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Regioselective synthesis of *N*-functionalized 12-membered azapyridinomacrocycles bearing trialkylcarboxylic acid side chains

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Abstract—Selective protection of primary amine moieties of diethylenetriamine by 2-nitrophenylsulfonyl chloride followed by alkylation of the central *N* atom generates functionalized disulfonamide building blocks. When reacted with 2,6-bis(bromomethyl)pyridine following the Richman–Atkins methodology, such compounds yield the corresponding pyridine-containing azamacrocycles. Smooth removal of the *N*-sulfonyl groups provides versatile azamacrocyclic intermediates with transannular secondary amine functions. Subsequent *N*-alkylation regioselectively leads to tri *N*-functionalized 12-membered azapyridinomacrocycles bearing a sequence of *N*-acetate and *N*-propionate side chains.

1. Introduction

Recent interest in polyazamacrocyclic chelates of paramagnetic and radioactive metal ions largely results from their biomedical applications, such as Magnetic Resonance Imaging (MRI) contrast agents[1] and diagnostic agents[2] as well as therapeutic radiopharmaceuticals.[3]

A large number of 12- and 14-membered tetraazamacrocycles have been studied[1b] and it appears that the selectivity of the complexation (i.e. the relative stability of the corresponding complexes) of such ligands towards various metal ions could be tuned by adjusting the ring size, the number and nature of coordinating subunits. Pyridine-containing azamacrocyclic ligands bearing three amines and three acidic side chains offer a chromophoric subunit as well as seven potential donor sites of various degrees of hardness able to coordinate a lanthanide ion in its first coordination sphere.[4] Potential applications of this type of ligand exploit the high stability of their complexes together with their ability to shield the encapsulated ion from interactions with the neighbouring environment.[5] Moreover, recent spectroscopic investigations involving such ligands were reported to allow UV-light induced Tb^{3+} and Eu^{3+} luminescence[4,6] thus extending the potential use of rare-earth complexes in biomedical imaging.

The regioselective *N*-functionalization of polyazamacrocycles is a synthetic challenge of interest as it may allow a fine tuning of their complexation properties by adjusting the nature of the coordinating subunits. Various approaches have been used for the desymmetrization of azamacrocycles.[7] Direct mono *N*-functionalization of unprotected polyazamacrocycles has been performed using a large excess of macrocycle relative to the electrophile reagent[8] or by using strictly controlled conditions.[9] These methods suffer from time-consuming purification steps and are precluded for unreadily available macrocyclic compounds. Monosubstitution was also achieved by alkylation of an organometallic complex derivative[10] or by previous regioselective protection.[11] However, these approaches have limited applicability as highly dependent on the nature of both the macrocyclic compound and the alkylating reagent.

An alternative synthetic route to regioselective *N*-functionalized azamacrocycles involves the differentiation of the amines of the polyamine skeleton at the early stage of the synthesis which requires the preparation of appropriately functionalized linear polyamine precursors. The synthesis of *N*-protected polyamines containing independently removable *N*-protecting groups has recently

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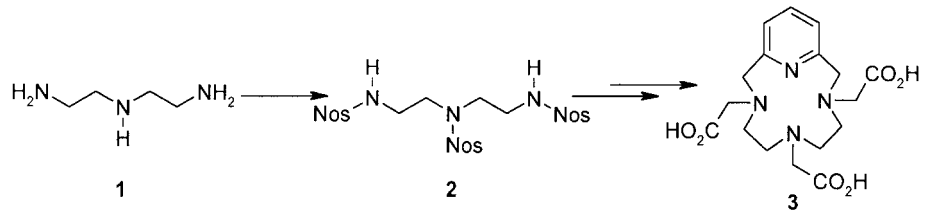


Scheme 1.

attracted a great deal of interest[12] since such compounds are valuable precursors for the synthesis of natural products. Multistep syntheses of regioselectively *N*-protected polyamines have been described;[13,14] however such syntheses are somewhat long.

We report here an approach involving a highly chemoselective protection and activation of primary amine of diethylenetriamine. Subsequent alkylation of the central amine moiety affords a versatile tri *N*-functionalized derivative that reacts with 2,6-bis(bromomethyl)pyridine in a macrocyclization process. A selective deprotection gives rise to a versatile pyridine-containing azamacrocycle with transannular secondary amine functions which can be further *N*-alkylated to yield 12-membered azamacrocyclic compounds with the desired sequence of *N*-acetate and *N*-propionate side chains.

2. Results and discussion

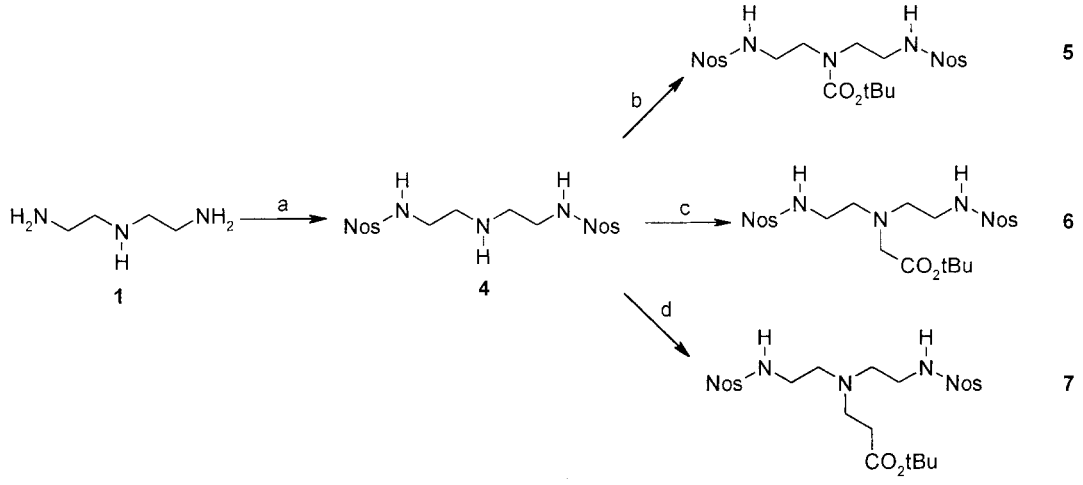
We have recently reported that the reaction of 3 equivalents of 2-nitrophenylsulfonyl chloride with diethylenetriamine **1** in heterogeneous $NaHCO_3$/THF system led to the formation of the tris(2-nitrophenylsulfonyl)-protected compound **2** (Scheme 1).[4] Treatment of **2** with 2,6-bis(bromomethyl)-pyridine in the presence of Na_2CO_3 gave the *N*-protected azamacrocycle. Removal of the three *N*-sulfonyl groups followed by alkylation with chloroacetic acid afforded ligand **3** with identical side chains in good yield.

For the synthesis of ligands with different side chains, we anticipated that the use of 2-nitrophenylsulfonyl chloride could be of interest for the construction of new orthogonally protected polyamine building blocks. Indeed, we have previously shown that differentiation of primary and secondary amine moieties of polyamines could be achieved with the use of 2-nitrophenylsulfonyl chloride.[15] So, by controlling the quantity of 2-nitrophenylsulfonyl chloride introduced (2 equivalents), the primary amine moieties of diethylenetriamine **1** have been selectively protected to produce the *N*-diprotected amine **4** in 79% yield (Scheme 2).

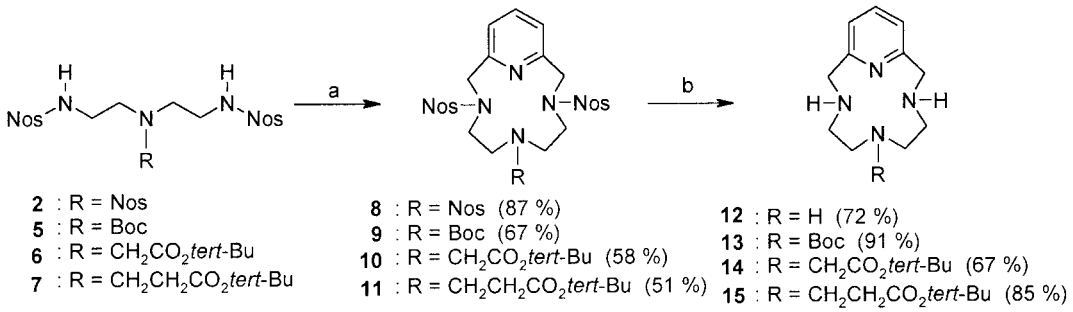
The central amine function of compound **4** was then functionalized following conventional methods (Scheme 2). The Boc derivative **5** was obtained in 87% yield by reaction of the corresponding anhydride in the presence of triethylamine. Such a compound is of interest for the preparation of monofunctionalized cyclens[7,16] or pyridine-containing azamacrocycles.[4,5,17]

The preparation of diethylenetriamine derivatives bearing *N*-alkylcarboxylate side chains was realized either by reaction of compound **4** with *tert*-butyl bromoacetate leading to the acetate product **6** in 82% yield or with *tert*-butyl acrylate leading quantitatively to the homologous propionate derivative **7**. Compounds **6** and **7** could serve to investigate the influence of the length of the side chains on the metal ion coordination of azapyridinomacrocyclic ligands.[18]

The macrocyclization step results from the Richman–Atkins protocol[16] (reaction of the functionalized 2-nitrophenylsulfonamide, i.e. **2**, **5**, **6** or **7**, with 2,6-bis(bromomethyl)pyridine in the presence of anhydrous Na_2CO_3)[4]



Scheme 2. (a) 2 eq. $ClSO_2(2\text{-}NO_2Ph)$, $NaHCO_3$, THF, 79%; (b) Boc_2O, THF, TEA, 87%; (c) *tert*-butyl bromoacetate, THF, Et_3N, 82%; (d) *tert*-butyl acrylate, MeOH, 98%.



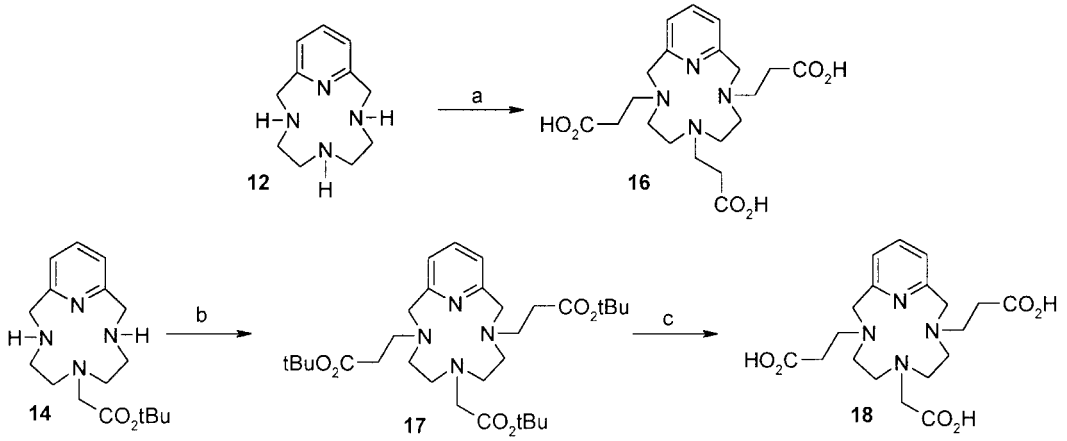
Scheme 3. (a) 2,6- bis(bromomethyl)pyridine, Na_2CO_3, DMF, 100°C; (b) PhSH, Na_2CO_3, DMF, r.t.

which produces the corresponding expected macrocycles **8**–**11** (Scheme 3) in medium to good yields. However, it should be noted that the macrocyclization yield decreases when the steric hindrance at the central *N*-atom decreases. This result gives further support to the idea that steric and conformational factors resulting from the presence of bulky tosyl or nosyl groups play a key role in determining the efficiency of Richman–Atkins cyclizations.[16,19] Indeed, central *N*-nosylated compound **2** should adopt the required conformation for cyclization more readily than the less bulky substrates **5–7** and, therefore, would cyclize more readily (Thorpe–Ingold effect).[20]

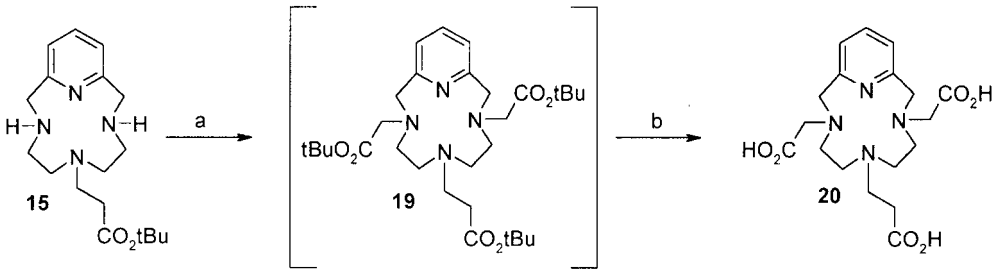
The nosyl groups of macrocyclic compounds **8**–**11** could be cleaved by aromatic nucleophilic substitution with thioglycolic acid in the presence of LiOH in DMF at room temperature.[21] However, purification of the water soluble amine **12** is complicated by the fact that both the excess of thioglycolic acid and the thioether by-product are water soluble. So, replacing the thioglycolic acid reagent by thiophenol gives rise to a lipophilic thioether by-product that facilitates the purification step. The nosylated macrocycles **8**–**11** were all treated under these conditions and gave compounds **12**–**15** bearing secondary amine functions in good to excellent yields (Scheme 3). It should be noted that the regioselectively mono *N*-functionalized compounds **13**–**15** with transannular secondary amine functions could be intermediates of choice for the synthesis of various bismacrocycles or cryptands.[7,14]

The desired 12-membered azapyridinomacrocycles bearing trialkylcarboxylic acid side chains **3**, **16**, **18** and **20** could be prepared from the parent amines **12**, **14** or **15** (Schemes 1, 4 and 5). Alkylation of compound **12** has been studied under various conditions.[22] The macrocycles **3** and **16** with identical side chains were obtained under forcing conditions (excess of alkylating reagent, pH 10 at 80°C for 2 days). In the case of the parent macrocyclic amines with the central *N*-atom already substituted **14**–**15**, milder conditions were used. Compound **17** was obtained in 43% yield by treating the amine **14** with an excess of *tert*-butyl acrylate. The *tert*-butyl ester derivative was then cleaved with dry hydrogen chloride leading to **18** in 56% yield.

Further alkylation of the propionate derivative **15** proved to be more problematic as, under classical conditions of reaction and treatment, the intermediate **19** could not be isolated (Scheme 5). We found that a one-pot alkylation/deprotection procedure leads to the desired macrocyclic compound **20** in 59% yield. It should be noted that NMR and SM analyses revealed the presence of a small proportion of compound **3** in the crude mixture (**20/3**: 80/20). The formation of such a by-product can be rationalized by a retro-Michael process occurring at the *N*-propionate subunit of **15** and the resulting secondary amine is alkylated in the presence of the excess of *tert*-butyl bromoacetate to give compound **3** as a by-product. Furthermore, such a retro reaction can explain the poor stability of **19** that precludes its isolation.



Scheme 4. (a) acrylic acid, NaOH/H_2O (pH=10), 54%; (b) *tert*-butyl acrylate, MeOH, 43%; (c) HCl-Et_2O sat., 56%.



Scheme 5. (a) *tert*-butyl bromoacetate, TEA, THF then (b) HCl-Et_2O sat., 59%.

3. Conclusion

In this paper, we have shown that the selective protection/activation of primary amines of diethylenetriamine **1** with 2-nitrophenylsulfonyl chloride provides a straightforward route to versatile intermediates for the synthesis of functionalized azamacrocycles. This protocol enabled us to prepare two monosubstituted macrocyclic amines, **14** and **15**, for the synthesis of symmetrical macrocycles **18** and **20** with the desired sequence of *N*-acetate and *N*-propionate side chains. The four 12-membered azapyridinomacrocycles prepared will allow an extension to the study aimed at optimizing the complexation selectivity of this class of compounds towards metallic cations.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere. Reactions were monitored by TLC or HPLC. ^1H and ^{13}C NMR spectra were recorded on a Brucker AM400. Mass spectrometry was obtained from Ecole Normale Supérieure (24 rue Lhomond, 75231 Paris Cedex 05). Spectral data for compounds **2**, **8**, **12** and **3** have been previously published.[15,22]

4.1.1. 1,7-Bis(2-nitrophenylsulfonyl)-1,4,7-triazaheptane (4). A solution of 2-nitrophenylsulfonyl chloride (2.21 g, 10 mmol) in 100 mL of tetrahydrofuran was added dropwise to a stirred suspension of **1** (0.50 g, 5 mmol) and dried $NaHCO_3$ (1.68 g, 20 mmol) in 50 mL of tetrahydrofuran at 0°C. The resulting mixture was allowed to warm to room temperature and stirred for further 12h, filtered and concentrated under vacuum. The crude product was purified by chromatography on silica gel (CH_2Cl_2/MeOH: 100/0 to 95/5) and yielded **4** as a white solid; 2.6 g, (79%). ^1H NMR (DMSO-d_6) δ: 2.48 (t, 4H, J=6.3 Hz), 2.88 (t, 4H, J=6.3 Hz), 7.84–7.99 (m, 8H). ^{13}C NMR (DMSO-d_6) δ: 42.5, 47.7, 124.2, 129.3, 132.4, 132.5, 133.8, 147.5. HRMS (FAB): found *m/z* 474.0759 ($[M+H]^+$); calcd for $C_{16}H_{20}N_5O_8S_2$ 474.0753.

4.1.2. 4-(*tert*-Butoxycarbonyl)-1,7-bis(2-nitrophenylsulfonyl)-1,4,7-triazaheptane (5). To a solution of **4** (9.43 g, 20 mmol) and triethylamine (5.46g, 54 mmol) in 100 mL of tetrahydrofuran at 0°C was added di-*tert*-butyl dicarbonate (6.54 g, 30 mmol). The reaction mixture was stirred at room temperature for 24 h. 150 mL of a saturated aqueous solution of ammonium chloride was added. The crude mixture was concentrated under vacuum and the resulting aqueous layer was extracted with dichloromethane. The organic layer was dried over sodium sulfate, concentrated under vacuum and gave a crude oil that was purified by chromatography on silica gel (ethyl acetate/heptane: 5/5 to 7/3) to afford compound **5** as a yellow oil; 9.90g (87%). ^1H NMR ($CDCl_3$) δ: 1.45 (s, 9H), 3.30 (m, 4H), 3.40 (m, 4H), 5.60 (m, 1H), 5.80 (m, 1H), 7.80–8.20 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 28.2, 42.4, 81.1, 125.2, 130.8, 132.8, 133.2, 133.6, 147.9, 155.7. HRMS (FAB): found *m/z* 596.1096 ($[M+Na]^+$); calcd for $C_{21}H_{27}N_5O_{10}S_2Na$ 596.1097.

4.1.3. 4-((*tert*-Butoxycarbonyl)methyl)-1,7-bis(2-nitrophenylsulfonyl)-1,4,7-triazaheptane (6). To a solution of **4** (0.94 g, 2 mmol) and triethylamine (1.24g, 12 mmol) in 25 mL of tetrahydrofuran was added *tert*-butyl bromoacetate (1.68 mL, 6 mmol). The reaction mixture was refluxed overnight and then allowed to cool to room temperature. 50 mL of a saturated aqueous solution of ammonium chloride was added. The crude mixture was concentrated under vacuum and the aqueous layer was extracted with dichloromethane. The organic layer was dried over sodium sulfate, and the solvent was evaporated to afford an oil. After a chromatography on silica gel (ethyl acetate/heptane: 5/5 to 8/2) the desired compound **6** was obtained as a yellow oil; 0.97g (82%). ^1H NMR ($CDCl_3$) δ: 1.39 (s, 9H), 2.75 (t, 4H, J=5.8 Hz), 3.05 (m, 4H), 3.10 (s, 2H), 5.96 (m, 2H), 7.70–8.05 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 27.9, 41.6, 54.2, 55.6, 81.8, 125.2, 130.6, 132.6, 133.1, 133.6, 147.9, 170.6. HRMS (FAB): found 588.1446 ($[M+H]^+$); calcd for $C_{22}H_{30}N_5O_{10}S_2$: 588.1434.

4.1.4. 4-(2-(*tert*-Butoxycarbonyl)ethyl)-1,7-bis(2-nitrophenylsulfonyl)-1,4,7-triazaheptane (7). Compound **4** (16.50 g, 35 mmol) was dissolved in a mixture of *tert*-butyl acrylate (13.46 g, 105 mmol) and methanol (20 mL). The reaction mixture was refluxed overnight and then concentrated under vacuum. The crude product was purified by chromatography on silica gel (ethyl acetate/heptane: 5/5 to 8/2) yielding **7** as a yellow oil; 20.7 g (98%). ^1H NMR ($CDCl_3$) δ: 1.43 (s, 9H), 2.32 (t, 2H, J=6.5 Hz), 2.56 (t, 4H, J=5.8 Hz), 3.10 (m, 4H), 3.15 (t, 2H, J=6.5 Hz), 5.84 (m, 2H), 7.70–8.10 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 27.9, 32.9, 41.2, 48.7, 53.6, 81.1, 125.2, 130.7, 132.5, 133.2, 133.4, 148.0, 171.8. HRMS (FAB): found 602.1559 ($[M+H]^+$); calcd for $C_{23}H_{31}N_5O_{10}S_2$: 602.1591.

4.1.5. General procedure for the macrocyclization: reaction of 2,6-bis(bromomethyl)pyridine with bis(2-nitrophenylsulfonamide) compounds 5-7. In a typical procedure, a solution of 2,6-bis(bromomethyl)pyridine

(2.38 g, 9 mmol) in anhydrous *N*,*N*-dimethylformamide (125 mL) was added dropwise to a stirred suspension of the disulfonamide building block (9 mmol) and Na_2CO_3 (3.81 g, 36 mmol) in anhydrous *N*,*N*-dimethylformamide (125 mL) at 100°C. The reaction mixture was heated overnight and then concentrated under vacuum. The residue was taken up in dichloromethane. The organic phase was washed with an aqueous solution of sodium hydroxide (0.1M) then dried over sodium sulfate and concentrated.

4.1.6. *tert*-Butyl 3,9-bis(2-nitrophenylsulfonyl)-3,6,9,15-tetraazabicyclo[9.3.1]pentadecane-1(15),11,13-triene-6-carbamate (9). Compound **9** was obtained after recrystallization in acetone as a white solid; 4.1 g (67%). ^{1}H NMR (DMSO-d_6) δ: 1.38 (s, 9H), 3.53 (m, 8H), 4.60 (s, 4H), 7.35 (m, 2H), 7.80–8.10 (m, 9H). ^{13}C NMR (DMSO-d_6) δ: 27.8, 44.5, 45.3, 49.6, 49.8, 55.0, 78.6, 122.3, 124.4, 129.2, 130.9, 132.5, 134.4, 138.2, 147.7, 154.4, 155.6. HRMS (FAB): found 677.1696 ($[M+H]^+$); calcd for $C_{28}H_{33}N_6O_{10}S_2$ 677.1700.

4.1.7. *tert*-Butyl 3,9-bis(2-nitrophenylsulfonyl)-3,6,9,15-tetraazabicyclo[9.3.1]pentadecane-1(15),11,13-triene-6-acetate (10). Compound **10** was obtained after chromatography on silica gel (ethyl acetate/heptane: 5/5 to 8/2) as a white solid; 3.60 g (58%). ^{1}H NMR ($CDCl_3$) δ: 1.39 (s, 9H), 2.55 (t, 4H, *J*=7.6 Hz), 3.17 (s, 2H), 3.30 (t, 4H, *J*=7.6 Hz), 4.56 (s, 4H), 7.42 (d, 2H, *J*=7.7 Hz), 7.82–8.06 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 28.1, 44.8, 51.1, 54.2, 57.4, 81.1, 124.1, 124.2, 130.7, 131.8, 132.6, 133.7, 139.0, 148.1, 154.5, 1709. HRMS (FAB): found 691.1824 ($[M+H]^+$); calcd for $C_{29}H_{35}N_6O_{10}S_2$ 691.1856.

4.1.8. *tert*-Butyl 3,9-bis(2-nitrophenylsulfonyl)-3,6,9,15-tetraazabicyclo[9.3.1]pentadecane-1(15),11,13-triene-6-propanoate (11). Compound **11** was obtained after chromatography on silica gel (ethyl acetate/heptane: 5/5 to 5/0) as a yellow oil; 3.23 g (51%). ^{1}H NMR ($CDCl_3$) δ: 1.39 (s, 9H), 2.22 (t, 2H, *J*=7.1 Hz), 2.45 (t, 4H, *J*=7.7 Hz), 2.64 (t, 2H, *J*=7.1 Hz), 3.25 (t, 4H, *J*=7.7 Hz), 4.57 (s, 4H), 7.45 (d, 2H, *J*=7.7 Hz), 7.68–8.05 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 28.1, 35.2, 44.4, 50.2, 50.7, 54.3, 80.1, 124.1, 124.3, 130.8, 131.8, 132.6, 133.7, 139.1, 148.2, 154.6, 171.5. HRMS (FAB): found *m/z* 705.2014 ($[M+H]^+$); calcd for $C_{30}H_{37}N_6O_{10}S_2$ 705.2013.

4.1.9. General procedure for the cleavage of the nosylate group of dinosylated macrocycles 9–11. In a typical procedure, anhydrous sodium carbonate (0.85 g, 8 mmol) was added to a solution of dinosylated macrocycle (1 mmol) and thiophenol (0.27 g, 2.5 mmol) in N,*N*-dimethylformamide (20 mL). The reaction mixture was stirred at room temperature overnight and then concentrated under vacuum. The residue was taken up in dichloromethane and the organic phase was washed with water then dried over sodium sulfate and concentrated.

4.1.10. *tert*-Butyl 3,6,9,15-tetraazabicyclo[9.3.1]pentadecane-1(15),11,13-triene-6-carbamate (13). Compound **13** was obtained after chromatography on silica gel (MeOH/NH_3 aq 32%: 100/0 to 95/5) as a colourless oil; 0.28 g (91%). ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 9H), 2.59 (t, 4H, *J*=5.3 Hz), 2.95 (m, 2H), 3.50 (m, 4H), 3.92 (s, 4H), 6.91 (d, 2H, *J*=7.6 Hz), 7.5 (dd, 1H, *J*=7.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 28.3, 48.5, 50.5, 51.8, 78.8, 120.0, 136.3, 157.2, 157.9. HRMS (FAB): found *m/z* 307.2130 ($[M+H]^+$); calcd for $C_{16}H_{27}N_4O_2$ 307.2134.

4.1.11. *tert*-Butyl 3,6,9,15-tetraazabicyclo[9.3.1]pentadecane-1(15),11,13-triene-6-acetate (14). Compound **14** was obtained after chromatography on neutral alumina (CH_2Cl_2/MeOH: 99/1) as a colourless oil; 0.21 g (67%). ^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 9H), 2.54 (m, 4H), 2.64 (m, 4H), 3.39 (s, 2H), 3.98 (s, 4H), 4.39 (m, 2H), 7.00 (d, 2H, *J*=7.6 Hz), 7.54 (dd, 1H, *J*=7.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 28.2, 47.7, 52.9, 56.3, 59.4, 81.3, 120.2, 136.8, 157.7, 171.3. HRMS (FAB): found *m/z* 321.2301 ($[M+H]^+$); calcd for $C_{17}H_{29}N_4O_2$ 321.2291.

4.1.12. *tert*-Butyl 3,6,9,15-tetraazabicyclo[9.3.1]pentadecane-1(15),11,13-triene-6-propanoate (15). Compound **15** was obtained after chromatography on neutral alumina (CH_2Cl_2/MeOH: 100/0 to 98/2) as a colourless oil; 0.28 g (85%). ^{1}H NMR ($CDCl_3$) δ: 1.38 (s, 9H), 2.52 (t, 2H, *J*=6.2 Hz), 2.60 (m, 4H), 2.70 (m, 4H), 2.92 (t, 2H, *J*=6.2 Hz), 4.15 (s, 4H), 5.85 (m, 2H), 7.10 (d, 2H, *J*=7.7 Hz), 7.66 (dd, 1H, *J*=7.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 27.9, 33.7, 47.2, 51.2, 53.2, 55.7, 80.9, 120.7, 137.6, 154.8, 172.7. HRMS (FAB): found *m/z* 334.2371 ($[M+H]^+$); calcd for $C_{18}H_{30}N_4O_2$ 334.2369.

4.1.13. 3,6,9,15-Tetraazabicyclo[9.3.1]pentadecane-1(15),11,13-triene-3,6,9-tripropanoic acid (16). Compound **12** (1.26 g, 4 mmol) was dissolved in water (16 mL). Acrylic acid (4.32 g, 60 mmol) was added and the pH of the solution was adjusted to 10 with an aqueous solution of NaOH (3N). The reaction mixture was heated at 80°C for 48 h, then concentrated, and the residue was pre-purified by chromatography on an ion-exchange resin (Dowex 1×8, formate form) eluting with formic acid (0.02N). The resulting product was further purified by gel-filtration (Sephadex G-10 eluting with water) and compound **16** was obtained as a white solid; 0.92g, 54%. ^{1}H NMR (D_2O/NaOD) δ: 2.31 (m, 4H), 2.43 (t, 2H, *J*=6.7 Hz), 2.50 (t, 4H, *J*=7.9 Hz), 2.61 (m, 6H), 2.97 (t, 4H, *J*=7.9 Hz), 3.85 (s, 4H), 7.43 (d, 2H, *J*=7.7 Hz), 7.95 (dd, 1H, *J*=7.7 Hz).^{13}C NMR (NaOD) δ: 37.6, 37.7, 49.4, 49.5, 53.3, 56.4, 61.4, 126.8, 141.7, 158.2, 183.6. HRMS (FAB): found *m/z* 423.2238 ($[M+H]^+$); calcd for $C_{20}H_{31}N_4O_6$ 423.2244.

4.1.14. Di-*tert*-butyl 6-[(*tert*-butoxycarbonyl)methyl]-3,6,9,15-tetraazabicyclo[9.3.1]pentadecane-1(15),11,13-triene-3,9-dipropanoate (17). Compound **14** (2.66 g, 8.29 mmol) was dissolved in *tert*-butyl acrylate (12.5 g, 99.5 mmol) and methanol (5 mL). The reaction mixture was refluxed for 48 h and then cooled to room temperature. The crude mixture was concentrated under vacuum and the residue was purified by chromatography on neutral alumina (ethyl acetate) yielding **17** as a yellow oil; 2.05 g (43%). ^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 27H), 2.45 (m, 8H), 2.55 (t, 4H, *J*=7.3 Hz), 2.94 (t, 4H, *J*=7.3 Hz), 3.10 (s, 2H), 3.79 (s, 4H), 7.16 (d, 2H, *J*=7.6 Hz), 7.65 (dd, 1H, *J*=7.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 28.1, 34.4, 49.3, 49.8, 53.1, 58.0, 60.5, 80.3, 122.7, 137.2, 157.4, 171.9. HRMS (FAB): found *m/z* 577.3984 ($[M+H]^+$); calcd for $C_{31}H_{53}N_4O_6$ 577.3965.

4.1.15. 6-(Carboxymethyl)-3,6,9,15-tetraazabicyclo[9.3.1]-pentadecane-1(15),11,13-triene-3,9-dipropanoic acid (18). Compound **17** (2.05 g, 3.55 mmol) was dissolved in 25 mL of anhydrous diethylether. The reaction mixture was then cooled to 0°C and 100 mL of a saturated solution of HCl in diethylether was added. The reaction mixture was stirred overnight. The white precipitate obtained was filtered and then pre-purified on an ion-exchange resin (Dowex 1X8, formate form) eluting with formic acid (0.02N). The residue was purified by gel filtration (Sephadex G-10 eluting with water) yielding **18** as a white solid; 0.81 g, 56%. ^{1}H NMR (D_2O) δ: 2.84 (m, 2H), 3.03 (t, 4H, J=6.9 Hz), 3.18 (m, 2H), 3.51 (m, 2H), 3.59 (m, 2H), 3.68 (s, 2H), 3.79 (m, 4H), 4.80 (s, 2H), 4.95 (s, 2H), 7.53 (d, 2H, J=7.8 Hz), 8.04 (dd, 1H, J=7.8 Hz).^{13}C NMR (D_2O) δ: 31.1, 52.6, 54.5, 56.6, 57.4, 60.3, 124.7, 142.9, 151.4, 176.7, 177.4. HRMS (FAB): found *m/z* 409.2108 ($[M+H]^+$); calcd for $C_{19}H_{29}N_4O_6$ 409.2087.

4.1.16. 3,9-Bis(carboxymethyl)-3,6,9,15-tetraazabicyclo-[9.3.1]pentadecane-1(15),11,13-triene-6-propanoic acid (20). Compound **15** (0.62 g, 1.85 mmol) was dissolved in 60 mL of anhydrous tetrahydrofuran. Triethylamine (0.9 mL, 7.00 mmol) and *tert*-butyl bromoacetate (1.5 mL, 10.2 mmol) were then added. The reaction mixture was heated at 70°C during 3 h and then concentrated under vacuum. The residue was taken up in dichloromethane (90 mL), washed with water (30 mL). The organic phase was dried over sodium sulfate, concentrated under vacuum and dissolved in 30 mL of diethylether. 150 mL of a saturated solution of HCl in diethylether was added and the reaction mixture was stirred overnight. The white precipitate was filtered and then pre-purified by gel filtration (Sephadex G-10 eluting with water). The residue was further purified by chromatography on an ion-exchange resin (Dowex 1X8, formate form) eluting with formic acid (0.02N) to provide compound **20** as a white solid; 0.43 g (59%). ^{1}H NMR (D_2O) δ: 2.95 (t, 2H, J=6.7 Hz), 3.20 (broad m, 4H), 3.38 (broad m, 4H), 3.57 (t, 2H, J=6.7 Hz), 3.99 (s, 4H), 4.60 (s, 4H), 7.78 (d, 2H, J=7.9 Hz), 8.38 (dd, 1H, J=7.9 Hz).^{13}C NMR (D_2O) δ: 30.5, 51.9, 53.6, 54.7, 59.1, 60.5, 126.5, 148.2, 154.2, 176.5, 177.0. HRMS (FAB): found *m/z* 395.1921 ($[M+H]^+$); calcd for $C_{18}H_{27}N_4O_6$ 395.1931.

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