A Short and Versatile Route to a Key Intermediate for Lactacystin Synthesis

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Potassium benzyloxycarbonyl acetate

A solution of KOH (9.8 g, 0.176 mol) in benzyl alcohol (176 ml) was added gradually to a solution of dibenzyl malonate (50 g, 0.176 mol) in benzyl alcohol (440 ml). The reaction mixture was stirred for four hours at ambient temperature, and diluted with diethyl ether (2.5 L), resulting in a white precipitate. The mixture was stirred for thirty minutes and the product removed by filtration, washed with diethyl ether (3 x 200 ml), and air-dried to give a colourless solid (33.4 g, 82%); mp 201 °C; (Found: C, 51.59%; H, 3.75%. $C_{10}H_9KO_4$ requires C, 51.71%; H, 3.91%); $\nu_{\max}(\text{mull})/\text{cm}^{-1}$: 1724; (Found: MH^+ , 233.02131. $C_{10}H_9KO_4$ requires 232.01379); m/z : 233 ($M+1$, 18), 192 (100), 154 (41), 136 (34); $\delta_H(D_2O, 400\text{MHz})$: 3.35 (2H, s), 5.16 (2H, s), 7.38-7.46 (5H, m); $\delta_C(D_2O, 100\text{MHz})$: 47.57, 70.11, 131.08, 131.47, 131.73, 138.44, 174.03, 176.78.

N-Benzylglycine ethyl ester

Ethyl bromoacetate (24.4 ml, 0.22 mol) in THF (120 ml) was added gradually to a solution of benzylamine (42.9 ml, 0.484 mol) in THF (120 ml) at 0 °C, resulting in a white mixture. The mixture was stirred at ambient temperature for four hours, and evaporated to dryness. Diethyl ether (150 ml) was added, the mixture filtered, and the filtrate concentrated to give the product (40.2g, 95%). The product was purified for analytical purposes by column chromatography on silica gel using diethyl ether as eluent, but can be used crude. $\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 3339, 1736, 1027; (Found: M^+ , 193.11030. $C_{11}H_{15}NO_2$ requires 193.11028); m/z : 193 (M^+ , 4%), 120 (54), 106 (30.), 91 (100); $\delta_H(CDCl_3, 400\text{MHz})$: 1.17 (3H, t, $J = 8.0$ Hz), 1.86 (1H, br s), 3.30 (2H, s), 3.70 (2H, s), 4.08 (2H, q, $J = 4.0$ Hz), 7.14-7.23 (5H, m); $\delta_C(CDCl_3, 100\text{MHz})$: 13.20, 49.08, 52.25, 59.64, 126.10, 127.23, 127.40, 138.55, 171.36.

N-Benzyl-N-ethoxycarbonylmethyl malonic acid monoamide benzyl ester 3

Potassium benzyloxycarbonyl acetate (33 g, 0.142 mol) was suspended in toluene (300 ml), and oxalyl chloride (37.2 ml, 0.462 mol) added. The reaction was stirred at 34 °C for twenty-four hours, and the solvent and excess oxalyl chloride removed to give the acid chloride. The crude acid chloride was dissolved in dichloromethane (200 ml), and added to a solution of N-benzylglycine ethyl ester (33 g, 0.17 mol) in dichloromethane (200 ml) at 0 °C. Pyridine (13.8 ml, 0.17 mmol) and DMAP (0.86 g, 7.1 mmol) were added at 0 °C, the mixture was allowed to reach ambient temperature, and stirred for four hours. The reaction mixture was washed with 5% HCl (2 x 100 ml) and water (2 x 100 ml), dried ($MgSO_4$), and the solvents

removed to give **3** as an orange oil (49.8 g, 83%), $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 3030, 2982, 1740, 1662, 1453, 1265, 1196, 733; (Found: M^+ , 369.15703. $\text{C}_{21}\text{H}_{23}\text{NO}_5$ requires 369.15762); m/z : 369 (M^+ , 3%), 278 (7), 192 (99), 118 (12), 91 (100); $^1\text{H}(\text{CDCl}_3, 400\text{MHz})$: 1.13 (3H, t, $J = 6.8$ Hz, minor rotamer), 1.15 (3H, t, $J = 9.2$ Hz, major rotamer), 3.45 (2H, s, minor rotamer), 3.52 (2H, s, major rotamer), 3.84 (2H, s, minor rotamer), 3.96 (2H, s, major rotamer), 4.04 (2H, q, $J = 7.2$ Hz, minor rotamer), 4.07 (2H, q, $J = 7.2$ Hz, major rotamer), 4.53 (2H, s, major rotamer), 4.59 (2H, s, minor rotamer), 5.08 (2H, s, major rotamer), 5.11 (2H, s, minor rotamer), 6.99-7.27 (20H, m); $^{13}\text{C}(\text{CDCl}_3, 100\text{MHz})$: 14.11 (minor rotamer), 14.14 (major rotamer), 41.07 (major rotamer), 41.34 (minor rotamer), 47.16 (major rotamer), 49.02 (minor rotamer), 49.92 (minor rotamer), 52.79 (major rotamer), 61.26 (major rotamer), 61.78 (minor rotamer), 67.28 (major rotamer), 67.37 (minor rotamer), 126.96-136.08, 166.52 (minor rotamer), 166.90 (major rotamer), 167.03 (major rotamer), 167.21 (minor rotamer), 168.76 (minor rotamer), 168.80 (major rotamer).

N*-Benzyl-3-methylpyrrolidin-2,4-dione 3-carboxylic acid benzyl ester **9*

Tetrabutylammonium fluoride (174 ml of a 1 M solution, 174 mmol) was added to a solution of the diester **3** (32 g, 86.6 mmol) and in diethyl ether (250ml), the mixture stirred under N_2 at ambient temperature for *ca* thirty minutes, and the colourless solid removed by filtration and washed with diethyl ether (2 x 100 ml). The solid was suspended in THF (250 ml) at ambient temperature, and methyl iodide (10.8ml, 173.2mmol) added. The mixture was stirred at ambient temperature for twenty-four hours, and evaporated to dryness. The crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (7/3) and ethyl acetate as eluents to give the product **9** as a yellow powder (15.6 g, 53%), mp 62 °C, (Found: C, 70.83%; H, 5.57%; N, 3.95%. $\text{C}_{20}\text{H}_{19}\text{NO}_4$ requires C, 71.2%; H, 5.68%; N, 4.15%); $\nu_{\text{max}}(\text{CH}_2\text{Cl}_2)/\text{cm}^{-1}$: 1777, 1741, 1685, 1115; (Found: M^+ , 337.13135. $\text{C}_{20}\text{H}_{19}\text{NO}_4$ requires 337.13141); m/z : 337 (M^+ , 7%), 246 (45), 202 (65), 91 (100); $^1\text{H}(\text{CDCl}_3, 400\text{MHz})$: 1.56 (3H, s), 3.66 (1H, d, $J = 17.6$ Hz), 3.87 (1H, d, $J = 17.5$ Hz), 4.36 (1H, d, $J = 14.8$ Hz), 4.93 (1H, d, $J = 14.8$ Hz), 5.13 (1H, d, $J = 12.4$ Hz), 5.17 (1H, d, $J = 12.4$ Hz), 7.15-7.34 (10H, m); $^{13}\text{C}(\text{CDCl}_3, 100\text{MHz})$: 15.25, 46.14, 54.95, 59.03, 68.13, 127.76-134.70, 165.30, 169.40, 202.14; and the enol ether by-product as a yellow oil (4.67 g, 16%), $\nu_{\text{max}}(\text{CH}_2\text{Cl}_2)/\text{cm}^{-1}$: 1718, 1618, 1068; (Found: M^+ , 337.13052. $\text{C}_{20}\text{H}_{19}\text{NO}_4$ requires 337.13141); m/z : 337 (M^+ , 2%), 246 (5), 189 (7), 108 (100), 91 (41); $^1\text{H}(\text{CDCl}_3, 400\text{MHz})$: 3.85 (2H, s), 3.89 (3H, s), 4.58 (2H, s), 5.29 (2H, s), 7.20-7.46 (10H, m); $^{13}\text{C}(\text{CDCl}_3, 100\text{MHz})$: 45.81, 47.70, 59.07, 66.36, 102.10, 128.14-137.16, 162.21, 168.03, 177.53.

N*-Benzyl-3-methylpyrrolidin-2,4-dione 3-carboxylic acid benzyl ester **9*

Tetrabutylammonium fluoride (15 ml of a 1 M solution, 15 mmol) was added to a solution of the lactam **6** (4 g, 12.4 mmol) in THF (140 ml), followed by methyl iodide (1.6 ml, 24.8 mmol). The resulting orange solution was stirred at ambient temperature for twenty-four hours, and the solvent removed to give an orange solid. The crude material was purified by column chromatography on silica gel using petroleum

ether/ ethyl acetate (6/4) as eluent to give the desired compound **9** as a yellow crystalline solid (2.31 g, 70%). The spectroscopic data for **9** is given above.

N*-Benzyl-3-methylpyrrolidin-2,4-dione 3,5-dicarboxylic acid 3-benzyl ester 5-methyl ester **8*

LHMDS (5.92 ml, 5.92 mmol) and DMPU (0.72 ml, 5.92 mmol) were added to THF (10 ml) under N₂, and the mixture cooled to -78 °C. A solution of lactam **9** (1 g, 2.96 mmol) in THF (3 ml) was added gradually, and the resulting orange solution stirred at -78 °C for one hour. Methyl cyanofornate (0.47 ml, 5.92 mmol) was added, and the solution stirred at -78 °C for a further two hours, saturated aqueous NH₄Cl (10 ml) added, and the mixture diluted with dichloromethane (50 ml). The solution was washed with water (2 x 20 ml) and brine (2 x 20 ml), dried (MgSO₄), and the solvents removed. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (7/3) as eluent to give the product **8** as a 5:1 mixture of inseparable diastereoisomers (0.87 g, 75%). (Found: C, 66.29%; H, 5.28%; N, 3.51%. C₂₂H₂₁NO₆ requires C, 66.83%; H, 5.35%; N, 3.54%); ν_{max} (neat)/cm⁻¹: 1789, 1749, 1707, 1218; (Found MH⁺, 396.14494, C₂₂H₂₁NO₆H⁺ requires 396.14472); *m/z*: 395 (M⁺, 2%), 304 (22), 260 (37), 105 (76), 91 (100), 77 (97); δ_{H} (CDCl₃, 400MHz): 1.56 (3H, s major isomer), 1.60 (3H, s, minor isomer), 3.46 (3H, s minor isomer), 3.74 (3H, s major isomer), 4.00 (1H, d, *J* = 14.8 Hz, major isomer), 4.23 (1H, d, *J* = 14.8 Hz, minor isomer), 4.31 (1H, s, minor isomer), 4.48 (1H, s, major isomer), 5.04 (1H, d, *J* = 12.4 Hz, minor isomer), 5.08 (1H, d, *J* = 12.4 Hz, major isomer), 5.19 (1H, d, *J* = 12.4 Hz, major isomer), 5.22 (1H, d, *J* = 12.4 Hz, minor isomer), 5.35 (1H, d, *J* = 14.8 Hz, major isomer), 5.39 (1H, d, *J* = 14.8 Hz, minor isomer), 7.09-7.35 (20H, m); δ_{C} (CDCl₃, 100MHz): 15.96, 16.03, 45.15 (major isomer), 45.36 (minor isomer), 52.84 (minor isomer), 53.23 (major isomer), 58.14 (minor isomer), 58.42 (major isomer), 66.69 (minor isomer), 67.53 (major isomer), 68.14 (minor isomer), 68.30 (major isomer), 126.9-134.5, 163.73, 164.70, 164.80, 164.95, 167.65, 168.81, 195.78 (minor isomer), 196.85 (major isomer).

N*-Benzyl-3-methylpyrrolidin-2,4-dione 5-carboxylic acid methyl ester **14*

Keto-ester **8** (300 mg, 0.76 mmol) and Pd(OH)₂/C (30 mg) were added to THF (15 ml) and the mixture degassed with nitrogen. The mixture was treated with hydrogen under balloon pressure for 20 minutes at room temperature, filtered through celite and evaporated to dryness to give the title compound **14** as a colourless solid (188 mg, 95%), mp 123-124 °C, ν_{max} (mull)/cm⁻¹: 3038, 1746, 1212; (Found: M⁺, 261.10021. C₁₄H₁₅NO₄ requires 261.10011); *m/z*: (M⁺, 15%), 202 (21), 91 (100), 65 (10); δ_{H} (CDCl₃, 400MHz): 1.35 (3H, d, *J* = 7.6 Hz, major isomer), 1.42 (3H, d, *J* = 7.6 Hz, minor isomer), 2.95 (1H, q, *J* = 7.6 Hz, minor isomer), 3.11 (1H, q, *J* = 7.6 Hz, major isomer), 3.71 (3H, s, major isomer), 3.74 (3H, s, minor isomer), 4.07 (1H, d, *J* = 14.4 Hz, minor isomer), 4.19 (1H, d, *J* = 14.6 Hz, major isomer), 4.28 (1H, s, major), 4.40 (1H, s, minor isomer), 5.18 (1H, d, *J* = 14.8 Hz, major isomer), 5.28 (1H, d, *J* = 14.8 Hz, minor isomer), 7.21-7.35 (10H, m); δ_{C} (CDCl₃, 100MHz): 9.76 (major isomer), 11.98 (minor isomer), 44.43 (major isomer), 44.65 (minor isomer), 45.16 (minor isomer), 15.28 (major isomer), 53.38, 67.91, 127.64-1129.50,

134.44, 165.34 (major isomer), 165.49 (minor isomer), 171.88 (major isomer), 172.26 (minor isomer), 200.29 (major isomer), 201.26 (minor isomer).