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3-Amino-2-piperidones as Constrained Pseudopeptides: Preparation of a New Ser-Leu Surrogate

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Abstract.– We describe a stereoselective preparation of 3-amino-2-piperidone **1**, a new conformationally constrained Ser-Leu surrogate. The key steps of the synthesis of compound **1** are the lactamisation of the secondary aminolactone **4** and the amination of the 3-position *via* the sulfite **2**.

Keywords.– peptide mimetics, lactamisation, piperidinone, amino acids and derivatives

In the context of our studies on the synthesis of 3-amino-2-piperidones as conformationally restricted pseudopeptides,[1] we have focused on the Ser-Leu surrogate **1**, in which the serine χ angle is constrained and the peptide bond is fixed in a "*trans*" conformation. 3-Aminolactams mimic β-turn conformations,[2] and the known biological activities of hydroxylactams as cancer cell metastasis inhibitors[3] and as antiinflammatories[4] lend an added significance to our target molecule.

The synthesis of compound **1** was planned using D-ribonolactone as the source of the desired chirality. Thus, if the lactamisation reaction of 5-aminolactones[5] could be applied on the secondary 5-aminolactone **4** (Figure 1), we would obtain hydroxylactam **3** in one step as a single isomer. The subsequent amination of C3 would be carried out *via* the sulfite **2**, by treatment with NaN_3[6] followed by reduction.

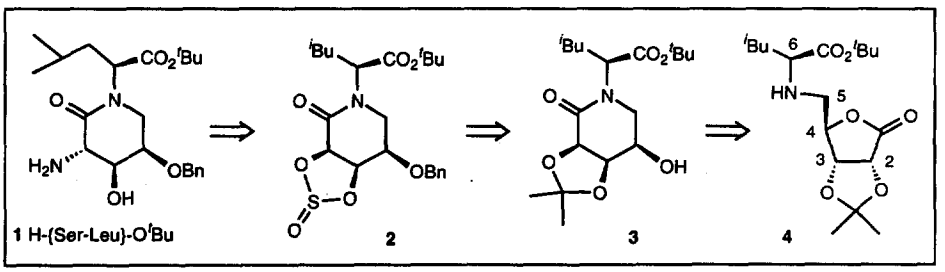

Figure 1

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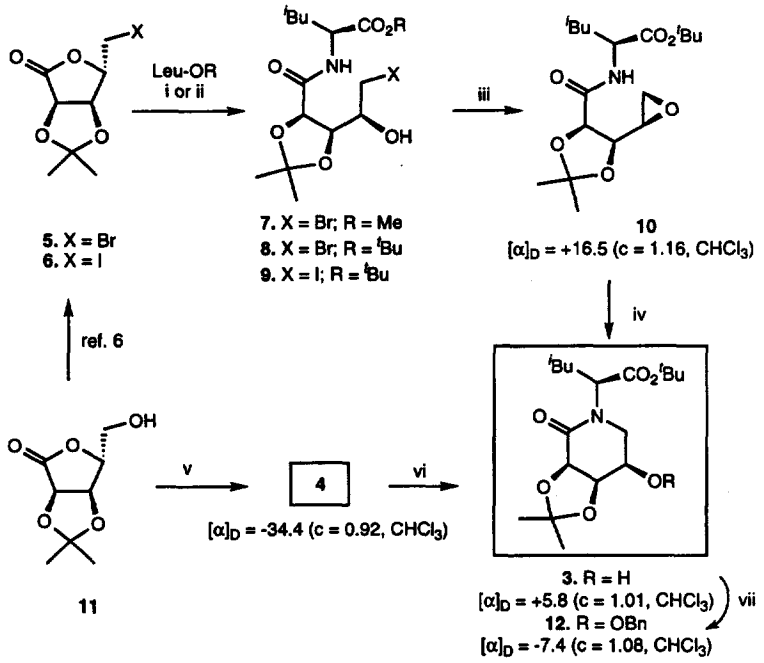
We first attempted to obtain lactone **4** (Figure 2) by reaction of leucine methyl and *t*-butyl esters with halides **5** and **6**.[7] The only product obtained from reaction of bromide **5** with Leu-OMe in THF using Et_3N as the base was unequivocally identified as the amide **7** from its 2D TOCSY NMR spectrum. The use of different reaction conditions and of iodide as a better leaving group led to the same result. Although butyrolactones are usually difficult to open,[8] our result can be explained by the extra strain on the ring that results from it being part of a 5,5-bicyclic system.

Compounds **8** and **9** were quantitatively converted to epoxide **10** by treatment with K_2CO_3 and the reaction of the epoxide **10** with NaH gave the desired lactam **3**, but in very low yield. Compound **3** shows analytical data characteristic of a substituted lactam ring.[9]

In order to avoid the lactone ring opening, we performed the S_N2 reaction on the triflate of compound **11**, with Leu-O^{t}Bu at room temperature using 2,6-lutidine as the base. We obtained lactone **4**[10] in satisfactory yield and differentiated it from amides **7-9** by its 2D TOCSY NMR spectrum. Treatment of lactone **4** with NaOAc in MeOH[11] yielded 2-piperidone **3** in 90% yield. The benzylation of the C5 hydroxy group was carried out with BnBr in the presence of KI to obtain compound **12**.



Reagents and conditions: i) NEt_3 (2 equivalents), THF, Δ (**7**: 62%); ii) 2,6-lutidine (1.2 equivalents), CH_2Cl_2, Δ (**8**: 95%; **9**: 70%); iii) K_2CO_3 (1.5 equivalents), CH_3CN, Δ (quantitative); iv) NaH (1 equivalent), THF (10-20%); v) 1. Tf_2O (1 equivalent), CH_2Cl_2, 2,6-lutidine (1 equivalent), 15 min, 0°C. 2. Leu-O^{t}Bu, 12 h, room temperature (73%); vi) NaOAc (2.5 equivalents), MeOH, Δ, 48 h (90%); vii) K_2CO_3 (1 equivalent), BnBr (3 equivalents), KI (1 equivalent), CH_3CN, Δ, 32 h (70%).

Figure 2

Hydrolysis of the acetal was achieved by treatment of compound **12** with PPTS (Figure 3). We then proceeded to the amination of the 3-position using the conditions described by Dodd *et al.*[6] The reaction of dihydroxylactam **13** with $SOCl_2$ in the presence of Et_3N converted it quantitatively to an equimolar epimeric mixture of the corresponding sulfites **2a,b**. The two isomers were separated by column chromatography (SiO_2) and fully characterised. Their treatment with NaN_3 in HMPA yielded azide **14** as a single isomer, by an *anti* attack of the azide on the 3-position. The azide was then hydrogenated using Lindlar's catalyst to obtain the target Ser-Leu surrogate **1**.[12]

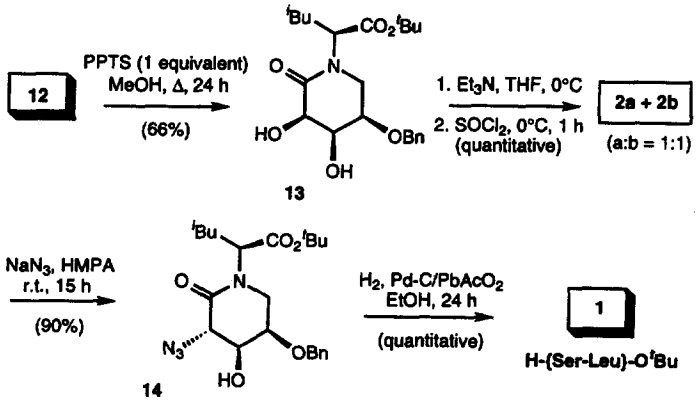


Figure 3

We intend to adapt this efficient method to the solid phase asymmetric synthesis of 3-amino-2-piperidones, and to build pseudodipeptide libraries in a combinatorial fashion by using primary amines other than leucine. Other functional transformations of the lactam ring will also be pursued.

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9. Lactam **3**: $[\alpha]_D$ = +5.8 (c = 1.01, $CHCl_3$). IR (NaCl) 3450 (OH), 1731 (CO), 1634 (CO) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 0.93 (d, *J* = 3 Hz, 3H, H-10), 0.96 (d, *J* = 3 Hz, 3H, H-10'), 1.41 (s, 3H, $O_2C(CH_3)_2$), 1.45 (s, 9H, $CO_2C(CH_3)_3$), 1.36-1.75 (m, 3H, H-8, H-9), 1.51 (s, 3H, $O_2C(CH_3)_2$), 2.3 (br s, 1H, OH), 3.23 (ddd, *J* = 12, 4 and 1 Hz, 1H, H-6), 3.34 (dd, *J* = 12 and 9 Hz, 1H, H-6'), 4.1 (dt, *J* = 9 and 4 Hz, 1H, H-5), 4.56 (ddd, *J* = 7, 4 and 1 Hz, 1H, H-4), 4.59 (d, *J* = 7 Hz, 1H, H-3), 5.15 (dd, *J* = 10 and 5 Hz, 1H, H-7); ^{13}C-NMR ($CDCl_3$, 75.4 MHz) 21.3 (C-10), 23.2 (C10'), 24.2 ($O_2C(CH_3)_2$), 24.9 (C9), 26.0 ($O_2C(CH_3)_2$), 28.0 ($CO_2C(CH_3)_3$), 37.7 (C8), 43.7 (C6), 54.6 (C7), 65.9 (C5), 74.5 (C4), 75.0 (C3), 82.0 ($CO_2C(CH_3)_3$), 110.8 ($O_2C(CH_3)_2$), 166.6 (CO), 170.6 (CO). MS *m/z* (%) 358 (M^+, 1), 359 (25), 256 (78), 198 (31), 57 (100). Anal. Calcd for $C_{18}H_{31}NO_6$: C, 60.48; H, 8.74; N, 3.92. Found: C, 60.60; H, 8.73; N, 3.94.

10. Aminolactone **4**: $[\alpha]_D$ = -34.4 (c = 0.92, $CHCl_3$). IR (NaCl) 3770 (NH), 1779 (CO), 1716 (CO) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 0.90 (d, *J* = 7 Hz, 3H, H-9), 0.92 (d, *J* = 7 Hz, 3H, H-9'), 1.39 (s, 3H, $O_2C(CH_3)_2$), 1.40 (m, 2H, H-7), 1.46 (s, 9H, $CO_2C(CH_3)_3$), 1.47 (s, 3H, $O_2C(CH_3)_2$), 1.60-1.75 (m, 1H, H-8), 2.50 (dd, *J* = 13.5 and 2 Hz, 1H, H-5), 3.07 (dd, *J* = 8 and 7 Hz, 1H, H-6), 3.25 (dd, *J* = 13.5 and 3 Hz, 1H, H-5), 4.61 (dd, *J* = 3 and 2 Hz, 1H, H-4), 4.64 (d, *J* = 6 Hz, 1H, H-3), 4.83 (d, *J* = 6 Hz, 1H, H-2); ^{13}C-NMR ($CDCl_3$, 75.4 MHz) 21.9 (C9), 22.7 (C9'), 24.9 (C8), 25.5 ($O_2C(CH_3)_2$), 26.7 ($O_2C(CH_3)_2$), 28.1 ($CO_2C(CH_3)_3$), 42.5 (C7), 48.3 (C5), 61.7 (C6), 75.6 (C2), 79.4 (C3), 81.4 ($CO_2C(CH_3)_3$), 82.5 (C4), 113.1 ($O_2C(CH_3)_2$), 174.0 (CO), 174.4 (CO); MS *m/z* (%) 358 (M^+, 4), 256 (100), 198 (52), 57 (61). Anal. Calcd for $C_{18}H_{31}NO_6$: C, 60.48; H, 8.74; N, 3.92. Found: C, 60.00; H, 8.78; N, 3.98.

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12. 3-Amino-2-piperidone **1**: IR (KBr) 3360 (br s, OH and NH_2), 1730 and 1650 (CO) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 0.87 and 0.89 (2d, *J* = 7 Hz, 3H each, H-10), 1.42 (s, 9H, $CO_2C(CH_3)_3$), 1.40-1.60 (m, 1H, H-9), 1.80-1.90 (m, 2H, H-8), 3.35 (dd, J_{ABX} = 12 and 4 Hz, 1H, H-6), 3.40 ((dd, J_{ABX} = 12 and 4 Hz, 1H, H-6), 3.75 (d, *J* = 8 Hz, 1H, H-3), 3.72 (br d, *J* = 8 Hz, 1H, H-4), 4.25 (br s, $W_{1/2}$ = 7 Hz, 1H, H-5), 4.70 (d, J_{AB} = 13 Hz, 1H, CH_ABn), 4.79 (d, J_{AB} = 13 Hz, 1H, CH_BBn), 5.22 (t, *J* = 7 Hz, 1H, H-7), 7.32 (br s, 5H, Ph); ^{13}C-NMR ($CDCl_3$, 75.4 MHz) 21.2 (C-10), 23.3 (C10'), 24.2 (C9), 27.9 ($O_2C(CH_3)_2$), 36.6 (C8), 43.8 (C6), 54.1 (C7). 54.5 (C3), 72.2 (C4), 72.3 (CH_2Bn), 73.4 (C5), 81.6 ($CO_2C(CH_3)_3$), 127.3, 127.6 and 128.3 (Ph), 137.8 (Ph-*i*), 170.4 and 172.0 (CO). MS *m/z* (%) 350 (5), 305 (M^+-$CO_2{}^t$Bu, 13), 91 (100), 57(95).