Reaction of polyamines with diethyloxalate: a convenient route for the synthesis of tetraazacycloalkanes

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Dedicated to Professor Armand Lattes on his 50th years teaching and research

Abstract

The reactivity of various polyamines with diethyloxalate has been investigated. It appears that, in similar experimental conditions, primary diamines give predominantly [2+2] adducts while the use of secondary benzylated polyamines results in [1+1] condensation. Although the intermediate tetraamides formed in the first case are extremely poorly soluble and show very slow reactivity towards reducing agents, cyclam has been obtained by using ultrasounds during the reaction of the corresponding tetraoxomacrocycle with BH_3/THF. The [1+1] cyclization reaction of diversely *N*-benzylated linear tetraamines, whose selective syntheses have been devised herein, gives access to various *N*-benzylated cyclens and cyclams. New macrocyclic ligands containing both amine and amide type nitrogen atoms have been formed as intermediates in these syntheses. Two compounds containing an aminal function exhibit an unexpected reactivity, leading to the formation of new bisaminal products whose structures have been established by X-ray diffraction.

Keywords: Diethyloxalate, polyamines, tetraazacycloalkanes, aminal, reduction, selective benzylation

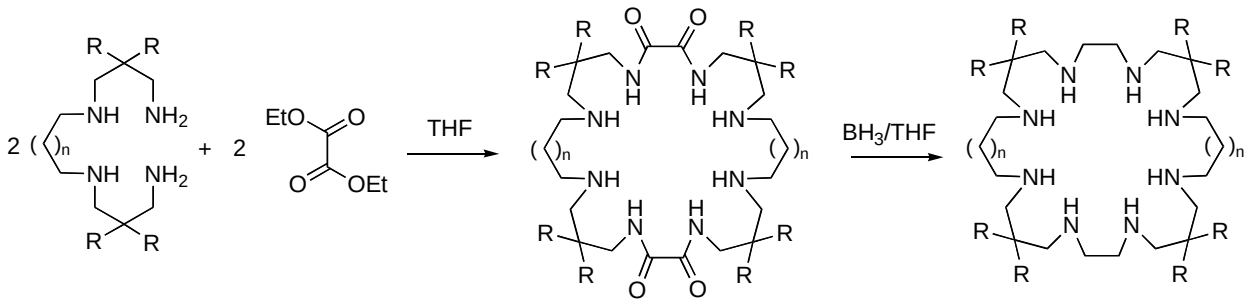
Introduction

The chemistry of tetraazacycloalkanes, especially cyclen and cyclam, has undergone a considerable development in the last thirty years, owing to their coordination properties. Indeed, these macrocyclic polyamines are able to form stable complexes with transition metals as well as lanthanides, actinides, and other heavy metals.[1] The affinity and selectivity towards the metal ion can be tuned by varying the size of the macrocyclic core as well as the nature and the number of pendant coordinating arms on the nitrogen atoms. Since the first syntheses of cyclen and cyclam

in the early 70's, there has been a still growing interest in the search of more convenient approaches for the preparation of these tetraazacycloalkanes and their derivatives. This interest is due to the usefulness of these macrocycles in many different fields including removal of metals from liquids,[2] purification of gases,[3] catalysis,[4] sensors and probes,[5] as well as medical applications.[6]

Particular efforts have been devoted to the preparation of selectively functionalized tetraazacycloalkanes and the so-called bifunctional chelating agents, containing two kinds of functional groups, one for the coordination of the metal, the other one for binding the macrocycle to a macromolecule such as an antibody, or onto a solid support.[7]

Many methods have been devised for the synthesis of cyclen, cyclam, and their functionalized derivatives, including high dilution techniques, use of metal cations as template, protection/deprotection sequences, functionalization on either nitrogen or carbon atoms. A recent key step in this chemistry is the use of bisaminal intermediates, both for the synthesis of cyclen or cyclam and their *N*- and/or *C*-functionalized derivatives.[8] A few years ago, we have shown that the condensation of linear tetraamines with diethyloxalate in the appropriate conditions (solvent, concentration, temperature) yields mainly the [2+2] adduct, thus providing a very convenient route towards large polyazamacrocycles after reduction of the tetraamide intermediates (Scheme 1).[9] Similar results have been recently reported by others.[10]



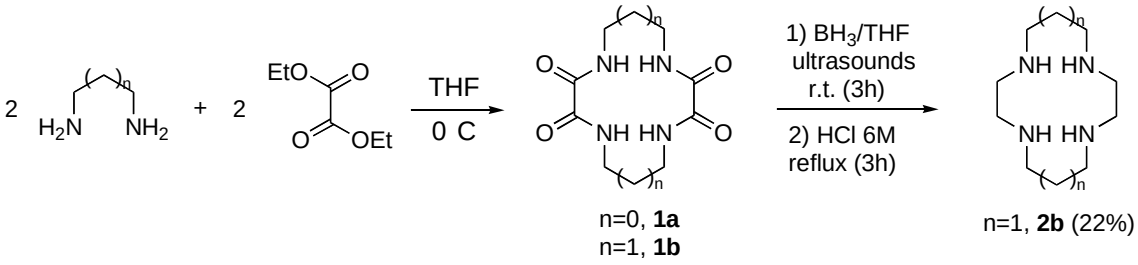
Scheme 1

As a part of our program for the development of convenient methods for the synthesis of tetraazacycloalkanes derivatives, we have investigated the reaction of diethyloxalate with diamines and *N*-benzylated polyamines.[11] The main results are reported herein.

Results and Discussion

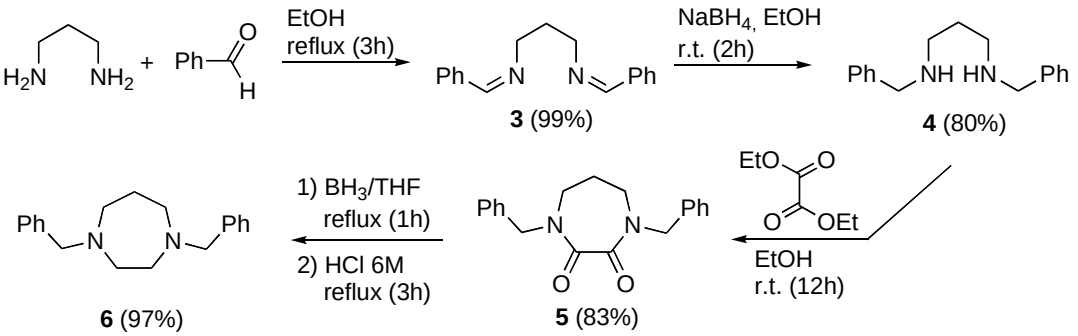
We have firstly investigated the condensation of diethyloxalate with two diamines, ethylenediamine and 1,3-propanediamine, in the conditions described in our previous paper

(Scheme 2). The expected cyclic tetraamide intermediates **1a** and **1b** are extremely poorly soluble in both organic solvents and water, therefore we were not able to isolate, purify and characterize these compounds. However, infra-red data show the presence of amide type carbonyl groups at 1670 cm^{-1}, indicating that the cyclization reaction occurs. First attempts to reduce these compounds with borane in THF failed. A strong intra- and/or inter-molecular hydrogen bonds network is probably responsible for both the insolubility of these compounds and their exceptional reluctance towards reduction. Reduction of intermediate **1b** was finally performed by using ultrasounds, which probably break hydrogen bonds and therefore facilitate the reduction reaction. A solution of **1b** and 1.5 equivalent of BH_3 in THF was stirred for 3 hours at room temperature under sonication (750 watts, 20 KHz). After acidic treatment, NaOH was added and the solution was extracted with dichloromethane. The colourless oil obtained upon evaporation was taken in diethylether to give cyclam **2b** as a white solid in 19 % overall yield.



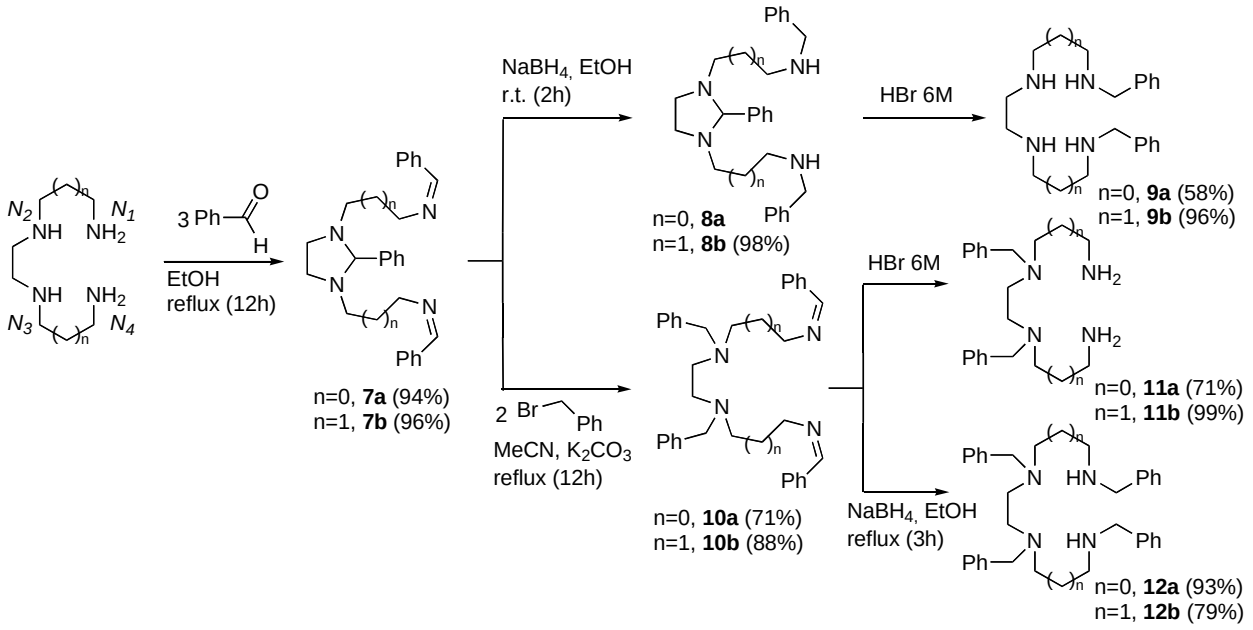
Scheme 2

In order to overcome the formation of a hydrogen bonds network, we have decided to use *N*-benzylated diamines as starting material. Indeed, the presence of benzyl groups on nitrogen atoms should increase the lipophilic character and consequently the solubility in organic solvents. Moreover, the use of secondary amines should prevent the formation of hydrogen bonds and benzyl groups can be easily removed by catalytic hydrogenolysis. The *N*,*N*'-dibenzylated 1,3-propanediamine **4** was prepared in 80 % yield by reduction of the corresponding diimine intermediate **3** obtained quantitatively by reacting 1,3-propanediamine with benzaldehyde (Scheme 3). The condensation of compound **4** with diethyloxalate, in either THF or ethanol, results in the formation of the [1+1] adduct **5**, with no trace of [2+2] derivative, even in relatively high concentration conditions (0.08 mol L^{-1}), as shown by mass spectrometry. This diamide was easily reduced by BH_3/THF to yield the dibenzylated seven-membered heterocycle **6**. This experiment shows that, as expected, the reduction of benzylated polyamides is facilitated, but unfortunately secondary diamines behave differently from primary diamines when treated with diethyloxalate. The main formation of the [1+1] cyclization product also indicates that the hydrogen bonds network could be a driving force in the formation of the [2+2] adduct. This result, which has been previously described,[12] prompted us to investigate the cyclization of benzylated tetraamines with diethyloxalate.



Scheme 3

Firstly, we have developed a convenient procedure for the synthesis of selectively benzylated tetraamines (Scheme 4). Some of these compounds have been reported previously.[13] In the first step, the reaction of three equivalents of benzaldehyde with triethylenetetraamine and *N*,*N*'-bis-(3-aminopropyl)-ethylenediamine in refluxing ethanol gives the corresponding diimine intermediates containing one aminal function **7a** and **7b** in very good yields (Figures 1 and 2). Depending on the subsequent treatment, these intermediates may yield the N^1,N^4- or the N^2,N^3-dibenzylated tetraamines, or the fully benzylated compounds.

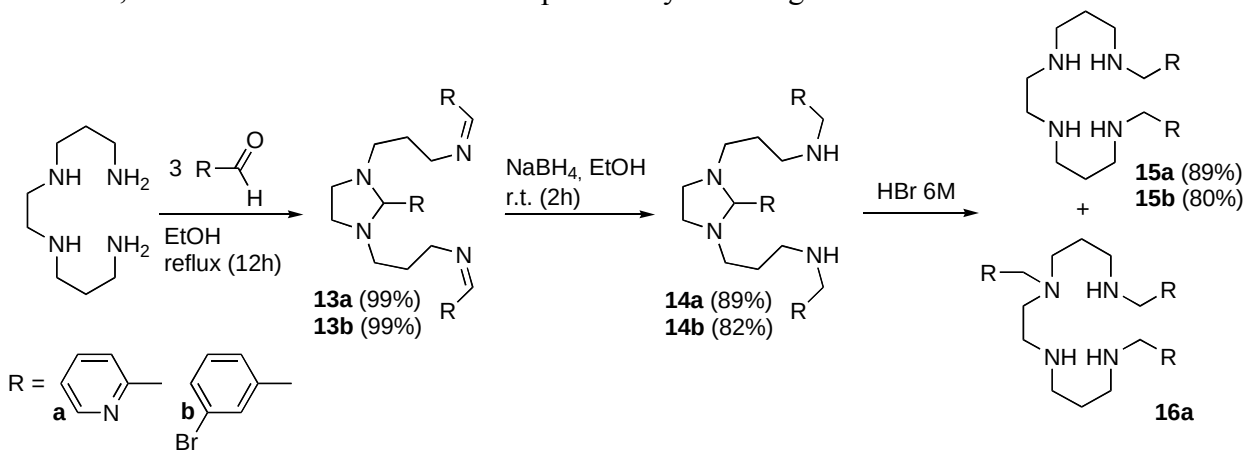


Scheme 4

The reduction of the Schiff bases **7a-b** with $NaBH_4$ in ethanol at room temperature gives the dibenzylated monoaminal compounds **8a-b**. The compound **8a** was not isolated because a rearrangment was observed during the work-up (vide infra). The acidic hydrolysis of **8a-b** allows

the removal of the aminal group to release the N_1,N_4-dibenzylated tetraamines **9a-b** in good overall yields (54.5 and 90 % respectively). The reaction of intermediates **7a-b** with two equivalents of benzyl bromide in refluxing acetonitrile results in the quantitative formation of the N_2,N_3-dibenzylated diimines **10a-b**. It is noteworthy that lower yields are observed when using only one equivalent of benzyl bromide. The reaction should proceed through the nucleophilic attack of one aminal type nitrogen on one equivalent of benzyl bromide, followed by the loss of one equivalent of benzaldehyde, which can be easily detected, and finally the reaction of the resulting secondary amine with the second equivalent of benzyl bromide. The presence of water in the solvent can explain the formation of benzaldehyde. The two imine functions in **10a-b** can be either hydrolysed with hydrobromic acid solution to give after neutralization and extraction the corresponding N_2,N_3-dibenzylated tetraamines **11a-b** in 48 and 95 % overall yields respectively, or reduced with $NaBH_4$ in refluxing ethanol to yield the tetrabenzylated tetraamines **12a-b**.

This methodology can be applied to different aromatic aldehydes, allowing the *N*-functionalization with other groups than the protecting benzyl groups. For instance, we have used 3-bromobenzaldehyde and 2-pyridinecarboxaldehyde to prepare difunctionalized tetraamines **15a-b** (Scheme 5). The aminal group linked to a pyridine appears to be more reluctant towards hydrolysis. Indeed, the action of a 4M HBr solution in ethanol at 0°C, i.e. conditions used to remove the aminal group obtained with benzaldehyde and 3-bromobenzaldehyde, gives a 50/50 mixture of di- and tribenzylated tetraamines **15a** and **16a**. However, **15a** can be obtained as the sole product by refluxing the solution.

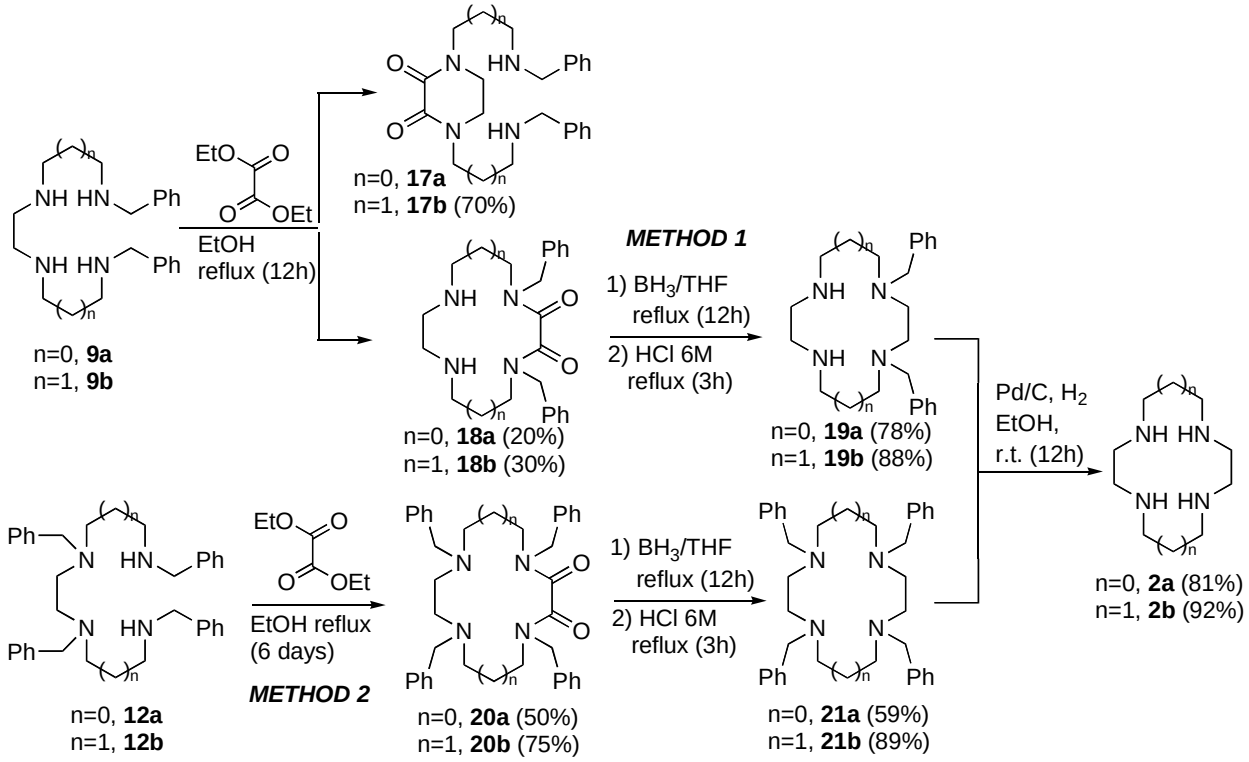


Scheme 5

The next step was to investigate the cyclization reaction of the different benzylated tetraamines with diethyloxalate. The reaction of N_1,N_4-dibenzylated tetraamines **9a-b** with the diester in refluxing ethanol gives the aimed dioxodibenzylcyclen **18a** and dioxodibenzylcyclam **18b** in 20 % and 30 % yields respectively, after optimisation of the reaction conditions, i.e. solvent, concentration, temperature (Scheme 6, Method 1). The formation of stable six-

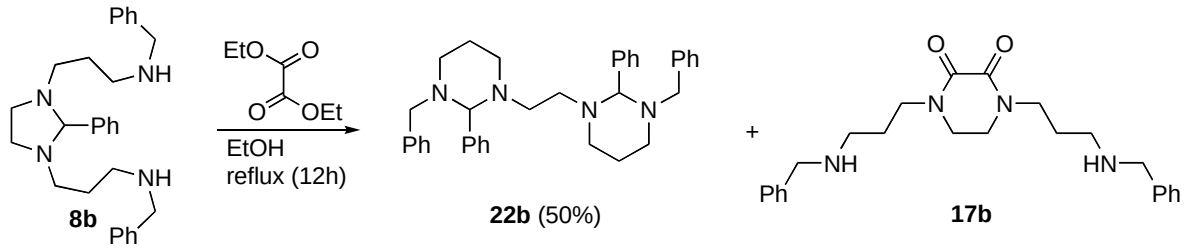
membered rings is predominant and the major products are the dioxopiperazine derivatives **17a-b**. The ratio **17b/18b** can be increased up to 91/9 by lowering the temperature (-10 °C). It has to be noted that **17a** was not isolated as a pure compound since for such a series the formation of a six-membered ring can lead to another isomer. The reduction of dioxomacrocycles **18a-b** with borane in THF allows the synthesis of 1,4-dibenzyltetraazacycloalkanes **19a-b**. The benzyl groups can be removed to give respectively cyclen **2a** and cyclam **2b**. More interestingly, intermediates **19a** and **19b** are valuable precursors of macrocyclic polyamines functionalized on two adjacent nitrogen atoms when the *N*-functionalization is performed before the deprotection step. Such 1,4-difunctionalized cyclens and cyclams are difficult to prepare using known methodologies.[14]

The cyclization reaction of tetrabenzylated tetraamines **12a-b** with diethyloxalate gives the expected dioxomacrocycles **20a** and **20b** in 50 % and 75 % yields respectively (Scheme 6, Method 2). In this case, the formation of six-membered rings does not occur due to the presence of the two tertiary amines. However, six days in refluxing ethanol were necessary to perform the cyclization reaction in good yields, thus illustrating the deactivating effect of the benzyl groups on the reactivity of the secondary amines. The reduction of compounds **20a-b** with BH_3/THF leads to the tetrabenzylated cyclen and cyclam **21a-b**, which can be deprotected to yield finally cyclen and cyclam.



Scheme 6

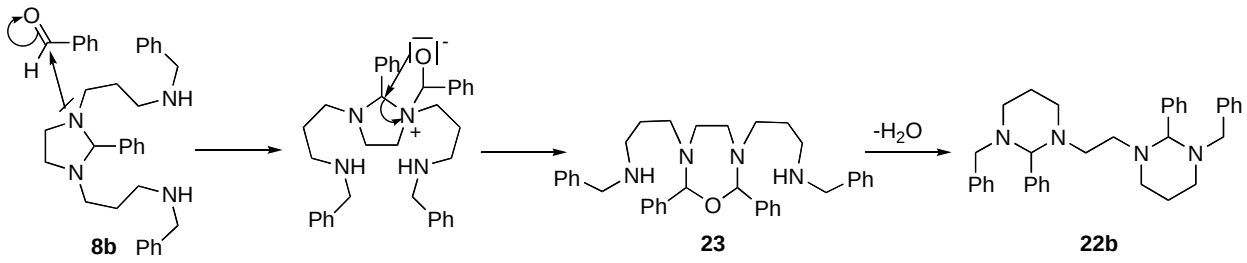
Unexpected products have been obtained from the reaction of aminal diimine derivative **8b** with diethyloxalate (Scheme 7). Indeed, this reaction does not lead to the aimed dioxoaminal macrocycle but to the rearranged product **22b** (Figure 4) containing two aminal moieties, together with the dioxopiperazine derivative **17b**. The formation of this cyclic diamide can be explained by the initial attack of diethyloxalate on one aminal nitrogen atom, implying the loss of one equivalent of benzaldehyde, as observed in the reaction of aminal derivatives **7a-b** with benzyl bromide, followed by the cyclization to yield the six-membered aminal ring. The formed benzaldehyde can then react faster than diethyloxalate with starting material **8b**, to give the bisaminal compound **22b**. Due to this rearrangement, the aminal moiety cannot be used as a protecting group. The compound **8a** behaves in a similar manner, since the bisaminal **22a** (Figure 3) is obtained directly from **7a**, together with the dibenzylated tetraamine **9a** in a 1:1 ratio, by reduction with $NaBH_4$ followed by hydrolysis. In this case, the intermediate **8a** was not isolated, thus indicating that the formation of two five-membered rings to give **22a** occurs more readily than the formation of two six-membered rings to yield **22b**. The compound **22b** was also obtained without using diethyloxalate, together with the dibenzylated product **9b** in a 1:1 ratio, by refluxing **8b** in water.



Scheme 7

It has to be noted that the reaction of one equivalent of benzaldehyde with the dibenzylated tetraamine **9b** gives the monoaminal product **8b**, which is almost quantitatively converted to the rearranged product **22b** by addition of a second equivalent of benzaldehyde. This experiment indicates that the rearrangement is induced by the attack of an electrophilic reagent, for instance diethyloxalate or in the latter case a second equivalent of benzaldehyde, on the tertiary nitrogen atom rather than on the terminal secondary amines. Thus, the reaction should proceed via the formation of the intermediate **23**, which after nucleophilic attack of the secondary amines and loss of a water molecule, gives the bisaminal product (Scheme 8). The first step of this reaction, corresponding to the insertion of the double-bond into the C-N aminal bond is in agreement with the mecanism postulated earlier for the reaction of aminals with polarized double bonds.[15] Moreover, we were able to prove the formation of such an intermediate by reacting formaldehyde with the monoaminal diimine **7b**. Indeed, the rearrangement was in this case prevented by the presence of the two imine functions, and the formation of the product resulting

from the insertion of the carbonyl group into the C-N aminal bond is evidenced by MALDI-TOF mass spectrometry.



Scheme 8

All compounds have been fully characterized by NMR spectroscopy, including ^{1}H-^{1}H and ^{1}H-^{13}C correlations experiments. It is clear that only one out of the three possible diastereoisomers (EE, ZZ, and EZ regarding the two C=N configurations) is obtained for the monoaminal diimines **7a** and **7b**. The EZ isomer is not compatible with the symmetry of the molecule in agreement with the number of signals on the NMR spectra. Single crystals were obtained from recrystallization of **7a** and **7b** in ethanol and THF respectively. In both cases, the most stable EE configuration was undoubtedly confirmed by X-ray diffraction (Figures 1 and 2).

The symmetry observed in solution is not preserved in the solid state, especially in the case of **7b**. Indeed, one C-N aminal bond is considerably longer than the other one (1.470 Å vs 1.452 Å). The distortion of the five-membered ring can result from interactions between the methylenic protons of the propylene chain and the π electrons of the benzyl groups of an adjacent molecule. The loss of symmetry in the solid state is also evidenced by CP-MAS ^{13}C NMR. Indeed, the ^{13}C spectrum of **7b** in the solid state exhibits a splitting or broadening of all signals.

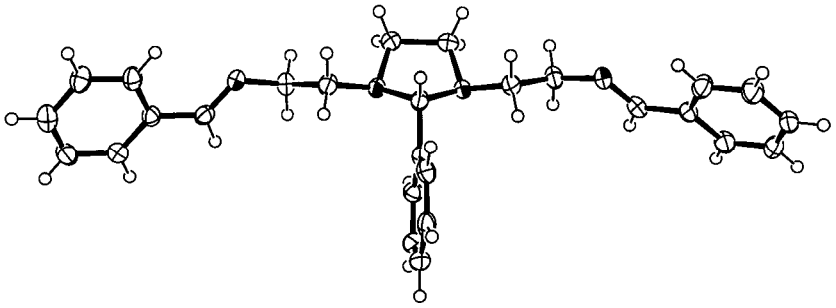


Figure 1. ORTEP view of **7a**, showing thermal ellipsoids at 50 % probability level.

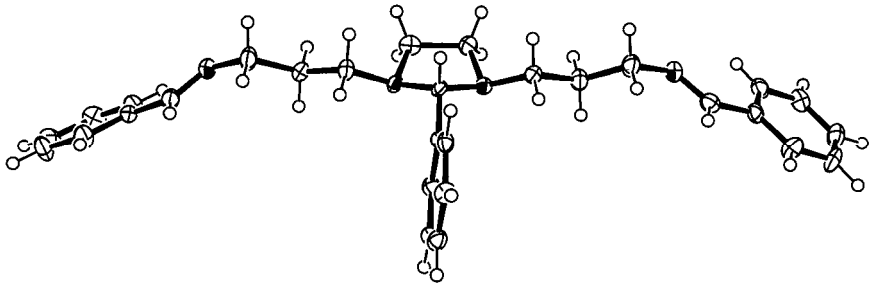


Figure 2. ORTEP view of **7b**, showing thermal ellipsoids at 50 % probability level.

The bisaminal compounds **22a** and **22b** resulting from the rearrangement of **8a** and **8b** can also exist as different stereoisomers, due to the presence of two identical asymmetric carbon atoms, i.e. a meso compound and a racemic mixture of two enantiomers. The ^{13}C NMR of **22b** recorded in $CDCl_3$, exhibits twelve signals in the 20-90 ppm region corresponding to the aliphatic carbon atoms. However, both diastereoisomers are symmetrical and should exhibit only six signals in this region. One may deduce that both compounds are present in this solution. Surprisingly, the spectrum was simplified when recorded in C_6D_6. In this solvent, only six signals appear in the region of interest, showing that only one diastereoisomer is present in the solution. The rearrangement gives probably only one compound, which then isomerizes in acidic solvent such as $CDCl_3$, to give a mixture of diastereoisomers. The NMR data given in the experimental section for compounds **22a** and **22b** are those obtained in C_6D_6 as solvent. The structures of bisaminal compounds **22a** and **22b** have been established unequivocally by single crystal X-ray diffraction (Figures 3 and 4). In both cases, the meso compound is obtained.

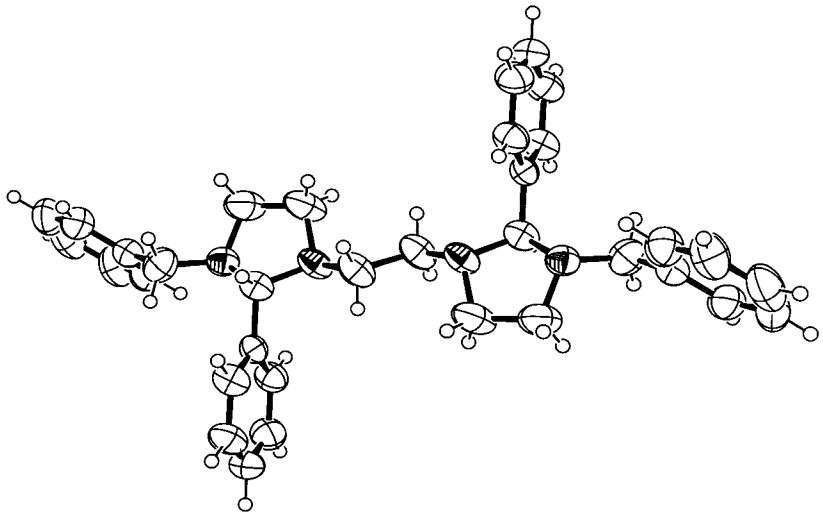


Figure 3. ORTEP view of **22a**, showing thermal ellipsoids at 50 % probability level.

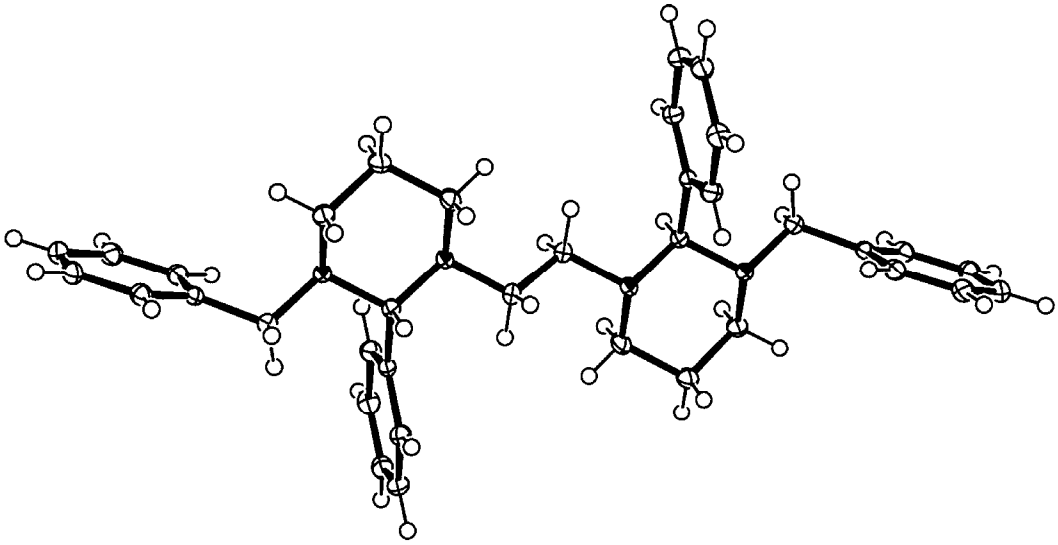


Figure 4. ORTEP view of **22b**, showing thermal ellipsoids at 50 % probability level.

Conclusions

Diethyloxalate proved to be a valuable precursor for the synthesis of polyazacycloalkanes. The cyclization reaction can be performed in good yields without using high dilution conditions, probably due to the conformational rigidity of the diester. However, the nature of the starting polyamine is a key parameter since [1+1] or [2+2] adducts can be preferably obtained depending on the presence or not of benzyl groups on the terminal nitrogen atoms. Indeed, the reaction of ethylene diamine or 1,3-propanediamine with diethyloxalate gives tetraamides which appear to be quite reluctants towards reduction, although cyclam can be obtained in 19 % overall yield, in only two steps, providing that ultrasounds are used during the reduction step. Convenient routes for the synthesis of various di- or tetrabenzylated linear tetraamines have been devised, implying the use of aminal intermediates obtained by reaction of the linear tetraamines with aldehydes. The cyclization of these *N*-benzylated tetraamines with diethyloxalate leads to various 2,3-dioxo *N*-benzylated tetraazamacrocycles, which after reduction and removal of benzyl groups, can yield cyclen or cyclam. Beside the synthesis of these two tetraazacycloalkanes, the interest of the synthetic routes described herein also lies in the intermediates. Thus, 1,4-dibenzylcyclen and cyclam are valuable cis-diprotected macrocycles for the preparation of new tetraazamacrocyclic ligands. Diamide intermediates also represent a new class of ligands and the coordination properties of these macrocycles incorporating both amine and amide type nitrogen atoms will be studied. Finally, we have shown that the reactivity of five-membered cyclic aminal compounds forbids the use of this moiety as protecting group in the cyclization reaction, but allows the stereoselective synthesis of new bisaminal compounds.

Experimental Section

General Procedures. ^{1}H (200 or 500 MHz) and ^{13}C NMR (50 or 125 MHz) spectra were recorded on Bruker AC 200 or Bruker DRX-500 spectrometers at the "Centre de Spectroscopie Moléculaire de l'Université de Bourgogne (CSM FR 2604)". Chemical shifts (δ) were measured by reference to the residual protons or carbon signals of the deuterated solvent. IR spectra were recorded on a Bruker IFS 66v spectrometer. MALDI-TOF mass spectra were recorded on a Bruker Daltonics Proflex III device using dithranol as a matrix. The melting points were determined using a Büchi B-545 apparatus and are uncorrected. Elemental analyses were carried out with a Fisons EA 1108 CHNS instrument at the CSM or done at the "Service Central d'Analyses du CNRS" in Vernaison.

X-Ray data collection and structure refinement. Colourless single-crystals of **7a**, **7b, 22a** and **22b,** were obtained from ethanol, THF, dichloromethane and acetone/dichloromethane (50/50) respectively. For compounds **7a**, **7b** and **22b,** data collections were carried out at low temperature (T = 110(2) K) on a Nonius KappaCCD diffractometer equipped with a nitrogen jet stream low-temperature system (Oxford Cryosystems), and for compound **22a** data were collected at room temperature on a Enraf-Nonius CAD4. In all experiments the X-ray source was graphite monochromatized Mo-Kα radiation (λ= 0.71073 Å) from a sealed tube. Intensity data were recorded as φ and ω scans with κ offsets in the former diffractometer, and as a θ/2θ scan mode in the later. No significant intensity decay was observed during data collections. No diffractometer or temperature problems occurred during the experiments. A psi-scan absorption correction[16] was carried out for compound **22a**.

In the case of **7b**, inspection of the X-ray pattern on the collected images indicated a severe twinning, which did not permit to fit the lattice parameters in an initial stage. Thus, using the data reduction software (DENZO program[17]) we omitted a subset of the data, permitting us both to fit good unit-cell parameters and to integrate reflections properly. This procedure led to a completeness of only 52 % up to θ_{max}= 25.0°, and therefore to a quite small ratio $N_{reflections}/N_{parameters}$ = 4.5. In spite of that, the structure could be solved (the best phase set in the solving procedure gave all the positions for the non-H atoms) and the refinement was very stable and fast converged to the final model.

All the structures were solved by direct methods using the SIR92 program.[18] While for **7a**, **7b** and **22b** the refinements were carried out by full-matrix least squares on F^2 using the SHELXL97 program[19] and the complete set of reflections, in the case of **22a** the refinement was done by full-matrix least squares on F using the LSFM OpenMolEN program[20] and the 1220 observed reflections ($I > 3\sigma(I)$). Anisotropic thermal parameters were refined for non-hydrogen atoms in the four structure determinations. Then, hydrogen atoms were located by Fourier synthesis and placed at calculated positions by using a riding model. They were refined with a global isotropic thermal factor in each structural model.

Table 1. Crystal and structure refinement data for compounds **7a**, **7b**, **22a** and **22b**.

Compound	**7a**	**7b**	**22a**	**22b**
Chemical formula	$C_{27}H_{30}N_4$	$C_{29}H_{34}N_4$	$C_{34}H_{38}N_4$	$C_{36}H_{42}N_4$
Formula weight	410.55	438.60	502.71	530.74
Temperature / K	110(2)	110(2)	294(2)	110(2)
Wavelength / Å	0.71073	0.71073	0.71073	0.71073
Crystal system	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic
Space group	$P\ 2_12_12_1$	$P\ 2_12_12_1$	C 2/c	$P\ 2_1$/c
a / Å	5.5430(2)	5.675(1)	21.885(5)	15.1330(2)
b / Å	16.6730(6)	8.873(1)	5.654(1)	5.5580(1)
c / Å	25.2380(12)	49.325(5)	24.591(6)	18.3100(3)
α / °	90	90	90	90
β / °	90	90	109.47(2)	108.087(1)
γ / °	90	90	90	90
Volume / Å^3	2332.46(16)	2483.7(6)	2868.8(12)	1463.94(4)
Z, D_{calc} / Mg m^{-3}	4, 1.16	4, 1.17	4, 1.16	2, 1.20
μ / mm^{-1}	0.070	0.070	0.069	0.071
Crystal size / mm^3	0.20x0.18x0.16	0.24x0.22x0.14	0.33x0.28x0.24	0.25x0.20x0.10
Collected reflections	5215	1634	3271	8511
Unique reflections	3075	1355	3197	5523
R_{int}	0.0591	0.0206	0.0360	0.0310
θ_{max} / °	27.5	25.0	27.3	33.0
Index ranges	0<= h <= 7 0<= k <= 21 -32<= l <= 32	0<= h <= 6 0<= k <= 10 -53<= l <= 58	-27<= h <= 25 -7<= k <= 0 0<= l <= 30	0<= h <= 23 0<= k <= 8 -28<= l <= 26
Data/parameters	3075/282	1355/300	1220/172	5523/182
$R1$, $wR2$[a] ($I > 2\sigma(I)$)	0.0468, 0.0901	0.0341, 0.0745	0.042, 0.054	0.0461, 0.1147
$R1$, $wR2$[a] (all data)	0.0974, 0.1105	0.0406, 0.0786	0.133, 0.148	0.0587, 0.1247
$\Delta\rho_{max}$, $\Delta\rho_{min}$ / eÅ^{-3}	0.189, -0.198	0.121, -0.127	0.134, -0.193	0.394, -0.230

[a]$R1 = \Sigma||F_o-F_c||/\Sigma|F_o|$ and $wR2 = [\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

As far as heavy atoms are not present in the non-centrosymmetric crystal structures of **7a** and **7b**, their absolute structures were not determined and Friedel pairs were merged in both cases.

For **22b**, the first twenty residual peaks observed at the convergence ($0.25 < \Delta\rho_{res} < 0.39$ eÅ^{-3}) correspond to the deformation of the electron distribution in the middle of the covalent bonds and in lone pairs regions.

Table 1 shows crystal data and structure refinement details.

The X-ray diffraction data have been deposited at the Cambridge Crystallographic Data Centre under the registration numbers 295408 (**7a**), 295409 (**7b**), 295410 (**22a**), 295411 (**22b**).

1,4,8,11-Tetraazacyclotetradecane (2b) via the 1,4,8,11-tetraazacyclotetradecane-2,3,9,10-tetraone (1b). A solution of diethyloxalate (9.85 g, 67.4 mmol) in THF (60 mL) was added dropwise to a solution of 1,3-propanediamine (5.0 g, 67.4 mmol) in THF (70 mL) at 0°C and stirred vigorously. The white precipitate formed (7.2 g, 87%) was filtered and washed with cold THF. Under Ar atmosphere, a 1M BH_3/THF solution (6.0 mL, 6.0 mmol) was added dropwise to a suspension of this solid (1.0 g, 3.9 mmol) in THF (50 mL) sonicated with a Sonicator cell disruptor W-375 apparatus (50 KHz). The solution was stirred and sonicated at room temperature for 3 h. After cooling at 0°C, water (20 mL) was added. After evaporation of THF, a 6M HCl solution (50 mL) was added and the solution was heated at reflux for 3 h. After cooling at room temperature, KOH pellets were added (pH > 11), and the solution was extracted 6 times with dichloromethane (100 mL). The combined organic solutions were dried over anhydrous $MgSO_4$ and evaporated to afford **2b** (cyclam) as a white solid (0.17 g, 22%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.73 (4H, q), 2.47 (4H, s), 2.68 (8H, s), 2.75 (8H, t); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 30.1, 49.9, 50.7; MS *m/z*: 201 (M^++1); *Anal.* Calcd. $C_{10}H_{24}N_4$: C, 59.96; H, 12.08; N, 27.97. Found: C, 59.81; H, 11.91; N 28.12.

1,7-Diphenyl-2,6-diazahepta-1,6-diene (3). A solution of benzaldehyde (14.3 g, 134.9 mmol) in ethanol (15 mL) was added dropwise to a solution of 1,3-propanediamine (5.0 g, 67.4 mmol) in refluxing ethanol (100 mL). The mixture was stirred under reflux for 3 h. The solution was evaporated to afford the crude compound **3** as a pale yellow solid (16.8 g, 99%, M.p. 81-83°C); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.14 (2H, q), 3.73 (4H, t), 7.38 (10H, m), 7.73 (2H, s); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 32.1, 59.3, 128.2, 128.7, 130.7, 136.4, 161.4; IR (KBr, $\nu_{C=N}$ cm^{-1}) 1650; MS *m/z*: 251 (M^++1); *Anal.* Calcd. $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 82.10; H, 7.04; N, 11.66.

***N,N'*-Dibenzyl-1,3-propanediamine (4).** An excesss of sodium borohydride (6.0 g, 159.6 mmol) was added to a solution of **3** (10.0 g, 39.9 mmol) in ethanol (150 mL). The mixture was stirred at room temperature for 2 h, cooled to 0°C and 15 mL of water were added. The solution was evaporated and the residue was dissolved in the minimum amount of water. The aqueous phase was extracted 6 times with dichloromethane (100 mL). The combined organic solutions were dried over anhydrous $MgSO_4$ and evaporated to give **4** as a colorless oil (8.1 g, 80%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.73 (2H, q), 2.01 (2H, s), 2.70 (4H, t), 3.78 (4H, s), 7.29 (10H, m);

^{13}C-NMR (50 MHz, $CDCl_3$) δ 30.3, 48.1, 54.2, 126.0, 128.2, 128.7, 140.6; MS *m/z*: 254 (M^+); *Anal.* Calcd. $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found: C, 80.69; H, 8.04; N, 11.46.

***N,N'*-Dibenzyl-1,4-diazacycloheptane-2,3-dione (5).** A solution of diethyloxalate (11.5 g, 7.9 mmol) in ethanol (30 mL) was added dropwise to a solution of **4** (2.0 g, 7.9 mmol) in ethanol (50 mL) at room temperature. The solution was stirred at room temperature for 12 h and then evaporated. The white solid obtained was washed with cold ethanol and recrystallized from ethanol to give **5** as white spangles (2.0 g, 83%, M.p. = 156°C). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.27 (2H, q), 3.27 (4H, t), 4.59 (4H, s), 7.28 (10H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 27.9, 43.8, 50.0, 127.8, 128.4, 130.1, 137.1, 164.9; IR (KBr, $\nu_{C=O}$ cm^{-1}) 1670; MS *m/z*: 309 (M^++1); *Anal.* Calcd. $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.09; H, 6.79; N, 9.32.

***N,N'*-Dibenzyl-1,4-diazacycloheptane (6).** Under Ar atmosphere, a 1M BH_3/THF solution (13 mL, 13 mmol) was added dropwise to a solution of **5** (1.0 g, 3.25 mmol) in anhydrous THF (40 mL). The solution was heated at reflux for 1 h. After cooling at 0°C, water (20 mL) was added. THF was evaporated, a 6M HCl solution (50 mL) was added and the solution was heated at reflux for 3 h. After cooling at room temperature, KOH pellets were added (pH > 11), and the solution was extracted 6 times with dichloromethane (100 mL). The combined organic solutions were dried over anhydrous $MgSO_4$ and evaporated to afford **6** as a colorless oil (0.88 g, 97%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.77 (2H, q), 2.68 (4H, s), 2.77 (4H, t), 3.65 (4H, s), 7.28 (10H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 28.2, 55.0, 55.6, 63.3, 127.4, 128.7, 129.4, 140.3; MS *m/z*: 280 (M^+); *Anal.* Calcd. $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 10.00. Found: C, 81.89; H, 8.28; N, 9.82.

2-Phenyl-1,3-bis[(3'-aza-4'-phenyl)-but-3'-enyl]-1,3-imidazolidine (7a). A solution of benzaldehyde (21.8 g, 205 mmol) in anhydrous ethanol (35 mL) was added dropwise to a solution of *N,N'*-triethylenetetraamine (10.0 g, 68 mmol) in refluxing anhydrous ethanol (110 mL). The mixture was stirred under reflux for 12 h. The solution was evaporated to afford a yellow oil. Cold ethanol (10 mL) was added to the crude product and the white precipitate was filtered and washed with cold acetone to give **7a** as a white solid (26.5 g, 94%, M.p. = 87-88°C) which can be recrystallized in THF or used without further purification in the following steps. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.5-2.8 (6H, m), 2.5-3.7 (7H, m), 7.2-7.5 (15H, m), 7.7 (2H, s); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 51.7, 53.2, 60.4, 89.4, 127.9, 128.3, 128.4, 129.3, 129.5, 130.4, 136.0, 140.0, 161.7; IR (KBr, $\nu_{C=N}$ cm^{-1}) 1650; MS *m/z*: 410 (M^+); *Anal.* Calcd. $C_{27}H_{30}N_4$: C, 78.99; H, 7.37; N, 13.65. Found: C, 79.52; H, 7.23; N, 14.01.

2-Phenyl-1,3-bis[(4'-aza-5'-phenyl)-pent-4'-enyl]-1,3-imidazolidine (7b). According to the procedure used for the synthesis of **7a**, a solution of benzaldehyde (18.2 g, 171 mmol) in anhydrous ethanol (30 mL) and a solution of *N,N'*-bis-(3-aminopropyl)-ethylenediamine (10.0 g, 57 mmol) in anhydrous ethanol (100 mL) were reacted to afford **7b** as a white solid (24.1 g, 96%, M.p. = 100-101°C) which can be recrystallized in abs. ethanol or used without further purification in the following steps. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.76 (4H, m), 2.22 (2H, m), 2.45 (2H, m), 2.55 (2H, m), 3.35 (2H, m), 3.45 (2H, m), 3.75 (2H, m), 3.80 (1H, s), 7.25-7.68 (15H, m), 8.02 (2H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 29.5, 50.4, 50.9, 59.2, 90.0, 125.2, 126.6,

127.4, 128.3, 129.4, 130.5, 136.3, 140.8, 161.3; IR (KBr, $\nu_{C=N}$ cm^{-1}) 1650; MS *m/z*: 438 (M^+); *Anal.* Calcd. $C_{29}H_{34}N_4$: C, 79.41; H, 7.81; N, 12.77. Found: C, 79.35; H, 7.83; N, 12.52.

2-(2-Pyridyl)-1,3-bis[4'-aza-5'-(2-pyridyl)-pent-4'-enyl]-1,3-imidazolidine (13a). According to the procedure used for the synthesis of **7a**, a solution of 2-pyridinecarboxaldehyde (18.4 g, 172 mmol) in anhydrous ethanol (30 mL) and a solution of *N*,*N*'-bis-(3-aminopropyl)-ethylenediamine (10.0 g, 57 mmol) in anhydrous ethanol (100 mL) were reacted to afford **13a** as a pale yellow solid (25.1 g, 99%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.63 (4H, q), 2.01-2.52 (6H, m), 3.22-3.78 (7H, m), 6.75-8.43 (14H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 29.4, 50.7, 51.1, 58.9, 90.4, 121.2, 122.9, 124.6, 136.5, 136.7, 147.9, 148.2, 149.3, 154.4, 161.6, 161.9; IR (KBr, $\nu_{C=N}$ cm^{-1}) 1650; MS *m/z*: 442 (M^++1); *Anal.* Calcd. $C_{26}H_{31}N_7$: C, 70.72; H, 7.08; N, 22.20. Found: C, 70.32; H, 7.53; N, 23.01.

2-(3-Bromophenyl)-1,3-bis[4'-aza-5'-(3-bromophenyl)-pent-4'-enyl]-1,3-imidazolidine (13b). According to the procedure used for the synthesis of **7a**, a solution of 3-bromobenzaldehyde (31.8 g, 172 mmol) in anhydrous ethanol (30 mL) and a solution of *N*,*N*'-bis-(3-aminopropyl)-ethylenediamine (10.0 g, 57 mmol) in anhydrous ethanol (100 mL) were reacted to afford **13b** as a pale yellow oil (38.2 g, 99%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.73 (4H, q), 2.15-2.66 (8H, m), 3.25-3.42 (5H, m), 6.91-7.92 (14H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 29.1, 50.1, 50.9, 58.6, 89.3, 122.3, 122.8, 126.8, 128.1, 129.6, 130.1, 130.7, 131.5, 132.1, 133.3, 138.2, 143.8, 159.6; IR (KBr, $\nu_{C=N}$ cm^{-1}) 1650; MS *m/z*: 673 (M^++1); *Anal.* Calcd. $C_{29}H_{31}N_4Br_3$: C, 51.58; H, 4.63; N, 8.30. Found: C, 52.21; H, 4.83; N, 8.61.

2-Phenyl-1,3-bis[4'-aza-5'-(phenyl)-pentyl]-1,3-imidazolidine (8b). According to the procedure used for the synthesis of **4**, sodium borohydride (3.5 g, 91.2 mmol) and a solution of **7b** (10.0 g, 23 mmol) in ethanol (100 mL) were reacted to afford **8b** as a colorless oil (9.9 g, 98%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.38 (2H, s), 1.57 (4H, m), 2.10-2.64 (12H, m), 3.41 (1H, s), 3.64 (4H, s), 7.24 (15H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 28.5, 47.7, 50.9, 50.9, 54.1, 90.2, 125.4, 125.9, 126.8, 128.1, 129.5, 131.5, 134.9, 140.5; MS *m/z*: 443 (M^++1); *Anal.* Calcd. $C_{29}H_{38}N_4$: C, 78.69; H, 8.65; N, 12.66. Found: C, 79.01; H, 8.99; N, 12.95.

2-(2-Pyridyl)-1,3-bis[4'-aza-5'-(2-pyridyl)-pentyl]-1,3-imidazolidine (14a). According to the procedure used for the synthesis of **4**, sodium borohydride (3.42 g, 90.4 mmol) and a solution of **13a** (10.0 g, 22.6 mmol) in ethanol (100 mL) were reacted to afford **14a** as a pale yellow oil (9.0 g, 89%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.47 (4H, q), 1.72 (2H, s), 2.01-2.75 (10H, m), 3.11-3.39 (2H, m), 3.55-3.83 (5H, m), 6.82-8.42 (12H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 28.8, 47.8, 51.1, 51.3, 55.4, 90.5, 122.5, 122.7, 122.9, 123.1, 136.5, 136.7, 148.1, 149.2, 159.9, 162.5; MS *m/z*: 446 (M^++1); *Anal.* Calcd. $C_{26}H_{35}N_7$: C, 70.08; H, 7.92; N, 22.00. Found: C, 70.62; H, 7.43; N, 21.81.

2-(3-Bromophenyl)-1,3-bis[4'-aza-5'-(3-bromophenyl)-pentyl]-1,3-imidazolidine (14b). According to the procedure used for the synthesis of **4**, sodium borohydride (2.25 g, 59.6 mmol) and a solution of **13b** (10.0 g, 14.9 mmol) in ethanol (100 mL) were reacted to afford **14b** as a pale yellow oil (8.2 g, 82%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.52 (4H, q), 1.89 (2H, s), 2.12-2.71 (12H, m), 3.39 (1H, s), 3.58 (4H, s), 7.0-7.5 (12H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 28.4, 47.5,

50.8, 50.9, 53.5, 89.3, 122.4, 122.5, 126.6, 126.7, 127.9, 129.9, 130.0, 131.1, 131.7, 132.0, 143.1, 143.8; MS *m/z*: 677 (M^++1); *Anal.* Calcd. $C_{29}H_{35}N_4Br_3$: C, 51.27; H, 5.19; N, 8.25. Found: C, 52.01; H, 5.88; N, 8.51.

1,10-Dibenzyl-1,4,7,10-tetraazadecane (9a). An excesss of sodium borohydride (3.5 g, 91.2 mmol) was added to a solution of **7a** (10.0 g, 24 mmol) in ethanol (100 mL). The mixture was stirred at room temperature for 2 h, cooled to 0°C and a 6M HBr solution (30 mL) was added. The white solid formed was filtered, washed with cold ethanol and dissolved in the minimum amount of water. KOH pellets were added (pH > 11) and the solution was extracted 6 times with dichloromethane (100 mL). The combined organic solutions were dried over anhydrous $MgSO_4$ and evaporated to afford **9a** as a pale yellow oil (4.55 g, 58%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.60 (4H, s), 2.55 (4H, s), 2.59 (8H, m), 3.63 (4H, s), 7.10 (10H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 48.8, 49.3, 49.3, 53.9, 126.9, 128.1, 128.4, 140.5; MS *m/z*: 326 (M^+); *Anal.* Calcd. $C_{20}H_{30}N_4$: C, 73.58; H, 9.26; N, 17.16. Found: C, 74.21; H, 9.82; N, 16.67.

1,12-Dibenzyl-1,5,8,12-tetraazadodecane (9b). A 6M HBr solution (30 mL) was added to a solution of **8b** (9.9 g, 22.3 mmol) in ethanol (100 mL). The white solid formed was filtered, washed with cold ethanol and dissolved in the minimum amount of water. KOH pellets were added (pH > 11) and the solution was extracted 6 times with dichloromethane (100 mL). The combined organic solutions were dried over anhydrous $MgSO_4$ and evaporated to afford **9b** as a colorless oil (7.6 g, 96%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.28 (4H, s), 1.60 (4H, q), 2.57 (4H, t), 2.61 (4H, t), 2.64 (4H, s), 3.69 (4H, s), 7.22 (10H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 30.4, 47.9, 48.5, 49.6, 54.1, 126.8, 128.1, 128.4, 140.6; MS *m/z*: 354 (M^+); *Anal.* Calcd. $C_{22}H_{34}N_4$: C, 74.53; H, 9.67; N, 15.80. Found: C, 74.08; H, 9.82; N, 16.02.

1,14-Bis(2-pyridyl)-2,6,9,13-tetraazatetradecane (15a). According to the procedure used for the synthesis of **9b**, a 6M HBr solution (15 mL) and a solution of **14a** (5.0 g, 11.2 mmol) in ethanol (50 mL) were reacted to afford a mixture (1/1 ratio) of **15a** and 1,14-bis(2-pyridyl)-6-(2-pyridylmethyl)-2,6,9,13-tetraazatetradecane (**16a**) which were separated by chromatography on alumina [CH_2Cl_2 then CH_2Cl_2-MeOH (100:5)]. The compound **15a** was obtained as the sole product when the reaction was performed in refluxing water (3.6 g, 89%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.59 (4H, q), 2.26 (4H, s), 2.53 (4H, t), 2.56 (4H, s), 2.62 (4H, t), 3.78 (4H, s), 6.8-8.5 (8H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 30.3, 47.9, 48.2, 49.4, 55.2, 121.9, 122.3, 136.5, 149.2; 159.7; MS *m/z*: 356 (M^+); *Anal.* Calcd. $C_{20}H_{32}N_6$: C, 67.38; H, 9.05; N, 23.57. Found: C, 68.21; H, 9.53; N, 22.91.

1,14-Bis(3-bromophenyl)-2,6,9,13-tetraazatetradecane (15b). According to the procedure used for the synthesis of **9b**, a 6M HBr solution (15 mL) and a solution of **14b** (5.0 g, 7.4 mmol) in ethanol (50 mL) were reacted to afford **15b** as a pale yellow oil (3.0 g, 80%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.40 (4H, s), 1.61 (4H, q), 2.56 (4H, t), 2.57 (4H, t), 2.63 (4H, s), 3.68 (4H, s), 7.1-7.5 (8H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ30.3, 47.9, 48.5, 49.6, 53.5, 122.6, 126.7, 129.9, 130.0, 131.1, 143.1; MS *m/z*: 610 (M^+); *Anal.* Calcd. $C_{22}H_{32}N_4Br_2$: C, 51.58; H, 6.30; N, 10.94. Found: C, 52.20; H, 6.53; N, 11.32.

5,8-Dibenzyl-1,12-diphenyl-2,5,8,11-tetraazatetradodecane-1,11-diene (10a). Benzyl bromide (8.34 g, 48.7 mmol) was added dropwise to a solution of **7a** (10.0 g, 24.3 mmol) and K_2CO_3 (20 g, 145 mmol) in refluxing acetonitrile (200 mL). The mixture was stirred under reflux for 12 h. The solid was filtered off and the solution was evaporated to afford a yellow oil which was chromatographed on alumina [CH_2Cl_2 then CH_2Cl_2-MeOH (100:5)] to give **10a** as a colorless oil (8.71 g, 71%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.71 (4H, s), 2.81 (4H, t), 3.52 (4H, t), 3.66 (4H, s), 7.2-8.2 (20H, m), 8.31 (2H, s); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 52.7, 55.1, 59.6, 60.0, 126.9, 128.2, 128.7, 128.9, 129.1, 129.9, 136.4, 139.9, 161.9; IR (neat, $\nu_{C=N}$ cm^{-1}) 1650; MS *m/z*: 503 (M^++1); *Anal.* Calcd. $C_{34}H_{38}N_4$: C, 81.24; H, 7.62; N, 11.15. Found: C, 79.92; H, 7.17; N, 10.89.

6,9-Dibenzyl-1,14-diphenyl-2,6,9,13-tetraazatetradecane-1,13-diene (10b). According to the procedure used for the synthesis of **10a**, benzyl bromide (11.7 g, 68 mmol) and a solution of **7b** (15.0 g, 34 mmol) K_2CO_3 (30 g, 220 mmol) in acetonitrile (300 mL) were reacted to afford **10b** as a colorless oil (15.9 g, 88%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.83 (4H, q), 2.49 (4H, t), 2.58 (4H, s), 3.56 (4H, s), 3.57 (4H, t), 7.1-7.9 (20H, m), 8.02 (2H, s); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 28.4, 52.0, 52.1, 59.0, 59.6, 126.8, 128.1, 128.2, 128.6, 128.9, 130.5, 136.4, 139.9, 161.1; IR (neat, $\nu_{C=N}$ cm^{-1}) 1650; MS *m/z*: 530 (M^+); *Anal.* Calcd. $C_{36}H_{42}N_4$: C, 81.47; H, 7.98; N, 10.56. Found: C, 81.01; H, 8.31; N, 11.20.

4,7-Dibenzyl-1,4,7,10-tetraazadecane (11a). According to the procedure used for the synthesis of **9b**, a 6M HBr solution (15 mL) and a solution of **10a** (5.0 g, 10 mmol) in ethanol (50 mL) were reacted to afford **11a** as a pale yellow oil (2.31 g, 71%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.49 (4H, s), 2.43 (4H, t), 2.54 (4H, s), 2.64 (4H, t), 3.49 (4H, s), 7.22 (10H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 39.8, 52.3, 57.4, 59.3, 127.0, 128.3, 128.9, 139.6; MS *m/z*: 326 (M^+); *Anal.* Calcd. $C_{20}H_{30}N_4$: C, 73.58; H, 9.26; N, 17.16. Found: C, 73.10; H, 8.86; N, 16.82.

5,8-Dibenzyl-1,5,8,12-tetraazadodecane (11b). According to the procedure used for the synthesis of **9b**, a 6M HBr solution (15 mL) and a solution of **10b** (5.0 g, 9.4 mmol) in ethanol (50 mL) were reacted to afford **11b** as a pale yellow oil (3.32 g, 99%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.53 (4H, q), 1.68 (4H,s), 2.40 (4H, t), 2.52 (4H, s), 2.62 (4H, t), 3.49 (4H, s), 7.21 (10H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 31.1, 40.5, 51.9, 51.9, 59.2, 126.9, 128.2, 128.9, 139.9; MS *m/z*: 354 (M^+); *Anal.* Calcd. $C_{22}H_{34}N_4$: C, 74.53; H, 9.67; N, 15.80. Found: C, 75.21; H, 9.97; N, 16.22.

1,4,7,10-Tetrabenzyl-1,4,7,10-tetraazadecane (12a). An excesss of sodium borohydride (1.51 g, 39.8 mmol) was added to a solution of **10a** (5.0 g, 10 mmol) in ethanol (50 mL). The mixture was stirred under reflux for 3 h, cooled to 0°C and 15 mL of water were added. The solution was evaporated and the residue was dissolved in the minimum amount of water. The aqueous phase was extracted 6 times with dichloromethane (100 mL). The combined organic solutions were dried over anhydrous $MgSO_4$ and evaporated to give **12a** as a pale yellow oil (4.7 g, 93%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.15 (2H, s), 2.58 (4H, s), 2.62 (4H, t), 3.53 (4H, s), 3.63 (4H, t), 3.69 (4H, s); 7.3 (20H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 46.8, 52.3, 53,9, 54,3, 59.4, 127.0, 127.2, 128.3, 128.5, 128.9, 130.1, 139.7, 140.5; MS *m/z*: 507 (M^++1); *Anal.* Calcd. $C_{34}H_{42}N_4$: C, 80.59; H, 8.35; N, 11.06. Found: C, 80.66; H, 8.48; N, 10.87.

1,5,8,12-Tetrabenzyl-1,5,8,12-tetraazadodecane (12b). According to the procedure used for the synthesis of **12a**, sodium borohydride (2.85 g, 75 mmol) and a solution of **10b** (10.0 g, 18 mmol) in ethanol (100 mL) were reacted to afford **12b** as a pale yellow oil (7.96 g, 79%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.71 (4H, q), 2.21 (2H,s), 2.49 (4H, t), 2.58 (4H, s), 2.63 (4H, t), 3.55 (4H, s), 3.75 (4H, s), 7.29 (20H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 27.5, 48.0, 52.0, 52.7, 54.3, 59.2, 126.9, 127.2, 128.2, 128.4, 128.9, 129.1, 139.9, 140.3; MS *m/z*: 535 (M^++1); *Anal.* Calcd. $C_{36}H_{46}N_4$: C, 80.85; H, 8.67; N, 10.48. Found: C, 81.38; H, 9.01; N, 10.51.

1,4-Dibenzyl-1,4,7,10-tetraazacyclododecane-2,3-dione (18a). A solution of diethyloxalate (4.48 g, 30 mmol) in anhydrous ethanol (20 mL) was added dropwise to a solution of **9a** (10.0 g, 30 mmol) in refluxing anhydrous ethanol (250 mL). The solution was stirred under reflux for 12 h. The white solid formed was filtered and washed with ethanol to give **18a** (2.38 g, 20%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.80 (2H, s), 3.42 (4H, t), 3.52 (4H, t), 3.66 (4H, s), 4.62 (4H, s), 7.26 (10H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 43.3, 43.8, 44.0, 50.6, 128.4, 129.0, 135.6, 139.5, 160.1; IR (KBr, $\nu_{C=O}$ cm^{-1}) 1670; MS *m/z*: 381 (M^++1); *Anal.* Calcd. $C_{22}H_{28}N_4O_2$: C, 69.45; H, 7.42; N, 14.72. Found: C, 68.70; H, 7.22; N, 14.37.

1,4-Dibenzyl-1,4,8,11-tetraazacyclotetradecane-2,3-dione (18b). According to the procedure used for the synthesis of **18a**, a solution of diethyloxalate (4.13 g, 28 mmol) in anhydrous ethanol (20 mL) and a solution of **9b** (10.0 g, 28 mmol) in anhydrous ethanol (250 mL) were reacted to afford **18b** as a white solid (3.42 g, 30%). ^{1}H-NMR (200 MHz, D_2O) δ 1.65 (4H, q), 3.32 (4H, t), 3.36 (4H, t), 3.62 (4H, s), 4.61 (4H, s), 7.32 (10H, m); ^{13}C-NMR (50 MHz, D_2O) δ 27.5, 43.2, 44.4, 44.8, 49.6, 128.3, 128.6, 129.0, 136.4, 161.1; IR (KBr, $\nu_{C=O}$ cm^{-1}) 1670; MS *m/z*: 408 (M^+); *Anal.* Calcd. $C_{24}H_{32}N_4O_2$: C, 70.56; H, 7.89; N, 13.71. Found: C, 71.01; H, 7.71; N, 13.50.

1,4-Bis[4'-aza-5'-phenylpentyl]-piperazine-2,3-dione (17b). The filtrate obtained after filtration of **18b** in the previous synthesis was evaporated to afford **17b** as a pale yellow oil (8.0 g, 70%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.71 (4H, q), 1.96 (2H, s), 2.57 (4H, t), 3.33 (4H, s), 3.45 (4H, t), 3.70 (4H, s), 7.24 (10H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 27.5, 44.6, 45.4, 46.0, 54.0, 127.0, 128.3, 128.5, 140.2, 157.5; IR (KBr, $\nu_{C=O}$ cm^{-1}) 1670; MS *m/z*: 408 (M^+); *Anal.* Calcd. $C_{24}H_{32}N_4O_2$: C, 70.56; H, 7.89; N, 13.71. Found: C, 70.18; H, 7.38; N, 14.21.

1,4,7,10-Tetrabenzyl-1,4,7,10-tetraazacyclododecane-2,3-dione (20a). A solution of diethyloxalate (1.15 g, 7.9 mmol) in anhydrous ethanol (20 mL) was added to a solution of **12a** (4.0 g, 7.9 mmol) in anhydrous ethanol (100 mL). The solution was stirred under reflux for 6 days and then evaporated. The residual colorless oil was dissolved in the minimum amount of ethanol and diethylether was added. The white solid formed was filtered, washed with diethylether to afford **20a** (2.21 g, 50%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.50 (4H, s), 2.52 (4H, t), 2.92 (4H, t), 3.52 (4H, s), 3.96 (4H, s), 7.25 (20H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 44.0, 49.9, 50.9, 51.9, 57.3, 126.9, 127.1, 128.8, 129.1, 129.6, 130.2, 138.3, 138.7, 163.3; IR (KBr, $\nu_{C=O}$ cm^{-1}) 1670; MS *m/z*: 560 (M^+); *Anal.* Calcd. $C_{36}H_{40}N_4O_2$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.82; H, 7.29; N, 10.07.

1,4,8,11-Tetrabenzyl-1,4,8,11-tetraazacyclotetradecane-2,3-dione (20b). According to the procedure used for the synthesis of **20a**, a solution of diethyloxalate (1.37 g, 9.3 mmol) in anhydrous ethanol (20 mL) and a solution of **12b** (5.0 g, 9.3 mmol) in anhydrous ethanol (100 mL) were reacted to afford **20b** as a white solid (4.13 g, 75%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.81 (4H, q), 2.41 (4H, t), 2.42 (4H, s), 2.84 (4H, t), 3.56 (4H, s), 3.97 (4H, s), 7.24 (20H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 23.9, 45.4, 50.9, 51.1, 51.4, 59.3, 127.1, 127.2, 128.3, 128.9, 130.0, 131.7, 138.9, 139.3, 161.1; IR (KBr, $\nu_{C=O}$ cm^{-1}) 1670; MS *m/z*: 588 (M^+); *Anal.* Calcd. $C_{38}H_{44}N_4O_2$: C, 77.52; H, 7.53; N, 9.52. Found: C, 76.29; H, 7.83; N, 9.01.

1,4-Dibenzyl-1,4,7,10-tetraazacyclododecane (19a). Under Ar atmosphere, a 1M BH_3/THF solution (23.2 mL, 23.2 mmol) was added to a solution of **18a** (2.2 g, 5.8 mmol) in anhydrous THF (60 mL). The solution was heated at reflux for 12 h. After cooling at 0°C, a water/THF (1/3) solution (30 mL) was added to quench excess borane. THF was evaporated, a 6M HCl solution (100 mL) was added and the solution was heated at 100°C for 3 h. After cooling at room temperature, KOH pellets were added (pH > 11), and the solution was extracted 6 times with dichloromethane (100 mL). The combined organic solutions were dried over anhydrous $MgSO_4$ and evaporated to afford **19a** as a colorless oil (1.59 g, 78%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.32 (4H, t), 2.39 (2H, s), 2.60 (4H, t), 2.74 (4H, s), 3.01 (4H, s), 3.60 (4H, s), 7.20 (10H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 45.6, 48.1, 51.3, 52.0, 57.8, 128.1, 128.5, 129.3, 140.5; MS *m/z*: 352 (M^+); *Anal.* Calcd. $C_{22}H_{32}N_4$: C, 74.96; H, 9.15; N, 15.89. Found: C, 74.21; H, 9.01; N, 15.21.

1,4-Dibenzyl-1,4,8,11-tetraazacyclotetradecane (19b). According to the procedure used for the synthesis of **19a**, a 1M BH_3/THF solution (29.2 mL, 29.2 mmol) and a solution of **18b** (3.0 g, 7.3 mmol) in anhydrous THF (75 mL) were reacted to afford **19b** as a colorless oil (2.44 g, 88%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.71 (4H, q), 2.01 (2H, s), 2.57 (4H, t), 2.59 (4H, s), 2.61 (4H, t), 3.13 (4H, s), 3.50 (4H, s), 7.26 (10H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 27.7, 49.6, 51.8, 52.7, 54.1, 60.9, 126.9, 128.2, 128.9, 139.6; MS *m/z*: 381 (M^++1); *Anal.* Calcd. $C_{24}H_{36}N_4$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.26; H, 9.45; N, 14.21.

1,4,7,10-Tetrabenzyl-1,4,7,10-tetraazacyclododecane (21a). According to the procedure used for the synthesis of **19a**, a 1M BH_3/THF solution (14.4 mL, 14.4 mmol) and a solution of **20a** (2.0 g, 3.6 mmol) in anhydrous THF (40 mL) were reacted to afford **21a** as a white solid (1.12 g, 59%, M.p. = 140-142°C). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.71 (16H, s), 3.47 (8H, s), 7.2-7.4 (20H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 46.6, 59.4, 126.2, 127.9, 128.8, 139.8; MS *m/z*: 533 (M^++1); *Anal.* Calcd. $C_{36}H_{44}N_4$: C, 81.16; H, 8.32; N, 10.52. Found: C, 80.42; H, 8.21; N, 10.08.

1,4,8,11-Tetrabenzyl-1,4,8,11-tetraazacyclotetradecane (21b). According to the procedure used for the synthesis of **19a**, a 1M BH_3/THF solution (34.8 mL, 34.8 mmol) and a solution of **20b** (5.0 g, 8.7 mmol) in anhydrous THF (80 mL) were reacted to afford **21b** as a white solid (4.41 g, 89%, M.p. = 152-154°C). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.76 (4H, q), 2.54 (8H, t), 2.63 (8H, s), 3.46 (8H, s), 7.26 (20H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 23.8, 50.5, 51.5, 59.5, 126.8, 128.1, 129.0, 140.1; MS *m/z*: 561 (M^++1); *Anal.* Calcd. $C_{38}H_{48}N_4$: C, 81.38; H, 8.63; N, 9.99. Found: C, 82.12; H, 8.75; N, 10.38.

1,4,7,10-Tetraazacyclododecane (2a) via the 1,4-dibenzyl-1,4,7,10-tetraazacyclododecane (19a). Activated Pd/C (1.0 g) was added to a solution of **19a** (1.0 g, 2.8 mmol) in ethanol (40 mL). The mixture was stirred under H_2 atmosphere for 12 h. After filtration over a celite plug, the solution was evaporated to give **2a** (cyclen) as a white solid (0.39 g, 81%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.12 (4H, s), 3.67 (16H, s); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 46.9; MS *m/z*: 173 (M^++1); *Anal.* Calcd. $C_8H_{20}N_4$: C, 55.78; H, 11.70; N, 32.52. Found: C, 55.02; H, 11.58; N, 31.97.

1,4,8,11-tetraazacyclotetradecane (2b) via the 1,4-dibenzyl-1,4,8,11-tetraazacyclotetradecane (19b). According to the procedure used for the synthesis of **2a**, activated Pd/C (3.0 g) and a solution of **19b** (4.0 g, 10.5 mmol) in ethanol (100 mL) were reacted to afford **2b** (cyclam) as a white solid (1.93 g, 92%).

1,2-Bis[(3-benzyl-2-phenyl)-1,3-imidazolidyl]ethane (22a). According to the procedure used for the synthesis of **4**, sodium borohydride (0.43 g, 11.4 mmol) and a solution of **7a** (1.0 g, 2.85 mmol) in ethanol (20 mL) were reacted to afford a colorless oil. The white solid formed upon addition of ethanol (15 mL) to this oil was filtrated and washed with cold ethanol to give **22a** (0.71 g, 50%, M.p. = 182°C) which can be recrystallized from dichloromethane. The oil isolated upon evaporation of the filtrate was identified as **9a**. ^{1}H-NMR (500 MHz, C_6D_6) δ 2.11-2.45 (6H, m), 2.61-2.85 (2H, m), 2.80-3.35 (6H, m), 3.51 (2H, d), 3.75 (2H, d), 7.0-7.7 (20H, m); ^{13}C-NMR (125 MHz, C_6D_6) δ 52.0, 52.2, 52.3, 58.1, 89.7, 127.0, 128.4, 128.6, 128.7, 128.9, 129.9, 140.1, 141.9; MS *m/z*: 503 (M^++1); *Anal.* Calcd. $C_{34}H_{38}N_4$: C, 81.24; H, 7.62; N, 11.15. Found: C, 80.92; H, 7.78; N, 11.00.

1,2-Bis[(3-benzyl-2-phenyl)-1,3-pyrimidinyl]ethane (22b). According to the procedure used for the synthesis of **18a**, a solution of diethyloxalate (0.66 g, 4.5 mmol) in anhydrous ethanol (5 mL) and a solution of **8b** (2.0 g, 4.5 mmol) in anhydrous ethanol (25 mL) were reacted to afford **22b** as a white solid (1.18 g, 50%) which can be recrystallized in acetone/dichloromethane (50/50). The oil isolated upon avaporation of the filtrate was identified as **17b**. ^{1}H-NMR (500 MHz, C_6D_6) δ 1.21 (4H, m), 1.80-2.00 (4H, m), 2.00-2.10 (2H, m), 2.62 (2H, d), 2.76 (2H, d), 2.83-2.86 (2H, m), 2.97 (2H, m), 3.55 (2H, s), 3.71 (2H, d), 7.0-7.7 (20H, m); ^{13}C-NMR (125 MHz, C_6D_6) δ 24.9, 51.7, 52.4, 52.6, 58.7, 88.7, 127.0, 128.4, 128.5, 129.1, 130.2, 130.3, 140.4, 142.9; MS *m/z*: 530 (M^+); *Anal.* Calcd. $C_{36}H_{42}N_4$: C, 81.47; H, 7.98; N, 10.56. Found: C, 81.07; H, 7.99; N, 10.53.

Acknowledgements

This work was supported through grants from the Conseil Régional de Bourgogne, Air Liquide SA, the CNRS and the French Ministry for Research.

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