Total Synthesis and Biological Activity of the Arachidonic Acid Metabolite Hemiketal E_2

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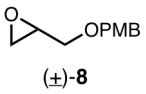
Supporting Information

1. General Procedure: All non-aqueous reactions were performed in flame-dried or oven dried round-bottomed flasks under an atmosphere of argon. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive liquids. Reaction temperatures were controlled using a thermocouple thermometer and analog hotplate stirrer. Reactions were conducted at room temperature (approximately 23 °C) unless otherwise noted. Flash column chromatography was conducted using silica gel 230-400 mesh. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F254 plates and visualized using UV, and potassium permanganate stain. Yields were reported as isolated, spectroscopically pure compounds.

2. Materials: Solvents were obtained from either an MBraun MB-SPS solvent system or freshly distilled (tetrahydrofuran was distilled from sodium-benzophenone; toluene was distilled from calcium hydride and used immediately; dimethyl sulfoxide and dimethylformamide were distilled from calcium hydride and stored over 4 Å molecular sieves). Commercial reagents were used as received. The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).

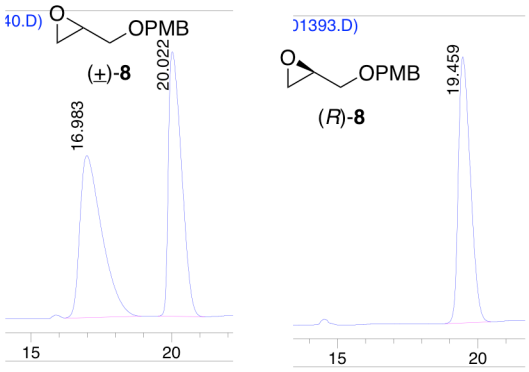
3. Instrumentation: Infrared spectra were obtained as thin films on NaCl plates using a Thermo Electron IR100 series instrument and are reported in terms of frequency of absorption (cm^{-1}). ^{1}H NMR spectra were recorded on Bruker 400, 500, or 600 MHz spectrometers and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad, app = apparent), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on Bruker 100, 125, or 150 MHz spectrometers and are reported relative to deuterated solvent signals. LC/MS was conducted and recorded on an Agilent Technologies 6130 Quadrupole instrument. High-resolution mass spectra were obtained from the Department of Chemistry and Biochemistry, University of Notre Dame using either a JEOL AX505HA or JEOL LMS-GCmate mass spectrometer.

4. Compound Preparation



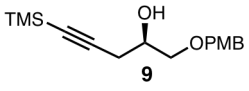
(±)-**8**

Glycidyl ether (±)-8: To a stirred suspension of NaH (60% dispersion in mineral oil, 4.75 g, 119 mmol) in DMF (250 mL) at 0 °C was added PMBCl (16.1 g, 119 mmol) dropwise. After 25 min, (±)-glycidol (neat) (8.00 g, 108 mmol) was added dropwise *via* syringe pump over 45 min, at which point the reaction was allowed to warm to room temperature. After 20 h, the mixture was poured into sat. aq. NH_4Cl (100 mL) and EtOAc (250 mL). The organic phase was washed with 10% aq. $NaHCO_3$ (100 mL) and water (150 mL) and the combined aqueous washes were extracted with EtOAc (100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford 17.1 g (82%) of ether **8** as a colorless oil. The spectral data matched reported values.[1]



Glycidyl ether (*R*)-8: To a solution of (±)-glycidyl ether **8** (6.35 g, 32.7 mmol) in acetic acid (37 μL, 0.654 mmol) was added (*S*,*S*)-(+)-*N*,*N*-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (98 mg, 0.163 mmol). The mixture was stirred at room temperature for 20 min before being cooled to 0 °C. THF (300 μL) and water (323 μL, 18.0 mmol) were added and the mixture was maintained at 0 °C for 1 h before being warmed to rt and stirred for 16 h. The mixture was distilled under reduced pressure to give 2.71 g (43%) of (*R*)-**8** as a clear colorless oil.

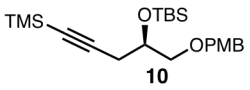
Enantiomeric excess was determined to be > 98% by Chiral HPLC analysis (Chiralpak® IA, 98:2 hexanes : iPrOH, 1 mL / min, λ = 254 nm, t_R(minor) = 15.807 min, t_R(major)= 18.523 min). The spectral data and optical rotation [Lit. for (*S*)-**8**, $[\alpha]_D^{24}$ = - 2.9° (*c* 3.0, $CHCl_3$); Obs. $[\alpha]_D^{24}$ = + 2.3° (*c* 2.5, $CHCl_3$)] matched reported values.[2]



9

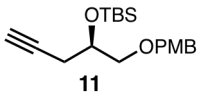
(*R*)-1-((4-methoxybenzyl)oxy)-5-(trimethylsilyl)pent-4-yn-2-ol (9): To a solution of trimethylsilylacetylene (1.46 g, 14.8 mmol) in THF (30 mL) cooled to -78 °C was added *n*-BuLi (6.40

mL, 14.8 mmol, 2.3 *M* in hexanes) dropwise. The solution was stirred at -78 °C for 15 min, at which point a solution of epoxide (*R*)-**2** (2.40 g, 12.4 mmol) in THF (12 mL) was added dropwise, followed by addition of BF_3•OEt_2 (1.83 mL, 14.8 mmol). The reaction mixture was allowed to stir at -78 °C for 2 h, and reaction was quenched with sat. aq. NH_4Cl (20 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford 3.00 g (83%) of **9** as a colorless oil. The spectral data matched reported values.[3]



10

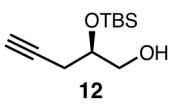
(*R*)-*tert*-butyl((1-((4-methoxybenzyl)oxy)-5-(trimethylsilyl)pent-4-yn-2-yl)oxy)dimethylsilane (10): To a solution of alcohol **9** (0.783 g, 2.68 mmol) in DMF (4.00 mL) at 0 °C was added TBSCl (0.806 g, 5.35 mmol), imidazole (0.547 g, 8.04 mmol), and DMAP (16.0 mg, 0.134 mmol). The reaction was allowed to stir at 0 °C for 2 h, quenched with water (8 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with water (2 x 30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to afford 1.03 g (95%) of **10** as a colorless oil: $[\alpha]_D^{20}$ = + 3.52° = (*c* 3.5, $CHCl_3$); IR (neat) 2856, 2178, 1613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.47 (s, 2 H), 3.92-3.98 (m, 1H), 3.80 (s, 3 H), 3.43 (app d, *J* = 5.4 Hz, 2H), 2.51 (dd, *J* = 5.5, 16.9 Hz, 1H), 2.35 (dd, *J* = 6.6, 16.9 Hz, 1H), 0.89 (s, 9H), 0.13 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.4, 129.1, 113.7, 104.3, 85.9, 73.5, 73.0, 70.5, 55.2, 26.2, 25.7, 18.1, -0.02, -4.63, -4.70.



11

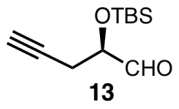
(*R*)-*tert*-butyl((1-((4-methoxybenzyl)oxy)pent-4-yn-2-yl)oxy)dimethylsilane (11): To a solution of alkynylsilane **10** (1.00 g, 2.46 mmol) in MeOH (25 mL) was added K_2CO_3 (0.340 g, 2.46 mmol). The reaction was allowed to stir at room temperature for 5 h. The MeOH was removed *in vacuo* and the resulting residue was dissolved in water (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to yield 0.795 g (97%) of **11** as a colorless oil: $[\alpha]_D^{20}$ = + 0.71° (*c* 2.45, $CHCl_3$); IR (neat) 3310, 3000, 2954, 2122, 1615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.48 (s, 2H), 3.93-3.99 (m, 1H), 3.81 (s, 3H), 3.48 (dd, *J* = 5.4, 9.7 Hz, 1H), 3.45

(dd, J = 5.4, 9.7 Hz, 1H), 2.47 (ddd, J = 2.7, 5.9, 16.7 Hz, 1H), 2.35 (ddd, J = 2.7, 6.0, 16.7 Hz, 1H), 1.95 (app t, J = 2.7 Hz, 1H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.4, 129.1, 113.6, 81.4, 73.2, 73.0, 70.2, 69.7, 55.2, 25.7, 24.6, 18.1, -4.61, -4.70; HRMS (ESI) calcd for $C_{19}H_{30}NaO_3Si$ [M+Na]$^+$: 357.1862; found: 357.1854.



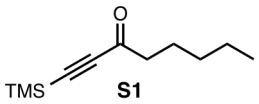
12

(*R*)-2-((*tert*-butyldimethylsilyl)oxy)pent-4-yn-1-ol (12): To a solution of ether **11** (1.65 g, 4.90 mmol) in CH_2Cl_2 (50 mL) was added DDQ (1.22 g, 5.39 mmol) and water (6 mL). The reaction was allowed to stir for 1.5 h at room temperature, during which time the color changed from dark green to red-orange. The reaction mixture was filtered through a plug of Celite and the resulting yellow mixture was washed with 10% aq. $NaHCO_3$ (50 mL) and water (2 x 100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The reaction product, alcohol **12**, was not purified but used directly in the next reaction.



13

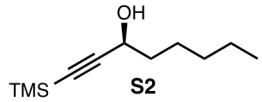
(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)pent-4-ynal (13): To a solution of crude alcohol **12** in CH_2Cl_2/DMSO (1:1, 20 mL) at 0 °C was added IBX (1.52 g, 5.42 mmol). The reaction stirred at 0 °C for 1 h, was subsequently allowed to warm to room temperature, and stirred at that temperature for 16 h. The mixture was diluted with CH_2Cl_2/H_2O (ca. 1:1, 100 mL) and the aqueous layer extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with water (2 x 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient of 1-2% Et_2O in hexanes) to afford 830 mg (78% over two steps) of aldehyde **13** as a light yellow oil: $[\alpha]_D^{20}$ = +17.9 (*c* 1.28, $CHCl_3$); IR (neat) 3313, 2955, 2930, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, J = 1.2 Hz, 1H), 4.11 (ddd, J = 1.2, 5.7, 6.9 Hz, 1H), 2.59 (ddd, J = 2.7, 5.7, 16.9 Hz, 1H), 2.48 (ddd, J = 2.7, 7.0, 16.9 Hz, 1H), 2.03 (s, 1H), 0.93 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 79.2, 75.7, 70.8, 25.6, 23.0, 18.1, -4.85, -4.89; HRMS (ESI) calcd for $C_{11}H_{20}NaO_2Si$ [M+Na]$^+$: 235.1131; found: 235.1112.



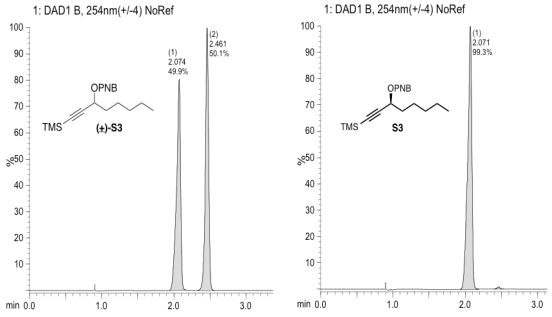
S1

1-(Trimethylsilyl)oct-1-yn-3-one (S1): To a suspension of $AlCl_3$ (10.3 g, 77.2 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added a solution of hexanoyl chloride (8.00 g, 59.4 mmol) and bistrimethylsilylacetylene (10.1 g, 59.4 mmol) in CH_2Cl_2 (100 mL) via cannula over a period of 10 min. The resulting yellow solution was allowed to warm to room temperature over 30 min, at which point the reaction was cooled to 0 °C

and quenched by slow addition of 1*N* HCl (100 mL). The resulting solution was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to afford 9.90 g (85%) of alkynone **S1** as a yellow oil. The spectral data matched reported values.[4]



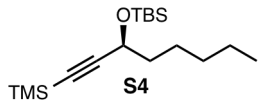
(*S*)-1-(trimethylsilyl)oct-1-yn-3-ol (**S2**): A mixture of alkynone **S1** (4.00 g, 20.4 mmol) and Ru[(1*S*, 2*S*)-p-TsNCH(C_6H_5)CH(C_6H_5)NH](η⁶-p-cymene) (0.855 g, 1.43 mmol) in 2-propanol (200 mL) was stirred at rt for 16 h. The mixture was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (silica gel, 10 % EtOAc in hexanes) to provide 3.53 g (88%) of **S2** as a light yellow oil. The spectral data and optical rotation [Lit. $[\alpha]_D^{24}$ = - 2.5° (*c* 10.15, $CHCl_3$); Obs. $[\alpha]_D^{24}$ = - 2.1° (*c* 8.5, $CHCl_3$)] matched reported values.[5]



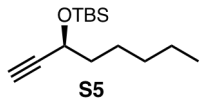
Enantiomeric excess analysis of 4-nitrobenzoate of S3: To a solution of alcohol **S2** (0.068 g, 0.343 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (0.144 mL, 1.03 mmol), p-nitrobenzoyl chloride (0.127 g, 0.686 mmol), and DMAP (2.0 mg, 0.017 mmol). The reaction was allowed to stir at rt for 1 h, at which point the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to provide 100 mg (85%) of **S3** as a dark yellow oil.

The *ee* of **S3** was determined to be 98% by Chiral SFC analysis (Lux Cellulose 2, 5% to 30% 2-propanol, 3.5 mL / min, λ = 254 nm, t_R(major) = 2.071 min, t_R(minor)= 2.462 min). $[\alpha]_D^{20}$ = -10.9° (*c* 2.50, $CHCl_3$); IR (neat) 2958, 2863, 2180, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.9 Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 2H), 5.63 (app t, *J* = 6.6 Hz, 1H), 1.86-1.93 (m, 2H), 1.47-1.54 (m, 2H), 1.31-1.36 (m, 4H), 0.89 (app t, *J* = 6.9 Hz, 3H), 0.17 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 150.7, 135.6, 131.0, 123.6, 102.1, 91.4, 66.2, 34.9, 31.3, 24.8, 22.5, 14.0, -0.140; HRMS (ESI) calcd for $C_{18}H_{25}NNaO_4Si$

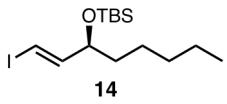
[M+Na]$^+$: 370.1451; found: 370.1478.



(*S*)-*tert*-butyldimethyl((1-(trimethylsilyl)oct-1-yn-3-yl)oxy)silane (S4): To a solution of alcohol **S2** (1.76 g, 8.87 mmol) in DMF (8 mL) at 0 °C was added TBSCl (2.67 g, 17.7 mmol), imidazole (1.81 g, 26.6 mmol), and DMAP (0.050 g, 0.444 mmol). The reaction was allowed to stir at 0 °C for 2 h, at which point the reaction was quenched with water (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to provide 2.60 g (95%) of **S4** as a colorless oil: $[\alpha]_D^{20}$ = -45.2° (*c* 3.20, $CHCl_3$); IR (neat) 2956, 2859, 1467, 1408 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (dd, *J* = 6.1, 7.0 Hz, 1H), 1.57-1.71 (m, 2H), 1.32-1.49 (m, 2H), 1.24 – 1.37 (m, 4H), 0.90 (s, 9H), 0.89 (app t, 3H), 0.15 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.9, 88.1, 63.3, 38.4, 31.3, 25.7, 24.8, 22.4, 18.2, 13.9, -0.255, -4.56, -5.03; HRMS (ESI) calcd for $C_{17}H_{36}NaOSi_2$ [M+Na]$^+$: 335.2202; found: 335.2164

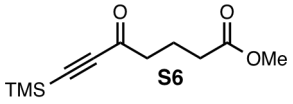


(*S*)-*tert*-butyldimethyl(oct-1-yn-3-yloxy)silane (S5): To a solution of silane **S4** (2.60 g, 8.32 mmol) in MeOH (50 mL) was added K_2CO_3 (1.15 g, 8.32 mmol). The reaction was allowed to stir room temperature for 1 h, at which point the MeOH was removed *in vacuo*. The resulting residue was taken up in water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to yield 1.88 g (95%) of alkyne **S5** as a colorless oil. The spectral data matched reported values.[6]

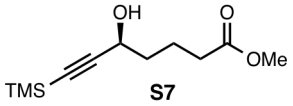


(*S*,*E*)-*tert*-butyl((1-iodooct-1-en-3-yl)oxy)dimethylsilane (14): To a solution of alkyne **S5** (0.680 g, 2.83 mmol) in THF (30 mL) was added half the required amount of zirconocene hydrochloride (0.456 g, 1.76 mmol). The mixture was allowed to stir at room temperature for 20 min, over which time the reaction changed from cloudy to clear. At this point, the remainder of zirconocene hydrochloride (0.456 g, 1.76 mmol) was added and the mixture was allowed to stir at room temperature for 20 min. Iodine (0.718 g, 2.83 mmol) was added and the mixture changed color from light yellow to dark brown. The reaction was allowed to stir for 5 min, at which point the mixture was diluted with hexanes (10 mL) and filtered through a pad of Celite. The resulting solution was washed with sat. aq.

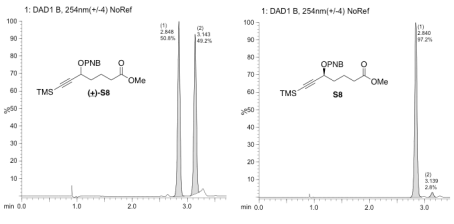
$Na_2S_2O_3$ (2 x 15 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, hexanes) to afford 0.948 g (91%) of vinyl iodide **14** as a colorless oil. The spectral data matched reported values.[7]



Methyl 5-oxo-7-(trimethylsilyl)hept-6-ynoate (S6): To a suspension of $AlCl_3$ (12.6 g, 94.8 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added a solution of methyl 4-(chloroformyl)butyrate (12.0 g, 72.9 mmol) and bistrimethylsilylacetylene (12.4 g, 72.9 mmol) in CH_2Cl_2 (90 mL) via cannula over a period of 10 min. The resulting yellow solution was allowed to warm to room temperature over 30 min, at which point the reaction was cooled to 0 °C and quenched by slow addition of 1*N* HCl (90 mL). The resulting solution was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford 9.90 g (60%) of **S6** as a light yellow oil. Spectral data matched reported values.[8]



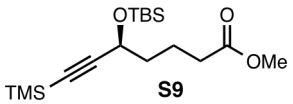
Methyl (*S*)-5-hydroxy-7-(trimethylsilyl)hept-6-ynoate (S7): A mixture of alkynone **S6** (3.00 g, 13.3 mmol) and Ru[(1*S*, 2*S*)-p-TsNCH(C_6H_5)CH(C_6H_5)NH] (η^6-p-cymene) (0.398 g, 0.665 mmol) in 2-propanol (130 mL) was stirred at room temperature for 1 h. The mixture was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to provide 2.87 g (95%) of alcohol **S7** as a yellow oil. The spectral data and optical rotation rotation [Lit. $[\alpha]_D^{24}$ = - 0.7° (*c* 1.1, $CHCl_3$); Found $[\alpha]_D^{24}$ = - 1.1° (*c* 5.5, $CHCl_3$)] matched reported values.[8]



Enantiomeric excess analysis of 4-nitrobenzoate of S8: To a solution of alcohol **S7** (0.050 g, 0.221 mmol) in CH_2Cl_2 (2.2 mL) was added triethylamine (0.300 mL, 2.21 mmol), p-nitrobenzoyl chloride (0.205mg, 1.10 mmol), and DMAP (ca. 1 mg, 0.008 mmol). The reaction was allowed to stir at room temperature for 1 h, at which point the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried ($MgSO_4$),

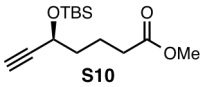
filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to provide 0.068 g (82%) of **S8** as a dark yellow oil.

The *ee* of **S8** was determined to be 95% by Chiral SFC analysis (Lux Cellulose 2, 5% to 30% 2-propanol, 3.5 mL / min, λ = 254 nm, t_R(major) = 2.840 min, t_R(minor)= 3.139 min). $[\alpha]_D^{20}$ = -11.3° (*c* 2.10, $CHCl_3$); IR (neat) 2957, 1734, 1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.9 Hz, 2H), 8.21 (d, J = 8.9 Hz, 2H), 5. 64 (app t, *J* = 6.2 Hz, 1H) 3.65 (s, 3H), 2.40 (app t, *J* = 7.2 Hz, 2H), 1.91-1.98 (m, 2H), 1.80-1.88 (m, 2H), 0.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 163.4, 150.6, 135.2, 130.9, 123.4, 101.2, 91.7, 65.4, 51.5, 34.0, 33.2, 20.3, -0.383; HRMS (ESI) calcd for $C_{18}H_{23}NNaO_6Si$ $[M+Na]^+$: 400.1192; found: 400.1206.



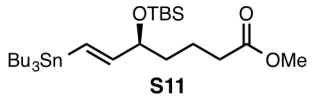
S9

Methyl (*S*)-5-((*tert*-butyldimethylsilyl)oxy)-7-(trimethylsilyl)hept-6-ynoate (S9): To a solution of alcohol **S7** (2.87 g, 12.6 mmol) in DMF (15 mL) at 0 °C was added TBSCl (3.79 g, 25.1 mmol), imidazole (2.57 g, 37.7 mmol), and DMAP (0.077, 0.630 mmol). The reaction was allowed to stir at 0 °C for 2 h, at which point the reaction was quenched with water (20 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to provide 4.10 g (94%) of silyl ether **S9** as a colorless oil: $[\alpha]_D^{20}$ = -42.2° (*c* 3.51, $CHCl_3$); IR (neat) 2953, 2859, 2172, 1743, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.35 (app t, *J* = 6.1 Hz, 1H), 3.67 (s, 3H), 2.35 (app t, *J* = 7.2 Hz, 2H), 1.65-1.87 (m, 4H), 0.90 (s, 9H), 0.16 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 107.2, 86.7, 62.9, 51.3, 37.6, 33.5, 25.7, 20.7, 18.1, -0.310, -4.58, -5.08.



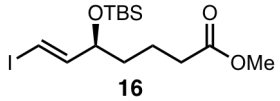
S10

Methyl (*S*)-5-((*tert*-butyldimethylsilyl)oxy)hept-6-ynoate (S10): To a solution of silane **S9** (0.770 g, 2.25 mmol) in MeOH (20 mL) was added K_2CO_3(0. 311 g, 2.25 mmol). The reaction was allowed to stir at room temperature for 1h, at which point the MeOH was removed *in vacuo*. The resulting residue was taken up in water (20 mL) and EtOAc (20 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to yield 547 mg (90%) of alkyne **S10** as a colorless oil. The spectral data matched reported values.[9]



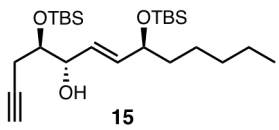
S11

Methyl (*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-(tributylstannyl)hept-6-enoate (S11): To a solution of alkyne **S10** (2.00 g, 7.39 mmol) in benzene (150 mL) was added Bu_3SnH (6.00 mL, 22.2 mmol) and AIBN (0.200 g, 1.48 mmol). The reaction was heated to 80 °C and stirred for 2 h. The mixture was then cooled to rt and the benzene was removed *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient of 0% to 2% Et_2O/hexanes) to provide 3.35 g (81 %) of **S11** as a clear, colorless oil: $[\alpha]_D^{20}$ = -12.2° (*c* 3.19, $CHCl_3$); IR (neat) 2956, 2928, 2856, 1744, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 0.8, 19.0 Hz, 1H), 5.89 (dd, *J* = 5.7, 19.0 Hz, 1H), 4.04 (ddd, *J* = 1.0, 5.7, 12.3 Hz, 1H), 3.65 (s, 3H), 2.31 (app t, *J* = 7.4 Hz, 2 H), 1.56-1.72 (m, 2H), 1.43-1.52 (m, 8H), 1.25-1.34 (m, 6H), 0.83-0.94 (m, 24H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 151.3, 126.9, 76.2, 51.3, 37.2, 34.0, 29.0, 27.1, 25.8, 20.8, 18.2, 13.6, 9.35, -4.38, -4.91. HRMS (ESI) calcd for $C_{26}H_{54}NaO_3SiSn$ $[M+Na]^+$: 585.2762; found: 585.2789.



16

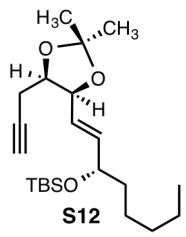
Methyl (*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-iodohept-6-enoate (16): To a solution of stannane **S11** (0.300 g, 0.534 mmol) in CH_2Cl_2 (2 mL) was added a solution of I_2 (0.200 g, 0.801 mmol) in CH_2Cl_2 (3 mL) dropwise until the resulting solution maintained a light pink color. The reaction was allowed to stir for 10 min, at which point sat. aq. $Na_2S_2O_3$ (5 mL), water (5 mL), and sat. aq. $NaHCO_3$ (5 mL) were added. The mixture stirred for an additional 5 min, at which time the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% Et_2O in hexanes) to provide 200 mg (90%) of **16** as a light yellow oil: $[\alpha]_D^{20}$ = -25.8° (*c* 1.70, $CHCl_3$); IR (neat) 2952, 2856, 1739, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 6.0, 14.4 Hz, 1H), 6.22 (dd, *J* = 1.1, 14.4 Hz, 1H), 4.10 (ddd, *J* = 1.3, 5.9, 11.8 Hz, 1H), 3.66 (s, 3H) 2.31 (app t, *J* = 7.3 Hz, 2H), 1.57-1.71 (m, 2H), 1.46-1.56 (m, 2H), 0.882 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 148.7, 75.9, 74.7, 51.4, 36.7, 33.8, 25.7 , 20.2, 18.1, -4.62, -5.00. HRMS (ESI) calcd for $C_{14}H_{27}INaO_3Si$ $[M+Na]^+$: 421.0672; found: 421.0677.



15

(5*R*,6*S*,9*S*,*E*)-2,2,3,3,11,11,12,12-octamethyl-9-pentyl-5-(prop-2-yn-1-yl)-4,10-dioxa-3,11-disilatridec-7-en-6-ol (15): To a solution of vinyl iodide **14** (2.69 g, 7.30 mmol) in THF (14 mL) at -78°C was added a solution of *t*-BuLi (8.6

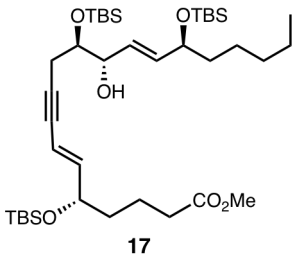
mL, 14.6 mmol, 1.7 *M* in pentane) dropwise. The mixture was allowed to stir at -78 °C for 1.5 h, at which point a solution of Me_2Zn (4.40 mL, 4.40 mmol, 1.0 *M* in heptane) was added dropwise. The reaction mixture was stirred at -78 °C for 15 min, at which point a solution of aldehyde **13** (620 mg, 2.92 mmol) in THF (12 mL) was added dropwise. The reaction stirred at -78 °C for 3 h and was quenched by addition of sat. aq. NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient of 1-4% EtOAc in hexanes) to provide 806 mg (61%) of alcohol **15** as a pale yellow oil: $[\alpha]_D^{20}$ = -8.49 (*c* 3.24, $CHCl_3$); IR (neat) ν_{max} = 3429, 2954, 2856, 1635, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (dd, *J* = 5.9, 15.5 Hz, 1H), 5.60 (dd, *J* = 6.5, 15.5 Hz, 1H), 4.24 (m, 1H), 4.12 (app q, *J* = 5.9 Hz, 1H), 3.89 (ddd, *J* = 3.2, 6.5, 6.5 Hz, 1H), 2.36 (ddd, *J* = 2.7, 6.8, 16.9 Hz, 1H), 2.28 (ddd, *J* = 2.7, 6.2, 16.9 Hz, 1H), 2.08 (d, *J* = 5.2 Hz, 1H), 1.96 (app t, *J* = 2.7 Hz, 1H), 1.42-1.52 (m, 2H) 1.23-1.36 (m, 6H), 0.91 (s, 9H), 0.90 (s, 9H), 0.88 (app t, *J* = 7.0 Hz, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 126.5, 81.5, 74.6, 74.3, 73.0, 70.3, 38.5, 32.0, 26.0, 25.9, 25.0, 22.8 (2 C), 18.4, 18.2, 14.2, -4.16, -4.25, -4.56, -4.60. HRMS (ESI) calcd for $C_{25}H_{50}NaO_3Si_2$ $[M+Na]^+$: 477.3196; found: 477.3221.



***tert*-butyl(((*S*,*E*)-1-((4*S*,5*R*)-2,2-dimethyl-5-(prop-2-yn-1-yl)-1,3-dioxolan-4-yl)oct-1-en-3-yl)oxy)dimethylsilane (S12)**: To a solution of **15** (0.100 g, 0.220 mmol) in THF (2 mL) at 0 °C was added a solution of TBAF (1.1 mL, 1.10 mmol, 1.0 *M* in THF). The reaction was allowed to stir at 0 °C for 2 h, at which point it was quenched with water (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and water (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The reaction product was not purified, but used directly in the next reaction.

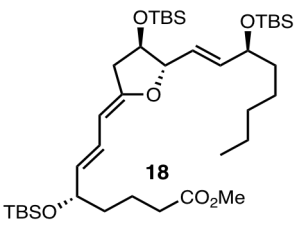
To a solution of crude diol (70.0 mg, 0.205 mmol) in acetone (1 mL) was added 2,2-dimethoxypropane (0.163 mL, 1.33 mmol) and *p*TSA (ca. 1 mg). The reaction was allowed to stir for 1 h, at which point the reaction was quenched with satd. aq. $NaHCO_3$ (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford 0.055 g (70%) of **S12** as a yellow oil: $[\alpha]_D^{20}$ = -13.3° (*c* 1.16, $CHCl_3$); IR (neat) ν_{max} = 3313, 2985, 2930, 2123, 1732, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (dd, J = 5.4, 15.4 Hz, 1H), 5.62

(dd, J = 7.4, 15.4 Hz, 1H), 4.62 (app t, J = 6.75 Hz, 1H), 4.30 (app q, J = 6.49 Hz, 1H), 4.15 (app q, J = 6.49 Hz, 1H), 2.41 (ddd, J = 2.7, 7.2, 16.6 Hz, 1H), 2.29 (ddd, J = 2.7, 6.4, 16.7 Hz, 1H), 1.99 (app t, J = 2.7 Hz, 1H), 1.50 (s, 3H), 1.41-1.48 (m, 2H), 1.38 (s, 3H), 1.26-1.32 (m, 6H), 0.90 (s, 9H), 0.88 (app t, J = 6.7, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 123.6, 108.7, 80.5, 78.5, 76.6, 72.3, 69.8, 38.0, 31.8, 28.0, 25.8, 25.5, 24.6, 22.5, 21.1, 18.1, 13.9, -4.48, -4.88. HRMS (ESI) calcd for $C_{22}H_{40}NaO_3Si$ $[M+Na]^+$: 403.2644; found: 403.2616.



17

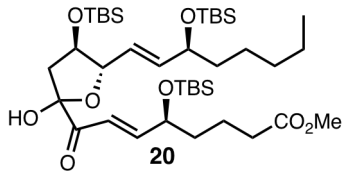
Methyl (5*S*,6*E*,11*R*,12*S*,13*E*,15*S*)-5,11,15-tris((*tert*-butyldimethylsilyl)oxy)-12-hydroxyicosa-6,13-dien-8-ynoate (17): To a solution of vinyl iodide **16** (0.188 g, 0.472 mmol) in Et_3N/dioxane (1:1, 0.500 mL) was added $PdCl_2(PPh_3)_2$ (6.00 mg, 0.00858 mmol) and CuI (3.30 mg, 0.0172 mmol). The reaction stirred for 5 min at which point a solution of alkyne **15** (0.195 g, 0.429 mmol) in Et_3N/dioxane (1:1, 0.500 mL) was added. The reaction stirred at room temperature for 12 h. The solvent was removed *in vacuo* and the resulting residue was taken up in Et_2O (5 mL) and water (5 mL). The aqueous layer was extracted with Et_2O (2 x 5 mL) and the combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient elution 0% to 5% Et_2O in hexanes) to afford 0.227 g (73%) of enyne **17** as a yellow oil: $[\alpha]_D^{20}$ = -25.0 (*c* 3.1, $CHCl_3$); IR (neat) 3505, 2953, 2856, 2360, 2220, 1741 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 6.13 (dd, *J* = 5.8, 15.8 Hz, 1H), 5.89 (dd, *J* = 5.7, 15.4 Hz, 1H), 5.82 (dd, *J* = 1.4, 15.8 Hz, 1H), 5.80 (dd, *J* = 6.0, 15.6 Hz, 1H), 4.30-4.34 (m, 1H), 4.14 (app q, *J* = 5.8 Hz, 1H), 3.96-4.01 (m, 2H), 3.33 (s, 3H), 2.68 (ddd, *J* = 2.0, 7.3, 16.9 Hz, 1H), 2.58 (ddd, *J* = 1.9, 5.6, 16.9 Hz, 1H), 2.07 (app t, *J* = 7.3 Hz, 2H), 1.80 (d, *J* = 4.3 Hz, 1H), 1.56-1.70 (m, 4H), 1.36-1.49 (m, 2H), 1.22-1.35 (m, 6H), 1.04 (s, 9H), 0.99 (s, 9H), 0.96 (s, 9H), 0.91 (app t, *J* = 6.84 Hz, 3H), 0.16 (s, 3H), 0.14 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ173.1, 145.4, 136.9, 110.1, 88.5, 80.9, 75.3, 74.8, 73.4, 72.7, 60.0, 51.0, 38.8, 37.5, 33.9, 32.3, 26.2, 26.1, 26.0, 25.4, 24.4, 23.1, 20.9, 18.5 (2C), 18.4, 14.3, -3.93, -4.27, -4.30, -4.45, -4.52, -4.73. HRMS (ESI) calcd for $C_{39}H_{76}NaO_6Si_3$ $[M+Na]^+$: 747.4847; found: 747.4828.



18

Methyl (*S*,6*E*,8*Z*)-5-((*tert*-butyldimethylsilyl)oxy)-8-((4*R*,5*S*)-4-((*tert*-butyldimethylsilyl)oxy)-5-((*S*,*E*)-3-((*tert*-butyldimethylsilyl)oxy)oct-1-en-1-

yl)dihydrofuran-2(3*H*)-ylidene)oct-6-enoate (18): To a solution of AuCl (ca. 1 mg) and powdered 4Å molecular sieves (150 mg) in THF (2.00 mL) was added a solution of enyne **17** (20.0 mg, 0.0276 mmol) in THF (0.500 mL). The reaction stirred at rt for 30 min, over which time the solution changed color from light yellow to deep purple. The reaction was filtered and the sieves were washed with Et_2O (3 x 5 mL). The resulting filtrate was washed with sat. aq. $NaHCO_3$ (10 mL) and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (pH = 7 buffered SiO_2, 50:1 hexanes: EtOAc) to provide 15.0 mg (75%) of furan **18** as a colorless oil: $[\alpha]_D^{20}$ = +3.44 (*c* 1.8, C_6D_6); IR (neat) 2953, 2928, 1741, 1675 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.01 (dd, *J* = 10.9, 15.4 Hz, 1H), 5.98 (ddd, *J* = 1.0, 5.3, 15.4 Hz, 1H), 5.80 (ddd, *J* = 1.2, 6.4, 15.4 Hz, 1H), 5.66 (dd, *J* = 7.0, 15.5 Hz, 1H), 5.15 (d, *J* = 10.8 Hz, 1H), 4.68 (app t, *J* = 5.3 Hz, 1H), 4.26 (app q, *J* = 6.3 Hz, 1H), 4.20 (app q, *J* = 5.5 Hz, 1H), 4.10 (app q, *J* = 5.5, 1H), 3.44 (s, 3H), 2.70 (dd, *J* = 6.2, 16.1 Hz, 1H), 2.53 (dd, *J* = 5.4, 16.1 Hz, 1H), 2.24 (app t, *J* = 7.4 Hz, 2H), 1.69-1.77 (m, 2H), 1.46-1.65 (m, 6H), 1.26-1.42 (m, 7H), 1.15 (s, 9H), 1.13 (s, 9H), 1.01 (s, 9H), 0.27 (s, 3H), 0.22 (s, 3H), 0.22 (s, 3H), 0.21 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 173, 155, 137, 130, 126, 124, 98.8, 88.1, 75.2, 73.8, 72.4, 50.6, 38.5, 38.3, 38.2, 33.8, 31.9, 26.0, 25.9, 25.6, 24.9, 22.7, 21.1, 18.2, 18.1, 17.9, 14.0, -4.04, -4.31, -4.83, -4.86, -4.89, -4.94.

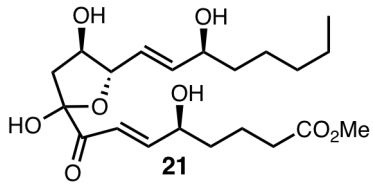


20

Methyl (5*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-8-((4*R*,5*S*)-4-((*tert*-butyldimethylsilyl)oxy)-5-((*S*,*E*)-3-((*tert*-butyldimethylsilyl)oxy)oct-1-en-1-yl)-2-hydroxytetrahydrofuran-2-yl)-8-oxooct-6-enoate (20): A solution of vinyl ether **18** (21.0 mg, 0.0290 mmol) in CH_2Cl_2 (1.00 mL) was cooled to 0 °C. A solution of dimethyldioxirane (0.500 mL, 0.058 *M* solution in acetone, 0.0290 mmol,) was added dropwise. The reaction stirred for 2 min and was concentrated *in vacuo*. The diol product (**19**) was not purified but used directly in the next reaction.

The crude diol (**19**) was taken up in CH_2Cl_2 (1.00 mL) and DMSO (1.00 mL) and cooled to 0 °C. IBX (16.0 mg, 0.0579 mmol) was added and the reaction was allowed to warm to rt and stirred for 6 h. The reaction was diluted with CH_2Cl_2 and water (1:1, 2 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with H_2O (3 x 5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, gradient

elution 2% to 5% EtOAc in hexanes) to yield 15.2 mg (70%) of a mixture of hemiketals **20** as a light yellow oil: $[\alpha]_D^{20}$ = -12.8 (*c* 2.3, $CHCl_3$); IR (neat) 3482, 2955, 2858, 2360, 1741, 1704, 1635 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.12, 7.08 (dd, dd; *J* = 4.7, 15.5 Hz, *J* = 4.8, 15.6 Hz; isomers, 1H), 6.85, 6.71 (dd, dd; *J* = 1.5, 15.5 Hz, *J* = 1.5, 15.6 Hz; isomers, 1H), 5.76, 5.67-5.71(dd, m; *J* = 5.5, 15.4 Hz; isomers, 1H), 5.48, 5.67-5.71 (ddd, m; *J* = 1.3, 6.5, 15.4 Hz; isomers 1H), 4.63, 4.32-4.42 (dd, m; *J* = 2.6, 6.4 Hz; isomers, 1H), 4.32-4.42, 4.11-4.17 (m, 2H), 4.11, 4.08 (m, app q; *J* = 5.7 Hz; isomers, 1H), 3.66, 3.65 (s; isomers, 3H), 2.50, 2.32 (dd, m; *J* = 5.9, 13.8 Hz; isomers, 1H), 2.32 (app t, J = 6.8 Hz, 2H), 2.29, 1.97 (dd, dd; *J* = 6.9, 14.4 Hz, *J* = 7.1, 13.2 Hz; isomers, 1H), 1.64-1.29 (m, 12H), 0.92 (s, 9H), 0.90, 0.89 (s, isomers, 9H), 0.88 (s, 9H), 0.10, 0.09 (s, isomers, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 0.03 (s, isomers, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 195.5, 193.3 (isomers); 173.7, 173.6 (isomers); 152.7, 151.9 (isomers); 137.6, 136.7 (isomers); 127.4, 125.8 (isomers); 121.9, 120.9 (isomers); 105.0, 103.0 (isomers); 88.5, 87.3 (isomers), 76.4; 72.4, 72.3 (isomers); 71.6; 51.5, 51.4 (isomers); 44.9 41.8 (isomers); 38.1, 38.0 (isomers); 36.5, 36.4 (isomers); 33.8; 31.8, 31.7 (isomers); 26.1, 26.0 (isomers); 25.9 25.9 (isomers); 25.8; 22.7; 20.7, 20.6 (isomers); 18.4; 18.3; 18.1, 18.0 (isomers); 14.2; -4.12, -4.18 (isomers); -4.34, -4.49 (isomers); -4.51, -4.55 (isomers); -4.61, -4.64 (isomers); -4.66, -4.70 (isomers); -4.72, -4.81 (isomers).



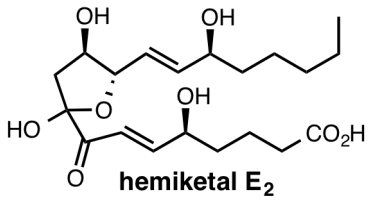
21

Methyl ester of HKE$_2$ (21): To a solution of hemiketal **14** (8.0 mg, 0.010 mmol) in CH_3CN (0.4 mL) at 0 °C was added HF•NEt_3 complex (0.086 mL, 0.528 mmol, 50 eq) dropwise slowly. The reaction mixture was warmed to room temperature and stirred for 5 h. The reaction was quenched with sat. aq. $NaHCO_3$ (2 mL) and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash column chromatography (silica gel, gradient elution 0% to 6% MeOH in CH_2Cl_2) to provide 3.0 mg (68%) of an inseparable mixture of diastereomers of methyl ester **21** as a light yellow oil. When the NMR is recorded in $CDCl_3$, a 3:1 mixture of isomers is observed. When recorded in CD_3OD, a 1:1 mixture of isomers is observed.

Major Isomer: ^1H NMR (600 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 3.7, 15.5 Hz, 1H), 6.81 (dd, *J* = 1.5, 15.5 Hz, 1H), 5.86 (dd, *J* = 5.3, 16.0 Hz, 1H), 5.70 (dd, *J* = 5.5, 16.0 Hz, 1H), 4.82 (d, *J* = 3.9 Hz, 1H), 4.43-4.46 (m, 1H), 4.37-4.39 (m, 1H), 4.28-4.30 (m, 1H), 4.12-4.16 (m, 1H), 3.67 (s, 3H), 2.49 (dd, *J* = 5.5, 13.7 Hz, 1H), 2.37 (app t, *J* = 6.9 Hz, 2H),

2.07 (d, J = 13.6 Hz, 1H), 1.24-1.82 (m, 12H), 0.86-0.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 174.4, 152.3, 136.2, 127.2, 120.9, 104.6, 88.6, 76.4, 71.8, 70.9, 51.9, 42.0, 36.9, 35.6, 33.6, 31.9, 25.2, 22.7, 20.6, 14.2.

Minor Isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (dd, J = 3.6, 15.5 Hz, 1H), 6.96 (d, J = 15.6 Hz, 1H), 5-76-5.88 (m, 2H), 4.82 (d, J = 3.9 Hz, 1H), 4.43-4.46 (m, 1H), 4.37-4.39 (m, 1H), 4.28-4.30 (m, 1H), 4.12-4.16 (m, 1H), 3.67 (s, 3H), 2.37 (app t, J = 6.9 Hz, 2 H), 2.17-2.22 (m, 1H), 2.07 (d, J = 13.6 Hz, 1H), 1.64-1.82 (m, 4H), 1.48-1.55 (m, 2H), 1.24-1.32 (m, 6H), 0.86-0.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 174.3, 152.4, 137.2, 129.0, 121.0, 103.8, 88.4, 76.0, 72.2, 70.9, 51.9, 43.5, 37.2, 35.7, 33.7, 29.9, 25.2, 22.7, 20.7, 14.3.



hemiketal E_2

Hemiketal E_2: To a solution of methyl ester 15 (3.0 mg, 0.007 mmol) in MeOH (2 mL) was added 15 % KOH (3.7 mL, 0.014 mmol). The reaction stirred at rt for 0.5 min. The reaction was acidified to pH = 4 with 5 N HCl, and the mixture was passed through a Waters HLB (hydrophilic/lipophilic balance) C18 cartridge. The combined organic layers were concentrated. The resulting residue was purified by reverse phase HPLC (Waters Symmetry C18, 5 μM, 250 x 4.6 mm, H_2O/MeCN/AcOH 60/40/0.01, R_t = 3.7 min) to afford **HKE$_2$** (1.0 mg). ^{1}H NMR (600 MHz, CD_3CN) δ: 7.00, 6.98 (dd, dd; J = 3.9, 4.5 Hz, J = 4.0, 4.4 Hz; isomers, 1H), 6.82, 6.69 (dd, J = 1.7, 15.6 Hz, J = 1.7, 15.6 Hz; isomers, 1H), 5.79, 5.76 (d, d; J = 5.7, J = 5.7 Hz; isomers, 1H), 5.72 (dd, J = 4.4, 6.4 Hz, 1H), 5.69 (dd, J = 5.8, 6.5 Hz, 2H), 5.66 (d, J = 6.6 Hz, 1H), 5.58, 5.56 (dd, dd; J = 0.5, 6.4 Hz; J = 0.5, 6.4 Hz, isomers, 1H), 4.5 (dd, J = 4.3, 6.2 Hz, 2H), 4.30-4.27, 4.35-4.20 (m, m; isomers, 2H), 4.13, 4.11-4.06 (ddd, m; J = 2.6, 6.5, 9.2 Hz, isomers, 2H), 4.05-3.94 (m, 2H), 2.48, 2.45 (d, d; J = 2.8, J = 2.7, Hz, isomers, 1H), 2.30 (t, t; J = 7.5, J = 7.5 Hz, isomers, 2H), 1.88, 1.85 (d, d; J = 4.0, J = 4.0 Hz, isomers, 1H), 1.69-1.52, 148-1.40 (m, m; isomers, 4H), 1.35-1.28 (m, 4H), 0.9-0.87 (m, 4H); ^{13}C NMR (150 MHz, CD_3CN) δ 196.1, 194.8 (isomers), 175.0, 174.9 (isomers); 152.6, 152.6 (isomers); 137.9, 137.5 (isomers); 129.3, 129.2 (isomers); 128.0, 128.0 (isomers); 122.5, 122.3 (isomers); 105.7, 105.1 (isomers); 88.6, 87.8 (isomers); 76.6, 76.2, 76.1 (isomers); 72.6, 72.5 (isomers); 72.2, 72.0 (isomers); 71.1, 71.1 (isomers); 43.8, 42.5 (isomers); 38.2, 38.1 (isomers); 37.0, 36.4 (isomers); 34.0, 33.9 (isomers); 32.7, 32.6 (isomers); 26.0, 25.9 (isomers); 23.4, 23.4 (isomers); 21.5, 21.5 (isomers); 14.4. HRMS (ESI) calcd for $C_{20}H_{32}O_8$ $[M-H]^-$: 399.2019; found: 357.2031.

5. Platelet aggregation assay: Hemiketal E_2 (HKE_2) inhibits platelet aggregation comparable to PGE_2 Hemiketal E_2 inhibits human platelet aggregation in a dose dependent member comparable to the well-known platelet aggregation inhibitor prostaglandin E_2 (Figure 1). In this experiment platelets were either preincubated (5 min) with increasing concentrations of HKE_2 (0.1 to 5 uM; red traces in Figure 1) or vehicle (ethanol; blue traces), and aggregation was induced by the thromboxane receptor agonist, U46,619. PGE_2 (0.1 uM) reduced platelet aggregation by 6% whereas HKE_2 resulted in a reduction by 87% (5 uM), 86% (0.5 uM), and 5% (0.1 uM).

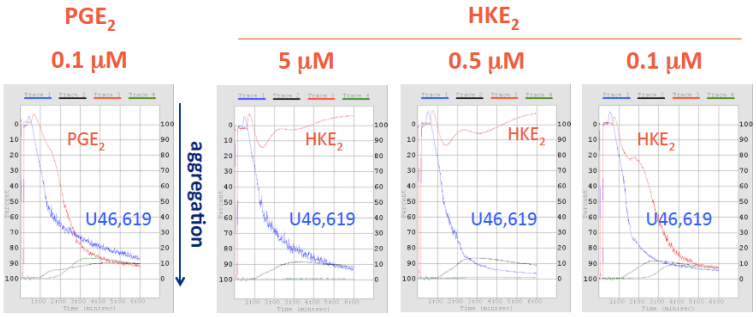


Figure 1. Hemiketal E_2 inhibits platelet aggregation.

6. References and footnotes

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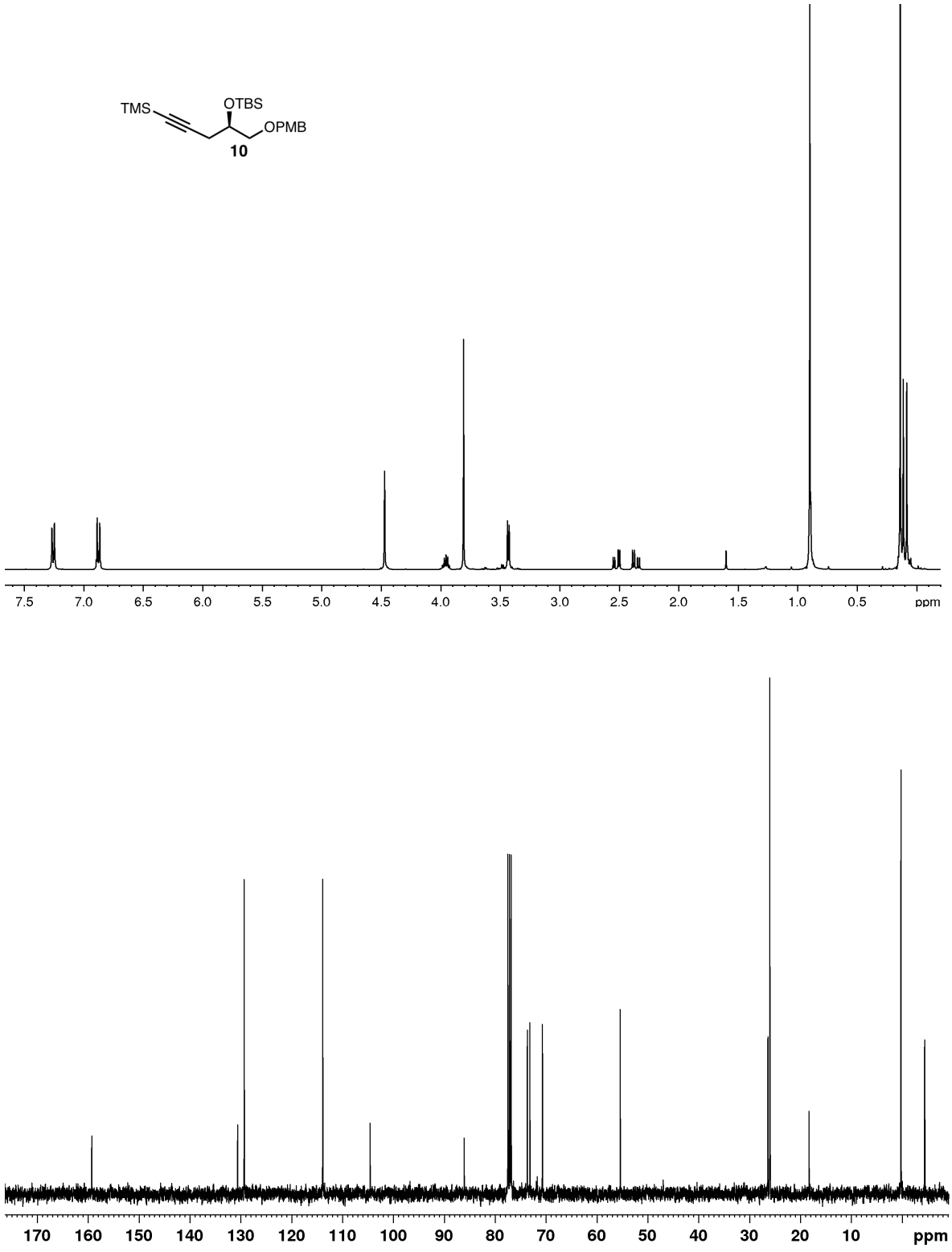
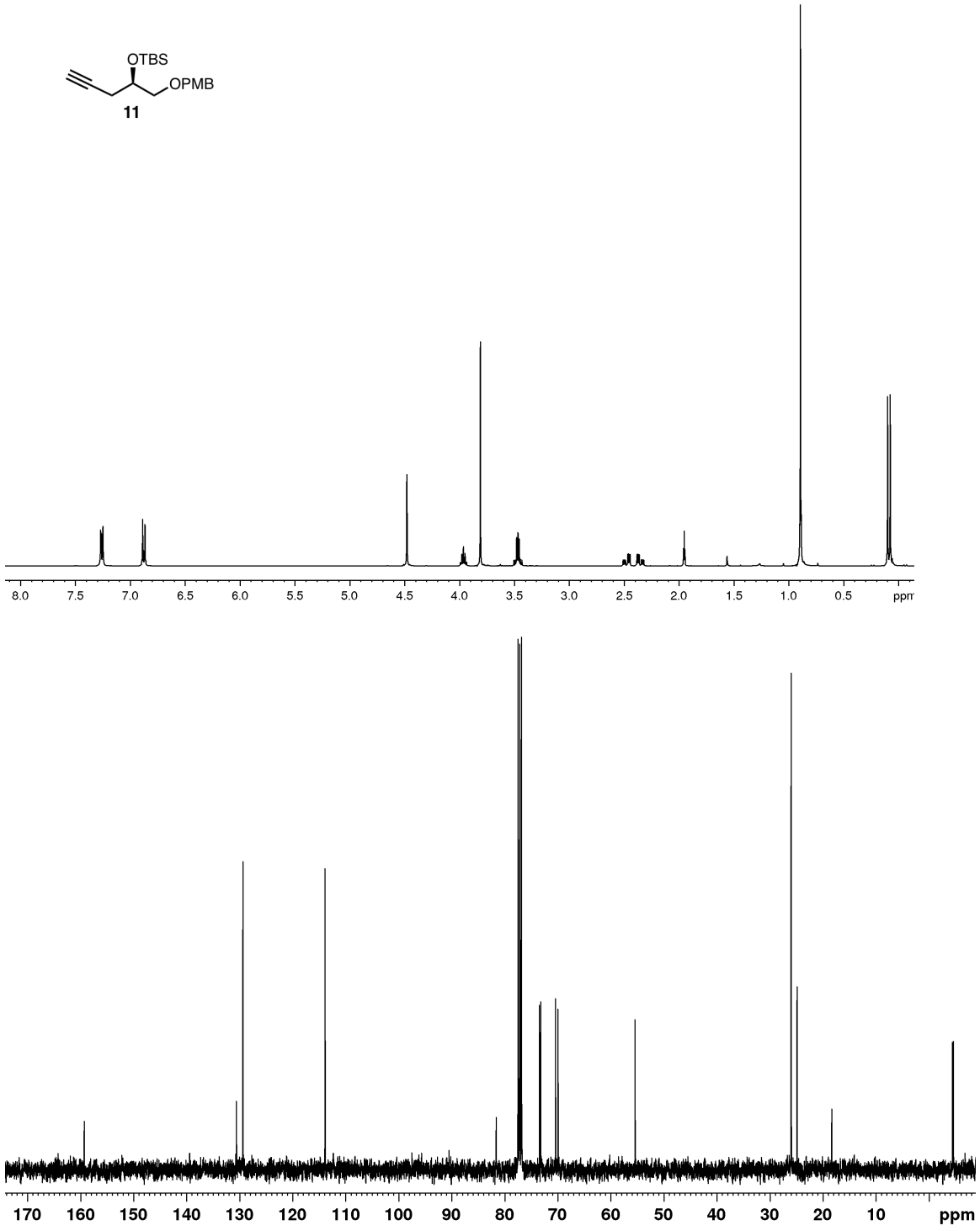
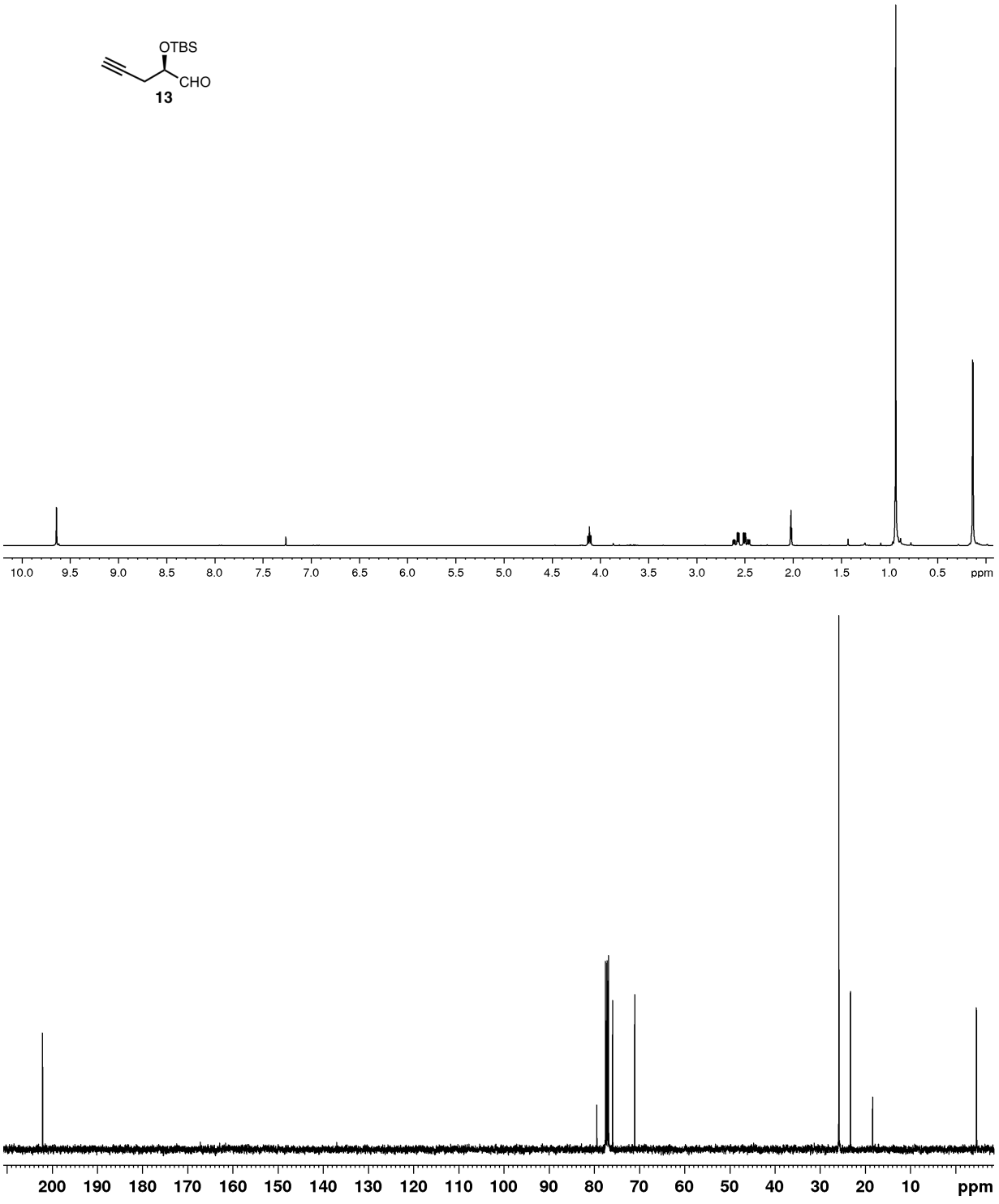
7. Copy of ^{1}H, ^{13}C NMR and 2D Spectra



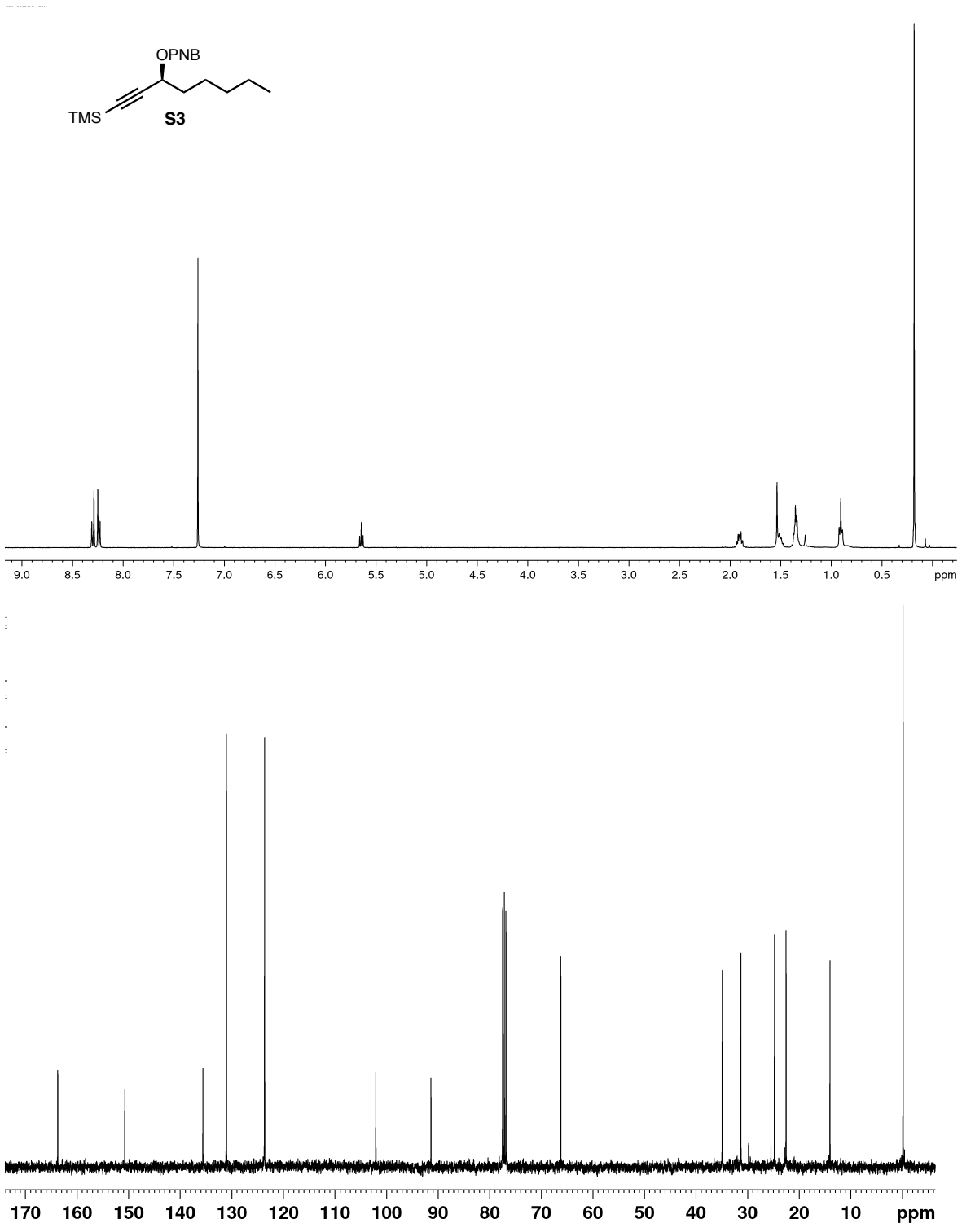
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz $CDCl_3$) spectra of silyl ether **10**



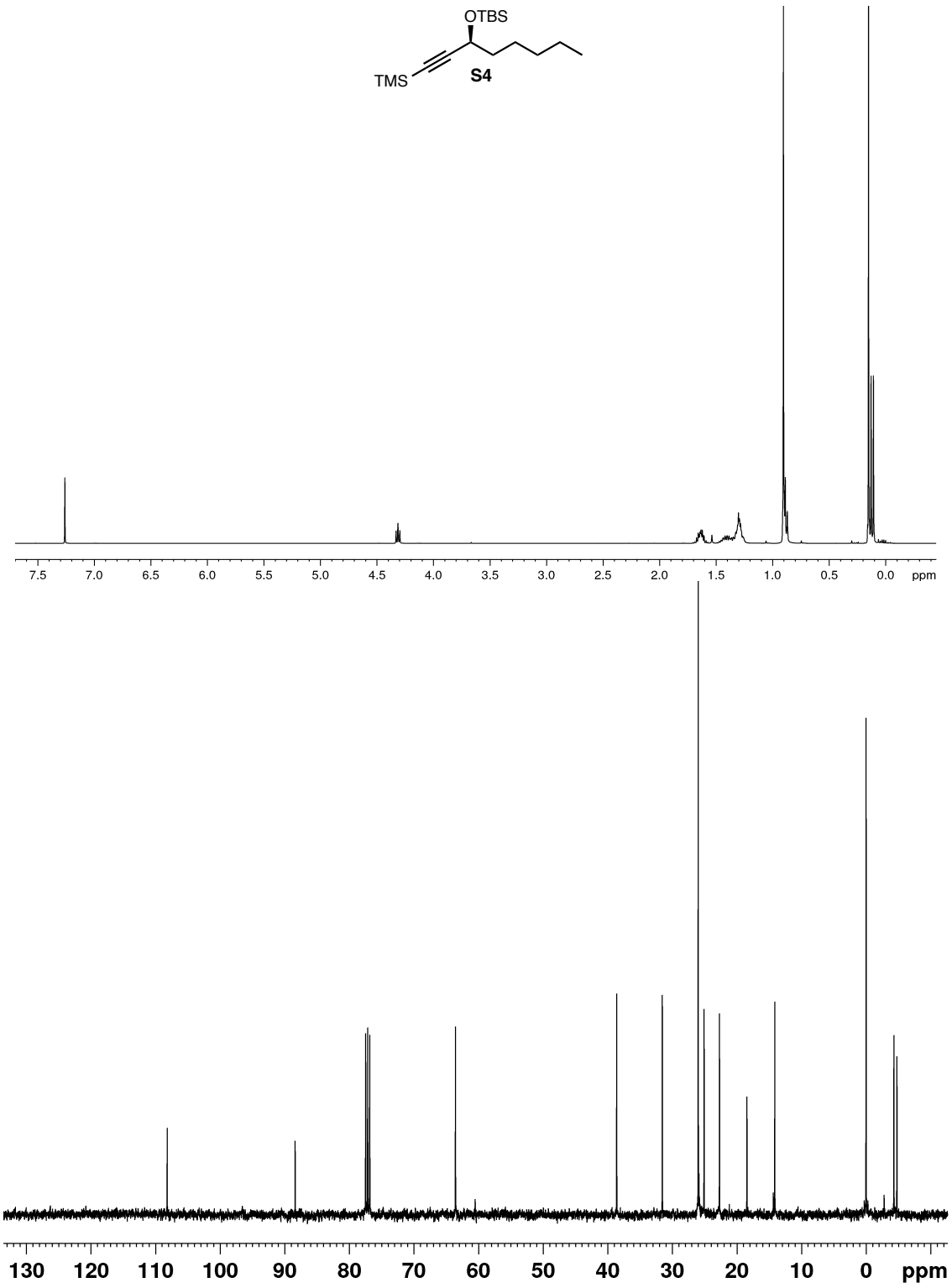
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz $CDCl_3$) spectra of alkyne **11**



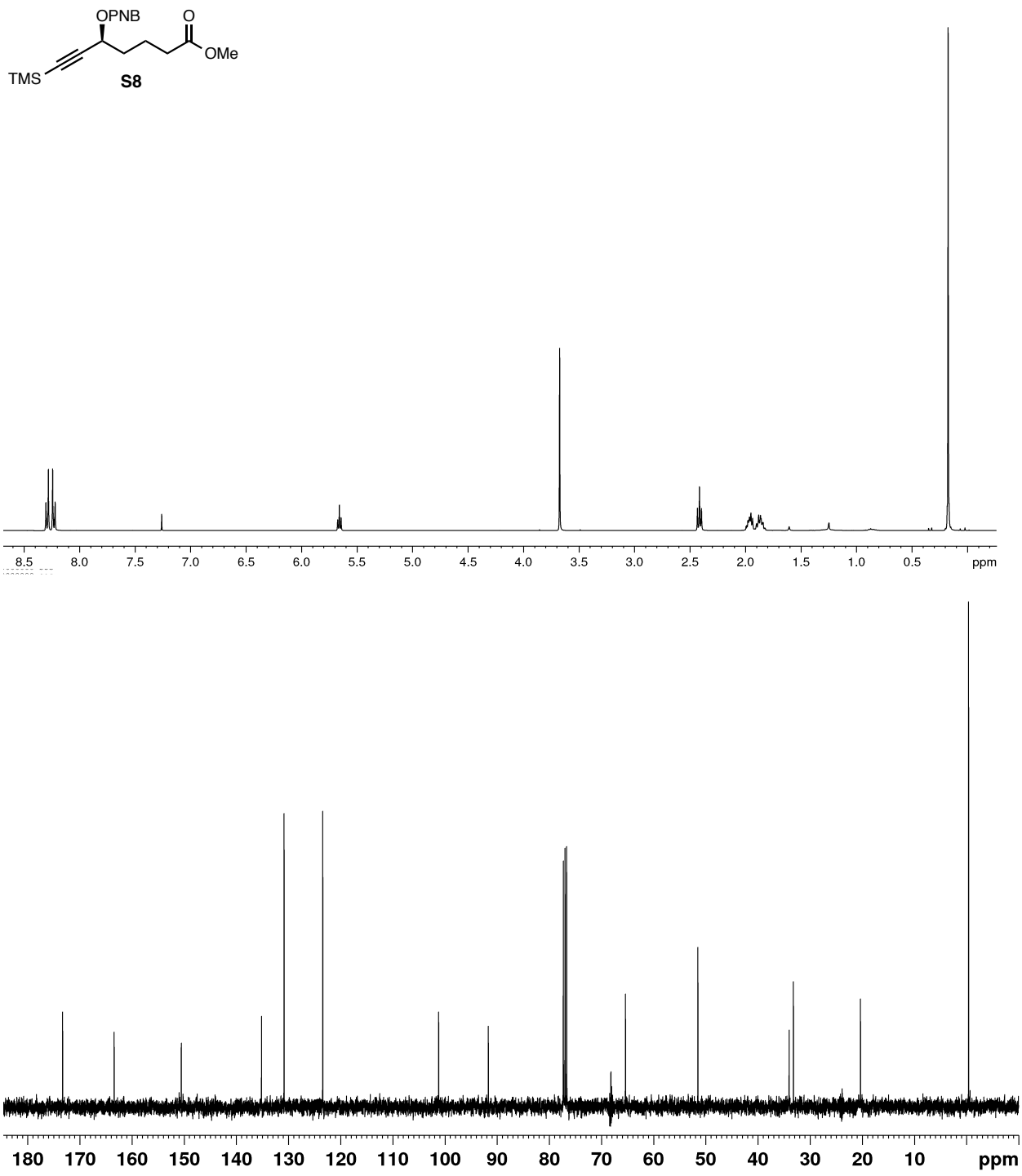
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz $CDCl_3$) spectra of aldehyde **13**



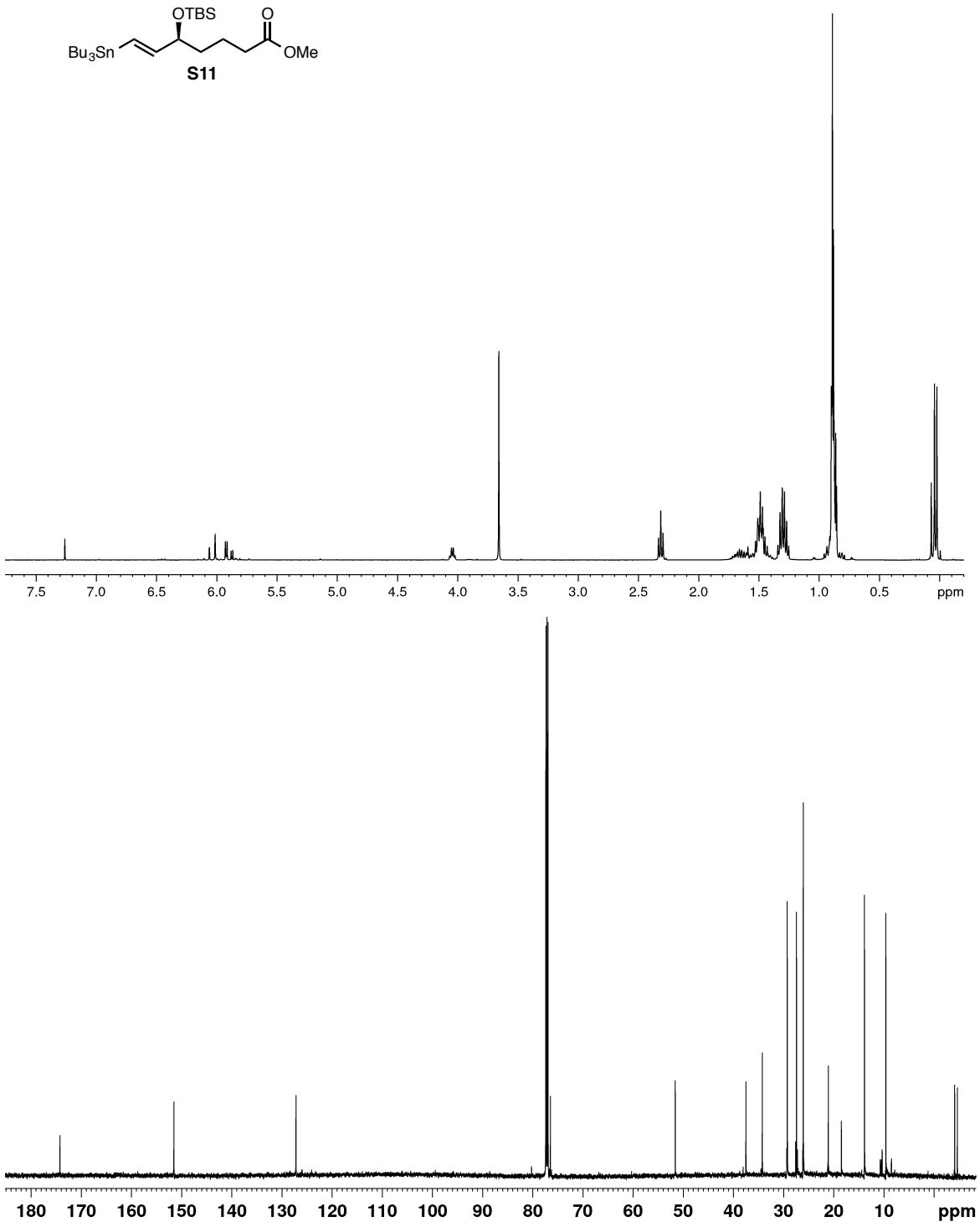
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz $CDCl_3$) spectra of p-nitrobenzoate **S3**



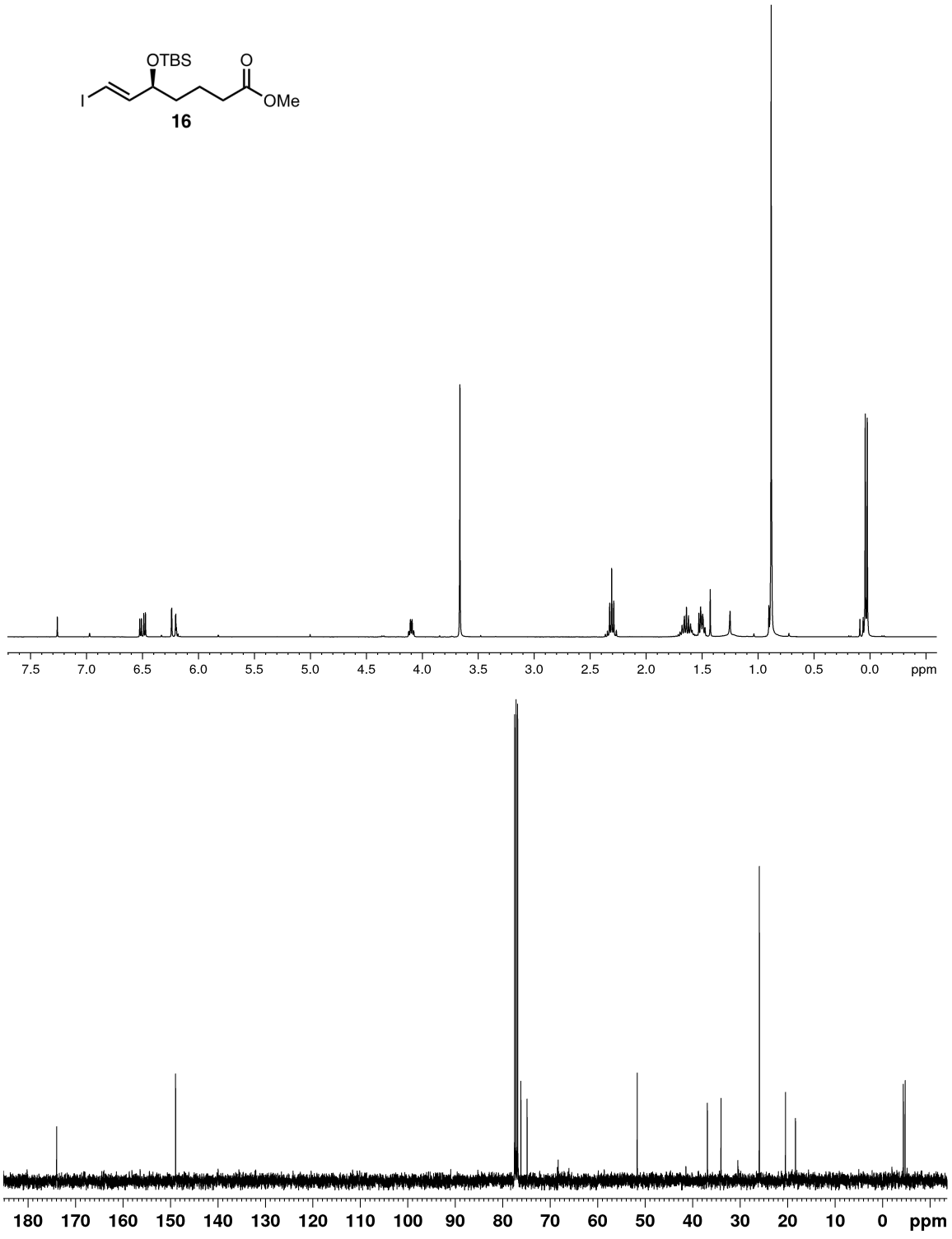
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz $CDCl_3$) spectra of TBS ether **S4**



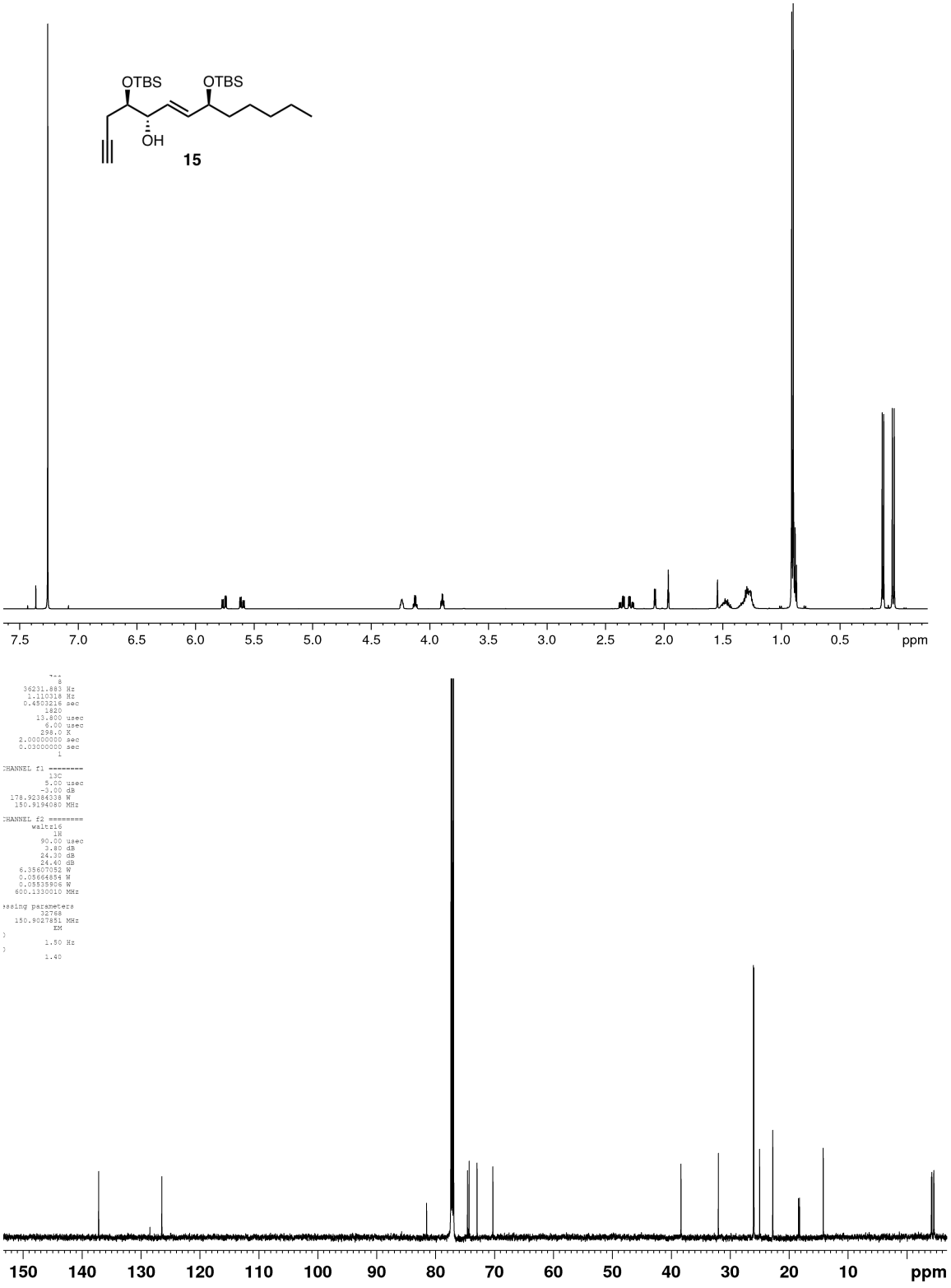
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz $CDCl_3$) spectra of p-nitrobenzoate **S8**



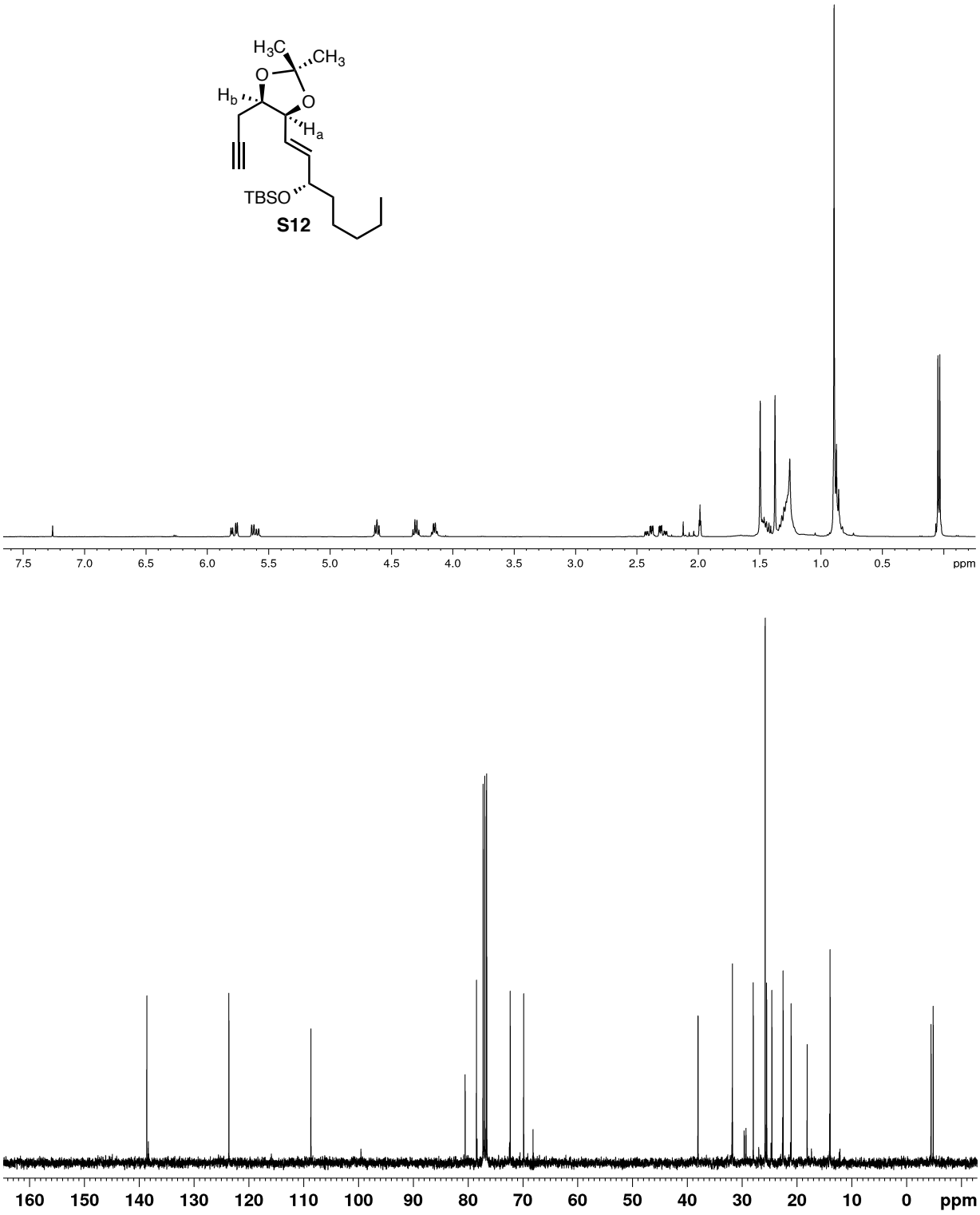
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz $CDCl_3$) spectra of vinyl stannane **S11**



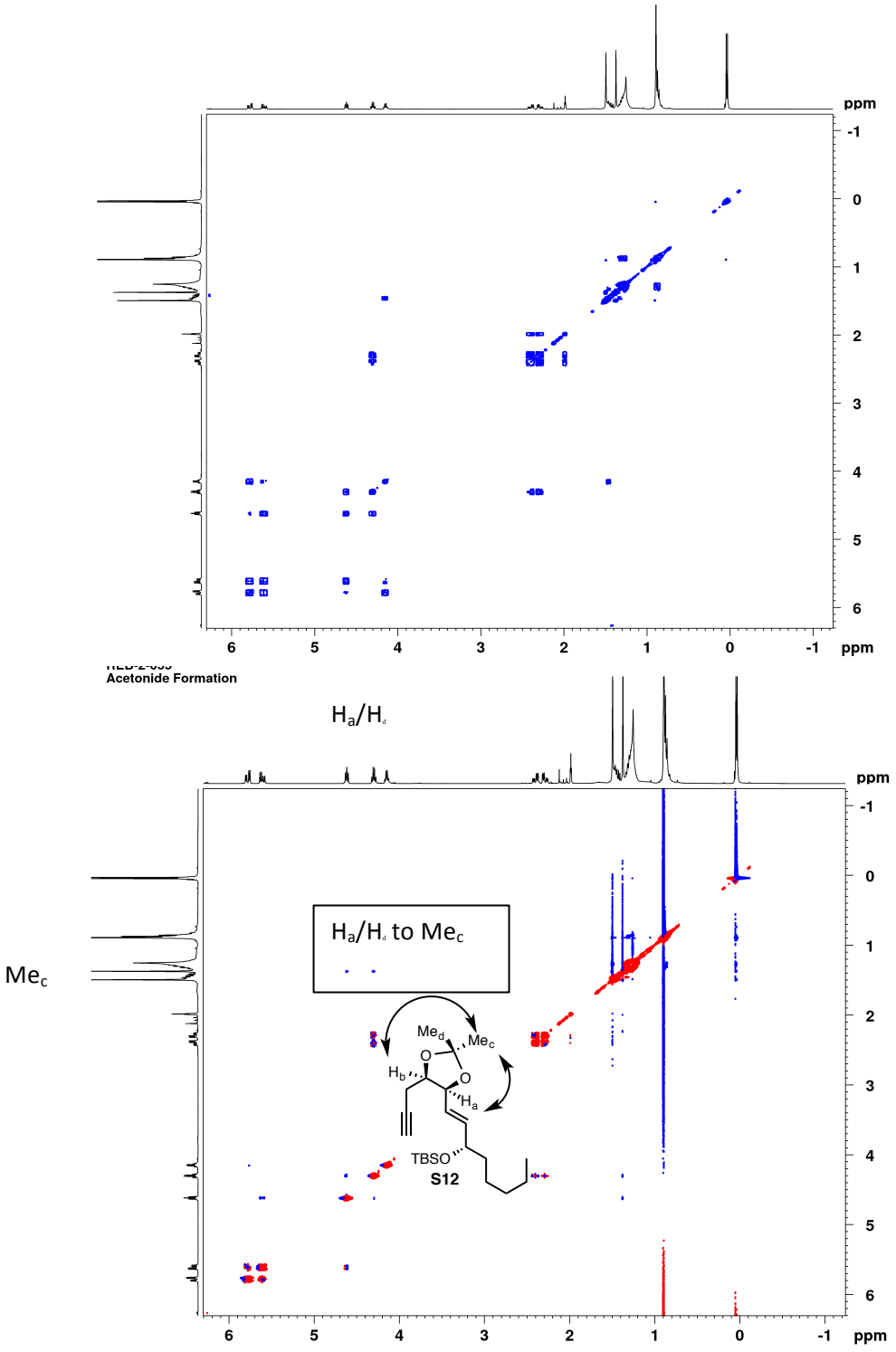
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz $CDCl_3$) spectra of vinyl iodide **16**



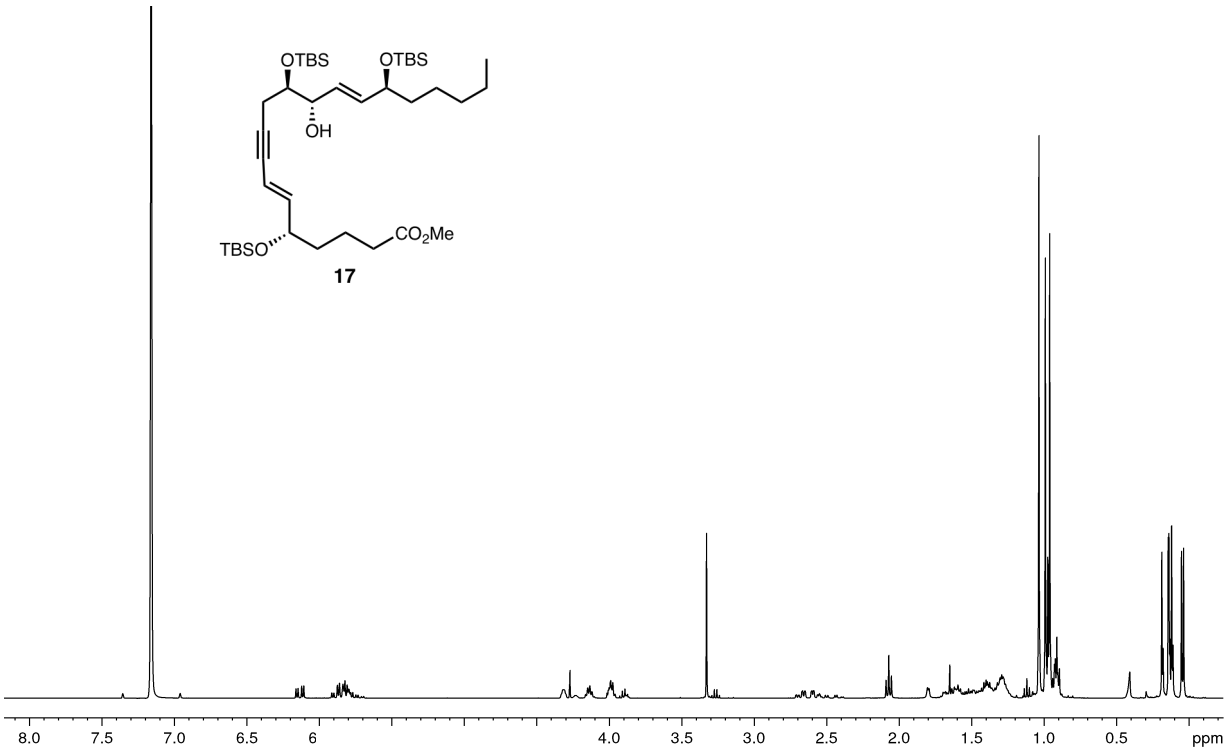
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz $CDCl_3$) spectra of alcohol **15**

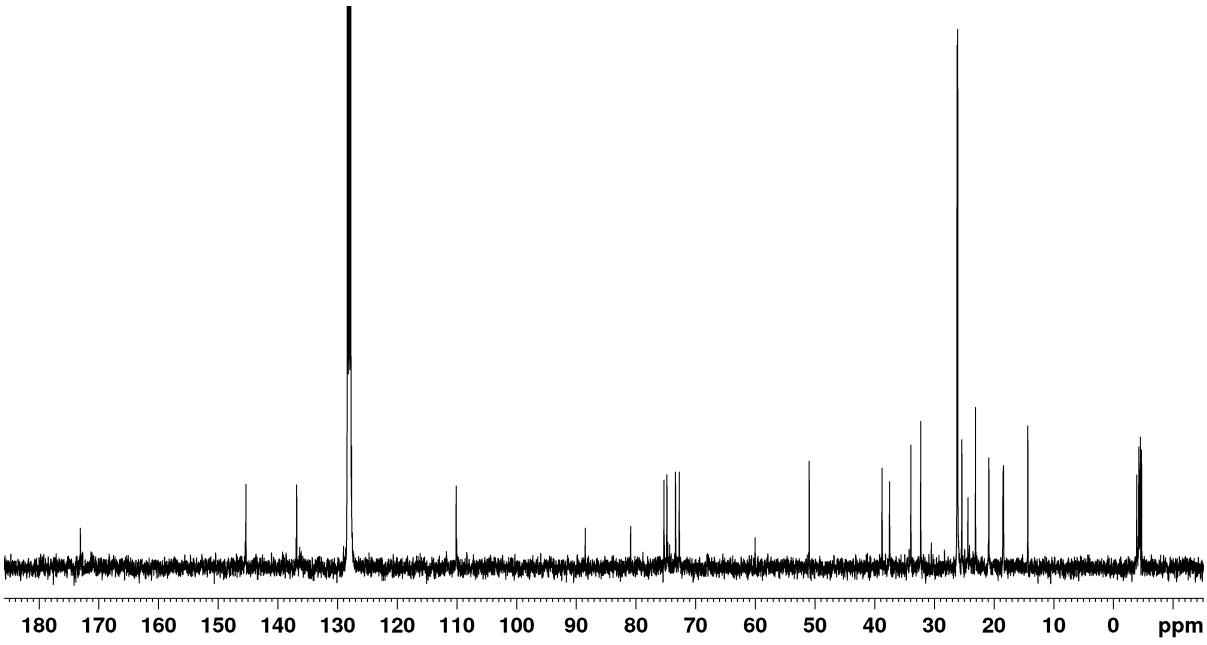


^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of acetonide **S12**

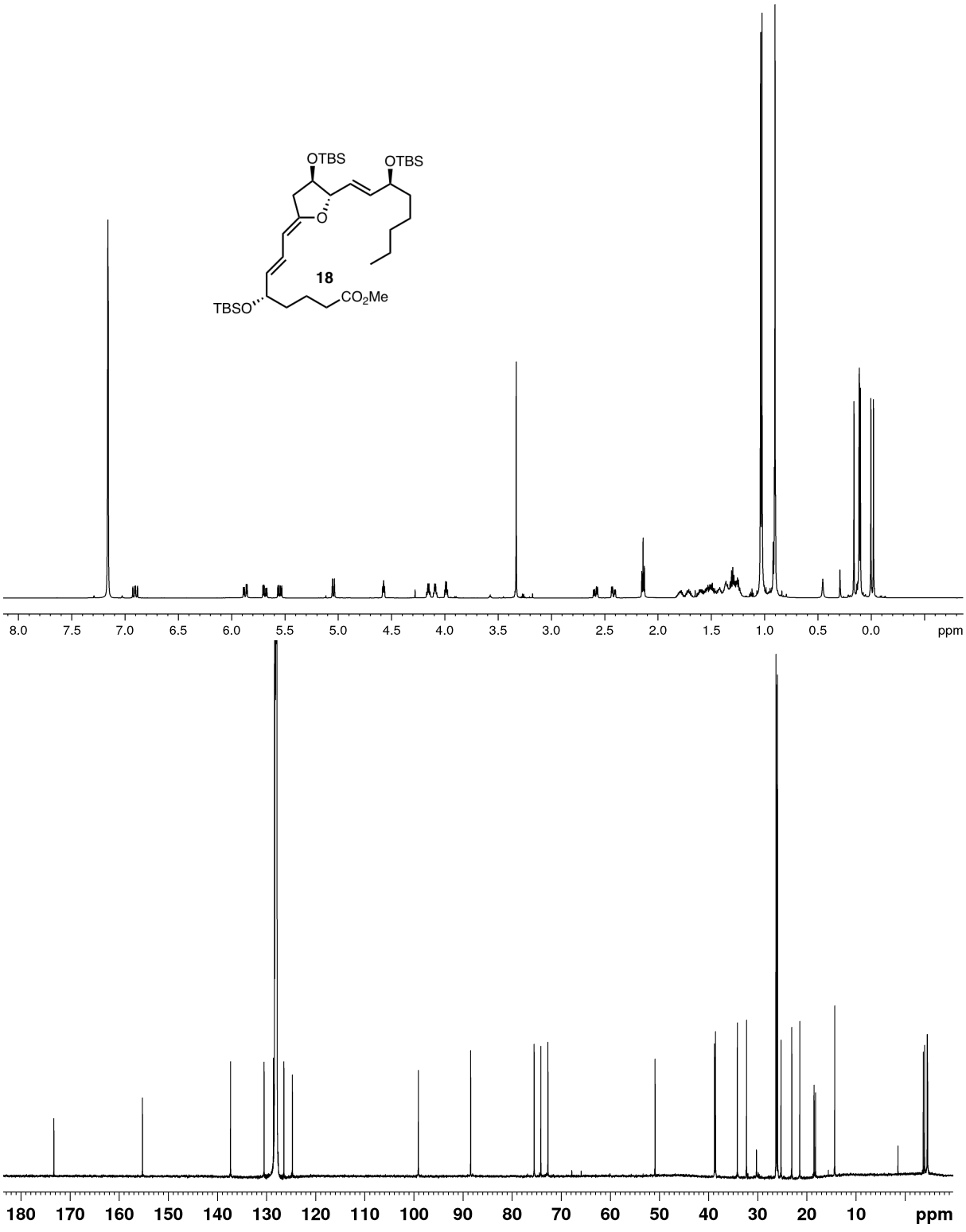


COSY (400 MHz, $CDCl_3$) and NOESY Spectrum (400MHz, $CDCl_3$) of acetonide **S12**

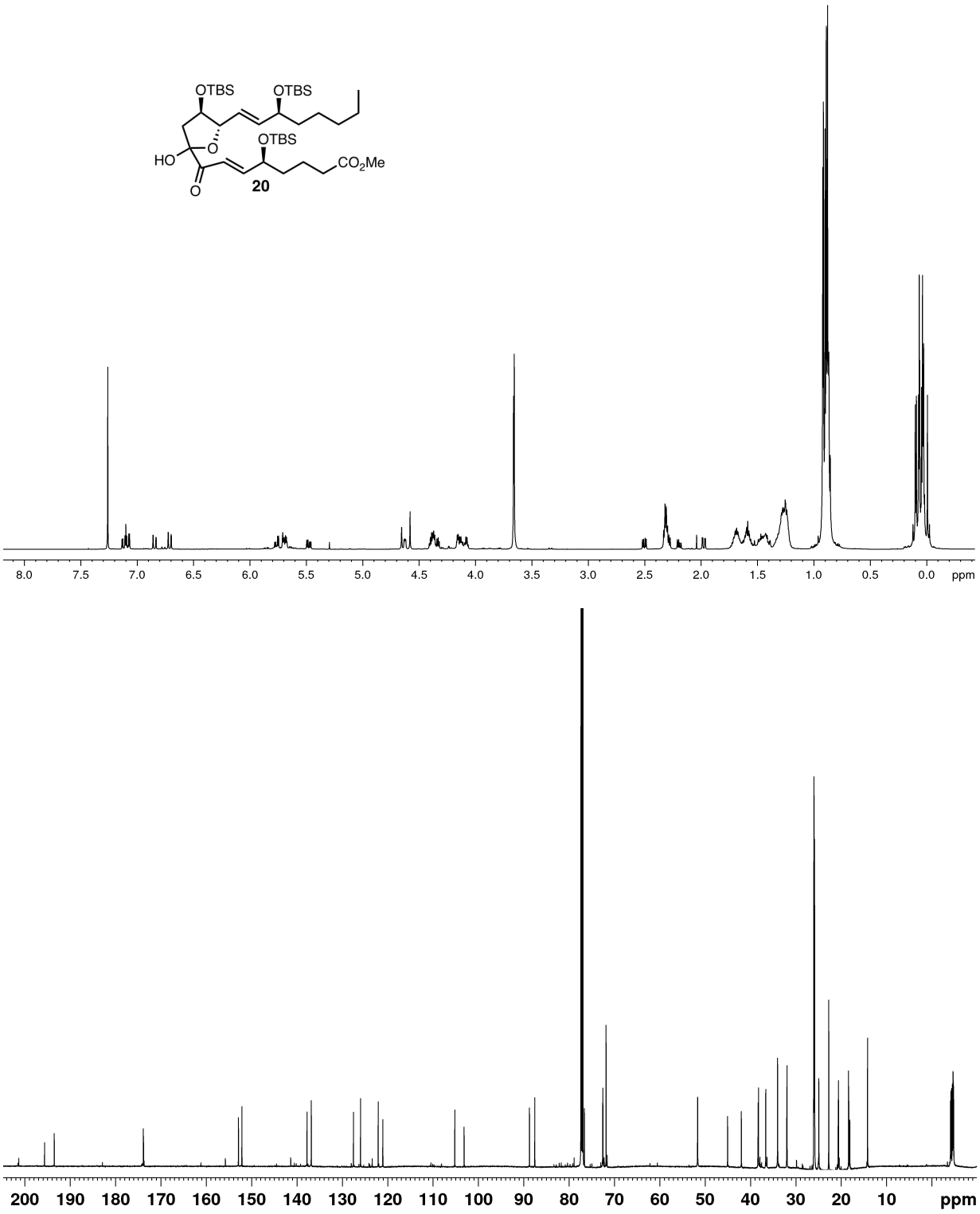




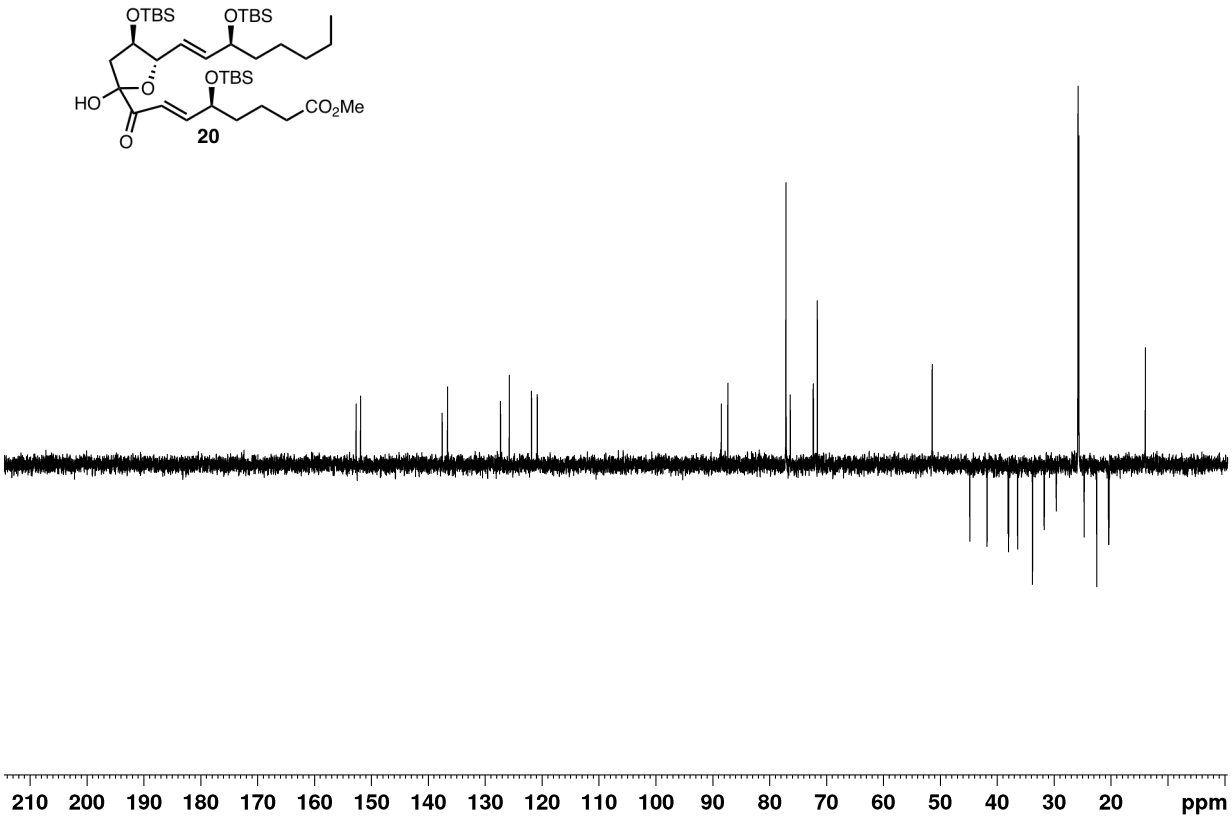
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz $CDCl_3$) spectra of alcohol enyne **17**

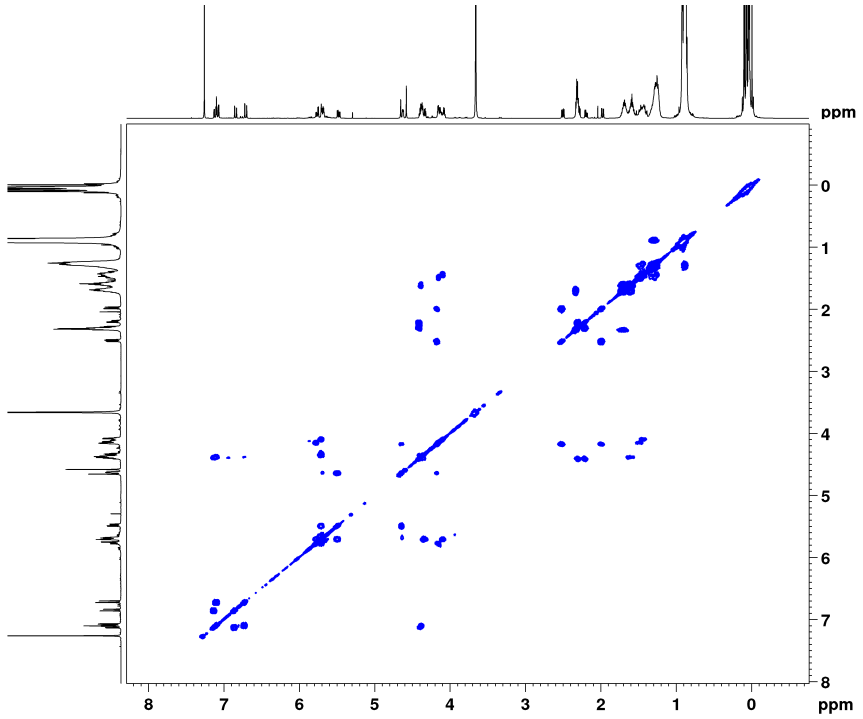


^{1}H NMR (400 MHz, C_6D_6) and ^{13}C NMR (100 MHz C_6D_6) spectra of vinyl ether **18**

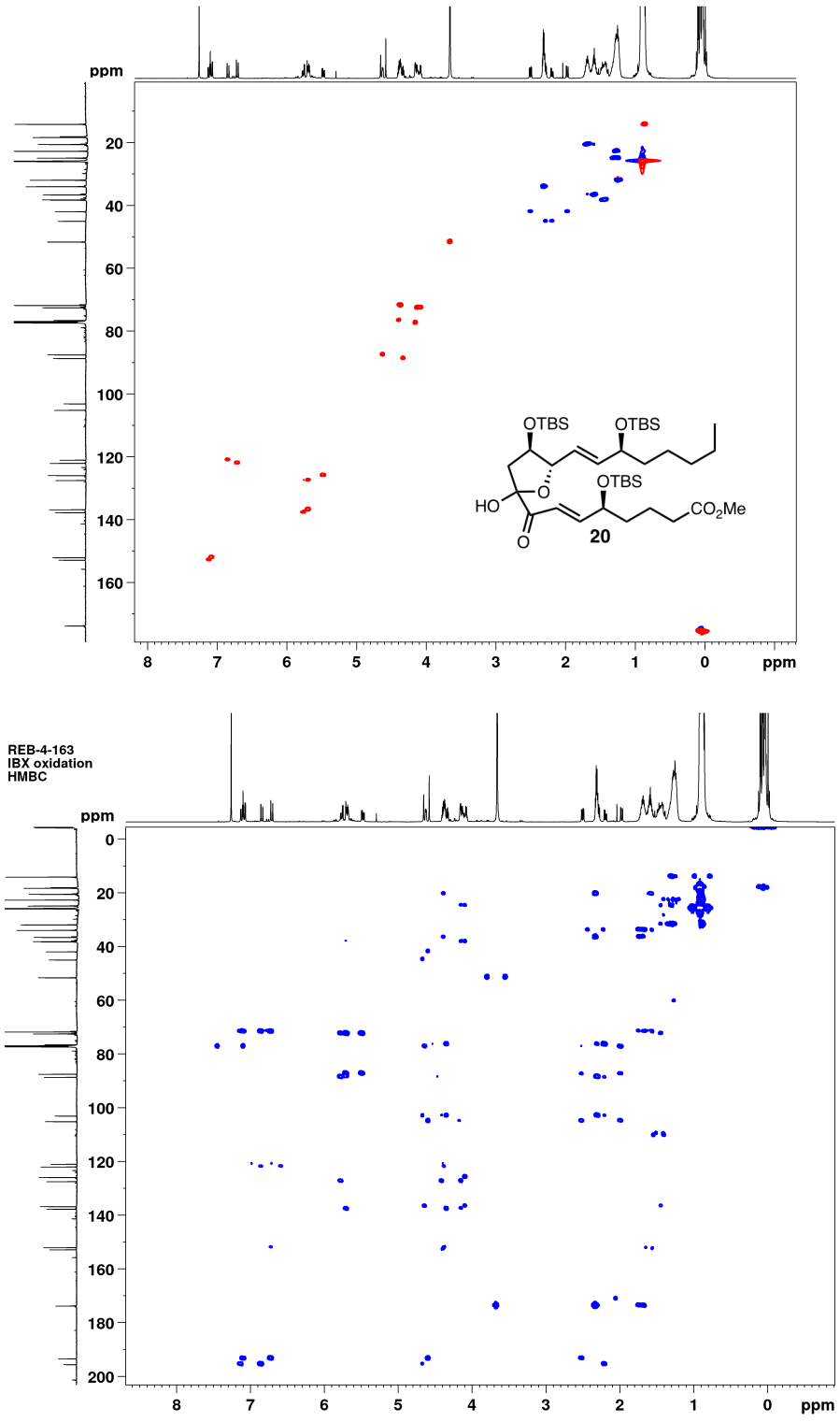


^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz $CDCl_3$) spectra of hemiketal **20**

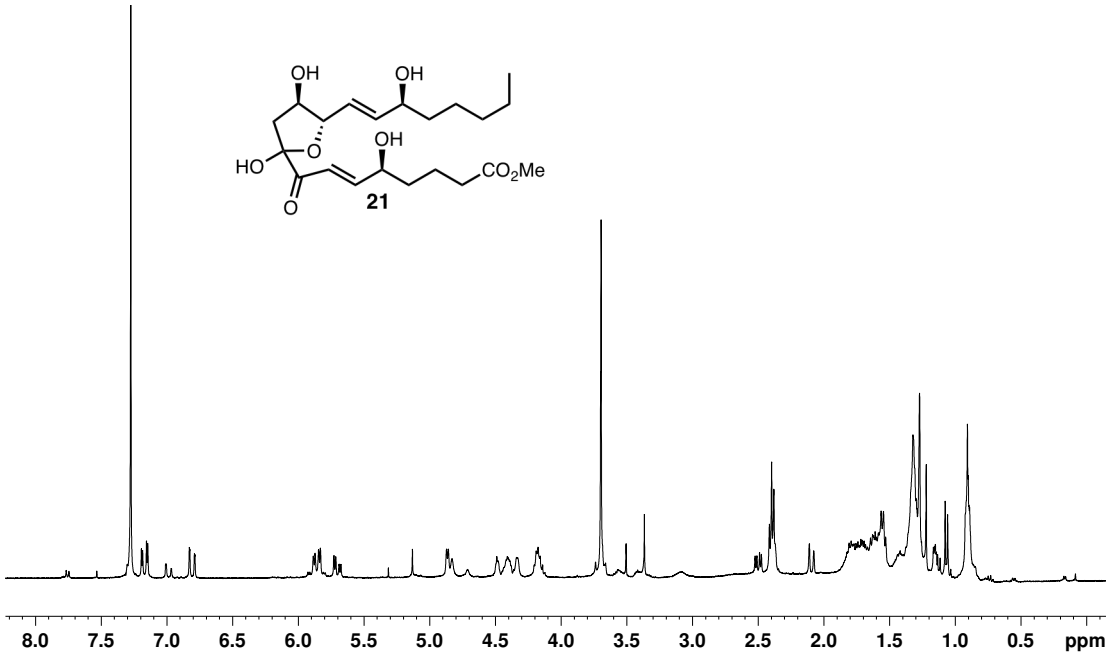


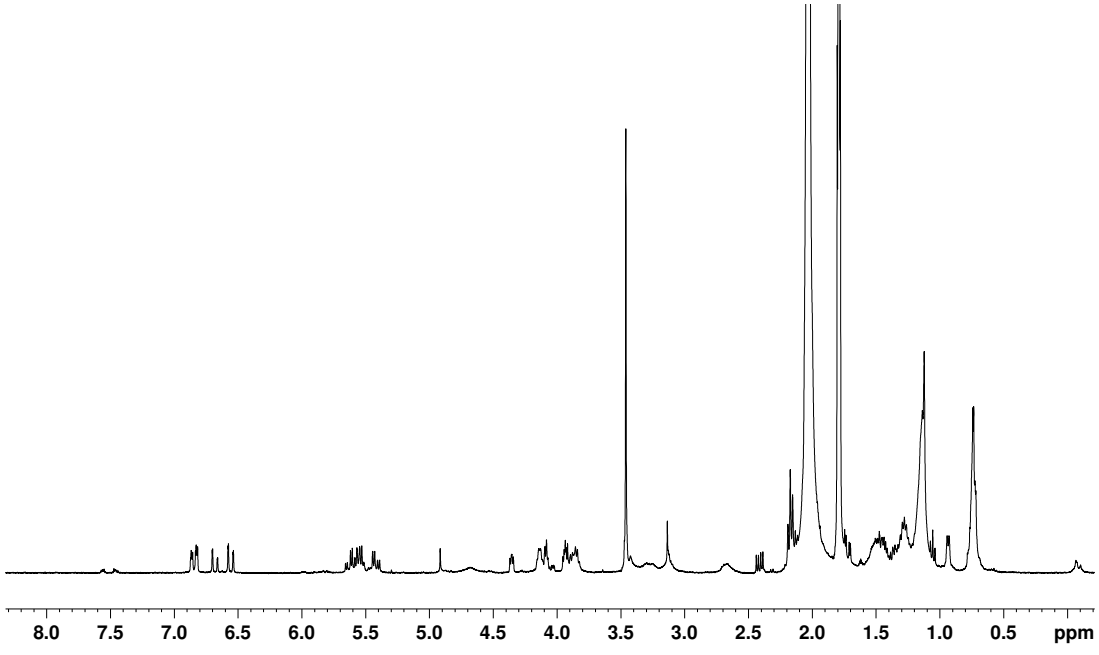


DEPT-135 NMR (150 MHz, $CDCl_3$) and COSY Spectrum (600 MHz, $CDCl_3$) of hemiketal **20**

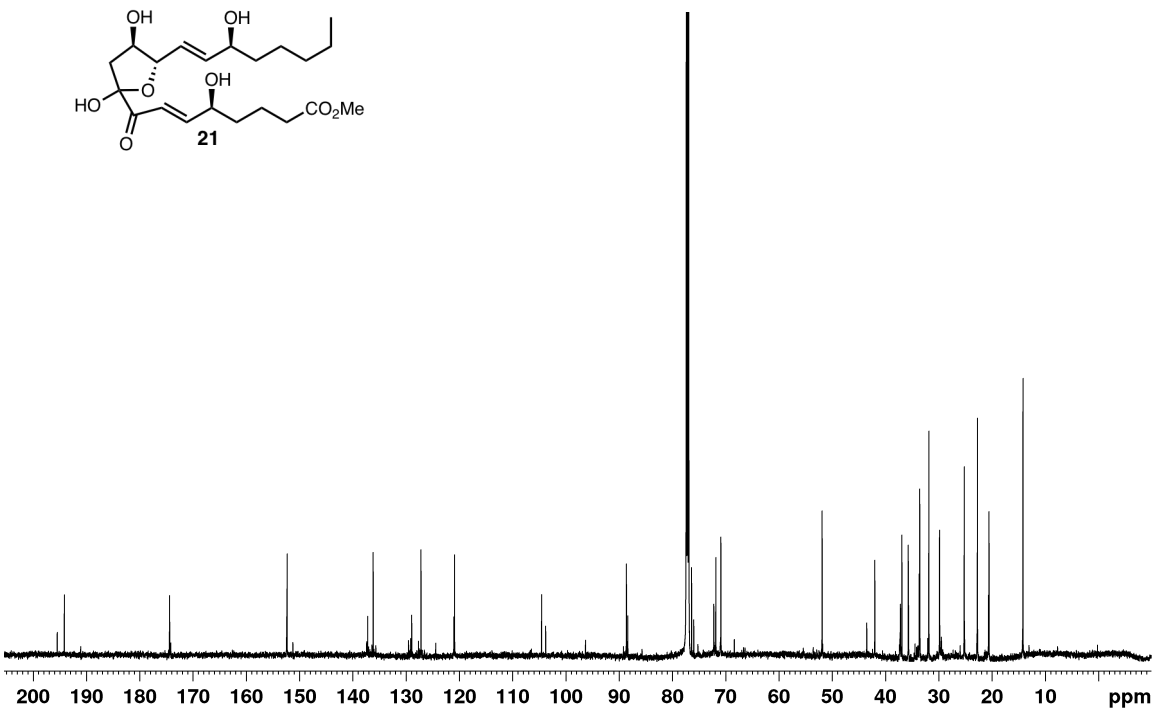


HSQC Spectrum (600 MHz, $CDCl_3$) and HMBC Spectrum (600 MHz, $CDCl_3$) of hemiketal **20**

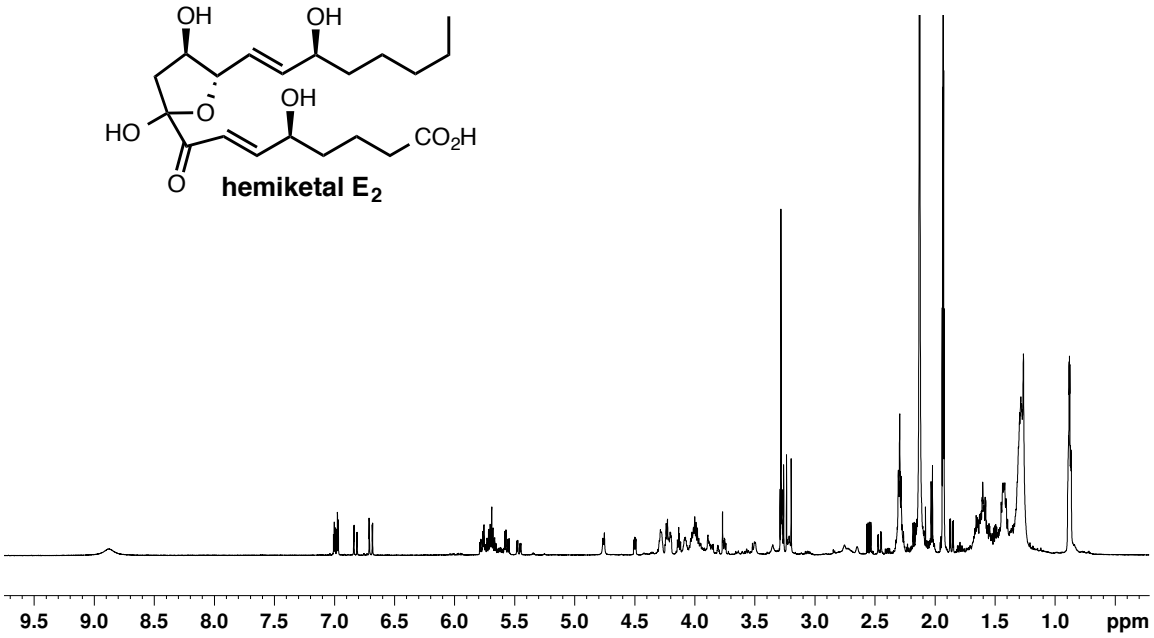


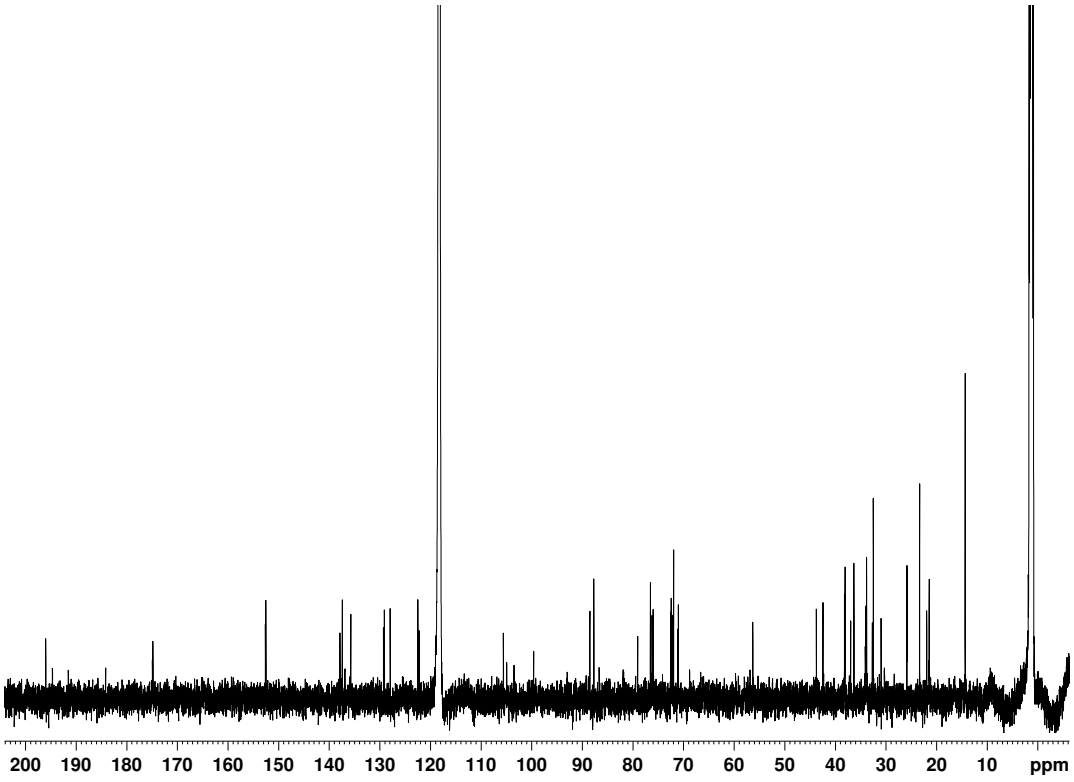


^{1}H NMR (600 MHz, $CDCl_3$, ca. 3:1 ratio) and (600 MHz, CD_3CN, ca. 1:1) isomers of methyl ester **21**

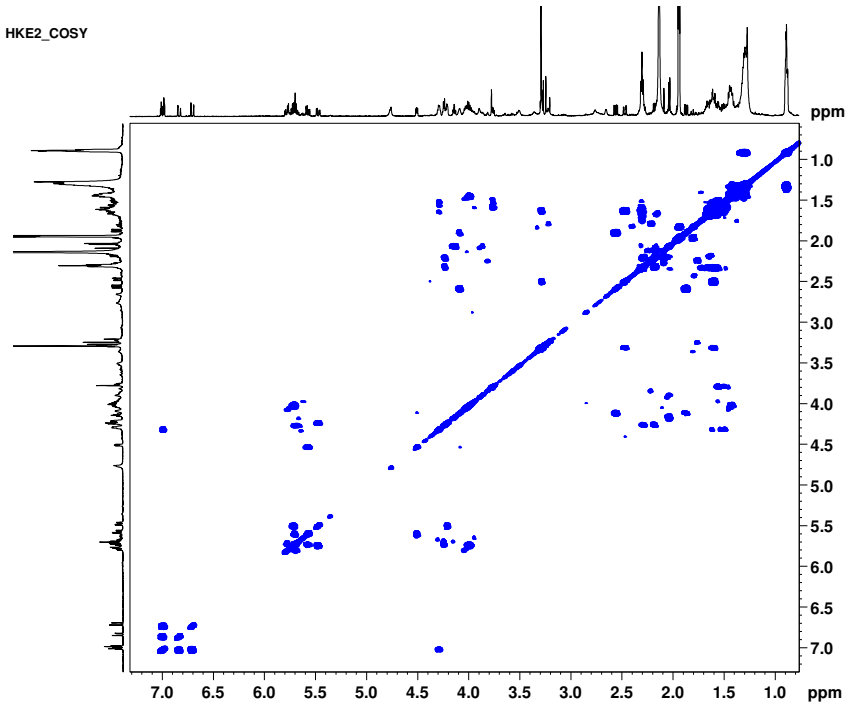


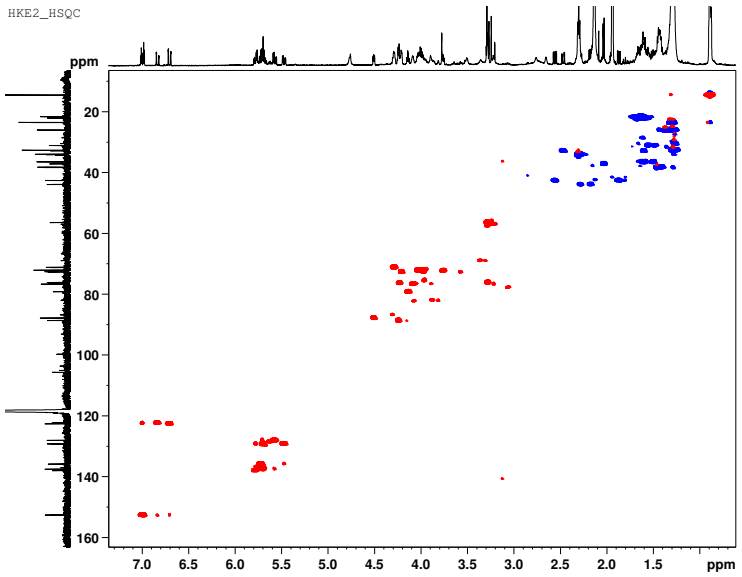
^{13}C NMR (100 MHz $CDCl_3$, ca. 3:1 ratio) spectra of methyl ester **21**



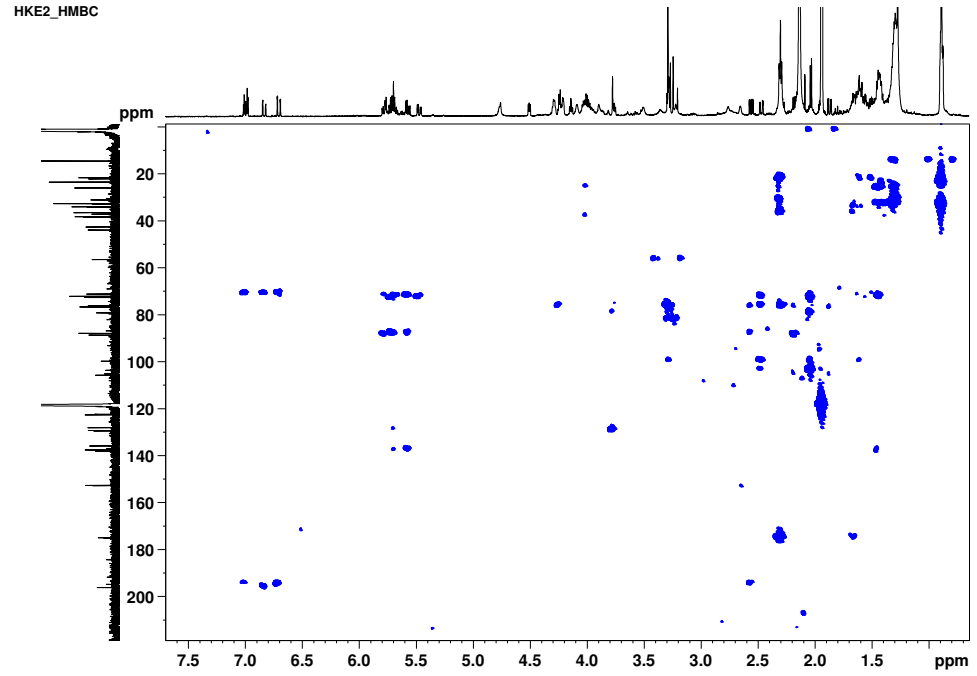


^{1}H NMR (600 MHz, CD_3CN) and ^{13}C NMR (100 MHz CD_3CN) spectra of hemiketal E_2 (**3**)

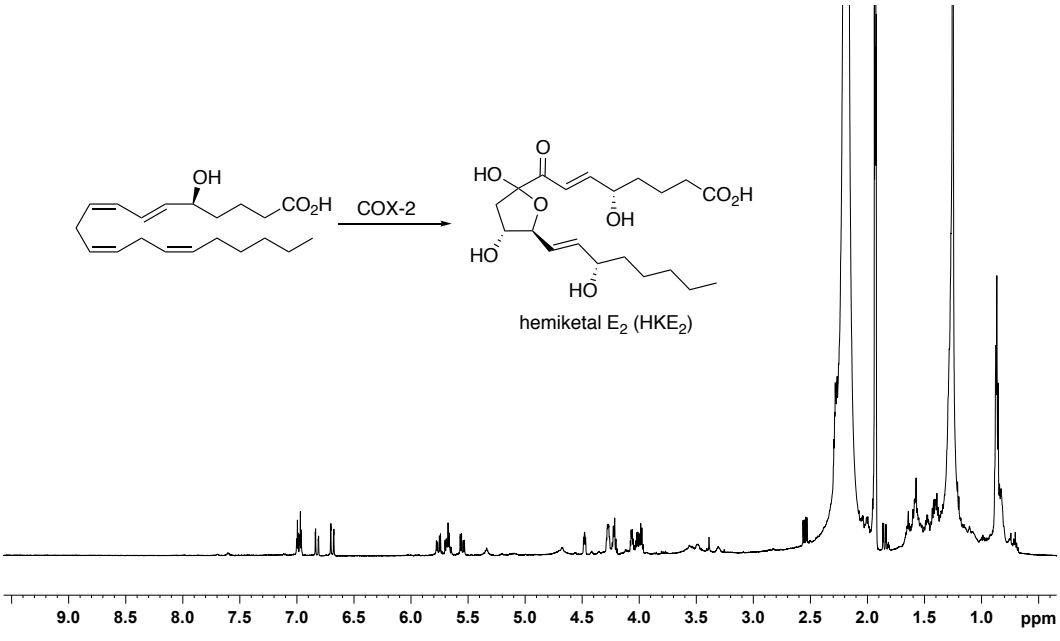




COSY Spectrum (600 MHz, $CDCl_3$) and HSQC Spectrum (600 MHz, CD_3CN) of hemiketal E_2 (**3**)



HMBC Spectrum (600 MHz, $CDCl_3$) and HMBC Spectrum (600 MHz, CD_3CN) of hemiketal E_2 (**3**)



^1H NMR (600 MHz, CD_3CN) spectrum of COX-2 derived hemiketal E_2 (**3**)