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First Unequivocal Synthesis of Dissymmetrical trans N,N'-difunctionalized 1,4,8,11-Tetraazacyclotetradecane.

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Abstract : The first unequivocal synthesis of disymmetrical trans N,N'-difunctionalized tetraazamacrocycles in cyclam series is reported. This convenient four-step method can be used for the synthesis of various trans N,N'-difunctionalized tetraazamacrocycles bearing two different pendant donor arms. © 1999 Published by Elsevier Science Ltd. All rights reserved.

The chemistry of polyazamacrocycles with coordinating side arms has known an increasing interest during the last decade due to their interest as coordinating ligands[1-4]. For example, the synthesis of 1,4,8,11-tetraazacyclotetradecane (cyclam) derivatives N-substituted by donor groups has been widely investigated. Indeed, such a substitution onto the macrocycle may increase its selectivity towards metal sequestration as well as the stability of the formed complexes[5].

A large number of tetra N-functionalized ligands starting from tetraazacycloalkanes bearing four identical pendant donor chains has already been synthesized[6-9]. Moreover, various methods for synthesis of mono N-functionalized tetraazamacrocycles have been reported[10-14]. Conversely, N,N'-disubstituted tetraazacycloalkanes were far less studied due to their rather difficult synthesis[15-20]. Furthermore, to our knowledge, no convenient and unequivocal syntheses of dissymmetrical N,N'-difunctionalized cyclam derivatives were described starting from the free tetraazamacrocycle ligand.

A new general method for the dissymmetrical 1,8-difunctionalization of "cyclam" is herein reported starting from the diprotected 1,4,8,11-tetraazatricyclo[9.3.1.$1^{4,8}$]hexadecane. In a previous communication, we described a new synthesis of a symmetrical trans di-substituted tetraazacyclotetradecane using this latter diprotected derivative[21]. By adding an excess of an alkylating agent to this compound, the bis-ammonium salt (Scheme 1) is obtained and after hydrolysis, the trans symmetrically di-substituted macrocycle is formed. In order to synthesize a dissymmetrical derivative, we isolated first the mono ammonium salt by slow addition of one equivalent of the alkylating agent to a solution of 1,4,8,11-tetraazatricyclo[9.3.1$1^{4,8}$] hexadecane (**1**, Scheme 2) in anhydrous ether at room temperature. This intermediate can be then reacted with another different alkylating agent giving thus a disymmetrical bis-ammonium salt. Further hydrolysis (NaOH 3M) leads to the trans di-substituted cyclam (Scheme 2).

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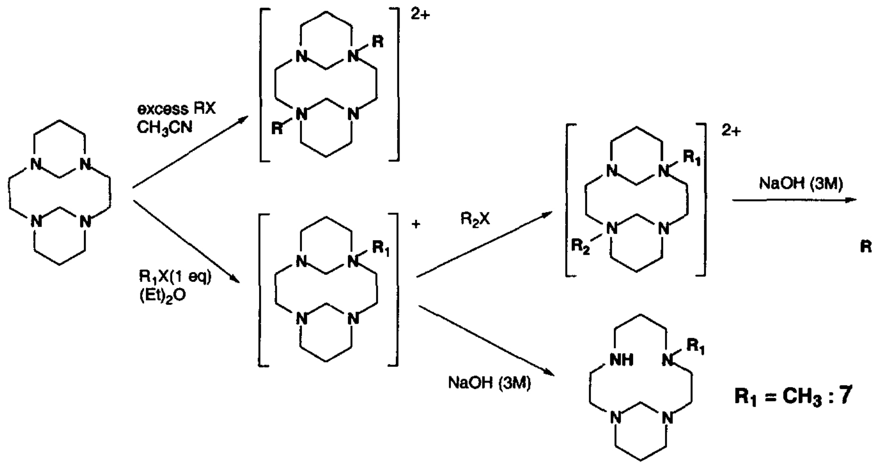
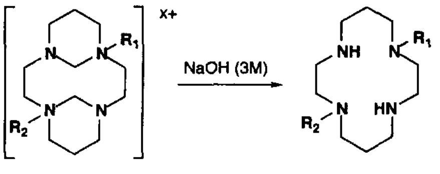


Scheme1

As an example, the slow addition at room temperature of one equivalent of methyl iodide in anhydrous ether to a solution of **1** (Scheme 2) readily gives a white precipitate which is filtrated, washed with ether, and recristallized in dichloromethane to give colorless crystals of **2** in 88 % yield (Scheme 2). This chiral monoammonium salt (**2**, Scheme 2) is allowed to react with 1.5 equivalent of 2-picolyl chloride ($-CH_2oPy$) in refluxing acetonitrile for four hours. Then, the mixture is gradually cooled down and the resulting white solid is filtered, washed with dichloromethane and recristallized from acetonitrile. Colorless crystals of **3** (Scheme 2) are obtained in 40 % yield. When 2-chloro-N,N'-dimethylacetamide is used as alkylating agent, **4** (Scheme 2) is formed in 86 % yield.

	x	R_1	R_2
1	0	/	/
2	1	Me	/
3	2	Me	CH_2oPy
4	2	Me	$CH_2CON(Me)_2$



	R_1	R_2
5	Me	CH_2oPy
6	Me	$CH_2CON(Me)_2$

Scheme 2

The dissymmetrical chiral ammonium salts **3**, **4** are quantitatively hydrolyzed using a sodium hydroxide solution (3M) at 50°C for 2 hours to give the aimed macrocycles **5**, **6** (Scheme 2). It is interesting to note that the direct hydrolysis of **2** leads to the monobridged N-methyl derivative **7** (Scheme 1) previously obtained by

Kaden et al.[22] from catalytic hydrogenation of **1** (Scheme 1). The overall yields for the synthesis of **5**, **6** are 31 and 68 % starting from cyclam respectively.

All the macrocycles were characterized by ^1H, ^{13}C NMR and ^1H-^1H, ^1H-^{13}C 2D-correlated spectrocopy and by EI mass spectrometry (except for the ammonium salts **2**, **3**, **4**)[23-25]. Satisfactory elemental analyses have been obtained[23-25]. It is noteworthy that the mono- and di-ammonium salts have respectively four chiral centers (nitrogen atoms of the macrocycles) but their synthesis affords only two enantiomers due to the blocked geometry of the starting material (**1**).

This convenient method is currently applied for the synthesis of various trans N,N'-difunctionalized cyclam derivatives bearing two different pendant donor arms.

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(23) Macrocycle 5: δ^{13}C (CDCl$_3$, 125 MHz) : 26.4 (-CH$_2$**CH$_2$**CH$_2$N(Me)-); 26.5 (-CH$_2$**CH$_2$**CH$_2$N(oPy)-); 43.0 (-N(**CH$_3$**)-); 47.9 (-NHCH$_2$**CH$_2$**N(oPy)-, -**CH$_2$**CH$_2$CH$_2$N(Me)-); 49.9 (-NH**CH$_2$**CH$_2$CH$_2$N(oPy)-); 51.8 (-NH**CH$_2$**CH$_2$N(Me)-); 53.4 (-CH$_2$CH$_2$**CH$_2$**N(oPy)-); 55.2 (-NHCH$_2$**CH$_2$**N(Me)-); 58.3 (-CH$_2$CH$_2$**CH$_2$**N(Me)-); 58.4 (-NH**CH$_2$**CH$_2$N(oPy)-); 60.8 (-N**CH$_2$**oPy); 122.3 (**-oPy**); 123.1 (**-oPy**); 136.8 (**-oPy**); 149.3 (**-oPy**); 160 (**-oPy**). δ^{1}H (CDCl$_3$, 500 MHz) : 1.67 (q, 4.5Hz, 2H, -CH$_2$**CH$_2$**CH$_2$N(Me)-); 1.82 (q, 5.5Hz, 2H, -CH$_2$**CH$_2$**CH$_2$N(oPy)-); 2.24 (s, 3H, -N(**CH$_3$**)-; 2.42 (t, 4.5Hz, 2H, -CH$_2$CH$_2$**CH$_2$**N(Me)-); 2.47 (m, 4H, -NH**CH$_2$**CH$_2$N(oPy)-, -N(Me)**CH$_2$**CH$_2$NH-), 2.56 (t, 5.5 Hz, 2H, -CH$_2$CH$_2$**CH$_2$**N(oPy)-); 2.60 (m, 4H, -N(Me)CH$_2$CH$_2$**CH$_2$**NH-, -NH**CH$_2$**CH$_2$N(Me)-); 2.66 (m, 2H, -NH**CH$_2$**CH$_2$N(oPy)-); 2.70 (m, 2H, -N(oPy)CH$_2$CH$_2$**CH$_2$**-); 3.20 (bs, 2H, **-NH-**); 3.68 (s, 2H, -**CH$_2$**oPy); 7.07 (m, 1H, **-oPy**); 7.47 (d, 7.8 Hz, 1H, **-oPy**); 7.58 (td, 7.8 and 2.8 Hz, 1H, **-oPy**); 8.43 (d, 5.4 Hz, 1H, **-oPy**). Found : C. 63.64; H. 10.42; N. 21.61. ($C_{17}H_{31}N_5$) H$_2$O requires : C.63.12; H.10.28; N.21.65. MS (EI) : m/z (%) 305 (53) $[M]^{+\cdot}$.

(24) Macrocycle 6: δ^{13}C (CDCl$_3$, 125 MHz) : 26.3 and 26.4 (-CH$_2$**CH$_2$**CH$_2$-); 35.8 and 37.0 (-CON(**CH$_3$**)$_2$); 42.4 (-N**CH$_3$**); 47.5; 48.1; 49.7; 51.2; 53.1; 55.0 (-**CH$_2$**CO-); 55.3; 57.7; 58.2; 170.2 (-**CO**N(CH$_3$)$_2$). δ^{1}H (CDCl$_3$, 500 MHz) : 1.70 (m, 4H, -CH$_2$**CH$_2$**CH$_2$ -); 2.15 (s, 3H, -N(**CH$_3$**)-); 2.41 (m, 4H); 2.58 (m, 2H, -N**CH$_2$**CH$_2$N-); 2.70 (m, 10H); 2.85 (s, 3H, -CON(**CH$_3$**)$_2$); 2.95 (s, 3H, -CON(**CH$_3$**)$_2$); 3.20 (s, 2H, -**CH$_2$**CO-); 3.48 (bs, 2H, **-NH-**). Found : C. 52.77; H 10.73; N. 19.98. ($C_{15}H_{33}N_5O$) 2.5 H$_2$O requires : C.52.30; H.11.12; N.20.33. MS (EI) : m/z (%) 300 (15) $[M+H]^{+\cdot}$.

(25) Macrocycle 7: δ^{13}C (CDCl$_3$, 125 MHz, 320K) : 22.4 and 25.2 (-CH$_2$**CH$_2$**CH$_2$-); 32.8 (-**CH$_3$**); 47.3; 47.9; 49.4; 52.7; 52.8; 53.6; 53.7; 58.1; 71.2 (-N**CH$_2$**N-). δ^{1}H (CDCl$_3$, 500 MHz, 320K) : 1.61 (bs, 2H); 1.71 (m, 2H); 2.16 (s, 3H, -**CH$_3$**); 2.43 (bs, 2H); 2.48 (t, 5 Hz, 2H); 2.68 (m, 12H); 3.59 (bs, 1H, **-NH-**); 5.25(s, 2H, -N**CH$_2$**N-). found : C. 62.45; H. 11.71; N. 24.02. ($C_{12}H_{26}N_4$) 0.25 H$_2$O requires : C. 62.43; H. 11.56 ; N. 24.27 . MS (EI) : m/z (%) 226 (78) $[M]^{+\cdot}$.