A Concise Route to Benzofused Macrolactones via Ynolides: Cycloproparadicicol

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Supporting Information Available: Experimental procedure and physical data for all new compounds (PDF). This material is available free of charge via the internet at <http://pubs.acs.org>.

Supplementary Material

General Methods: Reagents obtained from commercial suppliers were used without further purification unless otherwise noted. THF, toluene, and methylene chloride was obtained from a dry solvent system (passed through a prepacked column of alumina) and used without further drying. All air and water sensitive reactions were performed in oven or flame-dried glassware. NMR (^1H and ^{13}C) spectra were recorded on Bruker AMX-400 MHz or Bruker Advance DRX-500 MHz as noted individually, referenced to CDCl_3 (7.27 ppm for ^1H and 77.23 ppm for ^{13}C). Optical rotations were obtained on a JASCO model DIP-370 digital polarimeter. Low resolution mass spectra (ESI) were determined with a PEsCiex AP 130 spectrometer. High resolution mass spectra (FAB) were determined at Chemistry Department of Columbia University. Flash chromatography was performed with silica gel (230-400 mesh) from EM Science as the stationary phase. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F254 plates. Compounds which were not UV active were visualized by dipping the plates in phosphomolybdic acid solution and heating. Preparative thin layer chromatography was performed using the indicated solvent on Whatman® (LK6F Silica gel 60 Å 250 μM or Pk6F Silica Gel 60 Å 1000 μM) TLC plate.

Acid **6**. To a suspension of activated zinc (15 g, 230 mmol) in dry THF (50 mL) at 0 °C was added propargyl bromide **4** (19.2 mL 80 wt% in toluene, 172 mmol). The resulting mixture was stirred at 0 °C for 1 hr, and sorbaldehyde **5** (12.7 mL, 115 mmol) was added. After 1 hr at 0 °C, additional zinc (4.5 g, 69 mmol) was added, and stirring was continued for 2.5 hrs at room temperature (the reaction was exothermic and ice bath was needed occasionally to keep the temperature down). The reaction was

quenched by slow addition of sat. aqueous NH_4Cl (500 mL), followed by diluting with Et_2O (1 L). The layers were separated, and the organic layer was washed with H_2O (300 mL), brine (300 mL), dried (Na_2SO_4), filtered and concentrated in vacuum. The residue was dissolved in CH_2Cl_2 (750 mL) with imidazole (9.8 g, 144 mmol), *t*-butyldimethylsilyl chloride (19 g, 126 mmol) and 4-(dimethylamino)pyridine (1.4 g, 11.5 mmol), and stirred at room temperature for 3 hrs. Additional imidazole (4.9 g, 72 mmol) and *t*-butyldimethylsilyl chloride (9.5 g, 63 mmol) were added, and stirring was continued for 9 hrs. The reaction was quenched by addition of sat. aqueous NH_4Cl (200 mL). The layers were separated, and the organic layer was washed with H_2O (200 mL), brine (200 mL), dried (Na_2SO_4), filtered and concentrated in vacuum. The residue was purified by flash chromatography (silica, 0 to 10% Et_2O in hexane) to give the terminal alkyne precursor of **6** (15 g, 52%). ^1H NMR (CDCl_3 , 400 MHz) δ 6.18 (dd, J = 15.1, 10.5 Hz, 1H), 6.03 (ddd, J = 15.0, 10.6, 1.3 Hz, 1H), 5.72 (dd, J = 14.9, 6.9 Hz, 1H), 5.61 (dd, J = 15.1, 6.4 Hz, 1H), 4.30 (q, J = 6.3 Hz, 1H), 2.43 (ddd, J = 16.5, 6.2, 2.7 Hz, 1H), 2.34 (ddd, J = 16.5, 6.8, 1.7 Hz, 1H), 2.60 (t, J = 2.6 Hz, 1H), 1.77 (d, J = 6.8 Hz, 3H), 0.91 (s, 9H), 0.09, 0.06 (2s, 6H); ^{13}C NMR (CDCl_3 , 100 Hz) δ 132.5, 131.1, 130.7, 130.0, 81.7, 72.1, 70.1, 28.9, 26.1, 18.4, -2.7; IR (film) ν_{max} 3313, 2956, 2930, 2856, 2121, 1255, 1115, 1079, 987, 837; ESIMS m/z 273 ($[\text{M} + \text{Na}^+]$, $\text{C}_{15}\text{H}_{26}\text{NaOSi}$ requires 273).

To a solution of the terminal alkyne precursor of **6** (15.0 g, 59.9 mmol) in Et_2O (270 mL) at -78°C , was added a solution of BuLi (1.6 M in hexane, 41.5 mL, 66.4 mmol). After 45 min, excess crushed dry ice was added and the reaction was allowed to warm to room temperature. The solution was acidified by addition of 0.5 M aqueous citric acid (300 mL). The layers were separated, and the aqueous layer was extracted with additional Et_2O (300 mL x 2). The combined organic layers were dried (MgSO_4), filtered and concentrated in vacuum. The residue was purified by flash chromatography (silica, 50% to 100% EtOAc in hexane) to give the product as a light yellow solid (17.5 g, 99%). ^1H NMR (CDCl_3 , 400 MHz) δ 6.19 (dd, J = 15.1, 10.4 Hz, 1H), 6.03 (ddd, J = 14.9, 10.6, 1.3 Hz, 1H), 5.75 (dd, J = 15.0, 6.8 Hz, 1H), 5.55 (dd, J = 15.1, 6.4 Hz, 1H), 4.36 (q, J = 6.3 Hz, 1H), 2.61-2.48 (m, 2H), 1.77 (d, J = 6.8 Hz,

3H), 0.91 (s, 9H), 0.10, 0.06 (2s, 6H); ^{13}C NMR (CDCl_3 , 100 Hz) δ 157.6, 131.6, 131.3, 130.7, 89.7, 74.0, 71.4, 29.3, 26.0, 18.4, 18.3, -4.3, -4.7; IR (film) ν_{max} 2956, 2930, 2857, 2242, 1689, 1281, 1257, 1080; ESIMS m/z 317 ($[\text{M} + \text{Na}^+]$, $\text{C}_{16}\text{H}_{26}\text{NaO}_3\text{Si}$ requires 317).

Alkynoic ester **8**. To a solution of DIAD (14.7 mL, 72.9 mmol) in dry THF (350 mL) was added Ph_3P (15.8 g, 60.2 mmol), and the mixture was stirred at room temperature for one hour. At $-20\text{ }^\circ\text{C}$, a solution of acid **6** (13.1 g, 44.4 mmol) in 100 mL THF was added. After 15 min, a solution of alcohol **7** (4.0 g, 31.7 mmol) in 150 mL THF was added, and stirring was continued for 2 hours at $-20\text{ }^\circ\text{C}$. The reaction was quenched by addition of 250 mL of pH 7.2 phosphate buffer, followed by warming to room temperature and diluting with EtOAc (1.5 L). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 250 mL). The combined organic layers were washed with brine (250 mL), dried (Na_2SO_4), filtered and concentrated in vacuum. The residue was purified by flash chromatography (silica, 50:1 $\rightarrow$ 20:1 hexanes/EtOAc) to give ester **8** as a mixture of two inseparable diastereoisomers (5.9 g, 47%). ^1H NMR (CDCl_3 , 400 MHz) δ 6.17 (dd, $J = 15.1, 10.5$ Hz, 1H), 6.03 (ddd, $J = 12.3, 10.6, 1.4$ Hz, 1H), 5.70 (dd, $J = 14.8, 6.8$ Hz, 1H), 5.55 (dd, $J = 15.2, 6.4$ Hz, 1H), 5.37 (ddd, $J = 17.1, 10.2, 8.7$ Hz, 1H), 5.06 (q, $J = 6.4$ Hz, 1H), 5.03 (dd, $J = 17.0, 1.5$ Hz, 1H), 4.84 (dd, $J = 10.2, 1.6$ Hz, 1H), 4.34 (q, $J = 6.4$ Hz, 1H), 2.56-2.42 (m, 2H), 1.76 (d, $J = 6.8$ Hz, 3H), 1.57-1.53 (m, 2H), 1.29 (d, $J = 6.4$ Hz, 3H), 1.20-1.10 (m, 1H), 0.90 (s, 9H), 0.79-0.68 (m, 1H), 0.65-0.57 (m, 2H), 0.10, 0.05 (2s, 6H); ^{13}C NMR (CDCl_3 , 100 Hz) δ 154.5, 141.4, 131.8, 131.1, 130.8, 130.4, 112.1, 86.2, 74.9, 73.0, 71.5, 39.7, 29.2, 26.0, 22.4, 19.8, 18.4, 18.3, 17.2, 13.7, -4.3, -4.7; IR (film) ν_{max} 2955, 2930, 2856, 2238, 1710,

1253, 1068; ESIMS m/z 437 ($[M + Cl]^-$, $C_{24}H_{38}ClO_3Si$ requires 437); HRMS (FAB⁺) m/z 403.2687 ($[M + H]^+$, $C_{24}H_{39}O_3Si$ requires 403.2668).

Cobalt complex **9**. To a solution of acid **6** (192 mg, 0.653 mmol) and 5-hexen-1-ol (0.118 mL, 0.979 mmol) in dry CH_2Cl_2 (3 mL) was added EDCI (150 mg, 0.784 mmol) and 4-(dimethylamino)pyridine (8.0 mg, 0.065 mmol). After 3 hrs at room temperature, the reaction mixture was loaded on PTLC plates and purified (12:1 hexane/EtOAc) to give the model ester (146 mg, 59%). ¹H NMR ($CDCl_3$, 400 MHz) δ 6.18 (dd, $J = 15.1, 10.5$ Hz, 1H), 6.04 (ddd, $J = 15.0, 10.5, 1.5$ Hz, 1H), 5.79 (ddt, $J = 17.1, 10.3, 7.2$ Hz, 1H), 5.71 (dq, $J = 15.0, 6.8$ Hz, 1H), 5.56 (dd, $J = 15.1, 6.4$ Hz, 1H), 5.03 (dq, $J = 17.1, 1.6$ Hz, 1H), 4.97 (dd, $J = 10.2, 1.6$ Hz, 1H), 4.35 (q, $J = 6.3$ Hz, 1H), 4.16 (t, $J = 6.6$ Hz, 2H), 2.57-2.44 (m, 2H), 2.09 (q, $J = 7.2$ Hz, 1H), 1.77 (d, $J = 6.9$ Hz, 3H), 1.74-1.63 (m, 2H), 1.52-1.44 (m, 2H), 0.90 (s, 9H), 0.10, 0.06 (2s, 6H); ¹³C NMR ($CDCl_3$, 100 Hz) δ 154.0, 138.4, 131.8, 131.1, 130.8, 130.5, 115.1, 86.6, 74.6, 71.5, 65.9, 33.4, 29.3, 28.1, 26.0, 25.3, 18.4, 18.3, -4.3, -4.7; IR (film) ν_{max} 2955, 2930, 2856, 2238, 1713, 1249, 1072; ESIMS m/z 399 ($[M + Na]^+$, $C_{22}H_{36}NaO_3Si$ requires 399). HRMS (FAB⁺) m/z 375.2363 ($[M - H]^+$, $C_{22}H_{35}O_3Si$ requires 375.2355).

To a solution of the above alkynoic ester (77.8 mg, 0.207 mmol) in toluene (9 mL) was added $Co_2(CO)_8$ (99.0 mg, 0.289 mmol). The mixture was stirred at room temperature for 45 min, and then concentrated in vacuum. The dark residue was purified by PTLC (15:1 hexane/EtOAc) to give cobalt complex **9** (117.5 mg, 86%) as a red oil. ¹H NMR ($CDCl_3$, 400 MHz) δ 6.17 (dd, $J = 15.3, 10.6$ Hz, 1H), 6.03 (ddd, $J = 15.3, 11.3$ Hz, 1H), 5.68 (dd, $J = 14.9, 6.9$ Hz, 1H), 5.61 (dd, $J = 15.2, 6.8$ Hz, 1H), 5.38 (ddd, $J = 17.1, 10.1, 8.7$ Hz, 1H), 5.10 (q, $J = 6.4$ Hz, 1H), 5.04 (dd, $J = 17.1, 1.3$ Hz, 1H), 4.85 (dd, $J = 10.3, 1.4$ Hz, 1H), 4.41, (m, 1H), 3.20-3.15 (m, 2H), 1.76 (d, $J = 6.7$ Hz, 3H), 1.59 (t, $J = 6.6$ Hz, 2H), 1.32 (d, $J =$

6.2 Hz, 3H), 1.22-1.17 (m, 1H), 0.90 (s, 9H), 0.82-0.72 (m, 1H), 0.66-0.59 (m, 2H), 0.09, 0.08 (2s, 6H); ^{13}C NMR (CDCl_3 , 100 Hz) δ 198.7, 169.2, 141.4, 134.3, 132.5, 132.4, 132.2, 131.0, 130.2, 128.8, 127.2, 127.1, 112.0, 93.0, 81.0, 73.7, 73.6, 73.1, 40.0, 26.1, 22.4, 19.9, 18.6, 18.4, 17.4, 13.9, 13.5, -4.2, -4.3, -4.6; IR (film) ν_{max} 2956, 2930, 2858, 2097, 2058, 2029, 1703, 1221, 1065; ESIMS m/z 685 ($[\text{M} + \text{Na}^+]$, $\text{C}_{28}\text{H}_{36}\text{Co}_2\text{NaO}_9\text{Si}$ requires 685).

RCM product **10**. To a solution of cobalt complex **9** (16 mg, 0.024 mmol) in dry CH_2Cl_2 (120 mL) was added tricyclohexyl phosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]-[bezyli-dene] ruthenium(IV) dichloride (second generation Grubbs catalyst) (6.1 mg, 0.0072 mmol). The resulting solution was heated to 45 °C for 1 hr and 10 min, then cooled to room temperature and filtered through a plug of silica gel. The solvent was removed under reduced pressure. The residue was purified by PTLC (15:1 hexane/EtOAc) to give cyclic product **10** (10.5 mg, 71%). ^1H NMR (CDCl_3 , 400 MHz) δ 6.44 (dd, $J = 15.3, 10.8$ Hz, 1H), 5.97 (t, $J = 10.8$ Hz, 1H), 5.58 (dd, $J = 15.4, 7.5$ Hz, 1H), 5.54 (dt, $J = 10.1, 4.5$ Hz, 1H), 4.57-4.47 (m, 2H), 4.25-4.20 (m, 1H), 3.45-3.36 (m, 2H), 2.45-2.37 (m, 1H), 2.13-1.05 (m, 1H), 1.99-1.79 (m, 1H), 1.80-1.62 (m, 2H), 1.51-1.41 (m, 1H), 0.92 (s, 9H), 0.11, 0.08 (2s, 6H); ^{13}C NMR (CDCl_3 , 100 Hz) δ 199.9, 170.4, 135.2, 132.7, 129.0, 127.1, 92.8, 77.4, 73.1, 65.0, 45.2, 26.4, 26.1, 25.4, 18.5, 1.2, -4.2, -4.6; IR (film) ν_{max} 2955, 2930, 2857, 2098, 2059, 2027, 1702, 1213, 1057; ESIMS m/z 643 ($[\text{M} + \text{Na}^+]$, $\text{C}_{25}\text{H}_{30}\text{Co}_2\text{NaO}_9\text{Si}$ requires 643).

Model cyclic alkyne **11**. To a solution of compound **10** (35.6 mg, 0.0574 mmol) in acetone at -10 °C was added ammonium cerium (IV) nitrate (189 mg, 0.344 mmol) portionwise. After 10 min at -10 °C, the reaction was quenched by addition of diisopropylethylamine (0.18 mL, 1.03 mmol). The resulting mixture was filtered through a plug of neutral alumina, and the solvent was removed under reduced pressure. Purification by PTLC (15:1 hexane/EtOAc) afforded cyclic alkyne **11** (17.6 mg, 92%). ¹H NMR (CDCl₃, 400 MHz) δ 6.64 (dd, *J* = 15.5, 11.1 Hz, 1H), 6.07 (t, *J* = 11.0 Hz, 1H), 5.53 (dd, *J* = 15.5, 7.1 Hz, 1H), 5.40 (dt, *J* = 10.4, 4.8 Hz, 1H), 4.41-4.25 (m, 2H), 4.06-4.01 (m, 1H), 2.69-2.62 (m, 1H), 2.56 (dd, *J* = 17.1, 4.4 Hz, 1H), 2.46 (dd, *J* = 17.1, 9.5 Hz, 1H), 2.26-2.21 (m, 1H), 1.75-1.61 (m, 4H), 0.89 (s, 9H), 0.08, 0.07 (2s, 6H); ¹³C NMR (CDCl₃, 100 Hz) δ 153.9, 133.2, 132.9, 128.5, 128.2, 87.7, 77.0, 72.9, 68.0, 29.0, 28.2, 26.7, 26.0, 25.6, 18.3, -4.3, -4.7; IR (film) ν_{max} 2954, 2929, 2857, 2238, 1716, 1245, 1110, 1075, 837; ESIMS *m/z* 357 ([M + Na⁺], C₁₉H₃₀NaO₃Si requires 357). HRMS(FAB⁺) *m/z* 333.1888 ([M - H]⁺, C₁₉H₂₉O₃Si requires 333.1886).

Diels-Alder product **13**. Cyclic alkyne **11** (27 mg, 0.081 mmol) and excess diene **12** (0.30 mL, 0.90 mmol) were mixed and heated in a sealed vial to 140 °C for 48.5 hours. The mixture was cooled to room temperature, loaded onto a PTLC plate, and purified (4:1 hexane/EtOAc) to afford aromatic product **13** (20 mg, 60%). ¹H NMR (CDCl₃, 400 MHz) δ 11.64, (s, 1H), 6.38 (dd, *J* = 15.4, 10.9 Hz, 1H), 6.35 (d, *J* = 2.6 Hz, 1H), 6.30 (d, *J* = 2.6 Hz, 1H), 6.23 (t, *J* = 10.6 Hz, 1H), 5.95 (s, 1H), 5.78 (dd, *J* = 15.3, 8.4 Hz, 1H), 5.60 (q, *J* = 9.9 Hz, 1H), 4.69 (q, *J* = 9.1 Hz, 1H), 4.12 (t, *J* = 8.5 Hz, 2H), 3.63 (d, *J* = 13.0 Hz, 1H), 2.62 (dd, *J* = 13.1, 8.9 Hz, 1H), 2.50-2.40 (m, 1H), 2.12-2.05 (m, 1H), 1.87-1.76 (m, 2H), 1.56-1.44 (m, 2H), 0.78 (s, 9H), -0.20, -0.25 (2s, 6H); ¹³C NMR (CDCl₃, 100 Hz) δ 172.2, 165.7, 160.3, 144.8, 135.4, 131.0, 129.9, 126.0, 113.0, 105.3, 102.2, 78.7, 64.3, 46.6, 25.9, 24.2, 23.7, 23.0, 18.4, -4.7,

-5.0; IR (film) $\nu_{\max}$ 3380, 2954, 2929, 2856, 1648, 1620, 1254, 1169, 1106, 1061, 837; ESIMS m/z 441 ($[M + Na^+]$, $C_{23}H_{34}NaO_5Si$ requires 441). HRMS (FAB⁺) m/z 418.2173 ($[M]^+$, $C_{23}H_{34}O_5Si$ requires 418.2176).

Cobalt complex **14**. To a solution of alkyne **8** (526 mg, 1.31 mmol) in toluene (60 mL) was added $Co_2(CO)_8$ (625 mg, 1.83 mmol). The mixture was stirred at room temperature for 30 min, and the solvent was removed under reduced pressure. The dark residue was purified by flash chromatography (silica, 0 to 5% EtOAc in hexane) to give cobalt complex **14** (902 mg, 100%) as an inseparable mixture of two diastereomers. 1H NMR ($CDCl_3$, 400 MHz) δ 6.17 (dd, $J = 15.3, 10.6$ Hz, 1H), 6.03 (ddd, $J = 15.3, 11.3$ Hz, 1H), 5.68 (dd, $J = 14.9, 6.9$ Hz, 1H), 5.61 (dd, $J = 15.2, 6.8$ Hz, 1H), 5.38 (ddd, $J = 17.1, 10.1, 8.7$ Hz, 1H), 5.10 (q, $J = 6.4$ Hz, 1H), 5.04 (dd, $J = 17.1, 1.3$ Hz, 1H), 4.85 (dd, $J = 10.3, 1.4$ Hz, 1H), 4.41, (m, 1H), 3.20-3.15 (m, 2H), 1.76 (d, $J = 6.7$ Hz, 3H), 1.59 (t, $J = 6.6$ Hz, 2H), 1.32 (d, $J = 6.2$ Hz, 3H), 1.22-1.17 (m, 1H), 0.90 (s, 9H), 0.82-0.72 (m, 1H), 0.66-0.59 (m, 2H), 0.09, 0.08 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 198.7, 169.2, 141.4, 134.3, 132.5, 132.4, 132.2, 131.0, 130.2, 128.8, 127.2, 127.1, 112.0, 93.0, 81.0, 73.7, 73.6, 73.1, 40.0, 26.1, 22.4, 19.9, 18.6, 18.4, 17.4, 13.9, 13.5, -4.2, -4.3, -4.6; IR (film) $\nu_{\max}$ 2956, 2930, 2858, 2097, 2058, 2029, 1703, 1221, 1065; ESIMS m/z 711 ($[M + Na^+]$, $C_{30}H_{38}Co_2NaO_9Si$ requires 711).

RCM product **15**. To a solution of alkyne-cobalt complex **14** (67 mg, 0.097 mmol) in dry CH_2Cl_2 (485 mL) was added tricyclohexyl phosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]

[bezylidene] ruthenim(IV) dichloride (second generation Grubbs catalyst) (21 mg, 0.025 mmol). The resulting mixture was heated to 45 °C for 1.5 hours, and filtered through a short column of silica gel. The filtrate was concentrated in vacuum. The residue was purified by PTLC (15:1 hexanes/EtOAc) to give cyclic product **15** as a 2:1 mixture of two separable diastereomers. Major isomer (23.1 mg, 37%): ¹H NMR (CDCl₃, 400 MHz) δ 6.49 (dd, *J* = 15.4, 10.9 Hz, 1H), 5.84 (t, *J* = 10.6 Hz, 1H), 5.50 (dd, *J* = 15.4, 8.5 Hz, 1H), 5.06 (dd, *J* = 10.5, 6.9 Hz, 1H), 5.02-4.94 (m, 1H), 4.81-4.75 (m, 1H). 3.48-3.36 (m, 2H), 2.22-2.25 (m, 1H), 1.58-1.50 (m, 1H), 1.50-1.46 (m, 1H), 1.32 (d, *J* = 6.2 Hz, 3H), 0.91 (s, 9H), 0.90-0.80 (m, 1H), 0.89 (s, 9H), 0.67-0.63 (m, 1H), 0.59-0.55 (m, 1H), 0.12, 0.09 (2s, 6H); ¹³C NMR (CDCl₃, 100 Hz) δ 199.0, 170.4, 135.7, 134.9, 129.2, 127.8, 92.0, 77.5, 72.5, 72.1, 45.5, 38.0, 26.1, 10.3, 18.4, 16.4, 16.0, -4.2, -4.6; IR (film) ν_{max} 2955, 2928, 2854, 2097, 2060, 2029, 1692, 1232, 1056; ESIMS *m/z* 669 ([M + Na⁺], C₂₇H₃₂Co₂NaO₉Si requires 669); [α]_D²⁵ -127 (*c* 0.11, CHCl₃). Minor isomer (12.6 mg, 20%): ¹H NMR (CDCl₃, 500 MHz) δ 6.60 (dd, *J* = 15.7, 9.9 Hz, 1H), 5.86 (t, *J* = 10.3 Hz, 1H), 5.81 (dd, *J* = 15.7, 4.4 Hz, 1H), 5.12-5.05 (m, 1H), 4.99 (t, *J* = 9.9 Hz, 1H), 4.46-4.44 (m, 1H), 3.58 (dd, *J* = 15.3, 9.4 Hz, 1H), 3.32 (dd, *J* = 15.3, 4.2 Hz, 1H), 2.16 (dt, *J* = 15.3, 4.2 Hz, 1H), 1.65-1.59 (m, 2H), 1.36 (d, *J* = 6.5 Hz, 3H), 0.94 (s, 9H), 0.64-0.59 (m, 2H), 0.14 (s, 6H); ¹³C NMR (CDCl₃, 125 Hz) δ 198.6, 169.7, 135.9, 132.6, 126.8, 126.5, 92.0, 80.7, 73.4, 73.0, 41.8, 37.7, 26.1, 19.3, 18.5, 18.4, 15.1, 13.7, -4.5, -4.6; IR (film) ν_{max} 2929, 2856, 2097, 2059, 2028, 1702, 1220, 1059; ESIMS *m/z* 669 ([M + Na⁺], C₂₇H₃₂Co₂NaO₉Si requires 669). [α]_D²⁵ +48 (*c* 0.19, CHCl₃).

Cyclic alkyne **16**. The major isomer of **15** (23.1 mg, 0.0358 mmol) was dissolved in dry THF (1 mL). At 0 °C, a solution of I₂ (135 mg, 0.536 mmol) in THF (5 mL) was added. After 35 minutes at 0 °C, the reaction was quenched by the addition of a 2 mL 1:1 mixture of sat. aqueous Na₂S₂O₃ and NaHCO₃,

followed by warming to room temperature and diluting with EtOAc (20 mL). The layers were separated, and the organic layer was washed with sat. aqueous NH_4Cl , dried (Na_2SO_4), filtered and concentrated. The residue was purified by PTLC (15:1, hexanes/EtOAc) to cyclic alkyne **16** as colorless oil (8.9 mg, 69%). ^1H NMR (CDCl_3 , 400 MHz) δ 6.70 (dd, $J = 15.6, 11.1$ Hz, 1H), 5.98 (t, $J = 10.8$ Hz, 1H), 5.51 (dd, $J = 15.6, 7.7$ Hz, 1H), 5.20-5.14 (m, 1H), 4.92 (t, $J = 10.7$ Hz, 1H), 4.38-4.33 (m, 1H), 2.59 (dd, $J = 16.8, 4.3$ Hz, 1H), 2.41 (dd, $J = 16.7, 10.9$ Hz, 1H), 2.07 (dt, $J = 14.8, 1.8$ Hz, 1H), 1.74-1.67 (m, 1H), 1.33 (d, $J = 6.5$ Hz, 3H), 1.19-1.12 (m, 1H), 0.93-0.87 (m, 1H), 0.89 (s, 9H), 0.69-0.65 (m, 1H), 0.63-0.58 (m, 1H), 0.07 (s, 6H); ^{13}C NMR (CDCl_3 , 100 Hz) δ 153.4, 136.5, 132.5, 128.3, 125.4, 85.7, 77.4, 73.8, 72.0, 38.6, 29.2, 26.0, 20.4, 18.4, 18.2, 14.6, 12.8; IR (film) ν_{max} 2954, 2928, 2856, 2238, 1706, 1252, 1105, 1072, 1004; ESIMS m/z 383 ($[\text{M} + \text{Na}^+]$, $\text{C}_{21}\text{H}_{32}\text{NaO}_3\text{Si}$ requires 383); HRMS (FAB^+) m/z 360.2130 ($[\text{M}]^+$, $\text{C}_{21}\text{H}_{32}\text{O}_3\text{Si}$ requires 360.2121). $[\alpha]_{\text{D}}^{25} +56$ (c 0.95, CHCl_3).

Diels-Alder product **17**. Compound **16** (156 mg, 0.43 mmol) was dissolved in diene **12** (0.75 mL, 2.3 mmol) and heated to 140 °C in a sealed vial for 66 hours. The reaction mixture was cooled to room temperature and purified by PTLC (4:1, hexanes/EtOAc) to give **17** (143 mg, 75%). ^1H NMR (CDCl_3 , 400 MHz) δ 11.58 (s, 1H), 6.56 (dd, $J = 15.9, 9.3$ Hz, 1H), 6.38 (d, $J = 2.4$ Hz, 1H), 6.33 (d, $J = 2.4$ Hz, 1H), 5.94 (t, $J = 9.5$ Hz, 1H), 5.68 (dd, $J = 15.9, 6.8$ Hz, 1H), 5.46-5.43 (m, 1H), 5.34 (dd, $J = 10.1, 4.3$ Hz, 1H), 4.51 (q, $J = 6.7$ Hz, 1H), 3.79 (dd, $J = 13.6, 6.2$ Hz, 1H), 2.81 (dd, $J = 13.1, 8.9$ Hz, 1H), 1.99-1.81 (m, 2H), 1.44 (d, $J = 6.5$ Hz, 3H), 1.21-1.13 (m, 1H), 0.93-0.87 (m, 1H), 0.88 (s, 9H), 0.58-0.51 (m, 2H), -0.02 (s, 6H); ^{13}C NMR (CDCl_3 , 100 Hz) δ 164.8, 160.5, 143.8, 134.8, 133.7, 129.6, 128.0, 112.3, 106.1, 102.1, 75.7, 72.9, 42.6, 38.0, 26.1, 18.7, 18.4, 16.4, 16.1, 14.8, 1.4, -4.4, -4.6; IR (film) ν_{max} 3376,

2954, 2928, 2856, 1644, 1619, 1257, 1062, 835; ESIMS m/z 467 ($[M + Na]^+$, $C_{25}H_{36}NaO_5Si$ requires 467). HRMS (FAB⁺) m/z 444.2336 ($[M]^+$, $C_{25}H_{36}O_5Si$ requires 444.2332). $[\alpha]^{25}_D +3.1$ (c 1.3, $CHCl_3$).

To a solution of **17** (243 mg, 0.546 mmol) in anhydrous DMF (13.5 mL) was added acetic anhydride (2.9 mL) and 4-(dimethylamino)pyridine (12.0 mg, 0.0546 mmol) sequentially. After 30 min at room temperature, the reaction was quenched by addition of 50 mL of pH 7.2 phosphate buffer. The resulting mixture was diluted with EtOAc (75 mL), separated and the aqueous layer was extracted with additional EtOAc (2 x 50 mL). The combined organic layers were washed with 5% aqueous NaCl (2 x 45 mL). The combined washings were extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with sat. aqueous NaCl (30 mL), dried (Na_2SO_4), filtered and concentrated. Purification of the residue by PTLC (4:1 hexane/EtOAc) gave diacetate **18** (250 mg, 87%). 1H NMR ($CDCl_3$, 400 MHz) δ 6.96 (d, $J = 2.1$ Hz, 1H), 6.88 (d, $J = 2.1$ Hz, 1H), 6.59 (dd, $J = 16.0, 10.5$ Hz, 1H), 5.89 (t, $J = 10.5$ Hz, 1H), 5.66 (dd, $J = 16.1, 4.9$ Hz, 1H), 5.26-5.23 (m, 2H), 4.51 (q, $J = 5.8$ Hz, 1H), 3.12-3.02 (m, 2H), 2.28, 2.23 (2s, 6H), 1.47 (d, $J = 6.2$ Hz, 3H), 1.46-1.39 (m, 1H), 1.14 (ddd, $J = 14.9, 10.1, 2.0$ Hz, 1H), 0.96-0.87 (m, 1H), 0.87 (s, 9H), 0.52-0.48 (m, 2H), -0.01, -0.02 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 168.6, 168.4, 166.4, 151.4, 148.7, 139.1, 135.9, 133.6, 129.2, 127.2, 125.6, 120.4, 114.7, 73.8, 73.2, 43.2, 40.0, 26.0, 21.3, 21.0, 19.3, 18.3, 16.9, 16.2, 17.7, -4.6, -4.7; IR (film) ν_{max} 2954, 2928, 2856, 1775, 1720, 1612, 1191, 1134, 1069; ESIMS m/z 551 ($[M + Na]^+$, $C_{29}H_{40}NaO_7Si$ requires 551); HRMS (FAB⁺) m/z 528.2569 ($[M]^+$, $C_{29}H_{40}O_7Si$ requires 528.2543). $[\alpha]^{25}_D -38$ (c 1.1, $CHCl_3$).

Cyclopropamonocillin **19**. To a solution of diacetate **18** (250 mg, 0.473 mmol) in THF (10.2 mL) at 0 °C was added pyridine (3.4 mL) and HF-Pyridine complex (1.7 mL) sequentially. The resulting mixture was stirred at room temperature for 10.5 hrs. TMSOMe (30 mL) was added, and stirring was continued for 45 min to quench the remaining HF. The solvents were removed under reduced pressure. The alcohol isolated was dried under high vacuum, and dissolved in CH₂Cl₂ (15 mL) and cooled to 0 °C. Dess-Martin periodinane (301 mg, 0.710 mmol) was added, and the resulting mixture was stirred at room temperature for 15 min. The solution was then directly loaded on PTLC plates and purified (1:1 hexane/EtOAc) to give the desired ketone (133 mg, 68%). ¹H NMR (CDCl₃, 500 MHz) δ 8.01 (dd, *J* = 16.1, 11.3 Hz, 1H), 6.97 (d, *J* = 1.4 Hz, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.20 (t, *J* = 10.4 Hz, 1H), 5.96 (d, *J* = 16.0 Hz, 1H), 5.60 (dd, *J* = 10.0, 7.2 Hz, 1H), 5.47-5.41 (m, 1H), 4.20 (d, *J* = 13.8 Hz, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 2.31 (dt, *J* = 15.3, 4.4 Hz, 1H), 2.25, 2.24 (2s, 6H), 1.73-1.71 (m, 1H), 1.50 (d, *J* = 6.5 Hz, 3H), 1.26-1.21 (m, 1H), 1.00-0.97 (m, 1H), 0.75-0.69 (m, 2H); ¹³C NMR (CDCl₃, 125 Hz) δ 198.4, 168.5, 165.0, 152.1, 149.2, 145.6, 143.7, 135.7, 129.6, 128.8, 124.6, 119.1, 115.6, 72.8, 43.0, 38.3, 21.2, 18.2, 16.7, 16.5, 15.6; IR (film) ν_{max} 2928, 1774, 1728, 1657, 1621, 1586, 1290, 1190, 1132, 1029; ESIMS *m/z* 435 ([M + Na⁺], C₂₃H₂₄NaO₇ requires 435); HRMS (FAB⁺) *m/z* 413.1616 ([M + H]⁺, C₂₃H₂₅O₇ requires 413.1600). [α]_D²⁵ -269 (*c* 1.43, CHCl₃).

The above ketone (169 mg, 0.409 mmol) was dissolved in 26 mL 1:1 MeOH and 5% aqueous NaHCO₃, and stirred at room temperature for 14 hrs to remove the phenolic acetates. The resulting solution was diluted with sat. aqueous NH₄Cl (80 mL) and EtOAc (100 mL) and separated. The aqueous layer was extracted with additional EtOAc (3 x 75 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated in vacuum. Purification by PTLC (1:1 hexane/EtOAc) provided **19** (124 mg, 92%). ¹H NMR (CDCl₃, 500 MHz) δ 11.33 (s, 1H), 8.36 (dd, *J* = 16.1, 11.7 Hz, 1H), 6.48 (d, *J* = 1.6 Hz, 1H), 6.40 (d, *J* = 2.5 Hz, 1H), 6.20 (t, *J* = 11.3 Hz, 1H), 6.01 (d, *J* = 15.9 Hz, 1H), 5.72 (dd, *J* = 9.8, 6.2 Hz, 1H), 5.49-5.45 (m, 1H), 5.32 (d, *J* = 13.6 Hz, 1H), 3.51 (d, *J* = 13.7 Hz, 1H), 2.31 (dt, *J* = 15.8, 3.3 Hz, 1H), 1.61-1.55 (m, 1H), 1.55 (d, *J* = 6.7 Hz, 3H), 1.32-1.28 (m, 1H), 1.03-0.97 (m, 1H), 0.74-0.72

(m, 1H), 0.64-0.63 (m, 1H); ^{13}C NMR (CDCl_3 , 125 Hz) δ 201.8, 170.1, 165.6, 161.6, 145.3, 139.2, 129.5, 128.5, 109.4, 104.5, 102.7, 73.5, 43.2, 27.6, 17.9, 17.2, 15.9, 13.9; IR (film) ν_{max} 3260, 1650, 1618, 1586, 1447, 1259, 1160, 1099, 996, 854; ESIMS m/z 351 ($[\text{M} + \text{Na}^+]$, $\text{C}_{19}\text{H}_{20}\text{NaO}_5$ requires 351); HRMS (FAB^+) m/z 329.1382 ($[\text{M} + \text{H}]^+$, $\text{C}_{19}\text{H}_{21}\text{O}_5$ requires 329.1389). (+)-(R, R, S)-**19**: $[\alpha]^{25}_{\text{D}}$ -189 (c 0.77, CH_2Cl_2).

Cycloproparadicicol **2**. Compound **19** (26.5 mg, 0.081 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and cooled to 0 °C. A solution of SO_2Cl_2 in CH_2Cl_2 (4.5 mL, diluted from 0.123 mL 1 M solution in CH_2Cl_2 , 0.123 mmol) was added dropwise. After 45 minutes, the reaction was quenched by the addition of 5 mL of 5% NH_4Cl , and diluted with CH_2Cl_2 . The layers were separated, and the organic phase was washed with brine, dried (MgSO_4), filtered and concentrated in vacuum. Purification of the residue by PTLC (3:1, hexanes/ EtOAc) gave **2** as a white solid (17.8 mg, 61%). ^1H NMR (CDCl_3 , 500 MHz) δ 10.89 (s, 1H), 8.00 (dd, $J = 15.9, 11.3$ Hz, 1H), 6.63 (s, 1H), 6.42 (s, 1H), 6.13 (t, $J = 11.2$ Hz, 1H), 6.04 (d, $J = 16.3$ Hz, 1H), 5.62 (dd, $J = 9.9, 5.8$ Hz, 1H), 5.46-5.42 (m, 1H), 4.90 (broad d, $J = 15.9$ Hz, 1H), 3.77 (bs, 1H), 2.22 (dt, $J = 15.8, 3.2$ Hz, 1H), 1.60-1.52 (m, 1H), 1.48 (d, $J = 6.7$ Hz, 3H), 1.15-1.11 (m, 1H), 0.90-0.85 (m, 1H), 0.69-0.65 (m, 1H), 0.57-0.54 (m, 1H); ^{13}C NMR (CDCl_3 , 125 Hz) δ 199.2, 169.4, 162.7, 155.6, 143.5, 142.5, 136.9, 129.9, 128.9, 115.6, 107.8, 103.5, 74.4, 46.4, 37.4, 17.9, 17.3, 15.6, 13.6; IR (film) ν_{max} 3341, 1716, 1651, 1609, 1578 cm^{-1} ; ESIMS m/z 385 ($[\text{M} + \text{Na}^+]$, $\text{C}_{19}\text{H}_{19}\text{NaO}_5\text{Cl}$ requires 385); HRMS (ESI) m/z 385.0820 ($[\text{M} + \text{Na}^+]$, $\text{C}_{19}\text{H}_{19}\text{NaO}_5\text{Cl}$ requires 385.0819). (+)-(R, R, S)-**2**: $[\alpha]^{25}_{\text{D}}$ +69 (c 0.87, CH_2Cl_2).