SUPPORTING INFORMATION

Total Synthesis of Aquatolide

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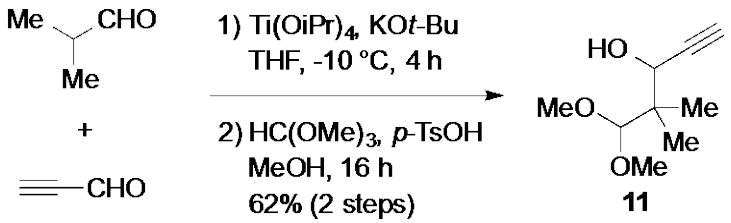
General Experimental Remarks

All non-aqueous reactions were performed under an argon atmosphere in flame-dried glassware with rigid exclusion of moisture from the reaction setup. Propynal was synthesized according to a recent literature procedure.[1] 3-Benzyloxy-1-bromopropane was prepared in two steps from 1,3-propanediol, as described recently.[2] All other reagents were obtained from commercial sources and were used without any extra purification. Anhydrous THF and CH_2Cl_2 were obtained by distillation under nitrogen atmosphere from appropriate drying agents. Other anhydrous solvents were used as received from Sigma-Aldrich. The photoreactions were carried out in a quartz reaction vessel with a Rayonet RPR 300 nm. ^{1}H NMR and ^{13}C NMR (APT) spectra were recorded in $CDCl_3$ on a Bruker Avance ARX 400 (^{13}C 100 MHz) or Varian Mercury 300 spectrometer. Chemical shifts (δ in ppm) and coupling constants (J in Hz) were determined by reference to residual solvent resonances. Acid labile compounds were measured in $CDCl_3$, filtered over Fluka neutral aluminum oxide. IR spectra were recorded on a Bruker IFS 28 FT-spectrophotometer and wavelengths are reported in cm^{-1}. High and low resolution mass measurements were performed with an AccuTOF GC-MS equipped with the ionization methods EI, FI and FD. Optical rotations ($[\alpha]^{20}_D$) were measured on a Perkin-Elmer 241 polarimeter. Chiral HPLC analysis was performed using a Shimadzu LC-20AD with a Shimadzu SPD-M20A Diode Array detector. Chiral resolution was performed using a Shimadzu SCL-10Avp equipped with Shimadzu LC8-A preparative pumps, Shimadzu SPD-10Avp UV-VIS detector and a Gilson 215 Liquid Handler Fraction Collector. Flash column chromatography purifications were carried out on Biosolve 60 Å (0.032–0.063 mm) silica gel using the indicated eluent. Progress of the reactions was monitored by thin layer chromatography using Merck silica gel 60 F_{254} pre-coated plates. Compounds were visualized by UV absorbance at 254 nm and by staining with aqueous potassium permanganate.

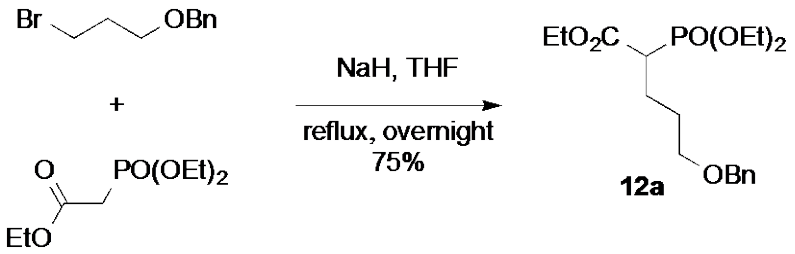
Experimental procedures



5,5-Dimethoxy-4,4-dimethylpent-1-yn-3-ol (11)

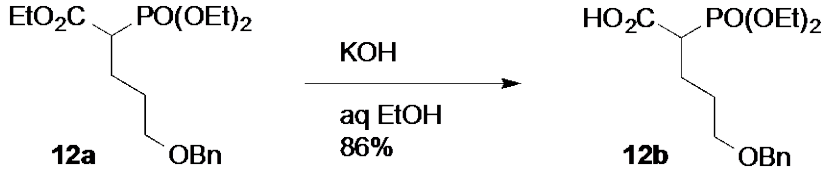
A solution of Ti(O*i*Pr)$_4$ (3.79 mL, 12.5 mmol, 2.5 equiv) and KO*t*-Bu (1.40 g, 12.5 mmol, 2.5 equiv) in anhydrous THF (15 mL) was mixed for 10 min at rt. This yellowish solution was subsequently cooled to -10 °C, after which a solution of propynal (0.41 g, 7.5 mmol, 1.5 equiv) and isobutyraldehyde (0.36 g, 5 mmol, 1 equiv) in anhydrous THF (10 mL) was added dropwise in 10 min. After stirring this mixture for 4 h between -10 and 0 °C the reaction was quenched with 2 N HCl solution (30 mL) and extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was partially removed until 5 mL remained in the flask. To this mixture methanol (50 mL), trimethyl orthoformate (1.64 mL, 15 mmol, 3 equiv) and *p*-toluenesulfonic acid (0.19 g, 1 mmol, 20 mol%) were respectively added and the brownish mixture was stirred overnight at rt. Next, the reaction was quenched by the addition of saturated $NaHCO_3$ solution (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. After purification by flash column chromatography (petroleum ether/EtOAc, 5:1), the title compound was obtained as

pale yellow oil in a yield of 0.554 g (3.22 mmol, 62%). TLC (petroleum ether/EtOAc, 5:1 v/v): R_f = 0.38. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (s, 1H), 4.20 (d, *J* = 2.0 Hz, 1H), 3.51 (s, 3H), 3.49 (s, 3H), 2.41 (d, *J* = 2.2 Hz, 1 H), 0.98 (s, 3H), 0.94 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ 111.83, 111.80, 67.95, 67.90, 59.11, 57.85, 18.85, 18.78, 18.23, 18.20. IR (neat): ν_{max} (cm^{-1}) = 3443, 3290, 1066, 646. HRMS (FD): m/z calculated for $C_9H_{17}O_3$ $(M+H)^+$ 173.1172, found 173.1176.



Ethyl 5-(benzyloxy)-2-(diethoxyphosphoryl)pentanoate (12a)

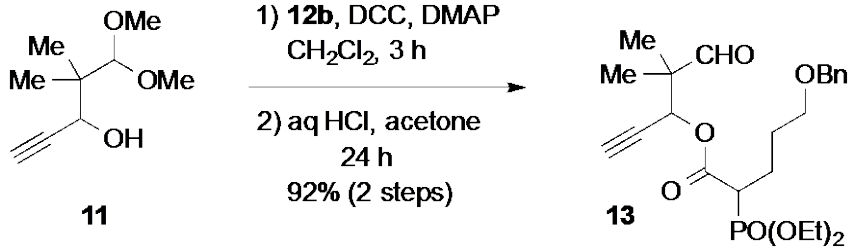
To a suspension of sodium hydride (60 wt% in mineral oil, 1.19 g, 29.8 mmol, 1.3 equiv) in anhydrous THF (20 mL), a solution of triethyl phosphonoacetate (5.65 g, 25.2 mmol, 1.1 equiv) in anhydrous THF (20 mL) was added dropwise. After mixing for 30 min, 3-benzyloxy-1-bromopropane (5.25 g, 22.9 mmol, 1 equiv) was added and the yellow mixture was refluxed overnight. The reaction was subsequently quenched with saturated NH_4Cl solution (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. After purification by flash column chromatography (petroleum ether/EtOAc, 1:2), the title compound was obtained as colorless oil in a yield of 6.38 g (17.1 mmol, 75%, 85% based on recovered starting material). TLC (petroleum ether/EtOAc, 1:2 v/v): R_f = 0.25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.24 (2m, 5H), 4.45 (s, 2H), 4.21-4.07 (m, 6H), 3.45 (dt, *J* = 6.2, 1.2 Hz, 2H), 2.96 (ddd, *J* = 22.7, 10.7, 4.2 Hz, 1H), 2.08-1.91 (m, 2H), 1.72-1.57 (m, 2H), 1.32-1.23 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.19, 169.14, 138.41, 128.33, 127.57, 127.52, 72.87, 69.46, 62.65 (dd, *J* = 11.7, 6.6 Hz), 61.34, 46.14, 44.83, 28.34 (d, *J* = 14.7 Hz), 23.98 (d, *J* = 4.8 Hz), 16.34 (dd, *J* = 24.0, 9.2 Hz), 14.14. IR (neat): ν_{max} (cm^{-1}) = 1730, 1247, 1017, 960. LRMS (FD): m/z calculated for $C_{18}H_{30}O_6P$ $(M+H)^+$ 373.2, found 372.2.



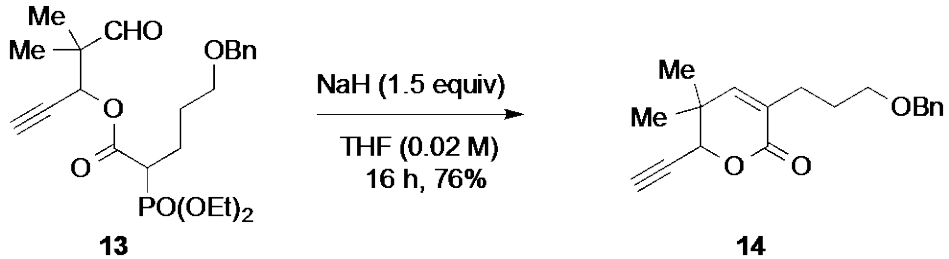
5-(Benzyloxy)-2-(diethoxyphosphoryl)pentanoic acid (12b)

To a solution of **12A** (6.38 g, 17.1 mmol, 1 equiv) in EtOH (50 mL), a solution of potassium hydroxide (4 M in water, 6.43 mL, 25.7 mmol, 1.5 equiv) was added at 0 °C. The temperature was allowed to come to rt while mixing overnight. Next, the solvent was removed and the concentrate was redissolved in water (100 mL). This aqueous solution was subsequently washed with Et_2O (3 x 50 mL) and then acidified to pH < 2 with concentrated hydrochloric acid. Next, the product was extracted from the water layer with EtOAc (4 x 100 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was obtained as a brownish oil in a yield of 5.08 (14.8 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 5H), 4.49 (s, 2H), 4.18 (dq, *J* = 23.6, 7.6 Hz, 4H), 3.53-3.45 (m, 2H), 3.01 (ddd, *J* = 23.0, 10.7, 4.0 Hz, 1H), 2.11–1.88 (m, 2H), 1.83–1.61 (m, 2H), 1.33 (td, *J* = 7.1, 3.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.79, 138.22,

128.28, 127.59, 127.50, 72.74, 69.31, 63.23 (dd, *J* = 56.3, 24.8 Hz), 45.14 (d, *J* = 131.3 Hz), 28.07 (d, *J* = 14.9 Hz), 23.82 (d, *J* = 4.9 Hz), 16.22 (d, *J* = 6.1 Hz). IR (neat): ν_{max} (cm^{-1}) = 1729, 1211, 1022. LRMS (FD): m/z calculated for $C_{16}H_{26}O_6P$ $(M+H)^+$ 345.1, found 345.2.

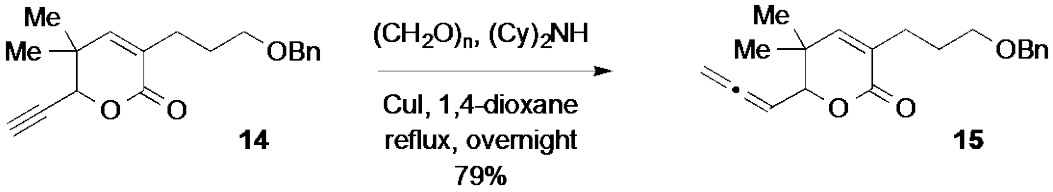


4,4-Dimethyl-5-oxopent-1-yn-3-yl 5-(benzyloxy)-2-(diethoxyphosphoryl)pentanoate (13)
To a solution of **11** (14.9 g, 86 mmol, 1 equiv), **12b** (30.6 g, 88 mmol, 1.03 equiv) and 4-dimethylaminopyridine (1.05 g, 8.6 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (200 mL), *N,N'*-dicyclohexylcarbodiimide (26.6 g, 129 mmol, 1.5 equiv) was added at 0 °C as a solid. After stirring for 3 h at 0 °C, full conversion was indicated by TLC. The reaction mixture was concentrated *in vacuo* and redissolved in acetone (440 mL). To this solution a 10% HCl solution (440 mL) was added at 0 °C. After mixing for 24 h, the product was extracted with CH_2Cl_2 (3 x 300 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. After purification by flash column chromatography (petroleum ether/EtOAc, 1:2), the title compound was obtained as a brownish oil in a yield of 36 g (79.6 mmol, 92%). The product is a mixture of two diastereoisomers. TLC (petroleum ether/EtOAc, 1:2 v/v): R_f = 0.30. TLC (petroleum ether/EtOAc, 1:1 v/v): R_f = 0.18. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 9.59 (s, 1H), 7.35-7.28 (m, 10H), 5.57 (d, *J* = 2.1 Hz, 1H), 5.55 (d, *J* = 2.1 Hz, 1H), 4.49 (s, 4H), 4.18-4.10 (m, 8H), 3.49-3.46 (m, 4H), 3.04 (dd, *J* = 10.3, 4.4 Hz, 1H), 2.99 (dd, *J* = 10.2, 4.5 Hz, 1H), 2.55 (s, 1H), 2.54 (s, 1H), 2.14-1.96 (m, 4H), 1.77-1.58 (m, 4H), 1.35-1.31 (m, 12H), 1.27 (s, 3H), 1.26 (s, 3H), 1.19 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.67, 201.57, 167.48 (d, *J* = 4.9 Hz), 167.15 (d, *J* = 5.3 Hz), 138.10, 128.04, 127.96, 127.20, 127.14, 76.17, 76.15, 72.39, 72.34, 68.97, 68.89, 68.82 67.52, 67.34, 62.50-62.29 (m), 49.07, 45.43 (d, *J* =120.4 HZ), 44.30, (d, *J* = 123.6 Hz) 27.73 (d, *J* = 10.2), 27.59 (d, *J* = 10.9 Hz), 23.82 (d, *J* = 4.5 Hz), 23.49 (d, *J* = 4.6 Hz), 18.58, 18.55, 17.28, 17.17, 16.13-15.88 (m). IR (neat): ν_{max} (cm^{-1}) = 3278, 1737, 1240, 1022, 698. HRMS (FD): m/z calculated for $C_{23}H_{34}O_7P$ $(M+H)^+$ 453.2037, found 453.2051.



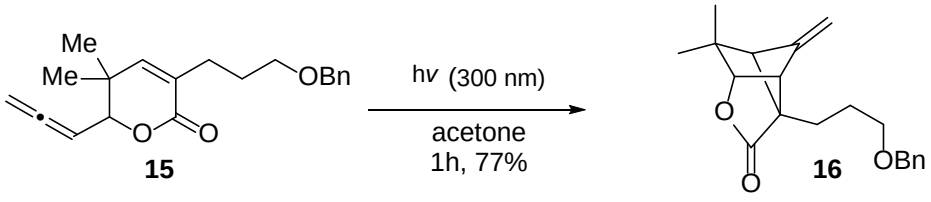
3-(3-(Benzyloxy)propyl)-6-ethynyl-5,5-dimethyl-5,6-dihydro-2H-pyran-2-one (14)
To a suspension of sodium hydride (60 wt% in mineral oil, 1.33 g, 33.2 mmol, 1.5 equiv) and anhydrous THF (1000 mL), a solution of **13** (10 g, 22.1 mmol, 1 equiv) in anhydrous THF (100

mL) was dropwise added in 30 min. After mixing overnight at rt, the reaction was quenched with saturated NH_4Cl solution (500 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 500 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. After purification by flash column chromatography (petroleum ether/EtOAc, 4:1), the title compound was obtained as colorless oil in a yield of 5.22 g (17.5 mmol, 76%). TLC (petroleum ether/EtOAc, 4:1 v/v): R_f = 0.26. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.24 (m, 5H), 6.30 (s, 1H), 4.74 (d, *J* = 2.3 Hz, 1H), 4.48 (s, 2H), 3.47 (t, *J* = 6.2 Hz, 2H), 2.54 (d, *J* = 2.3 Hz, 1H), 2.44–2.29 (m, 2H), 1.86–1.71 (m, 2H), 1.18 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.76, 149.43, 138.51, 129.48, 128.48, 127.85, 127.70, 76.32, 75.93, 73.02, 69.24, 36.06, 28.32, 27.51, 24.69, 21.62. IR (neat): ν_{max} (cm^{-1}) = 3281, 1722, 1102, 698. LRMS (FD/FI): m/z calculated for $C_{19}H_{22}O_3$ $(M)^+$ 298.2, found 298.2.



3-(3-(Benzyloxy)propyl)-5,5-dimethyl-6-(propa-1,2-dien-1-yl)-5,6-dihydro-2H-pyran-2-one (15)

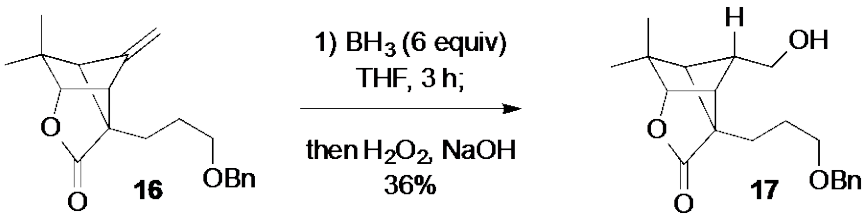
A dried 500 mL round-bottom flask was charged sequentially with paraformaldehyde (1.31 g, 43.8 mmol, 2.5 equiv), copper(I) iodide (1.67 g, 8.75 mmol, 0.5 equiv), 1,4-dioxane (200 mL), **14** (5.22 g, 17.5 mmol, 1 equiv) and dicyclohexylamine (6.27 mL, 31.5 mmol, 1.8 equiv) and was stirred under reflux. After completion of the reaction, as monitored by TLC, the mixture was cooled to rt. Next the mixture was diluted with EtOAc and respectively washed with 0.5 M HCl solution, saturated $NaHCO_3$ solution and brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. After purification by flash column chromatography (petroleum ether/EtOAc, 6:1), the title compound was obtained as pale yellow oil in a yield of 4.80 g (15.4 mmol, 79%). TLC (petroleum ether/EtOAc, 4:1 v/v): R_f = 0.39. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.25 (m, 5H), 6.29 (bs, 1H), 5.22 (dt, *J* = 8.4, 6.6 Hz, 1H), 4.96–4.83 (m, 2H), 4.56 (d, *J* = 8.4 Hz, 1H), 4.49 (s, 2H), 3.47 (t, *J* = 6.2 Hz, 2H), 2.47–2.26 (m, 2H), 1.85–1.72 (m, 2H), 1.06 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 209.90, 158.73, 150.48, 138.61, 129.56, 128.54, 127.91, 127.75, 86.60, 83.75, 73.09, 69.41, 36.26, 28.48, 27.48, 24.97, 20.46. IR (neat): ν_{max} (cm^{-1}) = 1958, 1719, 1364, 1104. LRMS (FD/FI): m/z calculated for $C_{20}H_{24}O_3$ $(M)^+$ 312.2, found 312.2.



2-(3-(Benzyloxy)propyl)-6,6-dimethyl-8-methylene-4-oxatricyclo[3.3.0.0^{2,7}]octan-3-one (16)

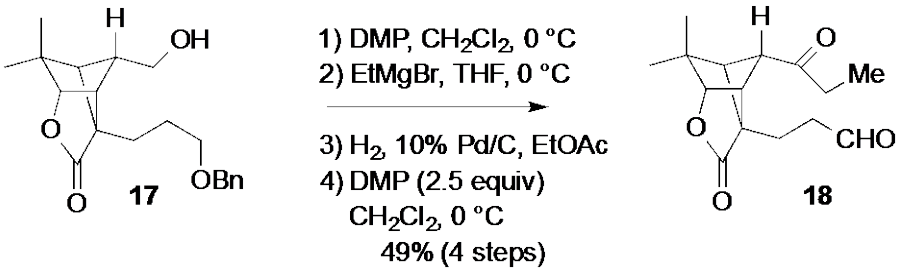
A solution of **15** (2.0 g, 6.4 mmol) in acetone (300 mL) in a quartz reaction vessel was degassed by bubbling a stream of argon through the solution for 30 min. The mixture was irradiated for 1 h

in a Rayonet RPR at 300 nm while maintaining an argon flow to homogenize the reaction mixture. The mixture was concentrated and purified by flash column chromatography (petroleum ether/EtOAc, 6:1). The title compound was isolated as pale yellow oil in a yield of 1.53 g (4.9 mmol, 77%). TLC (petroleum ether/EtOAc, 3:1 v/v): R_f = 0.58. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.26 (m, 5H), 4.71 (s, 1H), 4.70 (s, 1H), 4.49 (s, 2H), 4.37 (t, *J* = 2.2 Hz, 1H), 3.49 (t, *J* = 6.4 Hz, 2H), 3.34 (dd, *J* = 7.0, 2.5 Hz, 1H), 2.54 (d, *J* = 6.6 Hz, 1H), 1.97–1.78 (m, 2H), 1.70–1.62 (m, 2H), 1.08 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.90, 147.69, 138.66, 128.47, 127.77, 127.62, 97.90, 84.89, 72.83, 70.25, 64.12, 61.90, 59.10, 40.71, 26.79, 24.07, 22.38, 21.31. IR (neat): ν_{max} (cm^{-1}) = 3029, 1771, 1697, 1101. HRMS (FD/FI): m/z calculated for $C_{20}H_{24}O_3$ $(M)^+$ 312.1725, found 312.1728.



2-(3-(Benzyloxy)propyl)-8-(hydroxymethyl)-6,6-dimethyl-4-oxatricyclo[3.3.0.0^{2,7}]octan-3-one (17)

To a solution of **16** (711 mg, 2.28 mmol, 1 equiv) in anhydrous THF (7 mL), borane THF complex (1 M in THF, 13.7 mL, 13.66 mmol, 6 equiv) was added at rt. After completion of the reaction in 3h, as monitored by TLC, the reaction was cooled to –20 °C and very slowly a NaOH solution (3 M in water, 7.67 mL, 22.8 mmol, 10 equiv) was added. Cautious addition is required due to a vigorous evolution of hydrogen gas. Next, a H_2O_2 solution (30% in water, 2.3 mL, 22.8 mmol, 10 equiv) was added at the same temperature and was mixed for an additional 1 h. The reaction was then quenched with saturated NH_4Cl solution (20 mL) and extracted with Et_2O (4 x 15 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. After purification by flash column chromatography (petroleum ether/EtOAc, 1:1), the title compound was obtained as colorless oil in a yield of 267 mg (0.81 mmol, 36%). TLC (petroleum ether/EtOAc, 1:1 v/v): R_f = 0.17. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.28 (m, 5H), 4.49 (s, 2H), 4.43 (s, 1H), 4.06 (dd, *J* = 7.3, 2.6 Hz, 2H), 3.57–3.44 (m, 2H), 3.01 (dd, *J* = 7.2, 2.3 Hz, 1H), 2.47 (t, *J* = 7.3 Hz, 1H), 2.29 (dd, *J* = 7.1, 1.5 Hz, 1H), 2.18–2.11 (m, 1H), 1.98–1.90 (m, 1H), 1.62 (dt, *J* = 14.5, 6.7 Hz, 2H), 1.18 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.66, 138.46, 128.47, 127.73, 127.68, 84.93, 72.99, 70.06, 62.51, 61.03, 58.66, 53.58, 46.61, 42.24, 26.91, 25.14, 23.51, 23.25. IR (neat): ν_{max} (cm^{-1}) = 3440, 2963, 2874, 2359, 2340, 1765, 1095, 983. HRMS (FD/FI): m/z calculated for $C_{20}H_{26}O_4$ $(M)^+$ 330.1831, found 330.1848.

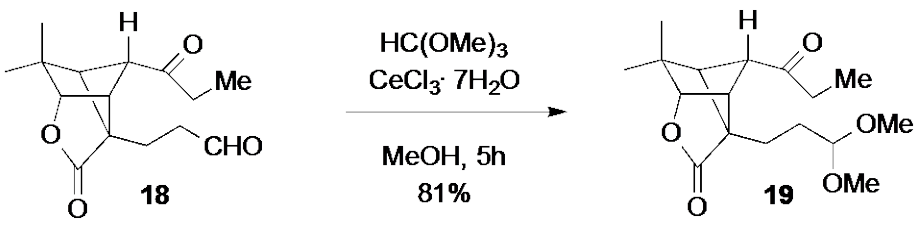


3-(6,6-Dimethyl-3-oxo-8-propionyl-4-oxatricyclo[3.3.0.0^{2,7}]octan-2-yl)propanal (18)

To a solution of **17** (167 mg, 0.51 mmol, 1 equiv) in anhydrous CH_2Cl_2 (10 mL), Dess–Martin periodinane (321 mg, 0.75 mmol, 1.5 equiv) was added at 0 °C. After mixing for 1 h, full conversion was obtained, as observed by TLC, and the mixture was filtered over celite and concentrated *in vacuo*. After purification by flash column chromatography (petroleum ether/EtOAc, 3:1), the title compound was obtained as colorless oil in a yield of 145 mg (0.45 mmol, 87%). TLC (petroleum ether/EtOAc, 2:1 v/v): R_f = 0.23. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 7.32–7.24 (m, 5H), 4.45 (s, 2H), 4.44 (s, 1H), 3.48–3.40 (m, 2H), 3.38 (dd, *J* = 7.1, 2.2 Hz, 1H), 2.83 (s, 1H), 2.68 (dd, *J* = 7.1, 1.5 Hz, 1H), 1.65–1.49 (m, 4H), 1.17 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.64, 177.29, 138.50, 128.29, 127.59, 83.68, 72.44, 69.64, 62.84, 58.46, 55.12, 52.75, 42.14, 25.33, 23.51, 23.11, 22.66. IR (neat): νmax (cm^{-1}) = 2963, 2863, 2360, 2341, 1770, 1712, 1094. HRMS (FD/FI): m/z calculated for $C_{20}H_{24}O_4$ $(M)^+$ 328.1675, found 328.1692.

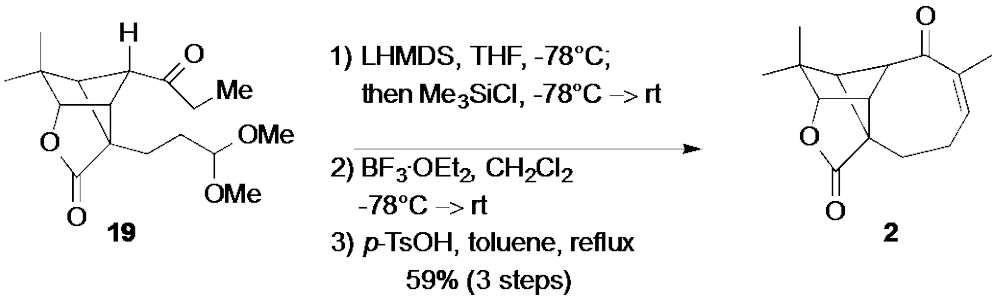
The obtained aldehyde was dissolved in anhydrous THF (8 mL), and ethylmagnesium bromide (3 M in Et_2O, 0.4 mL, 1.2 mmol, 2 equiv) was added to the solution at 0 °C. After completion of the reaction in 2 h, as monitored by TLC, the reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with Et_2O (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The secondary alcohol was obtained in a crude yield of 177 mg (0.49 mmol, 82%). The crude product was a mixture of diastereoisomers in a ratio of 1:1.36 (based on integrals of R-CHOH-R proton in ^{1}H NMR spectrum). ***Major isomer***: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.30 (m, 5H), 4.52 (ABq, J_{AB} = 7.9 Hz, 2H), 4.45 (t, 1H), 4.13 (td, *J* = 10.0, 3.8 Hz, 1H), 3.63–3.42 (m, 2H), 2.87 (dd, *J* = 7.2, 2.3 Hz, 1H), 2.48 (dd, *J* = 7.2, 1.7 Hz, 1H), 2.24–2.13 (m, 3H), 1.74–1.48 (m, 2H), 1.41–1.29 (m, 2H), 1.21 (s, 3H), 1.06 (s, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ***Minor Isomer***: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.27 (m, 5H), 4.52 (ABq, J_{AB} = 7.9 Hz, 2H), 4.44 (t, 1H), 4.23 (td, *J* = 8.6, 3.0 Hz, 1H), 3.63–3.41 (m, 3H), 3.13 (dd, *J* = 7.2, 2.3 Hz, 1H), 2.23–2.10 (m, 2H), 1.47–1.35 (m, 2H), 1.18 (s, 3H), 1.03 (s, 3H), 0.91 (t, *J* = 7.4 Hz, 3H).

The crude mixture of diastereoisomers was redissolved in EtOAc (10 mL) and Pd/C (10 wt%, 17 mg) was added to this solution. The flask was equipped with a balloon of H_2 and was stirred for 1 h until full conversion, as monitored by TLC. The suspension was filtered over a pad of celite and concentrated *in vacuo*. The diol was obtained as a colorless oil in quantitative yield. Next, the diol was redissolved in anhydrous CH_2Cl_2 (15 mL) and cooled to 0 °C. To this solution, Dess–Martin periodinane (520 mg, 1.23 mmol, 2.5 equiv) was added and mixed for 2 h at 0 °C. Next, the mixture was filtered over celite and concentrated *in vacuo*. After purification by flash column chromatography (petroleum ether/EtOAc, 2:1 –> 1:1), the title compound was obtained as colorless oil in a yield of 88 mg (0.33 mmol, 68%). Overall yield over three steps is 56%. TLC (petroleum ether/EtOAc, 2:1 v/v): R_f = 0.23. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.63 (s, 1H), 4.41 (t, *J* = 2.0 Hz, 1H), 3.27 (dd, *J* = 7.2, 2.3 Hz, 1H), 2.86 (s, 1H), 2.66–2.56 (m, 2H), 2.53–2.41 (m, 2H), 2.37 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.09-2.02 (m, 1H), 1.56-1.48 (m, 1H), 1.16 (s, 3H), 1.01 (t, *J* = 7.3 Hz, 3H), 0.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.60, 200.76, 177.34, 84.13, 62.15, 59.98, 55.04, 53.62, 42.74, 40.06, 34.51, 23.31, 22.91, 19.34, 7.83. IR (neat): ν_{max} (cm^{-1}) = 2975, 2939, 1766, 1718, 1704, 1125.



2-(3,3-Dimethoxypropyl)-6,6-dimethyl-8-propionyl-4-oxatricyclo[3.3.0.0^{2,7}]octan-3-one (19)

To a solution of **18** (88 mg, 0.33 mmol, 1 equiv) in MeOH (4 mL), cerium(III) chloride heptahydrate (123 mg, 0.33 mmol, 1 equiv) and trimethyl orthoformate (0.18 mL, 1.66 mmol, 5 equiv) were respectively added. After completion of the reaction in 5 h, as monitored by TLC, the reaction was quenched by the addition of saturated $NaHCO_3$ solution (10 mL) and extracted with Et_2O (3 x 15 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. After purification by flash column chromatography (petroleum ether/EtOAc, 2:1), the title compound was obtained as colorless oil in a yield of 84 mg (0.27 mmol, 81%). TLC (petroleum ether/EtOAc, 2:1 v/v): R_f = 0.36. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (br s, *J* = 2.0 Hz, 1H), 4.27 (t, *J* = 5.5 Hz, 1H), 3.32 (dd, *J* = 7.1, 2.2 Hz, 1H), 3.26 (s, 4H), 2.84 (s, 1H), 2.72–2.59 (m, 2H), 2.59-2.45 (m, 1H), 1.91-1.77 (m, 1H), 1.68–1.59 (m, 1H), 1.54–1.45 (m, 1H), 1.38-1.31 (m, 1H), 1.19 (s, 2H), 1.08 (t, *J* = 7.2 Hz, 2H), 1.04 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 209.34, 177.64, 103.83, 84.13, 62.65, 59.43, 54.99, 53.54, 52.54, 42.56, 34.47, 28.23, 23.35, 22.91, 21.79, 7.69. IR (neat): ν_{max} (cm^{-1}) = 2976, 2362, 2336, 1770, 1704, 1130, 1063. HRMS (EI): m/z calculated for $C_{16}H_{23}O_4$ $(M\text{-}CH_3O)^+$ 279.1591, found 279.1605.



Mukaiyama aldol condensation to Aquatolide (2)

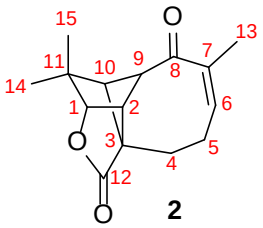
A stock solution of LiHMDS (0.38 M in THF) was prepared by addition of *n*-butyllithium (1.6 M in hexanes) to a solution of hexamethyldisilazane in anhydrous THF at 0 °C which was stirred for 30 min. In a separate flask a solution of **19** (69 mg, 0.22 mmol, 1 equiv) in anhydrous THF (1.5 mL) was made and to this solution the solution of LiHMDS in THF (3 mL, 1.11 mmol, 5 equiv) was added at -78 °C. After mixing for 1 h, chlorotrimethylsilane (0.14 mL, 1.11 mmol, 5 equiv) was added, and the mixture was stirred for an additional 30 min at this temperature. Next, the temperature was raised to rt and after completion of the reaction in 1 h, as monitored by TLC, the reaction was quenched by the addition of saturated $NaHCO_3$ solution (5 mL). The product was extracted with Et_2O (3 x 10 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

The silyl enol ether was redissolved in anhydrous CH_2Cl_2 (2 mL) and was cooled to -78 °C. To this solution, boron trifluoride diethyl etherate (0.03 mL, 0.24 mmol, 1.1 equiv) was added. The mixture was allowed to reach rt while stirring overnight. This mixture was then quenched by the addition of saturated $NaHCO_3$ solution (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

The complex mixture of diastereoisomers was subjected to elimination of MeOH by refluxing the Mukaiyama aldol product in toluene (10 mL) and *p*-toluenesulfonic acid (63 mg, 0.33 mmol, 1.5 equiv) for 4 h until completion, as monitored by TLC. The mixture was cooled to rt and was quenched with saturated $NaHCO_3$ solution (5 mL). The product was extracted with Et_2O (3 x 5 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. After

purification by flash column chromatography (petroleum ether/EtOAc, 5:1), the racemic title compound was obtained as a white solid in a yield of 32 mg (0.13 mmol, 59%). TLC (petroleum ether/EtOAc, 4:1 v/v): R_f = 0.20; mp 148-149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 (m, 1H), 4.50 (t, *J* = 2.0 Hz, 1H), 3.28 (dd, *J* = 7.2, 2.4 Hz, 1H), 2.94 (s 1H), 2.66 (dd, *J* = 7.2, 1.7 Hz, 1H), 2.54 (dd, *J* = 14.5, 7.1 Hz, 1H), 2.43-2.32 (m, 1H), 2.12-1.93 (m, 2H), 1.89 (q, *J* = 1.6 Hz, 3H), 1.21 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.63, 177.22, 134.84, 130.81, 99.88, 83.95, 62.57, 62.34, 54.28, 54.20, 41.59, 28.36, 22.57, 22.34, 21.93, 21.89. IR (neat): ν_{max} (cm^{-1}) = 2973, 1776, 1765, 1678, 1120, 978. HRMS (FD/FI): m/z calculated for $C_{15}H_{18}O_3$ M^+ 246.1256, found 246.1262.
The enantiomers were separated using preparative HPLC [Chiralcel AD-H (250 x 4.6 mm 5 μm), 1 mL/min, T_{column}: 25 °C, heptane/isopropanol, 9:1 v/v].
Natural compound: $[\alpha]_D$ +27.7 *[(c, 1.0, $CHCl_3$), lit: $[\alpha]_D$: +29.2° (c, 0.05, $CHCl_3$) or $[\alpha]_D$: +66.3° (c, 0.45, $CHCl_3$)]*. m.p.: 180-182 °*C (lit: 175-176°C or 142-143°C)*.
Other enantiomer: $[\alpha]_D$: -29.0° (c: 1.0, $CHCl_3$). m.p.: 180-182 °C

NMR Comparison between Synthetic and Isolated Aquatolide



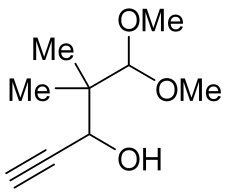
2

	^{1}H NMR chemical shifts (ppm)		^{13}C NMR chemical shifts (ppm)	
Nucleus	Reference[3]	Experimental	Reference[3]	Experimental
1	4.48	4.47	84.20	84.18
2	3.26	3.25	54.24	54.43
3			62.83	62.81
4	2.52	2.51	22.15	22.13
	1.96	1.97		
5	2.35	2.35	28.63	28.60
	2.03	2.03		
6	5.85	5.85	131.10	131.06
7			135.08	135.07
8			211.94	211.85
9	2.92	2.92	54.45	54.52
10	2.64	2.64	62.59	62.58
11			41.86	41.82
12			177.50	177.44
13	1.87	1.87	22.22	22.16
14	1.05	1.05	22.62	22.57
15	1.19	1.19	22.84	22.81

Table S-1: NMR comparison of synthesized aquatolide and isolated aquatolide.

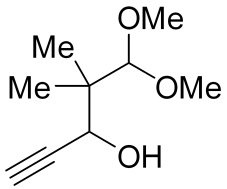
References

1. Liau, J.; Ma, S.; *Synthesis*, **2013**, *47*, 1624
2. Frankowski, K.J.; Golden, J.E.; Zeng, Y.; Lei, Y.; Aubé, J.; *J. Am. Chem. Soc.* **2008**, *130*, 6018.
3. Lodewyck, M. W.; Soldi, C.; Jones, P. B.; Olmstead, M. M.; Rita, J.; Shaw, J. T.; Tantillo, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 18550.



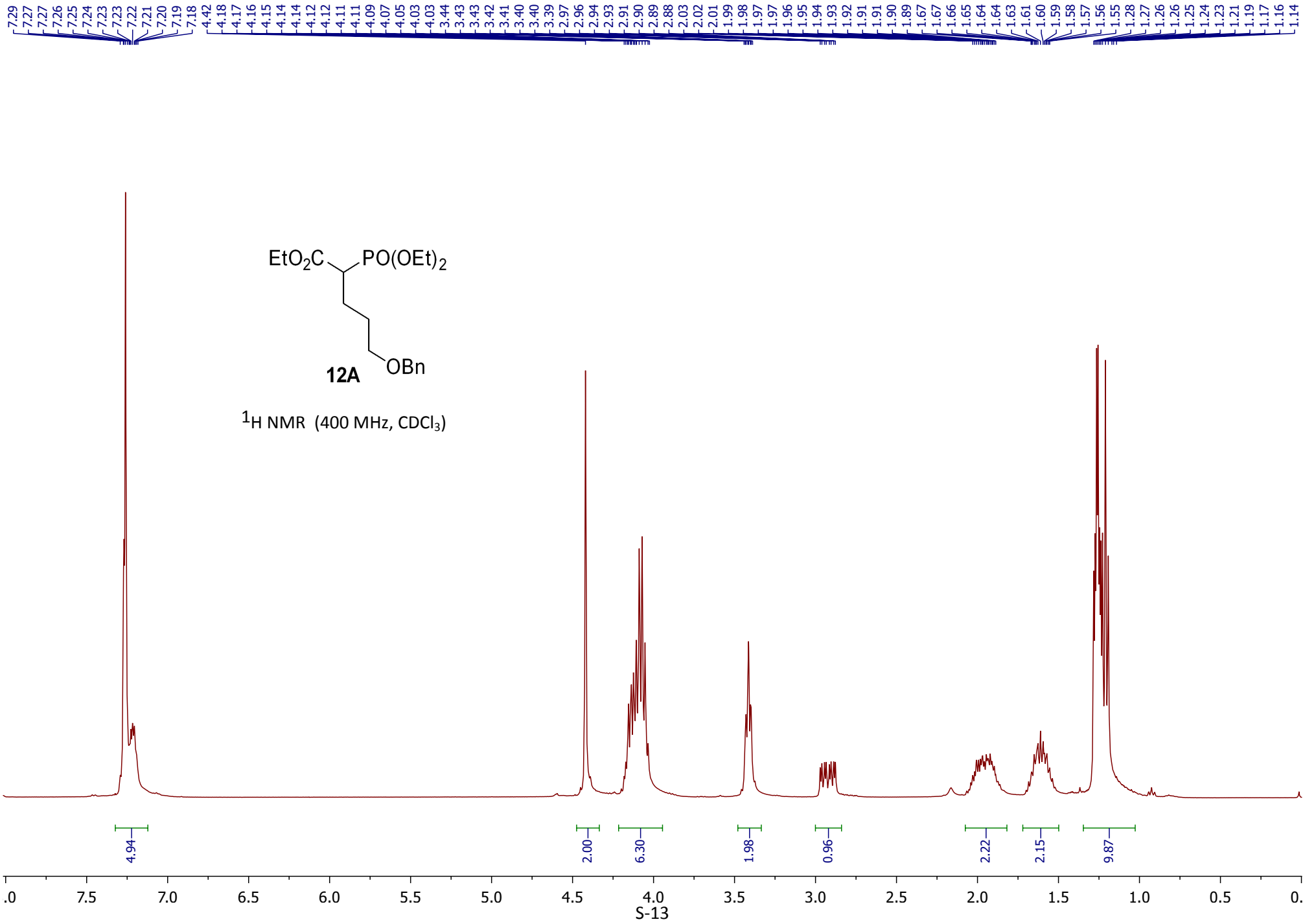
11

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



11

^{13}C NMR (APT; 101 MHz, $CDCl_3$)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4.42 4.18 4.17 4.16 4.15 4.14 4.14 4.12 4.12 4.11 4.11 4.09 4.07 4.05 4.03 4.03 3.44 3.43 3.43 3.42 3.41 3.40 3.40 3.39 2.97 2.96 2.94 2.93 2.91 2.90 2.89 2.88 2.03 2.02 2.01 1.99 1.98 1.97 1.97 1.96 1.95 1.94 1.93 1.92 1.91 1.91 1.90 1.89 1.67 1.67 1.66 1.65 1.64 1.64 1.63 1.61 1.60 1.59 1.58 1.57 1.56 1.55 1.28 1.27 1.26 1.26 1.25 1.24 1.23 1.21 1.19 1.17 1.16 1.14
EtO2C
PO(OEt)2
OBn
12A
1H NMR (400 MHz, CDCl3)
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2.00
6.30
1.98
0.96
2.22
2.15
9.87
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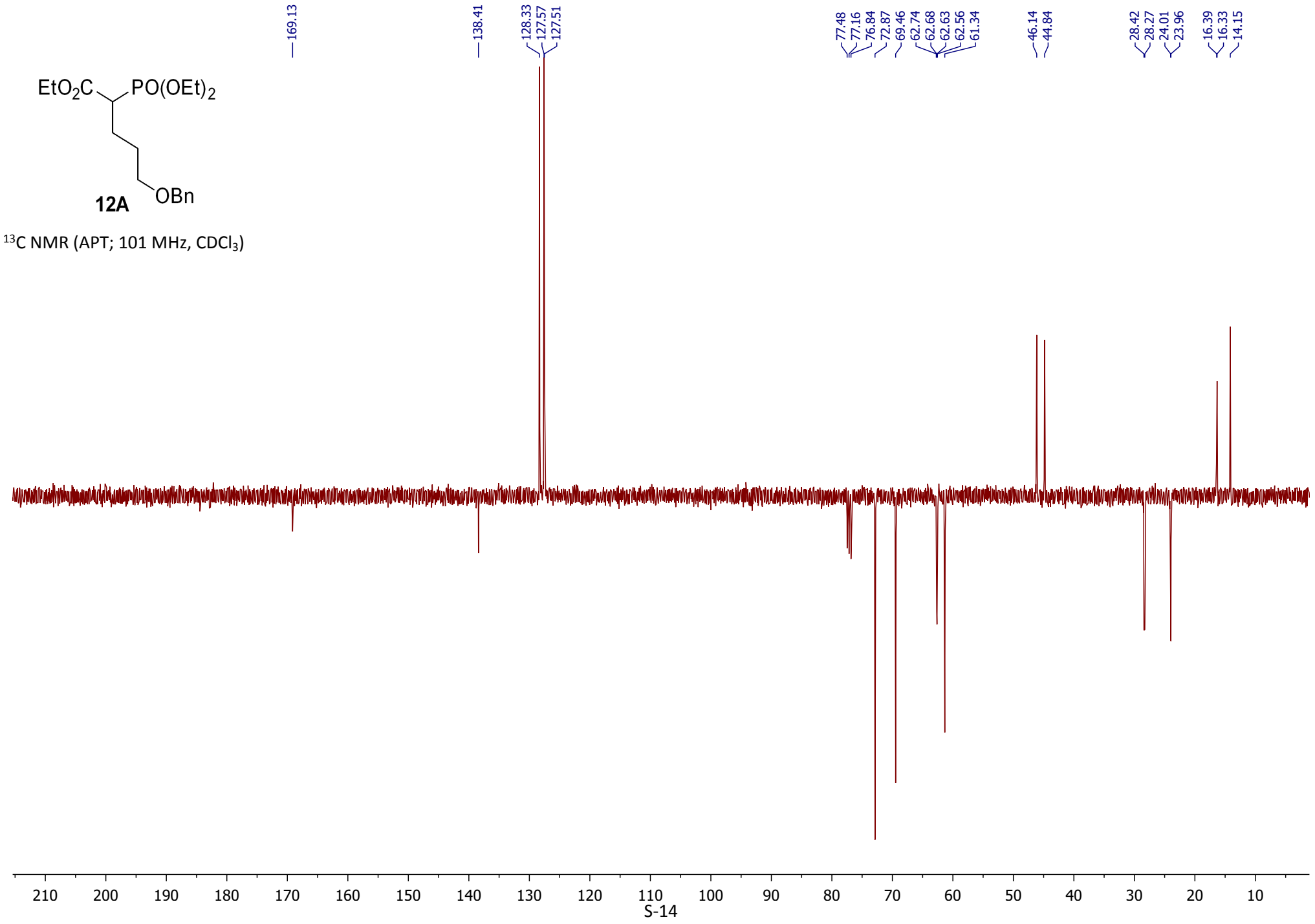
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62.56
61.34
46.14
44.84
28.42
28.27
24.01
23.96
16.39
16.33
14.15
EtO2C
PO(OEt)2
OBn
12A
13C NMR (APT; 101 MHz, CDCl3)
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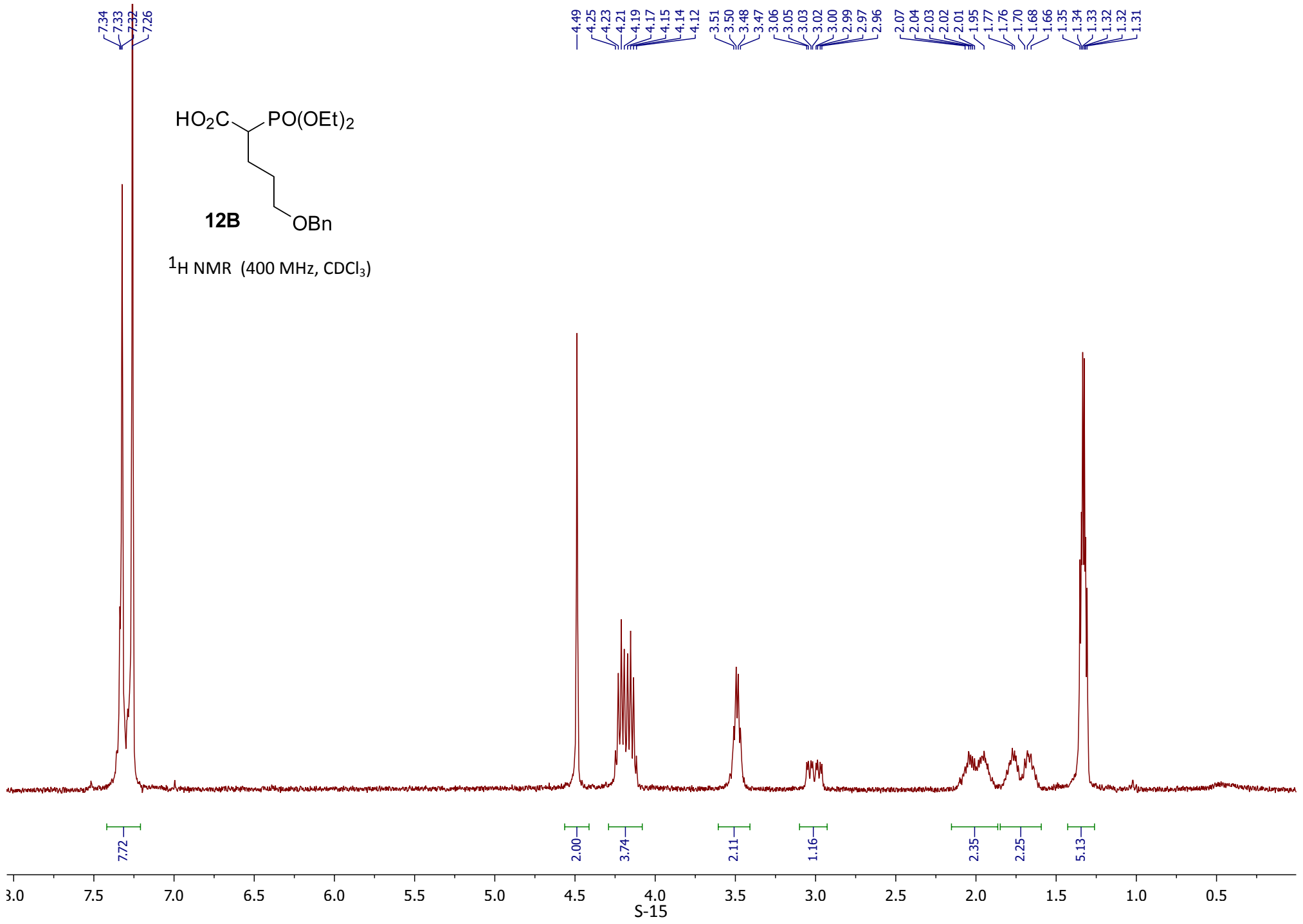
40
30
20
10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2.02
2.01
1.95
1.77
1.76
1.70
1.68
1.66
1.35
1.34
1.33
1.32
1.31
HO2C
PO(OEt)2
12B
OBn
1H NMR (400 MHz, CDCl3)
7.72
2.00
3.74
2.11
1.16
2.35
2.25
5.13
7.5
7.0
6.5
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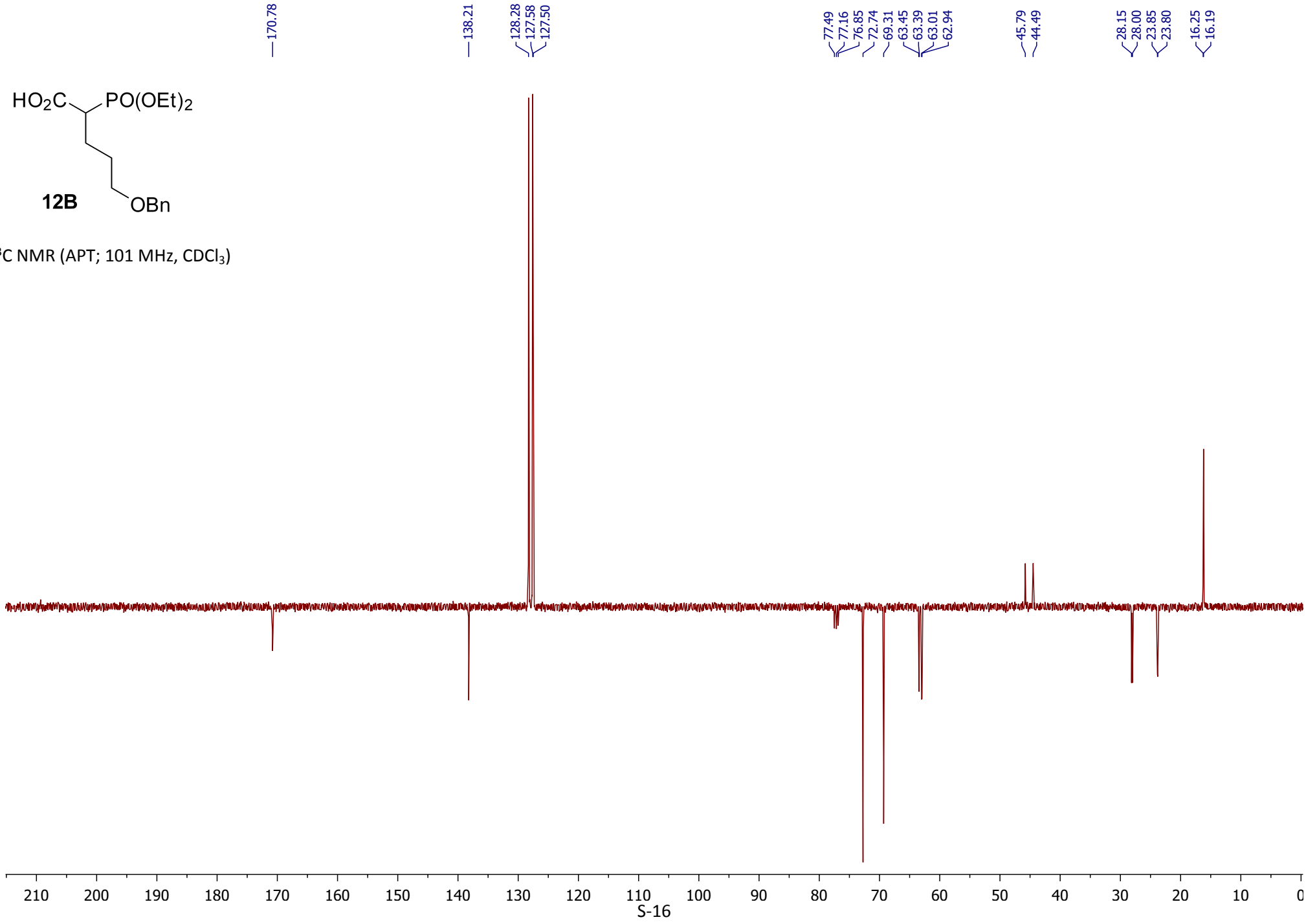
0.5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45.79
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23.85
23.80
16.25
16.19
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PO(OEt)2
12B
OBn
13C NMR (APT; 101 MHz, CDCl3)
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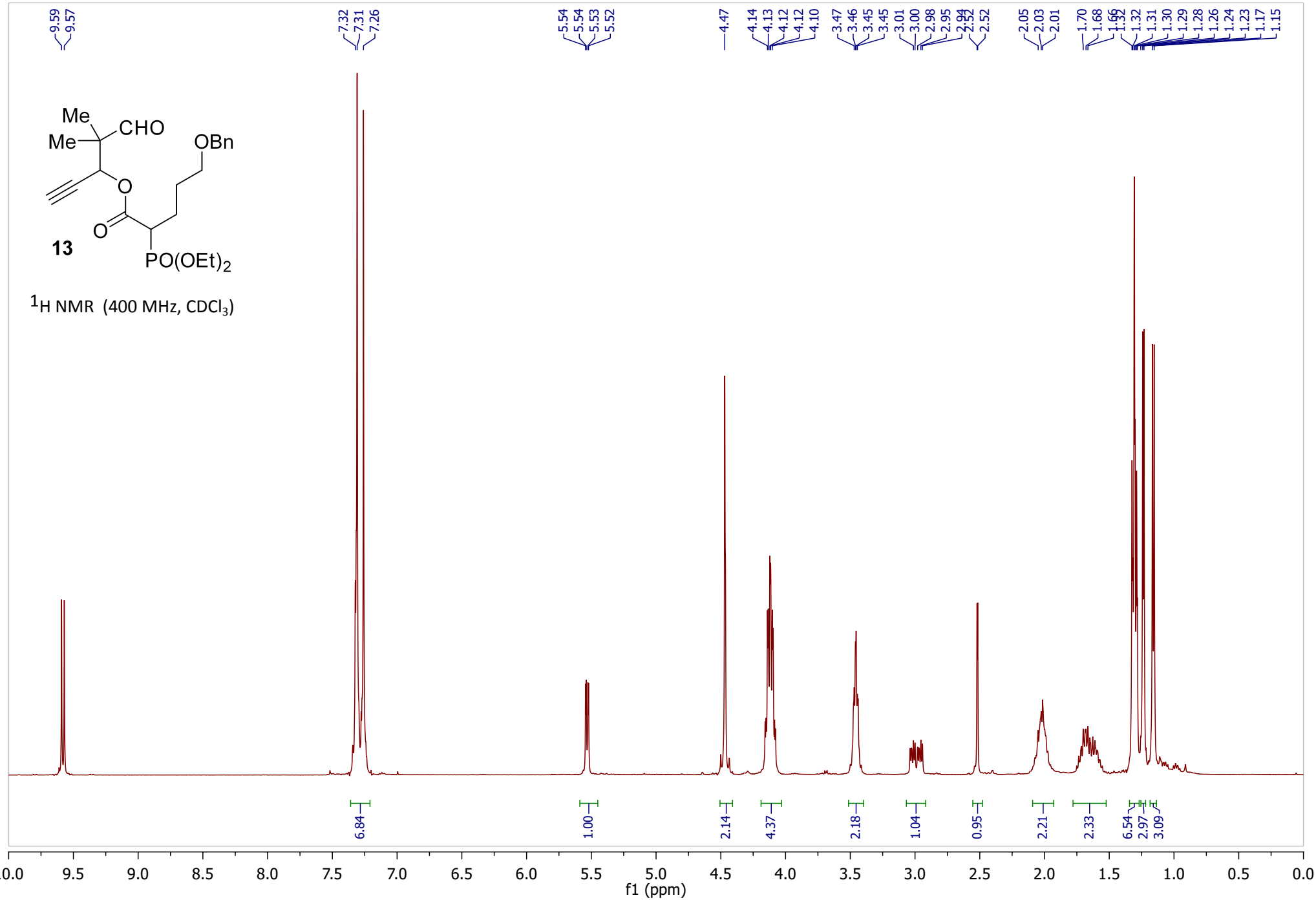
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1.70
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1.32
1.31
1.30
1.29
1.28
1.26
1.24
1.23
1.17
1.15
Me
Me
CHO
OBn
O
O
PO(OEt)2
13
1H NMR (400 MHz, CDCl3)
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2.14
4.37
2.18
1.04
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2.21
2.33
6.54
2.97
3.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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2.5
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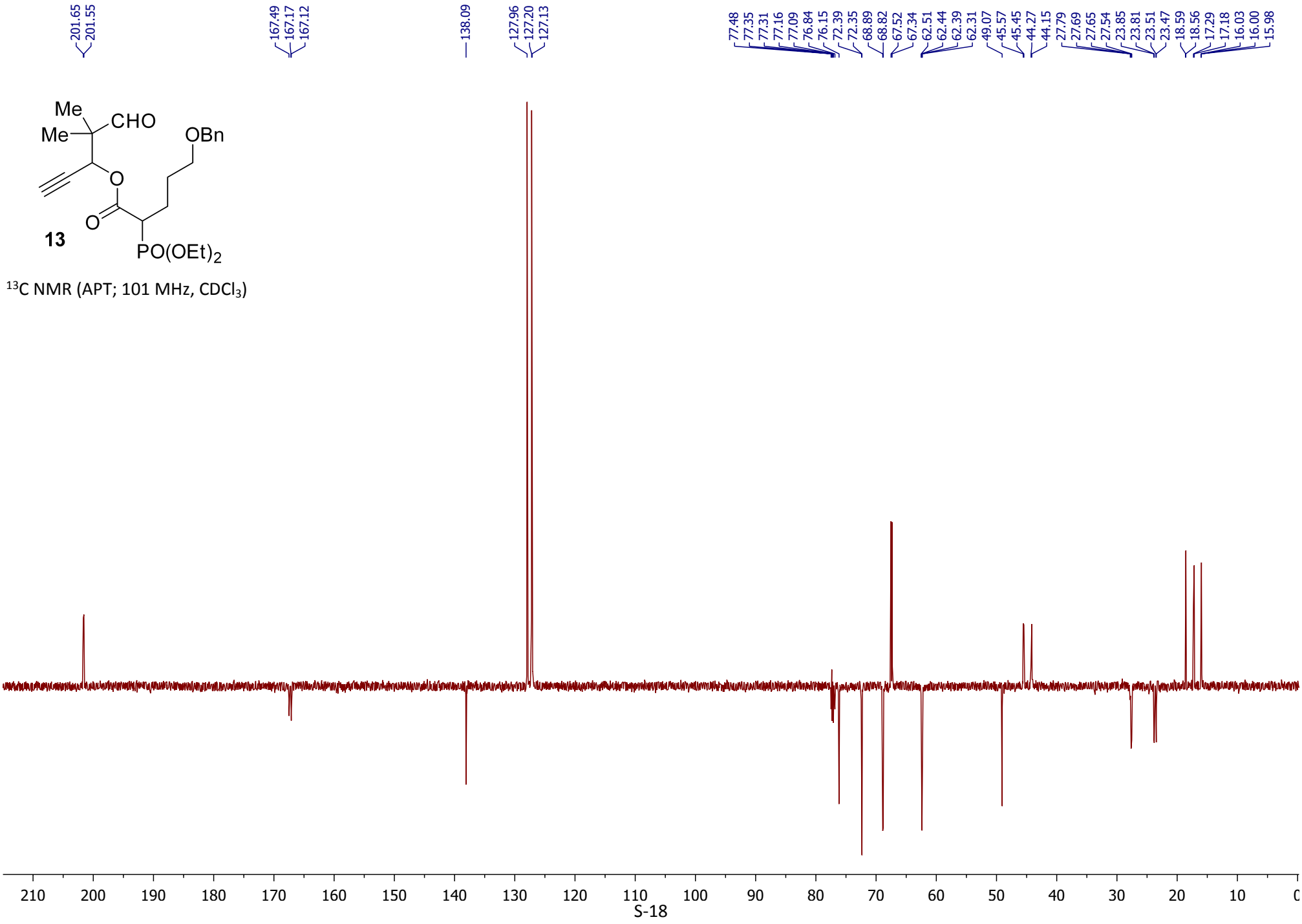
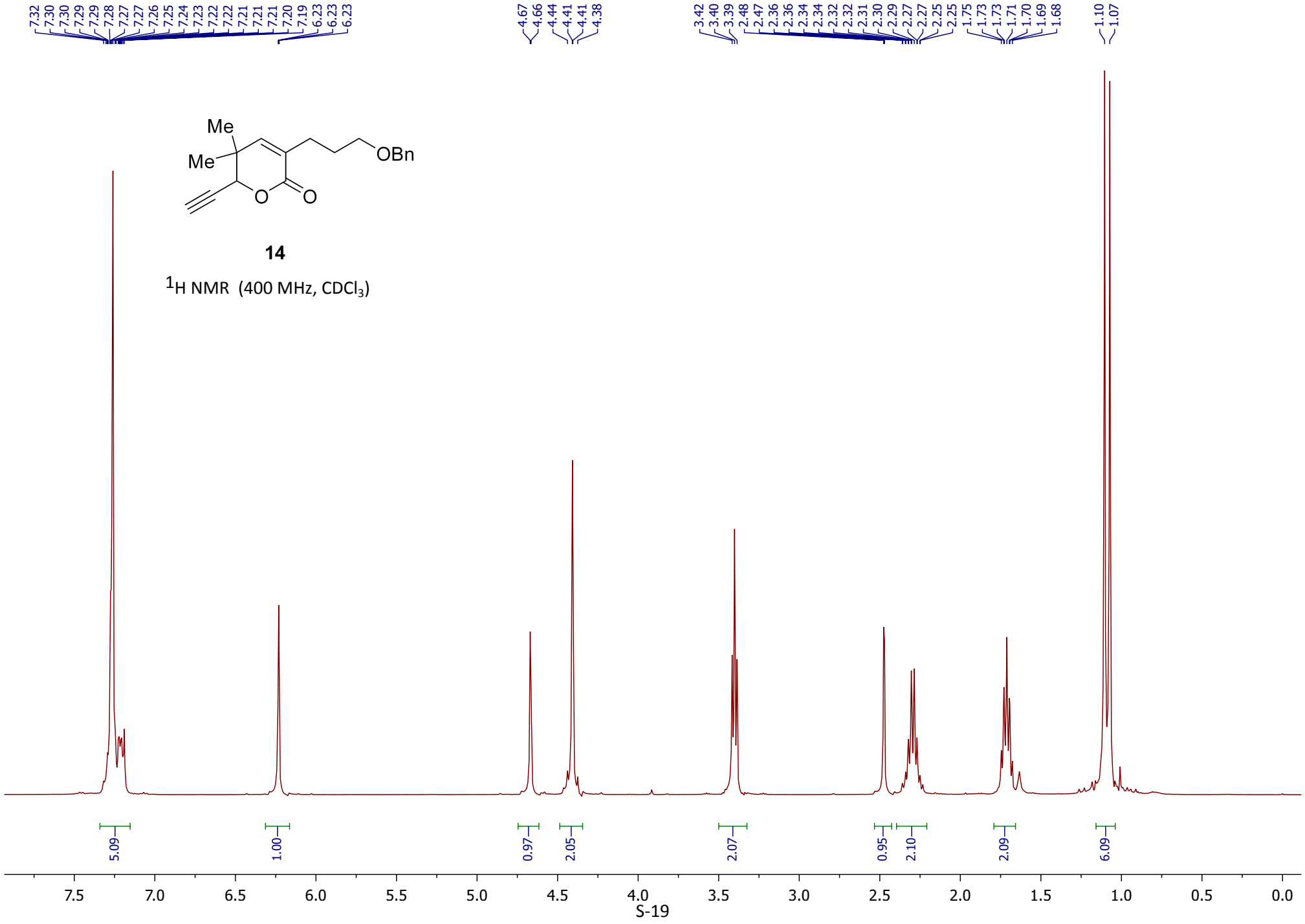
f1 (ppm)



^{13}C NMR (APT; 101 MHz, $CDCl_3$)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1.10 1.07
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Me
OBn
O
O
14
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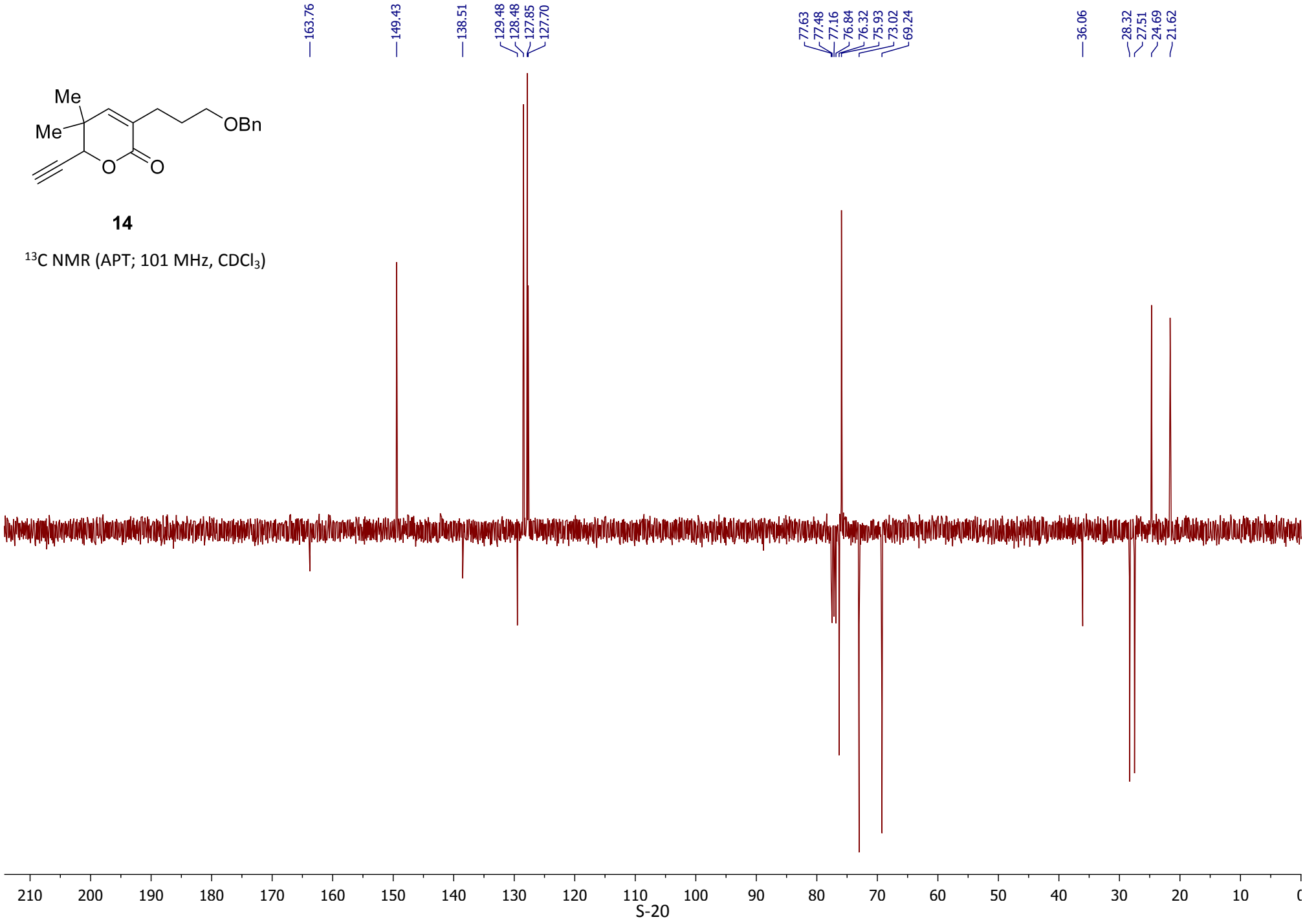
1.00
0.97
2.05
2.07
0.95
2.10
2.09
6.09
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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28.32
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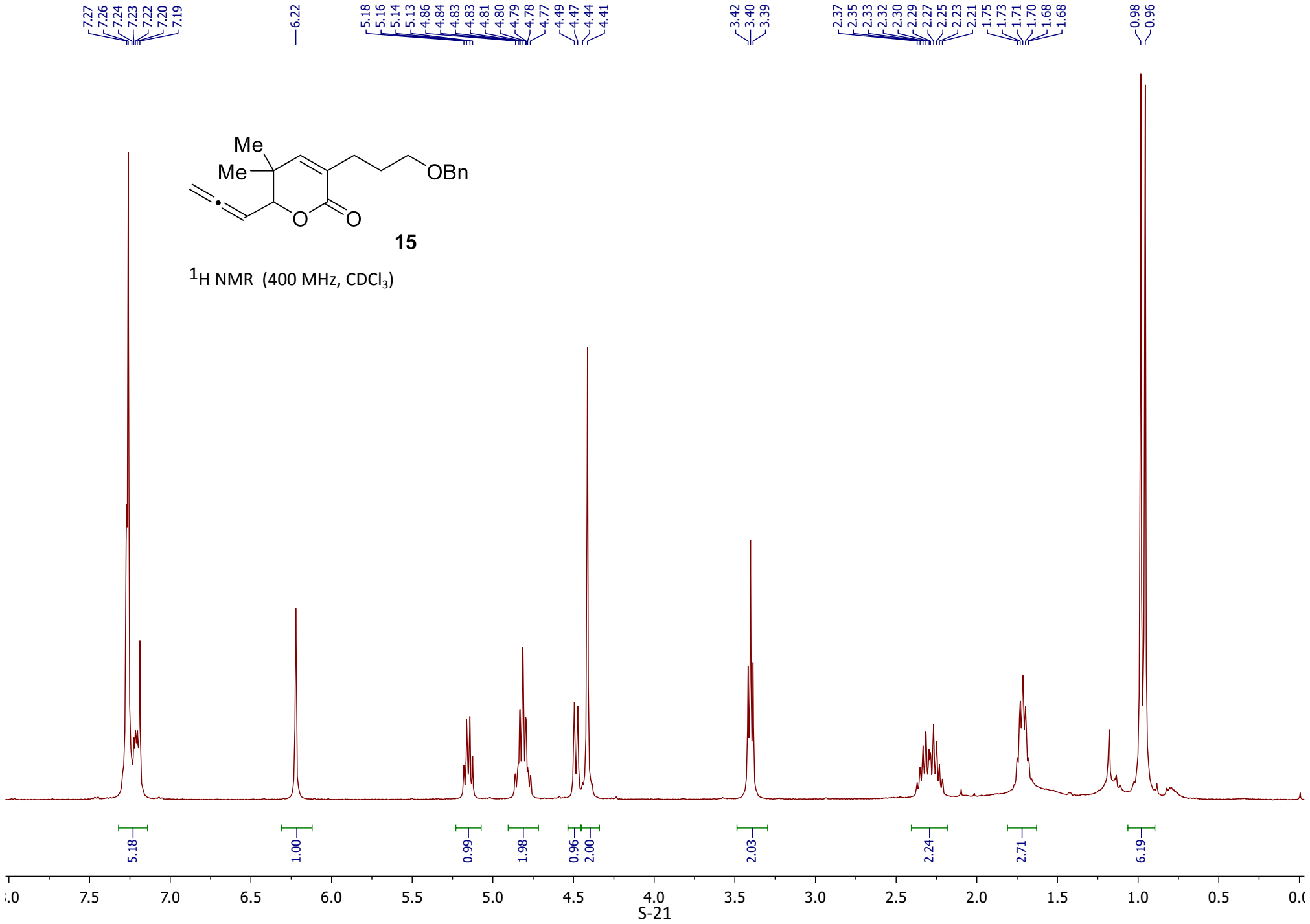
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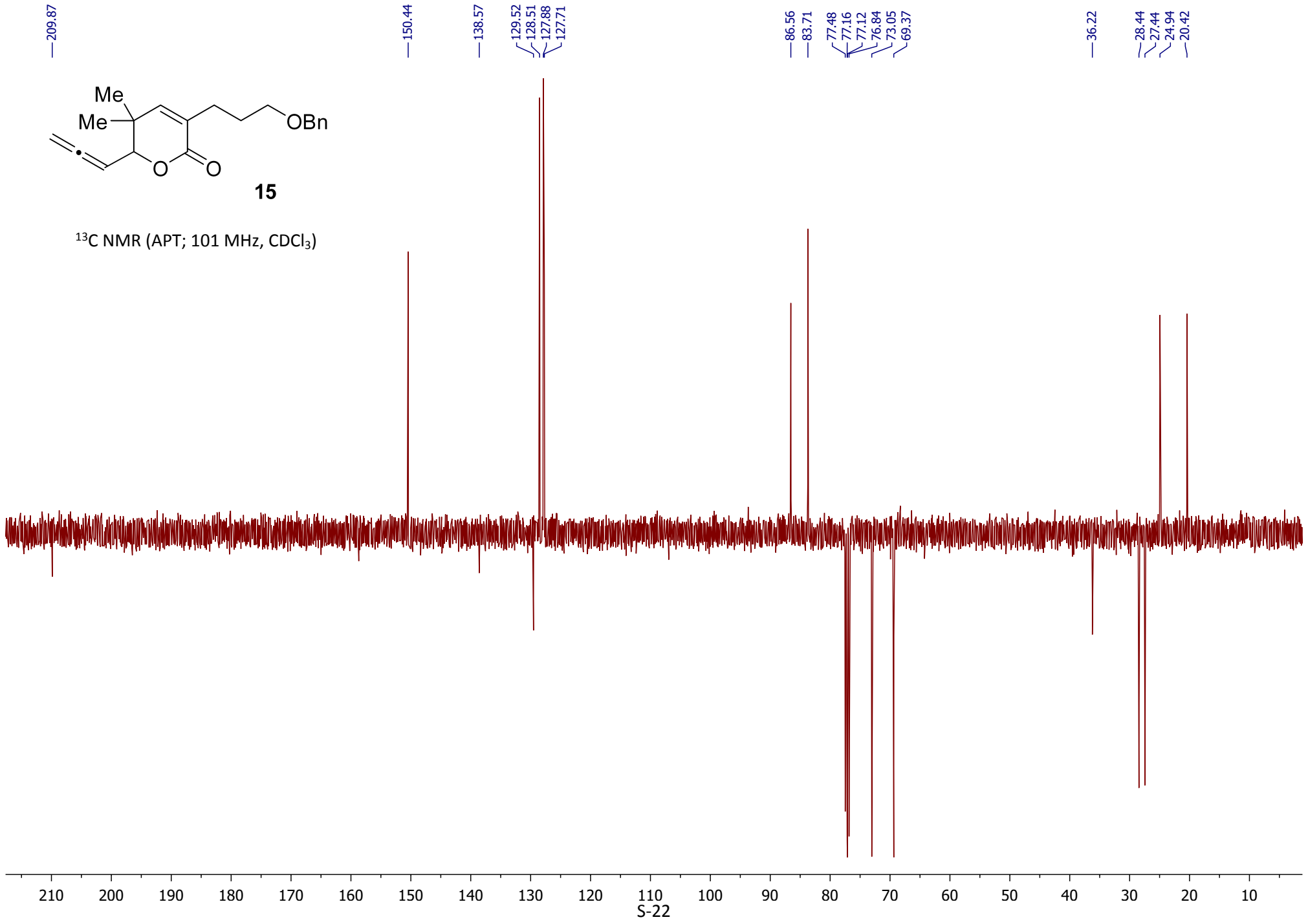
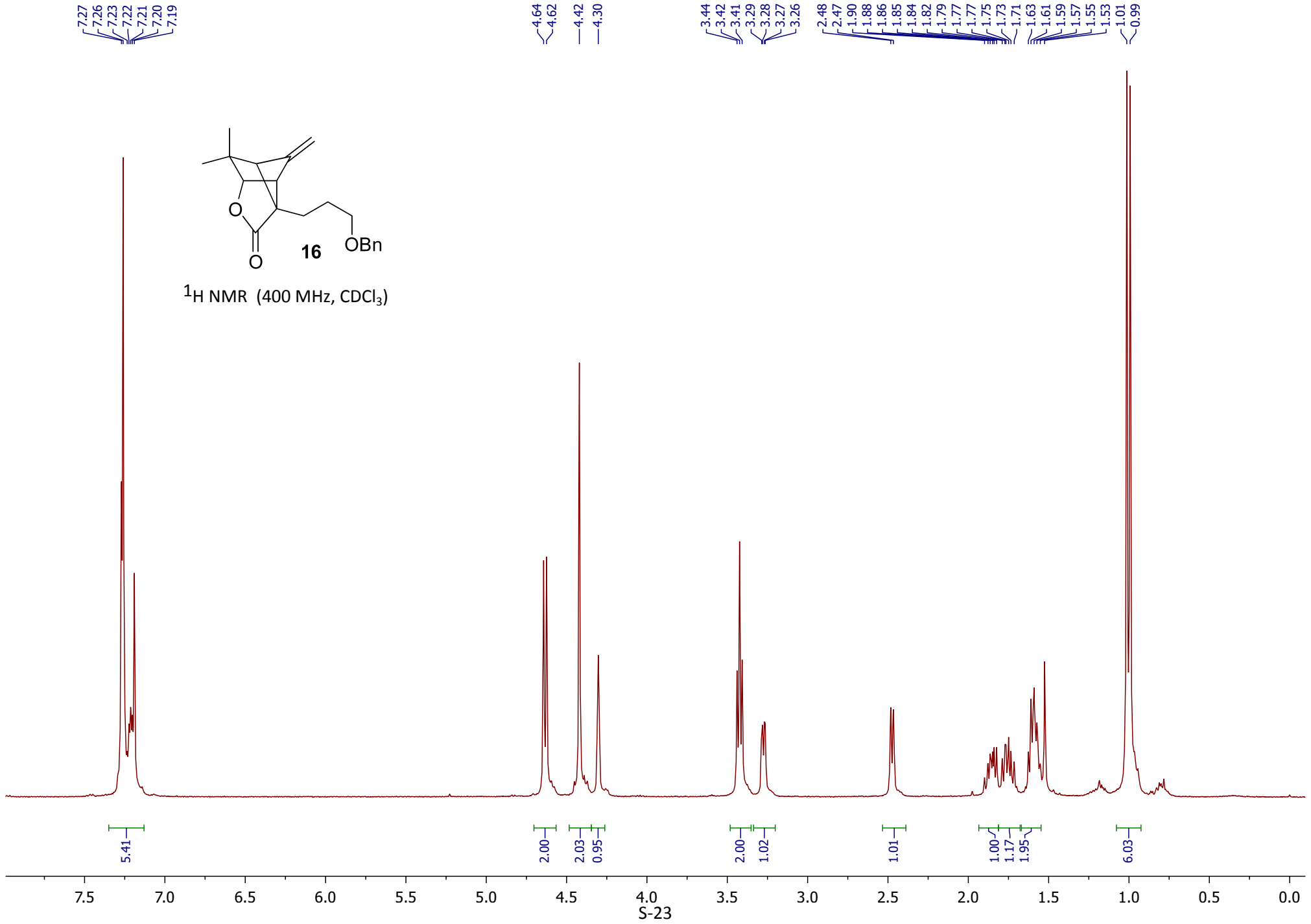
15
1H NMR (400 MHz, CDCl3)
5.18
1.00
0.99
1.98
0.96
2.00
2.03
2.24
2.71
6.19
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

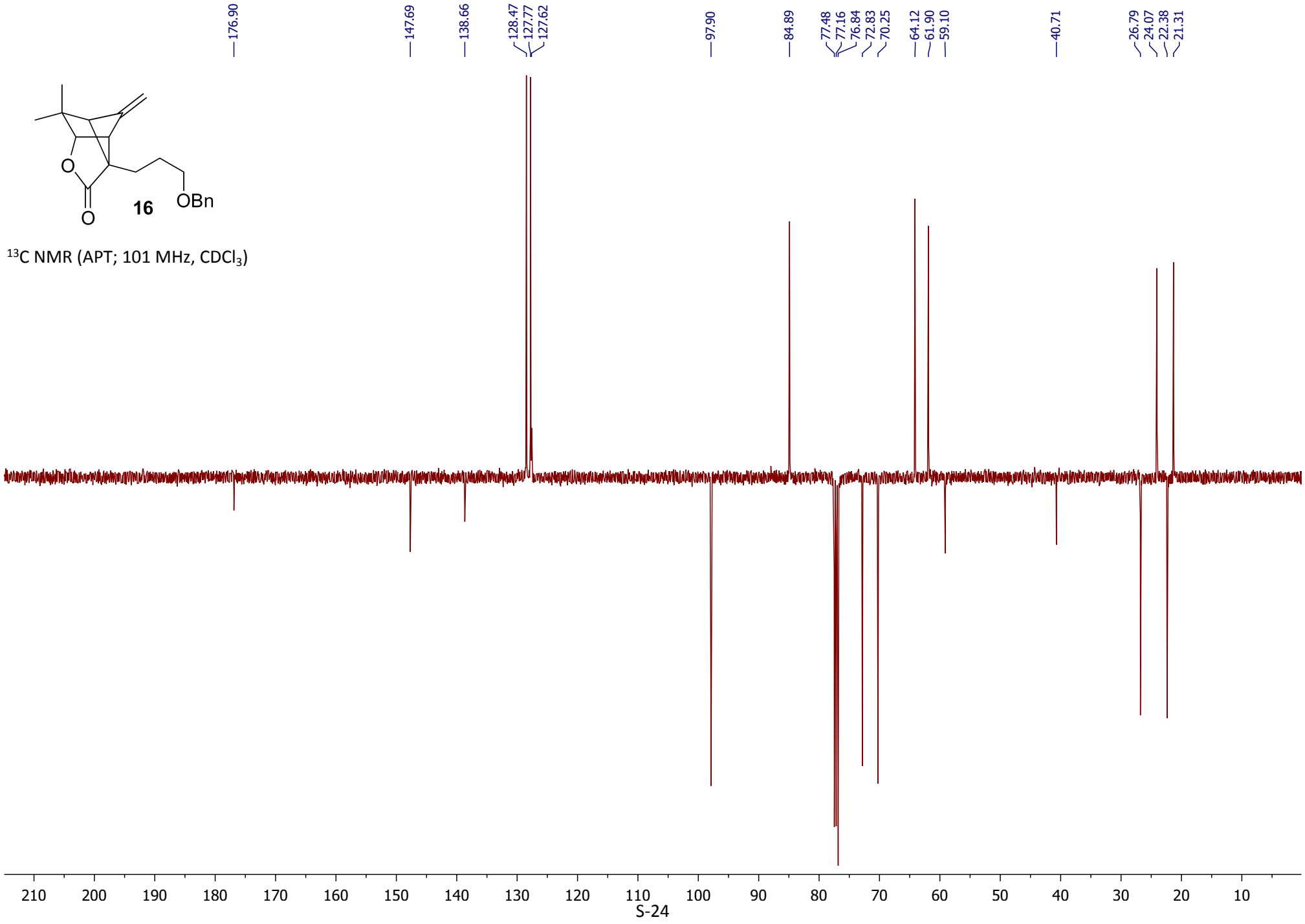


15

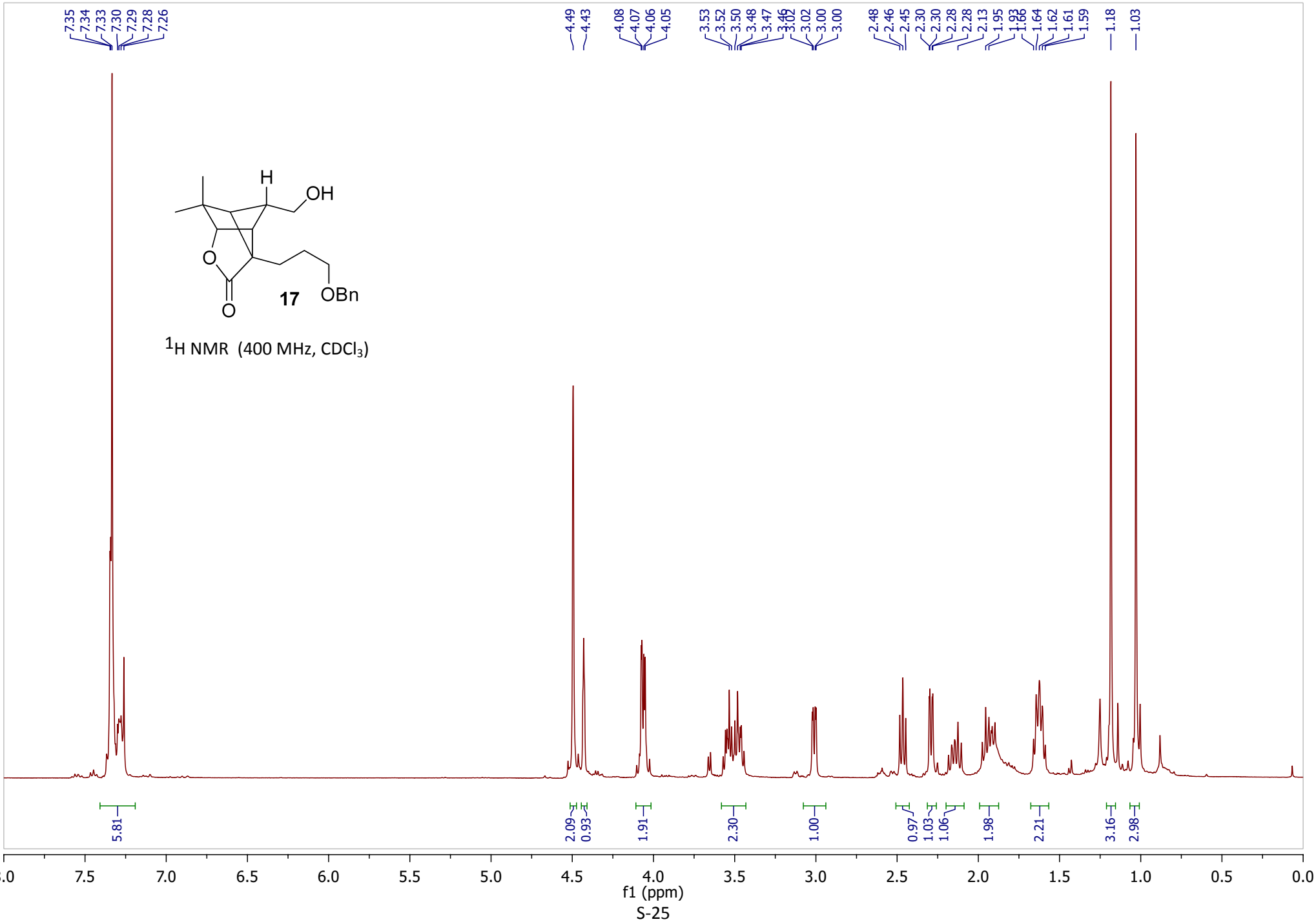
^{13}C NMR (APT; 101 MHz, $CDCl_3$)



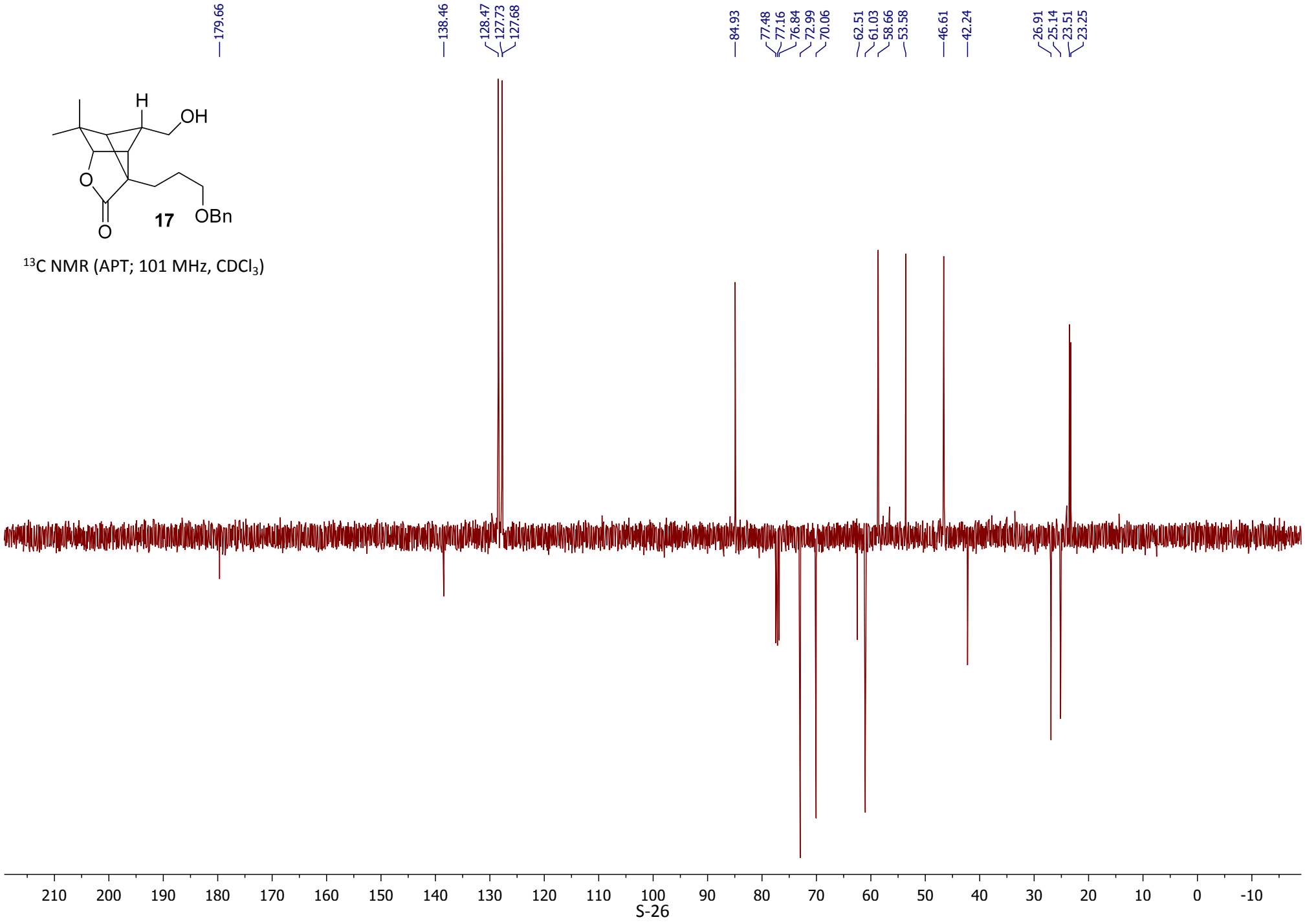
^{1}H NMR (400 MHz, $CDCl_3$)



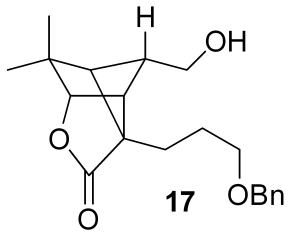
^{13}C NMR (APT; 101 MHz, $CDCl_3$)



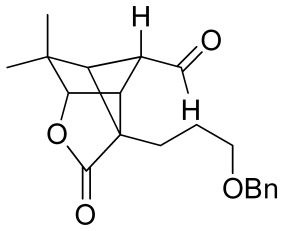
^{1}H NMR (400 MHz, $CDCl_3$)



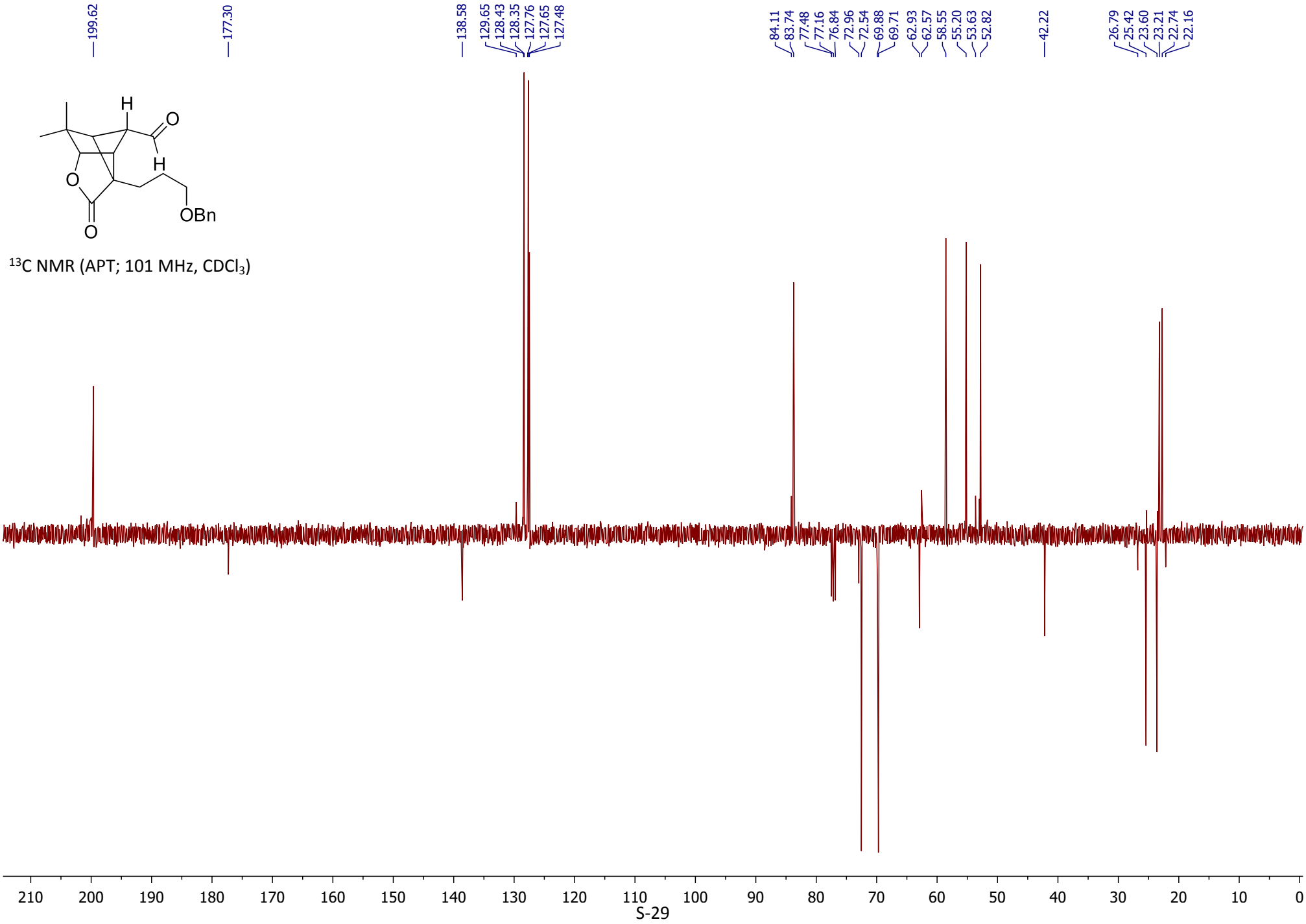
^{13}C NMR (APT; 101 MHz, $CDCl_3$)



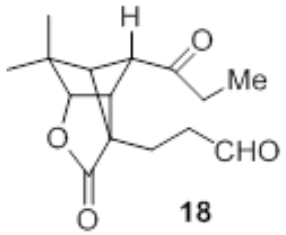
^{1}H NMR (1D NOE; 400 MHz, $CDCl_3$)



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

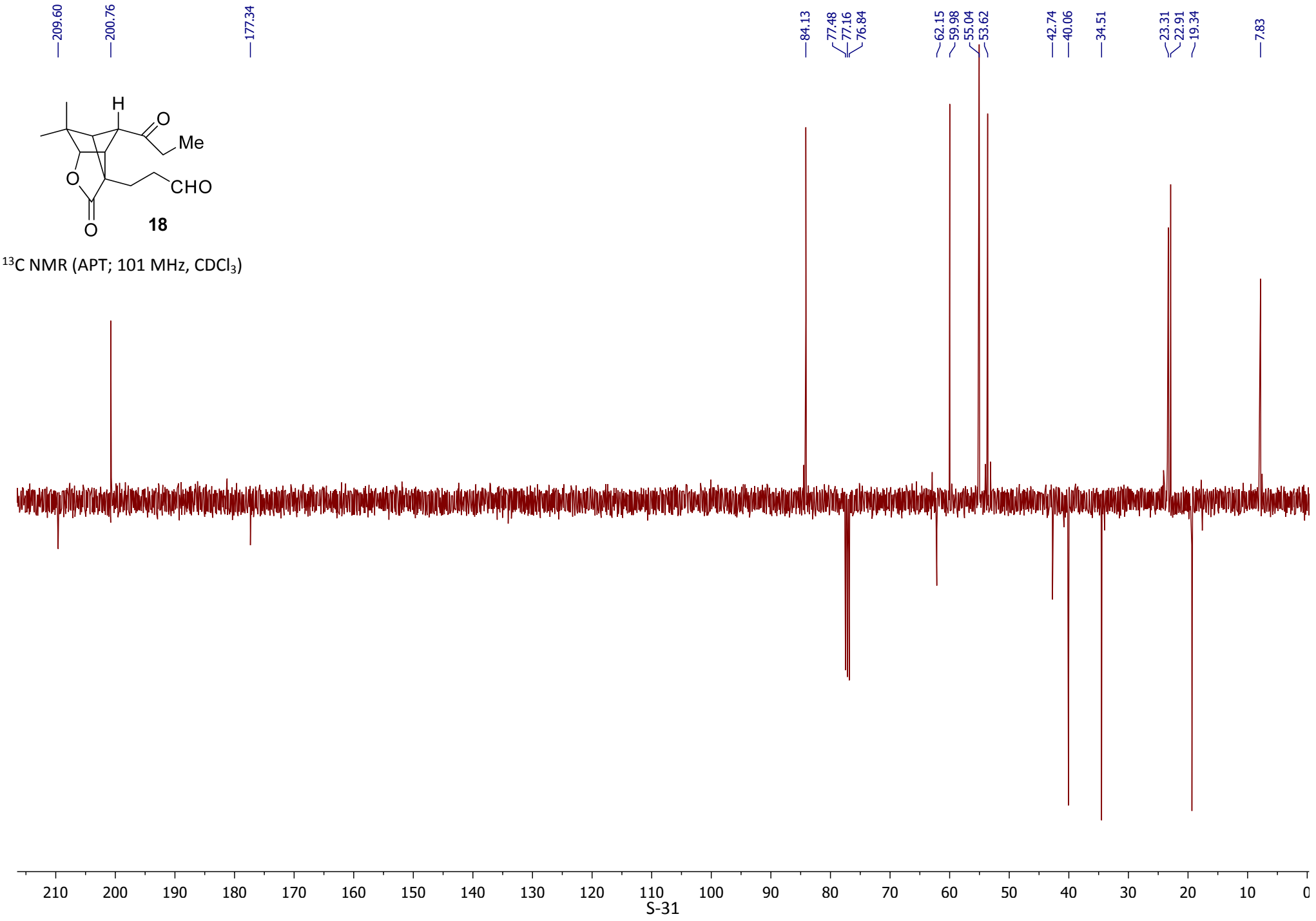


^{13}C NMR (APT; 101 MHz, $CDCl_3$)

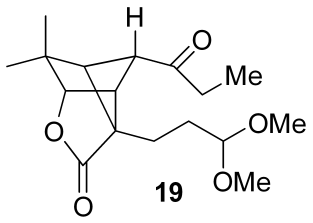


18

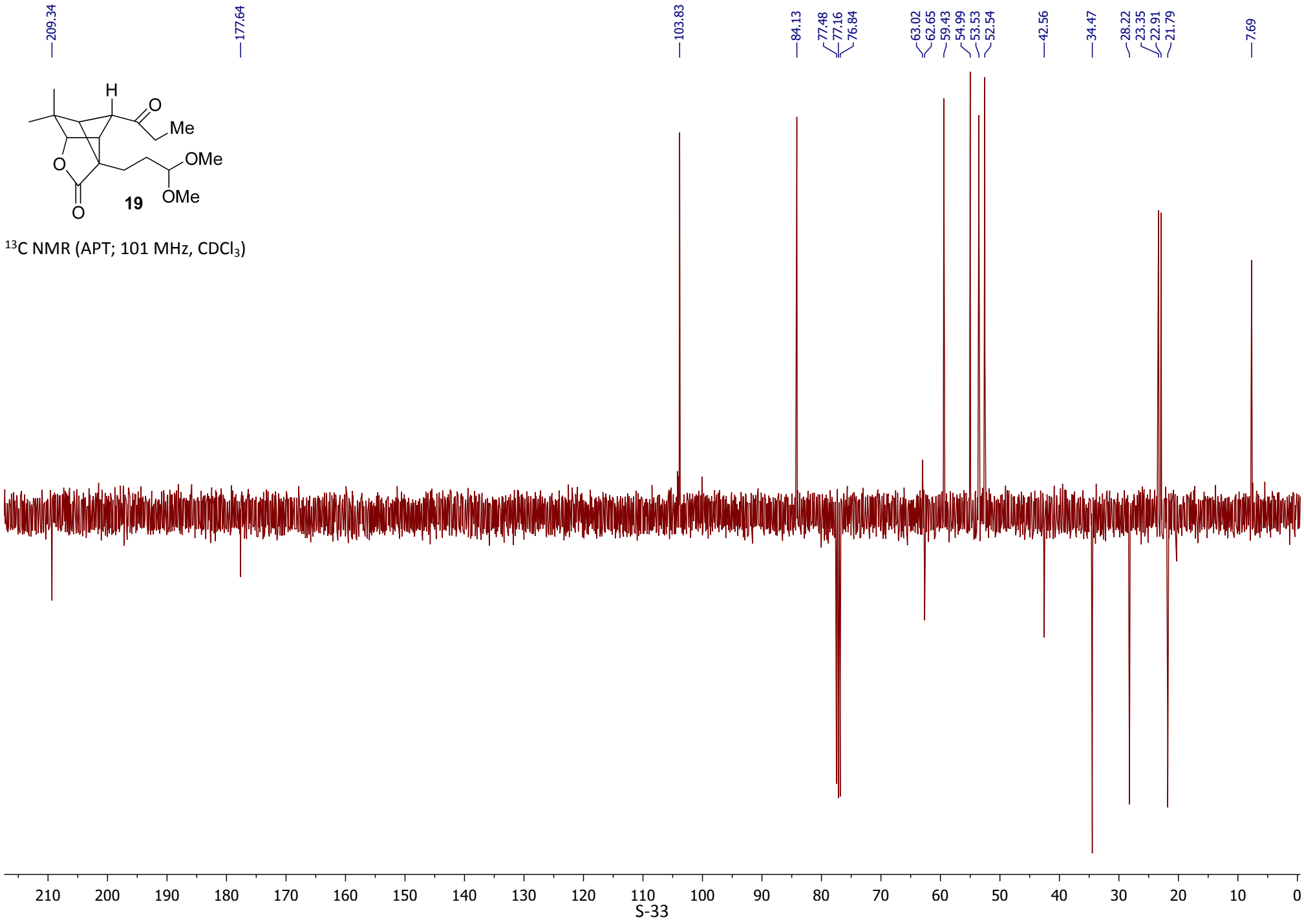
^{1}H NMR (400 MHz, $CDCl_3$)



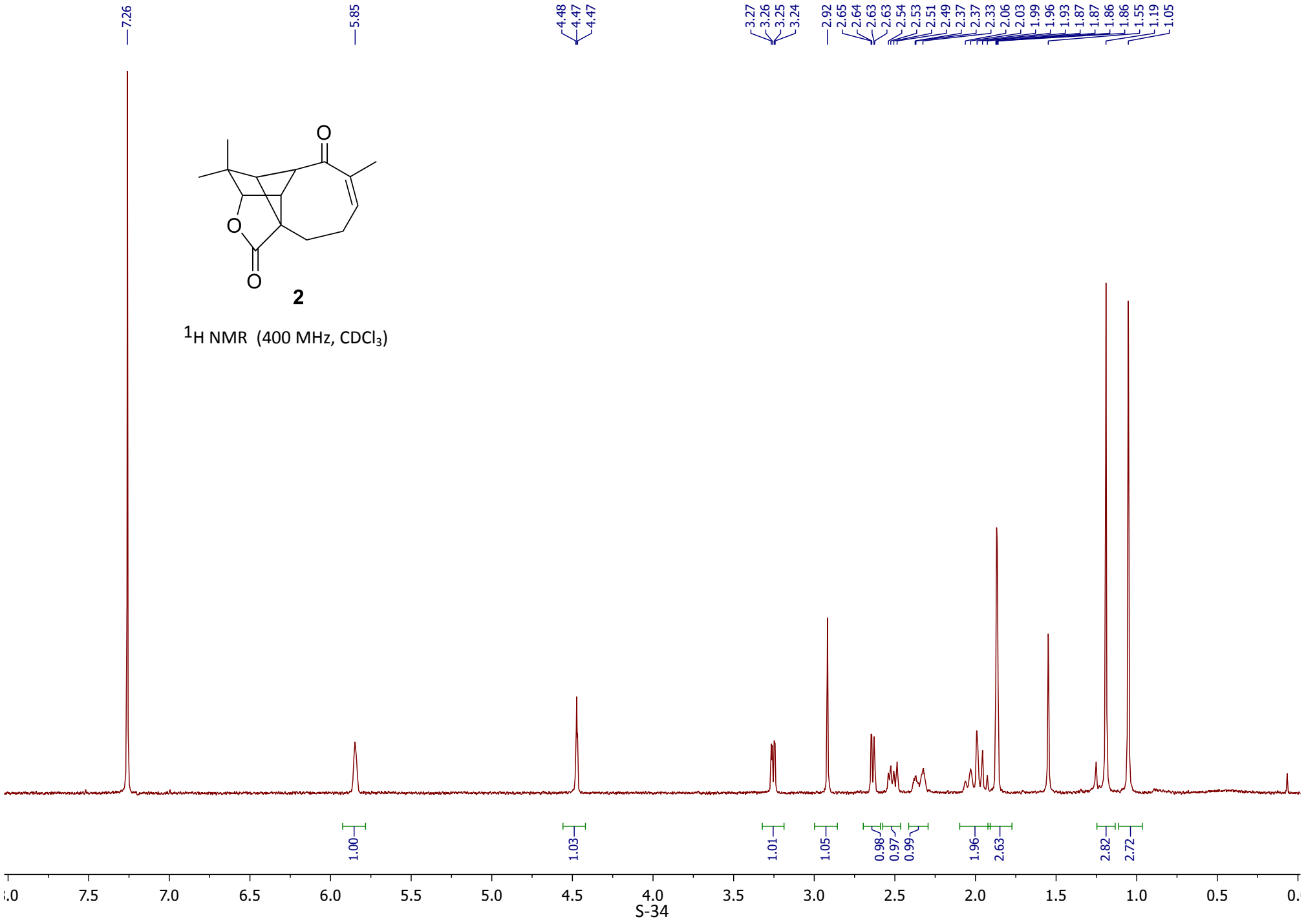
^{13}C NMR (APT; 101 MHz, $CDCl_3$)

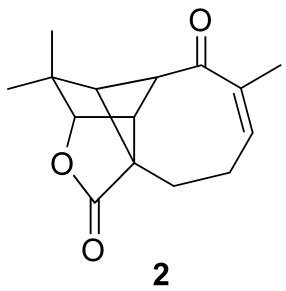


^{1}H NMR (400 MHz, $CDCl_3$)



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


7.26
5.85
4.48
4.47
4.47
3.27
3.26
3.25
3.24
2.92
2.65
2.64
2.63
2.63
2.54
2.53
2.51
2.49
2.37
2.37
2.33
2.06
2.03
1.99
1.96
1.93
1.87
1.87
1.86
1.86
1.55
1.19
1.05
O
O
O
2
1H NMR (400 MHz, CDCl3)
1.00
1.03
1.01
1.05
0.98
0.97
0.99
1.96
2.63
2.82
2.72
7.5
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



2

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

Biomolecular Synthesis Shimadzu HPLC Analysis Report

Racemic aquatolide

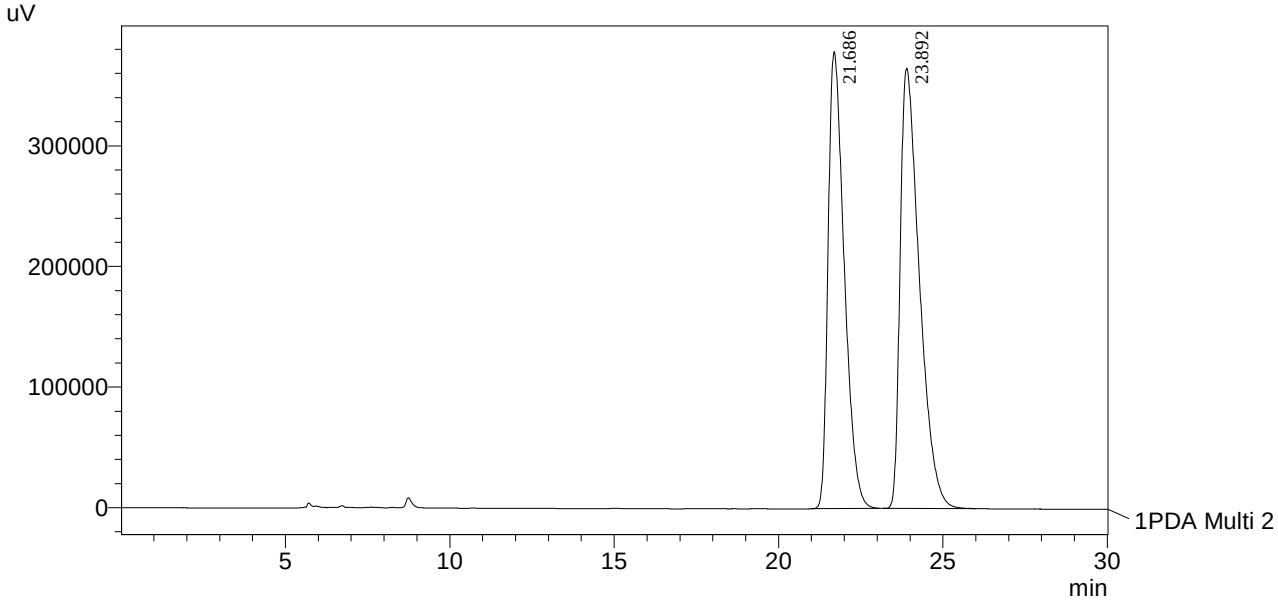
Injection Volume : 10 uL

Method

[Pump A Mobile Phase A]
Heptane
Pump A: Heptane, B: 2-Propanol

Pump A	:LC-20AD
Total Flow	:0.5000 mL/min
B.Conc	:10.0 %
C.Conc	:0.0 %
D.Conc	:0.0 %
PressMax	:100 bar
PressMin	:0 bar

Chromatogram



1 PDA Multi 2 / 254nm 4nm

Results

PeakTable

PDA Ch2 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.686	12940406	378951	46.541	50.940
2	23.892	14863668	364966	53.459	49.060
Total		27804074	743917	100.000	100.000

Biomolecular Synthesis Shimadzu HPLC Analysis Report

(+)-Aquatolide

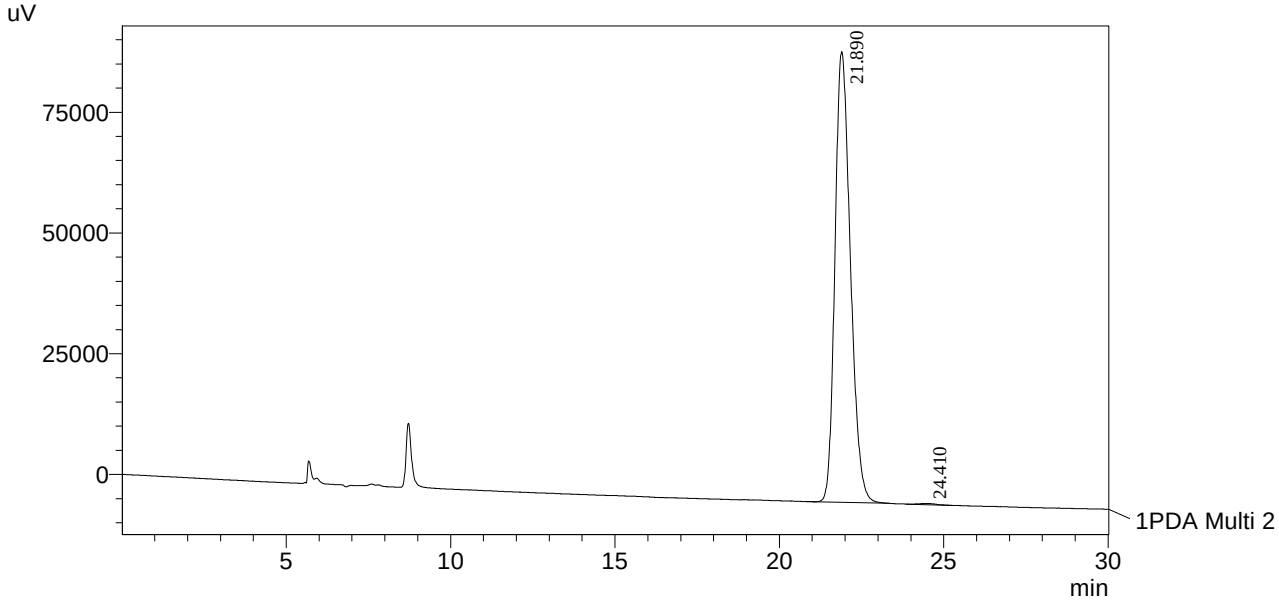
Injection Volume : 10 uL

Method

[Pump A Mobile Phase A]
Heptane
Pump A: Heptane, B: 2-Propanol

Pump A	:LC-20AD
Total Flow	:0.5000 mL/min
B.Conc	:10.0 %
C.Conc	:0.0 %
D.Conc	:0.0 %
PressMax	:100 bar
PressMin	:0 bar

Chromatogram



1 PDA Multi 2 / 254nm 4nm

Results

PeakTable

PDA Ch2 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.890	3048862	93328	99.735	99.751
2	24.410	8112	233	0.265	0.249
Total		3056974	93561	100.000	100.000

Biomolecular Synthesis Shimadzu HPLC Analysis Report

(-)-Aquatolide

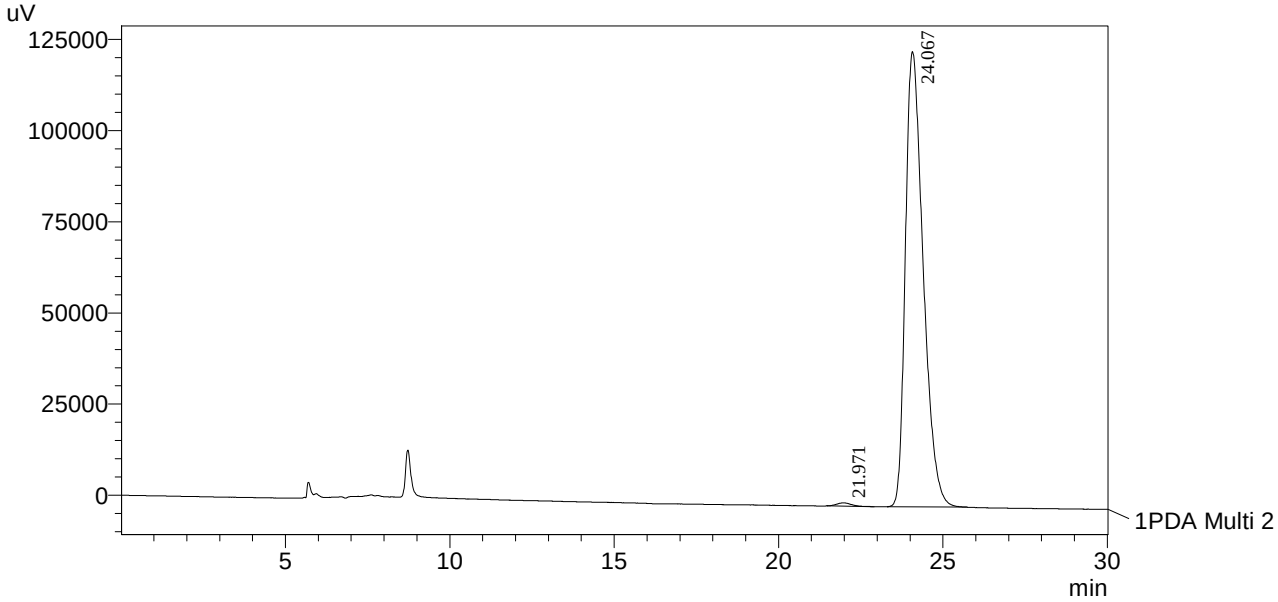
Injection Volume : 10 uL

Method

[Pump A Mobile Phase A]
Heptane
Pump A: Heptane, B: 2-Propanol

Pump A	:LC-20AD
Total Flow	:0.5000 mL/min
B.Conc	:10.0 %
C.Conc	:0.0 %
D.Conc	:0.0 %
PressMax	:100 bar
PressMin	:0 bar

Chromatogram



1 PDA Multi 2 / 254nm 4nm

Results

PeakTable

PDA Ch2 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.971	28069	910	0.595	0.724
2	24.067	4692927	124800	99.405	99.276
Total		4720995	125710	100.000	100.000