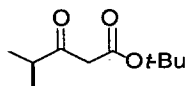
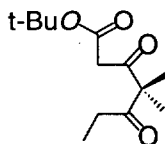


Supplementary Material

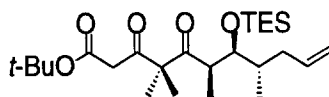


tert-Butyl 4-methyl-3-oxopentanoate. Meldrum's acid (80 g, 555 mmol) was dissolved in 600 mL of CH₂Cl₂ and cooled to 0 °C. Freshly distilled pyridine (87.8 g, 1.11 mol) was added to the CH₂Cl₂ solution and then *iso*-butyryl chloride (65.0 g, 610.5 mmol) was added to the mixture *via* a pressure equalizing addition funnel. The reaction was stirred at 0 °C for 1 hr and then warmed to rt and stirred for 2 hr. Then, the reaction was quenched with water (200 mL) and washed with 0.5 M HCl (x2), water (x1), and brine (x1). The organic layer was dried over MgSO₄ and concentrated *in vacuo*. The crude product was azeotropically dried with benzene (250 mL), and then dissolved in 200 mL of benzene and 200 mL of *tert*-butanol was added. The resultant reaction was heated at reflux for 4 hr. After this period, the volatiles were removed *in vacuo* and the product then distilled on the high vacuum pump (bp 62-63 °C, 0.1 mm Hg). The desired β-keto ester was obtained (58.6 g, 315.5 mmol) in 57% yield as a clear, colorless, light oil with spectral properties identical to the previously prepared compound.¹



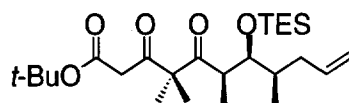
tert-Butyl 4,4-Dimethyl-3,5-dioxoheptanoate (11). *tert*-Butyl 3-oxopentanoate (55.0 g, 295.3 mmol) was added dropwise in 50 mL of dry THF to a slurry of NaH (9.7 g, 60% dispersion in mineral oil, 383.9 mmol) in 1.15 L of dry THF. The reaction mixture was stirred at 0 °C for 30 min and then the cold bath was cooled to -50 °C. Propionyl chloride (27.3 g, 295.3 mmol) was added rapidly (neat) by syringe to the cold solution. The reaction was monitored by TLC and the cold bath was maintained below -30 °C until the reaction was complete. After 1 hr, the reaction was quenched by pouring into a solution of saturated aqueous NH₄Cl and subjected to an aqueous workup. The aqueous layer was extracted with Et₂O (x2, 200 mL). Flash column chromatography with 2% EtOAc/hexanes

afforded the desired tricarbonyl **11** (50.7 g, 209.6 mmol) in 71% yield; (a 4:1 mixture of keto:enol tautomers) ^1H NMR (400 MHz, CDCl_3): δ 12.43 (s, 0.2H), 5.07 (s, 0.2H), 3.36 (s, 1.6H), 2.47 (q, $J = 7.13$ Hz, 2H), 1.44 (s, 9H), 1.35 (s, 6H), 1.03 (t, $J = 7.18$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 209.7, 202.9, 166.1, 81.91, 62.53, 43.34, 31.67, 27.82 (3), 21.03 (2), 7.82; IR (neat) 3411.8, 1742.6, 1718.5, 1702.0, 1644.2, 1460.6, 1156.1 cm^{-1} ; HR- $\text{CI}(\text{CH}_4)$ calcd for $\text{C}_{13}\text{H}_{23}\text{O}_4$: 243.1596 $[\text{M}+\text{H}]^+$; found: 243.1585 $[\text{M}+\text{H}]^+$.

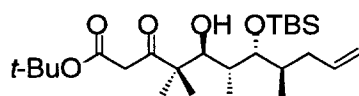


tert-Butyl (6R*,7S*,8S*)-3,5-dioxo-4,4,6,8-tetramethyl-7-(triethylsilyloxy)-10-undecenoate (15b, major). Tricarbonyl **11** (119 mg, 0.49 mmol) in 15 mL of dry THF was cooled to 0 °C, and then LDA (0.69 mL of a 2.0 M solution in THF, 2.8 equiv) was added dropwise to the cooled solution. The reaction mixture was removed from the ice bath and warmed to rt and stirred for 0.5 h. After this period of time, the reaction mixture was placed in a -50 °C cold bath and stirred for 5-10 min and then the aldehyde **13a** (0.26 g, 0.51 mmol) was added rapidly in one portion. The reaction was quenched after 10 min with saturated aqueous NH_4Cl , subjected to an aqueous workup, and dried over MgSO_4 . The crude product was azeotropically dried, x3, with benzene and then subjected directly to the following reaction conditions: The crude product was dissolved in 10 mL of dry DMF and treated successively with TESCl (0.46 g, 3.1 mmol) and imidazole (0.42 g, 6.18 mmol). The resultant reaction mixture was stirred at ambient temperature for 24 h and then quenched with water and subjected to an aqueous workup. Flash column chromatography with 20:1 hexanes:EtOAc afforded the desired tricarbonyl as a 3-4:1 mixture of diastereomeric products **15b/16b** in ca. 60% yield that were not separable by chromatography; ^1H NMR (400 MHz, CDCl_3): δ 5.68 (m, 1H), 4.96 (m, 2H), 3.86-3.76 (m, 1H), 3.39 (s, 1H), 3.16-2.99 (m, 1H), 2.20-2.07 (m, 1H), 1.90-1.69 (m, 1H), 1.48 (s, 6H), 1.43 (s, 9H), 1.29 (m, 1.5H), 1.06 (m, 0.5H), 0.95 (t, $J = 7.98$ Hz, 6H), 0.88 (d, $J = 6.82$ Hz, 2.5H), 0.83 (d, $J = 6.82$ Hz, 2.5H), 0.79 (d, $J = 6.81$ Hz, 0.5H), 0.74 (d, $J = 6.78$ Hz, 0.5H), 0.63 (m, 9H); ^{13}C

NMR (100 MHz, CDCl₃): δ 212.98, 212.74, 202.39, 202.31, 178.46, 172.60, 166.19, 137.85, 137.56, 137.51, 115.87, 115.78, 115.53, 90.59, 81.80, 81.40, 77.44, 76.29, 63.28, 54.19, 46.68, 45.85, 45.35, 45.06, 39.06, 37.91, 37.69, 35.34, 28.19, 37.69, 22.65, 22.40, 21.73, 61.69, 21.59, 21.54, 17.36, 17.10, 15.98, 15.70, 15.34, 13.15, 7.04, 7.01, 5.49, 5.39.

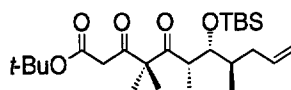


tert-Butyl (6R*,7S*,8R*)-3,5-dioxo-4,4,6,8-tetramethyl-7-(triethylsilyloxy)-10-undecenoate (16b, minor). ¹H NMR (400 MHz, CDCl₃): δ 5.67 (m, 1H), 5.18 (s, 1H), 4.92 (m, 2H), 3.79 (dd, *J* = 7.57, 1.76 Hz, 0.5H), 3.72 (dd, *J* = 6.11, 3.13 Hz, 0.5H), 3.09 (m, 1H), 2.22 (m, 0.5H), 2.09 (m, 0.5H), 1.83 (m, 0.5H), 1.70 (m, 0.5H), 1.43 (s, 9H), 1.23 (s, 6H), 1.05 (m, 2H), 0.94 (m, 9H), 0.84 (d, *J* = 6.78 Hz, 1.5H), 0.75 (m, 4.5H), 0.62 (m, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 213.48, 168.31, 167.69, 164.84, 137.98, 137.70, 115.63, 115.52, 99.34, 99.12, 79.02, 77.85, 56.46, 56.37, 45.15, 44.69, 39.36, 37.92, 37.65, 35.47, 29.69, 28.28, 23.34, 23.26, 23.01, 22.85, 22.69, 17.35, 16.81, 15.82, 13.10, 7.11, 6.98, 5.99, 5.55, 5.44, 5.20.

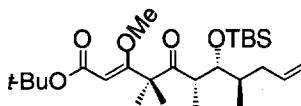


tert-Butyl (5R,6R,7R,8R)-7-(tert-butyldimethylsilyloxy)-5-hydroxy-3-oxo-4,4,6,8-tetramethyl-10-undecenoate (18). The previously described C-5 alcohol, **17**, was treated with the Dess Martin reagent according to the general procedure outlined for the preparation of **19** (below) and then subjected directly to the following conditions. The TPS ether (0.22 g, 0.32 mmol), was treated with buffered HF-pyridine (6 mL of a solution prepared from 4.2 g HF-pyridine, 11.4 mL pyridine, and 20 mL of THF) at ambient temperature for 2 h. Then the reaction mixture was poured into excess saturated aqueous NaHCO₃ and extracted with Et₂O. The organic layer was washed with saturated CuSO₄, saturated aqueous NaHCO₃, dried over Na₂SO₄, and concentrated *in vacuo*. Flash column chromatography with 15% EtOAc/hexanes afforded the desired C-7 alcohol **18** (0.146 g, 0.32

mmol) in 79% isolated yield (2 steps); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.76 (m, 1H), 5.01 (m, 2H), 4.01 (m, 1H), 3.62 (m, 1H), 3.46 (m, 1H), 2.50 (m, 2H), 1.84 (m, 2H), 1.74 (m, 1H), 1.55 (s, 1H), 1.43 (s, 9H), 1.2 (d, 3H), 1.18 (s, 3H), 1.16 (s, 3H), 0.93 (s, 9H), 0.81 (d, 3H), 0.10 (s, 3H), 0.12 (s, 3H).

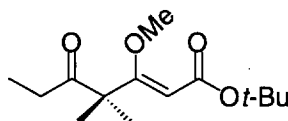


tert-Butyl (6R,7R,8R)-7-(tert-butyldimethylsilyloxy)-3,5-dioxo-4,4,6,8-tetramethyl-10-undecenoate (19). The C-7 alcohol, **18** (0.146 g, 0.32 mmol), was dissolved in 10 mL of dry CH_2Cl_2 and treated with the Dess Martin reagent (0.42 g, 0.96 mmol) at 0 °C for 1 h and then at ambient temperature for 1 h. The reaction mixture was quenched with a 1:1 mixture of $\text{NaHCO}_3:\text{Na}_2\text{S}_2\text{O}_3$. An aqueous workup followed by flash column chromatography with 2-3% EtOAc/hexanes afforded the desired tricarbonyl (0.13 g, 0.28 mol) in 88% yield; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.71 (m, 1H), 5.14 (s, 0.33H), 4.95 (m, 2H), 3.82 (m, 1H), 3.41 (s, 0.67H), 3.15 (m, 1H), 2.21 (m, 1H), 1.80 (m, 1H), 1.54 (s, 2H), 1.50 (s, 3H), 1.45 (s, 9H), 1.31 (m, 3H), 1.06 (m, 3H), 0.91 (s, 9H), 0.86 (d, $J = 6.91$ Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H).



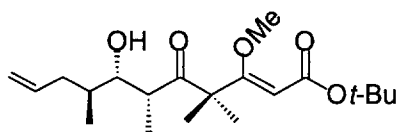
tert-Butyl (6R,7R,8R)-7-(tert-butyldimethylsilyloxy)-3-methoxy-5-oxo-4,4,6,8-tetramethyl-2,10-undecadienoate (20). Tricarbonyl **19** (22.2 mg, 0.049 mmol) was dissolved in acetone and treated with dimethylsulfate (50 μL) at reflux for 2 h. Then the reaction was cooled to ambient temperature and filtered through a short plug of Celite. The reaction mixture was concentrated *in vacuo* and subjected to flash column chromatography with 1-2% EtOAc/hexanes to afford the desired methyl enol ether, **20**. The $^1\text{H NMR}$ of this compound prepared from intermediates in a previously reported synthesis of epothilone B in these laboratories² was identical to the $^1\text{H NMR}$ spectrum of material prepared from an independent synthesis of **20** *via* the aldol reaction of **13a** and **21a** after

protection of the C-7 hydroxyl group as the TBS ether; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.73 (m, 1H), 5.20 (s, 1H), 4.98 (m, 2H), 3.88 (s, 3H), 3.79 (dd, $J = 2.88, 6.10$ Hz, 1H), 3.09 (m, 1H), 2.22 (m, 1H), 1.78 (m, 1H), 1.29 (s, 3H), 1.27 (s, 3H), 1.06 (d, $J = 6.98$ Hz, 3H), 0.91 (s, 9H), 0.89 (d, $J = 6.91$ Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H).



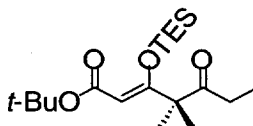
***tert*-Butyl-4,4-dimethyl-3-methoxy-5-oxo-2-heptenoate (21a).**

Trimethylsilyldiazomethane (TMSCHN_2 , 46.2 mL of a 2.0 M solution in THF, 92.4 mmol) was added by syringe to a stirred solution of the tricarbonyl (16.0 g, 66.0 mmol) and diisopropylethylamine (Hunig's base, 16.1 mL, 92.4 mmol) in 330 mL of a 9:1 solution of acetonitrile:methanol at rt. The resultant reaction mixture was stirred at rt for 18-20 hr. After this period of time, the reaction mixture was quenched with saturated aqueous NaHCO_3 and the enol ether extracted with Et_2O (x3, 50 mL). The combined organic layers were washed with brine and then dried over MgSO_4 , filtered and concentrated *in vacuo*. Flash column chromatography of the crude product (2% EtOAc /hexanes) afforded the desired enol ether **21a** (12.5 g, 48.4 mmol) in 74% yield; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.18 (s, 1H), 3.88 (s, 3H), 2.45 (q, $J = 7.33$ Hz, 2H), 1.48 (s, 9H), 1.25 (s, 6H), 1.02 (t, $J = 7.21$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 211.0, 173.1, 164.8, 96.94, 79.77, 62.17, 54.82, 30.46, 28.01, 22.83, 8.03; HR-Cl (CH_4) calcd for $\text{C}_{14}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}]^+$: 257.1753; found: 257.1749 $[\text{M}+\text{H}]^+$.



(6*R*,7*R*,8*S*)-7-Hydroxy-5-oxo-4,4,6,8-tetramethyl-3-methoxy-2,10-undecadieno-ate, *tert*-butyl ester (22a). The keto enol ether **21a** (8.0 g, 31.3 mmol) in 750 mL of dry THF was cooled to -30 °C in a cold bath ($\text{CO}_2(\text{s})/\text{CH}_3\text{CN}$) and then a solution of LDA (37.5 mmol, 0.90 M in THF) was added dropwise via syringe over 10 min. The reaction mixture was stirred at -30 to -33 °C for 20 min. Then the reaction vessel was placed in a -120 °C cold bath ($\text{N}_2(\text{liq})/\text{pentane}$)

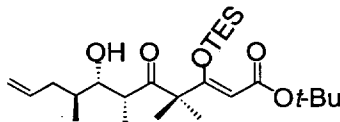
and the reaction mixture was stirred for 10 min. Finally, the aldehyde **13a**²³ (3.6 g, 36.7 mmol) was added via syringe in 5 mL of CH₂Cl₂. The reaction was complete after 10 min and was quenched by pouring into a solution of saturated aqueous NH₄Cl. The desired aldol product **22a** (5.2 g, 14.7 mmol) was isolated in 47% yield (yield of the major product of a 5.5:1 mixture of diastereomers, epimeric at C-8) after flash column chromatography with 6-8% EtOAc/hexanes; (major diastereomer, high R_f): ¹H NMR (400 MHz, CDCl₃): δ 5.78 (m, 1H), 5.18 (s, 1H), 4.98 (m, 2H), 3.90 (s, 3H), 3.37 (m, 1H), 3.35 (s, 1H), 3.35 (s, 1H), 3.12 (q, *J* = 7.74 Hz, 1H), 2.53 (m, 1H), 1.87 (dt, *J* = 13.8, 8.47 Hz, 1H), 1.61 (m, 1H), 1.55 (s, 1H), 1.48 (s, 9H), 1.28 (s, 3H), 1.27 (s, 3H), 1.05 (d, *J* = 6.91 Hz, 3H), .079 (d, *J* = 6.76 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): 217.7, 171.2, 164.8, 137.0, 116.3, 97.29, 80.22, 74.67, 62.17, 56.05, 41.05, 37.31, 34.99, 28.13, 22.69, 22.67, 15.00, 10.44.; (minor diastereomer, low R_f): ¹H NMR (400 MHz, CDCl₃): δ 5.76 (m, 1H), 5.19 (s, 1H), 5.06 (m, 2H), 1.48 (s, 3H), 3.41 (m, 1H), 3.17 (m, 1H), 3.12 (m, 1H), 2.11 (m, 1H), 1.86 (m, 1H), 1.63 (m, 1H), 1.48 (s, 9H), 1.28 (s, 3H), 1.27 (s, 3H), 1.07 (s, *J* = 6.91 Hz, 3H), 0.99 (d, *J* = 6.64 Hz, 3H); HR-FAB calcd for C₂₀H₃₄O₅Na: 377.2304 [M+Na]⁺; found: 377.2305 [M+Na]⁺.



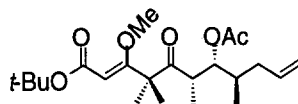
***tert*-Butyl-4,4-dimethyl-3-(trimethylsilyloxy)-5-oxo-2-heptenoate (21b).**

Tricarbonyl **11** (5.0 g, 60.7 mmol) was dissolved in 20 mL of dry THF and added slowly dropwise via syringe to a 0 °C cooled solution of NaH (0.99 g, 60% dispersion in mineral oil, 24.8 mmol) in 50 mL of dry THF. The resultant slurry was stirred at 0 °C for 30 min, then cooled to -50 °C, and finally TESOTf (6.6 g, 25.0 mmol) was added rapidly in one portion. The reaction mixture was stirred at -50 °C for 0.5 h and then quenched with saturated aqueous NaHCO₃. An aqueous workup followed by flash column chromatography with 2% EtOAc/hexanes afforded the desired TES enol ether (5.33 g, 15.0 mmol) in 73% yield; ¹H NMR (400 MHz, CDCl₃): δ 5.16 (s, 1H), 2.48 (q, *J* = 7.24 Hz, 2H), 1.45 (s, 9H), 1.24 (s, 6H), 1.02 (t, *J* = 7.24 Hz, 3H), 0.95 (t, *J* = 8.13 Hz, 9H), 0.74 (q, *J* = 8.13 Hz, 6H);

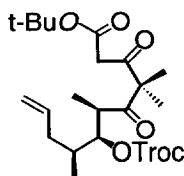
^{13}C NMR (100 MHz, CDCl_3): δ 211.17, 169.43, 165.06, 97.77, 78.93, 55.54, 30.33, 28.21, 22.94, 8.15, 6.78, 6.02; IR (neat) 1712, 1619, 1384, 1243, 1150 cm^{-1} .



tert-Butyl (6R,7R,8S)-7-hydroxy-5-oxo-4,4,6,8-tetramethyl-3-triethylsilyloxy-2,10-undecadienoate (22b). The keto enol ether **21b** (7.80 g, 22.0 mmol) in 175 mL of dry THF was cooled to $-30\text{ }^\circ\text{C}$ in a cold bath ($\text{CO}_2(\text{s})/\text{CH}_3\text{CN}$) and then, a cooled solution of LDA (27.2 mmol, 0.90 M in THF) was added dropwise via syringe over 5 min. Immediately after the addition of the keto enol ether, the reaction vessel was placed in a $-120\text{ }^\circ\text{C}$ cold bath ($\text{N}_2(\text{liq})/\text{pentane}$) and the reaction mixture was stirred for 10 min. Then, the aldehyde **13a** (2.0 g, 20.0 mmol) was added via syringe in 1 mL of dry THF. The reaction was complete after 30 min and was quenched by pouring into a solution of saturated aqueous NaHCO_3 . The desired aldol product **22b** (6.0 g, 13.2 mmol) was isolated in 60% yield (yield of the major product of a 5.5:1 mixture of diastereomers, epimeric at C-8) after flash column chromatography with 6-8% $\text{Et}_2\text{O}/\text{hexanes}$; (major diastereomer, higher R_f): ^1H NMR (400 MHz, CDCl_3): δ 5.78 (m, 1H), 5.22 (m, 1H), 5.05 (m, 2H), 3.37 (m, 2H), 3.18 (q, $J = 7.08$ Hz, 1H), 2.52 (m, 1H), 1.85 (dt, $J = 14.0, 8.37$ Hz, 1H), 1.62 (m, 1H), 1.55 (s, 3H), 1.46 (s, 9H), 1.22 (s, 3H), 1.25 (s, 3H), 1.04 (d, $J = 6.90$ Hz, 3H), 0.95 (t, $J = 7.94$ Hz, 6H), 0.76 (q, $J = 8.26$ Hz, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 217.8, 168.1, 164.6, 137.1, 116.2, 99.03, 79.21, 74.82, 56.74, 40.65, 37.39, 35.06, 28.24, 22.53, 22.29, 14.77, 10.54, 6.95, 6.04; (minor diastereomer, lower R_f) ^1H NMR (400 MHz, CDCl_3): δ 5.73 (m, 1H), 5.23 (s, 1H), 5.02 (m, 2H), 3.43 (d, $J = 8.74$ Hz, 1H), 3.21 (m, 2H), 2.06 (m, 1H), 1.84 (m, 1H), 1.62 (m, 1H), 1.55 (s, 3H), 1.46 (s, 9H), 1.27 (s, 3H), 1.24 (s, 3H), 1.06 (d, $J = 6.91$ Hz, 3H), 0.96 (t, $J = 8.06$ Hz, 9H), 0.77 (q, $J = 7.53$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 217.8, 168.5, 165.0, 136.8, 116.8, 99.46, 79.62, 75.47, 57.17, 41.43, 37.86, 35.58, 30.70, 28.66, 28.31, 22.90, 22.74, 16.53, 11.77, 7.37, 6.44.



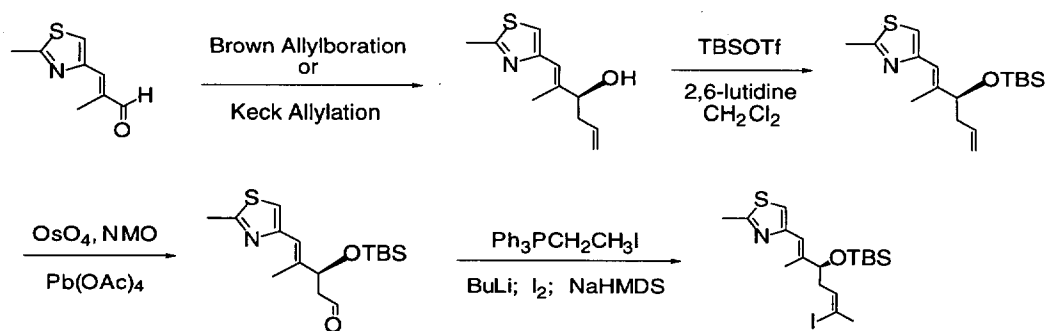
tert-Butyl (6R,7R,8S)-7-acetoxy-5-oxo-4,4,6,8-tetramethyl-3-methoxy-2,10-undecadienoate (23a). The C-7 alcohol **22a** (35 mg, 0.10 mmol) was dissolved in 5 mL of dry CH₂Cl₂ and treated successively with Ac₂O (20 mg, 0.20 mmol), Et₃N (40 mg, 0.40 mmol), and catalytic DMAP. The resultant reaction mixture was stirred at ambient temperature for 18 h and then quenched with 0.1N HCl and subjected to an aqueous workup. The resultant crude product was subjected to flash column chromatography with 1-2% EtOAc/hexanes to afford the desired C-7 acetate **23a** in 98% yield. The proton NMR spectrum of **23a** prepared from the aldol reaction of **21b** and **13a** was identical to the ¹H NMR spectrum obtained from the aldol reaction of tricarbonyl **11** and aldehyde **13a** thus providing a self-consistent proof of the stereochemistry of these compounds, see Scheme 4; ¹H NMR (400 MHz, CDCl₃): δ 5.69 (m, 1H), 5.20 (s, 1H), 4.97 (m, 2H), 3.70 (s, 3H), 3.19 (m, 1H), 2.16 (m, 1H), 2.07 (s, 3H), 1.64 (m, 2H), 1.55 (s, 1H), 1.48 (s, 9H), 1.33 (s, 3H), 1.24 (s, 3H), 1.04 (d, *J* = 6.76 Hz, 3H), .088 (d, *J* = 6.52 Hz, 3H).



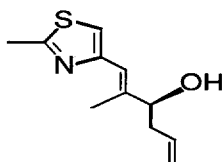
Synthesis of the tricarbonyl, 30, using TES protecting group at C3. (6R,7R,8S)-7-Trichloroethoxyethylcarbonate-3,5-dioxo-4,4,6,8-tetramethyl-10-undecenoate, tert-butyl ester (30). The alcohol, **22b**, (1.61 g, 3.55 mmol) was dissolved in 20 mL of dry CH₂Cl₂ and cooled to 0 °C in an ice bath. Then, pyridine (1.12 g, 14.2 mmol) and trichloroethoxyethylcarbonyl chloride (TrocCl) (1.50 g, 7.10 mmol) were added via syringe in that order. The reaction was stirred at 0 °C for 5 min and then the ice bath was removed and the reaction was allowed to come to rt and stir for 30 minutes. After this period of time, TLC analysis showed the complete consumption of the starting material. The reaction mixture was cooled to 0 °C and the TES enol ether was hydrolyzed by the addition of 20 mL of 0.5 M methanolic HCl. The reaction mixture was

stirred for 5 min at 0 °C and then quenched by pouring into a solution of saturated aqueous NaHCO₃. The desired tricarbonyl, **30** (1.54 g, 3.01 mmol), was isolated after an aqueous workup and flash column chromatography with 7-9% Et₂O/hexanes; ¹H NMR (400 MHz, CDCl₃): δ 12.63 (s, 0.25H), 5.70 (m, 1H), 5.15 (s, 0.25H), 5.08-4.88 (m, 2H), 4.91 (dd, *J* = 6.60, 5.01 Hz, 0.30H), 4.78 (m, 1H), 4.77 (dd, *J* = 7.86, 3.58 Hz, 0.70H), 4.72 (dd, *J* = 11.8, 9.66 Hz, 1H), 3.48 (d, *J* = 16.2 Hz, 0.75H), 3.42 (d, *J* = 16.2 Hz, 0.75H), 3.36 (m, 0.30H), 3.30 (m, 0.70H), 1.88 (m, 2H), 1.50 (s, 3H), 1.46 (s, 9H), 1.39 (s, 3H), 1.12 (d, *J* = 6.88 Hz, 0.70H), 1.10 (d, *J* = 6.88 Hz, 1.3H), 0.93 (d, *J* = 6.63 Hz, 1.3H), 0.88 (d, *J* = 6.86 Hz, 0.70H); ¹³C NMR (100 MHz, CDCl₃): δ 210.5, 209.5, 203.16, 178.3, 172.6, 166.2, 154.1, 135.9, 135.6, 117.2, 116.9, 94.69, 94.56, 90.69, 82.68, 81.98, 81.65, 81.53, 63.58, 54.34, 46.56, 41.99, 41.62, 36.41, 35.84, 34.49, 34.44, 31.56, 28.23 (3), 27.94 (3), 22.62, 22.08, 21.56, 20.80, 15.95, 15.58, 14.09, 13.02, 12.98, 11.35; IR (neat) 1757.9, 1718.9, 1700.2, 1642.2, 1620.7, 1250.6, 1156.3 cm⁻¹.

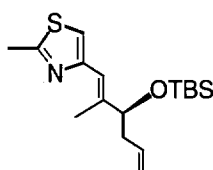
The vinyl iodide used in the new synthesis of dEpoB was prepared according to the previously reported synthesis as outlined in Scheme 1 (below):



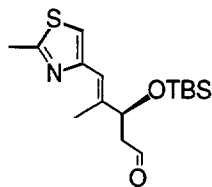
Scheme 1. Preparation of vinyl iodide moiety.



(1E,3S)-1-(2-Methylthiazoyl)-2-methyl-hexa-1,5-dien-1-ol.³ A mixture of (*S*)-(-)-1,1'-bi-2-naphthol (1.37 g, 4.8 mmol), Ti(O-*i*-Pr)₄ (1.36 g, 4.8 mmol), and 4 Å sieves (11 g) in CH₂Cl₂ (300 mL) was heated at reflux for 1 h. The mixture was cooled to rt and aldehyde **52**⁴ (8.0 g, 47.9 mmol) was added. After 10 min, the suspension was cooled to -78 °C, and allyl tri-*n*-butyltin (20.9 g, 67.1 mmol) was added. The reaction mixture was stirred for 10 min at -78 °C and then placed in a -20 °C freezer for 70 h. Saturated aqueous NaHCO₃ solution (2 mL) was added, and the mixture was stirred for 1 h, poured over Na₂SO₄, and then filtered through a pad of MgSO₄ and celite. The crude material was purified by flash chromatography with EtOAc/hexanes (5%-->10%-->15%-->20%-->25%-->30%, two column volumes each) to give the desired alcohol as a yellow oil (6.0 g, 88.0 mmol) in 60% yield; [α]_D = -15.9 (c 4.9, CHCl₃); IR (film) 3360, 1641, 1509, 1434, 1188, 1017, 914 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 6.92 (s, 1 H), 6.55 (s, 1 H), 5.82 (m, 1 H), 5.13 (dd, *J* = 17.1, 1.3 Hz, 1 H), 5.09 (d, *J* = 10.2 Hz, 1 H), 4.21 (t, *J* = 6.0 Hz, 1 H), 2.76 (br s, 1 H), 2.69 (s, 3 H), 2.40 (m, 2 H), 2.02 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃): δ 164.5, 152.6, 141.5, 134.6, 119.2, 117.6, 115.3, 76.4, 39.9, 19.0, 14.2; HRMS calcd. for C₁₁H₁₅NOS: 209.0874; found: 209.0872 (M+H).

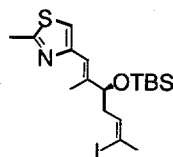


(1E,3S)-1-(2-Methylthiazoyl)-2-methyl-3-(tert-butyldimethylsilyl)-hexa-1,5-diene. **General Procedure for the TBS protection of alcohols.** (1E,3S)-1-(2-Methylthiazoyl)-2-methyl-hexa-1,5-dien-1-ol (5.70 g, 27.3 mmol) was dissolved in 50 mL of dry CH₂Cl₂ and cooled to -78 °C. Then, 2,6-lutidine (7.6 g, 70.9 mmol) and TBSOTf (9.36 g, 35.4 mmol) were added *via* syringe successively and in that order. The reaction mixture was stirred at this temperature for 30 minutes and then quenched by pouring the reaction mixture into saturated aqueous NaHCO₃. An aqueous workup followed by flash column chromatography with 2% EtOAc/hexanes afforded the previously characterized TBS ether (7.37 g, 22.8 mmol) in 84% yield.⁴



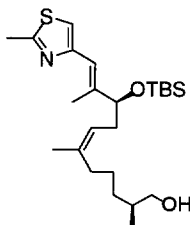
(3S,4E)5-(2-Methylthiazoyl)-2-methyl-3-(tert-butyldimethylsilyloxy)-4-pentenal. To a solution (1E,3S)-1-(2-Methylthiazoyl)-2-methyl-3-(tert-butyldimethylsilyl)-hexa-1,5-diene (prepared above) (7.37 g, 22.8 mmol) in acetone (150 mL) at 0 °C was added 6.7 g of a 60% solution of *N*-methyl-morpholine-*N*-oxide (NMO) in water (34.2 mmol), OsO₄ (0.039 M in THF, 6 mL, 0.23 mmol). The resultant mixture was stirred at 0 °C for 2 h and then quenched with saturated aqueous Na₂SO₃ solution (100 mL). The solution was poured into H₂O (100 mL) and extracted with EtOAc (8 x 50 mL). The combined organic layer was dried over MgSO₄, filtered, concentrated, and flashed through a short plug of silica gel to afford (7.8 g, 21.8 mmol) the crude diol in 96% yield.

To a solution of the crude diol⁵ (7.8 g, 21.8 mmol) in 400 mL benzene at 0 °C was added Pb(OAc)₄ (19.4 g, 43.7 mmol) and Na₂CO₃ (9.24 g, 87.2 mmol). The reaction mixture was stirred at 0 °C for 10 min and then rt for 1.5 hr. After this period of time, the reaction mixture was quenched by pouring into brine. The reaction was filtered through Celite and then the resultant aqueous layer was extracted with EtOAc (5 x 50 mL) dried over MgSO₄. Flash column chromatography on silica gel with 20% EtOAc/hexanes on a short pad of silica gave the previously characterized aldehyde as a yellow oil (5.02 g, 15.5 mmol) in 71% yield.⁴



3-(tert-Butyldimethylsilyl)-6-iodo-2-methyl-1-(2-methylthiazolyl)hepta-1,5-diene (31).⁶ *n*-BuLi (2.5 M in hexanes, 22.6 mL, 55.4 mmol) was added to a suspension of ethyl triphenylphosphonium iodide (23.2 g, 55.4 mmol) in THF (100 mL) at 25 °C. After 30 min, the clear red solution was transferred dropwise by syringe to a vigorously stirred solution of I₂ (14.1 g, 55.4 mmol) in THF (1.1 L) at -78 °C. After addition of the Wittig reagent was completed, the resulting pale

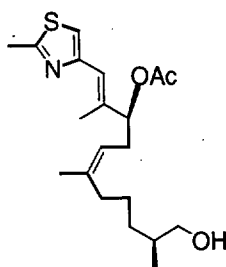
yellow suspension was stirred rapidly and warmed to $-20\text{ }^{\circ}\text{C}$. Then, NaHMDS (1.0 M soln in THF, 55.4 mL, 55.4 mmol) was added dropwise by syringe. During the addition of the NaHMDS, the reaction mixture changed from a yellow-orange slurry and to bright red solution. (3*S*,4*E*)-5-(2-Methylthiazoyl)-2-methyl-3-(*tert*-butyldimethylsilyloxy)-4-pentenal (6.0 g, 18.5 mmol) was then added in THF. After 30 min, the reaction mixture was poured into hexanes (400 mL) and then 0.5 mL brine was added. The solution was then passed through a plug of SiO₂ eluting with 2:1 hexanes/Et₂O. The iodide was purified by flash chromatography on SiO₂ eluting with hexanes/ethyl acetate (20:1 to 15:1) to afford the previously characterized the vinyl iodide **31**²⁴ (5.0 g, 10.2 mmol, 55%) as a yellow oil: $[\alpha]_{\text{D}} = -1.05$ (c 0.265, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 6.95 (s, 1H), 6.50 (s, 1H), 5.45 (dt, $J = 1.5, 6.8$ Hz, 1H), 4.22 (t, $J = 6.4$ Hz, 1H), 2.73 (s, 3H), 2.48 (s, 3H), 2.39 (m, 2H), 2.02 (s, 3H), 0.90 (s, 9H), 0.06 (3, s), 0.02 (3, s); ¹³C NMR (100 MHz, CDCl₃): δ 164.86, 153.46, 142.17, 132.54, 119.23, 115.68, 102.79, 77.70, 44.40, 39.09, 26.35, 19.65, 18.63, 14.54, -4.59, -4.84; IR (neat) 2928, 1470, 1252, 1068 cm⁻¹.



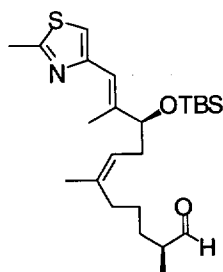
(2*S*,6*Z*,9*R*,10*E*) **9-(*tert*-Butyldimethylsilyloxy)-11-(2-Methylthiazoyl)-2,6,10-trimethyl-6,10-undecadien-1-ol (25a)**. In a 25-mL round bottom flask, (2*S*) 2-methyl-4-penten-1-ol, TES ether⁷ (208 mg, 0.97 mmol) was dissolved in 10 mL of dry THF and treated with 9-BBN (3.9 mL of a 0.5 M solution in THF) over a period of 1 h. The reaction mixture was then stirred an additional 2-3 hr until TLC analysis revealed the complete consumption of the olefin.

In a separate 50-mL round bottom flask, the vinyl iodide **31** (300 mg, 0.64 mol) was dissolved in 10 mL of DMF and then Cs₂CO₃ (63 mg, 1.94 mmol), Ph₃As (20 mg, 0.065 mmol), and catalytic PdCl₂(dppf)₂ (53 mg, 0.065 mmol), and H₂O (0.4 mL, 23.3 mmol) were added successively, and in that order, to the vigorously stirred reaction mixture. Then, the borane, prepared above, was added *via*

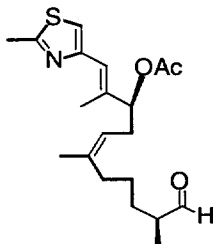
syringe to the vigorously stirred solution and the reaction mixture slowly turned from a light yellow color to a dark brown solution. The dark brown reaction mixture was stirred at ambient temperature for 2 hr and then quenched with water. An aqueous workup afforded the desired coupled product. The crude product was subject to flash column chromatography with 5% EtOAc/hexanes. Then, the crude product was then dissolved in 5 mL of Et₂O and cooled to 0 °C and treated with 5 mL of TBAF for 10-20 min. The reaction was quenched with brine and then subjected to an aqueous workup. Flash column chromatography with 60% EtOAc/hexanes afforded the desired C-1 alcohol (198 mg) in 82% yield, 2 steps; ¹H NMR (400 MHz, CDCl₃): δ 6.94 (s, 1H), 6.56 (s, 1H), 5.15 (m, 1H), 4.11 (m, 1H), 3.50 (dd, *J* = 6.06, 10.4 Hz, 1H), 3.42 (dd, *J* = 6.40, 10.37 Hz, 1H), 2.73 (s, 3H), 2.24 (m, 2H), 2.05 (m, 2H), 1.99 (s, 3H), 1.67 (s, 1H), 1.59 (m, 4H), 1.39 (m, 3H), 1.25 (m, 2H), 1.09 (m, 2H), 0.89 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H).



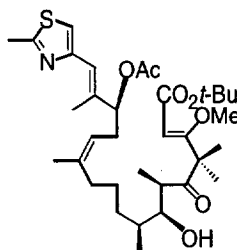
(2*S*,6*Z*,9*R*,10*E*)-9-Acetoxy-11-(2-methylthiazoyl)-2,6,10-trimethylundeca-6,10-dien-1-ol (25b). Prepared as above for **25a**; ¹H NMR (400 MHz, CDCl₃): δ 6.95 (s, 1H), 6.52 (s, 1H), 5.22 (t, *J* = 6.88 Hz, 1H), 5.07 (t, *J* = 7.76 Hz, 1H), 3.45 (m, 2H), 2.74 (s, 3H), 2.45 (m, 2H), 2.06 (m, 2H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 (m, 1H), 1.66 (s, 3H), 1.60 (m, 3H), 1.51-1.35 (m, 4H), 0.91 (d, *J* = 6.71 Hz, 3H).



(2*S*,6*Z*,9*R*,10*E*)-9-(*tert*-Butyldimethylsilyl)oxy-11-(2-methylthiazoyl)-2,6,10-trimethylundeca-6,10-dienal (26a). The C-1 alcohol, **25a** (198 mg, 0.45 mmol), was dissolved in CH₂Cl₂ and added slowly dropwise to the Swern reagent, prepared from the dropwise addition of 129 μL (1.82 mmol) of DMSO to 80 μL (0.91 mmol) of oxalyl chloride. The reaction mixture was stirred at -78 °C for 2 h and then Et₃N (320 μL, 2.27 mmol) was added and the reaction mixture was warmed to rt and quenched with water. An aqueous workup followed by flash column chromatography with 5% EtOAc/hexanes afforded the desired aldehyde in 87% yield; ¹H NMR (400 MHz, CDCl₃): δ 9.60 (s, 1H), 6.93 (s, 1H), 6.41 (s, 1H), 5.16 (m, 1H), 4.08 (m, 1H), 2.71 (s, 3H), 2.24 (m, 3H), 2.03 (m, 3H), 2.00 (s, 3H), 1.66 (s, 3H), 1.34 (m, 4H), 1.08 (d, *J* = 7.01 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H).

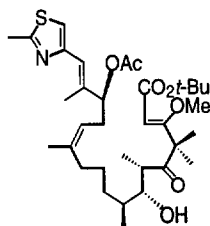


(2*S*,6*Z*,9*R*,10*E*)-9-Acetoxy-11-(2-methylthiazoyl)-2,6,10-trimethylundeca-6,10-dienal (26b). Prepared as **26a** above; ¹H NMR (400 MHz, CDCl₃): δ 9.60 (s, 1H), 6.96 (s, 1H), 6.52 (s, 1H), 5.22 (m, 1H), 5.10 (m, 1H), 2.71 (s, 3H), 2.48-2.22 (m, 4H), 2.07 (s, 3H), 2.06 (s, 3H), 1.66 (m, 3H), 1.66 (m, 3H), 1.44-1.21 (m, 5H), 1.08 (d, *J* = 7.01 Hz, 3H).

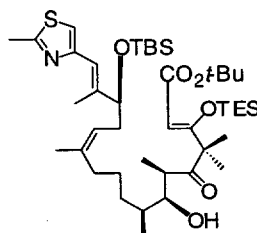


***tert*-Butyl (2*Z*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-15-acetoxy-4,4,6,8,12,16-hexamethyl-7-hydroxy-3-methoxy-17-(2-methylthiazole)-5-oxo-heptadeca-2,12,16-trienoate (27b,**

major). Prepared as **28a**, below, by the condensation of enol ether **21a** and aldehyde **26b** to afford **27b** as a 2.5:1 mixture of diastereomeric products epimeric at C6 and C7 in 62% combined yield; ^1H NMR (400 MHz, CDCl_3): δ 6.94 (s, 1H), 6.51 (s, 1H), 5.22 (t, $J = 6.64$ Hz, 1H), 5.18 (s, 1H), 5.06 (m, 1H), 3.89 (s, 3H), 3.34 (m, 1H), 2.70 (s, 3H), 2.54-2.27 (m, 3H), 2.05 (s, 3H), 1.81-2.05 (m, 5H), 1.75 (m, 1H), 1.66 (s, 3H), 1.48 (s, 9H), 1.42 (m, 2H), 1.27 (s, 3H), 1.27 (s, 3H), 1.25 (s, 1H), 1.03 (d, $J = 6.92$ Hz, 3H), 1.08 (d, $J = 6.98$ Hz, 2H), 0.78 (d, $J = 6.70$ Hz, 3H).

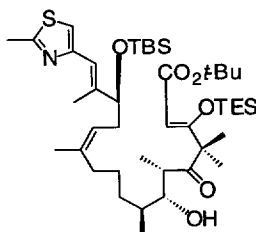


tert-Butyl (2Z,6R,7S,8R,12Z,15S,16E)-15-acetoxy-4,4,6,8,12,16-hexamethyl-7-hydroxy-3-methoxy-17-(2-methylthiazole)-5-oxo-heptadeca-2,12,16-trienoate (27b, minor). ^1H NMR (400 MHz, CDCl_3): δ 6.96 (s, 1H), 6.52 (s, 1H), 5.23 (m, 1H), 5.20 (s, 1H), 5.07 (m, 1H), 3.89 (s, 3H), 3.43 (dd, $J = 7.37, 2.90$ Hz, 1H), 3.14 (m, 2H), 2.70 (s, 3H), 2.45 (m, 3H), 2.07 (s, 3H), 1.98 (m, 1H), 1.68 (s, 3H), 1.48 (s, 9H), 1.29 (s, 3H), 1.28 (s, 3H), 1.24 (m, 5H), 1.08 (d, $J = 6.83$ Hz, 3H), 0.96 (d, $J = 6.58$ Hz, 3H), 0.95-0.80 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 217.35, 171.53, 164.75, 132.67, 122.16, 97.29, 80.11, 75.13, 62.23, 56.04, 41.87, 36.06, 31.56, 28.29, 28.14, 27.98, 27.96, 25.80, 22.80, 22.73, 17.90, 15.94, 11.41.



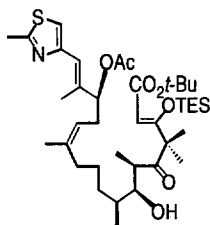
tert-Butyl (2Z,6R,7S,8S,12Z,15S,16E)-15-(tert-butyldimethylsilyloxy)-4,4,6,8,12,16-hexamethyl-7-hydroxy-17-(2-methylthiazolyl)-5-oxo-3-(triethylsilyloxy)-heptadeca-2,12,16-trienoate (28a, major). The enol ether **21b**, (46 mg,

0.13 mmol) was dissolved in 10 mL of dry THF and cooled to $-78\text{ }^{\circ}\text{C}$ in a cold bath. Then, LDA (645 mL of a 0.2M solution in THF) was added dropwise *via* syringe. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 45 min and then cooled further to $-100\text{ }^{\circ}\text{C}$. Then the aldehyde **26a** (33 gm, 0.076 mmol) was added in 2 mL of dry THF and the resultant reaction mixture stirred 30 min at reduced temperature. After this period of time, the reaction mixture was quenched with saturated aqueous NH_4Cl and subjected to an aqueous workup. Flash column chromatography with 20% EtOAc/hexanes afforded the desired aldolate, **28a**, as a mixture of diastereomeric products that were epimeric at C6 and C7 in a 2.5:1 ratio in 68% combined yield. A small amount of recovered starting material was also apparent, approx. 25%; ^1H NMR (400 MHz, CDCl_3): δ 6.92 (s, 1H), 6.51 (s, 1H), 5.21 (s, 1H), 5.09 (m, 1H), 4.07 (m, 1H), 3.37 (s, 1H), 3.34 (m, 1H), 3.18 (m, 1H), 2.71 (s, 3H), 2.50 (m, 1H), 2.24 (m, 2H), 2.03 (m, 2H), 1.99 (s, 3H), 1.73 (m, 2H), 1.66 (s, 3H), 1.51 (s, 1H), 1.45 (s, 9H), 1.34 (m, 1H), 1.26 (s, 3H), 1.24 (s, 3H), 1.10 (m, 3H), 1.02 (d, $J = 6.87\text{ Hz}$, 3H), 0.94 (t, $J = 7.94\text{ Hz}$, 9H), 0.88 (s, 9H), 0.77 (q, $J = 7.53\text{ Hz}$, 6H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 218.24, 168.57, 165.05, 137.42, 121.70, 118.98, 115.28, 99.39, 79.61, 79.45, 75.62, 57.15, 41.19, 35.67, 33.36, 32.80, 28.676, 26.25, 25.61, 23.91, 22.97, 22.73, 19.58, 18.63, 15.51, 14.30, 10.97, 7.38, 6.45.

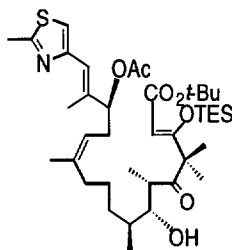


tert-Butyl (2*Z*,6*R*,7*S*,8*R*,12*Z*,15*S*,16*E*)-15-(*tert*-butyldimethylsilyloxy)-4,4,6,8,12,16-hexamethyl-7-hydroxy-3-(triethylsilyloxy)-17-(2-methylthiazole)-5-oxo-heptadeca-2,12,16-trienoate (**28a**, minor). ^1H NMR (400 MHz, CDCl_3): δ 6.92 (s, 1H), 6.46 (s, 1H), 5.22 (s, 1H), 5.12 (m, 1H), 4.08 (m, 1H), 3.40 (m, 1H), 3.19 (m, 1H), 2.71 (s, 3H), 2.22 (m, 2H), 1.99 (s, 3H), 1.99 (s, 3H), 1.94 (m, 2H), 1.67 (s, 3H), 1.45 (s, 9H), 1.43 (m, 4H), 1.27 (s, 3H), 1.28-1.24 (m, 3H), 1.25 (s, 3H), 1.05 (d, $J = 6.87\text{ Hz}$, 3H), 0.95 (m, 9H), 0.93 (m,

2H), 0.88 (s, 9H), 0.76 (t, $J = 7.86$ Hz, 6H), 0.00 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 217.3, 168.1, 164.6, 136.7, 121.5, 118.7, 114.9, 99.00, 79.16, 79.01, 75.43, 56.71, 41.21, 35.34, 32.70, 32.22, 38.28, 25.83, 25.25, 23.59, 22.63, 22.47, 19.17, 18.23, 15.62, 13.91, 11.59, 6.97, 6.04.

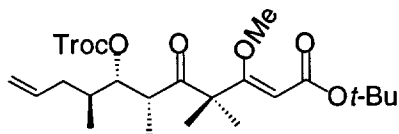


***tert*-Butyl (2Z,6R,7S,8S,12Z,15S,16E)-15-acetoxy-4,4,6,8,12,16-hexamethyl-7-hydroxy-3-(triethylsilyloxy)-17-(2-methylthiazolyl)-5-oxo-heptadeca-2,12,16-trienoate (28b, major).** Prepared as **28a**, above, by the condensation of enol ether **21b** and aldehyde **26b** to afford a 2.5:1 mixture of diastomeric products epimeric at C6 and C7 in 67% combined yield; ^1H NMR (400 MHz, CDCl_3): δ 6.94 (s, 1H), 6.51 (s, 1H), 5.22 (s, 1H), 5.21 (m, 1H), 5.02 (m, 1H), 3.35 (m, 2H), 3.18 (m, 1H), 2.71 (s, 3H), 2.47-2.33 (m, 2H), 2.06 (s, 3H), 2.01 (m, 3H), 1.73 (m, 1H), 1.66 (s, 3H), 1.57 (m, 2H), 1.46 (s, 9H), 1.52-1.41 (m, 3H), 1.33 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H), 1.03 (d, $J = 6.91$ Hz, 3H), 0.96-0.92 (m, 9H), 0.80-0.74 (m, 9H), 1.81-0.90 (m, 2H).

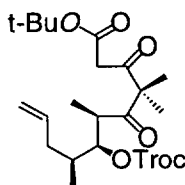


***tert*-Butyl (2Z,6R,7S,8R,12Z,15S,16E)-15-acetoxy-4,4,6,8,12,16-hexamethyl-7-hydroxy-3-(triethylsilyloxy)-17-(2-methylthiazolyl)-5-oxo-heptadeca-2,12,16-trienoate (28b, minor).** ^1H NMR (400 MHz, CDCl_3): δ 6.96 (s, 1H), 6.52 (s, 1H), 5.22 (s, 2H), 5.04 (m, 1H), 3.42 (m, 1H), 3.18 (m, 2H), 2.71 (m, 3H), 2.40 (m, 2H), 2.06 (s, 6H), 1.98 (m, 2H),

1.67 (s, 3H), 1.67 (m, 2H), 1.50-1.61 (m, 3H), 1.45 (s, 9H), 1.48-1.40 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H), 1.06 (d, $J = 6.89$ Hz, 3H), 0.95 (m, 9H), 0.83-0.73 (m, 9H).

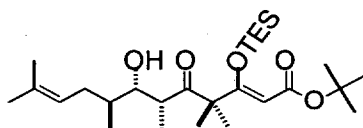


(6R,7R,8S)-7-(2,2,2-Trichloroethoxycarbonyl)-5-oxo-4,4,6,8-tetramethyl-3-methyl-2,10-undecadienoate, tert-butyl ester (29). The alcohol **22a** (5.2 g, 14.7 mmol) was dissolved in 70 mL of dry CH_2Cl_2 and cooled to 0 °C in an ice bath. Then, pyridine (4.65 g, 58.8 mmol) and trichloroethoxyethylcarbonoyl chloride (TrocCl) (6.23 g, 29.4 mmol) were added by syringe in that order. The reaction was stirred at 0 °C for 5 min and then the ice bath was removed and the reaction was allowed to come to rt and stir for 30 minutes. After this period of time, TLC analysis showed the complete consumption of the starting material. The reaction mixture was quenched by pouring it into a solution of saturated aqueous NaHCO_3 . Flash column chromatography with 3% EtOAc/hexanes through a short plug of silica gel afforded the desired enol ether which was subjected immediately to hydrolysis; ^1H NMR (400 MHz, CDCl_3): δ 5.71 (m, 1H), 5.21 (s, 1H), 5.02 (m, 2H), 4.86 (d, $J = 11.9$ Hz, 1H), 4.85 (m, 1H), 4.72 (d, $J = 11.9$ Hz, 1H), 3.91 (s, 3H), 3.25 (m, 1H), 2.26 (m, 1H), 1.87 (m, 1H), 1.81 (m, 1H), 1.48 (s, 9H), 1.31 (s, 3H), 1.26 (s, 3H), 1.11 (d, $J = 6.85$ Hz, 3H), 0.91 (d, $J = 6.64$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 211.30, 171.77, 164.80, 154.02, 135.89, 116.96, 97.75, 94.69, 82.37, 80.13, 80.21, 70.68, 62.29, 56.01, 41.38, 36.08, 34.47, 28.12, 23.26, 22.84, 15.90, 12.46; HR-FAB calcd for $\text{C}_{23}\text{H}_{35}\text{Cl}_3\text{O}_7\text{Na}$: 551.1346 $[\text{M} + \text{Na}]^+$; found: 551.1361 $[\text{M} + \text{Na}]^+$.



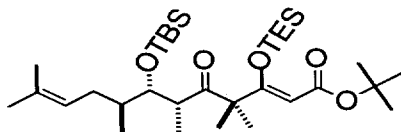
(6R,7R,8S)-7-(2,2,2-Trichloroethoxycarbonyl)-3,5-dioxo-4,4,6,8-tetramethyl-10-undecenoate, tert-butyl ester (30). The enol ether **29** (as above) was dissolved in acetone and

treated with 300 mg (catalytic) of *p*-TsOH at rt for 5-6 hrs. The reaction was monitored by TLC and after complete consumption of the starting enol ether was apparent, the reaction mixture was quenched with saturated aqueous NaHCO₃. The desired tricarbonyl **30** (6.8 g, 12.8 mmol), 87% (2 steps) was isolated after an aqueous workup and flash column chromatography with 7-9% EtOAc/hexanes; $[\alpha]_D = -57.4$ (c 0.275, CHCl₃); (a *ca.* 3:1 mixture of keto and enol tautomers) ¹H NMR (400 MHz, CDCl₃): δ 12.63 (s, 0.25H), 5.70 (m, 1H), 5.15 (s, 0.25H), 5.08-4.88 (m, 2H), 4.91 (dd, *J* = 6.60, 5.01 Hz, 0.30H), 4.78 (m, 1H), 4.77 (dd, *J* = 7.86, 3.58 Hz, 0.70H), 4.72 (dd, *J* = 11.8, 9.66 Hz, 1H), 3.48 (d, *J* = 16.2 Hz, 0.75H), 3.42 (d, *J* = 16.2 Hz, 0.75H), 3.36 (m, 0.30H), 3.30 (m, 0.70H), 1.88 (m, 2H), 1.50 (s, 3H), 1.46 (s, 9H), 1.39 (s, 3H), 1.12 (d, *J* = 6.88 Hz, 0.70H), 1.10 (d, *J* = 6.88 Hz, 1.3H), 0.93 (d, *J* = 6.63 Hz, 1.3H), 0.88 (d, *J* = 6.86 Hz, 0.70H); ¹³C NMR (100 MHz, CDCl₃): δ 210.5, 209.5, 203.16, 178.3, 172.6, 166.2, 154.1, 135.9, 135.6, 117.2, 116.9, 94.69, 94.56, 90.69, 82.68, 81.98, 81.65, 81.53, 63.58, 54.34, 46.56, 41.99, 41.62, 36.41, 35.84, 34.49, 34.44, 31.56, 28.23 (3), 27.94 (3), 22.62, 22.08, 21.56, 20.80, 15.95, 15.58, 14.09, 13.02, 12.98, 11.35; IR (neat) 1757.9, 1718.9, 1700.2, 1642.2, 1620.7, 1250.6, 1156.3 cm⁻¹; HR-FAB calcd for C₂₂H₃₃Cl₃O₇Na: 537.1190 [M+Na]⁺; found: 537.1206 [M+Na]⁺.

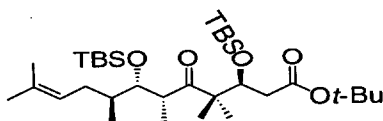


tert-Butyl (2Z,6R,7S,8S)-7-hydroxy-4,4,6,8-tetramethyl-3-(triethylsilyloxy)dodeca-2,10-dienoate (38). Prepared from the aldol condensation of **13b** and **21b** as described for the general aldol condensation described for **50d** below to afford the desired aldolate in 61% yield as a 4.5:1 mixture of diastereomeric products; ¹H NMR (400 MHz, CDCl₃): δ 5.15 (s, 1H), 5.01 (bt, *J* = 6.26 Hz, 1H), 3.32 (d, *J* = 8.60 Hz, 1H), 3.26 (s, 1H), 3.11 (q, *J* = 7.08 Hz, 1H), 2.30 (m, 2H), 1.76 (dt, *J* = 14.12, 5.70 Hz, 1H), 1.62 (s, 3H), 1.53 (s, 3H), 1.38 (s, 9H), 1.18 (d, *J* = 8.80 Hz, 6H), 0.96 (d, *J* = 6.80 Hz, 3H), 0.88 (t, *J* = 8.02 Hz, 9H), 0.71 (t, *J* = 7.40 Hz, 6H), 0.65 (d, *J* = 6.3 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 217.4, 168.1, 164.6, 132.5, 122.6,

98.9, 79.1, 74.9, 56.7, 40.7, 35.9, 31.2, 28.2, 25.2, 22.5, 22.3, 17.8, 15.2, 10.6, 6.9, 6.1; IR (neat) 5524, 2965, 1713, 1620, 1456, 1380, 1245, 1150, 979, 740 cm^{-1} .



tert-Butyl (2Z,6R,7S,8S)-7-(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-3-(triethylsilyloxy)dodeca-2,10-dienoate. Prepared by TBS protection of the C-7 hydroxyl group of **38** according to the general procedure outlined above to afford the desired C-7 TBS ether in 95% yield; ^1H NMR (500 MHz, CDCl_3): δ 5.21 (s, 1H), 5.02 (bm, 1H), 3.76 (m, 1H), 3.14 (m, 1H), 2.02 (bd, $J = 15.3$ Hz, 1H), 1.82 (m, 1H), 1.68 (s, 3H), 1.58 (s, 3H), 1.45 (s, 9H), 1.26 (s, 3H), 1.06 (d, $J = 6.9$ Hz, 3H), 1.24 (s, 3H), 0.95 (t, $J = 7.87$, 9H), 0.92 (s, 9H), 0.83 (d, $J = 6.84$ Hz, 3H), 0.78 (q, $J = 7.73$ Hz, 6H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 213.5, 168.5, 164.8, 131.9, 123.7, 99.0, 78.9, 56.3, 44.8, 39.9, 29.5, 28.3, 26.3, 25.8, 23.3, 23.0, 18.5, 17.9, 17.3, 16.0, 7.0, 6.0, 5.4, -3.7, -4.0; IR (neat) 2958, 1714, 1617, 1461, 1381, 1249, 1150, 1021, 853, 775, 738 cm^{-1} .

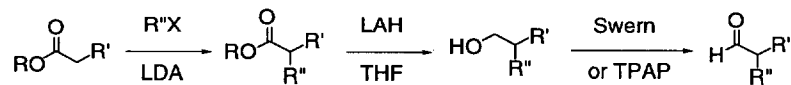


tert-Butyl (2Z,6R,7S,8S)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-dodeca-10-enoate (41). Prepared from *tert*-butyl (2Z,6R,7S,8S)-7-(*tert*-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-3-(triethylsilyloxy)dodeca-2,10-dienoate by subjection of the TES enol ether to the standard Noyori asymmetric reduction conditions described in the Experimental Section. Subsequent protection of the C-3 alcohol as the C-3 TBS ether, according to the above standard procedure, afforded the desired bis(*tert*-butyldimethylsilyloxy)ether in 76% yield (2 steps) which could be converted to the previously characterized monosubstituted terminal olefin by ozonolysis and Wittig reaction; ^1H NMR (400 MHz, CDCl_3): δ 5.03 (m, 1H), 4.32 (dd, $J = 3.92, 5.48$ Hz, 1H), 3.77 (dd, J

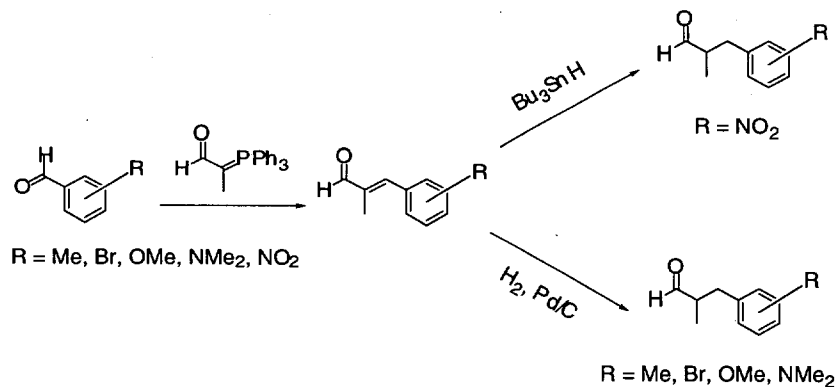
= 2.11, 7.14 Hz, 1H), 3.20 (m, 1H), 2.43 (dd, $J = 3.85, 17.2$ Hz, 1H), 2.17 (dd, $J = 5.58, 17.2$ Hz, 1H), 2.04 (m, 1H), 1.86 (m, 1H), 1.69 (s, 3H), 1.59 (s, 3H), 1.44 (s, 9H), 1.33 (m, 1H), 1.23 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.85 (d, $J = 6.90$ Hz, 3H), 0.07 (s, 6H), 0.06 (s, 6H).

The aldehydes used in these aldol reactions were prepared by either one of three procedures:

1. Substrates **49a** and **49b** were prepared according to the previously described Overman synthesis⁸ of these compounds. Substrate **49h** was prepared according to the previously described procedure.⁹ Substrate **49f** is commercially available.
2. As outlined in Scheme 2, the appropriate ester functionality could be alkylated with an appropriate alkyl halide followed by reduction to the corresponding alcohol and subsequent Swern or TPAP/NMO oxidation to the desired aldehyde. This method was utilized in the synthesis of substrates: **49c,d,e,g,i**
3. Substrates **49j-p** were prepared by Wittig olefination of the appropriate aldehyde with the appropriate Wittig reagent, Scheme 3, and subsequent reduction of the olefin by either Pd/C hydrogenation (**49j-o**) or a radical method mediated by Bu₃SnH (**49p**).

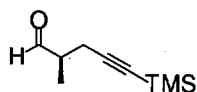


Scheme 2. Preparation of Aldehyde Substrates using alkylation.

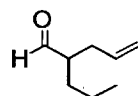


Scheme 3. Preparation of Aldehyde Substrates using Wittig olefination.

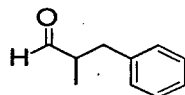
The following aldehyde substrates were readily prepared as described above and were characterized for purity by ^1H NMR spectra and used directly.



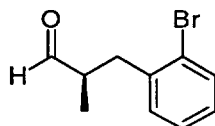
2-Methyl-5-trimethylsilyl-4-pentynal (49e). Prepared from 2-methyl-5-trimethylsilyl-4-pentyn-1-ol by TPAP oxidation to the desired aldehyde in 84% yield; ^1H NMR (400 MHz, CDCl_3): δ 9.58 (s, 1H), 2.42 (m, 2H), 2.27 (m, 1H), 1.08 (d, $J = 5.56$ Hz, 3H), -0.02 (s, 9H).



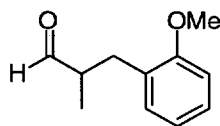
2-Propyl-4-pentenal (49g). Prepared from 2-propyl-4-penten-1-ol by Swern oxidation to afford the desired aldehyde in 86% yield: ^1H NMR (400 MHz, CDCl_3): δ 9.60 (s, 1H), 5.71 (m, 1H), 5.06 (m, 2H), 2.34 (m, 2H), 2.21 (m, 1H), 1.62 (m, 1H), 1.43 (m, 1H), 1.36 (m, 2H), 0.89 (t, $J = 7.16$ Hz, 3H).



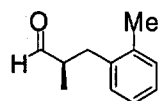
2-Methyl-3-phenylpropanal (49i). Prepared by Swern oxidation of 2-methyl-3-phenylpropan-1-ol to afford the desired aldehyde in 85% yield: ^1H NMR (400 MHz, CDCl_3): δ 10.14 (s, 1H), 7.70-7.28 (m, 5H), 3.29 (dd, $J = 5.63, 13.3$ Hz, 1H), 2.92-2.73 (m, 2H), 1.29 (d, $J = 6.82$ Hz, 3H).



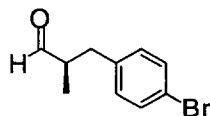
3-(2-Bromophenyl)-2-methylpropanal (49j). Prepared from 3-(2-bromophenyl)-2-methyl-2-propenal by hydrogenation with Pd/C to afford the desired aldehyde in 98% yield; ^1H NMR (400 MHz, CDCl_3): δ 9.64 (s, 1H), 7.45 (m, 1H), 7.13 (m, 2H), 6.99 (m, 1H), 3.15 (dd, $J = 13.7, 6.24$ Hz, 1H), 2.72 (m, 1H), 2.58 (dd, $J = 13.7, 8.07$ Hz, 1H), 1.02 (d, $J = 7.06$ Hz, 3H).



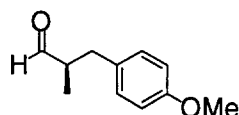
3-(2-Methoxyphenyl)-2-methylpropanal (49k). Prepared from 3-(2-methoxyphenyl)-2-methyl-2-propenal by hydrogenation with Pd/C to afford the desired aldehyde in 97% yield; ^1H NMR (400 MHz, CDCl_3): δ 9.66 (s, 1H), 7.19 (m, 1H), 7.09 (m, 1H), 6.87 (m, 2H), 3.79 (s, 3H), 3.05 (dd, $J = 13.2, 6.39$ Hz, 1H), 2.73 (m, 1H), 2.62 (m, 1H), 1.03 (d, $J = 6.89$ Hz, 3H).



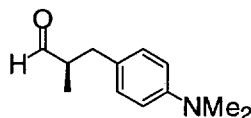
3-(2-Methylphenyl)-2-methylpropanal (49l). Prepared from 3-(2-methylphenyl)-2-methyl-2-propenal by hydrogenation with Pd/C to afford the desired aldehyde in 98% yield; ^1H NMR (400 MHz, CDCl_3): δ 9.95 (s, 1H), 7.40 (m, 4H), 3.33 (dd, $J = 13.8, 5.91$ Hz, 1H), 2.89 (m, 1H), 2.80 (dd, $J = 8.42, 13.8$ Hz, 1H), 2.55 (s, 3H), 1.34 (d, $J = 7.02$ Hz, 3H).



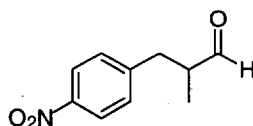
3-(4-Bromophenyl)-2-methylpropanal (49m). Prepared from 3-(4-bromophenyl)-2-methyl-2-propenal by hydrogenation with Pd/C to afford the desired aldehyde in 96% yield; ^1H NMR (400 MHz, CDCl_3): δ 9.87 (s, 1H), 7.62 (d, $J = 8.25$ Hz, 2H), 7.26 (d, $J = 8.27$ Hz, 2H), 3.26 (dd, $J = 6.21, 13.6$ Hz, 1H), 2.83 (m, 1H), 2.74 (m, 1H), 1.28 (d, $J = 7.06$ Hz, 3H).



3-(4-Methoxyphenyl)-2-methylpropanal (49n). Prepared from 3-(4-methoxyphenyl)-2-methyl-2-propenal by hydrogenation with Pd/C to afford the desired aldehyde in 98% yield; ^1H NMR (400 MHz, CDCl_3): δ 9.90 (s, 1H), 7.28 (d, $J = 8.51$ Hz, 2H), 7.02 (d, $J = 8.56$ Hz, 2H), 3.98 (s, 3H), 3.21 (dd, $J = 5.66, 13.3$ Hz, 1H), 2.86-2.73 (m, 2H), 1.27 (d, $J = 6.71$ Hz, 3H).

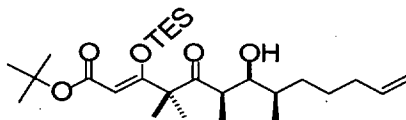


3-(4-*N,N*-Dimethylamino)-2-methylpropanal (49o). Prepared from 3-(4-*N,N*-dimethylamino)-2-methyl-2-propenal by hydrogenation with Pd/C to afford the desired aldehyde in 96% yield; ^1H NMR (400 MHz, CDCl_3): δ 9.51 (s, 1H), 6.83 (d, $J = 8.54$ Hz, 2H), 6.48 (d, $J = 8.59$ Hz, 2H), 2.77 (dd, $J = 5.84, 13.4$ Hz, 1H), 2.71 (s, 6H), 2.42 (m, 1H), 2.32 (dd, $J = 8.08, 13.5$ Hz, 1H), 0.86 (d, $J = 6.91$ Hz, 3H).



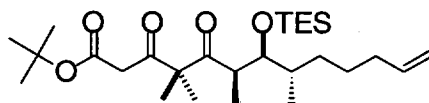
3-(4-Nitro)-2-methylpropanal (49p). Prepared from 3-(4-nitro)-2-methyl-2-propenal by reduction with Bu_3SnH to afford the desired aldehyde in 76% yield; ^1H NMR (400 MHz, CDCl_3): δ 9.89 (s, 1H), 7.16 (d, 2H), 6.76 (d, 2H), 3.03 (s, 6H), 2.95 (m, 2H), 2.79 (m, 2H).

The stereochemistry of the aldol condensation of **21a/b** and aldehyde **13b(49a)**, **21b/49f**, and **21b/49h** were determined by independent synthesis through a route with known stereochemistry. The stereochemistry of the diastereomers of these compounds (**50/51a,f** and **h**) and the remainder of the aldol products could be determined by comparing the ^1H NMR spectrum of the major and minor diastereomeric products--obtained on the crude, unfractionated aldol product. The most characteristic peaks used to determine the stereochemistry in these aldol condensations were the methyl doublets arising from the C6 and C8 methyl groups. In particular, in the major diastereomer, the methyl doublet that occurs further upfield was consistently at lower frequencies than the minor diastereomer. Although R_f was not used to determine the stereochemistry of the diastereomers, the R_f of the major diastereomer of these aldol products was consistently higher than the R_f of the minor diastereomer.

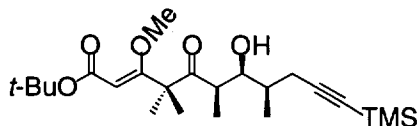


tert-Butyl (2Z,6R*,7S*,8S*)-7-hydroxy-5-oxo-4,4,6,8-tetramethyl-3-(triethylsilyloxy)trideca-2,12-dienoate (**50d**, minor). **General Procedure for the Aldol Reaction of Enolates 21a/b and Aldehydes 49a-p.** In a 100-mL round bottom flask equipped with a magnetic spin bar and under argon was added 20 mL of dry THF and the enol ether **21b** (0.34 g, 0.95 mmol). The resultant solution was cooled to $-30\text{ }^\circ\text{C}$. Then LDA (prepared from *i*-Pr₂NH (0.24 g, 2.38 mmol) and BuLi (0.95 mL of a 2.5 M solution)) was added slowly dropwise to the ketone and the resultant reaction mixture stirred at $-30\text{ }^\circ\text{C}$ for 10-15 min. After this period of time, the reaction mixture was cooled further to $-120\text{ }^\circ\text{C}$ and the aldehyde **49d** (0.17 g, 1.23 mmol) was added in one portion as a solution in 2 mL of dry THF. The reaction mixture was stirred at $-120\text{ }^\circ\text{C}$ for 10-15 min and then quenched by pouring into a solution of saturated aqueous NaHCO₃. An aqueous workup followed by flash column chromatography afforded the desired aldolate as a mixture of diastereomeric products epimeric at C-8 in a 2:1 mixture (**51d:50d**); (lower R_f) ^1H NMR (400 MHz, CDCl₃): δ 5.81 (ddt, $J =$

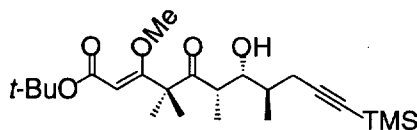
17.06, 10.27, 6.70 Hz, 1H), 5.21 (s, 1H), 4.98 (dd, $J = 16.98, 1.64$ Hz, 1H), 4.93 (dd, $J = 10.15, 0.85$ Hz, 1H), 3.36 (d, $J = 9.50$ Hz, 1H), 3.32 (s, 1H), 3.18 (app q, $J = 6.95$ Hz, 1H), 2.03 (m, 2H), 1.43 (d, $J = 4.65$ Hz, 3H), 1.74 (m, 1H), 1.58 (d, $J = 6.76$ Hz, 1H), 1.48 (m, 1H), 1.45 (s, 9H), 1.26 (s, 3H), 1.23 (s, 3H), 1.03 (d, $J = 6.97$ Hz, 3H), 0.94 (t, $J = 7.72$ Hz, 9H), 0.78 (m, 8H).



tert-Butyl (2Z,6R*,7S*,8R*)-7-hydroxy-5-oxo-4,4,6,8-tetramethyl-3-(triethylsilyloxy)-12-tridecenoate (**51d**, major). (higher R_f) $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.78 (m, 1H), 5.13, (s, 0.2H), 5.21 (s, 0.25H), 5.03 (m, 1H), 4.93 (bd, $J = 10.1$ Hz, 1H), 3.80 (m, 1H), 3.41 (s, 0.75H), 3.40 (s, 0.25H), 3.09 (m, 1H), 2.05 (m, 1H), 1.50 (bs, 3H), 1.45 (s, 9H), 1.42 (s, 3H), 1.37 (s, 3H), 1.30 (m, 3H), 1.06 (m, 3H), 0.96 (t, $J = 7.94$ Hz, 9H), 0.89 (m, 2H), 0.62 (q, $J = 7.98$ Hz, 6H).

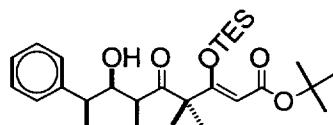


tert-Butyl (2Z,6R*,7S*,8S*)-7-hydroxy-3-methoxy-5-oxo-4,4,6,8-(tetramethyl)undeca-2-ene-10-ynoate (**50e**, minor). Prepared from the aldol condensation of **21a** and **49e** according to the same procedure outlined for the preparation of **50d** described above to afford the desired aldolate as a 3.3:1 mixture of diastereomeric products (**51e:50e**); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.20 (s, 1H), 3.90 (s, 3H), 3.50 (m, 1H), 3.20 (m, 2H), 2.17 (dq, $J = 5.24, 17.2$ Hz, 2H), 1.75 (m, 1H), 1.49 (s, 9H), 1.30 (s, 3H), 1.28 (s, 3H), 1.09 (d, $J = 6.69$ Hz, 3H), 1.06 (d, $J = 6.97$ Hz, 3H), 0.13 (s, 9H).

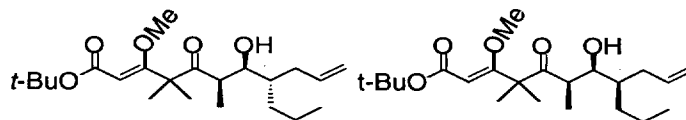


tert-Butyl (2Z,6R*,7S*,8R*)-7-hydroxy-3-methoxy-5-oxo-4,4,6,8-(tetramethyl)undeca-2-ene-10-ynoate (**51e**, major). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.18 (s,

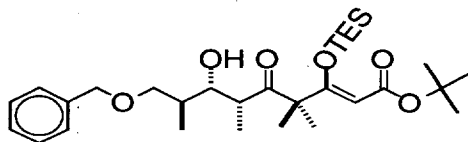
1H), 3.89 (s, 3H), 3.43 (m, 1H), 3.34 (m, 1H), 3.10 (m, 1H), 2.54 (dd, $J = 16.9, 3.60$ Hz, 1H), 2.26 (dd, $J = 16.9, 7.64$ Hz, 1H), 1.70 (m, 1H), 1.48 (s, 9H), 1.26 (s, 3H), 1.25 (s, 3H), 1.03 (d, $J = 6.93$ Hz, 3H), 0.94 (d, $J = 6.78$ Hz, 3H), 0.12 (s, 9H).



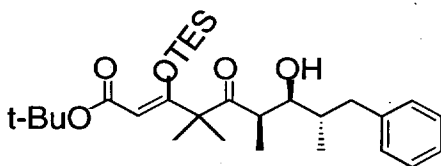
tert-Butyl (2Z,6R*,7S*,8R*)-7-hydroxy-5-oxo-8-phenyl-4,4,6,8-tetramethyl-3-(triethylsilyloxy)-2-octenoate (50f, major). Prepared from the aldol condensation of **21b** and **49f** to afford the desired aldolate **50f** as an 11:1 mixture of diastereomeric (**50f:51f**) products; ^1H NMR (400 MHz, CDCl_3): δ 7.35-7.05 (m, 5H), 4.91 (s, 1H), 3.87 (d, $J = 9.89$ Hz, 1H), 3.52 (s, 1H), 2.72 (m, 2H), 1.49 (ap s, 11H), 1.33 (d, $J = 6.75$ Hz, 3H), 1.08 (d, $J = 4.61$ Hz, 6H), 0.96 (q, $J = 7.76$ Hz, 9H), 0.78 (t, $J = 7.72$ Hz, 6H); ^{13}C NMR (100MHz, CDCl_3): δ 217.9, 167.6, 164.5, 143.9, 128.6, 127.4, 126.3, 98.8, 78.9, 75.4, 56.5, 43.1, 40.8, 28.3, 22.4, 22.1, 20.1, 10.4, 6.9, 5.9; IR (neat) 3516, 2963, 1712, 1621, 1455, 1372, 1243, 1149, 978, 740 cm^{-1} .



tert-Butyl (2Z,6R*,7S*,8R*/S*)-7-hydroxy-3-methoxy-8-propyl-4,4,6-trimethyl-10-undecenoate (50/51g). Prepared from aldol condensation of **21a** and **49g** to afford the desired aldolate in 58% yield as a 2:1 mixture of diastereomers (**51g:50g**) that were unseparable by flash column chromatography; ^1H NMR (400 MHz, CDCl_3): δ 5.75 (m, 1H), 5.17 (s, 0.67 (CH=)), 5.16 (s, 0.33 (CH=)), 5.06-4.97 (m, 2H), 3.88 (s (CH₃), 1H), 3.87 (s (CH₃), 2H), 3.51 (m, 1H), 3.24 (m, 0.33H), 3.20 (m, 0.67H), 3.14 (m, 0.33H), 3.07 (m, 0.67H), 2.33 (m, 0.63H), 2.15 (m, 0.71H), 2.05 (m, 0.33H), 1.98 (m, 0.33H), 1.56 (s, 2H), 1.46 (m, 9H), 1.34-1.12 (m, 9H), 1.03 (m, 3H), 0.88 (m, 3H).

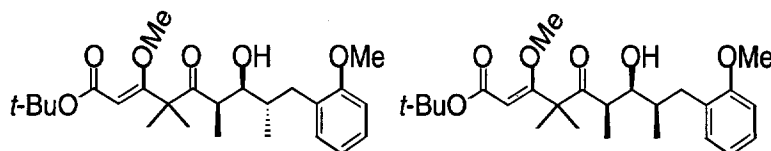


tert-Butyl (2Z,6R*,7S*,8R*)-7-hydroxy-10-oxa-5-oxo-11-phenyl-4,4,6,8-tetramethyl-3-(triethylsilyloxy)-2-undecenoate (51h, major). Prepared from the aldol condensation of **21b** and **49h** to afford the desired aldolate **51h** as the major diastereomer of a 4:1 mixture of diastereomeric products; (higher R_f) ^1H NMR (400 MHz, CDCl_3): δ 7.40-7.26 (m, 5H), 5.22 (s, 1H), 4.50 (q, unresolved, 2H), 3.66 (dd, $J = 9.03, 3.87$ Hz, 2H), 3.59 (d, $J = 9.2$ Hz, 1H), 3.43 (s, 2H), 3.40 (d, $J = 6.97$ Hz, 1H), 3.15 (q, $J = 6.91$ Hz, 1H), 1.85 (m, 1H), 1.58 (s, 1H), 1.50 (s, 1H), 1.46 (s, $J = 9\text{H}$), 1.25 (s, 1H), 1.06 (d, $J = 6.86$ Hz, 3H), 0.92 (q, $J = 7.90$ Hz, 9H), 0.77 (t, $J = 7.70$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 216.8, 168.2, 164.7, 138.6, 128.3, 127.6, 127.4, 99.0, 79.2, 73.4, 73.1, 56.7, 41.1, 36.1, 28.2, 22.7, 22.4, 13.8, 10.8, 6.9, 6.0; IR (neat): 3516, 2968, 2877, 1712, 1620, 1456, 1366, 1244, 1149, 980 cm^{-1} .

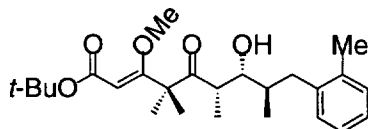


tert-Butyl (2Z,6R*,7S*,8R*)-7-hydroxy-5-oxo-9-phenyl-4,4,6,8-tetramethyl-3-(triethylsilyloxy)-2-nonenoate (51i, major). Prepared by the aldol condensation of **21b** and **49i** to afford the desired β -hydroxy ester as a 5:1 mixture of diastereomeric products in 63% yield (yield of major diastereomer): (higher R_f) ^1H NMR (400 MHz, CDCl_3): δ 7.32-7.15 (m, 5H), 5.21 (s, 1H), 3.51 (s, 1H), 3.44 (d, $J = 9.55$ Hz, 1H), 3.25 (dd, $J = 13.4, 3.17$ Hz, 1H), 3.21 (q, $J = 7.08$ Hz, 1H), 2.18 (dd, $J = 9.96, 9.95$ Hz, 1H), 1.80 (m, 1H), 1.44 (s, 9H), 1.27 (s, 3H), 1.24 (s, 3H), 1.07 (d, $J = 6.95$ Hz, 3H), 0.95 (t, $J = 7.72$ Hz, 9H), .077 (m, 6H), 0.65 (d, $J = 6.73$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 217.92, 168.12, 164.61, 141.06, 129.60 (2), 128.05 (2), 125.61, 99.01, 79.22,

75.10, 56.77, 40.67, 39.31, 37.48, 28.24 (3), 22.55, 22.27, 14.67, 10.57, 6.98 (3), 6.02 (3); IR (neat) 3518.6, 1707.5, 1619.3, 1454.8, 1378.4, 1243.3, 1149.3 cm^{-1} .

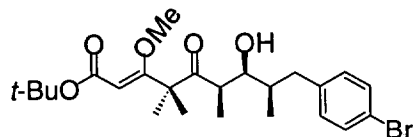


tert-Butyl (2Z,6R*,7S*,8R*/S*)-7-hydroxy-3-methoxy-9-(2-methoxyphenyl)-5-oxo-4,4,6,8-tetramethyl-2-nonenoate (50/51k). Prepared from the aldol condensation of 3-(2-methoxyphenyl)-2-methylpropanal and **21a** to afford the desired β -hydroxy ester as a 1.2:1 mixture in 51% yield.: ^1H NMR (400 MHz, CDCl_3): δ 7.17 (m, 1.5H), 7.07 (m, 0.5H), 6.82 (m, 2H), 5.18 (s, 0.45H), 5.15 (s, 0.55H), 3.87 (s, 1.2H), 3.84 (s, 1.8H), 3.77 (s, 3H), 3.43 (m, 1H), 3.30 (dq, $J = 7.41, 14.2$ Hz, 1H), 3.17 (dq, $J = 3.46, 13.3$ Hz, 1H), 3.13 (m, 0.50H), 2.75 (dd, $J = 4.73, 12.9$ Hz, 0.50H), 2.30 (dd, $J = 9.88, 13.2$ Hz, 0.50H), 2.10 (dd, $J = 9.43, 12.9$ Hz, 0.50H), 1.97 (m, 1H), 1.45 (s, 4.9H), 1.43 (s, 4.1H), 1.26 (s, 6H), 1.08 (d, $J = 6.85$ Hz, 1.5H), 1.09 (d, $J = 6.90$ Hz, 1.5H), 0.87 (d, $J = 6.57$ Hz, 1.5H), 0.66 (d, $J = 6.76$ Hz, 1.5H); ^{13}C NMR (100 MHz, CDCl_3): δ 217.7, 217.5, 171.98, 171.7, 165.2, 165.17, 158.2, 157.8, 131.6, 131.4, 129.8, 129.3, 127.6, 127.3, 120.6, 120.6, 110.7, 110.6, 97.90, 97.75, 80.51, 80.46, 75.80, 75.74, 62.62, 62.54, 56.41 (3), 55.63, 55.49, 42.58, 41.86, 36.73, 36.25, 35.12, 33.43, 23.27, 23.20, 23.15, 16.14, 15.46, 12.04, 10.94; IR (neat) 3512.8, 1709.3, 1626.3, 1461.6, 754.9 cm^{-1} .

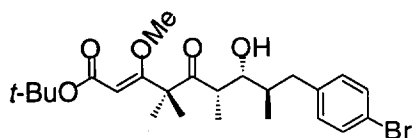


tert-Butyl (2Z,6R*,7S*,8R*)-7-hydroxy-3-methoxy-9-(2-methylphenyl)-5-oxo-4,4,6,8-tetramethyl-12-nonenoate (51l, major). Prepared from the aldol condensation of **21a** and **49l** according to the general procedure described above to afford the desired aldolate as a 2.8:1 (**51l**:**50l**) mixture of diastereomeric products; ^1H NMR (400 MHz, CDCl_3): δ 7.13 (m, 4H), 5.22 (s,

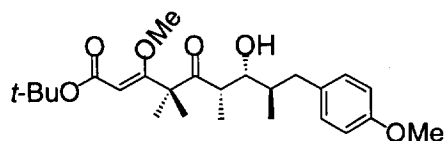
1H), 3.91 (s, 3H), 3.51 (m, 1H), 3.46 (m, 1H), 3.37 (m, 1H), 3.17 (m, 1H), 2.33 (s, 3H), 2.11 (dd, $J = 8.40, 8.49$ Hz, 1H), 1.78 (m, 1H), 1.26 (s, 3H), 1.25 (s, 3H), 1.06 (d, $J = 6.95$ Hz, 3H), 0.69 (d, $J = 6.70$ Hz, 3H).



tert-Butyl (2Z,6R*,7S*,8S*)-9-(4-bromophenyl)-7-hydroxy-3-methoxy-5-oxo-4,4,6,8-tetramethyl-12-nonenoate (50m, minor). Prepared from the aldol condensation of **21a** and **49m** according to the general procedure described above to afford the desired aldolate as a 4.2:1 (**51m:50m**) mixture of diastereomeric products; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.38 (d, $J = 8.26$ Hz, 2H), 7.04 (d, $J = 8.28$ Hz, 2H), 5.21 (s, 1H), 3.87 (s, 3H), 3.48 (m, 1H), 3.17 (m, 1H), 3.02 (bs, 1H), 2.66 (dd, $J = 4.15, 10.8$ Hz, 1H), 2.22 (dd, $J = 10.9, 7.47$ Hz, 1H), 1.81 (m, 1H), 1.47 (s, 9H), 1.27 (s, 3H), 1.26 (s, 3H), 1.07 (d, $J = 5.51$ Hz, 3H), 0.89 (d, $J = 5.28$ Hz, 3H).

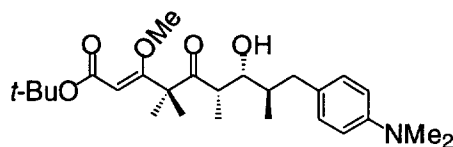


tert-Butyl (2Z,6R*,7S*,8R*)-9-(4-bromophenyl)-7-hydroxy-3-methoxy-5-oxo-4,4,6,8-tetramethyl-12-nonenoate (51m, major). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.37 (d, $J = 8.26$ Hz, 2H), 7.06 (d, $J = 8.29$ Hz, 2H), 5.17 (s, 1H), 3.82 (s, 3H), 3.50 (s, 1H), 3.36 (d, $J = 9.55$ Hz, 1H), 3.13 (m, 1H), 3.10 (m, 1H), 2.28 (dd, $J = 9.34, 13.4$ Hz, 1H), 1.78 (m, 1H), 1.46 (s, 9H), 1.27 (s, 3H), 1.26 (s, 3H), 1.06 (d, $J = 6.95$ Hz, 3H), 0.67 (d, $J = 6.77$ Hz, 3H).

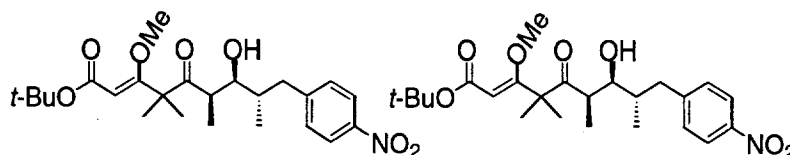


tert-Butyl (2Z,6R*,7S*,8R*)-7-hydroxy-3-methoxy-9-(4-methoxyphenyl)-5-oxo-4,4,6,8-tetramethyl-12-nonenoate (51n, major). Prepared from **21b** and **49n** according to the general procedure described above to afford the desired aldolate as a 5:1 (**51n:50n**) mixture of

diastereomeric products; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.08 (d, $J = 9.84$ Hz, 2H), 6.81 (d, $J = 8.55$ Hz, 2H), 5.17 (s, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.38 (d, $J = 9.44$ Hz, 1H), 3.10 (m, 2H), 2.25 (dd, $J = 9.42, 13.4$ Hz, 1H), 1.76 (m, 2H), 1.47 (s, 9H), 1.27 (s, 3H), 1.26 (s, 3H), 1.08 (d, $J = 6.95$ Hz, 3H), 0.69 (d, $J = 6.75$ Hz, 3H).



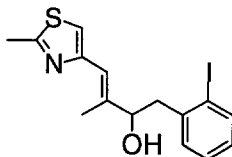
tert-Butyl (2Z,6R*,7S*,8R*)-9-(4-N,N-dimethylaminophenyl)-7-hydroxy-3-methoxy-5-oxo-4,4,6,8-tetramethyl-12-nonenoate (51o, major). Prepared from **21b** and **49o** according to the general procedure described above to afford the desired aldolate as a 5.4:1 (**51o:50o**) mixture of diastereomeric products; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.89 (d, $J = 8.51$ Hz, 2H), 6.50 (d, $J = 8.49$ Hz, 2H), 4.99 (s, 1H), 3.65 (s, 3H), 3.29 (m, 1H), 3.21 (m, 1H), 2.93 (m, 2H), 2.73 (s, 3H), 2.01 (dd, $J = 9.46, 13.4$ Hz, 1H), 1.57 (m, 1H), 1.29 (s, 9H), 1.09 (s, 3H), 1.08 (s, 3H), 0.99 (d, $J = 6.90$ Hz, 3H), 0.52 (d, $J = 6.74$ Hz, 3H).



tert-Butyl (2Z,6R*,7S*,8S*)-7-hydroxy-3-methoxy-9-(4-nitrophenyl)-5-oxo-4,4,6,8-tetramethyl-2-nonenoate (50p, minor). Prepared from the aldol condensation of **21b** and **49p** according to the general procedure described above to afford the desired aldolate as a 1.2:1 (**51p:50p**) mixture of diastereomeric products; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.15 (m, 2H), 7.34 (m, 2H), 5.26 (s, 1H), 3.93 (s, 3H), 3.40 (m, 1H), 3.21 (m, 2H), 2.72 (m, 1H), 1.84 (m, 2H), 1.05 (d, $J = 6.91$ Hz, 3H), 1.13 (d, $J = 6.99$ Hz, 3H), 1.31 (s, 3H), 1.32 (s, 3H), 1.48 (s, 9H).

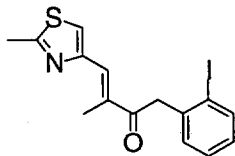
tert-Butyl (2Z,6R*,7S*,8R*)-7-hydroxy-3-methoxy-9-(4-nitrophenyl)-5-oxo-4,4,6,8-tetramethyl-2-nonenoate (51p, major). (higher R_f) $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.10 (d, $J = 8.65$ Hz, 2H), 7.33 (d, $J = 8.62$ Hz, 2H), 5.16 (s, 1H), 3.81 (s, 3H), 3.35 (d, $J = 9.63$

Hz, 2H), 3.24 (dd, $J = 13.3, 3.19$ Hz, 1H), 3.09 (q, $J = 6.84$ Hz, 1H), 2.42 (dd, $J = 9.34, 13.3$ Hz, 1H), 1.83 (m, 1H), 1.44 (s, 9H), 1.26 (s, 3H), 1.24 (s, 3H), 1.04 (d, $J = 6.98$ Hz, 3H), 0.67 (d, $J = 6.77$ Hz, 3H).

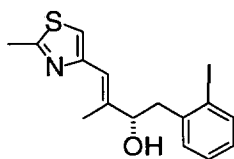


***rac*-(1*E*)-4-(2-Iodophenyl)-2-methyl-1-(2-methylthiaz-4-yl)-1-buten-3-ol (54).**

Naphthalene (4.64 g, 36.2 mmol) and Li (248 mg, 35.7 mmol) were stirred in THF (20 mL) until the Li was dissolved (~3 hr). A solution of ZnCl₂ (2.43 g, 17.8 mmol) in THF (20 mL) was added dropwise *via* a canula. The mixture was stirred 20 min at rt, then cooled to 0°C. A solution of 2-iodo-benzyl bromide (5.30 g, 17.8 mmol) in THF (5 mL) was added dropwise. The mixture was stirred for 30 min then added to a solution of LiCl (1.59 g, 37.6 mmol) and CuCN (1.60 g, 17.8 mmol) in THF (20 mL) at -20°C. The mixture was cooled to -78°C. BF₃•OEt₂ (4.13 mL, 33.6 mmol) was added, followed by a solution of the enal **52** (2.24 g, 13.4 mmol) in THF (5 mL). The mixture was allowed to warm to -30°C and stir for 1 hr. Then the reaction was quenched with saturated NH₄Cl, poured into EtOAc, and washed with H₂O and brine. The organic phase was dried (MgSO₄) and concentrated *in vacuo*. Purification by flash column chromatography (gradient elution: 20 to 30 to 40% EtOAc/hexanes) afforded 3.44 g (67%) of racemic alcohol **54** as a colorless solid; ¹H NMR (CDCl₃, 400 MHz): δ 7.80 (d, $J = 8.0$, 1H), 7.29-7.22 (m, 2H), 6.90 (s, 1H), 6.88 (td, $J = 7.3, 2.1$, 1H), 6.59 (s, 1H), 4.41 (dd, $J = 9.2, 3.8$, 1H), 3.06 (dd, $J = 13.7, 3.8$, 1H), 2.89 (dd, $J = 13.7, 9.3$, 1H), 2.83 (s, 1H), 2.58 (s, 3H), 2.11 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 167.73, 152.51, 141.89, 141.29, 139.45, 131.29, 128.20, 128.05, 118.70, 115.40, 100.87, 76.08, 46.68, 18.86, 14.72; IR (neat) 3280, 2922 cm⁻¹; HR-FAB calcd for C₁₅H₁₇INOS [M+H]⁺: 386.0076; found: 386.0073 [M+H]⁺.

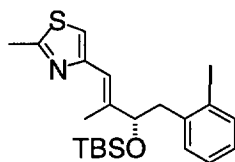


(1E)-4-(2-Iodophenyl)-2-methyl-1-(2-methylthiaz-4-yl)-1-buten-3-one (55). To a solution of alcohol *rac*-**54** (2.423 g, 6.29 mmol) and DMSO (1.79 mL, 25.2 mmol) in CH₂Cl₂ (50 mL) at -78°C was added oxalyl chloride (2M solution in CH₂Cl₂, 6.29 mL, 12.6 mmol). The mixture was stirred at -78°C for 40 min., then was treated with TEA (5.26 mL, 37.8 mmol) and warmed to rt. The mixture was diluted with EtOAc, washed with H₂O and brine, dried (MgSO₄), and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc/hexanes) afforded 2.18 g (90%) of enone **55** as a colorless solid; ¹H NMR (CDCl₃, 400 MHz): δ 7.82 (d, *J* = 7.9, 1H), 7.66 (s, 1H), 7.37 (s, 1H), 7.29 (t, *J* = 7.4, 1H), 7.18 (d, *J* = 7.4, 1H), 6.93 (t, *J* = 7.5, 1H), 4.28 (s, 2H), 2.74 (s, 3H), 2.29 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 198.21, 165.41, 151.57, 139.22, 139.1, 136.95, 131.22, 130.71, 128.46, 128.21, 121.83, 101.37, 49.36, 19.19, 13.52; IR (neat) 2920, 1667, 1626 cm⁻¹; HR-FAB calcd for C₁₅H₁₅INOS [M+H]⁺: 383.9919; found: 383.9909 [M+H]⁺.

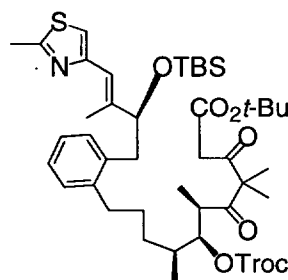


(1E,3S)-4-(2-Iodophenyl)-2-methyl-1-(2-methylthiaz-4-yl)-1-buten-3-ol [(S)-54]. A solution of (R)-2-Me-CBS-oxazolidinone in toluene (1M, 266 μL, 0.266 mmol) was evaporated *in vacuo*, and the residue was dissolved in CH₂Cl₂ (10 mL). BH₃•SMe₂ (533 μL, 5.33 mmol) was added and the mixture was stirred for 5 min. A solution of enone **55** (1.02 g, 2.66 mmol) in CH₂Cl₂ (5 mL) was added dropwise over 1.5 hr. The mixture was stirred for 30 min and then quenched with MeOH (5 mL) followed by addition of ethanolamine (3 mL). The mixture was stirred for 12 hr, then poured into EtOAc. The organic phase was washed with saturated aqueous NH₄Cl, H₂O, and brine, dried (MgSO₄), and then concentrated *in vacuo*. Purification by flash column chromatography (gradient

elution: 20 to 30% EtOAc/hexanes) afforded 907 mg (89%) of the desired chiral alcohol. Mosher ester analysis of the crude product showed a 4:1 ratio of diastereomers with a ^1H NMR spectrum that was identical to *rac*-**54**; HR-FAB calcd for $\text{C}_{15}\text{H}_{17}\text{INOS}$ $[\text{M}+\text{H}]^+$: 386.0076; found: 386.0062 $[\text{M}+\text{H}]^+$.

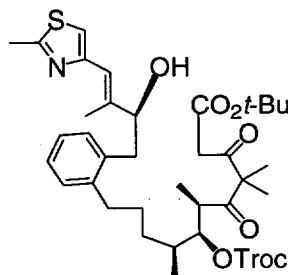


(1E,3S)-3-(tert-Butyldimethylsilyloxy)-4-(2-iodophenyl)-2-methyl-1-(2-methylthiaz-4-yl)-1-butene (56). To a solution of alcohol (*S*)-**54** (900 mg, 2.34 mmol) and 2,6-lutidine (381 μL , 3.27 mmol) in CH_2Cl_2 (12 mL) at -78°C , was added TBSOTf (644 μL , 2.80 mmol). The mixture was stirred at -78°C for 30 min, then quenched with H_2O . The mixture was diluted with EtOAc, washed with H_2O and brine, dried (MgSO_4), and concentrated *in vacuo*. Purification by flash column chromatography (15% EtOAc/hexanes) yielded 1.073 g (92%) of silyl ether **56** as a colorless oil; ^1H NMR (CDCl_3 , 400 MHz): δ 7.84 (d, $J = 7.8$, 1H), 7.27 (d, $J = 4.3$, 2H), 6.98 (s, 1H), 6.94-6.90 (m, 1H), 6.65 (s, 1H), 4.48 (dd, $J = 9.4$, 3.2, 1H), 3.04 (dd, $J = 13.3$, 3.4, 1H), 2.92 (dd, $J = 13.3$, 9.6, 1H), 2.76 (s, 3H), 2.19 (s, 3H), 0.83 (s, 9H), -0.14 (s, 3H), -0.34 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 164.47, 152.79, 142.32, 141.39, 139.11, 132.29, 127.97, 127.64, 118.33, 115.09, 100.79, 77.05, 47.93, 25.73, 19.06, 17.96, 14.31, -5.22, -5.72; IR (neat) 2953, 2920, 2884, 2854 cm^{-1} ; HR-FAB calcd for $\text{C}_{21}\text{H}_{31}\text{INOSSi}$: 500.0940 $[\text{M}+\text{H}]^+$; found: 500.0965 $[\text{M}+\text{H}]^+$.



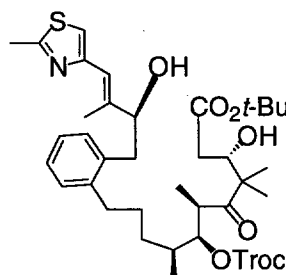
tert-Butyl (6R,7S,8S)-11-[[[(2S)-2-(tert-butyldimethylsilyloxy)-3-methoxy-4-(2-methylthiaz-4-yl)-3E-butenyl]phenyl]-3,5-dioxo-4,4,6,8-tetramethyl-7-(2,2,2-

trichloroethoxycarbonyl)-undecanoate. Prepared from Suzuki coupling of aryl iodide **56** and tricarbonyl **30** according to the general procedure outlined for the preparation of **32** (above) to afford the desired coupled product. Purification by flash column chromatography (gradient elution: 10 to 15 to 20% EtOAc/hexanes) afforded 612 mg (70%) of coupled product as an inseparable 4:1 mixture of diastereomers; $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 12.78 (s, 0.3 H), 7.40-7.31 (m, 4H), 7.16 (s, 1H), 6.72 (s, 1H), 5.31 (s, 0.3H), 5.04-4.92 (m, 3H), 4.46-4.43 (m, 1H), 3.64 (q, $J = 20.0$, 1.4H), 3.57-3.47 (m, 1H), 3.03-2.92 (m, 3H), 2.94 (s, 3H), 2.78-2.75 (m, 1H), 2.32 (s, 3H), 2.00-1.81 (m, 3H), 2.75-2.48 (m, 5H), 1.71 (s, 3H), 1.66 (s, 9H), 1.32-1.28 (m, 3H), 1.15-1.11 (m, 3H), 0.97 (s, 9H), 0.00 (s, 3H), -0.18 (s, 3H); HR-FAB calcd for $\text{C}_{43}\text{H}_{65}\text{Cl}_3\text{NO}_8\text{SSi}$: 888.3266 $[\text{M}+\text{H}]^+$; found: 888.3294 $[\text{M}+\text{H}]^+$.

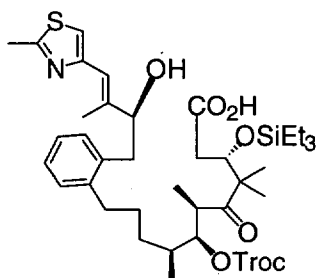


tert-Butyl (6R,7S,8S)-11-{[(2S)-2-hydroxy-3-methyl-4-(2-methylthiaz-4-yl)-3E-butenyl]phenyl}-3,5-dioxo-4,4,6,8-tetramethyl-7-(2,2,2-trichloroethoxycarbonyl)-undecanoate (57). To a solution of *tert*-butyl 11-{[(2S)-2-(*tert*-butyldimethylsilyloxy)-3-methyl-4-(2-methylthiaz-4-yl)-3-butenyl]phenyl}-3,5-dioxo-4,4,6,8-tetramethyl-7-(2,2,2-triethoxyethoxycarbonatyl)-undecanoate, above, (612 mg, 0.691 mmol) in THF (5 mL) at 0°C was added HF•pyridine. The mixture was stirred at rt for 30 min, then added to EtOAc/saturated aqueous NaHCO_3 . The phases were separated and the organic phase was washed with saturated aqueous NaHCO_3 and brine, dried (MgSO_4), and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexanes) afforded 368 mg (72%) of alcohol **57** as an inseparable 4:1 mixture of diastereomers; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 12.57 (s, 0.2H), 7.21-7.13 (m, 4H), 6.96 (s, 1H), 6.59 (s, 1H), 5.09 (s, 0.2H), 4.80-4.68 (m, 3H), 4.35-4.30 (m, 1H), 3.41 (q, $J = 16.2$,

1.6H), 3.33-3.21 (m, 1H), 2.95-2.77 (m, 2H), 2.72 (s, 3H), 2.63 (t, $J = 7.6$, 2H), 2.12 (s, 3H), 1.78-1.62 (m, 3H), 1.54-1.32 (m, 9H), 1.42 (s, 9H), 1.10-1.05 (m, 3H), 0.93-0.0.88 (m, 3H); HR-FAB calcd for $C_{37}H_{51}Cl_3NO_8S$: 774.2401 $[M+H]^+$; found: 774.2385 $[M+H]^+$.

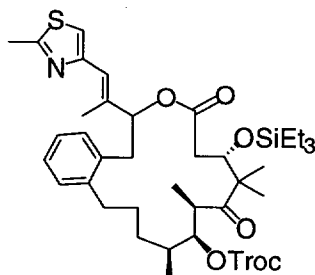


tert-Butyl (3*S*,6*R*,7*S*,8*S*)-3-hydroxyl-11-[[*(2S)*-2-hydroxy-3-methy-4-(2-methylthiaz-4-yl)-3*E*-butenyl]phenyl]-5-oxo-4,4,6,8-tetramethyl-7-(2,2,2-trichloroethoxycarbonyl)-undecanoate. Prepared from the above β -keto ester (531 mg, 0.689 mol) according to the general procedure outlined above for the preparation of **43** to afford the desired C-3 alcohol. Purification by flash column chromatography (40% EtOAc/hexanes) afforded 433 mg (82%) of the desired diol as an inseparable 4:1 mixture of diastereomers; 1H NMR ($CDCl_3$, 500 MHz): δ 7.21-7.14 (m, 4H), 6.99 (s, 1H), 6.62 (s, 1H), 4.89 (t, $J = 5.9$, 1H), 4.82-4.72 (m, 2H), 4.37-4.35 (m, 1H), 4.14-4.12 (m, 1H), 4.32 (t, $J = 6.6$, 1H), 3.35 (br. s, 1H), 2.97-2.82 (m, 2H), 2.76 (s, 3H), 2.66-2.64 (m, 2H), 2.37-2.23 (m, 2H), 2.13 (s, 3H), 1.74 (br. s, 1H), 1.76-1.70 (m, 3H), 1.63-1.59 (m, 2H), 1.44 (s, 9H), 1.15-1.08 (m, 9H), 0.97-0.95 (m, 3H); HR-FAB calcd for $C_{37}H_{53}Cl_3NO_8S$: 776.2557 $[M+H]^+$; found: 776.2546 $[M+H]^+$.



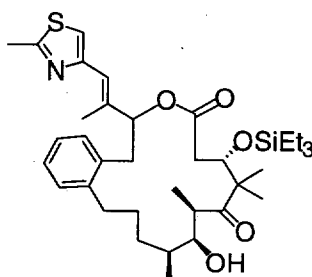
(3*S*,6*R*,7*S*,8*S*)-11-[[*(2S)*-2-Hydroxy-3-methy-4-(2-methylthiaz-4-yl)-3*E*-butenyl]phenyl]-5-oxo-4,4,6,8-tetramethyl-7-(2,2,2-trichloroethoxycarbonyl)-3-

(triethylsilyloxy)undecanoic acid. To a solution of diol (above) (430 mg, 0.553 mmol) in CH_2Cl_2 (6 mL) at -78°C , was added 2,6-lutidine (387 μL , 3.32 mmol) and TESOTf (374 μL , 1.66 mmol). The mixture was stirred at rt for 1 hr, then cooled to -78°C . The mixture was treated with 2,6-lutidine (902 μL , 7.75 mmol) and TESOTf (872 μL , 3.87 mmol), then stirred at rt for 20 hr. The mixture was poured into EtOAc. The organic phase was washed with sat. NaHCO_3 and brine, dried (MgSO_4), and concentrated *in vacuo* to afford 721 mg of the persilylated material, which was used without further purification. The residue was dissolved in THF (10 mL), cooled to 0°C and treated portionwise with 0.12 M HCl/MeOH (~8 mL). The mixture was diluted with EtOAc and the organic phase was washed with H_2O (3X) and brine, dried (MgSO_4), and concentrated *in vacuo*. Purification by flash column chromatography (50% EtOAc/hexanes) afforded the desired hydroxy acid (193 mg) followed by the diol acid (157 mg) upon elution with 10% $\text{MeOH}/\text{CH}_2\text{Cl}_2$. The diol acid was recycled to afford an additional 113 mg for a total of 306 mg (65% overall) of the desired hydroxy acid as an inseparable 4:1 mixture of diastereomers; $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.22-7.15 (m, 4H), 7.00-6.98 (m, 1H), 6.72 (s, 1H), 4.77-4.65 (m, 4H), 4.41-4.36 (m, 3H), 3.42-3.38 (m, 1H), 2.98-2.94 (m, 1H), 2.85-2.82 (m, 1H), 2.73 (s, 3H), 2.72-2.53 (m, 3H), 2.33-2.28 (m, 1H), 2.13-2.07 (m, 1H), 2.09 (s, 3H), 1.78-1.68 (m, 2H), 1.55-1.48 (m, 2H), 1.33-1.26 (m, 2H), 1.15 (s, 3H), 1.08 (s, 6H), 1.00-0.93 (m, 9H), 0.63 (q, $J = 7.9$, 6H); IR (neat) 295, 2876, 1757, 1707, 1250 cm^{-1} ; HR-FAB calcd for $\text{C}_{39}\text{H}_{59}\text{Cl}_3\text{NO}_8\text{SSi}$: 834.2796 $[\text{M}+\text{H}]^+$; found: 834.2801 $[\text{M}+\text{H}]^+$.



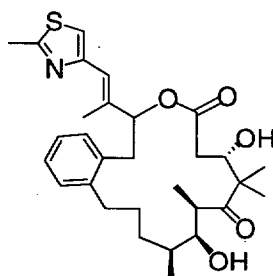
**(6S,10S,13R,14S,15S)-6-[1-Methyl-2-(2-methylthiazol-4-yl)-vinyl]-
11,11,13,15-tetramethyl-14-(2,2,2-trichloroethoxycarbonyl)-10-triethylsilyloxy-14-**

(2,2,2-trichloroethoxycarbonyl)-5,6,10,11,13,14,15,16,17,18-decahydro-9H-7-oxabenzocyclohexadecene-8,12,-dione. Prepared from the above C-15 hydroxy acid according to the general procedure outlined above for the preparation of **45**. The crude products was purified by flash column chromatography (gradient elution: 10 to 15% EtOAc/hexanes) to afford 105 mg (57%) of the desired macrolactone; $[\alpha]_D +12.0$ (c 1.00, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 7.20-7.07 (m, 4H), 6.99 (s, 1H), 6.62 (s, 1H), 5.18 (t, $J = 10.1$, 2H), 4.81 (q, $J = 11.9$, 2H), 3.93 (d, $J = 9.8$, 1H), 3.38-3.25 (m, 2H), 2.89 (t, $J = 11.6$, 1H), 2.78-2.65 (m, 2H), 2.70 (s, 3H), 2.21 (s, 3H), 1.84-1.73 (m, 3H), 1.31 (q, $J = 8.9$, 1H), 1.16 (s, 3H), 1.11 (s, 3H), 1.10 (d, $J = 6.4$, 3H), 1.04 (d, $J = 6.8$, 3H), 0.62 (t, $J = 7.9$, 9H), 0.34-0.24 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 212.50, 170.72, 164.73, 154.62, 152.39, 141.77, 138.40, 135.44, 130.49, 129.00, 126.72, 125.84, 120.03, 116.51, 94.82, 86.71, 83.10, 76.50, 53.40, 45.92, 39.04, 37.45, 35.19, 31.66, 31.46, 31.36, 25.08, 23.46, 19.24, 19.03, 16.42, 14.97, 6.59, 4.87; IR (neat) 2952, 2876, 1760, 1698 cm⁻¹; HR-FAB calcd for C₃₉H₅₇Cl₃NO₇SSi: 816.2691 [M+H]⁺; found: 816.2704 [M+H]⁺.



(6S,10S,13R,14S,15S)-14-Hydroxy-6-[1-methyl-2-(2-methylthiazol-4-yl)-vinyl]-11,11,13,15-tetramethyl-10-triethylsilyloxy-5,6,10,11,13,14,15,16,17,18-decahydro-9H-7-oxabenzocyclohexadecene-8,12,-dione. Prepared from the above Troc ester according to the general procedure outlined for the preparation of **46**. The crude product was purified by flash column chromatography (35% EtOAc/hexanes) to afford 82.0 mg (70%) of the desired C-7 hydroxy lactone; ¹H NMR (CDCl₃, 400 MHz): δ 7.21-7.08 (m, 4H), 6.99 (s, 1H), 6.64 (s, 1H), 5.26

(d, $J = 9.8$, 1H), 3.99 (dd, $J = 9.8$, 2.2, 1H), 3.84 (t, $J = 3.5$, 1H), 3.33 (dd, $J = 14.5$, 10.8, 1H), 3.05-3.02 (m, 1H), 2.93-2.87 (m, 1H), 2.85 (br. s, 1H), 2.72-2.63 (m, 3H), 2.71 (s, 3H), 2.59-2.55 (m, 1H), 2.21 (s, 3H), 1.83-1.79 (m, 1H), 1.62-1.59 (m, 1H), 1.50 (t, $J = 6.9$, 2H), 1.16 (s, 3H), 1.12 (d, $J = 6.7$, 3H), 1.08 (s, 3H), 1.06 (d, $J = 7.2$, 3H), 0.654 (t, $J = 7.9$, 9H), 0.35-0.22 (m, 6H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 218.18, 171.09, 165.16, 152.74, 141.83, 138.85, 135.90, 130.46, 128.95, 127.18, 126.34, 120.46, 116.78, 82.94, 76.28, 73.68, 54.04, 43.87, 39.96, 38.09, 37.29, 33.06, 32.17, 29.95, 24.35, 23.21, 19.60, 17.99, 15.73, 14.55, 7.15, 5.29; IR (neat) 3383, 2955, 2934, 2875, 1743, 1693 cm^{-1} ; $[\alpha]_{\text{D}} = -23.5$ (c 1.00, CHCl_3); HR-FAB calcd for $\text{C}_{36}\text{H}_{56}\text{NO}_5\text{Si}$: 642.3649 $[\text{M}+\text{H}]^+$; found: 642.3627 $[\text{M}+\text{H}]^+$.



(6S,10S,13R,14S,15S)-10,14-Dihydroxy-11,11,13,15-tetramethyl-6-[1-methyl-2-(2-methylthiazol-4-yl)-vinyl]-5,6,10,11,13,14,15,16,17,18-decahydro-9H-7-oxabenzocyclohexadecene-8,12,-dione (58). Prepared from the above C7-hydroxy lactone according to the general procedure outlined for the preparation of 47. Purification of the crude product by flash column chromatography (40% EtOAc/hexanes) afforded 57.7 mg (86%) of 58 as a colorless solid; ^1H NMR (CDCl_3 , 400 MHz): δ 7.21-7.13 (m, 4H), 7.00 (s, 1H), 6.68 (s, 1H), 5.40 (d, $J = 9.0$, 1H), 4.24 (d, $J = 9.4$, 1H), 3.84 (br. s, 1H), 3.74 (s, 1H), 3.27-3.21 (m, 2H), 2.97 (br. s, 1H), 2.86-2.67 (m, 3H), 2.72 (s, 3H), 2.36 (dd, $J = 14.4$, 10.7, 1H), 2.22-2.17 (m, 1H), 2.17 (s, 3H), 1.80-1.74 (m, 3H), 1.61-1.58 (m, 1H), 1.37-1.35 (m, 1H), 1.30 (s, 3H), 1.15 (d, $J = 6.9$, 3H), 1.07 (d, $J = 6.7$, 3H), 1.04 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 220.47, 170.38, 165.44, 151.29, 141.39, 135.39, 129.46, 129.23, 126.75, 126.11, 118.70, 115.69, 81.16, 73.08, 72.04, 53.60, 41.91, 39.54,

36.29, 35.98, 33.04, 30.92, 28.23, 22.63, 18.78, 18.11, 16.52, 15.83, 12.56; IR (neat) 3465, 2930, 1736, 1686 cm^{-1} ; $[\alpha]_{\text{D}}$ -54.9, (c 1.00, CHCl_3): HR-FAB calcd for $\text{C}_{30}\text{H}_{42}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 528.2784; found 528.2786.