CHIRAL LACTAMS AS TEMPLATES FOR ENZYME INHIBITORS: A SIMPLIFIED ROUTE TO THE EXPANDED POOL†

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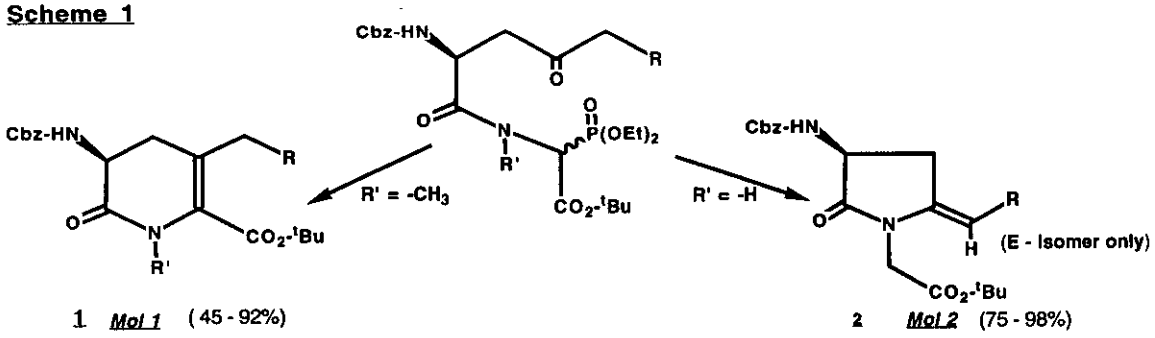
Abstract - A new class of dipeptide lactam templates first prepared using glycine phosphonates is now expanded to contain other amino acids and primary amine derivatives in a simplified general approach.

Recent advances in genetics, biophysics and protein structure analysis provide an unique opportunity to apply the principles of organic synthesis and molecular modelling to our increased understanding of protein structure and function to develop newer approaches to 'inhibitor design'.[1] Our goal was to design a molecular framework and confer upon it the selective biological properties by careful control of reactivity and geometry through structure manipulation. Choosing peptidases (Penicillin Recognizing Enzymes) as the *target enzyme* class, we recently reported the design of two new class of chiral lactams (**1** and **2**) and their first simple synthesis through an intramolecular Wadsworth-Horner-Emmons (WHE) reaction (scheme 1).[2]

Scheme 1



1 *Mol 1* (45 - 92%) **2** *Mol 2* (75 - 98%)

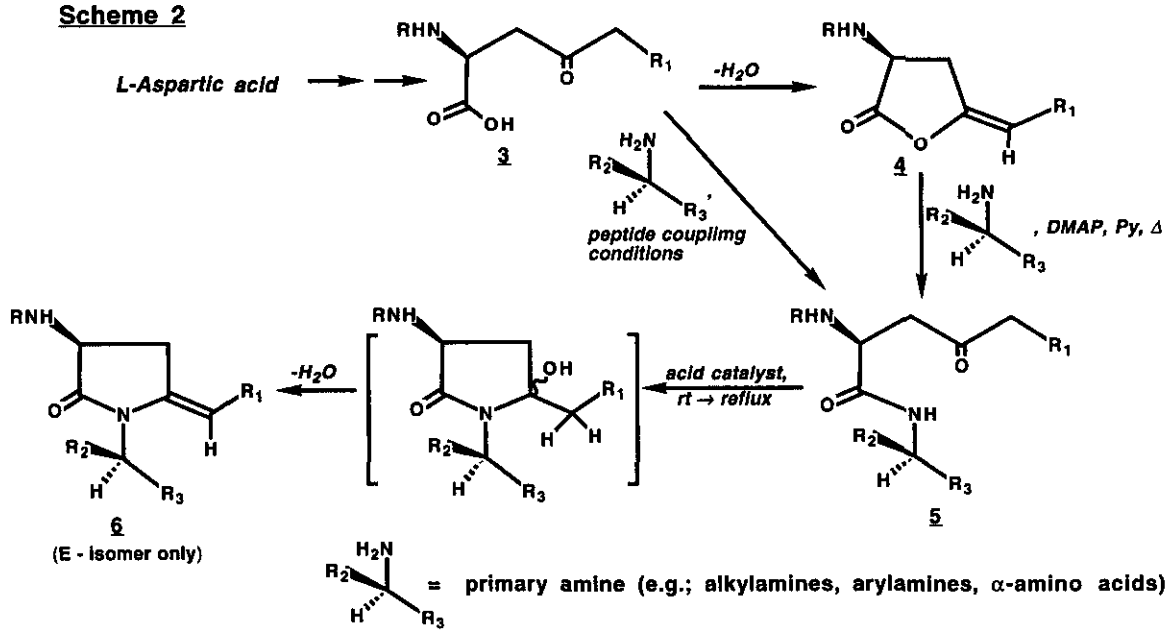
Exploratory investigations encouraged us for more detailed studies on the derivatives of 3-aminopyrrolidinones (**2**) and we decided to build a combinatorial library of peptide and non-peptide derivatives of **2** . Chiral substituents on the pyrrolidone nitrogen were determined to be essential for the conformational control of these lactams. Although the WHE reaction offered a very convenient route to Type 2 lactam, the use of glycine

† Dedicated to the memory of the late Prof. Yoshio Ban

phosphonate precluded the incorporation of the critical chiral substituents derived from primary α-amino acids on the pyrrolidone nitrogen.

In the new simplified direct approach (Scheme 2), the protected ketoacid (**3**) prepared from aspartic acid as before[2] was coupled with a primary amine derivative under standard conditions of peptide synthesis to furnish the ketoacyl derivative, **5** in moderate to high yields. The ene lactone (**4**) was obtained as the major side product. Although unreactive under these conditions, **4** (conveniently prepared from **3** with DCC/succinic acid) reacted very efficiently with the primary amine derivatives in warm pyridine in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP)[3] to furnish **5**. The combinatorial pool included keto-peptides prepared from (**R_2** and **R_3** in Scheme 2) alkylamines, arylamines, α-amino acids (L and D series) and 6-aminopenicillanic acid. The ketodipeptide (**5**) on treatment with an acid catalyst (PTSH or PPTS) underwent Mannich annulation to **6**.

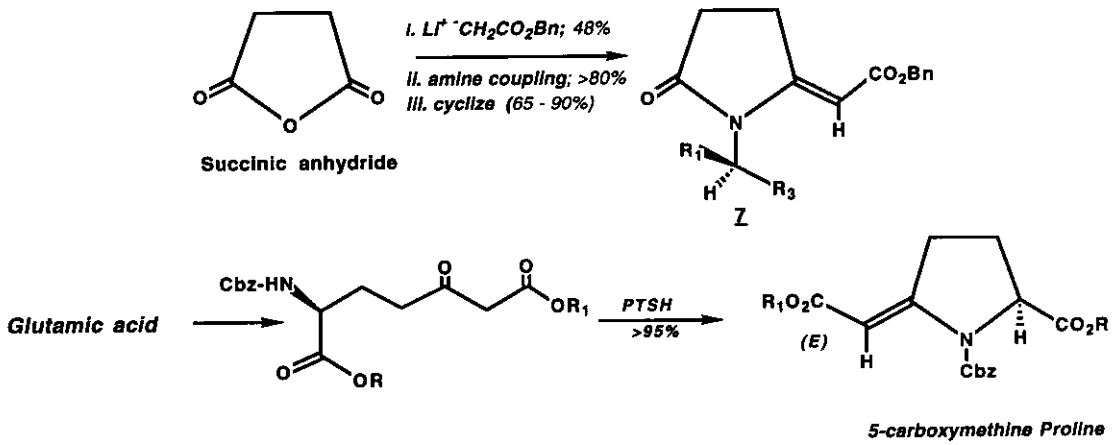
Scheme 2



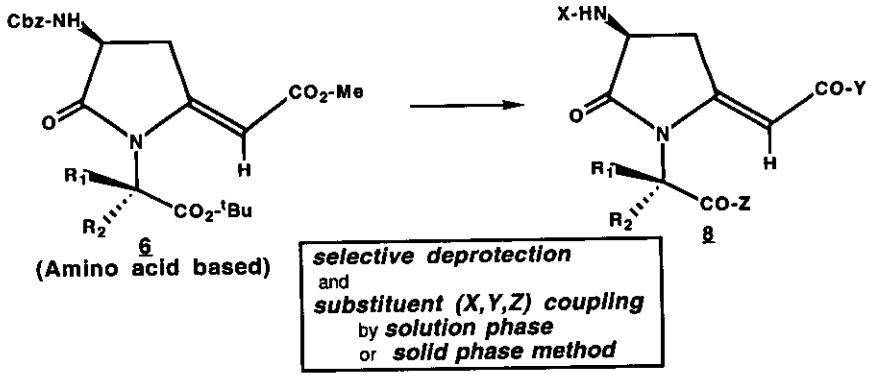
The corresponding 3-deamino analogs (**7**) were readily prepared from succinic anhydride. Orthogonal protection of functional groups in **6** allows further manipulation through solid or solution phase methods (Scheme 3). The keto acid

prepared from glutamic acid was extremely acid sensitive and furnished 5-carboxymethine proline, an important synthetic intermediate.[4]

Scheme 3



Preliminary results show that skilful variation of residues (X,Y and Z) in **8** to regulate the sub-site interactions leads to modulation of the bacterial growth inhibitory activity.



Due to unique structural features, these templates can lead to the development of conformationally defined peptide mimics, unique reverse turn mimics, branched peptides and chiral reagents. Two new class of polypeptides (Figure 1) with unusual conformational features can be envisioned from amino acid based templates.[5]

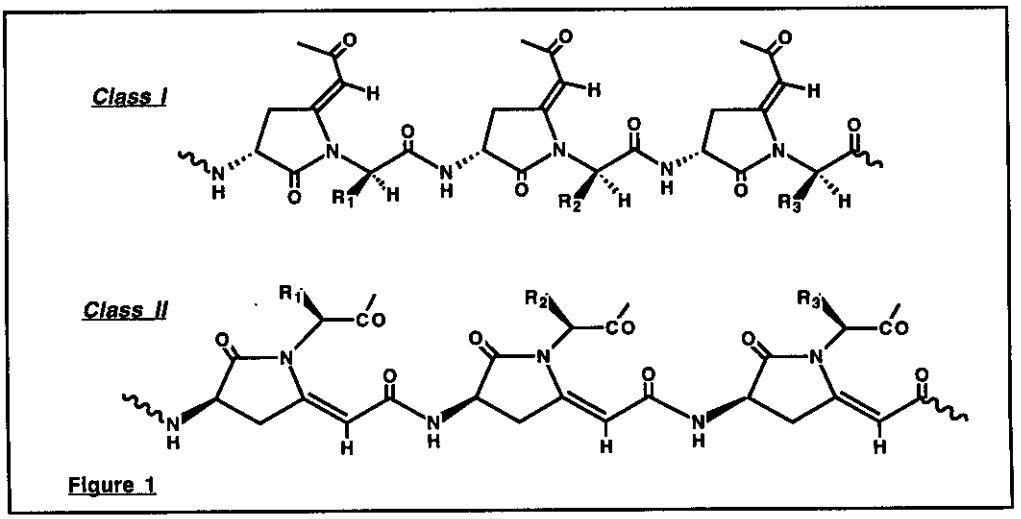


Figure 1

Work is currently in progress towards these and other goals.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

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4. e.g., see a) D. Fasseur, B. Rico, C. Ledue, P. Cauliez and D. Couturier, *J. Heterocycl. Chem.*, **1992**, *29*, 1285; b) F. C. Fang and S. Danishefsky, *Tetrahedron Lett.*, **1989**, *30*, 3621; c) T. Nagasaka, A. Tsukada and F. Hamaguchi, *Heterocycles*, **1986**, *24*, 2015
5. For development of other classes of polypeptide mimics, see *ref. 1*
6. All compounds gave satisfactory physical data.

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