Supporting information for Total Synthesis of (–)-18-*epi*-Peloruside A: An Alkyne Linchpin Strategy.

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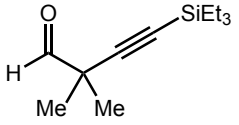
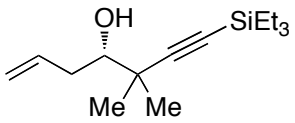
General Information:

All reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glassware with magnetic stirring, unless otherwise indicated. Solvents were dried by J. C. Meyer's Solvent Purification System. (*R,R*)- and (*S,S*)-Prophenol ligands was obtained from Sigma-Aldrich. Molecular sieves (4Å) were dried by heating with a propane torch in a round bottom flask under hi-vacuum (0.3 torr) for 5 minutes. Flash Chromatography was performed with EM Science silica gel (0.040-0.063μm grade). Analytical thin-layer chromatography was performed with 0.25 mm coated commercial silica gel plates (E. Merck, DC-Plastikfolien, kieselgel 60 F254). Proton nuclear magnetic resonance (^{1}H-NMR) data were acquired on a Mercury 400 (400 MHz), on a Varian Unity Inova-500 (500 MHz), or on a Varian Inova-600 (600 MHz) Spectrometer. Chemical shifts are reported in delta (δ) units, in parts per million (ppm) downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet, m, multiplet, br, broad. Carbon-13 nuclear magnetic resonance (^{13}C-NMR) data were acquired at 100 MHz on a Mercury 400, at 125 MHz on a Varian Unity Inova 500, or at 150 MHz on a Varion Inova-600 spectrometer. Chemical shifts are reported in ppm relative to the center line of a triplet at 77.23 ppm for chloroform-*d*. Infrared (IR) data were recorded as films on sodium chloride plates on a Thermo Scientific Nicolet IR100 FT-IR spectrometer. Absorbance frequencies are reported in reciprocal centimeters (cm^{-1}). Chiral HPLC analyses were performed on a Themo Separation Products Spectra Series P-100 or 200 and UV100 (254 nm) using Chiralcel® columns (OD-H, OB-H, OJ, AD, AS, OC, IA, IB or IC) eluting with heptane / *iso*-propanol mixtures indicated. Optical rotations were measured on a Jasco P-2000 digital polarimeter using 5 cm cells and the sodium D line (589 nm) at ambient temperature in the solvent and concentration indicated.

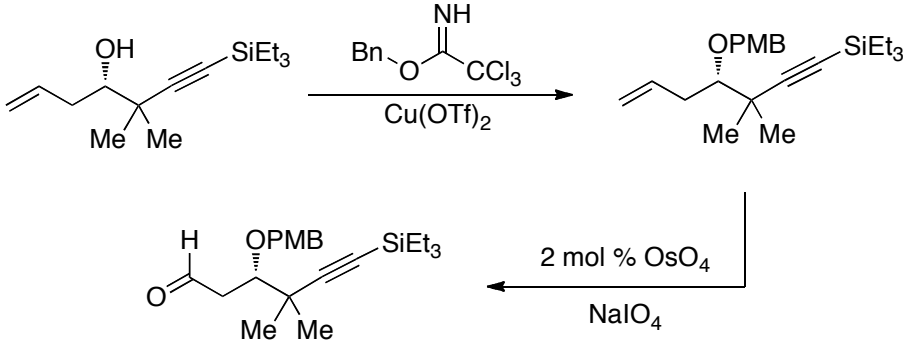


2,2-dimethyl-4-(triethylsilyl)but-3-ynal (7): 3-methyl propyne (1.5 ml, 14.7 mmol) was dissolved in Et_2O (12.5 ml) and the solution was cooled to -20 °C , n-BuLi (13 ml, 2.25 M in hexane, 29.4 mmol) was added, followed by TMEDA (2.2 ml, 14.7 mmol). The off white suspension was heated to 55 °C for 16 hours to give an orange solution. The reaction was cooled to – 78 °C and a solution of DMF (1.14 ml, 14. 7 mmol) in THF (20 ml + 4 ml for rinsing) was added via cannula, resulting in almost complete decoloration. The reaction was stirred at –78 °C for 11 h. TESCl (1.24 ml, 7.35 mmol) was added dropwise and the reaction was warmed to room temperature over 12 hours and then heated to 45 °C for 3 h. Saturated $NaHSO_4$ (20 ml) was added, the reaction was stirred vigorously for 25 minutes and then extracted with Et_2O. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (100 % petroleum ether –> 10 % Et_2O/petroleum ether) to give 2.0 g (66 %) of the title compound. TLC R_f = 0.65 (20% ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (s, 1H), 1.31 (s, 6H), 0.96 (t, J = 8.1 Hz, 9H), 0.56 (q, J = 8.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ 198.3, 107.6, 86.7, 43.7, 23.1, 7.6, 4.4; IR (thin film): νmax 2957, 2876, 2806, 2173, 1737, 1458, 1415, 1227, 1016, 975, 895, 774, 727 cm^{-1}.

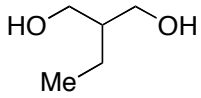


(*S*)-5,5-dimethyl-7-(triethylsilyl)hept-1-en-6-yn-4-ol (S5): To a solution of aldehyde **7** (128 mg, 0.51 mmol) in diethyl ether (2.0 mL) was added a commercially available solution of (−)-B-allyldiisopinocampheylborane (0.5 ml of a 1M solution in pentane) at -78 ºC. The reaction mixture was stirred at -78 ºC for 4h. The reaction mixture was quenched with methanol (0.25 mL), warmed to room temperature, and concentrated. The resulting oil is dissolved in 1:1 THF:pH 7 buffer and sodium perborate (405 mg, 4.07 mmol) is added. The reaction mixture is stirred at room temperature for 24 h, diluted with diethyl ether (10 mL) and poured into a separatory funnel. The organic layer is collected and the aqueous layer is extracted with diethyl ether (3 x 5 mL). The organic layers are combined, filtered through a pipette charged with sodium chloride, and the eluent is concentrated under reduced pressure. Silica gel chromatography using 10% Et_2O/hexanes afforded 115 mg (89%) the desired product as a colorless oil. TLC R_f = 0.33 (10% Et_2O/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (dddd, *J* = 17.2, 10.1, 7.4, 6.3 Hz, 1H), 5.16-5.10 (m, 1H), 3.40-3.36 (d, *J* = 10 Hz, 1H), 2.53-2.46 (m, 1H), 2.20-2.11 (m, 1H), 1.84 (d, *J* = 5.8 Hz, 1H), 1.24 (s, 3H), 1.21 (s, 3H), 0.97 (t, *J* = 8.2 Hz, 9H), 0.57 (q, *J* = 8.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 117.2, 113.1, 83.3, 76.7, 37.8, 36.9, 25.3, 25.0, 7.5, 4.5 ppm; IR (thin film): ν_{max} 3478, 2956, 2876, 2161, 1017, 726 cm^{-1}; Tr = 7.3 and 7.7 (major) (minor) (Chiracel® AD Chiral HPLC, λ = 210 nm, heptane:*i*-PrOH = 99.8:0.2, 0.8 mL/min).

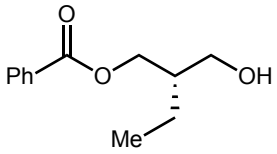


(*S*)-3-(4-methoxybenzyloxy)-4,4-dimethyl-6-(triethylsilyl)hex-5-ynal (5): (*S*)-triethyl(4-(4-methoxybenzyloxy)-3,3-dimethylhept-6-en-1-ynyl)silane: To a solution of alcohol (115 mg, 0.46 mmol) and *p*-methoxybenzyl trichloroacetimidate (182 mg, 0.720 mmol, 1.56 equiv) in toluene (10 mL) was added $Cu(OTf)_2$ (17 mg, 0.046 mmol, 0.1 equiv). The resulting mixture was stirred at room temperature for 10 h, filtered through a pipette containing silica gel eluting with 30% diethyl ether/hexanes. The eluent was concentrated and carried directly to the next step. To the resulting oil in 3:1 dioxane:H_2O (4.0 mL total volume) in a test tube was added 2,6-lutidine (96 mg, 0.89 mmol), OsO_4 (50 uL, 4% w/v in H_2O, 0.0082 mmol, 0.02 equiv), and $NaIO_4$ (350 mg, 1.64 mmol). The reaction was stirred for 1h, quenched with concentrated aqueous sodium sulfite (1.0 mL), and diluted with methylene chloride (5.0 mL). The bottom layer was pipetted out of the tube and additional methylene chloride (2.0 mL) was added. The organic layers were combined and concentrated. Silica gel chromatography using a gradient of 5-15% EtOAc/hexanes afforded 100 mg (58% over two steps) of the desired product as a colorless oil. TLC R_f = 0.45 (20% EtOAc/hexanes – CAM stain); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (dd, *J* = 2.3, 1.3 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 4.60 (d, *J* = 10.8 Hz, 1H), 4.56 (d, *J* = 10.8 Hz, 1H), 3.91 (dd, *J* = 7.8, 3.5 Hz, 1H), 3.80 (s, 3H), 2.93 (ddd, *J* = 17.1, 3.4, 1.3 Hz, 1H), 2.74 (ddd, *J* = 17.1, 7.9, 2.3 Hz, 1H), 1.29 (s, 3H), 1.20 (s, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.55 (q, *J* = 7.9 Hz, 6H) ppm; ^{13}C NMR

(100 MHz, $CDCl_3$): δ 201.0, 159.3, 130.5, 129.4, 113.8, 113.8, 83.4, 79.8, 73.6, 55.4, 46.8, 37.4, 27.0, 23.8, 7.7, 4.6 ppm.

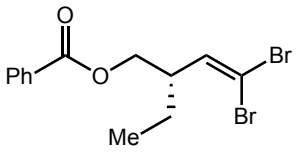


2-ethylpropane-1,3-diol (8): Solid $LiAlH_4$ (12.0 g, 0.32 mol) and anhydrous hexanes (100 mL) were sequentially added to a two-neck 1L flame-dried round bottomed flask charged with a reflux condenser. To this mixture was added anhydrous THF (200 mL) (the addition of anhydrous THF directly to solid $LiAlH_4$ causes rapid gas evolution, however, the process is controlled when hexanes is first added). To this suspension is added 2-ethyl-diethylmalonate (40 g, 0.212 mol) via syringe pump over 2h (caution: exothermic). Upon complete addition, the thick gray suspension is warmed to 60 ºC, and stirred for 12h. The suspension is diluted with THF (500 mL), cooled to 0 ºC, and finely ground Na_2SO_4•$10H_2O$ (100-150 g) is carefully added. The reaction is stirred for 3-4h until the gray suspension has completely turned into a fluffy white solid. The reaction mixture is poured through a sintered glass funnel, concentrated, and purified by vacuum distillation to afford 16.6 g (75%) of the desired product as a colorless oil. Spectral data matches literature results.[1] ^{1}H NMR (400 MHz, $CDCl_3$); δ 3.87-3.80 (m, 2H), 3.72-3.64 (m, 2H), 2.16 (t, J = 4.5 Hz, 2H), 1.75-1.65 (m, 1H), 1.31 (dq, J = 7.3, 7.3 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H). IR (neat): ν_{max} 3340, 2960, 2930, 2877, 1042 cm^{-1}.



(*S*)-2-(hydroxymethyl)butyl benzoate (9): *Preparation of the dinuclear zinc catalyst*: Diethyl zinc (1.92 mL, 1.92 mmol, 1.0 M in toluene) was added dropwise to a solution of (*S*,*S*)-ProPhenol ligand (613 mg, 0.96 mmol) in anhydrous toluene (37 mL) while stirring under nitrogen. The light yellow catalyst solution (0.026 M) was stirred for 30 min at room temperature and then transferred to the reaction mixture via cannula.

Asymmetric Desymmetrization: To a flame dried tube containing 2-ethyl-propane-1,3-diol (2.0 g, 19.2 mmol) and vinyl benzoate (14.22 g, 96.0 mmol) at room temperature, was added anhydrous toluene (120 mL). To this solution was added a stock solution of the pre-prepared catalyst at -78 ºC under a positive flow of nitrogen. The reaction was sealed and stirred at -20 ºC for 36h (stirring was essential to the yield of the reaction as the reaction is heterogeneous at this temperature, when the reaction was conducted at -20 ºC without stirring, similar enantioselectivity was obtained, however, significantly lowered yields were observed). The crude product was directly applied to a silica gel column, and eluted with 20% → 50% ethyl acetate/hexanes to afford 3.99 g (100%, 86% ee) of the desired product as a light yellow oil. When conducted on 10.04 g (96.5 mmol), 17.93 g product isolated, 89% yield, 86% ee R_f = 0.44 (50% ethyl acetate/hexanes); $[\alpha]_{25}^{D}$ -1.89 (86% ee, c. 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (dd, J = 8.4, 1.4 Hz, 2H), 7.60 (tt, J = 7.4, 1.4 Hz, 1H), 7.48 (dt, J = 8.4, 7.4 Hz, 2H), 4.51 (dd, J = 11.2, 4.3 Hz, 1H), 4.39 (dd, J = 11.2, 6.3 Hz, 1H), 3.71 (m, 1H), 3.63 (m, 1H), 2.05 (t, J = 6.3 Hz, 1H), 1.90 (m, 1H), 1.50 (m, 2H), 1.02 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 133.4, 130.3, 129.9, 128.7, 64.9, 62.6, 42.7, 21.1, 11.8; IR (neat): ν_{max} 3332, 2963, 2932, 2879, 1719, 1464, 1381, 1044, 1008, 969, 767 cm^{-1}; Tr = 18.3 and 21.6 min (major) (Chiralcel® OBH Chiral HPLC, λ = 254 nm, heptane:*i*-PrOH = 98:2, 0.8 mL/min); ee = 86%. Elemental Analysis Theoretical C69.21, H7.74 Found C69.19, H7.60. values matched those previously reported.[2]



(*S*)-4,4-dibromo-2-ethylbut-3-en-1-yl benzoate (10): *Oxidation of alcohol*: To a flask with 2-(hydroxymethyl)butyl benzoate (7.99 g, 38.4 mmol) dissolved in dichloromethane (50 mL) was added iodobenzene diacetate (14.54 g, 45.1 mmol, 1.18 equiv) and TEMPO (640 mg, 4.10 mmol, 0.11 equiv) at room temperature. The reaction was stirred for 3h (monitored by TLC using 20% ethyl acetate/hexanes) and concentrated to ~ 6 mL. Silica gel chromatography using a gradient of 5-10% ethyl acetate/hexanes afforded the desired compound, which was immediately taken forward to the next step. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.77 (d, *J* = 2.0 Hz, 1H), 7.99 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.56 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.43 (dd, *J* = 8.0 Hz, 2H), 4.58 (dd, *J* = 11.5, 7.0 Hz, 1H), 4.55 (dd, *J* = 11.5, 5.0 Hz, 1H), 2.73-2.66 (m, 1H), 1.90-1.80 (m, 1H), 1.70-1.62 (m, 1H), 1.04 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.1, 166.0, 132.9, 129.3, 129.3, 128.1, 62.1, 52.3, 18.7, 11.0; IR (neat): ν_{max} 3065, 2967, 2939, 2879, 2729, 1728, 1602, 1453, 1378, 1315, 1273, 1177, 1112, 1071, 1027, 712 cm^{-1}.

Corey-Fuchs Olefination: To a solution of triphenylphosphine (41 g, 156.3, 4.1 equiv) dissolved in CH_2Cl_2 (300 mL) was added carbon tetrabromide (23.5 g, 78.15 mmol, 2 equiv) at 0 ºC. The solution was stirred 30 min at 0 ºC and to the solution was added neat product from above. The reaction was stirred 4h, concentrated, and passed through a plug of silica gel eluting with 5% ethyl acetate/hexanes. The filtrate containing the desired product was concentrated and chromatographed using 2.5% diethyl ether/hexanes to afford 11.93 g (86%) of the desired product as a white solid. R_f = 0.69 (20% ether:hexanes – UV active); m.p. = 48-50 ºC; $[\alpha]_D^{25}$ +17.8 (c. 1.61, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06-8.03 (m, 2H), 7.59-7.55 (m, 1H), 7.48-7.43 (m, 2H), 6.32 (d, *J* = 9.6 Hz, 1H), 4.30 (dd, *J* = 10.9, 5.6 Hz, 1H), 4.23 (dd, *J* = 10.9, 7.2 Hz, 1H), 2.83 (m, 1H), 1.69-1.59 (m, 1H), 1.52-1.43 (m, 1H), 0.99 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 139.1, 133.0, 129.9, 129.6, 128.4, 90.7, 65.7, 44.8, 23.7, 11.4; IR (neat): $\acute{\imath}_{max}$ 2963, 1721, 1452, 1314, 1271, 1111, 1070, 769, 710 cm^{-1}.

(*R*)-4,4-dibromo-2-ethylbut-3-en-1-yl benzoate (*ent*-10*)*: Prepared according to the proceedure described above. (*R*,*R*)-ProPhenol ligand was employed in the desymmetrization reaction, providing the diol product in 86% ee. Subsequent conversion to the dibromoolefin as described above provided *ent*-**10**. $[\alpha]_D^{24}$ –16.9 (c. 1.6, EtOAc)

Determination of absolute configuration of desymmetrization reaction:

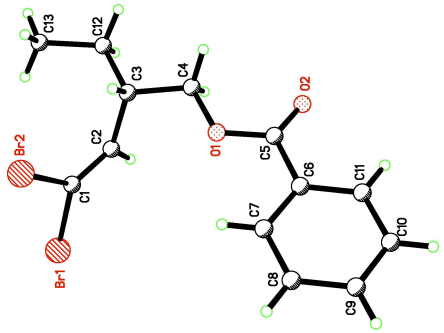
To confirm the absolute configuration of the desymmetrization reaction, we initially performed a synthetic study to intercept an intermediate (**S3**) from the De Brabander synthesis of (–)-peloruside A.[3] Since De Brabander synthesized the enantiomer of the natural product, we employed the dibromoolefin obtained from desymmetrization with the (*R*,*R*)-Prophenol catalyst, which we believed would provide the ethyl stereocenter matching that from the De Brabander synthesis. Thus, conversion of our dibromoolefin into (*R*,*Z*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methylhept-3-en-2-one (**S3**) was accomplished as described below. When the optical rotation of our product matched that from the De Brabander synthesis, we believed that the (*R,R*)-Prophenol catalyst did indeed generate the undesired ethyl stereocenter. Later studies, in fact, proved this analogy to be incorrect.

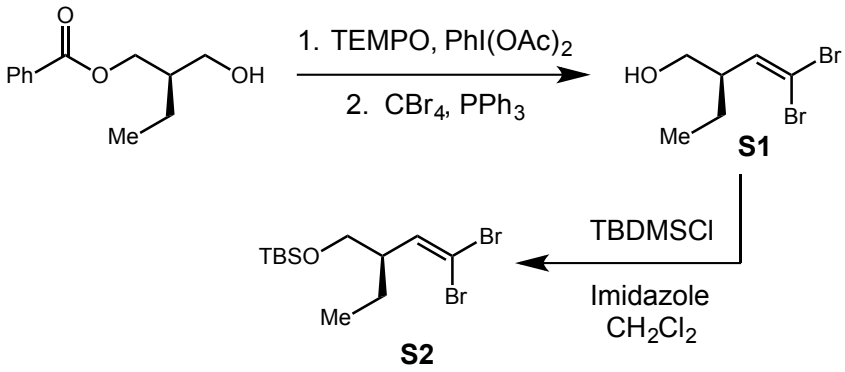
Finding discrepancies in the spectra of our final product from those of the natural product, we re-purified **S3** and obtained an optical rotation of -0.54, suggesting that our analysis had been incorrect. When **S3** was re-synthesized from the dibromoolefin obtained from the (*S,S*)-Prophenol catalyst, an $[\alpha]_D$

of +50.6 was obtained. This suggested that the (*S,S*)-Prophenol ligand in fact produced the same stereocenter as obtained in the De Brabander synthesis, and thus the wrong stereocenter for the natural enantiomer of the natural product.

In order to clear up these discrepancies, a single crystal X-ray analysis was performed on the dibromoolefin. This analysis confirmed that the ethyl stereocenter obtained from the (*S,S*)-Prophenol was indeed of the (*S*) configuration, and thus the wrong stereocenter for the synthesis of the natural isomer of peloruside A (Figure S1). This led to the synthesis of (–)-18-*epi*-peloruside A.

Figure S1. Single crystal X-ray analysis of dibromide **7** obtained from desymmetrization with (*S,S*)-Prophenol.

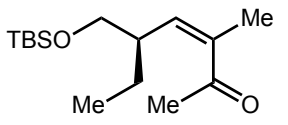




(*R*)-4,4-dibromo-2-ethylbut-3-en-1-ol (S1): To a solution of (*R*)-4,4-dibromo-2-ethylbut-3-en-1-yl benzoate (535 mg, 1.48 mmol) in methanol (10 mL) was added finely powdered K_2CO_3 (80 mg, 0.58 mmol). The reaction was stirred at room temperature for 12h, concentrated to ~ 2 mL, diluted with 30 mL ethyl acetate, and washed with saturated aqueous NH_4Cl. The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. Silica gel chromatography using 50 % ethyl acetate/hexanes afforded 351 mg (92%) of the desired compound as a clear oil. This product was directly taken forward to the next step.

(*R*)-tert-butyl((4,4-dibromo-2-ethylbut-3-en-1-yl)oxy)dimethylsilane (S2): To a solution of alcohol (319 mg, 1.25 mmol) in dichloromethane (10 mL) was added *tert*-butyldimethylchlorosilane (226 mg, 1.50 mmol) and imidazole (119 mg, 1.75 mmol). The reaction mixture was stirred at room temperature for 24h, diluted with dichloromethane (10 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Silica gel chromatography using a gradient of 0.5-1% diethyl ether/hexanes afforded 410 mg (89%) of the desired product as a clear oil. R_f = 0.8 (5% diethyl ether/hexanes – $KMnO_4$ stain); $[\alpha]_D^{25}$ +0.4 (c. 1.42, EtOAc); $[\alpha]_D^{25}$ +0.4 (c. 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.24 (d, *J* = 9.8 Hz, 1H), 3.55 (d, *J* = 5.8 Hz, 2H), 2.45 (m, 1H), 1.57 (m, 1H), 1.33 (m, 1H), 0.91 (t, *J* = 8.5 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0, 89.2, 64.6, 48.3, 26.1, 23.6, 18.5, 11.7, -5.2, -5.2 ppm; IR (neat): í$_{max}$ 2958, 2885, 2858, 1461, 1257, 1105, 835, 775 cm^{-1}; HRMS (ES$^+$) calcd for $C_{12}H_{25}Br_2OSi^+$ [M+H$^+$] calculated 371.0041 found 370.9856 (MNa$^+$).



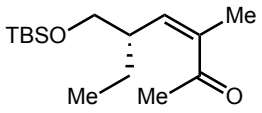
S3

α_D = +12, C = 0.1, $CHCl_3$

α_D = + 18, C = 0.1, $CHCl_3$ (lit. for enantiomer)

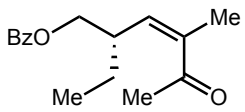
α_D = -0.47, C = 0.1, CHCl
(after re-purification)

(*R*,*Z*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methylhept-3-en-2-one (S3): To a suspension of CuI (77 mg, 0.41 mmol, 3 equiv) in diethyl ether (0.3 mL) was added a solution of methyllithium (500 uL of a 1.6 M solution in diethyl ether, 6 equiv) at -10 ºC. During this time the solution turned from a white suspension to a deep yellow suspension to a clear solution. The reaction was stirred at -10 ºC for 20 minutes, cooled to -78 ºC and to the reaction was added (*S*)-4,4-dibromo-2-ethylbut-3-en-1-ol (50 mg, ~38 uL, 0.135 mmol). The solution was stirred at -78 ºC for 1h and quenched with neat acetyl bromide (133 mg, 1.08 mmol, 8.0 equiv). The reaction was stirred at -78 ºC for 2h. The thick suspension was quenched by adding it into a rapidly stirring 1:1 mixture of diethyl ether/saturated $NaHCO_3$ (40 mL). The flask was quickly rinsed with an additional 20 mL of this mixture. The suspension was filtered through sand and concentrated under reduced pressure. Crude ^{1}H NMR analysis revealed a 5:1 mixture of the desired and undesired *Z* and *E* olefin isomers. The crude mixture was chromatographed using Chlorosil® and 5% ethyl acetate/hexanes to afford 17 mg (46%) of the desired product as a clear oil. R_f = 0.66 (20% EtOAc/hexanes – $KMnO_4$ stain); $[\alpha]_D^{25}$ +12.0 (c. 0.1, $CHCl_3$), -0.54 after repurification; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.44 (dq, *J* = 10.8, 1.6 Hz, 1H), 3.52 (d, *J* = 6.0 Hz, 2H), 2.76 (m, 1H), 2.28 (s, 3H), 1.95 (d, *J* = 1.6 Hz, 3H), 1.58-1.46 (m, 1H), 1.26-1.12 (m, 1H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H) ppm. Spectra were in agreement with previously reported values.[2]



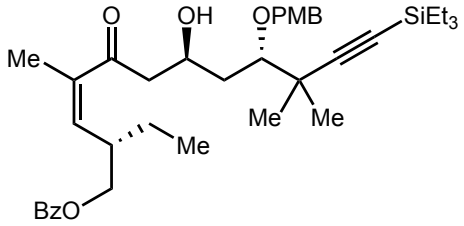
S4

(*S*,*Z*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methylhept-3-en-2-one (S4): Prepared as described using the dibromoolefin (after recrystallization from hexanes, 99% ee) obtained from desymmetrization using the (*S,S*)-Prophenol ligand. $[\alpha]_D^{25}$ +50.6 (c. 0.2, $CHCl_3$);



(*S*,*Z*)-2-ethyl-4-methyl-5-oxohex-3-enyl benzoate (*ent*-4): To a suspension of copper iodide (4.024 g, 21.13 mmol, 3 equiv) in anhydrous diethyl ether (26.5 mL) was added methyllithium (26.5 mL of a 1.6 M solution in diethyl ether, 6.0 equiv) at -20 ºC. The reaction was stirred at -20 ºC for 30 min, cooled to -78 ºC, and to it was added a solution of (*S*)-4,4-dibromo-2-ethylbut-3-enyl benzoate (2.55 g, 7.04 mmol) in diethyl ether (7.54 mL) dropwise over 10 minutes. The reaction was stirred at -78 ºC for 45 minutes. The resulting organge slurry was added via cannula to a 250ml round bottom containing acetyl bromide (5.2 ml, 70.4 mmol, 10 equiv) in THF (42 ml) at -78 ºC. Note: The THF solution of Acetyl bromide was prepared by addition of acetyl bromide to 42 ml of THF at -78 ºC. Acetyl bromide causes ring-opening of THF at room temperature. The reaction mixture was stirred at -78 ºC for 2h and quenched by adding

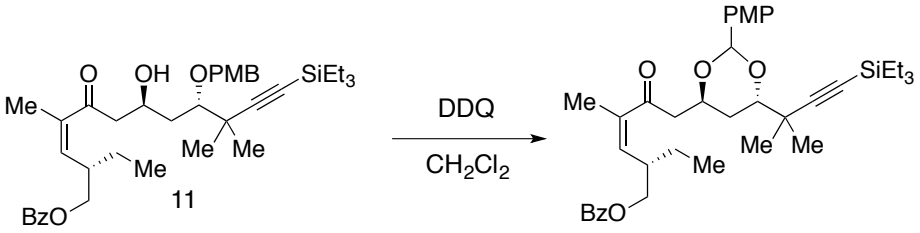
saturated aqueous $NaHCO_3$ (20 ml) and the semi-frozen mixture was immediately poured directly into a 500 mL Erlenmeyer flask containing 400 mL of 1:1 diethyl ether: saturated aqueous $NaHCO_3$ at 0 ºC. The white suspension was stirred for 5 min and filtered through a bed of sand using a fritted funnel. The filtrate was poured into a separatory funnel and the organic layer was collected. The aqueous layer was extracted with diethyl ether (2 x 150 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. Silica gel chromatography using 10:1 then 8:1 hexanes:diethyl ether afforded 1.51 g (83%) of the desired product as a light yellow oil. (with 6.93 g dibromoolefine, 18.9 mmol scale = 3.72 g, 75% yield, using 12.0 g dibromoolefin, 33 mmol scale = 6.08 g, 71% yield). $[\alpha]_{28}^{D}$ -14.0 (c. = 1.0, $CHCl_3$, +12.1 – *R* enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 2H), 5.47 (dq, *J* = 10.3, 1.4 Hz, 1H), 4.23 (d, *J* = 6.2 Hz, 2H), 3.2-3.08 (m, 1H), 2.23 (s, 3H), 1.96 (d, *J* = 1.4 Hz, 3H), 1.67-1.55 (m, 1H), 1.43-1.31 (m, 1H), 0.92 (t, *J* = 7.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.1, 166.5, 137.8, 137.8, 132.9, 130.3, 129.5, 128.3, 67.5, 39.8, 29.9, 29.7, 24.8, 21.1, 11.5 ppm; IR (neat): $\acute{\imath}_{max}$ 2963, 2929, 2358, 1720, 1670, 1270, 1111 cm^{-1}; HRMS (ES^+) calcd for $C_{16}H_{20}NaO_3^+$ 283.1310 found 283.1317 (MNa^+).



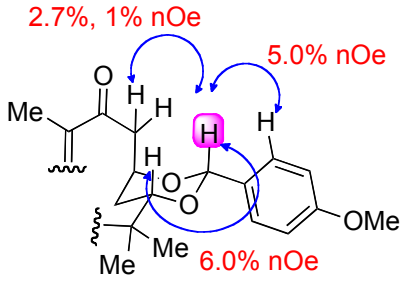
(2*R*,7*S*,9*S*,*E*)-2-ethyl-7-hydroxy-9-(4-methoxybenzyloxy)-4,10,10-trimethyl-5-oxo-12-(triethylsilyl)dodec-3-en-11-ynyl benzoate (11): *Preparation of LDA*: To a solution of Diisopropylamine (200 uL, 1.42 mmol) in toluene (0.86 mL) was added a solution of *n*-butyllithium (0.712 uL of a 2.0 M solution in hexanes) at 0 ºC. The reaction was stirred at 0 ºC for 30 min prior to use. This provided a 0.8 M solution of LDA in toluene.

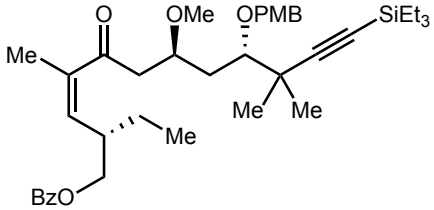
Aldol addition: LDA (1.85 mL of a 0.8 M solution in toluene) was added to a solution of enone ***ent*-4** (350 mg, 0.85 mmol) in toluene (7.8 mL) at -78 ºC. After stirring at this temperature for 45 min the solution was transferred via cannula to a suspension of aldehyde **5** (504 mg, 1.34 mmol) and zinc chloride (184 mg, 0.845 mmol) in toluene (4.95 mL) and 3 ml CH_2Cl_2 cosolvent at -78 ºC. The mixture was stirred at -78 ºC for 45 minutes, quenched by rapidly adding pH 7 buffer and the bath was removed. The resulting mixture was diluted with additional pH 7 buffer (5 mL) and EtOAc (20 mL) and poured into a separatory funnel. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. *Based on crude NMR integration a 4:1 ratio of diastereomers was obtained. The determination was based upon comparison of NMR d 2.62 (dd, J = 17.9, 9.0 Hz, 1H) ppm – undesired diastereisomer to d 2.32 (dd, J = 17.9, 9.0 Hz, 1H) ppm – desired diastereisomer.* Silica gel chromatography using 2% ethyl acetate/toluene afforded 642 mg (74%) of the desired product – this yield represents the isolated yield of the desired product only. TLC R_f = 0.29 in 2% ethyl acetate/benzene (major) and R_f = 0.17 in 2% ethyl acetate/ benzene (minor); ^{1}H NMR (400 MHz; C_6D_6): δ 8.08-8.05 (m, 2H), 7.29 (d, *J* = 8.7 Hz, 1H), 7.07-7.05 (m, 4H), 6.75 (d, *J* = 8.7 Hz, 2H), 5.50 (dd, J = 10.3, 1.5 Hz, 1H), 4.70 (s, 3H), 4.39-4.33 (m, 1H), 4.15 (dd, *J* = 10.8, 7.3, 1H), 4.07 (dd, *J* = 10.8, 5.5 Hz, 1H), 3.89 (dd, *J* = 10.4, 1.7 Hz, 1H), 3.47 (d, *J* = 2.2 Hz, 1H), 3.26 (s, 3H), 3.22-3.14 (m, 1H), 2.32 (dd, *J* = 17.9, 9.0 Hz, 1H), 2.19 (dd, *J* = 17.9, 2.6 Hz, 1H), 1.44 (d, *J* = 1.5 Hz, 3H), 1.40-1.42 (m, 1H), 1.32 (s, 3H), 1.26 (s, 3H), 1.04 (t, *J* = 7.9 Hz, 9H), 0.77 (t, *J* = 7.4 Hz, 3H), 0.58 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6): δ 206.3, 166.6, 159.1, 139.1, 137.3, 133.0, 131.3, 130.3, 129.6, 129.4, 128.5, 115.1, 82.1, 81.4, 75.0, 67.5, 64.5, 55.4, 49.0, 40.0, 38.1, 37.2, 26.2, 25.1, 24.9, 21.0, 11.7, 7.6, 4.6 ppm.

The 1,3-*anti* relationship of the oxygen centers was confirmed by formation of the cyclic PMP acetal via oxidation of the PMB ether with DDQ, then through NOE correlations.



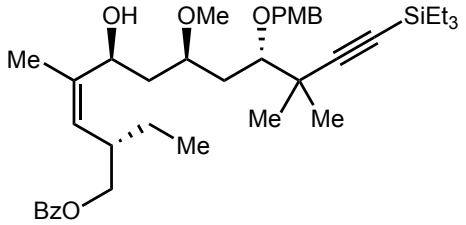
(*2S,Z*)-2-ethyl-6-((*4S,6S*)-2-(4-methoxyphenyl)-6-(2-methyl-4-(triethylsilyl)but-3-yn-2-yl)-1,3-dioxan-4-yl)-4-methyl-5-oxohex-3-enyl benzoate: To a solution of the alcohol (7.0 mg, 0.011 mmol) in anhydrous CH_2Cl_2 (0.3 mL) was added DDQ (3.0 mg, 0.013 mmol, 1.2 equiv). The reaction was stirred at room temperature for 4 hours. The reaction mixture was directly loaded onto a preparative thin layer chromatography plate and developed with 10% EtOAc/hexanes where the less polar band was collected to afford 4.5 mg (64%) of the desired acetal as a clear oil. The assignment of structure was based on nOe analysis:





2*R*,7*S*,9*S*,*Z*)-2-ethyl-7-methoxy-9-((4-methoxybenzyl)oxy)-4,10,10-trimethyl-5-oxo-12-(triethylsilyl)dodec-3-en-11-yn-1-yl benzoate (S6): To a solution of alcohol **11** (2.35 g, 3.7 mmol) in CH_2Cl_2 (66 mL) in a 250 ml flask was added proton sponge (3.97 g, 18.5 mmol, 5.0 equiv) at 0 ºC. To this reaction was added Me_3O^+ BF_4^- (2.19 g, 14.8 mmol, 4 equiv). Upon addition, the reaction mixture was placed into a room temperature water bath and stirred for 30 min. An additional 0.6 equiv Me_3O^+ BF_4^- was then added and the reaction was allowed to stir an additional 20 min. The reaction was then diluted with 100 ml 4:1 hexanes:EtOAc, filtered through a short plug of celite, and the organic phase washed with 50 ml of 5% aqueous $NaHSO_4$ and 50 ml PH7 phosphate buffer. The organic layer was then dried (Na_2SO_4) and concentrated under reduced pressure. Silica gel chromatography using a gradient of 9:1 then 8:1 hexanes:EtOAc afforded 2.0 g (83%) of the desired product as a light yellow oil. TLC R_f = 0.25 in 10% ethyl acetate/hexanes; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 8.0, 13 Hz, 2H), 7.54 (tt, *J* = 80 Hz, 1.3 Hz, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 5.45 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.74 (d, *J* = 11.0 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 4.28-4.20 (m, 2H), 4.07-4.0 (m, 1H), 3.78 (s, 3H), 3.56 (dd, *J* = 10.5, 2 Hz, 1H), 3.29 (s, 3H), 3.08-2.99 (m, 1H), 2.89 (dd, *J* = 16.7, 6.8 Hz, 1H), 2.54 (dd, *J* = 16.7, 5.1 Hz, 1H), 1.96-1.90 (m, 4H), 1.66-1.55 (m, 1H), 1.43-1.32 (m, 2H), 1.26 (s, 3H), 1.18 (s, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.54 (q, *J* = 7.9 Hz, 6H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.8, 166.5, 159.0, 138.1, 137.3, 132.8, 131.1, 130.3, 129.6, 129.0, 128.3, 115.0, 113.6, 82.1, 74.3, 74.1, 67.5, 56.1, 55.2, 47.0, 39.8, 37.3, 36.7, 26.2, 24.8, 24.7, 20.8, 11.5, 7.5, 4.5; IR (thin film): $\acute{\imath}_{max}$ 2959, 2874, 2160, 1721, 1514, 1272, 1249, 1097, 1028, 712 cm^{-1}.

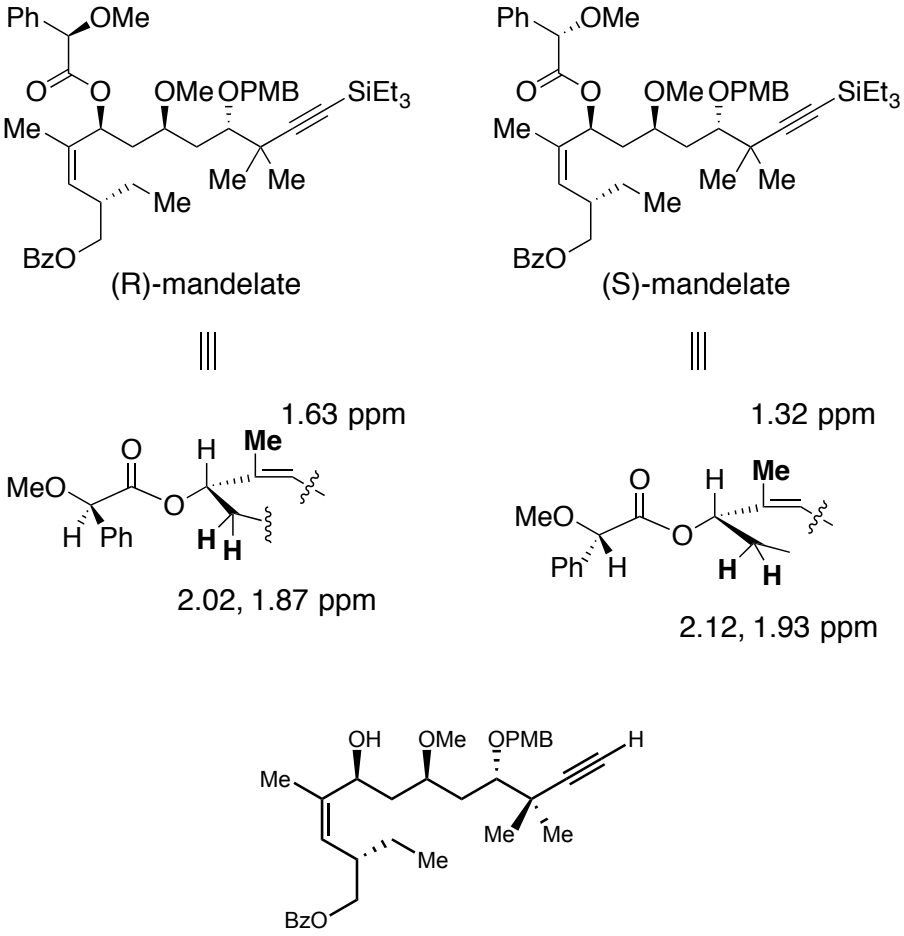


(2*R*,5*S*,7*R*,9*S*,*Z*)-2-ethyl-5-hydroxy-7-methoxy-9-((4-methoxybenzyl)oxy)-4,10,10-trimethyl-12-(triethylsilyl)dodec-3-en-11-yn-1-yl benzoate (S7): The protocol employed for this reaction was analogous to the one reported previously:[4] To a -78 ºC solution of the β-methoxy ketone **S6** (1.032 g, 1.59 mmol) in CH_2Cl_2 (50 mL) was added a solution of Me_2AlCl (2.23 ml of a 1 M in hexanes solution, 2.23 ml, 1.4 equiv). The reaction mixture was stirred for 2 min at this temperature and then freshly distilled Bu_3SnH (0.642 ml, 2.39 mmol, 1.5 equiv) was added. The reaction was stirred 2 hrs at -78 ºC and then additional Me2AlCl (0.6 ml) and Bu_3Sn (0.2 ml) were added. After stirring an additional 2 hours, the reaction was quenched with a saturated aqueous solution of $NaHSO_4$. The aqueous layer was extracted with EtOAc, the combined organic layers dried over Na_2SO_4, and the solvent removed under reduced pressure. Purification on a column of silica gel and eluting with 6:1 then 4:1 hexanes:EtOAc provided the desired compound (0.9237 g, 92%) as a colorless oil as a 5:1 mixture of diastereomers. Major: TLC R_f = 0.35 (30% ethyl acetate/hexanes – CAM stain); ^{1}H (500 MHz, $CDCl_3$): δ 8.05-7.99 (m, 2H), 7.55-7.52 (m, 1H), 7.44-7.40 (m, 2H), 7.29-7.25 (m, 2H), 6.84 (m, 2H), 5.04-5.01 (m, 1H), 4.74-4.69 (m, 2H), 4.59 (d, *J* = 10.6 Hz, 1H), 4.20-4.16 (m, 1H), 4.09 (dd, *J* = 10.8, 6.7 Hz, 1H), 3.77 (s, 3H), 3.76-3.72 (m, 1H), 2.83-2.76 (m, 1H), 2.05-1.92 (m, 2H), 1.75 (d, *J* = 1.4 Hz, 3H), 1.68-1.60 (m, 2H), 1.41-1.28 (m, 2H), 1.28 (s, 3H), 1.17 (s, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.54 (q, *J* = 7.9 Hz, 6H) ppm.

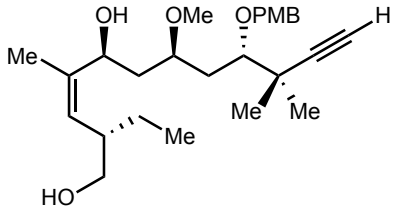
The absolute configuration of the allylic alcohol center was confirmed via formation of the (R) and (S)-O-methylmandelate ester and then comparison of the resulting 1H NMR spectra as previously described.[6] Conversion to the mandelate ester was accomplished as follows: Into a 10 ml round bottom flask was placed S7 (0.047 g, 0.07 mmol) in 1 ml CH_2Cl_2 and (R)- or (S)-O-methylmandelic acid (0.024 g, 0.14 mmol, 2 equiv) was added, followed by a catalytic amount of DMAP. EDC-HCl (0.0415 g, 0.217 mmol, 3 equiv) was then added and the reaction allowed to stir under a nitrogen atmosphere at room temperature for 24 hours. The reaction was then quenched by addition of 3 ml saturated $NaHCO_3$ solution and the mixture was extracted with 3X5 ml CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the solvent was removed. The crude material was purified on a column of silica gel and eluted with 20% EtOAc in heaxanes to provide the clean mandelate esters (0.0363 g for (R)-O-methylmandelic acid (66% yield) and 0.0255 g (46.4% yield) for (S)-O-methylmandelic acid) as colorless oils.

According to the mandelate ester analysis for determining absolute configuration of alcohol stereocenters,[6] the allylic alcohol of intermediate S7 was assigned as (S) as depicted below.

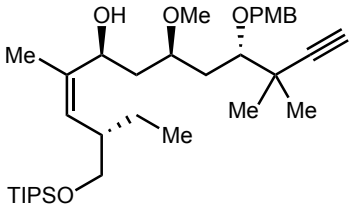
NMR shifts for (R)- and (S)-O-methylmandelate esters confirming absolute stereochemistry.



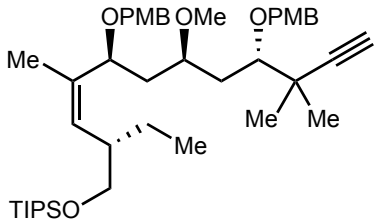
(2*S*,5*S*,7*R*,9*S*,*Z*)-2-ethyl-5-hydroxy-7-methoxy-9-((4-methoxybenzyl)oxy)-4,10,10-trimethyldodec-3-en-11-yn-1-yl benzoate (12): Into a 100 ml round bottom flask was added the Tes-Alkyne **S6** (1.79 g, 2.75 mmol) and 54 ml THF. In a separate vial was placed TBAF (6.86 ml of a 1M THF solution, 6.86 mmol, 2.5 equiv) and acetic acid (0.081 ml, 1.37 mmol, 0.5 equiv). This solution was then added via syringe to the alkyne solution at room temperature, and the reaction allowed to stir 1 hr. The reaction was then quenched by addition of PH7 phosphate buffer, the aqueous extracted with EtOAc, and the combined organic layers dried over Na_2SO_4 and concentrated. Purification by silica gel chromatography and eluting with 5:1 then 3:1hexanes:EtOAc provided the desired product (1.4312 g, 97%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.97-8.02 (m, 2H), 7.54 (tt, J = 1.3, 7.4 Hz, 1H), 7.39-7.46 (m, 2H), 7.25-7.32 (m, 2H), 6.81-6.89 (m, 2H), 5.02 (dd, J = 0.7, 10.1 Hz, 1H), 4.72 (dd, J = 2.5, 9.9 Hz, 1H), 4.65 (d, J = 10.7 Hz, 1H), 4.59 (d, J = 10.7 Hz, 1H), 4.08-4.22 (m, 2H), 3.77 (s, 3H), 3.69-3.76 (m, 1H), 3.49 (dd, J = 1.9, 9.3 Hz, 1H), 3.35 (s, 3H), 2.73-2.86 (m, 2H), 2.14 (s, 1H), 2.02 (ddd, J = 2.1, 9.7, 14.4 Hz, 1H), 1.90 (ddd, J = 1.9, 8.0, 14.9 Hz, 1H), 1.76 (d, J = 1.3 Hz, 3H), 1.71 (ddd, J = 3.9, 9.6, 14.7 Hz, 1H), 1.63 (ddd, J = 4.7, 7.4, 13.4 Hz, 1H), 1.39 (ddd, J = 2.9, 4.7, 14.6 Hz, 1H), 1.28-1.34 (m, 1H), 1.27 (s, 3H), 1.21 (s, 3H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 11.8, 18.4, 24.4, 25.3, 26.6, 36.3, 36.8, 38.7, 39.0, 54.9, 55.4, 68.2, 69.1, 69.7, 74.6, 77.4, 81.8, 90.7, 113.9, 127.5, 128.6, 129.5, 129.7, 130.5, 131.1, 133.1, 139.9, 159.3, 166.7.



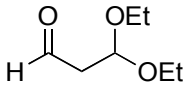
(2*S*,5*S*,7*R*,9*S*,*Z*)-2-ethyl-7-methoxy-9-((4-methoxybenzyl)oxy)-4,10,10-trimethyldodec-3-en-11-yne-1,5-diol (S8): Into a 50 ml round bottom flask containing the benzoate ester (1,392 g, 2.59 mmol) is placed 25 ml MeOH and K_2CO_3 (0.717 g, 5.18 mmol, 2 equiv) at room temperature. The reaction is the heated for 4 hrs at 35 °C, at which time TLC showed complete consumption of starting material. The reaction was then quenched with water, extracted with EtOAc, the organics dried over Na2SO4, and the solvent removed. Purification on a column of silica gel and eluting with 2:1 then 1:1 hexanes:EtOAc provided the title compound (0.980 g, 87% yield) as a colorless oil. At this stage, the incorrect diastereomer generated from the directed reduction was separated, providing an additional 0.139 grams product diastereomeric at the allylic alcohol stereocenter (12% yield). Rf = 0.40 (4:1 Hexanes:EtOAc); IR (film): υ = 3423 (br), 3305, 2960, 1613, 1514, 1462, 1249, 1093, 1036; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28-7.32 (m, 2H), 6.85-6.90 (m, 2H), 4.99 (dd, J = 1.1, 10.3 Hz, 1H), 4.66 (d, J = 10.6 Hz, 1H), 4.58 (dd, J = 5.7, 7.9 Hz, 1H), 4.56 (d, J = 10.6 Hz, 1H), 3.80 (s, 3H), 3.71-3.78 (m, 1H), 3.55 (dd, J = 4.6, 5.6 Hz, 1H), 3.49 (dd, J = 1.6, 10.0 Hz, 1H), 3.34 (s, 3H), 3.25 (t, J = 9.7 Hz, 1H), 2.67 (bs, 1H), 2.57-2.66 (m, 1H), 2.16 (s, 1H), 1.99-2.07 (m, 2H), 1.73 (d, J = 1.0 Hz, 3H), 1.66 (ddd, J = 3.4, 10.0, 14.7 Hz, 1H), 1.58 (dt, J = 4.9, 14.5 Hz, 1H), 1.34-1.43 (m, 1H), 1.30 (s, 3H), 1.22 (s, 3H), 1.06-1.16 (m, 1H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 12.1, 19.3, 24.2, 25.1, 26.8, 35.7, 36.8, 38.2, 42.4, 53.0, 55.5, 66.6, 69.7, 75.0, 76.1, 82.0, 90.7, 113.9, 129.7, 130.6, 131.0, 139.5, 159.3.



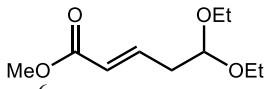
(3S,6S,8R,10S,Z)-8-methoxy-10-((4-methoxybenzyl)oxy)-5,11,11-trimethyl-3-(((triisopropylsilyl)oxy)methyl)tridec-4-en-12-yn-6-ol (**S9**): Into a 100 ml round bottom flask containing a stir bar is placed (2R,5S,7R,9S,Z)-2-ethyl-7-methoxy-9-((4-methoxybenzyl)oxy)-4,10,10-trimethyldodec-3-en-11-yne-1,5-diol (1.0133 g, 2.34 mmol) in 39 ml CH_2Cl_2. Imidazole (1.102 g, 16.4 mmol, 7 equiv) is added, followed by chlorotriisopropylsilane (1.50 ml, 7.03 mmol, 3 equiv). The reaction is stirred at ambient temperature until TLC shows complete consumption of starting material (5 hours). The reaction was then quenched with 40 ml $NaHCO_3$ (sat., aqueous), layers separated, and the aqueous extracted with 3 X 40 ml EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed. Purification on a column of silica gel with 8:1 then 6:1 Hexanes:EtOAc as eluent provided the title compound (1.3315 g, 97% yield) as a clear oil. $[\alpha]_D$ = +4.09 (c = 1.80, $CHCl_3$, 24.1 °C); Rf = 0.57 (4:1 Hexanes:EtOAc); IR (film): υ = 3444 (br), 3310, 2943, 2866, 2113 (sm), 1613, 1514, 1463, 1249, 1098; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.31 ($d_{(app)}$, J = 8.6 Hz, 2H), 6.87 ($d_{(app)}$, J = 8.6 Hz), 4.94 (dd, J = 1.2, 10.3 Hz, 1H), 4.66 (d, J = 10.7 Hz, 1H), 4.63 (d, J = 10.7 Hz, 1H), 4.54 (dd, J = 3.1, 9.7 Hz, 1H), 3.81 (s, 3H), 3.71-3.78 (m, 1H), 3.52-3.58 (m, 2H), 3.44 (dd, J = 7.1, 9.3 Hz, 1H), 3.36 (s, 3H), 3.06 (s (br), 1H), 2.62-2.72 (m, 1H), 2.15 (s, 1H), 2.06 (ddd, J = 6.3, 9.8, 14.4 Hz, 1H), 1.93 (ddd, J = 1.6, 8.7, 14.8 Hz, 1H), 1.79 (ddd, J = 3.3, 9.7, 14.4 Hz, 1H, 1.74 (d, J = 1.3 Hz, 3H), 1.54 (ddd, J = 4.6, 7.4, 12.2 Hz, 1H), 1.49 (ddd, J = 3.1, 6.0, 14.2 Hz, 1H), 1.30 (s, 3H), 1.24 (s, 3H), 1.03-1.06 (m, 21 H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 12.0, 12.1, 17.9, 18.2, 19.9, 24.6, 24.9, 26.7, 36.4, 36.8, 39.3, 42.0, 55.0, 55.5, 67.2, 69.6, 69.7, 74.7, 76.7, 81.8, 90.8, 113.9, 129.4, 129.5, 131.2, 139.4, 159.3. HRMS (ESI): $C_{35}H_{60}O_5Si$ (M+Na) calculated: 611.4108, found 611.4097.



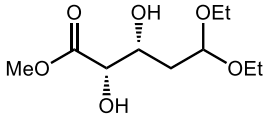
(((2S,5S,7R,9S,Z)-2-ethyl-7-methoxy-5,9-bis((4-methoxybenzyl)oxy)-4,10,10-trimethyldodec-3-en-11-yn-1-yl)oxy)triisopropylsilane (**13**): Into a 5 dram vial containing a stir bar was placed **40** (0.7047 g, 1.20 mmol) in 7 ml DMF. The reaction was cooled to 0 °C in an ice water bath and sodium hydride (0.1436 g 60% dispersion in mineral oil, 3.59 mmol, 3 equiv) was added in one portion. The reaction was then stirred for 1 hour at 0 °C, at which time p-methoxybenzyl chloride (0.65 ml, 4.79 mmol, 4 equiv) and tetrabutylammonium iodide (0.044 g, 0.12 mmol, 0.1 equiv) were sequentially added. The reaction was stirred 1 hour at 0 °C, then allowed to warm to room temperature and stirred for an additional 8 hours. The reaction was then quenched by careful addition of Brine (30 ml) and the mixture extracted with 4 X 30 ml Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed. Purification on a long column of silica gel (~12 inches) with 9:1 Hexanes:EtOAc as eluent provided the title compound (**41**) (0.7489 g, 92% yield) as a clear oil. $[\alpha]_D$ = +2.58 (c = 1.10, $CHCl_3$, 23.8 °C); Rf = 0.73 (5:1 Hexanes:EtOAc); IR (film): υ = 3309, 2942, 2866, 1614, 1514, 1249, 1095; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29 ($d_{(app)}$, J = 8.6 Hz, 2H), 7.21 ($d_{(app)}$, J = 8.7 Hz, 2H), 6.81 ($d_{(app)}$, J = 8.7 Hz, 2H), 6.75 ($d_{(app)}$, J = 8.6 Hz, 2H), 5.19 (d, J = 10.0 Hz, 1H), 4.68 (d, J = 10.6 Hz, 1H), 4.59 (d, J = 10.6 Hz, 1H), 4.32-4.38 (m, 2H), 4.14 (d, J = 11.0 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.70-3.78 (m, 1H), 3.60 (dd J = 1.6, 10.5 Hz, 1H), 3.57 (dd, J = 5.1, 9.4 Hz, 1H), 3.47 (dd, J = 6.7, 9.4 Hz, 1H), 3.32 (s, 3H), 2.38-2.47 (m, 1H), 2.19 (ddd, J = 3.6, 10.3, 14.1 Hz, 1H), 2.11 (s, 1H), 1.85 (ddd, J = 1.4, 10.2, 14.1 Hz, 1H), 1.75 (ddd, J = 2.3, 10.5, 14.0 Hz, 1H), 1.68 (ddd, J = 5.0, 7.6, 13.0 Hz, 1H), 1.72 (d, J = 1.0 Hz, 3H), 1.43 (ddd, J = 3.1, 8.2, 14.1 Hz, 1H), 1.27 (s, 3H), 1.22 (s, 3H), 1.22-1.26 (m, 1H), 1.02-1.06 (m, 21H), 0.90 (t, J = 7.4 Jz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 12.1, 12.2, 18.3, 24.9, 25.1, 26.6, 36.7, 37.7, 41.9, 55.38, 55.43, 67.0, 69.4, 70.1, 73.8, 74.9, 75.1, 81.8, 90.9, 113.8, 113.9, 129.3, 129.4, 131.1, 131.4, 131.6, 136.4, 159.1, 159.2. HRMS (ESI): $C_{43}H_{68}O_6Si$ (M+Na) calculated: 731.4677, found 731.4678.



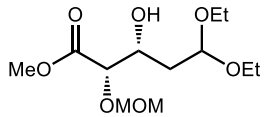
3,3-diethoxypropanal (S10): To a solution of methyl 3,3-diethoxypropanoate (10.0 g, 52.6 mmol) in anhydrous dichloromethane (260 mL) was added a solution of DIBAL (78.8 mL of a 1.0 M solution in toluene, 78.8 mmol, 1.5 equiv.) over 20 minutes at -78 °C. Upon complete addition, the reaction was stirred at -78 °C for an additional 45 minutes after which methanol (15 mL) was added. The reaction was then warmed to room temperature and stirred for 30 minutes. To the reaction was sequentially added water (~5 mL), stirred 10 minutes, and added solid Na_2SO_4 (30 g). Upon stirring for 10 minutes the reaction mixture was filtered and concentrated undezr reduced pressure. Silica gel chromatography using a gradient of 20%-60% pentane/diethyl ether afforded 6.14 g (80%) of the desired product compound as a colorless oil. Note: due to the volatility of this compound the majority of the toluene is removed during chromatography and the use of pentane and diethyl ether minimizes product loss during rotoray evaporation. R_f = 0.21 (20% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.76 (t, J = 2.5 Hz, 1H), 4.96 (t, J = 7.0 Hz, 1H), 3.73-3.45(m, 4H), 2.74 (dd, J = 5.5, 2.5 Hz, 2H), 1.24-1.19 (m, 6H) ppm; ^{13}C ($CDCl_3$, 100 MHz): δ 199.6, 98.0, 62.5, 48.2, 16.8 ppm; IR (thin film) ν_{max} 2977, 2882, 1728, 1375, 1120, 1062 cm^{-1}; this compound has been reported previously.[5]



(E)-methyl 5,5-diethoxypent-2-enoate (**15**)[6]: Into a flame dried 100 ml round bottom flask with a stir bar was placed sodium hydride (0.589 g, 14.72 mmol, 1.14 equiv) and 39 ml dry THF and the slurry is cooled to 0 °C. Trimethylphosphonoacetate (2.55 ml, 15.75 mmol, 1.22 equiv) is then added dropwise and the mixture warmed to room temperature and stirred for 30 min. 3,3-Diethoxypropanal **S10** was then added as a solution in 5 ml THF. The reaction iw stirred 30 minutes, the quenched with PH 7 phosphate buffer (50 ml) and extracted with 3 X 50 ml EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed. The mixture was purified on a column of silica gel with 6% EtOAc in hexanes as eluent to give the title compound (1.99 g, 76% yield) as a light yellow oil. Rf = 0.57 (3:1 Hexanes:EtOAc); IR (film): υ = 2978, 2884, 1727, 1273, 1123, 1061; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.96 (dt, J = 7.3, 15.7 Hz, 1H), 5.91 (dt, J = 1.4, 15.7 Hz, 1H), 4.58 (t, J = 5.6 Hz, 1H), 3.73 (s, 3H), 3.67 ($q_{(app)}$, J = 7.0 Hz, 1H), 3.65 ($q_{(app)}$, J = 7.0 Hz, 1H), 3.52 ($q_{(app)}$, J = 7.0 Hz, 1H), 3.51 ($q_{(app)}$, J = 7.0 Hz, 1H), 2.54 (ddd, J = 1.4, 5.6, 7.2 Hz, 1H), 1.21 (t, J = 7.0 Hz, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 15.4, 37.2. 51.6, 61.7, 101.5, 123.5, 144.1, 166.9.

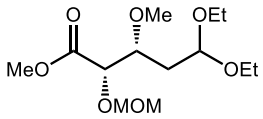


(2S,3R)-methyl 5,5-diethoxy-2,3-dihydroxypentanoate (**16**): To a solution of (E)-methyl 5,5-diethoxypent-2-enoate (**15**) (3.72 g, 18.4 mmol) in *tert*-butanol (64 ml) was added water (64 ml), K_3FeCN_6 (15.93 g, 48.41 mmol, 2.63 equiv), potassium carbonate (6.69 g, 48.4 mmol, 2.63 equiv), and $(DHQD)_2Pyr$ ligand (0.194 g, .221 mmol, 0.012 equiv) sequentially in that order. The reaction was then cooled to 0 °C and OsO_4 (0.70 ml 4% solution in water, 0.110 mmol, 0.006 equiv) was added via syringe and the reaction stirred 24 hours at 0 °C. The reaction was then quenched by addition of 75 ml 0.5 M $Na_2S_2O_3$ and the mixture extracted with EtOAC (3 X 150 ml). The combined organics were dried over Na_2SO_4, filtered and the solvent was removed. Purification on a column of silica gel and eluting with 1:1 hexanes:EtOAc provided the desired diol (3.723 g, 15.76 mmol, 86% yield) as a clear oil. $[\alpha]_D$ = +1.48 (c = 1.49, $CHCl_3$, 23.5 °C); Rf = 0.29 (1:1 Hexanes:EtOAc); IR (film): υ = 3461 (br), 2976, 2932, 2899, 1744, 1441, 1378, 1259, 1219, 1125, 1058; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.77 (t, J = 5.2 Hz, 1H), 4.17-4.23 (m, 1H), 4.07 (dd, J = 2.0, 7.4 Hz, 1H), 3.83 (s, 3H), 3.66-3.76 (m, 2H), 3.50-3.59 (m, 2H), 3.31 (d, J = 4.4 Hz, 1H), 3.16 (d, J = 7.3 hz, 1H), 2.07 (dddd, J = 5.6, 9.8, 14.5, 15.1, 1H), 1.86 (dddd, J = 2.8, 4.8, 7.8, 14.5 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 15.4, 15.5, 37.1, 52.6, 62.0, 69.6, 74.0, 102.0, 173.7. HRMS (ESI): $C_{10}H_{20}O_6$ (M+Na) calculated: 259.1152, found 259.1158.

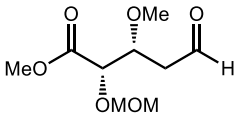


(2S,3R)-methyl 5,5-diethoxy-3-hydroxy-2-(methoxymethoxy)pentanoate (**S11**): Into a 50 ml flame dried round bottom flask was placed sodium hydride (0.3485 g 60% dispersion in mineral oil, 8.7 mmol, 1 equiv) in 12.8 ml THF. This slurry was cooled to –20 °C in a dry ice-cooled acetone bath and **16** (2.053 g, 8.7 mmol) was added slowly as a solution in12.8 ml dry THF. The reaction was then allowed to warm to 0 °C and was stirred at this temperature for 30 minutes. Tetrabutylammonium iodide (3.21 g, 8.7 mmol, 1 equiv), followed by chloromethylmethyl ether (0.86 ml, 11.3 mmol, 1.3 equiv) were sequentially added and the reaction was allowed to stir for 2 hours. The reaction was then quenched with PH 7 phosphate buffer (30 ml) and extracted with 3 X 30 ml EtOAc. The combined organics were dried with

brine, the Na_2SO_4, filtered, and the solvent was removed on a rotary evaporator under reduced pressure. The mixture was purified on a column of silica gel and eluted with 1.6:1 hexanes:EtOAc to give the title compound (1.0317 g, 42% yield) as a colorless oil. $[\alpha]_D$ = -36.9 (c 0.5, $CHCl_3$, 24.2 °C); Rf = 0.33 (1:1 hexanes:EtOAc); IR (film): υ = 3473 (br), 2975, 2932, 2900, 1752, 1440, 1213, 1153, 1119, 1051; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.77 (d, J = 6.9 H, 1H), 4.73-4.77 (m, 1H), 4.72 (d, J = 6.9 Hz, 1H), 4.16-4.23 (m, 1H), 4.11 (d, J = 3.5 Hz, 1H), 3.78 (s, 3H), 3.64-3.75 (m, 2H), 3.49-3.59 (m, 2H), 3.41 (s, 3H), 3.06 (d, J = 5.0 Hz, 1H), 1.98 (ddd, J = 5.0, 10.1, 14.3 Hz, 1H), 1.83 (ddd, J = 3.1, 5.7, 14.3 Hz, 1H), 1.22 (td, J = 1.5, 6.8 Hz, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 15.46, 15.5, 37.1, 52.4, 56.5, 62.2, 62.4, 69.5, 78.4, 96.7, 101.6, 171.3. HRMS (ESI): $C_{12}H_{24}O_7$ (M+Na) calculated: 303.1414, found 303.1419.

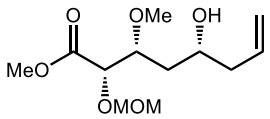


(2S,3R)-methyl 5,5-diethoxy-3-methoxy-2-(methoxymethoxy)pentanoate (**S12**): Trimethyloxonium tetrafluoroborate is washed with CH_2Cl_2 before use as follows: Into a oven dried 5 dram vial was placed 4 g Me_3OBF_4 and the vial purged with nitrogen. CH_2Cl_2 (5 ml) was then added via syringe to the vial and the contents swirled for 20 seconds. The CH_2Cl_2 was then removed with a syringe, discarded, and the remaining solids dried on the Hi-Vac for 5 minutes. The resulting solid was used in the reaction as follows: Into a flame dried 250 ml round bottom flask containing a stir bar was placed **S11** (1.7571 g, 6.27 mmol) in 126 ml CH_2Cl_2 and the reaction was cooled to 0 °C. Proton Sponge (6.72 g, 31.36 mmol, 5 equiv) was then added, followed by Me_3OBF_4 (3.71 g, 25.1 mmol, 4 equiv) in one portion. The reaction was stirred at 0 °C for 1 hour, at which time TLC showed complete consumption of starting material. The reaction was then filtered through a small plug of cotton, washed with 100 ml 5% $NaHSO_4$ solution and 50 ml brine. The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed. The mixture was then purified on a column of silica gel eluting with 1.7:1 hexanes:EtOAc to provide 1.7304 g (94% yield) of the title compound as a colorless oil. $[\alpha]_D$ = –26.03 (c = 1.41, $CHCl_3$, 22.7 °C); Rf = 0.55 (2:1 Hexanes:EtOAc); IR (film): υ = 2976, 2933, 2899, 2830, 1572, 1441, 1377, 1207, 1154, 1117, 1060; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.73 (q, J = 7.0 Hz, 2H), 4.67 (dd, J = 4.3, 7.4 Hz, 1H), 4.21 (d, J = 3.8 Hz, 1H), 3.78 (s, 3H), 3.76-3.81 (m, 1H), 3.61-3.73 (m, 2H), 3.48-3.56 (m, 2H), 3.42 (s, 3H), 3.40 (s, 3H), 1.97 (dddd, J = 4.3, 8.4, 12.5, 14.4 Hz, 1H), 1.89 (dddd, J = 5.1, 7.5, 12.3, 14.2 Hz, 1H), 1.22 ($q_{(apparent)}$, J = 7.90 Hz, 5H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 15.5, 15.5, 34.9, 52.2, 56.5, 59.0, 61.6, 76.9, 78.7, 96.8, 100.5, 171.4.



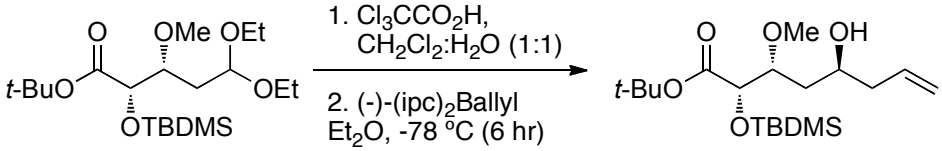
(2S,3R)-methyl 3-methoxy-2-(methoxymethoxy)-5-oxopentanoate (**17**): Into a oven dried 50 ml round bottom flask containing a stir bar was placed **S12** (1.1950 g, 4.06 mmol) in 25 ml CH_2Cl_2. Water (25 ml) was then added, followed by trichloroacetic acid (3.31 g, 20.31 mmol, 5 equiv). The reaction was stirred at ambient temperature for 1 hour, then quenched by addition 25 ml of a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous layer extracted with 2 X 50 ml CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed. The resulting oil was the dried under high vacuum (>0.3 torr) for several hours to give the title compound (**38**) (0.8647 g, 97% yield) as a clear oil. $[\alpha]_D$ = –55.2 (c = 1.44, $CHCl_3$, 22.8 °C); Rf = 0.22 (2:1 Hexanes:EtOAc); IR (film): υ = 2954, 2832, 2734, 1748, 1727, 1434, 1201, 1154, 1104, 1040; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.84 (dd, J = 1.3, 1.8 Hz, 1H), 4.73 (d, J = 6.9 Hz, 1H), 4.68 (d, J = 7.0 Hz, 1H), 4.31 (d, J = 4.0 Hz, 1H), 4.20 (ddd, J = 4.0, 5.5, 6.4 Hz, 1H), 3.79 (s, 3H), 3.42 (s, 3H), 3.39 (s, 3H), 2.84 (ddd, J = 1.0, 5.4, 17.7

Hz, 1H), 2.76 (ddd, J = 1.8, 6.4, 17.7 Hz, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 44.5, 52.3, 56.6, 58.8, 76.5, 96.8, 170.7, 200.2.



(2S,3R,5R)-methyl 5-hydroxy-3-methoxy-2-(methoxymethoxy)oct-7-enoate (**S13**): Into a 25 ml round bottom flask containing a stir bar was placed aldehyde **17** (0.8647 g, 3.93 mmol) in 20 ml dry Et_2O. The reaction was cooled to –78 °C and a solution of (+)-*B*-allyldiisopinocampheylborane (3.93 ml, 1M solution in pentanes, 3.93 mmol, 1 equiv) was added dropwise. The reaction was stirred 5 hours at this temperature, then quenched by addition of methanol (3.3 ml) and allowed to warm to room temperature over about 10 minutes by removing the cold bath. The solvent was then removed under reduce pressure and dry THF (11 ml), PH 7 phosphate buffer (5.4 ml), and 30% H_20_2 solution (4.4 ml) were sequentially added. The reaction was stirred for 24 hours, diluted with PH7 phosphoate buffer (20 ml) and extracted with EtOAc (3 X 30 ml). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed. Purification on a column of silica gel with 1:1 Hexanes:EtOAc as eluent provided the title compound (**S13**) containing a small amount of impurities. This mixture was taken directly to the next reaction. Rf = 0.23 (1:1 Hexanes:EtOAc); IR (film): υ = 3489 (br), 3076, 2953, 2932, 2830, 1752, 1438, 1211, 1153, 1099, 1041; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.83 (ddt, J = 7.2, 10.4, 16.9 Hz, 1H), 5.09-5.16 (m, 2H), 4.72 (q, J = 6.9 Hz, 2H), 4.29 (d, J = 4.0 Hz, 1H), 3.83-3.89 (m, 2H), 3.78 (s, 3H), 3.45 (s, 3H), 3.40 (s, 3H), 2.98 (broad s, 1H), 2.26 (dt, J [0.6, 7.1 Hz, 2H], 1.80 (ddd, J = 3.0, 5.4, 14.5 Hz, 1H), 1.71-1.77 (m, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 36.5, 42.7, 52.4, 56.6, 58.6, 69.7, 76.6, 81.3, 96.8, 118.2, 134.6, 171.4.

The stereochemical assignment for the allylic stereocenter generated above was performed by synthesizing the allylation product of an intermediate from an earlier route from both the (+)- and (–)-IPC_2-allylborane, and then by formation of the (R)- and (S)-O-methylmandelate esters and analysis of the ^{1}H NMR spectra as described below:

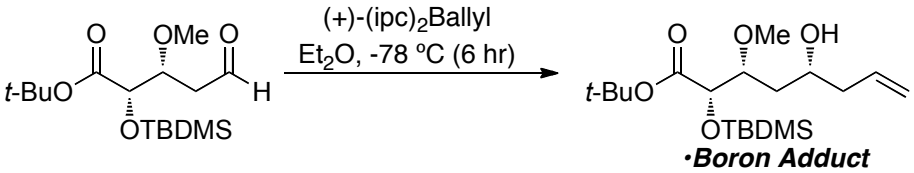


·Boron Adduct

(2*S*,3*R*,5*S*)-*tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-5-hydroxy-3-methoxyoct-7-enoate

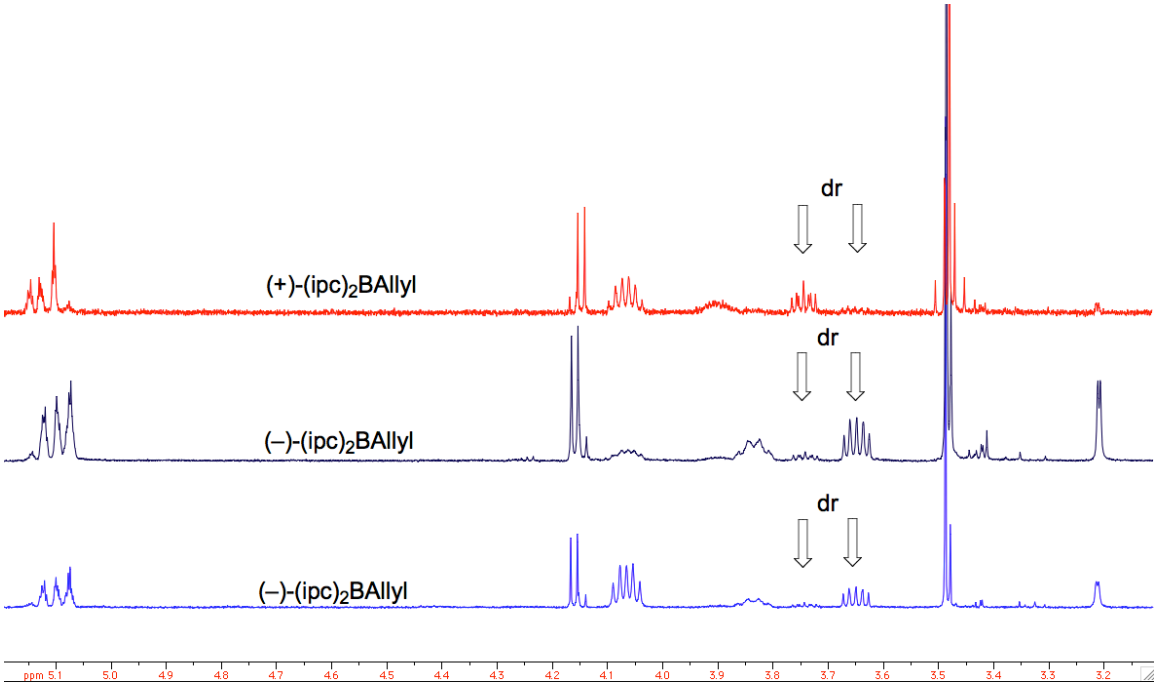
To a bi-layer or CH_2Cl_2/H_2O (40 mL, 1:1) was added (2S,3R)-*tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-5,5-diethoxy-3-methoxypentanoate (1.31 g, 3.22 mmol) and trichloroacetic acid (2.63 g, 16.10 mmol, 5.0 equiv). The reaction was stirred for 1h at room temperature, quenched with saturated aqueous sodium bicarbonate, and poured into a separatory funnel containing CH_2Cl_2 (90 mL). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure to afford 1.07 g (100%) of the desired compound as a colorless oil. TLC Rf = 0.31 in 20% ethyl acetate/hexanes (stains with CAM and DNPH); To a solution of the resulting aldehyde (1.07 g, 3.22 mmol) in diethyl ether (16 mL) was added a solution of (-)-Ipc_2B(allyl)borane (3.2 mL of a 1M solution in pentane) at -78 ºC. The reaction was stirred at this temperature for 4h, quenched with methanol, warmed to room temperature by removing bath, and concentrated under reduced pressure. To the resulting mixture was added THF (10 mL), pH 7 buffer (3 mL), and 30% aqueous hydrogen peroxide (2 mL). The mixture was stirred for 24 hours, diluted with pH 7 buffer (20 mL) and diethyl ether (50 mL), and poured into a separatory funnel. The organic layer was

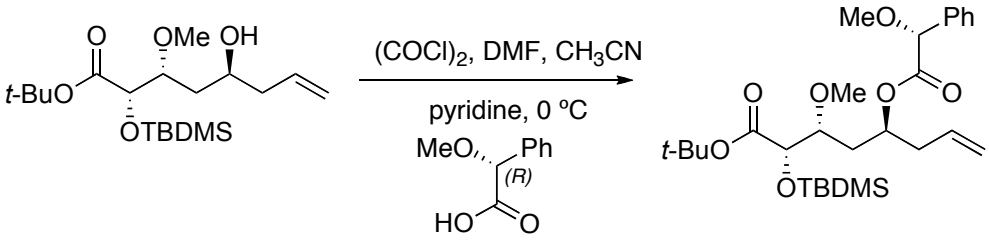
collected and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The organic layers were combined, concentrated under reduced pressure, redissolved in diethyl ether (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Filtration through silica gel eluting with 10-20% EtOAc/hexanes afforded 1.31 g of the desired product as a light yellow oil as an uncharacterized boron adduct that can be taken forward directly to the next step. R_f = 0.43 (20% EtOAc/hexanes) CAM and $KMnO_4$ stain; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.12-5.06 (m, 2H), 4.14 (d, *J* = 6.0 Hz, 1H), 3.84-3.80 (m, 1H), 3.66-3.62 (m, 1H), 3.47 (s, 3H), 3.20 (d, *J* = 1.8 Hz, 1H), 2.25-2.20 (m, 2H), 1.60-1.55 (m, 3H), 1.47 (s, 9H), 0.90 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); HRMS (ES^+) calcd for $C_{19}H_{38}NaO_5Si^+$ 397.2386 found 397.2393. This compound was isolated as a boron adduct and ^{13}C spectra for this compound was complicated by a large number of peaks corresponding to byproducts; full characterization is presented for the corresponding mandelate ester as this material was not carried forward in the synthesis.



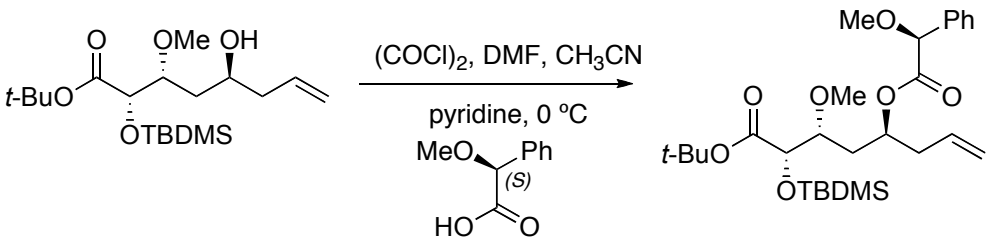
(2*S*,3*R*,5*R*)-*tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-5-hydroxy-3-methoxyoct-7-enoate: To a solution of (2*S*,3*R*)-*tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-methoxy-5-oxopentanoate (1.35 g, 4.0 mmol) in diethyl ether (20 mL) was added a solution of (+)-Ipc_2B(allyl)borane (4.0 mL of a 1M solution in pentane) at -78 ºC. The reaction was stirred at this temperature for 4h, quenched with methanol, warmed to room temperature by removing bath, and concentrated under reduced pressure. To the resulting mixture was added THF (10 mL), pH 7 buffer (5 mL), and 30% aqueous hydrogen peroxide (4 mL). The mixture was stirred for 24 hours, diluted with pH 7 buffer (20 mL) and diethyl ether (50 mL), and poured into a separatory funnel. The organic layer was collected and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The organic layers were combined, concentrated under reduced pressure, redissolved in diethyl ether (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Filtration through silica gel eluting with 10-20% EtOAc/hexanes afforded 2.37 g of the desired product as a light yellow oil as an uncharacterized boron adduct that can be taken forward directly to the next step. R_f = 0.43 (20% EtOAc/hexanes) CAM and $KMnO_4$ stain; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88-5.76 (M, 1H), 5.15-5.08 (m, 2H), 4.14 (d, *J* = 4.8 Hz, 1H), 3.94-3.86 (m, 1H), 3.74 (ddd, *J* = 8.0, 5.0, 3.2 Hz, 1H), 3.48 (s, 3H), 2.25-2.20 (m, 2H), 1.60-1.55 (m, 3H), 1.48 (s, 9H), 0.91 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H) ppm; HRMS (ES^+) calcd for $C_{19}H_{38}NaO_3Si^+$ 397.2387 found 397.2393 (MNa^+); Material carried forward as a boron complex.

Comparison of 1H NMR spectra of diastereomeric alcohols from (+)- and (–)-IPC-allylborane addition





(2*S*,3*R*,5*S*)-*tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-methoxy-5-((*R*)-2-methoxy-2-phenylacetoxy)oct-7-enoate: Oxalyl chloride (16.8 mg, 0.13 mmol, 2.0 equiv) was added dropwise to a solution of DMF (13.15 mg, 0.18 mol, 2.7 equiv) in acetonitrile (400 ul) at 0 ºC. (*R*)-*O*-Methylmandelic acid (20 mg, 0.12 mmol, 1.8 equiv) was added and the reaction was stirred for 5 min at 0 ºC. A solution of the title alcohol as an unknown boron adduct (25 mg, 0.067 mmol) in pyridine (100 uL) was then added and the reaction was stirred at 0 ºC for 1h. Upon complete conversion (judged by TLC), the reaction mixture was diluted with diethyl ether (3 mL) and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. Preparative TLC using 10% EtOAc/hexanes afforded 8.0 mg of the desired product as a colorless oil. Since the starting material was an uncharacterized boron adduct the yield for this transformation was not calculated based on starting material. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.29 (m, 5H), 5.41 (ddd, J = 17.3, 14.7, 10.5, 7.9 Hz, 1H), 5.11-5.03 (m, 1H), 4.83-4.70 (m, 3H), 4.17 (d, J = 4.1 Hz, 1H), 3.48 -3.43 (m, 1H), 3.42 (s, 3H), 3.32 (s, 3H), 2.27-2.11 (m, 2H), 1.90 (ddd, J = 14.4, 6.1, 5.0 Hz, 1H), 1.80 (ddd, J = 14.4, 8.0, 7.0 Hz, 1H), 1.46 (s, 9H), 0.90 (s, 9H), 0.1 (s, 3H), 0.05 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 170.3, 136.3, 132.5, 128.6, 128.5, 127.2, 118.2, 82.6, 81.2, 79.7, 73.8, 71.7, 57.7, 57.4, 38.6, 33.3, 28.0, 25.8, 25.7, 18.2, -4.6, -5.4 ppm; IR (thin film): ν_{max} 2929, 2856, 2360, 1747, 1367, 1116 cm^{-1}; HRMS (ES$^+$) calcd for $C_{28}H_{46}NaO_7Si^+$ 545.2911 found 545.2911.

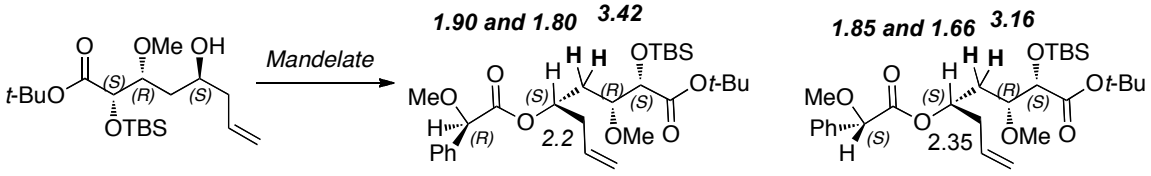


(2*S*,3*R*,5*S*)-*tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-methoxy-5-((S)-2-methoxy-2-phenylacetoxy)oct-7-enoate: Oxalyl chloride (16.8 mg, 0.13 mmol, 2.0 equiv) was added dropwise to a solution of DMF (13.15 mg, 0.18 mol, 2.7 equiv) in acetonitrile (400 uL) at 0 ºC. (*S*)-*O*-Methylmandelic acid (20 mg, 0.12 mmol, 1.8 equiv) was added and the reaction was stirred for 5 min at 0 ºC. A solution of the title alcohol as an unknown boron adduct (25 mg, 0.067 mmol) in pyridine (100 uL) was then added and the reaction was stirred at 0 ºC for 1h. Upon complete conversion (judged by TLC), the reaction mixture was diluted with diethyl ether (3 mL) and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. Preparative TLC using 10% EtOAc/hexanes afforded 8.0 mg of the desired product as a colorless oil. Since the starting material was an uncharacterized boron adduct the yield for this transformation was not calculated based on starting material. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.29 (m, 5H), 5.70 (m ,1H), 5.10-5.00 (m, 2H), 4.72 (s, 1H), 4.10 (d, *J* = 4.0 Hz, 1H), 3.42 (s, 1H), 3.16 (ddd, *J* = 8.6, 6.8, 4.0 Hz, 1H), 3.05 (s, 3H), 2.40-2.24 (m, 2H), 1.85 (ddd, *J* = 14.5, 6.9, 4.6 Hz, 1H), 1.68 (ddd, *J* = 14.5, 8.4, 6.0 Hz, 1H), 1.42 (s, 9H), 0.88 (s, 9H), 0.073 (s, 3H), 0.011 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.3, 136.4, 133.0, 128.6, 128.6, 127.2, 118.2, 82.6, 81.1, 79.2, 73.7, 71.6, 57.4, 57.4, 38.9, 33.3, 28.0, 25.8, 25.7, 18.2, -4.6, -5.4 ppm; IR (thin film): ν_{max} 2928, 2855, 1748, 1255, 1174, 1148, 1117, 838 cm^{-1}; HRMS (ES$^+$) calcd for $C_{28}H_{46}NaO_7Si^+$ 545.2911 found 545.2926.

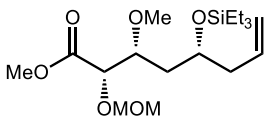
iH NMR analysis of

Mandelic ester analysis for the resulting allylic esters esters is illustrated below. Based on the ^{1}H NMR shift, the absolute stereochemical determination using the mandelate ester analysis is consistent with the predicted stereochemistry in Brown allylation.[7]

Mandelate ester analysis

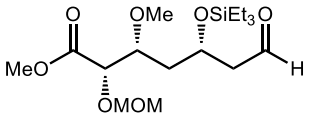


3.61 **3.62**

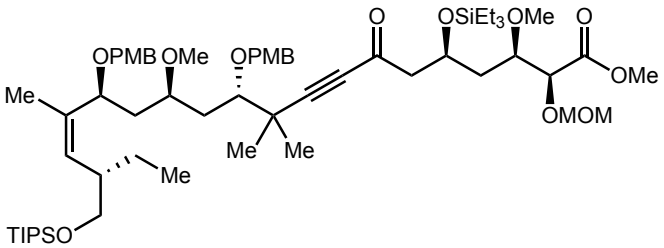


(2S,3R,5R)-methyl 3-methoxy-2-(methoxymethoxy)-5-((triethylsilyl)oxy)oct-7-enoate (**S14**): Into a 100 ml round bottom flask was placed **S13** (assume 100% yield from previous transformation, 3.93 mmol) in 54 ml CH_2Cl_2. Imidazole (2.68 g, 39.3 mmol, 10 equiv) was then added, followed by chlorotriethylsilane (3.3 ml, 19.65 mmol, 5 equiv). The reaction was allowed to stir for 2 hours, quenched with 50 ml of a

saturated solution of $NaHCO_3$ and extracted with 3 X 50 ml Et_2O. The mixture was run through a short column of silica gel and the product isolated and taken directly to the next transformation. $[\alpha]_D$ = –49.76 (c = 1.34, $CHCl_3$, 23.4 °C); Rf = 0.85 (1:1 Hexanes:EtOAc); IR (film): υ = 3076, 2954, 2879, 2828, 1753, 143, 1207, 1154, 1104, 1049; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.82 (ddt, J = 7.1, 10.3, 24.6 Hz, 1H), 5.03-5.11 (m, 2H), 4.75 (d, J = 7.1 Hz, 1H), 4.69 (d, J = 7.1 Hz, 1H), 4.20 (d, J = 3.3 Hz, 1H), 3.78-3.86 (m, 2H), 3.77 (s, 3H), 3.39 (s, 3H), 3.35 (s, 3H), 2.22-2.36 (m, 2H), 1.79 (td, J = 2.6, 6.7 Hz, 2H), 0.97 (t, J = 7.7 Hz, 9H), 0.62 (q, J = 7.7 Hz, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 5.2, 7.1, 36.9, 42.5, 52.2, 56.6, 58.3, 69.0, 78.8, 78.9, 96.8, 117.7, 134.7, 171.6.



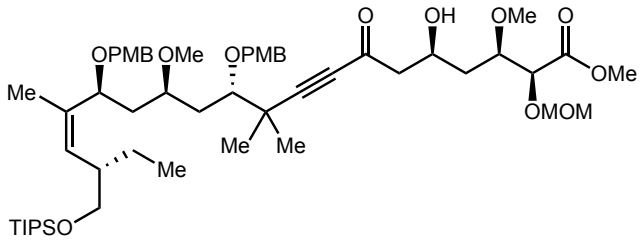
(2S,3R,5S)-methyl 3-methoxy-2-(methoxymethoxy)-7-oxo-5-((triethylsilyl)oxy)heptanoate (**2**): Into a 100 ml round bottom flask was placed the **S14** (assume 100% yield from previous 2 transformations, 3.93 mmol) in 75 ml CH_2Cl_2 and the reaction was cooled to –78 °C. Ozone was then bubbled through the reaction for 5 minutes or until a deep blue color persisted. The ozone line was the removed and a stream of dry nitrogen was bubbled through the solution until the blue color faded to clear (about 30-45 min). Triphenyl phosphine (2.06 g, 2 equiv) was the added and the cold bath removed and the solution allowed to warm to ambient temperature. After 1 hour, if TLC did not show complete consumption of the ozonide, an additional 0.5 equiv. PPh_3 was added and the reaction stirred 30 min. The solvent was then removed on the rotory evaporator under reduced pressure, and the crude product purified on a column of silica gel and eluted with 4:1 hexanes:EtOAc to give the title compound (1.222 g, 3.23 mmol, 82% yield over 3 steps) as a colorless oil. $[\alpha]_D$ = –18.66 (c = 1.31, $CHCl_3$, 23.8 °C); Rf = 0.14 (4:1 Hexanes:EtOAc); IR (film): υ = 2955, 2914, 2879, 2829, 1751, 1729, 1460, 1209, 1110., 1048; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.81 (t, J = 2.2 Hz, 1H), 4.73 (d, J = 7.1 Hz, 1H), 4.70 (d, J = 7.1 Hz, 1H), 4.37 (p, J = 6.1 Hz, 1H), 4.20 (d, J = 3.8 Hz, 1H), 3.75-3.80 (m, 1H), 3.78 (s, 3H), 3.40 (s, 3H), 3.38 (s, 3H), 2.65 (ddd, J = 1.8, 5.3, 16.1 Hz, 1H), 2.60 (ddd, J = 2.4, 6.2, 16.3 Hz, 1H), 1.91 (ddd, J = 5.7, 8.2, 14.3 Hz, 1H), 1.80 (ddd, J = 5.1, 6.2, 14.3 Hz, 1H), 0.96 (t, J = 7.9 Hz, 9H), 0.62 (q, J = 7.9 Hz, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 5.1, 5.2, 7.0, 38.3, 51.1, 52.3, 56.5, 58.4, 65.2, 76.7, 78.4, 96.8, 171.3, 201.9. HRMS (ESI): $C_{17}H_{34}O_7Si$ (M+Na) calculated: 401.1963, found 401.1958.



(2S,3R,5S,11S,13R,15S,18S,Z)-methyl 3,13-dimethoxy-11,15-bis((4-methoxybenzyl)oxy)-2-(methoxymethoxy)-10,10,16-trimethyl-7-oxo-5-((triethylsilyl)oxy)-18-(((triisopropylsilyl)oxy)methyl)icos-16-en-8-ynoate (**S15**): Into a 5 dram vial is placed **13** (0.1251 g, 0.184 mmol) in 1.8 ml THF and the reaction was cooled to –78 °C. To this solution is the added *n*-butyllithium (2.22 M in hexanes, 0.91 ml, 0.203 mmol, 1.1 equiv) and the solution is stirred 1.5 hrs. A solution of $MgBr_2$ (1.5 M, 0.147 ml, 1.2 equiv, prepared by slow addition of 0.650 ml 1,2-dibromoethane to a mixture of 0.182 g magnesium metal in 4.3 ml THF, followed by refluxing for 1 hour, then addition of 0.7 ml benzene for solubility). The resulting slurry is removed from the dry ice-acetone bath and allowed to slowly warm until a homogeneous solution is formed. The reaction is then re-cooled to –78 °C and a solution of aldehyde **2** in 0.6 ml THF is added dropwise. All dry ice was then removed from the acetone bath and the bath was allowed to slowly warm to ~–10 °C over a period of 3 hours. The reaction

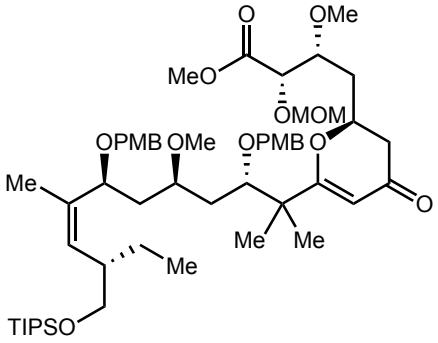
was then quenched with 5 ml $NaHCO_3$ (sat., aqueous) and extracted with 4X10 ml Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed. Purification on a column of silica gel with 3:1 then 2:1 Hexanes:EtOAc provided the alkyne addition product **18** as a mixture of 2 diastereomers (0.1724 g, 85% yield) and as a clear oil. With 0.75 g **13** and 0.46 g **2** (1.1 mmol scale), 0.95 g product **18** was isolated (79% yield) This crude mixture was then taken directly to the subsequent oxidation reaction without further characterization.

Into a 5 dram vial containing a stir bar is placed the alkyne addition product **18** from above (0.8324 g, 0.765 mmol) in 8 ml CH_2Cl_2. To this solution at room temperature was added MnO_2 (4.16 g, 5 weight equiv) and the reaction was stirred for 1 hour until complete consumption of the starting material was observed by TLC. The reaction was diluted with 8 ml hexanes and loaded directly onto a column of silica gel. The mixture was eluted with 4:1 then 3:1 hexanes:EtOAc and the product **S15** (0.6956 g, 84% yield) was obtained as a colorless oil. $[\alpha]_D$ = +4.78 (c = 1.04, $CHCl_3$, 25.0 °C); Rf = 0.40 (3:1 Hexanes:EtOAc); IR (film): υ = 2953, 2868, 2208, 1749, 1672, 1514, 1249, 1096; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.27 ($d_{(app)}$, J = 8.6 Hz, 2H), 7.19 ($d_{(app)}$, J = 8.6 Hz, 2H), 6.80 ($d_{(app)}$, J = 8.7 Hz, 2H), 6.74 ($d_{(app)}$, J = 8.7 Hz), 5.20 (d, J = 10.2 Hz, 1H), 4.73 (d, J = 7.0 Hz, 1H), 4.72 (d, J = 10.4 Hz, 1H), 4.69 (d, J = 7.1 Hz, 1H), 4.58 (d, J = 10.4 Hz, 1H), 4.31-4.40 (m, 3H), 4.16 (d, J = 3.6 Hz, 1H), 4.14 (d, J = 11 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.65-3.79 (m, 1H), 3.56 (dd, J = 5.3, 9.3 Hz, 1H), 3.47 (dd, J = 6.7, 9.2 Hz, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 3.31 (s, 3H), 2.75 (dd, J = 7.0, 15.9 Hz, 1H), 2.68 (dd, J = 5.4, 16.0 Hz, 1H)., 2.39-2.47 (m, 1H), 2.17 (ddd, J = 3.8, 10.7, 14.1 Hz, 1H), 1.82 (ddd, J = 5.7, 7.5, 14.2 Hz, 1H), 1.72 (d, J = 1.1 Hz, 3H), 1.63-1.78 (m, 4H), 1.44 (ddd, J = 3.4, 7.8, 14.3 Hz, 1H), 1.27 (s, 3H), 1.23 (s, 3H), 1.01-1.08 (m, 21H), 0.94 (t, J = 8.0 Hz, 9H), 0.91 (t, J = 7.5 Hz, 3H), 0.60 (q, J = 8.0 Hz, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 0.2, 5.1, 7.1, 12.1, 12.2, 18.2, 18.26, 18.29 24.6, 24.8, 25.0, 36.3, 37.2, 37.5, 38.2, 41.9, 52.2, 53.5, 55.3, 55.4, 56.6, 58.4, 65.7, 67.0, 70.1, 73.8, 74.6, 75.2, 76.9, 78.5, 81.3, 82.1, 96.8, 100.2, 113.9, 129.2, 129.4, 131.05, 131.08, 131.7, 136.3, 159.1, 159.2, 171.5, 185.8. HRMS (ESI): $C_{60}H_{100}O_{13}Si_2$ (M+Na) calculated: 1107.6595, found 1107.6593.

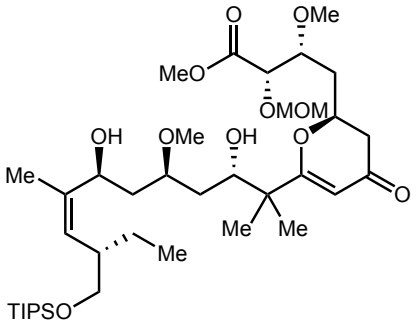


(2S,3R,5S,11S,13R,15S,18S,Z)-methyl 5-hydroxy-3,13-dimethoxy-11,15-bis((4-methoxybenzyl)oxy)-2-(methoxymethoxy)-10,10,16-trimethyl-7-oxo-18-(((triisopropylsilyl)oxy)methyl)icos-16-en-8-ynoate (**19**): Into a 5 dram vial was placed **S15** (0.638 g, 0.59 mmol) in 12 ml *i*-PrOH and the reaction was cooled to –40 °C in a dry ice acetone bath. Fluorosilicic acid solution (34% in water, 380 µl, 1.18 mmol, 2.0 equiv) was then added and the bath was allowed to slowly warm to –20 °C over the course of ~2 hrs, then stirred at this temperature an additional 2 hours. The reaction was then quenched by addition of 20 ml PH 7 phosphate buffer, and the mixture extracted with 5 X 20 ml Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed. Purification on a column of silica gel with 2:1 then 1:1 Hexanes:EtOAc as eluent provided the title compound (**19**) (0.5532 g, 97% yield) as a clear oil. $[\alpha]_D$ = +2.37 (c = 1.22, $CHCl_3$, 25.0 °C); Rf = 0.19 (2:1 Hexanes:EtOAc); IR (film): υ = 3509 (br), 2943, 2866, 2209, 1753, 1672, 1514, 1249, 1096; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.27 ($d_{(app)}$, J = 8.7 Hz, 2H), 7.20 ($d_{(app)}$, J = 8.7 Hz, 2H), 6.81 ($d_{(app)}$, J = 8.7 Hz, 2H), 6.74 ($d_{(app)}$, J = 8.7 Hz, 2H), 5.19 (d, J = 10.1 Hz, 1H), 4.73 (d, J = 7.0 Hz, 1H), 4.69 (d, J = 10.9 Hz, 1H), 4.69 (d, J = 7.0 Hz, 1H), 4.59 (d, J = 7.0 Hz, 1H), 4.35 (d, J = 11 Hz, 1H), 4.34 (dd, J = 2.8, 10.2 Hz, 1H), 4.26 (d, J = 3.6 Hz, 1H), 4.22-4.28 (m, 1H), 4.14 (d, J = 11.1 Hz, 1H), 3.87 (ddd, J = 3.7, 6.5, 6.6 Hz, 1H), 3.77 (s, 6H), 3.75 (s, 3H), 3.69-3.74 (m, 1H), 3.67 (dd, J = 2.0, 9.9 Hz, 1H), 3.56 (dd, J = 5.3, 9.4 Hz, 1H), 3.47 (dd, J = 6.6, 9.5 Hz, 1H), 3.39

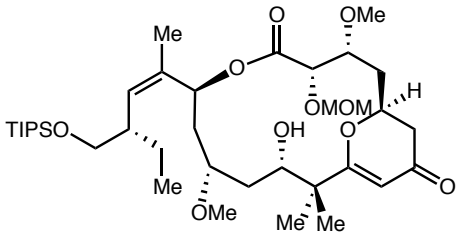
(s, 3H), 3.37 (s, 3H), 3.33 (s, 3H), 3.27 (d, J = 2.8 Hz, 1H), 2.70 (dd, J = 8.5, 17.4 Hz, 1H), 2.61 (dd, J = 3.6, 17.4 Hz, 1H), 2.38-2.47 (m, 1H), 2.18 (ddd, J = 3.5, 10.5, 14.1 Hz, 1H), 1.72 (d, J = 1.1 Hz, 3H, 1.58-1.80 (m, 5H), 1.44 (ddd, J = 2.9, 7.9, 13.7 Hz, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 1.19-1.27 (m, 1H), 1.01-1.07 (m, 21H) 0.91 (t, J = 7.5 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 12.08, 12.13, 18.23, 18.24, 18.3, 24.5, 24.9, 25.0, 36.3, 26.7, 37.3, 37.5, 41.9, 52.352.6, 55.4, 55.6, 56.5, 58.4, 65.4, 67.0, 70.7, 73.7, 74.9, 75.3, 76.4, 79.9, 81.4, 81.6, 96.8, 101.1, 113.89, 113.91, 129.2, 129.3, 130.96, 130.99, 131.7, 136.3, 159.1, 159.3, 171.3, 186.9.



Methyl (2*S*,3*R*)-3-methoxy-4-((*S*)-6-((3*S*,5*R*,7*S*,10*S*,*Z*)-5-methoxy-3,7-bis((4-methoxybenzyl)oxy)-2,8-dimethyl-10-(((triisopropylsilyl)oxy)methyl)dodec-8-en-2-yl)-4-oxo-3,4-dihydro-2*H*-pyran-2-yl)-2-(methoxymethoxy)butanoate (**S16**): Into a 5 dram vial was placed **19** (0.8118 g, 0.836 mmol) in 38 ml CH_2Cl_2 under a nitrogen atmosphere. To this solution was added $NaHCO_3$ (0.702 g, 8.36 mmol, 10 equiv), the reaction was cooled to 0 °C, and (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (0.0161 g, .021 mmol, 0.025 equiv) was added. The reaction was allowed to warm to room temperature and stirred 1 hour. The mixture was then filtered through a pipet containing florisil (~2 cm plug). The solvent was removed and the product purified on a column of silica gel and eluting with 2:1 then 1:1 Hexanes:EtOAc to give the title compound **S16** (0.7640 g, 94% yield) as a colorless oil. $[\alpha]_D$ = –23.12 (c = 1.57, $CHCl_3$, 25.1 °C); Rf = 0.42 (1:1 Hexanes:EtOAc); IR (film): υ = 2943, 2866, 1752, 1668, 1596, 1514, 1249, 1096, 1038; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.21 ($d_{(app)}$, J = 8.8 Hz, 2H), 7.17 ($d_{(app)}$, J = 8.8 Hz, 2H), 6.79 ($d_{(app)}$, J = 8.8 Hz, 2H), 6.73 ($d_{(app)}$, J = 8.8 Hz, 2H), 5.54 (s, 1H), 5.19 (d, J = 10.4 Hz, 1H), 4.72 (d, J = 7.2 Hz, 1H), 4.69 (d, J = 7.2 Hz, 1H), 4.53 (d, J = 10.6 Hz, 1H) 4.46 (d, J = 10.6 Hz, 1H), 4.40-4.45 (m, 1H), 4.35 (d, J = 11.0 Hz, 1H), 4.30 (dd, J = 2.5, 10.6 Hz, 1H), 4.27 (d, J = 3.6 Hz, 1H), 4.10 (d, J = 11.2 Hz, 1H), 3.94 (dd, J = 1.2, 10.1 Hz, 1H), 3.90 (ddd, J = 3.6, 6.5, 6.5 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.66-3.73 (m, 1H), 3.54 (dd, J = 5.4, 9.4 Hz, 1H), 3.47 (dd, J = 6.7, 9.4 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 3.33 (s, 3H), 2.46 (dd, J = 13.6, 16.6 Hz, 1H), 2.38 (dd, J = 3.4, 16.6 Hz, 1H), 2.35-2.44 (m, 1H) 2.14-2.23 (m, 2H), 2.10-2.08 (m, 1H), 1.71 (d, J = 1.0 Hz, 3H), 1.60-1.70 (m, 2H), 1.53 (ddd, J = 1.0, 10.5, 12.7 Hz, 1H), 1.37 (ddd, J = 3.1, 8.2, 14.2 Hz, 1H), 1.19-1.27 (m, 1H), 1.18 (s, 3H), 1.08 (s, 3H), 1.01-1.06 (m, 21H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 12.08, 12.14, 18.2, 18.3, 21.5, 22.0, 25.0, 34.9, 36.5, 37.8, 41.2, 41.9, 45.4, 52.4, 55.4, 55.5, 56.6, 58.5, 67.0, 70.0, 73.8, 74.9, 75.0, 76.2, 76.4, 78.0, 80.1, 96.9, 103.6, 113.9, 129.0, 129.1, 131.0, 131.1, 131.7, 136.3, 159.1, 159.2, 171.1, 182.8, 193.1. HRMS (ESI): $C_{54}H_{86}O_{13}Si$ (M+Na) calculated: 993.5730, found 993.5734.



Methyl (2*S*,3*R*)-4-((*S*)-6-((3*S*,5*R*,7*S*,10*S*,*Z*)-3,7-dihydroxy-5-methoxy-2,8-dimethyl-10-(((triisopropylsilyl)oxy)methyl)dodec-8-en-2-yl)-4-oxo-3,4-dihydro-2*H*-pyran-2-yl)-3-methoxy-2-(methoxymethoxy)butanoate (**20**): Into a 5 dram vial containing **S16** (0.764 g, 0.79 mmol) was added dry CH_2Cl_2 (21 ml) and PH 7 Phosphate buffer (4.9 ml). The reaction was cooled to 0 °C and DDQ (2,3-Dichloro-5,6-dicyano-*p*-benzoquinone, 0.8927 g, 3.93 mmol, 5 equiv) was added in one portion. The reaction was warmed to room temperature and stirred 30 min. A second batch of DDQ (0.8927 g, 3.93 mmol, 5 equiv) was then added and the reaction stirred 30 min. A third portion of DDQ (0.45 g, 2.5 equiv) was added and the reaction stirred 30 minutes. The reaction was then quenched with 20 ml $NaHCO_3$ (sat., aqueous) and extracted with 4X20 ml CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed. Purification on a column of silica gel with 2% then 5% MeOH in CH_2Cl_2 provided the title compound (0.5175 g, 90% yield) as a clear oil. $[\alpha]_D = -34.36$ (c = 1.43, $CHCl_3$, 25.4 °C). Rf = 0.32 (5% MeOH in CH_2Cl_2); IR (film): υ = 3442 (br), 2943, 2866, 1750, 1655, 1592, 1100, 1062; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.50 (s, 1H), 4.93 (d, J = 10.5 Hz, 1H), 4.74 (d, J = 7.0 Hz, 1H), 4.70 (d, J = 7.0 Hz, 1H), 4.42-4.50 (m, 2H), 4.34 (d, J = 3.4 Hz, 1H), 3.95 (d, J = 10.2 Hz, 1H), 3.90 (ddd, J = 3.6, 6.8, 7.0 Hz, 1H), 3.79 (s, 3H), 3.67 (p, J = 5.4 Hz, 1H), 3.60 (dd, J = 5.3, 9.2 Hz, 1H), 3.50-3.70 (m, 2H, (OH)), 3.41 (s, 3H), 3.38 (s, 6H), 3.32-3.41 (m, 1H), 2.73-2.82 (m, 1H), 2.49 (dfd, J = 13.9, 16.8 Hz, 1H), 2.40 (dd, J = 3.3, 16.8 Hz, 1H), 2.18 (ddd, J = 6.8, 8.2, 14.6 Hz, 1H), 2.00-2.12 (m, 2H), 1.79 (ddd, J = 5.5, 10.8, 14.6 Hz, 1H), 1.72 *d, J = 0.7 Hz, 1H), 1.69 (dd, J = 3.3, 5.5 Hz, 1H), 1.58 (dd, J = 4.4, 14.5 Hz, 1H), 1.47 (ddd, J = 4.5, 7.5, 13.2 Hz, 1H), 1.16 (s, 3H), 1.13 (s, 3H), 1.01-1.07 (m, 21H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 12.1, 18.1, 20.7, 21.3, 21.6, 25.0, 34.1, 34.8, 38.4, 41.6, 41.8, 45.1, 52.4, 56.6, 56.8, 58.4, 67.2, 69.8, 73.3, 76.0, 76.7, 78.1, 78.9, 96.9, 104.1, 129.6, 139.6, 171.2, 182.6, 193.2. HRMS (ESI): $C_{38}H_{70}O_{11}Si$ (M+Na) calculated: 753.4580, found 753.4582.

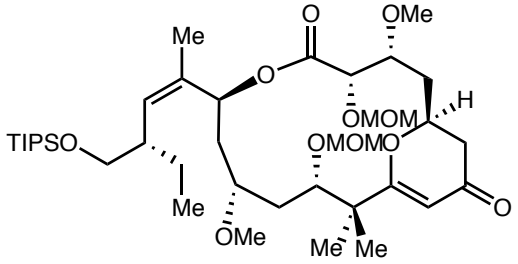


(1*S*,3*R*,4*S*,7*S*,9*S*,11*S*)-11-hydroxy-3,9-dimethoxy-4-(methoxymethoxy)-12,12-dimethyl-7-((*S*,*Z*)-4-(((triisopropylsilyl)oxy)methyl)hex-2-en-2-yl)-6,17-dioxabicyclo[11.3.1]heptadec-13-ene-5,15-dione (**21**): Into a 10 ml reaction vial is placed Pyranone **20** (0.0186 g, 0.26 mmol) and trimethyltin hydroxide (0.050 g, 0.27 mmol, 10 equiv) and the vial is purged with argon. Freshly distilled and degassed (argon) dichloroethane (2.6 ml) was added and the reaction was heated to 80 °C for 48 hours. The mixture was then cooled to room temperature, diluted with 5 ml EtOAc and 4 ml 1M HCL added. The layers were separated, the aqueous extracted with EtOAC (3X5 ml), and the combined organics were washed with 1M HCl (5 ml) before being dried over Na_2SO_4 and the solvent removed. Benzene (10 ml) was added and

then removed on the rotary evaporator to azeotropically dry the resulting acid before taking the crude acid to the next reaction.

The crude acid from above was dissolved in 0.55 ml THF and cooled to 0 °C. Triethylamine (21 µl, 0.153 mmol, 6 equiv) was then added and the reaction stirred about 1 minute before 2,4,6-trichlorobenzoyl chloride (12 µl, 0.077 mmol, 3 equiv) was added. The ice bath was then removed and the reaction allowed to warm to ambient temperature and stir 2 hours. The mixture was then diluted with 8 ml freshly distilled toluene, and the resulting solution was added via syringe pump to a 45 °C solution of 4-dimethylaminopyridine (0.025 g, 0.20 mmol, 8 equiv) in toluene (22 ml) over a period of 20 hours. After an additional 4 hours, the solvent was removed under reduced pressure and the product purified on a column of silica gel and eluted using 4:1 CH_2Cl_2:acetone to provide the desired macrolactone (0.010 g, 0.014 mmol) in 57% yield as a colorless oil. $[\alpha]_D$ = –39.0 (c = 1.68, $CHCl_3$, 23.1 °C). Rf = 0.8 (3:1 CH_2Cl_2:acetone); IR (film): υ = 3429 (br), 2942, 2866, 1731, 1663, 1592, 1463, 1244, 1098; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.80 (dd, J = 1.3, 10.1 Hz, 1H), 5.53 (s, 1H), 5.06 (d, J = 10.2 Hz, 1H), 4.77 (d, J = 7.1 Hz, 1H), 4.73 (d, J = 7.1 Hz, 1H), 4.55 (d, J = 2.5 Hz, 1H), 4.49 (ddt, J = 3.1, 10.1, 14.1 Hz, 1H), 4.22-4.28 (m, 2H), 3.78-3.85 (m, 1H), 3.57-3.63 (m, 1H), 3.47-3.54 (m. 1H), 3.40 (s, 3H), 3.39 (s, 3H), 3.37 (s, 3H), 2.92 (broad d, J = 1.8 Hz, 1H), 2.58-2.66 (m, 1H), 2.57 (dd, J = 14.4, 16.9 Hz, 1H), 2.38 (dd, J = 2.6, 17.0 Hz, 1H), 2.15-2.24 (m, 2H), 2.08 (ddd, J = 3.6, 9.9, 14.0 Hz, 1H), 1.98 (ddd, J = 1.9, 11.1, 15.1 Hz, 1H), 1.80 (ddd, J = 4.0, 10.9, 14.3, 1H), 1.71 (d, J = 1.0 Hz, 3H), 1.57 (ddd, J = 5.3, 7.6, 13.5 Hz, 1H), 1.43 (dd, J = 5.2, 13.9 Hz, 1H), 1.15 (s, 3H), 1.12 (s, 3H), 1.01-1.07 (m, 21H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 11.8, 12.2, 18.2, 18.3, 18.5, 19.9, 22.9, 24.8, 33.9, 35.8, 36.5, 42.1, 42.6, 44.5, 56.4, 57.6, 58.7, 67.3, 70.5, 73.5, 75.2, 76.8, 77.4, 96.9, 104.9, 131.7, 133.7, 169.5, 182.9, 193.7. HRMS (ESI): $C_{37}H_{66}O_{10}Si$ (M+H) calculated: 699.4498, found 699.4498.

Mom-protection of macrolactone **21**: Interception of Taylor Synthesis:[8]



S17: Into a 3 dram vial was placed pyranone **21** (0.0075 g, 0.011 mmol) and 1.1 ml CH_2Cl_2 and the reaction was cooled to 0 °C. Hünigs base (47 µl, 0.27 mmol, 25 equiv) was added, followed by chloromethyl methyl ether (16 µl, 0.215 mmol, 20 equiv). The reaction was allowed to warm to ambient temperature and stirred 24 hours. A saturated solution of $NaHCO_3$ was then added (2 ml) and the aqueous phase extracted with EtOAc (3X5 ml). The combined organic layers were dried over Na_2SO_4, the solvent was removed, and the product purified on a column of silica gel and eluted with 1:1 Hexanes:EtOAc to give the product (0.0029 g, 36% yield) as a colorless oil. $[\alpha]_D$ = –31.6 (c = 0.25, $CHCl_3$, 24.0 °C) (Lit:[3] $[\alpha]^{22}_D$= -81.2° (c 0.005, $CHCl_3$);. IR (film): υ = 2886, 2825, 1705, 1644, 1573, 1442, 1362, 1136, 1082, 1020; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.79 (dd, J = 1.5, 8.7 Hz, 1H), 5.50 (s, 1H), 5.07 (d, J = 10.3 Hz, 1H), 4.65-4.76 (m, J = 4 H), 4.34-4.41 (m, 1H), 4.22 (d, J = 6.2 Hz, 1H), 3.90-3.94 (m, 1H), 3.54-3.59 (m, 3H), 3.47-3.53 (m, 1H), 3.45 (s, 3H), 3.40 (s, 3H), 3.38 (s, 3H), 3.31 (s, 3H), 2.58-2.65 (m, 1H), 2.57 (dd, J = 13.8, 16.9 Hz, 1H), 2.38 (dd, J = 3.3, 16.9 Hz, 1H), 2.21-2.30 (m, 1H), 1.92-2.11 (m, 3H), 1.69 (s, 3H), 1.61-1.67 (m, 2H), 1.48-1.53 (m, 1H), 1.28-1.33 (m, 1H), 1.26 (s, 3H), 1.18 (s, 3H), 1.02-1.07 (m, 21H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 11.7, 12.2, 14.3, 18.2, 18.3, 20.9, 22.8, 24.8, 25.0, 29.9, 35.2, 35.8, 38.7, 40.7, 42.1, 45.1, 56.3, 56.7, 58.1, 67.2, 70.9, 74.6, 76.5, 76.7, 78.8, 84.6,

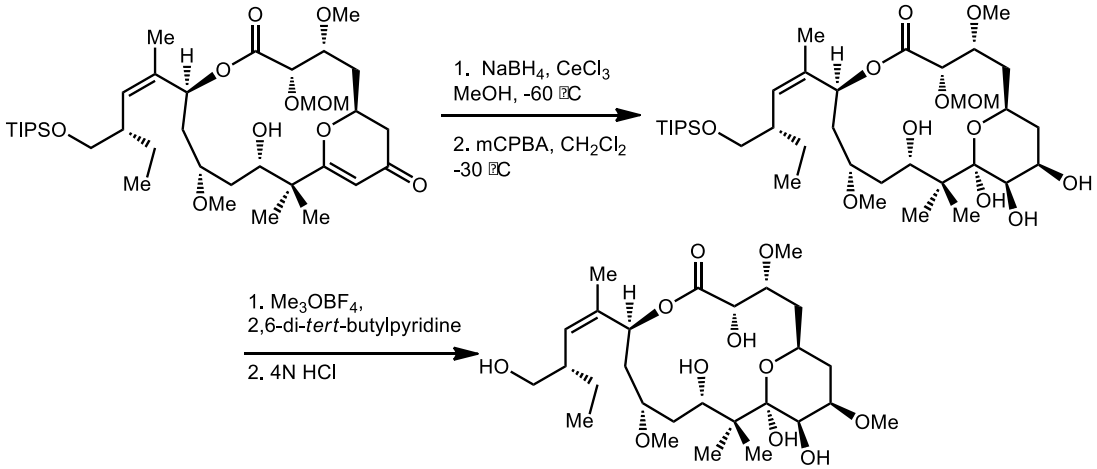
96.5, 99.4, 104.9, 131.7, 133.8, 169.5, 181.0, 193.3. HRMS (ESI): $C_{39}H_{70}O_{11}Si$ (M+Na) calculated: 765.4580, found 765.4577.

Our first indication of the incorrect assignment of the absolute stereochemistry of the ethyl stereocenter came from discrepancies in the ^{1}H and ^{13}C NMR spectra of intermediate **S17** and the same compound reported by the Taylor group. See a comparison of the ^{13}C chemical shifts below, and of the 1H spectra in the figures section.

Chemical Shift comparison between our reported intermediate 19a and the same compound from the Taylor synthesis:

Center Peak of CHCl3 referenced to 77.23 ppm	Center Peak of CHCl3 referenced to 77.0 ppm	Intermediate from Taylor Synthesis
11.74	11.51	
12.22	11.99	12.21
14.34	14.11	
18.23	18	18.18
18.28	18.05	18.29
20.91	20.68	20.53
22.88	22.65	
24.76	24.53	24.7
25.01	24.78	25.15
29.92	29.69	29.96
35.23	35	34.84
35.82	35.59	36.34
38.7	38.47	38.45
40.74	40.51	40.99
42.11	41.88	41.97
45.09	44.86	45.15
56.25	56.02	56.22
56.73	56.5	56.71
58.21	57.98	58.33
67.19	66.96	65.89
70.88	70.65	70.63
74.58	74.35	74.67
76.53	76.3	76.42
76.73	76.5	76.75
		77.47
78.75	78.52	79.16
84.58	84.35	85.01
96.48	96.25	96.35
99.39	99.16	99.37
104.91	104.68	105.17
131.73	131.5	131.54
133.8	133.57	133.11

169.49	169.26	169.39
181.03	180.8	180.99
193.24	193.01	193.35



(–)-18-*epi*-Peloruside A: We found it easiest to perform the following 4-step sequence without intermediate characterization. This final 4 step sequence follows modified procedures based on the Taylor synthesis of (+)-peloruside A.

Into a 3 dram vial was placed pyranone **21** (0.0084 g, 0.012 mmol) in 1.1 ml MeOH and cerium trichloride heptahydrate (0.0030 g, 0.012 mmol, 1 equiv) was added. The reaction was cooled to -60 °C. In a separate vial is placed $NaBH_4$ (0.0054 g) and the vial was cooled to 0 °C before 2.0 ml of MeOH was added. The vial was swirled until all $NaBH_4$ was dissolved and then 0.30 ml (0.00081 mg, 1.9 equiv) of this solution was quickly removed and added to the reaction dropwise. The reaction was stirred at -60 °C for 45 minutes and the quenched with 1ml brine and 2 ml PH 7 phosphate buffer. The mixture was then extracted with EtOAc (4X5 ml), CH_2Cl_2 (1X5 ml), the combined organics dried over Na_2SO_4, and the solvent removed under reduced pressure in a cold (>20 °C) water bath. The crude product was azeotroped with benzene one time before carrying on to the next reaction.

The crude material from above was dissolved in 1.3 ml CH_2Cl_2 and treated with solid $NaHCO_3$ (0.0055g, 5 equiv) followed by mCPBA (0.0022g, 0.0127 mmol, 1.05 equiv) at -30 °C. The reaction was stirred at this temperature for 45 minutes, quenched with 1.5 ml saturated aqueous NH_4Cl, and extracted with EtOAc (4x4 ml). The combined organics were washed with 5 ml $NaHCO_3$ solution, dried over Na_2SO_4, and the solvent removed under reduced pressure. The mixture was purified on a column of silica gel with 10% EtOH in toluene as eluent. Spot with Rf = 0.37 (10% EtOH in toluene) was collected and carried onto the next reaction sequence (0.0058 g, 63% yield, 2 steps).

Into a 3 dram vial was placed the purified material from above (0.0041 g, .0056 mmol) in 2.4 ml CH_2Cl_2. The reaction was cooled to 0 °C and treated with 2,6-di-*tert*-butylpyridine (19 µl, 0.0836 mmol, 15 equiv) followed by Me_3OBF_4 (0.0083g, 0.0557 mmol, 10 equiv). The reaction was stirred at 0 °C for 30 minutes, at which time additional Me_3OBF_4 (0.0020g, 2.4 equiv) was added. After an additional 20 minutes of stirring, Me_3OBF_4 (0.0020g, 2.4 equiv) was again added. The reaction was then stirred 15 min and quenched by addition of saturated aqueous $NaHCO_3$ (4 ml) and extracted with 4X5 ml. The combined organics were dried over Na_2SO_4 and the solvent was removed. The crude product was dissolved in CH_2Cl_2 and loaded onto a small plug of silica gel, and 5 ml CH_2Cl_2 was passed through the plug to elute the 2,6-di-*tert*-butylpyridine. The crude product was then eluted with 10 ml 10% MeOH in CH_2Cl_2 and the solvent removed. The crude product was dissolved in 1.2 ml THF, cooled to 0 °C, and 4N HCl (1.2 ml) was added. The reaction was allowed to warm to ambient temperature and stirred 3 hours. The mixture was then made basic by addition of saturated aqueous $NaHCO_3$ and extracted with 4X15 ml EtOAc. The combined organics were dried over Na_2SO_4, the solvent was removed, and the

product was purified on a column of silica gel and eluted with 1%–10% MeOH in CH_2Cl_2 to give the desired product (–)-18-*epi*-peloruside A (0.0012 g, 39% yield, 2 steps) as a white solid after lyophilization from benzene. Rf = 0.39 (10% MeOH in CH_2Cl_2). $[\alpha]_D$ = -21.7 (c = 0.05, $CHCl_3$, 24.0 °C). IR (film): υ = 3340 (br), 2921, 2878, 2810, 1713, 1425, 1394, 1243, 1076, 1008, 789; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.80 (br s, 1H), 5.68 (d, J = 11.2 Hz, 1H), 5.03 (d, J = 10.2 Hz, 1H), 4.86-4.92 (m, 1H), 4.56 (d, J = 9.0 hz, 1H), 4.47 (s, 1H), 4.26-4.31 (m, 1H), 4.01 (d, J = 2.5 Hz, 1H), 4.27 (dd, J = 4.9, 11.1 Hz, 1H), 3.93-3.99 (m, 1H), 3.82 (ddd, J = 2.9, 5.0, 11.4 Hz, 1H), 3.58-3.66 (m, 1H), 3.47 (s, 3H), 3.38 (s, 3H), 3.35 (t, J = 10.2 Hz, 1H), 3.30 (s, 3H), 2.72 (d, J = 9.2 Hz, 1H), 2.66-2.75 (m, 1H), 2.26 (dd, J = 10.3, 14.4 Hz, 1H), 1.95-2.16 (m, 3H), 1.70-1.83 (m, 3H), 1.69 (d, J = 0.7 Hz, 3H), 1.39-1.48 (m, 2H), 1.28-1.35 (m, 1H), 1.12 (s, 3H), 1.08 (s, 3H), 0.98 (t, J = 7.6 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.0, 136.5, 130.41, 102.2, 78.3, 78.1, 76.2, 74.1, 70.5, 70.1, 67.0, 66.7, 66.5, 59.4, 56.4, 55.9, 42.7, 42.5, 36.1, 32.0, 24.9, 21.0, 18.9, 18.2, 16.0, 11.9. HRMS (ESI): $C_{27}H_{48}O_{11}Na$ (M+Na) calculated: 571.3089, found 571.3083.

The coupling constant between the hydrogens at the 7 and 8 positions of peloruside A is 2.5 Hz (see doublet at 4.02), confirming a syn relationship between the hydroxyl group and methoxy group on the pyran ring of our final compound, (–)-epi-peloruside A. See West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem.* **2000**, *65,* 445.

For a comparison of 1H spectra, see Spectral Images section.

Comparison of ^{13}C spectra for (–)-18-*epi*-peloruside A and natural and synthetic materials:

18-*epi*-Peloruside A	Peloruside A (Natural Material)	Synthetic Material (Taylor)
172.74	174	174.01
136.26	136.1	136.09
130.18	131.1	131.18
101.97	101.9	101.91
78.09	78.3	78.28
77.86	77.9	77.93
75.93	75.9	75.9
73.87	73.9	73.89
70.29	70.9	70.91
69.83	70.3	70.3
66.81	66.9	67
66.43	66.8	66.85
66.30	63.5	63.49
59.13	59.1	59.11
56.18	56.1	56.09
55.69	55.7	55.7
42.47	43.6	43.6
42.27	43.3	43.37
35.90	35.7	35.7
32.93	33	33.92
31.74	32.6	32.59
24.64	31.7	31.67
20.81	24.6	24.6
18.67	20.8	20.81

17.99	17.5	17.45
15.78	15.8	15.84
11.63	12.2	12.24

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