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Michal Achmatowicz[a]; Agnieszka Szczepańska[ab]; Daniel T. Gryko[a]; Piotr Salański[a]; Janusz Jurczak[ab]
[a] Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw [b] Department of Chemistry, University of Warsaw, Warsaw, Poland

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The Simple Synthesis of Chiral Polyazaoxacoronands Derived from α-Amino Acids

MICHAŁ ACHMATOWICZ[a], AGNIESZKA SZCZEPAŃSKA[ab], DANIEL T. GRYKO[a], PIOTR SAŁAŃSKI[a] and JANUSZ JURCZAK[ab*]

[a]*Institute of Organic Chemistry, Polish Academy of Sciences, 01–224 Warsaw and* [b]*Department of Chemistry, University of Warsaw, 02–093 Warsaw, Poland*

Bisamidation of oxaloyl chloride using L-amino acid methyl ester hydrochlorides afforded chiral diesters. The following reactions of diesters with 2,2-(ethylenedioxy)diethylamine, afforded tetramides possessing C_2 symmetry. Coupling of *N*-hydroxysuccinimide ester of *N*-benzyloxycarbonyl-L-alanine with 1,5-diamino-3-oxapentane, followed by cleavage of protecting groups, afforded an optically active diamine, which was transformed consequently into tetramide *via* the reaction with diglycolic acid dimethyl ester under high pressure conditions.

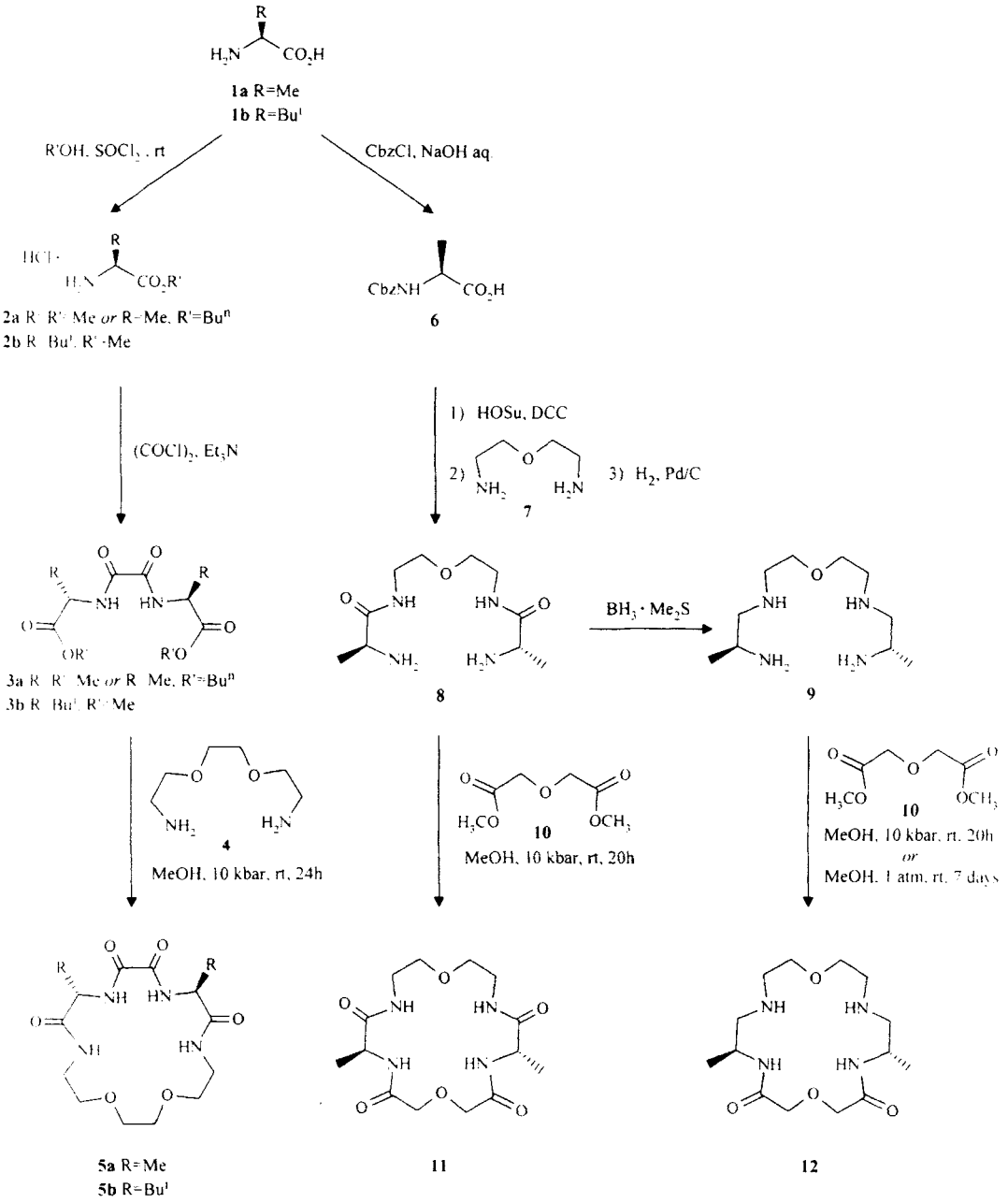
Keywords: macrocyclization, polyazaoxacoronands, α-amino acids, high pressure

There are several papers describing preparation of cyclic diamides as intermediates in the synthesis of diazacoronands [1]. An interesting approach to this problem has been reported by Tabushi *et al.* [2], namely a condensation of primary α,ω-diamine with dimethyl ester of malonic or oligoglycolic acids in boiling ethanol. Recently, we have found [3–6] that the method can be extended to more complex dicarboxylic esters; this has also been confirmed by other authors [7–9]. In this communication we would like to present two isosteric pathways for the synthesis of optically active polyazaoxacoronands from α-amino acids.

Our first approach relied on preparation of two diesters **3a** and **3b** starting with L-alanine (**1a**) and L-leucine (**1b**). The amino acids were first transformed into methyl ester hydrochlorides **2a** and **2b** by the standard procedure, then reacted with half equivalent of oxaloyl chloride in the presence of triethylamine.

Macrocyclization reactions were carried out in methanol with 1 equivalent of diamine and DBU as a catalyst. The time after which all diester was consumed, varied from 1 day to 1 week depending on amount of DBU used, which ranged from 0.1 to 1 equivalent. The reaction mixture was then concentrated and the macrocyclic product was separated by flash chromatography to give 25% of **5a**. In the case of macrocyclization reaction of diester **3b**, an additional product was detected. After characterization by ^1H and ^{13}C NMR and mass spectrometry it became evident that it was the *meso* isomer which resulted from epimerization of diester **3b**. This result put under a question the usefulness of DBU as a catalyst. Since the macrocyclization reaction failed to proceed in the absence of basic catalysis, we have tried some other basic catalysts such as cyanides (NaCN), acetates (CH_3COOK) and triethylamine. In all cases, the reaction proceeded

* Author for correspondence.



with racemization or failed to yield a macrocycle. Thus we abandoned the basic catalysis and tried to utilize the high pressure methodology. Since diester **3a** (R'=Me) is very poorly soluble in methanol, we had to transform it into some more soluble derivative. Our choice was to substitute methyl ester with some more lipophylic one to increase its solubility. After several experiments we ended up with dibutyl ester **3a** (R'=Bu^n) which happened to have the most useful molec-

ular mass/solubility ratio. After 20h time which was sufficient for substrates to react under 10 kbar, we separated cyclic product in high yields (60–65%) and virtually without racemization.

The second approach to the synthesis of polyazaoxacoronands also consisted in bisamidation reaction. Tetramide **11** was obtained only under high pressure conditions (10 kbar, rt, 20 h) in methanol in 9% yield. Afterwards diamine **8** was transformed into diamine **9** by the reaction with $BH_3 \cdot Me_2S$ complex in THF, and used to yield diamide **12**. Reactions were carried out under high pressure as well as normal conditions in 37% and 66% yields, respectively. All macrocycles were purified by column chromatography.

On the basis of our investigations, we found out that the presence of carbonyl groups makes the macrocyclization reaction somewhat difficult and only diamines lacking of amide bonds gave acceptable yields. The obtained amides, after reduction, can be used for synthesis of more complex polyazamacrocyclic compounds.

Acknowledgements

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