The Total Synthesis of Monatin

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Condensation Products **15**: A dry ice-jacketed cannula covered with a TYGON® tube was used to deliver reagents at –78 °C. This device was necessary to maintain the reaction temperature below –76 °C. To prepare LDA, 1.6N *n*-butyllithum in hexanes (4.9 mL, 7.9 mmol) was added to DIPA (1.2 mL, 8.5 mmol) in THF (30 mL) in a 100 mL three-necked round bottom flask at –60 °C under a dry N_2 atmosphere. The temperature was allowed to rise to 0 °C over 30 min. A solution of compounds **2** at –78 °C (2.7 g, 7.2 mmol) in THF (6.0 mL) was added dropwise to the LDA solution cooled to –78 °C using the dry ice-jacketed cannula. The reaction temperature was maintained below –76 °C. After generation of the enolates of **2** over 10 min, a solution of **14** (1.5 g, 6.5 mmol) in THF (3.0 mL) at –78 °C was added dropwise to the enolate solution under –76 °C using the dry ice-jacketed cannula. The orange color of the reaction solution turned green after 2 h. Saturated NH_4Cl aq. (23 mL) was added to the reaction solution at –78 °C and the reaction mixture was allowed to warm to rt over a period of 1 h. The product was extracted with ether (2 x 100 mL) and the combined organic layer washed with H_2O and brine, and dried over anhyd. $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was taken to dryness under reduced pressure. Purification of the residual oil was accomplished using flash column chromatography (250 g silica gel, dry-packed). Elution with hexanes/ether = 1:0 to 5:1 resulted in the stereoisomeric mixture of **15** (3.0 g, 53%). Rf = 0.47 (hexanes/ether, 1:1); MS (ESI, 70 eV): *m/z*: 625 [M+Na$^+$], 601 [M-H$^-$].

Lactams **19a** and **19b**: Diastereoisomeric mixture **18a** and **18b** (56 mg, 0.1 mmol) was dissolved in 0.1N HCl/HCO$_2$H (0.5 mL) at rt. After 3 h, H$_2$O (3.0 mL) was added and the solvent was removed under reduced pressure. To remove the acid completely, this operation was repeated twice. The residue was dissolved in MeOH (1 mL) and 3N KOH (0.1 mL) was added at 0 °C. After one minute, the reaction solution was acidified to approximatley pH 6 with DOWEX® 50W (H$^+$). After removing the resin by filtration, the filtrate was purified by HPLC under the conditions described below. Both diastereoisomers **19a** (6.6 mg, 0.024 mmol, 24%) and **19b** (8.8 mg, 0.032 mmol, 32%) were isolated: **19a**: IR (film): ν_{max} = 3399-3343, 1701, 1458, 1434, 1287, 1236, 747 cm^{-1}; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 ^{o}C): δ = 10.88 (s, 1H; COO*H*), 7.95 (s, 1H; lactam N*H*), 7.60 (d, *J* = 8.0 Hz, 1H; indole C*H*=CH), 7.31 (d, *J* = 8.0 Hz, 1H; indole C*H*=CH), 7.14 (d, *J* = 2.0 Hz, 1H; indole NH-C*H*=CH), 7.03 (ddd, *J* = 8.0, 8.0, 0.8 Hz, 1H; indole C*H*=CH), 6.95 (ddd, *J* = 8.0, 8.0, 0.8 Hz, 1H; indole C*H*=CH), 3.44 (dd, *J* = 8.0, 6.8 Hz, 1H; C*H*-COOH), 2.96 (d, *J* = 14.0 Hz, 1H; arom-CH_2), 2.87 (d, *J* = 14.0 Hz, 1H; arom-CH_2), 2.37 (dd, *J* = 13.2, 8.0 Hz, 1H; CH_2-C), 1.77 (dd, *J* = 13.2, 6.8 Hz, 1H; CH_2-C); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 ^{o}C): δ = 177.3, 173.2, 135.5, 127.8, 124.4, 120.5, 118.5, 118.2, 111.0, 108.6, 75.7, 51.3, 37.2, 32.2; HR-MS (MALDI) calcd for $C_{14}H_{15}N_2O_4$ [M+H$^+$]: 275.1026; found 275.1032.

Monatin·HCl (**1**): To an EtOH solution (5 mL) of optically pure **19a** (14.0 mg, 51.0 μmol), was added 3N aq. NaOH (86.7 μl, 0.26 mmol). After the reaction was allowed to reflux for 3 h, the mixture was acidified with 1N HCl and the solvent removed under reduced pressure. Purification by HPLC under the conditions described below resulted in synthetic Monatin·HCl (**1**, 7.75 mg, 26.5 μmol, 52%): $[\alpha]_D^{25} = -8.8$ (1N HCl, $c = 0.23$), reported $[\alpha]_D^{25} = -7.6$ (1N HCl, $c = 0.23$); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 ^{o}C): δ = 10.83 (s, 1H; COO*H*), 7.55 (d, J = 8.0 Hz, 1H; indole C*H*=CH), 7.29 (d, J = 8.0 Hz, 1H; indole C*H*=CH), 7.12 (s, 1H; indole NH-C*H*=CH), 7.01 (dd, J = 8.0, 8.0 Hz, 1H; indole C*H*=CH), 6.93 (dd, J = 8.0, 8.0 Hz, 1H; indole C*H*=CH), 3.55 (dd, J = 8.0, 5.0 Hz, 1H; C*H*-COOH), 3.05 (br s, 2H; arom-CH_2), 2.29 (dd, J = 15.0, 5.0 Hz, 1H; CH_2-C), 1.87 (dd, J = 15.0, 8.0 Hz, 1H; CH_2-C); HR-MS (MALDI) calcd for $C_{14}H_{17}N_2O_5$ [M+H$^+$]: 293.1137; found 293.1129.

A VYDAC™ Protein & Peptide C18 column (2.5 x 25 cm) was employed for the HPLC purification of compounds **1**, **13**, **19a**, **19b**, **20**. The initial chromatography conditions involved solvent mixtures of CH_3CN containing 0.1% TFA and H_2O containing 0.1% TFA in a ratio of 10:90. The ratio of CH_3CN was increased from 10% to 25% over 30 min. The eluates containing the product were lyophilized to yield the product. DIPA = diisopropylamine, [D$_6$]DMSO = dimethyl-d$_6$-sulfoxide, TFA = trifluoroacetic acid.