# A New Versatile Synthesis of Macrotricyclic Tetraazacycloalkane-Based Ligands from Bis-aminal Derivatives

Stéphanie Develay,[a] Raphaël Tripier,[a] Françoise Chuburu,[a] Michel Le Baccon,[a] and Henri Handel*[a]

**Keywords:** Bis-aminals / Amines / Nitrogen heterocycles / Alkylation

A new powerful synthesis of symmetrical (two-step) or dissymmetrical (three-step) macrotricyclic cyclen- or cyclam-based ligands is reported. In this procedure, the starting materials are bis-aminals derived from condensation of cyclen or cyclam with glyoxal. The two macrocyclic subunits are linked by two aromatic spacers through nitrogen atoms.

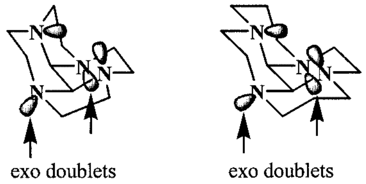
## Introduction

Polyazacycloalkanes are versatile ligands well-known for their high binding affinity for transition metals;[1,2] their synthesis and their selective N-alkylation have both been a very popular objective of research groups over the last thirty years.[3] Like bis-macrocycles, macrotricyclic ligands are of great interest because of their ability to behave as multi-site receptors in the trapping of various substrates or to coordinate metals.[4−7] Macrotricycles are formed by linking two rings with two spacer bridges which define three cavities: the two lateral macrocycles, and a central one delimited by the linkers. The consequence of such a construction is that the metals coordinated by two face-to-face macrocyclic subunits are constrained to stay at a close distance, which induces possible metal-metal interactions and therefore particular electronic properties. Moreover, one may assume that the delineated central cavity can function as an excellent host for anionic species, according to the distance between the two macrocyclic centers, the degree of protonation of the macrocycles or, alternatively, the nature of the complexed metals.

Despite their importance,[8−12] the development of cylindrical tetraazacycloalkanes-based macrotricycles is restrained mainly because of their difficult multi-step syntheses.[3,13−16] In the continuation of our work on bis-tetraazamacrocycles we report here a new route to polyazamacrotricycles based on the use of bis-aminals as building blocks.

## Result and Discussion

The bis-aminals of linear or cyclic tetraamines proved to be an excellent tool for tetraazacycloalkane synthesis and modification.[17−21] They are easily obtained from the direct condensation of an α-dicarbonyl compound with the corresponding tetraamine: so, glyoxal reacts with cyclen (1,4,7,10-tetraazacyclododecane) or cyclam (1,4,8,11-tetraazacyclotetradecane) in methanolic solution at room temperature to give quantitatively the decahydro-2a,4a,6a,8a-tetraaza-cyclopenta[fg]acenaphthylene (**1**; cyclen-glyoxal) or decahydro-3a,5a,8a,10a-tetraazapyrene (**2**; cyclam-glyoxal). These compounds present a bent *cis* configuration,[21] which induces a discrimination between the two pairs of opposite nitrogen atoms: the one which possesses its lone pairs directed towards the convex side of the molecular structure exhibits a much more marked nucleophilic character (Figure 1).



**1** **2**

Figure 1. Molecular structures of cyclen-glyoxal **1** and cyclam-glyoxal **2**

The reaction of one equivalent of an electrophile with **1** or **2** led to a monoalkylated derivative, and this reaction was used both to obtain mono N-alkylated cyclam or cyclen[20] and on the other hand to prepare bis-tetraazamacrocycles.[21] With two equivalents of electrophile, a second (slower) attack occurs on the opposite nitrogen atom which leads to an $N_1$-$N_7$ ($n = 0$) and $N_1$-$N_8$ ($n = 1$)

---

[a] UMR CNRS 6521, "Chimie, Electrochimie Moléculaire et Analytique", Université de Bretagne Occidentale,
B. P. 809, 6 avenue Le Gorgeu, 29285 Brest Cedex, France
Fax: (internat.) +33-(0)2/9801−6594
E-mail: henri.handel@univ-brest.fr

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

**DOI: 10.1002/ejoc.200300188**

Table 1. Macrotricycles obtained and overall yields

| | Bis-aminals | Diammonium salts | | Tetraammonium salts | | Macrotricycles overall yields | |
|---|---|---|---|---|---|---|---|
| Symmetric | **1** | o | **3a** | o-o | **3b** | **3c** | 60% |
| | | m | **4a** | m-m | **4b** | **4c** | 98% |
| | | p | **5a** | p-p | **5b** | **5c** | 91% |
| | | py | **6a** | py-py | **6b** | **6c** | 98% |
| | **2** | m | **7a** | m-m | **7b** | **7c** | 68% |
| | | p | **8**a | p-p | **8b** | **8c** | 61% |
| Dissymmetric | **1** | | | m-p | **9b** | **9c** | 75% |
| | | | | m-py | **10b** | **10c** | 80% |
| | **2** | | | m-p | **11b** | **11c** | 63% |

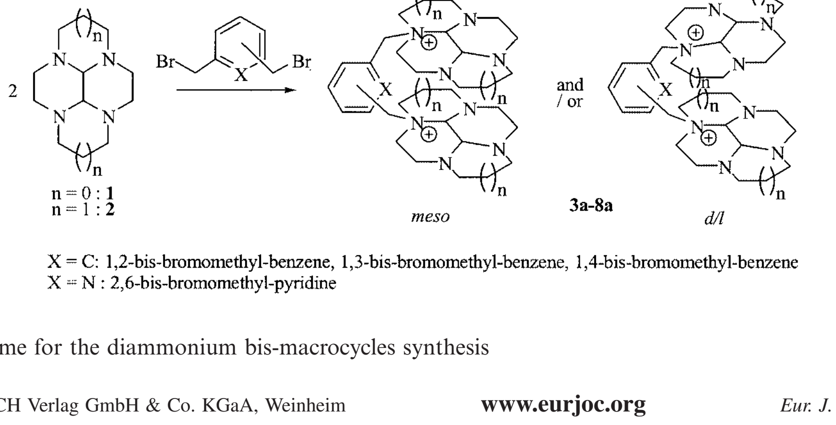
dialkylation of the macrocycle via a diquat salt. Furthermore, this second attack takes place on the same side as the first one,[20] leading to a *cis* entry of the electrophilic moieties. This occurrence is favourable to a [2+2] reaction and opens the way to cylindrical macrotricycles. Moreover, according to the Dreiding molecular models the formation of the macrobicycle by [1+1] cyclisation[3] is, a priori, not favoured.

As a matter of fact, we observed that when an equivalent of 1,3-bis(bromomethyl)benzene were added to the cyclen-glyoxal **1** at room temperature, the subsequent macrotricyclic tetraammonium salt **4b** was obtained in good yields. However, when the reaction was quenched after a short time, the bis-macrocyclic diammonium salt **4a** was detected. Furthermore, the preparation of **4b** by reaction between the bis-salt **4a** and the corresponding bis-electrophile confirmed the intermediacy of the diammonium salt. Consequently, it appeared that the [2+2] reaction consists of two consecutive steps, consistent with the fast alkylation of the first nitrogen atom, whereas the second one reacts more slowly.[21]

A general synthetic pathway was deduced from these observations in order to obtain cylindrical macrotricycles from cyclen- or cyclam-glyoxal bis-aminals **1** and **2** (Schemes 1 and 2) using 1,2-bis(bromomethyl)benzene, 1,3-bis(bromomethyl)benzene, 1,4-bis(bromomethyl)benzene and 2,6-bis(bromomethyl)pyridine as electrophiles. The subsequent links are respectively referenced o, m, p, py in Table 1.

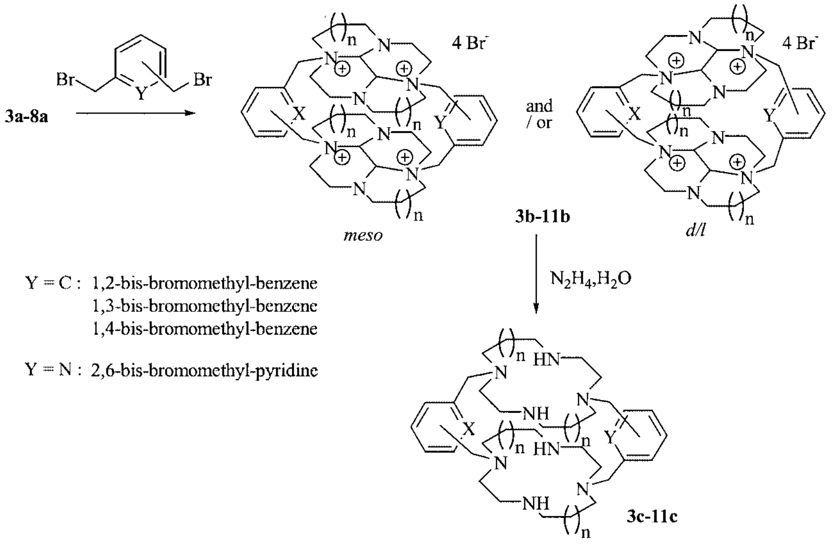
In a typical experiment the macrotricycle synthesis proceeded through the initial preparation of the bis-macrocyclic diammonium salts **3a−8a** (Scheme 1). This route allowed the use of two different linkers. Subsequent addition of the desired second bis-electrophile (Scheme 2), which may or may not differ from the first one, led to symmetrical (**3b−8b**) or dissymmetrical (**9b−11b**) macrotricyclic tetraammonium salts in good yields. The deprotection of the tetraammonium salts **3b−11b** was performed in hydrazine monohydrate as described previously,[21] leading to the free macrotricycles **3c−11c** in good yields (Table 1).

One can note that upon the formation of the diammonium salts **3a−8a**, the four nitrogen atoms and the aminal carbon atoms become centers of chirality. The *cis* configuration of the aminal bridge and the entry of the electrophile on the same side as the two aminal hydrogen atoms induce the formation of two possible configurations, the racemic (*d*/*l*) and meso diastereoisomers, which have been observed in some cases and reported in previous papers.[21] This situation is maintained after the addition of the second bis-electrophile, making the $^{13}$C NMR spectra recorded of some compounds more complicated. Thus, **3b**, **5b** and **10b** exhibit two series of signals of nearly equal intensity due to the coexistence of these two configurations. The presence of the two isomers has no impact on the end product. Finally, the symmetrical macrotricyclic tetraammonium salts **3b−8b** can also be obtained in one pot by reaction of the bis-aminals **1−2** with two equivalents of the bis-electrophile.



X = C: 1,2-bis-bromomethyl-benzene, 1,3-bis-bromomethyl-benzene, 1,4-bis-bromomethyl-benzene
X = N : 2,6-bis-bromomethyl-pyridine

Scheme 1. Reaction scheme for the diammonium bis-macrocycles synthesis



Scheme 2. Reaction scheme for the macrotricycles synthesis

## Conclusion

In conclusion, we have reported a new, easy-to-run and versatile two- or three-step route to cylindrical macrotricycles based on the great interest of bis-aminal for tetraazamacrocycle alkylation. Moreover, no high dilution conditions are required, which is an important improvement of this method. Various new cylindrical macrotricycles were obtained in high overall yields and fully characterised, as were their intermediate tetraammonium salts. According to well as the reactants' stoichiometry, the alkylation reaction can be directed either to the unequivocal symmetrical macrotricycles or to a specific combination leading to the dissymmetrical macrotricyclic compounds. In order to obtain a large range of cylindrical macrotricycles, we are currently extending the scope of this method to cylindrical entities composed of two different macrocyclic rings. In other respects the study of the new and interesting macrotricyclic tetraaminal tetraammonium intermediates salts, which can also present a strong affinity towards specific guests, is also one of our main objectives.

## Experimental Section

**General:** All reagents were of commercial quality and solvents were dried using standard procedures. Elemental analyses were performed at the Service de Microanalyse, CNRS, 91198 Gif sur Yvette, France. Mass spectrometry analyses were performed at the Centre Régional de Mesures Physiques de l'Ouest, Rennes, France. Among the bis-macrocyclic diammonium salts **3a−8a** synthesised in $CH_3CN$ as previously reported,[21] **3a** and **6a** are new compounds.

Experimental data are available as Supporting Information (see footnote on the first page of this article).

**General Procedure for the Synthesis of Macrotricycles 3b−11b:** A solution of the desired bis-electrophile in $CH_3CN$ or DMF (0.75 M) was added dropwise to a solution of the tetraaminal bis-macrocycle diammonium salt in $CH_3CN$ or DMF (0.75 M) at room temperature with vigorous stirring. After two days for cyclen derivatives, and one week for cyclam derivatives, filtration of the white precipitate formed led to the macrotricyclic tetraaminal tetraammonium salts **3b−11b**.

**One-Step Synthesis of 3b−8b**: The desired bis-electrophile ($CH_3CN$ for **1** or DMF for **2**; 0.75 M) was added dropwise to a solution of the bis-aminal macrocycle ($CH_3CN$ or DMF) 0.75 M) at room temperature with vigorous stirring. After two days for **1** and one week for **2**, filtration of the white precipitate formed gave the macrotricyclic tetraaminal tetraammonium salts **3b−8b**.

**General Procedure for the Synthesis of 3c−11c:** The tetra-salts **3b−11b** were refluxed in hydrazine monohydrate as described previously.[21] If required the free compounds were purified by recrystallization from acetone.

## Acknowledgments

We thank M. P. Friocourt for her valuable help.

---

[1] R. B. Lauffer, *Chem. Rev.* **1987**, *87*, 901−927.
[2] R. M. Izatt, K. Pawlak, J. S. Bradshaw, R. L. Bruening, *Chem. Rev.* **1995**, *95*, 2529−2586.
[3] F. Denat, S. Brandès, R. Guilard, *Synlett* **2000**, *5*, 561−574.
[4] H. An, J. S. Bradshaw, R. M. Izatt, *Chem. Rev.* **1992**, *92*, 543−572.
[5] J.-M. Lehn, *Pure Appl. Chem.* **1980**, *52*, 2441−2459.
[6] K. E. Krakowiack, J. S. Bradshaw, X. Kou, N. K. Dalley, *J. Heterocycl. Chem.* **1995**, 931−935.
[7] S. Quici, A. Manfredi, L. Raimondi, A. Sironi, *J. Org. Chem.* **1995**, *60*, 6379−6388.
[8] A. Ingham, M. Rodopoulos, K. Coulter, T. Rodopoulos, S. Subramanian, A. McAuley, *Coord. Chem. Rev.* **2002**, 233−234, 255−271.
[9] J. D. Chartres, L. F. Lindoy, G. V. Meehan, *Coord. Chem. Rev.* **2001**, 216−217, 249−286.
[10] R. Ballardini, V. Balzani, A. Credi, M. T. Gandolfi, F. Kotzyba-Hibert, J.-M. Lehn, L. Prodi, *J. Am. Chem. Soc.* **1994**, 5741−5746.

[11] A. Bencini, M. A. Bernardi, A. Bianchi, M. Ciampolini, V. Fusi, N. Nardi, F. Pina, B. Valtancoli, *J. Chem. Soc., Perkin Trans. 2* **1998**, 413−418.

[12] M. Lachkar, R. Guilard, A. Atmani, A. De Cian, J. Fisher, R. Weiss, *Inorg. Chem.* **1998**, *37*, 1575−1584.

[13] I. M. Helps, D. Parker, J. R. Morphy, J. Chapman, *Tetrahedron* **1989**, *45*, 219−226.

[14] L. Fabbrizzi, T. A. Kaden, A. Perotti, B. Seghi, L. Siegfried, *Inorg. Chem.* **1986**, *25*, 321−327.

[15] T. Koike, T. Watanabe, S. Aoki, E. Kimura, M. Shiro, *J. Am. Chem. Soc.* **1996**, *118*, 12696−12703.

[16] D. A. Tomalia, L. R. Wilson, *Patent*, US4517122, **1985**.

[17] G. Hervé, H. Bernard, N. Le Bris, J. J. Yaouanc, H. Handel, *Tetrahedron Lett.* **1998**, *39*, 6861−6864.

[18] G. Hervé, H. Bernard, N. Le Bris, M. Le Baccon, J. J. Yaouanc, H. Handel, *Tetrahedron Lett.* **1999**, *40*, 2517−2520.

[19] F. Chuburu, R. Tripier, M. Le Baccon, H. Handel, *Eur. J. Org. Chem.* **2003**, *6*, 1050−1055.

[20] J. Kotek, P. Hermann, P. Vojtisek, J. Rohovec, I. Lukes, *Collect. Czech. Chem. Commun.* **2000**, *65*, 243−266.

[21] M. Le Baccon, F. Chuburu, L. Toupet, H. Handel, M. Soibinet, I. Deschamps-Olivier, J.-P. Barbier, M. Aplincourt, *New J. Chem.* **2001**, *25*, 1168−1174.

Received March 20, 2003