Enantioselective formal synthesis of the marine macrolide (–)-callyspongiolide

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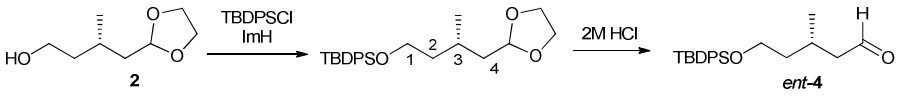
Supporting Information Available

Experimental procedures and spectroscopic data

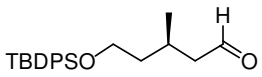
General Procedures. All air sensitive reactions were carried out under a dry argon or nitrogen atmosphere, with dry, freshly distilled solvents using standard procedures. Drying of organic extracts during the work-up of reactions was performed over anhydrous $MgSO_4$ or Na_2SO_4. Evaporation of solvent was accomplished with a rotatory evaporator. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located by UV and either a 1% $KMnO_4$ solution or 3% ethanolic *p*-anysaldehyde. Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, 230-400 mesh). NMR spectra were recorded at 400 MHz (^{1}H) and 100.6 MHz (^{13}C), and chemical shifts are reported in δ values, in parts per million (ppm) relative to Me_4Si (0 ppm) or relative to residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity, coupling constant (*J*) in Hertz (Hz), integrated intensity, and assignment (when possible). Assignments and stereochemical determinations are given only when they are derived from definitive two-dimensional NMR experiments (*g*-HSQC-COSY). IR spectra were performed in a spectrophotometer Nicolet Avatar 320 FT-IR and only noteworthy IR absorptions (cm^{-1}) are listed. Optical rotations were measured in a Perkin-Elmer 241 polarimeter, using a Na lamp. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. High-resolution mass spectra (HRMS) were performed by the *Centres Científics i Tecnològics de la Universitat de Barcelona.*



2 *ent*-**4**

(*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-3-methyl-1-pentanal (*ent*-4): *tert*-Butyldiphenylsilyl chloride (7.1 mL, 27.3 mmol) and imidazole (2.04 g, 29.96 mmol) were added to a solution of alcohol **2**[1] (4.35 g, 27.13 mmol) in anhydrous CH_2Cl_2 (230 mL), and the mixture was heated at reflux temperature for 15 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (hexane to 98:2 hexane-Et_2O) to afford the protected alcohol (9.72 g, 90%) as an oil. $[\alpha]^{22}_D$ –6.32 (*c* 1.02, $CHCl_3$); IR (film): ν = 2930, 1428, 1112 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.91 (d, *J* = 6.8 Hz, 3H, CH_3), 1.04 [s, 9H, $(CH_3)_3$], 1.38-1.52 (m, 2H, H-2 or H-4), 1.62-1.72 (m, 2H, H-2 or H-4), 1.83-1.92 (m, 1H, H-3), 3.65-3.73 (m, 2H, H-1), 3.79-3.89 (m, 2H, O*C*$H_2$$CH_2$O), 3.90-3.99 (m, 2H, O*C*$H_2$$CH_2$O), 4.87 (t, *J* = 5.2 Hz, 1H, CHO), 7.35-7.42 (m, 6H, ArH), 7.66-7.68 (m, 4H, ArH); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) 19.2 [*C*$(CH_3)_3$], 20.0 (CH_3), 26.2 (C-3), 26.8 [C(*C*$H_3)_3$], 39.8 (C-2 or C-4), 40.2 (C-2 or C-4), 61.9 (C-1), 64.6 (O*C*$H_2$$CH_2$O), 64.7 (O*C*$H_2$$CH_2$O), 127.5 (C-*o*), 103.7 (OCH), 130.0 (C-*p*), 134.0 (C-*i*), 135.5 (C-*m*); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{24}H_{35}O_3Si$ 399.235, found 399.2348.

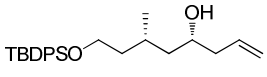
HCl (2.41 mL of a 2.0 M solution in water, 4.82 mmol) was added to a solution of the above acetal (96 mg, 0.24 mmol) in THF (10 mL), and the solution was heated at 50 ºC for 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the THF was removed under vacuum. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (hexane to 97:3 hexane-Et_2O) to afford pure aldehyde *ent*-**4** (55 mg, 64 %) as a colorless oil: $[\alpha]^{22}_D$ –5.12 (*c* 0.95, $CHCl_3$); IR (film): ν = 2859, 2713, 1726 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.93 (d, *J* = 6.8 Hz, 3H, CH_3), 1.05 [s, 9H, $(CH_3)_3$], 1.44-1.63 (m, 2H, H-4), 2.20 (ddd, *J* = 15.4, 7.8, 2.6 Hz, 1H, H-2), 2.25-2.33 (m, 1H, H-3), 2.39 (ddd, *J* = 15.4, 5.2, 2.0 Hz, 1H, H-2), 3.70 (t, *J* = 6.8 Hz, 2H, H-5), 7.36-7.42 (m, 6H, ArH), 7.65-7.68 (m, 4H, ArH), 9.71 (m, 1H, CHO); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) 19.2 [*C*$(CH_3)_3$], 20.0 (CH_3), 25.0 (C-3), 26.9 [C(*C*$H_3)_3$], 39.6 (C-4), 50.8 (C-2), 61.5 (C-5), 127.6 (C-*o*), 129.6 (C-*p*), 133.8 (C-*i*), 135.5 (C-*m*), 200.8 (CHO); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{22}H_{31}O_2Si$ 355.2088, found 355.2093.



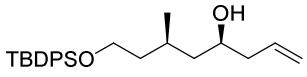
(*R*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-3-methyl-1-pentanal (4): Dess-Martin periodinane (1.66 g, 3.91 mmol) was added at room temperature to a solution of alcohol **3**[2] (696 mg,

[1] A. K. Ghosh, K. A. Shurrush and Z. L. Dawson, *Org. Biomol. Chem*., 2013, **11**, 7768-7777.
[2] H. Ito, T. Inove and K. Iguchi, *Org. Lett.,* 2008, **10**, 3873-3876.

1.95 mmol) in anhydrous CH_2Cl_2 (19 mL), and the resulting mixture was stirred for 1 h 30 min. The solution was poured into saturated aqueous solutions of $Na_2S_2O_3$ (7.5 mL) and $NaHCO_3$ (7.5 mL), and the mixture was stirred at room temperature for 1 h. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, filtered, and concentrated. Flash chromatography (97:3 hexane-Et_2O) of the residue gave aldehyde **4** (623 mg, 90%) as a colorless oil: $[\alpha]^{22}_D$ +6.21 (*c* 0.97, $CHCl_3$);

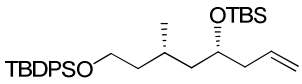


(4*R*,6*S*)-8-[(*tert*-Butyldiphenylsilyl)oxy]-6-methyl-1-octen-4-ol (*ent*-5): (*S*,*S*)-2-Allyl-1,3-bis-(4-bromobenzyl)-chlorooctahydro-2-(1*H*)-1,3,2-benzodiazasilole (Leighton reagent; 1.13 g, 2.03 mmol) and scandium triflate (41.7 mg, 85 μmol) were added to a solution of aldehyde ***ent*-4** (603 mg, 1.7 mmol) in anhydrous CH_2Cl_2 (17 mL). After stirring at 0 ºC for 5 h and at room temperature for 15 h, a TLC still showed starting material. More scandium triflate (40 mg, 81 μmol) was added and the mixture was stirred for an additional 5 h. Then, tetrabutylammonium fluoride (1.69 mL of a 1.0 M solution in THF, 1.69 mmol) was added, the resulting mixture was stirred at room temperature for 30 min, and the solvent was evaporated. Flash chromatography (8:2 to 1:1 hexane-CH_2Cl_2) of the residue gave alcohol ***ent*-5** (583 mg, 87%) as a colorless oil: $[\alpha]^{22}_D$ −7.15 (*c* 1.02, $CHCl_3$); IR (film): ν = 3369, 2929, 1428 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.87 (d, *J* = 6.8 Hz, 3H, CH_3), 1.05 [s, 9H, $(CH_3)_3$], 1.32-1.38 (m, 3H, H-5, H-7), 1.70-1.77 (m, 1H, H-7), 1.77-1.85 (m, 1H, H-6), 2.06-2.14 (m, 1H, H-3), 2.24-2.30 (m, 1H, H-3), 3.65-3.76 (m, 3H, H-4, H-8), 5.10-5.15 (m, 2H, H-1), 5.77-5.87 (m, 1H, H-2), 7.36-7.44 (m, 6H, ArH), 7.65-7.68 (m, 4H, ArH); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) 19.2 [$C(CH_3)_3$], 20.5 (CH_3), 26.4 (C-6), 26.8 [$C(CH_3)_3$], 39.1 (C-7), 42.1 (C-3), 44.3 (C-5), 62.0 (C-8), 68.6 (C-4), 118.0 (C-1), 127.5 (C-*o*), 129.5 (C-*p*), 133.8 (C-*i*), 135.5 (C-2), 135.6 (C-*m*); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{25}H_{37}O_2Si$ 397.2557, found 397.2550.

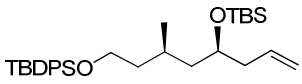


(4*S*,6*R*)-8-[(*tert*-Butyldiphenylsilyl)oxy]-6-methyl-1-octen-4-ol (5): DBU (1.5 mL, 10.03 mmol) and allyltrichlorosilane (0.53 mL, 3.64 mmol) were successively added to a cooled (0 ºC) solution of diaminophenol **11**[3] (976 mg, 3.34 mmol) in anhydrous CH_2Cl_2 (11 mL), and the mixture was stirred at room temperature for 1 h. The resulting mixture was recooled to 0 ºC, aldehyde **4** (1.08 g, 3.04 mmol) was added, and the solution was stirred at room temperature for 15 h. After cooling the mixture to 0 ºC, *n*-Bu_4NF (3.04 mL of a 1 M solution in THF, 3.04 mmol) was added, and the stirring was continued at room temperature for 40 min. The solution was concentrated, and the resulting residue was chromatographed (6:4 to 1:1 hexane-CH_2Cl_2) to afford alcohol **5** (925 mg, 77%): $[\alpha]^{22}_D$ +8.26 (*c* 1.02, $CHCl_3$).

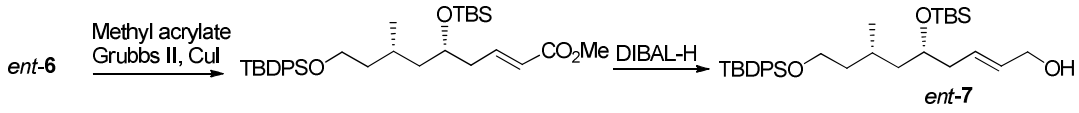
[3] L. M. Suen, M. L. Steigerwald and J. L. Leighton, *Chem. Sci.*, 2013, **4**, 2413-2417.



(4*R*,6*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-8-[(*tert*-butyldiphenylsilyl)oxy]-6-methyl-1-octene (*ent*-6): Et_3N (0.46 mL, 3.28 mmol) and TBSOTf (0.47 mL, 2.05 mmol) were added to a solution of alcohol *ent*-**5** (348 mg, 0.82 mmol) in anhydrous CH_2Cl_2 (6.8 mL) at −78 ºC. The mixture was stirred at −30 ºC for 2 h and at room temperature for 18 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the resulting solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, filtered, and concentrated. The resulting residue was chromatographed (9:1 to 8:2 hexane-CH_2Cl_2) to give *ent*-**6** (338 mg, 80%): $[\alpha]^{22}_D$ −6.21 (*c* 1.0, $CHCl_3$); IR (film): ν = 1640, 1472, 1428 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.04 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si), 0.85 (d, *J* = 6.8 Hz, 3H, CH_3), 0.88 [s, 9H, $(CH_3)_3$], 1.05 [s, 9H, $(CH_3)_3$], 1.21-1.29 (m, 1H, H-5), 1.31-1.46 (m, 2H, H-7, H-5), 1.60-1.73 (m, 2H, H-6, H-7), 2.11-2.17 (m, 1H, H-3), 2.22-2.28 (m, 1H, H-3), 3.63-3.72 (m, 2H, H-8), 3.74-3.80 (m, 1H, H-4), 5.00 (m, 1H, H-1), 5.02-5.05 (m, 1H, H-1), 5.77-5.88 (m, 1H, H-2), 7.36-7.45 (m, 6H, ArH), 7.66-7.69 (m, 4H, ArH); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) -4.4 (CH_3Si), -4.3 (CH_3Si), 18.1 [*C*$(CH_3)_3$], 19.2 [*C*$(CH_3)_3$], 20.2 (CH_3), 25.9 [C(*C*$H_3)_3$], 26.3 (C-6), 26.9 [C(*C*$H_3)_3$], 39.9 (C-7), 41.7 (C-3), 44.7 (C-5), 62.1 (C-8), 70.2 (C-4), 116.6 (C-1), 127.6 (CHAr), 129.5 (CHAr), 134.0 (C-*i*), 135.4 (C-2), 135.6 (CHAr); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{31}H_{51}O_2Si_2$ 511.3422, found 511.3440.



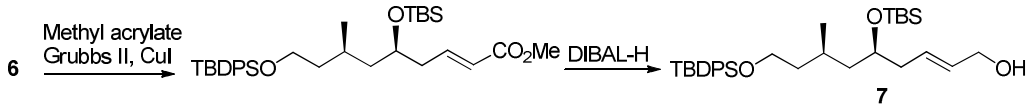
(4*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-8-[(*tert*-butyldiphenylsilyl)oxy]-6-methyl-1-octene (6) was prepared from alcohol **5** by the same procedure as described for *ent*-**6**. Specific rotation of **6**: $[\alpha]^{22}_D$ +5.68 (*c* 1.04, $CHCl_3$).



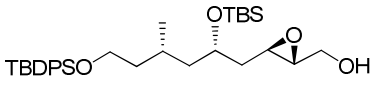
(5*S*,7*S*,*E*)-5-[(*tert*-Butyldimethylsilyl)oxy]-9-[(*tert*-butyldiphenylsilyl)oxy]-7-methyl-2-nonen-1-ol (*ent*-7): Methyl acrylate (0.82 mL, 9.10 mmol), Grubbs 2nd generation catalyst (51.4 mg, 60.6 µmol), and CuI (17.3 mg, 91 µmol) were added to a solution of alkene *ent*-**6** (1.55 g, 3.03 mmol) in anhydrous ethyl ether (32 mL). The mixture was heated at 40 ºC for 4 h, cooled to room temperature, and concentrated. The residue was purified by flash chromatography (7:3 to 1:1 hexane-CH_2Cl_2) to give the unsaturated ester (1.61 mg, 94%) as a yellowish oil: $[\alpha]^{22}_D$ –0.11 (*c* 2.2, $CHCl_3$); IR (film): ν = 1728, 1658, 1473 cm^{-1}; δ_H (400 MHz; $CDCl_3$, Me_4Si, COSY, *g*-HSQC) 0.03 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si), 0.84 (d, *J* = 6.4 Hz, 3H, CH_3), 0.87 [s, 9H, $(CH_3)_3$], 1.05 [s, 9H, $(CH_3)_3$], 1.26-1.35 (m, 2H, H-6 and H-8), 1.37-1.43 (m, 1H, H-6), 1.58-1.69 (m, 2H, H-7 and H-8), 2.20-2.28 (m, 1H, H-4),

2.35-2.42 (m, 1H, H-4), 3.62-3.71 (m, 2H, H-9), 3.73 (s, 3H, OCH_3), 3.81-3.87 (m, 1H, H-5), 5.83 (dt, *J* = 15.6, 1.2 Hz, 1H, H-2), 6.95-7.02 (m, 1H, H-3), 7.36-7.44 (m, 6H, ArH), 7.65-7.68 (m, 4H, ArH); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) -4.5 (CH_3Si), -4.4 (CH_3Si), 18.0 [*C*$(CH_3)_3$], 19.2 [*C*$(CH_3)_3$], 20.0 (CH_3), 25.8 [C(*C*$H_3)_3$], 26.3 (C-7), 26.9 [C(*C*$H_3)_3$], 39.9 (C-8), 40.0 (C-4), 45.1 (C-6), 51.4 (OCH_3), 61.9 (C-9), 69.5 (C-5), 122.9 (C-2), 127.6 (CHAr), 129.5 (CHAr), 134.0 (C-*i*), 135.5 (CHAr), 146.4 (C-3), 166.8 (C-1); HRMS (ESI-TOF) *m/z* $[M + Na]^+$ Calcd for $C_{33}H_{52}NaO_4Si_2$ 591.3296, found 591.3296.

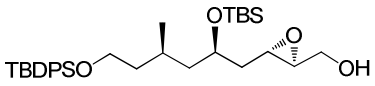
DIBAL-H (6.22 mL of a 1.0 M solution in CH_2Cl_2, 6.22 mmol) was added dropwise under an argon atmosphere to a solution of the above ester (1.61 mg, 2.83 mmol) in anhydrous CH_2Cl_2 (85 mL) at −78º, and the resulting mixture was stirred for 2 h. The temperature was raised to −30 ºC, methanol (2.5 mL) was added, and the mixture allowed to reach 0 ºC. Saturated aqueous potassium sodium tartrate (12 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, filtered, and concentrated. Flash chromatography (9:1 hexane-EtOAc) of the residue afforded alcohol *ent*-**7** (1.53 g, quantitative) as a colorless oil: $[\alpha]^{22}_D$ −3.39 (*c* 1.06, $CHCl_3$); IR (film): ν = 3351, 1589, 1471, 1427, 1112 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.03 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si), 0.84 (d, *J* = 6.8 Hz, 3H, CH_3), 0.87 [s, 9H, $(CH_3)_3$], 1.04 [s, 9H, $(CH_3)_3$], 1.17-1.23 (m, 1H, H-4), 1.32-1.44 (m, 2H, H-4 and H-8), 1.59-1.71 (m, 2H, H-7 and H-8), 2.08-2.15 (m, 1H, H-6), 2.21-2.27 (m, 1H, H-6), 3.62-3.71 (m, 2H, H-9), 3.73-3.79 (m, 1H, H-5), 4.07 (t, *J* = 4.6 Hz, 2H, H-1), 5.60-5.74 (m, 2H, H-2 and H-3), 7.35-7.44 (m, 6H, ArH), 7.65-7.68 (m, 4H, ArH); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) -4.4 (CH_3Si), -4.3 (CH_3Si), 18.1 [*C*$(CH_3)_3$], 19.2 [*C*$(CH_3)_3$], 20.2 (CH_3), 25.9 [C(*C*$H_3)_3$], 26.3 (C-7), 26.9 [C(*C*$H_3)_3$], 40.0 (C-6 and C-8), 44.8 (C-4), 62.0 (C-9), 63.8 (C-1), 70.2 (C-5), 127.6 (CHAr), 129.5 (CHAr), 129.6 (C-2 or C-3), 131.2 (C-2 or C-3), 135.5 (C-*i*), 135.6 (CHAr); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{32}H_{53}O_3Si_2$ 541.3528, found 541.3547.



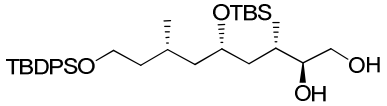
(5*R*,7*R*,*E*)-5-[(*tert*-Butyldimethylsilyl)oxy]-9-[(*tert*-butyldiphenylsilyl)oxy]-7-methyl-2-nonen-1-ol (7) was prepared from alkene **6** operating as in the above preparation of *ent*-**7.** Specific rotation of the unsaturated ester $[\alpha]^{22}_D$ + 0.10 (*c* 1.09, $CHCl_3$). Specific rotation of alcohol **7**: $[\alpha]^{22}_D$ + 3.25 (*c* 1.0, $CHCl_3$).



(2*R*,3*R*,5*S*,7*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-9-[(*tert*-butyldiphenylsilyl)oxy]-2,3-epoxy-7-methyl-1-nonanol (*ent*-8): Titanium isopropoxide (885 µL, 2.98 mmol) was added dropwise to a solution of diisopropyl (**–**)-tartrate (790 µL, 3.74 mmol) in anhydrous CH_2Cl_2 (25 mL) containing 4Å molecular sieves (500 mg) at −40 ºC, and the mixture was stirred for 30 min. Cumene hydroperoxide (1.84 mL, 9.94 mmol) and, after an additional 30 min, a solution of alcohol *ent*-**7** (1.34 g, 2.49 mmol) in CH_2Cl_2 (10 mL) were added dropwise. The mixture was stirred at −25 ºC overnight. 10% Aqueous tartaric acid (100 mL) was added, and the mixture was stirred at room temperature for 1 h. Et_2O (10 mL) and H_2O (10 mL) were added, the phases were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, filtered, and concentrated. The residue was purified by flash chromatography (9:1 hexane-EtOAc) to give epoxide *ent*-**8** (1.24 mg, 90%) as a colorless oil: $[\alpha]^{22}_D$ +23.5 (*c* 0.96, $CHCl_3$); IR (film): ν = 3444, 1589, 1471 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.06 (s, 3H, CH_3Si), 0,08 (s, 3H, CH_3Si), 0.84 (d, *J* = 6.4 Hz, 3H, CH_3), 0.89 [s, 9H, $(CH_3)_3$], 1.04 [s, 9H, $(CH_3)_3$], 1.30-1.40 (m, 2H, H-6 and H-8), 1.43-1.49 (m, 1H, H-6), 1.60-1.66 (m, 4H, H-4, H-7 and H-8), 2.91 (ddd, *J* = 4.6, 2.4, 2.4 Hz, 1H, H-2), 3.09 (ddd, *J* = 7.0, 5.2, 2.4 Hz, 1H, H-3), 3.57-3.73 (m, 3H, OCH_2), 3.87-3.96 (m, 2H, H-5 and OCH_2), 7.35-7.42 (m, 6H, ArH), 7.65-7.67 (m, 4H, ArH); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) -4.6 (CH_3Si), -4.3 (CH_3Si), 18.0 [*C*$(CH_3)_3$], 19.2 [*C*$(CH_3)_3$], 19.9 (CH_3), 25.9 [C(*C*$H_3)_3$], 26.3 (C-7), 26.9 [C(*C*$H_3)_3$], 39.1 (C-4), 40.2 (C-8), 45.6 (C-6), 53.4 (C-3), 59.0 (C-2), 61.6 (OCH_2), 61.9 (OCH_2), 68.3 (C-5), 127.6 (CHAr), 129.5 (CHAr), 133.9 (C-*i*), 135.5 (CHAr); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{32}H_{53}O_4Si_2$ 557.3477, found 557.3470.

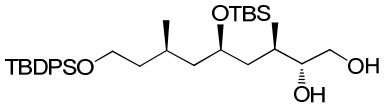


(2*S*,3*S*,5*R*,7*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-9-[(*tert*-butyldiphenylsilyl)oxy]-2,3-epoxy-7-methyl-1-nonanol (8) was prepared from alcohol *ent*-**7** operating as in the above preparation of epoxide *ent*-**8**, but using diisopropyl (+)-tartrate. Specific rotation of **8**: $[\alpha]^{22}_D$ −24.6 (*c* 0.97, $CHCl_3$).

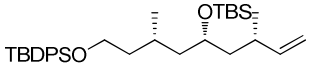


(2*S*,3*S*,5*S*,7*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-9-[(*tert*-butyldiphenylsilyl)oxy]-3,7-dimethyl-1,2-nonadiol (*ent*-9): $AlMe_3$ (540 µL of a 2.0 M solution in hexanes, 1.08 mmol) was added dropwise to a solution of epoxide *ent*-**8** (200 mg, 0.36 mmol) in anhydrous hexane (1.5 mL) containing anhydrous Na_2SO_4 (100 mg) at 0 ºC. After stirring for 1 h, the

mixture was poured into saturated aqueous $NaHCO_3$ and potassium sodium tartrate (1:1, 4 mL) and extracted with EtOAc. The combined organic extracts were washed with brine, dried, filtered, and concentrated. The residue was purified by flash chromatography (CH_2Cl_2) to give diol *ent*-**9** (160 mg, 66%) as a colorless oil: $[\alpha]^{22}_D$ +3.10 (*c* 1.0, $CHCl_3$).IR (film): ν = 3384, 1447, 1427, 1255, 1112, 1086 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.09 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si), 0.84 (d, *J* = 6.8 Hz, 3H, CH_3), 0.85 (d, *J* = 6.4 Hz, 3H, CH_3), 0.90 [s, 9H, $(CH_3)_3$], 1.04 [s, 9H, $(CH_3)_3$], 1.28-1.39 (m, 2H, H-4 and H-6), 1.56-1.70 (m, 4H, H-4, H-6 and H-8), 1.76-1.83 (m, 1H, H-3), 3.34 (ddd, *J* = 8.0, 8.0, 3.0 Hz, 1H, H-2), 3.43-3.51 (m, 1H, H-1 or H-9), 3.65-3.75 (m, 3H, H-1 and H-9), 3.94-3.99 (m, 1H, H-5), 7.36-7.44 (m, 6H, ArH), 7.65-7.68 (m, 4H, ArH); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) -4.6 (CH_3Si), -4.5 (CH_3Si), 18.0 (CH_3), 18.0 [$C(CH_3)_3$], 19.2 [$C(CH_3)_3$], 19.4 (CH_3), 25.8 [$C(CH_3)_3$], 26.3 (C-7), 26.9 [$C(CH_3)_3$], 32.2 (C-3), 40.4 (C-4), 42.0 (C-8), 43.2 (C-6), 61.7 (OCH_2), 64.9 (OCH_2), 69.8 (C-5), 75.9 (C-2), 127.6 (CHAr), 129.5 (CHAr), 133.9 (C-*i*), 134.0 (CHAr); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{33}H_{57}O_4Si_2$ 573.3790, found 573.3789.

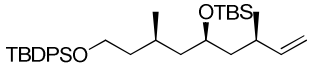


(2*R*,3*R*,5*R*,7*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-9-[(*tert*-butyldiphenylsilyl)oxy]-3,7-dimethyl-1,2-nonadiol (9) was prepared from epoxide **8** operating as in the above preparation of diol *ent*-**9**. Specific rotation of **9**: $[\alpha]^{22}_D$ –2.96 (*c* 1.06, $CHCl_3$).



(3*S*,5*S*,7*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-9-[(*tert*-butyldiphenylsilyl)oxy]-3,7-dimethyl-1-nonene (*ent*-10): Ph_3P (740 mg, 2.82 mmol), imidazole (192 mg, 2.82 mmol), and I_2 (537 mg, 2.12 mmol) were added to a stirred solution of diol *ent*-**9** (404 mg, 0.71 mmol) in anhydrous CH_2Cl_2 (3.4 mL) at 0 ºC, and the mixture was stirred at room temperature for 5 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, filtered, and concentrated. The residue was dissolved in Et_2O cooled with an ice bath and filtered to remove Ph_3PO. The organic solvent was evaporated, and the resulting residue was chromatographed (Biotage®, 95:5 to 60:40 hexane-CH_2Cl_2) to afford compound *ent*-**10** (339 mg, 89%) as a colorless oil: $[\alpha]^{22}_D$ + 17.8 (*c* 1.01, $CHCl_3$); IR (film): ν = 1640, 1472, 1427, 1112 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.02 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si), 0.81 (d, *J* = 6.4 Hz, 3H, CH_3), 0.88 [s, 9H, $(CH_3)_3$], 0.98 (d, *J* = 6.8 Hz, 3H, CH_3), 1.04 [s, 9H, $(CH_3)_3$], 1.20-1.26 (m, 1H, H-4 or H-6), 1.27-1.36 (m, 2H, H-4 or H-6 and H-8), 1.37-1.46 (m, 2H, H-4 or H-6), 1.56-1.61 (m, 1H, H-8), 1.63-1.68 (m, 1H, H-7), 2.28-2.37 (m, 1H, H-3), 3.63-3.75 (m, 3H, H-5 and H-9), 4.91-4.99 (m, 2H, H-1), 5.67 (ddd, *J* = 7.6, 10.4, 17.2 Hz, 1H, H-2), 7.35-7.44 (m, 6H, ArH), 7.66-7.68 (m, 4H, ArH); δ_C (100.6 MHz; $CDCl_3$;

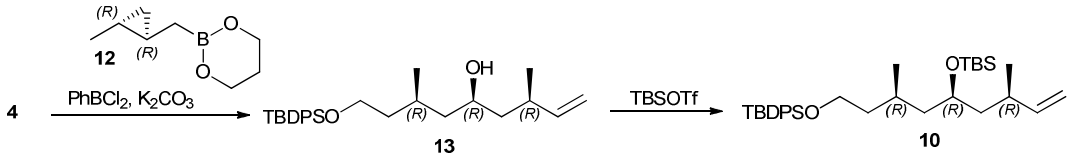
Me_4Si) -4.2 (CH_3Si), -3.9 (CH_3Si), 18.1 [$C(CH_3)_3$], 19.2 [$C(CH_3)_3$], 20.0 (CH_3), 21.4 (CH_3), 26.0 [$C(CH_3)_3$], 26.3 (C-7), 26.9 [$C(CH_3)_3$], 34.1 (C-3), 40.4 (C-8), 44.3 (C-4 or C-6), 45.7 (C-4 or C-6), 62.0 (C-9), 68.9 (C-5), 112.7 (C-1), 127.6 (CHAr), 129.5 (CHAr), 134.1 (C-*i*), 135.6 (CHAr), 144.6 (C-2); HRMS (ESI-TOF) *m/z* $[M + NH_4]^+$ Calcd for $C_{33}H_{58}NO_2Si_2$ 556.4001, found 556.3997.



(3*R*,5*R*,7*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-9-[(*tert*-butyldiphenylsilyl)-oxy]-3,7-dimethyl-1-nonene (10)

Method A: Compound **10** was prepared from diol **9** operating as in the above preparation of *ent*-**10**. Specific rotation of alkene **10**: $[\alpha]^{22}_D$ – 17.0 (*c* 1.01, $CHCl_3$).

Method B:

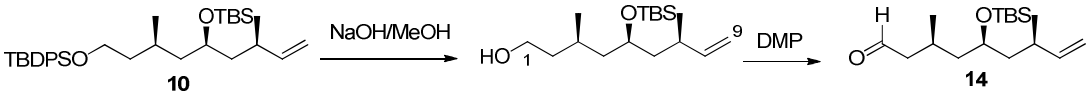


$PhBCl_3$ (530 µL, 4.1 mmol) and K_2CO_3 (2.24 g, 16.2 mmol) were added under an argon atmosphere to a solution of boronate **12**[4] (1.25 mg, 8.2 mmol) in CH_2Cl_2 (23 mL) at room temperature. Then, a solution of aldehyde **4** (959 mg, 2.7 mmol) in CH_2Cl_2 (4 mL) was added, and the mixture was stirred at room temperature for 17 h. The solution was quenched by adding 3M aqueous NaOH (24 mL) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried, filtered, and concentrated. The resulting residue was chromatographed (3:7 to 1:1 hexane-CH_2Cl_2) to give **(3*R*,5*R*,7*R*)-9-[(*tert*-Butyldiphenylsilyl)oxy]-3,7-dimethyl-1-nonen-5-ol (13)** (870 mg, 76%) as a colorless oil: $[\alpha]^{22}_D$ –2.41 (*c* 0.99, $CHCl_3$); IR (film): ν = 3406, 1428, 1313, 1111 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.85 (d, *J* =6.8 Hz, 3H, CH_3), 1.01 (d, *J* = 6.8 Hz, 3H, CH_3), 1.05 [s, 9H, $(CH_3)_3$], 1.31-1.39 (m, 5H, H-4, H-6, H-8), 1.60-1.68 (m, 1H, H-4), 1.74-1.83 (m, 1H, H-7), 2.38-2.45 (m, 1H, H-3), 3.65-3.76 (m, 3H, H-5 and H-9), 4.97 (ddd, *J* = 10.2, 1.9, 0.8 Hz, 1H, H-1), 5.03 (ddd, *J* = 17.2, 1.9, 1.0 Hz, 1H, H-1), 5.67 (ddd, *J* = 17.2, 10.2, 8.4 Hz, 1H, H-2), 7.36-7.43 (m, 6H, ArH), 7.66-7.68 (m, 4H, ArH); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) 19.2 [$C(CH_3)_3$], 20.5 (CH_3), 21.3 (CH_3), 26.3 (C-7), 26.9 [$C(CH_3)_3$], 34.7 (C-3), 39.2 (C-4), 44.4 (C-6 or C-8), 45.5 (C-6 or C-8), 62.1

[4] Reagent **12** was prepared (5 steps, 59% yield) following the original procedure,[4a,b] with two modifications: i) in the first step, 1-propenylboronic acid was quantitatively prepared by hydrolysis (silica gel and water) of the corresponding potassium trifluoroborate[4c] instead of hydroboration of propine; ii) the lithium halocarbenoid, needed for the homologation of the cyclopropylboronate in the last step, was generated (75%) by reaction with MeLi·LiBr[4d] instead of with *n*-BuLi. (a) H. Lin, W. Pei, H. Wang, K. N. Houk and I. J. Krauss, *J. Am. Chem. Soc.*, 2013, **135**, 82-85; (b) H. Lin, L. Tian and I. J. Krauss, *J. Am. Chem. Soc.*, 2015, **137**, 13176-13182; (c) G. A. Molander, L. N. Cavalcanti, B. Canturk, P.-S. Pan and L. E. Kennedy, *J. Org. Chem.*, 2009, **74**, 7364-7369; (d) S. Monticelli, M. Rui, L. Castoldi, G. Missere and V. Pace, *Monatsh. Chem.*, 2018, **149**, 1285-1291.

(C-9), 67.6 (C-5), 113.4 (C-1), 127.6 (CHAr), 129.5 (CHAr), 134.0 (C-*i*), 135.6 (CHAr), 144.2 (C-2); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{27}H_{41}O_2Si$ 425.2870, found 425.2867.

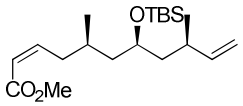
Operating as in the preparation of *ent*-**6**, from alcohol **13** (450 mg, 1.1 mmol) in CH_2Cl_2 (9.5 mL), Et_3N (610 µL, 4.3 mmol), and TBSOTf (620 µL, 2.71 mmol), alkene **10** (458 mg, 80%) was obtained after flash chromatography (85:15 hexane-CH_2Cl_2).



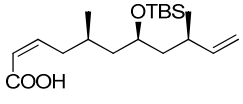
10 **14**

(3*S*,5*R*,7*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3,7-dimethyl-8-nonen-1-al (14): A solution of **10** (458 mg, 0.85 mmol) in 10% NaOH-MeOH (8.5 mL) was stirred at 78 ºC for 5 h. Then, additional 10% NaOH-MeOH (8.5 mL) was added, and the solution was heated at reflux overnight. CH_2Cl_2 (20 mL) was added and the phases were separated. The organic layer was washed with water and brine, dried, filtered, and concentrated. Flash chromatography (hexane to 9:1 hexane-EtOAc) of the residue afforded the primary alcohol (230 mg, 90%) as a colorless oil. $[\alpha]^{22}_D$ –25.2 (*c* 0.8, $CHCl_3$); IR (film): ν = 3345, 1639 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.05 (s, 6H, $SiCH_3$), 0.89 [s, 9H, $(CH_3)_3$], 0.89 (d, *J* = 6.4 Hz, 3H, CH_3), 0.99 (d, *J* = 6.8 Hz, 3H, CH_3), 1.29-1.47 (m, 5H, H-4, H-6 and H-8), 1.58-1.67 (m, 2H, H-2 and H-3), 2.29-2.36 (m, 1H, H-7), 3.65-3.71 (m, 2H, H-1), 3.72-3.79 (m, 1H, H-5), 4.92-5.00 (m, 2H, H-9), 5.68 (ddd, *J* = 17.6, 10.2, 7.6 Hz, 1H, H-8); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) -4.2 ($SiCH_3$), -3.9 ($SiCH_3$), 18.1 [*C*$(CH_3)_3$], 20.0 (C-3*C*H_3), 21.2 (C-7*C*H_3), 25.9 [C(*C*$H_3)_3$], 26.3 (C-3), 34.1 (C-7), 40.4 (C-2), 44.3 (C-4 or C-6), 45.6 (C-4 or C-6), 60.9 (C-1), 68.8 (C-5), 112.8 (C-9), 144.6 (C-8); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{17}H_{37}O_2Si$ 301.2557, found 301.2558.

Dess-Martin periodinane (635 mg, 1.5 mmol) and $NaHCO_3$ (285 mg, 3.39 mmol) were added to a solution of the above alcohol (300 mg, 0.99 mmol) in CH_2Cl_2 (21 mL) at 0 ºC. The mixture was stirred at room temperature for 1.5 h and concentrated. The resulting residue was chromatographed (hexane to 9:1 hexane-EtOAc) to afford aldehyde **14** (274 mg, 92%) as a yellowish oil: $[\alpha]^{22}_D$ –23.9 (*c* 0.91, $CHCl_3$); IR (film): ν = 2857, 2709, 1728, 1641 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.04 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.89 [s, 9H, $(CH_3)_3$], 0.95 (d, *J* = 6.4 Hz, 3H, CH_3), 0.99 (d, *J* = 6.8 Hz, 3H, CH_3), 1.35-1.49 (m, 4H, H-4, H-6), 2.13-2.19 (m, 1H, H-3), 2.23 (dd, *J* = 8.0, 2.0 Hz, 1H, H-2), 2.28-2.33 (m, 1H, H-7), 2.44-2.51 (m, 1H, H-2), 3.72-3.78 (m, 1H, H-5), 4.93 (ddd, *J* = 10.4, 2.0, 0.8 Hz, 1H, H-9), 4.98 (ddd, *J* = 17.2, 2.0, 0.8 Hz, 1H, H-9), 5.63-5.72 (ddd, *J* = 17.2, 10.4, 8.0 Hz, 1H, H-8), 9.75 (dd, *J* = 2.0, 1.6 Hz, 1H, CHO); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) -4.1 ($SiCH_3$), -4.0 ($SiCH_3$), 18.1 [*C*$(CH_3)_3$], 20.5 (CH_3), 21.1 (CH_3), 24.8 (C-3), 25.9 [C(*C*$H_3)_3$], 32.4 (C-7), 44.2 (C-4 or C-6), 44.9 (C-4 or C-6), 51.2 (C-2), 68.2 (C-5), 112.8 (C-9), 144.4 (C-8), 202.6 (CO); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{17}H_{35}O_2Si$ 299.2401, found 299.2392.

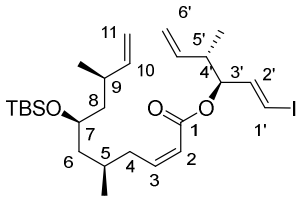


Methyl (5*R*,7*R*,9*R*,*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]-5,9-dimethyl-2,10-undecadienoate (15): Potassium bis(trimethylsilyl)amide (1.51 mL of a 0.5 M solution in toluene, 0.76 mmol) and $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ (160 µL, 0.76 mmol) were added to a solution of 18-crown-6 (200 mg, 0.76 mmol) in anhydrous THF (14.7 mL) at −78 ºC. After stirring the solution at this temperature for 15 min, a solution of aldehyde **14** (112 mg, 0.38 mmol) in anhydrous THF (4.2 mL) was added dropwise, and the stirring was continued overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (8:2 hexane-CH_2Cl_2) of the residue afforded methyl ester **15** (118 mg, 88%): $[\alpha]^{22}_D$ −18.6 (*c* 0.98, $CHCl_3$); IR (film): ν = 1727, 1644, 1173 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.04 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.88 [s, 9H, $(CH_3)_3$], 0.90 (d, *J* = 6.8 Hz, 3H, CH_3), 0.98 (d, *J* = 6.8 Hz, 3H, CH_3), 1.30-1.37 (m, 2H, H-6 or H-8), 1.39-1.49 (m, 2H, H-6 and H-8), 1.64-1.72 (m, 1H, H-5), 2.28-2.35 (m, 1H, H-9), 2.53-2.67 (m, 2H, H-4), 3.71 (s, 3H, OCH_3), 3.72-3.78 (m, 1H, H-7), 4.93 (ddd, *J* = 10.0, 1.8, 0.8 Hz, 1H, H-11), 4.97 (ddd, *J* = 17.5, 1.8, 1.2 Hz, 1H, H-11), 5.68 (ddd, *J* = 17.5, 10.0, 7.3 Hz, 1H, H-10), 5.83 (dt, *J* = 11.5, 1.7 Hz, 1H, H-2), 6.22 (ddd, *J* = 11.5, 8.0, 7.4 Hz, 1H, H-3); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) -4.2 ($SiCH_3$), -4.0 ($SiCH_3$), 18.1 [$C(CH_3)_3$], 19.9 (C-5CH_3), 21.2 (C-9CH_3), 26.0 [C(CH_3)$_3$], 29.8 (C-5), 34.1 (C-9), 36.2 (C-4), 44.4 (C-6 or C-8), 45.1 (C-6 or C-8), 51.0 (OCH_3), 68.7 (C-7), 112.7 (C-11), 120.2 (C-2), 144.6 (C-10), 149.4 (C-3), 166.9 (CO); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{20}H_{39}O_3Si$ 355.2663, found 355.2656.

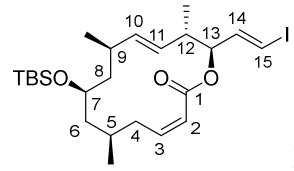


(5*R*,7*R*,9*R*,*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]-5,9-dimethyl-2,10-undecadienoic acid (16): $LiOH{\cdot}H_2O$ (166 mg of a 56% w/w, 2.22 mmol) was added to a solution of methyl ester **15** (175 mg, 0.49 mmol) in THF:MeOH:H_2O (19 mL:4 mL:11 mL) at 0 ºC, and the mixture was stirred at room temperature for 15 h. The temperature was lowered to 0 ºC, additional $LiOH{\cdot}H_2O$ (74 mg of a 56% w/w, 0.99 mmol) was added, and the mixture was stirred at room temperature for 5 h. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were dried, filtered, and concentrated. Flash chromatography (hexane to 8:2 hexane-EtOAc) of the residue afforded carboxylic acid **16** (122 mg, 73%) as a yellowish oil: $[\alpha]^{22}_D$ −10.9 (*c* 0.5, $CHCl_3$); IR (film): ν = 2957, 1698, 1640, 1462, 1252 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.04 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.88 [s, 9H, $(CH_3)_3$], 0.90 (d, *J* = 6.8 Hz, 3H, C-5CH_3), 0.99 (d, *J* = 6.4 Hz, 3H, C-9CH_3), 1.32-1.38 (m, 2H, H-6), 1.39-1.49 (m, 2H, H-8), 1.66-1.74 (m, 1H, H-5), 2.28-2.35 (m, 1H, H-9), 2.59-2.63 (m, 2H, H-4), 3.72-3.79 (m, 1H, H-7), 4.91-4.99 (m, 2H, H-11), 5.68 (ddd, *J* =

17.6, 10.2, 7.4 Hz, 1H, H-10), 5.85 (dt, *J* = 11.6, 1.6 Hz, 1H, H-2), 6.34 (dt, *J* = 11.6, 7.6 Hz, 1H, H-3); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) -4.1 ($SiCH_3$), -3.9 ($SiCH_3$), 18.1 [$C(CH_3)_3$], 19.9 (C-5CH_3), 21.1 (C-9CH_3), 25.9 [$C(CH_3)_3$], 29.8 (C-5), 34.1 (C-9), 36.4 (C-4), 44.4 (C-6), 45.0 (C-8), 68.7 (C-7), 112.7 (C-11), 19.7 (C-10), 144.5 (C-2), 151.8 (C-3), 170.6 (COOH); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{19}H_{35}O_3Si$ 339.2361, found 339.2369.



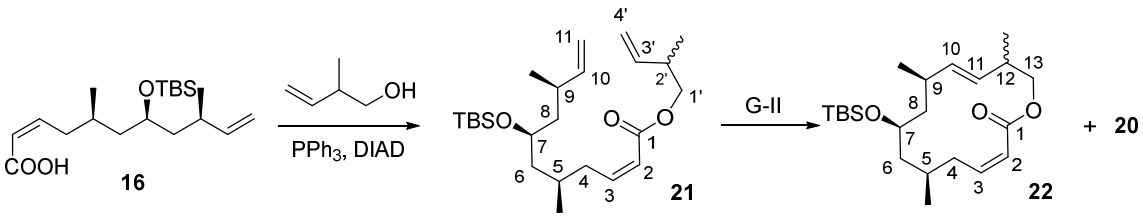
Z-unsaturated ester (18): Diisopropyl azodicarboxylate (120 µL, 0.59 mmol) was added to a solution of alcohol **17**[5] (59 mg, 0.24 mmol) and carboxylic acid **16** (99 mg, 0.29 mmol) in anhydrous THF (1.5 mL). The solution was cooled to 0 ºC, and PPh_3 (154 mg, 0.59 mmol) was added. After stirring at room temperature for 18 h under an argon atmosphere, the reaction was quenched with H_2O and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried, filtered, and concentrated. Flash chromatography (hexane to 8:2 hexane-CH_2Cl_2) of the residue afforded unsaturated ester **18** (70 mg, 51%) as a colorless oil: $[\alpha]^{22}_D$ −58.2 (*c* 2.3, $CHCl_3$); δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.04 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.88 [s, 9H, $(CH_3)_3$], 0.89 (d, *J* = 6.8 Hz, 3H, CH_3), 0.98 (d, *J* = 6.8 Hz, 3H, CH_3), 1.03 (d, *J* = 6.4 Hz, 3H, CH_3), 1.29-1.37 (m, 2H, H-6), 1.39-1.48 (m, 2H, H-8), 1.64-1.72 (m, 1H, H-9), 2.50-2.66 (m, 2H, H-4), 3.72-3.78 (m, 1H, H-7), 4.91-4.99 (m, 2H, H-11), 5.05-5.11 (m, 2H, H-6'), 5.18 (t, *J* = 6.6 Hz, 1H, H-3'), 5.63-5.76 (m, 2H, H-10 and H-5'), 5.81 (dt, *J* = 11.5, 1.8 Hz, 1H, H-2), 6.24 (ddd, *J* = 11.5, 8.0, 7.2 Hz, 1H, H-3), 6.40 (dd, *J* = 14.4, 0.8 Hz, 1H, H-1'), 6.49 (dd, *J* = 14.4, 6.8 Hz, 1H, H-2'); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) -4.1 ($SiCH_3$), -3.9 ($SiCH_3$), 15.4 (C-4'*C*H_3), 18.1 [$C(CH_3)_3$], 19.9 (C-5*C*H_3), 21.2 (C-9*C*H_3), 25.9 [$C(CH_3)_3$], 29.8 (C-5), 34.1 (C-9), 36.4 (C-4), 41.3 (C-4'), 44.4 (C-6), 45.1 (C-8), 68.7 (C-7), 77.9 (C-3'), 80.3 (C-1'), 112.7 (C-11), 116.2 (C-6'), 120.1 (C-2), 138.6 (C-5'), 142.1 (C-2'), 144.5 (C-10), 150.1 (C-3), 165.2 (C-1); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{26}H_{46}IO_3Si$ 561.2255, found 561.2255.



Macrolide 19: Second-generation Hoveyda-Grubbs catalyst (12 mg, 19.4 µmol) was added to a solution of ester **18** (23 mg, 64.6 µmol) in anhydrous toluene (26 mL) at room temperature, and the resulting mixture was heated at 80 ºC for 3 h. The solvent was evaporated, and

[5] H. Fuwa, T. Suzuki, H. Kubo, T. Yamori and M. Sasaki, *Chem. Eur. J.*, 2011, **17**, 2678-2688.

the resulting residue was chromatographed (hexane to 8:2 hexane-CH_2Cl_2) to afford macrolide **19** (3.4 mg, 16%), cyclooctene **20** (2.7 mg, 25%), and unsaturated ester **18** (6 mg). Macrolide **19**: $[\alpha]^{22}_D$ –60.8 (*c* 0.51, $CHCl_3$); δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.09 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.87 [s, 9H, $(CH_3)_3$], 0.89 (d, *J* = 6.8 Hz, 3H, CH_3), 0.92 (m, 1H, H-6 or H-8), 0.96 (d, *J* = 6.8 Hz, 3H, CH_3), 1.00 (d, *J* = 7.2 Hz, 3H, CH_3), 1.05-1.11 (m, 1H, H-6 or H-8), 1.28-1.37 (m, 2H, H-6 and H-8), 1.95 (ddd, *J* = 14.4, 6.0, 2.8 Hz, 1H, H-4), 2.01-2.09 (m, 1H, H-5), 2.14-2.25 (m, 2H, H-9 and H-12), 3.43-3,48 (m, 1H, H-7), 3.62 (ddd, *J* = 14.4, 12.6, 4.2 Hz, 1H, H-4), 5.03 (dd, *J* = 15.2, 9.2 Hz, 1H, H-11), 5.11-5.17 (m, 2H, H-10 and H-13), 5.84 (dd, *J* = 11.6, 2.8 Hz, 1H, H-2), 6.23 (td, *J* = 11.6, 4.2 Hz, 1H, H-3), 6.45 (d, *J* = 14.4 Hz, 1H, H-15), 6.52 (dd, *J* = 14.4, 7.6 Hz, 1H, H-14); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) -3.4 ($SiCH_3$), -3.2 ($SiCH_3$), 17.4 (CH_3), 18.4 [$C(CH_3)_3$], 20.1 (CH_3), 22.6 (CH_3), 26.0 [$C(CH_3)_3$], 27.5 (C-12), 31.2 (C-4), 34.6 (C-5 or C-9), 42.3 (C-5 or C-9), 44.7 (C-6 or C-8), 47.6 (C-6 or C-8), 68.4 (C-7), 77.6 (C-13), 80.8 (C-15), 121.5 (C-2), 131.0 (C-10), 138.3 (C-11), 143.3 (C-14), 146.4 (C-3), 164.8 (C-1). HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{24}H_{42}IO_3Si$ 533.1942, found 533.1931. Cyclooctene **20**: δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.05 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.86 (d, *J* = 6.8 Hz, 3H, CH_3), 0.88 [s, 9H, $(CH_3)_3$], 1.03 (d, *J* = 6.4 Hz, 3H, CH_3), 1.36-1.45 (m, 1H, H-4 or H-6), 1.51-1.56 (m, 1H, H-4 or H-6), 1.61-1.71 (m, 2H, H-4 and H-6), 1.78-1.83 (m, 1H, H-8), 1.86-1.94 (m, 1H, H-7), 2.38-2.45 (m, 1H, H-8), 2.46-2.52 (m, 1H, H-3), 3.64 (ddd, *J* = 10.4, 7.6, 3.0 Hz, 1H, H-5), 5.39 (dd, *J* = 6.4, 10.4 Hz, 1H, H-1 or H-2) 5.43-5.48 (m, 1H, H-1 or H-2); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) -4.6 ($SiCH_3$), 18.2 [$C(CH_3)_3$], 21.2 (CH_3), 23.3 (CH_3), 25.9 [$C(CH_3)_3$], 28.8 (C-3), 30.8 (C-7), 31.3 (C-8), 44.9 (C-4 or C-6), 48.8 (C-4 or C-6), 73.3 (C-5), 124.3 (C-1), 138.2 (C-2); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{16}H_{33}OSi$ 269.2295, found 269.2282.

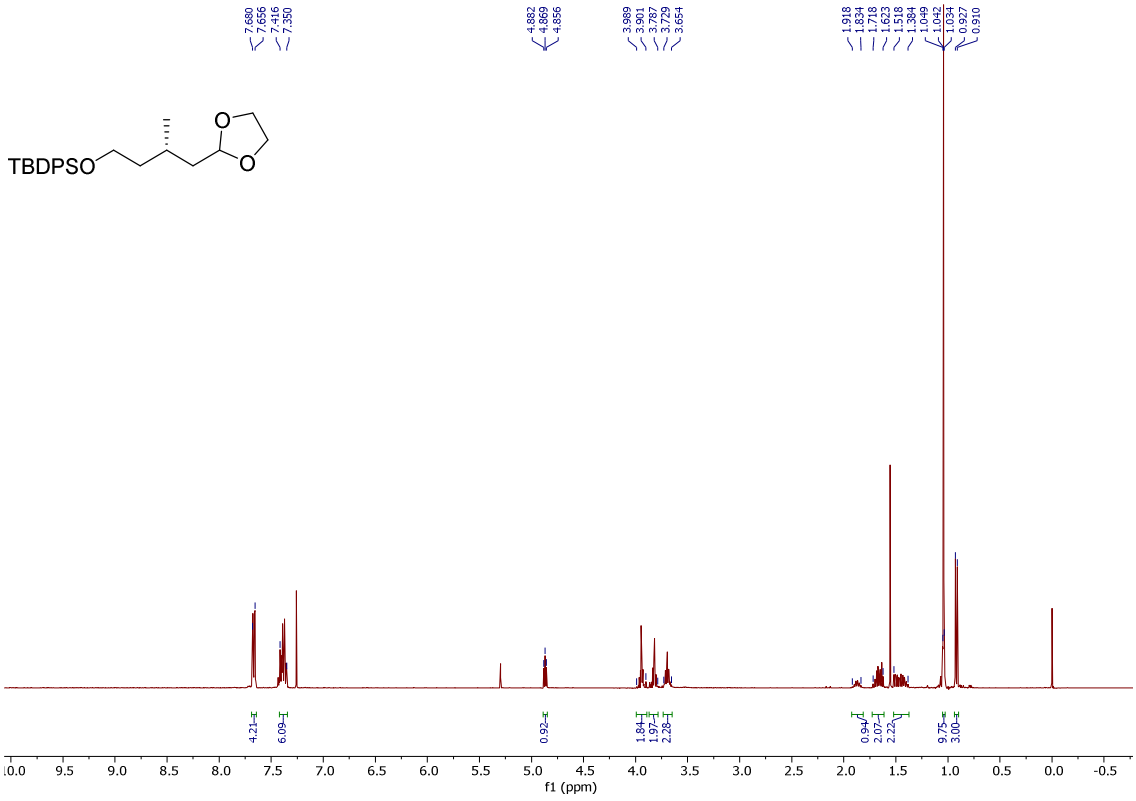


Macrolactone 22: Diisopropyl azodicarboxylate (95 µL, 0.48 mmol) was added under an argon atmosphere to a solution of commercial 2-methyl-4-penten-1-ol (25 µL, 0.24 mmol) and carboxylic acid **16** (100 mg, 0.29 mmol) in anhydrous THF (1.5 mL). The solution was cooled to 0 ºC and PPh_3 (127 mg, 0.48 mmol) was added. After stirring at room temperature for 18 h, the reaction was quenched with H_2O and the resulting mixture was extracted with EtOAc. The organic phase was washed with brine, dried, filtered, and concentrated. Flash chromatography (hexane to 9:1 hexane-EtOAc) of the residue afforded *Z*-unsaturated ester **21** (70 mg, 66%) as a mixture of C-2'epimers indistinguishable by NMR: δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC) 0.04 (s, 3H, $SiCH_3$), 0.05

(s, 3H, $SiCH_3$), 0.88 [s, 9H, $(CH_3)_3$], 0.89 (d, *J* = 6.8 Hz, 3H, CH_3-H5), 0.98 (d, *J* = 6.8 Hz, 3H, CH_3-H9), 1.06 (d, *J* = 6.8 Hz, 3H, CH_3-H2'), 1.29-1.37 (m, 2H, H-6), 1.39-1.48 (m, 2H, H-8), 1.63-1.74 (m, 1H, H-5), 2.28-2.35 (m, 1H, H-9), 2.51-2.66 (m, 3H, H-4 and H-2'), 3.72-3.78 (m, 1H, H-7), 3.95-4.07 (m, 2H, H-1'), 4.91-4.99 (m, 2H, H-11), 5.03-5.11 (m, 2H, H-4'), 5.63-5.79 (m, 2H, H-10 and H-3'), 5.81-5.85 (m, 1H, H-2), 6.17-5.23 (m, 1H, H-3); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) -4.2 ($SiCH_3$), -3.9 ($SiCH_3$), 16.5 (CH_3-C2'), 18.1 [*C*$(CH_3)_3$], 19.9 (CH_3-C5), 21.2 (CH_3-C9), 25.9 [C(*C*$H_3)_3$], 29.9 (C-5), 34.1 (C-9), 36.3 (C-4), 36.9 (C-2'), 44.4 (C-6), 45.1 (C-8), 67.9 (C-1'), 68.7 (C-7), 112.7 (C-11), 114.9 (C-4'), 120.5 (C-2), 140.2 (C-3'), 144.6 (C-10), 149.1 (C-3), 166.5 (C-1).

Second-generation Grubbs catalyst (18 mg, 21 μmol) was added to a stirred solution of ester **20** (43 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (44 mL) at room temperature, and the resulting mixture was heated at reflux for 3 h. The solvent was evaporated, and the resulting residue was chromatographed (8:2 hexane-CH_2Cl_2) to afford macrolactone **22** (15 mg, 38%) as a mixture of C-12 epimers, and cyclooctene **20** (14.4 mg, 50%): **22**: δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, *g*-HSQC, from a mixture of C_{12} epimers) 0.04 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.87 [s, 9H, $(CH_3)_3$], 0.88 [s, 9H, $(CH_3)_3$], 0.90 (d, *J* = 6.8 Hz, 3H, CH_3), 0.94-0.96 (m, 12H, 4CH_3), 1.03 (d, *J* = 6.8 Hz, 3H, CH_3), 1.47-1.58 (m, 4H, H-4 and 2H, H-6), 1.80-1.88 (m, 1H, H-5 and 2H, H-8), 2.22-2.31 (m, 1H, H-5 and 2H, H-9), 2.36-2.40 (m, 2H, H-8), 2.53-2.60 (m, 2H, H-12), 3.59-3.71 (m, 2H, H-7), 3.91-3.96 (dd, *J* = 11.0, 8.8 Hz, 2H, H-13 minor), 4.18-4.24 (m, 2H, H-13 major), 4.98-5.04 (dd, *J* = 15.2, 8.8 Hz, 1H, H-10 minor), 5.01-5.12 (dd, *J* = 15.2, 8.8 Hz, 1H, H-11 minor), 5.22-5.28 (dd, *J* = 16.0, 6.8 Hz, 1H, H-10 major), 5.36-5.42 (dd, *J* = 16.0, 7.2 Hz, 1H, H-11 major), 5.67-5.74 (m, 2H, H-2), 6.88-7.02 (m, 2H, H-3); δ_C (100.6 MHz; $CDCl_3$; Me_4Si). Data of the major diastereomer from a mixture of C-12 epimers: -3.4 ($SiCH_3$), 16.2 (CH_3), 18.3 [*C*$(CH_3)_3$], 20.6 (CH_3), 24.2 (CH_3), 26.0 [C(*C*$H_3)_3$], 31.6 (C-5), 32.2 (C-9), 36.4 (C-12), 42.4 (C-8), 47.7 (C-4), 48.4 (C-6), 67.0 (C-13), 71.4 (C-7), 121.3 (C-2), 129.8 (C-10), 136.1 (C-11), 148.6 (C-3), 165.8 (C-1); Data of the minor diastereomer from a mixture of C-12 epimers: δ -3.2 ($SiCH_3$), -2.8 ($SiCH_3$),16.8 (CH_3), 18.4 [*C*$(CH_3)_3$], 22.6 (CH_3), 24.2 (CH_3), 25.9 [C(*C*$H_3)_3$], 30.4 (C-5), 34.6 (C-9), 37.4 (C-12), 42.4 (C-8), 47.7 (C-4), 48.4 (C-6), 67.6 (C-13), 71.3 (C-7), 121.6 (C-2), 131.7 (C-10), 138.5 (C-11), 149.5 (C-3), 165.7 (C-1); HRMS (ESI-TOF) *m/z* $[M + H]^+$ Calcd for $C_{22}H_{41}O_3Si$ 381.2819, found 381.2818.

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



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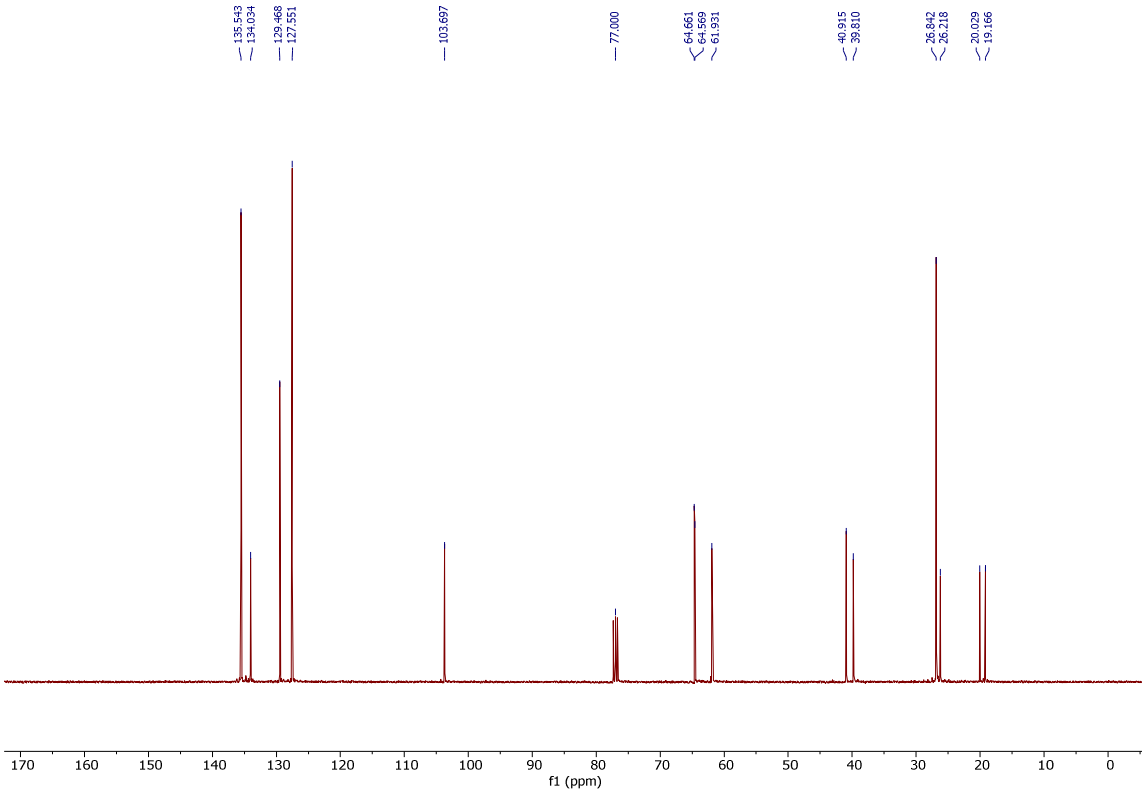

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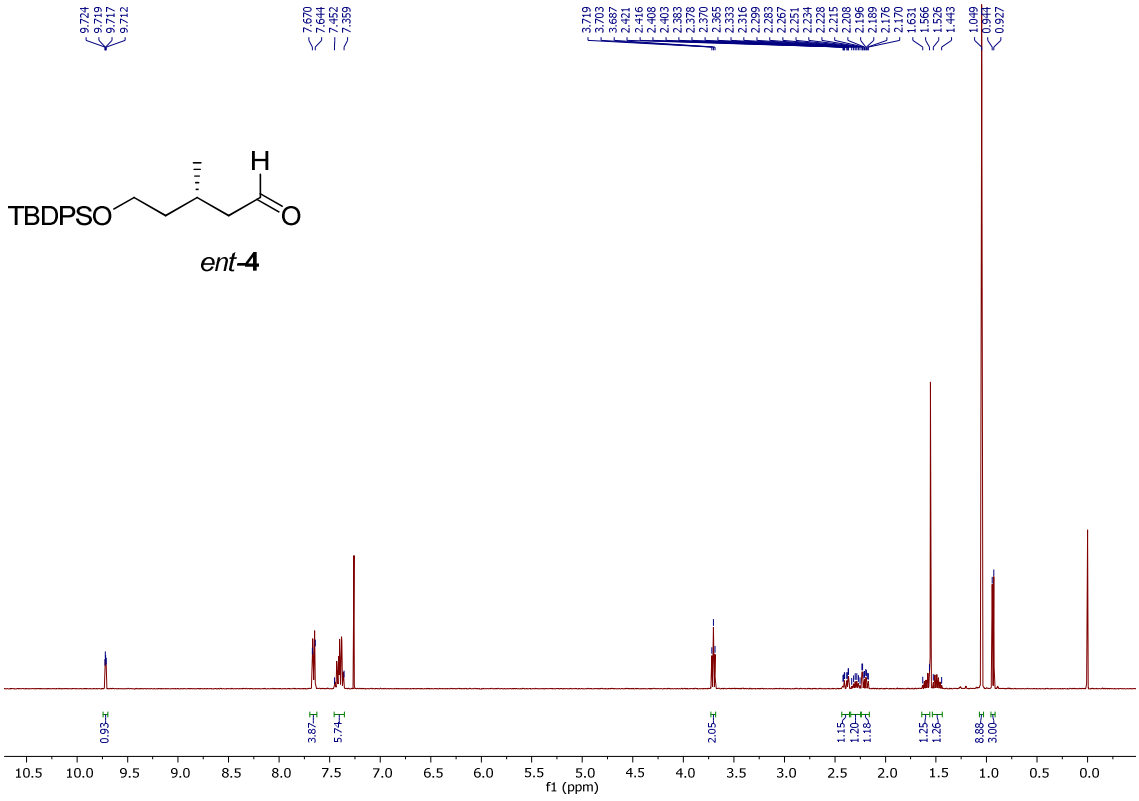

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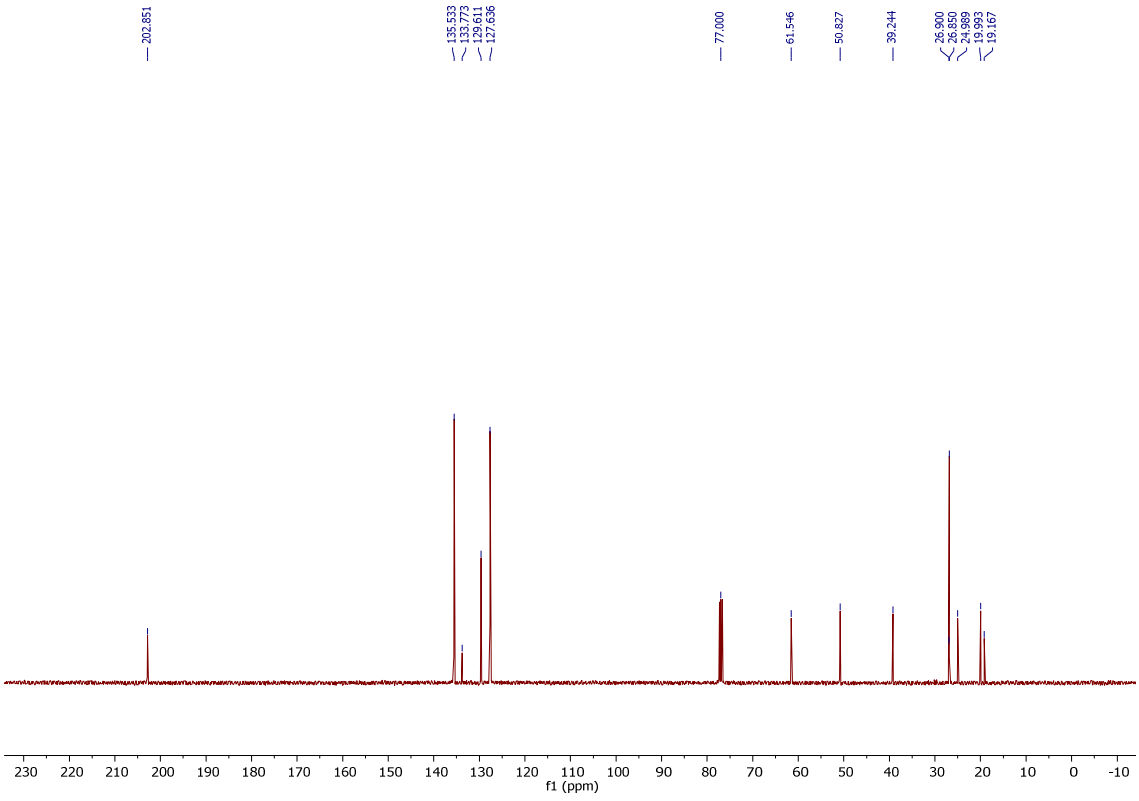

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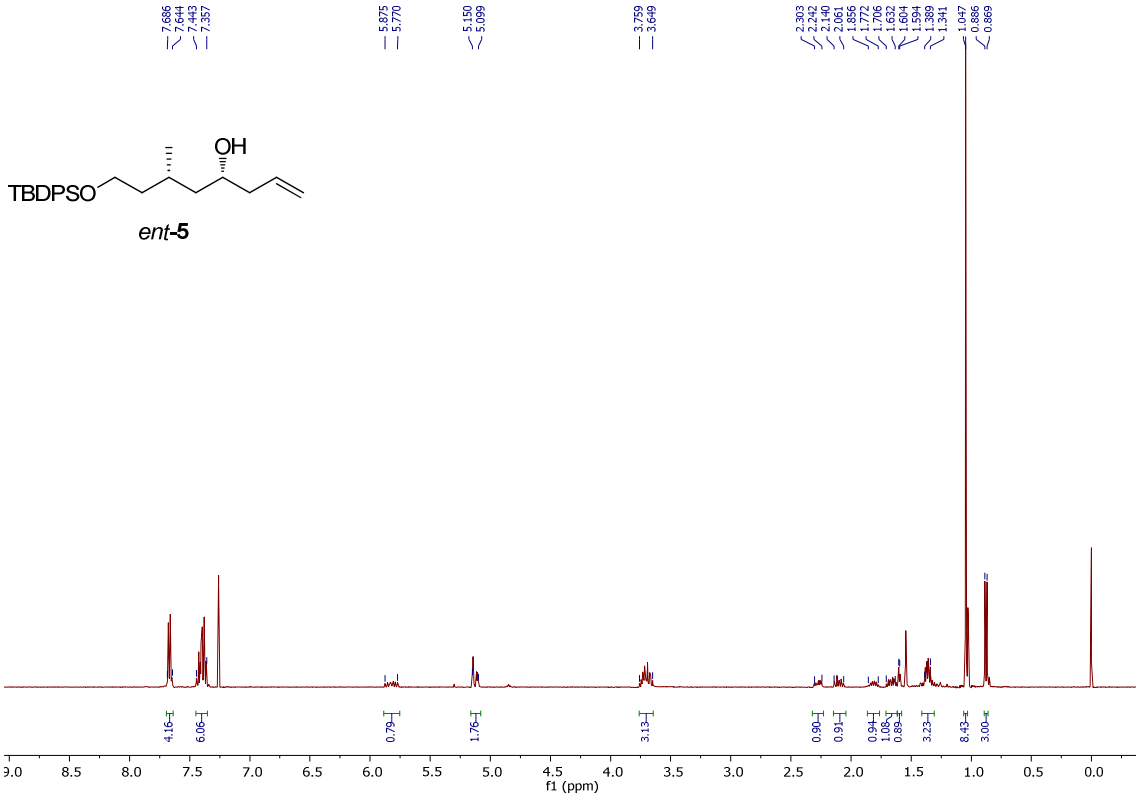

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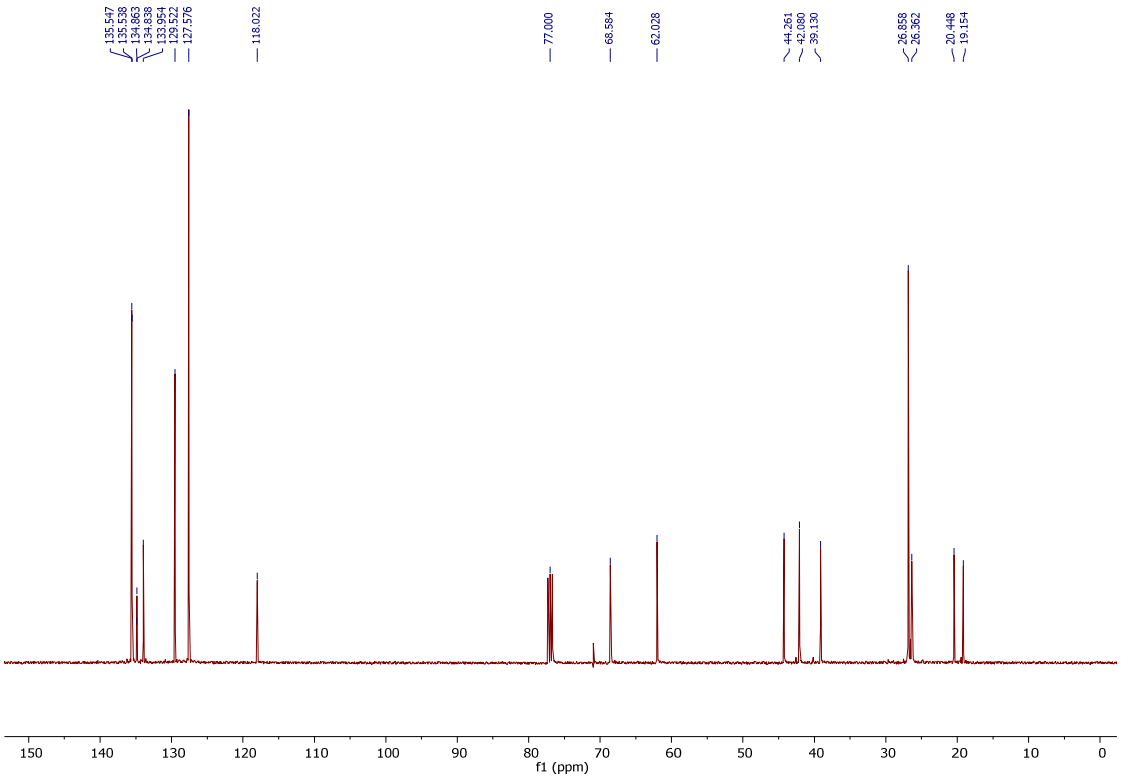

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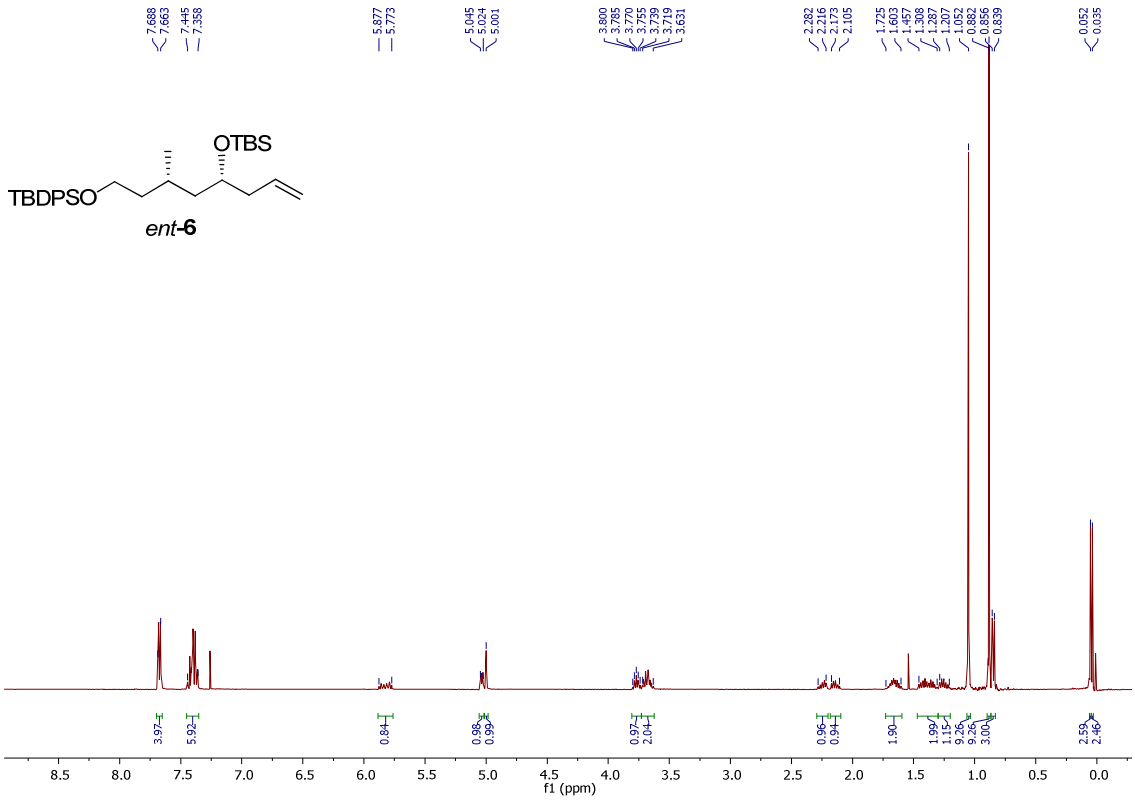

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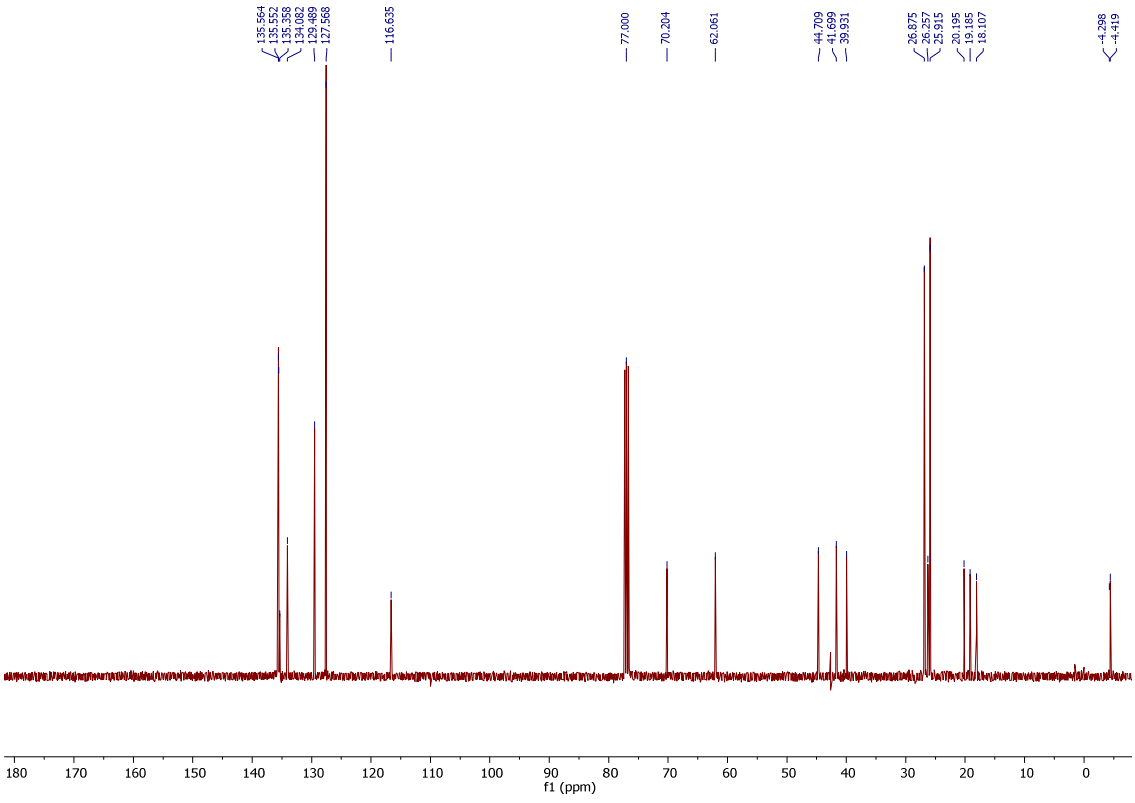

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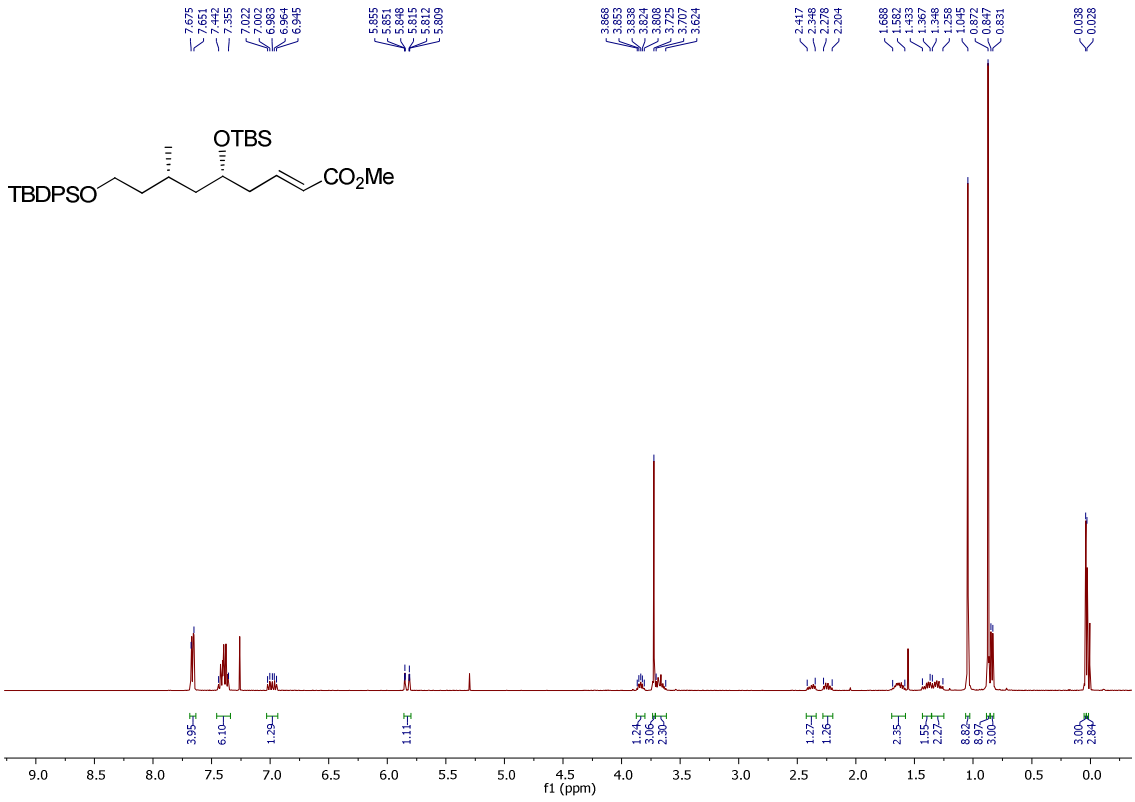
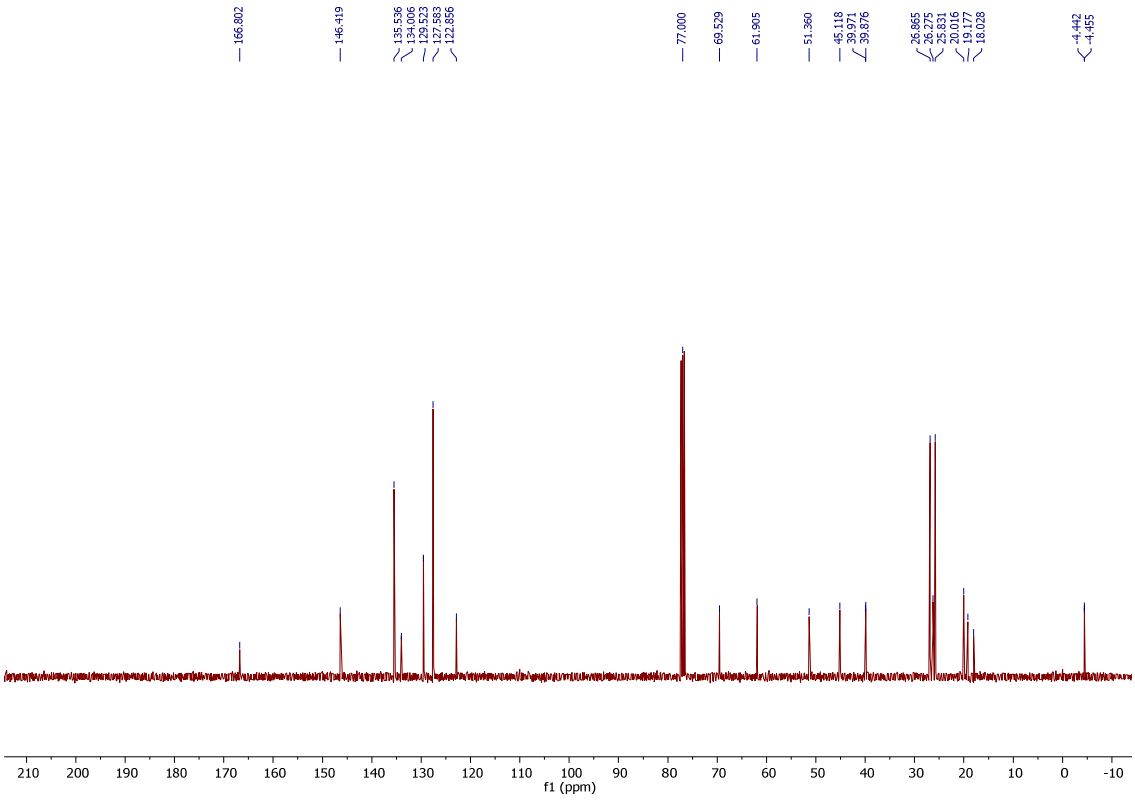
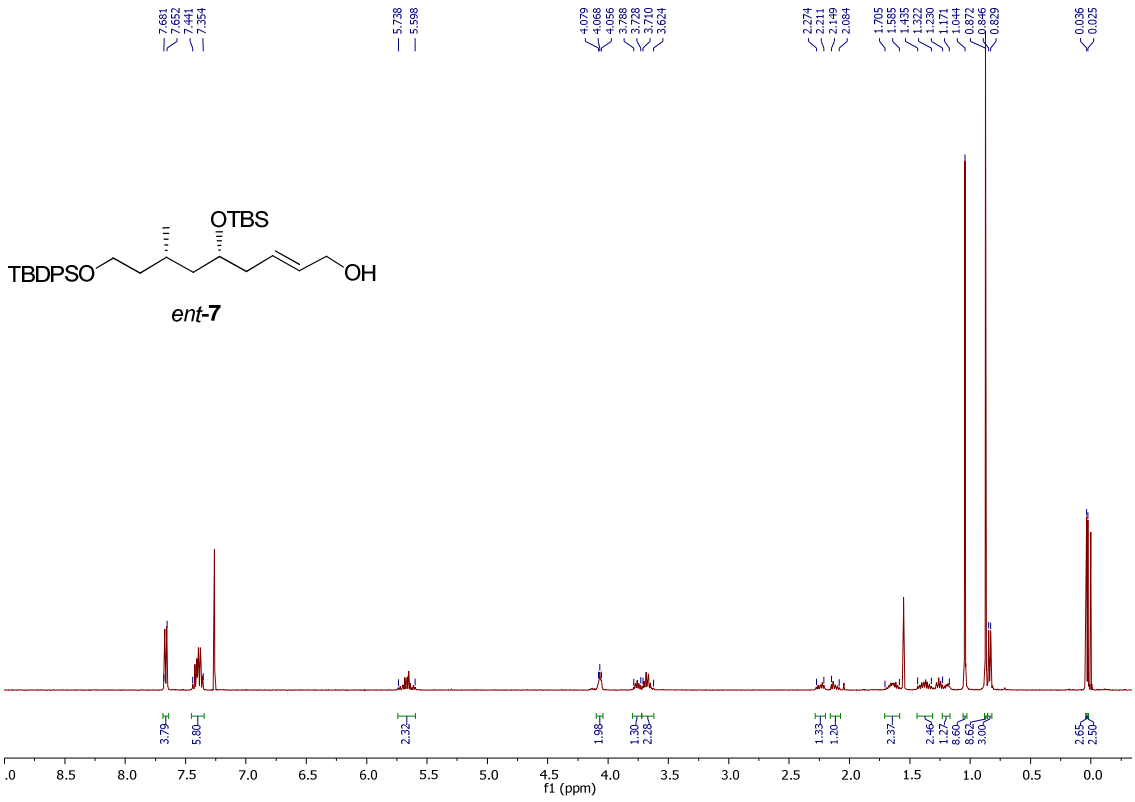


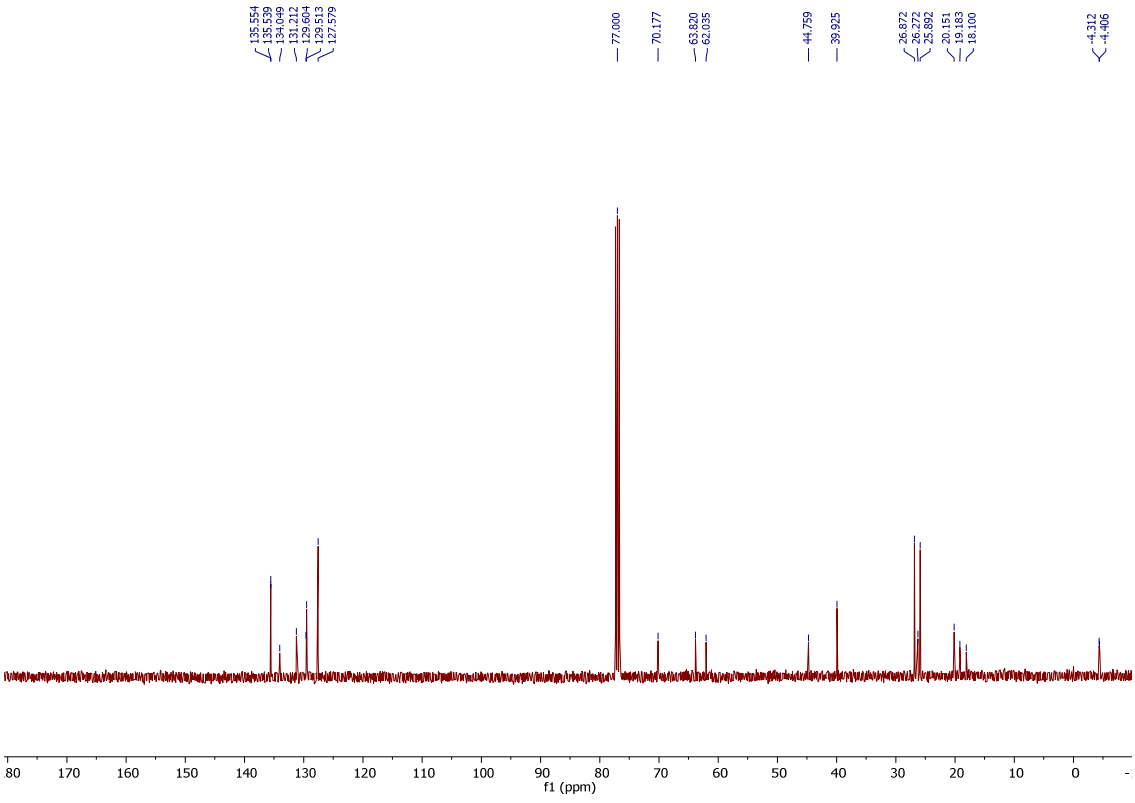
^{13}C NMR (100.6 MHz, $CDCl_3$)



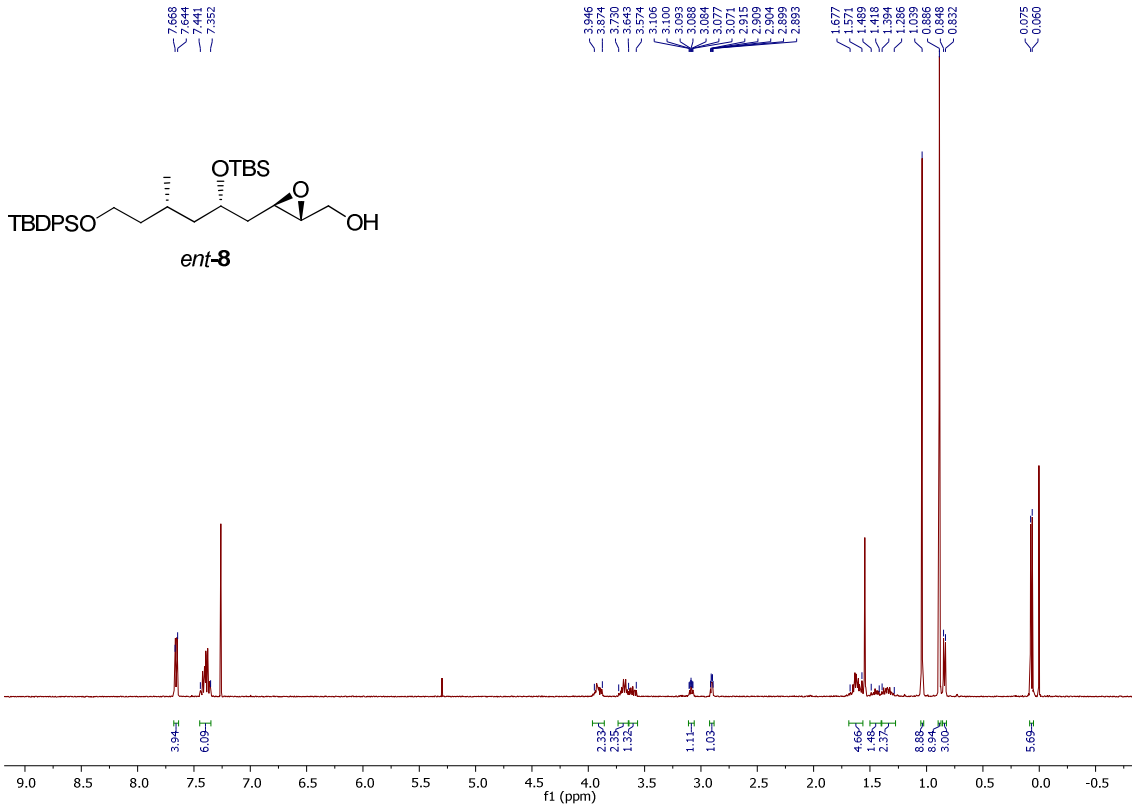
^{1}H NMR (400 MHz, $CDCl_3$)



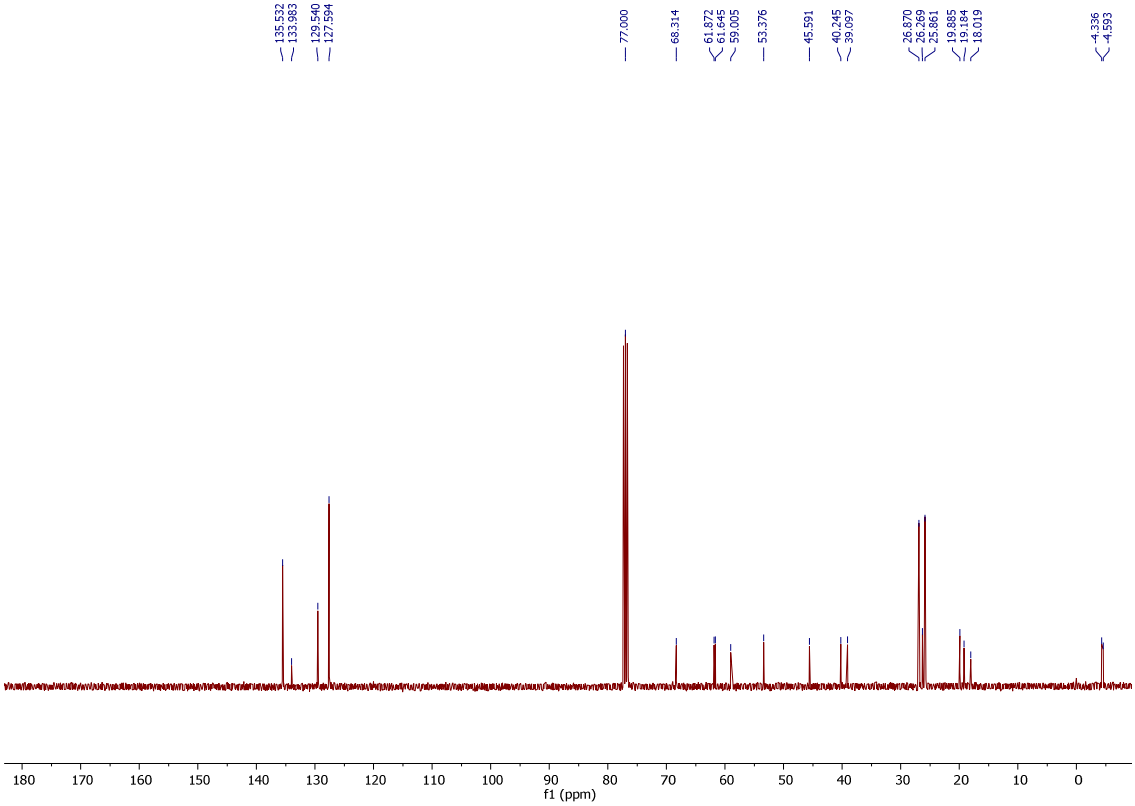
^{13}C NMR (100.6 MHz, $CDCl_3$)



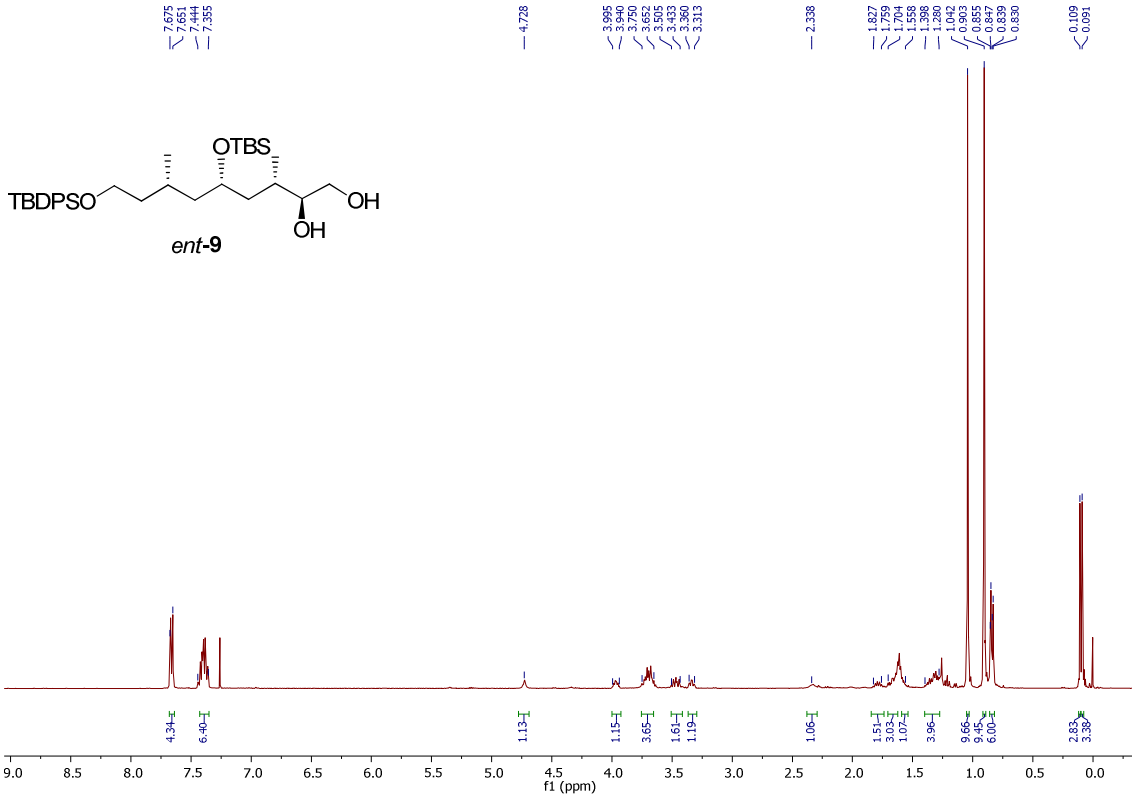
^{1}H NMR (400 MHz, $CDCl_3$)



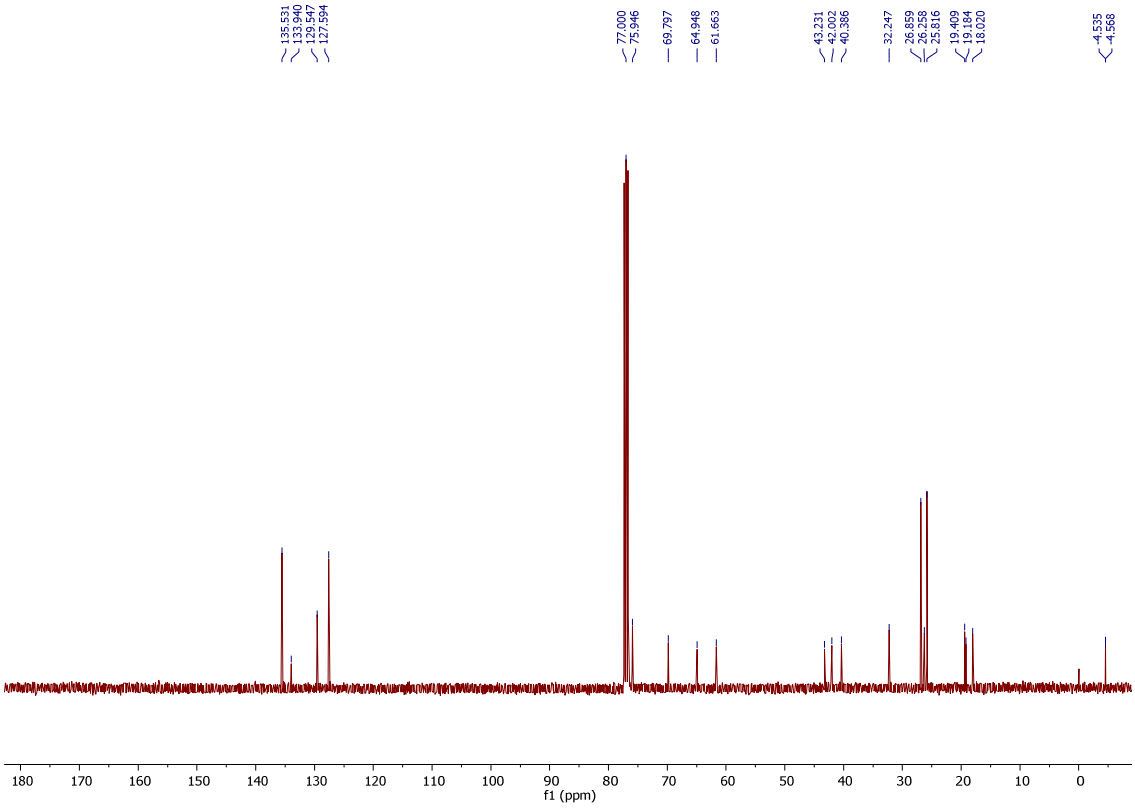
^{13}C NMR (100.6 MHz, $CDCl_3$)



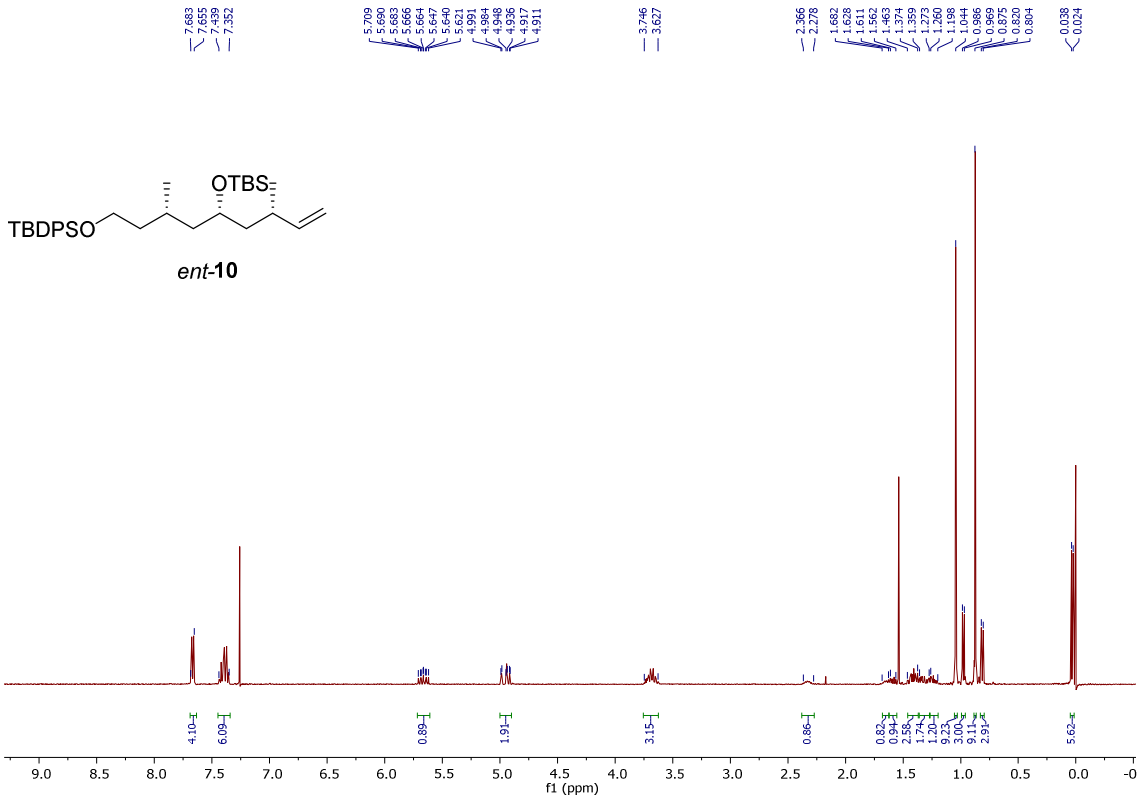
^{1}H NMR (400 MHz, $CDCl_3$)



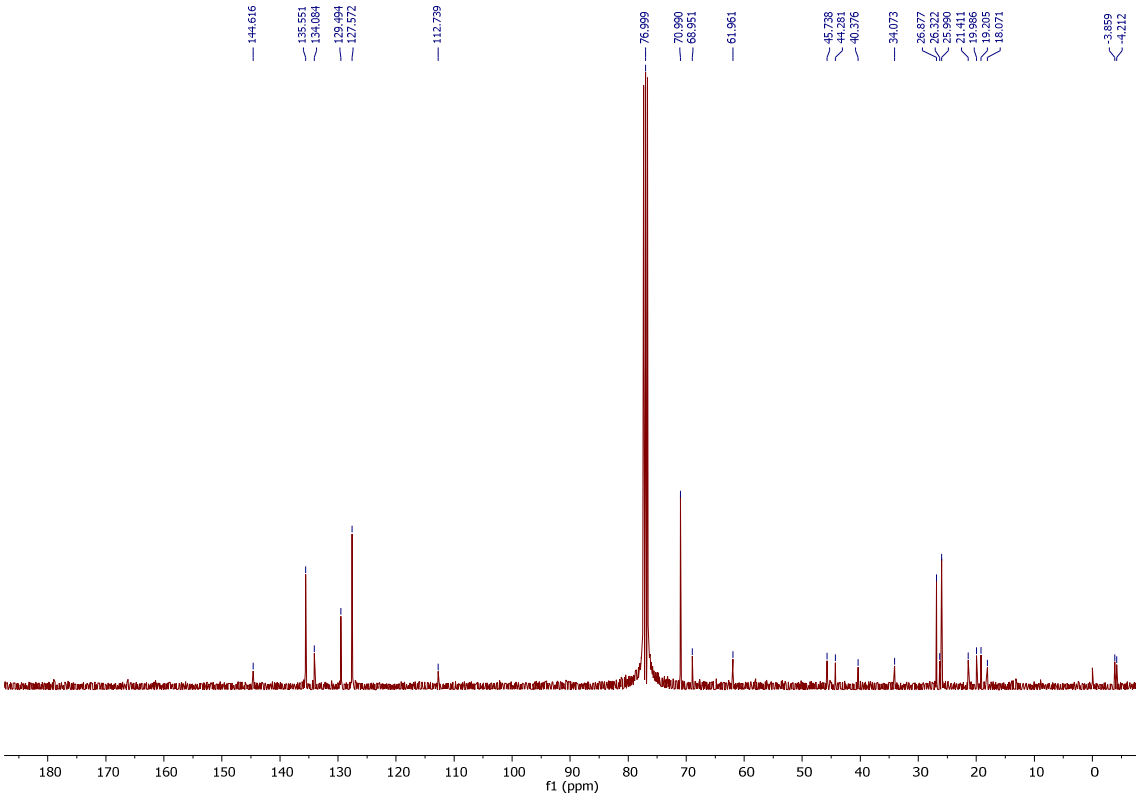
^{13}C NMR (100.6 MHz, $CDCl_3$)



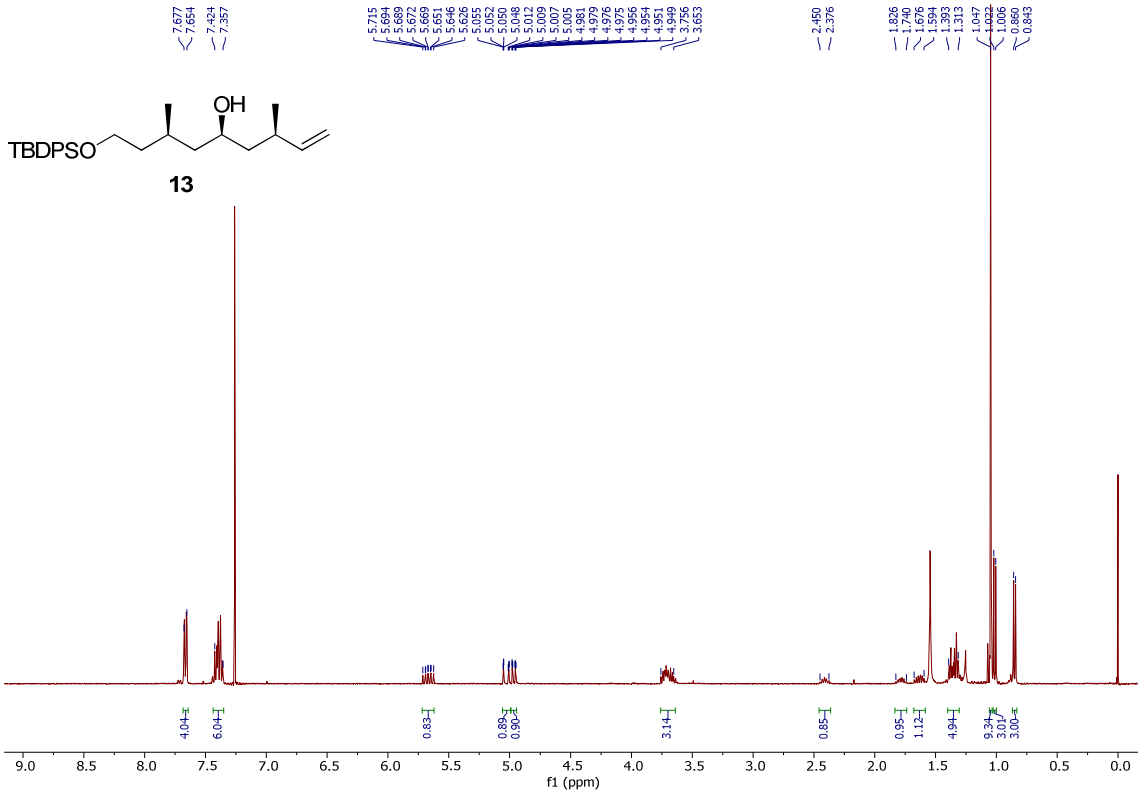
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100.6 MHz, $CDCl_3$)



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



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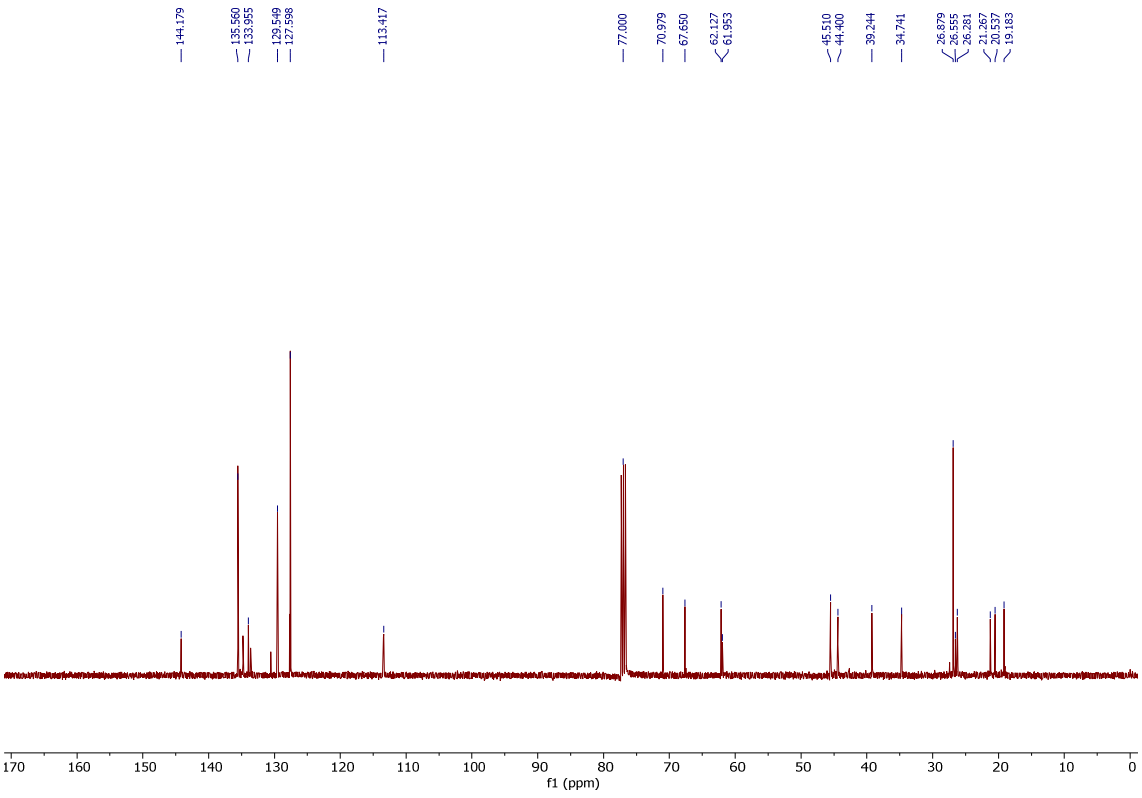

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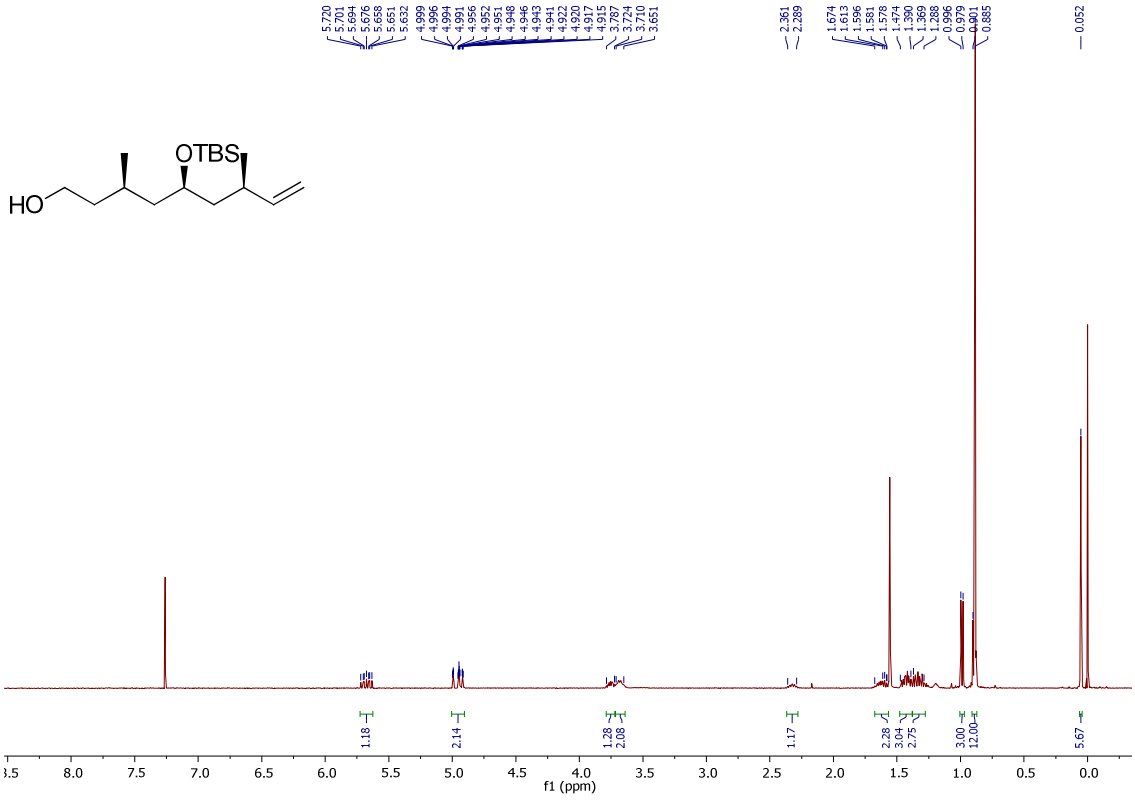
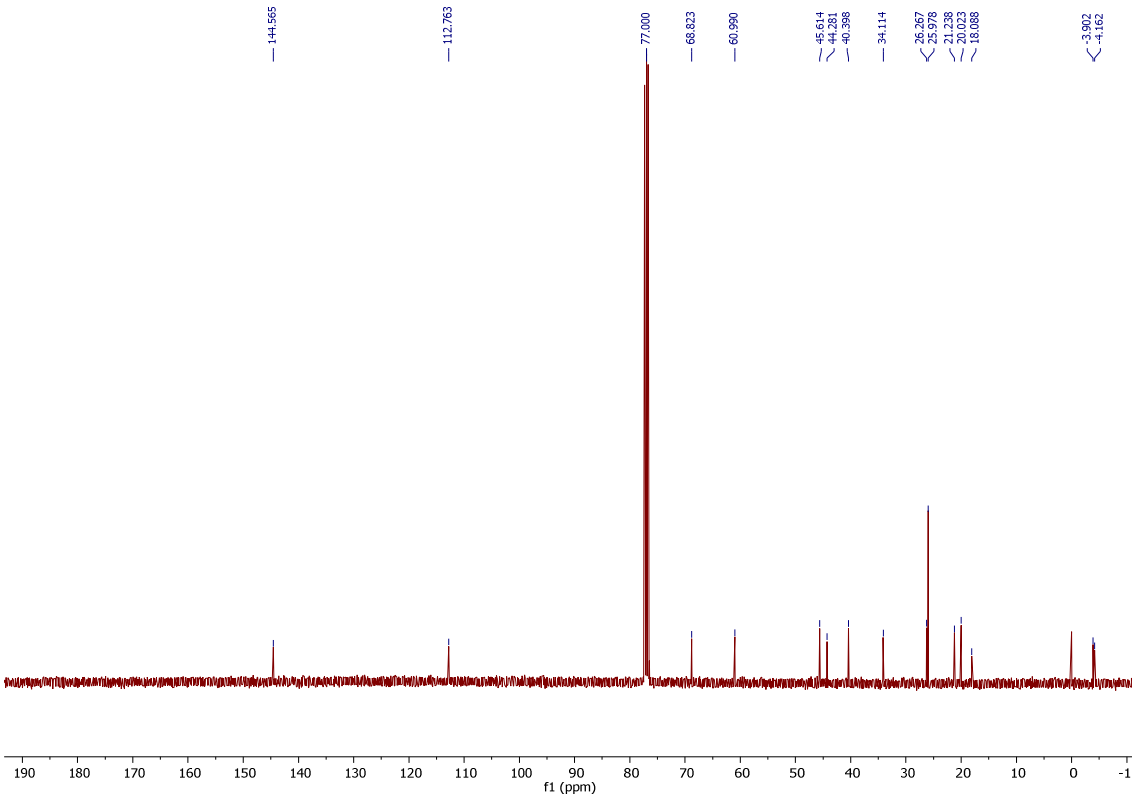
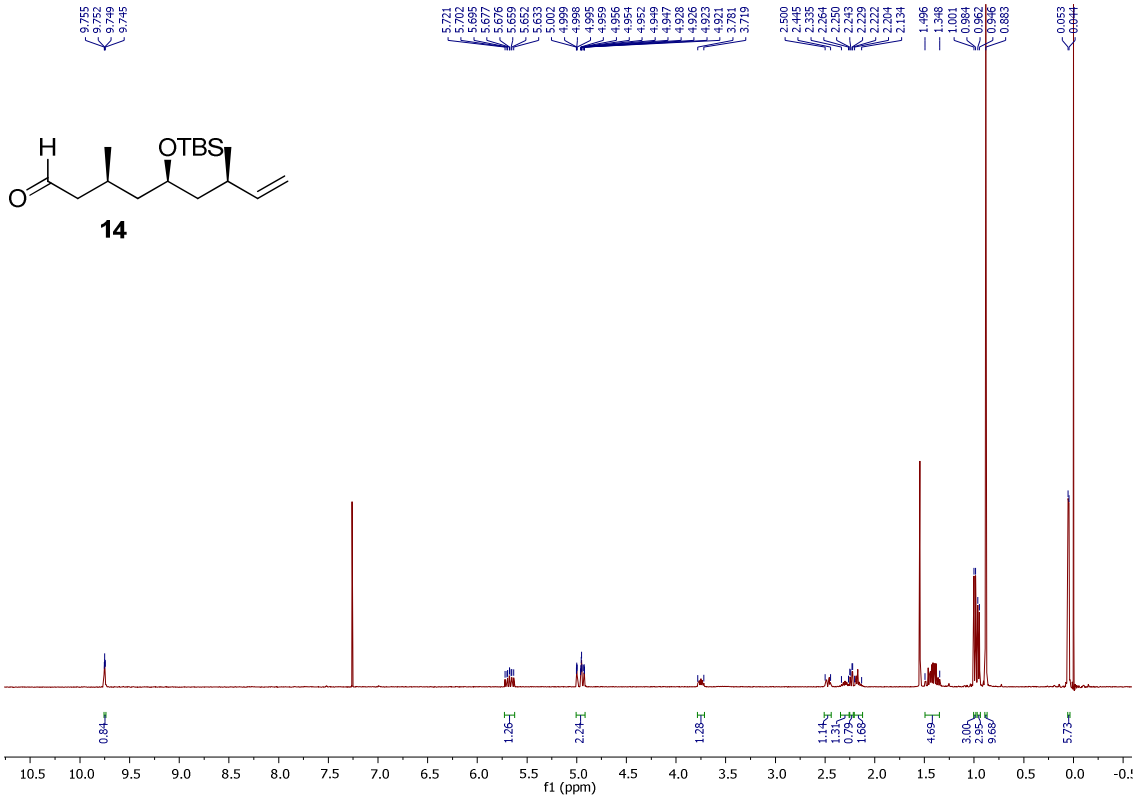


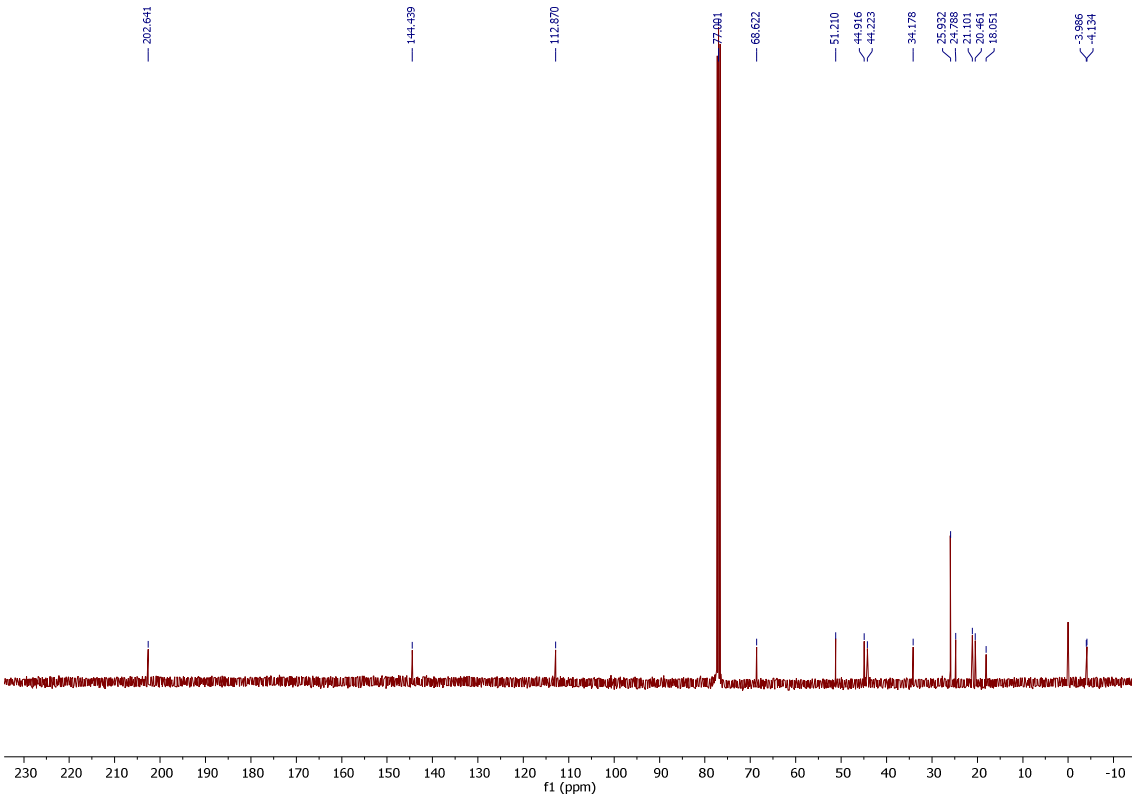
^{13}C NMR (100.6 MHz, $CDCl_3$)



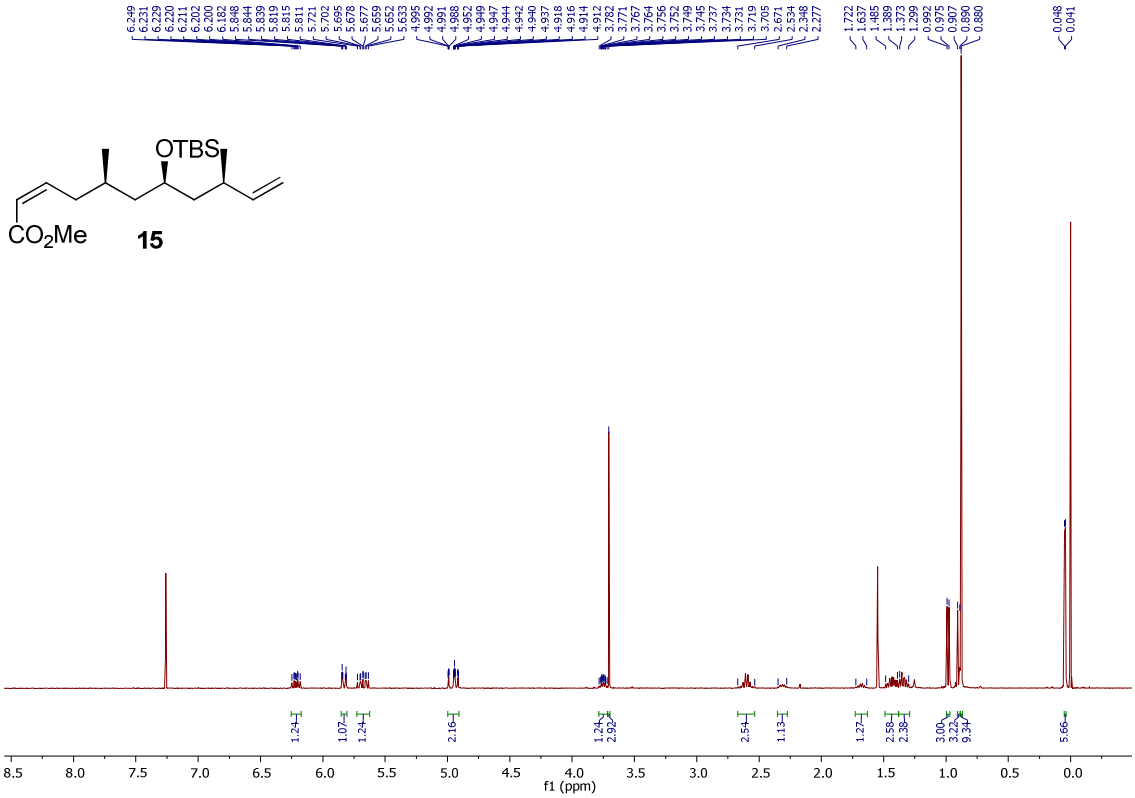
^{1}H NMR (400 MHz, $CDCl_3$)



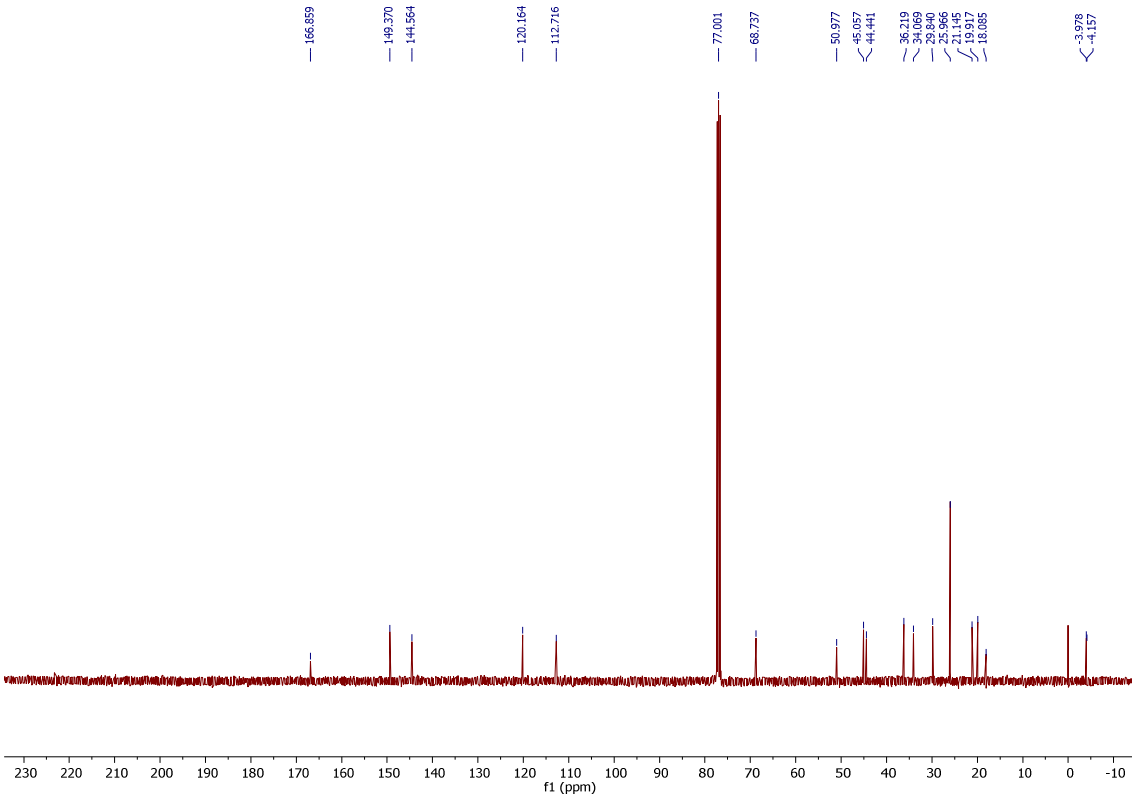
^{13}C NMR (100.6 MHz, $CDCl_3$)



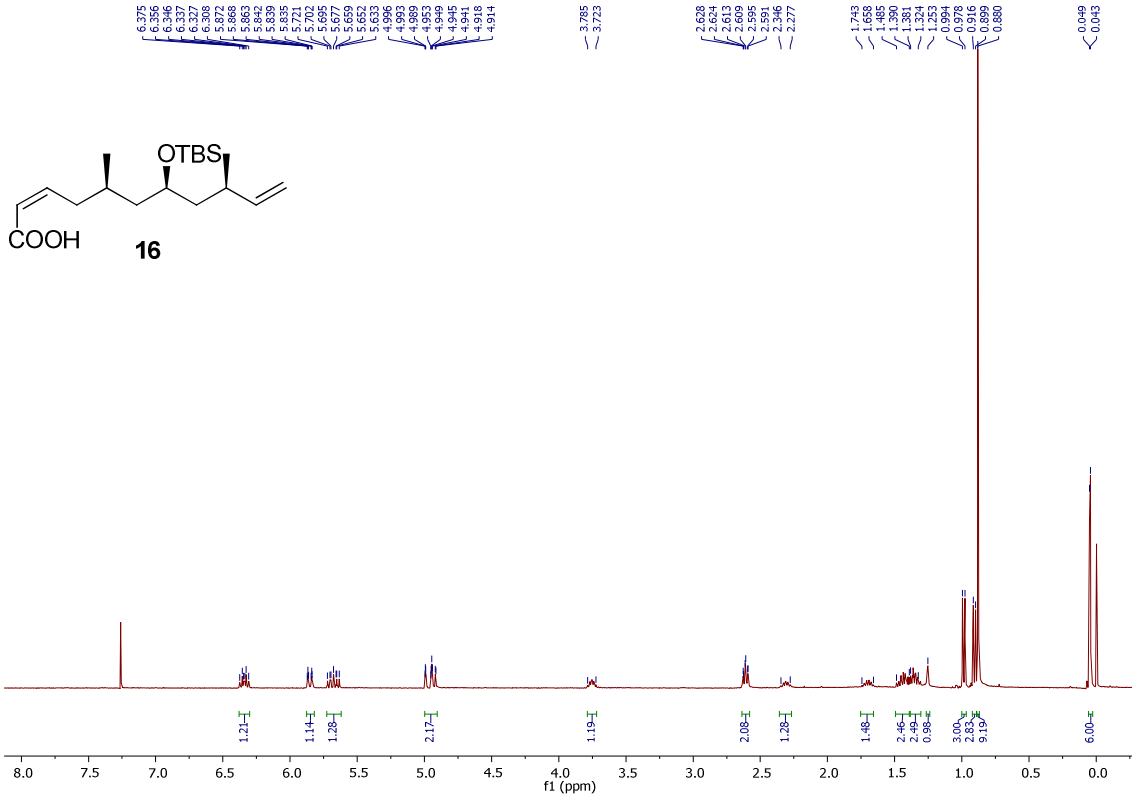
^{1}H NMR (400 MHz, $CDCl_3$)



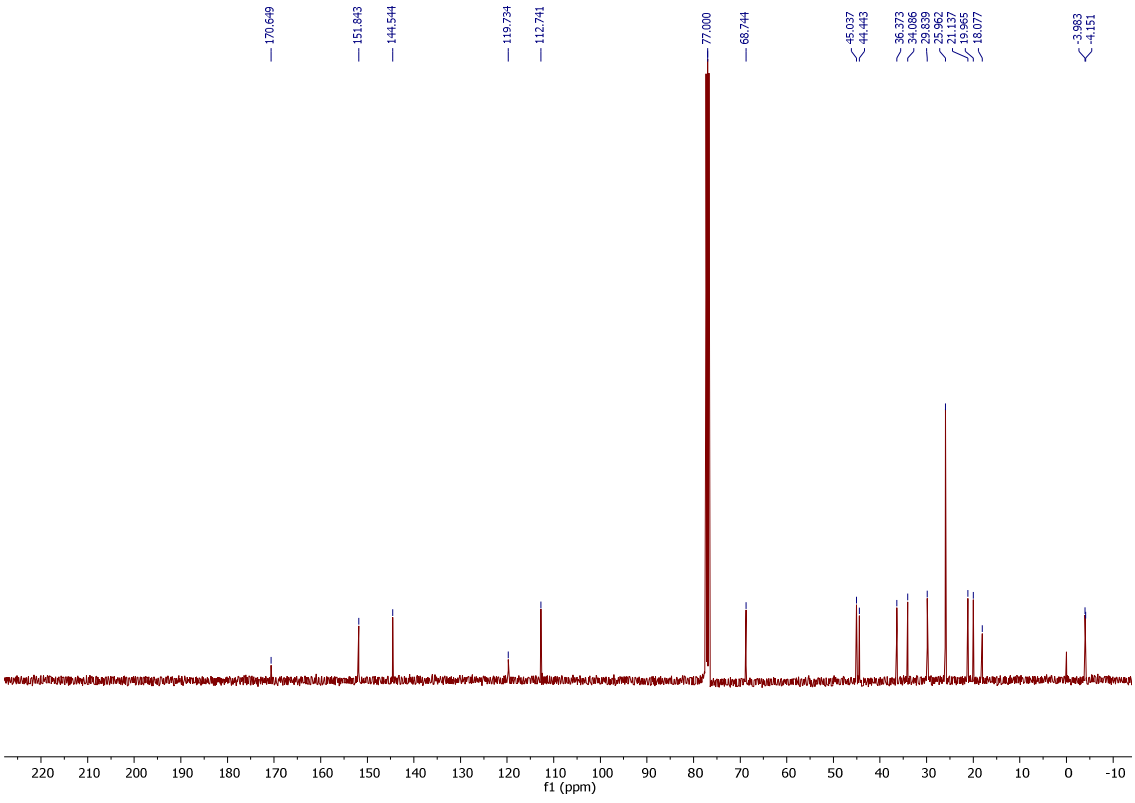
^{13}C NMR (100.6 MHz, $CDCl_3$)



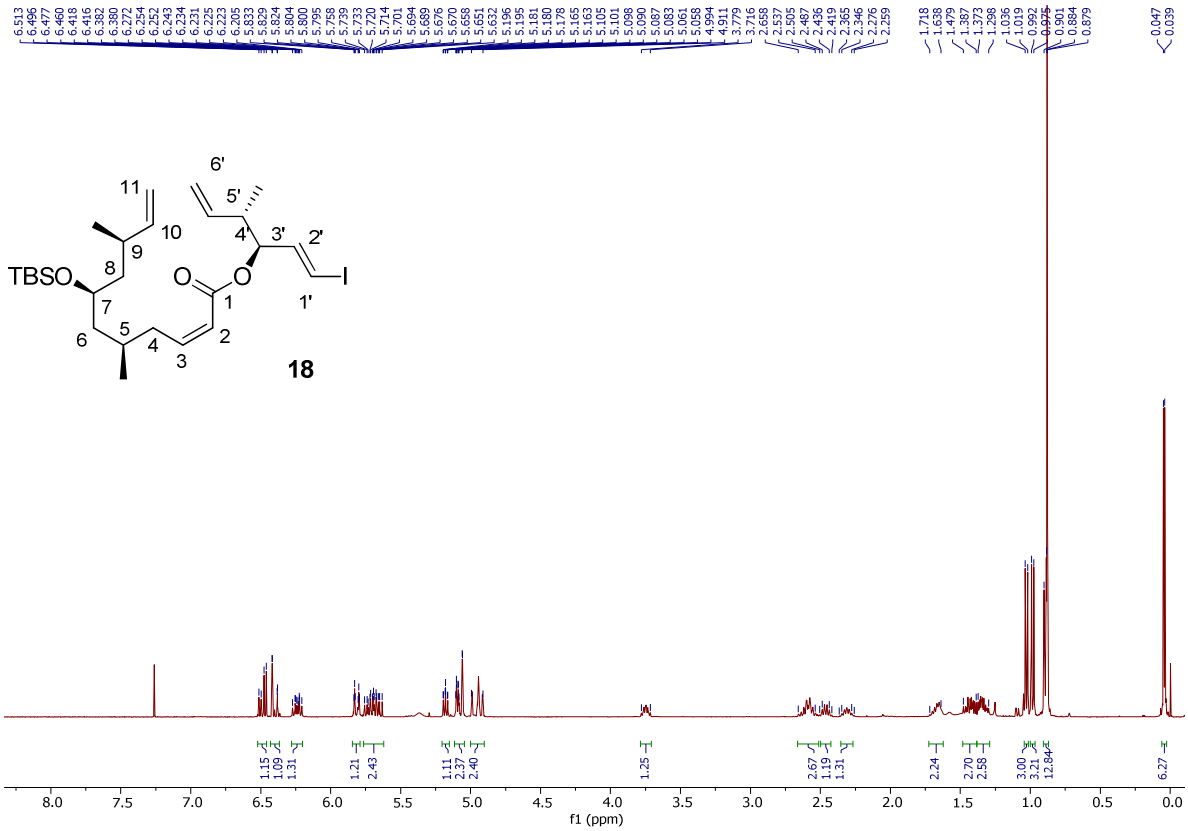
^{1}H NMR (400 MHz, $CDCl_3$)



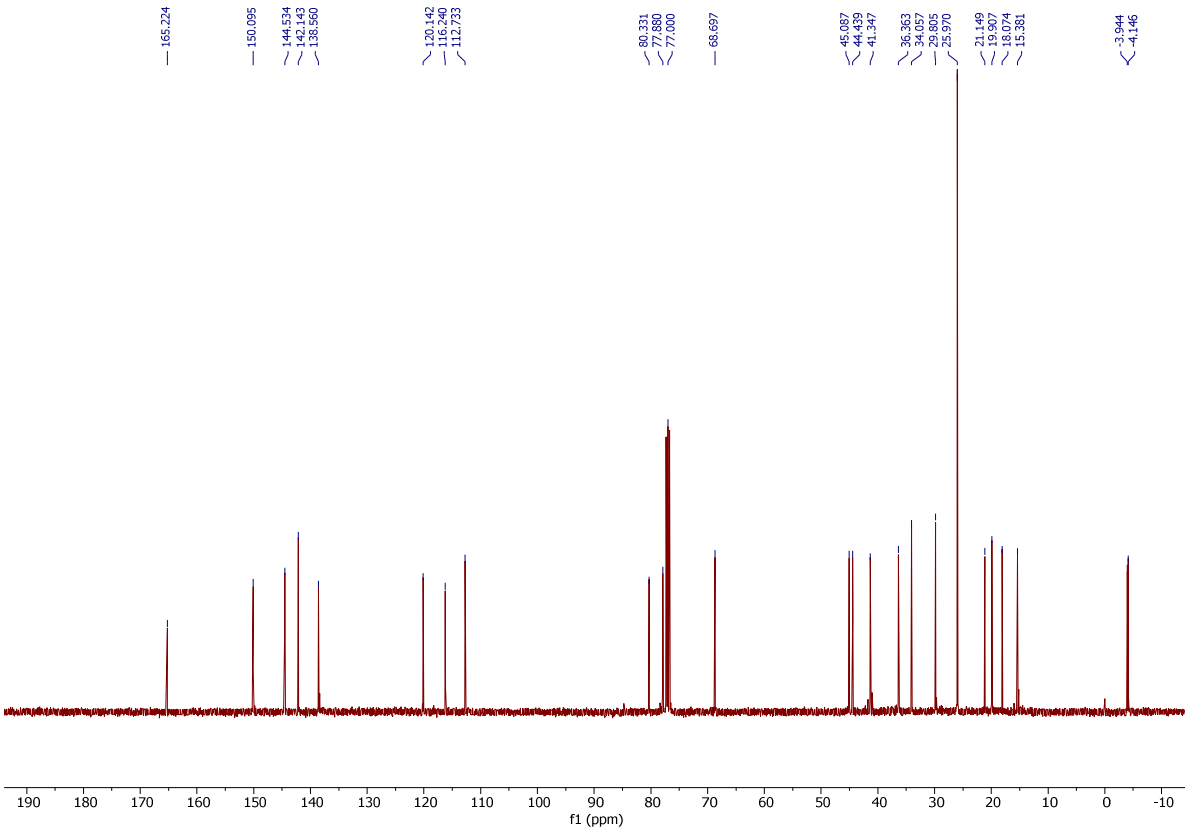
^{13}C NMR (100.6 MHz, $CDCl_3$)



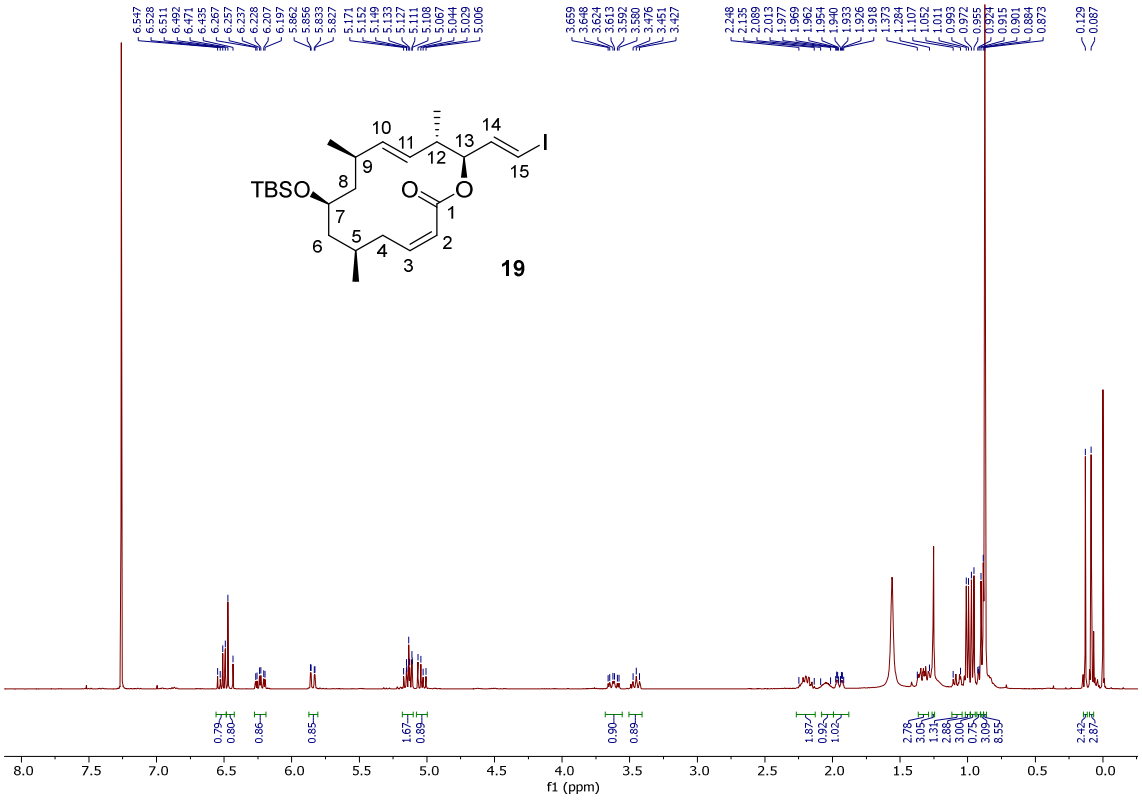
^{1}H NMR (400 MHz, $CDCl_3$)



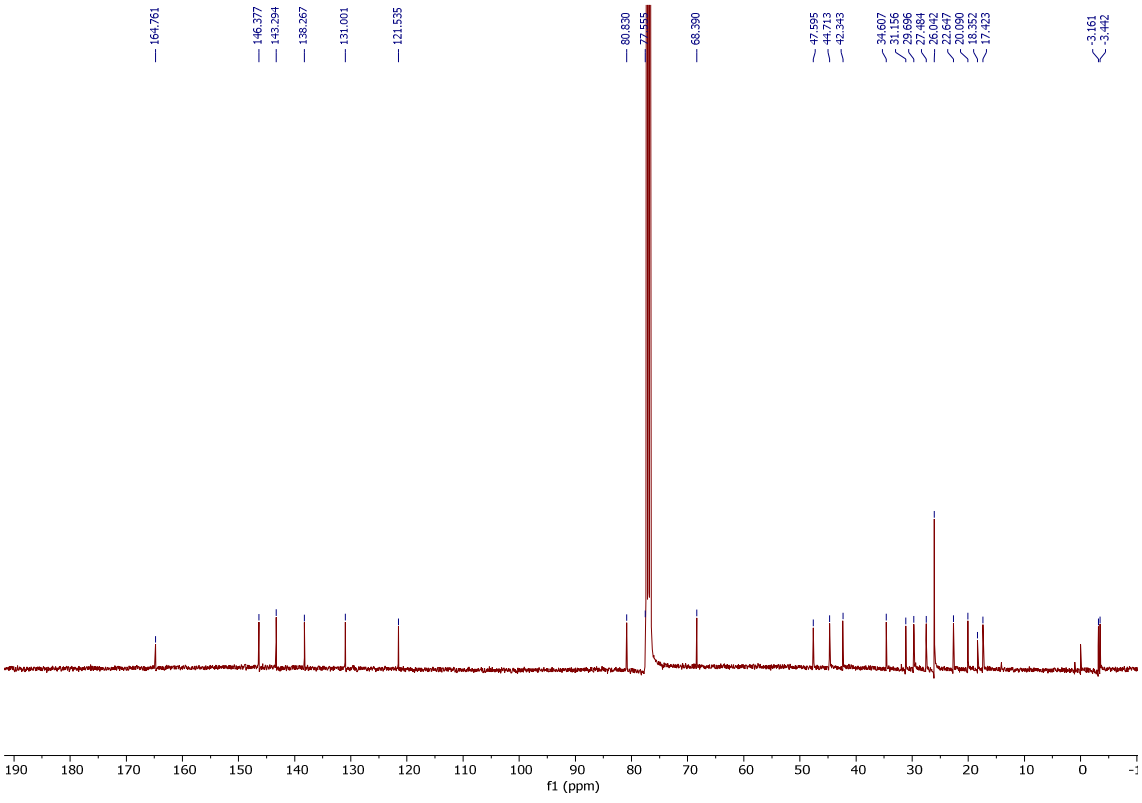
^{13}C NMR (100.6 MHz, $CDCl_3$)



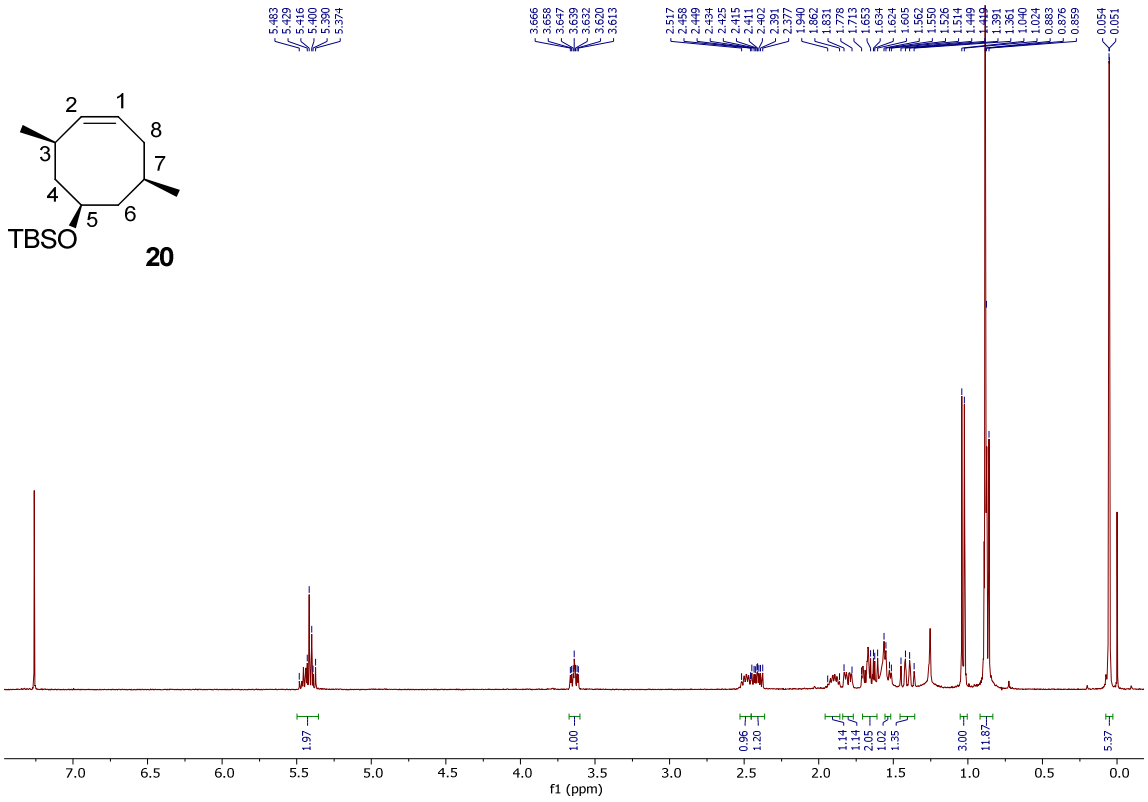
^{1}H NMR (400 MHz, $CDCl_3$)



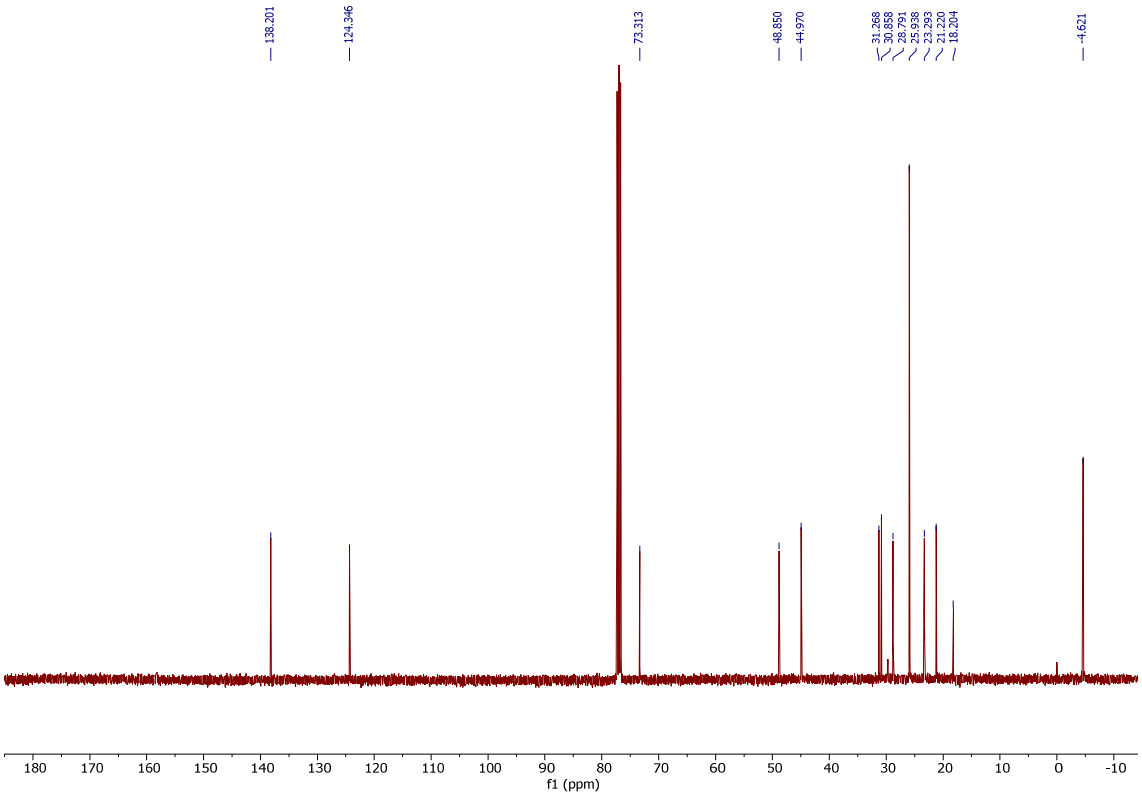
^{13}C NMR (100.6 MHz, $CDCl_3$)



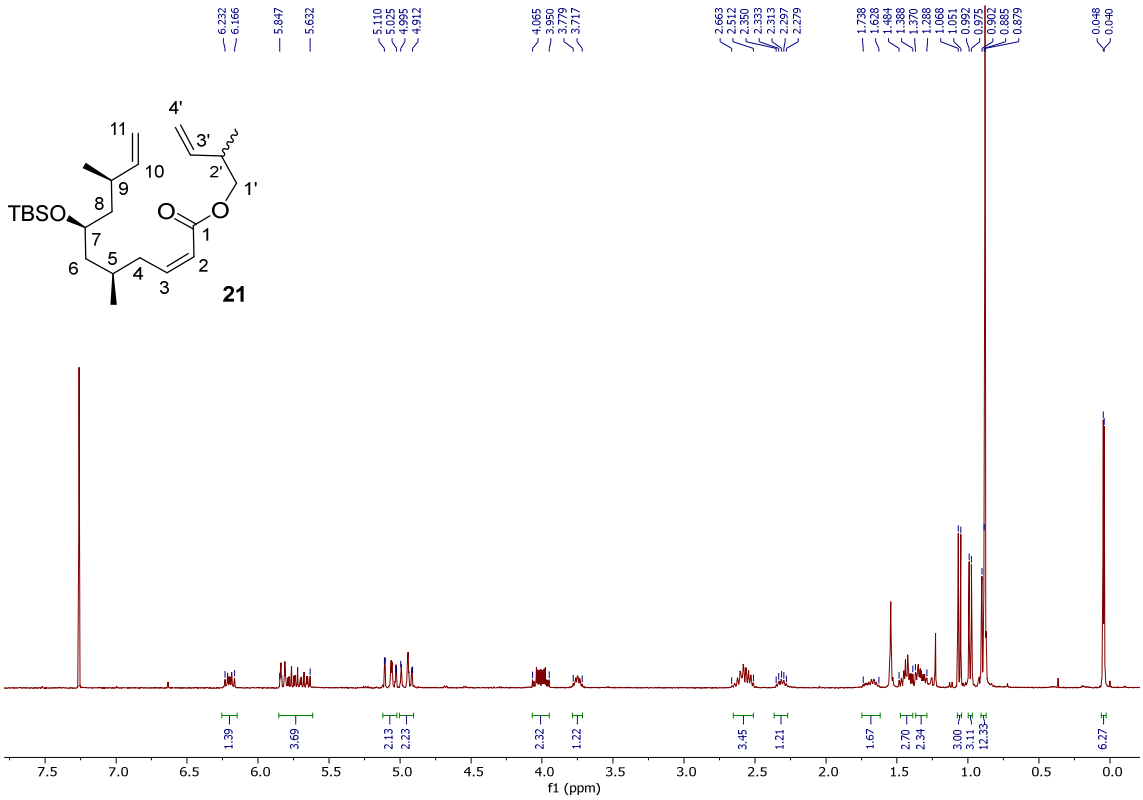
^{1}H NMR (400 MHz, $CDCl_3$)



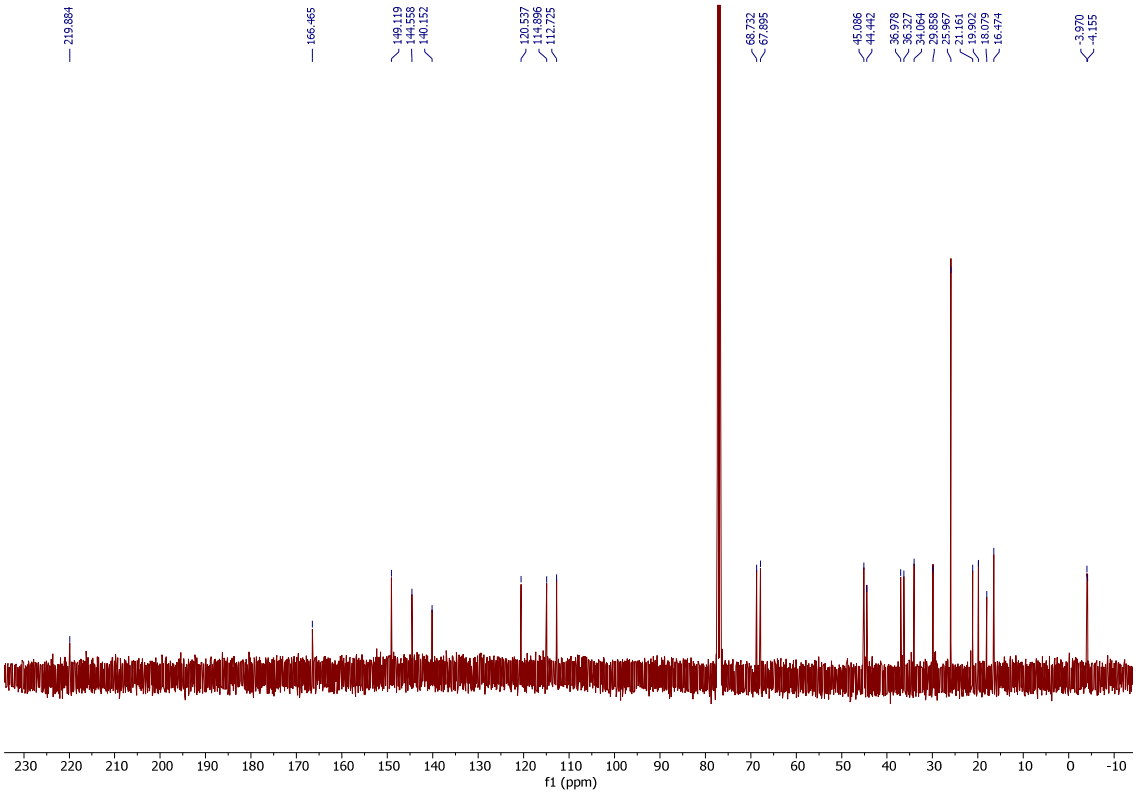
^{13}C NMR (100.6 MHz, $CDCl_3$)



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



^{13}C NMR (100.6 MHz, $CDCl_3$)



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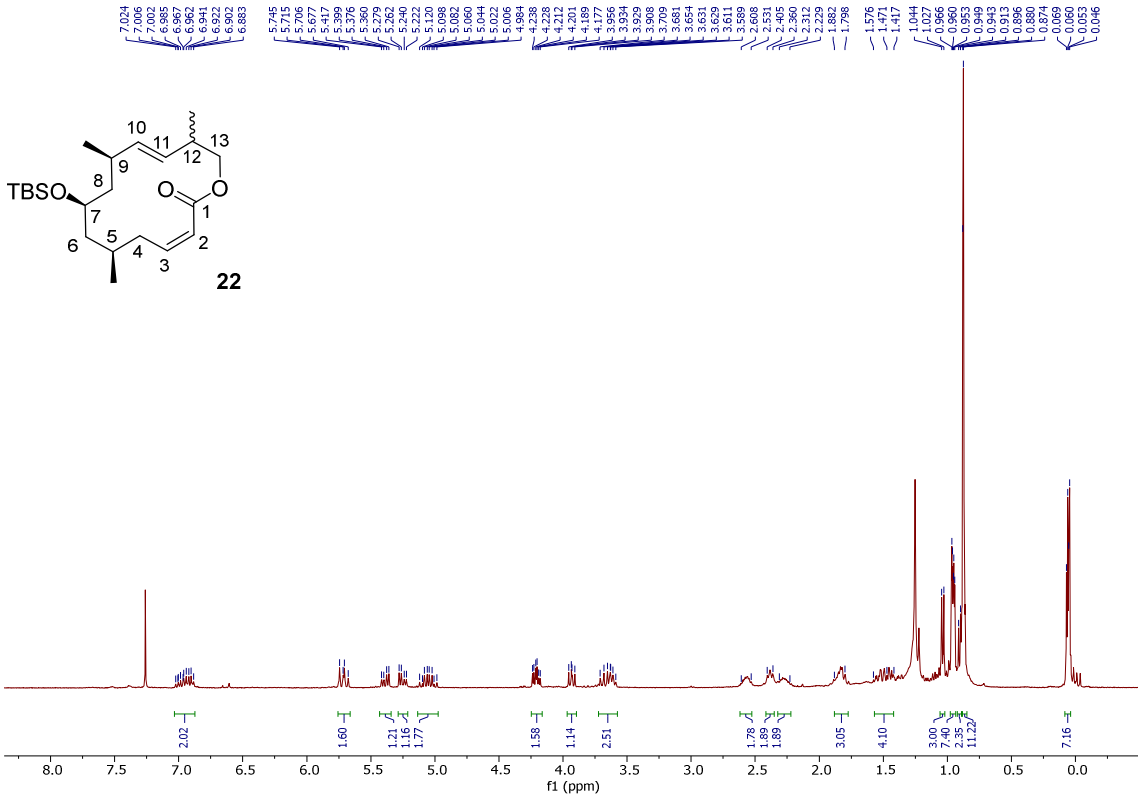

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^{13}C NMR (100.6 MHz, $CDCl_3$)