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First Unequivocal Synthesis of 1 or 8-N-Monosubstituted 1,4,8,12-Tetraazacyclopentadecane

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Abstract: *A novel method derived from Kaden's modification[1] of the Richman and Atkins's cyclization[2] using tosylated synthons allows the unequivocal synthesis of 1 and 8-monofunctionalized 1,4,8,12-tetraazacyclo-pentadecane. Both syntheses are described.*

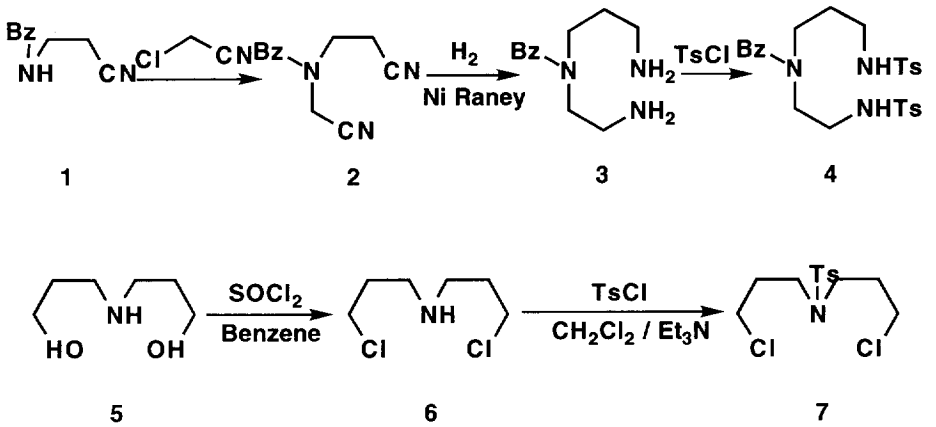
Despite the ever growing interest in the coordinating properties of macrocycles such as crown-ethers, cryptands or cyclophanes[3,4] most studies involving N-monosubstituted derivatives of tetraazamacrocycles have been made either on cyclam or isocyclam. The N-monofunctionalization of the former was achieved by reacting five equivalents of the parent "free-base" with one equivalent (to avoid polysubstitution) of halogenated derivative[5]. Still, removing the excess of cyclam from the final product remains time consuming and therefore, prior to the substitution, it can be interesting to protect three of the nitrogens as recently described[6,7]. On the other hand, the synthesis of N-monosubstituted derivatives of isocyclam involves the condensation of symmetrical synthons[8,9]. We report here the results of our research on the synthesis of N-monosubstituted tetraazamacrocycles by reaction of an unsymmetrical synthon with a symmetrical one. The method is partially derived from that used by Kaden and al.[1] involving a macrocycle in which one nitrogen is discriminated.

Condensation of N-cyanoethylbenzylamine **1** with chloroacetonitrile[10] yielded after careful distillation the N-cyanomethyl-N-cyanoethyl-benzylamine **2** (52%) (**Scheme 1**). Hydrogenation[11] of **2** gave 4-benzyl-1,4,8-triazaoctane **3** in a quantitative yield. Tosylation of **3** was performed by dropwise addition over a period of 5 hours of tosyl chloride in an etheral solution on a stirred solution of **3** in presence of two equivalents of sodium hydroxyde leading to the first synthon **4** in a quantitative yield.

The second fragment **7**[12,13] was obtained from dipropanolamine **5** resulting from the condensation of propanolamine on chloropropanol[14]. The necessary transformations of dipropanolamine in a fragment suitable for cyclization with **4** were performed in two steps.

To a cooled benzene solution (5 °C) of dipropanolamine **5**, an excess of thionylchloride was added dropwise under efficient stirring and then refluxed for three hours after which the reaction mixture was left to stand overnight. After neutralization of the excess of thionylchloride with sodium hydroxyde (1N), the desired compound **6** was extracted with chloroform (97%). Tosylation of **6** was achieved by addition of tosyl chloride in dichloromethane on a stirred solution of dichloropropylamine and triethylamine in the same solvent (97%).

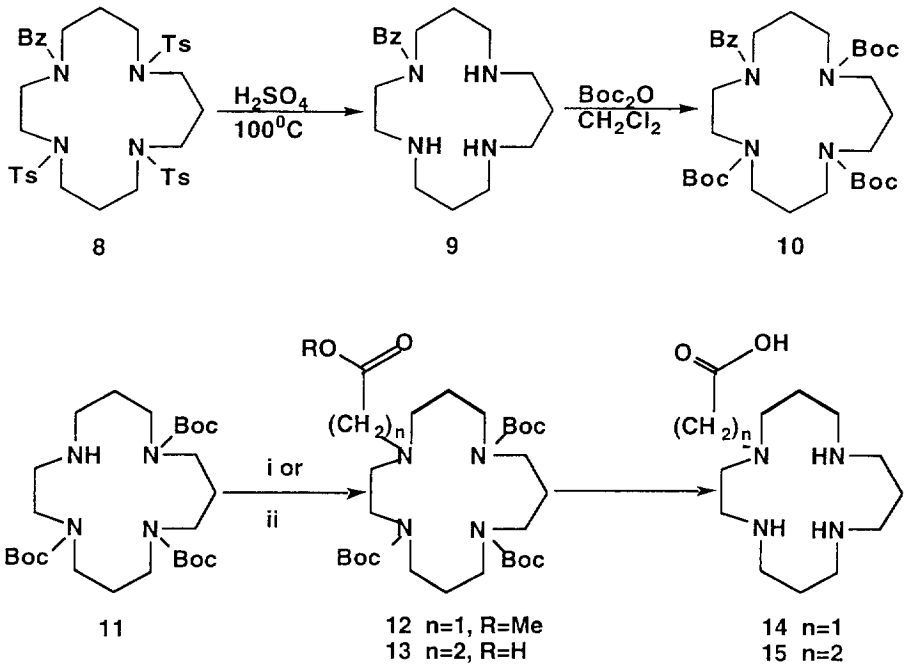
Scheme 1.



After a Richman and Atkins-like cyclization[2] of **4** and **7**, 1-benzyl-4,8,12-tritosyl-1,4,8,12-tetraazacyclopentadecane **8** was isolated and recrystallized from dichloromethane / methanol(1/4) (**Scheme 2**) (yield 46%). Detosylation was performed in concentrated sulfuric acid at 100 °C, without alteration of the benzyl protecting group. The resulting N-monosubstituted product **9** was isolated after classical treatment[2] (74%). Protection of the three free nitrogens proceeded *via* addition of di-*tert*-butyldicarbonate in CH_2Cl_2 to a solution of **9** in the same medium. Compound **10** was then purified by chromatography (silica gel-CH_2Cl_2 / MeOH 95 / 5) (97%).

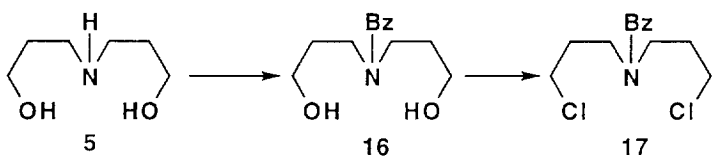
By hydrogenolysis of **10** in acetic acid over palladium on activated carbon, the benzyl protecting group was removed and the tri-N-protected macrocycle **11** was obtained in a quantitative yield. Finally substitution with methyl bromoacetate affords the ester **12**. After treatment of a methanolic solution of **12** with four equivalents of sodium hydroxyde, evaporation and elimination of the Boc protecting group with a four molar hydrochloric solution, the pH was raised to 12 and the solution was evaporated to dryness. The remaining solid was taken up in ethanol and the sodium chloride was eliminated by filtration. The final compound **14** was isolated by addition of concentrated hydrochloric acid[5] (50%).

Scheme 2.



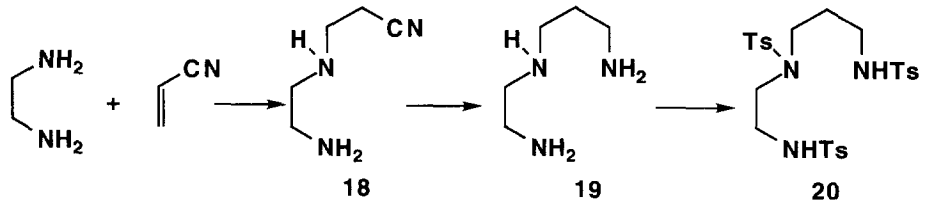
The preparation of the second isomer (8 instead of 1 substituted) was performed in a similar way (**Scheme 3**). N-Benzyl-dipropanolamine **16** was obtained by condensation of benzyl bromide on **5** in acetonitrile with potassium carbonate as deprotonating agent (76%), and was further chlorinated to give **17** as described previously for the synthesis of **6** (86%).

Scheme 3.



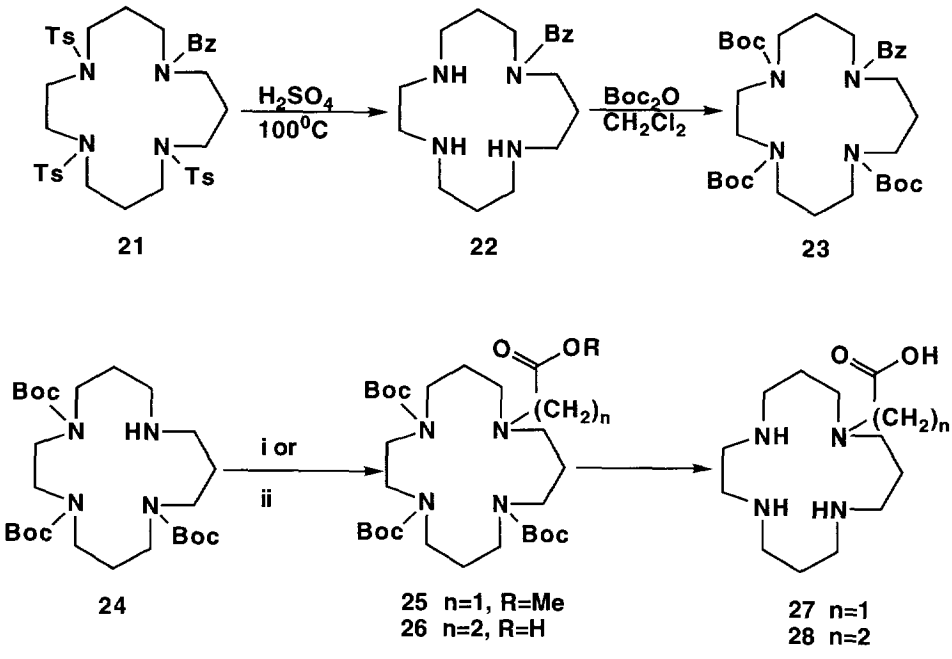
In parallel (**Scheme 4**), 1,4,8-tritosyl-1,4,8-triazaoctane **20** was prepared in three steps : the condensation of one equivalent of acrylonitrile on ethylene diamine led to N-(2-cyanoethyl)ethylenediamine **18** (46%). This was followed by reduction of the cyano group as described for **3** (85%), and finally, by tosylation of the three amines yielding the second synthon **20** (100%)

Scheme 4.



Cyclisation of **17** and **20** gave 8-benzyl-1,4,12-tritosyl-1,4,8,12-tetraazacyclopentadecane **21** (36%) which is the isomer of **8** (**Scheme 5**). The same steps described for the preparation of **14**, were applied to **21**, successively yielding 8-benzyl-1,4,8,12-tetraazacyclopentadecane **22** (71%), 8-benzyl-1,4,12-tri-Boc-1,4,8,12-tetraazacyclo-pentadecane **23** (99%), 1,4,12-tri-Boc-1,4,8,12-tetraazacyclopentadecane **24** (100%), and finally (1,4,8,12-tetraazacyclo-pentadecane-8-yl) acetic acid **27** (53%) through (1,4,8,12-tetraazacyclo-pentadecane-8-yl) methyl acetate **25**.

Scheme 5.



i = Methyl bromoacetate
ii = Acrylic acid

Finally **11** and **24** were reacted with acrylic acid yielding after treatment by hydrochloric acid both isomers bearing a propionic acid pendant arm **15** and **28** after treatment by hydrochloric acid.

Experimental (All compounds were characterized by ^{1}H and ^{13}C NMR using a Bruker WM 400 FT-NMR)

Bz stands for benzyl, Ts for p-toluenesulfonyl, Boc for $(CH_3)C\text{-}CO\text{-}O\text{-}$ and Ph for phenyl

N-cyanoethyl-benzylamine (1) [15]

N-(2-cyanoethyl)-N-cyanomethyl-benzylamine (2)

A mixture of N-cyanoethyl-benzylamine **1** (22g), chloroacetonitrile (18 ml), triethylamine (20 ml) in ethanol (40 ml) was refluxed over a period of 24 hours. The ethanol was evaporated and the remaining oily product taken up in chloroform. This organic layer was extracted twice with water, dried over magnesium sulfate, filtered, and finally evaporated. The remaining brown oil was distilled to yield the desired N-cyanoethyl-N-cyanomethyl-benzylamine as a colorless oil (b.p. 172-174°C/10^{-4} mbar; m= 14.7g; yield= 52%). ^{1}H NMR δ($CDCl_3$): 2.56 (t, 2H, N-CH_2-*CH_2*-CN); 2.94 (t, 2H, N-*CH_2*-CH_2-CN); 3.51 (s, 2H, N-*CH_2*-CN); 3.74 (s, 2H, *$CH_{2(Bz)}$*); 7.28-7.37 (m, 5H, *$C_6H_{5(Bz)}$*). ^{13}C RMN δ($CDCl_3$): 17.56 (1C, CH_2-*CH_2*-CN); 42.1; 49.9; 58.5 (3C, N-*CH_2*-CH_2-CN, N-*CH_2*-CN et *$CH_{2(Bz)}$*); 115.4; 118.91 (2C, -*CN*); 128.7; 129.4; 129.6; 136.9 (6C, *$C_6H_{5(Bz)}$*). Elemental analysis ($C_{12}H_{13}N_3$) Found : C, 72.4; H, 6.6; N, 21.0 Calc. : C, 72.34; H, 6.58; N, 21.09

N-benzyl-1,4,8-triazaoctane (3)

N-cyanoethyl-N-cyanomethyl-benzylamine **2** (26g) and sodium hydroxide (5.77g) were dissolved in 95% ethanol (273ml). Raney nickel (10g) was added and the suspension vigorously stirred under hydrogen pressure (40 bar) for 3 days. The nickel was then filtered off and the organic solvent was evaporated to leave a saturated sodium hydroxide solution. The desired compound was extracted with chloroform. The organic layer was then dried over magnesium sulfate, filtered and evaporated. The product can be used without any further purification (m= 26.7g; yield= 100%). ^{1}H NMR δ($CDCl_3$): 1.58 (q, 2H, N-CH_2-*CH_2*-CH_2-NH_2); 1.75 (bs, 4H, *NH_2*); 2.42; 2.43; 2.68; 2.72 (4t, 8H, N-*CH_2*-CH_2-*CH_2*-NH_2 and N-*CH_2*-*CH_2*-NH_2); 3.51 (s, 2H, *$CH_{2(Bz)}$*); 7.14-7.3 (m, 5H, *$C_6H_{5(Bz)}$*). ^{13}C RMN δ($CDCl_3$): 30.91 (1C, N-CH_2-*CH_2*-CH_2-NH_2); 39.58; 40.19; 51.47; 56.87; 58.87 (5C, N-*CH_2*-CH_2-*CH_2*-NH_2, N-*CH_2*-*CH_2*-NH_2 et *$CH_{2(Bz)}$*); 126.87; 128.2; 128.77; 139.72 (6C; *$C_6H_{5(Bz)}$*). Elemental analysis ($C_{12}H_{21}N_3$) Found : C, 69.6; H, 10.2; N, 20.2 Calc. : C, 69.52; H, 10.21; N, 20.27

4-benzyl-1,8-ditosyl-1,4,8-triazaoctane (4)

4-benzyl-1,4,8-triazaoctane **3** (24g) and sodium hydroxide (9.6g) were dissolved in water (120ml). A solution of p-toluenesulfonylchloride (49g) in diethyl ether (520ml) was added dropwise under efficient stirring.

The mixture was stirred for an additional 4 hours and allowed to stand to separate the two phases. Dichloromethane (≈200ml) was added and the two layers were separated. The organic phase was dried over magnesium sulfate, filtered and evaporated to leave a thick glassy orange oil containing traces of unreacted p-toluenesulfonylchloride. The compound was used with no further purification (m=61g; yield=100%). ^{1}H NMR δ($CDCl_3$): 1.62 (q, 2H, N-CH_2-*CH_2*-CH_2-NHTs); 2.40; 2.43 (2s, 6H, *$CH_{3(Ts)}$*); 2.46; 2.49; 2.90; 2.93 (4t, 8H, 2N-*CH_2*-CH_2-*CH_2*-NHTs and N-*CH_2*-*CH_2*-NHTs); 3.40 (s, 2H, *$CH_{2(Bz)}$*); 7.20-7.30; 7.65-7.75 (2m, 13H, *$C_6H_{4(Ts)}$* and *$C_6H_{5(Bz)}$*). RMN ^{13}C δ($CDCl_3$): 21.92 (2C, *$CH_{3(Ts)}$*); 26.94 (1C, N-CH_2-*CH_2*-CH_2-NHTs); 40.99; 42.09; 51.82; 53.01 (4C, N-*CH_2*-CH_2-*CH_2*-NHTs, N-*CH_2*-*CH_2*-NHTs) 58.75 (1C, *$CH_{2(Bz)}$*); 127.53; 127.69; 128.90; 129.36; 130.15; 130.77; 137.53; 138.80; 143.71 (18C, *$C_6H_{5(Bz)}$* and *$C_6H_{4(Ts)}$*). Elemental analysis ($C_{26}H_{33}N_3S_2O_4$) Found : C, 60.6; H, 6.45; N, 8.1; S, 12.4 Calc. : C, 60.56; H, 6.45; N, 8.15; S, 12.43

Dipropanolamine (5)

A mixture of 3-amino-1-propanol (145ml), 1-chloro-3-hydroxypropane (80ml) and water (450ml) was refluxed over 24 hours. Potassium hydroxide was then added. After dissolution, the whole of the water was evaporated to leave a viscous oil and large quantities of potassium chloride. These were filtered and washed with dried acetone or dichloromethane. The organic phase was dried over magnesium sulfate, filtered and evaporated to leave a dark brown oil. The desired dipropanolamine was obtained, by distillation of this oil, as a colorless liquid (b.p.= 180°C/18 mbar; m= 81g; yield= 64%). ^{1}H NMR δ($CDCl_3$): 1.54 (q, 4H, N-CH_2-*CH_2*-CH_2-OH); 2.59 (t, 4H, N-CH_2-CH_2-*CH_2*-OH); 3.51 (t, 4H, N-*CH_2*-CH_2-CH_2-OH). ^{13}C NMR δ($CDCl_3$): 32.2 (N-CH_2-*CH_2*-CH_2-OH); 48.46 (N-CH_2-CH_2-*CH_2*-OH); 62.07 (N-*CH_2*-CH_2-CH_2-OH).

Di-(3-chloropropyl)amine (6)

Dipropanolamine **5** (20 g) in benzene (300 l) was cooled down to 5 °C. At this temperature, thionyl chloride (45 ml) was then added dropwise under efficient stirring. After the addition the reaction mixture was refluxed over 4 hours then brought down to room temperature and left to stand overnight. After cooling down again to 5°C, a solution of sodium carbonate (10%) was added until the pH was basic. The organic layer was then separated, dried over magnesium sulfate, filtered and evaporated to yield the dichloropropylamine (m=24.8 g; yield = 97 %). RMN ^{1}H δ($CDCl_3$): 1.15-1.35 (bs, 1H, *NH*); 1.91 (q, 4H, N-CH_2-*CH_2*-CH_2-Cl); 2.76; 3.61 (2t, 8H, N-*CH_2*-CH_2-*CH_2*-Cl). RMN ^{13}C δ($CDCl_3$): 33.39 (2C,N-CH_2-*CH_2*-CH_2-Cl); 35.86; 40.66 (4C,N-*CH_2*-CH_2-*CH_2*-Cl)

N-tosyl-di-(chloropropyl)amine (7)

Di-(3-chloropropyl)amine **6** (24.8 g) was dissolved in a mixture of methylene chloride (200 ml) and triethylamine (22 ml). A solution of tosyl chloride (27.8 g) in methylene chloride (100 ml) was added under stirring. After 5 hours the reaction mixture was extracted with water (3 times 50 ml), the organic phase was dried over magnesium sulfate, filtered and the solvent evaporated to leave a paste that slowly solidifies (m=46 g; yield = 97 %). RMN ^{1}H δ($CDCl_3$): 1.81 (q, 2H, N-CH_2-*CH_2*-CH_2-Cl); 2.41 (s, 3H, *$CH_{3(Ts)}$*); 3.22; 3.76(2t, 8H, N-*CH_2*-CH_2-*CH_2*-Cl); 7.31; 7.71 (2d, 4H, *$C_6H_{4(Ts)}$*).

RMN ^{13}C δ($CDCl_3$): 21.85 (1C, $CH_{3(Ts)}$); 32.25 (2C, N-CH_2-CH_2-CH_2-Cl); 42.47; 47.1 (4C, N-CH_2-CH_2-CH_2-Cl); 118.43; 127.6; 130.28; 144.04 (6C, $C_6H_{4(Ts)}$). Elemental analysis ($C_{13}H_{19}N_1S_1O_2Cl_2$) Found : C, 48.1 H, 5.9; N, 4.3; S, 9.8; Cl, 21.9 Calc. : C, 48.15; H, 5.92; N, 4.32; S, 9.82; Cl, 21.87

1-benzyl-4,8,12-tritosyl-1,4,8,12-tetraazacyclopentadecane (8)

4-benzyl-1,8-ditosyl-1,4,8-triazaoctane **4** (40g) was dissolved in dry DMF (800ml). The solution was placed under argon and sodium hydride (20g; 50% in paraffin) was added by small portions. The reaction mixture was heated up to 50°C until hydrogen evolution ceases and the suspension turned dark brown. While maintaining under argon, the reaction mixture was brought back to room temperature and filtered to eliminate the excess of sodium hydride. The solution was heated up to 80°C and a solution of N-tosyl-dichloropropylamine **7** (25g) in dry DMF (500ml) was added dropwise. The reaction mixture was maintained under stirring at 80°C for an additional 24 hours after which it was cooled to room temperature and filtered to remove the sodium chloride. The whole of the solvent was evaporated to leave a thick black oil which was taken up in water (350ml). A light grey-brown suspension was obtained and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered and evaporated. The last traces of DMF were removed under reduced pressure (10^{-2} mbar) to give a light brown paste. This was dissolved in the minimum of hot dichloromethane (≈ 45ml). Then methanol (≈160ml) was added over the hot dichloromethane. After several hours at room temperature the desired tetrasubstituted macrocycle was isolated as a yellow solid (m=26.5g; yield= 46%). RMN ^1H δ($CDCl_3$): 1.72; 1.94 (2q, 6H, N-CH_2-CH_2-CH_2-N); 2.39 2.41; 2.42 (3s, 9H, $CH_{3\ (Ts)}$); 2.47; 2.63 (2t, 4H, $CH_{2(Bz)}$-CH_2-); 2.93-3.21 (m, 12H, N-CH_2-); 3.54 (1s, 2H, N-$CH_{2(Bz)}$); 7.20-7.33; 7.48-7.66 (2m, 17H, $C_6H_{5(Bz)}$ and $C_6H_{4(Ts)}$). ^{13}C NMR δ($CDCl_3$): 21.89 (3C, $CH_{3(Ts)}$); 28.47; 30.22; 31.1 (3C, N-CH_2-CH_2-CH_2-N); 48.23; 48.36; 48.59; 49.03; 52.55; 53.75 (8C, N-CH_2-); 60.51 (1C; $CH_{2(Bz)}$); 127.70; 127.79; 128.81; 129.58; 130.23; 130.34; 139.58; 143.76; 144.01(24C; $C_6H_{5(Bz)}$ and $C_6H_{4(Ts)}$). Elemental analysis ($C_{39}H_{50}N_4S_3O_6$) Found : C, 61.1; H, 6.6; N, 7.3; S, 12.5; Calc. : C, 61.07; H, 6.57; N, 7.30; S, 12.54

1-Benzyl-1,4,8,12-tetraazacyclopentadecane (9)

1-benzyl-4,8,12-tritosyl-1,4,8,12-tetraazacyclopentadecane **8** (26.1 g) was dissolved in concentrated sulfuric acid (100 ml). The solution was then heated up (up to 85-90°C), under vigorous stirring and for 24 hours after which the reaction mixture was cooled to 0°C. Ethanol (250 ml) followed by ether (250 ml) were slowly added. The brown solid that precipitated was decanted and isolated. It was then taken up in water (250 ml), neutralized by sodium hydroxyde until pH ≈ 12. The monobenzylated derivative was extracted in chloroform (m=10.4 g; yield = 74 %). RMN ^1H δ($CDCl_3$): 1.63; 1.69 (2q, 6H, N-CH_2-CH_2-CH_2-N); 2.42-2.76 (m, 16H, N-CH_2-); 3.47 (1s, 2H, N-$CH_{2(Bz)}$); 7.18-7.29 (m, 5H, $C_6H_{5(Bz)}$). Elemental analysis ($C_{18}H_{32}N_4$) Found : C, 71.0; H, 10.6; N, 18.4 Calc. : C, 71.01; H, 10.59; N, 18.4

1-Benzyl-4,8,12-tri-Boc-1,4,8,12-tetraazacyclopentadecane (10)

1-benzyl-1,4,8,12-tetraazacyclopentadecane **9** (6 g) was diluted in dichloromethane (60 ml). A solution of di-*tert*-butyldicarbonate (12.9 g) in dichloromethane (60 ml) was slowly added under stirring. The solvent was evaporated and the residu was purified over a silica gel column eluting with CH_2Cl_2-MeOH 95/5 (m=10.1 g; yield = 97 %). RMN ^1H δ($CDCl_3$): 1.34; 1.40; 1.46 (3s, 27H, CH_{3Boc}); 1.68 (1bq, 2H, CH_2-CH_2-CH_2); 1.83 (2bq, 2H, CH_2-CH_2-CH_2); 2.40; 2.56 (2bt, 4H, Bz-N-CH_2); 3.21-3.31 (1bm, 12H, CH_2-CH_2-CH_2); 3.56 (1s, 2H, $CH_{2(Bz)}$); 7.25 (s, 5H, $C_6H_{5(Bz)}$). RMN ^{13}C δ($CDCl_3$): 29.91; 30.35 (12C); 46.25; 47.27; 51.96 (8C); 60.29 (1C, $CH_{2(Bz)}$); 79.70; 79.81; 80.04 (3C, $C(CH_3)_3$); 127.37; 129.83; 129.17; 139.75 (6C, $C_6H_{5(Bz)}$); 155.74; 155.97; 156.19 (3C, COO-t-Bu). Elemental analysis ($C_{32}H_{56}N_4O_6$) Found : C, 65.5; H, 9.3; N, 9.3 Calc. : C, 65.53; H, 9.33; N, 9.26

4,8,12-tri-Boc-1,4,8,12-tetraazacyclopentadecane (11)

1-benzyl-4,8,12-tri-Boc-1,4,8,12-tetraazacyclopentadecane **10** (8.7 g) and Pd/C 10% (0.5g) were placed under hydrogen (1 atm.) in acetic acid (100ml) with efficient stirring. The reaction was followed by t.l.c. (silica gel/$CHCl_3$). When t.l.c. showed no starting material left, the suspension was filtered over celite and the filtrate evaporated. The residue was taken up in water and the pH brought to 12 by addition of a molar sodium hydroxide solution. The water solution was then extracted with chloroform. The organic layer was dried over sulfate magnesium, filtered and evaporated to yield 4,8,12-tri-Boc-1,4,8,12-tetraazacyclopentadecane as a light yellow solid (m=7.5 g; yield = 100 %). RMN ^1H δ($CDCl_3$): 1.43 (1s, 27H, CH_{3Boc}); 1.71; 1.78; 1.86 (3 q, 6H, CH_2-CH_2-CH_2); 2.67; 2.78 (t, 4H, NH-CH_2); 3.11-3.39 (m, 12H, CH_2-CH_2-CH_2). RMN ^{13}C δ(CDCl3): 28.92; 29.29 (3C); 30.36 (9C, CH_{3Boc}); 45.75; 46.52; 46.67; 46.96; 47.75; 49.01; 49.41 (8C); 79.70; 79.82; 79.95 (3C, $C(CH_3)_3$); 156.01; 156.16; 156.34 (3C, *COO*-t-Bu). Elemental analysis ($C_{26}H_{50}N_4O_6$) Found : C, 60.7; H, 9.8; N, 10.8 Calc. : C, 60.67; H, 9.79; N, 10.89

(1,4,8,12-tetraazacyclopentadecane-1-yl)-acetic acid (14)

4,8,12-tri-Boc-1,4,8,12-tetraazacyclopentadecane **11** (7.5 g) was dissolved in acetonitrile (180 ml). Potassium carbonate (18.75 g) and methylbromoacetate (2.2 ml) were successively added. The reaction mixture was stirred over 24 hours, filtered and evaporated to remove any trace of methylbromoacetate. The ester derivative of the macrocycle **12** was obtained as a very thick oil (7.8 g; 91 %). It was taken up (1.1g) in methanol (10 ml) and the resulting solution cooled down to 5 °C. A sodium hydroxyde solution (0.3 g in 10 ml) was slowly added while keeping the solution under 5°C. When t.l.c (silica gel-CH_2Cl_2/MeOH-15/2) showed no trace of the initial ester left, the solvent was evaporated. The white residue was dissolved in water at 0°C and hydrochloric acid was added until a four molar solution was obtained. After gas evolution ceased, the solution was neutralized by addition of sodium hydroxyde until pH reached 12-12.1, the water was evaporated and the white solid was taken up in ethanol. The insoluble sodium chloride was filtered off and the filtrate was kept at -10°C for a few hours. Cold concentrated hydrochloric acid was added and the desired macrocycle precipitated as its hydrochloric salt. RMN ^1H δ(D_2O): 1.89 (1q, 2H, CH_2-CH_2-CH_2); 2.14; 2.17 (2q, 4H, CH_2-CH_2-CH_2); 2.90; 3.09 (2t, 4H, CO_2H-CH_2-N-CH_2); 3.19-3.34 (m, 12H, CH_2-CH_2-CH_2); 3.57 (1s, 2H, N-CH_2-CO_2H).

RMN ^{13}C δ(D_2O): 23.06; 23.80; 24.6 (3C, CH_2-*CH_2*-CH_2); 45.10; 45.28; 45.44; 45.61; 46.02; 46.71; 53.20; 55.31 (8C, *CH_2*-CH_2-*CH_2*); 58.48 (1C, N-*CH_2*-CO_2H); 174.27 (1C, *CO_2H*). Elemental analysis ($C_{13}H_{28}N_4O_2$, 4HCl, $2H_2O$) Found : C, 34.3; H, 8.0; N, 12.6 ; Cl, 31.1 Calc. : C, 34.36; H, 7.93; N, 12.34, Cl, 31.27

3-(1,4,8,12-tetraazacyclopentadecane-1-yl)-propionic acid (15)

4,8,12-tri-Boc-1,4,8,12-tetraazacyclopentadecane **11** (1 g) was dissolved in ethanol (10 ml). Acrylic acid (267 µl) was added and the solution refluxed over 24 hours to give the acid derivative **13**. The protecting groups were eliminated by action of a four molar hydrochloric acid solution at 0°C. After gas evolution ceased, the solution was treated as described for the preparation of **14**. RMN ^1H δ(D_2O): 2.04 (1q, 2H, CO_2H-CH_2-N-CH_2-*CH_2*-CH_2); 2.12; 2.15 (2q, 4H, CH_2-*CH_2*-CH_2); 2.73; 3.07 (2t, 4H, CO_2H-CH_2-*CH_2*-N-*CH_2*); 3.19-3.33 (m, 14H, *CH_2*-CH_2-*CH_2*); 3.43 (1t, 2H, N-CH_2-*CH_2*-CO_2H). RMN ^{13}C δ(D_2O): 22.27; 22.7; 23.06 (3C, CH_2-*CH_2*-CH_2); 31.72 (1C, N-*CH_2*-CH_2-COOH); 42.21; 44.57; 44.78; 44.84; 44.91; 45.93; 50.04; 52.57(8C, *CH_2*-CH_2-*CH_2* et N-*CH_2*-*CH_2*-N); 54.08 (1C, N-CH_2-*CH_2*-COOH); 176.24 (1C, *CO_2H*). Elemental analysis ($C_{14}H_{30}N_4O_2$, 4.9HCl, $2H_2O$). Found : C, 34.6; H, 7.8; N, 11.3 ; O, 12.7; Cl, 34.6 Calc. : C, 33.60; H, 7.78; N, 11.2, O, 12.8; Cl, 34.79

N-Benzyl-dipropanolamine (16)

Dipropanolamine **5** (62 g) and benzyl bromide(66 ml) in acetonitrile (250 ml) with potassium carbonate (130 g) were refluxed during 48 hours. The solid was filtered off and the solvent was evaporated. The desired compound was obtained after distillation of the residu (b.p.= 178-182 °C/10^{-2} mbar; m= 73 g; yield = 70 %). RMN ^1H δ($CDCl_3$): 1.73 (q, 2H, N-CH_2-*CH_2*-CH_2-OH); 2.59 (t, 4H, N-*CH_2*-CH_2-CH_2-OH); 3.54 (s, 2H, *$CH_{2(Bz)}$*); 4.14 (t, 4H, N-CH_2-CH_2-*CH_2*-OH); 7.28 (s, 5H, *$C_6H_{5(Bz)}$*). RMN ^{13}C δ(CDCl3): 28.76 (2C,N-CH_2-*CH_2*-CH_2-OH); 52.02 (2C,N-*CH_2*-CH_2-CH2-OH); 58.68 (1C); 61.79 (2C,N-CH2-CH_2-*CH_2*-OH); 127.27 (1C, *$CH_{2(Bz)}$*); 128.41; 129.18; 138.02 (6C, *$C_6H_{5(Bz)}$*)

N-Benzyl-di-(3-chloropropyl)amine (17)

17 was obtained starting from **16** and using the same method as described for the synthesis of di-(3-chloropropyl)amine **(6)** (b.p.= 148-150 °C/10^{-2} mbar; yield = 86 %). RMN ^1H δ($CDCl_3$): 1.91 (q, 2H, N-CH_2-*CH_2*-CH_2-OH); 2.57 (t, 4H, N-*CH_2*-CH_2-CH_2-Cl); 3.54 (s, 2H, *$CH_{2(Bz)}$*); 3.57 (t, 4H, N-CH_2-CH_2-*CH_2*-Cl); 7.28 (s, 5H, Ph). RMN ^{13}C δ(CDCl3): 30.87 (2C,N-CH_2-*CH_2*-CH_2-Cl); 43.49; 51.31 (4C,N-*CH_2*-CH_2-*CH_2*-Cl); 59.28 (1C, *$CH_{2(Bz)}$*); 127.43; 128.71; 129.13; 139.80 (6C, *$C_6H_{5(Bz)}$*). Elemental analysis ($C_{13}H_{19}N_1Cl_2$) Found : C, 60.0; H, 7.4; N, 5.4; Cl, 27.2 Calc. : C, 60.01; H, 7.36; N, 5.38; Cl, 27.25

N-(Cyanoethyl)-ethylenediamine (18)

Acrylonitrile (98 ml) was added dropwise to ethylenediamine (100 ml) at 0°C. After 48 hours under stirring, N-(Cyanoethyl)-ethylenediamine was purified by distillation (b.p.=98-100 °C/10^{-2} mbar ; m=77 g; yield = 46 %). RMN ^1H δ($CDCl_3$): 2.54; 2.57; 2.78; 2.84 (4t, 2H, N-*CH2-CH2*-CN et N-*CH2-CH2*-N)

1,4,8-triazaoctane (19)

The reduction of **18** proceeded via the same method used for the hydrogenation of **2** (yield = 85 %). RMN ^{1}H δ($CDCl_3$): 1.57 (q, 2H, N-CH_2-*CH_2*-CH_2-NH_2); 2.53-2.76 (m, 8H, N-*CH_2*-CH2-*CH_2*-NH_2 et N-*CH_2*-*CH_2*-NH_2). RMN ^{13}C δ($CDCl_3$): 33.29 (1C, N-CH_2-*CH_2*-CH_2-NH_2); 39.86; 41.13; 47.09; 52.12 (4C, N-*CH_2*-CH2-*CH_2*-NH_2 et N-*CH_2*-*CH_2*-NH_2)

1,4,8-tritosyl-1,4,8-triazaoctane (20)

Tosylation of 1,4,8-triazaoctane **19** was performed in the same conditions as described for **4** (yield = 100 %). RMN ^{1}H δ($CDCl_3$): 1.72 (1q, 2H, N-CH_2-*CH_2*-CH_2-NHTs); 2.36; 2.40 (2s, 9H, *$CH_{3(Ts)}$*); 2.93; 2.96; 3.09 (4t, 8H, N-*CH_2*-CH_2-*CH_2*-NHTs et N-*CH_2*-*CH_2*-NHTs); 7.26-7.29; 7.57-7.74 (2m, 12H, *$C_6H_{4(Ts)}$*.) Elemental analysis ($C_{26}H_{33}N_3S_3O_6$) Found : C, 53.9; H, 5.7; N, 7.3; S, 16.7 Calc. : C, 53.87; H, 5.74; N, 7.25; S, 16.59

8-Benzyl-1,4,12-tritosyl-1,4,8,12-tetraazacyclopentadecane (21)

8-Benzyl-1,4,12-tri-tosyl-1,4,8,12-tetraazacyclopentadecane was synthesized from 1,4,8-tritosyl-1,4,8-triazaoctane **20** (47.3 g) and N-tosyl-di(chloropropyl)amine **17** (21.3 g) following the same preparation as for 1-benzyl-4,8,12-tritosyl-1,4,8,12-tetraazacyclopentadecane (yield = 36 %). RMN ^{1}H δ(CDCl3): 1.64; 1.68; 1.91 (3q, 6H, N-CH_2-*CH_2*-CH_2-N); 2.42 (t, 2H, *$CH_{2(Bz)}$*-*CH_2*-); 2.43; 2.44; 2.45 (3s, 9H, *$CH_{3\ (Ts)}$*); 2.48 (t, 2H, *$CH_{2(Bz)}$*-*CH_2*-); 2.96-3.19 (m, 8H, N-*CH_2*-); 3.21 (1s, 4H, N-*CH_2*-*CH_2*-N); 3.48 (1s, 2H, N-*$CH_{2(Bz)}$*); 7.18-7.36; 7.59-7.74 (2m, 17H, *$C_6H_{5(Bz)}$* and *$C_6H_{4(Ts)}$*). ^{13}C NMR δ($CDCl_3$): 22.04 (3C, *$CH_{3\ (Ts)}$*); 27.86; 29.35; 29.98 (3C, N-CH_2-*CH_2*-CH_2-N); 48.34; 48.68; 48.75; 48.82; 49.12; 49.15; 52.05; 52.26 (8C, N-*CH_2*-); 60.98 (1C; *$CH_{2(Bz)}$*); 127.60; 127.77; 127.96; 127.98; 128.78; 129.52; 130.33; 130.45; 135.95; 136.23; 139.90; 144; 144.22(24C; *$C_6H_{5(Bz)}$* and *$C_6H_{4(Ts)}$*). Elemental analysis ($C_{39}H_{50}N_4S_3O_6$) Found : C, 61.2; H, 6.5; N, 7.3; S, 12.6; Calc. : C, 61.07; H, 6.57; N, 7.30; S, 12.54

8-Benzyl-1,4,8,12-tetraazacyclopentadecane (22)

The preparation of **22** from 8-Benzyl-1,4,12-tritosyl-1,4,8,12-tetraaza-cyclopentadecane **21** followed the same receipe as described for the synthesis of **9** (yield = 71 %). RMN ^{1}H δ(CDCl3): 1.54; 1.56 (2q, 6H, N-CH_2-*CH_2*-CH_2-N); 2.38-2.69 (m, 16H, N-*CH_2*-); 3.51 (1s, 2H, N-*$CH_{2(Bz)}$*); 7.19-7.31 (m, 5H, *$C_6H_{5(Bz)}$* and *$C_6H_{4(Ts)}$*). Elemental analysis ($C_{18}H_{32}N_4$) Found : C, 70.0; H, 11.1; N, 18.9 Calc. : C, 71.01; H, 10.59; N, 18.4

8-Benzyl-1,4,12-tri-Boc-1,4,8,12-tetraazacyclopentadecane (23)

23 was prepared from 8-Benzyl-1,4,8,12-tetraazacyclopentadecane **22** as described for the synthesis of **10** (yield = 99 %). RMN ^{1}H δ($CDCl_3$): 1.44 (3s, 27H, *CH_{3Boc}*); 1.64; 1.66 (2bq, 2H, CH_2-*CH_2*-CH_2); 1.87 (2bq, 2H, CH_2-CH_2-CH_2); 2.38; 2.42 (2bt, 4H, Bz-N-*CH_2*); 3.21-3.31 (1bm, 12H, *CH_2*-CH_2-*CH_2*); 3.54 (1s, 2H, *$CH_{2(Bz)}$*); 7.28 (s, 5H, *$C_6H_{5(Bz)}$*).

^{13}C NMR δ($CDCl_3$): 28.15; 28.85; 29.33 (12C); 46.6.46; 47.09; 47.52; 51.81; 52.15 (8C); 60.51 (1C, $CH_{2(Bz)}$); 79.67; 79.93 (3C, $C(CH_3)_3$); 127.31; 128.54; 129.31; 139.81 (6C, $C_6H_{5(Bz)}$); 155.74; 156.08 (3C, *C*OO-t-Bu). Elemental analysis ($C_{32}H_{56}N_4O_6$) Found : C, 65.5; H, 9.4; N, 9.2 Calc. : C, 65.53; H, 9.33; N, 9.26

1,4,12-tri-Boc-1,4,8,12-tetraazacyclopentadecane (24)

The preparation of **24** from 1,4,12-tri-Boc-1,4,8,12-tetraazacyclopentadecane **23** was performed as described for the synthesis of **11** (yield = 100 %). RMN ^1H δ($CDCl_3$): 1.44; 1.45 (3s, 27H, CH_{3Boc}); 1.67; 1.69 (3 q, 6H, CH_2-*CH_2*-CH_2); 2.62; 2.64 (t, 4H, NH-*CH_2*); 3.22-3.36 (m, 12H, *CH_2*-CH_2-*CH_2*). ^{13}C NMR δ($CDCl_3$): 28.98 (9C, CH_{3Boc}); 29.34; 30.41 (3C); 45.65; 45.87; 46.61; 46.88; 47.55; 47.74 (8C); 79.74; 80.01 (3C, $C(CH_3)_3$); 155.96; 156.16(3C, *COO*-t-Bu). Elemental analysis ($C_{26}H_{50}N_4O_6$) Found : C, 60.6; H, 9.8; N, 10.9 Calc. : C, 60.67; H, 9.79; N, 10.89

(1,4,8,12-tetraazacyclopentadecane-8-yl)-acetic acid (27)

The preparation of **27** from 1,4,12-tri-Boc-1,4,8,12-tetraazacyclopentadecane **24** was performed as described for the synthesis of **14**. RMN ^1H δ(D_2O): 2.17; 2.20 (3q, 6H, CH_2-*CH_2*-CH_2); 3.3-3.4 (m, 12H, *CH_2*-CH_2-*CH_2*); 3.59 (1s, 4H, N-*CH_2*-*CH_2*-N); 3.84 (1s , 2H, N-*CH_2*-CO_2H). ^{13}C NMR δ(D_2O): 23.54, 24.08 (3C, CH_2-*CH_2*-CH_2); 44.53; 46.16; 47.06; 47.14; 54.59; 54.71 (8C, *CH_2*-CH_2-*CH_2* et N-*CH_2*-*CH_2*-N); 60.00 (1C, N-*CH_2*-COOH); 172.47 (1C, *CO_2H*). Elemental analysis ($C_{13}H_{28}N_4O_2$, 4.5HCl, $3H_2O$) Found : C, 31.8; H, 7.9; N, 11.6 ; Cl, 32.4 Calc. : C, 31.82; H, 7.85; N, 11.42, Cl, 32.58

3-(1,4,8,12-tetraazacyclopentadecane-8-yl)-propionic acid (28)

The preparation of **28** from 1,4,12-tri-Boc-1,4,8,12-tetraazacyclopentadecane **24** was performed as described for the synthesis of **15**. RMN ^1H δ(D_2O): 2.33; 2.35 (3q, 6H, CH_2-*CH_2*-CH_2); 3.08 (1t, 2H, CO_2H-CH_2-*CH_2*-N); 3.47-3.69 (m, 12H, *CH_2*-CH_2-*CH_2*); 3.74 (1t, 2H, N-CH_2-*CH_2*-CO_2H); 3.79 (1s, 4H, N-*CH_2*-*CH_2*-N). ^{13}C NMR δ(D_2O): 22.08; 22.09; 23.45 (3C, CH_2-*CH_2*-CH_2); 32.09 (1C, N-*CH_2*-CH_2-COOH); 43.67; 43.68; 45.14; 45.33; 46.05; 46.37; 52.27; 53.92 (8C, *CH_2*-CH_2-*CH_2* et N-CH_2-*CH_2*-COOH); 176.07 (1C, *CO_2H*). Elemental analysis ($C_{14}H_{30}N_4O_2$, 4.6HCl, $2H_2O$) Found : C, 34.3; H, 8.0; N, 11.5 ; Cl, 33.0 Calc. : C, 34.29; H, 7.88; N, 11.43, Cl, 33.34

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