Einhorn Reaction for the Synthesis of Aromatic Building Blocks for Macrocyclization

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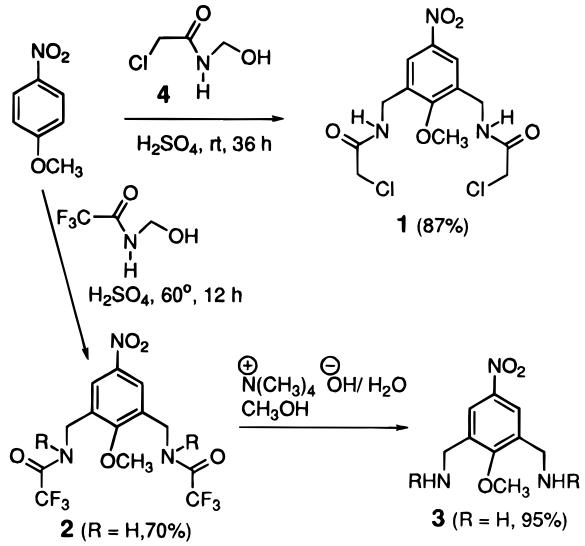
Introduction

In spite of the numerous synthetic pathways reported for the preparation of azacrown macrocycles,[1] they are still relatively unavailable because of their high cost and the tedious and many-step procedures for their syntheses and isolation. A recently reported synthesis gave cyclen (1,4,7,10-tetraazacyclododecane) in a two-step process in a yield of 57%.[2] Improved methods to prepare the azacrown macrocycles are actively being studied. Our studies have been concerned with simple and general methods to prepare benzoazamacrocyclic compounds. We have introduced aromatic subunits into the azamacrocyclic framework using the Mannich aminomethylation of phenols by bissecondary amines and formaldehyde.[3] The Einhorn amidomethylation reaction has been used only once in macrocyclic chemistry,[4] although this reaction is well known in open-chain synthetic organic chemistry[5] and could provide a valuable alternative to the Mannich method. The electrophilic reactivity of the intermediate *N*-acylmethylenimmonium ions in the amidomethylation process is generally greater than that of the aminomethylating agents of the Mannich process. Thus, aromatic molecules less reactive than phenol undergo amidomethylation.[5b,c] This allows the preparation of new building blocks for macrocyclization by introducing amino, amido, and halomethylamido interacting sites into aromatic rings containing different functionalities.

The present study concerns the synthesis of bis(α-haloacetamidomethyl) and benzyldiamine sythons **1**−**3** (Scheme 1) through amidomethylation and their application for the preparation of benzoazamacroheterocycles. These synthons are useful as rigid building blocks

Scheme 1. Preparation of New Synthons 1−3



containing the chromophoric NO_2 group. The methoxy function could be converted to the phenolic OH after ring closure,[6] providing a proton-ionizable group in the macrocyclic cavity. We show three synthetic routes to prepare benzoazamacrocycles using synthons **1**−**3**.

Results and Discussion

Application of the bis(α-chloroacetamide)s for the synthesis of azamacroheterocycles has been reported.[7] The preparation of the bis(α-chloroacetamide)s was carried out by acylation of the appropriate diamines with chloroacetyl chloride. They are then used for cyclization with diamine intermediates followed by reduction to form the azamacrocycle.[7] This method, developed in our laboratory, allowed the preparation of a great number of azamacrocycles from linear aliphatic fragments.[7f] The same transformations can be used to introduce aromatic subunits into the macrocyclic ring using aromatic diamines. However, only a few simple aromatic diamine intermediates are available. For this reason, azamacrocycles containing aromatic subcyclic units are usually prepared from the corresponding aromatic dialdehydes and/or bisalkylating or bisacylating reagents. The unavailability of bifunctional aromatic compounds requires that the final aromatic azamacrocycles be prepared by many-step syntheses and in low overall yields.

We used the amidomethylation reaction (Einhorn reaction) to prepare bis(α-chloroacetamide) **1** in one step from commercially available starting materials in 87% yield (Scheme 1). The *N*-acylmethylenimmonium ions formed from starting *N*-(hydroxymethyl)-α-chloroacetamide (**4**) in strong acid are so reactive that they react with aromatic rings that contain deactivating functional groups.[5b,c] Scheme 2 shows the application of **1** in the

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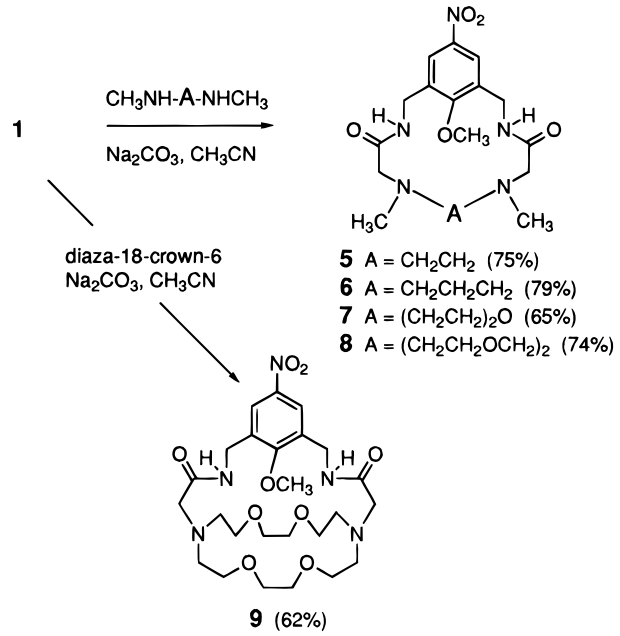
Scheme 2. Preparation of *p*-Nitroanisole-Containing Tetraazacrown Macrocycles from Synthon 1

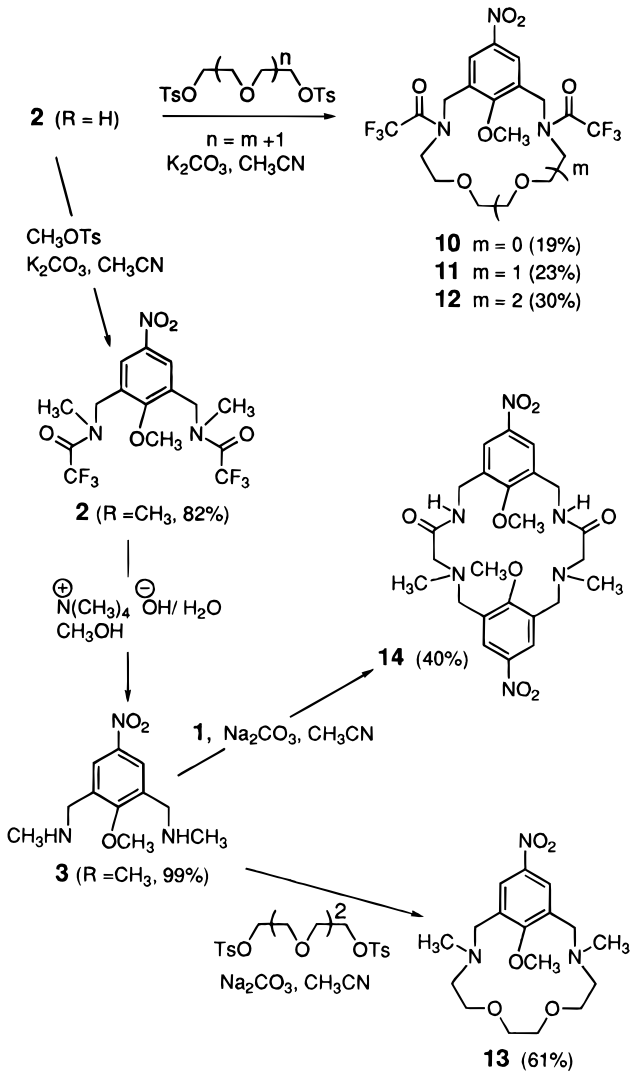


synthesis of several macrocyclic ligands. Monocyclic benzoazacrown ethers **5**−**8** were prepared in excellent yields by treating **1** with the appropriate diamines and Na_2CO_3 in refluxing CH_3CN. Synthon **1** was used to prepare cryptand **9** from diaza-18-crown-6 under the same conditions indicated for the preparation of **5**−**8**. As mentioned above, the *p*-nitroanisole fragment can be useful for the synthesis of chromogenic ligands. The cleavage of the internal methoxy group of mono- and polycyclic anisole-containing crown macrocycles occured smoothly.[6] Thus, because of the relative simplicity and high yields in these reactions, the methods presented in Schemes 1 and 2 could be convenient for the preparation of different UV-responsive azamacroheterocycles.

Synthon **2** is another example of simple bifunctional aromatic building blocks (Scheme 1). Amidomethylation of *p*-nitroanisole with *N*-(hydroxymethyl)trifluoroacetamide in concentrated sulfuric acid gave **2** in a 70% yield. Synthon **2** was used to form the azamacrocycles by two methods. First, the direct alkylation of **2** (R = H) with the oligoethylene glycol ditosylates and K_2CO_3 in refluxing CH_3CN gave macrocycles **10**−**12** (Scheme 3). Second, intermediates **2** (R = H and CH_3) were treated with aqueous $(CH_3)_4NOH$ to form intermediates **3** (R = H and CH_3) (Schemes 1 and 3, repectively). This procedure gave the primary and secondary bisamines **3** in 95% (R = H) and 99% (R = CH_3) yields. Moreover, alkylation of amide **2** (R = H) using methyl tosylate also occured in an excellent yield (Scheme 3). Thus, the benzylamine nitrogens of a macrocycle can be functionalized before the final cyclization step. The second approach to form a macrocyclic ring from sython **2**, then, is its conversion to bisamine **3** followed by ring closure with the proper bisalkylating reagent as shown by the preparation of **13** and **14** (Scheme 3).

The X-ray crystal structure of **5**[8] showed that it had the structure shown in Scheme 2. The 4-nitroanisole ring

Scheme 3. Preparation of *p*-Nitroanisole-Containing Azacrown Macrocycles from Synthons 2 and 3



of **5** is tilted out of the plane of the microring cavity, giving the molecule a pseudo *C*2-symmetry. The ^{1}H NMR spectra of **5** and **6** have two sets of peaks at δ 4.22 and 4.72 (for **5**) and δ 4.36 and 4.56 (for **6**) attributable to the hydrogen atoms on the carbons next to the anisole ring. Those peaks for **6** coalesced into a doublet at 55 °C in $CDCl_3$ but did not coalesce in the case of **5** at 62 °C. The larger macrocycle **7** has a doublet in the ^{1}H NMR spectrum at δ 4.46 that separated into two peaks at temperatures below −25 °C. Those peaks coalesced at −15 °C. The calculated free energies of activation $\Delta G^{\ddagger}$ for these conformational transformations were 14.9 kcal/mol for **6** and 12.1 kcal/mol for **7**.[9,10] These values are similar to those for the conformational transformations of the *N*-hydroxide derivatives of pyridono-14-crown-4 ($\Delta G^{\ddagger}$ = 15.5 kcal/mol) and pyridono-15-crown-5 ($\Delta G^{\ddagger}$ = 12.8 kcal/mol).[11]

Experimental Section

The ^{1}H NMR spectra were obtained at 200 MHz in $CDCl_3$. CI and low-voltage ionization were used to record the mass

(8) X-ray experimental details and structure data for **5** are available from the Cambridge Crystallographic Data Centre. The experimental details, atomic coordinates and bond lengths and angles can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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spectra. Starting materials and solvents were purchased from commercial sources where available.

2,6-Bis[(2-chloroacetamido)methyl]-4-nitroanisole (1) (Scheme 1). To a stirred solution of 4-nitroanisole (9.4 g, 60 mmol) in concd H_2SO_4 (60 mL) at rt was added *N*-(hydroxymethyl)-2-chloroacetamide (**4**) (30.3 g, 240 mmol). After being stirred for 36 h, the mixture was poured into 200 g of ice. The resulting aqueous suspension was filtered. The solid was washed with a large amount of water, dried, and recrystallized from ethanol to give 19 g (87%) of **1**: mp 178−179 °C; ^{1}H NMR δ (DMSO-d_6) 3.88 (s, 3 H), 4.19 (s, 4 H), 4.44 (d, J = 5.9 Hz, 4 H), 8.09 (s , 2 H), 8.92 (t, J = 5.9 Hz, 2 H); MS m/z 364 (M^+). Anal. Calcd for $C_{13}H_{15}Cl_2N_3O_5$: C, 42.87; H, 4.15. Found: C, 43.00; H, 4.36.

2,6-Bis[(trifluoroacetamido)methyl]-4-nitroanisole (2, R = H) (Scheme 1). A mixture of 15.3 g (0.1 mol) of 4-nitroanisole, 42.9 g (0.3 mol) of *N*-(hydroxymethyl)trifluoroacetamide, and 150 mL of H_2SO_4 (95%) was stirred at 60 °C for 12 h and poured into 500 g of ice. One L of ether was added, and the mixture was shaken and transferred to a separatory funnel. The organic phase was separated, dried (Na_2SO_4), and evaporated. The residue was recrystallized from toluene/C_2H_5OH (10:1) to give 28.2 g (70%) of **2** (R = H): mp 158−160 °C; ^{1}H NMR δ (DMSO-d_6) 3.90 (s, 3 H), 4.55 (d, J = 5.4 Hz, 4 H), 8.16 (s, 2 H), 10.10 (t, J = 5.4 Hz, 2 H); MS m/z 404 $[M + 1]^+$. Anal. Calcd for $C_{13}H_{11}F_6N_3O_5$: C, 38.72; H, 2.75. Found: C, 38.80; H, 2.73.

2,6-Bis(aminomethyl)-4-nitroanisole (3, R = H) (Scheme 1). A mixture of 1 g (2.5 mmol) of diamide **2** (R = H), 6 mL of a 10% solution of $(CH_3)_4NOH$, and 4 mL of CH_3OH was stirred under reflux for 0.5 h. CH_3OH was removed under reduced pressure, and product was extracted three times with 10-mL portions of $CHCl_3$. After drying (Na_2SO_4), the $CHCl_3$ was evaporated under reduced pressure to give 0.5 g (95%) of **3** (R = H): mp 57−59 °C; ^{1}H NMR δ 1.50 (s, 4 H), 3.85 (s, 3 H), 3.94 (s, 4 H), 8.17 (s, 2 H); MS m/z 212 $[M + 1]^+$. Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20. Found: C, 51.24; H, 6.25.

2,6-Bis[(*N*-methyltrifluoroacetamido)methyl]-4-nitroanisole (2, R = CH_3) (Scheme 3). A mixture of 1 g (2.5 mmol) of diamide **2** (R = H), 1.03 g (5.5 mmol) of methyl tosylate, 7 g (0.05 mol) of K_2CO_3, and 50 mL of CH_3CN was stirred under reflux for 5 h. The mixture was cooled and filtered, and the CH_3CN was removed. The residue was treated with 100 mL of H_2O and 100 mL of $CHCl_3$. The organic phase was dried (Na_2SO_4), and the solvent was evaporated. The residue was recrystallized from CCl_4/C_2H_5OH (4:1) to give 0.88 g (82%) of **2** (R = CH_3): mp 125−127 °C; ^{1}H NMR δ 3.16 (s, 6 H), 3.88 (s, 3 H), 4.76 (s, 4 H), 8.01 (s, 2 H); MS m/z 432 $[M + 1]^+$. Anal. Calcd for $C_{15}H_{15}F_6N_3O_5$: C, 41.77; H, 3.51. Found: C, 41.85; H, 3.54.

2,6-Bis[(*N*-methylamino)methyl]-4-nitroanisole (3, R = CH_3) (Scheme 3). Compound **3** (R = CH_3) was synthesized as above for **3** (R = H) from 0.5 g (1.16 mmol) of diamide **2** (R = CH_3), 3 mL of a 10% solution of $(CH_3)_4NOH$, and 3 mL of CH_3OH and refluxed for 1.5 h. The product (0.27 g, 99%) was isolated as an oil: ^{1}H NMR δ 1.40 (s, 2 H), 2.45 (s, 6 H), 3.80 (s, 4 H), 3.85 (s, 3 H), 8.18 (s, 2 H); MS m/z 240 $[M + 1]^+$. Anal. Calcd for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16. Found: C, 55.18; H, 7.12.

6,9-Dimethyl-18-methoxy-16-nitro-3,6,9,12-tetraazabicyclo[12.3.1]heptadeca-1(18),14,16-triene-4,11-dione (5) (Scheme 2). A mixture of 0.267 g (3 mmol) of *N*,*N*′-dimethylethylenediamine, 1.1 g (3 mmol) of diamide **1**, 10 g (0.09 mol) of anhydrous Na_2CO_3, and 1 L of CH_3CN was refluxed for 24 h under N_2. The Na_2CO_3 was filtered, and the CH_3CN was evaporated. The solid residue was chromatographed on silica gel using NH_4OH/THF (1:20) as eluant to give 0.86 g (75%) of **5**, which was recrystallized from CH_3OH to give white prisms: mp 232−233 °C dec; ^{1}H NMR δ 2.02 (m, 2 H), 2.24 (s, 6 H), 2.30 (m, 2 H), 2.85 (d, J = 16.2 Hz, 2 H), 2.93 (d, J = 16.2 Hz, 2 H), 3.91 (s, 3 H), 4.22 (dd, J = 14.3, 5.12 Hz, 2 H), 4.72 (dd, J = 14.3, 6.96 Hz, 2 H), 7.47 (t, J = 5.58 Hz, 2 H), 8.09 (s, 2 H); MS m/z 379 (M^+). Anal. Calcd for $C_{17}H_{25}N_5O_5$: C, 53.82; H, 6.64. Found: C, 53.62; H, 6.78.

6,10-Dimethyl-19-methoxy-17-nitro-3,6,10,13-tetraazabicyclo[13.3.1]octadeca-1(19),15,17-triene-4,12-dione (6) (Scheme 2). Compound **6** was obtained as above for **5** from 0.316 g (3 mmol) of *N*,*N*′-dimethyl-1,3-propanediamine, 1.1 g (3 mmol) of diamide **1**, and 10 g (0.09 mol) of Na_2CO_3. Macrocycle **6** (0.93 g, 79%) was isolated after column chromatography and recrystallization from CH_3OH/CH_3CN: mp 205−207 °C dec; ^{1}H NMR δ 1.30−1.70 (m, 2 H), 1.95−2.03 (m, 4 H), 2.26 (s, 6 H), 2.81 (d, J = 16.5 Hz, 2 H), 2.99 (d, J = 16.5 Hz, 2 H), 3.94 (s, 3 H), 4.36 (dd, J = 14.3, 5.0 Hz, 2 H), 4.56 (dd, J = 14.3, 7.7 Hz, 2 H), 7.76 (t, J = 6.0 Hz, 2 H), 8.13 (s, 2 H); MS m/z 393 (M^+). Anal. Calcd for $C_{18}H_{27}N_5O_5$: C, 54.95; H, 6.92. Found: C, 55.16; H, 7.02.

9-Oxa-6,12-dimethyl-21-methoxy-19-nitro-3,6,12,15-tetraazabicyclo[15.3.1]eicosa-1(21),17,19-triene-4,14-dione (7) (Scheme 2). Compound **7** was obtained as above for **5** from 0.404 g (3 mmol) of *N*,*N*′-dimethyl-1,5-diamino-3-oxapentane, 1.1g (3 mmol) of **1**, and 10 g (0.09 mol) of Na_2CO_3. Macrocycle **7** (0.826 g, 65%) was isolated after column chromatography and recrystillization from toluene: mp 131−133 °C dec; ^{1}H NMR δ 2.24 (s, 6 H), 2.34 (t, J = 5.6 Hz, 4 H), 2.96 (s, 4 H), 3.31 (t, J = 5.6 Hz, 4 H), 3.86 (s, 3 H), 4.46 (d, J = 5.9 Hz, 4 H), 7.69 (t, J = 5.9 Hz, 2 H), 8.12 (s, 2 H); MS m/z 423 (M^+). Anal. Calcd for $C_{19}H_{29}N_5O_6$: C, 53.89; H, 6.90. Found: C, 54.00; H, 6.94.

9,12-Dioxa-6,15-dimethyl-24-methoxy-22-nitro-3,6,15,18-tetraazabicyclo[18.3.1]tricosa-1(24),20,22-triene-4,17-dione (8) (Scheme 2). Compound **8** was obtained as above for **5** from 0.54 g (3 mmol) of N,N′-dimethyl-1,8-diamino-3,6−dioxaoctane, 1.1 g (3 mmol) of **1**, and 10 g (0.09 mol) of Na_2CO_3. Macrocycle **8** (1.04 g, 74%) was isolated after column chromatography and recrystallization from CH_3CN/C_6H_{14}: mp 140−142 °C dec; ^{1}H NMR δ 2.30 (s, 6 H), 2.42 (t, J = 5.4 Hz, 4 H), 3.06 (s, 4 H), 3.15 (s, 4 H), 3.27 (t, J = 5.4 Hz, 4 H), 3.81 (s, 3 H), 4.50 (d, J = 5.9 Hz, 4 H), 7.94 (t, J = 5.9 Hz, 2 H), 8.05 (s, 2 H); MS m/z 467 (M^+). Anal. Calcd for $C_{21}H_{33}N_5O_7$: C, 53.95; H, 7.11. Found: C, 53.76; H, 7.10.

18,21,26,29-Tetraoxa-32-methoxy-8-nitro-1,4,12,15-tetraazatricyclo[13.8.8.1^{6,10}]dotriacosa-6,8,10(32)-triene-3,13-dione (9) (Scheme 2). Compound **9** was synthesized as above for **5** from 0.787 g (3 mmol) of diaza-18-crown-6, 1.1 g (3 mmol) of **1**, and 10 g (0.09 mol) of Na_2CO_3. Macrobicycle **9** (1.03 g, 62%) was isolated after column chromatography and recrystallization from toluene/hexane: mp 178−180 °C dec; ^{1}H NMR δ 2.57 (m, 4 H), 2.72 (m, 4 H), 3.18 (s, 4 H), 3.27−3.43 (m, 16 H), 3.85 (s, 3 H), 4.54 (d, J = 5.1 Hz, 4 H), 8.15 (m, 4 H); MS m/z 553 (M^+). Anal. Calcd for $C_{25}H_{39}N_5O_9$: C, 54.24; H, 7.10. Found: C, 54.46; H, 7.13.

6-Oxa-3,9-bis(trifluoroacetyl)-15-methoxy-13-nitro-3,9-diazabicyclo[9.3.1]tetradeca-1(15),11,13-triene (10) (Scheme 3). A mixture of 2.02 g (5 mmol) of diamide **2** (R = H), 2.07 g (5 mmol) of diethylene glycol ditosylate, 15 g (0.11 mol) of K_2CO_3, and 250 mL of CH_3CN was stirred under reflux for 120 h. The mixture was filtered, and the solvent was evaporated under reduced pressure. To the residue was added a mixture of 100 mL of $CHCl_3$ and 100 mL of THF. The mixture was filtered, and solvents were evaporated. The product was isolated after column chromatography on silica gel using $CHCl_3$/THF (12:1) as eluant to give 0.44 g (19%) of **10**: mp 123−125 °C; ^{1}H NMR δ 2.40−5.55 (m, 12 H), 3.80 (s, 3 H), 8.21 (m, 2 H); MS m/z 474 $[M + 1]^+$. Anal. Calcd for $C_{17}H_{17}F_6N_3O_6$: C, 43.14; H, 3.62. Found: C, 43.18; H, 3.70.

6,9-Dioxa-3,12-bis(trifluoroacetyl)-18-methoxy-16-nitro-3,12-diazabicyclo[12.3.1]heptadeca-1(18),14,16-triene (11) (Scheme 3). Compound **11** was synthesized as above for **10** from 2.02 g (5 mmol) of diamide **2** (R = H), 2.29 g (5 mmol) of triethylene glycol ditosylate, and 15 g (0.11 mol) of K_2CO_3. Macrocycle **11** (0.59 g, 23%) was isolated after column chromatography as a solid: mp 125−128 °C; ^{1}H NMR δ 2.40−5.35 (m, 16 H), 3.82 (s, 3 H), 7.95 (m, 2 H); MS m/z 518 $[M + 1]^+$. Anal. Calcd for $C_{19}H_{21}F_6N_3O_7$: C, 44.11; H, 4.10. Found: C, 44.10; H, 4.17.

6,9,12-Trioxa-3,15-bis(trifluoroacetyl)-21-methoxy-19-nitro-3,15-diazabicyclo[15.3.1]eicosa-1(21),17,19-triene (12) (Scheme 3). Compound **12** was obtained as above for **10** from 2.02 g (5 mmol) of diamide **2** (R = H), 2.51 g (5 mmol) of tetraethylene glycol ditosylate, and 15 g (0.11 mol) of K_2CO_3. Macrocycle **12** (0.85 g, 30%) was isolated after column chromatography as a solid: mp 154−156 °C; ^{1}H NMR δ 3.52 (m, 16 H), 3.83 (s, 3 H), 5.05 (m, 4 H), 7.91 (m, 2 H); MS m/z 562 $[M + 1]^+$. Anal. Calcd for $C_{21}H_{25}F_6N_3O_8$: C, 44.93; H, 4.49. Found: C, 45.01; H, 4.43.

6,9-Dioxa-3,12-dimethyl-18-methoxy-16-nitro-3,12-diazabicyclo[12.3.1]heptadeca-1(18),14,16-triene (13) (Scheme 3). A mixture of 0.19 g (0.8 mmol) of diamine **3** (R = CH_3), 0.36

g (0.8 mmol) of triethylene glycol ditosylate, 1.06 g (0.01 mol) of Na_2CO_3, and 50 mL of CH_3CN was stirred under reflux for 100 h. The mixture was filtered, and the solvent was removed. The residue was treated with 20 mL of H_2O and 50 mL of $CHCl_3$. The organic phase was separated and dried (Na_2SO_4), and the $CHCl_3$ was evaporated. The residue was purified on silica gel using CH_3OH as the eluant to give 0.172 g (61%) of **13** as an oil: ^{1}H NMR δ 2.25−3.95 (m, 22 H), 4.00 (s, 3 H), 8.15 (m, 2 H); MS m/z 354 $[M + 1]^+$. Anal. Calcd for $C_{17}H_{27}N_3O_5$: C, 57.77; H, 7.70. Found: C, 57.85; H, 7.68.

6,14-Dimethyl-23,24-dimethoxy-10,21-dinitro-3,6,14,17-tetraazatricyclo[17.3.1^{1,19}.1^{8,12}]tricosa-1(23),19,21,8,10,12(24)-hexaene-4,16-dione (14) (Scheme 3). Compound **14** was obtained as above for **13** from 0.35 g (1.5 mmol) of diamine **3** (R = CH_3), 0.533 g (1.5 mmol) of diamide **1**, and 2 g (0.019 mol) of Na_2CO_3. Compound **14** (0.31 g, 40%) was isolated after column chromatography on silica gel using $CHCl_3$/THF (1:1) as eluant: mp 225−228 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 6 H), 3.02 (s, 4 H), 3.50 (s, 3 H), 3.60 (s, 3 H), 3.72 (s, 4 H), 4.35 (d, J = 6.6 Hz, 4 H), 7.70 (t, J = 6.6 Hz, 2 H), 8.05 (s, 2 H), 8.21 (s, 2 H); MS m/z 531 $[M + 1]^+$. Anal. Calcd for $C_{24}H_{30}N_6O_8$: C, 54.33; H, 5.70. Found: C, 54.38; H, 5.76.

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