



Trivalent protecting groups for the synthesis of symmetrical and unsymmetrical bis-tetraazamacrocycles

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Abstract : Facile syntheses of bis-tetraazamacrocycles are reported starting from triprotection of tetraazamacrocycles. The triprotected macrocycle was mono N-alkylated and then this compound reacted with another macrocycle to give symmetrical or unsymmetrical bis-tetraazamacrocycles.
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The properties of symmetrical or unsymmetrical bis-tetraazamacrocycles have not been extensively investigated because of their difficult synthesis. A new important application of this class of compounds should concern the biomedical field since the potent and selective inhibition of immunodeficiency virus HIV-1 and HIV-2 by bis-tetraazamacrocycles have been recently reported¹.

These molecules are generally obtained according to a procedure previously described by Fabbrizzi and al.² based on the use of N-tosyl or N-mesyl triprotected tetraazamacrocyclic intermediates which requires an additional purification step. The main drawback of this synthetic route lies in the statistical conditions of the first step, as the best results are obtained when two equivalents of tosyl chloride are allowed to react with one equivalent of the tetraazamacrocycle. Under these conditions the yields do not exceed 50%. The condensation of two equivalents of this intermediate with one equivalent of a X-R-X fragment (X = O-Ts, Br) leads, after H₂SO₄ deprotection, to the symmetrical bis-macrocycle². Unsymmetrical ones are obtained with poor yields since the key-step of the synthesis consists in the reaction of the triprotected intermediate with an excess of a X-R-X fragment¹.

Recently we have proposed the stoichiometric easy-to-run triprotection of a variety of tetraazamacrocycles involving the use of trivalent groups such as metal carbonyl³, phosphoryl⁴, thiophosphoryl⁵, boron⁶ or trimethylsilyl⁷ entities, stable in various conditions but easily removable.

In this work, we wish to show the interest of these triprotections for the synthesis of both symmetrical and unsymmetrical bis-tetraazamacrocycles.

A. Symmetrical bis-tetraazamacrocycles

The reaction of two equivalents of a triprotected tetraazamacrocycle with one equivalent of a bis-electrophile leads to the symmetrical bis-tetraazamacrocycles. This synthesis constitutes a simple extension of the previously published mono N-alkylation of tetraazamacrocycles^{4,6}. Some examples of compounds obtained in this way, using either boron or phosphoryl protected cyclam are summarized in Fig 1.

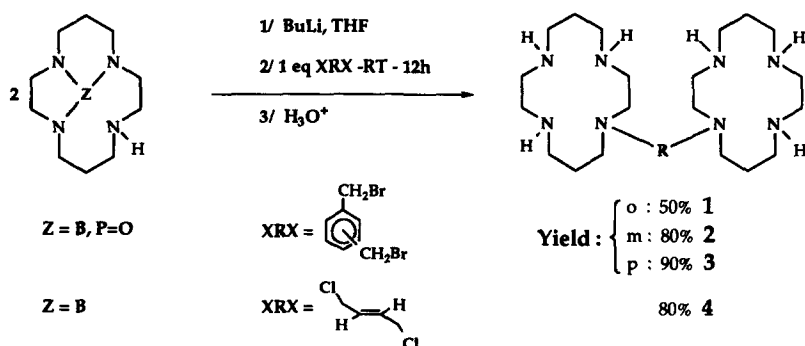


Fig. 1 : Synthesis of symmetrical bis-tetraazamacrocycles

After the removal of the protecting group, by treatment with an excess of concentrated hydrochloric acid in ethanol, the compound was precipitated and isolated as hydrochlorides. The symmetrical bis-macrocycles **1**, **2**, **3**, **4** were then obtained as free base after neutralisation on a strongly basic exchange resin⁹.

B. Unsymmetrical bis-tetraazamacrocycles.

The first step of the synthesis consists in the preparation of a mono N-substituted tetraazamacrocycle carrying a pendant side-chain at the end of which a reactive group is present. For this purpose, the phosphoryl and thiophosphoryl triprotection seems to us the most appropriate because of the stability of the intermediates in various conditions. We used two different approaches to prepare these key-derivatives.

1) The macrocycle is allowed to react with an electrophile which possesses a second group reactive in a different process. In the following examples, using propargyl chloride, a nucleophile substitution in a first step leads to the previously described compound **5**¹⁰. The second triprotected macrocycle is then introduced *via* a Mannich reaction (Fig. 2). In this reaction, formaldehyde is condensed with the secondary amine function of the protected macrocycle and the alkylated triprotected cyclam **5** containing an active propargylic hydrogen.

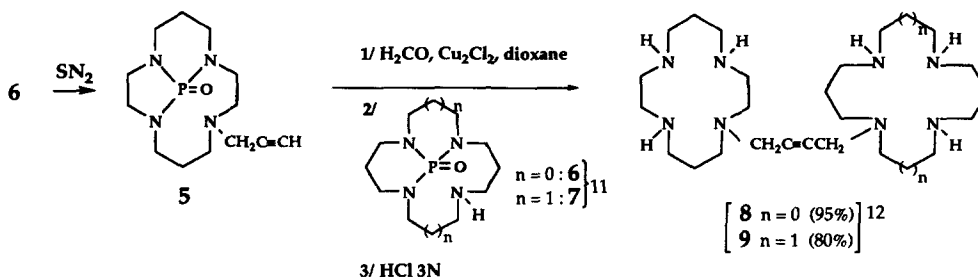


Fig. 2

2) The macrocycle is allowed to react with a bis-electrophile bearing two functions of well differentiated reactivities. A successful approach of this synthesis was described by Sessler⁹ in the reaction between N,N'-ditosyl-1,4,7-triazanonane and 4-chlorobutyrylchloride. Thus the amide functionality that is created prevents subsequent attack on the terminal carbon atom. In a similar manner, the reaction of a phosphoryl or thiophosphoryl protected macrocycle with 6-bromohexanoylchloride leads to stable intermediates **11**, **12**, **13**¹⁴ in high yield. The unsymmetrical protected bis-macrocycle is then easily obtained by grafting another triprotected tetraazamacrocycle. Reduction of the amide group is accomplished by using $\text{BH}_3 \cdot \text{SMe}_2$; after reaction the acidic hydrolysis resulted in the formation of the deprotected hexyl bridged bismacrocycle **14**, **15**, **16**¹⁵ (Fig.3).

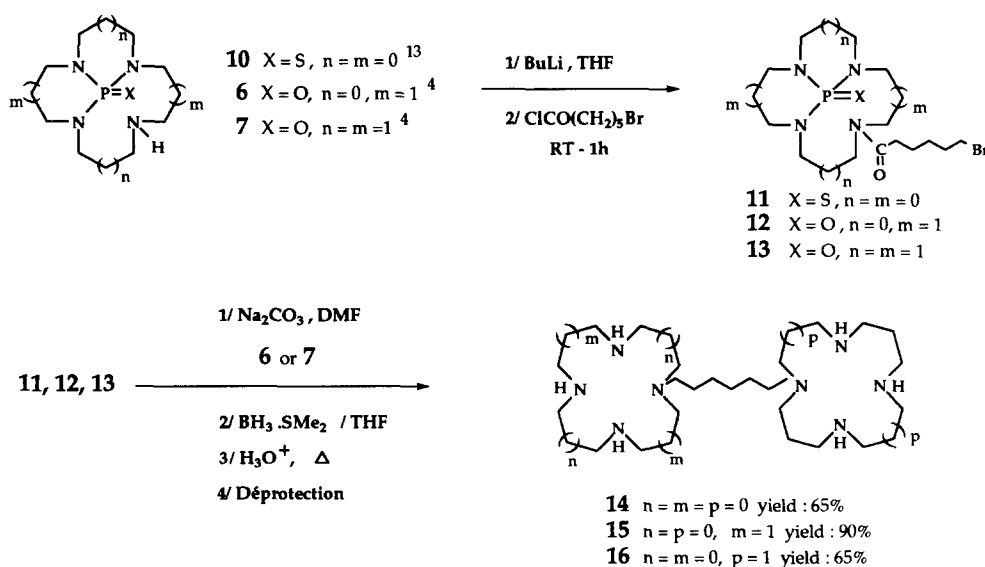


Fig.3

These examples establish the usefulness of these trivalent protecting groups for the synthesis of symmetrical and unsymmetrical bis-tetraazamacrocycles. In all steps the reaction is unequivocal, easy to run and avoids the vigorous deprotection conditions of tosyl groups. This approach could provide a new route for the facile synthesis of a variety of bis-macrocycles.

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References and notes

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8. Infrared spectra were obtained on a Bomem Michelson 100 spectrophotometer. All ^1H and ^{13}C were recorded on Bruker AC300 spectrometer (75,45MHz for C) in CDCl_3 ; chemical shifts are given in ppm downfield from external TMS reference. ^{31}P NMR were recorded on JEOL FX 100 spectrometer (40,26 MHz); chemical shifts are given in ppm downfield from external 85% H_3PO_4 . ^1H -NMR data of Compound **1**: 1,80 (8H, m, NCH_2CH_2), 2,70 (32H, m, NCH_2), 3,60 (4H, s, $\text{NCH}_2\text{C}_6\text{H}_4\text{CH}_2\text{N}$), 7,40 (4H, m, C_6H_4). ^{13}C -NMR: 26,1; 27,9 (NCH_2CH_2), 47,1; 47,4; 48,0; 48,4; 48,8; 50,2; 53,3; 54,3; 55,2 (NCH_2), 126,5; 129,4; 137,5 (C_6H_4).
Compounds **2** and **3** are already described in reference 2.
 ^1H -NMR data of compound **4**: 1,70 (8H, m, NCH_2CH_2), 2,60 (32H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 3,10 (4H, m, CH_2CH), 5,60 (2H, m, $\text{CH}=\text{CH}$). ^{13}C -NMR: 28,3; 25,5 (NCH_2CH_2), 46,9; 47,6; 48,4; 49,1; 49,2; 50,4; 52,6; 53,4; 53,7 (NCH_2), 129,1 ($\text{CH}=\text{CH}$).
9. Sessler, J.L., Sibert, J.W., *Tetrahedron*, **1993**, *39*, 8727-8738 and references therein.
10. ^{13}C -NMR data of compound **5**: 25,2; 21,9 (NCH_2CH_2), 40,6 (d, $\text{J}_{\text{P-C}} = 3,3$ Hz); 40,9; 43,9 (d, $\text{J}_{\text{P-C}} = 11,2$ Hz), 45,5 (d, $\text{J}_{\text{P-C}} = 15,4$ Hz); 41,4; 41,7; 48,8; 50,7; 52,9 (NCH_2), 71,5 (CH), 79,5 ($\text{C}\equiv$). ^{31}P -NMR (CDCl_3): $\delta = 25,8$ ppm.
11. Compounds **6** and **7** are already described in reference 4.
12. Compound **8**: ^1H -NMR: 1,72 (8H, m, NCH_2CH_2), 2,68 (32H, m, NCH_2), 3,49 (4H, s, $\text{CH}_2\text{C}\equiv$). ^{13}C NMR: 28,5; 25,0 (NCH_2CH_2), 39,2; 46,3; 47,7; 48,7; 49,0; 50,1; 50,2; 51,4; 53,7 (NCH_2), 78,1 ($\text{C}\equiv$).
Compound **9**: ^1H -NMR: 1,62 (12H, m, NCH_2CH_2), 2,60 (32H, m, NCH_2), 3,35; 3,47 (4H, 2s, $\text{CH}_2\text{C}\equiv$). ^{13}C NMR: 26,2 (2C); 28,6 (2C) ($\text{NCH}_2\text{CH}_2(3333)$), 25,4; 28,9 ($\text{NCH}_2\text{CH}_2(2323)$), 39,5; 41,1; 46,7; 47,0; 47,6 (2C); 48,0 (4C); 49,3 (2C); 50,4 (2C); 49,0; 50,5; 51,6; 54,0 (NCH_2), 77,4; 79,4 ($\text{C}\equiv$).
13. Compound **10** is already described in reference 5.
14. Compound **11**: ^{13}C -NMR: 23,1; 26,9; 31,7; 32,1; 33,3 ($(\text{CH}_2)_5$), 44,0 (d, $\text{J}_{\text{P-C}} = 4,4$ Hz); 45,9 (d, $\text{J}_{\text{P-C}} = 4,2$ Hz), 50,0 (m), 50,6 (m) (NCH_2), 172,7 ($\text{C}=\text{O}$). ^{31}P -NMR (CDCl_3): $\delta = 82,9$ ppm. IR (KBr) 1640 cm^{-1} .
Compound **12**: ^{13}C -NMR: 23,7; 27,2; 31,9; 33,2 (2C) ($(\text{CH}_2)_5$), 21,1; 25,6 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 40,1; 41,4; 42,0; 43,6; 44,2 (d, $\text{J}_{\text{P-C}} = 6,1$ Hz); 44,9; 48,1; 49,2 (d, $\text{J}_{\text{P-C}} = 5,3$ Hz) (NCH_2), 174,1 ($\text{C}=\text{O}$). ^{31}P -NMR (CDCl_3): $\delta = 24,7$ ppm. IR (KBr) 1640 cm^{-1} . Compound **13**: ^{13}C -NMR: 24,0; 27,5; 32,2; 33,0; 33,5 ($(\text{CH}_2)_5$), 23,1 (d, $\text{J}_{\text{P-C}} = 4,1$ Hz); 23,2 (d, $\text{J}_{\text{P-C}} = 4,6$ Hz); 27,3; 29,5 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 43,6; 46,7 (2C); 46,1; 46,9; 47,5; 47,6; 47,8 (d, $\text{J}_{\text{P-C}} = 4,9$ Hz) (NCH_2), 172,7 ($\text{C}=\text{O}$). ^{31}P -NMR (CDCl_3): $\delta = 14,0$ ppm. IR (KBr) 1630 cm^{-1} .
15. Compound **14**: ^{13}C -NMR: 24,8; 25,4; 26,6 (2C); 26,7; 27,9 ($\text{NCH}_2\text{C}_4\text{H}_8\text{CH}_2\text{N} + \text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 47,3; 47,6; 48,1; 49,1; 49,2; 50,6; 51,8; 53,4; 53,5; 53,8 ($\text{NCH}_2(2323) + \text{NCH}_2(\text{CH}_2)_4\text{CH}_2\text{N}$), 44,2 (2C); 45,3 (2C); 46,1 (2C); 50,6 (2C) ($\text{NCH}_2(2222)$). ^1H -NMR: 1,25 (4H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1,40 (4H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1,68 (4H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 2,57 (36H, m, NCH_2). Compound **15**: ^{13}C -NMR: 24,9; 25,6; 27,0; 28,3 ($\text{NCH}_2\text{C}_4\text{H}_8\text{CH}_2\text{N} + \text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 47,1; 47,5; 48,2; 48,9; 49,0; 50,5; 51,8; 53,1; 54,0 (NCH_2). ^1H -NMR: 1,24 (4H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1,38 (4H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1,70 (8H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 2,60 (36H, m, NCH_2).
Compound **16**: ^{13}C -NMR: 26,3; 26,9; 27,0; 27,1 ($\text{NCH}_2\text{C}_4\text{H}_8\text{CH}_2\text{N}$), 26,4 (2C); 28,2 (2C) ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 53,8; 54,0 ($\text{NCH}_2\text{C}_4\text{H}_8$), 47,5 (4C); 51,0 (2C); 51,2 (2C) ($\text{NCH}_2(3333)$), 44,7 (2C); 45,6 (2C); 46,6 (2C); 47,3 (2C) ($\text{NCH}_2(2222)$). ^1H -NMR: 1,28 (4H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1,44 (4H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1,64 (8H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 2,50 (36H, m, NCH_2).