A De Novo Enantioselective Total Synthesis of Laulimalide

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Supporting Information

General Information: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_D^{25}$ (c g/100mL). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^1H NMR spectra were recorded on Bruker DPX 301/302 (300 MHz), Avance 500 (500 MHz), or LC-NMR 600 (600 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CHCl_3 : δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR spectra were recorded on a Bruker DPX 301/302 (75 MHz) or Avance 500 (125 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuteriochloroform: δ 77.0 ppm). Mass spectra were obtained on a VG-7070 or Fisons Autospec high resolution magnetic sector mass spectrometer. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described on 230-240 mesh silica gel.¹ Analytical gas liquid chromatography (GLC) was performed on a Hewlett-Packard 5890 Series II gas chromatograph with a flame ionization detector and split mode capillary injection system, using a Chiraldex™ G-TA column (20 m x 0.25 mm) (Advanced Separation Technologies Inc.). Hydrogen was used as the carrier gas at the indicated pressures. Analytical high performance liquid chromatograph (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm), using a Daicel Chiralcel™ OD-H column (250 x 4.6 mm) (Daicel Inc.). HPLC grade isopropanol and hexanes were used as the eluting solvents.

All experiments were carried out under a nitrogen atmosphere in oven or flame-dried glassware using standard inert atmosphere techniques for introducing reagents and solvents. Commercially available solvents and reagents were purified and dried using standard procedures. The catalyst complex **4** was prepared according to the published procedure.²

(4R)-4-Methyloxetan-2-one (5): To a -78 °C solution of 1.3 g of aluminum complex **4** (2.27 mmol) and 14.6 g of tetra-*n*-butylammonium bromide (45.4 mmol) in 91 mL of CH_2Cl_2 was added 6.72 mL of $i\text{Pr}_2\text{NEt}$ (38.6 mmol) followed by 3.20 mL of acetyl bromide (43.1 mmol). The resulting yellow solution was stirred two minutes at -78 °C whereupon 1.27 mL of acetaldehyde (22.7 mmol) was added dropwise via syringe. The reaction was maintained at -78 °C for 12h before the reaction mixture was poured into ice-cold hexanes (300 mL). The resulting mixture was eluted through silica gel (40% EtOAc/Hex) and the eluant was concentrated to yield 1.7 g (87%, crude) of **5** as a pale yellow liquid that was sufficiently pure to use in subsequent transformations. Separation of the enantiomers by chiral GC [Chiraldex G-TA column, flow rate 1.5 mL/min, method: 80 °C for 5.0 min, ramp @ 5.0 °C/min to 100 °C for 10.0 min, ramp @ 5.0 °C to 130 °C for 5 min. T_r 8.04 min (*R*) and 9.05 min (*S*)] determined the enantiomeric excess to be 99%. ^1H NMR (300 MHz,

¹ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923-2925.

² Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, 121, 9742-9743.

CDCl₃): δ 4.61 (ddq, J = 4.2, 6.0, 12.0 Hz, 1H), 3.48 (dd, J = 5.7, 16.3 Hz, 1H), 2.98 (dd, J = 4.3, 16.3 Hz, 1H), 1.47 (d, J = 8.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 168.0, 67.7, 44.0, 20.2.

(3R)-3-Hydroxy-N-methoxy-N-methylbutyramide: To a 0 °C solution of 6.32 g of *N,O*-dimethylhydroxylamine hydrochloride (65.1 mmol) in 30 mL CH₂Cl₂ was added 65 mL of dimethylaluminum chloride (65 mmol of 1 M hexanes solution). The resulting solution was allowed to warm to ambient temperature and stirred for 2 h. To the resulting suspension was added a solution of **5** in 5 mL of CH₂Cl₂ via cannula. The reaction mixture was maintained at ambient temperature overnight whereupon 36 mL (3 mL/mmol Me₂AlCl) of pH 8 phosphate buffer was added. The reaction mixture was filtered through Celite to remove the solid aluminum salts and the layers of the filtrate were separated. The aqueous portion was extracted with CH₂Cl₂ (3x100 mL) and the combined organics were dried over Na₂SO₄, filtered, and concentrated. The crude oil was purified by silica gel chromatography (Et₂O) to provide 3.8 g (81%) of the β -hydroxyl amide as a pale yellow oil: [α]_D = -58 (*c* 3.0, CHCl₃); IR (thin film): 3448, 3008, 2974, 2938, 1642, 1420, 1389, 1216, 1002, 754 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.21 (ddq, J = 2.6, 6.3, 9.0 Hz, 1H), 3.70 (s, 3H), 3.20 (s, 3H), 2.67 (d, J = 16.7 Hz, 1H), 2.44 (dd, J = 9.5, 16.8 Hz, 1H), 1.24 (d, J = 6.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 173.6, 64.0, 61.2, 39.7, 31.7, 22.2; HRMS calcd for C₆H₁₃NO₃: 147.0895, found 147.0895.

(3R)-3-(*tert*-Butyldiphenylsilyloxy)-N-methoxy-N-methylbutyramide (6): To a 0 °C solution of 0.730 g of the β -hydroxyl amide (4.96 mmol) in 8 mL of CH₂Cl₂ was added 1.73 mL of ⁱPr₂NEt (9.93 mmol), 1.42 mL of TBDPSCl (5.46 mmol), and 0.607 g of DMAP (4.96 mmol). The resulting solution was warmed to ambient temperature and maintained for 18 h. Saturated aqueous NaHCO₃ (20 mL) was added and the mixture was extracted with CH₂Cl₂ (3x20 mL). The combined organics were washed with 1 M HCl (50 mL) and brine (50 mL), dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexanes) to afford 1.8 g (94%) of **6** as a pale yellow oil. [α]_D = -9.1 (*c* 3.8, CHCl₃); IR (thin film): 3069, 3045, 2964, 2930, 2856, 1660, 1472, 1385, 1178, 1002, 940 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.71-7.79 (m, 4H), 7.36-7.46 (m, 6H), 4.45 (sextet, J = 6.0 Hz, 1H), 3.61 (s, 3H), 3.14 (s, 3H), 2.84 (dd, J = 6.0, 15.0 Hz, 1H), 2.44 (dd, J = 6.0, 15.0 Hz, 1H), 1.16 (d, J = 6.0 Hz, 3H), 1.07 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 171.9, 135.8, 135.7, 134.5, 134.0, 129.5, 129.4, 127.4, 127.3, 66.9, 61.1, 41.8, 31.4, 26.9, 23.7, 19.1; HRMS calcd for C₂₂H₃₀NO₃Si: 384.1995, found 384.1976.

(3R)-3-(*tert*-Butyldiphenylsilyloxy)butyraldehyde: To a -78 °C solution of 0.700 g of **6** (1.82 mmol) in 11 mL of Et₂O was added 2 mL of a 1.0 M hexanes solution of ⁱBu₂AlH (2.00 mmol) dropwise. The resulting colorless solution was maintained at -78 °C for 30 min whereupon a 1 M HCl solution (20 mL) was added and the resulting mixture was extracted with Et₂O (3x20 mL). The combined organics were washed with brine (30 mL) and filtered through Celite. The filtrate was then dried over Na₂SO₄, filtered, and concentrated. Purification of the crude oil by flash chromatography (5% EtOAc/hexanes) afforded 0.569 g (95%) of the title aldehyde as a clear, colorless liquid. [α]_D = +7.5 (*c* 2.9, CHCl₃); IR (thin film) 3069, 3048, 2961, 2930, 2893, 2859, 2720, 1728, 1425, 1379, 1110, 823 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 9.78 (t, J = 2.6 Hz, 1H), 7.69-7.75 (m, 4H), 7.38-7.49 (m, 6H), 4.38 (sextet, J = 6.0 Hz, 1H), 2.57 (ddd, J = 2.9, 6.0, 15.8 Hz, 1H), 2.49 (ddd, J = 2.2, 5.6, 15.8 Hz, 1H), 1.21 (d, J = 6.0 Hz, 3H), 1.08 (s, 9H); ¹³C NMR (75 MHz,

CDCl₃): δ 202.1, 136.1, 134.4, 134.0, 130.2, 130.0, 128.0, 127.9, 66.0, 53.1, 27.2, 24.1, 19.5; HRMS calcd for C₁₆H₁₇O₂Si: 269.0998, found 269.0999.

(4R, 2'R)-4-[2-*tert*-Butyldiphenylsilyloxy)propyl]oxetan-2-one (7): To a $-50\text{ }^{\circ}\text{C}$ solution of 0.870 g of aluminum complex **4** (1.50 mmol) in 25 mL of CH₂Cl₂ was added 4.43 mL of ¹Pr₂NEt (25.4 mmol) followed by 2.10 mL of acetyl bromide (28.4 mmol). To the resulting yellow solution was added a solution of 4.88 g of aldehyde (prepared above; 15.0 mmol) in 5 mL of CH₂Cl₂. The reaction was maintained at $-50\text{ }^{\circ}\text{C}$ 12 h and was then quenched by pouring into ice-cold hexanes (150 mL). The resulting mixture was filtered through silica gel (50% EtOAc/Hex) and concentrated. The crude product was then purified by flash chromatography (3% EtOAc/hexanes) to afford 4.77 g (86%) of **7** as a white solid. $[\alpha]_{\text{D}} = +17$ (*c* 2.6, CHCl₃); IR (thin film): 3072, 3051, 2964, 2930, 2893, 2859, 1824, 1425, 1376, 1110, 909 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.66-7.70 (m, 4H), 7.38-7.45 (m, 6H), 4.69 (dq, *J* = 4.4, 6.7 Hz, 1H), 4.04 (dddd, *J* = 6.1, 6.1, 6.1, 12.1 Hz, 1H), 3.29 (dd, *J* = 5.8, 16.3 Hz, 1H), 2.95 (dd, *J* = 4.3, 16.3 Hz, 1H), 2.13 (ddd, *J* = 6.3, 6.3, 14.0 Hz, 1H), 1.81 (ddd, *J* = 5.0, 7.0, 14.0 Hz, 1H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.09 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 168.4, 136.2, 136.1, 134.3, 134.0, 130.2, 130.1, 128.1, 127.9, 68.8, 66.7, 44.0, 43.6, 27.3, 23.6, 19.5; HRMS calcd for C₁₈H₁₉O₃Si: 311.1103, found 311.1107.

(3S, 5R)-5-(*tert*-Butyldiphenylsilyloxy)-3-methylhexanoic acid (8): To a $-50\text{ }^{\circ}\text{C}$ solution of 2.69 g of CuBr (18.8 mmol) in 185 mL of THF and 20 mL of dimethylsulfide was slowly added 12.5 mL of a 3.0 M ethereal solution of methylmagnesium bromide (37.5 mmol) dropwise. The resulting pale green solution was stirred at $-50\text{ }^{\circ}\text{C}$ for 30 min then warmed to $-30\text{ }^{\circ}\text{C}$ for 30 min. The reaction was then cooled to $-50\text{ }^{\circ}\text{C}$ and 4.6 g of **7** (12.5 mmol) in 15 mL of THF was added via cannula. After maintaining the reaction at $-50\text{ }^{\circ}\text{C}$ for 45 min, 2.4 mL of TMSCl (18.8 mmol) was added and the reaction was allowed to warm to $25\text{ }^{\circ}\text{C}$ overnight. A mixture of saturated NH₄Cl (500 mL) and 1 M HCl (200 mL) was added and the resulting mixture was extracted with Et₂O (4X150 mL). The combined organics were washed with saturated NH₄Cl and brine (50 mL), dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography (10% EtOAc/hexanes) to afford 3.85 g (80%) of **8** as a viscous pale yellow oil. $[\alpha]_{\text{D}} = +6.7$ (*c* 2.2, CHCl₃); IR (thin film): 3070, 3045, 2961, 2928, 2853, 1704, 1426, 1373, 1108, 909, 820 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.77-7.82 (m, 4H), 7.41-7.52 (m, 6H), 3.92-4.02 (m, 1H), 2.20-2.32 (m, 2H), 2.06-2.15 (m, 1H), 1.69 (ddd, *J* = 5.1, 7.5, 13.3 Hz, 1H), 1.32 (ddd, *J* = 4.6, 7.7, 12.9 Hz, 1H), 1.15-1.18 (m, 12H), 0.91 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 179.6, 135.9, 134.8, 134.2, 129.6, 129.4, 127.5, 127.4, 67.5, 46.7, 41.9, 27.0, 26.7, 24.0, 19.7, 19.3; HRMS calcd for C₁₉H₂₃O₃Si: 327.1416, found 327.1419.

(3S, 5R)-5-(*tert*-Butyldiphenylsilyloxy)-3-methylhexanal (9): To a $25\text{ }^{\circ}\text{C}$ solution of 3.75 g of carboxylic acid **8** (9.76 mmol) in 50 mL of Et₂O was slowly added 7.3 mL of a 2.0 M THF solution of H₃B•SMe₂ (14.6 mmol) dropwise. The resulting clear, colorless solution was heated to reflux and maintained 1 h. After cooling to $25\text{ }^{\circ}\text{C}$, the solvent was evaporated and the remaining viscous residue was dissolved in 50 mL of CH₂Cl₂. To this colorless solution was added 5.26 g of pyridinium chlorochromate (24.4 mmol) and the resulting brown suspension was heated to reflux and maintained for 2.5 h. The reaction was then cooled to $25\text{ }^{\circ}\text{C}$, diluted with Et₂O, filtered through Celite, and concentrated. The crude product was purified by flash chromatography (5% EtOAc/hexanes) to afford 3.05 g (85%) of **9** as a pale yellow oil: $[\alpha]_{\text{D}} = -1.0$ (*c* 2.6, CHCl₃); IR (thin film): 3067, 3048, 2959, 2928, 2853, 2708, 1726, 1426, 1373, 1111, 1067, 823 cm⁻¹; ¹H NMR

(300 MHz, CDCl₃): δ 9.63 (t, J = 2.5 Hz, 1H), 7.67-7.72 (m, 4H), 7.36-7.44 (m, 6H), 3.81-3.91 (m, 1H), 2.07-2.23 (m, 2H), 1.55 (ddd, J = 5.0, 7.7, 13.0 Hz, 1H), 1.23 (ddd, J = 4.7, 8.2, 13.4 Hz, 1H), 1.09 (d, J = 6.0 Hz, 3H), 1.06 (s, 9H), 0.78 (d, J = 6.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 202.6, 135.9, 134.7, 134.2, 129.6, 129.5, 127.6, 127.4, 67.5, 51.3, 47.1, 27.1, 24.9, 24.0, 20.0, 19.3.

(4R, 2'S, 4'R)-4-[4'-(tert-Butyldiphenylsilyloxy)-2-methylpentyl]oxetan-2-one

(10): To a -50 °C solution of 0.704 g of aluminum triamine catalyst **4** (1.21 mmol) in 16 mL of CH₂Cl₂ was added 2.40 mL of *i*Pr₂NEt (13.7 mmol) followed

by 1.13 mL of acetyl bromide (15.3 mmol). The resulting yellow solution was stirred at -50 °C whereupon 2.97 g of aldehyde **9** (8.07 mmol) in 5 mL of CH₂Cl₂ was added slowly dropwise via syringe. The reaction was maintained at -50 °C for 16 h, whereupon the reaction was quenched by pouring into ice-cold hexanes (100 mL). The resulting mixture was filtered through silica gel (50% EtOAc/Hex eluant) and the filtrate concentrated. The crude product mixture was purified by flash chromatography (11% hexanes/benzene) to afford 2.76 g (84%) of **10** as a white solid: $[\alpha]_D$ = +21 (*c* 2.3, CHCl₃); IR (thin film): 3070, 3048, 2965, 2931, 2853, 1828, 1426, 1376, 1200, 1111, 1061, 820 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.66-7.72 (m, 4H), 7.35-7.47 (m, 6H), 4.45 (dtd, J = 4.5, 5.6, 8.0 Hz, 1H), 3.80-3.90 (m, 1H), 3.45 (dd, J = 5.7, 16.2 Hz, 1H), 2.95 (dd, J = 4.3, 16.2 Hz, 1H), 1.73-1.84 (m, 1H), 1.67 (ddd, J = 5.2, 7.8, 13.7 Hz, 1H), 1.54 (ddd, J = 5.2, 7.6, 13.4 Hz, 1H), 1.37 (ddd, J = 5.3, 7.9, 13.6 Hz, 1H), 1.20 (ddd, J = 4.9, 8.2, 12.7 Hz, 1H), 1.10 (d, J = 6.0 Hz, 3H), 1.05 (s, 9H), 0.76 (d, J = 6.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 168.2, 135.9, 134.7, 134.3, 129.6, 129.5, 127.6, 127.4, 69.7, 67.4, 47.2, 43.4, 42.2, 27.0, 26.7, 24.1, 19.6, 19.3; HRMS calcd for C₂₁H₂₅O₃Si: 353.1572, found 353.1559.

(2R, 2'S, 4'R)-2-[4-(tert-Butyldiphenylsilyloxy)-2-methylpentyl]-2,3-

dihydropyran-4-one (11): To a 0 °C solution of 0.690 mL of diisopropylamine

(4.93 mmol) in 20 mL of THF was added 2.95 mL of a 1.6 M solution of *n*BuLi in hexanes (4.68 mmol) slowly dropwise. The resulting solution was maintained at

0 °C for 30 min whereupon 0.590 mL of acetaldehyde *N*-piperidine hydrazone (4.93 mmol) was added. The resulting heterogeneous mixture was stirred at 0 °C for 1 h then cooled to -78 °C whereupon 1.01 g of **10** (2.46 mmol) in 2 mL of THF was added via cannula. The resulting yellow solution was maintained at -78 °C overnight. The reaction was quenched with saturated NaHCO₃ and extracted with EtOAc (3X20 mL). The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The remaining residue was dissolved in THF and treated with 2.8 g of camphorsulfonic acid (12.1 mmol) and the reaction was warmed to 60 °C over the course of 1 h and then allowed to cool to ambient temperature. The reaction was quenched with saturated NaHCO₃ and extracted with EtOAc. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. Purifying the crude product mixture by flash chromatography (8% EtOAc/hexanes) afforded 0.665 g (62%) of **11** as a yellow oil. $[\alpha]_D$ = +68 (*c* 2.1, CHCl₃); IR (thin film): 3073, 3051, 2962, 2931, 2860, 1673, 1593, 1429, 1274, 1114, 909 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.68-7.73 (m, 4H), 7.35-7.47 (m, 6H), 7.29 (d, J = 6.0 Hz, 1H), 5.39 (dd, J = 1.0, 6.0 Hz, 1H), 4.40 (dddd, J = 4.0, 4.0, 8.3, 13.2 Hz, 1H), 3.84-3.94 (m, 1H), 2.43 (dd, J = 12.5, 16.8 Hz, 2H), 1.81-1.97 (m, 1H), 1.67 (ddd, J = 4.5, 9.5, 14.2 Hz, 1H), 1.52 (ddd, J = 5.7, 7.3, 13.4 Hz, 1H), 1.12 (d, J = 6.0 Hz, 3H), 1.06 (s, 9H), 0.76 (d, J = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 192.5, 163.0, 135.9, 134.7, 134.3, 129.5, 129.4, 127.5, 127.4, 106.9, 67.5, 47.6, 47.1, 42.4, 41.9, 27.0, 25.3, 24.0, 19.4, 19.2; HRMS calcd for C₂₃H₂₇O₃Si: 379.1729, found 379.1729.

(2R, 2'S, 4'R, 4S)-2-[4-(*tert*-Butyldiphenylsilyloxy)-2-methylpentyl]-3,4-dihydro-2H-pyran-4-yl-acetate: To a 0 °C solution of 0.408 g of **11** (0.936 mmol) and 0.418 g of CeCl₃·7H₂O (1.12 mmol) in 10 mL of MeOH was added 0.039 g of NaBH₄ (1.03 mmol) portionwise. After stirring 40 min at 0 °C, the

reaction was quenched by adding 10 mL of water. The mixture was extracted with CH₂Cl₂ (4x20 mL) and the combined organics were dried over Na₂SO₄, filtered, and concentrated to afford the corresponding allylic alcohol. The crude alcohol (0.410 g, 0.936 mmol) was dissolved in 8 mL of CH₂Cl₂ and cooled to 0 °C. To this solution was added 0.391 mL of Et₃N (2.81 mmol), 0.011 g of DMAP (0.0936 mmol), and 0.135 mL of acetic anhydride (1.40 mmol). The resulting clear, colorless solution was maintained at ambient temperature for 2 h whereupon the reaction mixture was concentrated and purified by flash chromatography (hexanes/ Et₃N 50:1) to afford 0.404 g (90%) of the allylic acetate as a clear colorless oil. [α]_D = +17 (*c* 2.0, CHCl₃); IR (thin film): 3070, 3048, 2961, 2931, 2856, 1729, 1645, 1429, 1370, 1231, 1108, 1040, 912 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.68-7.73 (m, 4H), 7.35-7.43 (m, 6H), 6.41 (d, *J* = 6.2 Hz, 1H), 5.38 (tq *J* = 1.5, 6.6 Hz, 1H), 4.72 (ddd, *J* = 2.2, 3.8, 6.2 Hz, 1H), 3.95-4.03 (m, 1H), 3.83-3.94 (m, 1H), 2.10-2.16 (m, 1H), 2.05 (s, 3H), 1.78-1.95 (m, 1H), 1.57-1.69 (m, 1H), 1.47-1.56 (m, 1H), 1.19 (ddd, *J* = 5.3, 8.0, 13.5 Hz, 1H), 1.06-1.10 (m, 12H), 0.75 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 171.8, 146.7, 135.9, 134.9, 134.4, 129.5, 129.4, 127.5, 127.3, 100.8, 72.2, 67.6, 65.7, 47.7, 42.2, 34.0, 27.0, 25.5, 24.0, 21.2, 19.5, 19.2; EI-MS *e/v* 423 (M⁺-*t*Bu), 363 (M⁺-*t*Bu-AcOH), 253, 199, 147; HRMS calcd for C₂₃H₂₇O₂Si: 363.1780, found 363.1765.

(2R, 4S, 2'S)-(2-methyl-4-oxopentyl)-3,4-dihydro-2H-pyran-4-yl-acetate (13): To a 0 °C solution of 0.400 g of the allylic acetate (prepared above; 0.833 mmol) in 0.25 mL of THF was slowly added 1.95 mL of a 1.0 M THF solution of tetrabutylammonium fluoride (1.95 mmol) dropwise. The reaction was warmed to

ambient temperature and maintained for 6 h then diluted with EtOAc (100 mL). The resulting solution was washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude alcohol was dissolved in 6 mL of CH₂Cl₂ and 1.0 g of 4 Å molecular sieves was added followed by 0.784 g of pyridinium dichromate (2.08 mmol). The resulting brown suspension was maintained at ambient temperature for 1.5 h before being diluted with Et₂O (100 mL) and filtered through Celite. The filtrate was concentrated and the crude product mixture was purified by flash chromatography (hexanes/Et₃N 50:1) to afford 0.160 g (80%) of **13** as a colorless oil. [α]_D = +9.8 (*c* 2.5, CHCl₃); IR (thin film): 3067, 2960, 2930, 1729, 1644, 1372, 1232, 1042, 1023, 805 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.40 (d, *J* = 6.2 Hz, 1H), 5.33-5.38 (m, 1H), 4.69-4.72 (m, 1H), 3.97-4.05 (m, 1H), 2.22-2.50 (m, 3H), 2.13-2.20 (m, 1H), 2.10 (s, 3H), 2.02 (s, 3H), 1.61-1.73 (m, 2H), 1.27 (ddd, *J* = 3.3, 8.4, 14.0 Hz, 1H), 0.92 (d, *J* = 6.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 208.1, 170.7, 146.4, 100.9, 72.2, 65.5, 51.4, 41.7, 34.0, 30.2, 25.7, 21.1, 19.6.

(2R, 6R, 2'S)-4-[6-(2-Methyl-4-oxopentyl)-5,6-dihydro-2H-pyran-2-yl]but-2-ynoic acid, *tert*-butyl ester (2): To a -78 °C solution of 0.064 g of **13** (0.267 mmol) in 1 mL of CH₂Cl₂ was slowly added 0.457 g of **14**

(1.07 mmol) in 0.5 mL of CH₂Cl₂. To the resulting solution was added a solution of 0.129 g of tributyltin trifluoromethanesulfonate (0.293 mmol) in 1 mL of CH₂Cl₂ via cannula. The reaction was maintained at -78 °C for 2 h then allowed to slowly warm to ambient temperature. Saturated aqueous NaHCO₃ (5 mL) was added and the mixture was extracted with CH₂Cl₂ (4 x 6 mL). The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude product

mixture was purified by flash chromatography (2% EtOAc/hexanes) to afford 0.068 g (80%) of **2** as a clear colorless oil. $[\alpha]_D = -72$ (*c* 1.5, CHCl₃); IR (thin film): 3039, 2980, 2931, 2241, 1706, 1369, 1282, 1160, 1074, 912, 732 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.85-5.92 (m, 1H), 5.74-5.79 (m, 1H), 4.34-4.46 (m, 1H), 3.74 (dddd, *J* = 3.6, 8.5, 8.5, 12.5 Hz, 1H), 2.61 (dd, *J* = 7.0, 16.9 Hz, 1H), 2.50 (dd, *J* = 6.9, 17.0 Hz, 1H), 2.44 (dd, *J* = 6.9, 17.0 Hz, 1H), 2.22-2.33 (m, 2H), 2.11 (s, 3H), 1.82-2.02 (m, 3H), 1.53 (ddd, *J* = 4.5, 9.7, 14.0 Hz, 1H), 1.45 (s, 9H), 1.22 (ddd, *J* = 3.1, 8.3, 12.9 Hz, 1H), 0.92 (d, *J* = 6.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 208.6, 152.5, 127.4, 125.9, 83.3, 82.9, 75.9, 70.1, 66.1, 51.6, 42.1, 30.8, 30.0, 28.0, 26.0, 24.6, 19.6; EI-MS *m/z* 321 (M⁺+H), 265, 181, 163, 123, 105, 57.

(4S)-(tert-Butyldiphenylsiloxy)methyl-oxetane-2-one (16):² To a -50 °C methylene chloride solution of 58 mg of aluminum triamine catalyst **4** (0.10 mmol) in 5.7 mL of CH₂Cl₂ was added 0.30 mL of DIPEA (1.7 mmol) followed by 0.14 mL of acetyl bromide (1.9 mmol). The resulting yellow solution was stirred at -50 °C whereupon 0.298 g of 2-tert-butyldiphenylsiloxyacetaldehyde (1.0 mmol) was added dropwise via syringe. After maintaining at -50 °C for 12 h, the reaction mixture was diluted with 10 mL of pentane, filtered through silica gel (30% EtOAc/hexanes), and concentrated. The resulting residue was purified by silica gel chromatography (10% EtOAc/hexanes) to provide 0.30 g of **16** (92%) as a white crystalline solid in 92% ee; HPLC (90/10 hexanes/*i*PrOH, 1.0 mL/min) *T_r*(min) = 7.63 (*R*), 13.27 (*S*).

(3S)-4-(tert-Butyldiphenylsiloxy)-hydroxy-N-

methoxy-N-methylbutyramide:

To a 0 °C solution of 1.36 g of methoxymethylamine hydrochloride (14 mmol) in 30 mL of CH₂Cl₂ was added 14 mL of a 1 M hexanes solution of dimethylaluminum chloride (14 mmol). The resulting solution was allowed to warm to ambient temperature and maintained for 1 h. To the resulting suspension was added a solution of 2.39 g of **16** (7.0 mmol) in 5 mL of CH₂Cl₂ via cannula. The reaction mixture was maintained for 2 h at ambient temperature, then quenched with 42 mL of pH 8 hydrogen phosphate buffer. The resulting mixture was filtered through a pad of celite and the biphasic filtrate was separated and the aqueous layer was extracted with CH₂Cl₂ (2X10 mL). The combined organics were dried over MgSO₄, filtered, and concentrated. The crude product mixture was purified by silica gel chromatography (30% EtOAc/hexanes) to provide 2.64 g (94%) of the title β-hydroxyl amide as a white solid. $[\alpha]_D = -16$ (*c* 1.1, CHCl₃); IR (thin film): 3441.6, 3069, 3046, 2954, 2931, 2891, 2855, 1640, 1465, 1426, 1386, 1184, 1109, 998, 828, 741, 705, 610 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.72 (dd, *J* = 1.8, 5.0 Hz, 4H), 7.44-7.36 (m, 6H), 4.24 (m, 1H), 3.85 (d, *J* = 3.2 Hz, 1H), 3.80 (dd, *J* = 4.7, 10.1 Hz, 1H), 3.72 (dd, *J* = 5.0, 10.0 Hz, 1H), 3.64 (s, 3H), 3.16 (s, 3H), 2.78 (d, *J* = 15.6 Hz, 1H), 2.67 (dd, *J* = 8.3, 15.2 Hz, 1H), 1.11 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 173.1, 135.4, 133.2, 129.7, 127.7, 68.6, 67.0, 61.1, 53.4, 34.9, 31.7, 26.8, 19.2; HRMS calcd for C₂₂H₃₁NO₄Si: 344.1322, found 344.1318.

(3S)-4-(tert-Butyldiphenylsiloxy)-N-methoxy-(4-methoxybenzyloxy)-N-methylbutyramide (17):

To a solution of 0.511 g of the β-hydroxyl amide (prepared above, 1.27 mmol) in 2.5 mL of diethyl ether was added 0.790 mL of *p*-methoxybenzyltrichloroacetimidate (3.82 mmol) and 0.010 mL of trifluoromethanesulfonic acid via syringe. After stirring for 30 min at ambient temperature, 5 mL of saturated aqueous NaHCO₃ was added to the reaction. The aqueous and organic layers were separated and the aqueous layer was extracted with diethyl ether (2X10 mL). The combined organic layers were dried over MgSO₄, filtered,

and concentrated. The crude product mixture was purified by silica gel chromatography (20% EtOAc/hexane); elution of the title compound was coincident with trichloroacetamide. The isolated product was triturated from the solid trichloroacetamide using pentane (5X10 mL). The combined pentane washings were concentrated to provide 0.50 g (77%) of **17** as a colorless oil. $[\alpha]_D = -9.5$ (c 1.1, CHCl_3); IR (thin film): 3006, 2954, 2931, 2851, 1707, 1655, 1509, 1461, 1422, 1244, 1109, 820, 756, 701 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.68 (dd, $J = 1.1, 7.5$ Hz, 4H), 7.46–7.35 (m, 6H), 7.21 (d, $J = 8.6$ Hz, 2H), 6.83 (d, $J = 8.6$ Hz, 2H), 4.53 (dd, $J = 5.7, 16.5$ Hz, 2H), 4.12 (m, 1H), 3.79 (s, 3H), 3.76 (dd, $J = 5.2, 7.2$ Hz, 1H), 3.68 (dd, $J = 5.2, 8.8$ Hz, 1H), 3.61 (s, 3H), 3.20 (s, 3H), 2.95–2.55 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (CDCl_3): δ 172.4, 156.8, 135.6, 133.3, 130.9, 129.7, 129.4, 127.7, 113.6, 76.5, 72.3, 65.6, 61.2, 55.2, 34.7, 32.0, 26.8, 19.2; HRMS calcd for $\text{C}_{30}\text{H}_{39}\text{NO}_5\text{Si}$: 464.1893, found 464.1893.

(3S)-4-(tert-Butyldiphenylsilyloxy)-(4-methoxybenzyloxy) butyraldehyde: To

a -78°C solution of 61 mg of **17** (0.117 mmol) in 1.0 mL of THF was added 0.129 mL of DIBAL-H (0.129 mmol) as a 1 M solution in hexanes. After stirring at -78°C for 45 min, the reaction was poured into 5 mL of a 0°C mixture of 1:1 diethyl ether and 1 M HCl. The resulting biphasic mixture was stirred at ambient temperature for 30 min. The ether layer was separated and washed with brine (1X5 mL). The organic portion was dried over MgSO_4 , filtered, and concentrated. The crude product mixture was purified by silica gel chromatography (20% EtOAc/hexanes) to provide 0.044 g (80%) of the title aldehyde as a colorless oil. $[\alpha]_D = -20$ (c 0.7, CHCl_3); IR (thin film): 3065, 3050, 2994, 2954, 2931, 2855, 2725, 1723, 1608, 1584, 1513, 1469, 1422, 1248, 1113, 1034, 820, 737, 705 cm^{-1} ; ^1H NMR (CDCl_3): δ 9.78 (t, $J = 2.0$ Hz, 1H), 7.67 (dd, $J = 1.7, 6.1$ Hz, 4H), 7.43–7.37 (m, 6H), 7.19 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 4.48 (dd, $J = 11.1, 34.1$ Hz, 2H), 4.03 (m, $J = 5.5$ Hz, 1H), 3.80 (s, 3H), 3.77 (dd, $J = 4.9, 10.6$ Hz, 1H), 3.67 (dd, $J = 5.7, 10.5$ Hz, 1H), 2.70 (dd, $J = 1.9, 6.1$ Hz, 2H), 1.06 (s, 9H); ^{13}C NMR (CDCl_3): δ 201.4, 159.4, 135.7, 133.2, 130.3, 130.0, 129.5, 127.9, 113.9, 74.6, 71.9, 65.3, 55.3, 46.4, 26.9, 19.3; EI-MS (70 eV) 419 ($\text{M}^+ - \text{CH}_2\text{CHO}$), 405 ($\text{M}^+ - \text{Bu}$), 391, 333, 327, 309, 267, 241, 199, 181, 163, 135, 121, 105.

(2E)(5S)-6-(tert-Butyldiphenylsilyloxy)-(4-methoxybenzyloxy)hex-2-enoic acid, ethyl ester: To a 0°C suspension of 1.06 g of

methyltriphenylphosphonium bromide (3.0 mmol) in 5 mL of THF was added via syringe 4.53 mL of KHMDS (2.27 mmol) as a 0.5 M solution in toluene. To the resulting orange solution was added via cannula 0.70 g of the aldehyde (prepared above; 1.5 mmol) as a solution in 5 mL of THF. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated and purified by silica gel chromatography (25% EtOAc/hexanes) to provide 0.758 g (95%) of the title (*E*)-enoate ester as a colorless oil. $[\alpha]_D = -16$ (c 2.5, CHCl_3); IR (thin film): 3069, 3050, 2954, 2931, 2851, 1719, 1655, 1612, 1584, 1513, 1469, 1430, 1362, 1299, 1248, 1172, 1113, 1034, 820, 741, 705, 610 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.67 (d, $J = 6.8$ Hz, 4H), 7.56–7.40 (m, 6H), 7.20 (d, $J = 8.6$ Hz, 2H), 6.95 (ddd, $J = 7.9, 7.9, 15.6$ Hz, 1H), 6.85 (d, $J = 8.6$ Hz, 2H), 5.87 (d, $J = 15.6$ Hz, 1H), 4.46 (dd, $J = 11.4, 31.2$ Hz, 2H), 4.20 (q, $J = 7.0$ Hz, 2H), 3.81 (s, 3H), 3.74 (m, 1H), 3.60 (dd, $J = 5.2, 6.0$ Hz, 2H), 2.49 (dd, $J = 6.9, 14.3$ Hz, 2H), 1.35 (t, $J = 7.2$ Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (CDCl_3): δ 166.5, 159.3, 145.5, 135.7, 133.4, 133.3, 130.5, 129.9, 129.5, 127.9, 123.6, 113.8, 78.1, 71.8, 65.4, 60.3, 55.3, 34.8, 26.9, 19.3, 14.4; EI-MS (70 eV) 475 ($\text{M}^+ - \text{tBu}$), 429, 337 (475-OPMB), 309, 267, 241, 227, 223, 199, 121 (PMB).

(2E)(5S)-6-(tert-Butyldiphenylsiloxy)-(4-methoxybenzyloxy)hex-2-en-1-ol:

To a -78°C solution of 0.328 g of the (*E*)-enoate ester (prepared above; 0.617 mmol) in 3.1 mL of THF was added 1.3 mL of a 1 M hexanes solution of DIBAL-H (1.29 mmol). The reaction was allowed to warm slowly to 0°C over a 90 min. The reaction mixture was poured into a 0°C mixture of 10 mL of diethylether and 10 mL of 1 M HCl and the resulting biphasic mixture was stirred for 15 min. The organic and aqueous layers were separated and the aqueous layer was saturated with brine and extracted with diethylether (3x10 mL). The combined organics were dried over MgSO_4 , filtered, and concentrated. The crude product mixture was purified by silica gel chromatography (15% EtOAc/hexanes) to provide 0.267 g (89%) of the title allylic alcohol as a colorless oil. $[\alpha]_{\text{D}} = -13$ (c 1.1, CHCl_3); IR (thin film): 3418, 3065, 3046, 2954, 2931, 2851, 1612, 1509, 1461, 1422, 1244, 1109, 1030, 820, 741, 701 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.68 (d, $J = 6.2$ Hz, 4H), 7.44–7.36 (m, 6H), 7.23 (d, $J = 8.5$ Hz, 2H), 6.86 (d, $J = 8.5$ Hz, 2H), 5.66–5.63 (m, 2H), 4.51 (dd, $J = 11.3$, 34.1 Hz, 2H), 4.04 (dd, $J = 4.3$, 9.4 Hz, 2H), 3.81 (s, 3H), 3.72 (dd, $J = 5.7$, 10.7 Hz, 1H), 3.64 (dd, $J = 5.1$, 10.5 Hz, 1H), 3.53 (dd, $J = 5.5$, 5.5 Hz, 1H), 2.34 (ddd, $J = 6.6$, 9.2, 9.9 Hz, 2H), 1.07 (s, 9H); ^{13}C NMR (CDCl_3): δ 159.2, 135.8, 135.7, 133.6, 133.5, 131.7, 130.9, 129.9, 129.8, 129.6, 129.5, 128.7, 127.8, 113.8, 79.0, 71.6, 65.5, 63.6, 55.3, 34.4, 27.0, 19.3; EI-MS (70 eV) 433 ($\text{M}^+ - t\text{Bu}$), 415 (433- H_2O), 333, 295, 279, 241, 223, 211, 199, 181, 163, 135, 121, 105.

(2E)(5S)-6-(tert-Butyldiphenylsiloxy)-(4-methoxybenzyloxy)hex-2-en-triphenylmethylether (18):

To a solution of 0.181 mL of 2,6-lutidine (1.56 mmols), 0.289 g of chlorotriphenylmethane (1.04 mmol), and 0.383 g of tetra-*n*-butylammonium iodide (1.04 mmol) in 2 mL of CH_2Cl_2 was added a solution of 0.508 g of allylic alcohol (prepared above; 1.04 mmol) in 1 mL CH_2Cl_2 via syringe. The golden-brown reaction mixture was stirred at room temperature for 5.5 h. The reaction mixture was then concentrated and purified by silica gel chromatography (10/90 EtOAc/hexanes) to provide 0.678 g (92%) of **18** as a colorless oil. IR (thin film): 3057, 3026, 2955, 2927, 2856, 1960, 1881, 1818, 1616, 1509, 1450, 1426, 1386, 1362, 1299, 1248, 1176, 1109, 1054, 1034, 820, 760, 744, 700 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.74 (d, $J = 6.5$ Hz, 4H), 7.53 (d, $J = 7.3$ Hz, 6H), 7.48–7.28 (m, 15H), 6.86 (d, $J = 8.5$ Hz, 2H), 5.88–5.65 (m, 2H), 4.58 (dd, $J = 11.3$, 26.5 Hz, 2H), 3.87–3.65 (m, 3H), 3.83 (s, 3H), 3.60 (d, $J = 4.6$ Hz, 2H), 2.43 (ddd, $J = 6.4$, 9.63, 10.0 Hz, 2H), 1.13 (s, 9H); ^{13}C NMR (CDCl_3): δ 159.2, 144.6, 135.8, 133.7, 131.1, 130.0, 129.8, 129.5, 129.4, 128.8, 128.6, 128.0, 127.9, 127.1, 113.9, 86.9, 79.3, 71.8, 65.7, 65.0, 55.4, 34.9, 27.0, 19.4.

(4E)(2S)-(4-methoxybenzyloxy)-6-(triphenylmethyloxy)hex-4-en-1-ol:

To a solution of 100 mg of **18** (0.137 mmols) in 1.4 mL of THF was added 0.164 mL of tetrabutylammonium fluoride (0.164 mmol) as a 1 M solution in THF via syringe. The reaction was maintained for 2 h at ambient temperature, then added directly to a silica gel column and eluted with 30% EtOAc/hexanes to afford 67 mg (99%) of the title alcohol as a colorless oil. $[\alpha]_{\text{D}} = 8.0$ (0.8, CHCl_3); IR (thin film): 3434, 3081, 3061, 3030, 2931, 2867, 1640, 1612, 1513, 1446, 1244, 1172, 1030, 824, 745, 709 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.48 (d, $J = 7.2$ Hz, 6H), 7.35–7.23 (m, 11H), 6.89 (d, $J = 6.6$ Hz, 2H), 5.95–5.65 (m, 2H), 4.57 (dd, $J = 11.1$, 41.0 Hz, 2H), 3.80 (s, 3H), 3.74–3.40 (m, 3H), 2.39 (ddd, $J = 6.5$, 9.8, 13.0 Hz, 2H), 1.95 (m, 1H); ^{13}C NMR (CDCl_3): δ 159.4, 144.3, 130.5, 129.9, 129.6, 128.8, 128.0, 127.6, 127.1, 114.1, 86.9, 79.1, 71.5, 64.8, 64.3, 55.4, 34.2; HRMS calcd for $\text{C}_{33}\text{H}_{34}\text{O}_4$: 493.2373, found 493.2379.

(4E)(2S)-(4-methoxybenzyloxy)-6-(triphenylmethyloxy)hex-4-en-1-al (15): To a solution of 0.133 g of the alcohol (0.19 mmol) in 15 mL of CH₂Cl₂ at ambient temperature was added 0.094 g of Dess-Martin periodinane (0.22 mmol) portionwise. The resulting turbid white mixture was stirred 30 min. Saturated aqueous NaHCO₃ (5 mL) was added and the mixture was extracted with CH₂Cl₂ (3x15 mL). The combined organics were washed with brine (15 mL), dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (20% EtOAc/Hex) to afford 0.124 g (94%) of **15** as a colorless oil. $[\alpha]_D = -8$ (0.8, CHCl₃); IR (thin film): 3550, 3085, 3058, 3032, 2932, 2860, 1732, 1612, 1513, 1490, 1448, 1248, 1174, 1035, 763, 738, 706 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 9.67 (d, $J = 1.9$ Hz, 1H), 7.49 (d, $J = 7.2$ Hz, 6H), 7.42–7.18 (m, 11H), 6.89 (d, $J = 8.5$ Hz, 2H), 5.90–5.71 (m, 2H), 4.62 (dd, $J = 11.3, 21.7$ Hz, 2H), 3.88–3.73 (m, 4H), 3.61 (d, $J = 4.2$ Hz, 2H), 2.51 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 203.5, 144.3, 134.9, 130.8, 129.9, 129.7, 128.8, 128.0, 128.0, 127.3, 127.1, 125.9, 114.1, 87.0, 82.8, 72.4, 64.7, 55.4, 33.6, 29.9. FAB-MS m/z 515 (M+Na)⁺.

(3S)-E-5-Methyl-1-tributylstannanylhexas-1,5-dien-3-ol: To a –78 °C solution of 0.119 g of allyl(-)-icp₂B **20** (0.348 mmol) in 1.5 mL of Et₂O was added 0.100 g of β -tributylstannyl acrolein (0.290 mmol) slowly dropwise. The resulting colorless solution was maintained for 1 h at –78 °C and then slowly warmed to 0 °C. An aqueous solution of 3N NaOH (0.3 mL) and 30% H₂O₂ (0.3 mL) were added, the colorless, biphasic solution was then stirred for 2 h at ambient temperature. The mixture was extracted with Et₂O (3x10 mL). The combined organics were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (2% EtOAc/Hex) to afford 0.112 g (96%) of the homoallylic alcohol as a colorless oil. The enantiomeric purity of this compound was determined using the procedure outlined below. $[\alpha]_D = -9.3$ (c 1.1, CHCl₃); IR (thin film): 3365, 2957, 2926, 2871, 2853, 1460, 1376, 1073, 989, 889 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.12 (dd, $J = 1.1, 19.1$ Hz, 1H), 6.04 (dd, $J = 5.1, 19.1$ Hz, 1H), 4.86 (dd, $J = 1.2, 79.5$ Hz, 1H), 4.24–4.23 (m, 1H), 2.28–2.24 (m, 2H), 1.93 (d, $J = 3.4$ Hz, 1H), 1.80 (s, 3H), 1.55–1.47 (m, 6H), 1.36–1.34 (m, 6H), 0.94–0.89 (m, 14H); ¹³C NMR (75 MHz, CDCl₃): δ 150.1, 142.2, 127.6, 113.6, 72.4, 46.0, 30.0, 27.2, 22.4, 13.6, 9.4; HRMS calcd for C₁₅H₂₉OSn [M-ⁿBu]⁺: 345.1240, found 345.1251.

(3S)-E-Benzoic acid, 3-methyl-1-(2-tributylstannanylviny)but-3-enyl ester (enantiomeric purity assay): To a solution of 0.092 g of the homoallylic alcohol (prepared above; 0.23 mmol) in 0.1 mL pyridine was added 0.03 mL of benzoyl chloride (0.28 mmol) and 0.001 g of DMAP (0.01 mmol) sequentially. The resulting white suspension was maintained for 20 min at ambient temperature. The reaction mixture was quenched with saturated NaHCO₃ (2 mL), and the aqueous layer was extracted with Et₂O (3x6 mL). The combined organics were washed with brine (4 mL), dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (2% EtOAc/Hex) to afford 0.113g (97%) of the title ester as a colorless oil. $[\alpha]_D = -9.2$ (c 7.1, CHCl₃); IR (thin film): 2956, 2926, 2871, 2853, 1721, 1271, 1111, 710 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.11 (d, $J = 8.5$ Hz, 2H), 7.59 (m, 1H), 7.50–7.45 (m, 2H), 6.32 (d, $J = 18.9$ Hz, 1H), 6.07 (dd, $J = 5.5, 19.1$ Hz, 1H), 5.70–5.68 (m, 1H), 4.83 (s, 1H), 2.57–2.48 (m, 2H), 1.84 (s, 1H), 1.53 (m, 6H), 1.33 (m, 7H), 0.91 (m, 14H); ¹³C NMR (75 MHz, CDCl₃): δ 165.7, 145.3, 141.1, 132.7, 130.6, 129.6, 128.3, 113.6, 75.3, 43.1, 29.0, 27.6, 27.2, 22.6, 13.7, 9.4; HRMS calcd for C₂₂H₃₃O₂Sn [M-ⁿBu]⁺: 449.1503, found 449.1484. Separation of the enantiomers by chiral HPLC [Daicel Chiracel[®] OD-H column, flow rate 0.5 mL/min,

0.5% *i*PrOH, 99.5% hexane, Tr: 9.7 min (*R*), 10.8 min (*S*)] provided the enantiomer ratio: 3*S* : 3*R* = 98 : 1 (98 %ee).

((3*S*)-*E*-3-Allyloxy-5-methylhexa-1,5-dienyl)tributylstannane (21**):** To a $-78\text{ }^{\circ}\text{C}$ solution of 0.662 g of the homoallylic alcohol (prepared above; 1.65 mmol) in 10 mL of THF was added 7.90 mL of a 0.5 M toluene solution of KHMDS (1.82 mmol) slowly dropwise. After 15 min, 0.94 mL of allyl bromide (4.95 mmol) was added and the resulting solution was warmed to ambient temperature and maintained for 2h. The reaction was quenched with brine and the aqueous layer was extracted with Et₂O (3x12 mL). The combined organics were dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (2% EtOAc/hexanes) to afford 0.699 g (97%) of **21** as a colorless oil. $[\alpha]_{\text{D}} = -38$ (*c* 2.3, CHCl₃); IR (thin film): 3077, 2957, 2926, 2871, 2852, 1460, 1077, 992, 920, 888 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.10 (d, *J* = 9.5 Hz, 1H), 5.96-5.87 (m, 1H), 5.79 (dd, *J* = 7.2, 19.0 Hz, 1H), 5.25 (dd, *J* = 1.6, 17.1 Hz, 1H), 5.15 (d, *J* = 10.4 Hz, 2H), 4.75 (d, *J* = 10.8 Hz, 1H), 4.06 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.87-3.79 (m, 2H), 2.39 (dd, *J* = 7.1, 13.9 Hz, 1H), 2.21 (dd, *J* = 6.3, 13.9 Hz, 1H), 1.75 (s, 3H), 1.56-1.46 (m, 6H), 1.37-1.25 (m, 7H), 0.96-0.82 (m, 14H); ¹³C NMR (75 MHz, CDCl₃): δ 148.4, 142.2, 135.1, 131.2, 116.5, 112.6, 82.0, 69.1, 44.0, 29.1, 27.2, 22.9, 13.7, 9.4; HRMS calcd for C₁₈H₃₃OSn [M-ⁿBu]⁺: 377.1580, found 377.1597.

Tributyl-[(*E*)-2-((2*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)vinyl]stannane (22**):**

To a 25 $^{\circ}\text{C}$ solution of 0.081 g of freshly prepared Schrock's catalyst (0.11 mmol)³ in 11 mL of degassed toluene was added 0.661 g of **21** (1.5 mmol). After maintaining the reaction at ambient temperature for 25 min, to the resulting dark brown solution was added another portion of 0.081 g of Schrock's catalyst (0.11 mmol). After 30 min, the reaction was exposed to air for 2 h. The reaction mixture was concentrated and the crude product was purified by flash chromatography (0.6% EtOAc/hexanes) to afford 0.465 g (81%) of **22** as a brown oil. $[\alpha]_{\text{D}} = -73$ (*c* 1.1, CHCl₃); IR (thin film): 2957, 2926, 2872, 2851, 1460, 1378, 1123, 988 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.25 (d, *J* = 19.2 Hz, 1H), 6.09 (dd, *J* = 4.8, 19.2 Hz, 1H), 5.43 (s, 1H), 4.22 (s, 2H), 4.00 (m, 1H), 2.10-1.91 (m, 2H), 1.73 (s, 3H), 1.61-1.47 (m, 6H), 1.39-1.27 (m, 6H), 0.94-0.86 (m, 15H); ¹³C NMR (75 MHz, CDCl₃): δ 148.3, 131.5, 128.5, 119.6, 76.4, 65.6, 35.5, 29.0, 27.2, 22.9, 13.6, 9.3; HRMS calcd for C₁₆H₂₉OSn [M-ⁿBu]⁺: 357.1240, found 357.1248.

(2*S*)-2-[(*E*)-2-Iodovinyl]-4-methyl-3,6-dihydro-2*H*-pyran (23**):** To a $-20\text{ }^{\circ}\text{C}$ solution of

0.226 g of **22** (0.55 mmol) in 10 mL of THF was slowly added a solution of 0.123 g of NIS (0.55 mmol) in 0.8 mL of THF dropwise. After stirring 30 min at $-20\text{ }^{\circ}\text{C}$, the resulting yellow solution was poured into brine (6 mL) and the mixture was extracted with Et₂O (3x15 mL). The combined organics was washed with saturated Na₂S₂O₃ (8 mL), dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (10% CH₂Cl₂/pentane) to afford 0.131 g (96%) of **23** as a yellow oil. $[\alpha]_{\text{D}} = -106$ (*c* 0.76, CHCl₃); IR (thin film): 3026, 2963, 2908, 2823, 1381, 1368, 1124, 1059, 1013, 667, 682 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.61 (dd, *J* = 5.5, 14.5 Hz, 1H), 6.39 (dd, *J* = 0.9, 14.6 Hz, 1H), 5.39 (s, 1H), 4.16 (s, 2H), 3.97 (m, 1H), 2.04-1.87 (m, 2H), 1.68 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 145.9, 131.0, 119.7, 78.0, 75.5, 65.6, 35.0, 23.0; HRMS calcd for C₈H₁₁OI: 249.9855, found 249.9860.

³ Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

(1E, 6E)(3S, 4S)-4-(4-Methoxybenzyloxy)-1-[(2S)-4-methyl-3,6-dihydro-2H-pyran-2-yl]-8-trityloxyocta-1,6-dien-3-ol (24): To a 25 °C suspension of 0.173 g of Mg powder (7.1 mmol) in 5 mL of Et₂O was slowly added 0.57 mL of 1,2-dibromoethane (6.7 mmol) in 1.70 mL of benzene dropwise. After the reaction exotherm subsided, the slightly turbid gray solution was stirred for another 30 min and then allowed to stand for 1.5 h without stirring. The molarity of the resulting MgBr₂ is approximately 1.0 M.

To a -78 °C solution of 0.104 g of **23** (0.42 mmol) in 3.5 mL of Et₂O was slowly added 0.60 mL of a 1.39 M pentane solution of ^tBuLi (0.83 mmol) dropwise. After maintaining the resulting pale yellow solution at -78 °C for 1 h, 1.00 mL of the 1.0 M ethereal magnesium bromide (1.0 mmol) solution (prepared above) was added dropwise. The reaction solvent was evaporated under reduced pressure maintaining the reaction solution at -78 °C. The resulting white, solid residue was dissolved by adding 6.0 mL of CH₂Cl₂ cooled to -78 °C via cannula. To the resulting clear, colorless solution was added 0.158 g of **15** (0.33 mmol) in 0.7 mL of CH₂Cl₂ dropwise. After stirring for 20 min at -78 °C, 1.5 mL of water and 2.5 mL of brine were added to quench the reaction. The aqueous layer was extracted with CH₂Cl₂ (3X10 mL). The combined organics was dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (35% EtOAc/Hex) to afford 1.910 g (96%) of **24** as a colorless oil: [α]_D = -32 (*c* 3.0, CHCl₃); IR (thin film): 3436, 3013, 2928, 2856, 1513, 1249, 1216, 1034, 757, 705 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.58-7.56 (m, 6H), 7.38-7.26 (m, 11H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.97-5.78 (m, 4H), 5.48 (s, 1H), 4.65 (dd, *J* = 10.9, 44.7 Hz, 2H), 4.25 (s, 3H), 4.14 (m, 1H), 3.78 (s, 3H), 3.69 (d, *J* = 4.4 Hz, 2H), 3.52 (m, 1H), 2.93 (s, 1H), 2.56 (m, 1H), 2.43 (m, 1H), 2.16 (m, 1H), 2.08 (s, 1H), 1.99 (m, 1H), 1.77 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 159.1, 144.1, 133.1, 131.2, 130.0, 129.7, 129.6, 129.4, 128.4, 127.6, 127.5, 126.8, 119.5, 113.7, 86.6, 81.2, 73.1, 72.1, 65.4, 64.5, 60.2, 55.0, 35.5, 33.4, 22.8, 20.9, 14.0; FAB-MS *m/z* 639 (M+Na)⁺.

tert-Butyl-[(4E)(1S, 2S)-2-(4-methoxy-benzyloxy)-1-[(1E)-2-((2S)-4-methyl-3,6-dihydro-2H-pyran-2-yl)-vinyl]-6-trityloxy-hex-4-enyloxy]dimethylsilane: To a 0 °C solution of 0.682 g of **24** (1.1 mmol) and 0.238 g of imidazole (3.4 mmol) in 5 mL of DMF was added 0.513 g of TBSCl (3.4 mmol). The reaction was warmed to ambient temperature and stirred for 4.5 h. The reaction was quenched by adding 15 mL of saturated NaHCO₃ and 20 mL of EtOAc and the layers were shaken and separated. The aqueous layer was extracted with EtOAc (3X15 mL) and the combined organics were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (10% EtOAc/Hex) to afford 0.799 g (98%) of the silyl ether as a yellow oil. [α]_D = -52 (*c* 2.1, CHCl₃); IR (thin film): 3058, 3005, 2954, 2929, 2855, 1513, 1448, 1249, 1105, 1036, 836, 775, 758, 706, 632 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.65-7.62 (m, 6H), 7.49-7.37 (m, 11H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.05-5.77 (m, 4H), 5.58 (s, 1H), 4.73 (dd, *J* = 11.3, 19.0 Hz, 2H), 4.47 (dd, *J* = 4.6, 4.6 Hz, 1H), 4.30 (s, 2H), 4.20 (m, 1H), 3.90 (s, 3H), 3.71 (d, *J* = 4.9 Hz, 2H), 3.54 (m, 1H), 2.52 (m, 1H), 2.32-2.21 (m, 2H), 2.07 (m, 1H), 1.06 (s, 9H), 0.2 (s, 3H), 0.19 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 159.1, 144.3, 131.6, 131.4, 130.8, 130.2, 129.6, 129.4, 128.6, 127.7, 126.8, 119.7, 113.7, 86.6, 82.1, 73.6, 73.1, 72.5, 65.5, 64.8, 55.2, 35.7, 33.2, 25.9, 25.6, 23.0, 18.1, -4.5, -4.9; FAB-MS *m/z* 753 (M+Na)⁺. Satisfactory high-resolution mass data could not be obtained; copies of the ¹H and ¹³C NMR spectra are provided.

(2E,7E)(5S,6S)-6-(tert-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-8-((2S)-4-methyl-3,6-dihydro-2H-pyran-2-yl)-octa-2,7-dien-1-ol:

To a 0 °C solution of 0.440 g of the silyl ether (prepared above; 0.61 mmol) in 28 mL of nitromethane was slowly added 3.9 mL of formic acid dropwise. The resulting yellow solution was stirred for 20 min whereupon 40 mL of ice-cold saturated NaHCO₃ and 30 mL of EtOAc were added. The layers were separated and the aqueous portion was extracted with EtOAc (3x40 mL). The combined organics were washed with brine (40 mL), dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (35% EtOAc/Hex) to afford 0.250 g (86%) of the title allylic alcohol as a yellow oil. $[\alpha]_D = -83$ (c 4.0, CHCl₃); IR (thin film): 3442, 2999, 2929, 2856, 1513, 1249, 1098, 1037, 972, 836, 777 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.34 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 5.87 (m, 2H), 5.72 (m, 2H), 5.50 (s, 1H), 4.62 (dd, *J* = 11.5, 29.6 Hz, 2H), 4.37 (dd, *J* = 4.5, 4.5 Hz, 1H), 4.26 (s, 2H), 4.13 (s, 3H), 3.89 (s, 3H), 3.44 (m, 1H), 2.37 (m, 1H), 2.16-2.11 (m, 2H), 1.79 (m, 1H), 0.98 (s, 9H), 0.11 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 159.2, 131.5, 131.4, 130.9, 130.8, 130.2, 130.1, 129.5, 119.7, 113.6, 81.8, 73.5, 73.1, 72.3, 65.6, 63.8, 55.3, 35.7, 32.8, 25.9, 23.0, 18.1, -4.5, -4.9; HRMS calcd for C₂₄H₃₅O₅Si [M-^tBu]⁺: 431.2253, found 431.2275.

(2E, 7E)(5S, 6S)-6-(tert-Butyldimethylsilyloxy)-5-(4-methoxy-benzyloxy)-8-((2S)-4-methyl-3,6-dihydro-2H-pyran-2-yl)-octa-2,7-dienal (3):

To a 25 °C solution of 0.117 g of the allylic alcohol (prepared above; 0.16 mmol) in 10 mL of CH₂Cl₂ was added 0.139 g of Dess-Martin periodinane (0.33 mmol) portionwise. The resulting turbid mixture was stirred 30 min then 8 mL of saturated NaHCO₃ solution was added. The mixture was extracted with CH₂Cl₂ (3x15 mL) and the combined organics were washed with brine (15 mL), dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (15% EtOAc/hexanes) to afford 0.117 g (100%) of **3** as a pale yellow oil. $[\alpha]_D = -86$ (c 3.9, CHCl₃); IR (thin film): 2955, 2930, 2887, 2856, 1692, 1513, 1250, 1111, 1036, 837, 778 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 9.55 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 6.2 Hz, 2H), 6.89 (ddd, *J* = 7.3, 7.3, 15.6 Hz, 1H), 6.22 (dd, *J* = 7.9, 15.6 Hz, 1H), 5.96 (t, *J* = 3.0 Hz, 2H), 5.56 (s, 1H), 4.75 (d, *J* = 11.5 Hz, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.32 (m, 1H), 4.19 (m, 1H), 3.95 (s, 3H), 3.26 (m, 1H), 2.68 (dddd, *J* = 0.5, 4.5, 7.5, 16.5 Hz, 1H), 2.48 (dddd, *J* = 0.5, 3.0, 4.0, 16.5 Hz, 1H), 2.19 (m, 1H), 2.04 (m, 1H), 1.84 (br s, 3H), 1.04 (s, 9H), 0.19 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 194.0, 159.4, 156.6, 134.1, 132.2, 131.3, 130.0, 129.7, 129.0, 119.7, 113.8, 80.5, 73.3, 72.4, 65.6, 55.3, 35.7, 33.4, 25.8, 22.9, 18.1, -4.6, -5.0; HRMS calcd for C₂₄H₃₃O₅Si [M-^tBu]⁺: 429.2097, found 429.2077.

4-((2R, 6R)-6-((7E, 12E)(2R, 6S, 10S, 11S)-6,11-Bis-(tert-butyl-dimethylsilyloxy)-10-(4-methoxybenzyloxy)-2-methyl-13-((2S)-4-methyl-3,6-dihydro-2H-pyran-2-yl)-4-oxotrideca-7,12-dienyl)-5,6-dihydro-2H-pyran-2-yl)-but-2-ynoic acid, tert-butyl ester:

To a 0 °C suspension of 0.800 g of (1R,2R)-N,N'-Bis(paranitrobenzenesulfonyl)-1,2-diphenylethylenediamine (1.4 mmol) in 71 mL of 1,2-dichloroethane was slowly added 2.75 mL of a 1.0 M CH₂Cl₂ solution of boron tribromide (2.8 mmol) dropwise. After 5 min, the reaction mixture was warmed to 50 °C and maintained for 8 h. The solvent was evaporated under reduced pressure and the yellow residue was dissolved in 50 mL toluene whereupon the solvent was again evaporated; the process of dissolution

and subsequent evaporation was repeated two more times until the bromo borane reagent **26** was obtained as a white powder.

To a $-78\text{ }^{\circ}\text{C}$ solution of 0.117 g of the boron reagent **26** (0.17 mmol) in 4 mL of CH_2Cl_2 was slowly added 0.056 g of **2** (0.17 mmol) as a solution in 0.5 mL of CH_2Cl_2 . After stirring the resulting colorless solution for 2 h, a solution of 0.072 g of **3** (0.15 mmol) in 0.5 mL of CH_2Cl_2 was added dropwise. After stirring 1 h at $-78\text{ }^{\circ}\text{C}$, 1 mL of MeOH and 5 mL of phosphate buffer (pH 7) were added sequentially. The reaction mixture was allowed to warm to ambient temperature and stirred for 30 min. The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 x 9 mL). The combined organics were dried over MgSO_4 , filtered, and concentrated to provide the crude product mixture containing **27**.

To a $0\text{ }^{\circ}\text{C}$ DMF solution (4 mL) of the resulting yellow residue (**27**) and 0.059 g of imidazole (1.1 mmol) was added 0.126 g of TBSCl (1.0 mmol). The reaction was warmed to ambient temperature and stirred 7 h whereupon 10 mL of saturated NaHCO_3 and 20 mL of CH_2Cl_2 were added. The layers were separated with the aqueous layer being extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine (20 mL), dried over MgSO_4 , filtered, and concentrated. The crude product mixture was purified by flash chromatography (15% EtOAc/Hex) to afford 0.141 g (89%) of the silyl-protected aldol adduct as a yellow oil. Separation of the C_{15} epimers by HPLC [Zorbax column, flow rate 0.3 mL/min, 3.5 % i -PrOH, 96.5% hexane, T_r : 65.2 (15*S*), 67.8 (15*R*)] provided the diastereomer ratio: 15*S* : 15*R* = 9 : 1. $[\alpha]_D = -82$ (c 2.1, CHCl_3); IR (thin film): 2955, 2929, 2856, 2239, 1708, 1253, 1704, 837, 777 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.25 (d, $J = 8.6\text{ Hz}$, 2H), 6.86 (d, $J = 8.6\text{ Hz}$, 2H), 5.93-5.61 (m, 5H), 5.48-5.41 (m, 2H), 4.56-4.435 (m, 3H), 4.39 (br t, 1H), 4.27 (t, $J = 4.3, 4.3\text{ Hz}$, 1H), 4.17 (s, 2H), 4.06-4.00 (m, 1H), 3.79 (s, 3H), 3.79-3.76 (m, 1H), 3.30 (m, 1H), 2.63-2.55 (m, 3H), 2.38-2.28 (m, 6H), 2.03-1.92 (m, 6H), 1.70 (s, 3H), 1.48 (s, 9H), 0.93 (d, $J = 6.1\text{ Hz}$, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.01 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3): δ 208.7, 159.2, 152.7, 134.3, 131.6, 131.5, 130.9, 130.1, 129.5, 128.1, 127.5, 125.9, 119.8, 113.8, 83.2, 82.4, 76.2, 73.6, 72.8, 72.5, 70.2, 70.0, 66.2, 65.7, 55.4, 52.4, 51.5, 42.1, 35.8, 32.7, 30.9, 28.1, 26.0, 25.3, 24.8, 23.1, 19.7, 18.7, 18.3, 18.2, $-4.1, -4.4, -4.8$ (2C); HRMS calcd for $\text{C}_{53}\text{H}_{84}\text{O}_9\text{Si}_2$ $[\text{M}+\text{Na}]^+$: 943.5552, found 943.5579.

Acid alcohol 28: To a $25\text{ }^{\circ}\text{C}$ solution of 0.063 g of the silyl-protected aldol adduct (prepared above; 0.069 mmol) in 12 mL of CH_2Cl_2 and 6 mL of phosphate buffer (pH = 7) was added 0.134 g of DDQ (0.48 mmol) portionwise. After stirring 4 h, the reaction was diluted with CH_2Cl_2 (20 mL). The separated organic layer was washed with saturated NaHCO_3 (2x15 mL) until it was colorless. The combined organic extracts were dried, filtered, and concentrated to give a yellow oil that was dissolved in 8 mL of CH_2Cl_2 . To the resulting yellow solution was cooled to $-50\text{ }^{\circ}\text{C}$ and 0.34 mL of 2,6-di-*tert*-butylpyridine (1.4 mmol) and 0.15 mL of trimethylsilyl trifluoromethanesulfonate (0.7 mmol) were added sequentially. The reaction mixture was warmed to $0\text{ }^{\circ}\text{C}$ and stirred 2.5 h whereupon 2.0 mL of buffer solution (pH = 5) was added at $0\text{ }^{\circ}\text{C}$ and the reaction was stirred vigorously for another 1 h. The separated aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were washed with brine (30 mL), dried over MgSO_4 , filtered, and concentrated. The crude product mixture was purified by flash chromatography (20% EtOAc/Hex to 15% EtOH/EtOAc) to afford 0.050 g (94%) of **28** as a yellow oil. $[\alpha]_D = -70$ (c 2.5, CHCl_3); IR (thin film): 3395, 3035, 2953, 2929, 2852, 2237, 1713, 1470, 1359, 1252, 1091, 837, 778 cm^{-1} ; ^1H NMR (300

MHz, CDCl₃): δ 5.95-5.85 (m, 1H), 5.80-5.46 (m, 5H), 5.42 (br s, 1H), 4.62 (m, 1H), 4.42 (m, 1H), 4.19 (brs, 2H), 4.13-3.95 (m, 3H), 3.74 (m, 1H), 3.55 (m, 1H), 2.80-2.55 (m, 2H), 2.54-2.37 (m, 2H), 2.35-2.20 (m, 2H), 2.13-1.88 (m, 6H), 1.71 (s, 3H), 1.65-1.50 (m, 1H), 1.36-1.20 (m, 2H), 0.95 (d, J = 5.7 Hz, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.04 (brs, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 209.5, 154.8, 135.3, 134.3, 133.6, 131.2, 130.5, 127.4, 126.3, 125.6, 119.5, 86.3, 75.7, 74.5, 73.4, 70.4, 69.4, 66.0, 65.4, 52.3, 50.3, 42.3, 35.4, 35.1, 31.0, 25.9, 24.3, 22.9, 20.0, 18.1, 0.44, -3.9, -4.3, -4.8, -5.0; HRMS calcd for C₄₁H₆₈O₈Si₂ [M+Na]⁺: 767.4370, found 767.4345.

Lactone 29: To a 0 °C solution of 0.0228 g of 4-pyrrolidinopyridine (0.15 mmol) and 0.050 mL of *i*Pr₂NEt (0.30 mmol) in 5.8 mL of toluene was slowly added 0.024 mL of 2,4,6-trichlorobenzoyl chloride (0.15 mmol) dropwise. The resulting pale yellow suspension was stirred for 15 min at 0 °C whereupon a solution of 0.0056 g of **28**

(0.077 mmol) in 2.4 mL of toluene was added over 2 h at 0 °C. The resulting pale yellow suspension was stirred for 16 h at 0 °C. The reaction was quenched by adding 5 mL of brine and the separated aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated. The crude product mixture was purified by flash chromatography (15% EtOAc/Hex) to afford 0.0051 g (93%) of **29** as a yellow oil. [α]_D = -67 (*c* 2.2, CHCl₃); IR (thin film): 3033, 2956, 2929, 2856, 2237, 1713, 1471, 1361, 1250, 1094, 1067, 964, 837 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.91-5.79 (m, 2H), 5.70 (dd, J = 6.0, 15.6 Hz, 1H), 5.65-5.51 (m, 3H), 5.43 (br s, 1H), 4.95 (ddd, J = 2.4, 6.8, 9.3 Hz, 1H), 4.66 (br d, J = 9.0 Hz, 1H), 4.43 (br d, J = 9.0 Hz, 1H), 4.20-4.16 (m, 3H), 4.07 (ddd, J = 3.0, 3.0, 9.1 Hz, 1H), 3.61-3.53 (m, 1H), 2.67 (dd, J = 11.1, 17.6 Hz, 2H), 2.45-2.25 (m, 5H), 2.20-2.02 (m, 4H), 1.72 (s, 3H), 1.95-1.89 (m, 2H), 1.39 (dd, J = 10.1, 12.5 Hz, 1H), 1.14 (dd, J = 7.6, 13.5 Hz, 1H), 1.01 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H), 0.00 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 209.9, 153.2, 137.1, 133.6, 131.3, 128.9, 127.5, 126.7, 123.6, 119.8, 86.7, 73.8, 73.6, 73.2, 71.4, 68.4, 65.9, 65.5, 54.1, 49.8, 41.8, 35.7, 31.6, 26.8, 25.9, 25.8, 23.9, 22.9, 22.6, 21.4, 18.1, 18.0, 14.1, -4.4, -4.4, -4.9, -5.2; ESI-MS: 749.3 (M⁺Na)⁺; HRMS calcd for C₄₁H₆₆O₇Si₂ [M+Na]⁺: 749.4245, found 749.4279.

Keto lactone 30: To a solution of 8.5 mg of **29** (11.7 μ mol) in 3 mL of EtOAc and 3 mL of 1-hexene containing 0.014 mL of quinoline was added 15 mg of Lindlar's catalyst (5% Pd by wt.). The resulting black suspension was subjected to 1 atmosphere H₂ (ballon) (*CAUTION: Dihydrogen gas is extremely flammable.*) and stirred 1 h at ambient temperature. The reaction flask was then purged with N₂ and the

reaction mixture was filtered through Celite and the filtrate was concentrated. The crude product mixture was purified by flash chromatography (2% EtOAc/hexanes) to afford 7.5 mg (88%) of **30** as a clear, colorless oil. [α]_D = -155 (*c* 1.2, CHCl₃); IR (thin film): 2955, 2927, 2855, 1720, 1651, 1419, 1111, 837 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.35 (ddd, J = 4.1, 9.6, 11.4 Hz, 1H), 5.90-5.77 (m, 3H), 5.73-5.49 (m, 4H), 5.43 (br s, 1H), 4.86 (ddd, J = 2.1, 6.0, 11.1 Hz, 1H), 4.59 (ddd, J = 6.0, 6.0, 6.0 Hz, 1H), 4.31 (br d, J = 9.8 Hz, 1H), 4.23-4.19 (m, 3H), 4.06 (ddd, J = 4.4, 9.3 Hz, 1H), 3.79-3.65 (m, 2H), 2.61 (dd, J = 6.2, 16.2 Hz, 1H), 2.46 (dd, J = 6.6, 16.3 Hz, 1H), 2.41-2.31 (m, 2H), 2.25 (dddd, J = 2.6, 2.6, 2.6, 16.6 Hz, 1H), 2.16-2.01 (m, 5H), 1.95-1.85 (m, 2H), 1.72 (s, 3H), 1.51 (dddd, J = 7.7, 7.7, 7.7, 7.7 Hz, 1H), 1.27 (ddd, J = 3.6, 6.1, 9.9 Hz, 1H), 0.91 (d, J = 6.4 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 209.2, 165.3, 148.4, 135.8, 132.9, 131.3, 129.0, 128.8, 125.7, 124.9, 121.4, 119.8, 75.1, 73.3, 73.2,

73.0, 68.6, 66.9, 65.5, 51.8, 51.3, 42.5, 35.7, 33.6, 31.6, 31.3, 28.7, 25.8, 25.7, 22.9, 21.0, 18.1, 18.0, –4.5 (2C), –4.9, –5.0; HRMS calcd for $C_{41}H_{68}O_7Si_2$ $[M+K]^+$: 767.4141, found 767.4158.

Protected desepoxylaualimalide 31: To a suspension of 0.365 g of zinc (5.58 mmol) and 0.025 g of lead (II) iodide (0.054 mmol) in THF (5 mL) was added 0.250 mL of CH_2I_2 (3.10 mmol). The resulting pale yellow suspension was maintained for 30 min at ambient temperature then cooled to 0 °C. To the 0 °C suspension was added 0.25 mL of a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (0.25 mmol) and the resulting dark

brown suspension was warmed to ambient temperature and maintained for an additional 30 min. The resulting brown suspension was drawn into a syringe and added in portions to a 0 °C solution of 10.8 mg of **30** (14.8 μ mol) in THF (1 mL); the reaction was monitored by TLC immediately after each portionwise addition and addition was continued until the starting ketone was completely consumed. A 1:1 mixture of saturated aqueous $NaHCO_3$ and brine was added to the reaction mixture and the resulting mixture was diluted with Et_2O . The aqueous and organic layers were separated with the aqueous portion being extracted with Et_2O (3 $\times$ 10 mL). The combined organics were washed with brine, dried over $NaSO_4$, filtered, and concentrated. Purifying the crude product mixture by flash chromatography (5% $EtOAc$ /hexanes) afforded 9.1 mg (85%) of **31** as a clear, colorless oil. $[\alpha]_D = -118$ (c 1.4, $CHCl_3$); IR (thin film): 2955, 2928, 2856, 1723, 1074, 836, 776 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 6.32 (ddd, $J = 4.8, 9.8, 10.2$ Hz, 1H), 5.91-5.82 (m, 2H), 5.80-5.67 (m, 3H), 5.53-5.49 (m, 2H), 5.43 (br s, 1H), 4.89 (ddd, $J = 2.4, 6.1, 10.4$ Hz, 1H), 4.77 (br s, 1H), 4.75 (br s, 1H), 4.30-4.15 (m, 5H), 4.06 (ddd, $J = 4.3, 4.3, 9.2$ Hz, 1H), 3.80 (m, 1H), 3.68 (ddd, $J = 10.0, 10.0, 15.2$ Hz, 1H), 2.37-2.22 (m, 3H), 2.19-2.02 (m, 6H), 1.94-1.82 (m, 3H), 1.71 (s, 3H), 1.62-1.54 (m, 1H), 1.17 (ddd, $J = 4.9, 6.8, 12.0$ Hz, 1H), 0.88 (br s, 21H), 0.07 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 147.0, 144.7, 136.3, 132.8, 131.3, 129.0, 128.6, 125.3, 124.9, 121.6, 119.7, 113.4, 75.6, 73.3, 73.1, 72.2, 72.1, 67.0, 65.5, 45.0, 44.7, 43.1, 35.7, 33.8, 31.6, 31.4, 28.8, 25.9, 25.7, 22.9, 20.3, 18.2, 18.0, –4.3, –4.5, –4.8, –4.9; HRMS calcd for $C_{42}H_{70}O_6Si_2$ $[M+Na]^+$: 749.4609, found 749.4586.

Desepoxylaualimalide: To a 0 °C solution of 13 mg of silyl ether **31** (17.9 μ mol) in THF (2 mL) was added 1.0 mL of HF -pyridine complex dropwise via syringe. The reaction was maintained for 1 h at ambient temperature, then poured into a 0 °C mixture of saturated aqueous $NaHCO_3$ (50 mL) and $EtOAc$ (30 mL). The layers were separated and the aqueous portion was extracted with $EtOAc$ (3 $\times$ 20 mL). The

combined organics were washed with brine, dried over $NaSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (40% $EtOAc$ /hexanes) to obtain 8.0 mg (90%) of desepoxy-laualimalide as a pale yellow oil. $[\alpha]_D = -171$ (c 0.7, $CHCl_3$); IR (thin film): 3415, 2924, 2853, 1720, 1415, 1165 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 6.36 (ddd, $J = 5.3, 9.9, 11.4$ Hz, 1H), 5.94-5.82 (m, 3H), 5.79-5.69 (m, 2H), 5.64-5.61 (m, 2H), 5.42 (brs, 1H), 5.00 (app q, $J = 6.6$ Hz, 1H), 4.87 (br s, 2H), 4.23-4.12 (m, 5H), 4.05 (ddd, $J = 4.4, 4.4, 9.1$ Hz, 1H), 3.92-3.84 (m, 1H), 3.56 (dddd, $J = 1.3, 8.0, 9.9, 18$ Hz, 1H), 2.39-2.32 (m, 2H), 2.31-2.22 (m, 2H), 2.20-2.08 (m, 3H), 2.07-1.97 (m, 1H), 1.96-1.84 (m, 3H), 1.83-1.74 (m, 3H), 1.70 (s, 3H), 1.67-1.61 (m, 1H), 1.14 (ddd, $J = 4.0, 7.5, 11.7$ Hz, 1H), 0.87 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 147.3, 144.9, 135.4, 133.9, 131.3, 129.0, 128.3, 126.5, 124.8, 121.2, 119.7, 114.3, 75.3, 73.7, 73.1, 71.3, 69.8, 67.6, 65.6,

44.8, 43.3, 42.3, 35.7, 34.4, 33.6, 30.9, 28.3, 22.9, 19.7; HRMS calcd for $C_{30}H_{42}O_6$ $[M+Na]^+$: 512.2879, found 521.2880.

(-)-Laulimalide (1): To a $-20\text{ }^{\circ}\text{C}$ suspension of 0.130 g of 4 Å molecular sieves in CH_2Cl_2 (4 mL) was added 5 μL of (+)-DIPT (22.5 μmol) followed by 5 μL of titanium tetraisopropoxide (16.1 μmol). The reaction mixture was maintained at $-20\text{ }^{\circ}\text{C}$ for 30 min then treated with 4 μL of a 4.3 M solution of $t\text{BuOOH}$ in toluene (1 equiv, 16 μmol).

The reaction was maintained for an additional 30 min at $-20\text{ }^{\circ}\text{C}$ whereupon a solution of 8 mg of desepoxy-laulimalide (16 μmol) in CH_2Cl_2 (2 mL) was added dropwise via syringe and the reaction was stirred at $-20\text{ }^{\circ}\text{C}$ for 2 h. A mixture of 4N NaOH (0.5 mL) and brine (1.5 mL) was added to the reaction mixture and the resulting mixture was warmed to $0\text{ }^{\circ}\text{C}$ and stirred 90 min. The mixture was extracted with CH_2Cl_2 (3 $\times$ 10 mL) and the combined organic layers were washed with brine and filtered through Celite. The filtrate was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography (25% EtOAc/hexanes) to provide a pale yellow oil that was then triturated with 5% $i\text{PrOH}$ /hexanes to afford 5.5 mg (69%) of (-)-laulimalide (**1**) as a white solid. $[\alpha]_D = -198$ (c 0.1, CHCl_3); IR (thin film): 3423, 3071, 3032, 2917, 2846, 1719, 1642, 1422, 1383, 1213, 1169, 894 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ 6.45 (ddd, $J = 3.8, 10.1, 11.4$ Hz, 1H), 5.94-5.83 (m, 3H), 5.77 (dd, $J = 5.7, 15.7$ Hz, 1H), 5.72-5.69 (m, 2H), 5.43 (br s, 1H), 5.17 (ddd, $J = 1.6, 5.2, 11.2$ Hz, 1H), 4.88 (br s, 1H), 4.86 (br s, 1H), 4.32 (br d, $J = 9.4$ Hz, 1H), 4.24 (ddd, $J = 5.5, 5.5, 5.5$ Hz, 1H), 4.19 (m, 2H), 4.07 (m, 1H), 4.04 (ddd, $J = 4.5, 4.5, 9.7$ Hz, 1H), 3.79-3.72 (m, 2H), 3.08 (ddd, $J = 3.3, 3.3, 9.1$ Hz, 1H), 2.91 (ddd, $J = 2.6, 2.6, 2.6$ Hz, 1H), 2.40-2.37 (m, 2H), 2.22 (dddd, $J = 2.7, 2.7, 2.7, 16.8$ Hz, 1H), 2.13 (brd, $J = 15.3$ Hz, 1H), 2.07-1.85 (m, 7H), 1.79 (dd, $J = 10.0, 12.8$ Hz, 1H), 1.70 (br s, 3H), 1.54-1.43 (m, 2H), 1.37-1.31 (m, 1H), 0.84 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 166.0, 150.3, 144.8, 133.9, 131.2, 128.7, 128.5, 125.2, 120.5, 119.7, 112.5, 73.4, 73.2, 73.1, 72.3, 67.9, 66.5, 65.6, 60.7, 52.1, 45.5, 43.4, 37.1, 35.6, 33.8, 33.3, 31.6, 29.7, 22.9, 20.7; HRMS calcd for $C_{30}H_{42}O_7$ $[M+Na]^+$: 537.2828, found 537.2816.

Exp-889-c

EXP-901-1

ajk-1auiimalid cdc13 rt 500MHz 1H delay 12sec (in sol 17 hours) 5/29/02

Current Data Parameters

NAME	ajk-1auiimalid
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	5/29/02
Time	9.12
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PULPROG	zg
TD	32768
SOLVENT	CDCl3
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DS	0
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FIDRES	0.22911 Hz
AQ	2.1823988 sec
RG	724.1
DW	66.600 usec
DE	6.00 usec
TE	290.0 K
D1	12.00000000 sec
P1	5.20 usec
DE	6.00 usec
SFO1	500.133008 MHz
NUC1	1H
PL1	0.00 dB

F2 - Processing parameters

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SF	500.130023 MHz
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LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

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F1P	8.500 ppm
F1	4254.10 Hz
F2P	0.150 ppm
F2	75.02 Hz
PPMCM	0.41750 ppm/cm
HZCM	208.80431 Hz/cm