Synthesis of the Entire Framework of Tartrolon B Utilizing a Silicon-Tethered Ring-Closing Metathesis Strategy

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Supporting Information

Materials and Methods

Commercially available chemicals were used without further purification. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone, and dichloromethane (CH₂Cl₂) was distilled from CaH₂ under nitrogen atmosphere. Hexanes were also distilled prior to use. Flash chromatography was performed using silica gel (60 Å porosity, 32-63 µm particle size) from Sorbent Technologies. Reactions were monitored by thin layer chromatography (TLC) using 250 µm E. Merck pre-coated silica gel 60 F₂₅₄ (particle size 40 –63 µm). ¹H NMR and ¹³C NMR spectra were obtained on a Bruker AC-300, Varian MercuryPlus-300, or on a Varian UNITY-500 spectrometer. Chemical shifts are reported in δ values relative to an internal standard of tetramethylsilane (TMS). High-resolution mass spectra were obtained using Leu5-enkephalin or erythromycin as a lock mass on an ESI-TOF spectrometer equipped with Z-spray and a reflectron.

Experimental

To a stirred mixture of potassium *tert*-butoxide (5.0 g, 44.6 mmol), THF (31 mL), and *cis*-2-butene (10.0 mL, 89.3 mmol), *n*-butyllithium in hexanes (2.5 M, 44.6 mmol) was

added slowly at $-78\text{ }^{\circ}\text{C}$ under N_2 atmosphere. After complete addition of *n*-butyllithium, the mixture was stirred at $-45\text{ }^{\circ}\text{C}$ for 10 min. The resulting solution was cooled back to $-78\text{ }^{\circ}\text{C}$, and to it was added drop-wise (+)-B-methoxydiisopinocampheylborane in ether (1 M, 53.6 mmol). After the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min, $\text{BF}_3\cdot\text{OEt}_2$ (8.0 mL, 67 mmol) was added dropwise. Then aldehyde **7** (9.5 g, 73.0 mmol) was added drop-wise as a solution in Et_2O at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred at this temperature for 3h then treated with 41 mL of 3 M NaOH and 17 mL 30% H_2O_2 , and the contents were refluxed for 1h. The organic layer was separated and washed with water and brine, dried over MgSO_4 , filtered, and concentrated in vacuo. An inseparable mixture of the desired crotylation product and isopinocampheyl alcohol (ca. 1:2, 19.0g) was obtained after silica gel column chromatography (12:1 to 3:1 hexane:ethyl acetate), and was used directly without further purification.

To a cooled ($0\text{ }^{\circ}\text{C}$) solution of the alcohol (9.5 g crude mixture) in DMF (85 mL) was added NaH (60% dispersed in mineral oil, 1.6 g). The mixture was stirred for 30 min and 4-methoxybenzyl chloride (3.2 mL) was added at $0\text{ }^{\circ}\text{C}$. The mixture was then stirred for 2 h and quenched with saturated aqueous NH_4Cl . The mixture was diluted with Et_2O (80 mL) and washed with water ($2 \times 40\text{ mL}$), then with brine. The organic layer was dried with MgSO_4 , filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (12:1 to 3:1 hexane:ethyl acetate) to provide 3.9 g of **8** (41% over 2 steps) as a colorless oil; $[\alpha]_{\text{D}}^{25} +34.5$ (*c* 1.64, CHCl_3); **^1H NMR (300 MHz, CDCl_3):** δ 7.28 (m, 2H), 6.89 (m, 2H), 5.85 (ddd, $J = 7.4, 10.0, 17.6\text{ Hz}$, 1H), 5.00-5.10 (m, 2H), 4.65 (ABq , $J = 10.9\text{ Hz}$, 1H), 4.55 (ABq , $J = 10.9\text{ Hz}$, 1H), 4.16 (ddd, $J = 4.9, 6.3, 7.2\text{ Hz}$, 1H), 3.98 (dd, $J = 6.3, 8.1\text{ Hz}$, 1H), 3.89 (dd, $J = 7.3, 7.9\text{ Hz}$, 1H), 3.80 (s, 3H), 3.51 (dd, $J = 5.2, 5.5\text{ Hz}$, 1H), 2.37 (m, 1H), 1.43 (s, 3H), 1.35 (s, 3H), 1.07 (d, $J = 6.8\text{ Hz}$, 3H); **^{13}C NMR (300 MHz, CDCl_3):** δ 159.29, 141.35, 130.92, 129.58 $\times 2$, 114.73, 113.86 $\times 2$, 108.78, 82.23, 77.05, 74.31, 65.77, 55.41, 40.55, 26.77, 25.61, 15.49; **HRMS:** calcd for $\text{C}_{18}\text{H}_{26}\text{O}_4$ [MNa^+] m/z 329.1729, found 329.1726.

To a cooled (0 °C) solution of **8** (580 mg, 1.9 mmol) in THF (20 mL) under N₂ atmosphere, was added a solution of 9-BBN in THF (0.5 M, 6.78 mL, 3.39 mmol) drop-wise via syringe over 30 min. The reaction was gradually allowed to warm to room temperature overnight. The resulting mixture was cooled back to 0 °C, and aqueous 3 M NaOH (8.5 mL) and 30% H₂O₂ (1.13 mL) was added. This mixture was allowed to warm to room temperature and stirred for 3 h, after which the volatiles were removed in vacuo. The residue was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over MgSO₄, filtered, concentrated, and purified by column chromatography (5:1 hexane:ethyl acetate to 100% ethyl acetate) to afford 1.778 g of **8-a** (98%) as a viscous oil; $[\alpha]_D^{25} +24.4$ (*c* 1.64, CHCl₃); **¹H NMR (300 MHz, CDCl₃):** δ 7.25 (m, 2H), 6.88 (m, 2H), 4.60 (ABq, *J* = 10.9 Hz, 1H), 4.55 (ABq, *J* = 10.9 Hz, 1H), 4.17 (dd, *J* = 6.2, 12.7 Hz, 1H), 4.04 (dd, *J* = 6.2, 8.2 Hz, 1H), 3.89 (dd, *J* = 6.9, 8.2 Hz, 1H), 3.80 (s, 3H), 3.56-3.75 (m, 2H), 3.50 (dd, *J* = 3.2, 5.9 Hz, 1H), 1.97 (m, 1H), 1.76 (m, 1H), 1.74 (br s, 1H), 1.53 (m, 1H), 1.42 (s, 3H), 1.35 (s, 3H), 0.97 (d, *J* = 6.9 Hz, 3H); **¹³C NMR (300 MHz, CDCl₃):** δ 159.35, 130.60, 129.52 × 2, 113.91 × 2, 108.67, 82.72, 76.83, 73.76, 66.91, 61.37, 55.40, 36.70, 32.66, 26.79, 25.39, 15.39; **IR (neat)** 3446, 2936, 1613, 1514 cm⁻¹; **HRMS:** calcd for C₁₈H₂₈O₅ [MNa⁺] *m/z* 347.1834, found 347.1823.

To a cooled (-78 °C), stirring solution of oxalyl chloride (1.35 mL, 15.2 mmol) in CH₂Cl₂ (32 mL) under N₂ atmosphere, was added DMSO (2.4 mL, 34.9 mmol) as a solution in CH₂Cl₂ (6.5 mL), and stirred for 20 min. A solution of alcohol **8-a** (4.32 g, 13.3 mmol) in CH₂Cl₂ (15.5 mL) was then added drop-wise and stirred for 30 min, at which point Et₃N (9.25 mL, 66.4 mmol) was added and warmed gradually to room temperature. The mixture was stirred for approximately 1h then diluted with CH₂Cl₂ and

washed with water and brine. The solution was dried over MgSO_4 , filtered, and solvent removed in vacuo. The resulting residue was purified by silica gel chromatography (8:1 to 3:1 hexane:ethyl acetate) to yield 4.0 g of **9** (93%) as a yellowish oil; $[\alpha]_D^{+10.8}$ (*c* 1.64, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 9.71 (t, $J = 1.7$ Hz, 1H), 7.23 (m, 2H), 6.88 (m, 2H), 4.55 (ABq, $J = 11.2$ Hz, 1H), 4.48 (ABq, $J = 11.2$ Hz, 1H), 4.12–4.13 (m, 2H), 3.86 (dd, $J = 6.0, 7.8$ Hz, 1H), 3.80 (s, 3H), 3.48 (dd, $J = 3.0, 6.1$ Hz, 1H), 2.43–2.60 (m, 2H), 2.35 (ddd, 2.2, 6.9, 15.3 Hz, 1H), 1.42 (s, 3H), 1.34 (s, 3H), 1.00 (d, $J = 6.6$ Hz, 3H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ 202.23, 159.42, 130.39, 129.58 ($\times 2$), 113.94 ($\times 2$), 108.85, 81.188, 76.70, 73.58, 67.07, 55.40, 47.90, 30.48, 26.79, 25.38, 15.21; **IR** (neat) 2985, 2719, 1723, 1612, 1514 cm^{-1} ; **HRMS**: calcd for $\text{C}_{18}\text{H}_{26}\text{O}_5$ [MNa^+] m/z 345.1678, found 345.1661.

To a suspension of (methoxymethyl)triphenylphosphonium chloride (34.2 g, 99.8 mmol) in THF (150 mL) under N_2 at -78 $^\circ\text{C}$, was added NaHMDS (96.8 mL, 1 M in THF) drop-wise and stirred at that temperature for 1 h. A solution of aldehyde **9** (4.8 g, 14.9 mmol) in THF (51 mL) was then slowly added via syringe and stirred for an additional 2 h at -78 $^\circ\text{C}$. The mixture was then warmed to room temperature and stirred for 30-45 min. until complete. The reaction was then quenched with a saturated aqueous NaHCO_3 solution, extracted into Et_2O and washed with brine. The organic layer was then dried over MgSO_4 , filtered, concentrated in vacuo, and purified by silica gel column chromatography (12:1 to 7:1 hexane:ethyl acetate) to afford 4.2 g (80%) of the methyl enol ether **10** as a colorless oil (ca. 1.5:1 *E:Z*); $^1\text{H NMR}$ (300 MHz, CDCl_3): **mixture of *E:Z* isomers (ca. 1.5:1)** δ 7.24-7.29 (m, 4H), 6.85-6.90 (m, 4H), 6.26 (d, $J = 12.6$ Hz, 1H, *E*-isomer), 5.94 (dt, $J = 5.2, 1.3$ Hz, 1H, *Z*-isomer), 4.51–4.71 (m, 5H), 4.34 (q, $J = 7.0$ Hz, 1H), 4.11-4.19 (overlapping q, $J = 6.3$ Hz, 1H $\times 2$), 3.99-4.05 (m, 2H), 3.86-3.93 (m, 2H), 3.80 (s, 6H), 3.57 (s, 3H), 3.54-3.56 (m, 2H), 3.50 (s, 3H), 2.29 (m, 1H), 1.96-2.15 (m, 2H), 1.86 (m, 1H), 1.69-1.79 (m, 2H), 1.43 (s, 6H), 1.35 (s, 6H), 0.94 (d, $J = 6.0$ Hz, 3H), 0.92 (d, $J = 6.0$ Hz, 3H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ 159.25, 159.20,

148.23, 147.09, 131.30, 131.07, 129.44, 129.35, 113.86, 113.82, 108.56, 108.55, 105.07, 101.27, 81.60, 81.42, 77.42, 77.29, 74.31, 73.98, 66.62, 66.55, 59.59, 56.03, 55.39, 36.82, 35.99, 32.37, 28.50, 26.84, 25.52, 25.43, 14.80, 14.40; **HRMS**: calcd for $C_{20}H_{30}O_5$ $[MNa^+]$ m/z 373.1991, found 373.1994.

To a cooled (-20 °C) solution of *N*-bromosuccinamide (490 mg, 2.75 mmol) in THF:H₂O (25 mL:4.3 mL), was added a solution of the methyl enol ether **10** in THF (3 mL) and stirred for 30-45 min. The volatiles were removed from the mixture in vacuo and the residue was diluted in ethyl acetate, and organic layer was separated and washed with brine. After drying over MgSO₄, filtered, and concentrated in vacuo, the crude material was used directly in the next reaction without purification.

The crude α -bromoaldehyde was dissolved in wet THF (9.6 mL), glacial acetic acid (324 mg, 5.5 mmol) was added, and the solution cooled to 0 °C. To a vigorously stirring solution was then added Zn dust (350 mg, 5.5 mmol) portion-wise, and the mixture was allowed to gradually warm to room temperature. After stirring for 2 h, the reaction was diluted in Et₂O and washed with H₂O, saturated NaHCO₃, and brine. The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (5:1 to 1:1 hexane:ethyl acetate) to yield 790 mg (87% over 2 steps) of aldehyde **10-a** as a colorless oil; **¹H NMR (300 MHz, CDCl₃)**: δ 9.74 (t, J = 1.5 Hz, 1H), 7.25 (m, 2H), 6.87 (m, 2H), 4.60 (ABq, J = 10.9, 1H), 4.53 (ABq, J = 10.9, 1H), 4.13 (dd, J = 6.2, 12.5 Hz, 1H), 4.05 (dd, J = 6.2, 7.9 Hz, 1H) 3.90 (dd, J = 6.6, 7.9 Hz, 1H), 3.80 (s, 3H), 3.47 (dd, J = 3.0, 6.0 Hz, 1H), 2.32-2.55 (m, 2H), 1.72-1.88 (m, 2H), 1.56 (m, 1H), 1.42 (s, 3H), 1.35 (s, 3H), 0.94 (d, J = 7.0 Hz, 3H); **¹³C NMR (300 MHz, CDCl₃)**: δ 202.51, 159.36, 130.70, 129.52 $\times$ 2, 113.91 $\times$ 2, 108.69, 82.20, 76.94, 73.87, 66.87, 55.41, 42.16, 35.09, 26.83, 26.00, 25.38, 14.50; **HRMS**: calcd for $C_{19}H_{28}O_5$ $[MNa^+]$ m/z 391.2097, found 391.2109.

To a stirred mixture of potassium *tert*-butoxide (1.35g, 12.0 mmol), THF (2.0 mL), and *trans*-2-butene (2.2 mL, 4.1 mmol), *n*-butyllithium in hexanes (2.5 M, 12.0 mmol) was added slowly at $-78\text{ }^{\circ}\text{C}$ under N_2 atmosphere. After complete addition of *n*-butyllithium, the mixture was stirred at $-45\text{ }^{\circ}\text{C}$ for 10 min. The resulting solution was cooled back to $-78\text{ }^{\circ}\text{C}$, and to it was added drop-wise (+)-B-methoxy-diisopinocampheylborane in ether (1 M, 14.5 mmol). After the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min, $\text{BF}_3\cdot\text{OEt}_2$ (2.0 mL, 16.1 mmol) was added drop-wise. Then aldehyde **10-a** (9.5 g, 73.0 mmol) was added drop-wise as a solution in Et_2O at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred at this temperature for 4h then treated with 4.2 mL of 3 M NaOH and 1.7 mL 30% H_2O_2 , and the contents were refluxed for 1h. The organic layer was separated and washed with water and brine, dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (9:1 to 3:1 hexane:ethyl acetate) to afford 1.8 g (57%) of crotylation product **11** as a colorless oil; **^1H NMR (300 MHz, CDCl_3):** δ 7.25 (m, 2H), 6.87 (m, 2H), 5.74 (ddd, $J = 10.9, 16.6, 8.2$ Hz, 1H), 5.13 (s, 1H), 5.08 (m, 1H), 4.62 (ABq , $J = 11.0$ Hz, 1H), 4.54 (ABq , $J = 11.0$ Hz, 1H), 4.15 (m, 1H), 4.03 (dd, $J = 6.3, 8.1$ Hz, 1H), 3.90 (dd, $J = 7.0, 7.9$ Hz, 1H), 3.79 (s, 3H), 3.50 (dd, $J = 3.6, 5.6$ Hz, 1H), 3.35 (m, 1H), 2.18 (m, 1H), 1.73 (m, 1H), 1.39-1.51 (m, 4H), 1.43 (s, 3H), 1.35 (s, 3H), 1.02 (dd, $J = 6.9$ Hz, 3H), 0.93 (dd, $J = 6.9$ Hz, 3H); **^{13}C NMR (300 MHz, CDCl_3):** (major diastereomer) δ 159.22, 140.37, 131.00, 129.43, 116.43, 113.81, 108.54, 82.46, 77.16, 74.68, 74.02, 66.60, 55.34, 44.29, 35.59, 32.10, 29.87, 26.80, 25.43, 16.40, 14.75; (distinguishable signals from minor diastereomer) δ 82.32, 77.09, 72.26, 71.99, 66.73, 37.27, 27.92, 22.82, 14.21; **HRMS:** calcd for $\text{C}_{23}\text{H}_{36}\text{O}_5$ [MNa^+] m/z 415.2460, found 415.2451.

To a cooled (0 °C) solution of **11** in CH₂Cl₂ (8.0 mL) was added DIEA (diisopropylethylamine, 395mg, 3.1 mmol) drop-wise followed by MOM-Cl (chloromethyl methyl ether, 246 mg, 3.1 mmol). The solution was gradually warmed to room temperature until reaction was determined to be complete by TLC, at which point it was quenched with saturated NH₄Cl and diluted with CH₂Cl₂. The organic layer was washed with saturated NH₄Cl, H₂O, then brine, and dried over MgSO₄. The solution was filtered, concentrated in vacuo and purified by silica gel column chromatography (9:1 to 5:1 hexane:ethyl acetate) to afford 333 mg (75%) of **12** as a colorless oil; **¹H NMR (300 MHz, CDCl₃):** δ 7.24 (m, 2H), 6.87 (m, 2H), 5.78 (m, 1H), 5.03 (m, 2H), 4.67 (ABq, *J* = 6.8 Hz, 1H), 4.63 (ABq, *J* = 6.8 Hz, 1H), 4.60 (ABq, *J* = 11.2 Hz, 1H), 4.52 (ABq, *J* = 11.2 Hz, 1H), 4.13 (m, 1H), 4.02 (dd, *J* = 6.3, 8.1 Hz, 1H), 3.90 (dd, *J* = 6.8, 8.0 Hz, 1H), 3.80 (s, 3H), 3.48 (dd, *J* = 3.4, 5.5 Hz, 1H), 3.42 (m, 1H), 3.38 (s, 3H), 2.44 (m, 1H), 1.72 (m, 1H), 1.32-1.59 (m, 4H), 1.42 (s, 3H), 1.35 (s, 3H), 1.03 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H); **¹³C NMR (300 MHz, CDCl₃):** (major diastereomer) δ 159.28, 140.71, 131.08, 129.32 × 2, 114.89, 113.85 × 2, 108.56, 96.32, 82.66, 81.80, 77.16, 74.06, 66.70, 55.81, 55.37, 41.07, 35.80, 30.03, 29.16, 26.82, 25.44, 15.09, 14.71; (distinguishable signals from minor diastereomer): δ 95.57, 82.61, 77.79, 55.62, 34.11, 32.39, 29.56, 27.61, 22.99, 14.79, 14.21; **HRMS:** calcd for C₂₅H₄₀O₆ [MNa⁺] *m/z* 459.2723, found 459.2712.

To a solution of the alkene **12** (197 mg, 0.45 mmol) in DMF (4.0 mL), THF (0.6 mL), and water (0.6 mL) was added CuCl (62 mg, 0.60 mmol) and PdCl₂ (20 mg, 0.11 mmol). The solution was flushed with oxygen for 15-20 min. and then stirred under an atmosphere of oxygen for 2.5 days at room temperature. The reaction mixture was diluted with ethyl acetate and poured into water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NH₄Cl, saturated aqueous NaHCO₃, brine, and the dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (6:1 to 2:1 hexane:ethyl acetate) to afford 144 mg (71%) ketone **13** as a colorless oil along with a

trace amount of an inseparable regioisomeric side product aldehyde. **¹H NMR (300 MHz, CDCl₃):** δ 7.25 (m, 2H), 6.87 (m, 2H), 4.61 (ABq, *J* = 10.8 Hz, 1H), 4.53 (ABq, *J* = 10.8 Hz, 1H), 4.59 (s, 2H), 4.14 (q, *J* = 6.3 Hz, 1H), 4.02 (dd, *J* = 6.3, 8.0 Hz, 1H), 3.89 (dd, *J* = 6.8, 8.0 Hz, 1H), 3.77-3.85 (m, 1H), 3.80 (s, 3H), 3.47 (dd, *J* = 3.4, 5.7 Hz, 1H), 3.32 (s, 3H), 2.83 (quintet, *J* = 7.1 Hz, 1H), 2.18 (s, 3H), 1.72 (m, 1H), 1.24-1.58 (m, 4H), 1.42 (s, 3H), 1.35 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); **¹³C NMR (300 MHz, CDCl₃):** δ 211.36, 159.22, 130.95, 129.33 × 2, 113.81 × 2, 108.57, 96.31, 82.88, 79.09, 76.97, 74.03, 66.69, 55.92, 55.34, 50.20, 35.74, 29.96, 28.90, 28.47, 26.79, 25.43, 14.51, 12.15; (trace amount of aldehyde side product from Wacker oxidation): 202.34, 82.71, 81.91, 77.03, 47.57, 31.48, 16.49, 14.57; **HRMS:** calcd for C₂₅H₄₀O₇ [MNa⁺] *m/z* 475.2672, found 475.2666.

18 (and 11-epimer, 86:14)

To a cooled (0 °C) solution of (-)-*B*-chlorodiisopinocampheylborane (194 mg, 0.60 mmol) in Et₂O (2 mL) was added Et₃N (0.13 mL, 0.93 mmol) under N₂ atmosphere. A solution of ketone **13** (100 mg, 0.22 mmol) in Et₂O (2 mL) was added via syringe and the reaction was maintained at 0 °C for 90-100 min. The reaction mixture was then cooled to -78 °C and a solution of 5-hexenal in Et₂O (1.5 mL) was added via syringe. The reaction mixture was maintained at -78 °C for 3.5 h and then warmed to -20 °C and maintained at that temperature overnight. The reaction mixture was quenched by sequential addition of MeOH (1.7 mL), pH 7 buffer (0.6 mL), and 30 % H₂O₂ (0.6 mL). The resulting mixture was then diluted with CH₂Cl₂ and poured into water. The aqueous layer was extracted with CH₂Cl₂, and the combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (8:1 to 1:1 hexanes:ethyl acetate) to afford 85 mg of **18** (72%,

86:14 of **18** and it's C-11 epimer); **¹H NMR (300 MHz, CDCl₃)**: (major diastereomer) δ 7.25 (m, 2H), 6.87 (m, 2H), 5.82 (ddt, *J* = 6.6, 10.3, 17.0 Hz, 1H), 4.95–5.08 (m, 2H), 4.61 (ABq, *J* = 10.8 Hz, 1H), 4.52 (ABq, *J* = 10.8 Hz, 1H), 4.53–4.62 (m, 2H), 4.14 (q, *J* = 6.3, 1H), 4.05 (m, 1H), 4.03 (dd, *J* = 6.3, 7.9 Hz, 1H), 3.89 (dd, *J* = 7.1, 7.9 Hz, 1H), 3.81 (m, 1H), 3.80 (s, 3H), 3.46 (dd, *J* = 3.4, 5.5 Hz, 1H), 3.30 (s, 3H), 3.19 (d, *J* = 3.5 Hz, 1H), 2.82 (m, 1H), 2.53–2.72 (m, 2H), 2.07–2.29 (m, 2H), 1.71 (m, 1H), 1.45–1.67 (m, 5H), 1.42 (s, 3H), 1.35 (s, 3H), 1.25 (m, 1H), 1.01 (d, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); **¹³C NMR (300 MHz, CDCl₃)**: (major diastereomer) δ 214.60, 159.26, 138.27, 130.95, 129.27, 114.94, 113.84, 108.59, 96.28, 82.94, 79.27, 76.98, 73.97, 66.96, 66.73, 55.97, 55.33, 49.78, 49.75, 35.78, 35.58, 29.82, 28.86, 28.08, 26.78, 25.42, 14.52, 12.45; **HRMS**: calcd for C₃₀H₄₈O₈ [MNa⁺] *m/z* 559.3247, found 559.3263

19

To a cooled (–10 °C) solution of **18** (446 mg, 0.83 mmol) in THF (2.8 mL) under N₂ atmosphere, was added acetaldehyde (0.22 mL, 4.16 mmol). To this solution was added SmI₂ (0.83 mmol, 0.1 M in THF) slowly in the dark. After stirring for 1.5 h in the dark at –10 °C, the reaction was diluted with ethyl acetate, washed with saturated NaHCO₃, brine, dried over MgSO₄. The solution was filtered, concentrated in vacuo, and the residue purified by silica gel column chromatography (2:1 hexanes:ethyl acetate) to afford 480 mg (99%) of product **19** as an oil; **¹H NMR (300 MHz, CDCl₃)**: (major diastereomer) δ 7.26 (m, 2H), 6.87 (m, 2H), 5.79 (m, 1H), 5.11 (m, 1H), 4.94–5.05 (m, 2H), 4.53–4.66 (m, 4H), 4.16 (q, *J* = 6.2 Hz, 1H), 4.03 (dd, *J* = 6.2, 8.0 Hz, 1H), 3.90 (dd, *J* = 6.8, 8.0 Hz, 1H), 3.81 (s, 3H), 3.74 (br m, 1H), 3.47 (dd, *J* = 3.4, 5.6 Hz, 1H), 3.36 (s, 3H), 3.26 (d, *J* = 3.7 Hz, 1H), 2.08, (s, 3H), 2.06–2.15 (m, 2H), 1.88 (m, 1H), 1.44–1.78 (m, 8H), 1.42 (s, 3H), 1.35 (s, 3H), 0.93, (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H);

^{13}C NMR (300 MHz, CDCl_3): (major diastereomer) δ 172.26, 159.25, 137.63, 131.08, 129.32, 115.27, 113.86, 108.55, 96.19, 83.09, 79.56, 77.06, 74.13, 71.44, 68.79, 66.72, 55.90, 55.37, 41.90, 40.02, 35.72, 34.37, 29.95, 29.59, 28.08, 26.80, 25.44, 21.19, 14.52, 11.16; **HRMS:** calcd for $\text{C}_{32}\text{H}_{52}\text{O}_9$ $[\text{MNa}^+]$ m/z 603.3509, found 603.3487.

19-a

To a cooled (0 °C) solution of **19** (480 mg, 0.83 mmol) in CH_2Cl_2 (9.0 mL) was added DIEA (*N,N*-diisopropylethylamine, 323 mg, 2.5 mmol) drop-wise followed by MOMCl (chloromethyl methyl ether, 201 mg, 2.5 mmol). The solution was gradually warmed to room temperature until reaction was determined to be complete by TLC, at which point it was quenched with saturated NH_4Cl and diluted with CH_2Cl_2 . The organic layer was washed with saturated NH_4Cl , H_2O , then brine, and dried over MgSO_4 . The solution was concentrated in vacuo and purified by silica gel column chromatography (5:1 to 2:1 hexane:ethyl acetate) to afford 390 mg (76%) of **19-a** as an oil; **^1H NMR (300 MHz, CDCl_3):** (major diastereomer) δ 7.25 (m, 2H), 6.86 (m, 2H), 5.80 (m, 1H), 5.08 (m, 1H), 5.0 (m, 2H), 4.52-4.65 (m, 6H), 4.16 (q, J = 6.5 Hz, 1H), 4.02 (dd, J = 6.5, 8.0 Hz, 1H), 3.90 (dd, J = 6.9, 8.0 Hz, 1H), 3.79 (s, 3H), 3.74 (m, 1H), 3.47 (dd, J = 3.8, 5.5 Hz, 1H $\times$ 2), 3.42 (m, 1H), 3.37 (s, 3H), 3.34 (s, 3H), 2.07 (dd, J = 7.4, 14.6 Hz, 2H), 2.02 (s, 3H), 1.60-1.79 (m, 9H), 1.42 (s, 3H), 1.35 (s, 3H), 1.35 (m, 1H), 0.94 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 7.0 Hz, 3H); **^{13}C NMR (300 MHz, CDCl_3):** (major diastereomer) δ 170.67, 159.21, 137.94, 130.95, 129.29, 114.92, 113.79, 108.56, 96.81, 96.38, 83.06, 79.65, 76.97, 75.53, 74.09, 71.17, 66.61, 56.00, 55.93, 55.33, 39.61, 36.04, 34.99, 34.46, 29.53, 29.47, 28.46, 26.78, 25.44, 21.32, 14.55, 10.35; **HRMS:** calcd for $\text{C}_{34}\text{H}_{56}\text{O}_{10}$ $[\text{MNa}^+]$ m/z 647.3771, found 647.3781.

To a solution of **19-a** (340 mg, 0.54 mmol) in methanol (6.0 mL) was added K_2CO_3 (298 mg, 2.16 mmol) and stirred vigorously at reflux for 2-3 h. The reaction mixture was diluted with ethyl acetate, quenched with pH 7 buffer, and the organic layer was separated and washed with brine. The solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (3:1 to 1:1 hexanes:ethyl acetate) to afford 291 mg (92%) of **20** as an oil; **1H NMR (300 MHz, $CDCl_3$):** (major diastereomer) δ 7.26 (m, 2H), 6.88 (m, 2H), 5.86 (m, 1H), 5.04 (m, 1H), 4.96 (m, 1H), 4.52-4.67 (overlapping doublets, 6H), 4.15 (q, $J = 7.0$ Hz, 1H), 4.02 (dd, $J = 6.4, 8.0$ Hz, 1H), 3.90 (dd, $J = 7.0, 8.0$ Hz, 1H), 3.81-3.89 (m, 2H), 3.80 (s, 3H), 3.48 (m, 2H), 3.39 (s, 3H), 3.38 (s, 3H), 3.03 (d, $J = 4.0$ Hz, 1H), 2.08-2.30 (m, 2H), 2.02 (sextet, $J = 7.0$ Hz, 1H), 1.37-1.83 (m, 9H), 1.42 (s, 3H), 1.35 (s, 3H), 0.94 (d, $J = 6.9$ Hz, 3H), 0.84 (d, $J = 6.9$ Hz, 3H); **^{13}C NMR (300 MHz, $CDCl_3$):** (major diastereomer) δ 159.22, 138.80, 130.97, 129.29, 114.67, 113.82, 108.57, 96.72, 96.38, 82.91, 79.56, 77.03, 76.63, 74.02, 67.33, 66.65, 56.19, 56.01, 55.35, 39.92, 37.61, 36.94, 35.98, 30.26, 29.13, 28.93, 26.80, 25.44, 14.68, 10.53; **HRMS:** calcd for $C_{32}H_{54}O_9$ $[MNa^+]$ m/z 605.3666, found 605.3642.

To a stirring solution of phenyltriethynylsilane (136 mg, 0.75 mmol) and alcohol **21-a** (83 mg, 0.38 mmol) in dry hexanes (1.6 mL) was added NaH (60% dispersion in mineral oil, 1.5 mg, 38 μ mol) and stirred at room temperature for 1-2 h. The reaction mixture

was filtered through a pad of celite, concentrated in vacuo, and the residue purified by silica gel chromatography (10 % ether in hexanes) to afford silyl ether **21** (89 mg, 63 %); **¹H NMR (300 MHz, CDCl₃):** δ 7.79 (m, 2H), 7.25-7.50 (m, 8H), 5.66 (m, 2H), 4.49 (s, 3H), 4.22 (sextet, *J* = 6.1 Hz, 1H), 3.95 (d, *J* = 5.8 Hz, 2H), 2.63 (s, 1H), 2.62 (s, 1H), 2.16 (m, 2H), 1.47-1.76 (m, 2H), 1.28 (d, *J* = 6.0 Hz, 3H); **¹³C NMR (300 MHz, CDCl₃):** δ 138.57, 134.43, 134.26, 131.19, 128.49, 128.21, 127.92, 127.67, 126.62, 95.67, 95.59, 84.60, 84.49, 72.00, 71.03, 70.98, 38.29, 28.56, 23.23; **HRMS:** calcd for C₂₄H₂₆O₂Si [MNa⁺] *m/z* 397.1600, found 397.1592.

22 (diastereomeric mixture)

To a solution of secondary alcohol **20** (140 mg, 0.24 mmol) and silyl ether **21** (89 mg, 0.24 mmol) in hexanes (3.0 mL) was added NaH (60% dispersion in mineral oil, 1.0 mg, 24.0 μmol) and stirred over gentle heating for 4-5 h. The reaction mixture was filtered through a pad of celite, concentrated in vacuo, and the residue purified by silica gel chromatography (5:1 to 3:1 hexane:ethyl acetate) to afford 129 mg (58%) of silaketel **22**; **¹H NMR (300 MHz, CDCl₃):** (mixture of two diastereomers) δ 7.73 (m, 2H × 2), 7.23-7.43 (m, 10H × 2), 6.86 (d, *J* = 8.5 Hz, 2H × 2), 5.46-5.89 (m, 3H × 2), 4.88-5.05 (m, 2H × 2), 4.42-4.70 (overlapping doublets, 8H × 2), 4.27 (m, 1H × 2), 4.15 (m, 2H × 2), 3.85-4.04 (m, 5H × 2), 3.79 (s, 3H × 2), 3.47 (m, 2H × 2), 3.32, 3.30, 3.28, 3.26 (s, 3H × 4), 2.56, 2.55 (s, 1H × 2), 2.01-2.20 (m, 6H × 2), 1.62-1.78 (m, 5H × 2), 1.46-1.60 (m, 5H × 2), 1.42 (s, 3H × 2), 1.35 (s, 3H × 2), 1.25, 1.16 (d, *J* = 5.4 Hz, 3H × 2), 0.93, 0.91 (d, *J* = 6.6 Hz, 3H × 2), 0.85, 0.82 (d, *J* = 7.0 Hz, 3H × 2); **¹³C NMR (300 MHz, CDCl₃):** (mixture of two diastereomers) δ 159.25, 138.59, 134.38, 134.35, 134.31, 134.24, 133.37,

133.34, 131.12, 130.70, 129.30, 128.46, 127.96, 127.88, 127.64, 126.60, 126.54, 114.51, 113.85, 108.55, 97.45, 96.57, 96.53, 94.89, 94.54, 85.04, 84.76, 83.19, 79.70, 79.60, 77.43, 77.08, 77.08, 74.12, 72.00, 71.99, 71.23, 71.08, 71.02, 70.98, 69.87, 69.69, 66.63, 55.87, 55.81, 55.75, 55.37, 40.57, 40.54, 38.58, 38.45, 38.30, 37.40, 37.16, 36.05, 36.01, 29.35, 29.30, 28.96, 28.93, 28.49, 28.38, 26.82, 25.49, 23.34, 23.32, 14.58, 10.61, 10.58; **HRMS**: calcd for C₅₄H₇₈O₁₁Si [MNa⁺] *m/z* 953.5211, found 953.5242.

23 (diastereomeric mixture)

To a solution of silaketel **22** (129 mg, 0.14 mmol) in dry CH₂Cl₂, flushed with N₂, was added Grubb's second-generation catalyst (10 mg, 8.5 mol%). The solution was refluxed under N₂ atmosphere for 2 h (*R_f* = 0.6 for both starting material and product, 3:1 hexanes:ethyl acetate). The solution was stirred at room temperature in open atmosphere for 1 h, at which point it was concentrated in vacuo. The brown residue was purified by silica gel column chromatography (5:1 to 4:1 hexane:ethyl acetate) to afford 91 mg (84 %) of bicycle **23** as a colorless oil; **¹H NMR (300 MHz, CDCl₃)**: (mixture of two diastereomers) δ 7.58-7.67 (m, 2H × 2), 7.32-7.41 (m, 3H × 2), 7.22-7.27 (m, 2H × 2), 6.86 (m, 2H × 2), 6.50 (t, *J* = 7.9 Hz, 1H × 2), 6.28, 6.25 (d, *J* = 11.6 Hz, 1H × 2), 5.26-5.48 (m, 1H × 2), 5.00 (d, *J* = 6.7 Hz, 1H), 4.54-4.74 (m, 5H × 2), 4.40 (m, 1H), 4.12-4.22 (m, 1H × 2), 4.15 (m, 1H), 4.02 (dd, *J* = 7.9, 6.4 Hz, 1H × 2), 3.88-3.93 (m, 2H × 2), 3.79 (s, 3H × 2), 3.42-3.60 (m, 2H × 2), 3.39, 3.37, 3.36, 3.27, (s, 3H × 4), 2.06-2.57 (m, 4H × 2), 1.53-1.99 (m, 10H × 2), 1.28-1.50 (m, 2H × 2), 1.42 (s, 3H × 2), 1.35 (s, 3H × 2), 1.25, 1.09 (d, *J* = 6.2 Hz, 3H × 2), 0.96, 0.95 (d, *J* = 6.0 Hz, 3H × 2), 0.86, 0.84 (d, *J* = 6.0 Hz, 3H × 2); **¹³C NMR (300 MHz, CDCl₃)**: (mixture of two diastereomers) δ 159.25,

154.28, 146.08, 138.68, 136.82, 135.99, 135.56, 134.35, 134.26, 134.07, 134.00, 132.46, 131.16, 130.28, 129.98, 129.32, 129.15, 128.02, 127.99, 125.93, 113.85, 108.56, 98.51, 97.33, 96.85, 96.73, 83.18, 79.68, 79.63, 77.84, 77.35, 74.16, 70.55, 68.96, 68.18, 66.64, 65.88, 56.11, 56.04, 55.79, 55.78, 55.38, 41.01, 40.47, 38.90, 38.34, 37.29, 36.99, 36.10, 35.07, 29.69, 29.62, 28.77, 28.65, 27.48, 26.83, 26.41, 25.51, 24.99, 24.54, 23.73, 23.66, 14.60, 10.49, 10.45; **HRMS**: calcd for $C_{44}H_{66}O_{10}Si$ $[MNa^+]$ m/z 805.4323, found 805.4320.

24

To a solution of **23** (45 mg, 0.06 mmol) in THF (1.7 mL) under N_2 atmosphere, was added TBAF (tetrabutylammonium fluoride, 0.1 M, 0.17 mmol). The solution was stirred at room temperature for 3 h, at which point it was quenched with saturated aqueous NH_4Cl and diluted with ethyl acetate. The organic layer was separated, washed with water, brine, dried over $MgSO_4$, and filtered. The solution was concentrated in vacuo to give a yellow residue, which was purified by silica gel column chromatography (3:1 hexane:ethyl acetate to 100 % ethyl acetate) to afford 23 mg (59 %) of diol **24** as a colorless oil; **1H NMR (300 MHz, $CDCl_3$)**: δ 7.25 (m, 2H), 6.87 (m, 2H), 6.37 (dd, J = 11.1, 14.3 Hz, 1H), 5.97 (t, J = 11.1, 1H), 5.69 (m, 1H), 5.31 (dd, J = 7.7, 18.3 Hz, 1H), 4.51-4.67 (overlapping doublets, 6H), 4.15 (m, 1H), 4.02 (dd, J = 6.3, 7.7 Hz, 1H), 3.90 (m, 1H), 3.83-3.98 (m, 3H), 3.80 (s, 3H), 3.48 (m, 2H), 3.39 (s, 3H), 3.37 (s, 3H), 3.04 (d, J = 3.4 Hz, 1H), 2.25 (m, 4H), 2.01 (m, 1H), 1.72 (m, 1H), 1.38-1.67 (m, 10H), 1.42 (s, 3H), 1.35 (s, 3H), 1.20 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 7.2 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H); **^{13}C NMR (300 MHz, $CDCl_3$)**: δ 159.28, 134.69, 129.40, 129.32, 129.25, 125.88, 113.86, 108.61, 96.76, 96.43, 82.96, 79.61, 77.06, 76.67, 74.04, 67.66, 67.30, 66.68, 56.21, 56.03, 55.38, 39.97, 39.07, 37.64, 37.27, 36.00, 29.30, 29.17, 28.93, 26.81, 25.45,

24.23, 23.72, 14.69, 10.54; **HRMS:** calcd for $\text{C}_{38}\text{H}_{64}\text{O}_{10}$ $[\text{MNa}^+]$ m/z 703.4397, found 703.4380.

18 (and 11-epimer, 86:14)

19-a

21

22 (diastereomeric mixture)

Chemical structure of **22** (diastereomeric mixture): CCCCC/C=C\CCOC(=O)c1ccccc1

¹H NMR spectrum (CDCl₃) of **22** (diastereomeric mixture). The spectrum shows peaks from 0 to 9 ppm. Key features include a broad peak at ~8.2 ppm (OH), a multiplet at ~7.2 ppm (aromatic), a multiplet at ~6.2 ppm (alkene), a large singlet at ~4.2 ppm (CH₂-OBn), a multiplet at ~3.2 ppm (CH₂-CH₂-), and a multiplet at ~1.2 ppm (CH₃). Integration values are shown below the baseline.

[illegible]