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An Efficient β-Turn Directed Cyclization of Simple Peptidomimetics

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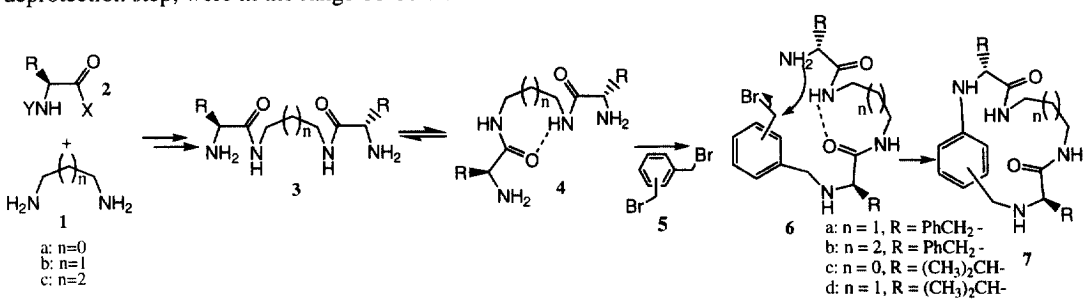
Abstract: Chiral polyaza[n]para- and metacyclophanes are easily assembled starting from the appropriate bis(bromomethyl)arene and diamides obtained from aminoacids and alkylidenediamines. The corresponding ortho-derivatives could not be obtained. Molecular dynamics calculations suggest that those results can be explained through the participation of a β-turn like structure in the open chain intermediate, which is only important for para- and meta- derivatives.

The preparation of cyclic peptidomimetics is a very important target, both for molecular recognition and biomedical studies as well as for catalytic purposes.[1] A simple analysis of the structures of some peptidomimetics able to form β-turns suggest that the preorganization afforded by the structural units associated with β-turns could favor intramolecular processes over the intermolecular ones and provide a simple route for the synthesis of macrocyclic peptidomimetic receptors. This should allow for the preparation of novel compounds with potential catalytic or biomedical applications.[2] Here we report on the evidence for the efficiency of such an approach when a judicious selection of the starting materials is made.

Compounds such as **3** represent some of the simplest peptidomimetics for which a β-turn can be expected, according to the general structure **4**. Preliminary molecular mechanics calculations on compounds **3** showed that conformations in which such a β-turn occurs are prevalent for them (**3**, n=0,1,2). These open-chain peptidomimetics could be easily prepared starting from the corresponding diamines **1** and the N-Cbz protected aminoacids **2** (Y=Cbz, X=OH) through the formation of their activated N-hydroxysuccinimide esters (**2**, Y=Cbz, X=$ONC_4H_4O_2$) (see Scheme 1).[3] Overall yields for the preparation of compounds **3**, after the final deprotection step, were in the range 60-80 %.



Scheme 1

According to our ongoing studies in the preparation of polyazamacrocycles,[4] we evaluated the cyclization reaction shown in the Scheme 1, in which peptidomimetics **3** were reacted with different *bis*(bromomethyl)benzenes **5** in order to obtain the corresponding cyclic compounds **7**.

Some results are gathered in Table 1. Yields refer to the pure products obtained after chromatographic purification of the crude of the reaction. Reactions were carried out in refluxing CH_3CN, using K_2CO_3 as the base and concentrations of ca. 10^{-3}M. No important differences were obtained when high dilution conditions

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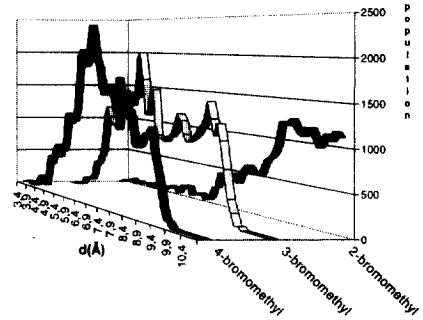
were used. All compounds were fully characterized by elemental analysis, IR, ^{1}H and ^{13}C NMR spectroscopy as well as by mass spectrometry. As can be seen in the Table very good results were obtained when 1,3- or 1,4-*bis*(bromomethyl)benzene were used, but the expected cyclic compounds were not be isolated when the 1,2-derivative was used. Instead, a mixture of oligomeric compounds was obtained. The formation of 1,2-dihydroisoindol derivatives could not be detected.[5]

Table 1. Results obtained in the synthesis of macrocyclic diamides **7.**

***Bis*(bromomethyl) reagent**	**Diamide 4**	**Yield (%)**
para-	4a	68
para-	4b	40
para-	4c	55
para-	4d	70
meta-	4a	48
meta-	4d	66
ortho-	4a	-
ortho-	4d	-

Figure 1. Distribution of -NH_2 - C-Br distances for compounds **6** (R = Ph_2CH_2-, n = 1) obtained by MD analysis.



In order to understand better these results, as well as the exact role played by the intramolecular hydrogen-bonding, extensive molecular dynamics calculations were carried out using the MacroModel software.[6] For compounds **6** derived from 1,3- or 1,4-bis(bromomethyl)benzene folded conformations are clearly prevalent and accordingly, conformations with shorter N - C-Br distances predominate (see Figure 1). The situation is however very different for derivatives of 1,2-*bis*(bromomethyl)benzene for which the unfolded conformations predominate and the nucleophilic nitrogen atom cannot easily approach the C-Br bond

In conclusion, the present method represents a simple and efficient procedure for the preparation of cyclic peptidomimetics that does not require the use of high dilution techniques or the use of complex synthetic methodologies.

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