Studies in Macrolide Antibiotic Synthesis: The Role of Tethered Alkoxides in Titanium Alkoxide-mediated Regioselective Reductive Coupling Reactions

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SUPPORTING INFORMATION-1:

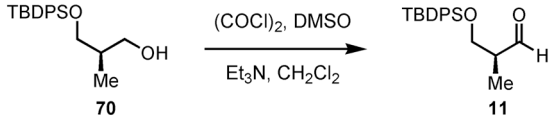
General. All reactions were conducted in flame dried glassware under nitrogen using anhydrous solvents. Toluene was dried by distillation over sodium benzophenone ketyl. Dichloromethane, tetrahydrofuran and diethylether were used after passing through activated alumina columns. Methyl sulfoxide was purchased from Aldrich Chemical Company in Sure/Seal™ containers and used as received. Triethylamine was dried by distillation over CaH_2. All chiral aldehydes were obtained from a Swern or Dess-Matin oxidation of the corresponding primary alcohol and used without purification. All other commercially available reagents were used as received.

^{1}H NMR data were recorded at 500 MHz or 400 MHz using a Bruker AM-500, a Bruker Avance DPX-500 or a Bruker AM-400 instrument. ^{1}H NMR chemical shifts are reported relative to residual $CHCl_3$ (7.27 ppm) or C_6H_6 (7.16 ppm). ^{13}C NMR data were recorded at 126 MHz using a Bruker AM-500 or a Bruker Avance DPX-500 instrument. ^{13}C chemical shifts are reported relative to the central line of $CDCl_3$ (77.23 ppm) or C_6D_6 (128.00 ppm). Infrared spectra were recorded using a Midac Spectrometer M-series. Low resolution mass spectrometry was performed on a Waters Micromass® ZQ™ instrument using electrospray ionization (EI). Optical rotations were measured on Perkin Elmer Model 341 polarimeter using a 1 mL capacity micro cell with a 10 cm path length.

Chromatographic purifications were performed using 60Å, 35-75μm particle size silica gel from Silicycle. All compounds purified by chromatography were sufficiently pure for use in further experiments, unless indicated otherwise.

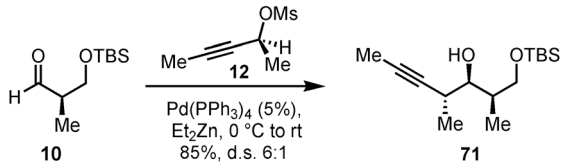
For all reductive coupling reactions, the major diastereomer was tentatively assigned as the product derived from net Felkin-selective addition in accord with our previous observations.[2] (Compounds **7a', 7a", 43-50, 54-69**)

General procedure for the Swern oxidation:



Methyl sulfoxide (177 μL, 2.47 mmol) in CH_2Cl_2 (1.6 mL) was added via cannula to a cooled solution of $(COCl)_2$ (106 μL, 1.23 mmol) in CH_2Cl_2 (2.6 mL) at −78 °C. After stirring for 15 min, alcohol **70** (270 mg, 0.82 mmol) in CH_2Cl_2 (1.6 mL) was added slowly via cannula. The resulting cloudy solution was stirred for 1 h before adding Et_3N (0.52 mL, 3.70 mmol) neat. The reaction was then warmed to 0 °C and stirred for 15 min after which 1.5 mL of water was added. The reaction mixture was then poured into a separatory funnel containing 15 ml of EtOAc and the organic layer was washed with water (2 × 10 mL), sat. NH_4Cl (3 × 10 mL), sat. $NaHCO_3$ (1 × 10 mL) and brine successively. Crude aldehyde **11** was obtained after drying over anhydrous $MgSO_4$ followed by solvent removal. The aldehyde was further dried by azeotropic removal of water (concentration 3 × from anhydrous benzene).

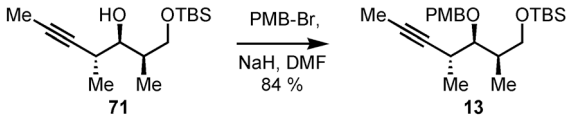
1. Assembly of the seco-acid precursor of (9*S*)-dihydroerythronolide A (1st generation approach).



(2*R*,3*R*,4*R*)-1-(*tert*-butyldimethylsilanyloxy)-2,4-dimethyl-5-heptyn-3-ol, 15:[1]

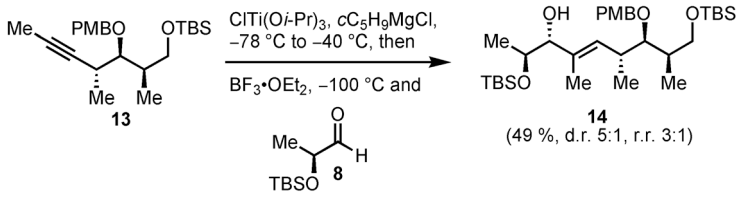
A solution of mesylate **12** (7.15 g, 44.1 mmol) in THF (10 mL) and a solution of aldehyde **10** (5.00 g, 24.5 mmol) in THF (10 mL) were added successively via cannula to

a stirring solution of $Pd(PPh_3)_4$ (1.41 g, 1.22 mmol) in THF (117 mL) at room temperature. The flask was cooled to 0 °C before adding a freshly prepared solution of Et_2Zn (58.3 mmol, 58.3 mL, 1.0 M in hexanes) dropwise over 1 h via cannula. The reaction was slowly warmed to room temperature and stirred for 8 h. The flask was then cooled to 0 °C and 50 mL of a saturated solution of NH_4Cl was added. The aqueous layer was extracted with EtOAc (3 × 70 mL) and the combined organic layer was washed with sat $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. The crude material was purified by flash column chromatography on silica gel eluting successively with 2 %, 4 % and 6 % EtOAc/ hexanes to provide 5.63 g (85 %) of **71** as 6:1 mixture of diastereomers as determined after analysis of the crude. Alcohol **71** was immediately used in the next step.



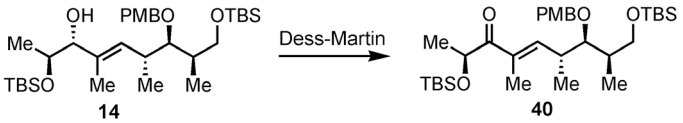
(2*R*,3*R*,4*R*)-1-(*tert*-butyldimethylsilanyloxy)-3-(*p*-methoxybenzyloxy)-2,4-dimethyl-5-heptyn, 13. Sodium hydride (310 mg, 7.75 mmol) was added at once to a stirring solution of homopropargyl alcohol **71** (d.r. = 6:1; 1.91 g, 7.05 mmol) and PMB-Br (1.84 g. 9.16 mmol) in DMF (47 mL) at −20 °C. The reaction was allowed to reach room temperature and stirred for 48 h before pouring into a separatory funnel containing EtOAc (100 mL) and water (80 mL). The phases were separated and the organic layer further washed with water (3 × 80 mL), sat. $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The residue obtained after solvent removal was purified by flash column chromatography on silica gel eluting successively with 1 %, 2 % and 3 % EtOAc/ hexanes to afford 1.89 g (84 %) of pure **13**. $[\alpha]_{589}^{20}$ −16.3° (*c* 0.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.30 (m, 2H), 6.89-6.86 (m, 2H), 4.74 (A of AB, J = 13.5 Hz,

1H), 4.53 (B of AB, J = 13.5 Hz, 1H), 3.81 (s, 3H), 3.57 (dd, J = 12.3, 6.1 Hz, 1H), 3.48 (dd, J = 12.3, 7.6 Hz, 1H), 3.44 (dd, J = 8.8, 5.1 Hz, 1H), 2.75-2.69 (m, 1H), 1.98-1.89 (m, 1H), 1.81 (d, J = 3.0 Hz, 3H), 1.14 (d, J = 8.8 Hz, 3H), 0.91 (s, 9H), 0.89 (d, J = 8.7 Hz, 1H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 131.6, 129.9, 129.7, 113.8, 82.4, 82.2, 74.4, 65.8, 55.5, 38.4, 29.7, 26.1, 18.4, 11.4, 3.9, −5.1, −5.2; IR (thin film, NaCl) 2955, 2929, 2858, 1514, 1249, 1093, 1039, 836, 775 cm^{-1}; LRMS (EI, Na) calcd for $C_{23}H_{38}O_3Si$, 413.63 *m/z* (M + Na); observed, 413.42 (M + Na)$^+$ *m/z*



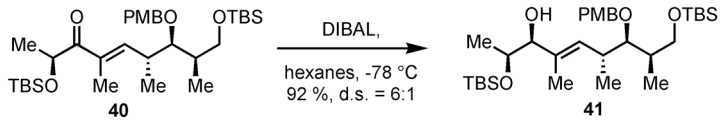
(*E*)-(2*R*,3*R*,4*R*,7*R*,8*S*)-1,8-di(*tert*-butyldimethylsilanyloxy)-3-(*p*-methoxybenzyloxy)-2,4,6-trimethylnon-5-ene-7-ol, 14. To a −78 °C solution of alkyne **13** (500 mg, 1.29 mmol; d.r. = 6:1) in 13 mL of toluene, was added sequentially ClTi(O*i*-Pr)$_3$ (1.0 M in hexanes; 2.84 mL, 2.84 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 2.84 mL, 5.68 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to −40 °C and stirred for 1 h during which the reaction turned dark brown. The flask was then cooled to −78 °C and $BF_3{\cdot}OEt_2$ (360 μL, 2.84 mmol) was added in a dropwise manner. Following a stirring period of 10 min at −78 °C, the flask was further cooled to −100 °C by immersing into a liquid N_2/ pentane bath. Aldehyde **8** (778 mg, 4.13 mmol) was then added as a solution in toluene (0.5 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.5 mL). Stirring was maintained for 1 h at −100 °C, before warming to −78 °C. Saturated NH_4Cl solution (10 mL) was then added and the

suspension was allowed to reach ambient temperature before partitioning between EtOAc (20 mL) and water (10 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 40 mL), brine (1 × 40 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography on silica gel eluting successively with 2 %, 4 %, 6 %, 10 % and 15 % EtOAc -hexanes to provide 370 mg (49 %) of a diastereomeric mixture of **14** (d.r. = 5:1 at C7). $[\alpha]_{589}^{20}$ –5.1° (*c* 0.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (m, 2H), 6.87-6.85 (m, 2H), 5.57 (d, *J* = 9.6 Hz, 1H), 4.55 (A of AB, *J* = 10.8 Hz, 1H), 4.46 (B of AB, *J* = 10.8 Hz, 1H), 3.96 (d, *J* = 3.5 Hz, 1H), 3.96-3.93 (m, 1H), 3.80 (s, 3H), 3.52 (dd, *J* = 9.7, 7.0 Hz, 1H), 3.44 (dd, *J* = 9.7, 6.1 Hz, 1H), 3.39 (dd, *J* = 6.7, 4.0 Hz, 1H), 2.80-2.68 (m, 1H), 1.87-1.81 (m, 1H), 1.61 (s, 3H), 0.98 (d, *J* = 9.1 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.93-0.91 (m, 21H), 0.097 (s, 3H), 0.088 (s, 3H), 0.045 (s, 3H), 0.038 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 132.6, 132.1, 130.0, 129.3, 113.8, 83.4, 79.2, 74.5, 70.8, 66.0, 55.5, 38.8, 35.6, 26.2, 26.0, 18.5, 18.3, 18.1, 17.1, 14.1, 11.6, –4.3, –4.7, –5.13, –5.15; IR (thin film, NaCl) 2955, 2929, 2856, 1514, 1471, 1463, 1249, 1087, 1039, 836, 775, 668 cm^{-1}; LRMS (EI, Na) calcd for $C_{32}H_{60}O_5Si_2$, 603.99 *m/z* (M + Na); observed, 603.46 $(M + Na)^+$ *m/z*.



(*E*)-(2*R*,3*R*,4*R*,8*S*)-1,8-di(*tert*-butyldimethylsilanyloxy)-3-(*p*-methoxybenzyloxy)-2,4,6-trimethylnon-5-ene-7-one, 40. To a stirring solution of **14** (370 mg, 0.637 mmol) in dichloromethane (12 mL, reagent grade from a bottle) was added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (540 mg, 1.28 mmol) at room temperature. After 1

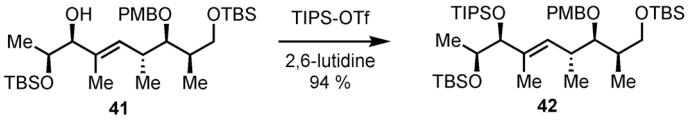
h of stirring, the reaction was diluted with a solution of 20 % EtOAc/ hexanes (10 mL) and most of the solvent was removed. The residue was dissolved in 30 mL of EtOAc/ hexanes and washed with a 1:1 mixture of 10 % $Na_2S_2O_3$ and sat $NaHCO_3$ until a clear organic layer was obtained. The organic layer was then washed with brine and dried over anhydrous Na_2SO_4. The solvent was concentrated and the residue was purified by flash column chromatography eluting with 10 % EtOAc/ hexanes to afford 335 mg of enone **40** (91 %). Enone **40** was immediately used in the following step.



40 **41**

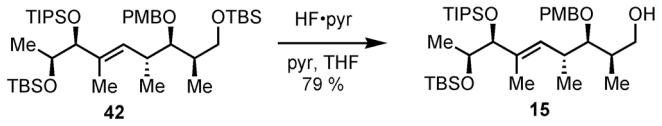
(*E*)-(2*R*,3*R*,4*R*,7*S*,8*S*)-1,8-di(*tert*-butyldimethylsilanyloxy)-3-(*p*-methoxybenzyloxy)-2,4,6-trimethylnon-5-ene-7-ol, 41. To a cooled solution of enone **40** (573 mg, 0.990 mmol) in hexanes at −78 °C was added DIBAL (1.0 M in hexanes; 1.48 mL, 1.48 mmol) slowly via syringe down the side of the flask. After stirring for 10 min, 2.0 mL of MeOH was added followed by 5 mL of saturated Rochelle salt solution. The suspension was allowed to reach room temperature before diluting with EtOAc (10 mL) and water (10 mL). The phases were separated and the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layer was then washed with $NaHCO_3$ (2 × 20 mL) and brine. After drying over anhydrous Na_2SO_4, the solvent was removed and the residue was purified by flash column chromatography eluting with 8 % EtOAc/ hexanes affording 528 mg of unsaturated alcohol **41** (92 %, d.s. = 6:1 from ^{1}H NMR of crude product). $[\alpha]_{589}^{20}$ +12.8 ° (*c* 0.67, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.27 (m, 2H), 6.87-6.86 (m, 2H), 5.48 (d, *J* = 9.8 Hz, 1H), 4.56 (A of AB, *J* = 10.6 Hz, 1H), 4.45 (B of AB, *J* = 10.6 Hz, 1H), 3.80 (s, 3H), 3.77-3.68 (m, 2H), 3.53 (dd, *J* =

9.8, 6.7 Hz, 1H), 3.46 (dd, *J* = 9.8, 6.0 Hz, 1H), 3.38 (dd, *J* = 6.2, 4.4 Hz, 1H), 2.76-2.69 (m, 1H), 1.87-1.78 (m, 1H), 1.64 (d, *J* = 1.1 Hz, 3H), 1.05 (d, *J* = 5.9 Hz, 3H), 0.94-0.91 (m, 24H), 0.12 (s, 3H), 0.11 (s, 3H), 0.051 (s, 3H), 0.049 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ159.2, 133.5, 133.2, 131.9, 129.6, 113.8, 83.3, 74.6, 71.3, 66.0, 55.5, 38.9, 35.7, 26.2, 26.1, 20.3, 18.5, 18.3, 18.1, 12.1, 11.8, –3.8, –4.5, –5.13, –5.15; IR (thin film, NaCl) 2956, 2929, 2856, 1249, 1132, 1087, 1040, 1005, 835, 776, 671 cm^{-1}; LRMS (EI, Na) calcd for $C_{32}H_{60}O_5Si_2$, 603.99 *m/z* (M + Na); observed, 603.43 $(M + Na)^+$ *m/z*.



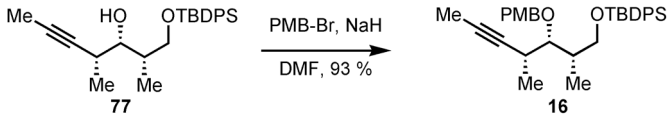
(*E*)-(2*R*,3*R*,4*R*,7*S*,8*S*)-1,8-di(*tert*-butyldimethylsilanyloxy)-3-(*p*-methoxybenzyloxy)-7-(*tri*-isopropylsilanyloxy)-2,4,6-trimethylnon-5-ene, 42. To a cooled solution of allylic alcohol **41** (198 mg, 0.339 mmol) and 2,6-lutidine (0.12 mL, 1.0 mmol) in dichloromethane (3.4 mL) at 0 °C, was added TIPS-OTf (0.14 mL, 0.51 mmol) dropwise. The reaction was held at 0 °C for 1 h before diluting with 20 % EtOAc/ hexanes (10 mL). The organic layer was then washed with saturated $NaHCO_3$ (2 × 10 mL), brine and dried over anhydrous Na_2SO_4. The solvent was concentrated and the residue was purified by flash column chromatography eluting with 2 % EtOAc/ hexanes affording 237 mg of **42** (94 %). $[\alpha]_{589}^{20}$ −24.0° (*c* 0.84, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.27-7.26 (m, 2H), 6.86-6.85 (m, 2H), 5.62 (d, *J* = 9.6 Hz, 1H), 4.60 (A of AB, *J* = 10.9 Hz, 1H), 4.48 (B of AB, *J* = 10.9 Hz, 1H), 4.12 (d, *J* = 4.4 Hz, 1H), 3.91-3.86 (m, 1H), 3.81 (s, 3H), 3.48 (dd, *J* = 9.7, 5.6 Hz, 1H), 3.44 (dd, *J* = 9.7, 5.9 Hz, 1H), 3.36 (dd, *J* = 5.2, 5.2 Hz, 1H), 2.80-2.71 (m, 1H), 1.85-1.76 (m, 1H), 1.68 (d, *J* = 0.8 Hz, 3H), 1.052-1.046 (m, 21H), 0.99-.096 (m, 9H), 0.91 (s, 9H), 0.88 (s, 9H), 0.05 (s, 3H),

0.039(s, 3H), 0.038 (s, 3H), 0.031 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 133.9, 132.1, 129.6, 129.0, 113.7, 84.1, 79.7, 74.3, 72.9, 66.0, 55.5, 18.5, 18.37, 18.36, 18.3, 18.2, 18.1, 15.4, 12.9, 1.7, –4.35, –4.40, –5.2; IR (thin film, NaCl) 2956, 2929, 2856, 1513, 1463, 1249, 1105, 835, 774, 680 cm^{-1}; LRMS (EI, Na) calcd for $C_{41}H_{80}O_5Si_3$, 760.33 *m/z* (M + Na); observed, 760.77 $(M + Na)^+$ *m/z.*



(*E*)-(2*R*,3*R*,4*R*,7*S*,8*S*)-8-di(*tert*-butyldimethylsilanyloxy)-3-(*p*-methoxybenzyloxy)-7-(*tri*-isopropylsilanyloxy)-2,4,6-trimethylnon-5-ene-1-ol, 15. To a solution of **42** (237 g, 0.321 mmol) in 5 mL of THF was added successively 0.72 mL of pyridine and 0.97 mL of HF•pyr complex. After stirring at room temperature for 2 h, the reaction flask was immersed in an ice-bath and saturated $NaHCO_3$ (10 mL) was added carefully. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was concentrated and the residue was purified by flash column chromatography eluting successively with 2 % and 30 % EtOAc/ hexanes to afford 159 mg of **15** (79 %). $[\alpha]_{589}^{20}$ –29.7° (*c* 0.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.28-7.26 (m, 2H), 6.88-6.85 (m, 2H), 5.63 (d, *J* = 9.8 Hz, 1H), 4.63 (A of AB, *J* = 11.1 Hz, 1H), 4.49 (B of AB, *J* = 11.1 Hz, 1H), 4.14 (d, *J* = 4.3 Hz, 1H), 3.92-3.88 (m, 1H), 3.81 (s, 3H), 3.59 (dd, *J* = 10.7, 6.4 Hz, 1H), 3.50 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.41 (dd, *J* = 4.9, 4.9 Hz, 1H), 2.88-2.77 (m, 1H), 1.98-1.90 (m, 1H), 1.70 (d, *J* = 1.0 Hz, 3H), 1.05-0.99 (m, 30H), 0.88 (s, 9H), 0.054 (s, 3H), 0.048 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ159.2, 134.3, 131.4, 129.4, 129.2, 128.6, 113.9, 84.8, 79.6, 73.6, 72.9, 66.7, 55.5, 38.2,

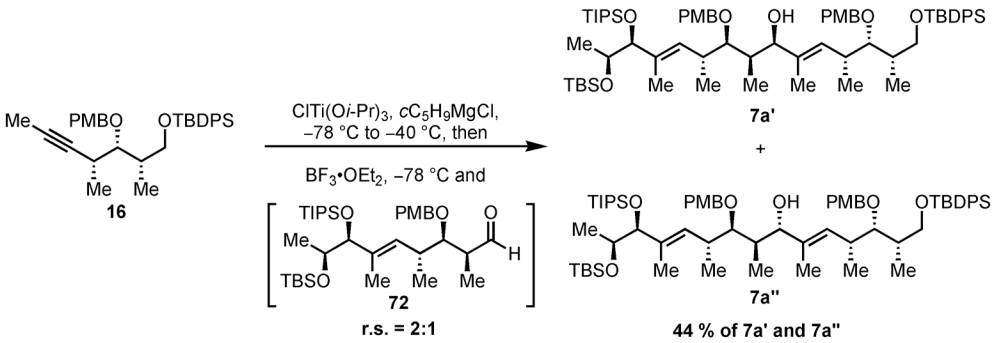
35.1, 26.1, 18.44, 18.36, 18.2, 18.0, 15.5, 12.6, 12.5, −4.3, −4.4; IR (thin film, NaCl) 3419, 2958, 2867, 1514, 1463, 1389, 1249, 1101, 1039, 883, 835, 735, 678 cm^{-1}; LRMS (EI, Na) calcd for $C_{35}H_{66}O_5Si_2$, 645.07 *m/z* (M + Na); observed, 645.75 $(M + Na)^+$ *m/z*.



(2*S*,3*S*,4*R*)-1-(*tert*-butyldiphenylsilanyloxy)-3-(*p*-methoxybenzyloxy)-2,4-dimethyl-5-heptyn, 16. Sodium hydride (137 mg, 3.43 mmol) was added at once to a stirring solution of homopropargyl alcohol **77**[2] (1.23 g, 3.12 mmol) and PMB-Br (755 mg, 3.74 mmol) in DMF (16 mL) at −20 °C. The reaction was allowed to reach room temperature and stirred overnight before pouring into a separatory funnel containing EtOAc (30 mL) and water (20 mL). The phases were separated and the organic layer further washed with water (3 × 20 mL), sat. $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The residue obtained after solvent removal was purified by flash column chromatography on silica gel eluting successively with 1 %, 2 % and 3 % EtOAc/ hexanes to afford 1.49 g (93 %) of pure **16**. $[\alpha]_{589}^{20}$ −1.32° (*c* 0.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.68 (m, 4H), 7.46-7.37 (m, 6H), 7.23-7.21 (m, 2H), 6.86-6.84 (m, 2H), 4.60 (A of AB, *J* = 11.1 Hz, 1H), 4.55 (B of AB, *J* = 11.1 Hz, 1H), 3.81 (s, 3H), 3.67-3.34 (m, 2H), 3.55 (dd, *J* = 9.8, 5.7 Hz, 1H), 2.68-2.61 (m, 1H), 2.37-2.29 (m, 1H), 1.83 (d, *J* = 2.4 Hz, 3H), 1.27 (d, *J* = 2.9 Hz, 3H), 1.10 (s, 9H), 0.85 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 135.9, 135.8, 134.2, 134.1, 131.4, 129.8, 129.5, 127.9, 127.8, 113.9, 82.5, 81.9, 74.9, 66.8, 55.5, 38.8, 29.9, 27.1, 19.5, 18.6, 14.4, 10.6, 3.8; IR (thin film, NaCl) 2965, 2933, 2958, 1514, 1465, 1428, 1248, 112, 1079, 1039,

824, 702 cm^{-1}; LRMS (EI, Na) calcd for $C_{33}H_{42}O_3Si$, 537.77 *m/z* (M + Na); observed, 537.55 $(M + Na)^+$ *m/z*

(*E*)-(2*R*,3*R*,4*R*,8*S*)-1,8-di(*tert*-butyldimethylsilanyloxy)-3-(*p*-methoxybenzyloxy)-2,4,6-trimethylnon-5-ene-1-al, 72. To a stirring solution of **15** (20 mg, 0.032 mmol) in dichloromethane (0.64 mL, reagent grade from a bottle) at 0 °C was added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (27 mg, 0.064 mmol) at once. The reaction was stirred at 0 °C for 1 h and at room temperature for 30 min before diluting with a solution of 20 % EtOAc/ hexanes (2 mL). Most of the solvent was removed. The residue was dissolved in 5 mL of EtOAc/ hexanes and washed with a 1:1 mixture of 10 % $Na_2S_2O_3$ and sat $NaHCO_3$ until a clear organic layer was obtained. The organic layer was then washed with brine and dried over anhydrous $MgSO_4$. Crude aldehyde **72**, obtained after solvent removal, was further dried by azeotropic removal of water (concentration 3 × from anhydrous benzene). The aldehyde was used in the subsequent experiment without further purification.



Synthesis of diene 7a' and 7a'' via titanium reductive coupling. To a –78 °C solution of alkyne **16** (50 mg, 0.097 mmol) in 0.97 mL of toluene, was added sequentially

$ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in hexanes; 150 μL, 0.150 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 150 μL, 0.300 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to –40 °C and stirred for 2 h during which the reaction turned dark brown. The flask was then cooled to –78 °C and $BF_3 \bullet OEt_2$ (18 μL, 0.15 mmol) was added in a dropwise manner. Following a stirring period of 10 min at –78 °C, aldehyde **72** (20 mg, 0.032 mmol) was then added as a solution in toluene (0.1 mL) down the side of the flask via a gas tight syringe. The transfer was quantitated with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at –78 °C, before the addition of saturated NH_4Cl solution (0.3 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chomatography eluting successively with 2 %, 3 %, 5 %, 7 %, 10 % and 15 % EtOAc/ hexanes to provide 16 mg (44 %) of **7a'** and **7a"** as the major regioisomer. Compound **7a'** was obtained as an inseparable mixture with some of the minor regioisomer. The amount of this minor contaminant was determined from analysis of the ^1H spectrum and was not included in the yield reported.

Regioselectivity data for 7a' and 7a". The residue obtained after a titanium reductive coupling as described above was filtered through a short pad of silica eluting successively with 2 % (50 mL) and 4 % (50 mL) EtOAc/ hexanes until all traces of reduced alkyne **16** were removed. All remaining organics were removed by washing the

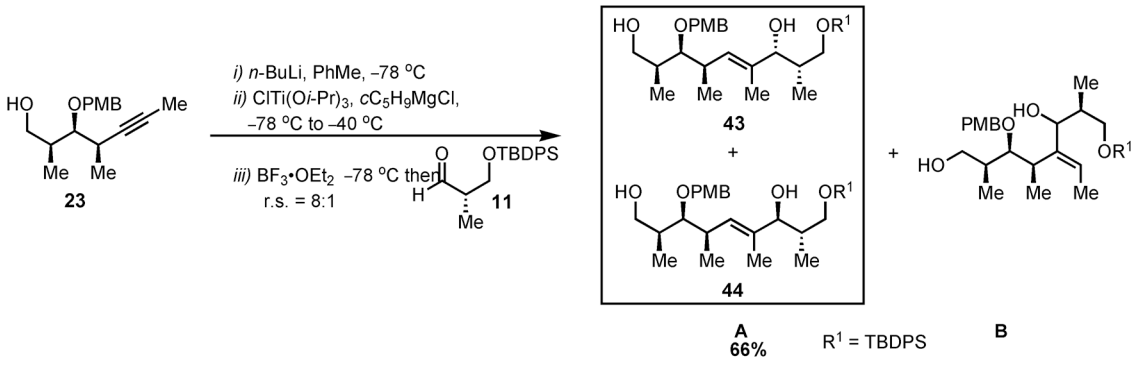
silica with 200 mL of 100 % EtOAc. Analysis of the partially purified mixture by ^{1}H NMR shows an approximately 2:1 mixture of regioisomers.

Data for major diastereomer (*E,E*)-(2*S*,3*S*,4*R*,7*R*,8*R*,9*R*,10*R*,13*S*,14*S*)-1-(*tert*-butyldiphenylsilanyloxy)-3,9-di(*p*-methoxybenzyloxy)-13-(*tri*-isopropylsilanyloxy)-14-(*tert*-butyldimethylsilanyloxy)-2,4,6,8,10,12-hexamethylpentadec-5,11-diene-7-ol, 7a'. $[\alpha]_{589}^{20}$ −13.4 ° (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66-7.63 (m, 4H), 7.44-7.32 (m, 6H), 7.31-7.29 (m,2H), 7.23-7.21 (m, 2H), 6.88-6.82 (m, 4H), 5.60 (d, *J* = 9.6 Hz, 1H), 5.34 (d, *J* = 10.1 Hz, 1H), 4.77 (A of AB, *J* = 10.1 Hz, 1H), 4.43 (B of AB, *J* = 10.1 Hz, 1H), 4.54 (m, 2H), 4.17 (d, *J* = 3.8 Hz, 1H), 4.09 (s, 1H), 3.95-3.89 (m, 1H), 3.81-3.75 (m, 5H), 3.64 (dd, *J* = 9.6 Hz, 1H), 3.56-3.50 (m, 4H), 3.04-2.96 (m, 1H), 2.74-2.66 (m, 1H), 1.97-1.92 (m, 1H), 1.74 (s, 3H), 1.53 (s, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.07-1.03 (m, 33H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.90-0.89 (m, 12H), 0.76 (d, *J* = 6.9 Hz, 3H), 0.062 (s, 3H), 0.043 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 159.2, 135.82, 135.79, 134.7, 134.6, 134.2, 134.1, 131.7, 131.1, 129.8, 129.5, 129.3, 127.9, 114.0, 113.9, 87.0, 83.4, 79.4, 79.2, 75.2, 73.1, 72.8, 66.9, 55.50, 55.48, 39.2, 37.8, 36.4, 35.3, 27.1, 26.1, 19.5, 18.41, 18.36, 18.2, 17.84, 17.77, 16.1, 14.1, 12.7, 10.8, 7.7, –4.36, –4.45; IR (thin film, NaCl) 3483, 2958, 2931, 2864, 1612, 1514, 1463, 1248, 1108, 1039, 842, 775, 701 cm^{-1}; LRMS (EI, Na) calcd for $C_{68}H_{108}O_8Si_3$, 1160.84 *m/z* (M + Na); observed, 1144.02 $(M + Na)^+$ *m/z.*

Data for minor diastereomer (*E,E*)-(2*S*,3*S*,4*R*,7*S*,8*R*,9*R*,10*R*,13*S*,14*S*)-1-(*tert*-butyldiphenylsilanyloxy)-3,9-di(*p*-methoxybenzyloxy)-13-(*tri*-isopropylsilanyloxy)-14-(*tert*-butyldimethylsilanyloxy)-2,4,6,8,10,12-hexamethylpentadec-5,11-diene-7-ol, 7a". $[\alpha]_{589}^{20}$ +4.42 ° (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66-7.63 (m, 4H),

7.42-7.35 (m, 6H), 7.28-7.27 (m,2H), 7.21-7.19 (m, 2H), 6.84-6.83 (m, 4H), 5.68 (d, J = 9.4 Hz, 1H), 5.21 (d, J = 10.0 Hz, 1H), 4.66-4.54 (m, 4H), 4.17 (d, J = 3.9 Hz, 1H), 3.94-3.91 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.66-3.62 (m, 2H), 3.53-3.50 (m, 2H), 2.87-2.83 (m, 1H), 2.74-2.65 (m, 1H), 2.00-1.91 (m, 1H), 1.74 (s, 3H), 1.60 (s, 3H), 1.10 (d, J = 6.7 Hz, 3H), 1.08-1.05 (m, 27H), 1.02 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.89 (m, 12H), 0.83 (d, J = 7.0 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H), 0.059 (s, 3H), 0.041 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.24, 159.17, 135.8, 135.7, 134.2, 133.98, 133.94, 131.7, 131.6, 129.81, 129.79, 129.4, 129.3, 127.9, 113.94, 113.89, 83.3, 80.8, 79.4, 75.2, 73.2, 73.1, 66.8, 55.50, 55.46, 39.2, 37.7, 36.3, 35.3, 27.1, 26.1, 19.5, 19.0, 18.4, 18.3, 18.2, 17.9, 15.7, 12.7, 12.3, 11.3, 10.5, −4.31, −4.42; IR (thin film, NaCl) 3487, 2930, 2863, 1613, 1514, 1463, 1248, 1108, 1039, 883, 825, 701, 668 cm^{-1}; LRMS (EI, Na) calcd for $C_{68}H_{108}O_8Si_3$, 1160.87 *m/z* (M + Na); observed, 1144.16 $(M + Na)^+$ *m/z*.

***Table 1*. The role of a tethered free hydroxyl in titanium alkoxide-mediated reductive coupling reactions.**

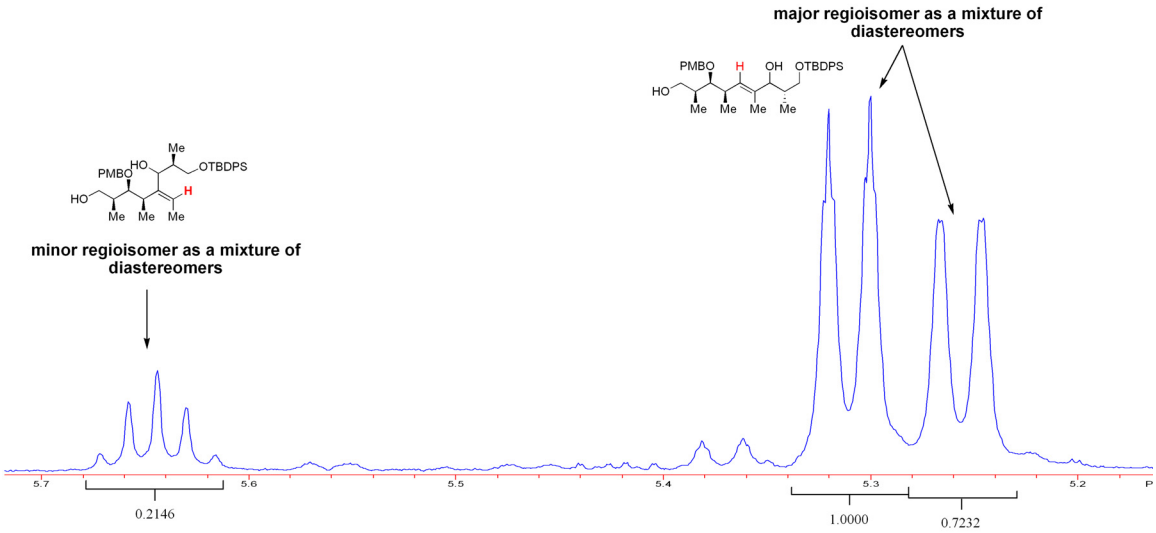


Entry 1 - synthesis of ene-diol 43 and 44. To a −78 °C solution of alkyne **23** (20 mg, 0.072 mmol) in 0.72 mL of toluene, was added sequentially, *n*-BuLi (2.27 M in hexanes; 35 μL, 0.080 mmol), $ClTi(Oi\text{-}Pr)_3$ (1.0 M in hexanes; 160 μL, 0.16 mmol) and

c-C_5H_9MgCl (2.0 M in diethyl ether; 160 μL, 0.32 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to −40 °C and stirred for 2 h during which the reaction turned dark brown. The flask was then cooled to −78 °C and BF_3•OEt_2 (29 μL, 0.23 mmol) was added in a dropwise manner. Following a stirring period of 10 min at −78 °C, aldehyde **11** (76 mg, 0.23 mmol) was added as a solution in toluene (0.2 mL) down the side of the flask via a gas tight syringe. The transfer was quantitated with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at −78 °C, before the addition of saturated NH_4Cl solution (0.4 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography eluting successively with 5 % (100 mL), 7% (50 mL), 10 % (100 mL), 15 %(50 mL), 20 % (100 mL) and 30 % (200 mL) EtOAc/ hexanes to provide 29 mg (66 %) of **43** and **44** as the major regioisomer **A**. Compound **44** was obtained with a small amount (10%) of the minor regioisomer as contaminant. The amount of this contaminant was included in the yield reported.

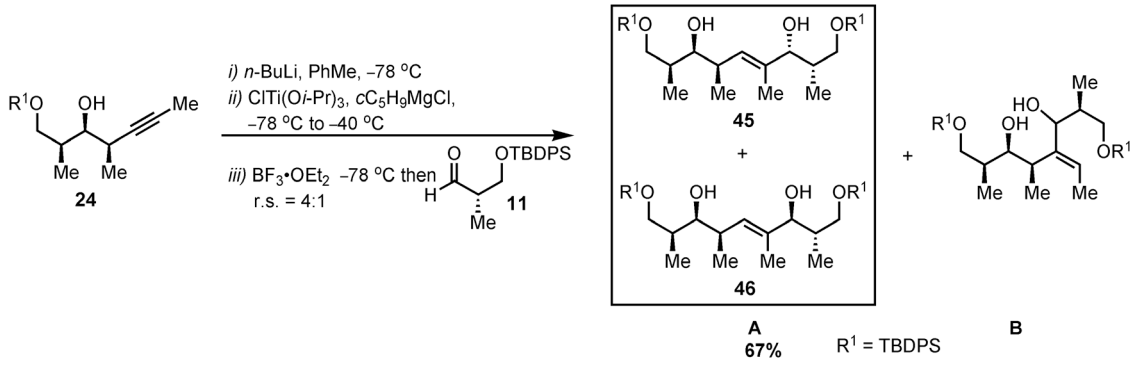
Entry 1 - Regioselectivity data A:B. The residue obtained after a titanium reductive coupling using the above procedure was filtered through a short pad of silica eluting successively with 5 % (50 mL), 7 % (50 mL), 10 % (50 mL) and 15 % (50 mL) EtOAc/ hexanes until all traces of the partially reduced olefinic product of alkyne **23** were removed. All remaining organics were removed by washing the silica with 200 mL

of 100 % EtOAc. Analysis of the partially purified mixture by ^{1}H NMR shows an approximately 8:1 mixture of regioisomers.



Data for major diastereomer (*E*)-(2*S*,3*R*,6*R*,7*S*,8*S*)-1-(*tert*-butyldiphenylsilanyloxy)-7-(*p*-methoxybenzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,9-diol, 43. $[\alpha]_{589}^{20}$ +16.8 ° (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.67 (m, 4H), 7.47-7.39 (m, 6H), 7.31-7.28 (m, 2H), 6.90-6.88 (m, 2H), 5.31 (d, *J* = 10.1 Hz, 1H), 4.62 (A of AB, *J* = 10.8 Hz, 1 H), 4.52 (B of AB, *J* = 10.8 Hz, 1 H), 4.22 (s, 1 H), 3.81 (s, 3H), 3.72-3.64 (m, 2H), 3.58-3.57 (m, 2H), 3.43-3.41 (m, 1H), 2.76-2.68 (m, 1H), 2.65 (s br, 1H), 1.93-1.83 (m, 2H), 1.62 (s br, 1H), 1.57 (s, 3H), 1.08 (s, 9H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 135.89, 135.83, 134.8, 133.5, 133.3, 131.2, 130.01, 129.96, 129.6, 128.3, 127.96, 127.95, 114.0, 84.4, 77.9, 74.9, 68.4, 66.6, 55.5, 38.8, 37.8, 36.2, 27.1, 19.4, 19.1, 13.6, 10.8, 10.6; IR (thin film, NaCl) 3396, 2962, 2931, 2859, 1613, 1514, 1472, 1428, 1249, 1113, 1089, 1033, 824, 739, 702 cm^{-1}; LRMS (EI, Na) calcd for $C_{37}H_{52}O_5Si$, 627.89 *m/z* (M + Na); observed, 627.55 $(M + Na)^{+}$ *m/z*.

Data for minor diastereomer (*E*)-(2*S*,3*S*,6*R*,7*S*,8*S*)-1-(*tert*-butyldiphenylsilanyloxy)-7-(*p*-methoxybenzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,9-diol, 44. $[\alpha]_{589}^{20}$ +20.3 ° (*c* 0.23, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.69 (m, 4H), 7.46-7.41 (m, 6H), 7.30-7.29 (m, 2H), 6.89-6.88 (m, 2H), 5.25 (d, *J* = 9.9 Hz, 1H), 4.60 (A of AB, *J* = 10.8 Hz, 1 H), 4.54 (B of AB, *J* = 10.8 Hz, 1 H), 4.00 (s br, 1 H), 3.91 (d, *J* = 8.6 Hz, 1H), 3.81 (s, 3H), 3.79 (dd, *J* = 13.1, 6.9 Hz, 1H), 3.67-3.63 (m, 1H), 3.59-3.53 (m, 2H), 3.41 (d, *J* = 9.1 Hz, 1H), 2.77-2.72 (m, 1H), 2.00-1.94 (m, 1H), 1.88-1.82 (m, 1H), 1.67 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.08 (s, 9H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.65 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 135.84, 135.83, 135.4, 132.9, 131.6, 131.2, 130.1, 129.6, 128.0, 84.2, 84.1, 77.8, 74.9, 69.6, 66.5, 55.5, 38.8, 37.8, 36.3, 27.0, 19.3, 18.3, 13.8, 11.3, 10.8; IR (thin film, NaCl) 3422, 2959, 2931, 2857, 1612, 1514, 1463, 1428, 1248, 1036, 823, 741 cm^{-1}; LRMS (EI, Na) calcd for $C_{37}H_{52}O_5Si$, 627.89 *m/z* (M + Na); observed, 627.51 $(M + Na)^+$ *m/z*.



Entry 2 - synthesis of ene-1,5-diol 45 and 46. To a −78 °C solution of alkyne **47** (30 mg, 0.076 mmol) in 0.76 mL of toluene, was added sequentially, *n*-BuLi (2.27 M in hexanes; 37 μL, 0.084 mmol), $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in hexanes; 170 μL, 0.17 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 170 μL, 0.34 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to −40 °C and stirred

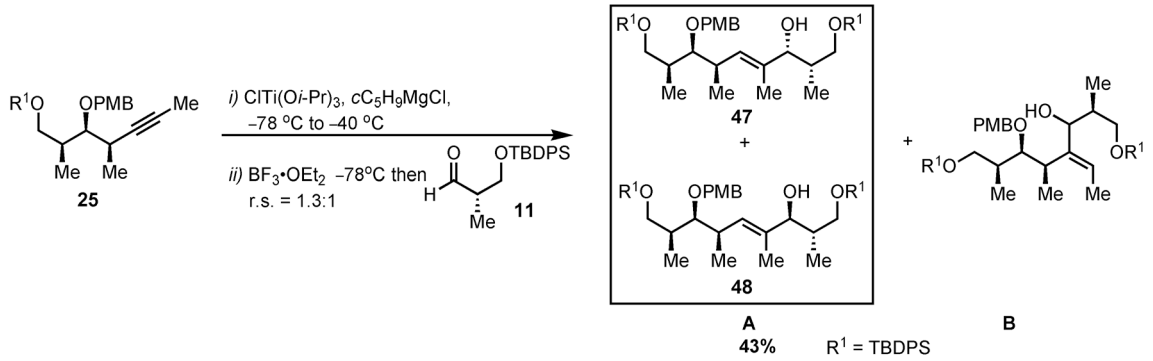
for 2 h during which the reaction turned dark brown. The flask was then cooled to −78 °C and BF_3•OEt_2 (31 μL, 0.24 mmol) was added in a dropwise manner. Following a stirring period of 10 min at −78 °C, aldehyde **11** (79 mg, 0.24 mmol) was then added as a solution in toluene (0.2 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at −78 °C, before the addition of saturated NH_4Cl solution (0.4 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography eluting successively with 2 % (100 mL), 4 % (100 mL), 7 % (50 mL), 10 % (50 mL), 15 % (100 mL) and 20 % (100 mL) EtOAc/ hexanes to provide 37 mg (67 %) of **45** and **46** as the major regioisomer **A**.

Entry 2 - Regioselectivity data A:B. The residue obtained after a titanium reductive coupling using the above procedure was filtered through a short pad of silica eluting successively with 2 % (100 mL), 4 % (50 mL) and 6 % (50 mL) EtOAc/ hexanes until all traces of the partially reduced olefinic product of alkyne **24** were removed. All remaining organics were removed by washing the silica with 200 mL of 100 % EtOAc. Analysis of the partially purified mixture by ^{1}H NMR shows an approximately 4:1 mixture of regioisomers.

Data for major diastereomer (*E*)-(2*S*,3*R*,6*R*,7*S*,8*S*)-1,9-di(*tert*-butyldiphenylsilanyloxy)-2,4,6,8-tetramethylnon-4-ene-3,7-diol, 45. $[\alpha]_{589}^{20}$ +9.3 ° (*c* 0.84, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68-7.67 (m, 8H), 7.44-7.30 (m, 12H), 5.24

(d, J = 10.1 Hz, 1H), 4.23 (d, J = 3.0 Hz, 1H), 3.81 (dd, J = 10.2, 3.7 Hz, 1H), 3.72-3.63 (m, 4H), 2.59-2.51 (m, 1H), 1.87-1.82 (m, 1H), 1.80-1.73 (m, 1H), 1.61 (s, 3H), 1.075 (s, 9H), 1.068 (s, 9H), 1.05 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 7.1 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.0, 135.89, 135.85, 135.8, 135.1, 133.5, 133.4, 133.2, 130.1, 130.01, 129.98, 128.00, 127.97, 127.96, 127.94, 127.88, 127.7, 78.8, 77.7, 70.0, 68.4, 37.7, 37.2, 36.5, 27.13, 27.11, 19.43, 19.42, 18.0, 13.8, 10.4, 9.6; IR (thin film, NaCl) 3471, 2959, 2930, 2858, 1472, 1427, 1113, 998, 823, 740, 701, 614 cm^{-1}; LRMS (EI, Na) calcd for $C_{45}H_{62}O_4Si_2$, 746.14 *m/z* (M + Na); observed, 746.72 $(M + Na)^+$ *m/z*.

Data for minor diastereomer (*E*)-(2*S*,3*S*,6*R*,7*S*,8*S*)-1,9-di(*tert*-butyldiphenylsilanyloxy)-2,4,6,8-tetramethylnon-4-ene-3,7-diol, 46. $[\alpha]_{589}^{20}$ +12.5 ° (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.65 (m, 8H), 7.49-7.380 (m, 12H), 5.13 (d, J = 10.1 Hz, 1H), 3.87 (d, J = 8.7 Hz, 1H), 3.78-3.76 (m, 2H), 3.67-3.61 (m, 3H), 2.60-2.52 (m, 1H), 1.98-1.93 (m, 1H), 1.72-1.63 (m, 1H), 1.67 (s, 3H), 1.11 (d, J = 6.5 Hz, 3H), 1.07 (s, 18H), 0.91 (d, J = 7.0 Hz, 3H), 0.59 (d, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.9, 135.83, 135.8, 135.6, 133.3, 133.1, 133.94, 132.92, 131.3, 130.11, 130.10, 130.06, 130.01, 128.00, 127.98, 127.97, 84.2, 78.6, 69.8, 69.6, 37.6, 37.3, 36.6, 27.1, 27.01, 19.4, 19.3, 17.0, 13.7, 11.3, 9.5; IR (thin film, NaCl) 3472, 2958, 2930, 2857, 1427, 1112, 740, 701 cm^{-1}; LRMS (EI, Na) calcd for $C_{45}H_{62}O_4Si_2$, 746.14 *m/z* (M + Na); observed, 746.63 $(M + Na)^+$ *m/z*.



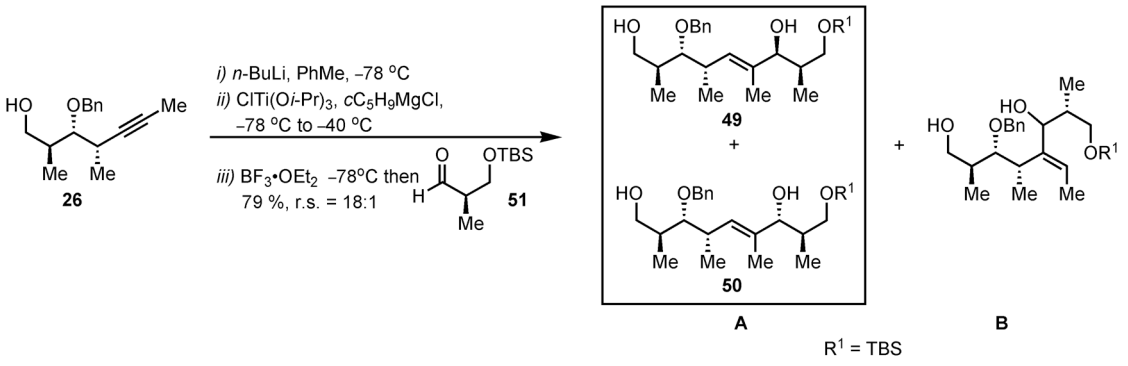
Entry 3 - synthesis of enol 47 and 48. To a −78 °C solution of alkyne **25** (35 mg, 0.068 mmol) in 0.68 mL of toluene, was added sequentially, $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in hexanes; 150 μL, 0.15 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 150 μL, 0.30 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to −40 °C and stirred for 2 h during which the reaction turned dark brown. The flask was then cooled to −78 °C and BF_3•OEt_2 (19 μL, 0.15 mmol) was added in a dropwise manner. Following a stirring period of 10 min at −78 °C, aldehyde **11** (71 mg, 0.22 mmol) was then added as a solution in toluene (0.2 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at −78 °C, before the addition of saturated NH_4Cl solution (0.4 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography eluting successively with 2 % (100 mL), 4 % (100 mL), 7 % (100 mL), 10 % (50 mL), 15 % (100 mL) and 20 % (100 mL) EtOAc/ hexanes to provide 24 mg (43 %) of **47** and **48** as the major regioisomer **A**.

Entry 3 - Regioselectivity data A:B. The residue obtained after a titanium reductive coupling using the above procedure was filtered through a short pad of silica eluting successively with 2 % (100 mL) and 4 % (50 mL) EtOAc/ hexanes until all traces of the partially reduced olefinic product of alkyne **25** were removed. All remaining organics were removed by washing the silica with 200 mL of 100 % EtOAc. Analysis of the partially purified mixture by ^{1}H NMR shows an approximately 1.3:1 mixture of regioisomers.

Data for major diastereomer (*E*)-(2*S*,3*R*,6*R*,7*S*,8*S*)-1,9-di(*tert*-butyldiphenylsilanyloxy)- 7-(*p*-methoxybenzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,7-diol, 47. $[\alpha]_{589}^{20}$ +9.21 ° (*c* 0.89, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68-7.66 (m, 8H), 7.42-7.38 (m, 12H), 7.22-7.20 (m, 2H), 6.85-6.83 (m, 2H), 5.33 (d, *J* = 10.1 Hz, 1H), 4.54 (s, 2H), 4.23, (s, 1H), 3.80 (s, 3H), 3.74-3.61 (m, 3H), 3.57-3.51 (m, 2H), 2.72-2.65 (m, 1H), 1.98-1.91 (m, 1H), 1.90-1.82 (m, 1H), 1.57 (s, 3H), 1.09 (s, 9H), 1.06 (s, 9H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 135.9, 135.84, 135.82, 135.80, 134.7, 134.2, 134.1, 133.6, 133.4, 131.7, 130.00, 129.97, 129.8, 129.5, 128.4, 127.96, 127.95, 127.87, 127.85, 113.9, 83.3, 77.9, 75.2, 68.4, 66.9, 55.5, 39.2, 37.8, 36.3, 27.15, 27.12, 19.51, 19.46, 18.3, 13.7, 10.5, 10.4; IR (thin film, NaCl) 3496, 2962, 2859, 1427, 1248, 1112, 740, 701 cm^{-1}; LRMS (EI, Na) calcd for $C_{53}H_{70}O_5Si_2$, 866.29 *m/z* (M + Na); observed, 866.72 $(M + Na)^+$ *m/z.*

Data for minor diastereomer (*E*)-(2*S*, 3*S*,6*R*,7*S*,8*S*)-1,9-di(*tert*-butyldiphenylsilanyloxy) -7-(*p*-methoxybenzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,7-diol, 48. $[\alpha]_{589}^{20}$ +19.6 ° (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.63 (m,

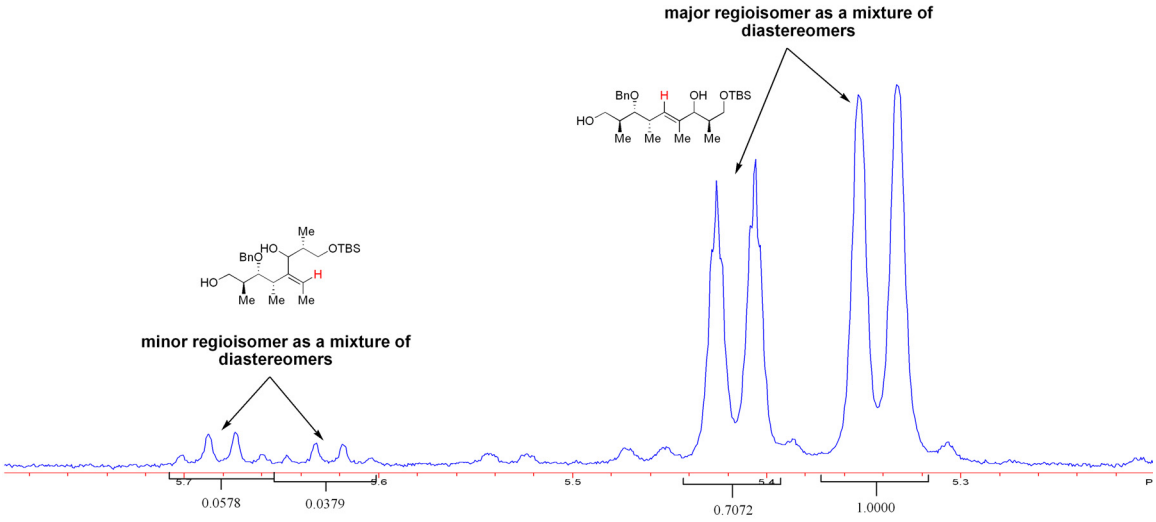
8H), 7.45-7.33 (m, 12H), 7.22-7.20 (m, 2H), 6.85-6.84 (m, 2H), 5.22 (d, J = 10.0 Hz, 1H), 4.55 (s, 2H), 3.98, (s, 1H), 3.92 (d, J = 8.9 Hz, 1H), 3.80 (s, 3H), 3.70-3.62 (m, 2H), 3.55-3.49 (m, 2H), 2.74-2.68 (m, 1H), 2.01-1.93 (m, 1H), 1.91-1.84 (m, 1H), 1.66 (s, 3H), 1.12(d, J = 6.5 Hz, 3H), 1.08 (s, 9H), 1.06 (s, 9H), 0.76 (d, J = 6.8 Hz, 3H), 0.62 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 135.85, 135.78, 135.74, 135.2, 134.1, 133.03, 132.99, 132.1, 131.6, 130.1, 129.80, 129.78, 129.4, 128.05, 128.04, 127.9, 127.8, 113.9, 84.4, 83.2, 75.3, 69.8, 66.8, 55.5, 39.2, 37.8, 36.3, 27.1, 27.0, 19.5, 19.3, 18.3, 13.7, 11.1, 10.4; IR (thin film, NaCl) 3492, 2960, 2931, 2858, 1514, 1472, 1428, 1248, 1112, 1038, 823, 740, 701, 614 cm^{-1}; LRMS (EI, Na) calcd for $C_{53}H_{70}O_5Si_2$, 866.29 *m/z* (M + Na); observed, 866.72 (M + Na)$^+$ *m/z.*



Entry 4 - synthesis of ene-diol 49 and 50. To a −78 °C solution of alkyne **26** (20 mg, 0.081 mmol) in 0.81 mL of toluene, was added sequentially, *n*-BuLi (2.27 M in hexanes; 39 μL, 0.089 mmol), $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in hexanes; 180 μL, 0.18 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 180 μL, 0.36 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to −40 °C and stirred for 2 h during which the reaction turned dark brown. The flask was then cooled to −78 °C and BF_3•OEt_2 (33 μL, 0.260 mmol) was added in a dropwise manner. Following a stirring period of 10 min at −78 °C, aldehyde **51** (53 mg, 0.26 mmol) was then added as a

solution in toluene (0.2 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at −78 °C, before the addition of saturated NH_4Cl solution (0.4 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography eluting successively with 5 % (100 mL), 7% (50 mL), 10 % (100 mL), 15 % (50 mL), 20 % (100 mL) and 30 % (200 mL) EtOAc/ hexanes to provide 29 mg (79 %) of an inseparable mixture of regioisomers **A** and **B**.

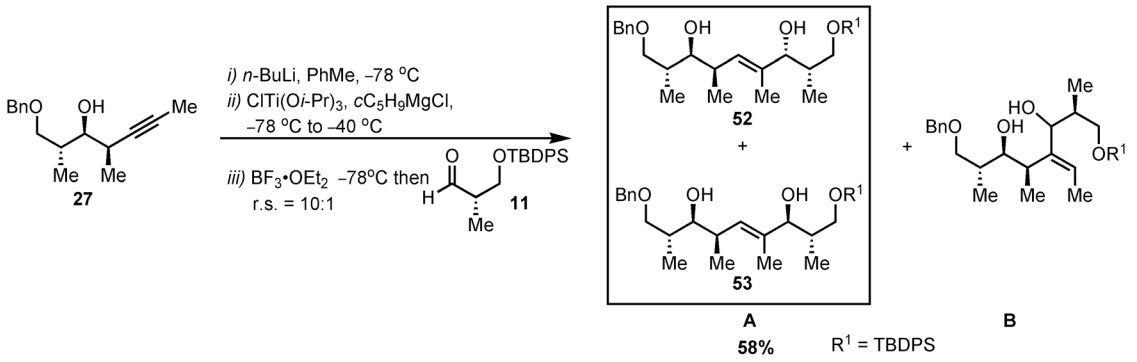
Entry 4 - Regioselectivity data A:B. The residue obtained after a titanium reductive coupling using the above procedure was filtered through a short pad of silica eluting successively with 5 % (100 mL), 7 % (50 mL), 10 % (50 mL) and 15 % (50 mL) EtOAc/ hexanes until all traces of the partially reduced olefinic product of alkyne **26** were removed. All remaining organics were removed by washing the silica with 200 mL of 100 % EtOAc. Analysis of the partially purified mixture by ^1H NMR shows an approximately 18:1 mixture of regioisomers.



Data for major diastereomer (*E*)-(2*R*,3*S*,6*S*,7*R*,8*S*)-1-(*tert*-butyldimethylsilanyloxy)-7-(benzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,9-diol, 49. $[\alpha]_{589}^{20}$ –22.3° (*c* 1.37, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 5.34 (d, *J* = 9.8 Hz, 1H), 4.66 (A of AB, *J* = 10.8 Hz, 1 H), 4.59 (B of AB, *J* = 10.8 Hz, 1 H), 4.14 (s br, 1 H), 3.85 (d, *J* = 8.2 Hz, 1H), 3.81-3.76 (m, 2H), 3.62-3.54 (m, 2H), 3.27 (dd, *J* = 6.5, 5.1 Hz, 1H), 2.85-2.77 (m, 1H), 2.76-2.60 (s br, 1H), 1.94-1.83 (m, 2H), 1.66 (d, *J* = 0.73 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 7.2 Hz, 3H), 0.92 (s, 9H), 0.71 (d, *J* = 7.0 Hz, 3H), 0.10 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 135.9, 131.4, 128.7, 128.05, 127.98, 89.9, 84.2, 76.0, 68.9, 65.7, 37.7, 37.5, 36.3, 26.0, 18.3, 16.8, 16.0, 13.9, 11.7, –5.4, –5.5; IR (thin film, NaCl) 3425, 2958, 2929, 2858, 1471, 1456, 1253, 1089, 1005, 836, 777, 697 cm^{-1}; LRMS (EI, Na) calcd for $C_{26}H_{46}O_4Si$, 473.73 *m/z* (M + Na); observed, 473.49 $(M + Na)^+$ *m/z*.

Data for minor diastereomer (*E*)-(2*R*,3*R*,6*S*,7*R*,8*S*)-1-(*tert*-butyldimethylsilanyloxy)-7-(benzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,9-diol, 50. $[\alpha]_{589}^{20}$ –17.7° (*c* 0.9, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.29 (m, 5H), 5.42 (d,

J = 9.9 Hz, 1H), 4.68 (A of AB, *J* = 10.8 Hz, 1 H), 4.61 (B of AB, *J* = 10.8 Hz, 1 H), 4.19 (s, 1 H), 3.80 (d, *J* = 10.8 Hz, 1H), 3.76 (dd, *J* = 9.9, 4.0 Hz, 1H), 3.68 (dd, *J* = 9.8, 4.6 Hz, 1H), 3.55-3.53 (m, 1H), 3.30 (dd, *J* = 7.1, 4.6 Hz, 1H), 3.07 (s br, 1H), 2.85-2.78 (m, 1H), 2.75 (s br, 1H), 1.93-1.82 (m, 2H), 1.60 (s, 3H), 1.11 (d, *J* = 2.65 Hz, 3H), 1.10 (d, *J* = 2.15 Hz, 3H), 0.92 (s, 9H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.085 (s, 3H), 0.080 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 135.0, 128.7, 128.07, 128.05, 90.2, 78.3, 76.2, 68.3, 65.6, 37.6, 37.4, 36.5, 26.1, 18.4, 17.1, 16.1, 14.0, 10.3, –5.35, –5.39; IR (thin film, NaCl) 3410, 2957, 2929, 2857, 1471, 1454, 1256, 1094, 1028, 836, 777, 698 cm^{-1}; LRMS (EI, Na) calcd for $C_{26}H_{46}O_4Si$, 473.73 *m/z* (M + Na); observed, 473.49 (M + Na)$^+$ *m/z*.



Entry 5 - synthesis of ene-1,5-diol 52 and 53. To a −78 °C solution of alkyne **27** (20 mg, 0.081 mmol) in 0.81 mL of toluene, was added sequentially, *n*-BuLi (2.27 M in hexanes; 39 μL, 0.089 mmol), $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in hexanes; 180 μL, 0.18 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 180 μL, 0.36 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to −40 °C and stirred for 2 h during which the reaction turned dark brown. The flask was then cooled to −78 °C and BF_3•OEt_2 (33 μL, 0.26 mmol) was added in a dropwise manner. Following a stirring period of 10 min at −78 °C, aldehyde **11** (85 mg, 0.26 mmol) was then added as a

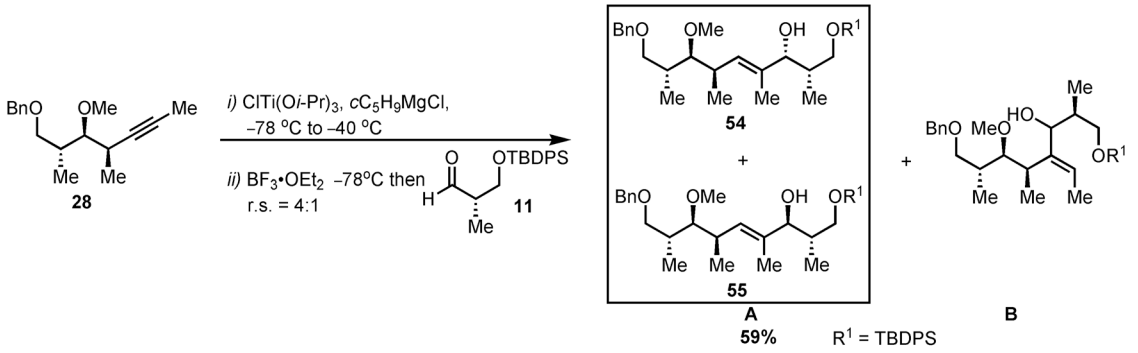
solution in toluene (0.2 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at −78 °C, before the addition of saturated NH_4Cl solution (0.4 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography eluting successively with 2 % (100 mL), 4 % (100 mL), 7 % (50 mL), 10 % (50 mL), 15 % (100 mL) and 20 % (200 mL) EtOAc/ hexanes to provide 27mg (58 %) of **52** and **53** as the major regioisomer **A**.

Entry 5 - Regioselectivity data A:B. The residue obtained after a titanium reductive coupling using the above procedure was filtered through a short pad of silica eluting successively with 2 % (100 mL), 4 % (50 mL) and 6 % (50 mL) EtOAc/ hexanes until all traces of the partially reduced olefinic product alkyne **27** were removed. All remaining organics were removed by washing the silica with 200 mL of 100 % EtOAc. Analysis of the partially purified mixture by ^{1}H NMR shows an approximately 10:1 mixture of regioisomers.

Data for (*E*)-(2*R*,3*S*,6*R*,7*S*,8*R*)-1,9-di(benzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,7-diol, 52. $[\alpha]_{589}^{20}$ +29.6° (*c* 0.73, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.68 (m, 4H), 7.68-7.28 (m, 11H), 5.33 (d, *J* = 9.6 Hz, 1H), 4.53 (A of AB, *J* = 12.0 Hz, 1 H), 4.48 (B of AB, *J* = 12.0 Hz, 1 H), 3.91-3.90 (m, 2H), 3.78 (dd, *J* = 10.1, 4.1 Hz, 1H), 3.64 (dd, *J* = 10.1, 7.9 Hz, 1H), 3.61 (dd, *J* = 9.2, 4.2 Hz, 1H), 3.43 (dd, *J* = 9.0, 5.2 Hz, 1H), 3.28 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.03 (d, *J* = 6.1 Hz, 1H), 2.55-2.48 (m, 1H),

1.97-1.82 (m, 2H), 1.58 (d, J = 1.1 Hz, 3H), 1.07 (s, 9H), 1.06 (d, J = 2.3 Hz, 3H), 1.04 (d, J = 2.8 Hz, 3H), 0.63 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 135.8, 135.0, 133.0, 131.9, 130.1, 128.7, 128.02, 127.96, 83.9, 80.2, 74.1, 73.8, 69.5, 37.7, 36.5, 36.0, 27.0, 19.3, 15.9, 15.4, 13.9, 11.3; IR (thin film, NaCl) 3451, 2959, 2858, 1428, 1112, 1078, 822, 739, 701, 613 cm^{-1}; LRMS (EI, Na) calcd for $C_{36}H_{50}O_4$ Si, 597.87 *m/z* (M + Na); observed, 597.50 $(M + Na)^+$ *m/z.*

Data for (*E*)-(2*S*,3*R*,6*R*,7*S*,8*R*)-1,9-di(benzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,7-diol, 53. $[\alpha]_{589}^{20}$ +15.6° (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4H), 7.46-7.36 (m, 6H), 7.36-7.28 (m, 5H), 5.36 (d, J = 9.7 Hz, 1H), 4.53 (A of AB, J = 12.0 Hz, 1 H), 4.48 (B of AB, J = 12.0 Hz, 1 H), 4.17 (d, J = 3.9 Hz, 1H), 3.64 (dd, J = 5.0, 2.6 Hz, 1H), 3.61 (dd, J = 9.0, 4.1 Hz, 1H), 3.43 (dd, J = 9.1, 5.0 Hz, 1H), 3.31 (dd, J = 11.8, 5.8 Hz, 1H), 3.01 (d, J = 6.0 Hz, 1H), 2.53-2.45 (m, 2H), 1.93-1.81 (m, 2H), 1.47 (d, J = 0.94 Hz, 3H), 1.07 (s, 9H), 1.06 (d, J = 7.2 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.1, 135.9, 135.8, 134.7, 133.6, 133.5, 129.96, 129.93, 128.9, 128.7, 128.00, 127.96, 127.93, 127.92, 80.2, 78.1, 74.0, 73.8, 68.0, 38.0, 36.5, 35.9, 27.1, 19.3, 16.0, 15.5, 13.3, 10.9; IR (thin film, NaCl) 3440, 2960, 2930, 2858, 1454, 1428, 1112, 1089, 1006, 823, 739, 701, 614 cm^{-1}; LRMS (EI, Na) calcd for $C_{36}H_{50}O_4$ Si, 597.87 *m/z* (M + Na); observed, 597.50 $(M + Na)^+$ *m/z*.

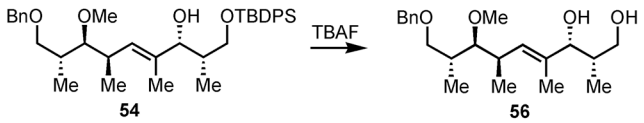


Entry 6 - synthesis of allylic alcohols 54 and 55. To a −78 °C solution of alkyne **28** (20 mg, 0.075 mmol) in 0.75 mL of toluene, was added sequentially, ClTi(O*i*-Pr)$_3$ (1.0 M in hexanes; 170 μL, 0.17 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 170 μL, 0.34 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to −40 °C and stirred for 2 h during which the reaction turned dark brown. The flask was then cooled to −78 °C and BF_3•OEt_2 (21 μL, 0.17 mmol) was added in a dropwise manner. Following a stirring period of 10 min at −78 °C, aldehyde **11** (78 mg, 0.24 mmol) was then added as a solution in toluene (0.2 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at −78 °C, before the addition of saturated NH_4Cl solution (0.4 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography eluting successively with 2 % (100 mL), 4 % (100 mL), 7 % (100 mL), 10 % (50 mL), 15 % (100 mL) and 20 % (200 mL) EtOAc/ hexanes to provide

26 mg (59 %) of **54** and **55** as the major regioisomer **A**. Compound **54** was contaminated with an impurity. This contaminant was not included in the yield.

Entry 6 - Regioselectivity data A:B. The residue obtained after a titanium reductive coupling using the above procedure was filtered through a short pad of silica eluting successively with 2 % (50 mL) and 4 % (50 mL) EtOAc/ hexanes until all traces of the partially reduced product of alkyne **28** were removed. All remaining organics were removed by washing the silica with 200 mL of 100 % EtOAc. Analysis of the partially purified mixture by ^{1}H NMR shows an approximately 4:1 mixture of regioisomers.

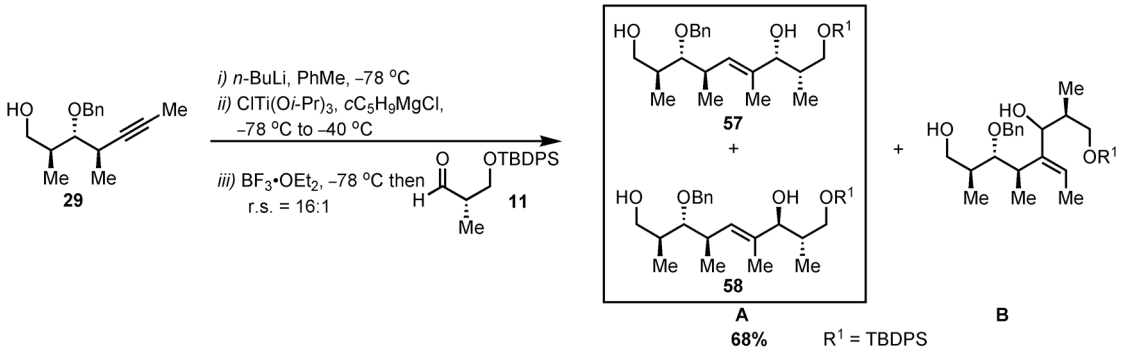
Entry 6 – Characterization data for 54. Due to contamination of allylic alcohol **54** with an unidentified impurity, characterization was performed on diol **56** obtained after a TBAF deprotection.



54 56

Data for diol 56. $[\alpha]_{589}^{20}$ +12.5 ° (*c* 0.36, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 5.37 (d, *J* = 9.6 Hz, 1H), 4.51 (A of AB, *J* = 12.1 Hz, 1 H), 4.47 (B of AB, *J* = 12.1 Hz, 1 H), 4.09 (d, *J* = 4.6 Hz, 1H), 3.66 (d, *J* = 5.1 Hz, 2H), 3.54 (dd, *J* = 8.9, 4.1 Hz, 1H), 3.44 (s, 3H), 3.39 (dd, *J* = 7.5, 7.5 Hz, 1H), 2.94 (dd, *J* = 2.9, 2.9 Hz, 1H), 2.69-2.62 (m, 1H), 2.00-1.94 (m, 1H), 1.94-1.86 (m, 1H), 1.81 (s br, 2H), 1.56 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 135.2, 129.4, 128.5, 127.9, 127.7, 88.1, 79.1, 73.3, 72.3, 67.1, 61.6, 38.0, 37.1, 35.2, 16.1, 15.7, 13.4, 11.1; IR (thin film, NaCl) 3395, 2965, 2925, 2875, 1454, 1453, 1110, 1086, 1028, 734, 695 cm^{-1}; LRMS (EI, Na) calcd for $C_{21}H_{34}O_4$, 373.49 *m/z* (M + Na); observed, 373.40 $(M + Na)^+$ *m/z*.

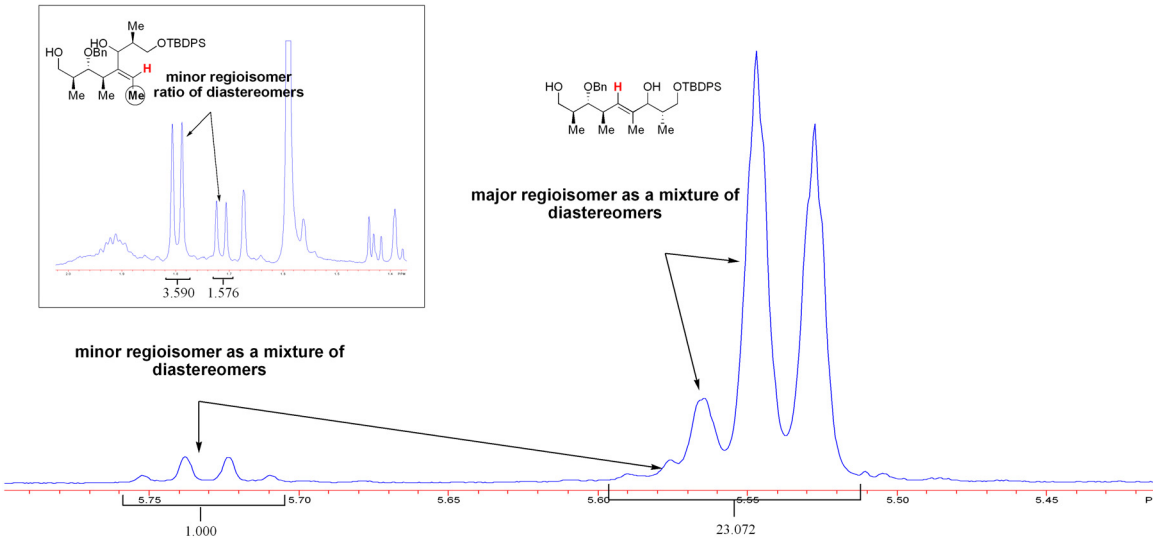
Data for minor diastereomer (*E*)-(2*S*,3*S*,6*R*,7*S*,8*S*)-11-(*tert*-butyldiphenylsilanyloxy)-7-(methoxy)- 9-(benzyloxy)--2,4,6,8-tetramethylnon-4-ene-3-ol, 55. $[\alpha]_{589}^{20}$ +14.8° (*c* 1.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.69 (m, 4H), 7.48-7.40 (m, 6H), 7.34-7.31 (m, 5H), 5.34 (d, *J* = 9.9 Hz, 1H), 4.49 (A of AB, *J* = 12.1 Hz, 1 H), 4.48 (B of AB, *J* = 12.1 Hz, 1 H), 3.93 (s, 1H), 3.90 (d, *J* = 8.6 Hz, 1H), 3.79 (dd, *J* = 4.0, 10.1 Hz, 1H), 3.65 (dd, *J* = 7.9, 10.0 Hz, 1H), 3.53 (dd, *J* = 8.9, 4.1 Hz, 1H), 3.41 (s, 3H), 3.38-3.35 (m, 1H), 2.90 (dd, *J* = 5.9, 5.9 Hz, 1H), 2.68-2.60 (m, 1H), 1.99-1.90 (m, 2H), 1.60 (d, *J* = 1.1 Hz, 3H), 1.08 (s, 9H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.66 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 135.84, 135.83, 135.0, 133.0, 132.4, 130.1, 128.5, 128.0, 127.8, 127.6, 88.2, 84.1, 73.2, 72.3, 69.6, 61.5, 37.8, 37.1, 35.2, 27.1, 19.3, 16.0, 15.6, 13.8, 11.2; IR (thin film, NaCl) 3481, 2961, 2930, 2856, 1472, 1456, 1428, 1089, 1006, 739, 701 cm^{-1}; LRMS (EI, Na) calcd for $C_{37}H_{52}O_4Si$, 611.89 *m/z* (M + Na); observed, 611.47 $(M + Na)^+$ *m/z*.



Entry 7 – synt hesis of ene-diol 57 and 58. To a –78 °C solution of alkyne **29** (20 mg, 0.081 mmol) in 0.81 mL of toluene, was added sequentially, *n*-BuLi (2.27 M in hexanes; 39 μL, 0.089 mmol), $ClTi(Oi\text{-}Pr)_3$ (1.0 M in hexanes; 180 μL, 0.18 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 180 μL, 0.36 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to –40 °C and stirred

for 2 h during which the reaction turned dark brown. The flask was then cooled to −78 °C and BF_3•OEt_2 (33 μL, 0.26 mmol) was added in a dropwise manner. Following a stirring period of 10 min at −78 °C, aldehyde **11** (85 mg, 0.26 mmol) was then added as a solution in toluene (0.2 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at −78 °C, before the addition of saturated NH_4Cl solution (0.4 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography eluting successively with 5 % (100 mL), 7 % (50 mL), 10 % (100 mL), 15 %(50 mL), 20 % (100 mL) and 30 % (200 mL) EtOAc/ hexanes to provide 32 mg (68 %) of diastereomers **57** and **58** as the major regioisomer **A**.

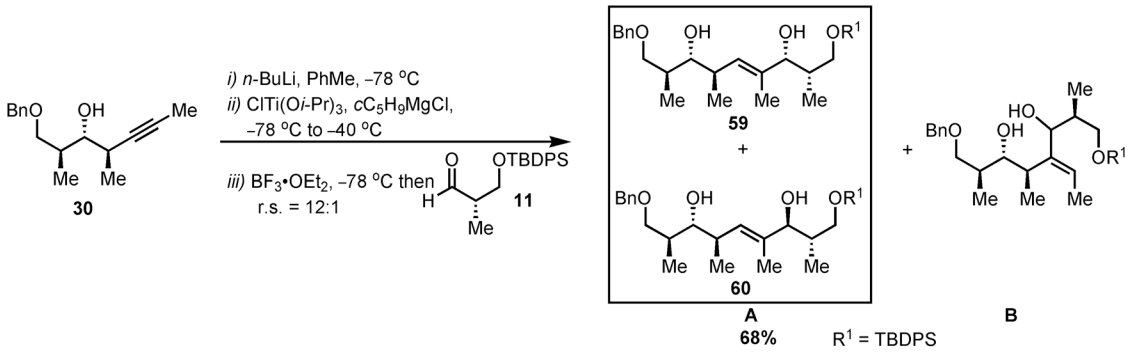
Entry 7 - Regioselectivity data A:B. The residue obtained after a titanium reductive coupling using the above procedure was filtered through a short pad of silica eluting successively with 5 % (100 mL), 7 % (50 mL), 10 % (50 mL) and 15 % (50 mL) EtOAc/ hexanes until all traces of the partially reduced olefinic product alkyne **29** were removed. All remaining organics were removed by washing the silica with 200 mL of 100 % EtOAc. Analysis of the partially purified mixture by ^1H NMR shows an approximately 16:1 mixture of regioisomers.



Data for major diastereomer (*E*)-(2*S*,3*R*,6*R*,7*R*,8*S*)-1-(*tert*-butyldimethylsilanyloxy)-7-(benzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,9-diol, 57. $[\alpha]_{589}^{20}$ –8.1° (*c* 3.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.67 (m, 4H), 7.44-7.28 (m, 11H), 5.54 (d, *J* = 9.7 Hz, 1H), 4.72 (A of AB, *J* = 11.1 Hz, 1H), 4.61 (B of AB, *J* = 11.1 Hz, 1H), 4.80 (d, *J* = 4.4 Hz, 1H), 3.71 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.66-3.61 (m, 3H), 3.31 (dd, *J* = 7.1, 4.1 Hz, 1H), 2.83-2.76 (m, 1H), 2.47 (s br, 1H), 1.91-1.84 (m, 2H), 1.57 (s, 3H), 1.08 (s, 9H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 135.98, 135.88, 135.80, 133.6, 133.5, 129.92, 129.89, 128.6, 127.93, 127.90, 127.34, 89.1, 78.3, 75.4, 68.0, 66.5, 38.2, 38.1, 35.7, 27.1, 19.4, 18.3, 15.5, 13.3, 11.1; IR (thin film, NaCl) 3422, 2961, 2930, 2859, 1473, 1456, 1362, 1112, 999, 824, 739, 701, 614 cm^{-1}; LRMS (EI, Na) calcd for $C_{36}H_{50}O_4Si$, 597.87 *m/z* (M + Na); observed, 597.51 $(M + Na)^+$ *m/z*.

Data for minor diastereomer (*E*)-(2*S*,3*S*,6*R*,7*R*,8*S*)-1-(*tert*-butyldimethylsilanyloxy)-7-(benzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,9-diol, 58.

$[\alpha]_{589}^{20}$ –24.5° (*c* 0.69, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.68 (m, 4H), 7.42-7.30 (m, 11H), 5.55 (d, *J* = 9.3 Hz, 1H), 4.73 (A of AB, *J* = 11.0 Hz, 1 H), 4.61 (B of AB, *J* = 11.0 Hz, 1 H), 3.96 (d, *J* = 8.7 Hz, 1H), 3.78 (dd, *J* = 10.1, 4.1 Hz, 1H), 3.68-3.61 (m, 3H), 3.31 (dd, *J* = 7.9, 3.5 Hz, 1H), 2.84-2.77 (m, 1H), 2.00-1.92 (m, 1H), 1.83-1.78 (m, 1H), 1.68 (d, *J* = 1.1 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.07 (s, 9H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.63 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 136.2, 135.8, 132.94, 132.92, 130.0, 128.7, 128.04, 128.02, 127.98, 127.95, 88.7, 84.4, 75.5, 70.0, 66.8, 38.7, 37.6, 35.7, 27.1, 19.3, 18.5, 15.2, 13.8, 11.2; IR (thin film, NaCl) 3440, 2960, 2929, 2858, 1471, 1454, 1428, 1112, 1028, 1006, 823, 738, 701, 614 cm^{-1}; LRMS (EI, Na) calcd for $C_{36}H_{50}O_4$ Si, 597.87 *m/z* (M + Na); observed, 597.00 $(M + Na)^+$ *m/z.*observed, $(M + Na)^+$ *m/z.*



Entry 8 - synthesis of ene-1,5-diol 59 and 60. To a –78 °C solution of alkyne **30** (20 mg, 0.081 mmol) in 0.81 mL of toluene, was added sequentially, *n*-BuLi (2.27 M in hexanes; 39 μL, 0.089 mmol), $ClTi(Oi\text{-}Pr)_3$ (1.0 M in hexanes; 180 μL, 0.18 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 180 μL, 0.36 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to –40 °C and stirred for 2 h during which the reaction turned dark brown. The flask was then cooled to –78 °C and BF_3•OEt_2 (33 μL, 0.26 mmol) was added in a dropwise manner. Following a stirring

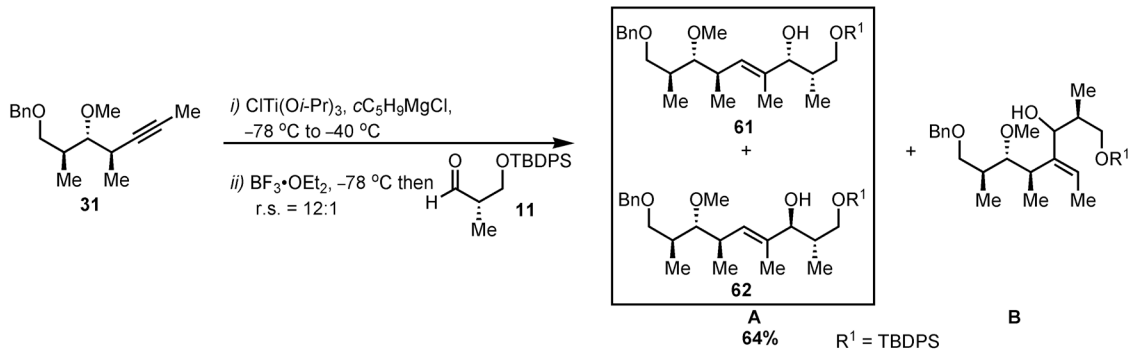
period of 10 min at −78 °C, aldehyde **11** (85 mg, 0.26 mmol) was then added as a solution in toluene (0.2 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at −78 °C, before the addition of saturated NH_4Cl solution (0.4 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography eluting successively with 2 % (100 mL), 4 % (100 mL), 7 % (50 mL), 10 % (50 mL), 15 % (100 mL) and 20 % (200 mL) EtOAc/ hexanes to provide 32 mg (68 %) of diastereomers **59** and **60** as the major regioisomer **A**.

Entry 8 - Regioselectivity data A:B. The residue obtained after a titanium reductive coupling using the above procedure was filtered through a short pad of silica eluting successively with 2 % (100 mL), 4 % (50 mL) and 6 % (50 mL) EtOAc/ hexanes until all traces of the partially reduced olefinic product alkyne **30** were removed. All remaining organics were removed by washing the silica with 200 mL of 100 % EtOAc. Analysis of the partially purified mixture by ^{1}H NMR shows an approximately 12:1 mixture of regioisomers.

Data for major diastereomer (*E*)-(2*R*,3*S*,6*R*,7*R*,8*S*)-1-(*tert*-butyldiphenylsilanyloxy)- 9-(benzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,7-diol, 59. $[\alpha]_{589}^{20}$ +13.8° (*c* 2.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.68 (m, 4H), 7.45-7.28 (m, 11H), 5.57 (d, *J* = 9.8 Hz, 1H), 4.55-4.50 (m, 2H), 4.21 (d, *J* = 4.0 Hz, 1H),

3.68-3.63 (m, 2H), 3.58 (dd, *J* = 9.2, 4.5 Hz, 1H), 3.54-3.51 (m, 1H), 3.40 (dd, *J* = 7.5, 4.1 Hz, 1H), 2.63-2.57 (m, 1H), 1.93-1.86 (m, 2H), 1.56 (s, 3H), 1.08 (s, 9H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 136.1, 135.9, 135.8, 133.6, 133.5, 129.91, 129.89, 128.7, 127.94, 127.90, 127.89, 126.4, 80.3, 78.1, 75.5, 73.7, 68.0, 38.1, 36.6, 35.5, 27.1, 19.4, 18.0, 14.4, 13.5, 10.9; IR (thin film, NaCl) 3447, 2960, 2930, 2858, 1454, 1427, 1112, 1028, 824, 739, 701, 614 cm^{-1}; LRMS (EI, Na) calcd for $C_{36}H_{50}O_4Si$, 597.87 *m/z* (M + Na); observed, 597.52 $(M + Na)^+$ *m/z*.

Data for minor diastereomer (*E*)-(2*R*,3*R*,6*R*,7*R*,8*S*)-1-(*tert*-butyldiphenylsilanyloxy)- 9-(benzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,7-diol, 60. $[\alpha]_{589}^{20}$ +19.6° (*c* 1.31, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.70 (m, 4H), 7.48-7.40 (m, 6H), 7.36-7.28 (m, 5H), 5.54 (d, *J* = 9.7 Hz, 1H), 4.52 (A of AB, *J* = 12.1 Hz, 1H), 4.51 (B of AB, *J* = 12.1 Hz, 1H), 3.97 (d, *J* = 8.9 Hz, 1H), 3.79 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.67 (dd, *J* = 9.9, 8.3 Hz, 1H), 3.57 (dd, *J* = 9.2, 4.2 Hz, 1H), 3.50 (dd, *J* = 8.2, 8.2 Hz, 1H), 3.41 (dd, *J* = 8.0, 3.7 Hz, 1H), 2.64-2.58 (m, 1H), 2.01-1.92 (m, 1H), 1.88-1.79 (m, 1H), 1.67 (d, *J* = 0.8 Hz, 3H), 1.09-1.07 (m, 12H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.65 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.9, 136.1, 135.8, 133.0, 130.1, 129.6, 129.7, 128.03, 128.01, 127.99, 127.92, 84.3, 80.4, 75.9, 73.7, 69.8, 37.6, 36.7, 35.5, 27.0, 19.4, 18.0, 14.1, 13.8, 11.1; IR (thin film, NaCl) 3469, 2960, 2929, 2858, 1454, 1428, 1113, 1087, 1005, 823, 739, 701, 615 cm^{-1}; LRMS (EI, Na) calcd for $C_{36}H_{50}O_4Si$, 597.87 *m/z* (M + Na); observed, 597.52 $(M + Na)^+$ *m/z*.



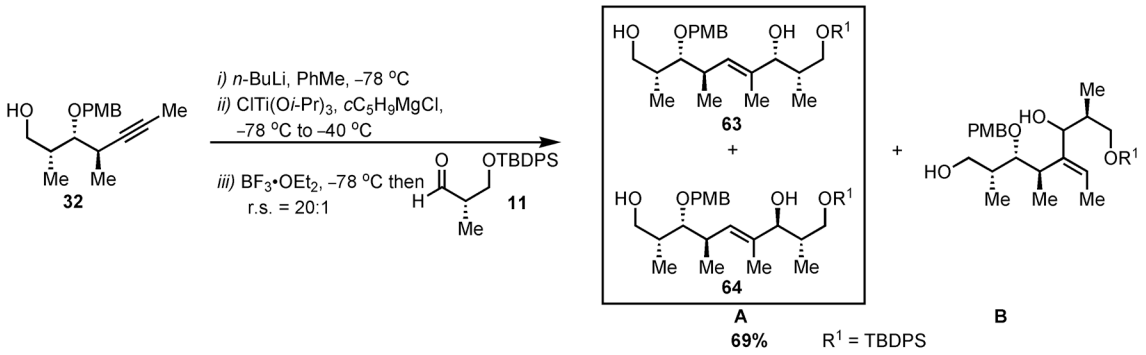
Entry 9 - synthesis of enol 61 and 62. To a −78 °C solution of alkyne **31** (20 mg, 0.075 mmol) in 0.75 mL of toluene, was added sequentially, $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in hexanes; 170 μL, 0.17 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 170 μL, 0.34 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to −40 °C and stirred for 2 h during which the reaction turned dark brown. The flask was then cooled to −78 °C and $BF_3{\bullet}OEt_2$ (21 μL, 0.17 mmol) was added in a dropwise manner. Following a stirring period of 10 min at −78 °C, aldehyde **11** (78 mg, 0.24 mmol) was then added as a solution in toluene (0.2 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at −78 °C, before the addition of saturated NH_4Cl solution (0.4 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography eluting successively with 2 % (100 mL), 4 % (100 mL), 7 % (100 mL), 10 % (50 mL), 15 % (100 mL) and 20 % (200 mL) EtOAc/ hexanes to provide 29 mg (64 %) of **61** and **62** as the major regioisomer **A**.

Entry 9 - Regioselectivity data A:B. The residue obtained after a titanium reductive coupling using the above procedure was filtered through a short pad of silica eluting successively with 2 % (50 mL) and 4 % (50 mL) EtOAc/ hexanes until all traces of the partially reduce olefinic product alkyne **31** were removed. All remaining organics were removed by washing the silica with 200 mL of 100 % EtOAc. Analysis of the partially purified mixture by ^{1}H NMR shows an approximately 10:1 mixture of regioisomers.

Data for major diastereomer (*E*)-(2*S*,3*R*,6*R*,7*S*,8*S*)-1-(*tert*-butyldiphenylsilanyloxy)-7-(methoxy)- 9-(benzyloxy)- 2,4,6,8-tetramethylnon-4-ene-3-ol, 61. $[\alpha]_{589}^{20}$ +1.08° (*c* 3.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.68 (m, 4H), 7.46-7.35 (m, 10H), 7.31-7.28 (m, 1H), 5.51 (d, *J* = 9.8 Hz, 1H), 4.54-4.49 (m, 2H), 4.18 (d, *J* = 4.2 Hz, 1H), 3.65-3.64 (m, 2H), 3.52-3.51 (m, 2H), 3.43 (s, 3H), 3.00 (dd, *J* = 8.2, 3.4 Hz, 1H), 2.68-2.62 (m, 1H), 2.44-2.18 (s br, 1H), 1.90-1.80 (m, 2H), 1.54 (s, 3H), 1.08 (s, 9H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 135.9, 135.81, 135.77, 135.3, 129.90, 129.88, 128.5, 128.1, 127.95, 127.90, 127.76, 127.61, 126.9, 87.5, 78.3, 73.2, 72.8, 68.1, 61.4, 38.1, 37.7, 35.0, 27.1, 19.4, 18.6, 15.1, 13.3, 11.0; IR (thin film, NaCl) 3465, 2961, 2930, 2858, 1471, 1428, 1362, 1112, 1008, 824, 739, 701, 614 cm^{-1}; LRMS (EI, Na) calcd for $C_{37}H_{52}O_4Si$, 611.89 *m/z* (M + Na); observed, 611.48 $(M + Na)^+$ *m/z*.

Data for minor diastereomer (*E*)-(2*S*,3*S*,6*R*,7*S*,8*S*)-11-(*tert*-butyldiphenylsilanyloxy)-7-(methoxy)- 9-(benzyloxy)--2,4,6,8-tetramethylnon-4-ene-3-ol, 62. $[\alpha]_{589}^{20}$ +5.6° (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.69 (m, 4H), 7.45-7.40 (m, 6H), 7.36-7.33 (m, 5H), 5.46 (d, *J* = 9.8 Hz, 1H), 4.51 (A of AB, *J* = 12.2

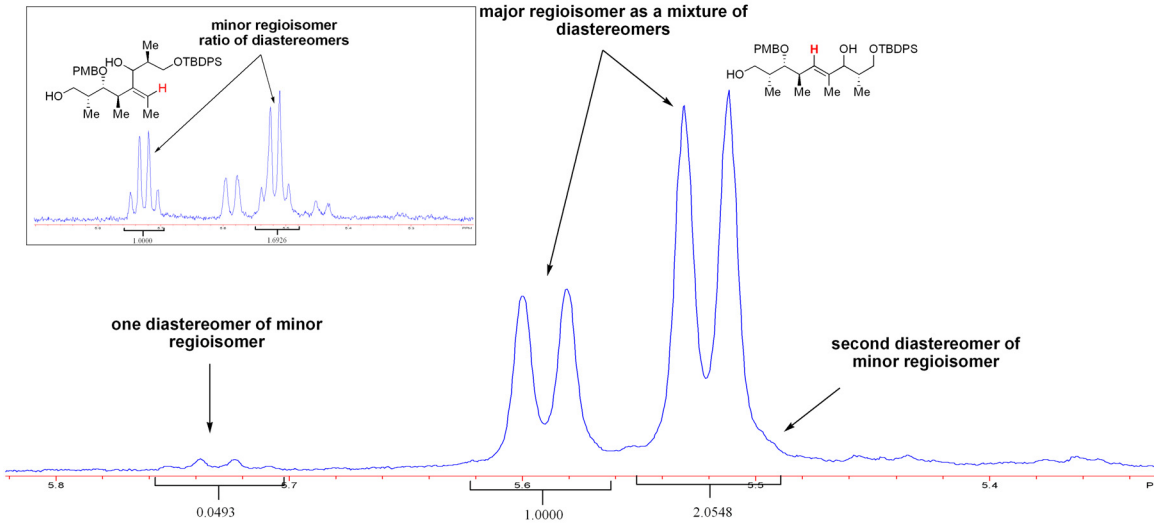
Hz, 1H),), 4.49 (B of AB, *J* = 12.2 Hz, 1H), 3.95 (d, *J* = 9.0 Hz, 1H), 3.77 (dd, *J* = 10.1, 4.2 Hz, 1H), 3.65 (dd, *J* = 9.9, 7.8 Hz, 1H), 3.52 (dd, *J* = 8.9, 5.6 Hz, 1H), 3.48 (dd, *J* = 8.8, 3.6 Hz, 1H), 3.44 (s, 3H), 3.02 (dd, *J* = 6.8, 3.7 Hz, 1H), 2.71-2.64 (m, 1H), 2.00-1.93 (m, 1H), 1.77-1.71 (m, 1H), 1.65 (d, *J* = 0.7 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.07 (s, 9H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.62 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 135.8, 135.7, 133.0, 130.1, 128.5, 128.03, 128.00, 127.7, 127.6, 87.3, 84.4, 73.2, 72.8, 69.9, 61.5, 38.0, 37.6, 35.1, 27.0, 19.3, 18.6, 14.9, 13.7, 10.9; IR (thin film, NaCl) 3490, 2960, 2930, 2858, 1454, 1428, 1362, 1112, 1094, 1006, 823, 739, 701, 614 cm^{-1}; LRMS (EI, Na) calcd for $C_{37}H_{52}O_4Si$, 611.89 *m/z* (M + Na); observed, 611.55 $(M + Na)^+$ *m/z*.



Entry 10 - synthesis of ene-diol 63 and 64. To a –78 °C solution of alkyne **32** (20 mg, 0.072 mmol) in 0.72 mL of toluene, was added sequentially, *n*-BuLi (2.27 M in hexanes; 35 μL, 0.080 mmol), $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in hexanes; 160 μL, 0.16 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 160 μL, 0.32 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to –40 °C and stirred for 2 h during which the reaction turned dark brown. The flask was then cooled to –78 °C and BF_3•OEt_2 (29 μL, 0.23 mmol) was added in a dropwise manner. Following a stirring period of 10 min at –78 °C, aldehyde **11** (76 mg, 0.23 mmol) was then added as a

solution in toluene (0.2 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at −78 °C, before the addition of saturated NH_4Cl solution (0.4 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography eluting successively with 5 % (100 mL), 7% (50 mL), 10 % (100 mL), 15 % (50 mL), 20 % (100 mL) and 30 % (200 mL) EtOAc/ hexanes to provide 30 mg (69 %) of diastereomers **63** and **64** as the major regioisomer **A**.

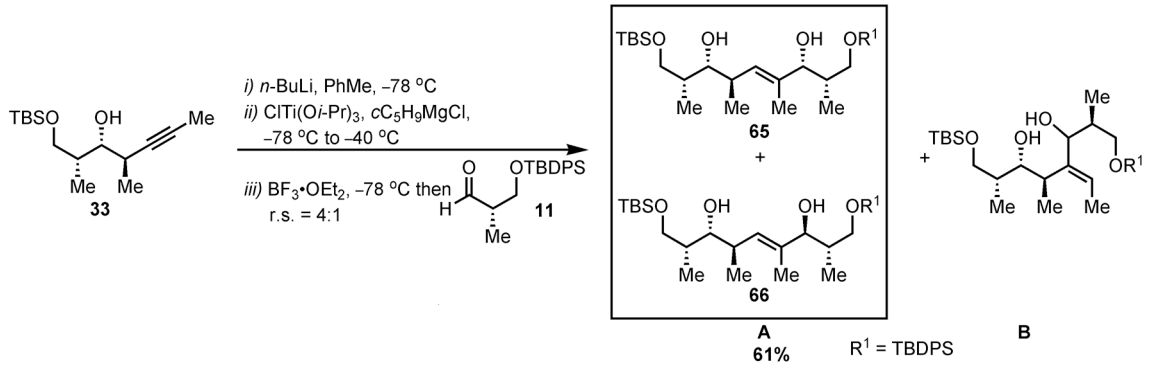
Entry 10 - Regioselectivity data A:B. The residue obtained after a titanium reductive coupling using the above procedure was filtered through a short pad of silica eluting successively with 5 % (100 mL), 7 % (50 mL), 10 % (50 mL) and 15 % (50 mL) EtOAc/ hexanes until all traces of the partially reduced olefinic product of alkyne **32** were removed. All remaining organics were removed by washing the silica with 200 mL of 100 % EtOAc. Analysis of the partially purified mixture by ^1H NMR shows an approximately 20:1 mixture of regioisomers.



Data for major diastereomer (*E*)-(2*S*,3*R*,6*R*,7*R*,8*R*)-1-(*tert*-butyldiphenylsilanyloxy)-7-(*p*-methoxybenzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,9-diol, 63. $[\alpha]_{589}^{20}$ +1.31° (*c* 2.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.63 (m, 4H), 7.45-7.37 (m, 6H), 7.31-7.21 (m, 2H), 6.92-6.82 (m, 2H), 5.52 (d, *J* = 9.5 Hz, 1H), 4.58 (A of AB, *J* = 11.0 Hz, 1 H), 4.50 (B of AB, *J* = 11.0 Hz, 1 H), 4.12 (d, *J* = 6.2 Hz, 1H), 3.80 (s, 3H), 3.61-3.57 (m, 3H), 3.52 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.41-3.39 (m, 1H), 2.78-2.72 (m, 1H), 2.00-1.93 (m, 1H), 1.90-1.82 (m, 1H), 1.57 (s, 3H), 1.08 (s, 9H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 135.9, 135.8, 135.5, 133.7, 133.6, 131.3, 129.91, 129.87, 129.4, 129.2, 127.9, 84.7, 78.7, 73.8, 67.9, 66.5, 55.5, 38.3, 37.9, 35.0, 27.1, 19.5, 18.5, 13.0, 12.0, 11.6; IR (thin film, NaCl) 3401, 2959, 2929, 2858, 1514, 1458, 1427, 1248, 1113, 1033, 823, 739, 702 cm^{-1}; LRMS (EI, Na) calcd for $C_{37}H_{52}O_5$ Si, 627.89 *m/z* (M + Na); observed, 627.56 $(M + Na)^+$ *m/z*.

Data for minor diastereomer (*E*)-(2*S*,3*S*,6*R*,7*R*,8*R*)-1-(*tert*-butyldiphenylsilanyloxy)-7-(*p*-methoxybenzyloxy)-2,4,6,8-tetramethylnon-4-ene-3,9-

diol, 64. $[\alpha]_{589}^{20}$ +4.8° (*c* 1.33, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.70-7.68 (m, 4H), 7.47-7.39 (m, 6H), 7.27-7.25 (m, 2H), 6.87-6.86 (m, 2H), 5.59 (d, *J* = 10.0 Hz, 1H), 4.59 (A of AB, *J* = 10.0 Hz, 1 H), 4.50 (B of AB, *J* = 10.0 Hz, 1 H), 3.95 (d, *J* = 8.3 Hz, 1H), 3.80 (s, 3H), 3.78 (dd, *J* = 10.1, 4.0 Hz, 1H), 3.66-3.63 (m, 1H), 3.58 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.49 (dd, *J* = 10.7, 5.1 Hz, 1H), 3.40 (dd, *J* = 4.6, 4.6 Hz, 1H), 2.82-2.75 (m, 1H), 2.00-1.90 (m, 2H), 1.67 (s, 3H), 1.07 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.67 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 135.84, 135.83, 135.8, 133.0, 133.6, 131.3, 131.2, 130.1, 129.4, 128.02, 128.01, 114.0, 84.6, 84.0, 73.9, 69.5, 55.5, 38.2, 37.7, 35.2, 27.0, 19.3, 18.7, 13.9, 12.0, 11.6; IR (thin film, NaCl) 3430, 2959, 2930, 2860, 1514, 1471, 1428, 1248, 1113, 1036, 822, 742, 702, 668, 613 cm^{-1}; LRMS (EI, Na) calcd for $C_{37}H_{52}O_5Si$, 627.89 *m/z* (M + Na); observed, 627.49 (M + Na)$^+$ *m/z*.



Entry 11 - synthesis of ene-diol 65 and 66. To a –78 °C solution of alkyne **33** (20 mg, 0.074 mmol) in 0.74 mL of toluene, was added sequentially, *n*-BuLi (2.27 M in hexanes; 36 μL, 0.08 mmol), $ClTi(Oi\text{-}Pr)_3$ (1.0 M in hexanes; 160 μL, 0.16 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 160 μL, 0.32 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to –40 °C and stirred for 2 h during which the reaction turned dark brown. The flask was then cooled to –78 °C

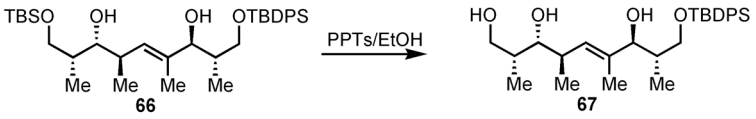
and BF_3•OEt_2 (30 μL, 0.24 mmol) was added in a dropwise manner. Following a stirring period of 10 min at −78 °C, aldehyde **11** (77 mg, 0.24 mmol) was then added as a solution in toluene (0.2 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at −78 °C, before the addition of saturated NH_4Cl solution (0.4 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography eluting successively with 2 % (100 mL), 4% (100 mL), 7 % (50 mL), 10 % (50 mL), 15 % (100 mL) and 20 % (100 mL) EtOAc/ hexanes to provide 27 mg (61 %) of diastereomers **65** and **66** as the major regioisomer **A**.

Entry 11 - Regioselectivity data A:B. The residue obtained after a titanium reductive coupling using the above procedure was filtered through a short pad of silica eluting successively with 2 % (100 mL), 4 % (50 mL) and 6 % (50 mL) EtOAc/ hexanes until all traces of the partially reducedproduct of alkyne **33** were removed. All remaining organics were removed by washing the silica with 200 mL of 100 % EtOAc. Analysis of the partially purified mixture by ^{1}H NMR shows an approximately 4:1 mixture of regioisomers.

Data for major diastereomer (*E*)-(2*S*,3*R*,6*R*,7*R*,8*R*)-1-(*tert*-butyldiphenylsilanyloxy)-9-(*tert*-butyldimethylsilanyloxy)-2,4,6,8-tetramethylnon-4-ene-3,9-diol, 65. $[\alpha]_{589}^{20}$ +6.3° (*c* 1.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79-7.66

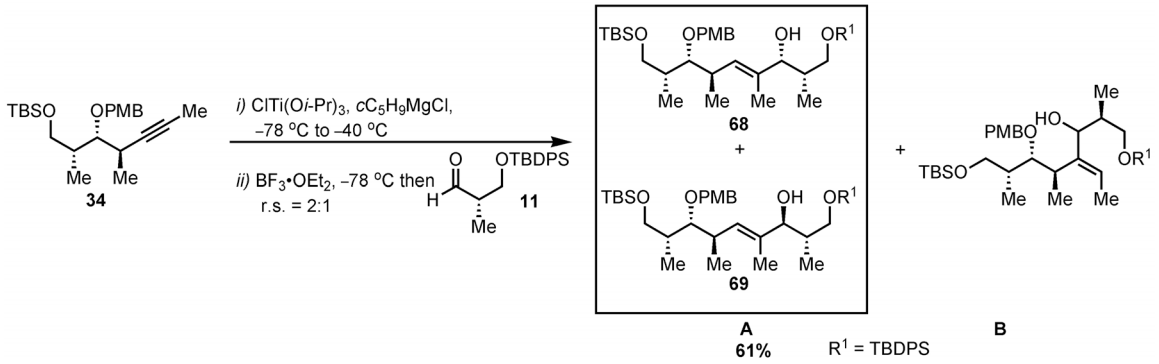
(m, 4H), 7.44-7.38 (m, 6H), 5.40 (d, J = 9.5 Hz, 1H), 4.20 (s, 1H), 3.69-3.64 (m, 4H), 3.52 (d, J = 8.6 Hz, 1H), 2.57-2.53 (m, 1H), 2.41-2.10 (s br, 2H), 1.89-1.79 (m, 2H), 1.59 (s, 3H), 1.08 (s, 9H), 0.96-0.91 (m, 15H), 0.84 (d, J = 6.7 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.3, 135.9, 135.8, 133.6, 133.5, 129.96, 129.93, 129.1, 127.9, 78.3, 68.1, 68.0, 37.9, 36.9, 36.1, 27.1, 26.2, 19.5, 18.5, 17.2, 13.6, 11.1, 9.7, –5.2; IR (thin film, NaCl) 3434, 2959, 2930, 2858, 1514, 1256, 1113, 1094, 1006, 836, 778, 701, 614 cm^{-1}; LRMS (EI, Na) calcd for $C_{33}H_{58}O_4Si$, 622.00 *m/z* (M + Na); observed, 622.64 $(M + Na)^+$ *m/z*.

Entry 11 – Characterization data for 66. Due to contamination of enol-1,5-diol **66** with an unidentified impurity, characterization was performed on triol **67** obtained after a selective removal of the TBS group.



66 **67**

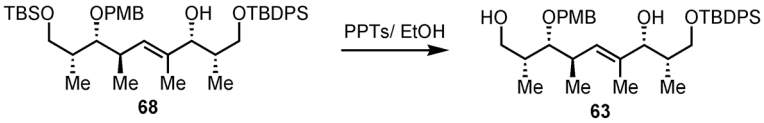
Data for triol 67. $[\alpha]_{589}^{20}$ +22.4° (*c* 0.59, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.68 (m, 4H), 7.48-7.39 (m, 6H), 5.31 (d, J = 9.7 Hz, 1H), 3.98 (d, J = 8.2 Hz, 1H), 3.82 (dd, J = 10.2, 3.9 Hz, 1H), 3.76 (dd, J = 10.7, 4.1 Hz, 1H), 3.69 (dd, J = 10.6, 5.7 Hz, 1H), 3.65 (dd, J = 10.1, 2.3 Hz, 1H), 3.51 (dd, J = 9.0, 2.4 Hz, 1H), 2.66-2.58 (m, 1H), 2.00-2.92 (m, 1H), 1.92-1.83 (m, 1H), 1.70 (d, J = 0.8 Hz, 3H), 1.08 (s, 9H), 1.01 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 0.72 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.4, 135.84, 135.82, 132.9, 130.8, 130.2, 128.1, 83.8, 77.9, 69.4, 67.9, 37.4, 36.4, 36.0, 27.0, 19.3, 16.9, 14.1, 14.0, 12.2, 9.2; IR (thin film, NaCl) 3411, 2960, 2929, 2858, 1458, 1427, 1113, 1083, 1024, 823, 740, 701 cm^{-1}; LRMS (EI, Na) calcd for $C_{29}H_{44}O_4Si$, 507.74 *m/z* (M + Na); observed, 507.47 $(M + Na)^+$ *m/z*.



Entry 12 - synthesis of allylic alcohols 68 and 69. To a −78 °C solution of alkyne **34** (20 mg, 0.052 mmol) in 0.74 mL of toluene, was added sequentially, ClTi(O*i*-Pr)$_3$ (1.0 M in hexanes; 110 μL, 0.11 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 110 μL, 0.22 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to −40 °C and stirred for 2 h during which the reaction turned dark brown. The flask was then cooled to −78 °C and BF_3•OEt_2 (14 μL, 0.11 mmol) was added in a dropwise manner. Following a stirring period of 10 min at −78 °C, aldehyde **11** (54 mg, 0.17 mmol) was then added as a solution in toluene (0.2 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at −78 °C, before the addition of saturated NH_4Cl solution (0.4 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography eluting successively with 2 % (100 mL), 4% (100 mL), 7 % (50 mL), 10 % (100 mL), 15 % (100 mL) and 20 % (100 mL) EtOAc/ hexanes to provide 23 mg (61 %) of diastereomers **68** and **69** as the major regioisomer **A**.

Entry 12 - Regioselectivity data A:B. The residue obtained after a titanium reductive coupling using the above procedure was filtered through a short pad of silica eluting successively with 2 % (100 mL), 4 % (50 mL) and 6 % (50 mL) EtOAc/ hexanes until all traces of the partially reduced olefinic product of alkyne **33** were removed. All remaining organics were removed by washing the silica with 200 mL of 100 % EtOAc. Analysis of the partially purified mixture by ^{1}H NMR shows an approximately 2:1 mixture of regioisomers.

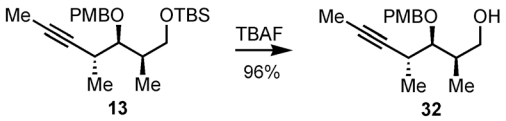
Entry 12 – Characterization data for 68. Due to contamination of enol **68** with an unidentified impurity, characterization was performed on ene-diol **63** (see entry 10) obtained after a selective removal of the TBS group.



Data for minor diastereomer (*E*)-(2*S*,3*S*,6*R*,7*R*,8*R*)-1-(*tert*-butyldiphenylsilanyloxy)-7-(*p*-methoxybenzyloxy)-9-(*tert*-butyldimethylsilanyloxy)-2,4,6,8-tetramethylnon-4-ene-3-ol, 69. $[\alpha]_{589}^{20}$ –2.1° (*c* 0.49, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.68 (m, 4H), 7.47-7.39 (m, 6H), 7.26-7.24 (m, 2H), 6.86-6.84 (m, 2H), 5.54 (d, *J* = 9.5 Hz, 1H), 4.55 (A of AB, *J* = 10.9 Hz, 1H), 4.48 (B of AB, *J* = 10.9 Hz, 1H), 3.94 (d, *J* = 8.6 Hz, 1H), 3.80 (s, 3H), 3.77 (dd, *J* = 10.2, 4.1 Hz, 1H), 3.63 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.49 (dd, *J* = 9.8, 6.2 Hz, 1H), 3.42 (dd, *J* = 9.7, 5.9 Hz, 1H), 3.37 (dd, *J* = 5.3, 5.3 Hz, 1H), 2.76-2.69 (m, 1H), 1.97-1.92 (m, 1H), 1.80-1.76 (m, 1H), 1.65 (d, *J* = 0.8 Hz, 3H), 1.07 (s, 9H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.62(d, *J* = 6.9 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 135.8, 135.4, 133.0, 131.9, 131.8, 130.1, 129.2, 128.03, 128.01, 113.8, 84.3,

83.6, 74.5, 69.7, 65.8, 39.2, 37.6, 35.7, 27.0, 26.1, 19.3, 18.52, 18.48, 13.9, 12.5, 11.3, −5.17, −5.19; IR (thin film, NaCl) 3487, 2957, 2929, 2858, 1464, 1249, 1113, 1113, 1086, 1036, 832, 771, 701, 668 cm^{-1}; LRMS (EI, Na) calcd for $C_{43}H_{66}O_5Si_2$, 742.15 *m/z* (M + Na); observed, 742.71 $(M + Na)^+$ *m/z*.

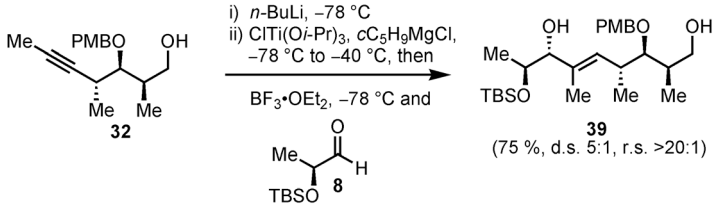
2. Assembly of the seco-acid precursor of (9*S*)-dihydroerythronolide A (2nd generation approach).



(2*R*,3*R*,4*R*)-3-(*p*-methoxybenzyloxy)-2,4-dimethyl-5-heptyn-1-ol, 32.

To a stirring solution of **13** (150 mg, 0.39 mmol) in 3.9 mL of THF, was added TBAF (1.0 M in THF; 0.58 mL, 0.58 mmol) in a dropwise manner. The reaction was stirred overnight at room temperature before pouring in a separatory funnel containing 10 mL of EtOAc and 8 mL of sat. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layer was then washed with brine (1 × 20 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography on silica gel eluting successively with 30 % EtOAc -hexanes to provide 103 mg (96 %) of a pure **32** $[\alpha]_{589}^{20}$ –19.4° (*c* 2.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.30 (m, 2H), 6.89-6.87 (m, 2H), 4.74 (A of AB, *J* = 11.0 Hz, 1H), 4.57 (B of AB, *J* = 11.0 Hz, 1H), 3.81 (s, 3H), 3.66-3.59 (m, 2H), 3.42 (dd, *J* = 6.0, 4.4 Hz, 1H), 2.81-2.75 (m, 1H), 2.07-1.94 (m, 1H), 1.88, (s br, 1H), 1.82 (d, *J* = 2.4 Hz, 3H), 1.17 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 130.9 129.9, 114.0, 83.1, 82.0, 77.3, 73.6, 60.1, 55.5, 37.4, 28.8, 18.3, 11.9, 3.9; IR (thin film, NaCl)

3415, 2929, 2917, 2858, 1514, 1456, 1249, 1173, 1035, 821 cm^{-1}; LRMS (EI, Na) calcd for $C_{17}H_{24}O_3$, 299.37 *m/z* (M + Na); observed, 299.20 $(M + Na)^+$ *m/z*



(*E*)-(2*R*,3*R*,4*R*,7*R*,8*S*)-3-(*p*-methoxybenzyloxy)-8-(*tert*-butyldimethyl silanyloxy)-2,4,6-trimethylnon-5-ene-1,7-diol, 39. To a −78 °C solution of alkyne **32** (300 mg, 1.09 mmol) in 11 mL of toluene, was added sequentially *n*-BuLi (2.5 M in hexanes; 0.48 mL, 1.2 mmol), $ClTi(Oi\text{-}Pr)_3$ (1.0 M in hexanes; 2.4 mL, 2.4 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 2.4 mL, 4.8 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to −40 °C and stirred for 1 h during which the reaction turned dark brown. The flask was then cooled to −78 °C and $BF_3{\cdot}OEt_2$ (0.44 mL, 3.5 mmol) was added in a dropwise manner. Following a stirring period of 10 min at −78 °C, aldehyde **8** (660 mg, 3.5 mmol) was then added as a solution in toluene (0.5 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.5 mL). Stirring was maintained for 1 h at −78 °C. Saturated NH_4Cl solution (7 mL) was then added and the suspension was allowed to reach ambient temperature before partitioning between EtOAc (20 mL) and water (10 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 40 mL), brine (1 × 40 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chromatography on silica gel eluting successively with 5 %, 10 %, 15 %, 20 % and 30 % EtOAc -hexanes to provide 379 mg (75 %) of a diastereomeric

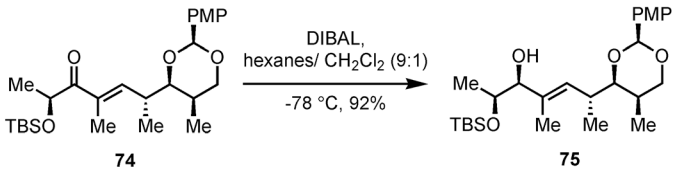
mixture of **39** (d.s. = 5:1 at C7). $[\alpha]_{589}^{20}$ +1.98° (*c* 0.81, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.25 (m, 2H), 6.87-6.86 (m, 2H), 5.64 (d, *J* = 9.8 Hz, 1H), 4.59 (A of AB, *J* = 11.0 Hz, 1H), 4.49 (B of AB, *J* = 11.0 Hz, 1H), 3.98-3.94 (m, 2H), 3.81 (s, 3H), 3.59 (dd, *J* = 10.8, 7.0 Hz, 1H), 3.54 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.40 (dd, *J* = 6.3, 3.9 Hz, 1H), 2.82-2.76 (m, 1H), 2.35-2.00 (s br, 2H), 2.00-1.93 (m, 1H), 1.63 (d, *J* = 1.1 Hz, 3H), 1.00-0.96 (m, 9H), 0.91 (s, 9H), 0.096 (s, 3H), 0.091 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 132.8, 131.3, 129.8, 129.6, 129.4, 113.9, 84.7, 79.0, 73.8, 70.6, 66.6, 55.5, 37.7, 35.0, 26.0, 18.3, 17.0, 14.3, 11.7, –4.3, –4.7; IR (thin film, NaCl) 3422, 2957, 2929, 2856, 1514, 1463, 1249, 1086, 1035, 835, 777, 668 cm^{-1}; LRMS (EI, Na) calcd for $C_{26}H_{46}O_5Si$, 489.73 *m/z* (M + Na); observed, 489.48 $(M + Na)^+$ *m/z*.

(*E*)-(2*R*,3*R*,4*R*,7*R*,8*S*)-1,3-O-(4-methoxy-benzylidene)-8-(*tert*-butyldimethylsilanyloxy)-2,4,6-trimethylnon-5-ene-7-ol, 73. To a stirring mixture of **39** (280 mg, 0.64 mmol) and 0.76 mg of activated 4Å molecular sieves powder in 3.8 mL of CH_2Cl_2 at 0 °C was added a solution of DDQ (175 mg, 0.77 mmol) in 11.2 mL of CH_2Cl_2 dropwise via cannula. The resulting slurry was stirred for an additional 20 min at 0 °C before filtering through Celite. The filtrate was washed successively with sat $NaHCO_3$ and brine before drying over anhydrous Na_2SO_4. The solvent was concentrated and the residue was purified by flash column chromatography eluting with 8 % EtOAc/ hexanes to afford 232 mg (83 %) of **73**. $[\alpha]_{589}^{20}$ +21.8° (*c* 0.82, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 7.62-7.59 (m, 2H), 6.83-6.80 (m, 2H), 5.58 (d, *J* = 9.1 Hz, 1H), 5.34 (s,

1H), 4.08 (s, 1H), 3.97-3.93 (s, 1H), 3.81-3.79 (m, 1H), 3.68 (dd, *J* = 11.0, 1.9 Hz, 1H), 3.31 (dd, *J* = 9.7, 1.9 Hz, 1H), 3.26 (s, 3H), 2.74-2.66 (m, 1H), 2.46-2.40 (s br, 1H), 1.71 (d, *J* = 1.1 Hz, 3H), 1.22-1.18 (m, 1H), 1.16 (m, 3H), 1.06 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.008 (s, 3H), – 0.005 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 160.2, 134.4, 132.5, 130.2, 128.5, 128.3, 127.9, 113.6, 102.0, 83.9, 79.5, 73.7, 71.6, 54.6, 34.1, 30.3, 25.9, 18.2, 17.5, 15.6, 14.1, 11.2, –4.5, –4.9; IR (thin film, NaCl) 3477, 2958, 2929, 2855, 1519, 1463, 1249, 1108, 1081, 1033, 967, 832, 777 cm^{-1}; LRMS (EI, Na) calcd for $C_{26}H_{44}O_5Si$, 487.71 *m/z* (M + Na); observed, 487.42 (M + Na)$^+$ *m/z*.

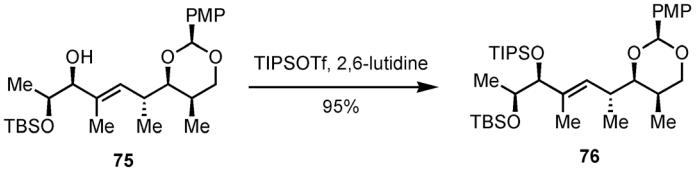
73 74

(*E*)-(2*R*,3*R*,4*R*,8*S*)-1,3-O-(4-methoxy-benzylidene)-8-(*tert*-butyldimethylsilanyloxy)-2,4,6-trimethylnon-5-ene-7-one, 74. To a cooled solution of **73** (232 mg, 0.50 mmol) in dichloromethane at 0 °C was added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (424 mg, 1.0 mmol) at once. After stirring for 1 h at 0 °C and 30 min at rt, the reaction was diluted with 10 mL of 30 % EtOAc/hex solution. Most of the solvent was evaporated and the residue was diluted 10 mL of 30 % EtOAc/hex solution. The white cloudy solution was washed with a 1:1 mixture of 10 % $Na_2S_2O_3$ and sat $NaHCO_3$ until a clear organic layer is obtained. The organic layer was then washed with brine and dried over anhydrous Na_2SO_4. The solvent was concentrated and the residue was purified by flash column chromatography eluting with 5 % EtOAc/ hexanes to afford 213 mg of enone **74** (92 %). Enone **74** was immediately used in the next step.



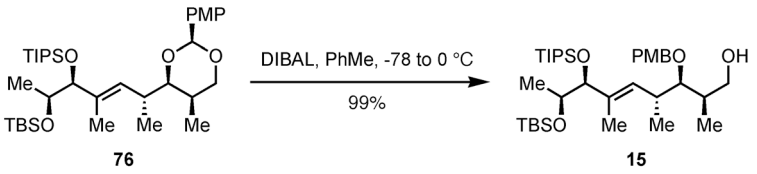
(*E*)-(2*R*,3*R*,4*R*,7*S*,8*S*)-1,3-O-(4-methoxy-benzylidene)-8-(*tert*-butyldimethylsilanyloxy)-2,4,6-trimethylnon-5-ene-7-ol, 75. A solution of **74** (210 mg, 0.45 mmol) in hexanes/dichloromethane (9:1, 4.5 ml) was cooled to –78 °C before adding DIBAL (1.0 M in hexanes; 1.1 mL, 1.1 mmol) in a dropwise manner. After 10 min of stirring, 0.5 mL of methanol was added slowly followed by 2 mL of saturated Rochelle salt solution. The resulting slurry was warmed to room temperature before pouring into a separatory funnel containing 10 mL of ethyl acetate and 7 mL of sat. Rochelle salt solution. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layer was washed with saturated $NaHCO_3$ (2 × 20 mL), brine and dried over anhydrous Na_2SO_4. The solvent was concentrated and the residue was purified by flash column chromatography eluting with 5 % EtOAc/ hexanes affording 194 mg of **75** (92 %). $[\alpha]_{589}^{20}$ +61.5° (*c* 0.13, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.38 (m, 2H), 6.87-6.85 (m, 2H), 5.42 (s, 1H), 5.37 (d, *J* = 8.8 Hz, 1H), 4.07-4.01 (m, 1H), 3.79 (s, 3H), 3.74-3.69 (m, 1H), 3.67-3.65 (m, 1H), 3.60 (dd, *J* = 9.4, 2.0 Hz, 1H), 2.72-2.62 (m, 1H), 1.72-1.69 (m, 1H), 1.65 (d, *J* = 0.95 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.0 Hz, 3H), 0.94-0.90 (m,12 H), 0.079 (s, 6H); ^{13}C NMR (126 MHz, C_6D_6) δ 160.2, 135.6, 132.40, 132.38, 128.3, 128.1, 127.9, 113.7, 101.8, 83.6, 83.0, 73.7, 71.8, 54.6, 34.2, 30.4, 26.0, 20.4, 18.2, 15.5, 13.1, 11.2, –4.2, –4.6 IR (thin film, NaCl) 3544, 2957, 2929, 2856, 1518, 1463, 1249, 1114, 1034,

832, 777 cm^{-1}; LRMS (EI, Na) calcd for $C_{26}H_{44}O_5Si$, 487.77 *m/z* (M + Na); observed, 487.46 $(M + Na)^+$ *m/z*.



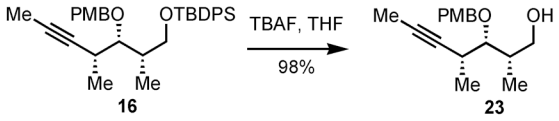
75 **76**

(*E*)-(2*R*,3*R*,4*R*,7*S*,8*S*)-1,3-O-(4-methoxy-benzylidene)-7-(*tri*-isopropylsilanyloxy)-8-(*tert*-butyldimethylsilanyloxy)-2,4,6-trimethylnon-5-ene, 76. To a cooled solution of enol **75** (150 mg, 0.32 mmol) and 2,6-lutidine (0.11 mL, 0.97 mmol) in dichloromethane (3.2 mL) at 0 °C, was added TIPS-OTf (0.13 mL, 0.50 mmol). The reaction was held at 0 °C for 1 h before diluting with 20 % EtOAc/ hexanes (10 mL). The organic layer was then washed with saturated $NaHCO_3$ (2 × 10 mL), brine and dried over anhydrous Na_2SO_4. The solvent was concentrated and the residue was purified by flash column chromatography eluting with 2 % EtOAc/ hexanes affording 190 mg of **76** (95 %). $[\alpha]_{589}^{20}$ +14.5 ° (*c* 0.64, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 7.61-7.58 (m, 2H), 6.87-6.86 (m, 2H), 5.55 (d, *J* = 9.1 Hz, 1H), 5.37 (s, 1H), 4.31 (d, *J* = 4.2 Hz, 1H), 4.09-4.04 (m, 1H), 3.80 (dd, *J* = 11.0, 0.9 Hz, 1H), 3.71 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.38 (dd, *J* = 9.6, 1.9 Hz, 1H), 3.33 (s, 3H), 2.80-2.72 (m, 1H), 1.87 (d, *J* = 1.0 Hz, 3H), 1.23-1.20 (m, 1H), 1.19-1.14 (m, 27H), 0.98 (s, 9H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.14 (s, 3H), 0.075 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 160.2, 134.9, 132.6, 130.9, 128.3, 128.1, 113.6, 102.3, 84.2, 80.1, 73.7, 73.3, 54.7, 34.3, 30.4, 26.1, 18.42, 18.39, 18.3, 16.0, 15.8, 12.8, 11.2, –4.45, –4.44; IR (thin film, NaCl) 2959, 2865, 1519, 1463, 1249, 1108, 1000, 883, 834, 774, 680 cm^{-1}; LRMS (EI, Na) calcd for $C_{35}H_{64}O_5Si_2$, 644.05 *m/z* (M + Na); observed, 644.62 $(M + Na)^+$ *m/z*.



76 **15**

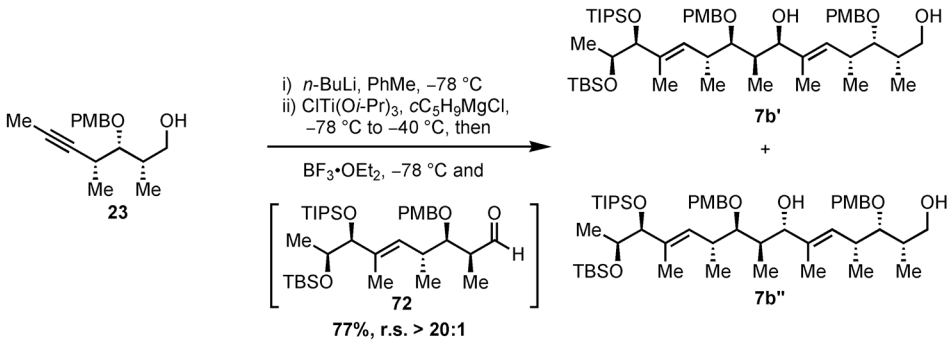
(*E*)-(2*R*,3*R*,4*R*,7*S*,8*S*)-3-(*p*-methoxybenzyloxy)-7-(*tri*-isopropylsilanyloxy)-8-di(*tert*-butyldimethylsilanyloxy)-2,4,6-trimethylnon-5-ene-1-ol, 15. To a solution of **76** (190 g, 0.31 mmol) in 3 mL of toluene at –78 °C was added DIBAL (1.0M in hexanes; 0.97 mL, 0.97 mmol). The reaction was slowly warmed to 0 °C and kept at this temperature for 30 min. The reaction was cooled to –78 °C and 0.5 mL of methanol was added followed by 1.5 mL of Rochelle salt solution. The resulting slurry was warmed to room temperature before pouring into a separatory funnel containing 6 mL of ethyl acetate and 3 mL of sat. Rochelle salt solution. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 6 mL). The combined organic layer was washed with saturated $NaHCO_3$ (2 × 15 mL), brine and dried over anhydrous Na_2SO_4. The solvent was concentrated and the residue was purified by flash column chromatography eluting with 15 % EtOAc/ hexanes affording 188 mg of **15** (99 %).



16 **23**

(2*S*,3*S*,4*R*)-3-(*p*-methoxybenzyloxy)-2,4-dimethyl-5-heptyn-1-ol, 23. To a stirring solution of **16** (188 mg, 0.37 mmol) in 3.6 mL of THF, was added TBAF (1.0 M in THF; 0.55 mL, 0.55 mmol) in a dropwise manner. The reaction was stirred overnight at room temperature before pouring in a separatory funnel containing 10 mL of EtOAc and 8 mL of sat. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layer was then washed with brine (1 × 20 mL) and dried over

anhydrous Na_2SO_4. The crude material was purified by flash column chromatography on silica gel eluting successively with 30 % EtOAc -hexanes to provide 100 mg (98 %) of pure **32** $[\alpha]_{589}^{20}$ +0.91° (*c* 0.44, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 6.90-6.87 (m, 2H), 4.62 (A of AB, *J* = 10.9 Hz, 1H), 4.53 (B of AB, *J* = 10.9 Hz, 1H), 3.81 (s, 3H), 3.60 (dd, *J* = 5.6, 5.6 Hz, 1H), 3.48 (dd, *J* = 8.7, 2.7 Hz, 1H), 2.73-2.64 (m, 1H), 2.29-2.21 (m, 1H), 1.79, (d, *J* = 2.4 Hz, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 130.9 129.7, 114.1, 83.3, 81.5, 77.7, 74.5, 66.5, 55.5, 38.7 29.8, 18.7, 10.9, 3.8; IR (thin film, NaCl) 3416, 2967, 2919, 2876, 1612, 1514, 1456, 1302, 1249, 1174, 1035, 825 cm^{-1}; LRMS (EI, Na) calcd for $C_{17}H_{24}O_3$, 299.37 *m/z* (M + Na); observed, 299.20 $(M + Na)^+$ *m/z*



(*E*)-(2*R*,3*R*,4*R*,7*S*,8*S*)-3,9-di(*p*-methoxybenzyloxy)-13-(*tri*-isopropyl silanyloxy)-14-(*tert*-butyldimethylsilanyloxy)-2,4,6,8,10,12-hexamethylpentadec-5,11-diene-1-ol. To a −78 °C solution of alkyne **23** (27 mg, 0.097 mmol) in 0.97 mL of toluene, was added sequentially *n*-BuLi (2.5 M in hexanes; 43 μL, 0.11 mmol), ClTi(O*i*-Pr)$_3$ (1.0 M in hexanes; 150 μL, 0.15 mmol) and *c*-C_5H_9MgCl (2.0 M in diethyl ether; 150 μL, 0.30 mmol) in a dropwise manner via a dry gas-tight syringe. The resulting yellow solution was slowly warmed to −40 °C and stirred for 2 h during which the reaction turned dark brown. The flask was then cooled to −78 °C and BF_3•OEt_2 (32 μL,

0.25 mmol) was added in a dropwise manner. Following a stirring period of 10 min at −78 °C, aldehyde **72** (20 mg, 0.032 mmol) was then added as a solution in toluene (0.1 mL) down the side of the flask via a gas tight syringe. The transfer was completed with additional toluene (2 × 0.1 mL). Stirring was maintained for 1 h at −78 °C, before the addition of saturated NH_4Cl solution (0.3 mL). The suspension was allowed to reach ambient temperature before partitioning between EtOAc (5 mL) and water (3 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. The crude material was purified by flash column chomatography eluting successively with 5 %, 7 %, 10 %, 15%, 20 % and 30 % EtOAc/ hexanes to provide 22 mg (77 %) of **7b'** and **7b"** as the major regioisomer.

Regioiselectivity data for 7b' and 7b". The residue obtained after a titanium reductive coupling as described above was filtered through a short pad of silica eluting successively with 5 % (50 mL), 7 % (50 mL), 10 % (50 mL) and 15 % (50 mL) EtOAc/ hexanes until all traces of the partially reduced olefinic product of alkyne **23** were removed. All remaining organics were removed by washing the silica with 200 mL of 100 % EtOAc. Analysis of the partially purified mixture by ^{1}H NMR shows a ≥ 20:1 mixture of regioisomers.

Data for major diastereomer (*E,E*)-(2*S*,3*S*,4*R*,7*R*,8*R*,9*R*,10*R*,13*S*,14*S*)-3-(*p*-methoxybenzyloxy)-7-(*tri*-isopropylsilanyloxy)-8-di(*tert*-butyldimethylsilanyloxy)-2,4,6-trimethylnon-5-ene-1-ol, 7b'. $[\alpha]_{589}^{20}$ +3.2 ° (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 4H), 6.89-6.86 (m, 4H), 5.65 (d, *J* = 9.4 Hz, 1H), 5.21 (d, *J* = 9.9 Hz, 1H), 4.65 (A of AB, *J* = 11.0 Hz, 1H), 4.59 (A of AB, *J* = 10.8 Hz, 1H), 4.55 (B of

AB, J = 10.8 Hz, 1H), 4.51 (B of AB, J = 11.0 Hz, 1H), 4.15 (d, J = 4.0 Hz, 1H), 3.94-3.88 (m, 2H), 3.813 (s, 3H), 3.809 (s, 3H), 3.62 (dd, J = 6.0, 2.1 Hz, 1H), 3.58-3.57 (m, 2H), 3.40 (dd, J = 8.9, 2.0 Hz, 1H), 2.88-2.80 (m, 1H), 2.77-2.65 (m, 1H), 2.02-1.92 (m, 1H), 1.90-1.79 (m, 1H), 1.72 (s, 3H), 1.60 (s, 3H), 1.11 (d, J = 6.6 Hz, 3H), 1.04 (s, 21H), 1.00 (d, J = 6.2 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.88-0.85 (m, 12H), 0.83 (d, J = 8.1 Hz, 3H), 0.052 (s, 3H), 0.036 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ159.4, 159.2, 135.8, 134.1, 131.4, 131.1, 130.9, 129.7, 129.6, 129.3, 114.0, 113.9, 84.3, 83.6, 80.6, 79.2, 77.4, 74.9, 73.0, 66.5, 55.5, 38.8, 37.5, 36.2, 35.2, 26.1, 18.8, 18.42, 18.36, 18.2, 17.8, 15.8, 12.6, 12.3, 11.6, 10.8, –4.35, –4.45; IR (thin film, NaCl) 3429, 2957, 2930, 2866, 1616, 1514, 1457, 1249, 1104, 1039, 882, 827, 775 cm^{-1}; LRMS (EI, Na) calcd for $C_{52}H_{90}O_8Si_2$, 922.44 *m/z* (M + Na); observed, 921.88 $(M + Na)^+$ *m/z*.

Data for minor diastereomer (*E*,*E*)-(2*S*,3*S*,4*R*,7*S*,8*R*,9*R*,10*R*,13*S*,14*S*)-3-(*p*-methoxybenzyloxy)-7-(*tri*-isopropylsilanyloxy)-8-di(*tert*-butyldimethylsilanyloxy)-2,4,6-trimethylnon-5-ene-1-ol, 7b". $[\alpha]_{589}^{20}$ –10.8 ° (*c* 0.90, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.26 (m, 4H), 6.88-6.86 (m, 4H), 5.59 (d, J = 9.6 Hz, 1H), 5.31 (d, J = 9.9 Hz, 1H), 4.76 (A of AB, J = 10.7 Hz, 1H), 4.59 (B of AB, J = 10.8 Hz, 1H), 4.54 (B of AB, J = 10.8 Hz, 1H), 4.43 (B of AB, J = 10.7 Hz, 1H), 4.16 (d, J = 4.2 Hz, 1H), 4.08 (s, 1H), 3.95-3.90 (m, 1H), 3.809 (s, 3H), 3.806 (s, 3H), 3.82-3.75 (m, 1H), 3.59 (s br, 2H), 3.51 (dd, J = 5.3, 3.6 Hz, 1H), 3.42 (d, J = 8.6 Hz, 1H), 3.02-2.95 (m, 2H), 2.76-2.69 (m, 1H), 1.99-1.86 (m, 2H), 1.73 (d, J = 0.7 Hz, 3H), 1.54 (s, 3H), 1.10 (d, J = 6.6 Hz, 3H), 1.08-1.02 (m, 24H), 0.99 (d, J = 6.2 Hz, 3H), 0.88-0.81 (m, 15H), 0.060 (s, 3H), 0.043 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 159.3, 134.8, 134.7, 131.2, 131.0, 129.6, 129.3, 129.1, 12 8.0, 114.02, 113.93, 86.9, 84.5, 79.4, 79.2, 74.9, 72.9, 72.8, 66.7,

55.5, 38.9, 37.8, 36.3, 35.3, 26.1, 18.4, 18.3, 18.2, 17.8, 17.7, 16.0, 14.0, 12.6, 10.7, 7.7, –4.37, –4.40; IR (thin film, NaCl) 3408, 2956, 2931, 2865, 1613, 1514, 1463, 1248, 1102, 1039, 883, 825, 775, 680 cm^{-1}; LRMS (EI, Na) calcd for $C_{52}H_{90}O_8Si_2$, 922.44 *m/z* (M + Na); observed, 922.93 $(M + Na)^+$ *m/z.*

References:

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2. Bahadoor, A.B.; Flyer, A.; Micalizio, G.C. *J. Am. Chem. Soc.* **2005**, *127*, 3694-3695.