SUPPORTING INFORMATION

Total Synthesis of (+)-Asteltoxin

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Experimental Section

General methods. All solvents were purified prior to use. Benzene, toluene, ethyl ether, and tetrahydrofuran were distilled from sodium and benzophenone under an atmosphere of nitrogen. Methylene chloride was distilled from calcium hydride. Amine bases—pyridine, triethylamine, diisopropylethylamine, and diisopropylamine—were dried and stored over potassium hydroxide pellets. DMSO and DMF were dried and stored over 4Å molecular sieves.

All moisture- or oxygen-sensitive reactions were conducted under nitrogen. All glassware, syringes, needles, and magnetic stirring bars used in moisture-sensitive reactions were oven-dried at 140 °C and stored in a desiccator. Upon work-up, solvents were evaporated under reduced pressure using a rotary evaporator, followed under high vacuum. Reactions were monitored by thin-layer chromatography (TLC). TLC glass plates (Kieselgel 60 F_{254} from E.M. Merck), pre-coated with a 0.25 mm layer of silical

gel, were used. TLC spots were visualized under ultraviolet (UV) light (254 nm), and also by one of three methods: anisaldehyde stain, molybdenum stain, or iodine vapor. Preparative TLC was used for separations of <20 mg of crude products with a 20x20 cm silica gel plate as described above. Column chromatography was performed using silica gel 60 (70□230 mesh), mostly by gravity. In general, the amount of silica gel used was ten to twenty times the weight of crude products.

Melting points (mp) were measured with a Thomas Hoover open capillary melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded in CH_2Cl_2 solutions with a Nicolet spectrophotometer, which was calibrated with polystyrene film (1601 cm^{-1}) as standard. The dimensions of $[\alpha]_D$ values are given in deg cm^2 g^{-1}, and concentration *c* is reported in g/100 mL.

High resolution mass spectra (HRMS) were obtained under EI mode (70 eV) from a VG Autospec mass spectrometer at The University of Alabama. NMR spectra were measured on commercially available spectrometers. Proton NMR spectra were recorded in $CDCl_3$ at 360 MHz, unless otherwise stated. The chemical shifts are reported in parts per million (ppm) from tetramethylsilane. Multiplicities are denoted as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), and br (broad). Coupling constants (*J*) are reported in hertz (Hz). Data are presented as follows: chemical shift, multiplicity, coupling constant, and relative area. ^{13}C NMR spectra were recorded at 90 MHz, relative to □ 77.0 ppm resonance of $CDCl_3$, unless otherwise stated. HRMS and IR data are listed for only one isomer, except as noted. Unless otherwise specified, all

compounds purified by chromatography were sufficiently pure (>95% by ^{1}H analysis) for use in subsequent reactions. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA.

(2*S*,3*S*,4*R*)-2,3-Epoxy-4-*O*-(*tert*-butyldimethylsiloxy)-2-methyl-5-*O*-(triisopropylsiloxy)-pent-1-ol (16b). To a mixture of (+)-DIPT (130 μL, 0.62 mmol) and 0.5 g of 4Å molecular sieves in CH_2Cl_2 (5 mL) at −40 °C was added Ti(O-*i*-Pr)$_4$ (148 μL, 0.5 mmol). After this mixture had been stirred for 10 min, a solution of alcohol **15b** (1 g, 2.49 mmol) in CH_2Cl_2 (5 mL) was added and the resulting mixture was stirred for 30 min. A 2 M TBHP solution (2.5 mL) in CH_2Cl_2 was then added slowly. The resulting mixture was stirred for 6 h at −20 °C and diluted with CH_2Cl_2 (10 mL). A 1 N NaOH solution was added, and the resulting mixture was then stirred at room temperature for 30 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the product by chromatography using 25:1 hexane–EtOAc afforded 832 mg (80%) of **16b**: R_f 0.37 (1:1 hexane–EtOAc); $[\alpha]_D$ = −13.09 (*c* 2.43, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.09 (s, 3 H), 0.15 (s, 3 H) 0.92 (s, 9 H), 1.02 (s, 21 H), 1.47 (s, 3 H), 3.04 (d, *J* = 7.9 Hz, 1 H), 3.54 (dd, *J* = 8.6, 12.3 Hz, 1 H), 3.60–3.74 (m, 4

H); ^{13}C NMR (90 MHz, $CDCl_3$) δ −0.9, −4.5, 11.9, 15.6, 18.0, 25.8, 61.5, 62.9, 65.4, 66.0, 72.4.

(3*RS*,4*S*,5*S*,6*R*)-4,5-Epoxy-2,4-dimethyl-6-*O*-(*tert*-butyldimethylsiloxy)-7-*O*-(triisopropylsiloxy)-3-*O*-(trimethylsiloxy)-1-heptene (17b). To a solution of **16b** (1.0 g, 2.39 mmol) in CH_2Cl_2 (20 mL) were added powdered 4Å molecular sieves (1.0 g), NMO (840 mg, 7.17 mmol), and TPAP (84 mg, 0.24 mmol). The mixture was stirred at room temperature for 30 min and filtered through a pad of Celite and silica gel. The filtrate was concentrated under reduced pressure to give 950 mg (95%) of the crude aldehyde, which was used immediately without further purification for the next step: R_f 0.76 (1:1 hexane–EtOAc).

To a 1 M solution of propenylmagnesium bromide (2.5 mL, 1.1 equiv) in THF at −20 °C was added dropwise (during 15 min) a solution of the previously prepared aldehyde (950 mg) in THF (20 mL). The reaction mixture was stirred for 30 min at the same temperature and quenched with aqueous saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the crude product by chromatography using 10:1 hexane–ether gave 837 mg (80%) of the alcohol as a diastereomeric mixture (colorless oil).

Spectral data for the R_f 0.44 diastereomer (5:1 hexane–ether): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.09 (s, 3 H), 0.12 (s, 3 H), 0.92 (s, 9 H), 1.06 (s, 21 H), 1.29 (s, 3 H), 1.75 (s, 3 H), 3.17 (d, *J* = 8.0 Hz, 1 H), 3.62 (td, *J* = 5.9, 8.0 Hz, 1 H), 3.70 (d, *J* = 5.9 Hz, 2 H), 4.06 (s, 1 H), 4.95 (q, *J* = 1.6 Hz, 1 H), 5.07 (s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ −4.8, −4.5, 11.9, 15.8, 17.7, 18.0, 25.8, 61.8, 62.1, 66.0, 73.0, 115.1, 143.1.

Spectral data for the R_f 0.36 diastereomer (5:1 hexane–ether): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.09 (s, 3 H), 0.12 (s, 3 H), 0.91, (s, 9 H), 1.04 (s, 21 H), 1.25 (s, 3 H), 1.74 (s, 3 H), 2.15 (d, *J* = 5.0 Hz, 1 H), 3.0 (d, *J* = 8.0 Hz, 1 H), 3.59 (td, *J* = 5.8, 8.0 Hz, 1 H), 3.70 (d, *J* = 5.8 Hz, 2 H), 3.73 (br s, 1 H), 4.94 (s, 1 H), 5.11 (s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ −4.8, −4.5, 11.9, 13.0, 17.7, 18.0, 19.2, 25.8, 62.8, 64.2, 66.0, 72.8, 78.9, 112.3, 143.2.

A solution of the alcohol (1.9 g, 4.14 mmol) in CH_2Cl_2 (80 mL) was treated sequentially at −20 °C with 2,6-lutidine (1.93 mL, 16.6 mmol) and TMSOTf (1.6 mL, 8.3 mmol). The reaction mixture was stirred for 30 min at the same temperature, quenched with aqueous saturated NH_4Cl, and warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography using 25:1 hexane–EtOAc to provide 2.2 g (99%) of **17b** as a mixture of two diastereomers.

Spectral data for the R_f 0.82 diastereomer (10:1 hexane EtOAc): ^{1}H NMR (360 MHz, $CDCl_3$) 0.08 (s, 9 H), 0.09 (s, 3 H), 0.12 (s, 3 H), 0.91 (s, 9 H), 1.07 (s, 21 H), 1.18 (s, 3 H), 1.70 (s, 3 H), 2.93 (d, *J* = 8.1 Hz, 1 H), 3.55 (td, *J* = 5.7, 8.1 Hz, 1 H), 3.68 (d, *J* = 5.7 Hz, 2 H), 3.84 (s, 1 H), 4.86 (t, *J* = 1.5 Hz, 1 H), 4.95 (s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) 4.8, 4.5, 0.0, 11.9, 14.9, 18.0, 25.9, 31.6, 61.7, 62.0, 66.1, 73.8, 79.0, 112.9, 145.2, 151.3; MS *m/z* 487 (M^+ *i*-Pr, 10), 357 (21), 203 (46), 175 (28), 157 (30), 144 (100), 133 (76), 115 (52), 103 (30); HRMS (M^+ *i*-Pr) calcd 487.3095 for $C_{24}H_{51}O_4Si_3$, found 487.3050.

(2*S*,3*R*,4*R*)-2-Methyl-2-(2-propenyl)-4-*O*-(*tert*-butyldimethylsiloxy)-5-*O*-(triisopropylsiloxy)-3-hydroxy-pentan-1-al (18). To a solution of **17b** (2.2 g, 4.15 mmol) in CH_2Cl_2 (80 mL) at 78 °C was added dropwise a 1 M solution of $TiCl_4$ (5.4 mL, 1.5 equiv) in CH_2Cl_2. The reaction mixture was stirred for 20 min at the same temperature, quenched with aqueous saturated NH_4Cl, and warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by chromatography using 50:1 hexane EtOAc to yield 1.77 g (93 %) of **18**: R_f 0.46 (10:1 hexane EtOAc): ^{1}H NMR (360 MHz, $CDCl_3$) 0.09 (s, 3 H), 0.10 (s, 3 H), 0.89 (s, 9 H), 1.06 (s, 21 H), 1.18 (s, 3 H), 1.77 (s, 3 H), 2.84 (d, *J* = 9.0 Hz, 1 H, O*H*), 3.63(dd, *J* = 5.5, 8.3 Hz, 1 H), 3.65 (t, *J* = 8.3 Hz, 1 H), 3.82 (dd, *J* =

5.5, 8.3 Hz, 1 H), 4.47 (d, *J* = 9.0 Hz, 1 H), 4.92 (s, 1 H), 5.10 (s, 1 H), 9.54 (s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) □ □4.4, □3.3, 11.9, 13.6, 18.0, 21.4, 26.0, 64.4, 64.5, 65.3, 69.7, 71.4, 108.3, 114.2, 146.1, 202.4; MS *m/z* 458 (M^+, 1), 239 (23), 203 (31), 157 (73), 132 (77), 115 (100), 103 (90).

(3*S*,4*R*,5*R*)-2,3-Dimethyl-3-(1,3-dioxolan-2-yl)-4-hydroxy-5-*O*-(*tert*-butyldimethylsiloxy)-6-*O*-(triisopropylsiloxy)-1-hexene-4-ol (19). A solution of **18** (1 g, 2.07 mmol) in THF (10 mL) was treated with 2,2-dimethyl-1,3-dioxolane (3.4 mL, 31 mmol), ethylene glycol (1.1 mL, 20 mmol), and a 1 M solution (0.2 mL) of HCl in ether. (Alternatively *p*-TsOH·H_2O (0.1 equiv) was used in place of HCl.) Progress of the reaction was monitored by TLC until **18** disappeared (2 or 3 days). The reaction mixture was then diluted with THF (10 mL), and solid $NaHCO_3$ was added to neutralize HCl. Water was then added, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography using 20:1 hexane□EtOAc afforded 1.8 g (82%) of **19**: $[\alpha]_D$ = □20.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) □ 0.09 (s, 3 H), 0.10 (s, 3 H), 0.90 (s, 9 H), 1.06 (s, 21 H), 1.12 (s, 3 H), 1.83 (s, 3 H), 2.80 (d, *J* = 8.7 Hz, 1 H, O*H*), 3.53 (dd, *J* = 4.9, 9.0 Hz, 1 H), 3.61 (t, *J* = 9.0 Hz, 1 H), 3.79□3.97 (m, 5 H), 4.26 (d, *J* = 8.7 Hz, 1 H), 4.94 (s, 1 H), 4.99 (s, 1 H), 5.01 (q, *J* = 1.3 Hz, 1 H); ^{13}C NMR (90

MHz, $CDCl_3$) δ −4.4, −3.3, 11.9, 13.6, 18.0, 21.4, 26.0, 50.2, 64.4, 64.5, 65.3, 69.7, 71.4, 108.3, 114.2, 146.1.

(3*S*,4*R*,5*R*)-2,3-Dimethyl-3-(1,3-dioxolan-2-yl)-4-*O*-(4-methoxybenzyloxy)-5-*O*-(*tert*-butyldimethylsiloxy)-6-*O*-(triisopropylsiloxy)-1-hexene (20). A solution of **19** (1.0 g, 1.84 mmol) in THF (8 mL) was treated with KH (630 mg, 5.5 mmol; 35% in mineral oil) and PMBCl (373 μL, 2.7 mmol). The reaction mixture was heated at reflux for 2 h and cooled to room temperature. An excess amount of KH was then quenched by slow addition of water. EtOAc (10 mL) was added, and the mixture was washed with aqueous saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The organic extracts were dried over $MgSO_4$, concentrated, and purified by chromatography using 50:1 hexane–EtOAc to provide 1 g (82%) of **20**: R_f 0.57 (10:1 hexane–EtOAc); $[\alpha]_D$ = 4.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.05 (s, 21 H), 1.28 (s, 3 H), 1.84 (s, 3 H), 3.61 (d, *J* = 10.0 Hz, 2 H), 3.79–3.80 (m, 2 H), 3.80 (s, 3 H), 3.85 (m, 1 H), 3.89–3.94 (m, 2 H), 4.23 (d, *J* = 1.6 Hz, 1 H), 4.71 (d, *J* = 4.1 Hz, 2 H), 4.93 (s, 1 H), 4.96 (d, *J* = 1.4 Hz, 1 H), 5.01 (s, 1 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 7.31 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ −3.9, −3.5, 11.9, 15.8, 18.0, 18.2, 22.1, 26.1, 50.3, 55.2, 64.5, 65.0, 65.2, 73.0, 74.2, 78.0, 108.4, 113.4, 114.6, 128.3, 132.4,

146.0; MS *m/z* 652 (M^+, 5), 621 (M^+–OMe, 75), 373 (11), 157 (39), 121 (100), 115 (25).

(2*S*,3*S*,4*R*,5*R*)-5-(Hydroxymethyl)-2-methoxy-4-(4-methoxybenzyloxy)-3-methyl-3-(2-propenyl)oxolane (21). A solution of **20** (1 g, 1.53 mmol) in THF (30 mL) was treated with a 1 M solution (3.8 mL, 2.5 equiv) of tetrabutylammonium fluoride in THF. The reaction mixture was stirred at room temperature for 2 h and quenched with aqueous saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Purification by chromatography using 10:1 to 3:1 hexane–EtOAc gave 513 mg (95%) of the corresponding diol: R_f 0.44 (1:1 hexane–EtOAc): $[\alpha]_D$ = 4.5 (*c* 2.1, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.22 (s, 3 H), 1.81 (s, 3 H), 2.1 (br s, 1 H, O*H*), 3.39–3.42 (m, 2 H), 3.65 (br s, 1 H), 3.86 (s, 3 H), 3.87–3.96 (m, 5 H), 4.55 (d, A of AB q, *J* = 10.5 Hz, 1 H), 4.72 (d, B of AB q, *J* = 10.5 Hz, 1 H), 4.95 (s, 1 H), 4.98 (s, 1 H), 5.05 (br s, 1 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 7.26 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.8, 22.4, 50.2, 55.2, 64.8, 65.0, 66.2, 70.0, 74.7, 78.9, 107.6, 113.7, 115.2, 129.4, 130.2, 144.9, 159.3; MS *m/z* 338 (M^+, 1), 240 (10), 210 (15), 182 (35), 138 (50), 121 (100), 107 (42).

A solution of the diol (610 mg, 1.73 mmol) in MeOH (17 mL) was treated with a 1 M solution (3.5 mL) of HCl in ether, stirred at room temperature for 2 h, and HCl gas was then removed by bubbling nitrogen through the solution. Solid $NaHCO_3$ was added and filtered off. The solvent was evaporated *in vacuo*, and the crude product was purified by chromatography using 5:1 hexane–ether to provide 470 mg (84%) of **21**: R_f 0.29 (2:1 hexane–EtOAc): $[\alpha]_D$ = 45.8 (*c* 2.0, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.18 (s, 3 H), 1.86 (br s, 3 H), 2.31 (br s, 1 H, O*H*), 3.46 (s, 3 H), 3.76 (dd, *J* = 5.1, 11.7 Hz, 1 H), 3.80 (s, 3 H), 3.82 (dd, *J* = 5.6, 11.7 Hz, 1 H), 3.87 (d, *J* = 4.6 Hz, 1 H), 4.31 (apparent t, ddd, *J* = 4.6, 5.1, 5.6 Hz, 1 H), 4.39 (d, A of AB q, *J* = 10.8 Hz, 1 H), 4.52 (d, B of AB q, *J* = 10.8 Hz, 1 H), 4.90 (br s, 1 H), 5.00 (q, *J* = 1.3 Hz, 1 H), 5.15 (s, 1 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 7.21 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.8, 21.7, 54.6, 55.2, 56.8, 62.1, 73.8, 78.7, 87.4, 108.1, 112.6, 113.8, 129.4, 129.8, 145.1, 159.2; MS *m/z* 322 (M^+, 3), 178 (10), 135 (8), 122 (22), 121 (100), 113 (10); HRMS (M^+–H) calcd 321.1702 for $C_{18}H_{25}O_5$, found 321.1724.

(2*S*,3*S*,4*R*,5*R*)-2-Methoxy-4-(4-methoxybenzyloxy)-3-methyl-3-(2-propenyl)-5-(triisopropylsiloxymethyl)oxolane (22). A solution of **21** (400 mg, 1.24 mmol), imidazole (169 mg, 2.5 mmol), and DMAP (7.6 mg, 0.06 mmol) in CH_2Cl_2 (24 mL) was treated with triisopropylsilyl chloride (292 μL, 1.36 mmol). The reaction mixture was stirred at room temperature overnight and diluted with

CH_2Cl_2 (20 mL). After aqueous saturated NH_4Cl solution had been added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification of the crude product by column chromatography using 20:1 hexane–EtOAc gave 580 mg (98%) of **22**: R_f 0.36 (10:1 hexane–EtOAc); $[\alpha]_D$ = 12.3 (*c* 0.9, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.08 (s, 21 H), 1.14 (s, 3 H), 1.78 (s, 3 H), 3.48 (s, 3 H), 3.80 (s, 3 H), 3.81 (d, *J* = 3.2 Hz, 1 H), 3.86 (dd, *J* = 5.5, 9.9 Hz, 1 H), 3.91 (dd, *J* = 8.4, 9.9 Hz, 1 H), 4.34 (ddd, *J* = 3.2, 5.5, 8.4 Hz, 1 H), 4.46 (d, A of AB q, *J* = 11.0 Hz, 1 H), 4.73 (d, B of AB q, *J* = 11.0 Hz, 1 H), 4.76 (br s, 1 H), 4.91 (br s, 1 H), 5.18 (s, 1 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 7.22 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.9, 12.3, 17.7, 18.0, 18.6, 21.0, 54.6, 55.2, 57.1, 61.3, 73.7, 79.9, 85.8, 108.3, 111.5, 113.6, 129.0, 130.8, 145.9, 159.0; MS *m/z* 478 (M^+, 1), 233 (10), 201 (20), 173 (20), 121 (100), 103 (20).

(2*RS*,3*R*,4*R*,5*R*)-5-(Hydroxymethyl)-3-[(2*R*)-1,2-dihydroxy-2-propyl]-2-methoxy-4-(4-methoxybenzyloxy)-3-methyloxolane (23). A solution of **22** (340 mg, 0.71 mmol) in 1:2 acetone–water (7 mL) was treated with NMO (1.09 g, 1.0 mmol) and OsO_4 (12.5 mg, 0.1 mmol). The reaction mixture was stirred at room temperature for 4 h, quenched by solid sodium thiosulfate, stirred for an additional 30 min, and filtered through a pad of Celite. The filter cake was washed

thoroughly with EtOAc. The combined organic filtrates were evaporated *in vacuo*. Purification of the crude product by column chromatography using 3:1 hexane–EtOAc afforded 304 mg (85%) of **23** as an anomeric mixture: R_f 0.52 (1:1 hexane–EtOAc); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.9, 16.0, 16.3, 18.0, 20.8, 21.6, 54.6, 55.2, 55.6, 56.6, 60.3, 67.4, 67.5, 74.4, 74.6, 75.2, 76.1, 79.7, 80.2, 89.0, 89.1, 105.4, 106.2, 114.09, 114.14, 128.9, 129.0, 129.8, 130.0, 159.6, 159.7.

(2*RS*,3*R*,4*R*,5*R*)-3-[(2*R*,3*R*)-2,3-Dihydroxy-2-pentyl]-5-(triisoproplsiloxymethyl)-2-methoxy-4-(4-methoxybenzyloxyl)-3-methyloxolane (24). To a solution of oxalyl chloride (153 μL, 1.7 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added slowly a solution of DMSO (218 μL, 3.4 mmol) in CH_2Cl_2 (2 mL). After the mixture had been stirred for 10 min, a solution of **23** (224 mg, 0.44 mmol) in CH_2Cl_2 (1 mL) was added and stirring was continued for an additional 30 min. Triethylamine (612 μL, 4.4 mmol) was then added at the same temperature. After 10 min, the mixture was allowed to warm to 0 °C, and 1:10 water–CH_2Cl_2 (3 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were washed with aqueous saturated sodium bicarbonate, dried over $MgSO_4$, and concentrated under reduced pressure. The crude aldehyde thus obtained was used for the next step without further purification.

To a 1 M solution of ethylmagnesium bromide (4.4 mL) in THF at room temperature was added a solution of the crude aldehyde in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 30 min, quenched with aqueous saturated NH_4Cl, and stirred for an additional 10 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were concentrated under reduced pressure. Purification of the crude product by chromatography using 10:1 hexane–EtOAc afforded 160 mg (68%) of **24** as a mixture of the two anomers.

Spectral data of the R_f 0.52 anomer (1:1 hexane–EtOAc): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.5 Hz, 3 H), 1.11 (s, 21 H), 1.38–1.49 (m, 1 H), 1.62–1.72 (m, 1 H), 1.94 (d, *J* = 6.0 Hz, 1 H), 3.46 (s, 3 H), 3.50 (dd, *J* = 2.2, 6.0 Hz, 0.5 H), 3.53 (dd, *J* = 2.2, 6.0 Hz, 0.5 Hz), 3.82 (s, 3 H), 3.95 (s, 1 H), 3.97 (d, *J* = 2.0 Hz, 1 H), 4.25 (d, *J* = 2.2 Hz, 1 H), 4.33 (qt, *J* = 2.0, 7.1 Hz, 1 H), 4.57 (d, A of AB q, *J* = 10.6 Hz, 1 H), 4.93 (d, B of AB q, *J* = 10.6 Hz, 1 H), 5.34 (s, 1 H), 5.50 (s, 1 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 7.30 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.3, 11.9, 16.6, 18.0, 22.9, 23.6, 29.6, 55.3, 56.6, 60.4, 74.2, 76.6, 77.3, 79.4, 89.7, 105.1, 114.1, 129.0, 123.0, 160.0.

(1*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-5,6-Dimethyl-7-ethyl-4-(4-methoxybenzyloxy)-3-(triisopropylsiloxymethyl)-2,8-dioxabicyclo[3.3.0]octan-6-ol (25). A solution of **24** (73 mg, 0.135 mmol) in CH_2Cl_2 (7 mL) was treated with *p*-TsOH (25 mg, 0.13 mmol) and 4Å molecular sieves (70 mg). The mixture was stirred at room

temperature for 1.5 h. Solid $NaHCO_3$ was added to neutralize p-TsOH, and the solvent was then removed *in vacuo*. The cruce product was purified by column chromatography using 4:1 hexane–EtOAc as eluent to give **25** (65 mg, 95%): R_f 0.15 (50:1 hexane–EtOAc); $[\alpha]_D$ = +15.7 (*c* 0.74, $CHCl_3$); IR (film) 3471 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.5 Hz, 3 H), 1.01–1.09 (21 H), 1.23 (s, 3 H), 1.24 (s, 3 H), 1.42–1.55 (m, 2 H), 3.61 (d, *J* = 1.7 Hz, 1 H), 3.81 (s, 3 H), 3.94 (d, *J* = 5.7 Hz, 1 H), 4.10 (d, *J* = 5.7 Hz, 1 H), 4.07–4.15 (m, 1 H), 4.35 (dd, *J* = 5.3, 7.5 Hz, 1 H), 4.42 (d, A of AB q, *J* = 10.9 Hz, 1 H), 4.89 (d, B of AB q, *J* = 10.9 Hz, 1 H), 5.17 (s, 1 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 7.23 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.2, 11.9, 18.0, 21.2, 55.2, 60.4, 61.7, 73.8, 81.0, 83.3, 85.0, 88.6, 111.2, 113.7, 128.6, 130.1, 159.0; HRMS (M^+–C_3H_7) calcd for $C_{25}H_{41}O_6Si$ 465.2672, found 465.2680.

(1*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-5,6-Dimethyl-7-ethyl-3-(hydroxymethyl)-4-(4-methoxybenzyloxy)-2,8-dioxabicyclo[3.3.0]octan-6-ol (26). A solution of **25** (80 mg, 0.157 mmol) in THF (3 mL) was treated with a 1 M solution of tetrabutylammonium fluoride (0.24 mL, 1.5 equiv) in THF. The reaction mixture was stirred at room temperature for 30 min and quenched with aqueous saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by chromatography

using 10:1 to 3:1 hexane–EtOAc gave 55 mg (100%) of **26**: R_f 0.32 (1:1 hexane–EtOAc): $[\alpha]_D$ = +75.8 (*c* 0.85, $CHCl_3$) {lit[2c] $[\alpha]_D$ = +53.2 (*c* 0.3, MeOH)}; IR (film) 3424 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.5 Hz, 3 H; C-1), 1.22 (s, 3 H; Me at C-5), 1.26 (s, 3 H; Me at C-4), 1.46–1.55 (m, 2 H), 3.61 (d, *J* = 3.4 Hz, 1 H; C-7), 3.81 (s, 3 H), 3.85 (dd, *J* = 5.2, 11.2 Hz, 1 H; H-9), 3.97 (dd, *J* = 6.6, 11.2 Hz, 1 H; H-9'), 4.21 (ddd, *J* = 3.4, 5.2, 6.6 Hz, 1 H; H-8), 4.30 (dd, *J* = 4.7, 8.1 Hz, 1 H; H-3), 4.44 (d, A of AB q, *J* = 10.8 Hz, 1 H), 4.51 (d, B of AB q, *J* = 10.8 Hz, 1 H), 5.22 (s, 1 H; H-6), 6.87 (d, *J* = 8.6 Hz, 2 H), 7.23 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.2, 17.0, 17.2, 21.2, 55.2, 61.3, 62.1, 74.5, 80.9, 83.4, 86.1, 88.6, 111.3, 113.8, 129.0, 129.3, 159.3; MS *m/z* 352 (M^+, 3), 291 (12), 136 (43), 124 (44), 121 (100), 109 (74); HRMS (M^+) calcd for $C_{19}H_{28}O_6$ 352.1886, found 352.1854.

15c: IR (film) 3339 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.03 (m, 42 H), 1.68 (d, *J* = 1.2 Hz, 3 H), 3.48 (dd, *J* = 6.9, 9.6 Hz, 1 H), 3.74 (dd, *J* = 5.6, 9.6 Hz, 1 H), 3.98 (s, 2 H), 4.54 (m, 1 H), 5.37 (qd, *J* = 1.2, 8.5 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.9, 12.3, 14.4, 17.6, 17.9, 68.2, 68.3, 70.3, 128.1, 136.0; HRMS (M^+–C_3H_7) calcd for $C_{21}H_{45}O_3Si_2$ 401.2907, found 401.2895. Anal. Calcd for $C_{24}H_{52}O_3Si_2$: C, 64.8; H, 11.8. Found: C, 64.7; H, 11.8.

(2*S*,3*S*,4*R*)-2,3-Epoxy-4,5-bis(triisopropylsiloxy)-2-methylpentan-1-ol (16c). To a mixture of (+)-DET (386 μL, 2.25 mmol) and 0.5 g of 4Å molecular sieves in CH_2Cl_2 (5 mL) at −40 °C was added Ti(O-*i*-Pr)$_4$ (665 μL, 2.25 mmol). After this mixture had been stirred for 10 min, a solution of alcohol **15c** (R^4 = R^5 = TIPS; 1 g, 2.25 mmol) in CH_2Cl_2 (5 mL) was added. The resulting mixture was stirred for 30 min, and a 2 M TBHP solution (2.3 mL) in CH_2Cl_2 was then added. The reaction mixture was stirred for 6 h at −20 °C and diluted with CH_2Cl_2 (10 mL). A 30% NaOH/brine solution was then added, and the resulting mixture was stirred at room temperature for 30 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography using 25:1 hexane–EtOAc afforded epoxide **16c** (0.91 g, 88%) as a colorless oil: R_f 0.48 (5:1 hexane–EtOAc); $[\alpha]_D$ = −16.23 (*c* 1.06, $CHCl_3$); IR (film) 3444 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.00–1.10 (m, 42 H), 1.34 (s, 3 H), 1.78 (br s, 1 H, O*H*), 3.07 (d, *J* = 8.0 Hz, 1 H), 3.54 (dd, *J* = 7.5, 12.0 Hz, 1 H), 3.66 (m, 2 H), 3.76 (dd, *J* = 4.4, 8.1 Hz, 1 H), 3.81 (dd, *J* = 4.4, 8.1 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.9, 12.4, 15.7, 17.9, 18.0, 61.3, 63.3, 65.4, 66.2, 72.4; MS *m/z* 287 (66), 245 (60), 157 (84), 131 (73), 115 (100); HRMS (M^+–OC_3H_7) calcd for $C_{21}H_{45}O_3Si_2$ 401.2907, found 401.2908. Anal. Calcd for $C_{24}H_{52}O_4Si_2$: C, 62.6; H, 11.4. Found: C, 62.4; H, 11.4.

(2*R*,3*S*,4*S*,5*RS*)-3,4-Epoxy-1,2-bis(triisopropylsiloxy)-4,6-dimethyl-6(*E*)-non-6-en-5-ol (30). To a solution of oxalyl chloride (0.75 mL, 8.25 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added slowly a solution of DMSO (0.7 mL, 9.90 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 10 min, and a solution of **16c** (0.76 g, 1.65 mmol) in CH_2Cl_2 (5 mL) was then added. After the resulting mixture had been stirred for an additional 30 min, triethylamine (2.3 mL, 16.5 mmol) was added. The reaction mixture was then allowed to warm to 0 °C, stirred for an additional 10 min at 0 °C, and quenched by addition of 1:10 water−CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with aqueous saturated NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The crude aldehyde thus obtained was used immediately for the next step.

To a solution of (*E*)-2-bromo-2-pentene (**29b**) (368 mg, 2.48 mmol) in THF (10 mL) at −78 °C was added *t*-BuLi (2.4 mL of a 1.5 M solution in pentane, 3.6 mmol). After the resulting mixture had been stirred for 2 h at −78 °C, a solution of $MgBr_2$ (2.53 mL of a 1 M solution in ether; prepared from magnesium and 1,2-dibromoethane in ether) was added. The resulting mixture was stirred for an additional 20 min at −78 °C, and a solution of the crude aldehyde in THF (3 mL) was then added. The reaction mixture was stirred for 2 h at −78 °C, quenched with aqueous NH_4Cl, and diluted with EtOAc (30 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification of the residue by chromatography using 50:1 hexane−ether gave **30** (697 mg,

80%) as a mixture of two epimers: IR (film) 3472, 1098, 1065 cm^{-1}; MS *m/z* 485 (2), 359 (27), 287 (22), 185 (30), 157 (90), 145 (100); HRMS ($M^+ - C_3H_7$) calcd for $C_{26}H_{53}O_4Si_2$ 485.3482, found 485.3469. Anal. Calcd for $C_{29}H_{60}O_4Si_2$: C, 65.8; H, 11.4. Found: C, 65.6; H, 11.5.

Spectral data for the R_f 0.49 isomer (10:1 hex–EtOAc): $[\alpha]_D$ = +21.9 (*c* 2.3, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.5 Hz, 3 H), 1.01–1.12 (m, 42 H), 1.26 (s, 3 H), 1.63 (s, 3 H), 2.05 (m, 2 H), 2.25 (s, 1 H, O*H*), 3.22 (d, *J* = 7.4 Hz, 1 H), 3.65–3.81 (m, 3 H), 3.99 (s, 1 H), 5.50 (t, *J* = 7.1 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.3, 11.9, 12.5, 13.8, 16.1, 18.0, 18.1, 20.9, 62.3, 62.4, 66.1, 73.2, 79.0, 132.3, 132.5.

Spectral data for the R_f 0.44 isomer (10:1 hex–EtOAc): $[\alpha]_D$ = –5.80 (*c* 2.29, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.5 Hz, 3 H), 1.07 (m, 42 H), 1.21 (s, 3 H), 1.61 (s, 3 H), 2.05 (dq, *J* = 6.2, 7.5 Hz, 2 H), 3.02 (d, *J* = 7.1 Hz, 1 H), 3.64–3.80 (m, 4 H), 5.50 (t, *J* = 7.0 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.9, 12.5, 12.6, 12.7, 13.9, 13.9, 18.0, 18.1, 20.7, 62.6, 63.7, 66.2, 72.8, 79.2, 129.1, 132.7.

(2*R*,3*S*,4*S*,5*RS*)-3,4-Epoxy-5-trimethylsilyloxy-1,2-bis(triisopropylsiloxy)-4,6-dimethyl-6(*E*)-nonene (31). To a solution of **30** (697 mg, 1.32 mmol) in CH_2Cl_2 (20 mL) at –78 °C were added sequentially 2,6-lutidine (340 μL, 2.9 mmol) and TMSOTf (225 μL, 1.45 mmol). The reaction mixture was stirred for 30 min at the same temperature and quenched with aqueous saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined

organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography using 50:1 hexane–ether provided **31** (650 mg, 82%) as a mixture of two diastereomers: IR (film) 1250, 1099, 1067 cm^{-1}; MS *m/z* 359 (43), 287 (27), 171 (80), 145 (100); HRMS ($M^+ - C_3H_7$) calcd for $C_{26}H_{53}O_4Si_2$ 557.3878, found 557.3881.

Spectral data for the R_f 0.33 isomer (35:1 hexane–EtOAc): ^1H NMR (360 MHz, $CDCl_3$) δ 0.04 (s, 9 H), 0.95 (t, *J* = 7.5 Hz, 3 H), 1.03–1.11 (m, 42 H), 1.17 (s, 3 H), 1.56 (s, 3 H), 2.01 (dq, *J* = 6.2, 7.5 Hz, 2 H), 3.06 (m, 1 H), 3.65–3.78 (m, 3 H), 3.91 (s, 1 H) 5.35 (t, *J* = 7.1 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 0.0, 11.5, 12.0, 12.5, 13.8, 16.0, 18.0, 18.1, 20.7, 61.8, 61.8, 66.4, 73.9, 80.1, 130.1, 134.5.

Spectral data for the R_f 0.28 isomer (35:1 hexane–EtOAc): ^1H NMR (360 MHz, $CDCl_3$) δ 0.09 (s, 9 H), 0.96 (t, *J* = 7.5 Hz, 3 H), 1.07 (m, 42 H), 1.18 (s, 3 H), 1.60 (s, 3 H), 2.02 (dq, *J* = 6.2, 7.5 Hz, 2 H), 2.87 (m, 1 H), 3.62 (s, 3 H), 3.65–3.73 (m, 2 H), 3.75 (m, 1 H), 5.47 (t, *J* = 7.2 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 0.2, 11.9, 12.5, 13.2, 13.8, 14.0, 18.0, 18.1, 20.7, 62.7, 63.8, 66.3, 73.3, 81.2, 128.4, 133.5.

(2*S*,3*R*,4*R*)-2-Methyl-2-[2(*E*)-penten-2-yl]-3-hydroxy-4,5-bis(triisopropylsiloxy)pentanal (32). To a solution of **31** (650 mg, 1.08 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added dropwise a 1.0 M solution of $TiCl_4$ (1.4 mL) in CH_2Cl_2. The mixture was stirred for 20 min at the same temperature, and quenched with aqueous saturated NH_4Cl, and warmed to room temperature. The organic layer was

separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by chromatography using 50:1 hexane–EtOAc gave aldehyde **32** (559 mg, 98%) as a colorless oil: R_f 0.48 (10:1 hexane–EtOAc); $[\alpha]_D$ = –57.00 (*c* 0.45, $CHCl_3$); IR (film) 3541, 1724, 1463 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.5 Hz, 3 H), 1.07 (s, 42 H), 1.21 (s, 3 H), 1.62 (s, 3 H), 2.07 (dq, *J* = 6.2, 7.5 Hz, 2 H), 2.80 (d, *J* = 9.0 Hz, 1 H), 3.65 (dd, *J* = 4.6, 9.0 Hz, 1 H), 3.70 (t, *J* = 9.0 Hz, 1 H), 3.94 (dd, *J* = 4.6, 9.2 Hz, 1 H), 4.51 (d, *J* = 8.4 Hz, 1 H), 5.39 (t, *J* = 6.7 Hz, 1 H), 9.48 (s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.9, 13.2, 13.8, 14.0, 17.9, 18.1, 18.2, 21.5, 59.8, 63.9, 69.4, 71.3, 131.7, 132.0, 202.7; MS *m/z* 309 (45), 157 (94), 145 (100); HRMS {M^+–61 (C_3H_7+H_2O)} calcd for $C_{26}H_{52}O_3Si_2$ 467.3377, found 467.3364.

(2*R*,3*R*,4*S*)-3-Hydroxy-4-(1,3-dioxolan-2-yl)-4,5-dimethyl-1,2-bis(triisopropylsiloxy)-5(*E*)-octene (33). A solution of aldehyde **32** (559 mg, 1.06 mmol), ethylene glycol (1.8 mL, 31.8 mmol), and *p*-TsOH•H_2O (10 mg, 0.05 mmol) in benzene (30 mL) was heated at reflux overnight with removal of water by using a Dean-Stark trap. The reaction mixture was cooled to room temperature, diluted with EtOAc (30 mL), washed with aqueous saturated NH_4Cl, dried over $MgSO_4$, and evaporated *in vacuo*. Purification of the residue by column chromatography using 50:1 hexane–EtOAc gave **33** (576 mg, 95%) as a white solid: R_f 0.33 (10:1 hexane–EtOAc); mp 58–60 °C; $[\alpha]_D$ = –26.50 (*c* 0.84, $CHCl_3$); IR (CH_2Cl_2) 3416 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ

0.95 (t, J = 7.5 Hz, 3 H), 1.06 (s, 42 H), 1.13 (s, 3 H), 1.67 (s, 3 H), 2.0–2.1 (m, 2 H), 2.80 (d, J = 9.2 Hz, 1 H), 3.58 (dd, J = 4.7, 8.8 Hz, 1 H), 3.68 (t, J = 9.1 Hz, 1 H), 3.77–3.93 (m, 5 H), 4.32 (d, J = 9.2 Hz, 1 H), 5.01 (s, 1 H), 5.39 (t, J = 6.5 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) 11.9, 13.5, 14.0, 14.0, 14.2, 17.9, 18.2, 18.3, 21.3, 50.4, 64.4, 64.5, 65.2, 69.9, 72.0, 105.2, 108.8, 129.8, 135.0; MS *m/z* 359 (25), 295 (30), 157 (79), 145 (100); HRMS (M^+–C_3H_7) calcd for $C_{28}H_{57}O_5Si_2$ 529.3745, found 529.3743. Anal. Calcd for $C_{31}H_{64}O_5Si_2$: C, 65.0; H, 11.3. Found: C, 65.0; H, 11.2.

(2*R*,3*R*,4*S*)-3-(4-Methoxybenzyloxy)-4-(1,3-dioxolan-2-yl)-4,5-dimethyl-1,2-bis(triisopropylsiloxy)-5(*E*)-octene (34). A solution of alcohol **33** (576 mg, 1.01 mmol) in THF (3 mL) was added at room temperature to KH (463 mg, from 35% suspension in mineral oil), which had been pre-washed with hexane. The mixture was stirred for 1 h, and PMBCl (137 L, 1.01 mmol) was then added. After the reaction mixture had been stirred for overnight, excess KH was quenched by slow addition of water. The mixture was extracted with EtOAc (2 x 10 mL). The organic extracts were washed with aqueous saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. Purification of the crude product by column chromatography using 50:1 hexane–EtOAc provided **34** (559 mg, 80%) as a white solid: R_f 0.48 (10:1 hexane–EtOAc); mp 53–55 °C; $[\alpha]_D$ = +3.50 (*c* 0.39, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) 0.96 (t, J = 7.5 Hz, 3 H), 1.06 (br s, 21 H), 1.07 (br s, 21 H), 1.30 (s, 3 H), 1.70 (s, 3 H), 2.05 (dq, J = 6.2, 7.5 Hz, 2 H), 3.68–3.70 (m, 2 H), 3.80 (s, 3 H), 3.78–3.86 (m, 4 H), 3.89 (m, 1 H), 4.01 (dd, J = 6.3, 8.0 Hz, 1 H),

4.74 (s, 2 H), 4.96 (s, 1 H), 5.41 (t, *J* = 6.3 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 7.32 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) □ 11.9, 13.8, 14.0, 14.8, 16.1, 18.0, 18.3, 21.4, 50.6, 55.2, 64.6, 64.8, 64.9, 73.4, 74.2, 78.0, 108.9, 113.3, 128.1, 130.2, 132.6, 134.7, 158.5; MS *m/z* 692 (M^+□C_3H_7, 3), 373 (18), 359 (15), 295 (60), 157 (72), 121 (100); HRMS (M^+□C_3H_7) calcd for $C_{36}H_{65}O_6Si_2$ 649.4320, found 649.4328. Anal. Calcd for $C_{39}H_{72}O_6Si_2$: C, 67.6; H, 10.5. Found: C, 67.8; H, 10.6.

(2*R*,3*R*,4*S*)-3-(4-Methoxybenzyloxy)-4-(1,3-dioxolan-2-yl)-4,5-dimethyloct-5(*E*)-en-1, 2-diol (42). A solution of **34** (559 mg, 0.81 mmol) in THF (10 mL) was treated at 0 °C with a 1 M solution of tetrabutylammonium fluoride (1.8 mL) in THF. The reaction mixture was stirred at room temperature for 3 h and quenched by addition of aqueous saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by chromatography using 10:1 to 2:1 hexane□EtOAc gave diol **42** (293 mg, 95%) as a colorless oil: R_f 0.22 (2:1 hexane:EtOAc); $[\alpha]_D$ = +13.10 (*c* 1.08, $CHCl_3$); IR (film) 3434, 1514 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) □ 0.96 (t, *J* = 7.5 Hz, 3 H), 1.19 (s, 3 H), 1.67 (s, 3 H), 2.05 (dq, *J* = 6.7, 7.5 Hz, 2 H), 3.40 (dd, *J* = 7.5, 11.1 Hz, 1 H), 3.44 (dd, *J* = 4.5, 11.1 Hz, 1 H), 3.62 (m, 1H), 3.80 (s, 3 H), 3.82□3.94 (m, 5 H), 4.55 (d, A of AB q, *J* = 10.5 Hz, 1 H), 4.73 (d, B of AB q, *J* = 10.5 Hz, 1 H), 5.01 (s, 1 H), 5.41 (t, *J* = 6.7 Hz, 1 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 7.26 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (90 MHz,

$CDCl_3$) δ 14.0, 14.8, 15.0, 21.5, 50.4, 55.2, 64.8, 65.1, 66.3, 69.3, 74.6, 79.1, 108.0, 113.8, 129.4, 130.3, 131.0, 133.4, 159.3; MS *m/z* 287 (14), 261 (14), 149 (43), 137 (56), 121 (100); HRMS (M^+−CH_3) calcd for $C_{20}H_{29}O_6$ 365.1964, found 365.1988.

(2*S*,3*S*,4*R*,5*R*)-5-(Hydroxymethyl)-2-methoxy-4-(4-methoxybenzyloxy)-3-methyl-3-[2(*E*)-penten-2-yl]oxolane (35). A solution of **42** (288 mg, 0.75 mmol) in MeOH (14 mL) was treated with a 1 M solution (1.5 mL) of HCl in ether. After the mixture had been stirred at room temperature for 1.5 h, HCl was removed by bubbling nitrogen through the solution, followed by addition of solid $NaHCO_3$. The mixture was filtered, and the solvent was removed *in vacuo*. The crude product was purified by chromatography using 5:1 hexane-ether to provide 345 mg (88%) of **35**: R_f 0.29 (2:1 hexane-EtOAc); $[\alpha]_D$ = +37.1 (*c* 2.8, $CHCl_3$); IR (film) 3440, 1514, 1463, 1034 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.5 Hz, 3 H), 1.15 (s, 3 H), 1.72 (s, 3 H), 2.08 (ddq, *J* = 2.0, 6.2, 7.4 Hz, 2 H), 3.49 (s, 3 H), 3.80 (s, 3 H), 3.74-3.86 (m, 3 H), 4.30 (q, *J* = 5.0 Hz, 1 H), 4.36 (d, A of AB q, *J* = 10.8 Hz, 1 H) 4.50 (d, B of AB q, *J* = 10.8 Hz, 1 H), 5.18 (s, 1 H), 5.30 (dt, *J* = 1.2, 6.8 Hz, 1 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 7.19 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.1, 15.0, 18.8, 21.4, 55.3, 55.4, 57.0, 62.2, 73.8, 78.7, 87.7, 108.2, 113.9, 128.0, 129.3, 130.1, 134.1, 159.4; MS *m/z* 350 (1), 197 (10), 140 (17), 121 (100); HRMS (M^+) calcd for $C_{20}H_{30}O_5$ 350.2093, found 350.2094.

(2*R*,3*R*,4*R*,5*R*,6*R*)-3-(4-Methoxybenzyloxy)-4-(1,3-dioxolan-2-yl)-4,5-dimethyloct-1,2,5,6-tetrol (43). A mixture of *t*-butyl alcohol (2.5 mL), water (2.5 mL), and AD-mix-□ [containing $K_3Fe(CN)_6$ (762 mg, 2.3 mmol; 3 equiv), K_2CO_3 (106 mg, 0.77 mmol), $(DHQD)_2$-PHAL (302 mg, 0.39 mmol; 0.5 equiv), and OsO_4 (49 mg, 0.19 mmol; 0.25 equiv)] was stirred at room temperature and two phases were produced, the lower aqueous phase being yellow. Methanesulfonamide (74 mg, 0.78 mmol) was added at this point. The resulting mixture was cooled to 0 °C, and a solution of **42** (293 mg, 0.77 mmol) in 1:1 *t*-BuOH/H_2O (20 mL) was added. The heterogeneous slurry was stirred vigorously at 4 °C overnight, and solid sodium sulfite (2.9 g, 23 mmol) was added at 4 °C. The reaction mixture was then allowed to warm to room temperature, stirred for an additional 3 h, and diluted with EtOAc (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 2 N KOH (3 mL) and dried over Na_2SO_4. The crude product was purified by column chromatography (1:4 hexane□EtOAc□ EtOAc) to afford pure tetrol **43** (236 mg, 74%) as a white solid, free from its diastereomer: R_f 0.15 (1:4 hexane□EtOAc); mp 80□82 °C; $[\alpha]_D$ = +38.67 (*c* 0.45, $CHCl_3$); IR (CH_2Cl_2) 3382, 1612, 1514 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) □ 0.86 (t, *J* = 7.3 Hz, 3 H), 1.11 (s, 3 H), 1.20 (s, 3 H), 1.38 (m, 1 H), 1.58 (m,1 H), 1.67 (br, 1 H, O*H*), 2.34 (br, 1H, O*H*), 3.61 (dd, *J* = 4.2, 9.7 Hz, 1 H), 3.80 (s, 3 H), 3.70□4.01 (m, 8 H), 4.11 (dd, *J* = 5.5, 7.2 Hz, 1 H), 4.41 (br, 1 H, O*H*), 4.51 (d, *J* = 10.3 Hz, 1 H), 4.66 (d, *J* = 10.3 Hz, 1 H), 5.20 (s, 1 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 7.26 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) □ 11.1, 16.3,

20.3, 25.0, 52.3, 55.3, 64.3, 64.7, 65.9, 70.6, 74.8, 76.4, 79.0, 83.3, 105.5, 114.0, 129.4, 129.6, 159.6; MS *m/z* 291 (5), 249 (15), 189 (11), 121 (100); HRMS (M^+) calcd for $C_{21}H_{34}O_8$ 414.2254, found 414.2268.

(1*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-5,6-Dimethyl-7-ethyl-3-(hydroxymethyl)-4-(4-methoxybenzyloxy)-2,8-dioxabicyclo[3.3.0]octan-6-ol (26). A solution of tetraol **43** (236 mg, 0.57 mmol) in MeOH (57 mL) was treated with a 1 M solution (1.1 mL) of HCl in ether. After the reaction mixture had been stirred overnight, HCl was neutralized by bubbling nitrogen through and subsequent addition of solid $NaHCO_3$. After methanol had been removed, the concentrate was then dissolved in 20:1 EtOAc–brine (30 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (4 x 10 mL). The combined organic extracts were concentrated *in vacuo* to give the crude product. Purification by column chromatography using 1:4 hexane–EtOAc as eluent provided the bis(tetrahydrofuran) **26** (181 mg, 90%), which proved to be identical, in every aspect, to the bis(tetrahydrofuran) from the first-generation synthesis (*vide supra*).

(1*S*,3*R*,4*R*,5*S*,6*S*,7*R*)-5,6-Dimethyl-7-ethyl-3-(hydroxymethyl)-4-(4-methoxybenzyloxy)-2,8-dioxabicyclo[3.3.0]octan-6-ol (39a). A mixture of *t*-butyl alcohol (0.2 mL), water (0.2 mL), and AD-mix-β [containing $K_3Fe(CN)_6$ (37.2 mg, 0.11 mmol; 3 equiv), K_2CO_3 (7.8 mg, 0.06 mmol), $(DHQ)_2$-PHAL (14.7 mg, 0.02 mmol; 0.5 equiv), and OsO_4 (2.9 mg, 0.01 mmol; 0.3 equiv)] was stirred at room temperature and two phases were produced, the lower aqueous phase being yellow. Methanesulfonamide (3.6 mg, 0.04 mmol) was added at this point. The resulting mixture was

cooled to 0 °C, and a solution of **42** (14.3 mg, 0.04 mmol) in 1:1 *t*-BuOH–H_2O (2.5 mL) was then added. The heterogeneous slurry was stirred vigorously at 4 °C overnight, and solid sodium sulfite (0.15 g, 1.2 mmol) was added at 4 °C. The reaction mixture was then allowed to warm to room temperature, stirred for an additional 3 h, and diluted with EtOAc (5 mL). After the organic layer had been separated, the aqueous layer was extracted with EtOAc (4 x 15 mL). The combined organic extracts were washed with 2 N KOH (3 mL) and dried over Na_2SO_4. The crude product was partially purified by filtration through a column of silica gel (1:4 hexane–EtOAc→ EtOAc) to afford the tetraol.

A solution of the tetraol thus obtained (8.2 mg, 0.02 mmol) in MeOH (2 mL) was treated with a 1 M solution (0.04 mL) of HCl in ether. After the reaction mixture had been stirred overnight, HCl was neutralized by bubbling nitrogen through and subsequent addition of solid $NaHCO_3$. After methanol had been removed, the concentrate was then dissolved in 20:1 EtOAc–brine (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were concentrated *in vacuo* to give the crude product. Purification by column chromatography using 1:4 hexane–EtOAc as eluent provided **26** (0.9 mg) and **39a** (5.7 mg, 43% overall yield): R_f 0.50 (1:4 hexane–EtOAc); $[\alpha]_D$ = –13.0 (*c* 0.19, $CHCl_3$); IR (film) 3485, 1514, 1032 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ (Asteltoxin numbering is used to indicate the protons.) 1.02 (t, *J* = 7.5 Hz, 3 H; C-1), 1.16 (s, 3 H; Me at C-5), 1.20 (s, 3 H; Me at C-4), 1.48–1.60 (m, 1 H; C-2), 1.73–1.84 (m, 1 H; C-2'), 3.62 (dd, *J* = 3.1, 9.5 Hz, 1 H; C-3), 3.80 (dd, *J* = 4.2, 12.1 Hz, 1 H; C-9), 3.82 (s, 3H), 4.09 (dd, *J* = 6.1, 12.1 Hz, 1 H; C-9'), 4.14 (d, *J* = 7.8 Hz, 1H; C-7), 4.28 (ddd, *J* = 4.2, 6.1, 7.8 Hz, 1 H; C-8), 4.54 (d, A of AB q, *J* = 11.1 Hz, 1 H), 4.62 (d,

B of AB q, J = 11.1 Hz, 1 H), 5.01 (s, 1 H; C-6), 6.09 (d, J = 6.9 Hz, 2 H), 7.25 (d, J = 6.9 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) □ 11.3, 21.4, 21.7, 21.9, 55.3, 57.9, 61.7, 74.9, 80.6, 81.5, 88.6, 90.4, 112.1, 114.1, 128.7, 129.8, 159.8.

(1*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-Ethyl 3-{5,6-Dimethyl-7-ethyl-6-hydroxy-4-(4-methoxy-benzyloxy)-2,8-dioxabicyclo[3.3.0]oct-3-yl}-prop-2-enoate (47). A solution of DMSO (237 □L, 3.1 mmol) in CH_2Cl_2 (1 mL) was added slowly at □78 °C to a solution of oxalyl chloride (220 □L, 2.5 mmol) in CH_2Cl_2 (5 mL). After the mixture had been stirred for 15 min, a solution of **26** (180 mg, 0.51 mmol) in CH_2Cl_2 (10 mL) was added. The resulting mixture was stirred for 30 min at the same temperature, and triethylamine (0.86 mL, 6.2 mmol) was then added. After the reaction mixture had been stirred for an additional 10 min, it was allowed to warm to 0 °C and quenched by addition of brine (3 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude aldehyde **44** was used immediately without purification for the next olefination step.

A solution of (i-PrO)$_2$P(O)CH_2CO_2Et (**46**) (486 □L, 2.0 mmol) in THF (7 mL) was treated at 0 °C with a 1 M solution of t-BuOK (1.9 mL, 3.8 equiv) in THF. After the mixture had been stirred for 2 h at the same temperature, it was cooled to □40 ~ □50 °C, and a solution of previously prepared **44** in THF (10 mL) was then added. The reaction mixture was allowed to slowly warm to 0 °C and quenched with aqueous saturated

NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were evaporated *in vacuo* to give the crude product. Purification by chromatography using 3:1 to 1:1 hexane–EtOAc afforded **47** (169 mg, 79%) as a colorless oil: R_f 0.57 (1:2 hexane–EtOAc); $[\alpha]_D$ = –18.30 (*c* 1.65, $CHCl_3$); IR (film) 3499, 1715, 1515 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.5 Hz, 3 H), 1.23 (s, 3 H), 1.26 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 1.41–1.53 (m, 2 H), 3.57 (d, *J* = 3.2 Hz, 1 H), 3.79 (s, 3 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 4.29 (d, A of AB q, *J* = 10.3 Hz, 1 H), 4.30 (dd, *J* = 4.9, 7.6 Hz, 1 H), 4.37 (d, B of AB q, *J* = 10.3 Hz, 1 H), 4.66 (ddd, *J* = 1.1, 3.2, 6.5 Hz, 1 H), 5.23 (s, 1 H), 6.21 (dd, *J* = 1.1, 15.7 Hz, 1 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 7.09 (dd, *J* = 6.5, 15.7 Hz, 1 H), 7.18 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.1, 14.2, 16.9, 17.2, 21.2, 55.2, 60.4, 62.1, 74.2, 80.9, 82.2, 87.7, 88.6, 111.7, 113.7, 123.9, 128.9, 129.4, 142.4, 159.3, 165.9; MS *m/z* 420 (M^+, 5), 136 (30), 134 (45), 121 (100), 109 (25); HRMS (M^+) calcd for $C_{23}H_{32}O_7$ 420.2148, found 420.2144.

The ^1H NMR spectral data of its epimer which was obtained in <5% yield: (360 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.5 Hz, 3 H), 1.22 (s, 3 H), 1.26 (s, 3 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 1.40–1.60 (m, 2 H), 3.80 (s, 3 H), 3.90 (d, *J* = 3.1 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 4.33 (d, A of AB q, *J* = 10.7 Hz, 1 H), 4.38 (dd, *J* = 4.7, 8.2 Hz, 1 H), 4.44 (d, B of AB q, *J* = 10.7 Hz, 1 H), 5.21 (s, 1 H), 5.53 (m, 1 H), 5.93 (dd, *J* = 1.6, 11.7 Hz, 2 H), 6.56 (dd, *J* = 7.0, 11.7 Hz, 1 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 7.16 (d, *J* = 8.6 Hz, 2 H).

(1*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-5,6-Dimethyl-7-ethyl-3-(3-hydroxyprop-1(*E*)-enyl)-4-(4-methoxybenzyloxy)-2,8-dioxabicyclo[3.3.0]octan-6-ol (48). To a solution of **47** (169 mg, 0.4 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added dropwise a 1 M solution of diisobutylaluminum hydride (0.9 mL) in hexane. After the mixture had been stirred for 2 h at the same temperature, it was allowed to warm to 0 °C, diluted with CH_2Cl_2 (50 mL), and quenched by addition of 1:1 MeOH–water (0.2 mL). The resulting gel was stirred for an additional 30 min and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. Purification of the crude product by chromatography using 1:2 hexane–EtOAc to EtOAc provided **48** (119 mg, 78%) as a white solid: R_f 0.46 (EtOAc); mp 123–125 °C; $[\alpha]_D$ = +10.90 (*c* 1.00, $CHCl_3$); IR (CH_2Cl_2) 3418, 1613, 1015 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.5 Hz, 3 H), 1.20 (s, 3 H), 1.23 (s, 3 H), 1.40–1.55 (m, 2 H), 2.01 (s, 3 H), 3.45 (d, *J* = 3.0 Hz, 1 H), 3.78 (s, 3 H), 4.11 (d, *J* = 4.1 Hz, 2 H), 4.32 (d, A of AB q, *J* = 10.7 Hz, 1 H), 4.33 (m, 1 H), 4.46 (d, B of AB q, *J* = 10.7 Hz, 1 H), 4.53 (dd, *J* = 3.0, 7.0 Hz, 1 H), 5.17 (s, 1 H), 5.95 (td, *J* = 7.0, 15.8 Hz, 1 H), 5.98 (td, *J* = 4.1, 15.8 Hz, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.2, 16.9, 17.1, 21.2, 55.2, 62.0, 62.7, 73.9, 80.9, 83.6, 87.6, 88.5, 111.2, 113.7, 126.4, 128.9, 129.4, 134.1, 159.1; MS *m/z* 297 (5), 171 (64), 121 (100); HRMS (M^+) calcd for $C_{21}H_{30}O_6$ 378.2042, found 378.2065.

(1*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-3-(3-Acetoxyprop-1(*E*)-enyl)-4,6-dihydroxy-5,6-dimethyl-7-ethyl-2,8-dioxabicyclo[3.3.0]octane (51). To a solution of **48** (10 mg, 0.026 mmol) in

CH_2Cl_2 (0.5 mL) were added pyridine (0.5 mL), acetic anhydride (50 μL, 0.52 mmol), and 4-(dimethylamino)pyridine (3.3 mg, 0.025 mmol). The resulting mixture was stirred for 3 h at room temperature. After solvents were evaporated *in vacuo*, the residue was dissolved in EtOAc (5 mL), washed with aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 hexane–EtOAc) to afford the acetate (9.63 mg, 91%) as a colorless oil: R_f 0.64 (1:4 hexane–EtOAc); $[\alpha]_D$ = –11.45 (*c* 1.45, $CHCl_3$); IR (film) 3485, 1739, 1514 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.4 Hz, 3 H), 1.21 (s, 3 H), 1.24 (s, 3 H), 1.43–1.56 (m, 2 H), 1.96 (s, 3 H), 3.46 (d, *J* = 3.0 Hz, 1 H), 3.80 (s, 3 H), 4.32 (d, A of AB q, *J* = 10.7Hz, 1 H), 4.37 (dd, *J* = 5.1, 7.6 Hz, 1 H), 4.46 (d, B of AB q, *J* = 10.7 Hz, 1 H), 4.53 (dd, *J* = 3.0, 6.5 Hz, 2 H), 4.55–4.60 (m, 2 H), 5.19 (s, 1 H), 5.97 (dd, *J* = 4.8, 15.7 Hz, 2 H), 5.99 (dd, *J* = 6.5, 15.7 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 7.21 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.2, 16.9, 17.1, 20.7, 21.2, 55.2, 62.0, 63.8, 73.9, 80.9, 83.4, 87.6, 88.5, 111.4, 113.7, 128.7, 128.7, 129.2, 129.4, 159.2, 170.6; MS *m/z* 171 (31), 149 (28), 131 (100), 121 (84); HRMS (M^+–CH_3) calcd for $C_{22}H_{29}O_7$ 405.1913, found 405.1928. Anal. Calcd for $C_{23}H_{32}O_7$: C, 65.7; H, 7.7. Found: C, 65.3; H, 7.7.

A solution of the resulting acetate (9.6 mg, 0.024 mmol) in 18:1 CH_2Cl_2–H_2O (10.5 mL) was treated with DDQ (16.4 mg, 0.072 mmol). The reaction mixture was stirred overnight at room temperature and quenched by addition of solid $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted by EtOAc (2 x 10 mL). The

combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography eluting with 1:4 hexane–EtOAc to afford **51** (6.63 mg, 92%) as a colorless oil: R_f 0.50 (1:4 hexane–EtOAc); $[\alpha]_D$ = +22.13 (*c* 0.24, $CHCl_3$); IR (film) 3453, 1727 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.05 (t, *J* = 7.5 Hz, 3 H), 1.18 (s, 3 H), 1.38 (s, 3 H), 1.52 (s, 1 H, O*H*), 1.53–1.59 (m, 2 H), 1.78 (d, 1 H, O*H*), 2.08 (s, 3 H), 3.70 (dd, *J* = 2.9, 4.8 Hz, 1 H), 4.28 (dd, *J* = 5.3, 7.4 Hz, 1 H), 4.64–4.70 (m, 3 H), 5.27 (s, 1 H), 5.82 (dd, *J* = 4.8, 15.7 Hz, 1 H), 6.09 (dtd, *J* = 1.3, 5.5, 15.7 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.2, 16.0, 17.9, 20.9, 21.6, 62.1, 64.0, 78.5, 80.9, 82.5, 89.6, 111.7, 127.6, 129.4, 170.7; MS *m/z* 182 (37), 157 (25), 127 (46), 125 (100); HRMS (M^+–$COCH_3$) calcd for $C_{13}H_{21}O_5$ 257.1389, found 257.1384.

(1*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-3-(3-Acetoxyprop-1(*E*)-enyl)-4,6-bis(trimethylsiloxy)-5,6-dimethyl-7-ethyl-2,8-dioxabicyclo[3.3.0]octane (52). 2,6-Lutidine (0.5 mL, 4.3 mmol) and TMSOTf (85 μL, 0.44 mmol) were added sequentially to a solution of **51** (6.6 mg, 0.022 mmol) in CH_2Cl_2 (5 mL) at –78 °C. The reaction mixture was stirred for 3 h at the same temperature, quenched with aqueous saturated NH_4Cl, and allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product. Purification of column chromatography using 5:1 hexane–EtOAc provided **52** (8.80 mg, 90%) as a colorless oil:

R_f 0.30 (5:1 hexane–EtOAc); $[\alpha]_D$ = +74.29 (*c* 0.07, $CHCl_3$); IR (film) 1743, 1462 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.12 (s, 9 H), 0.15 (s, 9 H), 1.03 (t, *J* = 7.5 Hz, 3 H), 1.12 (s, 3 H), 1.35 (s, 3 H), 1.36–1.48 (m, 2 H), 2.06 (s, 3 H), 3.84 (d, *J* = 3.9 Hz, 1 H), 4.21 (dd, *J* = 3.5, 8.9 Hz, 1 H), 4.56 (dd, *J* = 3.9, 8.0 Hz, 1 H), 4.59 (m, 2 H), 5.22 (s, 1 H), 5.83 (dt, *J* = 5.5, 15.6 Hz, 1 H), 5.96 (dd, *J* = 8.0, 15.6 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 0.8, 2.8, 11.5, 17.7, 18.1, 20.9, 22.7, 62.9, 64.0, 81.0, 84.9, 85.0, 90.2, 112.2, 128.2, 131.4, 170.7; MS *m/z* 301 (31), 245 (64), 231 (56), 214 (100), 158 (56); HRMS (M^+) calcd for $C_{21}H_{40}O_6Si_2$ 444.2363, found 444.2384.

Phosphonate 5:[3e] mp 138–140 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 1.87 (s, 3 H), 2.72 (dd, *J* = 7.5, 23.0 Hz,), 3.68 (dd, *J* = 10.8 Hz, 6 H), 3.75 (s, 3 H), 5.42 (s, 1 H), 6.36 (dd, *J* = 4.6, 15.3 Hz,), 6.50 (qd, *J* = 7.5, 15.3 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 8.6, 30.0 (d, *J* = 139 Hz), 52.7 (d, *J* = 8 Hz), 56.0, 89.0, 107.8, 123.0 (d, *J* = 15 Hz), 126.5 (d, *J* = 12 Hz), 152.8, 170.4.

Bis(trimethylsilyl) ether of asteltoxin (54). To a solution of **52** (8.44 mg, 0.019 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added a 1 M solution of diisobutylaluminum hydride (42 μL) in hexane. After the reaction mixture had been stirred for 2 h at the same temperature, it was allowed to warm to –10 °C and diluted with 10 mL of CH_2Cl_2, followed by addition of 1:1 MeOH–water (50 μL). The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure.

Purification of the concentrate by chromatography using 2:1 hexane–EtOAc provided the corresponding alcohol (7.18 mg, 94%) as a colorless oil: R_f 0.25 (2:1 hexane–EtOAc); $[\alpha]_D$ = +14.2 (*c* 0.16, $CHCl_3$): IR (film) 3425 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.13 (s, 9 H), 0.15 (s, 9 H), 1.03 (t, *J* = 7.5 Hz, 3 H), 1.12 (s, 3 H), 1.35 (s, 3 H), 1.38–1.49 (m, 2 H), 3.84 (d, *J* = 3.8 Hz, 1 H), 4.19 (d, *J* = 3.2 Hz, 2 H), 4.22 (dd, *J* = 3.5, 8.8 Hz, 1 H), 4.57 (dd, *J* = 3.8, 7.1 Hz, 1 H), 5.22 (s, 1H), 5.81–5.99 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 0.8 (2 C's), 2.8, 11.5, 17.6, 18.1, 22.7, 63.0, 81.0, 84.9, 85.2, 90.2, 112.2, 128.7, 133.7; MS *m/z* 301 (33), 245 (60), 231 (71), 172 (100), 143 (86); HRMS (M^+–OH) calcd for $C_{19}H_{37}O_4Si_2$ 385.2230, found 385.2218.

A solution of the allylic alcohol (6.83 mg, 0.017 mmol) in CH_2Cl_2 (2 mL) was treated with 30 mg (20 equiv) of MnO_2. The reaction mixture was stirred at room temperature for 5 h and filtered through a short column of silica gel. The filtrate was concentrated *in vacuo* to give crude aldehyde **53**, which was used immediately without further purification for the next step.

A solution of phosphonate **5** (49 mg, 0.17 mmol) in THF (1 mL) was treated at –78 °C with LiHMDS (153 μL, a 1.0 M solution in THF). After the solution had been stirred for 4 h, a solution of crude aldehyde **53** in THF (1 mL) was added via a cannula. The reaction mixture was then stirred for 5 h at the same temperature and quenched by addition of aqueous saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 x 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the crude product by chromatography using 2:1 hexane–EtOAc provided TMS-protected asteltoxin

54 (8.4 mg, 88% in two steps): R_f 0.21 (2:1hexane□EtOAc); $[\alpha]_D$ = +61.1 (*c* 0.2, $CHCl_3$); IR (film) 1721, 1710, 1453 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) □ 0.11 (s, 9 H), 0.15 (s, 9 H), 1.03 (t, *J* = 7.5 Hz, 3 H), 1.13 (s, 3 H), 1.35 (s, 3 H), 1.96 (s, 3 H), 3.83 (s, 3 H), 3.84 (d, *J* = 3.8 Hz, 1 H), 4.22 (dd,, *J* = 3.5, 8.9 Hz, 1 H), 4.61 (dd, *J* = 3.8, 7.9 Hz, 1 H), 5.24 (s, 1H), 5.49 (s, 1 H), 5.96 (dd, *J* = 7.9, 15.3, Hz, 1 H), 6.29□6.40 (m, 2 H), 6.36 (d, *J* = 15.0 Hz, 1 H), 6.50 (dd, *J* = 10.5, 14.8 Hz, 1 H), 7.20 (dd, *J* = 11.2, 15.0 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) □ 0.9, 2.8, 8.9, 11.5, 17.7, 18.1, 22.7, 56.1, 63.1, 81.3, 85.0, 85.2, 88.9, 90.2, 108.0, 112.3, 119.5, 132.1, 132.8, 133.8, 135.8, 137.2, 154.3, 163.5, 170.5; MS *m/z* 562 (13), 332 (29), 319 (100), 293 (33), 158 (48); HRMS (M^+) calcd for $C_{29}H_{46}O_7Si_2$ 562.2782, found 562.2762.

Asteltoxin ((+)-1). To a solution of **54** (7.9 mg, 0.014 mmol) in THF (5 mL) at 0 °C was added a solution of a 1 M tetrabutylammonium fluoride (31 □L) in THF. The reaction mixture was stirred at 4 °C for 1.5 days and quenched with aqueous saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by chromatography using a 3:2 CH_2Cl_2□EtOAc solution gave asteltoxin **1** (5.09 mg, 87%): R_f 0.12 (3:2 CH_2Cl_2□EtOAc); $[\alpha]_D$ = +21.3 (*c* 0.06, MeOH) {lit[1a,7b] $[\alpha]_D$ = +20.0 (*c* 1.15, MeOH)}; IR (CH_2Cl_2) 3434, 1727, 1692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) □ 1.06 (t, *J* = 7.5 Hz, 3 H), 1.19 (s, 3 H), 1.39 (s, 3 H), 1.51□1.62 (m, 2 H), 1.76 (d, *J* = 4.8 Hz, 1 H, O*H*), 1.97 (s, 3 H), 3.73 (dd, *J*

= 3.0, 4.8 Hz, 1 H), 3.83 (s, 3 H), 4.30 (dd, *J* = 5.2, 7.5 Hz, 1 H), 4.75 (m, 1 H), 5.29 (s, 1 H), 5.50 (s, 1 H), 5.87 (dd, *J* = 5.0, 15.2 Hz, 1 H), 6.39 (d, *J* = 15.0 Hz, 1 H), 6.41 (dd, *J* = 11.0, 14.7 Hz, 1 H), 6.51 (dd, *J* = 10.8, 14.7 Hz, 1 H), 6.65 (ddd, *J* = 1.5, 10.8, 15.2 Hz, 1 H), 7.18 (dd, *J* = 11.0, 15.0 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) □ 8.9, 11.2, 16.0, 17.9, 21.6, 56.2, 62.1, 78.6, 80.9, 83.0, 89.0, 89.7, 108.4, 111.7, 120.2, 129.2, 132.8, 134.0, 135.3, 136.2, 154.1, 163.6, 170.5; MS *m/z* 247 (8), 219 (9), 171 (27), 121 (100); HRMS (M^+) calcd for $C_{23}H_{30}O_7$ 418.1992, found 418.1998.