A NEW APPROACH TO THE SYNTHESIS OF CHIRAL TETRAAZACORONANDS DERIVED FROM L-ALANINE*

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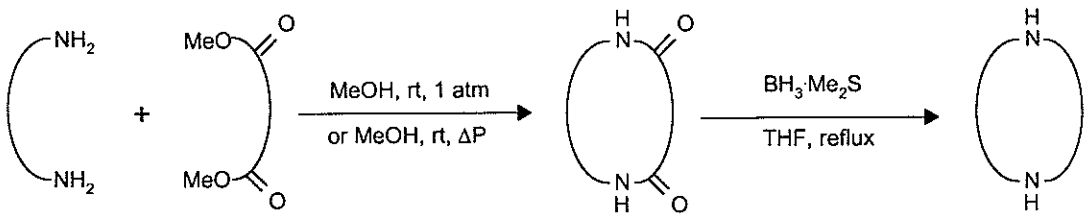
Abstract - Dimethyl α,ω-dicarboxylates react under high pressure or ambient conditions with chiral primary diamino ethers derived from L-alanine to give the chiral cyclic diamides or tetramides in satisfactory yields. The effective preparation of chiral amino components starting from L-alanine is also described.

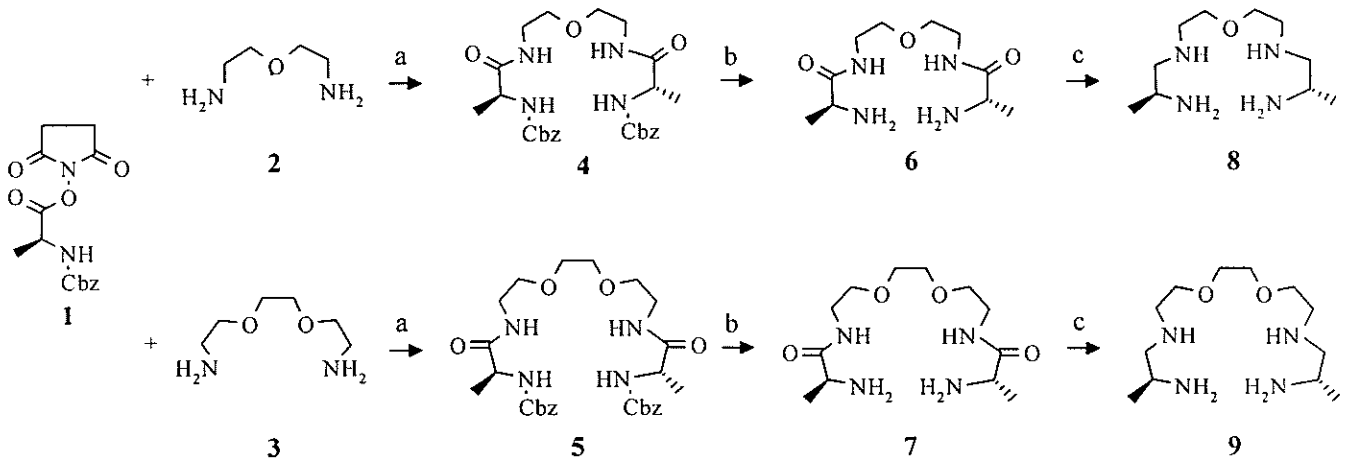
There are several papers describing the preparations of cyclic diamides as intermediates in the synthesis of diazacoronands.[1] An interesting approach to this problem has been reported by Tabushi *et al.*[2] as a condensation of primary α,ω-diamine with dimethyl ester of malonic or oligoglycolic acids in boiling ethanol. Recently, we have found[3] that this method can be extended to other, more complex dicarboxylic esters. This finding constitutes a very efficient and versatile procedure for the synthesis of various macrocyclic diamides, as schematically shown in Scheme 1.



Scheme 1

*Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

We investigated the usefulness of this method for the preparation of chiral polyazacoronands derived from L-alanine. After protecting the amino group, we synthesized the active *N*-hydroxysuccinimide ester (**1**), which was subjected to reactions with amines (**2**) and (**3**), respectively (Scheme 2). The resulting products (**4**) and (**5**) were treated with hydrogen in the presence of the 5% Pd/C catalyst to afford the amines (**6**) and (**7**), respectively, which were then reduced using $BH_3{\cdot}Me_2S$ (BMS) to form amines (**8**) and (**9**), respectively.



Scheme 2. Reagents and conditions: (a) THF, rt; (b) H_2, 5% Pd/C, MeOH, rt; (c) $BH_3{\cdot}Me_2S$, THF, reflux.

Table 1. Double-amidation reactions leading to chiral tetraazacoronands[a,b]

Entry	Diamine	Diester	Tetraaza-coronand	Pressure	Time	Yield [%]	$[\alpha]_D^{20}$
1	**6**	**10**	**13**	10 kbar	24 h	9	-5.0
2	**6**	**11**	**14**	10 kbar	24 h	10	-21.1
3	**6**	**12**	**15**	10 kbar	24 h	11	-19.8
4	**7**	**10**	**16**	10 kbar	24 h	10	-12.8
5	**7**	**11**	**17**	10 kbar	24 h	10	-2.0
6	**7**	**12**	**18**	10 kbar	24 h	8	-7.9
7	**8**	**10**	**19**	10 kbar	24 h	37	-15.8
8	**8**	**10**	**19**	1 atm	7 days	66	
9	**8**	**11**	**20**	10 kbar	24 h	23	-7.6
10	**8**	**11**	**20**	1 atm	7 days	18	
11	**8**	**12**	**21**	10 kbar	24 h	43	-5.8
12	**8**	**12**	**21**	1 atm	7 days	55	
13	**9**	**10**	**22**	10 kbar	24 h	37	-3.3
14	**9**	**10**	**22**	1 atm	7 days	54	
15	**9**	**11**	**23**	10 kbar	24 h	29	-5.2
16	**9**	**11**	**23**	1 atm	7 days	30	
17	**9**	**12**	**24**	10 kbar	24 h	34	-2.6
18	**9**	**12**	**24**	1 atm	7 days	41	

[a] All reactions were carried out at room temperature and in methanol as a solvent.
[b] Optical rotations were measured for 1% solutions in ethanol.

The resulting amines (**8**) and (**9**), as well as starting amines (**6**) and (**7**), were subjected to cyclisation reactions with the methyl esters of carboxylic acids derived from di-, tri-, and tetraethylene glycols (**10**, **11**, and **12**, respectively) as shown in Table 2.[4,5] The reaction yields are shown in Table 1. The yields are generally good and they are higher for amines (**8**) and (**9**) than for (**6**) and (**7**).

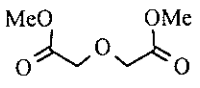
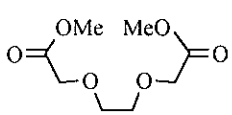
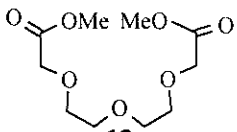
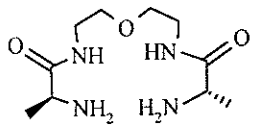
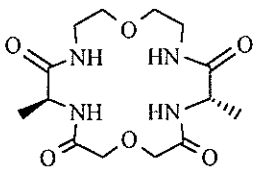
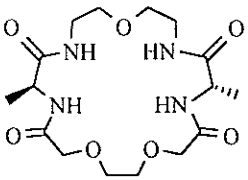
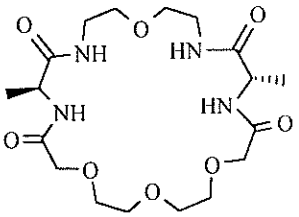
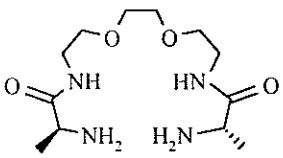
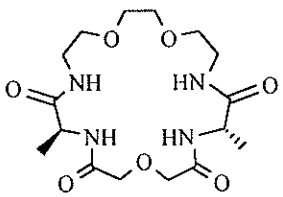
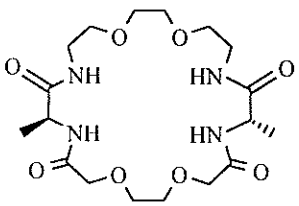
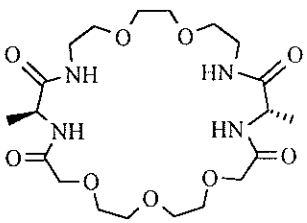
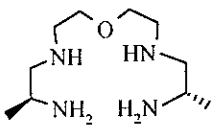
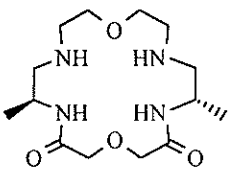
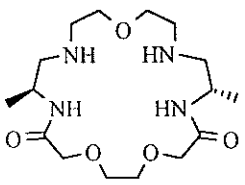
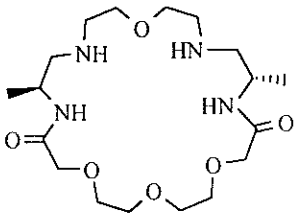
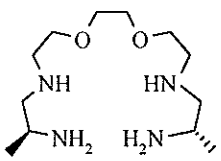
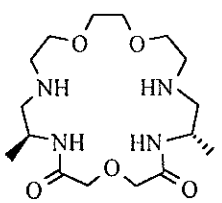
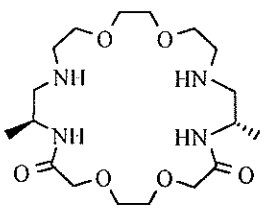
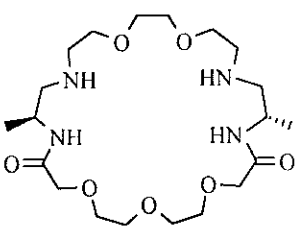
	 **10**	 **11**	 **12**
 **6**	 **13**	 **14**	 **15**
 **7**	 **16**	 **17**	 **18**
 **8**	 **19**	 **20**	 **21**
 **9**	 **22**	 **23**	 **24**

Table 2

The results presented here demonstrate that chiral α,ω-diamines obtained from L-alanine can be efficiently transformed into various macrocyclic diamides and tetraamides with satisfactory yields. Investigations on the application of other α-amino acids to this problem are in progress.

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Financial support from the National Commitee for Scientific Research (KBN grant 3 T09A 127 15) is gratefully acknowledged.

REFERENCES AND NOTES

1. For recent comprehensive reviews see:
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2. a) I. Tabushi, H. Okino, and Y. Kuroda, *Tetrahedron Lett.*, 1976, 4339.
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3. a) J. Jurczak, S. Kasprzyk, P. Sałański, and T. Stankiewicz, *J. Chem. Soc., Chem. Commun.*, 1991, 957.
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   d) P. Lipkowski, D. T. Gryko, J. Jurczak, and J. Lipkowski, *Tetrahedron Lett.*, 1998, **39**, 3833.
4. All macrocyclic compounds obtained (**13-24**) have correct high-resolution MS, and ^{1}H and ^{13}C NMR spectra.
5. Typical procedure: An equimolar 0.1 M methanolic solution of α,ω-diamine and dimethyl α,ω-dicarboxylate was left at ambient temperature over a period of 7 days. Then the solvent was evaporated and the residue was chromatographed on the silica gel column using 0.5-3% mixtures of MeOH in $CHCl_3$. The high-pressure procedure was identical to that reported earlier: D. T. Gryko, P. Piatek, and J. Jurczak, *Synthesis*, 1999, 336.

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