An Iterative Shimizu Non-aldol Approach for the Stereoselective Synthesis of C13-C22 Fragment of Callystatin A

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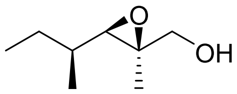
Supporting Information

Experimental section

General:

Unless and otherwise noted, all the starting materials and reagents were obtained from commercial suppliers and used after further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl, toluene from sodium. Dichloromethane, hexane were freshly distilled from calcium hydride. All solvents for routine isolation of products and chromatography were reagent grade and glass distilled. Air and moisture sensitive reactions were performed under an argon/ UHP nitrogen atmosphere. Flash chromatography was performed using silica gel (100-200 mesh, Aceme) with indicated solvents. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid and heat as developing agents. Optical rotation were recorded on Rudolph Autopol IV digital polarimeter. High-resolution mass spectra (HRMS) were recorded on a micromass ESI TOF (time of flight) mass spectrometer. IR spectra were recorded on a Thermo Nicolete Avater 320 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded either on Varian AS 400 or Bruker AV 400 MHz instrument in $CDCl_3$. The following abbreviations are used in reporting NMR data: s, singlet; br, broad; d, doublet; t, triplet; q, quartet;; dd, doublet of doublets; dt, doublet of triplets; tq, triplet of quartets; ddd, doublet of doublet of doublets; m, multiplet.

((2*R*,3*R*)-3-*sec*-Butyl-2-methyloxiran-2-yl)methanol (14):



14

To a suspension of activated powdered 4Å molecular sieves (2 g) and CaH_2 (0.12 g, 2.96 mmol) in CH_2Cl_2 (70 mL) were added D-(–)-diisopropyl tartrate (0.62 mL, 2.96 mmol) and $Ti(O^iPr)_4$ (0.97 mL, 3.26 mmol) at –25 °C. After being stirred for another 10 min, a solution of ^{t}BuOOH (3M in toluene, 9.8 mL, 29.6 mmol) was added and the reaction mixture was stirred for another 1 h before a solution of alcohol **17** (1.9 g, 14.8 mmol) in CH_2Cl_2 (20 mL) was added. The reaction mixture was stirred for additional 4 h at the same temperature and slowly allowed to warm to –20 °C before quenching with a solution of 10% NaOH in saturated aq. NaCl (10 mL). After warming to –10 °C, the reaction mixture was diluted with diethyl ether (150 mL), treated with mixture of Na_2SO_4 (10 g) and Celite (2.5 g), and stirred for an additional 15 min. The whole suspension was then allowed to settle for 1 h before filtering through a pad of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure to afford a crude residue which was purified on a silica gel column chromatography (50% ethyl acetate/hexanes) to afford the epoxide **14** (1.8 g, 84%) as a colorless liquid.

R$_f$ = 0.29 (20% ethyl acetate/hexanes);

$[\alpha]^{20}_D$ = +33.5 (*c* 0.7, $CHCl_3$);

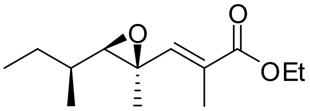
IR (neat): 3430, 2675, 1383, 1217, 1161, 1041, 949, 761 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.67 (dd, *J* = 12.5, 4.8 Hz, 1H), 3.55 (dd, *J* = 12.5, 7.7 Hz, 1H), 2.71 (d, *J* = 9.2 Hz, 1H), 1.77 (dd, *J* = 8.4, 4.4 Hz, 1H), 1.40-1.30 (m, 3H), 1.29 (s, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 65.5, 65.4, 62.0, 33.6, 26.5, 17.5, 14.6, 11.4;

HRMS (ESI): calcd. for $C_8H_{16}O_2Na$: 167.1048, found: 167.1046.

(*E*)-ethyl 3-((2*R*,3*R*)-3-sec-butyl-2-methyloxiran-2-yl)-2-methylacrylate (18):



18

A solution of alcohol **14** (1.8 g, 12.5 mmol) in 120 mL of ethyl acetate was treated with IBX (5.4 g, 18.7 mmol) and refluxed for 6 h. The reaction mixture was allowed to cool at rt, filtered through a pad of Celite and washed thoroughly with ethyl acetate. The filtrate was concentrated under reduced pressure to afford the aldehyde, which was immediately used in the next step.

To a solution of the above aldehyde in anhydrous toluene (80 mL) was added ethyl-2-(triphenylphosphoranylidene) propionate (5.88 g, 16.2 mmol) at rt and the stirring was continued for 3 h. The solvent was evaporated and the resultant residue was purified by column chromatography (4% ethyl acetate/hexanes) to afford the unsaturated ester **18** (2 g, 71% yield for two steps) as a colorless oil.

R$_f$ = 0.59 (10% ethyl acetate/hexanes);

$[\alpha]^{20}_D$ = +12.5 (*c* 0.3, $CHCl_3$);

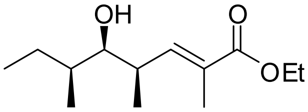
IR (neat): 2966, 2928, 2344, 1736, 1465, 1381, 1259, 1025 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (dq, *J* =10.2, 1.1 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 2.58 (d, *J* = 8.8 Hz, 1H), 1.95 (d, *J* = 1.1 Hz, 3H), 1.52-1.32 (m, 3H), 1.42 (s, 3H), 1.29 (t, *J* = 7.3 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, CDCl$_3$): δ 167.9, 140.5, 129.6, 68.9, 60.8, 60.0, 34.3, 26.3, 17.4, 16.9, 14.2, 13.2, 11.4;

HRMS (ESI): calcd. for $C_{13}H_{23}O_3$: 227.1647, found: 227.1653.

(4*R*,5*R*,6*S*,*E*)-ethyl 5-hydroxy-2,4,6-trimethyloct-2-enoate (19):



19

To the mixture of $Pd_2(dba)_3CHCl_3$ (0.27 g, 0.26 mmol) in dioxane (13 mL) was added ^{n}Bu$_3$P (66 μL, 0.26 mmol) at rt. To this was added a solution of formic acid (0.71 mL, 17.6 mmol) and triethylamine (6.2 mL, 44.2 mmol) in dioxane (26 mL) and the mixture was stirred for 5 min. The alkenyloxirane **18** (2.0 g, 8.84 mmol) in dioxane (39 mL) was added to the above brown suspension, and the mixture was stirred for 5 h. The solution was passed through a pad of Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography (10% ethyl acetate/hexanes) to give alcohol **19** (1.7 g, 85%).

R$_f$ = 0.33 (10% ethyl acetate/hexanes);

$[\alpha]^{20}_D$ = +13.6 (*c* 0.3, CHCl$_3$);

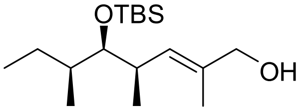
IR (neat): 3417, 2964, 1695, 1463, 1276, 1218, 1020 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$): δ 6.55 (d, *J* = 10.3 Hz, 1H), 4.19 (q, *J* = 6.9 Hz, 2H), 3.42-3.36 (m, 1H), 2.67-2.61 (m, 1H), 1.87 (s, 3H), 1.46-1.35 (m, 2H), 1.30 (t, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (100 MHz, CDCl$_3$): δ 168.2, 143.9, 127.0, 77.9, 60.5, 37.7, 37.2, 27.0, 16.2, 14.2, 12.5, 12.2, 11.7;

HRMS (ESI): calcd. For $C_{13}H_{24}O_3Na$: 251.1623, found: 251.1635.

(4*R*,5*R*,6*S*,*E*)-5-(tert-butyldimethylsilyloxy)-2,4,6-trimethyloct-2-en-1-ol (20):



20

To a stirred solution of the alcohol **19** (1.7 g, 7.45 mmol) in dry CH_2Cl_2 (45 mL), Et_3N (4.18 mL, 29.8 mmol) was added and cooled to –10 °C. After adding TBSOTf (2.22 mL, 9.69 mmol) the resulting solution was stirred at same temperature for additional 30 min and solvent was evaporated under the reduced pressure. The residue thus obtained was purified by column chromatography (2% ethyl acetate/hexanes) to afford the corresponding silyl ether (2.3 g, 90%) as a colorless oil.

R*f* = 0.76 (5% ethyl acetate/hexanes);

$[\alpha]^{20}_{D}$ = +15.7 (*c* 2.5, $CHCl_3$);

IR (neat): 2959, 2931, 2857, 1714, 1462, 1367, 1462, 1367, 1255, 1232, 1095, 836 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ 6.60 (dq, *J* = 10.8, 1.4 Hz, 1H), 4.23-4.12 (m, 2H), 3.41 (dd, *J* = 7.0, 2.9 Hz, 1H), 2.70-2.60 (m, 1H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.47-1.31 (m, 2H), 1.29 (t, *J* = 7.3 Hz, 3H), 1.26-1.03 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 145.8, 125.9, 78.9, 60.4, 39.8, 37.5, 26.8, 26.1, 18.4, 16.5, 14.2, 14.0, 12.4, 12.2, –3.6, –3.9;

HRMS (ESI): calcd. For $C_{19}H_{38}O_3NaSi$: 365.2488, found: 365.2505.

To a stirred solution of the above silyl ether (2.3 g, 6.72 mmol) in CH_2Cl_2 (65 mL) at –30 °C was added a solution of DIBAL-H (15.5 mL, 1M in toluene, 15.5 mmol) and the resultant mixture was stirred for 2 h at –20 °C. The reaction was then diluted with EtOAc (60 mL) and saturated aq. solution of Na, K-tartarate was added. After being stirred for an additional 2 h at rt, two layers were separated and aq. layer was further extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography (10% ethyl acetate/hexanes) to afford the allylic alcohol **20** (1.7 g, 85%) as colorless oil.

R*f* = 0.28 (10% ethyl acetate/hexanes).

$[\alpha]^{20}_{D}$ = +7.7 (*c* 1.0, $CHCl_3$);

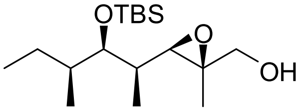
IR (neat): 3367, 2959, 2930, 2858, 1463, 1256, 1064, 1020, 836 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ 5.21 (dq, *J* = 10.2, 1.1 Hz, 1H), 3.98 (d, *J* = 5.5 Hz, 2H), 3.33 (dd, *J* = 7.7, 2.6 Hz, 1H), 2.58–2.49 (m, 1H), 1.62 (d, *J* = 1.1 Hz, 3H), 1.44-1.34 (m, 2H), 1.29 (t, *J* = 5.8 Hz, 1H), 1.25-1.09 (m, 1H),0.93 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 132.9, 130.7, 79.6, 69.1, 39.3, 36.3, 27.0, 26.2, 18.5, 17.7, 13.9, 13.8, 12.3, –3.6;

HRMS (ESI): calcd. for $C_{17}H_{36}O_2NaSi$: 323.2382, found: 323.2393.

((2*R*,3*R*)-3-((2*R*,3*R*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-4-methylhexan-2-yl)-2-methyloxiran-2-yl)methanol (12):



12

To a stirred solution of the alcohol **20** (1.7 g, 5.66 mmol) in dry CH_2Cl_2 (60 mL) at –42 °C, $Ti(O^iPr)_4$ (2.26 mL, 8.49 mmol) was added. After being stirred for 15 min, ^tBuOOH (2.26 mL, 3M, 6.8 mmol) was introduced and solution was stirred for 9 h. at same temperature and then at –23 °C for another 12 h. Reaction was quenched by the addition of half saturated Na-K tartarate with removal of cooling bath. Stirring was continued for an additional 2 h and then solution was poured into 150 mL of ether. Two layers were separated and aq. layer was further extracted with EtOAc (3 x 20 mL). Combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated to afford the residue which upon purification with flash chromatography (20% ethyl acetate/hexanes) gave the epoxy alcohol **12** (1.5 g, 84%) as a colorless viscous oil.

R*f* = 0.37 (20% ethyl acetate/hexanes);

$[\alpha]^{20}_D$ = +7.6 (*c* 0.5, $CHCl_3$);

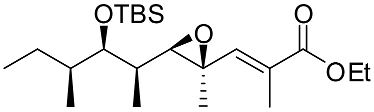
IR (neat): 3440, 2959, 2930, 2857, 1463, 1257, 1026, 836, 673 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (dd, *J* = 12.3, 4.0 Hz, 1H), 3.53 (dd, *J* = 12.3, 8.6 Hz, 1H), 3.47 (t, *J* = 3.6 Hz, 1H), 2.92 (d, *J* = 9.4 Hz, 1H), 1.79 (dd, *J* = 8.2, 4.0 Hz, 1H), 1.49–1.43 (m, 2H), 1.29 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.86 (t, *J* = 7.0 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 76.9, 65.3, 64.1, 62.2, 39.8, 36.0, 26.4, 26.1, 18.4, 15.0, 14.8, 13.2, 12.3, –3.7, –4.2;

HRMS (ESI): calcd. for $C_{17}H_{36}O_3NaSi$: 339.2331, found: 339.2320.

(*E*)-ethyl 3-((2*R*,3*R*)-3-((2*R*,3*R*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-4-methylhexan-2-yl)-2-methyloxiran-2-yl)-2-methylacrylate (21):



21

A solution of **12** (1.5 g, 4.75 mmol) in 50 mL of ethyl acetate was treated with IBX (2 g, 7.12 mmol) and refluxed for 6 h. The reaction mixture was cooled to rt and filtered through a pad of

Celite and washed thoroughly with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure to afford an aldehyde, which was immediately used in the next step.

To the solution of above aldehyde in anhydrous toluene (40 mL) was added ethyl-2-(triphenylphosphoranylidene)propionate (2.23 g, 6.17 mmol) at rt and the stirring was then continued for 3 h. The solvent was evaporated and the resultant residue was purified by column chromatography (5% ethyl acetate/hexanes) to afford the unsaturated ester **21** (1.6 g, 85% for two steps) as a colorless oil.

R*f* = 0.59 (10% ethyl acetate/hexanes);

[α]^{20}$_D$ = –31.0 (*c* 1.0, $CHCl_3$);

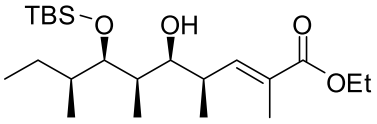
IR (neat): 2960, 2933, 2858, 1716, 1655, 1463, 1383, 1259, 1027, 837, 672 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (s, 1H), 4.17 (q, *J* = 7.3 Hz, 2H), 3.55 (t, *J* = 3.7 Hz, 1H), 2.73 (d, *J* = 9.5 Hz, 1H), 1.96 (d, *J* = 1.1 Hz, 3H), 1.69-1.60 (m, 1H), 1.58-1.53 (m, 2H), 1.42 (s, 3H), 1.28 (t, *J* = 7.3 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.88 (m, 15H), 0.08 (s, 3H), 0.05 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 140.5, 129.9, 77.1, 67.2, 60.8, 60.6, 40.2, 36.0, 26.4, 26.1, 18.4, 17.9, 14.9, 14.2, 13.3, 12.4, 12.1, –3.7, –3.9;

HRMS (ESI): calcd. for $C_{22}H_{42}O_4NaSi$: 421.2750, found: 421.2757.

(4*R*,5*S*,6*R*,7*R*,8*S*,*E*)-ethyl 7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,4,6,8-tetramethyldec-2-enoate (11):



11

To the mixture of $Pd_2(dba)_3CHCl_3$ (0.125 g, 0.12 mmol) in dioxane (8 mL) was added PPh_3 (0.031 g, 0.12 mmol) at rt and stirred for 1 min. To this was added a solution of formic acid (0.32 mL, 8.08 mmol) and triethylamine (2.04 mL, 20 mmol) in dioxane (16 mL) and the mixture was stirred for 5 min. The alkenyloxirane **21** (1.6 g, 4.04 mmol) in dioxane (24 mL) was added to the above brown suspension, and the mixture was stirred for 16 h. The solution was passed through a pad of Celite and filtrate was concentrated under reduced pressure and residue was purified by flash chromatography (5% ethyl acetate/hexanes) to afford **11** (1.3 g, 81%).

R*f* = 0.49 (20% ethyl acetate/hexanes);

[α]^{20}$_D$ = +13.6 (*c* 1.0, $CHCl_3$);

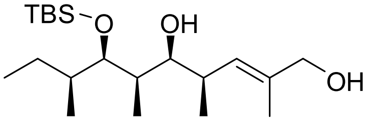
IR (neat): 2960, 2933, 1713, 1464, 1374, 1217, 1023, 836 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$): δ 6.49 (dq, *J* = 10.2, 1.1 Hz, 1H), 4.23-4.15 (m, 2H), 3.65-3.61 (m, 1H), 3.48-3.46 (m, 1H), 2.67-2.57 (m, 1H), 2.15 (d, *J* = 4.0 Hz, 1H), 1.86 (d, *J* = 1.1 Hz, 3H), 1.69-1.53 (m, 4H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.87 (d, *J* = 7.4 Hz, 3H), 0.84 (d, *J* = 7.2 Hz, 3H), 0.82 (t, *J* = 6.9 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H);

^{13}C NMR (100 MHz, CDCl$_3$): δ 168.1, 143.6, 127.3, 79.8, 78.6, 60.4, 39.9, 38.0, 37.6, 26.1, 26.0, 25.7, 18.3, 16.5, 14.6, 14.2, 12.4, 8.2, –3.5, –4.3;

HRMS (ESI): calcd. for $C_{22}H_{45}O_4Si$: 401.3087, found: 401.3076.

(4*R*,5*S*,6*R*,7*R*,8*S*,*E*)-7-(*tert*-butyldimethylsilyloxy)-2,4,6,8-tetramethyldec-2-ene-1,5-diol:



To a solution of ester **11** (0.10 g, 0.25 mmol) in CH_2Cl_2 (6 mL) was added DIBAL-H (0.6 mL, 0.6 mmol, 1M in toluene) at –78 °C. The solution was stirred at the same temperature for 1 h. The reaction mixture was treated with a saturated solution of Na, K-tartarate (5 mL) and the mixture was stirred until the solution became clear. The organic layer was separated from the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with water, brine and dried over Na_2SO_4. Concentration of the solution followed by silica gel column purification (12% ethyl acetate/hexanes) afforded the diol (0.08 g, 90%) as a viscous oil.

R*$_f$* = 0.30 (20% ethyl acetate/hexanes);

$[\alpha]^{20}_D$ = +11.0 (*c* 2.0, CHCl$_3$);

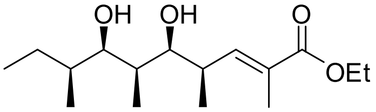
IR (neat): 3390, 2959, 2930, 2858, 1650, 1463, 1379, 1254, 1054, 836 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.14 (dq, *J* = 9.9, 1.1 Hz, 1H), 3.98 (s, 2H), 3.61 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.35 (dd, *J* = 9.2, 1.8 Hz, 1H), 2.54-2.46 (m, 1H), 1.79-1.70 (m, 2H), 1.68 (d, *J* = 1.1 Hz, 3H), 1.63-1.49 (m, 2H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.87 (d, *J* = 7.4 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.81 (t, *J* = 6.9 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H);

^{13}C NMR (100 MHz, CDCl$_3$): δ 134.5, 128.7, 79.8, 79.0, 68.7, 39.9, 37.5, 36.3, 26.1, 25.8, 18.3, 17.4, 14.6, 13.9, 12.5, 8.4, –3.4, –4.2;

HRMS (ESI): calcd. for $C_{20}H_{42}O_3SiNa$: 381.2801, found: 381.2795.

(4*R*,5*S*,6*S*,7*R*,8*S*,*E*)-ethyl 5,7-dihydroxy-2,4,6,8-tetramethyldec-2-enoate (22):



22

To a stirred solution of silyl ether **11** (0.05 g, 0.13 mmol) in THF (2.5 mL) at 0 °C was added the solution of TBAF (0.19 mL, 1 M in THF, 0.19 mmol) and the reaction mixture was stirred at 0 °C for 30 min, then at rt for 3 h. 1 mL of water was added to the reaction mixture and extracted with EtOAc (4 x 5 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. Concentration of the solution followed by silica gel column purification (30% ethyl acetate/hexanes) afforded the diol **22** (0.03 g, 85%)

R*f* = 0.27 (30% ethyl acetate/hexanes);

$[\alpha]^{20}_D$ = +16.4 (*c* 1.0, $CHCl_3$);

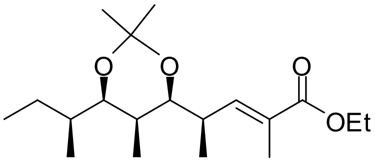
IR (neat): 3422, 2967, 2934, 1709, 1650, 1463, 1369, 1227, 1156, 1096, 970 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.49 (dq, *J* = 10.2, 1.1 Hz, 1H), 4.25–4.13 (m, 2H), 3.61 (d, *J* = 9.5 Hz, 1H), 3.46 (dd, *J* = 8.8, 1.8 Hz, 1H), 3.39 (bs, 1H), 2.72–2.64 (m, 1H), 2.34 (bs, 1H), 1.88 (d, *J* = 1.1 Hz, 3H), 1.55–1.45 (m, 1H), 1.40–1.32 (m, 2H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 143.5, 127.7, 81.8, 80.8, 60.7, 37.9, 37.7, 36.5, 25.5, 16.9, 15.1, 14.4, 12.7, 10.9, 4.9;

HRMS (ESI): calcd. for $C_{16}H_{30}O_4Na$: 309.2042, found: 309.2041.

(*R*,*E*)-ethyl-4-((4*S*,5*S*,6*R*)-6-*sec*-butyl-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylpent-2-enoate (23):



23

To the stirred solution of above diol **22** (0.03 g, 0.1 mmol) in 2,2-dimethoxy propane (4 mL) was added PPTS (5 mg) and the mixture was stirred for 1.5 h at 50 °C. The reaction mixture was then quenched by adding water and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed successively with water, brine and dried over Na_2SO_4. Concentration of the solution followed by silica gel column purification (8% ethyl acetate/hexanes) afforded the ester **23** (0.025 g, 74%)

R*f* = 0.83 (20% ethyl acetate/hexanes);

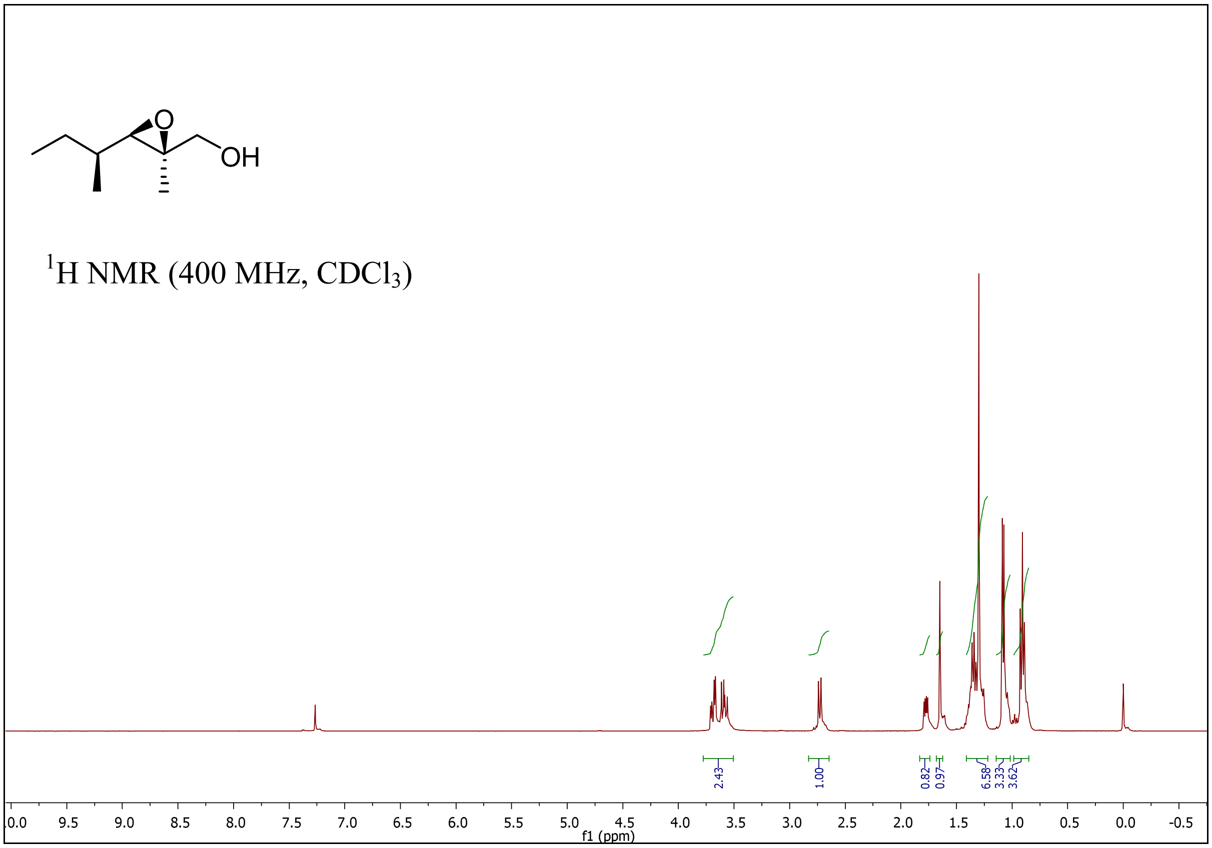
[α]^{20}$_D$ = +6.2 (*c* 2.0, $CHCl_3$);

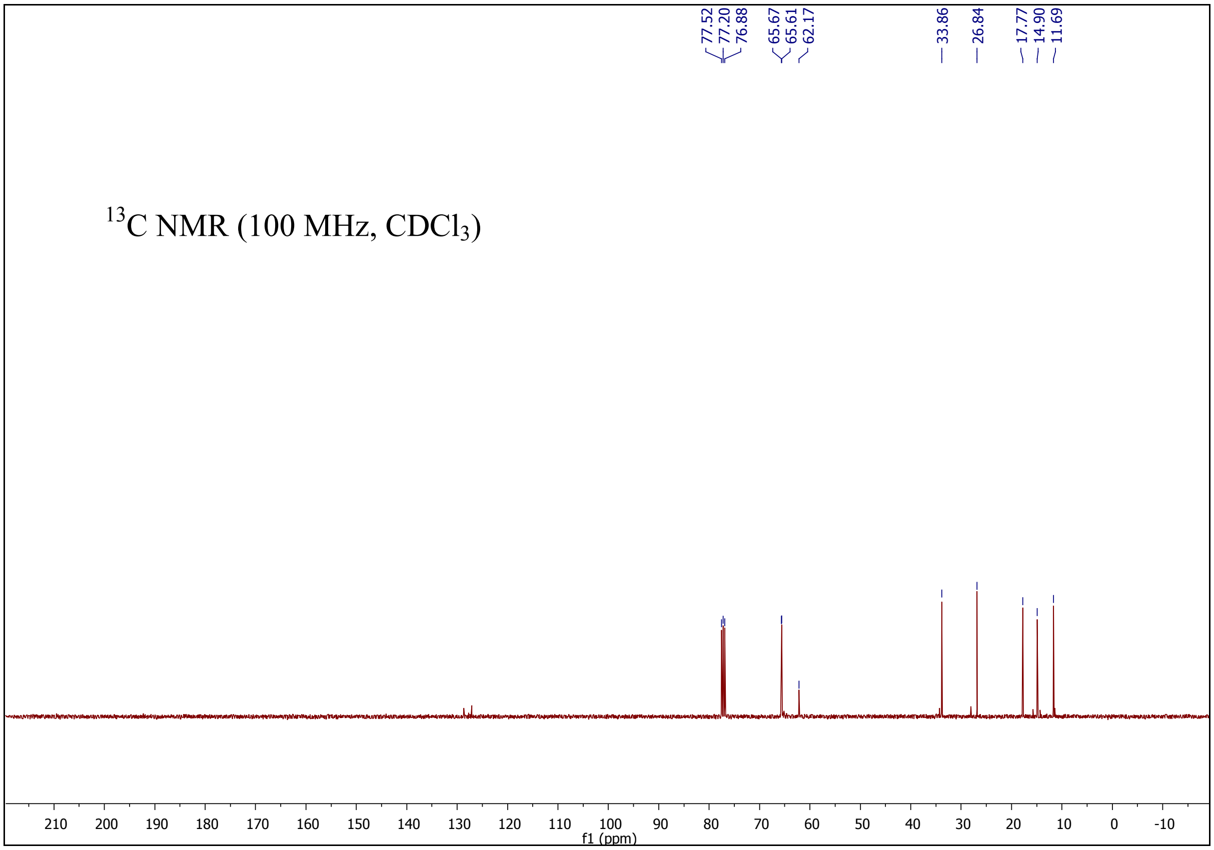
IR (neat): 2968, 2939, 1706, 1650, 1460, 1380, 1217, 1179, 1096, 1013 cm^{-1};

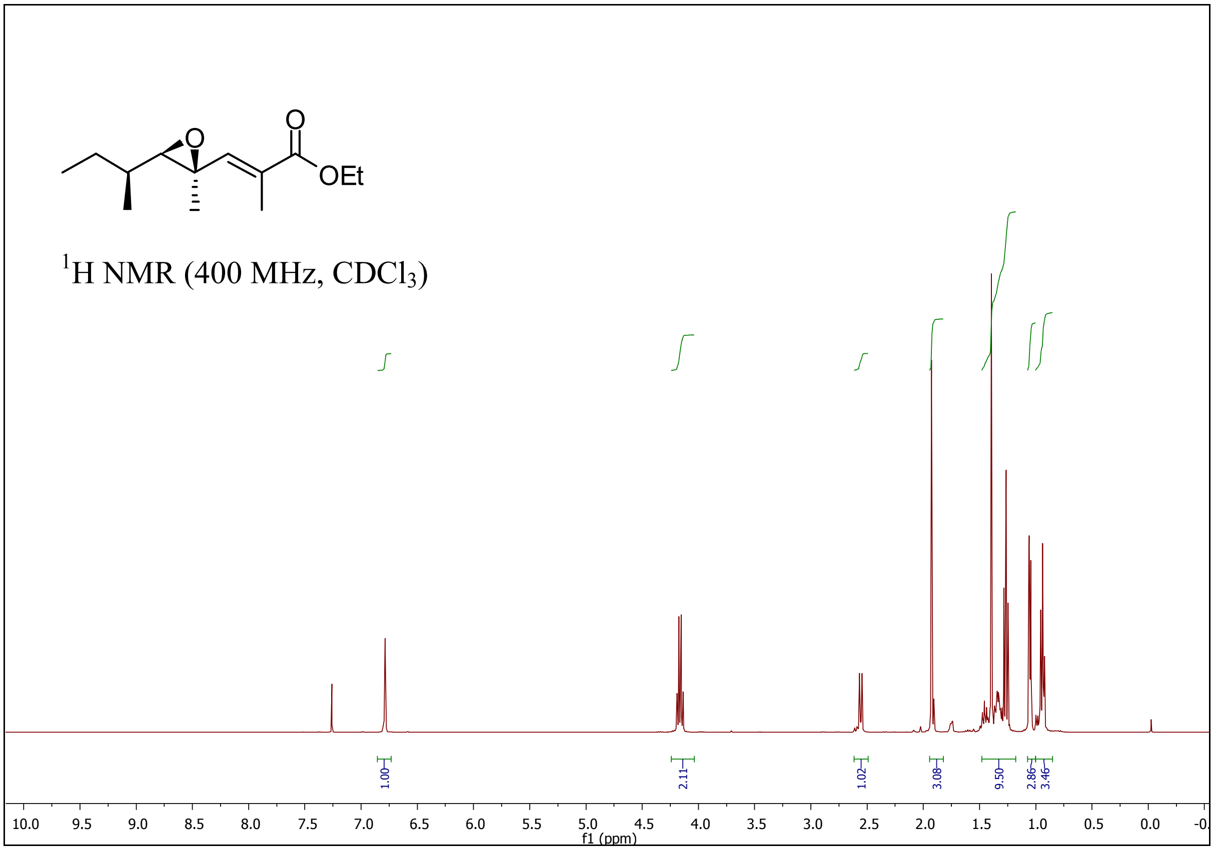
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.50 (dq, *J* = 10.2, 1.1 Hz, 1H), 4.20 (q, *J* = 7.3 Hz, 2H), 3.60 (dd, *J* = 9.5, 1.8 Hz, 1H), 3.34 (dd, *J* = 9.9, 1.8 Hz, 1H), 2.69-2.61 (m, 1H), 1.88 (d, *J* = 1.1 Hz, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.30 (t, *J* = 7.3 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.73 (d, *J* = 7.0 Hz, 3H);

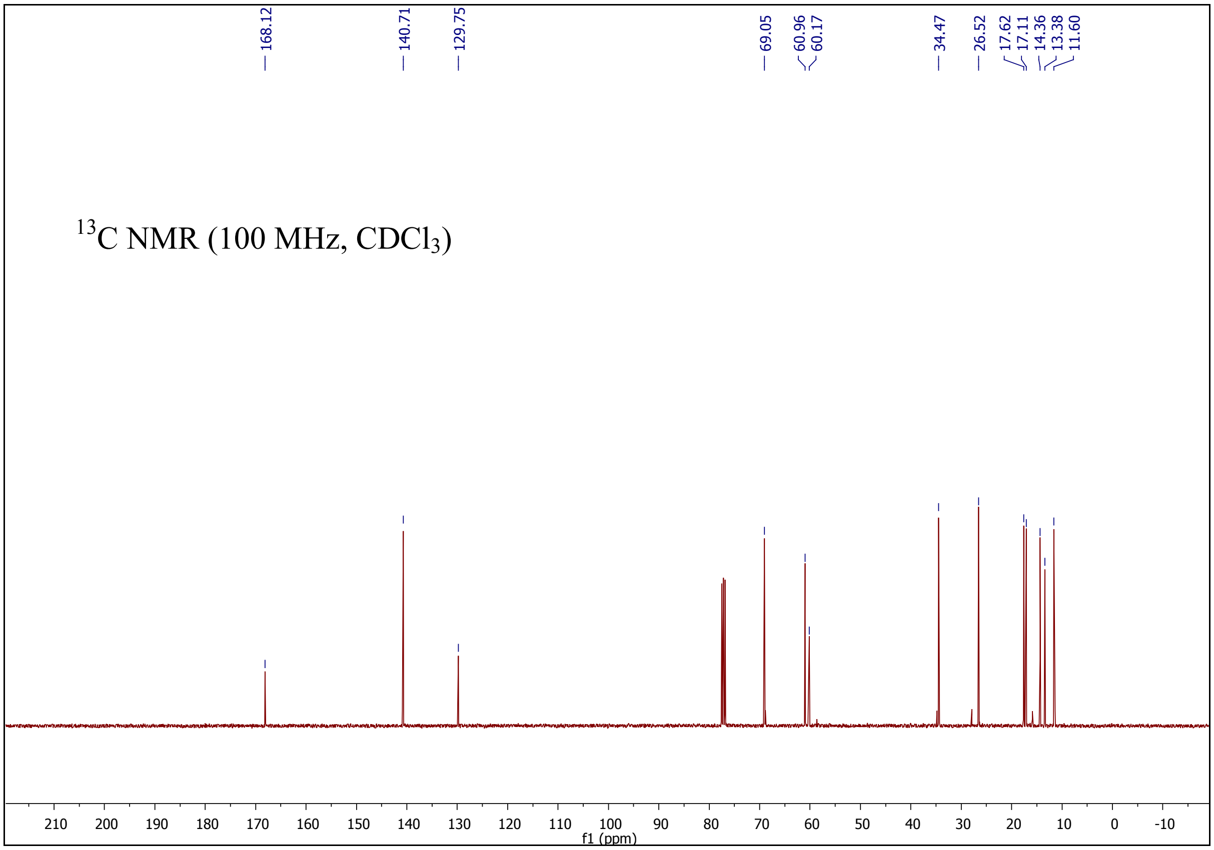
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 142.4, 127.8, 98.9, 78.0, 77.5, 60.5, 35.7, 35.5, 31.9, 29.9, 23.5, 19.5, 16.8, 15.4, 14.2, 12.5, 10.9, 5.0;

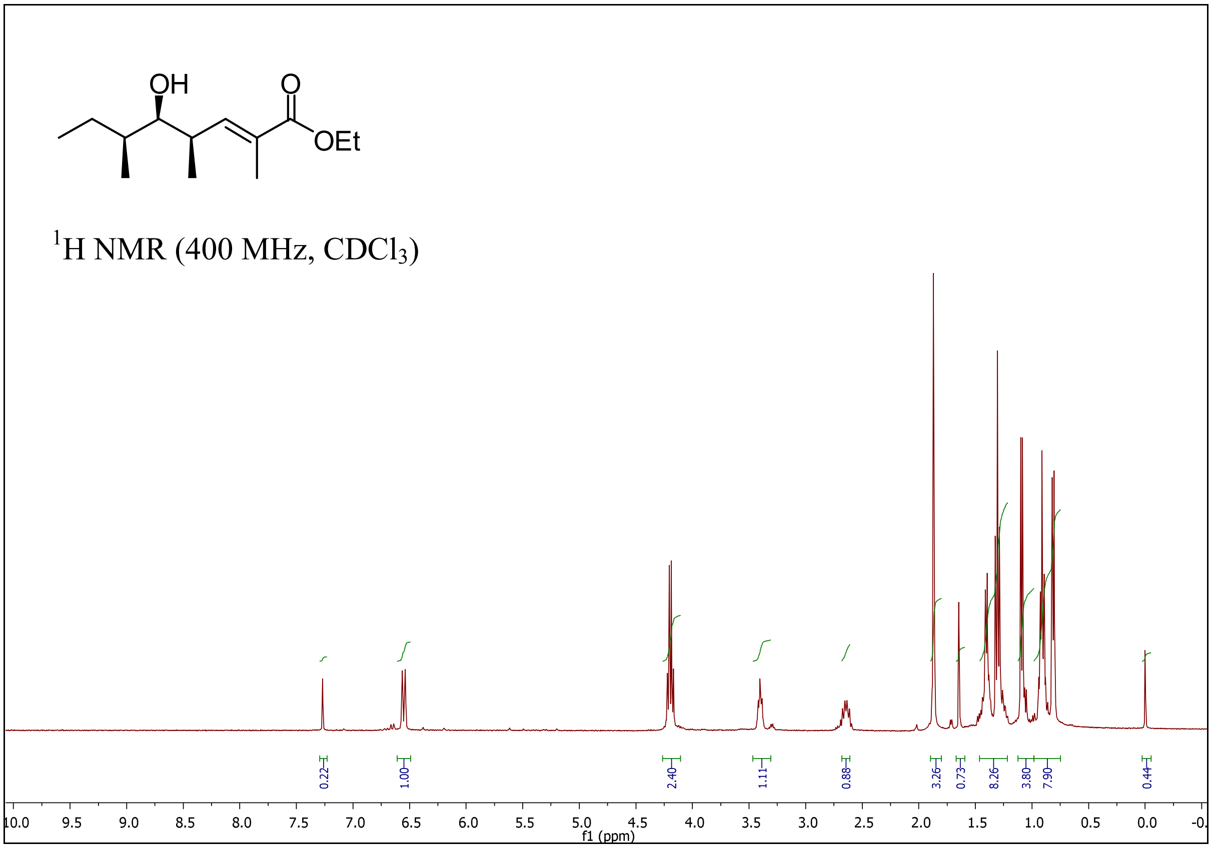
HRMS (ESI): calcd. for $C_{19}H_{34}O_4Na$: 349.2355, found: 349.2345.

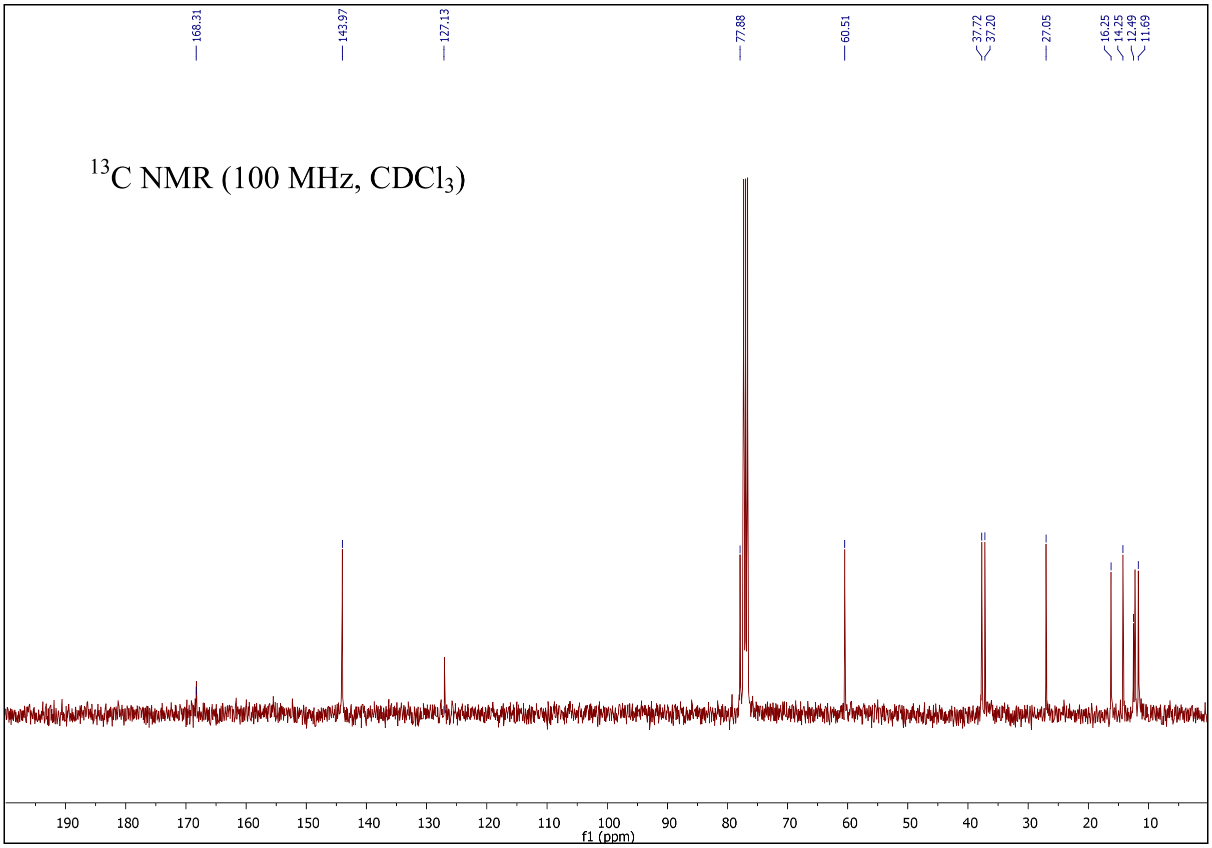

OH
O
^{1}H NMR (400 MHz, CDCl$_3$)
2.43
1.00
0.82
0.97
6.58
3.33
3.62
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

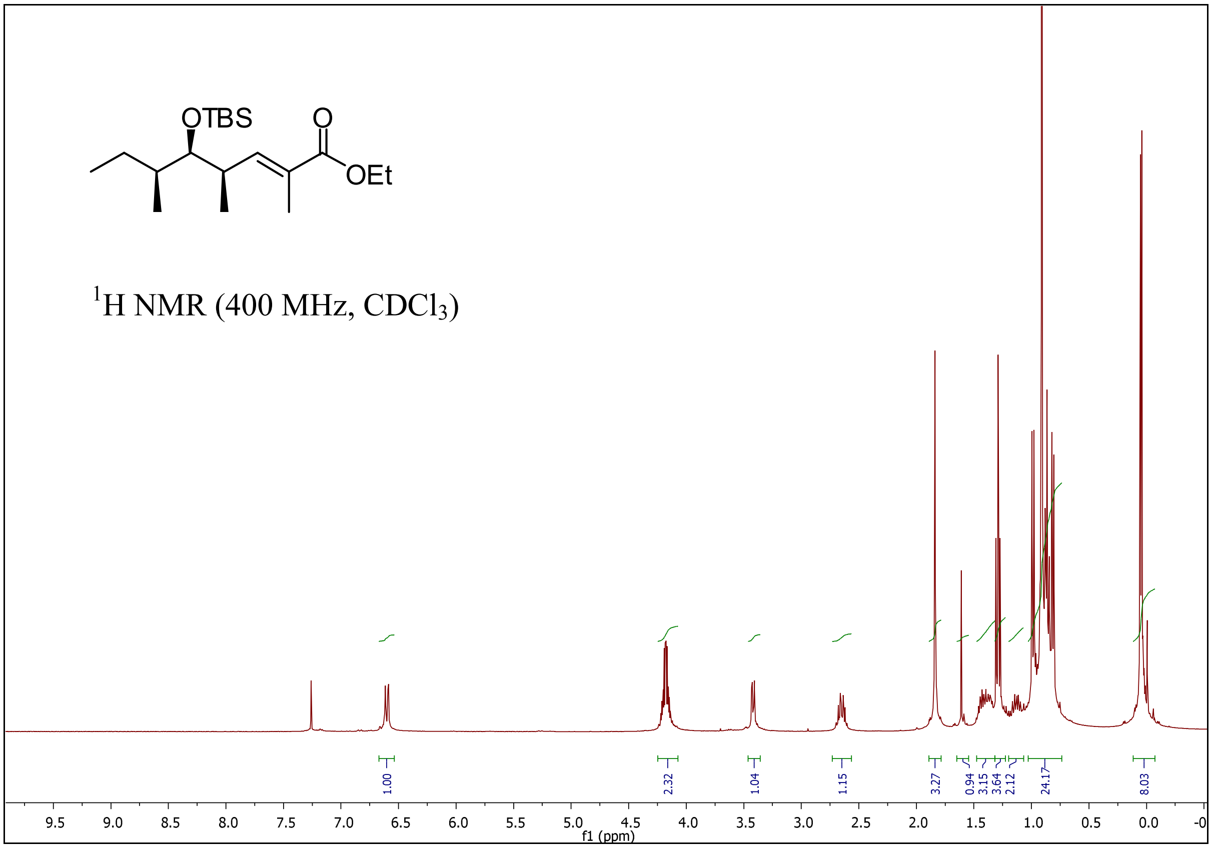

77.52
77.20
76.88
65.67
65.61
62.17
33.86
26.84
17.77
14.90
11.69
^{13}C NMR (100 MHz, CDCl$_3$)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

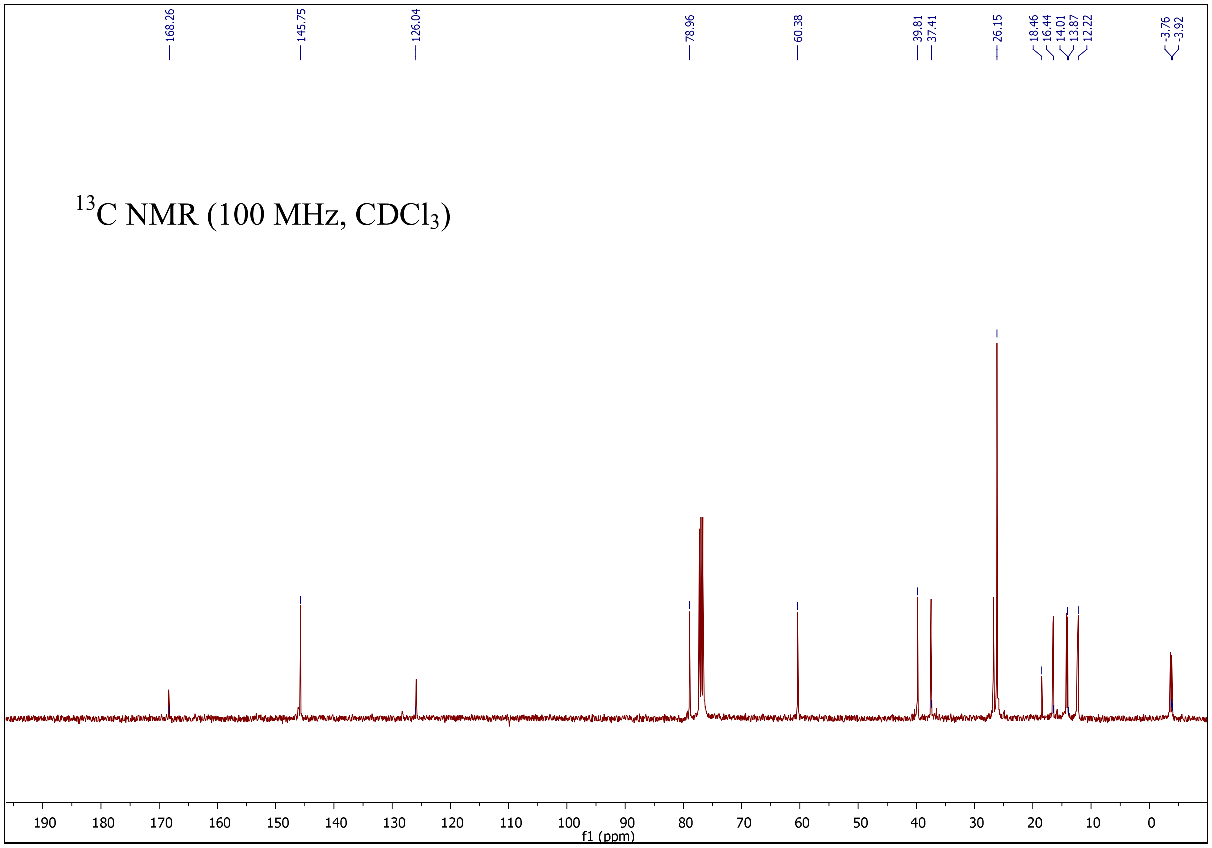

O
O
OEt
^{1}H NMR (400 MHz, CDCl$_3$)
1.00
2.11
1.02
3.08
9.50
2.86
3.46
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

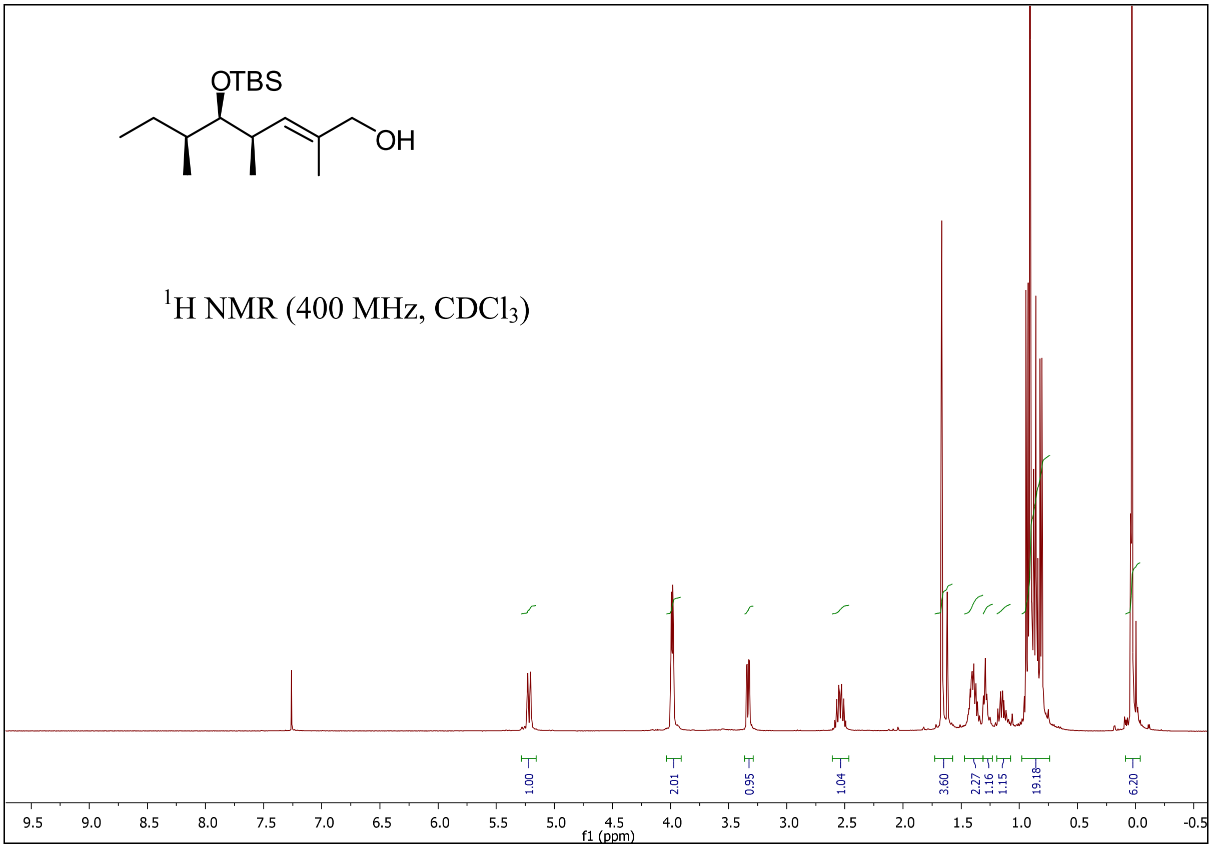

168.12
140.71
129.75
69.05
60.96
60.17
34.47
26.52
17.62
17.11
14.36
13.38
11.60
^{13}C NMR (100 MHz, CDCl$_3$)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

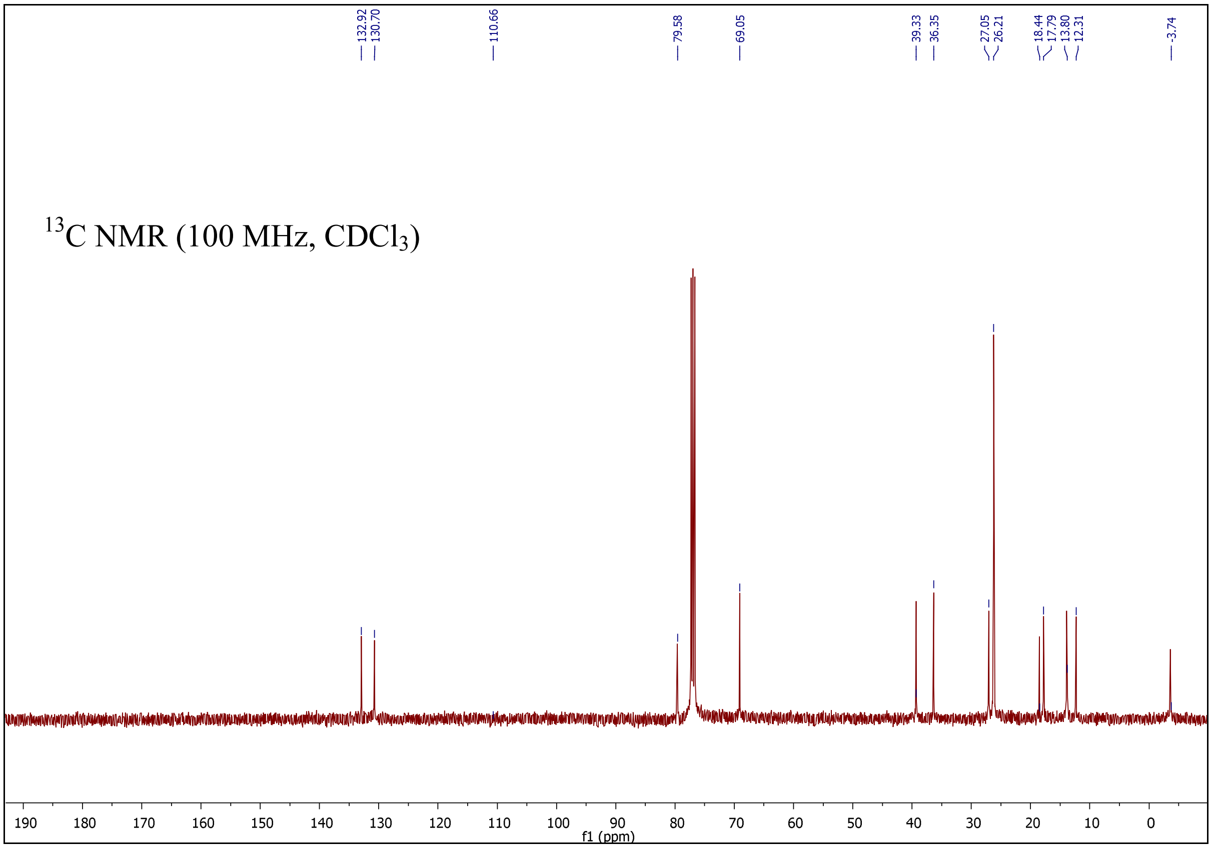

OH
O
OEt
^{1}H NMR (400 MHz, CDCl$_3$)
0.22
1.00
2.40
1.11
0.88
3.26
0.73
8.26
3.80
7.90
0.44
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.
f1 (ppm)

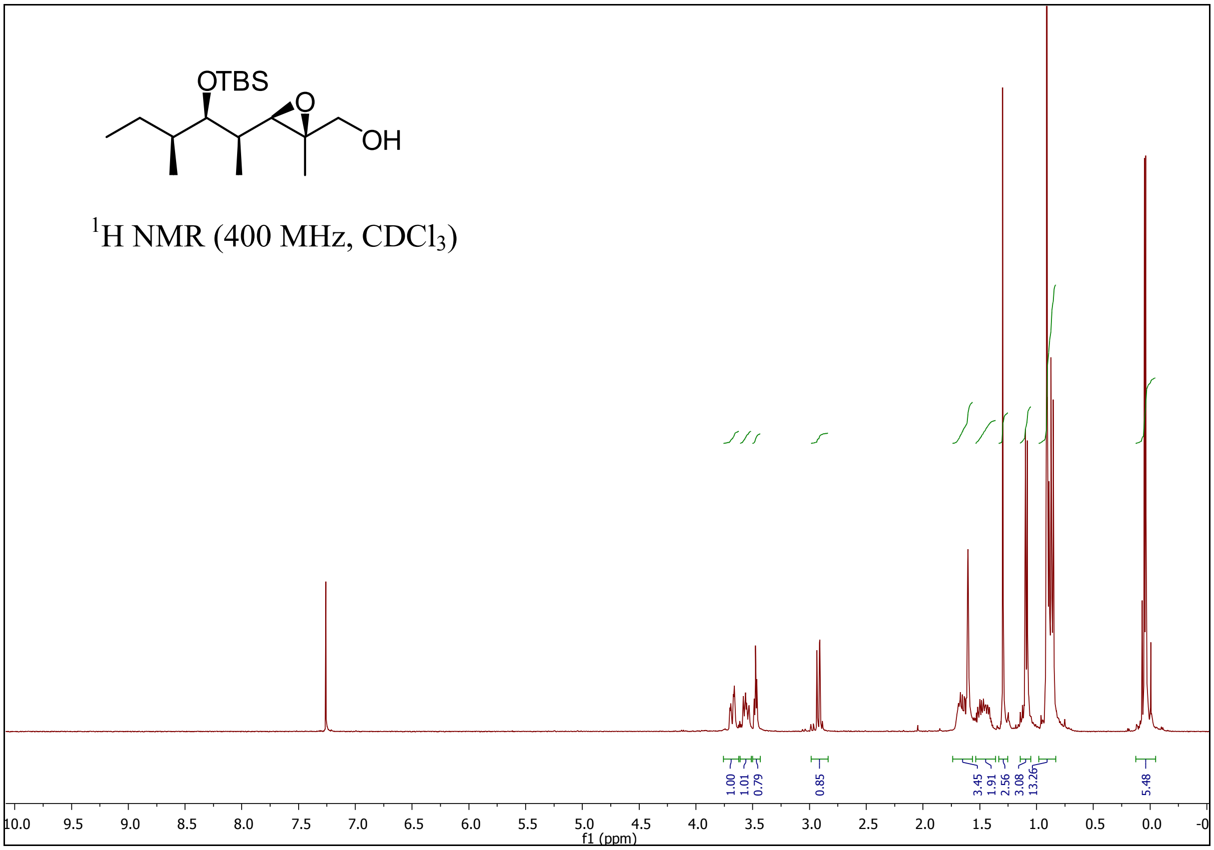

168.31
143.97
127.13
77.88
60.51
37.72
37.20
27.05
16.25
14.25
12.49
11.69
^{13}C NMR (100 MHz, CDCl$_3$)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

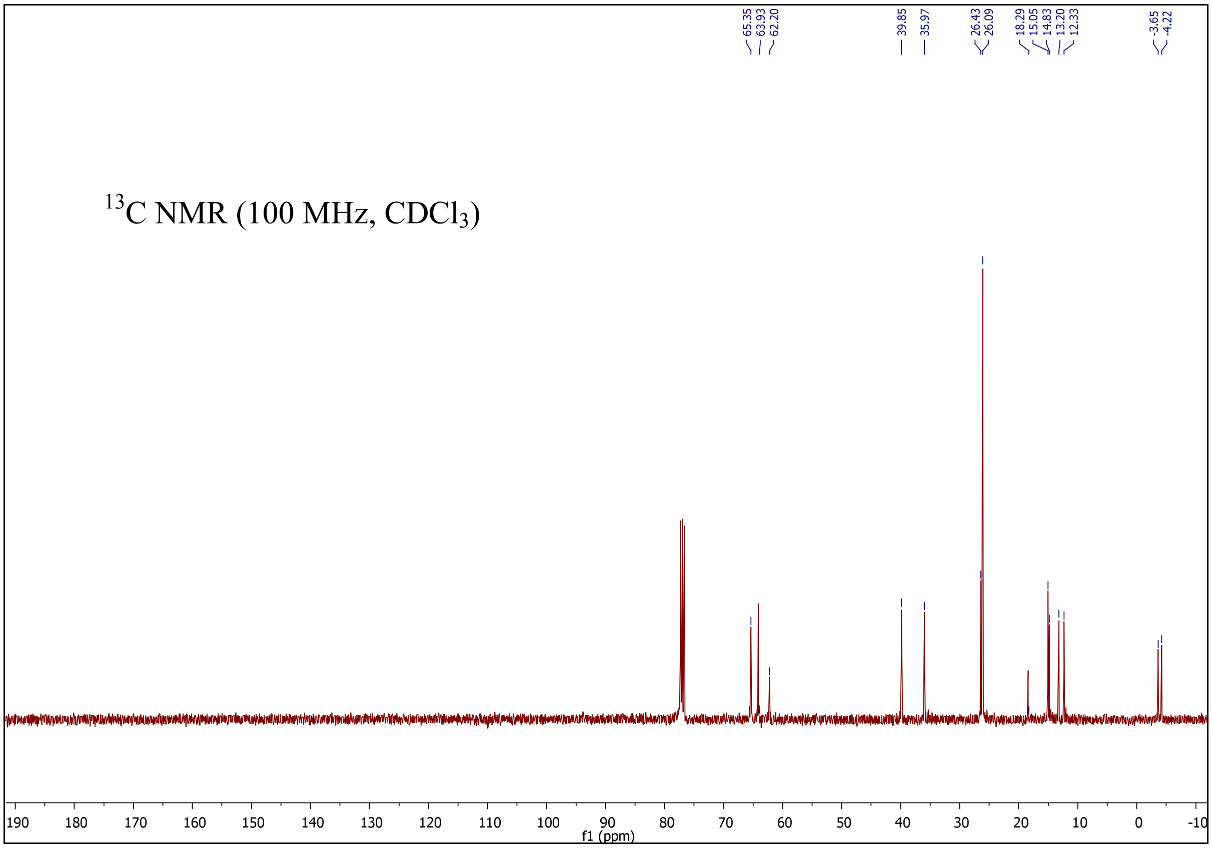

OTBS
O
OEt
^{1}H NMR (400 MHz, CDCl$_3$)
1.00
2.32
1.04
1.15
3.27
0.94
3.15
3.64
2.12
24.17
8.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

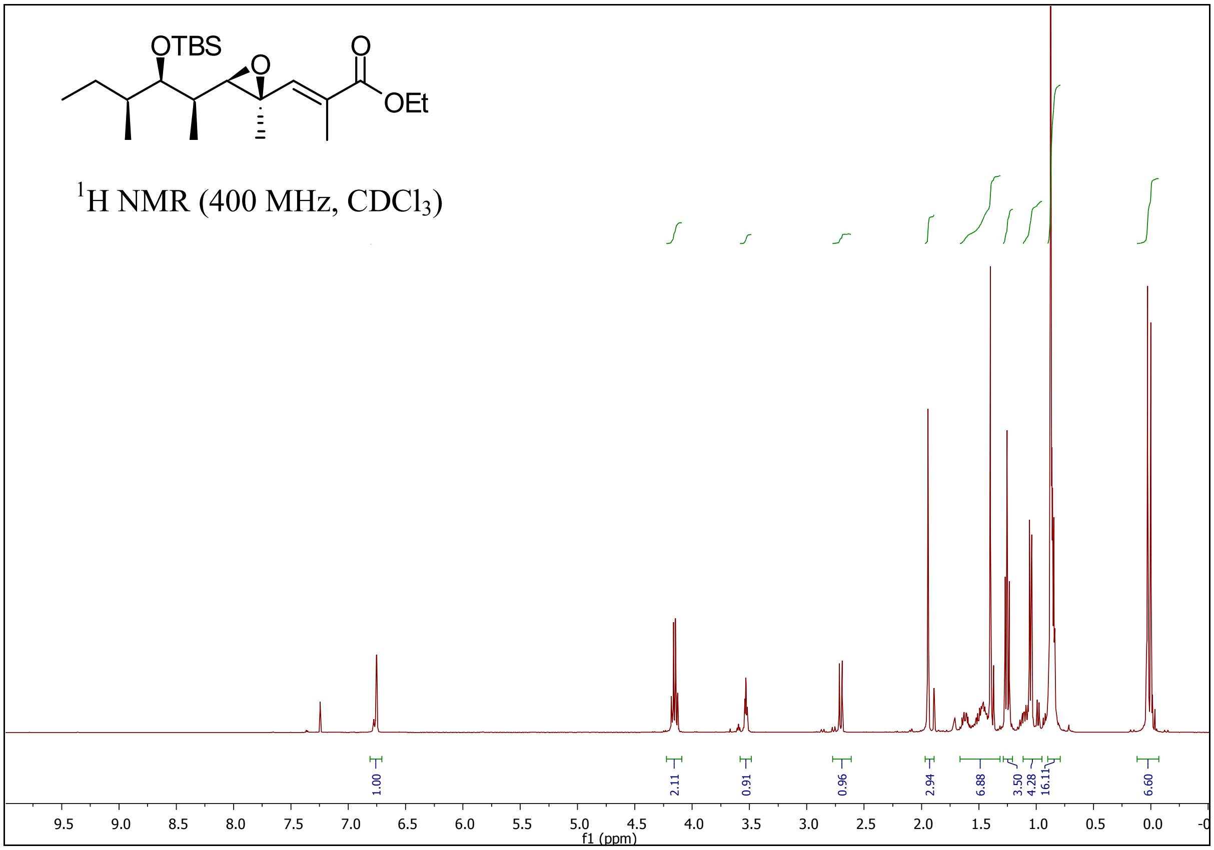

168.26
145.75
126.04
78.96
60.38
39.81
37.41
26.15
18.46
16.44
14.01
13.87
12.22
-3.76
-3.92
^{13}C NMR (100 MHz, CDCl$_3$)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

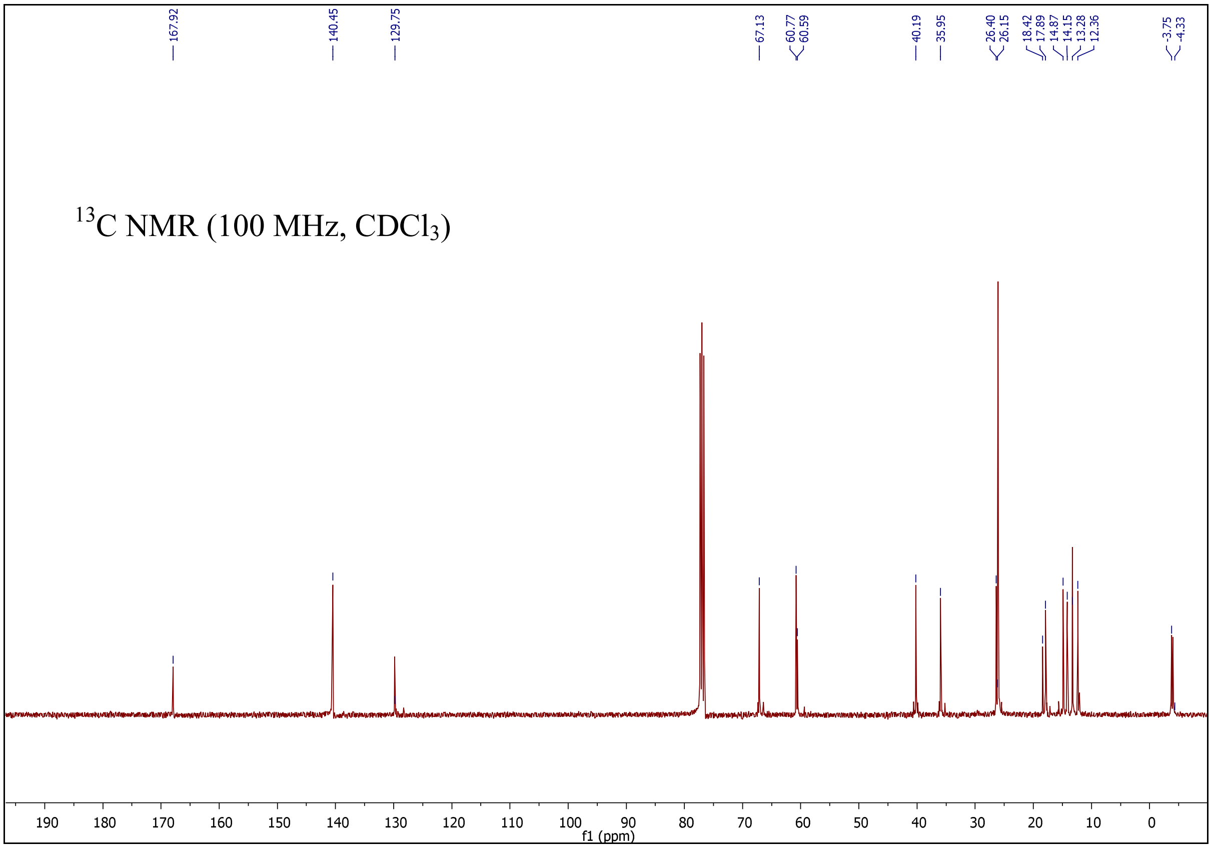

OTBS
OH
^{1}H NMR (400 MHz, CDCl$_3$)
1.00
2.01
0.95
1.04
3.60
2.27
1.16
1.15
19.18
6.20
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

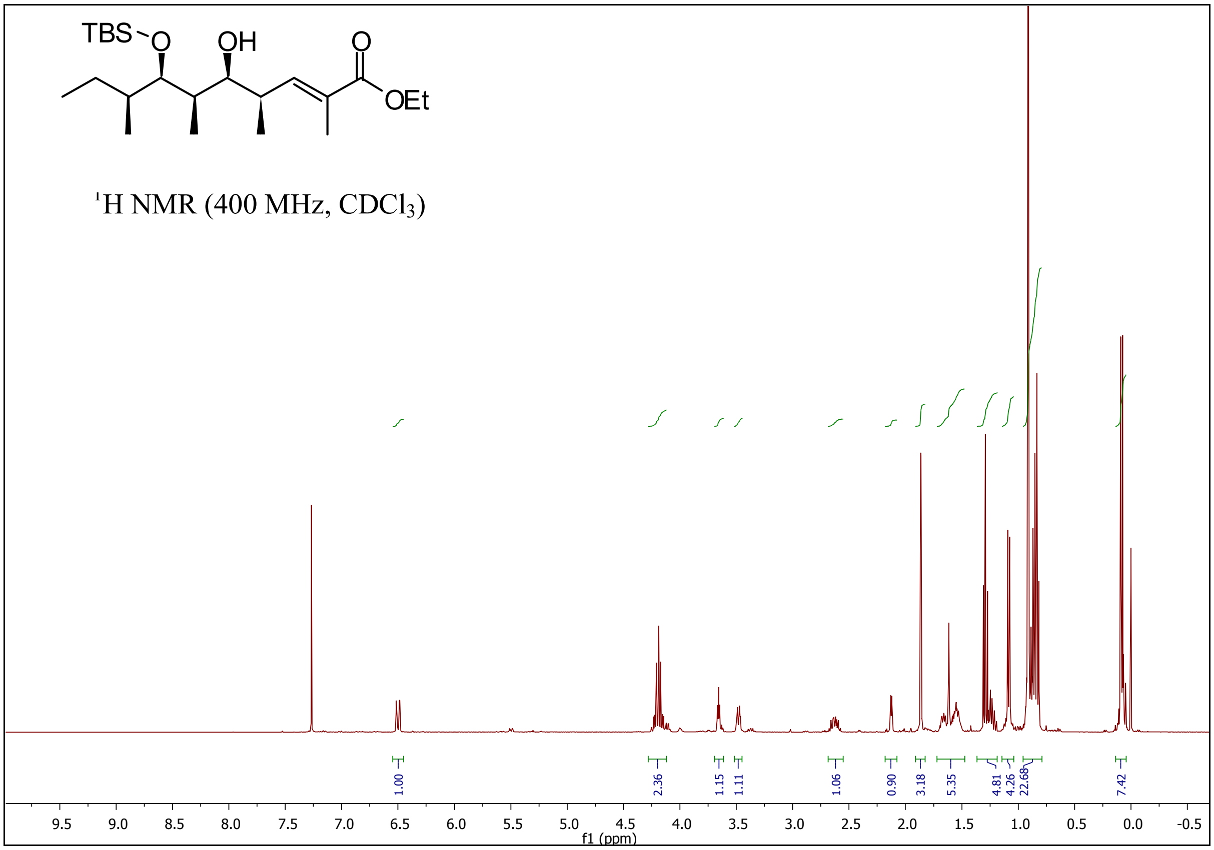

132.92
130.70
110.66
79.58
69.05
39.33
36.35
27.05
26.21
18.44
17.79
13.80
12.31
-3.74
^{13}C NMR (100 MHz, CDCl$_3$)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

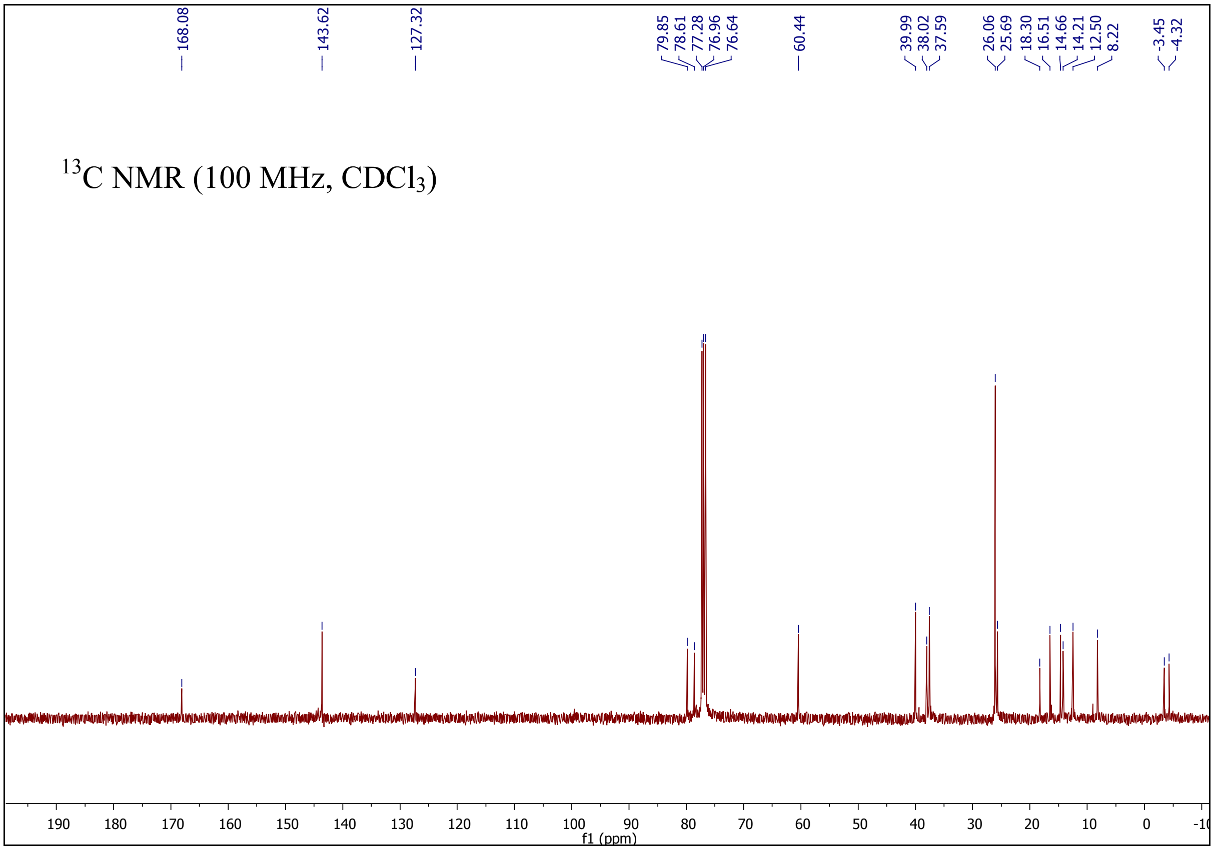

OTBS
O
OH
^{1}H NMR (400 MHz, CDCl$_3$)
1.00
1.01
0.79
0.85
3.45
1.91
2.56
3.08
13.26
5.48
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

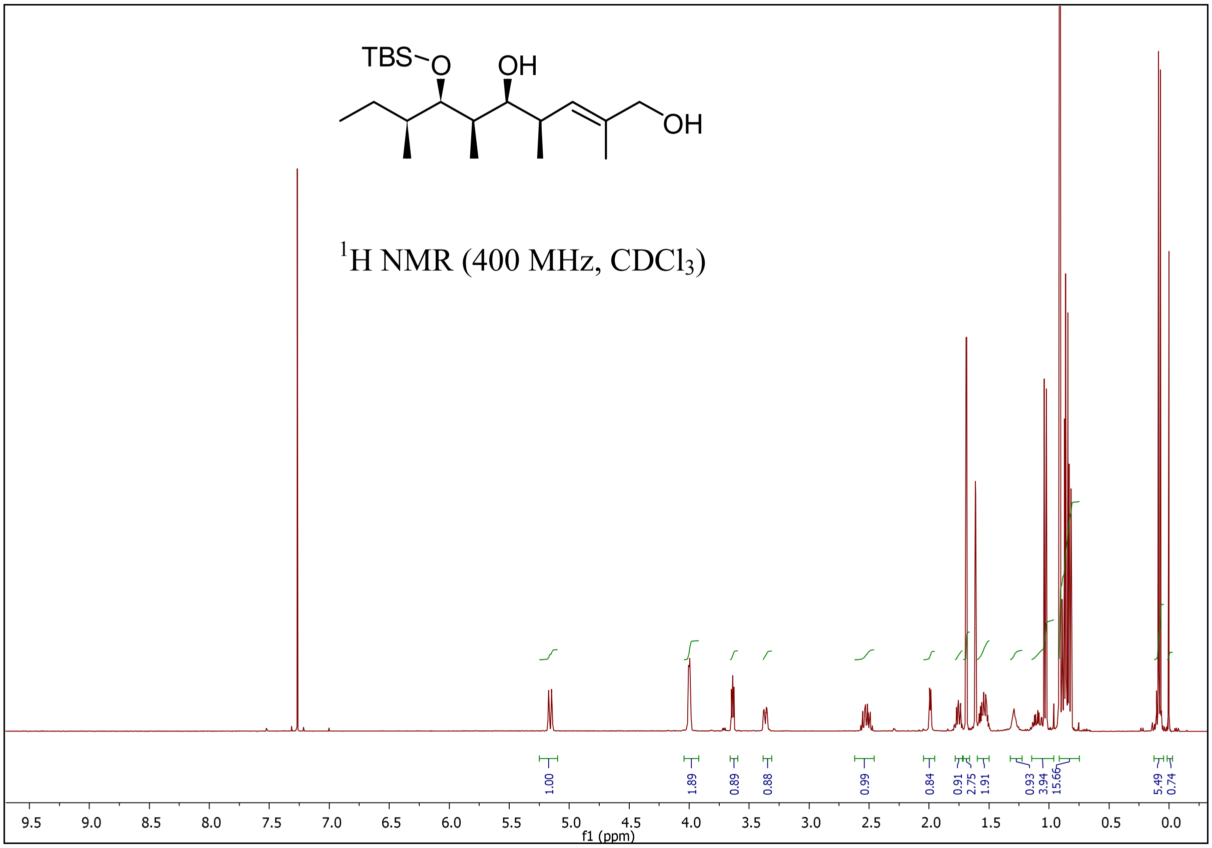

65.35
63.93
62.20
39.85
35.97
26.43
26.09
18.29
15.05
14.83
13.20
12.33
-3.65
-4.22
^{13}C NMR (100 MHz, CDCl$_3$)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

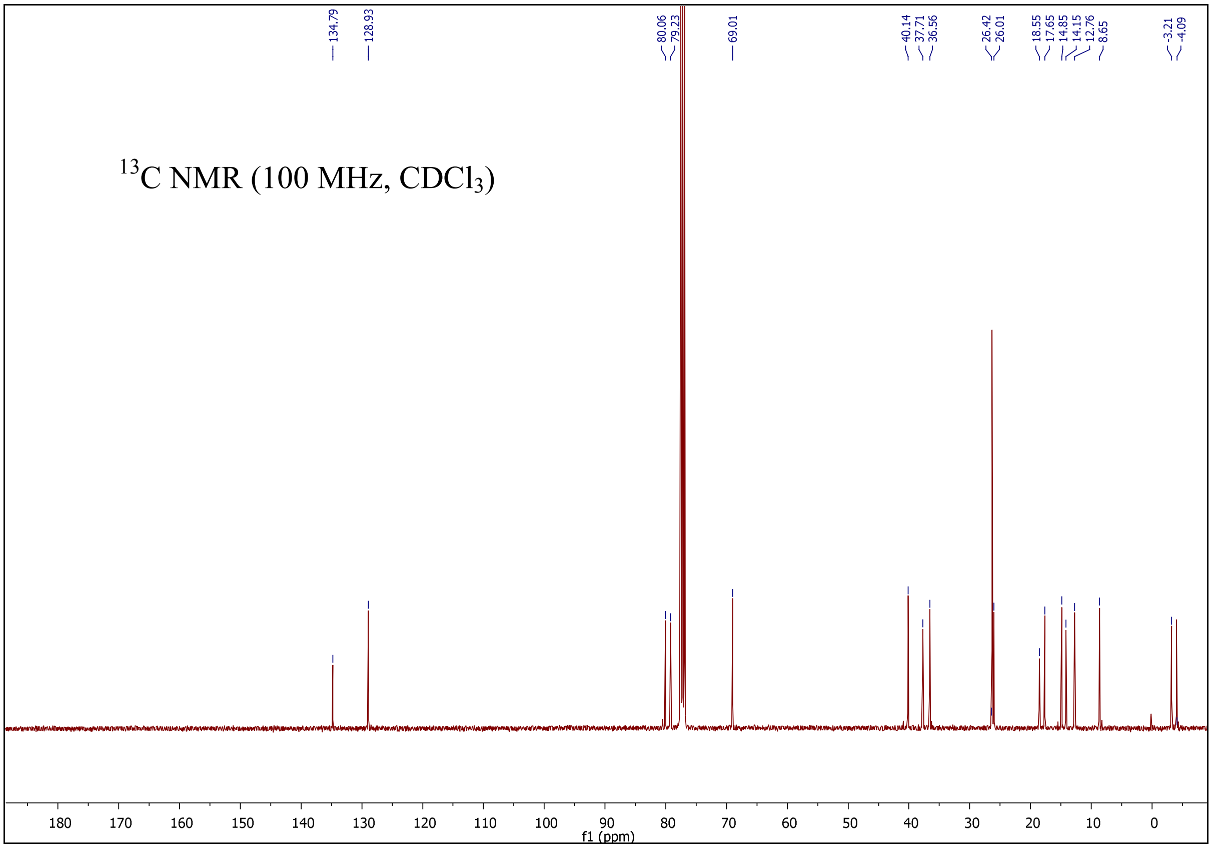

OTBS
O
O
OEt
^{1}H NMR (400 MHz, CDCl$_3$)
1.00
2.11
0.91
0.96
2.94
6.88
3.50
4.28
16.11
6.60
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

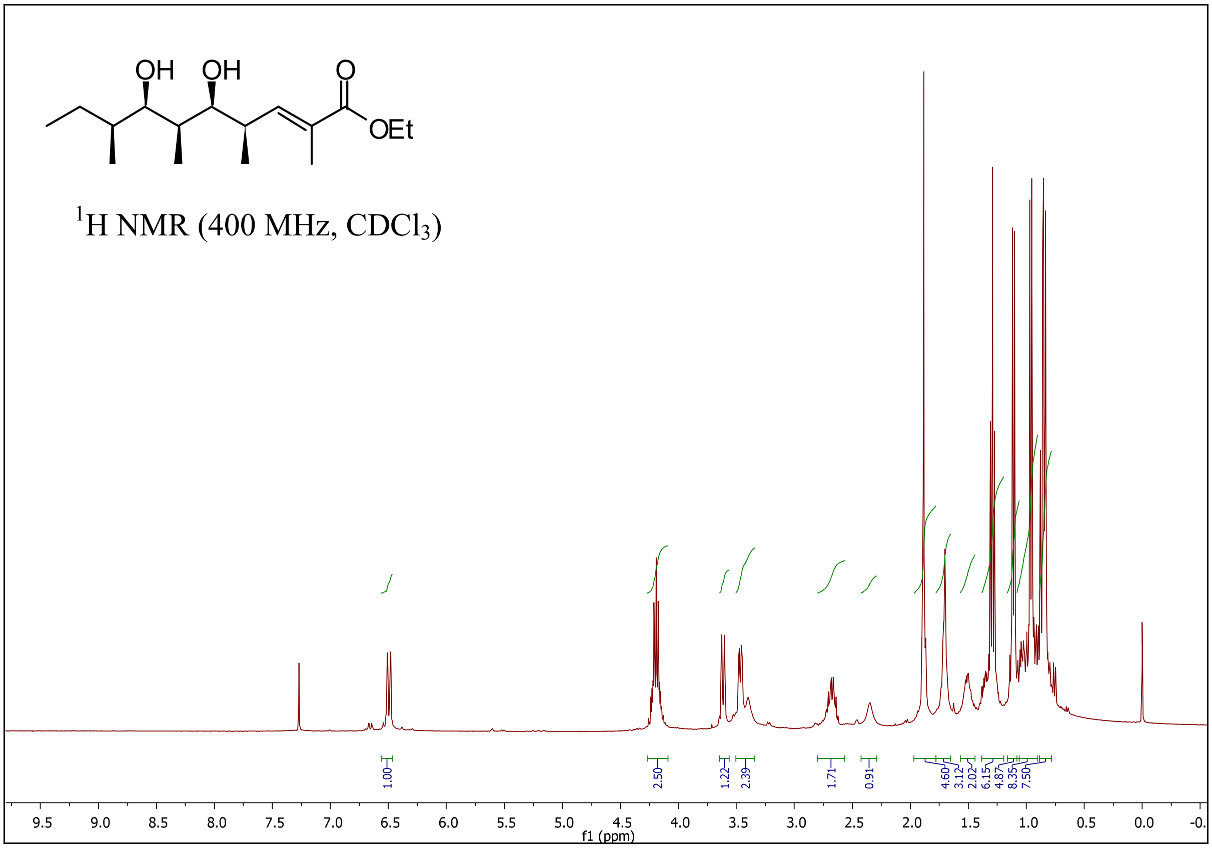

167.92
140.45
129.75
67.13
60.77
60.59
40.19
35.95
26.40
26.15
18.42
17.89
14.87
14.15
13.28
12.36
-3.75
-4.33
^{13}C NMR (100 MHz, CDCl$_3$)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

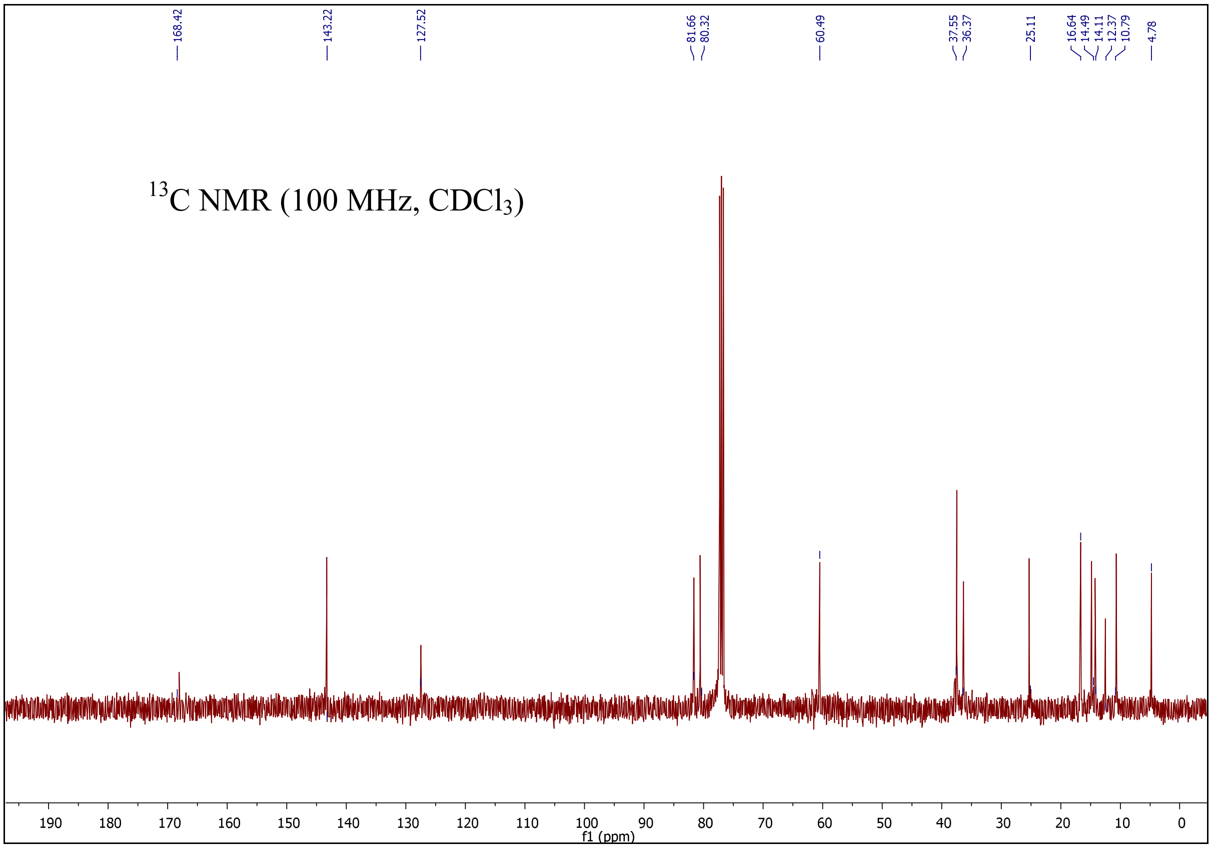

TBS
O
OH
O
OEt
^{1}H NMR (400 MHz, CDCl$_3$)
1.00
2.36
1.15
1.11
1.06
0.90
3.18
5.35
4.81
4.26
22.68
7.42
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

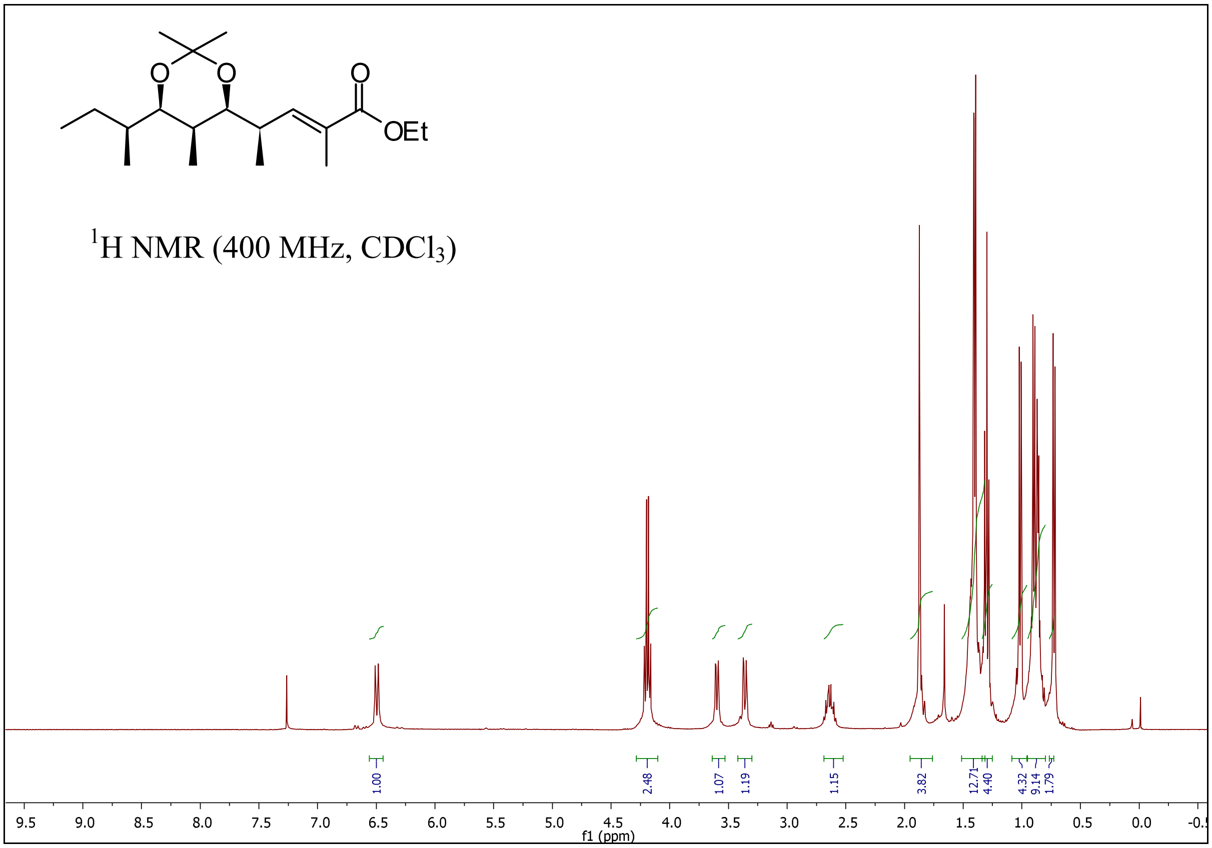

168.08
143.62
127.32
79.85
78.61
77.28
76.96
76.64
60.44
39.99
38.02
37.59
26.06
25.69
18.30
16.51
14.66
14.21
12.50
8.22
-3.45
-4.32
^{13}C NMR (100 MHz, CDCl$_3$)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

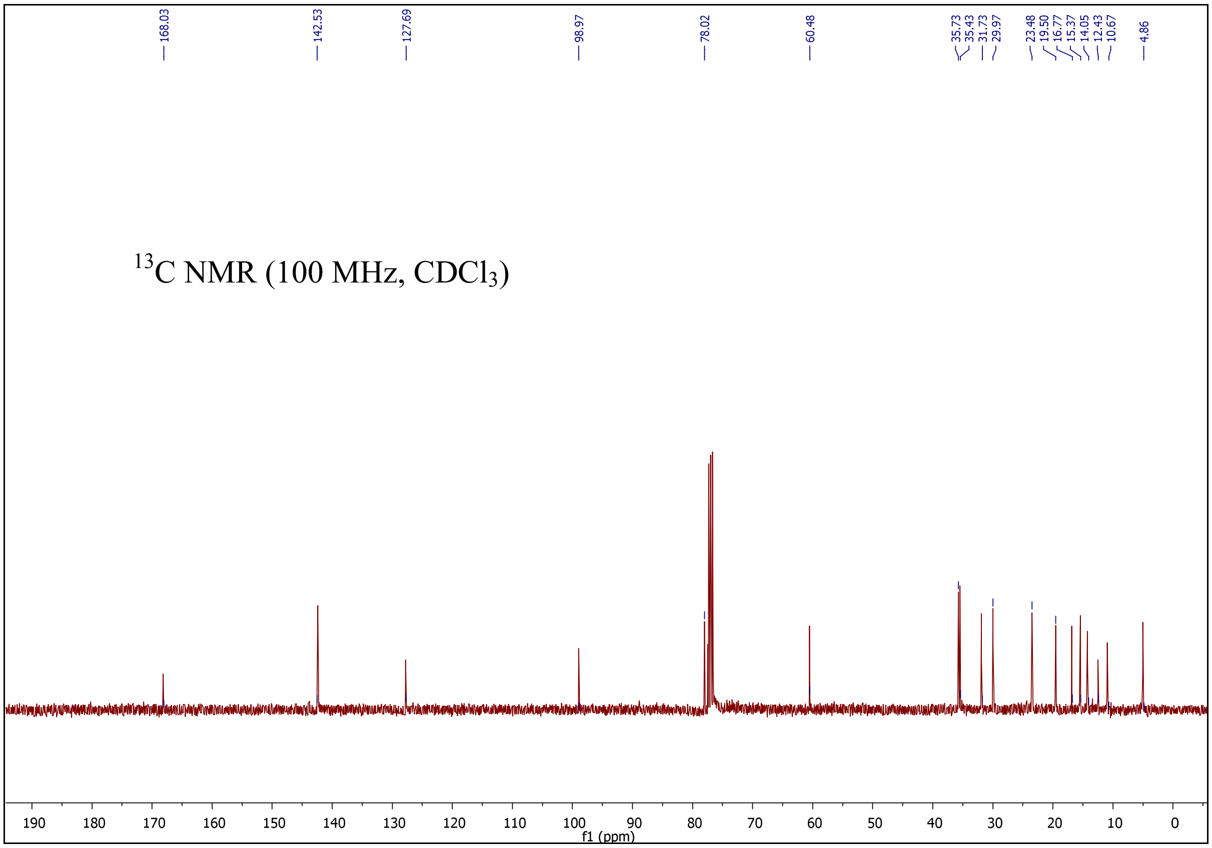

TBS
O
OH
OH
^{1}H NMR (400 MHz, CDCl$_3$)
1.00
1.89
0.89
0.88
0.99
0.84
0.91
2.75
1.91
0.93
3.94
15.66
5.49
0.74
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


134.79
128.93
80.06
79.23
69.01
40.14
37.71
36.56
26.42
26.01
18.55
17.65
14.85
14.15
12.76
8.65
-3.21
-4.09
^{13}C NMR (100 MHz, CDCl$_3$)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
OH
O
OEt
^{1}H NMR (400 MHz, CDCl$_3$)
1.00
2.50
1.22
2.39
1.71
0.91
4.60
3.12
2.02
6.15
4.87
8.35
7.50
9.5
9.0
8.5
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.
f1 (ppm)


168.42
143.22
127.52
81.66
80.32
60.49
37.55
36.37
25.11
16.64
14.49
14.11
12.37
10.79
4.78
^{13}C NMR (100 MHz, CDCl$_3$)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
O
OEt
1H NMR (400 MHz, CDCl3)
1.00
2.48
1.07
1.19
1.15
3.82
12.71
4.40
4.32
9.14
1.79
9.5
9.0
8.5
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
f1 (ppm)


168.03
142.53
127.69
98.97
78.02
60.48
35.73
35.43
31.73
29.97
23.48
19.50
16.77
15.37
14.05
12.43
10.67
4.86
13C NMR (100 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

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