A Concise and Straightforward Total Synthesis of (±)-Salinosporamide A, based on a Biosynthesis Model

Nicholas P Mulholland,[a] Gerald Pattenden,[a] and Iain A.S. Walters.[b]*

[a] School of Chemistry, University of Nottingham, Nottingham, NG7 2RD, England
[b] AstraZeneca R & D Charnwood, Medicinal Chemistry, Bakewell Road, Loughborough, LE11 5RH, England

Additional experimental procedures and data.

Diethyl-1-Benzyl-3-hydroxy-3-methyl-5-oxo-pyrrolidine-2,2-dicarboxylate (16). A solution of the amine **14b** (3.0g, 11 mmol) and 2,2,5-trimethyl-4*H*-1,3-dioxin-4-one **15** (1.8 mL, 14 mmol) in dry toluene (11 mL) and acetic acid (2.7 mL) was heated at 120°C for 1 hr under a nitrogen atmosphere. The mixture was allowed to cool to room temperature, and then concentrated *in vacuo.* The residue was purified by flash column chromatography, using petroleum ether-diethyl ether (1:3) as eluent, to give the pyrrolidinone (2.96 g, 75%) as a pale orange oil, whose spectroscopic data were identical with those presented in the literature.[14]

Diethyl 1-Benzyl-3-methyl-5-oxo-3-trimethylsilanyloxy-pyrrolidine-2,2-dicarboxylate (17). Trimethylsilyl chloride (910 µL, 7.1 mmol) was added dropwise over 5 min to a stirred solution of the pyrrolidinone alcohol **16** (1.65 g, 4.7 mmol), triethylamine (2.0 mL, 14 mmol) and DMAP (770 mg, 4.7 mmol) in anhydrous dichloromethane (6.6 mL) at 0 °C under a nitrogen atmosphere. The solution was stirred at 0 °C for 0.5 hr, and then quenched with a saturated aqueous solution of sodium hydrogen carbonate (10 mL). The mixture was diluted with ethyl acetate (50 mL) and the separated aqueous layer was then extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with saturated aqueous copper(II) sulfate (10 mL), brine (10 mL), then dried and concentrated *in vacuo* to leave the *silyl ether* **17** (1.85 g, 93%) as a pale yellow oil. A small portion was purified by chromatography, using petroleum ether-diethyl ether (1:1) as eluent, to give the silyl ether as a colourless oil; (Found: C 59.4; H, 7.4; N 3.2; $C_{21}H_{31}NO_6Si$ requires C, 59.4; H, 7.4; N, 3.3); ν_{max} ($CHCl_3$)/ cm^{-1} 1738, 1698; δ_H (360 MHz, $CDCl_3$) 7.56-7.19 (5H, m, C_6H_5), 5.04 (1H, d, *J* 15.2, NCH*H*Ph), 4.71 (1H, d, *J* 15.2 NC*H*HPh) 4.25 (1H, qd, *J* 7.2 and 10.8, OCH*H*CH_3), 4.11 (1H, qd, *J* 7.2 and 10.8, OC*H*HCH_3), 3.63 (2H, overlapping qd, *J* 7.2 and 10.5, OCH_2CH_3), 2.84 (1H, d, *J* 16.4, C*H*HC(=O)NBn), 2.64 (1H, d, *J* 16.4, CH*H*C(=O)NBn), 1.62 (3H, s, CCH_3), 1.26 (3H, t, *J* 7.2, OCH_2CH_3), 1.07 (3H, t, *J* 7.2, OCH_2CH_3), 0.15 (9H, s, OTMS); δ_c (90 MHz, $CDCl_3$) 174.3 (s), 167.3 (s), 166.1 (s), 136.6 (s), 128.8 (d) x 2, 128.0 (d) x 2, 127.2 (d), 80.9 (s), 79.5 (s), 77.2 (t), 61.8 (t), 61.4 (t), 45.7 (t), 23.5(q), 13.9 (q), 13.6 (q), 1.9 (q) x 3; *m/z* (ES) 444.1839 (M + Na^+, $C_{21}H_{31}NO_6SiNa$ requires 444.1813).

(2*S,3*S**)-Ethyl-1-Benzyl-2-formyl-3-methyl-5-oxo-3-trimethylsilanyloxy-pyrrolidine-2-carboxylate (18).** A solution of Super-hydride® (4.8 mL, 4.8 mmol, 1.0 M in THF) was added dropwise over 15 min to a stirred solution of the diester **17** (1.85 g, 4.39 mmol) in anhydrous dichloromethane (20 mL) at –78 °C under a nitrogen atmosphere. The solution was stirred for 0.5 hr, then water (20 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography, using petroleum ether-diethyl ether (1:1) then diethyl ether as eluent, to give the *aldehyde* **18** (1.14 g, 69%) as a colourless oil; (Found: C 60.2; H, 7.3; N 3.6; $C_{19}H_{27}NO_5Si$ requires C, 60.45; H, 7.2; N, 3.7); ν_{max} ($CHCl_3$)/ cm^{-1} 2960, 2872, 1754, 1724, 1693; δ_H (360 MHz, $CDCl_3$) 9.98 (1H, s, C*H*O), 7.29-7.19 (5H, m, C_6H_5), 4.98 (1H, d, *J* 14.6, NCH*H*Ph), 4.37 (1H, d, *J* 14.6, NC*H*HPh) 3.91 (1H, qd, *J* 7.2 and 10.8, OCH*H*CH_3), 3.74 (1H, qd, *J* 7.2 and 10.8, OC*H*HCH_3), 2.93 (1H, d, *J* 16.1, C*H*HC(=O)NBn), 2.45 (1H, d, *J* 16.1, CH*H*C(=O)NBn), 1.42 (3H, s, CCH_3), 1.11 (3H, t, *J* 7.2, OCH_2CH_3), 0.15 (9H, s, OTMS); δ_c (90 MHz, $CDCl_3$) 197.1 (d), 173.3 (s), 167.4 (s), 135.6 (s), 129.5 (d) x 2, 128.1 (d) x 2, 127.9 (d), 81.5 (s), 79.5 (s), 61.8 (t), 45.7 (t), 45.4 (t), 30.2 (q), 13.7 (q), 1.7 (q) x 3; *m/z* (ES) 410.1983 (M + MeOH + H^+, $C_{20}H_{32}NO_6Si$ requires 410.1993). ^{1}H NMR nOe experiments (360 MHz, $CDCl_3$): irradiation at δ 9.98 (C*H*O) gave an enhancement of 1.7% at δ 1.42 (C*Me*), and irradiation at δ 1.42 gave a corresponding enhancement of 2.4% at δ 9.98 ppm. In addition, irradiation at δ 3.74 (CH_2CH_3) gave an enhancement of 0.8% at δ 0.15 (SiMe_3) ppm.

(2*R,3*S**)-Ethyl-2-((*R**)-Acetoxy-(*S**)-cyclohex-2-enyl-methyl)-1-benzyl-3-methyl-5-oxo-3-trimethylsilanyloxy-pyrrolidine-2-carboxylate (19b).** A catalytic amount of dimethylaminopyridine was added to a stirred solution of the alcohol **19a** (394 mg, 0.86 mmol) in acetic anhydride (2 mL) and anhydrous pyridine (2 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 23 hr and then diluted with ethyl acetate (60 mL). The mixture was washed with water and saturated aqueous copper(II) sulfate (1:1, 30 mL), then with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo* to leave the *acetate* **19b** (378 mg, 87%) as a pale yellow oil; ν_{max} ($CHCl_3$)/ cm^{-1} 2942, 1756, 1694; δ_H (400 MHz, $CDCl_3$) 7.37-7.17 (5H, m, C_6H_5), 5.76 (1H, m, CH_2CH=), 5.44 (1H, app. dd *J* 10.4, 2.2, CH_2CH=C*H*), 5.38 (1H, d, *J* 3.8, C*H*(OAc)), 4.88 (1H, d, *J* 15.6, NC*H*HPh), 4.63 (1H, d, *J* 15.6, NCH*H*Ph), 4.19-4.05 (2H, m, O*CHH*CH_3), 2.52-2.44 (1H, br. s, CH_2CH=CHC*H*), 2.50 (1H, d, *J* 16.8, CH*H*C(=O)NBn), 2.45 (1H, d, *J* 16.8, C*H*HC(=O)NBn), 2.06 (3H, s, O*Ac*), 1.99-1.93 (2H, br. s, CH_2CH_2CH=), 1.79-1.72

(3H, m, C*H*HCH$_2$CH=, =CHCH(R)C*H*H, =CHCH(R)CH*H*), 1.58 (3H, s, CC*H$_3$*), 1.52-1.41 (1H, m, CH*H*CH$_2$CH=), 1.12 (3H, t, *J* 7.2, OCH$_2$C*H$_3$*), 0.17 (9H, s, OTMS); δ_c (100 MHz, CDCl$_3$) 174.0 (s), 169.5 (s), 167.9 (s) , 138.2 (s), 130.1 (d), 127.7 (d) x 2, 126.5 (d) x 2, 126.1 (d), 124.4 (d), 82.0 (s), 81.2 (s), 77.1 (d), 61.4 (t), 48.0 (t), 46.2 (t), 37.8 (d), 29.4 (t), 24.5 (t), 22.5 (q) 21.4 (q), 21.1 (t), 13.7 (q), 2.0 (q) x 3; *m/z* (ES) 502.2650 (M + H$^+$, $C_{27}H_{40}NO_6Si$ requires 502.2619).

(2*R,3*S**)-Ethyl-2-((*R**)-Acetoxy-(*S**)-cyclohex-2-enyl-methyl)-1-benzyl-3-hydroxy-3-methyl-5-oxo-pyrrolidine-2-carboxyloate (20a).** Potassium fluoride (1.0 g, 10 mmol) was added in one portion to a stirred solution of the silyl ether **19b** (522 mg, 1.0 mmol) in methanol-acetic acid (10 ml, 5:1) at room temperature and the mixture was then stirred at room temperature for 18 hr. The mixture was diluted with ethyl acetate (30 mL) and water (30 mL) and the separated aquous layer was then extracted with ethyl actate (2 x 30 mL). The combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, using ethyl acetate-petroleum ether (1:4) as eluent, to give the corresponding *tertiary alcohol* **20a** (355 mg, 78%, over three steps) as a colourless solid; mp 176-179°C (from benzene:ethyl acetate); (Found: C 66.9; H, 7.3; N 3.2; $C_{24}H_{31}NO_6$ requires C, 67.1; H, 7.3; N, 3.3); ν_{max} ($CHCl_3$)/ cm^{-1} 3600 (br), 2940, 1746, 1698; δ_H (400 MHz, $CDCl_3$) 7.39-7.18 (5H, m, C$_6$*H$_5$*), 5.77-5.72 (1H, m, CH$_2$C*H*=), 5.38 (1H, d, *J* 4.5, C*H*(OAc)), 5.34 (1H, dd, *J* 2.2 and 10.3, CH$_2$CH=C*H*), 4.87 (1H, d, *J* 15.5, NC*H*HPh), 4.67 (1H, d, *J* 15.5, NCH*H*Ph), 4.24 (1H, qd, *J* 7.2 and 10.8 C*H*CH$_3$), 4.13 (1H, qd, *J* 7.2 and 10.8, C*H*CH$_3$), 2.55-2.50 (1H, br s, CH$_2$CH=CHC*H*), 2.52 (1H, d, *J* 17.2, CH*H*C(=O)NBn), 2.44 (1H, d, *J* 17.2, C*H*HC(=O)NBn), 2.06 (3H, s, OAc), 1.96-1.95 (2H, br. s, CH$_2$C*H$_2$*CH=), 1.78-1.65 (3H, m, C*H*HCH$_2$CH=, =CHCH(R)C*H*H, =CHCH(R)CH*H*), 1.52 (3H, s, CC*H$_3$*), 1.52-1.53 (1H, m, CH*H*CH$_2$CH=), 1.71 (3H, t, *J* 7.2, OCH$_2$C*H$_3$*); δ_c (100 MHz, $CDCl_3$) 174.2 (s), 169.4 (s), 168.3 (s), 138.0 (s), 130.3 (d), 128.1 (d) x 2, 126.9 (d) x 2, 126.5 (d), 124.3 (d), 80.9 (s), 77.8 (s), 77.4 (d), 61.9 (t), 48.1 (t), 46.1 (t), 37.6 (d), 29.2 (t), 24.6 (t), 22.3 (q), 21.2 (q), 21.2 (t), 13.8 (q); *m/z* (ES) 430.2224 (M + H$^+$, $C_{24}H_{32}NO_6$ requires 430.2230).