A Method for Constructing the C44-C55 Side Chain of Altohyrtin C

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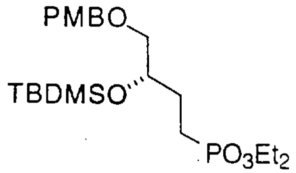
Supporting Information

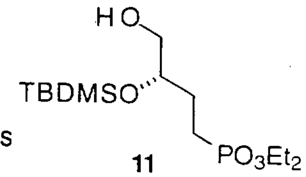
General. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and diethylether were distilled under N_2 from Sodium/benzophenone ketyl. Dichloromethane, triethylamine, diisopropylamine, diisopropylethylamine and trimethylsilyl chloride (TMSCl) were distilled under N_2 from CaH_2 prior to use. Unless otherwise specified, all reactions were carried out in oven-dried or flame-dried glassware under an atmosphere of dry Ar. The concentration of commercially available *n*-butyllithium (Acros) was determined by titration with diphenylacetic scid. Silica gel chromatography was carried out on ICI Silitech 32-63 DA silica gel. Thin layer chromatography (TLC) was performed with Merck F-245 TLC plates. ^{1}H NMR and ^{13}C NMR were measured in $CDCl_3$ with an internal reference of 7.24 (^{1}H) and 77.0 (^{13}C). IR spectra were measured as thin films on NaCl plates. Analytical analyses was performed at the Microanalytical Laboratory operated by the University of California Berkeley College of Chemistry



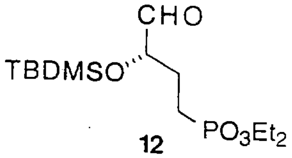
10

Compound 10: A solution of diethyl methylphosphonate (9.94 g, 65.34 mmol) in THF (65 mL) at -78°C was treated with butyllithium (2.2 M in hexanes, 238.4 mL, 65.43 mmol) and stirred for 15 minutes at -78 °C. Epoxide **9** (4.23 g, 21.78 mmol) in THF (20 mL) was added to the solution via cannula (5 mL rinse), followed by BF_3OEt_2 (11.04 mL, 87.12 mmol). The mixture was stirred for 1 h at -78 °C then quenched by addition of saturated aqueous NH_4Cl (100 mL) and warmed to room temperature. The reaction was diluted with ethyl acetate (200 mL) and the aqueous layer was further extracted with ethyl acetate (200 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concebtrated. Flash chromatography (hexane/acetone, 1:1) provided the 2° alcohol contaminated with a considerable amount of $CH_3PO_3Et_2$ (ca 1 eq) which was inseparable from the desired alcohol. The alcohol was taken on to the next step without further purification.

A solution of imidazole (5.94 g, 87.2 mmol) in DMF (30 mL) was treated with *t*-butyldimethylsilyl chloride (6.56 g, 43.6 mmol) and stirred for 15 min. The crude alcohol in DMF (10 mL) was added via cannula and the reaction mxture was stirred for three hours. The mixture was partitioned between ether and water (100 mL ea) and the aqueous layer extracted with ether (2 X 100 mL). The combined ether layers were washed with brine (150 mL), dried with $MgSO_4$, filtered and concentrated. Flash chromatography (acetone/hexane, 1:1) providedved (–)-**10**, (3.33 g, 33% yield, 2 steps) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J*=8.7 Hz, 2H), 6.85 (d, *J*=8.7 Hz, 2H), 4.41 (dd, *J*=11.6, 15.0 Hz, 2H), 4.10-4.0 (m, 4H), 3.83-3.80 (m, 1H), 3.78 (s, 3H), 3.46 (dd, *J*=5.4, 9.5 Hz, 1H), 3.26 (dd, *J*=6.1, 9.5 Hz, 1H), 1.84-1.68 (m, 4H), 1.29 (t, *J*=7.1 Hz, 4H), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.2, 129.2, 113.7, 73.4, 72.9, 70.7 (J_{cp}=17.6), 61.3, 55.4, 26.4, 25.8, 21.0 (J_{cp}=147.5), 18.0, 16.4 (J_{cp}=6.1), -4.5, -4.9; IR (thin film) 2930, 1248 cm^{-1}; $[\alpha]_D^{20}$ -11.8° (c=2.0, $CHCl_3$); Analysis calc'd for $C_{20}H_{41}O_6PSi$: C, 57.37; H, 8.97; found: C, 57.04; H, 9.09.

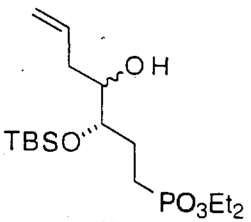

11

Compound 11: A solution of of (–)-**10** (2.35 g, 5.11 mmol) in dichloromethane-water (18:1, 32 mL) was treated with DDQ (2.32 g, 10.2 mmol) and stirred for 1h. Saturated aqueous $NaHCO_3$ (30 mL) was added and the layers separated. The aqueous layer was extracted with dichloromethane (2 X 40 mL) and the combined organic layers washed with water then brine (50 mL ea), dried with $MgSO_4$, filtered and concentrated. Flash chromatography (acetone/hexanes, 75:25) provided (+)-**11** (1.58 g, 91% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.11-4.02 (m, 4H), 3.80-3.77 (m, 1H), 3.54-3.43 (m, 2H), 2.02 (t, *J*=6.9 Hz, 1H), 1.83-1.67 (m, 4H), 1.30 (t, *J*=7.1 Hz, 6H), 0.87 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.0 (J_{cp}=16.1), 65.4, 61.5 (J_{cp}=8.1), 26.3, 25.7, 20.9 (J_{cp}=142.6), 17.9, 16.3 (J_{cp}=6.0), -4.67, -4.70; IR (thin film) 3391, 1251 cm^{-1}; $[\alpha]_D^{20}$ +5.9° (c=1.1, $CHCl_3$); Analysis calc'd for $C_{14}H_{33}O_5PSi$: C, 49.40; H, 9.70; found: C, 49.46; H, 9.63.


12

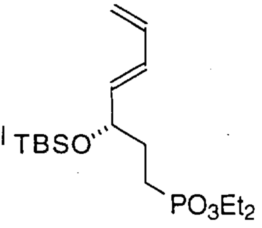
Compound 12: A solution of oxalyl chloride (0.99 mL, 11.3 mmol) in dichloromethane (10 mL) at -78 ° C was treated with dimethylsulfoxide (1.61 mL, 22.74 mmol) dropwise via syringe and the mixture stirred for 10 min. Alcohol (+)-**11**

(1.93 g, 5.67 mmol) in dichloromethane (10 mL) was added to the -78°C reaction via cannula and resultant cloudy solution stirred 15 min further. Diisopropylethyl amine (4.06 mL, 22.25 mmol) was then added dropwise via syringe. The resultant clear mixture was stirred for 5 min at -78°C then warmed to room temperature. The reaction was partitioned between water and dichloromethane (50 mL ea). The aqueous layer was extracted with dichloromethane (2 X 50 mL) and the combined organic layers washed with brine (75 mL), dried with $MgSO_4$, filtered and concentrated providing crude aldehyde **11** (1.93 g, 100% yield) as a pale yellow oil . The aldehyde was sufficiently pure to take on to the next reaction. A small sample was purified by flash chromatography (ethyl acetate) for analytical purposes providing (–)-**12** as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, J=0.8 Hz, 1H), 4.12-4.0 (m, 5H), 1.94-1.72 (m, 4H), 1.30 (t, J=7.1 Hz, 6H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 76.8 (J_{cp}=6.8), 61.5 (J_{cp}=6.4), 25.57, 25.55, 20.6 (J_{cp}=143.4), 18.0, 16.3 (J_{cp}=6.0), -4.8, -5.1; IR (thin film) 1736, 1248 cm^{-1}; $[\alpha]_D^{20}$ -29.35° (c=2.35, $CHCl_3$); Analysis calc'd for $C_{14}H_{31}O_5PSi$: C, 49.68; H, 9.23; found: C, 49.30; H, 9.49.



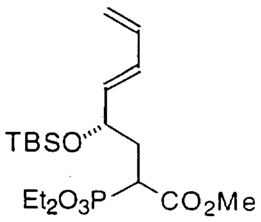
13

Compound 13: A solution of crude aldehyde **12** (1.9 g, 5.67 mmol) and allyl bromide (1.02 g, 8.51 mmol) in THF (10 mL) and saturated aqueous NH_4Cl (10 mL) at 0°C was treated with Zn dust (0.57 g, 8.51 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was partitioned between ethyl acetate and water (50 mL ea) and the aqueous layer extracted with ethyl acetate (2 X 50 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Flash chromatography (ethyl acetate) provided **13** (1.9 g, 88% yield) as a colorless oil as an inseparable mxture of diastereomers (ca. 2-3:1). Data for major isomer only given. ^1H NMR (400 MHz, $CDCl_3$) δ 5.87-5.77 (m, 1H), 5.14-5.06 (m, 2H), 4.16-4.00 (m, 4H), 3.65-3.60 (m, 1H), 2.46 (s, 1H), 2.28 (2.11, J=m Hz, 2H), 1.92-1.70 (m, 4H), 1.30 (t, J=7.1 Hz, 6H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 117.6, 74.1 (J_{cp}=15.7), 72.6, 61.4 (J_{cp}=6.4), 37.0, 25.7, 24.1, 20.7 (J_{cp}=142.3), 17.9, 16.3, -4.3, -4.6; IR (thin film) 3381, 1640, 1252 cm^{-1}; Analysis calc'd for $C_{17}H_{33}O_5PSi$: C, 53.66; H, 9.80; found: C, 53.64; H, 9.88.



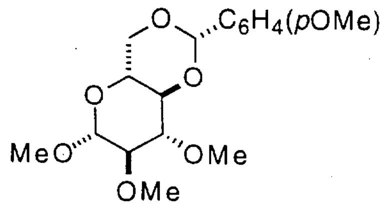
14

Compound 14: A solution of alcohol **13** (84.8 mg, 0.223 mmol) in dichloromethane (2 mL) was treated with Martin's sulfurane (300 mg, 0.446 mmol) . The reaction was stirred for thirty minutes and concentrated. Flash chromatography (ethyl acetate) provided (+)-**14** (67.1 mg, 83% yield) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.32 (dt, *J*=16.9, 10.4 Hz, 1H), 6.16 (dd, *J*=14.9, 10.5 Hz, 1H), 5.61 (dd, *J*=15.2, 6.2 Hz, 1H), 5.18 (2, *J*=16.6 Hz, 1H), 5.08 (d, *J*=10.2 Hz, 1H), 4.20-4.15 (m, 1H), 4.13-4.03 (m, 4H), 1.80-1.67 (m, 4H), 1.32 (t, *J*=6.9 Hz, 6H), 0.90 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 136.3, 136.0, 130.8, 117.1, 72.2 (J_{cp}=18.6), 61.4 (J_{cp}=6.4), 30.6, 25.8, 20.9 (J_{cp}=142.6), 18.2, 16.3 (J_{cp}=5.9), -4.1, -4.9; IR (thin film) 1251, 1031 cm^{-1}; $[\alpha]_D^{20}$ 3.25° (c=1.2, CHCl$_3$); Analysis calc'd for : C, 56.32; H, 9.73; found: C, 56.24; H, 9.73.



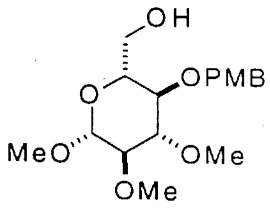
7

Compound 7: *n*-BuLi (2.2 M, 1.2 mL, 2.63 mmol) was added to a solution of diisopropyl amine (0.37 mL, 2.63 mmol) in THF (5 mL) at 0 °C, the mixture stirred for 15 min and cooled to -78 °C. A solution of phosphonate (+)-**14** (221 mg, 0.584 mmol) in THF (3 mL) was added to the -78 °C solutuion of LDA via cannula (2 mL rinse). The mixture was stirred for 30 min at -78 °C and then dimethylcarbonate (0.22 mL, 2.63 mmol) was added dropwise via syringe. The mixture was slowly warmed to 0 °C (1 hr) and then treated with 1 N HCl until ca. pH 3. The mixture was partitioned between water and ethyl acetate (25 mL ea) and the aqueous layer extracted with ethyl acetate (2 X 25 mL). The combined organic layers were dried with MgSO$_4$, filtered and concentrated. Flash chromatography (ethyl acetate) provided 7 (212 mg, 86% yield) as a colorless oil as an inseparable mixture of diastereomers (ca 1:1). Data given for mixture of isomers. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.32-6.09 (m, 4H), 5.60-5.50 (m, 2H), 5.19-1.03 (m, 4H), 4.26 (4.20, *J*=m Hz, 1H), 4.13-4.05 (m, 5H), 3.72 (s, 3H), 3.67 (s, 3H), 3.27-3.10 (m, 2H), 2.31-1.87 (m, 4H), 0.93 (s, 9H), 0.85 (s, 9H), 0.043 (s, 3H), 0.039 (s, 3H), 0.013 (s, 3H), 0.003 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.8 (J_{cp}=5.2), 169.5 (J_{cp}=5.0), 136.1, 135.8, 135.1, 131.1, 130.9, 117.3, 117.2, 70.9 (J_{cp}=5.4), 70.8 (J_{cp}=5.6), 32.7 (J_{cp}=6.2), 62.5 (J_{cp}=6.6), 52.3, 52.2, 41.1 (J_{cp}=130.3), 40.8 (J_{cp}=130.5), 34.8 (J_{cp}=4.3), 34.4 (J_{cp}=4.5), 25.69, 25.67, 18.04, 17.99, 16.22 (J_{cp}= 6.0), 16.21 (J_{cp}=3.6), -4.4, -4.7, -5.0, -5.3; IR (thin film) 2950, 11735, 1255, 1052, 1025 cm^{-1}.



16

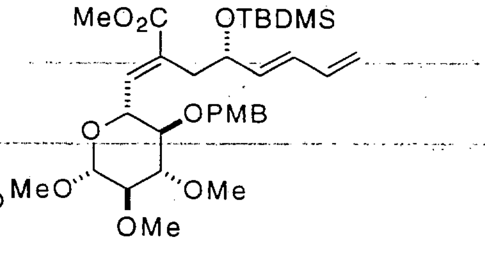
Compound 16: Diol **15** (5.6 g, 17.9 mmol) was added to a solution of NaH (60% dispersion in mineral oil, 5.7 g, 144 mmol, washed with 50 mL petroleum ether) in DMF (110 mL) at 0 °C. Methyl iodide (10.2 g, 71.6 mmol) was then added dropwise via syringe. The reaction mixture was stirred at 0 °C for 5 min then warmed to room temperature. The reaction was then cooled to 0°C and quenched with methanol (50 mL) then partitioned between water (100 mL) and ether (250 mL). The aqueous layer was extracted further with ether (2 X 250 mL). The combined ether extracts were washed with brine, water (250 mL each), dried with $MgSO_4$, filtered and concentrated affording **16** as a white solid (6.1 g, 100% yield). m.p. 135-137°; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J=8.7 Hz, 2H), 6.86 (d, J=8.7 Hz, 2H), 5.47 (s, 1H), 4.31-4.27 (m, 1H), 4.28 (d, J=7.5 Hz, 1H), 3.77 (s, 3H), 3.74 (t, J=10.3 Hz, 1H), 3.60 (s, 3H), 3.57 (s, 3H), 3.54-3.50 (m, 1H), 3.53 (s, 3H), 3.38-3.33 (m, 2H), 3.04 (t, J=7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 129.7, 127.3, 113.5, 104.8, 101.1, 83.6, 82.6, 81.2, 68.6, 65.8, 60.8, 57.2, 55.2; IR (thin film) 1516, 1250, 1169, 1090 cm^{-1}; $[\alpha]_D^{20}$ -54.2° (c=2.56, $CHCl_3$); Analysis calc'd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11; found: C, 60.31; H, 7.50.



17

Compound 17: A 250 mL 3-neck round bottom flask was fitted with a stopper reflux condenser and a solid addition funnel. The flask was charged with **16** (3.0 g, 8.8 mmol) and THF (90 mL). Solid lithium aluminum hydride (95%, 1.05 g, 26.4 mmol) was added to flask in one portion. Aluminum chloride (2.94 g, 22.0 mmol) was added to the solid addition funnel. The reaction mixture was heated to reflux and the $AlCl_3$ was added in small portions over 1 hour, so as not to create an overly vigorous reaction. The reaction was kept at reflux for 7 hours. The reaction was charged with with ethyl acetate (50 mL) to consume the $LiAlH_4$ and stirred 1 h further, then cooled to 0 °C. Saturated aqueous NH_4Cl (100 mL) was carefully added added and the solid aluminum salts filtered off. The organic filtrate was washed with brine, dried with $MgSO_4$, filtered and concentrated. Flash chromatagrphy afforded (–)-**17** (1.67 g, 62% yield) as a white solid. m.p. 70-71°; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J=8.5 Hz, 2H), 6.88 (d, J=8.5 Hz, 2H), 4.78 (d, J=10.8 Hz, 1H), 4.58 (d, J=10.6 Hz, 1H), 4.2 (d, J=7.8 Hz, 1H), 3.86-3.82 (m, 1H), 3.80 (s, 3H), 3.70-3.67 (m, 1H), 3.66 (s, 3H), 3.59 (s, 3H), 3.53 (s, 3H), 3.45-3.40 (m, 1H), 3.30-3.27 (m, 2H), 2.99

(apparent t, *J*=8.3 Hz, 1H), 2.15 (broad s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 130.1, 129.8, 113.8, 104.3, 86.5, 83.9, 77.3, 74.8, 74.5, 61.9, 61.0, 60.5, 57.1, 55.2; IR (thin film) 3568, 1612, 1514, 1248, 1081 cm^{-1}; $[\alpha]_D^{20}$ -12.0° (c=2.0, $CHCl_3$); Analysis calc'd for $C_{17}H_{26}O_7$: C, 59.64; H, 7.65; found: C, 59.49; H, 7.98.

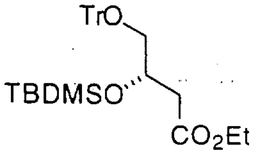


18

Compound 18: A solution of dimethyl sulfoxide (0.023 mL, 0.07 mmol) was added to a solution of oxalyl chloride (0.015 mL, 0.15 mmol) in dichloromethane (1 mL) at -78 °C. The mixture was stirred for 10 min and a solution of **17** (25 mg, 0.07 mmol) in dichloromethane (1 mL) was added to the reaction via cannula and the resultant cloudy solution stirred for 15 minutes. Diisopropylethylamine (0.05 mL, 0.30 mmol) was then added, the mixture stirred 5 min further at -78 °C and then warmed to room temperature. The mixture was quenched with water (10 mL) and then extracted with dichloromethane (3 X 30 mL). The combined organic layers were washed with brine (40 mL), dried with $MgSO_4$, filtered and concentrated affording crude aldehyde **6** (25 mg, 99 % yield) The crude aldehyde was unstable to chromatography and was thus used in the next reaction without purification.

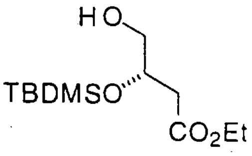
A stock solution of LDA (0.2 M) was added to a solution of 7 (30.0 mg, 0.07 mmol) in THF (0.5 mL) at 0 °C. The mixture was stirred for 15 at 0°C and then cooled to -78 °C. The crude aldehyde in THF (0.5 mL) was added via cannula and the mixture stirred for 15 min at -78 °C, warmed to room temperature and stirre for 16 h. The reaction was quenched with NH_4Cl (10 mL) and extracted with ether (3 X 20 mL). The combined ether extracts were dried with $MgSO_4$, filtered and concentrated. Flash chromatography (hexanes/ethyl acetate ,70:30) provided (–)-**18** (17 mg, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J*=8.6 Hz, 2H), 6.82 (d, *J*=8.6 Hz, 2H), 6.60 (d, *J*=8.3 Hz, 1H), 6.25 -6.08, m, 2H), 5.64 (dd, *J*=15.1, 5.9 Hz, 1H), 5.14 (d, *J*=16.3 Hz, 1H), 5.01 (d, *J*=10.4 Hz, 1H), 4.64 (d, *J*=10.7 Hz, 1H), 4.44 (d, *J*=10.7 Hz, 1H), 4.33-4.28 (m, 1H), 4.14 (d, *J*=7.7 Hz, 1H), 4.05-4.01 (m, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.64 (s, 3H), 3.58 (s, 3H), 3.50 (s, 3H), 3.25-3.22 (m, 2H), 3.02-2.99 (m, 1H), 2.62-2.59 (m, 2H), 0.88 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 159.2, 139.1, 136.3, 136.0, 132.3, 130.0, 129.84, 129.78, 116.8, 113.6, 104.1, 86.4, 83.7, 80.6, 74.6, 71.6, 61.1, 60.4, 57.0, 55.1, 51.8, 36.7, 25.8, 18.1, -4.8,

-5.0; IR (thin film) 2952, 1718, 1612, 1078 cm^{-1}; $[\alpha]_D^{20}$ -25.11.0° ($CHCl_3$); Analysis calc'd for $C_{32}H_{50}O_9Si$: C, 63.34; H, 8.31; found: C, 63.09; H, 8.12.



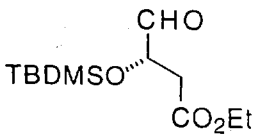
20

Compound 20: A solution of **19** (9.6g, 24.6 mmol) in *N,N,*-dimethyl formamide (DMF) (25 mL) was treated with imidazole (4.02 g, 59.1 mmol) and then *t*-butyldimethylsilyl chloride (4.45 g, 29.5 mmol) and stirred at ambient temperature for 30 min. The mixture was partitioned between water (100 mL) and ether (100 mL) and the layers separated. The aqueous layer was further extracted with ether (2 X 100 mL) and the combined organic layers washed with water, brine (150 mL each), dried with $MgSO_4$, filtered and concentrated. Flash chromatography (hexanes/ethyl acetate, 90:10) provided (–)-**20** (12.2 g, 98 % yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.23 (m, 15H), 4.29-4.23 (m, 1H), 4.16-4.03 (m, 2H), 3.14 (dd, J=4.8, 9.2 Hz, 1H), 3.02 (dd, J=7.0, 9.1 Hz, 1H), 2.76 (dd, J=4.5, 14.8 Hz, 1H), 2.48 (dd, J=8.0, 14.8 Hz, 1H), 1.24 (t, J=7.2 Hz, 3H), 0.82 (s, 9H), 0.01 (s, 3H), -0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 171.7, 143.5, 128.6, 127.7, 126.7, 86.5, 68.8, 37.2, 60.2, 40.9, 40.4, 25.6, 17.8, 14.1, -4.7, -5.2; IR (thin film) 1736 cm^{-1}; $[\alpha]_D^{20}$ -17.9° (c=1.2, $CHCl_3$); Analysis calc'd for $C_{31}H_{40}O_4Si$: C, 73.77; H, 7.99; found: C, 73.71; H, 8.30.



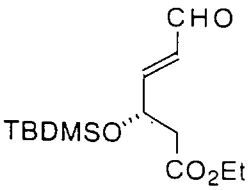
21

Compound 21: A solution of (–)-**20** (8.3 g, 16.54 mmol) in absolute ethanol (100 mL) was treated with 10% palladium on carbon (1.6 g, 1.6 mmol Pd) and placed in a Parr shaking hydrogenator (40 psi H_2) for 24 h. The mixture was filtered through Celite, the filter bed washed with ether (500 mL) and concentrated. Flash chromatography (gradient elution, ethyl acetate/hexanes, 10:90 → ethyl acetate/hexanes, 30:70) provided (–)-**21** (3.25 g, 75% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23-4.18 (m, 1H), 4.17-4.01 (m, 2H), 3.63-3.5 (m, 2H), 2.54 (dd, J=1.9, 6.1 Hz, 2H), 2.00 (dd, J=5.4, 7.5 Hz, 1H), 1.26 (t, J=7.1 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 69.6, 66.1, 60.4, 39.3, 25.5, 17.9, 14.1, -4.8, -5.0; IR (thin film) 3483, 1736 cm^{-1}; $[\alpha]_D^{20}$ -8.5° (c=3.13, $CHCl_3$); Analysis calc'd for $C_{12}H_{26}O_4Si$: C, 54.92; H, 9.99; found: C, 55.00; H, 9.75.



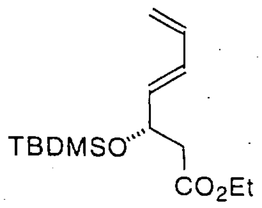
22

Compound 22: A solution of oxalyl chloride (0.23 mL, 2.67 mmol) in dichloromethane (2.6 mL) at -78 °C was treated with dimethyl sulfoxide (0.38 mL, 5.34 mmol) dropwise via syringe and then stirred for 10 min. (–)-**21** (330.7 mg, 1.26 mmol) in dichloromethane (2.6 mL) was added to the reaction via cannula. The mixture was stirred for 20 min and then diisoproplyethylamine (0.91 mL, 5.47 mmol) was added via syringe, stirred for 5 min at -78°C and then warmed to room temperature (30 min). The mixture was partitioned between water and dichloromethane (10 mL each) and the layers separated. The aqueous layer was extracted with dichloromethane (2 X 10 mL) and the combined organic layers washed with brine (15 mL), dried with $MgSO_4$, filtered and concentrated. The crude aldehyde was triturated with ether to precipitate the amine salts, filtered and concentrated providing (–)-**22** (313 mg, 96% yield), which was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 4.40-4.37 (m, 1H), 4.18-4.14 (m, 2H), 2.72-2.63 (m, 2H), 1.27 (t, *J*=7.2 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 170.1, 74.2, 30.8, 38.6, 25.5, 17.9, 14.1, -4.9, -5.2; IR (thin film) 1738 cm^{-1}; $[\alpha]_D^{20}$ -39.8° (c=1.16, $CHCl_3$).



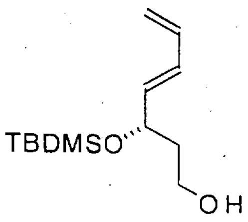
23

Compound 23: A solution of (–)-**22** (3.7 g, 14.3 mmol) in toluene (30 mL) was treated with triphenylphosphorylidene acetaldehyde (5.0 g, 16.4 mmol) and heated to 70 °C for 60 min. The dark red mixture was diluted with ether (100 mL) and filtered through sand to remove the solid material. The filtrate was washed with water and brine (100 mL each), dried with $MgSO_4$, filtered and concentrated. The crude aldehyde was triturated with ether to precipitate the amine salts, filtered and concentrated. Flash chromatography (ethyl acetate:hexanes, 10:90) provided (–)-**23** (3.39 g, 82% yield) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (d, *J*=7.9 Hz, 1H), 6.85 (dd, *J*=4.5, 15.6 Hz, 1H), 6.29 (dd, *J*=7.9, 14.4 Hz, 1H), 4.87-4.84 (m, 1H), 4.17-4.10 (m, 2H), 2.62-2.50 (m, 2H), 1.25 (t, 7.1H), 0.87 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 17.01, 157.8, 131.0, 68.5, 60.7, 42.4, 25.5, 17.9, 14.1, -4.8, -5.3; IR (thin film) 1736, 1693 cm^{-1}; $[\alpha]_D^{20}$ -6.71° (c=2.1, $CDCl_3$); Analysis calc'd for $C_{14}H_{26}O_4Si$: C, 58.70; H, 9.15; found: C, 58.68; H, 9.03.



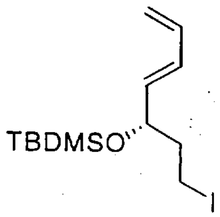
24

Compound 24: A solution of methyltriphenylphosphonuim iodide (2.55 g, 6.31 mmol) in THF (20 mL) at 0 °C was treated with sodium bis(trimethylsilyl)amide (2 M in THF, 3.03 mL, 6.06 mmol), warmed to room temperature and stirred for 30 min. The mixture was cooled to -78°C and a solution of (–)-**23** (1.45 g, 5.05 mmol) in THF (10 mL) was added via cannula, stirred for 5 min and then warmed to room temperature (ca. 30 min). The reaction was quenched with water (20 mL) and extracted with ether (3 X 50 mL). The combined organic layers were washed with water, brine (50 mL each), dried with $MgSO_4$, filtered and concentrated. Flash chromatography (10:90, ethyl acetate:hexane) provided (–)-**24** (1.19 g, 82% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.37-6.17 (m, 1H), 5.94 (dd, J=6.6, 14.9 Hz, 1H), 5.2 (d, J=16.6 Hz, 1H), 5.09 (d, J=9.7 Hz, 1H), 4.66-4.61 (m, 1H), 4.19-4.10 (m, 2H), 2.57-2.28 (m, 2H), 1.26 (t, J=10 Hz, 2H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 136.1, 135.5, 130.6, 117.4, 70.1, 60.3, 43.8, 25.8, 18.0, 14.1, -4.5, -5.2; IR (thin film) 1740 cm^{-1}; $[\alpha]_D^{20}$ -1.3° (c=2.5, $CHCl_3$); Analysis calc'd for $C_{15}H_{29}O_3Si$: C, 63.11; H, 10.24; found: C, 63.40; H, 10.05.



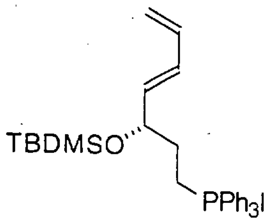
25

Compound 25: A solution of (–)-**24** (1.25 g, 4.37 mmol) in dichloromethane (20 mL) was cooled to -78 °C and treated with DIBAL (1 M in hexanes, 8.75 mL, 8.75 mmol) dropwise, stirred for 30 min at -78 °C and then warmed to 0 °C. The reaction was cooled to -78 °C and then treated with MeOH (2 mL) followed by saturated aqueous Rochelle's salt (20 mL). The mixture was warmed to room temperature and stirred vigorously until the mixture became biphasic (ca. 1 h). The layers were separated and the aqueous layer extracted with dichloromethane (2 X 50 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Flash chromatography (30:70, ethyl acetate:hexanes) provided (–)-25 (768.9 mg, 73% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (dd, J=10.2, 16.8 Hz, 1H), 6.18 (dd, J=10.6, 15.2 Hz, 1H), 5.70 (dd, J=6.4, 15.2 Hz, 1H), 5.19 (d, J=16.6 Hz, 1H), 5.08 (d, J=9.8 Hz, 1H), 4.46 (dq, J=5.6, 11.3 Hz, 1H), 3.85-3.78 (m, 1H), 3.77-3.68 (m, 1H), 2.54 (broad s, 1H), 1.89-1.80 (m, 1H), 1.76-1.69 (m, 1H), 0.91 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 136.0, 130.4, 117.1, 117.1, 72.4, 60.1, 39.3, 25.7, 18.0, -4.4, -5.1; IR (thin film) 3370, 1605 cm^{-1}; $[\alpha]_D^{20}$ -16.0° (c=2.45, $CHCl_3$); Analysis calc'd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81; found: C, 64.17; H, 10.97.



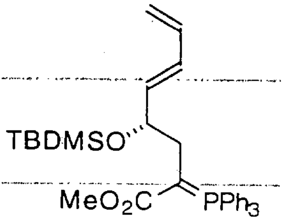
26

Compound 26: A solution of (–)-**25** (2.80 g, 11.6 mmol) in dichloromethane (250 mL) at 0 °C was treated with triethylamine (4.8 mL, 34.7 mmol) then methaneulfonyl chloride (1.32 mL, 17.33 mmol) and stirred for 5 min. The mixture was warmed to room temperature, stirred for 1 h and poured into water (100 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 X 100 mL). The combine organic layers were washed with water, brine (100 mL each), dried with $MgSO_4$, filtered and concentrated. The crude mesylate was dissolved in acetone (100 mL), treated with sodium iodide (8.7 g, 57.8 mmol) and then heated to reflux for 2 h. The mixture was cooled to room temperature, partitioned between water and ether (100 mL each) and the aqueous layer extracted with ether (2 X 100 mL). The combined organic layers were washed with saturated aqueoues $Na_2S_2O_3$ (100 mL), brine (100 mL), dried with $MgSO_4$, filtered and concentrated. Flash chromatography (gradient elution, hexanes → hexanes/ethyl acetate, 10:90) provided (+)-**26** (3.53 g, 86% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36-6.16 (m, 2H), 5.64 (dd, J=6.8, 15.1 Hz, 1H), 5.21 (d, J=16.4 Hz, 1H), 5.10 (d, J=9.7 Hz, 1H), 4.24 (dd, J=6.8, 11.9 Hz, 1H), 3.26-3.16 (m, 2H), 2.08-1.93 (m, 1H), 0.91 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.7, 130.8, 117.4, 72.8, 41.7, 25.8, 18.1, 2.6, -4.3, -4.8; IR (thin film) 2950, 1605, 1255, 1082 cm^{-1}; $[\alpha]_D^{20}$ +11.5° (c=3.0, $CHCl_3$); Analysis calc'd for $C_{13}H_{25}IOSi$: C, 44.32; H, 7.15; found: C, 44.59; H, 7.49.



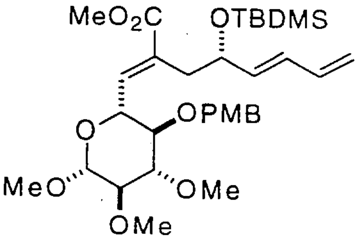
27

Compound 27: A solution of (+)-**26** (662.9 mg, 1.88 mmol) in benzene (2.0 mL) was treated with triphenylphosphine (493.5 mg, 1.88 mmol) and the mixture was heated to reflux for 14 h. The mixture was cooled to room temperature and concentrated affording a off-white solid. The solid was washed with hexane (5 X 100 mL) to remove residual PPh_3 affording (–)-**27** (1.131 g, 98% yield) as a white solid. m.p. 67-71°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.71 (m, 15H), 6.31-6.26 (m, 2H), 5.68 (dd, J=6.4, 13.8 Hz, 1H), 5.20 (d, J=15.3 Hz, 1H), 5.07 (d, J=9.2 Hz, 1H), 4.65-4.62 (m, 1H), 3.87-3.80 (m, 1H), 3.48-3.38 (m, 1H), 1.90-1.69 (m, 2H), 0.87 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.2 (J_{CP}=2.9), 134.7, 133.5 (J_{CP}=10.0), 131.8, 130.6 (J_{CP}=12.5), 117.93, 117.86 (J_{CP}=86.5), 71.4 (J_{CP}=16.6), 30., 25.8, 18.6 (J_{CP}=52.8), 18.0, -4.3, -4.5; IR (thin film) 2930, 1587, 1437, 1111, 836 cm^{-1}; $[\alpha]_D^{20}$ -1.0° (c=1.43, $CHCl_3$); Analysis calc'd for $C_{31}H_{40}IOSiP$: C, 60.58; H, 6.56; found: C, 60.21; H, 6.92.



8

Compound 8: A solution of phosphonium salt **27** (61.4 mg, 0.1 mmol) in THF (1 mL) at -78 °C was treated with NaHMDS (2 M in THF, 0.2 mL, 0.4 mmol) and the resultant red/brown solution stirred for 1 h. Methyl chloroformate (0.009 mL, 0.1 mmol) was added via syringe. The mixture was stirred for 30 at -78 °C and then warmed to room temperature and quenched with saturated aqueous $NaHCO_3$ (10 mL), then extracted with dichloromethane (3 X 25 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Flash chromatography (ethyl acetate/ethanol, 90:10) provided **8** (42.5 mg, 78% yield) as an yellow/orange gum. ^1H NMR reveals that the phodphorylidene exists as a mixture of E and Z isomers (ca. 1:1) in the zwitterionic form. Data given for mixture of isomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.27 (m, 30H), 6.16-6.09 (m, 4H), 5.37 (dd, *J*=14.1, 7.1 Hz, 2H), 5.09 (d, 15.92H), 4.96 (d, *J*=8.9 Hz, 2H), 4.44 (m, 1H), 4.22 (m, 1H), 3.60 (broad s, 3H), 3.10 (broad s, 3H), 2.68-2.48 (m, 2H), 1.95-1.75 (m, 2H), 0.85 (s, 9H), 0.84 (s, 9H), 0.02 (broad s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8 (J_{CP}=7.7), 138.6 (J_{CP}=7.0), 136.9, 133.8, 133.7, 132.0, 131.94, 131.86, 131.83, 131.5, 130.2, 128.5, 128.32 (J_{CP}=11.8), 128.31 (J_{CP}=8.8), 127.8 (J_{CP}=4.0), 115.5, 74.9, 73.5, 49.7, 48.6, 35.5, 35.4, 25.9, 18.2, -4.6; IR (thin film) 1629, 1604, 1436, 1101 cm^{-1}.

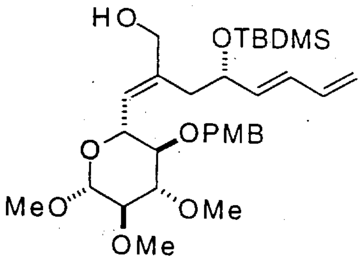


18

Compound 18: A solution of dimethyl sulfoxide (0.092 mL, 1.3 mmol) was added to a solution of oxalyl chloride (0.055 mL, 0.65 mmol) in dichloromethane (2 mL) at -78 °C. The mixture was stirred for 10 min and a solution of **6** (73 mg, 0.215 mmol) in dichloromethane (2 mL) was added to the reaction via cannula and the resultant cloudy solution stirred for 15 minutes. Diisopropylethylamine (0.23 mL, 1.32 mmol) was then added, the mixture stirred 5 min further at -78 °C and then warmed to room temperature. The mixture was quenched with water (10 mL) and then extracted with dichloromethane (3 X 30 mL). The combined organic layers were washed with brine (40 mL), dried with $MgSO_4$, filtered and concentrated affording crude aldehyde **6** (72 mg, 99% yield)

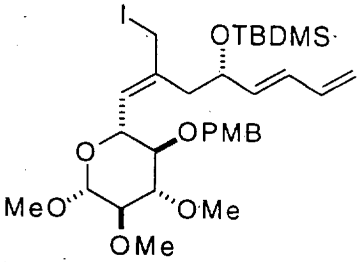
The crude aldehyde was unstable to chromatography and was thus used in the next reaction without purification.

The crude aldehyde was dissolved in dichloromethane/benzene (1/1, 2 mL) and treated with phosphorylidene **8** (235 mg, 0.43 mmol). The mixture was stirred for 5 days at room temperature then partitioned between water and dichloromethane (25 mL ea) and the aqueous layer extracted with dichloromethane (2 X 25 mL). The combined organic layers were washed with brine (30 mL) dried with $MgSO_4$, filtered and concentrated. Flash chromatography (gradient elution, ethyl acetate/hexanes, 30:70 -> ethyl acetate-> ethanol/ethyl acetate, 10:90) afforded (–)-**18** (90 mg, 70% yield, 2 steps), equivalent in all respects to material obtained via the HWE reaction, and recovered **8** (80 mg, 35 %).



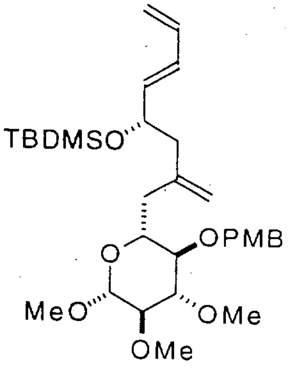
37

Compound 37: A solution of ester **18** (11.7 mg, 0.02 mmol) in dichloromethane (1 mL) at -78 °C was treated with diisobutylaluminum hydride (1 M in toluene, 0.04 mL, 0.04 mmol) and stirred for 5 min. The reaction was quenched with methanol (0.1 mL) then saturated aqueous Rochelle's salt (5 mL), warmed to room temperature and diluted with dichloromethane (5 mL). The mixture was stirred vigorously until the layers partitioned (ca 30 min). The aqueous layer was extracted further with dichloromethane (2 X 10 mL) and the combined organic layers dried with $MgSO_4$, filtered and concentrated. Flash chromatography (ethyl acetate/hexanes, 30:70) provided (–)-**28** (11.1 mg, 99% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J*=8.6 Hz, 2H), 6.84 (d, *J*=8.6 Hz, 2H), 6.23 (dt, *J*=16.9, 10.3 Hz, 1H), 6.06 (dd, *J*=15.1, 10.6 Hz, 1H), 5.65 (dd, *J*=15.1, 6.7 Hz, 1H), 5.42 (d, *J*=8.6 Hz, 1H), 5.15 (d, *J*=16.6 Hz, 1H), 5.05 (d, *J*=10.3 Hz, 1H), 4.65 (d, *J*=10.7 Hz, 1H), 4.51 (d, *J*=10.7 Hz, 1H), 4.32-4.27 (m, 1H), 4.16 (d, *J*=7.7 Hz, 1H), 4.06 (broad s, 2H), 3.93 (apparent t, *J*=8.0 Hz, 1H), 2.58 (broad s, 1H), 2.50 (dd, *J*=13.9, 5.5 Hz, 1H), 2.31 (dd, *J*=13.9, 7.5 Hz, 1H), 0.89 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 145.9, 141.8, 136.2, 136.1, 130.4, 130.3, 129.8, 124.6, 117.3, 113.6, 104.2, 86.3, 83.7, 81.3, 74.5, 73.3, 71.3, 67.4, 61.0, 60.4, 56.9, 55.2, 327.5, 25.8, 18.1, -4.5, -4.8; IR (thin film) 3453, 1612 cm^{-1}; $[\alpha]_D^{20}$ -32.5° (c=0.5, $CHCl_3$); Analysis calc'd for $C_{31}H_{50}O_8Si$: C, 64.33; H, 8.71; found: C, 64.34; H, 8.70.



38

Compound 38: A solution of alcohol **28** (127 mg, 0.22 mmol) in dichloromethane (2 mL) was treated with triethylamine (0.12 mL, 0.88 mmol) and then cooled to 0 °C. Methanesulfonyl chloride (0.035 mL. 0.44 mmol) was added, the mixture warmed to room temperature and stirred for 30 min. The reaction was partitioned between ether and water (20 mL ea) and the aqueous layer extracted further with ether (2 X 30 mL). The combined ether layers were washed with brine, dried with $MgSO_4$, filtered and concentrated. The crude mesylate was used without further purification. A solution of the crude mesylate in acetone (5 mL) was treated with sodium iodide (264 mg, 1.76 mmol) then heated to reflux for 1 h. The mixture was partitioned between ether and water (20 mL ea) and the aqueous layer extracted with ether (2 X 20 mL). The combined organic layers were washed with brine (40 mL), dried with $MgSO_4$, filtered and concentrated. Flash chromatography (hexanes:ethyl acetate, 80:20) provided (–)-**29** (126 mg, 86% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J*=8.6 Hz, 2H), 6.84 (d, *J*=8.6 Hz, 2H), 6.24 (dt, *J*=16.9, 10.3 Hz, 1H), 6.10 (dd, *J*=15.0, 10.6 Hz, 1H), 5.64 (dd, *J*=15.0, 6.2 Hz, 1H), 5.62 (d, *J*=8.7 Hz, 1H), 5.15 (d, *J*=16.6 Hz, 1H), 5.04 (d, *J*=10.1 Hz, 1H), 4.59 (d, *J*=10.3 Hz, 1H), 4.53 (d, *J*=10.3 Hz, 1H), 4.30-4.25 (m, 1H), 4.12 (d, *J*=7.8 Hz, 1H), 4.06 (d, *J*=8.8 Hz, 1H), 3.99 (d, *J*=8.9 Hz, 1H), 3.88 (t, *J*=8.8 Hz, 1H), 3.77 (s, 3H), 3.61 (s, 3H), 3.56 (s, 3H), 3.48 (s, 3H), 3.22-3.13 (m, 2H), 2.97 (apparent t, *J*=8.0 Hz, 1H), 2.57 (dd, *J*=13.9, 6.2 Hz, 1H), 2.45 (dd, *J*=13.9, 7.5 Hz, 1H), 0.87 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 159.2, 139.8, 136.1, 130.22, 130.19, 129.9, 128.3, 117.3, 113.6, 104.1, 85.9, 83.7, 81.2, 74.3, 72.6, 71.8, 61.2, 60.5, 57.0, 55.2, 38.2, 25.8, 18.1, 14.2, -4.6, -4.8; IR (thin film) 1612, 1071 cm^{-1}; $[\alpha]_D^{20}$ -55.8° (c=1.2, $CHCl_3$); Analysis calc'd for $C_{31}H_{49}IO_7Si$: C, 54.06; H, 7.34; found: C, 54.42; H, 7.17.



4

Compound 4: A solution of **30** (45.8 mg, 0.66 mmol) in ethanol/1-hexene (1:1, 1 mL) was treated with hydrazine monohydrate (0.07 mL, 1.53 mmol) and heated to 40 °C for 1 h. The reaction was diluted with water/brine (1:1, 10 mL) and extracted with methanol/dichloromethane (5:95, 3 X 30 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, filtered and concentrated. TLC analysis revealed air oxidation of the allylic hydrizine species had already commenced. The crude allylic hydrazine was stirred under air atmosphere in dichloromethane/1-hexene (1:1, 2 mL) for 3 h to complete the air oxidation. The mixture was concentrated and flash chromatography (hexanes/ethyl acetate, 80:20) provided (+)-**4** (19 mg, 51% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J*=8.8 Hz, 2H), 6.89 (d, *J*=8.5 Hz, 2H), 6.30 (dt, *J*=16.9, 10.3 Hz, 1H), 6.14 (dd, *J*=15.2, 10.7 Hz, 1H), 5.(67, *J*=dd, 15.2, 6.3 Hz, 1H), 5.16 (d, *J*=16.6 Hz, 1H), 5.05 (d, *J*=10.2 Hz, 1H), 4.87 (apparent t, *J*=15.0 Hz, 2H), 4.81 (d, *J*=10.6 Hz, 1H), 4.56 (d, *J*=10.6 Hz, 1H), 4.27 (apparent q, *J*=6.5 Hz, 1H), 4.09 (d, *J*=7.8 Hz, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 3.59 (s, 3H), 3.47 (s, 3H), 3.33-3.22 (m, 2H), 3.12 (t, *J*=9.0 Hz, 1H), 3.01 (t, *J*=8.0 Hz, 1H), 2.54 (d, *J*=14.8 Hz, 1H), 2.31-2.20 (m, 2H), 2.08 (dd, *J*=14.9, 9.8 Hz, 1H), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 142.4, 136.4, 136.5, 136.4, 129.8, 129.6, 116.5, 114.2, 113.7, 104.0, 86.8, 84.1, 81.1, 74.5, 73.8, 71.6, 60.9, 60.3, 56.6, 55.2, 45.4, 38.1, 25.8, 18.1, -4.5, -4.9; IR (thin film) 935, 1613, 1514, 1250, 1079 cm^{-1}; $[\alpha]_D^{20}$ +6.4° (c=0.8, $CHCl_3$); Analysis calc'd for $C_{31}H_{50}O_7Si$: C, 66.16; H, 8.95, found: C, 66.52; H, 9.26.