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A FACILE SYNTHESIS OF 8-AMINO-3-OXOINDOLIZIDINE DERIVATIVES AS CONFORMATIONALLY RESTRICTED ORNITHYL PSEUDODIPEPTIDES

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Abstract: One pot procedure for the synthesis of 8-amino-3-oxoindolizidines from Z^{δ}-protected ornithyl ketomethylene pseudodipeptide derivatives is described. This procedure, involving hydrogenolysis of the Z-group, intramolecular reductive amination and γ-lactamization, provides readily access to a variety of 3-oxoindolizidines of defined stereochemistry at C-8 and C-8a.

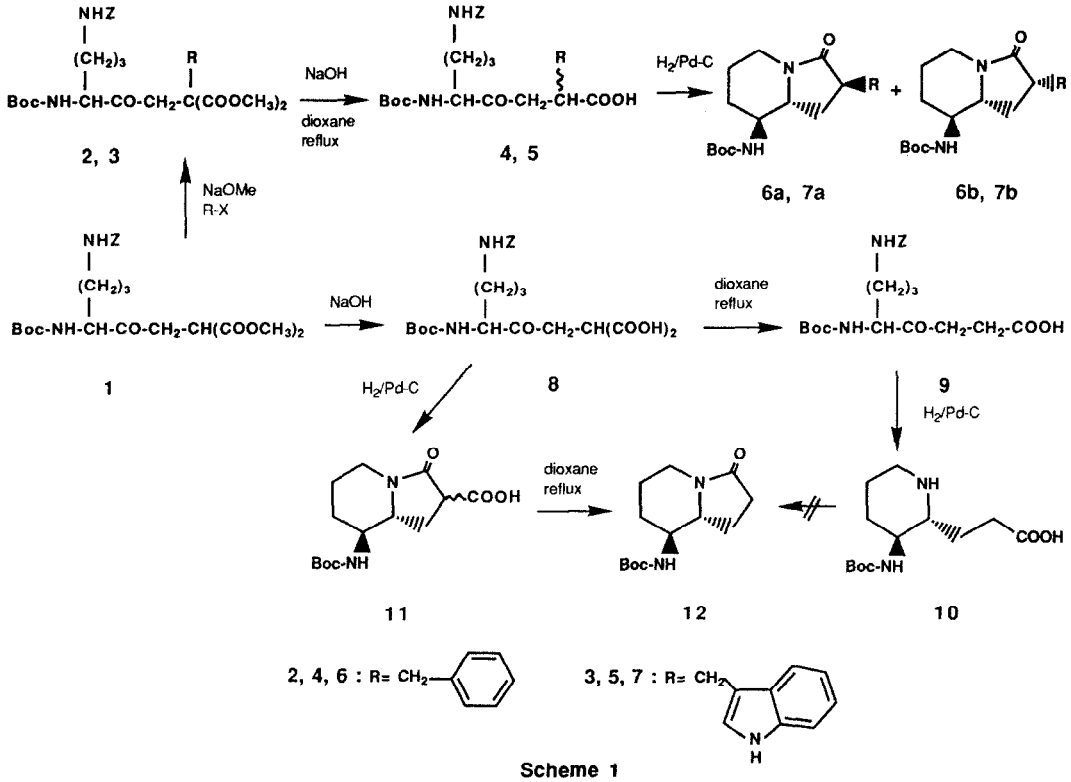
Replacement of the peptide backbone by a non-peptide framework bearing the amino acid side-chain groups of the peptide is an encouraging approach to the design of peptidomimetics.[1] Lactam containing dipeptides are being extensively used as conformational constraint in peptides.[2-6] Moreover, nitrogen bridged bicyclic lactams, such as indolizidine derivatives[7] and related structures,[8] have been described to mimic the central part of a ß-turn.[9] These facts directed our attention towards suitable substituted 3-oxoindolizidines as conformationally restricted analogues of dipeptides.

Our approach was based on the known ability of ornithyl and arginyl derivatives to intramolecular cyclizations.[2,10] Thus, it was expected that, under reductive conditions, δ-deprotected ornithyl ketomethylene dipeptides cyclized to the corresponding piperidines which, on intramolecular acylation, could provide the 3-oxoindolizidine bicyclic system. Similar approaches were used for the synthesis of indolizidine related natural products, such as swainsonine[11] and tylophorine.[12]

As shown in Scheme 1, the starting material for the synthesis of 3-oxoindolizidines **6**, **7**, and **12**, was the 4-ketodiester **1**, which was prepared by alkylation of dimethyl malonate with the corresponding ornithine halomethyl ketone.[13,14] According to this approach, 4-ketodiacids **4**, **5** and **9** were selected as precursors of the 3-oxoindolizidines **6**, **7** and **12**, analogues of Orn-Phe, Orn-Trp and Orn-Gly, respectively.

The introduction of the Phe and Trp side-chain in **4** and **5** was carried out by reaction of the sodium derivative of **1** with benzyl bromide and methiodide of gramine, respectively, to give **2** (88%) and **3** (76%). Saponification and decarboxylation of **2** and **3** provided **4** (92%, foam, 12:1 $CHCl_3$/MeOH) and **5** (61%, foam, 9:1 $CHCl_3$/MeOH), in which the C-terminal amino acid residues are fully racemic. Catalytic hydrogenation of these 2-substituted-4-ketoacids, for 15-24 h[15] at room temperature and 30 psi of pressure, using Pd-C as catalyst, directly gave the 2-substituted-3-oxoindolizidines **6** (86%, syrup,

4:1 $CHCl_3$/MeOH) and **7** (45%, foam, 4:1 $CHCl_3$/MeOH) which, in the case of **6**, could be separated into the two diastereomers **6a** and **6b**. However, a similar treatment of compound **9** gave the piperidine derivative **10**, as the only reaction product. No γ-lactamization of **10** was observed either by prolonged hydrogenation or by refluxing in different solvents in the presence of triethylamine. On the contrary, the 3-oxoindolizidine-2-carboxylic acid **11** (85%) was directly formed when the diacid **8** was hydrogenated in the above conditions. Decarboxylation of **11** led to the desired indolizidine **12** (52%, 20:1 $CHCl_3$/MeOH). The fact that compounds **10** and **12** were single isomers indicated the stereoselectivity of the intramolecular reductive amination.



Scheme 1

The ^{1}H-NMR of compounds **6a**, **6b** and **12** allowed us to assign the R configuration for C-8a, based on the $J_{8,8a}$ coupling constant values (Table 1) which indicated a trans disposition between the H-8 and H-8a protons. The observed shielding for H-8a (≈ 0.3 ppm) in compound **6a** when compared to the same proton in **6b** and **12** suggested that H-8a and benzyl group are in the same side of the ring. This suggestion was corroborated by a similar, but slight, shielding for H-8 proton in **6b** that indicated that the H-8 and the

aromatic ring are cis. The large difference in chemical shift for H-5 protons ($\Delta\delta_{5ax,5eq}$ 1.5 ppm, Table 1) means a trans-disposition between the H_{5eq} and the nitrogen lone pair and, therefore, a trans-fused conformation for the indolizidine ring.[16] ^{13}C-NMR values (Table 2) were also in agreement with this favoured trans-fused conformation.[16,17]

Table 1. ^{1}H-NMR data of 3-oxoindolizidines **6, 7, 11** and **12** (300 MHz, $CDCl_3$)

	δ (ppm)							
Compound	H-1	H-2	H-5	H-6	H-7	H-8	H-8a	$J_{8,8a}$ (Hz)
6a	1.98 1.85	2.75	4.07 2.42	1.68 1.43	2.03 1.15	3.27	2.67	10.1
6b	2.22 1.60	2.62	4.08 2.50	1.75 1.40	2.05 1.23	3.15	2.95	8.6
7[a,b]	2.0-2.2	2.8-3.2	3.86 2.40-2.59	1.69 1.37	1.98 0.89	2.8-3.2		-
11[a]	2.50 2.12	3.28	4.07 2.60	1.78 1.43	2.08 1.25	3.45	3.28	-
12	2.17 1.93	2.38	4.07 2.52	1.74 1.48	2.08 1.26	3.28	3.08	9.8

[a] Mixture of diastereomers. [b] Spectrum recorded in CD_3OD.

Table 2. ^{13}C-NMR data of 3-oxoindolizidines **6, 7, 11** and **12** (75 MHz)

Compound	Solvent	C-3	C-2	C-8	C-8a	Ring CH_2			
6a	DMSO-d_6	177.1	43.9	54.05	61.6	40.7	32.1	28.2	25.1
6b	DMSO-d_6	177.0	44.9	53.4	61.0	40.6	32.1	29.9	24.8
7[a]	CD_3OD	177.9 177.7	43.7 42.2	55.3 54.2	61.6 61.0	41.1 40.6	32.2 32.0	30.2 30.0	24.9 24.8
11[a]	DMSO-d_6	172.1 171.9	48.5 48.3	53.6 52.7	59.6 58.6	39.5[b]	30.8 30.6	27.4 26.8	23.6 23.4
12	$CDCl_3$	173.6	31.4	53.2	61.9	39.2	29.8	23.7	22.1

[a] Mixture of diastereomers. [b] Included in DMSO-d_6 signal.

In conclusion the most important aspect of this approach is the rapid construction of the 3-oxoindolizidine skeleton in one step, involving two consecutive intramolecular cyclizations from simple molecules, with high degree of stereocontrol at C-8 and C-8a. In the field of alkaloids, it could provide an easy access to δ-coniceine and derivatives from

the appropiate δ-amino acid.[18] Attempts to prepare suitably protected 8-amino-3-oxoindolizidine-2-carboxylic acid derivatives for being introduced as a spacer into higher peptides are now in progress.

REFERENCES AND FOOTNOTES

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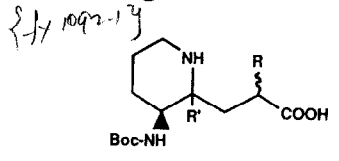
15. When compound **5** was hydrogenated in the presence of Pd-C as catalyst for 1 h, compounds **13** (42%) and **14** (18%) were obtained as mixtures of two diastereomers as shown by their ^{1}H- and ^{13}C-NMR spectra. Hydrogenation for 4 h gave exclusively **14** in 67% yield. Hydrogenation of **4** for 2 h gave compound **15** (69%) as the only reaction product. Compounds **14** and **15** suffered spontaneous cyclization to the corresponding indolizidines **11** and **12** in MeOH or DMF solution (24-48 h).



13: R=CH_2-indole, R'=OH
14: R=CH_2-indole, R'=H
15: R=CH_2-Ph, R'=H

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