Mannich Reaction as a Key Strategy for the Synthesis of Benzoazacrown Ethers and Benzocryptands

Victor N. Pastushok,[†] Jerald S. Bradshaw,*[,†] Andrei V. Bordunov,[‡] and Reed M. Izatt[†]

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602, and IBC Advanced Technologies, Inc., P.O. Box 98, American Fork, Utah 84003

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A convenient method for the synthesis of mono- and polycyclic azacrown macrocycles containing aromatic fragments using the Mannich condensation of phenols and secondary diamines has been studied. This new approach allowed the synthesis of bisphenols connected by oligoazaoxaalkane units in good yields without the need to protect the phenolic OH groups. These bisphenols (**13**−**16**) were alkylated with ditosylates of polyethylene glycols to give benzoazacrown ethers **25**−**30**. Intermediate bisphenols **13**−**15** were also treated with three bis(methoxymethyl)-substituted diamines to form benzoazacrowns **10**−**12** containing internal phenolic functions. Phenol-containing mono- (**11**) and bicyclic (**3**, $n = 1$) compounds, which were synthesized via the Mannich aminomethylation process, were used as building blocks for construction of bi- (**32**) and tricyclic (**33**) ligands.

Introduction

Introducing aromatic fragments into the crown macrocyclic framework increases the rigidity of those ligands and improves their preorganization for binding particular ions or organic guest molecules. The aromatic units facilitate the modification of macrocyclic hosts with various UV and/or fluorescent active groups,[1] proton-ionizable fragments,[2] and functional groups which can be polymerized or attached to solid supports to form solid phases for analysis, catalysis, and separations[3] or attached to proteins to provide radionuclide carriers for medical diagnosis and therapy.[4]

The majority of the synthetic methods to introduce aromatic subunits into azacrown macrocycles are based on the reactions of functional groups which are already attached to the aromatic ring either directly or through a connecting linkage.[5] Aminomethyl groups of the benzylamine type are widely used connectors between aromatic subunits and their nonaromatic chains. Known methods for benzylamine bond formation used in macrocyclization reactions include the alkylation of NHR end functions with benzyl halides or acylation of the diamine intermediates with aromatic diacid chlorides followed by reduction as shown in Scheme 1, part a. Scheme 1, part b shows the preparation of the same type of macrocycles using starting compounds with the interacting groups on the opposite aromatic and nonaromatic parts.

Schiff base formation (Scheme 1, part c) was reported as a ring closure method to synthesize different supramolecular systems.[6] Reduction of the macrocyclic Schiff bases leads to benzyamine connections between the aromatic rings and nonaromatic chains. Methods for benzylamine bond formation shown in Scheme 1, parts a−c, use aromatic building blocks with at least two functionalities. These bifunctional reactants can be difficult to prepare. Moreover, acylation and Schiff base formation each require an additional step after cyclization to convert the amides or Schiff bases to the benzylamines.

Recently, we reported a general method to construct polycyclic phenol-containing structures using a modified Mannich reaction.[7] Interaction of bisphenol **1**, having unoccupied positions *ortho* to the OH groups, with methoxymethyl-substituted derivatives of diazacrown ethers **2** gave direct substitution on the phenol rings by the macrocycle-containing aminomethyl groups (Scheme 1, part d). Formation of benzylamine bonds occurred when the phenols had either electron-donating or electron-withdrawing substituents.[8] This process alleviates the need to functionalize the aromatic fragments after the cyclization step or after attachment of the phenol groups to the azamacrocycle.

[†] Brigham Young University.

[‡] IBC Advanced Technologies, Inc.

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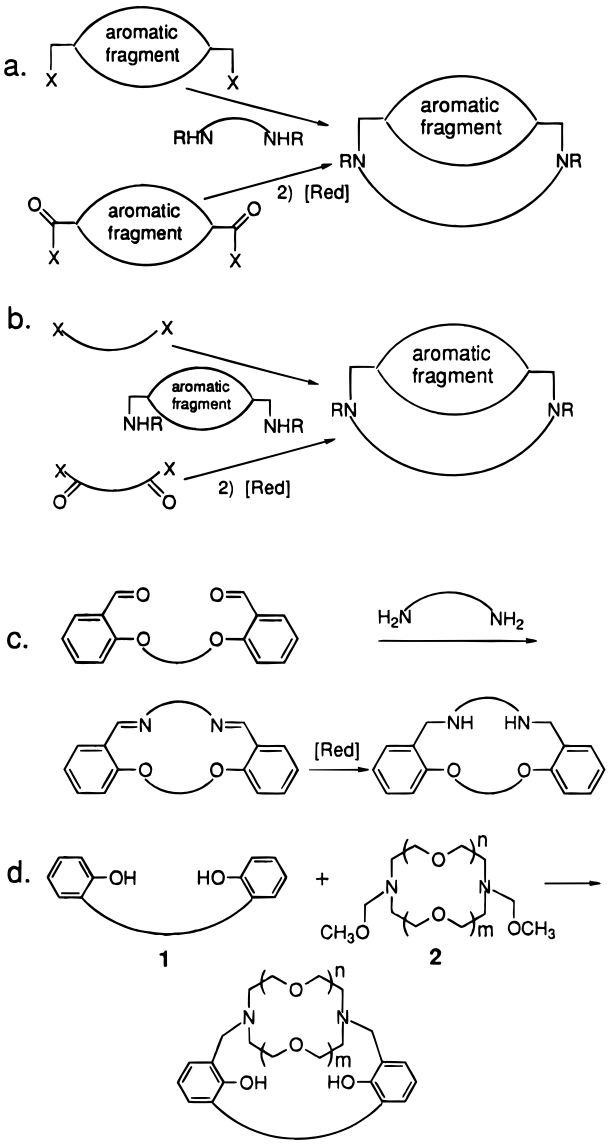
Scheme 1



This modified Mannich condensation method was applied successfully to functionalize the azacrown macrocycles with various ligating groups.[8,9] The intermolecular coordination of *N*,*N*′-bis(methoxymethyl)-diazacrown ethers (intermediates for the modified Mannich condensation) and the appropriate bisphenols allowed the synthesis of complicated bi- and tricyclic molecules in good yields by simple, mostly one-step precedures and easy product isolation steps.[7]

The present study is a continuation of our efforts to develop simple, general methods for the preparation of azamacroheterocycles. We have expanded our methodology (the modified Mannich condensation between phenolic and secondary amine building blocks) to the synthesis of benzoazacrown ethers and new benzocryptands. We have shown the possiblilities of the Mannich reaction to design different molecular topologies using positions *ortho* to the OH phenolic group and the OH groups themselves as interacting sites.

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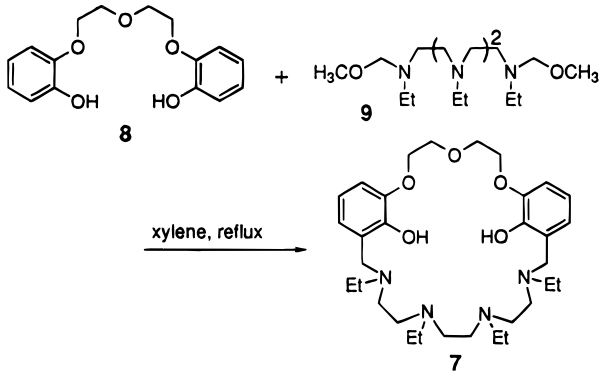
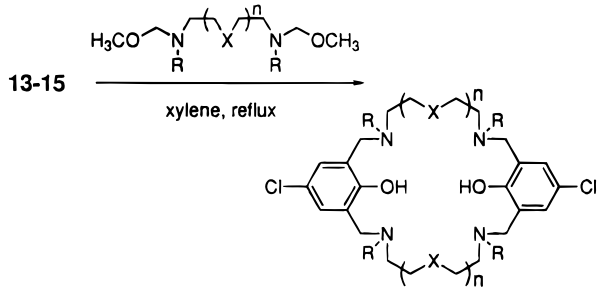
Scheme 2



Scheme 3



10 n = 2, R = C_2H_5, X = NC_2H_5
11 n = 1, R = CH_3, X =O
12 n = 2, R = CH_3, X =O

Results and Discussion

The location of the connecting linkages and OH groups are geometrically favorable for construction of monocylic as well as bicyclic molecular frameworks on the bisphenol **1** baseplate (Scheme 1, part d). There are two ring closure approaches to convert linear building block **1** to a macrocycle. First, the Mannich reaction of **1** with bisaminomethylating reagents to close the ring on positions *ortho* to the OH groups (Scheme 1, part d). Aminomethylation of phenols with methoxymethylamines usually occures in the position *ortho* to the phenolic OH group even if the *para* position is unsubstituted.[8a] Bicyclic cryptands **3**−**6** (Figure 1) were prepared according to this strategy.[7] A similar approach was developed to synthesize the monocyclic benzoazacrown ethers from bisphenols and linear aminomethylating blocks. Benzoazacrown **7** (Scheme 2) was prepared by treating bisphenol **8** with bis(methoxymethyl) derivative **9** in refluxing xylene. Compound **9** was used without isolation after treating the corresponding bis-secondary amine with paraformaldehyde in methanol and evaporating the solvent. The method shown in Scheme 2 allows the preparation of macrocycles containing internal phenolic OH groups and various other structural subunits in the connecting chains. The free *para* positions on the benzo units of the final macrocycles are attractive sites for functionalization because of their high reactivity toward electrophilic aromatic substitution.

Benzoazacrown ethers **10**−**12** were also synthesized by ring closure of bisphenols **13**−**15** on postions *ortho* to the OH groups (Scheme 3). Starting intermediates **13**−**15** were prepared from *p*-chlorophenol, the appropriate secondary diamines, and paraformaldehyde in refluxing aqueous dioxane (Scheme 4). Using a reflux temperature of 100 °C or less[8a] allows only one aminomethyl fragment to be introduced into one *ortho* position. The second substitution to form **10**−**12** requires a higher tempera-

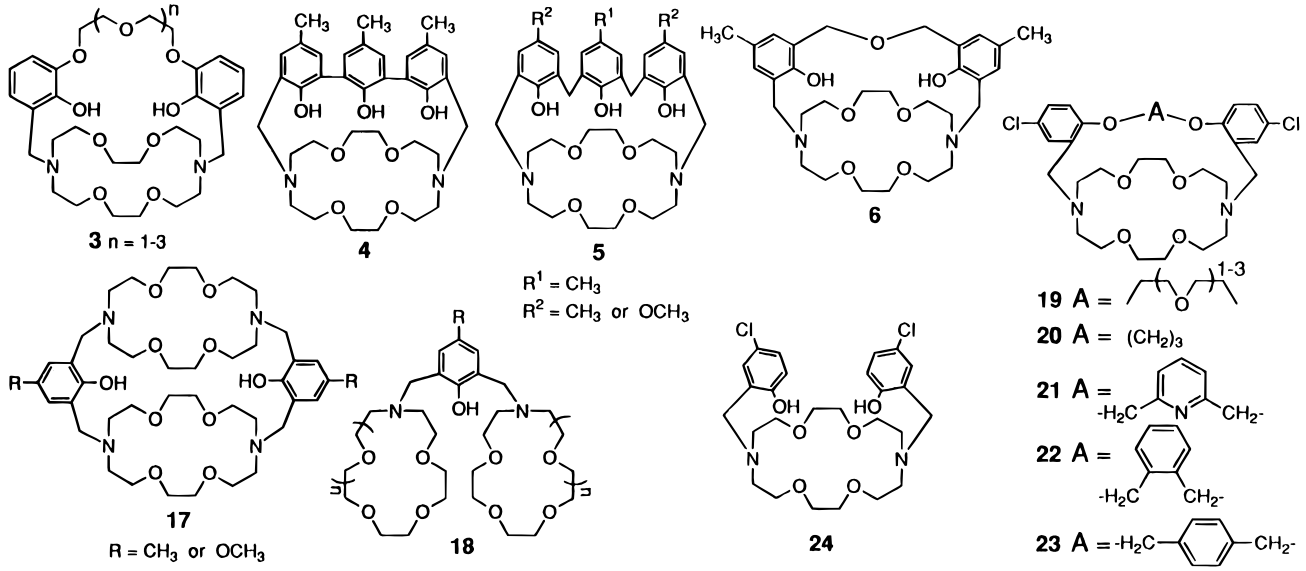
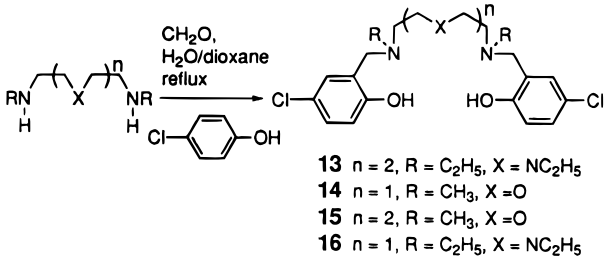
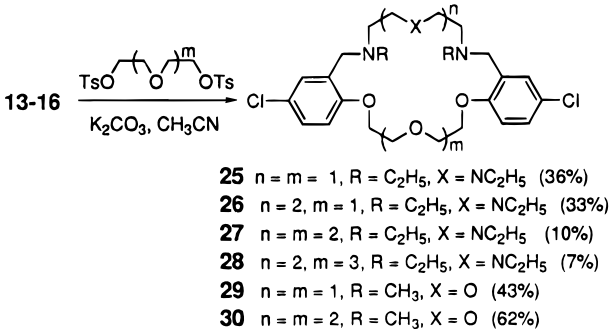


Figure 1.

Scheme 4



Scheme 5



ture (Scheme 3). Refluxing xylene was used as the solvent in the cyclization step to obtain cryptands **17** (Figure 1) according to Scheme 1, part d.[7] Preparation of macrocycles **10**−**12** was performed using similar conditions (treatment of the bisphenol with the bis(methoxymethylamine) in refluxing xylene) (Scheme 3). The 4-chlorophenol group was used in the synthesis of **13**−**16** to avoid *para* substitution of the aromatic ring at high temperature. The different interacting abilities of the starting unsubstituted phenols and the monoaminomethylated phenols allow the controlled preparation of mono-*ortho*- or di-*ortho*-substituted phenols. We already reported the preparation of the bis(azacrown) ethers **18** (Figure 1) using a two-step procedure. The first aminomethyl fragment was introduced into the phenol ring at 80 °C (refluxing CCl_4 or benzene), and the second substitution occurred at 144 °C (refluxing xylene).[10] The above approach allows the synthesis of unsymmetric macrocyclic systems from two different aminomethylating blocks introduced into the phenol ring in a stepwise fashion.

Another method to construct the benzoazamacrocycles using bisphenol intermediates **1** (Scheme 1, part d) includes the synthesis of the bisphenols from phenol and bisaminomethylating building blocks (see Scheme 4) followed by treating the phenolic OH groups with the proper bisalkylating reagents (Scheme 5). A number of benzocryptands (**19**−**23**, Figure 1) have been synthesized from bisphenol **24** and the appropriate ditosylate or benzyl halide.[11] The same reaction conditions (K_2CO_3, CH_3CN, reflux) have been used to prepare benzoazacrown ethers **25**−**30** (Scheme 5) from bisphenols **13**−**16** and ditosylates of the polyethylene glycols. Macrocycles having similar topology were prepared by Lindoy and coworkers by a different process.[6d−f] Salicylaldehyde was first treated with a dihalide followed by condensation with a diamine to form a cyclic diimine which was reduced (Scheme 1, part c). The authors also reversed the process by first treating salicylaldehyde with the diamine followed by the dihalide.[6e] The Mannich condensation (Scheme 4) followed by cyclization of the OH groups in the last step (Scheme 5) shortens Lindoy's procedure for the preparation of monocylcic ligands. It also facilitates the synthesis of three-dimensional benzoazamacrocycles since the required starting intermediates, such as the bisphenols, can be prepared in one high yield step (Scheme 4) in contrast to the several step syntheses for the benzyl dihalides[12] or aromatic diacid chlorides.[13]

A metal ion could be important in these cyclization reactions. Ring closure reactions of bisphenols **13**−**16**

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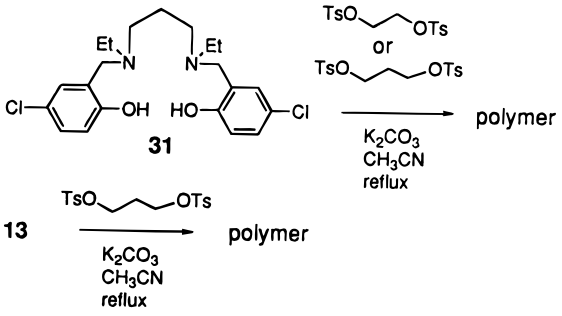
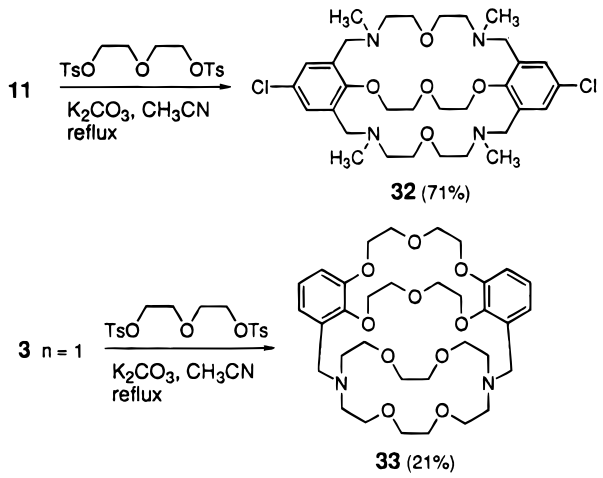
Scheme 6



Scheme 7



(Scheme 5) and **24**[11] were performed using K_2CO_3 as the base. Macrocycles **29** and **30** were isolated in higher yields than **25** and **27**, respectively (Scheme 5). The oxygen atoms in the benzylamine bridge of **29** and **30** provide stronger binding to K^+ than the substituted nitrogen atoms of the benzylamine chains of **25** and **27**. We did not observe cyclization products for the interaction of bisphenols **31** and **13** with the ditosylates of ethylene glycol and 1,3-propanediol, respectively (Scheme 6). Starting materials were not observed at the end of these reactions as determined by TLC. The reactions gave polymeric material as indicated in Scheme 6. The absence of oxygen heteroatoms in the benzylamine linkages of **31** and **13** and in the ditosylates probably preclude a metal ion assisted process. On the other hand, the yields of benzocryptands **19**−**22** (Figure 1) prepared by treating **24** with the appropriate bisalkylating agents and K_2CO_3 in refluxing CH_3CN were 35−71%.[11] Evidently, the heteroatoms of the diazacrown ring and alkylating fragments promote the cyclization of **24** on the metal ion. This could explain the low yield (9%) of **23**[11] since the phenoxy oxygens would be too far away to be efficient in metal ion assisted coordination of the interacting molecular fragments.

The Mannich reaction between phenols and bisamine building blocks followed by ring closure of the phenolic OH groups allowed the preparation of three-dimensional benzoazamacrocycles **32** and **33** (Scheme 7). This strategy can be applied to form different mono- and polycyclic macrocycles by varying the geometric parameters of the introduced chains. The efficiency of the final ring closure step depends on the conformations of the bisphenols and especially on the mutual positions of the cyclizing OH groups. As shown in Scheme 7, compound **32** was obtained in a 71% yield from an intermediate (**11**) which has OH groups in favorable positions for cyclization with diethylene glycol ditosylate. On the other hand, benzocryptand **33** was isolated in a 21% yield probably due to intermolecular strain.

Experimental Section

The ^1H NMR spectra were recorded in $CDCl_3$ at 200 MHz. CI and low-voltage ionization were used to record the mass spectra. Solvents and starting materials were purchased from commercial sources where available. Compound **3** ($n = 1$) was synthesized as described.[8a]

30,31-Dihydroxy-15,18,21,24-tetraethyl-2,5,8-trioxa-15,-18,21,24-tetraazatricyclo[24.3.1.1^{9,13}]untriaconta-1(30),9,-11,13(31),26,28-hexaene (7) (Scheme 2). To a solution of 2.07 g (0.069 mol) of paraformaldehyde in 50 mL of CH_3OH was added 8.9 g (0.034 mol) of 1,4,7,10-tetraethyl-1,4,7,10-tetraazadecane. After the solution was allowed to stand for 15 min, the CH_3OH was evaporated. The residue was added to a solution of bisphenol **8** (10.0 g, 0.034 mol) in 300 mL of xylene. The mixture was stirred under reflux for 24 h, and xylene was evaporated under reduced pressure. The product was isolated by column chromatography on neutral Al_2O_3 using 15/1 $C_6H_5CH_3/CH_3OH$ as eluant to give 0.58 g (3%) of **7** as an oil: ^1H NMR δ 0.96 (t, $J = 7.3$ Hz, 6 H), 1.07 (t, $J = 7.4$ Hz, 6 H), 2.55 (m, 20 H), 3.68 (s, 4 H), 4.10 (m, 8 H), 6.72 (m, 6 H); MS, m/z 573 $[M + 1]^+$. Anal. Calcd for $C_{32}H_{52}N_4O_5$: C, 67.10; H, 9.15. Found: C, 67.27; H, 9.15.

Preparation of 1,10-Bis(5-chloro-2-hydroxybenzyl)-1,4,7,10-tetraethyl-1,4,7,10-tetraazadecane (13) (Scheme 4). A solution of 2.8 g (0.09 mol) of paraformaldehyde in 6 mL of H_2O was added to a solution of 12 g (0.05 mol) of 1,4,7,-10-tetraethyl-1,4,7,10-tetraazadecane in 55 mL of dioxane. After the solution was allowed to stand for for 15 min, 30 g (0.23 mol) of 4-chlorophenol was added. The mixture was stirred under reflux for 120 h. Dioxane was evaporated under reduced pressure. The residue was dissolved in a saturated aqueous solution of tartaric acid, and the excess of 4-chlorophenol was extracted four times with 50-mL portions of ethyl acetate. The water phase was neutralized with Na_2CO_3 and brought to pH 8 with $NaHCO_3$. The product was extracted four times with 100-mL portions of $CHCl_3$. The combined $CHCl_3$ phases were separated, dried (Na_2SO_4), and evaporated. The crude material was purified on silica gel using 1/1 $CHCl_3$/THF as eluant to give 10.5 g (42%) of **13** as an oil: ^1H NMR δ 0.99 (t, $J = 7.4$ Hz, 6 H), 1.02 (t, $J = 7.5$ Hz, 6H), 2.52 (m, 20 H), 3.62 (s, 4 H), 6.89 (m, 6 H), 10.69 (s, 2 H); MS, m/z 540 $[M + 1]^+$. Anal. Calcd for $C_{28}H_{44}Cl_2N_4O_2$: C, 62.33; H, 8.22. Found: C, 62.47; H, 8.12.

1,7-Bis(5-chloro-2-hydroxybenzyl)-1,7-dimethyl-4-oxa-1,7-diazaheptane (14) (Scheme 4). Compound **14** was obtained in the same manner as above for **13** from 7.5 g (0.06 mol) of 1,7-dimethyl-4-oxa-1,7-diazaheptane, 3.41 g (0.11 mol) of paraformaldehyde, and 40.11 g (0.31 mol) of 4-chlorophenol. **14** (20.6 g, 88%) was isolated after column chromatography as an oil: ^1H NMR δ 2.33 (s, 6 H), 2.70 (t, $J = 5.8$ Hz, 4 H), 3.60 (t, $J = 5.8$ Hz, 4 H), 3.70 (s, 4 H), 7.10 (m, 6 H), 10.2 (s br, 2 H); MS, m/z 414 $[M + 1]^+$. Anal. Calcd for $C_{20}H_{26}Cl_2N_2O_3$: C, 58.12; H, 6.34. Found: C, 58.33; H, 6.43.

1,10-Bis(5-chloro-2-hydroxybenzyl)-1,10-dimethyl-4,7-dioxa-1,10-diazadecane (15) (Scheme 4). Compound **15** was obtained in the same manner as above for **13** from 7.5 g (0.04 mol) of 1,10-dimethyl-4,7-dioxa-1,10-diazadecane, 2.56 g (0.08 mol) of paraformaldehyde, and 30.1 g (0.23 mol) of 4-chlorophenol. **15** (18 g, 92%) was isolated after column chromatography as an oil: ^1H NMR δ 2.30 (s, 6 H), 2.68 (t, $J = 5.7$ Hz, 4 H), 3.65 (m, 12 H), 7.00 (m, 6 H), 10.23 (s br, 2 H); MS, m/z 458 $[M + 1]^+$. Anal. Calcd for $C_{22}H_{30}Cl_2N_2O_4$: C, 57.77; H, 6.61. Found: C, 57.93, H, 6.40.

1,7-Bis(5-chloro-2-hydroxybenzyl)-1,4,7-triethyl-1,4,7-triazaheptane (16) (Scheme 4). Compound **16** was obtained in the same manner as above for **13** from 9.4 g (0.05 mol) of 1,4,7-triethyl-1,4,7-triazaheptane, 3.0 g (0.1 mol) of paraformaldehyde, and 32 g (0.25 mol) of 4-chlorophenol. **16** (11.7 g, 50%) was isolated after column chromatography as an oil: ^1H NMR δ 1.01 (t, $J = 7.4$ Hz, 3 H), 1.06 (t, $J = 7.5$ Hz, 6 H), 2.55 (m, 14 H), 3.65 (s, 4 H), 6.91 (m, 6 H), 10.73 (s, 2 H); MS, m/z

469 $[M + 1]^+$. Anal. Calcd for $C_{24}H_{35}Cl_2N_3O_2$: C, 61.53; H, 7.53. Found: C, 61.63; H, 7.46.

16,33-Dichloro-35,36-dihydroxy-3,6,9,12,20,23,26,29-octaethyl-3,6,9,12,20,23,26,29-octaazatricyclo[29.3.1.1^{14,18}]hexatriaconta-1(35),14,16,18(36),31,33-hexaene (10) (Scheme 3). Compound **10** was synthesized as above for **7** from 0.24 g (8 mmol) of paraformaldehyde, 1.0 g (4 mmol) of 1,4,7,10-tetraethyl-1,4,7,10-tetraazadecane, and 2.1 g (4 mmol) of bisphenol **13**. Crude **10** was purified on silica gel with 15/1 and 4/1 CH_3OH/NH_4OH as eluants. The solvents were evaporated under reduced pressure. The residue was dissoved in 100 mL of benzene, and the solution was dried (Na_2SO_4) and evaporated to give 1.26 g (40%) of **10** as an oil: ^{1}H NMR δ 1.00 (t, J = 7.5 Hz, 12 H), 1.18 (t, J = 7.5 Hz, 12 H), 2.56 (m, 40 H), 3.62 (s, 8 H), 7.03 (s, 4 H); MS, m/z 412 $[M/2 + 1]^+$. Anal. Calcd for $C_{44}H_{78}Cl_2N_8O_2$: C, 64.29; H, 9.56. Found: C, 63.98; H, 9.36.

13,27-Dichloro-29,30-dihydroxy-3,9,17,23-tetramethyl-6,20-dioxa-3,9,17,23-tetraazatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11,13,15(30),25,27-hexaene (11) (Scheme 3). Compound **11** was synthesized as above for **7** from 1.14 g (0.038 mol) of paraformaldehyde, 2.5 g (0.019 mol) of 1,7-dimethyl-4-oxa-1,7-diazaheptane, and 7.84 g (0.019 mol) of bisphenol **14**. After column chromatography on silica gel using 40/1 $MeOH/NH_4OH$ as eluant, the solvents were evaporated and the residue was dissolved in 150 mL of benzene. The solution was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. To the residue was added 70 mL of EtOEt. The pure product was precipitated, filtered, and washed with EtOEt to give 1.1 g (10%) of **11** as a solid: mp 150−152 °C; ^{1}H NMR δ 2.3 (s, 12 H), 2.68 (t, J = 5.6 Hz, 8 H), 3.55 (t, J = 5.6 Hz, 8 H), 3.60 (s, 8 H), 6.99 (s, 4 H); MS, m/z 570 $[M + 1]^+$. Anal. Calcd for $C_{28}H_{42}Cl_2N_4O_4$: C, 59.04; H, 7.33. Found: C, 59.05; H, 7.32.

16,33-Dichloro-35,36-dihydroxy-3,12,20,29-tetramethyl-6,9,23,26-tetraoxa-3,12,20,29-tetraazatricyclo[29.3.1.1^{14,18}]hexatriaconta-1(35),14,16,18(36),31,33-hexaene (12) (Scheme 3). Compound **12** was prepared as above for **7** from 0.85 g (0.028 mol) of paraformaldehyde, 2.5 g (0.014 mol) of 1,10-dimethyl-4,7-dioxa-1,10-diazadecane, and 6.49 g (0.014 mol) of bisphenol **15** to give 1.8 g (20%): mp 108−110 °C; ^{1}H NMR δ 2.25 (s, 12 H), 2.67 (t, J = 5.7 Hz, 8 H), 3.64 (m, 24 H), 7.02 (s, 4 H); MS, m/z 658 $[M + 1]^+$. Anal. Calcd for $C_{32}H_{50}Cl_2N_4O_6$: C, 58.44; H, 7.66. Found: C, 58.52; H, 7.67.

12,26-Dichloro-16,19,22-triethyl-2,5,8-trioxa-16,19,22-triazatricyclo[22.4.0.0^{9,14}]octacosa-1(24),9,11,13,25,27-hexaene (25) (Scheme 5). A mixture of 1.45 g (3 mmol) of **16,** 1.28 g (3 mmol) of diethylene glycol ditosylate, 8.5 g (0.06 mol) of K_2CO_3, and 50 mL of CH_3CN was stirred under reflux for 72 h. The solvent was evaporated under reduced pressure, and 100 mL of hot H_2O was added to the residue. After being cooled to rt, the mixture was extracted three times with 50-mL portions of $CHCl_3$, and the organic phase was separated, dried (Na_2SO_4), and evaporated. The crude product was purified on neutral Al_2O_3 using 20/1 $CHCl_3$/THF as eluant to give 0.6 g (36%) of **25** as an oil: ^{1}H NMR δ 1.02 (t, J = 7.5 Hz, 3 H), 1.08 (t, J = 7.6 Hz, 6 H), 2.51, (m, 14 H), 3.6 (s, 4 H), 3.57 (t, J = 5.0 Hz, 4 H), 4.14 (t, J = 5.0 Hz, 4 H), 7.07 (m, 6 H); MS, m/z 539 $[M + 1]^+$. Anal. Calcd for $C_{28}H_{41}Cl_2N_3O_3$: C, 62.45; H, 7.67. Found: C, 62.28; H, 7.59.

12,29-Dichloro-16,19,22,25-tetraethyl-2,5,8-trioxa-16,19,22,25-tetraazatricyclo[25.4.0.0^{9,14}]untriaconta-1(27),9,11,13,28,30-hexaene (26) (Scheme 5). Compound **26** was synthesized in the same manner as above for **25** from 1.58 g (3 mmol) of **13,** 1.21 g (3 mmol) of diethylene glycol ditosylate, and 8.3 g (0.06 mol) of K_2CO_3. **26** (0.6 g, 33%) was isolated as an oil after column chromatography on Al_2O_3 using 10/1 $CHCl_3$/THF as eluant: ^{1}H NMR δ 1.04 (m, 12 H), 2.53 (m, 20 H), 3.59 (s, 4 H), 3.97 (t, J = 5.1 Hz, 4 H), 4.12 (t, J = 5.1 Hz, 4 H), 7.10 (m, 6 H); MS, m/z 610 $[M + 1]^+$. Anal. Calcd for $C_{32}H_{50}Cl_2N_4O_3$: C, 63.04; H, 8.27. Found: C, 62.98; H, 8.16.

15,32-Dichloro-19,22,25,28-tetraethyl-2,5,8,11-tetraoxa-19,22,25,28-tetraazatricyclo[28.4.0.0^{12,17}]tetratriaconta-1(30),12,14,16,31,33-hexaene (27) (Scheme 5). Compound **27** was obtained in the same manner as above for **25** from 1.78 g (3.3 mmol) of **13**, 1.51 g (3.3 mmol) of triethylene glycol ditosylate, and 9.1 g (0.066 mol) of K_2CO_3. **27** (0.22 g, 10%) was isolated as an oil after column chromatography on Al_2O_3 using 3/1 $CHCl_3$/THF as eluant: ^{1}H NMR δ 0.99 (t, J = 7.3 Hz, 6 H), 1.02 (t, J = 7.4 Hz, 6 H), 2.52 (m, 20 H), 3.54 (s, 4 H), 3.78 (s, 4 H), 3.88 (t, J = 5.5 Hz, 4 H), 4.10 (t, J = 5.5 Hz, 4 H), 7.08 (m, 6 H); MS, m/z 653 (M^+). Anal. Calcd for $C_{34}H_{54}Cl_2N_4O_4$: C, 62.47; H, 8.33. Found: C, 62.57; H, 8.12.

18,35-Dichloro-22,25,28,31-tetraethyl-2,5,8,11,14-pentaoxa-22,25,28,31-tetraazatricyclo[31.4.0.0^{15,20}]heptatriaconta-1(33),15,17,19,34,36-hexaene (28) (Scheme 5). Compound **28** was obtained in the same manner as above for **25** from 1.95 g (3.6 mmol) of **13**, 1.82 g (3.6 mmol) of tetraethyelene glycol ditosylate, and 10 g (0.072 mol) of K_2CO_3. **28** (0.18 g, 7%) was isolated as an oil after column chromatography on Al_2O_3 using THF as eluant: ^{1}H NMR δ 1.00 (t, J = 7.5 Hz, 6 H), 1.03 (t, J = 7.4 Hz, 6 H), 2.50 (m, 20 H), 3.55 (s, 4 H), 3.69 (s, 8 H), 3.82 (t, J = 5.2 Hz, 4 H), 4.06 (t, J = 5.2 Hz, 4 H), 7.06 (m, 6 H); MS, m/z 698 $[M + 1]^+$. Anal. Calcd for $C_{36}H_{58}Cl_2N_4O_5$: C, 61.97; H, 8.38. Found: C, 61.81; H, 8.22.

12,26-Dichloro-16,22-dimethyl-2,5,8,19-tetraoxa-16,22-diazatricyclo[22.4.0.0^{9,14}]octacosa-1(24),9,11,13,25,27-hexaene (29) (Scheme 5). Compound **29** was synthesized as above for **25** from 2.1 g (5 mmol) of **14**, 2.11 g (5 mmol) of diethylene glycol ditosylate, and 13.8 g (0.1 mol) of K_2CO_3. **29** (1.06 g, 43%) was isolated as an oil after column chromatography on Al_2O_3 using 5/1 $CHCl_3$/THF as eluant: ^{1}H NMR δ 2.25 (s, 6 H), 2.75 (t, J = 5.8 Hz, 4 H), 3.61 (s, 4 H), 3.69 (t, J = 5.8 Hz, 4 H), 3.98 (t, J = 5.5 Hz, 4 H), 4.14 (t, J = 5.5 Hz, 4 H), 6.98 (m, 6 H); MS, m/z, 484 $[M + 1]^+$. Anal. Calcd for $C_{24}H_{32}Cl_2N_2O_4$: C, 59.63; H, 6.67. Found: C, 59.50; H, 6.53.

15,32-Dichloro-19,28-dimethyl-2,5,8,11,22,25-hexaoxa-19,28-diazatricyclo[28.4.0.0^{12,17}]tetratriaconta-1(30),12,14,16,31,33-hexaene (30) (Scheme 5). Compound **30** was obtained in the same manner as above for **25** from 2.27 g (5 mmol) of **15**, 2.28 g (5 mmol) of triethylene glycol ditosylate, and 13.8 g (0.1 mol) of K_2CO_3. **30** (1.78 g, 62%) was isolated after column chromatography on Al_2O_3 using 1/1 $CHCl_3$/THF as eluant: mp 75−78 °C; ^{1}H NMR δ 2.23 (s, 6 H), 2.75 (t, J = 5.7 Hz, 4 H), 3.69 (m, 16 H), 3.85 (t, J = 5.6 Hz, 4 H), 4.08 (t, J = 5.6 Hz, 4 H), 6.95 (m, 6 H); MS, m/z 572 $[M +1]^+$. Anal. Calcd for $C_{28}H_{40}Cl_2N_2O_6$: C, 58.84; H, 7.05. Found: C, 59.00; H, 7.22.

13,27-Dichloro-3,9,17,23-tetramethyl-6,20,30,33,36-pentaoxa-3,9,17,23-tetraazatetracyclo[23.3.1.7^{29,37}.1^{11,15}]heptatriaconta-1(28),11,13,15(37),25,27-hexaene (32) (Scheme 7). Compound **32** was obtained as described above for **25** from 1.07 g (2 mmol) of crown compound **11,** 0.78 g (2 mmol) of diethylene glycol ditosylate, and 5.5 g (40 mmol) of K_2CO_3. Cryptand **32** (0.85 g, 71%) was isolated as an oil after column chromatography on silica gel using 40/1 and 20/1 $MeOH/NH_4OH$ as eluants: ^{1}H NMR δ 2.24 (s, 12 H), 2.70 (t, J = 5.7 Hz, 8 H), 3.55 (m, 16 H), 3.87 (t, J = 5.1 Hz, 4 H), 4.20 (t, J = 5.1 Hz, 4 H), 7.20 (s, 4 H); MS, m/z 640 $[M + 1]^+$. Anal. Calcd for $C_{32}H_{48}Cl_2N_4O_5$: C, 60.09; H, 7.56. Found: C, 60.12; H, 7.66.

9,12,15,26,29,34,37,40,43,46-Decaoxa-1,23-diazapentacyclo[21.8.8.7^{7,17}.0^{16,21}.0^{3,8}]hexatetraconta-3,5,7,16,18,20-hexaene (33) (Scheme 7). Compound **33** was obtained as described above for **25** from 1 g (1.7 mmol) of cryptand **3** (n = 1), 0.72 g (1.7 mmol) of diethylene glycol ditosylate, and 5 g (0.035 mol) of K_2CO_3. Cryptand **33** (0.24 g, 21%) was isolated as a solid (mp 147−150 °C) after column chromatography on neutral Al_2O_3 using 40/1 MePh/MeOH as eluant: ^{1}H NMR δ 2.70 (m, 8 H), 3.53 (m, 20 H), 4.14 (m, 16 H), 6.83 (m, 6 H); MS, m/z 647 $[M + 1]^+$. Anal. Calcd for $C_{34}H_{50}N_2O_{10}$: C, 63.14; H, 7.79. Found: C, 63.27; H, 7.68.

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