DOI: 10.1002/ejoc.200901183

Efficient Synthesis of New *C*-Functionalized Macrocyclic Polyamines

Yoann Rousselin,[a] Nicolas Sok,[a] Frédéric Boschetti,[b] Roger Guilard,[a] and Franck Denat*[a]

Keywords: Amines / N ligands / Bifunctional chelating agents / Macrocycles

A powerful synthetic route for the preparation of new polyazamacrocycles, valuable precursors of bifunctional chelating agents with applications in nuclear medicine, is reported. The desired functional group was introduced onto the macrocycle backbone during the cyclization step, thus avoiding the tedious preparation of a *C*-functionalized synthon. The regioselective reaction of macrocycles bearing an aminomethyl pendant arm with aldehydes is also described.

Introduction

Cyclic tetraamines (cyclen, cyclam, and [13]aneN4 and their derivatives) have attracted increasing attention owing to their versatile coordination properties which allow their use in many fields, especially for medical purposes.[1] Indeed, gadolinium chelates based on cyclen (e.g., DOTA-like ligands) are widely used for magnetic resonance imaging (MRI),[2] macrocyclic complexes with radioactive metals (^{64}Cu, ^{111}In, ^{68}Ga, and ^{90}Y ...) are good candidates for labeling biological vectors for either diagnosis or therapeutic purposes,[3] and macrocycles incorporating Eu^{III} and Tb^{III} are very useful as fluorescent probes and labels.[4]

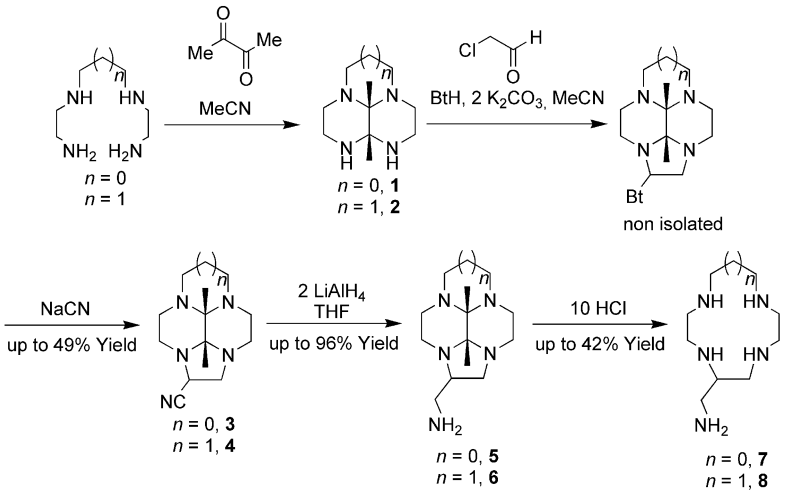
There is clearly a strong need for finely tailored ligands that are multifunctional [so-called BFCs or **b**ifunctional **c**helating **a**gents (BCAs)] and have very specific properties, and the search for powerful synthetic routes towards tetraazacycloalkanes and their *N*- and/or *C*-functionalized derivatives has become a real economic challenge. To date, many routes have been proposed for the selective *N*-functionalization of such frameworks.[5] However, the attachment of the targeting biomolecule to a carbon atom of the macrocyclic BFC may be preferred because the four nitrogen atoms then remain available for further functionalization with chelating arms. This approach also avoids the previous multistep syntheses of sophisticated pendant arms bearing both a chelating group and a grafting functionality.[6] Several strategies have been used for the synthesis of such *C*-functionalized tetraazacycloalkanes.[7] The main drawback of these approaches is the preparation of the precursor bearing the desired function on a carbon atom, which can be tedious in some cases. The size of the macrocycle is also very important for tuning the coordination properties of the chelating agent. [13]aneN4 derivatives have been much less investigated than their smaller and larger analogues, cyclen and cyclam derivatives, respectively, although it has been reported that such 13-membered ring compounds could show original properties.[8] The selective alkylation of [13]aneN4 is clearly more difficult than that of the more symmetrical cyclen and cyclam macrocycles, which may explain why less attention has been paid to this tetraazacycloalkane.

We wish to report in this paper a powerful route for the synthesis of new macrocyclic tetraamines bearing an additional aminomethyl group on a carbon atom in both the cyclen and [13]aneN4 series. These macrocycles represent a new class of ligands, the coordination properties of which are currently under investigation. These compounds are also valuable precursors of new bifunctional chelating agents for labeling biomolecules. Indeed, the four secondary amine groups of the ring can be further functionalized, for instance, with acetate groups, after selective protection of the primary amine function. A second approach is to introduce another functionality onto the pendant amino group by using a suitable reagent prior to ring functionalization. We will also report herein an example of such a regioselective reaction, that is, the condensation with various aldehydes, which after reduction yield exclusively the compound *N*-alkylated on the exocyclic nitrogen atom.

Results and Discussion

The conditions used for the cyclization step in the procedure described herein allow the introduction of a functional group onto a carbon atom of the cyclic backbone without needing to prepare a sophisticated precursor. The starting linear tetraamines, triethylenetetraamine and *N*,*N*-

[a] Institut de Chimie Moléculaire de l'Université de Bourgogne, UMR 5260, CNRS-Univ. Bourgogne,
9 Avenue Alain Savary, 21078 Dijon Cedex, France
Fax: +33-3-80396117
E-mail: Franck.Denat@u-bourgogne.fr
[b] CheMatech,
9 Avenue Alain Savary, 21078 Dijon Cedex, France
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901183.



Scheme 1. Synthesis of the *C*-aminomethyl macrocycles **7** and **8**.

bis(aminoethyl)propane-1,3-diamine, were first rigidified by reaction with 2,3-butanedione to give the bis-aminal compounds **1** and **2** (Scheme 1).[5b,9] This "bis-aminal approach" has been widely used in the last decade to prepare macrocyclic tetraamines in high yields without using high-dilution conditions or a metal cation as a template.[9b,10] It has also been shown that *C*-functionalized and regioselectively *N*-functionalized derivatives as well as cross-bridged macrocycles can readily be obtained via such bis-aminal intermediates.[5b,7,11]

Condensation of chloroacetaldehyde with the bis-aminal compounds **1** and **2** in the presence of 1 equiv. of benzotriazole and potassium carbonate in acetonitrile gave the corresponding cyclic adducts, which were not isolated (Scheme 1). The benzotriazole-assisted reaction of secondary amines with aldehydes has been extensively studied by Katritzky et al.[12] and we have previously successfully used this very convenient method for the synthesis of macrocyclic polyamines.[13] Indeed, the reaction of a suitable bis-aminal compound with glyoxal assisted by benzotriazole has proved to be a powerful route for the large-scale preparation of cyclen. The benzotriazole moiety in these adducts can be displaced by any kind of nucleophilic reagent. In this work we chose cyanide ions as the nucleophilic agent and compounds **3** and **4** were isolated in 30 and 49% yields, respectively, after the addition of sodium cyanide. The NMR spectra of these compounds are quite complicated because both **3** and **4** were obtained as pairs of enantiomers that have a diastereomeric cross-relation. Moreover, the presence of many diastereotopic protons in these polycyclic derivatives gives rise to a large number of signals in the ^{1}H NMR spectra. However, we were able to recrystallize a couple of enantiomers in both series. The crystal structures of these compounds are shown in Figure 1. In the cyclen derivative **3**, the cyanide group is pointing away from the bis-aminal bridge, whereas the cyanide and the two methyl groups on the bis-aminal carbon atoms in compound **4** are located on the same side of the mean plane.

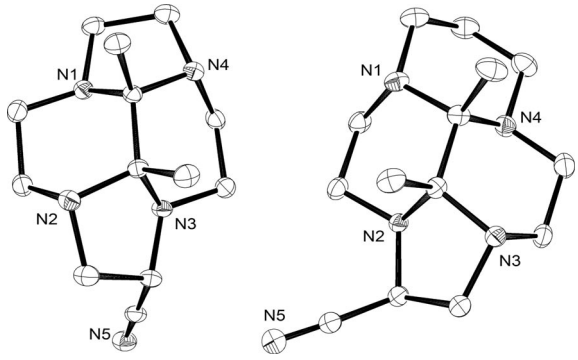


Figure 1. ORTEP[14] views of one *anti* stereoisomer of **3** (left) and one *syn* stereoisomer of **4** (right), showing thermal ellipsoids at the 50% probability level. Hydrogen atoms have been omitted for clarity.

Reduction of compounds **3** and **4** with 2 equiv. of $LiAlH_4$ gave the corresponding aminomethyl bis-aminal derivatives **5** and **6**, respectively, which were converted into the target macrocycles **7** and **8** after removal of the bis-aminal bridge by acidic hydrolysis.

The structure of the penta-protonated form of the new cyclen derivative **7** is shown in Figure 2. According to Dale's nomenclature the macrocycle adopts a (3,3,3,3)-A conformation, the four nitrogen atoms being located at the vertices of a square. Note that this structure resembles that of cyclen tetrahydrochloride. In the structure shown in Figure 2, the absolute configuration of the carbon atom bearing the aminomethyl group is *S*, but compound **7** is obtained as a racemic mixture.

The crystal structure of compound **8** presented in Figure 3 shows that two macrocycles, held together in a head-to-tail arrangement by intermolecular hydrogen bonds, are present in the unit cell with N–H···N distances of 3.208 and 3.346 Å for N3A–N4B and N5A–N4B, and 3.329 and 3.282 Å for N5B–N4A and N3B–N4A, respectively. The conformation of this macrocycle is thus imposed by inter-

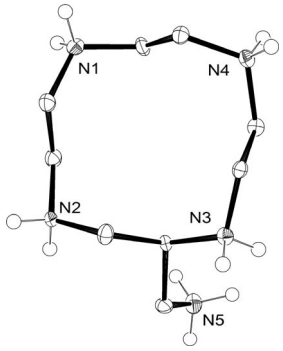


Figure 2. ORTEP[14] view of the penta-protonated form of **7**, showing thermal ellipsoids at the 50% probability level. Hydrogen atoms attached to carbon atoms of the cyclic backbone, water molecules, and counterions have been omitted for clarity.

molecular hydrogen bonds as well as by intramolecular hydrogen bonds, as shown by the following N–H···N distances: N2A–N3A 2.815 Å, N2A–N1A 2.879 Å, N2B–N3B 2.832 Å, N2B–N1B 2.870 Å, N4A–N1A 3.129 Å, N4B–N1B 3.146 Å.

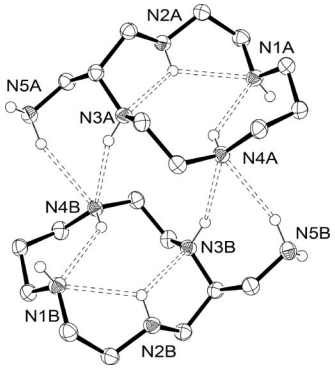


Figure 3. ORTEP[14] view of compound **8**, showing thermal ellipsoids at the 50% probability level. Hydrogen atoms attached to carbon atoms of the cyclic backbone have been omitted for clarity. Hydrogen bonds are indicated by dashed lines.

The *C*-aminomethyl macrocycles **7** and **8** represent a new class of ligands, which by themselves may exhibit original chelating properties towards metal cations. Several complexes have already been prepared and the study of the coordination properties of these cyclic pentaamines will be reported elsewhere.

To protect the primary amine group for appending additional coordinating arms onto the four nitrogen atoms of the macrocycle, compound **8** was treated with 1 equiv. of benzaldehyde. Only traces of the expected Schiff base were observed, with both ^{1}H and ^{13}C NMR spectra exhibiting signals characteristic of the presence of an aminal moiety. It was proven by X-ray analysis of the [13]aneN4 derivative **10** (Figure 4) that the initial reaction of the primary amine with the aldehyde was followed by the thermodynamically favored formation of a hexahydropyrimidine six-membered ring (Scheme 2). Similar results were obtained with other aldehydes as well as with the cyclen series. The X-ray structure of the cyclen derivative **9** containing an anthracene moiety is shown in Figure 4.

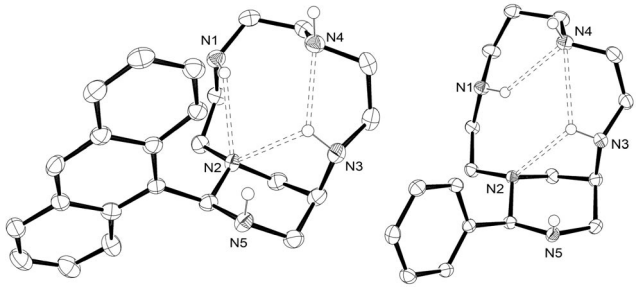
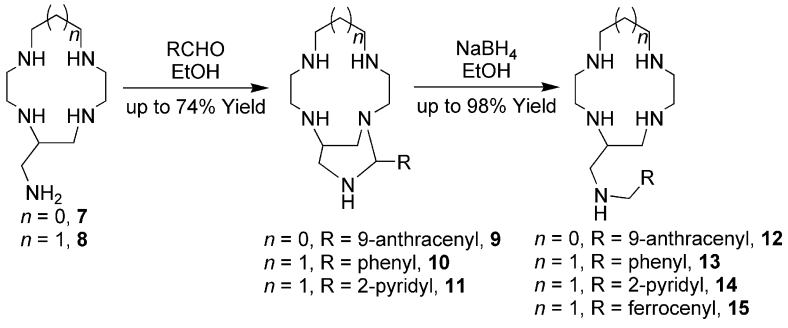


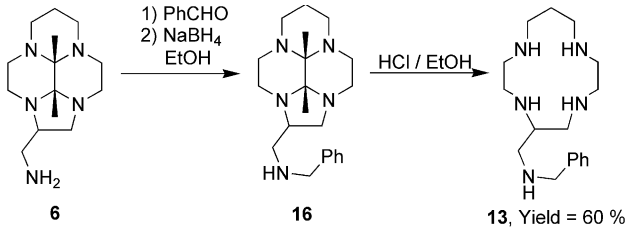
Figure 4. ORTEP[14] view of compounds **9** (left) and **10** (right), showing thermal ellipsoids at the 50% probability level. Hydrogen atoms attached to carbon atoms of the cyclic backbone have been omitted for clarity. Hydrogen bonds are indicated by dashed lines. Intramolecular N–H···N distances are 2.897, 2.904, and 2.964 Å for N1–N2, N3–N4, and N3–N2, respectively, in **9** and 3.142, 2.903, and 2.984 Å for N1–N4, N3–N2, and N3–N4, respectively, in **10**.

The aminal intermediates were quantitatively reduced by sodium borohydride in ethanol. Because two compounds could result from the opening of the aminal bridge, compound **13** was synthesized following another route, that is, the bis-aminal intermediate **6** was first treated with benzaldehyde before reduction and removal of the protecting bis-aminal group in the last step (Scheme 3).

The superimposition of the NMR spectra of the two compounds prepared by the two different routes proved unambiguously that the cleavage of the aminal group in **10** occurred selectively leading to the formation of the



Scheme 2. Selective *N*-alkylation of macrocycles **7** and **8**.



Scheme 3. Alternative route to macrocycle **13**.

(benzylamino)methyl-[13]aneN4 derivative **13**. This remarkable reaction provides a convenient access to new macrocycles functionalized on the exocyclic nitrogen atom. Indeed, any aliphatic or aromatic aldehyde, such as 2-pyridinecarbaldehyde or ferrocenecarbaldehyde, can be used.

Conclusions

We have devised a very efficient synthesis of *C*-functionalized tetraazacycloalkanes. Aminomethyl derivatives of cyclen and [13]aneN4 have been prepared in quite good overall yields. We are currently investigating the reactivity of the benzotriazole bis-aminal adduct with nucleophilic agents other than the cyanide ion. Preliminary results have shown that various Grignard reagents as well as other carbanions, such as the malonate ion, could be successfully used, which means that the scope of this reaction is not limited to the preparation of compounds described herein. We would also like to point out the peculiar reactivity of the *C*-aminomethyl macrocycles with aldehydes, which results in the highly regioselective *N*-functionalization of the pendant primary amine group. This reaction provides a very efficient access to a wide range of valuable bifunctional chelating agents based on the cyclen and [13]aneN4 macrocycles.

Experimental Section

General: NMR spectra were recorded with a Bruker 300, 500, or 600 spectrometer (300, 500, or 600 MHz for ^{1}H; 75, 125, or 150 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to the residual peak of [D]chloroform (δ = 7.25 or 77.00 ppm for ^{1}H or ^{13}C). The following abbreviations are used; s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br.: broad. Elemental analyses were performed at the PACSMUB at the University of Burgundy. Mass spectra were obtained by the MALDI-TOF (matrix-assisted laser desorption ionization time of flight) method with a Bruker DALTONICS Proflex III spectrometer or by ESI (electrospray ionization) with a Bruker MicroTOF-Q spectrometer. Infrared spectra were recorded with a Bruker Vector 22 spectrometer in ATR mode. CCDC-749971 (for **3**), -749972 (for **4**), -749973 (for **7**), -749974 (for **8**), -749975 (for **9**), and -749976 (for **10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

***cis*-9b,9c-Dimethyldecahydro-2a,4a,6a,8a-tetraazacyclopenta[*fg*]acenaphthylene-1-carbonitrile (3):** A solution of 2,3-butanedione (33.5 g, 0.39 mol) was added to a solution of dry triethylenetetraamine (57.0 g, 0.39 mol) and calcium hydroxide (57.70 g, 0.78 mol) in acetonitrile (2 L) at 0 °C. The mixture was stirred at this temperature for 2 h. After filtration, an orange solution was obtained and benzotriazole (46.4 g, 0.39 mol, 1 equiv.) and K_2CO_3 (107.6 g, 0.78 mol, 2 equiv.) were added at 0 °C. A solution of chloroacetaldehyde dried with $MgSO_4$ (60.84 g, 0.39 mol) in acetonitrile (500 mL) was slowly added at 0 °C and the resulting mixture was stirred for 3 h. NaCN (19.21 g, 1 equiv.) was added. The mixture was stirred overnight at room temperature. The solution was filtered through Celite and the solid was washed with acetonitrile (500 mL). The filtrate was evaporated. The resulting solid was dissolved in chloroform (1 L). After filtration, the solvent was removed and the residual brown solid was taken up in diethyl ether (2 L) and stirred at room temperature overnight. The impurities were eliminated by filtration and the solvent was removed. The residual solid was purified by aluminium oxide chromatography [solvent: CH_2Cl_2/pentane (95:5)]. Two diastereoisomers were obtained as a yellow oil (yield 28.5 g, 0.12 mol, 29%). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 1.07 (m, 9 H), 1.31 (s, 3 H), 2.48–3.22 (m, 26 H), 3.34–3.52 (m, 3 H), 4.21 (m, 1 H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 300 K): δ = 13.8, 14.0, 14.4, 16.4 (CH_3), 42.6, 42.8, 43.8, 44.2, 45.8, 46.5, 47.4, 47.9, 49.6, 49.7, 50.3, 50.7, 51.1, 53.4 (CH_2-α), 55.7, 56.5 (CH), 78.0, 78.3, 79.5, 80.0 (N-C-N), 119.7, 120.4 (CN) ppm. IR: $\tilde{\nu}$ = 2233 (CN) cm^{-1}. MS (MALDI-TOF): *m*/*z* = 247.76 [M]$^+$.

***cis*-9b,9c-Dimethyldecahydro-2a,4a,7a,9a-tetraazacyclopenta[*cd*]-phenylene-1-carbonitrile (4):** A solution of 2,3-butanedione (27.45 g, 0.319 mol) in acetonitrile (10 mL) was added to a solution of *N*,*N*-bis(aminoethyl)propane-1,3-diamine (51.1 g, 0.319 mmol) in acetonitrile (1.5 L) at 0 °C. The mixture was stirred at this temperature for 2 h. Benzotriazole (38.1 g, 1 equiv.) and K_2CO_3 (88.2 g, 2 equiv.) were added. A solution of 50% chloroacetaldehyde in water (50.1 g, 0.319 mol) was slowly added at 0 °C and the resulting mixture was stirred for 3 h. NaCN (15.6 g, 1 equiv.) was added and the mixture was stirred overnight at room temperature. Then the solution was filtered through Celite and washed with acetonitrile (100 mL). The filtrate was evaporated. The resulting solid was dissolved in CH_2Cl_2 (500 mL). After filtration, the organic phase was washed with a 3 M NaOH solution (200 mL). After extraction, the organic phase was dried with $MgSO_4$ and the solvent was evaporated. The residual brown solid was purified by aluminium oxide chromatography (eluent: CH_2Cl_2). Compound **4** was obtained as a white powder; m.p. 152.1(5) °C; yield 40.73 g, 0.156 mol, 49%. Single crystals of **4** were obtained by slow evaporation of cyclohexane. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 1.03 (s, 3 H), 1.12 (m, 2 H), 1.29 (s, 6 H), 1.31 (s, 3 H), 2.26–3.69 (m, 32 H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 300 K): δ = 11.5, 11.7, 13.5, 14.9 (CH_3), 18.1 (×2) (CH_2-β), 42.3, 43.9, 45.4 (×2), 45.5, 45.6, 47.3, 47.4, 47.6, 47.9, 48.0, 49.5, 49.6, 49.7 (CH_2-α), 56.3 (×2) (CH), 72.6, 72.9, 80.2, 80.4 (N-C-N), 119.2, 120.3 (CN) ppm. IR: $\tilde{\nu}$ = 2228 (CN) cm^{-1}. MS (MALDI-TOF): *m*/*z* = 261.97 [M]$^+$.

***cis*-(9b,9c-Dimethyldecahydro-2a,4a,6a,8a-tetraazacyclopenta[*fg*]acenaphthylen-1-yl)methanamine (5):** A solution of **3** (28.5 g, 0.12 mol) in dry THF was slowly added to a suspension of $LiAlH_4$ (5.25 g, 0.14 mol) in THF (250 mL) under nitrogen at –78 °C. The resulting mixture was stirred overnight. Water (50 mL) was carefully added at –78 °C to the mixture to neutralize the excess $LiAlH_4$. After removal of the solvent, the residual white solid was taken up in chloroform (500 mL), insoluble impurities were eliminated by filtration and washed with NaOH (8 M) solution. Two diastereoisomers were obtained as a yellow oil (yield 28.0 g, 0.11 mol, 96%). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 1.05–1.55 (m, 16 H), 2.36–3.44 (m, 34 H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 300 K): δ = 13.9, 14.0, 16.6, 23.0 (CH_3), 43.3, 43.9, 44.4 (×2), 44.8,

45.2, 45.6, 46.1, 46.4, 48.6, 50.1, 50.5, 51.3, 51.4, 52.3, 55.7 (CH_2-α), 60.5, 63.3 (CH), 77.3, 78.4, 79.4, 80.3 (N-C-N) ppm. MS (MALDI-TOF): *m*/*z* = 251.32 $[M]^+$.

***cis*-(9b,9c-Dimethyldecahydro-2a,4a,7a,9a-tetraazacyclopenta[*cd*]-phenylen-1-yl)methanamine (6):** A solution of **4** (40.73 g, 0.156 mol) in dry THF (50 mL) was slowly added to a suspension of $LiAlH_4$ (11.8 g, 0.31 mol, 2 equiv.) in THF (200 mL) under nitrogen at –78 °C. The resulting mixture was stirred overnight. Ethyl acetate (100 mL) and then water (25 mL) were carefully added. After removal of the solvent, the residual white-grey solid was taken up in chloroform (2 × 200 mL) and insoluble products were eliminated by filtration. Compound **6** was obtained as a colorless oil (yield 32.16 g, 78%) as two diastereoisomers. ^1H NMR (300 MHz, $CDCl_3$, 300 K): δ = 1.04 (s, 3 H), 1.12 (s, 3 H), 1.27 (s, 2.9 H), 1.28 (s, 2.9 H), 1.76 (m, 1.3 H), 2.2–3.6 (m, 26.6 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 300 K): δ = 11.9, 12.3 (×2), 13.4 (CH_3), 18.7, 25.8 (CH_2-β), 44.8, 44.9, 45.7, 45.9, 46.5, 46.6, 47.2 (×2), 48.0, 48.3, 48.4, 49.4, 50.0, 50.1, 51.0, 51.1 (CH_2-α), 61.8, 68.1 (C-H), 73.2, 73.4, 79.3, 80.5 (N-C-N) ppm. MS (MALDI-TOF): *m*/*z* = 265.82 $[M]^+$.

(1,4,7,10-Tetraazacyclododecan-2-yl)methanamine (7): A solution of 35% hydrochloric acid (40 mL, 0.4 mol, 7 equiv.) was slowly added to compound **5** (15.0 g, 0.06 mol). The mixture was heated at reflux overnight. After cooling at room temperature, a precipitate was formed. The light-brown solid was filtered and washed successively with ethanol and with diethyl ether. A white powder was obtained. Then the solid was taken up in a 16 M NaOH solution (20 mL) and extracted with chloroform. Compound **7** was obtained as a yellow oil (yield 4.3 g, 0.02 mol, 39%). ^1H NMR (300 MHz, $CDCl_3$, 300 K): δ = 1.75 (s, 6 H), 2.49–2.66 (m, 17 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 300 K): δ = 44.1, 44.6, 46.0, 46.3, 46.4, 46.7, 46.8, 48.9 (CH_2-α), 57.2 (CH) ppm. MS (MALDI-TOF): *m*/*z* = 201.75 $[M]^+$.

(1,4,7,10-Tetraazacyclotridecan-5-yl)methanamine (8): A solution of 35% hydrochloric acid (107 mL, 1.2 mol, 10 equiv.) was added to a solution of **6** (32.16 g, 0.12 mol) in ethanol (200 mL). The resulting mixture was heated at reflux for 4 h. After cooling, the solution was filtered and washed with ethanol (50 mL) and then diethyl ether (100 mL). The solid was dissolved in a saturated 15 M NaOH solution (10 mL). After extraction with chloroform (2 × 150 mL), the organic phase was dried with $MgSO_4$ and the solvent was evaporated. Compound **8** was obtained as a white solid; m.p. 78.8(5) °C; yield 11.02 g, 42%. Single crystals of **8** were obtained by slow evaporation of pentane. ^1H NMR (300 MHz, $CDCl_3$, 300 K): δ = 1.63 (m, 2 H), 1.87 (s, 6 H), 2.67–2.76 (m, 17 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 300 K): δ = 28.9 (CH_2-β), 44.3, 46.2, 47.7, 49.0, 49.0, 49.7, 49.8, 50.8 (CH_2-α), 59.0 (CH) ppm. MS (MALDI-TOF): *m*/*z* = 215.68 $[M]^+$. $C_{10}H_{25}N_5 \cdot 0.2H_2O$ (221.62): calcd. C 54.86, H 11.69, N 31.99; found C 55, H 11.57, N 31.81.

14-(Anthracen-9-yl)-1,4,7,10,13-pentaazabicyclo[9.3.1]pentadecane (9): Anthracene-9-carbaldehyde (0.25 g, 1.25 mmol) was added to a solution of **7** (0.25 g, 1.25 mmol) in ethanol (20 mL) at room temperature. The mixture was stirred at room temperature for 12 h. Then the solvent was removed and the residual oil was taken up in diethyl ether (50 mL). The insoluble salts were removed by filtration and after 12 h crystals appeared. After filtration, compound **9** was obtained as yellow needles; m.p. 153.4(5) °C; yield 0.3 g, 0.5 mmol, 61%. ^1H NMR (600 MHz, $CDCl_3$, 300 K): δ = 2.08–3.06 (m, 36 H), 3.14–3.25 (m, 4 H), 3.53 (m, 1 H), 3.84–4.08 (m, 2 H), 5.64–5.86 (m, 1 H), 7.40–7.51 (m, 8 H), 7.92–8.08 (m, 4 H), 8.47 (m, 4 H), 9.43 (m, 2 H) ppm. $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, 300 K): δ = 43.3, 44.9, 45.2, 46.0, 46.2, 46.6, 46.7, 46.7, 46.8, 48.3, 48.6, 50.0, 50.2, 52.2, 52.7, 52.9, 55.5, 66.2 (CH_2-α), 77.9, 81.5 (CH-aminal), 123.2, 124.5, 124.6, 124.8 (×2), 125.2, 125.3 (×2), 125.4 (×2), 125.6, 126.2, 126.8 (×2), 128.3, 128.7, 128.9 (×2), 129.0, 129.3, 129.4, 129.6, 129.7, 130.0, 130.5, 130.7, 131.5, 132.2 (C_{ar}) ppm. ESI: *m*/*z* = 390.26 $[M^+ + H]$. $C_{24}H_{31}N_5$ (389.54): calcd. C 74.00, H 8.02, N 17.98; found C 73.61, H 8.80, N 18.26.

15-Phenyl-1,4,8,11,14-pentaazabicyclo[10.3.1]hexadecane (10): Benzaldehyde (0.3 mL, 3.5 mmol) was added at 0 °C to a solution of **8** (0.76 g, 3.5 mmol) in ethanol (50 mL). The mixture was stirred at this temperature for 5 h. The solvent was evaporated and the residual oil was taken up in pentane (50 mL). The insoluble impurities were removed by filtration. Compound **10** was obtained as colorless crystals upon slow evaporation of the solvent; m.p. 93.8(5) °C; yield 0.74 g, 2.4 mmol, 70%. Two diastereoisomers were obtained. ^1H NMR (300 MHz, $CDCl_3$, 300 K): δ = 1.43–3.30 (m, 46 H), 3.96 (s, 1 H), 4.37 (s, 1 H), 7.26–7.56 (m, 10 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 300 K): δ = 32.0, 32.5 (CH_2-β), 51.0 (×2), 51.7, 51.8, 53.0, 53.1, 53.7, 54.6, 54.7, 54.9, 55.5, 55.6, 56.1, 56.5, 57.1, 57.2 (CH_2-α), 67.9 (×2) (CH), 85.8, 90.0 (N-C-N), 131.0 (×3), 131.8, 132.1, 132.2 (×3), 132.5 (×2) (CH_{ar}), 145.0, 145.4 (C_{ar}) ppm. MS (MALDI-TOF): *m*/*z* = 304.09 $[M + H]^+$. $C_{17}H_{29}N_5$ (303.45): calcd. C 67.09, H 9.63, N 23.08; found C 67.31, H 9.66, N 22.40.

15-(Pyridin-2-yl)-1,4,8,11,14-pentaazabicyclo[10.3.1]hexadecane (11): 2-Pyridinecarbaldehyde (0.22 g, 2 mmol) was added at 0 °C to a solution of **8** (0.44 g, 2 mmol) in ethanol (50 mL). The mixture was stirred at this temperature overnight. The solvent was evaporated, and the residual oil was taken up in pentane (50 mL). The insoluble impurities were removed by filtration. After evaporation of the solvent, compound **11** was obtained as a colorless oil; yield 0.45 g, 1.5 mmol, 74%. Two diastereoisomers were obtained. ^1H NMR (300 MHz, $CDCl_3$, 300 K): δ = 1.15–3.19 (m, 46 H), 4.06 (s, 1 H), 4.41 (s, 1 H), 7.15 (m, 2 H), 7.36 (m, 2 H), 7.51 (m, 2 H), 8.49 (m, 2 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 300 K): δ = 28.2, 28.8 (CH_2-β), 47.1, 47.2, 48.0, 49.2 (×2), 49.5, 50.6, 50.8, 51.1, 51.6, 51.7, 51.8, 52.3, 52.6, 53.5, 53.6 (CH_2-α), 64.5 (×2) (CH), 82.8, 86.2 (N-C-N), 122.1, 122.2, 123.2, 123.3, 136.6, 137.0, 149.4, 149.5 (CH_{ar}), 160.0, 160.7 (C_{ar}) ppm.

***N*-[(1,4,7,10-Tetraazacyclododecan-2-yl)methyl]-1-(anthracen-9-yl)-methanamine (12):** $NaBH_4$ (0.15 g, 3.84 mmol) was added to a solution of **9** (0.3 g, 0.77 mmol) in ethanol (10 mL) at room temperature. The mixture was stirred at room temperature for 12 h. The solvent was then removed and the residual orange oil was taken up in diethyl ether (20 mL). The insoluble salts were removed by filtration through CLARCEL®. After evaporation of the solvent compound **12** was obtained as a yellow oil; yield 0.20 g, 0.51 mmol, 67%. ^1H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.89 (br. s, 4 H), 2.25–2.73 (m, 18 H), 4.50 (m, 2 H), 7.31 (m, 4 H), 7.80 (m, 2 H), 8.19 (m, 3 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 300 K): δ = 44.3, 45.9 (×2), 46.0, 46.3, 46.8, 47.0, 49.0, 52.7 (CH_2-α), 55.1 (CH), 124.3, 124.9, 126.0, 127.0, 129.0, 130.3, 131.5, 131.9 (C_{ar}) ppm.

***N*-[(1,4,7,10-Tetraazacyclotridecan-5-yl)methyl]-1-phenylmethanamine (13):** $NaBH_4$ (0.11 g, 3 mmol, 10 equiv.) was added at 0 °C to a solution of **10** (90 mg, 297 μmol) in ethanol (25 mL). The mixture was heated at reflux overnight. The solvent was evaporated and the residual solid was taken up in chloroform (50 mL). After filtration and evaporation of the solvent, the residual oil was taken up in pentane (30 mL). The insoluble impurities were removed by filtration. After evaporation of the solvent, compound **13** was obtained as a colorless oil; yield 90 mg, 297 μmol, 98%. ^1H NMR (300 MHz, $CDCl_3$, 300 K): δ = 1.60 (m, 2 H), 2.19 (s, 5 H), 2.44–

2.72 (m, 17 H), 3.70 (s, 2 H), 7.22 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 300 K): δ = 32.5 (CH_2-β), 49.8, 51.3, 52.4, 52.8, 53.3 (×2), 54.7, 55.5, 57.8 (CH_2-α), 60.7 (CH), 130.4, 131.6 (×2), 131.9 (×2) (CH_{ar}), 139.5 (C_{ar}) ppm. MS (MALDI-TOF): *m*/*z* = 306.10 $[M]^+$.

***N*-[(1,4,7,10-Tetraazacyclotridecan-5-yl)methyl]-1-(pyridin-2-yl)-methanamine (14):** $NaBH_4$ (0.55 g, 14 mmol, 10 equiv.) was added to a solution of **11** (0.44 g, 1.4 mmol) in ethanol (50 mL) at room temperature. The mixture was heated at reflux overnight. The solvent was evaporated and the residual solid was taken up in chloroform (50 mL). After filtration and evaporation of the solvent, compound **14** was obtained as a colorless oil (yield 0.44 g, 1.4 mmol, 100%). ^1H NMR (300 MHz, $CDCl_3$, 300 K): δ = 1.63 (m, 2 H), 2.4–2.6 (m, 18 H), 3.84 (s, 2 H), 7.06 (s, 1 H), 7.22 (s, 1 H), 7.56 (s, 1 H), 8.49 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 300 K): δ = 32.8 (CH_2-β), 49.8, 51.4, 52.4, 52.8, 53.3 (×2), 54.8, 55.8, 59.1 (CH_2-α), 60.7 (CH), 125.5, 125.8, 140.0, 152.9 (CH_{ar}), 163.6 (C_{ar}) ppm. MS (MALDI-TOF): *m*/*z* = 307.03 $[M]^+$.

***N*-[(1,4,7,10-Tetraazacyclotridecan-5-yl)methyl]-1-(ferrocenyl)methanamine (15):** Ferrocenecarbaldehyde (1.07 g, 5 mmol) was added to a solution of **8** (1.08 g, 5 mmol) in ethanol (50 mL) at room temperature. The mixture was stirred at room temperature for 2 h. $NaBH_4$ (1.9 g, 50 mmol, 10 equiv.) was added and the mixture was heated at reflux overnight. The solvent was evaporated and the residual solid was taken up in chloroform (50 mL). After evaporation of the solvent, the residual oil was taken up in acetonitrile (50 mL). The insoluble impurities were removed by filtration. After evaporation of the solvent, compound **15** was obtained as a brown oil; yield 1.16 g, 2.8 mmol, 56%. ^1H NMR (300 MHz, $CDCl_3$, 300 K): δ = 1.81 (m, 2 H), 2.65–2.80 (m, 17 H), 3.62 (s, 2 H), 4.22–4.31 (m, 9 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 300 K): δ = 27.0 (CH_2-β), 44.4, 45.8, 46.8, 47.0 (×2), 47.2 (×2), 49.2, 50.4 (CH_2-α), 55.1 (CH), 74.9 (×2), 75.3 (×2), 75.7 (×5) (CH_{ar}), 85.4 (C_{ar}) ppm. MS (MALDI-TOF): *m*/*z* = 414.06 $[M]^+$.

***N*-[(1,4,7,10-Tetraazacyclotridecan-5-yl)methyl]-1-phenylmethanamine (13) (alternative route):** Benzaldehyde (2.34 g, 22.07 mmol) was added to a solution of **6** (5.86 g, 22.07 mmol) in ethanol (100 mL) at room temperature. The mixture was stirred at room temperature for 12 h. Then $NaBH_4$ (1.66 g, 44.0 mmol, 2 equiv.) was added and the resulting mixture was stirred for 12 h. The solvent was removed and the residual white solid was taken up in dichloromethane (50 mL). The insoluble salts were removed by filtration through CLARCEL®. The solvent was removed by evaporation to yield the bis-aminal intermediate **16** as an oil, which was taken up in ethanol (50 mL). A solution of 37% hydrochloric acid (10 equiv., 20 mL) was added and the mixture was heated at reflux for 12 h. The solvent was removed by evaporation and the residual oil was taken in a 16 M solution of NaOH (10 mL). Chloroform (50 mL) was added and the organic phase was extracted and dried with magnesium sulfate. After filtration and evaporation of the solvent, compound **13** was obtained as a yellow oil; yield 4.14 g, 13.56 mmol, 59.7%.

Supporting Information (see footnote on the first page of this article): Experimental procedures for the synthesis of all compounds and X-ray data for compounds **3**, **4**, and **7**–**10**.

Acknowledgments

This work was supported by the Centre National de la Recherche Scientifique (CNRS), the French Ministry of Research, and the Regional Council of Burgundy. Y. R. and N. S. especially acknowledge the French Ministry for Research for Ph. D. grants.

[1] a) X. Y. Liang, P. J. Sadler, *Chem. Soc. Rev.* **2004**, *33*, 246; b) R. Delgado, V. Felix, L. M. P. Lima, D. W. Price, *Dalton Trans.* **2007**, 2734.

[2] a) V. Jacques, J.-F. Desreux, *Top. Curr. Chem.* **2002**, *221*, 123; b) A. E. Toth, E. Merbach, *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging* **2001**, Wiley, Chichester; c) L. M. De Leon-Rodriguez, Z. Kovacs, *Bioconjugate Chem.* **2008**, *19*, 391.

[3] a) S. Liu, D. S. Edwards, *Bioconjugate Chem.* **2001**, *12*, 7; b) S. Liu, *Adv. Drug Delivery Rev.* **2008**, 1347; c) K. Tanaka, K. Fukase, *Org. Biomol. Chem.* **2008**, *6*, 815.

[4] T. Gunnlaugsson, J. P. Leonard, *Chem. Commun.* **2005**, 3114.

[5] a) F. Denat, S. Brandès, R. Guilard, *Synlett* **2000**, 561; b) F. Boschetti, F. Denat, E. Espinosa, A. Tabard, Y. Dory, R. Guilard, *J. Org. Chem.* **2005**, *70*, 7042; c) J. Massue, S. E. Plush, C. S. Bonnet, D. A. Moore, T. Gunnlaugsson, *Tetrahedron Lett.* **2007**, *48*, 8052; d) A. Barge, L. Tei, D. Upadhyaya, F. Fedeli, L. Beltrami, R. Stefania, S. Aime, G. Cravotto, *Org. Biomol. Chem.* **2008**, *6*, 1176; e) C. Wängler, B. Wängler, M. Eisenhut, U. Haberkorn, W. Mier, *Bioorg. Med. Chem.* **2008**, *16*, 2606; f) M. Suchy, R. H. E. Hudson, *Eur. J. Org. Chem.* **2008**, 4847.

[6] K.-P. Eisenwiener, P. Powell, H. R. Mäcke, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2133.

[7] a) F. Boschetti, F. Denat, E. Espinosa, J.-M. Lagrange, R. Guilard, *Chem. Commun.* **2004**, 588; b) E. A. Lewis, C. C. Allan, R. W. Boyle, S. J. Archibald, *Tetrahedron Lett.* **2004**, *45*, 3059.

[8] R. Ruloff, E. Toth, R. Scopelliti, R. Tripier, H. Handel, A. E. Merbach, *Chem. Commun.* **2002**, 2630.

[9] a) F. Boschetti, F. Denat, E. Espinosa, R. Guilard, *Chem. Commun.* **2002**, 312; b) G. Hervé, H. Bernard, N. Le Bris, J. J. Yaouanc, H. Handel, *Tetrahedron Lett.* **1998**, *39*, 6861.

[10] a) R. W. Sandnes, J. Vasilevskis, K. Undheim, M. Gacek, WO 96/28432, **1996**; b) M. Argese, G. Ripa, A. Scala, V. Valle, WO 97/49691, **1997**; c) R. W. Sandnes, M. Gacek, K. Undheim, *Acta Chem. Scand.* **1998**, *52*, 1402; d) J. Platzek, K. Hoyer, K.-D. Graske, B. Radüchel, WO 00/32581, **2000**.

[11] a) W. C. Baker, M. J. Choi, D. C. Hill, J. L. Thompson, P. A. Petillo, *J. Org. Chem.* **1999**, *64*, 2683; b) J. Rohovec, R. Gyepes, I. Cisarova, J. Rudovsky, I. Lukes, *Tetrahedron Lett.* **2000**, *41*, 1249; c) N. Bernier, R. Tripier, V. Patinec, M. Le Baccon, H. Handel, *C. R. Chim.* **2007**, *10*, 832; d) A. D. Averin, A. V. Shukhaev, A. K. Buryak, F. Denat, R. Guilard, I. P. Beletskaya, *Tetrahedron Lett.* **2008**, *49*, 3950.

[12] A. R. Katritzky, W. Q. Fan, C. Fu, *J. Org. Chem.* **1990**, *55*, 3209.

[13] F. Boschetti, F. Chaux, F. Denat, R. Guilard, H. Ledon, WO **2005**/000823, **2005**.

[14] L. Farrugia, *J. Appl. Crystallogr.* **1997**, *30*, 565.

Received: October 19, 2009
Published Online: February 16, 2010

