Pergamon

Tetrahedron Letters 39 (1998) 853–856

TETRAHEDRON LETTERS

Syntheses of New Unsymmetrical Bispolyazamacrocycles

J. Dessolin, G. Quéléver, M. Camplo and J.L. Kraus*

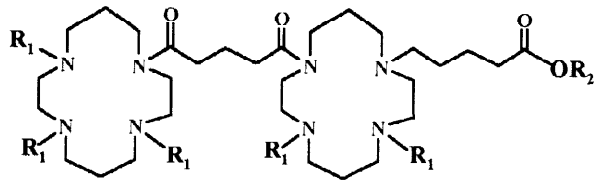
Laboratoire de Chimie Biomoléculaire, Faculté des Sciences de Luminy, case 901,
Université de la Méditerranée, 70 route Léon Lachamp 13288 Marseille cedex 9, France.

Received 23 July 1997; accepted 30 November 1997

Abstract : We report the synthesis of an original unsymmetrical bismacrocycle bearing a carboxylic side-arm. Two different synthetic pathways were investigated, both involving a Schotten-Baumann like reaction. The first route allowed us to obtain a mixture of compounds whilst the second one was direct and non-ambiguous.

In order to prepare various functionalized cyclams, the tosyl protecting group was initially used.[1] In some model containing amide linkages, the tosyl deprotection represents a crucial step because the removal agents can induce side reactions. For these reasons, the *tertio*butyloxycarbonyl group (Boc) has been recently used in the cyclam series.[2] The preparation of various di-protected cyclams by the Boc group, their NMR characterization and the application of the 1,8-diboc cyclam in the synthesis of bridged biscyclams have been reported.[2,3] Such derivatives are potential anti-HIV agents;[5,6] they could also provide an effective means for labelling antibodies in order to produce radioimmunodiagnostic agents.[4] Previously, the best anti-HIV activities were obtained with symmetrical bispolyazamacrocycles. Although the structural feature seems to be that an aromatic bridge was preferable to an aliphatic one, it could not be predicted whether this latter condition was applicable to unsymmetrical bispolyazamacrocycles. Here we report the synthesis of a new unsymmetrical bistetraazamacrocycle (Figure 1), bearing a terminal carboxylic acid functionalized side-chain.

Figure 1



10 R_1 = Boc R_2 = Et

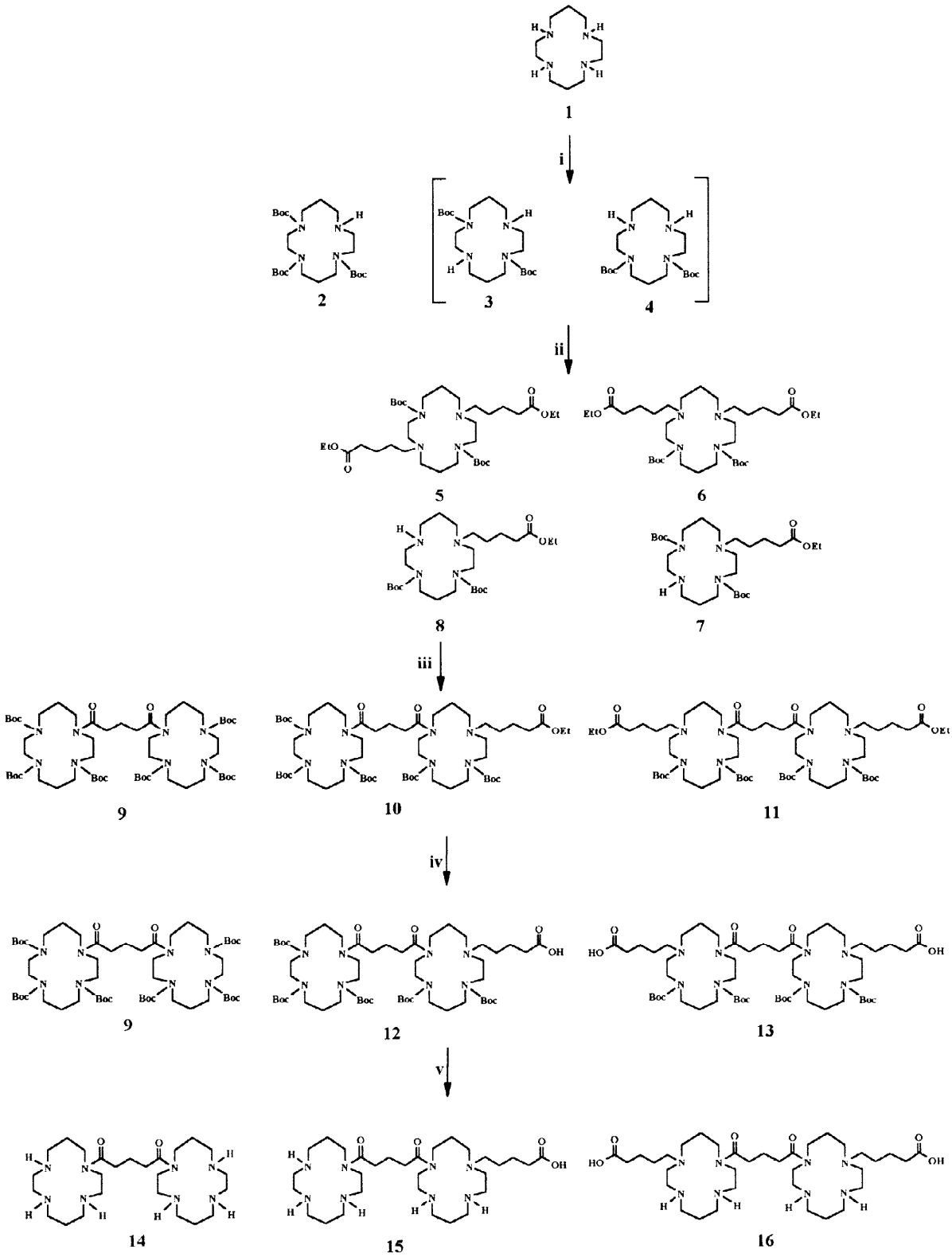
15 R_1 = H R_2 = H

The reaction of 1.8 equivalent of di-*tert*-butyl dicarbonate with 1 equivalent of cyclam **1** can afford a mixture of various products : tetra-, tri-, di- and monoboc-cyclams (Scheme 1). While the tetra-protected cyclam was found as traces, the triboc compound **2** was isolated in 24% yield and the more polar compounds were isolated as a mixture of different products **3**, **4** as revealed by TLC. The NMR spectrum of this crude mixture indicated di-protected cyclams as major components.

Fax : (33) 491 82 92 50
E-mail : kraus@luminy.univ-mrs.fr

0040-4039/98/$19.00
PII: S0040-4039(97)10748-1

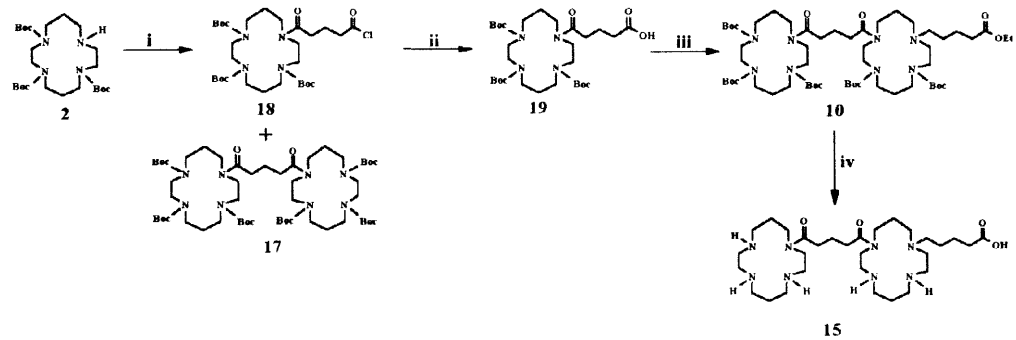
Scheme 1



i : Boc_2O, CH_2Cl_2. ii : Br-$(CH_2)_4$-CO_2Et, K_2CO_3, CH_3CN. iii : Glutaryl dichloride, 2, CH_2Cl_2, $NaHCO_3$aq. iv : NaOH 10M, THF. v : HCl 1M, THF.

In order to identify these products, the mixture was submitted to a condensation reaction with an ω-bromo ester in acetonitrile in the presence of K_2CO_3. Four functionalized compounds (**5**, **6**, **7** and **8**) were then isolated and clearly identified by NMR ^1H COSY experiments. The minor and less polar compounds **5** and **6** corresponding to the N1,N8-diester (trans) and the N1,N11-diester (cis) respectively were characterized by NMR and Mass Spectrometry. These compounds were obtained in low yields (respectively 3% and 7%) while the major mono-functionalized products **7** and **8** were obtained in 15% and 65% yields respectively. The major and most polar compound **8** was identified by NMR (COSY ^1H) as the analogue N1,N11-di-Boc-N4-ester (cis). Diboc functionalized cyclam **8** was converted into the bismacrocycle through a biphasic solvent system using a mixture of dichloromethane and aqueous bicarbonate solution (v/v) in the presence of 1 equivalent of N-triboc cyclam **2** and 1 equivalent of glutaryl dichloride. In these experimental conditions, three bismacrocycles could be obtained : the two symmetrical compounds **9** and **11**, resulting from the dimerization of **2** and **8** respectively, and the unsymmetrical desired compound **10**. At this stage, flash chromatography did not allowed us to separate compounds **9**, **10** and **11**. However, the saponification (NaOH 10M in THF) of the product mixture led to the corresponding compounds **9**, **12**, and **13** which were easily purified by flash column chromatography. The symmetrical analogues **9** and **11** and the unsymmetrical bismacrocycle **12** were fully characterized by NMR spectroscopy (COSY ^1H) and FAB^+ mass spectrum. Total synthesis is summarized in Scheme 1. Bismacrocycle **10** was also synthesized through the following sequences (Scheme 2). Starting from triboc protected cyclam **2**, through a Schotten-Baumann like reaction, involving a two phase system similar to the one previously described in the presence of 1 equivalent of glutaryl dichloride, it is possible to isolate after basic hydrolysis of mono-adduct **18**, the carboxylic acid cyclam derivative **19**. This latter analogue was converted into the bismacrocycle **10**[7] using a second coupling reaction which involved activation by dicyclohexylcarbodiimide / 1-hydroxybenzotriazole (DCC / HOBt) coupling reagents in the presence of diboc cyclam **8**. Acid hydrolysis (HCl 1M in THF) of the Boc-protected bismacrocycle **9**, **10**, **12** and **13** led to the corresponding desired biscyclam N-carboxypentyl analogues **14**, **15**[8] and **16**. It should be underlined that in the experimental hydrolysis conditions, besides the Boc deprotection of compound **10**, the hydrolysis of the ethyl ester occurred.

Scheme 2



i : Glutaryl dichloride, CH_2Cl_2, $NaHCO_3$aq. ii : NaOH 10M, THF. iii : 8, DCC, HOBt, DIEA. iv : HCl 1M, THF

In conclusion, the synthesis of a new unsymmetrical bispolyazamacrocycle bearing a carboxylic side-arm was achieved. Two synthetic pathways using a Schotten-Baumann like reaction were investigated. The new analogues were fully characterized through NMR sequences and Mass Spectrometry; they will be tested on the one hand as possible substrates for labelling antibodies, and on the other hand as anti-HIV candidates.

Acknowledgements.

The authors thanks INSERM for financial support.

References and Notes.

1- Helps, I.M. ; Parker, D. ; Morphy, J.R. ; Chapman, J. *Tetrahedron* **1989**, *45*, 219-226.

2- Boitrel, B. ; Andrioletti, B. ; Lachkar, M. ; Guilard, R. *Tetrahedron Lett.* **1995**, *35*, 4995-4998.

3- Brandes, S. ; Gros, C. ; Denat, F. ; Pullumbi, P. ; Guilard, R. *Bull. Soc. Chim. Fr.* **1996**, *133*, 65-73.

4- a) Franz, J. ; Volkert, W.A. ; Barefield, E.K. ; Holmes, R.A. *Nucl. Med. Biol.* **1987**, *14*, 569-572. b) Franz, J. ; Freeman, G.M. ; Barefield, E.K. ; Volkert, W.A. ; Ehrhardt, G.J. ; Holmes, R.A. *Nucl. Med. Biol.* **1987**, *14*, 479-484.

5- Bridger, G.J. ; Skerlj, R.T. ; Thornton, D. ; Padmanabhan, S. ; Martellucci, S.A. ; Henson, G.W. ; Abrams, M.J. ; Yamamoto, N. ; De Vreese, K. ; Pauwels, R. ; De Clercq, E. *J. Med. Chem.* **1995**, *38*, 366-378.

6- Trabaud, C. ; Dessolin, J. ; Camplo, M. ; Kraus, J.L. *Synth. Commun.* **1997** (in press).

7- Compound **10** : MS FAB$^+$ (GT) : 1125 $(M+H)^+$. RMN ^1H 250 MHz ($CDCl_3$) : 1.25 (t, J = 7.10 Hz, 3H, CH_3) ; 1.45 (brs, 47H, t-Bu and -C<u>H</u>$_2$-$(CH_2)_2$-CO_2Et) ; 1.50-1.83 (m, 6H, -C<u>H</u>$_2$-CH_2-CO_2Et and $(CO-CH_2)_2$-C<u>H</u>$_2$- and Boc-N-CH_2-C<u>H</u>$_2$-N-$(CH_2)_4$-CO_2Et) ; 1.85-2.05 (m, 6H, (Boc-N-CH_2)-C<u>H</u>$_2$) ; 2.28 (t, j = 7.35 Hz, 2H, -C<u>H</u>$_2$-CO_2Et) ; 2.38 (brs, 6H, N-C<u>H</u>$_2$-$(CH_2)_3$-CO_2Et and -$(C\underline{H}_2)_2$-N-CH_2-$(CH_2)_3$-CO_2Et) ; 2.55 (brs, 4H, N-CO-C<u>H</u>$_2$-) ; 3.07-3.43 (m, 28H, -C<u>H</u>$_2$-N-CO and -C<u>H</u>$_2$-N-Boc) ; 4.11 (q, J = 7.10 Hz, 2H, -O-C<u>H</u>$_2$-CH_3). Anal ($C_{57}H_{104}N_8O_4$) : C, H, N.

8- Compound **15** : MS FAB$^+$ (GT) : 597 $(M+H)^+$. RMN ^1H 250 MHz (D_2O) : 1.62 (m, 2H, -C<u>H</u>$_2$-CH_2-CO_2H) ; 1.72-2.38 (m, 12H, -(HN-CH_2)$_2$-C<u>H</u>$_2$- and $(CO-CH_2)_2$-C<u>H</u>$_2$- and -C<u>H</u>$_2$-$(CH_2)_2$-CO_2H and CON-CH_2-C<u>H</u>$_2$-CH_2-N) ; 2.40-2.63 (m, 6H, -C<u>H</u>$_2$-CO_2H and CO-C<u>H</u>$_2$-) ; 3.17-4.24 (m, 34H, -C<u>H</u>$_2$-N). Anal ($C_{30}H_{66}N_8O_4Cl_6.2H_2O$) : C, H, N.