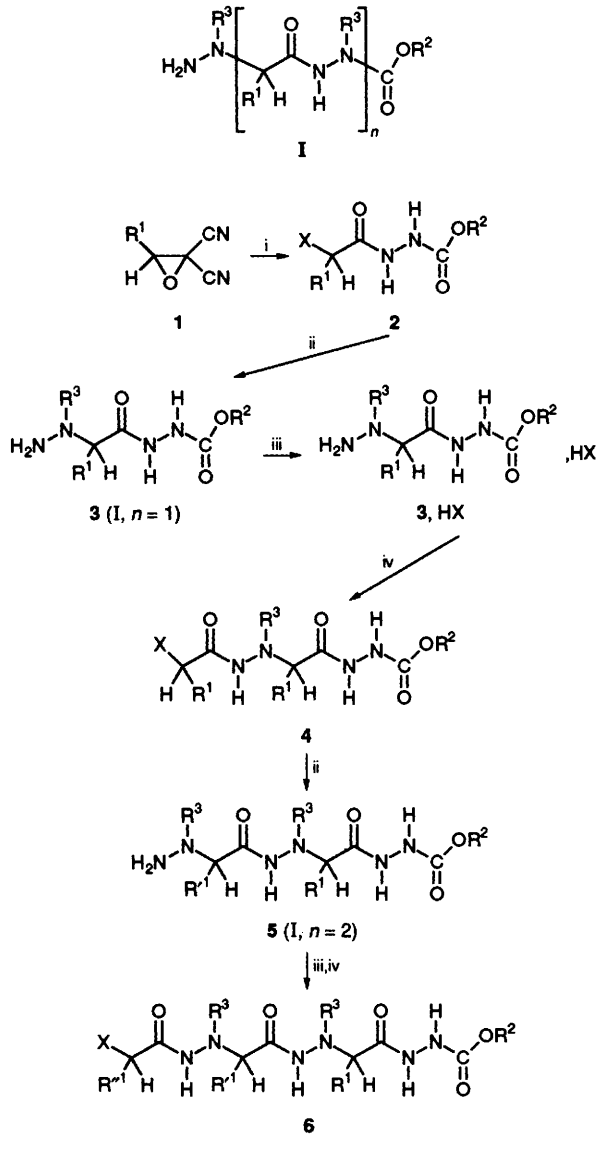
Design and Synthesis of a New Series of Peptide Analogues: the Hydrazinopeptides

C. Barré, P. Le Grel, A. Robert and M. Baudy-Floc'h*

Groupe de Recherches de Chimie Structurale Université de Rennes I, URA CNRS 704, Avenue du Général Leclerc, 35042 Rennes Cédex, France

Hydrazinopeptides, a new series of peptide analogues, have been obtained in good yield, by a general synthetic strategy; these new analogues are also polyhydrazides as well as polyamides.

As peptides are essential components of all living systems, their chemistry and biochemistry have been extensively studied.[1,2] Many peptide analogues have been synthesized to date through the modification not only of the amino acid side chain, *e.g.* by exchanging one amino acid for another, but also of a part of the backbone structure, *e.g.* the azapeptides (the α-CH group of some amino acid residues in the peptide chain are replaced by an N atom[3]) or the hydrazinopeptides [some amide blocks (RCH–CO–NH) in the peptide chain are replaced by hydrazide blocks (RCH–CO–NHNH)[4–6]].



Scheme 1 *Reagents and conditions*: for $R^1 = p\text{-}ClC_6H_4$, $R^2 = R^3 = Me$, X = Br, i, $H_2NNHCO_2R^2$ HX, MeCN, room temp., 12 h, 99%; ii, H_2NNHR^3, MeCN, 10 min, 73% iii, HBr, dioxane–diethyl ether, 10 min, 90%; iv, 1, MeCN, room temp., 16 h, 87%

Until now, there has been no strategy to prepare hydrazinopeptides, **I**, where the whole peptidic backbone consists of hydrazide motifs.

Our previous work in the field of α-functionalized hydrazides[7,8] prompted us to design a procedure for the synthesis of this new class of peptide analogues **I**. Our strategy, described in Scheme 1, consists of reacting the *gem* dicyanoepoxides **1** with carbazate halohydrates to lead to α-halohydrazides **2**,[7] then the reaction of substituted hydrazines with α-halohydrazides **2** affords α-hydrazinohydrazides. It is worth noting that when the reactant is methyl hydrazine the substituted nitrogen attacks the α-halogenohydrazides to give chemioselectively the α-hydrazinohydrazides **3**. The halohydrate of these α-hydrazinohydrazides **3** can react with another molecule of epoxide **1** to yield hydrazino peptides **4**. If we repeat the reactional sequence from **2** to **4** (steps ii, iii and iv) we obtain the trihydrazinopeptides **5** and **6**.

The hydrazinopeptides **3–6** are obtained with good yields, but as a mixture of diastereoisomers. In this hydrazinopeptide preparation, we have to separate two diastereoisomers **5** before going further in the synthesis. Nevertheless, it is quite easy to separate the diastereoisomers **5**, only one pure diastereoisomer **5** precipitates in the reaction medium. At this time the relative configurations of the asymetric carbons of **4**, **5** and **6** are unknown.

Despite the absence of diastereoselectivity, the merit of the procedure is that it is the first to allow the synthesis of peptide analogues with complete replacement of amide blocks by hydrazide blocks, **I**. Moreover, the efficiency of this synthesis is due to good yields in each step and to its versatility. Indeed, we can keep the same substituents R^1 and R^3 all along the sequence, but we can also change these substituents in a predictable manner by reacting different epoxides (R^1 = alkyl, aryl) and different substituted hydrazines (R^3 = Me, CH_2Ph, CF_3 CH_2) at selected steps of the reaction. This step by step strategy, allows also, for instance, the linkage of an optically active aminoester to halogenated hydrazinopeptides **4** to **6**.

Received, 20th October 1993; Com. 3/06281C

References

1 R. M. Williams, *Synthesis of optically active α-amino acids*, Pergamon, 1989.
2 M. Bodanszky, *Principles of Peptide Synthesis*, Springer, 1984.
3 J. Gante, *Synthesis*, 1989, 405.
4 R. Grupe and H. Niedrich, *Chem. Ber.*, 1966, **99**, 3914.
5 P. H. Bentley and J. S. Morley, *J. Chem. Soc. (C)*, 1966, 60.
6 H. Niedrich, *Chem. Ber.*, 1967, **100**, 3273.
7 P. Le Grel, M. Baudy-Floc'h and A. Robert, *Synthesis*, 1987, 306.
8 P. Le Grel, M. Baudy-Floc'h and A. Robert, *Tetrahedron*, 1988, **44**, 4805.