

Synthesis of the Potent Antimalarials Calothrixin A and B

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Supporting Information:

TMS trapping experiment.

Diethylamide **7** (100 mg, 0.44 mmol, 1.0 equiv) was dissolved in 5 mL of dry THF and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. LDA (2.0 M commercial solution in heptane/tetrahydrofuran/ethylbenzene, 440 μL , 2.0 equiv) was added dropwise over 2-3 min, with the solution slowly turning yellow and then dark brown and finally green. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 45 min and then neat TMSCl (110 μL , 2.0 equiv) was added dropwise over 1-2 min. The resulting mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, with a white precipitate forming. After 1 h, TLC (silica, EtOAc/hexanes 2:1) showed formation of a new, less polar compound and some remaining starting material. The reaction mixture was allowed to warm to room temperature overnight and then it was diluted with EtOAc (5 mL) and washed with H_2O (2-3 mL). The organic layer was separated, dried over Na_2SO_4 and the solvent evaporated under reduced pressure furnishing a crude oil. ^1H NMR (CDCl_3 , 300 MHz) of this oil showed the presence of about 50 % of starting material and 50 % of the TMS-trapped product **9** in which TMS had been incorporated on the pyridine ring next to the diamide group. The characteristic peaks are a singlet at 9.00 ppm (vs a doublet at 8.93 ppm for the starting amide) and the disappearance of a doublet at 7.20 ppm present in the ^1H NMR of the starting amide.

Preparation of MOM-protected Calothrixin

A lithium 2,2,6,6-tetramethylpiperidide solution was prepared by adding 2,2,6,6-tetramethylpiperidine (freshly distilled from KOH, 2.9 mL, 17 mmol, 4.0 equiv) dropwise (over less than 1 min) to a cold ($-70\text{ }^{\circ}\text{C}$, MeOH/liquid nitrogen) solution of *n*-BuLi (2.5 M in hexanes, 7.0 mL, 17 mmol, 4.0 equiv) in 64 mL of dry THF, under nitrogen, and then stirring the mixture at -5 to $0\text{ }^{\circ}\text{C}$ (still in the same cold bath; this temperature was achieved by adding room-temperature MeOH slowly to the bath over 30 min) for 1 h. The temperature was then reduced to $-90\text{ }^{\circ}\text{C}$ (by adding more liquid nitrogen to the bath) and a solution of diethylamide **7** (1.0 g, 4.3 mmol, 1.0 equiv) in 32 mL of dry THF was added dropwise over 10-15 min. The resulting yellow solution

became brown and finally deep green within about 15 min. The mixture was stirred at $-90\text{ }^{\circ}\text{C}$ for 35 min and then a solution of aldehyde **6** (372 mg, 1.75 mmol, 0.41 equiv) in 16 mL of dry THF was added dropwise over 5 min. The reaction solution remained the same color. The flask was then taken out of the cold bath and left standing just above the level of the bath liquid to slowly reach room temperature (about 2 h). During this time the solution turned first dark gray and finally deep purple. The mixture was left standing overnight at room temperature, then quenched with water (50 mL) and extracted with EtOAc (2 x 100 mL). The orange organic layer was dried over Na_2SO_4 and the solvent was evaporated to furnish an orange residue. The residue was purified by filtration through silica (EtOAc/hexane 2:3) using a conical column. This operation was carried out in a 500 mL Squibb separatory funnel (such as Aldrich Z14,301-4; the approximate dimensions of the column were 18 cm high and 9 and 1 cm upper and lower diameters, respectively), giving 149 mg of the desired product (**13**) as an amorphous red/orange solid (12 % from **7**, 26 % from **6**) which could be further purified by crystallization from hot EtOAc.

MOM-protected calothrixin B (13). mp: 234-235 $^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ 9.74 (s, 1H), 9.56 (d, $J = 8.4$ Hz, 1H), 8.40 (d, $J = 8.0$ Hz, 1H), 8.17 (d, $J = 8.4$ Hz, 1H), 7.83 (t, $J = 8.0$ Hz, 1H), 7.75 (t, $J = 8.4$ Hz, 1H), 7.61 (d, $J = 8.4$ Hz, 1H), 7.49 (t, $J = 8.0$ Hz, 1H), 7.41 (t, $J = 8.0$ Hz, 1H), 6.12 (s, 2H), 3.43 (s, 3H). ^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$): δ 182.1, 181.3, 152.3, 147.8, 140.2, 135.5, 133.3, 131.6, 130.5, 130.3, 128.4, 127.7, 125.5, 124.3, 124.0, 123.3, 123.2, 118.6, 112.1, 75.7, 56.9. MS (EI): m/z 342, 327, 312, 299. HRMS (EI): $[\text{M}^+]$ 342.1005; $\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}_3$ requires 342.1004.

MOM cleavage:

To a solution of **13** (227 mg, 0.66 mmol) in THF (100 mL) was added concentrated hydrochloric acid (45 mL) at room temperature. The resulting dark red suspension was stirred at 50-55 $^{\circ}\text{C}$ for 48 h, when TLC (silica, hexanes/EtOAc 1:1) showed the absence of starting material. The mixture was carefully neutralized with saturated NaHCO_3 solution (*ca* 430 mL) and extracted with CHCl_3 (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to furnish an orange residue. This material was purified by chromatography on a 4 x 15 cm standard silica column (EtOAc in hexanes 1:3 to 1:0) to give 146 mg of **2** (74 %).

Calothrixin B (2). mp: $\geq 300\text{ }^{\circ}\text{C}$ (dec). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 13.17 (bs, 1H), 9.63 (s, 1H), 9.58 (d, $J = 8.4$ Hz, 1H), 8.19 (d, $J = 8.0$ Hz, 1H), 8.18 (d, $J = 8.0$ Hz, 1H), 7.96 (t, $J = 6.8$ Hz, 1H), 7.89 (t, $J = 6.8$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.48 (t, $J = 6.8$ Hz, 1H), 7.40 (t, $J = 6.8$ Hz, 1H). ^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$): δ 180.5, 180.0, 150.9, 147.2, 138.2, 137.8, 132.4, 131.4, 130.0, 129.6, 127.0, 126.9, 124.7, 124.1, 123.2, 122.4, 122.1, 115.4, 113.8. UV λ_{max} (EtOH) 282, 352, 406 nm (ϵ 28,500; 6,030; 4,200). λ_{max} (EtOH + NaOH) 286, 330 (sh), 470 nm (ϵ 22,000; 11,000;

3,086). MS (EI): m/z 298 (100), 270 (22), 242, 214, 168, 141. HRMS (EI): $[M^+]$ 298.0743; $C_{19}H_{10}N_2O_2$ requires 298.0742.

Oxidation to calothrixin A:

To a suspension of calothrixin B (**2**, 30 mg, 0.10 mmol) in CH_2Cl_2 (50 mL), under nitrogen, was added in one portion *m*-CPBA (Aldrich 50-60 % peracid, 150 mg, excess) in CH_2Cl_2 (50 mL). The mixture was heated at reflux until (ca 14 h) no starting material could be detected by TLC (EtOAc/hexanes 1:1). The resulting suspension was diluted with 550 mL of CH_2Cl_2 to afford a red-orange solution, which was washed with saturated K_2CO_3 solution (3 x 15 mL). The organic layer was washed with water until the wash was neutral, dried over Na_2SO_4 and evaporated to give an orange-red solid. CH_2Cl_2 was added and the insoluble solid was collected by centrifugation and washed several times with small volumes of CH_2Cl_2 . The title compound was obtained as an amorphous orange-red solid (22 mg, 71 %).

Calothrixin A (1). mp: ≥ 280 °C. 1H NMR (400 MHz, $DMSO-d_6$): δ 13.22 (br s, 1H), 9.68 (br d, $J = 9.5$ Hz, 1H), 8.88 (s, 1H), 8.60 (br d, $J = 9.5$ Hz, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 8.1-7.95 (m, 2H), 7.60 (d, $J = 8.4$ Hz, 1H), 7.45 (t, $J = 6.8$ Hz, 1H), 7.38 (t, $J = 6.8$ Hz, 1H). UV λ_{max} (EtOH) 288, 360, 413 nm (ϵ 31,000; 6,880; 5,300). λ_{max} (EtOH + NaOH) 281, 310 (sh), 357 (sh), 365, 482 nm (ϵ 29,000; 20,400; 14,400; 16,300; 4,500). MS (FAB): m/z 315.2. HRMS (FAB): $[(M+1)^+]$ 315.0769; $C_{19}H_{10}N_2O_3$ requires 315.0770.