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3,6-Dioxoperhydropyrrolo[1,2-*a*]pyrazines. A New Approach to Conformationally Restricted Tripeptides

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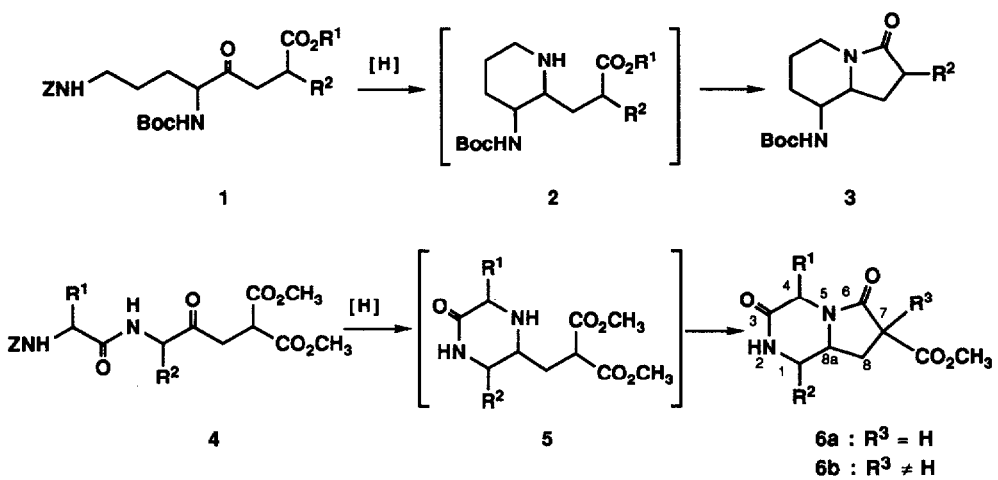
Abstract. *Catalytic hydrogenation of the 4-ketodiesters, obtained fom Z-Xaa-Gly (Xaa= Ala, Phe) halomethyl ketones and dimethyl malonate, provides readily access to the corresponding 4-substituted-3,6-dioxoperhydropyrrolo[1,2-a]pyrazine-7-carboxylic acid derivatives with high degree of stereocontrol at the new chiral centers. Alkylation of these bicyclic bis-lactams with benzyl bromide gave the corresponding Xaa-Gly-Phe restricted tripeptides.*

Lactams as conformational constraints in peptide backbones are effective structural tools for probing the active conformations of bioactive peptides.[1-5] Although several synthetic routes to lactam-bridged modified peptides are known,[1-6] these methods commonly lack provision for retention of the amino acid side chain as a substituent on the lactam. Taking into account that the amino acid side chains of peptides play an important role in receptor recognition,[5,7] we directed our attention towards new non-peptide molecules that could carry the side-chain residues.

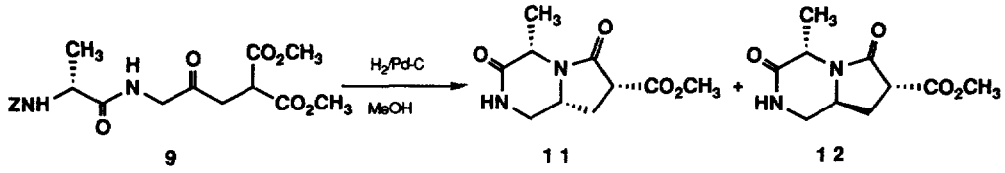
In previous papers, [8,9] we have reported a procedure for the synthesis of the 8-amino-3-oxoindolizidines **3** from the 4-ketodiesters **1**, obtained from Boc-Orn(Z)-chloromethyl ketone. This procedure, involving hydrogenolysis of the Z-group, intramolecular reductive amination and γ-lactamization of the resulting piperidine intermediates **2**, leads, in one step, to the elaboration of the 3-oxoindolizidine skeleton. With this in mind, it could be expected that, under similar conditions, the 4-ketodiester analogues **4**, derived from dipeptides, cyclized to the 2-ketopiperazines **5**, which, on lactamization, could provide the 3,6-dioxoperhydopyrrolo[1,2-a]pyrazine-7-carboxylate **6a** of defined stereochemistry at C_1 and C_4 (Scheme 1).



Scheme 1

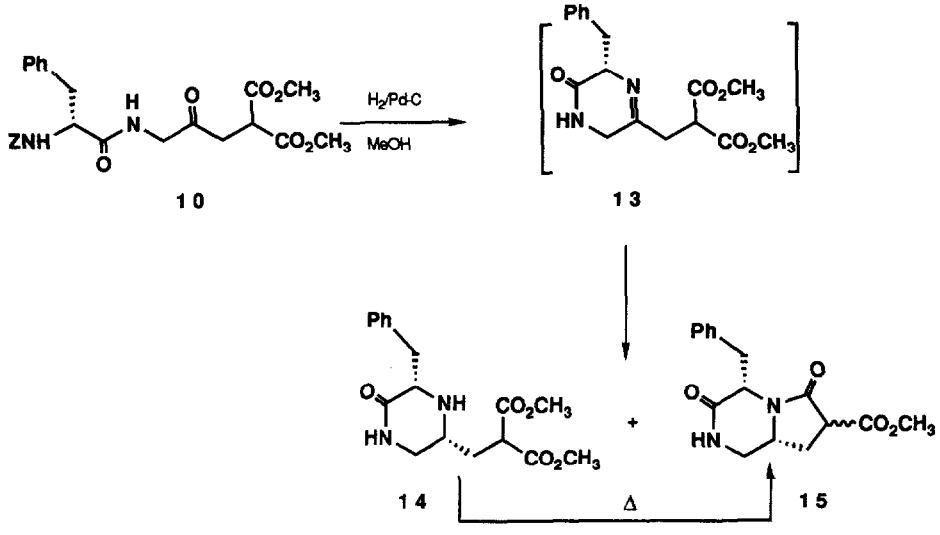
Compounds **6a** can be considered restricted analogues of Xaa-Gly-Gly in which the Gly at C-terminus could be replaced with other amino acids by introduction of the suitable side chain at C_7 position to give **6b**. Additionally, compounds **6** could be incorporated into higher peptides.

According to this approach, the 4-ketodiesters **9** and **10** [10] were prepared by alkylation of dimethyl malonate with Z-Ala-Gly and Z-Phe-Gly halomethyl ketones, previously obtained from the corresponding dipeptides, following the procedure described for the 4-ketodiester **1** ($R^1 = CH_3$, $R^2 = CO_2CH_3$). [11,12] Catalytic hydrogenation of compound **9** for 2 days at room temperature and 30 psi of pressure, using 10% Pd-C as catalyst, directly gave the 4-methyl perhydropyrrolo[1,2-*a*]pyrazines **11** (79%, 20:1 CH_2Cl_2/MeOH) and **12** (15%), that could be considered restricted analogues of the tripeptide Ala-Gly-Gly (Scheme 2).



Scheme 2

A similar treatment of the 4-ketodiester **10** (H_2/Pd-C, 5 days, r. t., 30 psi) gave a mixture of the 3,5-disubstituted 2-ketopiperazine **14**, [10] as a single isomer, and the bicyclic bis-lactam **15** in a 5:1 ratio (69% overall yield, 40:1 CH_2Cl_2/MeOH). Compound **14** was quickly lactamized to the bicyclic derivative **15** by refluxing in toluene (Scheme 3). The imine **13**, intermediate of the reductive amination, was isolated when the reaction was stopped after disappearance of the starting material (5h, r.t.).[13]

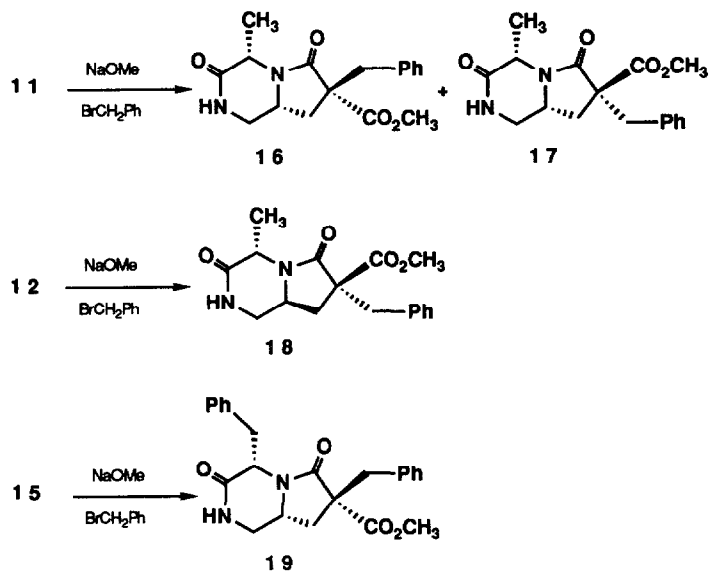


Scheme 3

The high or total stereoselectivity found at C_{8a} could be explained through the imine intermediates, in a way that hydrogenation of the C=N double bond takes place, preferently or exclusively, by the opposite side to the CH_3 or the CH_2Ph substituents.

The assignment of the absolute stereochemistry at the new chiral centers, C_7 and C_{8a}, in compounds **11** and **12** was based on their ^{1}H-NMR data (Table 1) and NOE experiments. Thus, major compound **11** shows strong dipolar exchanges of magnetization (NOE) between H_{8a}-H_{1e} and H_{8a}-H_8 and small NOE's between H_{8a}-H_4 and H_{8a}-H_7, indicating that all these protons are in the same side of the heterocyclic ring. As the stereochemistry at C_4 was fixed by the starting dipeptide, compound **11** has 4*S*, 7*R*, 8a*R* configuration. Although no clear NOE's were observed for the H_{8a} proton in compound **12**, the 8a*S* stereochemistry was indirectly established from the synthesis of its 7-alkyl derivative. Assignment of the stereochemistry at C_{8a} in compound **15**, obtained as a mixture of diastereoisomers at C_7, was made by correlation of its ^{1}H-NMR spectrum with those of the Ala derivatives **11** and **12**.

In order to test the possibility of introducing an amino acid side chain different from glycine at C-terminus, compounds **11**, **12** and **15** were alkylated with benzyl bromide in the presence of sodium methoxide .



Scheme 4

As shown in scheme 4, alkylation of compound **11** gave a mixture of 7-benzyl derivatives **16** (35%, 75:1 CH_2Cl_2/MeOH) and **17** (15%), while a similar reaction of **12** and **15** afforded compounds **18** (46%) and **19** (49%), respectively, as single diastereoisomers. The absolute stereochemistry at C_7 of all these benzyl derivatives was established on the basis of the chemical shifts of their H_{8a} protons. Thus, the observed shielding for this proton in compounds **16**, **18** and **19**, when compared to the same proton in the parent bicyclic derivatives **11**, **12** and **15**, indicated that the 7-benzyl group and the H_{8a} are in *cis* disposition (Table 1).

In conclusion, we have described an efficient route to the preparation of 4,7-disubstituted 3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazine-7-carboxylate derivatives, bicyclic bis-lactams of potential interest in the field of conformationally restricted peptides. The most important aspect of this approach is the rapid construction of the pyrrolopyrazine skeleton in one step, and the high degree of stereocontrol obtained for the new chiral centers. Studies with 4-ketodiesters derived from other Z-dipeptides are in progress.

Table 1. Selected ^{1}H-NMR data of compounds **11, 12, 15-19** (300 MHz, $CDCl_3$)[(∂ ppm), (J Hz)]

Compd	H-1	H-2	H-4	H-7	H-8	H-8a	$J_{1,8a}$	$J_{7,8}$	$J_{8,8a}$
11	3.49 3.31	7.29	4.21	3.55	2.41 2.16	3.75	3.4 11.0	8.2 11.2	5.1 9.7
12	3.48 3.21	6.23	4.57	3.55	2.68 1.96	4.11	9.0 11.2	5.4 9.9	8.0 4.7
15[a]	2.82 1.52	6.85	4.44	3.50	2.16 1.77	3.56	6.3 11.7	7.8 11.3	5.6 11.3
	2.84 1.52	6.89	4.44	3.45	2.25 1.45	3.86	7.6 11.7	5.7 9.7	5.7 12.7
16	3.16 3.07	6.99	3.92	-	2.22	2.32	3.4 9.7	-	b
17	3.27 2.65	7.01	4.19	-	2.39 1.61	3.84	4.4 11.0	-	6.2 9.2
18	3.21	6.74	4.38	-	2.36 2.27	3.09	b	-	8.4 5.0
19	2.57 1.54	6.40	4.21	-	1.98	2.09	2.9 10.9	-	b

[a] Mixture of two diastereoisomers. [b] They can not be exactly measured.

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12. García-López, M.T.; González-Muñiz, R.; Harto,J.R. *Tetrahedron* , **1988**, *44*, 5131-5138.
13. *3(S)-Benzyl-5-[(2,2-dimethoxycarbonyl)ethyl]-2-oxo-1,2,3,6-tetrahydropyrazine* (**13**). ^{1}H-NMR (300 MHz, $CDCl_3$) : ∂ 7.34-7.08 (m, 5H, Ph), 6.52 (d, 1H, H-1), 4.44 (m, 1H, H-3), 4.03 (dd, 1H, $CH_2\underline{CH}$), 3.78 and 3.72 (2s, 6H, CO_2CH_3), 3.64 (ddd, 1H, H-6), 3.23 (dd, 1H, 3-CH_2), 3.12 (dd, 1H, 3-CH_2), 2.96 (dd, 1H, H-6), 2.78 (ddd, 1H, $C\underline{H}_2CH$), 2.70 (ddd, 1H, $C\underline{H}_2CH$). ^{13}C-NMR (50 MHz, $CDCl_3$): ∂ 69.9 and 169.4 (C-2 and CO_2), 161.7 (C-5), 61.6 (C-3), 52.6 (OCH_3),47.6 (C-6), 45.9 (C-5''), 38.8 (C-3'), 34.6 (C-5').

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