Synthesis of the C6-C21 Segment of Amphidinolide E

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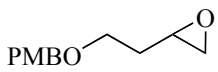
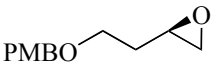
Supporting Information: Experimental procedures for all new compounds 17 pages



(±)-4-(*p*-Methoxybenzyloxy)-1,2-epoxybutane

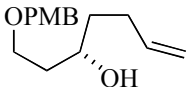
To a stirring solution of *p*-methoxybenzyl 3-butenyl ether (33.7 g, 0.18 mol) in CH_2Cl_2 (1.2 L) was added MCPBA (77%, 50.0 g, 0.22 mmol) After stirring overnight, the reaction mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$. A 10% aqueous solution of NaOH was added dropwise to dissolve the resultant solids and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (0.05 mm/Hg, 160^{o}C) to give 31.7 g (87%) of epoxide as a clear liquid. ^{1}H NMR (300 MHz, $CDCl_3$) _ 7.32 (d, *J* = 1.77 Hz, 2H), 6.93 (d, *J* = 1.70 Hz, 2H), 4.56 (s, 2H), 3.79 (s, 3H), 3.53 (t, *J* = 5.7 Hz, 2H), 3.01 (m, 1H), 2.78 (m, 1H), 2.52 (m, 1H), 2.02 (m, 2H).



Epoxide 1

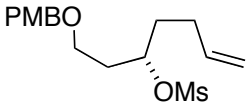
To a flame-dried round-bottomed flask equipped with a stirbar was added the (*R,R*)-(salen)Co(II) precatalyst (491 mg, 0.813 mmol) followed sequentially by freshly distilled (±)-PMB epoxy ether (33.87 g, 163 mmol) and AcOH (186 μL, 3.25 mmol). After the reaction mixture turned from a red suspension to a dark brown solution (0.25 h), the solution was cooled to 0 ^{o}C and THF (2 mL) and water (1.30 mL, 81.3 mmol) were added. The reaction mixture was allowed to warm to room temperature over 2 h and stirred overnight. The (*S*)-PMB epoxy ether was removed by careful bulb-to-bulb distillation (0.05 mm/Hg, 160 ^{o}C) from the reaction mixture to yield 15.9 g (47%) of epoxide **1** as a clear oil. $[\alpha]^{20}_D$ – 12.3 (*c* 1.00, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) _ 7.32

(d, *J* = 1.77 Hz, 2H), 6.93 (d, *J* = 1.70 Hz, 2H), 4.50 (s, 2H), 3.78 (s, 3H), 3.52 (t, *J* = 5.7 Hz, 2H), 3.06 (m, 1H), 2.78 (m, 1H), 2.52 (m, 1H), 2.02 (m, 2H).



Alcohol 2

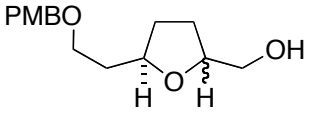
To a suspension of freshly purified CuI (1.34 g, 7.04 mmol) in THF (315 mL) at -30 ^{o}C was added allylmagnesium chloride (2M in Et_2O, 35.2 mL) over 0.25 h. The reaction mixture was stirred an additional 5 min followed by the addition of a solution of epoxide **1** (10.5 g, 50.4 mmol) in THF (53 mL) over 0.25 h. The reaction mixture was allowed to warm to 0 ^{o}C and stirred for an additional 0.5 h. The reaction mixture was quenched with aqueous NH_4Cl/NaOH (9:1) and Et_2O and transferred to a separatory funnel. The aqueous layer was separated and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The solution was concentrated to give 12.6 g (100%, crude) of alcohol **2** which was used in the next step with no further purification. $[\alpha]^{20}_{D}$ – 8.3 (*c* 1.00, $CHCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$) _ 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.84 (m, 1H), 5.07-4.96 (m, 2H), 4.45 (s, 2H), 3.83 (m, 1H), 3.81 (s, 3H), 3.70 (m, 1H), 3.63 (m, 1H), 2.20 (m, 1H), 2.12 (m, 1H), 1.74 (m, 2H), 1.58 (m, 1H), 1.52 (m, 1H).



Mesylate 3

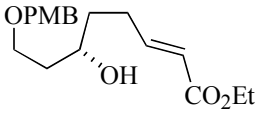
To a stirring solution of alcohol **2** (0.250 g, 0.999 mmol) in CH_2Cl_2 (10 mL) at 0 °C was sequentially added triethylamine (0.278 mL, 2.00 mmol) and MsCl (0.116 mL, 1.500 mmol). After stirring for 0.5 h, the reaction mixture was quenched with water, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The

combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 0.312 g (95% over two steps) of mesylate **3** as a light yellow oil which was used without further purification. $[\alpha]^{20}_D$ + 9.3 (*c* 1.00, $CHCl_3$): ^{1}H NMR ($CDCl_3$, 300 MHz); δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 5.79 (ddd, *J* = 1.5, 1.5, 15.0 Hz, 1H), 5.08 (m, 2H), 5.01 (m, 1H), 4.98 (m, 1H), 4.42 (q, *J* = 6.9 Hz, 2H), 3.88 (s, 3H), 3.58 (m, 2H), 2.97 (s, 3H), 2.17 (m, 2H), 1.99 (m, 2H), 1.84 (m, 2H).



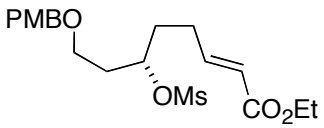
Tetrahydrofuran 4

To a solution of mesylate **3** (123 mg, 0.304 mmol) in *t*-BuOH/water/acetone (2:2:1, 5 mL) was added NMO (53.5 mg, 1.02 mmol) and OsO_4 (2.5 wt% in toluene, 0.095 μmol). After stirring overnight, the reaction mixture was quenched by the addition of solid Na_2SO_3 and stirred for an additional 1 h. Diethyl ether was added to the mixture and the layers were separated. The aqueous layer was further extracted with Et_2O and the combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The solution was concentrated under reduced pressure and the residue was chromatographed on silica gel (gradient elution with 50% to 100% EtOAc/hexanes) to give (72%) of hydroxy ether **4** as a viscous light yellow oil. $[\alpha]^{20}_D$ + 2.4 (*c* 1.00, $CHCl_3$): ^{1}H NMR ($CDCl_3$, 300 MHz); δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 4.44 (s, 2H), 4.05 (m, 2H), 3.80 (s, 3H), 3.72-3.48 (m, 4H), 2.02-1.58 (m, 6H).



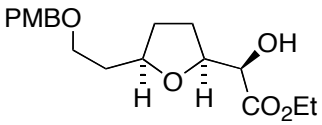
Unsaturated Ester 5

To a solution of olefin **2** (159 mg, 0.639 mmol) in CH_2Cl_2 (6 mL) was added ethyl acrylate (383 mg, 3.830mmol) and Hoveyda-Grubbs II catalyst (12 mg, 0.019 mmol). After 3-4 h at reflux the reaction was judged complete by TLC analysis at which point the mixture was concentrated under reduced pressure and subjected directly to column chromatography on silica gel (10:1 to 3:1 hexanes:ether) to give ester **5** (160 mg, 80%) as a colorless oil: $[\alpha]^{20}_D$ -14.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) _ 7.24 (d, *J* = 8.5 Hz, 2H), 7.06 (dt, *J* = 6.9, 1.2, 6.9 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.88 (d, 12.5 Hz, 1H), 4.47 (s, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.65 (m, 2H), 3.12 (d, *J* = 2.9 Hz, 1H), 2.37 (m, 2H), 1.64 (m, 4H) 1.31 (t, *J* = 7.1 Hz, 3H).



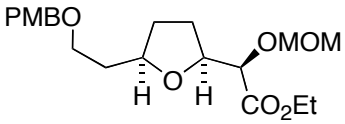
Mesylate 6

To a stirring solution of alcohol **5** (5.72 g, 17.7 mmol) in CH_2Cl_2 (175 mL) at 0 °C was sequentially added triethylamine (4.94 mL, 35.5 mmol) and MsCl (2.06 mL, 26.7 mmol). After stirring for 0.5 h, the reaction mixture was quenched with water, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 7.16 g (100%) of mesylate **6** as a light yellow oil which was used without further purification. $[\alpha]^{20}_D$ + 4.2 (*c* 1.00, $CHCl_3$): ^{1}H NMR ($CDCl_3$, 300 MHz); δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.95 (m, 1H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.86 (ddd, *J* = 1.5, 1.5, 15.0 Hz, 1H), 5.60 (m, 1H), 4.42 (d, *J* = 5.1 Hz, 2H), 4.19 (q, *J* = 6.9 Hz, 2H), 3.81 (s, 3H), 3.55 (m, 2H), 2.97 (s, 3H), 2.33 (m, 2H), 1.96 (m, 2H), 1.88 (m, 2H), 1.28 (t, *J* = 6.9 Hz, 3H).



Tetrahydrofuran 7

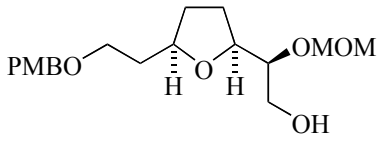
To a well stirred suspension of AD-mix-α (4.75 g, 1.4 g/mmol) in *t*-BuOH/H_2O (1:1, 30 mL) was added methanesulfonamide (323 mg, 3.39 mmol) with stirring until both phases were nearly clear (~0.25 h). The reaction mixture was cooled to 0 °C and mesylate **6** (1.36 g, 3.39 mmol) was added with a *t*-BuOH/H_2O rinse (4 mL). The mixture was allowed to warm to rt and stirred for 1d. The reaction was quenched by the addition of aqueous Na_2SO_3 (5.09 g) and stirred for 1h. The mixture was extracted with CH_2Cl_2 and Et_2O and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient elution with 20% to 50% EtOAc/hexanes) to give 987 mg (87%) of tetrahydrofuran **7** as a mostly separable mixture of 850 mg (75%) cis and 137 mg (12%) of mixed cis and trans fractions as light yellow oils. (Note: there is no difference in the R_f of the starting material and product.) $[\alpha]^{20}_D$ + 8.0 (*c* 1.00, $CHCl_3$):^{1}H NMR ($CDCl_3$, 300 MHz); δ 7.25 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.43 (d, *J* = 3.3 Hz, 2H), 4.21 (m, 3H), 4.05 (m, 2H), 3.80 (s, 3H), 3.54 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.10 – 1.50 (m, 6H), 1.29 (dd, *J* = 6.9, 6.9 Hz, 3H).



MOM Ether 8

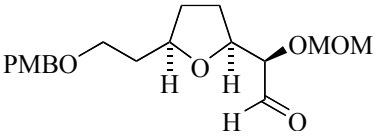
To a stirring solution of alcohol **7** (4.54 g, 13.4 mmol) in CH_2Cl_2 was sequentially added Hunig's base (16.3 mL, 94.0 mmol), MOMCl (6.06 mL, 80.4 mmol), and TBAI (2.27 g, 6.15 mmol). The reaction vessel was shielded from light by wrapping the round bottomed flask in aluminum foil, and the reaction mixture was

stirred overnight. The reaction was quenched by the addition of an aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 . The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography on silica gel (gradient elution with 25% to 50% EtOAc/hexanes) gave 5.20 g (100%) of MOM ether **8** as a light yellow oil. $[\alpha]^{20}_D$ + 19.5 (*c* 1.00, $CHCl_3$): ^{1}H NMR ($CDCl_3$, 300 MHz); δ 7.25 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.72 (s, 2H), 4.42 (d, *J* = 3.3 Hz, 2H), 4.21 (m, 3H), 4.06 (m, 1H), 4.02 (m, 1H), 3.80 (s, 3H), 3.54 (dd, *J* = 6.6, 6.6 Hz, 2H), 3.39 (s, 3H), 1.94 – 1.87 (m, 5H), 1.57 (m, 1H), 1.31 (dd, *J* = 6.9,6.9 Hz, 3H).



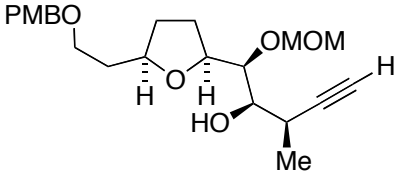
Alcohol 9

To a stirring suspension of $LiAlH_4$ (345 mg, 9.09 mmol) in THF (8 mL) at -78 ^{o}C was added a solution of ester **8** (580 mg, 1.52 mmol) in THF (7 mL) slowly over 0.25 h. The reaction mixture was warmed to rt and stirred for 1.5 h. The reaction was quenched at 0 ^{o}C by the sequential addition of water (0.340 mL), 10% NaOH (0.510 mL), and water (1.0 mL) with 0.25 h of stirring between each addition. The mixture was filtered though a plug of Celite to give 456 mg (88%) of alcohol **9** as a clear oil which was used without purification $[\alpha]^{20}_D$ -30.1 (*c* 1.00, $CHCl_3$); : ^{1}H NMR (300 MHz, $CDCl_3$) _ 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.74 (dd, *J* = 6.8, 8.2 hz, 2H), 4.42 (d, *J* = 2.3 Hz, 2H), 4.13 (m, 2H), 3.83 (s, 3H), 3.76 (m, 2H), 3.54 (m, 3H), 3.43 (s, 3H), 1.9 (m, 6H).



Aldehyde 10

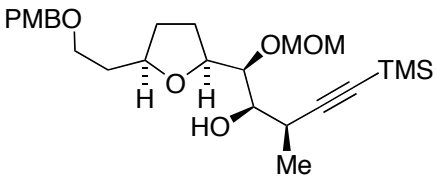
To a solution of alcohol **9** (456 mg, 1.34 mmol) in CH_2Cl_2 (13 mL) was added anhydrous $NaHCO_3$ (1.12 g, 13.4 mmol), and Dess-Martin periodinane reagent (830 mg, 2.01 mmol) successively. After 1 h TLC analysis indicated the reaction was complete and saturated aqueous $NaHCO_3$, and saturated aqueous $Na_2S_2O_3$ were added simultaneously and the mixture was extracted with ether. The ether extracts were separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an oil that was chromatographed on deactivated silica gel with 10:1 hexanes/Et_2O as eluant to afford aldehyde **10** (349 mg, 77%); $[\alpha]^{20}_D$ +4.4 (*c* 1.00, $CHCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$) _ 9.70 (d, *J* = 1.7 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.75 (d, *J* = 2.1 Hz, 2H), 4.43 (d, *J* = 2.3 Hz, 2H), 4.25 (m, 1H) 3.96 (m, 2H) 3.80 (s, 3H), 3.55 (t, *J* = 6.5 Hz, 2H), 3.41 (s, 3H), 2.04 (m, 6H).



Tetrahydrofuran Alcohol 12b

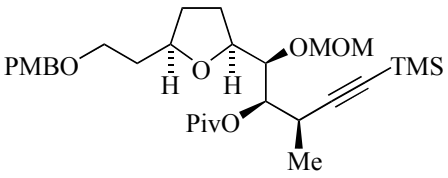
To a stirring solution of $InBr_3$ (43.0 mg, 0.124 mmol) in EtOAc (1.2 mL) at -78 ^{o}C was added aldehyde **10** (40.0 mg, 0.118 mmol) and the *(M)*-allenylstannane deived from mesylate **11b** (68.0 mg, 1.99 mmol) and the mixture was warmed to 0 ^{o}C. After stirring for 2 h, the mixture was quenched with water and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and chromatographed on silica gel (elution with 5% EtOAc/hexanes) to give 43.5 mg (94% including some tin byproduct) of alcohol **12b** as a 95:5 mixture of homopropargylic

alcohol adducts as a clear oil. $[\alpha]^{20}_{D}$ -25.8 (*c* 1.00, $CHCl_3$): ^{1}H NMR ($CDCl_3$, 300 MHz); δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.83 (d, *J* = 6.6 Hz, 1H), 4.76 (d, *J* = 6.6 Hz, 1H), 4.43 (s, 3H), 4.13 (m, 1H), 3.98 (m, 1H), 3.81 (s, 3H), 3.52 (m, 3H), 3.43 (s, 3H), 2.81 (m, 1H), 2.12 (d, *J* = 2.7 Hz, 1H), 1.97 – 1.55 (m, 6H), 1.28 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.2, 7.2 Hz, 3H).



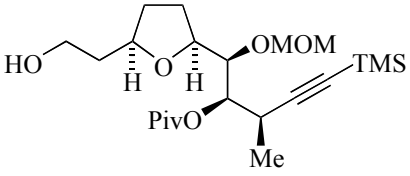
Tetrahydrofuran Alcohol 12c.

To a stirring solution of THF:HMPA (3:1, 1.5 mL) was added aldehyde **10** (100 mg, 0.296 mmol) followed by $Pd(OAc)_2$ (4.0 mg, 0.018 mmol) and PPh_3 (4.7 mg, 0.018 mmol). Upon complete dissolution of the PPh_3 the solution was cooled to 0 °C. InI beads (107 mg, 0.443 mg) were pulverized in a mortar and added to the solution followed by TMS mesylate **11c** (91.0 mg, 0.414 mmol). The solution was then stirred at 0 °C for 0.25 h before being warmed to rt. Upon completion of the reaction as judged by TLC analysis (~ 0.5 h) the reaction mixture was quenched with 10% HCl and diluted with Et_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with 10% EtOAc/hexanes) to give 113 mg (83%) of alcohol **12c** as a light yellow oil. $[\alpha]^{20}_{D}$ -27.0 (*c* 1.00, $CHCl_3$): ^{1}H NMR ($CDCl_3$, 500 MHz); δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.89 (d, *J* = 10.0 Hz, 1H), 4.75 (d, *J* = 10.0 Hz, 1H), 4.43 (s, 3H), 4.13 (m, 1H), 3.97 (m, 1H), 3.81 (s, 3H), 3.52 (m, 4H), 3.42 (s, 3H), 2.85 (m, 1H), 1.97 – 1.65 (m, 6H), 1.25 (d, *J* = 7.9 Hz, 3H), 0.15 (m, 9H).



Pivalic Ester 13

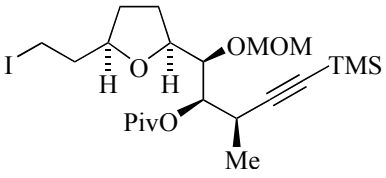
To a stirred solution of alcohol **12c** (0.150 g, 0.718 mmol) in pyridine (2 mL) at 25 ^{o}C was added pivalic chloride (0.114 mL, 0.933 mmol) and DMAP (cat.), with stirring at reflux. After 12 h TLC analysis indicated the reaction was complete and H_2O was added and the mixture was extracted with ether. The combined ether extracts were washed 3x with saturated aqueous $CuSO_4$ then with water and brine successively and then dried over $MgSO_4$. Concentration under reduced pressure gave pivalate **13** as an oil (0.210 g, 100%). This oil was taken on without further purification: $[\alpha]^{20}_{D}$ -24.5 (*c* 1.00, $CHCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$) _ 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.00 (t, *J* = 5.6 Hz, 1H), 4.87-4.71 (dd, *J* = 6.7, 13.0 Hz, 2H), 4.43 (s, 2H), 3.97 (m, 2H), 3.83 (s, 3H), 3.68 (m, 1H), 3.55 (t, *J* = 1 Hz, 2H), 3.43 (s, 3H), 3.05 (m, 1H), 1.99 (m, 2H), 1.86 (m, 4H), 1.26 (s, 9H), 1.24 (d, *J* = 2.0 Hz, 3H), 0.16 (s, 9H).



Alcohol 14

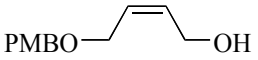
To a solution of crude pivalic ester **13** (0.089 g, 0.162 mmol) in CH_2Cl_2 (1.62 mL) and pH 7 potassium phosphate monobasic-sodium hydroxide buffer 0.05 M (0.09 mL) was added DDQ (0.055 g, 0.243 mmol) with stirring at rt. After 1.5 h TLC analysis indicated the reaction was complete and saturated aqueous $NaHCO_3$ was added and the mixture was extracted with ether. The combined ether extracts were washed with saturated aqueous $NaHCO_3$ and brine successively and then dried over $MgSO_4$. Concentration under reduced

pressure followed by silica gel chromatography (2:1 hexanes/Et_2O) gave alcohol **14** as a pale yellow oil (0.070 g, 90%): $[\alpha]^{20}_D$ -18.3 (*c* 1.00, $CHCl_3$): ^1H NMR (300 MHz, $CDCl_3$) _ 5.03 (t, *J* = 5.6 Hz, 1H), 4.86 (dd, *J* = 6.7, 13.0 Hz, 2H), 4.04 (q, *J* = 2.6 Hz, 2H), 3.82 (m, 2H), 3.68 (t, *J* = 5.9 Hz, 1H), 3.49 (s, 3H), 3.0, (m, 1H), 2.03 (m, 2H), 1.66 (m, 4H), 1.33 (s, 9H), 1.25 (d, *J* = 2.0 Hz, 3H), 0.29 (s, 9H).



Iodide 15

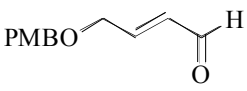
To a solution of the above alcohol **14** (60 mg, 0.154 mmol) in a 3:1 solution of ether:acetonitrile (1.16 mL: 0.385 mL) at 0 ^oC was added imidazole (33 mg, 0.485 mmol), PPh_3 (69 mg, 0.262 mmol), and iodine beads (66 mg, 0.262 mmol) successively. The reaction was then allowed to warm to room temperature and was monitored by TLC until complete ~1 h. Saturated $Na_2S_2O_3$ was then added and the mixture was extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give an oil that was chromatographed on silica gel with 2:1 hexanes/ether as eluant to afford iodide **15** (57 mg, 70%): $[\alpha]^{20}_D$ -32.6 (*c* 1.00, $CHCl_3$): ^1H NMR (300 MHz, $CDCl_3$) _ 5.04 (t, *J* = 5.6 Hz, 1H), 4.81 (dd, *J* = 6.7, 13.0 Hz, 2H), 4.02 (m, 1H), 3.94 (m, 1H), 3.76 (t, *J* = 5.6 Hz, 1H), 3.44 (s, 3H), 3.33 (m, 2H), 3.12 (m, 1H), 2.08 (m, 4H), 1.78 (m, 1H), 1.57 (m, 1H), 1.3 (s, 9H), 1.26 (d, *J* = 2.0 Hz, 3H), 0.23 (s, 9H).



4-(*p*-Methoxybenzyloxy)-2-buten-1-ol (17)

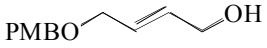
To a mixture of NaH (60% wt., 1.07 g, 44.4 mmol) in THF (90 mL) at 0 ^oC was added (*Z)*-2-butene-1,4-diol (3.87 g, 44.4 mmol). After the mixture was stirred for 1 h PMBCl

(6.60 g, 44.4 mmol) was added, and the solution was stirred at rt. After 2 h TLC analysis indicated the reaction was complete and aqueous 10% K_2CO_3 was added and the mixture was extracted with ether. The ether extracts were separated, dried over $MgSO_4$, filtered, and concentrated to give 9.35 g of crude oil **17** which was taken on without purification. ^{1}H NMR (300 MHz, $CDCl_3$) _ 7.32 (d, *J* = 1.77 Hz, 2H), 6.93 (d, *J* = 1.70 Hz, 2H), 5.81 (m, 2H), 4.49 (s, 2H), 4.19 (d, *J* = 5.6 Hz, 2H), 4.03 (d, *J* = 5.9 Hz, 2H), 3.85 (s, 3H).



4-(*p*-Methoxybenzyloxy)-2-butenal (18)

To a solution of (Z) allylic alcohol **17** (1.35 g, 6.46 mmol) in CH_2Cl_2 (20 mL) was added 4Å MS (2.5 g) and PCC (1.81 g, 8.40 mmol) at 0 ^{o}C and the mixture was stirred for 2 days at rt. After 3 days TLC analysis indicated the reaction was complete and the mixture was filtered through a pad of Celite and concentrated under reduced pressure to give a dark red oil **18** (2.34 g) that was taken on to the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$) _ 9.62 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 1.77 Hz, 2H), 6.93 (d, *J* = 1.70 Hz, 2H), 6.8 (m, 1H), 6.44 (dq, *J* = 2.0, 5.9 Hz, 1H) 4.55 (s, 2H), 4.28 (d, *J* = 2.0 Hz, 2H), 3.84 (s, 3H).



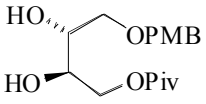
4-(*p*-Methoxybenzyloxy)-2-buten-1-ol (19)

To a stirred solution of aldehyde **18** (0.500 g, 2.39 mmol) in CH_2Cl_2 (23 mL) at -78 ^{o}C was added DIBAL-H (1.0 M in hexanes, 3.60 mL, 3.60 mmol). The solution was stirred for 30 min. then poured into a mixture of 50 mL of saturated Rochelle's salt solution and 50 mL of ether. Upon clarification, the organic layer was separated, dried over $MgSO_4$, filtered and concentrated to yield an oil **19** (0.734 g) that was taken on without

purification. ^{1}H NMR (300 MHz, $CDCl_3$) _ 7.32 (d, *J* = 1.77 Hz, 2H), 6.93 (d, *J* = 1.70 Hz, 2H), 5.91 (m, 2H), 4.49 (s, 2H), 4.20 (d, *J* = 4.7 Hz, 2H), 4.05 (d, *J* = 4.6 Hz, 2H), 3.84 (s, 3H).

(*E*)-4-(*p*-Methoxybenzyloxy)-2-butenyl Pivalate (20)

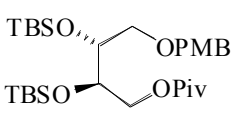
To a stirred solution of allylic alcohol **19** (0.150 g, 0.718 mmol) in pyridine (2 mL) at 25 ^{o}C was added pivalic anhydride (0.114 mL, 0.933 mmol) and DMAP (cat.), with stirring. After 0.5 h TLC analysis indicated the reaction was complete and H_2O was added and the mixture was extracted with ether. The combined ether extracts were washed 3x with saturated aqueous $CuSO_4$ then with water and brine successively and then dried over $MgSO_4$. Concentration under reduced pressure gave pivalate **20** as an oil (0.210 g, 100%). This oil was taken on without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) _ 7.32 (d, *J* = 1.77 Hz, 2H), 6.93 (d, *J* = 1.70 Hz, 2H), 5.89 (m, 2H), 4.61 (m, 2H), 4.97 (d, *J* = 1.6 Hz, 2H), 4.04 (m, 2H), 3.84 (d, *J* = 1.8 Hz, 3H), 1.25 (s, 9H).



(2*R*,3*R*)-1-Pivaloxy-4-(*p*-methoxybenzyloxy)-2,3-butanediol (21)

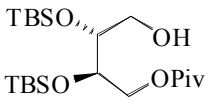
To a well stirred suspension of AD-mix-α (0.477 g, 1.4g/mmol) in *t*-BuOH/H_2O (1:1, 3.5 mL) was added methanesulfonamide (0.032 g, 0.341 mmol) with stirring until both phases were nearly clear (~15 min). The reaction mixture was cooled to 0 ^{o}C and olefin **20** (0.100 g, 0.341 mmol) was added with a *t*-BuOH/H_2O rinse (1 mL). The mixture was allowed to warm to rt and stirred overnight. After 18 h TLC analysis indicated the reaction was complete and saturated aqueous $Na_2S_2O_3$ was added and the mixture was stirred for 1h. The mixture was extracted with ether (3x) and the combined

ether extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel 2:1 Et_2O/hexanes to give diol **21** (0.066 g, 60%): $[\alpha]^{20}_D$ + 3.3 (*c* 1.00, $CHCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$) _ 7.30 (d, *J* = 7.7 Hz, 2H), 6.93 (d, *J* = 7.0 Hz, 2H), 4.52 (s, 2H), 4.20 (d, *J* = 4.84 Hz, 2H), 3.90 (m, 1H), 3.84 (s, 3H), 3.80 (m, 1H), 3.63 (m, 2H), 1.24 (s, 9H).



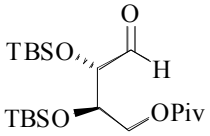
(2*R*,3*R*)-2,3-(bis-*tert*-Butyldimethylsilyloxy)-4-(*p*-methoxybenzyloxy)butyl Pivalate (22)

To a solution of crude diol **21** (0.053 g, 0.162 mmol) in CH_2Cl_2 (1.0 mL) were added triethylamine (0.225 mL, 1.62 mmol) and *t*-butyldimethylsilyl trifluoromethanesulfonate (0.171 g, 0.648 mmol), and the mixture was stirred at 0 ^oC. After 0.5 h TLC analysis indicated the reaction was complete and ether and water were added. The ether extracts were separated and washed with saturated aqueous $NaHCO_3$ and brine successively and then dried over $MgSO_4$. Concentration under reduced pressure gave the bis-silyl ether **22** as an oil (0.150 g). This oil was taken on without purification to give fully protected **22** in 100% yield. $[\alpha]^{20}_D$ + 25.1 (*c* 1.00, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) _ 7.32 (d, *J* = 1.77 Hz, 2H), 6.93 (d, *J* = 1.70 Hz, 2H), 4.48 (s, 2H), 4.27 (dd, *J* = 3.6, 2.6 Hz, 1H), 4.01 (dd, *J* = 5.7, 5.5 Hz, 1H), 3.97 (m, 2H), 3.84 (s, 3H), 3.67 (dd, *J* = 1.1, 7.7 Hz, 1H), 3.40 (dd, *J* = 6.8, 2.8, 1H), 1.23 (s, 9H), 0.90 (s, 18H), 0.12 (s, 12H).



(2*R*, 3*R*)-4-Pivaloxy-2,3-(bis-*tert*-butyldimethylsilyloxy)butan-1-ol (23)

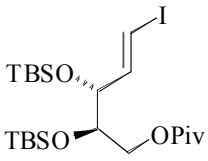
To a solution of crude bis-protected silyl ether **22** (0.089 g, 0.162 mmol) in CH_2Cl_2 (1.62 mL) and pH 7 potassium phosphate monobasic-sodium hydroxide buffer 0.05 M (0.09 mL) was added DDQ (0.055 g, 0.243 mmol) with stirring at rt. After 1.5 h TLC analysis indicated the reaction was complete and saturated aqueous $NaHCO_3$ was added and the mixture was extracted with ether. The combined ether extracts were washed with saturated aqueous $NaHCO_3$ and brine successively and then dried over $MgSO_4$. Concentration under reduced pressure followed by silica gel chromatography (2:1 hexanes/Et_2O) gave alcohol as a pale yellow oil (0.070 g, 99% over two steps) which was contaminated with inseparable *p*-methoxybenzaldehyde side products: ^{1}H NMR (300 MHz, $CDCl_3$) _ 4.35 (dd, *J* = 2.8 Hz, 1H), 4.03 (m, 1H), 3.89 (m, 1H), 3.75 (m, 2H), 3.61 (m, 1H), 1.20 (s, 9H), 0.91 (s, 18H), 0.10 (s, 12H).



(2*R*, 3*R*)-4-Pivaloxy-2,3-(bis-*tert*-butyldimethylsilyloxy)butanal (24)

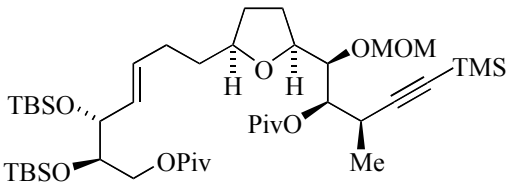
To a solution of alcohol **23** (100 mg, 0.246 mmol) in CH_2Cl_2 (3 mL) was added anhydrous $NaHCO_3$ (203 mg, 2.41 mmol), and Dess-Martin periodinane reagent (203 mg, 0.492 mmol) successively. After 1 h TLC analysis indicated the reaction was complete and saturated aqueous $NaHCO_3$, and saturated aqueous $Na_2S_2O_3$ were added simultaneously and the mixture was extracted with ether. The ether extracts were separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an oil that was chromatographed on deactivated silica gel with 10:1 hexanes/Et_2O as eluant to afford aldehyde **24** $[\alpha]^{20}_D$ +31.2 (*c* 1.00, $CHCl_3$): ^{1}H

NMR (300 MHz, $CDCl_3$) _ 9.74 (s, 1H), 4.20 (m, 1H), 4.05 (m, 3H), 1.17 (s, 9H), 0.91 (s, 9H), 0.87 (s, 9H), 0.09 (s, 12H).



(*E*)-(3*R*, 4*R*)-5-Pivaloxy-3,4-(bis-*tert*-butyldimethylsilyloxy)-1-iodo-1-pentene (25)

To a solution of $CrCl_3$•$(THF)_3$ (0.030 g, 0.074 mmol), zinc dust (0.144 g, 2.21 mmol), and thoroughly dried NaI (0.055 g, 0.368 mmol) in dioxane (3.68 mL) was added freshly distilled TMSCl (0.281 mL, 2.21 mmol) at 25 ^oC. After the mixture was stirred at 25 ^oC for 40 min., a solution of aldehyde **25** (0.161 g, 0.368 mmol) and iodoform (0.289 g, 0.736 mmol) in dioxane (3.68 mL) was added at 25 ^oC over a period of 4 h. After 8 h TLC analysis indicated the reaction was complete and the reaction mixture was poured into water and extracted with hexane. The hexane extracts were washed with saturated aqueous $Na_2S_2O_3$ and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on deactivated silica gel (hexane) gave vinyl iodide **25** (0.155 g, 73%) as a colorless oil: $[\alpha]^{20}_D$ + 15.8 (*c* 1.00, $CHCl_3$): ^1H NMR (300 MHz, $CDCl_3$) _ 6.72 (dd, *J* = 4.35, 10.0 Hz, 1H), 6.33 (dd, *J* = 1.7, 12.7 Hz, 1H), 4.23 (dd, *J* = 1.9, 8.6 Hz, 1H), 4.24 (m, 1H), 3.9 (m, 2H), 1.17 (s, 9H), 0.91 (s, 9H), 0.87 (s, 9H), 0.09 (s, 12H).



Tetrahydrofuran 27

To a solution of alkyl iodide **25** (0.057 g, 0.106 mmol) in Et_2O (1.43 mL) at -78 ^oC was added MeO-9-BBN (1.0 M solution in THF, 0.249 mL, 0.249 mmol) and *t*-BuLi (0.189 mL, 0.284 mmol) successively with stirring for 5 min. After 5 min THF (1.42 mL) was added and the mixture was warmed to 25 ^oC with stirring for an additional 1 h. After 1 h K_3PO_4 (3M solution 0.230 mL, 0.70 mmol), vinyl iodide **25** (0.041 g, 0.071 mmol), and Pd(dppf)Cl_2 (0.005 g, 0.007 mmol) were added successively with stirring. After 10 h TLC analysis indicated the reaction was complete and water was added and the mixture was extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give an oil that was chromatographed on deactivated silica gel with 1:1 hexanes/Et_2O as eluant to afford Suzuki adduct **27** (0.050 g, 82%): $[\alpha]^{20}_D$ -18.6 (*c* 1.00, $CHCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$) _ 5.62 (m, 2H), 5.00 (m, 1H), 4.91 (d, *J* = 6.7 Hz, 1H), 4.76 (d, *J* = 6.2 Hz, 1H), 4.25 (m, 1H), 4.14 (m, 1H), 4.00 (m, 1H), 3.77 (m, 1H), 3.44 (s, 3H), 3.07 (m, 1H),), 2.20 (m, 2H), 1.85 (m, 2H), 1.80 (m, 2H), 1.62 (m, 2H), 1.27 (d, *J* = 1.9 Hz, 6H), 0.98 (d, *J* = 8.8 Hz, 18H), 0.25 (s, 6H), 0.18 (s, 6H), 0.08 (dt, *J* = 1.5, 5.9 Hz, 9H).