Ruthenium–Catalyzed Alkene–Alkyne Coupling: Synthesis of the Proposed Structure of Amphidinolide A

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Supplementary Material

Ester 6.

2-Butynoic acid (1.00g, 11.89 mmol), 9-fluorenylmethanol (2.334g, 11.89 mmol) and camphorsulfonic acid (138 mg, 0.59 mmol) were dissolved in 40 mL of toluene. After 90 min the reaction was warmed to reflux and toluene was slowly distilled from the reaction mixture. After approximately 1 h approximately 30 mL of toluene had distilled over, another 30 mL of toluene was added. The slow distillation was continued, and after another 30 mL had distilled over, the reaction was allowed to cool to rt. The reaction was then poured into sat. aq. NaHCO₃ and extracted with Et₂O (3x), dried (MgSO₄) and concentrated. Purification by silica gel chromatography (20-50% Et₂O/petroleum ether) provided 2.211 g (71%) of the ester as a thick oil.

5.: R_f = 0.55 (30% Et₂O/70% petroleum ether); IR (film from CH₂Cl₂) 3058, 2958, 2243, 1709 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.77 (d, J = 7.6 Hz, 2H), 7.63 (d, J = 7.3 Hz, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.4 Hz, 2H), 4.42 (d, J = 7.6 Hz, 2H), 4.25 (t, J = 7.6 Hz, 1H), 2.05 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 153.7, 143.3, 141.2, 127.9, 127.1, 125.1, 120.0, 80.1, 72.3, 67.6, 46.4, 3.9. Anal calcd for C₁₈H₁₄O₂: C, 82.42 H, 5.38. Found: C, 82.37, H, 5.47.

Diene 2.

Allyltributyltin (7.02 mL, 20.4 mmol) was dissolved in 35 mL of THF and cooled to -78 °C. Butyllithium (1.6 M in hexanes, 8.43 mL, 13.49 mmol) was then slowly added. After 1 h the reaction was cannulated into a slurry of copper iodide (13.49 mmol, 2.57g) in 20 mL of THF at -78 °C. The reaction was allowed to warm to -25 °C for 1 h, and then recooled to -78 °C. Alkynoic ester X (2.211 g, 8.42 mmol) was then dissolved in 25 mL of THF, cooled to -78 °C, and added via cannula to the allyl copper. After 30 min the reaction was quenched at -78 °C with sat. aq. ammonium chloride and allowed to warm to rt. The reaction was then poured into brine and extracted with ethyl ether (3x), the combined extracts being dried (MgSO₄) and concentrated. Purification by silica gel chromatography (5-20% Et₂O/petroleum ether) gave 2.490 g (97%) of diene ester **2**.

2: R_f = 0.41 (10% Et₂O/90% petroleum ether); IR (film from CH₂Cl₂) 3067, 2940, 1954, 1908, 1714 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, J = 7.3 Hz, 2H), 7.61 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 6.8 Hz, 2H), 7.31 (t, J = 7.3 Hz, 2H), 5.75-5.86 (m, 2H), 5.17 (s, 1H), 5.12 (d, J = 7.1 Hz, 1H), 4.40 (d, J = 7.1 Hz, 2H), 4.24 (t, J = 7.1 Hz, 1H), 2.91 (d, J = 6.6 Hz, 2H), 2.14 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 166.6, 158.8, 144.0, 141.3, 134.1, 127.7, 127.0, 125.0, 120.0, 117.9, 116.0, 65.7, 46.8, 45.0, 18.8. Anal calcd for C₂₁H₂₀O₂: C, 82.86 H, 6.62. Found: C, 83.05, H, 6.49.

Sulfone Ester 8.

The starting sulfide (for the preparation of this sulfide, see Waissner, K.; Vanzura, J.; Hrabalck, A.; Vinsova, J.; Gresak, S. *Coll Czech. Chem. Comm.* **1991**, *56*, 2389) (897 mg, 3.58 mmol) was dissolved in 20 mL of CH₂Cl₂ and cooled to 0°C in an ice bath. MCPBA (4.54 g, 18 mmol) was then added in portions over 15 min. The reaction was then allowed to warm to rt. After 72 h the reaction was cooled to 0°C and quenched with the addition of sat. aq. Na₂S₂O₃. The reaction was then poured into brine and extracted with CH₂Cl₂ (4x), dried (MgSO₄) and concentrated. Purification by silica gel chromatography (75-100% Et₂O/petroleum ether) provided 827 mg (82%) of the sulfone ester as a white solid.

8.: *R_f* = 0.20 (75% Et₂O/25% petroleum ether); IR (film from CH₂Cl₂) 2922, 1746 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.59-7.67 (m, 5H), 4.69 (s, 2H), 3.77 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 167.9, 133.3, 130.3, 129.9, 123.7, 53.2, 34.8. Anal calcd for C₁₀H₁₀N₄O₄S : C, 42.55; H, 3.57; N, 19.85. Found: C, 42.72; H, 3.36; N, 19.98.

Unsaturated Sulfone.

Sulfone ester **8** (212 mg, 0.848 mmol), Cs₂CO₃ (1.5 mmol, 489 mg) and R,R-ligand **10** (31 mg, 0.045 mmol) were suspended in 8 mL of CH₂Cl₂ and degassed by bubbling Ar gas through the suspension for approximately 10 min. Pd₂(dba)₃-CHCl₃ (11.6 mg, 0.01125 mmol) was then added and the reaction stirred for approximately 10 min, during which time the color changed from purple to yellow. Carbonate **9** (178 mg, 1.125 mmol) was then added in 1 mL of CH₂Cl₂. After 3 h the reaction was poured into brine and extracted with CH₂Cl₂, dried (MgSO₄) and concentrated. Purification by silica gel chromatography (30% Et₂O/petroleum ether, *R_f* = 0.19) gave 220 mg (74%) of a 1:1 mixture of alkylated diastereomers as a yellow oil. Most of this mixture (176 mg, 0.503 mmol) was dissolved in 2 mL of DMSO. Sodium chloride (78 mg, 1.339 mmol) was then added and the reaction was warmed to 150 °C in an oil bath. After 4 h the reaction was cooled to rt, poured into brine and extracted with CH₂Cl₂, dried (MgSO₄) and concentrated. Purification by silica gel chromatography (30% Et₂O/petroleum ether) provided 95 mg (66% yield) of the unsaturated sulfone as a yellow oil.

Unsaturated sulfone: *R_f* = 0.27 (20% Et₂O/80% petroleum ether); IR (film from CH₂Cl₂) 2967, 1596, 1152 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.58-7.66 (m, 5H), 5.47-5.54 (m, 1H), 5.30 (dd, *J* = 15.3, 7.9 Hz, 1H), 3.85 (dd, *J* = 14.6, 7.3 Hz, 1H), 3.61 (dd, *J* = 14.6, 6.3 Hz, 1H), 2.93-3.34 (m, 1H), 1.59 (d, *J* = 7.3 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 153.9, 133.0, 132.2, 131.4, 129.6, 126.7, 125.1, 61.5, 32.0, 20.5, 17.7. [*α*]_D²³ = +40.4 (*c* 2.0, CH₂Cl₂).

Sulfone 12.

The unsaturated sulfone (103 mg, 0.352 mmol) was dissolved in 2 mL of ethanol. 100 mL of acetic acid was then added followed by Pd(OH)₂/C (20%, ~50% H₂O, 99 mg, 0.070 mmol). The reaction was then evacuated and put under a hydrogen balloon. After 5 h the reaction appeared slow, so more Pd(OH)₂/C (20%, ~50% H₂O, 99 mg, 0.070 mmol) was added. After another 1 h the reaction was filtered through celite with ethyl acetate and concentrated. Purification by silica gel chromatography (20% Et₂O/petroleum ether) provided 70 mg (68% yield) of the sulfone **12** as a thick oil.

12.: $R_f \sim 0.50$ (20% diethyl ether/petroleum ether). IR (film): 2962.0, 1595.8, 1498.1, 1462.7, 1338.4, 1153.2, 763.9, 685.5, 630.5 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 7.64-7.56 (m, 5 H), 3.80 (dd, $J = 14.7, 4.9$ Hz, 1 H), 3.56 (dd, $J = 14.4, 7.8$ Hz, 1 H), 2.25-2.40 (m, 1 H), 1.55-1.24 (m, 4 H), 1.14 (d, $J = 6.3$ Hz, 3 H), 0.88 (t, $J = 5.9$ Hz, 3 H). ^{13}C NMR (75 MHz, CDCl_3) δ : 153.98, 132.98, 131.36, 129.58, 125.08, 61.71, 38.57, 27.91, 19.58, 19.39, 13.80. $[\alpha]_D^{25} = +1.34$ (c 1.71, CH_2Cl_2).

Epoxide 14.

To a suspension of 21.8 g (0.544 mmol) of 60% sodium hydride dispersion in mineral oil in 500 mL of THF at rt was slowly added 47.9 g (0.544 mmol) of diol **13** *via* syringe over 20 minutes causing warming of the reaction mixture. The resulting heterogeneous mixture was stirred at rt for 3 h whereupon 2.5 g (6.8 μmol) of tetrabutylammonium iodide and 42.7 g (0.272 mmol) of freshly prepared *p*-methoxybenzylchloride were successively added. After stirring at rt for 16 h, the mixture was carefully quenched by addition of 100 mL of water followed by dilution with 500 mL of diethyl ether. The resulting clear layers were separated and the aqueous portion was extracted with diethyl ether (100 mL) and the combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford approximately 100 mL of the crude product as a yellow liquid. Flash chromatography on silica gel initially eluting with 50% diethyl ether in petroleum ether mixtures to remove some less polar material then increasing the eluant polarity to 75% diethyl ether in petroleum ether to collect the desired product. Concentration of these fractions *in vacuo* provided 30.0 g (53%) of the pure allylic alcohol as a yellow oil. TLC $R_f = 0.34$ (75% Et_2O in petroleum ether). IR (film): 3385.9, 2858.9, 1612.4, 1513.4, 1247.6, 1032.5, 819.0 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 7.26 (d, $J = 8.7$ Hz, 2 H), 6.88 (d, $J = 8.7$ Hz, 2 H), 5.81 (app dt, $J = 11.3, 5.1$ Hz, 1 H), 5.72 (app dt, $J = 11.3, 5.4$ Hz, 1 H), 4.45 (s, 2 H), 4.16 (d, $J = 6.0$ Hz, 2 H), 4.06 (d, $J = 5.8$ Hz, 2 H), 3.80 (s, 3 H), 1.98 (s, 1 H).

To a suspension of 27 g of freshly activated 3 Å powdered molecular sieves (heated to 140°C at 1 Torr for 14 h then cooled to rt) in 250 mL of methylene chloride was added a solution of 17.7 g (86 mmol) of freshly distilled (+)-diethyltartrate in 40 mL of methylene chloride. The resulting mixture was cooled to -30°C whereupon 20.5 g (21.2 mL, 72 mmol) of distilled titanium tetrakisopropoxide and 145 mL (72-86 mmol) of a 5-6 M stock solution of *t*BuOOH in decane (NOTE: the *t*BuOOH decane solution was predried over 4 Å molecular sieve pellets for 20 minutes just prior to use) were successively added and the resulting yellow mixture was stirred at -30°C for 30 minutes. During this time, a solution of 30.0 g (144 mmol) of the allylic alcohol in 150 mL of methylene chloride was predried over 4 Å molecular sieve pellets for 20 min, then the solution was transferred *via* cannula over 30 min into the previously prepared reaction mixture at -30°C. The reaction flask was then placed into a -20°C freezer and allowed to remain at that temperature without stirring for 40 h whereupon the mixture was filtered to remove the sieves and *slowly* poured into a well-stirred 0°C solution of 236 g (86 mmol) of iron sulfate heptahydrate and 143 g (86 mmol) of tartaric acid in 800 mL of water. After stirring at 0°C for 15 min, the layers were separated and the aqueous portion was extracted with diethyl ether (3 x 500 mL). The combined organic extracts were cooled to 0°C whereupon 140 mL of 30% aqueous sodium hydroxide was added. After stirring at 0°C for 1 h, 500 mL of water was added and the layers were separated. The aqueous portion was extracted with diethyl ether (3 x 300 mL) and the combined extracts were washed with brine (2 x 200 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator to afford approximately 100 mL of the crude product as a colorless suspension in residual decane. This material was purified by flash chromatography on silica gel beginning with 80% Et_2O in petroleum ether mixture as the eluant to remove the decane and less polar impurities. Finally, elution with 100% Et_2O afforded after concentration *in vacuo* 23.01 g (71%) of pure epoxide **14** as a yellow oil. The enantiomeric purity of **14** was determined to be 84% ee by chiral HPLC analysis: Chiralcel OD at 23°C, 1.0 mL/min flow rate, 15% isopropanol-heptane, $\lambda = 254$ nm, retention times for enantiomers of **14**: 13.66 min (minor), 16.17 min (major) as compared to a racemic

standard of **103**. TLC R_f = 0.22 (80% Et₂O in petroleum ether). IR (film): 3440.2, 2934.4, 1612.3, 1585.9, 1513.2, 1246.4, 1085.9, 1033.1, 821.4 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ : 7.26 (d, J = 8.5 Hz, 2 H), 6.88 (d, J = 8.6 Hz, 2 H), 4.55 (d, J = 11.3 Hz, 1 H), 4.46 (d, J = 11.3 Hz, 1 H), 3.81 (s, 3 H), 3.78-3.67 (m, 3 H), 3.60 (dd, J = 6.0, 5.1 Hz, 1 H), 3.30-3.20 (m, 2 H), 1.76 (br s, 1 H). $[\alpha]_D^{25}$ = -17.0 (c 2.15, CH₂Cl₂).

Oxetane 15.

To a slurry of 32.0 g (357 mmol) of copper cyanide in 350 mL of diethyl ether at -40°C was added 422.3 mL (663 mmol) of a 1.57 M solution of methyl lithium-lithium bromide complex in diethyl ether affording a cloudy, off-white colored mixture which was allowed to slowly warm from -40°C to -20°C over 1.5 h. The reaction mixture was then cooled to -50°C and a solution of 22.94 g (102 mmol) of the epoxide **14** in 50 mL of diethyl ether was added *via* cannula and the resulting mixture was allowed to slowly warm from -50°C to -20°C over 3.5 h. At this time, the reaction was carefully quenched at -20°C by a slow, dropwise addition of 100 mL of an aqueous solution of saturated ammonium chloride which had been buffered to a pH~9 with conc ammonium hydroxide. After allowing to warm to rt with vigorous stirring for 1 h, the mixture was partitioned between 400 mL of the ammonium chloride/ammonium hydroxide solution, 200 mL of water, and 300 mL of diethyl ether. The aqueous portion was extracted with additional diethyl ether (2 x 400 mL) and the combined cloudy organic extracts were filtered through a pad of celite and the resulting clear filtrate was concentrated *in vacuo* to afford the crude diol mixture as a 2-3:1 regioisomeric mixture of the 1,2-diol and 1,3-diol as determined by ¹H NMR analysis. Separation of the desired regioisomeric 1,3-diol from the 1,2-diol was accomplished by dissolving the crude mixture in 400 mL of 10% aqueous THF, cooling the resulting solution to 0°C, and adding 21.8 g (102 mmol) of sodium periodate. The mixture was warmed to rt and stirred for 1.5 h giving a thick, white heterogeneous mixture. After dilution with 1 L of chloroform, the mixture was decanted away from the white insoluble precipitate which had formed and the resulting solution was washed with brine (200 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to a yellow oil as the crude product mixture. Flash chromatography on silica gel initially eluting with 80% ethyl acetate in petroleum ether mixtures removed the aldehyde byproduct followed by eluting with 100% ethyl acetate to provide 16.7 g (68%) of pure 1,3 diol as a yellow oil. TLC R_f = 0.42 (80% EtOAc in petroleum ether). IR (film): 3405.6, 2910.9, 1612.8, 1514.0, 1248.6, 1096.6, 1033.8, 819.1 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ : 7.22 (d, J = 8.3 Hz, 2 H), 6.86 (d, J = 8.3 Hz, 2 H), 4.50-4.41 (m, 2 H), 3.98-3.92 (m, 1 H), 3.78 (s, 3 H), 3.60-3.58 (m, 2 H), 3.46 (d, J = 5.9 Hz, 2 H), 2.82 (br s, 2 H), 1.85-1.78 (br m, 1 H), 0.88 (d, J = 7.3 Hz, 3 H). ¹³C NMR (75 MHz, CDCl₃) δ : 159.24, 129.78, 129.39, 113.78, 73.02, 72.39, 72.05, 66.06, 55.19, 37.28, 11.00. Anal. Calcd for C₁₃H₂₀O₄: C, 64.98; H, 8.39. Found: C, 64.61; H, 8.32. $[\alpha]_D^{25}$ = +2.77 (c 1.70, CH₂Cl₂).

To a solution of 14.4 g (60 mmol) of the 1,3-diol in 280 mL of pyridine at 0°C was added 11.4 g (60 mmol) of freshly purified tosyl chloride in three portions over 15 min followed by stirring at 0-4°C (cold room temp) for 40 h. The cold mixture was then slowly poured into a well-stirred 0°C mixture of 10% aqueous HCl (400 mL) and diethyl ether (400 mL) and the resulting layers were separated. The organic layer was washed with additional ice-cold aqueous 10% HCl (300 mL) and the combined aqueous acidic portions were extracted with diethyl ether (3 x 300 mL). The combined organic extracts were successively washed with 300 mL of 10% aqueous HCl, 300 mL of 0.2 M aqueous copper sulfate solution, and brine (2 x 200 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator to a total volume of approximately 500 mL. This solution which still contained residual pyridine was washed again with 10% aqueous HCl (3 x 100 mL), 100 mL of 0.2 aqueous copper sulfate solution, and brine (2 x 100 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford a pale yellow oil as the crude tosylate intermediate. Due to the apparent instability of the tosylate, this intermediate was not purified further but was immediately dissolved in 50 mL of anhydrous THF and subjected directly to the next reaction. A relatively pure

sample of the tosylate could be obtained by rapid flash chromatography on silica gel (50% Et₂O in petroleum ether): TLC R_f = 0.37 (50% Et₂O in petroleum ether). IR (film): 3447.9, 2909.5, 1612.1, 1513.7, 1357.6, 1248.2, 1176.1, 965.7, 815.7 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 7.76 (d, *J* = 7.8 Hz, 2 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.22 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 4.43 (app s, 2 H), 4.03 (dd, *J* = 9.3, 6.8 Hz, 1 H), 3.90 (dd, *J* = 9.8, 5.9 Hz, 1 H), 3.85-3.82 (m, 1 H), 3.80 (s, 3 H), 3.43-3.33 (m, 2 H), 2.43 (s, 3 H), 2.35 (br s, 1 H), 2.04-1.93 (br m, 1 H), 0.87 (d, *J* = 6.8 Hz, 3 H). ¹³C NMR (75 MHz, CDCl₃) δ: 159.25, 144.72, 132.78, 129.79 (2), 129.34, 127.82, 113.79, 72.95, 72.14, 71.88, 69.49, 55.20, 35.42, 21.57, 10.63.

The THF solution of the crude tosylate was transferred *via* cannula into a suspension of 4.80 g (120 mmol) of 60% dispersion of sodium hydride in mineral oil in 100 mL of THF at rt and the resulting heterogeneous mixture was stirred at rt for 4 h. At this time, the reaction mixture was carefully quenched by a slow, dropwise addition of 20 mL of methanol followed by the addition of 100 mL of water and 100 mL of diethyl ether. The resulting layers were separated and the aqueous portion was extracted with diethyl ether (3 x 75 mL). The combined extracts were washed with brine (2 x 25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford a 15.2 g of a yellow oil as the crude oxetane. Flash chromatography on silica gel (50% diethyl ether in petroleum ether) afforded 10.9 g (82%) of pure oxetane as a pale yellow oil. TLC R_f = 0.57 (50% Et₂O in petroleum ether). IR (film): 2872.2, 1612.5, 1513.3, 1457.2, 1247.6, 1094.3, 1033.8, 969.6, 818.8 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 7.26 (d, *J* = 8.3 Hz, 2 H), 6.87 (d, *J* = 8.3 Hz, 2 H), 4.97-4.91 (m, 1 H), 4.76 (dd, *J* = 8.3, 5.9 Hz, 1 H), 4.50 (app q, *J* = 7.8 Hz, 2 H), 4.18 (app t, *J* = 6.3 Hz, 1 H), 3.79 (s, 3 H), 3.69 (d, *J* = 5.9 Hz, 2 H), 3.15 (app sextet, *J* = 6.8 Hz, 1 H), 1.16 (d, *J* = 7.3 Hz, 3 H).

Alcohol 16.

To a solution of 20.8 mL (14.4 g, 147 mmol) of trimethylsilylacetylene in 230 mL of THF at -78°C was added 92 mL (147 mmol) of a 1.6 M solution of *n*butyllithium in hexanes and the resulting clear, colorless solution was stirred at -78°C for 30 min then at 0°C for 45 minutes. The mixture was cooled to -78°C and 18.1 mL (20.9 g, 147 mmol) of freshly distilled boron trifluoride etherate was added followed by stirring for 10 min whereupon a solution of 10.9 g (49 mmol) of **15** in 30 mL of THF was added *via* cannula. After stirring at -78°C for 45 min, 100 mL of saturated aqueous ammonium chloride was added and the reaction mixture was allowed to warm to rt whereupon 100 mL of water and 100 mL of diethyl ether were added. The resulting layers were separated and the organic portion was washed with 5% aqueous HCl (2 x 100 mL). The aqueous portions were combined and extracted with diethyl ether (2 x 150 mL) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford 15.5 g of a yellow oil as the crude product. Flash chromatography on silica gel (40% diethyl ether in petroleum ether) then afforded 10.57 g (62%) of pure alcohol product as a pale yellow oil. TLC R_f = 0.43 (50% Et₂O in petroleum ether). IR (film): 3463.3, 2959.4, 2902.6, 2173.1, 1612.9, 1514.0, 1249.4, 843.4 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 7.24 (d, *J* = 8.3 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 4.46 (s, 2 H), 3.82 (m, 1 H), 3.78 (s, 3 H), 3.49 (dd, *J* = 9.8, 3.4 Hz, 1 H), 3.41 (apparent t, *J* = 9.8 Hz, 1 H), 2.41 (br m, 1 H), 2.31 (dd, *J* = 17.1, 6.4 Hz, 1 H), 2.17 (dd, *J* = 17.1, 6.8 Hz, 1 H), 1.80 (m, 1 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.13 (s, 9 H). ¹³C NMR (75 MHz, CDCl₃) δ: 159.21, 129.94, 129.31, 113.76, 105.70, 85.92, 72.92, 72.42, 72.28, 55.17, 35.06, 23.98, 14.22, 0.05.

Anal. Calcd for C₁₈H₂₈O₃Si: C, 67.46; H, 8.81. Found: C, 67.59; H, 8.83. $[\alpha]_D^{26} = +11.5$ (c 3.8, CH₂Cl₂).

The alcohol (75 mg, 0.234 mmol) was dissolved in 2 mL of DMF. Imidazole (21 mg, 0.304 mmol) was then added followed by TBDMSCl (46 mg, 0.304 mmol). After 22 h the reaction was taken up in diethyl ether and washed with water (1x) and brine (2x). The organic layer was then dried (MgSO₄) and concentrated. Purification by silica gel chromatography (2-6% Et₂O/petroleum ether) provided 94 mg (93%) of the silyl ether as a yellow oil.

$R_f = 0.37$ (5% Et₂O/95% petroleum ether); IR (film from CH₂Cl₂) 2959, 2859, 2170, 1609 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.35 (d, $J = 8.5$ Hz, 2H), 6.97 (d, $J = 8.5$ Hz, 2H), 4.54 (q, $J = 11.5$ Hz, 2H), 4.05-4.10 (m, 1H), 3.91 (s, 3H), 3.47 (d, $J = 6.1$ Hz, 2H), 2.30 (qd, $J = 16.8, 7.8$, 2H), 1.97-2.05 (m, 1H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.96 (s, 9H), 0.24 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.0, 130.4, 129.2, 113.6, 106.7, 85.4, 72.7, 72.6, 72.0, 55.2, 35.7, 25.9, 24.5, 18.1, 13.0, 0.1, -4.2, -5.0. $[\alpha]_D^{23} = -4.8$ (c 1.2, CH₂Cl₂). Anal calcd for C₂₄H₄₂O₃Si₂: C, 66.30; H, 9.74. Found: C, 66.49; H, 9.62.

The protected alcohol (155 mg, 0.357 mmol) was dissolved in 3 mL of dichloromethane. 1 mL of water was then added followed by DDQ (97 mg, 0.428 mmol). The reaction was then stirred for 1 h, after which it was poured into diethyl ether and washed with sat. aq. NaHCO₃ (3x). The organic layer was then dried (MgSO₄) and concentrated. Purification by silica gel chromatography (20-40% Et₂O/petroleum ether) provided 104 mg (93%) of alcohol **16** as a clear oil.

$R_f = 0.58$ (30% Et₂O/70% petroleum ether); IR (neat) 3402, 2949, 2170 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.79 (q, $J = 4.7$ Hz, 1H), 3.54-3.60 (m, 2H), 2.29 (dd, $J = 16.8, 6.0$, 1H), 2.16 (dd, $J = 16.8, 6.8$ Hz, 1H), 1.86-1.91 (m, 1H), 1.70 (s, 1H), 0.97 (d, $J = 7.1$ Hz, 3H), 0.90 (s, 9H), 0.14 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 106.0, 85.8, 74.5, 64.5, 35.6, 25.8, 23.8, 18.1, 14.6, 0.1, -4.3, -4.7. $[\alpha]_D^{23} = -5.7$ (c 1.0, CH₂Cl₂).

Allylic Alcohol 17.

Alcohol **16** (860 mg, 2.73 mmol) was dissolved in 8 mL of CH₂Cl₂. Dess-Martin Periodinane (1.39g, 3.28 mmol) was then added. After approximately 90 min, the reaction was diluted with petroleum ether and filtered through a plug of silica gel with 20% Et₂O/80% petroleum ether. The aldehyde was then concentrated and dissolved in 6 mL of DME. In a separate flask, potassium hexamethyldisilazide (499 mg, 2.5 mmol) was dissolved in 6 mL of DME and cooled in a dry ice/acetone bath. Sulfone **12** (736 mg, 2.5 mmol) was then added in 6 mL of DME. The solution turned bright yellow. After stirring for approximately 90 minutes, the solution of aldehyde in DME was added dropwise over approximately 10 min. The reaction was allowed to slowly warm to room temperature and stirred overnight (approximately 16 h). The reaction was then poured into brine and extracted with ethyl ether (4x), the combined organic extracts being dried (MgSO₄) and concentrated. Purification by silica gel chromatography (3-6% Et₂O/petroleum ether) provided 685 mg (72%) of the *trans* alkene as a clear oil. Proton NMR analysis of the crude reaction showed a greater than 20:1 preponderance of the *trans* olefin isomer.

$R_f = 0.34$ (2% Et₂O/98% petroleum ether); IR (film from CH₂Cl₂) 2959, 2171 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.42 (dd, $J = 15.6, 7.3$ Hz, 1H), 5.32 (dd, $J = 15.6, 6.8$ Hz, 1H), 4.05 (t, $J = 6.3$ Hz, 1H), 2.29 (dd, $J = 16.6, 6.1$ Hz, 1H), 2.01-2.15 (m, 2H), 1.56-1.72 (m, 1H), 1.21-1.33 (m, 4H), 0.95 (d, $J = 6.6$ Hz, 3H), 0.85-0.90 (bs, 15H), 0.15 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 137.6, 129.7, 107.0, 85.3, 75.8, 39.7, 39.2, 36.1, 25.9, 23.7, 20.6, 20.4, 18.2, 14.3, 14.1, 0.2, -4.1, -4.9. $[\alpha]_D^{23} = +1.4$ (c 1.0, CH₂Cl₂).

The *trans* alkene (650 mg, 1.71 mmol) was dissolved in 8 mL of THF. Tetrabutylammonium fluoride (1M in THF, 3.76 mL, 3.76 mmol) was then added. After approximately 24 h the reaction was poured into sat. aq. NaHCO₃ and extracted with ethyl ether (4x). The combined organic extracts were then

dried (MgSO₄) and concentrated. Purification by silica gel chromatography (20-30% Et₂O/petroleum ether) provided 305 mg (92%) of allylic alcohol **17** as a clear oil.

R_f = 0.43 (20% Et₂O/80% petroleum ether); IR (film from CH₂Cl₂) 3402, 3312, 2958, 2116 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.55 (dd, J = 15.6, 7.6 Hz, 1H), 5.40 (dd, J = 15.6, 7.0 Hz, 1H), 4.08 (t, J = 5.9 Hz, 1H), 2.33 (ddd, J = 16.6, 5.9, 2.7 Hz, 1H), 2.12-2.17 (m, 1H), 2.08 (ddd, J = 16.6, 7.3, 2.4 Hz, 1H), 1.98 (t, J = 2.4 Hz, 1H), 1.74-1.86 (m, 1H), 1.22-1.32 (m, 4H), 1.02 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 139.0, 128.6, 83.3, 75.5, 69.4, 39.1, 38.2, 36.2, 25.6, 22.1, 20.5, 14.5, 14.1. $[\alpha]_D^{23}$ = +2.7 (c 0.7, CH₂Cl₂).

Epoxide 3.

Alkene **17** (125 mg, 0.643 mmol) was dissolved in 5 mL of methylene chloride and cooled to 0 °C. MCPBA (68%, 171 mg, 0.675 mmol) was then added in small portions over 5 min. After approximately 2 h the reaction was poured into 40 mL of sat. aq. NaHCO₃ and extracted with ethyl ether (3x). The combined organic extracts were then dried (MgSO₄) and concentrated. Purification by silica gel chromatography (25% Et₂O/petroleum ether) provided 50 mg (37%) of the undesired trans epoxide and 56 mg (41%) of the *cis* epoxide **3** as clear oils.

Undesired epoxide: R_f = 0.41 (30% Et₂O/70% petroleum ether); IR (film from CH₂Cl₂) 3465, 3302, 2959, 2116 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.85-3.91 (m, 1H), 2.80-2.87 (m, 2H), 2.38 (ddd, J = 16.8, 6.8, 2.7 Hz, 1H), 2.24 (ddd, J = 16.8, 7.1, 2.7 Hz, 1H), 2.00 (t, J = 2.7 Hz, 1H), 1.87-1.98 (m, 2H), 1.20-1.49 (m, 5H), 1.06 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.3 Hz, 3H), 0.91 (t, J = 6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 82.7, 70.8, 69.7, 60.1, 58.9, 35.6, 35.5, 34.9, 22.7, 20.1, 16.6, 14.2, 14.0. HRMS calcd for C₁₀H₁₅O₂ (M-C₃H₇): 167.1072. Found: 167.1074. $[\alpha]_D^{23}$ = +1.0 (c 1.0, CH₂Cl₂).

Desired epoxide 3: R_f = 0.32 (30% Et₂O/70% petroleum ether); IR (film from CH₂Cl₂) 3457, 3311, 2958, 2116 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.54-3.61 (m, 1H), 2.82 (dd, J = 4.6, 2.2 Hz, 1H), 2.73 (dd, J = 7.1, 2.2 Hz, 1H), 2.36 (ddd, J = 16.8, 6.8, 2.7 Hz, 1H), 2.22 (ddd, J = 16.8, 6.8, 2.7 Hz, 1H), 2.11 (d, J = 5.1 Hz, 1H), 1.99 (t, J = 2.7 Hz, 1H), 1.86-1.94 (m, 2H), 1.20-1.53 (m, 4H), 1.07 (d, J = 6.8 Hz, 3H), 0.88-0.97 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 82.6, 72.7, 69.7, 61.0, 58.8, 37.0, 36.7, 35.0, 22.4, 20.0, 15.7, 14.2, 14.1. HRMS calcd for C₁₀H₁₅O₂ (M-C₃H₇): 167.1072. Found: 167.1076 $[\alpha]_D^{23}$ = +34.7 (c 1.1, CH₂Cl₂).

Silyl Ether 19.

To a solution of **18** (55.2 g, 313 mmol) in 350 mL of THF at -78°C was added 115 mL (297 mmol) of a 2.58 M solution of *n*-butyllithium in hexanes over 15 minutes. The resulting clear, pale yellow reaction mixture was allowed to stir at -78°C for 3.5 h whereupon 10.5 g (142 mmol) of ethyl formate was added dropwise via syringe over 5 min and the resulting mixture was stirred at -78°C for 1 h then allowed to warm to rt over 1 h. The reaction mixture was diluted with 300 mL of diethyl ether and 30 mL of saturated aqueous sodium bicarbonate was added dropwise followed by addition of 250 mL of water. The resulting layers were separated and the aqueous portion was extracted with additional diethyl ether (3 x 150 mL) and the combined organic extracts were washed with brine (3 x 100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo* to afford 65 g of the crude bispropargylic alcohol intermediate (TLC R_f = 0.58 in 75% Et₂O in petroleum ether) as a dark red/orange oil. This material was subjected to the next step without further purification due to its instability.

The crude alcohol was dissolved in 600 mL of THF and cooled to -40°C whereupon 149 mL (497 mmol) of 65% w/w solution of Red-Al in toluene was added dropwise via syringe over 30 min with concomitant hydrogen gas evolution. The resulting clear, reddish-orange mixture was allowed to stir while warming from -40°C to 0°C over 4.5 h. The reaction was then carefully quenched at 0°C by dropwise addition of 30 mL of a 1 M aqueous solution of Rochelle's salts causing vigorous gas evolution. The mixture was allowed to warm to rt whereupon and additional 150 mL of 1 M aqueous

Rochelle's salts, 100 mL of water, and 500 mL of diethyl ether were added followed by vigorous stirring for 2 h. The resulting homogeneous layers were then separated and the aqueous phase was diluted with 200 mL of additional water before being extracted with diethyl ether (3 x 150 mL). The combined organic extracts were washed with brine (3 x 100 mL), dried (MgSO₄), filtered, and concentrated on a rotary evaporator to afford 69.5 g of the crude alcohol containing residual solvents and 2-methoxyethanol from quenching of the Red-Al reagent. The residual solvents and 2-methoxyethanol were removed via Kugelrohr distillation at 70°C at 1 Torr over 20-30 min to afford 59.4 g of a dark yellow/brown oil which was purified by flash chromatography on silica gel (elution with 75% Et₂O/petroleum ether) to deliver 33.2 g (61%) of pure alcohol as a yellow oil. Due to the apparent instability of **59**, this material was not stored for prolonged periods but was converted to its more stable silyl ether derivative **60**. Physical data for the alcohol: TLC R_f = 0.35 (75% Et₂O in petroleum ether).

IR (film): 3414.6, 3001.4, 2838.7, 1612.3, 1585.9, 1246.6, 1033.3, 971.6, 818.5 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 7.24 (d, *J* = 8.8 Hz, 4 H), 6.86 (d, *J* = 8.8 Hz, 4 H), 5.85-5.71 (m, 4 H), 4.64 (br d, *J* = 3.9 Hz, 1 H), 4.42 (s, 4 H), 3.98 (d, *J* = 3.9 Hz, 4 H), 3.77 (s, 6 H), 2.24 (d, *J* = 3.9 Hz, 1 H). ¹³C NMR (75 MHz, CDCl₃) δ: 159.04, 133.77, 130.08, 129.28, 127.62, 113.65, 72.11, 71.82, 69.59, 55.13.

To a solution of alcohol (29.3 g, 0.076 mmol) in 100 mL of DMF at 0°C were successively added 15.5 g (0.228 mmol) of imidazole and 14.9 g (0.099 mmol) of *t*-butyldimethylsilyl chloride. The resulting mixture was allowed to warm to rt and stir for 48 h then poured into 300 mL of saturated aqueous ammonium chloride and 300 mL of diethyl ether. The mixture was stirred until two homogeneous layers resulted (~ 2 min) and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 150 mL) and the combined organic extracts were washed with water (3 x 80 mL), brine (3 x 50 mL), then dried (MgSO₄), filtered, and concentrated *in vacuo* to give 39.4 g of crude **19** as a golden yellow oil. Flash chromatography on silica gel (elution with 20% Et₂O in petroleum ether) afforded 33.7 g (89%) of pure **19** as pale yellow oil. TLC R_f = 0.40 (20% Et₂O in petroleum ether). IR (film): 2930.6, 2855.1, 1613.0, 1585.9, 1513.7, 1249.0, 1102.6, 835.9, 776.8 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 7.26 (d, *J* = 8.8 Hz, 4 H), 6.86 (d, *J* = 8.8 Hz, 4 H), 5.76 (dt, *J* = 15.6, 4.9 Hz, 2 H), 5.69 (dd, *J* = 15.6, 4.4 Hz, 2 H), 4.68 (app t, *J* = 4.4 Hz, 1 H), 4.43 (s, 4 H), 3.99 (d, *J* = 4.9 Hz, 4 H), 3.79 (s, 6 H), 0.91 (s, 9 H), 0.07 (s, 6 H). ¹³C NMR (75 MHz, CDCl₃) δ: 159.08, 134.94, 130.29, 129.31, 126.15, 113.68, 72.83, 71.56, 69.77, 55.19, 25.84, 18.30, -4.66. Anal. Calcd for C₂₉H₄₂SiO₅: C, 69.84; H, 8.49. Found: C, 69.70; H, 8.34.

Alcohol 20.

To a mixture of potassium hexaferrocyanide (59.1 g, 179 mmol), potassium carbonate (24.8 g, 179 mmol), sodium bicarbonate (15.1 g, 179 mmol), methanesulfonamide (5.69 g, 59.8 mmol), (DHQD)₂-PHAL (0.935 g, 1.20 mmol), potassium osmate(VI) dihydrate (0.220 g, 0.598 mmol) was added 300 mL of water and 250 mL of *tert*-butanol and the resulting mixture was stirred at rt for 15 min to afford a homogeneous solution. The mixture was then cooled to 0°C at which time a suspension of 29.8 g (59.8 mmol) of **19** in 50 mL of *tert*-butanol was added *via* pipette. The reaction mixture was vigorously stirred at 0°C for 38 h then quenched at 0°C by the addition of 82 g of sodium sulfite. The resulting mixture was allowed to warm to rt with stirring over 1 h then 250 mL of water and 500 mL of ethyl acetate were added. The resulting layers were separated and the aqueous portion was extracted with additional ethyl acetate (3 x 200 mL). The combined organic layers were then washed with 2 N aqueous sodium hydroxide solution (2 x 200 mL), water (2 x 150 mL), and brine (2 x 200 mL), then dried over MgSO₄, filtered, and concentrated *in vacuo* to afford 31.5 g of the crude diol as a dark

yellow/green oil. Purification of the product by flash chromatography on silica gel (elution with 70% Et₂O in petroleum ether) yielded 25.02 g (79%) of a pale yellow oil as the inseparable mixture of diols in a >15:1 diastereoselectivity.

Physical data for the major diastereomer: TLC R_f = 0.21 (50% Et₂O in petroleum ether). IR (film):

3474.6, 2953.9, 2856.6, 1613.2, 1586.3, 1248.8, 1099.8, 837.2, 778.9 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 7.24 (d, *J* = 8.8 Hz, 2 H), 7.22 (overlapping d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.84 (overlapping d, *J* = 8.8 Hz, 2 H), 5.82 (dt, *J* = 15.6, 4.9 Hz, 1 H), 5.72 (dd, *J* = 15.6, 5.9 Hz, 1 H), 4.46 (m, 2 H), 4.42 (s, 2 H), 4.36 (app t, *J* = 4.9 Hz, 1 H), 4.28 (br m, 1 H), 3.99 (d, *J* = 4.9 Hz, 2 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.54 (dd, *J* = 5.9, 1.5 Hz, 2 H), 3.48 (app t, *J* = 5.9 Hz, 1 H), 3.17 (d, *J* = 3.4 Hz, 1 H), 2.88 (d, *J* = 6.8 Hz, 1 H), 0.90 (s, 9 H), 0.11 (s, 3 H), 0.06 (s, 3 H). ¹³C NMR (75 MHz, CDCl₃) δ: 159.17, 159.08, 131.99, 130.13, 129.79, 129.36, 129.23, 129.03, 113.71, 113.68, 93.94, 75.75, 73.52, 73.13, 71.98, 71.56, 69.46, 68.62, 55.14, 22.74, 18.00, -4.46, -5.08. Anal. Calcd for C₂₉H₄₄SiO₇: C, 65.38; H, 8.32. Found: C, 65.16; H, 8.18.

Physical data for the minor diastereomer: TLC R_f = 0.21 (50% Et₂O in petroleum ether). ¹H NMR (300 MHz, CDCl₃) δ: 7.24 (d, *J* = 8.8 Hz, 4 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.84 (overlapping d, *J* = 8.8 Hz, 2 H), 5.82 (dt, *J* = 15.6, 4.9 Hz, 1 H), 5.72 (dd, *J* = 15.6, 5.9 Hz, 1 H), 4.46 (m, 2 H), 4.42 (m, 2 H), 4.27 (app t, *J* = 5.9 Hz, 1 H), 3.98 (d, *J* = 4.4 Hz, 2 H), 3.82 (m, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.53 (m, 2 H), 3.48-3.44 (m, 1 H), 3.17 (br s, 1 H), 2.80 (br s, 1 H), 0.88 (s, 9H), 0.06 (s, 3 H), 0.04 (s, 3 H).

A solution of the inseparable diastereomeric diols (25.2 g, 47.5 mmol) in 150 mL of CH₂Cl₂ and 61.8 g (475 mmol) of 1,1-dimethoxycyclopentane at 0°C was treated with *p*-toluenesulfonic acid (0.270 g, 1.42 mmol). After stirring at 0°C for 1.75 h, the reaction mixture was neutralized by the addition of solid NaHCO₃ (ca. 2 g) and allowed to warm to rt and stir overnight. Filtration of the mixture through a short pad of silica gel (3 x 7 cm) washing with 200 mL of additional diethyl ether then provided a clear filtrate which was concentrated *in vacuo* on a rotary evaporator to provide approximately 75 mL of the crude acetal intermediate (TLC R_f = 0.90, 70% Et₂O in petroleum ether) as a pale yellow liquid which contained some residual 1,1-dimethoxycyclopentane.

The crude material was dissolved in 100 mL of anhydrous THF and the solution was cooled to 0°C whereupon 57 mL (57.0 mmol) of a 1.0 M solution of TBAF in THF was added dropwise. The resulting mixture was stirred at 0°C for 2 h and at rt for 14 h then the mixture was partitioned between 50 mL of saturated aqueous ammonium chloride solution and 50 mL of diethyl ether and the layers were separated. The aqueous phase was extracted with additional diethyl ether (3 x 50 mL) and the combined organic extracts were washed with brine (3 x 30 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* on a rotary evaporator to afford the crude product as an orange liquid which contained residual 1,1-dimethoxycyclopentane. Purification by flash chromatography on silica gel initially eluting with 70% Et₂O in petroleum ether then increasing to 80% Et₂O in petroleum ether provided 21.5 g (94%) of an inseparable 13 : 1 diastereomeric mixture of **20** as a pale yellow oil.

Physical data for **20** (major diastereomer): TLC R_f = 0.31 (70% Et₂O in petroleum ether). IR (film):

3442.1, 2954.8, 2869.3, 1612.7, 1586.0, 1513.8, 1248.4, 1107.7, 1035.0, 975.3, 820.0 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 7.24 (d, *J* = 8.3 Hz, 2 H), 7.22 (overlapping d, *J* = 8.3 Hz, 2 H), 6.84 (d, *J* = 8.3 Hz, 4 H), 5.90 (dt, *J* = 15.6, 5.9 Hz, 1 H), 5.74 (dd, *J* = 15.6, 5.4 Hz, 1 H), 4.48 (s, 2H), 4.40 (s, 2 H), 4.21 (br m, 1 H), 4.06 (dd, *J* = 12.2, 5.4 Hz, 1 H), 3.96 (d, *J* = 5.4 Hz, 2 H), 3.76 (s, 6 H), 3.69 (dd, *J* = 7.3, 5.9 Hz, 1 H), 3.57 (dd, *J* = 10.3, 5.4 Hz, 1 H), 3.50 (dd, *J* = 10.3, 5.4 Hz, 1 H), 2.91 (br s, 1 H), 1.89-1.71 (m, 4 H), 1.71-1.64 (m, 4 H). ¹³C NMR (75 MHz, CDCl₃) δ: 159.12, 159.00, 130.99, 130.15, 129.48, 129.29, 129.21, 128.71, 119.20, 113.65, 113.58, 80.96, 76.81, 73.02, 71.56, 71.52, 70.30, 69.56, 55.06, 37.22, 37.07, 36.97, 23.42, 23.24. Anal. Calcd for C₂₈H₃₆O₇: C, 69.40; H, 7.49. Found: C, 69.19; H, 7.30.

Ketone 21.

To the alcohol **20** (21.5 g, 44.6 mmol) and 26.2 g (313 mmol) of sodium bicarbonate in 250 mL of methylene chloride at 0°C was added 24.6 g (57.9 mmol) of Dess-Martin periodinane as a solid over 1 minute. The resulting heterogeneous mixture was allowed to warm to rt and stir for 30 min, then the mixture was cooled to 0°C whereupon three 50 mL portions of 1 N aqueous sodium sulfite solution was slowly added over 15 minutes. After warming to rt and stirring vigorously for an additional 2 h, 50 mL of water was added and the resulting layers were separated. The aqueous portion was extracted with diethyl ether (3 x 75 mL). The combined extracts were washed with brine (2 x 75 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to afford 22.8 g of the crude enone as a yellow oil. Purification by flash chromatography (elution with 40% Et₂O in petroleum ether) provided 19.5 g (91%) of pure unsaturated ketone as a pale yellow oil. Enantiomeric purity of the ketone was determined to be 90% ee by chiral HPLC analysis: Chiralpak AD at 23°C, 1.0 mL/min flow rate, 20% isopropanol-heptane, λ = 254 nm, retention times for enantiomers of the ketone: 12.03 min (minor), 13.20 min (major) as compared to a racemic standard of unsaturated ketone. TLC R_f = 0.65 (60% Et₂O in petroleum ether). IR (film): 2955.9, 2869.4, 1691.8, 1629.7, 1612.7, 1513.9, 1248.4, 1110.8, 1034.7, 819.4 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ : 7.24 (d, *J* = 8.3 Hz, 4 H), 7.04 (dt, *J* = 15.6, 3.9 Hz, 1 H), 6.88-6.78 (m, 5 H), 4.52 (s, 2 H), 4.47 (s, 2 H), 4.32 (d, *J* = 7.3 Hz, 1 H), 4.25-4.20 (m, 1 H), 4.16-4.14 (m, 2 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.68 (dd, *J* = 10.7, 3.9 Hz, 1 H), 3.59 (dd, *J* = 10.7, 5.4 Hz, 1 H), 1.91-1.86 (m, 2 H), 1.83-1.76 (m, 2 H), 1.73-1.68 (m, 4 H). ¹³C NMR (75 MHz, CDCl₃) δ : 197.58, 159.22, 159.11, 145.15, 129.81, 129.57, 129.28, 129.19, 123.98, 120.86, 113.73, 113.65, 80.90, 77.31, 73.05, 72.37, 69.77, 68.51, 55.14, 36.73, 36.57, 23.56, 23.16. Anal. Calcd for C₂₈H₃₄O₇: C, 69.69; H, 7.10. Found: C, 69.72; H, 6.88. $[\alpha]_D^{26}$ = +8.43 (c 1.79, CH₂Cl₂).

A 1-L round-bottomed flask was charged with potassium hexaferrocyanide (40.2 g, 122 mmol), potassium carbonate (16.9 g, 122 mmol), sodium bicarbonate (10.2 g, 122 mmol), methanesulfonamide (3.86 g, 40.6 mmol), (DHQD)₂-PHAL (0.950 g, 1.22 mmol), and potassium osmate(VI) dihydrate (0.450 g, 1.22 mmol) and 175 mL of water and 100 mL of *tert*-butanol was added. The mixture was stirred vigorously at rt for 10 min then cooled to 0°C and stirred for an additional 15 minutes. At this time, a suspension of 19.5 g (40.6 mmol) of unsaturated ketone in 50 mL of *tert*-butanol was added *via* pipette. The flask was rinsed with 25 mL of additional *tert*-butanol and the rinse was added. The resulting orange, heterogeneous reaction mixture was vigorously stirred at 0-3°C for 24 h then quenched by the addition of 70 g of sodium sulfite along with 300 mL of water followed by warming to rt over 1 h with vigorous stirring. After adding 400 mL of ethyl acetate, the layers were separated and the aqueous portion was extracted with additional ethyl acetate (3 x 350 mL). The combined organic extracts were washed with 1 N aqueous sodium hydroxide (2 x 300 mL), water (4 x 300 mL), and brine (3 x 200 mL), then dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford a yellow-green oil as the crude diol. This material was dissolved in diethyl ether (~300 mL) and the solution was filtered through a short pad of silica gel (3 x 8 cm) eluting with an additional liter of diethyl ether. The resulting clear filtrate was concentrated *in vacuo* to afford 18.03 g of a white solid as the partially purified diol intermediate (TLC R_f = 0.25, 50% Et₂O in petroleum ether).

The diol mixture was dissolved in 400 mL of anhydrous methylene chloride and 52.8 g (406 mmol) of 1,1-dimethoxycyclopentane was added. After cooling the mixture to 0°C, 0.463 g (2.44 mmol) of *p*-toluenesulfonic acid hydrate was added and the resulting mixture was stirred at 0°C for 4 h then ca. 3 g of solid sodium bicarbonate was added and the mixture was warmed to rt and stirred overnight (14 h). The contents were filtered and concentrated on a rotary evaporator to remove the solvents to give the desired product which contained the excess 1,1-dimethoxycyclopentane. Since the

desired product appeared to be unstable to silica gel chromatography due to significant “streaking” of the product when analyzed by TLC (50% Et₂O in petroleum ether, R_f = 0.63), the 1,1-dimethoxypentane was removed by Kugelrohr distillation by heating the crude mixture to 60°C at 0.2 Torr for 30 minutes. The purified product (20.6 g, 88%) was then recovered from the distillation pot as an 8 : 1 diastereomeric mixture, as a yellow oil. The diastereomeric ratio of 8:1 was determined by the relative integration areas of the major diastereomer resonance at 4.29 ppm (m, 2 H) compared to the minor diastereomer resonance at 4.21 ppm (m, 2 H). Due to the apparent instability of the product, a satisfactory elemental analysis was not obtained. Physical data for **21** (major diastereomer) : TLC R_f = 0.63 (50% Et₂O in petroleum ether). IR (film): 2956.6, 2872.0, 1730.3, 1612.7, 1586.1, 1513.9, 1248.5, 1106.0, 973.8, 820.3 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 7.22 (d, *J* = 8.8 Hz, 4 H), 6.84 (d, *J* = 8.8 Hz, 4 H), 4.56 (d, *J* = 6.8 Hz, 2 H), 4.48 (s, 4 H), 4.29 (m, 2 H), 3.77 (s, 6 H), 3.63 (dd, *J* = 10.2, 4.4 Hz, 2 H), 3.57 (dd, *J* = 10.2, 5.4 Hz, 2 H), 1.83-1.81 (m, 4 H), 1.78-1.71 (m, 4 H), 1.64 (br s, 8 H). ¹³C NMR (75 MHz, CDCl₃) δ: 205.51, 159.19, 129.78, 129.34, 121.18, 113.69, 79.62, 76.68, 73.10, 69.75, 55.19, 36.86, 36.65, 23.56, 23.24.

Diol 22.

To a solution of 20.6 g (35.4 mmol) of **21** in 100 mL of THF at 0°C was added 106 mL (106 mmol) of a 1.0 M solution of trimethylsilylmethylmagnesium chloride in diethyl ether over 15 minutes. The resulting clear yellow solution was allowed to warm to rt and stir for 4 h then carefully quenched by a slow, dropwise addition of 50 mL of water causing vigorous bubbling of the reaction mixture. After 30 min, 200 mL of saturated aqueous ammonium chloride and 200 mL of diethyl ether were then added and the mixture was stirred vigorously for 1 h. The resulting layers were separated and the aqueous portion was extracted with additional diethyl ether (3 x 200 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 23.6 g of the crude hydroxysilane intermediate as a yellow oil.

The crude hydroxysilane was dissolved in 200 mL of anhydrous THF and 141.4 mL (70.7 mmol) of a 0.5 M solution of potassium hexamethyldisilazide (KHMDS) in toluene was added. The resulting mixture was stirred at rt for 18 h then partitioned between 300 mL of water and 200 mL of diethyl ether. The aqueous portion was extracted with diethyl ether (3 x 150 mL) and the combined organic extracts were washed with brine (3 x 100 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 20.3 g of a yellow oil as the crude product. Purification by flash chromatography on silica gel eluting with 35% diethyl ether in petroleum ether afforded 14.8 g (72%) of pure olefin in an 8:1 diastereomeric mixture as a pale yellow oil. The diastereomeric ratio was determined by the relative integration areas of the major diastereomer resonance at 5.36 ppm (s, 2 H) compared to the minor diastereomer resonance at 5.31 ppm (s, 2 H). Physical data for the olefin (major diastereomer) : TLC R_f = 0.70 (60% Et₂O in petroleum ether). IR (film): 2956.1, 2871.4, 1650.6, 1612.8, 1586.1, 1513.9, 1248.1, 1101.8, 1035.4, 820.2 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 7.22 (d, *J* = 8.8 Hz, 4 H), 6.84 (d, *J* = 8.8 Hz, 4 H), 5.36 (s, 2 H), 4.46 (s, 4 H), 4.22 (d, *J* = 7.8 Hz, 2 H), 4.07-4.02 (m, 2 H), 3.76 (s, 6 H), 3.56 (dd, *J* = 10.3, 3.4 Hz, 2 H), 3.48 (dd, *J* = 10.7, 5.4 Hz, 2 H), 1.86-1.82 (m, 4 H), 1.80-1.72 (m, 4 H), 1.66-1.58 (m, 8 H). ¹³C NMR (75 MHz, CDCl₃) δ: 159.09, 143.14, 129.94, 129.26, 119.07, 115.76, 113.61, 79.91, 78.00, 72.99, 69.36, 55.13, 37.34, 37.04, 23.53, 23.32. Anal. Calcd for C₃₄H₄₄O₈: C, 70.32; H, 7.64. Found: C, 70.34; H, 7.80.

To a 0°C solution of 11.5 g (19.8 mmol) of the olefin in 250 mL of methylene chloride at rt were successively added 7.6 mL of water and 13.5 g (59.4 mmol) of DDQ. The resulting dark green mixture was allowed to warm to rt and stir for 1.25 h and the resulting tan, heterogeneous mixture was

filtered through a pad of celite to remove the solids and the pad was washed with 200 mL of additional methylene chloride. The resulting filtrate was washed with saturated aqueous sodium sulfite (3 x 80 mL), saturated aqueous sodium bicarbonate (80 mL), and brine (100 mL). The solution was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to provide approximately 13 g of the crude diol mixture as a yellow liquid. Purification by flash chromatography (gradient elution from 80% Et₂O in petroleum ether to 100% Et₂O) initially afforded fractions containing the less polar minor diastereomer (TLC R_f = 0.48, 100 % Et₂O) with later fractions providing 5.6 g (83%) of the pure major diastereomer **22** as a pale yellow oil. Physical data for **22** (major diastereomer): TLC R_f = 0.36 (100% Et₂O). IR (film): 3431.3, 2958.6, 2874.4, 1649.8, 1334.5, 1112.0, 1039.7, 985.6 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 5.42 (s, 2 H), 4.32 (d, *J* = 8.3 Hz, 2 H), 3.98 (app dt, *J* = 7.8, 3.9 Hz, 2 H), 3.82 (dd, *J* = 12.2, 3.4 Hz, 2 H), 3.64 (dd, *J* = 12.2, 3.9 Hz, 2 H), 2.46 (br s, 2 H), 1.86-1.76 (m, 8 H), 1.71-1.57 (m, 8 H). ¹³C NMR (75 MHz, CDCl₃) δ: 142.61, 118.98, 115.66, 80.98, 77.26, 61.43, 37.23, 37.02, 23.23, 23.20. Anal. Calcd for C₁₈H₂₈O₆: C, 63.51; H, 8.29. Found: C, 63.67, H, 8.14. [α]_D²⁴ = + 6.44 (c 1.79, CH₂Cl₂).

Alkyne **23**.

To a suspension of 0.73 g (18.2 mmol) of 60% sodium hydride dispersion in mineral oil in 80 mL of THF at rt was added a solution of 5.9 g (17.3 mmol) of diol **22** in 30 mL of THF via cannula. The resulting mixture was allowed to stir at rt for 5 h affording a thick, heterogeneous mixture which became difficult to stir. As a result, 20 mL of additional THF was added to aid in stirring the mixture followed by the addition of 2.61 g (17.3 mmol) of *t*-butyldimethylsilyl chloride. After stirring at rt for 48 h, the mixture was partitioned between 100 mL of saturated aqueous ammonium chloride and 100 mL of diethyl ether. The aqueous portion was extracted with additional diethyl ether (3 x 70 mL) and the combined organic extracts were washed with brine (2 x 50 mL), dried over magnesium sulfate, and concentrated *in vacuo* to provide approximately 8 g of the crude product as a yellow oil. Purification by flash chromatography (elution with 35% Et₂O in petroleum ether) afforded 6.34 g (80%) of pure silyl ether as a colorless oil. TLC R_f = 0.38 (30% Et₂O in petroleum ether). IR (film): 3483.1, 2956.3, 2858.1, 1648.8, 1471.9, 1334.3, 1111.4, 836.5, 778.6 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 5.42 (s, 1 H), 5.36 (s, 1 H), 4.35 (d, *J* = 7.8 Hz, 1 H), 4.31 (d, *J* = 7.8 Hz, 1 H), 3.98-3.90 (m, 2 H), 3.83-3.75 (m, 2 H), 3.70-3.59 (m, 2 H), 2.33 (dd, *J* = 13.2, 7.3 Hz, 1 H), 1.83-1.73 (m, 8 H), 1.70-1.61 (m, 8 H), 0.85 (s, 9 H), 0.02 (s, 6 H). ¹³C NMR (75 MHz, CDCl₃) δ: 142.96, 118.89, 118.82, 115.88, 81.27, 80.77, 77.52, 62.42, 61.52, 37.39, 37.36, 37.17, 36.94, 25.81, 23.45, 23.32, 23.22, 18.29, -5.38, -5.53. Anal. Calcd for C₂₄H₄₂SiO₆: C, 63.40; H, 9.31. Found: C, 63.21; H, 9.52. [α]_D²⁴ = + 8.80 (c 1.95, CH₂Cl₂).

To a solution of 4.23 g (6.09 mL, 43.1 mmol) of trimethylsilylacetylene in 100 mL of THF at -78°C was added 23.1 mL (36.9 mmol) of a 1.6 M solution of *n*-butyllithium in hexanes and the resulting mixture was stirred at -78°C for 30 min then at 0°C for 1 h. During this time, in a separate flask was prepared a solution of 1.46 g (1.49 mL, 18.4 mmol) of pyridine in 55 mL of methylene chloride and the solution was cooled to -50°C whereupon 4.51 g (2.69 mL, 16.0 mmol) of trifluoromethanesulfonic anhydride from a freshly opened ampule was added followed by stirring at -50°C for 15 min giving a cloudy white, heterogeneous mixture. To this mixture was then added a solution of 5.59 g (12.3 mmol) of the alcohol in 44 mL of methylene chloride *via* cannula and the resulting mixture was stirred at -50°C for 40 minutes. The mixture was then diluted with 100 mL of petroleum ether at -50°C and the cold solution was poured directly onto a column of silica gel (6 x 16 cm) which had been "prewetted" with a mixture of 30% diethyl ether in petroleum ether. The cold reaction solution was rapidly eluted through the silica column washing the column with an additional 600 mL of the 30% diethyl ether in petroleum

ether mixture. The resulting clear filtrate was concentrated on a rotary evaporator to provide the crude triflate intermediate as a clear pale yellow oil (TLC R_f = 0.81, 30% Et₂O in petroleum ether). The sensitive triflate was then immediately dissolved in 30 mL of anhydrous THF.

At this time, to the previously prepared solution of the lithium acetylide at 0°C was added 25.8 mL of DMPU and the mixture was cooled to -78°C and the crude triflate solution was transferred *via* cannula into the lithium acetylide solution at -78°C. The resulting mixture was stirred at -78°C for 45 min, then the mixture was quenched at -78°C by the initial addition of 3 mL of methanol followed by the addition of 40 mL of saturated aqueous ammonium chloride. After warming to rt, the contents were partitioned between 20 mL of water and 75 mL of diethyl ether and the aqueous portion was extracted with additional diethyl ether (3 x 50 mL). The combined organic extracts were washed with water (4 x 50 mL), brine (50 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to deliver approximately 6.5 g of a yellow oil as the crude intermediate containing some residual DMPU.

This material was dissolved in 30 mL of THF and the solution was transferred *via* cannula into a well-stirred mixture of 36.9 mL (36.9 mmol) of a 1 M solution of TBAF in THF containing 2.11 mL (36.9 mmol) of acetic acid at rt. The resulting golden yellow solution was stirred at rt for 24 h then the mixture was partitioned between 30 mL of saturated aqueous sodium bicarbonate solution and 50 mL of diethyl ether. The aqueous portion was extracted with additional diethyl ether (3 x 50 mL) and the combined organic extracts were washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford approximately 6 g of the crude product mixture as a yellow oil. Flash chromatography on silica gel (elution with 45% Et₂O in petroleum ether) yielded 4.13 g (96%) of pure **23** as a pale yellow oil. TLC R_f = 0.34 (50% Et₂O in petroleum ether). IR (film): 3473.9, 3284.8, 2959.6, 2874.3, 2123.7, 1646.2, 1432.9, 1334.9, 1203.9, 1109.1, 1041.0 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ : 5.44 (s, 1 H), 5.42 (s, 1 H), 4.34 (d, J = 8.3 Hz, 1 H), 4.28 (d, J = 7.8 Hz, 1 H), 4.09-3.99 (m, 2 H), 3.84 (dd, J = 12.2, 2.9 Hz, 1 H), 3.66 (dd, J = 11.7, 3.9 Hz, 1 H), 2.64 (ddd, J = 17.1, 4.4, 2.4 Hz, 1 H), 2.48 (ddd, J = 17.1, 5.4, 2.4 Hz, 1 H), 2.03 (t, J = 2.4 Hz, 1 H), 1.99 (br s, 1 H), 1.88-1.77 (m, 8 H), 1.76-1.61 (m, 8 H). ¹³C NMR (75 MHz, CDCl₃) δ : 142.10, 119.11, 119.05, 116.91, 94.04, 80.92, 80.45, 79.73, 77.65, 70.82, 61.52, 37.62, 37.47, 37.23(2), 23.59, 23.43, 23.37(2), 22.04. Anal. Calcd for C₂₀H₂₈O₅: C, 68.94; H, 8.10. Found: C, 69.14; H, 7.91. $[\alpha]_D^{24}$ = +17.4 (c 2.26, CH₂Cl₂).

Alkyne 4.

To a solution of 4.06 g (11.6 mmol) of alkyne **23** in 80 mL of ethyl acetate at rt were successively added 2.26 mL (2.06 mL, 17.5 mmol) of quinoline and 0.50 g of Lindlar's catalyst (5 wt% of palladium/CaCO₃/Pb) and the resulting mixture was cooled to 0°C. The flask was purged with hydrogen gas using a balloon and the mixture was allowed to stir under a hydrogen atmosphere while closely monitoring the progress of the reaction by TLC analysis (50% diethyl ether in petroleum ether). After stirring at 0°C for 1.5 h, TLC analysis showed the complete conversion of the starting alkyne **23** (R_f ~ 0.34) to the slightly less polar alkene (R_f ~ 0.42). The reaction mixture was immediately filtered through a pad of celite to remove the catalyst and the resulting clear filtrate was washed with ice-cold 1 N HCl (3 x 25 mL), saturated aqueous sodium bicarbonate (2 x 25 mL), and brine (25 mL). The solution was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 4.2 g of the crude product as a pale yellow oil. Flash chromatography on silica gel (elution with 45% Et₂O in petroleum ether) afforded 3.92 g (96%) of pure alkene as a pale yellow oil. TLC R_f = 0.42 (50% Et₂O in petroleum ether). IR (film): 3473.3, 2960.0, 2874.3, 1642.6, 1433.4, 1334.5, 1204.5, 1109.1, 1037.7, 988.2, 917.1 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ : 5.85 (ddt, J = 17.1, 10.2, 6.8 Hz, 1 H), 5.46 (s, 1 H), 5.38 (s, 1 H), 5.14-5.07 (m, 2 H), 4.32 (d, J = 8.3 Hz, 1 H), 4.08 (d, J = 7.8 Hz, 1 H), 4.03-3.97 (m, 2

H), 3.84 (dd, $J = 11.7, 2.9$ Hz, 1 H), 3.67 (dd, $J = 12.2, 3.9$ Hz, 1 H), 2.48-2.43 (m, 1 H), 2.31 (app dt, $J = 15.1, 5.9$ Hz, 1 H), 2.02 (br s, 1 H), 1.87-1.73 (m, 8 H), 1.69-1.64 (m, 8 H). ^{13}C NMR (75 MHz, CDCl_3) δ : 142.57, 133.82, 118.94, 118.63, 117.45, 116.48, 81.24, 80.77, 79.26, 77.56, 61.50, 37.49, 37.43, 37.20 (2), 36.46, 23.45, 23.37, 23.33(2). Anal. Calcd for $\text{C}_{20}\text{H}_{30}\text{O}_5$: C, 68.55; H, 8.63. Found: C, 68.70; H, 8.78. $[\alpha]_{\text{D}}^{24} = +19.7$ (c 2.50, CH_2Cl_2).

To a solution of 0.330 g (0.227 mL, 2.60 mmol) of oxalyl chloride in 7 mL of methylene chloride at -78°C was slowly added 0.406 g (0.369 mL, 5.20 mmol) of anhydrous DMSO dropwise with concomitant gas evolution. After stirring at -78°C for 10 minutes, a solution of 0.700 g (2.00 mmol) of the starting alcohol in 5 mL of methylene chloride was added dropwise *via* cannula and the resulting heterogeneous mixture was stirred for 1 h at -78°C , then 2.09 mL (12.0 mmol) of diisopropylethylamine was added to afford a clear homogeneous solution which was stirred at -78°C for 5 min then warmed to -20°C for 45 minutes. The reaction was quenched at -20°C by the addition of saturated aqueous ammonium chloride (10 mL) followed by warming to rt. The resulting mixture was partitioned between 10 mL of water and 20 mL of methylene chloride and the aqueous portion was extracted with additional methylene chloride (2 x 20 mL). The combined organic extracts were successively washed with 1 N aqueous HCl (3 x 25 mL), saturated aqueous sodium bicarbonate (25 mL), and brine (25 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford 0.711 g of the crude aldehyde intermediate as a clear, colorless oil. Due to the instability of the aldehyde, this material was not purified further but was immediately dissolved in 8 mL of anhydrous THF and subjected directly to the next transformation. IR (film): 2961.2, 2874.7, 1737.7, 1643.6, 1335.8, 1107.0, 1035.3, 918.7 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 9.74 (s, 1 H), 5.84 (ddt, $J = 17.1, 10.2, 6.8$ Hz, 1 H), 5.47 (s, 1 H), 5.37 (s, 1 H), 5.14-5.07 (m, 2 H), 4.56 (d, $J = 6.8$ Hz, 1 H), 4.35 (dd, $J = 7.3, 1.9$ Hz, 1 H), 4.12 (d, $J = 7.8$ Hz, 1 H), 4.02-3.95 (m, 1 H), 2.48-2.39 (m, 1 H), 2.30 (dt, $J = 14.2, 7.3$ Hz, 1 H), 1.82-1.56 (m, 14 H).

A solution of 0.745 g (5.00 mmol) of dimethyldiazomethylphosphonate in 8 mL of THF was transferred *via* cannula into 0.565 mL (0.565 mmol) of a 1.0 M solution of sodium hexamethyldisilazide in THF at -78°C . The resulting bright yellow mixture was stirred at -78°C for 20 min whereupon the solution of the previously prepared aldehyde in 8 mL of THF was added dropwise *via* cannula over 10 min (1 mL THF rinse). The resulting mixture was stirred at -78°C for 30 min then warmed to rt and quenched with 10 mL of water. The layers were separated and the aqueous portion was extracted with additional diethyl ether (3 x 25 mL) and the combined extracts were washed with brine (25 mL), dried over anhydrous magnesium, filtered, and concentrated *in vacuo* to afford 0.708 g of the crude alkyne as a yellow oil. Flash chromatography on silica gel (elution with 5% diethyl ether in petroleum ether) provided 0.578 g (84%) of pure **4** as a pale yellow oil. TLC $R_f = 0.28$ (5% Et_2O in petroleum ether). IR (film): 3268.0, 3077.8, 2961.9, 2874.8, 2116.2, 1643.1, 1433.6, 1335.5, 1205.5, 1107.2, 1037.8, 919.5 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 5.84 (ddt, $J = 17.1, 10.3, 6.8$ Hz, 1 H), 5.47 (s, 1 H), 5.39 (s, 1 H), 5.14-5.06 (m, 2 H), 4.46 (s, 2 H), 4.14 (d, $J = 8.3$ Hz, 1 H), 3.98 (ddd, $J = 11.7, 7.3, 4.4$ Hz, 1 H), 2.53 (s, 1 H), 2.42 (app dt, $J = 14.6, 5.9$ Hz, 1 H), 2.30 (app dt, $J = 14.6, 6.8$ Hz, 1 H), 1.98-1.76 (m, 8 H), 1.74-1.61 (m, 8 H). ^{13}C NMR (75 MHz, CDCl_3) δ : 141.73, 133.79, 120.31, 118.71, 117.50, 117.24, 81.27, 81.17, 80.75, 79.28, 75.04, 70.32, 37.49, 37.26, 36.63(2), 36.36, 23.80, 23.46, 23.42, 23.12. Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{O}_4$: C, 73.23; H, 8.19. Found: C, 73.40; H, 8.33. $[\alpha]_{\text{D}}^{24} = +27.9$ (c 1.78, CH_2Cl_2).

Carboxylic Acid **24**.

Alkyne **4** (36 mg, 0.104 mmol) and alkene **2** (159 mg, 0.523 mmol) were dissolved in 300 μL of dichloroethane and warmed to 50°C in an oil bath. $\text{Cp}^*\text{Ru}(\text{MeCN})_3\text{PF}_6$ (5.1 mg, 0.01 mmol) was then

added in one portion. After approximately 2 h the reaction was placed atop a silica gel column and purified by silica gel chromatography (10-30% Et₂O/80% petroleum ether) which gave 31 mg (46%) of the desired Fmoc ester as a 3.5 : 1 mixture of branched and linear products. Further purification on silica gel of the mixture of starting materials with 40-80% CH₂Cl₂/petroleum ether provided 11mg of alkyne (30% recovered) and 108 mg of alkene (69% recovered).

Fmoc Ester: R_f = 0.41 (20% Et₂O/80% petroleum ether); IR (film from CH₂Cl₂) 2958, 2877, 1714 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.77 (d, J = 7.6 Hz, 2H), 7.62 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 6.13-6.19 (m, 2H), 5.82-5.90 (m, 2H), 5.48 (s, 1H), 5.47 (s, 1H), 5.24 (s, 1H), 5.09-5.19 (m, 2H), 5.01 (s, 1H), 4.35-4.43 (m, 3H), 4.26 (t, J = 7.3 Hz, 1H), 4.19 (d, J = 8.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 166.9, 152.8, 144.0, 143.3, 142.3, 141.2, 135.6, 134.2, 133.9, 127.7, 127.0, 125.1, 120.0, 119.0, 118.7, 118.0, 117.8, 117.4, 115.6, 84.0, 81.2, 79.7, 79.6, 65.8, 46.8, 37.6, 37.4, 37.3, 37.2, 36.3, 34.6, 23.5, 23.4, 23.3, 13.9. HRMS calcd for C₃₂H₃₂O₄ (M-C₁₀H₁₆O₂): 480.2301. Found: 480.2327.

The Fmoc ester (37 mg, 0.057 mmol) was dissolved in 1.5 mL of CH₂Cl₂. Piperidine (35 μ L, 0.354 mmol) was then added. After 30 min more piperidine (150 μ L, 1.52 mmol) was added. After 2 h the reaction was poured into CH₂Cl₂ and washed with 0.2 M H₂SO₄ (3x) and brine (1x), dried (MgSO₄) and concentrated. Purification by silica gel chromatography (5-15% MeOH/CHCl₃) gave 22 mg (85%) of the desired acid **24**.

24: R_f = 0.69 (10% MeOH/90% CHCl₃); IR (film from CH₂Cl₂) 3076, 2959, 1687 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.15-6.22 (m, 2H), 5.80-5.88 (m, 1H), 5.75 (bs, 1H), 5.47 (s, 1H), 5.46 (s, 1H), 5.22 (s, 1H), 5.08-5.13 (m, 2H), 4.99 (s, 1H), 4.39 (d, J = 8.4 Hz, 1H), 4.18 (d, J = 8.5 Hz, 1H), 4.04 (d, J = 8.1 Hz, 1H), 3.90 (dt, J = 7.9, 4.0, 1H), 3.05 (dd, J = 16.6, 4.4, 1H), 2.89 (dd, J = 16.5, 5.0 Hz, 1H), 2.39-2.44 (m, 1H), 2.29 (s, 3H), 2.24-2.29 (m, 1H), 1.62-1.93 (m, 17H); ¹³C NMR (125 MHz, CDCl₃) δ 172.2, 154.5, 143.2, 135.6, 134.8, 133.9, 119.1, 118.7, 117.8, 117.7, 117.4, 115.7, 84.0, 81.2, 79.7, 79.6, 37.6, 37.4, 37.3, 37.2, 36.3, 34.6, 23.5, 23.4, 23.2, 14.1. HRMS calcd for C₂₈H₃₈O₆: 470.2668. Found: 470.2662. $[\alpha]_D^{23}$ = +40.1 (c 1.2, CH₂Cl₂).

Ester 25.

Acid **24** (36 mg, 0.0764 mmol) and $[\text{RuCl}_2(p\text{-cymene})]_2$ (4.7 mg, 0.00764 mmol) were dissolved in 2 mL of toluene. Ethyl ethynyl ether (40% in hexanes, 20 μ L, 0.084 mmol) was then added. After 2 h the reaction was concentrated to a dark solid. Alcohol **3** (42 mg, 0.1997 mmol) was then added in 300 μ L of dichloroethane, followed by a solution of camphorsulfonic acid (1.8 mg, 0.00764 mmol) in 200 μ L of dichloroethane. After 2 h the reaction was quenched with 10 μ L of triethylamine, placed atop a silica gel column and purified by silica gel chromatography (20-40% Et₂O/ petroleum ether) to provide 33 mg (66%) of ester **25** and 27 mg of recovered epoxide **3**. Further elution with 10% methanol/chloroform **25:** R_f = 0.19 (10% Et₂O/90% petroleum ether); IR (film from CH₂Cl₂) 3303, 2559, 2116 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.14 (bs, 2H), 5.81-5.89 (m, 1H), 5.75 (s, 1H), 5.47 (s, 1H), 5.46 (s, 1H), 5.22 (s, 1H), 2.08-5.13 (m, 2H), 4.98 (s, 1H), 4.83 (t, J = 6.0 Hz, 1H), 4.38 (t, J = 8.5 Hz, 1H), 4.18 (d, J = 8.5 Hz, 1H), 4.04 (d, J = 8.1 Hz, 1H), 3.88 (m, 1H), 3.03 (d, J = 16.5 Hz, 1H), 2.92 (dd, J = 6.0, 2.2 Hz, 1H), 2.88 (dd, J = 15.9, 4.4 Hz, 1H), 2.68 (dd, J = 7.4, 2.2 Hz, 1H), 2.36-2.44 (m, 2H), 2.35 (dd, J = 5.1 Hz, 1H), 2.29 (s, 3H), 2.22-2.28 (m, 2H), 2.05-2.11 (m, 1H), 2.05-2.11 (m, 1H), 2.01 (t, J = 2.7 Hz, 1H), 1.59-1.90 (m, 13H), 1.20-1.46 (m, 6H), 1.13 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 166.1, 153.2, 143.3, 142.4, 135.6, 134.2, 133.9, 119.0, 118.7, 117.8, 117.4, 115.6, 84.1, 81.8, 81.2, 79.7, 79.6, 74.7, 70.2, 61.5, 56.8, 51.0, 37.6, 37.5, 37.4, 37.3, 37.2, 36.6, 36.2, 35.3, 35.1, 34.6, 29.7, 23.5, 23.4, 23.3, 20.0, 15.8, 15.2, 14.2. HRMS calcd for C₄₁H₅₈O₇: 662.4183. Found: 662.4187. $[\alpha]_D^{23}$ = +30.9 (c 0.75, CH₂Cl₂).

The Presumed Amphidinolide A (1)

Ester **25** (24 mg, 0.0362 mmol) was dissolved in 36 mL of dichloroethane and warmed to 50 °C in an oil bath. $\text{CpRu}(\text{MeCN})_3\text{PF}_6$ (1.5 mg, 0.0036 mmol) was then added. After 1 h the reaction was quenched with the addition of 50 μL of triethylamine and concentrated in vacuo. Purification by silica gel chromatography (10-30% Et_2O /petroleum ether) provided 14 mg (58%) of the macrocycle product as a yellow oil.

Macrocycle: R_f = 0.32 (20% Et_2O /80% petroleum ether); IR (film from CH_2Cl_2) 2958, 1714 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.16 (d, J = 16.0 Hz, 1H), 6.07-6.13 (m, 1H), 5.79 (bs, 1H), 5.75 (t, J = 7.4 Hz, 1H), 5.54 (s, 1H), 5.50 (s, 1H), 5.29 (s, 1H), 5.25 (dd, J = 15.1, 7.3 Hz, 1H), 5.17 (s, 1H), 4.80 (s, 1H), 4.71 (s, 1H), 5.54 (dd, J = 7.2, 3.7 Hz), 4.28 (d, J = 8.2 Hz, 1H), 4.20 (d, J = 8.3 Hz, 1H), 4.13 (t, J = 7.7 Hz, 1H), 3.85 (d, J = 7.8 Hz, 1H), 3.16 (dd, J = 13.8, 8.8 Hz, 1H), 3.03 (dd, J = 14.0, 5.0 Hz, 1H), 2.96 (dd, J = 7.2, 2.2 Hz, 1H), 2.71 (dd, J = 7.3, 2.1 Hz, 1H), 2.55-2.66 (m, 2H), 2.44 (dd, J = 13.8, 6.0 Hz, 1H), 2.30 (s, 3H), 2.12-2.18 (m, 1H), 1.80-1.95 (m, 8H), 1.62-1.79 (m, 8H), 1.22-1.56 (m, 6H), 1.04 (d, J = 7.2 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.0, 151.9, 146.0, 143.1, 142.5, 135.3, 135.2, 133.9, 133.3, 127.9, 118.9, 118.8, 117.2, 115.1, 111.7, 84.9, 82.3, 81.1, 78.2, 77.7, 61.5, 54.4, 39.3, 38.1, 37.6, 37.4, 37.3, 37.1, 36.7, 35.7, 35.5, 33.9, 29.7, 23.5, 23.4, 23.3, 23.3, 19.9, 17.2, 16.0, 14.3. HRMS calcd for $\text{C}_{41}\text{H}_{58}\text{O}_7$: 662.4183. Found: 662.4179. $[\alpha]_D^{23}$ = +59.6 (c 1.0, CH_2Cl_2).

The protected macrocycle (7.6 mg, 0.0115 mmol) was suspended in 300 μL of dioxane and 200 μL of water was added. Amberlyst-15 (15 mg, 0.0705 mmol) was then added and the reaction was warmed to 60 °C. After 60 h the reaction was still not done, so more amberlyst (30 mg, 0.141 mmol) was added and the temperature raised to 85 °C. After 6 h. the reaction was filtered than concentrated. The residue was the purified by HPLC (70% ethyl acetate/30% hexanes, 10 mL/min, semi-prep column, silica gel packed) to provide 3.7 mg (61%) of the tetraol **1**.

1: R_f = 0.41 (ethyl acetate); IR (film from CH_2Cl_2) 3384, 3284, 2922, 1714 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.18 (d, J = 15.6 Hz, 1H), 6.04-6.10 (m, 1H), 5.79 (s, 1H), 5.72-5.76 (m, 1H), 5.59 (s, 1H), 5.58 (s, 1H), 5.36 (s, 1H), 5.25 (d, J = 13.4 Hz, 1H), 4.86 (s, 1H), 4.77 (s, 1H), 4.53 (dd, J = 7.2, 3.8 Hz, 1H), 4.28 (s, 1H), 4.21 (d, J = 7.2 Hz, 1H), 3.82 (s, 1H), 3.22 (bd, J = 14.9, 1H), 3.11 (t, J = 15.5, 1H),

2.91 (d, $J = 6.2$ Hz, 1H), 2.74 (bd, $J = 13.8$ Hz, 1H), 2.63-2.70 (m, 3H), 2.52 (d, $J = 12.5$ Hz, 1H), 2.34 (bs, 1H), 2.29 (s, 3H), 2.11-2.20 (m, 2H), 2.01-2.09 (m, 1H), 1.77 (t, $J = 11.8$ Hz, 1H), 1.10-1.60 (m, 6H), 0.97 (d, $J = 6.7$ Hz, 3H), 0.86-0.92 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.6, 152.0, 145.2, 136.3, 134.9, 131.1, 130.2, 119.3, 115.4, 114.8, 113.8, 96.1, 94.3, 73.4, 72.5, 70.9, 69.6, 61.4, 60.4, 54.2, 38.5, 36.7, 35.4, 33.3, 31.9, 29.7, 29.3, 22.7, 22.3, 21.0, 14.2. $[\alpha]_{\text{D}}^{23} = +55.8$ (c 0.2, CHCl_2).