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Solid phase synthesis of enantiomerically pure polyhydroxyvalerolactams

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Abstract—A general method for the solid phase synthesis of type **2** 3,4,5-trihydroxypiperidin-2-ones is described. Amination of D-ribonolactone **4** was accomplished using a Mitsunobu reaction, and type **7** aminolactone underwent direct lactamisation upon treatment with NaOAc. For the solid phase synthesis, the aminoacid was anchored directly to a TentaGel® resin, and the lactamisation step was concomitant with the cleavage from the resin.

1. Introduction

We recently reported the synthesis of pseudodipeptide **1** as a conformationally restricted Ser-Leu surrogate (Fig. 1),[1] in which a protected derivative of compound **2** (R = ^{i}Bu) was obtained as an intermediate. Since polyhydroxylated lactams have been reported as having interesting biological activities, such as glycosidase inhibitors,[2] cancer cell metastasis inhibitors,[3] and anti-inflammatories,[4] we considered the possibility of synthesising a small collection of 3,4,5-trihydroxypiperidin-2-ones **2**, whose activity may be modulated by the side chain functionalisation of the aminoacid moiety.

For this purpose, we envisaged to apply the lactamisation strategy that we had established[1] to a solid phase synthesis in which the lactams would be released in the last step. In this way, we could perform their synthesis in parallel and obtain the products with a high degree of purity. Our strategy consisted of anchoring the terminal carboxyl of the aminoacid moiety to a TentaGel® resin,[5] perform the condensation with D-ribonolactone **4**, and lactamise. Since lactamisation is performed using NaOAc/MeOH, the cleavage of the molecule from the resin would be concomitant with the cyclisation,[6] and no linker would be necessary.[7] However, the reaction conditions of some transformations had to be adapted to make them compatible with the solid support, and the reaction sequence was first established in solution.

2. Results and discussion

First, we explored the possibility of aminating ribonolactone **4** using a Mitsunobu reaction, which is mild and suitable for solid phase synthesis.[8] This was satisfactorily achieved by *N*-alkylation of the sulphonamide derived from Leu (**5**) with **4** in the presence of DEAD and PPh_3, followed by cleavage of the arylsulfone group of compound **6**[9] with PhSH (Scheme 1).[10] Treat-

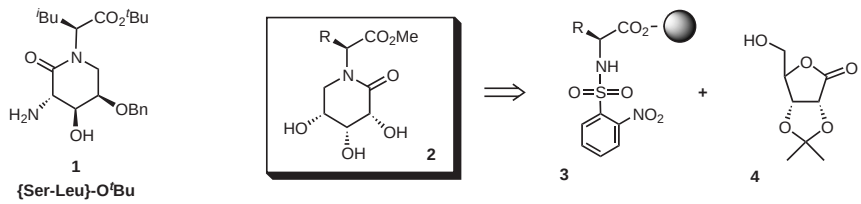

Figure 1.

Keywords: hydroxypiperidines; azasugars; hydroxylactams; solid phase synthesis.
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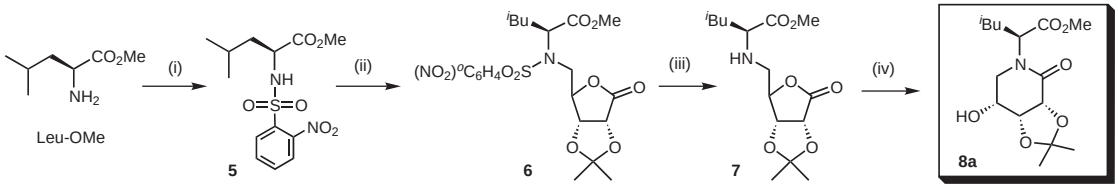
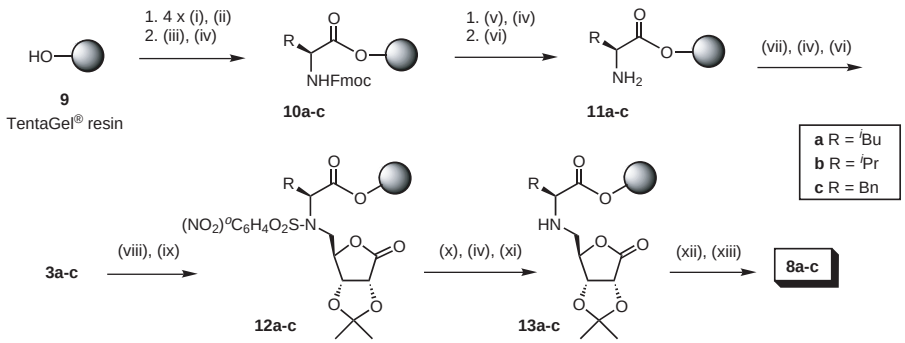


Scheme 1. Reagents and conditions: i) Et_3N (1.5 equiv.), *o*-NBSCl (1.5 equiv.), CH_2Cl_2, room temperature, 1.5 h (72%); ii) **4** (1.5 equiv.), PPh_3 (1.5 equiv.), DEAD (1.5 equiv.), CH_2Cl_2, 0°C, 5 min, room temperature, 12 h (80%); iii) PhSH (1.1 equiv.), K_2CO_3 (3 equiv.), DMF (87%); iv) NaOAc (5 equiv.), MeOH, reflux, 15 h (96%).

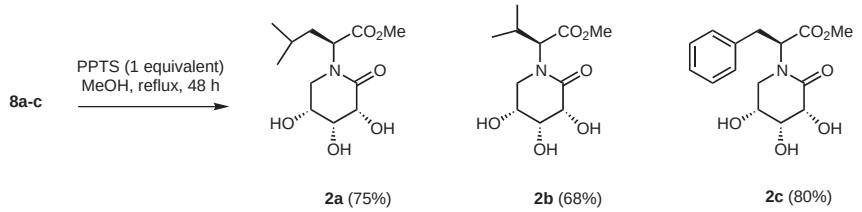
ment of the resulting secondary amine **7**[11] with NaOAc/MeOH yielded the expected lactam **8**.[12]

For the solid phase synthesis we followed Sieber's[13] and Liskamp's method[6] since the TentaGel® resin also swells conveniently in MeOH, which was necessary for an efficient lactamisation/cleavage step. The reaction sequence was applied in parallel to obtain the Leu (**8a**), Val (**8b**), and Phe (**8c**) derivatives (Scheme 2). Anchoring of the Fmoc protected aminoacids to the TentaGel® resin was achieved using DIC/DMAP/HOBt and repeating the process 4 times to obtain compounds **10a–c** in >95% yield.[14] After capping with Ac_2O, the Fmoc group was cleaved to obtain amines **11a–c**. Standard sulfonation of the amines gave the expected compounds **3a–c**.[15] The formation of the primary amines **11** and the sulphonamides **3** was confirmed by a positive and a negative ninhydrine test, respectively. Condensation of **3a–c** with **4**, followed by cleavage of the arylsulfone using PhSH, led to the secondary amines **13a–c**, which gave a positive chloranyl test. Subsequent lactamisation using NaOAc in MeOH resulted in the target lactams **8a–c**. After removal of the resin, the MeOH solvent was replaced by CH_2Cl_2 and the products filtered to yield **8a–c** in pure form.

Finally, hydrolysis of the acetal function of lactams **8a–c** using PPTS in MeOH yielded 3,4,5-trihydroxypiperidin-2-ones **2a–c** (Scheme 3), which were identified by their analytical data.[16]



Scheme 2. Reagents and conditions: i) Fmoc-Leu, Fmoc-Val, or Fmoc-Phe (5 equiv.), DIC (5 equiv.), DMAP (0.1 equiv.), HOBt (5 equiv.), DMF/CH_2Cl_2 (1:9, 6 ml/g of resin), 4 h, room temperature; ii) rinsing with CH_2Cl_2/MeOH/Et_2O (3 times each); iii) Ac_2O (1 equiv.), pyridine (2 equiv.), DMF (6 ml/g of resin), 1 h, room temperature; iv) rinsing with DMF/MeOH/Et_2O (3 times each); v) 3×20% piperidine–DMF (v/v, 6 ml/g of resin, 5–10–10 min), room temperature; vi) ninhydrine test; vii) Et_3N (5 equiv.), *o*-NBSCl (5 equiv.), DMF (6 ml/g of resin), room temperature, 1.5 h; viii) **4** (5 equiv.), PPh_3 (5 equiv.), DEAD (5 equiv.), THF (6 ml/g of resin), 0°C, 10 min, room temperature 12 h; ix) rinsing with THF/MeOH/Et_2O; x) PhSH (1.5 equiv.), K_2CO_3 (2 equiv.), DMF (6 ml/g of resin), room temperature, 40 min.; xi) chloranyl test; xii) NaOAc (5 equiv.), MeOH, reflux, 24 h; xiii) 1. filtration, 2. evaporation of the MeOH, 3. solution in CH_2Cl_2, 4. filtration, 5. evaporation of the solvent (40% total for **8a**; 27% total for **8b**, and 37% total for **8c**).



Scheme 3.

Acknowledgements

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9. Lactone **6**: $[\alpha]_D = +40$ ($c = 1.15$, $CHCl_3$); IR ($CHCl_3$) 1793 (CO), 1743 (CO), 1547 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.75 and 0.88 (2d, $J = 7$ Hz, 3H each, $(CH_3)_2CH$), 1.41 and 1.48 (2s, 3H each, $(CH_3)_2C$), 1.49–1.60 (m, 1H, $(CH_3)_2CH$), 1.74–1.84 (m, 2H, CH_2), 3.56 (dd, $J = 16$ and 7 Hz, 1H, H-5), 3.71 (s, 3H, CO_2CH_3), 3.75 (dd, $J = 16$ and 7 Hz, 1H, H-5′), 4.43 (dd, $J = 7$ and 6 Hz, 1H, NCH), 4.83–4.87(m, 2H, H-3 and H-4), 4.85 (br s, 1H, H-2), 7.68 (dd, $J = 7$ and 2 Hz, 1H, Ar-H3), 7.70–7.79 (m, 2H, Ar-H4 and Ar-H5), 8.09 (dd, $J = 6$ and 3 Hz, 1H, Ar-H6). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.5 and 22.3 ($(CH_3)_2CH$), 24.4 ($(CH_3)_2CH$), 25.6 and 26.7 ($(CH_3)_2C$), 38.3 (CH_2), 46.3 (C5), 52.7 (CO_2CH_3), 58.0 (NCH), 74.1 (C2), 77.3 (C3), 79.9 (C4), 113.8 ($(CH_3)_2C$), 124.3 (Ar-C3), 131.5 (Ar-C6), 131.8 and 134.3 (Ar-C2, Ar-C4 and Ar-C5), 147.8 (Ar-C1), 171.1 and 173.4 (CO).
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11. Lactone **7**: $[\alpha]_D = -42$ ($c = 1.10$, $CHCl_3$); IR ($CHCl_3$) 3300 (NH), 1785 (CO), 1736 (CO) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.90 and 0.92 (2d, $J = 7$ Hz, 3H each, $CH(CH_3)_2$), 1.39 and 1.47 (2s, 3H each, $C(CH_3)_2$), 1.41–1.44 (m, 2H, CH_2CH), 1.64–1.72 (m, 1H, $CH(CH_3)_2$), 2.48 (dd, $J = 13$ and 2 Hz, 1H, H-5), 3.22 (dd, $J = 8$ and 7 Hz, NCH), 3.26 (dd, $J = 13$ and 3 Hz, H-5), 3.72 (s, 3H, CO_2CH_3), 4.61 (dd, $J = 3$ and 2 Hz, 1H, H-4), 4.65 (d, $J = 6$ Hz, 1H, H-3), 4.82 (d, $J = 6$ Hz, 1H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.7 and 22.8 ($CH(CH_3)_2$), 24.9 ($(CH_3)_2CH$), 25.5 and 26.7 ($C(CH_3)_2$), 42.5 (CH_2CH), 48.6 (C5), 51.8 (CO_2CH_3), 60.8 (NCH), 75.6 (C2), 79.4 (C3), 82.8 (C4), 113.1 ($C(CH_3)_2$), 174.2 (CO), 175.1 (CO). Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 56.72; H, 7.86; N, 4.39.
12. Lactam **8a**: $[\alpha]_D = +5$ ($c = 1.02$, $CHCl_3$); IR ($CHCl_3$) 3400 (br, OH), 1742 (CO), 1650 (CO) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.94 and 0.96 (2d, $J = 3$ Hz, 3H each, $CH(CH_3)_2$), 1.41 and 1.52 (2s, 3H each, $C(CH_3)_2$),1.55–1.75 (m, 3H, $CH_2CH(CH_3)_2$), 2.60 (br s, 1H, OH), 3.23 (dd, $J = 12$ and 4 Hz, 1H, H-6), 3.37 (dd, $J = 12$ and 9 Hz, 1H, H-6), 3.70 (s, 3H, CO_2CH_3), 4.10–4..15 (m, 1H, H-5), 4.56–4.63 (m, 2H, H-3 and H-4), 5.3 (dd, $J = 10$ and 6 Hz, 1H, NCH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.3 and 23.2 ($CH(CH_3)_2$), 24.8 ($CH(CH_3)_2$), 24.8 and 26.0 ($C(CH_3)_2$), 37.5 (CH_2CH), 43.7 (C6), 52.3 (CO_2CH_3), 53.9 (NCH), 65.7 (C5), 74.4 and 74.8 (C3 and C4), 110.8 ($C(CH_3)_2$), 166.7 and 171.9 (CO). Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.28; H, 7.90; N, 4.46.
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16. Lactam **2a**: $[\alpha]_D = +11$ ($c = 1.20$, $CHCl_3$); IR ($CHCl_3$) 3450 (br, OH), 1740 (CO), 1648 (CO) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.95 (d, $J = 7$ Hz, 6H, $CH(CH_3)_2$), 1.48–1.61 (m, 1H, $CH(CH_3)_2$),1.67–1.83 (m, 2H, CH_2CH), 2.95 (br s, 1H, OH), 3.26 (br s, 1H, OH), 3.35 (dd, $J = 12$ and 8 Hz, 1H, H-6), 3.45 (dd, $J = 12$ and 6 Hz, 1H, H-6), 3.72 (s, 3H, CO_2CH_3), 4.01 (br s, 1H, OH), 4.09 (d, $J = 3$ Hz, 1H, H-3), 4.12–4.22 (m, 1H, H-5), 4.37 (t, $J = 3$ Hz, 1H, H-4), 5.23 (dd, $J = 10$ and 5 Hz, 1H, NCH);). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.3 and 23.3 ($CH(CH_3)_2$), 24.6 ($CH(CH_3)_2$), 37.0 (CH_2CH), 46.4 (C6), 52.4 (CO_2CH_3), 54.5 (NCH), 64.7 (C5), 68.9 (C4), 69.2 (C3), 170.5 and 171.6 (CO). Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.39; H, 7.57; N, 4.62. Lactams **2b** and **2c** show similar characteristic data. Lactam **2b**: $[\alpha]_D = -36$ ($c = 1$, $CHCl_3$). Lactam **2c**: $[\alpha]_D = -33$ ($c = 1$, $CHCl_3$).