Formal Synthesis of (□)- Apicularen A

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Supporting Information

General Procedures

All moisture- and air-sensitive reactions were carried out in flame- or oven-dried glassware using magnetic stirring under a positive pressure of nitrogen or argon gas. Thin layer chromatography was performed on Whatman silica gel PE SIL G/UV plates. Concentration *in vacuo* was performed using a Büchi rotary evaporator. Flash chromatography was performed on EM Science 230-400 mesh silica gel. Melting points were determined using an Electrothermal apparatus and are reported uncorrected. Infrared spectra were recorded on a MIDAC Grams/Prospect FT-IR. NMR spectra were recorded on a Bruker DXR 500 and a Bruker DRX 400 MHz FTNMR instruments. Proton NMR spectra were obtained using CDCl₃ as solvent, unless otherwise noted, and referenced to residual protiated solvent (□ 7.26 ppm) or to a TMS standard (□ 0.0 ppm). Carbon NMR spectra were recorded in ppm relative to the residual solvent signal: CDCl₃ (□ 77.00 ppm). Mass spectra were determined on an AE2-MS 30, a PG 7070E-HF, a CG Analytical 7070E, or a Fisons autospec spectrometer. Optical rotations were measured with a Jasco DIP-370 digital polarimeter. Tetrahydrofuran, diethylether, toluene and methylene chloride were dried by filtration through alumina according to the procedure by Grubbs.¹ Capillary GC analysis was performed on a Hewlett Packard Model 6890

¹ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*, **1996**, *15*, 1518-1520.

instrument equipped with a FID detector. Chiral capillary GC analysis was performed on a Hewlett Packard Model 5890 instrument equipped with a FID detector and beta-cyclodextrin permethylated hydroxypropyl column. All reagents were purchased from Aldrich Chemical Co. or Acros and were used as received, unless otherwise stated. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ).

12

Chloride 12. To a cooled solution ($-78\text{ }^{\circ}\text{C}$) of *E*-1-tributylstannyl-2-trimethylsilylethylene **11** (12.06 g, 30.98 mmol) dissolved in THF (300 mL) was added dropwise *n*-BuLi (12.5 mL, 31.3 mmol, 2.50 M in hexane). The mixture was stirred for 20 min. To the reaction was added sequentially $\text{BF}_3\cdot\text{OEt}_2$ (4.885 g, 34.4 mmol) and (*R*)-epichlorohydrin (3.037 g, 32.83 mmol). The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for another 60 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (300 mL). The aqueous layer was extracted with ethyl acetate (3 $\times$ 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to give an unpurified oil. Purification on silica gel (8% ethyl acetate/hexane) provided **12** as a clear oil (3.574 g, 60%): IR (neat) 3399, 2955, 2899, 1618, 1430, 1248, 1059, 993 cm^{-1} ; $[\alpha]_D^{23} +2.9$ (*c* 0.74, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 6.00 (ddd, $J = 18.5, 6.5, 6.5$ Hz 1H), 5.80 (d, $J = 18.5$ Hz, 1H), 3.89 (br s, 1H), 3.61 (dd, $J = 16.5, 5.5$ Hz 1H), 3.47 (dd, $J = 11.0, 6.5$ Hz, 1H), 2.40 (dd, $J = 7.0, 7.0$ Hz, 2H), 2.25 (s, 1H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.8, 135.2, 70.5, 49.5, 41.6, -1.3 ; HRMS (CI/ NH_3) m/z calcd for $\text{C}_8\text{H}_{17}\text{ClOSi}$ $[\text{M}]^+$ 192.0737, found: 192.0730.

13

Iodide 13. Alcohol **12** (2.35 g, 12.2 mmol) was dissolved in acetone (100 mL) and had

NaI added (80 g, 540 mmol). The reaction was heated to reflux for 6 d. The reaction was cooled to room temperature then diluted with ether (300 mL). The organic layer was washed with water (2 $\times$ 150 mL) then brine (100 mL). The combined aqueous layers were extracted with ether (3 $\times$ 200 mL). The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo* to give an unpurified oil. Purification on silica gel (5% ethyl acetate/hexane) provided **13** as a clear oil (3.43 g, 99%): IR (neat) 3424, 2956, 2913, 2878, 1618, 1247, 1042, 839 cm⁻¹; [α]_D²³ +6.8 (*c* 0.50, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 5.98 (ddd, *J* = 18.5, 6.5, 6.5 Hz, 1H), 5.80 (d, *J* = 18.5 Hz, 1H), 3.63 (m, 1H), 3.35 (dd, *J* = 10.0, 4.0, 1H), 3.22 (dd, *J* = 10.0, 6.5 Hz, 1H), 2.40 (dd, *J* = 6.5, 6.5 Hz, 2H), 2.11 (d, *J* = 5.5, 1H), 0.05 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 140.9, 135.3, 70.0, 43.8, 14.9, -1.3. HRMS (CI/NH₃) *m/z* calcd for C₇H₁₄IOSi [M-CH₃]⁺ 268.9859, found: 268.9857.

10

Iodide 10. Alcohol **13** (3.08 g, 10.8 mmol) was dissolved in CH₂Cl₂ (60 mL) and cooled to 0 °C. To the solution was added Et₃N (5 mL) then TESOTf (3.02 g, 11.4 mmol). The solution was stirred at 0 °C for 0.5 h, warmed to room temperature and stirred another 8 h. The reaction was quenched with saturated aqueous NH₄Cl (20 mL) and diluted with hexane (100 mL). The organic layer was washed with water (4 $\times$ 25 mL) then brine (20 mL). The combined aqueous layers were extracted with hexane (50 mL). The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo* to give an unpurified oil. Purification on silica gel (hexane) provided **10** as a clear oil (4.27 g, 99%): IR (neat) 2956, 2910, 2879, 1617, 1414, 1246, 1069, 1005 cm⁻¹; [α]_D²³ δ 4.0 (*c* 1.00, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 5.98 (ddd, *J* = 18.5, 6.5, 6.5 Hz, 1H), 5.76 (d, *J* = 18.5 Hz, 1H), 3.67 (dd, *J* = 5.5, 5.5, 1H), 3.17 (dd, *J* = 10.0, 4.0, 1H), 2.46 (dd, *J* = 14.0, 7.0 Hz,

1H), 2.36 (dd, $J = 14.0, 6.5$ Hz, 2H), 0.97 (t, $J = 8.0$, 9H), 0.62 (q, $J = 8.0$, 6H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.9, 134.2, 71.4, 44.4, 40.9, 6.9, 5.1, -1.3. HRMS (CI/NH_4^+) m/z calcd for $\text{C}_{14}\text{H}_{32}\text{IOSi}_2$ $[\text{M}+\text{H}]^+$ 399.1036, found: 399.1033.

15

Alcohol 15. A solution of benzeneruthenium(II) chloride dimer (54 mg, 0.11 mmol) and (R)-BINAP (134 mg, 0.22 mmol) in dry DMF (5 mL) was degassed by allowing argon to bubble through for 20 min. The slurry was heated to 100 °C for 10 min. The solution was allowed to cool then added via syringe to a Parr bomb containing a degassed solution of ketoester **14** (20.0 g, 79.7 mmol) in ethanol (ca. 100 mL). The bomb was pressurized with hydrogen gas (1200 psi). The apparatus was warmed to 60 °C for 4 d. The apparatus was cooled to room temperature and the bomb was vented. The solution was concentrated *in vacuo* to give an unpurified oil. Purification on silica gel (25% ethyl acetate/hexane) provided **15** as a clear oil (19.35 g, 96%): IR (neat) 3450, 2931, 2859, 1728 cm^{-1} ; $[\alpha]_D^{23}$ 11.8 (c 1.04, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.25-7.37 (m, 5H), 4.52 (s, 2H), 4.20-4.28 (m, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 3.69 (ddd, $J = 9.4, 6.4, 5.3$ Hz, 1H), 3.65 (ddd, $J = 9.4, 6.6, 5.4$ Hz, 1H), 3.39-3.42 (m, 1H), 2.49 (d, $J = 6.3$ Hz, 2H), 1.75-1.86 (m, 2H), 1.26 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.4, 138.0, 128.4, 127.7, 127.6, 73.2, 67.9, 66.9, 60.6, 41.5, 36.0, 14.1; HRMS (CI/NH_3) m/z calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 253.1144, found: 253.1442.

9a, 9b

Cyanohydrin acetonide 9. To a cooled solution (0 °C) of alcohol **15** (2.963 g, 11.75 mmol) and dry Et_3N (5 mL) in CH_2Cl_2 (100 mL) was added dropwise a solution of

trimethylsilyl chloride (1.31 g, 12.1 mmol) in CH₂Cl₂ (5 mL). The mixture was warmed to room temperature and was stirred for 4 h. The reaction was diluted with CH₂Cl₂ (100 mL) then washed with water (2 × 50 mL) and brine (30 mL). The organic phase was dried over Na₂SO₄ and concentrated *in vacuo* to provide the TMS ether as a clear oil. To a cooled (−78 °C) solution of the TMS ether of **15** (3.814 g, 11.75 mmol) in ethyl ether (50 mL) was added DIBALH (12.3 mL, 12.3 mmol, 1.0 M in toluene) dropwise over 15 min. The solution was stirred for 2 h then 0.5 mL ethyl formate was added and stirred an additional 10 min while warming to 0 °C. A saturated aqueous solution of Rochelles salt (75 mL) was added. The mixture warmed to room temperature and stirred 2 h. The aqueous layer was extracted with ethyl ether (3 × 50 mL). The combined organic phases were washed with brine (20 mL), dried over Na₂SO₄, and concentrated *in vacuo* to give an unpurified oil which was immediately dissolved in CH₂Cl₂ (3 mL) and cooled to 0 °C. A few crystals of 18 crown 6/KCN complex were added then TMSCN was added dropwise over 10 min. The mixture was warmed to room temperature and was stirred for 12 h. CSA (57 mg), acetone and dimethoxypropane (50 mL, 4:1) were added and stirring was continued for 1 d. To the mixture was added Et₃N (0.5 mL) then concentrated *in vacuo* to give 3.15 g of an unpurified oil. Purification on silica gel (7% ethyl acetate/hexane) provided a 1:1 mixture of *cis/trans* **9** as a clear oil (2.58 g, 80%) (the isomers can be separated by flash chromatography for characterization): IR (neat) 2996, 2928, 2870, 1455, 1383, 1263, 1204, 1129, 1093, 996 cm^{−1}; *anti*-diastereomer (**9b**); [α]_D²³ +26.3 (*c* 1.44, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.28-7.37 (m, 5H), 4.75 (m, 1H), 4.48 (dd, *J* = 19.1, 11.9 Hz, 2H), 4.08 (ddd, *J* = 13.4, 7.3, 5.1 Hz, 1H), 3.58 (ddd, *J* = 9.5, 8.0, 5.4 Hz, 1H), 3.48 (ddd, *J* = 11.7, 10.8, 5.4 Hz, 1H), 1.72-1.83 (m, 4H), 1.42 (s, 3H), 1.41 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 138.2, 128.4, 127.69, 127.68, 117.8, 100.0, 73.1, 65.3, 65.0, 59.1, 35.9, 34.5, 29.6, 19.2; HRMS (CI/NH₃) *m/z* calcd for C₁₆H₂₂NO₃ [M+H]⁺ 276.1601, found: 276.1596; *syn*-diastereomer (**9a**); [α]_D²³ +43.8 (*c* 1.41, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.28-7.37 (m, 5H), 4.83 (dd, *J* = 6.4, 2.4

Hz, 1H), 4.51 (s, 2H), 4.35 (dddd, $J = 9.0, 9.0, 5.1, 2.9$ Hz, 1H), 3.51-3.61 (m, 2H), 1.90 (ddd, $J = 13.5, 11.3, 6.4$ Hz, 1H), 1.78-1.84 (m, 3H), 1.66 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.2, 128.4, 128.3, 127.7, 119.9, 100.9, 73.1, 65.5, 62.9, 58.8, 35.8, 33.3, 29.8, 21.8; HRMS (CI/ NH_3) m/z calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 276.1601, found: 276.1598.

8

Nitrile 8. To a stirred solution of cyanohydrin acetone **9** (1.182 g, 4.29 mmol) and iodide **10** (1.482 g, 3.72 mmol) in THF (20 mL) at -78 °C was added DMPU (0.924 g, 7.2 mmol) and then 11.5 mL of an 0.4 M (4.6 mmol) LDA solution (in THF) prepared from freshly distilled diisopropyl amine and *n*-BuLi (2.50 M in hexane). The resulting pink mixture was stirred at -78 °C for 50 min then was warmed to -40 °C and stirred for 8 h. The reaction was quenched with saturated aqueous NH_4Cl (100 mL). The aqueous layer was extracted with ethyl acetate (3 $\times$ 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to give an unpurified oil. Purification on silica gel (3% ethyl acetate/hexane) provided **8** as a clear oil (1.877 g, 92%): IR (neat) 3086, 3028, 2953, 1602, 1495, 1454, 1383, 1248, 1205, 863 cm^{-1} ; $[\alpha]_D^{23} +30.7$ (c 1.47, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.28-7.38 (m, 5H), 6.03 (dt, $J = 18.5, 6.6$ Hz, 1H), 5.74 (dt, $J = 18.6, 1.2$ Hz, 1H), 4.52 (s, 2H), 4.36 (dddd, $J = 12.5, 6.1, 6.1, 1.7$ Hz, 1H), 4.13 (dddd $J = 5.6, 5.6, 5.4, 5.4$ Hz, 1H), 3.50-3.60 (m, 2H), 2.48 (ddd, $J = 13.9, 7.3, 6.6$ Hz, 1H), 2.34 (ddd, $J = 13.9, 7.0, 6.8$ Hz, 1H), 1.98, (dd, $J = 14.7, 5.1$ Hz, 1H), 1.92 (dd, $J = 10.0, 5.4$ Hz, 1H), 1.76 (m, 3H), 1.69 (s, 3H), 1.68 (dd, $J = 13.4, 11.5$ Hz, 1H), 1.38 (s, 3H), 0.97 (t, $J = 10.1$ Hz, 9H), 0.63 (q, $J = 10.1$ Hz, 6H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.4, 138.3, 133.9, 128.4, 127.7, 127.6, 122.1, 101.1, 73.1, 68.3,

67.4, 65.7, 63.7, 49.1, 45.8, 39.4, 35.9, 30.9, 21.5, 6.9, 5.1, -1.3; HRMS (CI/NH₃) *m/z* calcd for C₃₀H₅₂NO₄Si₂ [M+H]⁺ 546.3435, found: 546.3428.

16

Alcohol 16. To a solution of ammonia (ca. 100 mL), condensed into a flask and cooled to -78 °C, was added lithium wire (ca. 350 mg, 50 mmol). The solution turned deep blue. After all the lithium has dissolved, THF was added to the solution (70 mL). To the reaction mixture was added rapidly a solution of nitrile **8** (2.40 g, 4.40 mmol) dissolved in THF (20 mL). The reaction was stirred at -78 °C for 15 min then 3 mL of isoprene was added. The solution was immediately poured onto saturated aqueous NH₄Cl (500 mL) (violent bubbling occurs due to rapid boiling of ammonia). The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo* to give an unpurified oil. Purification on silica gel (15% ethyl acetate/hexane) provided **16** as a clear oil (1.668 g, 88%): IR (neat) 3419, 2993, 2952, 2879, 1617, 1380, 1248, 1005, 838 cm⁻¹; [α]_D²³ +8.9 (*c* 1.77, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.02 (ddd, *J* = 18.6, 6.6, 6.6 Hz, 1H), 5.67 (d, *J* = 18.6 Hz, 1H), 4.08 (dddd, *J* = 11.7, 7.3, 4.9, 2.2 Hz, 1H), 3.99 (dddd, *J* = 11.5, 5.9, 5.9, 2.2 Hz, 1H), 3.87 (dddd, *J* = 6.1, 6.1, 5.9, 5.9 Hz, 1H), 3.78 (m, 2H), 2.50 (br. s, 1H), 2.29 (m, 2H), 1.72 (m, 3H), 1.51 (dt, *J* = 13.9, 5.9 Hz, 1H), 1.47-1.50 (m, 1H), 1.45 (s, 3H), 1.35 (s, 3H), 1.27 (ddd, *J* = 12.7, 11.5, 11.5 Hz, 1H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.58 (q, *J* = 8.0 Hz, 6H), 0.03 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 143.3, 134.0, 98.5, 69.5, 68.5, 65.9, 61.0, 45.0, 43.9, 38.1, 37.0, 30.2, 19.8, 6.9, 5.1, -1.3; HRMS (CI/NH₃) *m/z* calcd for C₂₂H₄₇O₄Si₂ [M+H]⁺ 431.3013, found: 431.3017.

7a, 7b

Acetal 7. To a cooled (0 °C) solution of Dess-Martin periodinane (1.56 g, 3.67 mmol) dissolved in CH₂Cl₂ (80 mL) was added alcohol **16** (1.207 g, 2.80 mmol) dissolved in CH₂Cl₂ (10 mL). The solution was stirred at 0 °C for 20 min, then warmed to room temperature, and stirred 3 h. The reaction was quenched with 1 N NaOH (50 mL) and was stirred until the organic layer became clear. The aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo* to provide an unpurified oil. The residue was dissolved in methanol (30 mL) and DOWEX[®] 50X8-100 (ca. 1 g) was added. The mixture was stirred for 8 h. The resulting mixture was filtered to remove the resin, rinsing with methanol, while the filtrate was treated with Et₃N (3 mL). The organic phase was concentrated *in vacuo* to provide an oil. The oil was dissolved in CH₂Cl₂ (70 mL) and cooled to 0 °C. To the solution was added pyridine (4 mL), DMAP (30 mg, 0.2 mmol), then trifluoroacetic anhydride (1.26 g, 6.0 mmol) dropwise. The solution was stirred at 0 °C for 10 min, warmed to room temperature, and stirred another 8 h. The reaction was quenched with saturated aqueous sodium bicarbonate (50 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo* to give an unpurified oil. Purification on silica gel (10% ethyl acetate/hexane) provided **7** as a white solid (1.194 g, 89%): IR (neat) 2960, 2904, 2850, 1785, 1385, 1335, 1219, 1185, 1081, 1055, 839 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) major diastereomer (*syn*) δ 5.95 (ddd, *J* = 18.4, 7.2, 5.7 Hz, 1H), 5.82 (d, *J* = 18.4 Hz, 1H), 5.57 (dddd, *J* = 7.6, 7.6, 5.5, 5.5 Hz, 1H), 5.49 (ddd, *J* = 5.9, 2.9, 2.9 Hz, 1H), 4.55 (dd, *J* = 9.7, 1.9 Hz, 1H), 3.78 (dddd, *J* = 11.5, 9.6, 5.6, 2.2 Hz, 1H), 3.54 (s, 3H), 2.58 (dddd, *J* = 14.1, 6.0, 5.6, 1.0 Hz, 1H), 2.49 (ddd, *J* = 14.1, 7.6, 7.6 Hz, 1H), 2.13 (dq,

$J = 14.5, 2.0$ Hz, 1H), 1.84 (dd, $J = 7.6, 5.7$ Hz, 2H), 1.67 (dq, $J = 14.5, 2.0$ Hz, 1H), 1.75 (dddd, $J = 9.8, 9.8, 3.1, 3.1$ Hz, 1H), 1.66 (dddd, $J = 11.5, 11.5, 2.7, 2.7$ Hz, 1H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.9 (d, $J = 43$ Hz), 156.5 (d, $J = 43$ Hz), 139.1, 136.3, 114.4 (d, $J = 286$ Hz), 114.2 (d, $J = 286$ Hz), 99.1, 73.9, 73.5, 65.9, 56.6, 42.0, 39.3, 34.9, 34.6, -1.6 ; HRMS (CI/ NH_3) m/z calcd for $\text{C}_{18}\text{H}_{30}\text{F}_6\text{O}_6\text{SiN}$ $[\text{M}+\text{NH}_4]^+$ 498.1747, found: 498.1740.

6

Diene 6. To a cooled ($0\text{ }^\circ\text{C}$) solution of bis-trifluoroacetate **7** (750 mg, 1.56 mmol) in CH_3CN (50 mL) and 2,4-pentadienyltrimethylsilane² (710 mg, 5.06 mmol) was added $\text{BF}_3\cdot\text{OEt}_2$ (664 mg, 4.68 mmol) dropwise. The solution was stirred for 1 h at $0\text{ }^\circ\text{C}$ then quenched by addition of saturated aqueous potassium carbonate (30 mL) and methanol (10 mL). The biphasic solution was stirred vigorously for 4 h. The aqueous layer was extracted with ethyl acetate (3 $\times$ 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to provide an unpurified oil. Purification on silica gel (50% ethyl acetate/hexane) provided **6** as a clear oil (497 mg, 98%): IR (neat) 3367, 2941, 2919, 1617, 1418, 1318, 1246, 1092, 1003, 899 cm^{-1} ; $[\alpha]_D^{23}$ -9.5 (c 0.64, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 6.31 (dt, $J = 17.1, 10.2$ Hz, 1H), 6.11 (dd, $J = 15.2, 10.5$ Hz, 1H), 6.01 (dt, $J = 18.6, 6.6$ Hz, 1H), 5.73 (d, $J = 18.6$ Hz, 1H), 5.65 (dt, $J = 14.9, 7.6$ Hz, 1H), 5.11 (d, $J = 17.1$ Hz, 1H), 5.0 (d, $J = 11.2$ Hz, 1H), 4.29 (dddd, $J = 11.2, 8.0, 7.8, 3.6$ Hz, 1H), 3.95 (dddd, $J = 9.3, 9.3, 4.4, 4.4$ Hz, 1H), 3.84 (dddd, $J = 9.0, 6.1, 6.1, 2.7$ Hz, 1H), 3.80 (m, 1H), 2.45 (ddd, $J = 14.4, 7.3, 7.3$ Hz, 1H), 2.22-2.35 (m, 3H), 1.96 (dddd, $J = 13.0, 4.2, 4.2, 1.2$ Hz, 2H), 1.86 (dddd, $J = 14.4, 11.0, 9.3$ Hz, 1H), 1.77 (dddd,

² Seyferth, D.; Pornet, P.; Weinstein, R. *Organomet.* **1982**, 1651-1658.

$J = 13.0, 4.2, 4.2, 1.7$ Hz, 2H), 1.66 (dddd, $J = 9.5, 9.5, 5.4, 5.4$ Hz, 1H), 1.39 (dt, $J = 14.7, 2.9$ Hz, 1H), 1.31 (ddd, $J = 13.0, 9.3, 9.3$ Hz, 1H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.7, 136.8, 133.9, 133.7, 130.0, 115.9, 71.9, 71.4, 69.2, 64.4, 44.6, 39.2, 38.9, 38.7, 37.9, -1.2; HRMS (CI/ NH_3) m/z calcd for $\text{C}_{18}\text{H}_{33}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 325.2199, found: 325.2191.

5

Arylbromide 5. Diene **6** (25 mg, 0.077 mmol), methyl 3-bromopropiolate (125 mg, 0.77 mmol), and Otera's distannoxane catalyst **17**³ (16 mg) were dissolved in toluene (2 mL) in a resealable tube. The solution was cycled through a freeze/pump/thaw sequence three times. The sealed tube was heated to 110 °C for 12 h. The reaction tube was cooled to room temperature and back filled with argon. To the reaction mixture was concentrated *in vacuo* and the residue run through a plug of silica (10% ethyl acetate/hexane). The fraction was concentrated *in vacuo* and the residue taken up in toluene (3 mL). To the reaction mixture was added DDQ (45 mg, 0.20 mmol). The reaction was heated to 100 °C stirred for 10 h then concentrated *in vacuo* to provide an unpurified oil. The residue was run through a plug of silica (10% ethyl acetate/hexane). The collected fraction was concentrated *in vacuo* and the residue taken up in methanol (2 mL) and treated with NaOH (ca. 5 mg). The mixture was stirred for 10 min then concentrated *in vacuo* and the residue taken up in CH_2Cl_2 (2 mL). To the solution was added Et_3N (0.1 mL), and TBSOTf (20 mg, 0.077 mmol). The solution was stirred for 1 h. The reaction was quenched with saturated aqueous sodium bicarbonate (5 mL). The aqueous layer was

³ Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, 27, 2383.

extracted with ethyl acetate (3 $\times$ 3 mL). The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo* to give an unpurified oil. Purification on silica gel (10% ethyl acetate/hexane) provided **5** as a clear oil (19 mg, 44%): IR (neat) 2956, 2921, 2856, 1733, 1560, 1411, 1389, 1212, 1117, 867 cm⁻¹; [α]_D²³ +3.1 (*c* 1.00, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.41 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.12 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.14 (dt, *J* = 18.6, 6.6 Hz, 1H), 5.80 (dd, *J* = 18.6, 1.2 Hz, 1H), 5.66 (dddd, *J* = 11.9, 8.3, 4.6, 3.4 Hz, 1H), 4.36 (ddd, *J* = 9.5, 9.5, 2.7 Hz, 1H), 4.08 (dddd, *J* = 5.9, 5.9, 3.9, 3.9 Hz, 1H), 3.96 (dddd, *J* = 11.2, 6.1, 4.1, 1.5 Hz, 1H), 3.67 (dd, *J* = 14.7, 11.2 Hz, 1H), 2.60 (dddd, *J* = 14.7, 8.5, 5.9, 1.2 Hz, 1H), 2.40 (m, 2H), 1.93 (ddd, *J* = 13.4, 6.4, 3.7 Hz, 1H), 1.78 (ddd, *J* = 14.9, 11.2, 10.0 Hz, 1H), 1.58-1.65 (m, 3H), 1.49 (dd, *J* = 12.3, 3.7 Hz, 1H), 0.92 (s, 9H), 0.06 (s, 6H), 0.05 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 168.9, 141.5, 140.4, 137.5, 133.6, 130.5, 130.2, 129.4, 118.7, 74.5, 74.2, 65.3, 64.6, 42.0, 39.8, 39.5, 39.0, 37.5, 25.8, 17.9, -1.2, -4.8; HRMS (CI/NH₃) *m/z* calcd for C₂₇H₄₃O₄Si₂Br [M]⁺ 566.1883, found: 566.1871.

20

Phenol 20. To a cooled (-78 °C) solution of arylbromide **5** (11 mg, 0.019 mmol) in THF (2 mL) was added *n*-BuLi (12 μ L, 0.019 mmol, 1.60 M in hexanes) then after ca. 5 sec trimethylsilylperoxide (20 mg, 0.11 mmol) was added. The solution was stirred for 10 min then was quenched by addition of saturated aqueous NH₄Cl solution (3 mL). The aqueous layer was extracted with ethyl acetate (2 $\times$ 2 mL). The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo* to provide an unpurified oil. Purification on silica gel (2% ethyl acetate/hexane) provided **20** as clear oil (5 mg, 50%): IR (neat) 3435, 2954, 2854, 1732, 1619, 1559, 1437, 1260, 1100, 864 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.18 (dd, *J* = 8.1, 7.8 Hz, 1H), 7.14 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.12

(dd, $J = 7.8, 0.9$ Hz, 1H), 6.03 (ddd, $J = 18.6, 7.3, 5.4$ Hz, 1H), 5.88 (s, 1H), 5.80 (dd, $J = 18.6, 1.5$ Hz, 1H), 5.60 (dddd, $J = 11.9, 8.3, 4.9, 3.2$ Hz, 1H), 4.36 (ddd, $J = 9.5, 9.5, 3.9$ Hz, 1H), 4.03 (dddd, $J = 5.6, 5.6, 4.4, 4.4$ Hz, 1H), 3.79 (dddd, $J = 11.0, 6.4, 4.7, 1.7$ Hz, 1H), 3.65 (dd, $J = 13.7, 11.5$ Hz, 1H), 2.48 (m, 2H), 2.35 (dd, $J = 13.7, 2.0$ Hz, 1H), 1.88 (ddd, $J = 13.2, 5.6, 4.2$ Hz, 1H), 1.61-1.76 (m, 4H), 1.52 (ddd, $J = 12.9, 5.4, 4.1$ Hz, 1H), 0.90 (s, 9H), 0.08 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.5, 152.9, 141.4, 139.2, 134.8, 131.1, 122.5, 122.3, 115.3, 74.3, 73.2, 65.5, 65.2, 41.9, 40.8, 40.5, 38.3, 37.1, 25.8, 18.0, δ 1.3, δ 4.8; HRMS (ESI) m/z calcd for $\text{C}_{27}\text{H}_{44}\text{O}_5\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 527.2625, found: 527.2622.

21

Acetate 21. To a solution of phenol **20** (4.2 mg, 7.9 μmol), pyridine (20 μL), and DMAP (1 mg, 0.01 mmol) dissolved in CH_2Cl_2 (1 mL) was added acetic anhydride (10 mg, 0.1 mmol). The mixture was stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 1 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to provide an unpurified oil. Purification on silica gel (10% ethyl acetate/hexane) provided **21** as clear oil (4.1 mg, 94%): IR (neat) 2954, 2929, 2856, 1773, 1725, 1617, 1463, 1366, 1250, 1200, 1111, 1081, 840 cm^{-1} ; $[\alpha]_D^{23}$ δ 7.0 (c 0.20, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.30 (dd, $J = 8.1, 7.8$ Hz, 1H), 7.04 (d, $J = 7.8$ Hz, 1H), 7.03 (d, $J = 8.1$ Hz, 1H), 6.00 (dt, $J = 18.4, 7.6$ Hz, 1H), 5.80 (dd, $J = 18.6, 1.2$ Hz, 1H), 5.63 (dddd, $J = 9.3, 6.8, 6.8, 4.1$ Hz, 1H), 4.36 (ddd, $J = 9.5, 9.5, 3.4$ Hz, 1H), 4.03 (dddd, $J = 9.0, 6.4, 4.4, 2.7$ Hz, 1H), 3.88 (dddd, $J = 11.2, 6.1, 4.2, 1.7$ Hz, 1H), 3.60 (dd, $J = 13.9, 10.5$ Hz, 1H), 2.50 (dddd, $J = 14.1, 7.5, 5.9, 1.4$ Hz, 1H), 2.43 (dd, $J = 13.2, 2.0$ Hz, 1H), 2.38 (dddd, $J = 14.2, 8.2,$

7.0, 1.4 Hz, 1H), 2.22 (s, 3H), 1.90 (ddd, $J = 13.0, 5.6, 4.0$ Hz, 1H), 1.73 (ddd, $J = 15.1, 11.0, 11.0$ Hz, 1H), 1.58-1.68 (m, 3H), 1.50 (ddd, $J = 12.9, 5.6, 3.9$ Hz, 1H), 0.91 (s, 9H), 0.07 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.6, 168.2, 146.6, 140.8, 139.7, 134.3, 129.7, 129.1, 127.8, 120.6, 73.8, 73.4, 65.6, 65.4, 42.1, 39.9, 39.4, 38.7, 37.7, 25.8, 21.0, 18.0, δ 1.3, δ 4.8; HRMS (CI/ NH_3) m/z calcd for $\text{C}_{29}\text{H}_{47}\text{O}_6\text{Si}_2$ $[\text{M}+\text{H}]^+$ 547.2911, found: 547.2914.

3

Phenol 3. To a solution of acetate **21** (3.3 mg, 6.0 μmol) in CH_3CN (1 mL) was added *N*-iodosuccinimide (6 mg, 0.1 mmol). The mixture was stirred for 3 h. The reaction was quenched with saturated aqueous Na_2SO_3 (2 mL) stirring until the solution became clear. The aqueous layer was extracted with ethyl acetate (3 $\times$ 1 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to provide an unpurified oil. The residue was dissolved in methanol (1 mL) and treated with K_2CO_3 (ca. 10 mg). The mixture was stirred for 20 min then DOWEX[®] 50X8-100 was added (ca. 100 mg). The mixture was stirred for 6 h. The resulting solution was filtered to remove the resin rinsing with methanol and the filtrate treated with Et_3N (0.1 mL). The organic phase was concentrated *in vacuo* to provide an oil residue. Purification on silica gel (10% ethyl acetate/hexane) provided **3** as clear oil (2.1 mg, 78%): IR (neat) 3298, 2954, 2927, 2856, 1710, 1584, 1465, 1360, 1291, 1057, 762 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.20 (dd, $J = 8.1, 7.8$ Hz, 1H), 6.83 (d, $J = 8.0$ Hz, 1H), 6.75 (d, $J = 7.8$ Hz, 1H), 6.56 (ddd, $J = 14.4, 8.3, 6.6$ Hz, 1H), 6.25 (dd, $J = 14.5, 1.2$ Hz, 1H), 5.91 (s, 1H), 5.53 (dddd, $J = 11.7, 8.3, 5.6, 3.3$ Hz, 1H), 4.31 (dddd, $J = 9.5, 9.5, 4.6, 1.7$ Hz, 1H), 4.06 (m, 1H), 3.88 (dddd, $J = 11.2, 6.1, 4.2, 1.7$ Hz, 1H), 3.52 (dd, $J = 14.4, 11.3$ Hz, 1H), 2.78 (s, 1H), 2.45 (m, 2H),

1.90 (dt, $J = 12.7, 4.1$ Hz, 1H), 1.85 (m, 2H), 1.57-1.68 (m, 2H), 1.25 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.5, 153.1, 140.9, 138.6, 131.2, 122.6, 122.1, 115.3, 78.4, 73.2, 72.4, 66.4, 65.0, 41.1, 39.6, 39.3, 38.8, 37.4; HRMS (CI/ NH_3) m/z calcd for $\text{C}_{18}\text{H}_{21}\text{O}_5\text{I}$ $[\text{M}]^+$ 444.0434, found: 444.0432.

4

Phenol 4. To a solution of iodide **3** (0.9 mg, 2 μmol) in benzene (0.5 mL) was added tributyltinhydride (4 mg, 14 μmol) and AIBN (2 mg, 12 μmol). The mixture was warmed to 45 $^\circ\text{C}$ stirred for 4 h. The reaction was cooled to room temperature and concentrated *in vacuo* to provide an unpurified oil. Purification on silica gel (30% ethyl acetate/hexane) provided **4** as clear oil (0.5 mg, 80%): IR (neat) 3262, 2926, 1722, 1580, 1464, 1296 cm^{-1} ; $[\alpha]_D^{23} +5$ (c 0.03, CH_3OH); ^1H NMR (500 MHz, acetone- D_6) δ 8.40 (s, 1H), 7.11 (dd, $J = 8.3, 7.8$ Hz, 1H), 6.77 (d, $J = 8.3$ Hz, 1H), 6.69 (d, $J = 7.8$ Hz, 1H), 5.92 (dddd, $J = 17.6, 10.3, 7.6, 6.6$ Hz, 1H), 5.48 (dddd, $J = 13.2, 5.6, 5.6, 2.4$ Hz, 1H), 5.13 (ddd, $J = 17.1, 3.7, 1.5$ Hz, 1H), 5.03 (dddd, $J = 10.3, 2.2, 1.2, 1.2$ Hz, 1H), 4.26 (dddd, $J = 10.5, 6.6, 4.6, 1.9$ Hz, 1H), 3.96-4.02 (m, 1H), 3.88 (dddd, $J = 9.7, 8.1, 4.9, 1.7$ Hz, 1H), 3.79 (d, $J = 4.2$ Hz, 1H), 3.34 (dd, $J = 14.9, 10.0$ Hz, 1H), 2.44 (dd, $J = 14.9, 1.7$ Hz, 1H), 2.30-2.41 (m, 2H), 1.93 (dt, $J = 13.0, 4.1$ Hz, 1H), 1.83 (dt, $J = 14.3, 11.0$ Hz, 1H), 1.67 (dddd, $J = 12.5, 6.4, 6.4, 1.9$ Hz, 1H), 1.58 (dt, $J = 14.7, 2.2$ Hz, 1H), 1.45-1.54 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.2, 154.3, 140.2, 135.3, 130.3, 125.5, 122.3, 117.5, 114.4, 73.63, 73.60, 68.1, 64.9, 41.4, 40.1, 39.9, 39.7, 39.1; HRMS (CI/ NH_3) m/z calcd for $\text{C}_{18}\text{H}_{22}\text{O}_5$ $[\text{M}]^+$ 318.1467, found: 318.1470.

18

Diester 18. Diene **6** (20 mg, 0.062 mmol), methyl 3-bromopropiolate (100 mg, 0.62 mmol), and Otera's distannoxane catalyst **17** (12 mg) were dissolved in toluene (2 mL) in a resealable tube. The solution was cycled through a freeze/pump/thaw sequence three times. The sealed tube was heated to 110 °C for 8 h. The reaction tube was cooled to room temperature and back filled with argon. To the reaction mixture was concentrated *in vacuo* to give an unpurified oil. Purification on silica gel (5% ethyl acetate/hexane) provided **18** as a clear oil (5.4 mg, 15%): IR (neat) 2959, 2947, 1728, 1619, 1220, 870, 784 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.32 (dt, $J = 16.6, 10.3$ Hz, 1H), 6.13 (dd, $J = 15.7, 11.0$ Hz, 1H), 6.01 (dt, $J = 18.6, 6.6$ Hz, 1H), 5.74 (d, $J = 18.6$ Hz, 1H), 5.63 (ddd, $J = 15.2, 7.3, 7.3$ Hz, 1H), 5.10-5.18 (m, 3H), 5.02 (d, $J = 10.3$ Hz, 1H), 4.27 (m, 1H), 3.84-3.92 (m, 2H), 2.49 (ddd, $J = 14.2, 6.7, 6.7$ Hz, 1H), 2.24-2.36 (m, 2H), 2.01 (dt, $J = 13.4, 3.9$ Hz, 1H), 1.76-1.84 (m, 2H), 1.54 (dt, $J = 12.2, 8.1$ Hz, 1H), 1.48 (dt, $J = 14.2, 2.7, 2.7$ Hz, 1H), 1.32 (dt, $J = 14.2, 7.1$ Hz, 1H), 0.05 (s, 9H); HRMS (CI/ NH_3) m/z calcd for $\text{C}_{24}\text{H}_{31}\text{O}_5\text{SiBr}_2$ $[\text{M}+\text{H}]^+$ 585.0308, found: 585.0295.

19

Arylbromide 19. Diester **18** (5.4 mg, 9.2 μmol) and DDQ (15 mg, 0.06 mmol) were dissolved in toluene (1 mL), heated to 90 °C, and stirred for 8 h then concentrated *in*

vacuo to provide an unpurified oil. Purification on silica gel (10% ethyl acetate/hexane) provided **19** as clear oil (4.2 mg, 78%): IR (neat) 2956, 2919, 1716, 1245, 1703, 864, 837 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.44 (dd, $J = 7.8, 1.0$ Hz, 1H), 7.12 (t, $J = 7.8$ Hz, 1H), 7.18 (dd, $J = 7.8, 1.0$ Hz, 1H), 6.17 (dt, $J = 18.6, 6.6$ Hz, 1H), 5.87 (dd, $J = 18.5, 1.2$ Hz, 1H), 5.73 (dddd, $J = 11.2, 8.1, 5.1, 2.9$ Hz, 1H), 5.21 (ddd, $J = 12.0, 6.6, 5.4$ Hz, 1H), 4.34 (ddd, $J = 9.5, 9.5, 3.7$ Hz, 1H), 4.10 (ddd, $J = 11.5, 6.4, 5.1$ Hz, 1H), 3.57 (dd, $J = 14.7, 10.8$ Hz, 1H), 2.65 (dddd, $J = 14.7, 8.1, 6.1, 1.5$ Hz, 1H), 2.51 (dd, $J = 14.9, 1.5$ Hz, 1H), 2.46 (dddd, $J = 14.7, 6.4, 4.9, 1.2$ Hz, 1H), 2.10 (ddd, $J = 13.7, 5.6, 4.4$ Hz, 1H), 1.76-1.94 (m, 4H), 1.70 (ddd, $J = 14.9, 2.9, 1.5$ Hz, 1H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.7, 151.8, 141.1, 139.2, 137.2, 134.0, 130.9, 130.4, 129.5, 118.9, 73.9, 73.1, 72.7, 70.3, 65.7, 53.3, 42.0, 38.9, 38.7, 35.2, 33.6, δ 1.2; HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{28}\text{O}_5\text{SiBr}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 604.9971, found: 604.9981.