

SUPPLEMENTARY MATERIAL

An alternative stereoselective total synthesis of (-) – pyrenophorol

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S1 Experimental

1.1 General

All chemicals and solvents were purchased from Sigma Aldrich and Merck and used without further purification. All reactions were monitored by thin layer chromatography (TLC) on silica Merck 60 F254 precoated aluminum plates. ¹H and ¹³C NMR spectra were recorded in 500 MHz, 300 MHz, 150 MHz, and 75 MHz Bruker spectrometer. Chemical shifts are reported in δ units (ppm) with tetramethylsilane (TMS) as a reference. All coupling constants (J) are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet). FT-IR spectra were taken on IR spectrophotometer by using NaCl optics. Mass spectra were performed on direct inlet system or LC by MSD trap SL. Optical rotation values are recorded on digital polarimeter at 25 °C.

1.2 Procedures

1.2.1 (S)-*tert*-*Butyl(hex-5-en-2-yloxy) dimethylsilane* (7)

A suspension of Mg (3.97 g, 165.5 mmol) and dry ether (30 mL) was treated with allyl chloride (6.8 mL, 82.55 mmol) at room temperature and stirred for 30 min. It was cooled to -78 °C and a solution of **4** (4 mL, 55.17 mmol) in dry ether (10 mL) was added dropwise and the mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with aq. NH₄Cl solution (10 mL) and extracted with ether (2 x 50

mL). Combined extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated then afforded the crude alcohol **6** (5.0 g, 90%) as a colorless liquid. It was used as such for next reaction.

A mixture of the above alcohol **6** (5 g, 50 mmol) and imidazole (10.2 g, 150 mmol) in dry CH_2Cl_2 (50 mL) was treated with TBSCl (8.29 g, 55 mmol) at 0 °C under nitrogen atmosphere and stirred at room temperature for 4 h. The reaction mixture was quenched with aq. NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (60-120 Silica gel, *n*-Hexane) then furnished **7** (7.5 g, 70%) as a colorless liquid. $[\alpha]_D$ -62.3 (*c* 0.81, CHCl_3); ^1H NMR (200 MHz, CDCl_3): δ 5.72 (m, 1H, olefinic), 4.89 (dd, 2H, *J* = 17.3, 3.7 Hz, olefinic), 3.76 (q, 1H, *J* = 6.0 Hz, -CH), 2.02 (m, 2H, allylic - CH_2), 1.44 (m, 2H, - CH_2), 1.07 (d, 3H, *J* = 6.0 Hz, - CH_3), 0.84 (s, 9H, 3 x - CH_3), 0.08 (s, 6H, 2 x - CH_3); ^{13}C NMR (75 MHz, CDCl_3): δ 139.5, 114.2, 77.1, 32.0, 29.5, 26.2, 22.9, 14.2, -3.2; IR (neat): 2956, 2858, 1467, 1370, 1254, 1135, 1053, 997 cm^{-1} ; ESIMS: 237 ($\text{M}+\text{Na}$)⁺.

1.2.2 (*S*)-6-(*tert*.-Butyldimethylsilyloxy)hept-1-en-3-ol (3)

Ozone was bubbled through a cooled (-78 °C) solution of **7** (7.4 g, 34.57 mmol) in CH_2Cl_2 (70 mL) until the pale blue color persisted. Excess ozone was removed with Me_2S (2 mL) and stirred for 30 min at 0 °C. The reaction mixture was concentrated under reduced pressure then gave aldehyde **8**, which was used for further reaction.

A solution of vinylmagnesium bromide (2.0 *N* solution in THF) (20.5 mL, 41.5 mmol) was added dropwise to a stirred solution of above aldehyde **8** (7.1 g, 33.17 mmol) in dry THF (60 mL) at -40 °C. After the addition was complete, the reaction mixture was stirred for 4 h and treated with aq. NH_4Cl solution (30 mL) dropwise. The residue was filtered through celite and filtrate was extracted with ethyl acetate (2 x 50 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography (60-120 Silica gel, 10% EtOAc in pet. ether) then afforded **3** (6.8 g, 84%) as a colorless liquid. ^1H NMR (300 MHz, CDCl_3): δ 5.84 (m, 1H, olefinic), 5.11 (q, 2H, *J* = 14.6 Hz, olefinic), 4.02 (m, 1H, -

CH), 3.83 (m, 1H, -CH), 1.60-1.39 (m, 4H, 2 x -CH₂), 1.06 (dd, 3H, *J* = 5.2 Hz, -CH₃), 0.84 (s, 9H, 3 x -CH₃), 0.01 (s, 6H, 2 x -CH₃); ESIMS: 267 (M+Na)⁺.

1.2.3 (3*S*,6*S*)-6-(*tert*-*Butyldimethylsilyloxy*)hept-1-en-3-ol (10)

Dry DMSO (3.84 mL, 54.87 mmol) was added dropwise to a solution of oxalyl chloride (2.37 mL, 27.43 mmol) in dry CH₂Cl₂ (15 mL) at -78 °C, and stirred for 20 min. A solution of **3** (3.0 g, 18.29 mmol) in dry CH₂Cl₂ (15 mL) was added and stirred for 2 h at -78 °C. It was quenched with Et₃N (15.76 mL, 106.37 mmol) and diluted with CH₂Cl₂ (50 mL). The reaction mixture was washed with water (50 mL), brine (50 mL), dried (Na₂SO₄) evaporated and the obtained residue was purified by column chromatography (60-120 Silica gel, 10% EtOAc in pet. ether) then furnished the corresponding ketone **9** (2.63 g, 89%). [α]_D -37.4 (c 0.18, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 5.71 (m, 1H, olefinic), 5.13 (d, 1H, *J* = 14.8 Hz, olefinic), 5.01 (d, 1H, *J* = 10.4 Hz, olefinic), 3.99 (m, 1H, -CH), 3.78 (m, 1H, -CH), 1.60-1.37 (m, 4H, 2 x -CH₂), 1.06 (d, 3H, *J* = 5.4 Hz, -CH₃), 0.81 (s, 9H, 3 x -CH₃), 0.01 (s, 6H, 2 x -CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 141.5, 114.3, 72.1, 68.6, 33.1, 26.0, 23.3, 18.0, -4.8, -4.4; IR (neat): 3435, 2929, 2857, 1465, 1373, 1253, 1134, 1048, 833 cm⁻¹; ESIMS: 267 (M+Na)⁺.

1.2.4 *tert*-*Butyl*((2*S*,5*S*)-5-(benzyloxy)hept-6-en-2-yloxy)dimethylsilane (11)

NaH (0.59 g, 24.59 mmol) was added to a cooled (0 °C) solution of **10** (3.0 g, 12.29 mmol) in dry THF (30 mL), stirred for 30 min and treated with a solution of PMBBr (2.93 g, 14.74 mmol) in dry THF (15 mL). After 7.5 h stirring at room temperature, the reaction mixture was quenched with sat. NH₄Cl solution (10 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layers were washed with water (2 x 10 mL), brine (10 mL) and dried (Na₂SO₄). Solvent was evaporated under reduced pressure and purified the residue by column chromatography (60-120 Silica gel, 5% EtOAc in pet. ether) then furnished **11** (3.7 g, 82%) as a yellow liquid. [α]_D -23.6 (c 0.9, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.29 (m, 5H, ArH-Bn), 5.79-5.67 (heptet, 1H, *J*

δ = 7.5, 10.3 Hz, olefinic), 5.19 (q, 2H, J = 4.1, 10.3 Hz, olefinic), 4.54, 4.30 (2d, 2H, J = 11.8 Hz, -OCH₂ Ar), 3.78 (s, 3H, -OCH₃), 3.76-3.62 (m, 2H, 2 x -CH), 1.61-1.32 (m, 4H, 2 x -CH₂), 1.20 (d, 3H, J = 6.0 Hz, -CH₃), 0.85 (s, 9H, 3 x -CH₃) 0.00 (s, 6H, 2 x -CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 149.0, 131.5, 128.5, 128.2, 127.6, 121.0, 72.7, 57.80, 55.60, 35.3, 30.2, 25.8, 23.8, 22.4, -4.4; IR (neat): 2926, 2858, 1722, 1456, 1268, 1106 cm⁻¹; ESIMS: 335 (M+Na)⁺.

1.2.5 (4S,7S,E)-Methyl 7-(tert.-butyldimethylsilyloxy)-4-(benzyloxy)oct-2-enoate (12)

Ozone was bubbled through a cooled (-78 °C) solution of **11**(7.4 g, 34.57 mmol) in CH₂Cl₂ (70 mL) until the pale blue color persisted. Excess ozone was removed with Me₂S (2 mL) and stirred for 15 min at 0 °C. The reaction mixture was concentrated under reduced pressure to give aldehyde which was used for further reaction.

Solution of the above aldehyde in benzene (50 mL) was treated with (methoxy-carbonylmethylene)triphenyl phosphorane (3.54 g, 10.54 mmol) at reflux temperature. After 2 h, solvent was evaporated and purified the residue by column chromatography (60-120 Silica gel, 10% EtOAc in pet. ether) to furnish **12** (3.12 g, 84%) as a yellow liquid. First eluted was *E* isomer. $[\alpha]_D$ -54.7 (c 0.8, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 7.31 (m, 5H, ArH-Bn), 6.77 (dd, 1H, J = 6.1, 15.8 Hz, olefinic), 5.94 (d, 1H, J = 15.7Hz, olefinic), 4.44 (d, 1H, J = 11.7 Hz, benzylic), 4.32 (d, 1H, J = 11.7 Hz, benzylic), 4.04 (q, 2H, J = 7.6 Hz, -CH₂), 3.87 (q, 1H, J = 5.6, 12.1 Hz, -OCH), 3.73 (s, 3H, OCH₃), 3.61 (m, 1H, -OCH), 1.72-1.31 (br. m, 4H, 2 x -CH₂), 1.17 (t, 3H, J = 7.6 Hz, -CH₃), 1.07 (d, 3H, J = 6.0 Hz, -CH₃), 0.85 (s, 9H, 3 x -CH₃), 0.01 (s, 6H, 2 x -CH₃); ¹³C NMR (CDCl₃, 150 MHz): δ 166.5, 158.2, 147.4, 129.7, 128.6, 118.8, 113.5, 79.6, 71.2, 66.6, 55.4, 51.6, 35.4, 30.2, 25.6, 24.2, 18.2, -4.8; IR (neat): 2932, 1724, 1612, 1512, 1448, 1386, 1164, 1037 cm⁻¹; ESIMS: 429 (M+Na)⁺.

1.2.6 (4S,7S,E)-7-(tert.-Butyldimethylsilyloxy)-4-(benzyloxy)oct-2-enoic acid (13)

LiOH (0.45 g, 18.48 mmol) was added to a solution of **12** (2.6 g, 6.16 mmol) in THF: MeOH: water (3:1:1, 20 mL), and stirred at room temperature for 4 h. The pH of reaction mixture was adjusted to acidic with 1N HCl solution and extracted with ethyl

acetate (30 mL). Organic layers were washed with water (15 mL), brine (15 mL), dried (Na₂SO₄), evaporated under reduced pressure and purified the residue by column chromatography (60-120 Silica gel, 30% EtOAc in pet. ether) then gave **13** (2.02 g, 80%) as a colourless oil. [α]_D +14.6 (c 0.6, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 7.19 (d, 2H, J = 8.5 Hz, ArH-PMB), 6.94 (dd, 1H, J = 6.0, 15.6 Hz, olefinic), 6.81 (d, 2H, J = 8.5 Hz, ArH-PMB), 5.91 (d, 1H, J = 15.5 Hz, olefinic), 4.48 (d, 1H, J = 11.4 Hz, benzylic), 4.29 (d, 1H, J = 11.6 Hz, benzylic), 3.90 (q, 1H, J = 5.6, 12.1 Hz, -OCH), 3.79 (s, 3H, OCH₃), 3.49 (m, 1H, -OCH), 1.72-1.34 (br. m, 4H, 2 x -CH₂), 1.13 (d, 3H, J = 6.0 Hz, -CH₃); 0.85 (s, 9H, 3 x -CH₃), 0.09 (s, 6H, 2 x -CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 172.8, 158.4, 149.5, 130.6, 128.6, 119.6, 113.5, 78.8, 72.6, 66.6, 55.6, 36.2, 30.8, 25.9, 24.2, 17.6, -4.6; IR (neat): 3540, 3031, 2930, 2857, 1710, 1097 cm⁻¹; ESIMS: 401 (M+Na)⁺.

1.2.7 (4S,7S,E)-7-Hydroxy-4-(benzyloxy)oct-2-enoic acid (2)

TBAF (6.5 mL, 6.5 mmol) was added to a cooled (0 °C) solution of **13** (2.20 g, 5.40 mmol) in dry THF (15 mL) under nitrogen atmosphere, and stirred for 3 h. After completion of reaction, reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 x 50 mL). Organic layers were washed with water (2 x 10 mL), brine (10 mL), dried (Na₂SO₄), evaporated and purified the residue by column chromatography (60-120 Silica gel, 55% EtOAc in pet. ether) then gave **2** (1.38 g, 87%) as a liquid. [α]_D -32.6 (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 7.18 (d, 2H, J = 8.6 Hz, ArH-PMB), 6.95 (dd, 1H, J = 6.0, 15.6 Hz, olefinic), 6.80 (d, 2H, J = 8.6 Hz, ArH-PMB), 5.99 (d, 1H, J = 15.6 Hz, olefinic), 4.50 (d, 1H, J = 11.6 Hz, benzylic), 4.29 (d, 1H, J = 11.6 Hz, benzylic), 3.92 (q, 1H, J = 5.6, 12.1 Hz, -OCH), 3.79 (s, 3H, OCH₃), 3.76 (m, 1H, -OCH), 1.72-1.32 (br. m, 4H, 2 x -CH₂), 1.11 (d, 3H, J = 6.0 Hz, -CH₃); ¹³C NMR (CDCl₃, 75 MHz): δ 172.6, 158.2, 146.4, 132.6, 128.9, 118.3, 113.6, 78.8, 72.4, 68.2, 56.4, 34.2, 29.8, 23.2; IR (neat): 3451, 2929, 2857, 2102, 1722, 1612, 1514, 1360, 1041, 777 cm⁻¹; ESIMS: 265(M+H)⁺.

1.2.8 (3E,5S,8R,11E,13S,16R)-5,13-Bis(benzyloxy)-8,16-dimethyl-1,9-dioxacyclo-hexa-deca- 3,11-diene-2,10-dione (14)

A solution of **2** (0.225 g, 0.93 mmol) and Ph₃P (1.22 g, 4.67 mmol) in toluene: THF (10:1, 250 mL) DEAD (0.81 mL, 16.87 mmol) was added at -20 °C and stirred under N₂ atmosphere for 10 h. Solvent was evaporated under reduced pressure and purified the residue by column chromatography (60-120 Silica gel, 10% EtOAc in pet. ether) then afforded **14** (0.14 g, 56%) as a colorless oil. [α]_D -17.3 (c 1.14, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 7.18 (d, 4H, *J* = 8.7 Hz, ArH-PMB), 6.81 (d, 4H, *J* = 8.7 Hz, ArH-PMB), 6.61 (dd, 2H, *J* = 6.2, 11.6 Hz, olefinic), 5.82 (d, 2H, *J* = 11.6 Hz, olefinic), 5.01-4.91 (m, 2H, -OCH), 4.41 (d, 2H, *J* = 11.3 Hz, benzylic), 4.24 (d, 2H, *J* = 11.3 Hz, benzylic), 4.12 (m, 2H, -OCH), 3.61 (s, 6H, OCH₃), 1.79 (q, 4H, *J* = 6.4 Hz, -CH₂), 1.60 (m, 4H, -CH₂), 1.32 (d, 6H, *J* = 7.1 Hz, -CH₃); ¹³C NMR (75 MHz, CDCl₃): 166.6, 158.2, 146.2, 129.7, 128.8, 120.6, 113.6, 79.8, 72.4, 68.4, 56.2, 39.6, 28.4, 2.2; IR (neat): 3416, 3068, 2932, 2859, 1722, 1608, 1527, 1462, 1427, 1273, 1105, 918, 702 cm⁻¹; ESIMS: 515 (M+Na)⁺.

1.2.9 Pyrenophorol (**1**)

To a solution of **14** (0.12 g, 0.21 mmol) in aq. CH₂Cl₂ (2 mL, 19:1), DDQ (71 mg, 0.31 mmol) was added and stirred at room temperature for 3 h. The reaction mixture was quenched with sat. NaHCO₃ solution (1 mL), filtered and washed with CH₂Cl₂ (10 mL). The filtrate was washed with water (3 mL), brine (3 mL), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by column chromatography (60-120 Silica gel, 20% EtOAc in pet. ether) then furnished **1** (52 mg, 78%) as a white solid. m.p.: 137-139 °C; lit. m.p. 135 °C; [α]_D -3.7 (c 0.56, acetone); lit. [α]_D -3.0 (c 1.0, acetone); ¹H NMR (CDCl₃, 300 MHz): δ 6.81 (dd, 2H, *J* = 15.4, 5.1 Hz, olefinic), 5.87 (dd, 2H, *J* = 15.4, 2.0 Hz, olefinic), 5.11-4.99 (m, 2H, 2 x -OCH), 4.21-4.19 (m, 2H, 2 x -OCH), 2.29 (br. s, 2H, 2 x -OH), 2.03-1.93 (m, 4H, 2 x -CH₂), 1.77-1.58 (m, 4H, 2 x -CH₂), 1.23 (d, 6H, *J* = 6.0 Hz, 2 x -CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 167.5, 143.3, 121.3, 74.1, 68.6, 31.1, 28.9, 19.0; IR (neat): 3442, 2922, 2853, 1721, 1630, 1126, 835 cm⁻¹; ESIMS *m/z* [M+Na]⁺: 335.

Figure S1: ^1H NMR Spectrum of (*S*)-*tert*.-Butyl(hex-5-en-2-yloxy) dimethylsilane (7)

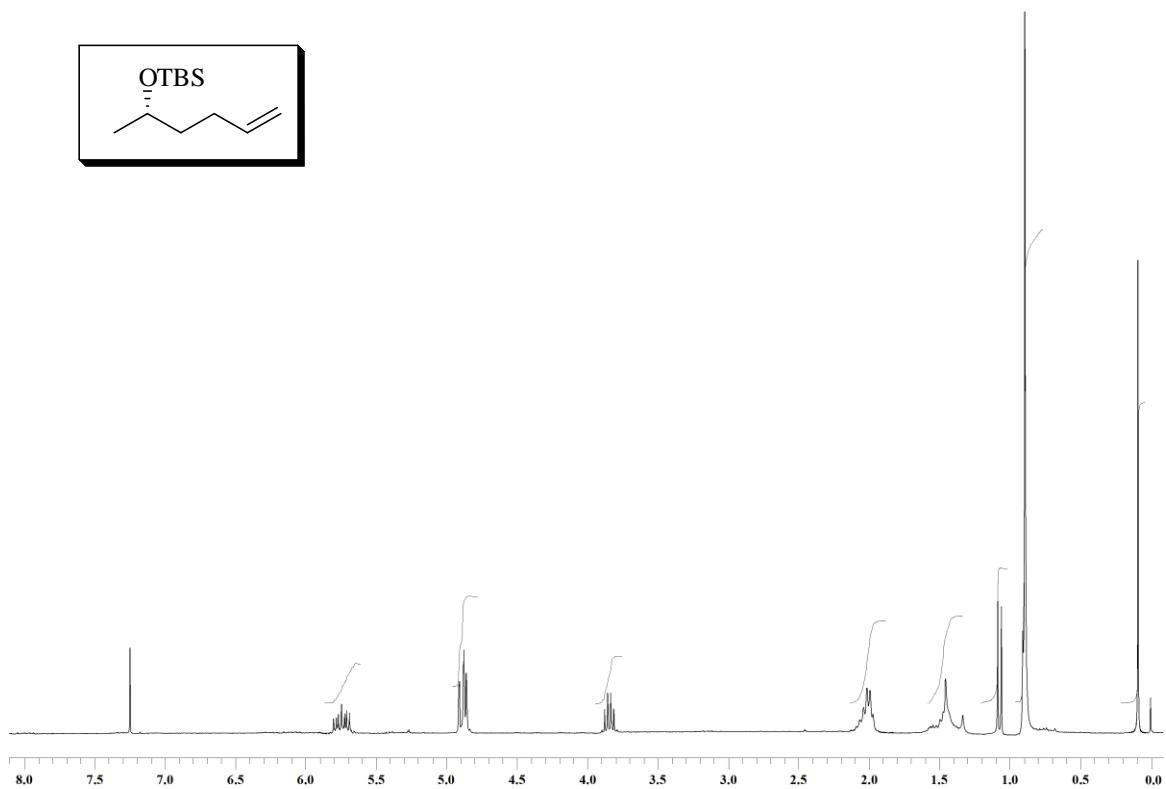


Figure S2: ^{13}C NMR Spectrum of (*S*)-*tert*.-Butyl(hex-5-en-2-yloxy) dimethylsilane (7)

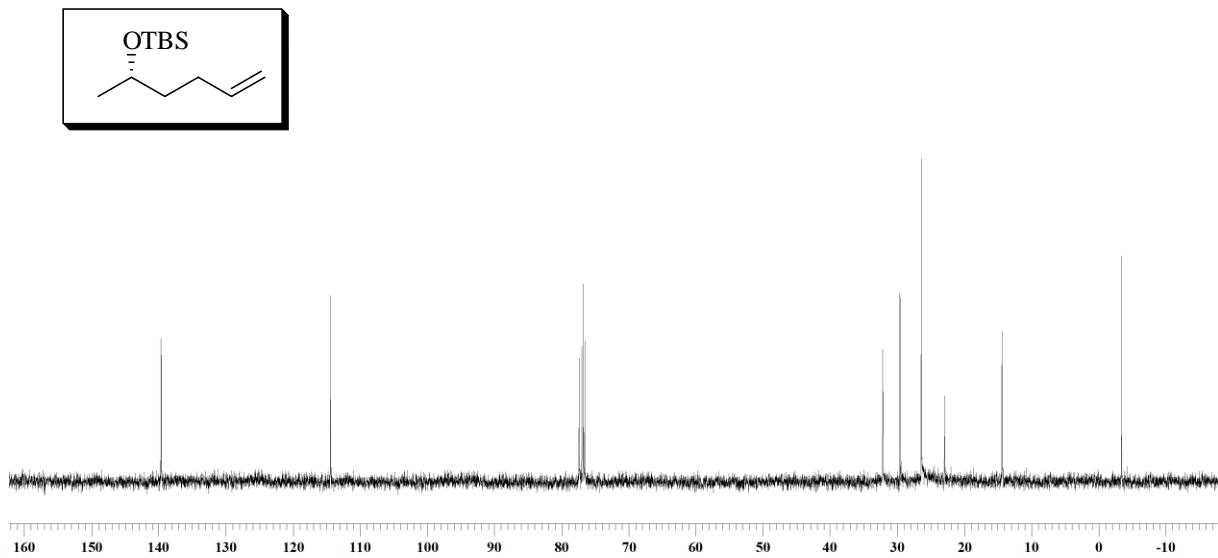


Figure S3: ^1H NMR Spectrum of (S)-6-(tert.-Butyldimethylsilyloxy)hept-1-en-3-ol (3)

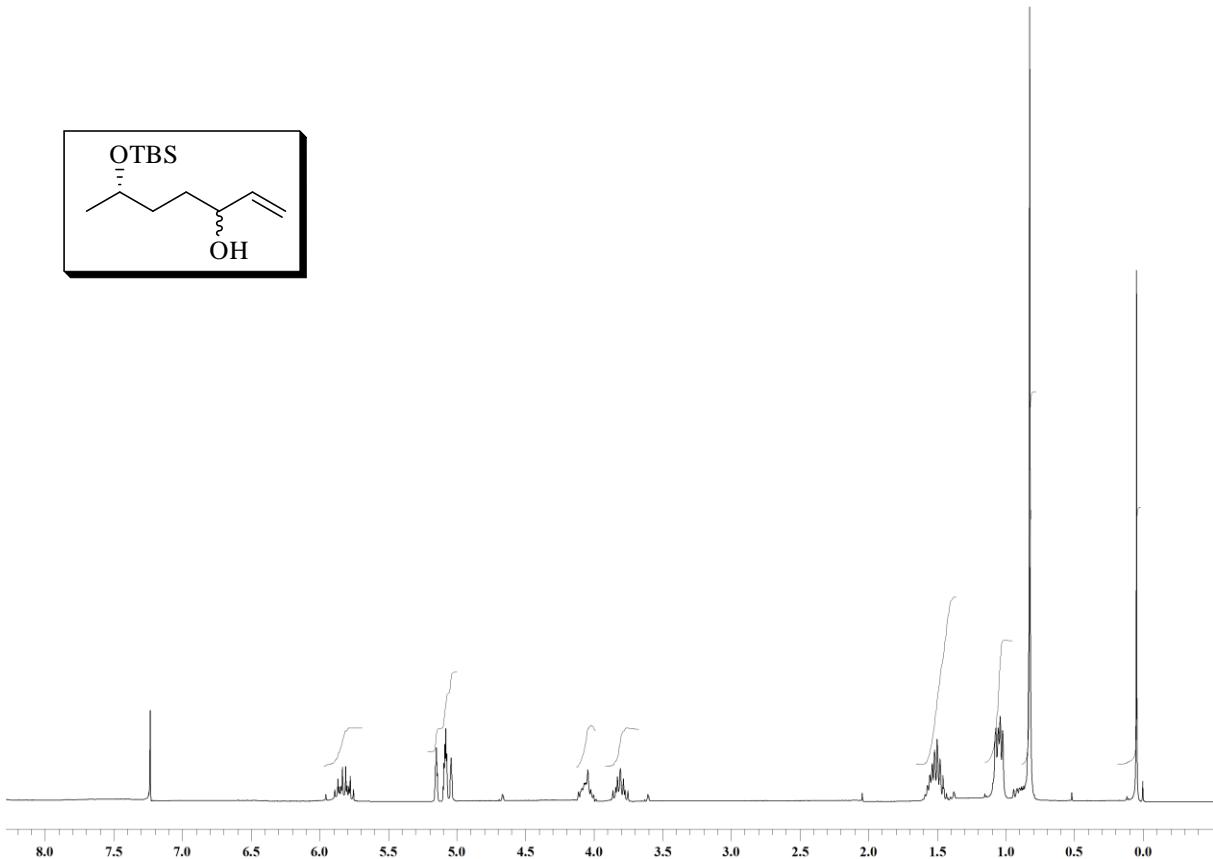


Figure S4: ^1H NMR Spectrum of (3*S*,6*S*)-6-(*tert*.-Butyldimethylsilyloxy)hept-1-en-3-ol (10)

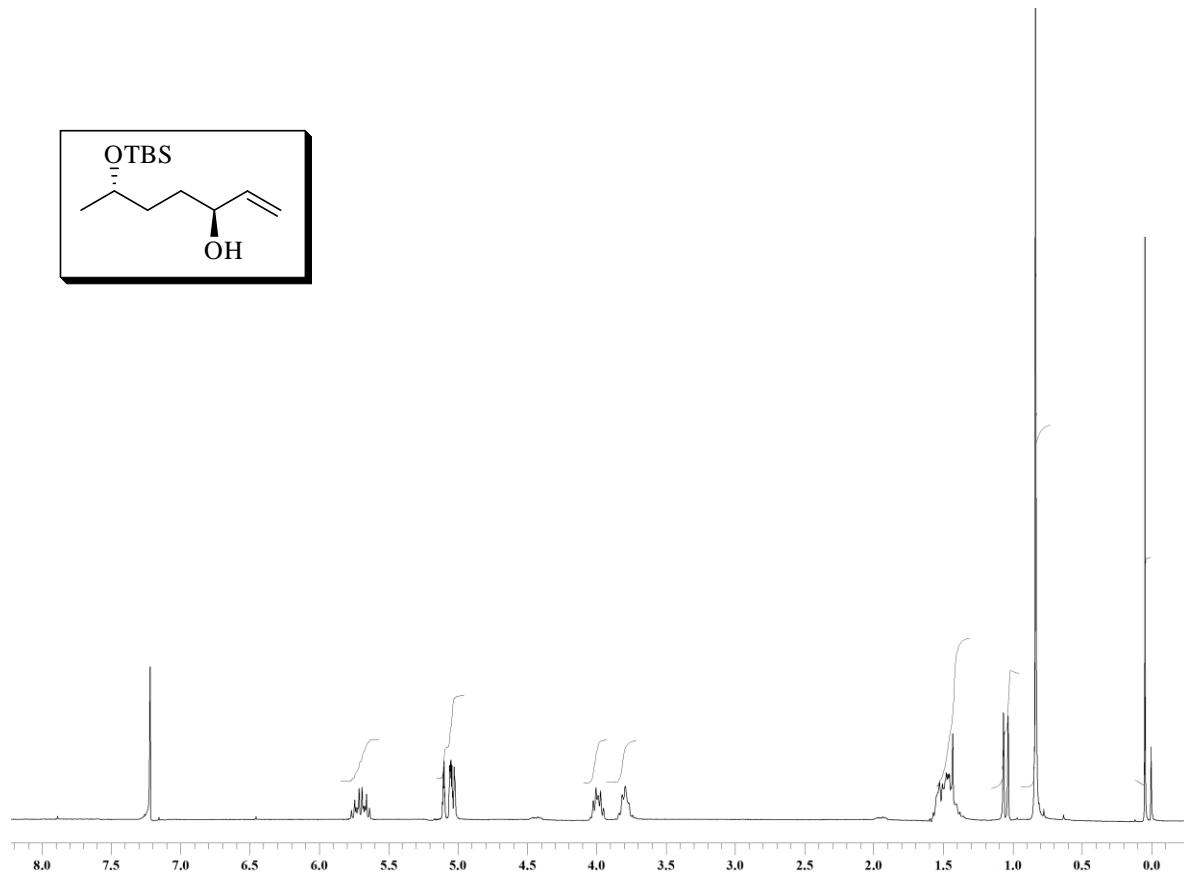


Figure S5: ^{13}C NMR Spectrum of (3*S*,6*S*)-6-(*tert*.-Butyldimethylsilyloxy)hept-1-en-3-ol (10)

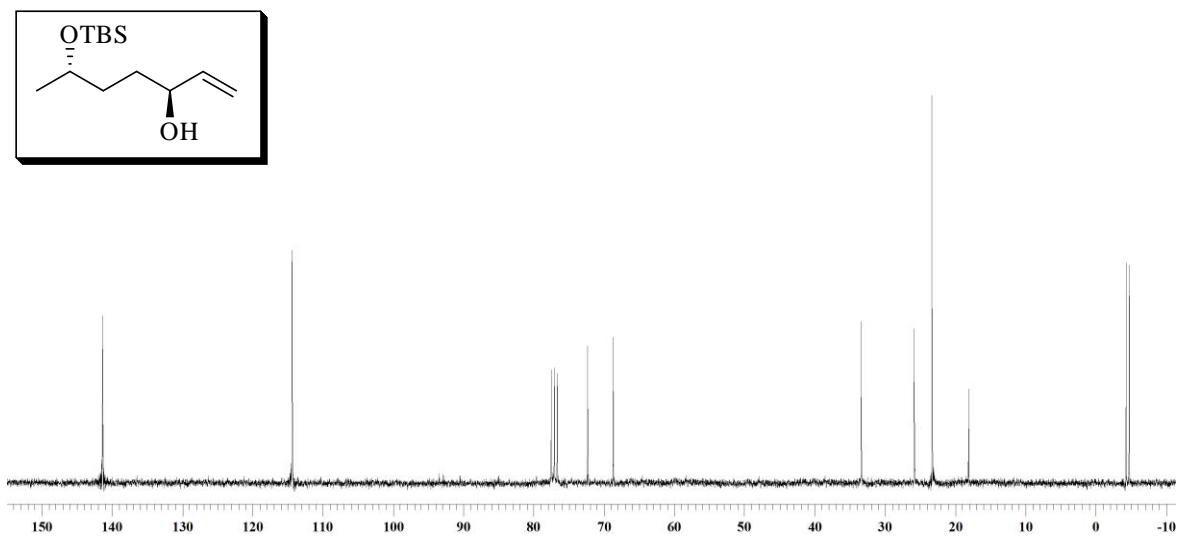


Figure S6: ^1H NMR Spectrum of *tert*-Butyl((2*S*,5*S*)-5-(benzyloxy)hept-6-en-2-yloxy)dimethyl silane (11)

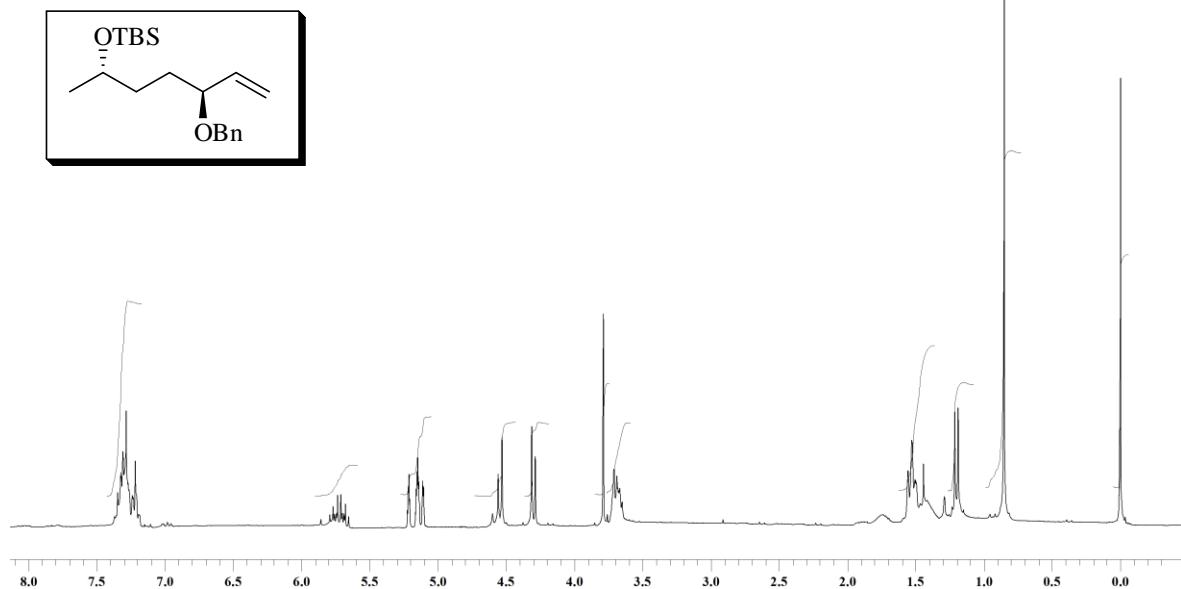


Figure S7: ^{13}C NMR Spectrum of *tert*-Butyl((2*S*,5*S*)-5-(benzyloxy)hept-6-en-2-yloxy)dimethyl silane (11)

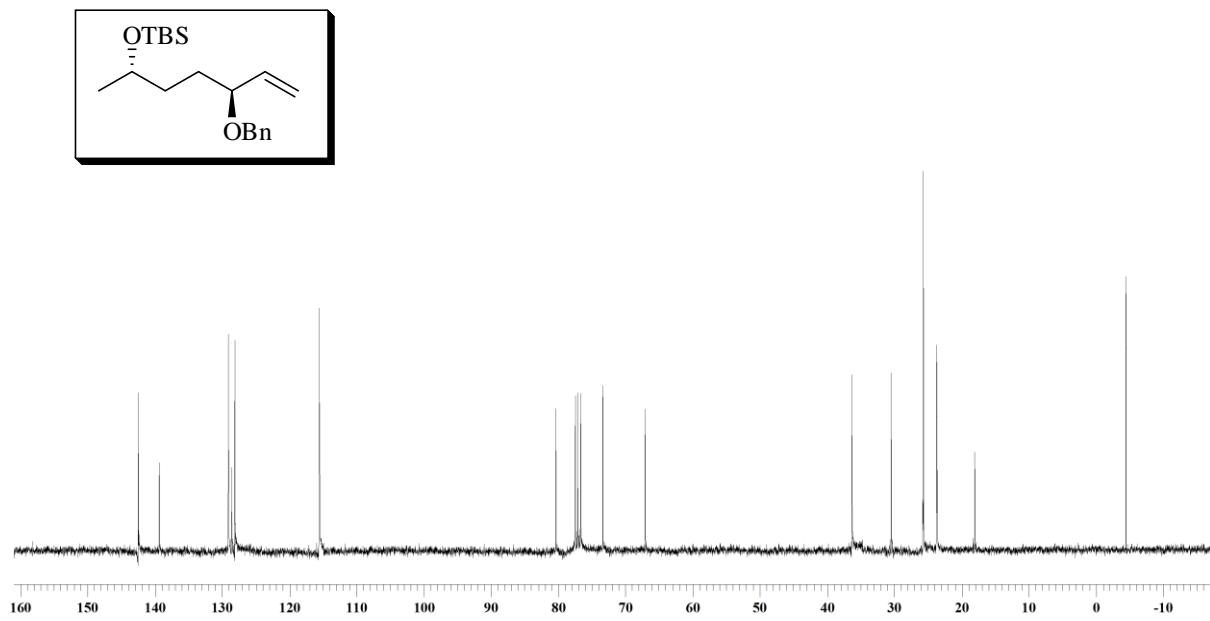


Figure S8: ^1H NMR Spectrum of (4*S*,7*S*,*E*)-Methyl 7-(*tert*.-butyldimethylsilyloxy)-4-(benzyloxy)oct-2-enoate (12)

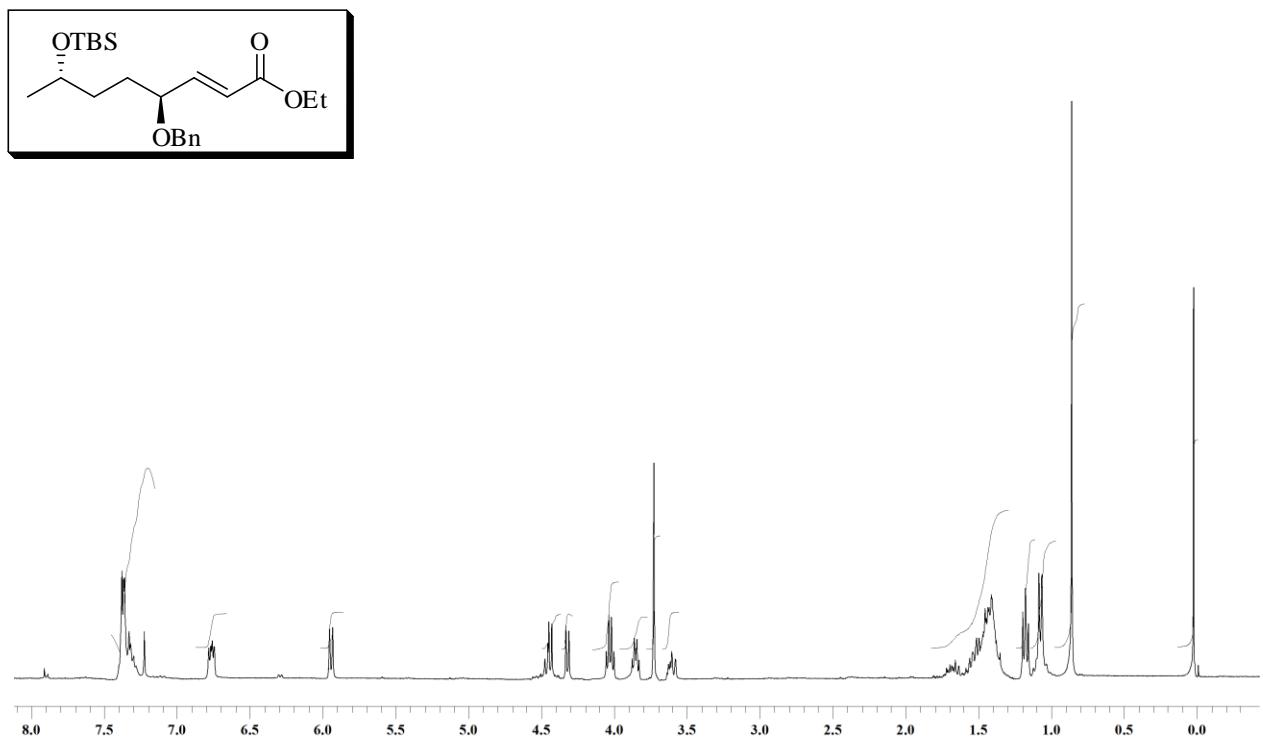


Figure S9: ^{13}C NMR Spectrum of (4*S*,7*S*,*E*)-Methyl 7-(*tert*.-butyldimethylsilyloxy)-4-(benzyloxy)oct-2-enoate (12)

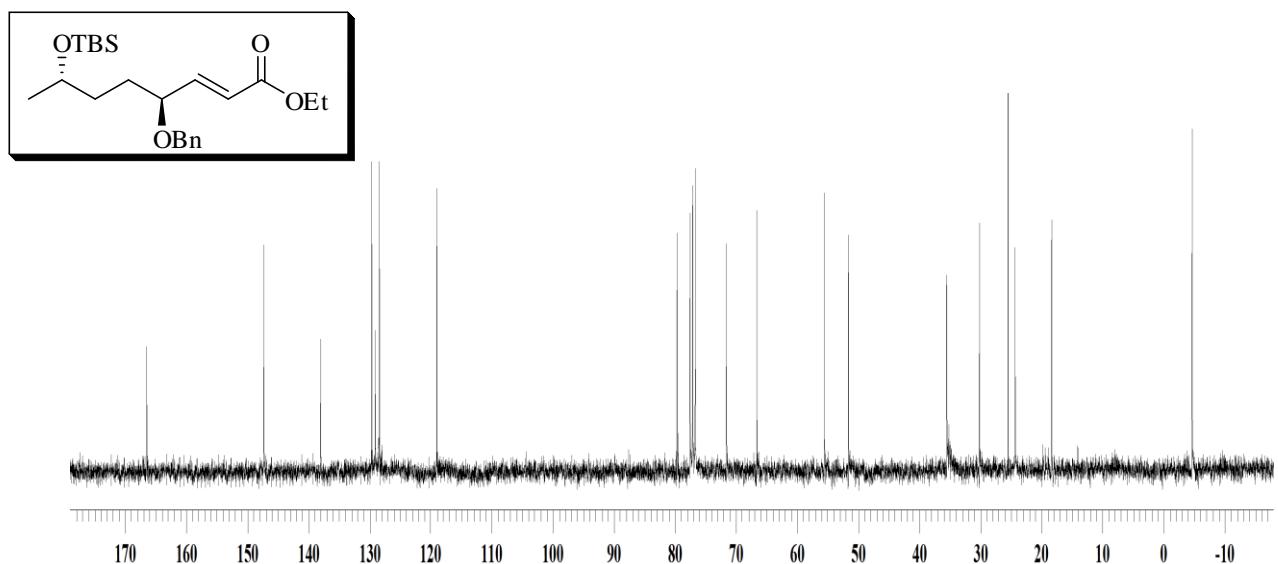


Figure S10: ^1H NMR Spectrum of (4*S*,7*S*,*E*)-7-(*tert*.-Butyldimethylsilyloxy)-4-(benzyloxy)oct-2-enoic acid (13)

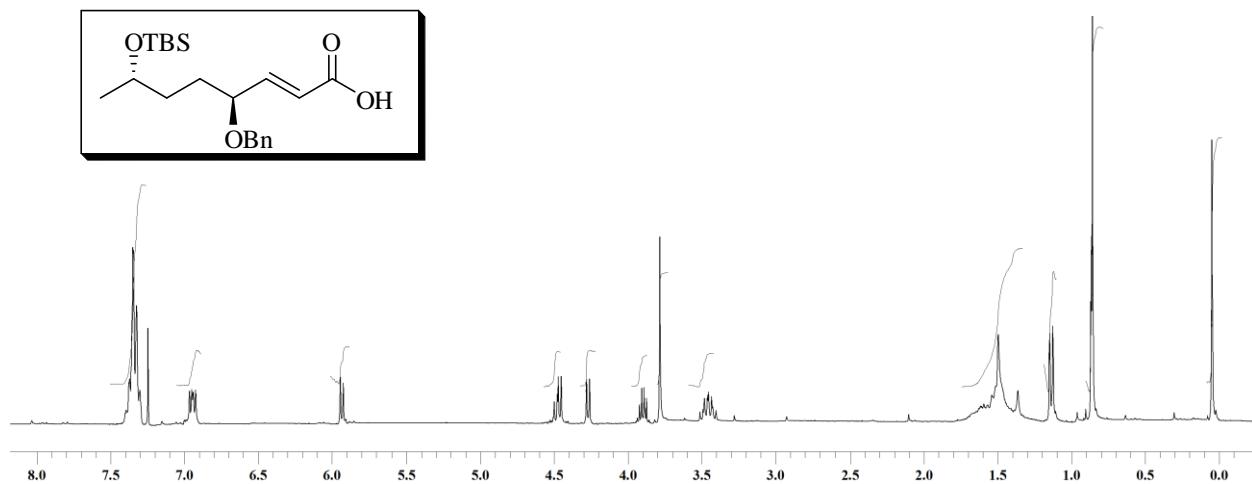


Figure S11: ^{13}C NMR Spectrum of (4*S*,7*S*,*E*)-7-(*tert*.-Butyldimethylsilyloxy)-4-(benzyloxy)oct-2-enoic acid (13)

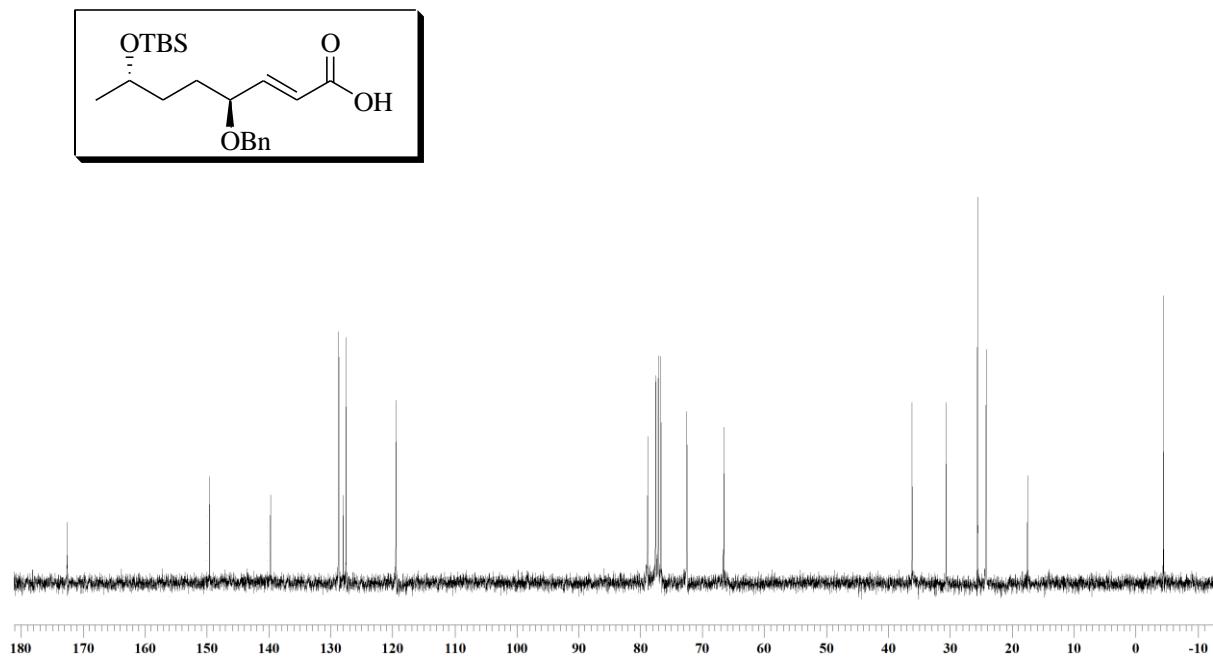


Figure S12: ^1H NMR Spectrum of (4*S*,7*S*,*E*)-7-Hydroxy-4-(benzyloxy)oct-2-enoic acid (2)

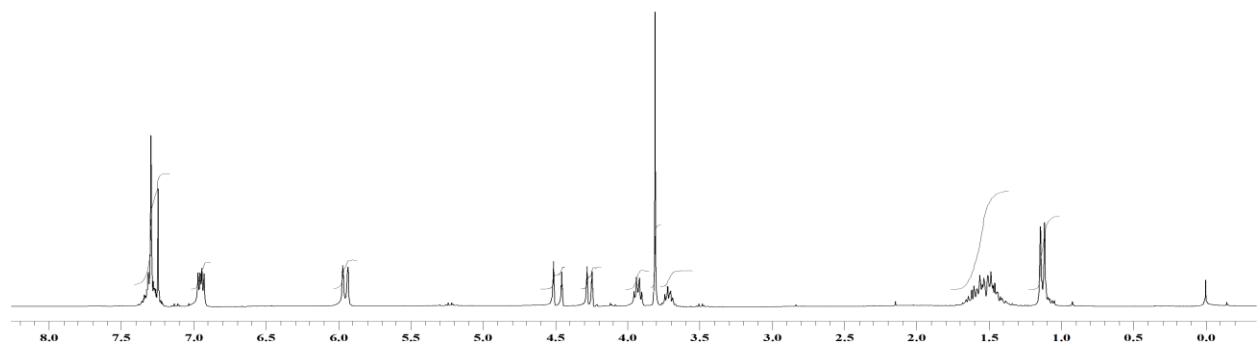
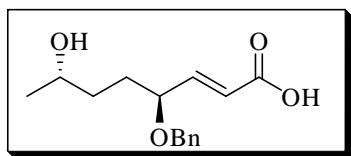


Figure S13: ^{13}C NMR Spectrum of (4*S*,7*S*,*E*)-7-Hydroxy-4-(benzyloxy)oct-2-enoic acid (2)

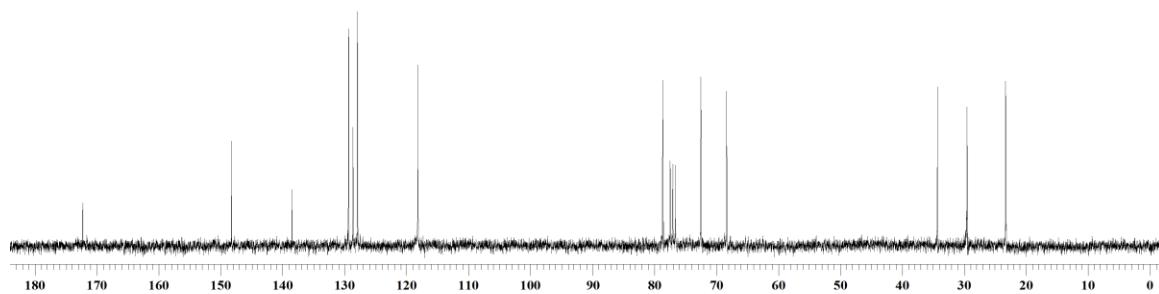
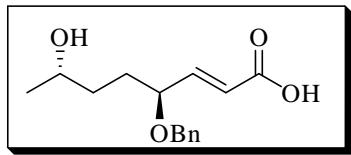


Figure S14: ^1H NMR Spectrum of (-) – Pyrenophorol (1)

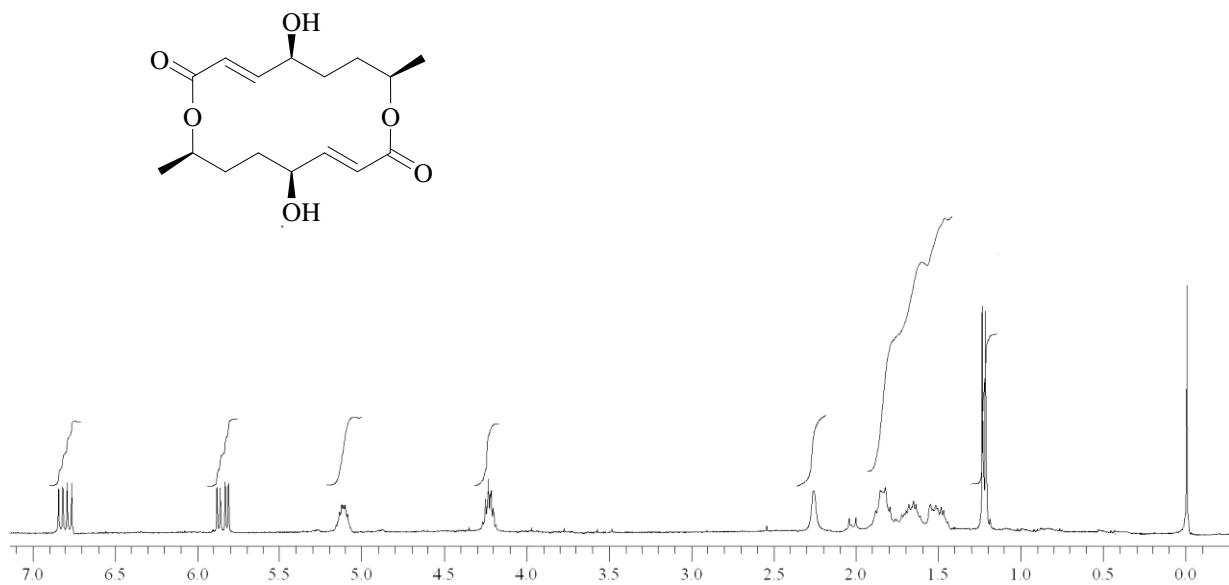


Figure S15: ^{13}C NMR Spectrum of (-) – Pyrenophorol (1)

