Asymmetric Total Synthesis of Rollicosin

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SUPPORTING INFORMATION

General. Unless otherwise noted, all non-aqueous reactions were performed in flame-dried glassware under nitrogen. Optical rotations were measured on a Perkin Elmer 341 polarimeter at room temperature. Concentrations (*c*) are reported in g/100 mL. Infrared spectra (**IR**) were obtained on a Perkin Elmer 1600 Series FT-IR. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra and were recorded on a Varian Inova-400 at 400 MHz and 100 MHz respectively. Chemical shifts are reported in ppm relative to CHCl_3 (δ 7.27) for ^1H NMR and the central resonance of CDCl_3 (δ 77.0) for ^{13}C NMR. High resolution fast atom bombardment mass spectra (**HRMS**) were obtained on a JEOL MStation JMS-700 mass spectrometer at the University of Massachusetts-Amherst.

EM Science DriSolv[®] solvents (CH_2Cl_2 , PhH, THF, PhCH_3) were used in moisture sensitive reactions. (*R,R*)-hexa-1,5-diene-3,4-diol **10** was prepared from D-mannitol using the protocol reported by Burke and Sametz.¹ Benzyl ether **8** was prepared from 10-undecen-1-ol as described by Chow and Kitching.² (5*S*)-Methyl-3-phenylsulfanyldihydrofuran-2-one **3** was prepared according to the procedure of White, Somers, and Reddy.³ Commercially available reagents and solvents were used as received without further purification.

Experimental Procedures.

Mono-TBS Ether of 10. To a solution of (*R,R*)-hexa-1,5-diene-3,4-diol **10** (3.075 g, 26.94 mmol) in CH_2Cl_2 (135 mL) at 0 °C was added imidazole (2.752 g, 40.41 mmol) and TBSCl (4.060 g, 26.94 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 18 h, after which time it was quenched by addition of H_2O (100 mL). The biphasic mixture was diluted with Et_2O (200 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous phase was extracted with Et_2O (3x150 mL). The combined organic phases were washed with 0.1 M HCl (150 mL) and brine (150 mL) and dried over MgSO_4 . The drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (6:1 pentane/ Et_2O) provided 4.430 g (72%) of the corresponding mono-TBS ether as a colorless oil. Data for the mono-TBS ether of **10**: $[\alpha]_D^{22} +80.1$ (*c* 2.21, CH_2Cl_2); **IR** (thin film) 3567, 3054, 2956, 2931, 2886, 2858 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 5.85 (ddd, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.82 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1H), 5.34 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.25 (ddd, *J* = 17.2, 1.6, 1.2 Hz, 1H), 5.22 (m, 1H), 5.19 (m, 1H), 4.00-3.93 (m, 2H), 2.54 (br s, 1H), 0.92 (s,

9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 137.7, 136.9, 117.1, 116.5, 77.4, 75.6, 25.8, 18.2, -4.2, -4.9; HRMS calcd for $\text{C}_{12}\text{H}_{25}\text{O}_2\text{Si}$ (MH^+) 229.1624, found 229.1660.

Acrylate Ester 9. To a solution of the mono-TBS ether of **10** (2.133 g, 9.33 mmol) in CH_2Cl_2 (93 mL) at 0 °C was added $i\text{Pr}_2\text{NEt}$ (6.5 mL, 37.32 mmol) followed by acryloyl chloride (1.52 mL, 18.66 mmol). The reaction mixture was warmed to room temperature and stirred for 12 h, after which time it was quenched with 100 mL of water and diluted with Et_2O (150 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3x100 mL). The combined organic phases were washed with saturated NH_4Cl (150 mL) and brine (150 mL) and dried over MgSO_4 . The drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (12:1 pentane/ Et_2O) gave acrylate ester **9** (2.371 g, 90%) as a colorless oil. Data for **9**: $[\alpha]_D^{22} +62.9$ (c 2.02, CH_2Cl_2); IR (thin film) 3095, 2957, 2930, 2887, 2858, 1734 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 6.45 (dd, $J = 17.4, 1.6$ Hz, 1H), 6.16 (dd, $J = 17.4, 10.5$ Hz, 1H), 5.88-5.78 (m, 2H), 5.86 (dd, $J = 10.5, 1.6$ Hz, 1H), 5.32-5.26 (m, 3H), 5.23 (dt, $J = 10.7, 1.4$ Hz, 1H), 5.19 (ddd, $J = 10.5, 2.0, 1.4$ Hz, 1H), 4.24 (tt, $J = 6.2, 1.4$ Hz, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 165.1, 136.6, 132.6, 131.0, 128.5, 118.0, 116.9, 77.1, 74.2, 25.7, 18.1, -4.6, -4.9; HRMS calcd for $\text{C}_{15}\text{H}_{27}\text{O}_3\text{Si}$ (MH^+) 283.1729, found 283.1733.

Metathesis Product 7. To a solution of acrylate ester **9** (1.020 g, 3.61 mmol) in PhH (360 mL) was added the benzyl ether of 10-undecen-1-ol **8** (2.820 g, 10.83 mmol). The mixture was heated to reflux, and a solution of second generation Grubbs' catalyst **11** (306.5 mg, 0.36 mmol) in PhH (10 mL) was added over a period of 10 hours by syringe pump. Heating was continued for 8 h after addition was complete. After cooling to room temperature, the mixture was filtered through a short pad of silica gel, and the filtrate was concentrated in vacuo. Purification by silica gel chromatography (3:1 hexanes/ Et_2O) gave metathesis product **7** (1.124 g, 64%) as a slightly yellow oil. Data for **7**: $[\alpha]_D^{22} -36.3$ (c 1.67, CHCl_3); IR (thin film) 3010, 2928, 2855, 1762 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.44 (dd, $J = 5.8, 1.6$ Hz, 1H), 7.36-7.26 (m, 5H), 6.15 (dd, $J = 5.8, 2.0$ Hz, 1H), 5.69 (dt, $J = 15.4, 6.8$ Hz, 1H), 5.26 (ddt, $J = 15.4, 7.2, 1.4$ Hz, 1H), 4.95 (dt, $J = 5.5, 1.8$ Hz, 1H), 4.51 (s, 2H), 4.33 (br t, $J = 6.3$ Hz, 1H), 3.47 (t, $J = 6.6$ Hz, 2H), 2.00 (q, $J = 6.8$ Hz, 2H), 1.62 (m, 2H), 1.39-1.21 (m, 12H), 0.90 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.9, 153.9, 138.7, 135.5, 128.3, 127.6, 127.4, 126.6, 122.8, 85.7, 73.6, 72.8, 70.5, 32.1, 29.7, 29.5, 29.4, 29.3, 29.0, 28.9, 26.2, 25.7, 18.1, -4.4, -5.0; HRMS calcd for $\text{C}_{29}\text{H}_{47}\text{O}_4\text{Si}$ (MH^+) 487.3244, found 487.3219.

Alcohol 17. To a solution of metathesis product **7** (995.6 mg, 2.05 mmol) in EtOAc (25 mL) at room temperature was added approximately 100 mg of 10 wt.% Pd on activated carbon. The reaction mixture was stirred under 1 atmosphere of H₂ for 8 hours after which time it was filtered through a pad of silica gel with EtOAc and concentrated in vacuo. Purification by silica gel column chromatography (3:1 hexanes/EtOAc) gave alcohol **17** (706.4 mg, 86%) as a colorless oil. Data for **17**: $[\alpha]_D^{22}$ -69.6 (*c* 1.70, CHCl₃); **IR** (thin film) 3462, 3019, 2929, 2856, 1768 cm⁻¹; **¹H NMR** (CDCl₃, 400 MHz) δ 4.41 (ddd, *J* = 7.6, 6.1, 4.3 Hz, 1H), 3.59 (td, *J* = 6.1, 4.5 Hz, 1H), 3.56 (t, *J* = 6.7 Hz, 2H), 2.49 (ddd, *J* = 18.0, 10.1, 6.2 Hz, 1H), 2.39 (ddd, *J* = 17.6, 10.1, 7.4 Hz, 1H), 2.14 (m, 1H), 1.95 (m, 1H), 1.57-1.45 (m, 3H), 1.40-1.12 (m, 18H), 0.81 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); **¹³C NMR** (CDCl₃, 100 MHz) δ 177.5, 81.6, 74.1, 63.0, 32.7, 32.6, 29.7, 29.5, 29.4, 29.3, 28.6, 25.8, 25.7, 25.2, 23.6, 18.0, -4.5; **HRMS** calcd for C₂₂H₄₅O₄Si (MH⁺) 401.3087, found 401.3074.

Alkene 6. To a solution of alcohol **17** (540.5 mg, 1.35 mmol) in CH₂Cl₂ (15 mL) at room temperature was added crushed 4 Å molecular sieves (~500 mg). The slurry was cooled to 0 °C, and NMO (237.8 mg, 2.03 mmol) and TPAP (94.9 mg, 0.27 mmol) were added sequentially. The greenish black slurry was stirred for 10 minutes at 0 °C. The reaction mixture was filtered through a short pad of silica gel with EtOAc, and the filtrate was concentrated in vacuo to give 499.0 mg of the corresponding aldehyde, which was used without purification in the next step.

The crude aldehyde (499.0 mg, 1.25 mmol) was dissolved in THF (12 mL), and the solution was cooled to -10 °C. In a separate flask, CH₃PPh₃Br (1.446 g, 4.05 mmol) in THF (15 mL) and cooled to 0 °C. 2.53 mL of a 1.6 M solution of *n*BuLi in hexanes (4.05 mmol) was added, and the resulting bright yellow solution was stirred for 30 minutes. The 0.23 M solution of Wittig reagent was added dropwise via syringe to the crude aldehyde until the yellow color persisted, and the slurry was stirred at -10 °C for an additional 5 minutes. The reaction was quenched by addition of H₂O (40 mL) and diluted with Et₂O (50 mL). The layers were separated, and the aqueous phase was extracted with Et₂O (3x50 mL). The combined organic layers were washed with 0.1 M HCl (40 mL) and brine (40 mL) and dried over MgSO₄. The drying agent was removed by filtration, and the filtrate was concentrated in vacuo. Purification by silica gel column chromatography (8:1 hexanes/EtOAc) gave alkene **6** (407.0 mg, 76% from **17**) as a colorless oil. Data for **6**: $[\alpha]_D^{22}$ -25.5 (*c* 1.54, CHCl₃); **IR** (thin film) 3076, 2926, 2855, 1784 cm⁻¹; **¹H NMR** (CDCl₃, 400 MHz) δ 5.73 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 4.93 (dq, *J* = 17.1, 1.2 Hz, 1H), 4.85 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 4.41 (ddd, *J* = 7.6, 6.1, 4.3 Hz, 1H), 3.59 (td, *J* = 6.1, 4.3 Hz, 1H), 2.49 (ddd, *J* = 17.8, 10.1, 6.2 Hz, 1H), 2.39 (ddd, *J* = 17.4, 10.1, 7.4 Hz, 1H), 2.13 (m, 1H), 2.00-1.91 (m, 3H), 1.52 (m, 1H), 1.39-1.17 (m, 17H), 0.81 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); **¹³C NMR** (CDCl₃, 100 MHz) δ 177.4, 139.2, 114.1, 81.6, 74.2, 33.8, 32.6, 29.7,

29.5, 29.4, 29.1, 28.9, 28.6, 25.8, 25.2, 23.6, 18.0, -4.5; **HRMS** calcd for C₂₃H₄₅O₃Si (MH⁺) 397.3138, found 397.3184.

Diol 18. Alkene **6** (593.1 mg, 1.50 mmol) was dissolved in 7.5 mL of *t*BuOH and 7.5 mL of H₂O and cooled to 0 °C. AD-mix-β (2.101 g) was added, and the slurry was stirred at 0 °C for 36 h. The reaction was quenched by addition of sat. Na₂S₂O₃ (15 mL), warmed to room temperature, and stirred for 1 h. The mixture was extracted with EtOAc (6x30 mL), and the organic extracts were dried over MgSO₄. The drying agent was removed by filtration, and the filtrate was concentrated in vacuo. Purification by silica gel column chromatography (2:1 EtOAc/hexanes) gave diol **18** (561.5 mg, 87%) as a colorless oil. Data for **18**: [α]_D²² +19.3 (*c* 1.05, CHCl₃); **IR** (thin film) 3422, 2928, 2855, 1773 cm⁻¹; **¹H NMR** (CDCl₃, 400 MHz) δ 4.43 (ddd, *J* = 7.6, 6.1, 4.3 Hz, 1H), 3.62 (m, 2H), 3.59 (dd, *J* = 10.9, 3.1 Hz, 1H), 3.37 (dd, *J* = 10.9, 7.6 Hz, 1H), 2.51 (ddd, *J* = 18.0, 10.1, 6.3 Hz, 1H), 2.40 (ddd, *J* = 17.6, 10.1, 7.6 Hz, 1H), 2.14 (m, 1H), 1.97 (m, 1H), 1.52 (sex, *J* = 7.0 Hz, 1H), 1.42-1.15 (m, 19H), 0.82 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); **¹³C NMR** (CDCl₃, 100 MHz) δ 177.5, 81.6, 74.1, 72.3, 66.8, 33.1, 32.6, 29.7, 29.6, 29.4, 28.6, 25.8, 25.5, 25.2, 23.6, 18.0, -4.5; **HRMS** calcd for C₂₃H₄₇O₅Si (MH⁺) 431.3193, found 431.3187.

Triflate 4. To a solution of diol **18** (231.1 mg, 0.54 mmol) and 2,6-lutidine (300 μL, 2.57 mmol) in CH₂Cl₂ (5.4 mL) at -78 °C was added Tf₂O (96 μL, 0.57 mmol). After 10 minutes, TBSOTf (190 μL, 0.81 mmol) was added, and the reaction mixture was stirred for an additional 30 minutes at 0 °C. The reaction was quenched by addition of sat. NH₄Cl (10 mL) and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (3x15 mL). The combined organic phases were washed with sat. NH₄Cl (15 mL), H₂O (15 mL), and brine (15 mL) and dried over Na₂SO₄. The drying agent was removed by filtration, and the filtrate was concentrated in vacuo. Purification by silica gel column chromatography (6:1 hexanes/EtOAc) gave triflate **4** (299.8 mg, 82%) as a colorless oil. The triflate was unstable and therefore used immediately in the next step.

Sulfide 19. (5*S*)-Methyl-3-phenylsulfanyldihydrofuran-2-one **3** (92.2 mg, 0.44 mmol) in THF (0.40 mL) was cooled to 0 °C, and 0.88 mL of a 0.5 M solution of KHMDS in PhCH₃ (0.44 mmol) was added. The resulting pale yellow

solution was stirred at 0 °C for 10 minutes after which time triflate **4** (299.8 mg, 0.44 mmol) in 0.4 mL of THF was added via syringe. The reaction mixture was warmed to room temperature and stirred for 16 h. The reaction was quenched by addition of sat. NH₄Cl (5 mL) and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic extracts were washed with sat. NH₄Cl (10 mL), H₂O (10 mL), and brine (10 mL) and dried over Na₂SO₄. The drying agent was removed by filtration, and the filtrate was concentrated in vacuo. Purification by silica gel column chromatography (6:1 hexanes/EtOAc) gave sulfide **19** (200.4 mg, 62%) as an inseparable 12:1 mixture of diastereomers. Data for **19**: **IR** (thin film) 3060, 2928, 2855, 1778 cm⁻¹; **¹H NMR** (CDCl₃, 400 MHz, major isomer) δ 7.58-7.32 (m, 5H), 4.55-4.47 (m, 2H), 4.26 (m, 1H), 3.68 (q, *J* = 5.6 Hz, 1H), 3.05 (dd, *J* = 14.1, 7.6 Hz, 1H), 2.57 (ddd, *J* = 17.8, 10.0, 6.1 Hz, 1H), 2.47 (ddd, *J* = 17.6, 10.0, 7.6 Hz, 1H), 2.21 (m, 1H), 2.09-1.95 (m, 2H), 1.88 (dd, *J* = 15.2, 8.6 Hz, 1H), 1.84 (dd, *J* = 14.1, 6.4 Hz, 1H), 1.60 (sex, *J* = 6.5 Hz, 1H), 1.50-1.19 (m, 22H), 0.91 (s, 9H), 0.90 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); **¹³C NMR** (CDCl₃, 100 MHz, major isomer) δ 177.6, 177.4, 136.7, 130.4, 129.6, 129.0, 81.6, 74.2, 73.3, 70.2, 69.5, 55.5, 41.2, 39.4, 38.5, 32.7, 29.7, 29.5, 28.6, 26.0, 25.9, 25.8, 25.2, 24.4, 23.6, 22.0, 18.1, 18.0, -3.9, -4.5; **HRMS** calcd for C₄₀H₇₁O₆SSi₂ (MH⁺) 735.4510, found 735.4493.

Butenolide 20. To a solution of sulfide **19** (90.2 mg, 0.12 mmol) in CH₂Cl₂ (2.4 mL) at 0 °C was added *m*CPBA (77% max., 29.6 mg, 0.13 mmol). After 30 minutes, the reaction was quenched by addition of sat. NaHCO₃ (5 mL) and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (2x10 mL). The combined organic extracts were washed with sat. NaHCO₃ (5 mL) and brine (5 mL) and dried over Na₂SO₄. The drying agent was removed by filtration, and the filtrate was concentrated in vacuo. The crude sulfoxide was dissolved in PhCH₃ (3 mL) and heated to 110 °C for 20 minutes. The solution was filtered through a short pad of silica gel with EtOAc to give butenolide **20** (65.9 mg, 88%) as a colorless oil, which was used without further purification. Data for **20**: [α]_D²² -37.7 (*c* 0.67, CHCl₃); **IR** (thin film) 2927.8, 2855, 1775, 1758, cm⁻¹; **¹H NMR** (CDCl₃, 400 MHz) δ 7.13 (br s, 1H), 5.01 (q, *J* = 6.7 Hz, 1H), 4.49 (q, *J* = 5.9 Hz, 1H), 3.95 (p, *J* = 5.5 Hz, 1H), 3.67 (q, *J* = 5.9 Hz, 1H), 2.61-2.42 (m, 4H), 2.21 (m, 1H), 2.04 (m, 1H), 1.60 (sex, *J* = 7.0 Hz, 1H), 1.47-1.20 (m, 19H), 1.42 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); **¹³C NMR** (CDCl₃, 100 MHz) δ 177.4, 174.0, 151.5, 130.8, 81.6, 77.5, 74.2, 70.2, 37.0, 32.7, 29.7, 29.6, 29.5, 28.6, 25.9, 25.8, 25.2, 25.1, 23.6, 19.0, 18.0, -4.5; **HRMS** calcd for C₃₄H₆₅O₆Si₂ (MH⁺) 625.4320, found 625.4356.

Rollicosin (1). To a solution of butenolide **20** (60.1 mg, 0.096 mmol) in MeOH (1 mL) at 0 °C was added 1 mL of 5% (v/v) AcCl in MeOH before being warmed to room temperature and stirred for 3 h. The solution was diluted

with CH_2Cl_2 , and solid NaHCO_3 was added until a neutral pH was reached. The mixture was filtered through a short pad of Celite with EtOAc, and the filtrate was concentrated in vacuo. Purification by silica gel column chromatography (96:4 $\text{CHCl}_3/\text{MeOH}$) gave rollicosin **1** (32.7 mg, 86%) as a white solid. Data for **1**: mp = 102-104 °C; $[\alpha]_D^{22}$ -23.3 (*c* 0.41, CHCl_3); **IR** (thin film) 3408, 2918, 2850, 1769, 1746 cm^{-1} ; **^1H NMR** (CDCl_3 , 400 MHz) δ 7.19 (d, J = 1.5 Hz, 1H), 5.06 (qd, J = 6.8, 1.5 Hz, 1H), 4.42 (td, J = 7.4, 4.9 Hz, 1H), 3.84 (m, 1H), 3.57 (dt, J = 7.4, 4.9 Hz, 1H), 2.62 (ddd, J = 17.8, 10.0, 5.1 Hz, 1H), 2.56-2.50 (m, 1H), 2.54 (dt, J = 17.8, 9.0 Hz, 1H), 2.40 (dd, J = 15.2, 8.4 Hz, 1H), 2.26 (m, 1H), 2.12 (m, 1H), 1.60-1.25 (m, 20H), 1.43 (d, J = 6.8 Hz, 3H); **^{13}C NMR** (CDCl_3 , 100 MHz) δ 177.2, 174.6, 151.9, 131.1, 82.9, 78.0, 73.6, 69.9, 37.3, 33.3, 32.9, 29.4, 28.7, 25.5, 25.4, 24.1, 19.1; **HRMS** calcd for $\text{C}_{22}\text{H}_{37}\text{O}_6$ (MH^+) 397.2590, found 397.2593.

References.

- (1) Burke, S. D.; Sametz, G. M. *Org. Lett.* **1999**, *1*, 72.
- (2) Chow, S.; Kitching, W. *Tetrahedron: Asymmetry* **2002**, *13*, 779.
- (3) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991.

^1H and ^{13}C NMR Spectra.