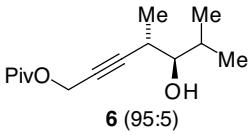
Progress Toward the Total Synthesis of Bafilomycin A_1: Stereoselective Synthesis of the C15-C25 Subunit by Additions of Allenylzinc Reagents to Aldehydes

James A. Marshall and Nicholas D. Adams

Department of Chemistry, McCormick Road, P.O. Box 400319, University of Virginia, Charlottesville, VA 22904

Supporting Information:

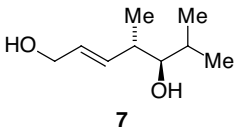
General. Chemical shifts are reported in ppm referenced to $CHCl_3$ at 7.26, C_6D_6 at 7.15, and DMSO-d_6 at 2.49 for ^1H, and $CDCl_3$ at 77.00, C_6D_6 at 128.00, and DMSO-d_6 at 39.7 ppm for ^{13}C. THF, ether and dichloromethane were dried by passing through activated alumina under argon gas. All reactions were performed under an atmosphere of argon or nitogen in flame dried glassware. Palladium (II) acetate was purchased from Aldrich Chemical Company in 99.9+% purity and used as is. All reagents were used as purchased without further purification unless otherwise stated. Combustion analyses were performed by Atlantic Microlabs, Inc. Norcross, Ga.



6 (95:5)

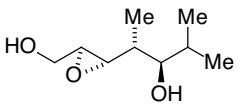
(3*R*,4*S*)-2,4-Dimethyl-7-pivaloxy-5-heptyn-3-ol (6). General procedure. To degassed THF (130 mL) was added $Pd(OAc)_2$ (197 mg, 0.88 mmol). Upon complete dissolution of the $Pd(OAc)_2$, the resultant orange solution was cooled to -78 °C and PPh_3 (231 mg, 0.88 mmol) was added. To the resultant solution was added mesylate **4** (6.0 g, 22.9 mmol), freshly distilled isobutyraldehyde (1.27 g, 17.6 mmol) followed by dropwise addition of diethylzinc (53.0 mL, 1 M in hexane, 53.0 mmol). The mixture was stirred for 5 min and warmed to -20 °C . The dark solution was stirred for 17 h and then quenched by carefully pouring into 100 mL of a stirred mixture of 9:1 v/v H_2O/conc. HCl and ether (100 mL) ***(Caution, vigorous evolution of ethane.)***. The mixture was stirred vigorously for 30

min and the layers were separated. The ether layer was washed with brine and the combined aqueous layers were extracted with ether. The extracts were dried over $MgSO_4$ and decolorizing Norit (*ca*. 2 g). After filtration through a pad of Celite over silica gel, the solution was concentrated under reduced pressure and the residue was chromatographed on silica gel (9:1 hexanes/EtOAc). To remove residual palladium salts, the resultant orange oil was further purified by Kügelrohr distillation (95 °C, 0.1 mm) to give 3.22 g (76%) of alcohol **6** and its *syn* diastereomer as a 95:5 inseparable mixture: R_f 0.45 (4:1 hexanes/EtOAc); $[\alpha]_D^{20}$ +4.8 (*c* 1.28, $CHCl_3$). IR (film) 3517 (broad), 2239, 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.59 (d, *J* = 1.8 Hz, 2H), 2.99 (dd, *J* = 7.2, 3.9 Hz, 1H), 2.67 (m, 1H), 1.71 (m, 1H), ~1.18 (d, *J* = ~7.0 Hz, 3H), 1.15 (s, 9H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.73, 87.40, 79.42, 77.12, 52.51, 38.58, 32.07, 30.40, 26.92, 19.35, 17.84. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H 10.07. Found: C, 70.00; H, 10.04.



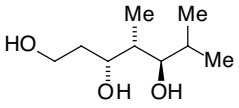
7

(2*E*,4*S*,5*R*)-4,6-Dimethyl-2-heptene-1,5-diol (7). To a cold (0 °C) suspension of $LiAlH_4$ (1.32 g, 32.9 mmol) in THF (80 mL) was added a solution of alkyne **6** (2.26 g, 9.40 mmol) in THF (10 mL) dropwise. After 10 min the suspension was allowed to reach rt, stirred for 10 min and heated to 55 °C. After 2 h, the mixture was cooled to 0 °C and quenched carefully by successive addition of H_2O (1.3 mL), 10% NaOH (1.3 mL) and H_2O (3.9 mL). After warming to rt, the suspension was stirred vigorously for 15 min, filtered through a pad of Celite with ether and concentrated under reduced pressure. The residue was chromatographed on silica gel (1:1 to 1:3 hexanes/EtOAc) to give 1.30 g (87%) of allylic alcohol **7** as a colorless oil: R_f 0.33 (3:1 EtOAc/hexanes); $[\alpha]_D^{20}$ -14.3 (*c* 0.90, $CHCl_3$). IR (film) 3374 (broad) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75-5.60 (m, 2H), 4.09 (d, *J* = 4.5, 2H), 3.08 (apparent t, *J* = 6.0 Hz, 1H), 2.34 (m, 1H), 2.31 (bs, 1H), 1.74 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.13, 130.27, 79.97, 63.21, 39.53, 30.34, 19.78, 17.30, 16.59.



8 (97:3)

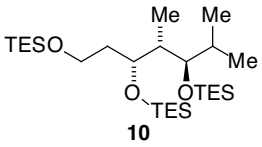
(2*S*,3*S*,4*S*,5*R*)-4,6-Dimethyl-2,3-epoxyheptane-1,5-diol (8). To a suspension of powdered 4 Å molecular sieves (*ca*. 0.50 g) in CH_2Cl_2 (90 mL) was added L-(+)-diisopropyl tartrate (2.4 mL, 11.2 mmol). The mixture was cooled to -40 °C and Ti(O*i*-Pr)$_4$ (2.7 mL, 9.23 mmol) was added. After 10 min *tert*-butyl hydroperoxide (2.9 mL, 5-6 M in decane, *ca*. 16.1 mmol) was added dropwise. The mixture was stirred for 30 min and then allylic alcohol **7** (1.27 g, 8.03 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 5 min. After 23 h the reaction mixture was quenched with a minimal amount of H_2O (3 mL), allowed to warm to rt and diluted with EtOAc. The resultant heterogeneous mixture was strirred vigorously for 15 min and filtered through a pad of Celite. Concentration under reduced pressure followed by chromatography on silica gel (1:1 hexanes/EtOAc) provided 1.20 g (86%) of epoxide **8** as a colorless oil: R_f 0.23 (3:1 EtOAc/hexanes); $[\alpha]_D^{20}$ -20.8 (*c* 0.60, $CHCl_3$). IR (film) 3400 (broad) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (d, *J* = 9.3, 1H), 3.70 (d, *J* = 12.6 Hz, 1H), 3.28 (dd, *J* = 7.2, 4.5 Hz, 1H), 3.11 (m, 1H), 2.97 (dd, *J* = 7.2, 2.7 Hz, 1H), 2.30 (bs, 1H), 2.20 (bs, 1H), 1.84 (m, 1H), 1.64 (m, 1H), 1.00 (d, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.56, 61.94, 59.40, 58.83, 38.30, 29.78, 19.98, 15.23, 13.82. Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H 10.41. Found: C, 61.77; H, 10.29.



9

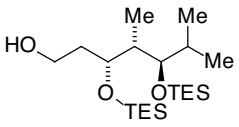
(3*R*,4*S*,5*R*)-4,6-Dimethylheptane-1,3,5-triol (9). To a cold (0 °C) solution of epoxide **8** (1.07 g, 6.14 mmol) in THF (60 mL) was added Red-Al (9.5 mL, 65 wt % in toluene, 30.7 mmol) dropwise. After 19 h at 0 °C, the reaction mixture was quenched carefully by dropwise addition of saturated aqueous sodium potassium tartrate (Rochelle's salt) ***(Caution, vigorous evolution of H_2 may result)***. EtOAc was added and the mixture was allowed to warm to rt. The organic layer was washed with brine and the combined aqueous layers were extracted several times with EtOAc. The combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (1:1 to 1:3 hexanes/EtOAc) to provide 1.0 g (93%) of triol **9** as a colorless oil: R_f 0.25 (9:1 CH_2Cl_2/MeOH); $[\alpha]_D^{20}$ +11.0 (*c* 1.25, $CHCl_3$). IR (film) 3352 (broad)

cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (dt, *J* = 10.8, 2.4 Hz, 1H), 3.88 (m, 2H), 3.40 (dd, *J* = 6.6, 5.4 Hz, 1H), 2.93 (bs, 1H), 1.86 (m, 3H), 1.53 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.72, 74.09, 62.27, 39.08, 34.46, 30.32, 19.81, 15.83, 12.13.



10

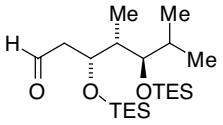
(3*R*,4*S*,5*R*)-4,6-Dimethyl-1,3,5-tris(triethylsilyloxy)heptane (10). To a cold (0 °C) solution of triol **9** (0.95 g, 5.39 mmol) in CH_2Cl_2 (55 mL) was added 2,6-lutidine (5.6 mL, 48.5 mmol) followed by dropwise addition of TESOTf (3.7 mL, 16.4 mmol). After 30 min, the mixture was quenched with saturated aqueous $NaHCO_3$, diluted with ether and allowed to warm to rt. The ether layer was washed with brine and the combined aqueous layers were extracted with ether. The extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (19:1 hexanes/EtOAc) to give 2.77 g (99%) of silyl ether **10** as a colorless oil: R_f 0.74 (19:1 hexanes/EtOAc); $[\alpha]_D^{20}$ +1.8 (*c* 0.74, $CHCl_3$). IR (film) 2952, 1458, 1238 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (m, 1H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.52 (dd, *J* = 6.6, 2.4 Hz, 1H), 1.85-1.71 (m, 3H), 1.53 (m, 1H), 0.99-0.93 (m, 27H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 7.5 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.66-0.57 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.19, 70.82, 59.81, 43.59, 39.01, 30.32, 21.52, 16.19, 10.46, 7.15, 6.79, 6.41, 5.81, 5.64, 4.40. Anal. Calcd for $C_{27}H_{62}O_3Si_3$: C, 62.48; H 12.04. Found: C, 62.75; H, 11.89.



11

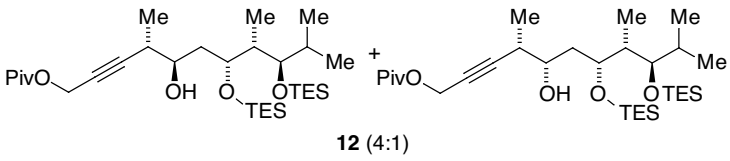
(3*R*,4*S*,5*R*)-4,6-Dimethyl-3,5-bis(triethylsilyloxy)heptan-1-ol (11). Silyl ether **10** (3.1 g, 5.96 mmol) was dissolved in a solution of H_2O, AcOH and THF (1:3:10, 100 mL). After 5 h, the solution was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ (200 mL). After 15 min the mixture was allowed to warm to rt, diluted with ether and stirred vigorously for 2 h. The organic layer was washed with brine and the combined aqueous layers were extracted with ether. The extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Chromatography on silica gel (19:1 to

4:1 hexanes/EtOAc) provided 0.44 g (14%) of the starting silyl ether **6** and 1.99 g (82%) of alcohol **11**: R_f 0.31 (9:1 hexanes/EtOAc); $[\alpha]_D^{20}$ +2.0 (*c* 0.70, $CHCl_3$). IR (film) 3344 (broad) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95 (m, 1H), 3.79 (m, 1H), 3.67 (m, 1H), 3.48 (m, 1H), 1.87 (m, 1H), 1.80-1.67 (m, 3H), 0.96 (t, *J* = 7.5 Hz, 18H), 0.90 (d, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.67-0.56 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.31, 72.38, 60.09, 42.85, 37.57, 30.54, 21.32, 16.63, 11.65, 7.09, 7.00, 6.56, 5.77, 5.54, 5.50. Anal. Calcd for $C_{21}H_{48}O_3Si_2$: C, 62.31; H 11.95. Found: C, 62.55; H, 12.06.



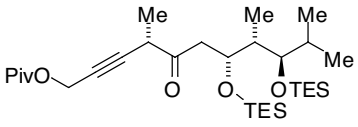
5

(3*R*,4*S*,5*R*)-4,6-Dimethyl-3,5-bis(triethylsilyloxy)heptanal (5). To a cold (-78 °C) solution of oxalyl chloride (0.62 mL, 7.10 mmol) in CH_2Cl_2 (25 mL) was added a solution of dimethyl sulfoxide (0.77 mL, 10.7 mmol) in CH_2Cl_2 dropwise. After 15 min, a solution of alcohol **11** (1.44 g, 3.55 mmol) in CH_2Cl_2 was added dropwise. The resultant solution was stirred for 10 min then triethylamine (2.5 mL, 17.8 mmol) was added. The reaction was maintained at -78 °C for 3 h, quenched with H_2O and allowed to warm to rt. The mixture was diluted with ether and the organic layer was washed with brine. The combined aqueous layers were extracted with ether and the extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was taken up in hexanes and filtered through a pad of Celite. Concentration of the filtrate under reduced pressure provided 1.42 g (99%) of aldehyde **5** as a yellow oil which was used without further purification. Pure aldehyde could be obtained as a colorless oil by silica gel chromatography (19:1 hexanes/EtOAc): R_f 0.52 (9:1 hexanes/EtOAc); $[\alpha]_D^{20}$ +2.2 (*c* 0.67, $CHCl_3$). IR (film) 1727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (t, *J* = 2.7 Hz, 1H), 4.29 (apparent q, *J* = 5.7 Hz, 1H), 3.47 (dd, *J* = 6.0, 3.9 Hz, 1H), 2.64 (dd, *J* = 5.7, 2.7 Hz, 2H), 1.78 (m, 1H), 1.69 (m, 1H), 0.99-0.90 (m, 24H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.66-0.57 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.24, 79.12, 69.44, 50.51, 43.90, 31.25, 20.81, 17.04, 12.78, 7.07, 6.92, 6.55, 5.77, 5.50, 5.38. Anal. Calcd for $C_{21}H_{46}O_3Si_2$: C, 62.62; H 11.51. Found: C, 62.79; H, 11.44.



12 (4:1)

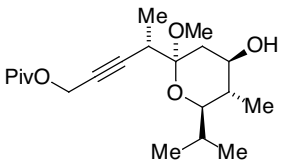
Alcohol 12. The general procedure described for alcohol **6** was employed with $Pd(OAc)_2$ (28 mg, 0.12 mmol), PPh_3 (33 mg, 0.12 mmol), mesylate **4** (1.30 g, 4.96 mmol), aldehyde **5** (1.0 g, 17.6 mmol) and diethylzinc (7.4 mL, 1 M in hexane, 7.4 mmol) in THF (25 mL) at -20 °C for 16 h. Purification by silica gel chromatogrphy (19:1 hexanes/EtOAc) provided 0.99 g (70%) of alcohol **12** as a 4:1 inseparable mixture: R_f 0.36 (9:1 hexanes/EtOAc); $[\alpha]_D^{20}$ -7.1 (*c* 1.20, $CHCl_3$). IR (film) 3513 (broad), 2240, 1737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.66 (m, 2H), 4.14 (m, 1H), 3.97 (m, 1H), 3.86 (m, 1H), 3.55 (dd, *J* = 7.5, 2.4 Hz, 1H), 3.48 (dd, *J* = 5.4, 3.3 Hz, 1H), 3.37 (d, *J* = 3.0 Hz, 1H), 2.57 (m, 1H), 1.92-1.60 (m, 4H), 1.21 (s, 9H), 1.01-0.80 (m, 30H), 0.69-0.58 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.75, 88.00, 78.56, 77.95, 76.56, 73.25, 72.41, 71.87, 71.03, 52.67, 43.10, 42.56, 39.46, 38.64, 38.37, 32.99, 30.61, 30.46, 27.02, 21.58, 20.98, 17.18, 16.20, 16.09, 15.96, 12.52, 10.39, 7.15, 7.07, 6.92, 5.80, 5.68, 5.45, 5.22. Anal. Calcd for $C_{31}H_{62}O_5Si_2$: C, 65.21; H 10.94. Found: C, 65.31; H, 10.81.



13

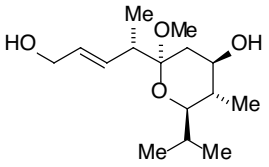
Ketone 13. To solution of alcohol **12** (0.91 g, 1.59 mmol) in CH_2Cl_2 (32 mL) was added solid $NaHCO_3$ (1.34 g, 15.9 mmol) and the Dess Martin periodinane reagent (0.87 g, 2.07 mmol). The suspension was stirred for 1.5 h and then quenched by simultaneous addition of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The mixture was diluted with ether and stirred vigorously for 30 min. The organic layer was washed with brine and the aqueous layer was extracted with ether. The extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 0.905 g (100%) of the ketone **13** which was used without further purification in the subsequent reaction. Pure ketone could be obtained as a colorless oil by silica gel chromatography (19:1 hexanes/EtOAc): R_f 0.59 (9:1 hexanes/EtOAc); $[\alpha]_D^{20}$ +30.9 (*c* 2.32, $CHCl_3$). IR (film) 1738, 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.67 (d, *J* = 2.1 Hz, 2H), 4.35 (m, 1H), 3.46 (dd, *J* = 6.0, 3.3 Hz, 1H), 3.30 (qt, *J* = 6.9, 2.1 Hz, 1H), 2.92 (d, *J* = 6.3 Hz, 2H), 1.81 (m, 1H), 1.55 (m,

1H), 1.29 (d, *J* = 6.9 Hz, 3H), 1.21 (s, 9H), 0.99-0.89 (m, 21H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.67-0.54 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.78, 177.70, 84.79, 79.15, 78.05, 69.43, 52.40, 47.20, 43.58, 39.61, 38.69, 31.12, 27.02, 20.89, 16.81, 15.82, 11.84, 7.11, 7.02, 5.46. Anal. Calcd for $C_{31}H_{60}O_5Si_2$: C, 65.44; H 10.63. Found: C, 65.70; H, 10.68.



3

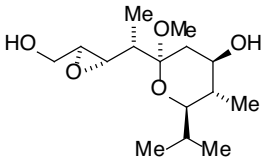
Pyranoside 3. To a solution of ketone **13** (0.905 g, 1.59 mmol) in MeOH (17 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (0.40 g, 1.59 mmol). After 1 h, the MeOH was removed under reduced pressure and the residue was taken up in ether and washed with brine. The aqueous layer was extracted with ether and the combined extracts were dried over $MgSO_4$. Filtration and concentration under reduced pressure followed by silica gel chromatography (9:1 to 4:1 hexanes/EtOAc) provided 437 mg (84%, 2 steps) of pyranoside **3** as a colorless oil: R_f 0.59 (9:1 hexanes/EtOAc); $[\alpha]_D^{20}$ +33.8 (*c* 0.80, $CHCl_3$). IR (film) 3429 (broad), 1736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (d, *J* = 2.1 Hz, 2H), 3.72 (td, *J* = 21.0, 4.8 Hz, 1H), 3.18 (s, 3H), 3.11 (dd, *J* = 10.2, 1.8 Hz, 1H), 2.98 (qt, *J* = 7.2, 2.1, 1H), 2.17 (dd, *J* = 12.6, 4.8, 1H), 1.92 (m, 1H), 1.55 (bs, 1H), 1.44 (dd, *J* = 12.3, 11.1 Hz, 1H), 1.33 (m, 1H), 1.20 (s, 9H), 1.19 (d, *J* ≈ 7 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.78, 100.94, 89.96, 77.60, 75.79, 70.03, 52.70, 46.91, 40.29, 38.68, 37.39, 31.58, 28.14, 27.04, 20.58, 16.15, 14.05, 12.07. Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H 9.67. Found: C, 67.98; H, 9.78.



14

Alcohol 14. To a cold (0 °C) solution of alkyne **3** (0.52 g, 1.47 mmol) in THF (15 mL) was added Red-Al (4.6 mL, 65 wt % in toluene, 14.7 mmol) dropwise. After 15 min the solution was allowed to warm to rt. After 18 h, the reaction mixture was cooled to 0 °C and quenched carefully by dropwise addition of saturated aqueous sodium potassium tartrate (Rochelle's salt) ***(Caution, vigorous evolution of H_2.)***. EtOAc was added and the mixture was allowed to warm to rt. The organic layer was washed with brine and the combined aqueous layers were extracted several times with EtOAc.

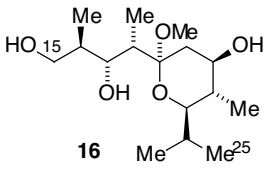
The combined extracts were dried over $MgSO_4$, filtered and concentrated first on a rotary evaporator and then under high vacuum (0.005 mm) to remove the ethylene glycol monomethyl ether, a contaminant which was present as a result of hydrolysis of the Red-Al, to provide 0.40 g (100%) of the allylic alcohol **14** which was used immediately in the subsequent reaction without further purification: R_f 0.22 (3:1 EtOAc/hexanes); $[\alpha]_D^{20}$ +29.6 (*c* 0.70, C_6H_6). IR (film) 3375 (broad) cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.77 (dd, *J* = 15.6, 6.9 Hz, 1H), 5.63 (dt, *J* = 15.6, 5.1 Hz, 1H), 4.09 (bs, 2H), 3.73 (m, 1H), 3.24 (m, 1H), 3.16 (m, 1H), 3.10 (dd, *J* = 10.8, 1.8 Hz, 1H), 3.03 (s, 3H), 2.67 (m, 1H), 2.03 (dd, *J* = 12.9, 4.8, 1H), 1.80 (m, 1H), 1.48 (dd, *J* = 12.6, 11.1, 1H), 1.40 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H) 1.05 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.3 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 131.71, 130.86, 102.59, 77.91, 70.11, 63.40, 46.48, 40.74, 40.00, 37.47, 28.61, 20.91, 14.94, 14.38, 12.24.



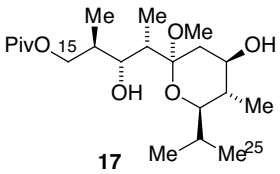
15 (>97:3)

Epoxide 15. To a suspension of powdered 4 Å molecular sieves (*ca*. 300 mg) in CH_2Cl_2 (25 mL) was added L-(+)-diisopropyl tartrate (0.44 mL, 2.06 mmol). The mixture was cooled to -20 °C and Ti(O*i*-Pr)$_4$ (0.50 mL, 1.69 mmol) was added. After 10 min, *tert*-butyl hydroperoxide (0.53 mL, 5-6 M in decane, *ca*. 2.9 mmol) was added dropwise. The mixture was stirred for 30 min and allylic alcohol **14** (0.40 g, 1.47 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 5 min. After 20 h, the reaction mixture was quenched with a minimal amount of H_2O (2 mL), allowed to warm to rt and diluted with EtOAc. The resultant heterogeneous mixture was strirred vigorously for 15 min and filtered through a pad of Celite. Concentration under reduced pressure followed by chromatography on silica gel (1:1 to 1:3 hexanes/EtOAc) provided 340 mg (80%, 2 steps) of epoxide **15** as a colorless syrup: R_f 0.16 (3:1 EtOAc/hexanes); $[\alpha]_D^{20}$ +31.1 (*c* 0.95, CH_2Cl_2). IR (film) 3392 (broad), 1463, 1378 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 3.71 (m, 2H), 3.50 (m, 1H), 3.09 (m, 2H), 2.96 (s, 3H), 2.82 (m, 1H), 2.30 (bs, 1H), 2.16 (dd, *J* = 12.9, 4.8 Hz, 1H), 1.99 (m, 1H), 1.91 (bs, 1H), 1.81 (m, 1H), 1.52 (dd, *J* = 12.6, 11.1 Hz, 1H), 1.37 (m, 1H), 1.05 (d, *J* = 7.5 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75

MHz, C_6D_6) δ 102.31, 77.78, 69.98, 61.86, 57.14, 55.89, 46.87, 40.51, 38.71, 38.40, 28.56, 20.80, 14.33, 12.32, 10.56. Anal. Calcd for $C_{15}H_{28}O_5$: C, 62.47; H 9.79. Found: C, 62.05; H, 9.89.

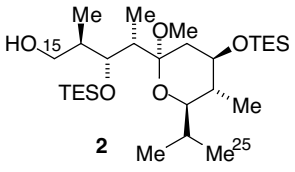


Triol 16. To a cold (-78 °C) suspension of CuCN (1.99 g, 22.2 mmol) in CH_2Cl_2 (12 mL) was added MeLi (31.7 mL, 1.4 M in ether, 44.4 mmol) dropwise. After 5 min, the mixture was allowed to warm to 0 °C, stirred for 30 min and then a solution of epoxy alcohol **15** (320 mg, 1.11 mmol) in CH_2Cl_2 (10 mL) was added. The resultant cloudy mixture was stirred for 10 min and allowed to warm to rt. After 19 h, the reaction mixture was carefully poured into a precooled (0 °C) solution of 9:1 saturated aqueous NH_4Cl/concentrated NH_4OH ***(Caution, vigorous evolution of gaseous methane)*** and diluted with ether. The mixture was stirred at rt until the organic layer cleared and the aqueous layer became bright blue in color. The organic layer was washed with brine and the combined aqueous layers were extracted several times with EtOAc. The extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 303 mg (90%) of triol **16** as a white solid. This material was used without further purification in the subsequent reaction. Pure triol **16** could be obtained as colorless crystals by recrystallization from EtOAc: mp 129-130 °C; R_f 0.19 (EtOAc); $[\alpha]_D^{20}$ +43.1 (*c* 0.55, EtOAc). IR (film) 3372 (broad) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.41 (m, 2H), 4.26 (d, *J* = 6.3 Hz, 1H), 3.53 (m, 1H), 3.42 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.29 (m, 2H), 2.96 (s, 3H), 2.94 (m, 1H), 2.02 (dd, *J* = 13.5, 4.5 Hz, 1H), 1.87 (m, 2H), 1.49 (m, 1H), 1.27 (dd, *J* = 13.5, 11.4 Hz, 1H), 1.11 (m, 1H), 0.92 (d, *J* = 7.2 Hz, 3H), 0.84-0.77 (m, 12H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 102.60, 76.60, 70.27, 68.55, 64.53, 45.67, 40.05, 39.78, 39.49, 38.65, 37.82, 27.84, 20.60, 14.18, 12.28, 7.65.



Pivalic Ester 17. To a cold (0 °C) solution of 150 mg (0.493 mmol) of triol **16** (Gentle warming was required to dissolve the triol.) was added triethylamine (206 μL, 1.48 mmol) and 2,2-dimethylpropionyl chloride (79

μL, 0.64 mmol) followed by 4-*N*,*N*-dimethylaminopyridine (3 mg, 0.03 mmol). After 2 h, an additional portion of acid chloride (18 μL, 0.148 mmol) was added and stirring was continued for 30 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with ether. The ether layer was washed with brine and the combined aqueous layers were extracted with ether. The extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (2.3:1 to 1:1 hexanes/EtOAc) to provide 167 mg (87%) of pivalic ester **17** as a white foam: R_f 0.74 (EtOAc); $[\alpha]_D^{20}$ +50.2 (*c* 0.55, EtOAc). IR (film) 3413 (broad), 1728 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 4.37 (dd, *J* = 10.8, 5.7 Hz, 1H), 4.25 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.81-3.67 (m, 2H), 3.13 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.01 (s, 3H), 2.42 (dd, *J* = 13.2, 4.5 Hz, 1H), 2.11 (apparent q, *J* = 6.9 Hz, 1H), 1.85-1.79 (m, 2H), 1.72 (dd, *J* = 12.9, 11.4 Hz, 1H), 1.43 (m, 1H), 1.18 (s, 9H), 1.13 (d, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 178.65, 103.48, 77.83, 70.64, 70.34, 67.32, 46.48, 40.64, 39.26, 38.57, 38.01, 28.64, 27.35, 20.91, 14.43, 14.26, 12.42, 7.54. Anal. Calcd for $C_{21}H_{40}O_6$: C, 64.92; H 10.38. Found: C, 64.76; H, 10.43.



Alcohol 2. To a cold (0 °C) solution of diol **17** (65 mg, 0.167 mmol) in CH_2Cl_2 (1 mL) was added imidazole (105 mg, 1.7 mmol) followed by dropwise addition of triethylsilyl chloride (140 μL, 0.835 mmol). After 15 min, the resultant cloudy suspension was allowed to warm to rt. After 19 h, the reaction mixture was quenched with water and diluted with ether. The ether layer was washed with brine and the combined aqueous layers were extracted with ether. The extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (99:1 hexanes/EtOAc) to give 97 mg (94%) of the triethylsilyl ether as a colorles oil: R_f 0.54 (19:1 hexanes/EtOAc); $[\alpha]_D^{20}$ +16.7 (*c* 1.00, EtOAc). IR (film) 1731 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 4.23 (m, 1H), 4.03 (dd, *J* = 11.4, 7.5 Hz, 1H), 3.96 (dd, *J* = 11.4, 6.3 Hz, 1H), 3.82 (td, *J* = 9.9, 5.5 Hz, 1H), 3.05 (dd, *J* = 10.2, 1.5 Hz, 1H), 2.99 (s, 3H), 2.15 (m, 1H), 2.08-2.00 (m, 2H), 1.81 (m, 1H), 1.72 (dd, *J* = 12.6, 10.5 Hz, 1H), 1.48 (m, 1H), 1.22 (s, 9H), 1.13 (d, *J* = 7.2

Hz, 3H), 1.10-1.04 (m, 21H), 0.92-0.89 (m, 9H), 0.77-0.66 (m, 12H); ^{13}C NMR (75 MHz, C_6D_6) δ 177.63, 103.35, 77.87, 71.92, 71.08, 66.66, 46.67, 40.94, 39.22, 38.98, 38.84, 28.95, 27.35, 20.87, 14.42, 13.11, 12.80, 10.92, 7.44, 7.30, 6.15, 5.71. Anal. Calcd for $C_{33}H_{68}O_6Si_2$: C, 64.23; H 11.11. Found: C, 64.45; H, 11.20.

To a cold (-78 °C) solution of the above pivalic ester (130 mg, 0.211 mmol) in CH_2Cl_2 (2 mL) was added DIBAL-H (0.46 mL, 1 M solution in hexanes, 0.46 mmol) dropwise. After 45 min, the reaction mixture was carefully poured into a stirred mixture of saturated aqueous sodium potassium tartrate (Rochelle's salt) (10 mL) and ether (10 mL). The mixture was stirred vigorously for 1 h at which time the organic layer cleared. The organic layer was washed with brine and the combined aqueous layers were extracted with ether. The extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (19:1 hexanes/EtOAc) provided 100 mg (92%) of alcohol **2** as a colorless oil: R_f 0.51 (9:1 hexanes/EtOAc); $[\alpha]_D^{20}$ +21.8 (*c* 0.51, EtOAc). IR (film) 3424 (broad) cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 4.27 (apparent t, *J* = 2.4 Hz, 1H), 3.85 (td, *J* = 10.2, 4.5 Hz, 1H), 3.41 (apparent bs, 2H), 3.09 (dd, *J* = 10.2, 1.8 Hz, 1H), 3.04 (s, 3H), 2.14-2.06 (m, 2H), 1.91 (m, 1H), 1.81 (td, *J* = 6.9, 1.8 Hz, 1H), 1.73 (dd, *J* = 12.6, 10.5 Hz, 1H), 1.36 (apparent bs, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.11-1.05 (m, 21H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.75 (q, *J* = 7.8 Hz, 6H), 0.71 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 103.40, 92.33, 77.83, 72.17, 71.92, 65.13, 46.81, 43.26, 40.98, 39.75, 39.54, 28.93, 20.83, 14.41, 13.55, 12.80, 11.23, 7.44, 7.32, 6.15, 6.00. Anal. Calcd for $C_{28}H_{60}O_5Si_2$: C, 63.10; H 11.35. Found: C, 62.89; H, 11.49.