Supporting Information for:

Concise Synthesis of a Lactonamycin Model System By Diastereoselective Dihydroxylation of a Highly Functionalized Naphthoquinone

Christopher Cox and Samuel J. Danishefsky*

General. All nonaqueous reactions were carried out in oven- or flame-dried glassware under argon, unless otherwise specified. All reagents used were commercially available from Sigma-Aldrich, unless indicated otherwise. Solvents were reagent grade and purified by standard techniques: THF and diethyl ether were distilled from Na-benzophenone; CH_2Cl_2 was distilled from CaH_2; all other solvents were Aldrich "anhydrous" grade solvents, unless indicated otherwise. Reactions were magnetically stirred and monitored by thin layer chromatography on Whatman 250 μm alumina-backed silica gel plates. Flash chromatography was performed with SAI silica gel 60 (particle size 32-63 μm), and Florisil was 200 mesh from Aldrich. Yields reported are for isolated, spectroscopically pure compounds unless otherwise indicated. Melting points are uncorrected. $CDCl_3$ was allowed to stand over K_2CO_3 and 4 Å MS to neutralize and dry it prior to NMR sample preparation. NMR spectra were recorded on Bruker DPX 300, DRX 300, 400 or DMX 500 MHz spectrometers. ^1H and ^{13}C chemical shifts were referenced to residual solvent peaks. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrometer, and solutions were approximately 5 mg/mL. High resolution mass spectra were acquired in the Columbia University Mass Spectral Core facility on a JEOL HX110 spectrometer.

Bromide 10. To a suspension of 1.27 g (32 mmol, 1.1 equiv) of NaH (60% suspension in oil) in 100 mL of THF at 0 ˚C was added 3.14 mL (30 mmol, 1.05 equiv) of benzyl alcohol. The mixture was stirred for 30 min, and then 10.4 g (29 mmol, 1 equiv) of 2-bromo-3-(bromomethyl)-1,4-dimethoxynaphthalene[1] dissolved in 40 mL of THF was added dropwise. Following the addition of 1.1 g (2.9 mmol, 10 mol%) of tetrabutylammonium iodide, the solution was warmed to rt and stirred for 8 h. The reaction was carefully quenched with 150 mL saturated NH_4Cl, and then extracted with 2 x 150 mL EtOAc. The combined organic layers were washed with 1 x 100 mL brine, dried with Na_2SO_4, concentrated by rotary evaporation, and the residue was recrystallized from Et_2O/pentane to yield 9.04 g (81%) of **10** as a white powder: mp = 76-77 ˚C. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.1 (2H, m), 7.6 (2H, m), 7.5 (2H, m), 7.4-7.3 (3H, m), 4.9 (3H, s), 4.8 (3H, s), 4.05 (3H, s), 4.0 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 152.7, 150.2, 138.1, 129.2, 128.3, 128.2, 127.9, 127.7, 127.3, 126.6, 123.0, 122.5, 116.5, 73.1,

66.7, 63.9, 61.3 ppm; IR (KBr) 2935, 1579, 1571, 1455, 1360, 1086 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{19}BrO_3$ $[M]^+$: 386.0518; found 386.0500.

Aldehyde 11. To a well stirred solution of 7.0 g (18.0 mmol, 1 equiv) of **10** in 140 mL of THF at -95 ˚C was added quickly 7.25 mL of a 2.5 M solution of nBuLi in hexanes (18.0 mmol, 1 equiv), followed 30 seconds later by 1.75 mL (22 mmol, 1.2 equiv) of freshly distilled ethyl formate. The resultant solution was stirred for 10 min at low temperature, and allowed to warm to rt over 30 min. The reaction was then poured into a separatory funnel containing 100 mL of saturated NH_4Cl, and extracted with 2 x 150 mL EtOAc. The organic layers were combined, washed with 1 x 100 mL brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by flash column chromatography with 4:1 hexanes:EtOAc to yield 4.87 g (80%) of **11** as a white powder: mp = 74-76 ˚C. ^1H NMR ($CDCl_3$, 300 MHz) δ 10.7 (1H, s), 8.3 (1H, m), 8.2 (1H, m), 7.8-7.6 (2H, m), 7.5-7.3 (5H, m), 5.1 (2H, s), 4.7 (2H, s), 4.1 (3H, s), 4.0 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 191.6, 159.1, 152.1, 138.3, 131.6, 129.3, 128.8, 128.3, 128.25, 127.6, 127.3, 125.0, 124.7, 123.4, 123.2, 73.4, 65.1, 63.7, 62.7 ppm; IR (KBr) 2938, 2889, 2838, 1685, 1357, 1067 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{20}O_4$ $[M + H]^+$: 337.1440; found 337.1451.

β-**Hydroxy ester 12a.** To 2.45 mL (17.5 mmol, 1.25 equiv) of diisopropylamine in 100 mL THF at 0 ˚C was added 7.0 mL of a 2.5 M solution of nBuLi in hexanes (17.5 mmol, 1.25 equiv). After 30 min, the solution was cooled to -78 ˚C and 2.35 mL (17.5 mmol, 1.25 equiv) of *t*-butyl acetate was added dropwise. After 45 min, 4.7g (14.0 mmol, 1 equiv) of **11** in 45 mL THF was added dropwise and the solution was stirred for 30 min. The reaction was quenched with 150 mL of saturated NH_4Cl, and extracted with 2 x 150 mL EtOAc. The organic layers were combined, washed with 1 x 100 mL brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by flash column chromatography with 3:1 hexanes:EtOAc to yield 6.3 g (100%) of **12a** as a highly viscous, colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.2-8.1 (2H, m), 7.6 (2H, m), 7.5-7.3 (5H, m), 5.8 (1H, dd, J = 9.8, 3.3 Hz), 5.15 (1H, d, J = 10.3 Hz), 4.95 (1H, d, J = 10.3 Hz), 4.75 (1H, d, J = 11.4 Hz), 4.70 (1H, d, J = 11.4 Hz), 4.2 (1H, s), 4.05 (3H, s), 3.9 (3H, s), 3.3 (1H, dd, J = 15.8, 9.8 Hz), 2.9 (1H, dd, J = 15.8, 3.3 Hz), 1.5 (9H, s) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.4, 151.8, 150.9, 137.5, 131.0, 128.8, 128.1, 128.0, 127.9, 127.5, 126.4, 126.2, 125.0, 122.7, 122.4, 80.3, 72.8, 66.5, 63.9, 63.1, 62.9, 43.2, 27.8 ppm; IR (neat) 3482, 2978, 2935, 2848, 1727, 1589, 1455, 1358, 1151, 1067 cm^{-1}; HRMS (FAB) calcd for $C_{27}H_{32}O_6$ $[M]^+$: 452.2199; found 452.2196.

Quinone 13a. To 850 mg (1.88 mmol, 1 equiv) of **12a** in 25 mL CH_3CN at 0 ˚C was added dropwise a solution of 2.6 g (4.7 mmol, 2.5 equiv) of ammonium cerium (IV) nitrate in 12.5 mL of water. The mixture was stirred for 30 min, and then quenched with 100 mL water. The mixture was extracted with 2

x 125 mL CH_2Cl_2, and the combined organic layers were washed with 2 x 100 mL water, dried over Na_2SO_4, and concentrated by rotary evaporation. The resultant oil was passed through a short pad of silica with 3:1 hexanes:EtOAc to provide 774 mg (97%) of **13a** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.1 (2H, m), 7.7 (2H, m), 7.4-7.2 (5H, m), 5.45 (1H, dt, *J* = 9.1, 4.0 Hz), 4.85 (1H, d, *J* = 11.0 Hz), 4.7-4.6 (3H, m), 3.9 (1H, d, *J* = 9.2 Hz), 2.95 (1H, dd, *J* = 15.4, 9.1 Hz), 2.75 (1H, dd, *J* = 15.4, 4.0 Hz), 1.4 (9H, s) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 186.4, 183.9, 170.0, 147.1, 141.4, 137.3, 134.1, 133.8, 131.9, 131.4, 128.4, 127.9, 127.8, 126.5, 126.2, 81.0, 73.6, 67.4, 61.8, 43.1, 28.0 ppm; IR (neat) 3512, 2978, 1728, 1662, 1593, 1290, 1149, 1074 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{26}O_6$ $[M + H]^+$: 423.1807; found 423.1807.

Spirocyclic lactone 15. To 1.70 g (4.0 mmol, 1 equiv) of quinone **13a** and 615 mg (5.25 mmol, 1.3 equiv) of N-methylmorpholine N-oxide in 85 mL of 50:50 acetone:water was added 1.6 mL (0.13 mmol, 3.25 mol%) of OsO_4 (2.5% solution in *t*-butanol). After stirring for 6 h at rt, the mixture was quenched with 100 mL of saturated $NaHSO_3$ and allowed to stir for an additional 12 h. The solution was then extracted with 2 x 100 mL EtOAc, the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The crude material was purified by flash column chromatography with 3:1 hexanes:EtOAc to yield 1.30 g (71%) of **14** as a crunchy white taffy. This material was dissolved in 25 mL of CH_2Cl_2, cooled to 0 ˚C, and 12.5 mL of 90% trifluoroacetic acid/water was added dropwise. The mixture was warmed to rt, allowed to stir for 12 h, and then carefully quenched by dumping into saturated $NaHCO_3$. After the layers were separated, the aqueous phase was extracted with 2 x 50 mL CH_2Cl_2, the combined organic phases were again washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated by rotary evaporation. The crude material was purified by flash column chromatography with 3:1 to 2:1 hexanes:EtOAc to yield 899 mg (83%) of **15** as a white powder: mp = 132-134 ˚C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.2 (1H, m), 8.1 (1H, m), 7.9-7.8 (2H, m), 7.2 (3H, m), 6.8 (2H, m), 5.1 (1H, m), 4.4 (1H, d, *J* = 11.9 Hz), 4.3 (2H, m), 4.2 (1H, s), 4.0 (1H, d, *J* = 9.7 Hz), 3.7 (1H, d, *J* = 9.7 Hz), 3.1 (1H, dd, *J* = 17.5, 9.1 Hz), 2.9 (1H, dd, *J* = 17.5, 8.1 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 195.6, 191.8, 171.4, 136.2, 135.4, 134.9, 134.85, 133.3, 128.2, 127.8, 127.2, 127.15, 86.8, 79.7, 73.6, 71.6, 69.0, 37.7 ppm; IR (KBr) 3520, 3467, 2934, 1794, 1698, 1596, 1406, 1277, 1194, 1122 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{18}O_7$ $[M + H]^+$: 383.1131; found 383.1130.

Acetonide 17. Spirocyclic lactone **15** (173 mg, 0.045 mmol, 1 equiv) was dissolved in 12 mL of CH_2Cl_2. After cooling to -78 ˚C, 1.35 mL (1.35 mmol, 3 equiv) of 1 M BBr_3 in CH_2Cl_2 was added dropwise and the resultant solution stirred for 30 min. The reaction was quenched with saturated NH_4Cl, extracted with 2 x 50 mL of EtOAc, washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by flash column chromatography with 1:1 hexanes:EtOAc to

provide 113 mg (85%) of the triol as a crunchy white taffy. This material was dissolved in 5 mL of acetone (freshly distilled from $CaSO_4$) and cooled to 0 ˚C. To the solution was added dropwise 115 mg (2 equiv) of $AlCl_3$ in 5 mL Et_2O. After stirring for 30 min at 0 ˚C, the reaction was quenched with ice cold saturated $NaHCO_3$, extracted with 2 x 15 mL EtOAc, washed with brine, and dried over Na_2SO_4. Following concentration by rotary evaporation, the product was purified by flash column chromatography with 1:1 hexanes:EtOAc to provide 100 mg (79%) of **17** as a white powder: mp = 228 ˚C (dec). ^{1}H NMR (d_6-acetone, 400 MHz) δ 8.15 (1H, m), 8.05 (1H, m), 7.9 (2H, m), 5.4 (1H, d, *J* = 5.4 Hz), 4.9 (1H, d, *J* = 9.0 Hz), 4.7 (1H, m), 4.2 (1H, d, *J* = 9.0 Hz), 2.95 (1H, dd, *J* = 17.4, 9.8 Hz), 2.85 (1H, s), 2.6 (1H, dd, *J* = 17.4, 8.6 Hz) ppm; ^{13}C NMR (d_6-acetone, 101 MHz) δ 192.0, 191.1, 172.7, 137.1, 135.8, 135.4, 135.2, 127.7, 127.1, 112.9, 90.6, 88.3, 70.9, 63.4, 36.9, 26.4, 25.8 ppm; IR (KBr) 3468, 2992, 1794, 1703, 1596, 1375, 1286, 1261, 1213, 1070 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{16}O_7$ [M + H]$^+$: 333.0974; found 333.0974.

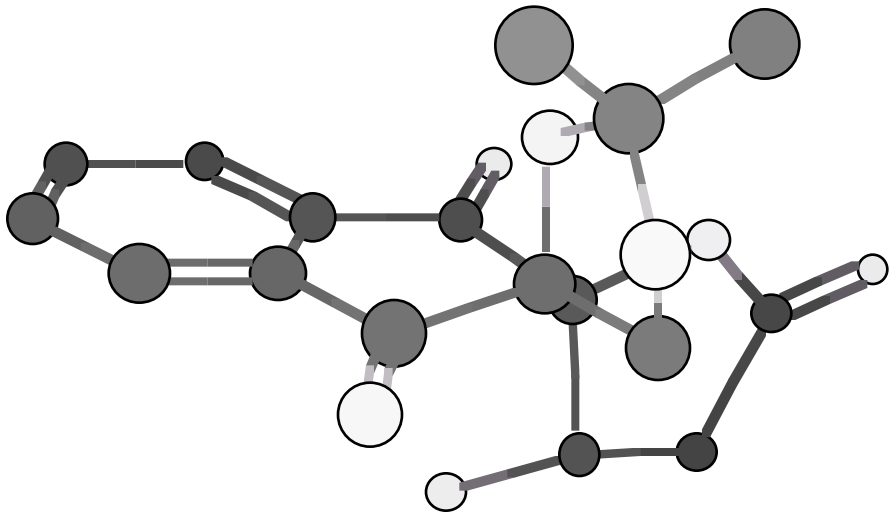
α-Iodo, β-OTMS lactone 20. To a solution of 210 mg (0.55 mmol, 1 equiv) of **15** in 7 mL of THF was added 245 μL (1.9 mmol, 3.5 equiv) of chlorotrimethylsilane. After cooling to -78 ˚C, 1.70 mL (1.7 mmol, 3.1 equiv) of a 1M solution of LiHMDS in THF was added dropwise, the resultant mixture was stirred for 30 min, and then 137 mg (0.60 mmol, 1.1 equiv) of N-iodosuccinimide in 1 mL THF was added. After stirring for 30 min at -78 ˚C, the reaction was quenched with saturated NH_4Cl, dumped into a separatory funnel, and extracted with 2 x 50 mL EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The crude material was purified by flash column chromatography with 19:1 to 9:1 hexanes:EtOAc to yield 307 mg (85%) of **20** as a 3:1 mixture of diastereomers as a thick, colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) **less polar product:** δ 8.1 (2H, m), 7.8 (2H, m), 7.4-7.3 (5H, m), 5.6 (1H, d, *J* = 8.0 Hz), 4.7 (3H, m), 4.1 (1H, d, *J* = 9.4 Hz), 3.9 (1H, d, *J* = 9.4 Hz), -0.1 (9H, s), -0.3 (9H, s) ppm; **more polar product:** δ 8.0 (2H, m), 7.8 (2H, m), 7.4-7.3 (5H, m), 4.7 (2H, m), 4.5 (1H, d, *J* = 10.4 Hz), 4.35 (1H, d, *J* = 7.8 Hz), 4.25 (1H, d, *J* = 9.1 Hz), 3.9 (1H, d *J* = 9.1 Hz), -0.1 (9H, s), -0.4 (9H, s) ppm; IR (neat) 3066, 3033, 2957, 1798, 1712, 1596, 1454, 1254, 1102 cm^{-1}; HRMS (FAB) calcd for $C_{27}H_{33}IO_7Si_2$ [M + H]$^+$: 653.0888; found 653.0909.

α,β-Unsaturated lactone 21a. To 44 mg (0.067 mmol, 1 equiv) of **20** dissolved in 3 mL of THF was added 12 μL (0.081, 1.2 equiv) of DBU. After stirring for 30 min, the volatiles were removed under vacuum, and the crude material was purified by flash column chromatography with 9:1 hexanes:EtOAc to provide 31 mg (82%) of **21a** as a sticky white taffy. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.2 (1H, m), 8.1 (1H, m), 7.85 (1H, s), 7.8 (2H, m), 7.3 (3H, m), 6.95 (2H, m), 4.35 (1H, d, *J* = 12.0 Hz), 4.3 (1H, d, *J* = 12.0 Hz), 3.65 (1H, d, *J* = 9.6 Hz), 3.6 (1H, d, *J* = 9.6 Hz), 0.2 (9H, s) ppm; ^{13}C NMR ($CDCl_3$,

75.5 MHz) δ 194.0, 186.7, 167.8, 156.3, 135.9, 135.2, 134.7, 134.5, 133.9, 128.4, 128.1, 127.6, 127.5, 127.1, 96.1, 87.4, 83.3, 73.9, 73.5, 1.9 ppm; IR (neat) 2955, 1781, 1709, 1595, 1251, 1200, 1102 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{23}IO_6Si$ $[M + H]^+$: 563.0387; found 563.0372.

α-Iodolactone 19. α,β-unsaturated lactone **21a** (24 mg, 0.043 mmol, 1 equiv) was dissolved in 3 mL of CH_2Cl_2. After cooling to -78 ˚C, 85 μL (.085 mmol, 2 equiv) of 1 M BBr_3 in CH_2Cl_2 was added dropwise and the resultant solution stirred for 15 min. The reaction was quenched with saturated NH_4Cl, extracted with 2 x 10 mL of CH_2Cl_2, washed with water, and dried over Na_2SO_4. After concentration by rotary evaporation and further drying under high vacuum, the residue was dissolved in 3 mL of $CHCl_3$ (dried and neutralized over 4 Å MS and K_2CO_3). After adding 100 mg of silica gel, the suspension was stirred for 3.5 h. The reaction was then concentrated and the crude product was purified by flash column chromatography with 3:1 followed by 2:1 hexanes:EtOAc to provide 17 mg (84%) of **19** as an inseparable 1.5:1 mixture of diastereomers as a sticky white taffy. ^1H NMR ($CDCl_3$, 400 MHz) **less polar product**: δ 8.3 (2H, m), 7.9 (2H, m), 4.85 (1H, s), 4.75 (1H, d, *J* = 8.5 Hz), 4.6 (1H, s), 3.9 (1H, d, *J* = 8.5 Hz), 0.1 (9H, s) ppm; **more polar product**: δ 8.3 (2H, m), 7.9 (2H, m), 4.95 (1H, d, *J* = 6.0 Hz), 4.8 (1H, d, *J* = 8.5 Hz), 4.45 (1H, d, *J* = 6.0 Hz), 3.85 (1H, d, *J* = 8.5 Hz), 0.1 (9H, s) ppm; IR (CH_2Cl_2) 1798, 1706, 1594, 1188 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{17}IO_6Si$ $[M + H]^+$: 472.9909; found 472.9904.

X-Ray Crystallography of 17. Crystals suitable for diffraction were grown by slow evaporation of THF. Crystal data for **17**: monoclinic, a = 13.194 (2) Å, b = 10.839 (2) Å, c = 10.957 (2) Å, α = 90.00˚ β = 97.282 (3)˚, γ = 90.00˚, space group = $P2_1/c$; G.O.F. = 1.045; R = 5.27%.



Supporting Figure 1. Chem-3D representation of the X-ray structure of **17**.

1. Silverman, R. B.; Oliver, J. S. *J. Med. Chem.* **1989**, *32*, 2138-2141.