Synthesis of New Pyridinoazacrown Ethers Containing Aromatic and Heteroaromatic Proton Ionizable Substituents

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Methods for the synthesis of pyridinocrowns functionalized with various proton ionizable groups have been elaborated. Sixteen new ligands containing pyridine rings as part of the macrocycle or as a side arm have been prepared. Different interactive abilities of the OH and NH functions of 3,9-dioxa-6-azaundecane-1,11-diol (**3**) in strong base allowed the synthesis of pyridinoazacrowns **1** and **2** by cyclization with 2,6-bis((tosyloxy)methyl)pyridine (**4**) and THP-protected 4-hydroxy-2,6-bis(tosyloxy)methyl)pyridine (**5**). Pyridinoazacrown **1** was functionalized with different proton ionizable side arms by treatment first with formaldehyde in methanol to form the *N*-methoxymethyl derivative **6** and then treating **6** with 5-chloro-8-hydroxyquinoline or the appropriate substituted phenol. Pyridinoaza-18-crown-6 ligands containing *p*-methylphenol (**7**), *p*-methoxyphenol (**8**), *p*-chlorophenol (**9**), *p*-fluorophenol (**10**), *p*-cyanophenol (**11**), 2-formyl-4-bromophenol (**12**), or 5-chloro-8-hydroxyquinoline (**13**) groups were prepared by this process. Pyridinoazacrowns **1** and **2** were alkylated with 2-hydroxy-5-nitrobenzyl chloride or 5-chloro-8-methoxy-2-(bromomethyl)quinoline followed by removal of the protecting groups to form *p*-nitrophenol- and 5-chloro-8-hydroxy-2-quinolinyl-substituted ligands (**16, 18**, and **21**). Macrocycles **22** and **23** containing proton ionizable triazole and phenol functions inside the macrocyclic cavity and a pyridine side arm were prepared by cyclization of the appropriate dihalide with 6-(2′-pyridylmethyl)-3,9-dioxa-6-azaundecane-1,11-diol followed by cleavage of the THP or methoxy protecting groups. Preliminary complexation data show that the phenol-substituted pyridinoaza-18-crown-6 ligands form strong complexes with various metal cations and exhibit high selectivity toward Ag^+. Macrocycle **16** containing a *p*-nitrophenol substituent formed a complex with benzylamine. The crystal structures for **16** and its benzylamine complex are also given here.

Introduction

Macrocyclic ethers with pyridine and other nitrogen-containing heterocyclic subunits are of interest because of their ability to form strong and selective interactions with various charged and neutral guest molecules. Heterocyclic groups incorporated in the macrocyclic ring provide rigidity and are able to participate in complexation through their soft nitrogen donor atoms. Pyridine-containing macrocycles are efficient complexing agents for metal cations.[1] They also displayed high log *K* values in complexation with ammonium salts.[1,2] The (*S*) and (*R*) isomers of chiral organic ammonium salts were recognized by chiral pyridino-18-crown-6 ligands.[3] Efficient separation of organic ammonium salt enantiomers was achieved when such chiral pyridine-containing macrocycles were attached to a solid support.[4] The attachment of pyridine moieties as side arms resulted in a number of lariat azacrown ethers which function as selective cation carriers for membrane transport.[5]

A great improvement in complexation ability and selectivity has been observed when proton ionizable units were attached to the crown ring as side arms or introduced inside the macrocyclic cavity. Proton ionizable crown ethers also alleviate the need to have hard anions (chloride, nitrate, sulfate) to cotransport with the metal cations across bulk liquid and liquid–surfactant membranes. Moreover the difference in UV or fluorescence spectra of protonated and deprotonated forms of the above macrocycles allows spectrophotometric determination of complexed cations. Phenolic groups are widely used proton ionizable substituents.[6] Phenol-containing lariat azacrown ethers have shown the ability to selectively extract cations from water into an organic phase. Many of those compounds were found to be efficient chromogenic reagents[7] for Li^+, K^+, Ca^{2+}, Sr^{2+}, and Ba^{2+}. Crown ethers containing the triazole subcyclic unit have also been shown to have a strong affinity toward metal cations and ammonium salts.[1,8] As a result of the acidity

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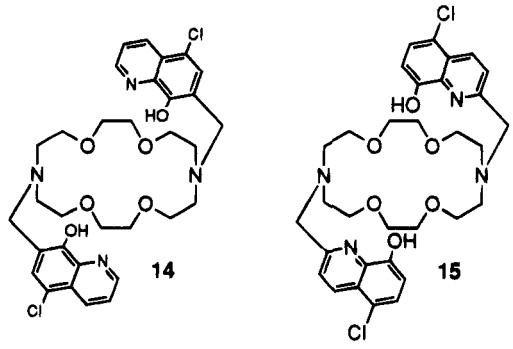


Figure 1. Macrocycles **14** and **15**.

of the triazole NH function, the triazolodiester crown ethers were able to form complexes with amines.[8b]

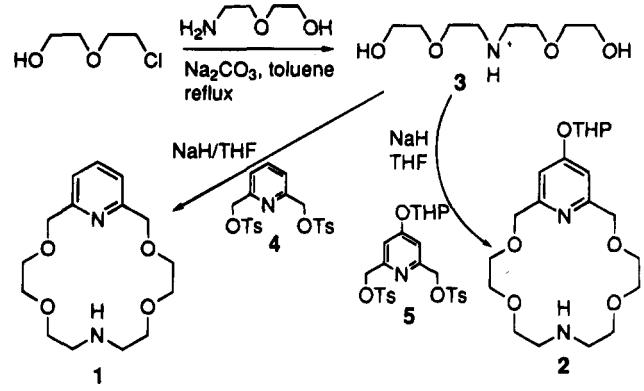
We now report new synthetic methods to combine the soft pyridine complexation site with proton ionizable (phenol and triazole) groups for cooperative interaction with cations or other complexed guest molecules. We are especially interested in preparation of pyridinocrowns functionalized by analytical chelating reagents. One of those reagents, 5-chloro-8-hydroxyquinoline, has already been attached to diaza-18-crown-6 and its 21- and 24-membered analogues.[9] Those diazacrowns (**14** and **15**, Figure 1) exhibited unique selectivities for Mg^{2+}, K^+, Ba^{2+}, and Cu^{2+} over other metal ions. In this paper, the preparation of a number of pyridino-, pyridono- and triazolocrown ethers containing various proton ionizable substituents is described as well as initial studies on their complexation behavior. Complete details of their interactions with metal and organic ammonium cations will be reported at a later date.

Results and Discussion

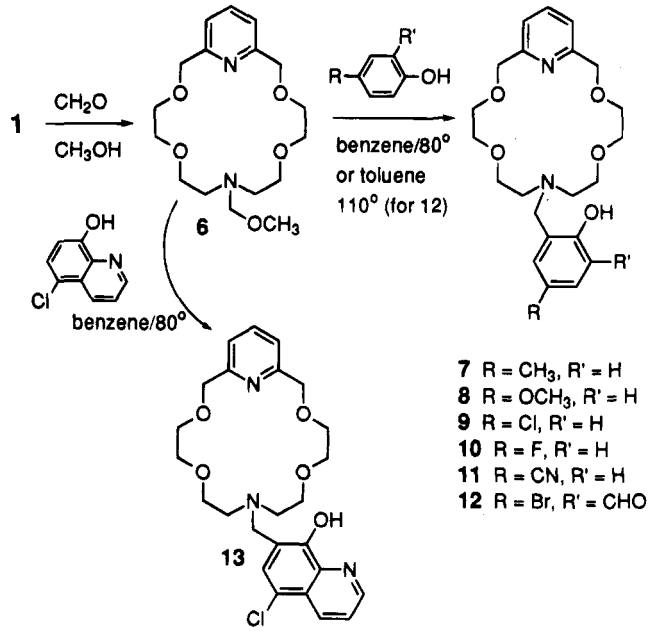
The most convenient way to functionalize the pyridinoazacrowns with proton ionizable side arms is to attach those side arms to the ring NH groups. Secondary nitrogens are able to undergo nucleophilic substitution with alkylating agents bearing protected or unprotected proton ionizable units.[7g,10] Another possibility is the conversion of secondary amines to (methoxymethyl)-amines, which are active electrophilic reagents in the Mannich reaction and react readily with electron rich aromatics such as phenols.[11]

Unsubstituted pyridinoazacrown **1** and its THP-protected hydroxypyridine analogue **2** were synthesized by treating diol **3** with ditosylates **4** and **5**, respectively (Scheme 1). The greater basicity of the primary OH groups in strongly alkaline media (NaH, THF) allowed the preparation of macrocycles **1** and **2** in yields of 32% and 30%, respectively, avoiding the necessity of protecting the NH function. The same conditions were also used for the cyclization of chiral secondary alcohol groups in the presence of an NH function.[12] Starting diol **3** was

Scheme 1. Preparation of Macrocycles 1 and 2



Scheme 2. Preparation of Macrocycles 6–13



obtained by treating β-(chloroethoxy)ethanol with a large excess of 2-(2-aminoethoxy)ethanol in refluxing toluene using Na_2CO_3 as a base.

We have reported the synthesis of monoazacrown ethers and bis(monoazacrown ether)s functionalized with different phenolic groups.[11,13] The modified Mannich reaction is a superior way to attach phenolic units with electron donating as well as electron withdrawing substituents to the azamacrocyclic ring. Methoxymethyl derivative **6** was prepared through the condensation of **1** with paraformaldehyde in dry methanol (Scheme 2). Following the evaporation of the solvent, the product was used without further purification. **6** was treated with various phenols in refluxing benzene to give the proton ionizable pyridinoazacrowns **7–11** (Scheme 2). In a similar fashion 4-bromosalicylaldehyde and 5-chloro-8-hydroxyquinoline could be attatched to the macrocycle to give **12** and **13**, respectively (Scheme 2). These side-arm substituents were chosen as a result of their known ability to form strong complexes with metal cations. For example, 8-hydroxyquinoline (oxine) is a well-known extraction, photometric, and precipitation reagent.[14] To improve its selectivity, proper pH and masking agents are necessary. CPK models show that the pyridine ring and side arms in **12** and **13** are in suitable positions for

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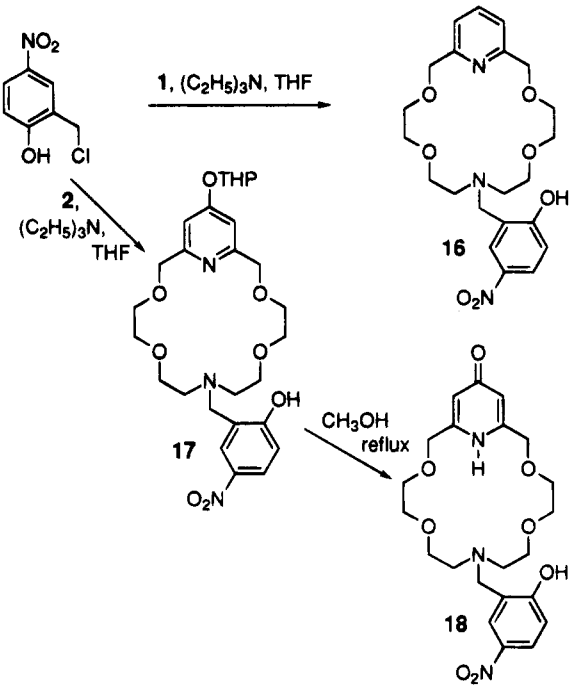
cooperative interaction with cations. Such a cooperative interaction and the conformational restriction arising from the preorganization of the macrocycle could increase the recognition ability of these functionalized pyridinocrowns as compared to **1** and the free salicylaldehyde or 8-hydroxyquinoline chelating reagents. An increase in the stability and selectivity of metal ion complexation has been demonstrated previously with the 5-chloro-8-hydroxyquinoline-substituted diazacrowns **14** and **15** (Figure 1).[9] 5-Chloro-8-hydroxyquinoline itself does not interact with K^+ and Mg^{2+} in methanol as shown by a calorimetric titration.[9] However, **14** interacts strongly with those cations resulting in log K values of 3.39 and 6.73, respectively. The reaction of **15** with K^+ has a log K value of 6.61. In addition, when compared with the parent diaza-18-crown-6, the 5-chloro-8-hydroxyquinoline-substituted crowns **14** and **15** show larger binding constants in methanol for most metal cations studied.[9]

We tried to attach a salicylaldehyde-derived side arm to the azacrown ring by derivatization of (methoxymethyl)azacrown **6**, but no reaction occurred in either refluxing CCl_4 or benzene.[13] This may be a result of intramolecular binding in salicylaldehyde (and *o*-nitrophenol which also does not react) which prevents the phenolic proton from being involved in the formation of the six-membered transition state necessary for aminomethylation under these conditions.[13] Using para-substituted 5-bromosalicylaldehyde and toluene as the solvent to allow for a higher reaction temperature, pyridinoazacrown **12** (Scheme 2) could be isolated in a 61% yield. Generally, blocking the para position in the starting phenol is not necessary for the selective aminomethylation of the ortho position.[11,15] Even unsubstituted phenol gave high yields of *o*-aminomethylation due to formation of the six-membered transition state. However, products of para substitution are also possible especially when high temperature is applied or the phenolic substrates contain groups which promote para substitution. For these reasons, we used 5-bromosalicylaldehyde and 5-chloro-8-hydroxyquinoline where the position para to the OH group is blocked.

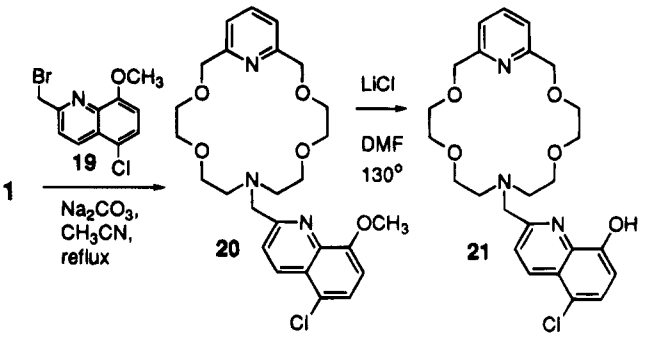
Alkylation of the NH functions of azacrowns with active benzylic halides is another way to attach a proton ionizable substituent onto the macrocyclic ring. Pyridino- and THP-protected hydroxypyridinoazacrown ethers **16** and **17**, containing *p*-nitrophenol substituents, were synthesized by treating macrocycles **1** and **2**, respectively, with 2-hydroxy-5-nitrobenzyl chloride in THF using triethylamine as the base (Scheme 3). The THP protecting group of **17** was cleaved by refluxing in methanol. In this case, the nitrophenol group is acidic enough to facilitate the deprotection reaction.

Lariat macrocycles **14** and **15** (Figure 1) having diazacrown units in the 2- and 7-positions of 5-chloro-8-hydroxyquinoline, respectively, exhibit quite different affinities toward alkali and transition metal cations.[9] For ligand **14**: log K_{Na^+} = 2.89; log K_{K^+} = 3.39; log $K_{Cu^{2+}}$ = 9.83 in methanol at 25 °C. For ligand **15**: log K_{Na^+} = 3.74, log K_{K^+} = 6.61, log $K_{Cu^{2+}}$ = 4.0. Thus, changing the 8-hydroxyquinoline attachment position to the crown moieties dramatically affects the selectivity of complex formation. Alkylation of **1** with 5-chloro-8-methoxy-2-(bromomethyl)quinoline (**19**) followed by cleavage of the methyl protecting group with LiCl in DMF at 130 °C gave ligand **21** (Scheme 4). Compound **21** is isomeric with **13**,

Scheme 3. Preparation of Nitrophenol-Substituted Macrocycles 16–18



Scheme 4. Preparation of Macrocycles 20 and 21



the only difference being the position of attatchment of the hydroxyquinoline to the pyridinoazacrown. Such a structural variation has been shown to have a dramatic effect on stability and selectivity of complexation as mentioned above.

The synthesis of compounds **22** and **23** containing a pyridine pendant arm demonstrates another approach for introducing pyridine substituents on the macrocyclic ring (Scheme 5). The pyridine pendant arms were attached to the aliphatic nitrogen before cyclization. Compounds **22** and **23** contain soft pyridine complexation sites outside the macrocycle and proton ionizable subunits (triazole and *p*-cresol) as part of the cavity. Ligand **23** was synthesized to allow a comparison of its binding properties with those of compound **7** (which contains pyridine as part of the macroring and *p*-cresol as a substituent). This allows an investigation of the influence of the position of the pyridine and phenolic units within these compounds on their complexation behavior. Starting diol **24** was prepared by alkylation of **3** with 2-picolyl chloride hydrochloride in the presence of Na_2CO_3 as a base. Macrocycles **25** and **26** were obtained by cyclization of **24** with dihalides **27** and **28**, respectively, using NaH as the base (Scheme 5). The THP protecting group of **25** was cleaved in methanol saturated with HCl. The methyl protecting group of **26** was removed by LiI in refluxing pyridine.[16]

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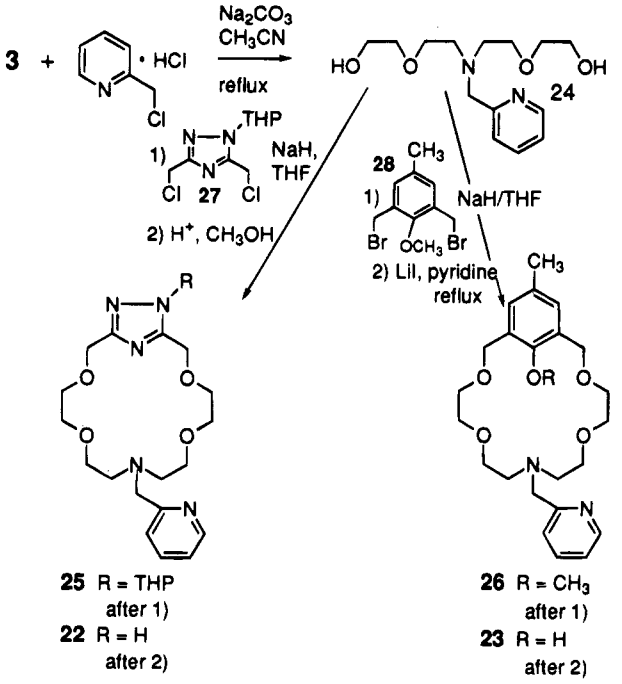
Scheme 5. Preparation of Pyridine-Substituted Macrocycles 22 and 23



Preliminary experiments show that these phenol-substituted pyridinoaza-18-crown-6 ligands exhibit strong interactions with metal cations. The log K values for the interaction of various cations with **1**, **7**–**9**, and **16** were measured in methanol at 25 °C using titration calorimetry.[17] Unsubstituted ligand **1** shows very weak interaction with Na^+, while the interaction of Na^+ with **7**–**9** and **16** gave log K values of 3.49 ± 0.05, 3.58 ± 0.04, 3.29 ± 0.04, and 3.06 ± 0.03, respectively. It is evident that introduction of the phenolic lariat group greatly improves complexation of these ligands with Na^+. These preliminary data also indicate that the presence of electron donating groups para to the phenolic OH lead to the formation of more stable complexes. Similar results were observed for interactions with K^+ where the log K for **8** (3.62 ± 0.03) is greater than that for **16** (3.17 ± 0.04). In addition, ligands **7**–**9** and **16** form very strong complexes with Ag^+ with log K values greater than 8. *p*-Nitrophenol-substituted **16** also formed a complex with benzylamine. Ligands **7**–**9** did not interact with benzylamine, possibly as a result of the weaker acidity of the phenolic groups. Complexation studies for these new lariat pyridinoazacrown ethers are in progress and will be reported in more detail at a later date.

The crystal structures of **16** and its benzylamine complex are shown in Figures 2 and 3, respectively. The crystal structures reveal that the diaza-18-crown-6 ring in **16** is somewhat disorganized. The rigid pyridine causes the crown ring to be strained, which is evident in the disorder of several atoms of that ring. It was possible to resolve the disorder for C5, C6, O13, and O16. For clarity, the figure shows only one of each of two half atoms at the disordered atom sites. The lariat arm does not lie over the cavity, but instead the phenol hydrogen

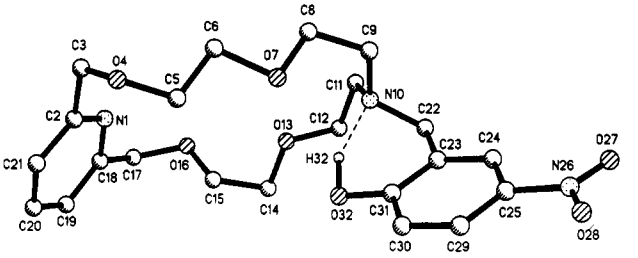


Figure 2. Computer drawing of **16** with atom labels. All hydrogen atoms except H32 are omitted for clarity.

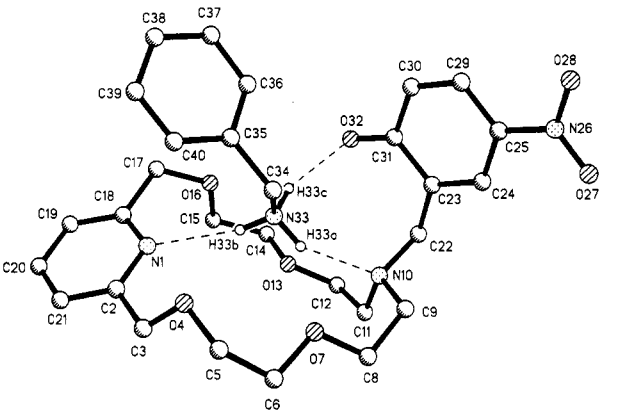


Figure 3. Computer drawing of the **16**–benzylamine complex. All hydrogen atoms except H33a, H33b, and H33c are omitted for clarity.

forms a hydrogen bond with N10. The dihedral angle between the least-squares plane of the donor atoms of the crown ring and the plane of the nitrophenol ring is 50.7°. The host molecule has the potential of donating the phenol proton to a benzylamine guest. As a result, the host becomes an anion and the guest a benzylammonium cation. This is significant in membrane transport because the complex is neutral and thus its transport is not conditional on the transport of an anion.

The host undergoes rearrangement during the complexation process with benzylamine as the two crown nitrogen atoms, which were on opposite sides of the least-squares plane of the ring in the uncomplexed host, are now on the same side of the ring (Figures 2 and 3). The crown nitrogen atoms are now in position to be acceptor atoms for hydrogen bonds formed with the NH_3^+ group of the guest. The crown oxygen donor atoms are not involved in hydrogen bonding. One of these atoms, O4, is disordered. The phenoxide oxygen is the acceptor atom for the third hydrogen bond. The three hydrogen bonds are shown in Figure 3. It was possible to locate the three hydrogen atoms involved in these interactions using the X-ray data. One other significant conformational change occurs in the host. The lariat arm of the host is rotated so its plane is now almost perpendicular to the least-squares plane of the crown donor atoms. The dihedral angle between these planes is 81.0°. This allows for the formation of a strong hydrogen bond between the phenoxide oxygen and the ammonium hydrogen. Experimental details, positional and thermal parameters of the atoms, bond lengths and angles, and hydrogen bond data for **16** and its complex are available.[18]

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(18) X-ray structural data and experimental details for **16** and the **16**–benzylamine complex are available from the Cambridge Crystallographic Data Centre. The experimental details, atomic coordinates and structural data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Experimental Section

The ^{1}H NMR spectra were recorded at 200 MHz. The CI method was used to record the mass spectra. Elemental analyses have been performed by MHW Laboratories, Phoenix, AZ. Solvents and starting materials were purchased from commercial sources where available. Compounds **4**,[3b] **5**,[19] **19**,[9] **27**,[8a] and **28**[20] were synthesized as described.

Preparation of 3,9-Dioxa-6-azaundecane-1,11-diol (3) (Scheme 1). A solution of β-(chloroethoxy)ethanol (74.4 g, 0.6 mol) in 150 mL of toluene was added dropwise to a refluxing mixture of 2-(2-aminoethoxy)ethanol (252.3 g, 2.4 mol), 1500 mL of toluene, and 70 g (0.66 mol) of Na_2CO_3. The mixture was stirred under reflux using a Dean–Stark adaptor for 2 days. The mixture was filtered, and toluene and excess 2-(2-aminoethoxy)ethanol were evaporated under reduced pressure. The residue was distilled (150 °C/0.15 mm) (lit.[21] 128 °C/0.02mm) to give 91.5 g (79%) of **3**: ^{1}H NMR ($CDCl_3$) δ 2.78 (t, J = 5.0 Hz, 4 H), 3.49–3.76 (m, 15 H); MS m/z 193 (M^+). Anal. Calcd for $C_8H_{19}NO_4$: C, 49.74; H, 9.84. Found: C, 49.60; H, 10.01.

6-(2′-Pyridylmethyl)-3,9-dioxa-6-azaundecane-1,11-diol (24) (Scheme 5). 2-Picolyl chloride hydrochloride (10 g, 0.061 mol), diol **3** (11g, 0.057 mol), and Na_2CO_3 (15 g, 0.14 mol) were refluxed in 220 mL of CH_3CN for 16 h. The mixture was filtered, and the solvent was evaporated. The residue was dissolved in 120 mL of $CHCl_3$ and extracted with a saturated brine solution. The $CHCl_3$ phase was separated, dried ($MgSO_4$), and evaporated. The crude material was purified on neutral Al_2O_3 using THF as eluent to give 10.7 g (66%) of **24** as an oil: ^{1}H NMR ($CDCl_3$) δ 2.80 (t, J = 5.1 Hz, 4 H), 3.48–3.75 (m, 14 H), 3.91 (s, 2 H) 7.17 (m, 1 H), 7.50 (m, 1 H), 7.68 (m, 1 H), 8.51 (m, 1 H); MS m/z 284 (M^+). Anal. Calcd for $C_{14}H_{24}N_2O_4$: C, 59.15; H, 8.45. Found: C, 59.26; H, 8.61.

3,6,12,15-Tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (1) (Scheme 1). Diol **3** (7.8 g, 0.04 mol) was dissolved in 150 mL of THF (distilled under $LiAlH_4$) and added dropwise to a stirred suspension of NaH (2.4 g, 0.1 mol) in 80 mL of THF under argon. After addition of the diol at 25 °C, the mixture was refluxed for 1 h and then cooled to 0 °C. Ditosylate **4** (18 g, 0.04 mol) in 300 mL of THF was added dropwise to the suspension of the disodium salt of **3** in THF. The reaction mixture was kept at rt over 2 days. THF was evaporated, and the residue was shaken with a mixture of ice, water, and CH_2Cl_2 (1:2:6). The organic layer was separated, dried ($MgSO_4$), and evaporated. The crude material was purified on neutral Al_2O_3 using $C_6H_5CH_3/CH_3OH$ (40/1) as eluent to give 3.8 g of **1** (32%) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.40 (brs, 1 H), 2.77 (t, J = 5.0 Hz, 4 H), 3.53–3.74 (m, 12 H), 4.75 (s, 4 H), 7.22 (d, 2 H), 7.65 (t, 1 H); MS m/z 296 (M^+). Anal. Calcd for $C_{15}H_{24}N_2O_4$; C, 60.81; H, 8.11. Found: C, 60.68; H, 8.03.

9-(2′-Hydroxy-5′-methylbenzyl)-3,6,12,15-tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (7) (Scheme 2). Compound **1** (1.5 g, 5.1 mmol) was dissolved in 10 mL of CH_3OH and added to a solution of paraformaldehyde (0.2 g, 6.7 mmol) in 15 mL of CH_3OH. The mixture was kept overnight at 25 °C. CH_3OH was evaporated, and methoxy derivative **6** was dried under high vacuum for 3 h. Compound **6** was used without purification in the reaction with *p*-cresol (1.6 g, 15.2 mmol). These reactants were refluxed in 40 mL of C_6H_6 for 24 h. After evaporation, the residue was dissolved in 50 mL of ethyl acetate and extracted twice with 10 mL portions of 20% aqueous tartaric acid. The aqueous phase was separated and extracted with 50 mL of ethyl acetate. The aqueous solution of **7** was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and evaporated. Crude macrocycle **7** was purified on neutral Al_2O_3 with $C_6H_5CH_3/CH_3OH$ (40/1) as eluent to give 1.0 g (51%) of **7** as an oil: ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3 H), 2.71 (t, J = 5.1 Hz, 4 H), 3.49–3.81 (m, 14 H), 4.71 (s, 4 H), 6.60–6.95 (m, 3 H), 7.28 (d, 2 H), 7.69 (t, 1 H); MS m/z 416 (M^+). Anal. Calcd for $C_{23}H_{32}N_2O_5$: C, 66.35; H, 7.69. Found: C, 66.25; H, 7.66.

9-(2′-Hydroxy-5′-methoxybenzyl)-3,6,12,15-tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (8) (Scheme 2). Compound **6** (1.7 g, 5.1 mmol) was refluxed with *p*-methoxyphenol (0.6 g, 5.1 mmol) in 40 mL of C_6H_6 for 24 h. After evaporation, crude macrocycle **8** was purified on neutral Al_2O_3 with $C_6H_5CH_3/CH_3OH$ (40/1) as eluent to give 1.2 g (55%) of **8** as an oil: ^{1}H NMR ($CDCl_3$) δ 2.75 (t, J = 5.1 Hz, 4 H), 3.50–3.81 (m, 17 H), 4.71 (s, 4 H), 6.51 (s, 1 H), 6.70 (s, 2 H), 7.28 (d, 2 H), 7.68 (t, 1 H); MS m/z 432 (M^+). Anal. Calcd for $C_{23}H_{32}N_2O_6$: C, 63.89; H, 7.41. Found: C, 63.72; H, 7.37.

9-(2′-Hydroxy-5′-chlorobenzyl)-3,6,12,15-tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (9) (Scheme 2). Compound **9** was obtained in the same manner as above for **8** from 1.7 g (5.1 mmol) of **6** and 0.7 g (5.4 mmol) of *p*-chlorophenol. **9** (1.2 g, 56%) was isolated after column chromatography: mp 61–62 °C; ^{1}H NMR ($CDCl_3$) δ 2.75 (t, J = 5.1 Hz, 4 H), 3.50–3.79 (m, 14 H), 4.70 (s, 4 H), 6.67–7.09 (m, 3 H), 7.28 (d, 2 H), 7.70 (t, 1 H); MS, m/z 437 (M^+). Anal. Calcd for $C_{22}H_{29}N_2O_5Cl$; C, 60.41; H, 6.64. Found: C, 60.27; H, 6.63.

9-(2′-Hydroxy-5′-fluorobenzyl)-3,6,12,15-tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (10) (Scheme 2). Compound **10** was obtained in the same manner as above for **8** from 1.7 g (5.1 mmol) of **6** and 0.6 g (5.4 mmol) of *p*-fluorophenol. **10** (0.3 g, 15%) was isolated as an oil after column chromatography using silica gel and $C_6H_5CH_3/CH_3OH$ (100/1) as eluent: ^{1}H NMR ($CDCl_3$) δ 2.72 (m, J = 5.1 Hz, 4 H) 3.50–3.63 (m, 8H), 3.76–3.81 (m, 6 H), 4.72 (s, 4 H), 6.60–6.88 (m, 3 H), 7.26 (d, 2 H), 7.68 (t, 1 H); MS m/z 420 (M^+). Anal. Calcd for $C_{22}H_{29}N_2O_5F$: C, 62.86; H, 6.90. Found: C, 62.68; H, 6.77.

9-(2′-Hydroxy-5′-cyanobenzyl)-3,6,12,15-tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (11) (Scheme 2). Compound **11** was obtained in the same manner as above for **8** from 1.7 g (5.1 mmol) of **6** and 0.7 g (5.9 mmol) of *p*-cyanophenol. **11** was purified by column chromatography using neutral Al_2O_3 and $C_6H_5CH_3/CH_3OH$ (100/1) as eluent to give a brown oil which solidified on standing and was recrystallized from ethanol: 0.4 g (20%); mp 166–167 °C; ^{1}H NMR ($CDCl_3$) δ 2.73 (t, J = 5.4 Hz, 4 H), 3.54 (t, J = 5.4 Hz, 4 H), 3.56–3.62 (m, 4 H), 3.73–3.80 (m, 6 H), 4.71 (s, 4 H), 6.75 (d, 1 H), 7.18 (d, 1 H), 7.29 (d, 2 H), 7.41 (dd, 1 H) 7.69 (t, 1 H). Anal. Calcd for $C_{23}H_{29}N_3O_5$: C, 64.64; H, 6.79. Found: C, 64.80; H, 6.73.

9-(2′-Hydroxy-3′-carbonyl-5′-bromobenzyl)-3,6,12,15-tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (12) (Scheme 2). **6** (1.7 g, 5.1 mmol) was refluxed with 1.3 g (6.5 mmol) of 5-bromosalisylaldehyde in 40 mL of toluene for 24 h under argon. The solvent was evaporated, and the residue was dissolved in 15 mL of 20% aqueous tartaric acid. The solution was extracted twice with 50 mL portions of ethyl acetate. The aqueous phase was neutralized with $NaHCO_3$ and extracted twice with 50 mL portions of $CHCl_3$. The organic layer was separated, dried (Na_2SO_4), and evaporated. The crude macrocycle was purified on silica gel with THF as eluent to give 1.6 g (61%) of **12** as an oil: ^{1}H NMR (CD_3OD) δ 2.80 (t, J = 5.0 Hz, 4 H), 3.54–3.69 (m, 12 H), 3.91 (s, 2 H), 4.69 (s, 4 H), 7.40 (m, 3 H), 7.62 (s, 1 H), 7.74 (t, 1 H), 10.04 (s, 1 H); MS m/z 510 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{29}BrN_2O_6$: C, 54.22; H, 5.70. Found: C, 54.42; H, 5.52.

9-((5′-Chloro-8′-hydroxy-7′-quinolinyl)methyl)-3,6,12,15-tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (13) (Scheme 2). **6** (1.7 g, 5.1 mmol) was refluxed with 0.7 g (3.9 mmol) of 5-chloro-8-hydroxyquinoline in 40 mL of benzene for 12 h. The benzene solution was filtered and evaporated. The residue was purified by column chromatography using silica gel with $THF/C_6H_5CH_3$ (2/1) as eluent to give 1.4 g (58%) of **13** as an oil: ^{1}H NMR (CD_3OD) δ 2.78 (t, J = 5.1 Hz, 4 H), 3.56 (m, 8 H), 3.72 (m, 4 H), 3.99 (s, 2 H), 4.68 (s, 4 H), 7.41 (m, 3 H), 7.58 (m, 1 H), 7.80 (t, 1 H), 8.50 (m, 1 H), 8.79 (m, 1 H); MS m/z 488 (M^+). Anal. Calcd for $C_{25}H_{30}ClN_3O_5$: C, 61.54; H, 6.15. Found: C, 61.33; H, 6.10.

9-(2′-Hydroxy-5′-nitrobenzyl)-3,6,12,15-tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (16) (Scheme 3). To a stirred solution of **1** (1.2 g, 4.1 mmol) and

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Et_3N (0.5 g, 5 mmol) in 50 mL of dry THF was added a solution of 2-(chloromethyl)-4-nitrophenol (0.8 g, 4.3 mmol) in 10 mL of THF at 0 °C. The mixture was kept overnight at 25 °C. The THF solution was filtered and evaporated. The residue was dissolved in 20 mL of 20% aqueous tartaric acid. The resulting solution was extracted twice with 50 mL portions of $CHCl_3$. The aqueous phase was neutralized with $NaHCO_3$ and extracted four times with 50 mL portions of $CHCl_3$. The combined organic layers were separated, dried (Na_2SO_4), and evaporated. The residue was refluxed with 100 mL of ethyl acetate and filtered. Evaporation of ethyl acetate gave 1.5 g (85%) of **16**: mp 114–115 °C; ^{1}H NMR ($CDCl_3$) δ 2.76 (t, J = 5.0 Hz, 4 H), 3.52–3.61 (m, 8 H) 3.75 (m, 4 H), 3.89 (s, 2 H), 4.71 (s, 4 H), 6.75 (d, 1 H), 7.28 (d, 2 H), 7.70 (t, 1 H), 7.89 (m, 1 H) 8.07 (m, 1 H); MS m/z 447 (M^+). Anal. Calcd for $C_{22}H_{29}N_3O_7Cl$: C, 59.06; H, 6.49. Found: C, 58.88; H, 6.56.

9-(2′-Hydroxy-5′-nitrobenzyl)-3,6,12,15-tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-17,20-dien-19(21*H*)-one (18) (Schemes 1 and 3). Diol **3** (3 g, 15.5 mmol) dissolved in 80 mL of dry THF was added dropwise to a stirred mixture of NaH (1 g, 41.7 mmol) and 40 mL of dry THF at 25 °C under argon. This mixture was stirred at reflux for 1 h and cooled to 0 °C. Ditosylate **5** (8.8 g, 16.1 mmol) in 200 mL of dry THF was added dropwise to the suspension of the disodium salt of **3** in THF. The reaction mixture was kept at rt for 2 days. THF was evaporated at 25 °C. The residue was extracted with an ice–water–CH_2Cl_2 mixture (1:2:6). The CH_2Cl_2 phase was separated. The aqueous layer was extracted twice with 80 mL portions of CH_2Cl_2. The organic fractions were combined, dried ($MgSO_4$), and evaporated at 25 °C. The crude product was passed through neutral Al_2O_3 using $C_6H_5CH_3$/THF (1/1) as eluent to give 1.8 g (30%) of **2** as a slightly impure oil. The product was dissolved in 50 mL of THF containing 0.9 mL of Et_3N (6.8 mmol). 2-(Chloromethyl)-4-nitrophenol (0.9 g, 4.5 mmol) in 70 mL of THF was added dropwise to this solution at 0 °C. The mixture was kept overnight at 25 °C. THF was evaporated, and the residue was washed with 80 mL of benzene. The benzene solution of **17** was filtered, and the solvent was removed under reduced pressure. The THP protecting group was cleaved by refluxing **17** in 100 mL of CH_3OH for 10 h. CH_3OH was evaporated, and the crude material was purified on a silica gel column (60–200 mesh) first with 1,4-dioxane then with 1,4-dioxane/CH_3OH (3/1) as eluents to give 1.5 g (21%) of **18** as an oil: ^{1}H NMR ($CDCl_3$), δ 2.83 (t, J = 5.0 Hz, 4 H), 3.56–3.75 (m, 12 H), 3.89 (s, 2 H), 4.47 (s, 4 H), 6.2 (s, 2 H), 6.67 (d, 1 H), 7.97–8.12 (m, 2 H). Anal. Calcd for $C_{22}H_{29}N_3O_8$: C, 57.02; H, 6.26. Found: C, 57.23; H, 6.35.

9-((5′-Chloro-8′-methoxy-2′-quinolinyl)methyl)-3,6,12,15-tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (20) (Scheme 4). A mixture of **19** (3.1 g, 10.8 mmol), **1** (3.2 g, 10.8 mmol), and Na_2CO_3 (2.2 g, 20.8 mmol) was refluxed in 80 mL of CH_3CN for 20 h. The solvent was evaporated, and the residue was dissolved in 50 mL of $CHCl_3$ and extracted with 20 mL of H_2O. The aqueous layer was extracted twice with 50 mL portions of $CHCl_3$. The organic phase was separated, dried (Na_2SO_4), and evaporated. The crude product was purified on neutral Al_2O_3 using $CHCl_3$/THF (10/1) as eluent to give 4.3 g (79%) of **20** as an oil: ^{1}H NMR ($CDCl_3$) δ 2.79 (t, J = 5.1 Hz, 4 H), 3.50–3.61 (m, 8 H), 3.73 (m, 4 H), 4.04 (s, 2 H), 4.06 (s, 3 H), 4.69 (s, 4 H), 6.92 (d, 1 H), 7.30 (d, 2 H), 7.47 (d, 1 H) 7.71 (t, 1 H), 7.91 (d, 1 H), 8.32 (d, 1 H); MS m/z 502 (M^+). Anal. Calcd for $C_{26}H_{32}N_3O_5Cl$: C, 62.21; H, 6.38. Found: C, 62.10; H, 6.31.

9-((5′-Chloro-8′-hydroxy-2′-quinolinyl)methyl)-3,6,12,15-tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (21) (Scheme 4). Compound **20** (1.2 g, 2.4 mmol) was dissolved in 15 mL of DMF and stirred with LiCl (2 g, 47.1 mmol) at 130 °C for 18 h. After cooling, the solvent was evaporated under reduced pressure. The residue was treated with three 30 mL portions of ether, and the mixture was acidified to pH ~7 by 10% HCl and extracted with $CHCl_3/H_2O$ (4:1). The $CHCl_3$ layer was separated and washed with aqueous $NaHCO_3$ and water. The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated. Crude **21** was purified by column chromatography on neutral Al_2O_3 using $C_6H_5CH_3$/THF (1/2) as eluent to give 0.6 g (48%) of **21** as an oil: ^{1}H NMR ($CDCl_3$) δ 2.79 (t, J = 5.1 Hz, 4 H), 3.50–3.62 (m, 8 H), 3.75 (m, 4 H), 3.99 (s, 2 H), 4.75 (s, 4 H), 7.03 (d, 1 H), 7.29 (d, 2 H), 7.42 (d, 1 H), 7.71 (m, 2 H), 8.30 (d, 1 H). Anal. Calcd for $C_{25}H_{30}N_3O_6Cl$; C, 61.54; H, 6.15. Found: C, 61.60; H, 6.31.

9-(2′-Pyridylmethyl)-3,6,12,15-tetraoxa-9,18,19,20-tetraazabicyclo[15.2.1]eicosa1(20),17-diene (22) (Scheme 5). A solution of diol **24** (2.7 g, 9.5 mmol) in 100 mL of THF was added dropwise to a suspension of NaH (0.7 g, 29.2 mmol) in 80 mL of THF at 25 °C under argon. The mixture was refluxed for 1 h and cooled to 0 °C. A solution of **27** (2.4 g, 9.6 mmol) in 300 mL of THF was added to the suspension of the disodium salt of **24**. The reaction mixture was kept at rt for 2 days. THF was evaporated at 25 °C. The residue was extracted with an ice–water–CH_2Cl_2 mixture (1:2:6) having a pH of 12. The CH_2Cl_2 phase was separated. The aqueous layer was extracted twice with 80 mL portions of CH_2Cl_2. The organic fractions were combined, dried ($MgSO_4$), and evaporated at 25 °C. The crude product was passed through neutral Al_2O_3 using $C_6H_5CH_3$/THF (1/2) and then pure THF as eluent to give 1.3 g (29%) of **25** as an impure oil. The product was dissolved in 30 mL of CH_3OH, and 4 mL of CH_3OH saturated with HCl was added. The mixture was allowed to stand for 2.5 h. The solvent was evaporated, and the residue was dissolved in 5 mL of H_2O. The solution was extracted with CH_2Cl_2, and the aqueous layer was neutralized by $NaHCO_3$ and extracted six times with 50 mL portions of CH_2Cl_2. The CH_2Cl_2 solution was dried ($MgSO_4$) and evaporated. The crude product was purified on silica gel with THF and then with THF/CH_3OH (30/1) as eluent to give 0.8 g (22%) of **22** as an oil: ^{1}H NMR ($CDCl_3$) δ 2.88 (t, J = 5.2 Hz, 4 H), 3.38–3.73 (m, 12 H), 3.79 (s, 2 H), 4.76 (s, 4 H), 5.31 (s, 1 H), 7.09 (m, 1 H), 7.29 (m, 1 H), 7.56 (m, 1 H), 8.43 (m, 1 H); MS m/z 377 (M^+). Anal. Calcd for $C_{18}H_{27}N_5O_4$: C, 57.29; H, 7.16. Found: C, 57.05; H, 7.37.

9-(2′-Pyridylmethyl)-3,6,12,15-tetraoxa-19-methyl-21-methoxy-9-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (26) (Scheme 5). A solution of diol **24** (4 g, 14.1 mmol) in 300 mL of THF was added dropwise to a suspension of NaH (1.0 g, 41.7 mmol) in 30 mL of THF at 25 °C under argon. The mixture was refluxed for 1 h and cooled to 0 °C. A solution of dibromide **28** (4.7 g, 14.3 mmol) in 200 mL of THF was added to the suspension of the disodium salt of **24**. The reaction mixture was kept at 25 °C for 2 days. THF was evaporated. The residue was extracted with a water–$CHCl_3$ mixture (1:4). The $CHCl_3$ phase was separated. The aqueous layer was extracted twice with 50 mL portions of $CHCl_3$. The $CHCl_3$ fractions were combined, dried (Na_2SO_4), and evaporated. Crude macrocycle **26** was purified on neutral Al_2O_3 using $C_6H_5CH_3/CH_3OH$ (50/1) as eluent. The resulting oil solidified on standing and was recrystallized from ether/hexane (2/1) to give 2.5 g (42%) of **26**: mp 58–60 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3 H), 2.65 (t, J = 5.5, 4 H), 3.33–3.56 (m, 12 H), 3.69 (s, 2 H), 4.04 (s, 3 H), 4.56 (s, 4 H), 7.08–7.42 (m, 5 H), 8.45 (m, 1 H); MS m/z 430 (M^+). Anal. Calcd for $C_{24}H_{34}N_2O_5$: C, 66.98; H, 7.91. Found: C, 67.12; H, 7.87.

9-(2′-Pyridylmethyl)-3,6,12,15-tetraoxa-19-methyl-21-hydroxy-9-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (23) (Scheme 5). Compound **26** (4.1 g. 9.5 mmol) and LiI (10 g, 74.6 mmol) were refluxed in 20 mL of dry pyridine under argon for 12 h. Pyridine was evaporated, and the residue was treated with 20 mL of 10% aqueous HCl. The resulting solution was extracted twice with 50 mL portions of ether. The aqueous phase was neutralized with $NaHCO_3$ and extracted twice with 80 mL portions of $CHCl_3$. The $CHCl_3$ layer was dried (Na_2SO_4) and evaporated. Crude macrocycle **23** was purified on silica gel using $CHCl_3/CH_3OH$ (10/1) as eluent to give 1.2 g (31%) as an oil: ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3 H), 2.89 (t, 4 H), 3.60–3.74 (m, 12 H), 3.86 (s, 2 H), 4.62 (s, 4 H), 7.00 (s, 2 H), 7.29 (m, 1 H), 7.68 (m, 2 H), 8.45 (m, 1 H); MS m/z 418 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{32}N_2O_5$: C, 66.35; H, 7.69. Found: C, 66.18; H, 7.69.

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