Supporting Information

Studies Towards Asymmetric Synthesis of 4(S)-11-Dihydroxydocosahexaenoic acid (diHDHA) Featuring Cross-Coupling of Chiral Stannane under Mild Conditions

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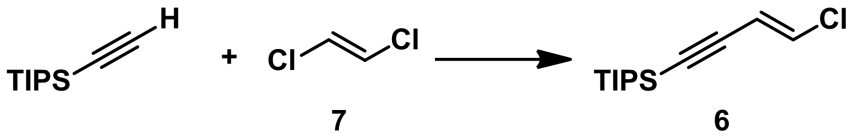
l. General introduction

All reactions were conducted open to air atmosphere unless otherwise stated. All solvents (CH_2Cl_2, CH_3CN and water) were purchased from Fisher Scientific Company and used without further purification. Flash chromatography (FC) was performed using E. Merck silica gel 60 (240–400 mesh). Thin layer chromatography (TLC) was performed using pre-coated plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on spectrometers at operating frequencies of 400 MHz (^{1}H) or 100 MHz (^{13}C) as indicated in the individual spectrum. Chemical shifts (δ) are given in ppm relative to residual solvent (usually chloroform δ = 7.26 for ^{1}H NMR or δ = 77.3 for proton decoupled ^{13}C NMR) and coupling constants (*J*) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quartet, and m for multiplet. Low resolution LC/MS spectra were obtained with an Agilent 1200 series API-LC/MSD spectrometer. High resolution mass spectral analyses were

kindly provided by Professor Kevin A. Schug at Department of Chemistry & Biochemistry, The University of Texas at Arlington.
All starting material compounds were purchased from Sigma-Aldrich or TCI America.

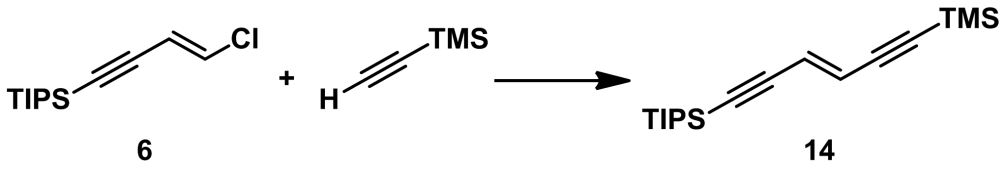
II. Experiment procedures and compounds characterization data

1. (*E*)-(4-chlorobut-3-en-1-yn-1-yl)triisopropylsilane (6)[1]



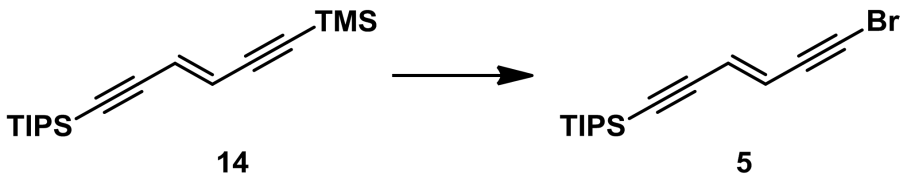
To a stirred solution of ethynyltriisopropylsilane (2.0 g, 11.0 mmol), (*E*)-1,2-dichloroethene (2.1 g, 21.9 mmol), $Pd(PPh_3)_2Cl_2$ (231.1mg, 0.3 mmol) and CuI (63.2 mg, 0.3 mmol) in ether (20 mL) under argon at room temperature was added piperidine (1.9 g, 21.9 mmol). The reaction was covered with aluminum foil and stirred for additional 5 h. The mixture was filtered though a pad of silica-gel, solvent was removed and purified by silica-gel column with eluent (pure hexane) to afford 2.6 g colorless oil in quantitative yield. R_f = 0.65 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (d, *J* = 13.6 Hz, 1H), 5.98 (d, *J* = 13.6 Hz, 1H), 1.09 (s, 3H), 1.07 (s, 18H).

2. (*E*)-triisopropyl(6-(trimethylsilyl)hexa-3-en-1,5-diyn-1-yl)silane (14)



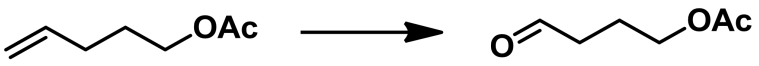
To a mixture of (*E*)-4-triisopropyl silyl-1-chloro-1-buten-3-yne (2.0 g, 8.2 mmol), ethynyltrimethylsilane (1.6 g, 16.5 mmol), $Pd(PPh_3)_2Cl_2$ (289.0 mg, 0.4 mmol) and CuBr (118.1 mg, 0.8 mmol) in toluene (40 mL) under argon at room temperature was added piperidine (1.4 g, 16.5 mmol). The reaction was covered with aluminum foil at ambient temperature continued for overnight. The mixture was filtered through a short pad of silica-gel, organic solvent was evaporated and then the crude product was purified by silica-gel flash chromatography with eluent (pure hexane) to afford 2.5 g light-yellow oil in quantitative yield. R_f = 0.50 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 16.0 Hz, 20.0 Hz, 2H), 1.09 (s, 3H), 1.07 (s, 18H), 0.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.1, 121.4, 104.9, 103.0, 100.4, 97.4, 18.6, 11.2, 0.2.

3. (*E*)-(6-bromohexa-3-en-1,5-diyn-1-yl)triisopropylsilane (5)



To a stirred solution of (*E*)-triisopropyl(6-(trimethylsilyl)hexa-3-en-1,5-diyn-1-yl)silane (0.7 g, 2.3 mmol), $AgNO_3$ (78.5 mg, 0.5 mmol) in anhydrous acetone (20 mL) under argon at ambient temperature was added NBS (491.2 mg, 2.8 mmol) in one portion. The reaction was covered with aluminum foil and continued for 3 h. After completion of the reaction, organic solvent was evaporated in *vacuo*, diluted with hexane (50 mL), washed with brine (50 mL x 2) and dried over Na_2SO_4. Solvent was removed in *vacuo*, and purified by silica-gel flash chromatography with eluent (pure hexane) to afford 690.4 mg light-yellow oil in 97% yield. R_f = 0.54 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (d, *J* = 16.0 Hz, 1H), 5.97 (d, *J* = 16.0 Hz, 1H), 1.09 (s, 3H), 1.07 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.8, 120. 9, 104.4, 97.9, 78.5, 55.1, 18.6, 11.2.

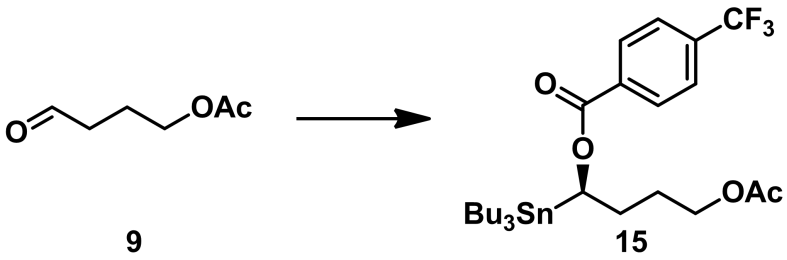
4. 4-oxobutyl acetate (9)[2,3,4]



10 **9**

4-Oxobutyl acetate was synthesized according to literature ozonolysis procedure. 4-Pentenyl Acetate (TCI, 10.0 g) was dissolved in 80 mL of anhydrous DCM in 250mL two-neck round bottom flask. One of the neck was connected with a drying tube filled with drierite, the other one was connected to a O_3 dispenser. After cooled to -78°C, O_3 was bubbled to the reaction with vigorous stirring until the reaction changed to pale blue color (~45min). Reaction was purged with argon to remove the excess O_3, then Ph_3P (22.5 g) was added. The reaction was warmed up to rt slowly, and stirred for another one hour at rt. To the reaction mixture was added hexane to precipitate most of the triphenylphosphine oxide. The solvent was decanted and concentrated in vacuum. Crude aldehyde was distilled under vacuum to afford 4-oxobutyl acetate (~9-10g).

5. (*R*)-4-acetoxy-1-(tributylstannyl)butyl 4-(trifluoromethyl)benzoate (15)[5]

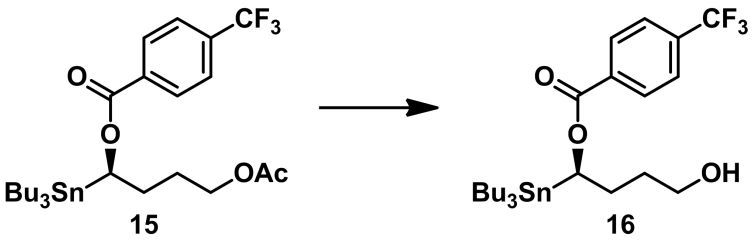


9 **15**

To a 250 mL RBF was charged with DME (40 mL) and a stirring bar under Argon, covered with aluminum foil, cooled to -78 °C. Diethyl zinc (1.0 M in hexane, 17.5 mL, 17.5 mmol) and tributyltin hydride (5.1 g, 17.5 mmol) were injected in sequence. The reaction was stirred for 5 min before moved to 4 °C. The mixture was stirred for 24 h at 4 °C. Then the reaction was diluted with DME (50 mL), cooled to -78 °C. Chiral ligand (253.3 mg, 1.0 mmol) dissolved in DME (30 mL) was added. After stirred for 5 min, 4-oxobutyl acetate (642.0 mg, 0.6 mL, 5.0 mmol) was added. The reaction was stirred at -25 °C covered with aluminum foil for overnight. The reaction was quenched slowly with Sat. NH_4Cl (100 mL). After warmed up to ambient temperature and stirred for additional 10 min, the organic solvent was evaporated in rotavapor,

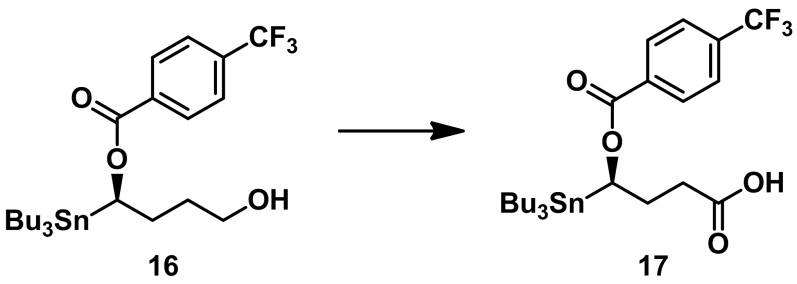
the aqueous residue was extracted with DCM (80 mL x 4), the DCM layer was dried over Na_2SO_4, concentrated in rotavapor. Crude residue was quickly filtered through a pad of silica gel (to remove the non-polar and polar tin byproducts), the flask and the silica gel pad was washed with hexane, then gradually increased to 10% EtOAc/ hexane. The crude product fractions (R_f = 0.15, 25% EtOAc in hexane) were combined and concentrated. The residue was stirred with 4-(trifluoromethyl)benzoyl chloride (1.6 g, 1.5 mL, 7.5 mmol), pyridine (0.8 g, 0.8 mL, 10.0 mmol) and catalytic amount of DMAP in DCM at room temperature. After 1 h, the reaction was quenched with brine, extracted with DCM (80 mL x 4). DCM layer dried over Na_2SO_4, concentrated in rotavapor. Crude product was purified by silica gel chromatography with eluent 20% EtOAc in hexane to give (*R*)-4-acetoxy-1-(tributylstannyl)butyl 4-(trifluoromethyl)benzoate in 60% yield. R_f = 0.5 (25% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 5.2 Hz, 2H), 7.71 (d, *J* = 4.0 Hz, 2H), 5.08 (s, 1H), 4.10 (s, 2H), 2.16-2.07 (m, 1H), 2.04 (s, 3H), 2.10-1.92 (m, 1H), 1.88-1.68 (m, 2H), 1.54-1.24 (m, 12H), 0.94-0.83 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 165.7, 134.4 (q, *J* = 33.0 Hz), 133.9, 130.1, 129.9, 125.6 (q, *J* = 4.0 Hz), 123.9 (q, *J* = 271.0 Hz), 72.7 (t, *J* = 163.0 Hz), 64.2, 29.7 (t, *J* = 10.0 Hz), 27.6 (t, *J* = 29.0 Hz), 27.1, 21.2, 13.9, 9.79 (t, *J* = 153.0 Hz).

6. (*R*)-4-hydroxy-1-(tributylstannyl)butyl 4-(trifluoromethyl)benzoate (16)



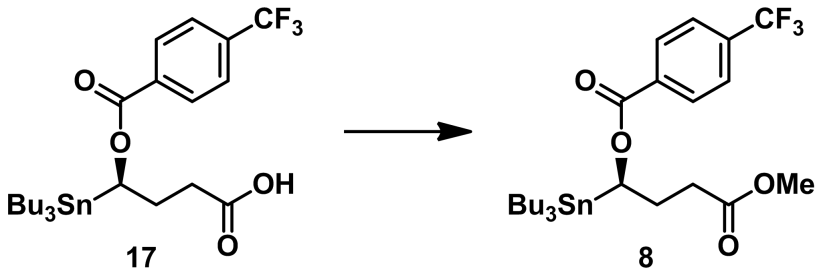
To a stirred solution of (*R*)-4-Acetoxy-1-(tributylstannyl)butyl 4-(trifluoromethyl)benzoate (1.1 g, 1.9 mmol) in anhydrous methanol (15 mL) under argon at ambient temperature was added catalytic amount of PTSA (25.6 mg, 0.1 mmol). The mixture was heated to 50 ^{o}C for 5 h. After the reaction was completed, sat.$NaHCO_3$ was added to quench the reaction, the organic phase was evaporated in rotavapor. The aqueous residue was extracted with DCM (50 mL x 3), the combined DCM extractions were dried over Na_2SO_4, concentrated in rotavapor and purified by silica-gel flash chromatography with eluent (20% EtOAc in henaxe) to give 1.5 g colorless oil in quantitative yield. R_f = 0.3 (25% EtOAc in hexane).

7. (*R*)-4-(tributylstannyl)-4-((4-(trifluoromethyl)benzoyl)oxy)butanoic acid (17)[6,7]



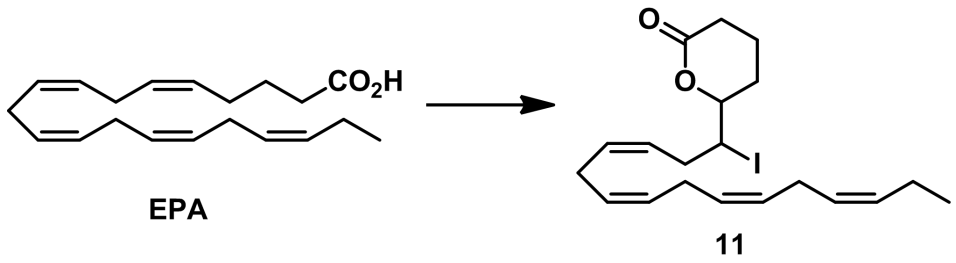
To a stirred solution of (*R*)-4-Hydroxy-1-(tributylstannyl)butyl 4-(trifluoromethyl)benzoate (1.5 g, 2.7 mmol) in anhydrous DMF (20 mL) under argon at room temperature was added PDC (3.0 g, 8.0 mmol) and AcOH (1.0 mL) in sequence. The reaction was stirred at ambient temperature for overnight. The reaction was quenched with brine (50 mL), extracted with EtOAc (50 mL x 3), organic layer was further washed with brine, dried over Na_2SO_4, concentrated in rotavapor. Crude acid was purified by silica-gel flash chromatography with eluent (30% EtOAc in hexane) to give 0.6 g white solid in 39% yield. R_f = 0.1 (25% EtOAc in hexane).

8. (*R*)-4-methoxy-4-oxo-1-(tributylstannyl)butyl 4-(trifluoromethyl)benzoate (8)



To a stirred solution of (*R*)-4-(tributylstannyl)-4-(4-(trifluoromethyl)benzoyloxy)butanoic acid (600.1 mg, 1.1 mmol) in anhydrous THF (20 mL) under argon at 0 °C was added diazomethane generated in situ (in wet ether) until the yellow color of the solution was not changed for 1 min. Solvent was removed and purified by silica-gel flash chromatography to afford 310.2 mg colorless oil in 50% yield. R_f = 0.6 (25% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 8.0 Hz, 2H), 5.30 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.91 (s, 3H), 2.80-2.62 (m, 3H), 2.52-2.44 (m, 1H), 1.84-1.50 (m, 12H), 1.23-1.11 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 165.7, 134.7 (q, *J* = 32.0 Hz), 133.8, 129.9, 125.6 (q, *J* = 4.0 Hz), 123.9 (q, *J* = 271.0 Hz), 72.4 (t, *J* = 158.0 Hz), 51.8, 33.1 (t, *J* = 19.0 Hz), 29.7, 29.2 (t, *J* = 10.0 Hz), 27.6 (t, *J* = 28.0 Hz), 13.8, 9.85 (t, *J* = 162.0 Hz). (The product was covered with aluminum foil, kept in -25°C freezer under argon when not using.)

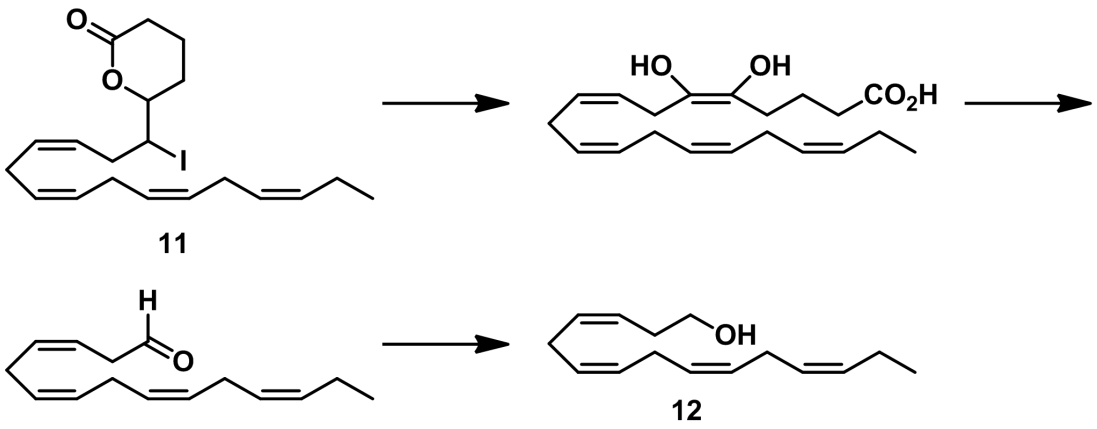
9. 6-((3*Z*,6*Z*,9*Z*,12*Z*)-1-iodopentadeca-3,6,9,12-tetraen-1-yl)tetrahydro-2H-pyran-2-one (11)



To a stirred solution of eicosapentaenoic acid (1.0 g, 3.3 mmol) in a mixture of THF (50 mL) and H_2O (25 mL) under argon at 0 °C was added $KHCO_3$ (1.5 g, 15.1 mmol), KI (2.1g, 13.0 mmol) and I_2 (6.2 g, 24.1 mmol) in sequence. The reaction was continued at 4 °C for 18h, the reaction was diluted with 50 mL water, quenched with sat. $Na_2S_2O_3$ solution until the black color changed to yellow then disappeared. Extracted with EtOAc (50 mL x 5), combined EtOAc layer

was washed with 10% HCl (20 mL), water (50 mL), brine (50 mL), dried over Na_2SO_4, concentrated in *vacuo*. Crude residue was purified by silica gel flash chromatography with eluent (30% EtOAc in hexane) to afford 1.1 g colorless oil in 78% yield. R_f = 0.4 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (dd, *J* = 16.0 Hz, 8.0 Hz, 1H), 5.41-5.25 (m, 7H), 4.08 (td, *J* = 8.0 Hz, 4.0 Hz, 1H), 3.93 (dt, *J* = 12.0 Hz, 4.0 Hz, 1H), 2.84-2.78 (m, 8H), 2.64-2.51 (m, 1H), 2.50-2.41 (m, 1H), 2.09-1.72 (m, 6H), 0.95 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 132.0, 131.4, 128.7, 128.6, 127.7, 127.4, 127.0, 126.9, 80.9, 37.0, 34.4, 29.6, 28.0, 25.9, 25.7, 25.6, 20.6, 18.3, 14.3.

10. (3*Z*,6*Z*,9*Z*,12*Z*)-pentadeca-3,6,9,12-tetraen-1-ol (12)[8]

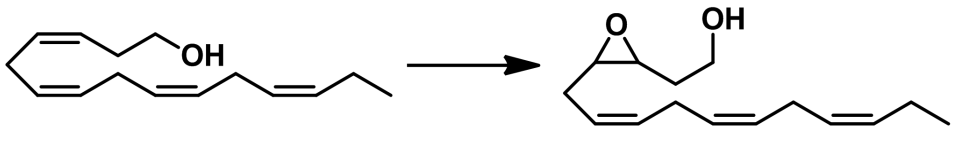


(3*Z,* 6*Z,* 9*Z,* 12*Z*)-pentadeca-3, 6, 9, 12-tetraen-1-ol was synthesized according to literature. To a stirred solution of lactone iodide (1.1 g, 2.5 mmol) in a mixture of MeOH (11.5 mL) and H_2O (0.5 mL) was added 5% KOH (3.0 mL) at 0 °C. The mixture was stirred under argon at 60 °C for 4 h. The reaction mixture was acidified with 5% aqueous HCl (10 mL) and extracted with EtOAc (50 mL x 4). The organic layer was combined and was washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, and concentrated in rotavapor. The crude product was immediately used for next step without further purification.

To a stirred solution of the crude residue in a mixture of THF (8.0 mL) and H_2O (4.0 mL) was added sodium periodate (0.8 g, 6.5 mmol) at 0 °C under argon. After 1 h, the reaction mixture was diluted with brine (80 mL), extracted with DCM (60 mL x 5). Combined DCM extractions were dried over Na_2SO_4, and concentrated in rotavapor. The crude product was immediately for next step without further purification.

To a stirred solution of the crude residue in anhydrous MeOH (15 mL) was treated with $NaBH_4$ (0.3 g, 7.9 mmol) at 0 °C for 30 min. The reaction was quenched with brine (80 mL) at 0 °C and extracted with DCM (60 mL x 5). Combined DCM extractions were dried over Na_2SO_4, and concentrated in rotavapor. Crude residue was purified by silica gel flash chromatography to afford 410.0 mg colorless oil in 76% yield for 3 steps. (All the reaction intermediates including the iodo starting material are not stable, so all these reactions should be finished in the same day! The product was covered with aluminum foil, kept in -78°C freezer under argon when not using.)

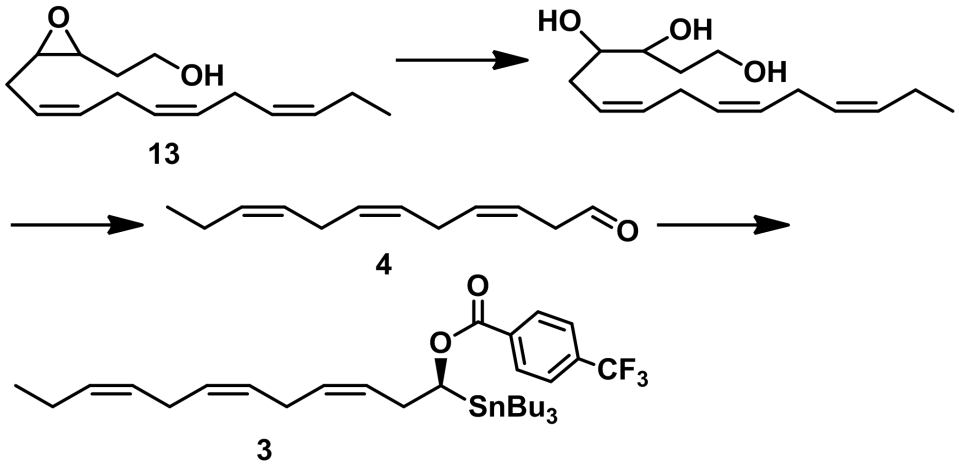
11. 2-(3-((2*Z*,5*Z*,8*Z*)-undeca-2,5,8-trien-1-yl)oxiran-2-yl)ethanol (13)[9]



12 **13**

Epoxidation of (3*Z*, 6*Z*, 9*Z*, 12*Z*)-pentadeca-3,6,9,12-tetraen-1-ol was performed following the literature procedure with modifications: A solution of the alcohol (0.41 g, 1.86 mmol) in toluene (15.0 mL) was cooled to 0 °C and $VO(acac)_2$ (25.0 mg, 0.093 mmol) added in one portion to give a green suspension. After stirred for 5min, *t*-BuOOH (6.0 M in decane, 0.62 mL, 3.72 mmol) was added dropwise and the reaction mixture allowed to warm up to ambient temperature (changed to reddish). After the reaction completed (in ~5h, if not, add more *t*-BuOOH), quenched by adding aqueous sodium sulfite solution (20% w/w) (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with aqueous sodium sulfite solution (20% w/w, 75 mL) and brine (75 mL), dried over Na_2SO_4, and concentrated in *vacuo*. Crude residue was purified by silica gel chromatography (R_f = 0.16, hexane/ EtOAc 2:1) to afford 2-(3-((2*Z*, 5*Z*, 8*Z*)-undeca-2,5,8-trien-1-yl)oxiran-2-yl)ethanol (0.33 g, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49-5.29 (m, 6H), 3.84-3.79 (m, 2H), 3.09 (dt, *J* = 8.0, 4.0 Hz, 1H), 2.97 (m, 1H), 2.83-2.76 (m, 4H), 2.43-2.35 (m, 1H), 2.26-2.19 (m, 1H), 2.08-2.01 (m, 2H), 1.90-1.83 (m, 1H), 1.74-1.67 (m, 1H), 0.95 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2, 130.9, 129.0, 127.6, 127.0, 124.2, 60.6, 56.2, 55.1, 30.7, 26.5, 25.9, 25.7, 20.7, 14.4. (The product was covered with aluminum foil, kept in -78^{o}C freezer under argon when not using.)

12. (*S*,3*Z*,6*Z*,9*Z*)-1-(tributylstannyl)dodeca-3,6,9-trien-1-yl-4-(trifluoromethyl)benzoate (12)[5]



13 **4** **3**

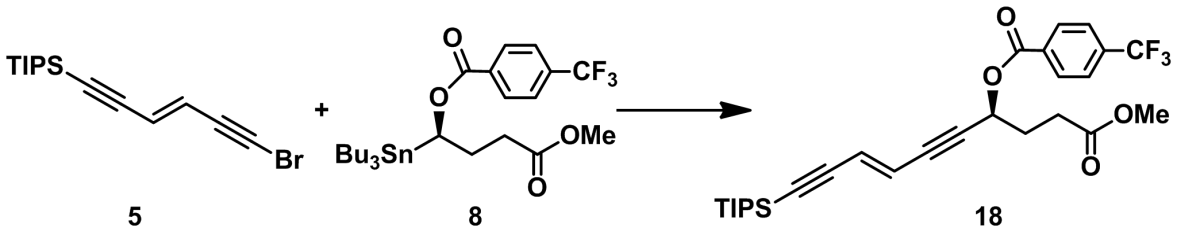
The epoxide was dissolved in DME (20 mL)/ H_2O (10 mL) under argon, cooled to 0^{o}C. Concentrated $HClO_4$ (60%, 1.5 mL) was injected. The reaction was warmed up to rt and stirred until all epoxide disappeared (followed by TLC, ~5h). Quenched with sat.$NaHCO_3$ solution (80 mL). After organic solvent was evaporated in rotavapor, the aqueous residue was extracted with

EtOAc (50 mL x 5). The combined EtOAc layers were washed with brine (60 mL), dried over Na_2SO_4, and concentrated in *vacuo*.

The crude residue was stirred with sodium periodate (600.0 mg) in THF/ H_2O (2:1, 20 mL) at 0°C under argon. After 1h, the reaction mixture was diluted with brine (80 mL), extracted with DCM (60mL x 5). Combined DCM extractions were dried over Na_2SO_4, and concentrated in rotavapor. Crude residue was again dissolved in 10% EtOAc/ Hexane, quickly filtered through a pad of silica gel (to remove the polar byproduct). The flask and the silica gel pad were washed with more 10% EtOAc/ Hexane. The aldehyde fractions was condensed to give crude (3*Z*, 6*Z*, 9*Z*)-dodeca-3,6,9-trienal (R_f = 0.49, hexane/ EtOAc 4:1) which was used immediately for the next step. (The Triol and aldehyde are not stable, so this reaction should be performed the next day after the setting up of the Et_2Zn/ Bu_3SnH reaction!)

Et_2Zn (1.0 M in hexane, 4.0 mL) was injected to anhydrous DME (10 mL) under argon. After cooled to -78 °C, Bu_3SnH (1.06 mL, 4.0 mmol) was injected. The reaction was stirred at -4 °C with aluminum foil cover and argon protection. After stirred for 1 day at 4 °C, the reaction was diluted with 20 mL more DME, cooled to -78 °C. Chiral ligand (48 mg, 0.2 mmol, dissolved in 5 mL DME under argon) was added. After stirred for 5 min, crude aldehyde (in 5 mL DME under argon) was added. The reaction mixture was stirred at -25 °C overnight covered with aluminum foil. After the reaction was complete (followed by TLC, ~15h. Alcohol R_f = 0.54 hexane/ EtOAc 6:1, strong PMA active), 4-(trifluoromethyl)benzoyl chloride (1.5 mL) was injected, the power of the Cryogenic Cooler was turned off to let the reaction slowly warmed up to rt, and stirred for another 1h. After carefully quenched with sat.$NaHCO_3$ (30 mL), the organic solvent was evaporated in rotavapor, the aqueous residue was extracted with DCM (30 mL x 4). Combined DCM extractions were washed with sat. NH_4Cl, H_2O, Brine, dried over Na_2SO_4, and concentrated in rotavapor. Crude product was purified by silica gel chromatography (R_f = 0.71 hexane/ EtOAc 6:1) to give (*S*, 3*Z*, 6*Z*, 9*Z*)-1-(tributylstannyl)dodeca-3,6,9-trien-1-yl 4-(trifluoromethyl)benzoate (220.0 mg, 27% from epoxide) as colorless oil (sometimes pale yellow if there is some impurity). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 5.46-5.31 (m, 6H), 5.11 (dd, *J* = 6.0, 3.0 Hz, 1H), 2.85-2.79 (m, 5H), 2.67-2.64 (m, 1H), 2.10-2.04 (m, 2H), 1.57-1.18 (m, 12H), 0.94-0.84 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 134.3 (q, *J* = 32.0 Hz), 134.1, 132.3, 130.3, 129.9, 128.9, 127.9, 127.1, 127.0, 125.5 (q, *J* = 4.0 Hz), 123.9 (q, *J* = 271.0 Hz), 72.2 (t, *J* = 155.0 Hz), 32.1, 29.3 (t, *J* = 10.0 Hz), 27.6 (t, *J* = 29.0 Hz), 26.0, 25.8, 20.8, 14.5, 13.9, 10.0 (t, *J* = 161.0 Hz). (The product was covered with aluminum foil, kept in -78 °C freezer under argon when not using.)

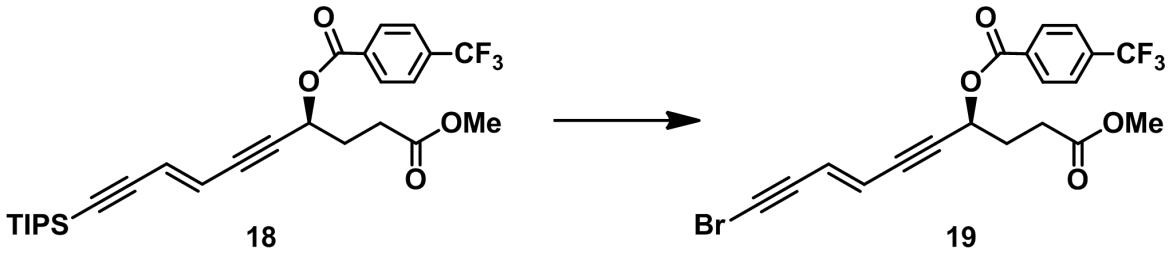
13. (*S*,*E*)-1-methoxy-1-oxo-10-(triisopropylsilyl)deca-7-en-5,9-diyn-4-yl 4-(trifluoromethyl) benzoate (18)[10,11,12]



Copper(I)-thiophene-2-carboxylate (CuTc) (5.0 mg, 0.026 mmol) was weighed into a 20 mL reaction vial charged with a stirring bar, sealed and argon purged. (*E*)-(6-bromohexa-3-en-1,5-diyn-1-

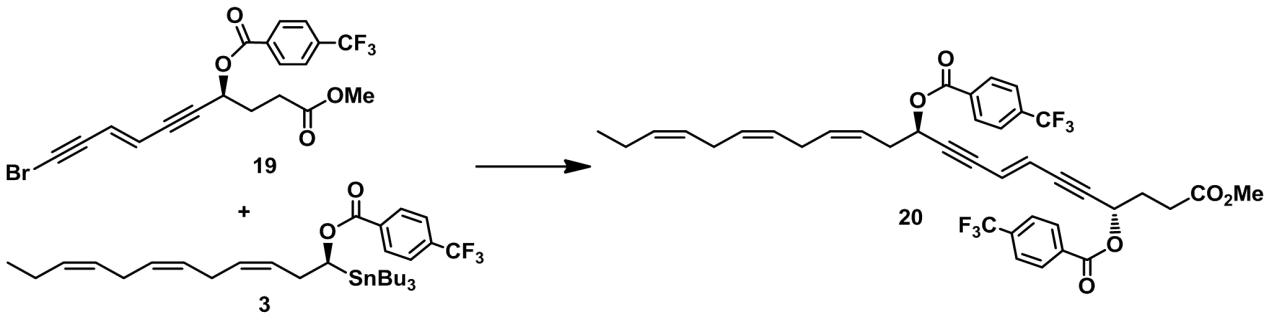
yl)triisopropylsilane (~3.0 equiv.) and (*R*)-4-methoxy-4-oxo-1-(tributylstannyl)butyl 4-(trifluoromethyl) benzoate (75.0 mg, 0.129 mmol) (in 4.0 mL of anhydrous dioxane under argon) was injected to the reaction. The reaction was allowed to stir at 90 °C under argon (covered with black cloth). After the reaction was complete (followed by TLC, ~20h), the crude mixture was diluted with hexane, filtered through a pad of celite. Reaction vial and the silica gel pad were washed with ether, concentrated. Crude residue was purified by silica gel chromatography (R_f = 0.48, 4:1 hexane/ EtOAc) to give (*S*, *E*)-1-methoxy-1-oxo-10-(triisopropylsilyl)deca-7-en-5,9-diyn-4-yl-4-(trifluoromethyl)benzoate as a yellow/ brown oil (45.0 mg, 67% yield). (If necessary, the product was dissolved in ether, passed quickly through a pad of 10% K_2CO_3/S iO_2 to remove the polar Sn byproduct.) The flask and the pad were washed with more ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 6.06 (d, *J* = 16.0 Hz, 1H), 6.00 (dd, *J* = 16.0, 2.0 Hz, 1H), 5.82 (td, *J* = 6.0, 2.0 Hz, 1H), 3.66 (s, 3H), 2.57 (t, *J* = 8.0 Hz, 2H), 2.28 (q, *J* = 7.0 Hz, 2H), 1.07-1.03 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 164.3, 135.0 (q, *J* = 33.0 Hz), 133.0, 130.4, 125.7 (q, *J* = 4.0 Hz), 123.8 (q, *J* = 271.0 Hz), 123.1, 120.3, 104.6, 98.2, 90.2, 84.8, 64.8, 52.1, 30.0, 29.8, 18.8, 11.4. (Sn byproduct will probably react with the AgF in next step thus affect the reaction.)

14. (*S*,*E*)-10-bromo-1-methoxy-1-oxodeca-7-en-5,9-diyn-4-yl 4-(trifluoromethyl) benzoate (19)



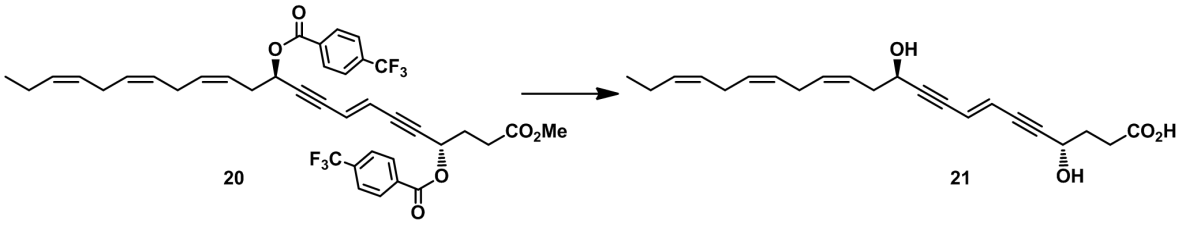
AgF (54.0 mg, 0.423 mmol) and NBS (82.0 mg, 0.461 mmol) were weighed into a 100 mL RBF charged with a stirring bar, sealed and argon purged. (*S, E*)-1-methoxy-1-oxo-10-(triisopropylsilyl)deca-7-en-5,9-diyn-4-yl 4-(trifluoromethyl)benzoate (in 20 mL CH_3CN under argon) was injected. The reaction was stirred at rt covered with aluminum foil. After the reaction was complete (followed by TLC, ~5h), the crude mixture was diluted with ether (80 mL), washed with brine (80 mL x 2). Ether layer was dried over Na_2SO_4, concentrated. Crude residue was again dissolved in ether, filtered through a pad of Celite, concentrated in *vacuo* to give (*S, E*)-10-bromo-1-methoxy-1-oxodeca-7-en-5,9-diyn-4-yl-4-(trifluoromethyl)benzoate (160.0 mg, 94% yield) as brown oil. Crude product (R_f = 0.37, 4:1 hexane/ EtOAc) was covered with aluminum foil, stored in -80 °C Freezer under argon. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 6.05 (dd, *J* = 16.0, 2.0 Hz, 1H), 6.00 (d, *J* = 16.0 Hz, 1H), 5.84 (td, *J* = 6.0, 1.0 Hz, 1H), 3.66 (s, 3H), 2.57 (t, *J* = 8.0 Hz, 2H), 2.28 (q, *J* = 7.0 Hz, 2H). (The compound should be used ASAP for the next cross-coupling step without further purification.)

15. (4*S*,7*E*,11*R*,13*Z*,16*Z*,19*Z*)-1-methoxy-1-oxodocosa-7,13,16,19-tetraen-5,9-diyne-4,11-diyl bis(4-(trifluoromethyl)benzoate) (20)[10,11,12]



Copper(I)-thiophene-2-carboxylate (CuTc) (2.4 mg, 0.0125 mmol) was weighed into a 20 mL reaction vial charged with a stirring bar, sealed and argon purged. (*S, E*)-10-bromo-1-methoxy-1-oxodeca-7-en-5,9-diyn-4-yl 4-(trifluoromethyl)benzoate (20.0 mg, 0.045mmol) and (*S*, 3*Z*, 6*Z*, 9*Z*)-1-(tributylstannyl)dodeca-3,6,9-trien-1-yl-4-(trifluoromethyl)benzoate (40.0 mg, 0.062 mmol) (in 4.0 mL of anhydrous dioxane under argon) was injected to the reaction. The reaction was allowed to stir at 90 °C under argon (covered with black cloth). After the reaction was complete (followed by TLC, ~20h), the crude mixture was diluted with hexane, filtered through a pad of celite. Reaction vial and the silica gel pad were washed with ether, concentrated. Crude residue was purified by silica gel chromatography (R_f = 0.38, 4:1 hexane/ EtOAc) to give (4*S*,7*E*,11*R*,13*Z*,16*Z*,19*Z*)-1-methoxy-1-oxodocosa-7,13,16,19-tetraen-5,9-diyne-4,11-diyl bis(4-(trifluoromethyl)benzoate) as a colorless oil (18.0 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.0 Hz, 2H), 7.70 (d, *J* = 7.0 Hz, 2H), 6.01 (t, *J* = 17.0 Hz, 2H), 5.82 (t, *J* = 6.0 Hz, 1H), 5.76 (t, *J* = 6.0 Hz, 1H), 5.61-5.24 (m, 6H), 3.61 (s, 3H), 2.85 (t, *J* = 7.0 Hz, 2H), 2.78 (t, *J* = 7.0 Hz, 2H), 2.75-2.70 (m, 2H), 2.56 (t, *J* = 7.0 Hz, 2H), 2.28 (q, *J* = 7.0 Hz, 2H), 2.08-2.01 (m, 2H), 0.94 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 164.4, 164.3, 135.0 (q, *J* = 33.0 Hz), 134.9 (q, *J* = 33.0 Hz), 133.1, 133.0, 132.5, 132.4, 130.4, 129.2, 127.5, 127.0, 125.69 (q, *J* = 4.0 Hz), 125.65 (q, *J* = 4.0 Hz), 123.77 (q, *J* = 272.0 Hz), 123.74 (q, *J* = 271.0 Hz), 123.0, 121.7, 121.1, 91.7, 90.7, 84.4, 83.9, 65.2, 64.8, 52.1, 33.0, 30.0, 29.8, 26.0, 25.8, 20.8, 14.5. (If necessary, the product was dissolved in ether, passed quickly through a pad of 10% K_2CO_3/ SiO_2 to remove the polar Sn byproduct. Washed the flask and the pad with more ether.)

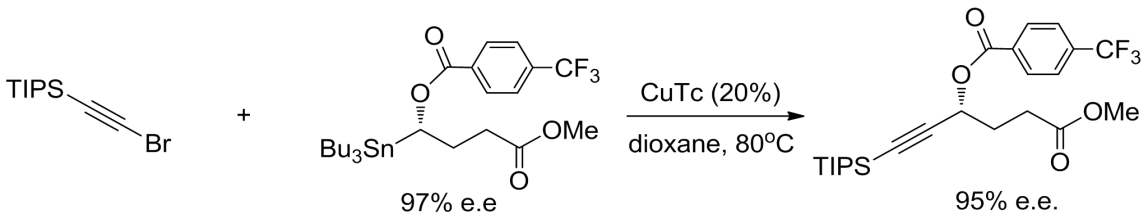
16. (4*S*,7*E*,11*R*,13*Z*,16*Z*,19*Z*)-4,11-dihydroxydocosa-7,13,16,19-tetraen-5,9-diynoic acid (21)



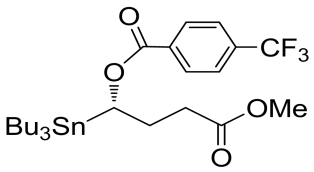
Starting material (24.0 mg, 0.0335 mmol) was stirred with LiOH (6.0 mg, 0.25 mmol) in THF (2 mL)/ H_2O (0.5 mL) at rt under argon. After the reaction was complete (followed by TLC, ~5h), acidified with 1N HCl solution, and further diluted with brine (50 mL). The aqueous was extracted with EtOAc (50mL x 5), combined EtOAc layer was washed with brine, dried over Na_2SO_4, concentrated in rotavapor. Crude product was purified by silica gel chromatography (R_f = 0.11, 4:1 DCM/ MeOH/ AcOH 100:5:1) to give the deprotected acid. Purified acid was stirred with sat. $NaHCO_3$ in THF/ H_2O for 10min, the organic solvent was evaporated in rotavapor. The

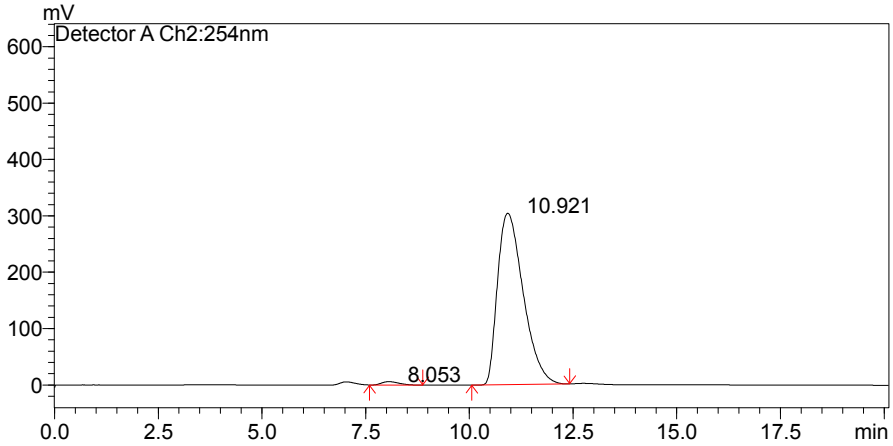
residue was stirred with Biobeads (prewashed with MeOH, then H_2O) for 30 min, filtered. The biobeads were washed with excess amount of H_2O, then MeOH. MeOH fraction was collected and concentrated in *vacuo* to give desired product in sodium form. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (t, *J* = 26.0 Hz, 2H), 5.53-5.26 (m, 6H), 4.49 (t, *J* = 6.0 Hz, 1H), 4.43 (t, *J* = 6.0 Hz, 1H), 2.85 (t, *J* = 5.0 Hz, 2H), 2.81 (t, *J* = 6.0 Hz, 2H), 2.45 (t, *J* = 6.0 Hz, 2H), 2.41-2.26 (m, 2H), 2.12-2.04 (m, 2H), 1.94 (q, *J* = 7.0 Hz, 2H), 0.96 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7, 131.6, 130.6, 128.3, 127.6, 126.9, 124.3, 120.6, 120.3, 95.6, 95.2, 82.1, 81.9, 62.1, 61.9, 35.6, 34.2, 33.7, 25.6, 25.2, 20.3, 13.5.

III. HPLC data of key compound 8



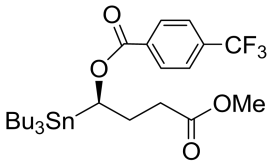
A. Condition: Chiralcel OD 4.6x250mm, hexane/IPA:100/0.1, 1mL/min, 205/254nm

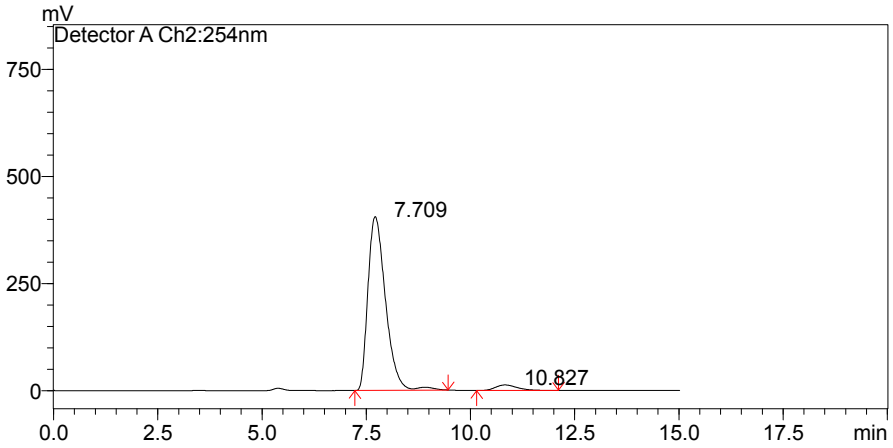




Coupling

Retention time (min)	Area %
8.053	1.32
10.921	98.68

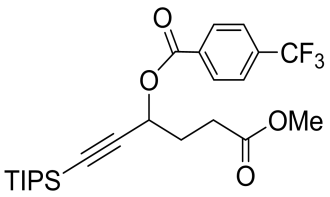




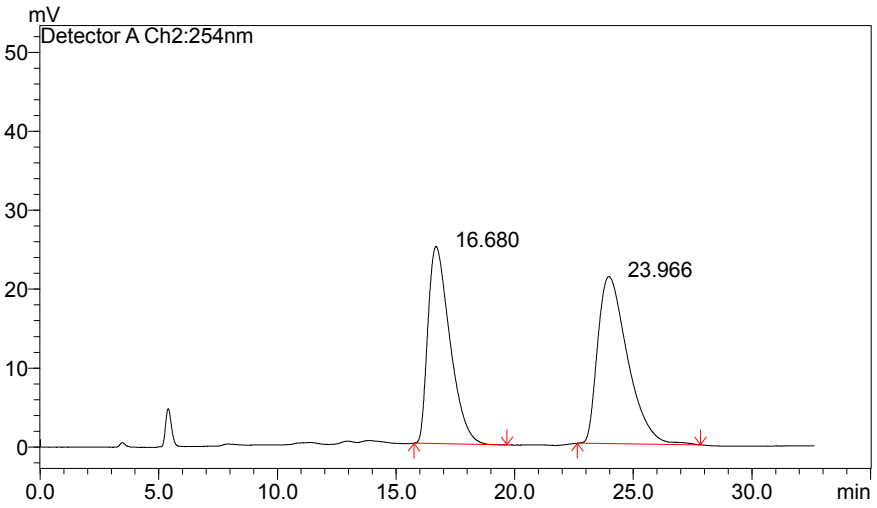
Coupling

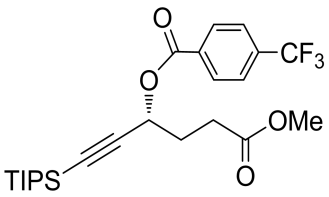
Retention time (min)	Area %
7.709	96.3
10.827	3.7

B. Condition: Chiralcel OD 4.6x250mm, hexane/IPA:100/0.1, 1mL/min, 205/254nm

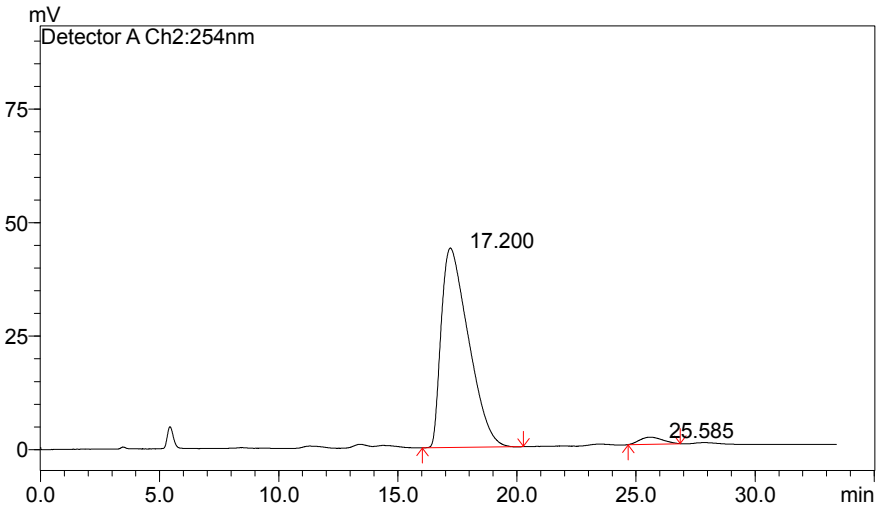


Racemic





Coupling



Retention time (min)	Area %
17.2	97.3
25.6	2.7

IV. References.

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