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Total Synthesis of Saturated and Unsaturated di-*trans*-*N*-substituted Cyclam-based Macrocycles Through a Versatile Intermediate

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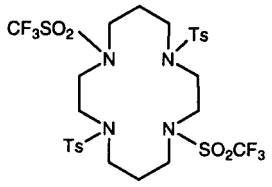
Abstract—A total synthesis of di-*trans*-*N*-substituted cyclam-type macrocycles through a versatile intermediate is described for the first time. This synthesis uses readily available low-cost commercial reagents. This synthesis was designed in such a way that the products and some intermediates could be selectively deprotected providing versatility both during the synthesis and for the utility of the final product. Thus, it should be possible to form cryptand molecules with *trans* bridges with good selectivity. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Polyazamacrocycles are well known[1] to form stable complexes with transition elements and heavy metal ions. The applications of these chelating ligands have been developed rapidly in areas such as chemistry and biochemistry:[2–5] analogous of enzymes, catalysis, purification of waste waters, radiochemical agents, selective coordination of dioxygen from air or potent inhibitors of HIV. The number and nature of the *N*-substituents can increase the selectivity for metal sequestration as well as the stability of the formed complexes. Numerous methods for the synthesis of poly-*N*-functionalized macrocycles have been described in literature[6–12] and normally for their interesting applications in the coordinating properties as cryptands or cyclophanes.[2,13–17] *trans*-Disubstituted macrocycles have been studied far less due to difficulties encountered in their preparation. This stems from their lack of symmetry which means that a stepwise strategy is necessary. Indeed, most of the reported syntheses of such compounds consist of the direct derivatisation of the non-protected macrocyclic molecule.[6,7] This approach has normally led to mixtures of isomers with low yields. For the above reasons we were stimulated to develop a protocol for the preparation of di-*trans*-*N*-substituted macrocycles, via a total synthesis, using relatively inexpensive reagents.

Our strategy for the synthesis of these cyclam-based compounds consisted in the systematic addition of arms to built a convenient open chain and a final cyclisation step to obtain the macrocycle. The advantages of this method are an easy functionalization of the *trans*-N atoms by using two different kinds of protecting groups and the possibility of synthesizing saturated or unsaturated macrocycles. These further ring systems give a rigidity to the overall cycle which influences the properties when interacting with anions.[16,17]



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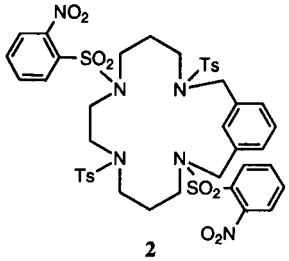

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Scheme 1.

Keywords: aza compounds; macrocycles; asymmetry; cyclisation.

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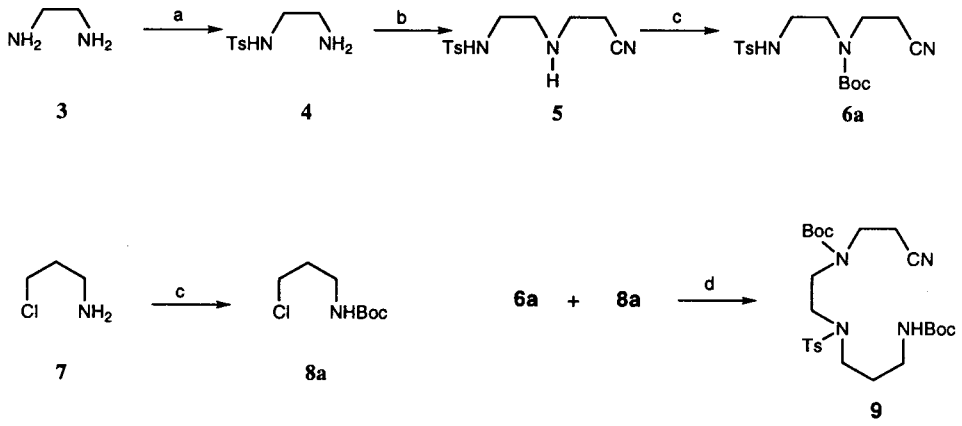
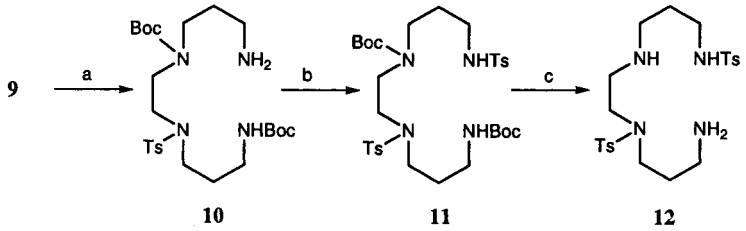


Scheme 2. (a) TsCl, benzene, 74%; (b) acrylonitrile, 93%; (c) $(Boc)_2O$, Net_3, 95%; (d) NaH, DMF, 87%.



Scheme 3. (a) $CoCl_2$, $NaBH_4$, methanol, 87%; (b) TsCl, pyridine, 80%; (c) CF_3COOH, 99%.

We report here the complete synthesis of two different *trans-N*-substituted azamacrocycles **1** and **2** (Scheme 1), obtained in 2 steps from the same precursor, namely 1,8-*N*,*N*′-bistosyl-1,5,8,12-tetraazadodecane **12**. The synthesis of this versatile intermediary **12** was accomplished in seven steps.

Results and Discussion

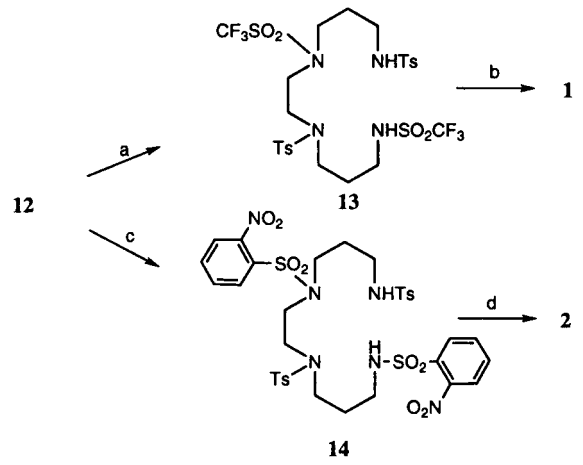
From the readily available diamine **3** (Scheme 2) we have prepared the monotosylated compound **4** as described by Kirsanov,[18] increasing the yield to 74% by a modification of the purification method. A conjugated addition of **4** to acrylonitrile in acetonitrile led to the derivative **5**, with a very good yield (93%).

Our synthetic strategy required the condensation of a third arm with the tosylated amine function just obtained **5**. This made necessary a selective protection of the secondary amine function. For this purpose we have tried three protecting groups, namely *tert*-butoxycarbonyl, *o*-nitrobenzenesulfonyl and benzoyl, leading to the compounds **6a**–**c** in 95, 50 and 83% yields, respectively.[†] Unfortunately, the direct condensation with the commercial hydrochloride amine **7** did not work and we recovered, in each case, the starting material. Therefore, we protected **7** with the same groups and obtained the three derivatives **8a**–**c** in 95, 72 and 93% yields, respectively. The results (yield, ease of purification and stability of the products) of the condensation between **6a**–**c** and **8a**–**c** respectively have compelled us to choose the double protected Boc-compound **9** for carrying on our synthetic route. The ^1H NMR spectrum of **9** displays the presence of the protective groups, namely *tert*-butoxycarbonyl (two singlets at 1.44 and 1.47 ppm) and tosyl (four aromatic protons). A broad signal at 4.90 ppm, which disappeared after addition of D_2O, proved the presence of one acidic proton that we have attributed to the amino group N-8. The characteristic band at 3387 cm^{-1} in its IR spectrum confirms this function. As further confirmation of the proposed structure we have attributed the signal at 118 ppm in the ^{13}C NMR spectrum to the carbon atom of the nitrile group and the band at 2245 cm^{-1} in the IR spectrum to the CN stretching vibration.

Attempted $LiAlH_4$ reduction of **9** led to complete degradation and the formation of an intractable mixture. We have achieved (Scheme 3) the desired reduction of the nitrile function to a primary amine by using $NaBH_4$ and $CoCl_2$.[19] A selective tosylation then furnished the tetra-*N*-substituted compound **11**, from which the *N*-Boc protective groups have been easily removed under acidic conditions affording **12** (nearly quantitative yield). The fact that the amine functions N-5 and N-12 of the so formed compound **12** could be protected with different groups, leading to various di-*trans*-*N*-substituted macrocycles after cyclisation, make it a very important and versatile intermediate.

Synthetic applications of **12** may be realized in many ways. For example, an activation of the amino groups (Scheme 4) with the trifluoromethanesulfonyl or *o*-nitrobenzenesulfonyl derivatives, leading to **13** and **14** in 70 and 74% yields, respectively, followed by a cyclisation with dibromoethane or α,α′-dibromo-*m*-xylene in presence of K_2CO_3, according

[†] We noticed, in the NMR spectra (^1H and ^{13}C NMR) of some of these compounds, the presence of rotational conformers.



Scheme 4. (a) $(CF_3SO_2)_2$, −70°C/rt, 70%; (b) 1,2-dibromoethane, K_2CO_3, DMF, 35%; (c) $ClSO_2(o\text{-}NO_2Ph)$, 74%; (d) α,α′-dibromoxylene, K_2CO_3, DMF, 64%.

to Panetta's procedure[20] gave the two expected azamacrocycles **1** and **2**.

Conclusion

In this report we have demonstrated that our strategy for the synthesis of large-ring compounds can be applied to the preparation of various di-*trans*-*N*-substituted macrocycles. Our examples show that compound **12** can be used as a very versatile synthon, prepared in seven steps in a overall 39% yield, in order to synthesize derivatives of cyclam family including cyclophanes. Two novel macrocycles **1** and **2** were synthesized using this process. These compounds offer the opportunity for selective deprotection[21,22] of the nitrogen atoms in the ring allowing the possibility of the preparation of a range of *trans*-substituted macrocycles.

Experimental

General

Reagents and solvents were purified before use.[23] All reactions were run under a positive pressure of dry argon. Flash chromatography was performed on silica gel from Macherey–Nagel (Kieselgel 60 M). Preparative TLC was performed on glass plates coated with 1 mm of silica gel (Macherey–Nagel, Kieselgel DGF_{254}). Analytical TLC: Aluminium-backed silica gel Merck 60 F_{254}. Melting points were determined with a capillary apparatus and were uncorrected. NMR spectra were recorded on a Bruker AMX-400 apparatus (^1H at 400 MHz and ^{13}C at 100 MHz) in $CDCl_3$ with chemical shift values (δ) in ppm downfield from tetramethylsilane. FT-IR ($\tilde{\nu}$, cm^{-1}) spectra were obtained using thin films on NaCl windows or in KBr pellets. Microanalyses were performed by the IST analytical services in Lisbon using a combustion apparatus.

***N*-Tosyl-ethylenediamine (4).** To a solution of ethylenediamine (40.11 mL, 0.60 mol) in benzene (80 mL)—CAUTION: very toxic—at 40°C was added slowly (1 h), under efficient stirring, tosyl chloride (38.13 g, 0.20 mol) dissolved in benzene (150 mL). The mixture was stirred for an additional 3 h. The white precipitated that appeared was filtered and treated with 1 M aqueous hydrochloric acid (100 mL). The remaining solid was filtered off and the filtrate was treated with NaOH until the appearance of white needles of the desired product **4** which was filtrated and dried (31.71 g, 74%). mp: 127–128°C (lit: 121–123°C)[18]. ^1H NMR δ 2.42 (s, 3H, CH_3 (Ts)), 2.79 (t, J=5.5 Hz, 2H, CH_2–NH_2), 2.80 (bs, 2H, NH_2), 2.95 (t, J=5.5 Hz, 2H, CH_2–NHTs), 7.30 (d, J=7.7 Hz, 2H, C_6H_4 (Ts)), 7.75 (d, J=7.7 Hz, 2H, C_6H_4 (Ts)). ^{13}C NMR δ 21.30 (CH_3 (Ts)), 40.64 (CH_2–NH_2), 45.21 (CH_2–NHTs), 126.90, 129.60, 136.80, 143.28 (C_6H_4 (Ts)). FT-IR (KBr): 3359 (NH_2), 3297 (NH), 1147 (SO_2). Anal. Calcd for $C_9H_{14}N_2O_2S$ (214.28): C 50.45, H 6.58, N 13.07, S 14.96. Found: C 50.64, H 6.60, N 13.04, S 14.96.

1-*N*-Cyanoethyl-4-*N′*-tosyl-ethylenediamine (5). A solution of **4** (30.00 g, 0.14 mol) in acetonitrile (100 mL) was heated at 40°C. After 30 min, acrylonitrile (11.27 mL, 0.17 mol) in acetonitrile (150 mL) was added. The reaction mixture was refluxed over three additional hours and then brought down to room temperature. Concentration of the solvents in vacuum afforded a pale yellow solid which was recrystallized (CH_2Cl_2/hexane) to give **5** as a white solid (34.81 g, 93%). mp: 56–58°C. ^1H NMR δ 2.42 (s, 3H, CH_3 (Ts)), 2.44 (t, J=6.6 Hz, 2H, CH_2–CN), 2.70 (t, J=5.5 Hz, 2H, CH_2–CH_2–NHTs), 2.78 (t, J=6.6 Hz, 2H, CH_2–CH_2–CN), 2.79 (bs, 1H, NH), 2.98 (t, J=5.5 Hz, 2H, CH_2–NHTs), 7.31 (d, J=8.0 Hz, 2H, C_6H_4 (Ts)), 7.74 (d, J=8.0 Hz, 2H, C_6H_4 (Ts)). ^{13}C NMR δ 18.73 (CH_2–CN), 21.49 (CH_3 (Ts)), 42.31, 44.31, 47.39 (3×CH_2–NH), 118.54 (CN), 127.10, 129.77, 136.63, 143.57 (C_6H_4 (Ts)). FT-IR (KBr): 3315, 3224 (NH), 2250 (CN), 1147(SO_2). Anal. Calcd for $C_{12}H_{17}N_3O_2S$ (267.34): C 53.91, H 6.41, N 15.72, S 11.99. Found: C 54.05, H 6.47, N 15.72, S 11.89.

1-*N*-(*tert*-Butoxycarbonyl)-1-*N*-cyanoethyl-4-*N′*-tosyl-ethylenediamine (6a). The diamine **5** (29.00 g, 0.11 mol) and triethylamine (23.0 mL, 0.17 mol) were mixed with 50 mL of chloroform. A solution of di-*tert*-butyldicarbonate (23.70 g, 0.11 mol) in chloroform was added slowly at room temperature. After the addition was completed, the temperature was raised to reflux for 2 h. The solution was then allowed to cool to room temperature and washed with 1 N aqueous hydrochloric acid (50 mL), water (2×25 mL), saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried over magnesium sulphate, and the solvent was evaporated to afford a pale yellow solid. Recrystallization (CH_2Cl_2/hexane) afforded **6a** as a white solid (37.70 g, 0.10 mol, 95%). mp: 120–122°C. ^1H NMR δ 1.45 (s, 9H, $(CH_3)_3C$), 2.42 (s, 3H, CH_3 (Ts)), 2.57 (bs, 2H, CH_2–CN), 3.07 (bs, 2H, CH_2–CH_2–NHTs), 3.38 (t, J=5.6 Hz, 2H, CH_2–CH_2–CN), 3.44 (bs, 2H, CH_2–NHTs), 5.40 (bs, 1H, NH), 7.30 (d, J=7.7 Hz, 2H, C_6H_4 (Ts)), 7.73 (d, J=7.7 Hz, 2H, C_6H_4 (Ts)). ^{13}C NMR δ 17.52 (CH_2–CN), 21.53 (CH_3 (Ts)), 28.30 ((CH_3)$_3$C), 42.07, 44.60, 48.10 (3×CH_2–N), 81.35 ((CH_3)$_3$*C*), 118.07 (CN), 127.04, 129.84, 136.83, 143.60 (C_6H_4 (Ts)), 155.50 (CO (Boc)). FT-IR (KBr): 3270 (NH), 2249 (CN), 1693 (CO). Anal. Calcd for $C_{17}H_{25}N_5O_4S$ (367.46): C 55.57, H

6.86, N 11.44, S 8.72. Found: C 55.60, H 6.89, N 11.35, S 8.67.

***N*-(*tert*-Butoxycarbonyl)-3-chloropropylamine (8a).** 3-Chloropropylamine hydrochloride (**7**) (11.0 g, 0.11 mol) and triethylamine (18.42 mL, 0.13 mol) were mixed in chloroform (50 mL). A solution of di-*tert*-butyldicarbonate (23.79 g, 0.11 mol) in 50 mL of chloroform was added slowly. Using the same work-up than the one for **6a**, a brown oil was obtained as a crude product. Kugelrohr distillation gave 20.05 g (95%) of **8a** as a colourless solid below 4°C. ^{1}H NMR δ 1.44 (s, 9H, $(CH_3)_3$C), 1.96 (m, 2H, CH_2–CH_2–CH_2), 3.28 (m, 2H, CH_2–NHBoc), 3.59 (t, J=6.4 Hz, 2H, CH_2–Cl), 4.80 (bs, 1H, NH). ^{13}C NMR δ 28.53 ($(CH_3)_3$C), 32.78 (CH_2–CH_2–CH_2), 38.10 (CH_2–NHBoc), 42.51 (CH_2–Cl), 79.00 ($(CH_3)_3C$), 156.00 (CO (Boc)). FT-IR (film): 3349 (NH), 1693 (CO). Anal. Calcd for $C_8H_{16}ClNO_2$ (193.67): C 49.61, H 8.33, N 7.23. Found: C 49.88, H 8.56, N 7.29.

1,8-*N*,*N*′-Bis(*tert*-butoxycarbonyl)-1-*N*-cyanoethyl-4-*N*″-tosyl-1,4,8-triazaoctane (9). To a solution of **6a** (35.00 g, 99.50 mmol) in DMF (100 mL) under argon at 0°C, was added sodium hydride (5.60 g, 60% paraffin, 0.11 mol) in small portions. After the addition was finished and no more hydrogen was evolved, the reaction was heated to 60°C. A solution of **8a** (18.40 g, 0.10 mol) in DMF (100 mL) was then added dropwise and the reaction mixture was maintained at 110°C during another 4 h. The solvent was then evaporated to leave a brown oil. This sticky oil was dissolved in dichloromethane (100 mL) and washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulphate and the solvent was evaporated to afford a pale brown oil. That was purified by flash column chromatography (acetone/ether/hexane 1:1:4) to yield 43.36 g (87%) of **9** as a colourless oil. Unchanged starting materials **6a** (3.50 g, 10%) and **8a** (1.80 g, 10%) were also recovered. ^{1}H NMR δ 1.44 (s, 9H, $(CH_3)_3$C), 1.47 (s, 9H, $(CH_3)_3$C), 1.70 (m, 2H, CH_2–CH_2–CH_2), 2.42 (s, 3H, CH_3 (Ts)), 2.60 (m, 2H, CH_2–CN), 3.16 (m, 6H, 3×CH_2–N), 3.47 (m, 4H, 2×CH_2–N), 4.95 (bs, 1H, NHBoc), 7.32 (d, J=7.7 Hz, 2H, C_6H_4 (Ts)), 7.68 (d, J=7.7 Hz, 2H, C_6H_4 (Ts)). ^{13}C NMR δ 17.45 (CH_2–CN), 21.33 (CH_3 (Ts)), 28.15, 28.25 (2×$(CH_3)_3$C), 28.86 (CH_2–CH_2–CH_2), 37.13, 44.59, 47.35, 47.90, 48.34 (5×CH_2–N), 78.95, 80.88 (2×$(CH_3)_3C$), 118.10 (CN), 127.02, 129.73, 135.4, 143.56 (C_6H_4 (Ts)), 154.70, 155.86 (2×CO (Boc)). FT-IR (film): 3387 (NH), 2249 (CN), 1697 (CO). Anal. Calcd for $C_{25}H_{40}N_4O_6S$ (524.68): C 57.23, H 7.68, N 10.68, S 6.11. Found: C 56.98, H 7.76, N 10.44, S 5.91.

1,8-*N*,*N*′-Bis(*tert*-butoxycarbonyl)-5-*N*″-tosyl-1,5,8,12-tetraazadodecane (10). To a solution of **9** (27.28 g, 52.00 mmol) in methanol was added 24.73 g (0.10 mol) of $CoCl_2{\cdot}6H_2O$. After stirring at rt for about 30 min, the dark-blue solution was cooled to 0°C and 7.87 g (0.21 mol) of sodium borohydride was added in small portions. A black precipitated [Co(II)B] appeared and hydrogen was involved. Once the addition was finished, tlc showed no remaining starting material. The solution was treated with 5 M aqueous hydrochloric acid (20 mL) in order to destroy the boride. The solvents were evaporated and the obtained brown oil was taken up in concentrated ammonia solution (300 mL) and CH_2Cl_2 (200 mL). The oil was then washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulphate. Solvent removal afforded 23.9 g (45.24 mmol, 87%) of the title compound as a very viscous brown oil that foamed under vacuum. The residue obtained was used in the next reaction without further purification. ^{1}H NMR δ 1.44 (s, 18H, 2×$(CH_3)_3$C), 1.65 (m, 2H, CH_2–CH_2–CH_2), 1.72 (m, 2H, CH_2–CH_2–CH_2), 2.43 (s, 3H, CH_3 (Ts)), 2.70 (bs, 2H, CH_2–NH_2), 3.16 (m, 6H, 3×CH_2–N), 3.30 (bm, 2H, CH_2–N), 3.35 (bs, 2H, CH_2–N), 5.00 (bs, 1H, NHBoc), 7.31 (d, J=7.7 Hz, 2H, C_6H_4 (Ts)), 7.68 (d, J=7.7 Hz, 2H, C_6H_4 (Ts)). ^{13}C NMR δ 22.00 (CH_3 (Ts)), 28.90 (2×$(CH_3)_3$C), 29.35, 31.12 (2×CH_2–CH_2–CH_2), 37.61, 39.84, 45.12, 47.40, 47.59, 47.81 (6×CH_2–N), 79.84, 80.10 (2×$(CH_3)_3C$), 127.60, 130.30, 136.10, 143.80 (C_6H_4 (Ts)), 155.90, 156.50 (2×CO (Boc)). FT-IR (film): 3370 (NH), absence of nitrile band, 1693 (CO).

1,8-*N*,*N*′-Bis(*tert*-butoxycarbonyl)-5,12-*N*″,*N*‴-bistosyl-1,5,8,12-tetraazadodecane (11). Compound **10** (20.0 g, 38.0 mmol) was dissolved in a mixture of chloroform (150 mL) and pyridine (7.48 mL, 76.00 mmol). Tosyl chloride (7.97 g, 41.80 mmol) was added in portions under stirring. After the addition was finished the reaction mixture was refluxed over 16 h and then cooled to rt. The solution was diluted with more chloroform (100 mL) and washed with 1 M hydrochloric acid (50 mL), water (2×50 mL), saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried over magnesium sulphate and the solvent was evaporated to afford a brown foam of crude product. The residue was placed on flash silica gel column and eluted with hexane/ether (1:5). Solvent evaporation afforded 20.8 g (30.4 mmol, 80%) of the title compound as a fine yellow powder. ^{1}H NMR δ 1.39 (s, 9H, $(CH_3)_3$C), 1.43 (s, 9H, $(CH_3)_3$C), 1.69 (m, 4H, 2×CH_2–CH_2–CH_2), 2.40 (s, 3H, CH_3 (Ts)), 2.41 (s, 3H, CH_3 (Ts)), 2.85 (bs, 2H, CH_2–N), 3.13 (m, 6H, 3×CH_2–N), 3.24 (m, 4H, 2×CH_2–N), 4.88 (bs, 1H, NHBoc), 5.90 (bs, 1H, NHTs), 7.30 (m, 4H, C_6H_4 (Ts)), 7.66 (d, J=7.6 Hz, 2H, C_6H_4 (Ts)), 7.73 (d, J=7.6 Hz, 2H, C_6H_4 (Ts)). ^{13}C NMR δ 22.00, 22.03 (2×CH_3 (Ts)), 28.54 (CH_2–CH_2–CH_2), 28.87, 28.96 (2×$(CH_3)_3$C), 29.61 (CH_2–CH_2–CH_2), 37.84, 40.30, 44.57 (3×CH_2–N), 47.49 (2×CH_2–N), 47.89 (CH_2–N), 79.71, 81.09 (2×$(CH_3)_3C$), 127.50, 127.60, 130.20, 130.40, 136.25, 138.04, 143.57, 144.29 (2×C_6H_4 (Ts)), 156.60 (2×CO (Boc)). FT-IR (film): 3394 (NH), 1686 (CO). Anal. Calcd for $C_{32}H_{50}N_4O_8S_2$ (682.89): C 56.28, H 7.38, N 8.20, S 9.39. Found: C 56.03, H 7.57, N 8.12, S 9.43.

1,8-*N*,*N*′-Bistosyl-1,5,8,12-tetraazadodecane (12). To a cooled solution (0°C) of **11** (9.59 g, 14.00 mmol) in chloroform (30 mL) was added dropwise trifluoroacetic acid (10.78 mL, 0.14 mol). After the addition was finished the temperature was allowed to warm at rt and the reaction mixture stirred for about 1 h more. Solvents were evaporated and the residue dissolved in dichloromethane (100 mL) and washed with aqueous sodium bicarbonate (50 mL) and brine (50 mL). After drying and evaporating the solvent the resulting brown foam (6.76 g, 99%) was used in the next reaction without further purification. ^{1}H NMR δ

1.59 (m, 2H, CH_2–*CH_2*–CH_2), 1.68 (m, 2H, CH_2–*CH_2*–CH_2), 2.42 (s, 6H, 2×CH_3 (Ts)), 2.58 (t, *J*=6.0 Hz, 2H, *CH_2*–N), 2.68 (t, *J*=5.8 Hz, 2H, *CH_2*–N), 2.76 (t, *J*=6.4 Hz, 2H, *CH_2*–N), 2.98 (t, *J*=5.6 Hz, 2H, *CH_2*–N), 3.03 (t, *J*=6.0 Hz, 2H, *CH_2*–N), 3.15 (m, 2H, *CH_2*–N), 7.31 (m, 4H, C_6H_4 (Ts)), 7.70 (d, *J*=8.0 Hz, 2H, C_6H_4 (Ts)), 7.74 (d, *J*=8.0 Hz, 2H, C_6H_4 (Ts)). ^{13}C NMR *δ* 21.29 (2×CH_3 (Ts)), 27.83, 31.32 (2×CH_2–*CH_2*–CH_2), 38.66, 42.68, 47.58, 47.84, 48.32, 48.80 (6×*CH_2*–N), 127.11, 127.33, 129.70, 129.87, 135.56, 137.20, 143.10, 143.65 (2×C_6H_4 (Ts)). FT-IR (film): 3583 (NH_2), 3290 (NH), absence of carbonyl band.

1,8-*N*,*N′*-Bistosyl-5,12-*N″*,*N‴*-bis(trifluoromethanesulfonyl)-1,5,8,12-tetraazadodecane (13). To compound **12** (1.00 g, 2.00 mmol) in CH_2Cl_2 (40 mL) was added triethylamine (1.10 mL, 8.00 mmol) under stirring. The mixture was cooled to −70°C and trifluoromethanesulfonic anhydride (1.35 mL, 8.00 mmol) added. The temperature was allowed to rise and the mixture was stirred for an additional 2 h at rt. The solution was then treated with 3 M NaOH (20 mL) and extracted with more CH_2Cl_2. The organic layer was washed with water (2×20 mL), 1 M hydrochloric acid (20 mL), water (20 mL), saturated aqueous sodium bicarbonate (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulphate and the solvent was evaporated to afford a pale yellow oil. Flash chromatography (AcOEt/hexane 3:2) yielded **13** (1.04 g, 70%) as a colourless oil. ^{1}H NMR *δ* 1.88 (m, 4H, 2×CH_2–*CH_2*–CH_2), 2.42 (s, 3H, CH_3 (Ts)), 2.44 (s, 3H, CH_3 (Ts)), 2.94 (m, 2H, *CH_2*–N), 3.21 (t, *J*=5.9 Hz, 2H, *CH_2*–N), 3.28 (t, *J*=7.5 Hz, 2H, *CH_2*–N), 3.38 (t, *J*=5.8 Hz, 2H, *CH_2*–N), 3.49 (bs, 2H, *CH_2*–N), 3.55 (bs, 2H, *CH_2*–N), 5.14 (t, *J*=6.2 Hz, 1H, NHTs), 6.26 (bs, 1H, NHTf), 7.31 (d, *J*=8.0 Hz, 2H, C_6H_4 (Ts)), 7.35 (d, *J*=8.2 Hz, 2H, C_6H_4 (Ts)), 7.69 (d, *J*=8.2 Hz, 2H, C_6H_4 (Ts)), 7.70 (d, *J*=8.0 Hz, 2H, C_6H_4 (Ts)). ^{13}C NMR *δ* 21.25 (2×CH_3 (Ts)), 28.39, 29.10 (2×CH_2–*CH_2*–CH_2), 39.85, 40.96, 46.81, 47.12, 47.84, 48.30 (6×*CH_2*–N), 119.72 (q, *J*=320 Hz, CF_3), 119.80 (q, *J*=322 Hz, CF_3), 127.05, 127.23, 129.96, 130.26, 134.72, 136.06, 144.04, 144.59 (2×C_6H_4 (Ts)). FT-IR (film): 3274 (NH), 721 (CF_3). Anal. Calcd for $C_{24}H_{32}F_6N_4O_8S_4$ (746.77): C 38.60, H 4.32, N 7.50, S 17.17. Found: C 38.87, H 4.27, N 7.31, S 16.93.

1,8-*N*,*N′*-Bistosyl-4,11-*N″*,*N‴*-bis(trifluoromethanesulfonyl)-1,4,8,11-tetraazacyclotetradecane (1). Dry DMF (10 mL) was added to a flask containing **13** (0.20 g, 0.20 mmol) and potassium carbonate (0.28 g, 10.20 mmol) under an argon atmosphere. The mixture was heated for 1 h at 80°C and then a solution of 1,2-dibromoethane (17.23 μl, 10.20 mmol)—CAUTION: very toxic—in 10 mL of DMF was added dropwise. The reaction mixture was maintained at 110°C for 24 h, then was cooled to rt. After solvent removal the residue was dissolved in dichloromethane (25 mL) and washed with saturated aqueous sodium bicarbonate (25 mL) and brine (25 mL). The residue was purified by preparative TLC (AcOEt/hexane 2:3) to yield **1** (54 mg, 35%). ^{1}H NMR *δ* 2.02 (m, 4H, 2×CH_2–*CH_2*–CH_2), 2.42 (s, 6H, 2×CH_3 (Ts)), 3.13 (bs, 4H, 2×*CH_2*–N), 3.26 (bm, 4H, 2×*CH_2*–N), 3.64 (bm, 8H, 4×*CH_2*–N), 7.34 (d, *J*=8.0 Hz, 4H, C_6H_4 (Ts)), 7.67 (d, *J*=8.0 Hz, 4H, C_6H_4 (Ts)). ^{13}C NMR *δ* 22.09 (2×CH_3 (Ts)), 28.17 (2×CH_2–*CH_2*–CH_2), 48.74, 48.91, 50.32, 50.95 (4×2×*CH_2*–N), 120.20 (q, *J*=323 Hz, 2×CF_3), 128.37, 130.89, 134.64, 145.23 (2×C_6H_4 (Ts)). FT-IR (film): Absence of amino band. Anal. Calcd for $C_{26}H_{34}{\cdot}F_6N_4O_8S_4$ (772.81): C 40.41, H 4.43, N 7.25, S 16.59. Found: C 40.63, H 4.31, N 7.16, S 16.26.

1,8-*N*,*N′*-Bis(2-nitrobenzenesulfonyl)-5,12-*N″*,*N‴*-bistosyl-1,5,8,12-tetraazadodecane (14). To a stirred solution of **12** (6.51 g, 13.50 mmol) in 50 mL of chloroform was added triethylamine (10 mL, 72,0 mmol) followed by 2-nitrobenzenesulfonyl chloride (6.60 g, 29.70 mmol) in portions. The reaction mixture was stirred at rt for 16 h. The solution was then diluted with more chloroform (100 mL) and washed with 1 N hydrochloric acid (50 mL), water (2×50 mL), saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried over magnesium sulphate and the solvent was evaporated to afford a pale green powder. The residue was purified by flash column chromatography. Elution with AcOEt/hexane (3:2) afforded **14** (8.52 g, 74%) as a pale green powder. ^{1}H NMR *δ* 1.84 (m, 4H, 2×CH_2–*CH_2*–CH_2), 2.41 (s, 3H, CH_3 (Ts)), 2.43 (s, 3H, CH_3 (Ts)), 2.96 (m, 3H, *CH_2*–N and CH*H*–N), 3.20 (m, 5H, 2×*CH_2*–N and CH*H*–N), 3.40 (t, *J*=6.8 Hz, 2H, *CH_2*–N), 3.50 (t, *J*=7.8 Hz, 2H, *CH_2*–N), 4.99 (t, *J*=6.4, 1H, NHTs), 5.82 (t, *J*=6.2, 1H, NHR), 7.30 (m, 4H), 7.71 (m, 3H), 7.74 (m, 6H), 7.83 (m, 1H), 8.02 (m, 1H), 8.12 (m, 1H), (2×C_6H_4 (Ts), 2×C_6H_4 (SO_2-*o*-(NO_2)Ph)). ^{13}C NMR *δ* 22.10 (2×CH_3 (Ts)), 29.22, 29.69 (2×CH_2–*CH_2*–CH_2), 40.74, 41.27, 47.31, 47.82, 48.59, 49.00 (6×*CH_2*–N), 124.80, 125.00 125.70, 125.90, 130.40, 130.60, 131.20, 131.40, 132.70, 132.90, 133.50, 134.20, 134.30, 134.60, 135.60, 137.20, 144.10, 144.60, 148.50, 148.60 (2×C_6H_4 (Ts), 2×C_6H_4 (SO_2-*o*-(NO_2)Ph)). FT-IR (film): 3305 (NH), 1542 (NO_2), 1336 (C–NO_2). Anal. Calcd for $C_{36}H_{42}N_6O_{12}S_4$ (852.97): C 47.88, H 4.73, N 9.85, S 15.03. Found: C 47.73, H 4.80, N 9.34, S 14.88.

2,9-*N*,*N′*-Bis(2-nitrobenzenesulfonyl)-6,13-*N″*,*N‴*-bistosyl-2,6,9,13-tetraaza [14] (1,5)benzenecyclophane (2). To a solution of **14** (6.40 g, 0.40 mmol) in dry DMF (20 mL) was added potassium carbonate (0.55 g, 4.00 mmol). After stirring 30 min at rt α,α′-dibromo-*m*-xylene (0.11 g, 0.40 mmol) was added. The reaction mixture was kept under reflux for 2 h; after this time the solvent was removed and the residue was dissolved in dichloromethane (50 mL), washed with saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried over magnesium sulphate and the solvent was evaporated to afford a pale yellow powder. Purification by flash chromatography (AcOEt/hexane 3:2) yielded **2** (0.38 g, 64%). ^{1}H NMR *δ* 1.59 (m, 4H, 2×CH_2–*CH_2*–CH_2), 2.42 (s, 3H, CH_3 (Ts)), 2.45 (s, 3H, CH_3 (Ts)), 2.72 (t, *J*=7.4 Hz, 2H, CH_2–*CH_2*–N), 2.92 (t, *J*=7.4 Hz, 2H, CH_2–*CH_2*–N), 3.00 (m, 4H, 2×CH_2–*CH_2*–N), 3.18 (t, *J*=7.0 Hz, 2H, CH_2–*CH_2*–N), 3.31 (t, *J*=7.4 Hz, 2H, CH_2–*CH_2*–N), 4.15 (s, 2H, N–*CH_2*–Ar), 4.48 (s, 2H, N–*CH_2*-Ar), 7.30 (m, 8H), 7.54 (d, *J*=8.0 Hz, 2H), 7.61 (m, 1H), 7.72 (m, 7H), 8.03 (m, 2H) (2×C_6H_4 (Ts), 2×C_6H_4 (SO_2-*o*-(NO_2)Ph), C_6H_4 (*m*-xyleno)). ^{13}C NMR *δ* 22.20 (2×CH_3 (Ts)), 29.25, 29.52 (2×CH_2–*CH_2*–CH_2), 47.57, 48.23, 48.43, 48.78, 53.89, 54.99 (8×*CH_2*–N), 124.70, 125.10, 128.00, 128.40, 128.70, 129.10, 130.00, 130.50, 130.70, 131.50, 132.30, 132.60,

132.70, 134.40, 134.60, 137.70, 138.20, 144.60 ($2\times C_6H_4$ (Ts), $2\times C_6H_4$ (SO_2-*o*-(NO_2)Ph), C_6H_4 (*m*-xyleno)). FT-IR (film): absence of amino band, 1544 (NO_2), 1344 (C–NO_2), 1160 (SO_2). Anal. Calcd for $C_{42}H_{46}N_6O_{12}S_4$ (955.11): C 52.82, H 4.85, N 8.80, S 13.43. Found: C 52.81, H 4.85, N 8.76, S 13.33.

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References

1. Lindoy, L. F. *The Chemistry of Macrocyclic Ligand Complexes*, Cambridge University Press: Cambridge, 1989.
2. Denat, F.; Lacour, S.; Brandès, S.; Guilard, R. *Tetrahedron Lett.* **1997**, *38*, 4417–4420.
3. Alfonso, I.; Astorga, C.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1999**, *10*, 2515–2522.
4. Kim, B. M.; So, S. M. *Tetrahedron Lett.* **1999**, *40*, 7687–7690.
5. Gaudinet-Hamann, B.; Zhu, J.; Fensterbank, H.; Larpent, C. *Tetrahedron Lett.* **1999**, *40*, 287–290.
6. Boitrel, B.; Andrioletti, B.; Lachkar, M.; Guilard, R. *Tetrahedron Lett.* **1995**, *36*, 4995–4998.
7. Helps, I. M.; Parker, D.; Morphy, J. R.; Chapman, J. *Tetrahedron* **1989**, *45*, 219–226.
8. Alfonso, I.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1999**, *10*, 367–374.
9. Lázár, I. *Tetrahedron Lett.* **1999**, *40*, 381–382.
10. Alcock, N. W.; Balakrishnan, K. P.; Moore, P.; Pike, G. A. *J. Chem. Soc., Dalton Trans.* **1987**, 889–894.
11. Alcock, N. W.; Moore, P.; Omar, H. A. A. *J. Chem. Soc., Dalton Trans.* **1986**, 985–989.
12. Dickins, R. S.; Howard, J. A. K.; Lehmann, C. W.; Moloney, J.; Parker, D.; Peacock, R. D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 521–523.
13. Royal, G.; Dahaoui-Gindrey, V.; Dahaoui, S.; Tabard, A.; Guilard, R.; Pullumbi, P. *Eur. J. Org. Chem.* **1998**, 1971–1975.
14. Bucher, C.; Royal, G.; Barbe, J. M.; Guilard, R. *Tetrahedron Lett.* **1999**, *40*, 2315–2318.
15. Weisman, G. R.; Rogers, M. E.; Wong, E. H.; Jasinski, J. P.; Paight, E. S. *J. Am. Chem. Soc.* **1990**, *112*, 8604–8605.
16. Burguete, M. I.; Escuder, B.; Luis, S. V.; Miravet, J. F.; García-España, E. *Tetrahedron Lett.* **1994**, *35*, 9075–9078.
17. Altava, B.; Burguete, M. I.; Escuder, B.; Luis, S. V.; García-España, E.; Muñoz, M. C. *Tetrahedron* **1997**, *53*, 2629–2640.
18. Kirsanov, A. V.; Kirsanova, N. A. *J. Gen. Chem. USSR Engl. Trans.* **1962**, *32*, 877–882.
19. Buhleier, E.; Wehner, W.; Vögtle, F. *Synthesis* **1978**, 155–158.
20. Panetta, V.; Yaouanc, J. J.; Handel, H. *Tetrahedron Lett.* **1992**, *33*, 5505–5508.
21. (a) Taber, D. F.; Wang, Y. *J. Am. Chem Soc.* **1997**, *119*, 22–26. (b) Gold, E. H.; Babad, E. *J. Org. Chem.* **1972**, *37*, 2208–2210.
22. (a) Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1966**, 1581–1583. (b) Ji, S.; Gortter, L. B.; Waring A. B.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, 5311–5312.
23. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: New York, 1980.