Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Enantioselective total syntheses of (-)-*clasto*-Lactacystin β-lactone and 7-*epi*-(-)-*clasto*-Lactacystin β-lactone

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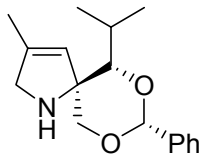
General Information

Reactions were performed in flame-dried glassware under an atmosphere of argon unless otherwise stated. Starting materials were obtained from commercial suppliers and used without further purification unless otherwise stated. THF was degassed and dried over alumina under nitrogen, and petrol refers to petroleum ether 40 – 60. Thin layer chromatography was carried out on Merck silica 60 gel glass-backed plates. Plates were visualised by exposure to UV light followed by staining with basic potassium permanganate solution. Flash chromatography was carried out using Merck silica gel 60 as the stationary phase. Melting points were recorded on Koffler hot stage apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 polarimeter and concentrations given as g/100 mL. Microanalytical data were obtained using an Exeter Analytical CE-440 elemental analyser. Proton NMR spectra were recorded using either a Bruker DRX500, AV400 or Jeol EX270 spectrometer at 298 K unless otherwise stated. Data are expressed as chemical shifts in parts per million (ppm) relative to residual chloroform (δ 7.27) or methanol (δ 3.31) as internal standard on the δ scale. The multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; app, apparent; br, broad. All coupling constants are quoted in Hertz (Hz). Carbon NMR spectra were recorded using either a Bruker DRX500, AV400 or Jeol EX270 spectrometer at 298 K. Data are expressed as chemical shifts in ppm relative to residual chloroform (δ 77.16) or methanol (δ 49.00) as internal standard on the δ scale. Infra-red spectra were recorded using a Perkin-Elmer 1600 FT spectrophotometer as either thin films or dilute solutions in chloroform. High-resolution mass spectra were acquired using an MM70E instrument using electrospray positive ionisation (ES, +ve).

(*5R, 6S, 8R*)-6-Isopropyl-3-methyl-8-phenyl-7,9-dioxa-1-aza-spiro-[4.5]-dec-3-ene (10) and But-2-ynyl-(*2R, 4S, 5R*)-4-isopropyl-2-phenyl-[1,3]-dioxan-5-yl) amine (11)



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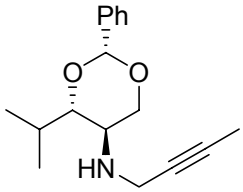


11

KHMDS (0.5M in toluene) (57.0 mL, 28.5 mmol) was added dropwise over 30 min to a stirring solution of vinyl bromide **7** (5.00 g, 14.2 mmol) in THF (80 mL) at -30 °C. The red solution was allowed to reach room temperature over 6 h and then quenched with a saturated aqueous solution of Na_2CO_3 (100 mL). The aqueous layer was extracted with Et_2O (3 × 150 mL) and the combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow oil. The crude material was purified by column chromatography using a pentane and EtOAc (6:1) with 1% Et_3N to give *acetylene* **11** (0.51 g, 13%) as a colourless oil and the polarity was increased to pentane and EtOAc (2:1) to give of *3-pyrroline* **10** (3.20 g, 83%) as colourless oil: 3-Pyrroline **10**: (Found C, 74.51 H, 8.50; N, 4.82. $C_{17}H_{23}NO_2$ requires C, 74.69; H, 8.48; N, 5.12%); $[\alpha]_D^{26}$ –8.47 (0.938 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2960, 2840, 1096; δ_H (400 MHz; $CDCl_3$) 7.54 – 7.51 (2H, m, ArH), 7.41 – 7.32 (3H, m, ArH), 5.82 (1H, m, C*H*=CCH_3), 5.53 (1H, s, CHPh), 3.90 (1H, d, *J* 10.4, C*H*HO), 3.73 (1H, dq, *J* 15.1 and 1.0, C*H*HN), 3.67 (1H, dq, *J* 15.1 and 1.0, CH*H*N), 3.65 (1H, d, *J* 10.4, CH*H*O), 3.39 (1H, d, *J* 4.4, CHO), 1.95 (1H, qqd, *J* 6.9, 6.8 and 4.4, C*H*$(CH_3)_2$), 1.77 (3H, m, =CC*H*$_3$), 1.45 (1H, br, s, NH_2), 1.06 (3H, d, *J* 6.9, CH_3), 1.01 (3H, d, *J* 6.7, CH_3); δ_C (100 MHz; $CDCl_3$) 138.9 (C), 137.2 (C), 128.7 (C), 128.3 (CH), 126.2 (CH), 125.4 (CH), 101.4 (CH), 89.2 (CH), 78.1 (CH_2), 68.8 (C), 56.9 (CH_2), 29.1 (CH), 22.0 (CH_3), 18.5 (CH_3), 14.3 (CH_3); *m/z* (ES, +ve) 274 ($M + H^+$) and 168 ($M + H^+$ - PhCHO); ($C_{17}H_{25}NO_2$ requires 274.1807. Found 274.1805); Acetylene **11**: (Found C, 74.67 H, 8.53; N, 5.09. $C_{17}H_{23}NO_2$ requires C, 74.69; H, 8.48; N, 5.12%); $[\alpha]_D^{26}$ –56.3 (1.052 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2965, 2923, 2877, 1099; δ_H (400 MHz; $CDCl_3$) 7.53 – 7.50 (2H, m, ArH), 7.40 – 7.32 (3H, m, ArH), 5.47 (1H, s, CHPh), 4.45 (1H, dd, *J* 10.7 and 4.8, C*H*HO), 3.39 (1H, dd, *J* 10.7 and 10.0, CH*H*O), 3.46 – 3.35 (3H, m, CH_2N and CHO), 3.05 (1H, *app* td, *J* 10.0 and 4.8, CHN), 2.18 (1H, qqd, *J* 6.9, 6.8 and 2.0, C*H*$(CH_3)_2$), 1.83 (3H, s, C≡CC*H*$_3$), 1.10 (3H, d, *J* 6.9, CH_3), 1.05 (3H, d, *J* 6.8, CH_3); δ_C (100 MHz; $CDCl_3$)

138.7 (C), 128.7 (CH), 128.2 (CH), 126.1 (CH), 100.9 (CH), 85.3 (CH), 79.5 (C), 71.0 (CH_2), 50.7 (CH), 36.8 (CH_2), 27.8 (CH), 20.1 (CH_3), 15.2 (CH_3), 3.5 (CH_3); *m/z* (ES, +ve) 274 ($M + H^+$) and 168 ($M + H^+$ - PhCHO); ($C_{17}H_{25}NO_2$ requires 274.1807. Found 274.1821).

General Procedure for the Oxidative Deprotection of Benzylidene Acetals 16 and 17

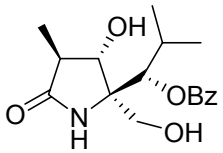
1. Preparation of DMDO

A single neck 3 l round bottom flask was equipped with an air condenser (wrapped with a polythene bag containing solid CO_2) connected to a 2 neck 500 mL round bottom receiving flask cooled to -78 °C. The 2 neck 500 mL flask was connected to a water aspirator. The 3 flask was charged with $NaHCO_3$ (29 g), H_2O (127 mL) and acetone (reagent grade)(96 mL) and cooled to between 0-3 °C. Oxone (12 g) was added in one portion, the suspension was vigorously stirred for 10 min and the ice bath was removed. Suction (~20mmHg) was applied and the yellow DMDO solution was distilled under reduced pressure into the receiving flask. The addition/ stirring/ distillation procedure was repeated 4 more times. After the last addition, the suspension was stirred for 30 min before distillation. The DMDO solution was allowed to reach 0 °C, dried with anhydrous K_2CO_3 and filtered into a precooled 100 mL round bottom flask. The solution was flushed with Ar, stoppered with a glass stopper and stored in the freezer at -25 °C until required. The concentration of DMDO was determined by iodometric titration as follows: 25 mL of 0.02 M aqueous solution of sodium thiosulfate (496 mg $Na_2S_2O_3.5H_2O$ in H_2O 100 mL) was placed in a 25 mL graduated burette. A 100 mL Erlenmeyer flask was charged with water (20 mL), glacial acetic acid (1 mL) a freshly prepared solution of sodium iodide (10 mL)(10 g NaI in 50 mL H_2O) and then the solution of DMDO (2 mL) was added. The solution was titrated rapidly with 0.02 M sodium thiosulfate until the disappearance of the yellow iodine colour. The concentration was calculated according to the following equation [(molarity of titrant) × (mL of titrant)]/[(mL of DMDO solution) × 2] and was in the range 0.05 to 0.07.

2. Oxidative Deprotection

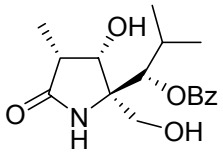
The benzylidene acetal was treated with a solution of DMDO (in acetone) (3 eq) and stirred at 0 - 3 °C for 18 h. The solution was allowed to reach room temperature, dried over $MgSO_4$ and concentrated *in vacuo*. The products of the reaction were suitably pure for the next reaction.

Benzoic acid (S)-1-((2*S*, 3*S*, 4*S*)-3-hydroxy-2-hydroxymethyl-4-methyl-5-oxo-pyrrolidin-2-yl)-2-methyl-propyl ester (18)



Using the general procedure described above: Lactam **16** (45.5 mg, 0.149 mmol) and DMDO solution (8.1 mL, 0.45 mmol) gave diol **18** (48.3 mg, 100 %) as a colourless solid: mp 70 -73 °C (MeOH); $[\alpha]_D^{30}$ +12.3 (c 0.55 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3421, 2969, , 1704 (s) (C=O); δ_H (500 MHz; $CDCl_3$) 8.09 (2H, m, ArH), 7.65 (1H, m, ArH), 7.52 – 7.48 (2H, m, ArH), 5.19 (1H, d, *J* 3.6, C*H*OBz), 4.01 (1H, d, *J* 8.6, C*H*OH), 3.99 (1H, d, *J* 11.6, C*H*HOH), 3.72 (1H, d, *J* 11.6, CH*H*OH), 2.58 (1H, dq, *J* 8.6 and 7.2, C*H*CH_3), 2.27 (1H, qqd, *J* 6.8, 6.8 and 3.6, C*H*$(CH_3)_2$), 1.16 (3H, d, *J* 7.2, CHC*H*$_3$), 1.04 (3H, d, *J* 6.8, CH_3), 1.01 (3H, d, *J* 6.8, CH_3); δ_c (126 MHz; $CDCl_3$) 180.0 (C), 167.8 (C), 134.5 (CH), 131.2 (C, Ph), 130.8 (CH), 129.7 (CH), 80.3 (CH), 78.9 (CH), 67.8 (C), 63.1 (CH_2), 45.9 (CH), 43.1 (CH), 22.6 (CH_3), 18.1 (CH_3), 14.1 (CH_3); *m/z* (ES, +ve) 344 ($M + Na^+$), and 322 ($M + H^+$); ($C_{17}H_{23}NNaO_5$ requires 344.1474. Found 344.1451).

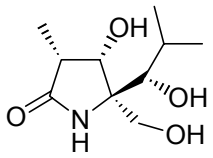
Benzoic acid (S)-1-((2*S*, 3*S*, 4*R*)-3-hydroxy-2-hydroxymethyl-4-methyl-5-oxo-pyrrolidin-2-yl)-2-methyl-propyl ester (23)



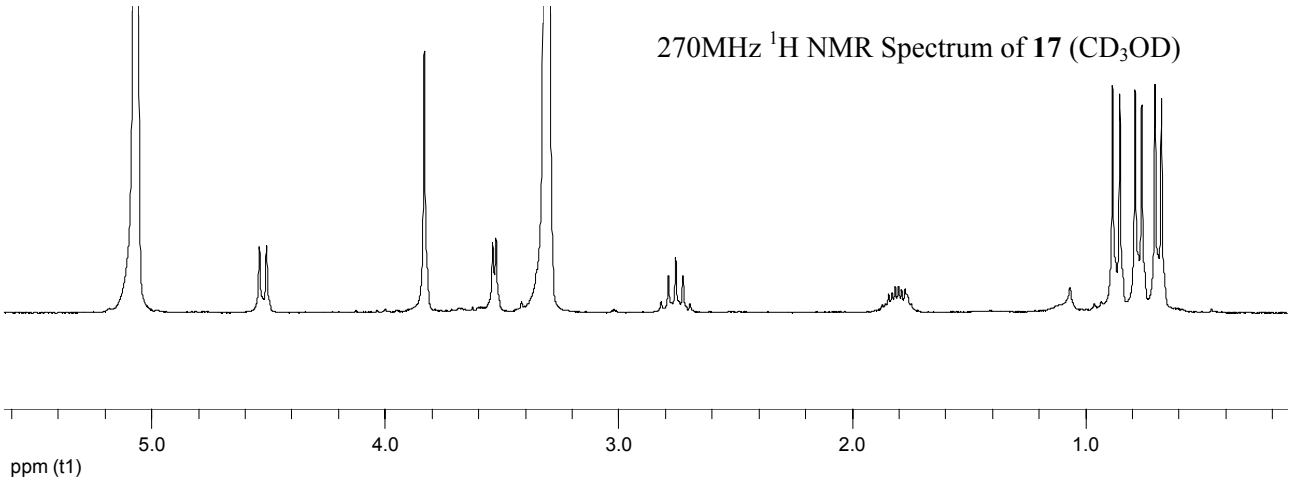
Using the general procedure described above: Lactam **15** (59.0 mg, 0.193 mmol) and DMDO solution (8.5 mL, 0.64 mmol) gave diol **23** (55.5 mg, 90 %) as a colourless foam: mp 157-159 °C (DCM); $[\alpha]_D^{29}$ +10.7 (0.690 in $CHCl_3$); ν_{max}/cm^{-1}($CHCl_3$) 3636, 3430, 2970, 1699 (s)(C=O); δ_H (500 MHz; CD_3OD) 8.05 – 8.04 (2H, m, ArH), 7.65 – 7.62 (1H, m, ArH), 7.52 – 7.49 (2H, m, ArH), 5.38 (1H, d, *J* 4.0, C*H*OBz), 4.39 (1H, d, *J* 7.2 C*H*OH), 3.84 (2H, s, CH_2OH), 2.64 (1H, qd, *J* 7.5 and 7.2, C*H*CH_3), 2.30 (1H, qqd, *J* 6.9, 6.7 and 4.0, C*H*$(CH_3)_2$), 1.06 (3H, d, *J* 7.5, CHC*H*$_3$), 1.05 (3H, d, *J* 6.9, CH_3), 1.02 (3H, d, *J* 6.7, CH_3); δ_C (126 MHz; CD_3OD) 181.5 (C), 167.6 (C), 134.6 (CH), 131.0 (C), 130.7 (CH), 129.8 (CH), 80.2 (CH), 74.0 (CH), 69.4

(C), 62.9 (CH_2), 42.7 (CH), 30.3 (CH), 22.5 (CH_3), 18.3 (CH_3), 9.4 (CH_3); *m/z* (ES, +ve) 344 ($M+Na^+$) and 322 ($M+H^+$); ($C_{17}H_{24}NO_5$ requires 322.1654. Found 322.1653).

(3*R*, 4*S*, 5*R*, 1'*S*)-4-Hydroxy-5-hydroxymethyl-5-(1'-hydroxy-2-methylpropyl)-3-methylpyrrolidin-2-one (17)[1]



A suspension of acetal **15** (2.3 mg, 7.5 μmol) , Pd/C (2.9 mg)and concentrated HCl (15 μL) in MeOH (1.2 mL) were stirred under a triple balloon of H_2 at room temperature for 17 h. $NaHCO_3$ solid (31 mg) was added and the suspension was filtered through a pad of celite and washed with MeOH (50 mL). The filtrate was concentrated *in vacuo* to give a colourless solid. The crude material was purified by column chromatography using $CHCl_3$:MeOH (4:1) to give triol **17** (1.3 mg, 79 %): ν_{max}/cm^{-1}(film) 3358, 2962, 1673; δ_H (270 MHz; CD_3OD) 4.40 (1H, d, *J* 7.6, C*H*OH, H-4), 3.78 (1H, s, CH_2OH, H-5'), 3.51 (1H, d, *J* 3.4, C*H*OH, H-1'), 2.81 (1H, app quin, *J* 7.6, C*H*CH_3, H-3), 2.01-1.90 (1H, m, C*H*$(CH_3)_2$, H-2'), 1.10 (3H, d, *J* 7.6, CHC*H*$_3$), 1.03 (3H, d, *J* 6.9, CH_3), 0.95 (3H, d, *J* 6.7, CH_3); δ_C (67 MHz; CD_3OD) 181.7 (C), 79.0 (CH), 74.4 (CH), 70.0 (C), 68.3 (CH_2), 42.7 (CH), 30.6 (CH), 22.7 (CH_3), 17.6 (CH_3), 9.5 (CH_3); *m/z* (ES, +ve) 218 ($M+H^+$).



1. Uno, H.; Baldwin, J. E.; Russell, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2139.