Stereoselective Synthesis of Medium-Sized Cyclic Ethers by Sequential Ring-Closing Metathesis and Tsuji-Trost Allylation

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Supporting Information

General Information

Air and/or moisture sensitive reactions were performed under an atmosphere of argon in flame dried apparatus. Tetrahydrofuran (THF), toluene, dichloromethane and diethyl ether were dried and purified using a Pure-SolvTM 500 Solvent Purification System. Other organic solvents and starting materials were obtained from commercial sources and used as received unless otherwise specified. Petroleum ether used for column chromatography was the 40−60 °C fraction.

Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F_{254} aluminium plates. TLC plates were visualised under UV light and stained using either potassium permanganate solution or acidic ethanolic anisaldehyde solution or phosphomolybdic acid solution. Flash column chromatography was performed on silica gel (Fluorochem LC60A 35–70 μm, or Geduran Si 60 35−70 μm).

IR spectra were recorded using a Shimadzu FT IR-8400S ATR instrument. The IR spectrum of each compound (solid or liquid) was acquired directly on a thin layer at ambient temperature.

^{1}H NMR spectra were recorded on Bruker Avance III 400 MHz and 500 MHz spectrometers at ambient temperature. ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz and 500 MHz spectrometers at 101 MHz and 126 MHz at ambient temperature.

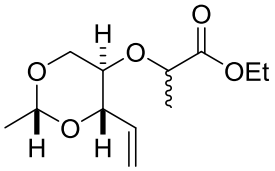
High resolution mass spectra (HRMS) were recorded using positive chemical ionization (CI+), positive ion impact (EI+) ionisation or fast atom bombardment (FAB) on a Jeol MStation JMS-700 instrument, or using positive or negative ion electrospray (ESI+/ESI–) techniques on a Bruker 2 micrOTOF-Q instrument.

Optical rotations were recorded with an error of 0.1 using an Autopol IV or Autopol V automatic polarimeter.

Elemental analyses were carried out on an Exeter Analytical Elemental Analyser EA 440.

Melting points were recorded with an Electrothermal IA 9100 apparatus.

Ethyl (2*R*)-{[(2*R*,4*S*,5*R*)-4-ethenyl-2-methyl-1,3-dioxan-5-yl]oxy}propanoate and ethyl (2*S*)-{[(2*R*,4*S*,5*R*)-4-ethenyl-2-methyl-1,3-dioxan-5-yl]oxy}propanoate (12).



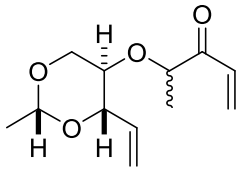
12

Sodium hydride (60% w/w in mineral oil, 604 mg, 25.2 mmol) was suspended in THF (50 mL). A solution of alcohol **10**[1] (2.80 g, 19.4 mmol) in THF (50 mL) was added dropwise and after complete addition the mixture was stirred for 20 min at room temperature. Ethyl 2-bromopropionate (3.0 mL 23 mmol) was added, followed by tetra-*n*-butylammonium iodide (286 mg, 0.774 mmol) and the mixture was heated at reflux for 2.5 h. The reaction was quenched by the addition of water (50 mL) and the mixture was extracted with diethyl ether (3 × 150 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 1:1) to give a diastereomeric mixture (1:1.7) of the ester **12** (4.70 g, 19.1 mmol, 99%) as a yellow oil. Complete separation of the diastereomers was difficult and small amounts of each isomer were obtained for characterization purposes. R_f = 0.40 (pet. ether-ethyl acetate, 4:1).

Less polar diastereoisomer: $[\alpha]_D^{25}$ +17.1 (*c* = 1.81, $CHCl_3$); ν_{max} 2986, 2942, 2862, 1748, 1732, 1447, 1404, 1279, 1196, 1139, 1115, 1037, 997, 928, 903, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (1H, ddd, *J* = 17.2, 10.5, 6.6 Hz), 5.43 (1H, ddd, *J* = 17.2, 1.6, 1.3 Hz), 5.28 (1H, ddd, *J* = 10.5, 1.6, 1.0 Hz), 4.69 (1H, q, *J* = 5.0 Hz), 4.29 (1H, dd, *J* = 10.9, 5.2 Hz), 4.23−4.10 (2H, m), 4.04 (1H, q, *J* = 6.9 Hz), 3.87 (1H, dd, *J* = 9.2, 6.6 Hz), 3.47 (1H, dd, *J* = 10.9, 10.3 Hz), 3.19 (1H, ddd, *J* = 10.3, 9.2, 5.2 Hz), 1.32 (3H, d, *J* = 5.0 Hz), 1.31 (3H, d, *J* = 6.9 Hz), 1.27 (3H, t, *J* = 7.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 135.2, 118.6, 98.7, 81.6, 75.9, 74.2, 69.4, 61.2, 20.7, 18.7, 14.3. HRMS (ESI) for $C_{12}H_{20}NaO_5$ $[M+Na]^+$ calcd 267.1203, found 267.1193.

More polar diastereoisomer: $[\alpha]_D^{25}$ −15.9 (*c* = 1.75, $CHCl_3$); ν_{max} 2987, 2940, 2907, 2876, 1732, 1647, 1449, 1406, 1373, 1329, 1200, 1121, 1042, 928, 903, 860, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.05 (1H, ddd, *J* = 17.3, 10.7, 5.5 Hz), 5.40 (1H, ddd, *J* = 17.3, 1.6, 1.5 Hz), 5.24 (1H, ddd, *J* = 10.7, 1.5, 1.4 Hz), 4.70 (1H, q, *J* = 5.1 Hz), 4.21−4.07 (3H, m), 4.03 (1H, q, *J* = 6.8 Hz), 3.92−3.86 (1H, m), 3.44 (1H, dd, *J* = 10.6, 10.0 Hz), 3.29 (1H, ddd, *J* = 10.0, 9.2, 5.0 Hz), 1.34 (3H, d, *J* = 6.8 Hz), 1.33 (3H, d, *J* = 5.1 Hz), 1.26 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 135.0, 117.3, 98.9, 80.2, 74.1, 72.5, 69.0, 61.1, 20.7, 19.1, 14.3; HRMS (ESI) for $C_{12}H_{20}NaO_5$ $[M+Na]^+$ calcd 267.1203, found 267.1194.

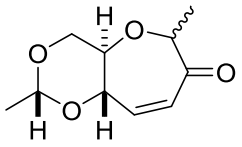
(4*R*)-{[(2*R*,4*S*,5*R*)-4-Ethenyl-2-methyl-1,3-dioxan-5-yl]oxy}pent-1-en-3-one and 4*R*)-{[(2*R*,4*S*,5*R*)-4-ethenyl-2-methyl-1,3-dioxan-5-yl]oxy}pent-1-en-3-one (14).



14

Methyltriphenylphosphonium bromide (6.57 g, 18.4 mmol) was suspended in THF (150 mL) and the mixture was cooled to −78 °C. *n*-Butyllithium (14.7 mL of 2.5 M solution in hexanes, 37 mmol) was added and the mixture was stirred at this temperature for 40 min. A solution of the ester **12** (4.50 g, 18.4 mmol) in THF (100 mL) was added and the mixture was allowed to warm to rt and then stirred for 3 h. The reaction was quenched by the addition of water (50 mL) and THF was removed under reduced pressure. The resulting mixture was extracted with ethyl acetate (3 × 150 mL) and the combined organic extracts were dried (Na_2SO_4) and then concentrated under reduced pressure. The crude phosphonium ylide **13** was dissolved in diethyl ether (100 mL) and pH 7 phosphate buffer (105 mL) was added followed by formaldehyde (13.6 mL of a 37% w/w solution in water, 181 mmol). The mixture was stirred for 2 h at rt and then extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 2:1) to deliver a diastereomeric mixture (1:1.7) of the enone **14** (3.80 g, 91% over 2 steps) as a yellow oil. R_f = 0.47 (pet. ether-ethyl acetate, 4:1); ν_{max} 2992, 2938, 2859, 1701, 1613, 1404, 1278, 11665, 1148, 1101, 986, 930, 905, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.73 (0.5H, dd, *J* = 17.4, 10.5 Hz), 6.61 (0.5H, dd, *J* = 17.4, 10.6 Hz), 6.39 (0.5H, dd, *J* = 17.4, 1.6 Hz), 6.38 (0.5H, dd, *J* = 17.4, 1.7 Hz), 5.93 (1H, dddd, *J* = 17.1, 10.5, 6.5, 2.0 Hz), 5.81 (0.5H, dd, *J* = 10.6, 1.6 Hz), 5.77 (0.5H, dd, *J* = 10.5, 1.7 Hz), 5.47−5.38 (1H, m), 5.32−5.26 (1H, m), 4.71 (0.5H, q, *J* = 5.1 Hz), 4.69 (0.5H, q, *J* = 5.1 Hz), 4.22−4.16 (1H, m), 4.16 (0.5H, q, *J* = 6.9 Hz), 4.09 (0.5H, q, *J* = 6.8 Hz), 3.93–3.86 (1H, m), 3.46 (1H, ddd, *J* = 10.8, 10.4, 2.0 Hz), 3.27 (0.5H, ddd, *J* = 10.1, 9.1, 5.0 Hz), 3.17 (0.5H, ddd, *J* = 10.1, 9.2, 5.1 Hz), 1.34 (1.5H, d, *J* = 5.1 Hz), 1.33 (1.5H, d, *J* = 5.1 Hz), 1.29 (1.5H, d, *J* = 6.8 Hz), 1.28 (1.5H, d, *J* = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 199.5, 135.1, 135.0, 131.3, 131.2, 130.1, 129.9, 118.9, 118.5, 98.9, 98.8, 81.4, 81.0, 80.9, 79.8, 76.8, 73.6, 72.6, 69.3, 69.3, 20.7, 18.4, 17.9; HRMS (ESI+) for $C_{12}H_{18}NaO_4$ $[M+Na]^+$ calcd 249.1097, found 249.1102.

(2*R*,4a*R*,6*R*,9a*S*)-4a,9a-Dihydro-2,6-dimethyl-4*H*-1,3-dioxino[5,4-*b*]oxepin-7(6*H*)-one and (2*R*,4a*R*,6*S*,9a*S*)-4a,9a-dihydro-2,6-dimethyl-4*H*-1,3-dioxino[5,4-*b*]oxepin-7(6*H*)-one (15).



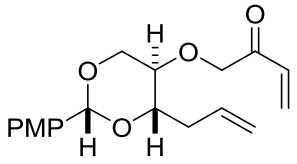
15

Diene **14** (0.10 g, 0.44 mmol) was dissolved in degassed dichloromethane (50 mL) and Grubbs second generation catalyst (1.1 mg, 13 μmmol) was added. The solution was heated at reflux for 18 h and the solvent was then removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 1:1) to give a diastereomeric mixture (1:1.7) of enone **15** (80 mg, 91%) as a yellow solid. Small amounts of each diastereomer were obtained for characterization purposes. R_f = 0.33 (pet. ether-ethyl acetate, 4:1).

Less polar diastereoisomer: m.p. 52−54 °C; $[\alpha]_D^{24}$ +45.7 (*c* = 0.110, $CHCl_3$); ν_{max} 2992, 2940, 2861, 1726, 1664, 1449, 1412, 1391, 1311, 1281, 1236, 1159, 1124, 1111, 1088, 1059, 1040, 1028, 1008, 903, 883, 847, 802 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 6.46 (1H, dd, *J* = 12.8, 2.3 Hz), 6.01 (1H, dd, *J* = 12.8, 2.7 Hz), 4.74 (1H, q, *J* = 5.0 Hz), 4.29 (1H, q, *J* = 6.8 Hz), 4.19 (1H, dd, *J* = 9.6, 4.0 Hz), 4.16 (1H, ddd, *J* = 8.6, 2.7, 2.3 Hz), 3.56 (1H, ddd, *J* = 10.1, 8.6, 4.0 Hz), 3.51 (1H, dd, *J* = 10.1, 9.6 Hz), 1.36 (3H, d, *J* = 5.0 Hz), 1.35 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4, 143.7, 128.2, 99.6, 83.8, 79.8, 73.9, 68.8, 20.5, 19.2; HRMS (ESI) for $C_{10}H_{14}NaO_4$ $[M+Na]^+$ calcd 221.0784, found 221.0777.

More polar diastereoisomer: m.p. 76−78 °C; $[\alpha]_D^{24}$ +114 (*c* = 0.725, $CHCl_3$); ν_{max} 2994, 2940, 2926, 2878, 1722, 1661, 1458, 1413, 1393, 1313, 1286, 1261, 1236, 1157, 1132, 1115, 1095, 1061, 1039, 1021, 1003, 897, 845, 812, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.48 (1H, dd, *J* = 12.6, 2.4 Hz), 6.04 (1H, dd, *J* = 12.6, 2.6 Hz), 4.75 (1H, q, *J* = 5.0 Hz), 4.42 (1H, q, *J* = 6.9 Hz), 4.22 (1H, ddd, *J* = 8.8, 2.6, 2.4 Hz), 4.09 (1H, dd, *J* = 10.8, 5.2 Hz), 3.68 (1H, ddd, *J* = 10.3, 8.8, 5.2 Hz), 3.52 (1H, dd, J = 10.8, 10.3 Hz), 1.45 (3H, d, *J* = 6.9 Hz), 1.37 (3H, d, *J* = 5.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 144.0, 128.7, 99.5, 80.5, 79.6, 69.1, 68.7, 20.5, 17.2. HRMS (ESI) for $C_{10}H_{14}NaO_4$ $[M+Na]^+$ calcd 221.0784, found 221.0775.

1-{[(2*R*,4*S*,5*R*)-2-(4-Methoxyphenyl)-4-(prop-2-en-1-yl)-1,3-dioxan-5-yl]oxy}but-3-en-2-one (19).

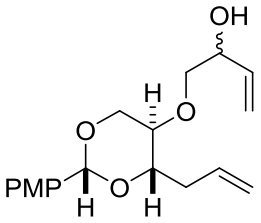


19

To a stirred suspension of sodium hydride (370 mg of a 60% w/w suspension in mineral oil, 9.25 mmol) in THF (7 mL) at 0 °C was added a solution of alcohol **16**[2] (1.78 g, 7.11 mmol) in THF

(15 mL) in a dropwise manner. The solution was allowed to warm to rt and phosphorane **17** (3.01 g, 8.53 mmol) was added, followed by tetra-*n*-butylammonium iodide (79 mg, 0.21 mmol). The reaction mixture was heated at reflux for 2 h and then cooled to rt. The reaction was quenched by the addition of water (15 mL) and the aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (chloroform-methanol, 97:3) to afford the crude phosphonium ylide **18** as a brown foam, which was immediately dissolved in diethyl ether (85 mL). To the solution of the ylide was added pH 7 phosphate buffer (70 mL) followed by formaldehyde (5.34 mL of a 37% w/v solution in water) and the reaction mixture was then stired at rt for 2 h. The aqueous phase was extracted with diethyl ether (3 × 100 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 3:1 → 2:1) to afford diene **19** (1.88 g, 83% over 2 steps) as a colorless oil. R_f = 0.81 (diethyl ether-methanol, 95:5); $[\alpha]_D^{25}$ −27 (*c* = 1.0, $CHCl_3$); ν_{max} 2930, 2857, 1717, 1614, 1516, 1395, 1302, 1248, 1171, 1101, 1028, 1011, 977, 932, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 8.7 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 6.50 (1H, dd, *J* = 17.6, 10.6 Hz), 6.34 (1H, dd, *J* = 17.6, 1.3 Hz), 5.98 (1H, dddd, *J* = 17.2, 10.2, 7.4, 6.4 Hz), 5.87 (1H, dd, *J* = 10.6, 1.3 Hz), 5.44 (1H, s), 5.18−5.08 (2H, m), 4.41 (1H, dd, *J* = 10.9, 5.0 Hz), 4.38 (1H, s), 4.38 (1H, s), 3.80 (3H, s), 3.78 (1H, ddd, *J* = 9.1, 7.2, 3.4 Hz), 3.66 (1H, dd, *J* = 10.9, 10.1 Hz), 3.38 (1H, ddd, *J* = 10.1, 9.1, 5.0 Hz), 2.70 (1H, dddt, *J* = 14.7, 6.4, 3.4, 1.5 Hz), 2.51−2.38 (1H, dddt, *J* = 14.7, 7.4, 7.2, 1.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1, 160.1, 134.3, 132.3, 130.4, 129.6, 127.5, 117.5, 113.7, 101.0, 79.9, 74.4, 73.9, 69.1, 55.4, 36.4; HRMS (ESI) for $C_{18}H_{22}NaO_5$ $[M+Na]^+$ calcd 341.1359, found 341.1351.

(2*R*)-1-{[(2*R*,4*S*,5*R*)-2-(4-Methoxyphenyl)-4-(prop-2-en-1-yl)-1,3-dioxan-5-yl]oxy}but-3-en-2-ol and (2*S*)-1-{[(2*R*,4*S*,5*R*)-2-(4-Methoxyphenyl)-4-(prop-2-en-1-yl)-1,3-dioxan-5-yl]oxy}but-3-en-2-ol (S1).

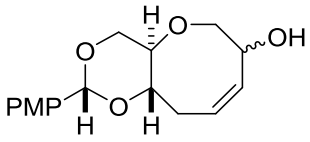


S1

To a stirred solution of enone **19** (560 mg, 1.76 mmol) in methanol (20 mL) were added at rt cerium(III) chloride heptahydrate (1.3 g, 3.5 mmol) and sodium borohydride (76 mg, 2.0 mmol). The resulting mixture was stirred for 45 min at rt. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 25 mL) and the combined organic extracts were washed with

brine (30 mL), dried ($MgSO_4$) and the concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether-diethyl ether, 9:1 to 1:1) to give a diastereomeric mixture (1:1) of the alcohol **S1** (510 mg, 90%) as a colorless oil. R_f = 0.38 (pet. ether-diethyl ether, 3:7); ν_{max} 3447, 3076, 2932, 2913, 2863, 2841, 1712, 1699, 1642, 1606, 1614, 1516, 1395, 1248, 1171, 1105, 1030, 1011, 922, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.7 Hz), 6.88 (2H, d, *J* = 8.7 Hz,), 5.97 (1H, dddd, *J* = 17.2, 10.2, 7.2, 6.5 Hz), 5.83 (1H, dddd, *J* = 17.3, 10.6, 5.6, 2.5 Hz), 5.42 (1H, s), 5.38 (1H, dt, *J* = 17.3, 1.5 Hz), 5.23 (1H, dt, *J* = 10.6, 1.5 Hz), 5.19−5.08 (2H, m), 4.39 (1H, ddd, *J* = 10.7, 5.0, 3.6 Hz), 4.33−4.23 (1H, m), 3.80 (3H, s), 3.73−3.35 (5H, m), 2.67−2.59 (1H, m), 2.48−2.38 (1H, m), 2.34 (0.5H, d, *J* = 3.6 Hz), 2.28 (0.5H, d, *J* = 3.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 136.4, 136.4, 134.4, 134.4, 130.4, 127.5, 117.3, 117.3, 117.0, 117.0, 113.7, 101.1, 79.9, 79.9, 74.2, 74.1, 73.4, 73.1, 72.0, 71.7, 69.3, 69.2, 55.4, 36.6, 36.5; HRMS (ESI) for $C_{18}H_{24}NaO_5$ $[M+Na]^+$ calcd 343.1516, found 343.1507; Anal. calcd for $C_{18}H_{24}O_5$: C, 67.48%; H, 7.55%. Found: C, 67.39%; H, 7.69%.

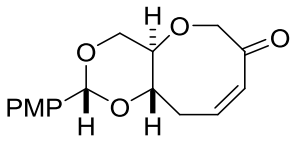
(2*R*,4a*R*,7*R*,10a*S*)-4,4a,6,7,10,10a-Hexahydro-2-(4-methoxyphenyl)-1,3-dioxino[5,4-*b*]-oxocin-7-ol and (2*R*,4a*R*,7*S*,10a*S*)-4,4a,6,7,10,10a-Hexahydro-2-(4-methoxyphenyl)-1,3-dioxino[5,4-*b*]-oxocin-7-ol (20).



20

To a stirred solution of alcohol **S1** (1:1 mixture of diastereoisomers) (495 mg, 1.54 mmol) in dry and degassed dichloromethane (1.5 L) at rt was added a solution of the Hoveyda-Grubbs second generation catalyst (48 mg, 80 μmol). The mixture was heated to reflux for 14 h and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (dichloromethane-methanol, 97:3 to 95:5) to afford a diastereomeric mixture (1:1) of the alcohol **20** (330 mg, 73%) as a colorless solid. R_f = 0.38 (dichloromethane−methanol, 96:4); m.p. 144−146 ºC; ν_{max} 3321, 3225, 3020, 2967, 2932, 2859, 1616, 1589, 1518, 1308, 1252, 1130, 1105, 1088, 1051, 1013, 953, 934, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, d, *J* = 8.7 Hz), 7.38 (1H, d, *J* = 8.7 Hz), 6.89 (1H, d, *J* = 8.7 Hz), 6.88 (1H, d, *J* = 8.7 Hz), 5.94−5.79 (1.5 H, m), 5.62 (0.5H, ddd, *J* = 10.7, 7.4, 1.5 Hz), 5.41 (0.5H, s), 5.39 (0.5H, s), 4.80−4.72 (0.5H, m), 4.56 (0.5H, dt, *J* = 9.7, 3.7 Hz), 4.22−4.16 (1H, m), 3.88 (0.5H, dd, *J* = 11.6, 3.7 Hz), 3.80 (1.5H, s), 3.79 (1.5H, s), 3.68 (0.5H, ddd, *J* = 10.3, 9.1, 4.6 Hz), 3.57 (0.5H, dd, *J* = 10.3, 10.2 Hz), 3.56−3.37 (2H, m), 3.30 (0.5H, dd, *J* = 10.9, 10.8 Hz), 2.82−2.73 (0.5H, m), 2.56−2.37 (3.5H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 137.4, 134.3, 130.3, 130.2, 127.6, 127.5, 127.0, 126.3, 113.8, 101.7, 101.2, 82.9, 79.9, 75.5, 75.4, 72.9, 71.9, 69.8, 69.6, 69.5, 67.4, 55.5, 33.7, 30.7; HRMS (EI+) for $C_{16}H_{20}O_5$ $[M]^+$ calcd 292.1311, found 292.1316; Anal. calcd for $C_{16}H_{20}O_5$: C, 65.74%; H, 6.90%. Found: C, 65.68%; H, 6.95%.

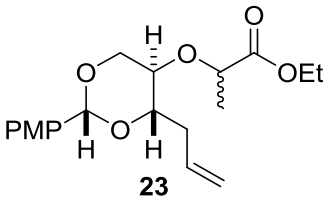
(2*R*,4a*R*,10a*S*)-4,4a,10,10a-Tetrahydro-2-(4-methoxyphenyl)-1,3-dioxino[5,4-*b*]oxocin-7(6*H*)-one (21).



21

To a stirred solution of allylic alcohols **20** (1:1 mixture of diastereomers) (59 mg, 0.20 mmol) in dry dichloromethane (4 mL) was added Dess-Martin periodinane (115 mg, 0.263 mmol). The mixture was stirred for 30 min at rt and the reaction was then quenched by the addition of a saturated aqueous solution of sodium sulfite (5 mL). The mixture was allowed to stir for 20 min at rt and then the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (pet. ether-diethyl ether, 9:1 → 1:1) to afford the cyclic enone **21** (51 mg, 86%) as a colorless solid. R_f = 0.40; (pet. ether-diethyl ether, 1:1); m.p. 166−167 °C; $[\alpha]_D^{18}$ −100 (*c* = 0.93, $CHCl_3$); ν_{max} 2939, 2918, 2866, 1680, 1614, 1582, 1518, 1395, 1366, 1296, 1267, 1242, 1132, 1111, 1093, 1038, 1015, 968, 937, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 8.7 Hz), 6.89 (2H, d, *J* = 8.7 Hz), 6.50 (1H, ddd, *J* = 12.4, 9.3, 7.8 Hz), 5.91 (1H, d, *J* = 12.4 Hz), 5.45 (1H, s), 4.54 (1H, dd, *J* = 17.6, 1.3 Hz), 4.29 (1H, d, *J* = 17.6 Hz), 4.27 (1H, dd, *J* = 10.3, 4.5 Hz), 3.81 (3H, s), 3.73 (1H, ddd, *J* = 9.7, 8.8, 1.2 Hz), 3.70 (1H, dd, *J* = 10.3, 10.1 Hz), 3.64 (1H, ddd *J* = 10.1, 8.8, 4.5 Hz), 2.82 (1H, dddd, *J* = 14.5, 9.7, 7.8, 1.6 Hz), 2.63 (1H, ddd, *J* = 14.5, 9.3, 1.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.0, 160.3, 137.0, 129.8, 129.6, 127.6, 113.9, 101.6, 82.5, 79.7, 77.7, 69.3, 55.5, 34.6; HRMS (EI+) for $C_{16}H_{18}O_5$ $[M]^+$ calcd 290.1154, found 290.1158.

Ethyl (2*R*)-{[(2*R*,4*S*,5*R*)-2-(4-methoxyphenyl)-6-(prop-2-en-1-yl)-1,3-dioxan-5-yl]oxy}-propanoate (23) and ethyl (2*S*)-{[(2*R*,4*S*,5*R*)-2-(4-methoxyphenyl)-6-(prop-2-en-1-yl)-1,3-dioxan-5-yl]oxy}-propanoate (23).



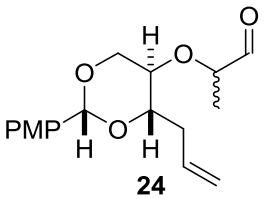
23

To a stirred suspension of sodium hydride (215 mg of a 60% w/w suspension in mineral oil, 5.37 mmol) in THF (10 mL) at rt was added a solution of alcohol **16** (1.03 g, 4.12 mmol) in THF (10 mL). The mixture was stirred at rt for 20 min, before the addition of ethyl 2-bromopropionate (0.643 mL, 4.95 mmol) followed by tetra-*n*-butylammonium iodide (60.9 mg, 0.165 mmol). The mixture was heated to reflux for 3 h and allowed to cool to rt before the reaction was quenched by the addition of water (25 mL). The aqueous phase was extracted with diethyl ether (3 × 75 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure.

The residue was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 5:1 → 3:1) to afford a diastereomeric mixture (1:1) of the ester **23** (1.42 g, 98%) as a colorless oil. A small amount of the less polar isomer was separated for characterization purposes.

Less polar diastereoisomer: R_f = 0.39 (pet. ether-ethyl acetate, 4:1); $[\alpha]_D^{24}$ +0.95 (*c* = 1.3, $CHCl_3$); ν_{max} 3075, 2982, 2938, 2909, 2861, 1746, 1614, 1302, 1248, 1203, 1171, 1111, 1084, 1032, 995, 978, 918, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 8.7 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 5.96 (1H, dddd, *J* = 17.6, 10.2, 7.5, 6.3 Hz), 5.42 (1H, s), 5.19−5.05 (2H, m), 4.40 (1H, dd, *J* = 11.0, 5.1 Hz), 4.27−4.16 (2H, m), 4.08 (1H, q, *J* = 6.9 Hz), 3.79 (3H, s), 3.73 (1H, ddd, *J* = 9.2, 7.0, 3.6 Hz), 3.66 (1H, dd, *J* = 11.0, 10.2 Hz), 3.37 (1H, ddd, *J* = 10.2, 9.2, 5.1 Hz), 2.61 (1H, dddt, *J* = 14.5, 6.3, 3.6, 1.7 Hz), 2.46−2.34 (1H, m), 1.41 (3H, d, *J* = 6.9 Hz), 1.30 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 160.1, 134.3, 130.5, 127.5, 117.4, 113.7, 100.9, 80.1, 76.0, 73.9, 69.7, 61.3, 55.4, 36.3, 19.0, 14.3; HRMS (ESI) for $C_{19}H_{26}NaO_6$ $[M+Na]^+$ calcd 373.1622, found 373.1607.

(2*R*/*S*)-2-{[(2*R*,4*S*,5*R*)-2-(4-Methoxyphenyl)-4-(prop-2-en-1-yl)-1,3-dioxan-5-yl]oxy}propanal (24).

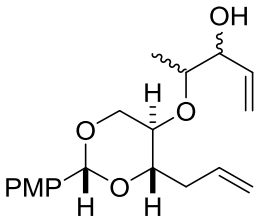


24

To a stirred solution of ester **23** (1.26 g, 3.60 mmol) in toluene (11 mL) at −78 °C was added diisobutylaluminium hydride (4.32 mL of a 1 M solution in heptane, 4.32 mmol) in a dropwise manner over 10 min. The mixture was stirred at −78 °C for 2 h before the reaction was quenched by the addition of methanol (5 mL). The mixture was allowed to warm to rt and diluted with diethyl ether (40 mL). A saturated aqueous solution of Rochelle salt (20 mL) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 50 mL) and the combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 7:1 then 3:1) to afford a diastereomeric mixture (1.4:1) of the aldehyde **24** (1.02 g, 93%) as a colorless oil. R_f = 0.21 (pet. ether-diethyl ether, 1:1); ν_{max} 3077, 2978, 2934, 1736, 1641, 1616, 1518, 1394, 1371, 1302, 1250, 1173, 1094, 1034, 1013, 986, 918, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.66 (0.4H, d, *J* = 1.5 Hz), 9.60 (0.6H, d, *J* = 1.2 Hz), 7.39 (2H, d, *J* = 8.8 Hz), 6.89 (2H, d, *J* = 8.8 Hz), 6.02−5.95 (1H, m), 5.45 (0.4H, s), 5.44 (0.6H, s), 5.17−5.08 (2H, m), 4.34 (1H, dd, *J* = 10.6, 5.1 Hz), 3.97−3.90 (1H, m), 3.80 (3H, s), 3.77−3.71 (1H, m), 3.66 (0.6H, dd, *J* = 10.6, 10.4 Hz), 3.63 (0.4H, dd, *J* = 10.5, 10.3 Hz), 3.48−3.39 (1H, m), 2.72 (0.4H, dddt, *J* = 14.8, 6.5, 3.4, 1.6 Hz), 2.64 (0.6H, dddt, *J* = 14.7, 6.5, 3.4, 1.6 Hz), 2.52−2.37 (1H, m), 1.33 (1.8H, d, *J* = 7.0 Hz), 1.30 (1.2H, d, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.2, 201.9,

160.2, 160.2, 134.2, 130.3, 130.3, 127.5, 117.6, 117.6, 113.8, 113.7, 101.0, 101.0, 80.6, 79.9, 79.9, 79.7, 72.7, 72.5, 69.6, 69.5, 55.4, 36.3, 36.2, 16.6, 15.6; HRMS (EI) for $C_{17}H_{22}O_5$ $[M]^+$ calcd 306.1467, found 306.1464.

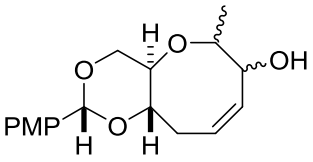
(3*R*/*S*,4*R*/*S*)-4-{[(2*R*,4*S*,5*R*)-2-(4-Methoxyphenyl)-4-(prop-2-en-1-yl)-1,3-dioxan-5-yl]oxy}pent-1-en-3-ol (25).



25

To a stirred solution of aldehyde **24** (200 mg, 0.653 mmol) in THF (2.6 mL) at −78 °C was added vinylmagnesium bromide (1.63 mL of a 1 M solution in THF, 1.63 mmol) in a dropwise manner. The reaction mixture was allowed to stir at −78 °C for 1 h and then warmed to rt. Stirring was continued for 1.5 h before the dropwise addition of further vinylmagnesium bromide (1.63 mL of a 1 M solution in THF, 1.63 mmol). The mixture was stirred for a further 2 h and the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL). The mixture was diluted with dichloromethane (15 mL) and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 7:1 → 3:1) to afford a mixture of all four diastereomers of the allylic alcohol **25** (144 mg, 66%) as a colorless oil. A small amount of the least polar isomer was separated for characterization purposes R_f = 0.24 (pet. ether-diethyl ether, 1:1); ν_{max} 3450, 3077, 2980, 2918, 2849, 1643, 1616, 1589, 1518, 1395, 1302, 1248, 1173, 1094, 1032, 991, 920, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.7 Hz), 6.89 (2H, d, *J* = 8.7 Hz), 5.97 (1H, dddd, *J* = 17.2, 10.2, 7.1, 6.8 Hz), 5.83 (1H, ddd, *J* = 17.2, 10.5, 6.2 Hz), 5.43 (1H, s), 5.32 (1H, ddd, *J* = 17.3, 1.7, 1.5 Hz), 5.24 (1H, ddd, J = 10.5, 1.7, 1.5 Hz), 5.18−5.07 (2H, m), 4.38 (1H, dd, *J* = 10.6, 4.8 Hz), 4.13−4.07 (1H, m), 3.80 (3H, s), 3.69−3.59 (2H, m), 3.58 (1H, dd, *J* = 10.6, 10.2 Hz), 3.50−3.44 (1H, m), 2.67−2.58 (1H, m), 2.43−2.34 (1H, m), 2.03 (1H, brs), 1.14 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 136.3, 134.4, 130.5, 127.5, 117.3, 117.3, 113.7, 101.0, 80.1, 77.5, 75.7, 70.7, 69.8, 55.4, 36.2, 14.7; HRMS (ESI) for $C_{19}H_{26}NaO_5$ $[M+Na]^+$ calcd 357.1672, found 357.1662.

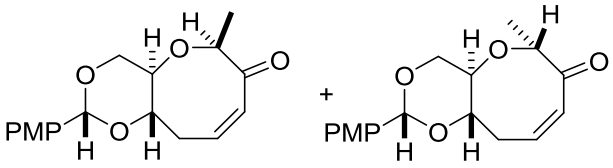
(2*R*,4a*R*,6*R*/*S*,7*R*/*S*,10a*S*)-4,4a,6,7,10,10a-Hexahydro-2-(4-methoxyphenyl)-6-methyl-1,3-dioxino[5,4-*b*]oxocin-7-ol (S2).



S2

To a stirred solution of allylic alcohol **25** (455 mg, 1.36 mmol) in dichloromethane (170 mL) at rt was added Grubbs second generation catalyst (34.6 mg, 42.0 µmol). The reaction mixture was heated under reflux for 18 h and subsequently concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 5:1 to 1:1) to afford **S2** (364 mg, 87%) as a colorless solid. The isomers were not separated and the diastereomeric mixture was used immediately in the subsequent oxidation reaction. R_f = 0.15 (pet. ether/diethyl ether, 1:1). ν_{max} 3333, 3240, 2940, 2870, 1613, 1520, 1389, 1304, 1250, 1173, 1095, 1034, 964, 826 cm^{-1}; HRMS (ESI) for $C_{17}H_{22}NaO_5$ $[M+Na]^+$ calcd 329.1359, found 329.1362.

(2*R*,4a*R*,6*S*,10a*S*)-2-(4-Methoxyphenyl)-6-methyl-4,4a,10,10a-tetrahydro-1,3-dioxino[5,4-b]-oxocin-7(6*H*)-one (22a) and (2*R*,4a*R*,6*R*,10a*S*)-2-(4-methoxyphenyl)-6-methyl-4,4a,10,10a-tetrahydro-1,3-dioxino[5,4-b]oxocin-7(6*H*)-one (22b).



22a **22b**

Hydrazone Alkylation Method

To a solution of the enone **21** (100 mg, 0.344 mmol) in benzene (8 mL) was added *N*,*N*-dimethylhydrazine (130 µL, 1.71 mmol) followed by anhydrous $MgSO_4$ (250 mg, 2.08 mmol). Glacial acetic acid (210 µL, 3.67 mmol) was added dropwise and the mixture was stirred at room temperature for 20 min before further anhydrous $MgSO_4$ (150 mg, 1.25 mmol) was added. The mixture was stirred at room temperature for 30 min before the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL). The mixture was extracted with ethyl acetate (3 × 30 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to furnish the crude hydrazone, which was used without further purification.

The crude hydrazone was dissolved in THF (8 mL) and cooled to −78 °C, *t*-butyllithium (0.25 mL of a 1.9 M solution in hexanes, 0.48 mmol) was added and the mixture was stirred for 15 min before addition of methyl iodide (0.22 mL, 3.5 mmol). The mixture was allowed to warm to rt and stirring was continued for 30 min. The reaction was quenched with water (15 mL) and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$)

and the solvent removed *in vacuo*. The residue was dissolved in a 10:1 mixture of THF and water (4.5 mL), copper(II) chloride (55 mg, 0.41 mmol) was added and the mixture was stirred at rt for 20 min. NH_3 (12 mL of a 28–30% w/w solution in water) and water (20 mL) were added and the mixture was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 4:1) to afford a diastereomeric mixture (4:1, **22a**:**22b**) of the enones (46.4 mg, 44% over 3 steps) as a colorless solid.

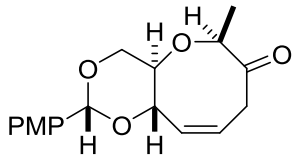
*Oxidation of Alcohol **S2***

To a stirred solution of **S2** (73 mg, 0.24 mmol) in dichloromethane (5 mL) at rt was added Dess-Martin periodinane (252 mg, 0.594 mmol). The mixture was stirred at rt for 2 h and the reaction was quenched by the addition of saturated aqueous sodium thiosulphate solution (7 mL). The mixture was stirred at rt for a further 20 min and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic extracts were washed with 50% saturated aqueous sodium bicarbonate solution (10 mL) then brine (10 mL) before being dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 5:1 to 1:1) to afford a diastereomeric mixture (1:1.3) of the enones **22a** and **22b** (69.1 mg, 95%) as a colorless solid.

22a: R_f = 0.56 (pet. ether-diethyl ether, 1:2); m.p. 113−115 °C; $[\alpha]_D^{25}$ −76.1 (*c* = 0.375, $CHCl_3$); ν_{max} 2976, 2936, 2860, 1676, 1616, 1518, 1371, 1302, 1248, 1173, 1101, 1086, 1030, 978, 912, 829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.7 Hz), 6.89 (2H, d, *J* = 8.7 Hz), 6.45 (1H, ddd, *J* = 12.5, 9.8, 7.8 Hz), 5.96 (1H, dd, *J* = 12.5, 0.9 Hz), 5.44 (1H, s), 4.32 (1H, q, *J* = 6.6 Hz), 4.26−4.18 (1H, m), 3.80 (3H, s), 3.71−3.63 (3H, m), 2.87−2.77 (1H, m), 2.58 (1H, dd, *J* = 13.9, 9.8 Hz), 1.34 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 160.3, 135.4, 130.5, 130.0, 127.6, 113.9, 101.6, 84.2, 81.4, 78.0, 69.9, 55.5, 34.2, 18.4; HRMS (ESI) for $C_{17}H_{20}NaO_5$ $[M+Na]^+$ calcd 327.1203, found 327.1187.

22b: R_f = 0.50 (pet. ether-diethyl ether, 1:2); m.p. 85−88 °C; $[\alpha]_D^{23}$ +42.5 (*c* = 0.215, $CHCl_3$); ν_{max} 2963, 2930, 2855, 1674, 1614, 1518, 1373, 1302, 1248, 1173, 1140, 1099, 1086, 1030, 827, 802, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 8.7 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 6.31 (1H, dt, *J* = 13.0, 5.5 Hz), 5.94 (1H, dd, *J* = 13.0, 1.9 Hz), 5.41 (1H, s), 4.38 (1H, q, *J* = 6.8 Hz), 4.19 (1H, dd, *J* = 10.2, 4.4 Hz), 4.03 (1H, ddd, *J* = 9.3, 8.0, 3.4 Hz), 3.94 (1H, dd, *J* = 10.5, 10.2 Hz), 3.87 (1H, ddd, *J* = 10.5, 9.3, 4.4 Hz), 3.80 (3H, s), 2.77−2.70 (2H, m), 1.33 (3H, d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5, 160.3, 136.7, 129.8, 127.6, 127.5, 113.9, 101.4, 76.6, 75.9, 73.0, 67.6, 55.5, 37.2, 19.3; HRMS (ESI) for $C_{17}H_{20}NaO_5$ $[M+Na]^+$ calcd 327.1203, found 327.1192.

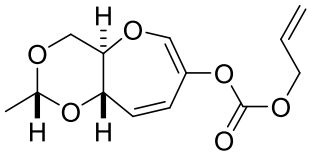
(2*R*,4a*R*,6*S*,10a*S*)-2-(4-Methoxyphenyl)-6-methyl-4,4a,8,10a-tetrahydro-1,3-dioxino[5,4-b]-oxocin-7(6*H*)-one (26)



26

To a stirred solution of the diastereomeric enones **22a** and **22b** (1:1.3 mixture, 89 mg, 0.29 mmol) in THF (9 mL) at rt was added DBU (90 µL, 0.60 mmol). The mixture was stirred at rt for 18 h before saturated aqueous ammonium chloride solution (20 mL) was added and the mixture was diluted with ethyl acetate (20 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 4:1) to afford ketone **26** (52.6 mg, 59%) as a colorless solid. R_f = 0.63 (pet. ether-diethyl ether, 1:2); m.p. 106−109 °C; $[\alpha]_D^{25}$ −479 (*c* = 0.710, $CHCl_3$); ν_{max} 2970, 2932, 2847, 1721, 1613, 1520, 1381, 1296, 1250, 1172, 1119, 1026, 980, 880, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 8.7 Hz), 6.90 (2H, d, *J* = 8.7 Hz), 5.92 (1H, ddd, *J* = 11.2, 4.6, 1.3 Hz), 5.65 (1H, dddd, *J* = 11.2, 9.3, 7.6, 2.2 Hz), 5.48 (1H, s), 4.58 (1H, dddd, *J* = 8.9, 4.6, 2.2, 0.5 Hz), 4.34 (1H, dd, *J* = 11.1, 5.5 Hz), 4.17 (1H, q, *J* = 6.9 Hz), 4.00 (1H, ddd, *J* = 11.0, 9.3, 1.3 Hz), 3.81 (3H, s), 3.71 (1H, dd, *J* = 11.1, 10.2 Hz), 3.51 (1H, ddd, *J* = 10.2, 8.9, 5.5 Hz), 2.88 (1H, dd, *J* = 11.0, 7.6 Hz), 1.28 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.8, 160.3, 135.2, 130.0, 127.6, 122.2, 113.9, 100.8, 81.7, 79.8, 77.3, 70.0, 55.5, 41.1, 18.2; HRMS (ESI) for $C_{17}H_{20}NaO_5$ $[M+Na]^+$ calcd 327.1203, found 327.1205.

(2*R*,4a*R*,9a*S*)-4a,9a-Dihydro-2-methyl-4*H*-1,3-dioxino[5,4-*b*]oxepin-7-yl prop-2-en-1-yl carbonate (27).

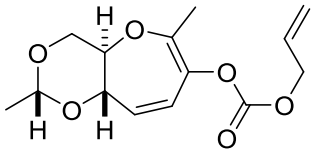


27

To a stirred solution of enone **11** (300 mg, 1.63 mmol) in THF (16 mL) at −78 °C was added allyl chloroformate (0.208 mL, 1.96 mmol) in a dropwise manner. The solution was stirred for 10 min before dropwise addition of sodium bis(trimethyl)silylamide (0.98 mL of a 2 M solution in THF, 2.0 mmol) over 15 min. The mixture was stirred at −78 °C for a further 2.5 h and then allowed to warm to rt. The reaction was quenched by the addition of potassium dihydrogen phosphate solution (15 mL of a 5% w/v in water) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 30 mL) and the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column

chromatography on silica gel (pet. ether-diethyl ether, 3:1) to afford enol carbonate **27** (435 mg, 99%) as a colorless solid. R_f = 0.61 (pet. ether-diethyl ether, 1:1); m.p. 66−68 °C; $[\alpha]_D^{21}$ −7.9 (*c* = 1.0, $CHCl_3$); ν_{max} 2996, 2941, 2899, 2879, 1746, 1620, 1411, 1364, 1273, 1248, 1227, 1211, 1157, 1128, 1115, 1042, 1028, 1001, 951, 939, 905, 882, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (1H, s), 5.95 (1H, ddt, *J* = 17.2, 10.4, 5.8 Hz), 5.84–5.75 (2H, m), 5.39 (1H, ddd, *J* = 17.2, 2.7, 1.5 Hz), 5.31 (1H, ddd, *J* = 10.4, 2.7, 1.2 Hz), 4.71 (1H, q, *J* = 5.0 Hz), 4.67 (2H, ddd, *J* = 5.8, 1.5, 1.2 Hz), 4.36 (1H, dd, *J* = 10.4, 4.6 Hz), 4.09–4.05 (1H, m), 3.60 (1H, ddd, *J* = 10.4, 6.8, 4.6 Hz), 3.53 (1H, dd, *J* = 10.4, 10.4 Hz), 1.38 (3H, d, *J* = 5.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 142.3, 133.6, 131.2, 129.7, 121.5, 119.6, 98.6, 77.1, 71.0, 69.3, 68.4, 20.5; HRMS (ESI) for $C_{13}H_{16}NaO_6$ $[M+Na]^+$ calcd 291.0839, found 291.0829. Anal. calcd for $C_{13}H_{16}O_6$: C, 58.20%; H, 6.01%. Found: C, 58.36%; H, 6.03%.

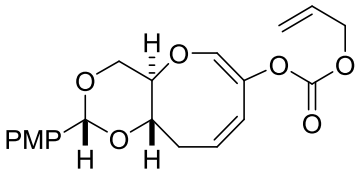
(2*R*,4a*R*,9a*S*)-4a,9a-Dihydro-2,6-dimethyl-4*H*-1,3-dioxino[5,4-*b*]oxepin-7-yl prop-2-en-1-yl carbonate (28).



28

To a stirred solution of enone **15** (173 mg, 0.873 mmol) in THF (17 mL) at −78 °C was added allyl chloroformate (0.112 mL, 1.05 mmol) in a dropwise manner. The solution was stirred for 10 min before dropwise addition of sodium bis(trimethyl)silylamide (0.53 mL of a 2 M solution in THF, 1.1 mmol) over 15 min. The reaction mixture was stirred at −78 °C for a further 2 h and then allowed to warm to rt. The reaction was quenched by the addition of potassium dihydrogen phosphate solution (10 mL of a 5% w/v in water) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 30 mL) and the combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 3:1) to afford the enol carbonate **28** (233 mg, 95%) as a colorless solid. R_f = 0.46 (pet. ether-ethyl acetate, 4:1); m.p. 97−100 °C; $[\alpha]_D^{24}$ +35.4 (*c* = 0.845, $CHCl_3$); ν_{max} 2296, 2920, 2874, 1742, 1664, 1629, 1368, 1273, 1256, 1159, 1132, 1119, 1064, 1034, 1001, 947, 984, 905, 853, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (1H, ddt, *J* = 17.2, 10.4, 5.8 Hz), 5.77 (1H, dd, *J* = 12.5, 2.4 Hz), 5.68−5.63 (1H, m), 5.39 (1H, dq, *J* = 17.2, 1.4 Hz), 5.31 (1H, dq, *J* = 10.4, 1.4 Hz), 4.70 (1H, q, *J* = 5.0 Hz), 4.68 (2H, dt, *J* = 5.8, 1.4 Hz), 4.34 (1H, dd, *J* = 10.5, 5.0 Hz), 4.06−4.01 (1H, m), 3.64 (1H, ddd, *J* = 10.5, 7.4, 5.0 Hz), 3.55 (1H, dd, *J* = 10.5, 10.5 Hz), 1.87 (3H, s), 1.37 (3H, d, *J* = 5.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 151.3, 131.4, 129.7, 126.9, 122.3, 119.5, 98.5, 76.8, 71.0, 69.2, 68.7, 20.5, 17.0; HRMS (ESI) for $C_{14}H_{18}NaO_6$ $[M+Na]^+$ calcd 305.0996, found 305.0998.

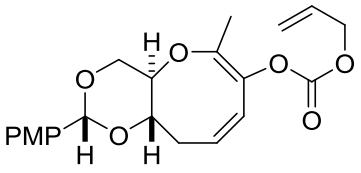
(2*R*,4a*R*,10a*S*)-4a,10a-Dihydro-2-(4-methoxyphenyl)-1,3-dioxino[5,4-b]oxocin-7-yl prop-2-en-1-yl carbonate (34).



34

To a stirred solution of enone **21** (380 mg, 1.31 mmol) in THF (40 mL) at −78 °C was added allyl chloroformate (0.167 mL, 1.57 mmol) in a dropwise manner. The solution was stirred for 10 min before dropwise addition of sodium bis(trimethyl)silylamide (0.81 mL of a 1.95 M solution in THF, 1.6 mmol) over 15 min. The mixture was stirred at −78 °C for a further 2 h and then allowed to warm to rt. The reaction was quenched by the addition of potassium dihydrogen phosphate solution (20 mL of a 5% w/v in water) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 75 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 4:1) to afford the enol carbonate **34** (419 mg, 86%) as a colorless solid. R_f = 0.53 (pet. ether-diethyl ether, 1:1); m.p. 120−122 °C; $[\alpha]_D^{23}$ = −82 (*c* = 0.38, $CHCl_3$); ν_{max} 2938, 2861, 1804, 1749, 1694, 1682, 1649, 1599, 1578, 1510, 1427, 1366, 1273, 1260, 1248, 1213, 1182, 1159, 1152, 1121, 1094, 1059, 1026, 964, 941, 914, 835, 824, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 8.7 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 6.58 (1H, s), 6.00−5.83 (3H, m), 5.45 (1H, s), 5.38 (1H, ddd, *J* = 17.2, 2.4, 1.2 Hz), 5.30 (1H, ddd, *J* = 10.4, 2.4, 1.2 Hz), 4.68−4.60 (3H, m), 4.25 (1H, dd, *J* = 10.4, 5.1 Hz), 3.80 (3H, s), 3.74 (1H, ddd, *J* = 9.0, 4.1, 2.8 Hz), 3.70 (1H, dd, *J* = 10.4, 10.4 Hz), 2.97 (1H, dddd, *J* = 14.2, 8.4, 4.1, 1.4 Hz), 2.63 (1H, ddd, *J* = 14.2, 7.1, 2.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 154.6, 141.4, 131.3, 130.4, 130.0, 128.4, 127.6, 126.4, 119.5, 113.8, 101.9, 73.7, 69.2, 69.2, 69.0, 55.5, 31.7; HRMS (ESI) for $C_{20}H_{22}NaO_7$ $[M+Na]^+$ calcd 397.1258, found 397.1242.

(2*R*,4a*R*,10a*S*)-4a,10a-Dihydro-2-(4-methoxyphenyl)-6-methyl-1,3-dioxino[5,4-b]oxocin-7-yl prop-2-en-1-yl carbonate (35).



35

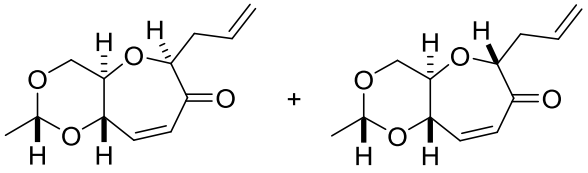
To a stirred solution of enone **22** (4:1 mixture of **a**:**b**, 100 mg, 0.329 mmol) in THF (10 mL) at −78 °C was added allyl chloroformate (42 µL, 0.40 mmol) in a dropwise manner. The was mixture stirred for 10 min before dropwise addition of sodium bis(trimethyl)silylamide (0.20 mL of a 2 M solution in THF, 0.39 mmol). Stirring was continued for 2.5 h, the reaction mixture was then warmed to ambient temperature and quenched with potassium dihydrogen phosphate solution

(10 mL of a 5% w/v in water). The mixture was extracted with diethyl ether (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pet. ether-diethyl ether, 4:1) to furnish the enol carbonate **35** (98 mg, 77%) as a colorless solid. R_f = 0.64 (pet. ether-ethyl acetate, 1:1); m.p. 114−117 °C; $[\alpha]_D^{27}$ = −66 (*c* = 0.41, $CHCl_3$); ν_{max} 2956, 2858, 1749, 1649, 1612, 1516, 1295, 1246, 1099, 1033, 1024, 956, 909, 809, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 8.7 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 5.95 (1H, ddt, *J* = 17.2, 10.5, 5.8 Hz), 5.93−5.88 (1H, m), 5.84 (1H, ddd, *J* = 10.8, 8.2, 7.0 Hz), 5.44 (1H, s), 5.38 (1H, dtd, *J* = 17.2, 1.4, 1.2 Hz), 5.29 (1H, dq, *J* = 10.5, 1.2 Hz), 4.66 (2H, ddd, *J* = 5.8, 1.4, 1.2 Hz), 4.38 (1H, ddd, J = 10.2, 9.0, 5.2 Hz), 4.25 (1H, dd, *J* = 10.4, 5.2 Hz), 3.80 (3H, s), 3.71 (1H, dd, *J* = 10.4, 10.2 Hz), 3.68 (1H, ddd, *J* = 9.0, 4.6, 3.6 Hz), 2.80 (1H, dddd, *J* = 13.8, 8.2, 3.6, 0.5 Hz), 2.59 (1H, ddd, *J* = 13.8, 7.0, 4.6 Hz), 1.87 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 153.6, 148.3, 131.4, 130.1, 129.3, 127.5, 127.4, 125.9, 119.0, 113.7, 101.7, 75.0, 69.8, 69.4, 68.8, 55.3, 32.0, 16.6. HRMS (CI+, isobutane) calcd for $C_{21}H_{25}O_7$ $[M+H]^+$ 389.1600, found 389.1598.

General procedure for Tsuji-Trost allylation reactions.

A solution of $Pd(PPh_3)_4$ (5 mol%) and PHOX ligand (12.5 mol%) in THF (10 mL) was prepared and allowed to stir at rt for 25 min, after which a solution of the enol carbonate (25−35 mmol) in THF (5 mL) was added. The mixture was stirred at rt for 2 h before being concentrated under reduced pressure. Subsequent purification of the residue by flash column chromatography on silica gel afforded the allylated products **32a**/**b**, **33a**/**b**, **36a**/**b** and **37a**/**b**.

(2*R*,4a*R*,6*S*,9a*S*)-4a,9a-Dihydro-2-methyl-6-(prop-2-enyl)-4*H*-1,3-dioxino[5,4-*b*]oxepin-7(6*H*)-one (32a) and (2*R*,4a*R*,6*R*,9a*S*)-4a,9a-Dihydro-2-methyl-6-(prop-2-enyl)-4*H*-1,3-dioxino[5,4-*b*]oxepin-7(6*H*)-one (32b).



32a + **32b**

Following the general procedure, the enol carbonate **27** (100 mg, 0.373 mmol) in THF (15 mL) was treated with the complex generated from the ligand **29** (18.1 mg, 46.7 μmol) and $(PPh_3)_4Pd$ (21.6 mg, 18.7 μmol) to give the enone **32a** (80.2 mg, 96%, dr >97:3) as a colorless oil.

Following the general procedure, the enol carbonate **27** (100 mg, 0.373 mmol) in THF (15 mL) was treated with the complex generated from the ligand **30** (18.1 mg, 46.7 μmol) and $(PPh_3)_4Pd$ (21.6 mg, 18.7 μmol) to give the enones **32a** and **32b** (63.0 mg, 75%, dr 13:87) as colorless oils.

Following the general procedure, the enol carbonate **27** (100 mg, 0.373 mmol) in THF (15 mL) was treated with the complex generated from the ligand **31** (16.8 mg, 46.7 mmol) and $(PPh_3)_4Pd$ (21.6 mg, 18.7 μmol) to give the enones **32a** and **32b** (77.3 mg, 92%, dr 69:31) as colorless oils.

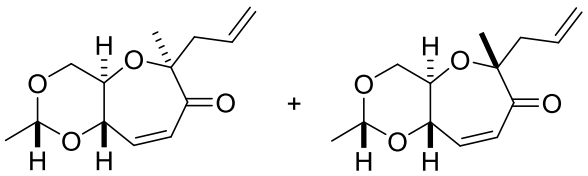
32a: R_f = 0.60 (pet. ether-diethyl ether, 1:1); $[\alpha]_D^{26}$ +31 (*c* = 0.93, $CHCl_3$); ν_{max} 3077, 2996, 2920, 2878, 1663, 1447, 1290, 1153, 1126, 1109, 1030, 1008, 907, 891, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.45 (1H, dd, *J* = 12.7, 2.2 Hz), 6.01 (1H, dd, *J* = 12.7, 2.7 Hz), 5.77 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz), 5.11−5.02 (2H, m), 4.74 (1H, q, *J* = 5.0 Hz), 4.24 (1H, dd, *J* = 7.4, 4.2 Hz), 4.19−4.12 (2H, m), 3.58−3.49 (2H, m), 2.56 (1H, dddt, *J* = 14.7, 6.9, 4.2, 1.4 Hz), 2.41 (1H, dddt, *J* = 14.7, 7.4, 6.9, 1.1 Hz), 1.35 (3H, d, *J* = 5.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 143.5, 133.3, 128.7, 118.0, 99.6, 87.1, 79.7, 73.9, 68.6, 37.8, 20.5; HRMS (ESI) for $C_{12}H_{16}NaO_4$ $[M+Na]^+$ calcd 247.0941, found 247.0936.

32b: R_f = 0.68 (pet. ether-diethyl ether, 1:1); $[\alpha]_D^{25}$ +44.1 (*c* = 0.305, in $CHCl_3$); ν_{max} 3077, 2996, 2920, 2861, 1663, 1645, 1447, 1413, 1389, 1306, 1290, 1271, 1236, 1153, 1107, 1065, 1030, 1009, 991, 982, 907, 889, 866, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (1H, dd, *J* = 12.6, 2.3 Hz), 6.05 (1H, dd, *J* = 12.6, 2.6 Hz), 5.82 (1H, dddd, *J* = 17.1, 10.1, 7.7, 6.2 Hz), 5.22−5.11 (2H, m), 4.74 (1H, q, *J* = 5.0 Hz), 4.34 (1H, dd, *J* = 9.9, 4.1 Hz), 4.23 (1H, ddd, *J* = 8.9, 2.6, 2.3 Hz), 4.12 (1H, dd, *J* = 10.8, 5.2 Hz), 3.72 (1H, ddd, *J* = 10.2, 8.9, 5.2 Hz), 3.49 (1H, dd, *J* = 10.8, 10.2 Hz), 2.69 (1H, dddt, *J* = 15.2, 6.2, 4.1, 1.6 Hz), 2.57 (1H, dddt, *J* = 15.2, 9.9, 7.7, 1.0 Hz), 1.37 (3H, d, *J* = 5.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.6, 144.4, 134.0, 128.8, 118.3, 99.5, 83.7, 79.6, 68.8, 68.7, 35.6, 20.5. HRMS (ESI) for $C_{12}H_{16}NaO_4$ $[M+Na]^+$ calcd 247.0941, found 247.0934.

Detailed Experimental Procedure for the Palladium-Mediated Allylation Reaction Performed on a Scale of Greater than 1 mmol.

To a stirred solution of $Pd_2(dba)_3$ (94.0 mg, 0.102 mmol) in degassed THF (95 mL) at 25 °C was added (*S*)-*t*-Bu-PHOX (**29**) (98.4 mg, 0.254 mmol). After 30 min, a solution of allyl enol carbonate **27** (1.1 g, 4.1 mmol) in degassed THF (30 mL) was added in a dropwise manner. The resulting mixture was stirred at 25 °C for 1 h, then filtered through Celite® and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether-diethyl ether, 9:1) to afford the enone **32a** (760 mg, 83%) as a colorless oil.

(2*R*,4a*R*,6*S*,9a*S*)-4a,9a-Dihydro-2,6-dimethyl-6-(prop-2-enyl)-4*H*-1,3-dioxino[5,4-*b*]oxepin-7(6*H*)-one (33a) and (2*R*,4a*R*,6*R*,9a*S*)-4a,9a-Dihydro-2,6-methyl-6-(prop-2-enyl)-4*H*-1,3-dioxino[5,4-*b*]oxepin-7(6*H*)-one (33b).



33a **33b**

Following the general procedure, the enol carbonate **28** (100 mg, 0.354 mmol) in THF (15 mL) wastreated with the complex generated from the ligand **29** (17.2 mg, 44.3 μmol) and $(PPh_3)_4Pd$ (20.5 mg, 17.7 μmol) to give the enone **33a** (80.2 mg, 95%, dr >97:3) as a colorless oil.

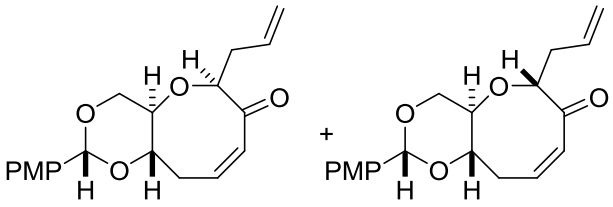
Following the general procedure, the enol carbonate **28** (100 mg, 0.354 mmol) in THF (15 mL) was treated with the complex generated from the ligand **30** (17.2 mg, 44.3 μmol) and $(PPh_3)_4Pd$ (20.5 mg, 17.7 μmol) to give the enones **33a** and **33b** (66.3 mg, 79%, dr 28:72) as colorless oils.

Following the general procedure, the enol carbonate **28** (100 mg, 0.354 mmol) in THF (15 mL) was treated with the complex generated from the ligand **31** (15.9 mg, 44.2 μmol) and $(PPh_3)_4Pd$ (20.5 mg, 17.7 μmol) to give the enones **33a** and **33b** (74.2 mg, 88%, dr 87:13) as colorless oils.

33a: R_f = 0.53 (pet. ether-ethyl acetate, 4:1); $[\alpha]_D^{20}$ = +46.5 (*c* = 1.10, $CHCl_3$); ν_{max} 2976, 2930, 2859, 1724, 1664, 1642, 1412, 1287, 1159, 1107, 1088, 1061, 1040, 1017, 907, 885, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.39 (1H, dd, *J* = 12.6, 2.4 Hz), 5.98 (1H, dd, *J* = 12.6, 2.7 Hz), 5.71 (1H, dddd, *J* = 17.3, 10.2, 7.5, 6.9 Hz), 5.06−4.96 (2H, m), 4.76 (1H, q, *J* = 5.0 Hz), 4.13−4.03 (2H, m), 3.58−3.49 (2H, m), 2.35 (1H, dddd, *J* = 14.0, 7.5, 1.2, 1.0 Hz), 2.28 (1H, dddd, *J* = 14.0, 6.9, 1.4, 1.2 Hz), 1.40 (3H, s), 1.36 (3H, d, *J* = 5.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.8, 142.0, 132.2, 129.0, 118.9, 99.4, 88.2, 79.4, 69.6, 69.1, 45.5, 22.1, 20.5; HRMS (ESI) for $C_{13}H_{18}NaO_4$ $[M+Na]^+$ calcd 261.1097, found 261.1098.

33b: R_f = 0.48 (pet. ether-ethyl acetate, 4:1); $[\alpha]_D^{25}$ +14.8 (*c* = 0.995, in $CHCl_3$); ν_{max} 2978, 2926, 2857, 1717, 1665, 1640, 1412, 1389, 1287, 1261, 1157, 1105, 1061, 1040, 1017, 907, 885, 866, 845, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.44 (1H, dd, *J* = 12.6, 2.4 Hz), 6.04 (1H, dd, *J* = 12.6, 2.6 Hz), 5.82 (1H, dddd, *J* = 16.9, 10.3, 8.1, 6.5 Hz), 5.22−5.14 (2H, m), 4.74 (1H, q, *J* = 5.1 Hz), 4.14 (1H, dd, *J* = 10.5, 4.9 Hz), 4.10 (1H, ddd, *J* = 8.3, 2.6, 2.4 Hz), 3.57 (1H, ddd, *J* = 10.2, 8.3, 4.9 Hz), 3.49 (1H, dd, *J* = 10.5, 10.2 Hz), 2.68 (1H, dd, *J* = 14.8, 6.5 Hz), 2.54 (3H, dddd, *J* = 14.8, 8.0, 1.2, 1.0 Hz), 1.35 (3H, d, *J* = 5.1 Hz), 1.22 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.3, 142.7, 132.6, 128.1, 119.3, 99.4, 87.4, 79.5, 70.0, 68.8, 40.3, 25.4, 20.5; HRMS (ESI) for $C_{13}H_{18}NaO_4$ $[M+Na]^+$ calcd 261.1097, found 261.1091.

(2*R*,4a*R*,6*S*,10a*S*)-2-(4-Methoxyphenyl)-6-(prop-2-enyl)-4,4a,10,10a-tetrahydro-1,3-dioxino-[5,4-b]-oxocin-7(6*H*)-one (36a) and (2*R*,4a*R*,6*R*,10a*S*)-2-(4-methoxyphenyl)-6-(prop-2-enyl)-4,4a,10,10a-tetrahydro-1,3-dioxino[5,4-b]oxocin-7(6*H*)-one (36b).



36a **36b**

Following the general procedure, the enol carbonate **34** (20 mg, 53 µmol) in THF (2.0 mL) was treated with the complex generated from the ligand **29** (5.3 mg, 14 µmol) and $(PPh_3)_4Pd$ (6.2 mg, 5.4 µmol) to give the enones **36a** and **36b** (14.0 mg, 79%, dr 94:6) as colorless solids.

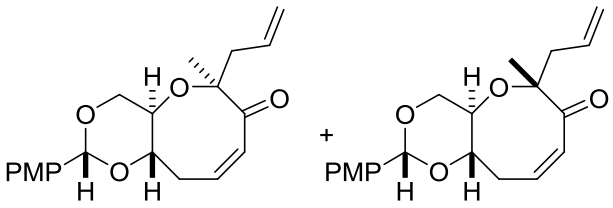
Following the general procedure, the enol carbonate **34** (100 mg, 0.267 mmol) in THF (15 mL) was treated with the complex generated from the ligand **30** (12.9 mg, 33.3 µmol) and $(PPh_3)_4Pd$ (15.5 mg, 13.4 µmol) to give the enones **36a** and **36b** (64.2 mg, 73%, dr 17:83) as colorless solids.

Following the general procedure, the enol carbonate **34** (100 mg, 0.267 mmol) in THF (15 mL) was treated with the complex generated from the ligand **31** (12.0 mg, 33.4 µmol) and $(PPh_3)_4Pd$ (15.5 mg, 13.4 µmol) to give the enones **36a** and **36b** (75.1 mg, 85%, dr 66:34) as colorless solids.

36a: R_f = 0.42 (pet. ether-diethyl ether, 1:1); m.p. 74−76 °C; $[\alpha]_D^{23}$ = −79 (*c* = 0.30, $CHCl_3$); ν_{max} 3069, 2972, 2916, 2872, 1694, 1663, 1640, 1616, 1589, 1516, 1387, 1373, 1335, 1302, 1248, 1173, 1097, 1035, 964, 912, 824, 808 cm^{-1},^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 8.7 Hz), 6.89 (2H, d, *J* = 8.7 Hz), 6.46 (1H, ddd, *J* = 12.6, 10.0, 7.9 Hz), 5.92 (1H, dd, *J* = 12.6, 0.9 Hz), 5.83 (1H, dddd, *J* = 17.0, 10.2, 7.5, 6.7 Hz), 5.44 (1H, s), 5.19−5.12 (2H, m), 4.26−4.21 (2H, m), 3.80 (3H, s), 3.70−3.60 (3H, m), 2.84 (1H, dddd, *J* = 14.2, 9.6, 8.1, 1.5 Hz), 2.65−2.59 (1H, m), 2.58 (1H, dd *J* = 14.0, 10.0 Hz), 2.31 (1H, dddt, *J* = 14.0, 9.2, 7.9, 0.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.3, 160.3, 136.0, 133.7, 130.9, 129.9, 127.5, 118.7, 113.9, 101.7, 87.7, 82.2, 77.8, 69.6, 55.5, 37.0, 34.2; HRMS (ESI) for $C_{19}H_{22}NaO_5$ $[M+Na]^+$ calcd 353.1359, found 353.1352.

36b: R_f = 0.44 (pet. ether-diethyl ether, 1:1); m.p. 92−94 °C; $[\alpha]_D^{25}$ −14.6 (*c* = 0.0950, in $CHCl_3$); ν_{max} 3078, 2963, 2924, 2862, 1674, 1613, 1520, 1373, 1304, 1250, 1173, 1096, 1026, 926, 826 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (2H, d, *J* = 8.8 Hz), 6.88 (2H, d, *J* = 8.8 Hz), 6.28 (1H, dt, *J* = 13.2, 5.1 Hz), 5.86 (1H, dt, *J* = 13.2, 2.3 Hz), 5.78 (1H, ddt, *J* = 17.2, 10.3, 7.0 Hz), 5.39 (1H, s), 5.17−5.08 (2H, m), 4.28 (1H, dd, *J* = 8.2, 4.6 Hz), 4.19−4.15 (1H, m), 4.04 (1H, ddd, *J* = 9.2, 7.5, 4.1 Hz), 3.98−3.86 (2H, m), 3.80 (3H, s), 2.77−2.71 (2H, m), 2.53−2.43 (1H, m), 2.41−2.32 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.1, 160.3, 137.0, 133.2, 129.7, 127.5, 127.2, 118.6, 113.9, 101.3, 80.0, 75.4, 73.5, 67.1, 55.5, 38.3, 37.8. HRMS (ESI) for $C_{19}H_{22}NaO_5$ $[M+Na]^+$ calcd 353.1359, found 353.1350.

(2*R*,4a*R*,6*S*,10a*S*)-2-(4-Methoxyphenyl)-6-methyl-6-(prop-2-enyl)-4,4a,10,10a-tetrahydro-1,3-dioxino[5,4-b]-oxocin-7(6*H*)-one (37a) and (2*R*,4a*R*,6*R*,10a*S*)-2-(4-methoxyphenyl)-6-methyl-6-(prop-2-enyl)-4,4a,10,10a-tetrahydro-1,3-dioxino[5,4-b]oxocin-7(6*H*)-one (37b).



37a **37b**

Following the general procedure, the enol carbonate **35** (36 mg, 93 µmol) in THF (1.5 mL) was treated with the complex generated from the ligand **29** (4.5 mg, 12 µmol) and $(PPh_3)_4Pd$ (5.2 mg, 4.5 µmol) to give the enone **37a** (26 mg, 81%, dr >97:3) as a colorless oil.

Following the general procedure, the enol carbonate **35** (29 mg, 75 µmol) in THF (1.5 mL) was treated with the complex generated from the ligand **30** (3.6 mg, 9.2 µmol) and $(PPh_3)_4Pd$ (3.4 mg, 2.9 mmol) to give the enones **37a** and **37b** (21 mg, 81%, dr 55:45) as colorless oils.

Following the general procedure, the enol carbonate **36** (30 mg, 77 µmol) in THF (1.5 mL) was treated with the complex generated from the ligand **31** (3.5 mg, 9.7 µmol) and $(PPh_3)_4Pd$ (3.6 mg, 3.1 µmol) to give the enones **37a** and **37b** (23 mg, 86%, dr 91:9) as colorless oils.

37a: R_f = 0.45 (pet. ether-ethyl acetate, 4:1); $[\alpha]_D^{26}$ = −93.4 (*c* = 1.01, $CHCl_3$); ν_{max} 2936, 2861, 1703, 1616, 1518, 1250, 1173, 1098, 1034, 990, 974, 924, 829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 8.7 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 6.16−6.09 (1H, m), 6.03 (1H, d, *J* = 12.8 Hz), 5.65 (1H, dddd, *J* = 17.1, 10.2, 7.8, 6.7 Hz), 5.41 (1H, s), 5.12 (1H, ddt, *J* = 10.2, 1.6, 1.1 Hz), 5.09 (1H, ddt, *J* = 17.1, 1.6, 1.4 Hz), 4.06 (1H, dd, *J* = 10.4, 4.6 Hz), 3.80 (3H, s), 3.75 (1H, ddd, *J* = 9.2, 8.9, 3.2 Hz), 3.66 (1H, ddd, *J* = 10.1, 8.9, 4.6 Hz), 3.60 (1H, dd, *J* = 10.4, 10.1 Hz), 2.50−2.39 (2H, m), 2.38 (1H, ddt, *J* = 13.8, 6.7, 1.4 Hz), 2.27 (1H, ddt, *J* = 13.8, 7.8, 1.1 Hz), 1.39 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.9, 160.2, 131.6, 131.4, 130.0, 129.9, 127.5, 119.4, 113.8, 101.0, 85.3, 78.4, 71.2, 70.1, 55.4, 43.8, 33.7, 17.9; HRMS (EI+) for $C_{20}H_{25}O_5$ $[M+H]^+$ calcd 345.1702, found 345.1705.

37b: R_f = 0.43 (pet. ether-ethyl acetate, 4:1); $[\alpha]_D^{24}$ = −12 (*c* = 0.40, $CHCl_3$); ν_{max} 2961, 2928, 2857, 1705, 1641, 1616, 1518, 1456, 1393, 1364, 1302, 1250, 1173, 1123, 1096, 1034, 991, 974, 926, 829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (2H, d, *J* = 8.7 Hz), 6.87 (2H, d, *J* = 8.7 Hz), 6.17 (1H, d, *J* = 12.4 Hz), 6.15−6.08 (1H, m), 5.80 (1H, dddd, *J* = 17.3, 10.2, 7.1, 6.8 Hz), 5.40 (1H, s), 5.24−5.16 (2H, m), 4.18 (1H, dd, *J* = 11.0, 4.6 Hz), 3.80 (3H, s), 3.77−3.55 (3H, m), 2.68 (1H, ddt, *J* = 15.2, 7.1, 1.2 Hz), 2.63 (1H, ddt, J = 15.2, 6.8, 1.4 Hz), 2.49−2.43 (2H, m), 1.25 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5, 160.2, 132.5, 131.2, 130.0, 129.9, 127.5, 119.4, 113.8, 101.1, 84.2, 79.0, 70.8, 70.2, 55.4, 36.8, 33.4, 23.3; HRMS (EI+) for $C_{20}H_{24}NaO_5$ $[M+Na]^+$ calcd 367.1516, found 367.1509.

References

1. (a) Giannis, A.; Münster, P.; Sandhoff, K.; Steglich W. *Tetrahedron* **1988**, *44*, 7177−7180. (b) Clark, J. S.; Grainger, D. M.; Ehkirch, A. A.-C.; Blake, A. J.; Wilson, C. *Org. Lett.* **2007**, *9*, 1033−1036.
2. Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127−130.

^{1}H and ^{13}C NMR Spectra

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^{1}H NMR spectrum of **14**	27
^{13}C NMR spectrum of **14**	28
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^{13}C NMR spectrum of **15** (less polar)	30
^{1}H NMR spectrum of **15** (more polar)	31
^{13}C NMR spectrum of **15** (more polar)	32
^{1}H NMR spectrum of **19**	33
^{13}C NMR spectrum of **19**	34
^{1}H NMR spectrum of **S1**	35
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^{13}C NMR spectrum of **20**	38
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^{13}C NMR spectrum of **21**	40
^{1}H NMR spectrum of **23**	41
^{13}C NMR spectrum of **23**	42
^{1}H NMR spectrum of **24**	43
^{13}C NMR spectrum of **24**	44
^{1}H NMR spectrum of **25**	45
^{13}C NMR spectrum of **25**	46
^{1}H NMR spectrum of **22a**	47
^{13}C NMR spectrum of **22a**	48
^{1}H NMR spectrum of **22b**	49
^{13}C NMR spectrum of **22b**	50
^{1}H NMR spectrum of **26**	51
^{13}C NMR spectrum of **26**	52
^{1}H NMR spectrum of **27**	53
^{13}C NMR spectrum of **27**	54
^{1}H NMR spectrum of **28**	55
^{13}C NMR spectrum of **28**	56
^{1}H NMR spectrum of **32a**	57

^{13}C NMR spectrum of **32a** 58
^{1}H NMR spectrum of **32b** 59
^{13}C NMR spectrum of **32b** 60
^{1}H NMR spectrum of **33a** 61
^{13}C NMR spectrum of **33a** 62
^{1}H NMR spectrum of **33b** 63
^{13}C NMR spectrum of **33b** 64
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^{13}C NMR spectrum of **34** 66
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^{13}C NMR spectrum of **36a** 70
^{1}H NMR spectrum of **36b** 71
^{13}C NMR spectrum of **36b** 72
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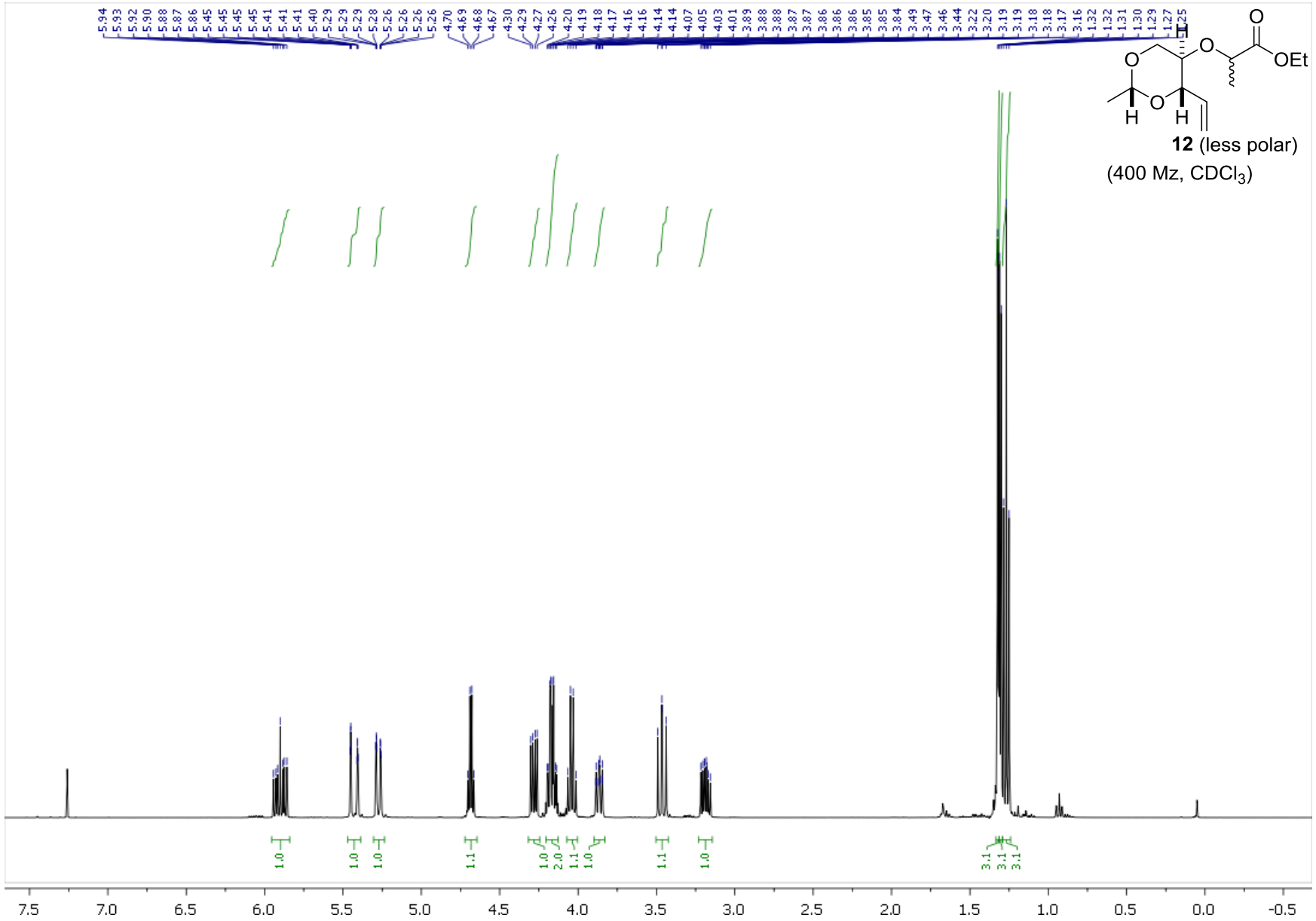
^{1}H NMR spectrum of **37b** 75
^{13}C NMR spectrum of **37b** 76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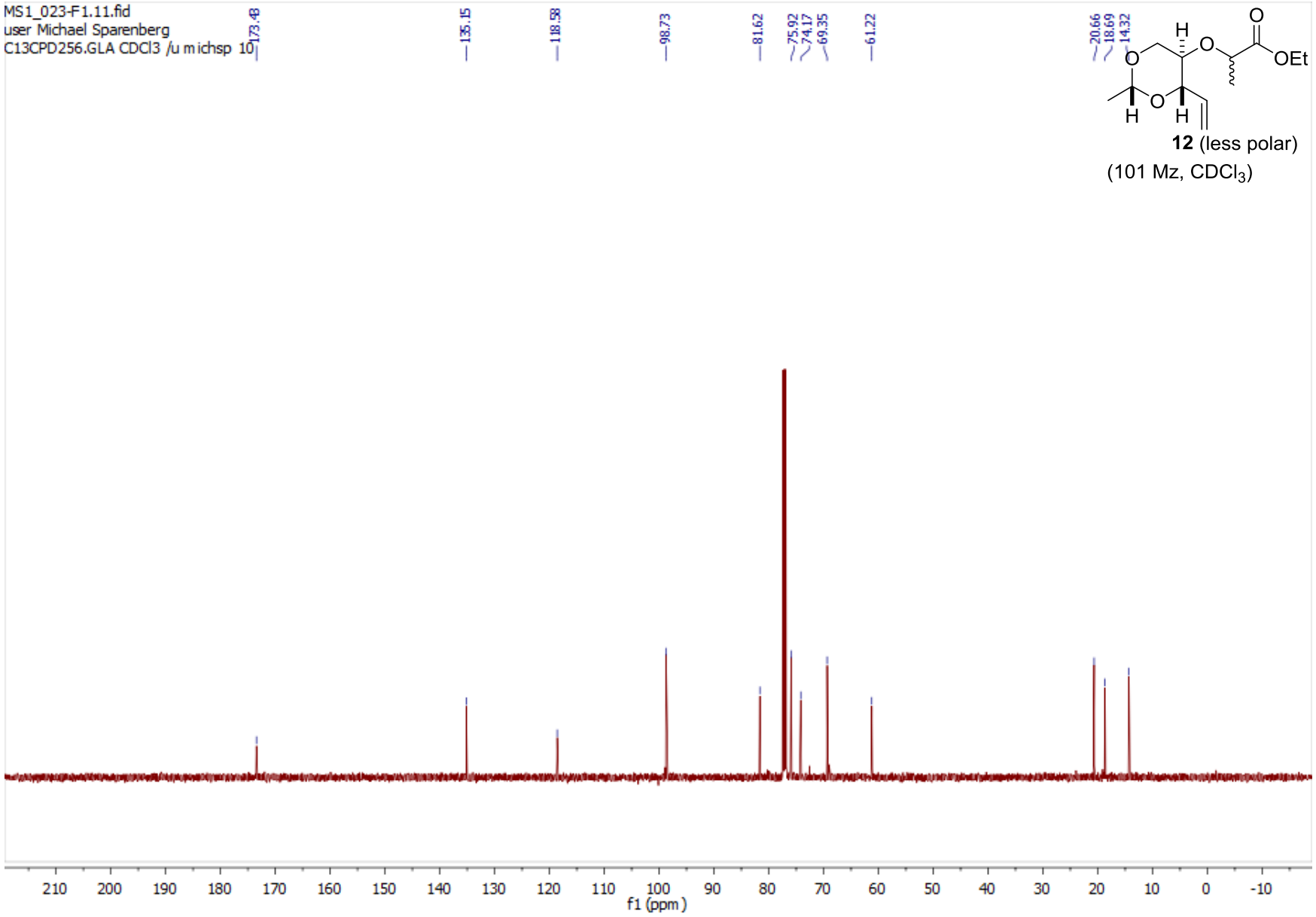
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135.15
118.58
98.73
81.62
75.92
74.17
69.35
61.22
20.66
18.69
14.32
O
H
O
OEt
O
O
H
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12 (less polar)
(101 Mz, CDCl3)
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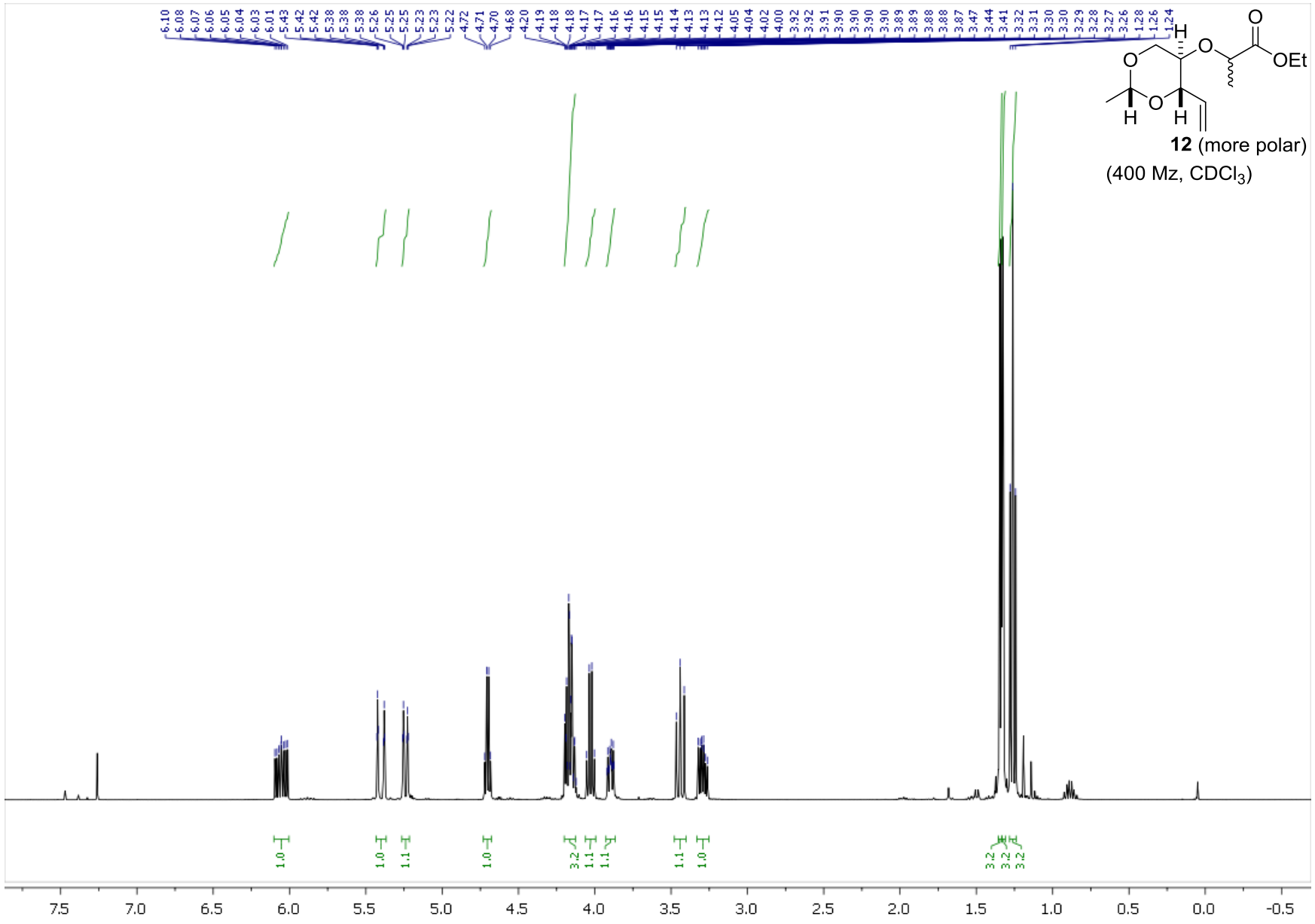
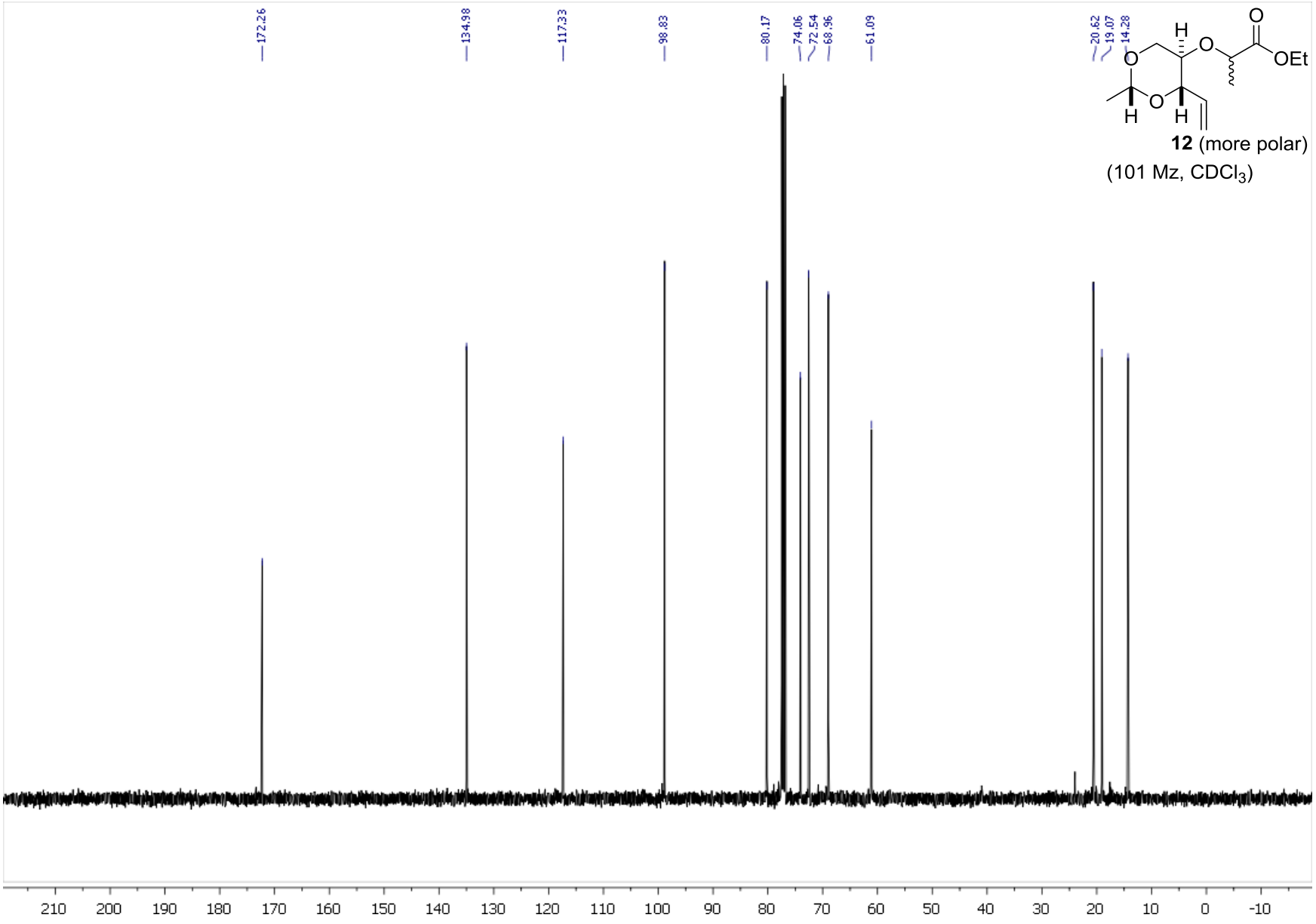
f1 (ppm)


12 (more polar)
(400 Mz, CDCl3)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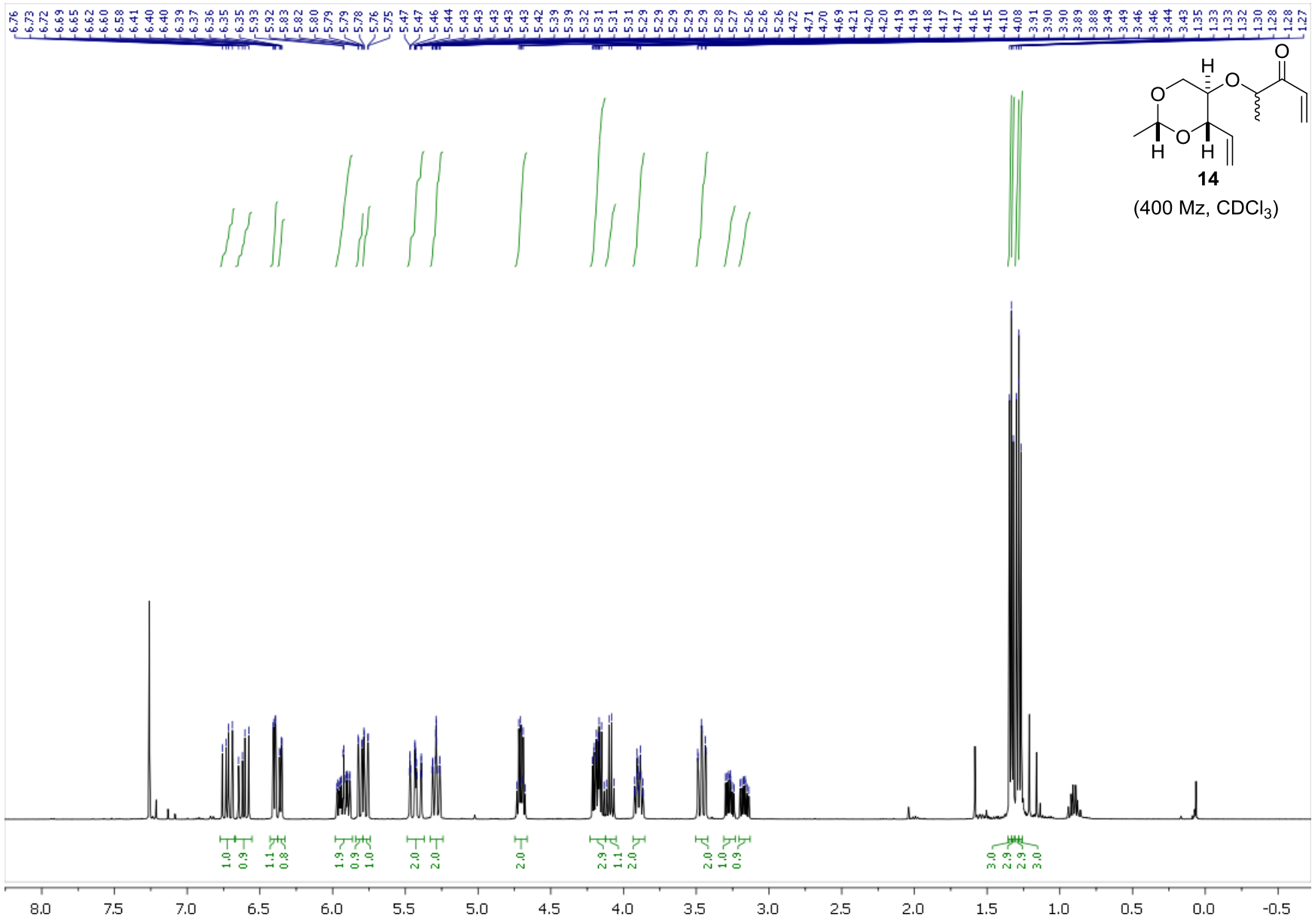
74.06
72.54
68.96
61.09
20.62
19.07
14.28
O
H
O
OEt
O
O
H
H
12 (more polar)
(101 Mz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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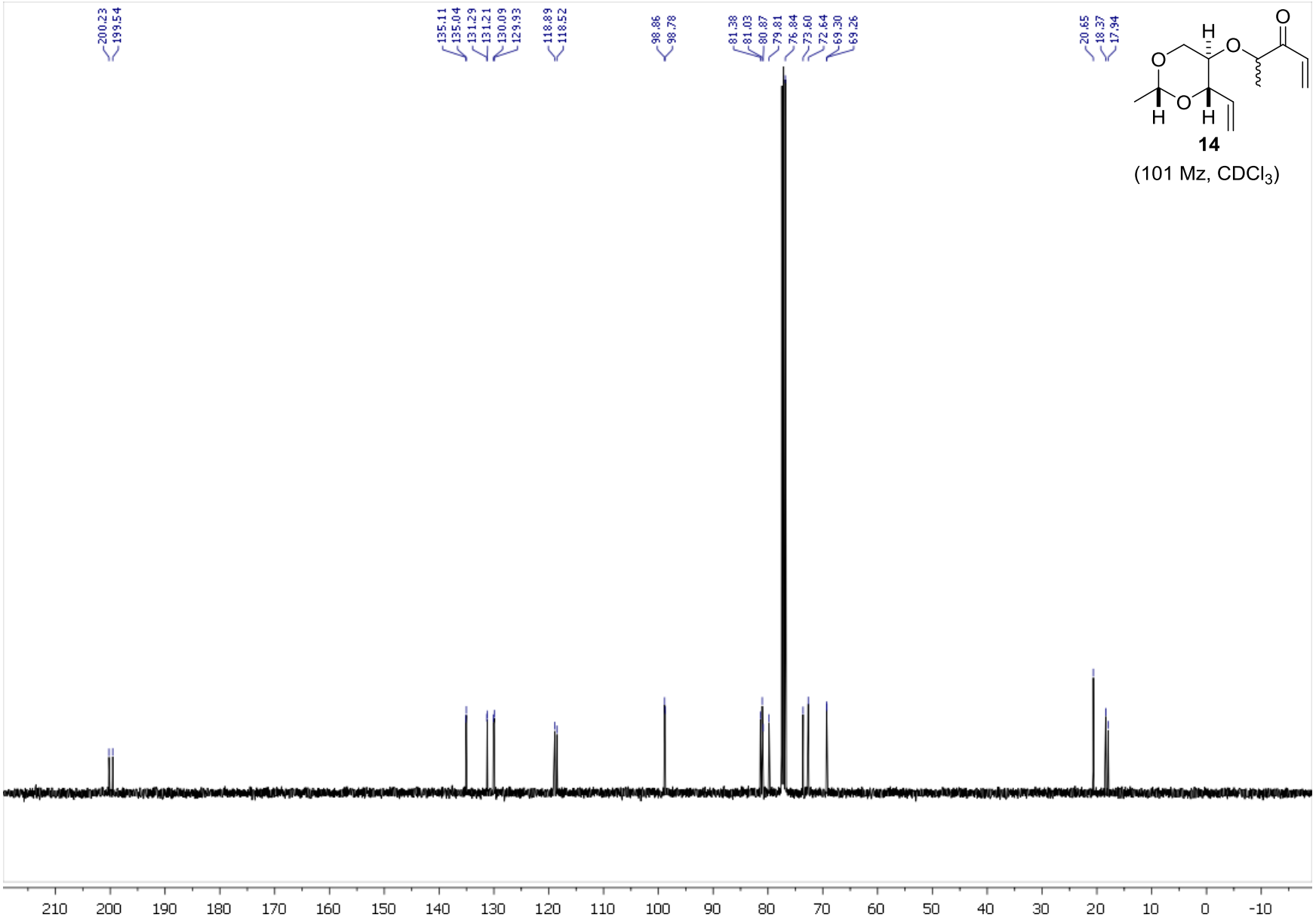
(400 Mz, CDCl3)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81.38
81.03
80.87
79.81
76.84
73.60
72.64
69.30
69.26
20.65
18.37
17.94
O
H
O
O
O
H
H
14
(101 Mz, CDCl3)
210
200
190
180
170
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140
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100
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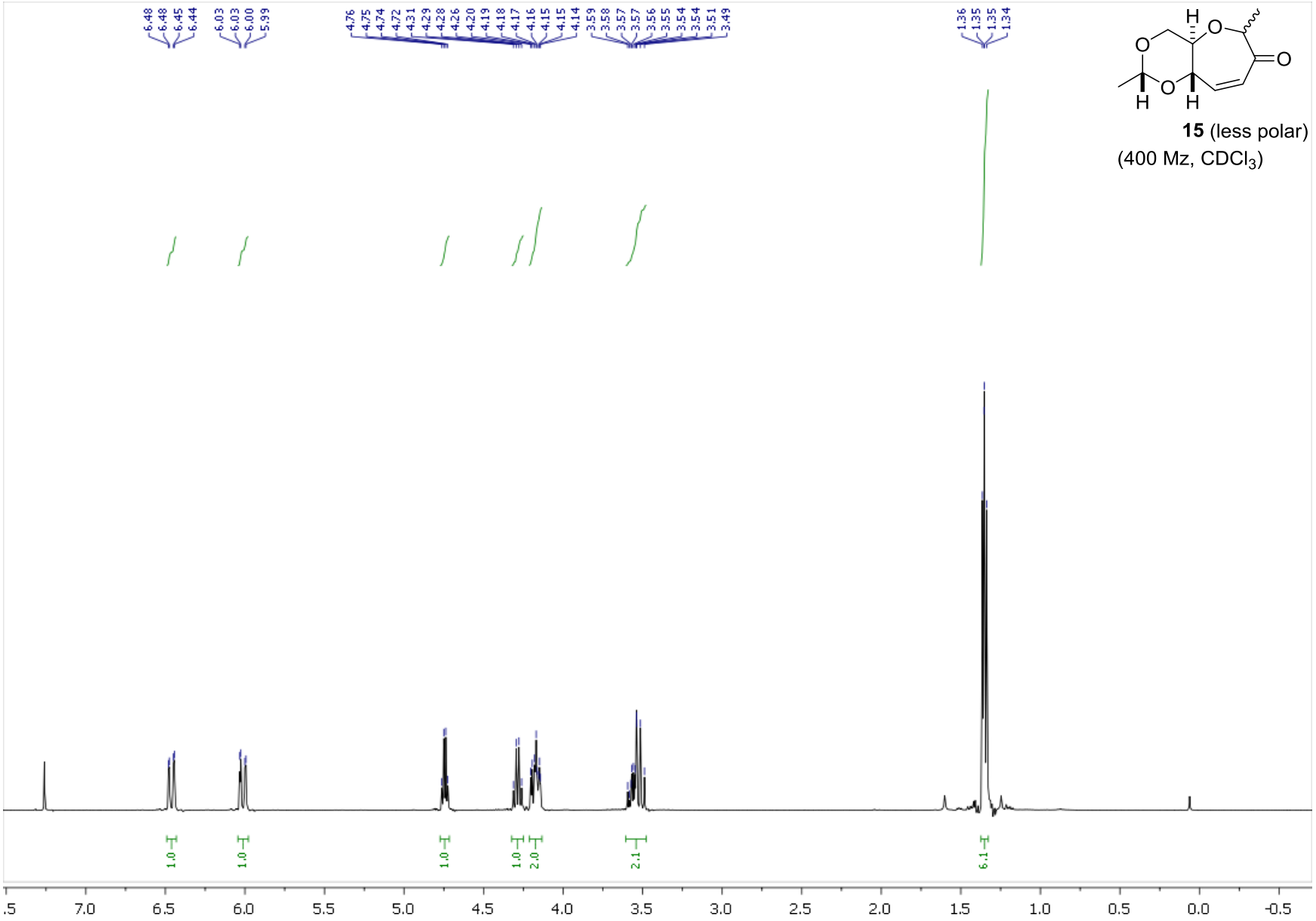

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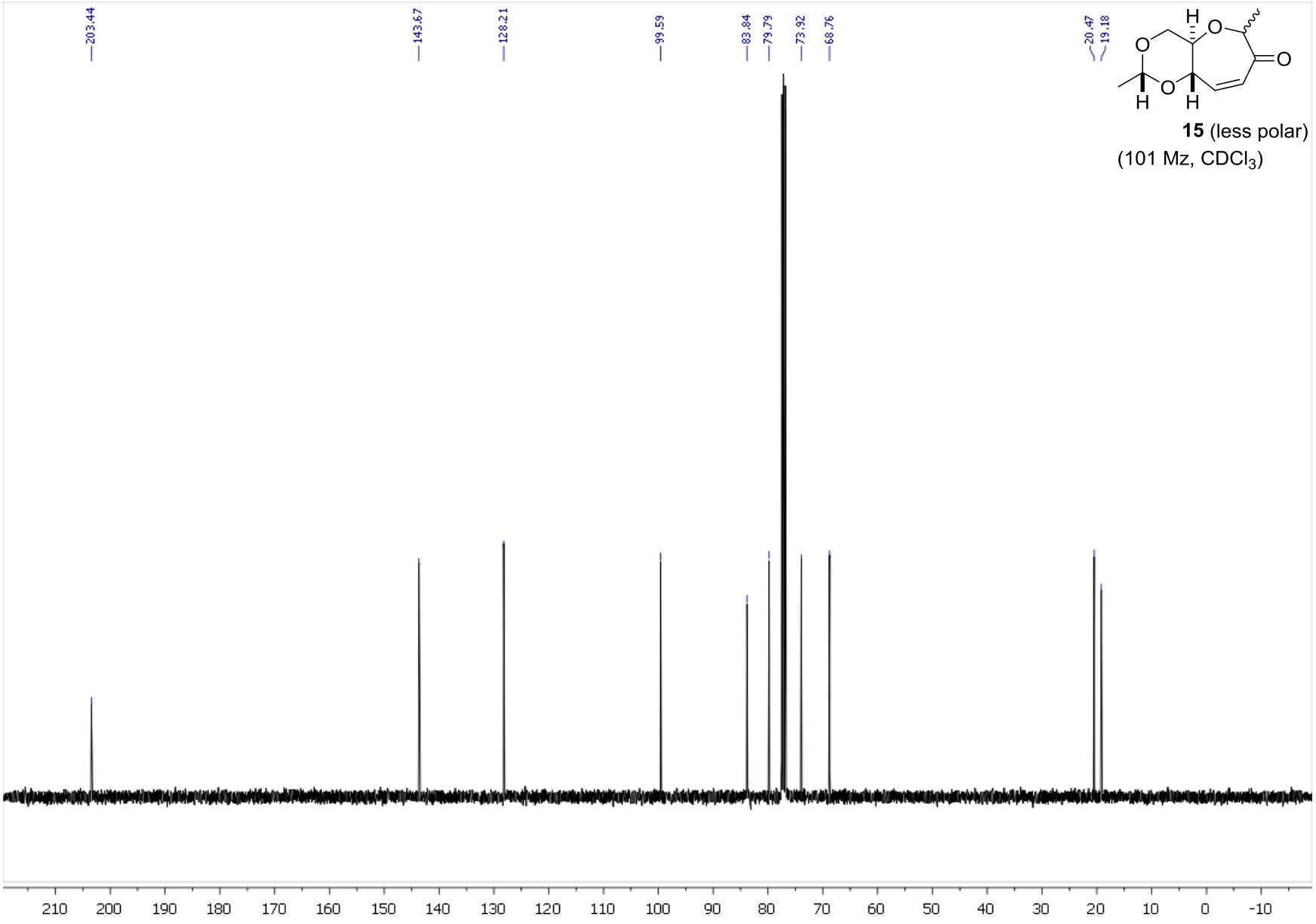

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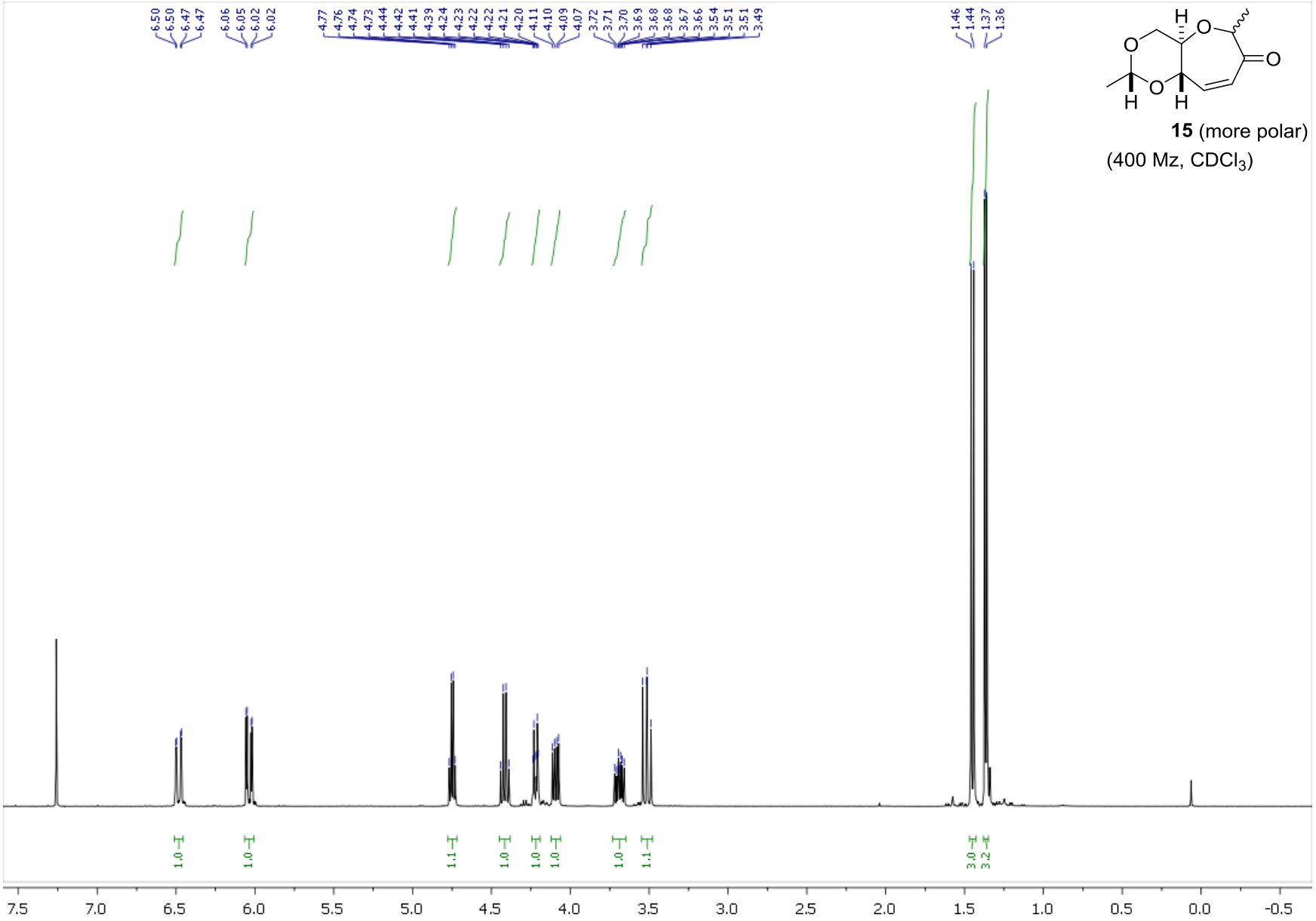
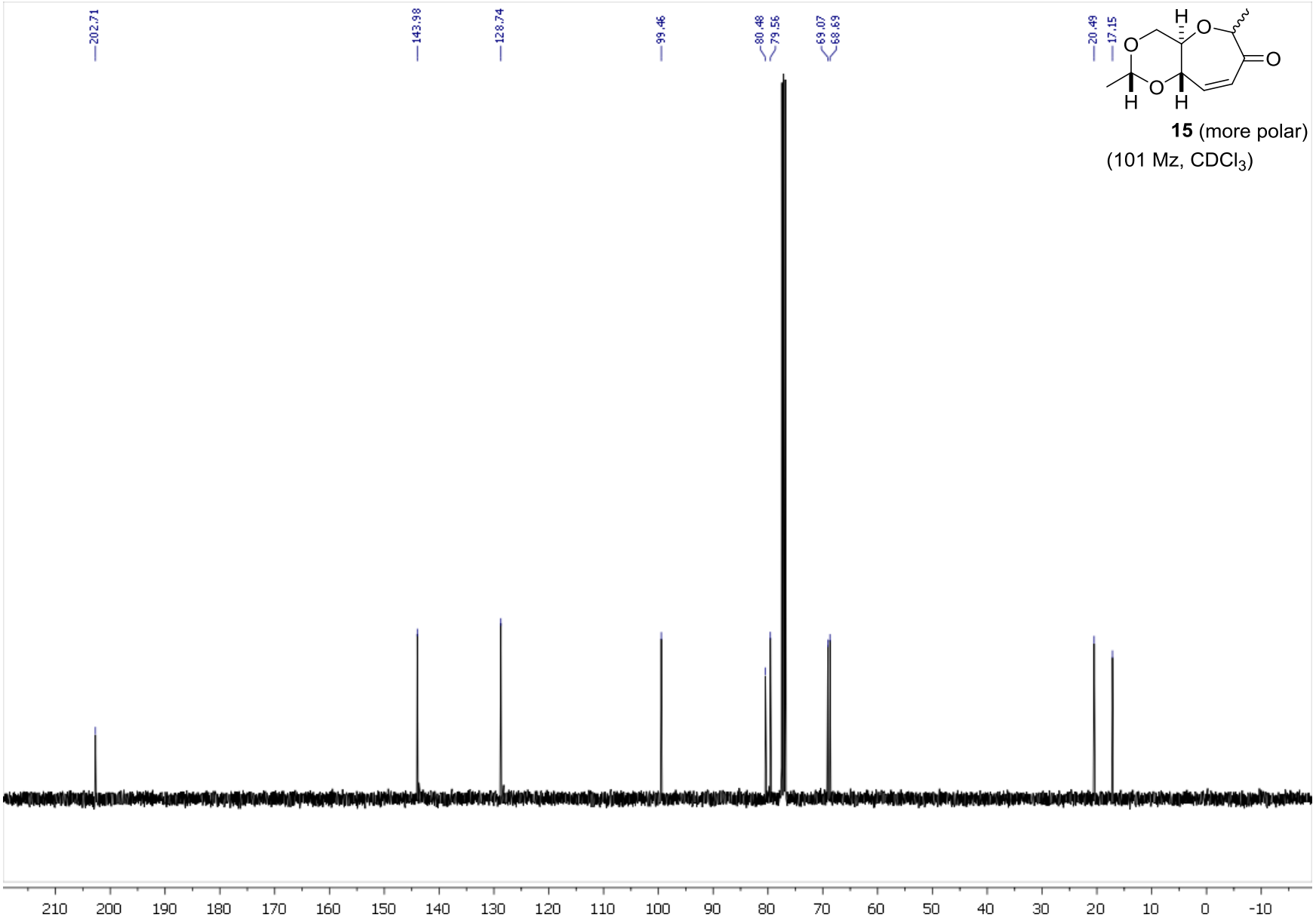


15 (more polar)

(400 Mz, $CDCl_3$)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20.49
17.15
H
O
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O
O
H
H
15 (more polar)
(101 Mz, CDCl3)
210
200
190
180
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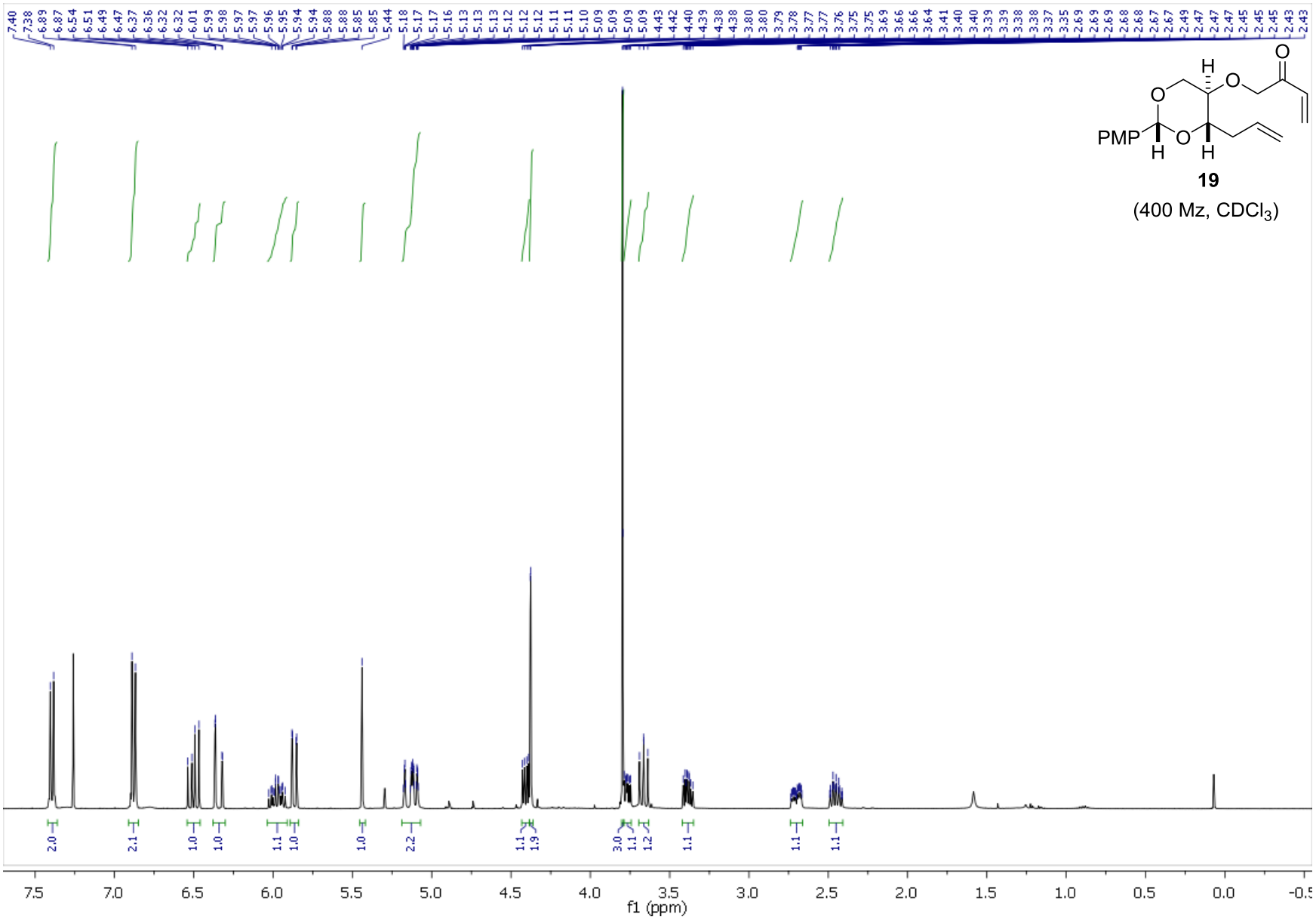
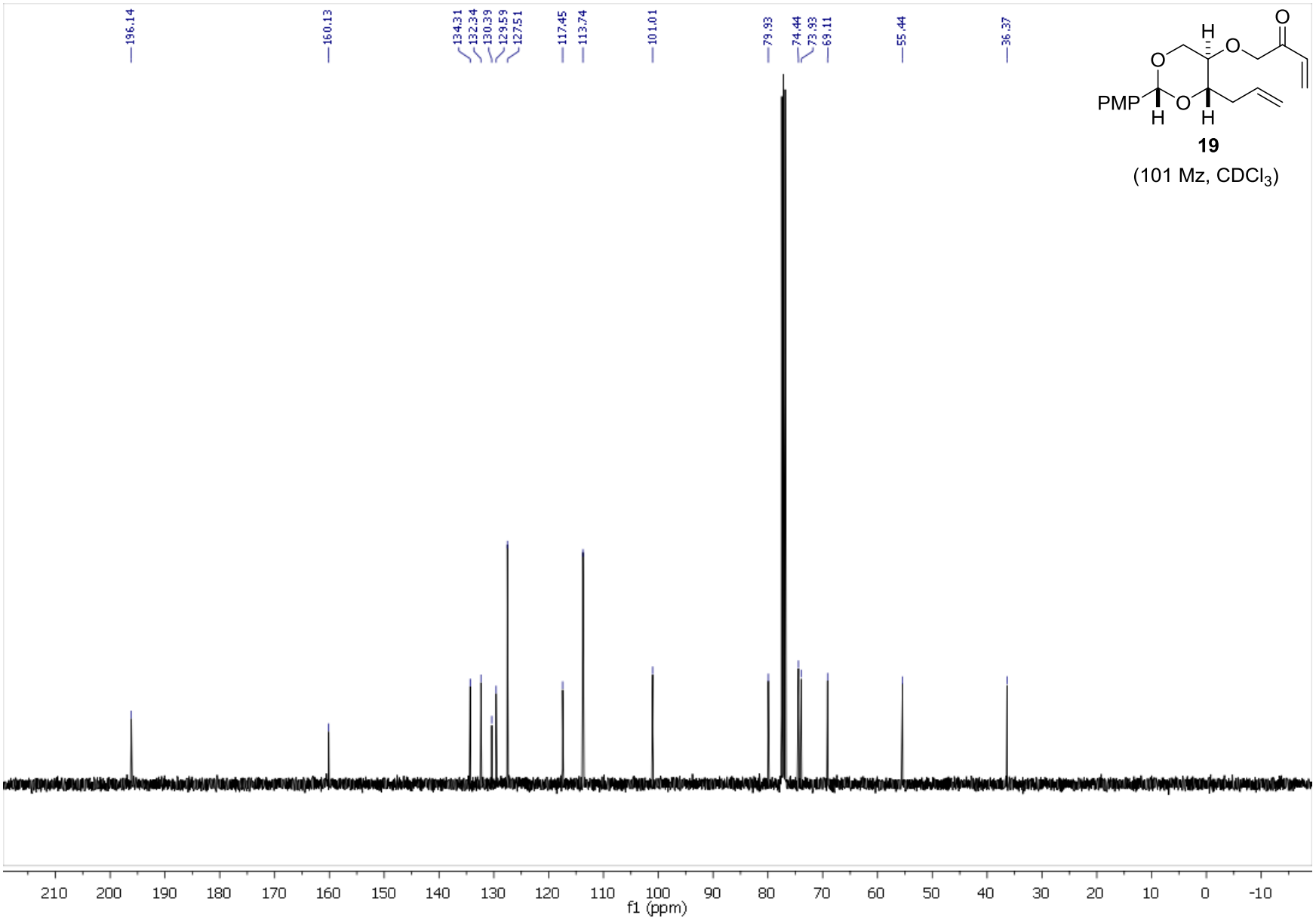

PMP
19
(400 Mz, CDCl3)
f1 (ppm)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69.11
55.44
36.37
PMP
H
O
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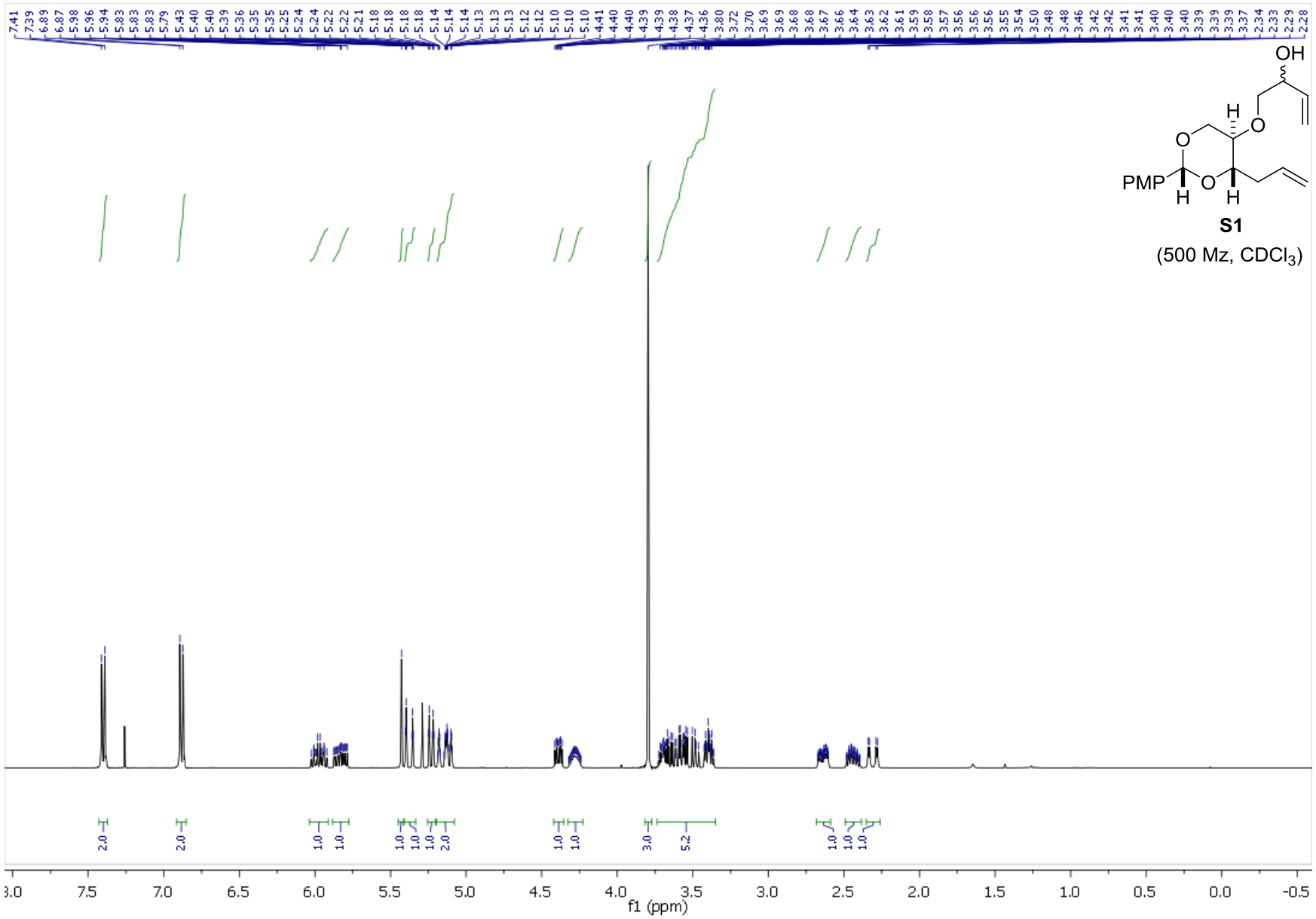
19
(101 Mz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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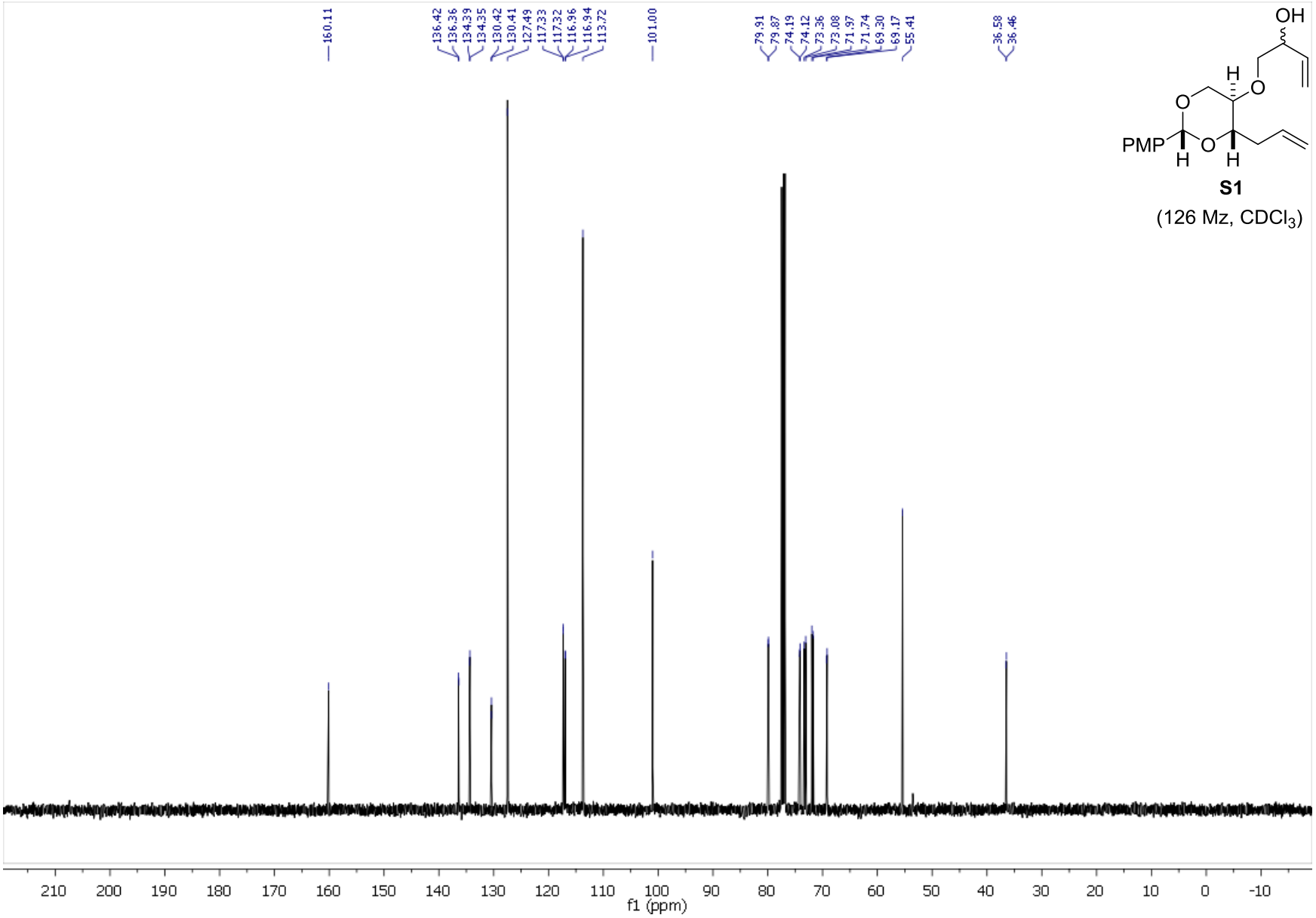
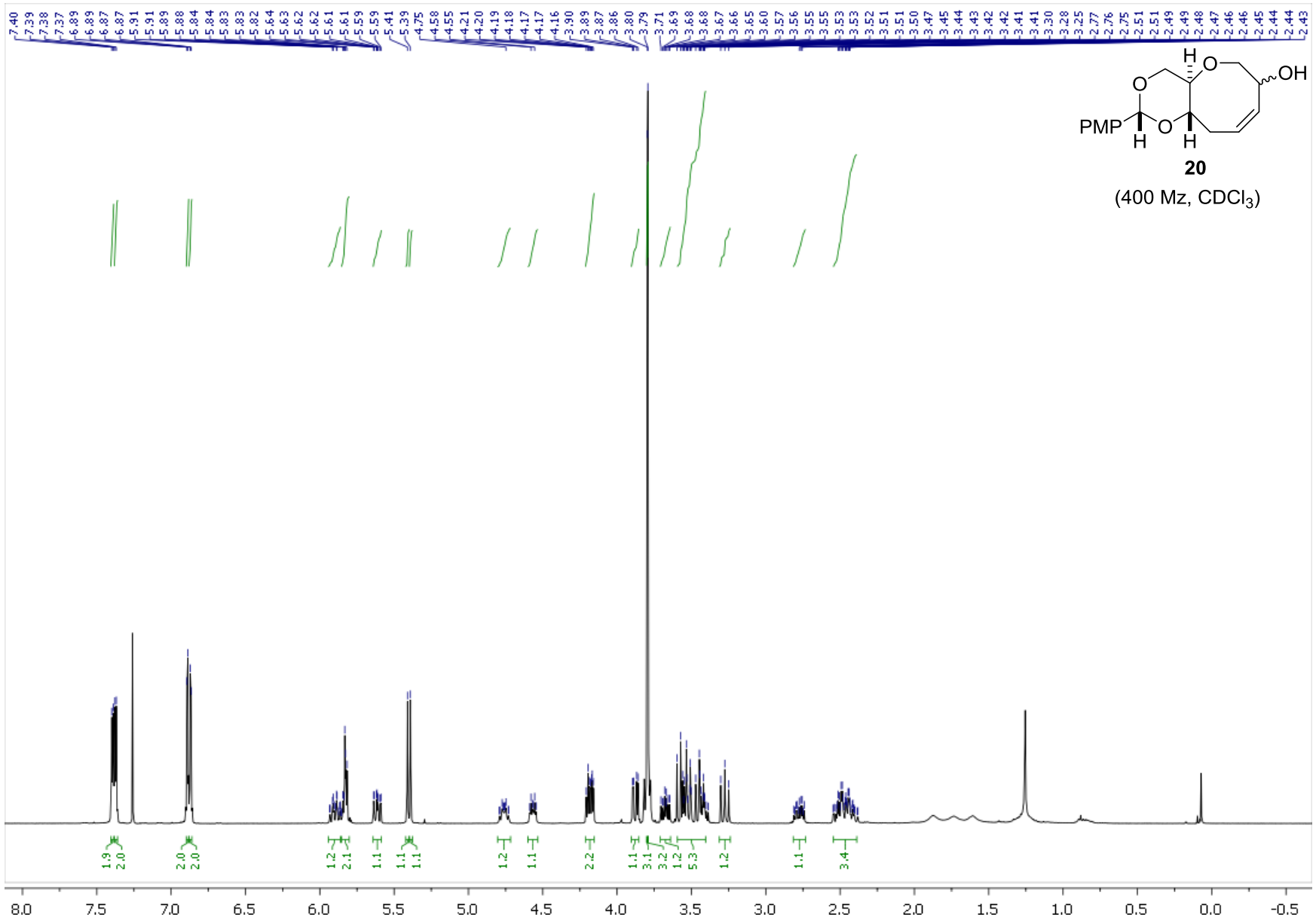
S1
(500 Mz, CDCl3)
f1 (ppm)



S1

(126 Mz, $CDCl_3$)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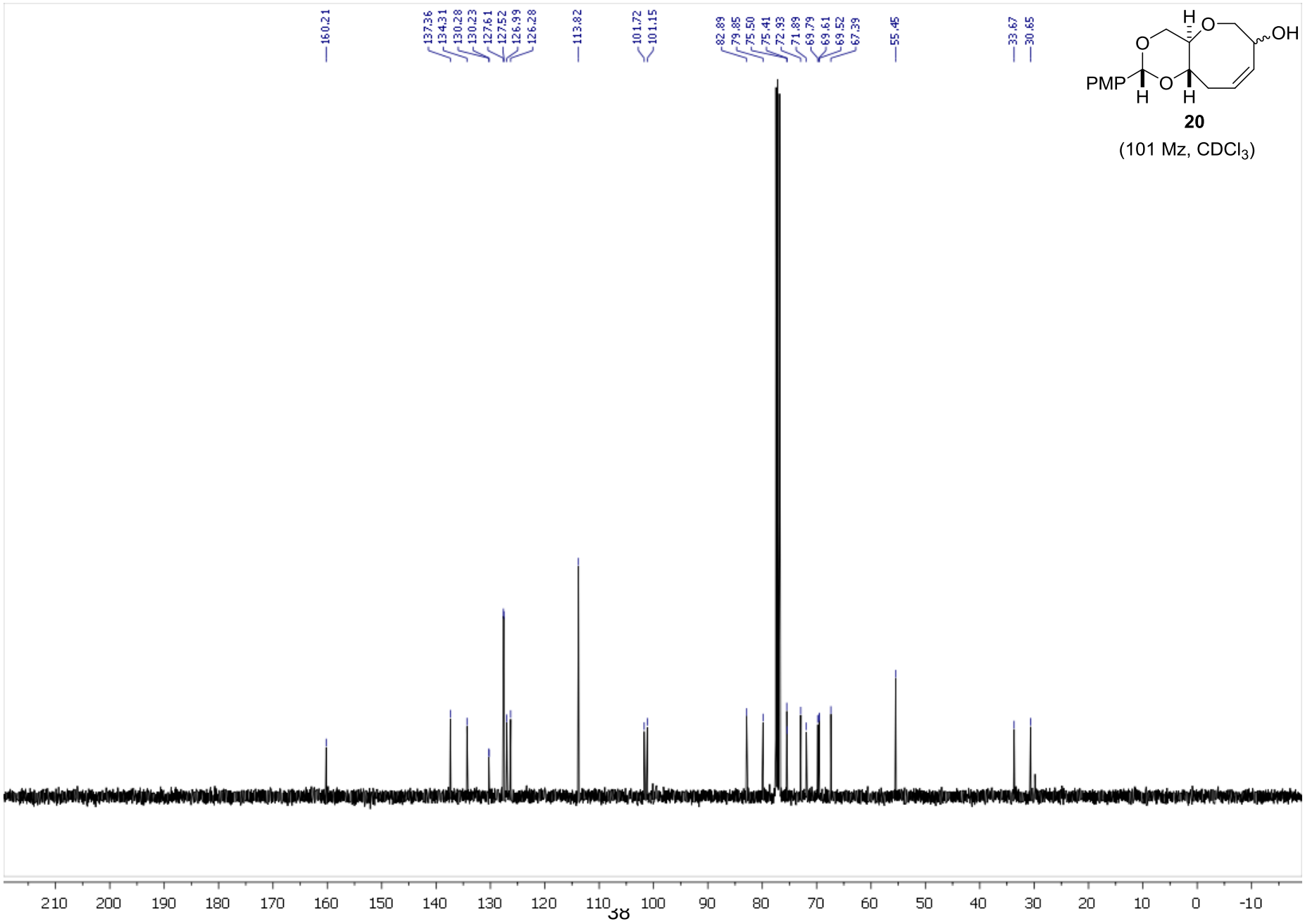
O
H
OH
20
(400 Mz, CDCl3)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113.82
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75.50
75.41
72.93
71.89
69.79
69.61
69.52
67.39
55.45
33.67
30.65
H
O
OH
O
PMP
O
H
H
20
(101 Mz, CDCl3)
210
200
190
180
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150
140
130
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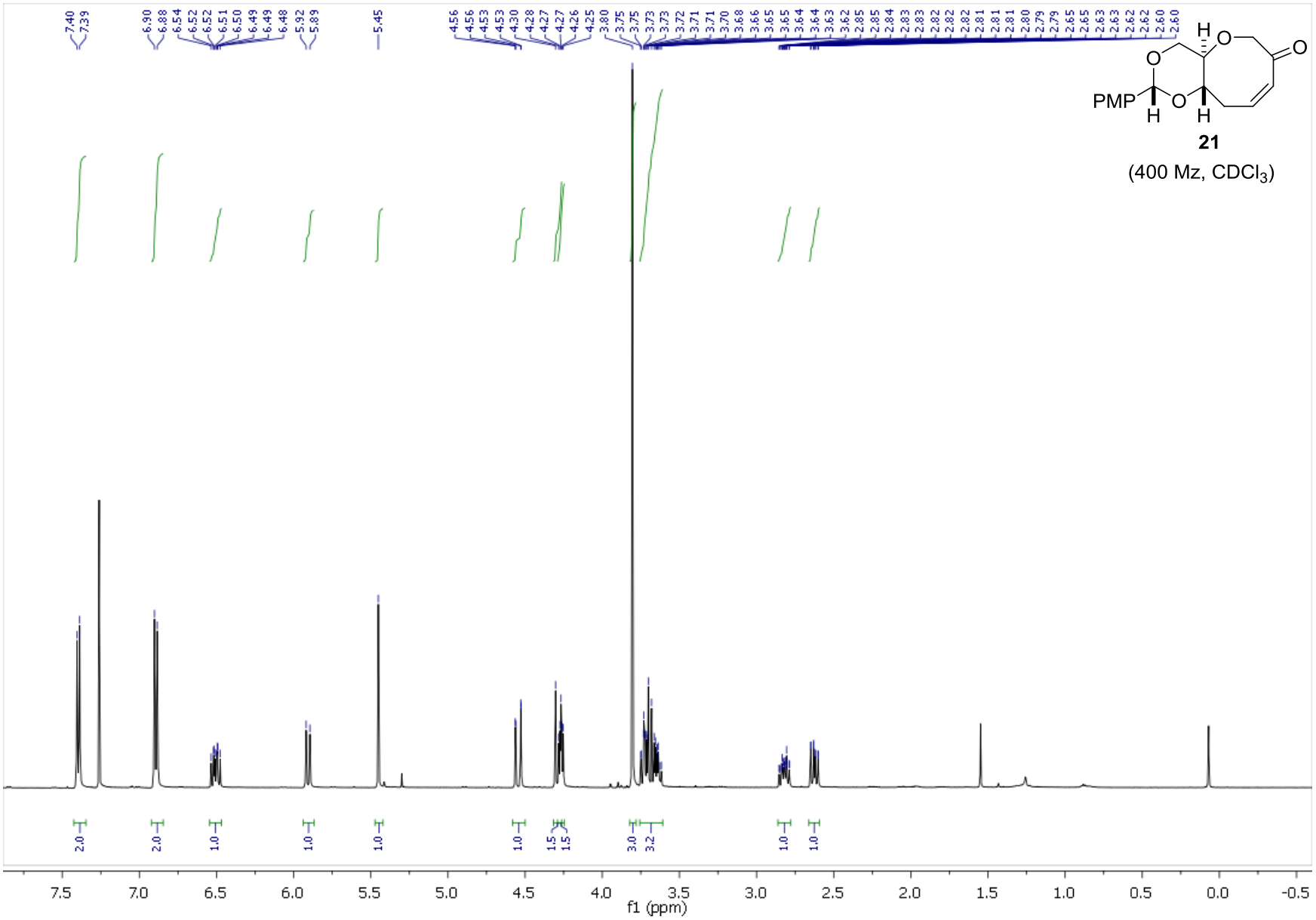
PMP
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H
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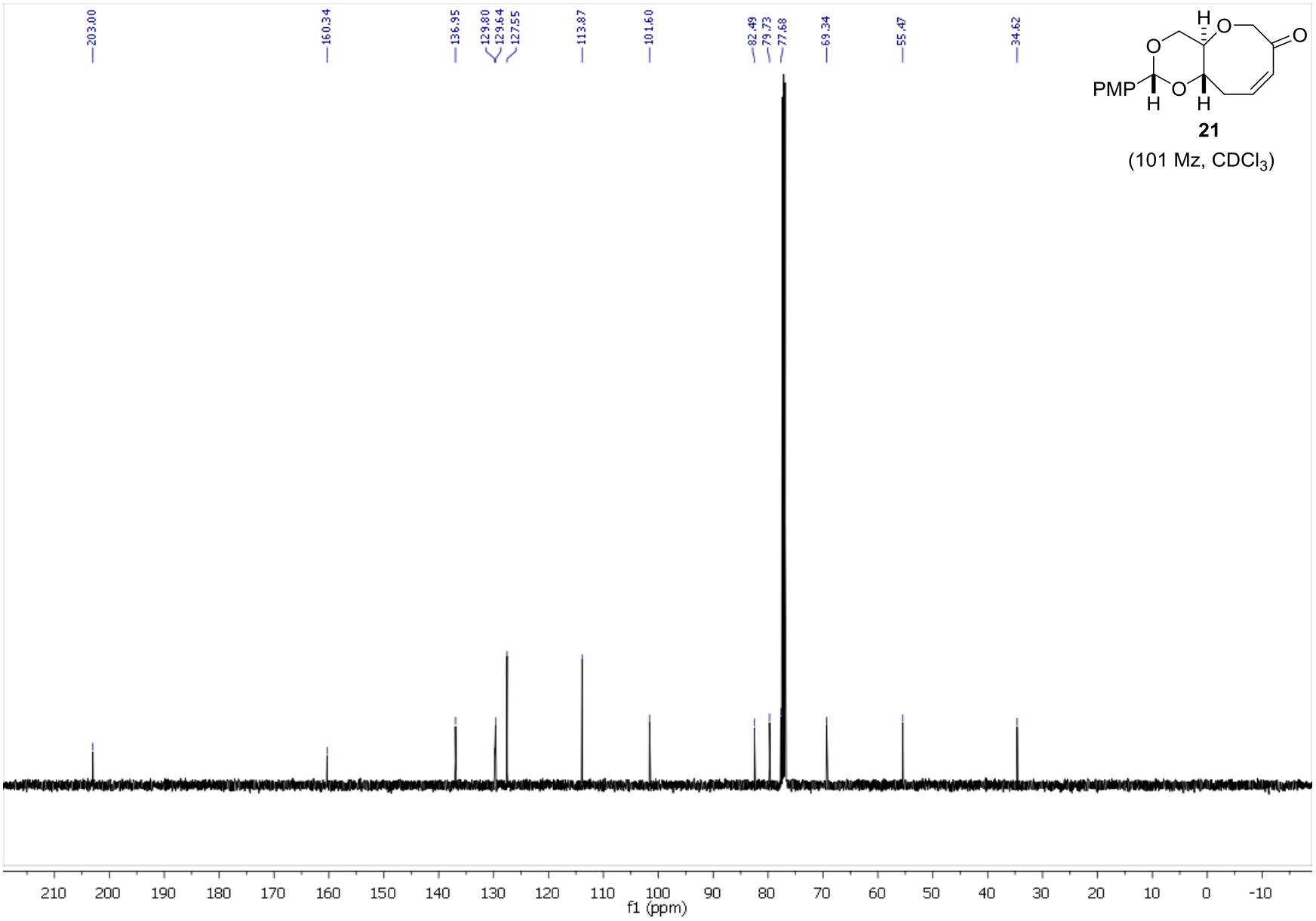
21
(400 Mz, CDCl3)
f1 (ppm)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79.73
77.68
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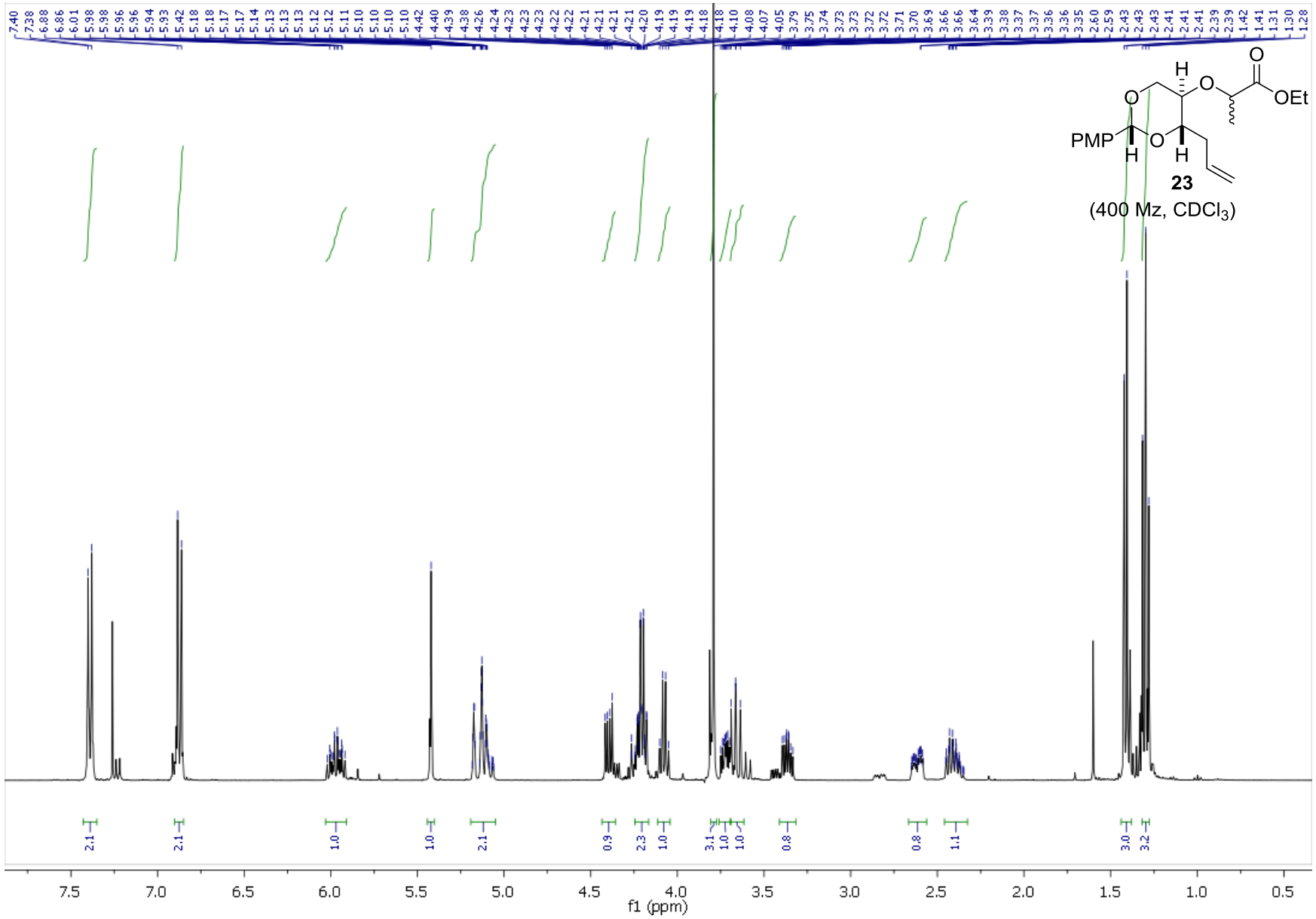
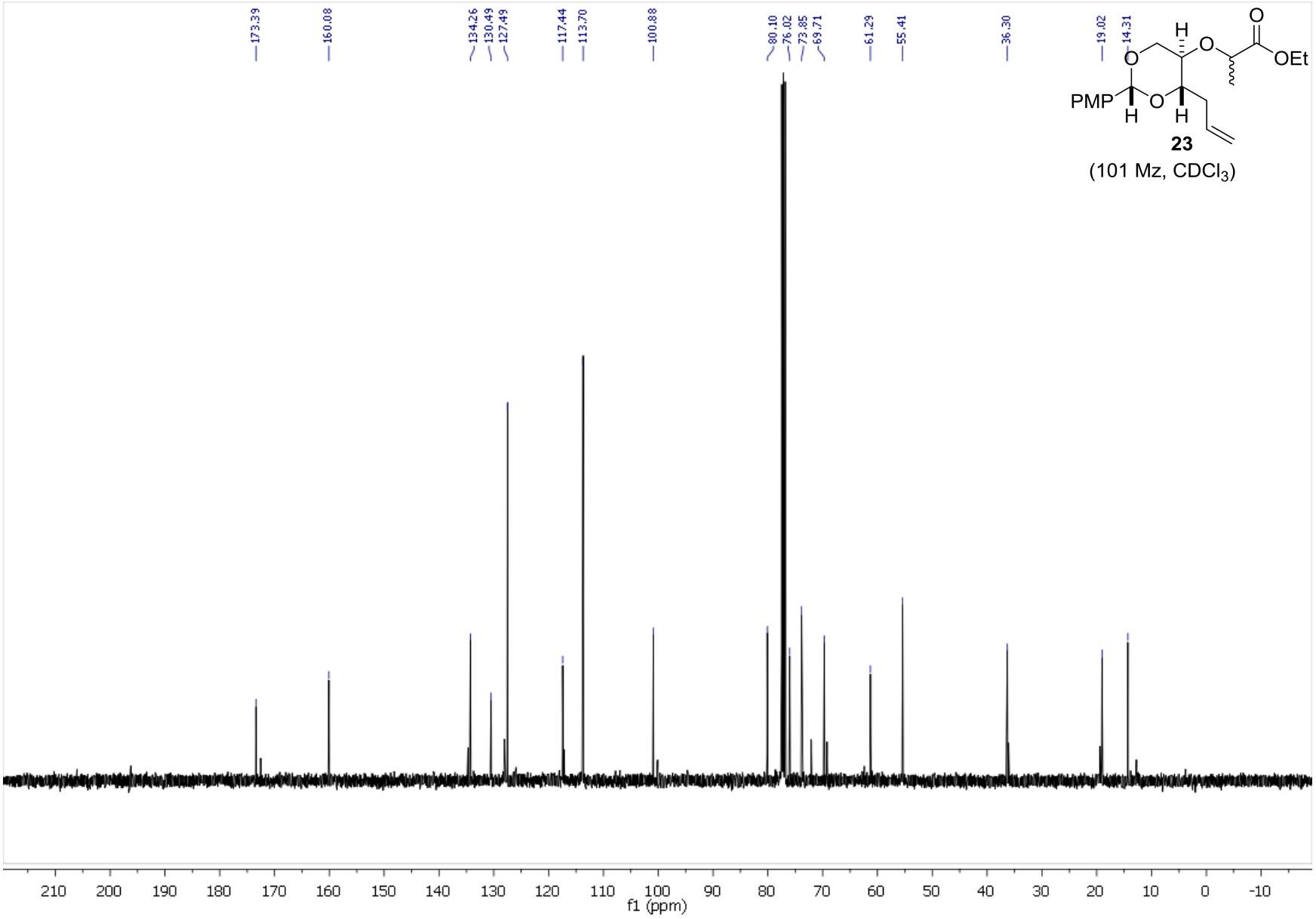
55.47
34.62
PMP
H
O
O
O
O
H
H
21
(101 Mz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


PMP
OEt
23
(400 Mz, CDCl3)
f1 (ppm)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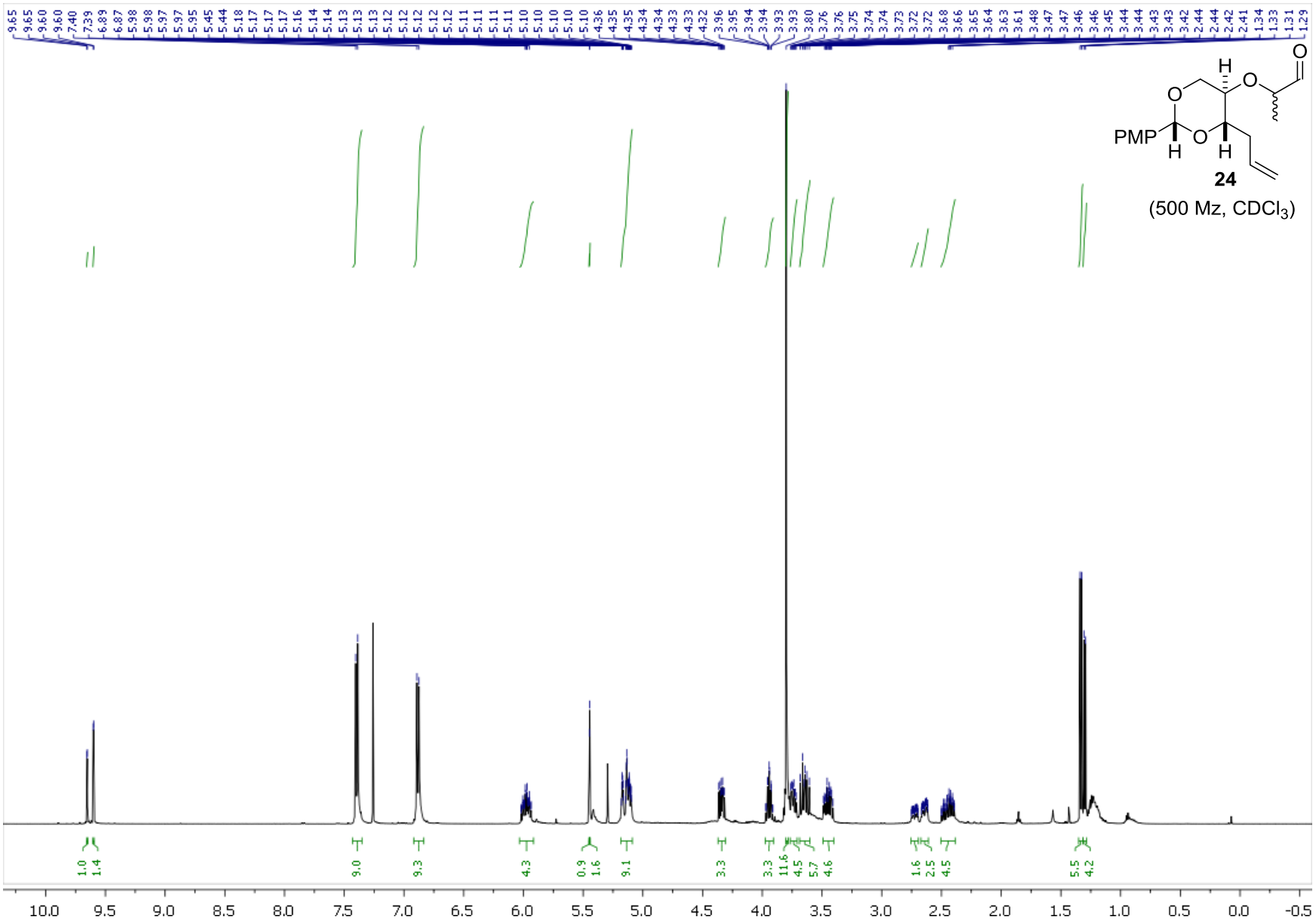
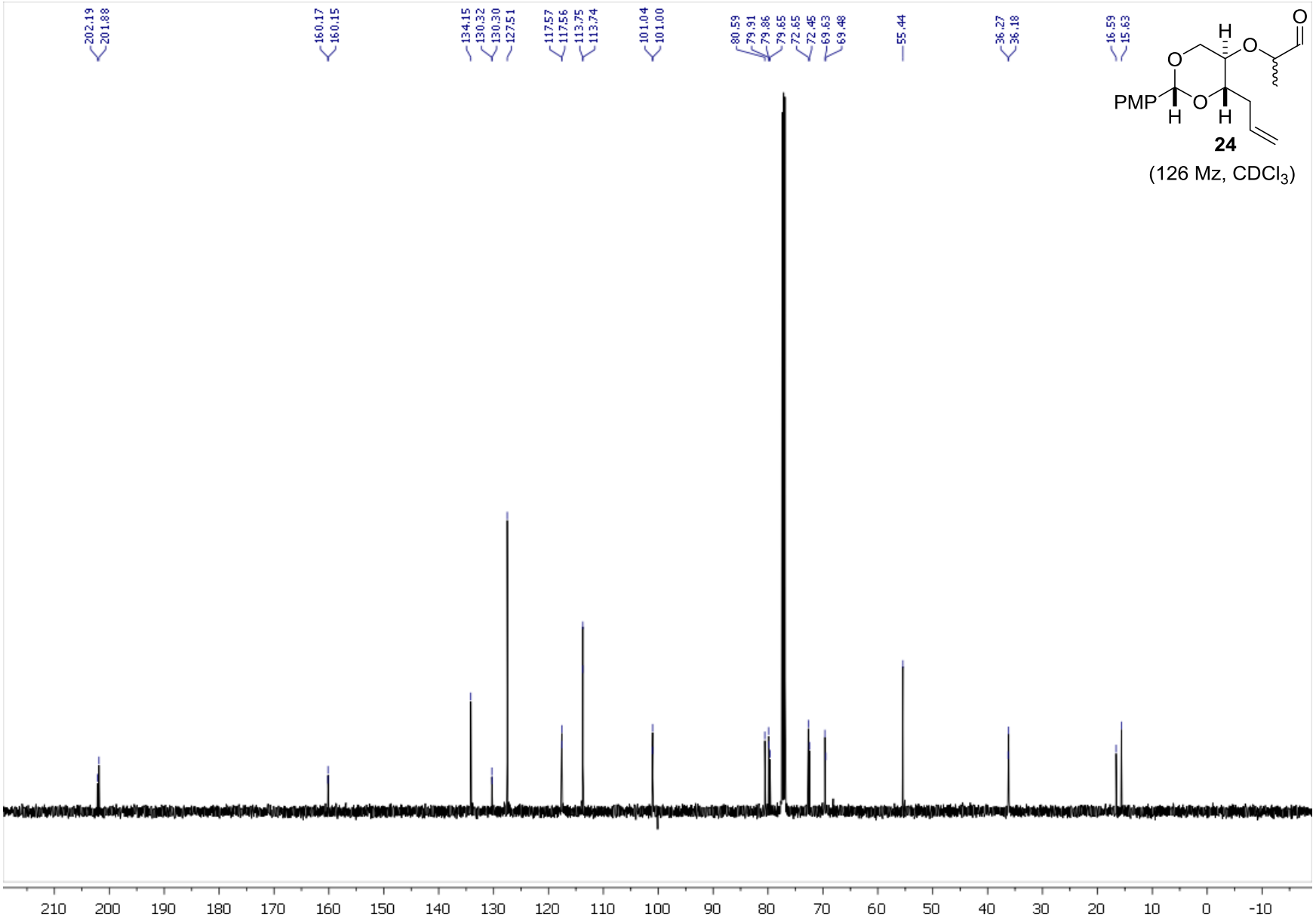
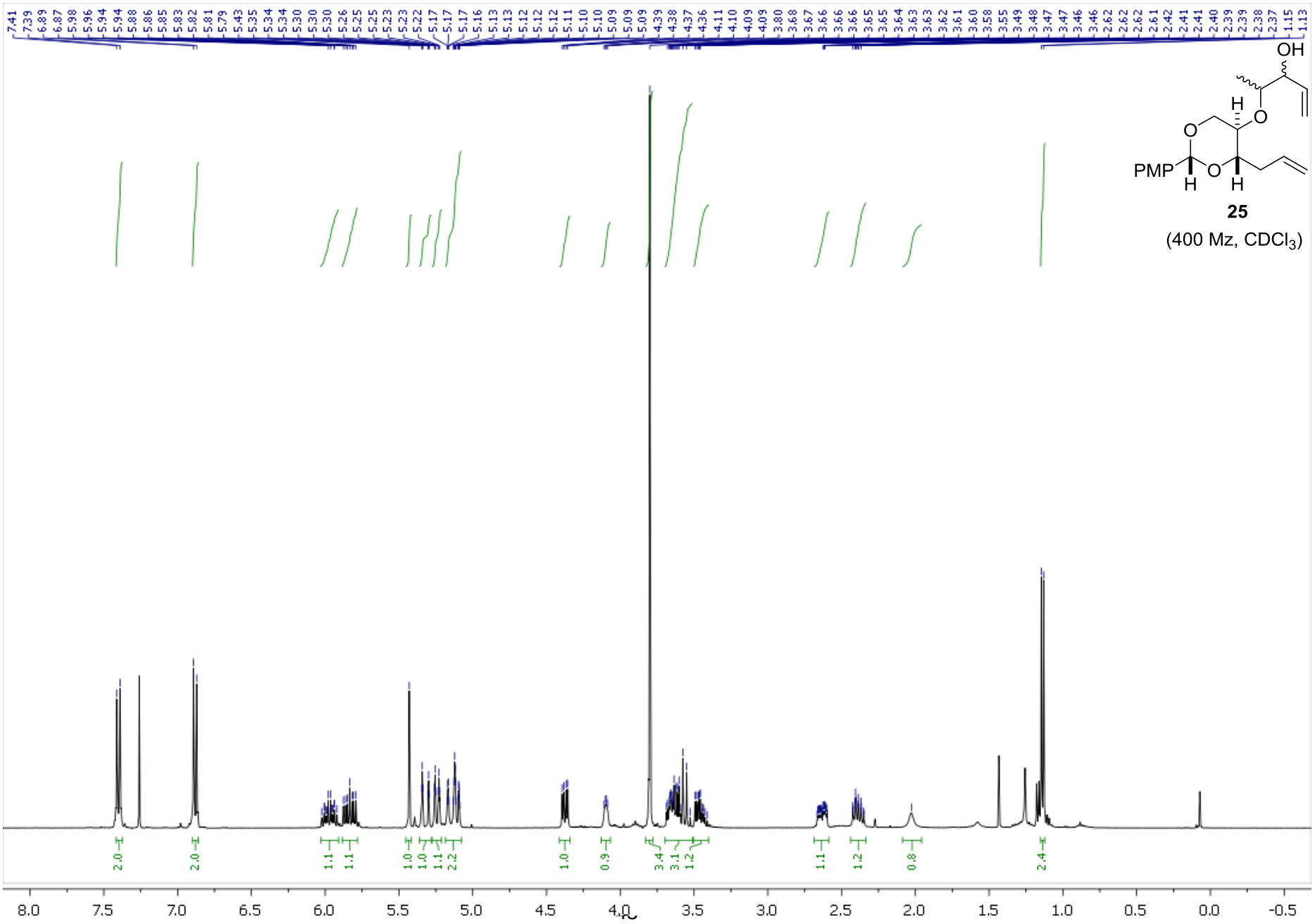
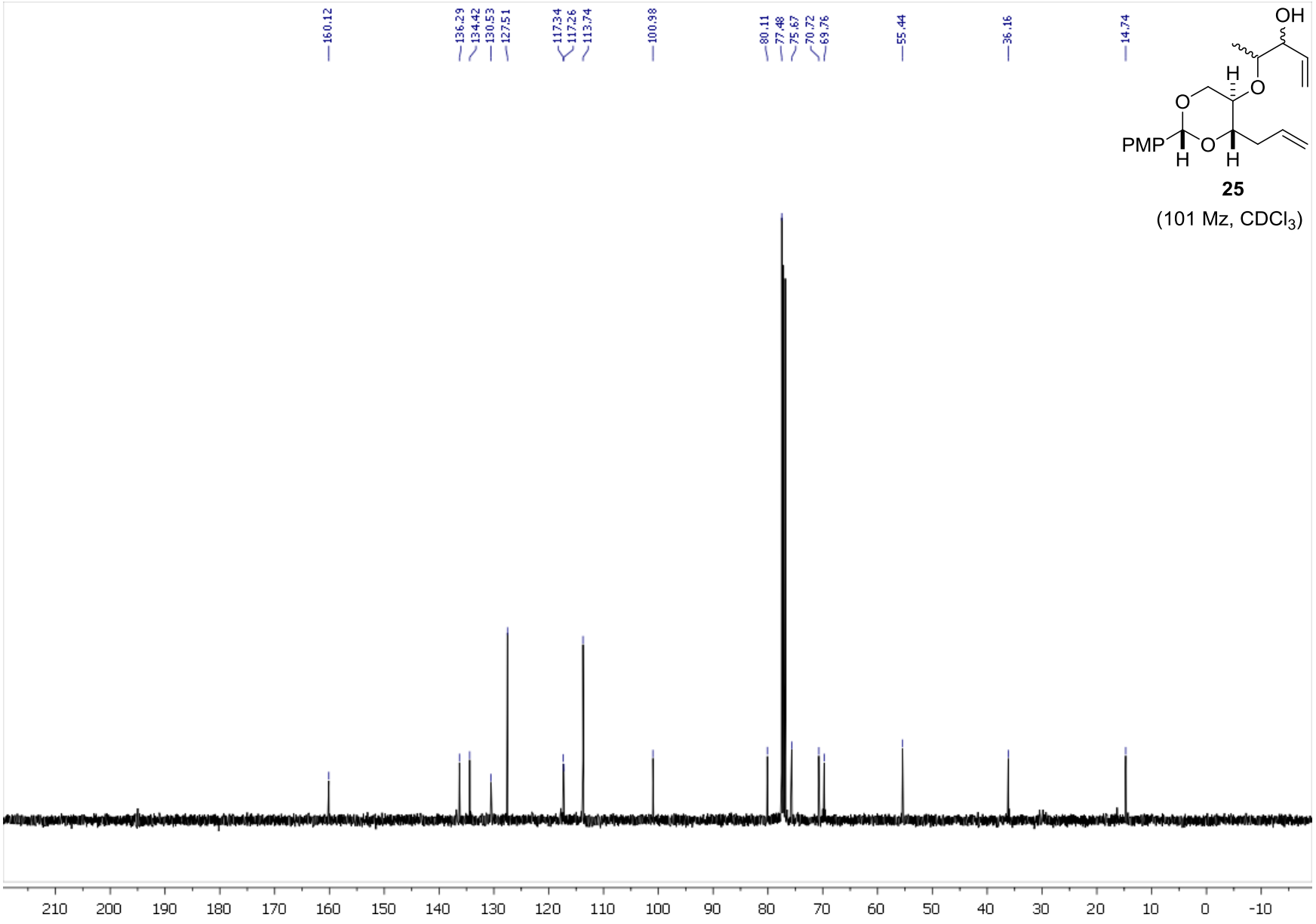
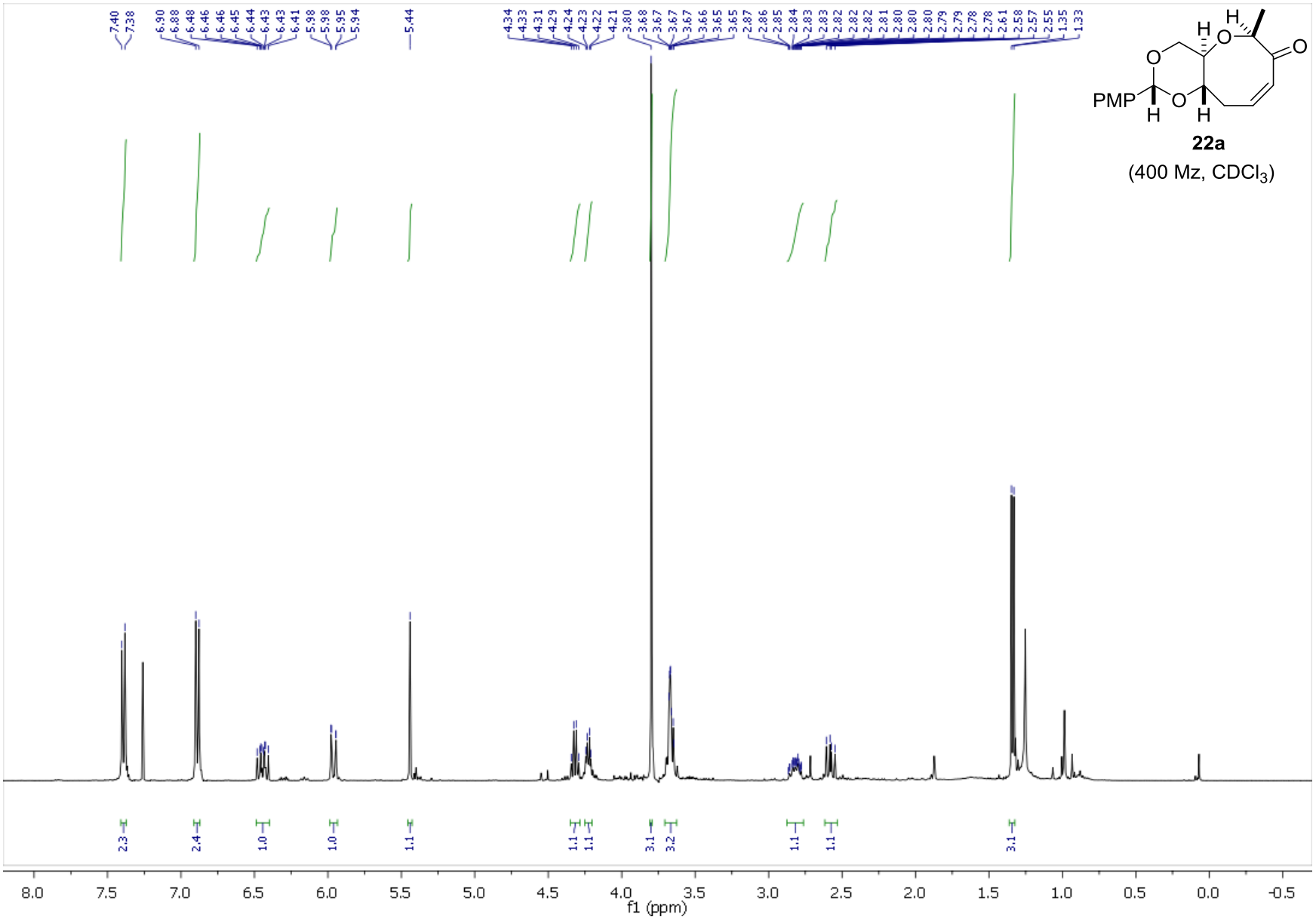
127.49
117.44
113.70
100.88
80.10
76.02
73.85
69.71
61.29
55.41
36.30
19.02
14.31
PMP
H
O
O
H
O
H
O
OEt
23
(101 Mz, CDCl3)
f1 (ppm)


PMP
24
(500 Mz, CDCl3)


202.19
201.88
160.17
160.15
134.15
130.32
130.30
127.51
117.57
117.56
113.75
113.74
101.04
101.00
80.59
79.91
79.86
79.65
72.65
72.45
69.63
69.48
55.44
36.27
36.18
16.59
15.63
PMP
24
(126 Mz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

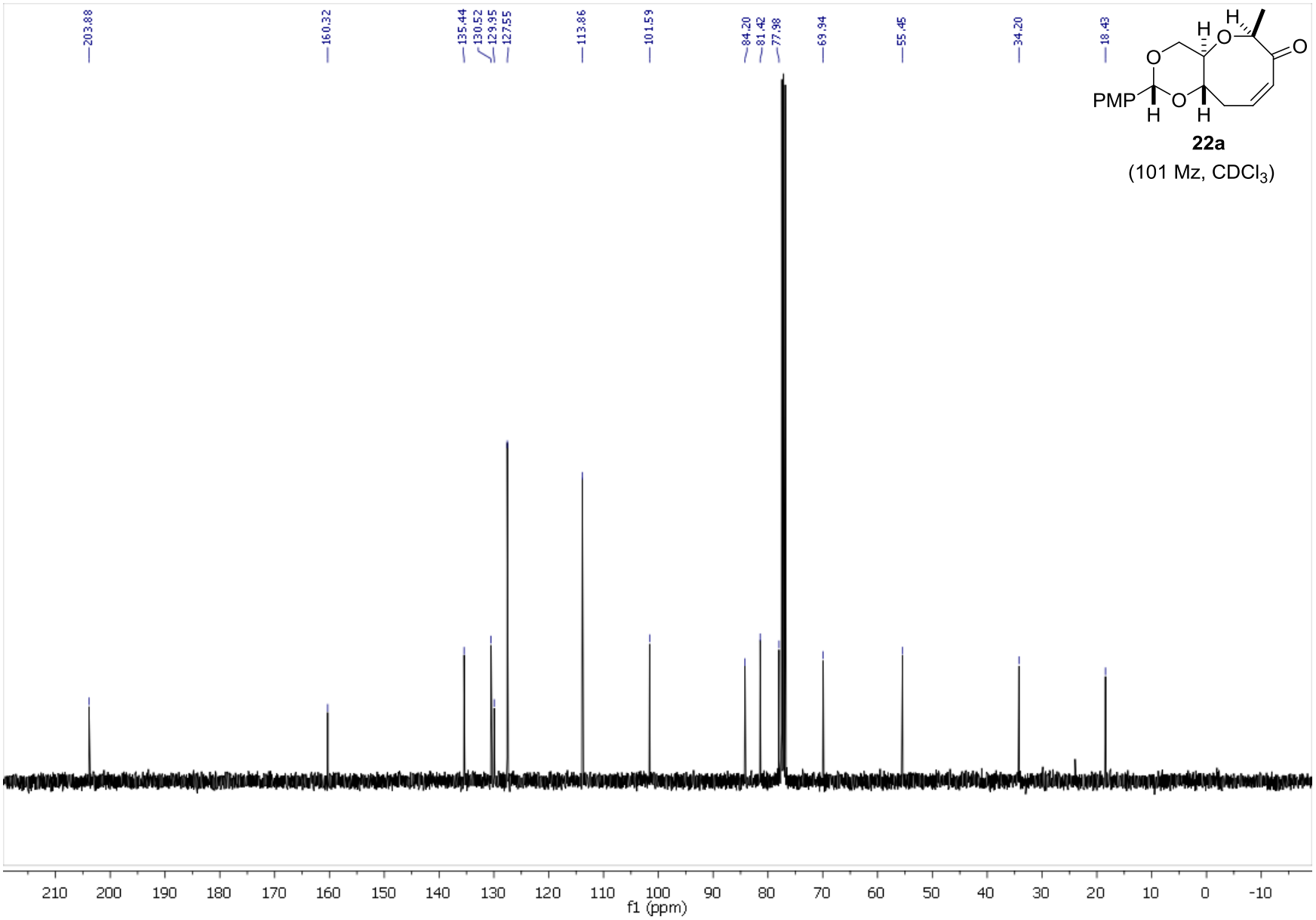

OH
H
O
O
PMP
O
H
H
25
(400 Mz, CDCl3)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

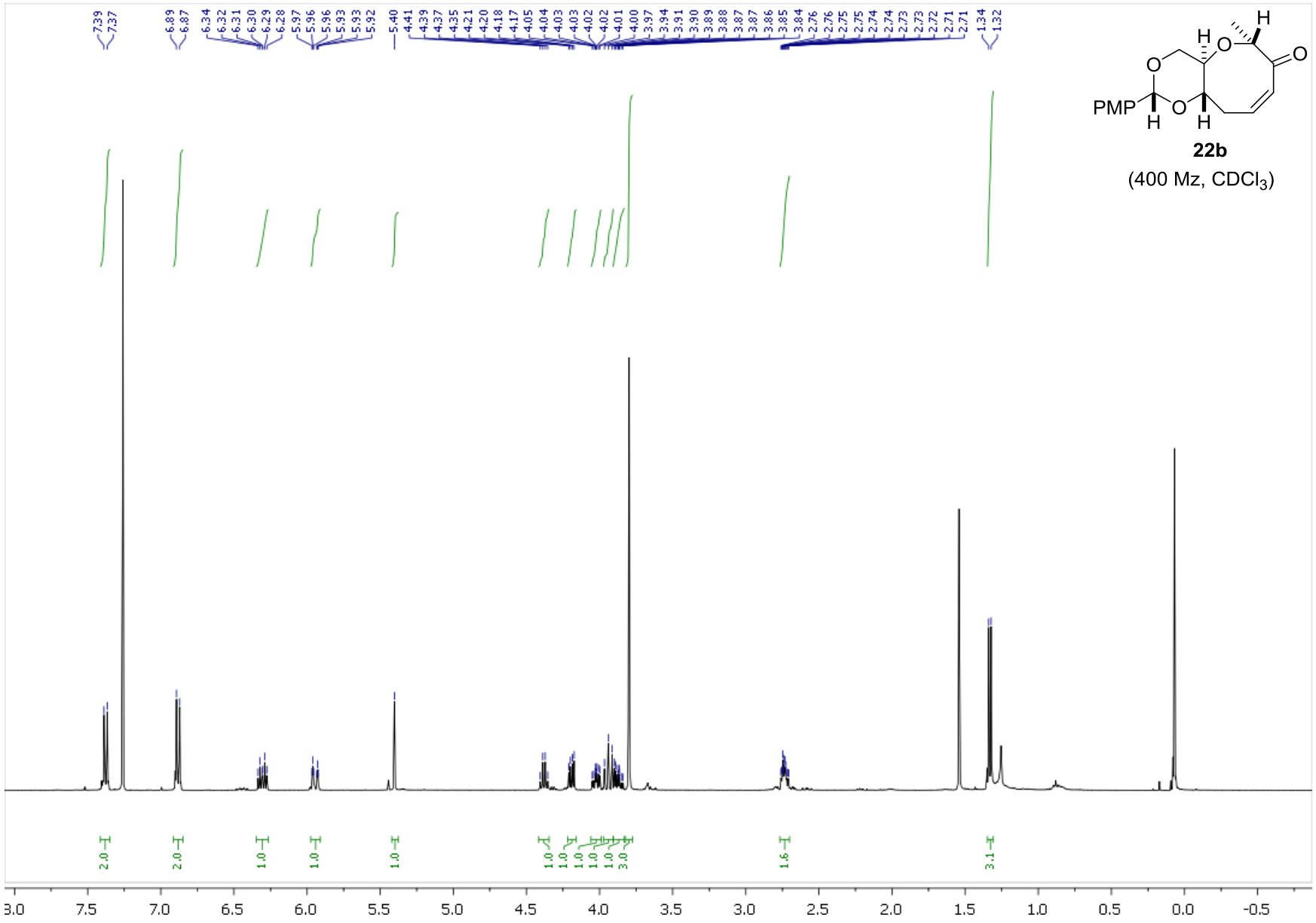

160.12
136.29
134.42
130.53
127.51
117.34
117.26
113.74
100.98
80.11
77.48
75.67
70.72
69.76
55.44
36.16
14.74
OH
H
O
O
PMP
H
O
H
25
(101 Mz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10



22a

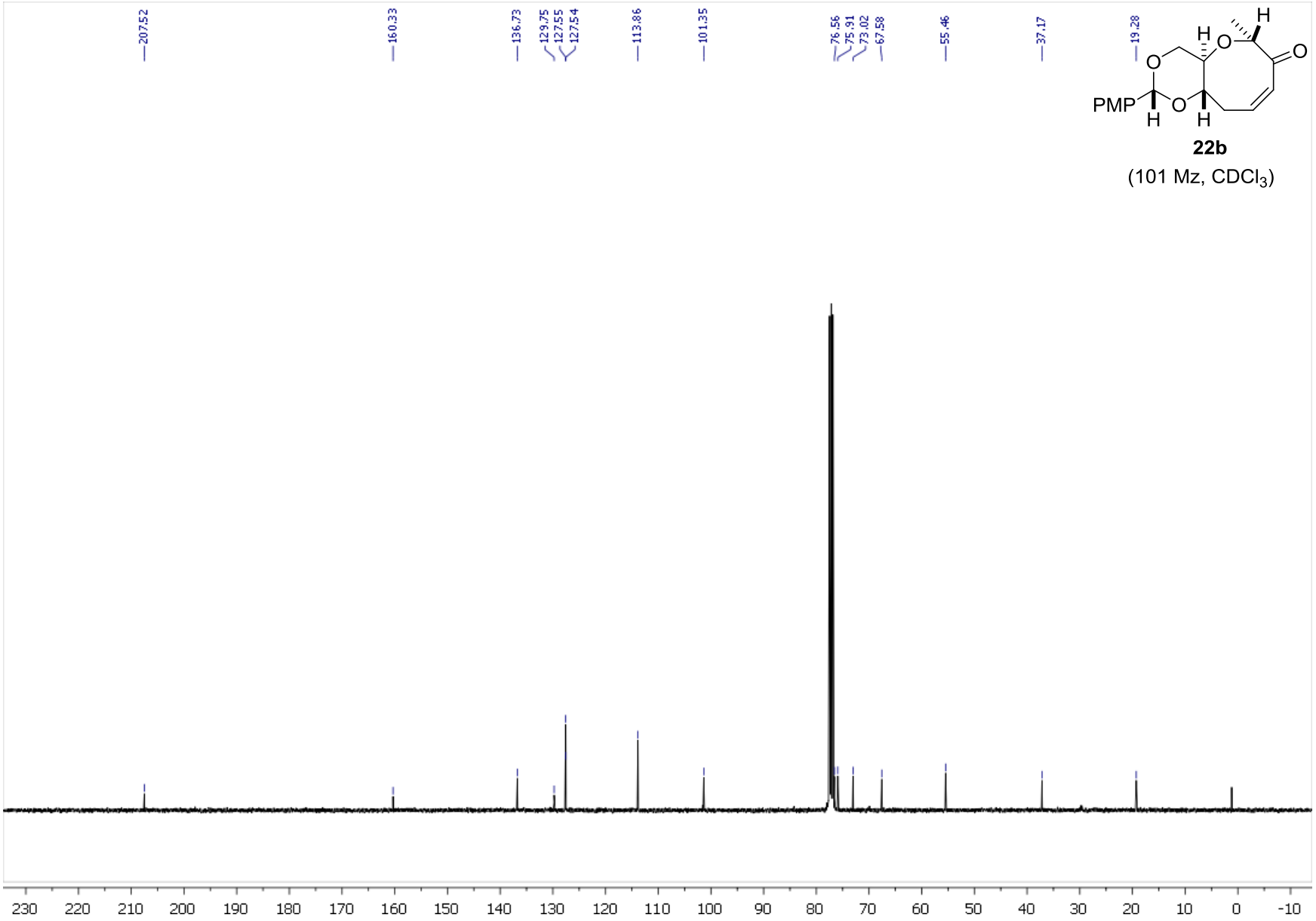
(400 Mz, $CDCl_3$)

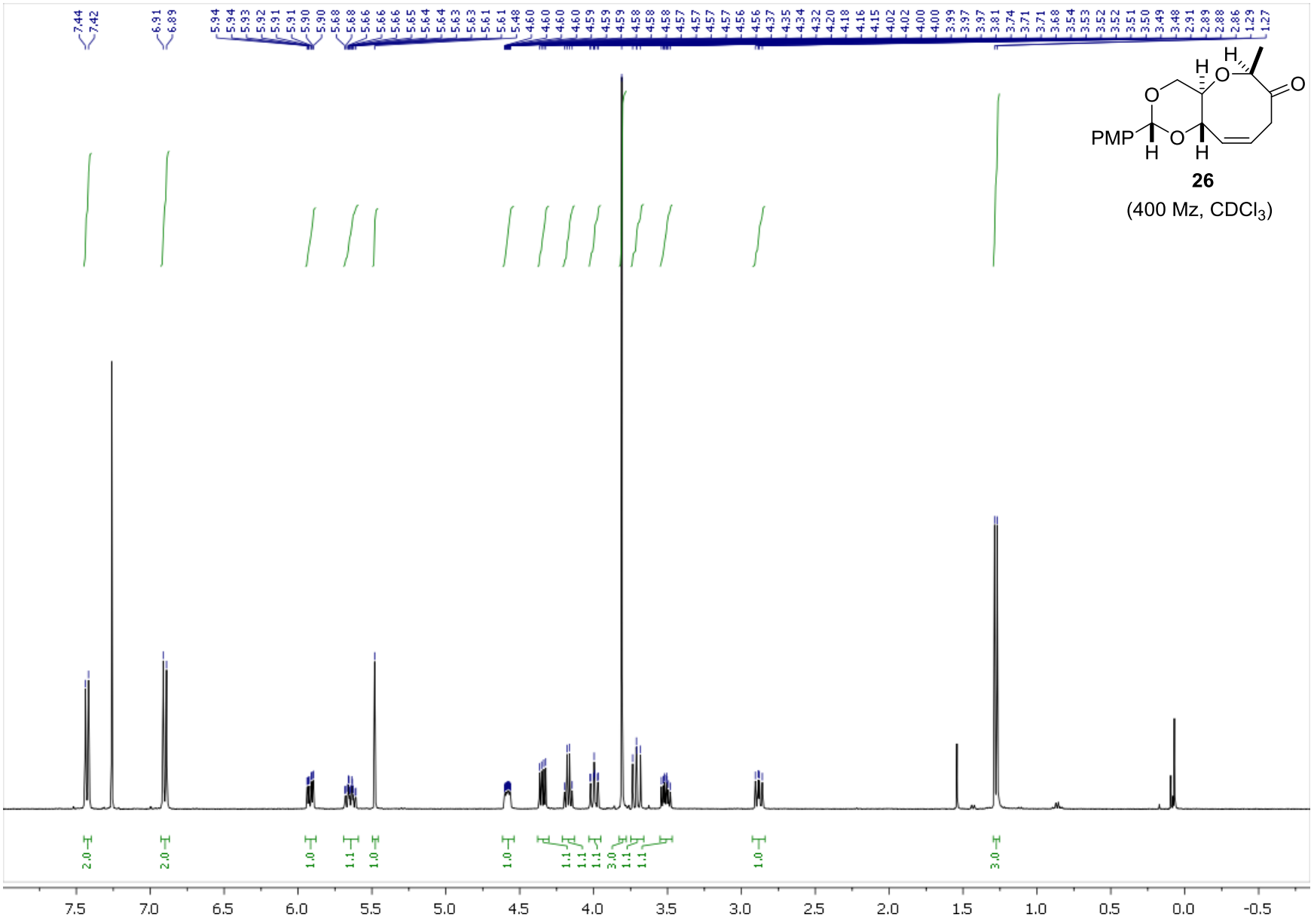

203.88
160.32
135.44
130.52
129.95
127.55
113.86
101.59
84.20
81.42
77.98
69.94
55.45
34.20
18.43
PMP
O
H
O
O
H
O
H
22a
(101 Mz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

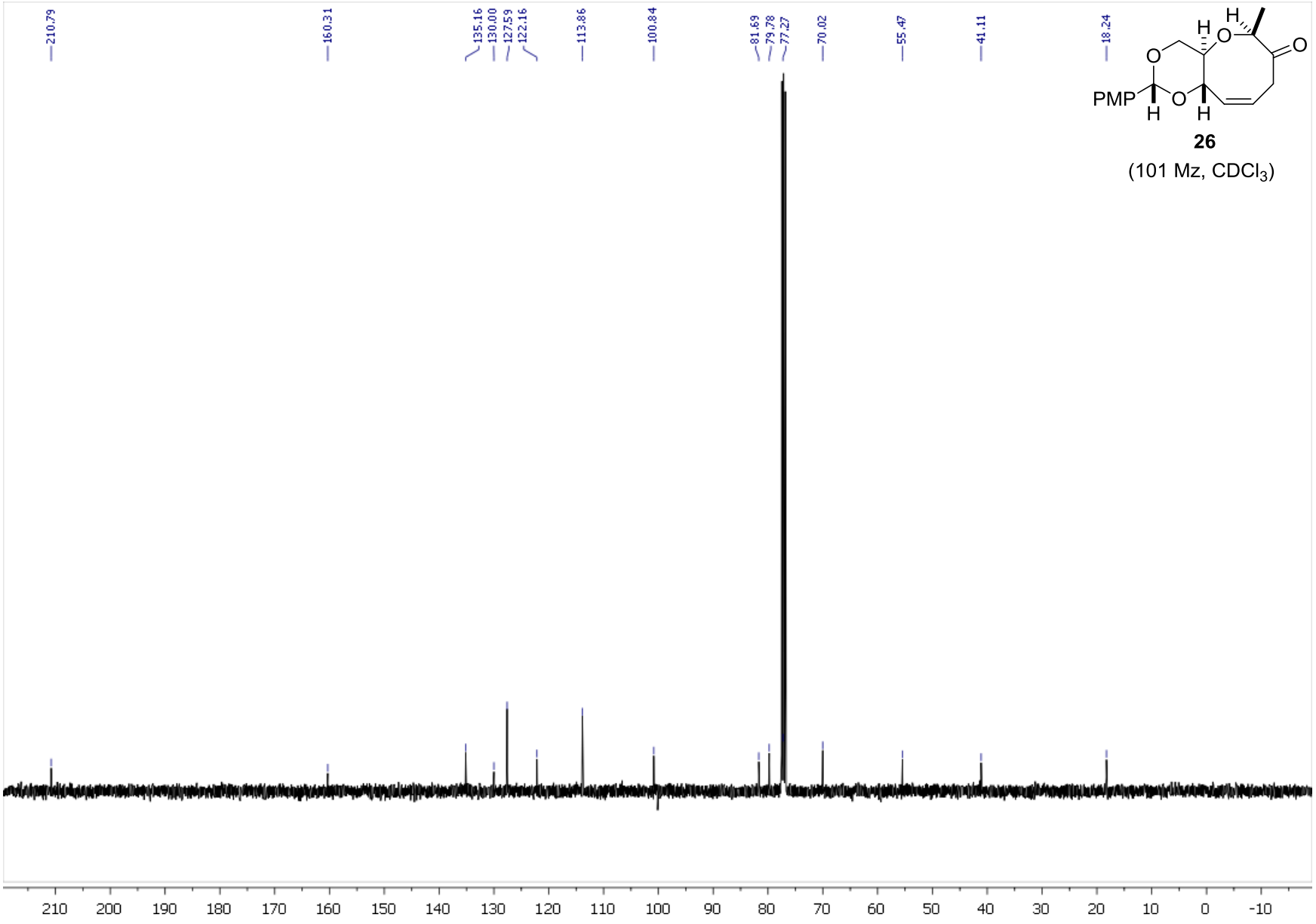


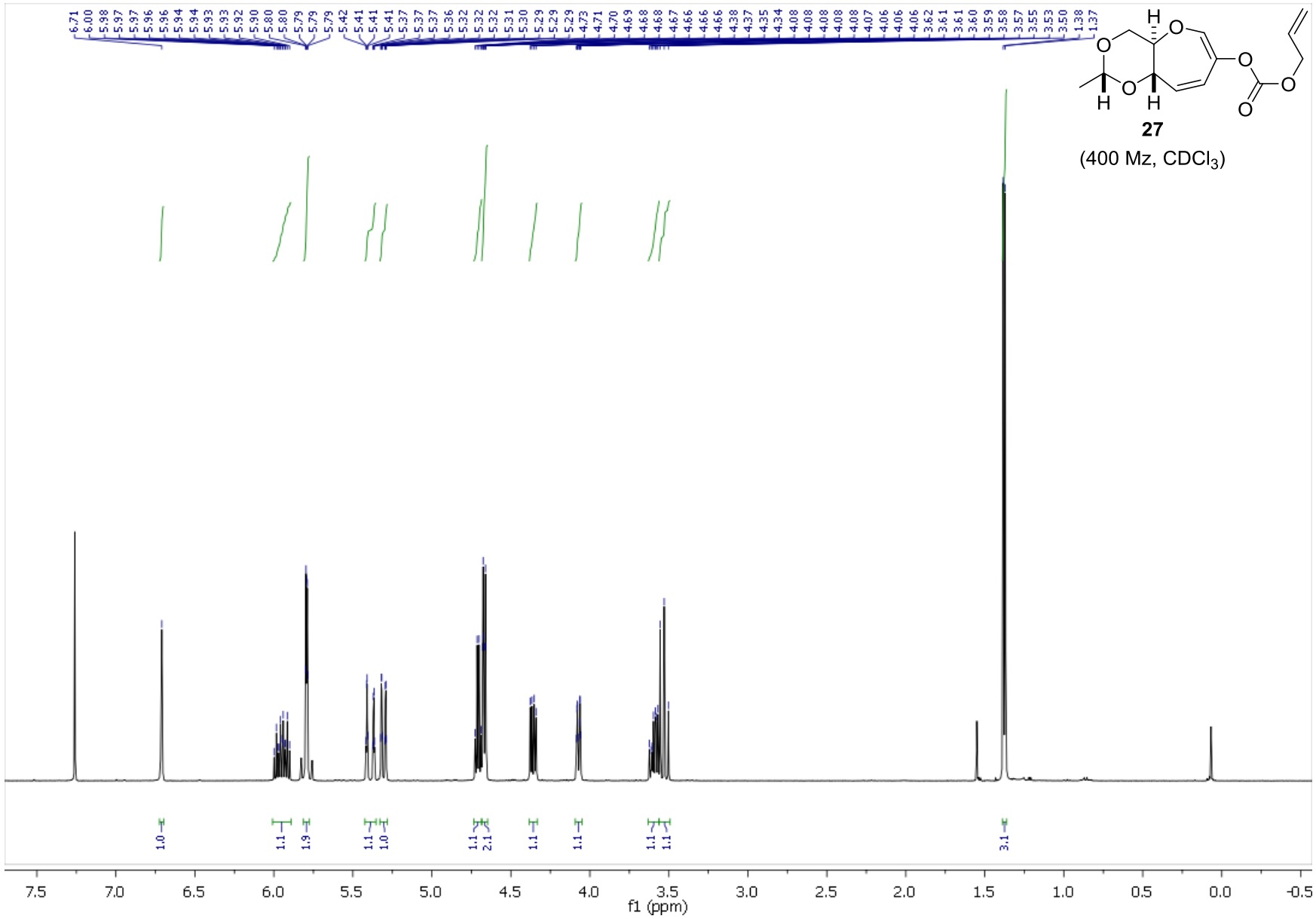
22b

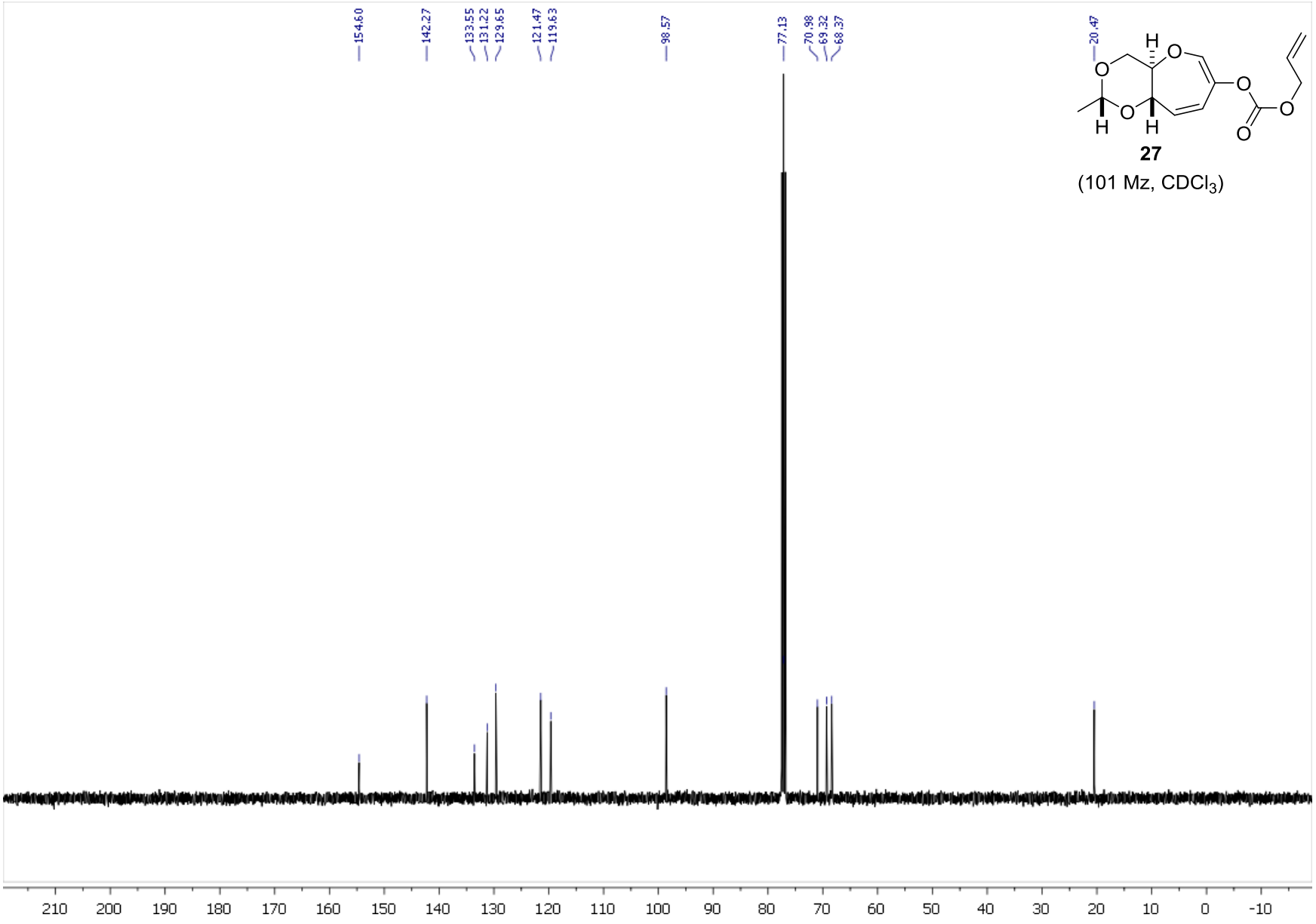
(400 Mz, $CDCl_3$)


207.52
160.33
136.73
129.75
127.55
127.54
113.86
101.35
76.56
75.91
73.02
67.58
55.46
37.17
19.28
PMP
H
O
O
O
O
H
H
H
22b
(101 Mz, CDCl3)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


PMP
O
O
O
O
H
H
H
26
(400 Mz, CDCl3)

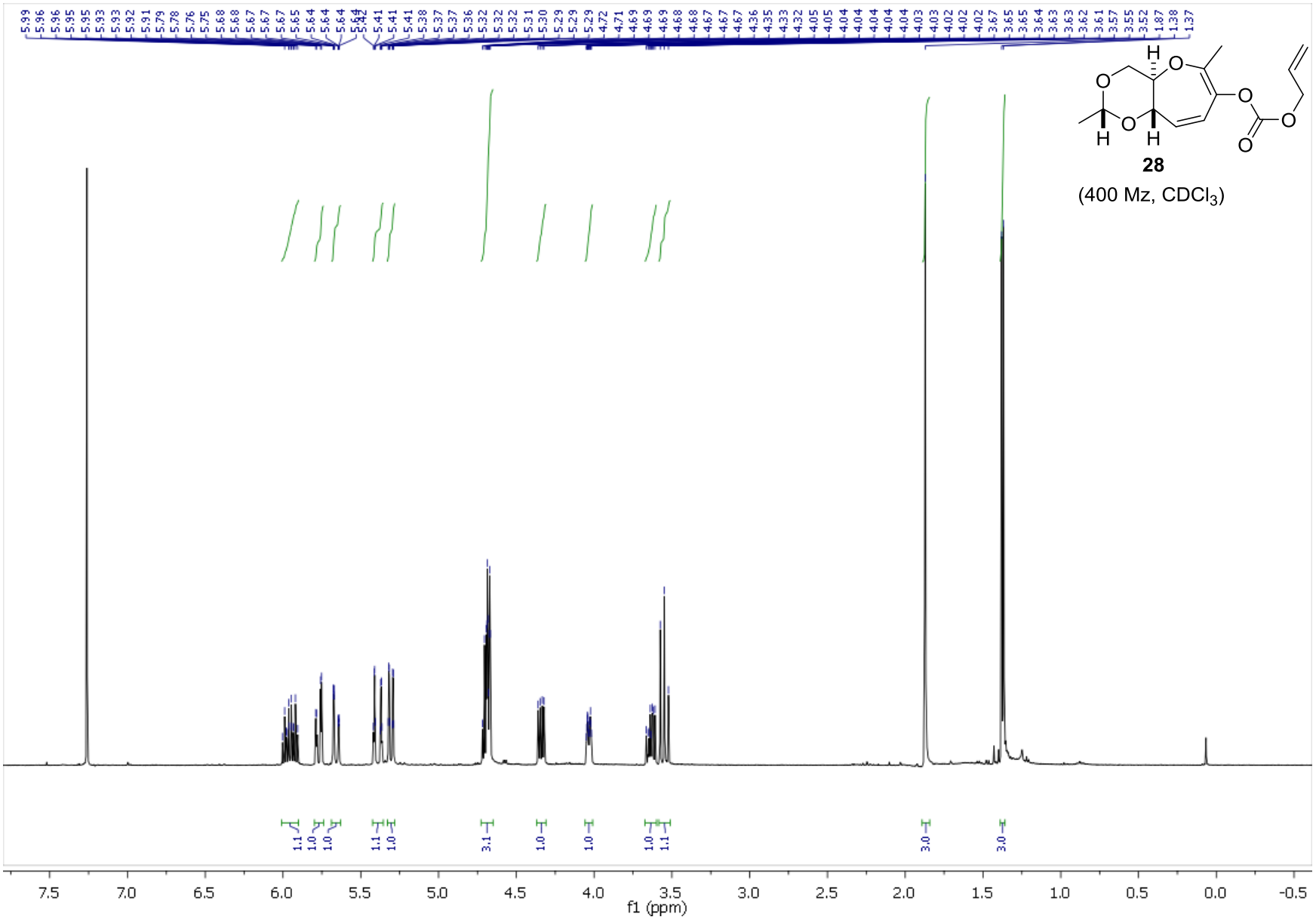

210.79
160.31
135.16
130.00
127.59
122.16
113.86
100.84
81.69
79.78
77.27
70.02
55.47
41.11
18.24
PMP
26
(101 Mz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

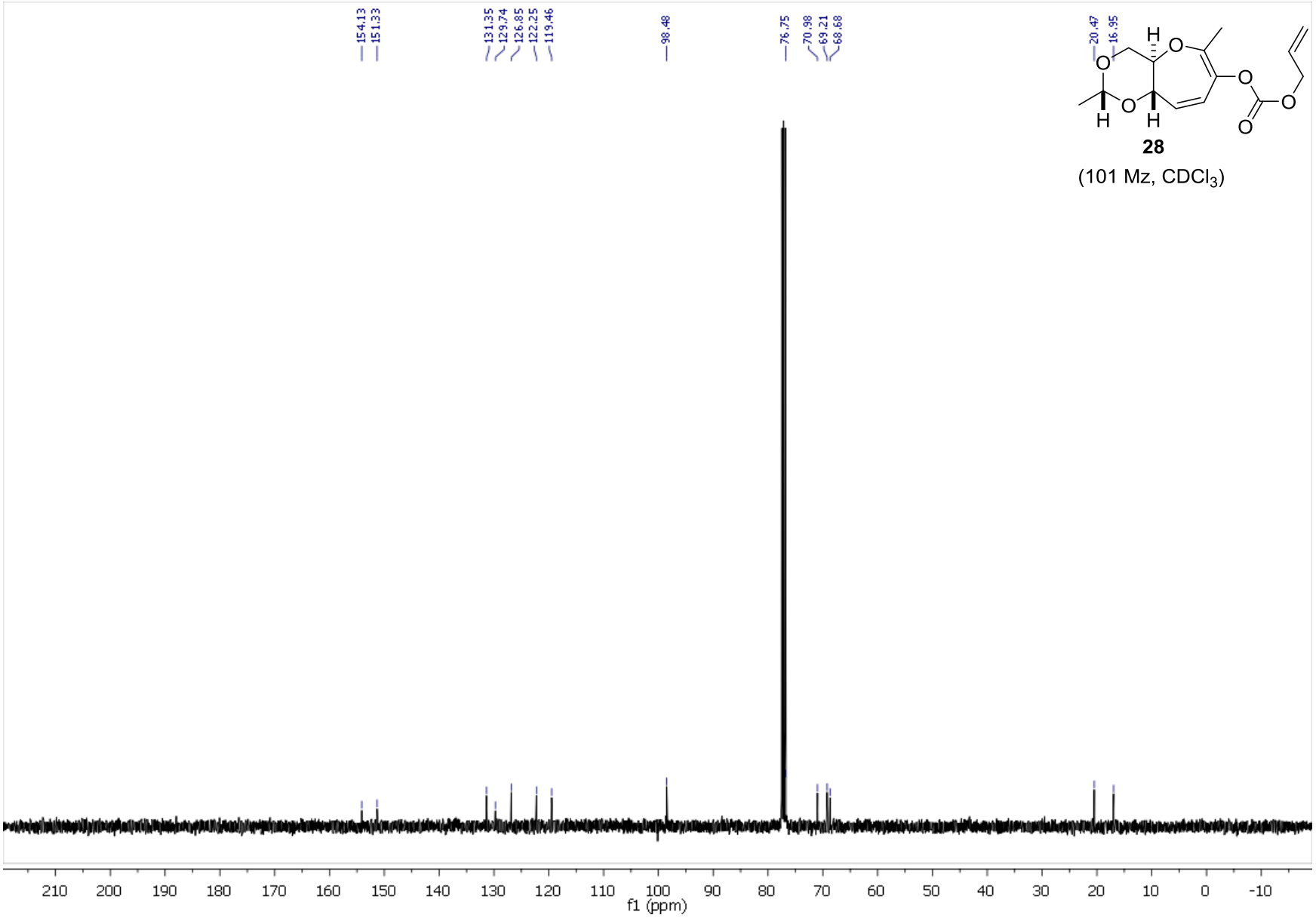

6.71 6.00 5.98 5.97 5.97 5.96 5.96 5.94 5.94 5.93 5.93 5.92 5.90 5.80 5.80 5.79 5.79 5.79 5.42 5.41 5.41 5.41 5.37 5.37 5.37 5.36 5.32 5.32 5.31 5.30 5.29 5.29 5.29 4.73 4.71 4.70 4.69 4.68 4.68 4.67 4.66 4.66 4.66 4.38 4.37 4.35 4.34 4.08 4.08 4.08 4.08 4.08 4.07 4.06 4.06 4.06 3.62 3.61 3.61 3.60 3.59 3.58 3.57 3.55 3.53 3.50 1.38 1.37
H
O
O
O
O
O
O
H
H
O
27
(400 Mz, CDCl3)
1.0
1.1
1.9
1.1
1.0
1.1
2.1
1.1
1.1
1.1
1.1
3.1
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 -0.5
f1 (ppm)

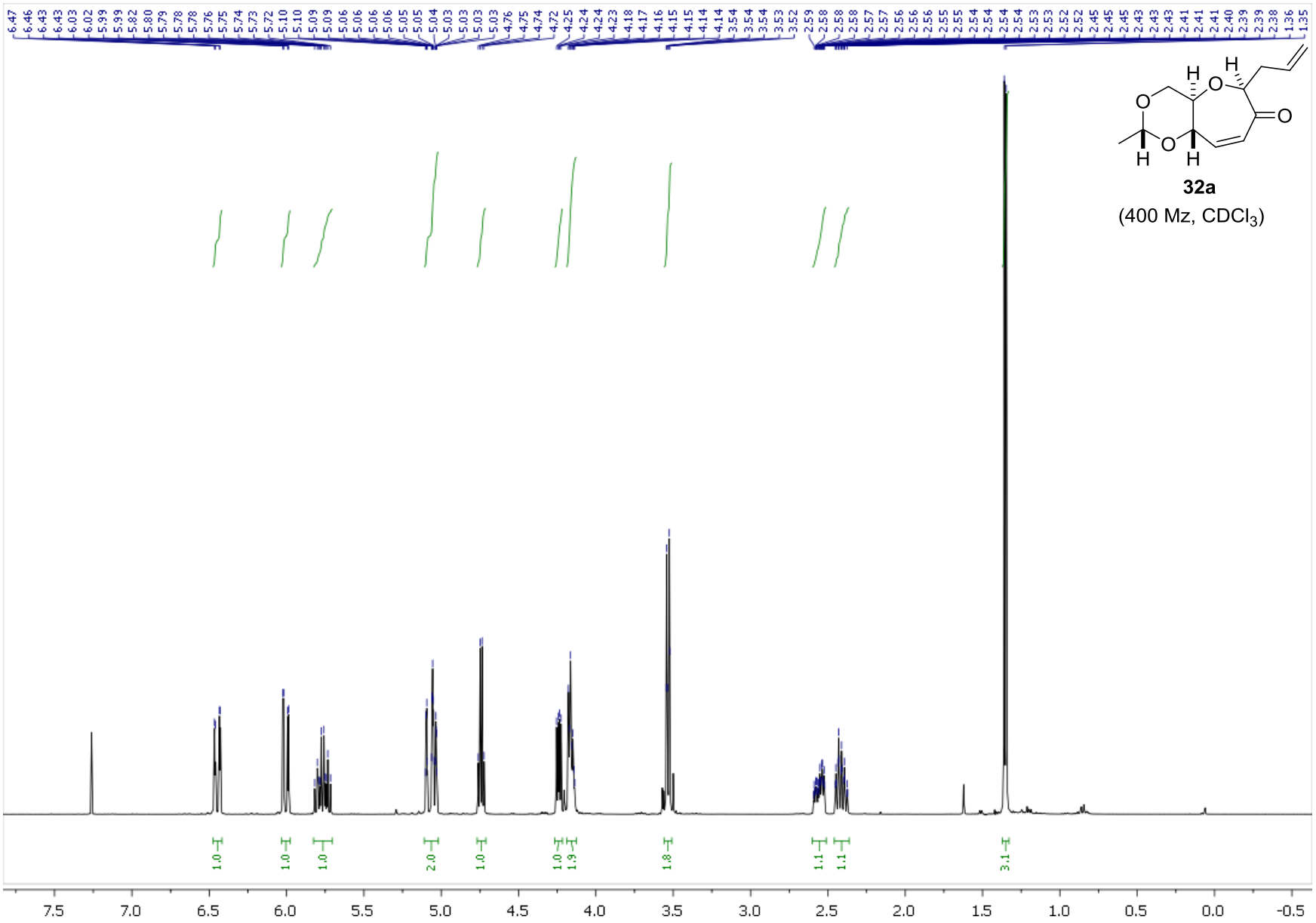


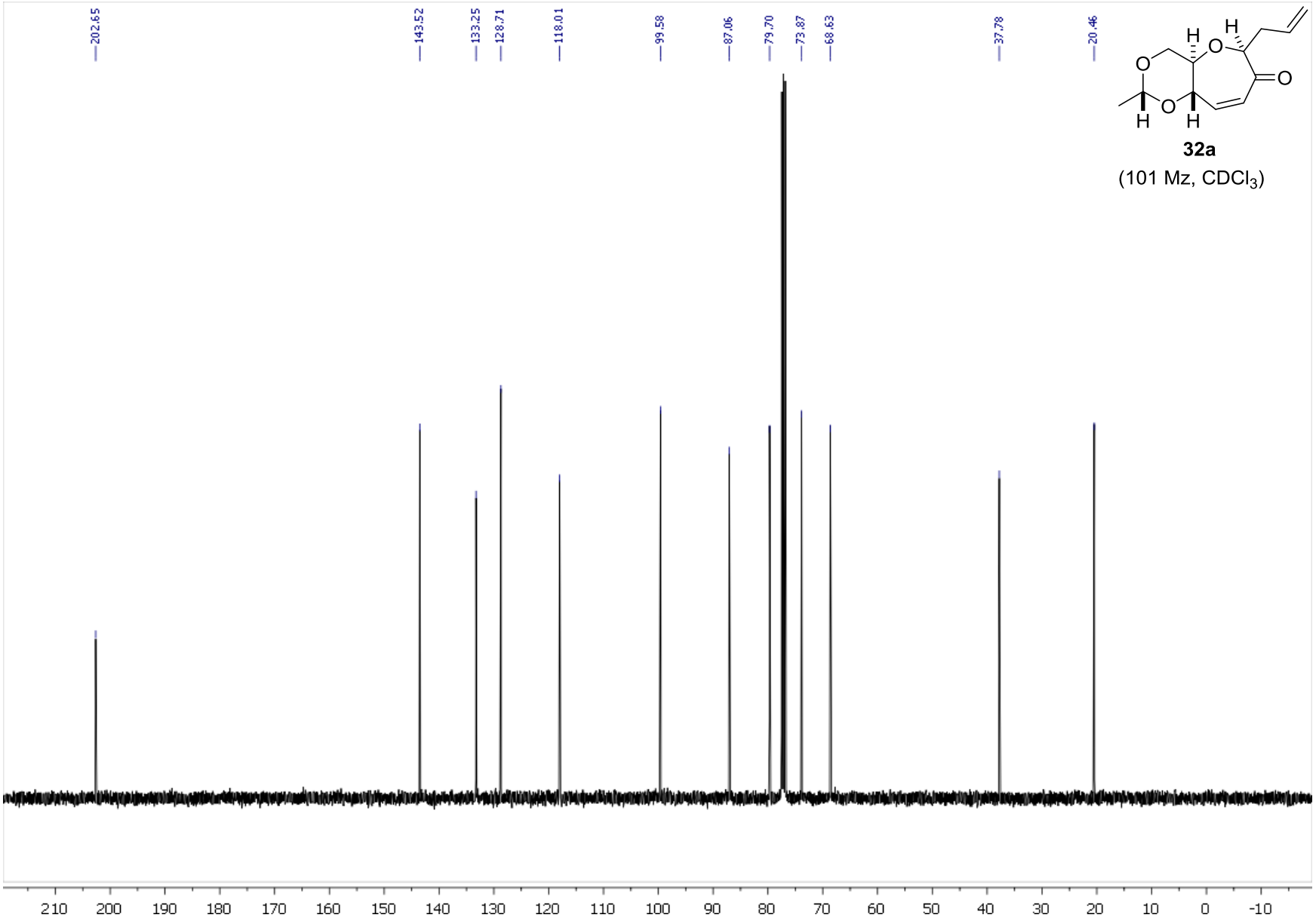
27

(101 Mz, $CDCl_3$)


28
(400 Mz, CDCl3)
f1 (ppm)

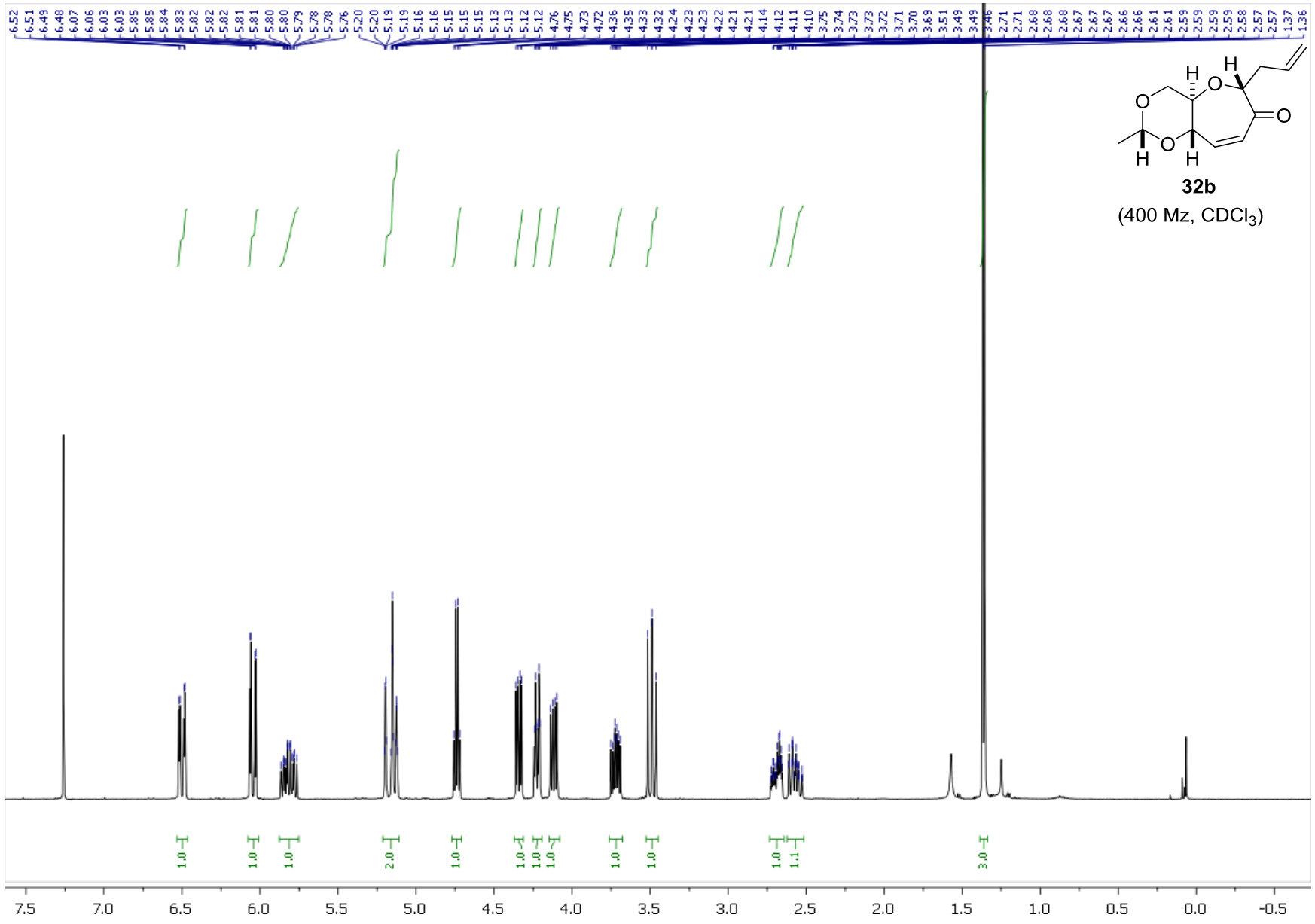

154.13
151.33
131.35
129.74
126.85
122.25
119.46
98.48
76.75
70.98
69.21
68.68
20.47
16.95
H
O
O
O
O
O
O
H
H
O
28
(101 Mz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

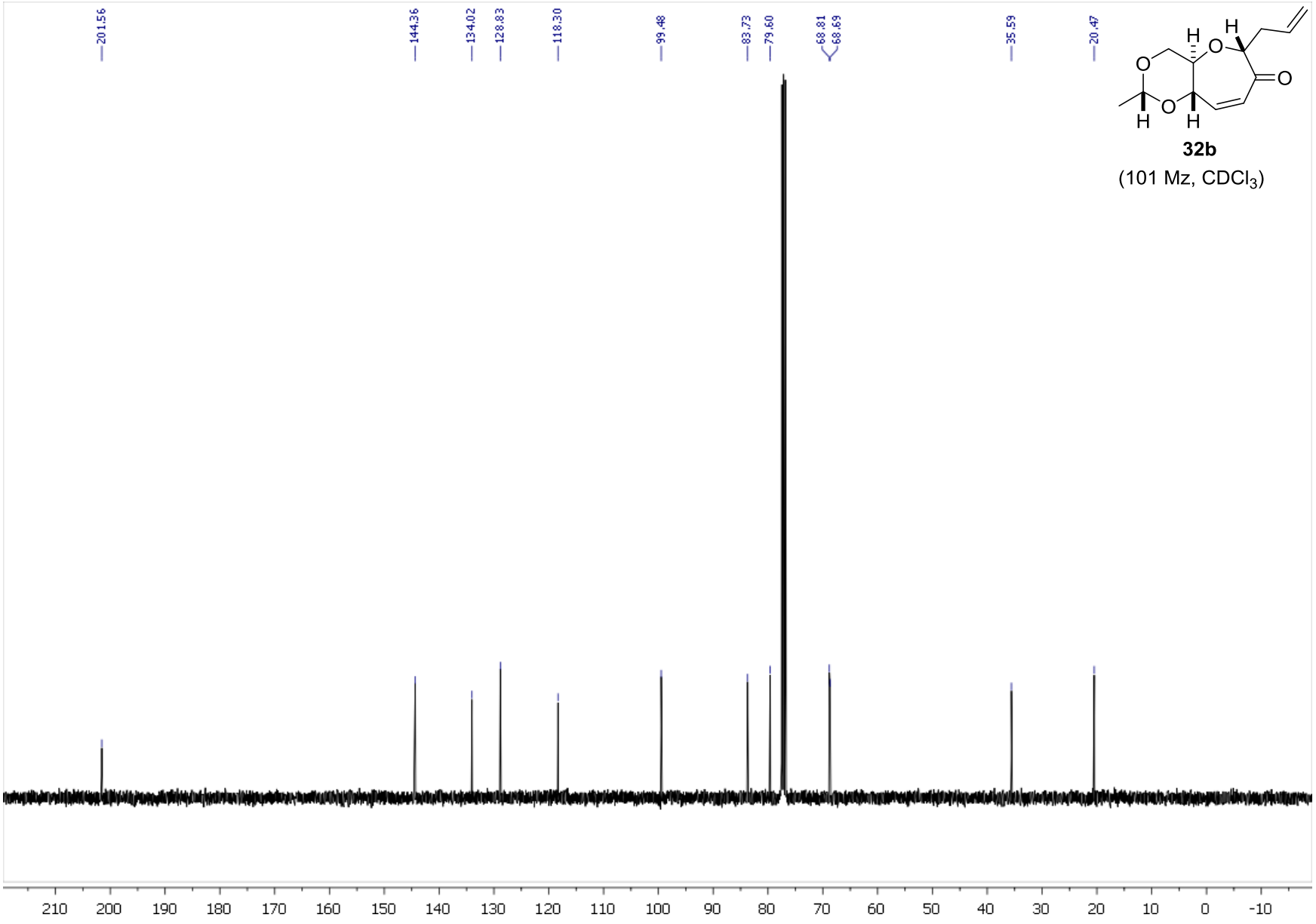

32a
(400 Mz, CDCl3)



32a

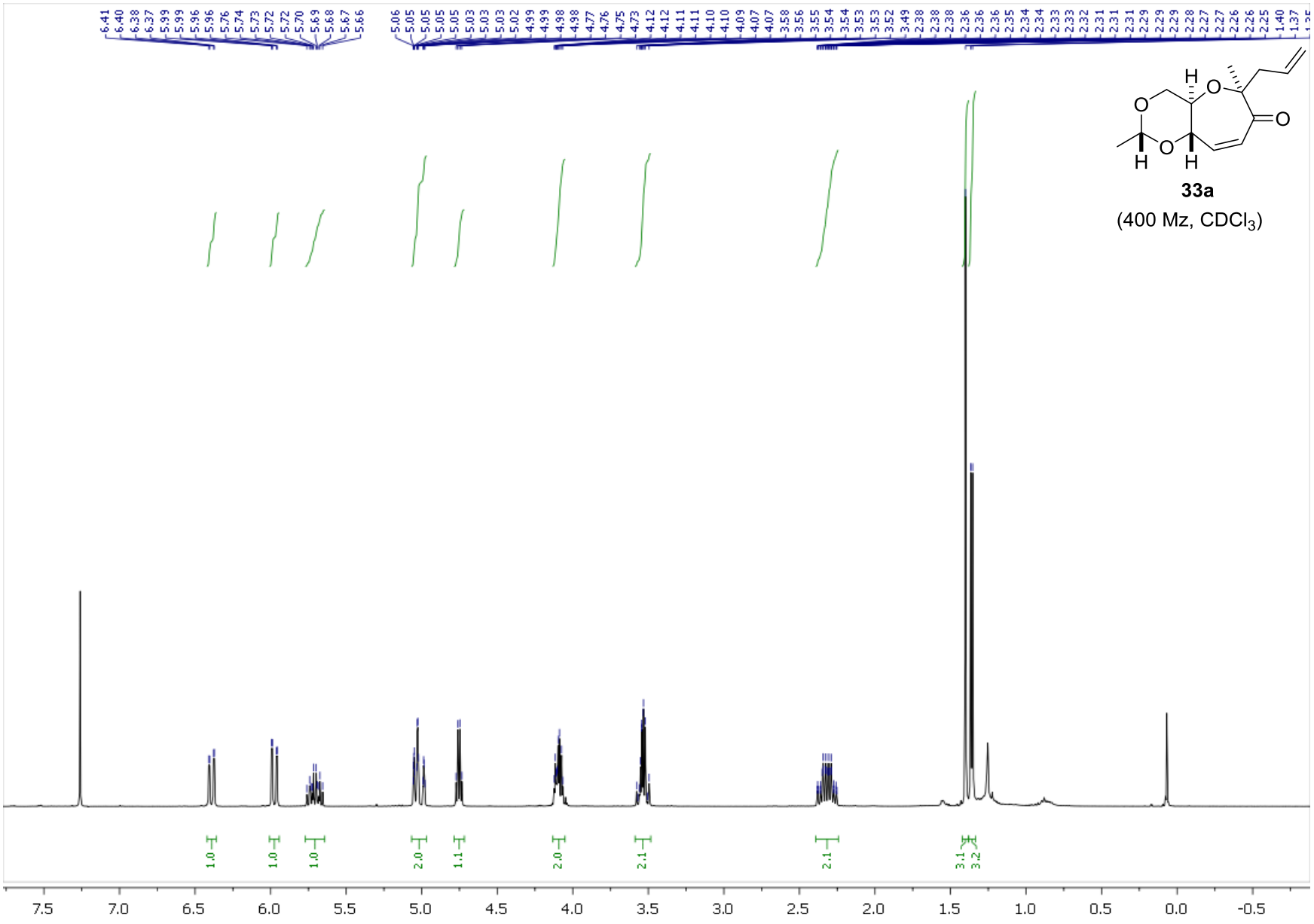
(101 Mz, $CDCl_3$)

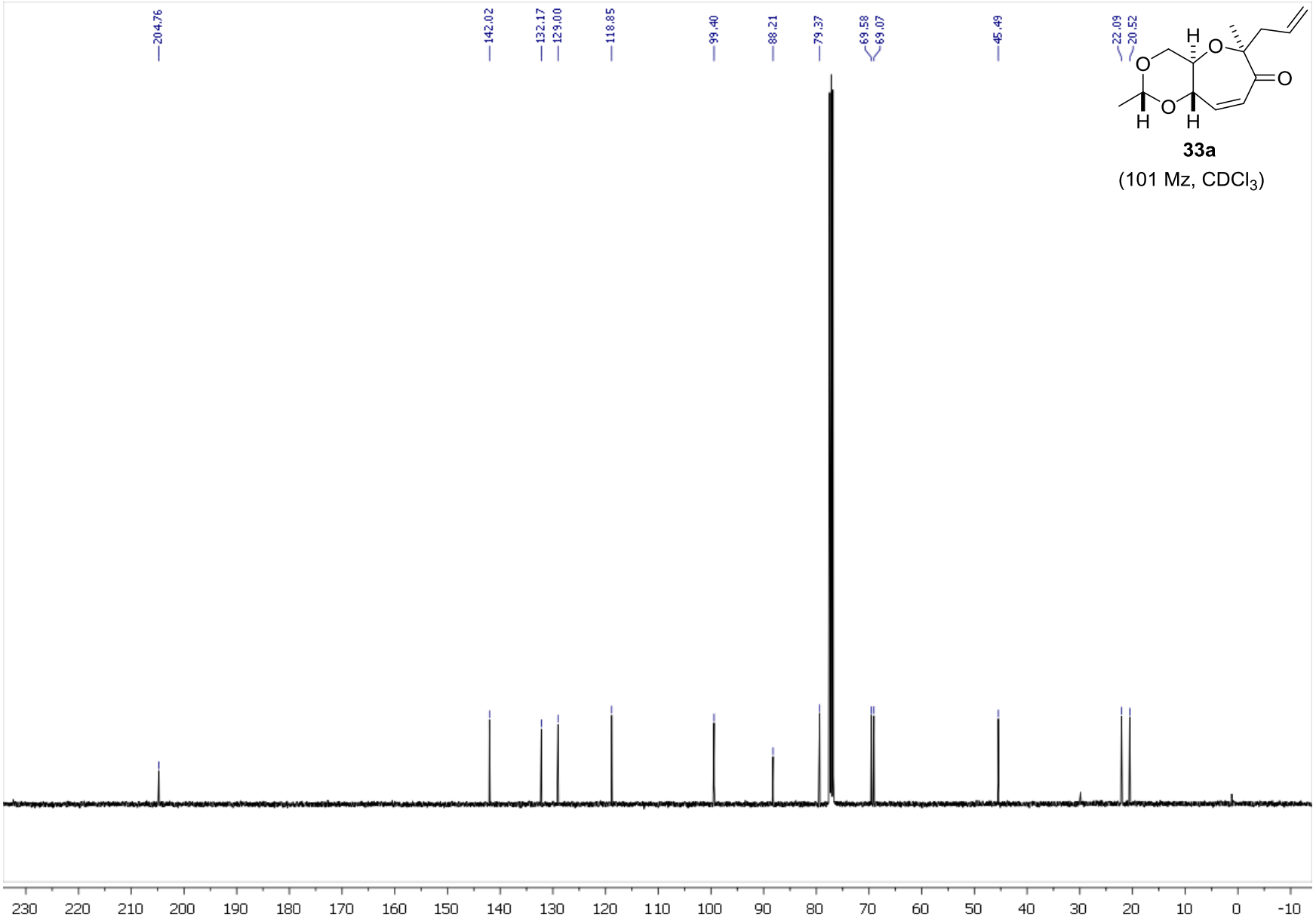

32b
(400 Mz, CDCl3)



32b

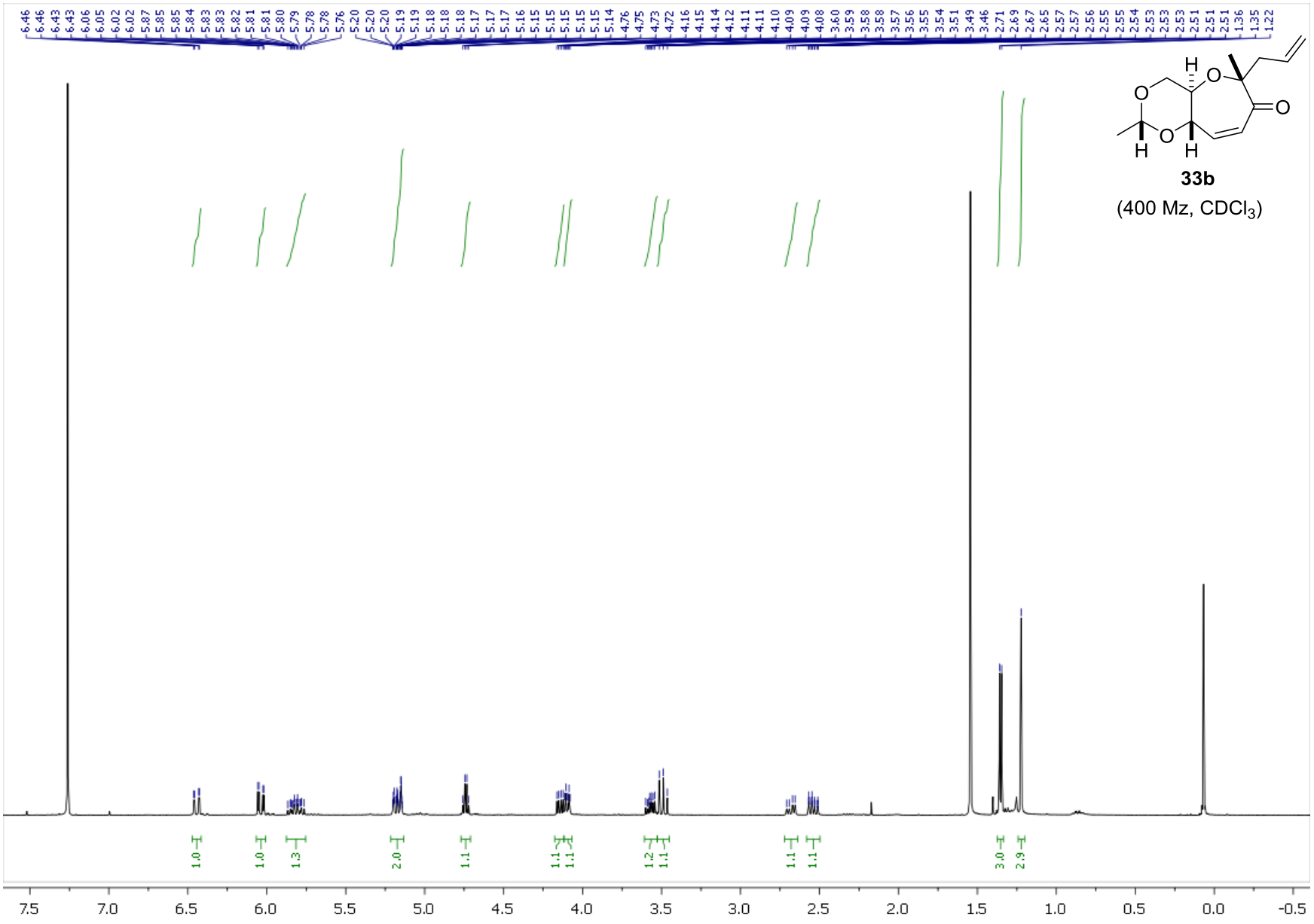
(101 Mz, $CDCl_3$)

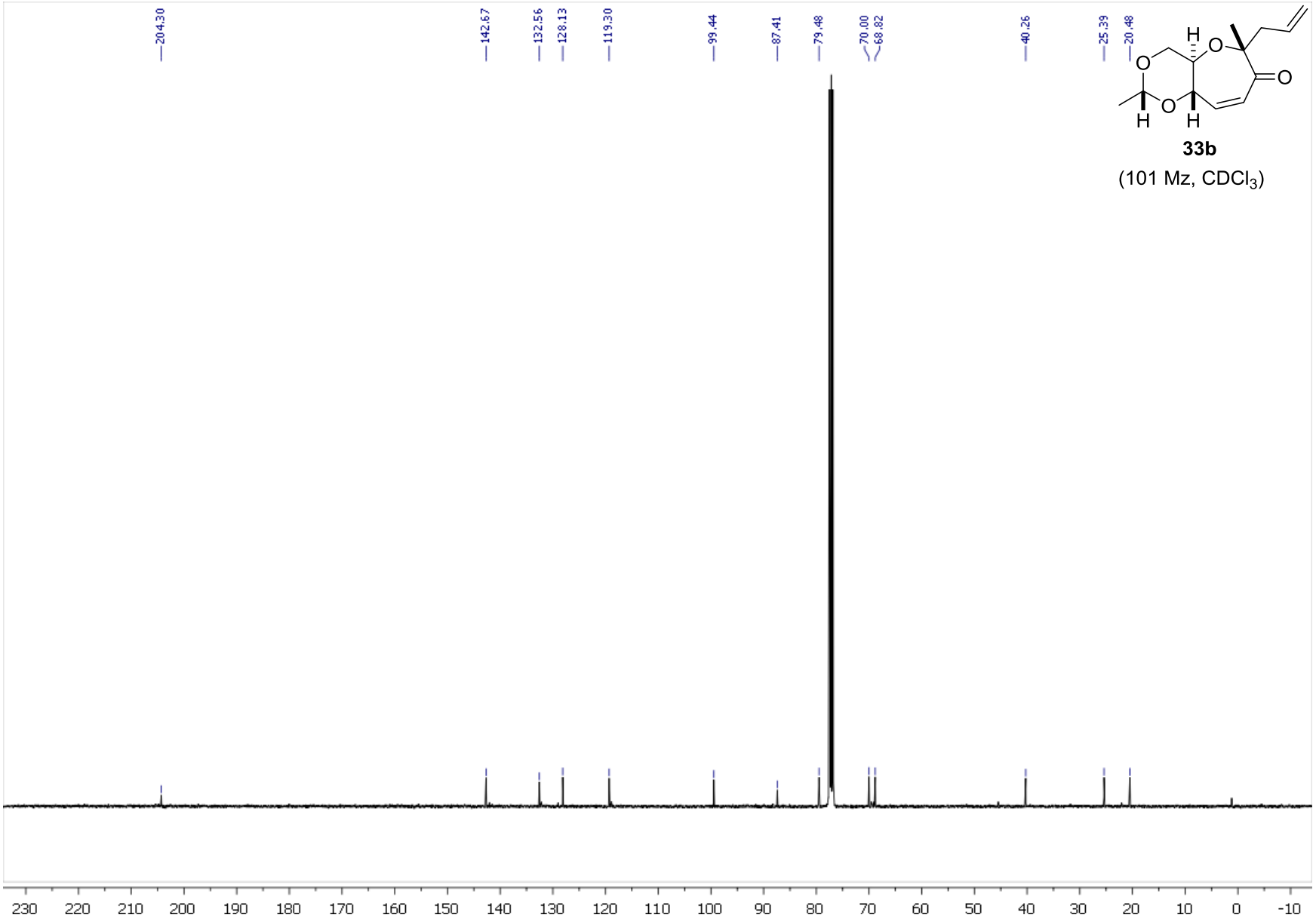

33a
(400 Mz, CDCl3)



33a

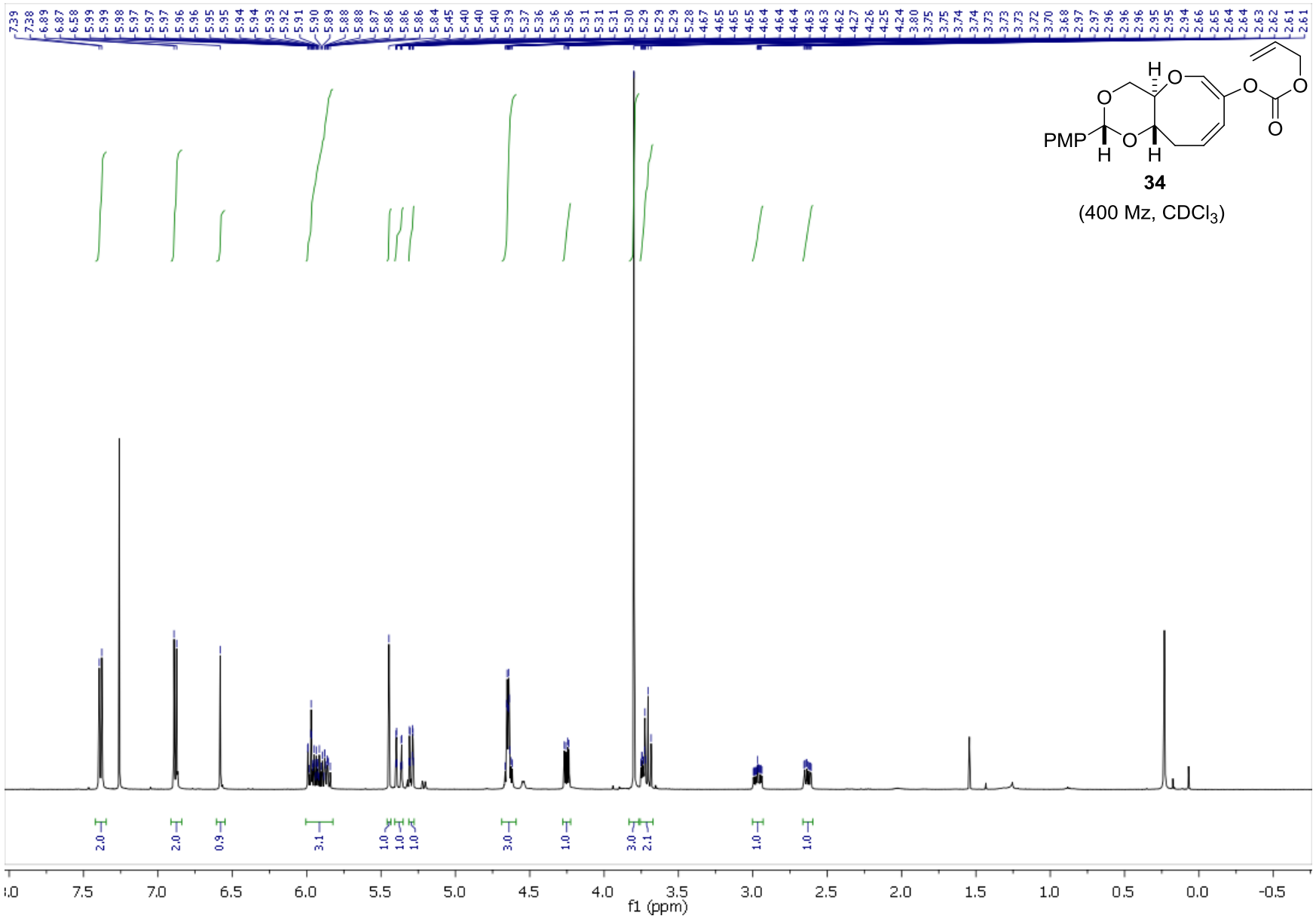
(101 Mz, $CDCl_3$)

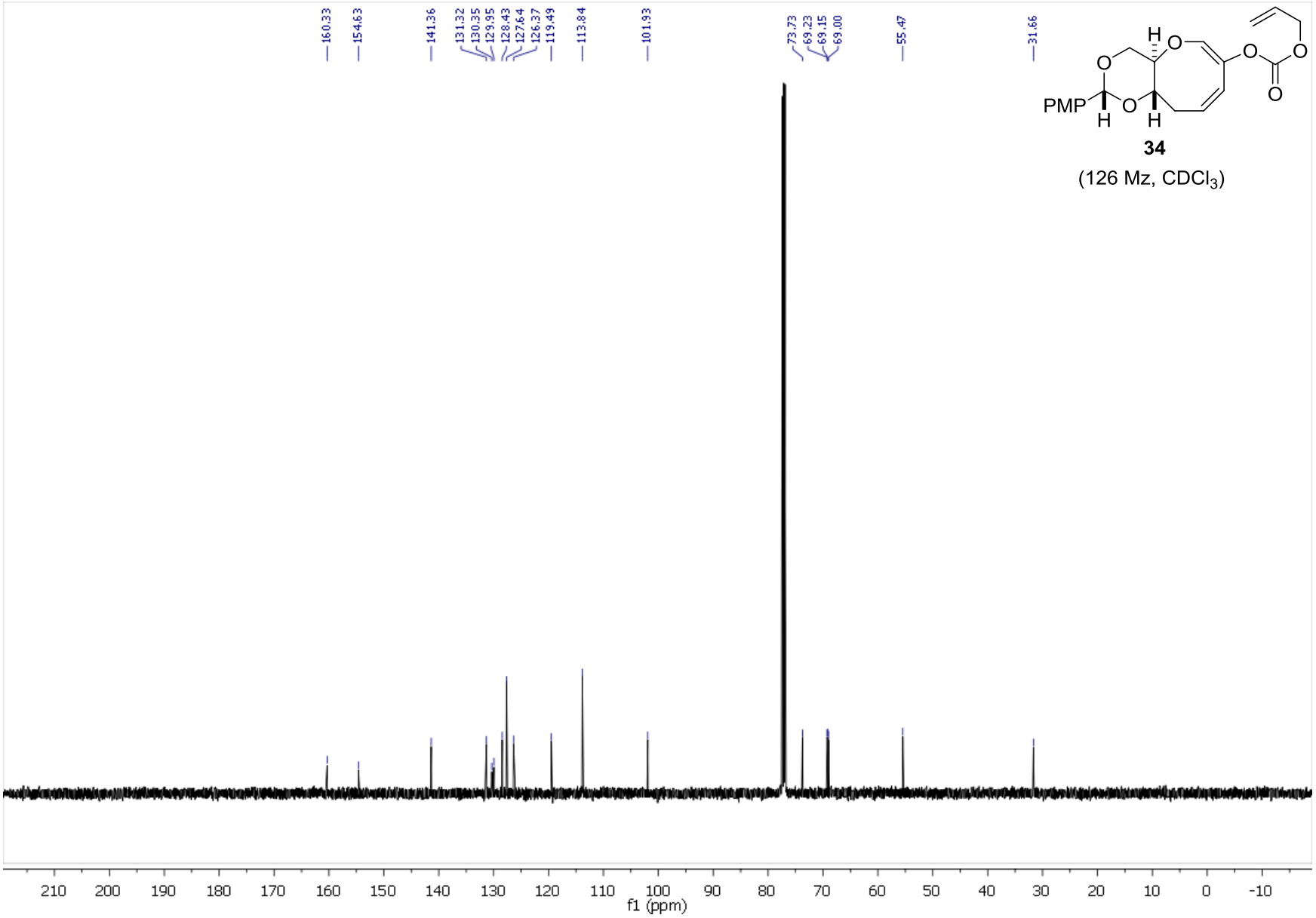

33b
(400 Mz, CDCl3)

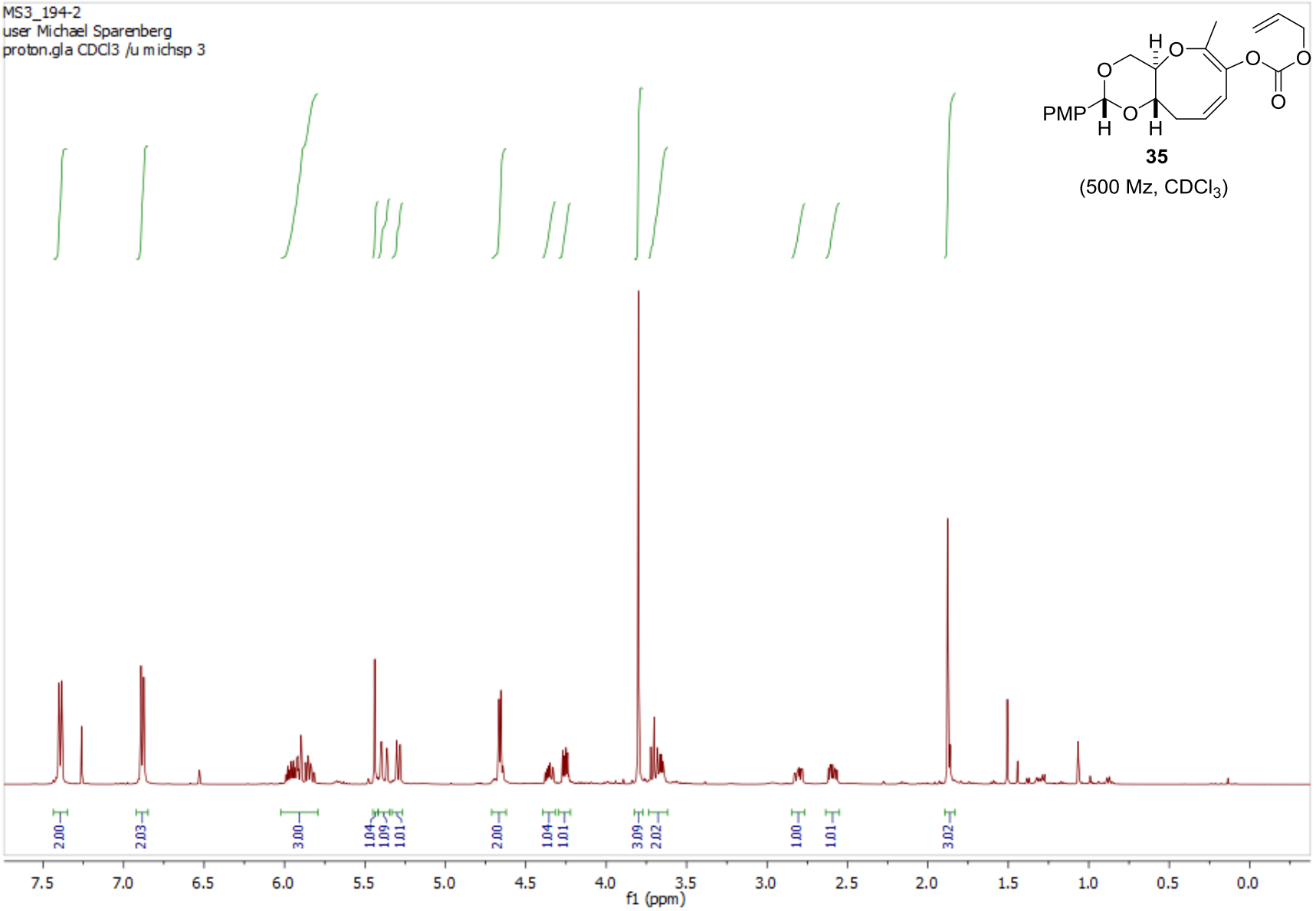


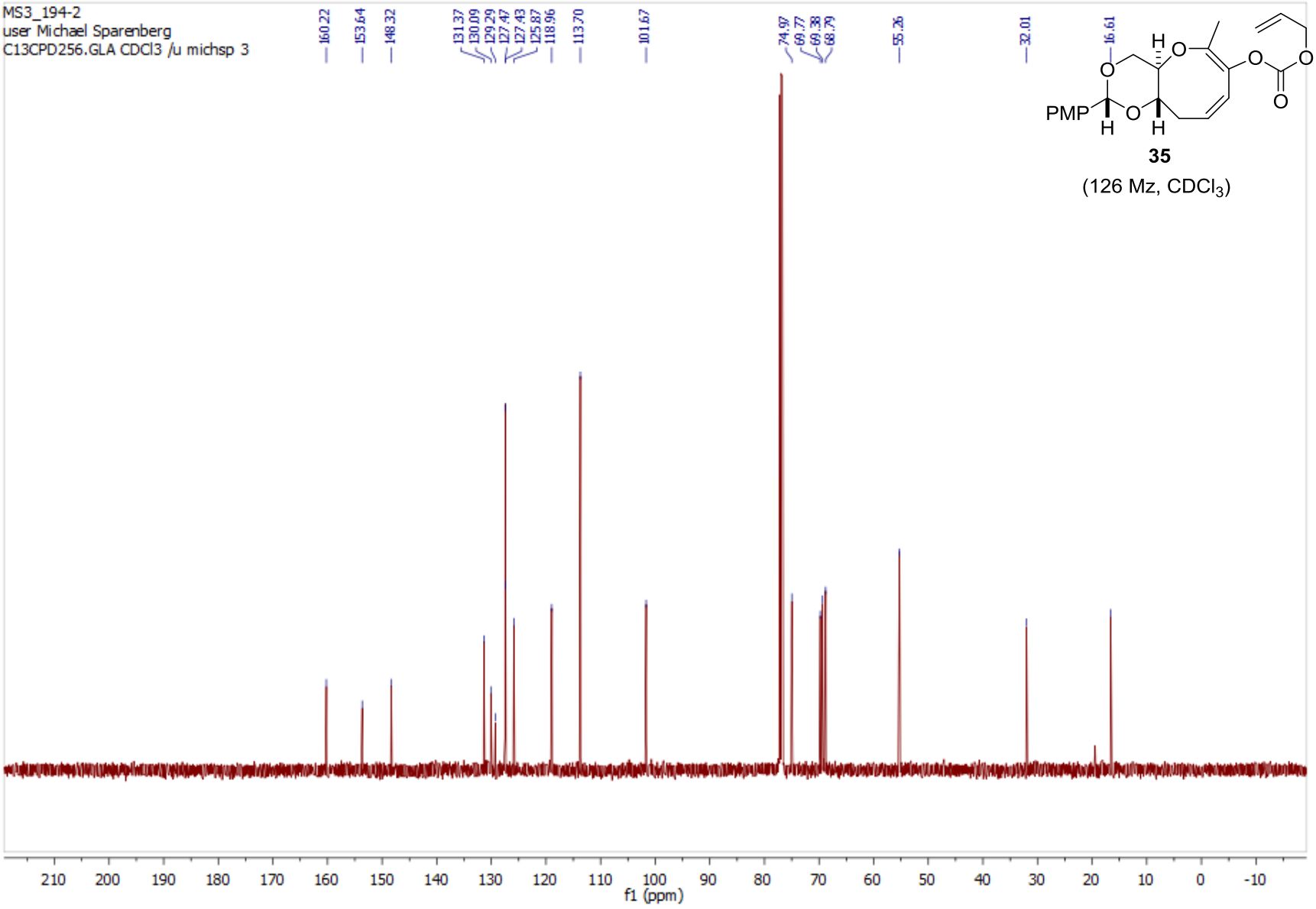
33b

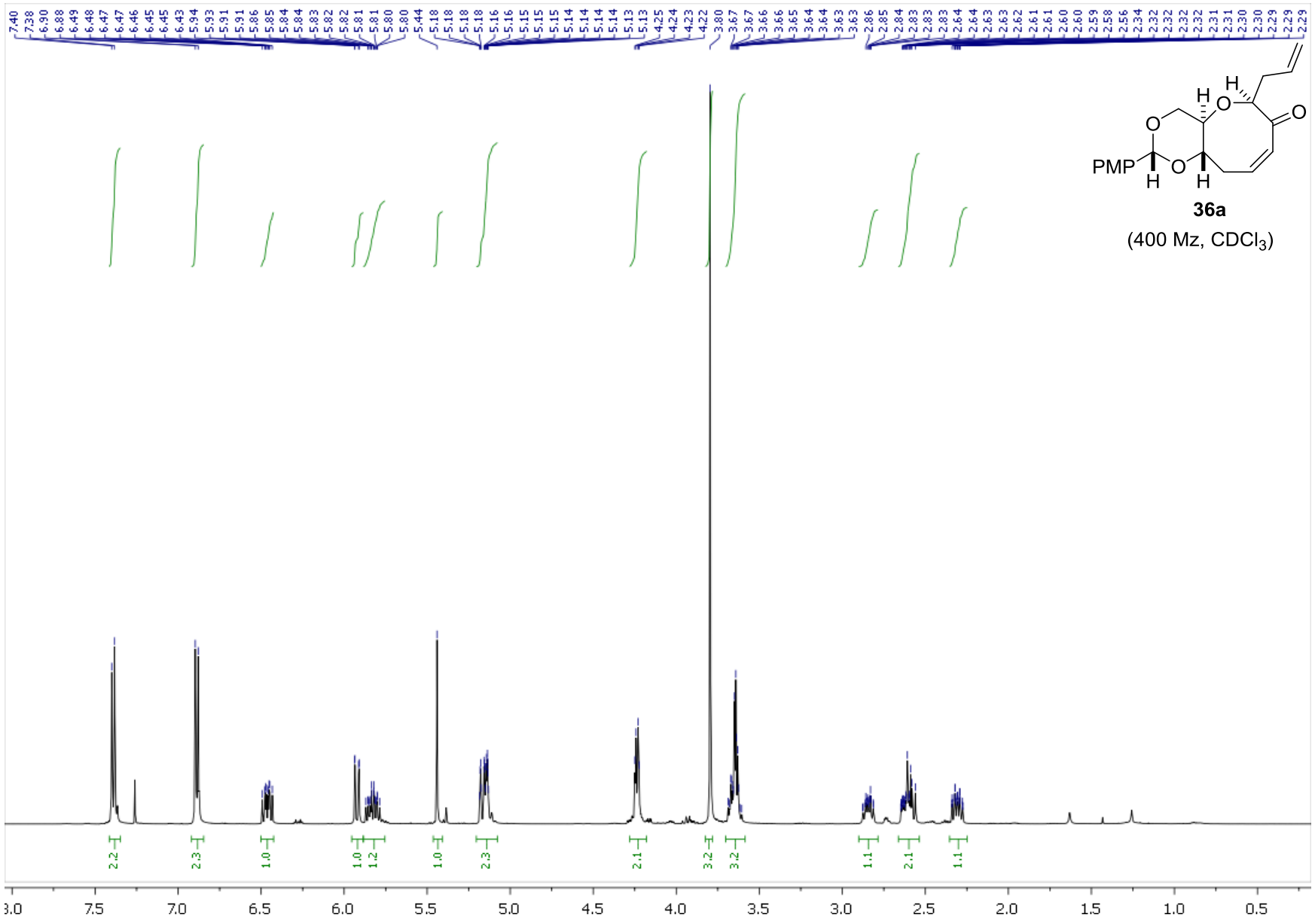
(101 Mz, $CDCl_3$)

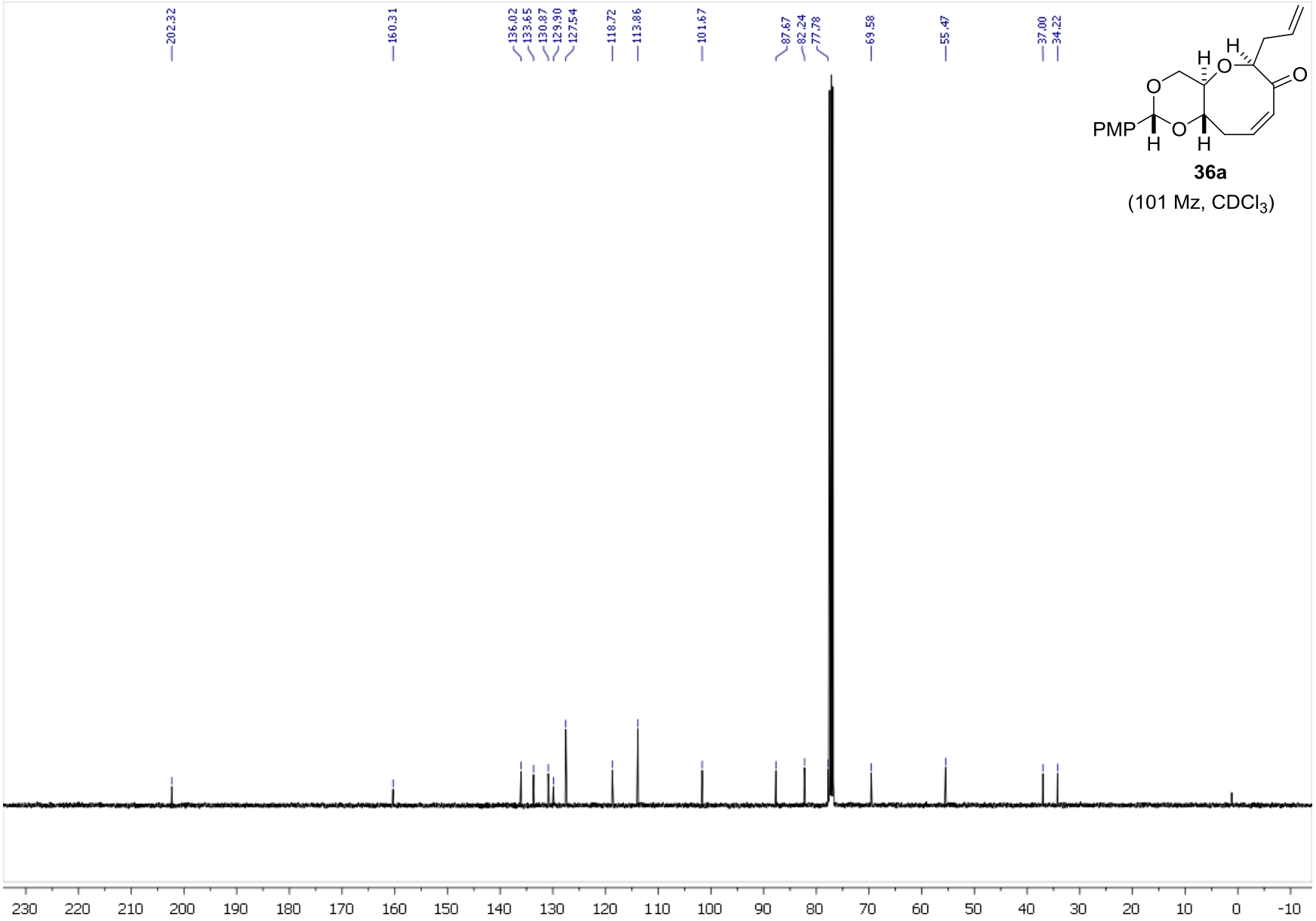

PMP
34
(400 Mz, CDCl3)
f1 (ppm)


160.33
154.63
141.36
131.32
130.35
129.95
128.43
127.64
126.37
119.49
113.84
101.93
73.73
69.23
69.15
69.00
55.47
31.66
PMP
H
O
O
O
O
O
O
H
H
34
(126 Mz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


MS3_194-2
user Michael Sparenberg
proton.gla CDCl3 /u michsp 3
PMP
35
(500 Mz, CDCl3)
2.00
2.03
3.00
1.04
1.09
1.01
2.00
1.04
1.01
3.09
2.02
1.00
1.01
3.02
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
f1 (ppm)

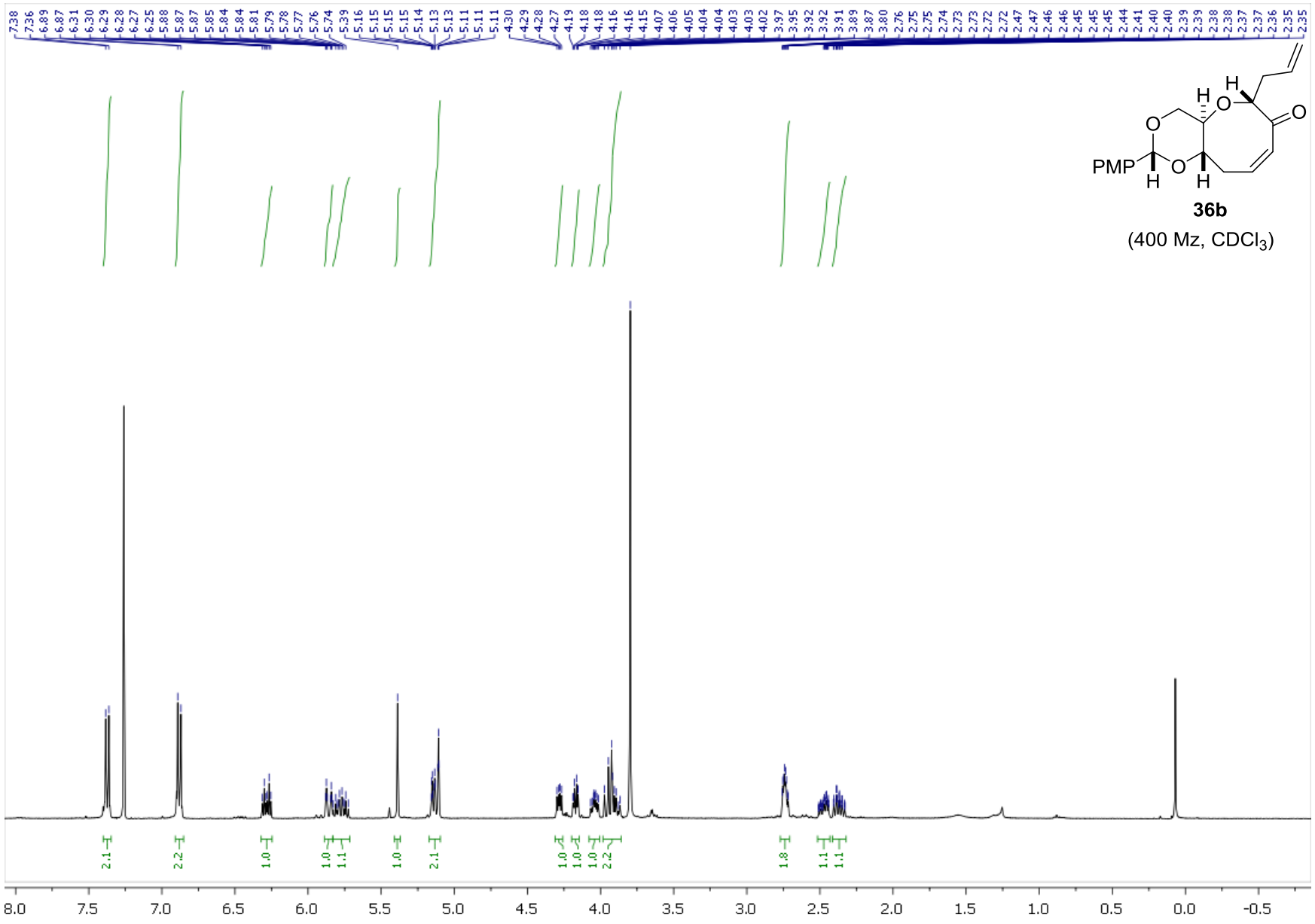

MS3_194-2
user Michael Sparenberg
C13CPD256.GLA CDCl3 /u michsp 3
160.22
153.64
148.32
131.37
130.09
129.29
127.47
127.43
125.87
118.96
113.70
101.67
74.97
69.77
69.38
68.79
55.26
32.01
16.61
PMP
H
O
O
O
O
O
H
H
35
(126 Mz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

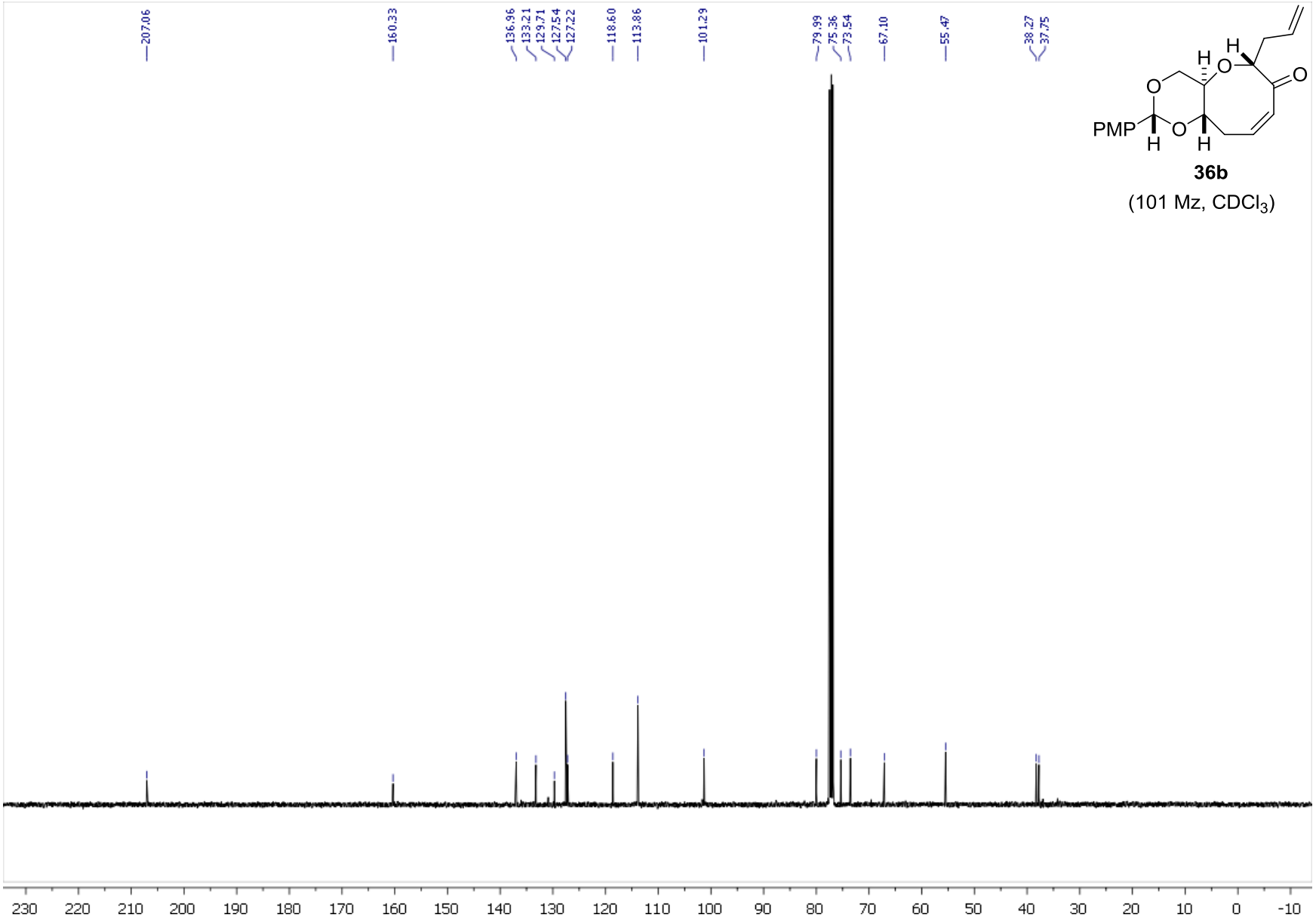

PMP
O
H
O
O
H
H
O
H
36a
(400 Mz, CDCl3)

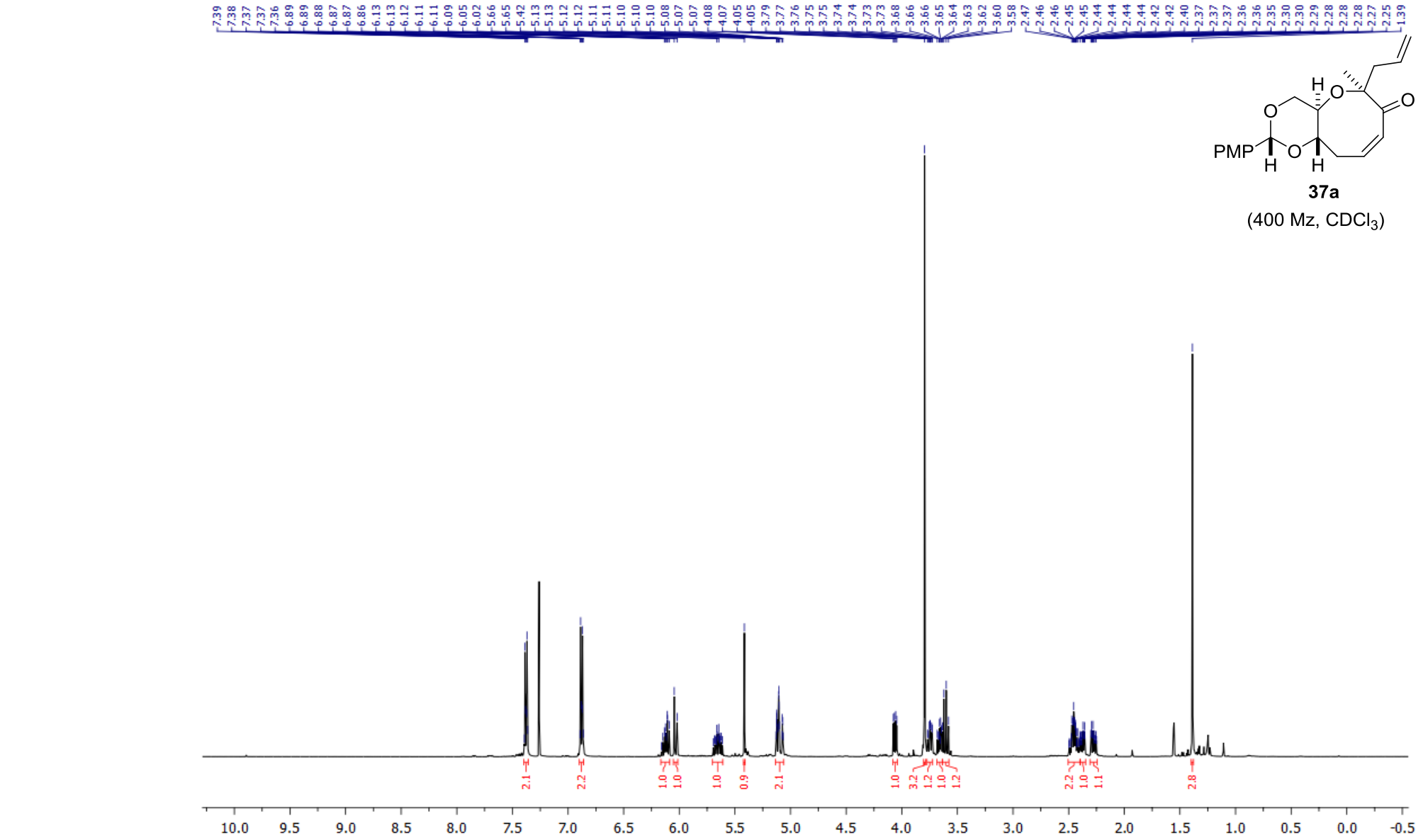


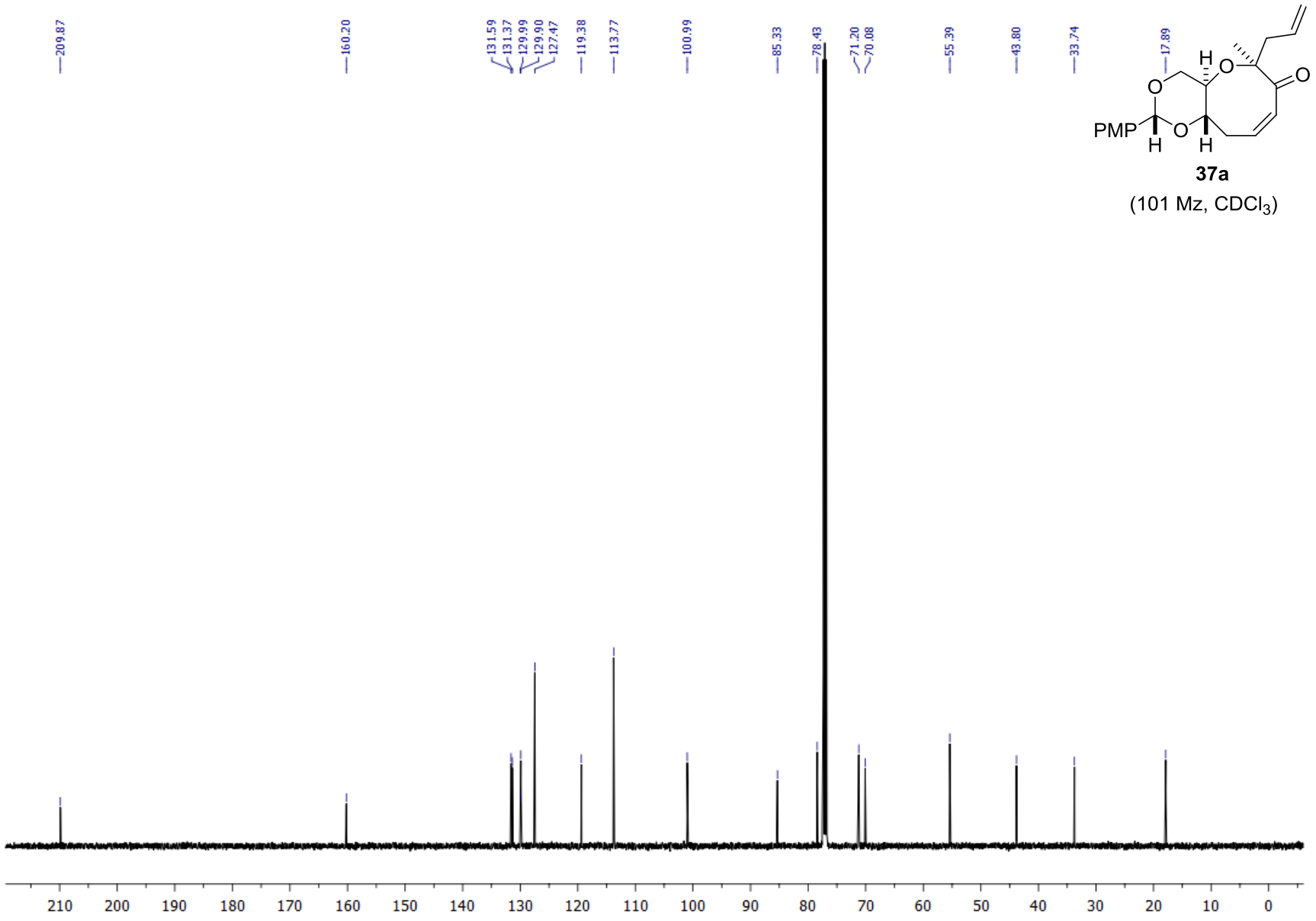
36a

(101 Mz, $CDCl_3$)


PMP
O
O
O
O
H
H
H
H
36b
(400 Mz, CDCl3)

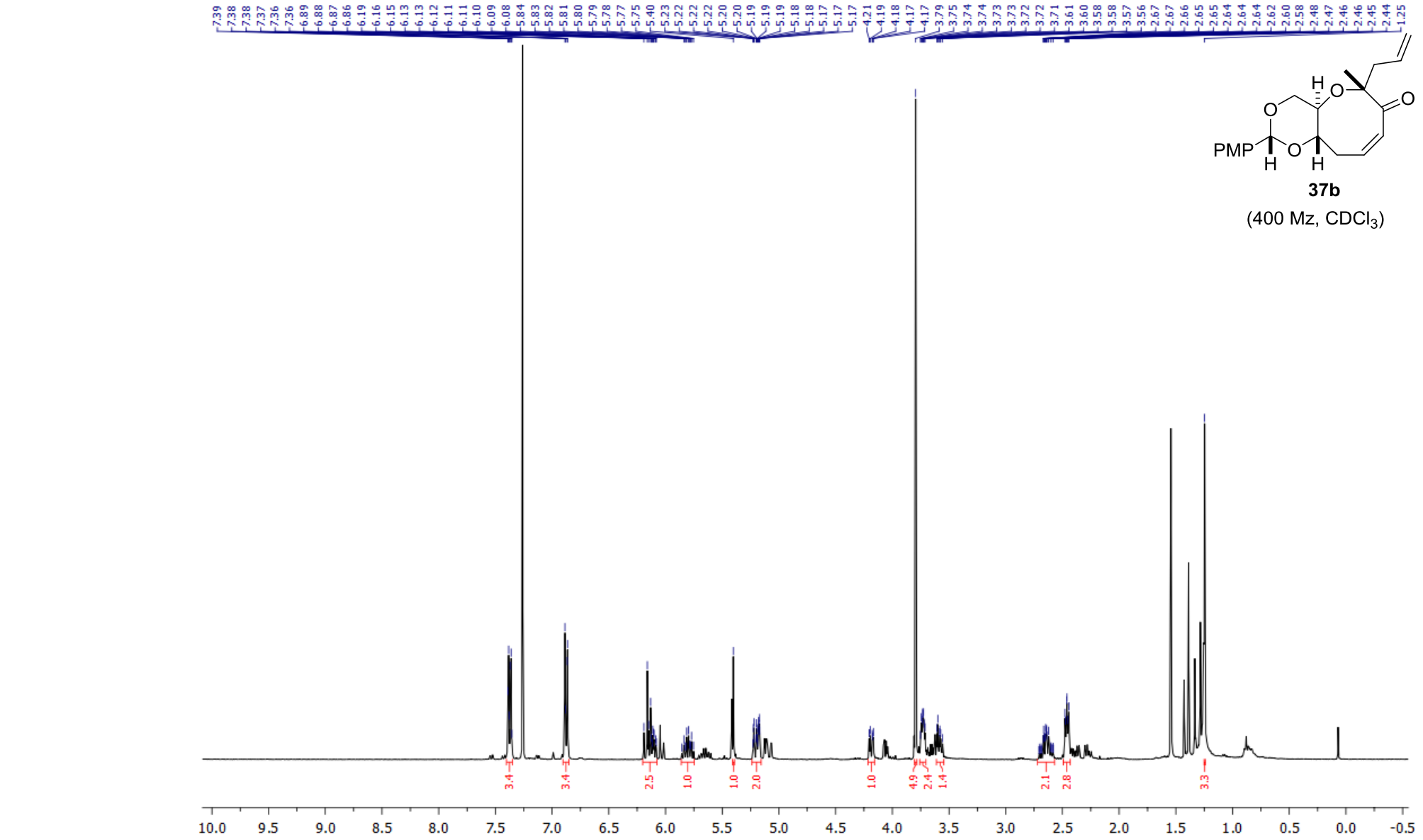

207.06
160.33
136.96
133.21
129.71
127.54
127.22
118.60
113.86
101.29
79.99
75.36
73.54
67.10
55.47
38.27
37.75
PMP
O
H
36b
(101 Mz, CDCl3)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

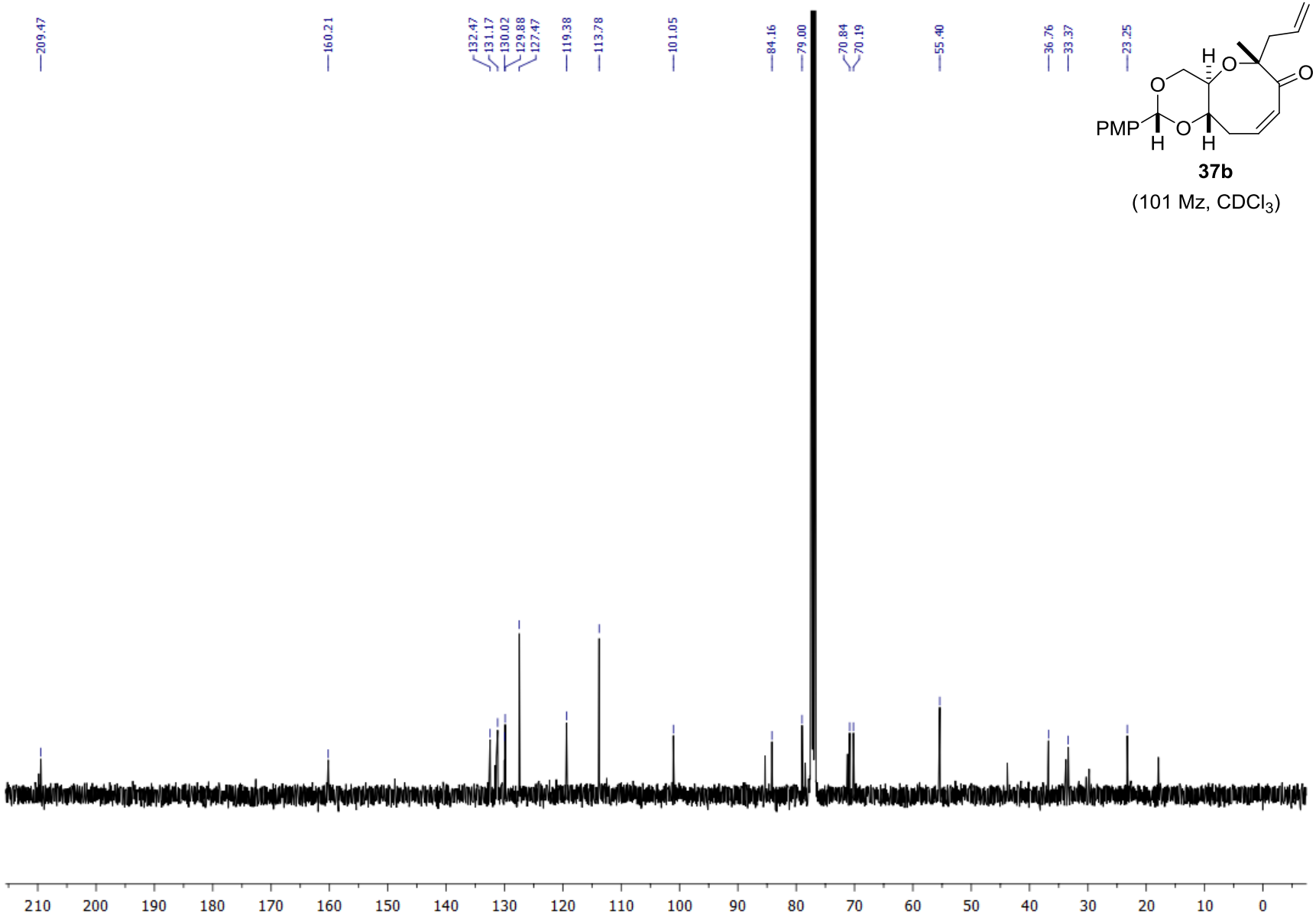

PMP
H
O
O
O
O
H
H
37a
(400 Mz, CDCl3)



37a

(101 Mz, $CDCl_3$)


PMP
H
O
O
O
O
H
H
37b
(400 Mz, CDCl3)



37b

(101 Mz, $CDCl_3$)