Synthesis of New Proton-Ionizable Crown Ether Compounds Containing Substituted 1*H*-Pyridin-4-one Subcyclic Units

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Five novel pyridono-18-crown-6 (**10**-**14**) and two new benzyloxy-substituted pyridino-18-crown-6 (**15** and **16**) ligands have been prepared. By the catalytic hydrogenative removal of the benzyl group from the benzyloxy moiety at position 4 of the pyridine ring of **15** and **16**, pyridono-18-crown-6 ethers **5** and **12** were obtained. These ligands were transformed to their 3,5-dibromo (**10** and **13**) and 3,5-dinitro derivatives (**11** and **14**) by treatment with bromine in methylene chloride and nitric acid in acetic anhydride, respectively. The latter proton-ionizable crown ethers have pK_a values of about 7.5 for **10** and **13** and 4.5 for **11** and **14**. Thus, they are good candidates for complexation and proton-coupled transport of selected cations.

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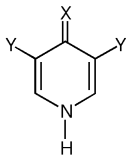
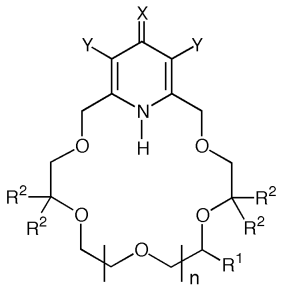
Introduction.

In order for an ionophore to perform optimum transport across the membrane of an aqueous source phase-lipophilic liquid membrane-aqueous receiving phase system, it should possess a relatively high ion-binding ability at the membrane phase-source phase interface, and have a relatively low ion-binding ability at the membrane phase-receiving phase interface. The solution for this seemingly contradictory requirement is to engineer into the ionophore a so-called "switching mechanism" which can create two different binding states. These two states can be reversibly interconverted by external forces such as redox, light, temperature, and *p*H gradients. Macrocycles having a *p*H switching mechanism have attracted the attention of many researchers [1].

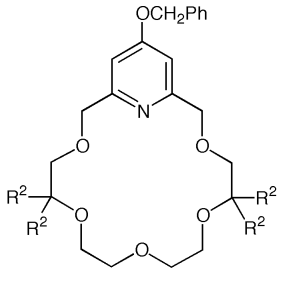
We are interested in crown ethers having a proton-ionizable moiety as a part of the macroring. These ionophores



1 X = O, Y = H
2 X = S, Y = H
3 X = O, Y = Br
4 X = O, Y = NO_2



5 X = O, Y = H, R^1,R^2 = H, n = 1
6 X = O, Y = H, R^1 = octyl, R^2 = H, n = 1
7 X = O, Y = H, R^1 = octyl, R^2 = H, n = 0
8 X = S, Y = H, R^1,R^2 = H, n = 1
9 X = S, Y = H, R^1 = octyl, R^2 = H, n = 1
10 X = O, Y = Br, R^1,R^2 = H, n = 1
11 X = O, Y = NO_2, R^1,R^2 = H, n =1
12 X = O, Y = H, R^1 = H, R^2 = hexyl, n = 1
13 X = O, Y = Br, R^1 = H, R^2 = hexyl, n = 1
14 X = O, Y = NO_2, R^1 = H, R^2 = hexyl, n = 1



15 R^2 = H
16 R^2 = hexyl

Figure 1. Structures of 1*H*-Pyridin-4-one Compounds (**1**-**4**), Proton-ionizable Crown Ethers Containing 1*H*-Pyridin-4-one and 1*H*-Pyridin-4-thione Subcyclic Units (**5**-**14**), and Pyridino-18-crown-6 Ligands **15** and **16**.

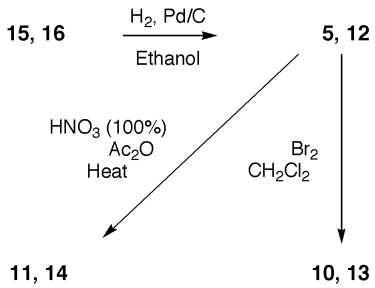
increase the cation-crown ether complex stability and allow selective proton-coupled transport of metal ions through various membrane systems without the need for an anion to accompany the macrocycle-cation complex [2]. Transport of the cations, in many cases, is *p*H dependent so that transport can be turned on and off by adjusting the *p*H [1,2b,3]. We have used water-insoluble proton-ionizable macrocycles containing the 1*H*-pyridin-4-one (**1**) (see Figure 1) and 1*H*-pyridin-4-thione (**2**) subcyclic units, such as **6**, **7**, and **9**, as carriers in the transport of metal ions in a H_2O-CH_2Cl_2-H_2O liquid membrane system [2b,2c,4]. The proton-ionizable macrocyclic carriers should have lipophilic substituents to insure that they remain in the organic membrane. Without a lipophilic side chain, no transport occurred, because the crown ether distributed into the aqueous phase so that it was not available as a carrier [2c]. In the case of pyridono ligands **6** and **7**, transport of alkali metal ions was observed for source phase *p*H values higher than 12, and in the case of thiopyridono ligand **9** higher than 10 [2c]. Since the pK_a values for removal of a proton from octyl-substituted **6** and **7** are presumably close to that for 4-pyridone **1** (11.09) [5] or non-alkyl-substituted **5** (10.98) [6] and the pK_a value for **9** is close to that for **8** (8.65) [7] or **2** (8.3) [8], respectively, transport can only take place when an appreciable amount of the macrocycle in question is ionized at the source phase-organic phase interface [2b,2c].

We have long wanted to prepare proton-ionizable macrocyclic ligands with pK_a values that would allow the transport of cations at relatively low source phase *p*H values. These more acidic *p*H-switched ligands would also be used to transport some of the heavy metal cations and ammonium and organic primary ammonium ions at relatively low source phase *p*H values [2c]. Since 3,5-dibromo-1*H*-pyridin-4-one (**3**) and 3,5-dinitro-1*H*-pyridin-4-one (**4**) have pK_a values of 7.73 [9] and 4.56]10], respectively, new non-lipophilic proton-ionizable ligands **10** and **11** containing these substituted pyridone subcyclic units (Figure 1) and their lipophilic tetrahexyl-substituted analogues **13** and **14** have been prepared for future proton-coupled cation transport studies. The preparation of new lipophilic macrocycle **12** and its known non-lipophilic analogue **5** [6] by a new straightforward method is also reported. A report of the cation transport properties of these interesting new proton-ionizable macrocycles will be published when that work is finished.

Results and Discussion.

The known pyridonocrown ether **5** [6] was obtained from the corresponding benzyloxy-substituted pyridinocrown ether **15** instead of from its tetrahydropyranyloxy analogue (Scheme 1). The benzyl protecting group is better than the THP protecting group for these kinds of syntheses [11]. The novel lipophilic pyridono ligand **12** was also obtained by the catalytic hydrogenation of pyridino macrocycle **16** in an excellent yield. Bromination of ligands **5** and **12** was carried out in dichloromethane at room temperature using a large excess of bromine. The yields of dibromo-substituted pyridono-crown ethers **10** and **13** were good to moderate (63% and 39%, respectively), although the same reaction conditions were used in both cases. Crude dibromo derivative **10** could be purified by crystallization, but the purification of **13** required chromatography. Nitration of pyridonocrown ethers **5** and **12** to form dinitro derivatives **11** and **14** was performed in a mixture of 100% nitric acid and acetic anhydride and required heat. The yields were low (30% for **11** and 25% for **14**) and chromatography was needed to purify the solid products. We plan to further investigate these reactions in order to obtain better yields for both bromination and nitration of the pyridonocrown ethers.

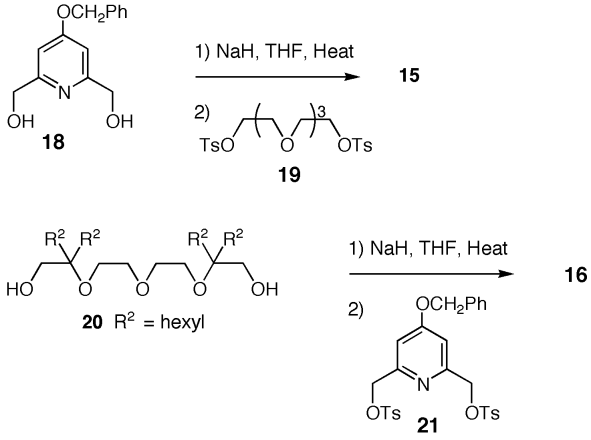
Scheme 1



Preparation of Proton-ionizable Pyridono-18-crown-6 Ligands **10**, **11**, **13**, and **14**.

Benzyloxy-substituted pyridinocrown ether **15** was prepared using a Williamson ether synthesis by treating the disodium salt of 4-benzyloxy-2,6-pyridinedimethanol (**18**) [12] with tetraethylene glycol ditosylate (**19**) [13] to give a 47% yield (Scheme 2). When 4-benzyloxy-2,6-pyridinedimethanol ditosylate (**21**) [14] and tetraethylene

Scheme 2

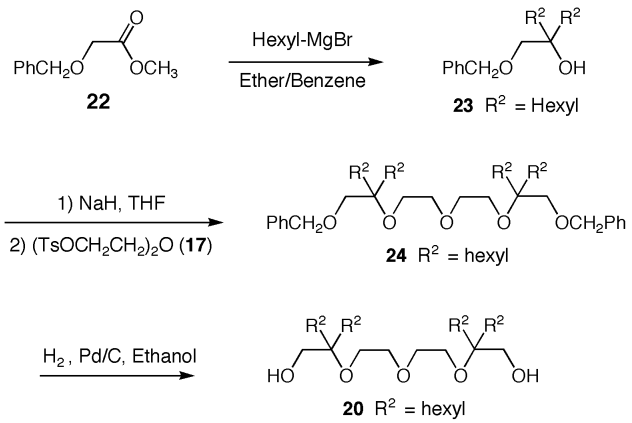


Preparation of Benzyloxypyridino-18-crown-6 Ethers **15** and **16**.

glycol were used in similar reaction conditions, a very low yield of crown ether **15** was obtained. (The latter reaction is not shown.) However, a good yield (49%) of **16** was obtained when ditosylate **21** was treated with the disodium salt of tetrahexyl-substituted tetraethylene glycol **20** under the above mentioned reaction conditions (Scheme 2). We presume that the solubility of the appropriate disodium salt in tetrahydrofuran plays an important role in this type of cyclization reaction.

In our previous studies of cation transport by lipophilic proton-ionizable crown ethers [2b,2c,4], a single long chain alkyl substituent was used to effect lipophilicity to the macrocycle (**6**, **7**, and **9**, for example). Using only one alkyl substituent creates a stereogenic center and could lead to complications in some complexation studies. Having only one long chain alkyl side arm causes the ligand to be surface active and results in foaming during the transport experiments. The four shorter hexyl arms secure lipophilicity for the ligand without causing foaming. Therefore, we have synthesized symmetric tetrahexyl-substituted crown ethers **12**-**14** and **16**. Preparation of tetrahexyl-substituted tetraethylene glycol **20** needed to prepare crown ether **16** was accomplished from the reported methyl benzyloxyacetate (**22**) [15] as shown in Scheme 3. Ester **22** was treated with an excess of hexylmagnesium bromide in a mixture of ether and benzene. When ester **22** in benzene was added to the ethereal Grignard reagent, a higher yield of **23** (95%) was obtained than when using only ether as a solvent. Dibenzyl-protected tetraethylene glycol **24** was obtained using the Williamson ether synthesis by treating alcohol **23** with diethylene glycol ditosylate (**17**). In this case, the yield was low (32%) probably the result of an unfavorable steric effect of the tertiary alcohol portion of **23**. Removal of the benzyl-protecting groups from **24** by catalytic hydrogenation went smoothly giving a good yield (94%) of tetrahexyl-substituted tetraethylene glycol **20**.

Scheme 3



Preparation of Tetrahexyl-substituted Tetraethylene Glycol (**20**).

EXPERIMENTAL

Infrared spectra were recorded on a Zeiss Specord IR 75 spectrometer. ^{1}H (500 MHz) and ^{13}C (125 MHz) nmr spectra were taken on a Bruker DRX-500 Avance spectrometer in deuteriochloroform unless otherwise indicated. Molecular weights were determined by a Perkin Elmer SIEX API 2000 triplequad mass spectrometer. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were taken on a Boetius micro melting point apparatus and were uncorrected. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. Silica gel 60 F_{254} (Merck) and aluminum oxide 60 F_{254} neutral type E (Merck) plates were used for tlc. Aluminum oxide (neutral, activated, Brockman I) and silica gel 60 (70-200 mesh, Merck) were used for column chromatography. Solvents were dried and purified according to well established methods [16]. Evaporations were carried out under reduced pressure unless otherwise stated.

3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]heneicosa-17,20-diene-19(21*H*)-one (**5**) (Scheme 1).

To 4.21 g (10 mmole) of benzyloxypyridinocrown ether monohydrate **15** was added under argon 0.4 g of 10% palladium on charcoal catalyst and then 280 ml of ethanol. The mixture was stirred under argon for 2 minutes, and then the argon was replaced by hydrogen and hydrogenation was carried out in the usual way at room temperature and at atmospheric pressure to give pyridonocrown ether **5** (3.25 g, 98%) which was purified by recrystallization from acetone to give white crystals of pure **5** (2.55 g, 77%) as a monohydrate identical in every aspect to that reported [6].

18,20-Dibromo-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]-heneicosa-17,20-diene-19(21*H*)-one (**10**) (Scheme 1).

To a stirred solution of pyridonocrown ether monohydrate **5** (166 mg, 0.5 mmole) in 10 ml of dichloromethane was added dropwise at room temperature a solution of bromine (1.02 ml, 3.3 g, 21 mmole) in 10 ml of dichloromethane. The reaction mixture was stirred at room temperature until the starting material disappeared according to tlc analysis (about 4 hours). After the reaction was completed, dichloromethane (10 ml) and aqueous triethylammonium acetate (30 ml of 1 *M* solution) was added. The phases were shaken well, and separated. The organic phase was shaken with 20 ml of water, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed. The residue was purified by recrystallization from methanol to give 143 mg (63%) of **10** as white crystals; mp 170-171°; R_f = 0.55 (silica gel tlc, 11% MeOH in CH_2Cl_2); ir (potassium bromide): 3328, 3024, 2872, 1608, 1584, 1572, 1516, 1504, 1468, 1432, 1348, 1288, 1264, 1248, 1104, 1088, 1064, 1056, 1048, 1008, 984, 940, 848, 712, 680 cm^{-1}; ^{1}H nmr: δ_H 3.67 (s, 8H), 3.79 (s, 8H), 4.58 (s, 4H), 10.4 (broad s, 1H, pyridone NH proton, shifted considerably by changing the temperature); ^{13}C nmr: δ_c 68.66, 70.11, 70.87, 70.91, 71.67, 109.27, 143.27, 168.28; ms: (electrospray) 472 $(M+1)^+$.

Anal. Calcd. for $C_{15}H_{21}Br_2NO_6$ (471.142): C, 38.24; H, 4.49; N, 2.97; Br, 33.92. Found: C, 37.96; H, 4.75; N, 3.14; Br, 33.66.

18,20-Dinitro-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-17,20-diene-19(21*H*)-one (**11**) (Scheme 1).

To pyridonocrown ether monohydrate **5**, (331 mg, 1 mmole) was added a mixture made previously from fuming nitric acid

(0.66 g, 10.5 mmole, 100% HNO_3, specific gravity, 1.52) and acetic anhydride (20 ml, 21.64 g, 212 mole) at room temperature. The reaction mixture was stirred at room temperature for 10 minutes then the temperature was raised to 60° and sustained until the starting material disappeared according to tlc analysis (about 3 hours). The volatile materials were removed and the residue was purified by preparative layer chromatography on silica gel (Merck PLC plates $60F_{254}$, 0.5 mm silica gel thickness, Art number: 1.05744) using 11% methanol in dichloromethane as eluent to give 138 mg (30%) of pure **11** as a yellow solid; mp > 360° (methanol); R_f = 0.48 (silica gel tlc, 11% MeOH in CH_2Cl_2); ir (potassium bromide): 3440, 3048, 2912, 1616, 1564, 1500, 1488, 1464, 1364, 1256, 1216, 1128, 1100, 1088, 1040, 952, 904, 824 cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 3.31 (2H, H_2O), 3.56 (s, 8H), 3.58 (s, 8H), 4.41 (s, 4H); ^{13}C nmr (DMSO-d_6): δ_C 69.37, 69.66, 69.71, 69.76, 69.81, 142.28, 149.62, 159.78; ms: (electrospray) 404 $(M+1)^+$.

Anal. Calcd for $C_{15}H_{21}N_3O_{10}$ •H_2O (421.36): C, 42.76; H, 5.50; N, 9.97. Found: C, 42.55; H, 5.52; N, 9.88.

5,5,13,13-Tetrahexyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-17,20-diene-19(21*H*)-one (**12**) (Scheme 1).

Macrocycle **12** was prepared as above for **5** from **16** (3.7 g, 5 mmole) using 0.2 g of 10% palladium on charcoal catalyst and 140 ml of ethanol as solvent. The crude product was purified by column chromatography on alumina using 2% ethanol in toluene as eluent to give **12** (3.5 g, 94%) as a colorless oil; R_f = 0.48 (silica gel tlc, 9% MeOH in CH_2Cl_2); ir (neat): 3516, 3267, 3063, 2930, 2860, 1634, 1584, 1531, 1455, 1377, 1103, 1026, 982, 965, 866, 727 cm^{-1}; ^1H nmr: δ_H 0.86 (tr, J = 7 Hz, 12H), 1.19-1.27 (m, 32H), 1.42-1.58 (m, 8H), 3.43 (s, 4H), 3.48-3.49 (m, 4H), 3.60-3,61 (m, 4H), 4.37 (s, 4H), 6.19 (s, 2H), 11.48 (broad s, 1H, pyridone NH proton, shifted considerably by changing the temperature); ^{13}C nmr: δ_C 14.20, 22.75, 23.47, 30.01, 31.87, 32.86, 61.06, 70.10, 71.31, 73.41, 79.81, 115.07, 147.29, 180.54; ms: (electrospray) 651 $(M+1)^+$.

Anal .Calcd for $C_{39}H_{71}NO_6$ (649.993): C, 72.07; H, 11.01; N, 2.15. Found: C, 71.93; H, 11.27; N, 2.09.

19,20-Dibromo-5,5,13,13-tetrahexyl-3,6,9,12,15- pentaoxa-21-azabicyclo[15.3.1]heneicosa-17,20-diene-19(21*H*)-one (**13**) (Scheme 1).

Macrocycle **13** was prepared as above for **10** from **12** (325 mg, 0.5 mmole) dissolved in 10 ml of dichloromethane using a solution of bromine (1.02 ml, 3.2 g, 21 mmole) in 10 ml of dichloromethane. The crude product was purified by preparative layer chromatography on silica gel using 2.4% methanol in dichloromethane as eluent to give **13** (139 mg, 34%) as an oil; R_f = 0.70 (silica gel tlc, 2.4% MeOH in CH_2Cl_2); ir (neat): 3324, 2955, 2931, 2859, 1606, 1576, 1466, 1378, 1352, 1262, 1216, 1120, 1069, 800, 758 cm^{-1}; ^1H nmr: δ_H 0.88 (tr, *J* = 7 Hz, 12H), 1.23-1.29 (m, 32H), 1.47-1.55 (m, 8H), 3.49 (s, 4H), 3.54-3.56 (m, 4H), 3.64-3.65 (m, 4H), 4.53 (s, 4H), 9.97 (broad s, 1H, pyridone NH proton, shifted considerably by changing the temperature); ^{13}C nmr: δ_C 14.22, 22.77, 25.28, 29.68, 31.31, 31.76, 61.63, 69.49, 74.18, 75.68, 78.08, 110.51, 143.16, 168.58; ms: (electrospray) 808 $(M+1)^+$.

Anal. Calcd for $C_{39}H_{69}Br_2NO_6$ (806.785): C, 58.06; H, 8.62; Br, 19.68, N, 1.74. Found: C, 57.82; H, 8.47; Br, 19.52; N, 1.68.

18,20-Dinitro-5,5,13,13-tetrahexyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-17,20-diene-19(21*H*)-one (**14**) (Scheme 1).

Macrocycle **14** was prepared as above for **11** from **12** (325 mg, 0.5 mmole) using 0.33 g (5.3 mmole) of 100% nitric acid and 10 ml of acetic anhydride. The crude product was purified by preparative layer chromatography on silica gel using 5% methanol in dichloromethane as eluent to give **14** (98 mg, 25%) as a yellow solid; mp 133-135°; R_f = 0.45 (silica gel tlc, 5% MeOH in CH_2Cl_2); ir (potassium bromide): 3436, 2931, 2859, 1620, 1522, 1468, 1357, 1330, 1261, 1222, 1135, 1117, 1082, 1025, 955, 829, 801 cm^{-1}; ^1H nmr: δ_H 0.89 (tr, *J* = 7 Hz, 12H), 1.26-1.29 (m, 32H), 1.50-1.53 (m, 8H), 3.54 (s, 4H), 3.66-3.67 (m, 4H), 3.69-3.70 (m, 4H), 4.56 (s, 4H); ^{13}C nmr: δ_C 14.29, 22.84, 23.39, 29.92, 30.06, 32.08, 59.17, 70.03, 71.11, 71.68, 78.91, 138.49, 152.77, 161.82; ms: (electrospray) 741 $(M+1)^+$.

Anal .Calcd for $C_{39}H_{69}N_3O_{10}$ •$2H_2O$ (776.019): C, 60.36; H, 9.48; N, 5.41. Found: C, 60.14; H, 9.42; N, 5.17.

19-Benzyloxy-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**15**) (Scheme 2).

To a well stirred suspension of sodium hydride (0.63 g, 21 mmole, 80% dispersion in mineral oil) in 5 ml of pure and dry tetrahydrofuran was added dropwise at 0° under argon a solution of 4-benzyloxy-2,6-pyridinedimethanol (**18**, 1.6 g, 6.52 mmole) in 30 ml of pure and dry tetrahydrofuran. After the addition was complete, the mixture was stirred at 0° for 10 minutes, at room temperature for 30 minutes and then at reflux temperature for 4 hours. The mixture was cooled to -60°, and a solution of tetraethylene glycol ditosylate (**19**, 3.5 g, 7 mmole) in 30 ml of pure and dry tetrahydrofuran was added. The mixture was stirred at -60° for 20 minutes and at room temperature for 5 days. The solvent was removed, and the residue was dissolved in a mixture of dichloromethane (100 ml) and ice cold water (50 ml). Phases were mixed and separated, and the aqueous phase was extracted with dichloromethane (3x50 ml). The combined organic phase was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed. The residue was purified by column chromatography on alumina using 1% ethanol in toluene as eluent to give 1.23 g (47%) of **15** as a colorless oil; R_f = 0.65 (alumina tlc, 5% MeOH in CH_2Cl_2); ir (neat): 3548, 3373, 3064, 3034, 2869, 1599, 1575, 1498, 1454, 1356, 1327, 1250, 1113, 1028, 990, 948, 861, 740, 699 cm^{-1}; ^1H nmr: δ_H 3.02 (broad s, 2H, H_2O) 3.55-3.58 (m, 8H), 3.63-3.66 (m, 4H), 3.70-3.72 (m, 4H), 4.67 (s, 4H), 5.10 (s, 2H), 6.85 (s, 2H), 7.31-7.40 (m, 5H); ^{13}C nmr: δ_c 69.63, 69.90, 70.49, 70.68, 71.05, 73.75, 107.62, 127.62, 128.38, 128.78, 135.91, 159.86, 166.00; ms: (electrospray) 404 $(M+1)^+$.

Anal. Calcd. for $C_{22}H_{29}NO_6$•H_2O (421.49): C, 62.69; H, 7.41; N, 3.32. Found: C, 62.44; H, 7.26; N, 3.14.

19-Benzyloxy-5,5,13,13-tetrahexyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**16**) (Scheme 2).

To a well stirred suspension of sodium hydride (0.32 g, 10.7 mmole, 80% dispersion in mineral oil) in 3 ml of pure and dry tetrahydrofuran was added dropwise at 0° under argon a solution of tetraethylene glycol **20** (1.75 g, 3.3 mmole) in 15 ml of pure and dry tetrahydrofuran. After the addition was completed, the mixture was stirred at 0° for 10 minutes, at room temperature for 30 minutes and then at reflux temperature for 4 hours. The mixture was cooled to –60°, and a solution of 4-benzyloxy-2,6-pyridinedimethanol ditosylate (**21**, 2.0 g, 3.6 mmole) in 15 ml of pure and dry tetrahydrofuran was added. The mixture was stirred at – 60° for 30 minutes and at room temperature for three days. The solvent was removed, and the residue was dissolved in a

mixture of dichloromethane (60 ml) and ice cold water (30 ml). Phases were shaken well and separated, and the aqueous phase was extracted with dichloromethane (3x30 ml). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed. The residue was purified by column chromatography on alumina using 0.4% ethanol in toluene as eluent to give **16** (1.2g, 49%) as a colorless oil; R_f = 0.55 (alumina tlc, 2% EtOH in toluene); ir (neat): 3030, 2928, 2870, 1600, 1544, 1456, 1368, 1328, 1104, 1052, 848, 736, 696 cm^{-1}; ^1H nmr: δ_H 0.88 (tr, *J* = 7 Hz, 12H), 1.19-1.27 (m, 32H), 1.43-1.515 (m, 8H), 3.43 (s, 4H), 3.45 (tr, *J* = 5 Hz, 4H), 3.52 (tr, *J* = 5 Hz, 4H), 4.66 (s, 4H), 5.11 (s, 2H), 6.87 (s, 2H), 7.33-7.43 (m, 5H); ^{13}C nmr: δ_C 14.11, 22.70, 23.10, 29.99, 31.86, 33.01, 60.55, 69.82, 70.93, 72.20, 74.05, 78.96, 107.56, 127.62, 128.36, 128.71, 135.84, 159.96, 165.90; ms: (electrospray) 741 $(M+1)^+$.

Anal Calcd. for $C_{46}H_{77}NO_6$ (740.117): C, 74.65; H, 10.49; N, 1.89. Found: C, 74.48; H, 10.62; N, 1.73.

2,2,8,8-Tetrahexyl-3,6,9-trioxaundecane-1,11-diol (**20**) (Scheme 3).

Compound **20** was prepared as above for **5** from **24** (3.56 g, 5 mmole) using 0.2 g of 10% palladium on charcoal catalyst and 140 ml of ethanol. The crude product was purified by column chromatography on silica gel using 8% acetone in cyclohexane as eluent to give **20** (2.5 g, 94%) as a colorless oil; R_f = 0.10 (silica gel tlc, 0.5% MeOH in CH_2Cl_2); ir (neat): 3432, 2928, 2888, 2864, 1464, 1376, 1248, 1084, 940, 724 cm^{-1}; ^1H nmr: δ_H 0.87 (tr, *J* = 7 Hz, 12H), 1.20-1.26 (m, 32H), 1.33-1.51 (m, 8H), 3.41 (s, 4H), 3.49-3.50 (m, 4H), 3.58-3.59 (m, 4H), 4.16 (broad s, 2H, hydroxyl protons, shifted considerably by changing the temperature); ^{13}C nmr: δ_C 14.01, 22.66, 23.31, 29.96, 31.81, 32.24, 59.86, 63.26, 71.17, 80.06.

7-Benzyloxymethyl-tridecane-7-ol (**23**) (Scheme 3).

To a well stirred solution of ethereal hexylmagnesium bromide, prepared from magnesium metal (14.6 g, 0.6 mole), hexyl bromide (99.05 g, 0.6 mole) and 350 ml of pure and dry ether, was added dropwise under argon a solution of methyl benzyloxyacetate (27.03 g, 0.15 mole) in 175 ml of pure and dry benzene. After the addition was completed, the reaction mixture was stirred at reflux temperature for 14 hours. The reaction mixture was cooled and first 1 liter of benzene and then 1 liter of saturated aqueous ammonium chloride solution were added. The mixture was transferred to a separatory funnel and mixed well. The aqueous phase was extracted twice with 500 ml portions of benzene. The combined organic phase was dried over magnesium sulfate, filtered, and the solvent was removed. The residue was purified by fractional distillation under reduced pressure to give 45.7 g (95%) of pure **23** as a colorless oil, bp 138-140° (0.2 mmHg); R_f = 0.55 (silica gel tlc, 0.5% MeOH in CH_2Cl_2); ir (neat): 3464, 3032, 2928, 2856, 1456, 1376, 1100, 736, 696 cm^{-1}; ^1H nmr: δ_H 0.92 (tr, *J* = 7 Hz, 6H), 1.30-1.34 (m, 16H), 1.51 (tr, *J* = 7 Hz, 4H), 2.24 (broad s, 1H), 3.35 (s, 2H), 4.57 (s, 2H), 7.30-7.39 (m, 5H); ^{13}C nmr: δ_c 14.25, 22.79, 23.53, 30.12, 31.98, 36.69, 73.54, 74.10, 75.81, 127.74, 127.78, 128.51, 138.46.

7,15-Bis(benzyloxymethyl)-7,15-dihexyl-8,11,14-trioxaheneicosane (**24**) (Scheme 3).

To a well stirred suspension of sodium hydride (3 g, 100 mmole, 80% dispersion in mineral oil) in 30 ml of pure and dry tetrahydrofuran was added dropwise at 0° under argon a solution of alcohol **23** (7.88 g, 24.6 mmole) in 200 ml of pure and dry tetrahydrofuran. After the addition was complete, the mixture was stirred at 0° for 10 minutes, at room temperature for 30 minutes and then at reflux temperature for 4 hours. The mixture was cooled to room temperature, and solid diethylene glycol ditosylate **17** (4.58 g, 11.1 mmole) was added in one portion. The mixture was stirred at room temperature for 20 minutes and at reflux temperature for 3 days. By that time the tlc analysis showed the total consumption of **17** and a large amount of unreacted **23**. The mixture was cooled to room temperature, and solid diethylene glycol ditosylate **17** (1.0 g, 4.8 mmole) was again added in one portion. Stirring was continued at room temperature for 20 minutes and then at reflux temperature for 2 days. The solvent was removed, and the residue was dissolved in a mixture of ether (300 ml) and ice cold water (250 ml). Phases were shaken well and separated, and the aqueous phase was extracted with ether (3x100 ml). The combined organic phase was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed. The residue was purified by column chromatography on silica gel using 0.5% methanol in dichloromethane as eluent to give 2.8. g (32%) of **24** as a colorless oil; R_f = 0.25 (silica gel tlc, 0.5% MeOH in CH_2Cl_2); ir (neat): 3064, 3048, 3032, 2928, 2888, 2864, 1492, 1456, 1372, 1208, 1104, 736, 696 cm^{-1}; ^1H nmr: δ_H 0.90 (tr, J = 7 Hz, 12H), 1.21-1.32 (m, 32H), 1.47-1.52 (m, 8H), 3.33 (s, 4H), 3.49 (tr, J = 7Hz, 4H), 3.59 (tr, J = 7Hz, 4H), 4.51 (s, 4H), 7.33-7.34 (m, 10H); ^{13}C nmr: δ_C 14.09, 22.66, 22.77, 29.88, 31.84, 33.24, 60.44, 71.01, 71.98, 73.21, 78.35, 127.44, 127.61, 128.23, 138.62.

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