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Preparation of hexaaza and heptaaza macrocycles functionalized with a single aminoalkyl pendant arm[†]

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Received 30th October 2002, Accepted 17th January 2003 First published as an Advance Article on the web 11th February 2003

A practical and reproducible route for the preparation of 1,4,7,10,13,16,19-heptaazacyclohenicosane (1), 1,4,7,10,13,16-hexaazacyclooctadecane (2), and 1,4,7,10,13,17-hexaazacycloicosane (3) bearing a single *N*-(2-aminoethyl) pendant arm has been developed. Richman–Atkins cyclization in the presence of caesium carbonate was applied to construct the macrocycle from 3-benzoyl- N^1 , N^5 -ditosyl-3-azapentane-1,5-diamine and the appropriate fully *N*-tosylated N^{α} , N^{ω} -bis(2-mesyloxyethyl) tri- or tetra-amine. The benzoyl group was selectively removed with potassium *tert*-butoxide, and the exposed nitrogen atom was reacted with *N*-tosylaziridine. The tosyl protections were removed with hydrogen bromide in acetic acid, and the product was converted to a free base with the aid of a strong anion exchange resin (OH⁻ form).

Introduction

Macrocyclic polyamines, the so-called azacrowns, have received increasing interest as artificial receptors and carriers of biologically important phosphoesters,¹ receptors of nucleic acid bases,²⁻⁵ catalysts of phosphoryl transfer reactions,⁶⁻⁹ and carriers of metal ions in simple chemical enzyme models.¹⁰⁻¹⁶ Many of these applications are dependent on covalent conjugation of the azacrown to a biomolecule that increases the overall lipophilicity of the conjugate¹⁷ or provides it with a desired bioaffinity.^{18,19} For efficient conjugation, the azacrown has to be derivatized with a pendant arm that bears the desired functionality. The ring nitrogen atoms obviously are potential sites for the attachment of such tethers, but the presence of several similar nitrogen atoms implies a synthetic challenge. Even relatively large azacrowns may be derivatized with a single pendant arm by using the azacrown in excess, as evidenced by the preparation of a monofunctionalized pentaaza macrocycle, 1,4,7,10,13-pentaazacyclopentadecane-1-(α -1,4-toluic acid),²⁰ but this approach wastes the precious azacrown and leads to tedious purification. More efficient synthetic methods that make use of orthogonal protecting groups on various nitrogen atoms upon the assembly of the azacrown from smaller fragments are undoubtedly needed to obtain reasonable yields. Considerable progress has recently been made in the field of N-functionalization of tri-²¹⁻²⁸ and tetra-azacycloalkanes.²⁹⁻³¹ In contrast, the data on derivatization of hexa- and hepta-aza cycloalkanes are scarce.³² In fact, among the fully saturated azacrowns, only a mixed dioxa hexaaza cycloalkane, 1,13dioxa-4,7,10,16,19,22-hexaazacyclotetracosane, has been been monofunctionalized with 2-aminoethyl, 2-hydroxyethyl and 2-mercaptoethyl tethers at N7.33 We now report on the synthesis of N-(2-aminoethylated) derivatives of three large fully saturated azacrowns, viz., 1,4,7,10,13,16,19-heptaazacyclohenicosane (1), 1,4,7,10,13,16-hexaazacyclooctadecane (2), and 1,4,7,10,13,17-hexaazacycloicosane (3). These compounds are expected to find applications as constituents of cleaving agents targeted towards polyphosphate bridges, such as the triphosphate bridge present in the 5'-cap structure of mRNA,³⁴ since large azacrowns have been shown to bind firmly pyrophosphate anion 35 and its organic derivatives. 36

Results and discussion

The pathway utilized to obtain *N*-(2-aminoethylated) azacrowns **1**–**3** is outlined in Scheme 1. Accordingly, the parent azacrowns having one of the ring nitrogen atoms benzoylated and all the rest tosylated were obtained by a slightly modified Richman–Atkins cyclization³⁷ between 3-benzoyl- N^1 , N^5 -ditosyl-3-azapentane-1,5-diamine (**8**) and the appropriate fully *N*tosylated N^{α} , N^{∞} -bis(2-mesyloxyethyl) polyamine (**11a–c**), as reported previously for smaller azacrowns.³⁸ The monofunctionalization was then achieved by removal of the benzoyl protection and treatment with *N*-tosylaziridine (**6**).³³ Finally, the tosyl protections were removed by repeated treatment with hydrogen bromide in acetic acid, and the products were converted to free bases by passing them through a strong anion exchange resin in the hydroxide ion form.

The building blocks employed in the cyclization were prepared as follows. N¹, N⁵-Ditosyl-3-azapentane-1, 5-diamine (7) was obtained in an almost quantitative yield by reacting N-(2aminoethyl)-p-toluenesulfonamide (4) with N-tosylaziridine (6), as described previously.³⁸ Benzoylation of the unprotected secondary nitrogen atom then gave the desired orthogonally protected triamine (8). The fully tosylated acyclic tri- and tetraamines (9a-c) were obtained in a 70% yield by tosylation of the corresponding unprotected amines. Previously the same compounds had been prepared by a stepwise elongation of N, N'-ditosylethane-1,2-diamine with N-(2-bromoethyl)-ptoluenesulfonamide,³⁹ but this approach led in our hands to a more complicated product mixture. Repeated chromatographic purification was needed, and the yield of the properly purified material ranged from 30 to 40%, making the reaction unsuitable for an early step reaction of a multi-step synthesis. By direct tosylation, the fully protected amines could easily be synthesized on a multi-gram scale. The N^{α} , N^{ω} -bis(2-mesyloxyethyl) building blocks (11a-c) were then obtained in a nearly quantitative yield by the reaction of the fully tosylated amines with ethylene carbonate and subsequent mesylation of the resulting diols (10a-c).40

The Richman–Atkins type coupling of the ditosylated amine (8) with the dimesylated diol (11a–c) was carried out under the conditions described previously for the preparation of closely related fully tosylated macrocyclic polyamines.⁴¹ Reasonably high yields were, however, obtained only when caesium carbonate was used as a base instead of potassium carbonate which was employed in the previously reported work. On using the latter base, the yield remained below 30% and was not repro-

† Electronic supplementary information (ESI) available: preparative details for compounds which have been reported previously. See http:// www.rsc.org/suppdata/ob/b2/b210663a/



Scheme 1 *a*) TsCl–pyridine, $-13 \,^{\circ}$ C, 2 h, 75%; *b*) TsCl–pyridine, $-40 \,^{\circ}$ C, 1 h, $-10 \,^{\circ}$ C, 1 h, $0 \,^{\circ}$ C, 1 h, 85%; *c*) KOH–benzene, 0.5 h, 95%; *d*) MeCN, reflux, 4 h, 75%; *e*) BzCl–toluene, 12 h, 90%; *f*) 1. ethylene carbonate–KOH, 160–170 $^{\circ}$ C, 4 h, 2. MeOH, reflux, 70–80%; *g*) MsCl–Et₃N–CH₂Cl₂, -15 to $-20 \,^{\circ}$ C, 0.5 h, 98%; *h*) Cs₂CO₃–DMF, 7 d, 60–70%; *i*) Me₃COK–THF, 2 h, reflux, 70–90%; *j*) **6**–MeCN–toluene, reflux, 3 d, 98%; *k*) HBr–AcOH, PhOH, 80 $^{\circ}$ C, 7 d, 60–75%.

ducible. Cyclization to **12a**, in particular, almost entirely failed; the yield was about 5%. Potassium carbonate, as well as sodium methoxide, resulted in formation of several side products, among which the elimination product **12d** predominated. In striking contrast, the fully protected heptaaza (**12a**) and hexaaza (**12b,c**) macrocycles were reproducibly obtained in a 60% and 70% yield, respectively, on using caesium carbonate as the base and keeping the concentration of the starting material below the effective molarity.⁴² In this manner the cyclization could be carried out on a multi-gram scale.

The *N*-benzoyl protection was readily removed with potassium *tert*-butoxide to yield **13a**–c.⁴³ In fact, it proved to be



advantageous to subject the crude reaction mixture of the Richman–Atkins coupling reaction as such to the debenzoylation, since the chromatographic purification of the deprotected macrocycle is easier than that of the fully protected azacrowns.

The monofunctionalized azacrowns were obtained in an

almost quantitative yield by reacting the debenzoylated macrocycles (13a-c) with 1.2 equiv. of N-tosylaziridine in a mixture of toluene and MeCN at 65-70 °C for about one week. The tosyl groups were then removed with 37% hydrogen bromide in acetic acid in the presence of a large excess of phenol.44,45 The deprotected products were hence obtained as hydrobromide salts. Unfortunately, the deprotection was not fully quantitative, though the situation improved at an elevated temperature. Evidently owing to limited solubility of partially deprotected starting material, even a prolonged treatment was not usually sufficient to remove all the tosyl groups, but traces of azacrowns bearing one or two tosyl groups could be detected by mass spectroscopy. Among the compounds studied, 14c proved to be easiest to deprotect, and the fully deprotected compound could be nicely precipitated with cold diethyl ether. 14a and 14b were more difficult to deblock entirely, and to get rid of mono- and ditosylated impurities, the deprotection was repeated. Precipitation with cold diethyl ether gave the fully deprotected material as a fine-grained powder. The fully deprotected products were finally converted to free bases (1-3) by passing them through a Dowex 1×8 resin in the hydroxide ion form.

In conclusion, an efficient and reproducible method for the preparation of large symmetric and asymmetric azacrowns that allows attachment of a pendant arm at a single nitrogen atom has been described. By optimizing both the synthesis of the tosylated acyclic precursors and the actual Richman–Atkins coupling/cyclization a protocol has been developed that enables multi-gram yields for individual laboratory scale syntheses. The most essential factors are the use of caesium carbonate as a base in the coupling/cyclization and proper control of the concentrations employed.

Experimental section

General

Dichloromethane, acetonitrile and dimethylformamide were distilled from CaH_2 and triethylamine from KOH, and subsequently stored over 4 Å molecular sieves. Pyridine was dried with BaO, followed by distillation from CaH_2 . Tetrahydrofuran, benzene and toluene were distilled from Na-benzophenone under N₂ atmosphere. The air- and moisture-sensitive reactions were carried out under N₂ using oven-dried glassware and a standard syringe/septum technique. All the other reagents (Aldrich, Lab Scan) were used as supplied unless otherwise stated.

The ¹H NMR and ¹³C NMR spectra were recorded on a JEOL JNM-GX 400 or Bruker 200 NMR spectrometer using Me₄Si as an internal reference. The IR spectra were recorded as KBr pellets on a Unicam SP 1100 spectrophotometer. The ESI-mass spectra were obtained with a Perkin Elmer Sciex API 365 triple quadrupole MS spectrometer. The HRMS spectra and the FAB⁺ spectra were recorded with a ZabSpecETOF instrument. The melting points reported are uncorrected.

Many of the compounds prepared to be used as intermediates of the synthesis of the desired monofunctionalized azacrowns (1-3) have been previously reported. They include N-(2-aminoethyl)-p-toluenesulfonamide (4),46-48 N-(2-tosyloxy-(5),^{38,45,49,50} ethyl)-p-toluenesufonamide N-tosylaziridine (6), $^{38,45,51} N^1, N^5$ -ditosyl-3-azapentane-1,5-diamine (7), 38 3-ben $zoyl-N^1, N^5$ -ditosyl-3-azapentane-1,5-diamine (8),³⁸ $N^1, 3, 6, N^8$ tetratosyl-3,6-diazaoctane-1,8-diamine (9a), ${}^{51-53}N^1$,3, N^5 -tritosyl-3-azapentane-1,5-diamine (9b),53-55 N¹,4,N⁷-tritosyl-4-azaheptane-1,7-diamine (9c),⁵⁶ 3,6,9,12-tetratosyl-3,6,9,12-tetraazatetradecane-1,14-diol (10a),57,58 3,6,9-tritosyl-3,6,9-triazaundecane-1,11-diol (10b),40,55,58 1,14-dimesyloxy-3,6,9,12-tetratosyl-3,6,9,12-tetraazatetradecane (11a)⁵⁸ and 1,11-dimesyloxy-3,6,9-tritosyl-3,6,9-triazaundecane (11b).^{39,58} N¹,3,N⁵-Tritosyl- N^1 , N^5 -divinyl-3-azapentane-1,5-diamine (12d), observed as a side product, is also a known compound.^{58,59} The experimental details for the preparation and characterization of these compounds are given as Electronic Supplementary Information. †

3,7,11-Tritosyl-3,7,11-triazatridecane-1,13-diol (10c)

A mixture of **9c** (1.78 g, 3.00 mmol), ethylene carbonate (0.58 g, 6.7 mmol) and powdered potassium hydroxide (5.1 mg, 0.091 mmol) was stirred at 160–170 °C for 4 h, allowed to cool to 90 °C, and a large excess of MeOH (50 cm³) was rapidly added. The white solid precipitate was separated by filtration and purified by silica gel chromatography to obtain **10c** in an 80% (1.64 g) yield. ¹H NMR (CDCl₃): 7.61 (d, *J* 8.0 Hz, 6H, *H*2 and 6 of Ts), 7.24 (d, *J* 8.0 Hz, *H*3 and 5 of Ts), 3.70 (q, *J* 5.3 Hz, 4H, *CH*₂OH), 3.07–3.12 (m, 12H, *CH*₂–N), 2.93 (t, *J* 5.4 Hz, 2H, O*H*), 2.34 (s, 9H, *CH*₃), 1.86–1.93 (m, 4H, CH₂CH₂CH₂). ¹³C NMR (CDCl₃): 143.6, 143.4, 135.7, 135.3, 129.8, 129.7, 127.2, 127.1, 61.5, 52.0, 48.4, 47.2, 28.9, 21.5. ν_{max} (KBr)/cm⁻¹ 3329, 1238, 1157. HRMS: required for C₃₁H₄₃-N₃O₈S₃ 682.2291(M + H⁺), found 682.2259.

1,13-Dimesyloxy-3,7,11-tritosyl-3,7,11-triazatridecane (11c)

A mixture of compound 10c (2.73 g, 4.00 mmol) and triethylamine (1.7 cm^3) in dry dichloromethane was cooled to -15 to -20 °C, and methanesulfonyl chloride (0.653 cm³) was added over 10 min. The mixture was transferred onto an ice bath, and the solution was stirred for 30 min. Crushed ice (100 cm³) and 10% aq. hydrogen chloride (50 cm³) were added, and the mixture was thoroughly shaken. The organic layer was washed with water, dried over MgSO₄, and evaporated to dryness to obtain a white solid. Purification by silica gel chromatography (CH₂Cl₂ : MeOH 200 : 1) gave **11c** in a 98% (3.28 g) yield. ¹H NMR (CDCl₃): 7.60 (d, J 8.0 Hz, 6H, H2 and 6 of Ts), 7.26 (d, J 8.0 Hz, 6H, H3 and 5 of Ts), 4.31 (t, J 5.8 Hz, 4H, CH₂-OMs), 3.33 (t, J 5.8 Hz, 4H, NCH2CH2OMs), 3.11 (t, J 7.3 Hz, 4H, C4-H₂ and C10-H₂), 3.06 (t, J 7.3 Hz, 4H, C6-H₂ and C8- H_2), 2.97 (s, 6H, OMs), 2.35 (s, 9H, CH₃ of Ts), 1.83–1.93 (quin., J 7.4 Hz, 4H, C5- H_2 and C9- H_2). ¹³C NMR (CDCl₃): 143.9, 143.6, 135.6, 135.1, 130.0, 129.9, 127.2, 127.1, 68.3, 48.2, 47.0, 37.3, 28.7, 21.5 (2C: Ms and Ts). HRMS: m/z required for $C_{33}H_{47}N_{3}O_{12}S_{5}$ 838.1842 (M + H⁺), found 838.1830.

1-Benzoyl-4,7,10,13,16,19-hexatosyl-1,4,7,10,13,16,19-heptaazacyclohenicosane (12a)

A mixture of compounds **8** (2.26 g, 4.39 mmol) and **11a** (5.30 g, 5.27 mmol) in 250 cm³ DMF was stirred in the presence of anhydrous caesium carbonate (14.30 g, 43.89 mmol) at ambient temperature for 7 d. The reaction mixture was filtered through Celite, and the solvent was removed under reduced pressure. The residue was chromatographed on a silica column (CH₂Cl₂ : MeOH 93 : 7) to afford **12a** as a colorless amorphous powder in a 70% (4.09 g) yield. Mp 149.9–150.2 °C. ¹H NMR (CDCl₃): 7.20–7.80 (m, 29H, Bz and Ts), 3.25–3.75 (m, 28H, CH₂), 2.43 (s, 9H, CH₃), 2.42 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 2.37 (s, 3H, CH₃). ¹³C NMR (CDCl₃): 173.1, 143.7, 135.8, 134.9, 134.2, 129.9, 129.6, 128.6, 127.5, 127.3, 126.9, 51.2, 50.9, 49.9, 49.7, 49.4, 49.1, 47.8, 44.9, 21.5. v_{max} (KBr)/cm⁻¹ 1632, 1599, 1341, 1159. HRMS: *m*/*z* required for C₆₃H₇₅N₇O₁₃S₆ 1330.3825 (M + H⁺), found 1330.3831.

1-Benzoyl-4,7,10,13,16-pentatosyl-1,4,7,10,13,16-hexaazacyclooctadecane (12b)

The reaction of **8** with **11b**, when conducted as described above for **12a**, afforded **12b** as a colorless amorphous powder in a 70% yield. ¹H NMR (CDCl₃): 7.10–7.69 (m, 25H, Bz and Ts), 3.05–3.55 (m, 24H, CH₂), 2.37 (s, 9H, CH₃), 2.35 (s, 3H, CH₃), 2.33 (s, 3H, CH₃). ¹³C NMR: 172.7, 144.1, 143.9, 143.8, 135.6, 135.3, 135.1, 135.0, 134.5, 129.9, 129.8, 129.7, 128.6, 127.4, 127.2, 126.7, 50.9, 50.7, 50.4, 50.3, 49.7, 49.4, 49.3, 49.2, 48.5, 47.6, 44.9, 21.5. v_{max} (KBr)/cm⁻¹ 1632, 1599, 1341, 1159. HRMS: m/z required for $C_{54}H_{64}N_6O_{11}S_5$ 1133.3315 (M + H⁺), found: 1133.3176.

7-Benzoyl-1,4,10,13,17-pentatosyl-1,4,7,10,13,17-hexaazacycloicosane (12c)

The reaction of **8** with **11c**, when conducted as described above for **12a**, afforded **12c** as a colorless amorphous powder in a 70% yield. ¹H NMR(CDCl₃): 7.15–7.70 (m, 25H, Bz and Ts), 3.5–3.7 (m, 4H, BzNCH₂), 2.96–3.33 (m, 20H, TsNCH₂), 2.35 (s, 9H, CH₃), 2.32 (s, 6H, CH₃), 1.98 (m, 2H, N-CH₂CH₂CH₂N), 1.85 (m, 2H, N-CH₂CH₂CH₂N). ¹³C NMR (CDCl₃): 172.9, 143.8, 143.7, 143.6, 143.5, 135.6, 135.4, 135.1, 134.7, 134.6, 134.3, 129.8, 128.6, 127.3, 127.1, 126.9, 51.0, 50.7, 49.6, 48.8, 48.4, 48.3 48.2, 48.1, 47.8, 47.4, 45.0, 29.4, 28.8, 21.5. v_{max} (KBr)/cm⁻¹ 1632, 1599, 1341, 1159. HRMS: *m*/*z* required for C₅₆H₆₈N₆O₁₁S₅ 1161.3628 (M + H⁺), found: 1161.3637.

1,4,7,10,13,16-Hexatosyl-1,4,7,10,13,16,19-heptaazacyclohenicosane (13a)

To a solution of macrocycle 12a (2.86 g, 2.16 mmol) in 50 cm³ THF, water (77.6 mg, 4.31 mmol) and potassium tert-butoxide (1.60 g, 14.22 mmol) were added under nitrogen. The mixture was refluxed and the progress of the debenzoylation of 12a was followed by TLC. After completion of the reaction, ice was added to the cooled solution, resulting in separation of two phases. The aqueous layer was extracted thoroughly with CH₂Cl₂. The combined organic layers were dried and evaporated under reduced pressure to obtain an orange solid that was chromatographed on a silica gel column (CH₂Cl₂ containing 1 to 3% MeOH) to obtain 13a as a white solid in a 90% yield. ¹H NMR (CDCl₂): 7.73 (d, J 8.4 Hz, 4H, H2 and 6 of Ts), 7.67 (d, J 8.3 Hz, 4H, H2 and 6 of Ts), 7.61 (d, J 8.4 Hz, 4H, H2 and 6 of Ts), 7.25-7.32 (m, 12H, H3 and 5 of Ts), 3.17-3.51 (m, 24H, TsNCH₂), 2.78–2.81 (m, 4H, HNCH₂), 2.47 (s, 3H, CH₂), 2.43 (s, 3H, CH₂), 2.40 (s, 3H, CH₂). ¹³C NMR (CDCl₃): 143.8, 143.7, 143.5, 135.9, 135.5, 135.0, 129.9, 129.8, 127.5, 127.4, 127.2, 50.9, 50.7, 50.3, 49.1, 48.8, 48.6, 48.4, 21.5. $v_{\rm max}$ (KBr)/ cm⁻¹ 3439, 1327, 1156 cm⁻¹. HRMS: *m/z* required for $C_{56}H_{71}N_7O_{12}S_6$ 1226.3563 (M + H⁺), found: 1226.3563.

1,4,7,10,13-Pentatosyl-1,4,7,10,13,16-hexaazacyclooctadecane (13b)

Debenzoylation of **12b** by the method described above for **13a** gave **13b** in a 90% yield. ¹H NMR (CDCl₃): 7.65 (d, *J* 8.3 Hz, 4H, *H*2 and 6 of Ts), 7.62 (d, *J* 8.3 Hz, 4H, *H*2 and 6 of Ts), 7.60 (d, *J* 8.3 Hz, 2H, *H*2 and 6 of Ts), 7.22–7.27 (m, 10H, *H*3 and 5 of Ts), 3.20–3.36 (m, 16H, TsNC*H*₂C*H*₂NTs), 3.08 (t, *J* 5.6 Hz, 4H, TsNC*H*₂CH₂NH), 2.65 (t, *J* 5.6 Hz, 4H, TsNC*H*₂C*H*₂NH), 2.35 (s, 15H, C*H*₃). ¹³C NMR (CDCl₃): 144.0, 143.8, 143.6, 135.5, 135.0, 134.2, 129.9, 129.8, 127.5, 127.3, 50.6, 50.5, 50.0, 49.4, 21.5. HRMS: *m*/*z* required for C₄₇H₆₀N₆O₁₀S₅ 1029.3053 (M + H⁺), found: 1029.3054. *v*_{max} (KBr)/cm⁻¹ 3437, 1633, 1338.

1,4,10,13,17-Pentatosyl-1,4,7,10,13,17-hexaazacycloicosane (13c)

Debenzoylation of **12c** by the method described above for **13a** gave **13c** in a 90% yield. ¹H NMR (CDCl₃): 7.63 (d, *J* 8.3 Hz, 4H, *H*2 and 6 of Ts), 7.60 (d, *J* 8.3 Hz, 4H, *H*2 and 6 of Ts), 7.55 (d, *J* 8.3 Hz, 2H, *H*2 and 6 of Ts), 7.22–7.28 (m, 10H, *H*3 and 5 of Ts), 3.21–3.27 (m, 8H, TsNCH₂CH₂NTs), 3.07–3.10 (m, 8H, TsNCH₂CH₂CH₂CH₂NTs), 2.95–3.01 (t, *J* 6.2 Hz, 4H, TsNCH₂CH₂NH), 2.77–2.80 (t, *J* 6.2 Hz, 4H, TsCH₂CH₂NH), 2.34 (s, 6H, CH₃), 2.32 (s, 9H, CH₃), 1.81–1.91 (m, 4H, TsNCH₂CH₂NTs). ¹³C NMR: 143.6, 135.0, 134.9, 129.8, 127.5, 127.3, 127.2, 50.6, 49.9, 49.5, 48.5, 48.1, 47.8, 29.3, 21.5.

 v_{max} (KBr)/cm⁻¹ 3437, 1633, 1338, 1159. HRMS: *m*/*z* required for C₄₉H₆₄N₆O₁₀S₅ 1057.3366 (M + H⁺), found: 1057.3373.

1-(*N*-Tosyl-2-aminoethyl)-4,7,10,13,16,19-hexatosyl-1,4,7,10,13, 16,19-heptaazacyclohenicosane (14a)

Equal amounts of debenzoylated macrocycle 13a and N-tosylaziridine (6) were heated in a mixture of toluene and MeCN under N₂ at 70 °C for several days. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (acetone : CH₂Cl₂ 1 : 4) to give 14a as a white solid in a 98% yield. ¹H NMR (CDCl₃): 7.65-7.74 (m, 14H, H2 and 6 of Ts), 7.18-7.32 (m, 14H, H3 and 5 of Ts), 5.48 (t, J 5.6 Hz, 1H, NHTs), 3.24-3.30 (m, 20H, TsNCH₂-CH2NTs), 3.10 (m, 4H, TsNCH2CH2N1), 2.93 (m, 2H, TsNH-CH2CH2N1), 2.63 (m, 6H, CH2N1), 2.40 (s, 6H, CH3), 2.39 (s, 6H, CH₃), 2.38 (s, 6H, CH₃), 2.34 (s, 3H, CH₃). ¹³C NMR (CDCl₃): 143.8, 143.6, 143.4, 143.0, 136.6, 135.4, 134.7, 134.4, 129.8, 129.7, 129.6, 129.5, 127.3, 127.1, 126.8, 53.7, 53.4, 52.8, 50.0, 49.9, 49.6, 49.4, 48.5, 47.9, 40.6, 30.7, 21.3. HRMS: m/z required for $C_{65}H_{82}N_8O_{14}S_7$ 1423.3896 (M + H⁺), found 1423.3810.

1-(*N*-Tosyl-2-aminoethyl)-4,7,10,13,16-pentatosyl-1,4,7,10,13, 16-hexaazacyclooctadecane (14b)

Compound **14b** was obtained by reacting **13b** with an equal amount of **6**, as described for **14a**. ¹H NMR (CDCl₃): 7.58–7.69 (m, 12H, *H*2 and 6 of Ts), 7.19–7.28 (m, 12H, *H*3 and 5 of Ts), 5.20 (t, *J* 5.8 Hz, 1H, N*H*Ts), 3.17–3.24 (m, 16H, TsNC*H*₂-C*H*₂NTs), 3.01–3.07 (m, 4H, TsNC*H*₂CH₂N1), 2.81–2.88 (m, 2H, TsNHC*H*₂CH₂N1), 2.55–2.59 (m, 4H, C2*H*₂ and C18*H*₂), 2.50–2.53 (m, 2H, TsNHC*H*₂C*H*₂N1), 2.39 (s, 6H, *CH*₃), 2.34 (s, 3H, *CH*₃), 2.31 (s, 3H, CH₃). ¹³C NMR (CDCl₃): 144.1, 144.0, 143.8, 143.3, 136.8, 135.6, 134.9, 134.5, 130.0, 129.9, 129.7, 127.5, 127.4, 127.3, 127.1, 53.8, 53.5, 50.5, 49.9, 49.1, 48.3, 40.8, 21.6. HRMS: *m*/*z* required for C₅₆H₇₁N₇O₁₂S₆ 1226.3563 (M + H⁺), found 1226.3414.

7-(*N*-Tosyl-2-aminoethyl)-1,4,10,13,17-pentatosyl-1,4,7,10,13, 17-hexaazacycloicosane (14c)

Compound **14c** was obtained by reacting **13c** with an equal amount of **6**, as described for **14a**. ¹H NMR (CDCl₃): 7.59–7.86 (m, 12H, H2 and 6 of Ts), 7.19–7.33 (m, 12H, H3 and 5 of Ts), 5.37 (t, J 5.8 Hz, 1H, NHTs), 2.81–3.32 (m, 22H, CH₂NTs), 2.70–2.74 (m, 4H, C2H₂ and C20H₂), 2.62–2.65 (m, 2H, TsN-HCH₂CH₂N1), 2.41 (s, 6H, CH₃), 2.40 (s, 6H, CH₃), 2.39 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 1.92–1.95 (m, 4H, TsNCH₂CH₂CH₂NTs). ¹³C NMR: 143.7, 143.6, 143.2, 136.8, 135.4, 135.3, 134.9, 134.8, 129.9, 129.7, 127.4, 127.3, 127.2, 127.1, 54.1, 53.8, 53.6, 49.8, 49.4, 48.6, 48.5, 47.8, 40.9, 29.7, 21.5. HRMS: *m/z* required for C₅₈H₇₅N₇O₁₂S₆ 1254.3876 (M + H⁺), found: 1254.3875.

1-(2-Aminoethyl)-1,4,7,10,13,16,19-heptaazacyclohenicosane (1)

The functionalized macrocycle **14a** (0.28 mmol; 400 mg) and excess of phenol (4.25 mmol; 400 mg) were dissolved in acetic acid containing 37% hydrogen bromide. The mixture was kept at 80 °C for 7 days. The solvent was evaporated under reduced pressure, the residue was dissolved in distilled water and washed with CH₂Cl₂, and finally with diethyl ether. The water phase was evaporated to dryness to obtain **1** as a yellow solid. This was dissolved in water, and passed through a Dowex 1 × 8 (OH⁻) resin to convert the product to a free base. ¹H NMR (D₂O): 3.26–3.59 (m, 20H, HNCH₂CH₂NH), 3.05 (m, 2H, CH₂NH₂), 2.80 (m, 6H, CH₂N1), 2.52 (m, 4H, C3H₂ and C20H₂). ¹³C NMR (D₂O): 50.8, 47.0, 44.6, 44.4, 43.9, 43.8, 43.7, 37.0, 35.7. HRMS: *m*/*z* required for C₁₆H₄₀N₈ 345.3454 (M + H⁺), found 345.3456.

1-(2-Aminoethyl)-1,4,7,10,13,16-hexaazacyclooctadecane (2)

Compound **14b** was deblocked as described above for **1** to obtain compound **2**. ¹H NMR (D₂O): 3.45–3.61 (m, 16H, HN-C H_2CH_2NH), 3.22 (m, 4H, C2 H_2 and C18 H_2), 3.02 (m, 2H, C H_2NH_2), 2.73 (m, 4H, C3 H_2 and C17 H_3), 2.67 (m, 2H, N1-C $H_2CH_2N_2$). ¹³C NMR (D₂O): 51.1, 49.5, 47.2, 45.6, 45.1, 45.0, 44,9, 36.2. HRMS: m/z required for C₁₄H₃₅N₇ 302.3032 (M + H⁺), found 302.3033.

7-(2-Aminoethyl)-1,4,7,10,13,17-hexaazacycloicosane (3)

Compound **14c** was deblocked as described above for **1** to obtain compound **2**. ¹H NMR (D₂O): 3.08–3.40 (m, 20H, CH₂NH), 2.97 (m, 2H, CH₂NH₂), 2.64–2.70 (m, 6H, CH₂N1), 1.99 (m, 4H, HNCH₂CH₂CH₂NH). ¹³C NMR (D₂O): 52.8, 52.4, 48.9, 47.5, 47.0, 46.1, 46.0, 38.8, 24.2. HRMS: *m/z* required for C₁₆H₃₉N₇ 330.3345 (M + H⁺), found 330.3347.

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