Synthesis of Selectively Protected Polyaza Macrocycles†

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A general route to selectively protected polyaza macrocycles has been developed using a mixture of diethylphosphoryl and tosyl groups for protection of linear chain polyamines. Condensation of *N*-(diethoxyphosphoryl)-*N'*,*N''*-ditosydiethylenetriamine (**1a**), *N*,*N''*-bis(diethoxyphosphoryl)-*N'*-tosyldiethylenetriamine (**1b**) and *N*,*N'*,*N''*-tris(diethoxyphosphoryl)diethylenetriamine (**1c**) with mesylates or tosylates **2** gave the corresponding macrocycles **3** in reasonable yield. The phosphoryl group was selectively removed with gaseous HCl in excellent yield.

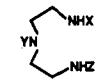
Macrocyclic polyamines are currently of scientific interest owing to their ability to complex transition metal ions as well as anions of biological interest. They are also capable of mimicking enzyme functions. The 24-membered ditopic macrocycle, 1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane ([24]N_6O_2), has been extensively studied with respect to its ability to catalyze phosphoryl transfer reactions reminiscent of the ATPases and kinases.[1,2] More recently, N-monosubstituted and symmetrically N,N'-disubstituted analogues of [24]N_6O_2 have been synthesized and examined as ATPase mimics.[3,4] In order to extend further the biomimetic studies on N-substituted macrocyclic polyamines, a more general and convenient method of synthesizing selectively protected macrocycles was sought.

The reaction of tosylamines with alkyl sulfates under basic conditions is currently the most widespread method for preparing macrocyclic polyamines.[5] Detosylation, however, has no selectivity. In order to accomplish selective deprotection, in the synthesis of N-substituted macrocyclic ligands, for example, a mixture of protective groups needs to be employed, so that certain groups can be removed at different times during the synthetic effort. In this respect, N-substituents such as tosyl and benzoyl have been used together.[3] However, primary amine groups protected as the benzamide do not react with alkylating reagents to form secondary amines; therefore, the use of benzoyl as a protective group in the synthesis of macrocycles is limited. Hence, it is of interest to develop protective groups that are not only able to activate primary amines to participate in alkylation reactions, but are also more easily deprotected after alkylation. An example of this type is the trifluoroacetyl group, which is found to give good protection to amines and is used to prepare secondary amines from their primary analogues in high yield.[6,7] Attempts to synthesize macrocycles using this protective group have failed, however.[7]

Herein is described the use of the diethylphosphoryl moiety as a protecting group. This method of protection not only meets the requirement of activating primary amines in order to cyclize and to form macrocyclic compounds in reasonable yield, but results in a more easily removable group compared to the tosyl analogue.

Results and Discussion

The protected diethylenetriamines **1** are the key precursors for a series of selectively protected polyaza macrocycles **4**. The procedure developed for the synthesis of compound **1a** utilizes a simple intermediate, *N*,*N'*-ditosylethylenediamine (**5**), which can readily be obtained by reacting ethylenediamine with tosyl chloride (Scheme I).[8] The monosodium salt of **5**, prepared in situ by mixing equivalent moles of NaH with **5** in DMF at room temperature, was treated with iodoacetonitrile to provide the monosubstituted derivative **6** in 29% yield, in addition to some of the disubstituted compound. Reduction of the nitrile of **6** with borane in THF followed by reaction with diethyl chlorophosphate afforded **1a** in good yield.



1 a. X=$(EtO)_2P(O)$, Y=Z= Ts
b. X=Z=$(EtO)_2P(O)$, Y= Ts
c. X=Y=Z= $(EtO)_2P(O)$

Diethanolamine was the precursor to **1b** and was tosylated in the presence of triethylamine in CH_2Cl_2 to give *N*,*O*,*O'*-tritosyldiethanolamine (**8**, Scheme II). Reaction of **8** with potassium phthalimide or phthalimide–K_2CO_3 in DMF readily gave **9**. Although **9** could also be obtained by treating **10** with tosyl chloride in pyridine, **10** was sometimes contaminated with *N'*-acetyl-*N*,*N''*-diphthaloyldiethylenetriamine, resulting from the reaction of diethylenetriamine with phthalic anhydride in acetic acid.[10] Hydrazinolysis of **9** in refluxing ethanol followed by reaction with diethyl phosphite in CCl_4 according to the procedure of Zwierzak[11] afforded **1b**. Compound **1c** was readily prepared by direct phosphorylation of diethylenetriamine with diethyl phosphite in CCl_4 or with diethyl chlorophosphate.

Diosylates **2a** and **b** were prepared by published methods.[3,12,13] Dimesylate **2c** was prepared from the diol **2d** in a similar manner, and the latter compound was obtained by following the reported procedure[3] except that the reaction of *N*,*N'*,*N''*-tritosyldiethylenetriamine with 2-[2-

† Dedicated to the memory of Matt Mertes.

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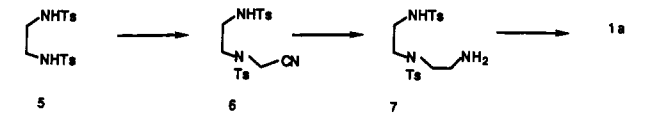
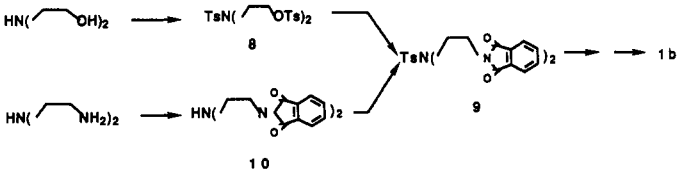
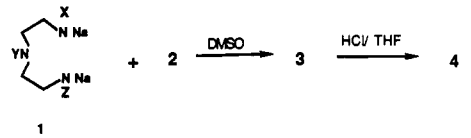
Scheme I

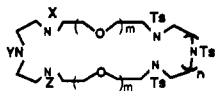


Scheme II



Scheme III

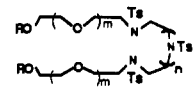




3 a. x= $(EtO)_2P(O)$, Y=Z= Ts, m= 1, n= 3
b. X=Z= $(EtO)_2P(O)$, Y= Ts, m= 1, n= 2
c. X=Z= $(EtO)_2P(O)$, Y= Ts, m= 1, n= 3
d. X=Z= $(EtO)_2P(O)$, Y= Ts, m= 2, n= 3
e. X=Y=Z= $(EtO)_2P(O)$, m= 1, n= 3

4 a. X= H, Y=Z= Ts, m= 1, n= 3
b. X=Z= H, Y= Ts, m= 1, n= 2
c. X=Z= H, Y= Ts, m= 1, n= 3
d. X=Z= H, Y= Ts, m= 2, n= 3
e. X=Y=Z= H, m= 1, n=3

(2-chloroethoxy)ethoxy]ethanol was accelerated by adding a catalytic amount of KI.



2 a. R= Me, m= 1, n=1
b. R= Ts, m= 1, n= 0
c. R= Me, m=2, n= 1
d. R= H, m= 2, n= 1

The ring closure reaction (Scheme III) was carried out in a manner similar to the cyclization of tosylamines with sulfonates with the exception that the disodium salts of **1** were not isolated.[5] The cyclization of tosylamides with sulfonates can also be achieved in the presence of a large excess of Cs_2CO_3[3,12,14] or K_2CO_3[15] in DMF, while NaH is superior in the cyclization of phosphoramidates with sulfates. The phosphoramidate condensation reactions gave yields ranging from 30 to 70%, which are reasonable compared to those reported for the analogous reactions of tosylamines. The reaction of **1a** with **2a** is low in yield possibly because of a difference in reactivity between the phosphoramidate and tosylamine in **1a**, which tends to form a dimer. No attempt was made to isolate and characterize side products.

The selective removal of the phosphoryl group can easily be accomplished in excellent yield by the procedure of Zwierzak[17] using dry gaseous HCl in THF to give the corresponding deprotected compounds **4a–e** (Scheme III). Deprotection is much more facile for the phosphoryl group compared to other protective groups such as benzoyl[3,17] and sulfonyl.[5]

In conclusion, the present work provides a convenient route leading to the synthesis of new selectively protected macrocyclic polyamines and broadens the synthetic range of N-monosubstituted, as well as symmetrically and unsymmetrically, N-polysubstituted polyaza macrocycles. The phosphoryl group may also be used instead of tosyl in the synthesis of macrocycles that are unstable to deprotection under vigorous reaction conditions, such as strong acids and bases, reduction, photolysis, and electrolysis.

Experimental Section

N,N'-Bis(*p*-tolylsulfonyl)ethylenediamine (**5**),[8] *N,N',N''*-tris(*p*-tolylsulfonyl)diethylenetriamine,[5] 1,17-bis(methylsulfoxy)-6,9,12-tris(*p*-tolylsulfonyl)-6,9,12-triaza-3,15-dioxaheptadecane (**2a**),[13] and 1,14-bis(*p*-tolylsulfoxy)-6,9-bis(*p*-tolylsulfonyl)-6,9-diazatetradecane (**2b**)[12] were prepared as previously described. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.43 MHz, respectively. Melting points were measured using capillary tubes without calibration.

***N,O,O'*-Tris(*p*-tolylsulfonyl)diethanolamine (8).** Tosyl chloride (233 g, 1.223 mol) was dissolved in CH_2Cl_2 (400 mL) in a 2-L flask at 0 °C with stirring. To this solution was added dropwise a solution of diethanolamine (42 g, 0.4 mol) and triethylamine (180 mL) in CH_2Cl_2 (200 mL) at 0 °C. Stirring was continued overnight at rt after the addition was completed. The precipitate generated from the reaction was filtered, and the solution was washed with water, dilute HCl, saturated $NaHCO_3$, and brine in turn, and dried (Na_2SO_4). After evaporation to dryness, 100 mL of ethanol was added. Crystals appeared after the solution stood at rt for several hours, which were collected and washed with cold 95% ethanol to give the product: yield 209 g (92%); mp 93–94 °C (lit.[9] mp 78–79 °C).

***N,N''*-Diphthaloyl-*N'*-(*p*-tolylsulfonyl)diethylenetriamine (9).** A solution of **8** (170 g, 0.3 mol) and potassium phthalimide (116.6 g, 0.63 mol) were dissolved in DMF (40 mL), stirred, and heated at 100 °C overnight. After being cooled to rt, the solution was poured into ice–water and the precipitate was collected by suction and washed with cold ethanol. The solid was dried in air and recrystallized from acetonitrile to give **9**: yield 111 g (72%); mp 219–221 °C; ^1H NMR δ 7.80, 7.72 (4 H each, m, phthaloyl), 7.50, 6.92 (2 H each, d, J = 8.4 Hz, Ts), 3.92, 3.73 (4 H each, t, J = 5 Hz, CH_2N), 2.14 (3 H, s, CH_3); ^{13}C NMR δ 168.08, 142.93, 137.40, 133.93, 132.06, 129.47, 126.84, 123.29, 44.48, 35.18, 21.48. Anal. Calcd for $C_{27}H_{23}N_3O_6S$: C, 62.66; H, 4.48; N, 8.12. Found: C, 62.90; H, 4.59; N, 8.00.

***N'*-(*p*-Tolylsulfonyl)diethylenetriamine (11).** A mixture of **9** (98.5 g, 0.19 mol) and hydrazine hydrate (85%, 30 mL) in 800 mL of absolute ethanol was refluxed for 24 h. After the mixture was cooled to rt, the resulting solid was filtered and washed with ethanol. The combined filtrates were concentrated to dryness, and the residue was diluted with CH_2Cl_2 (200 mL). Any additional precipitate that formed was filtered, and the solution was concentrated to dryness in vacuo to give the pure oil **11**: yield 47 g (96%); ^1H NMR δ 7.65 (2 H, d, J = 8.7 Hz, Ts), 7.26 (2 H, d, Ts), 3.08 (4 H, t, J = 6.3 Hz, CH_2N), 2.82 (4 H, t, CH_2N), 2.37 (3 H, s, CH_3), 1.27 (4 H, br s, NH); EIMS *m/e* (rel intens) 258 (M^+ + 1 H, 25), 227 (35), 215 (45), 198 (33), 155 (62). For elemental analysis the oil was transformed into the HCl salt and recrystallized from ethanol–ether, mp 268–270 °C. Anal. Calcd for $C_{11}H_{19}N_3O_2S$·2HCl: C, 40.00; H, 6.41; N, 12.72. Found: C, 40.00; H, 6.50; N, 12.58.

General Procedure for Phosphorylation of Amines. A mixture of amine (0.1 mol), diethyl phosphite (27.6 g, 0.2 mol), K_2CO_3 (55.2 g, 0.4 mol), $KHCO_3$ (20 g, 0.2 mol), and tetrabutylammonium bromide (3.2 g, 0.01 mol) in CCl_4 (60 mL) and CH_2Cl_2 (340 mL) was stirred at 0 °C and allowed to warm to rt overnight. The inorganic salts were filtered, and the solution was washed with water once, dried over Na_2SO_4, and then evaporated to give the product as an oil. The crude product was purified by chromatography on a silica gel column with an eluant of CH_2Cl_2–MeOH.

***N,N''*-Bis(diethoxyphosphoryl)-*N'*-tosyldiethylenetriamine (1b)** was isolated as an oil: yield 34.8 g (66%); ^1H NMR δ 7.62 (2 H, d, J = 8.4 Hz, Ts), 7.26 (2 H, d, Ts), 4.01 (8 H, m, OCH_2), 3.12 (8 H, m, CH_2N), 2.37 (3 H, s, $TsCH_3$), 1.29 (12 H, m, OCH_2CH_3); ^{13}C NMR δ 143.56, 135.36, 129.74, 127.15, 62.20, 62.15, 51.12, 51.05, 40.39, 21.36, 16.16, 16.06; EIMS *m/e* (rel intens)

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530 (M^+ + 1 H, 30), 374 (M^+ – Ts, 50); HRMS m/e for $C_{19}H_{37}N_3O_8P_2S$ + 1 H requires 530.1855, found 530.1855.

N,N',N''-Tris(diethoxyphosphoryl)diethylenetriamine (1c) was isolated as an oil: yield 35.8 g (70%); ^1H NMR δ 4.09–4.02 (12 H, m, OCH_2), 3.27 (2 H, br s, NH), 3.18–3.04 (8 H, m, CH_2N), 1.36–1.28 (18 H, m, CH_3); ^{13}C NMR δ 62.88, 62.81, 62.40, 62.33, 62.26, 47.78, 47.70, 47.64, 39.96, 16.31, 16.21, 16.13; EIMS m/e (rel intens) 512 (M^+ + 1 H, 25), 345 (75), 333 (28), 209 (75), 193 (75), 180 (70), 110 (100). Anal. Calcd for $C_{16}H_{40}N_3O_9P_3$: C, 37.58; H, 7.88; N, 8.22. Found: C, 37.48; H, 8.18; N, 8.00.

N-(Cyanomethyl)-N,N'-bis(p-tolylsulfonyl)ethylenediamine (6). A solution of N,N'-bis(p-tolylsulfonyl)ethylenediamine (3.68 g, 10 mmol) in DMF (40 mL) was added dropwise at rt to a stirring suspension of NaH (240 mg, 10 mmol, freshly washed with hexane) in DMF (10 mL). After the bubbles ceased, the mixture was heated to 60 °C, and iodoacetonitrile (1.67 g, 10 mmol) was added. Stirring was continued for 1 h at 60 °C. After the solvent was removed in vacuo, the residue was diluted with CH_2Cl_2 (100 mL), washed with water, and dried (Na_2SO_4). After the CH_2Cl_2 was concentrated to ~10 mL, the residue was allowed to sit at rt for precipitation. The undesired side product (dinitrile) precipitated and was filtered. The filtrate was chromatographed on a silica gel column with an eluant of CH_2Cl_2–MeOH (100:1) to give the product as a solid, which was recrystallized from CH_2Cl_2–ether: yield 1.18 g (29%); mp 131–132 °C; ^1H NMR δ 7.77, 7.70, 7.36, 7.33 (2 H each, d, J = 8.3 Hz, Ts); 5.34 (1 H, t, NH), 4.27 (2 H, s, CH_2CN), 3.29 (2 H, t, J = 5.8 Hz, CH_2), 3.20 (2 H, q, CH_2), 2.44 (6 H, s, $ArCH_3$); ^{13}C NMR δ 145.01, 143.79, 136.24, 133.68, 130.15, 129.85, 127.53, 127.10, 117.85 (CN), 47.27, 41.37, 36.51, 21.58, 21.49; IR (KBr) 3250 (NH), 1912 (CN) cm^{-1}. Anal. Calcd for $C_{18}H_{21}N_3O_4S_2$: C, 53.06; H, 5.19; N, 10.31. Found: C, 53.35; H, 5.18; N, 10.11.

N,N'-Bis(p-tolylsulfonyl)diethylenetriamine (7). To a solution of the nitrile 6 (1.18 g, 2.9 mmol) in THF (10 mL) was added a solution of borane–THF (1 M, 6 mL) under an inert atmosphere with stirring. The mixture was refluxed for 10 h and cooled to rt. The excess borane was decomposed by adding 4 mL of dilute HCl (4 N) with caution and refluxed for 1 h to decompose the complex. After the THF was removed in vacuo, the residue was neutralized to pH 10 with 10% aqueous NaOH, extracted with CH_2Cl_2 (3 × 20 mL), and dried (K_2CO_3). Evaporation of the CH_2Cl_2 gave the essentially pure product as a foam: yield 17 g (98%); ^1H NMR δ 7.70, 7.60, 7.20, 7.11 (2 H each, d, J = 7 Hz, Ts), 7.34 (1 H, s, TsNH), 3.10–3.00 (8 H, m, CH_2N), 2.74 (2 H, s, NH_2), 2.37 (3 H, s, $ArCH_3$), 2.32 (3 H, s, $ArCH_3$); ^{13}C NMR δ 142.97, 140.75, 139.58, 135.24, 129.38, 128.92, 126.88, 126.47, 52.04, 50.68, 43.77, 40.22, 21.13, 21.04; EIMS m/e (rel intens) 412 (M^+ + 1 H, 22), 256 (M^+ – Ts, 53); HRMS m/e for $C_{18}H_{25}N_3O_4S_2$ + 1 H 412.136, found 412.138.

N-(Diethoxyphosphoryl)-N',N''-bis(p-tolylsulfonyl)diethylenetriamine (1a). A solution of diethyl chlorophosphate (172.5 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of the amine 7 (411 mg, 1 mmol) and triethylamine (121.2 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) at 0 °C with stirring. After addition was complete, stirring was continued for 1 h at rt. The solution was then washed with cold dilute HCl (4 N) and a saturated $NaHCO_3$ solution and was dried (Na_2SO_4). Evaporation of the CH_2Cl_2 gave the pure product as a viscous oil: yield 545 mg (100%); ^1H NMR δ 7.76 (2 H, d, J = 8 Hz, Ts), 7.65 (2 H, m, Ts), 7.29 (4 H, d, Ts), 6.83 (1 H, t, TsNH), 4.07 (4 H, m OCH_2CH_3), 3.90 (1 H, m HN-P), 3.15 (8 H, m, CH_2N), 2.41 (6 H, s, $ArCH_3$), 1.31 (6 H, t, J = 7 Hz, OCH_2CH_3); ^{13}C NMR δ 143.44, 142.78, 136.95, 134.82, 129.55, 129.32, 126.97, 126.71, 62.21, 62.15, 51.17, 51.10, 49.73, 42.33, 39.98, 21.15, 15.93, 15.84. Anal. Calcd for $C_{22}H_{34}N_3O_7PS_2$: C, 48.26; H, 6.26; N, 7.67. Found: C, 48.00; H, 6.65; N, 7.28.

9,12,15-Tris(p-tolylsulfonyl)-9,12,15-triaza-3,6,18,21-tetraoxatricosane-1,23-diol (2d). A mixture of N,N',N''-tris(p-tolylsulfonyl)diethylenetriamine (5.65 g, 10 mmol), 2-[2-(2-chloroethoxy)ethoxy]ethanol (3.7 g, 22 mmol), K_2CO_3 (13.8 g, 100 mmol), and KI (0.5 g) in DMF (50 mL) was stirred at 90 °C for 3 d. The mixture was then cooled, and the inorganic precipitates were filtered. The filtrate was diluted with 200 mL of CH_2Cl_2 and washed with water containing a small amount of sodium thiosulfate for decoloration followed by brine. The organic layer was dried (Na_2SO_4) and was passed through a silica gel column with an eluant of CH_2Cl_2–MeOH (100:5) to give **2d** (7.45 g (90%)) as a viscous oil: ^1H NMR δ 7.75 (6 H, d, J = 8 Hz, Ts), 7.34 (6 H, m, Ts), 3.68–3.57 (20 H, m, CH_2O), 3.38 (12 H, m, CH_2N), 2.66 (2 H, br s, OH), 2.47 (3 H, s, $ArCH_3$), 2.44 (6 H, s, $ArCH_3$); ^{13}C NMR δ 143.64, 143.46, 135.76, 135.39, 129.74, 127.31, 127.25, 72.34, 70.27, 70.12, 69.88, 61.60, 49.50, 49.23, 49.07, 21.44; MS (FAB) m/e (rel intens) 830 (M^+ + 1 H, 38), 676 (100), 674 (40), 359 (82). Anal. Calcd for $C_{37}H_{55}N_3O_{12}S_3$: C, 53.54; H, 6.68; N, 5.06. Found: C, 53.35; H, 6.38; N, 4.99.

1,23-Bis(methylsulfoxy)-9,12,15-tris(p-tolylsulfonyl)-9,12,15-triaza-3,6,18,21-tetraoxatricosane (2c) was prepared according to the published method[3] and obtained as a viscous oil: yield 100%; ^1H NMR δ 7.73 (6 H, m, Ts), 7.34 (6 H, m, Ts), 4.38 (4 H, t, J = 4 Hz, CH_2OMs), 3.75–3.62 (16 H, m CH_2O), 3.39–3.32 (12 H, m, CH_2N), 3.06 (6 H, s, CH_3SO_2), 2.46 (3 H, s, $ArCH_3$), 2.44 (6 H, s, $ArCH_3$); ^{13}C NMR δ 143.65, 143.44, 135.69, 135.40, 129.78, 129.71, 127.13, 70.23, 70.13, 69.65, 69.21, 68.77, 49.07, 48.84, 37.45, 21.35. FABMS m/e (rel intens) 986 (M^+ + 1 H, 76), 832 (100), 830 (25), 802 (20), 437 (58). Anal. Calcd for $C_{39}H_{59}N_3O_{16}S_5$: C, 47.50; H, 6.03; N, 4.26. Found: C, 47.90; H, 5.78; N, 4.42.

General Procedure for Synthesis of Macrocycles 3a, 3d, and 3e. Into two dropping funnels were placed the two solutions to be cyclized. The first was prepared by adding the appropriate phosphoramidate 1 (1 mmol) in DMSO (15 mL) into a suspension of NaH (52.9 mg, 2.2 mmol, freshly washed from 60% NaH in oil with hexane) in DMSO (10 mL). The second solution was prepared by dissolving the appropriate dimesylate 2 (1 mmol) into DMSO (25 mL). In a three-necked flask equipped with the two dropping funnels was placed 25 mL of DMSO. The two solutions were added at the same rate at 70–75 °C with vigorous stirring for a period of 2 h. The DMSO was removed in vacuo, and the residue was diluted with CH_2Cl_2, washed with water and brine, and dried ($MgSO_4$). The mixture was purified by column chromatography on silica gel with an eluant of CH_2Cl_2–MeOH (100:3) to give the product as a foam.

1-(Diethoxyphosphoryl)-4,7,13,16,19-pentakis(p-tolylsulfonyl)-10,22-dioxa-1,4,7,13,16,19-hexaazacyclotetracosane (3a): yield 0.40 g (32%); ^1H NMR δ 7.70, 7.32 (10 H each, m, Ts), 4.02 (4 H, m, OCH_2CH_3), 3.59 (8 H, m, OCH_2), 3.39–3.29 (24 H, m, NCH_2), 2.41 (15 H, s, $ArCH_3$), 1.29 (6 H, t, OCH_2CH_3); ^{13}C NMR δ 143.36, 143.27, 143.18, 143.12, 135.89, 135.63, 135.56, 135.20, 129.54, 127.08, 126.97, 126.92, 70.64, 69.64, 62.06, 61.99, 49.10, 48.99, 48.77, 48.62, 47.64, 45.91, 45.64, 21.23, 15.96, 15.87; MS(FAB) m/e (rel intens) 1253 (M^+ + 1 H, 45), 1099 (100), 1098 (12), 1097 (14), 945 (48), 944 (25), 943 (40), 789 (20). Anal. Calcd for $C_{55}H_{77}N_6O_{15}PS_5 \cdot 0.5CH_2Cl_2$: C, 51.43; H, 6.07; N, 6.48. Found: C, 51.48; H, 6.0; N, 6.39.

1,7-Bis(diethoxyphosphoryl)-4,16,19,22-tetrakis(p-tolylsulfonyl)-1,4,7,16,19,22-hexaaza-10,13,25,28-tetraoxacyclotriacontane (3d): yield 0.56 g (42%); ^1H NMR δ 7.72 (8 H, m, Ts), 7.29 (8 H, m, Ts), 4.01 (8 H, m, OCH_2CH_3), 3.57 (16 H, m, CH_2O), 3.39–3.22 (24 H, m, CH_2N), 2.45 (3 H, s, $ArCH_3$), 2.42 (9 H, s, $ArCH_3$), 1.30 (12 H, t, J = 7 Hz, OCH_2CH_3); ^{13}C NMR δ 143.45, 143.28, 143.04, 136.29, 135.72, 135.34, 129.62, 129.52, 127.26, 127.15, 70.48, 70.03, 69.91, 69.80, 62.06, 61.99, 49.54, 49.04, 48.90, 47.12, 46.09, 45.58, 21.33, 16.07, 15.98; MS (FAB) m/e (rel intens) 1323 (M^+ + 1 H, 95), 1169 (100), 1167 (M^+ – Ts, 60), 1014 (38), 1012 (20).

1,4,7-Tris(diethoxyphosphoryl)-13,16,19-tris(p-tolylsulfonyl)-10,22-dioxa-1,4,7,13,16,19-hexaazacyclotetracosane (3e): yield 0.69 g (56%); ^1H NMR 7.58 (6 H, m, Ts), 7.22 (6 H, m, Ts), 3.98–3.85 (12 H, m, OCH_2CH_3), 3.49 (8 H, m, CH_2O), 3.26 (12 H, m, CH_2N), 3.09 (12 H, m, CH_2N), 2.33 (3 H, s, $ArCH_3$), 2.31 (6 H, m, CH_2N), 1.17 (18 H, t, J = 5.7 Hz, OCH_2CH_3); ^{13}C NMR 143.71, 143.48, 135.82, 135.25, 129.83, 129.78, 127.25, 127.17, 70.66, 69.79, 62.12, 62.05, 49.46, 49.38, 49.01, 46.15, 46.10, 45.90, 44.84, 21.43, 16.15, 16.05; MS (FAB) m/e (rel intens) 1217 (M^+ + 1 H, 100), 1063 (70), 908 (30). Anal. Calcd for $C_{49}H_{83}N_6O_{17}P_3S_3$: C, 48.35; H, 6.87; N, 6.90. Found: C, 48.40; H, 7.13; N, 6.89.

General Procedure for the Synthesis of Macrocycles 3b and 3c. A solution of the phosphoramidate 1 (5 mmol) in 100 mL of DMSO was added dropwise to a suspension of NaH (264 mg, 11 mmol, freshly washed with hexane) in DMSO (100 mL) at rt with stirring. After completion of the addition and cessation of bubbles (~20 min), the flask was heated to 70–80 °C, and a solution of the appropriate bisulfate 2 (5 mmol) in DMSO (100

mL) was added. The reaction mixture was stirred at 70–80 °C for 4 h followed by removal of the DMSO in vacuo. The residue was diluted with CH_2Cl_2, washed with water (3 times), and dried ($MgSO_4$). Chromatography of the mixture on silica gel with an eluant of CH_2Cl_2–MeOH (from 100:1 to 100:3), after evaporation of the solvent, gave the products as foams.

1,7-Bis(diethoxyphosphoryl)-4,13,16-tris(*p*-tolylsulfonyl)-10,19-dioxa-1,4,7,13,16-pentaazacycloheneicosane (3b): yield 2.8 g (54%); ^{1}H NMR δ 7.71 (6 H, *J* = 7.3 Hz, Ts), 7.33 (6 H, m, Ts), 4.04 (8 H, m, OCH_2CH_3), 3.59 (4 H, t, *J* = 5.3 Hz, OCH_2), 3.53 (4 H, t, *J* = 5 Hz, OCH_2), 3.37 (4 H, s, CH_2N), 3.31 (4 H, t, CH_2N), 3.22–3.17 (12 H, m, CH_2N), 2.45 (6 H, s, $ArCH_3$), 2.42 (3 H, s, $ArCH_3$), 1.32 (12 H, t, *J* = 7 Hz, OCH_2CH_3); ^{13}C NMR δ 143.48, 143.33, 135.91, 135.88, 129.73, 129.64, 127.15, 71.04, 69.95, 62.35, 62.27, 49.11, 48.86, 48.03, 46.56, 21.43, 16.14, 16.05; CIMS (NH_3) *m/e* (rel intens) 1038 (M^+ + 1 H, 30), 882 (M^+ – Ts, 25). Anal. Calcd for $C_{43}H_{89}N_5O_{14}P_2S_3$: C, 49.75; H, 6.70; N, 6.75. Found: C, 49.39; H, 6.80; N, 6.68.

1,7-Bis(diethoxyphosphoryl)-4,13,16,19-tetrakis(*p*-tolylsulfonyl)-10,22-dioxa-1,4,7,13,16,19-hexaazacyclotetracosane (3c): yield 4.5 g (73%); ^{1}H NMR δ 7.74–7.66 (8 H, m, Ts), 7.34–7.27 (8 H, m, Ts), 4.01 (8 H, m, OCH_2CH_3), 3.59 (4 H, t, *J* = 4.8 Hz, OCH_2), 3.54 (4 H, t, *J* = 4.8 Hz, OCH_2), 3.39–3.23 (24 H, m, CH_2N), 2.42 (9 H, s, $ArCH_3$, 2.39 (3 H, s, $ArCH_3$), 1.29 (12 H, t, OCH_2CH_3); ^{13}C NMR δ 143.60, 143.34, 143.02, 136.28, 135.91, 135.14, 129.75, 129.70, 129.55, 127.09, 126.99, 70.93, 69.95, 62.14, 62.05, 49.17, 49.13, 48.92, 46.90, 45.85, 21.33, 16.05, 15.98. Anal. Calcd for $C_{52}H_{80}N_6O_{16}P_2S_4$: C, 50.55; H, 6.50; N, 6.80. Found: C, 50.40; H, 6.50; N, 6.68.

General Procedure for Deprotection of the Phosphoryl Group. Into a solution of the macrocycles **3** (1 mmol) in 10 mL of THF was introduced gaseous HCl at 0 °C until the solution was totally saturated. After standing at rt overnight, the THF was removed in vacuo. The residue, which contained chloroalkanes such as dichlorobutane and chlorobutanol, precipitated after anhydrous ether was added. The ether solution was decanted or the solid was collected by filtration, as noted in the following text.

1,4,7,13,16-Pentakis(*p*-tolylsulfonyl)-10,22-dioxa-1,4,7,13,16,19-hexaazacyclotetracosane (4a) was isolated as the hydrochloride salt: yield 0.96 g (85%); mp 125 °C. It was converted to the free amine by neutralization: ^{1}H NMR δ 7.70, 7.32 (10 H each, m, Ts), 3.59 (6 H, m, CH_2O), 3.48 (2 H, t, CH_2O), 3.36 (18 H, m, CH_2N), 3.22 (2 H, t, CH_2N), 2.79 (2 H, t, CH_2N), 2.72 (2 H, t, CH_2N), 2.43 (15 H, s, $ArCH_3$); ^{13}C NMR δ 143.66, 143.54, 143.39, 143.30, 136.09, 135.97, 135.66, 135.58, 135.10, 70.47, 70.40, 70.28, 70.08, 49.83, 49.56, 49.35, 49.20, 49.12, 49.03, 48.87, 48.77, 48.60, 21.46; MS (FAB) *m/e* (rel intens) 1117 (M^+ + 1 H, 100), 963 (M^+ – Ts, 62), 809 (28). Anal. Calcd for $C_{51}H_{68}N_6O_{12}S_5 \cdot H_2O$: C, 53.94; H, 6.21; N, 7.40. Found: C, 53.80; H, 6.18; N, 7.18.

1,4,13-Tris(*p*-tolylsulfonyl)-7,19-dioxa-1,4,10,13,16-pentaazacycloheneicosane (4b). The solid was collected by suction filtration and recrystallized from ethanol–ether to give pure product: yield 0.79 g (94%); mp 126–131 °C. For NMR spectroscopy the solid was transformed to the amine as a foam by neutralization with NaOH (10%): ^{1}H NMR δ 7.86, 7.46 (4 H each, d, *J* = 8 Hz, Ts), 7.81, 7.43 (2 H, each, d, *J* = 8 Hz, Ts), 3.73 (4 H, t, *J* = 5 Hz, CH_2O), 3.66 (4 H, t, *J* = 4 Hz, CH_2O), 3.52 (4 H, s, CH_2N), 2.57 (6 H, s, $ArCH_3$), 2.55 (3 H, s, $ArCH_3$); ^{13}C NMR δ 143.36, 135.84, 134.96, 129.67, 129.61, 127.25, 127.16, 70.25, 70.06, 50.21, 49.68, 49.15, 48.39, 21.41, 21.38; CIMS (NH_3) (HCl salt) *m/e* (rel intens) 766 (M^+ + 1 H, 18), 612 (24), 610 (M^+ – Ts, 17), 456 (20), 432 (18), 302 (50), 241 (60). Anal. Calcd for $C_{35}H_{51}N_5O_8S_3 \cdot 2HCl$: C, 50.11; H, 6.37; N, 8.34. Found: C, 50.00; H, 6.48; N, 8.10.

1,4,7,16-Tetrakis(*p*-tolylsulfonyl)-10,22-dioxa-1,4,7,13,16,19-hexaazacyclotetracosane (4c) was isolated as an HCl salt and recrystallized from ethanol–ether: yield 0.98 g (95%); mp 229–231 °C. The salt was transformed into the free amine for NMR analysis: ^{1}H NMR δ 7.73, 7.35 (8 H each, m, Ts), 3.62 (4 H, br s, OCH_2), 3.53 (4 H, br s, OCH_2), 3.41 (12 H, m, CH_2N), 3.20 (4 H, t, *J* = 5 Hz, CH_2), 2.84–2.77 (10 H, m, CH_2N, N*H*), 2.44 (9 H, s, $ArCH_3$), 2.42 (3 H, s, $ArCH_3$); ^{13}C NMR δ 143.65, 143.37, 143.06, 135.83, 134.95, 129.68, 129.48, 127.16, 127.07, 70.24, 70.08, 49.69, 49.33, 49.03, 48.90, 48.74, 48.65, 21.34, 21.29: CIMS (NH_3) *m/e* (rel intens) 963 (M^+ + 1 H, 50), 809 (10), 808 (5), 807 (8), 653 (15). Anal. Calcd for $C_{44}H_{62}N_6O_{10}S_4 \cdot 2HCl$: C, 51.00; H, 6.22; N, 8.11. Found: C, 50.89; H, 6.18; N, 7.90.

1,4,7,19-Tetrakis(*p*-tolylsulfonyl)-1,4,7,16,19,22-hexaaza-10,13,25,28-tetraoxacyclotriacontane (4d). When ether was poured into the THF solution, an oil appeared, which remained an oil even after storage in the refrigerator. The ether was decanted thoroughly, and 10 mL of water was added to make an emulsion that was washed with ether (5 × 20 mL) to remove any chloro derivatives. The emulsion was then neutralized with 10% aqueous NaOH, extracted with CH_2Cl_2, and dried (K_2CO_3). Evaporation gave **4d** as a foam: yield 1.06 g (94%); ^{1}H NMR δ 7.76, 7.33 (8 H each, m, Ts), 3.65–3.54 (16 H, m, CH_2O), 3.41–2.74 (26 H, m, CH_2N,N*H*), 2.45 (3 H, s, $ArCH_3$), 2.42 (9 H, s, $ArCH_3$); ^{13}C NMR δ 143.34, 143.16, 142.92, 135.68, 135.60, 135.25, 129.51, 129.36, 127.17, 126.10, 70.18, 70.08, 69.94, 69.74, 49.61, 48.87, 48.71, 48.56, 21.28, 21.23; CIMS (NH_3) *m/e* 1051 (M^+ + 1 H), 895 (M^+ – Ts). Anal. Calcd for $C_{48}H_{70}N_6O_{12}S_4$: C, 54.84; H, 6.71; N, 7.99. Found: C, 54.80; H, 6.90; N, 7.80.

1,4,7-Tris(*p*-tolylsulfonyl)-10,22-dioxa-1,4,7,13,16,19-hexaazacyclotetracosane (4e) was collected as a highly hygroscopic solid. The solid was washed thoroughly with ether and then transformed into the free amine as a foam: yield 0.79 g (95%); ^{1}H NMR 7.62, 7.23 (6 H each, d, Ts), 6.50 (3 H, br s, N*H*), 3.68 (4 H, t, CH_2O), 3.55 (4 H, t CH_2), 3.32–3.28 (12 H, m, CH_2N), 2.97 (12 H, br s, CH_2N), 2.37 (3 H, s, Ts), 2.33 (6 H, s, Ts); ^{13}C NMR δ 143.65, 143.48, 135.56, 134.92, 129.72, 129.66, 127.09, 69.54, 67.13, 49.93, 48.83, 48.52, 47.20, 46.89, 45.34, 21.35, 21.29; MS (FAB) *m/e* (rel intens) 809 (M^+ + 1 H, 100). Anal. Calcd for $C_{37}H_{56}N_6O_8S_3 \cdot H_2O$: C, 53.73; H, 7.06; N, 10.16. Found: C, 53.80; H, 6.56; N, 10.00.

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Registry No. **1a**, 134209-53-3; **1b**, 134209-57-7; **1c**, 134209-58-8; **2a**, 110661-80-8; **2b**, 134209-68-0; **2c**, 134209-60-2; **2d**, 134209-59-9; **3a**, 134209-54-4; **3b**, 134209-63-5; **3c**, 134209-64-6; **3d**, 134209-61-3; **3e**, 134209-62-4; **4a**, 134209-55-5; **4a**·HCl, 134209-69-1; **4b**, 134237-98-2; **4b**·2HCl, 134209-71-5; **4c**, 134209-65-7; **4c**·2HCl, 134209-70-4; **4d**, 134209-66-8; **4e**, 134209-67-9; **5**, 4403-78-5; **6**, 134209-56-6; **7**, 134237-97-1; **8**, 16695-22-0; **9**, 23538-91-2; **11**, 23539-15-3; **11**·2HCl, 23538-67-2; $NH(CH_2CH_2OH)_2$, 111-42-2; $NH(CH_2CH_2NH_2)_2$, 111-40-0.