Pergamon

Tetrahedron Letters 40 (1999) 4865–4868

TETRAHEDRON LETTERS

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

Jordi Piró,[a] Mario Rubiralta,[a] Ernest Giralt,[b] Anna Diez[a]#

a. Laboratori de Química Orgànica. Facultat de Farmàcia. Universitat de Barcelona. 08028 - Barcelona, Spain

b. Departament de Química Orgànica. Facultat de Química. Universitat de Barcelona. 08028 - Barcelona, Spain

Received 18 March 1999; accepted 6 May 1999

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.

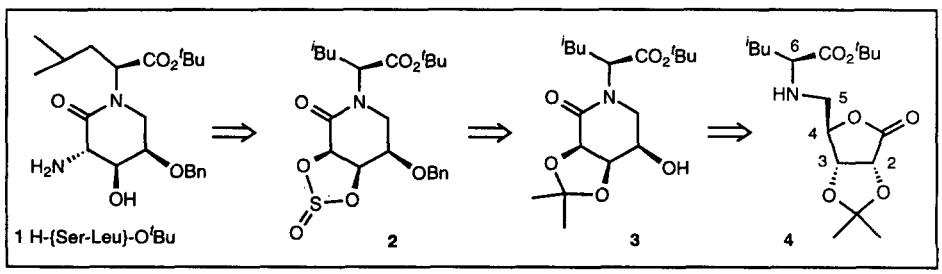


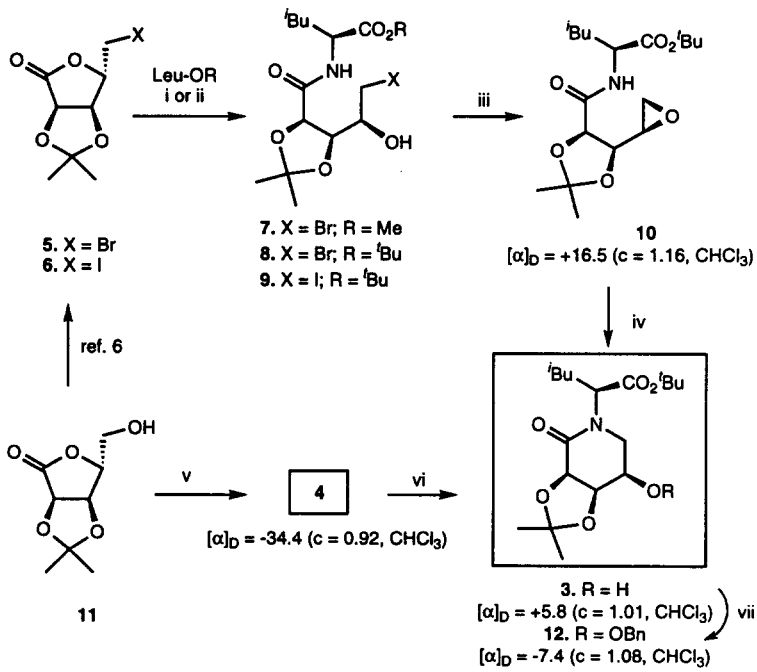
Figure 1

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00897-7

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]

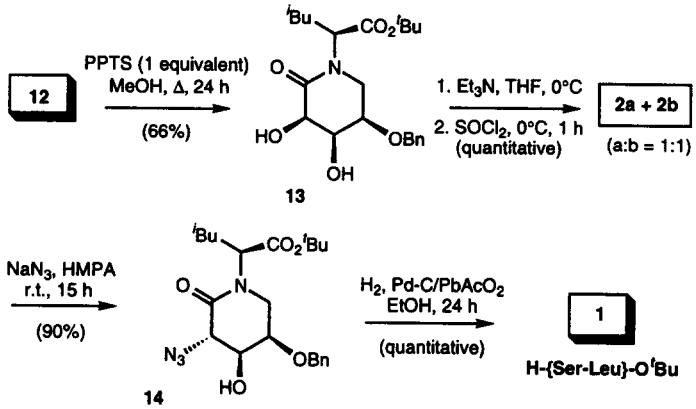


Figure 3

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.

Acknowledgements

Support for this research has been provided by the CIRIT (Generalitat de Catalunya) through grants QFN95-4703 and 1997SGR-00075, and by the DGICYT (Ministerio de Educación y Cultura, Spain) through grants PB97-0976 and 2FD97-0293. We also thank the CIRIT for a fellowship given to J. Piró.

References and Notes

To whom the correspondence should be addressed. Phone: 34-93-4024540. FAX: 34-93-4021896. E-mail: adiez@farmacia.far.ub.es

1. a. Rodríguez, R.; Estiarte, M.A.; Diez, A.; Rubiralta, M.; Colell, A.; García-Ruiz, C.; Fernández-Checa, J.C. *Tetrahedron*, **1996**, *52*, 7727-7736. b. Rodríguez, R.; Diez, A.; Rubiralta, M.; Giralt, E. *Heterocycles*, **1996**, *43*, 513-517. c. Estiarte, M.A.; de Souza, M.V.N.; del Río, X.; Dodd, R. H.; Rubiralta, M.; Diez, A. *Tetrahedron*, **1999**, in press.

2. a. Freidinger, R.M.; Perlow, D.S.; Veber, D.F., *J. Org. Chem.*, **1982**, *47*, 104-109. b. Nagai, U.; Sato, K. ; Nakamura, R.; Kato R. *Tetrahedron*, **1993**, *49*, 3577-3592. *c.* Müller, G. *Angew.Chem. Int. Ed. Engl.*, **1996**, *35*, 2767-2769.

3. Tsuruoka, T.; Nakabayashi, S.; Fukuyasu, H.; Ishii, Y.; Tsuruoka, T.; Yamamoto, H.; Inouye, S.; Kondo, S. EP 328111 A2, **1989**.
4. Tsuruoka, T.; Yuda, Y.; Nakabayashi, A.; Katano, K.; Sezaki, M.; Kondo, S. JP 63216867 A2, **1988**.
5. a. Herdeis, C.; Waibel, D. *Arch. Pharm. (Weinhein)*, **1991**, *324*, 269-274. b. Hanessian, S.J. *J. Org. Chem.*, **1969**, 34, 675-681.
6. Dauban, P.; Chiaroni, A.; Riche, C.; Dodd, R.H. *J. Org. Chem.*, **1996**, *61*, 2488-2496.
7. Bennett, S.M.; Biboutou, R.K.; Zhou, Z.; Pion, R. *Tetrahedron*, **1998**, *54*, 4761-4786.
8. Benz, G. in "Synthesis of Amides and Related Compounds" *"Comprehensive Organic Synthesis"*, Trost. B.M. and Flemming, I. Eds. Pergamon Press. Oxford, **1991**. p. 389.
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.
11. Zydowsky, T.M.; Dellaria, J.F., Jr.; Nellans, H.N. *J. Org. Chem.*, **1988**, *53*, 5607-5616.
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^+-$CO_2{}^tBu$, 13), 91 (100), 57(95).