Pergamon

*Tetrahedron Letters*, Vol. 35, No. 24, pp. 4091-4092, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0777-U

# Synthesis of 6,5-Fused Bicyclic Lactams as Potential Dipeptide β-Turn Mimetics

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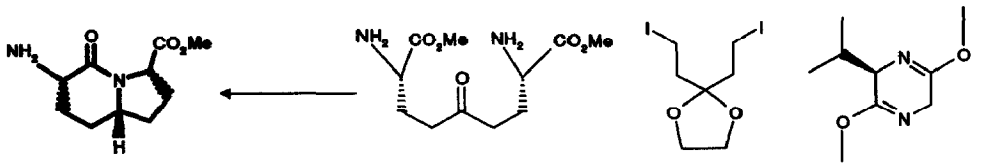
***Abstract:*** The first short synthesis of the dipeptide mimetic (3*S*, 6*S*, 9*S*)-6-amino-5-oxoindolizidine-3-carboxylic acid 1 and its Z-protected derivative 9 is described, employing the Schoellkopf bislactim-ether methodology, followed by a highly specific intramolecular reductive amination and spontaneous lactamization. These 6,5-fused bicyclic lactams may be viewed as conformationally restricted alanyl-proline β-turn mimetics.

Considerable research efforts have been concentrated over the past years on the generation of conformationally restricted peptides and their utilization in the synthesis of bioactive molecules. Studies have suggested, that the conformations of many peptides bound to their receptors (and possibly enzymes) contain β-turns and some increases in potency and duration of action have been observed for bicyclic lactam β-turn-bearing analogues [1]. This communication reports the synthesis of 6,5-fused bicyclic lactams, which may serve as suitable conformationally restricted dipeptide surrogates of Ala-Pro. Oxygen- and sulfur-analogues of the present molecule have been described in the past [2]; however, these molecules have the inherent disadvantage of being N/O and N/S acetals with potentially low metabolic stability and possibly short in vivo half lives. 7,6- and 7,5-fused bicyclic lactams have been recently prepared utilizing N-acyliminium ion cyclization chemistry [3], which prompted us to disclose our own results. Our synthesis of 6,5-fused bicyclic lactam 1 provides an excellent and short entry into this class of compounds and is based on the reductive amination-cyclization of dimethyl-(2*S*,8*S*)-2,8-diamino-5-oxononane-1,9-dicarboxylate 2.



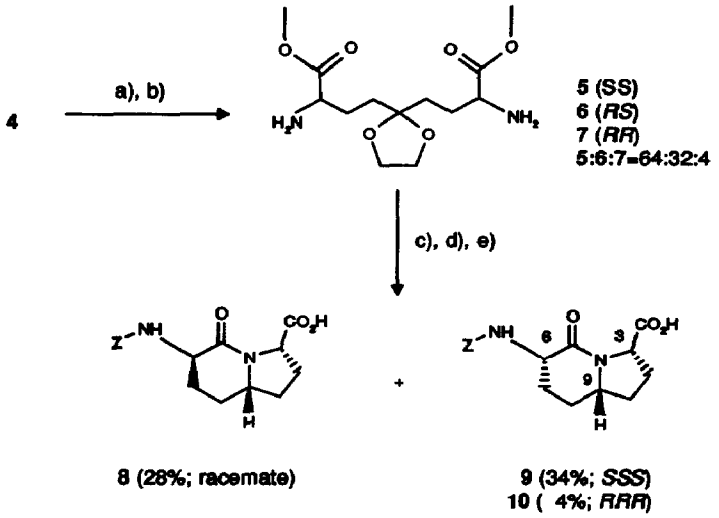

1 2 3 4

2 was prepared by applying the Schoellkopf bislactim-ether methodology [4] to control the configuration of C(2) and C(8). For this purpose, 2,2-bis(2-iodoethyl)-1,3-dioxolane 3 [5] was treated at -78° C with 2.6 equivalents of the Lithium salt of (2*R*)-(-)2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine 4 to provide in 81% yield the desired dialkylated ketals (*Scheme I*). The latter bis-dihydropyrazinyl-ketals were selectively hydrolized to a mixture of diaminoketals 5,6,7 (in a ratio of 64:32:4) under standard conditions with 0.25 N HCl and 75% yield after chromatographic separation from D-Val-OMe. Ketal hydrolysis and reductive amination followed by lactamization were performed in one pot, leading to the desired 6,5-fused lactam 1 derived from 5 and its analogues derived from 6 and 7. Upon treatment with benzylchloroformate, the mixture of Z-protected esters was easily separated by flash chromatography. Hydrolysis of the methyl esters with 0.4N NaOH in MeOH at r.t. provided the desired acids 8, 9 and 10 in good yield. Stereochemistry of the major product 9 was assigned to be *SSS*, based on an NOE (ROESY) between C-9 and C-6 protons (Indolizine numbering). No NOE could be observed in the 5-membered ring between C-9 and C-3 protons, which is in agreement with the findings of J.A.Robl in [3]. 8 is racemic, showed no NOE's between the crucial protons and was assigned the stereochemistry shown below. 8 [6] was obtained in crystalline form, 9 [7] resisted crystallization, however, together with its enantiomer 10 [8], it formed a crystalline racemate.

In spite of the limitations of the bislactim-ether methodology - resulting in an unspecific alkylation of 4 - we have used this synthesis to produce multigram quantities of 8, 9 and 10. Of specific note is the high selectivity of the reductive amination process. Overall, this method offers an easy access to dipeptide β-turn type II mimetics of the 6,5-fused bicyclic lactam

class, which can probably be extended to the preparation of n,(n-1)-fused bicyclic lactams (n>4).

*Scheme I*




a) 3, nBuLi, -78°C, 81%. b) 0.25N HCl $CH_2Cl_2/H_2O$, r.t. 2 hrs., 75%. c) EtOH/$HCl_{conc.}$, Pd/C, $H_2$, r.t. 14 hrs. quant. d) Z-Cl, $Na_2CO_3$, THF/$H_2O$, flash chromatography yields methyl esters of 8 (32%) and 9/10 (39%). e) 3 eq 0.4 N NaOH in MeOH, 88%.


## Acknowledgements:

The authors gratefully acknowledge Ms. T.Zardin and E.Buergin for the NOESY experiments and Mr. C.Quiqerez for the mass spectra.


## References and Notes: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[6] 8: m.p. 199° C.

[7] 9 resisted all attempts of obtaining crystals for X-ray analysis. 9 showed an optical rotation of $[\alpha]_D^{25}$ = -50.64 (c=1.00 in MeOH). $^1$H-NMR (360 MHz, DMSO-$d_6$): 1.45-2.20 (m, 8H, H-C(1,2,7,8)); 3.68-3.80 (m, 1H, H-C(9)); 4.05-4.16 (m, 1H, H-C(6)); 4.18-4.25 (m, 1H, H-C(3)); 5,03 (s, 2H, $CH_2$Ph)); 7.27-7.40 (m, 6H, Ph, NH); 12.5 (s, 1H, COOH). $^{13}$C-NMR (50.3 MHz, $CDCl_3$): 26.5; 26.7; 28.7; 31.5 (4$CH_2$: 1,2,7,8); 50.0; 57.1; 59.5; (3 CH:3,6,9); 66.8 ($CH_2$-Ph); 128.1; 128.5 (CH, Ph); 136.2 (C, $Ph_{ipso}$); 156.3; 169.9; 173.9 (C(5)=O, COOH, N-COO).

[8] 9/10 racemate: m.p. 148° C.


(*Received in Germany* 14 *March* 1994; *accepted* 15 *April* 1994)