Synthesis of (+)-Bullatacin via the Highly Diastereoselective [3+2] Annulation Reaction of a Racemic Aldehyde and a Non-Racemic Allylsilane

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Supporting Information – Part I

Experimental Details

General Experimental Details. All reaction solvents were dried before use. Tetrahydrofuran, dichloromethane, toluene, and diethyl ether were purified by passing through a solvent column composed of activated A-1 alumina. BF_3•OEt_2 and $SnCl_4$ were purified by fractional distillation and stored under nitrogen. Unless indicated, all other reagents and solvents were used as purchased without further purification.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were conducted on commercial 400 MHz or 500 MHz spectrometers. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the aforementioned instruments at 100 MHz and 125 MHz, respectively. The proton signal of residual non-deuterated solvent (7.26 ppm for $CHCl_3$) was used as an internal reference for ^{1}H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to the 77.2 ppm resonance of $CHCl_3$. Coupling constants are reported in Hz. Infrared (FT-IR) spectra were recorded as films. Optical rotations were measured using a quartz cell with 1 mL capacity and a 10 cm path length. Mass spectra were recorded on a ZVG 70-250-S spectrometer manufactured by Micromass Corp. (Manchester, UK). Combustion elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} glass plates pre-coated with a 0.25 mm thickness of silica gel. The TLC plates were visualized with UV light and/or by staining with Hanessian solution (ceric sulfate and ammonium molybdate in aqueous sulfuric acid). Column chromatography was generally performed using Kieselgel 60 (230-400 mesh) silica gel, typically using a 50-100:1 weight ratio of silica gel to crude product. All compounds were sufficiently pure after chromatographic purification for use in the next synthetic step.

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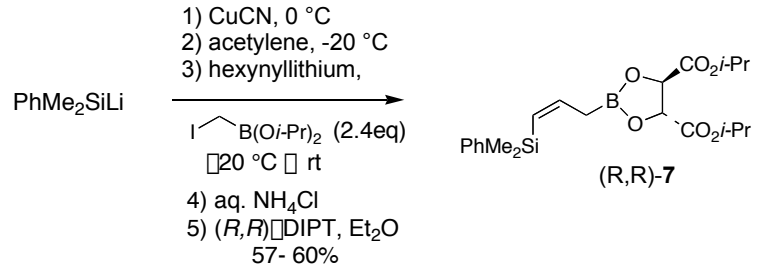
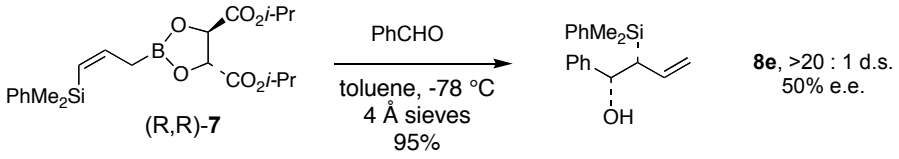


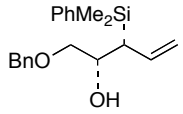
(Z)-γ-(Dimethylphenyl)silylallylboronate ((R,R)-7). Dimethylphenylsilyllithium was prepared by the addition of chlorodimethylphenylsilane (2 mL, 33.1 mmol) to a heterogeneous mixture of lithium metal (230 mg, 33.1 mmol) in THF (8 mL) at 0 °C. The reaction mixture was stirred vigorously at 0 °C for 6 h, and then stored at 0 °C for 12 h. The dark red solution was transferred by syringe to a slurry of CuCN (414 mg, 4.61 mmol) in THF (1 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min, cooled to -20 °C, and acetylene was bubbled through the reaction mixture via a needle at a slow and steady rate for 1 h. The brown reaction mixture was then further cooled to -78 °C and a solution of hexynyllithium (prepared by addition of *n*-butyllithium (2.5 mL of a 1.97 M solution in hexanes, 4.93 mmol) to 1-hexyne (560 μL, 4.87 mmol) in THF (2.5 mL) at -78 °C) was slowly added. The mixture was stirred for 5 min at -78 °C, then diisopropyl iodomethylborate (2.5 mL, 11.5 mmol) was added dropwise to the reaction mixture and the solution was allowed to warm slowly to 0 °C. After an additional 2.5 h at 0 °C, 5 mL of saturated aqueous NH_4Cl was added, followed immediately by 20 mL of diethyl ether. After vigorous stirring of the biphasic reaction mixture, the ether layer was transferred by cannula to a flask containing (*R*,*R*)-diisopropyl tartrate (1.47g, 6.28 mmol). The aqueous layer was extracted with more diethyl ether (2 × 20 mL) and these ether layers were transferred to the flask in the same manner and stirred over $MgSO_4$ for 3h. The solution was then filtered under a blanket of nitrogen and evaporated under reduced pressure to give Z-silylallylboronate ((R,R)-7) as a thick oil which was dried briefly under vacuum, and then stored at -20 °C as a 0.14M stock solution in toluene over 4Å molecular sieves. Based on ^{1}H NMR integration with respect to excess (*R*,*R*)-diisopropyl tartrate, the amount of Z-silylallylboronate ((R,R)-7) was determined to be 2.6 mmol, 57% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (dt, 1H, J = 13.9, 8.2 Hz), 5.69 (dt, 1H, J = 13.9, 1.4 Hz), 5.12 (sept, 2H, J = 6.3 Hz), 4.76 (s, 2H), 1.96 (d, 2H, J = 8.2 Hz), 1.30 (d, 12H, J = 6.2 Hz);

0.40 (s, 3H), 0.35 (s, 3H). This material was used in subsequent allylboration experiments without additional purification.



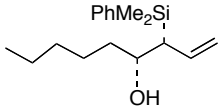
Representative Allylboration of Benzyaldehyde using Z-γ-silylallylboronate ((R,R)-7). A 3 mL aliquot (0.38 mmol) of the 0.125 M silylallylboronate stock solution in toluene was stirred over 4Å molecular sieves at -78 °C. To this was slowly added a -78 °C solution of benzaldehyde (72 μL, 0.71 mmol) in 0.5 mL of toluene. The reaction mixture was stirred at -78 °C for several hours, then was allowed to warm to 23 °C overnight. Et_3N (100 mL, 0.72 mmol) was then added and the reaction mixture was diluted with EtOAc (20 mL) and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, filtered, evaporated under reduced pressure and the residue was purified by chromatography (hexanes with 2% Et_3N to 5% v/v EtOAc-hexanes with 2% Et_3N) to provide the *syn*-α-hydroxyallylsilane **8e** (101 mg, 95%) as a light yellow oil. The enantiomeric purity of **8e** was determined to be 50% e.e. by Mosher ester analysis.

Data for (1*R*,2*R*)-2-[dimethyl(phenyl)silyl]-1-phenyl-3-buten-1-ol (8e) ^1H NMR (500 MHz, $CDCl_3$) δ 7.65-7.62 (m, 2H), 7.44-7.40 (m, 3H), 7.34-7.30 (m, 2H), 7.28-7.24 (m, 3H), 5.63 (dt, 1H, J = 17.1, 10.3 Hz), 4.91 (dd, 1H, J = 10.3, 2.0 Hz), 4.78 (m, 1H), 4.76 (m, 1H), 2.46 (dd, 1H, J = 10.3, 8.7 Hz), 1.93 (d, 1H, J = 4.4 Hz), 0.40 (s, 3H), 0.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.51, 138.19, 135.63, 134.42, 129.20, 128.26, 127.89, 127.60, 126.78, 115.49, 75.68, 44.70, -2.37, -3.41; IR (thin film) 3563.7, 3436.3, 3069.3, 3029.0, 2956.3, 2899.0, 1626.9, 1602.4, 1491.9, 1454.8, 1427.6, 1414.2, 1302.9, 1248.3, 1195.1, 1148.5, 1112.1, 1028.3, 998.1, 901.0, 840.5, 817.4, 778.5, 733.3, 700.4, 657.6, 631.5 cm^{-1}; HRMS (ES) calcd for $C_{18}H_{22}OSiNa$ $(M+Na)^+$, 305.1338 found, 305.1339.



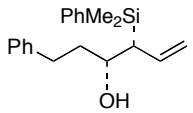
8a, 4 : 1 d.s.
75%, 56% .e.e

Data for (2*R*,3*R*)-3-[dimethyl(phenyl)silyl]-1-[(phenylmethyl)oxy]-4-penten-2-ol (8a). ^{1}H NMR (500 MHz, $CDCl_3$) □ 7.57-7.55 (m, 2H), 7.38-7.28 (m, 8H), 5.58 (dt, 1H, J = 17.0, 13.1 Hz), 4.93 (dd, 1H, J = 10.3, 1.6 Hz), 4.86 (m, 1H), 4.49 (s, 2H), 3.89 (m, 1H), 3.55 (dd, 1H, J = 9.5, 2.0 Hz), 3.29 (t, 1H, J = 8.7 Hz), 2.43 (d, 1H, J = 4.0 Hz), 2.07 (t, 1H, J = 9.7 Hz), 0.40 (s, 3H), 0.36 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) □ 138.20, 138.09, 136.03, 134.45, 129.10, 128.61, 127.93, 127.76, 114.73, 74.58, 73.47, 71.46, 39.75, -2.49, 3.02; IR (thin film) 3570.5, 3467.7, 3068.7, 2954.1, 2901.8, 2860.9, 1626.3, 1496.3, 1453.8, 1427.3, 1411.4, 1362.1, 1246.4, 1112.7, 1099.2, 1052.8, 1028.3, 998.6, 900.6, 834.3, 778.0, 732.3, 698.5, 655.9 cm^{-1}; HRMS (ES) calcd for $C_{20}H_{26}O_2SiNa$ $(M+Na)^+$, 349.1600 found, 349.1593.



8b, 9 : 1 d.s.,
74%, 64% e.e.

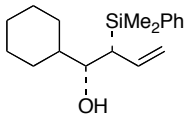
Data for (3*R*,4*R*)-3-[dimethyl(phenyl)silyl]-1-nonen-4-ol (8b). ^{1}H NMR (500 MHz, $CDCl_3$) □ 7.58-7.55 (m, 2H), 7.39-7.36 (m, 3H), 5.68 (dt, 1H, J = 17.1, 10.5 Hz), 5.02 (dd, 1H, J = 10.3, 2.0 Hz), 4.93 (dd, 1H, J = 17.1, 2.0 Hz), 3.69 (m, 1H), 2.08 (dd, 1H, J = 10.3, 7.1 Hz), 1.56-1.16 (m, 9H), 0.88 (t, 3H, J = 7.1 Hz), 0.37 (s, 3H), 0.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) □ 138.28, 136.13, 134.27, 129.22, 127.95, 115.45, 72.89, 44.53, 36.87, 31.91, 25.76, 22.80, 14.23, -2.67, -3.56; IR (thin film) 3570.2, 3467.8, 3070.8, 3051.6, 2956.5, 2930.8, 2858.4, 1626.1, 1466.9, 1427.8, 1413.9, 1378.6, 1300.9, 1249.1, 1112.8, 1037.4, 998.3, 898.9, 835.4, 815.0, 791.3, 776.1, 733.3, 700.7, 657.1 cm^{-1}; HRMS (ES) calcd for $C_{17}H_{28}OSiNa$ $(M+Na)^+$, 299.1807 found, 299.1809.



8c, 7 : 1 d.s.
95%, 54% e.e.

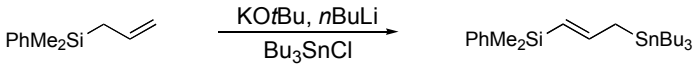
Data for (3*R*,4*R*)-4-[dimethyl(phenyl)silyl]-1-phenyl-5-hexen-3-ol (8c). ^{1}H NMR (500 MHz, $CDCl_3$) □ 7.57-7.53 (m, 2H), 7.41-7.36 (m, 3H), 7.29 (m, 2H), 7.20 (m, 1H), 7.15 (m, 2H), 5.69 (dt, 1H, J = 16.8, 10.3 Hz), 5.04 (d, 1H, J = 10.3 Hz), 4.95 (d, 1H, J = 16.9 Hz), 3.75 (m, 1H), 2.81 (ddd, 1H, J = 13.6, 10.3, 5.0 Hz), 2.56 (ddd, 1H, J = 13.7, 9.9, 6.7 Hz), 2.12 (dd, 1H, J = 10.9,

7.2 Hz), 1.85 (m, 1H), 1.63 (m, 1H), 1.37 (d, 1H, J = 6.7 Hz), 0.35 (s, 3H), 0.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.38, 138.04, 135.73, 134.25, 129.34, 128.64, 128.53, 128.04, 125.92, 115.88, 72.18, 44.53, 38.66, 32.44, -2.82, -3.71; IR (thin film) 3569.2, 3457.7, 3068.8, 3025.8, 2952.9, 1625.2, 1603.3, 1495.9, 1454.3, 1427.4, 1248.6, 1111.7, 1046.7, 1029.9, 998.3, 900.0, 836.2, 814.3, 774.8, 733.4, 699.5, 655.7 cm^{-1}; HRMS (ES) calcd for $C_{20}H_{26}OSiNa$ $(M+Na)^+$, 333.1651 found, 333.1652.



8d, 20 : 1 d.s.
81% , 55% .e.e

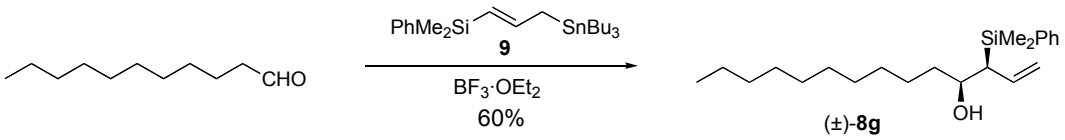
Data for (1*R*,2*R*)-1-cyclohexyl-2-[dimethyl(phenyl)silyl]-3-buten-1-ol (8d). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60-7.54 (m, 2H), 7.38-7.34 (m, 3H), 5.58 (dt, 1H, J = 17.1, 10.3 Hz), 4.92 (dd, 1H, J = 10.3, 1.6 Hz), 4.84 (m, 1H), 3.56 (ddd, 1H, J = 9.5, 6.3, 3.2 Hz), 2.18 (t, 1H, J = 9.9 Hz), 1.76-1.58 (m, 4H), 1.47 (m, 1H), 1.36 (m, 1H), 1.22-1.04 (m, 5H), 0.94 (m, 1H), 0.36 (s, 3H), 0.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.92, 137.15, 134.33, 129.14, 127.95, 113.93, 77.08, 41.81, 40.62, 30.92, 26.81, 26.74, 26.38, 24.58, -2.14, -3.48; IR (thin film) 3584.8, 3070.4, 3050.8, 2925.7, 2852.4, 1693.3, 1626.3, 1449.7, 1427.7, 1248.1, 1112.0, 1032.2, 998.6, 985.6, 896.2, 835.7, 816.3, 774.4, 732.1, 700.7, 655.7 cm^{-1}; HRMS (ES) calcd for $C_{18}H_{28}OSiNa$ $(M+Na)^+$, 311.1807 found, 311.1804.



9

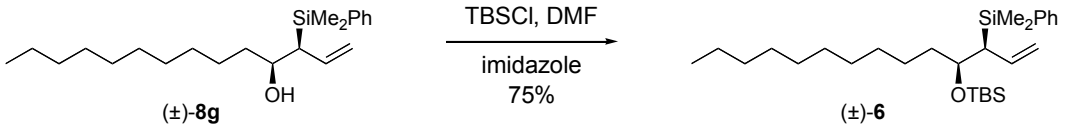
Dimethylphenyl-[(*E*)-3-(tributylstannyl)-1-propenyl]-silane (9). To a solution of potassium *t*-butoxide (3.54 g, 31.5 mmol) in THF (60 mL) at -78 °C was added phenyldimethylallylsilane (6.59 g, 37.0 mmol). A 2.5 M solution of *n*-butyllithium in hexanes (13.2 mL, 34.0 mmol) was added slowly dropwise to the –78 °C solution over 2 h. The resulting orange solution was gradually warmed to -50 °C and then stirred at this temperature for 1 h. Tri-*n*-butyltin chloride (10.0 mL, 36.7 mmol) was added dropwise to the reaction mixture. The solution was

slowly warmed to 23 °C and stirred for 12 h. The orange color dissipated during this period. Saturated aqueous $NaHCO_3$ was added, then the aqueous layer was separated and extracted with 30 mL of diethyl ether. The organic extract was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford **9** as a clear oil. This product was determined to be 66% pure by ^{1}H NMR analysis, with unreacted phenyl-dimethylallylsilane as the primary impurity. The crude product was satisfactory for use in subsequent reactions, as vacuum distillation of **9** was not successful due to its instability at temperatures > 110 °C. Additional purification was achieved through heating the crude product to 100 °C at 1.5 Torr to remove excess starting materials. The remaining yellow oil was dissolved in hexane and passed through a 1 inch silica gel plug to afford **9** as a colorless oil at 80% purity (determined via ^{1}H NMR integration): ^{1}H NMR (400 MHz, $CDCl_3$) □ 7.54-7.48 (m, 2H), 7.38-7.31 (m, 3H), 6.24 (dt, *J* = 18.3, 8.4 Hz, 1H), 5.46 (dt, *J* = 18.3, 1.1 Hz, 1H), 1.94 (dd, *J* = 8.4, 1.1 Hz, 2H), 1.47 (quint, *J* = 7.8 Hz, 6H), 1.28 (sextet, *J* = 7.6 Hz, 6H), 0.88 (t, *J* = 7.3 Hz, 9H), 0.88-0.84 (m, 6H), 0.28 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) □ 149.3, 140.1, 134.0, 128.8, 127.8, 121.0, 29.3, 27.5, 20.6, 13.9, 10.1, -1.9; IR (thin film) 3069, 2926, 2854, 2872, 1596, 1464, 1427, 1376, 1247, 1113, 1074, 982, 843, 791, 728, 699 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{33}SiSn$ *m/z* 409.1373 (M-*n*-butyl)$^+$, observed *m/z* 409.1366.



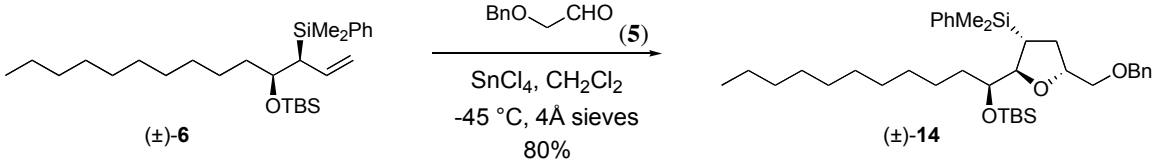
(3*S,4*S**)-3-(Dimethylphenylsilanyl)-4-hydroxy-tridec-1-ene (8g)**. $BF_3{\cdot}OEt_2$ (1.1 mL, 8.7 mmol) was added slowly dropwise to a -78 °C solution of crude allylstannane **9** (13 g, 17 mmol) in CH_2Cl_2 (75 mL). The reaction mixture was stirred at -78 °C for 10 min, and a solution of undecanal (1.8 mL, 8.7 mmol) in 10 mL of CH_2Cl_2 was added dropwise over 40 min. The reaction mixture was stirred at -78 °C for 4 h, then saturated aqueous $NaHCO_3$ (50 mL) was added. After the mixture warmed to room temperature, the organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and finally concentrated to a clear oil. Purification of the crude product by silica gel chromatography (5% v/v Et_2O-hexane ramped to 12% v/v Et_2O-hexane) furnished 1.80 g (60%,

based on undecanal) of **8g** as a clear oil containing trace amounts of unreacted undecanal. Additional purification was achieved through treatment of a methanol solution of the product at 0 °C with $NaBH_4$ for 5 h. The mixture was partitioned between water and ethyl acetate. The organic layer was separated and dried over Na_2SO_4, filtered, and concentrated to a clear oil. Purification of the crude product by silica gel chromatography (7% v/v Et_2O-hexane) afforded pure **8g** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.52 (m, 2H), 7.38-7.33 (m, 3H), 5.67 (dt, *J* = 16.8, 10.4 Hz, 1H), 4.99 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.91 (dd, *J* = 17.0, 1.4 Hz, 1H), 3.67 (bt, *J* = 7.1 Hz, 1H), 2.06 (dd, *J* = 10.7, 7.1 Hz, 1H), 1.58-1.38 (m, 2H), 1.36-1.10 (m, 17H), 0.89 (t, *J* = 6.9 Hz, 3H), 0.35 (s, 3H), 0.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 136.1, 134.3, 129.2, 127.9, 115.5, 72.9, 44.5, 36.9, 32.1, 29.8, 29.7, 29.5, 26.1, 22.9, 14.3, -2.7, -3.6; IR (thin film) 2922, 2847, 850, 668 cm^{-1}; MS (ESI, Na^+ added) *m/z* 269.2 $(M+Na)^+$. *Anal*. Calcd for $C_{22}H_{38}OSi$; C, 76.23; H, 11.05; Found: C, 76.40; H, 11.23.



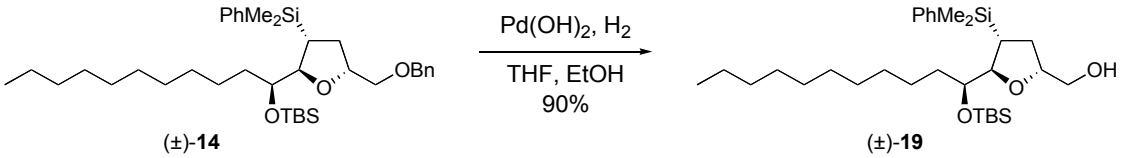
(3*S,4*S**)-3-(Dimethylphenylsilanyl)-4-(*tert*-butyldimethylsilanyloxy)-tridec-1-ene (6)**. To a 0 °C solution of **8g** (1.80 g, 5.2 mmol) in *N*,*N*-dimethylformamide (5 mL) was added imidazole (1.0 g, 15.0 mmol) and *tert*-butyldimethylsilyl chloride (0.98 g, 6.5 mmol). The resulting mixture was warmed to room temperature and stirred for 16 h. The reaction was again cooled to 0 °C, and 100 mL of Et_2O was added. The organic layer was washed with 200 mL of water, and then separated, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the crude product by silica gel chromatography (2.5 % v/v Et_2O-hexane ramped to 5 % v/v Et_2O-hexane) provided **6** (1.8 g, 75%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.38-7.31 (m, 3H), 5.85 (dt, *J* = 16.8, 10.3 Hz, 1H), 4.95 (dd, *J* = 10.0, 2.2 Hz, 1H), 4.80 (ddd, *J* = 16.8, 1.8, 0.7 Hz, 1H), 3.72 (ddd, *J* = 7.5, 3.9, 3.5 Hz, 1H), 2.10 (dd, *J* = 10.2, 2.9 Hz, 1H), 1.46-1.39 (m, 1H), 1.34-1.15 (m, 13H), 1.15-1.08 (m, 2H), 1.08-1.02 (m, 2H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.34 (s, 3H), 0.30 (s, 3H), -0.02 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 136.5, 134.2,

129.1, 127.8, 114.7, 74.3, 44.0, 35.9, 32.1, 29.8, 29.6, 29.5, 26.8, 26.2, 22.9, 18.4, 14.3, -3.0, -3.1, -3.9, -4.4; IR (thin film) 2957, 2855, 1472, 1253, 1112, 1066, 834, 773, 733, 699, 668 cm^{-1}, HRMS (ESI, Na^+ added) calcd for $C_{28}H_{52}OSi_2$ $(M + Na)^+$ *m/z* 483.3454, observed 483.3462. *Anal*. Calcd for $C_{28}H_{52}OSi_2$; C, 72.97; H, 11.37; Found: C, 73.02; H, 11.35.

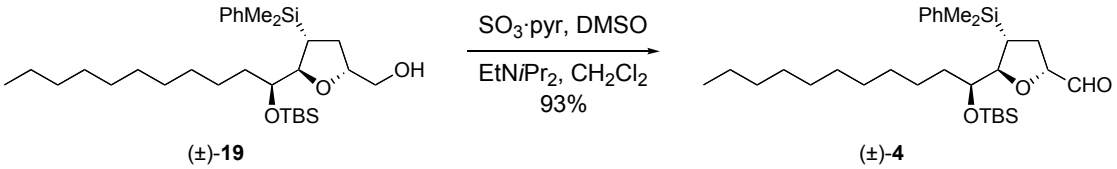


(2*S,3*R**,5*R**)-5-(Benzyloxymethyl)-2-[(1*S**)-1-(*tert*-butyldimethylsilanyloxy)-undecyl]-3-(dimethylphenylsilanyl)-tetrahydrofuran (14)**. A flame-dried round-bottom flask containing 4 Å molecular sieves was charged with a solution of allylsilane **6** (930 mg, 2.02 mmol) in CH_2Cl_2 (3.5 mL). The reaction mixture was cooled to -45 °C, and neat α-benzyloxyacetaldehyde (**5**) (3.91 mmol) was added. $SnCl_4$ (0.18 mL, 1 mmol) was added slowly dropwise to the cold solution, and the reaction mixture was stirred at -45 °C for 6 h. The reaction mixture was allowed to warm to -10 °C over a 10 h period. After this point, Et_3N (0.60 mL) was added dropwise to the 0 °C mixture, then the entire system was allowed to warm to room temperature. EtOAc (15 mL) and saturated aqueous $NaHCO_3$ (15 mL) were added to give a cloudy white suspension which was stirred at room temperature for 12 h. The organic layer was removed, and the aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a yellow oil. Purification of the crude product by silica gel chromatography provided **14** (1.0 g, 80%, based on allylsilane **6**) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.37 (m, 6H), 4.56 (A of AB_q, J_{AB} = 12.2 Hz, 1H), 4.52 (B of AB_q, J_{AB} = 12.2 Hz, 1H), 4.07 (dq, *J* = 9.0, 5.1 Hz, 1H), 3.97 (dd, *J* = 8.5, 2.7 Hz, 1H), 3.53 (ddd, *J* = 7.3, 4.4, 2.7 Hz, 1H), 3.47 (A of ABX, J_{AX} = 5.1 Hz, J_{AB} = 10.0 Hz, 1H), 3.47 (B of ABX, J_{BX} = 4.9 Hz, J_{AB} = 10.0 Hz, 1H), 2.09 (ddd, *J* = 11.7, 7.8, 6.1 Hz, 1H), 1.67 (dt, *J* = 11.7, 8.3 Hz, 1H), 1.58 (td, *J* = 11.5, 8.8, 1H), 1.41-1.34 (m, 1H), 1.34-1.17 (m, 14H), 1.00-1.16 (m, 5H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.32 (s, 3H), 0.27 (s, 3H), -0.01 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.2, 129.3, 128.5, 128.0, 127.8, 127.6, 124.0, 85.0, 78.1, 74.9, 73.5, 73.0, 33.1, 32.5, 32.1, 29.9,

29.8, 29.5, 26.2, 26.0, 22.9, 18.4, 14.3, -3.4, -4.0, -4.2, -4.3; IR (thin film) 2855, 1463, 1252, 1112, 835, 774, 733, 690 cm^{-1}, HRMS (ESI, Na^+ added) calcd $C_{37}H_{62}O_3Si_2$ $(M+Na)^+$ *m/z* 633.4135, observed 633.4147. *Anal*. Calcd for $C_{37}H_{62}O_3Si_2$: C, 72.73, H, 10.23. Found: C, 73.07, H, 10.47.

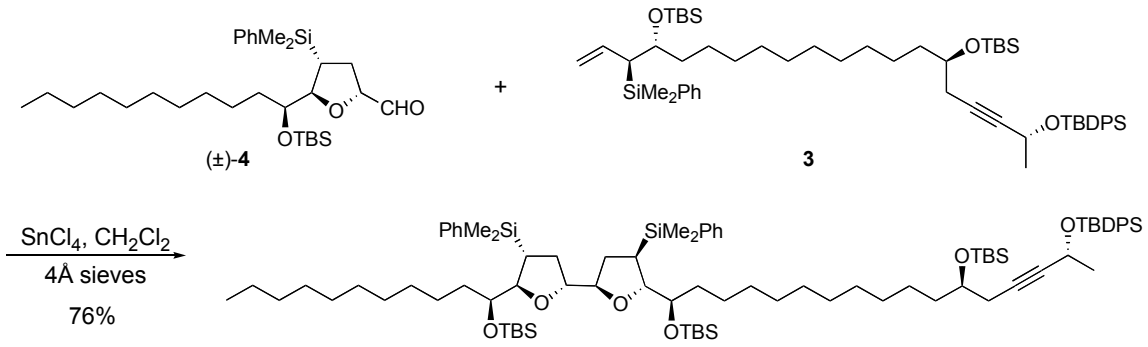


(2R*,4R*,5S*)-(±)-5-[(1S*)-1-(*tert*-Butyldimethylsilanyloxy)-undecyl]-4-(dimethylphenyl-silanyl)-tetrahydrofuran-2-yl]-methanol (19). Tetrahydrofuran **14** (370 mg, 0.61 mmol) and 10% $Pd(OH)_2/C$ (80 mg) were dissolved/suspended in THF (10 mL) and EtOH (1 mL). The reaction flask was evacuated and purged with hydrogen three times. The reaction was stirred at ambient temperature for 1 h and then filtered through Celite. The filtrate was concentrated and the crude product was purified by chromatography (SiO_2, 20% Et_2O-hexanes) to give 284 mg of alcohol **19** (90%): ^1H NMR (400 MHz, $CDCl_3$) d 7.52-7.46 (m, 2H), 7.38-7.32 (m, 3H), 4.02-3.92 (m, 2H), 3.70 (A of ABX, J_{AB} = 3.6 Hz, J_{AX} = 6.4 Hz, 1H), 3.66 (B of ABX, J_{AB} = 3.6 Hz, J_{BX} = 5.6 Hz, 1H), 3.51-3.46 (m, 1H), 3.44-3.37 (m, 1H), 2.04-1.95 (m, 1H), 1.77 (t, J = 6.4 Hz, 1H), 1.71-1.58 (m, 2H), 1.43-0.99 (m, 17H), 0.91-0.86 (m, 3H), 0.88 (s, 9H), 0.35 (s, 3H), 0.31 (s, 3H), -0.01 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 137.7, 133.8, 129.2, 127.9, 85.1, 79.2, 74.8, 64.4, 31.9, 31.8, 31.3, 29.7, 29.6, 29.3, 26.6, 26.0, 25.9, 22.7, 18.1, 14.1, -3.6, -4.2, -4.5, -4.6; IR (thin film) 3448, 2955, 2930, 2855, 1472, 1252, 1112, 836, 774, 732, 700, 668 cm^{-1}; HRMS calcd for $C_{30}H_{56}O_3Si_2$, 543.3666 *m/z* $(M+Na)^+$; observed 543.3677 *m/z*. *Anal*. Calcd for $C_{30}H_{56}O_3Si_2$; C, 69.17; H, 10.84. Found: C, 69.46; H, 10.73.



(±)-**19** (±)-**4**

(2R*,4R*,5S*)-(±)-5-[(1S*)-1-(*tert*-Butyldimethylsilanyloxy)-undecyl]-4-(dimethyl-phenylsilanyl)-tetrahydrofuran-2-carbaldehyde (4). To a solution of alcohol **19** (270 mg, 0.52 mmol), diisopropylethylamine (338 mg, 2.6 mmol), and DMSO (406 mg, 5.2 mmol) in CH_2Cl_2 (5 mL) at 0 ºC was added SO_3·pyridine (247 mg, 1.55 mmol). The reaction was stirred for 1 h and then quenched with aqueous sodium potassium tartrate and warmed to room temperature. The organic layer was separated, dried over $MgSO_4$, and concentrated. Purification of the crude product by chromatography (SiO_2, 3% to 5% Et_2O-hexanes) gave 251 mg of aldehyde **4** (93%): ^{1}H NMR (500 MHz, $CDCl_3$) □ 9.51 (d, *J* = 2.0 Hz, 1H), 7.52-7.48 (m, 2H), 7.42-735 (m, 3H), 4.19 (dt, *J* = 8.0, 2.0 Hz, 1H), 4.07 (dd, *J* = 9.0, 2.0 Hz, 1H), 3.58-3.54 (m, 1H), 2.31 (dt, *J* = 12.5, 7.5 Hz, 1H), 1.79 (ABX ddd, *J* = 20.5, 12.5, 8.0 Hz, 1H), 1.67 (dt, *J* = 10.5, 8.5 Hz, 1H), 1.42-0.96 (m, 18H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.36 (s, 3H), 0.33 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 203.3, 136.9, 133.8, 129.5, 128.0, 86.9, 82.8, 74.3, 32.0, 31.9, 31.6, 29.6, 29.6, 29.5, 29.3, 26.0, 25.9, 25.9, 22.7, 18.1, 14.1, -3.6, -4.3, -4.5, -4.7; IR (thin film) 2955, 2927, 2855, 1735, 1253, 1112, 836, 775, 734, 701 cm^{-1}; HRMS calcd for $C_{30}H_{54}O_3Si_2$, 541.3509 *m/z* $(M+Na)^+$; observed 541.3515 *m/z*. *Anal*. Calcd for $C_{30}H_{54}O_3Si_2$; C, 69.44; H, 10.49. Found: C, 69.26; H, 10.66.

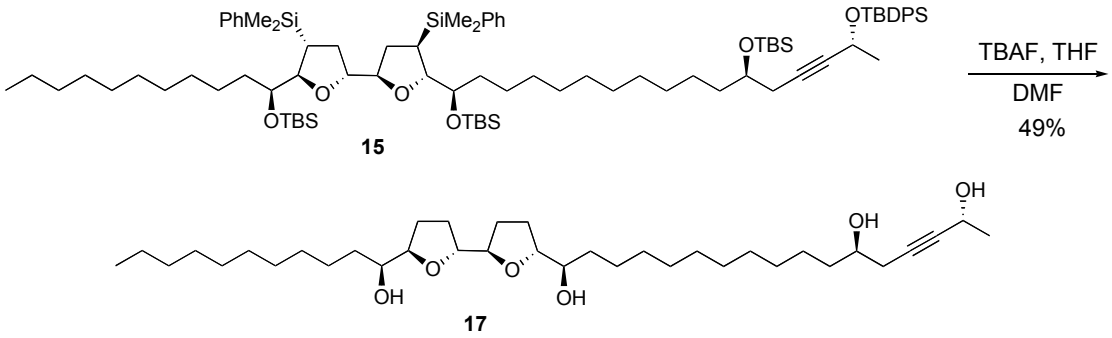


15, >20 : 1 d.s.

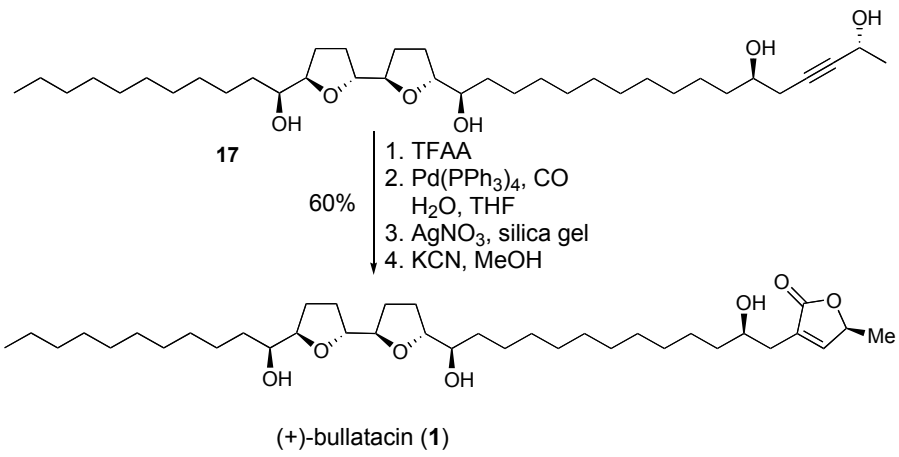
(2R, 2'R, 4R, 4'R, 5S, 5'S)-4,4'-bis-(Dimethylphenylsilanyl)-5-[(1S)-1-(*tert*-butyl-dimethylsilanyloxy)-undecyl]-5'-[(1R, 12R, 16R)-1,12-bis-(*tert*-butyldimethyl-silanyloxy)-16-

(*tert*-butyldiphenylsilanyloxy)-heptadec-14-yne]-octahydro-2,2'-bifuran (15). To a solution of racemic aldehyde **4** (241 mg, 0.46 mmol), highly enantiomerically enriched allylsilane **3**[1] (152 mg, 0.16 mmol), and flame-dried powdered 4Å sieves (200 mg) in CH_2Cl_2 (0.8 mL) at 0 ºC was added $SnCl_4$ (42 mg, 0.16 mmol) dropwise from a syringe. The reaction was stirred for 4 h and then quenched with triethylamine (0.5 mL) and warmed to room temperature. The reaction was diluted with hexanes (5 mL), Et_2O (5 mL), and saturated aqueous $NaHCO_3$ (5 mL) and stirred for 20 h. The organic layer was separated, dried over $MgSO_4$, concentrated, and the crude product purified by chromatography (SiO_2, 3% Et_2O-hexanes) to give 180 mg of bifuran **15** (76%): $[\alpha]_D^{23.0}$ = 36.4 (c 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dt, *J* = 6.5, 1.5 Hz, 2H), 7.69 (dt, *J* = 6.5, 1.5 Hz, 2H), 7.52-7.47 (m, 4H), 7.45-7.31 (m, 12H), 4.47 (q, *J* = 6.5 Hz, 1H), 3.93 (dd, *J* = 8.5, 3.0 Hz, 1H), 3.89 (dd, *J* = 9.0, 2.0 Hz, 1H), 3.80 (dt, *J* = 9.5, 6.0 Hz, 1H), 3.75-3.70 (m, 1H), 3.69-3.63 (m, 1H), 3.60-3.55 (m, 1H), 3.36 (dt, *J* = 6.0, 2.0 Hz, 1H), 2.25 (A of ABXX', J_{AB} = 16.5 Hz, J_{AX} = 5.0 Hz, $J_{AX'}$ = 2.0 Hz, 1H), 2.20 (B of ABXX', J_{AB} = 16.5 Hz, J_{BX} = 7.0 Hz, $J_{BX'}$ = 2.0 Hz, 1H), 1.96-1.90 (m, 1H), 1.87-1.81 (m, 1H), 1.69-1.60 (m, 4H), 1.58-1.51 (m, 1H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.47-0.97 (m, 37H), 1.08 (s, 9H), 0.90 (t, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.88 (s, 9H), 0.88 (s, 9H), 0.32 (s, 3H), 0.31 (s, 3H), 0.30 (s, 3H), 0.28 (s, 3H), 0.05 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.5, 136.2, 136.0, 134.3, 134.1, 134.1, 129.8, 129.8, 129.3, 128.1, 128.0, 127.8, 127.6, 84.6, 84.3, 83.5, 81.7, 81.6, 81.3, 75.1, 74.8, 71.4, 60.4, 53.7, 36.9, 34.5, 32.9, 32.6, 32.2, 32.2, 32.2, 30.2, 30.0, 30.0, 30.0, 29.9, 29.9, 29.6, 28.0, 27.1, 26.5, 26.4, 26.4, 26.3, 26.1, 26.0, 25.7, 25.5, 25.5, 23.0, 19.5, 18.5, 18.4, 18.3, 14.4, -3.3, -3.3, -3.8, -3.8, -4.0, -4.0, -4.1, -4.2, -4.4, -4.4; IR (thin film) 2928, 2855, 1472, 1251, 1111, 835, 774, 700 cm^{-1}; HRMS calcd for $C_{86}H_{146}O_6Si_6$, 1465.9633 *m/z* $(M+Na)^+$; observed 1465.9602 *m/z*. *Anal*. Calcd for $C_{86}H_{146}O_6Si_6$; C, 71.50; H, 10.19. Found: C, 71.24; H, 10.25.

[1] Tinsley, J. M.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, ASAP.



(2R, 2'R, 5R, 5'R)-5-[(1S)-1-hydroxyundecyl]-5'-[(1R, 12R, 16R)-1,12,16-trihydroxy-heptadec-14-yne]-octahydro-2,2'-bifuran (17). To a solution of **15** (85 mg, 0.059 mmol) in DMF (0.6 mL) was added TBAF (1M in THF, 0.6 mL, 0.59 mmol). The reaction was heated to 90 ºC for 20 h and then cooled to ambient temperature. The reaction was diluted with 1:1 Et_2O-hexanes (5 mL) and H_2O (5 mL) and the layers were separated. The organic layer was washed with 1M HCl (3 X 10 mL) and saturated aqueous $NaHCO_3$ (1 X 10 mL), filtered, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude product by chromatography (SiO_2, 2% to 4% MeOH-CH_2Cl_2) gave 17 mg of **17** (49%): $[\alpha]_D^{23.0}$ = 8.8 (c 1.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58-4.52 (m, 1H), 3.99-3.83 (m, 5H), 3.74 (q, J = 5.0 Hz, 1H), 3.44-3.38 (m, 1H), 2.46 (A of ABXX', J_{AB} = 16.5 Hz, J_{AX} = 4.0 Hz, $J_{AX'}$ = 1.5 Hz, 1H), 2.33 (B of ABXX', J_{AB} = 16.5 Hz, J_{BX} = 6.5 Hz, $J_{BX'}$ = 1.5 Hz, 1H), 2.40-2.10 (bm, 4H), 2.04-1.95 (m, 4H), 1.94-1.86 (m, 1H), 1.85-1.78 (m, 1H), 1.45 (d, J = 6.0 Hz, 3H), 1.72-1.23 (m, 40H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.1, 83.5, 83.1, 82.8, 82.6, 81.1, 74.3, 71.6, 70.2, 58.7, 36.4, 33.6, 32.6, 32.2, 29.9, 29.9, 29.8, 29.7, 29.6, 29.5, 29.5, 29.5, 29.4, 29.2, 29.2, 28.6, 27.9, 26.3, 25.7, 25.7, 24.9, 24.7, 22.9, 14.4; IR (thin film) 3402, 2925, 2854, 1465, 1070 cm^{-1}; HRMS calcd for $C_{36}H_{66}O_6$, 617.4757 *m/z* $(M+Na)^+$; observed 617.4763 *m/z*.



(+)-bullatacin (**1**)

(+)-Bullatacin (1). Intermediate **17** (16 mg, 0.027 mmol) was dissolved in trifluoroacetic anhydride (2.0 mL) and stirred at ambient temperature under a nitrogen atmosphere for 1 h. This mixture was concentrated at reduced pressure and dried on a vacuum pump for 1 h. The residue was dissolved in THF (0.30 mL) and water (0.03 mL) at ambient temperature under a CO atmosphere. $Pd(PPh_3)_4$ (0.6 mg, 0.00054 mmol) was added as a solution in THF (0.04 mL) and the reaction was stirred for 2 h. The reaction was diluted with Et_2O (5 mL) and dried over $MgSO_4$, then concentrated. The residue was dissolved in hexanes (0.2 mL) and CH_2Cl_2 (0.02 mL) and the flask was wrapped in aluminum foil to protect the contents from light. $AgNO_3/SiO_2$ (10 mg) was added and the reaction was stirred for 3 h. The reaction was filtered through Celite and concentrated and the residue was purified by chromatography (SiO_2, CH_2Cl_2). The purified material was dissolved in MeOH (1.0 mL) and KCN (2 mg, 0.04 mmol) was added to the reaction. After 20 minutes, the reaction was concentrated to 0.5 mL, diluted with Et_2O (5 mL), and washed with water (1 mL). The organic layer was dried over $MgSO_4$, concentrated, and purified by chromatography (SiO_2, 20% acetone/CH_2Cl_2). The purified material was dissolved in freshly distilled CH_3CN (20 mL) and washed with hexanes (10 x 10 mL). The CH_3CN layer was concentrated to give 10.0 mg (60%) of (+)-bullatacin (**1**): $[\alpha]_D^{23.0} = 15.3$ (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 5.05 (q, J = 7.2 Hz, 1H), 3.96-3.79 (m, 6H), 3.43-3.36 (m, 1H), 2.53 (d, J = 15.2 Hz, 1H), 2.38 (dd, J = 15.2, 8.0 Hz, 1H), 2.32 (br, 3H), 1.98-1.72 (m, 6H), 1.63-1.16 (m, 40H), 1.43 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 151.8, 131.2, 83.2, 82.8, 82.5, 82.3, 78.0, 74.1, 71.3, 69.9, 37.4, 33.4, 33.3, 32.4, 31.9, 29.7, 29.6, 29.5, 29.5, 29.5, 29.3, 28.9, 28.3,

26.0, 25.6, 25.6, 24.4, 22.7, 19.1, 14.1; IR (thin film) 3446, 2924, 2854, 1755, 1465, 1319, 1068, 953 cm^{-1}; HRMS calcd for $C_{37}H_{66}O_7$, 645.4706 *m/z* $(M+Na)^+$; observed 645.4708 *m/z*.

The ^{13}C NMR data (Table 2) for synthetic bullatacin compared favorably with data from the original isolation paper[2] and also the data from previous syntheses.[3, 4] The ^1H NMR data (Table 1) were difficult to interpret owing to overlapping signals and the presence of three hydroxyl signals that shift position depending on sample concentration. Consequently, the tris-Mosher esters of synthetic bullatacin were prepared and compared to the data published by Hoye (Table 3).[5]

Table 1. Comparison of ^1H NMR Data of Bullatacin (□)

Keinan[3]	Sasaki[4]	Roush (this study)[6]	Carbon No.[2]
7.17 (d, J = 1.4 Hz, 1H)	7.18 (d, J = 1.1 Hz, 1H)	7.18 (s, 1H)	35
5.04 (qq, J = 6.8, 1.4 Hz, 1H)	5.06 (dq, J = 6.9, 1.4 Hz, 1H)	5.05 (q, J = 7.2 Hz, 1H)	36
3.95-3.80 (m, 6H)	3.97-3.90 (m, 2H) 3.90-3.80 (m, 4H)	3.96-3.79 (m, 6H)	4, 16, 19, 20, 23, 24
3.38 (m, 1H)	3.43-3.38 (m, 1H)	3.43-3.36 (m, 1H)	15
2.73 (br, 1H)		2.32 (br, 3H)	O-H
2.60-2.28 (br, 2H)			O-H
2.50 (m, 1H)	2.55 (ddd, J=15.1, 3.3, 1.7 Hz, 1H)	2.53 (d, J = 15.2, 1H)	3a
2.38 (m, 1H)	2.41 (dd, J = 15.0, 8.3 Hz, 1H)	2.38 (dd, J = 15.2, 8.0 Hz, 1H)	3b
2.06-1.20 (m, bs, 51H)	2.04-1.94 (m, 42H)	1.98-1.72 (m, 6H) 1.63-1.16 (m, 40H)	5, 6-14, 17, 18, 21, 22, 25-33
1.41 (d, J = 6.8 Hz, 3H)	1.44 (d, J = 6.7 Hz, 3H)	1.43 (d, J = 6.8 Hz, 3H)	37
0.85 (t, J = 7.0 Hz, 3H)	0.86 (t, J = 6.7 Hz, 3H)	0.87 (t, J = 6.8 Hz, 3H)	34
71 protons reported	59 protons reported	66 protons reported	
$CDCl_3$, 400 MHz	$CDCl_3$, 500 MHz	$CDCl_3$, 500 MHz	

Molecular formula of bullatacin: $C_{37}H_{66}O_7$

[2] Hui, Y.-H.; Rupprecht, J. K.; Liu, Y. M.; Anderson, J. E.; Smith, D. L.; Chang, C.-J.; McLaughlin, J. L. *J. Nat. Prod.* **1989**, *52*, 463.
[3] Avedissian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035.
[4] Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419.
[5] Rieser, M. J.; Hui, Y.-H.; Rupprecht, J. K.; Koslowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203.
[6] Tinsley, J. M., Ph. D. Thesis, University of Michigan, 2005.

Table 2. Comparison of ^{13}C NMR Data for Bullatacin (1)

Isolation[2]	Keinan[3]	Roush (this study)[6]	Carbon No.[2]
174.5	174.4	174.6	1
151.7	151.5	151.8	35
131.1	131.4	131.2	2
83.2	83.2	83.2	16
82.8	82.9	82.8	23
82.4	82.4	82.5	19
82.2	82.1	82.3	20
77.9	77.8	78.0	36
74.1	74.0	74.1	15
71.3	71.7	71.3	24
69.9	70.0	69.9	4
37.3	37.5	37.4	5
33.2	33.5, 33.4	33.4, 33.3	3, 14
32.4	32.6	32.4	25
31.8	31.9	31.9	32
29.9, 29.5, 29.3	29.7, 29.6, 29.5, 29.3	29.7, 29.6, 29.5, 29.3	7-12, 27-31
28.9	28.8	28.9	17, 21
28.4	28.4	28.3	18, 22
26.0	26.5	26.0	6
25.5	25.6, 25.55	25.6	13, 26
	24.8	24.4	
22.6	22.6	22.7	33
19.1	19.1	19.1	37
14.1	14.1	14.1	34
$CDCl_3$, 50 MHz	$CDCl_3$, 100 MHz	$CDCl_3$, 125 MHz	

Table 3. Comparison of ^{1}H NMR Data for Tris-Mosher Ester Derivatives of (+)-Bullatacin (1)

Roush Observed for (S)-Esters[6]	Literature Value for (S)-Mosher Esters[5]	Carbon Number	Literature Value for (R)-Mosher Esters[5]	Roush Observed for (R)-Esters[6]
2.59-2.53	2.58-2.53	3	2.69, 2.61	2.67, 2.59
1.66	1.64	5	1.61	1.63
1.60	1.59	14	1.45	1.46
4.02	4.03	16	3.97	3.98
3.82-3.76	3.83-3.76	19,20	3.83, 3.65	3.82, 3.64
3.98	3.99	23	3.90	3.91
1.53	1.53	25	1.57	1.58
6.71	6.72	35	6.97	6.96
4.85	4.86	36	4.91	4.90
1.27	1.29	37	1.32	1.30
$CDCl_3$, 500 MHz	$CDCl_3$, 500 MHz		$CDCl_3$, 500 MHz	$CDCl_3$, 500 MHz