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Synthesis of Highly Functionalized γ-Lactam Derivatives for Use as Conformational Constraints in Peptides

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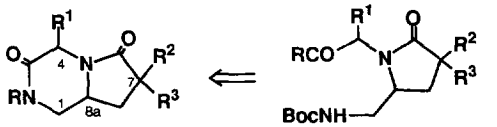
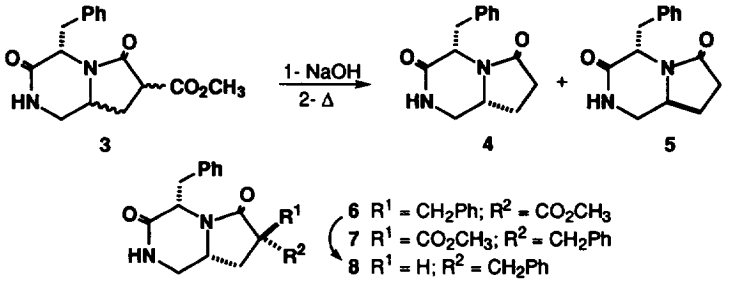
Abstract: A series of highly functionalized 2-oxopyrrolidine derivatives, as tripeptidemimetics in which the amino acid side chains are mounted on the γ-lactam template, were synthesized by nucleophilic opening of the δ-lactam system of the corresponding 3,6-dioxopyrrolo[1,2-*a*]pyrazine bicyclic analogues. Copyright © 1996 Elsevier Science Ltd

With the aim of circumventing the known limitations of peptides as potential drugs, various strategies have been devised for finding small non peptide molecules, referred to as peptidomimetics, that could bind to peptide receptors.[1] A useful step along the path towards the rational design of these compounds has been shown to be the incorporation of conformational constraints into peptides by replacing dipeptide or tripeptide fragments with lactams.[2-4] A more recent approach is that involving the selection of a template, or scaffold, onto which the pharmacophore amino acid side chains required for binding to the receptor can be attached in an appropriate orientation.[5] According to the pioneering proposal of Ariëns and Farmer,[6] nanomolar receptor binding affinity can be achieved with only three appropriately oriented pharmacophores. Based on this proposal, we have recently reported the construction of the bicyclic bis-lactam system **1** (R= H) as a fairly rigid template able to contain three amino acid side chains in different spatial orientations.[7] Although the eventual goal of peptidemimics is to produce a molecule that can only adopt one significant conformation, the availability of a broad range of templates permitting different conformational mobilities at the pharmacophore is essential in the progress towards this goal. This fact focused our attention on the controlled opening of compounds **1** (R= Boc) to provide monocyclic lactam analogues **2** as structurally related templates with greater conformational flexibility.



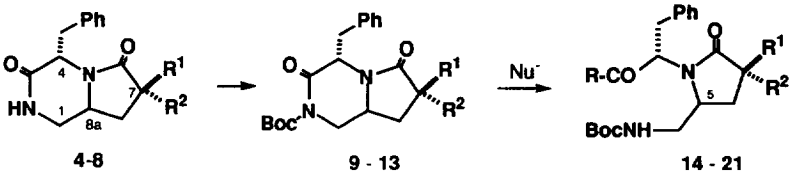
RESULTS AND DISCUSSION

The synthetic approach reported here was based on the amide-bond cleavage method that involves the regioselective hydrolysis of the corresponding Boc-imide derivatives.[8] As it happens with simple lactams,[9-11] it was expected that the opening of the 2-3 amide bond of the 3-oxopyrazine ring in compounds **1** could be performed using this methodology. To investigate this possibility, the Phe-Gly-Xaa (Xaa=Gly, Phe) restricted analogues **4-8** were selected as starting materials. Compounds **4** and **5** were prepared by saponification and decarboxylation of the diastereoisomeric mixture **3**[7] (Scheme 1). In a similar way, removal of the methoxycarbonyl group from compound **6**[7] allowed the preparation of the 4,7-dibenzyl derivative **8**.[12]



Scheme 1

Compounds **4-8** were easily transformed into the Boc-imide derivatives **9-13** by reaction with Boc_2O. In a typical experiment, the bicyclic derivative (1 equiv.) in CH_2Cl_2 was treated at room temperature with Boc_2O (2 equivs.), TEA (1 equiv.) and DMAP (0.2 equivs.) for 2.5 h (Scheme 2, Table 1).[13] These activated bicyclic lactams underwent regioselective hydrolysis, by treatment with NaOH, to the expected carboxylic acids (Compounds **14** and **18**, Table 2).[9-11,14,15] However, the nucleophilic opening with NH_3/MeOH did not afford the corresponding amide derivatives (R=NH_2), but the methyl ester analogues (R=OMe) were almost instantaneously formed, indicating that under these basic conditions the MeOH is acting as the nucleophile. The inefficacy of the NH_3 to act as nucleophile in this reaction was corroborated when compound **9** was allowed to stand with NH_3/dioxane for several days at room temperature, after which the starting bicyclic derivative remained unaltered. Finally, the amide derivative **16** was obtained from **9**, through ammonolysis of the initially formed methyl ester **15**, using NH_3/MeOH and prolonged reaction times (Table 2). The selective cleavage of (*S*)-5-(di-Boc-aminomethyl)-*N*^{1}-Boc-2-pyrrolidone to the corresponding amide derivative was described to proceed in NH_3/MeOH at room temperature for 5 days.[16] However, the possible participation of an intermediate methyl ester in this reaction was not mentioned. From our results, it seems that the nucleophilic opening of Boc-imide lactams using NH_3/MeOH and short reaction times, could constitute an alternate method to the described treatments with MeONa/MeOH[9,17] and HCl/MeOH[10] for the obtention of the corresponding methyl ester derivatives.



Scheme 2

Table 1.- Synthesis of Boc-Imide Derivatives **9-13**

Starting Compd.	R^1	R^2	Config. C_{8a}	Final Compd.	Yield[a] (%)
4[b]	H	H	*R*	**9**	64
5[b]	H	H	*S*	**10**	9
6	CH_2Ph	CO_2CH_3	*R*	**11**	90
7	CO_2CH_3	CH_2Ph	*R*	**12**	73
8	H	CH_2Ph	*R*	**13**	74

[a] Yield of isolated compounds. [b] Starting from a 7.5:1 mixture of compounds **4** and **5**, Boc-imide derivatives **9** and **10** where chromatographically separated in the indicated yield.

Table 2.- Synthesis of γ-Lactam Derivatives 14 -21

Starting Boc-imide	Nu^-	Time (h)	Final γ-lactam	R	R^1	R^2	Config. C_5	Yield[a] (%)
9	NaOH	2.5	**14**	OH	H	H	*R*	98
9	NH_3/MeOH	0.3	**15**	OMe	H	H	*R*	84
9	NH_3/MeOH	240	**16**	NH_2	H	H	*R*	95
10	NH_3/MeOH	0.3	**17**	OMe	H	H	*S*	84
11	NaOH	5	**18**[b]	OH	CH_2Ph	CO_2Me	*R*	68
11	NH_3/MeOH	0.3	**19**[c]	OMe	CH_2Ph	CO_2Me	*R*	95
12	NH_3/MeOH	0.3	**20**	OMe	CO_2Me	CH_2Ph	*R*	93
13	NH_3/MeOH	0.3	**21**	OMe	H	CH_2Ph	*R*	96

[a]Yield of isolated compounds. [b]The corresponding dicarboxylic acid (≈10%) was also isolated. [c]Also obtained by treatment of compound **18** with diazomethane

From the results indicated in Table 2, it can be concluded that neither the substituents in position 7 nor the configuration at C_7 and C_{8a} of the starting bicyclic lactam have any influence on the nucleophilic opening of 3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazine system to the corresponding highly functionalized monocyclic analogues. On the other hand, no racemization of the chiral centers was observed during the hydrolysis reactions, as demonstrated by coupling the corresponding *N*-Boc deblocked analogues of compounds **14-21** to amino acids.

Since the synthetic route to the starting bicyclic bis-lactams **1** allows the introduction of variable amino acid side chains with defined stereochemistry or in a stereocontrolled manner,[7] it is expected that a wide variety of γ-lactam derivatives **2** could be prepared using the method described here. Moreover, lactams **2** have protected amino and carboxylic groups that make them suitable for incorporation into peptide sequences and, therefore, they can be used as conformational constraints in higher peptides.

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12. Saponification and decarboxylation of compound **6** afforded the 7*R* derivative **8** (43%) along with an approximately 5% of the corresponding 7*S* diastereoisomer. The absolute configuration at the C_7 position of these 7-benzyl derivatives was established by means of n.O.e. experiments.
13. Representative procedure for the synthesis of Boc-imide derivatives.
A 7.5:1 mixture of compounds **4** and **5** (0.5 g, 2.04 mmol) was dissolved in CH_2Cl_2 (14 mL). Then, TEA (0.28 mL, 2.04 mmol), *N,N*-dimethylaminopyridine (0.025 g, 0.2 mmol) and di-*tert*-butyldicarbonate (0.92 g, 4.08 mmol) were added at room temperature. After 2.5 h of stirring, the solvent was evaporated and the resulting residue was purified on a silica gel column using EtOAc-hexane (1:2) as eluent, to give compounds **9** (0.46 g, 64%) and **10** (0.062 g, 9%).
Compound **9**: White solid, mp = 145-148°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28-7.08 (5H, m), 4.63 (1H, m), 3.92 (1H, dd, *J* = 13.5, 5.1), 3.60 (2H, m), 3.18 (1H, dd, *J* = 13.5, 2.7), 2.49 (2H, m), 2.07 (1H, m), 1.53 (9H, s), 1.35 (1H, m). Anal. Calcd. for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.08; H, 6.98; N, 7.85.
Compound **10**: Oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33-7.11 (5H, m), 4.81 (1H, m), 3.81 (1H, dd, *J* = 13.3, 3.5), 3.49 (1H, dd, *J* = 13.5, 4.0), 3.27 (1H, dd, *J* = 13.5, 5.7), 3.12 (1H, m), 2.89 (1H, m), 2.05 (1H, m), 1.54 (1H, m), 1.52 (9H, s). Anal. Calcd. for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 65.97; H, 7.21; N, 8.06.
14. Nucleophilic opening of 2-Boc-3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazines.
Hydrolysis with NaOH: A solution of the corresponding Boc-imide derivative (0.3 mmol) in THF (3 mL) was treated with 1N NaOH (0.3 mmol). After 2 h of reaction at room temperature, the solution was acidified to pH 3 with 1N HCl and extracted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4 and evaporated to dryness.
Reaction with NH_3-MeOH: The corresponding Boc-imide derivative (0.25 mmol) was treated with a saturated solution of NH_3 in MeOH (7 mL) at room temperature for the time indicated in Table 2. After evaporation of the solvents, the resulting residue was purified on a silica gel column using EtOAc-hexane (1:1) as eluent.
15. All new compounds gave analytical and spectroscopic data according to the proposed structures, as indicated for **15** and **17**:
15: White solid, mp = 131-133°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35-7.14 (5H, m), 5.52 (1H, d, *J* = 6.9), 3.86 (3H, s), 3.82 (1H, dd, *J* = 8.7, 4.0), 3.48 (2H, m), 3.32 (1H, dd, *J* = 13.5, 4.0), 2.95 (1H, m), 2.66 (1H, m), 2.34 (2H, m), 1.77 (2H, m), 1.42 (9H, s). Anal. Calcd. for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.50; N, 7.44. Found: C, 63.78; H, 7.25; N, 7.43.
17: Oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28-7.07 (5H, m), 4.71 (1H, dd, *J* = 11.7, 5.1), 4.56 (1H, m), 3.71 (3H, s), 3.55 (1H, m), 3.30 (3H, m), 2.70 (1H, m), 2.33 (1H, m), 2.07 (1H, m), 1.75 (2H, m), 1.35 (9H, s). Anal. Calcd. for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.50; N, 7.44. Found: C, 64.01; H, 7.18; N, 7.21.
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