Studies on the Synthesis of Pectenotoxin II: Synthesis of a C(11)-C(26) Fragment Precursor via [3+2]-Annulation Reactions of Chiral Allylsilanes

Glenn C. Micalizio and William R. Roush*

Department of Chemistry, University of Michigan, Ann Arbor, MI 48109

Email Address: roush@umich.edu

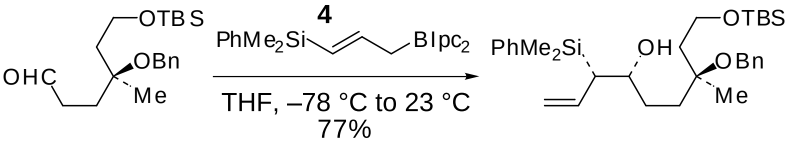
SUPPORTING INFORMATION

Experimental procedures for synthesis of **13-21** and **2** (11 pages).

General. All reactions were conducted in flame dried glassware under nitrogen. All solvents were purified before use. THF and Et_2O were dried by distillation from sodium benzophenone ketyl. CH_2Cl_2, pyridine, DMF were dried by distillation from CaH_2. Methanol was distilled from magnesium turnings. Toluene was dried by distillation from sodium. All other commercially available reagents and solvents were used as received.

^1H NMR data were recorded at either 500 MHz or 400 MHz using a Varian I-500 or a Varian XL-400 instrument respectively. ^1H NMR chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm). ^{13}C NMR data were recorded at either 125 MHz or 100 MHz using a Varian I-500 or a Varian XL-400 instrument respectively. ^{13}C chemical shifts are reported relative to the central line of $CDCl_3$ (77.0 ppm). Infrared spectra were recorded using a Perkin Elmer Spectrum 1000 FT-IR (thin film) . High resolution mass spectrometry was performed on a VG 70-250-S Micromass, Inc. mass spectrometer at the University of Michigan Mass Spectrometry Laboratory. Optical rotations were measured on a Rudolph Autopol III polarimeter using a 1 mL capacity quartz cell with a 10 cm path length. Elemental analyses were performed by the Elemental Analysis Laboratory at the University of Michigan.

Chromatographic purifications were performed using Kieselgel 60, 230-400 mesh, silica gel unless indicated otherwise. All compounds purified by chromatography were sufficiently pure for use in further experiments, unless indicated otherwise. Analytical and semi-preparative HPLC normal phase separations were performed using an HPLC system composed of two Rainin HXPL pumps, a Rheodyne 7125 injector, a Dynamax UV-C or RI-1 detector and Dynamax software on a Macintosh II SI to integrate the peaks.

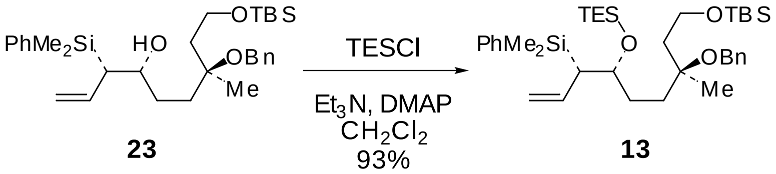


3

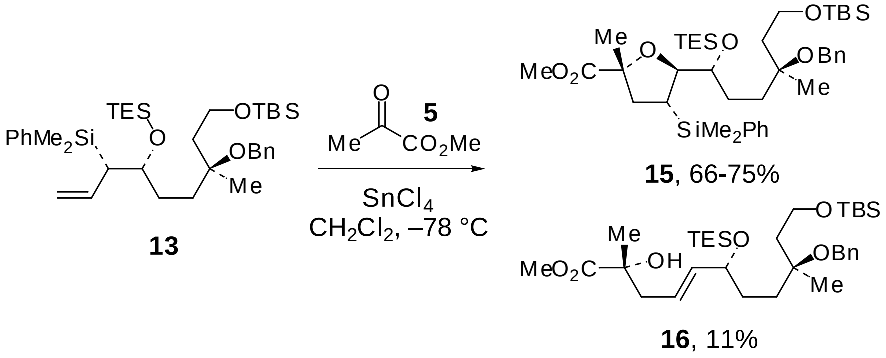
23

(3*S*,6*R*,7*S*)-1-*tert*-Butyldimethylsilanyloxy-3-benzyloxy-7-dimethyl-phenyl-silanyl-non-8-ene-6-ol (23). To a solution of dimethylphenylallylsilane (4.45 g, 18.7 mmol) in 10 mL of THF was added KO*t*-Bu (2.0 g, 18 mmol). The solution was then cooled to –78 °C and 7.65 mL of *n*-BuLi (2.35 M in hexanes, 18 mmol) was added dropwise via cannula. The solution was stirred at –78 °C for 15 min, then warmed to –45 °C and stirred for 15 min. The solution was recooled to –78 °C, and a solution of (–)-Ipc_2BOMe (5.69 g, 18 mmol in 16 mL of THF) was added dropwise via cannula. The solution was stirred at –78 °C for 45 min, after which time a solution of the crude aldehyde **3** (13.4 mmol in 30 mL of THF) was added dropwise via cannula. The solution was stirred at –78 °C for 4 h, then slowly warmed to 23 °C overnight. The solution was cooled to 0 °C and CH_3OH (20 mL) was added followed by pH 7 buffer (10 mL) and 7 mL of H_2O_2 (50%

aqueous). The solution was stirred at 0 °C for 2.5 h, then diluted with EtOAc and washed with pH 7 buffer, $NaHCO_3$ (sat) and brine. The combined aqueous layers were extracted with 200 mL of EtOAc, and this organic layer was washed with brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford a crude oil which was purified by flash column chromatography [300 g SiO_2 deactivated with a solution of 2% Et_3N in hexanes - 2% Et_3N in hexanes (600 mL); 18 : 1 hexanes : EtOAc - 2% Et_3N (2 L); 9 : 1 hexanes : EtOAc - 2% Et_3N (1 L)] affording 5.4 g (77%) of the β-hydroxy allylsilane **23** as ca. 13 : 1 mixture of diastereomers: $[\alpha]_D^{25.2}$ +1.8 (*c* 1.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2 H), 7.38-7.30 (m, 7 H), 7.27-7.24 (m, 1 J), 5.88-5.81 (m, 1 H), 5.06 (dd, *J* = 10.1, 2.1 Hz, 1 H), 4.93-4.90 (m, 1 H), 4.39-4.33 (m, 2 H), 3.74-3.68 (m, 3 H), 1.90 (dd, *J* = 10.6, 4.3 Hz, 1 H), 1.86-1.72 (m, 3 H), 1.58-1.46 (m, 3 H), 1.16 (s, 3 H), 0.90 (s, 9 H), 0.35 (s, 3 H), 0.31 (s, 3 H), 0.05 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 138.0, 135.2, 134.0, 129.0, 128.2, 127.7, 127.2, 127.1, 115.5, 76.2, 71.7, 63.2, 59.3, 42.3, 40.8, 34.9, 31.4, 26.0, 23.6, 18.3, –3.4, –4.0, –5.3; IR (thin film) 3459, 3069, 3029, 2954, 2930, 2884, 2857, 1808, 1725, 1624, 1497, 1471, 1463, 1428, 1385, 1361, 1304, 1252, 1090, 1065, 1028, 1006 cm^{-1}; HRMS (FAB) calcd for $C_{31}H_{50}O_3NaSi_2$, 549.3196 *m/z* $(M + Na)^+$; observed 549.3188 *m/z*.



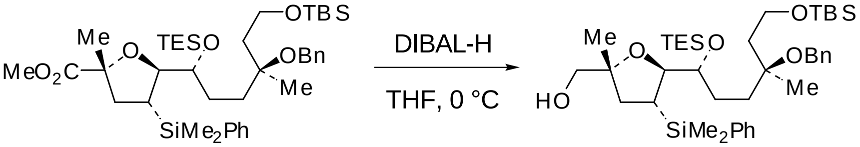
(3*S*,6*R*,7*S*)-1-*tert*-Butyldimethylsilanyloxy-3-benzyloxy-6-triethylsilanyloxy-7-dimethylphenylsilanyl-non-8-ene (13). To a solution of the β-hydroxy allylsilane **23** (5.4 g, 10.3 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (5.7 mL, 41 mmol) followed by DMAP (125 mg, 1 mmol) and TESCl (5.2 mL, 30.8 mmol). The solution was stirred at 23 °C for 36.5 h, after which time it was diluted with EtOAc and washed with $KHSO_4$ (1 N) followed by $NaHCO_3$ (sat) and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to give a crude oil which was purified by flash column chromatography [280 g SiO_2 deactivated with 1 L of 2% Et_3N in hexanes - 2% Et_3N in hexanes (1.5 L); 20 : 1 hexanes : EtOAc (1 L)] affording 6.1 g (93%) of the silyl ether **13**: $[\alpha]_D^{25.6}$ –5.4 (*c* 2.75, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2 H), 7.36-7.31 (m, 7 H), 7.27-7.24 (m, 1 H), 5.97-5.89 (m, 1 H), 4.99 (d, *J* = 10.5 Hz, 1 H), 4.82-4.78 (m, 1 H), 4.40 (A of AB, *J* = 11.4 Hz, 1 H), 4.34 (B of AB, *J* = 11.4 Hz, 1 H), 3.83-3.81 (m, 1 H), 3.78-3.68 (m, 2 H), 1.97 (d, *J* = 10.5 Hz, 1 H), 1.89-1.81 (m, 1 H), 1.80-1.74 (m, 1 H), 1.62-1.57 (m, 2 H), 1.46-1.40 (m, 1 H), 1.34-1.28 (m, 1 H), 1.19 (s, 3 H), 0.94-0.90 (m, 18 H), 0.58-0.53 (m, 6 H), 0.36 (s, 3H), 0.30 (s, 3 H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 138.7, 135.5, 134.1, 128.7, 128.2, 127.5, 127.1, 127.0, 114.6, 75.8, 73.9, 63.0, 59.4, 40.9, 40.7, 34.3, 30.5, 26.0, 23.9, 18.3, 7.0, 5.6, –3.3, –3.9, –5.3; IR (thin film) 3051, 3070, 3029, 2955, 2936, 2911, 2877, 2858, 1947, 1807, 1624, 1497, 1471, 1463, 1428, 1414, 1381, 1361, 1305, 1252, 1091, 1028, 1007 cm^{-1}; HRMS (FAB) calcd for $C_{37}H_{64}O_3NaSi_3$, 663.4061 *m/z* (M + Na)$^+$; observed 663.4065 *m/z*.



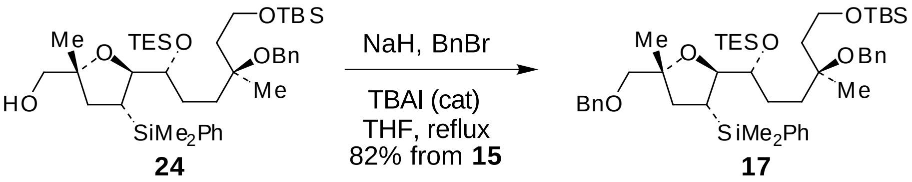
(2'*R*,4'*R*,5'*R*,6''*R*,3''*S*)-1-[5'-[6''-Triethylsilanyloxy-3''-benzyloxy-3''-methyl-1''-*tert*-butyldimethylsilanyloxy-hex-6'-yl]-4'-(dimethylphenylsilanyl)-2'-methyltetrahydrofuran-2-yl]-formic acid methyl ester (15). To a - 78° C solution of methyl pyruvate (435 µL, 4.8 mmol) and 4 Å mol. sieves in CH_2Cl_2 (1.5 mL) was added $SnCl_4$ (320 µL, 2.7 mmol) The solution was stirred for approximately 1.5 min, then a solution of allylsilane **13** (466 mg, 0.73 mmol in 1.5 mL of CH_2Cl_2) was added dropwise via cannula. The mixture was stirred for 10 min at –78 °C, then Et_3N (2 mL) was added. The cold solution was then transferred with EtOAc into a separatory funnel charged with $NaHCO_3$ (sat). The organic phase was washed with brine. The aqueous phase was filtered through Celite, then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford a crude oil which was purified by flash column chromatography [100 g SiO_2 - 100% hexanes (200 mL); 18 : 1 hexanes : EtOAc (500 mL)], affording 359 mg (66%) of the [3+2] annulation product **15** as well as 48 mg (11%) of the allylation product **16**. When performed on a 2 g (3 mmol) scale, the yield of **15** was 75% (homoallylic alcohol **16** was produced but not isolated).

Spectroscopic data for tetrahydrofuran **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2 H), 7.36-7.29 (m, 7 H), 7.25-7.22 (m, 1 H), 4.41 (A of AB, *J* = 11.2 Hz, 1 H), 4.36 (B of AB, *J* = 11.2 Hz, 1 H), 4.00 (dd, *J* = 10.7, 2.0 Hz, 1 H), 3.80-3.72 (m, 2 H), 3.64 (s, 3 H), 3.61-3.58 (m, 1 H), 2.14 (dd, *J* = 12.3, 12.3 Hz, 1 H), 1.94-1.71 (m, 5 H), 1.58-1.50 (m, 3 H), 1.35 (s, 3 H), 1.22 (s, 3 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 0.90 (s, 9 H), 0.58 (q, *J* = 7.9 Hz, 6 H), 0.33 (s, 3 H), 0.32 (s, 3 H), 0.06 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 139.6, 137.8, 133.8, 129.1, 128.2, 127.8, 127.2, 127.0, 85.7, 81.8, 75.9, 72.7, 63.0, 59.4, 52.0, 41.2, 40.8, 34.7, 27.4, 26.0, 25.4, 24.9, 23.8, 18.3, 7.0, 5.2, –3.2, –4.8, –5.3; IR (thin film) 3069, 3028, 2954, 2877, 1950, 1738, 1497, 1462, 1428, 1413, 1381, 1252, 1191, 1114, 1089, 1006 cm^{-1}; HRMS (FAB) calcd for $C_{41}H_{70}O_6NaSi_3$, 765.4378 *m/z* $(M + Na)^+$; observed 765.4377 *m/z*. *Anal.* Calcd for $C_{41}H_{70}O_6Si_3$; C, 66.26; H, 9.49. Found: C, 66.37; H, 9.63.

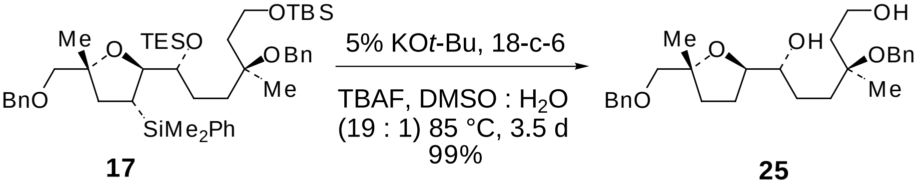
Spectroscopic data for allylation product **16**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.30 (m, 4 H), 7.26-7.23 (m, 1 H), 5.56-5.47 (m, 2 H), 4.38 (s, 2 H), 4.06-4.05 (m, 1 H), 3.77-3.73 (m, 5 H), 3.08 (s, 1 H), 2.51-2.47 (m, 1 H), 2.37-2.33 (m, 1 H), 1.91-1.78 (m, 2 H), 1.60-1.52 (m, 4 H), 1.40 (s, 3 H), 1.22 (s, 3 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 0.90 (s, 9 H), 0.57 (q, *J* = 7.9 Hz, 6 H), 0.05 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 139.6, 138.2, 128.2, 127.2, 127.0, 123.4, 75.9, 74.3, 73.2, 63.0, 59.3, 52.6, 43.1, 41.1, 33.9, 32.3, 25.9, 25.4, 23.7, 18.3, 6.9, 4.9, –5.3; IR (thin film) 3536, 3031, 2954, 2877, 1738, 1497, 1462, 1415, 1380, 1256, 1208, 1091, 1028, 1006 cm^{-1}; HRMS (FAB) calcd for $C_{33}H_{60}O_6NaSi_2$, 631.3826 *m/z* $(M + Na)^+$; observed 631.3850 *m/z*.



(2*R*,4*R*,5*R*,6'*R*,3'*S*)-2-Hydroxymethyl-2-methyl-4-dimethylphenylsilanyl-5-[6'-triethylsilanyloxy-3'-benzyloxy-3'methyl-1'-*tert*-butyldimethylsilanyloxy-hex-6'-yl]-tetrahydrofuran (24). To a 0 °C solution of the methyl ester **15** (805 mg, 1.08 mmol) in 8 mL of THF was added 3.2 mL of DIBAL-H (1.0 M in hexanes, 3.3 mmol). The solution was stirred for 30 min. at 0 °C, then CH_3OH (1mL) was added followed by Rochelle's salt (5 mL of a saturated solution). The solution was stirred for 40 min at 23 °C, then diluted with EtOAc and washed with $NaHCO_3$ (sat) followed by brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to afford a crude oil which was used without purification in the next step. A small amount of material was purified by flash column chromatography to afford analytically pure material [SiO_2 - 9 : 1 hexanes : EtOAc]: ^1H NMR (500 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2 H), 7.36-7.31 (m, 7 H), 7.26-7.24 (m, 1 H), 4.41 (A of AB, *J* = 11.4 Hz, 1 H), 4.36 (B of AB, *J* = 11.4 Hz, 1 H), 3.89-3.87 (m, 1 H), 3.81-3.72 (m, 2 H), 3.45-3.41 (m, 2 H), 3.34-3.30 (m, 1 H), 1.96-1.86 (m, 3 H), 1.84-1.78 (m, 2 H), 1.75-1.71 (m, 1 H), 1.58-1.55 (m, 1 H), 1.51-1.46 (m, 3 H), 1.22 (s, 3 H), 1.10 (s, 3 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 0.91 (s, 9 H), 0.56 (q, *J* = 7.9 Hz, 9 H), 0.34 (s, 6 H), 0.07 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 138.0, 133.8, 129.1, 128.2, 127.8, 127.15, 127.05, 84.9, 81.9, 75.9, 73.4, 68.5, 63.1, 59.4, 41.1, 37.2, 34.8, 28.0, 26.0, 25.8, 23.8, 23.7, 18.3, 7.0, 5.3, –3.4, –4.5, –5.3; IR (thin film) 3460, 3069, 3029, 2955, 2877, 1497, 1462, 1428, 1413, 1381, 1319, 1252, 1188, 1090, 1028, 1006 cm^{-1}; HRMS (FAB) calcd for $C_{40}H_{70}O_5NaSi_3$, 737.4429 *m/z* $(M + Na)^+$; observed 737.4452 *m/z*. *Anal.* Calcd for $C_{40}H_{70}O_5Si_3$; C, 67.17; H, 9.86. Found: C, 67.12; H, 9.67.

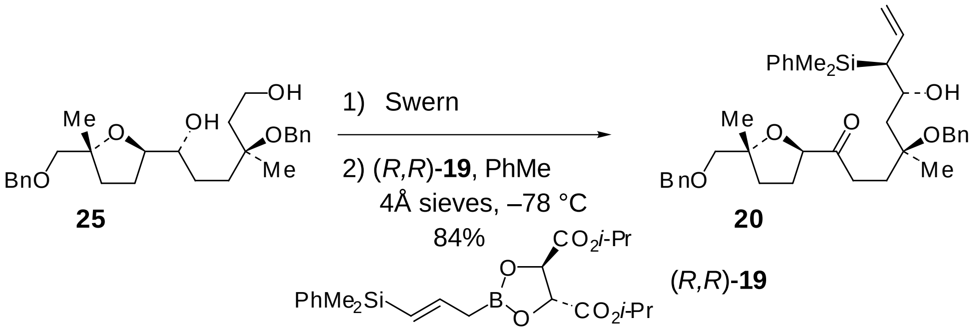


(2*R*,4*R*,5*R*,6'*R*,3'*S*)-2-Benzyloxymethyl-2-methyl-4-dimethylphenylsilanyl-5-[1'-triethylsilanyloxy-3'-benzyloxy-3'methyl-1'-*tert*-butyldimethylsilanyloxy-hex-6'-yl]-tetrahydrofuran (17). To a 0 °C solution of the crude primary alcohol **24** (1.1 mmol) in THF (4 mL) was added tetrabutylammonium iodide (TBAI; cat) followed by NaH (65 mg of a 60% dispersion in mineral oil, 1.6 mmol). To this solution was added benzyl bromide. The ice bath was removed and the solution was brought to reflux for 19 h. The solution was cooled to 23 °C and $NaHCO_3$ (sat) was added, then the solution was diluted with EtOAc and washed with $NaHCO_3$ (sat) followed by brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford a crude oil which was purified by flash column chromatography [120 g SiO_2 - 100% hexanes (500 mL); 25 : 1 hexanes : EtOAc (1 L); 18 : 1 hexanes : EtOAc (1 L); 7 : 1 hexanes : EtOAc (500 mL)] affording 716 mg (82%) of the benzyl ether **17**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2 H), 7.37-7.23 (m, 13 H), 4.54 (s, 2 H), 4.40 (A of AB, *J* = 11.2 Hz, 1 H), 4.36 (B of AB, *J* = 11.2 Hz, 1 H), 3.91 (d, *J* = 10.7 HJz, 1 H), 3.81-3.72 (m, 2 H), 3.59-3.56 (m, 1 H), 3.33 (A of AB, *J* = 9.6 Hz, 1 H), 3.28 (B of AB, *J* = 9.6 Hz, 1 H), 1.93-1.88 (m, 2 H), 1.83-1.72 (m, 3 H), 1.64-1.60 (m, 1 H), 1.56-1.46 (m, 3 H), 1.22 (s, 3 H), 1.14 (s, 3 H), 0.96-0.92 (m, 9 H), 0.91 (s, 9 H), 0.60-0.55 (m, 6 H), 0.34-0.33 (m, 6 H), 0.07 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 138.8, 138.4, 133.9, 128.9, 128.22, 128.16, 127.7, 127.4, 127.3, 127.2, 127.0, 115.3, 84.9, 80.9, 76.9, 76.0, 73.3, 73.1, 63.0, 59.4, 41.2, 38.7, 34.9, 27.4, 26.0, 25.6, 24.5, 23.7, 18.3, 7.0, 5.2, –3.0, –4.6, –5.3; IR (thin film) 3089, 3068, 3030, 2955, 2933, 2877, 2858, 1947, 1878, 1808, 1606, 1588, 1497, 1471, 1455, 1428, 1412, 1370, 1305, 1251, 1189, 1094, 1028, 1007 cm^{-1}; HRMS (FAB) calcd for $C_{47}H_{76}O_5NaSi_3$, 827.4898 *m/z* $(M + Na)^+$; observed 827.4882 *m/z*. *Anal*. Calcd for $C_{40}H_{70}O_5Si_3$; C, 70.09; H, 9.51. Found: C, 69.98; H, 9.67.



(2*R*,5*R*,1'*R*,3'*S*)-2-Benzyloxymethyl-2-methyl-5-[1',6'-dihydroxy-3'-benzyloxy-3'methyl-6'-hex-6'-yl]-tetrahydrofuran (25). To a solution of tetrahydrofuran **17** (189 mg, 0.23 mmol) and TBAF•3H_2O (218 mg, 0.69 mmol) in 2 mL of a 5% solution of KO*t*-Bu in DMSO : H_2O (19 : 1) was added 18-crown-6 (70 mg). The solution was heated at 85 °C for

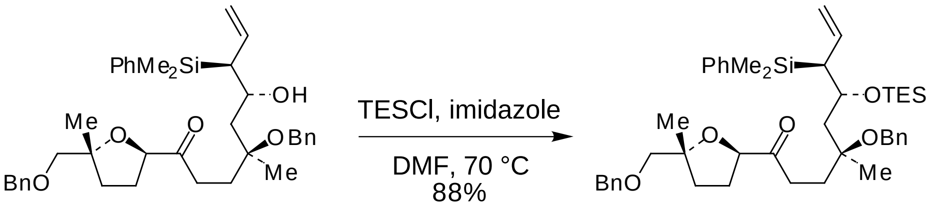
3.5 d after which time it was cooled to 23 °C, diluted with EtOAc and washed with $NaHCO_3$ (sat), then brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford a crude oil which was purified by flash column chromatography [40 g SiO_2 - 100% hexanes (150 mL); 2 : 1 hexanes : EtOAc (300 mL); 1 : 1 hexanes : EtOAc (400 mL); 1 : 2 hexanes : EtOAc (600 mL)] affording 103 mg (99%) of the desilylated diol **25**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.24 (m, 10 H), 4.58 (s, 2 H), 4.46 (A of AB, *J* = 10.90Hz, 1 H), 4.42 (B of AB, *J* = 10.9 Hz, 1 H), 3.87-3.83 (m, 2 H), 3.78-3.77 (m, 1 H), 3.39-3.36 (m, 3 H), 2.93 (s(br), 1 H), 2.52 (d, *J* = 3.7 Hz, 1 H), 2.04-1.93 (m, 4 H), 1.74-1.62 (m, 4 H), 1.56-1.45 (m, 2 H), 1.32 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.4, 128.4, 128.3, 127.5, 127.45, 127.43, 127.3, 83.1, 82.9, 78.3, 76.3, 74.7, 73.4, 63.5, 59.4, 39.9, 34.5, 34.1, 28.2, 27.8, 24.9, 23.0; IR (thin film) 3436, 3088, 3064, 3030, 2967, 2929, 2869, 1952, 1810, 1728, 1606, 1497, 1454, 1372, 1309, 1207, 1099, 1064, 1028 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{27}H_{42}NO_5$, 460.3063 *m/z* $(M + NH_4)^+$; observed 460.3079 *m/z*.



(2*R*,5*R*,4'*S*,6'*R*,7'*S*)-2-benzyloxymethyl-2-methyl-5-[4'-benzyloxy-4'-methyl-6'-hydroxy-7'-dimethylphenylsilanyl-8'-ene-1'-one-1'-yl]-tetrahydrofuran (20): To a –78 °C solution of DMSO (560 µL, 7.9 mmol) in CH_2Cl_2 (10 mL) was added $(COCl)_2$ (410 µL, 4.7 mmol) dropwise via syringe. The solution was stirred at –78 °C for 5 min, after which time diol **25** (694 mg, 1.57 mmol) was added as a solution in CH_2Cl_2 (8 mL) dropwise via cannula. Next, Et_3N (2.2 mL, 15.7 mmol) was added dropwise as a solution in CH_2Cl_2 (2 mL) and the –78 °C bath was removed. The solution was warmed to ca. 25 °C, then was diluted with EtOAc and washed twice with $KHSO_4$ (1N), then twice with $NaHCO_3$ (sat) and finally with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford the crude keto aldehyde **18** that was used in the subsequent allylboration without purification.

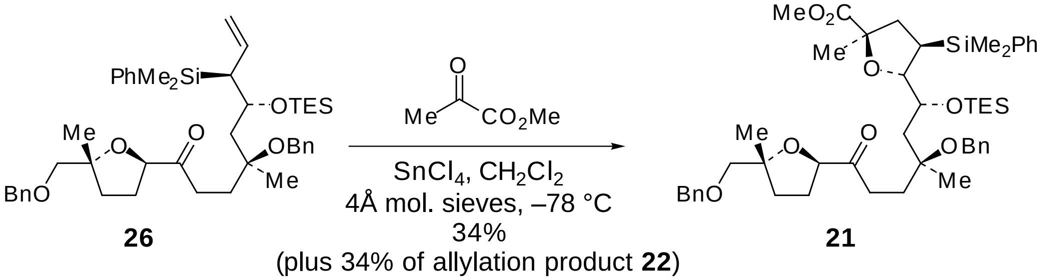
To a –78 °C solution of the crude keto aldehyde **18** from the preceding experiment and freshly activated 4Å mol. sieves in toluene (15 mL) was added the allylboronate (*R*,*R*)-**19** dropwise as a ca. 0.75 M solution in toluene (7 mL, ca. 5.3 mmol). The solution was stirred overnight; over this time, the temperature of the solution increased to 25 °C. The reaction mixture was diluted with EtOAc and Et_3N (3 mL) was added. The solution was washed with $NaHCO_3$ (sat), then brine, dried over

$MgSO_4$, filtered and concentrated to afford a crude oil which was purified by flash column chromatography [120 g SiO_2 deactivated with a 1% solution of Et_3N in hexanes (500 mL) - eluted with 1% Et_3N in hexanes (1 L), 18 : 1 hexanes : EtOAc (1 L + 10 mL Et_3N), 9 : 1 hexanes : EtOAc (1 L + 10 mL Et_3N)] affording 814 mg (84%) of the β-hydroxy allylsilane **20**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57-7.54 (m, 2 H), 7.38-7.25 (m, 13 H), 6.00-5.93 (m, 1 H),5.02-4.99 (m, 1 H), 4.84-4.80 (m, 1 H), 4.58 (s, 2 H), 4.43 (A of AB, *J* = 11.1 Hz, 1 H), 4.38 (B of AB, *J* = 11.1 Hz, 1 H), 4.37 (dd, *J* = 7.3 Hz, 1 H), 4.13 (d(br), *J* = 9.0 Hz, 1 H), 3.40-3.35 (m, 2 H), 3.31 (d, *J* = 1.0 Hz, 1 H), 2.56-2.52 (m, 2 H), 2.23-2.16 (m, 1 H), 2.07-2.00 (m, 2 H), 1.91-1.79 (m, 3 H), 1.71 (dd, *J* = 10.5, 3.2 Hz, 1 H), 1.63-1.58 (m, 1 H), 1.36 (d, *J* = 14.4 Hz, 1 H), 1.27 (s, 3 H), 1.20 (s, 3 H), 0.36 (s, 3 H), 0.32 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.9, 138.7, 138.3, 135.6, 134.1, 128.8, 128.4, 127.6, 127.5, 127.4, 127.3, 115.3, 114.6, 84.7, 84.3, 78.1, 76.1, 73.4, 68.0, 63.6, 44.5, 43.5, 33.9, 33.1, 30.6, 29.4, 24.4, 24.0, -3.7, -3.9; IR (thin film) 3486, 3068, 3031, 2970, 2873, 1953, 1777, 1715, 1624, 1497, 1454, 1428, 1410, 1373, 1306, 1246, 1207, 1113, 1028 cm^{-1}; HRMS (FAB) calcd for $C_{38}H_{50}O_5NaSi$, 637.3325 *m/z* (M + Na)$^+$; observed 637.3309 *m/z*.



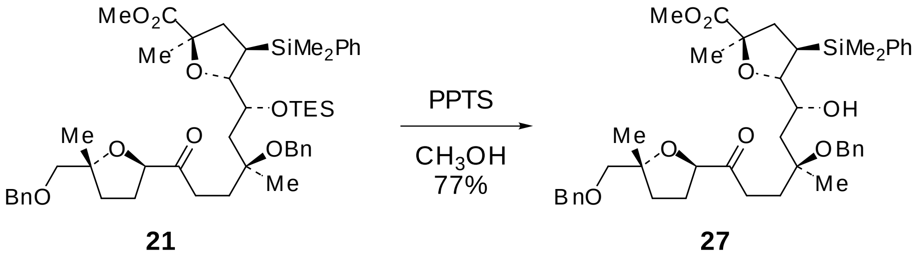
20 **26**

(2*R*,5*R*,4'*S*,6'*R*,7'*S*)-2-benzyloxymethyl-2-methyl-5-[4'-benzyloxy-4'-methyl-6'-triethylsilanyloxy-7'-dimethylphenylsilanyl-8'-ene-1'-one-1'-yl]-tetrahydrofuran (26): To a solution of the β-hydroxy allylsilane **20** (493 mg, 0.80 mmol) in 800 μL of anhydrous DMF was added imidazole (220 mg, 3.2 mmol) followed TESCl (270 μL, 1.6 mmol). The solution was stirred at ambient temperature for 1 h, then at 70 °C for 30 min. The solution was diluted with EtOAc and washed with $KHSO_4$ (1N), then $NaHCO_3$ (sat) followed by brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford a crude oil which was purified by flash column chromatography [40 g SiO_2 deactivated with 1% Et_3N in hexanes (300 mL) and eluted with 1% Et_3N in hexanes (500 mL); 18 : 1 hexanes : EtOAc (500 mL + 5 mL Et_3N] to give 514 mg of **26** (88%): $[\alpha]_D^{25.4}$ +26.4 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.41 (m, 2 H), 7.36-7.23 (m, 13 H), 5.90 (ddd, *J* = 17.6, 10.5, 10.5 Hz, 1 H), 4.93 (dd, *J* = 10.4, 2.2 Hz, 1 H), 4.67 (dd, *J* = 17.3, 2.2 Hz, 1 H), 4.57 (s, 2 H), 4.37 (dd, *J* = 7.6, 7.6 Hz, 1 H), 4.31-4.26 (m, 2 H), 4.18-4.17 (m, 1 H), 3.38-3.30 (m, 2 H), 2.66-2.53 (m, 2 H), 2.29 (d, *J* = 10.0 Hz, 1 H), 2.23-2.16 (m, 1 H), 2.09 (dd, *J* = 14.2, 8.3 Hz, 1 H), 2.02 (ddd, *J* = 12.3, 7.8, 7.8 Hz, 1 H), 1.92-1.83 (m, 2 H), 1.76-1.70 (m, 1 H), 1.63-1.56 (m, 1 H), 1.38 (dd, *J* = 14.2, 3.4 Hz, 1 H), 1.27 (s, 3 H), 1.18 (s, 3 H), 0.89 (t, *J* = 8.1 Hz, 9 H), 0.53 (q, *J* = 8.0 Hz, 6 H), 0.30 (s, 3 H), 0.21 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.5, 139.3, 138.7, 138.4, 135.9, 134.1, 128.6, 128.3, 128.8, 127.54, 127.47, 127.1, 127.0, 114.9, 84.7, 84.4, 76.2, 75.9, 73.4, 70.2, 63.1, 44.3, 41.8, 33.8, 32.3, 31.6, 29.6, 24.4, 23.4, 7.0, 5.7, -3.2, -3.8; IR (thin film) 3067, 3028, 2955, 2909, 2875, 1715, 1622, 1496, 1454, 1427, 1414, 1372, 1307, 1245, 1204, 1165, 1112, 1075, 1007 cm^{-1}; HRMS (FAB) calcd for $C_{44}H_{64}O_5NaSi_2$, 751.4190 *m/z* (M + Na)$^+$; observed 751.4180 *m/z*.

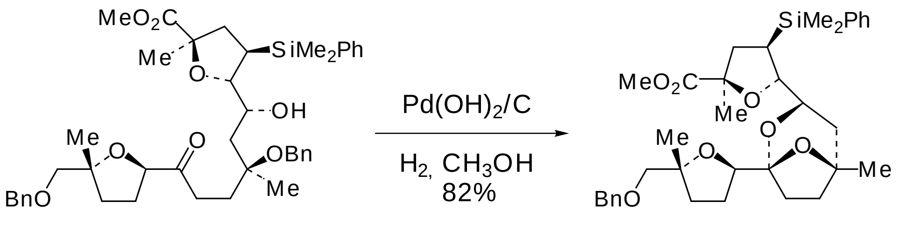


(4*S*,6*R*,2'*R*,5'*R*,2''*R*,4''*R*,5''*R*)-1-[2'-Methyl-2'-benzyloxymethyl-tetrahydrofuran-5'-yl]-6-[2''-methyl-2''-carbomethoxy-4''-dimethylphenylsilanyl-tetrahydrofuran-5''-yl]-4-benzyloxy-4-methyl-6-triethylsilanyloxy-hex-1-one (21): To a –78 °C solution of methyl pyruvate (182 µL, 2.0 mmol) and 4 Å mol. sieves in CH_2Cl_2 (1 mL), was added $SnCl_4$ (235 µL, 2.0 mmol). Next, the β-triethylsilyloxy allylsilane **26** (490 mg, 0.67 mmol) was added dropwise as a solution in 1.2 mL of CH_2Cl_2. The solution was stirred at –78 °C for 10 min, then Et_3N was added (1 mL). The solution was diluted with EtOAc and washed with Rochelle's salt (sat) (3x) followed by $KHSO_4$ (1N) (2x), $NaHCO_3$ (sat) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford a crude oil which was purified by flash column chromatography [100 g SiO_2 deactivated with 1% Et_3N in hexanes (500 mL) and eluted with 18 : 1 hexanes : EtOAc (500 mL), 9 : 1 hexanes : EtOAc (500 mL), 4 : 1 hexanes : EtOAc (1 L)] affording 190 mg of the desired annulation product **21** (34%) along with 160 mg (34%) of the product derived from allylation: $[\alpha]_{405}^{25.4}$ +12.9 (*c* 2.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.43 (m, 2 H), 7.36-7.21 (m, 13 H), 4.57-4.52 (m, 3 H), 4.40 (dd, *J* = 7.6, 7.6 Hz, 1 H), 4.27 (d, *J* = 11.0 Hz, 1 H), 4.26 (d, *J* = 9.0 Hz, 1 H), 3.76-3.74 (m, 1 H), 3.53 (s, 3 H), 3.38 (A of AB, *J* = 9.8 Hz, 1 H), 3.35 (B of AB, *J* = 9.8 Hz, 1 H), 2.66 (m, 2 H), 2.37 (dd, *J* = 14.7, 8.5 Hz, 1 H), 2.25-2.18 (m, 1 H), 2.11 (dd, *J* = 11.5, 11.5 Hz, 1 H), 2.03 (ddd, *J* = 12.5, 7.8, 7.8 Hz, 1 H), 1.97-1.82 (m, 4 H), 1.82-1.76 (m, 1 H), 1.65-1.60 (m, 1 H), 1.44-1.40 (m, 1 H), 1.39 (s, 3 H), 1.28 (s, 3 H), 1.16 (s, 3 H), 0.93 (t, *J* = 7.9 Hz, 9 H), 0.57-0.52 (m, 6 H), 0.23 (s, 3 H), 0.22 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 176.2, 139.5, 138.4, 137.6, 133.8, 129.1, 128.3, 128.1, 127.8, 127.5, 127.4, 127.3, 126.9, 85.4, 84.7, 84.3, 82.3, 76.2, 75.6, 73.4, 69.1, 62.9, 51.8, 42.0, 40.6, 33.8, 32.3, 31.4, 29.6, 25.6, 24.9, 24.4, 23.9, 7.1, 5.4, -4.1, -4.5; IR (thin film)

3067, 3030, 2953, 2910, 2876, 1732, 1715, 1496, 1454, 1428, 1412, 1373, 1283, 1250, 1207, 1167, 1115, 1060, 1028, 1009 cm^{-1}; HRMS (FAB) calcd for $C_{48}H_{72}O_8NaSi_2$, 855.4663 *m/z* (M + Na)$^+$; observed 853.4504 *m/z*.



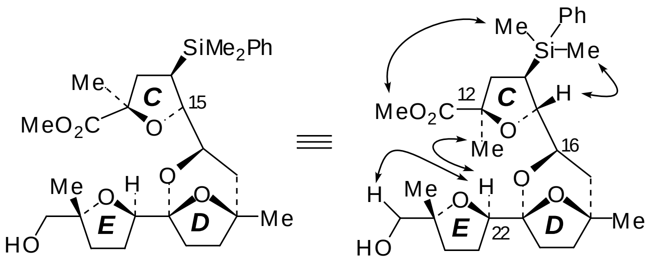
(4*S*,6*R*,2'*R*,5'*R*,2''*R*,4''*R*,5''*R*)-1-[2'-Methyl-2'-benzyloxymethyl-tetrahydrofuran-5'-yl]-6-[2''-methyl-2''-carbomethoxy-4''-dimethylphenylsilanyl-tetrahydrofuran-5''-yl]-4-benzyloxy-4-methyl-6-hydroxy-hex-1-one (27): To a solution of TES ether **21** (60 mg, 0.07 mmol) in CH_3OH (4 mL) was added PPTS (20 mg, 0.08 mmol). The solution was stirred for 15 min, after which time the solution was diluted with EtOAc and washed with $NaHCO_3$ (sat) followed by brine. The organic layers were dried over $MgSO_4$, filtered and concentrated to afford a crude oil which was purified via flash column chromatography [40 g SiO_2 eluted with 9 : 1 hexanes : EtOAc (500 mL), 4 : 1 hexanes : EtOAc (500 mL), 1 : 1 hexanes : EtOAc (500 mL)] affording 40 mg (77%) of the desired alcohol **27**: $[\alpha]_{405}^{25.6}$ +39 (*c* 2.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2 H), 7.37-7.23 (m, 13 H), 4.57 (s, 2 H), 4.41-4.33 (m, 3 H), 3.89-3.87 (m, 1 H), 3.66 (s, 3 H), 3.58-3.55 (m, 1 H), 3.39-3.34 (m, 2 H), 2.69-2.54 (m, 3 H), 2.25-2.10 (m, 2 H), 2.06-1.87 (m, 6 H), 1.85-1.77 (m, 1 H), 1.69 (dd, *J* = 14.9, 2.0 Hz, 1 H), 1.65-1.59 (m, 1 H), 1.44 (s, 3 H), 1.28 (s, 3 H), 1.20 (s, 3 H), 0.30 (s, 3 H), 0.28 (s, 3 H; ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1, 175.9, 139.0, 138.3, 137.0, 133.7, 129.3, 128.3, 128.2, 127.9, 127.53, 127.45, 127.3, 127.2, 87.2, 84.7, 84.3, 82.5, 76.9, 76.1, 73.4, 67.3, 63.3, 52.1; IR (thin film) 3500, 3064, 3029, 2951, 1732, 1715, 1496, 1453, 1428, 1403, 1372, 1281, 1252, 1207, 1165, 1113, 1027 cm^{-1}; HRMS (FAB) calcd for $C_{42}H_{56}O_8NaSi$, 739.3642 *m/z* (M + Na)$^+$; observed 739.3648 *m/z*.



27 **2**

(1*S*,3*R*,5*S*,2'*R*,5'*R*,2''*R*,4''*R*,5''*R*)-1-[2'-Methyl-2'-benzyloxymethyl-tetrahydrofuran-5'-yl]-3-[2''-methyl-2''-carbomethoxy-4''-dimethylphenylsilanyl-tetrahydrofuran-5''-yl]-5-methyl-2,8-dioxabicyclo-[3.2.1]octane (2): Dibenzyl ether **27** (39 mg, 0.05 mmol) was dissolved in CH_3OH (5 mL) and 30 mg of $Pd(OH)_2$ (Pearlman's catalyst) was added. Hydrogen was bubbled through the heterogeneous solution for ca. 2 h, after which time the solution was diluted with EtOAc, filtered through Celite and washed with $NaHCO_3$ (sat) then brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford a crude oil which was purified by flash column chromatography [30 g SiO_2 eluted with 2 : 1 hexanes : EtOAc (500 mL), 1 : 1 hexanes : EtOAc (500 mL)] affording 23 mg (82%) of the tetracycle **2**. Analytically pure material was obtained by HPLC [75% EtOAc/hexanes; 21 mm column; 10 mL/min; UV detection]: $[\alpha]_{365}^{26.4}$ +21 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2 H), 7.41-7.35 (m, 3 H), 4.02 (dd, *J* = 7.1, 7.1 Hz, 1 H), 3.93 (dd, *J* = 10.3, 1.5 Hz, 1 H), 3.70 (s, 3H), 3.49-3.39 (m, 3 H), 2.13-2.07 (m, 1 H), 2.05-1.89 (m, 7 H)1.68-1.64 (m, 1 H), 1.61-1.50 (m, 2 H), 1.44-1.38 (m, 1 H), 1.38 (s, 3 H), 1.32 (s, 3 H), 1.22 (s, 3 H), 1.17 (dd, *J* = 12.7, 3.4 Hz, 1 H), 0.34 (s, 3 H), 0.31 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 175.6, 137.8, 134.1, 129.6, 107.6, 85.0, 84.3, 83.0, 82.4, 80.7, 68.7, 68.4, 51.5, 40.7, 39.2, 34.3, 33.8, 32.1, 27.7, 26.0, 25.12, 25.09, 24.2, -3.5, -5.1; IR (thin film) 3479, 3069, 3047, 2966, 2930, 2873, 1737, 1455, 1428, 1374, 1350, 1325, 1252, 1193, 1168, 1151, 1115, 1050, 1011 cm^{-1}; HRMS (FAB) calcd for $C_{28}H_{42}O_7NaSi$, 541.2597 *m/z* $(M + Na)^+$; observed 741.2600 *m/z*.

The stereochemistry of **2** was confirmed by the ^1H NOE's summarized below.



2