Pergamon

Tetrahedron Letters, Vol. 38, No. 47, pp. 8197-8198, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10254-4

Easy Synthesis of a New C_2-Symmetric Diaza-crown Ether from L-Threonine

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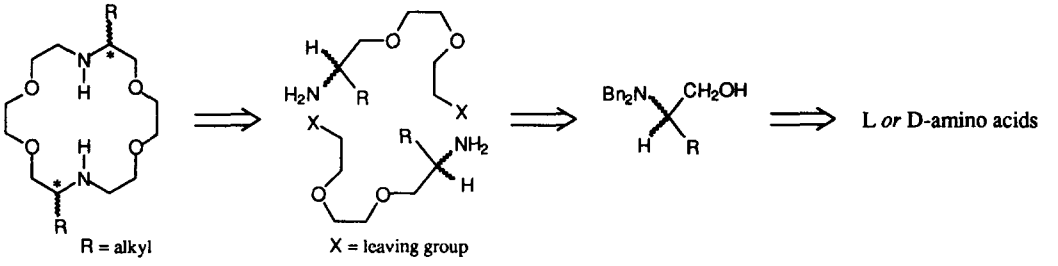
Abstract: The 1:1-cyclocondensation of a contrafunctional chiral amine easily obtained from L-threonine in four steps yielded the new C_2-symmetric diaza-crown ether **5**.

The chemistry of diaza-crown ethers is a very documented topic because they are indispensable starting materials for the synthesis of cryptands.[1] Nevertheless the access to chiral crown amino-ethers and related compounds remains a matter of considerable interest since highly functionalised macrocyclic systems can transport asymmetric anions selectively[2] or mimic the action of natural enzymes[3] and ion channels.[4]

The recent communication about a new method for the synthesis of dibenzo-diaza-crown ethers *via* the 1:1-cyclocondensation of α,ω-contrafunctional amines[5] prompts us to report some preliminary results along this line. Our general approach to the design of C_2-symmetric diaza-crown ethers from the chiral pool is outlined in Scheme 1:



Scheme 1: Retrosynthesis of C_2-symmetric diaza-crown ethers from chiral amino acids

The feasibility of such a cyclocondensation reaction between two *identical* chiral molecules is illustrated by the following sequence.

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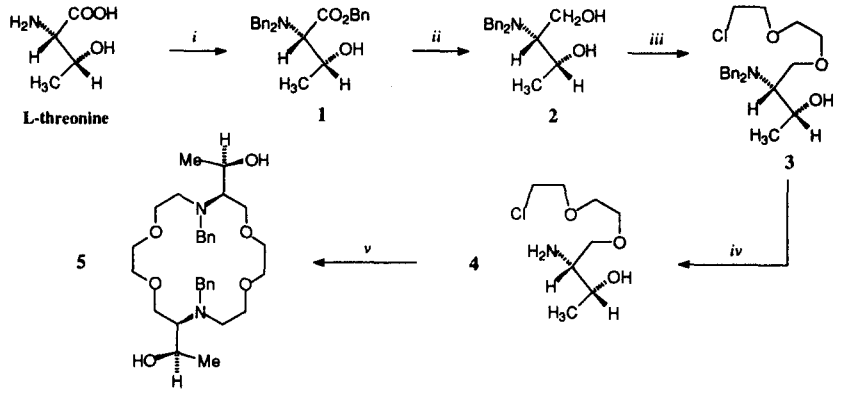

Scheme 2: Reagents and yields: *i*) BnBr, ref. EtOH/H_2O, 5 h, 70%; *ii*)[6] $LiAlH_4$, THF, rt →ref.; 2h, 96%; *iii*) $(ClCH_2CH_2)_2O$, 50% aq. NaOH, NBu_4HSO_4, rt, 18h, 78%; *iv*) H_2, Pearlman's catalyst[7], MeOH, rt, 14 h, ~99%; *v*) NaI, Na_2CO_3, ref. MeCN, 4d then BnBr, 14 h, 42%.

In a first attempt to prepare **5**[8], a THP-protected derivative of **1** (not described here) was prepared and used throughout the same sequence but this proved to be unnecessary since no *O*-alkylation on the secondary alcohol could be detected at step *iii*. The expected cyclization did not take place when sodium iodide was not added or when a monobenzylated amine[9] was used instead of the primary amine **4** at the last step.

We are currently studying extensions of this procedure to other amino acids or to the synthesis of [24-6]-diaza-macrocycles by using triethylenenglycol dichloride at step *iii*.[10]

References and notes

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8. All new compounds displayed satisfactory spectral data in full accord with their structures. For instance, **5**: yield 0.141 g (42%); HRMS (EI, 70 EV): obs'd 530.3353 ($M^{+\cdot}$ requires 530.3356 for $C_{30}H_{46}N_2O_6$) and 485.2 (100% RA) = $(M - C_2H_5O)^+$; IR (neat) 3443 cm^{-1}, broad, intramolecular H bond; ^1H NMR ($CDCl_3$ + ε D_2O), δ (ppm): 1.15 (6H, d, 2Me), 2.6 (2H, m, H_α Thr), 3.0 (4H, bm, $2CH_2$-N aliph.), 3.3-3.7 (20H, m, 2Hb, 8 OCH_2, $2H_\beta$), 3.9 (2H, d, 2Hb, J_{AB} =13 Hz), 7.2-7.4 (10H, m, arom.); ^{13}C NMR ($CDCl_3$) δ (ppm): 19.69 (CH_3), 50.40 (N-CH_2 aliph.), 56.10 (N-CH_2 arom.), 63.55 (C_α Thr), 67.30 (C_β Thr), 68.37, 70.46, and 70.75 (O-CH_2), 127.18, 128.44, 128.97, 139.58 (arom.).
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(*Received in France* 15 *August* 1997; *accepted* 1 *October* 1997)