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Efficient Synthesis of 1,4,7-Triazacyclononane and 1,4,7-Triazacyclononane-Based Bifunctional Chelators for Bioconjugation

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The reaction of diethylenetriamine with chloroacetaldehyde yielded a bicyclic aminal intermediate for the synthesis of 1,4,7-triazacyclononane (TACN), a macrocyclic polyamine the derivatives of which find applications as catalysts, bleaching agents, and chelators for medical imaging. This new synthetic protocol outperforms the synthetic methods described so far because it does not involve any cyclization step. Moreover, this aminal intermediate allowed access to a new family of TACN derivatives functionalized on the carbon skeleton, for example, *C*-aminomethyl-TACN. This novel compound is a precursor of valuable bifunctional chelating agents for nuclear medicine, in particular, for the preparation of PET imaging agents after bioconjugation and metallation with ^{68}Ga or ^{64}Cu.

Introduction

The interest in the synthesis of 1,4,7-triazacyclononane (TACN) and its derivatives has increased due to the use of their metal complexes in a wide range of applications, from catalysis to molecular imaging. This class of compounds has appeared in more than 300 patents in 30 years. Numerous metal complexes have been prepared, including $Mn^{II–V}$, Fe^{II}, Fe^{III}, $Ru^{II–IV}$ and Ru^{VI}, Co^{III}, Ga^{III}, Cu^{II}, and Zn^{II}.[1] The ability of triazacyclononane derivatives to stabilize high oxidation states of metal ions, in particular manganese, has led to the development of such complexes as oxidation catalysts. In particular, the ligand 1,4,7-trimethyl-1,4,7-triazacyclononane (MeTACN) has been the subject of many studies because of the catalytic activity of its binuclear manganese tris-oxo complex $[(MeTACN)_2Mn_2O_3]^{2+}$.[2] MeTACN–Mn^{IV} complexes have been used as bleaching agents in laundry formulations[2b] and as catalysts in olefin polymerization[3] and olefin epoxidation with hydrogen peroxide in water[4] or organic solvents[5] as well as in other oxidation processes.[6] Protein orientation at interfaces,[7] metalloenzyme biosite models,[8] and magnetic molecule clusters[9] are other examples of domains in which TACN derivatives have been exploited.

The interest in these macrocyclic molecules has continued to grow in the past 10 years in the field of nuclear medicine, particularly in the development of radiopharmaceuticals for diagnosis (imaging) and therapy (radioimmunotherapy).[10] Indeed, TACN derivatives provide versatile platforms for obtaining efficient bifunctional chelating agents (BFCA) capable of strongly coordinating a radio-metal (such as ^{111}In, $^{67/68}$Ga, $^{64/67}$Cu, and ^{90}Y for SPECT, PET imaging, or radiotherapy applications) and ensuring the attachment of the targeting vector. TACN is also an efficient chelator for the preparation of ^{99m}Tc radiopharmaceuticals.[10e] Derivatives bearing additional coordinating groups, such as carboxylates[11] and phosphinates,[12] have been particularly used in the development of BFCAs with optimal properties for Cu^{II} and Ga^{II} chelation.

Despite the interest in TACN derivatives, only a few synthetic methodologies have been reported in the literature. The only reported synthesis of TACN follows the general procedure for the preparation of macrocyclic polyamines developed by Richman and Atkins 40 years ago.[13] However, this method suffers from many drawbacks, for example, the use of tosyl groups to preorganize the intermediates to favor intramolecular cyclization is not atom-economic. Moreover, the method requires long reaction times and although the macrocyclization step is generally efficient, harsh conditions are required to remove the tosyl groups. The method has also been extended to the synthesis of *C*-functionalized TACN derivatives by using bis-electrophilic synthons that are functionalized on a carbon atom.[14] Such *C*-functionalized macrocycles are of special interest for the synthesis of BFCAs because the targeted biomolecule can be attached to a carbon atom of the TACN derivative with the three nitrogen atoms remaining available for further functionalization with coordinating arms. This approach, however, requires the preparation of a sophisticated *C*-functionalized precursor that must be resistant to the deprotec-

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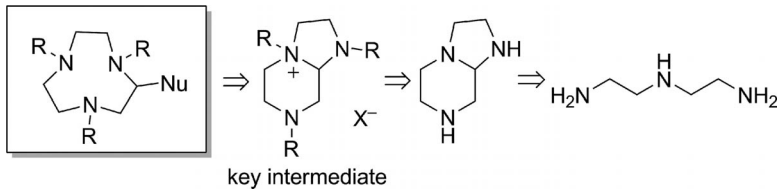


Figure 1. Retrosynthetic scheme for TACN and its *N*- and *C*-functionalized derivatives.

tion conditions. A method allowing functionalization of a carbon atom starting from MeTACN and involving a bicyclic pyrazinium salt as key intermediate has been reported in the literature,[15] however, this method requires the preliminary synthesis of MeTACN by the method of Richman and Atkins and is limited to the synthesis of *C*-functionalized MeTACN.

Inspired by the previous work, a new methodology using the "aminal tool" has been developed in our group to easily synthesize TACN and its *N*- and *C*-functionalized derivatives. The process involves three different steps: 1) The synthesis of an aminal intermediate from the commercially available linear diethylenetriamine, 2) functionalization of the secondary amines and quaternization of the tertiary amine of the aminal with a suitable electrophilic reagent, and 3) double-ring-opening by nucleophilic attack (Figure 1).

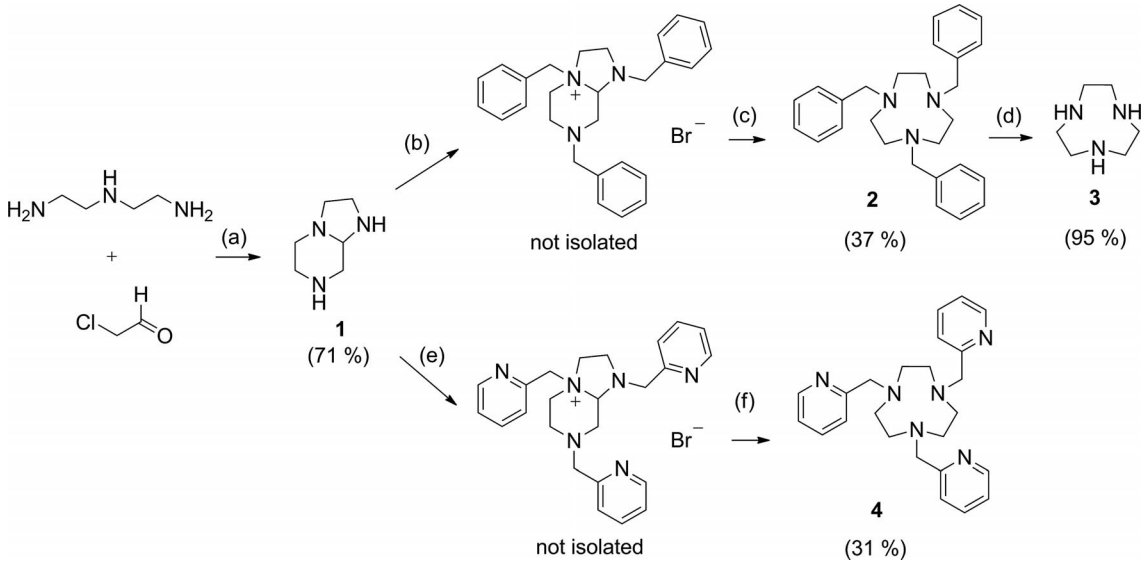
Results and Discussion

The aminal intermediate **1** was easily obtained by addition of chloroacetaldehyde to diethylenetriamine in the presence of potassium carbonate (Scheme 1). Next, 3 equiv. of benzyl bromide were added to compound **1** to yield the expected ammonium salt, which was not isolated. The ammonium salt was treated with $NaBH_4$ as a hydride nucleophilic agent, undergoing ring-opening and resulting in the formation of compound **2** in 37% yield after recrystallization in water.

The structure of **2** in its doubly protonated form was confirmed by X-ray diffraction (Figure 2). Compound **2** crystallizes with two chloride anions and three water molecules. The protons on the macrocycle were located in the Fourier difference map. The distances C2–N2, C3–N2, and C14–N2 [1.474(3), 1.467(3), and 1.482(3) Å, respectively] are shorter than those of protonated nitrogen atoms [C1–N1 1.512(3) Å, C6–N1 1.516(3) Å, C7–N1 1.535(3) Å, C5–N3 1.506(3) Å, C4–N3 1.504(3) Å, C21–N3 1.519(3) Å], which is in agreement with the protonation scheme.

Finally, the benzyl groups of **2** were cleaved by hydrogenolysis to give TACN **3** in 95% yield after recrystallization. The process reported herein is very efficient and reproducible. It gives access to TACN in three steps from the commercially available linear diethylenetriamine in 25% overall yield. Moreover, no tedious chromatographic work-up was necessary, all the compounds being isolated by recrystallization. This new synthetic procedure outperforms the approach described so far, it can be easily scaled up (see Exp. Sect.), and it has been patented.[16]

This reaction can also be used for the preparation of *N*-functionalized TACN by using the desired electrophilic reagent for the synthesis of the ammonium salt. For example,



Scheme 1. Synthesis of TACN and *N*-functionalized TACN. Reagents and conditions: (a) 2 equiv. K_2CO_3, CH_3CN, room temp.; (b) 3 equiv. BnBr, 4 equiv. K_2CO_3, CH_3CN, 10 °C, 24 h; (c) 1 equiv. $NaBH_4$, EtOH, –10 °C, 12 h; (d) H_2, Pd/C, CH_3CO_2H, room temp., 3 d; (e) 3 equiv. 2-(bromomethyl)pyridine hydrobromide, 10 equiv. K_2CO_3, CH_3CN, 10 °C, 12 h; (f) 1 equiv. $NaBH_4$, EtOH, –10 °C, 12 h.

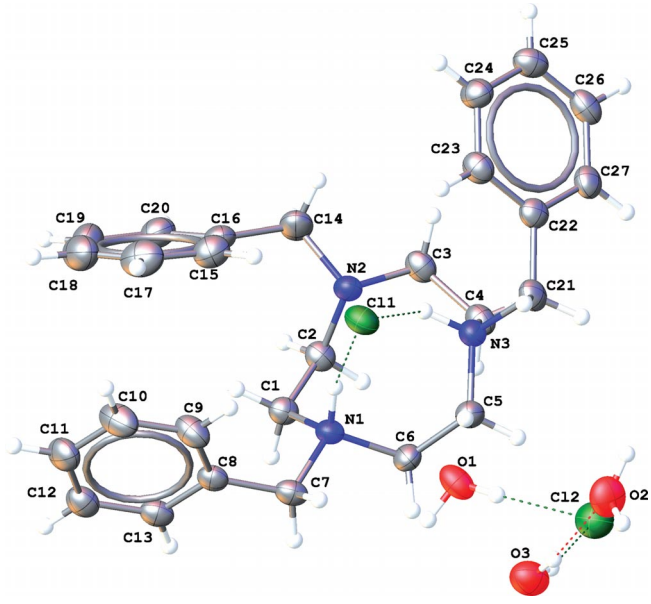
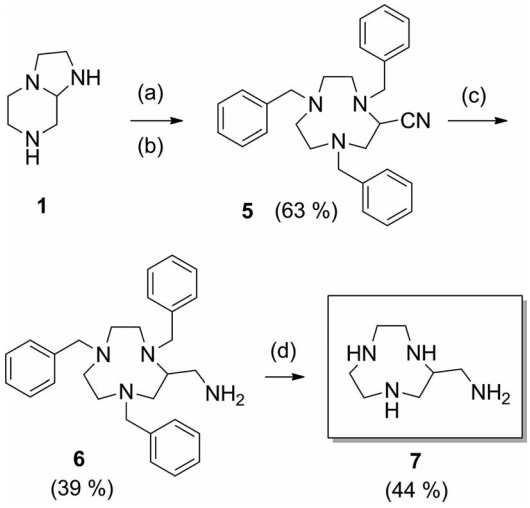


Figure 2. OLEX2[17] view of compound **2**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen bonds are shown as dashed lines.

the addition of 3 equiv. of a pyridine derivative instead of benzyl bromide gives access to compound **4** in three steps starting from the linear amine without the need for a protection/deprotection step (Scheme 1).

We then investigated the synthesis of new *C*-functionalized TACN derivatives. Thus, the addition of sodium cyanide to the quaternized ammonium salt yielded compound **5** in 63% yield (Scheme 2). The nitrile was reduced with $LiAlH_4$ and the benzyl groups then removed by hydrogenolysis to give the *C*-aminomethylTACN **7**.



Scheme 2. Synthesis of *C*-aminomethylTACN. Reagents and conditions: (a) 3 equiv. BnBr, 4 equiv. K_2CO_3, CH_3CN, 10 °C, 6 h; (b) 1 equiv. NaCN, room temp., 3 d; (c) 1.1 equiv. $LiAlH_4$, THF, –78 °C, 12 h; (d) H_2, Pd/C, $CH_3CO_2H/H_2O/THF$, room temp., 10 d.

Derivatives **6** and **7** were recrystallized and their structures elucidated by X-ray diffraction (Figures 3 and 4). Compound **6** is triprotonated and the protons were located in the Fourier difference maps on primary amine N4 and the two tertiary amines N1 and N3. The structure has four counter anions, and the compound crystallizes with a hydronium cation (O2) and one water molecule (O1). The protonation scheme of the macrocycle is also supported by the distances C2–N2, C3–N2, and C14–N2 [1.469(3), 1.469(3), and 1.474(3) Å, respectively], shorter than the ammonium C–N distance [C1–N1 1.505(3) Å, C6–N1 1.510(3) Å, C7–N1 1.521(3) Å, C4–N3 1.510(3) Å, C5–N3

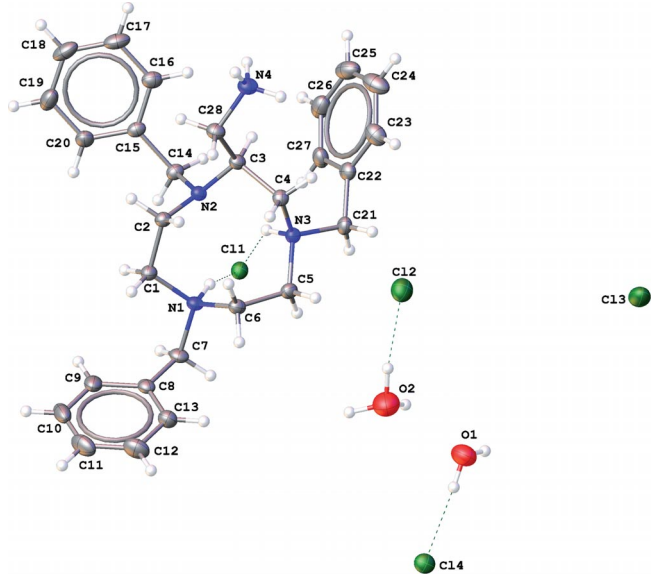


Figure 3. OLEX2[17] view of compound **6**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen bonds are shown as dashed lines.

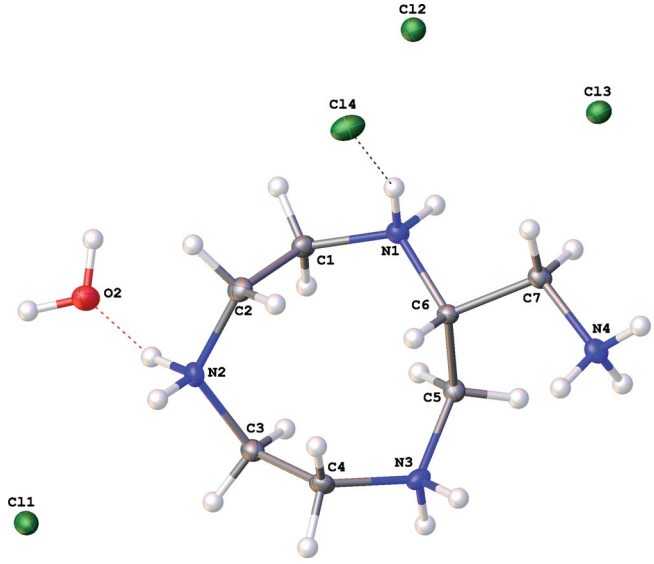
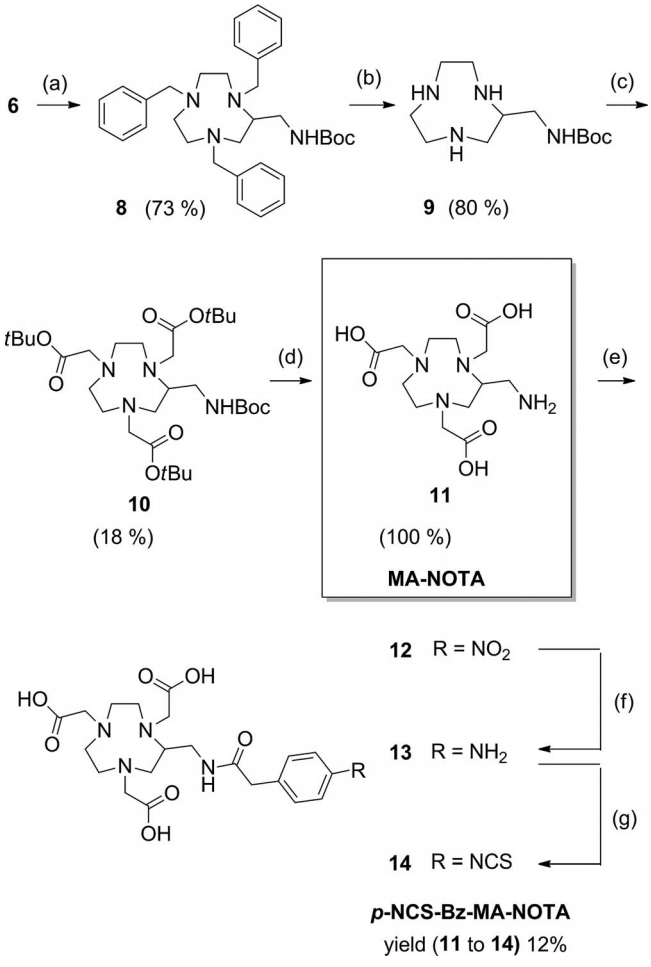


Figure 4. OLEX2[17] view of compound **7**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen bonds are shown as dashed lines.

1.511(3) Å, C21–N3 1.522(3) Å]. Compound **7**, which crystallizes with four chloride anions and one water molecule, was obtained in its fully protonated form. The protons on the amine were also located in the Fourier difference maps.

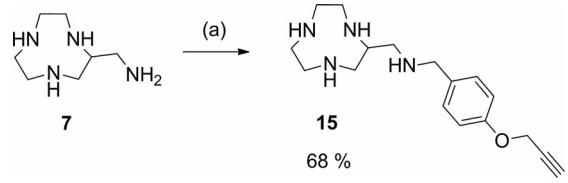
The protected and non-protected *C*-aminomethylTACNs **6** and **7**, respectively, represent highly valuable building blocks for the preparation of BFCAs. As a result of the powerful method described in this paper, a wide range of new promising BFCAs can be generated from these precursors by functionalization of the secondary and/or primary amino groups. To introduce various grafting functions, we used a protection/deprotection sequence starting from the synthon **6** (Scheme 3). The addition of 1 equiv. of Boc_2O to **6** followed by selective removal of the benzyl group by hydrogenolysis gave access to compound **9** in good yield. Such a strategy allows discrimination between primary and secondary nitrogen atoms and enables the introduction of various pendant coordinating arms for metal chelation prior to functionalization of the primary amine for further bioconjugation.



Scheme 3. Synthesis of the bifunctional chelating agents MA-NOTA and *p*-NCS-Bz-MA-NOTA. Reagents and conditions: (a) 1 equiv. Boc_2O, DCM, room temp., 12 h; (b) H_2, Pd/C, $CH_3CO_2H/H_2O/THF$, room temp., 2 d; (c) 3 equiv. *tert*-butyl bromoacetate, 7 equiv. K_2CO_3, DMF, 40 °C, 24 h; (d) TFA/CH_2Cl_2, room temp., 24 h; (e) *N*-succinimidyl 4-nitrophenylacetate, DIPEA, CH_3CN, room temp., 2 h; (f) H_2, 10% Pd/C, 1 d; (g) thiophosgene, CH_2Cl_2/H_2O, 3 h, room temp.

The three amines of the TACN ring of new precursor **9** were functionalized, followed by removal of the Boc protecting group (Scheme 3). Compound **10** was obtained by addition of 3 equiv. of *tert*-butyl bromoacetate followed by cleavage of all the protecting groups to give compound **11** (MA-NOTA). This method is highly versatile because any kind of grafting function can be introduced onto the primary amine in the last step. To demonstrate the potential use of compound **11** as a precursor of a new BFCA, we prepared a "ready-to-be-grafted" NOTA chelator, the so-called *p*-NCS-Bz-MA-NOTA (**14**). A pendant arm bearing a nitro functional group was easily introduced by using an activated ester precursor leading to compound **12**. The reaction was performed in a mixture of solvent (CH_3CN/water) to overcome solubility problems. After reduction of the nitro group by hydrogenolysis, the desired isothiocyanate function was introduced by the addition of thiophosgene.

Bearing in mind that compound **7** could also be modified without protection/deprotection steps, we investigated the reaction of **7** with aldehydes. Inspired by our previous work that revealed the versatility of using aldehyde to introduce a functional group selectively onto the amino pendant group of 13aneN4 derivatives,[18] we decided to explore this reaction by treating **7** with 1 equiv. of an aldehyde bearing an alkyne function. Treatment of the precursor **7** with 4-(prop-2-ynyloxy)benzaldehyde followed by reduction with $NaBH_4$ resulted in the formation of compound **15** in 68% yield (Scheme 4). Further functionalization of the secondary amines with coordinating arms will give access to new TACN-based BFCAs for site-specific bioconjugation using click chemistry.[19] Note that if the reaction of an aldehyde with **7** is selective towards the primary amine, the reaction with an activated carboxylic acid resulted in a mixture of products that we were not able to separate. In this case, an alternative synthetic strategy using intermediate **11** must be used.



Scheme 4. Synthesis of TACN precursor **15** for click chemistry. Reagents and conditions: (a) 4-(Prop-2-ynyloxy)benzaldehyde, EtOH, room temp., 48 h, 10 equiv. $NaBH_4$, EtOH, room temp., 12 h.

Conclusions

We have developed a new powerful methodology for the synthesis of TACN and *N*-functionalized TACNs via the key formation of an ammonium salt intermediate. The strategy was also used for the preparation of *C*-function-

alized derivatives, providing valuable building blocks for the synthesis of new BFCAs. Indeed, the use of suitable functionalization sequences allowed the selective introduction of coordinating pendant arms for metal chelation and grafting functions for bioconjugation. The chelator *p*-NCS-Bz-MA-NOTA bearing the isothiocyanate function is currently being used in our laboratory to label antibodies for immuno-PET applications. The extension of the method for the preparation of new BFCAs that contain other functional groups, such as maleimide or the thioctic moiety, which are suitable for attachment to cysteine or gold nanoparticles, respectively, is underway. Finally, the incorporation of a fluorescent dye will also give rise to a new class of SPECT or PET/optical probes for bimodal imaging applications.

Experimental Section

General: All chemicals were purchased from Acros and Aldrich and used without further purification. The precursor 3-(prop-2-ynyloxy)benzaldehyde was prepared as described in the literature.[20] Organic solvents were removed under reduced pressure by using a rotary evaporator. Water was removed from the products by lyophilization.

Octahydroimidazo[1,2-*a*]pyrazine (1): A solution of chloroacetaldehyde (50% in water, 111.8 g, 0.71 mol) in acetonitrile (500 mL) was added at 20 °C to a solution of diethylenetriamine (73.3 g, 0.71 mol) and K_2CO_3 (196.8 g, 1.42 mol, 2 equiv.) in acetonitrile (1 L). The mixture was stirred at this temperature for 6 h. After filtration through Celite, the solvent was evaporated. The oily residue was taken up in diethyl ether (800 mL) and insoluble impurities were removed by filtration. After evaporation of the solvent, compound **1** was isolated as a yellow oil (64.3 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 3.15 (dd, $^2J_{H,H}$ = 11.6, $^3J_{H,H}$ = 2.7 Hz, 1 H, C*H*$_2$CH), 3.06–2.96 (m, 2 H), 2.92–2.67 (m, 5 H), 2.48 (dd, $^2J_{H,H}$ = 11.6, $^3J_{H,H}$ = 8.0 Hz, 1 H, CH$_2$C*H*), 2.28–2.15 (m, 2 H), 1.72–1.62 (br. s, 2 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 75.9 (CH), 51.7 (CH$_2$α), 50.4, 48.6, 44.5, 42.2 ppm.

1,4,7-Tribenzyl-1,4,7-triazacyclononane (2): Benzyl bromide (353.97 g, 2.06 mol, 3 equiv.) was slowly added at 10 °C to a solution of **1** (87.61 g, 0.69 mol) and potassium carbonate (380 g, 2.76 mol, 4 equiv.) in acetonitrile (1.8 L). The mixture was stirred at room temperature overnight. After filtration through Celite, the solvent was removed. The product was then placed in ethanol (1.8 L) and sodium borohydride (26 g, 0.69 mol, 1 equiv) was added at –10 °C to the solution. After 12 h, the solvent was removed, the resulting mixture was taken up in chloroform (1.5 L), and insoluble salts were removed by filtration through Celite. After evaporation of the solvent, the residual oil was taken up in diethyl ether (1.5 L), and insoluble products were removed by filtration. The solvent was evaporated, the residual brown oil was placed in ethanol (200 mL), and hydrochloric acid (37%, 100 mL) was added. After evaporation of the solvent, acetone (500 mL) was added and the white precipitate thus formed was filtered and recrystallized from water (400 mL). The crystals were filtered and deprotonated with a 13 M NaOH solution until pH > 12. After extraction with chloroform, the organic phase was dried with $MgSO_4$. After filtration and evaporation of the solvent, compound **2** was obtained as a colorless oil (102 g, 0.255 mol, 37%). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.45–7.28 (m, 15 H), 3.70 (s, 6 H), 2.91 (s, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 140.4 (3 C$_{ar}$), 129.1 (6 C), 128.1 (6 C), 126.7 (3 CH$_{ar}$), 63.0 (3 CH$_2$), 55.4 (6 CH$_2$-α) ppm. MS (MALDI-TOF): *m*/*z* = 400 [M]$^+$. HRMS (ESI): calcd. for $C_{27}H_{33}N_3$ + H$^+$ 400.2747 [M + H]$^+$; found 400.2733. $C_{27}H_{33}N_3$·3HCl·1.5H_2O (534.21): calcd. C 60.50, H 7.33, N 7.84; found C 60.39, H 7.87, N 8.04.

1,4,7-Triazacyclononane (3): Compound **2** (84.77 g, 0.21 mol) was placed in acetic acid (1 L) with 10% Pd/C (9 g, 8 mmol, 0.04 equiv.) under H_2. After consumption of hydrogen (14.3 L, 0.63 mol, 3 equiv.), the solvent was removed. Hydrochloric acid (37%, 52 mL) and then ethanol (250 mL) were added. The precipitate thus formed was filtered, the white solid was washed with diethyl ether (200 mL), and compound **3** was obtained as a white solid (26 g, 0.20 mol, 95%). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 2.75 (s, 12 H), 2.07 (s, 3 H, N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 42.4 (CH$_2$-α) ppm. MS (MALDI-TOF): *m*/*z* = 129.70 [M]$^+$. HRMS (ESI): calcd. for $C_6H_{13}N_3$ + H$^+$ 130.1338 [M + H]$^+$; found 130.1332.

1,4,7-Tris(pyridin-2-ylmethyl)-1,4,7-triazacyclononane (4): 2-(Bromomethyl)pyridine hydrobromide (9.85 g, 39.0 mmol, 3 equiv.) was slowly added at 10 °C to a solution of **1** (1.62 g, 13.0 mmol) and K_2CO_3 (45.5 g, 330.0 mmol) in acetonitrile (90 mL). The mixture was stirred at room temperature overnight. After filtration through Celite, the solvent was removed. The oily residue was taken up overnight in diethyl ether (200 mL) and the resulting precipitate was filtered, washed with diethyl ether (2× 20 mL), and dried in vacuo to give 12.96 g of the intermediate. The intermediate (5.0 g, 10.3 mmol) was then placed in dry ethanol (45 mL) and $NaBH_4$ (3.9 g, 103.0 mmol) was added at –10 °C to the solution. After 12 h, the solvent was evaporated in vacuo and the resulting mixture taken up in diethyl ether (50 mL). Insoluble impurities were removed by filtration. After evaporation of the solvent, compound **4** was obtained as an orange oil (1.62 g, 31%). ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 150.3 (3 C), 145.6 (3 C), 143.5 (3 C), 127.3 (3 C), 126.4 (3 C), 56.3 (3 C), 49.3 (6 C) ppm. MS (ESI): *m*/*z* = 403.26 [M + H]$^+$. HRMS (ESI): calcd. for $C_{24}H_{30}N_6$ + H$^+$ 403.2605 [M + H]$^+$; found 403.2594.

1,4,7-Tribenzyl-1,4,7-triazacyclononane-2-carbonitrile (5): Benzyl bromide (259.3 g, 1.5 mol) was slowly added to a solution of **1** (64.3 g, 0.5 mol) and K_2CO_3 (278.8 g, 2.0 mol) in acetonitrile (1.1 L) at 10 °C and the resulting solution was stirred for 6 h. Then sodium cyanide (24.76 g, 0.5 mol) was carefully added and the mixture was stirred at room temperature for 3 d. After filtration through Celite, the solvent was evaporated in vacuo and the residual oil was taken up in diethyl ether (3 L). Insoluble impurities were removed by filtration. After evaporation of the solvent, compound **5** was obtained as a brown oil (137.2 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.40–7.16 (m, 15 H), 3.84–3.63 (m, 6 H), 3.53–3.42 (m, 1 H), 3.22–3.14 (m, 1 H), 2.99–2.95 (m, 1 H), 2.88–2.82 (m, 2 H), 2.74–2.66 (m, 1 H), 2.56–2.43 (m, 4 H), 1.78–1.53 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 140.0 (C$_{ar}$), 139.9, 139.4, 138.4, 129.5 (CH$_{ar}$), 129.2, 129.1 (2 C), 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 127.8, 127.2, 127.1, 126.9, 118.1 (CN), 66.1 (CH$_2$), 63.6, 62.3, 61.5, 58.9, 57.5, 56.5, 55.6, 54.8 (CH) ppm. IR: $\tilde{\nu}$ = 2250 (CN) cm^{-1}. MS (ESI): *m*/*z* = 425.25 [M + H]$^+$. HRMS (ESI): calcd. for $C_{28}H_{32}N_4$ + H$^+$ 425.2700 [M + H]$^+$; found 425.2694.

(1,4,7-Tribenzyl-1,4,7-triazacyclononan-2-yl)methanamine (6): A solution of **5** (112.7 g, 0.27 mol) in THF (450 mL) was slowly added at –78 °C to a suspension of $LiAlH_4$ (11.5 g, 0.32 mol, 1.2 equiv.) in THF (450 mL) under nitrogen. An emission of fumes was observed. The resulting mixture was stirred overnight and water (100 mL) was carefully added. After removal of the solvent, the residual green solid was taken up in chloroform (1 L), the solu-

tion was dried with $MgSO_4$, and insoluble impurities were removed by filtration through Celite. The residual brown oil was placed in acetone (200 mL) and a solution of HCl (37%, 200 mL) was carefully added. The white precipitate formed was filtered and recrystallized from water to give **6** (·3HCl) as a white solid. The resulting crystals were then dissolved in a 16 M NaOH solution until pH 14. After extraction with chloroform (2× 500 mL), the organic phase was dried with $MgSO_4$ and the solvent evaporated to give **6** as a yellow oil (45.3 g, 39%). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.35–7.11 (15 H), 3.71 (br. s, 1 H), 3.62–3.21 (m, 7 H), 2.98–2.90 (m, 1 H), 2.73–2.25 (m, 10 H), 1.30 (br. s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 141.2 (C_{ar}), 140.4, 140.2, 129.5 (CH_{ar}), 129.2, 128.8, 128.3 (C 9), 127.1, 127.0, 126.7, 64.3 (CH_2), 63.5, 62.8 (CH), 58.2 (CH_2), 57.9, 55.6, 55.1, 52.8, 51.1, 42.5 ppm. MS (ESI): *m*/*z* = 429.31 [M + H]$^+$. HRMS (ESI): calcd. for $C_{24}H_{30}N_6$ + H$^+$ 429.3012 [M + H]$^+$; found 429.3060.

(1,4,7-Triazacyclononan-2-yl)methanamine (7): Compound **6** (5.0 g, 11.7 mol) was dissolved in a mixture of acetic acid (29 mL), water (29 mL), and THF (98 mL) and then 10% Pd/C (500 mg, 0.47 mmol, 0.04 equiv.) was added under H_2. After consumption of hydrogen, the mixture was filtered to remove palladium. After evaporation of the solvent, the residue was dissolved in ethanol (100 mL). HCl (37%, 5 mL) was added and the resulting precipitate was filtered after 1 h, washed with acetone (20 mL), and dried under vacuum to give a white powder. The resulting precipitate was recrystallized from water. The white crystals were dissolved in a 16 M NaOH solution until pH 14. After extraction with chloroform (2× 50 mL), the organic phase was dried with $MgSO_4$ and the solvent evaporated in vacuo to give **7** as a yellow oil (0.79 g, 44%). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 2.50–2.03 (m, 13 H), 1.95–1.75 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 57.1 (CH), 48.7 ($CH_2\alpha$), 46.4, 46.3, 46.1, 45.8, 45.5 ppm. MS (ESI): *m*/*z* = 159.16 [M + H]$^+$. HRMS (ESI): calcd. for $C_7H_{18}N_4$ + H$^+$ 159.1604 [M + H]$^+$; found 159.1597.

***tert*-Butyl [(1,4,7-Tribenzyl-1,4,7-triazacyclononan-2-yl)methyl]carbamate (8):** A solution of Boc_2O (4.20 g, 19.2 mmol) in CH_2Cl_2 (100 mL) was slowly added to a solution of **6** (8.24 g, 19.2 mmol) in CH_2Cl_2 (150 mL). The solution was stirred overnight at room temperature. After evaporation of the solvent, the residual oil was purified by aluminium oxide chromatography (eluent: CH_3OH/CH_2Cl_2, 4:96) to give **8** as a yellow oil (7.42 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.35–7.12 (m, 15 H), 5.04–4.86 (br. s, 1 H), 4.13–3.92 (br. s, 1 H), 3.69–3.25 (m, 7 H), 3.17–2.81 (m, 3 H), 2.69–2.40 (m, 7 H), 2.34 (dd, $^2J_{H,H}$ = 13.1, $^3J_{H,H}$ = 2.1 Hz, 1 H), 1.43 (s, 9 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 156.2 (C=O), 140.6 (C_{ar}), 140.2, 140.0, 129.4 (2 CH_{ar}), 129.1 (2 C), 128.9 (2 C), 128.3 (6 C), 127.1, 126.9, 126.8, 78.9 (C), 64.1 (CH_2), 63.7, 58.5 (CH), 58.0 (CH_2), 57.8, 56.1, 55.2, 53.2, 50.5, 40.6, 28.7 (3 CH_3) ppm. MS (MALDI-TOF): *m*/*z* = 528.99 [M + H]$^+$. HRMS (ESI): calcd. for $C_{33}H_{44}N_4O_2$ + H$^+$ 529.3537 [M + H]$^+$; found 529.3515.

***tert*-Butyl [(1,4,7-Triazacyclononan-2-yl)methyl]carbamate (9):** Compound **8** (3.33 g, 6.30 mmol) was dissolved in a mixture of acetic acid (20 mL), water (20 mL), and THF (60 mL) and then 10% Pd/C (266 mg, 0.25 mmol) was added under H_2. After consumption of hydrogen, the mixture was filtered to remove palladium. After evaporation of the solvent, the residue was dissolved in ethanol (10 mL). A 3 M HCl solution (5 mL) was added and the resulting precipitate filtered after 1 hour, washed with ethanol (20 mL), and dried under vacuum to give a white powder. The resulting precipitate was then dissolved in a 3 M NaOH solution until pH 12. After extraction with chloroform (2× 50 mL), the organic phase was dried with $MgSO_4$ and the solvent evaporated to give **9** as a yellow oil (1.30 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 5.25 (s, 1 H, NHC=O), 3.16–2.98 (m, 3 H, NH), 2.98–2.45 (m, 13 H), 1.38 (s, 9 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 156.8 (C=O), 79.5 (C), 55.4 (CH), 46.8 (CH_2), 45.9, 45.6, 44.6, 44.0, 43.1, 28.6 (3 CH_3) ppm. MS (ESI): *m*/*z* = 203.15 [M – *t*Bu+2H]$^+$, 259.15 [M + H]$^+$. HRMS (ESI): calcd. for $C_{12}H_{26}N_4O_2$ + H$^+$ 259.2129 [M + H]$^+$; found 259.2116.

Tri-*tert*-butyl 2,2′,2′′-(2-{[(*tert*-Butoxycarbonyl)amino]methyl}-1,4,7-triazacyclononane-1,4,7-triyl)triacetate (10): A solution of compound **9** (471.1 mg, 1.84 mmol) in dimethylformamide (9.2 mL) was heated at 40 °C. *tert*-Butyl bromoacetate (0.803 mL, 5.51 mmol) and potassium carbonate (1.78 g, 12.9 mmol) were added to this solution and the reaction mixture was stirred overnight. The suspension was filtered through a bed of Celite and the filter cake was washed with chloroform. After evaporation of the solvents in vacuo, the crude compound was purified by flash chromatography on silica gel (eluent: CH_2Cl_2/CH_3OH, 94:6) and reversed-phase flash chromatography [eluent: (HCOOH/H_2O 0.01M)/CH_3CN 60:40]. Compound **10** was obtained as a light-yellow oil (181 mg, 18%). ^{1}H NMR (300 MHz, $CDCl_3$, 325 K): δ = 6.03 (br. s, 1 H, NHBoc), 3.79 (d, $^2J_{H,H}$ = 17.6 Hz, 1 H), 3.70 (d, $^2J_{H,H}$ = 17.6 Hz, 1 H), 3.68 (d, $^2J_{H,H}$ = 17.6 Hz, 1 H), 3.60 (d, $^2J_{H,H}$ = 17.6 Hz, 1 H), 3.43 (d, $^2J_{H,H}$ = 17.6 Hz, 1 H), 3.38–3.27 (m, 2 H), 3.26–2.64 (m, 12 H), 1.44, 1.43, 1.40, 1.39 (4 s, 36 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 171.3, 168.8, 167.3, 156.7 (NHC=OO*t*Bu), 83.1 (C_q*t*Bu), 82.5, 82.1, 79.6, 56.8, 56.4, 55.9, 53.3, 51.6, 39.3 (CH_2NH), 28.6 (CH_3), 28.3, 28.2, 28.1 ppm. MS (ESI): *m*/*z* = 601.46 [M + H]$^+$. HRMS (ESI): calcd. for $C_{30}H_{56}N_4O_8$ + H$^+$ 601.4171 [M + H]$^+$; found 601.4145. HPLC gradient: t_r = 26.75 min, purity 85%.

2,2′,2′′-[2-(Aminomethyl)-1,4,7-triazacyclononane-1,4,7-triyl]triacetic Acid (11, MA-NOTA): Trifluoroacetic acid (1 mL) was added to a stirred solution of compound **10** (49.5 mg, 0.08 mmol) in dichloromethane (2 mL). The resulting reaction mixture was then stirred overnight at room temperature before it was concentrated in vacuo. Compound **11**·3TFA was obtained as a light-yellow oil (54.0 mg, 100%) and directly used without purification. ^{1}H NMR (600 MHz, $CDCl_3$, 325 K): δ = 4.25–3.92 (m, 3 H), 3.88–3.53 (m, 4 H), 3.44–3.29 (m, 3 H), 3.27–3.20 (m, 2 H), 3.19–2.36 (m, 7 H) ppm. MS (ESI): *m*/*z* = 333.27 [M + H]$^+$. HRMS (ESI): calcd. for $C_{13}H_{24}N_4O_6$ + H$^+$ 333.1769 [M + H$^+$]; found 333.1757. $C_{13}H_{24}N_4O_6$3TFA: calcd. C 33.84, H 4.04, N 8.31; found C 33.64, H 3.73, N 7.94. HPLC gradient: t_r = 3.57 min, purity 86%.

2,2′,2′′-(2-{[2-(4-Nitrophenyl)acetamido]methyl}-1,4,7-triazacyclononane-1,4,7-triyl)triacetic Acid (12): *N*,*N*-Diisopropylethylamine (ca. 50 μL) was added dropwise to a stirred solution of **11** (27.2 mg, 0.082 mmol) in water (2 mL) until the pH reached 9.4. The solution was yellowish. A solution of *N*-succinimidyl 4-nitrophenylacetate (22.8 mg, 0.082 mmol) in acetonitrile (1 mL) was quickly added and the reaction mixture immediately turned red. The solution was stirred for 2 h and the solvents evaporated in vacuo and freeze-dried. The crude compound was dissolved in water (5 mL) and chloroform (5 mL). The aqueous phase was washed with chloroform (2× 5 mL) and the organic phase was extracted with water (5 mL). The combined aqueous layers were freeze-dried and **12** was obtained as a light-brown powder and used directly without purification. MS (ESI): *m*/*z* = 494.06 [M – H]$^-$.

2,2′,2′′-(2-{[2-(4-Aminophenyl)acetamido]methyl}-1,4,7-triazacyclononane-1,4,7-triyl)triacetic Acid (13): Compound **12** (40.1 mg, 0.082 mmol) was dissolved in water (1.4 mL) and 10% Pd/C (3.5 mg, 3 × 10^{-3} mmol, 0.04 equiv.) was added under H_2. The solu-

tion was stirred vigorously and after consumption of hydrogen the mixture was filtered through a bed of Celite to remove palladium and the filter cake was washed with water. The crude compound was freeze-dried and **13** was obtained as a light-yellow powder and used directly without purification. MS (ESI): *m*/*z* = 464.09 [M – H]$^-$.

2,2′,2′′-(2-{[2-(4-Isothiocyanatophenyl)acetamido]methyl}-1,4,7-triazacyclononane-1,4,7-triyl)triacetic Acid (14, *p*-NCS-Bz-MANOTA): Compound **13** (38.0 mg, 0.082 mmol) was dissolved in water (1.4 mL) and the solution stirred vigorously. Thiophosgene (37.8 μL, 0.49 mmol) was dissolved in dichloromethane (0.45 mL) in a test tube and the mixture was rapidly added to the previous solution. The resulting reaction mixture was stirred for 3 h. The aqueous phase was isolated and washed with chloroform. The crude compound was purified by semi-preparative HPLC (t_r = 32.3 min) to obtain **14** as a light-brown powder (5.0 mg, 0.010 mmol). The overall yield of the last three reactions was 12%. ^{1}H NMR (300 MHz, D_2O, 298 K): δ = 7.31 (s, 4 H, CH_{ar}), 4.05–3.65 (m, 5 H), 3.58 (s, 2 H, PhCH_2CO), 3.50–2.94 (m, 12 H), 2.91–2.78 (m, 1 H), 2.75–2.61 (m, 1 H) ppm. MS (ESI): *m*/*z* = 507.98 [M + H]$^+$. HRMS (ESI): calcd. for $C_{22}H_{29}N_5O_7S$ + Na^+ 530.1680 [M + Na]$^+$; found 530.1687. $C_{22}H_{29}N_5O_7S{\cdot}CHCl_3{\cdot}2H_2O$ (611.11): calcd. C 41.67, H 5.17, N 10.56, S 4.84; found C 41.32, H 5.23, N 10.75, S 3.06. HPLC gradient: t_r = 18.07 min, purity 90%.

***N*-[(1,4,7-Triazacyclononan-2-yl)methyl][4-(prop-2-ynyloxy)phenyl]methanamine (15):** Compound **7** (1.20 g, 7.5 mmol) was added to a solution of 4-(prop-2-ynyloxy)benzaldehyde (1.19 mg, 7.5 mmol) in ethanol (25 mL) and the mixture stirred at room temperature for 48 h. The solvent was evaporated to dryness and the residual oil was taken up in diethyl ether (25 mL). After stirring for 12 h, the insoluble impurities were removed by filtration. After evaporation of the solvent, $NaBH_4$ (250 mg, 6.7 mmol) was added in ethanol (10 mL) at 0 °C. The mixture was stirred overnight at room temperature. The solvent was evaporated and the resulting solid was dissolved in dichloromethane (25 mL). After filtration of the insoluble impurities, the solution was washed with 3 M NaOH (10 mL), dried with $MgSO_4$, and the solvent evaporated to give **15** as a very hygroscopic white foam (135 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.18 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H), 6.86 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H), 4.61 (d, $^4J_{H,H}$ = 2.3 Hz, 2 H, CH_2CCH), 3.65 (s, 2 H), 2.90–2.30 (m, 15 H), 1.60–1.10 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 156.6, 130.1, 129.3 (2 C), 114.8 (2 C), 78.8 (CH_2CCH), 75.6 (CH_2CCH), 55.9, 55.6, 53.6, 49.9, 47.3, 47.2, 47.0, 46.4, 46.0 ppm. MS (ESI): *m*/*z* = 303.22 [M + H]$^+$.

Crystal data for 2: $C_{27}H_{41}Cl_2N_3O_3$, M = 526.53, monoclinic, $P2_1/c$, a = 9.513(5), b = 34.739(5), c = 9.870(4) Å, β = 120.73(4)°, V = 2804(2) Å^3, Z = 4, T = 115(2) K, D_c = 1.247 g cm^{-3}, (Mo-$K_{\alpha1}$) = 0.71073 Å, μ = 0.264 mm^{-1}, 12685 reflections collected, 6437 unique, minimum and maximum residual electron densities: –0.601 and 0.528 e Å^{-3}. For $I > 2\sigma(I)$ and all data, R(1) = 0.0523 and 0.1035, and wR(2) = 0.1368 and 0.1561 , respectively.

Crystal Data for 6: $C_{28}H_{44}Cl_4N_4O_2$, M = 610.47, triclinic, $P\bar{1}$, a = 9.1187(2), b = 12.0008(2), c = 15.4937(3) Å, α = 70.1260(10), β = 86.6110(10), γ = 86.2630(10)°, V = 1589.90(5) Å^3, Z = 2, T = 115(2) K, D_c = 1.275 g cm^{-3}, (Mo-$K_{\alpha1}$) = 0.71073 Å, μ = 0.403 mm^{-1}, 11218 reflections collected, 7195 unique, minimum and maximum residual electron densities: –0.761 and 0.938 e Å^{-3}. For $I > 2\sigma(I)$ and all data, R(1) = 0.0501 and 0.0630, and wR(2) = 0.1456 and 0.1553, respectively.

Crystal Data for 7: $C_7H_{24}Cl_4N_4O$, M = 322.10, monoclinic, $P2_1/c$, a = 10.8478(3), b = 6.9249(2), c = 19.6388(7) Å, β = 102.912(2)°, V = 1437.96(8) Å^3, Z = 4, T = 115(2) K, D_c = 1.488 g cm^{-3}, (Mo-$K_{\alpha1}$) = 0.71073 Å, μ = 0.812 mm^{-1}, 6062 reflections collected, 3255 unique, minimum and maximum residual electron densities: –0.352 and 0.462 e Å^{-3}. For $I > 2\sigma(I)$ and all data, R(1) = 0.0327 and 0.0369, and wR(2) = 0.0705 and 0.0729, respectively.

CCDC-960359 (for **2**), -960360 (for **6**), and -960361 (for **7**) 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.

Supporting Information (see footnote on the first page of this article): Additional experimental details, data for compounds **1**–**15** (NMR, MS spectra, and HPLC chromatograms).

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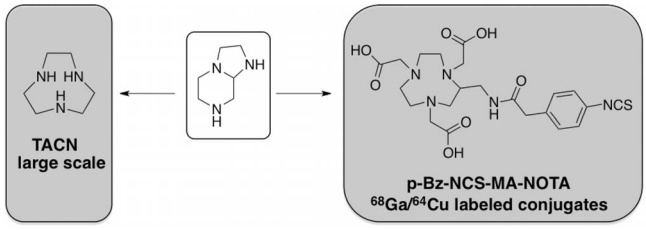

A new synthesis of 1,4,7-triazacyclononane and its *N*-functionalized derivatives is described. This powerful approach outperforms previous synthetic methods due to the use of an aminal intermediate. The method can be extended to the synthesis of valuable *C*-functionalized building blocks, giving access to a wide range of new bifunctional chelating agents, such as the *p*-NCS-Bz-MA-NOTA chelator.

Keywords: Synthetic methods / Nitrogen heterocycles / Amines / Macrocyclic polyamines / Chelates

