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SUPPORTING INFORMATION

Synthesis, Conformational Preferences, and Biological Activity of Conformational Analogues of the Microtubule-Stabilizing Agents, (–)-Zampanolide and (–)-Dactylolide

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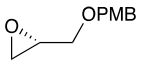
General Information

Unless otherwise noted, all materials were used as received from a commercial supplier without further purification. All anhydrous reactions were performed using oven-dried or flame-dried glassware, which was then cooled under vacuum and purged with nitrogen gas. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene (PhMe), and diethyl ether (Et_2O) were filtered through activated alumina under nitrogen. Triethylamine (TEA) and N,N-diisopropylethylamine (*i*-Pr_2NEt) were distilled over CaH_2 and stored over KOH pellets. 4 Å molecular sieves were oven-dried overnight and then cooled under high vacuum prior to use. All reactions were monitored by Silicycle analytical thin layer chromatography (TLC) plates (AL SIL G/UV, glass back) and analyzed with 254 nm UV light and/or anisaldehyde – sulfuric acid or potassium permanganate treatment. Silica gel for column chromatography was purchased from Silicycle (Silica Gel 60, 230-400 mesh). Unless otherwise noted, all ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO d6 using either Bruker 400 spectrometers operating at 400.13 MHz for ^1H and 100.61 MHz for ^{13}C, or Varian VNMRS 600 operating at 599.87 MHz for 1H and 150.84 MHz for ^{13}C. Chemical shifts (δ) were reported in ppm relative to residual $CHCl_3$ as an internal reference (^1H: 7.26 ppm, ^{13}C: 77.16 ppm). Coupling constants (J) were reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), x (septet), h (heptet), b (broad), and m (multiplet). Mass spectra (FAB) were obtained at the Department of Chemistry and Biochemistry, University of Notre Dame using either a JEOL AX505HA or JEOL JMS-GCmate mass spectrometer.

Experimental Methods

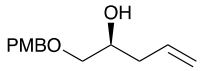


(S)-2-(((4-methoxybenzyl)oxy)methyl)oxirane: (4-methoxyphenyl)methanol (22 g, 20 mL, 1 eq, 0.16 mol) was slowly added to a vigorously stirred flask charged with 40% wt/wt NaOH (150 g NaOH in 230 mL of water) solution at 0 °C. 2-(chloromethyl)oxirane (60 g, 51 mL, 4 eq, 0.64 mol) was added by syringe pump over 30 min followed by tetrabutylammonium iodide (3.0 g, .05 Eq, 8.1 mmol). The solution was allowed to warm to 23 °C and stir for 3 days. The solution was diluted with water (250 mL) and Et_2O (250 mL). The aqueous layer was washed with Et_2O (100 mL x 3). The organics were dried with brine (100 mL), $MgSO_4$ and concentrated. The solution was purified via vacuum distillation (~.5 torr; 150° C) to afford 2-(((4-methoxybenzyl)oxy)methyl)oxirane (23 g, 74 %) as a clear oil.

In a round bottom flask charged with a stir bar and air, toluene (0.91 mL) was added to (*R,R*)-(−)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (193 mg, 0.0050 eq, 595 µmol) followed by an addition of acetic acid (71.4 mg, 0.07 mL, 0.010 eq, 1.19 mmol). The solution was stirred vigorously at room temp for 1 h. The solvent was removed to afford a brown residue. At this point 2-(((4-methoxybenzyl)oxy)methyl)oxirane (23.1 g, 1 eq, 119 mmol) in 1.00 mL of THF was added to the residue and stirred at 0 °C until the brown residue was

dissolved. Water (1.18 g, 1.18 mL, 0.55 eq, 65.4 mmol) was added dropwise to the solution and was allowed to slowly warm to 23° C and stirred for 16 hours. The resulting solution was concentrated *in vacuo.* The resulting residue was purified by vacuum distillation (~0.5 torr; 150° C) to afford (S)-2-(((4-methoxybenzyl)oxy)methyl)oxirane (9.70 g, 42 %) as a clear oil.

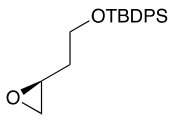
$[\alpha]_D^{23}$ = -3.5 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.28 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.55 (d, J = 11.5 Hz, 1H), 4.49 (d, J = 11.5 Hz, 1H), 3.81 (s, 3H), 3.73 (dd, J = 11.4, 3.1 Hz, 1H), 3.41 (dd, J = 11.4, 5.9 Hz, 1H), 3.20-3.16 (m, 1H), 2.80 (dd, J = 5.0, 4.3 Hz, 1H), 2.61 (dd, J = 5.0, 2.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 159.4, 130.1, 129.6, 114.0, 73.1, 70.7, 55.4, 51.0, 44.5; **HRMS-ESI** (m/z): calcd. for C11H14NaO3 [M + Na]+: 217.0841, found 217.0853



11

(S)-1-((4-methoxybenzyl)oxy)pent-4-en-2-ol:
(S)-2-(((4-methoxybenzyl)oxy)methyl)oxirane (3.00 g, 1.00 eq, 15.0 mmol), copper(I) iodide (730 mg, 0.25 eq, 3.75 mmol), and THF (80.0 mL, M = 0.15) were added to a round bottom flask charged with a stir bar and Ar. The solution was cooled to -78 °C and vinylmagnesium bromide (23.0 mL, 1.50 eq, 23.0 mmol) was added in one portion, stirred for 5 min and was warmed to rt. The deep purple solution was quenched with 4:1 NH_4Cl:NH_4OH buffer (100 mL) and stirred overnight. The solution was diluted with water (200 mL) and separated. The aqueous layer was extracted with EtOAc (50 mL x 3). The organic layer was washed with brine (100 mL), dried $MgSO_4$ and then concentrated. The solution was purified via flash column chromatography (2:1 Hex:Et_2O) to afford alcohol **11** (3.30 g, 96%) as a yellow oil.

$[\alpha]_D^{23}$ = +2.7 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.82 (ddt, J = 17.1, 10.1, 7.1 Hz, 1H), 5.14-5.08 (m, 2H), 4.49 (s, 2H), 3.90-3.84 (m, 1H), 3.81 (s, 3H), 3.49 (dd, J = 9.5, 3.4 = Hz, 1H), 3.34 (dd, J = 9.5, 7.5 Hz, 1H), 2.32 (s, br, 1H), 2.25 (t, J = 6.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 159.4, 134.4, 130.2, 129.5, 117.8, 114.0, 73.7, 73.2, 69.8, 55.4, 38.0 **HRMS-ESI** (m/z): calcd. for C13H18NaO3 [M + Na]+: 245.1154, found 245.1148.

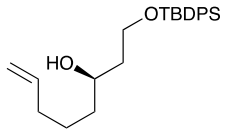


8

(S)-tert-butyl(2-(oxiran-2-yl)ethoxy)diphenylsilane: Epoxide **8** was prepared using known literature procedures.[1]

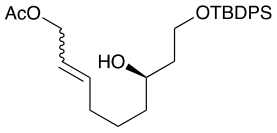
$[\alpha]_D^{23}$ = -6.3 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.62-7.66 (m, 4H), 7.45-7.26 (m, 6H), 3.87-3.78 (m, 2H), 3.13-3.08 (m, 1H), 2.79 (dd, J = 5.0, 4.1 Hz, 1H), 2.52 (dd, J = 5.1, 2.8 Hz, 1H),

1.80-1.75 (m, 2H), 1.06 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 135.7, 135.7, 133.8, 133.8, 129.8, 127.8, 61.0, 50.3, 47.4, 35.8, 27.0, 19.3 **HRMS-ESI** (m/z): calcd. for C20H27O2Si [M + H]+: 327.1780, found 327.1775.



(R)-1-((tert-butyldiphenylsilyl)oxy)oct-7-en-3-ol: In a flame-dried 100 mL two-necked flask containing a reflux condenser and stir bar was added magnesium turnings (1.70 g, 71.1 mmol, 3.00 eq), 1-butenyl bromide (7.21 mL, 71.1 mmol, 3.00 eq), 1,2-dibromoethane (1-2 drops), and dry THF (50 mL). The resulting solution was heated gently to reflux with stirring which initiated the Grignard reaction (CAUTION: extremely exothermic). The refluxing solution became dark grey and was stirred until the magnesium turnings dissolved completely. In a separate 500 mL round bottom flask was added the known epoxide **8** (7.76 g, 23.7 mmol, 1.00 eq), dry THF (50 mL, M = 0.24), and CuI (1.13 g, 5.92 mmol, 0.25 eq). This flask was then cooled to -78 °C using a dry ice/acetone bath. Once the Grignard reaction had completed, the freshly prepared Grignard reagent was added in one portion via syringe to the cooled epoxide/THF/CuI reaction mixture giving a deep purple solution. After 5 min at -78 °C, the resulting dark purple reaction mixture was warmed to 0 °C and stirred at this temperature for 1 h. After 1 h, the reaction mixture was quenched carefully with saturated aqueous NH4Cl (80 mL) at 0 °C followed by 28% NH_4OH aqueous solution (20 mL). The reaction mixture was stirred for 15 min and then diluted with water (80 mL). The layers were separated, and the aqueous layer extracted with Et_2O (50 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification was accomplished by flash chromatography on silica gel (10:1 Hex:EtOAc) provided the corresponding alcohol (8.96 g, 23.40 mmol, 99%) as a colorless oil.

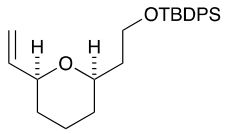
$[\alpha]_D^{23}$ = +5.5 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4H), 7.47-7.38 (m, 6H), 5.82 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.00 (d, J = 17.1 Hz, 1H), 4.95 (d, J = 10.2 Hz, 1H), 3.91-3.83 (m, 3H), 3.29 (d, J = 2.7 Hz, 1H), 2.11-2.05 (m, 2H), 1.79-1.61 (m, 2H), 1.59-1.50 (m, 2H), 1.49-1.40 (m, 2H), 1.05 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 139.0, 135.7, 135.7, 133.1, 133.0, 130.0, 130.0, 127.9, 114.6, 71.9, 63.8, 38.4, 37.1, 33.9, 26.9, 25.0, 19.2 **HRMS-ESI** (m/z): calcd. for C24H34NaO2Si [M + Na]+: 383.2406, found 383.2419.



(R)-9-((tert-butyldiphenylsilyl)oxy)-7-hydroxynon-2-en-1-yl acetate: In a flame-dried two-necked flask containing a reflux condenser and stir bar was added alkene-ol (1.02 g, 2.66 mmol, 1.00 eq)**,** (*Z*)-but-2-ene-1,4-diyl diacetate (4.57 g, 26.6 mmol, 10.0 eq) and DCM (30.0 mL, 0.10 M). The resulting solution was degassed with argon for 30 min. Grubbs II generation catalyst (113 mg, 0.13 mmol, 0.05 eq) was added in one portion, and the purple solution was heated to

reflux. After 18 h, the resulting brown solution was allowed to cool to room temperature and concentrated in vacuo. Purification[2] by flash chromatography on silica gel (20:1 →10:1→8:1→5:1→3:1→2:1 Pentane: Et_2O) provided the corresponding allylic acetate (1.18 g, 2.61 mmol, 98%, 9:1 *E:Z*) as a brown oil.

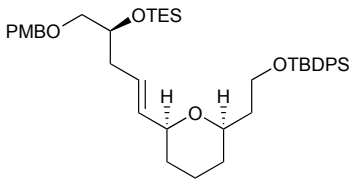
$[\alpha]_D^{23}$ = +7.9 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4H), 7.47-7.38 (m, 6H), 5.78 (td, J = 15.4 Hz, 1H), 5.58 (d, J = 15.4 Hz, 1H), 4.62 (d, J = 6.8 Hz, 0.2H), 4.51 (d, J = 6.5 Hz, 1.8H), 3.93-3.82 (m, 3H), 3.35 (s, br, 1H), 2.10-2.06 (m, 2H), 2.06 (s, 3H), 1.76-1.62 (m, 2H), 1.62-1.51 (m, 2H), 1.49-1.40 (m, 2H), 1.05 (s, 9H) **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 171.0, 136.4, 135.7, 135.6, 133.1, 132.9, 130.0, 130.0, 127.9, 124.1, 71.8, 65.4, 63.7, 38.4, 37.1, 32.3, 26.9, 24.9, 21.1, 19.1; **HRMS-ESI** (m/z): calcd. for C27H3O4Si [M + H]+: 455.2618, found 455.2512.



10

tert-butyldiphenyl(2-((2R,6S)-6-vinyltetrahydro-2H-pyran-2-yl)ethoxy)silane: In a flame-dried 25 mL cone shaped flask containing a stir bar was added freshly prepared $Pd_2(dba)_3{\cdot}CHCl_3$[3] (0.05 g, 0.04 mmol, 0.02 eq), (*S,S*)-DACH-phenyl Trost ligand[3] (0.091 g, 0.132 mmol, 0.06 eq), and dry DCM (15.0 mL, 0.15 M). The reaction mixture was stirred for 20 min allowing the initial purple homogenous solution to turn bright orange. In a separate flame-dried 100 mL round bottom flask containing a stir bar was added the allylic acetate (1.00 g, 2.20 mmol, 1.00 eq) and dry DCM (15.0 mL, 0.15 M) and the flask cooled to 0 °C. The catalyst solution was then added via cannula to the allylic acetate solution and the reaction mixture warmed to room temperature and stirred for 12 h. After 12 h, the reaction mixture was concentrated under reduced pressure giving an orange oil. Purification by flash chromatography on silica gel (10:1 Hex:EtOAc) provided *cis*-pyran **10** (0.82 g, 2.09 mmol, 95%, 10:1 dr) as a colorless oil.

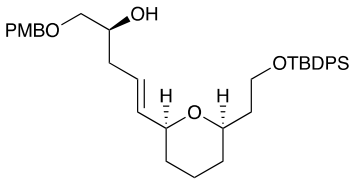
$[\alpha]_D^{23}$ = -16.4 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.68-7.65 (m, 4H), 7.43-7.34 (m, 6H), 5.86 (ddd, J = 17.3, 10.6, 5.2 Hz, 1H), 5.21 (td, J = 17.4, 1.6 Hz, 1H), 5.08 (td, J = 10.6, 1.6 Hz, 1H), 3.90-3.79 (m, 2H), 3.73 (td, J = 10.0, 5.5 Hz, 1H), 3.65-3.59 (m, 1H), 1.88-1.50 (m, 6H), 1.34-1.16 (m, 2H), 1.04 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 139.8, 135.7, 135.7, 134.2, 134.1, 129.6, 129.6, 127.7, 114.3, 78.2, 74.4, 60.4, 39.5, 31.6, 27.0, 23.8, 19.4, 0.14; **HRMS-ESI** (m/z): calcd. for C25H35O2Si+ [M + H]+: 395.2406, found 395.2401.



***tert*-butyl(2-((2*R*,6*S*)-6-((*S*,*E*)-5-((4-methoxybenzyl)oxy)-4-((triethylsilyl)oxy)pent-1-en-1-yl)tetrahydro-2*H*-pyran-2-yl)ethoxy)diphenylsilane:** To a flame-dried two-neck flask containing a stir bar and a reflux condenser, homoallylic alcohol **11** (0.56 g, 2.53 mmol, 2.00 eq), and vinyl pyran **10** (0.50 g, 1.27 mmol, 1.00 eq) was added dry DCM (12.5 mL, 0.11 M). This solution was deoxygenated with argon gas for 20 min and then Grubbs II generation catalyst (0.22 g, 0.25 mmol, 0.20 eq) was added resulting in a purple solution. The resulting reaction mixture was refluxed for 18 h. The dark brown solution was cooled to room temperature and concentrated under reduced pressure giving a brown oil. Purification of this crude oil by flash chromatography on silica gel (5:1 →3:1 Hex:EtOAc) provided an inseparable mixture of the homoallylic alcohol **11** and the cross metathesis product **7** as a yellow oil. The unreacted pyran starting material was re-isolated affording 60 mg (0.15 mmol, 12%) of the clear oil

The mixture of alcohols and DMF (5.0 mL, 0.30 M) were added to a flame-dried round bottom flask charged with a stir bar and argon. Imidazole (518 mg, 7.62 mmol, 6.00 eq) and TESCl (0.64 mL, 3.81 mmol, 3.00 eq) were added stirred for 18 h The brown solution was diluted with water (20 mL) and extracted with Et_2O (10 mL x 3). The organic layer was washed with brine (20 mL) and dried with $MgSO_4$. The solution was then concentrated under reduced pressure. The residue was purified via flash column chromatography (50:1 →20:1→10:1 Hex:Et_2O) to afford the silyl ether (0.70 g, 0.99 mmol, 78% (90% brsm)) as a clear colorless oil over two steps.

$[\alpha]_D^{23}$ = -11.7 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.65 (m, 4H), 7.43-7.34 (m, 6H), 7.24 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.63 (td, J = 15.7, 6.7 Hz, 1H), 5.52 (dd, J = 15.7, 5.5 Hz, 1H), 4.43 (s, 2H), 3.87-3.80 (m, 2H), 3.80 (s, 3H), 3.77-3.69 (m, 2H), 3.60-3.55 (m, 1H), 3.34 (d, J = 5.3 Hz, 2H), 2.30 (td, J = 14.0, 6.7 Hz, 1H), 2.20 (td, J = 14.0, 6.7 Hz, 1H), 1.84-1.75 (m, 2H), 1.73-1.64 (m, 2H), 1.56-1.46 (m, 2H), 1.29-1.16 (m, 2H), 1.04 (s, 9H), 0.93 (t, J = 7.9 Hz, 9H), 0.58 (q, J = 7.9, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 159.2, 135.7, 135.7, 134.3, 134.2, 134.1, 130.7, 129.6, 129.4, 129.3, 127.7, 127.2, 113.8, 78.0, 74.5, 74.1, 73.1, 71.5, 60.5, 55.4, 39.5, 38.1, 31.7, 31.6, 27.0, 23.8, 19.4, 7.0, 5.1; **HRMS-ESI** (m/z): calcd. for C42H63O5Si2 [M + H]+: 703.4214, found 703.4209.

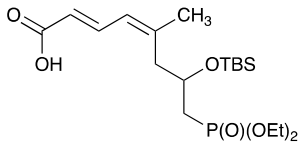


7

(*S*,*E*)-5-((2*S*,6*R*)-6-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)tetrahydro-2*H*-pyran-2-yl)-1-((4-methoxybenzyl)oxy)pent-4-en-2-ol: The silyl ether (0.62 g, 0.88 mmol, 1.00 eq) and MeCN:H_2O (2.81 mL, 8:1) were added to a round bottom flask charged with a stir bar and argon. The flask was cooled to 0 °C and TFA (0.31 mL) was added and stirred for 30 min. The cloudy solution was carefully quenched with $NaHCO_3$ (sat) (until the pH =7-8 by litmus paper; ~10 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (20 mL x 3). The organic layer was washed with brine (20 mL), dried $MgSO_4$, and concentrated in vacuo. The solution was purified via flash

column chromatography (5:1 →3:1 Hex:EtOAc) to afford alcohol **7** (485 mg, 0.82 mmol, 93%) as a clear colorless oil.

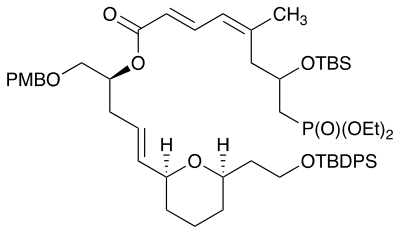
$[\alpha]_D^{23}$ = -12.3 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.68-7.64 (m, 4H), 7.42-7.34 (m, 6H), 7.25 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.63 (td, J = 15.7, 6.7 Hz, 1H), 5.56 (dd, J = 15.7, 4.9Hz, 1H), 4.46 (s, 2H), 3.87-3.82 (m, 2H), 3.80 (s, 3H), 3.77-3.75 (m, 1H), 3.72 (td, J = 10.0, 5.7 Hz, 1H), 3.61-3.55 (m, 1H), 3.47 (dd, J = 9.5, 3.4 Hz, 1H), 3.33 (dd, J = 9.5, 7.4 Hz, 1H), 2.30-2.17 (m, 2H), 1.84-1.75 (m, 2H), 1.73-1.65 (m, 2H), 1.61-1.51 (m, 2H), 1.32-1.14 (m, 2H), 1.04 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 159.4, 135.7, 135.7, 134.9, 134.2, 134.1, 130.2, 129.6, 129.6, 129.5, 129.5, 127.7, 126.2, 114.0, 77.8, 74.5, 73.7, 73.1, 70.0, 60.4, 55.4, 39.5, 36.7, 31.8, 31.5, 27.0, 23.7, 19.4; **HRMS-ESI** (m/z): calcd. for C36H49O5Si [M + H]+: 589.3349, found 589.3344.



6

(2*E*,4*Z*)-7-((*tert*-butyldimethylsilyl)oxy)-8-(diethoxyphosphoryl)-5-methylocta-2,4-dienoic acid: The acid prepared using the known procedure reported by Altmann and coworkers.[1]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (dd, J = 15.2, 11.7 Hz, 1H), 6.11 (d, J = 11.7 Hz, 1H), 5.77 (d, 15.2, 1H), 4.18-4.08 (m, 5H), 2.69 (dd, J = 13.4, 8.4, 1H), 2.54 (dd, J = 13.4, 8.4, 1H), 2.09-1.99 (m, 2H), 1.93 (s, 3H), 1.33 (dt, J = 7.1, 2.8 Hz, 6H), 0.84 (s, 9H), 0.05 (s, 3H), -0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ =171.5, 148.0, 143.0, 126.5, 118.8, 67.4, 6.19 (dd, J = 6.5, 1.3 Hz), 41.7 (d, J = 3.6 Hz), 35.2 (d, J = 134.7 Hz), 27.1, 25.9, 25.7, 18.0, 16.6 (d, J = 6.1 Hz), -4.6, -4.7; **HRMS-ESI** (m/z): calcd. for C19H38O6PSi [M + H]+: 421.2175, found 421.2170.

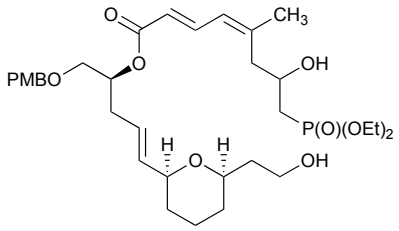


12

(*S*,*E*)-5-((2*S*,6*R*)-6-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)tetrahydro-2*H*-pyran-2-yl)-1-((4-methoxybenzyl)oxy)pent-4-en-2-yl-(2*E*,4*Z*)-7-((*tert*-butyldimethylsilyl)oxy)-8-(diethoxyphosphoryl)-5-methylocta-2,4-dienoate: A solution of acid **6** (1.24 g, 3.00 mmol, 1.30 eq) and NEt_3 (0.95 ml, 0.39 mmol, 3.00 eq) in toluene (11.0 mL, 0.10 M) was added to a flame-dried round-bottom flask with a stir bar under Ar. 2,4,6-trichlorobenzoyl chloride (0.64 ml, 4.10

mmol, 1.80 eq) was subsequently added at room temperature, producing a cloudy pale yellow solution and was stirred for 1 h; then a solution of alcohol **7** (1.34 g, 2.30 mmol, 1.00 eq) and DMAP (278 mg, 2.30 mmol, 1.00 eq) in toluene (9.00 ml (the mixture was sonicated to produce a clear solution); plus 2 x 0.5 ml from rinsing)) was added, resulting in the immediate formation of an off-white suspension. After 1 h of stirring, $NaHCO_3$ (sat) (10 mL) and EtOAc (20 mL) were added and the phases were separated. The aqueous layer was extracted with EtOAc (20 mL x 3), and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (1:3→1:1 EtOAc:Hex) afforded ester **12** (1.77 g, 1.80 mmol, 79%) as a clear yellow oil.

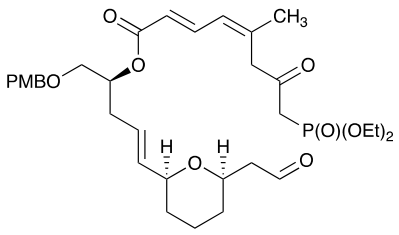
$[\alpha]_D^{23}$ = -9.2 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.64 (m, 4H), 7.59 (dd, J = 15.1, 11.7 Hz, 1H), 7.41-7.34 (m, 6H), 7.23 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.0 Hz, 2H), 6.06 (d, J = 11.4 Hz, 1H), 5.80 (d, J = 15.1 Hz, 1H), 5.54 (m, 2H), 5.10-5.05 (m, 1H), 4.49 (d, J = 11.7, 1H), 4.41 (dd, J =11.8, 2.9 Hz, 1H), 4.18-4.07 (m, 5H), 3.86-3.80 (m, 1H), 3.79 (s, 3H), 3.74-3.68 (m, 2H), 3.59-3.53 (m, 1H), 3.51 (d, J = 5.8 Hz, 2H), 2.64-2.53 (m, 2H), 2.41-2.39 (m, 2H), 2.01 (dd, J = 18.6, 6.2 Hz, 2H), 1.89 (s, 3H), 1.83-1.75 (m, 2H), 1.72-1.64 (m, 1H), 1.56-1.52 (m, 1H), 1.33 (dt, J = 7.1, 3.2, 6H), 1.28 (m, 2H), 1.03 (s, 9H), 0.83 (s, 9H), 0.05 (s, 3H), -0.03 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): (There were more C13 peaks than expected due to the diastereotopic nature of the compound) δ = 167.0, 159.3, 146.3 146.3, 141.5, 141.5, 135.7, 135.7, 135.1, 135.1, 134.2, 134.1, 130.3, 129.6, 129.5, 129.4, 127.7, 126.8, 125.4, 125.4, 119.7, 119.7, 113.9, 77.8, 74.5, 72.9, 72.1 (d, J = 5.1 Hz), 70.2, 66.9, 61.7 (dd, J = 6.5, 2.1 Hz), 60.4, 55.4, 41.8 (d, J = 4.7 Hz), 39.5, 35.9, 34.5, 34.1, 31.7, 31.5, 27.0, 25.9, 25.2,23.7, 19.4, 17.9, 16.6, 16.6, -4.7; **HRMS-ESI** (m/z): calcd. for C55H84O10PSi2 [M + H]+: 991.5341, found 991.5335.



(*S*,*E*)-5-((2*S*,6*R*)-6-(2-hydroxyethyl)tetrahydro-2*H*-pyran-2-yl)-1-((4-methoxybenzyl)oxy)pent-4-en-2-yl (2*E*,4*Z*)-8-(diethoxyphosphoryl)-7-hydroxy-5-methylocta-2,4-dienoate: Ester **12** (531 mg, 0.54 mmol, 1.00 eq) in THF (22.0 mL) was prepared in an oven-dried PTFE round-bottom flask equipped with a stir bar. 70% HF•py (5.30 mL) was carefully added at 0 °C. The mixture was warmed to room temperature after 5 min and continued stirring for 6 h. The solution was carefully pulled into a syringe and added to a vigorously stirred mixture of excess $NaHCO_3$ (sat) (200 mL) and EtOAc (200 mL); after ensuring the pH of the aqueous phase was neutral (pH = 7-8; litmus paper) the phases were separated. The aqueous phase was extracted with EtOAc (50 mL x 3). The combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography

(1:0 -> 1:1 EtOAc:Acetone) to afford the diol (307 mg, 0.48 mmol, 92%) as a colorless, viscous oil.

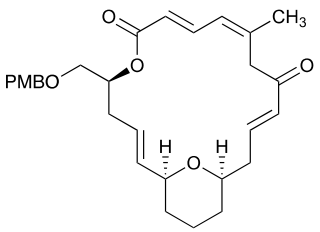
$[\alpha]_D^{23}$ = -14.6 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.55-7.49 (m, 1H), 7.21 (d, J = 7.7 Hz, 2H), 6.84 (d, J = 8.6 Hz 2H), 6.10 (d, J = 11.7 Hz, 1H), 5.80 (d, J = 15.0 Hz, 1H), 5.55-5.46 (m, 2H), 5.08-5.03 (m, 1H), 4.47 (dd, J = 11.7, 1.7 Hz, 1H), 4.40 (dd, J = 11.7, 2.3 Hz, 1H), 4.17-4.14 (m, 1H), 4.13-4.05 (m, 4H), 3.77 (s, 3H), 3.73-3.71 (m, 2H), 3.63 (s, br, 1H), 3.56-3.53 (m, 1H), 3.51-3.46 (m, 2H), 3.01 (s, br, 1H), 2.62-2.56 (m, 1H), 2.46-2.39 (m, 1H), 2.38-2.28 (m, 2H), 1.93-1.88 (m, 5H), 1.80-1.78 (m, 1H), 1.75-1.69 (m, 1H), 1.65-1.62 (m, 1H), 1.53-1.45 (m, 3H), 1.30 (t, J = 7.1 Hz, 6H), 1.27-1.22 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): (There were more C13 peaks than expected due to the diastereotopic nature of the compound) δ = 167.0, 167.0, 159.2, 145.6, 145.6, 140.5, 140.4, 134.7, 134.6, 130.2, 129.4, 126.7, 126.7, 125.8, 125.7, 120.1, 120.1, 113.8, 78.1, 78.0, 76.9, 72.8, 71.9, 70.2, 70.1, 65.3 (d, J = 4.6 Hz), 65.2 (d, J = 4.6 Hz), 62.1 (d, J = 6.3 Hz) 61.9 (d, J = 6.6 Hz), 61.3, 55.3, 41.3 (d, J = 4.7 Hz), 41.1 (d, J = 4.9 Hz), 38.2, 34.1, 34.0, 33.5, (d, J = 138.6 Hz), 33.4, (d, J = 138.6 Hz), 31.5, 31.3, 25.0, 24.9, 23.3, 16.5, (d, J = 2.4 Hz), 16.4, (d, J = 2.4 Hz); **HRMS-ESI** (m/z): calcd. for C33H52O10P [M + H]+: 639.3298, found 639.3293.



(*S*,*E*)-1-((4-methoxybenzyl)oxy)-5-((2*S*,6*R*)-6-(2-oxoethyl)tetrahydro-2*H*-pyran-2-yl)pent-4-en-2-yl (2*E*,4*Z*)-8-(diethoxyphosphoryl)-5-methyl-7-oxoocta-2,4-dienoate: The diol (261 mg, 0.41 mmol, 1.00 equiv) was charged in a flame-dried round bottom flask and dissolved in DCM (4.10 mL, M = 0.10). DMP (1.04 g, 0.41 mmol, 6.00 eq, addition in two equal portions, second addition after 30 min) was added at rt. After 2 h EtOAc (10 mL) and a mixture of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL) were added then stirring was continued for 1 h. When two clear phases had formed, the phases were separated. The aqueous phase was extracted with EtOAc (5 mL x 3), and the combined organic extracts were dried over $MgSO_4$. Concentration of the solution under reduced pressure and purification of the residue by flash chromatography (EtOAc, 1% AcOH to deactivate the stationary phase) gave the β-ketophosphonate ester (216 mg, 0.34 mmol, 83%) as a pale-yellow oil.

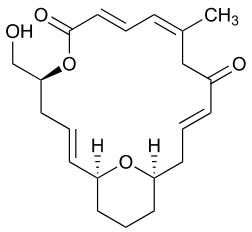
$[\alpha]_D^{23}$ = -7.4 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 9.76 (s, 1H), 7.38 (dd, J = 14.9, 11.7 Hz, 1H), 7.21 (d, J = 8.4, 2H), 6.85 (d, J = 8.5 Hz, 2H), 6.19 (d, J = 11.5 Hz, 1H), 5.85 (d, J = 15.0 Hz, 1H), 5.54-5.50 (m, 2H), 5.10-5.04 (m, 1H), 4.49-4.39 (m, 2H), 4.17-4.13 (m, 4H), 3.87-3.85 (m, 1H), 3.78 (s, 4H), 3.62 (s, 2H), 3.49-3.48 (m, 2H), 3.13 (s, 1H), 3.08 (s, 1H), 2.59 (ddd, J = 16.3, 7.5, 2.1 Hz, 1H), 2.45 (ddd, J = 16.3, 5.0, 1.6 Hz, 1H), 2.41-2.32 (m, 2H), 1.93-1.82 (m, 4H), 1.61-1.53 (m, 3H), 1.34-1.22 (m, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 201.7, 198.3, 166.8, 159.3, 140.9, 139.8, 134.5, 130.2, 129.4, 127.5, 125.8, 121.1, 113.9, 78.1, 73.0, 72.9, 72.1, 70.1, 62.9

(d, J = 6.4 Hz), 55.3, 50.1, 47.6, 42.7 (d, J = 127 Hz), 34.0, 31.3, 31.2, 25.0, 23.3, 16.4 (d, J = 6.1 Hz); **HRMS-ESI** (m/z): calcd. for C33H47NaO10P [M + Na]+: 657.2805, found 657.2791.



(1*S*,2*E*,5*S*,8*E*,10*Z*,14*E*,17*R*)-5-(((4-methoxybenzyl)oxy)methyl)-11-methyl-6,21-dioxabicyclo[15.3.1]henicosa-2,8,10,14-tetraene-7,13-dione: β-ketophosphonate ester (216 mg, 0.34 mmol, 1.00 eq) in THF/H_2O (40:1, 113 ml) was prepared in a round bottom flask with a stir bar. Freshly activated $Ba(OH)_2•8H_2O$ (140 mg, 0.44 mmol, 1.30 eq) was added at 0 °C. The orange solution was stirred for 30 min and warmed to room temperature. The solution was stirred for 4 h until it was quenched by adding EtOAc (100mL) followed by washing the organic layer with $NaHCO_3$ (50 mL) and then with brine (50 mL). The clear organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography (3:1 Hex:EtOAc) to afford the PMB-protected ether (80.0 mg, 0.17 mmol, 49%) as a colorless oil.

$[\alpha]_D^{23}$ = -99.6 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.60 (dd, J = 15.0, 11.6 Hz, 1H), 7.24 (d, J = 8.7 Hz, 2H), 6.89-6.82 (m, 3H), 6.10 (d, J = 11.6 Hz, 1H), 5.96 (d, J = 16.2 Hz, 1H), 5.89 (d, J = 15.0 Hz, 1H), 5.58 (ddd, J = 15.1, 9.5, 5.4 Hz, 1H), 5.42 (dd, J = 15.1, 6.4 Hz, 1H), 5.27-5.21 (m, 1H), 4.52-4.45 (m, 2H), 3.91 (d, J = 14.0 Hz, 1H), 3.80 (s, 3H), 3.74 (dd, J = 10.2, 6.6 Hz, 1H), 3.58 (dd, J = 10.2, 5.8 Hz, 1H), 3.51 (dd, J = 10.2, 5.2 Hz, 1H), 3.38 (ddd, J = 8.8, 8.8, 2.3 Hz, 1H), 3.23 (d, J = 14.0 Hz, 1H), 2.42-2.37 (m, 1H), 2.34-2.20 (m, 3H), 1.85-1.81 (m, 4H), 1.53-1.48 (m, 2H), 1.26-1.20 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 198.0, 166.9, 159.3, 146.6, 142.8, 139.4, 134.7, 131.4,130.2, 129.4, 126.0, 125.7, 121.3, 113.9, 78.1, 75.8, 73.0, 71.4, 70.9, 55.4, 44.9, 40.3, 35.4, 32.3, 31.6, 24.0, 23.5; **HRMS-ESI** (m/z): calcd. for C29H37O6 [M + H]+: 481.2590, found 481.2585.

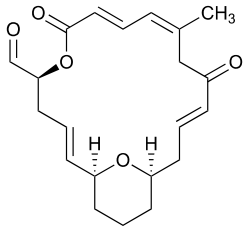


3

(1*S*,2*E*,5*S*,8*E*,10*Z*,14*E*,17*R*)-5-(hydroxymethyl)-11-methyl-6,21-dioxabicyclo[15.3.1]henicosa-2,8,10,14-tetraene-7,13-dione: PMB protected alcohol (118 mg, 0.25 mmol, 1.00 equiv) was dissolved in DCM:H_2O (5:1, 4.80 mL) buffer in a round bottom flask charged with a stir bar. DDQ (167 mg, 0.74 mmol, 3.00 equiv) was added at 0 °C, and the mixture was vigorously stirred for 4

h; the resulting reddish pink solution was quenched with $NaHCO_3$ (sat) (10 mL) and DCM (20 mL). The aqueous phase was extracted with DCM (10 mL x 3), and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (3:1→1:1 Hex:EtOAc) delivered alcohol **3** (59.0 mg, 0.16 mmol, 67%) as a colorless amorphous solid.

$[\alpha]_D^{23}$ = -93.4 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.59 (dd, J = 15.0, 11.6 Hz, 1H), 6.86 (ddd, J = 16.1, 8.0, 8.0 Hz, 1H), 6.11 (d, J = 11.5 Hz, 1H), 5.98 (d, J = 16.2 Hz, 1H), 5.88 (d, J = 15.0 Hz, 1H), 5.62 (ddd, J = 15.1, 9.1, 5.6 Hz, 1H), 5.44 (dd, J = 15.3, 6.2 Hz, 1H), 5.12-5.07 (m, 1H), 3.85 (d, J = 14.1 Hz, 1H), 3.77-3.72 (m, 3H), 3.41-3.37 (m, 1H), 3.28 (d, J = 14.1 Hz, 1H), 2.38-2.24 (m, 5H), 1.88-1.82 (m, 4H), 1.53-1.48 (m, 2H), 1.26-1.17 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 197.8, 167.4, 146.5, 143.2, 139.7, 134.7, 131.3, 125.7, 125.6, 120.9, 77.9, 75.8, 74.4, 65.0, 44.9, 40.2, 34.8, 32.2, 31.5, 24.1, 23.4; **HRMS-ESI** (m/z): calcd. for C21H29O5 [M + H]+: 361.2015, found 361.2010.

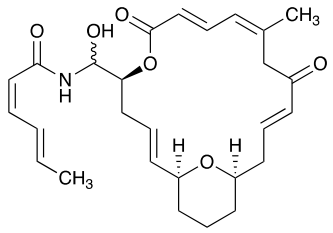


4

(1*S*,2*E*,5*S*,8*E*,10*Z*,14*E*,17*R*)-11-methyl-7,13-dioxo-6,21-dioxabicyclo[15.3.1]henicosa-2,8,10,14-tetraene-5-carbaldehyde: A solution of alcohol **3** (10.2 mg, 0.028 mmol, 1.00 eq) was dissolved in DCM (0.50 ml) in a flame-dried round bottom flask. DMP (48.0 mg, 0.11 mmol, 3.00 eq) added in 2 equal portions in 20 min intervals) at room temperature. Stirring was continued for 60 min then a mixture of $NaHCO_3$ (sat) (5 mL) and $Na_2S_2O_3$ (sat) (5 mL) was added and stirring was continued for 1 h until two clear phases were formed. The phases were separated and then the aqueous phase was extracted with DCM (5 mL x 3), the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified using flash chromatography (3:1 Hex:EtOAc) to afford aldehyde **4** (6.80 mg, 0.019 mmol, 66%) as a colorless solid.

$[\alpha]_D^{23}$ = -85.6 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.57 (d, J = 0.9 Hz, 1H), 7.55 (dd, J = 15.1, 11.7 Hz, 1H), 6.91 (ddd, J = 15.9, 8.0, 7.3 Hz, 1H), 6.18 (d, J = 11.6 Hz, 1H), 6.10 (d, J = 15.9 Hz, 1H), 5.87 (d, J = 15.1 Hz, 1H), 5.66 (ddd, J = 15.4, 7.5, 7.5 Hz, 1H), 5.54 (dd, J = 15.4, 5.2 Hz, 1H), 4.98 (dd, J = 9.9, 3.2 Hz, 1H), 3.77 (dd, J = 11.0, 4.8 Hz, 1H), 3.67 (d, J = 15.5 Hz, 1H), 3.52-3.45 (m, 2H), 2.60 (d, J = 14.7 Hz, 1H), 2.47-2.28 (m, 3H), 1.91-1.82 (m, 4H), 1.56-1.49 (m, 2H), 1.31-1.17 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 198.8, 196.9, 166.4, 146.1, 144.1, 140.7, 135.7, 131.2, 125.8, 123.7, 119.6, 78.0, 75.9, 44.8, 39.8, 32.6, 31.9, 31.4, 29.8, 25.1, 23.5; **HRMS-ESI** (m/z): calcd. for C21H27O5 [M + H]+: 359.1858, found 359.1853.

^{1}H NMR (600 MHz,$(CD_3)_3SO$) δ 9.50 (s, 1H), 7.35 (dd, J = 15.2, 11.6 Hz, 1H), 6.86 (dt, J = 15.2, 7.3 Hz, 1H), 6.26 (d, J = 11.5 Hz, 1H), 6.12 (d, J = 15.9 Hz, 1H), 5.90 (d, J = 15.2 Hz, 1H), 5.63 (dtd, J = 15.3, 7.6, 6.0, 1.4 Hz, 1H), 5.54 (dd, J = 15.5, 4.8 Hz, 1H), 4.99 (dd, J = 9.5, 3.7 Hz, 1H), 3.75 (dd, J = 10.4, 4.8 Hz, 1H), 3.68 (d, J = 16.6 Hz, 1H), 3.57 (d, J = 16.6 Hz, 1H), 3.48 (ddt, J = 11.3, 8.8, 2.7 Hz, 1H), 2.55 (dt, J = 15.0, 6.1, 4.8 Hz, 1H), 2.47 – 2.36 (m, 2H), 2.23 (dt, J = 14.9, 8.2 Hz, 1H), 1.87 (s, 3H), 1.81 – 1.69 (m, 2H), 1.51 (m, 4H).



5

(2*Z*,4*E*)-*N*-((*S/R*)-hydroxy((1*S*,2*E*,5*S*,8*E*,10*Z*,14*E*,17*R*)-11-methyl-7,13-dioxo-6,21-dioxabicyclo[15.3.1]henicosa-2,8,10,14-tetraen-5-yl)methyl)hexa-2,4-dienamide: Amide **13** (14 mg, 0.1 mmol, 4.6 eq) was dissolved in THF (0.50 mL) and DIBAL-H (1M in DCM, 0.10 mL, 0.1 mmol, 3.8 eq) was added. Stirring was continued at room temperature for 45 min. After that time a solution of aldehyde **4** (9.6 mg, 0.03 mmol, 1.0 eq) in THF (0.5 mL, flask rinsed once with 0.5 mL of THF) was added. Stirring continued for a total of 3 h was quenched Rochelle salt (sat) (1 mL) was added as well as EtOAc (1 mL) and stirring was continued for 15 min then brine (1mL) was added followed by separation of phases and extraction with EtOAc (3 mL x 3). The combined organic phases were dried over $MgSO_4$, and the residue was purified using flash chromatography on deactivated stationary phase (3:1 → 1:1 → 1:2 Hex:EtOAc, 2% NEt_3) giving hemiaminal **5** (5.8 mg, 0.01 mmol, 49%) as a 1.5:1.0 mixture of both C20 epimers as a white solid.

^{1}H NMR (400 MHz, $(CD_3)_3SO$): δ = 8.36 (d, J = 9.1 Hz, 1H, isomer 1), 8.28 (d, J = 9.0 Hz, 1H, isomer 2), 7.51-7.41 (m, 2H, isomer 1+2), 6.81-6.72 (m, 1H, isomer 1+2), 6.42- 6.33 (m, 1H, isomer 1+2), 6.24-6.18 (m, 1H, isomer 1+2), 6.11 (d, J = 5.0 Hz, 1H, isomer 2), 6.02-5.92 (m, 3H), 5.88 (d, J =15.0 Hz, 1H, isomer 2), 5.63 (d, J = 11.4 Hz, 1H, isomer 1+2), 5.59-5.52 (m, 1H, isomer 2), 5.51-5.42 (m, 1H, isomer 1), 5.40-5.31 (m, 2H), 4.93-4.88 (m, 1H, isomer 1), 4.86-4.82 (m, 1H, isomer 2), 3.90 (d, J = 14.6, 1H, isomer 1), 3.80 (d, J = 14.7 Hz, 1H, isomer 2), 3.68 (dd, J = 11.2, 7.0 Hz, 1H, isomer 1+2), 3.33-3.31 (m, 1H, isomer 2), 3.18 (d, J = 14.6 Hz, 1H, isomer 1), 2.45-2.42 (m, 1H, isomer 1+2), 2.34-2.12 (m, 4H),1.80-1.71 (m, 9H), 1.50-1.42 (m, 4H), 1.24-1.23 (m, 3H), 1.14-1.09 (m, 4H); **^{13}C NMR** (100 MHz, $(CD_3)_3SO$): δ = 197.2, 197.1, 165.9, 165.6, 165.3, 165.1, 146.2, 146.1, 143.1, 142.8, 140.9, 140.7, 139.7, 139.0, 137.5, 137.2, 134.5, 134.4, 130.7, 128.6, 125.4, 125.2, 125.2, 125.1, 121.1, 120.5, 119.2, 119.0, 77.2, 77.0, 75.1, 75.1, 73.5, 73.4, 72.5, 72.4, 45.7, 44.7, 33.3, 33.2, 31.8, 31.8, 31.1, 31.1, 24.0, 23.9, 22.9, 22.8, 18.4, 18.4; **HRMS-ESI** (m/z): calcd. for C27H35NNaO6 [M + Na]+: 492.2362, found 492.2357.

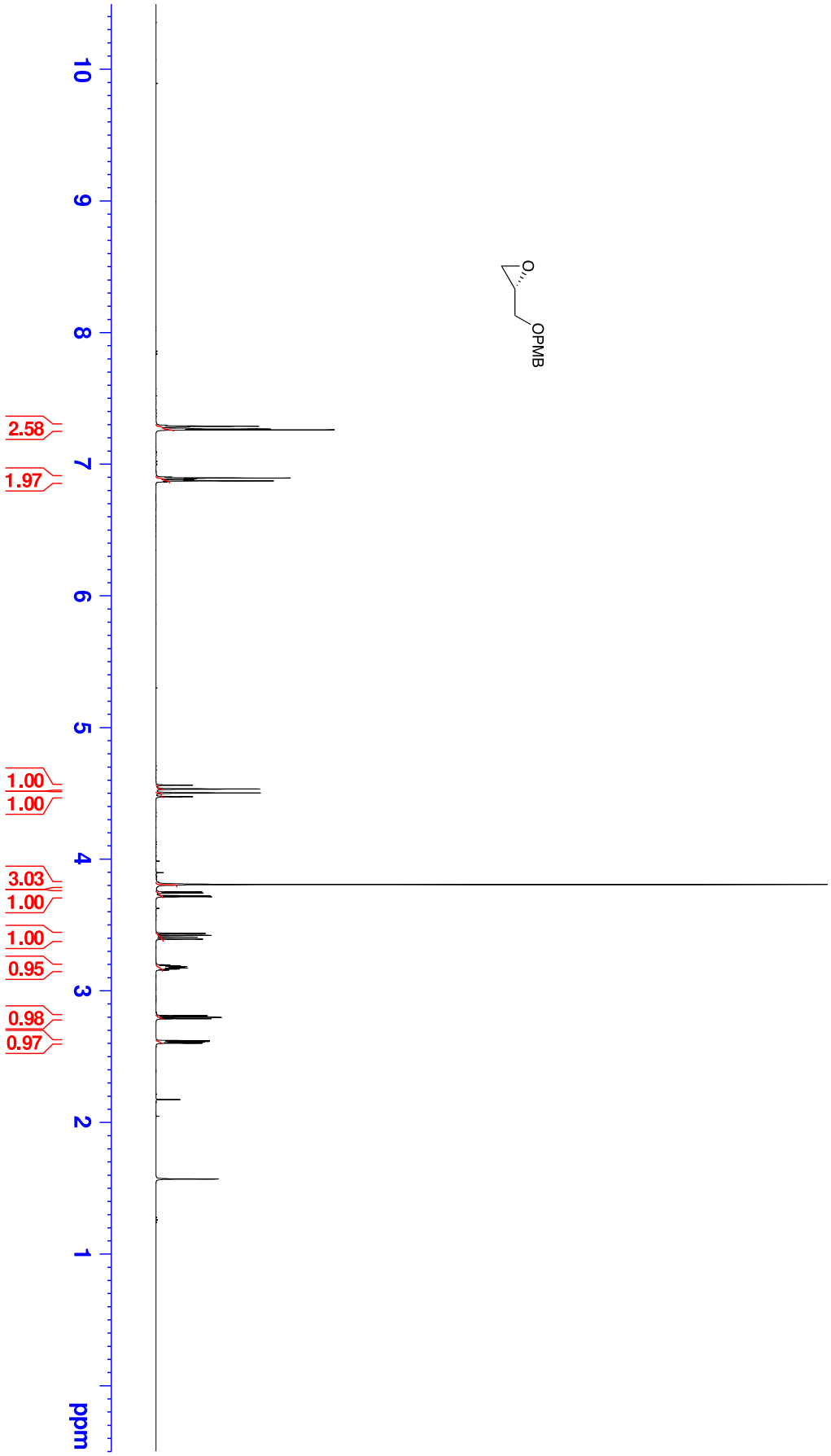
Cell Growth Inhibition by Compounds

PC3, human prostate cancer, and A549, human lung cancer cell lines were obtained from the NCI anticancer drug screen. A2780(1A9) cells, human ovarian cancer, were the kind gift of Dr. Tito Fojo, Medical Oncology Branch, NCI, NIH. All cells were maintained in DMEM medium supplemented with 10% fetal bovine serum. Growth inhibition was determined using the Cell-Titer Assay Reagent (Promega), following exposure to serial dilutions of each compound for 3 days prior to assay and GI(50) determinations as described.[4] Each compound was tested with an initial 10-dose dilution series, followed by narrower, replicate 6-dose series, each of which was a separate experiment. The results presented are mean GI(50) values based on multiple determinations, the SEM, and the number of replicates, *n*. Taxol was obtained through Millipore-Sigma and dactylolide and zampanolide were obtain via our previous total syntheses of the compounds.

ID	PC3			A549			1A9 (A2780/1A9)		
	GI(50)	SEM	n	GI(50)	SEM	n	GI(50)	SEM	n
Taxol	4.6	2	4	6	1.5	4	5.2	2	3
Zampanolide	3.2	0.4	3	5.2	2	4	2.1	1	3
Dactylolide	460	200	4	950	140	4	620	170	3
3	>30000		4	>30000		4	>30000		3
4	>30000		4	>30000		4	>30000		3
5	56	20	4	180	80	4	120	35	3

References:

1.) Zurwerra, D.; Gertsch, J.; Altmann, K-H. *Org. Lett.*, **2010**, *12*, 2302– 2305;
2.) The purification of the cross-metathesis product and (*Z*)-but-2-ene-1,4-diyl diacetate could be achieved by tedious column chromatography. However, when the reation was conducted on a large scale, the (*Z*)-but-2-ene-1,4-diyl could be removed via vacuum distillation to remove the coupling partner and then chromatographed on silica.
3.) The reaction could be conducted at 2 mol% palladium catalyst and 6 mol% ligand, but the reaction was particularly unreliable. Increasing the reaction to 10 mol% palladium catalyst and 30 mol% catalyst gave the most reproducible results.
4.) K. Präbst, H. Engelhardt, S. Ringgeler, H. Hübner, *Methods Mol. Biol.* **1601**, 1-17 (2017).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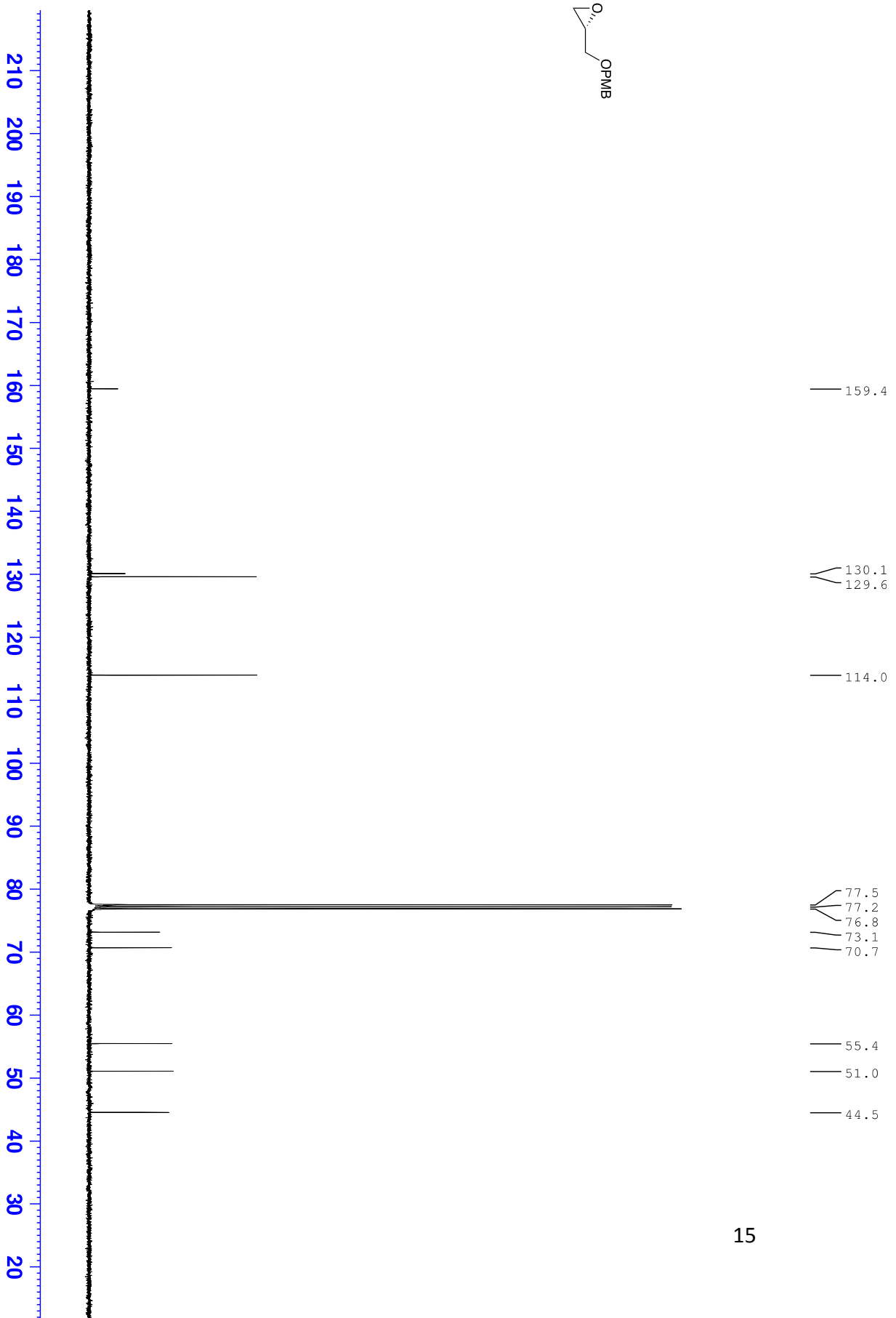
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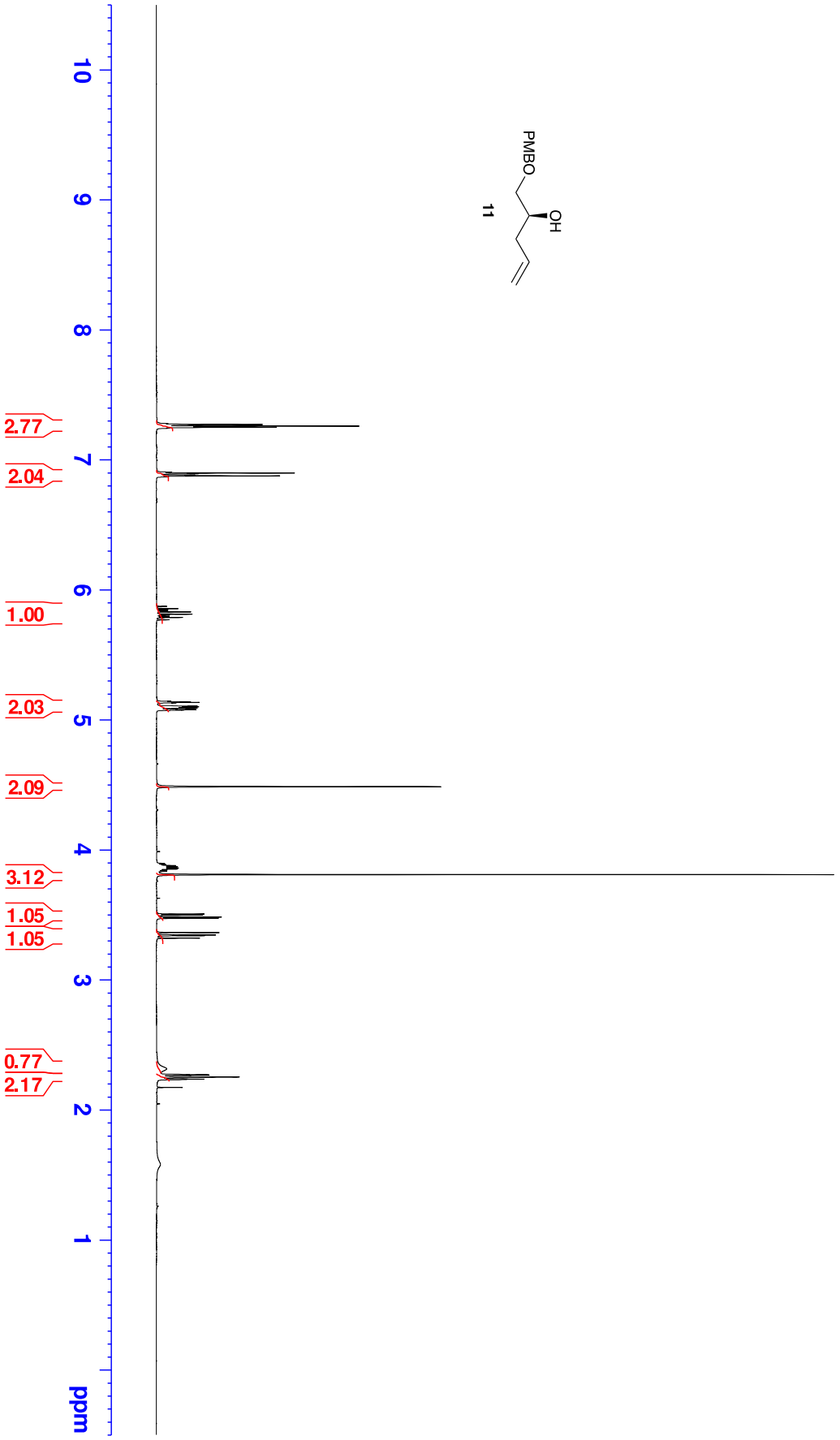
76.8
73.1
70.7
55.4
51.0
44.5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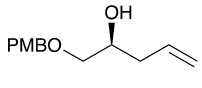
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PMBO

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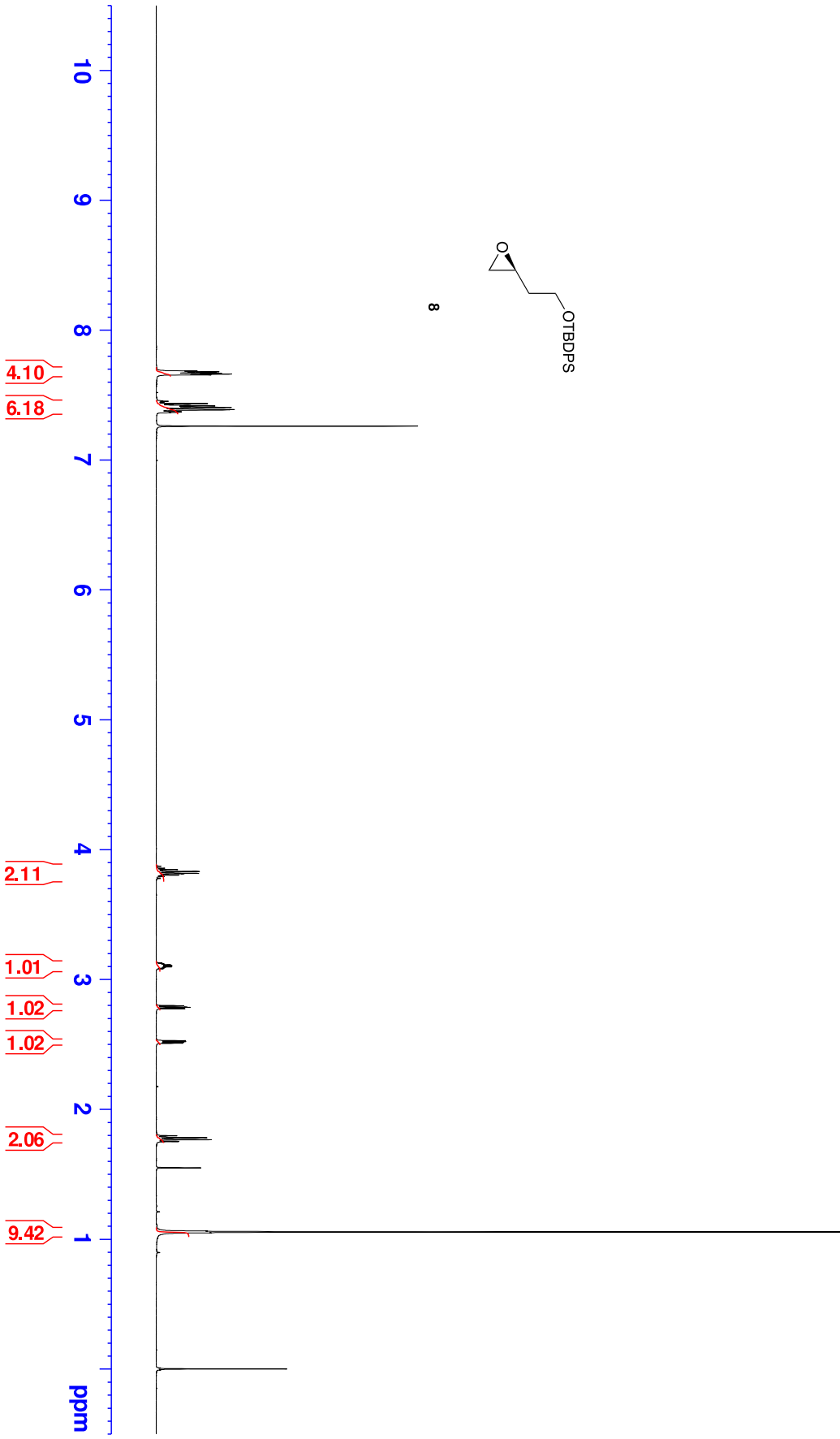
ppm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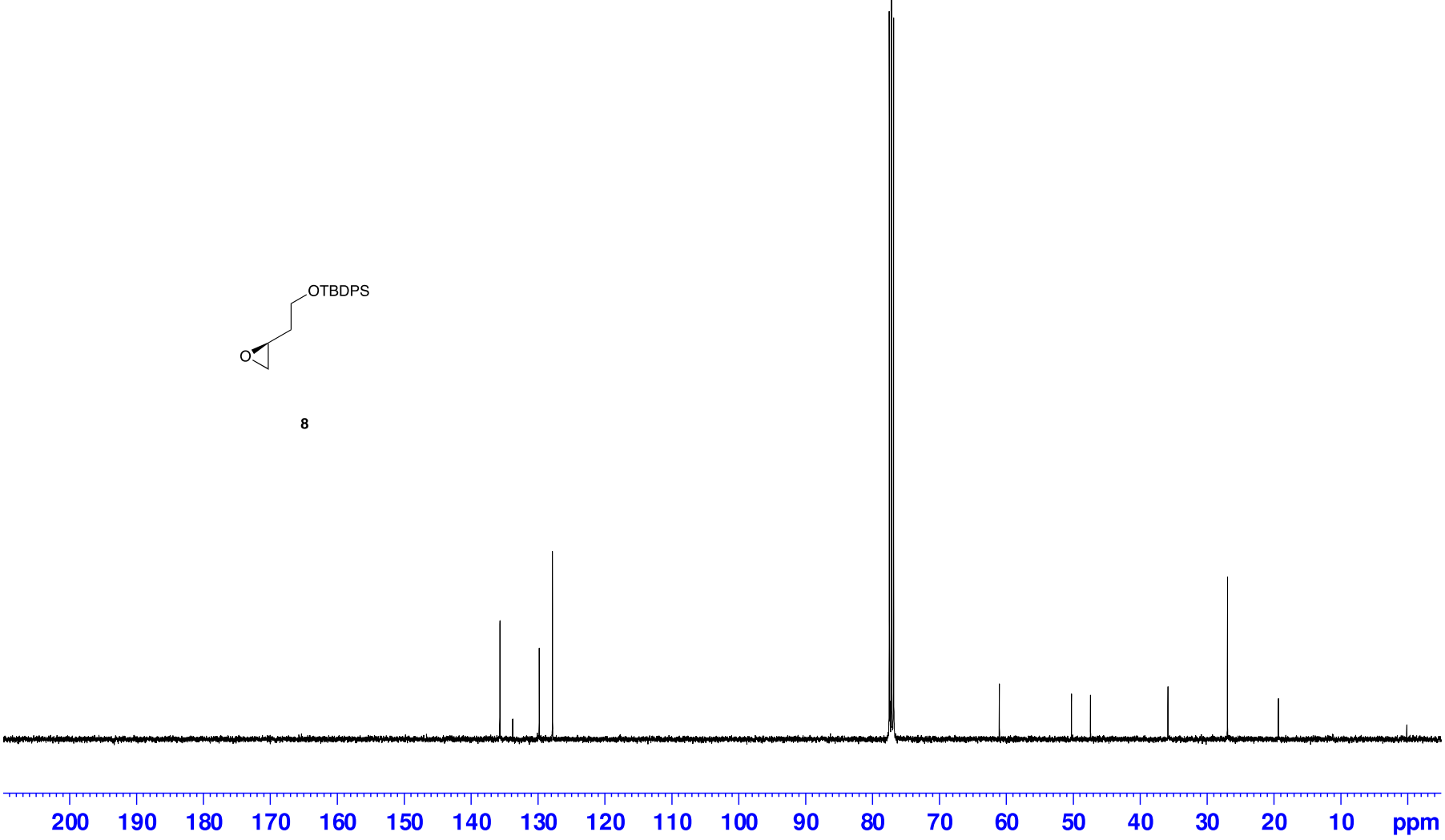
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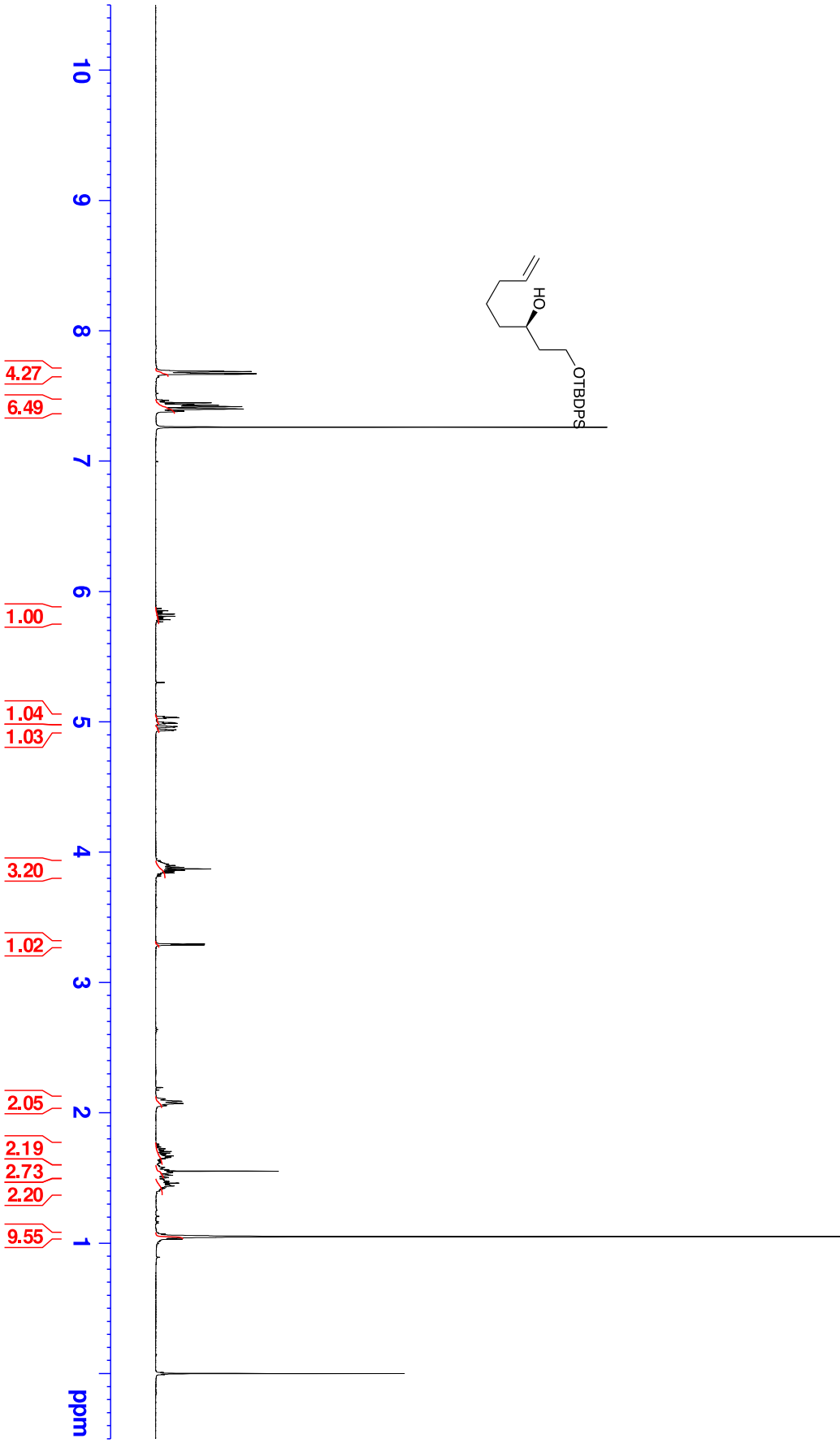
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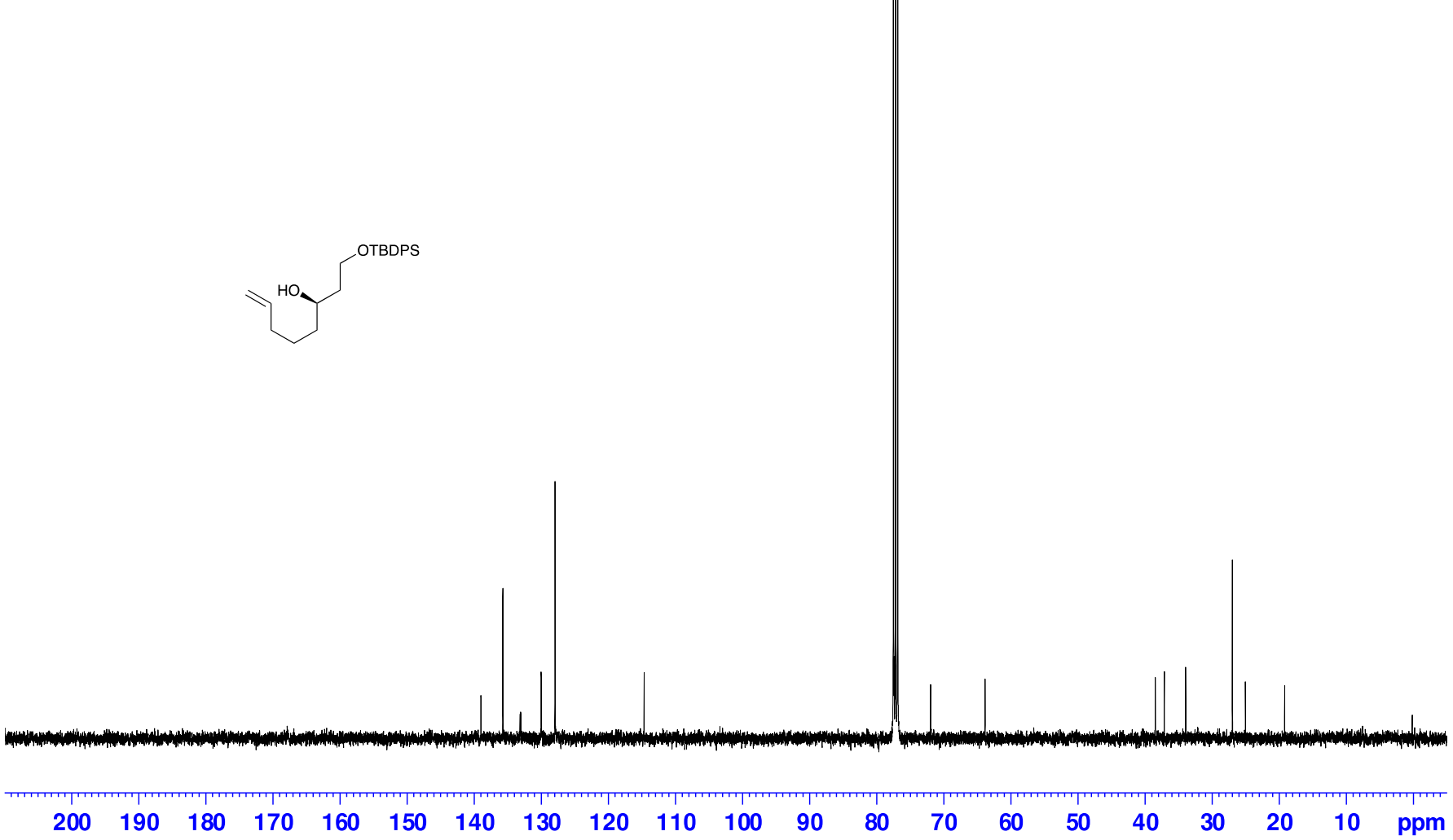
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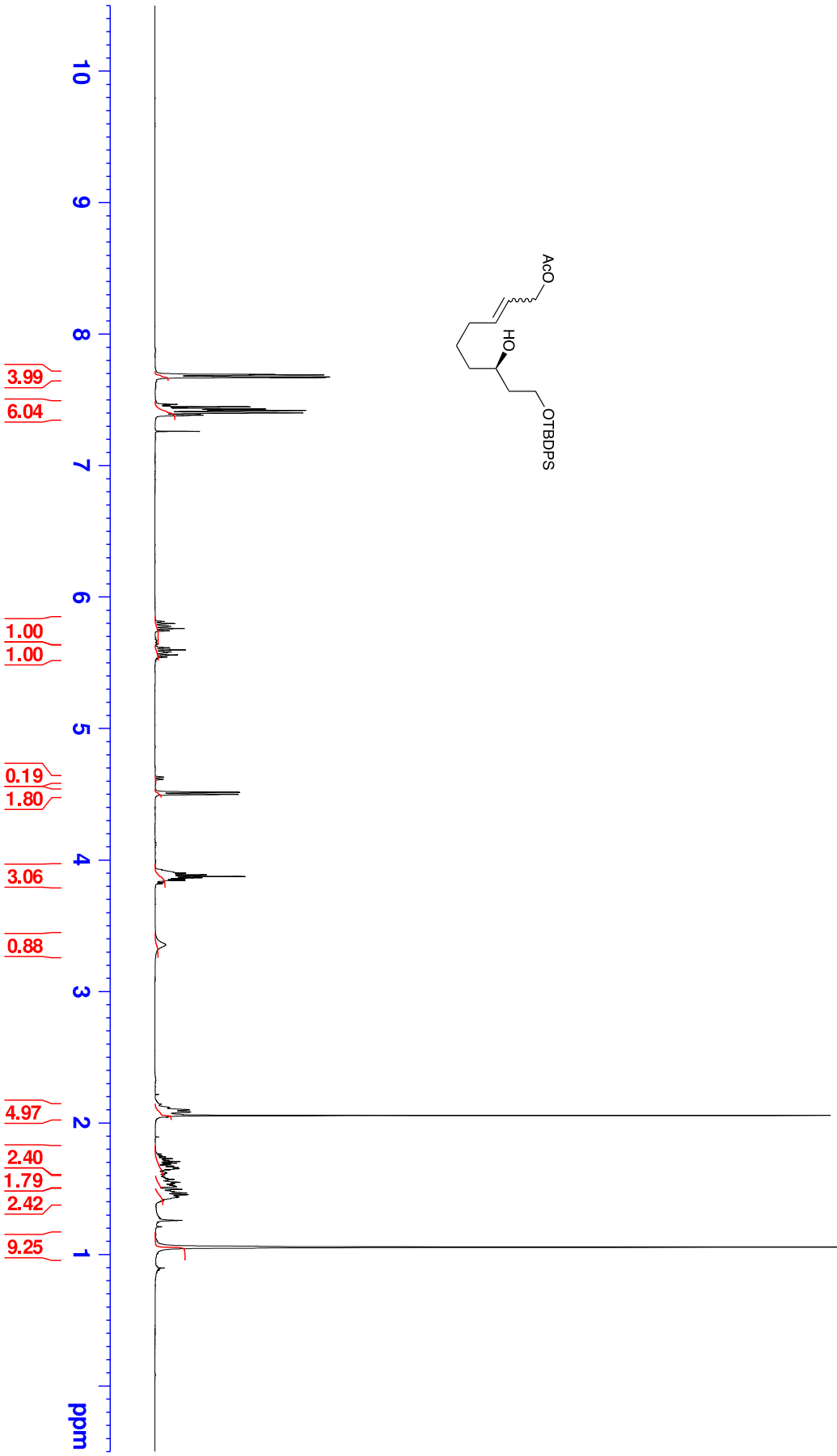
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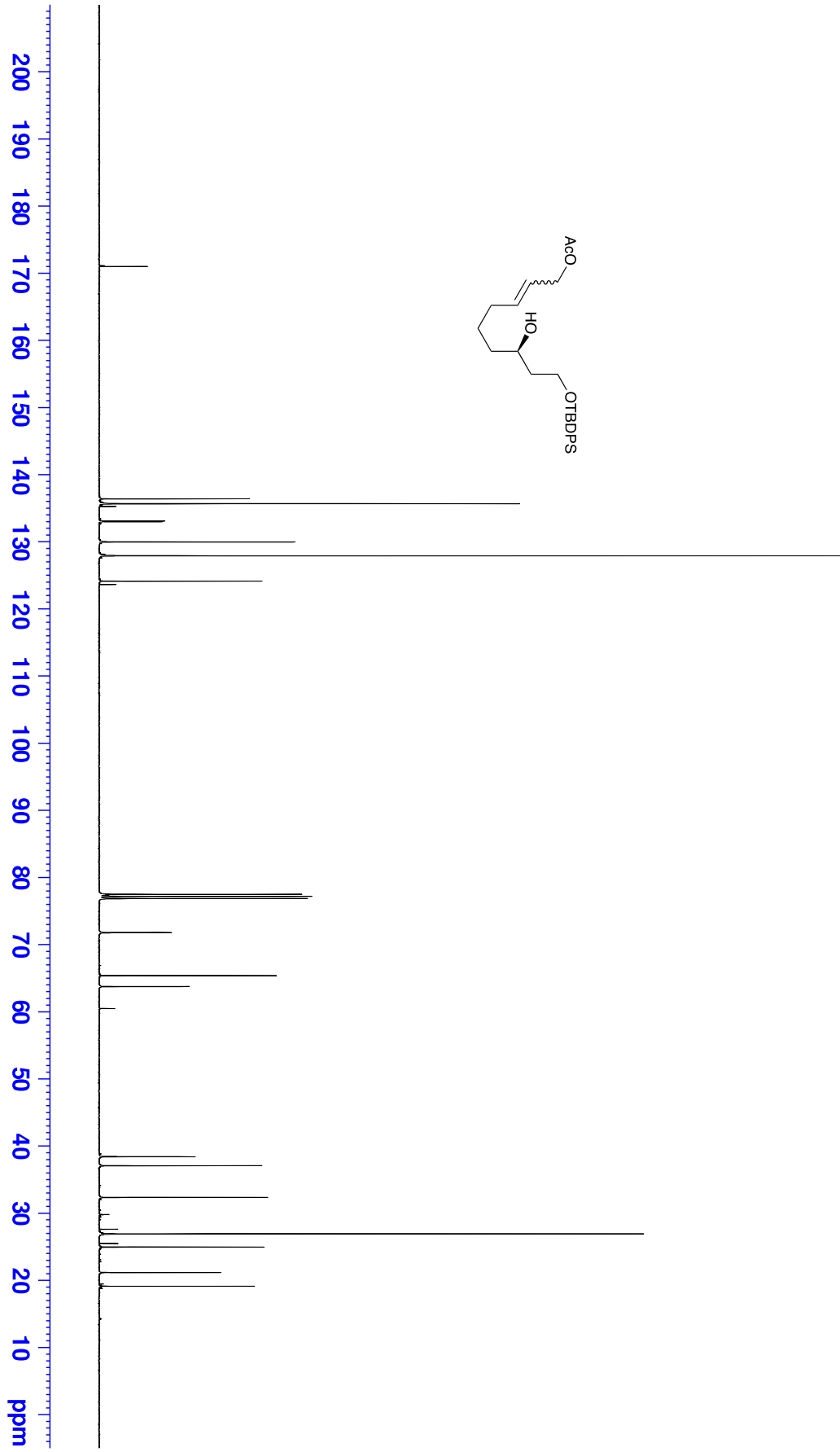
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30
20
10
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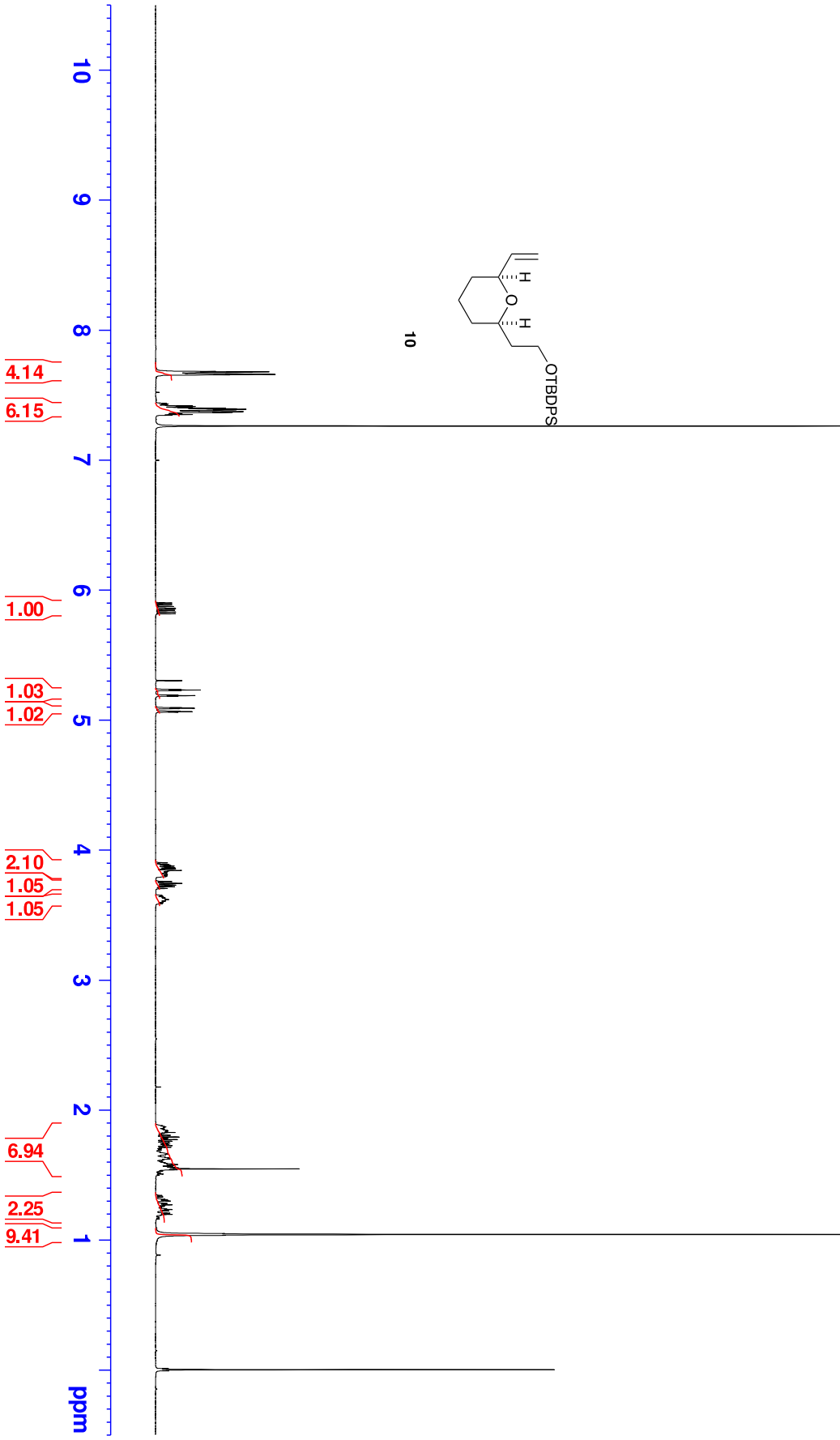
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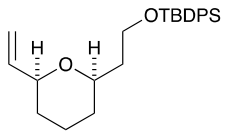
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H

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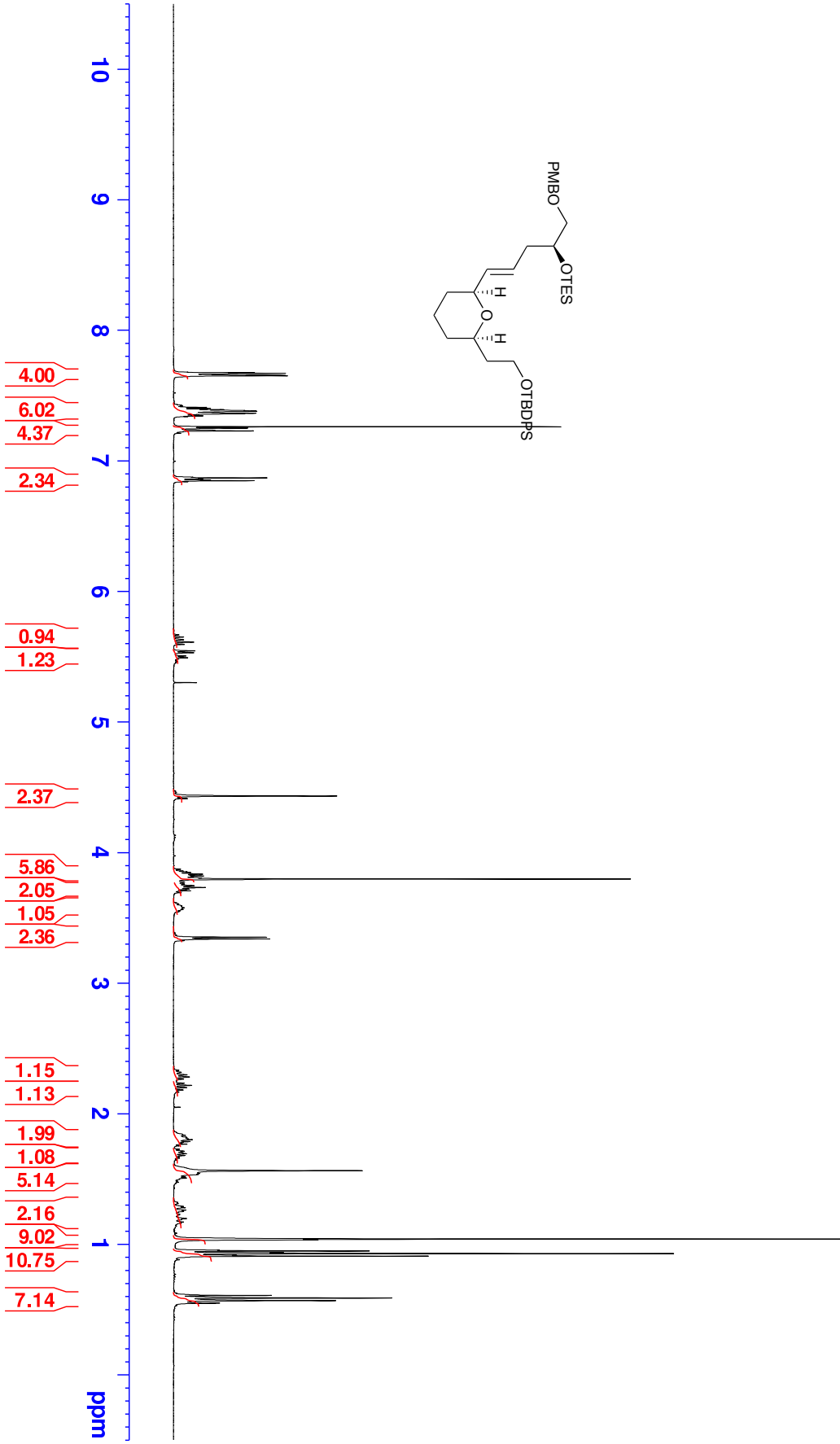
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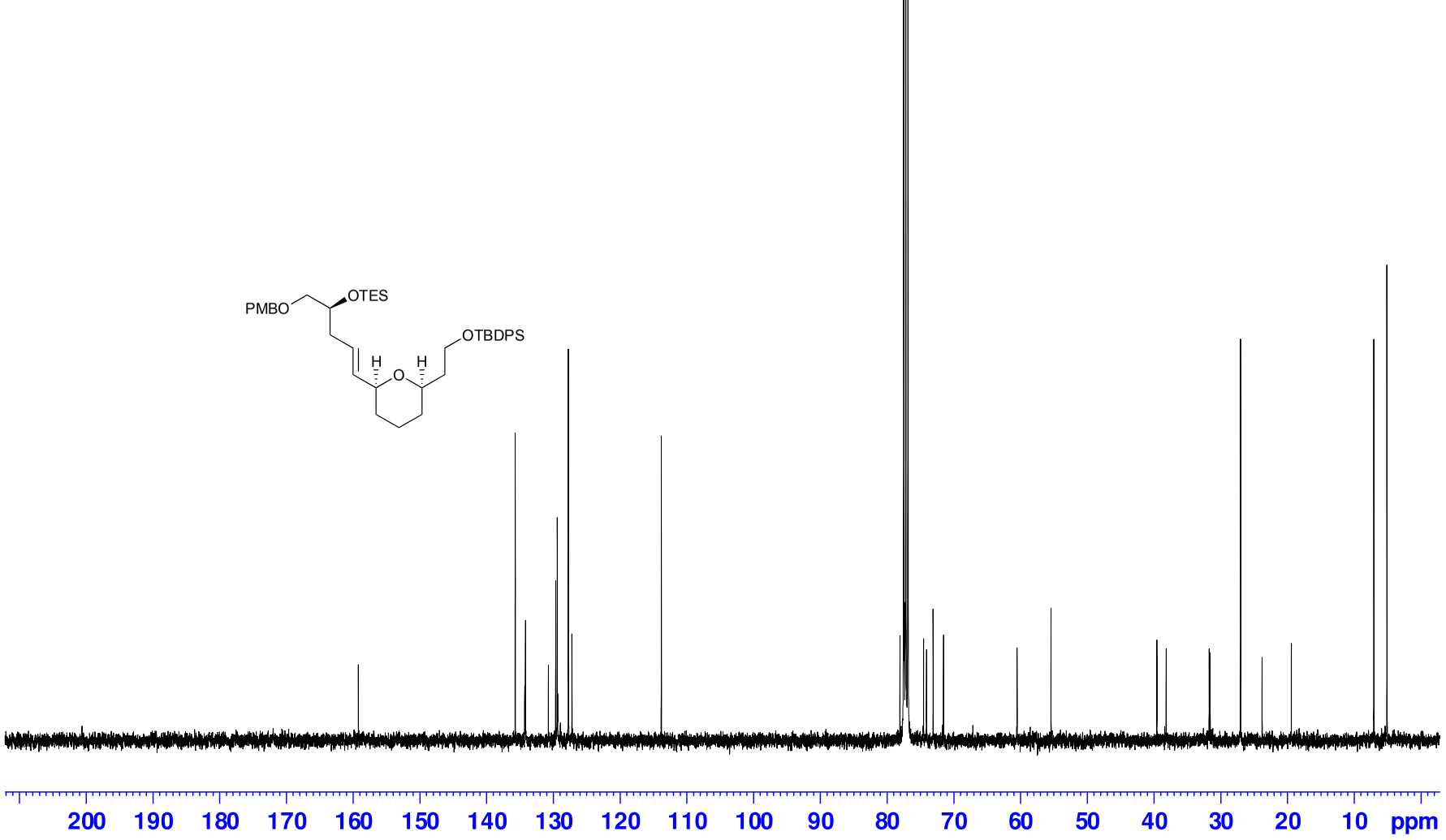
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O
H
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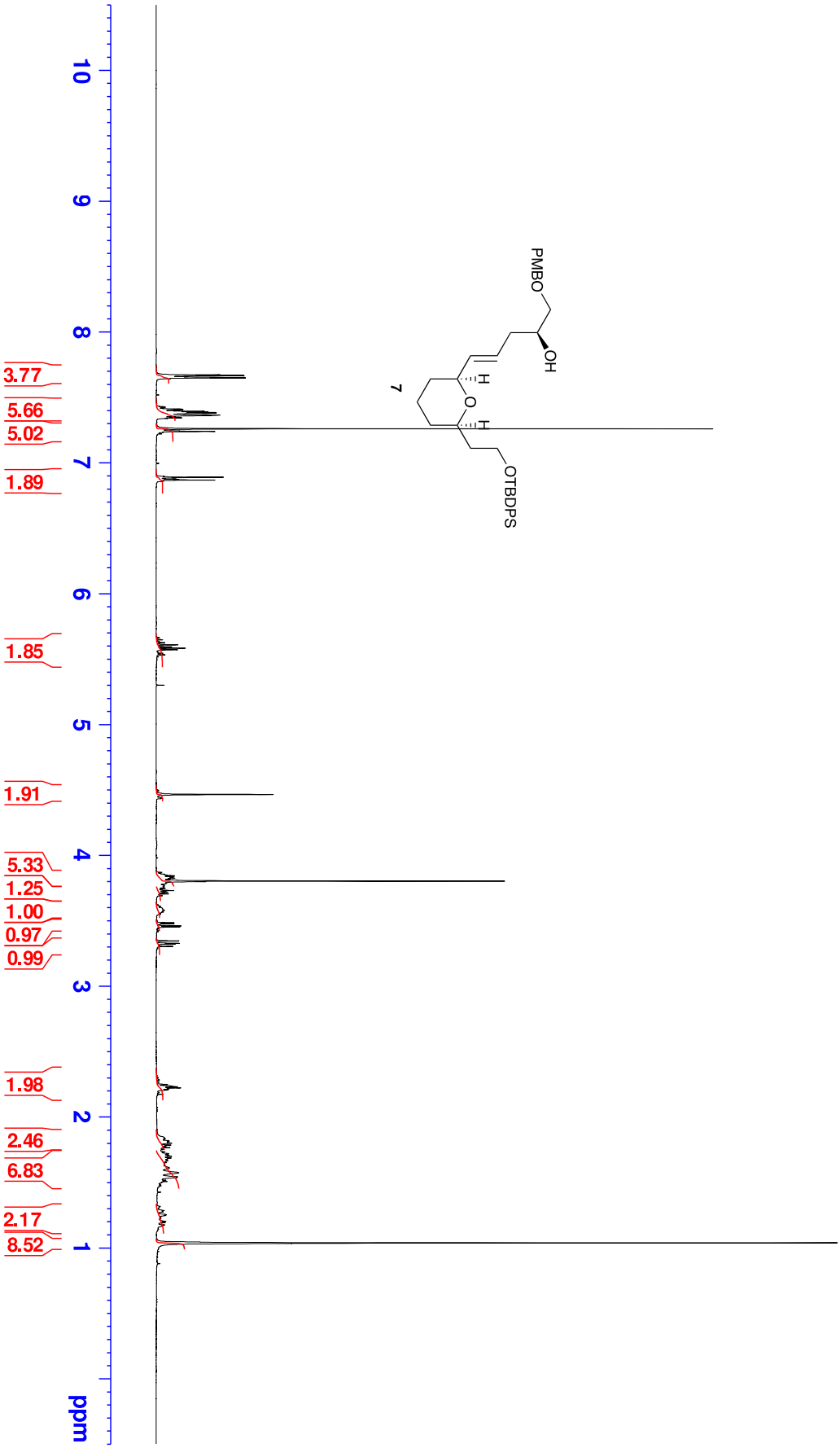
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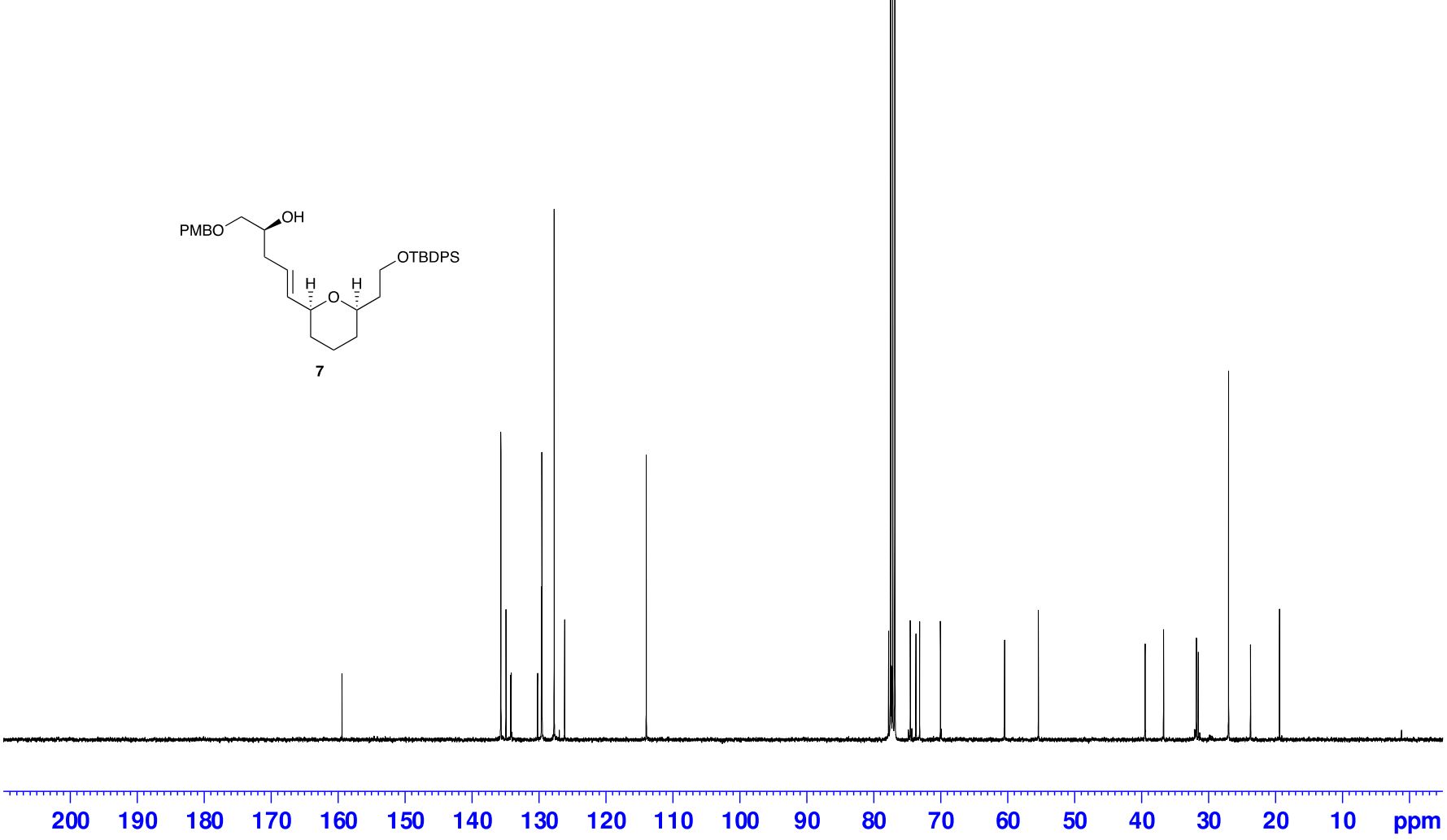
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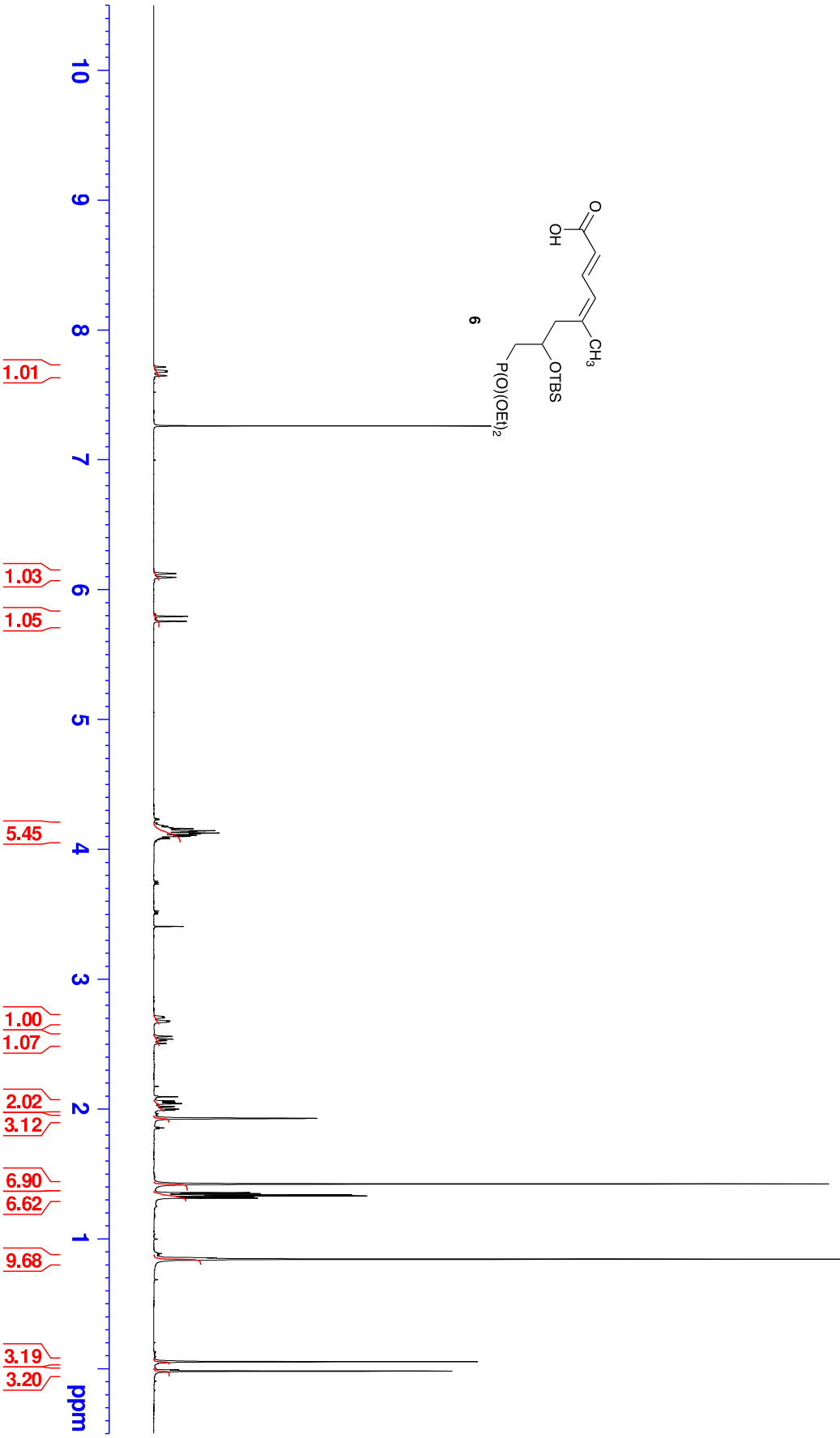
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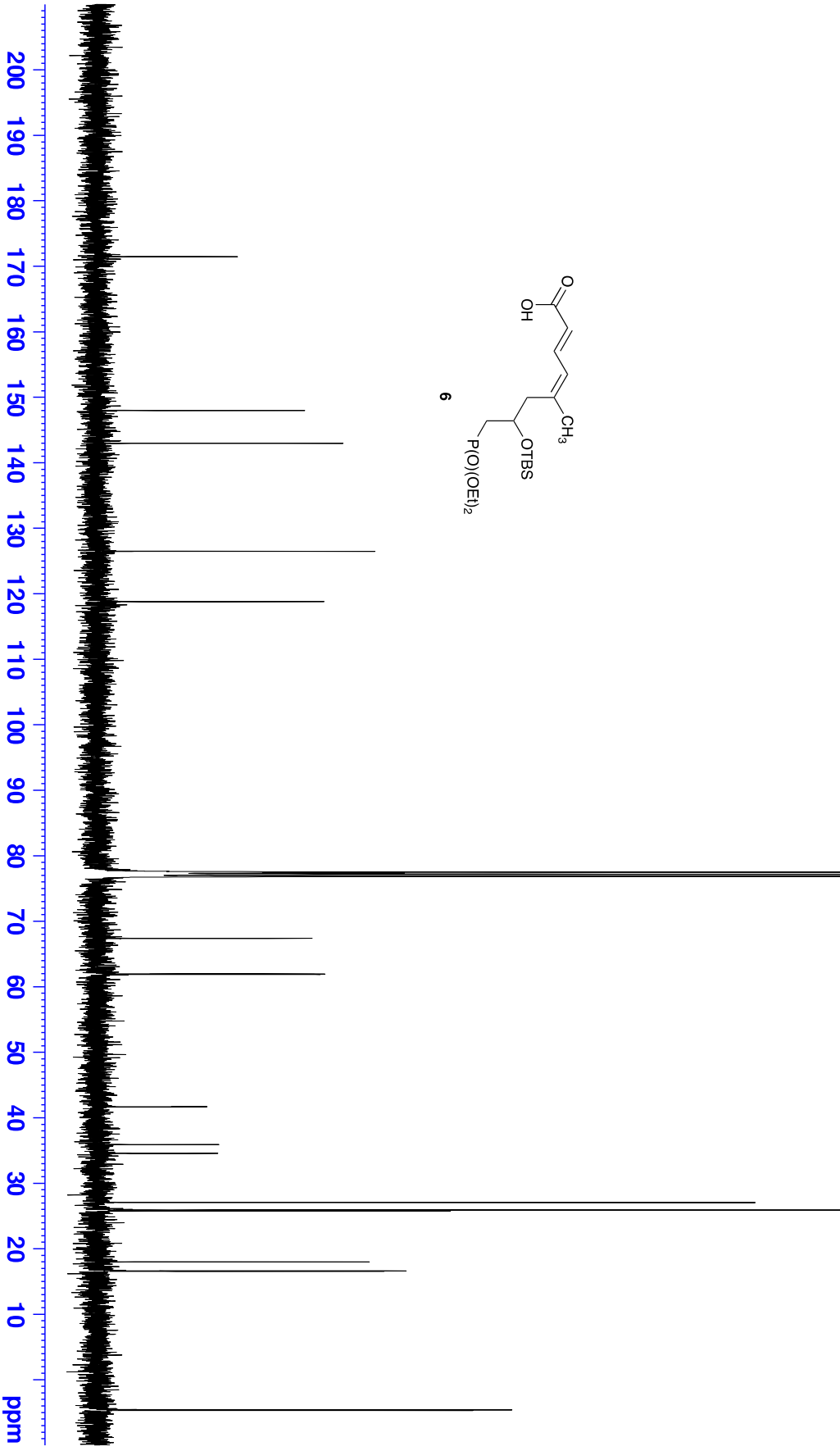
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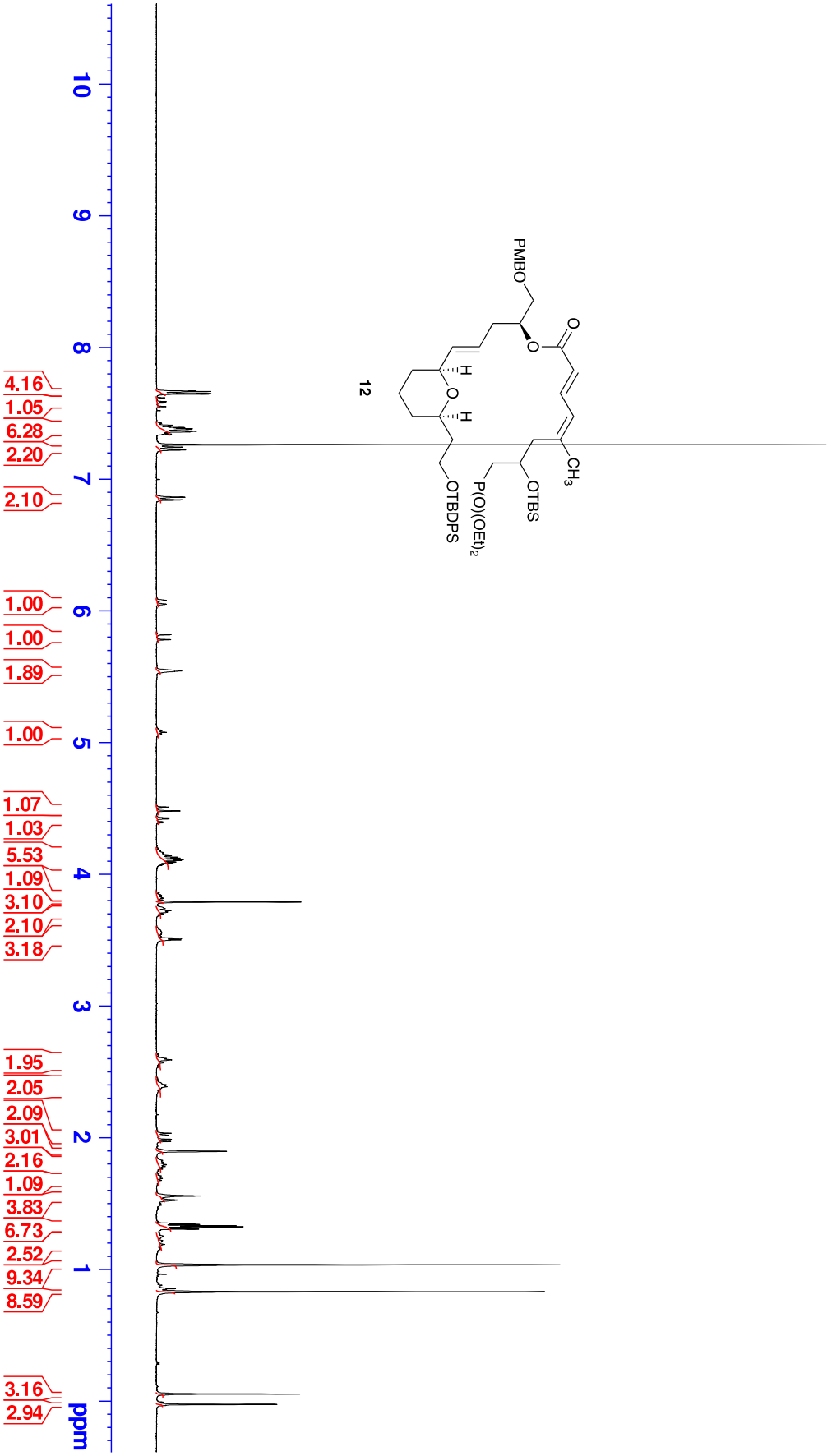
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H
CH3
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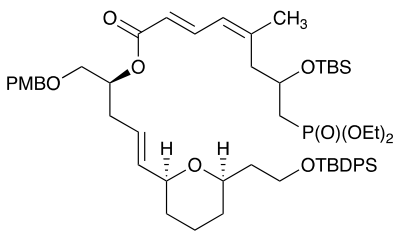
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PMBO
P(O)(OEt)2
H
H
O
OTBDPS

12

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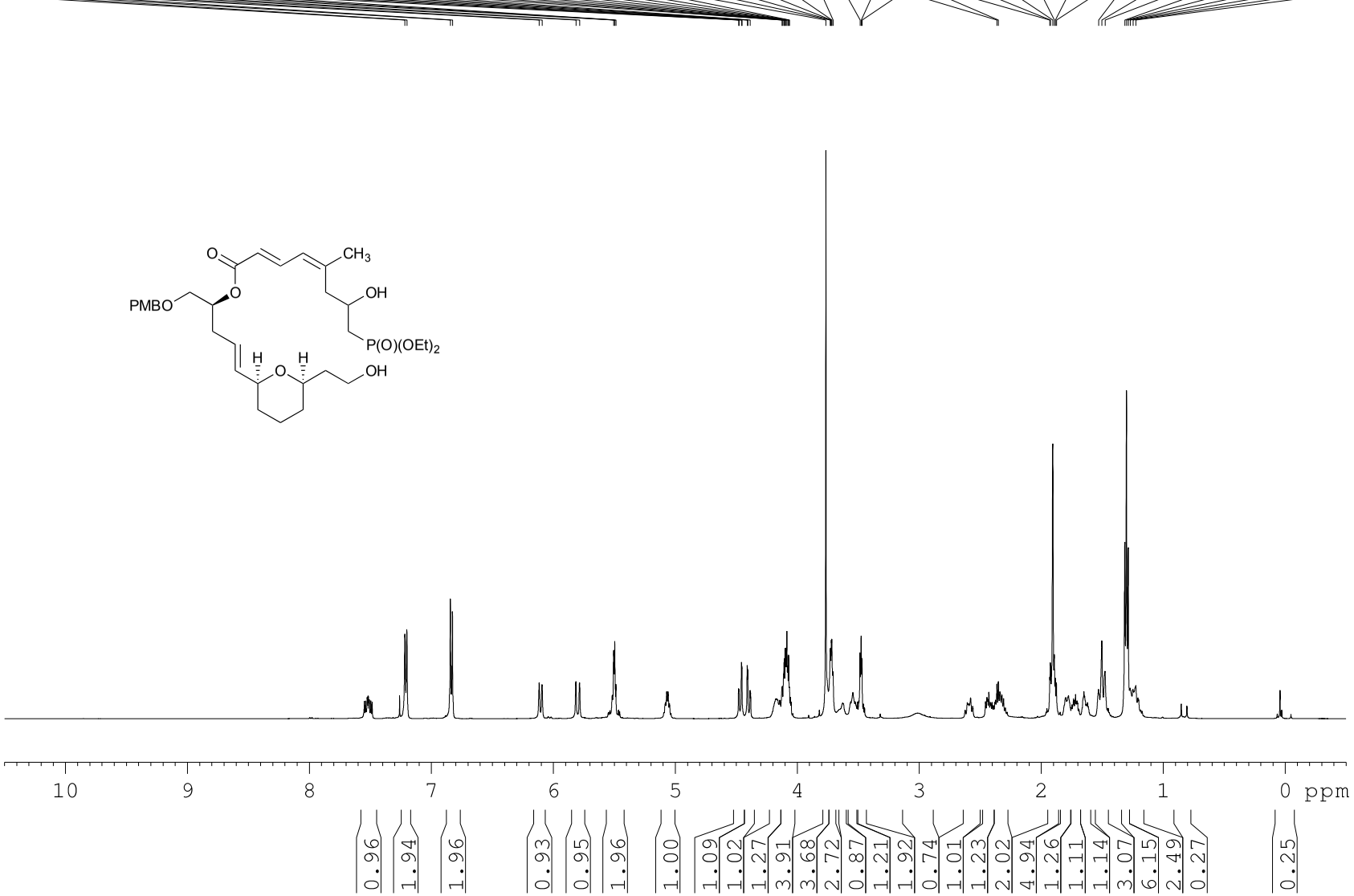
ppm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1.02
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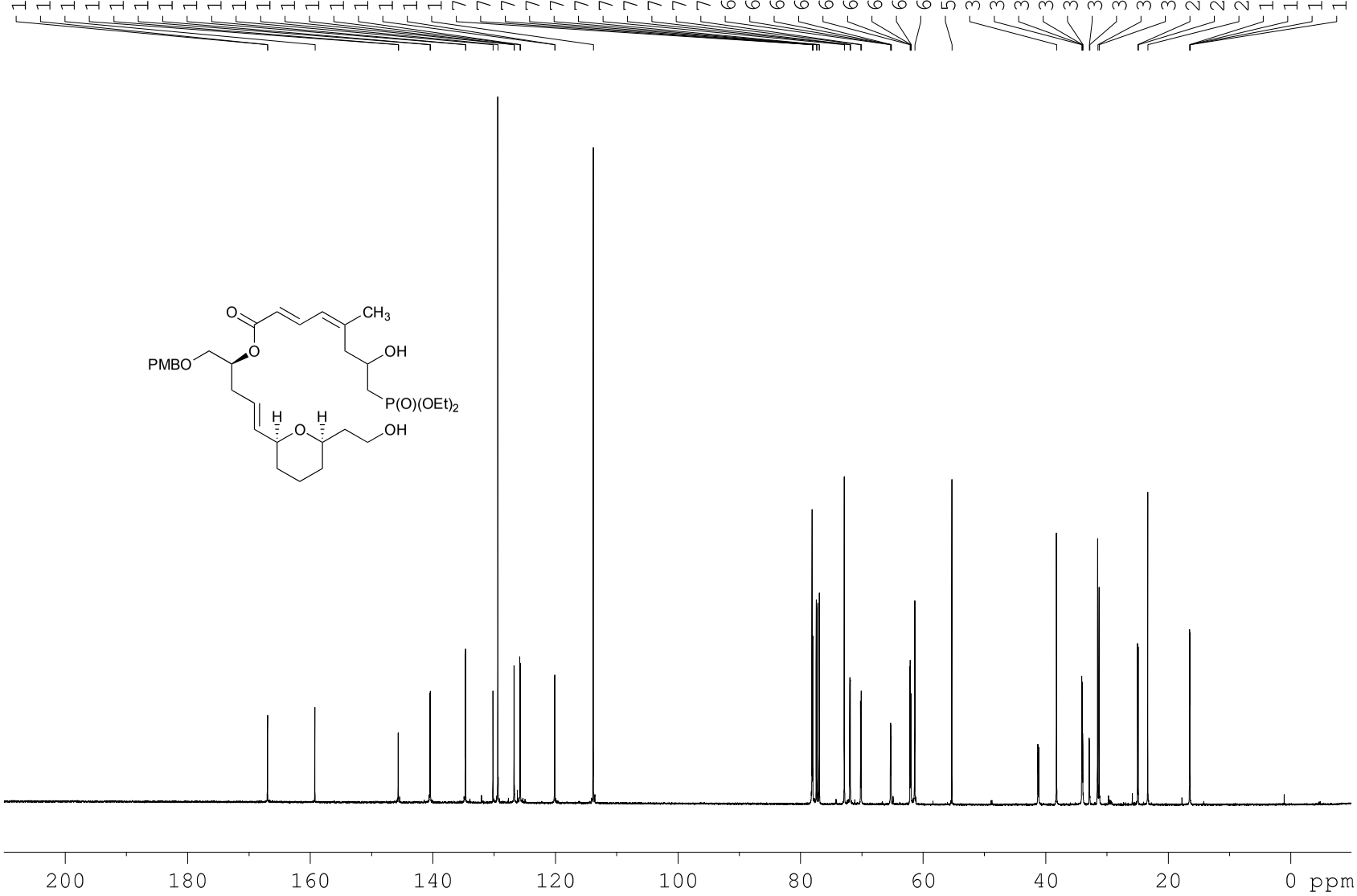
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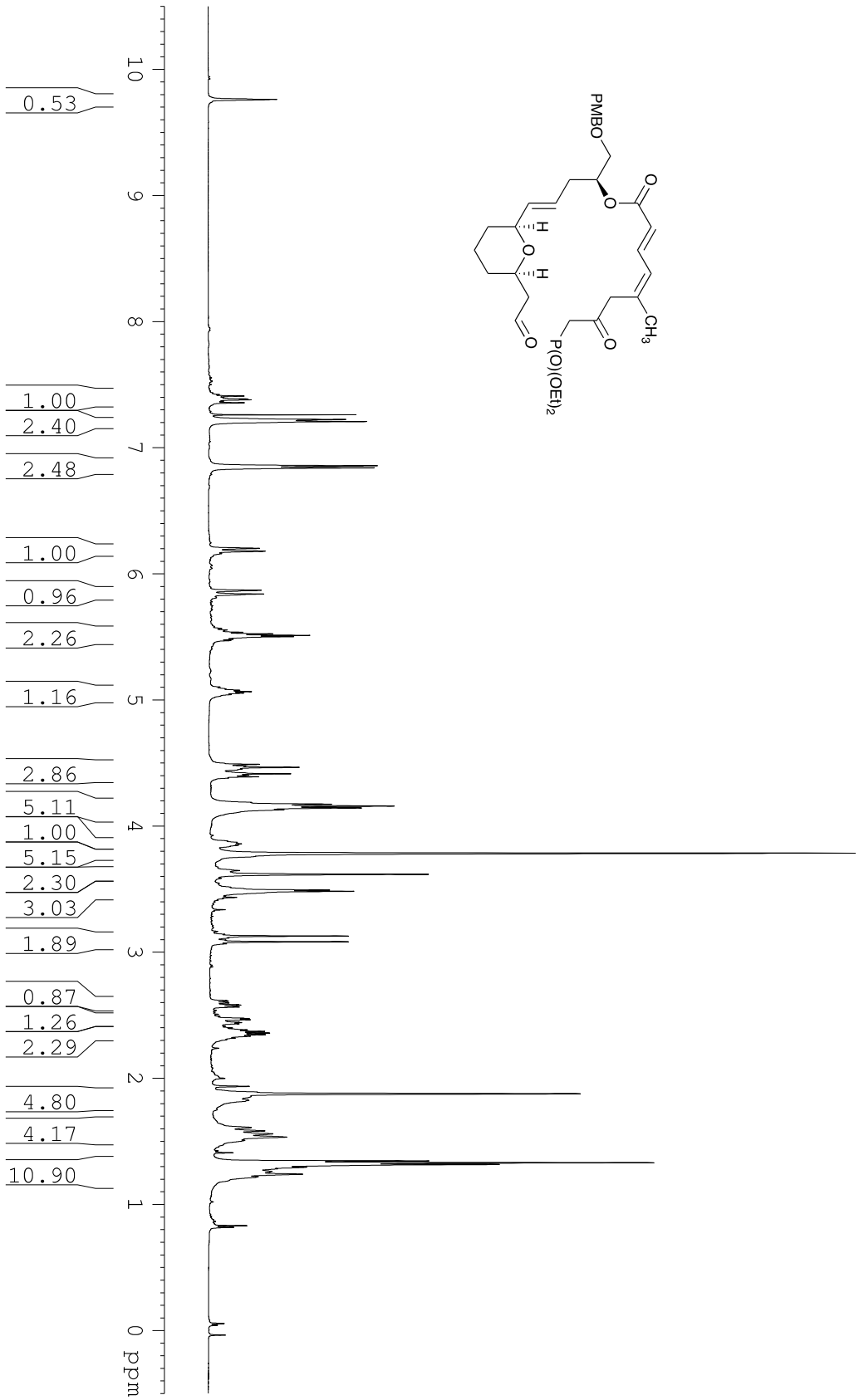
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5.11
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5.15
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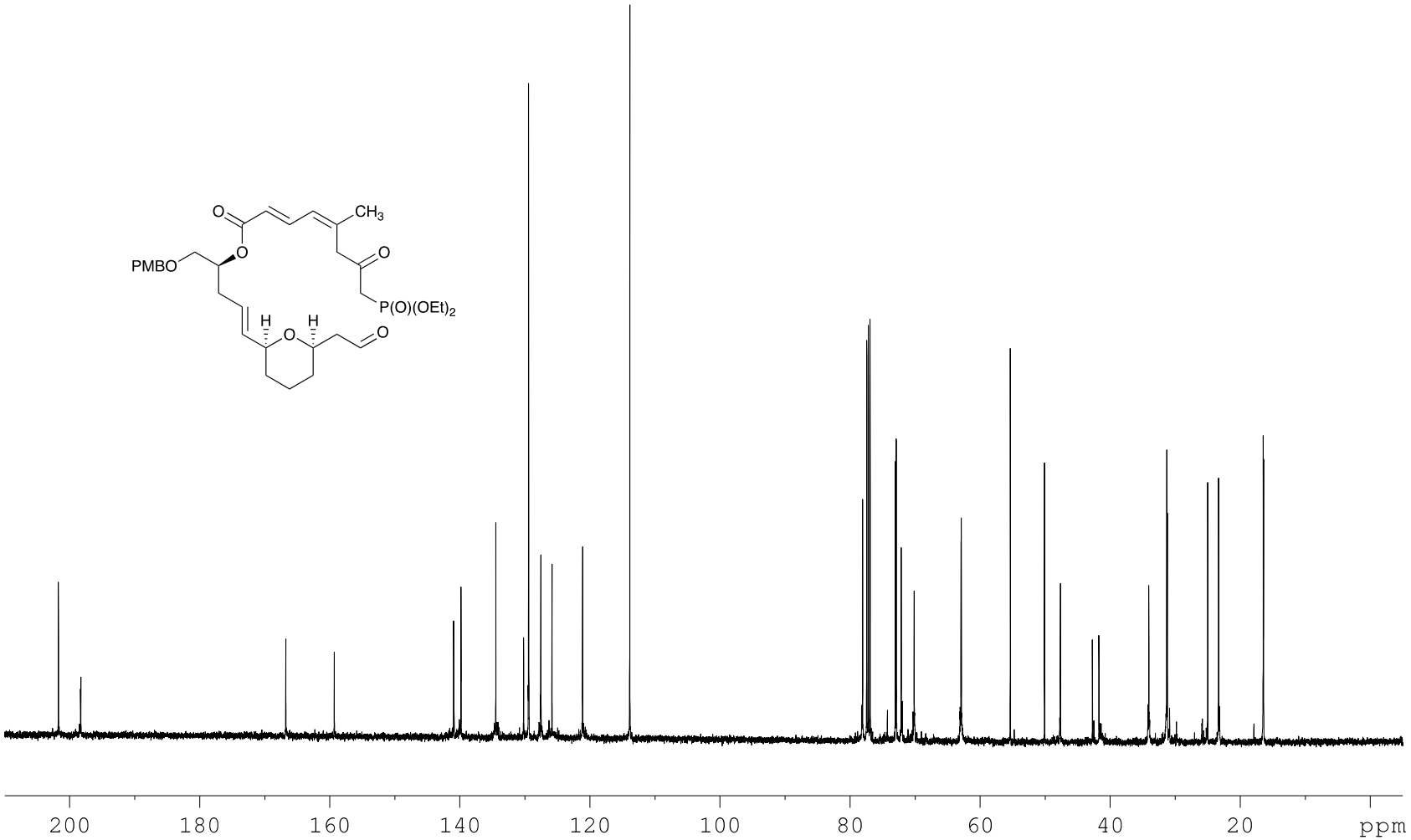
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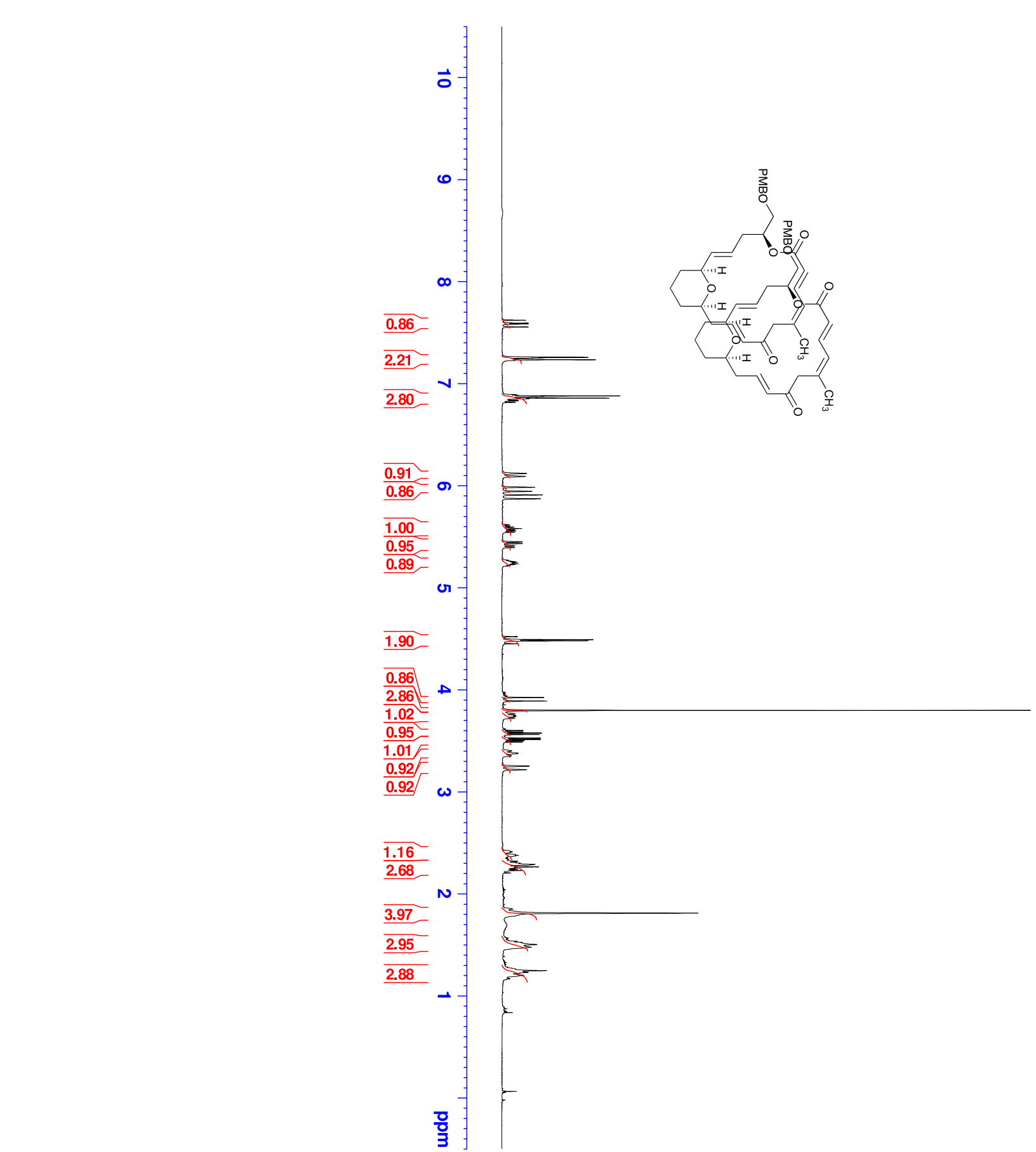
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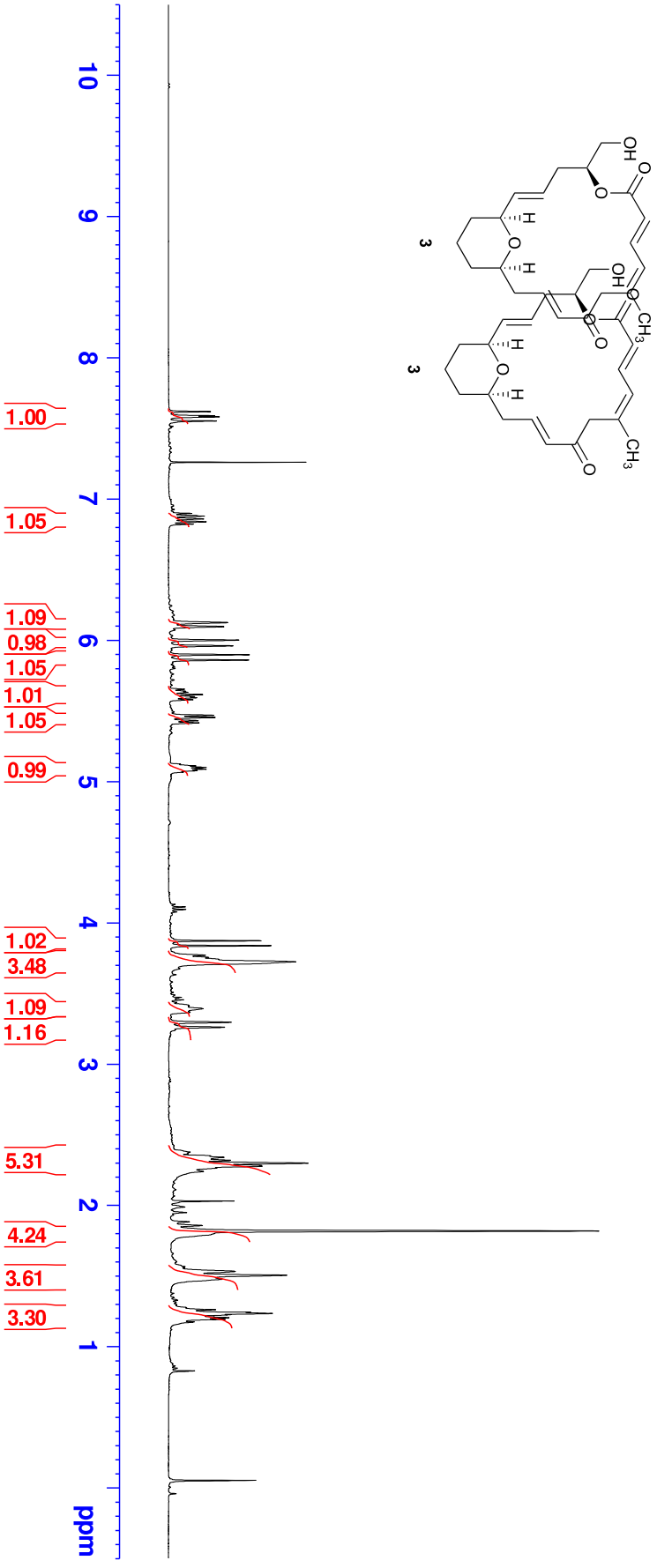
CH3
CH3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3.30
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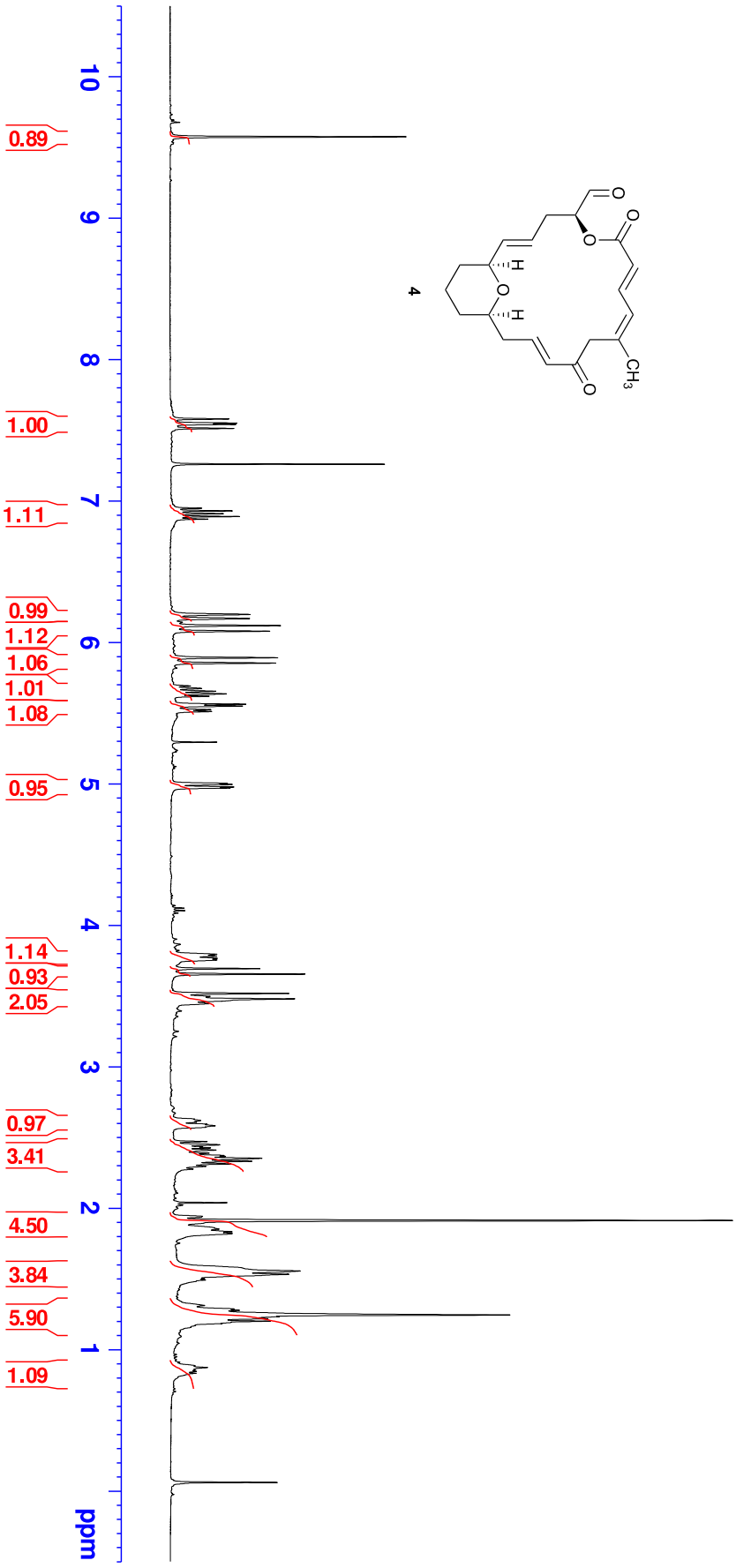
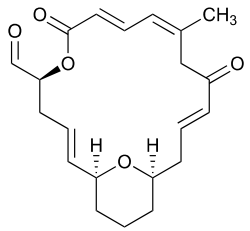
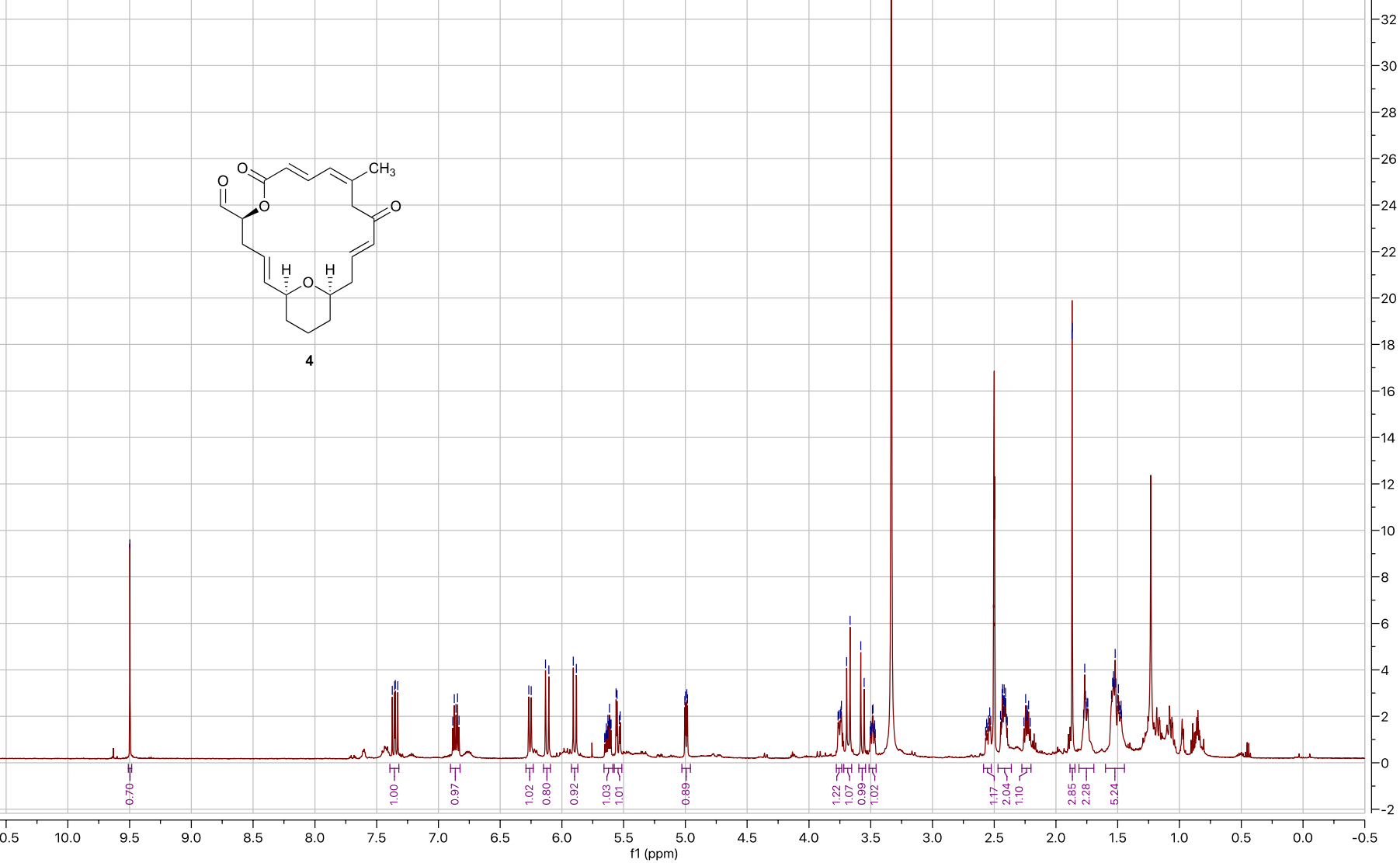
O
H
O
CH3
3


10
9
8
7
6
5
4
3
2
1
ppm
0.89
1.00
1.11
0.99
1.12
1.06
1.01
1.08
0.95
1.14
0.93
2.05
0.97
3.41
4.50
3.84
5.90
1.09
4
O
O
O
H
H
O
O
CH3

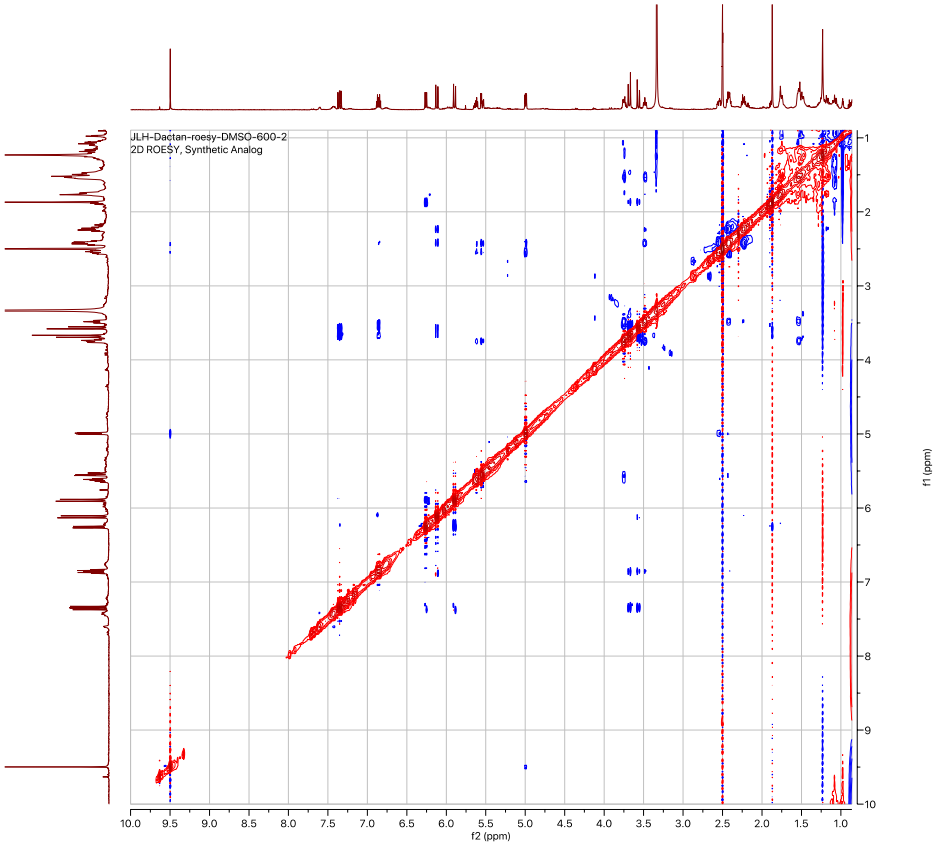

O
O
O
CH3
O
H
O
H

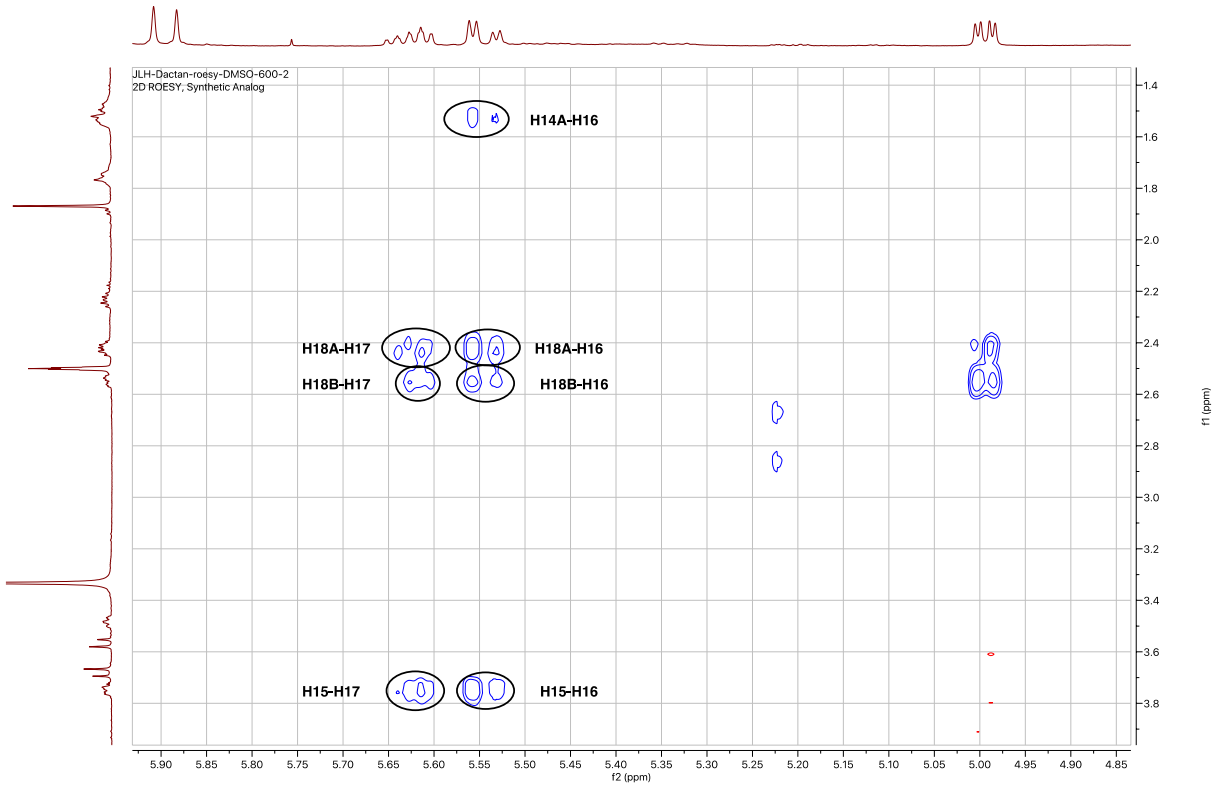
4

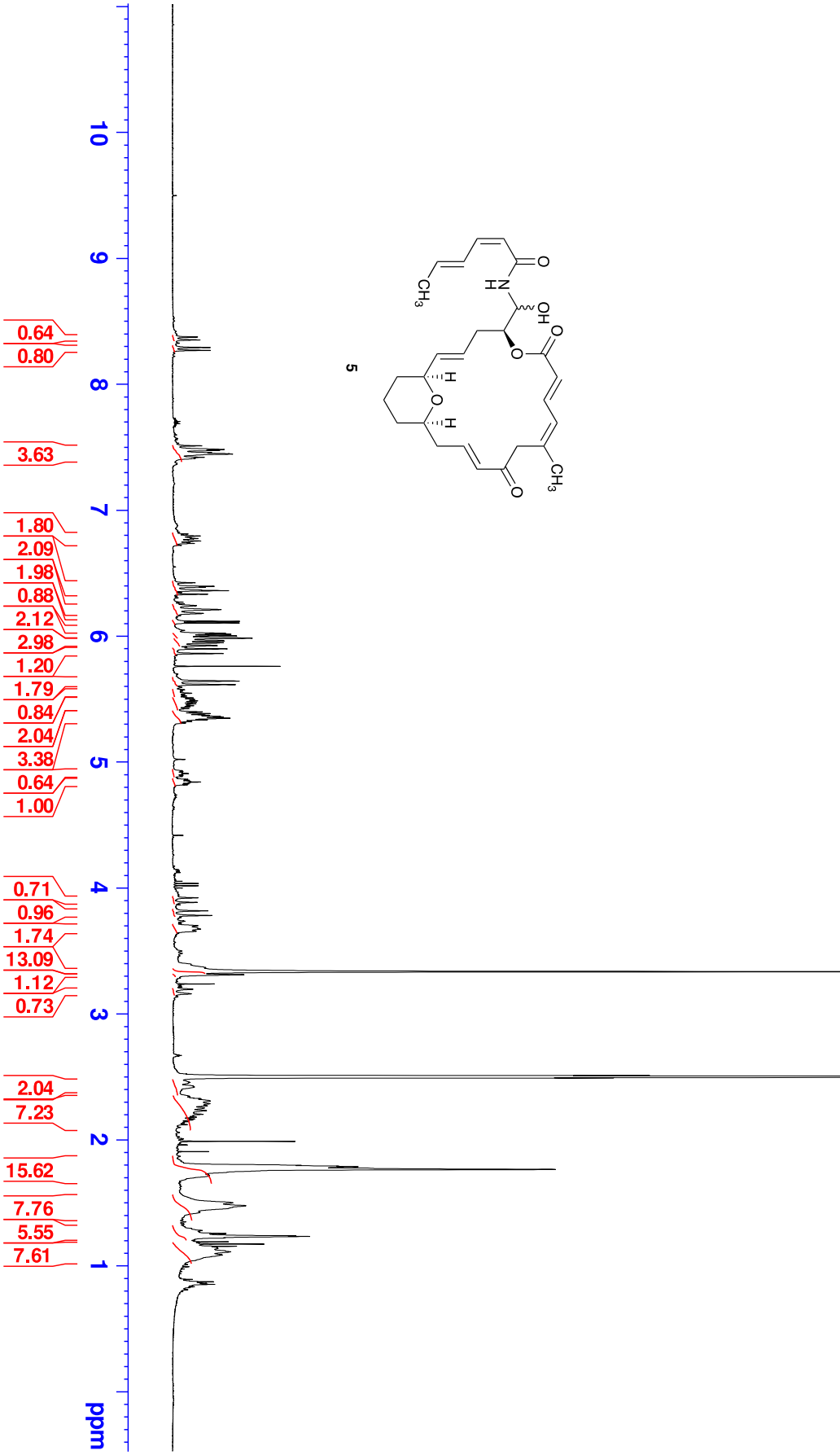
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

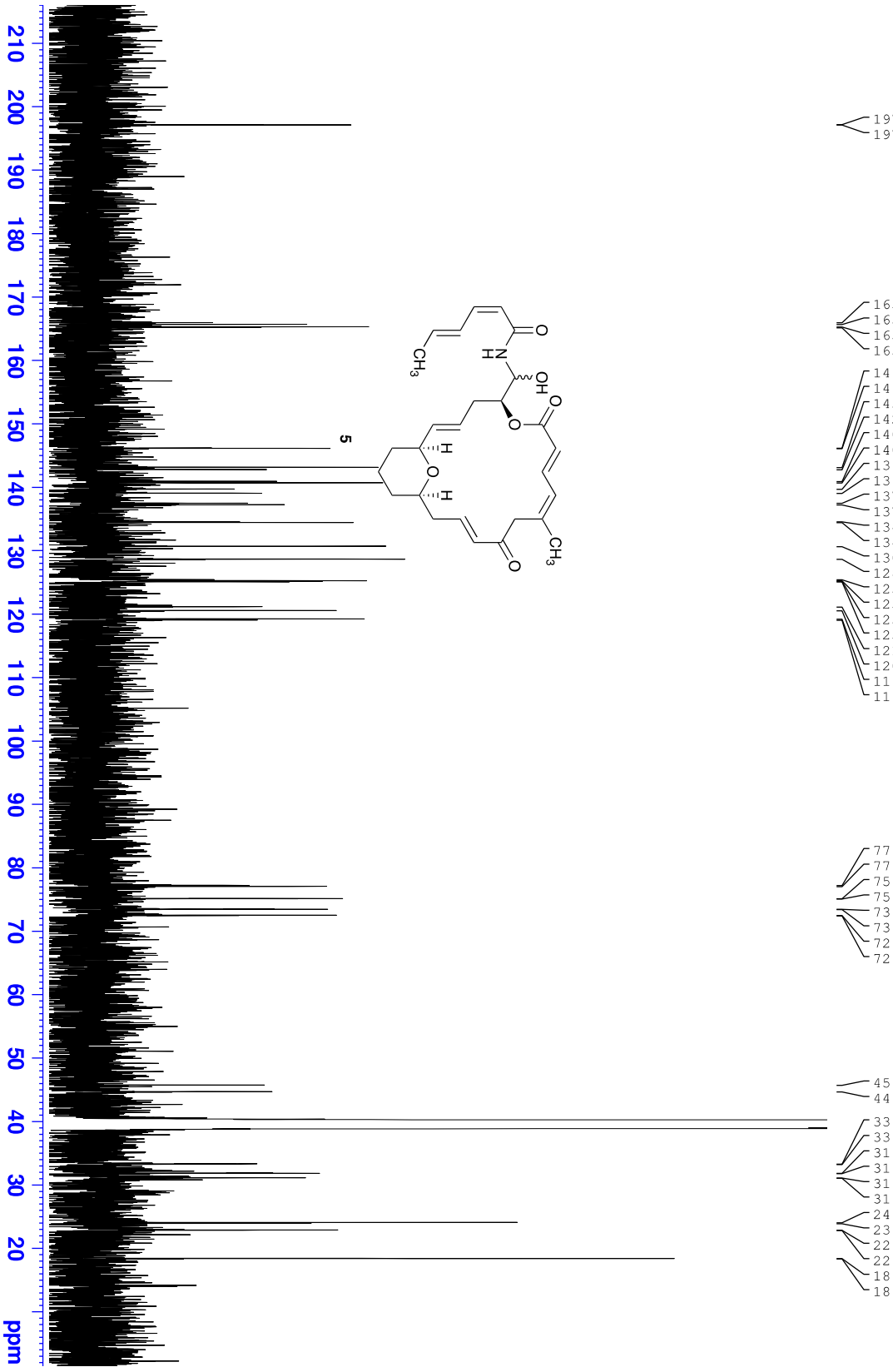

O
O
O
CH3
O
H
O
H
4
0.70
1.00
0.97
1.02
0.80
0.92
1.03
1.01
0.89
1.22
1.07
0.99
1.02
1.17
2.04
1.10
2.85
2.28
5.24
f1 (ppm)

Parameter	Value
Solvent	dmso
Temperature	22.0
Pulse Sequence	ROESY
Experiment	ROESY
Probe	AutoX_DB_PFG_8964
Number of Scans	40
Receiver Gain	48
Relaxation Delay	1.5000
Pulse Width	10.2500
Presaturation Frequency	
Acquisition Time	2.4999
Acquisition Date	2019-01-19T07:04:40
Modification Date	2019-01-24T08:32:14
Class	
2Spectrometer Frequency	(599.88, 599.88)
Spectral Width	(5787.0, 5787.0)
Lowest Frequency	(516.2, 514.9)
Nucleus	(1H, 1H)
Acquired Size	(14467, 100)
Spectral Size	(16384, 256)




JLH-Dactan-roesy-DMSO-600-2
2D ROESY, Synthetic Analog
H14A-H16
H18A-H17
H18A-H16
H18B-H17
H18B-H16
H15-H17
H15-H16
f2 (ppm)
f1 (ppm)


0.64
0.80
3.63
1.80
2.09
1.98
0.88
2.12
2.98
1.20
1.79
0.84
2.04
3.38
0.64
1.00
0.71
0.96
1.74
13.09
1.12
0.73
2.04
7.23
15.62
7.76
5.55
7.61
10
9
8
7
6
5
4
3
2
1
ppm
5
CH3
H
N
O
OH
O
O
H
O
H
O
CH3


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm
5
O
N
H
OH
O
O
H
O
H
CH3
CH3
O
O
19
19
16
16
16
16
14
14
14
14
14
14
13
13
13
13
13
13
13
12
12
12
12
12
12
12
11
11
77
77
75
75
73
73
72
72
45
44
33
33
31
31
31
31
24
23
22
22
18
18