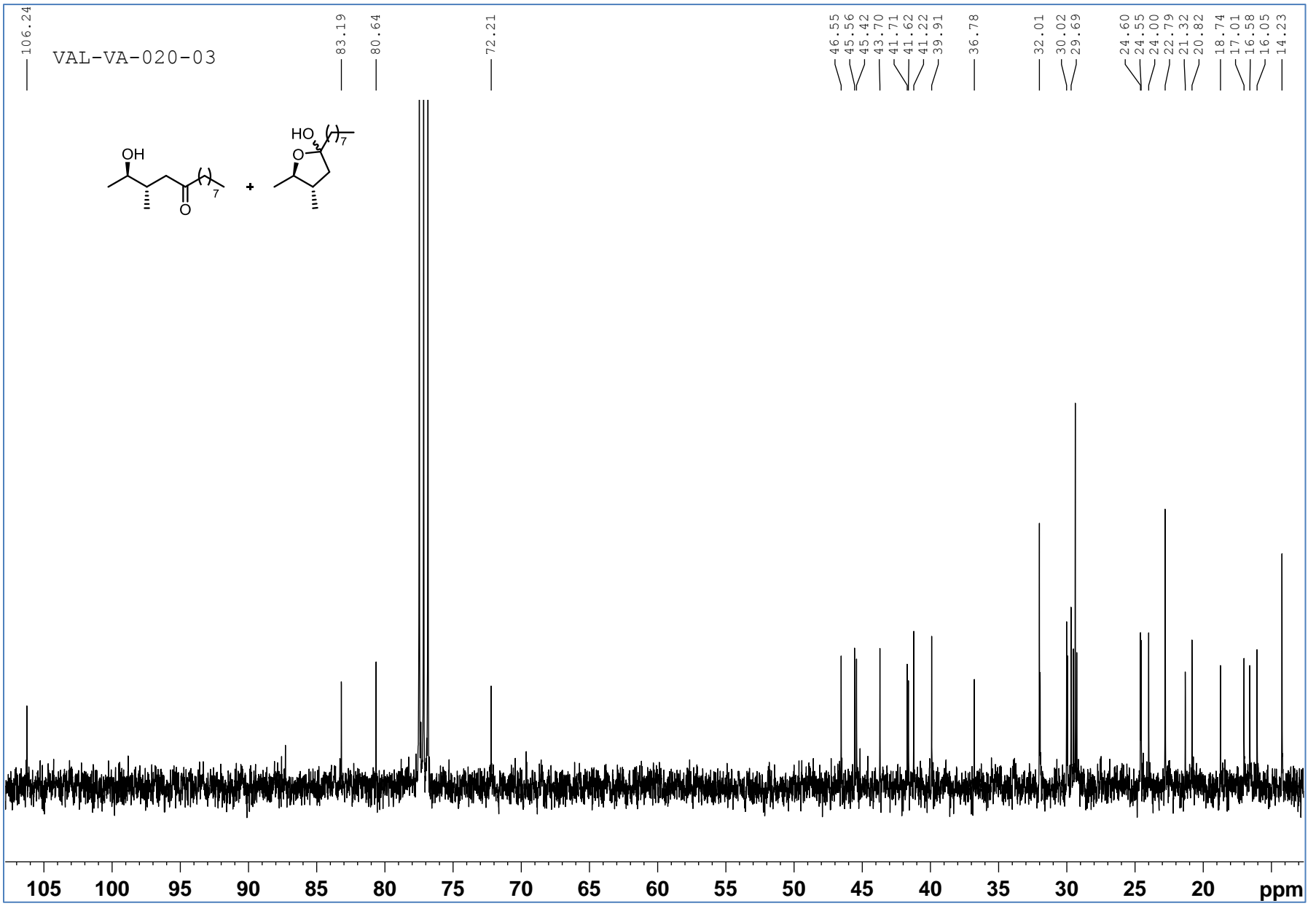


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1406.90

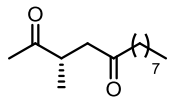
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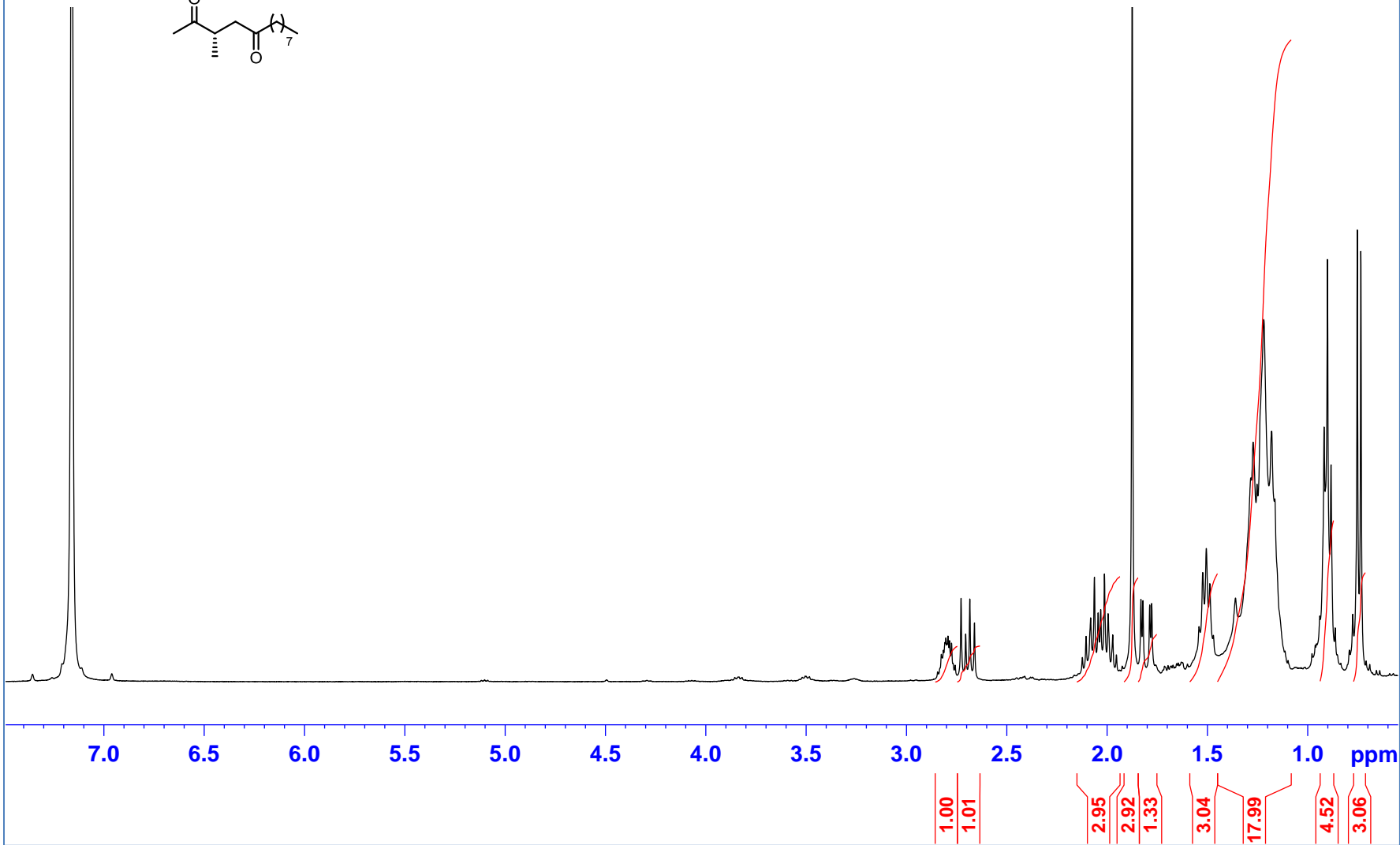




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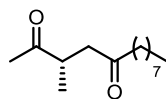


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- 842.11
- 825.51
- 805.42
- 788.94
- 750.08
- 732.72
- 728.68
- 715.23
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- 294.06

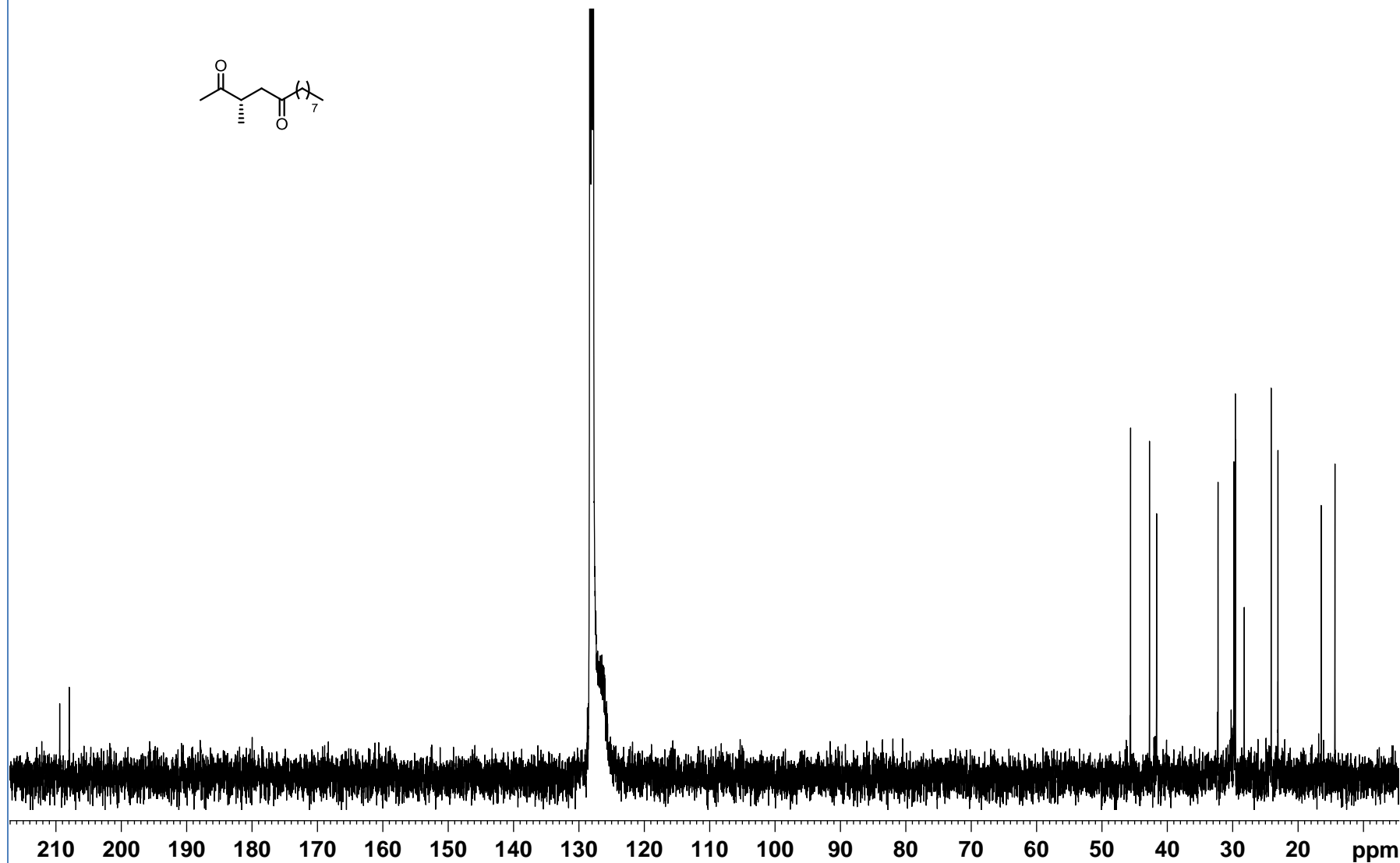


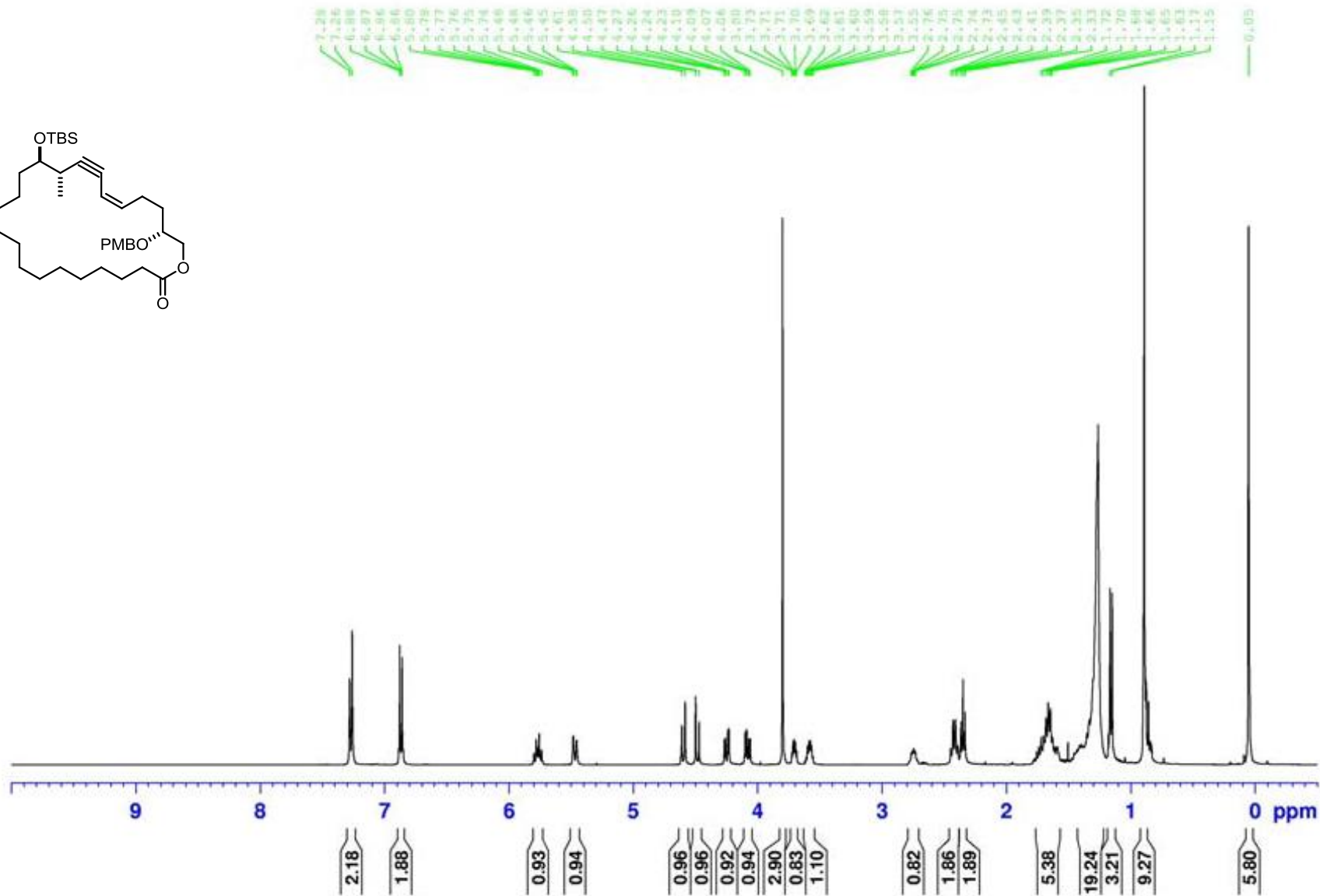
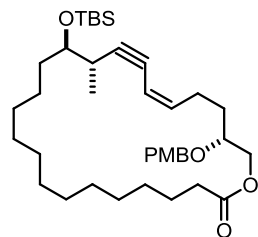
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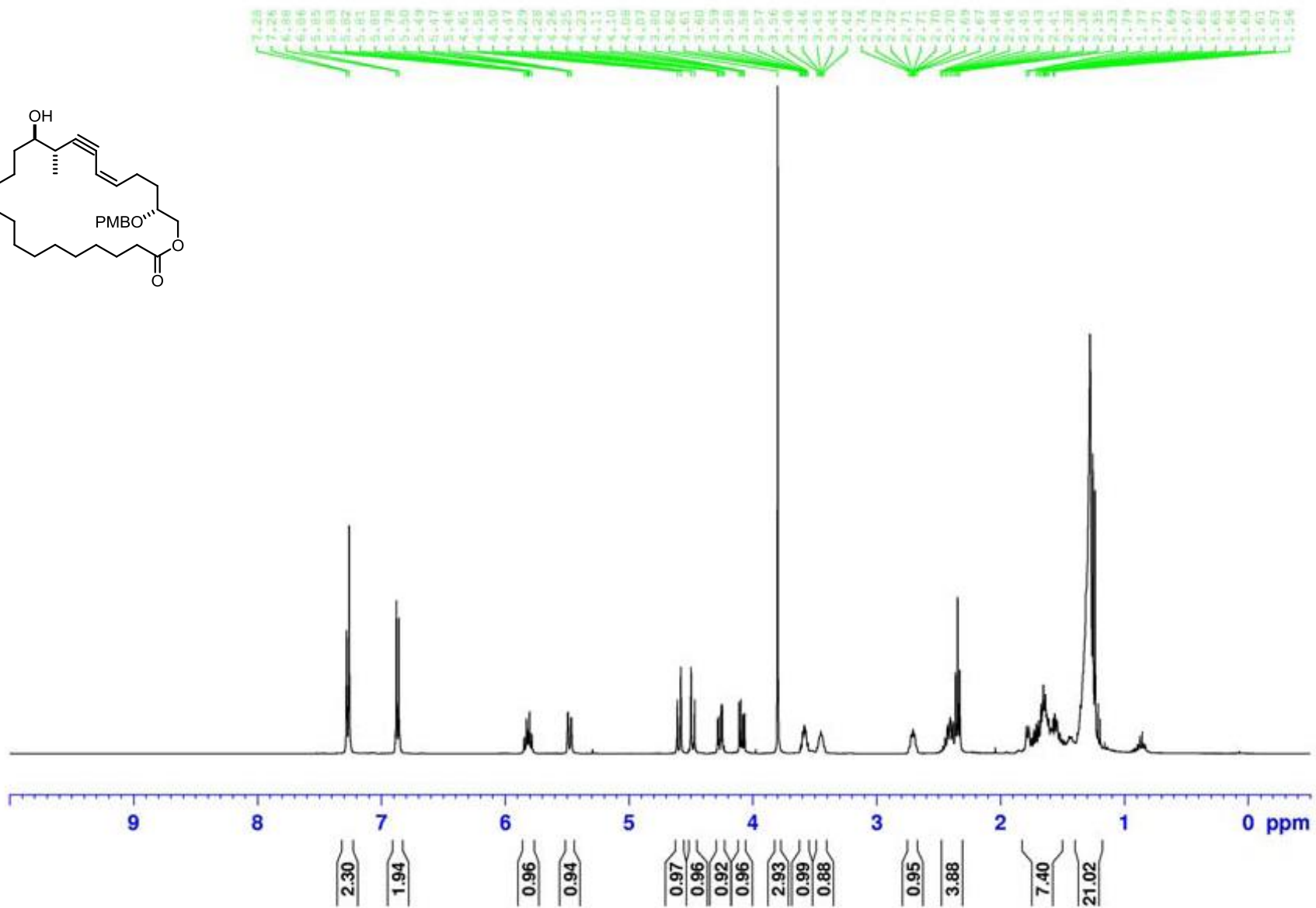
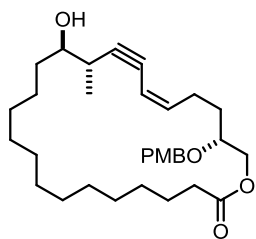
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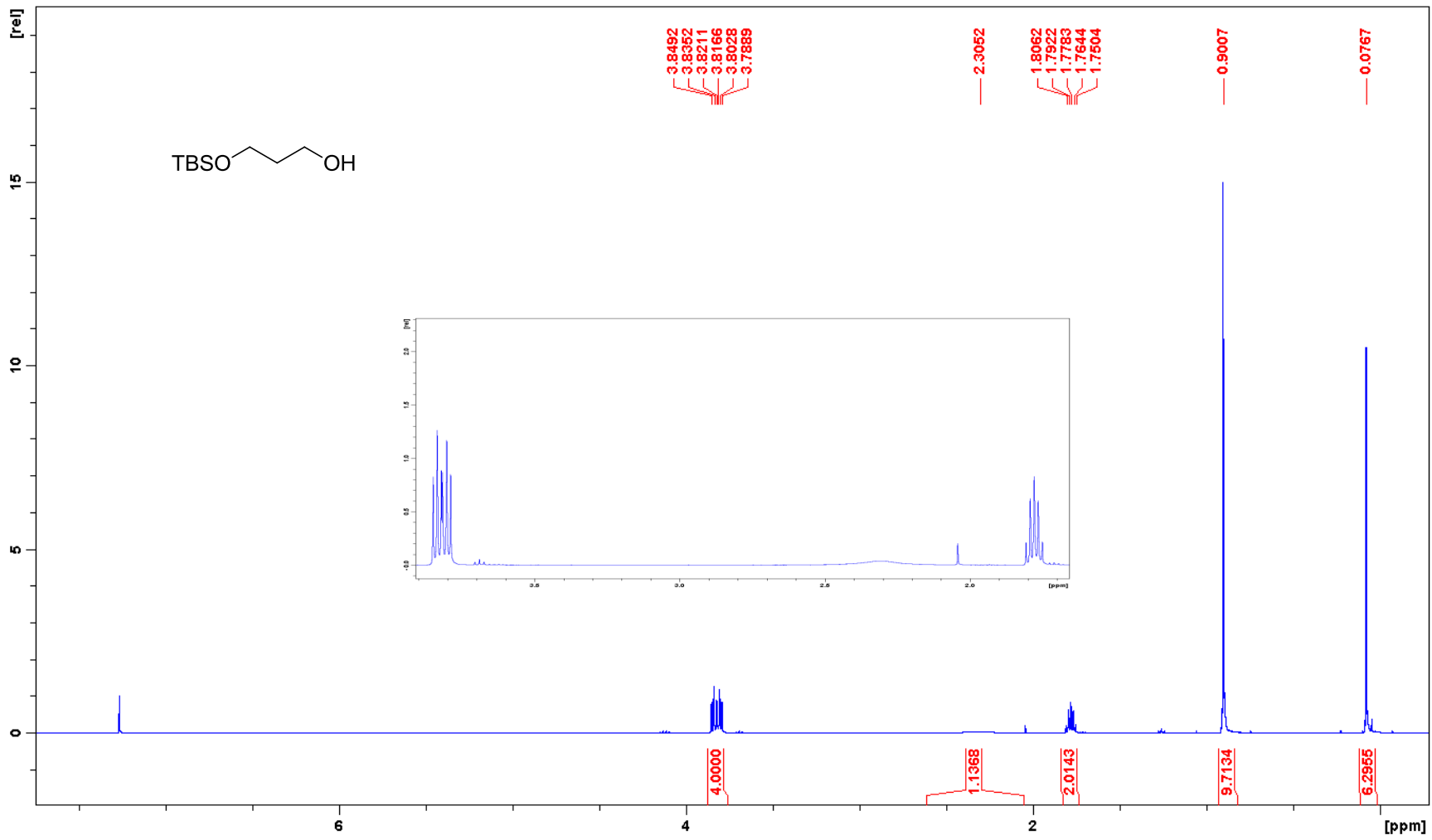


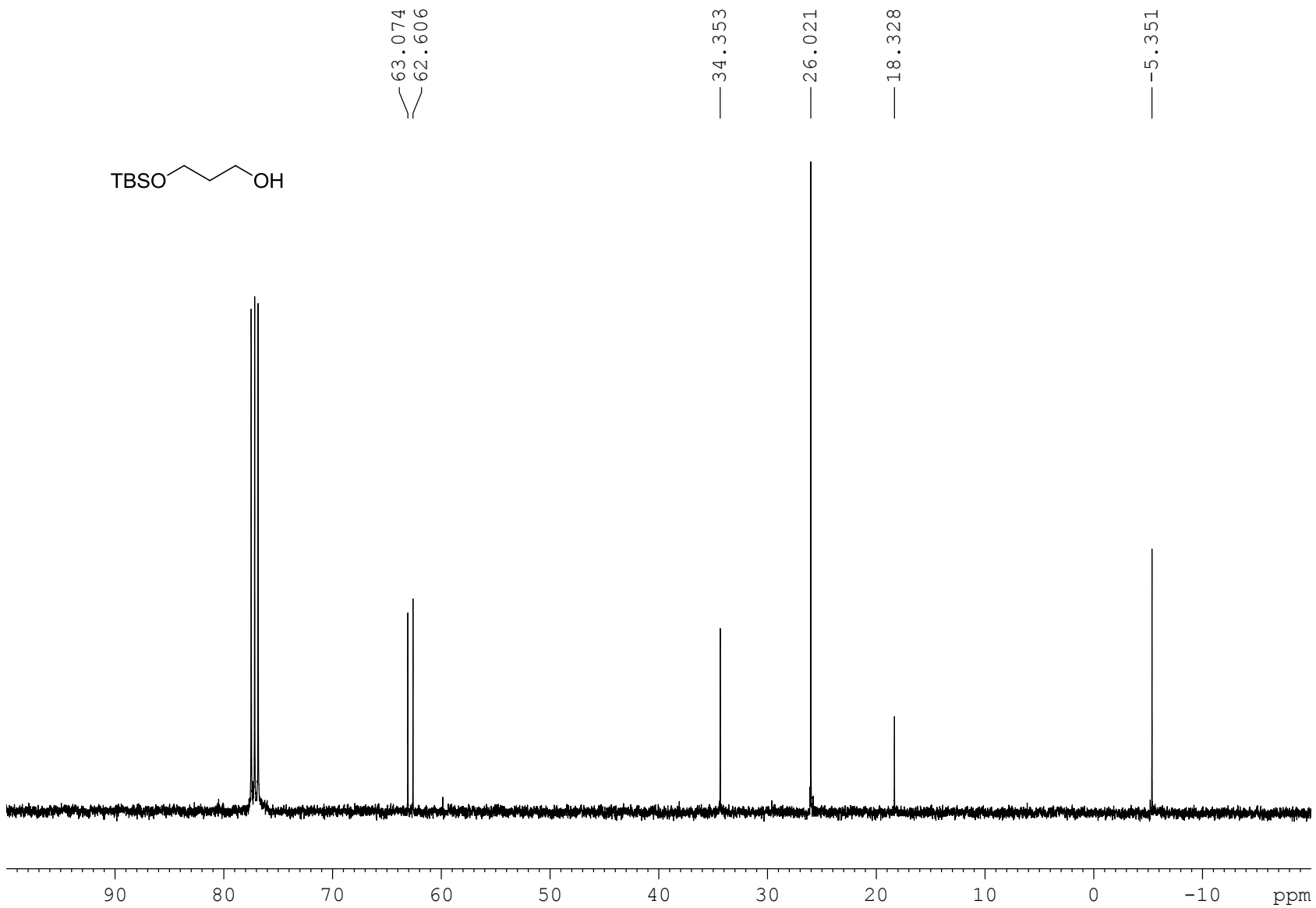
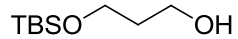
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14.35

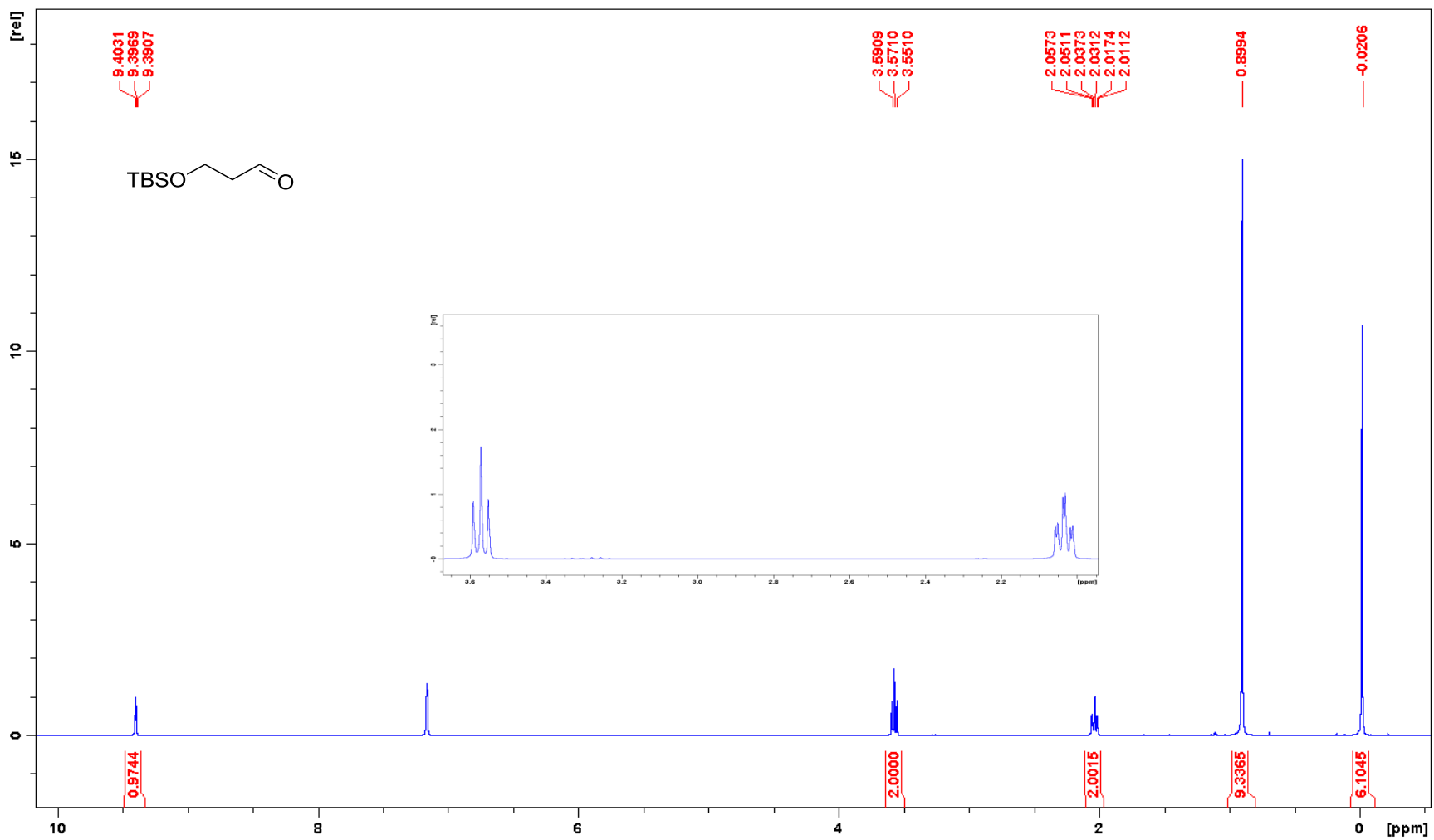


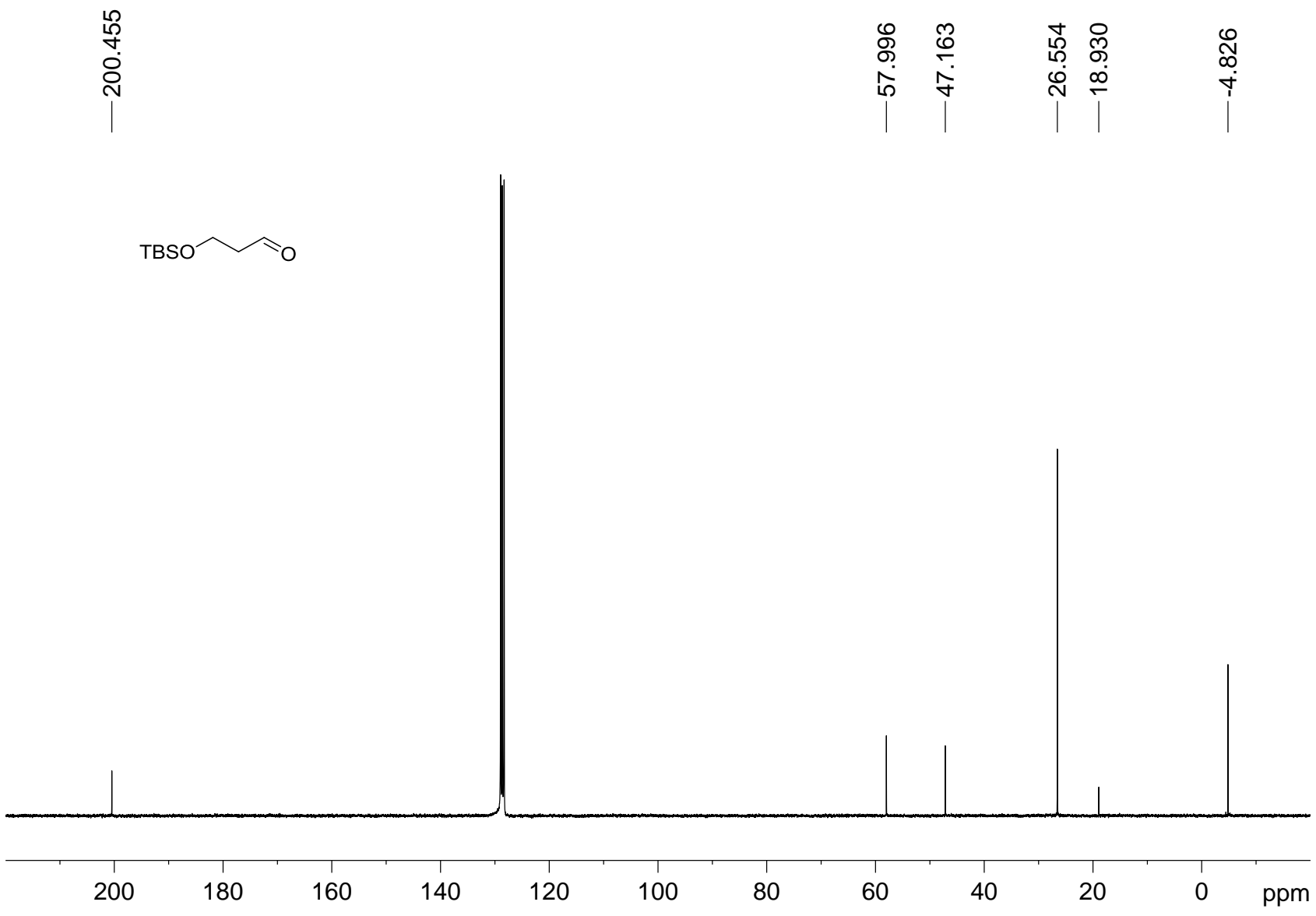


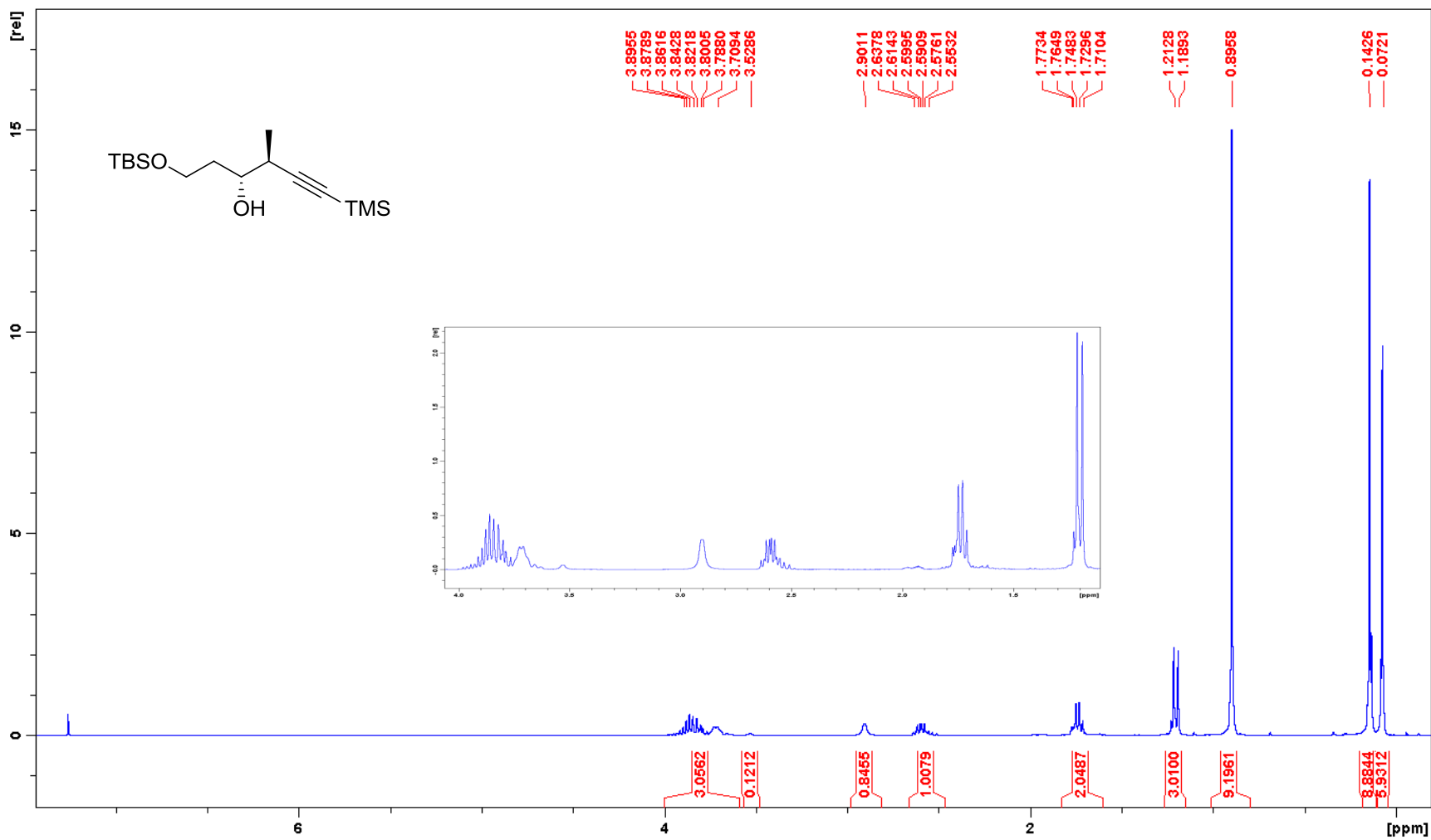


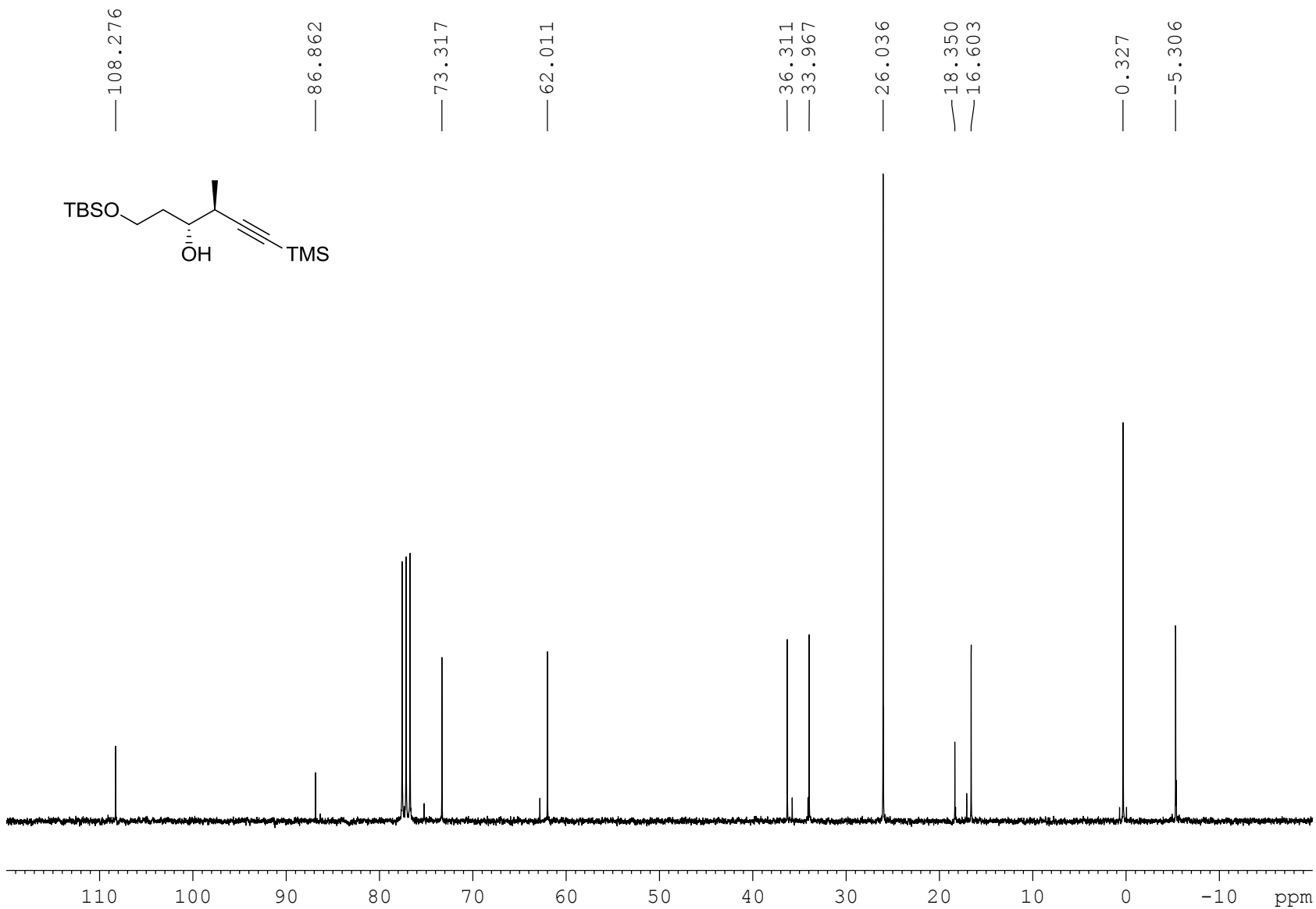
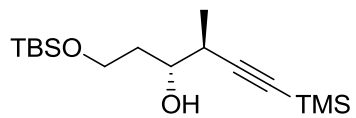


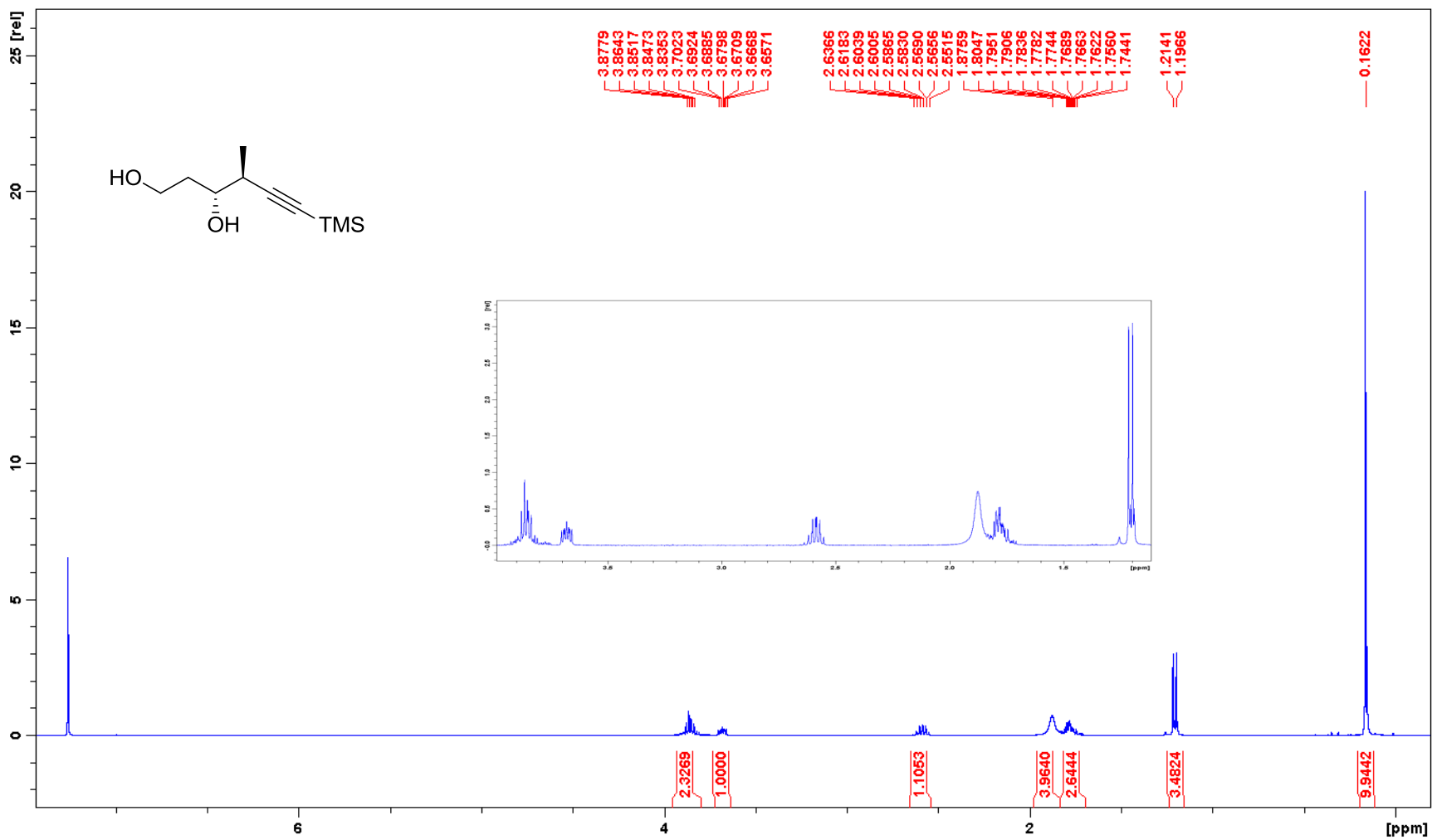


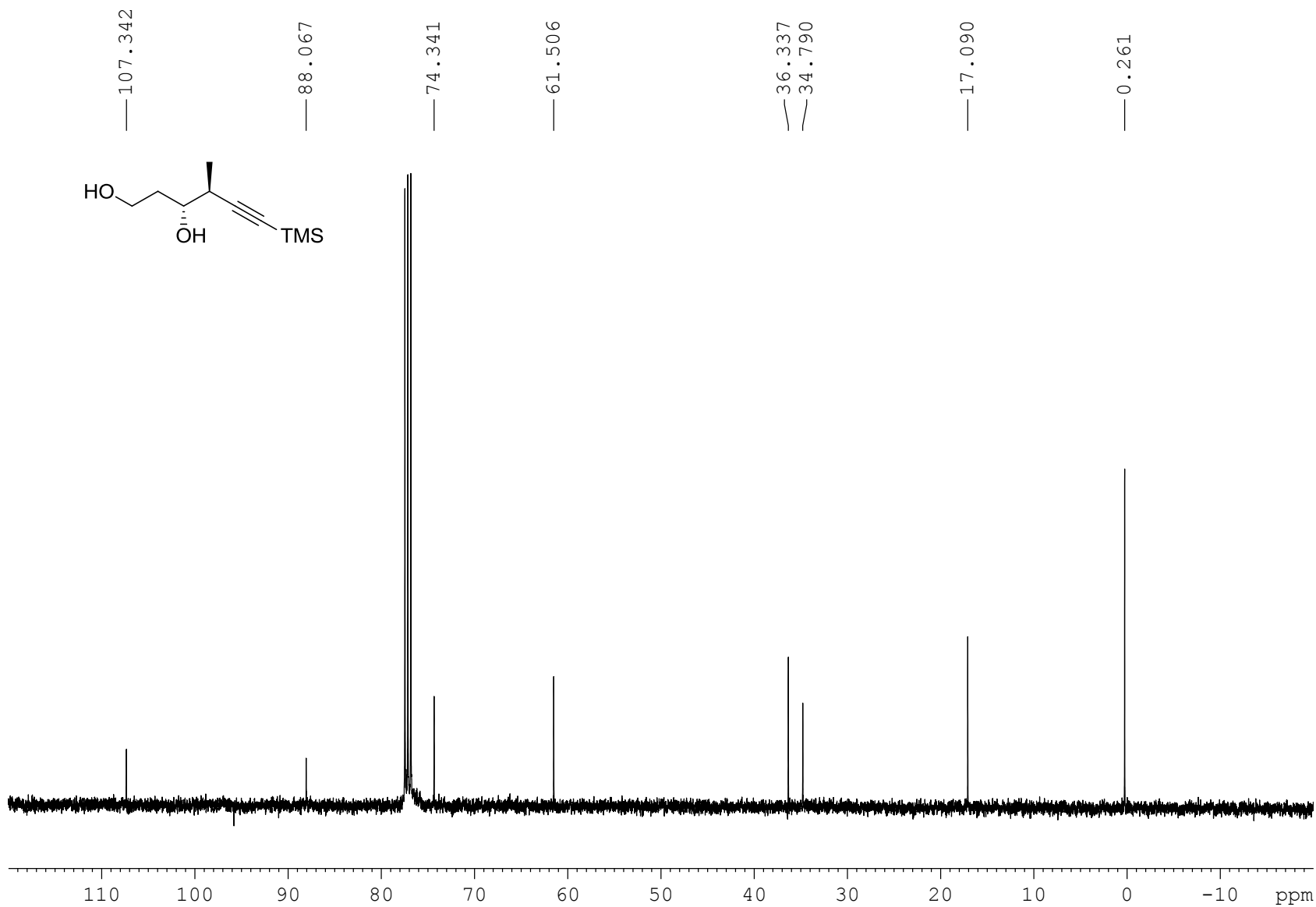
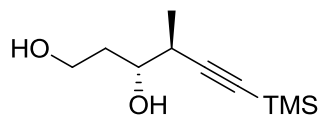


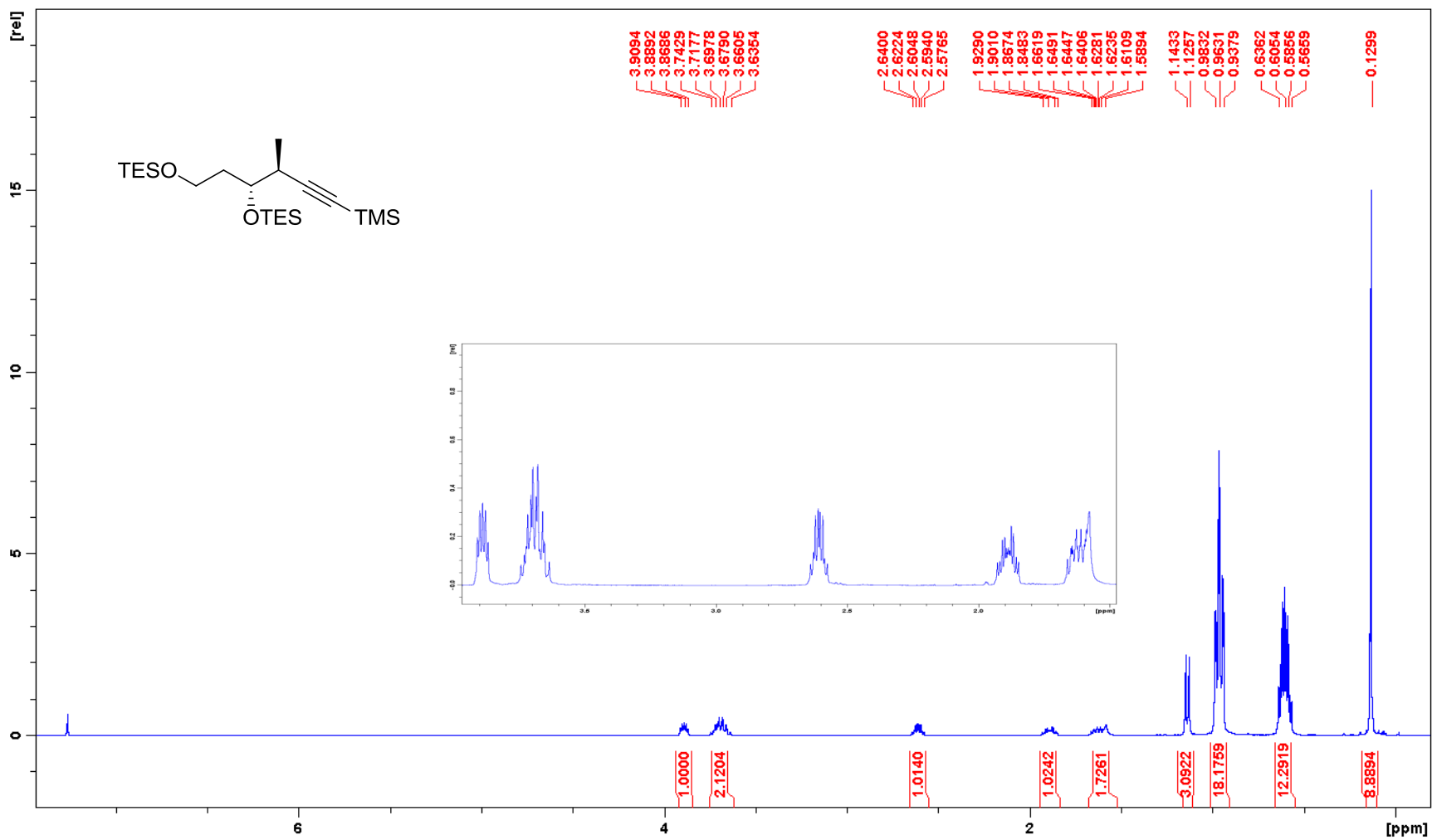


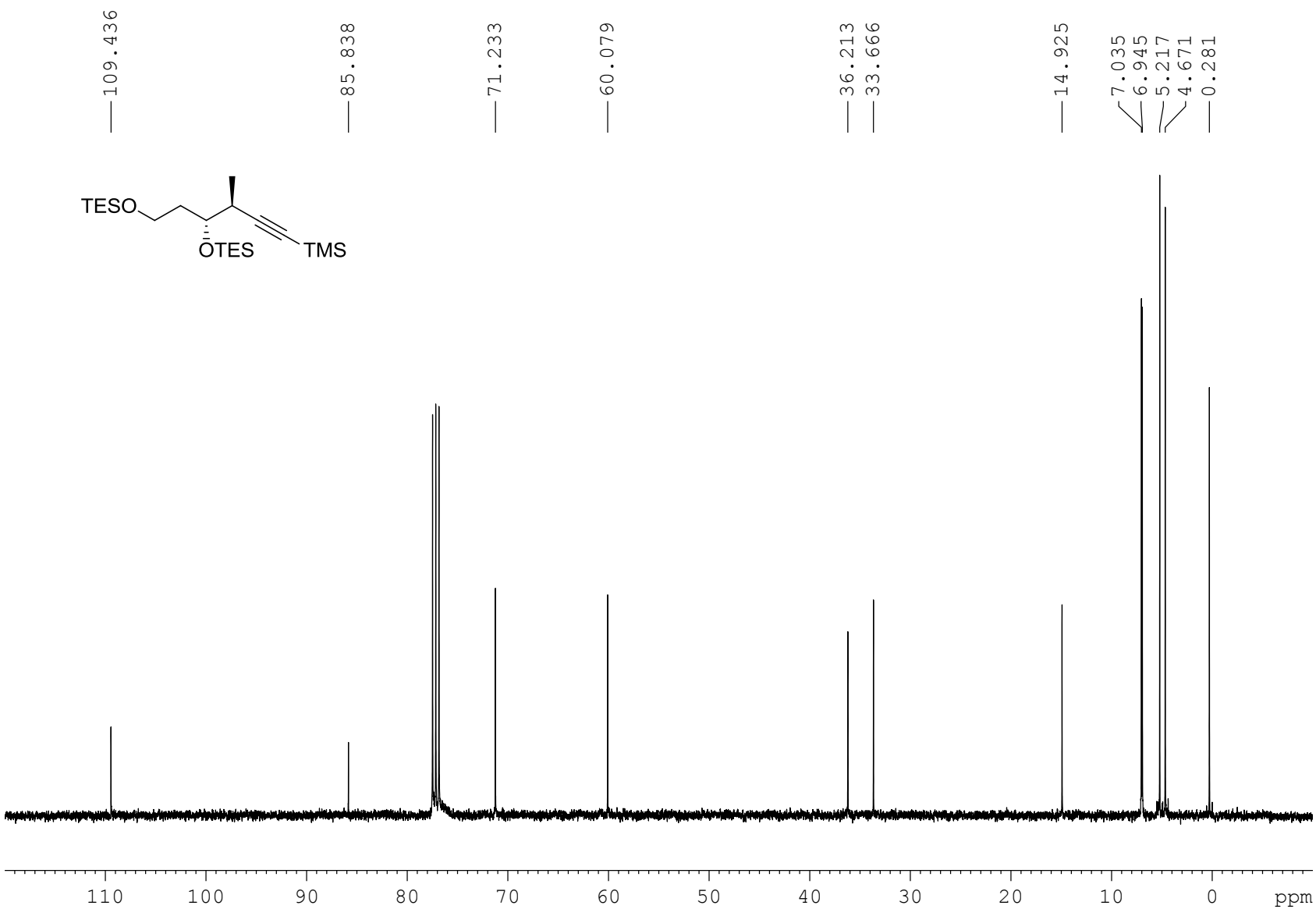
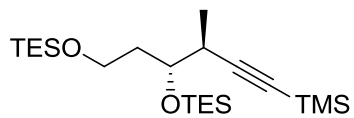


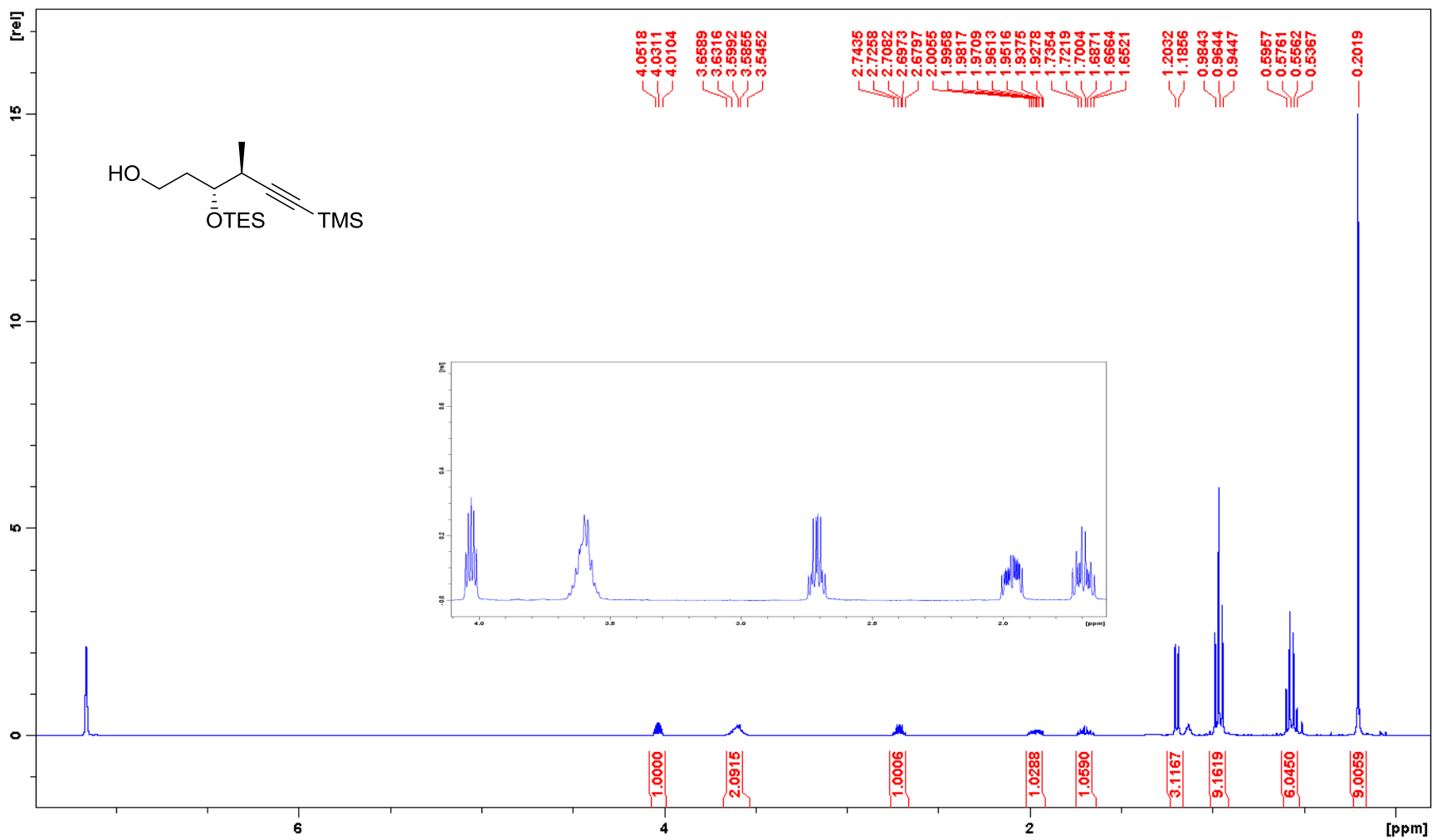


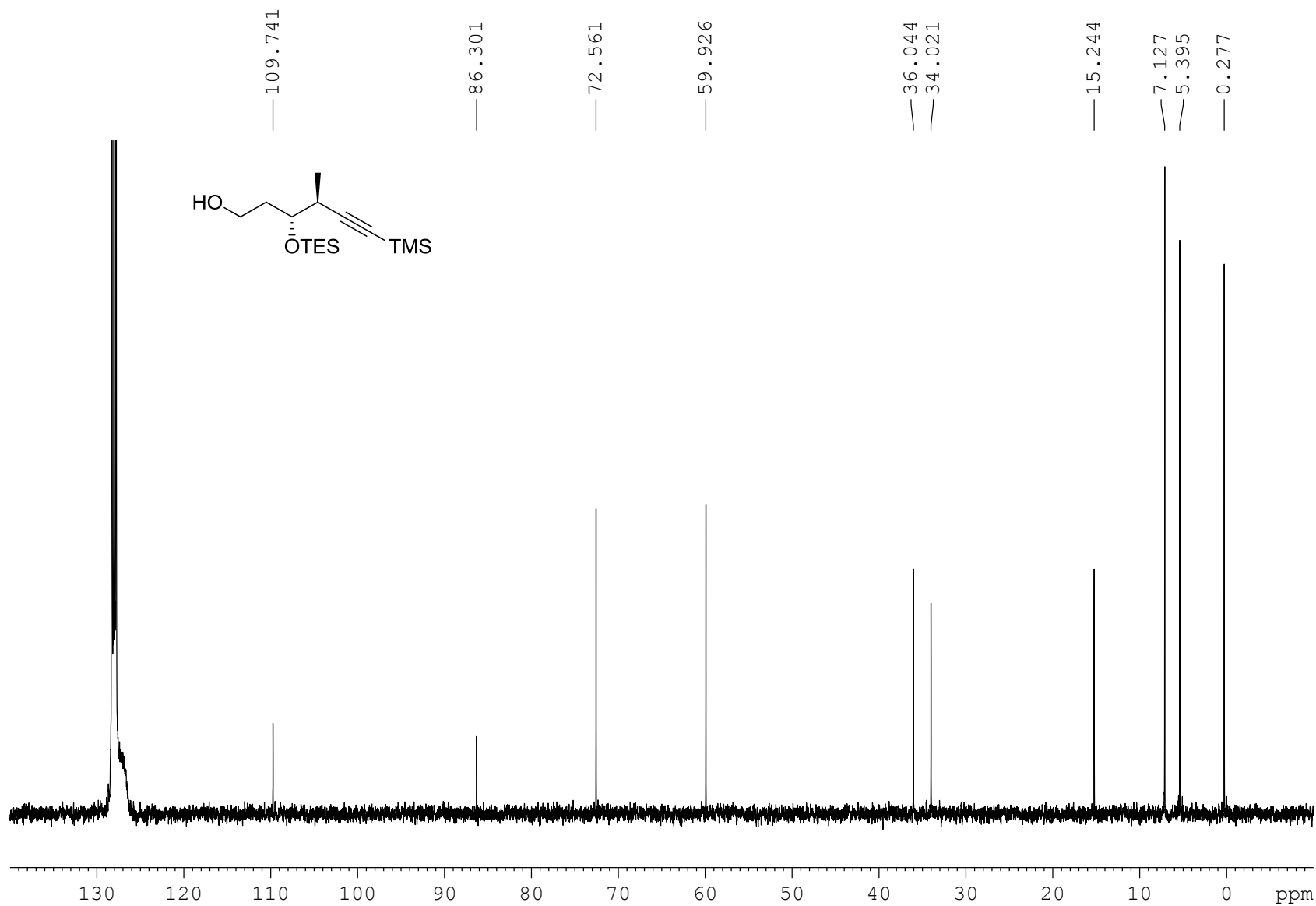
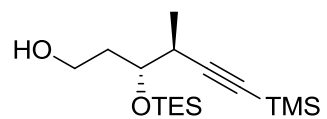


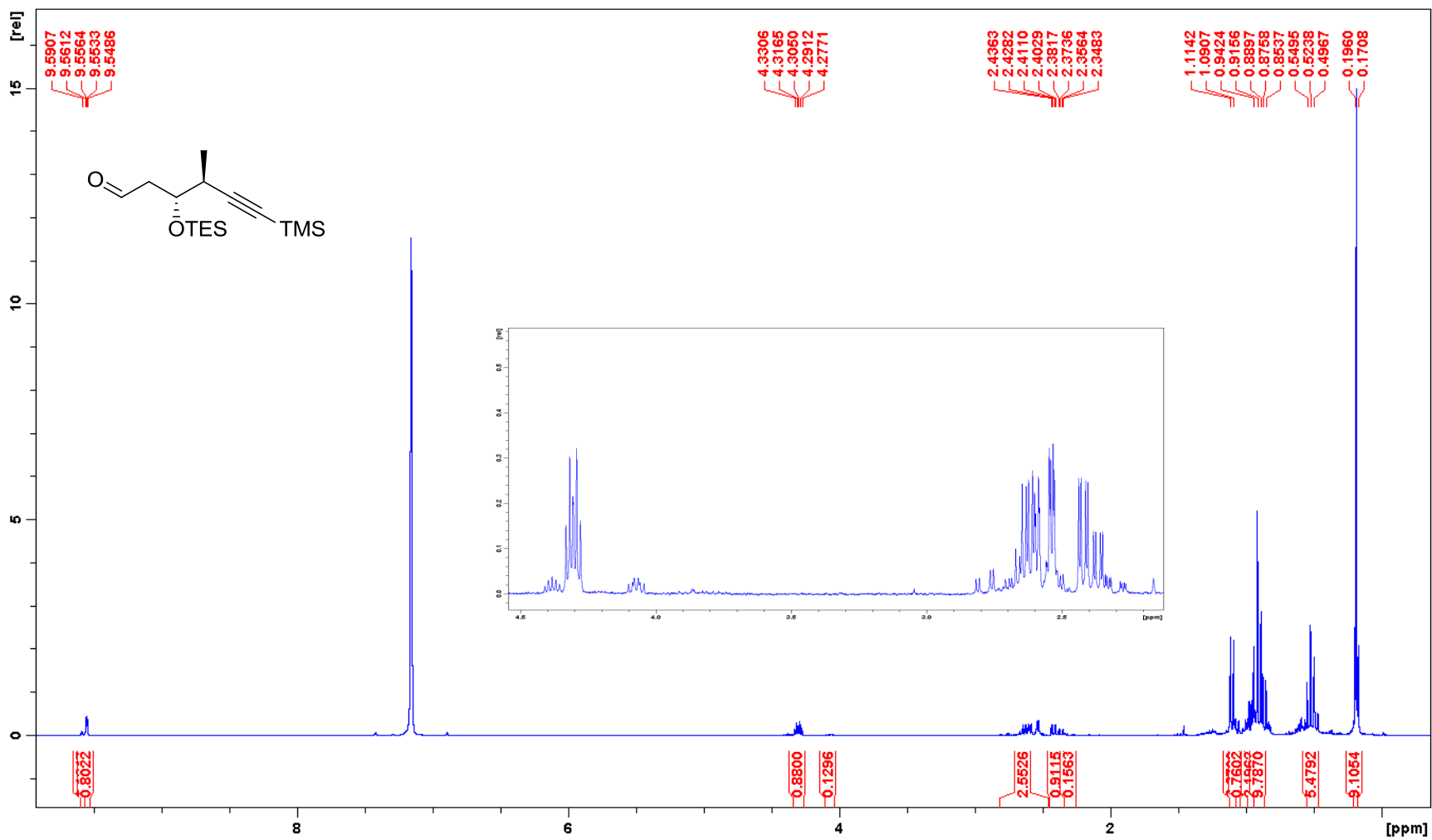


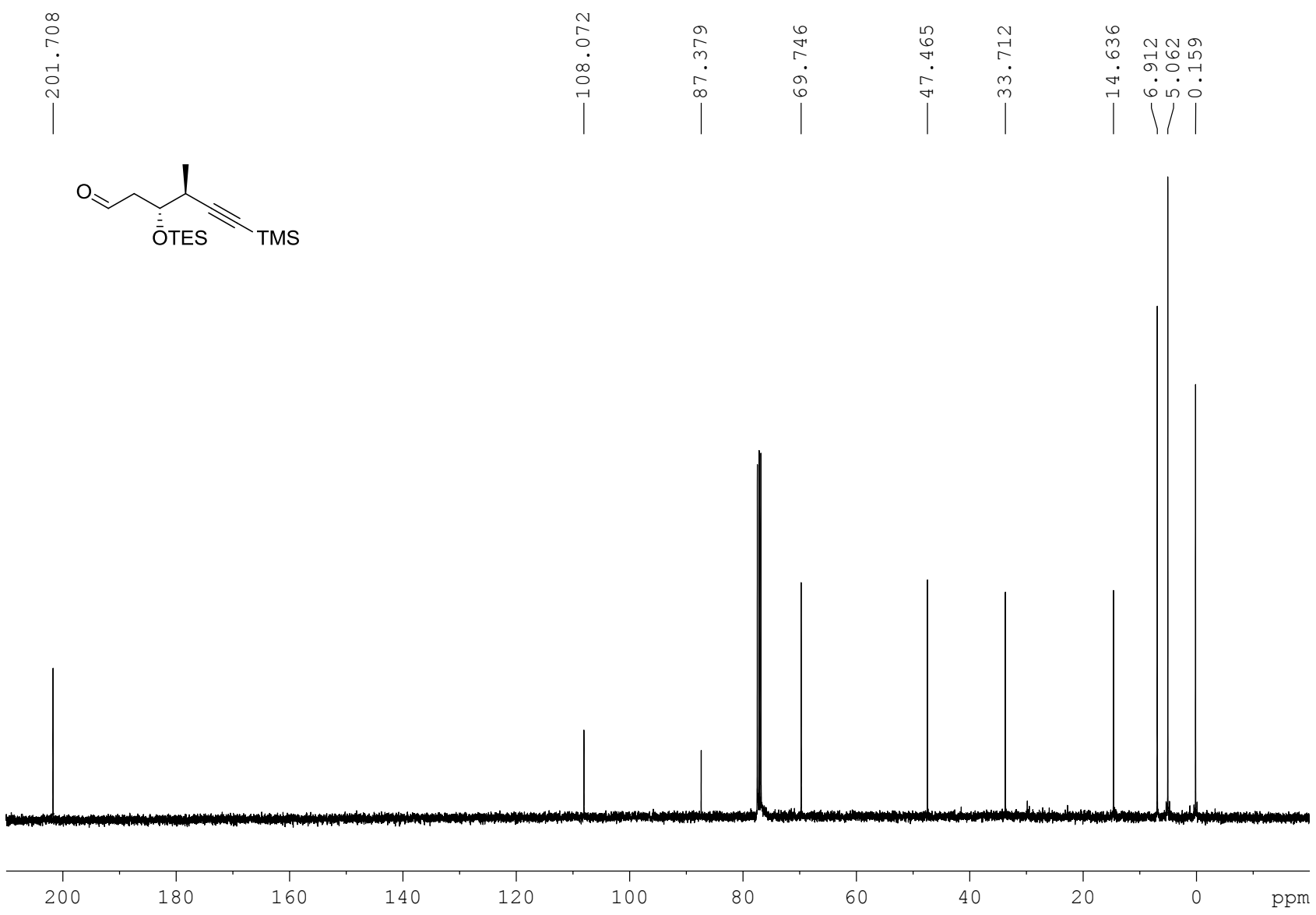


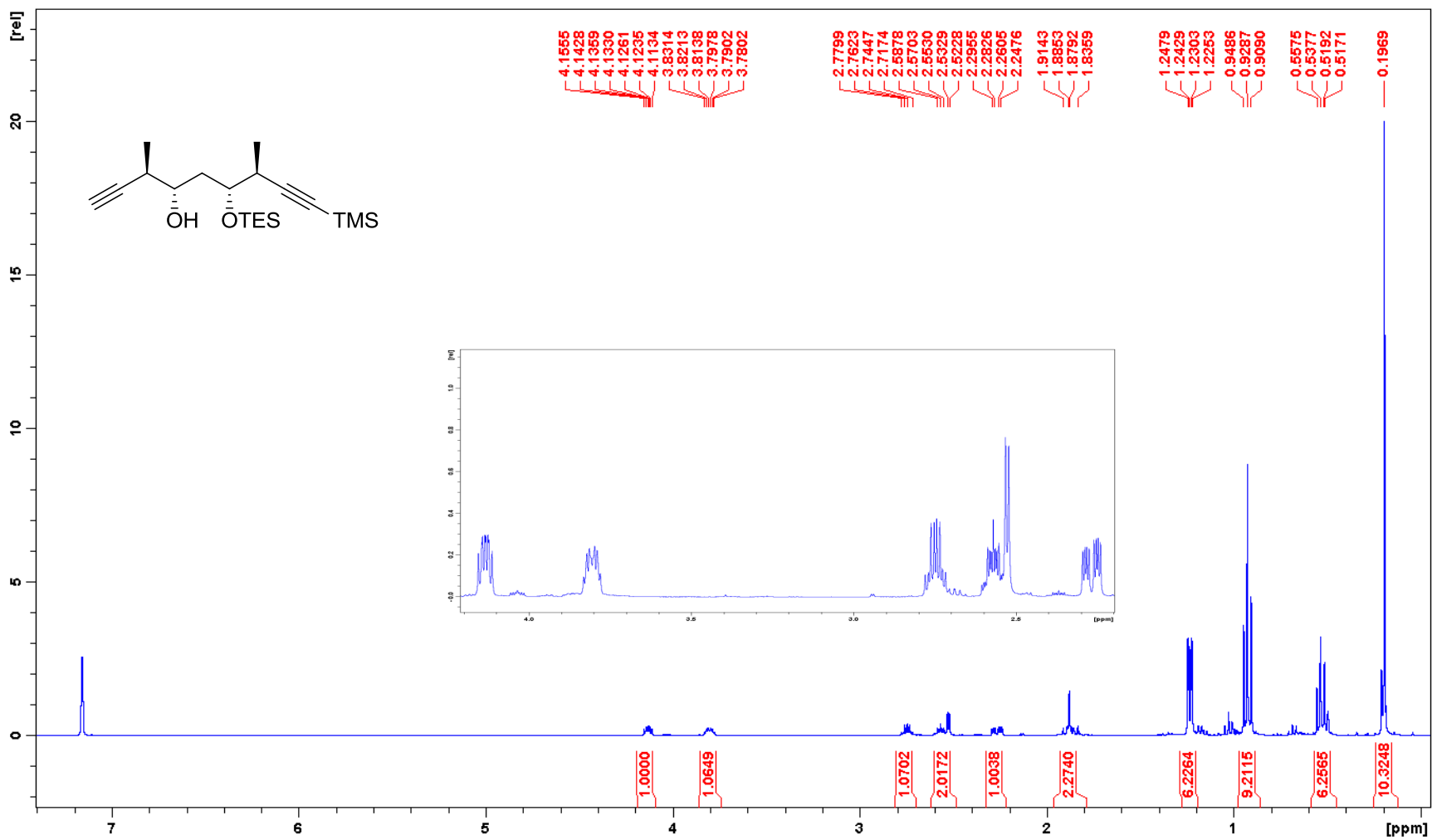


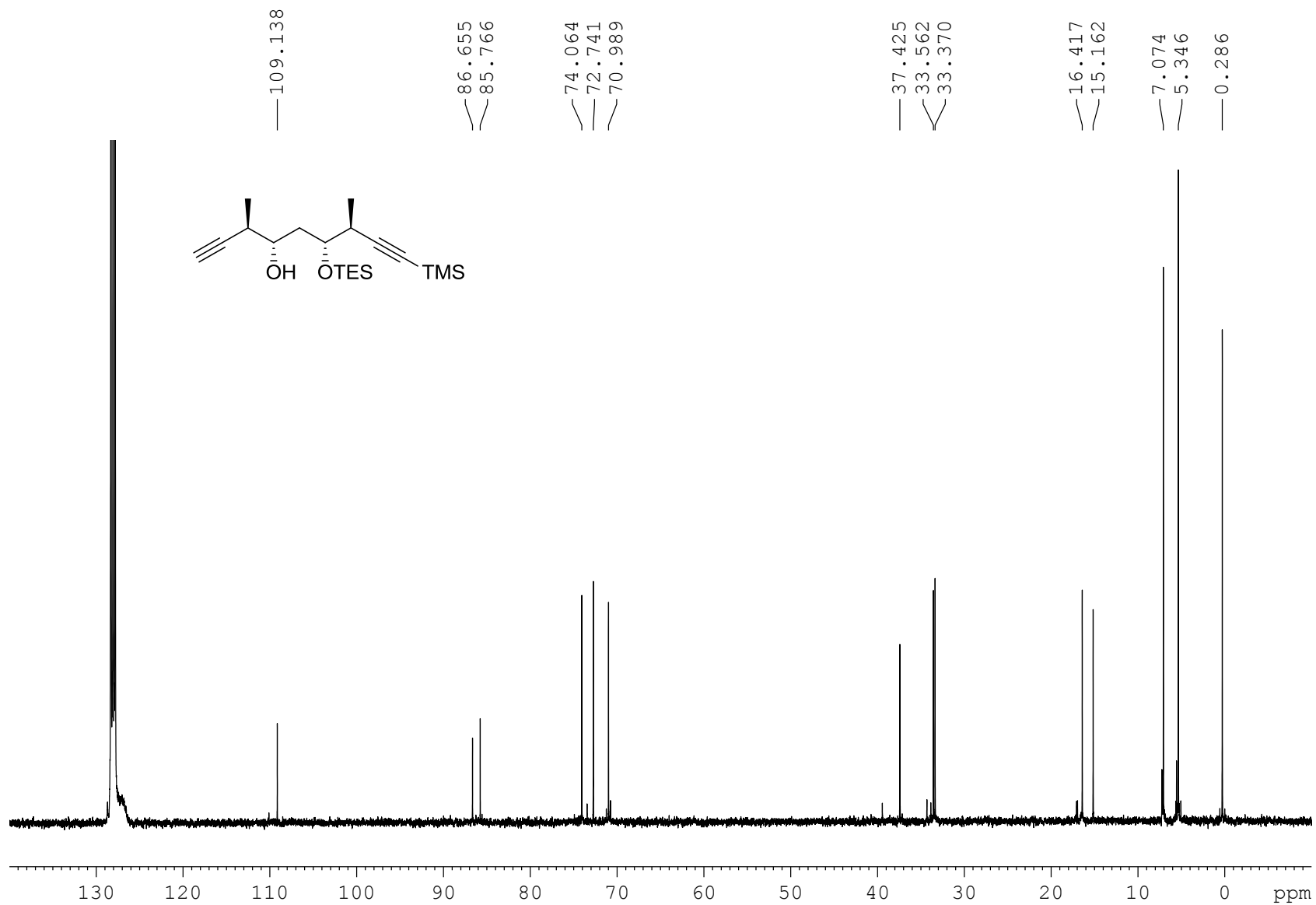


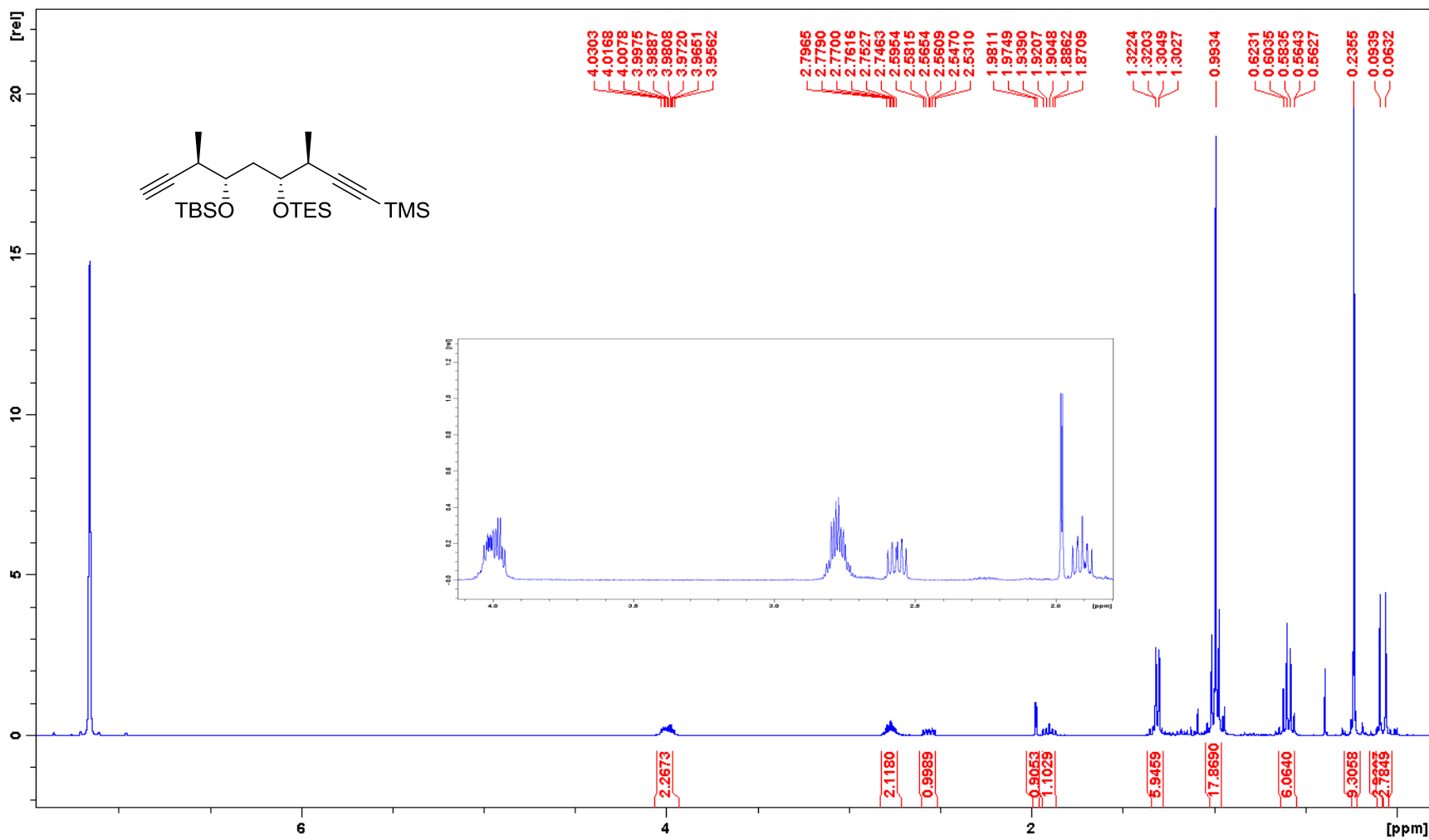


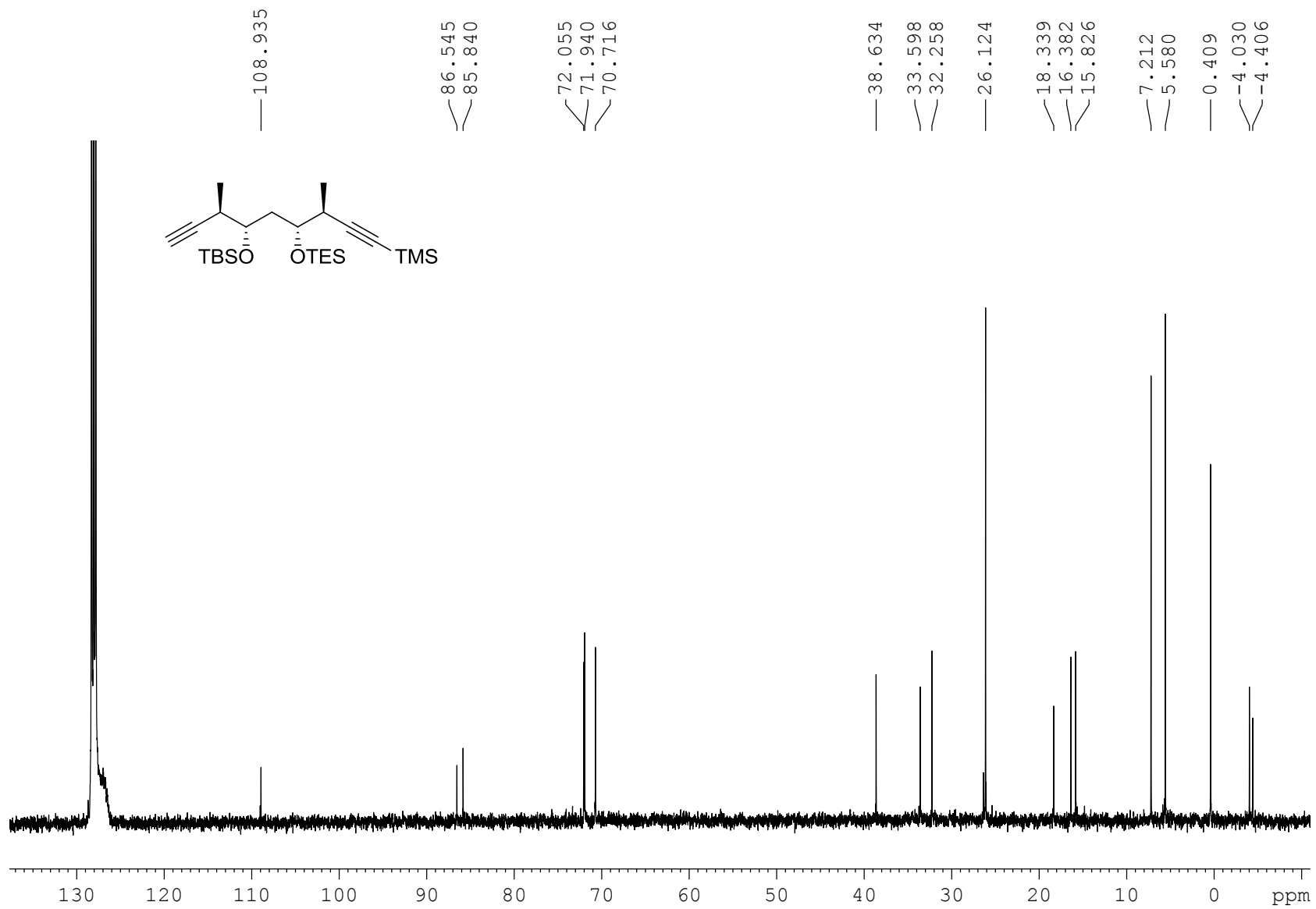


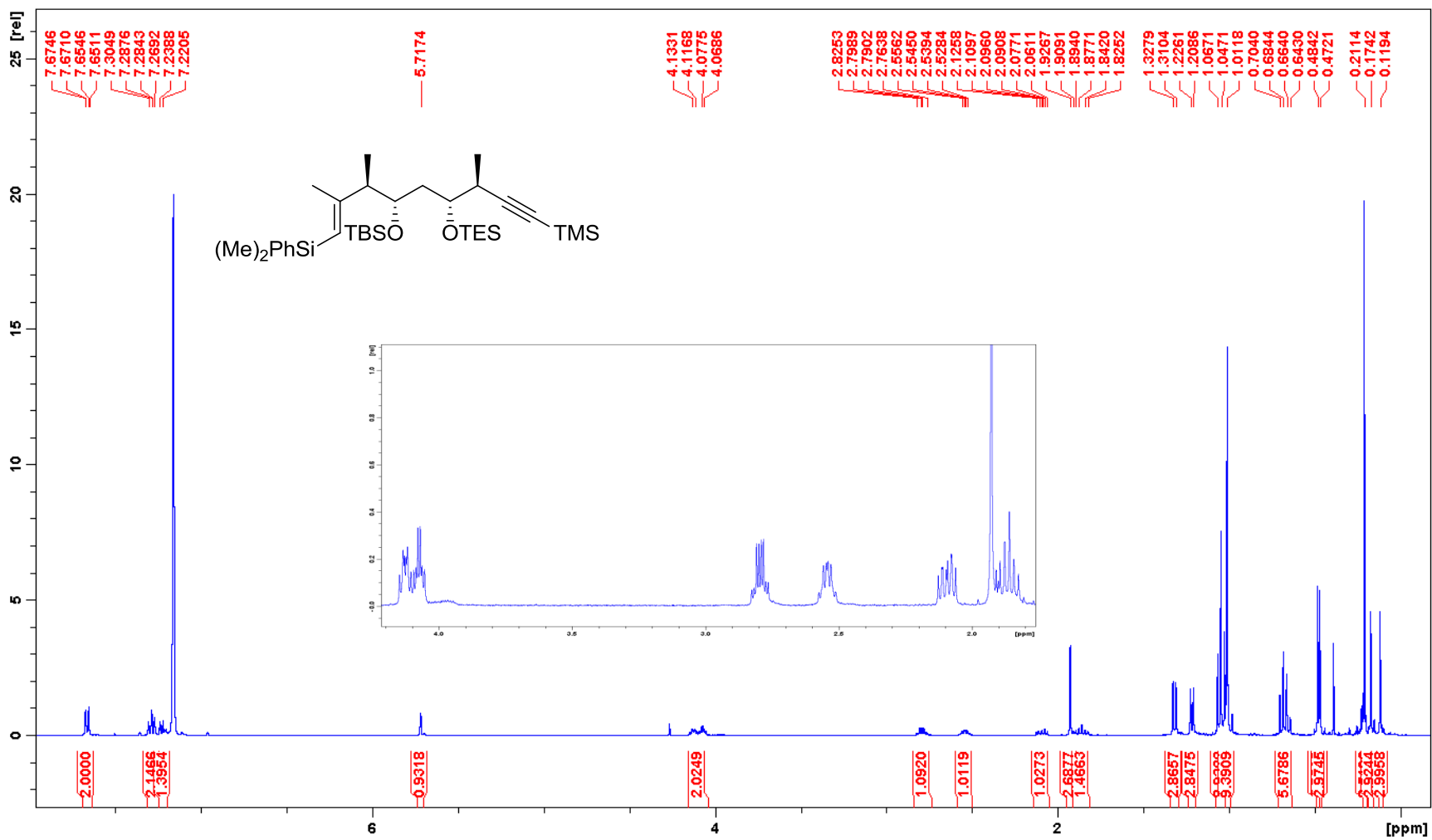


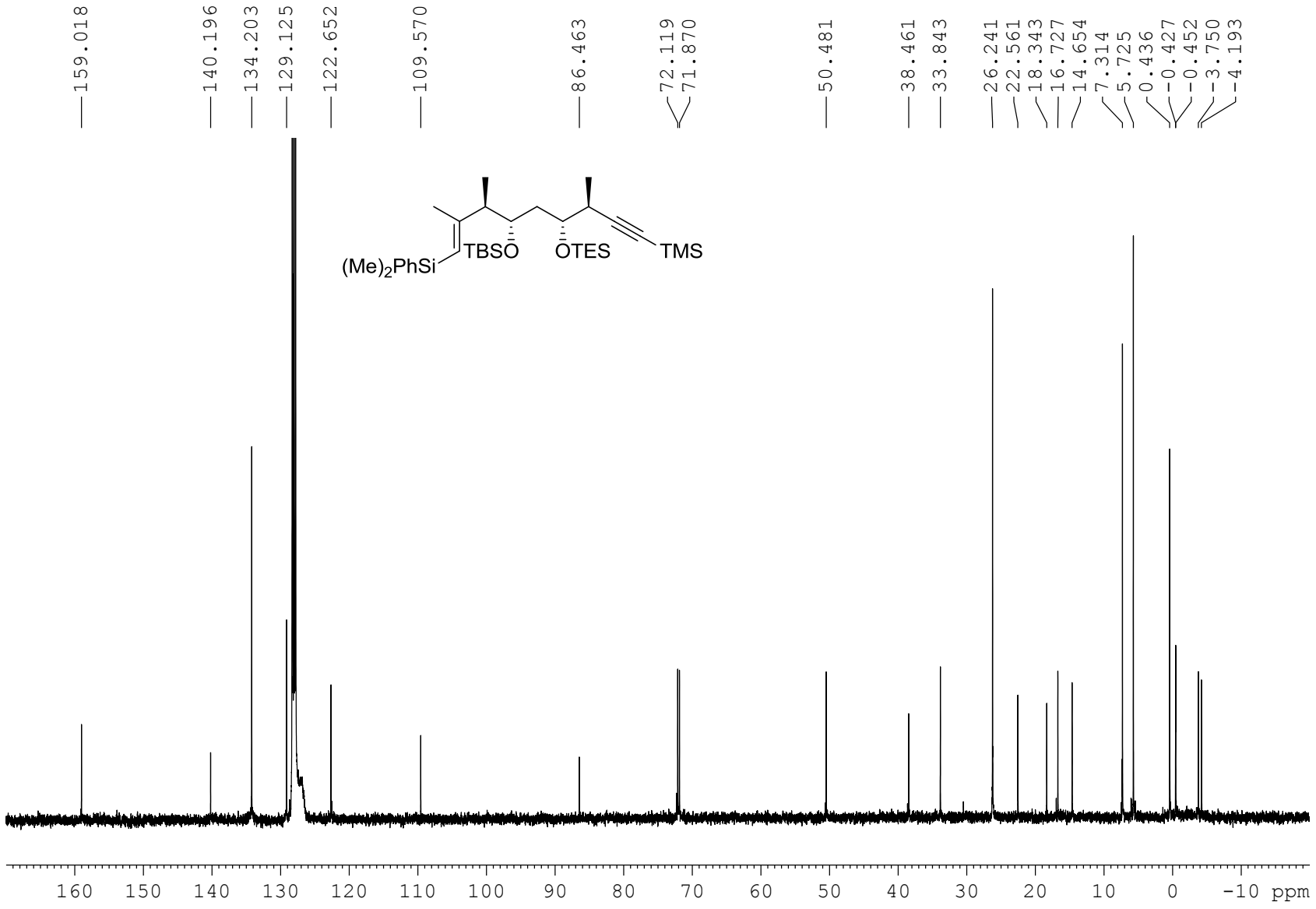


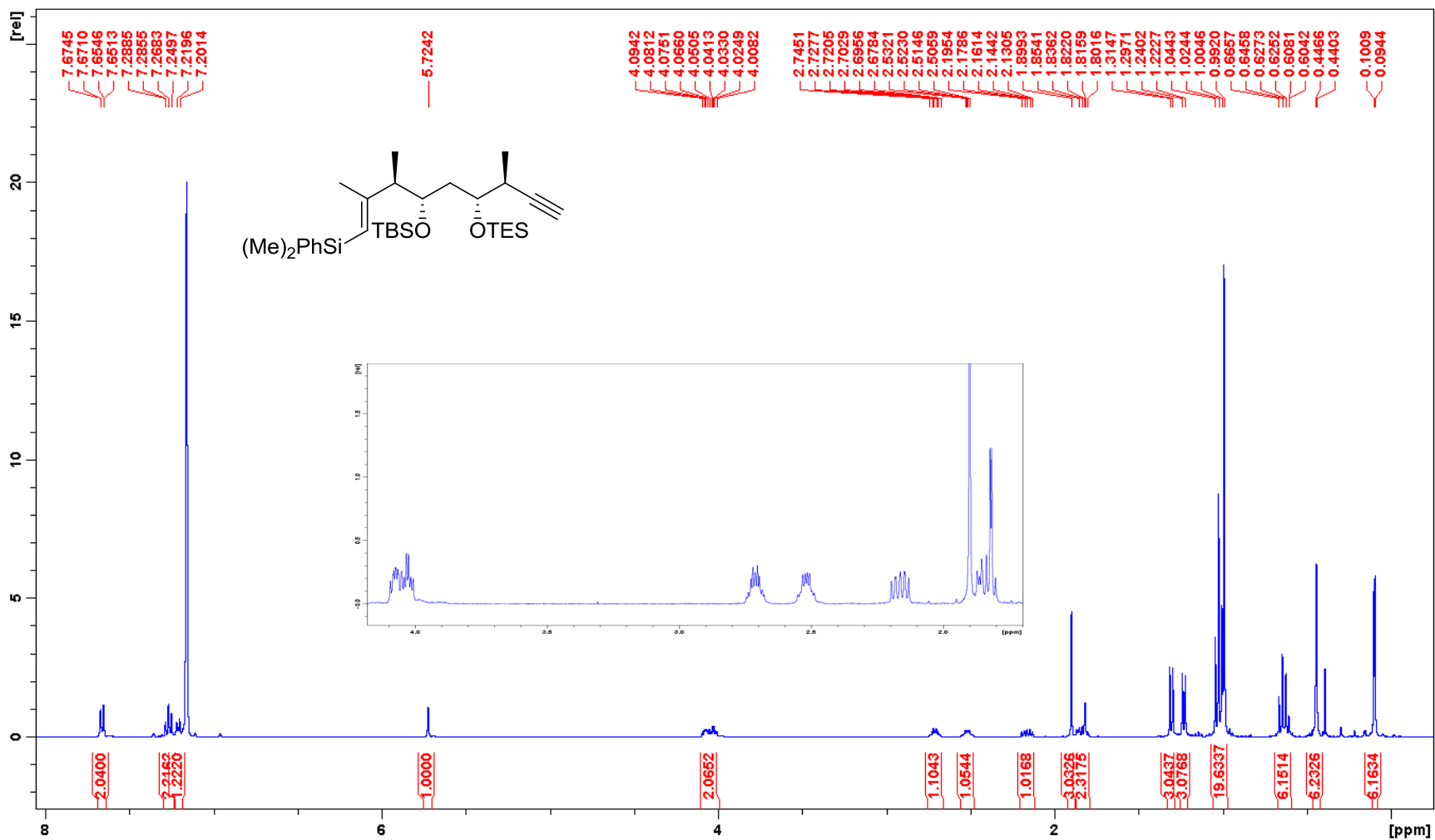


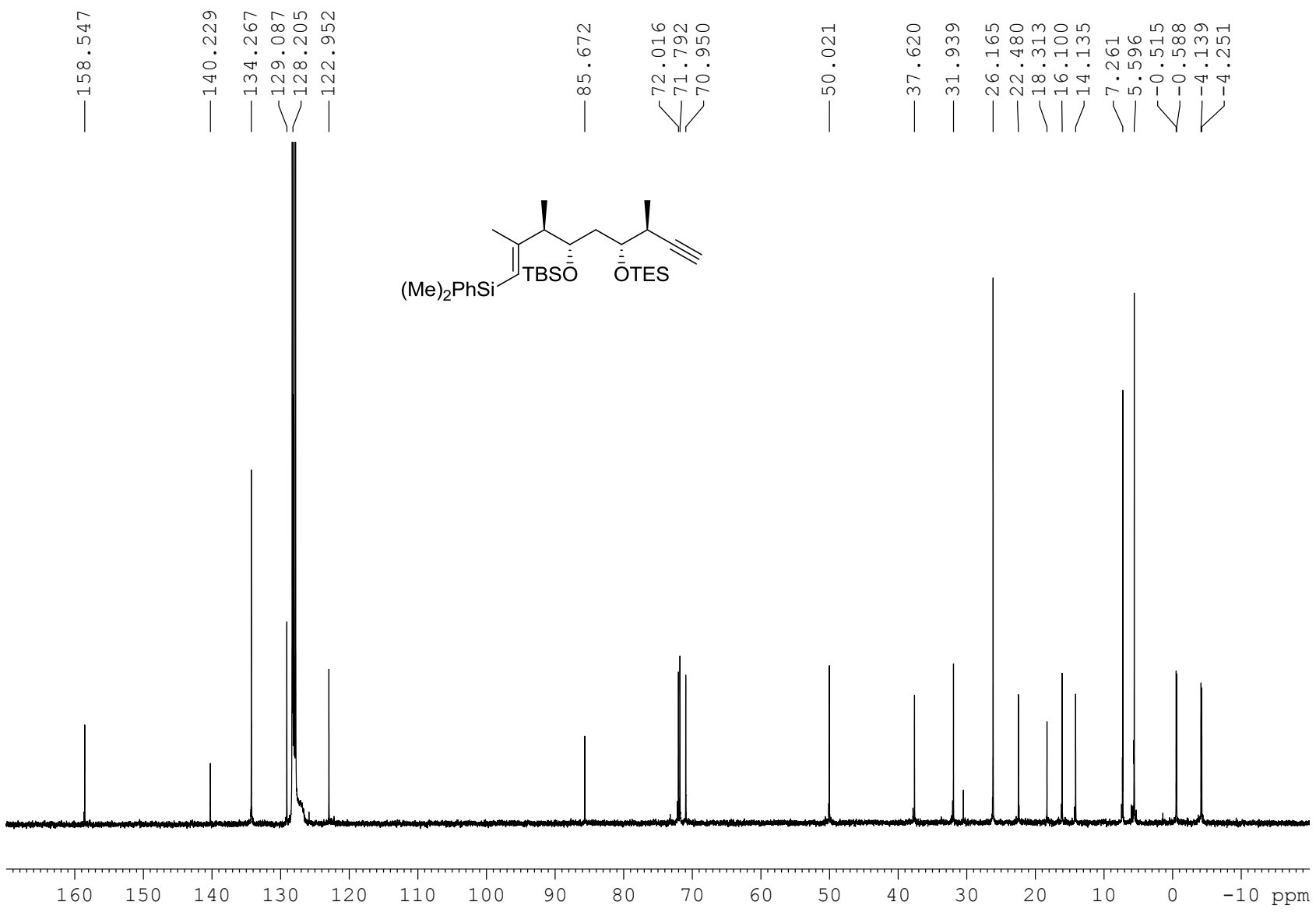


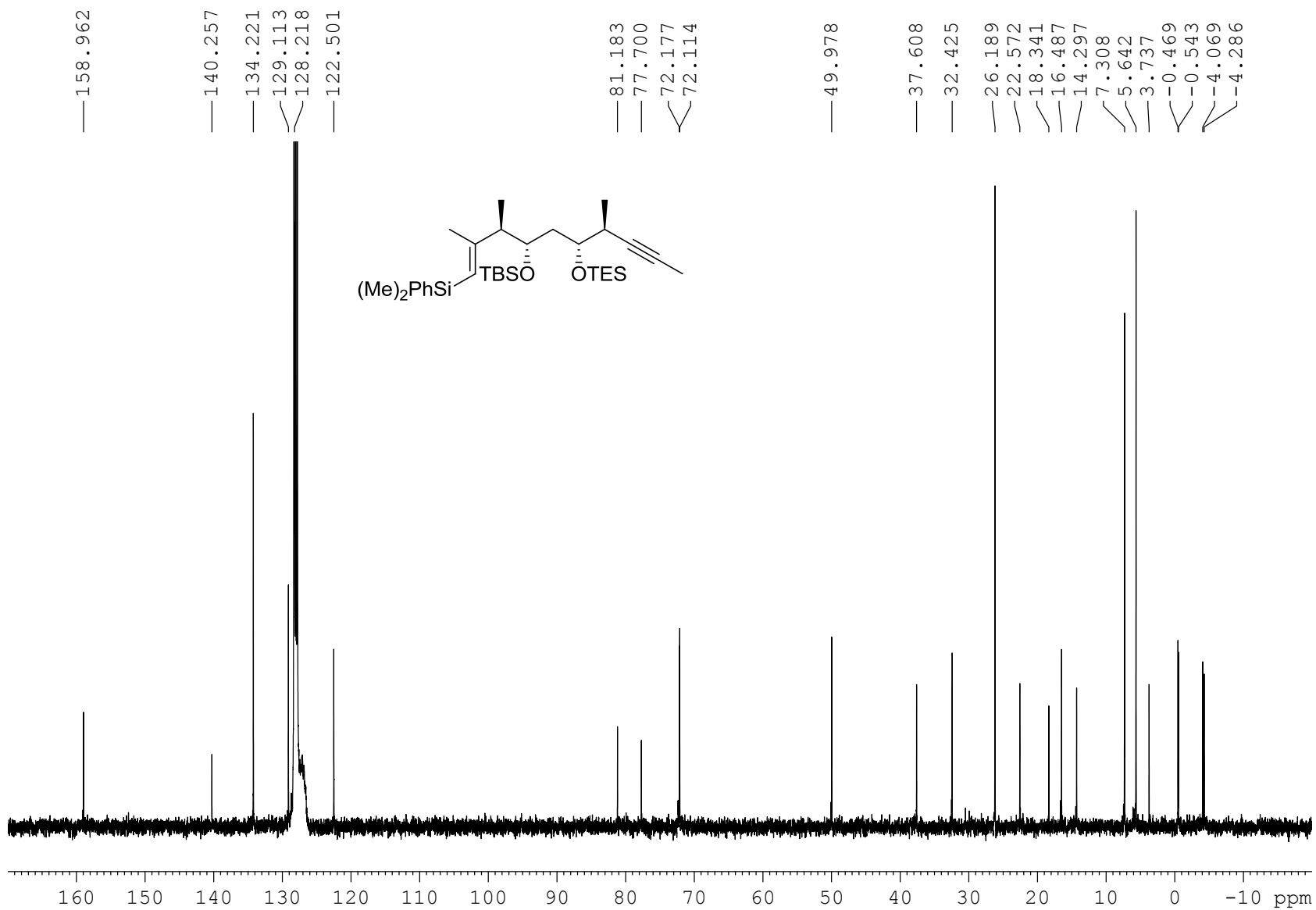


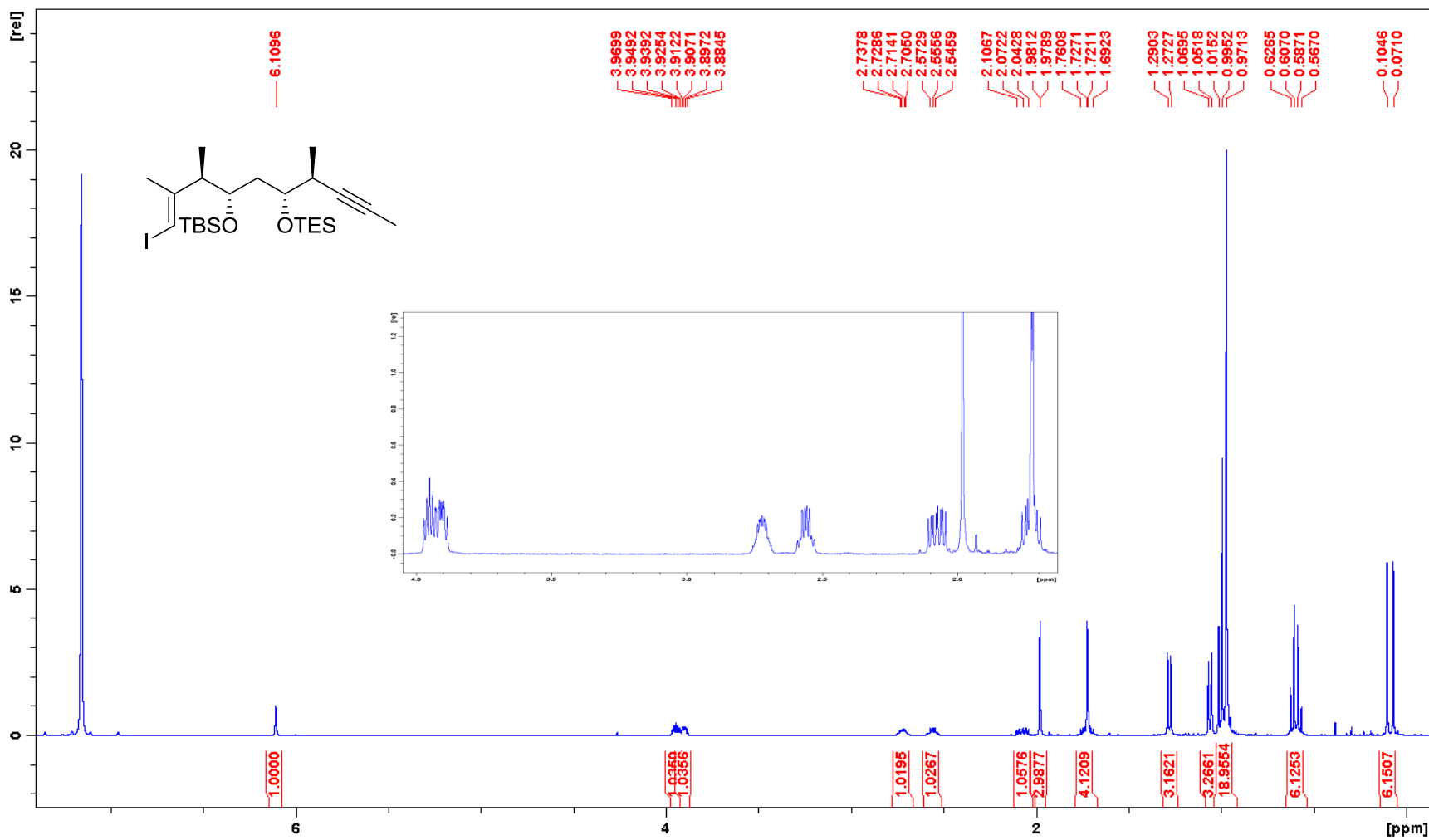


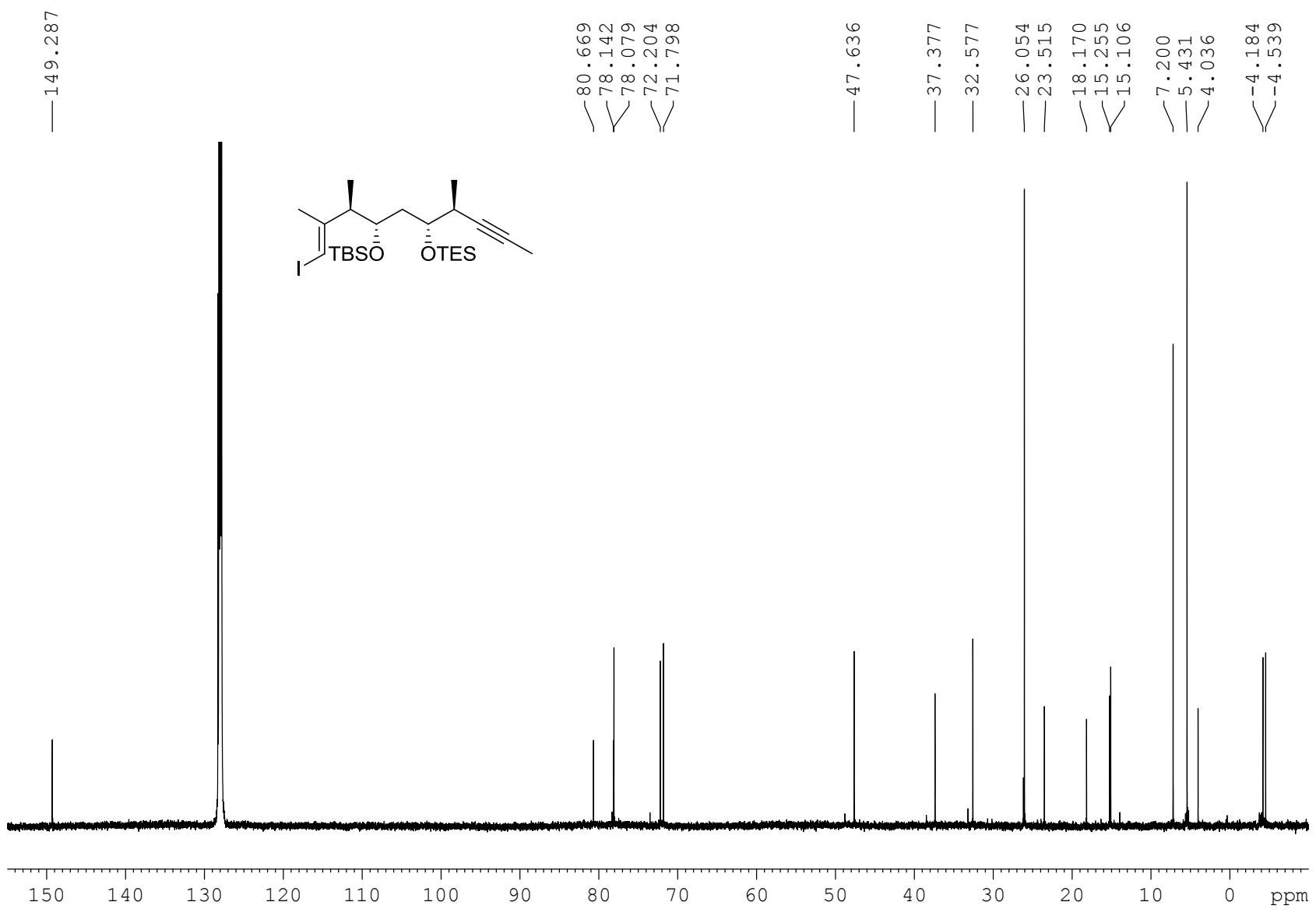


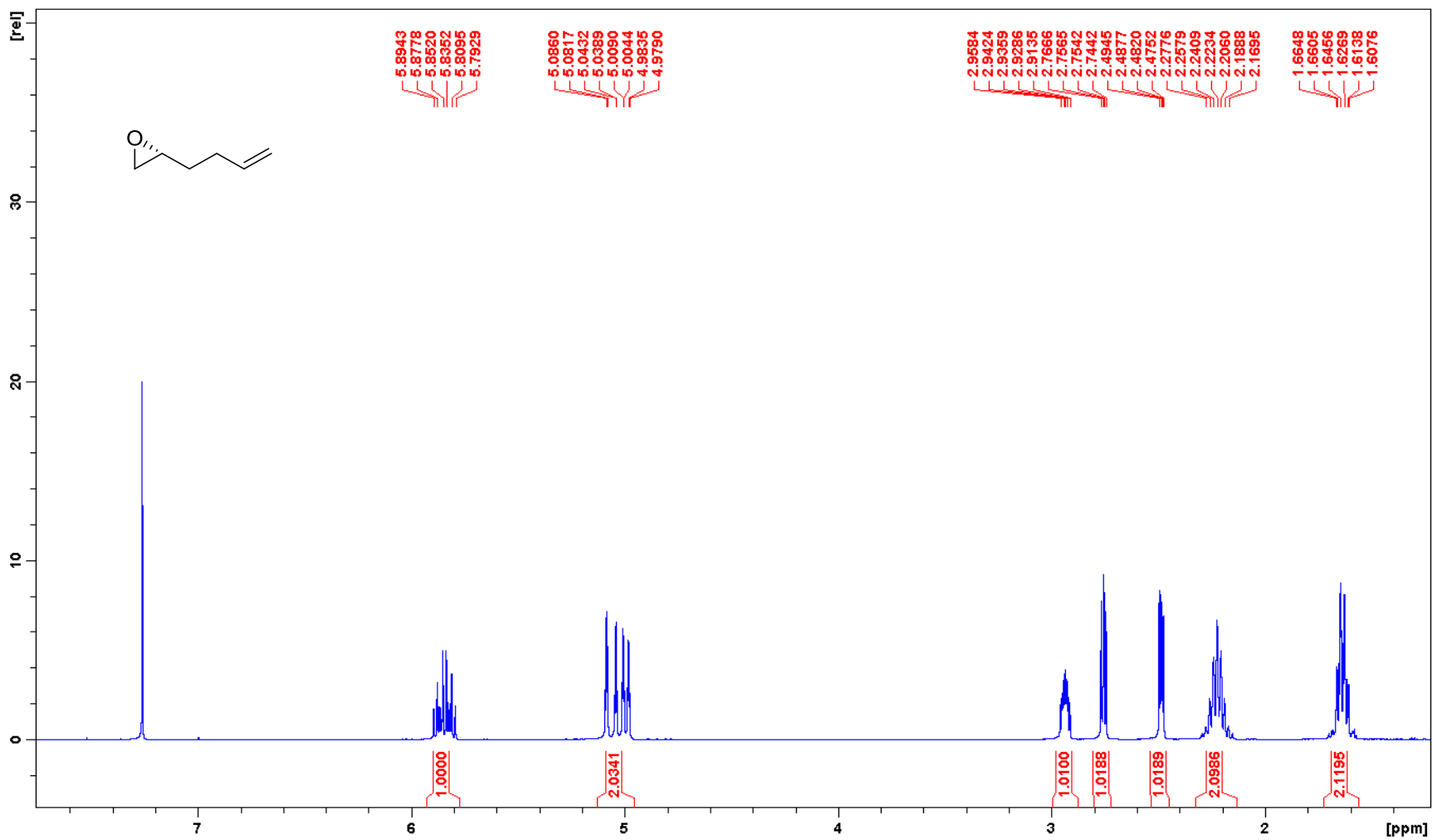


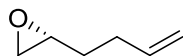












— 137.753

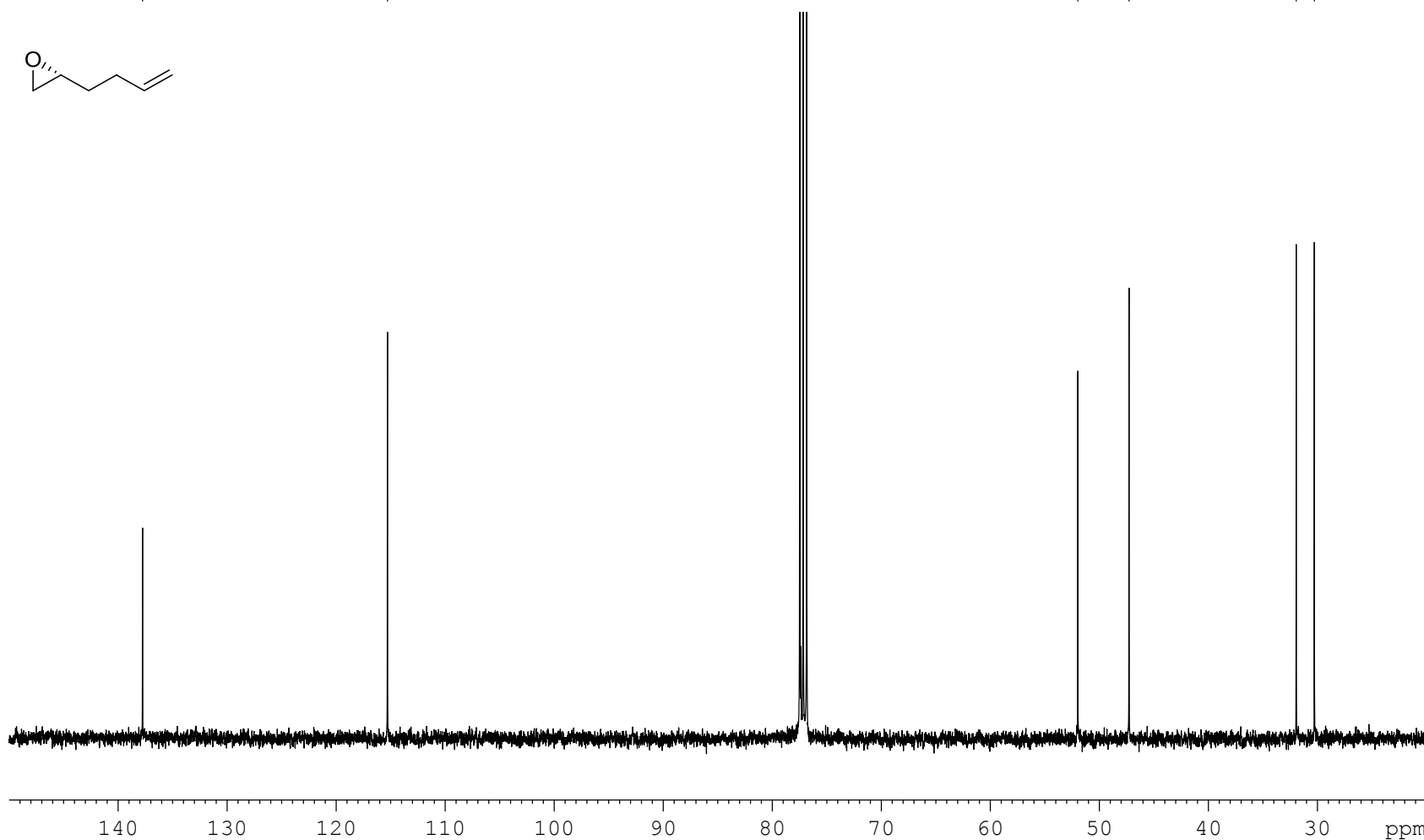
— 115.293

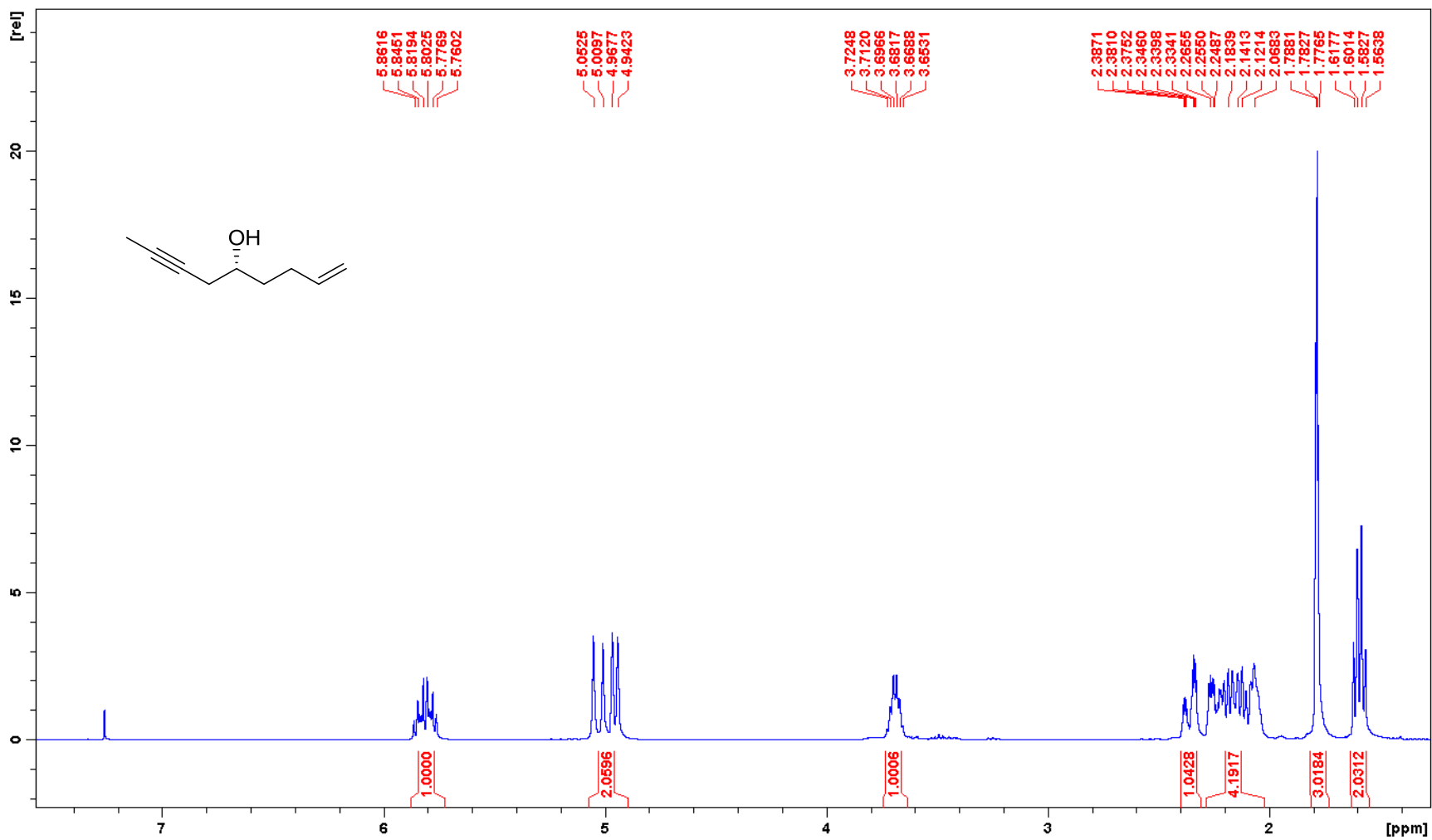
— 51.977

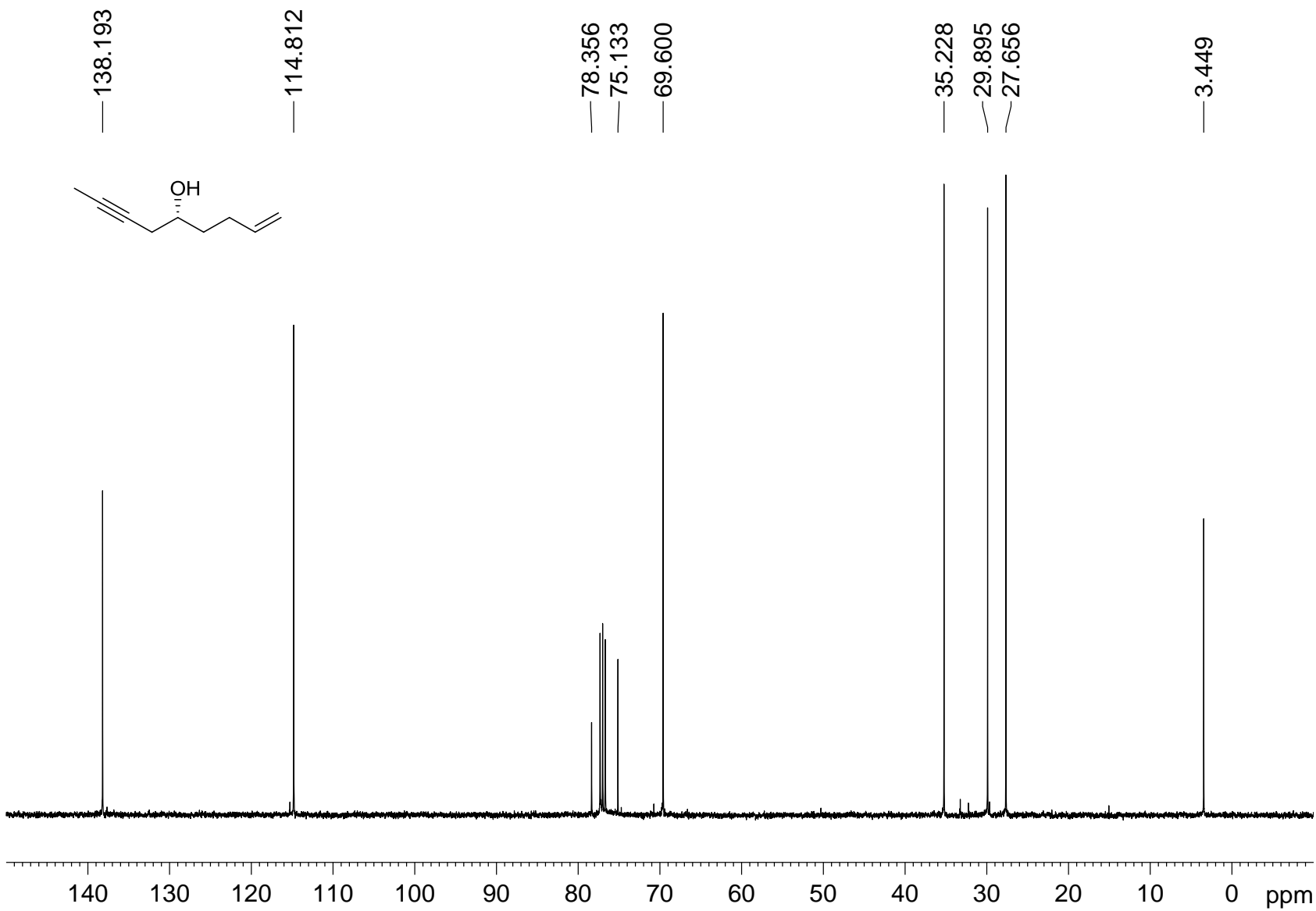
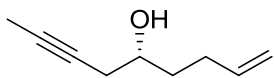
— 47.278

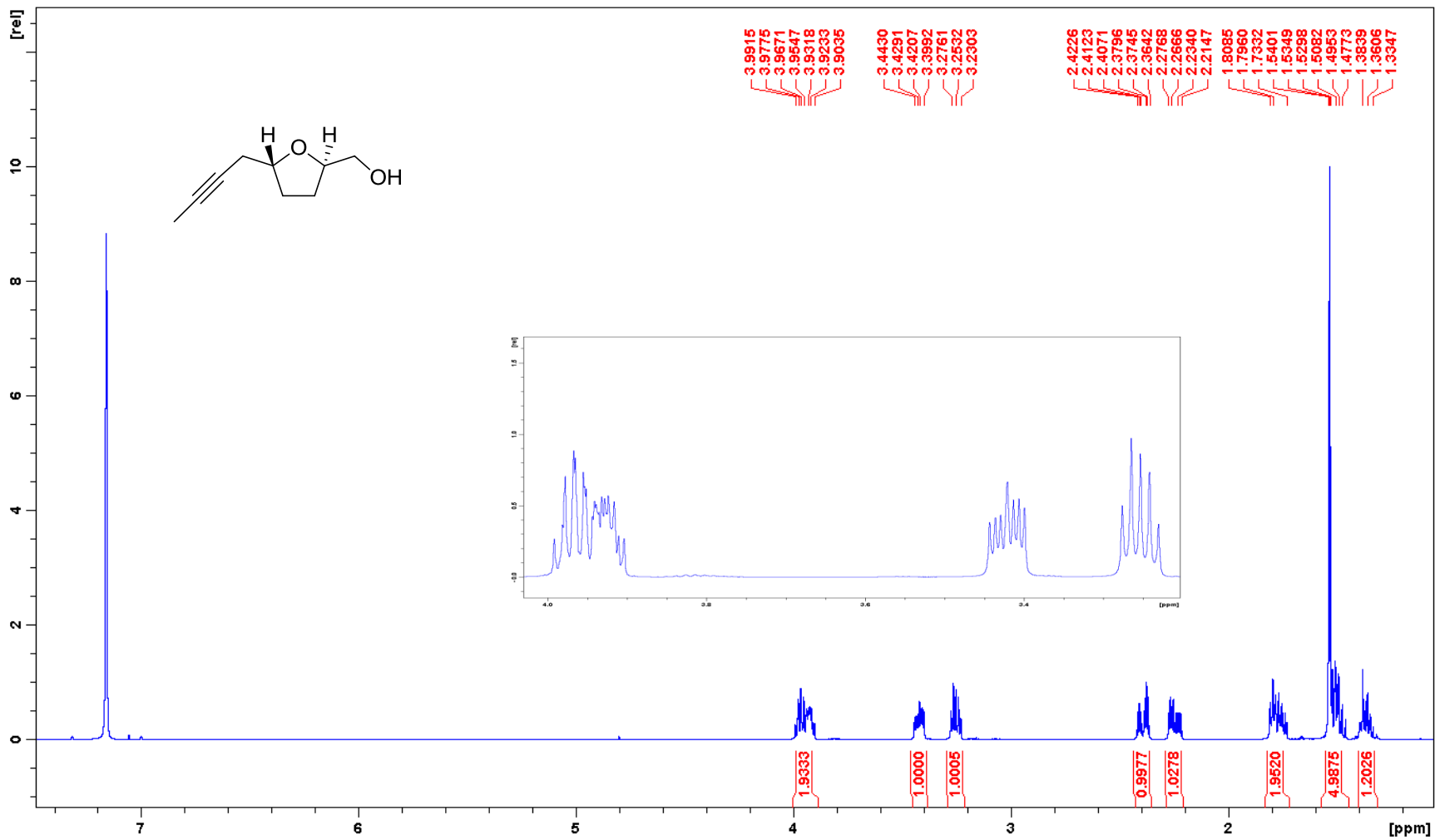
— 31.948

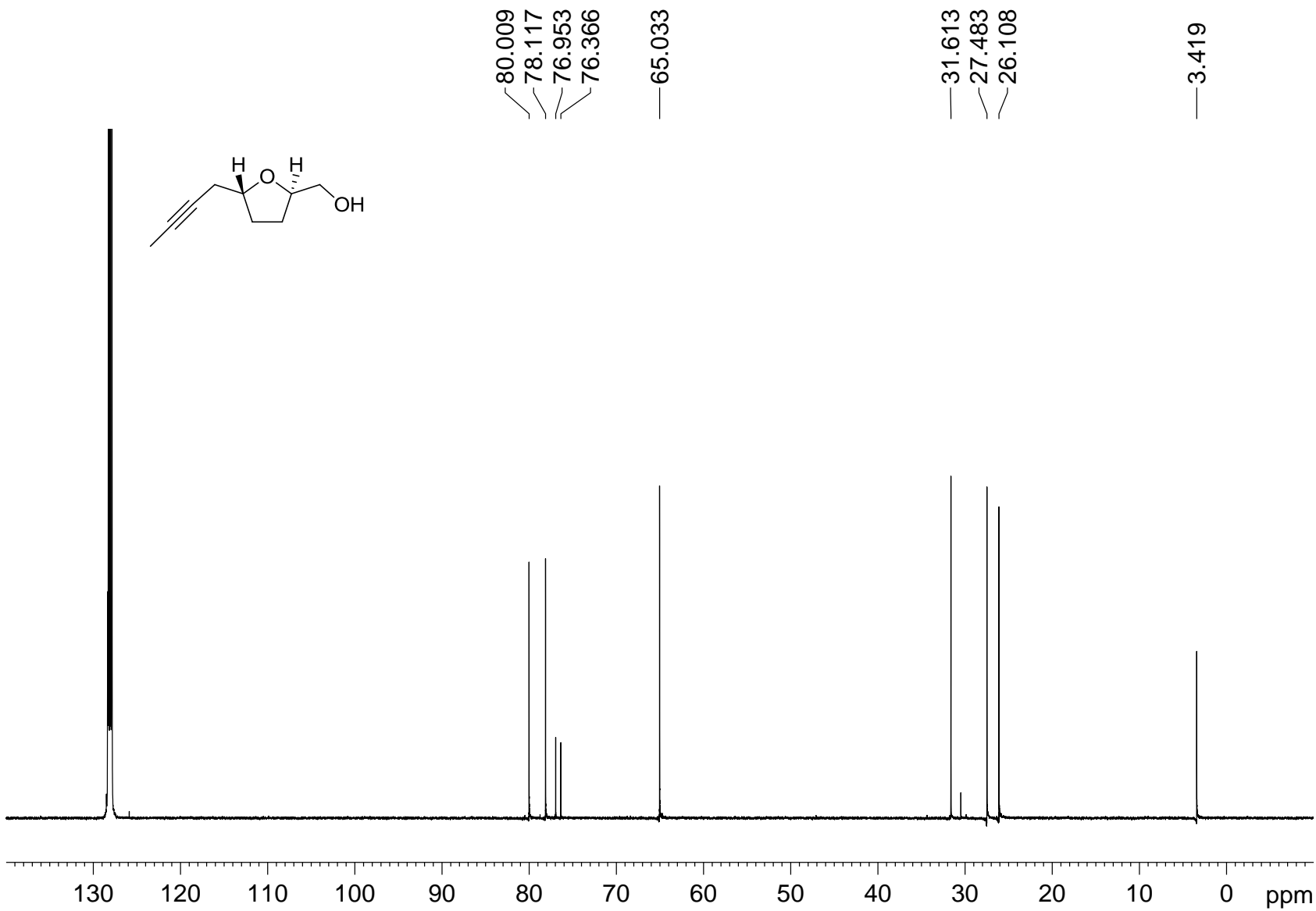
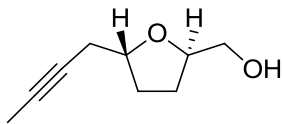
— 30.282

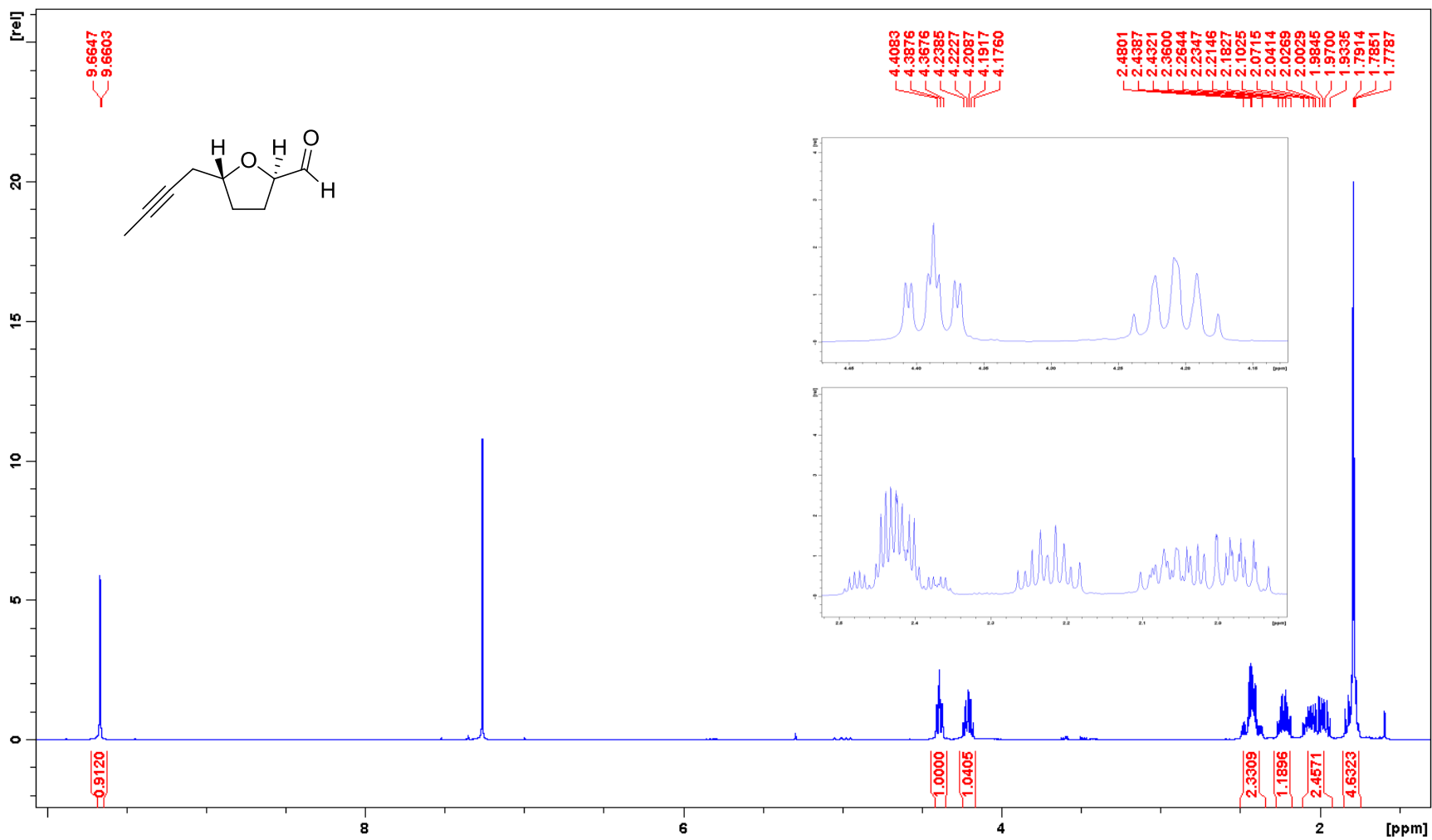




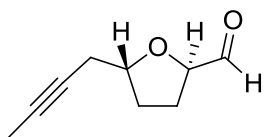








—202.800



83.362
79.462
77.364
75.085

30.441
27.328
25.471

—3.666



200

180

160

140

120

100

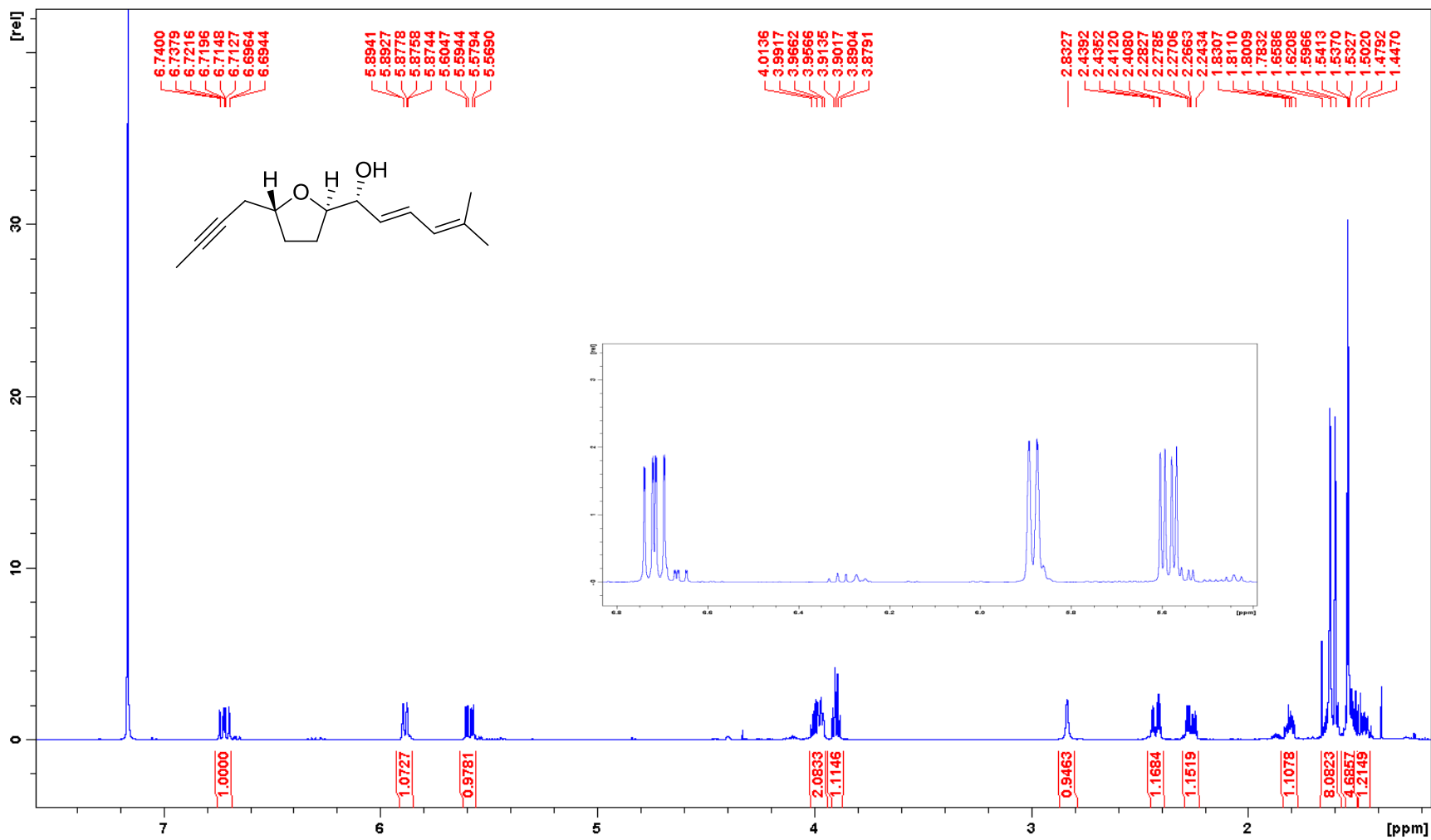
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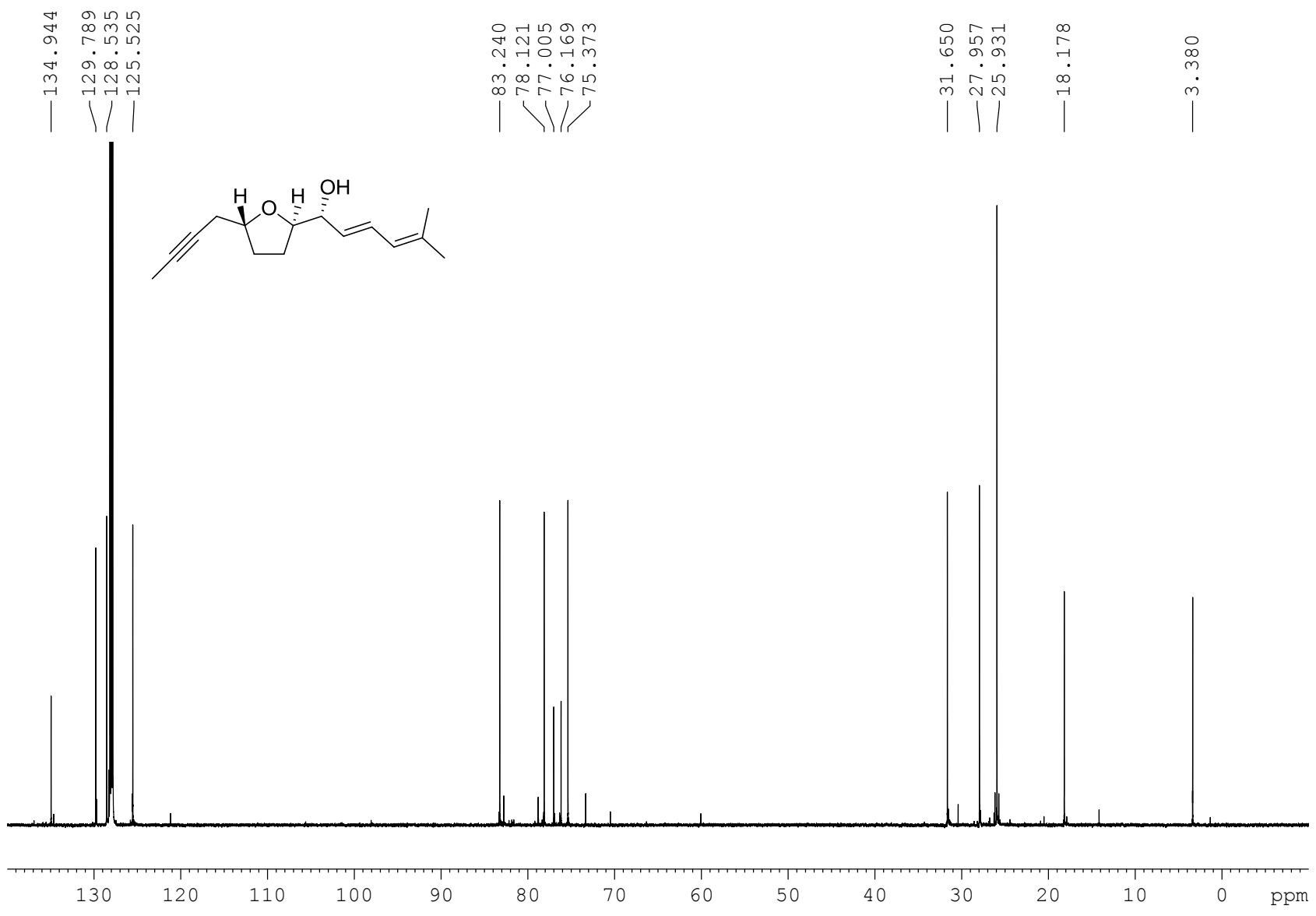
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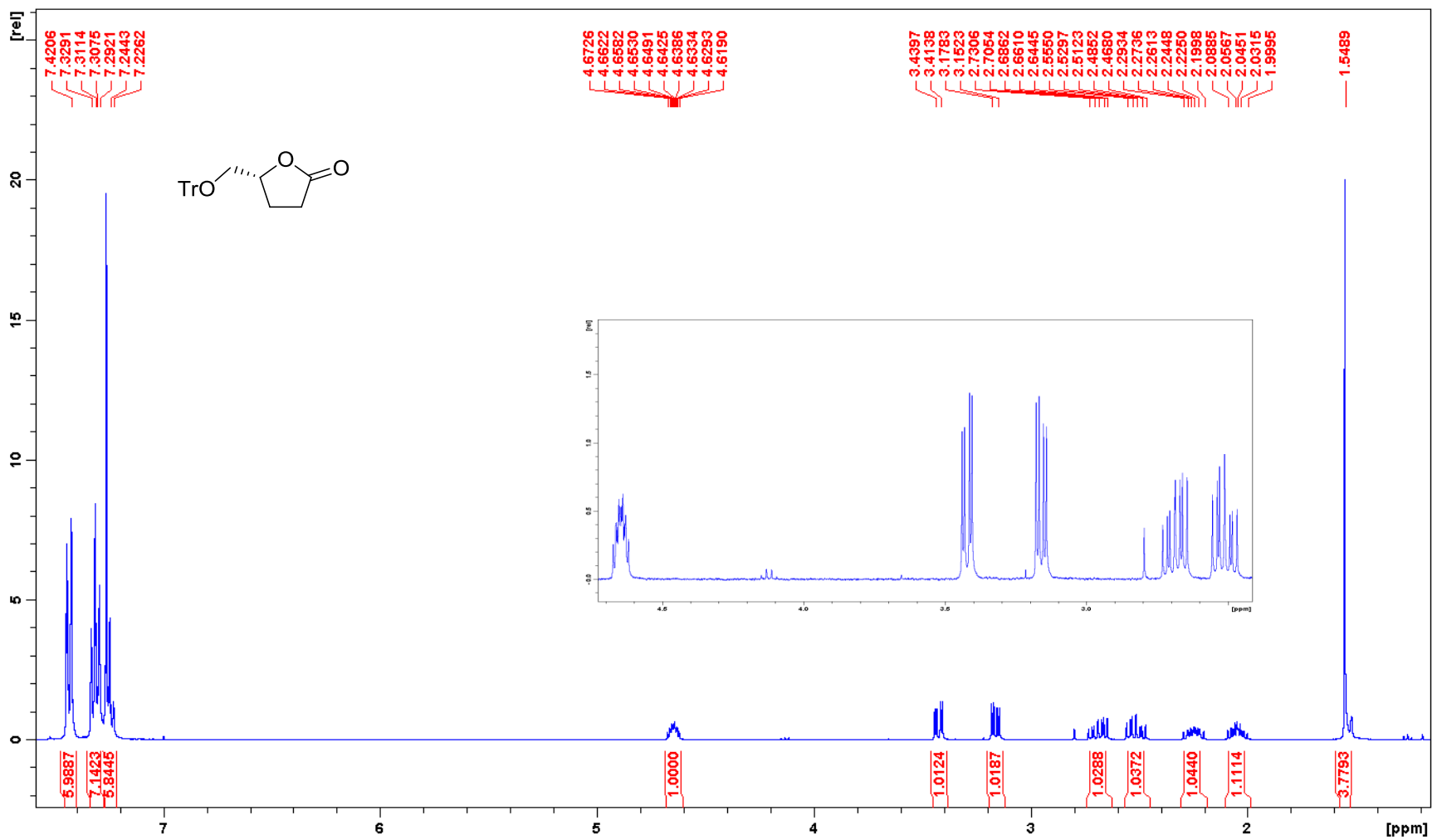
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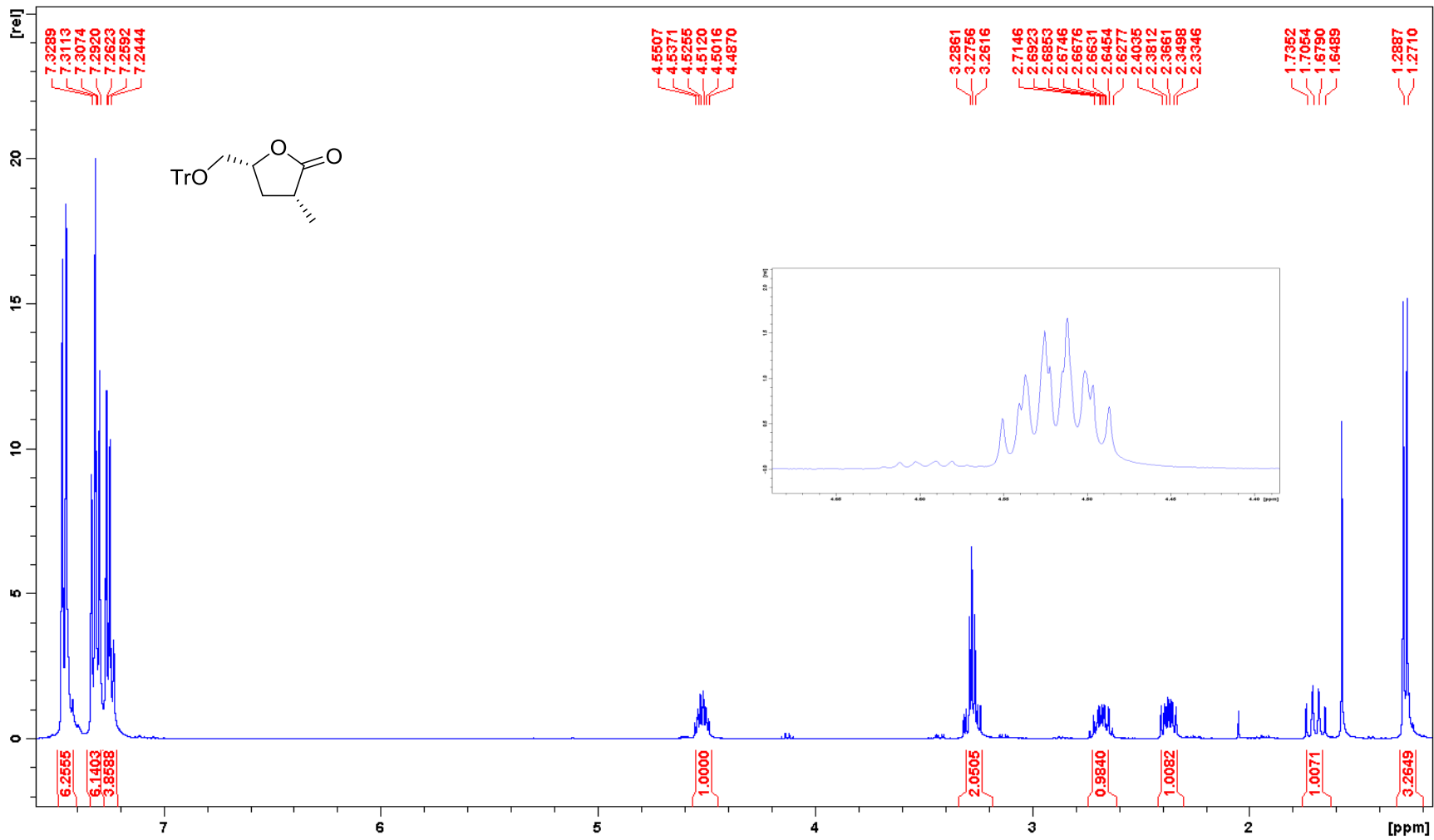
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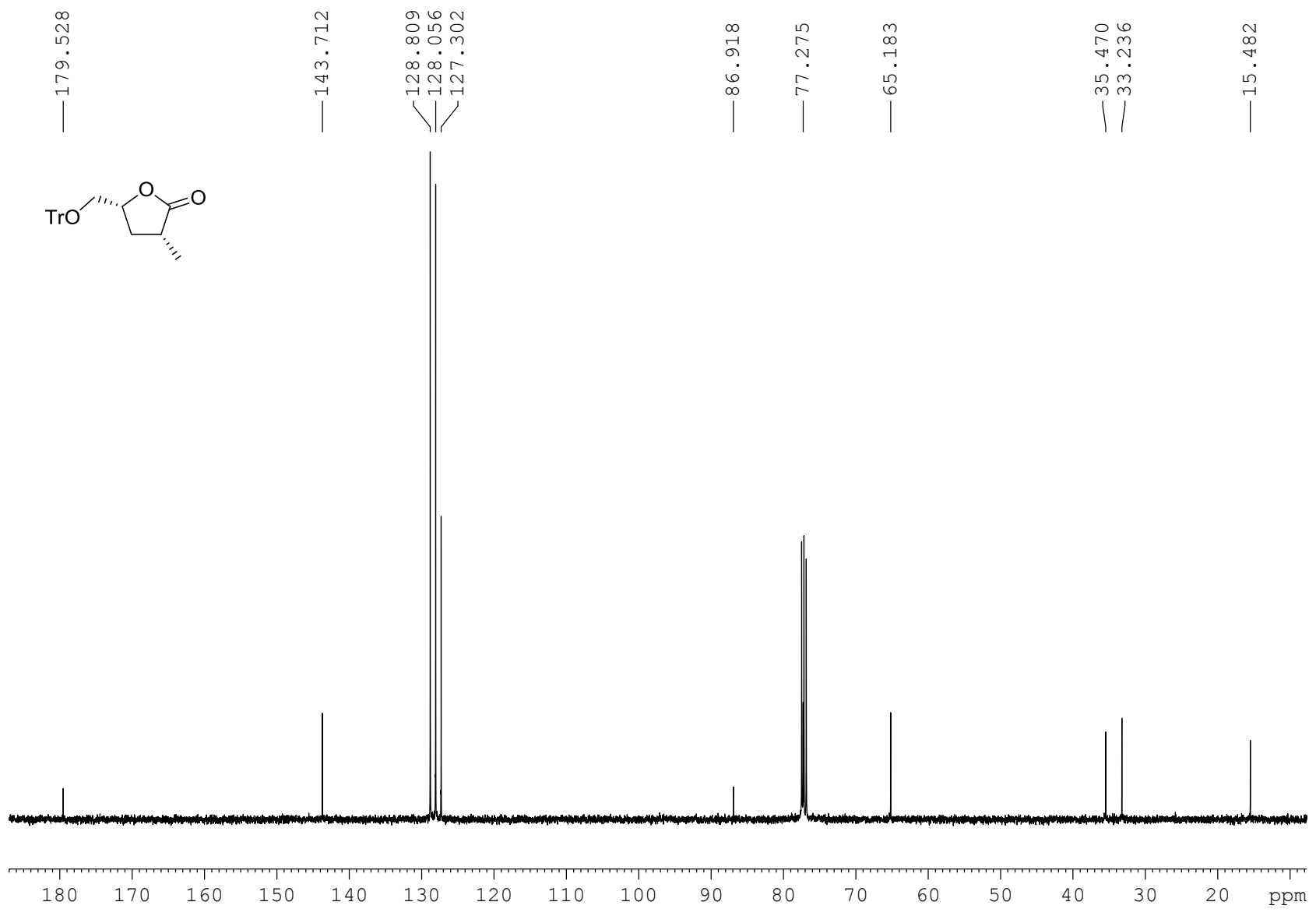
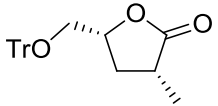
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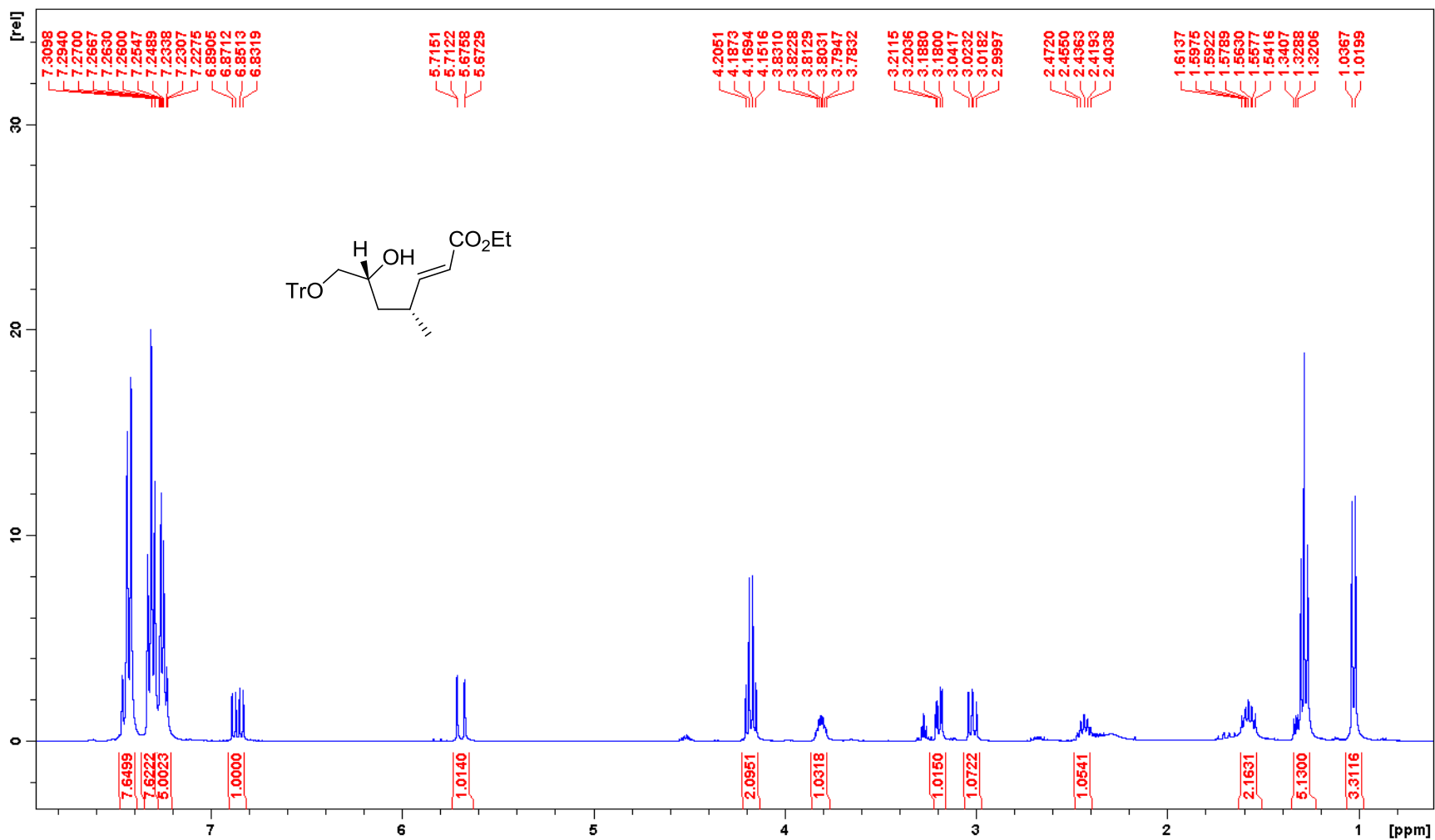


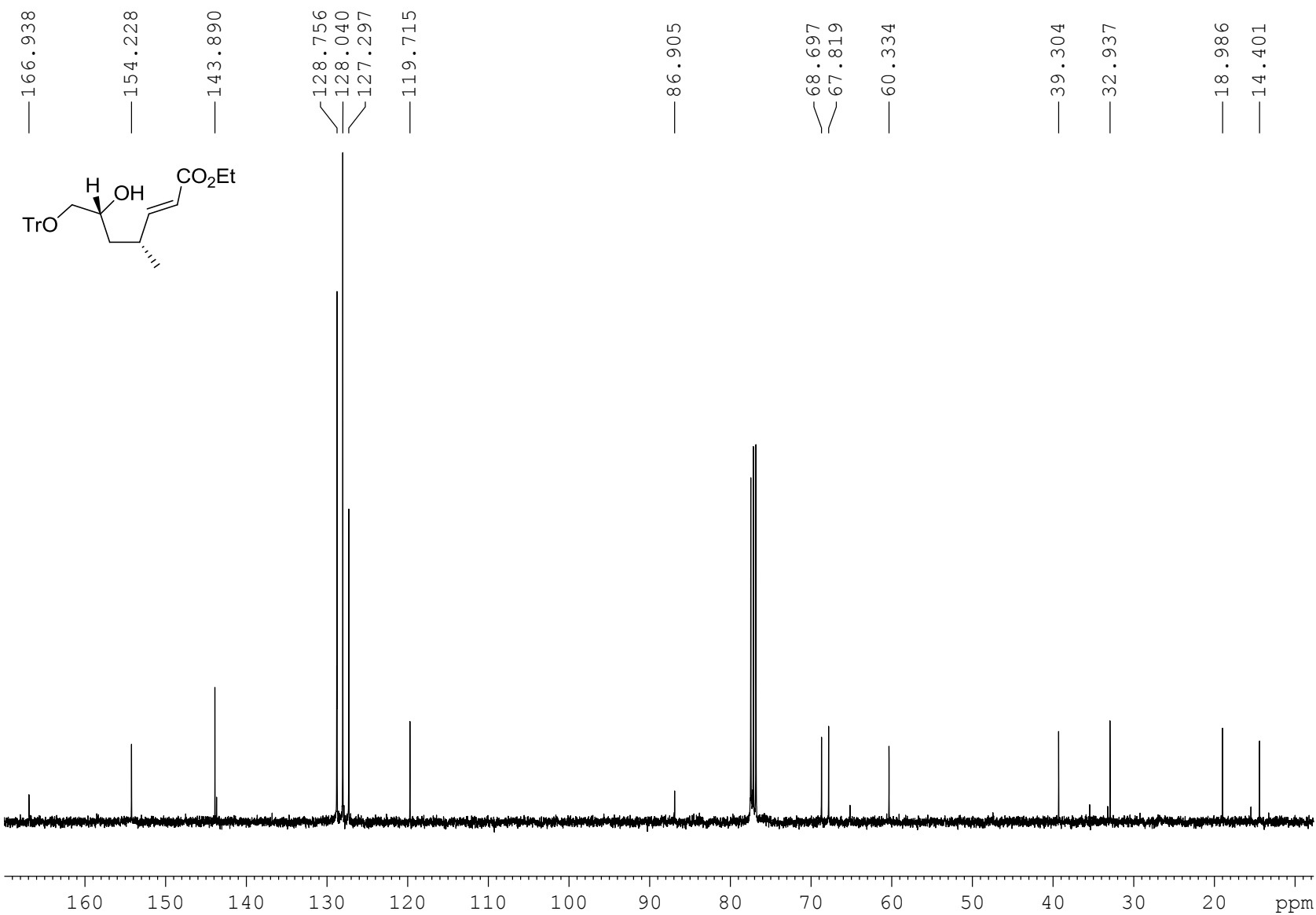


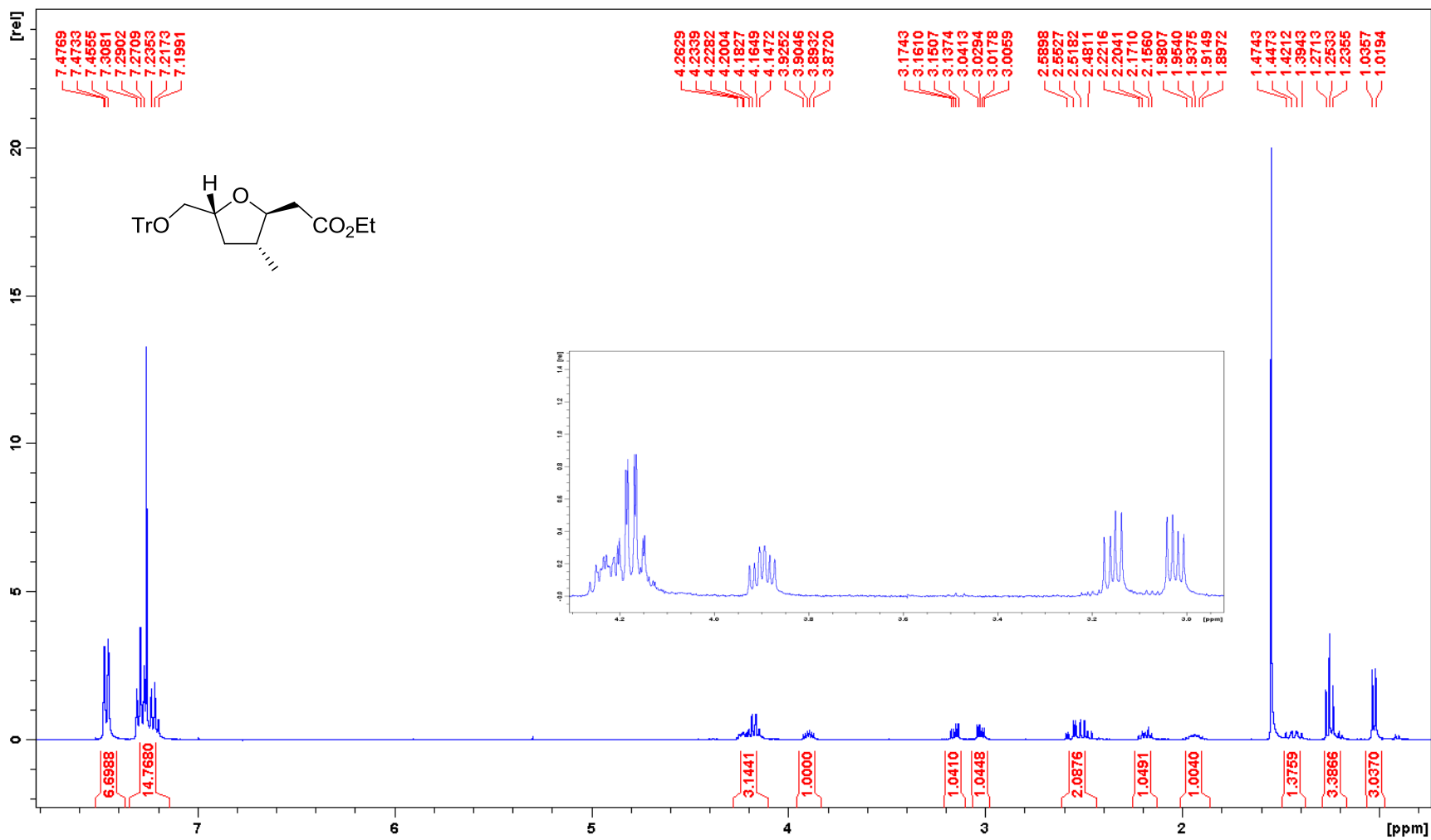


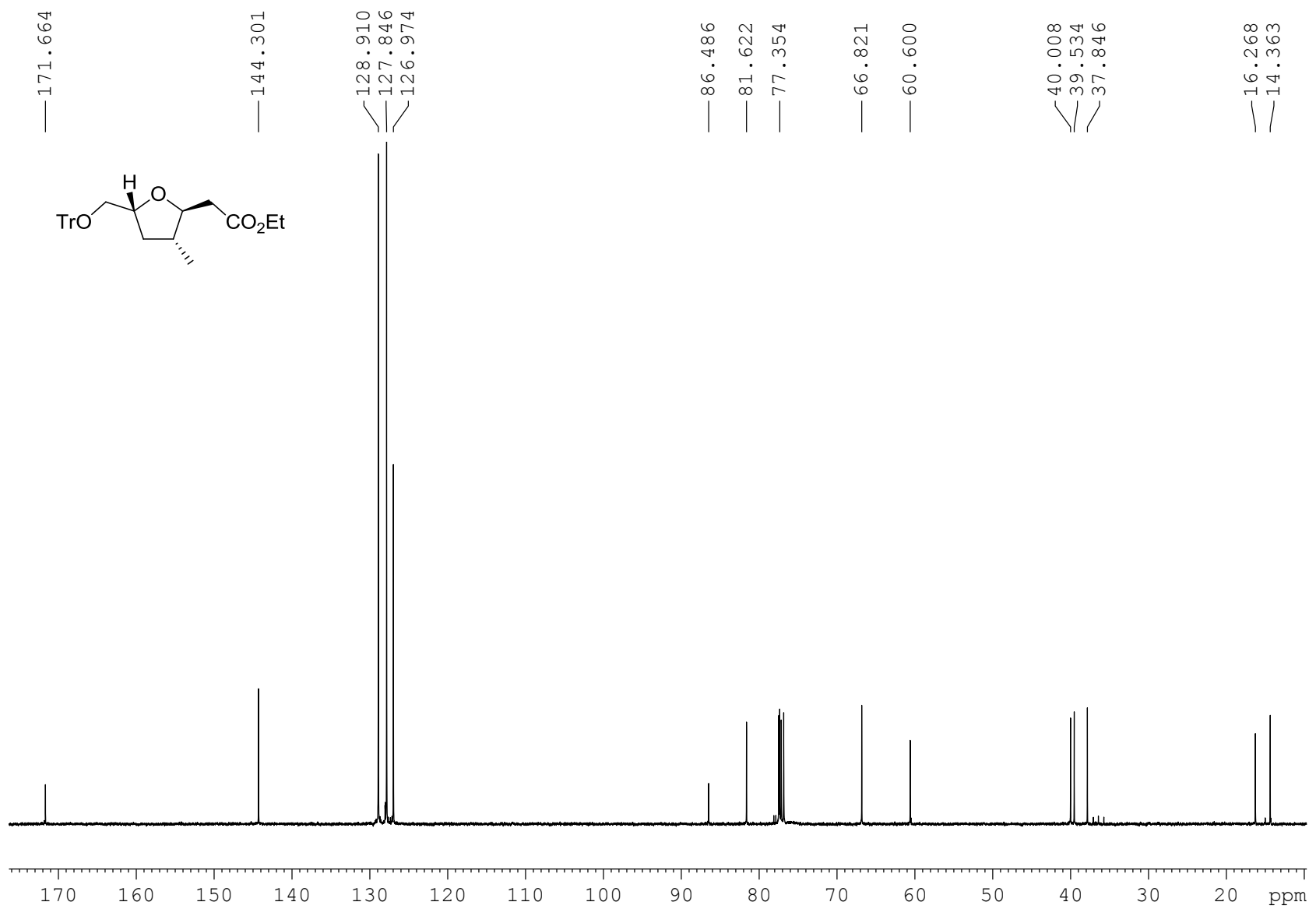


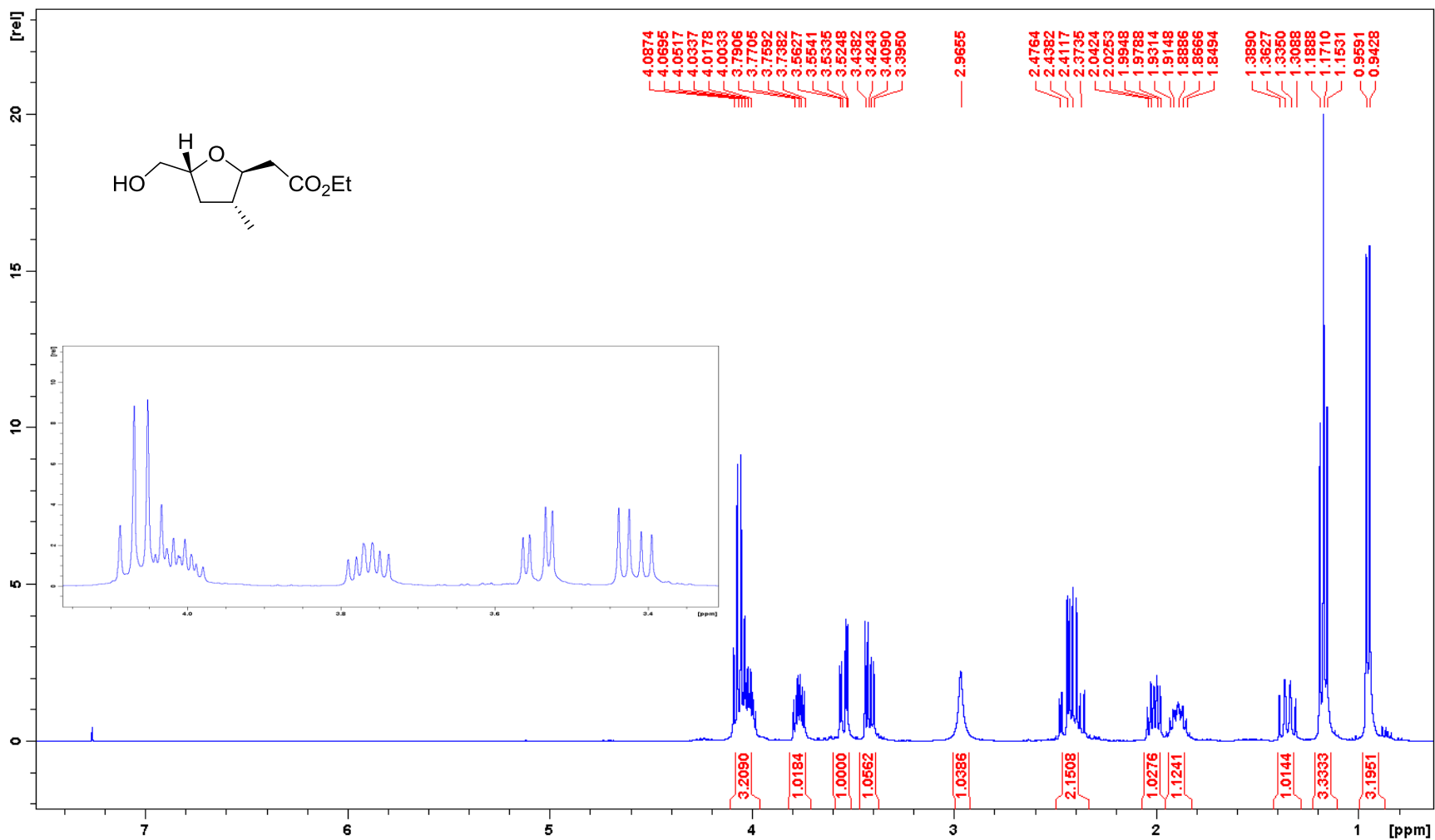




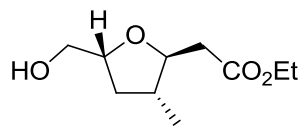








—171.524

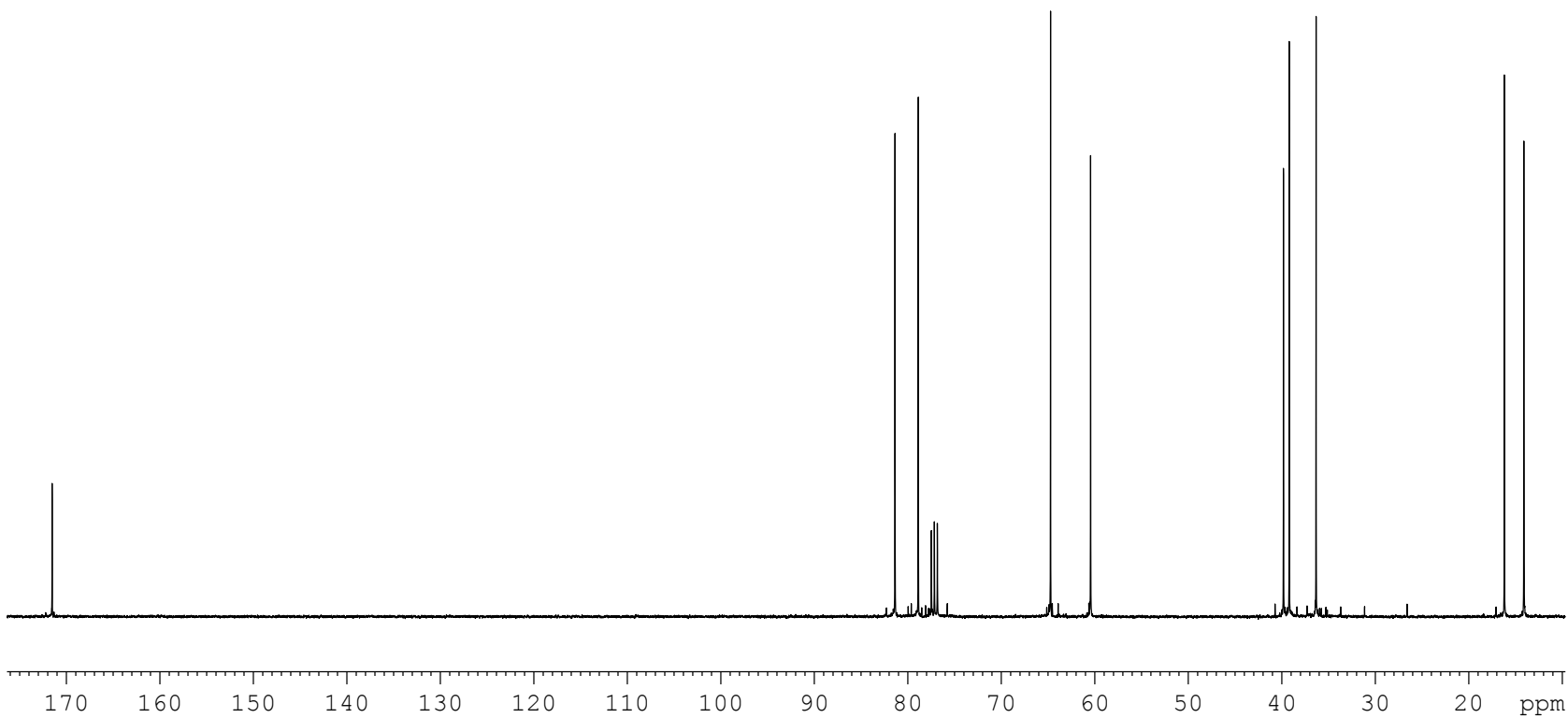


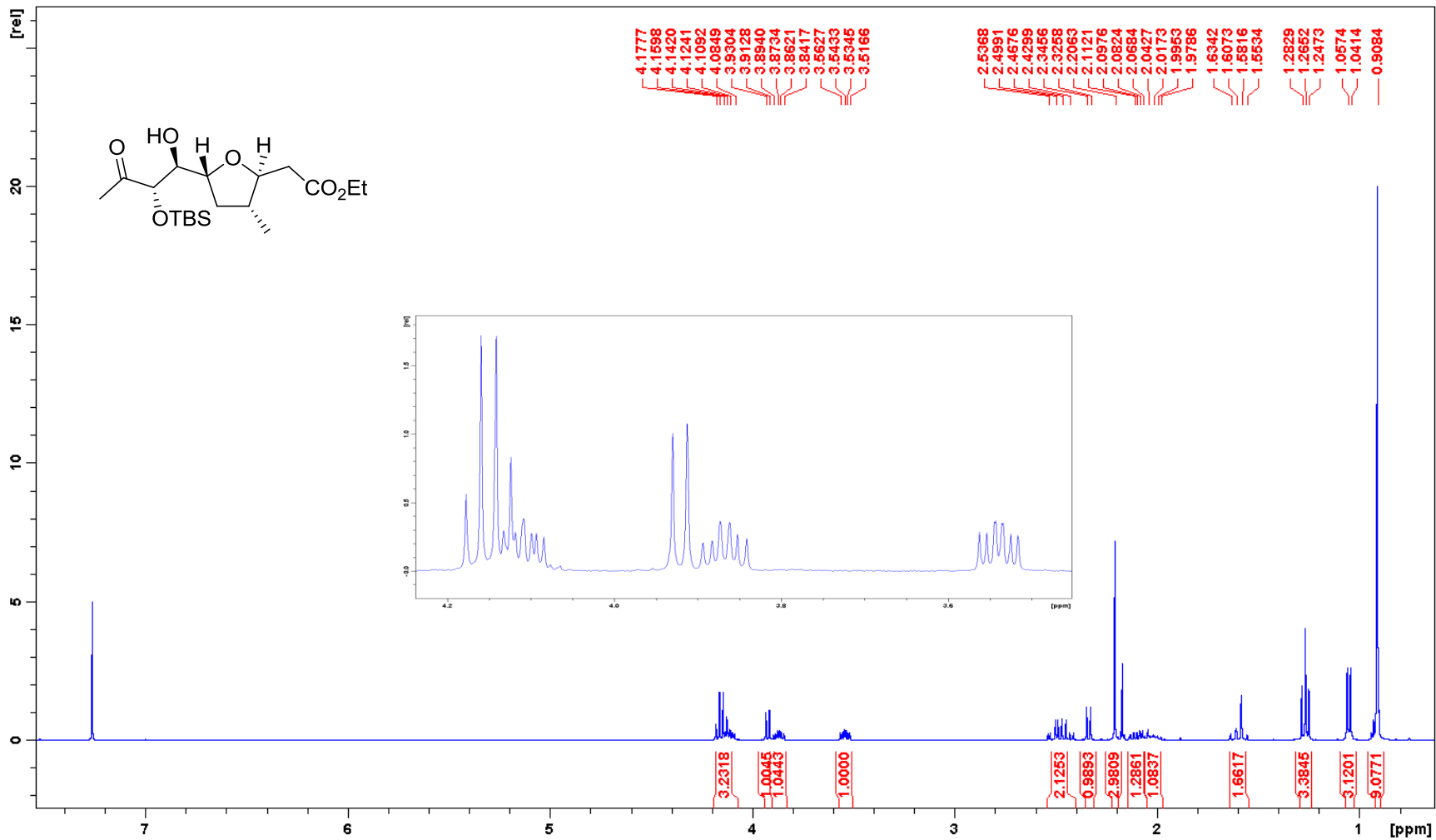
—81.368
—78.876

—64.732
—60.446

—39.820
—39.203
—36.330

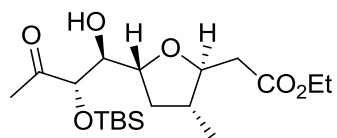
—16.193
—14.105





— 210.416

— 171.269



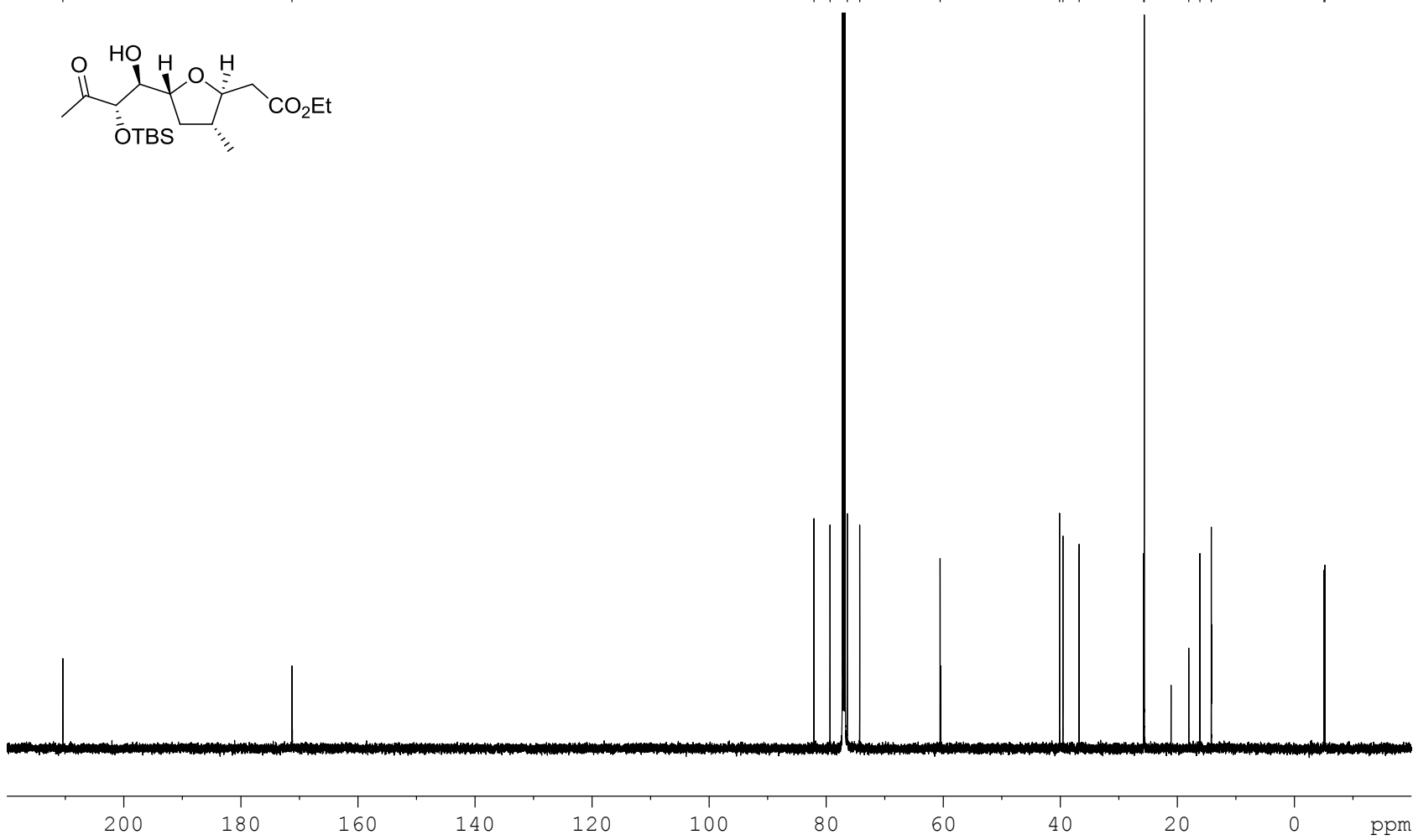
82.081
79.335
76.394
74.271

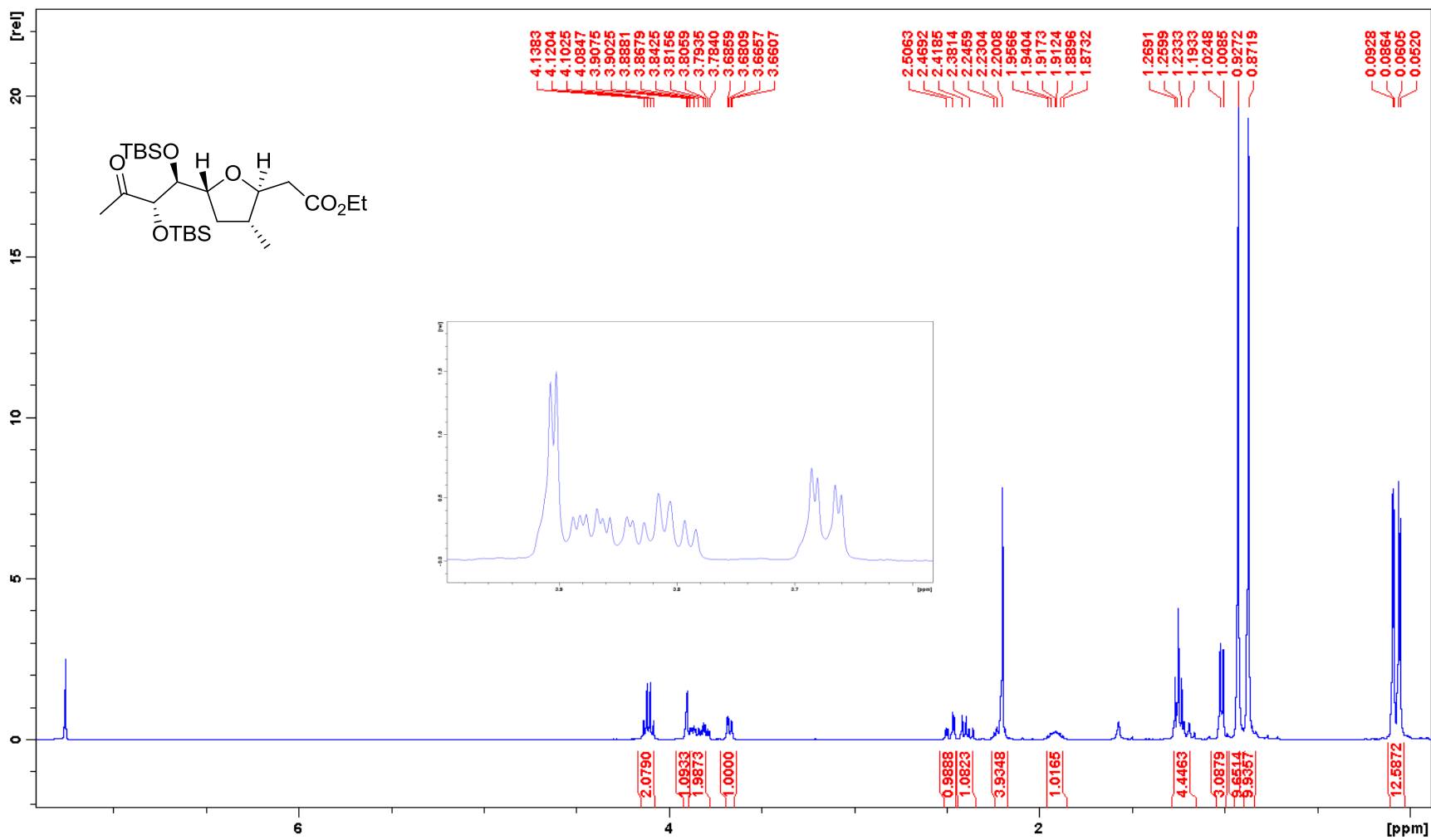
— 60.528

40.123
39.549
36.778

25.745
25.656
18.045
16.148
14.206

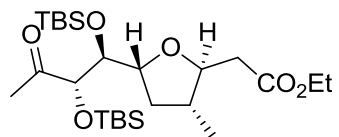
< -5.050
< -5.214





— 212.164

— 171.709

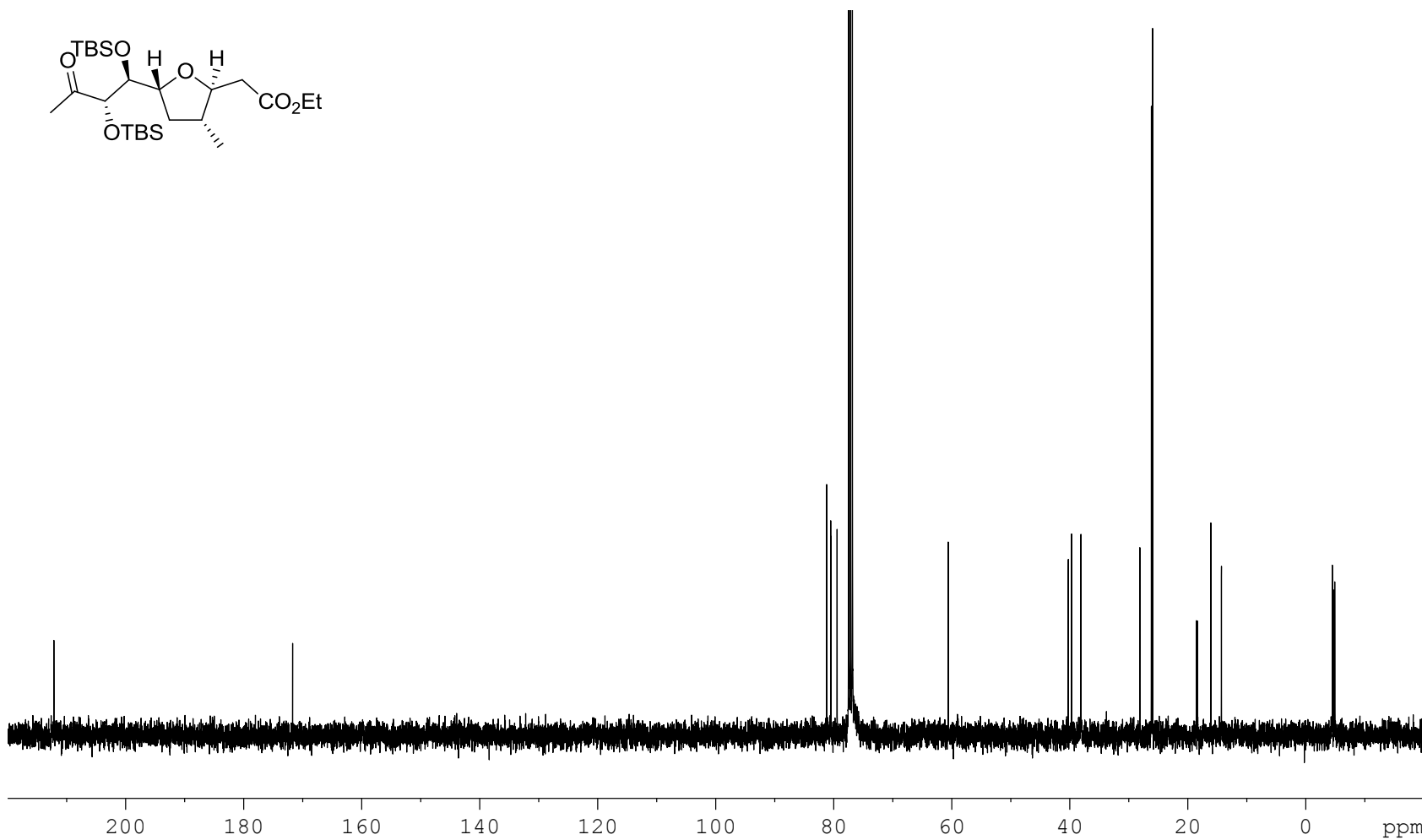


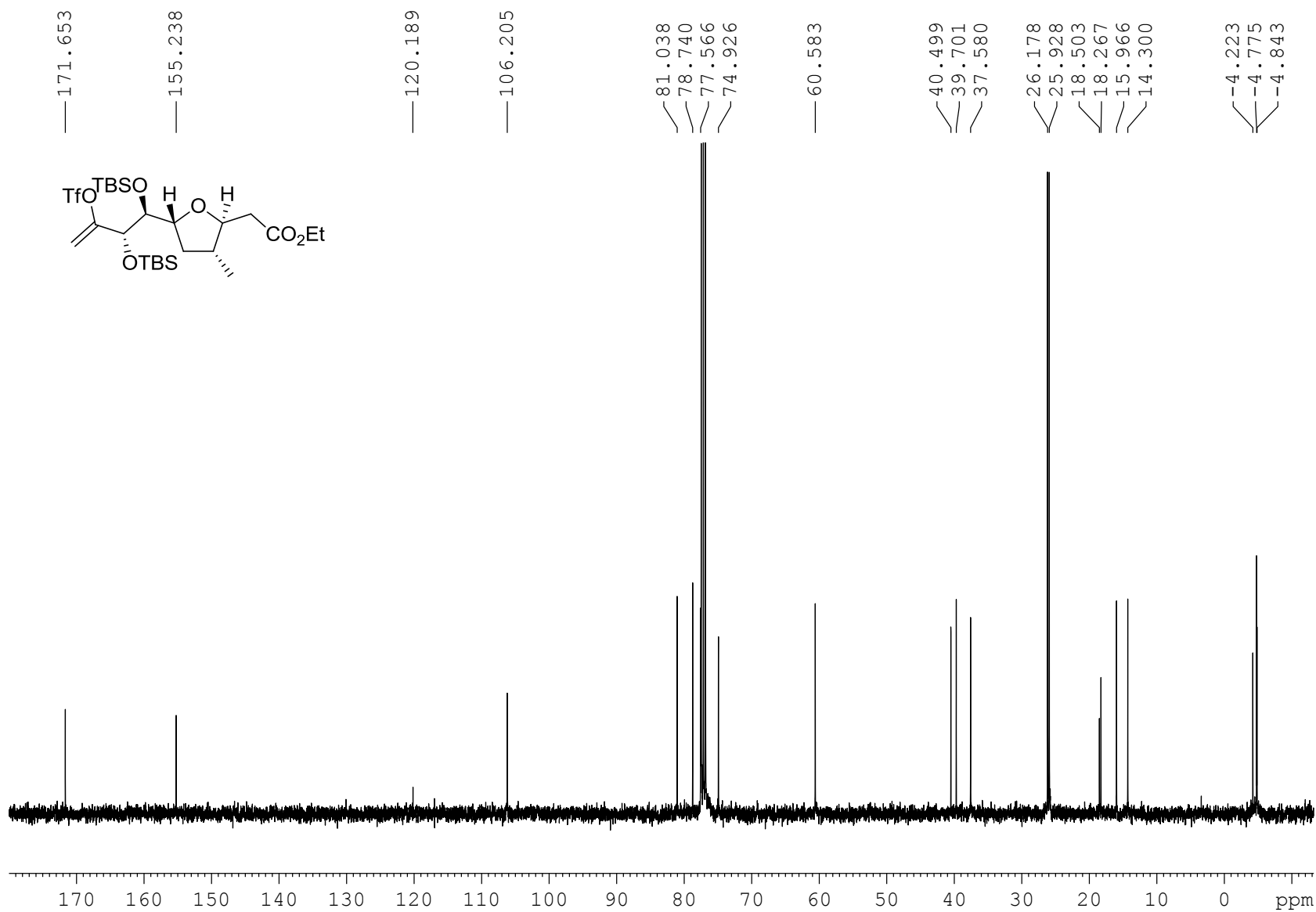
81.206
80.514
80.463
79.436

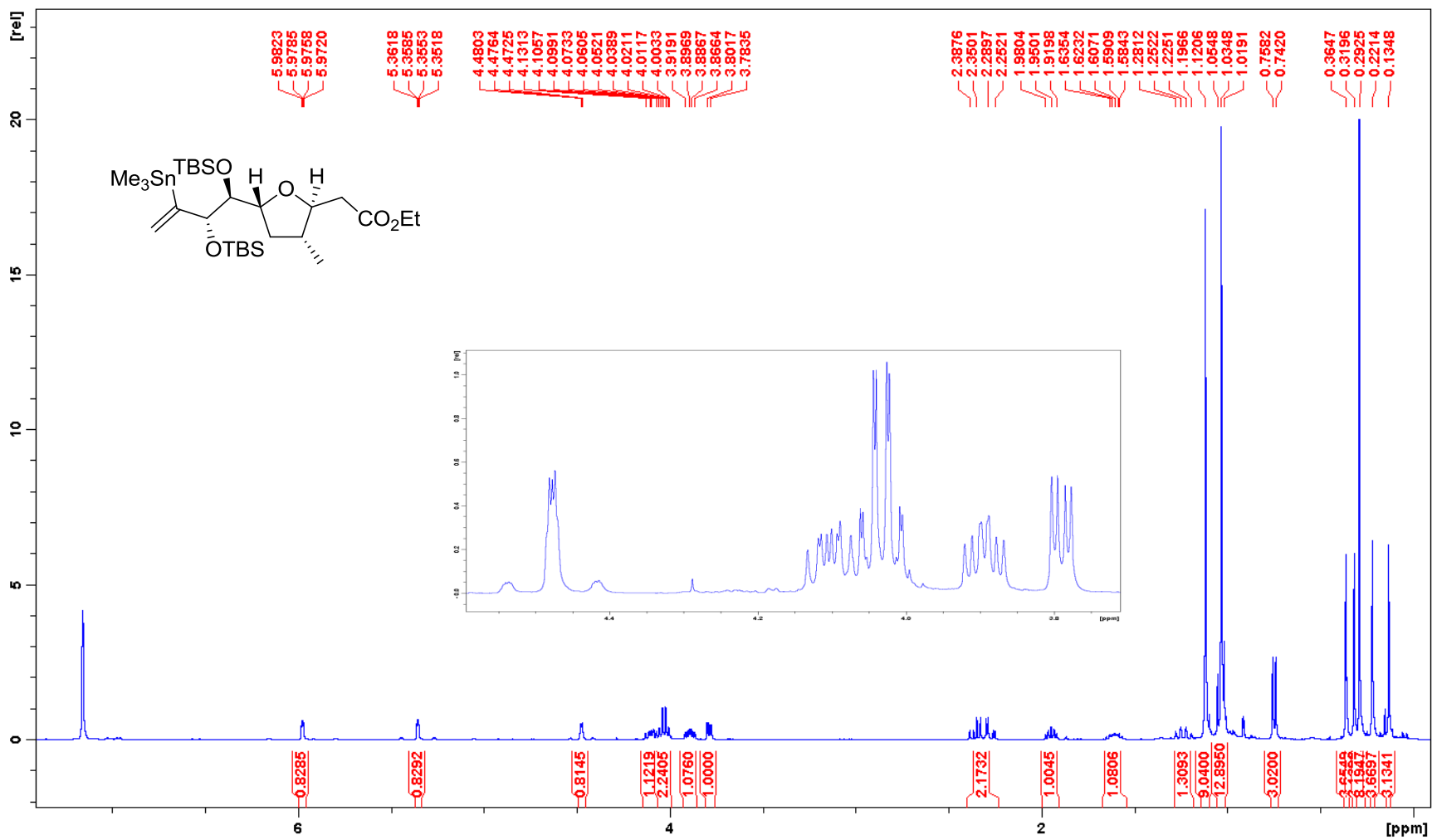
— 60.596

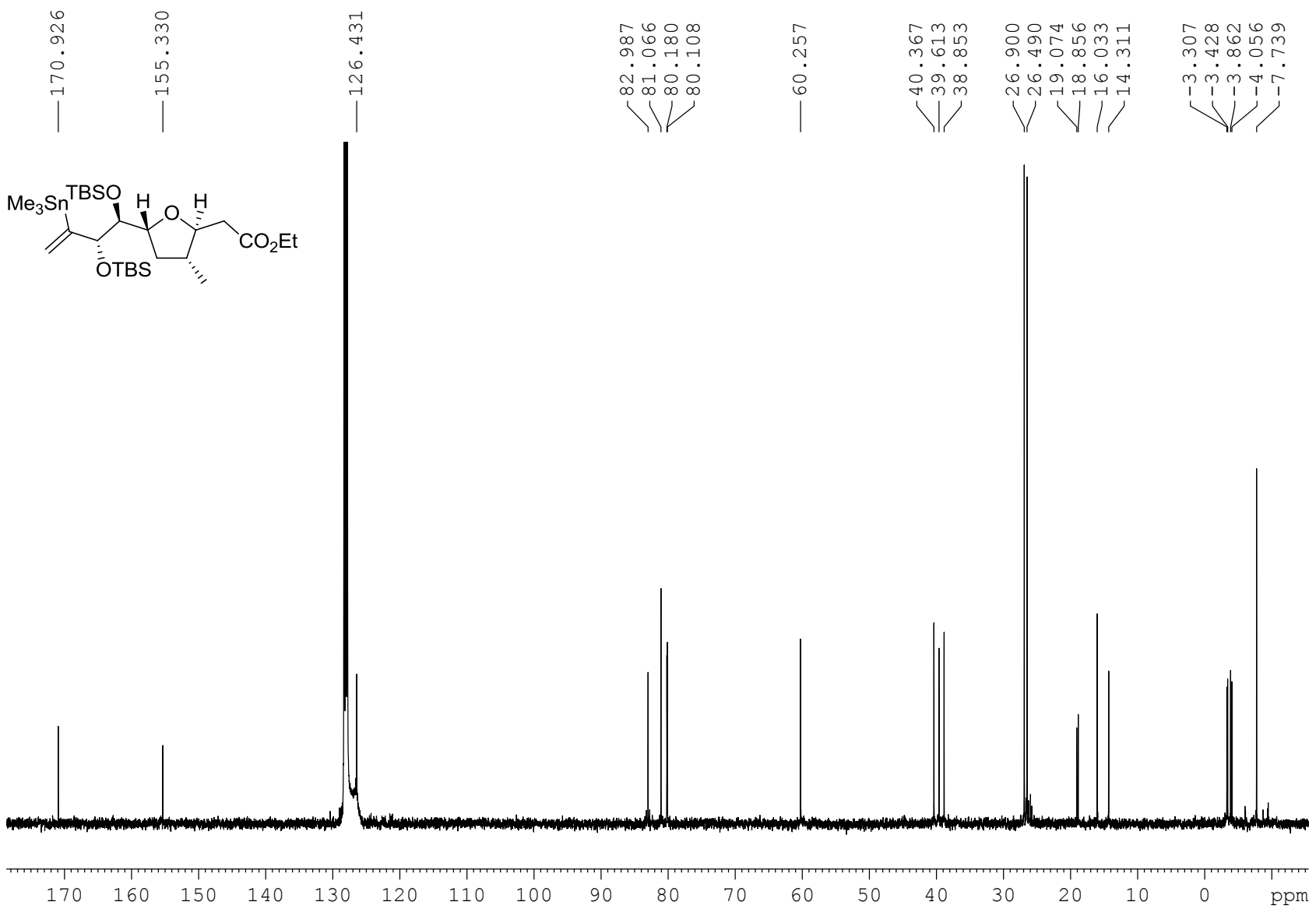
40.252
39.695
38.109
28.126
26.168
25.966
18.534
18.372
16.093
14.299

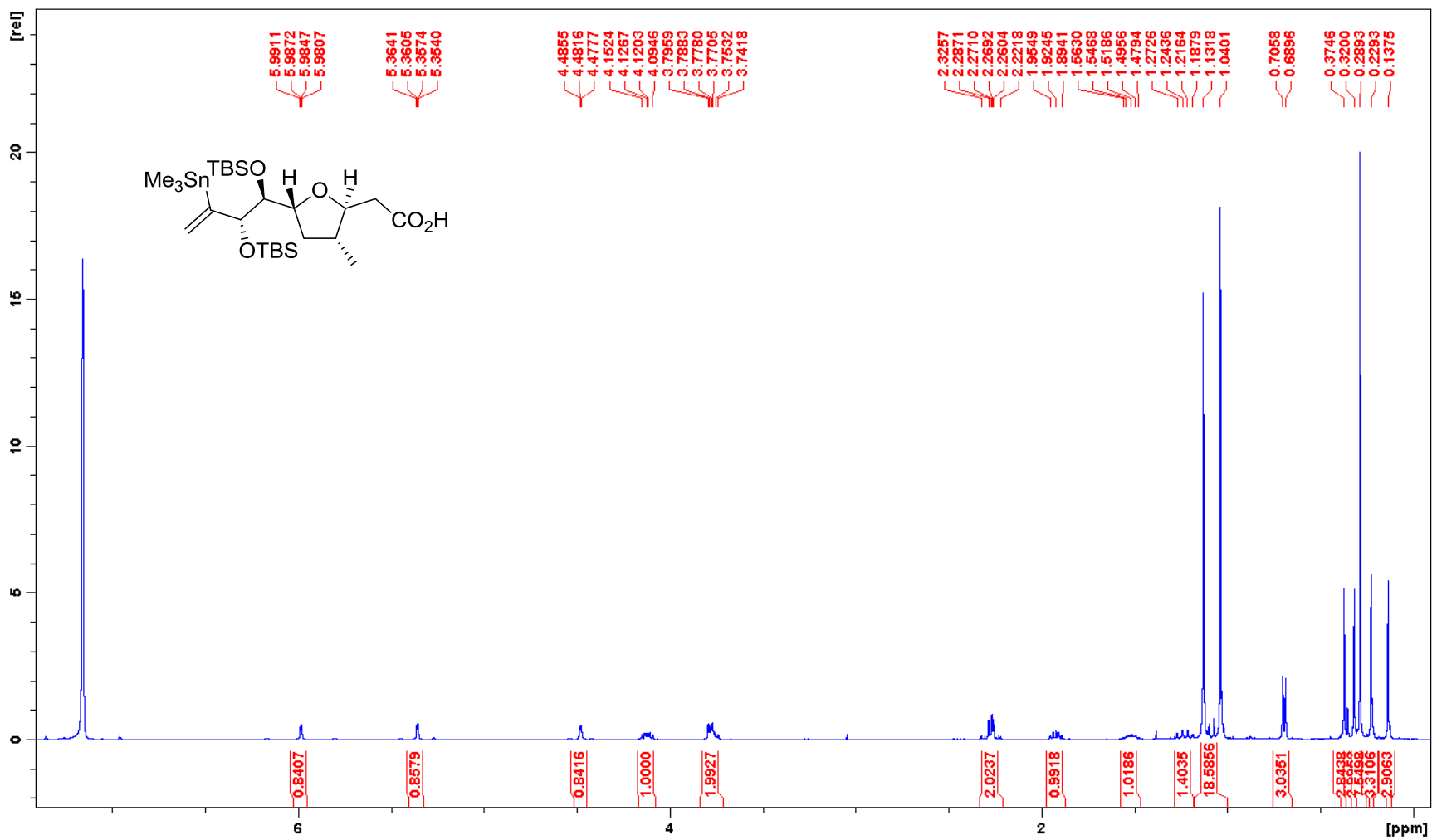
-4.498
-4.665
-4.910

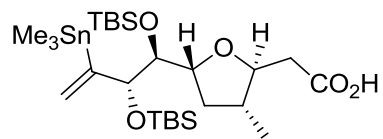












—177.089

—155.225

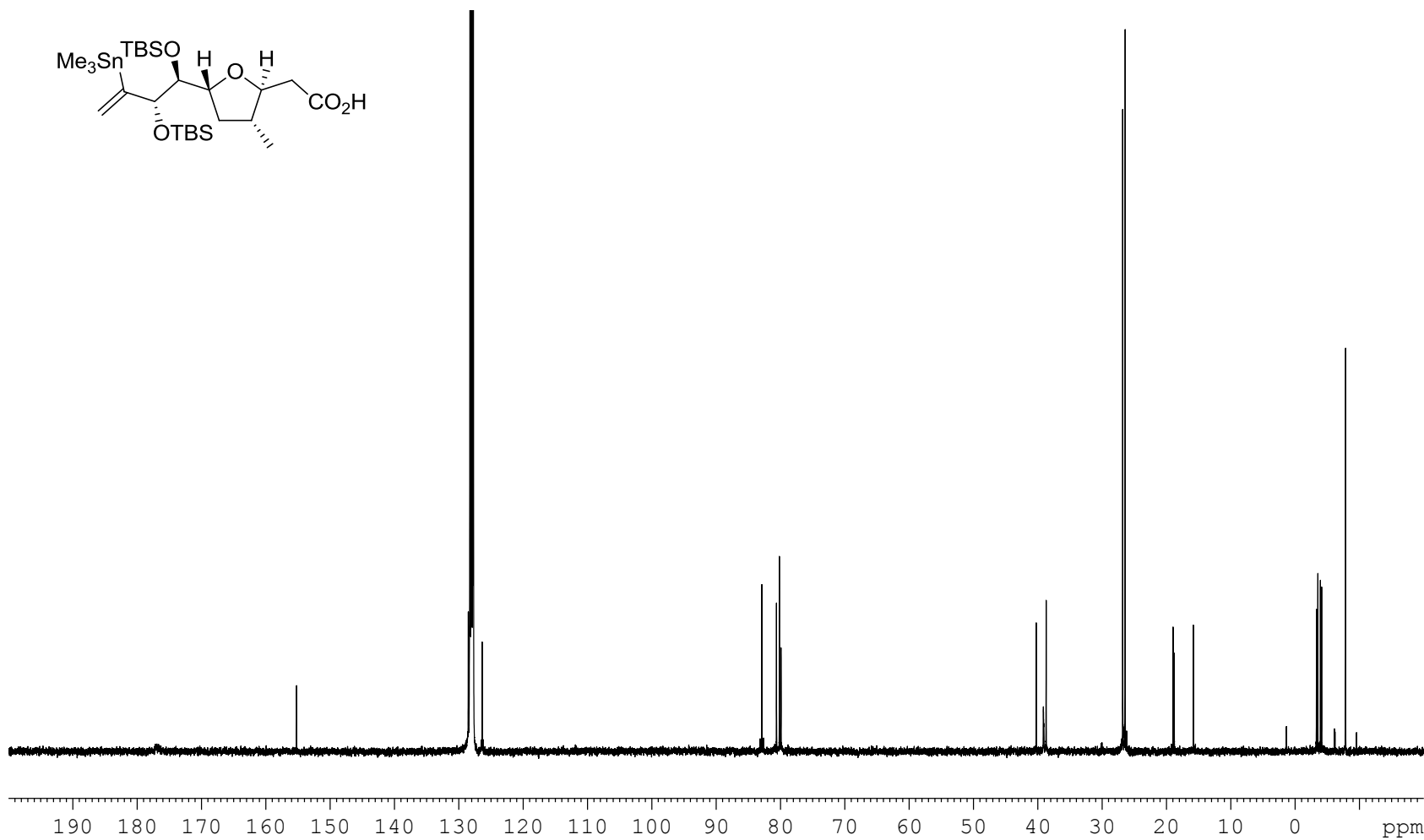
—126.376

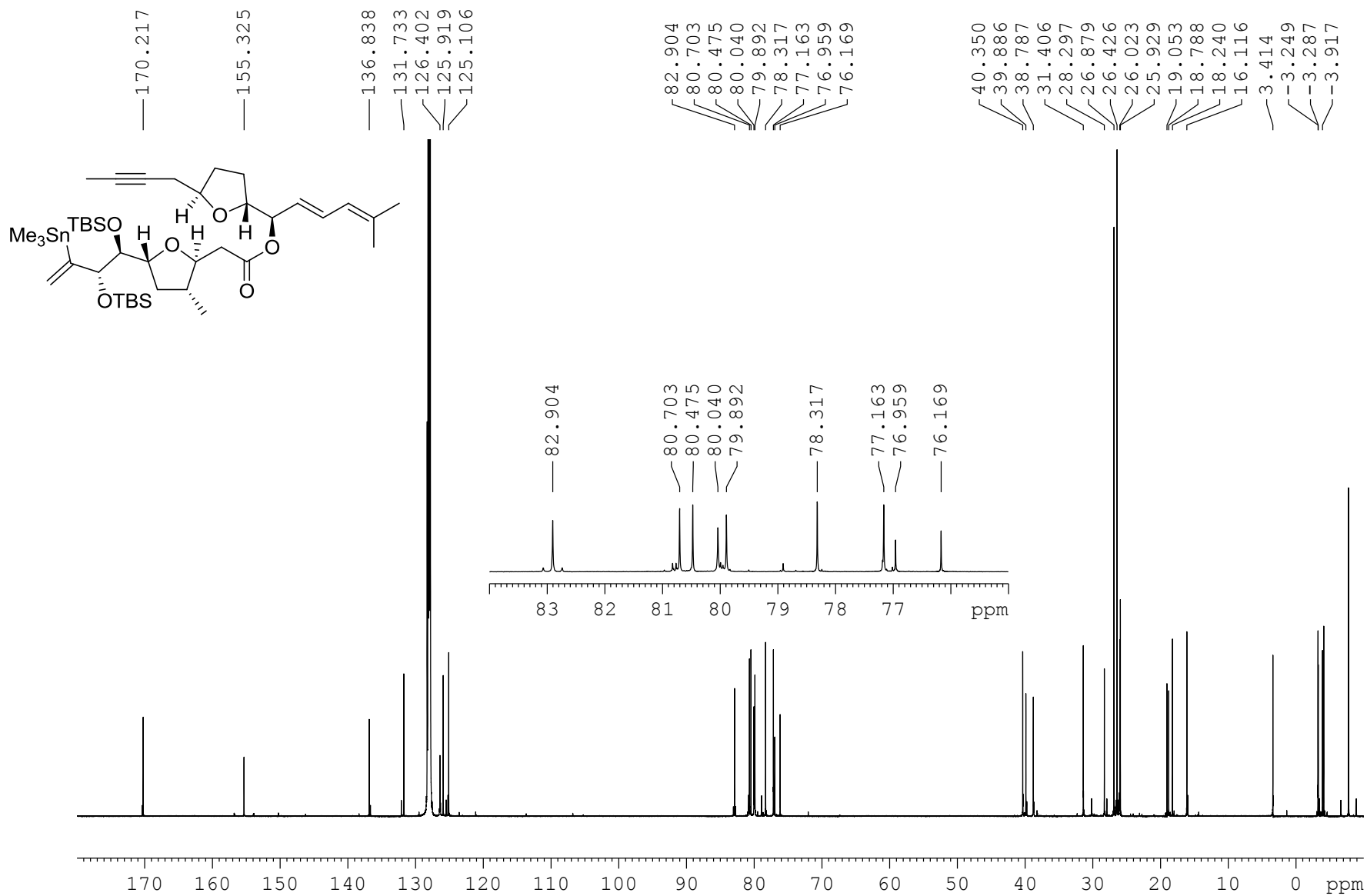
82.903
80.626
80.174
79.927

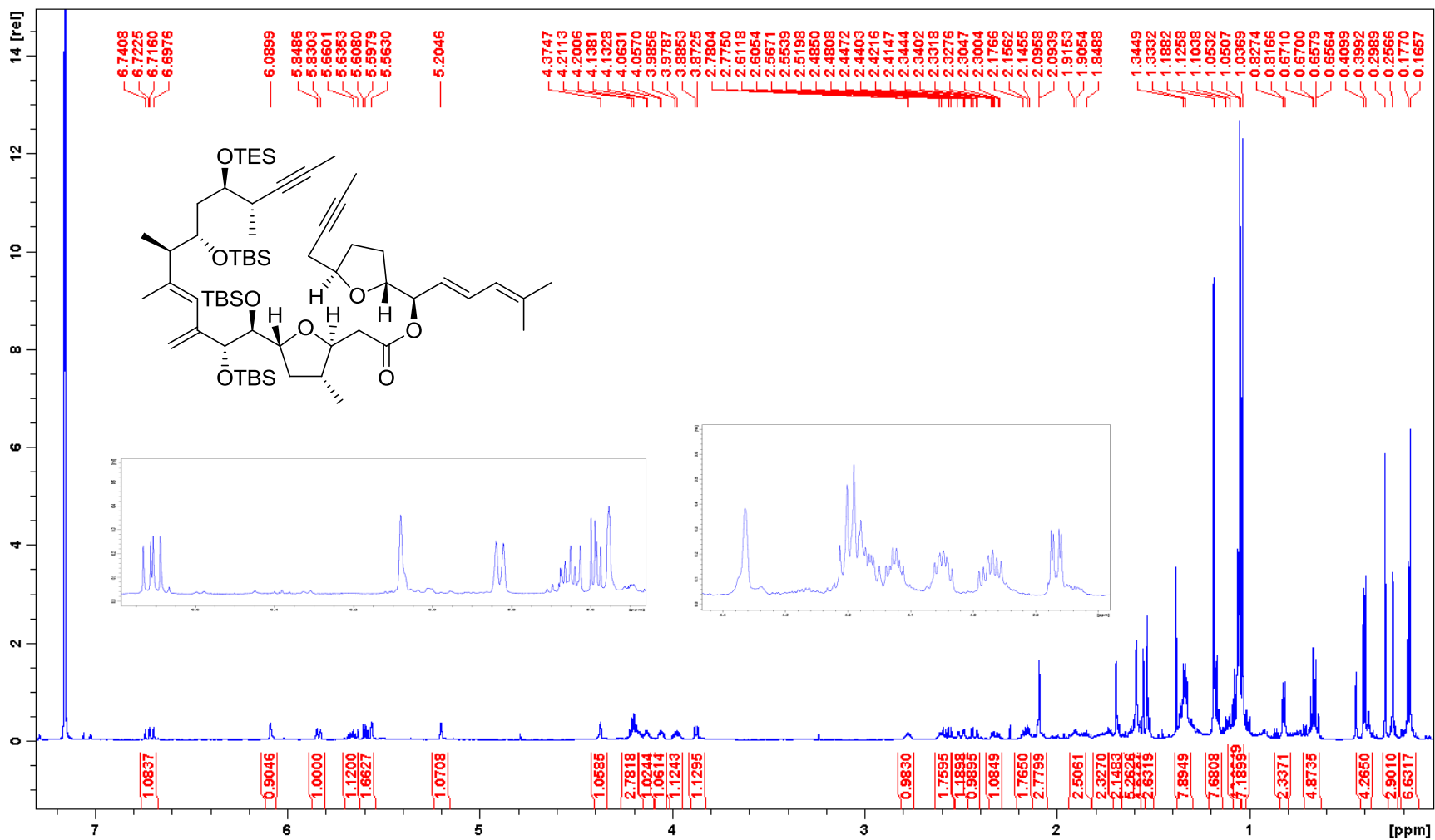
40.249
39.136
38.706

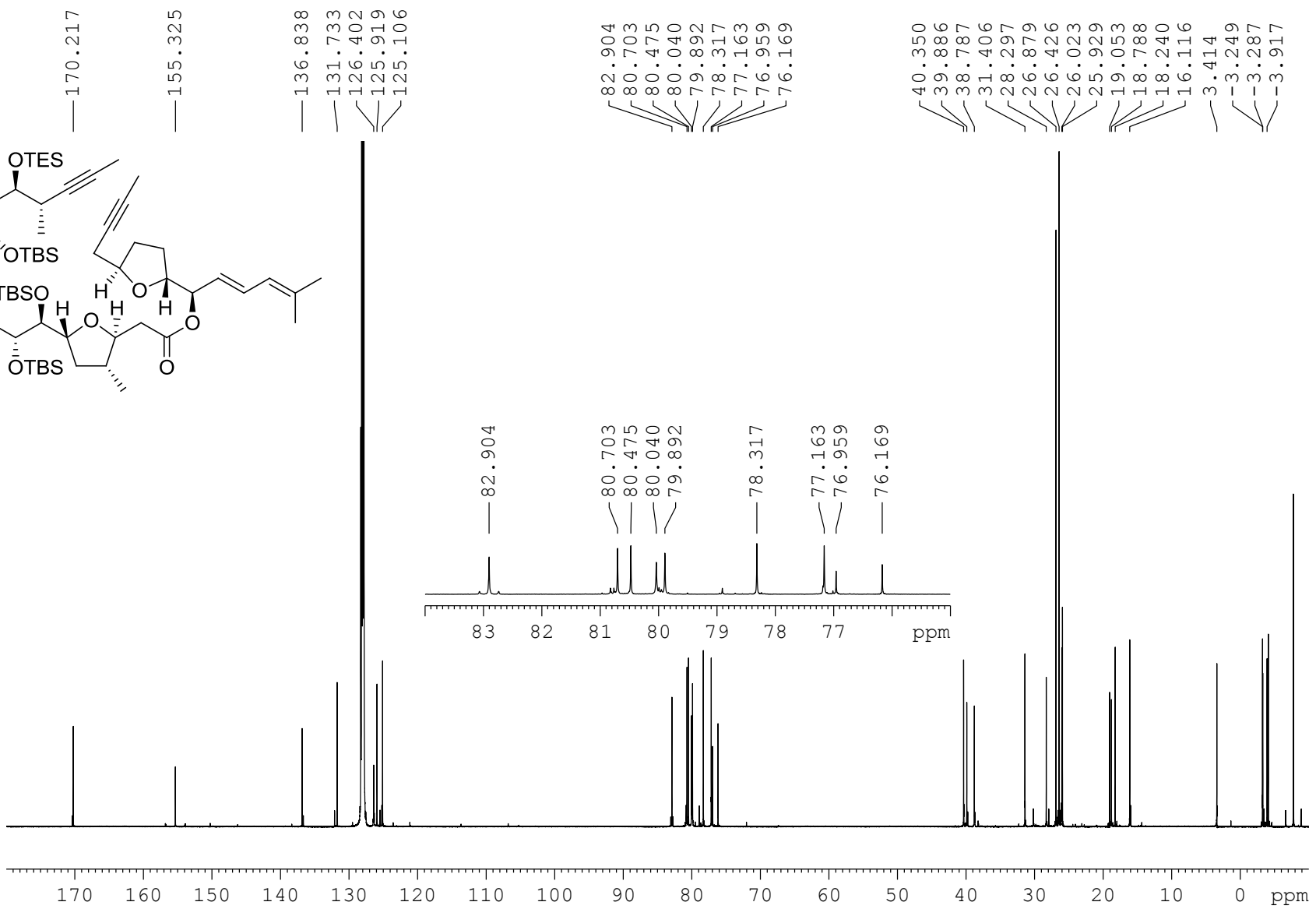
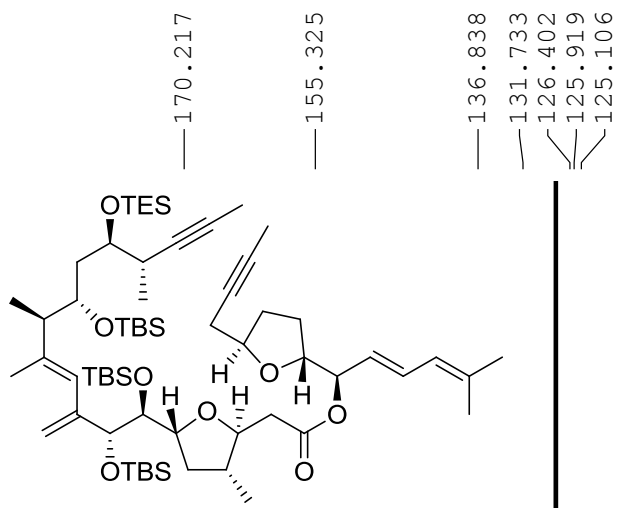
26.805
26.424
18.984
18.787
15.825

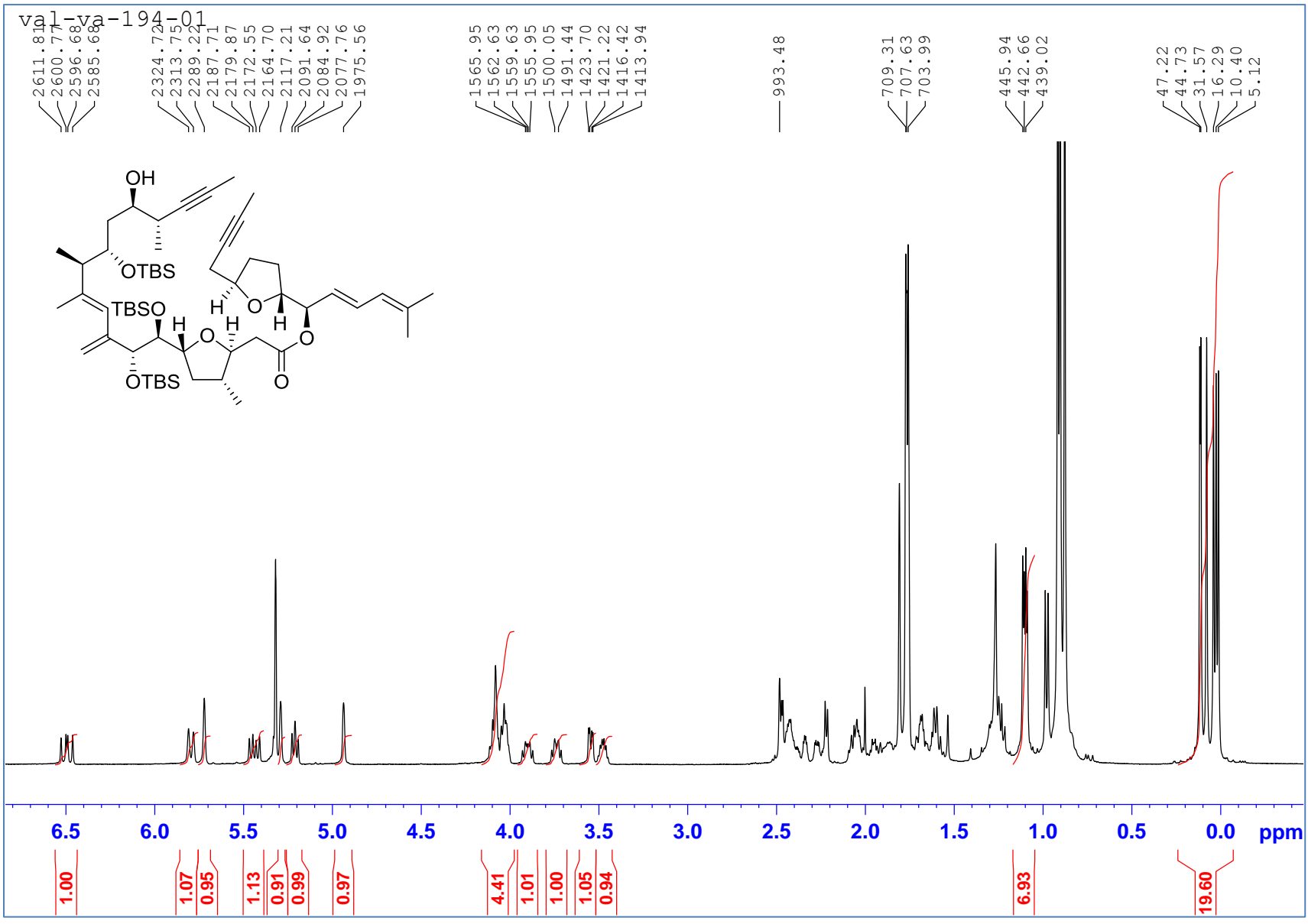
-3.312
-3.531
-3.929
-4.118
-7.845



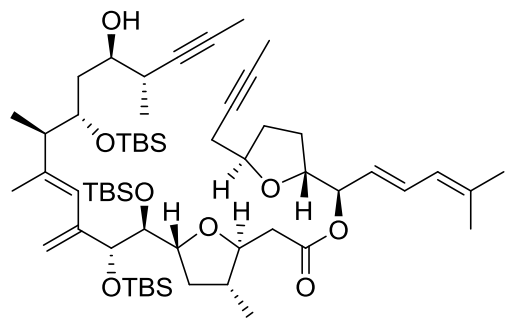








val-va-194-01

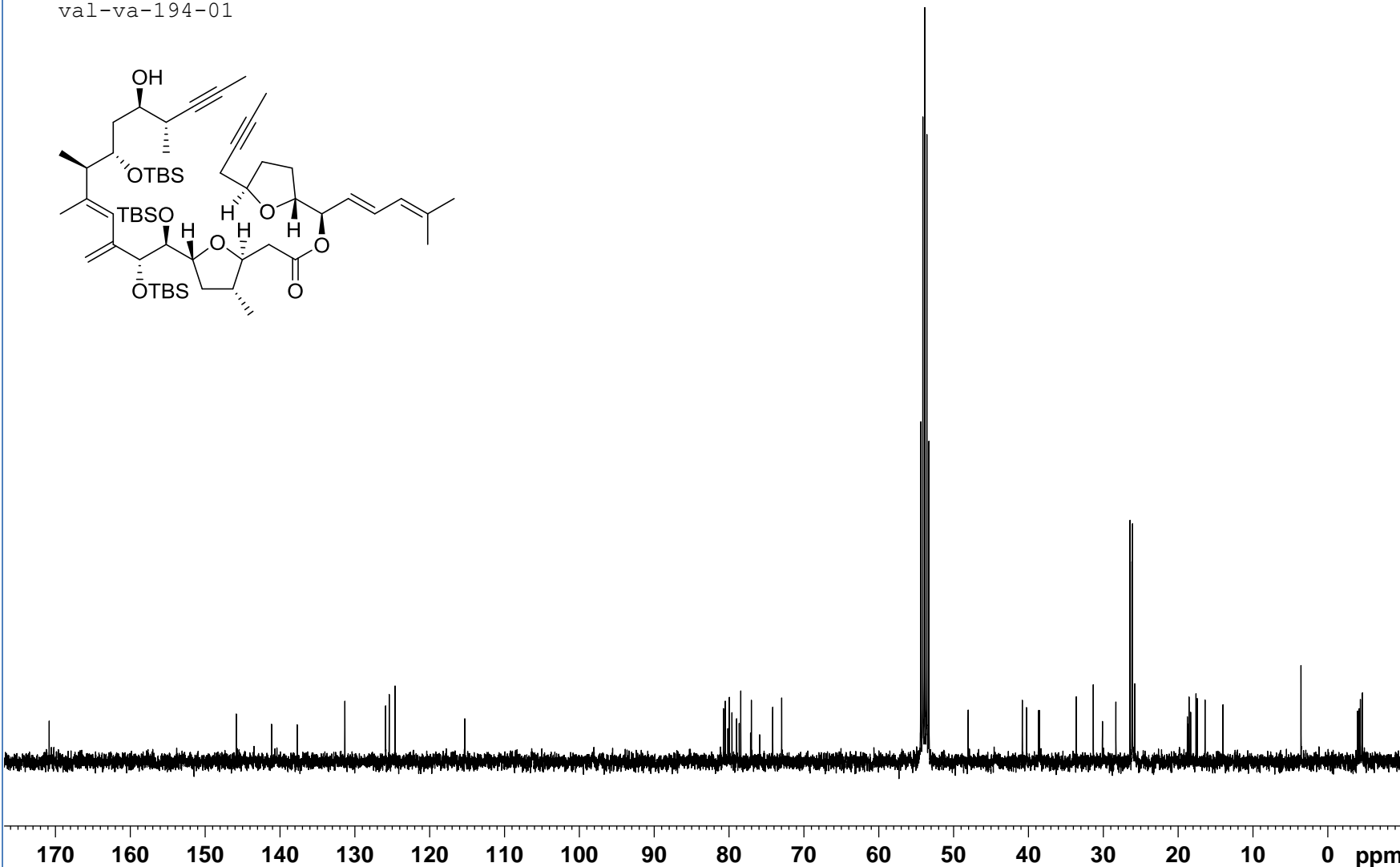


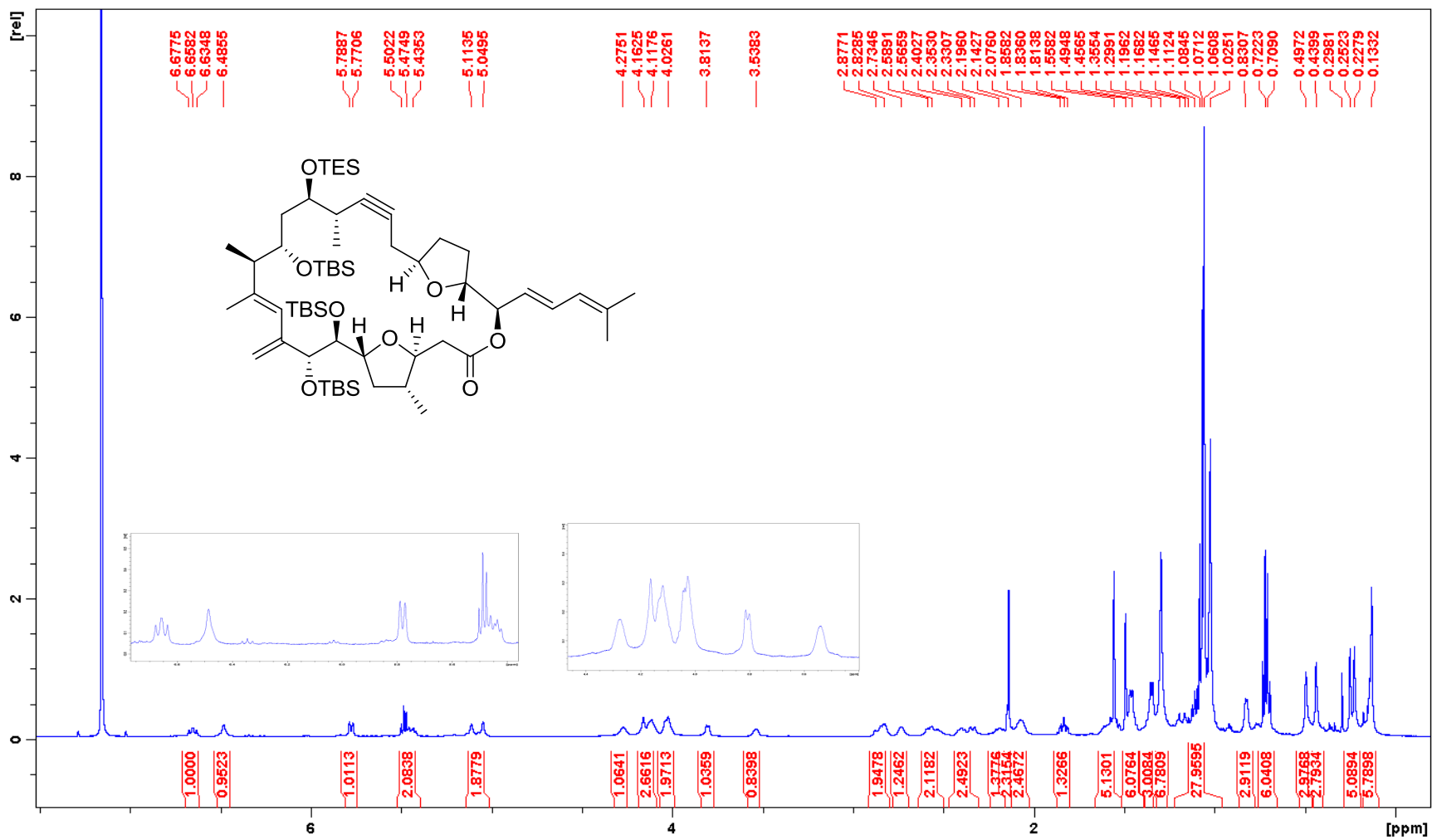
170.84
145.85
141.13
137.70
131.33
125.89
125.41
124.62
115.31

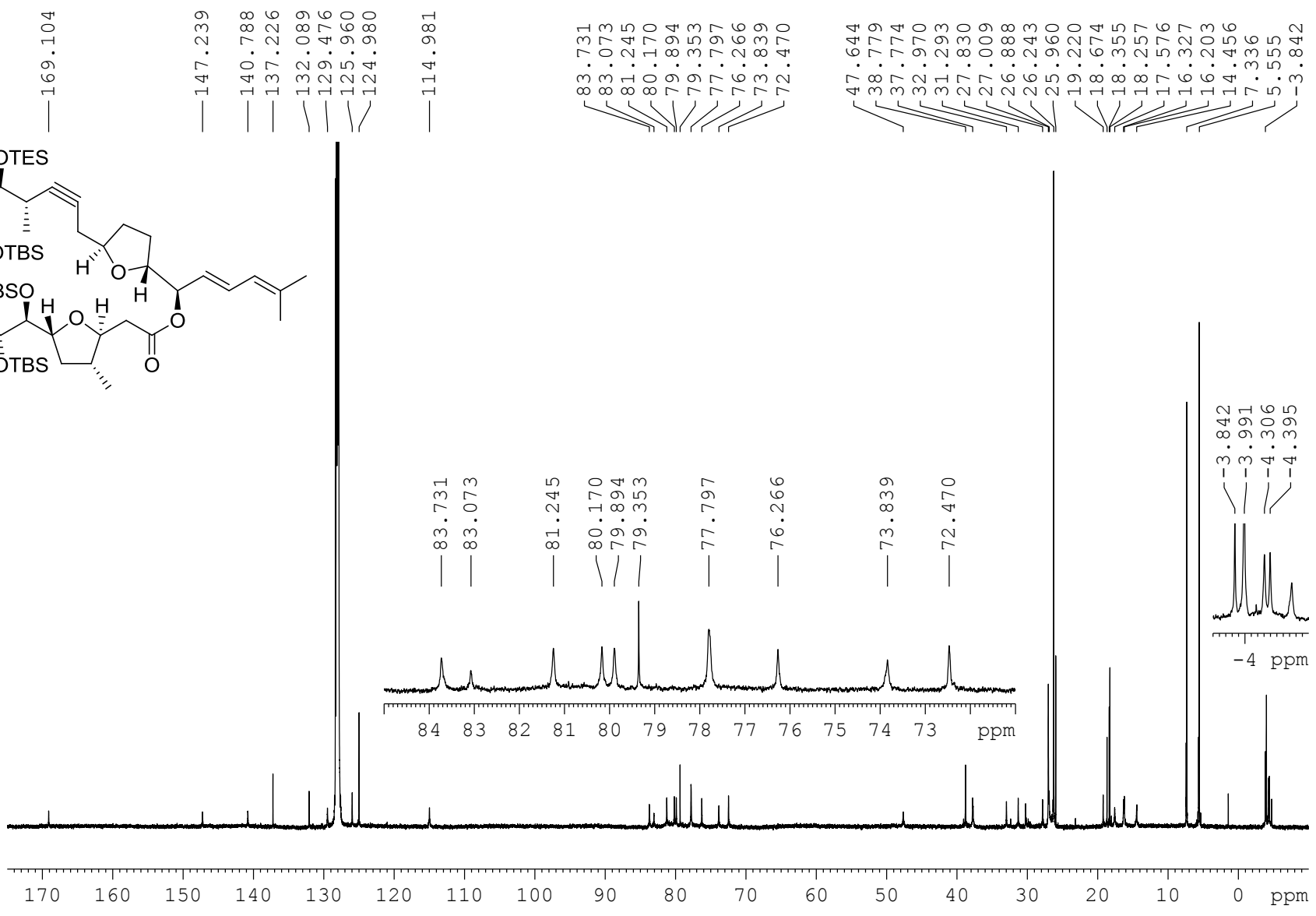
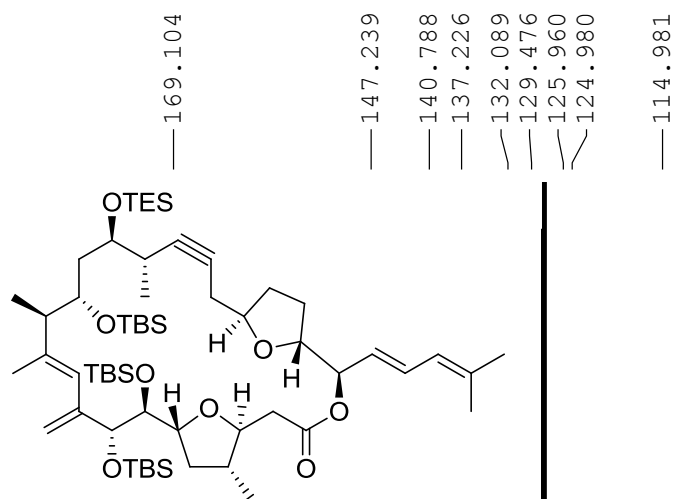
80.75
80.51
79.96
79.61
78.99
78.43
77.02
74.17
72.97

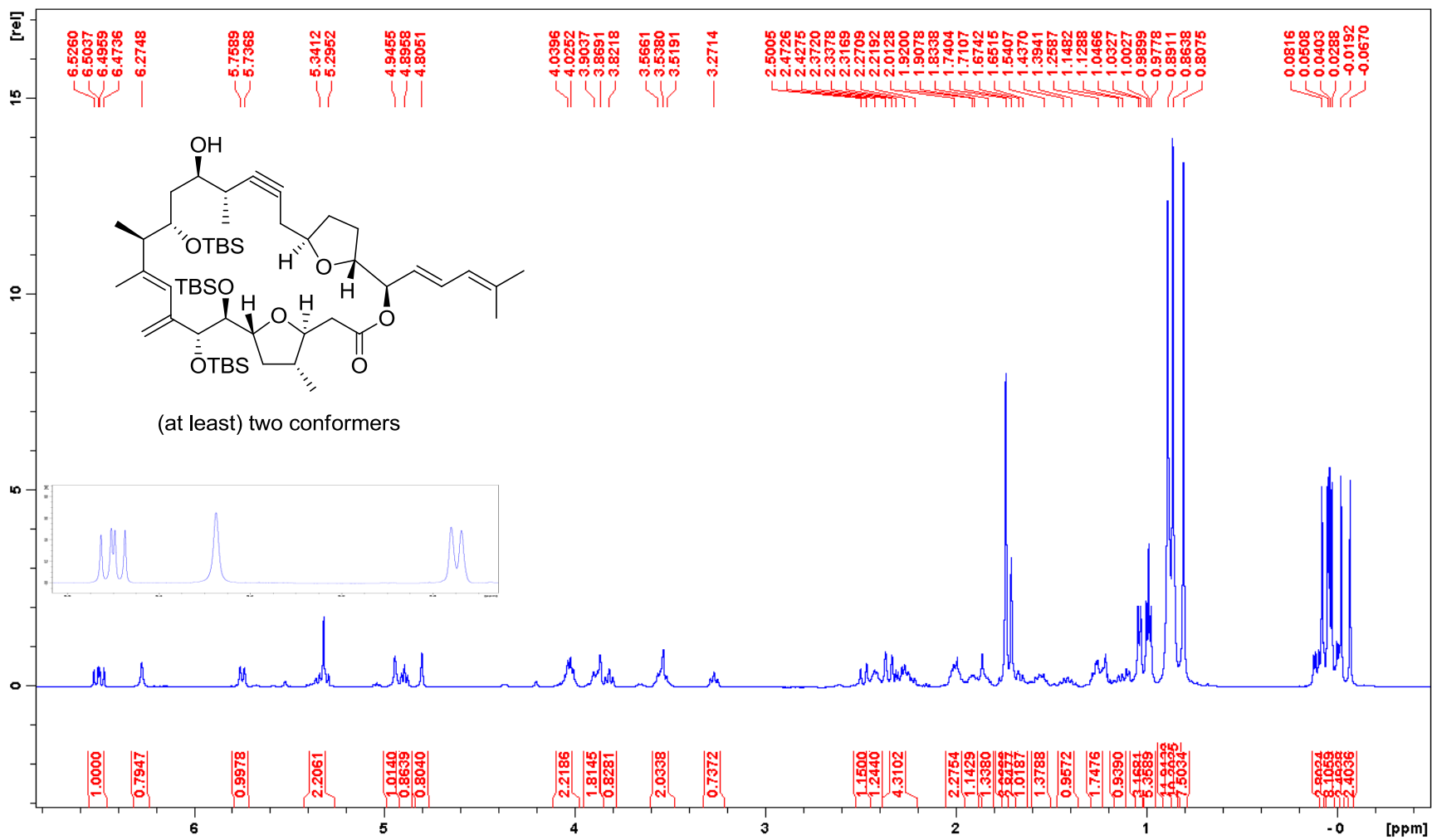
48.05
40.82
40.26
38.63
38.54
33.61
31.34
30.11
28.32
26.43
26.17
26.10
18.54
17.62
17.45
16.41
14.00

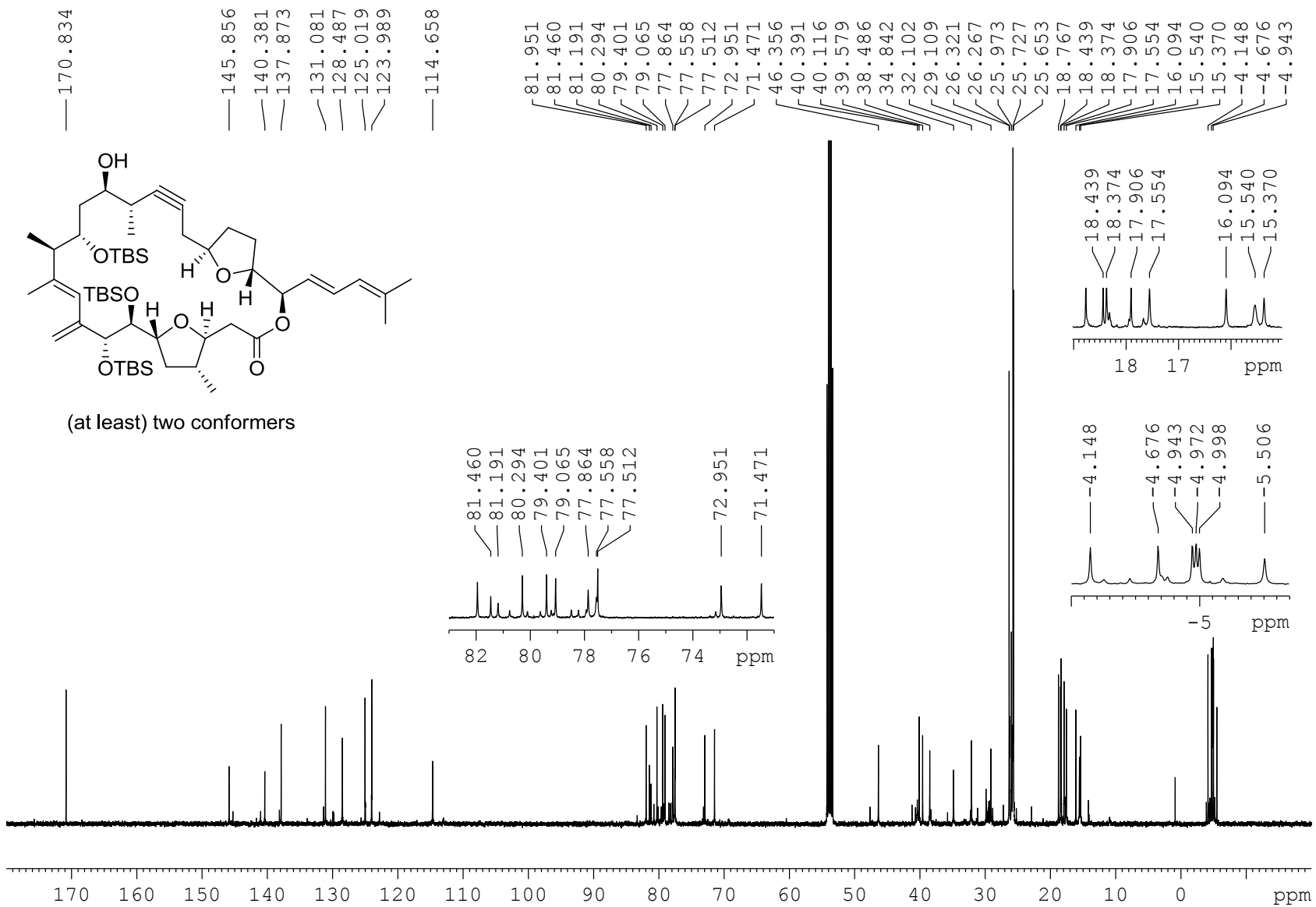
3.59
3.99
4.20
4.35
4.60
4.63

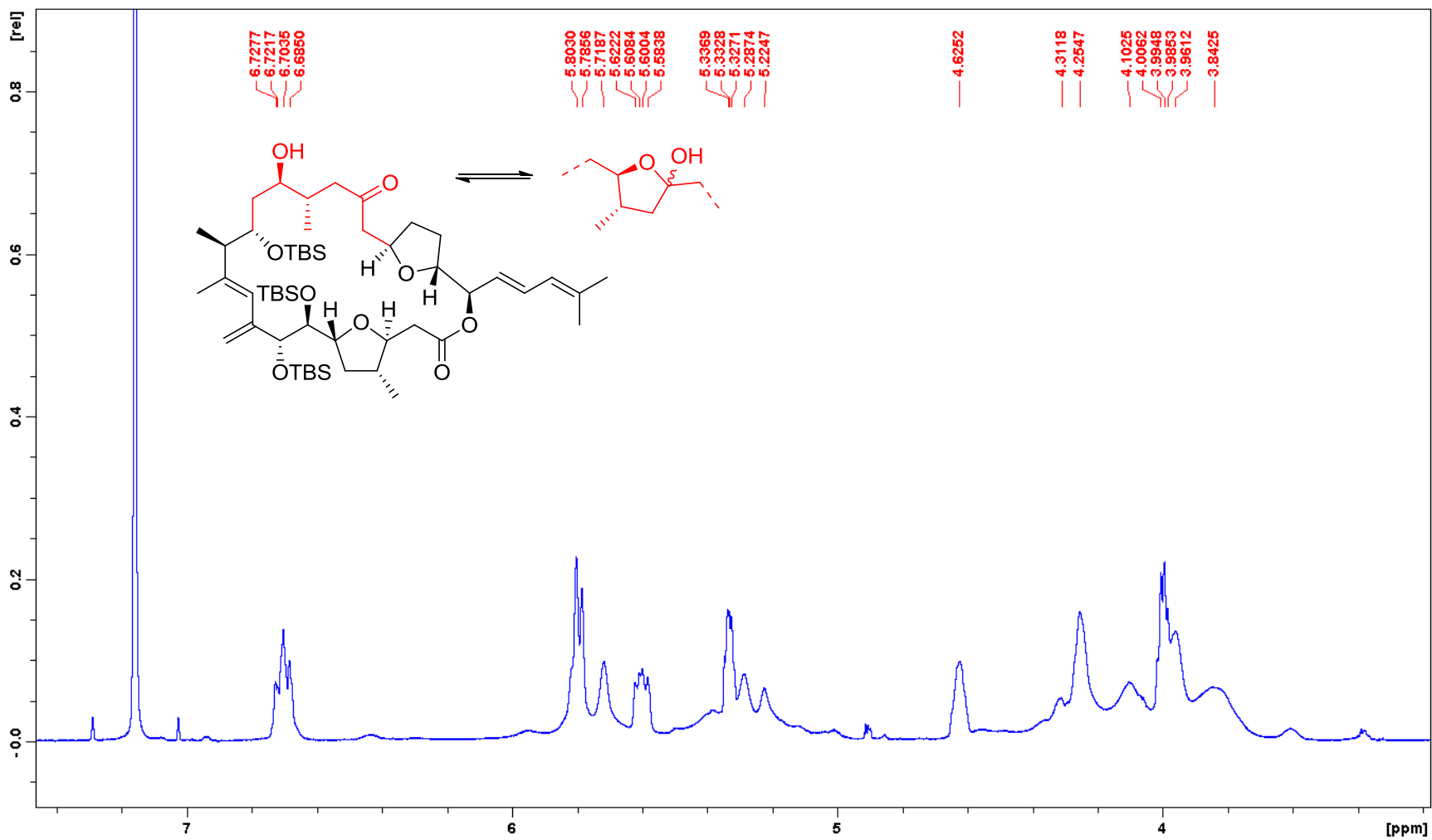


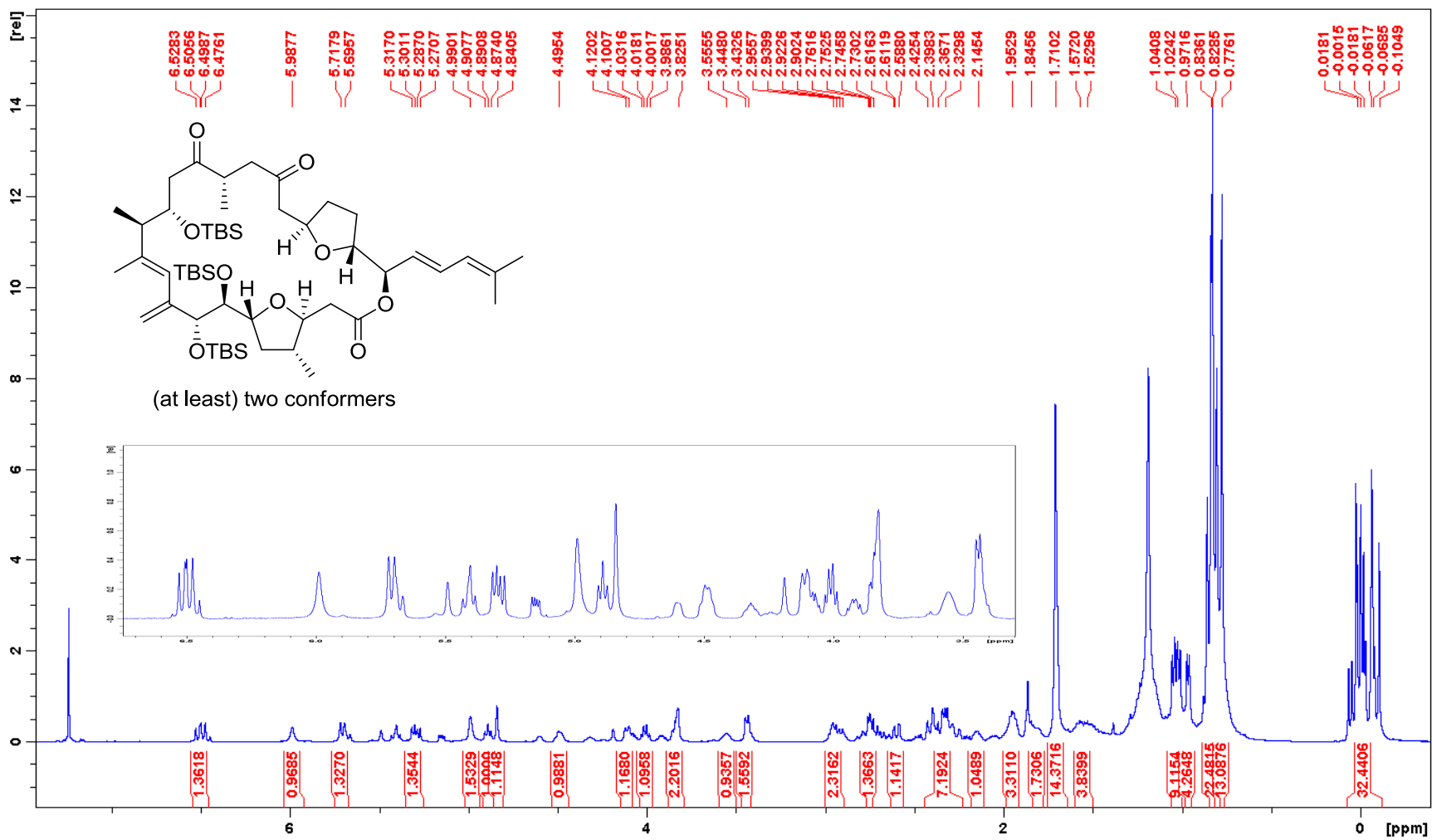


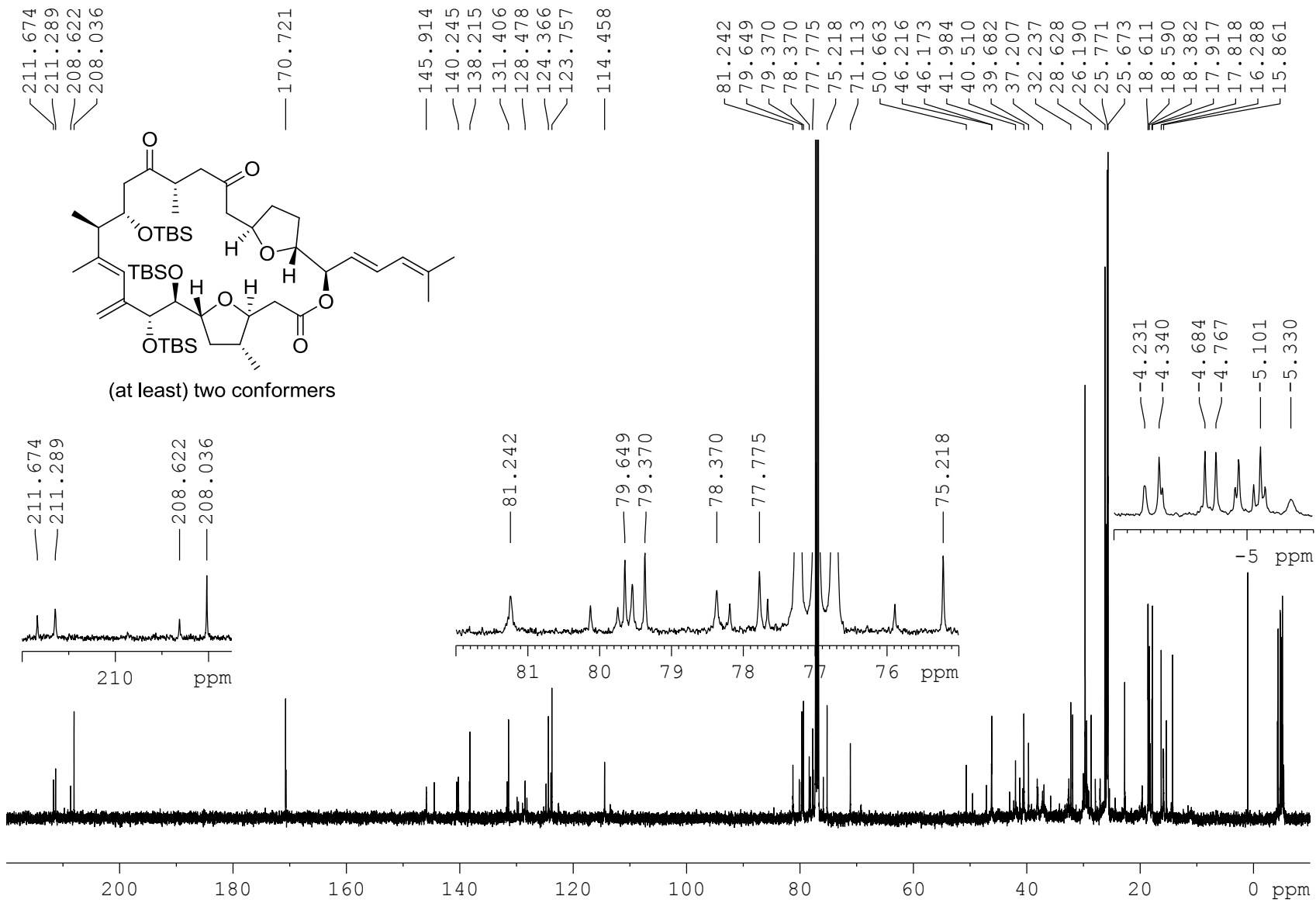




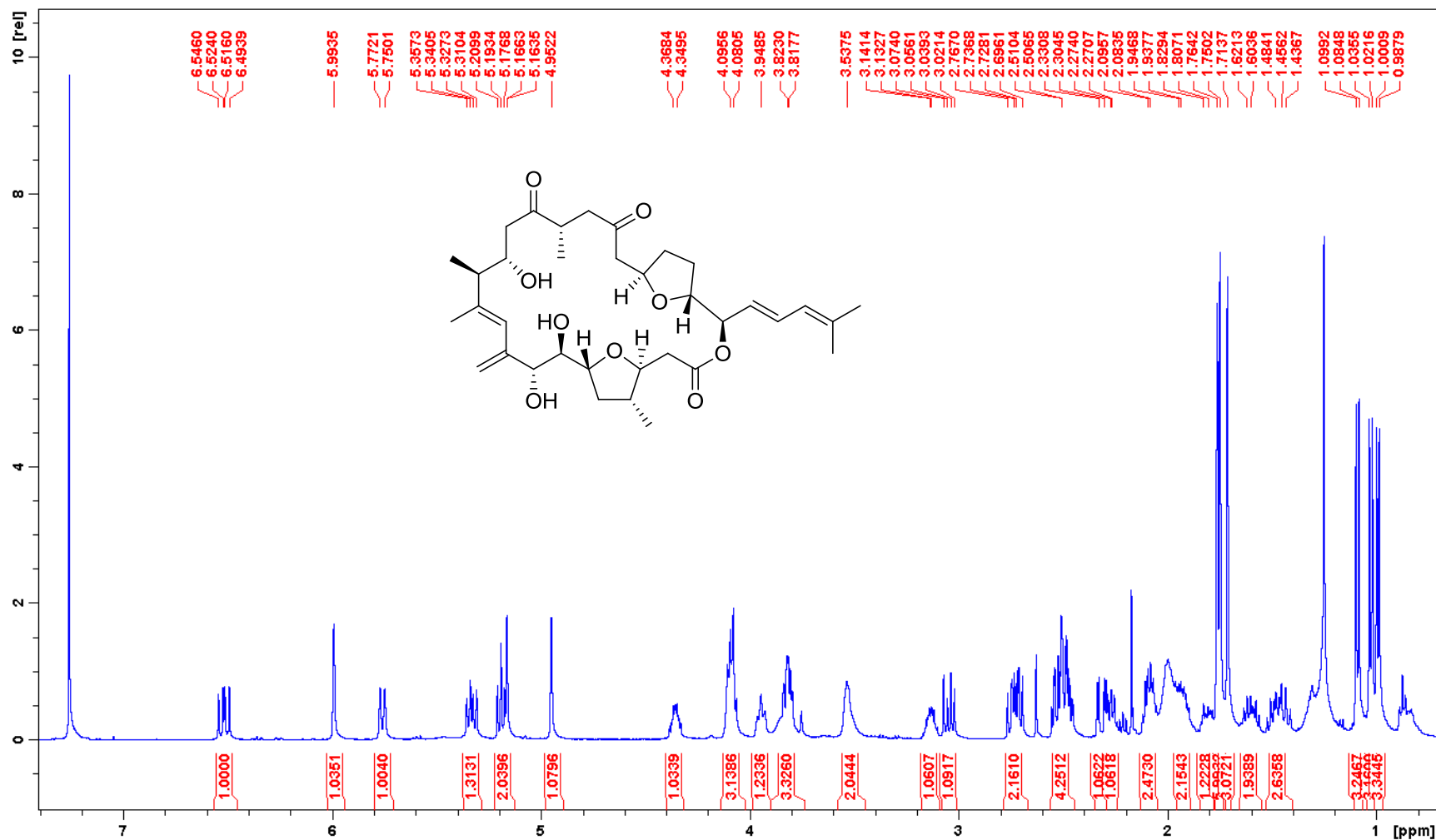




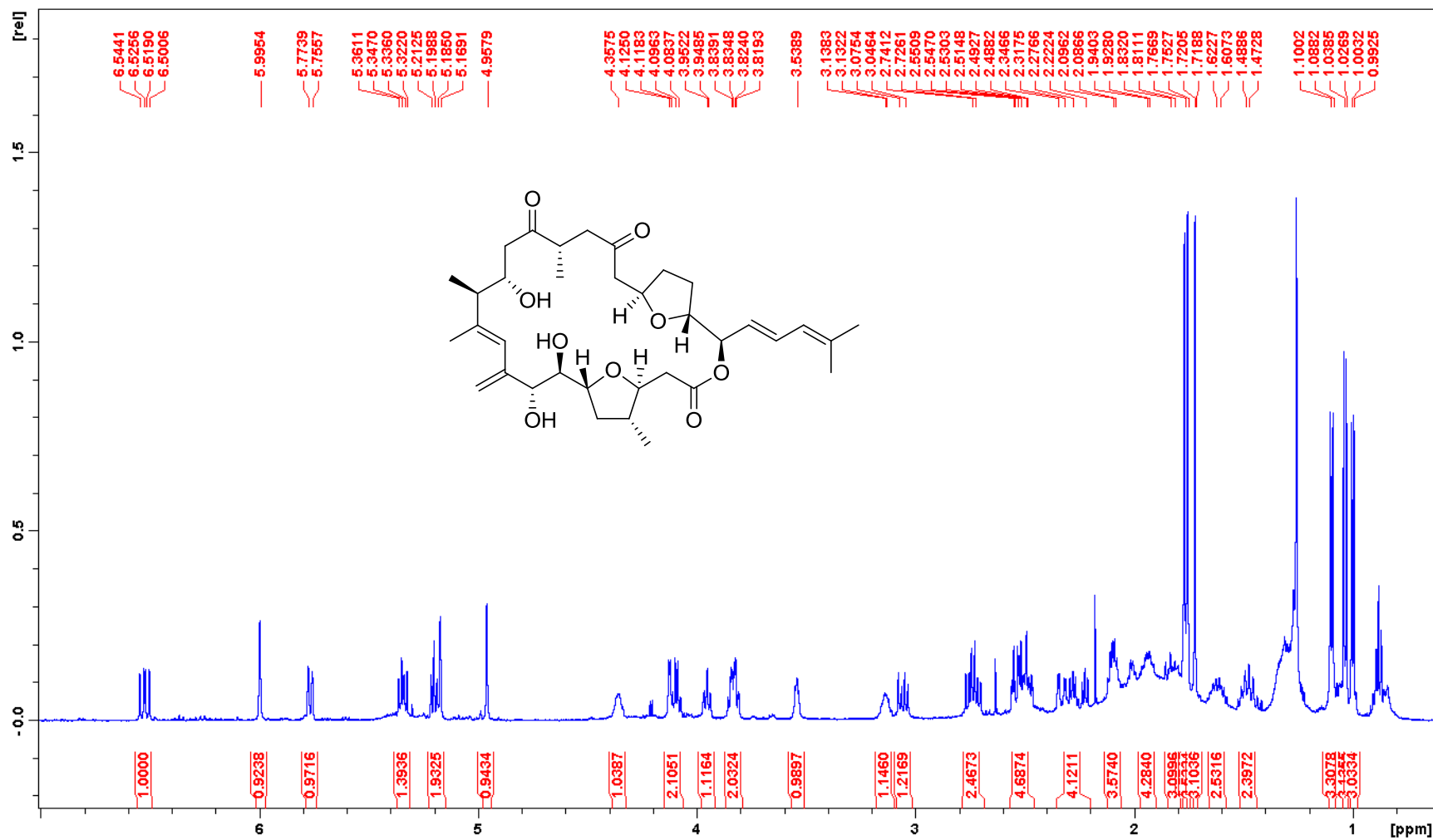


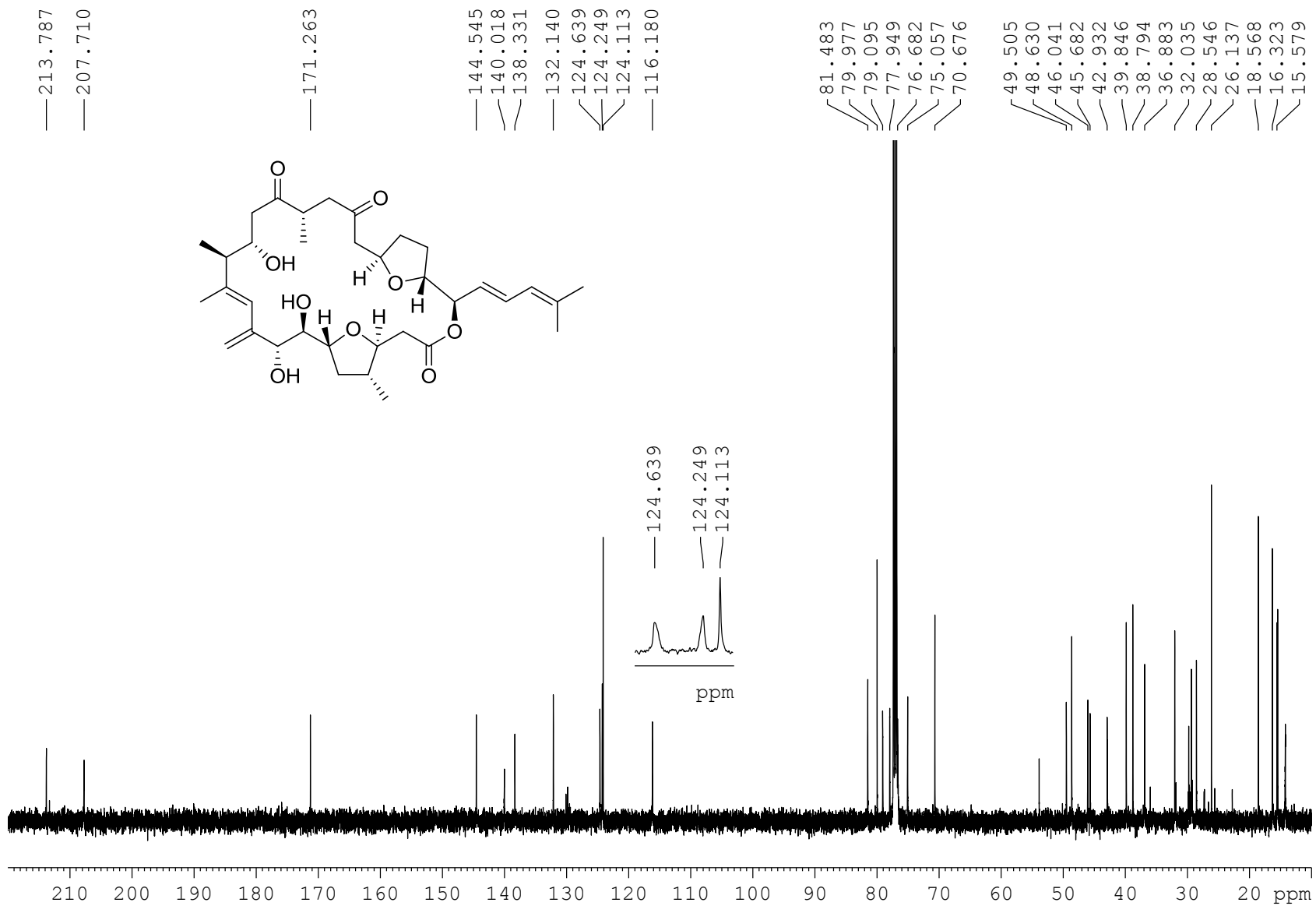


1.4 mg in 180 μ L – 500 MHz

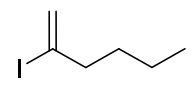


0.4 mg in 180 μ L – 600 MHz





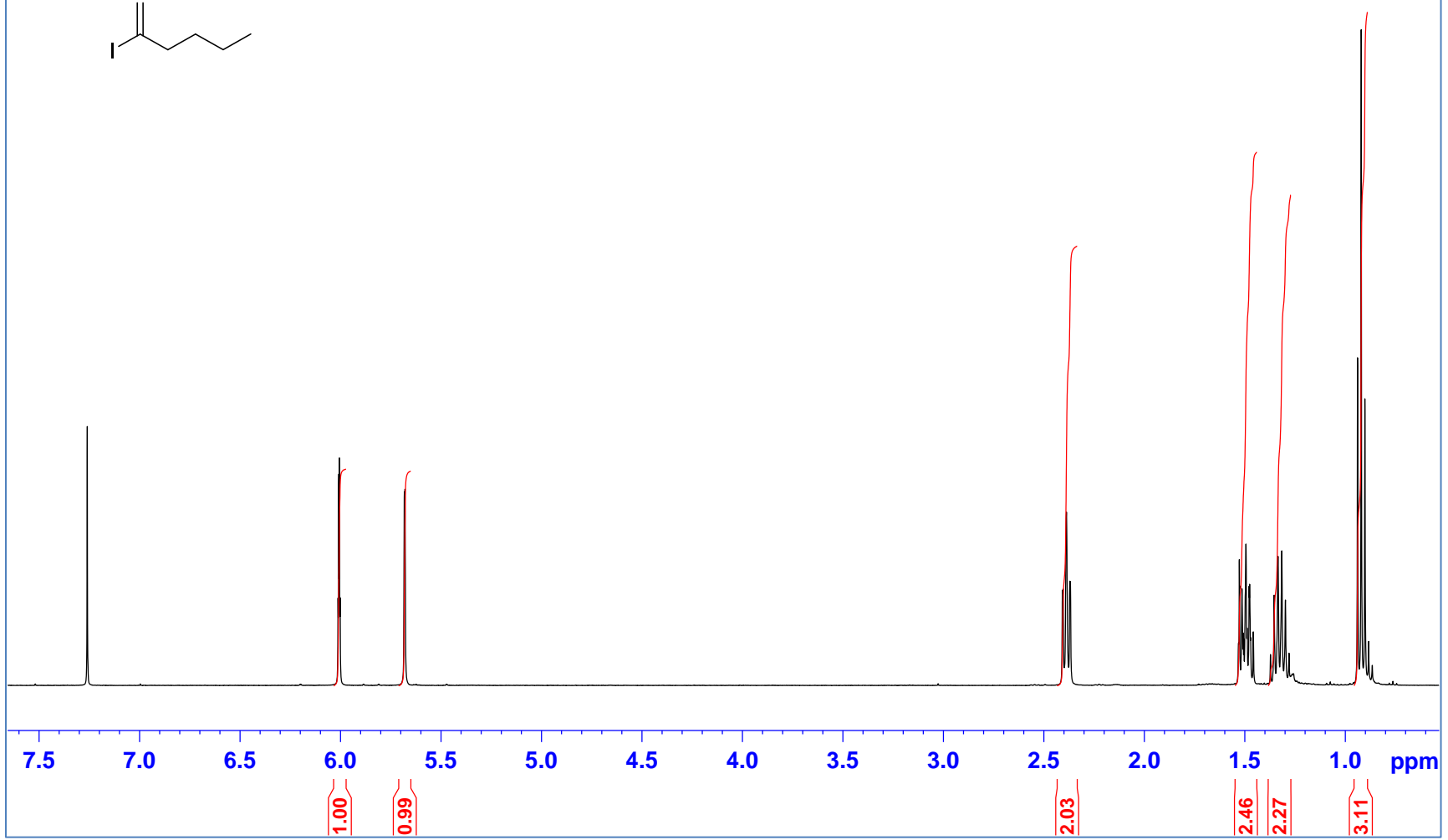
VAL-VA-226-01

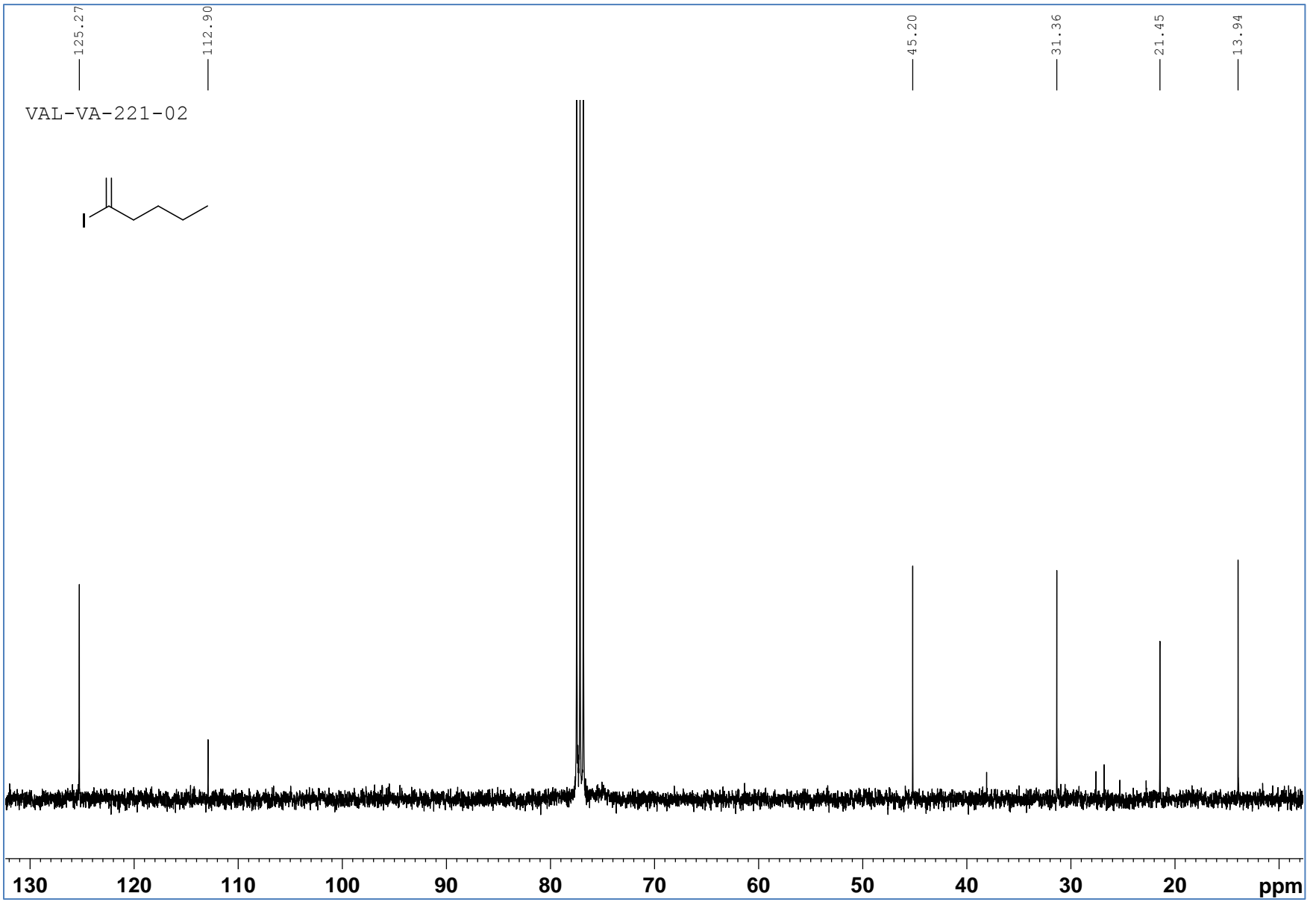


2405.62
2404.22
2402.86
2401.46
2273.62
2272.94
2272.30

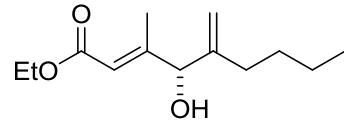
963.07
962.23
955.31
948.47
947.63

611.08
610.60
597.87
549.06
541.74
534.01
526.53
519.33
512.13
375.68
368.36
361.04





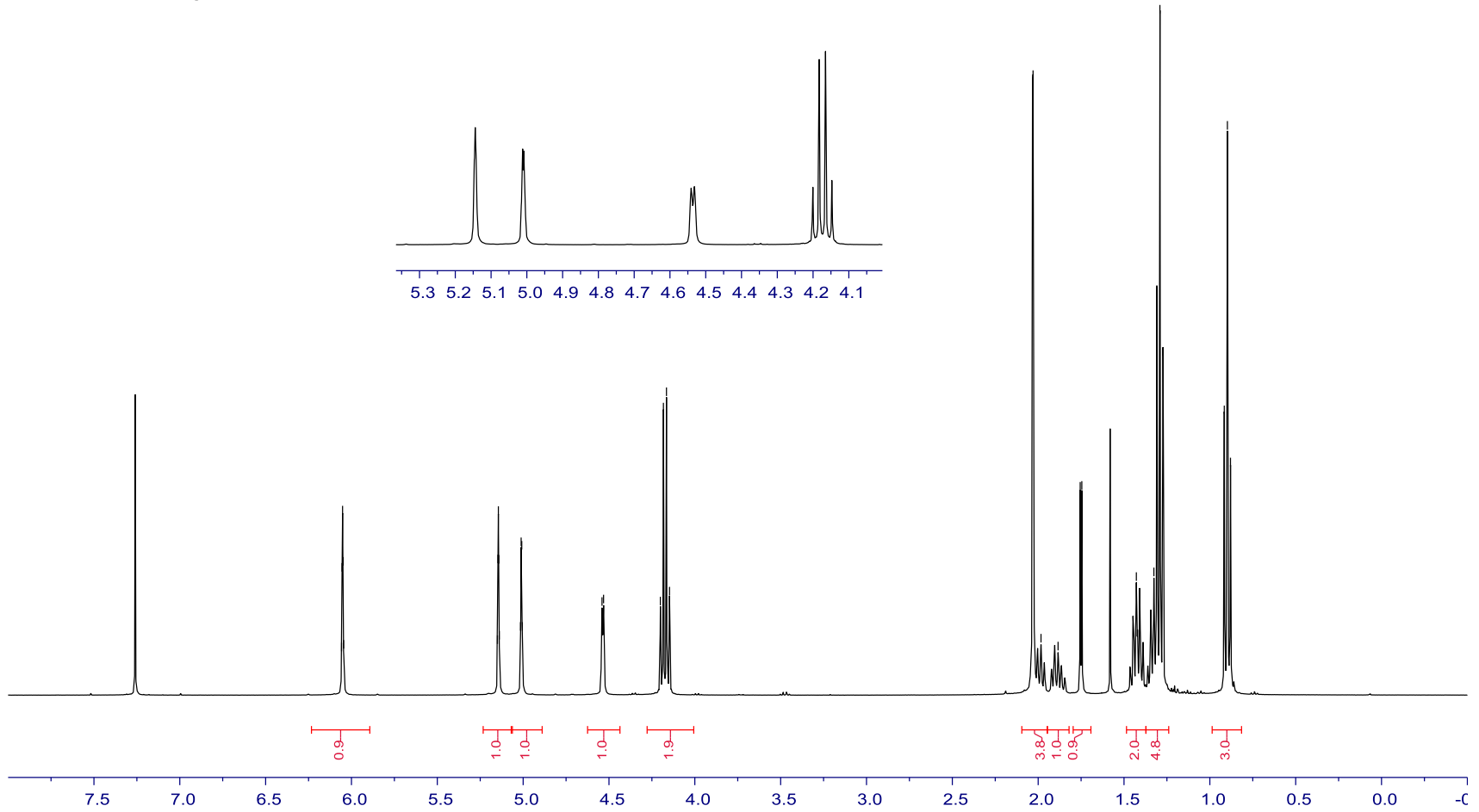
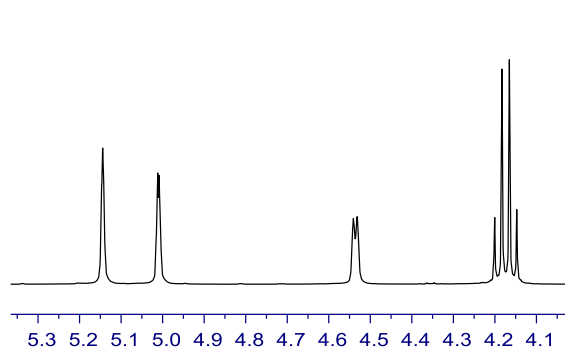
MID-MB-369-02



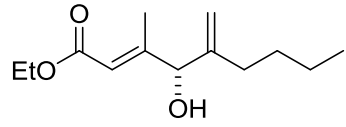
6.06
6.05
6.05
6.05

5.15
5.14
5.14
5.14
5.02
5.01
5.00
4.54
4.53
4.20
4.18
4.17
4.15

2.03
1.98
1.88
1.76
1.75
1.43
1.33
1.31
1.29
1.27
0.92
0.90
0.88



MID-MB-369-02



166.9

157.8

148.4

116.1

112.4

79.8

59.9

30.9

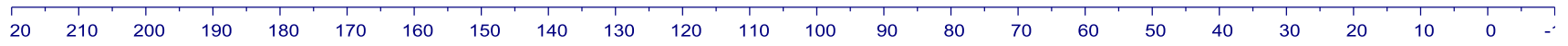
30.0

22.6

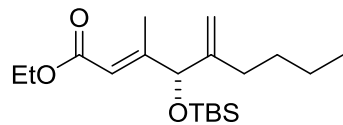
15.0

14.3

14.1



MID-MB-373-02



5.99
5.99
5.98
5.98

5.11
5.10
4.92
4.91
4.91

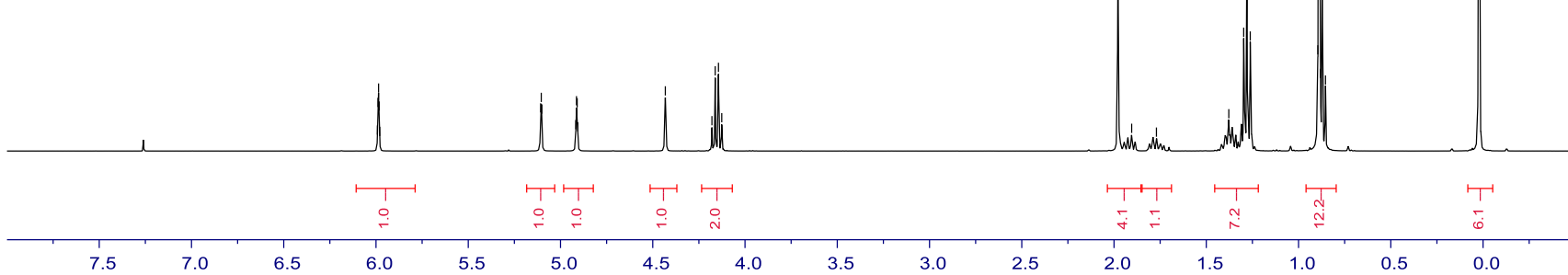
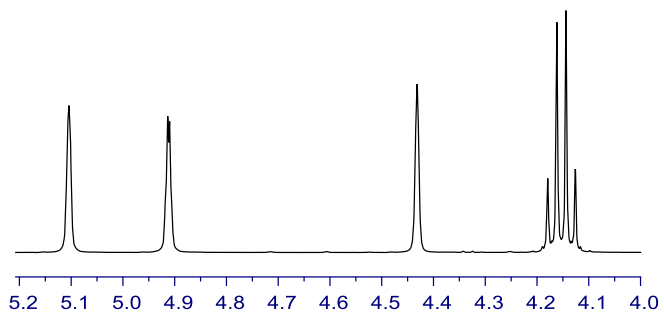
4.43
4.18
4.16
4.14
4.13

1.98
1.98
1.90

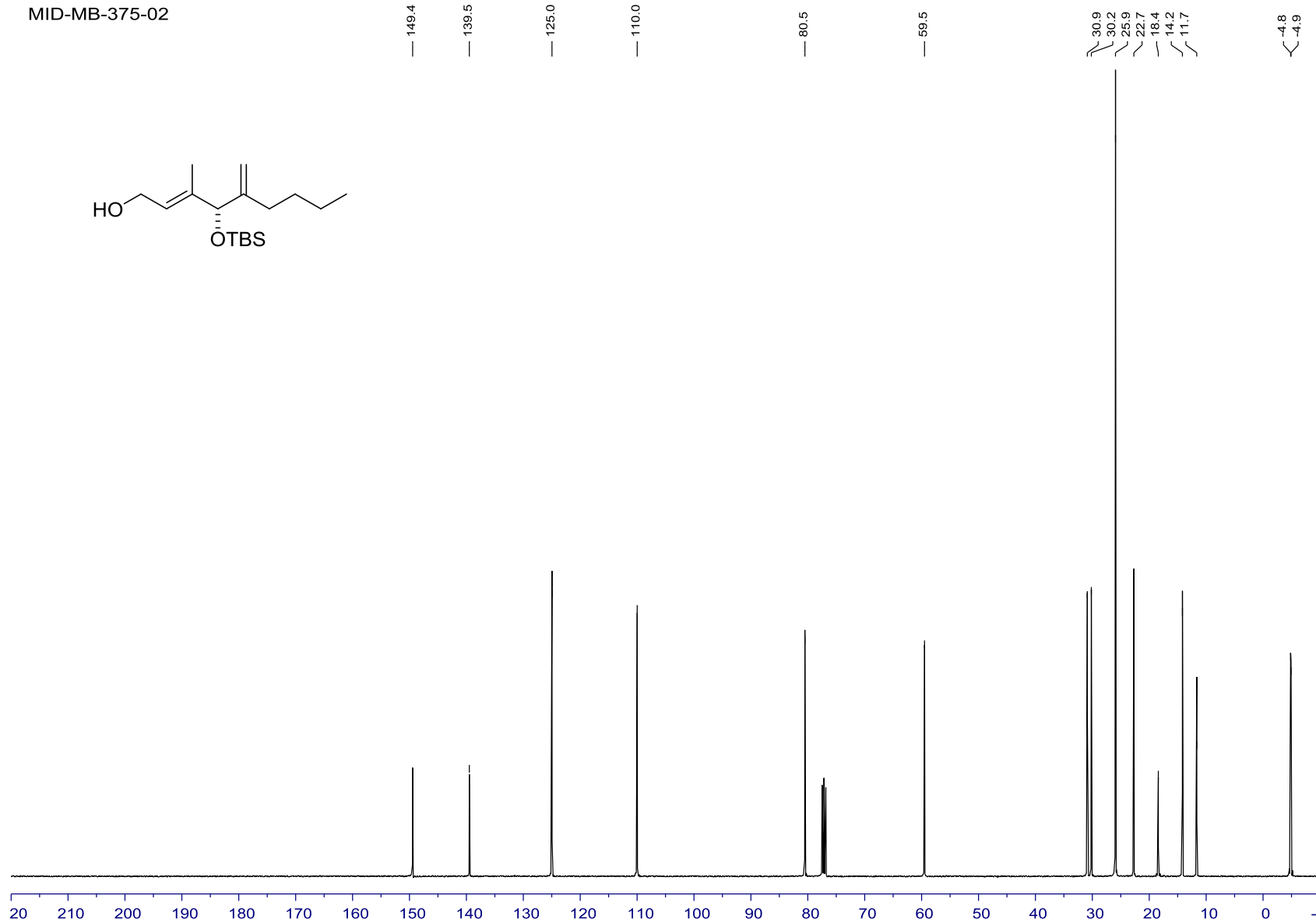
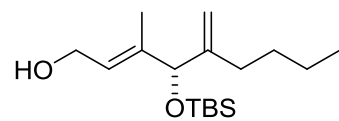
1.38
1.30
1.28
1.26

0.90
0.89
0.88
0.87
0.85

0.02
0.02



MID-MB-375-02



MID-MB-391-03

6.56
6.53
6.52
6.50

6.11
6.08

5.62
5.60
5.58
5.56

5.12

4.86

4.43

4.29

4.07

3.94
3.90

2.49

2.48

2.36

2.32

2.07

1.98

1.89

1.80

1.77

1.76

1.72

1.60

1.39

1.30

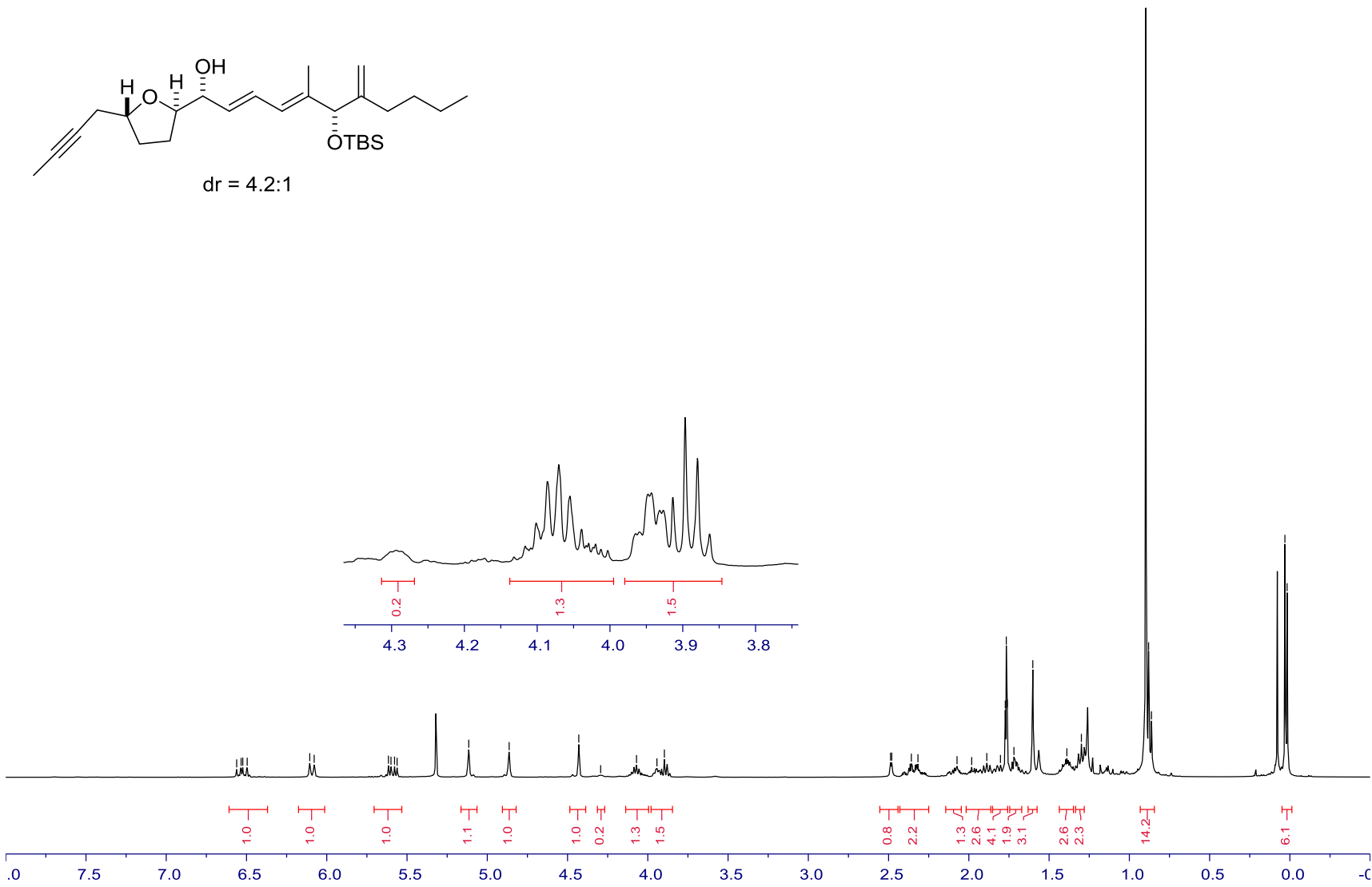
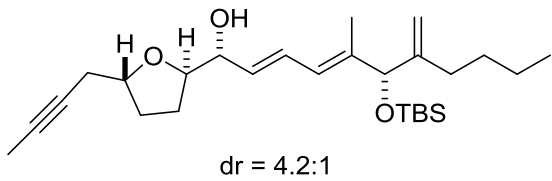
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0.88

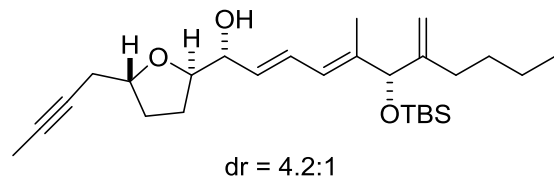
0.86

0.03

0.02



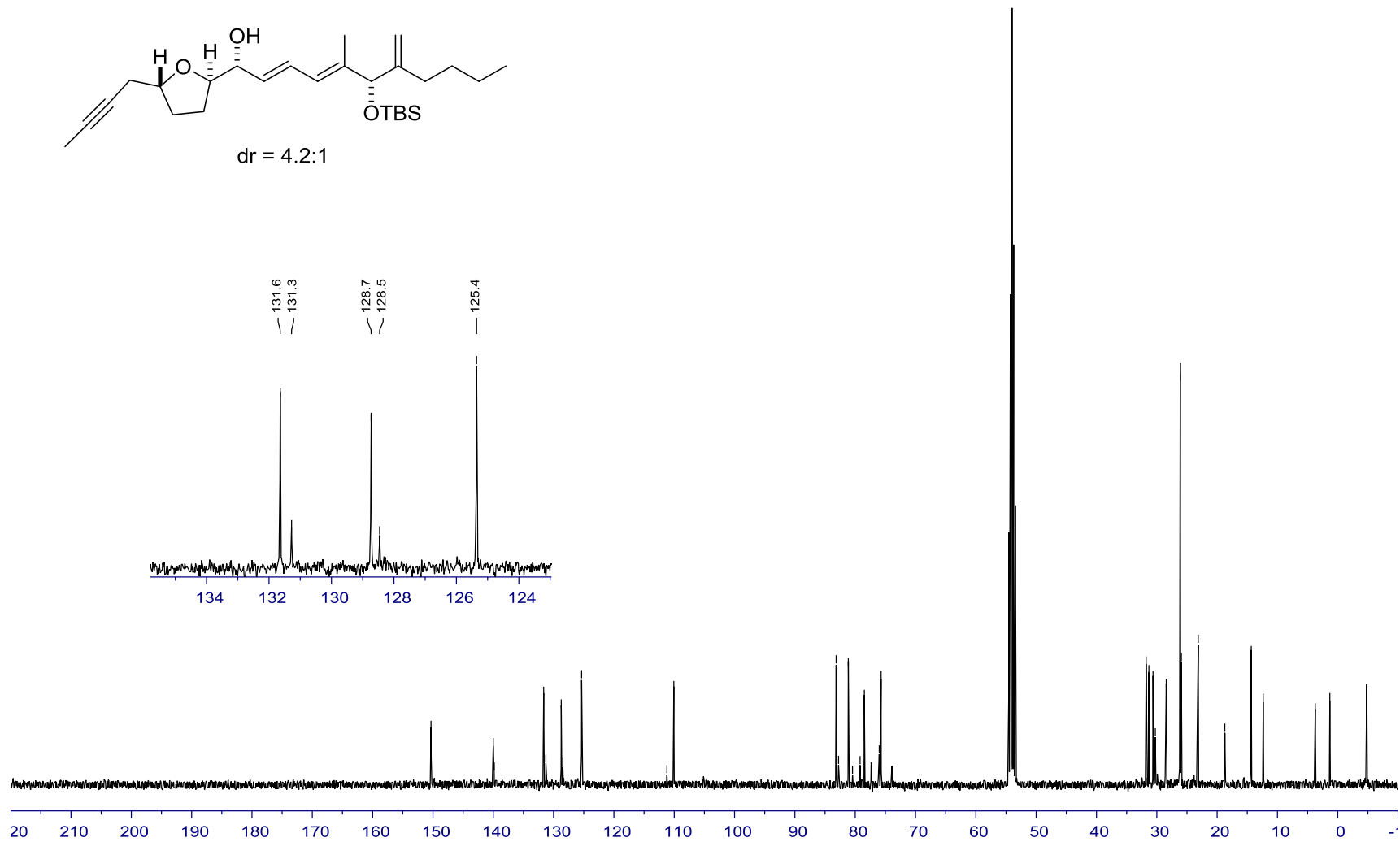
MID-MB-391-03



— 150.3
∩ 140.0
∩ 139.8
∩ 131.6
∩ 131.3
∩ 128.7
∩ 128.5
∩ 125.4
∩ 111.2
∩ 110.1

83.2
82.8
81.1
80.4
79.2
78.5
76.0
75.7

31.8
31.3
30.6
30.2
28.4
26.1
25.9
23.1
18.7
14.3
12.4
— 3.7
— 1.3
— -4.8



VAL-VC-047-01

6.57
6.56
6.54
6.53
6.50

6.11
6.08

5.62
5.60
5.58
5.57

5.12

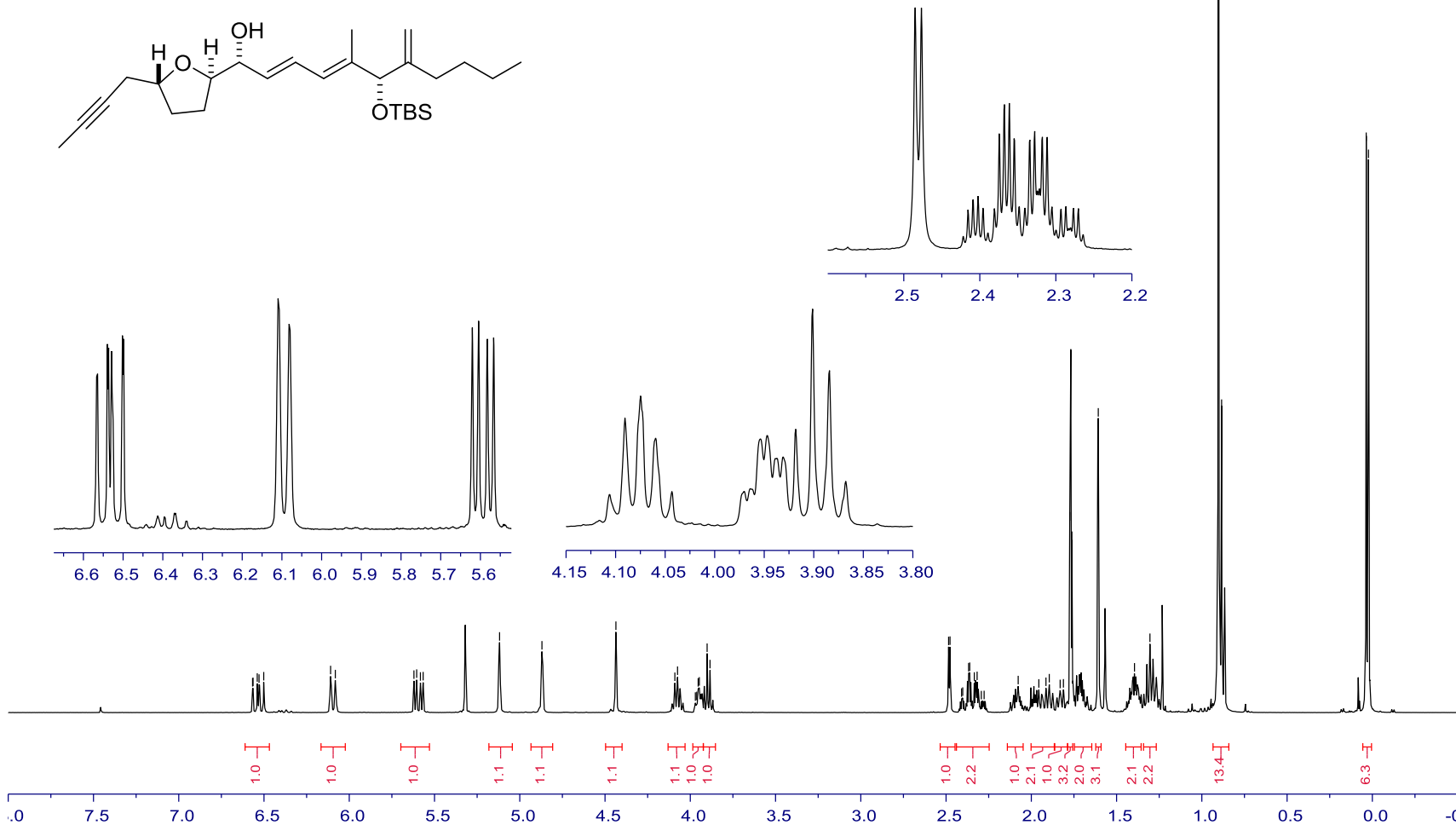
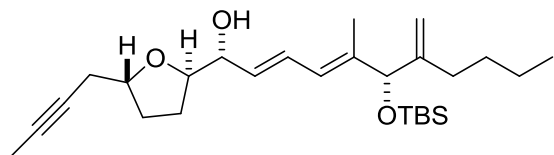
4.87

4.44
4.09
4.07
3.97
3.96
3.95
3.95
3.90
3.88

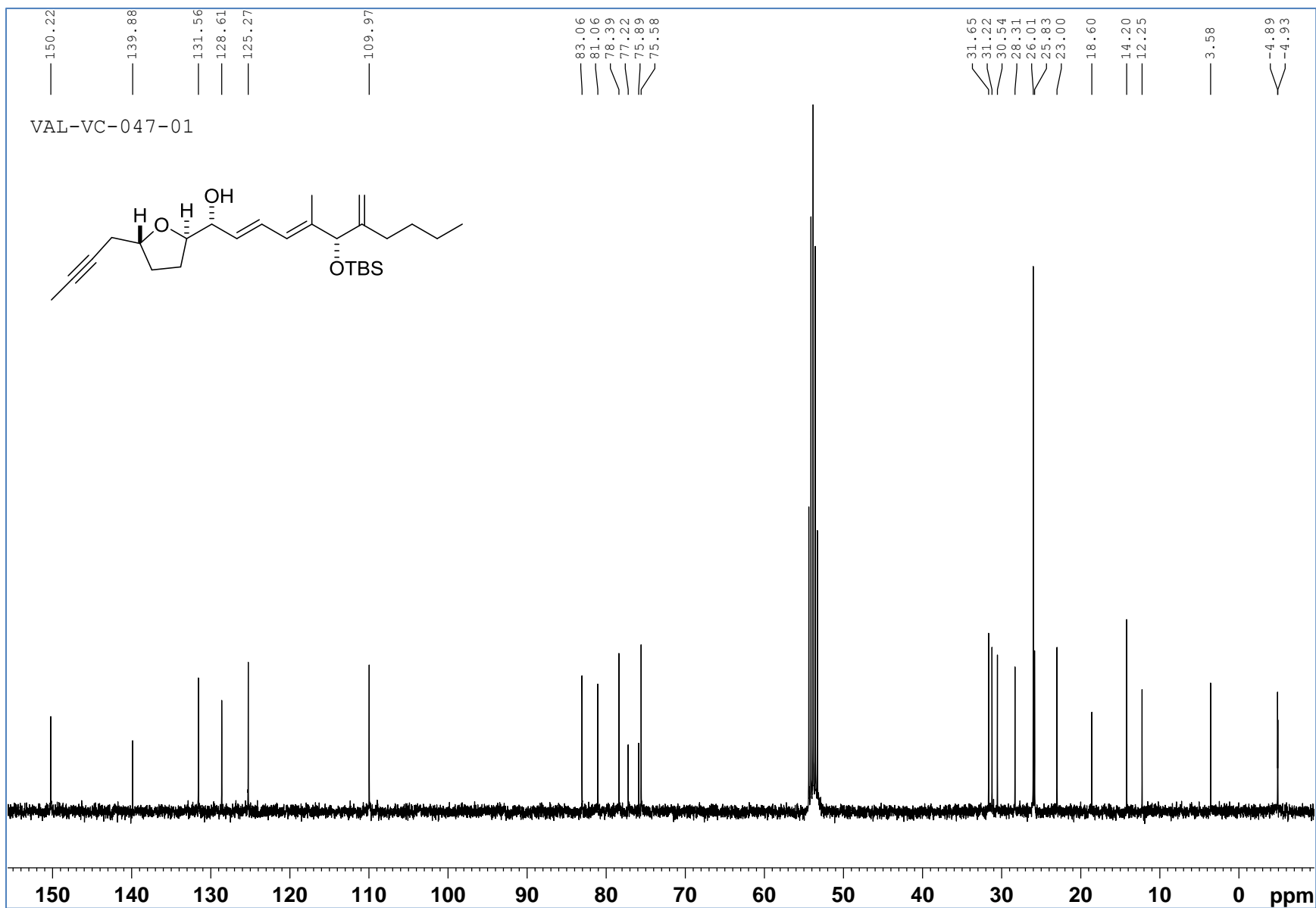
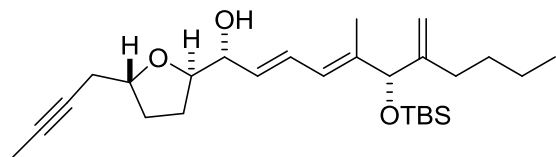
2.49
2.48
2.41
2.40
2.37
2.36
2.33
2.32
2.29
2.28
2.08
1.96
1.91
1.89
1.83
1.81
1.77
1.76
1.61
1.61
1.39
1.30

0.90
0.88

0.04
0.02

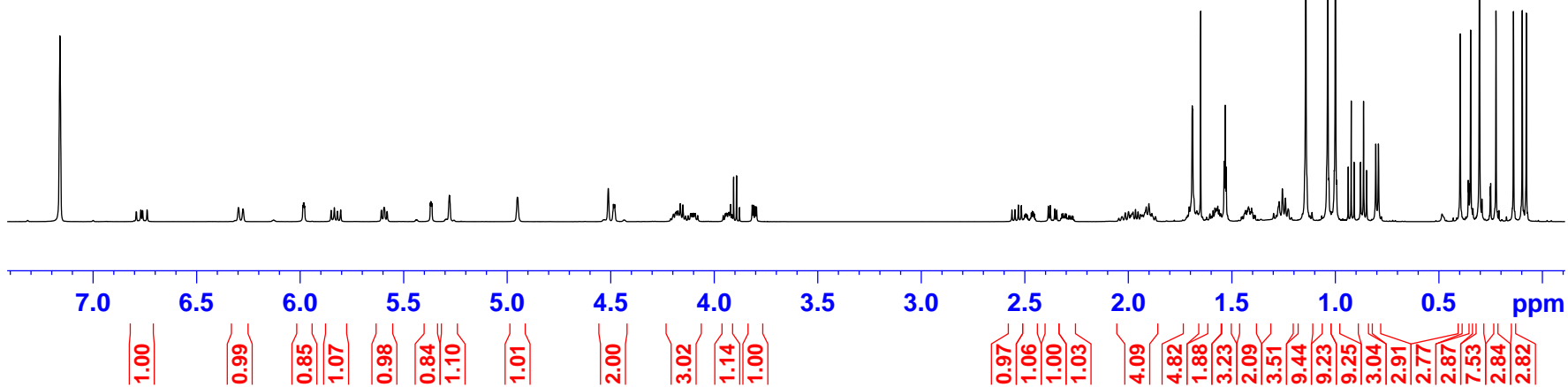
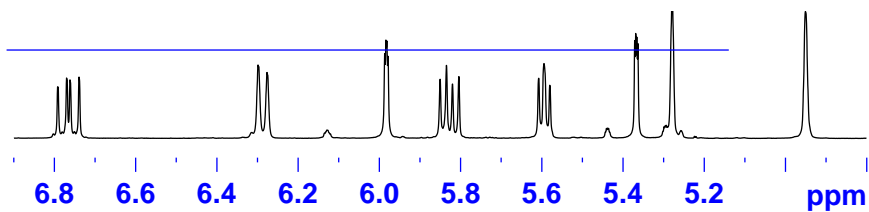
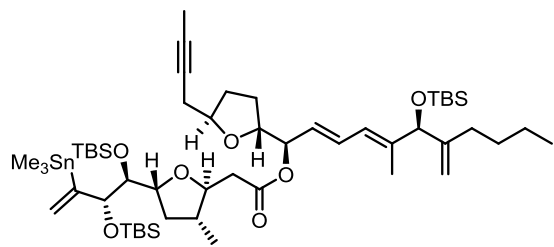


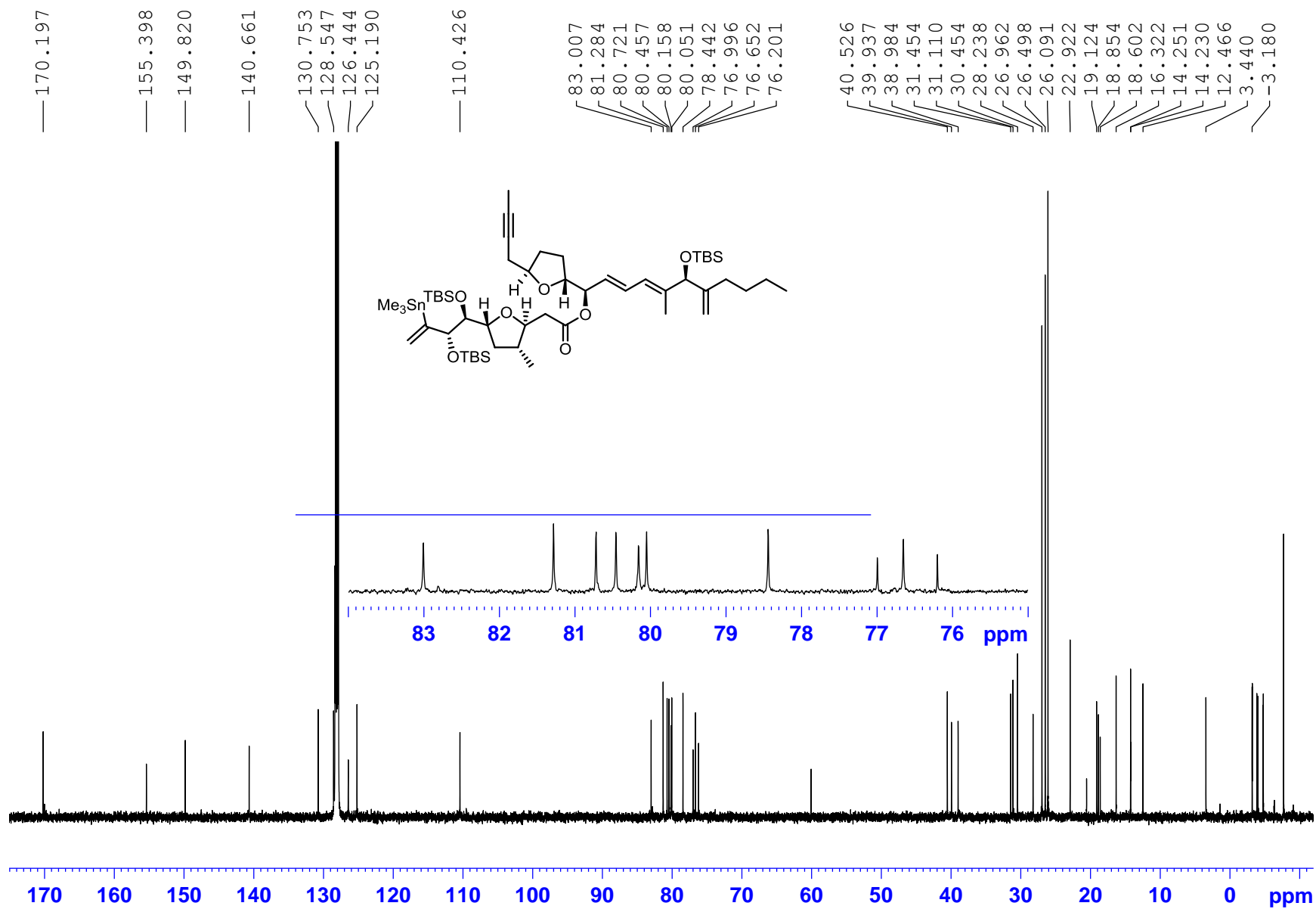
VAL-VC-047-01



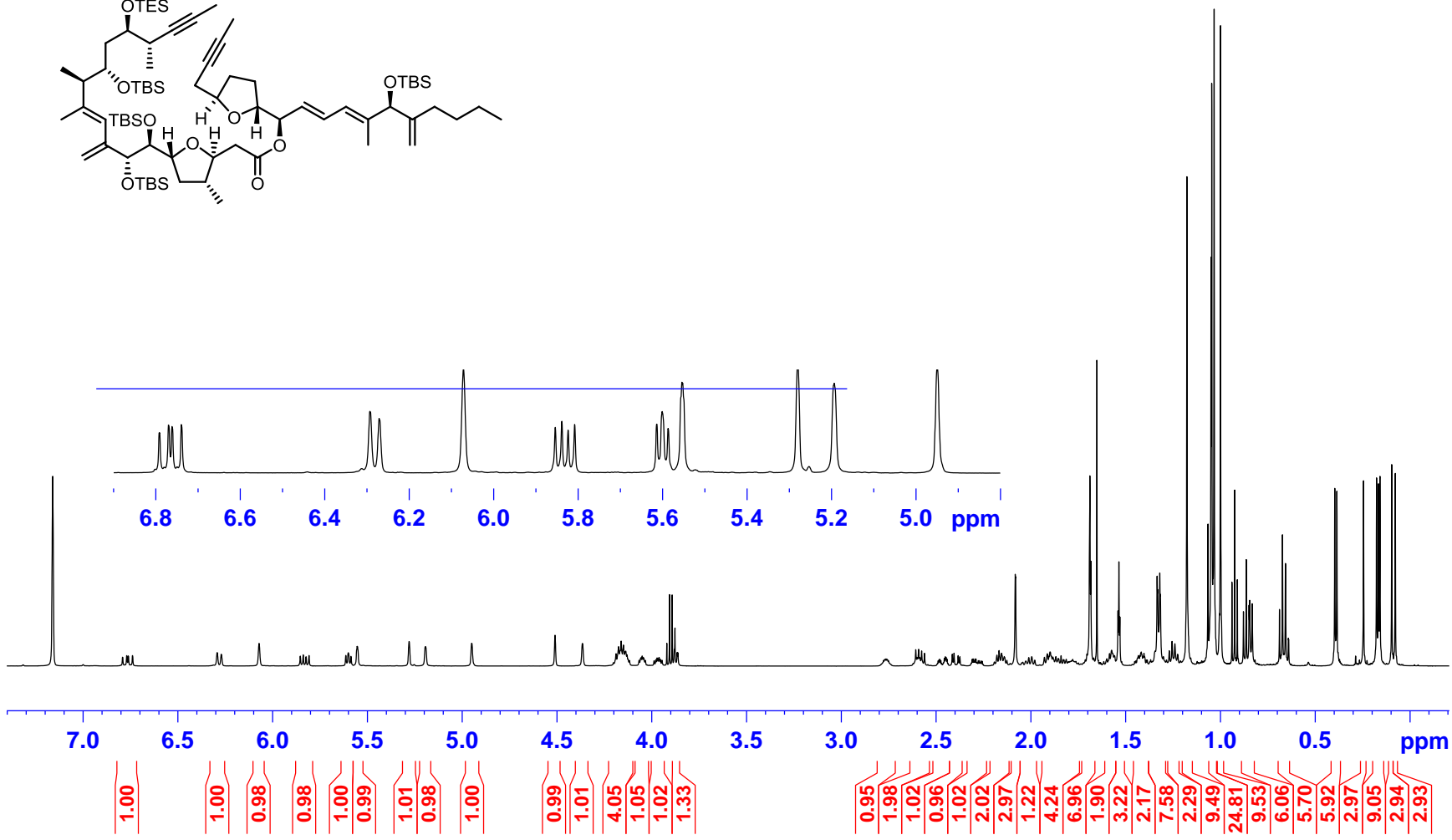
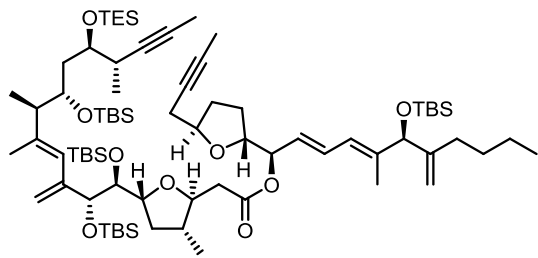
6.792
6.770
6.761
6.739
6.299
6.297
6.277
5.984
5.982
5.850
5.835
5.820
5.804
5.607
5.595
5.580
5.369
5.366
5.279
5.279
4.951
4.512
4.487
4.481
4.164
4.152
3.817
3.810
3.802
3.796

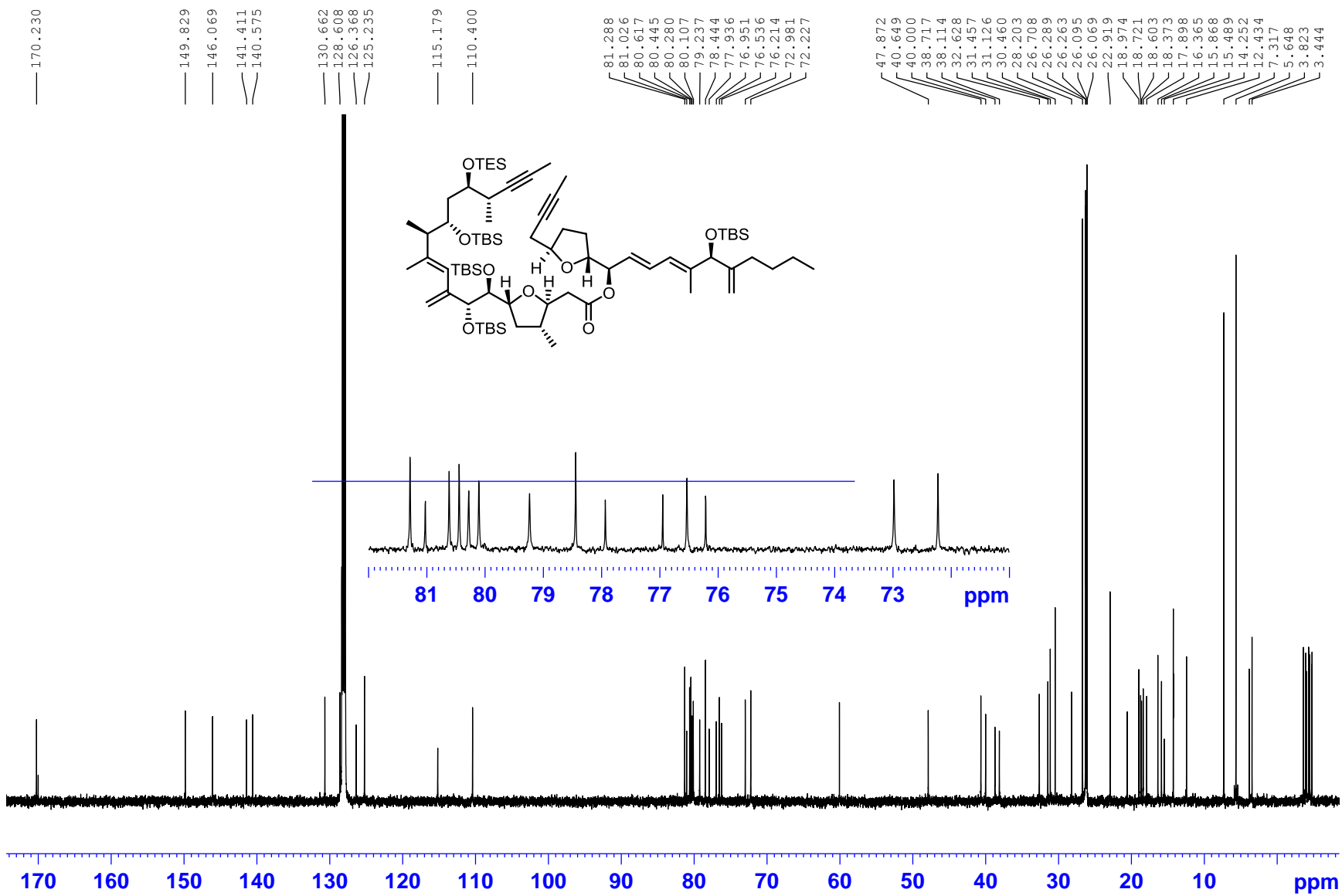
2.562
2.548
2.531
2.517
2.386
2.377
2.355
2.346
1.691
1.690
1.537
1.532
1.527
1.143
1.037
1.000
0.879
0.864
0.849
0.805
0.792
0.397
0.347
0.304





6.791
6.770
6.761
6.739
6.293
6.292
6.271
6.071
5.854
5.838
5.824
5.808
5.614
5.601
5.587
5.554
5.552
5.280
5.194
4.950
4.510
4.365
4.175
4.161
4.149
2.607
2.592
2.576
2.561
2.415
2.406
2.384
2.375
2.083
2.081
1.689
1.684
1.652
1.334
1.331
1.320
1.177
1.046
1.033
1.000
0.879
0.864
0.849
0.846
0.833
0.397
0.386
0.245
0.176
0.166
0.159
0.097
0.078

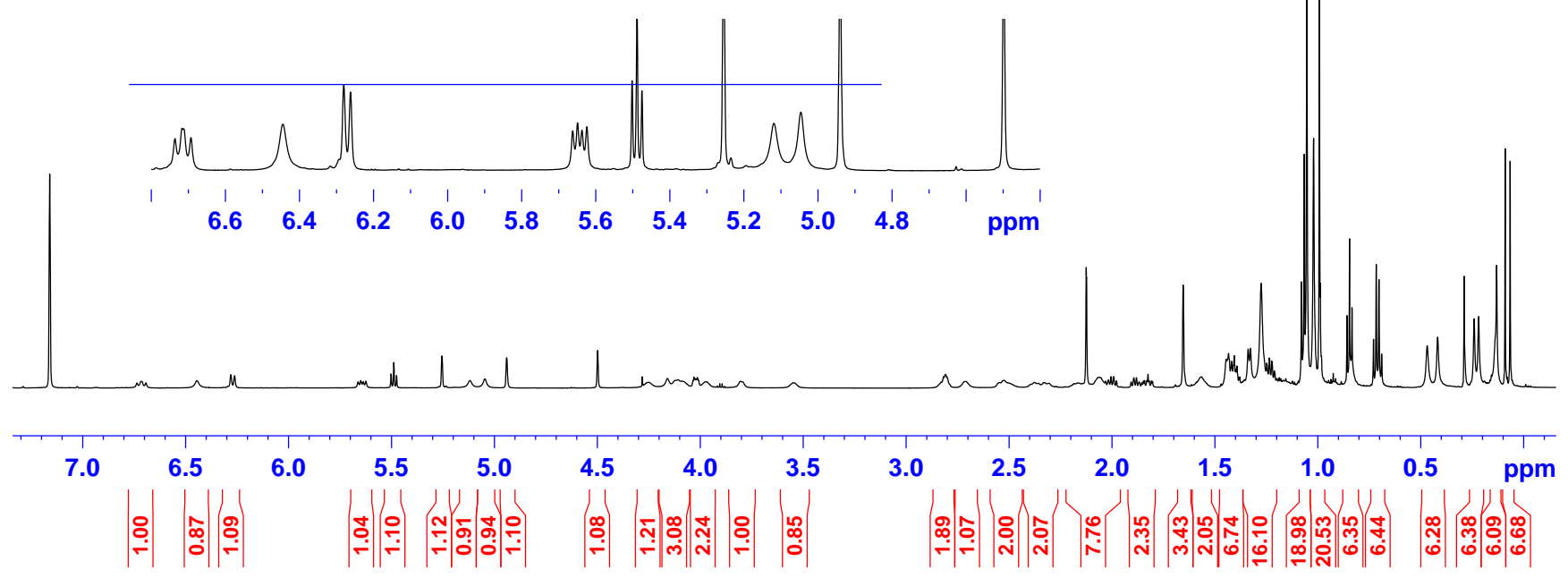
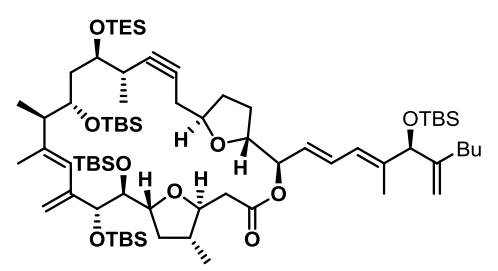


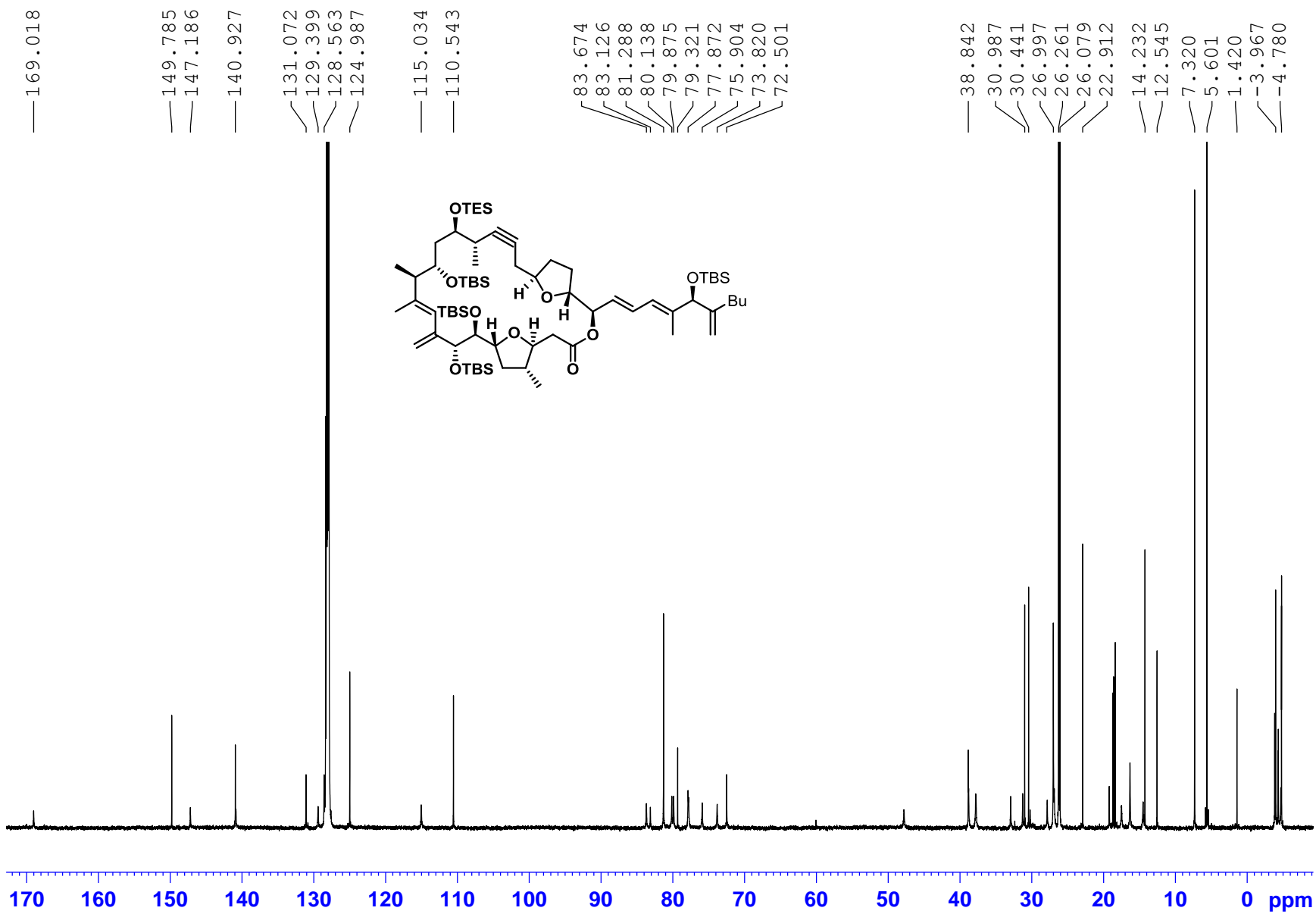


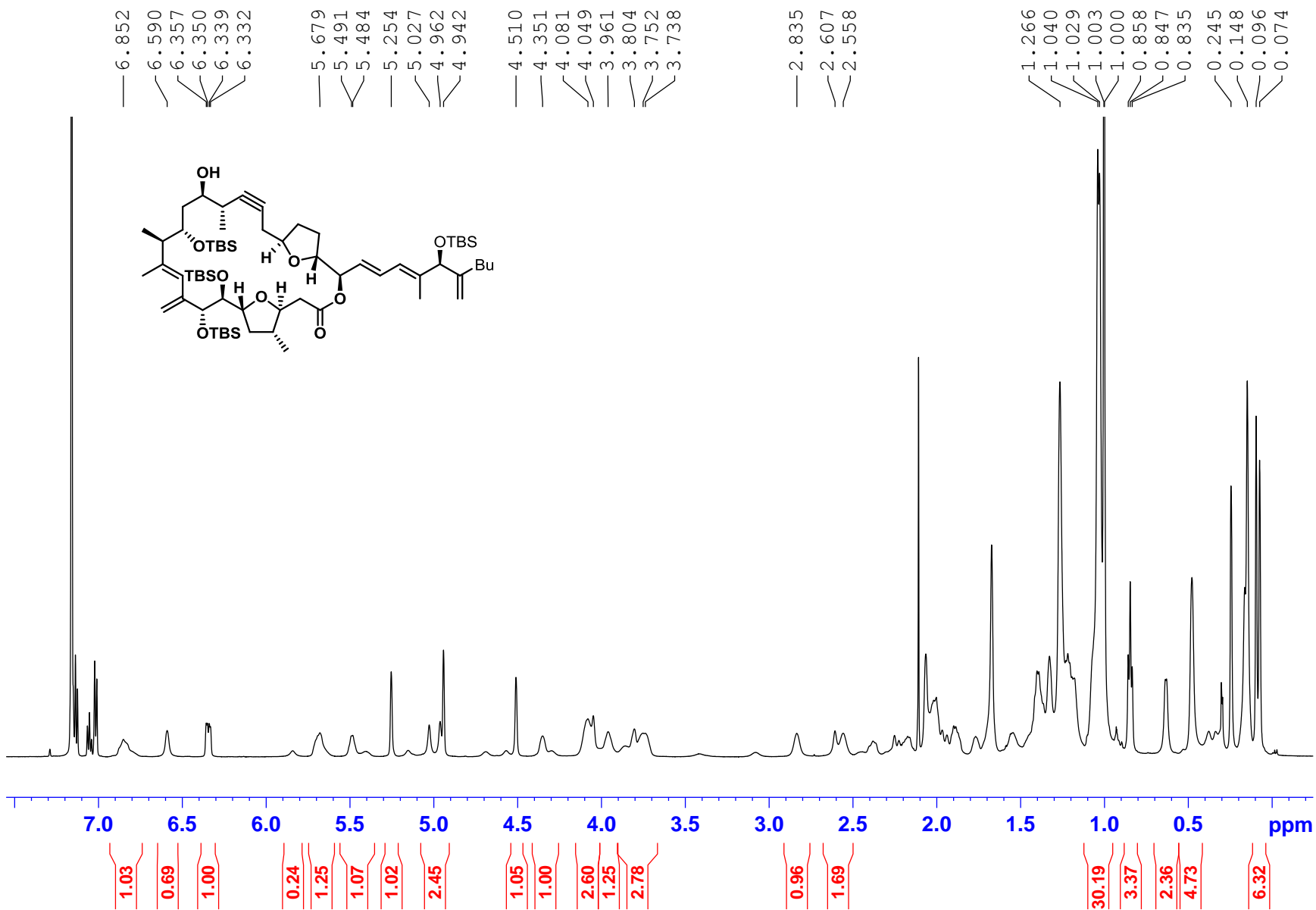
6.736
6.717
6.712
6.693
6.445
6.280
6.262
5.662
5.649
5.637
5.624
5.502
5.489
5.475
5.255
5.119
5.046
4.941

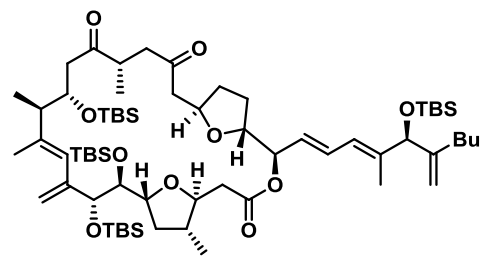
— 4.498
— 4.252
— 4.159
— 3.972
— 3.805
— 3.795
— 3.546

— 2.709
— 2.523
— 2.376
— 2.329
— 2.125
— 2.123
— 1.654
— 1.338
— 1.327
— 1.066
— 1.053
— 1.020
— 0.992
— 0.858
— 0.846
— 0.834
— 0.729
— 0.716
— 0.703
— 0.690
— 0.469
— 0.418









6.529
6.507
6.498
6.476
6.024
6.002
5.977

5.484
5.081
5.080
4.936
4.849

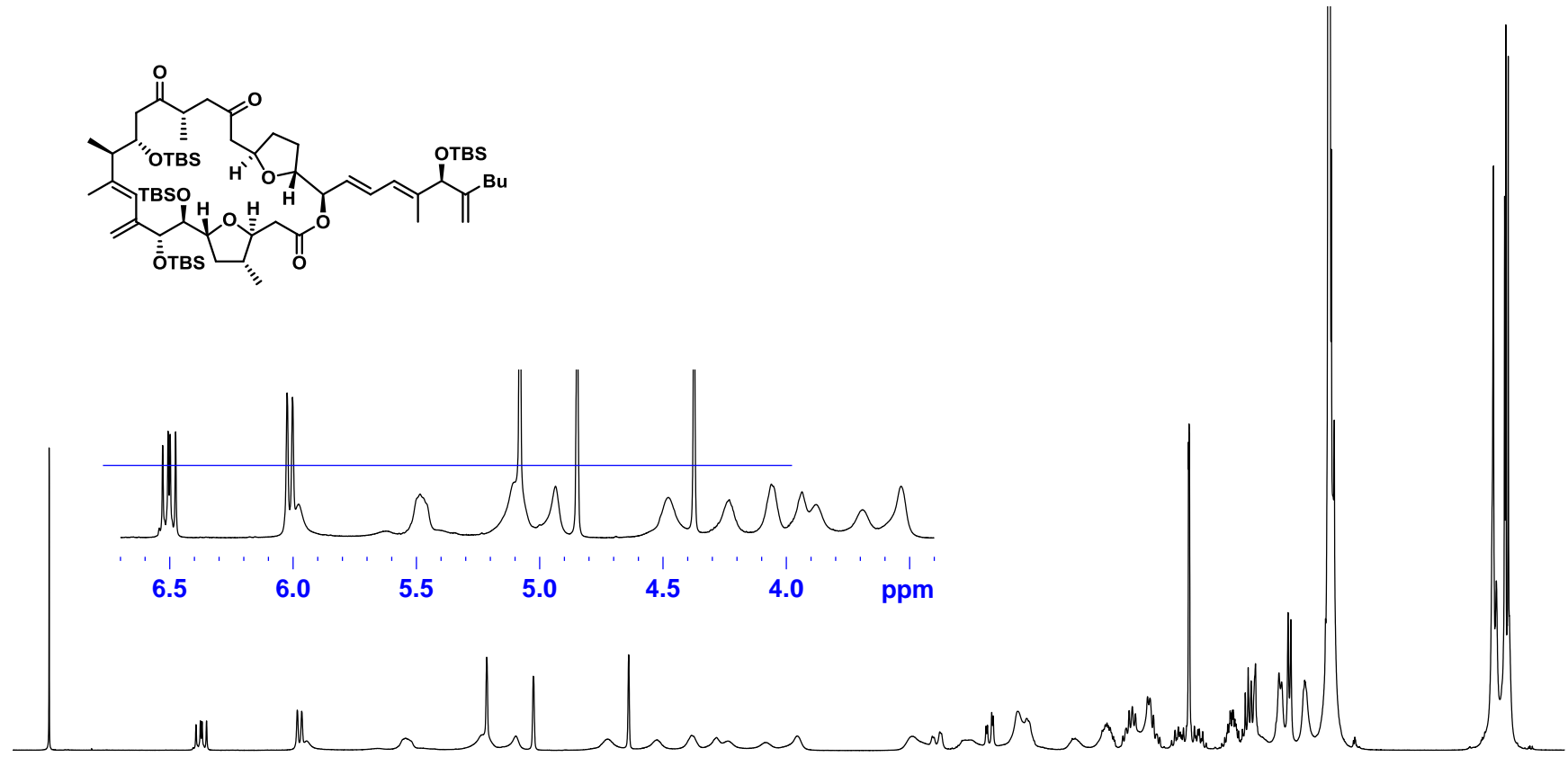
4.478
4.374
4.231
4.061
4.052
3.936
3.880
3.691
3.534

2.962
2.861
2.824
2.817
2.594
2.587
2.565
2.558
2.436
2.392

1.881
1.866
1.850
1.790
1.778
1.586
1.583
1.090
1.076

0.891
0.884
0.881

0.067
0.053
0.011
0.005



6.5
6.0
5.5
5.0
4.5
4.0
ppm

7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

1.00

1.63

1.08

2.74

0.95

1.02

1.11

1.11

0.95

1.12

1.63

0.77

1.15

2.62

1.32

1.28

4.76

1.00

2.18

6.26

6.32

2.25

5.06

3.35

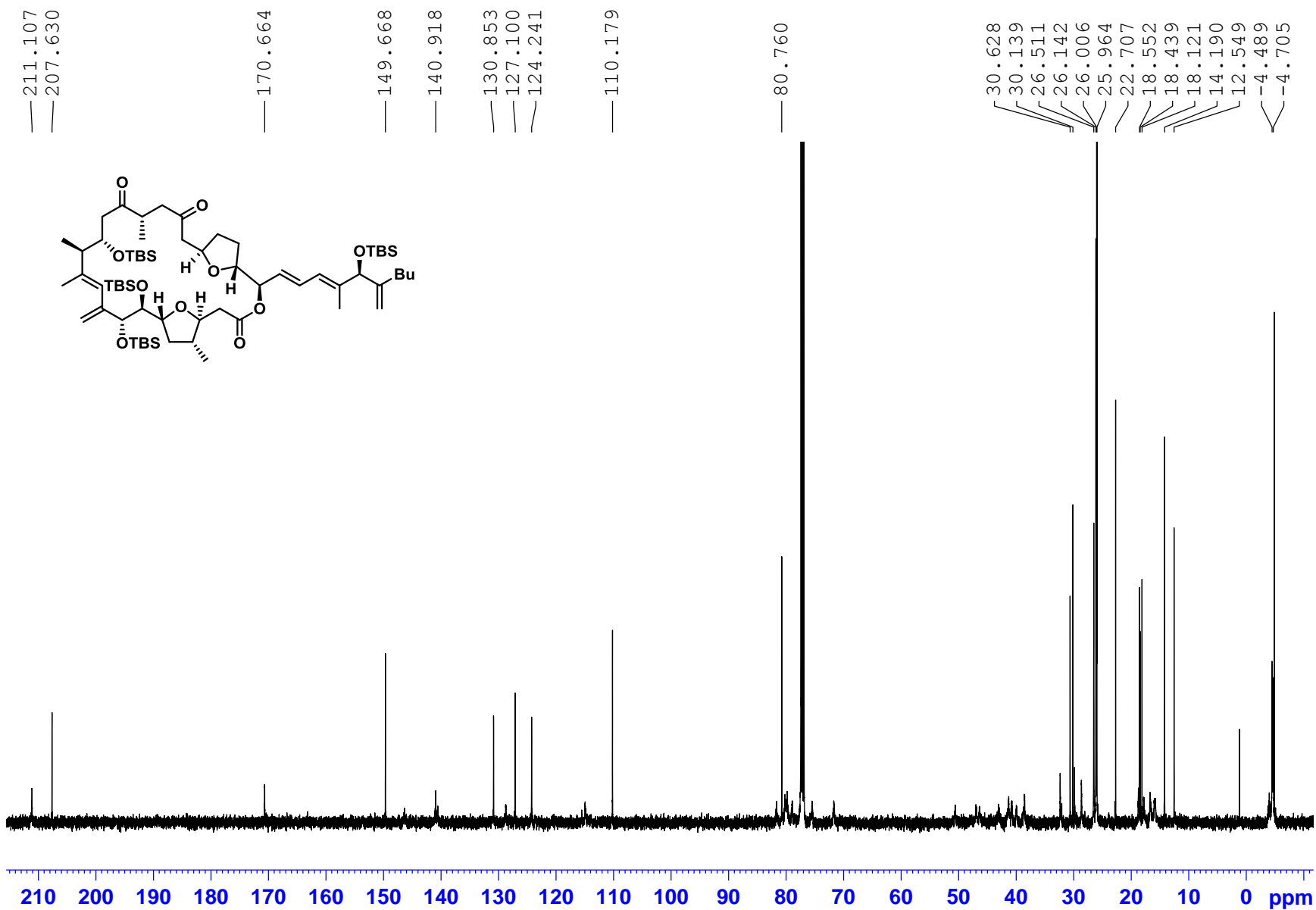
3.38

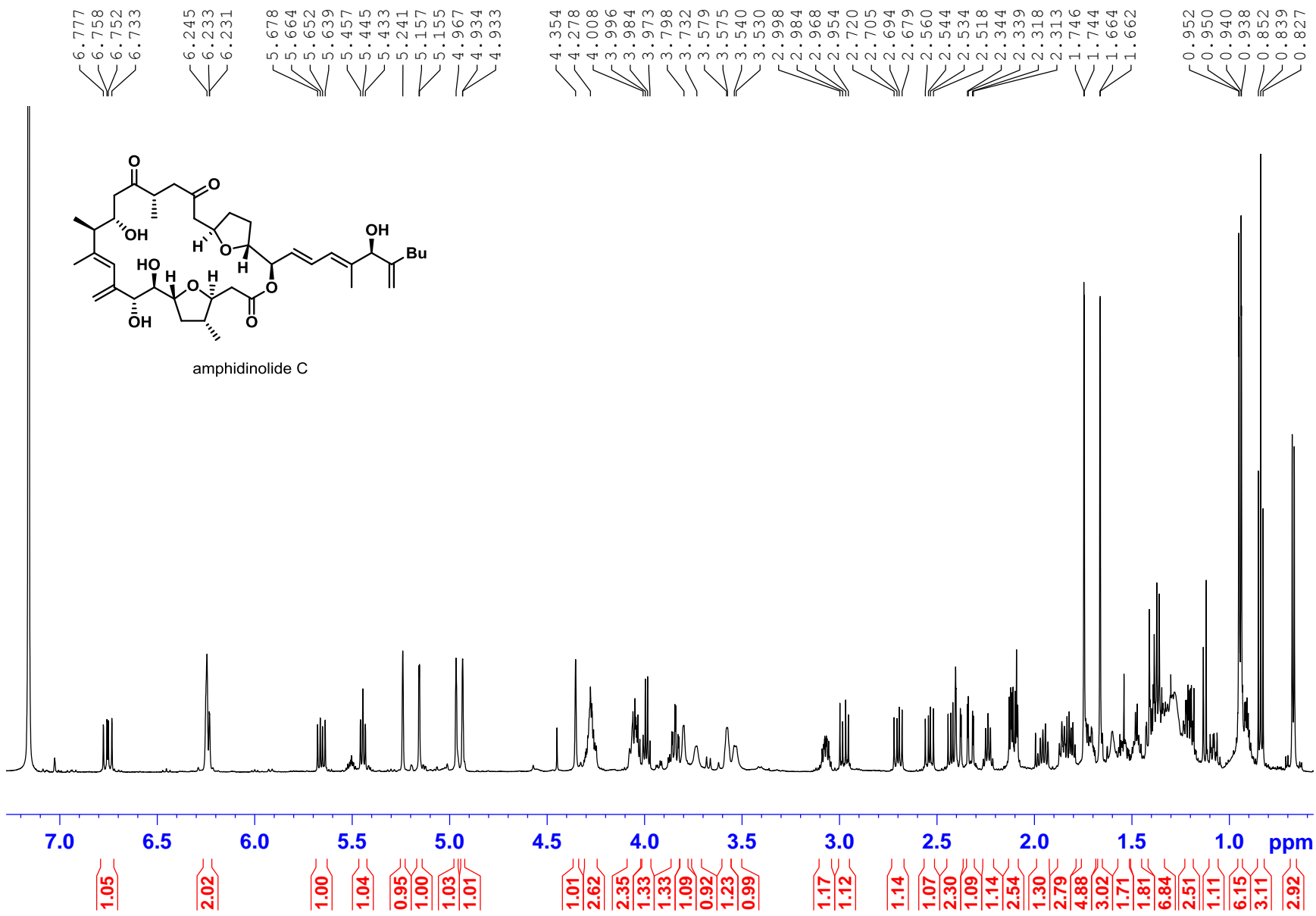
3.56

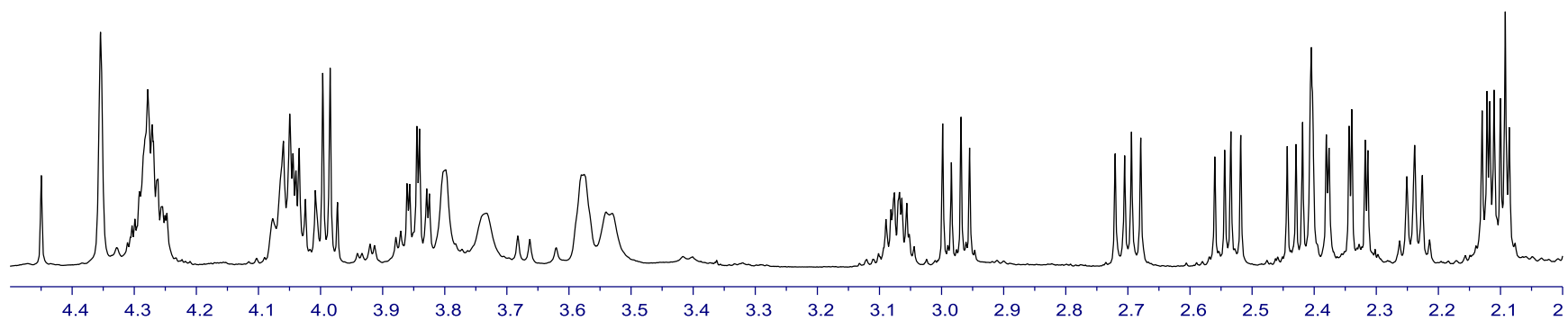
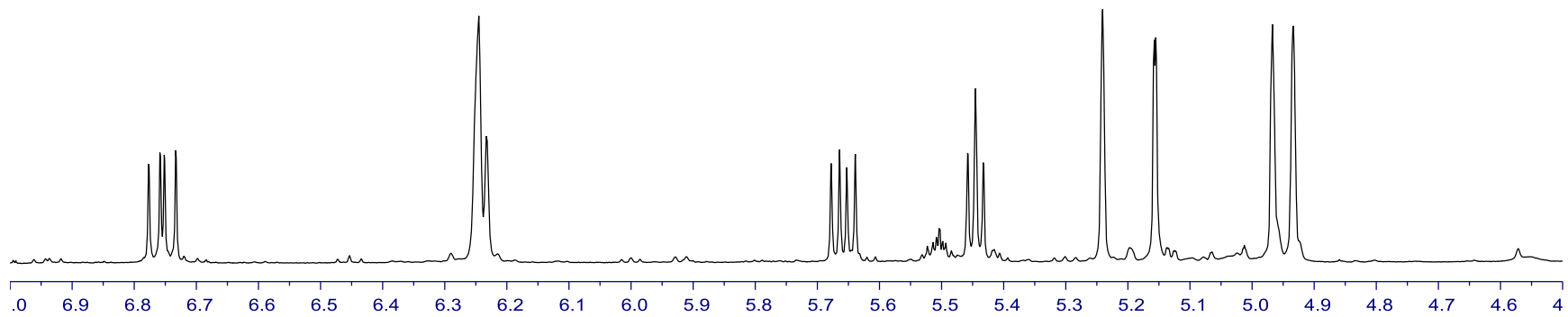
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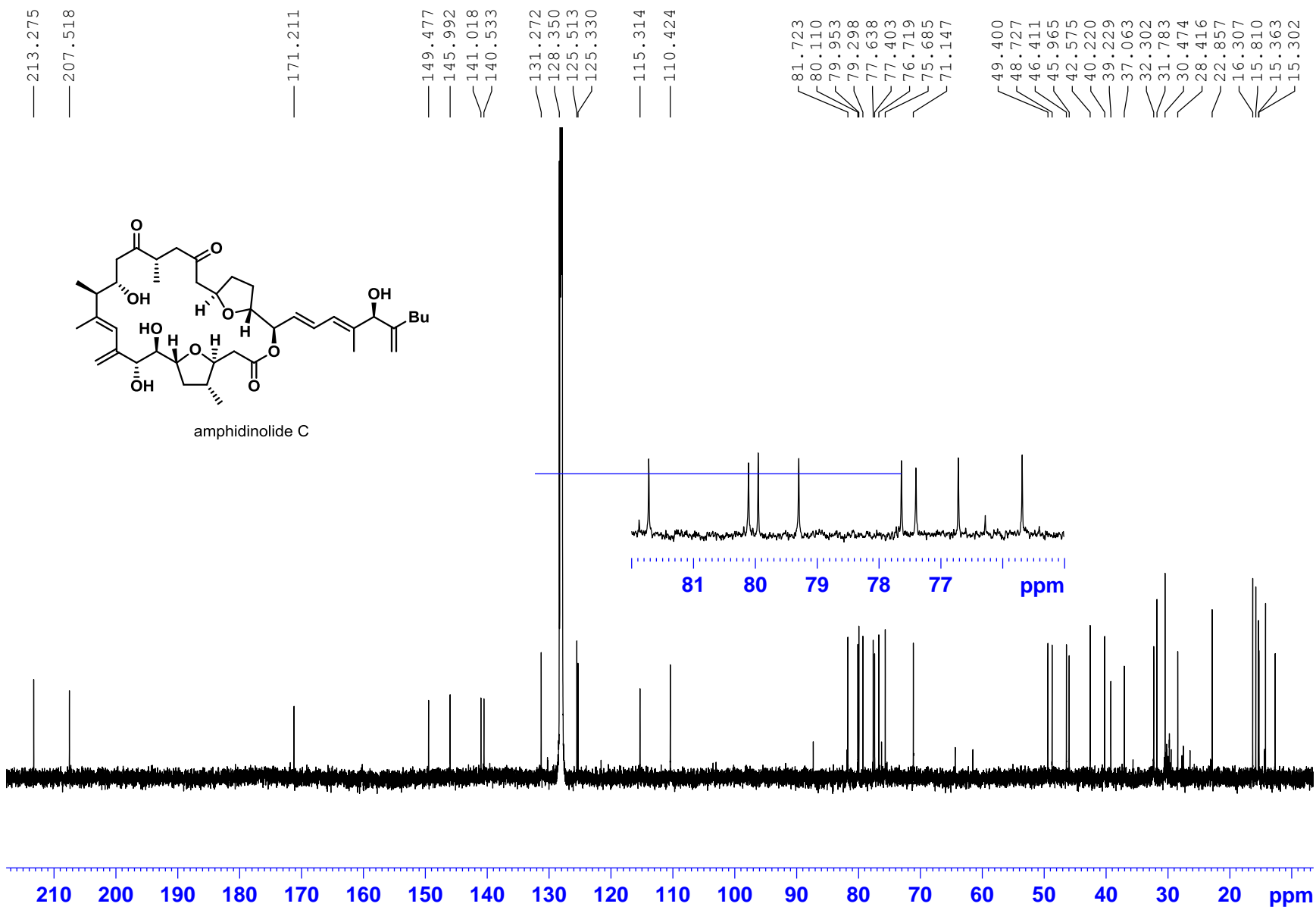
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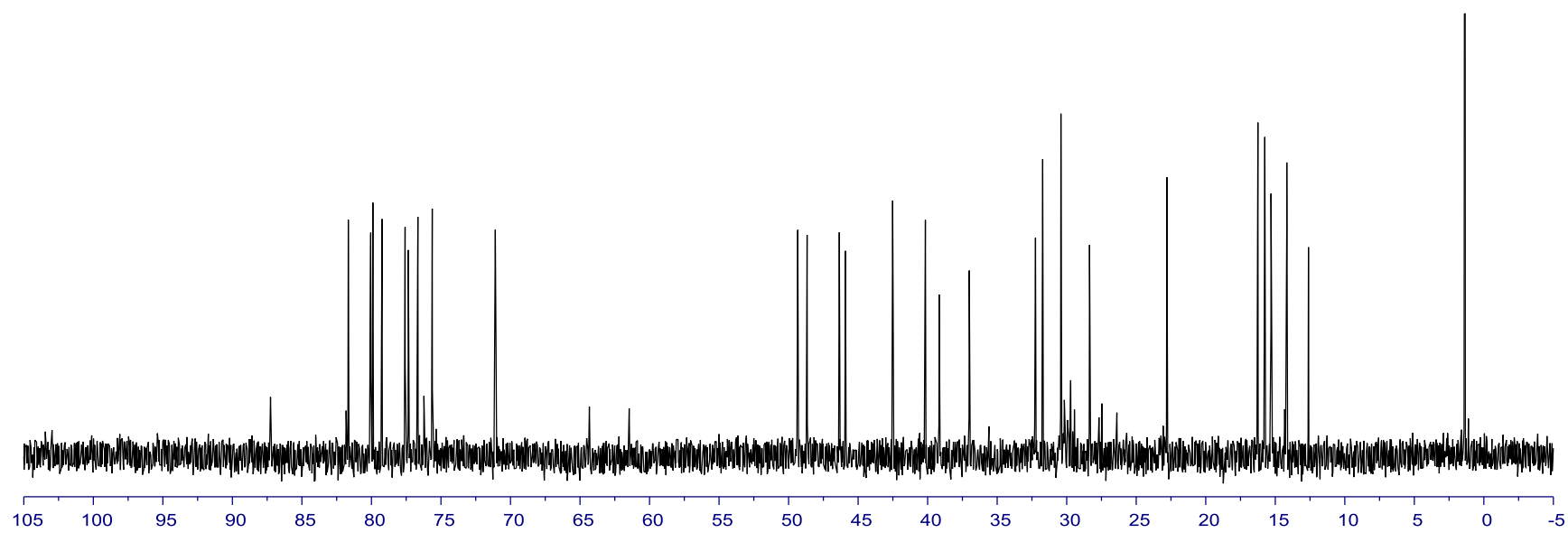
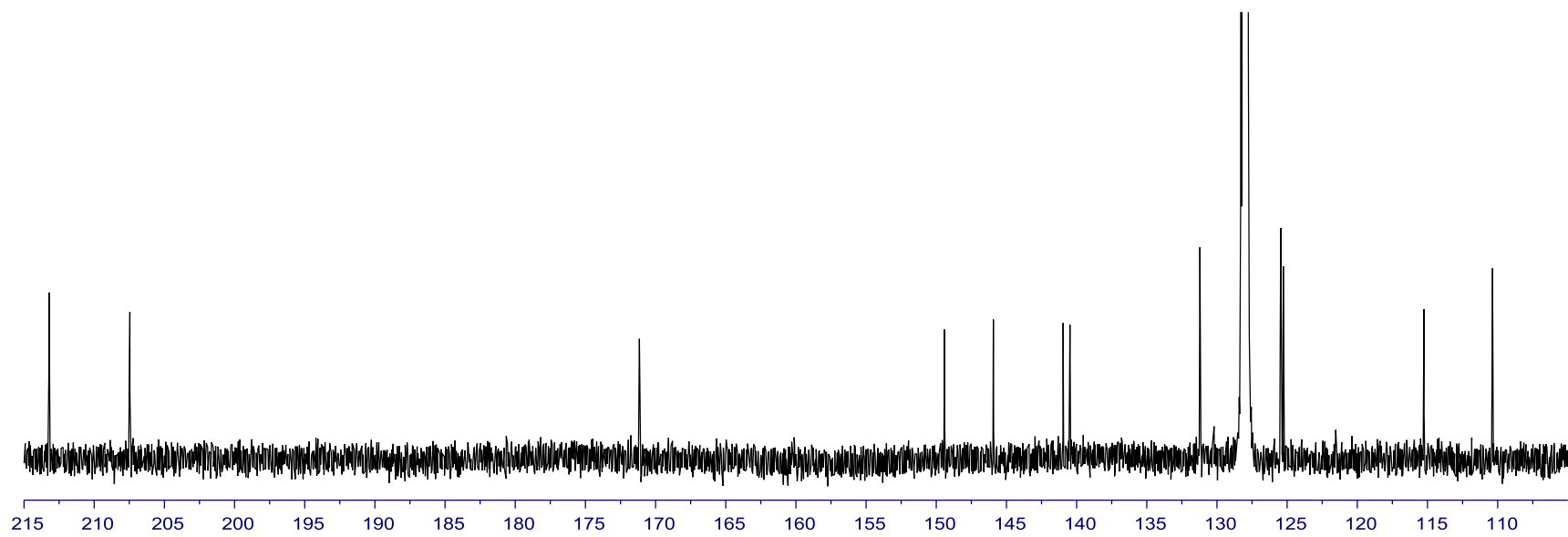
13.46



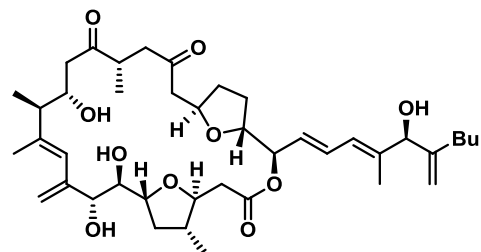




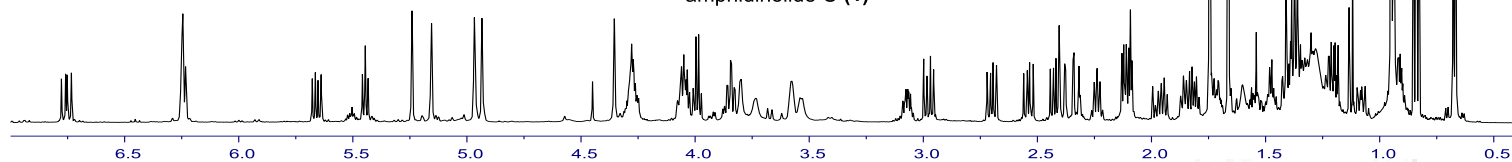




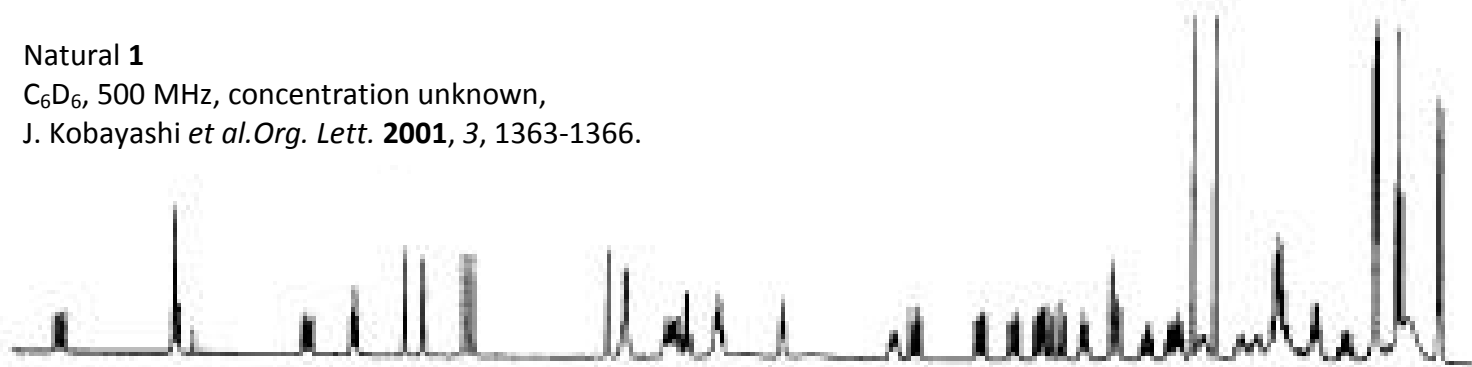
Synthetic **1**
C₆D₆, 600 MHz, 3.3 mg in 0.18 mL,
this study.



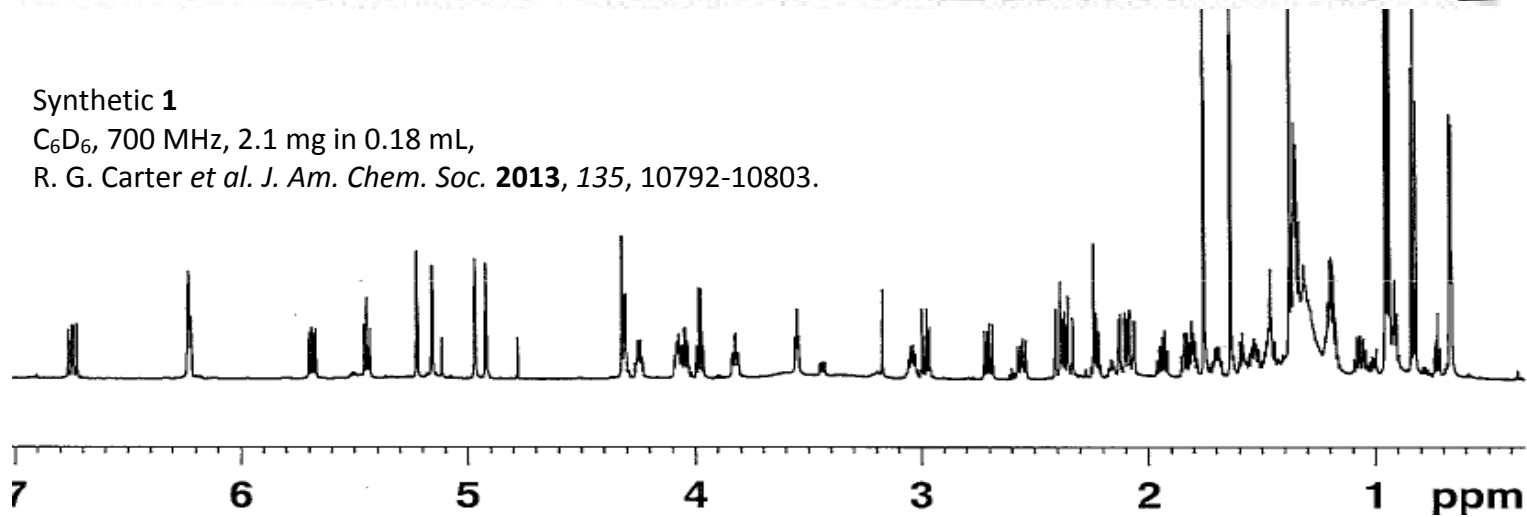
amphidinolide C (**1**)



Natural **1**
C₆D₆, 500 MHz, concentration unknown,
J. Kobayashi *et al. Org. Lett.* **2001**, *3*, 1363-1366.



Synthetic **1**
C₆D₆, 700 MHz, 2.1 mg in 0.18 mL,
R. G. Carter *et al. J. Am. Chem. Soc.* **2013**, *135*, 10792-10803.



Comparison of the ¹H NMR data of amphidinolide C (**1**)

