Preparation of Triazamacrocycles Containing Only Secondary Amine Functions Using Both Tosyl and BOC Protecting Groups

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1,8,15-Triazacycloheneicosane (**1**); 1,9,17-triazacyclotetracosane (**2**) and 1,10,19-triazacycloheptacosane (**3**) were prepared by treating the appropriate *N,N*-bis(ω-bromoalkyl)toluenesulfonamide **8-10** with the appropriate *N,N'*-ditosyl-α,ω-diaminoalkane **11-13** in dimethylformamide using sodium hydride as the base followed by phenol and 33% hydrobromic acid in acetic acid to remove the tosyl protecting groups. 2-Allyloxymethyl-4,11,18- triazaoxacycloheneicosane (**4**) was prepared in two ways. First, *N,N',N''*-tritosylbis(hexamethylene)triamine (**18**) was treated with 2-allyloxymethyl-3-oxa-1,6-hexanediol ditosylate (**23**) and cesium carbonate in dimethylformamide followed by sodium amalgam to remove the tosyl protecting groups. The second preparation of **4** was done by treating the tri-BOC analog of **18** with **23** followed by hydrochloric acid in isopropyl alcohol to remove the BOC protecting groups. The overall yields of **4** using these two processes were very close.

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Introduction.

The polyaza- and perazacrown compounds have received much attention in recent years [1-4]. These ligating compounds have many important applications such as in radioimmunotherapy [5] and as agents for the selective separation of specific metal ions or groups of metal ions [6].

The most common methods for the preparation of the azamacrocycles are from the reaction of α,ω-diamines and dihalides or ditosylates [1-4] or from the dihalides/ditosylates and *N,N'*-diprotected α,ω-diamines [7-9]. The tosyl group is the species most used to protect primary amine nitrogen atoms because it also activates the nitrogen atom as a nucleophile and often provides higher macrocyclization yields [7]. The main problem with using the tosyl group to protect the primary amine is removing it in the last step to form the azamacrocycles containing secondary amine functions. Other *N*-protecting groups have been tried. King and Krespan used the bis-trifluoroacetamide derivative to prepare a diazacrown but in a very low yield [10]. Other protected diamines that have been used to form the cyclic bissecondary amines include the bis-diethyl- or bis-dibenzylurethanes [11-14], bis-acetamides [15], bis-formamides [16], bis-phosphoramides [17,18] and more recently the bis-BOC-protected diamines [19]. The best overall yields for the protection, cyclization and deprotection steps are provided by the tosyl then phosphoryl and BOC protecting groups. The cyclization step is always best when *N*-tosyl groups are present but removal of the BOC and phosphoryl groups can be done in mild conditions and in better yields.

In this paper, we report the synthesis of three triazamacrocycles containing only secondary amine functions (Figure 1) using tosyl protecting groups. A triazacrown ether containing only secondary amines prepared using both tosyl and BOC protecting groups is also reported.

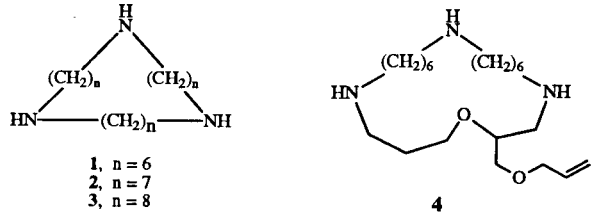


Figure 1. New Triazamacrocycles

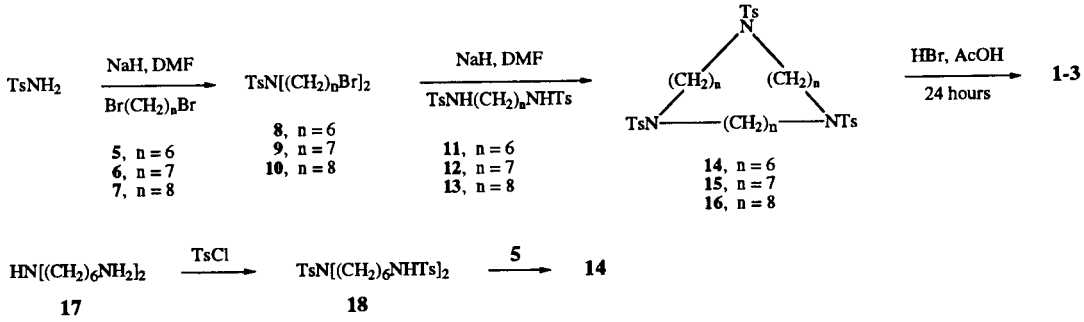
Azamacrocycles containing secondary amine functions are important intermediates for the synthesis of macropolycyclic ligating groups such as the supercryptands [20,21]. They also can be attached to antibodies for medicinal use [5] or to solid supports for other uses.

Results and Discussion.

Symmetric triazamacrocycles **1-3** were prepared by treating *N*-tosylbromides **8-10** with α,ω-bistosylamides **11-13** using sodium hydride as base and dimethylformamide as the solvent (Scheme 1). The *N*-tosyl protecting groups were removed from resulting pertosylmacrocycles **14-16** using hydrobromic acid in acetic acid. Macrocycle **1** was also prepared by treating tritosylated triamine **18** with 1,6-dibromohexane to give intermediate macrocycle **14** (Scheme 1). Macrocycle **1** has been prepared [22] from other intermediates.

We recently reported the use of BOC protecting groups for the preparation of diazacrown ethers [19]. The BOC groups are easy to introduce onto a primary amine and they are particularly easy to remove. The disadvantage of using BOC protecting groups for the synthesis of diazacrown ethers is the lower yield in the cyclocondensation step as compared to the bistosyl-protected diamine reactants. Triazamacrocycle **4** was prepared by two methods as shown in Scheme 2. First *N,N',N''*-tritosyl-7-aza-1,13-tridecanedi-

Scheme 1. Preparation of Triazamacrocycles **1-3**

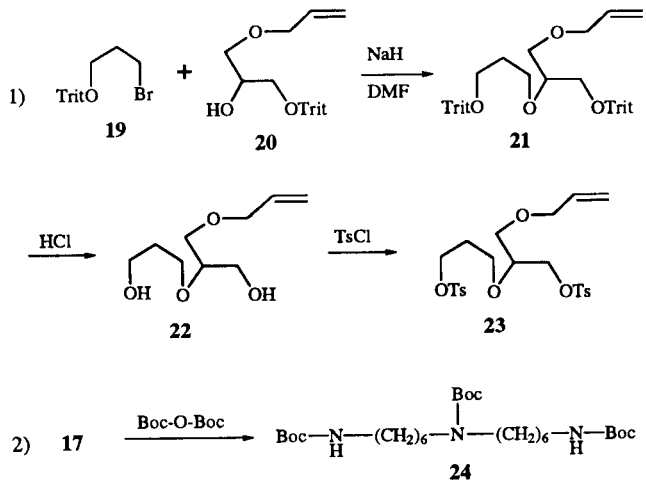


amine (**18**) was treated with 2-allyloxymethyl-3-oxa-1,6-hexanediol ditosylate (**23**) to give tritosyl-substituted triazacrown ether **25** (Scheme 2). The tosyl groups were removed using sodium amalgam. The yields of the two steps were 34% and 46%, respectively, giving an overall yield of 16%. In the second synthetic method for **4**, ditosylate **23** was treated with **24**, the tri-BOC analog of **18**, to give the tri-BOC-substituted triazacrown **26**. The BOC groups were removed by hydrochloric acid. In this case, the yields for the the two steps were 26% and 50%, respectively, giving an overall yield of 13%. No attempt was made to optimize the yields in any of these reactions. Even so, the two methods gave comparable yields for the preparation of **4**. The BOC method, though, uses a slightly easier procedure in that sodium amalgam is not necessary to remove the BOC groups. We suspect that the BOC method could give a higher cyclization yield if an excess of glycol ditosylate was used since the strong base conditions used in the reaction decomposes the glycol ditosylate reactants.

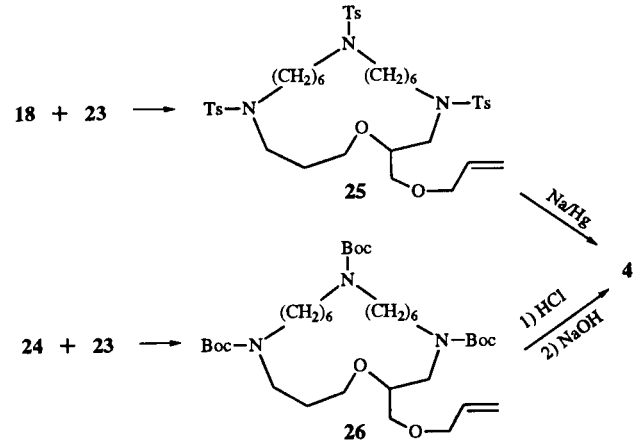
The various tosyl- and BOC-protected starting materials were prepared as shown in Schemes 1 and 2 and as outlined in the experimental section. These reactions lead to new triazamacrocycles which have secondary amine functions in the macroring. These materials could be used to prepare higher order macropolycyclic ligands or they could be attached to antibodies or solid supports.

Scheme 2. Preparation of Triazacrown **4**

A. Preparation of Intermediates



B. Preparation of Macrocycle **4**



EXPERIMENTAL

Proton nmr spectra were obtained at 200 MHz in deuteriochloroform. Molecular weights were determined by electon impact hrms. Starting compounds **19** and **20** were prepared as reported [23-26]. Other starting materials were puchased from the Aldrich Chemical Company. Silica gel (230-400 mesh) (Merck) was used for column chromatography. Combustion analyses were obtained from MHW Labs, Phoenix, Arizona.

Preparation of *N,N*-bis(6-Bromohexyl)toluenesulfonamide (**8**) (Scheme 1).

A solution of toluenesulfonamide (51.36 g, 0.3 mole) in 500 ml of dimethylformamide was treated with 14.40 g (0.6 mole) of sodium hydride at 60° for 30 minutes. 1,6-Dibromohexane (**5**) (219.60 g, 0.9 mole) was added to the mixture at room temperature. The resulting mixture was stirred at 60° for 3 hours and concentrated to dryness under vacuum. The residue was partitioned between ethyl acetate and hexane (8:2) and water. The organic layer was washed twice with water. After being dried over anhydrous magnesium sulfate, the solvent was evaporated. The residue was purified by column chromatography using hexane/ethyl acetate: 15/1 as eluant to give 35.81 g (24%) of **8**; ^{1}H nmr: δ 7.67

(d, J = 10.44 Hz, 2 H), 7.28 (d, J = 10.44 Hz, 2 H), 3.38 (t, J = 7.91 Hz, 4 H), 3.09 (t, J = 8.86 Hz, 4 H), 2.41 (s, 3 H), 1.94-1.73 (m, 4 H), 1.67-1.20 (m, 12 H).

Preparation of *N,N*-bis(7-Bromoheptyl)toluenesulfonamide (**9**) (Scheme 1).

Preparation of **9** followed the above procedure from toluenesulforamide (11.04 g, 0.064 mole), 1,7-dibromoheptane (**6**) (50 g, 0.19 mole) and sodium hydride (4.64 g, 0.19 mole) in 520 ml of dimethylformamide to give 13.0 g (38%) of **9**; ^{1}H nmr: δ 7.68 (d, J = 10.45 Hz, 2 H), 7.28 (d, J = 10.45 Hz, 2 H), 3.39 (t, J = 7.89 Hz, 4 H), 3.05 (t, J = 8.83 Hz, 4 H), 2.40 (s, 3 H), 1.92-1.75 (m, 4 H), 1.60-1.18 (m, 16 H).

Preparation of *N,N*-bis(8-Bromooctyl)toluenesulfonamide (**10**) (Scheme 1).

Preparation of **10** followed the same procedure described above from toluenesulfonamide (4.28 g, 0.025 mole), 1,8-dibromooctane (**8**) (20.40 g, 0.075 mole) and sodium hydride (1.52 g, 0.06 mole) in 200 ml of dimethylformamide to give 5.93 g (43%) of **10**; ^{1}H nmr: δ 7.68 (d, J = 10.43 Hz, 2 H), 7.28 (d, J = 10.43 Hz, 2 H), 3.39 (t, J = 7.85 Hz, 4 H), 3.07 (t, J = 8.75 Hz, 4 H), 2.41 (s, 3 H), 1.93-1.75 (m, 4 H), 1.63-1.15 (m, 20 H).

Preparation of *N,N',N''*-Tritosyl-1,8,15-triazacycloheneicosane (**14**) (Scheme 1).

A solution of *N,N'*-ditosyl-1,6-diaminohexane (**11**) (2.01 g, 4.74 mmoles) in 300 ml of dimethylformamide was treated with 0.26 g (10.4 mmoles) of sodium hydride at 60° for 30 minutes. To this solution was added a solution of **8** (2.49 g, 4.74 mmoles) in 50 ml of dimethylformamide. The resulting mixture was stirred at 60° for 3 hours. After evaporation of the solvent, the residue was partitioned between dichloromethane and water. The organic layer was washed twice with water, dried over anhydrous magnesium sulfate and concentrated to dryness. The crude product was purified by column chromatography using hexane/ethyl acetate: 7/1, then methylene chloride/ethyl acetate: 20/1 as eluants to give 1.30 g (36%) of **14**, ir: 2924, 2855, 1462, 1337, 1160, 1090, 550 cm^{-1}; ^{1}H nmr: δ 7.65 (d, J = 10.46 Hz, 6 H), 7.28 (d, J = 10.46 Hz, 6 H), 3.00 (t, J = 8.75 Hz, 12 H), 2.42 (s, 9 H), 1.68-1.48 (m, 12 H), 1.48-1.20 (m, 12 H); ^{13}C nmr: δ 143.6, 136.5, 130.1, 127.7, 50.4, 29.4, 27.0, 22.0; ms: m/z 760 (M$^+$), 603, 157.

Preparation of *N,N',N''*-Tritosyl-1,9,17-triazacyclotetracosane (**15**) (Scheme 1).

Compound **15** was prepared following the above procedure for **14** from **9** (4.90 g, 9.34 mmoles), *N,N'*-ditosyl-1,7-diaminoheptane (**12**) (4.10 g, 9.34 mmoles) and sodium hydride (0.52 g, 20.5 mmoles) in 800 ml of dimethylformamide to give 3.48 g (46%); ^{1}H nmr: δ 7.67 (d, J = 10.38 Hz, 12 H), 7.28 (d, J = 10.50 Hz, 6 H), 3.03 (t, J = 8.38 Hz, 12 H), 2.42 (s, 9 H), 1.68-1.41 (m, 12 H), 1.41-1.19 (m, 18 H).

N,N',N''-Tritosyl-1,10,19-triazacycloheptacosane (**16**) (Scheme 1).

Compound **16** was prepared following the same procedure as for **14** from **10** (5.58 g, 10.1 mmoles), *N,N'*-ditosyl-1,8-diaminooctane (**13**) (4.65 g, 10.1 mmoles) and sodium hydride (0.56 g, 22.2 mmoles) in 850 ml of dimethylformamide to give 2.17 g (26%); ir: 3026, 2930, 2856, 1724, 1599, 1494, 1464, 1337, 1158, 1091, 815, 755, 654 cm^{-1}; ^{1}H nmr: δ 7.68 (d, J = 10.35 Hz, 6 H), 7.29 (d, J = 10.35 Hz, 6 H), 3.04 (t, J = 8.29 Hz, 12 H), 2.42 (s, 9 H), 1.65-1.30 (m, 12 H), 1.30-1.15 (m, 24 H); ms: m/z 844 (M$^+$), 689, 533, 155.

Preparation of 1,8,15-Triazacycloheneicosane (**1**) (Scheme 1).

A mixture of **14** (27.01 g, 35.5 mmoles), phenol (11.69 g, 124 mmoles) and 200 ml of 33% hydrobromic acid in acetic acid was slowly warmed to 80° over a four-hour period and stirred at 80° overnight. After removal of the solvent, the residue was dissoved in water. The aqueous solution was extracted five times with ethyl ether and saturated with sodium hydroxide. The triazamacrocycle was extracted with methylene chloride from the saturated solution. The combined organic solutions were dried over anhydrous potassium carbonate. The mixture was filtered and the filtrate was concentrated. The crude product was chromatographed using methanol/ammonium hydroxide: 20/1 then 10/1 as eluants to give pure product **1** (8.66 g, 82%); ir (neat): 3293, 2928, 2852, 2801, 1461, 1467, 1130, 895 cm^{-1}; ^{1}H nmr: δ 2.57 (t, J = 8.25 Hz, 12 H), 1.60-1.17 (m, 24 H plus 3 NH); ^{13}C nmr (deuteriochloroform): δ 49.1, 29.3, 26.6; ms: m/z 298 (M$^+$).

These spectral properties were the same as those reported for **1** prepared by a different process [22].

Preparation of 1,9,17-Triazacyclotetracosane (**2**) (Scheme 1).

Macrocycle **2** was prepared using the same procedure as above for **1** from **15** (5.10 g, 6.36 mmoles), phenol (4.19 g, 44.5 mmoles) and 200 ml of 33% hydrobromic acid in acetic acid to give 1.81 g (84%); ^{1}H nmr: δ 2.61 (t, J = 8.10 Hz, 12 H), 1.60-1.29 (m, 30 H), 1.21 (s, 3 H); ^{13}C nmr: δ 49.7, 29.9, 29.2, 27.2; ms: m/z 340 (M$^+$), 239, 225, 125, 110.

Anal. Calcd for $C_{21}H_{45}N_3$: C, 74.27; H, 13.36. Found: C, 74.07; H, 13.58.

Preparation of 1,10,19-Triazacycloheptacosane (**3**) (Scheme 1).

Macrocycle **3** was prepared following the same procedure as for **1** from **16** (2.15 g, 2.55 mmoles), phenol (1.69 g, 17.8 mmoles) and 90 ml of 33% hydrobromic acid in acetic acid to give 0.80 g (82%); ^{1}H nmr: δ 2.55 (t, J = 8.52 Hz, 12 H), 1.56-1.35 (m, 12 H), 1.35-1.18 (m, 24 H), 1.12 (s, 3 H); ^{13}C nmr: δ 50.1, 30.2, 29.4, 27.3; ms: m/z 383 (M$^+$+1), 253, 140, 125.

Anal. Calcd for $C_{24}H_{51}N_3$: C, 75.52; H, 13.47. Found: C, 75.62; H, 13.44.

Preparation of *N,N',N''*-Tritosyl-7-aza-1,13-tridecanediamine (**18**) (Scheme 1).

To a solution of bis(hexamethylene)triamine (**17**) (21.54 g, 0.10 mole) and potassium carbonate (45.61 g, 0.33 mole) in 2500 ml of water was added 62.91 g (0.33 mole) of solid tosyl chloride at 70°. The resulting mixture was stirred for 24 hours at 70°. The solvent was decanted and the sticky crude product was dissolved in chloroform. The organic solution was washed twice with water and dried over anhydrous magnesium sulfate. Removal of the solvent gave 66.6 g (98%) of **18**. Tlc showed that the product was pure enough for the next reaction; ^{1}H nmr: δ 7.77 (d, J = 10.60 Hz, 4 H); 7.67 (d, J = 10.92 Hz, 2 H); 7.36-7.24 (overlap of two d, 6 H), 4.86 (t, J = 7.07 Hz, 2 H, NH), 3.02 (t, J = 8.35 Hz, 4 H), 2.95-2.80 (m, 4 H), 2.41 (s, 9 H), 1.60-1.38 (m, 8 H), 1.38-1.14 (m, 8 H).

Preparation of 1,8,15-triazacycloheneicosane (**14**) from **18** and **5** (Scheme 1).

To a stirred mixture of **18** (63.36 g, 0.094 mole) and cesium carbonate (73.11 g, 0.22 mole) in 1000 ml of dimethylformamide was slowly added a solution of **5** (22.80 g, 0.094 mole) in 500 ml of

dimethylformamide over 16 hours at 50°. The mixture was stirred for 24 hours at 50° and concentrated to dryness under vacuum. The residue was treated with water and filtered to collect a solid, which was partitioned between chloroform and water. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The crude product was purified by column chromatography using methylene chloride/ethyl acetate: 50/1, then 20/1 as eluants to give pure product **14** (27.01 g, 36%). All physical properties for **14** were the same as the compound prepared above.

Preparation of 2-Allyloxymethyl-3-oxa-1,6-hexanediol (**22**) (Scheme 2).

Compound **20** (18.6 g, 0.05 mole) was added under nitrogen to 100 ml of dimethylformamide containing 1.5 g (0.063 mole) of sodium hydride. After mixing for 0.5 hour, 18.5 g (0.05 mole) of **19** was added and the temperature was increased to 60°-70°. After 24 hours, the solvent was evaporated, water was added and the mixture was extracted two times with methylene chloride. The organic phase was dried using anhydrous magnesium sulfate. After filtration and evaporation of the solvent, the residue was chromatographed using methylene chloride/hexane: 3/2 as eluant. Crude dityl product **21** (26.1g, 78%) was collected. The crude product was dissolved in a mixture of 50 ml of methanol and 50 ml of methylene chloride. Hydrochloric acid (20 ml) was added and the mixture was stirred for 48 hours at 30°-35°. The reaction was checked by tlc (silica gel, ethyl acetate/ethanol: 5/1). After cooling, the solution was neutralized by adding sodium bicarbonate. The organic solvents were evaporated and water was added while the solution was stirred. The solid was filtered, the solution was evaporated to dryness, 100 ml of methylene chloride was added and the mixture was filtered again. After evaporation of the solvent and vacuum distilation (132-134°, 10.1 mm Hg), 3 g (41%) of glycol **22** was collected; ^{1}H nmr: δ 1.8 (m, 2 H), 3.0 (b, 2 H), 3.55 (m, 4 H), 3.75 (m, 5 H), 4.0 (d, 2 H), 5.2 (m, 2 H), 5.9 (m, 1 H).

Preparation of 2-Allyloxymethyl-3-oxa-1,6-hexanediol ditosylate (**23**) (Scheme 2).

Crude **22** (2.0 g, 0.011 mole) was added to 100 ml of pyridine. Tosyl chloride (6.0 g, 0.032 mole) was dropped into the pyridine solution at 0°-3°. The solution was stirred for 3 hours at 0°-5° and then kept refrigerated overnight. The mixture was poured onto ice containing 200 ml of hydrochloric acid. The aqueous solution was extracted with methylene chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered and the solution was evaporated. The residue was chromatographed using methylene chloride and then methylene chloride/ethyl acetate: 100/1 as eluants to give 4.2 g (80%) of **23**, mp 71°-72°; ^{1}H nmr: δ 1.8 (t, 2 H) 2.45 (s, 6 H), 3.4 (d, 2 H), 3.5 (m, 3 H), 3.9 (d, 2 H), 4.1 (m, 4 H), 5.2 (m, 42 H), 5.8 (m, 1 H), 7.35 (d, 4 H), 7.8 (d, 4 H).

Preparation of *N,N',N''*-*t*-butoxycarbonyl-7-aza-1,13-tridecanetriamine (**24**) (Scheme 2).

Triamine **17** (2.45 g, mole) in 20 ml of methylene chloride was droped into a stirred solution of 10 g of di-*t*-butyl dicarbonate in 200 ml of methylene chloride. After 12 hours, 300 ml of hexane was added and the solution was filtered. The filtrate was evaporated and the residue was chromatographed using methylene chloride/ethyl acetate: 10/1 and 5/1 as eluants to give 4.8 g (82%) of **24**; ^{1}H nmr: δ 1.3 (m, 8 H), 1.45 (s, 35 H), 3.1(m, 8 H), 4.5 (b, 2 H).

Preparation of 2-Allyloxymethyl-1-oxa-4,11,18-triaza-4,11,18-tritosylcycloheneicosane (**25**) (Scheme 2).

Ditosylate **23** (8.45 g, 0.017 mole) in 20 ml of dimethylformamide was dropped into a solution of 500 ml of dimethylformamide containing 11.43 g (0.017 mole) of tritosylate **18** and 40 g of cesium carbonate at 70°. The mixture was stirred at 70° for 48 hours. The solvent was evaporated and 400 ml of methylene chloride and 200 ml of water were added to the residue. The mixture was extracted two times with methylene chloride and the organic layers were combined and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated and the residue was chromatographed using methylene chloride/ethyl acetate: 50/1 as eluant to give 4.8 g (34%) of triazacrown **25**; ^{1}H nmr: δ 1.35 (m, 8 H), 1.55 (m, 8 H), 1.8 (m, 2 H), 2.4 (s, 9 H), 3.05 (m, 12 H), 3.45 (m, 3 H), 3.65 (m, 2 H), 4.0 (d, 2 H), 5.2 (m, 2 H), 5.9 (m, 1 H), 7.3 (m, 6 H), 7.65 (m, 6 H). A satisfactory elemental analysis was obtained for **4**, a derivative of **25**.

Preparation of 2-Allyloxymethyl-4,11,18-tris(*t*-butoxycarbonyl)-1-oxa-4,11,18- triazacycloheneicosane (**26**) (Scheme 2).

To tris-BOC-protected triamine **24** (4.2 g, 8.2 mmoles) in 400 ml of dimethylformamide 0.5 g (0.21 mmoles)of sodium hydride was added and, after 30 minutes, 4.1 g (8.2 mmole of ditorsylate **23** in 50 ml of dimethylformamide was added during 2 hours at room temperatrue. The mixture was stirred for 36 hours at room temperature and 5 hours at 60°. The solvent was evaporated and the residue was extracted two times with methylene chloride and water. The combined organic layers were dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under the vacuum and residue was chromatographed on silica gel using methylene chloride/ethyl acetate: 10/1 as eluant to give 1.6 g (26%) of **26**; ^{1}H nmr: δ 1.4 (m, 43 H), 1.8 (m, 2 H), 3.35 (m, 17 H), 4.0 (d, 2 H), 5.2 (m, 2 H), 5.9 (m, 1 H). A satisfactory elemental analysis was obtained for **4**, a derivative of **25**.

Preparation of 2-Allyloxymethyl-1-oxa-4,11,18-triazacycloheneicosane (**4**) from **25** (Scheme 2).

To 1.7 g (2 mmoles) of tritosyltriazacrown **25** in 30 ml of methanol and 200 ml of dioxane, 4.28 g of disodium hydrogen phosphate, 3.0 g of crushed sodium amalgam and 150 mg of anthracene were added. The mixture was refluxed for 5 days and then the solvent was decanted and evaporated. To the residue was added 20 ml of methylene chloride and the mixture was filtered. The solvent was evaporated and the residue was chromatographed using methanol/ammonium hydroxide: 20/1, then 10/1 and 5/1 as eluants. To the collected compound, 30 ml of methylene chloride was added and the mixture was filtered. After evaporation of solvent, 0.35 g (46%) of **4** was collected as an oil; ^{1}H nmr: δ 1.3 (m, 18 H), 1.7 (m, 2 H), 2.6 (m, 13 H), 3.5 (m, 2 H), 3.8 (m, 3 H), 3.95 (d, 2 H), 5.2 (m, 2 H), 5.85 (m, 1 H).

Anal. Calcd. for $C_{21}H_{43}N_3O_2$: C, 68.25; H, 11.73. Found: C, 68.03; H, 11.74.

Preparation of **4** from **26** (Scheme 2).

To 1.5 g (2.2 moles) of **26**, 50 ml of isopropyl alcohol saturated with hydrochloric acid was added and the mixture was stirred for 72 hours at room temperature and at 50° for 2 hours. The solvent was evaporated and to the residue was added 10 ml of saturated sodium hydroxide solution. The solution was extracted three times with methylene chloride. The organic layers

were dried over anhydrous magnesium sulfate, filtered and the organic solvent was evaporated. The residue was purified on silica gel using methanol/ammonium hydroxide: 20/1 as eluant to give 0.41 g (50%) of **4**. The physical properties were the same as those reported above.

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