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exo-Diastereoisomer of 10-aryl-1,4,7-triazabicyclo[5.2.1]decane as intermediary in specific derivatisation of triazacyclononane

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ABSTRACT

Reaction of triazacyclononane (tacn) and aromatic aldehydes leads to aminal adducts, which exhibit only the *exo* configuration. In these aminal compounds, secondary amine function possesses a higher reactivity towards electrophilic reactants than the two nitrogen atoms linked to aminal carbon, giving rise to the specific derivatisation of tacn by different functionalised groups. Study of this behaviour also permits the access to a ditopic tacn–cyclam bicyclic polyamine.

1. Introduction

The various applications of triazacyclononane (tacn) and derivatives generally imply their remarkable coordinating properties.[1] Protein orientation at interfaces,[2] metalloenzyme biosite models,[3] diagnostical or therapeutical metal carriers,[4] magnet molecule clusters,[5] sensors[6]… constitute examples of domains in which the potentialities of these small azamacrocycles are involved. Combination of tacn potentialities with different abilities of other chelators could extend the applications fields. A possible approach consists in synthesising polytopic ligands containing different workable characteristic sites. Such an association exists in ditopic cyclic-cyclic or cyclic-linear bispolyamines that have been investigated for biological or medicinal applications.[4,7]

In the previous different examples, the use of modified tacn, bearing one, two or three arms with- or without- coordinating atoms is usually required. The introduction on the triazamacrocycle of identical or different substituents necessitates to discriminate the amine functions of the macrocycle. The classical method consists in the introduction of the functional group before the cyclisation step leading to *N*-alkylated derivatives at the end of the synthetic process, which has, obviously, to be reconsidered when a new product is needed.[8] Recently, this way was used to synthesise tacn-containing cationic lipids with good buffering capacity, which is an important behaviour for non-viral gene delivery reagents.[9]

Statistic N-functionalisation also constitutes a synthetic strategy by reacting tacn and alkylating agent in a 1:1 or 1:2 ratio, but generally requires purification steps to separate non-reacted tacn and mono- or/and poly-substituted derivatives.[10] Reaction of tacn with BOC-ON in a 1:2 ratio has given rise to the diprotected 1,4-diBOC–tacn synthesis, which permitted for instance to obtain further Cu(II) complexes of tacn derivatives with alkyl- or xylyl-linked guanidinium groups studied as models compounds for cleaving the phosphonate ester backbone of DNA.[11] Protection of one or two nitrogen atoms of tacn has also been employed by tosylation,[12] carbamation[13] or pH controlled sulfomethylation,[14] including further purification and/or deprotection steps. Finally, a method based on an intermediate orthoamide has also been described and permits to graft independently one, two or three substituents on the tacn macrocycle by playing with the orthoamide hydrolysis.[15] Dipicolyl-tacn derivative studied in low spin–high spin iron molecular switching,[16] *N*-aminoalkyl-tacn derivatives suitable for functionalisation of carboxy terminated supports as self-assembled monolayers SAM[17] are examples of compounds issued from the orthoamide protection method.

These different routes are complementary methods and it is still important to develop such ways for grafting arms to cyclic polyamines in order to make it possible in various conditions offering more choice in the nature of substituents.

Reaction of tacn with anhydrous paraformaldehyde and dialkyloxyphosphine to give trimethylenephosphinate ester derivative was studied by D. Parker et al.[18] It was found to give a bicyclic aminal monophosphinate ester as a secondary product together with the expected trimethylenephosphinate ester. Acidic hydrolysis

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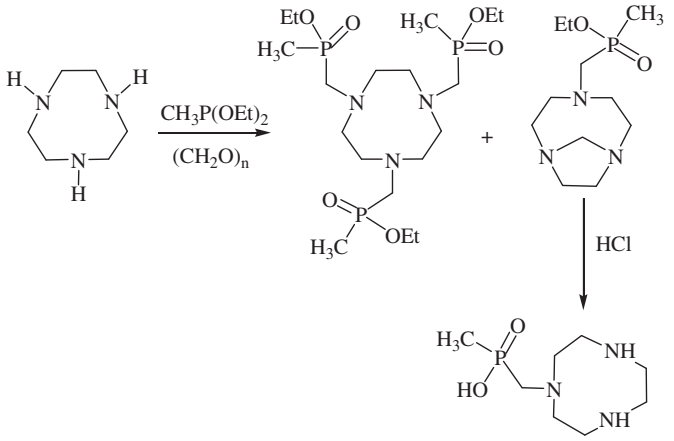
eliminated the aminal group and yielded the phosphinic acid substituent of tacn (Scheme 1). This result suggests a potential protecting role of the aminal group for two secondary amine functions, leaving the third one accessible to reactants. We therefore investigated the synthesis and characterisation of different aminal derivatives of tacn to evaluate further the opportunity to specifically substitute tacn and to apply the method to tacn-based ditopic ligands synthesis.



Scheme 1. Sequence described by D. Parker et al.[18]

2. Results and discussion

2.1. Aminal formation and characterisation

Our study was initialised by using paraformaldehyde showed by D. Parker et al.[18] The reaction took place in absolute ethanol at room temperature with molecular sieve for trapping liberated water. The white solid obtained after filtration and evaporation of the solvent was characterised as a mixture of the good aminal derivative **1** together with initial tacn and an other species in small amount containing two different kinds of aminal functions. According to ^{1}H NMR experiments, which exhibited an AB signal and a singlet one integrating, respectively, for 2:1 in the aminal protons area, this by-product was assumed to be a dimer **2** based on two units of **1** linked by a CH_2 aminal bridge (Fig. 1). Our different attempts by modifying the reaction conditions (concentration, solvent) did not permit to prevent the formation of this by-product.

Aqueous formaldehyde was then tested to replace paraformaldehyde. Formaldehyde was already used to synthesise cyclic aminal of cyclam (1,4,8,11-tetraazacyclotetradecane) in tetraazamacrocyclic analogues chemistry.[19] Aqueous formaldehyde (37%) (1 equiv) as carbonylated reactant was added to tacn in water at room temperature for 12 h. The reaction product contained essentially the attended aminal derivative 1,4,7-triazabicyclo[5.2.1] decane **1** and traces of the same precedent dimer. If an excess of paraformaldehyde or aqueous formaldehyde (1.5 equiv) was introduced in the reaction, the dimer appeared to be the main product showing the easiness of this bridge formation.

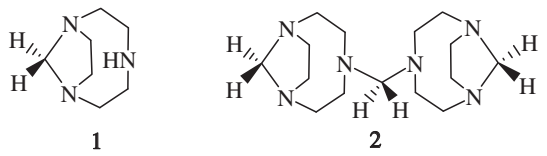
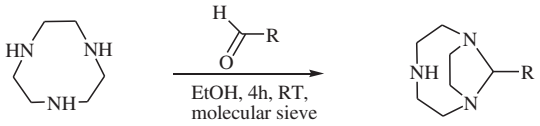


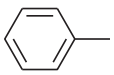
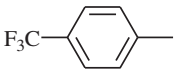
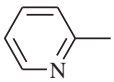
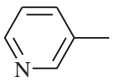
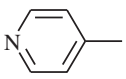
Fig. 1. Structure of aminal derivatives obtained with aqueous formaldehyde or paraformaldehyde.

Hindrance caused by the presence of substituent on aldehyde should not allow such an easy dimer formation. With the aim of obtaining a single aminal derivative without any trace of dimerisation, reactions of tacn with different substituted aldehydes were investigated in the experimental conditions previously described with paraformaldehyde (1 equiv of aldehyde, ethanol, molecular sieve). Several aromatic aldehydes like benzaldehyde, 4-fluorobenzaldehyde and 2-, 3- and 4-pyridinecarboxaldehyde gave rise to monomeric aminal formation. Nevertheless, hindered aldehyde as anthracenecarboxaldehyde never permitted total aminal formation whatever the experimental conditions. The products **3**–**7** were isolated with good to very good yields (Table 1).

For compounds **3**–**7**, ^{1}H NMR spectra exhibit a single peak for the aminal hydrogen showing the presence of only one of the two possible diastereoisomers between the *endo* and *exo* forms. 2D NMR sequences permitted to attribute the *exo* configuration, especially the NOESY sequence. Indeed, NOESY spectra of compounds **3** and **6** exhibited correlation between the hydrogen aminal (δ=5.66 ppm for **3** and 5.67 ppm for **6**) and the diastereotopic proton of the large bridge in the molecule (δ=3.32 ppm for **3** and 3.33 ppm for **6**) and a second correlation between an aromatic hydrogen (δ=7.50 ppm for **3** and δ=7.62 ppm and 8.57 ppm for **6**) and one of the diastereotopic hydrogen of a CH_2 of the small internal cycle (δ=3.07 ppm for **3** and 2.89 ppm for **6**) (Fig. 2).

Table 1
Synthesis of aminal derivatives



R	Compound	Yield (%)
	**3**	90
	**4**	80
	**5**	88
	**6**	77
	**7**	84

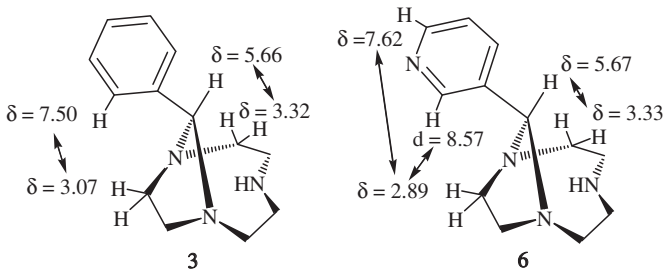


Fig. 2. NOESY correlations observed for *exo* configuration of aminal derivatives **3** and **6**.

2.2. Reactivity study

With the aim of verifying the efficiency of the protecting role of aminal bridge, electrophilic reagents were used to investigate their reactivity towards secondary amine and aminal functions. Different kinds of reactants were studied to better appreciate the protecting group capacity of the aminal function: activated reactants (benzyl and allyl bromides), non activated ones with hydrophobic chains (ethyl and decyl iodides) and electrophilic agents with coordinating groups (picolyl chlorides). Halogenoalkanes (1 equiv) were added to a solution of aminal derivatives in distilled acetonitrile with potassium carbonate and reaction mixture was kept under stirring at mild temperature (25–50 °C).

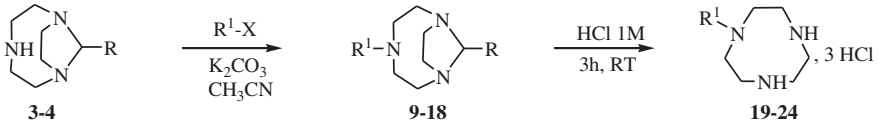
Reactivity of aminal **1** was first studied, even in the presence of traces of the dimeric by-product **2**, which was assumed to be kinetically less reactive towards electrophilic agent in the reaction conditions because all nitrogen atoms were engaged in aminal function. When benzyl bromide (1 equiv) was introduced into an acetonitrile solution of aminal **1**, one or several by-products together with the mono-*N*-alkylated derivative were obtained. After purification attempts by chromatography on silica, neutral or basic alumina, the results were not reproducible making difficult the characterisation of the secondary products.

The addition of benzyl bromide to compound **3** successfully produced a mono alkylated product **9** with a very good yield (Table 2). Surprisingly, reaction with allyl bromide gave rise to mono- and di-N-alkylation (respectively, **10** and **10′**) of tacn, implying that one of the nitrogen atoms of the aminal function was involved in the reaction. Compound **4** was studied in the same conditions in order to evaluate the effect of the electron-withdrawing CF_3 group on such a reactivity. In this case, reaction with allyl bromide resulted in the unique mono-N-alkylation of tacn (compound **12**) with an excellent yield, when benzyl bromide gave a lower yield than precedently (compound **11**) suggesting that the secondary amine function reactivity was also weakened. Other mono-N-functionalisations were successfully performed with **3** or **4** (Table 2) in good yields with aliphatic or aromatic substituents like ethyl **13**, 2-picolyl **16** or medium yields with decyl **15**, 4-picolyl **14** and bipyridinyl **17**. The aminal function of this last compound **17** was hydrolysed directly by the acidic silica gel during the purification step by column chromatography giving the mono-*N*-bipyridinyl-tacn with 32% yield. Deprotection step of other compounds was performed by hydrolysis in acidic conditions under stirring in a solution of hydrochloride acid 1 M at room temperature for 3 h. The final mono-*N*-substituted compounds were obtained in quantitative yield in their hydrochloride form after evaporation and washing with organic solvent. Obtention of product in their free base form could be easily performed by using an anion-exchange resin or by solubilisation of the chloride salt in water made basic (pH>12) followed by a simple extraction with an organic solvent like dichloromethane.

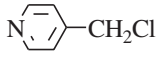
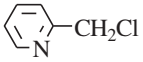
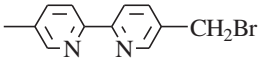
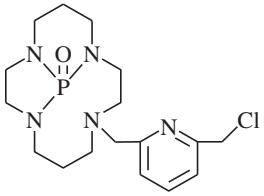
2.3. Application to ditopic polyamine synthesis

Multitopic polyamines, and especially ditopic ones (cyclic/cyclic or cyclic/linear), display a growing development due to the possible simultaneous characteristical interesting behaviours of both complexing sites. Synthesis of ligands that allow complexation of two metallic centres with identical or different nature in various coordination modes and geometries are thus omnipresent challenges. Indeed, such ditopic ligands can open access to bimodal sensors with diagnostic/therapeutic/magnetic… co-properties.

Table 2
Reaction of **3** and **4** with alkylating agents and hydrolysis step



3-4 **9-18** **19-24**

Compound	R^1–X	Product	Yield (%)	Product	Yield (%)
3	$C_6H_5CH_2Br$	**9**	99	**19**	100
3	CH_2=CH–CH_2Br	**10**+**10′**	(90)[a]	**20**	100
4	$C_6H_5CH_2Br$	**11**	72	**19**	100
4	CH_2=CH–CH_2Br	**12**	98	**20**	100
3	CH_3CH_2I	**13**	95	**21**	100
3		**14**	38	**22**	100
3	$C_{10}H_{21}I$	**15**	47	**23**	100
4		**16**	73	**24**	100
4		**17**	—	**25**	32[b]
3		**18**	97	**26**	70

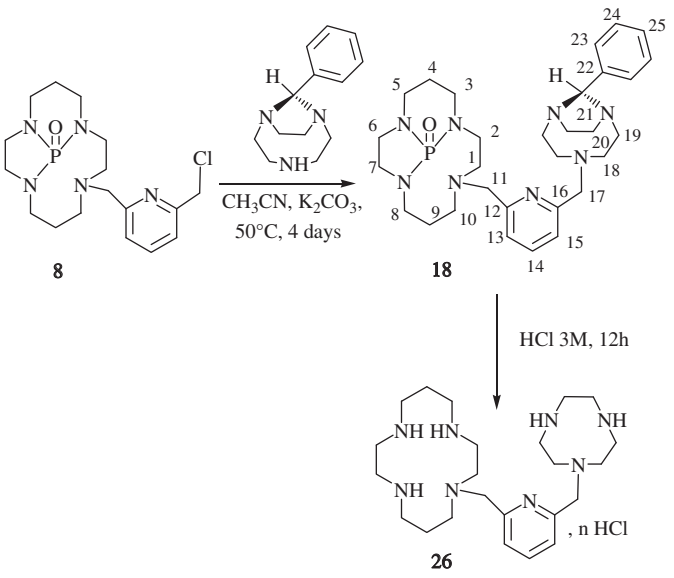
[a] Mixture of mono- and di-allylation.
[b] After acidic hydrolysis on silica gel column chromatography.

Several symmetric and dissymmetric bismacrocyclic polyamines are known like bistetraazacycloalkanes (cyclam-cyclam, cyclam-cyclen)[20] and bistriazacyclononane.[21] However, dissymmetric bismacrocycles containing two different sizes, for instance tacn–cyclam, are more scarce. In this context, a combination between tacn and a cyclic tetraamine like cyclam could offer the opportunity to complex two different metallic cations depending on the nature of the coordinating arms present, respectively, on each polyazamacrocycle.

Our group recently described the synthesis of ditopic polyammonium anion receptors made up of a cyclam and a linear polyamine.[7] It needed to protect both the tetraazamacrocycle and the linear polyamine by adapted ways. The cyclam was used in its phosphoryl form, which kept a single amine function free.[22] The nature of the electrophilic reactant is a phosphorylcyclam with a 2-methyl-6-(chloromethyl)pyridine arm bound to the amine function (compound **8** in Scheme 2). This electrophilic agent was obtained by reaction of cyclamphosphoryl with 2,6-bis(chloromethyl)pyridine in acetonitrile and was mixed with protected linear polyamine in solution to give the corresponding ditopic derivative.[7]

The concept could be extended to the cyclic triamine tacn in place of the linear polyamine. Aminal derivative 10-phenyl-1,4,7-triazabicyclo[5.2.1]decane **3** has been introduced in this reaction process with compound **8**.

The reaction of bismacrocyclic tacn–cyclam synthesis took place in similar conditions than those used for mono-N-alkylation of tacn. The acetonitrile solution of **8** and **3** was stirred at 50 °C for 4 days with potassium carbonate. A silica gel column chromatography using $CHCl_3$/MeOH (98:2) gave the dissymmetric diprotected bismacrocycle **18** with a good yield. Double multiplicity of some peaks appeared on ^{13}C NMR spectra. This phenomenon has been attributed to the presence of diastereotopic stereoisomers for **18** induced by the asymmetric nitrogen atoms of the rigid internal aminal cycle and the stereogenic phosphorus atom in the pyridinylcyclamphosphoryl group. This particularity disappeared after deprotection, which took place in HCl 3 M for 12 h at room temperature. These relatively mild conditions were efficient for eliminating both aminal and phosphoryl cores and hydrochloride deprotected derivative **26** was obtained in a good yield (Scheme 2). This product was purified by using anion-exchange resin, which allowed to obtain ditopic ligand **26** as a free base without any phosphate traces.



8 18 26

Scheme 2. Bismacrocyclic tacn–cyclam derivative synthesis.

3. Conclusion

A simple and easy-to-make method for mono-N-substitution of tacn has been described by using mild and rapid conditions of aminal formation with substituted aromatic aldehydes. This aminal function, which only presented the *exo* configuration played a protecting role when reaction with halogenoalkanes was achieved. Hydrolysis with hydrochloric acid easily resulted in various tacn derivatives bearing one grafted arm. This study offers an additional tool to those that are usually employed for making original triazamacrocyclic chelators.

The method showed its suitability to a larger application and was extended to a dissymmetric bismacrocycle tacn–cyclam synthesis. This tacn–cyclam compound opens the route to other ditopic products of the bismacrocyclic family by using adequate protection/deprotection steps. This aspect is under investigation with the aim of studying the coordination properties of new tacn-tetraazamacrocycle compounds.

4. Experimental section

4.1. General

1,4,7-Triazacyclononane and cyclam were purchased from CheMatech, Dijon, France. Other reagents were purchased from ACROS Organics or Aldrich Chemical Co. Elemental analyses were performed at the Service de Microanalyse (CNRS, 91198 Gif sur Yvette (C, H, N) and 69360 Solaize (Cl), France), NMR and mass spectrometry were investigated at the 'Services Communs' of the University of Brest. Mass spectrometry analyses were performed on an Autoflex MALDI TOF III LRF200 CID. ^1H, ^{15}N, ^{19}F, ^{31}P, ^{13}C NMR spectra were recorded with Advance 500 Bruker (500 MHz), Advance 400 Bruker (400 MHz) or AMX-3 300 Bruker (300 MHz) spectrometers. 2D NMR ^1H–^1H homonuclear, ^1H–^{13}C and ^1H–^{15}N heteronuclear correlations and homonuclear decoupling experiments permitted as much as possible the assignation of the ^1H and ^{13}C signals. The δ scales are relative to TMS (^1H, ^{13}C), CH_3NO_2 (^{15}N), H_3PO_4 (^{31}P) and $CFCl_3$ (^{19}F). The signals are indicated as follows: chemical shift (intensity, multiplicity (s, singlet; br s, broad singlet; d, doublet; t, triplet; m, multiplet; q, quartet), coupling constants *J* in hertz (Hz), assignation: H_α, C_α and H_β, C_β correspond to CH or CH_2 located in, respectively, α or β position of N; ar, pic, py were used, respectively, for aromatic, picolyl and pyridine).

Phosphorylcyclam,[22] 2,6-bis(chloromethyl)pyridine[23] and 5-(bromomethyl)-5′-methyl-2,2′-bipyridine[24] were synthesized as previously described.

4.2. General procedure for aminal synthesis

To a solution of 1,4,7-triazacyclononane (2 mmol) in distilled ethanol (50 mL) containing molecular sieve was added 1 equiv of aldehyde. The reaction mixture was stirred at room temperature. The solution was filtered and the filtrate was evaporated under reduced pressure to yield the aminal adduct.

*4.2.1. 1,4,7-triazabicyclo[5.2.1]decane (**1**).* Reaction with paraformaldehyde (60 mg, 2 mmol) for 4 h. White solid (267 mg, 95%). NMR ($CDCl_3$) ^1H (300 MHz) 2.65–2.84 (8H, m, H_α), 2.90–3.02 (5H, m, H_α+N*H*), 4.04 (d, 1H, *J* 9, H_{aminal}), 4.22 (d, 1H, *J* 9, H_{aminal}); ^{13}C (75 MHz) 48.6, 48.8, 57.4 (C_α), 76.8 (C_{aminal}).

*4.2.2. Bis(1,4,7-triazabicyclo[5.2.1]decan-4-yl)methane (**2**).* To a solution of 1,4,7-triazacyclononane (1.02 mmol) dissolved in distilled acetonitrile (20 mL) containing molecular sieve was added dropwise an acetonitrile solution (15 mL) of 1.5 equiv of

paraformaldehyde. The reaction mixture was stirred at room temperature during 24 h. Evaporation of CH_3CN under reduced pressure yielded the dimeric adduct as the major product. NMR ($CDCl_3$) ^{1}H (300 MHz) 2.66–2.79 (12H, m, H_α), 2.91–3.08 (12H, m, H_α), 3.24 (2H, s, H_{aminal}), 4.02 (2H, d, *J* 8, H_{aminal}), 4.11 (2H, d, *J* 8, H_{aminal}); ^{13}C (75 MHz) 48.7, 52.0, 55.2 (4C, C_α), 76.1 (2C, C_{aminal}), 80.8 (C_{aminal}).

*4.2.3. 10-Phenyl-1,4,7-triazabicyclo[5.2.1]decane (**3**).* Reaction with benzaldehyde (192 μL, 1.93 mmol) for 4 h. White solid (370 mg, 90%). NMR ($CDCl_3$) ^{1}H (300 MHz) 2.89–2.93 (4H, m, H_α), 2.99–3.03 (2H, m, H_α), 3.07–3.17 (4H, m, H_α), 3.32–3.39 (2H, m, H_α), 5.66 (1H, s, H_{aminal}), 7.18 (1H, t, *J* 7, H_{ar}), 7.29 (2H, t, *J* 7, H_{ar}), 7.50 (2H, d, *J* 7, H_{ar}); ^{13}C (75 MHz) 49.3 ($C_{\alpha N}$), 49.6 ($C_{\alpha NH}$), 58.8 ($C_{\alpha N}$), 88.3 (C_{aminal}), 126.6, 126.7 128.2 (CH_{ar}), 145.8 (C_{ar}); ^{15}N (50 MHz) −355 (*N*H), −331 (*N*); MALDI-TOF 216.1 $[M]^+$ 217.1 $[M+1]^+$. Anal. Calcd for $C_{13}H_{19}N_3\cdot 0.1C_2H_5OH$: C, 71.44; H, 8.90; N, 18.94. Found: C, 71.13; H, 8.88; N, 19.06.

*4.2.4. 10-(4-(Trifluoromethyl)phenyl)-1,4,7-triazabicyclo[5.2.1]decane (**4**).* Reaction with α,α,α-trifluorotolualdehyde (270 μL, 1.97 mmol) for 4 h. The residue was purified by silica gel chromatography ($CHCl_3$/Et_3N 9:1 then $CHCl_3$/MeOH/Et_3N 9:0.5:0.5) to yield an oily white solid (450 mg, 80%). NMR ($CDCl_3$) ^{1}H (500 MHz) 2.91–2.97 (6H, m, H_α), 3.08–3.12 (2H, m, H_α), 3.15–3.19 (2H, m, H_α), 3.31–3.37 (2H, m, H_α), 5.70 (1H, s, H_{aminal}), 7.53 (2H, d, *J* 8, H_{ar}), 7.61 (2H, d, *J* 8, H_{ar}); ^{13}C (125 MHz) 49.0 ($C_{\alpha NH}$), 49.3, 58.7 (C_α), 87.5 (C_{aminal}), 124.8 (*C*F$_3$, ^{1}*J* 272), 125.1 (CH_{ar}, ^{3}*J* 4), 127.1 (CH_{ar}), 129.0 (C_{ar}, ^{2}*J* 32), 149.7 (C_{ar}); ^{15}N (50 MHz) −356.8 (*N*H), −332.2 (*N*); ^{19}F (282 MHz) −62.77; MALDI-TOF *m*/*z* 286.1 $[M+1]^+$. Anal. Calcd for $C_{14}H_{17}F_3N_3\cdot 0.2H_2O$: C, 58.40; H, 6.09; N, 14.60. Found: C, 58.80; H, 6.22; N, 14.23.

*4.2.5. 10-(Pyridin-2-yl)-1,4,7-triazabicyclo[5.2.1]decane (**5**).* Reaction with 2-pyridinecarboxaldehyde (210 μL, 2.20 mmol) for 5 h. The residue was purified by silica gel chromatography ($CHCl_3$/Et_3N 9:1 then $CHCl_3$/MeOH/Et_3N 9:0.5:0.5) to yield an oily solid (425 mg, 88%). NMR ($CDCl_3$) ^{1}H (500 MHz) 2.72–2.76 (4H, m, $H_{\alpha NH}$), 2.89–2.93 (2H, m, $H_{\beta NH}$), 2.96–3.06 (4H, m, $H_{\alpha N}$), 3.18–3.25 (2H, m, $H_{\beta NH}$), 5.61 (1H, s, H_{aminal}), 6.91 (1H, dd, *J* 5, 7, H_{ar}), 7.29 (1H, d, *J* 8, H_{ar}), 7.42 (1H, dd, *J* 7, 8, H_{ar}), 7.42 (1H, d, *J* 5, H_{ar}); ^{13}C (126 MHz) 48.7 ($C_{\alpha NH}$), 48.9 ($C_{\alpha N}$), 58.0 ($C_{\beta NH}$), 89.2 (C_{aminal}), 119.6 (CH_{ar}), 121.0 (CH_{ar}), 135.8 (CH_{ar}), 149.0 (CH_{ar}), 163.7 (C_{ar}); ^{15}N (50 MHz) −357.1 (NH), −332.0 (N), −76.8 (N_{py}); MALDI-TOF *m*/*z* 219.1 $[M+1]^+$.

*4.2.6. 10-(Pyridin-3-yl)-1,4,7-triazabicyclo[5.2.1]decane (**6**).* Reaction with 3-pyridinecarboxaldehyde (213 μL, 2.30 mmol) for 4 h. The residue was purified by silica gel chromatography ($CHCl_3$/Et_3N 9:1 to $CHCl_3$/MeOH/Et_3N 9:0.5:0.5) to yield a brown solid (258 mg, 77%). NMR ($CDCl_3$) ^{1}H (500 MHz) 2.85–2.91 (6H, m, $4H_{\alpha NH}+2H_{\alpha N}$), 3.05–3.08 (2H, m, $H_{\beta NH}$), 3.12–3.13 (2H, m, $H_{\alpha N}$), 3.30–3.36 (2H, m, $H_{\beta NH}$), 5.55 (1H, s, H_{aminal}), 7.01 (1H, dd, *J* 4, 7, H_{ar}), 7.26 (1H, d, *J* 4, H_{ar}), 7.62 (1H, d, *J* 7, H_{ar}), 8.57 (1H, s, H_{ar}); ^{13}C (126 MHz) 49.1 ($C_{\alpha NH}$), 49.4 ($C_{\alpha N}$), 58.3 ($C_{\beta NH}$), 84.7 (C_{aminal}), 122.1 (CH_{ar}), 134.2 (CH_{ar}), 140.4 (C_{ar}), 147.9 (CH_{ar}), 148.5 (CH_{ar}); MALDI-TOF *m*/*z* 218.1 $[M]^+$.

*4.2.7. 10-(Pyridin-4-yl)-1,4,7-triazabicyclo[5.2.1]decane (**7**).* Reaction with 4-pyridinecarboxaldehyde (196 μL, 2.21 mmol) for 4 h. The residue was purified by silica gel chromatography ($CHCl_3$/Et_3N 9:1 then $CHCl_3$/MeOH/Et_3N 9:0.5:0.5) to yield a brown solid (385 mg, 84%). NMR ($CDCl_3$) ^{1}H (500 MHz) 2.84–2.98 (6H, m, $4H_{\alpha NH}+2H_{\alpha N}$), 3.04–3.07 (2H, m, $H_{\beta NH}$), 3.11–3.17 (2H, m, $H_{\alpha N}$), 3.26–3.32 (2H, m, $H_{\beta NH}$), 5.61 (1H, s, H_{aminal}), 7.38 (2H, d, *J* 5, CH_{ar}), 8.46 (2H, d, *J* 5, $CH_{ar}N$); ^{13}C (126 MHz) 49.2 ($C_{\alpha NH}$), 49.5 ($C_{\alpha N}$), 58.5 ($C_{\beta NH}$), 88.9 (C_{aminal}), 122.3 (CH_{ar}); 145.3 ($CH_{ar}N$), 152.7 (C_{ar}); MALDI-TOF 219.1 $[M+1]^+$.

4.3. General procedure for alkylation of aminal-protected tacn

Aminal-protected tacn (**3** or **4**) was dissolved in freshly distilled acetonitrile (25 mL) and halogenoalkane (1 equiv) and potassium carbonate (2.5 equiv) were added. The reaction mixture was stirred at room temperature. The solution was filtered and the filtrate was evaporated under reduced pressure to yield a brown oil.

*4.3.1. 4-Benzyl-10-phenyl-1,4,7-triazabicyclo[5.2.1]decane (**9**).* Reaction with **3** (370 mg, 1.70 mmol) and benzyl bromide (203 μL, 1.70 mmol) for 4 h. Yield 99% (529 mg). NMR ($CDCl_3$) ^{1}H (300 MHz) 2.48–3.34 (12H, m, H_α), 3.81 (2H, s, CH_2Ph), 5.72 (1H, s, H_{aminal}), 7.18–7.64 (10H, m, H_{ar}); ^{13}C (75 MHz) 49.6 ($C_{\alpha Naminal}$), 52.3 ($C_{\alpha N}$), 56.7 ($C_{\beta N}$), 62.8 (CH_2Ph), 87.7 (C_{aminal}) 126.7, 127.2, 128.2, 128.6, 128.8, 130.0 (CH_{ar}), 140.5 ($C_{ar}CH_2N$), 145.7 ($C_{ar}C_{aminal}$); MALDI-TOF 308.2 $[M+1]^+$.

*4.3.2. 4-Benzyl-10-(4-(trifluoromethyl)phenyl)-1,4,7-triazabicyclo[5.2.1]decane (**11**).* Reaction with **4** (254 mg, 0.89 mmol) and benzyl bromide (106 μL, 0.89 mmol) for 4 h. Yield 72% (240 mg). NMR ($CDCl_3$) ^{1}H (300 MHz) 2.58–3.25 (12H, m, H_α), 3.73 (2H, s, CH_2Ph), 5.66 (1H, s, H_{aminal}), 7.16–7.30 (5H, m, H_{ar}), 7.47 (2H, d, *J* 8, H_{ar}), 7.58 (2H, d, *J* 8, CH_{ar}–CCF_3); ^{13}C (75 MHz) 49.4 ($C_{\alpha Naminal}$), 55.2 ($C_{\alpha N}$), 56.6 ($C_{\beta N}$), 62.9 (CH_2Ph), 87.1 (C_{aminal}), 124.7 (*C*F$_3$, ^{1}*J* 250), 125.0 (CH_{ar}, ^{3}*J* 3), 127.2 (*C*–CF$_3$, ^{2}*J* 4), 127.3 (CH_{ar}), 128.5, 128.8 (CH_{ar}), 140.4 (C_{ar}–CH_2), 149.5 ($C_{ar}C_{aminal}$).

*4.3.3. 4-Allyl-10-(4-(trifluoromethyl)phenyl)-1,4,7-triazabicyclo[5.2.1]decane (**12**).* Reaction with **4** (235 mg, 0.82 mmol) and allyl bromide (70 μL, 0.82 mmol) for 4 h. Yield 98% (262 mg). NMR ($CDCl_3$) ^{1}H (300 MHz) 2.62–3.38 (14H, m, $H_\alpha+CH_{2allyl}$), 5.09 (1H, d, *J* 11, CH=*CH*$_2$), 5.14 (1H, d, *J* 18, CH=*CH*$_2$), 5.67 (1H, s, H_{aminal}), 5.77–5.95 (1H, m, *CH*=CH$_2$), 7.52 (2H, d, *J* 8, H_{ar}), 7.63 (2H, d, *J* 8, CH_{ar}–CCF_3); ^{13}C (75 MHz) 49.4 ($C_{\alpha Naminal}$), 55.0 ($C_{\alpha N}$), 56.8 ($C_{\beta N}$), 61.9 (CH_2CH=CH_2), 87.0 (C_{aminal}), 117.0 (CH=CH_2), 124.7 (*C*F$_3$, ^{1}*J* 272), 124.8 (CH_{ar}–CCF_3, ^{3}*J* 4), 127.1 (CH_{ar}), 128.8 (*C*–CF$_3$, ^{2}*J* 32), 136.7 (CH=CH_2), 149.6 (C_{ar}–C_{aminal}).

*4.3.4. 4-Ethyl-10-(4-(trifluoromethyl)phenyl)-1,4,7-triazabicyclo[5.2.1]decane (**13**).* Reaction with **4** (263 mg, 0.92 mmol) and iodoethane (74 μL, 0.92 mmol) for 64 h. Yield 95% (265 mg). NMR ($CDCl_3$) ^{1}H (300 MHz) 1.02 (3H, t, *J* 7, CH_3), 2.57–2.34 (14H, m, $H_\alpha+CH_2CH_3$), 5.73 (1H, s, H_{aminal}), 7.51 (2H, d, *J* 8, H_{ar}), 7.62 (2H, d, *J* 8, CH_{ar}–CCF_3); ^{13}C (126 MHz) 13.4 (CH_3), 49.4 ($C_{\alpha Naminal}$), 54.9 ($C_{\alpha N}$), 56.9 ($C_{\beta N}$), 52.6 (CH_2CH_3), 86.9 (C_{aminal}), 124.7 (*C*F$_3$, ^{1}*J* 273), 124.8 (C_{ar}–CCF_3, ^{3}*J* 4), 127.1 (CH_{ar}), 128.7 (*C*–CF$_3$, ^{2}*J* 32), 149.7(C_{ar}–C_{aminal}).

*4.3.5. 4-(4-Picolyl)-10-phenyl-1,4,7-triazabicyclo[5.2.1]decane (**14**).* Reaction with **3** (220 mg, 1.02 mmol) and 4-picolylchloride (100 mg, 0.79 mmol) for 140 h. The residue was purified by silica gel chromatography ($CHCl_3$/Et_3N 9:1 then $CHCl_3$/MeOH/Et_3N 9:0.5:0.5) to yield a brown oil (64 mg, 38%). NMR ($CDCl_3$) ^{1}H (300 MHz) 2.59–3.36 (12H, m, H_α), 3.82 (2H, s, CH_{2pic}), 5.63 (1H, s, H_{aminal}), 7.18–7.33 (7H, m, $C_6H_5+CH_{pic}$), 7.52 (2H, d, *J* 8, CH_{pic}); ^{13}C (75 MHz) 49.4 ($C_{\alpha N-Caminal}$), 55.5($C_{\alpha N}$), 56.4 ($C_{\beta N}$), 61.4 (CH_{2pic}), 87.8 (C_{aminal}), 123.6 (CH_{pic}), 126.7, 126.9, 128.2 (CH_{ar}), 145.3 (C_{ar}–C_{aminal}), 149.7 (C_{pic}), 150.1 (N=CH_{pic}).

*4.3.6. 4-Decyl-10-phenyl-1,4,7-triazabicyclo[5.2.1]decane (**15**).* Reaction of **3** (200 mg, 0.70 mmol) with 1-iododecane (150 μL, 0.70 mmol) for 4 days. After filtration and evaporation, the residue was purified by silica gel chromatography neutralised

with Et_3N ($CHCl_3$/hexane 1:1 then $CHCl_3$) to yield a brown oil (119 mg, 47%). NMR ($CDCl_3$) ^1H (300 MHz) 0.89 (3H, m, CH_3), 1.28 (16H, m, $C_{10}H_{21}$), 2.58–3.21 (12H, m, H_α), 3.33–3.37 (2H, m, N-CH_{2decyl}), 5.65 (1H, s, H_{aminal}), 7.18 (1H, t, *J* 7, H_{ar}), 7.29 (2H, t, *J* 7, H_{ar}), 7.50 (2H, d, *J* 7, H_{ar}); ^{13}C (75 MHz) 14.0 (*C*H_3), 22.6 (*C*H_2CH$_3$), 27.2, 28.5, 29.2, 29.6 (C_{decyl}), 31.9 (*C*H_2CH$_2$CH$_3$), 49.2 ($C_{\alpha N-Caminal}$), 55.2 ($C_{\alpha N}$), 56.5 ($C_{\beta N}$), 58.3 (*C*H_{2decyl}), 87.3 (C_{aminal}), 126.3, 127.8 (C_6H_5), 145.4 (C_{ar}–C_{aminal}).

*4.3.7. 4-(2-Picolyl)-10-(4-(trifluoromethyl)phenyl)-1,4,7-triazabicyclo[5.2.1]decane (**16**).* Reaction of **4** (500 mg, 1.75 mmol) with 4-picolylchloride (214 mg, 1.65 mmol) and sodium iodide (247 mg, 1.65 mmol) for 165 h. After filtration and evaporation, purification of the residue by silica gel chromatography ($CHCl_3$/Et_3N 9:1 then $CHCl_3$/MeOH/Et_3N 9:0.5:0.5) to yield a brown oil (443 mg, 73%). NMR ($CDCl_3$) ^1H (300 MHz) 2.70–2.75 (2H, m, $H_{\alpha N-Caminal}$), 2.88–2.94 (4H, m, $H_{\alpha N}$), 3.04–3.14 (4H, m, $2H_{\alpha N}$+$2H_{\alpha N-Caminal}$), 3.31–3.36 (2H, m, $H_{\alpha N}$), 3.97 (2H, s, CH_{2pic}), 5.65 (1H, s, H_{aminal}), 7.13 (1H, dd, *J* 5, 6, H_{pic}), 7.43 (1H, d, *J* 8, H_{pic}), 7.52 (2H, d, *J* 8, C*H*–CCF_3), 7.64 (3H, m, $2H_{ar}$+$1H_{pic}$), 8.52 (1H, d, *J* 5, H_{pic}); ^{13}C (75 MHz) 49.4 ($C_{\alpha N-Caminal}$), 55.2 ($C_{\alpha N}$), 56.2 ($C_{\beta N}$), 63.7 (CH_{2pic}), 87.2 (C_{aminal}), 122.2, 122.8 (*C*H$_{pic}$), 124.9 (*C*H=CCF_3, ^3J 4), 124.9 (*C*F_3, ^1J 279), 127.2 (*C*H=C–C_{aminal}), 128.9 (*C*–CF_3, ^2J 30), 136.6 (*C*H=CH–N), 149.4 (=*C*H–N), 149.6 (=*C*–C_{aminal}), 160.5 (*C*=N).

*4.3.8. 2-(6-((1,4,7-Triazabicyclo[5.2.1]decane)methyl)pyridinyl)-methylcyclamphosphoryl (**18**).* Reaction of **3** (250 mg, 1.15 mmol) and 2-(6-(chloromethyl)-pyridynyl)methylcyclamphosphoryl (**8**) (440 mg, 1.15 mmol) at 50 °C for 4 days. The solution was evaporated under reduced pressure to yield a yellow oil (640 mg, 97%), which was introduced into the next step without further purification. When necessary, purification by silica gel column chromatography neutralized with Et_3N was possible by eluting with $CHCl_3$, then $CHCl_3$/MeOH 98:2. NMR ($CDCl_3$) ^1H (400 MHz) 1.51–1.44 (2H, m, H^9), 1.68–1.78 (2H, m, H^4), 2.28–2.32 (2H, m, H^1), 2.38–2.41 (2H, m, H^2), 3.87 (18H, m, H_α), 3.23–3.33 (4H, m, H^3+H^5), 3.45–3.84 (4H, m, H^{11}+H_α), 3.87 (2H, s, H^{17}), 5.57 (1H, s, H^{21}), 7.09 (1H, m, H^{25}), 7.20 (3H, m, H^{24}+H^{15}), 7.41 (2H, m, H^{23}), 7.62 (1H, m, H^{14}), 7.77 (1H, m, H^{13}); ^{13}C (125 MHz) 21.7 (C^4), 26.2 (C^9), 40.6 (C^{10}), 41.6, 41.9 ($C_{\alpha cyclam}$), 44.1 ($C_{\alpha cyclam}$, ^2J 11), 45.3 ($C_{\alpha cyclam}$, ^2J 16), 48.7, 48.9 ($C_{\alpha N-Caminal}$), 51.5, 52.5, 52.6, 53.1 ($C_{\alpha cyclam}$), 54.5, 54.6 ($C_{\alpha Ntacn}$), 55.6, 55.7 ($C_{\alpha Ntacn}$), 58.2 ($C_{\alpha cyclam}$), 60.1 (N_{cyclam}–*C*H_2py), 62.8 (N_{tacn}–*C*H_2pyr), 87.2, 87.7 (C_{aminal}), 120.2 (C^{15}), 121.3 (C^{13}), 126.0 (C^{25}), 126.1 (C^{23}), 127.5 (C^{24}), 137.0 (C^{14}), 145.1 (C^{22}), 158.9 (C^{16}), 159.2 (C^{12}); ^{31}P (161.9 MHz) 25.9; MALDI-TOF *m*/*z* 565.3 $[M+1]^+$.

4.4. General procedure for aminal hydrolysis

Compounds **9**–**16** and **18** were dissolved in 25 mL of hydrochloric acid 1 M and stirred for 3 h at room temperature. The solution was evaporated under reduced pressure. The residue was washed by chloroform to yield hydrochloride compounds as white-off solids. Anion-exchange resin DOWEX gave the alkylated triazacyclononane as a free base.

*4.4.1. 1-Benzyl-1,4,7-triazacyclononane-1,4,7-trihydrochloride (**19**).* NMR (D_2O) ^1H (300 MHz) 3.01 (4H, t, *J* 5, H_α), 3.18 (4H, t, *J* 5, H_α), 3.57 (4H, s, $H_{\alpha NH}$), 3.88 (2H, s, CH_2Ph); 7.38 (5H, m, C_6H_5); ^{13}C (75 MHz) 44.9, 46.1, 50.3 (C_α), 61.9 (*C*H_2Ph), 133.3, 131.7, 133.1 (CH_{ar}), 138.1 (C_{ar}); MALDI-TOF *m*/*z* 220.2 $[M+1]^+$ for compound **19** as a free base. Anal. Calcd for $C_{13}H_{24}Cl_3N_3\cdot 3HCl\cdot 2.5H_2O$: C, 41.73; H, 7.82; N, 11.23; Cl, 28.42. Found: C, 41.37; H, 7.46; N, 11.27; Cl, 28.18.

*4.4.2. 1-Allyl-1,4,7-triazacyclononane-1,4,7-trihydrochloride (**20**).* NMR (D_2O) ^1H (300 MHz) 3.07 (4H, t, *J* 6, $H_{\alpha N}$), 3.31 (4H, t, *J* 6, $H_{\alpha N}$), 3.38 (2H, m, CH_2–CH=), 3.57 (4H, s, $H_{\alpha NH}$), 5.29 (1H, d, *J* 10, CH=CH_2), 5.32 (1H, d, *J* 6, CH=CH_2, H_2=C), 5.87 (1H, m, C*H*=CH_2); ^{13}C (75 MHz) 44.1, 44.4, 49.9 (C_α), 61.0 (*C*H_2–CH=), 125.0 (*C*H_2=), 133.5 (=*C*H); MALDI-TOF *m*/*z* 169.3 $[M]^+$ for compound **20** as a free base.

*4.4.3. 1-Ethyl-1,4,7-triazacyclononane-1,4,7-trihydrochloride (**21**).* NMR (D_2O) ^1H (300 MHz) 3.21 (3H, t, *J* 7, CH_3), 3.19 (2H, q, *J* 7, CH_2–CH_3), 3.55 (4H, br s, H_α), 3.57 (4H, br s, H_α), 3.68 (4H, br s, H_α); ^{13}C (75 MHz) 12.1 (*C*H_3), 43.3, 43.9, 49.7 (C_α), 54.7 (C_{aminal}); MALDI-TOF *m*/*z* 157.9 $[M]^+$as a free base.

*4.4.4. 1-(4-Picolyl)-1,4,7-triazacyclononane-1,4,7-trihydrochloride (**22**).* NMR (D_2O) ^1H (300 MHz) 3.16 (4H, t, *J* 6, H_α), 3.41 (4H, t, *J* 6, H_α), 3.73 (4H, br s, H_α), 4.26 (2H, s, CH_{2pic}), 8.09 (2H, d, *J* 6, C–CH_{ar}), 8.79 (2H, d, *J* 6, CH_{ar}–N); ^{13}C (75 MHz) 45.3, 46.7, 50.7 (C_α), 59.9 (C_{aminal}), 130.6 (*C*H_{ar}=C–N), 143.9 (*C*H_{ar}–N), 160.4 (C); MALDI-TOF *m*/*z* 221.0 $[M+1]^+$ as a free base.

*4.4.5. 1-Decyl-1,4,7-triazacyclononane-1,4,7-trihydrochloride (**23**).* NMR (D_2O) ^1H (300 MHz) 0.79 (3H, t, *J* 7.5, CH_3), 1.21 (14H, m, H_{decyl}), 1.56 (2H, m, $H_{\beta decyl}$), 2.88 (2H, m, H_{decyl}), 3.19 (4H, m, H_α), 3.38 (4H, m, H_α), 3.54 (4H, m, H_α); ^{13}C (75 MHz) 16.6 (*C*H_3), 25.3, 26.8, 29.7, 32.0 (2*C*), 32.2, 32.3 (C_{decyl}), 34.6 ($C_{\beta decyl}$), 44.3, 45.2, 50.4 (C_α), 54.5 ($C_{\alpha decyl}$).

*4.4.6. 1-(2-Picolyl)-1,4,7-triazacyclononane-1,4,7-trihydrochloride (**24**).* NMR (D_2O) ^1H (400 MHz) 1.13 (4H, t, *J* 5, H_α), 3.41 (4H, t, *J* 5, H_α), 3.71 (4H, br s, $H_{\alpha NH}$), 4.32 (2H, s, CH_{2pic}), 8.03 (1H, dd, *J* 6, 8, CH_{ar}=CH_{ar}–N), 8.11 (1H, d, *J* 8, CH_{ar}=C), 8.60 (1H, t, *J* 8, CH_{ar}=CH_{ar}), 8.77 (1H, d, *J* 6, CH_{ar}=N); ^{13}C (100 MHz) 45.3, 46.7, 50.9 (C_α), 58.1 (CH_{2pic}), 129. 4 (*C*H_{ar}=CH_{ar}–N), 131.1 (*C*H_{ar}=CH_{ar}), 144.8 (CH_{ar}=CH_{ar}–CH_{ar}), 150.2 (*C*H_{ar}=N), 153.1 (*C*).

*4.4.7. 1-((5′-Methyl-2,2′-bipyridin-5-yl)methyl)-1,4,7-triazacyclononane (**25**).* Compound **3** (216 mg, 1.00 mmol) and 5-(bromomethyl)-5′-methyl-2,2′-bipyridine[24] (262 mg, 1.00 mmol) were dissolved in distilled acetonitrile and potassium carbonate was added. The reaction mixture was stirred for 1 day at 50 °C. After cooling, the solution was filtered and the solvent evaporated. The residue (corresponding to 4-((5′-methyl-2,2′-bipyridin-5-yl) methyl)-10-phenyl-1,4,7-triazabicyclo[5.2.1]decane **17**) was purified by silica gel chromatography ($CHCl_3$ then $CHCl_3$/MeOH 98:2) to yield directly deprotected compound **25** as a white-off powder (100 mg, 32%). NMR ($CDCl_3$) ^1H (400 MHz) 2.35 (3H, s, CH_3), 2.66 (4H, m, H_α), 2.78 (4H, m, H_α), 3.02 (4H, m, H_α), 3.4 (2H, s, H_{aminal}), 7.58 (1H, d, *J* 8, CH_{ar}=CH_{ar}–C), 7.76 (1H, d, *J* 8, CH_{ar}=CH_{ar}–N), 8.22 (1H, d, *J* 8, CH_{ar}=C–N), 8.28 (1H, d, *J* 8, CH_{ar}=C–C), 8.46 (1H, s, H_{ar}), 8.57 (1H, s, H_{ar}); ^{13}C (75 MHz) 18.2 (*C*H_3), 45.7, 52.2, 55.4 (C_{tacn}), 58.3 (CH_{2bipy}), 120.4 (2C) (*C*H_{ar}=C–N), 133.2 (2C) (C_q–N), 137.3 (2C), 137.5(2C) (*C*H_{ar}=C–N), 149.5 (2*C*H_{ar}–N), 153.2, 155.2 (2*C*–CH=N); MALDI-TOF *m*/*z*: 312.1 $[M+1]^+$.

*4.4.8. Ditopic tacn-cyclam (**26**).* A solution of **18** (750 mg, 1.15 mmol) in hydrochloric acid 6 M (30 mL) was stirred at room temperature during 14 h. The solution was evaporated under reduce pressure. Work-up of the residue by anion-exchange resin Dowex yielded **26** as a free base. The very hygroscopic product was conserved as a hydrochloride salt.

$C_{23}H_{44}N_8\cdot 8HCl$ (**26**·8HCl) NMR (D_2O) ^1H (400 MHz) 1.86 (2H, m, H^4), 2.14 (2H, m, H^9), 2.78 (2H, m, H_α), 2.84 (2H, m, H_α), 2.96 (2H, m, H_α), 3.10 (4H, m, H_α), 3.23 (8H, m, H_α), 3.29 (2H, m, H_α), 3.35(4H, m, H_α), 3.87 (2H, s, H^{11}), 4.07 (2H, s, H^{17}), 7.36 (1H, d, *J* 8, H^{15}), 7.52 (1H, d, *J* 8, H^{13}), 7.93 (1H, dd, *J* 8, 8, H^{14}); ^{13}C (100 MHz) 22.2 (C^9), 25.0 (C^4), 42.7 ($C_{\alpha tacn}$), 42.8 ($C_{\alpha cyclam}$), 44.2 ($C_{\alpha tacn}$), 44.4 ($C_{\alpha cyclam}$), 45.0 (C^8), 46.5 ($C_{\alpha cyclam}$), 46.7 ($C_{\alpha cyclam}$), 48.6 ($C_{\alpha tacn}$), 49.7 ($C_{\alpha cyclam}$), 49.8 ($C_{\alpha cyclam}$), 51.5 ($C_{\alpha cyclam}$), 52.9 ($C_{\alpha cyclam}$), 57.5 (C^{11}),

60.5 (C^{17}), 123.8, 124.1 (C^{15}, C^{13}), 139.2 (C^{14}), 156.4, 157.2 (C^{16}, C^{12}). Anal. Calcd for $C_{23}H_{44}Cl_3N_8 \cdot 8HCl \cdot 5H_2O$ C, 33.92; H, 7.67; N, 13.76; Cl, 34.83. Found: C, 33.66; H, 7.72; N, 13.62; Cl, 34.89.

$C_{23}H_{44}N_8$ (**26**) NMR ($CDCl_3$) ^{1}H (400 MHz) 1.79 (2H, m, H^4), 1.88 (2H, m, H^9), 2.64 (2H, m, H^1), 2.75 (4H, m, H^{18}), 2.78–2.86 (16, m, $H_{\alpha cyclam}+H_{\alpha tacn}$), 2.98 (4H, s, H^{20}), 3.84 (2H, s, H^{11}), 3.88 (2H, s, H^{17}), 4.86 (5H, s, N*H*), 7.13 (1H, d, *J* 8, H^{15}), 7.33 (1H, d, *J* 8, H^{13}), 7.64 (1H, dd, *J* 8, 8, H^{14}); ^{13}C (100 MHz) 25.0 (C^9), 26.5 (C^4), 43.3 (C^{20}), 45.4 (C^{19}), 46.6 (C_α), 46.7 (C_α), 47.9 (C^8), 48.2 (C_α), 49.0 (C_α), 50.2 (C_α), 51.7 (C^{18}), 52.8 (C^{10}), 53.0 (C^1), 58.7 (C^{11}), 61.1 (C^{17}), 121.3 (C^{15}), 121.9 (C^{13}), 137.2 (C^{14}), 158.1 (C^{16}), 158.4 (C^{12}); MALDI-TOF *m*/*z* 433.38 $[M]^+$, 434.39 $[M+1]^+$.

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Supplementary data

NMR spectra (^{1}H, ^{13}C) of most of compounds and 2D NMR of compounds **3** and **6** are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.057.

References and notes

1. Bernhardt, P. V.; Lawrance, G. A. *Coord. Chem. Rev.* **1990**, *104*, 297–343; Wainwright, K. P. *Coord. Chem. Rev.* **1997**, *166*, 35–90.
2. Johnson, D. L.; Martin, L. L. *J. Am. Chem. Soc.* **2005**, *127*, 2018–2019.
3. Tolman, W. B. *Acc. Chem. Res.* **1997**, *30*, 227–237.
4. Mewis, R. E.; Archibald, S. J. *Coord. Chem. Rev.* **2010**, 1686–1712; Owadas, T. J.; Wong, E. H.; Weisman, G. R.; Anderson, C. J. *Chem. Rev.* **2010**, *110*, 2858–2902; Liang, F.; Wan, S.; Li, Z.; Xiong, X.; Yang, L.; Zhou, X.; Wu, C. *Curr. Med. Chem.* **2006**, *13*, 711–727.
5. Parker, R. J.; Spiccia, L.; Berry, K. J.; Fallon, G. D.; Moubaraki, B.; Murray, K. S. *Chem. Commun.* **2001**, 333–334; Sokol, J. J.; Lee, A. G.; Long, J. R. *J. Am. Chem. Soc.* **2002**, 7656–7657.
6. Tetilla, M. A.; Aragoni, M. C.; Arca, M.; Caltagirone, C.; Bazzicalupi, C.; Bencini, A.; Garau, A.; Isaia, F.; Laguba, A.; Lippolis, V.; Meli, V. *Chem. Commun.* **2011**, 3805–3807.
7. Pouessel, J.; Bazzicalupi, C.; Bencini, A.; Bernard, H.; Giorgi, C.; Handel, H.; Matera, I.; Le Bris, N.; Tripier, R.; Valtancoli, B. *Chem. Asian J.* **2011**, *6*, 1582–1594.
8. Chong, H.; Brechbiel, M. W. *Synth. Commun.* **2003**, *33*, 1147–1154.
9. Zhang, Q. F.; Yang, W. H.; Yi, W. J.; Zhang, J.; Ren, J.; Luo, T. Y.; Zhu, W.; Yu, X. Q. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7045–7049.
10. Kimura, S.; Bill, E.; Bothe, E.; Weyhermûller, T.; Wieghardt, K. *J. Am. Chem. Soc.* **2001**, *123*, 6025–6039; Kruper, W. J.; Rudolf, P. R.; Langhoff, C. A. *J. Org. Chem.* **1993**, *58*, 3869–3876.
11. Tjioe, L.; Joshi, T.; Forsyth, C. M.; Moubaraki, B.; Murray, K. S.; Brugger, J.; Graham, B.; Spiccia, L. *Inorg. Chem.* **2012**, *51*, 939–953; Tjioe, L.; Meininger, A.; Joshi, T.; Spiccia, L.; Graham, B. *Inorg. Chem.* **2011**, *50*, 4327–4339.
12. Sessler, J. L.; Sibert, J. W.; Lynch, V. *Inorg. Chem.* **1990**, *29*, 4143–4146.
13. Kovacs, Z.; Sherry, D. A. *Tetrahedron Lett.* **1995**, *36*, 9269–9272.
14. Van Westrenen, J.; Sherry, D. A. *Bioconjugate Chem.* **1992**, *3*, 524–532.
15. Atkins, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6365–6369; Weisman, G. R.; Vachon, D. J.; Johnson, V. B.; Gronbeck, D. A. *J. Chem. Soc., Chem. Commun.* **1987**, 886–887; Blake, A. J.; Fallis, I. A.; Gould, R. O.; Parsons, S.; Ross, S. A.; Schröder, M. *J. Chem. Soc., Chem. Commun.* **1994**, 2467–2469; Warden, A.; Graham, B.; Hearn, M. T. W.; Spiccia, L. *Org. Lett.* **2001**, *3*, 2855–2858; Battle, A. R.; Spiccia, L. *Tetrahedron* **2005**, *61*, 7499–7507.
16. Stavila, V.; Stortz, Y.; Franc, C.; Maurin, P.; Beuf, O.; Dufay, O.; Samarut, J.; Janier, M.; Hasserodt, J. *New J. Chem.* **2008**, *32*, 428–435; Touti, F.; Maurin, P.; Canaple, L.; Beuf, O.; Hasserodt, J. *Inorg. Chem.* **2012**, *51*, 31–33.
17. Sobieściak, T. D.; Zielenkiewicz, P. *J. Org. Chem.* **2010**, *75*, 2069–2072.
18. Broan, C. J.; Cole, E.; Jankowski, K. J.; Parker, D.; Pulukkody, K.; Boyce, B. A.; Beeley, N. R. A.; Millar, K.; Millican, A. T. *Synthesis* **1992**, 63–69.
19. Royal, G.; Dahaoui-Gindrey, V.; Dahaoui, S.; Tabard, A.; Guilard, R.; Pullumbi, P.; Lecomte, C. *Eur. J. Org. Chem.* **1998**, 1971–1975; Tripier, R.; Lagrange, J.-M.; Espinosa, E.; Denat, F.; Guilard, R. *Chem. Commun.* **2001**, 2728–2729.
20. Le Baccon, M.; Chuburu, F.; Toupet, L.; Handel, H.; Soibinet, M.; Deschamps-Olivier, I.; Barbier, J. P.; Aplincourt, M. *New J. Chem.* **2001**, *25*, 1168–1174; Timmons, J. C.; Hubin, T. J. *Coord. Chem. Rev.* **2010**, *254*, 1661–1685.
21. Wieghardt, K.; Tolksdorf, I.; Herrmann, W. *Inorg. Chem.* **1985**, *24*, 1230–1235; Blake, A. J.; Donlevy, T. M.; England, P. A.; Fallis, I. A.; Parsons, S.; Ross, S. A.; Schröder, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1981–1982; Brudenell, S. J.; Spiccia, L.; Bond, A. M.; Fallon, G. D.; Hockless, D. C.; Lazarev, G.; Mahon, P. J.; Tiekink, E. R. T. *Inorg. Chem.* **2000**, *39*, 881–892.
22. Filali, A.; Yaouanc, J. J.; Handel, H. *Angew. Chem.* **1991**, *103*, 563–564; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 560–561.
23. Rezzonico, B.; Grignon-Dubois, M. *J. Chem. Res. (S)* **1994**, *4*, 142–143.
24. Heck, R.; Dumarcay, F.; Marsura, A. *Chem.—Eur. J.* **2002**, *8*, 2438–2445.