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Regioselective N-Functionalization of Tetraazacycloalkanes

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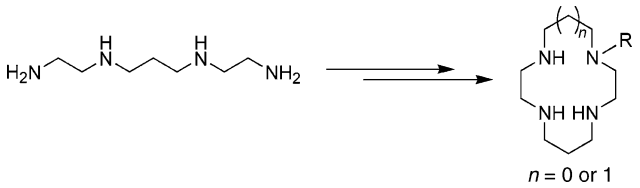

Bisaminal type compounds obtained by condensation of pyruvic aldehyde with the suitable open-chain tetraamine followed by cyclization with either dibromoethane or dibromopropane can be regioselectively quaternized by a wide range of alkylating agents. Removal of the bisaminal bridge yields the monosubstituted tetraazamacrocycle or bismacrocycle. Further functionalization allows the preparation of bifunctional ligands or trisubstituted macrocycles. The structure of six compounds was solved by X-ray diffraction, and the unexpected results are rationalized according to the molecular modeling calculations.

Introduction

Cyclic tetraamines have known a growing interest owing to their coordination properties and their wide range of applications.[1−7] The affinity of the macrocycle toward a specific guest, a metallic cation in most cases, might be tuned by varying the nature, the number, and the relative positions of the pendant arms on the nitrogen atoms. N-Functionalization with four identical pendant arms is straightforward. However, the preparation of only partially functionalized macrocycles is more synthetically demanding.[8] There is a significant interest in such ligands since further functionalization makes access to bifunctional chelating agents (BFCs or BCAs).[9] Indeed, macrocyclic amines bearing two kinds of functional groups, for both metal coordination and immobilization on a solid support or on a monoclonal antibody, have attracted special attention in recent years. Mono-N-functionalization is difficult to accomplish without resorting to the use of a large excess of the initial unsubstituted macrocycle. Different methods involve the protection of three secondary amines with protecting groups such as *tert*-butyloxycarbonyl (Boc)[10] or tosyl groups (Ts),[11] especially for preparing bismacrocycles. Another approach is to take advantage of the coordinating properties of the cyclic amine for the discrimination of one nitrogen atom over the three other ones. To this end, boron, phosphoryl, trimethylsilyl entities as well as metal carbonyls ($M(CO)_6$ where M = Cr, Mo, or W) have been utilized.[12,13] However, all of these methods are based on protection/deprotection strategies starting from the costly

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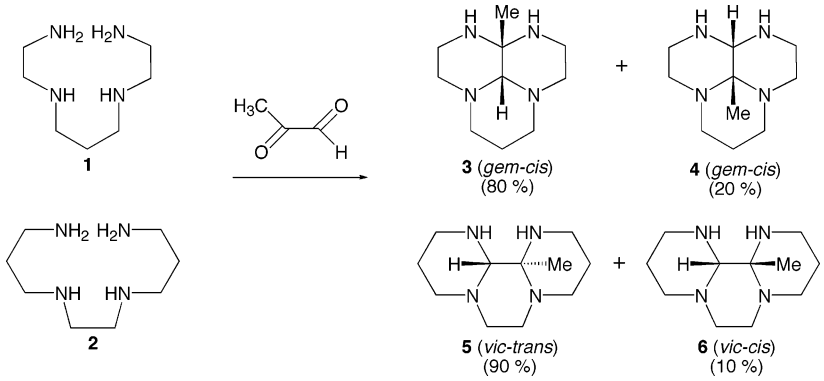
SCHEME 1



initial unsubstituted macrocycle. These drawbacks prompted us to develop new methods in regard to the two important concepts in synthetic efficiency: selectivity and atom economy.[14] The new syntheses should proceed in a minimum number of steps with high yields, as broad as possible regarding the nature of the macrocycle and the pendant arms. We have recently reported in a short communication the synthesis of selectively mono-N-benzylated cyclam and 1,4,7,10-tetraazacyclotridecane by using a bisaminal moiety acting both as a template and as a protecting group.[15] In this work, we describe the synthesis of various monofunctionalized macrocycles and bismacrocycles. The selectivity of the reaction of two linear tetraamines with pyruvic aldehyde, the cyclization of the bisaminal intermediates with biselectrophilic reagents, and the quaternization of the protected macrocycles are discussed on the basis of X-ray structure determinations and molecular modeling calculations.

Results and Discussion

Synthesis. First, we have studied the condensation of pyruvic aldehyde with linear tetraamines **1** and **2** (Scheme 1). Several isomers can be theoretically expected, compounds of *vic* type and more fused sytems called *gem* forms in which one of the two aminal-type carbon atoms is common to the three cycles.[16,17] Because of the dissymmetry of pyruvic aldehyde, two different *gem*-type compounds exist depending on the relative position of the methyl group. In addition, different stereoisomers can be formed for each of these compounds. The hydrogen atom and the methyl group of the bridge may lie either on the same side or the opposite sides of the average plane defined by the four nitrogen atoms, noted in the text as *cis* or *trans* isomers, respectively. The composition of the mixtures has been determined on the basis of the NMR spectra.

The reaction of *N*,*N*′-bis(2-aminoethyl)-1,3-propanediamine **1** with pyruvic aldehyde in acetonitrile at 4 °C quantitatively yields a mixture of two *gem-cis* isomers, **3** and **4**, in a 4:1 ratio. The structure of the major compound **3** has been confirmed by a single-crystal X-ray analysis (Figure 1a). The minor compound is the *cis* isomer **4** in which the methyl group is connected to the aminal type carbon located between the two tertiary amines. The *cis* configuration of this compound is confirmed by NMR spectroscopy since the ^{13}C NMR spectrum is temperature dependent.[17−19] The condensation of pyruvic aldehyde with *N*,*N*′-bis(3-aminopropyl)ethylenediamine **2** gives the *vic-trans* isomer **5** as the major compound when the reaction is performed in either acetonitrile at 4 °C or ethanol at 4 °C, together with a small amount (10%) of *cis* isomer **6**. No trace of *gem* isomers is observed.

The cyclization reaction of the different bisaminals with dibromoethane or dibromopropane should yield the corresponding bisaminal-protected macrocycle. In fact, these protected cyclic tetraamines can be obtained following a one-pot procedure without isolating the intermediates (Scheme 2). Starting from the linear tetraamine **1** or **2**, the condensation of pyruvic aldehyde is performed in acetonitrile at 4 °C, and then K_2CO_3 and the biselectrophilic reagent are added and the mixture is refluxed for 2 days. Yields indicated in Scheme 2 are the isolated yields starting from the linear tetraamine, after purification of compounds **7**−**10** by column chromatography.

Obviously, the best results are observed starting from tetraamine **1**, the protected macrocycles **7** and **8** being obtained in 69% and 68% yield, respectively. Bisaminal-protected macrocycles **9** and **10** have been prepared from the linear tetraamine **2** in 22% and 25% overall yield, respectively. A mixture of the compound **9** and the *cis* isomer **8** is obtained in 29% after chromatography and the ratio has been determined by integration of the ^1H NMR resonances. Compound **9** can be isolated as a pure compound after washing the mixture with cold acetone and its structure was solved by X-ray diffraction (Figure 1b).

Bisaminal adducts can be deprotected to release the corresponding free macrocycle, i.e., cyclam or 13aneN4. However, the interest of the method does not lie in the synthesis of the macrocycle itself after removal of the bisaminal bridge. In this regard, pyruvic aldehyde does not present a significant advantage over butanedione, for

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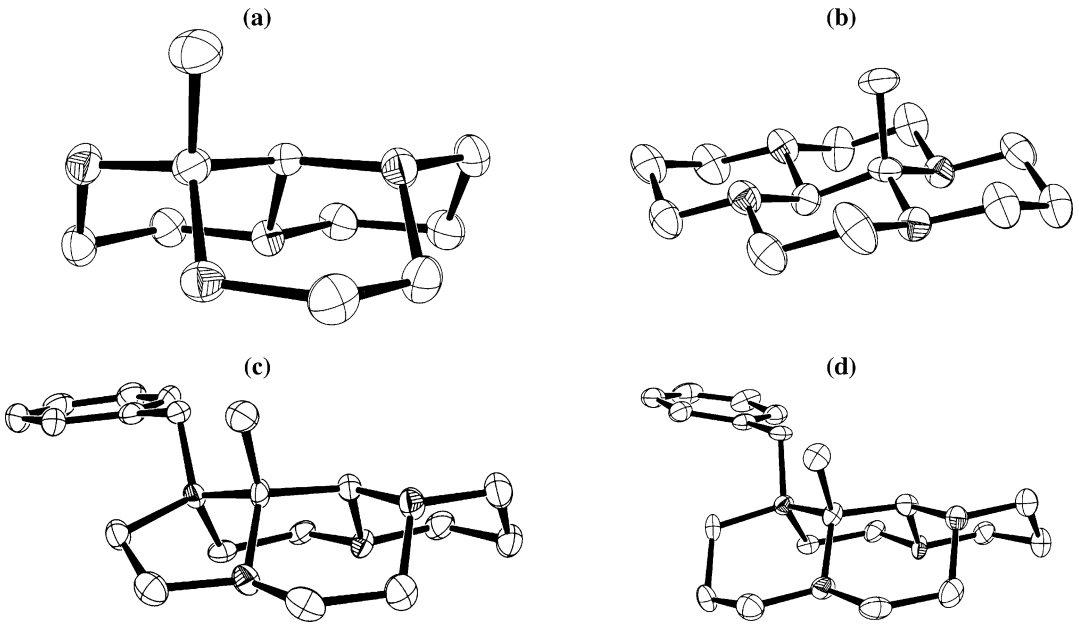
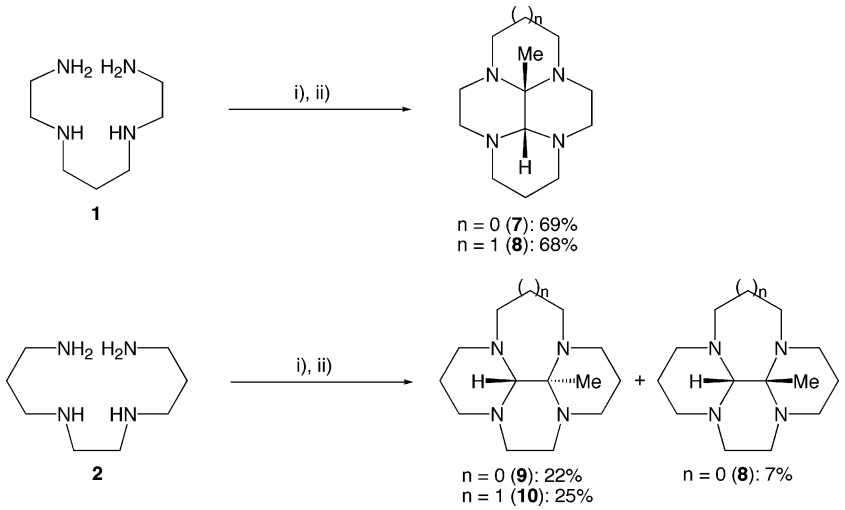


FIGURE 1. ORTEP views of (a) **3**, (b) **9**, (c) **11**, and (d) **19** (hydrogen atoms are omitted for clarity; ellipsoids are shown at 50% probability level).

SCHEME 2[a]



[a] Key: (i) pyruvic aldehyde, CH_3CN, 4 °C; (ii) dibromoethane ($n = 0$) or dibromoporpane ($n = 1$), K_2CO_3, CH_3CN, reflux.

example. Compared to glyoxal adducts, the bisaminal-protected macrocycles obtained with pyruvic aldehyde are less stable and the bridge can be removed under mild experimental conditions to release the macrocycle, as in the case of butanedione. Only the deprotection of compound **9** failed, but this is not unexpected regarding the very high stability of the similar *trans* cyclam/glyoxal adduct which cannot be deprotected even under very harsh conditions.[20] The principal advantage of pyruvic aldehyde when compared to the two other α-carbonyl compounds arises from its lower symmetry. Indeed, one may take advantage of the presence of the bisaminal moiety to perform selective mono-N-quaternization before removal of the protecting bridge (Schemes 3 and 4).

It has to be noted that the quaternization occurs selectively on the nitrogen atom linked to the aminal carbon bearing the methyl group as evidenced by X-ray structure determination of compounds **11** and **19** (Figure 1c,d). Consequently, only one isomer of the two possible mono-N-functionalized 13aneN4 derivatives is obtained after removal of the bisaminal bridge. Attempts to quaternize analogous butanedione protected macrocycles failed while quaternization of glyoxal cyclam adducts may lead to a mixture of the mono- and the 1,7-disubstituted compounds.[20] Moreover, the bisaminal bridge cannot be easily removed.

Various electrophilic reagents have been used and most reactions have been performed starting from protected macrocycle **7** (Schemes 3 and 4). The procedure has also been applied for the preparation of bismacrocycles (Scheme 5).

Most of the monofunctionalized 13aneN4 obtained after removal of the bisaminal bridge were not pre-

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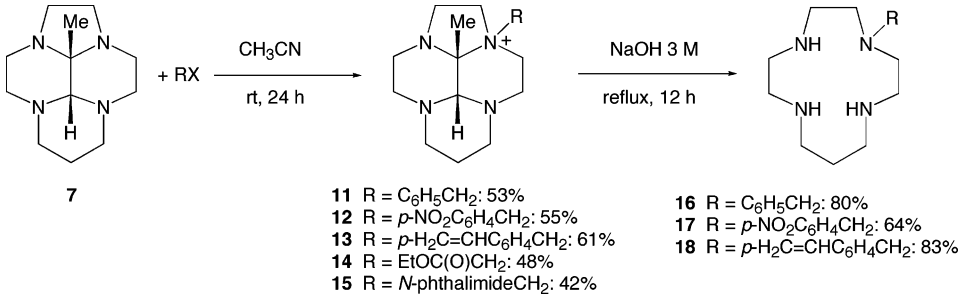
SCHEME 3



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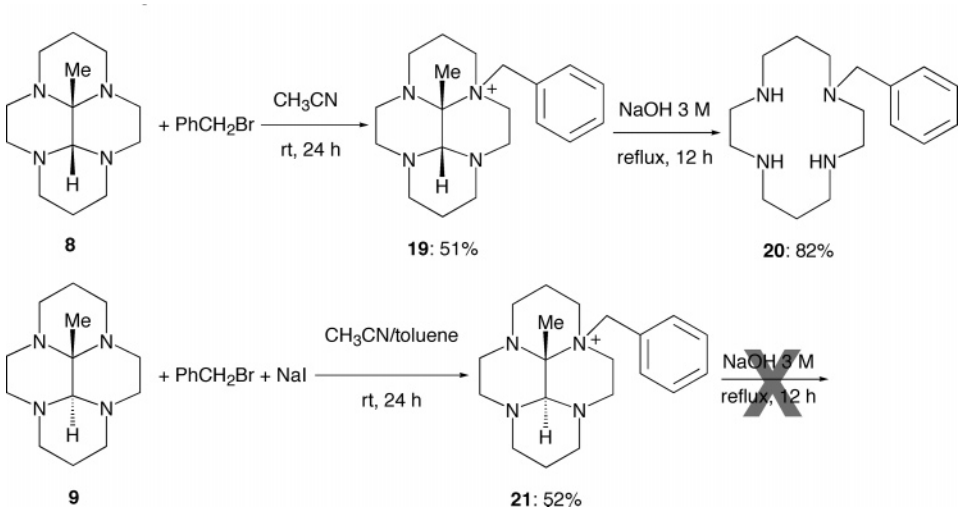

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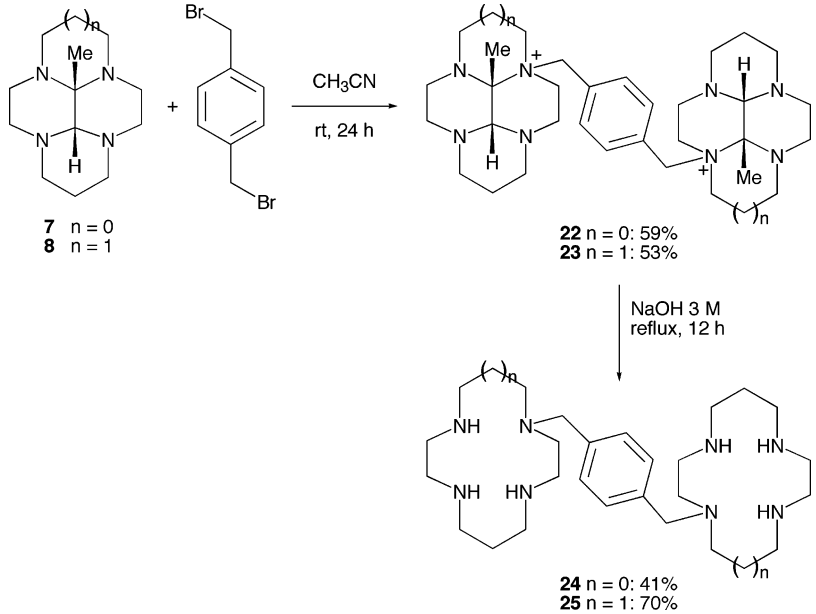

viously described in the literature. Attempts to isolate monoester from **14** failed due to the reactivity of the ester moiety, which can give the corresponding acid in the conditions used for the deprotection (NaOH or HCl aqueous solutions) and/or undergo lactamisation. Such intramolecular cyclization of 1,8-diacetic acid cyclam has already been reported.[21,22] We have also observed that cyclam monoester **26** synthesized by classical method (reaction of ethylbromoacetate with a large excess of cyclam) readily cyclizes to yield the novel bicyclic lactam **27** (Scheme 6 and Figure 2).

Many different procedures have been devised for the synthesis of the benzylated cyclam **20**[12,23−26] and the bismacrocycle **25**,[10,27] known as a highly potential anti-

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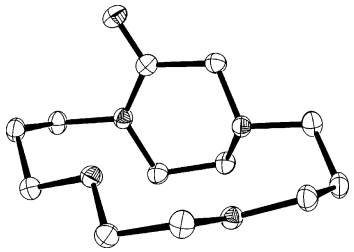
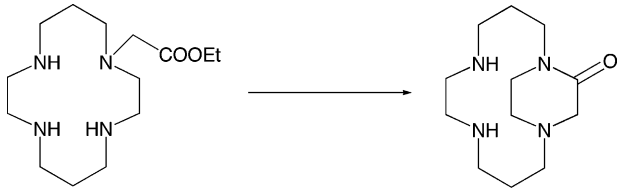


FIGURE 2. ORTEP view of **27** (hydrogen atoms are omitted for clarity, ellipsoids are shown at 50% probability level).

SCHEME 6



26 **27**

HIV compound named JM3100 or AMD3100 in its fully protonated form. However, the method described herein is much more convenient for the synthesis of such compounds. Glyoxal has already been used as a protecting group for the synthesis of monobenzylcyclam[20] as well as JM3100.[28] The authors added glyoxal to cyclam, the quaternization step was then performed then the bisaminal bridge was removed by using hydroxylamine. However, the use of glyoxal both as a template and as a protecting group has never been described before. Moreover, pyruvic aldehyde, which has never been used as a template or as a protecting group, replaces glyoxal advantageously since the deprotection of the bisaminal adduct is much easier. Butanedione is not convenient since the bisaminal adduct does not undergo quaternization (vide supra). In the case of the macrocycle 13aneN4, the use of pyruvic aldehyde presents an additional advantage, i.e., the control of the location of the N-substituent. Indeed, two different N-functionalized macrocycles exist because of the lack of symmetry of the cyclic amine. By using this approach, only one out the two regioisomers is obtained. This level of selectivity cannot be reached via any of the classical methods including direct functionalization or protection/deprotection sequences.

Finally, tri-N-functionalized tetraazacycloalkanes have been prepared starting from the selectively monobenzylated analogue. For instance, benzylated 13aneN4 **16** is further functionalized by reaction with ethyl bromoacetate to yield compound **28** which is easily deprotected to give the novel triester **29** (Scheme 7). It has to be noted that, unlike monoester **26**, **29** does not undergo any lactamisation reaction. A broad range of valuable bifunctional chelating agents can be designed starting from either the mono- or tri-N-functionalized macrocycles that are easily prepared according to this new method.

Discussion on the Formation and the Reactivity of the Bisaminal Intermediates. It appears from the experimental results reported herein as well as in the literature that the condensation of a linear tetraamine with a α-dicarbonyl compound, the cyclization of the resulting bisaminal intermediate, the quaternization reaction of the corresponding protected macrocycle, and the removal of the bisaminal bridge are strongly dependent on the nature of the tetraamine and the α-dicarbonyl compound. Indeed, the yields of these different reactions may range from 0 to 100% depending on the precursors. To rationalize these experimental observations, we have undertaken molecular modeling studies. These calculations, supported by X-ray structures, helped us in better understanding the reactivity of these rigid polycyclic bisaminal-type compounds.

First, we have investigated the condensation of *N*,*N*′-bis(2-aminoethyl)-1,3-propanediamine **1** and *N*,*N*′-bis(3-aminopropyl)ethylenediamine **2** with pyruvic aldehyde. The energies of the different adducts, regarding the orientation of the bisaminal bridge (*gem* or *vic* compounds), the *cis* or *trans* configuration of the substituents (H or Me) on the aminal carbons, the location of the methyl group, as well as the relative orientation of the lone pairs on the secondary amine type nitrogen atoms have been initially calculated by semiempirical AM1 calculations.[29] Then, the energies of the most stable compounds have been refined by DFT/B3LYP/6.31 G* calculations.[29] To determine the reliability of this procedure, the most stable geometries for the studied compounds were calculated and the molecular conformations were compared by overlay to the experimental structures (Table 1).[30] The accordance between the calculated and the experimental geometrical parameters is high, the root-mean square deviation (rmsd) being systematically lower than 0.079 Å.

The condensation of pyruvic aldehyde with tetraamine **1** in acetonitrile at 4 °C gives a mixture of two *gem*-*cis* isomers, **3** and **4**, in a 4:1 ratio (Scheme 1). The same selectivity has been observed in the case of butanedione.[31−33] No *vic*-isomer is observed because the formation of the adduct containing three six-membered rings is strongly favored. The difference between the calculated energies of the two most stable *trans* and *cis* isomers is too slight (0.43 kcal.mol^{-1}) to explain the absence of *trans* isomer. The *cis* isomer is certainly kinetically favored via

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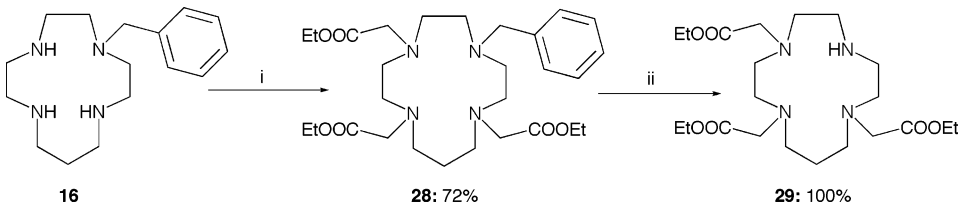
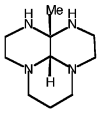
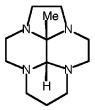
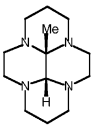
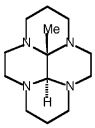
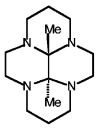
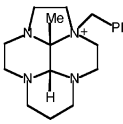
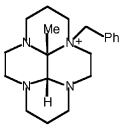
SCHEME 7 [a]



[a] Key: (i) $BrCH_2COOEt$, K_2CO_3, CH_3CN, reflux; (ii) H_2, Pd/C, EtOH, rt.

TABLE 1. Selected Experimental and Calculated (in Italics) Bond Lengths (Å)

Compound	**3**	**7**	**8**	**9**	**30**	**11**	**19**
							
$N_{unsubst}-C_{aminal}$	1.455(2)			1.461(3)	1.477(3)	1.451(5)	1.460(4)
	1.464	*1.466*	*1.463*	*1.469*	*1.481*		
	1.463(2)			1.457(3)	1.477(3)	1.472(5)	1.480(4)
	1.466	*1.473*	*1.475*	*1.469*	*1.483*		
	1.478(2)			1.484(3)	1.480(3)	1.477(4)	1.482(5)
	1.484	*1.474*	*1.476*	*1.482*	*1.483*		
	1.491(2)			1.482(3)	1.480(3)	-	-
	1.484	*1.474*	*1.488*	*1.482*	*1.484*		
$N^+_{subst}-C_{aminal}$	-	-	-	-	-	1.548(5)	1.582(4)
$N^+_{subst}-C_{subst}$	-	-	-	-	-	1.521(5)	1.539(5)
$\langle N^+_{subst}-C_{macr}\rangle$ [a]	-	-	-	-	-	1.519(7)	1.522(6)
$\langle N_{unsubst}-C_{macr}\rangle$ [a]	1.467(5)			1.463(8)	1.462(8)	1.465(11)	1.471(11)
	1.467	*1.465*	*1.464*	*1.461*	*1.460*		
$C_{aminal1}-C_{aminal2}$	1.544(2)			1.551(2)	1.552(4)	1.538(5)	1.561(5)
	1.556	*1.546*	*1.564*	*1.563*	*1.578*		
$C_{aminal2}-C_{methyl}$	1.527(2)			1.583(5)	1.538(3)	1.523(5)	1.543(5)
	1.536	*1.549*	*1.555*	*1.552*	*1.557*		
$C_{aminal1}-C_{methyl}$	-	-	-	-	1.538(3)	-	-
					1.556		

[a] Average distances.

the formation of iminium intermediates.[33] The energy comparison between the two *gem-cis* isomers, **3** and **4** (Scheme 1), indicates that the isomer **3** is more stable than **4** by 4.44 kcal·mol^{-1}. This difference agrees well with the experimental results. The most stable structure was found to be the *gem-cis* compound **3** in which one of the lone pairs, belonging to the secondary amine type nitrogen atoms is lying in axial position while the other one is in equatorial position. It is confirmed by the X-ray structure of compound **3** (Figure 1a). This perfect agreement between the experiment and the molecular modeling calculations shows the reliability of the theoretical results (Figure 3). It has to be noted that the condensation of the tetraamine **1** with glyoxal leads to a mixture of *gem-cis* and *gem-trans* compounds in slightly different ratios depending on the experimental conditions.[17,19,33−35] The preferential formation of the *trans* isomer reported by Fuchs and co-workers[36] is probably wrong since this result is contrary to a previous report of the same group.[34]

The condensation of pyruvic aldehyde with *N*,*N*′-bis-(3-aminopropyl)ethylenediamine **2** gives a mixture of *vic-trans* isomer **5** and *vic-cis* isomer **6** in a 9:1 ratio (Scheme

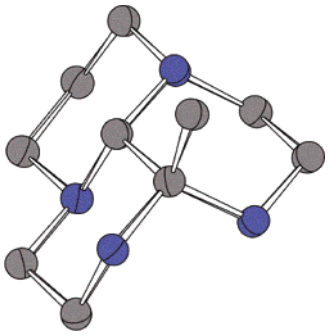


FIGURE 3. Chem3D overlay of the experimental RX and DFT/B3LYP/6.31 G* calculated structures of **3** (hydrogen atoms are omitted for clarity).

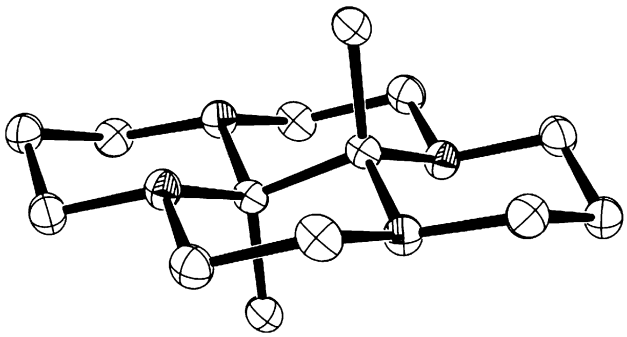


FIGURE 4. ORTEP view of **30** (hydrogen atoms are omitted for clarity; ellipsoids are shown at 50% probability level).

1). The B3LYP/6.31 G* DFT calculations indicate that the *vic-cis* isomer is slightly more stable than the *vic-trans* by only 0.85 kcal·mol^{-1}. The formation of the major *vic-trans* isomer is certainly due to kinetic parameters. No trace of *gem* isomer is obtained because of the much greater stability of the *vic* isomer which in this case is the one containing three six-membered rings. The behavior of pyruvic aldehyde toward the tetraamine **2** appears to be closer to that of glyoxal than that of butanedione. When glyoxal is used, the *vic-trans* compound is mainly obtained (90%),[17,20] while the *vic-cis* isomer is formed predominantly (75%) by using butanedione.[17,31,33]

The cyclization reaction of the bisaminal adducts depends strongly on the nature of the starting tetraamine and α-dicarbonyl compound. The bisaminal-protected macrocycles **7** and **8** are obtained in good overall yields while the bisaminal adducts obtained from **2** and pyruvic aldehyde cyclize with difficulty in the same conditions (Scheme 2). It has been reported that cyclization of bisaminal adducts **2**:butanedione (mostly the *vic-cis* isomer) with alkyl dibromides or ditosylates in the same conditions was unsuccessful.[31] However, the protected macrocycle **30**, in which the two methyl groups are in a *trans* position, is isolated in 8% yield (Figure 4, Scheme 8). It indicates that the cyclization step of the *trans* isomer occurs in 32% yield.

The reaction of the *vic-trans* isomer obtained from the condensation of glyoxal and tetraamine **2** with 1,2-dibromoethane in DMF in the presence of K_2CO_3 yielded the protected cyclam in 65% yield (58% overall yield from the linear tetraamine).[20] The cyclization may also be performed with glyoxal followed by reduction with sodium borohydride.[37,38] It appears from all these results that the main factor is the configuration of the bisaminal intermediate. The results obtained with the different α-dicarbonylated compounds could indicate that only the *vic-trans* isomer is able to undergo cyclization from **2**. However, the *cis* configuration with pyruvic aldehyde seems more suitable for the cyclization since the cyclization of the *vic-cis* isomer **6** occurs in 70% yield, while only a small ratio (24%) of the *vic-trans* isomer **5** is cyclized.

Figure 5 represents the most stable structures obtained from DFT/B3LYP/6.31 G* calculations for the bisaminal adducts of tetraamine **2** with butanedione and pyruvic aldehyde. In the *cis* intermediate obtained with butanedione, one of the two secondary amine type nitrogen atoms is involved in a hydrogen bond with the hydrogen bound to the other secondary amine type nitrogen (d(N4···HN1) = 2.186 Å, α = 113.8°) and thus is not available for nucleophilic substitution, while the lone pair of this nitrogen is hindered by the methyl group on the aminal carbon (Figure 5a). Moreover, the HN4 hydrogen atom is also involved in a weak hydrogen bonding interaction with N2 (d(N2···HN4) = 2.400 Å, α = 117.9°). Weaker interactions also exist in the glyoxal and pyruvic aldehyde intermediates (d(N2···HN4) = 2.694 and 2.616 Å, respectively). Consequently, the cyclization for the butanedione adduct is not possible. In the case of pyruvic aldehyde, due to the presence of only one methyl group on the bisaminal bridge, the nitrogen atom (N1) bound to the aminal carbon bearing the methyl group is no more hindered by the second methyl group and is able to attack the biselectrophilic reagent (Figure 5b).

The elimination of the hydrogen resulting from this nucleophilic substitution leaves the other secondary amine nitrogen free from any hydrogen-bonding interaction. Then the second nucleophilic substitution, i.e., the cyclization reaction, can occur. *Vic-trans* isomer **5** undergoes cyclization to a lesser extent than the analogous glyoxal adduct due to the steric hindrance of the methyl group on the rigid *trans* isomer. In the *trans* isomer, the presence of methyl groups is prejudicial to the cyclization reaction but does not completely forbid it, since compounds **9** or even **30** have been obtained (Figure 4).

The various *cis*-bisaminal protected macrocycles show different behaviors toward the quaternization reaction. Indeed, the bisaminal compounds obtained from glyoxal may undergo *trans* diquaternization, quaternization of corresponding butanedione adducts being not possible, while a selective monoquaternization occurs when pyruvic aldehyde is used as starting material. These different behaviors are easily explained on the basis of X-ray structures and molecular modeling. Indeed, protonation of such *cis*-bisaminal protected macrocycles occurs on the internal "concave" nitrogen atoms due to the convergence of the lone pairs of these two nitrogen atoms and the

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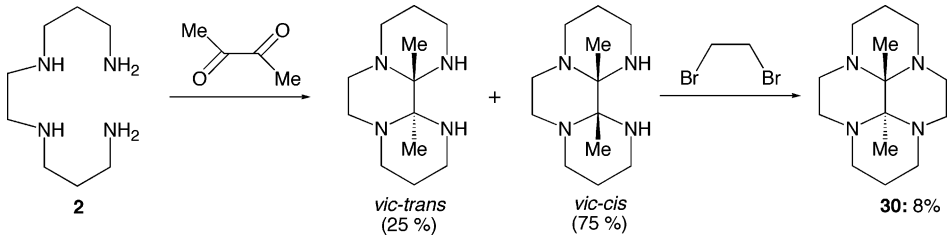
SCHEME 8



small size of the proton.[20] However, there is not enough room for any entity larger than hydrogen and quaternization with methyl iodide for example takes place

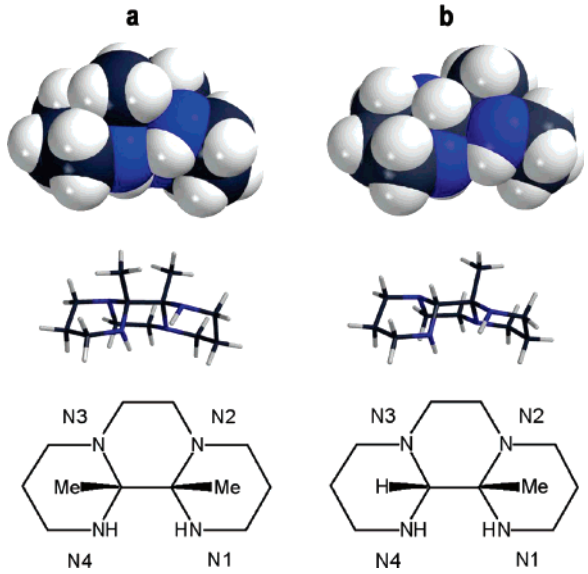


FIGURE 5. DFT/B3LYP/6.31 G* calculated structures of the *vic-cis* bis-aminal derived from 1,5,8,12-tetraazadodecane (323) and (a) butanedione or (b) pyruvic aldehyde.

on the "convex" nitrogen atoms, pointing outside the macrocyclic cavity. In the case of pyruvic aldehyde, only one of the two "convex" nitrogen atoms is accessible for quaternization. Indeed the "convex" nitrogen atom linked to the aminal carbon bearing the hydrogen atom is

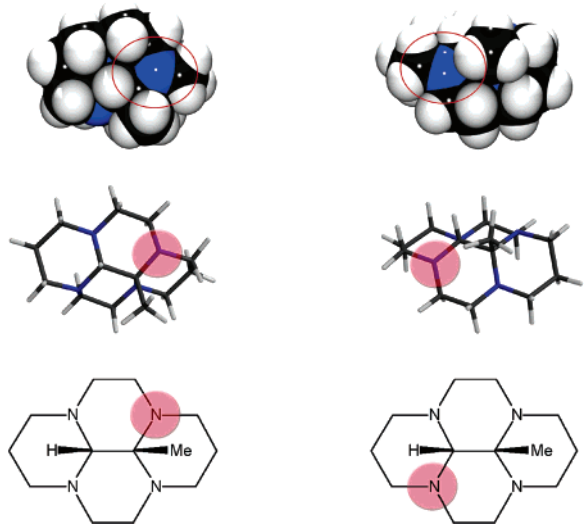


FIGURE 6. DFT/B3LYP/6.31 G* calculated structure of **8**.

partially hindered by the methyl group, as evidenced by the X-ray structure of compounds **11** and **19** (Figure 1c,d) and clearly shown in Figure 6. Thus, only selective monoquaternization is possible. When two methyl groups are present on the bisaminal bridge, in the case of butanedione adduct, the two "convex" nitrogen atoms are hindered. Therefore, none of the four nitrogen atoms is available for quaternization.

Conclusion

The method reported in this work is a very powerful route toward selectively functionalized tetraazacycloalkanes starting from linear tetraamines. This approach presents two main advantages when compared to previous conventional methods. The first important feature, which might be called the "organic template effect", is the rigidification of the linear tetraamine by the bisaminal bridge, favoring the cyclization reaction. This is a main answer according to the two important concepts in synthetic efficiency, i.e., atom economy and selectivity, since significant amounts of macrocycles can be prepared in good yields without using large volumes of solvents or producing two much wastes, two drawbacks often inherent to the synthesis of such cyclic compounds. The second key point of the method is the use of the bisaminal bridge as a protecting group before releasing the monofunctionalized tetraazacycloalkane. Not only does the same moiety play two crucial roles, but the bisaminal bridge is easily introduced and removed under mild conditions. The level of selectivity is higher than that of most of known procedures for the preparation of functionalized tetraazacycloalkanes, as evidenced by the formation of only one out the two monofunctionalized isomers in the 13aneN4 series. The scope of this method has been extended to various electrophilic reagents. Consequently this approach provides a very straightforward access to bismacrocycles.

Experimental Section

Materials and Equipment. The ^{1}H and ^{13}C NMR spectra were recorded on 300 or 500 MHz spectrometers at the "Centre de Spectroscopie Moléculaire de l'Université de Bourgogne (FR 2604)". The chemical shifts were measured by reference to the residual protons or carbon signals of the deuterated solvent. MALDI-TOF spectra were recorded using dithranol as a matrix. LSIMS spectra were recorded using *m*-nitrobenzyl alcohol as a matrix.

X-ray Diffraction Experiments and Data Processing. High-quality colorless single-crystal specimens were selected for the low-temperature X-ray diffraction experiments. The X-ray source was graphite monochromatized Mo Kα radiation from a sealed tube. Measurements were collected[39] on a diffractometer, equipped with a nitrogen jet stream low-

temperature system. For each crystal structure, the lattice parameters were obtained by a least-squares fit to the optimized setting angles of all collected reflections observed up to the maximum diffraction angle $2\theta_{max}$. Intensity data were recorded as φ and ω scans with κ offsets. Data reduction was done using the DENZO program.[40] Table S1 (Supporting Information) summarizes crystal data and some experimental conditions.

Structure Solution and Refinement. The structures were solved by direct methods using the SIR97 program.[41] Refinements were carried out by full-matrix least squares on F^2 using the SHELXL97 program[42] and the complete set of reflections. In all cases, the applied weighting scheme was $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$, a and b being updated parameters. Anisotropic thermal parameters were used for non H-atoms. In all structures, the hydrogens were located by Fourier synthesis and refined with a global isotropic thermal factor. While in **9**, **11**, and **19**[15] hydrogens were placed at calculated positions using a riding model, in **3**,[15] **27**, and **30** all H-atoms coordinates were refined. In **9**, the molecule was found to be disordered among two conformations A/B, both occupying the same regions in the unit cell and showing sites occupation factors of 0.5/0.5. The B conformer can be described as the inverted image of A by an $\bar{1}$-symmetry element placed on the middle of the C14−C23 bond, in such a way that all atomic sites (except those corresponding to the methyl group and the hydrogen H23) are shared by pairs of atoms corresponding to A and B conformers. Table S1 (Supporting Information) summarizes structure refinement details for the six compounds.

Molecular Modeling. All molecular modeling calculations were carried out using GAMESS (version 20 june 2002)[29] on a cluster at the "Centre des Ressources Informatiques de l'Université de Bourgogne". The lowest energy conformers were first located by low level calculations (semiempirical AM1 method). Then, for each derivative, all conformers having a relative energy below 4 kcal·mol^{-1} were calculated at the DFT/B3LYP/6-31 G* level.

Chemicals. *N*,*N*′-Bis(2-aminoethyl)-1,3-propanediamine **1** was synthesized according to literature procedure.[43] All other chemicals were purchased from commercial suppliers and used as received without further purification.

Typical Procedure for the Synthesis of Bisaminal Adducts. To a solution of tetraamine in acetonitrile (ca. 0.15 M for the synthesis of intermediates **3** and **4**, ca. 0.6 M for the synthesis of intermediates isomer **5** and **6**) cooled to 4 °C was added dropwise 1 equiv of pyruvic aldehyde (40 wt % solution in water). After completion of the reaction (4 h), the solution containing intermediates **3**−**6** was heated under reflux, potassium carbonate (5 equiv) and 1 or 2 equiv of dibromoethane or 1,3-dibromopropane were added for the synthesis of **7** and **8** or **9** and **10**, respectively. After 48 h, the mixture was filtered over a pad of Celite, the filtrate was evaporated, and the residue was chromatographed over an alumina plug using dichloromethane as eluent to yield pure compounds **7**−**10**.

***cis*-9a-Methyloctahydro-1,3a,6a,9-tetraazaphenalene 3** was prepared starting from *N*,*N*′-bis(2-aminoethyl)-1,3-propanediamine **1** (1.22 g; 7.65 mmol) and pyruvic aldehyde (40 wt % solution in water; 1.38 g; 7.65 mmol). The crude product was a mixture of the two isomers **3** and **4** in a 4:1 ratio as determined by integration of the signals corresponding to the methyl group in the ^{1}H NMR spectrum. This mixture was used for the next step without further purification. The minor isomer has not been fully characterized by NMR because of overlapped signals. Single crystals of **3** were obtained by slow evaporation of pentane. ^{1}H NMR of **3** (500 MHz, $CDCl_3$, 220 K) δ, ppm: 1.22 (m, 1H); 1.30 (s, 3H); 1.70 (s, 2H); 2.17−2.28 (m, 4H); 2.61−2.67 (m, 2H); 2.89 (s, 1H); 2.90−3.00 (m, 4H); 3.09 (m, 2H); 3.18 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 220 K) δ, ppm: (CH_3-) 19.6; (CH_2-β) 26.0; (CH_2-α) 39.3; 40.8; 44.9; 53.4; 55.1; 56.6; (NCN) 65.3; 81.3. MALDI-TOF: m/z = 196.28 $[M]^{+\bullet}$.

***trans*-4a-Methyldodecahydro-4,5,8a,10a-tetraazaphenanthrene 5** was prepared starting from *N*,*N*′-bis(3-aminopropyl)ethylenediamine **2** (5.06 g; 28.73 mmol) and pyruvic aldehyde (40 wt % solution in water; 5.16 g; 28.73 mmol). The crude product was a mixture of the two isomers **5** and **6** in a 9:1 ratio as determined by integration of the signals corresponding to the methyl group in the ^{1}H NMR spectrum. This mixture was used for the next step without further purification. The minor isomer has not been fully characterized by NMR because of overlapped signals. ^{1}H NMR of isomer **5** (500 MHz, $CDCl_3$, 300 K) δ, ppm: 1.05 (s, 3H); 1.33−1.40 (m, 2H); 1.50−1.60 (m, 2H); 1.96 (td; 1H, J = 3.1 Hz, 12.4 Hz); 2.15−2.23 (m, 2H); 2.30 (s, 1H); 2.36−2.48 (m, 4H); 2.52 (td, 1H, J = 3.4 Hz, 12.2 Hz); 2.67−2.69 (m, 2H); 2.74−2.78 (m, 2H); 2.91−2.95 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ, ppm: (CH_3-) 8.11; (CH_2-β) 27.1; 27.6; (CH_2-α) 39.5; 45.7; 48.0; 49.6; 54.3; 56.0; (NCN) 70.6; 85.5. LSIMS: m/z = 211.2 $[M + H]^+$.

***cis*-9b-Methyldecahydro-2a,4a,7a,9a-tetraazacyclopenta[*cd*]phenalene 7** was prepared starting from a crude mixture of **3** and **4** (1.50 g; 7.65 mmol), potassium carbonate (5.28 g; 38.25 mmol), and 1,2-dibromoethane (1.43 g; 7.65 mmol). Compound **7** was obtained as a colorless oil: yield 69%; m = 1.17 g; ^{1}H NMR (500 MHz, $CDCl_3$, 220 K) δ, ppm: 0.94 (s, 3H); 1.05 (m, 1H); 2.01 (m, 3H); 2.22−2.30 (m, 2H); 2.38−2.51 (m, 4H), 2.66−2.85 (m, 6H); 3.02 (m, 2H); 3.20 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 220 K) δ, ppm: (CH_3-) 1.8; (CH_2-β) 20.0; (CH_2-α) 45.6; 46.3; 46.7; 51.0; 51.8; 53.8; 54.5; 56.3; (NCN) 75.6; 81.8. LSIMS: m/z = 223.2 $[M + H]^+$. Anal. Calcd for $C_{12}H_{22}N_4$: C, 64.83; H, 9.97; N, 25.20. Found: C, 64.86; H, 9.52; N, 24.78.

***cis*-10b-Methyldecahydro-3a,5a,8a,10a-tetraazapyrene 8** was prepared starting from a crude mixture of **3** and **4** (12.24 g; 62.39 mmol), potassium carbonate (43.12 g; 311.97 mmol), and 1,3-dibromopropane (12.59 g; 62.39 mmol). Compound **8** was obtained as a colorless oil: yield m = 10.04 g; 68%; ^{1}H NMR (500 MHz, $CDCl_3$, 223 K) δ, ppm: 1.15−1.22 (m, 2H); 1.36 (s, 3H); 2.00−2.32 (m, 6H); 2.40−2.71 (m, 10H); 3.35 (m, 1H); 3.45 (m, 1H); 3.62 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 223 K) δ, ppm: (CH_3-) 13.5; (CH_2-β) 19.2; 19.4; (CH_2-α) 45.2; 45.2; 47.0; 49.2; 50.7; 53.3; 54.6; 56.9; (NCN) 70.8; 82.8. MALDI-TOF: m/z = 236.7 $[M]^{+\bullet}$.

***trans*-10b-Methyldecahydro-3a,5a,8a,10a-tetraazapyrene 9** was prepared starting from a crude mixture isomer of **5** and **6** (6.02 g; 28.73 mmol), potassium carbonate (19.86 g; 143.68 mmol), and 1,2-dibromoethane (10.78 g; 57.47 mmol). After chromatography (Al_2O_3, eluent: CH_2Cl_2), a mixture of **9** and of the corresponding *cis* isomer **8** (ratio: 3:1 determined by ^{1}H NMR) was obtained. Compound **9** was isolated as a white powder from the mixture after washing with cold acetone, yield 22%; m = 1.49 g. Single crystals of **9** were obtained by slow evaporation of acetone. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ, ppm: 1.08 (s, 3H); 1.34−1.48 (m, 2H); 1.75−2.00 (m, 5H); 2.33−2.40 (m, 4H); 2.45−2.48 (m, 4H); 2.58−2.63 (m, 4H); 2.80 (m, 2H).^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ, ppm: (CH_3-) 1.3; (CH_2-β) 24.6; 25.2; (CH_2-α) 47.6; 47.6; 48.8; 48.8; 54.5; 54.5; 54.8; 54.8; (NCN) 72.6; 89.6. MALDI-TOF: m/z = 236.7 $[M]^{+\bullet}$.

***trans*-11b-Methyldecahydro-3a,5a,8a,11a-tetraazacyclohepta[*def*]phenanthrene 10** was prepared starting from

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(43) Pruckmayr, G. Imparting durable press properties to cellulosic fabrics. US 3814580, 1974.

a crude mixture of isomers **5** and **6** (6.02 g; 28.73 mmol), potassium carbonate (19.86 g; 143.68 mmol), and 1,3-dibromopropane (11.55 g; 57.47 mmol). Compound **10** was obtained as a colorless oil, yield 25%; m = 1.80 g. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ, ppm: 1.31 (m, 1H); 1.33 (s, 3H); 1.68−1.71 (m, 2H); 1.74−1.95 (m, 3H); 2.01 (m, 1H); 2.29−2.33 (m, 2H); 2.53−2.69 (m, 9H); 2.85 (m, 1H); 2.98 (m, 1H); 3.13−3.19 (m, 2H); 3.34 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ, ppm: (CH_3-) 7.6; (CH_2-β) 23.8; 24.1; 26.3; (CH_2-α) 48.0; 49.7; 50.2; 50.3; 51.2; 52.0; 54.6; 55.1; (NCN) 75.2; 86.8. MALDI-TOF: m/z = 250.9 $[M]^{+\bullet}$. Anal. Calcd for $C_{14}H_{26}N_4$: C, 67.16; H, 10.47; N, 22.38. Found: C, 66.83; H, 10.81; N, 22.13.

Typical Procedure for the Quaternization of Bisaminal Adducts and Deprotection To Yield Monofunctionalized Macrocycles. Stoichiometric amounts of bisaminal adduct **7**−**9** and convenient electrophilic reagent were mixed together in acetonitrile (ca. 0.5 M, a mixture of acetonitrile/toluene 3:1 was used as a solvent for the synthesis of compound **21**, 1 equiv of NaI was added for the synthesis of compounds **13**, **21**, and **23**). The mixture was stirred at rt for 24 h, the white precipitate formed was filtered off and washed with diethyl ether, and the corresponding ammonium salt (**11**−**15**, **19**, **21**−**23**) was obtained as a white powder. The solid was dissolved in water (ca. 0.3 M), a 10-fold volume of 3 M aqueous NaOH solution was added, and the mixture was refluxed for 12 h. The solution was extracted three times with chloroform, and the combined organic phases were dried over $MgSO_4$ and evaporated to yield compounds **16**−**18**, **20**, **24**, and **25**.

***cis*-2a-Benzyl-9b-methyldecahydro-4a,7a,9a-triaza-2a-azoniacyclopenta[*cd*]phenalene bromide 11** was prepared starting from **7** (1.17 g; 5.27 mmol) and benzyl bromide (0.90 g; 5.27 mmol). Compound **11** was obtained as a white powder, yield 53%, m = 1.10 g. Single crystals of **11** were obtained by slow evaporation of acetonitrile. ^{1}H NMR (500 MHz, D_2O, 300 K) δ, ppm: 1.38 (m, 1H); 1.63 (s, 3H); 2.14 (m, 1H); 2.5−2.8 (m, 3H); 2.9−3.1 (m, 8H); 3.38 (m, 3H); 3.6 (m, 1H); 3.88 (s, 1H); 4.16 (m, 1H); 4.6 (d, 1H, J = 13.0 Hz); 4.86 (d, 1H, J = 13.0 Hz); 7.52−7.58 (m, 5H). ^{13}C NMR (125 MHz, D_2O, 300 K) δ, ppm: (CH_3-) 10.3; (CH_2-β) 18.5; (CH_2-α) 43.1; 44.7; 44.8; 47.0; 52.1; 53.2; 54.0; 58.7; (CH_2-Ph) 59.5; (NCN) 77.3; 87.3; (C-Ar) 127.9; (CH-Ar) 130.0; 131.2; 132.4. MALDI-TOF: m/z = 312.7 $[M - Br]^+$. Anal. Calcd for $C_{19}H_{29}N_4Br$: C, 58.14; H, 7.46; N, 14.28. Found: C, 58.26; H, 7.87; N, 14.16.

***cis*-9b-Methyl-2a-(4-nitrobenzyl)decahydro-4a,7a,9a-triaza-2a-azoniacyclopenta[*cd*]phenalene bromide 12** was prepared starting from **7** (1.94 g; 8.73 mmol) and p-nitrobenzyl bromide (1.88 g; 8.73 mmol). Compound **12** was obtained as a white powder, yield 55%, m = 2.10 g. ^{1}H NMR (500 MHz, D_2O, 300 K): 1.37 (m, 1H); 1.64 (s, 3H); 2.12 (m, 1H); 2.50 (m, 2H); 2.55 (m, 1H); 2.86−3.09 (m, 8H); 3.39 (m, 2H); 3.50 (m, 1H); 3.70 (m, 1H); 3.88 (s, 1H); 4.21 (m, 1H); 4.72 (d, 1H, J = 13.3 Hz); 5.01 (d, 1H, J = 13.3 Hz); 7.77 (d, 2H, J = 8.5 Hz); 8.27 (d, 2H, J = 8.5 Hz). ^{13}C NMR (125 MHz, D_2O, 300 K) δ, ppm: (CH_3-) 10.3; (CH_2-β) 18.5; (CH_2-α) 43.1; 44.7; 44.9; 46.9; 52.1; 53.8; 54.0; 57.5; (CH_2-$PhNO_2$) 59.7; (NCN) 77.3; 88.0; (CH-Ar) 124.9; 133.7; (C-Ar) 135.1; 149.3. MALDI-TOF: m/z = 358.2 $[M - Br]^+$.

***cis*-9b-Methyl-2a-(4-vinylbenzyl)decahydro-4a,7a,9a-triaza-2a-azoniacyclopenta[*cd*]phenalene iodide 13** was prepared starting from **7** (1.00 g; 4.50 mmol), 4-vinylbenzyl chloride (0.68 g; 4.50 mmol), and sodium iodide (0.67 g; 4.50 mmol). Compound **13** was obtained as a white powder, yield 61%, m = 1.28 g. ^{1}H NMR (500 MHz, D_2O, 300 K) δ, ppm: 1.33 (m, 1H); 1.56 (s, 3H); 2.08 (m, 1H); 2.45 (m, 2H); 2.65 (m, 1H); 2.82−2.98 (m, 7H); 3.08 (m, 1H); 3.25−3.40 (m, 3H); 3.58 (m, 1H); 3.78 (s, 1H); 4.06 (m, 1H); 4.54 (d, 1H, J = 13.2 Hz); 4.76 (d, 1H, J = 13.2 Hz); 5.33 (d, 1H, J = 11.0 Hz); 5.85 (d, 1H, J = 17.7 Hz); 6.74 (dd,1H, J = 11.0 Hz, 17.7 Hz); 7.42 (d, 2H, J = 8.2 Hz); 7.53 (d, 2H, J = 8.2 Hz). ^{13}C NMR (125 MHz, D_2O, 300 K) δ, ppm: (CH_3-) 12.1; (CH_2-β) 19.6; (CH_2-α) 43.7; 45.5; 45.7; 47.3; 52.8; 54.4; 54.7; 58.0; (CH_2-Ph) 60.0; (NCN) 76.9; 88.2; (CH_2=*C*H) 116.1; (CH-Ar) 127.2; (C-Ar) 127.4; (CH-Ar) 132.9; (CH_2=*C*H) 136.2; (C-Ar) 139.7. LSIMS: m/z = 339.2 $[M - I]^+$. Anal. Calcd for $C_{21}H_{32}N_4I$: C, 53.96; H, 6.90; N, 11.99. Found: C, 53.74; H, 6.79; N, 11.96.

***cis*-2a-Ethoxycarbonylmethyl-9b-methyldecahydro-4a,7a,9a-triaza-2a-azoniacyclopenta[*cd*]phenalene iodide 14** was prepared starting from **7** (11.00 g; 49.50 mmol) and iodoethyl acetate (10.59 g; 49.50 mmol). After the mixture was stirred for 24 h at rt, **14** was precipitated by addition of the mixture to 3 L of diethyl ether. Compound **14** was obtained as an off-white powder, yield 48%, m = 10.36 g. ^{1}H NMR (300 MHz, D_2O, 300 K) δ, ppm: 1.20 (t, 3H, J = 7.2 Hz); 1.25 (m, 1H); 1.42 (s, 3H); 2.05 (m, 1H); 2.41 (m, 2H); 2.63−2.98 (m, 8H); 3.32 (m, 2H); 3.67 (s, 1H); 3.76−3.95 (m, 3H); 4.06−4.25 (m, 3H); 4.35 (d, 1H, J = 16.6 Hz); 4.63 (d, 1H, J = 16.6 Hz). ^{13}C NMR (75 MHz, D_2O, 300 K) δ, ppm: (CH_3-) 10.6; 13.6; (CH_2-β) 18.4; (CH_2-α) 42.9; 44.8; 45.2; 47.0; 51.9; 53.9; 54.8; 55.8; 60.9; (−CH_2-O) 64.1; (NCN) 77.1; 88.6; (C=O) 165.1. MALDI-TOF: m/z = 309.2 $[M - I]^+$.

***cis*-2a-(1,3-Dioxo-1,3-dihydroisoindol-2-ylmethyl)-9b-methyldecahydro-4a,7a,9a-triaza-2a-azoniacyclopenta-[*cd*]phenalene bromide 15** was prepared starting from **7** (2.00 g; 9.00 mmol), *N*-(bromomethyl)phthalimide (2.16 g; 9.00 mmol). Compound **15** was obtained as an off-white powder, yield 42%, m = 1.75 g. ^{1}H NMR (500 MHz, D_2O, 300 K) δ, ppm: 1.46 (m, 1H); 1.76 (s, 3H); 2.16−2.26 (m, 1H); 2.56−2.62 (m, 2H); 2.81 (m, 1H); 2.95 (m, 1H, J = 4.0 Hz, 12.0 Hz); 3.00−3.14 (m, 5H); 3.31 (m, 1H, J = 13.3 Hz); 3.41−3.52 (m, 3H); 3.61−3.67 (m, 1H); 3.84 (m, 1H, J = 12.9 Hz); 3.93 (s, 1H); 4.29 (m, 1H, J = 5.0 Hz, 12.0 Hz); 5.30 (d, 1H, J = 13.1 Hz); 5.65 (d, 1H, J = 13.1 Hz); 7.97−8.05 (m, 4H). ^{13}C NMR (125 MHz, D_2O, 300 K) δ, ppm: (CH_3-) 11.0; (CH_2-β) 18.7; (CH_2-α) 43.2; 44.7; 44.9; 47.4; 52.3; 54.1; 54.4; 57.5; (CH_2-phthalimide) 59.9; (NCN) 77.9; 87.8; (CH-Ar) 125.2; (C-Ar) 131.4; (CH-Ar) 136.6; (C=O) 169.8. MALDI-TOF: m/z = 382.4 $[M - Br]^+$.

4-Benzyl-1,4,7,10-tetraazacyclotridecane 16 was prepared starting from **11** (1.10 g; 2.80 mmol). Compound **16** was obtained as a colorless oil, yield 80%, m = 0.62 g. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ, ppm: 1.70 (m, 2H); 2.20 (s, 3H); 2.58−2.66 (m, 10H); 2.75 (m, 4H); 2.8 (m, 2H); 3.62 (s, 2H); 7.26−7.30 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ, ppm: (CH_2-β) 28.9; (CH_2-α) 47.2; 47.9; 48.4; 48.4; 49.4; 50.7; 54.3; 54.4; (CH_2-Ph) 60.4; (CH-Ar) 127.3; 128.5; 129.4; (C-Ar) 139.7. MALDI-TOF: m/z = 276.7 $[M]^{+\bullet}$.

4-(4-Nitrobenzyl)-1,4,7,10-tetraazacyclotridecane 17 was prepared starting from **12** (1.00 g; 2.56 mmol). Compound **17** was obtained as a colorless oil, yield 64%, m = 0.53 g. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ, ppm: 1.61 (m, 2H); 2.49−2.91 (m, 19 H); 3.51 (s, 2H); 7.15 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ, ppm: (CH_2-β) 28.8; (CH_2-α) 47.1; 47.9; 48.3; 48.4; 49.5; 50.7; 54.1; 54.2; (CH_2-$PhNO_2$) 60.0; (CH-Ar) 126.9; 129.3; (C-Ar) 138.0; 141.6.

4-(4-Vinylbenzyl)-1,4,7,10-tetraazacyclotridecane 18 was prepared starting from **13** (1.00 g; 2.14 mmol). Compound **18** was obtained as a colorless oil, yield 83%, m = 0.54 g. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ, ppm: 1.71 (m, 2H); 2.60−2.82 (m, 19H); 3.62 (s, 2H); 5.20 (dd, 1H, J = 1.6 Hz, 10.8 Hz); 5.70 (dd, 1H, J = 1.6 Hz, 17.6 Hz); 6.68 (dd, 1H, J = 10.8 Hz, 17.6 Hz); 7.26 (d, 2H, J = 5.7 Hz); 7.34 (d, 2H, J = 5.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ, ppm: (CH_2-β) 29.0; (CH_2-α) 47.3; 48.0; 48.5; 48.5; 49.5; 50.8; 54.3; 54.5; (CH_2-Ph) 60.2; (CH_2=*C*H) 113.7; (CH-Ar) 126.5; 129.6; (C-Ar) 136.8; (CH_2=*C*H) 137.1; (C-Ar) 139.4. MALDI-TOF: m/z = 303.1 $[M + H]^+$.

***cis*-3a-Benzyl-10b-methyldecahydro-5a,8a,10a-triaza-3a-azoniapyrene bromide 19** was prepared starting from **8** (3.00 g; 12.70 mmol) and benzyl bromide (2.17 g; 12.70 mmol). Compound **19** was obtained as a white powder, yield 51%, m = 2.63 g. Single crystals of **19** were obtained by slow evaporation of chloroform. ^{1}H NMR (500 MHz, D_2O, 300 K) δ, ppm: 1.33 (m, 1H); 1.67 (m, 1H); 1.74 (s, 3H); 2.00−2.20 (m, 2H);

2.36 (dd, 1H, J = 11.5 Hz, 4.0 Hz); 2.56 (td, 1H, J = 12.5 Hz, 3.5 Hz); 2.65−3.01 (m, 9H); 3.16 (dd, 1H, J = 13.0 Hz, 4.5 Hz); 3.20 (td, 1H, J = 14.0 Hz, 2.5 Hz); 3.51 (td, 1H, J = 12.0 Hz, 5.0 Hz); 3.82 (td, 1H, J = 13.5 Hz, 4.5 Hz); 3.95 (s, 1H); 4.33 (td, 1H, J = 12.5 Hz); 4.33 (d, 1H, J = 13.0 Hz); 5.09 (d, 1H, J = 13.0 Hz); 7.50 (m, 5H). ^{13}C NMR (125 MHz, D_2O, 300 K) δ, ppm: (CH_3-) 9.9; (CH_2-β) 17.7; 18.7; (CH_2-α) 42.2; 46.2; 47.0; 47.4; 50.4; 52.3; 54.8; 56.2; (CH_2-Ph) 58.9; (NCN) 76.9; 86.0; (C-Ar) 126.3; (CH-Ar) 129.6; 131.2; 133.7. MALDI-TOF: m/z = 327.2 $[M - Br]^+$. Anal. Calcd for $C_{20}H_{31}N_4Br$, $CHCl_3$: C, 48.08; H, 6.15; N, 10.69. Found: C, 48.74; H, 6.78; N, 10.94.

1-Benzyl-1,4,8,11-tetraazacyclotetradecane 20 was prepared starting from **19** (2.70 g; 6.65 mmol). Compound **20** was obtained as a colorless oil, yield 82%, m = 1.58 g. NMR data for **20** were consistent with those reported in the literature.[12]

***trans*-3a-Benzyl-10b-methyldecahydro-5a,8a,10a-triaza-3a-azoniapyrene iodide 21** was prepared starting from **9** (0.30 g; 1.27 mmol), benzyl bromide (0.22 g; 1.27 mmol), and sodium iodide (0.18 g; 1.27 mmol). Compound **21** was obtained as a white powder, yield 52%, m = 0.30 g. ^{1}H NMR (500 MHz, D_2O, 300 K) δ, ppm: 1.70−1.85 (m, 3H); 1.94 (s, 3H); 2.28 (m, 1H); 2.51−2.54 (m, 2H); 2.60−2.75 (m, 2H); 2.80−2.89 (m, 2H); 2.93−3.05 (m, 4H); 3.11−3.15 (m, 2H); 3.34−3.49 (m, 5H); 5.19 (d, 1H, J = 13.9 Hz); 5.53 (d, 1H, J = 13.9 Hz); 7.56−7.65 (m, 5H). ^{13}C NMR (125 MHz, D_2O, 300 K) δ, ppm: (CH_3-) 8.9; (CH_2-β) 18.5; 23.4; (CH_2-α) 45.4; 47.4; 49.2; 51.4; 51.7; 52.0; 52.7; 53.4; (CH_2-Ph) 54.2; (NCN) 79.8; 86.5; (C-Ar) 128.2; 130.1; 131.4; 133.3.

***cis*-9b-Methyl-2a-[4-(9b-methyldecahydro-2a,4a,7a,9a-tetraazacyclopenta[*cd*]phenalen-2a-ylmethyl)benzyl]-decahydro-4a,7a,9a-triaza-2a-azoniacyclopenta[*cd*]phenalene dibromide 22** was prepared starting from **7** (1.00 g; 4.50 mmol) and α,α′-dibromo-*p*-xylene (0.59 g; 2.25 mmol). Compound **22** was obtained as a white powder, yield 59%, m = 0.94 g. ^{1}H NMR (300 MHz, D_2O, 300 K): 1.05 (m, 2H); 1.32 (s, 6H); 2.03 (m, 2H); 2.40−2.70 (m, 6H); 2.75−3.15 (m, 16H); 3.20−3.65 (m, 8H); 3.80 (s, 2H); 4.08 (m, 2H); 4.60 (d, 2H, J = 13.3 Hz); 4.86 (d, 2H, J = 13.3 Hz); 7.59 (s, 4H). ^{13}C NMR (75 MHz, D_2O, 300 K) δ, ppm: (CH_3-) 10.2; (CH_2-β) 18.4; (CH_2-α) 43.0; 44.6; 44.7; 46.8; 51.9; 53.4; 53.9; 57.8; (CH_2-Ph) 59.4; (NCN) 77.2; 87.5; (C-Ar) 130.5; (CH-Ar) 133.3. MALDI-TOF: m/z = 551.6 $[M - 2Br]^+$.

***cis*-10b-Methyl-3a-[4-(10b-methyldecahydro-3a,5a,8a,-10a-tetraazapyren-3a-ylmethyl)benzyl]decahydro-5a,-8a,10a-triaza-3a-azoniapyrene dibromide 23** was prepared starting from **8** (1.65 g; 6.98 mmol), α,α′-dibromo-*p*-xylene (0.92 g; 3.49 mmol), and sodium iodide (1.04 g; 6.98 mmol). Compound **23** was obtained as a white powder, yield m = 1.54 g, 53%. ^{1}H NMR (500 MHz, D_2O, 300 K) δ, ppm: 1.40 (m, 2H); 1.79 (m, 2H); 1.83 (s, 6H); 2.10−2.29 (m, 4H); 2.45 (m; 2H); 2.70−3.08 (m, 20H); 3.33 (m, 4H); 3.56 (m, 2H); 3.95 (m, 2H); 4.12 (s, 2H); 4.42−4.50 (m, 4H); 5.28 (d, 2H, J = 13.2 Hz); 7.72 (s, 4H). ^{13}C NMR (125 MHz, D_2O, 300 K) δ, ppm: (CH_3-) 10.2; (CH_2-β) 18.0; 19.0; (CH_2-α) 42.4; 46.4; 47.6; 47.6; 50.7; 52.5; 55.0; 56.7; (CH_2-Ph) 58.5; (NCN) 76.9; 86.6; (C-Ar) 129.3; (CH-Ar) 134.8. MALDI-TOF: m/z = 576.5 $[M - 2I]^+$.

4,4′-[1,4-Phenylenebis(methylene)]bis-1,4,7,10-tetraazacyclotridecane 24 was prepared starting from **22** (0.50 g; 0.71 mmol). Compound **24** was obtained as a colorless oil, yield 41%, m = 0.14 g.^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ, ppm: 1.40 (m, 4H); 2.30−2.90 (m, 38H); 3.48 (s, 4H); 7.17 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ, ppm: (CH_2-β) 28.8; (CH_2-α) 46.9; 47.8; 48.2; 48.3; 49.5; 50.7; 54.1; 54.1; (CH_2-Ph) 60.0; (CH-Ar) 129.4; (C-Ar) 138.5. MALDI-TOF: m/z = 476 $[M + H]^{+\bullet}$.

1,1′-[1,4-Phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane 25 was prepared starting from **23** (1.00 g; 1.20 mmol). Compound **25** was obtained as colorless oil, yield 70%, m = 0.46 g. NMR data for **25** were consistent with those reported in the literature.[10]

Synthesis of (1,4,8,11-Tetraazacyclotetradec-1-yl)acetic acid ethyl ester 26. To a mixture of cyclam (20.0 g; 0.10 mol) and potassium carbonate (8.00 g; 58.00 mmol) in 450 mL of chloroform was added dropwise a solution of ethylbromoacetate (3.34 g; 20.00 mmol) in 50 mL of chloroform. After being stirred at rt for 48 h, the mixture was filtered over a pad of Celite, the filtrate was evaporated under reduced pressure, and the residue was taken into petroleum ether. After filtration of the excess of cyclam, the filtrate was evaporated to give **26** as a slightly yellow oil, yield 97%. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ, ppm: 1.20 (t, 3H, J = 7.0 Hz); 1.65−1.71 (m, 4H); 2.56−2.71 (m, 19H); 3.31 (s, 2H); 4.07 (q, 2H, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ, ppm: (CH_3-) 14.7; (CH_2-β) 26.7; 29.4; (CH_2-α) 47.8; 48.3; 49.2; 49.4; 49.7; 51.2; 52.8; 53.6; 55.9; (CH_2-O) 60.5; (C═O) 171.5. MALDI-TOF: m/z = 286.9 $[M]^{+\bullet}$, 309.2 $[M + 23]^+$.

Synthesis of 1,5,8,12-Tetraazabicyclo[10.2.2]hexadecan-13-one 27. Compound **26** slowly undergoes intramolecular cyclization to give **27**. The conversion was almost complete after 10 days at room temperature, total after refluxing 48 h in acetonitrile. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ, ppm: 1.60−1.75 (m, 2H); 1.90−2.00 (m, 1H); 2.02−2.13 (m, 1H); 2.26−2.34 (td, 1H, J = 12.3 Hz, 4.9 Hz)); 2.47−2.86 (m, 10H); 2.91 (d, 1H, J = 15.5 Hz); 2.98 (dd, 1H, J = 12.0 Hz, 7.0 Hz); 3.05 (dd, 1H, J = 11.0 Hz, 5.5 Hz); 3.11 (dd, 1H, J = 11.5 Hz, 4.5 Hz); 3.29 (m, 1H); 3.37 (dd, 1H, J = 15.5 Hz, 3.4 Hz); 3.90 (td, 2H, J = 11.9 Hz, 6.5 Hz); 4.33 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ, ppm: (CH_2-β) 24.6; 26.8; (CH_2-α) 47.7; 48.1; 48.5; 48.8; 49.9; 50.2; 51.0; 56.4; 59.0 (C = O) 167.9. MALDI-TOF: m/z = 240.7 $[M]^{+\bullet}$.

Synthesis of (4-Benzyl-7,10-diethoxycarbonylmethyl-1,4,7,10-tetraazacyclotridec-1-yl)acetic Acid Ethyl Ester 28. To a suspension of **16** (1.62 g; 5.87 mmol) and potassium carbonate (4.87 g; 35.22 mmol) in 100 mL of acetonitrile was added ethyl bromoacetate (2.94 g; 17.61 mmol). The mixture was refluxed for 2 days and then filtered, and the solvent was removed under reduced pressure. The residual oil was taken up in pentane. After filtration, solvents were evaporated to give **28** as a pale yellow oil, yield 72%, m = 2.25 g. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ, ppm: 1.21−1.29 (m, 9H); 1.60 (m, 2H); 2.60 (m, 4H); 2.75 (m, 8H); 2.86 (m, 4H); 3.20 (s, 2H); 3.35 (s, 2H); 3.38 (s, 2H); 3.53 (s, 2H); 4.10−4.17 (m, 6H); 7.20−7.36 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ, ppm: (CH_3-) 14.9 (×3); (CH_2-β) 25.3; (CH_2-α) 51.2; 51.6; 52.1; 52.2; 52.6; 52.6; 52.9; 53.2; 55.5; 56.1; 56.4; (CH_2-Ph) 60.2; (CH_2-O) 60.6; 60.7; 60.8; (CH-Ar) 127.3; 128.7; 129.6; (C-Ar) 140.4; (C═O) 172.2; 172.3; 172.4. MALDI-TOF: m/z = 534.9 $[M]^{+\bullet}$.

Synthesis of (7,10-Diethoxycarbonylmethyl-1,4,7,10-tetraazacyclotridec-1-yl)acetic Acid Ethyl Ester 29. To a solution of **28** (2.20 g; 4.12 mmol) in 250 mL of ethanol was added Pd/C (300 mg). The mixture was stirred at room temperature under hydrogen atmosphere for 12 h. After filtration over a pad of Celite and evaporation of the solvent under reduced pressure, **29** was obtained quantitatively as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ, ppm: 1.15 (m, 9H); 1.60 (m, 2H); 2.60 (m, 9H); 2.71 (m, 2H); 2.97 (m, 2H); 3.02 (m, 4H); 3.22 (s, 2H); 3.38 (s, 2H); 3.39 (s, 2H); 4.04 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ, ppm: (CH_3-) 14.6 (×3); (CH_2-β) 23.8; (CH_2-α) 45.0; 46.3; 49.6; 50.9; 51.3; 51.5; 53.0; 54.0; 54.5; 56.6; 58.2; (CH_2-O) 60.8; 60.9; 61.0; (C═O) 171.3; 171.5; 171.5. MALDI-TOF: m/z = 445.3 $[M + H]^{+\bullet}$.

Synthesis of *trans*-10b,10c-Dimethyldecahydro-3a,5a,-8a,10a-tetraazapyrene 30. To a solution of *N*,*N*′-bis(3-aminopropyl)ethylenediamine **2** (2.78 g; 15.94 mmol) in 100 mL of acetonitrile cooled to 4 °C was added dropwise 1 equiv of butanedione (1.37 g; 15.94 mmol). After completion of the reaction (4 h), the solution was heated under reflux, and potassium carbonate (11.01 g; 79.70 mmol) and 2 equiv of dibromoethane (5.98 g; 31.87 mmol) were added. After 48 h, the mixture was filtered over a pad of Celite, the filtrate was evaporated, and the residue was chromatographed over an

alumina plug using dichloromethane as eluent to yield pure **30** as a white powder, yield 8%, $m = 0.30$ g. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ, ppm: 1.32 (s, 6H); 1.58 (m, 2H); 1.95−2.03 (m, 2H); 2.41−2.59 (m, 12H); 2.81 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ, ppm: (CH_3-) −0.2; (CH_2-β) 25.7; (CH_2-α) 48.5; 49.1; (NCN) 76.3. MALDI-TOF: $m/z = 250.8$ $[M]^{+\bullet}$.

Supporting Information Available: Crystal and structure refinement data for **3**, **9**, **11**, **19**, **27**, and **30** (Table S1). Computer modeling energies for the various studied structures. ^{1}H and ^{13}C spectra of **3**, **7**−**16**, **18**, **19**, **21**, **22**, **24**, and **26**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data corresponding to the structural analysis of **9**, **11**, **27**, and **30** have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 216209−216212. Copies of this information may be obtained from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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