New Pyrimidino-Crown Ether Ligands [1]

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Eight new macrocyclic ligands containing the pyrimidine subcyclic unit (**3-10**, Figure 1) have been prepared. Two of these new crown ethers are chiral. Pyrimidino-crowns **3-8** were prepared by treating the ditosylate derivative of the appropriate oligoethylene glycol with 4-methoxy-5-methyl-2,6-pyrimidinedimethanol in basic conditions. The yields were in the 30-50% range giving the crowns as viscous oils. Chiral dimethyl-substituted pyrimidino-crown **9** was prepared from 4-methoxy-5-methyl-2,6-pyrimidinedimethyl ditosylate and chiral dimethyl-substituted tetraethylene glycol. Treatment of dimethyl 4-methoxy-5-methyl-2,6-pyrimidinedicarboxylate with the diamine derivative of chiral dibenzyl-substituted tetraethylene glycol gave the chiral dibenzyl-substituted pyrimidino-crown diamide **10**. Starting 4-methoxy-5-methyl-2,6-pyrimidinedimethanol was prepared by a six step process from acetamidine hydrochloride and diethyl oxalpropionate.

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Introduction.

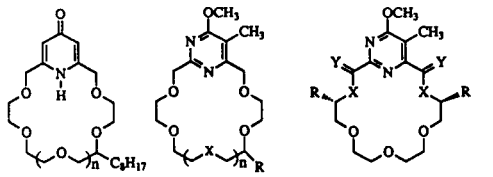
The synthesis and unique complexing characteristics of cyclic polyethers were first reported by Pedersen [2] about a quarter of a century ago. Since that landmark paper, a large variety and number of macrocyclic compounds have been prepared and their complexation properties have been studied [3,4]. As originally postulated [2] and later confirmed [5,6], there is a qualitative relationship between complex stability and the ratio of cation diameter to ligand cavity diameter. However, it is also evident that complex stability in these macrocyclic complexes depends on many other cation, ligand and ion/ligand parameters.

For the past three decades, work in this laboratory has been directed toward the systematic determination of the parameters that affect complex stability, and to understand that stability in terms of thermodynamic and kinetic data for complex formation [3,7-11]. In our studies, various structural changes have been made to the basic crown ether structure in an attempt to enhance the selectivity of these ligands and the stability of complexes formed with both metal and organic cations. Some of these modifications involve the substitution of ligand polyether oxygen donor atoms by sulfur and/or nitrogen atoms. Other substitutions have involved the insertion of aromatic and/or heterocyclic ring systems into the macroring.

Crown ethers containing a proton-ionizable group is an area of interest for many researchers [12,13]. We have reported a variety of proton-ionizable macrocycles. The majority of the ligands studied in our laboratory have the proton-ionizable moiety as a part of the macroring. The proton-ionizable macrocyclic ligands allow a proton-coupled transport of metal ions through various membrane systems without the need for an anion to accompany the macrocycle-ion complex [14-18]. The transport of these metal cations is *p*H dependent so that transport can be turned on or off by adjusting the *p*H [14,19,20]. Proton-ionizable ligands containing the 4-pyridone subcyclic unit (1 and 2, Figure 1) have shown promise as selective carriers in the transport of metal cations in some systems [14,15].

Enantiomeric recognition of organic amines and ammonium salts by chiral macrocycles is an area of molecular recognition that is receiving considerable attention at the present time [21-24]. Our interest in enantiomeric recognition has focused on the interaction of chiral pyridino-crown ligands with chiral organic ammonium salts [24]. In certain cases, these chiral pyridine-containing crowns have demonstrated appreciable enantiomeric recognition. These systems afford the possibility of systematically investigating how enantiomeric recognition varies with changes to the chiral host and chiral guest.

Figure 1. Macrocyclic Ligands



1, n = 0
2, n = 1

X = O
3, R = H; n = 0
4, R = H; n = 1
5, R = H; n = 2
6, R = C_8H_{17}; n = 1
X = S
7, R = H; n = 1
8, R = C_8H_{17}; n = 1

X = O
9, Y = H_2; R = CH_3
X = NH
10, Y = O; R = $CH_2C_6H_5$

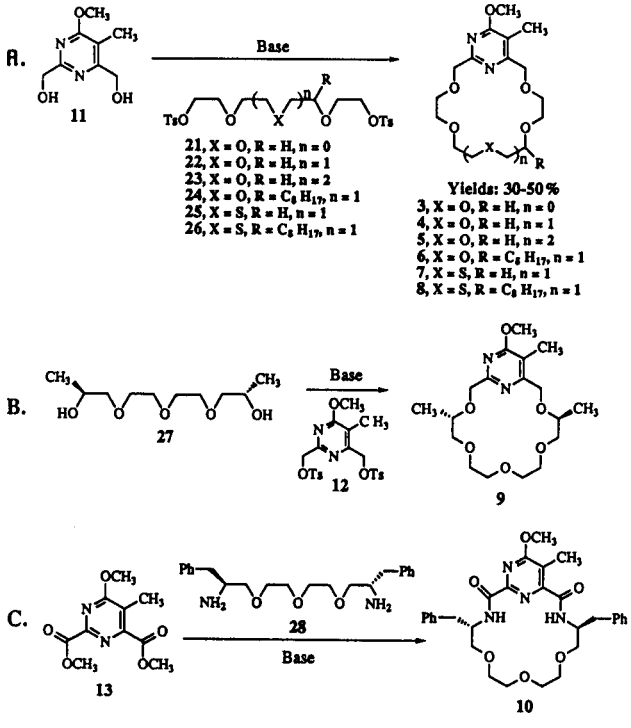
In view of the success of the pyridine-derived crowns in the above mentioned studies, we now report the synthesis and physical properties of pyrimidine-containing crown ethers **3-10** (Figure 1). We are currently converting some of these pyrimidino-crowns to the proton-ionizable pyrimidono-crowns by treatment with strong base. The new pro-

ton-ionizable crowns, as well as the results of a study of their use in complexing primary organic amines and ammonium salts, will be reported when that work is finished.

Results and Discussion.

The new pyrimidino-crown ethers were prepared as shown in Scheme I. Pyrimidino-crowns **3-8** were isolated as oils in 30 to 50% yields by treating 4-methoxy-5-methyl-2,6-pyrimidinedimethanol (**11**) with the approriate ditosylate **21-26** (Scheme I A). 4-Methoxy-5-methyl-2,6-pyrimidinedimethyl ditosylate (**12**) was treated with chiral dimethyl-substituted diol **27** to give chiral dimethyl-substituted pyrimidino-crown **9** in a 29% yield (Scheme I B).

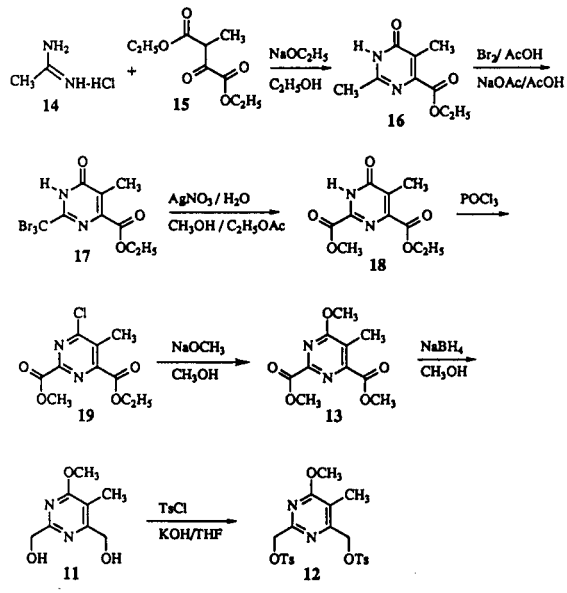
Scheme I. Preparation of Pyrimidino-crown Ethers

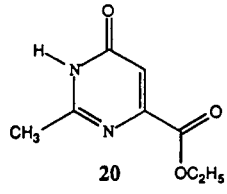


Chiral dibenzyl-substituted pyrimidino-crown diamide **10** was prepared in a 19% yield from dimethyl 4-methoxy-5-methyl-2,6-pyrimidinedicarboxylate (**13**) and the diamine derivative of chiral dibenzyl-substituted tetraethylene glycol **28** (Scheme I C). The structures proposed for these new macrocyclic compounds are consistent with data obtained from their ir, ^{1}H nmr and mass spectra, and combustion analyses. Macrocycle **6** proved to be a mixture of isomers as shown in the Experimental Section.

Starting pyrimidine-containing dimethanol **11**, ditosylate **12** and diester **13** were prepared as shown in Scheme II. Compounds **16-18** were prepared as reported [25] except in the case of compound **16**. When equimolar amounts of acetamidine hydrochloride (**14**) and diethyl oxalpropionate (**15**) were refluxed in ethanolic sodium ethoxide, ethyl 2,5-dimethyl-4-oxopyrimidine-6-carboxylate (**16**) separated in a 52% yield when the reaction mixture was cooled. Unfortunately, when a similar reaction was carried out using **14** and diethyl oxalacetate (or its sodium salt), the corresponding ethyl 2-methyl-4-oxopyrimidine-6-carboxylate (**20**) was isolated in only a 10% yield.

Scheme II. Preparation of Starting Pyrimidines 11-13





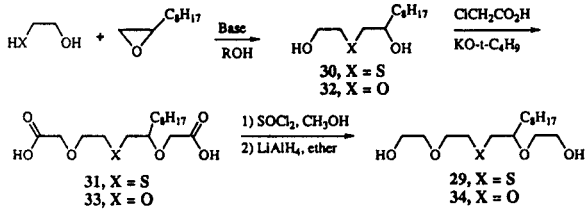
Selective bromination of **16** proceeded readily (92%) using a bromine-acetic acid-sodium acetate solution as reported by Hagmann and co-workers [25]. Treatment of tribromomethylpyrimidine **17** with 3 equivalents of aqueous silver nitrate in methanol and ethyl acetate gave the mixed diester derivative **18** as a solid in yields of about 90%. Refluxing **18** in phosphorus oxychloride gave ethyl 2-(carbomethoxy)-4-chloro-5-methylpyrimidine-6-carboxylate (**19**) (82%) as a white solid. When **19** was added to a solution of sodium methoxide in methanol at 4°, dimethyl 4-methoxy-5-methyl-2,6-pyrimidinedicarboxylate (**13**) was isolated in a 93% yield. Compound **13** was used to prepare chiral diamido-crown **10** shown in Scheme I C. Attempts to prepare compound **13** by treating mixed diester derivative **18** with thionyl chloride in methanol were unsuccessful.

Diester **13** was reduced quantitatively by sodium borohydride in methanol. Starting diester **13** was insoluable in methanol at 4° but the reaction mixture became clear when **13** was reduced to the desired 2,6-pyrimidinedimethanol (**11**). Diol **11** was isolated as a solid and used to pre-

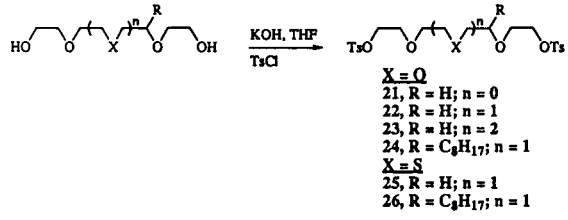
pare macrocyclic crown ethers as shown in Scheme I A. Diol **11** was also treated with tosyl chloride and potassium hydroxide in tetrahydrofuran to produce the ditosylated derivative **12**. Ditosylate **12** was then used to prepare chiral crown **9** as shown in Scheme I B.

These new pyrimidino-crowns can be treated with hot sodium hydroxide in methanol to give the corresponding pyrimidono-crown ethers. The synthesis of the proton-ionizable pyrimidono-crowns will be described in detail when that work is finished. A study of the complexing properties of the pyrimidino- and new pyrimidono-crowns will likewise be reported in a future publication when finished.

Scheme III. Preparation of Octyl-Substituted Tetraethylene Glycols



Scheme IV. Preparation of Ditosylate Starting Materials



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary tube melting point apparatus and are uncorrected. Infrared (ir) spectra were obtained on a Perkin Elmer 1600 FTIR spectrometer. The proton magnetic resonance (^{1}H nmr) spectra were obtained on a varian Gemini 200 MHz spectrometer in deuteriochloroform. Mass spectra were measured on a Finnegan 8430 high resolution mass spectrometer using electron impact and chemical ionization methods. Elemental analyses were performed by M. H. W. Laboratories, Phoenix, Arizona.

Acetamidine hydrochloride (**14**) and diethyl oxalpropionate (**15**) (Scheme II) were purchased from Aldrich Chemical Co. Compound **16** was prepared by a modification of the reported procedure [25] as described below. Compounds **17** and **18** were prepared as reported [25]. Starting unsubstituted glycol ditosylates **21-23** can be purchased from Aldrich Chemical Co. 3,9-Dioxa-6-thia-1,11-undecanediol, the precursor of **25** was prepared as reported [28]. Octyl-substituted tetraethylene glycol ditosylates **24** and **26** were prepared as reported [26-28] with some modifications of the procedures as noted (Schemes III and IV). Tosylation of all glycols was done using tosyl chloride and powdered potassium hydroxide as the base in tetrahydrofuran as reported for other alcohols [29,31] (Scheme IV). Optically active glycol **27** (Scheme I B) was prepared by the procedure of Cooper and Walborsky [30]. Chiral diamine **28** (Scheme I C) was prepared as reported by Huszthy, Bradshaw and co-workers [31]. All optical, physical, and spectra data obtained from chiral starting materials **27** and **28** matched those reported [30,31]. All reported yields are of isolated products.

Ethyl 2,5-Dimethyl-4-oxopyrimidine-6-carboxylate (**16**). (Scheme II).

A solution of 7.90 g (0.34 g-atom) of sodium metal in 150 ml of hplc grade ethanol was added dropwise to a solution of 32.0 g (0.34 mole) of acetamidine hydrochloride (**14**) in 250 ml of hplc grade ethanol under an argon atmosphere. The resulting salt was filtered. The filtrate (acetamidine free base) was added dropwise under argon to 65 ml (69.5 g, 0.34 mole) of diethyl oxalpropionate (**15**) and the mixture was stirred under reflux for 16 hours. The reaction mixture was cooled and solid **16** was filtered in three crops as the solvent evaporated. The product was recrystallized from ethyl acetate to give 35.1 g (52%) of **16** as colorless crystals, mp 172-173°. The physical and spectral properties of **16** matched those reported [25].

Ethyl 2-Methyl-4-oxopyrimidine-6-carboxylate (**20**).

Compound **20** was prepare as described above for **16** except diethyl oxalacetate was prepared and used instead of diethyl oxalpropionate. Compound **20** was isolated in a 10% yield as a light yellow solid, mp 180°; ir (potassium bromide): 3281, 3052, 1714, 1639, 1528, 1410, 1231, 1153, 1116, 1026 cm^{-1}; ^{1}H nmr: δ 2.40 (t, 3H), 2.58 (s, 3H), 4.43 (q, 2H), 7.1 (s, 1H), 10.8 (bs, 1H); ms: (low voltage), m/z 182 (M^+), 110 (base peak).

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.52. Found: C, 52.82; H, 5.67.

Ethyl 2-(Carbomethoxy)-4-chloro-5-methylpyrimidine-6-carboxylate (**19**). (Scheme II).

Compound **18** (20 g, 0.083 mole) was refluxed in 200 ml of freshly distilled phosphorus oxychloride for 2 hours. Excess phosphorus oxychloride was removed under reduced pressure. The resulting residue was dissolved in 400 ml of cold chloroform and poured over 100 g of ice. The phases were separated and the organic phase was extracted three times with 100 ml portions of cold water, and dried over anhydrous magnesium sulfate. The chloroform was evaporated and the desired chloropyrimidine was recrystallized from ether to give 17.6 g (82%) of **19** as microcrystals, mp 72-73°; ir (potassium bromide): 1752, 1714, 1531, 1467, 1434, 1385, 1344, 1300, 1260, 1197, 1166, 1131, 1030 cm^{-1}; ^{1}H nmr: δ 1.39 (t, 3 H), 2.54 (s, 3 H), 4.0 (s, 3 H), 4.45 (q, 2 H); ms: (low voltage), m/z 259 (M^+), 186 (base peak).

Anal. Calcd. for $C_{10}H_{11}N_2O_4Cl$: C, 46.43; H, 4.29. Found: C, 46.40; H, 4.50.

Dimethyl 4-Methoxy-5-methyl-2,6-pyrimidinedicarboxylate (**13**). (Scheme II).

Sodium metal (2.36 g, g-atom) was dissolved in 125 ml of hplc grade methanol and the mixture was cooled to 4°. Chloropyrimidine **19** (10 g, 0.004 mole) in 125 ml of methanol was added dropwise. The resulting mixture was stirred at 4° for 1 hour, then at room temperature for 1 hour. The reaction mixture was cooled to 4° and brought to a *p*H of 6 with 3 ml of acetic acid. The solvent was then evaporated. The residue was partitioned between 200 ml of methylene chloride and 100 ml of ice water and the water layer was extracted three times with 100 ml portions of methylene chloride. The combined organic layers were evaporated and the

desired compound was recrystallized from anhydrous ether or heptane to give 8.7 g (93%) of **13** as a white solid in two crops, mp 131-132°; ir (potassium bromide): 1747, 1724, 1571, 1474, 1441, 1390, 1373, 1265, 1246, 1080, 759 cm^{-1}; ^1H nmr: δ 2.38 (s, 3 H), 3.95 (s, 3 H), 3.98 (s, 3 H), 4.11 (s, 3 H).

Anal. Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04. Found: C, 50.01; H, 5.12.

4-Methoxy-5-methyl-2,6-pyrimidinedimethanol (**11**). (Scheme II).

Pyrimidine diester **13** (3.45 g, 0.014 mole) in 170 ml of hplc grade methanol was cooled to 4° under argon. To this mixture, 2.6 g (0.07 mole) of sodium borohydride was added in portions and the mixture was stirred for 1 hour.The methanol was removed under reduced pressure and the resulting residue was dissolved in 240 ml of chloroform and 100 ml of water. The water layer was extracted three times with chloroform. The combined organic layers were evaporated to give 2.64 g (100%) of **11**, mp 89-90°; ir (potassium bromide): 3400, 1581, 1475, 1372, 1043 cm^{-1}; ^1H nmr: δ 2.00 (s, 3 H), 3.95 (s, 3 H), 4.60 (s, 4 H); ms: m/z 184 (M^+ and base peak).

Anal. Calcd. for $C_8H_{12}N_2O_3$: C, 52.22; H, 6.56. Found: C, 52.28; H, 6.49.

4-Methoxy-5-methyl-2,6-pyrimidinedimethyl Ditosylate (**12**). (Scheme II).

Pyrimidine dimethanol **11** (4.4 g, 0.02 mole) was slowly added to a stirred mixture of 9.0 g of finely powdered potassium hydroxide in 100 ml of tetrahydrofuran under argon at 4°. This reaction mixture was stirred for 2 hours at 4° and then at room temperature for 1 hour. After the reaction was completed, the solvent was removed under reduced pressure. The residue was dissolved in a mixture of 300 ml of cold methylene chloride and 100 ml of ice water. The resulting mixture was shaken well and the phases were separated. The aqueous phase was shaken twice with 200 ml portions of cold methylene chloride and the combined organic phases were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the crude product was recrystallized from a dichloroethane and methanol mixture to give 9.2 g (78%) of **12** as a white solid; ir (neat) 2954, 2931, 2860, 1566, 1439, 1366, 1184, 1112 cm^{-1}; ^1H nmr: δ 2.20 (s, 3 H), 2.50 (s, 3 H), 2.51 (s, 3 H), 4.00 (s, 3 H), 5.1 (s, 4 H), 7.4 (m, 4 H), 7.9 (m, 4 H). A satisfactory elemental analysis was obtained for macrocycle **9**, a derivative of **12**.

4-Octyl-3,9-dioxa-6-thia-1,11 Undecanediol (**29**). (Scheme III).

This octyl-substituted thiaglycol was prepared as reported [27] except intermediate **30** was recrystallized from cold hexane instead of being distilled. This allowed **30** to be synthesized in a 100% yield. Furthermore, conversion of diacid **31** into its diester derivative allowed a more efficient reduction to diol **29** (65% *vs* 39% as reported [27]). All physical and spectral properties of **29** and **34** were as reported [27].

General Procedure for the Preparation of the Pyrimidino-crowns **3-8**. (Scheme I A).

In an oven-dried 500 ml three-necked round-bottom flask equipped with an addition funnel, argon inlet, and a stirring bar, were placed 200 ml of dry *tert*-butyl alcohol and 0.024 g -atom of potassium or sodium metal. Diol **11** (1.5 g, 8 mmoles) was added and the mixture was stirred for 30 minutes at 60°. The appropriate glycol ditosylate **21-26** (8 mmoles), dissolved in 50 ml of dry tetrahydrofuran or dioxane, was added dropwise. The resulting reaction mixture was stirred at 60° for 3 hours. overnight at room temperature, and refluxed for 15 minutes. The salts were filtered and the solvent was evaporated. The residue was purified and characterized as described below for each individual pyrimidino-crown ether.

16-Methoxy-15-methyl-3,6,9,12-tetraoxa-17,18-diazabicyclo-[12.3.1]octadecane-1(18),14,16-triene (**3**). (Scheme I A).

Crown **3** was prepared as described above using 3.7 g (8 mmoles) of **21**. The crude product was purified by column chromatography on neutral alumina using ethanol/toluene:1/80 and 1/40 as eluants to give 0.77 g (32%) of **3** as a clear viscous oil; ir (neat): 2868, 1730, 1578, 1465, 1414, 1367, 1293, 1250, 1190, 1106, 939, 856, 789 cm^{-1}; ^1H nmr: δ 2.07 (s, 3 H), 3.57-3.70 (m, 12 H), 3.9 (s, 3 H), 4.52 (s, 2 H), 4.54 (s, 2 H); ms: m/z 299 (M^+), 167 (base peak).

Anal. Calcd. for $C_{14}H_{22}N_2O_5$: C, 56.64; H, 7.43. Found: C, 56.81; H, 7.58.

19-Methoxy-18-methyl-3,6,9,12,15-pentaoxa-20,21-diazabicyclo-[15.3.1]heneicosa-1(21),17,19-triene (**4**) (Scheme I A).

Crown **4** was prepared as described above using 4.07 g (8.1 mmoles) of **22**. The crude product was purified by column chromatography on neutal alumina using ethanol/toluene: 1/80 and 1/20 as eluants to give 1.18 g (42%) of **4** as a clear viscous oil; ir (neat): 2866, 1725, 1676, 1465, 1413, 1369, 1249, 1190, 1121, 959, 870, 785 cm^{-1}; ^1H nmr: δ 2.1 (s, 3 H), 3.6-3.8 (m, 16 H), 3.9 (s, 3 H), 4.64 (s, 2 H), 4.66 (s, 2 H); ms: (low voltage), m/z 342 (M^+), 167 (base peak).

Anal. Calcd. for $C_{16}H_{26}N_2O_6$: C, 56.12; H, 7.65. Found: C, 56.00; H, 7.42.

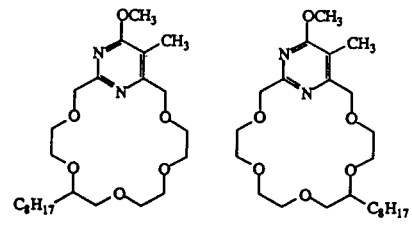
22-Methoxy-21-methyl-3,6,9,12,15,18-hexaoxa-23,24-diazabicyclo-[18.3.1]tetracosa-1(24),20,22-triene (**5**). (Scheme I A).

Macrocycle **5** was prepared as above using 5.0 g (8.1 mmoles) of **23**. The crude product was purified by column chromatography on neutral alumina using ethanol/toluene: 1/80 and 1/40 as eluants to give 1.2 g (38%) of **5** as a clear viscous oil; ir (neat): 2857, 1576, 1465, 1422, 1378, 1341, 1252, 1093, 1043 cm^{-1}; ^1H nmr: δ 2.1 (s, 3 H), 3.55-3.8 (bm, 20 H), 3.91 (s, 3 H), 4.56 (s, 2 H), 4.58 (s, 2 H); ms: (low voltage), m/z 386 (M^+), 167 (base peak).

Anal. Calcd. for $C_{18}H_{30}N_2O_7$: C, 55.94; H, 7.82. Found: C, 56.15; H, 8.00.

19-Methoxy-18-methyl-7 (and/or 11)-octyl-3,6,9,12,15-pentaoxa-20,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**6**). (Scheme I A).

Crown **6** was prepared as above using 5 g (8.1 mmoles) of **24**. The crude product was purified by column chromatography on neutral alumina using ethanol/toluene: 1/40 as eluant to give 1.85 g (50%) of **6** as a viscous oil; ir (neat): 2925, 2854, 1574, 1464, 1414, 1368, 1116 cm^{-1}; ^1H nmr: δ 0.84 (t, 3 H), 1.22 (bm, 14 H), 2.1 (d, 3 H), 3.45-3.7 (bm, 15 H), 3.93 (d, 3 H), 4.60-4.66 (m, 4 H); ms: (low voltage), m/z 454 (M^+), 149 (base peak). The doublets at δ 2.1 and 3.93 and the multiplet at 4.6-4.66 are due to equal amounts of the two isomeric forms of **6** as shown below:



Anal. Calcd. for $C_{24}H_{42}N_2O_6$: C, 63.41; H, 9.31. Found: C, 63.58; H, 9.20.

19-Methoxy-18-methyl-3,6,12,15-tetraoxa-9-thia-20,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**7**). (Scheme I A).

Thia-crown **7** was prepared as above using 5.2 g (8.1 mmoles) of sulfur-containing glycol **25**. The crude product was purified by column chromatography on neutral alumina using ethanol/toluene: 1/50 as eluant to give 1.35 g (46%) of **7** as a white waxy solid, mp 52-53°; ir (potassium bromide): 2921, 2870, 1574, 1476, 1407, 1374, 1348, 903, 799, 766, 733, 691, 668, 634, 557, 535, 507 cm^{-1}; ^1H nmr: δ 2.15 (s, 3 H), 2.73 (m, 4 H), 3.65-3.85 (bm, 12 H), 3.97 (s, 3 H), 4.64 (s, 4 H); ms: (low voltage), m/z 358 (M^+), 227 (base peak).

Anal. Calcd. for $C_{16}H_{26}N_2O_5S$: C, 53.61; H, 7.31. Found: C, 53.70; H, 7.20.

19-Methoxy-18-methyl-7 (and/or 11)-octyl-3,6,12,15-tetraoxa-9-thia-20,21-diaxabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**8**). (Scheme I A).

Macrocycle **8** was prepared as above from 5.13 g (8.1 mmoles) of glycol **26**. The crude product was purified by column chromatography on neutral alumina using ethanol/toluene: 1/40 as eluant to give 1.91 g (48%) of **8** as a viscous oil; ir (potassium bromide): 2924, 2855, 1575, 1464, 1414, 1369, 1290, 1191, 1102, 963, 730 cm^{-1}; ^1H nmr: δ 0.84 (t, 3 H), 1.22 (bm, 14 H), 2.15 (s, 3 H), 2.73 (m, 4 H), 3.45-3.85 (bm, 11 H), 3.97 (s, 3 H), 4.64 (s, 4 H); ms: m/z 471 (M^+), 74 (base peak).

Anal. Calcd. for $C_{24}H_{42}O_5N_2S$: C, 61.24; H, 8.99. Found: C, 61.51; H, 9.00.

(4*S*,14*S*)-19-Methoxy-4,14,18-trimethyl-3,6,9,12,15-pentaoxa-20,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**9**). (Scheme I B).

In an oven-dried 500 ml three-necked round-bottom flask equipped with an addition funnel, argon inlet, and a stirring bar, were placed 200 ml of dry *tert*-butyl alcohol and 0.024 g-atom of potassium or sodium metal. Chiral glycol **27** (1.8 g, 0.008 mole) was added and the mixture was stirred for 30 minutes. Pyrimidine ditosylate **12** (4.0 g, 0.008 mole) in 50 ml of dry tetrahydrofuran was added dropwise to the solution at 60°. The resulting mixture was stirred at 60° for 3 hours, overnight at room temperature, and refluxed for 15 minutes. The salts were filtered and the solvent was evaporated. The crude product was purified by column chromatography on neutral alumina using ethanol/toluene: 1/160 as eluant, and on silica using methanol/toluene: 1/4 as eluent to give 0.89 g (29%) of **9** as an oil; ir (neat): 2931, 2860, 1572, 1460, 1407, 1366, 1184, 1114, 996, 961, 920 cm^{-1}; ^1H nmr: δ 1.17 (t, 6 H), 2.16 (s, 3 H), 3.65-3.85 (bm, 14 H), 3.97 (s, 3 H), 4.71 (m, 4 H); ms: (low voltage), m/z 370 (M^+), 209 (base peak).

Anal. Calcd. for $C_{18}H_{30}N_2O_6$: C, 58.36; H, 8.16. Found: C, 58.25; H, 7.96.

(4*S*,14*S*)-4,14-Dibenzyl-19-methoxy-18-methyl-6,9,12-trioxa-3,15,20,21-tetraazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (**10**). (Scheme IC).

In an oven-dried 250 ml three-necked round-bottom flask equipped with an addition funnel, argon inlet, and a stirring bar, were placed 0.79 g (2.1 mmoles) of chiral dibenzyl-substituted **28**, 50 ml of dry diglyme, 1.51 g (2.1 mmoles) of pyrimidine diester **13**, and 0.41 g (5.2 mmoles) of sodium tosylate. The mixture was stirred at 135° for 12 days under argon. After the reaction was completed, the solvent was removed under reduced pressure. The residue was dissolved in 100 ml of methylene chloride and 30 ml of ice water. The resulting mixture was shaken well and the phases were separated. The aqueous phase was shaken twice with 50 ml portions of methylene chloride and the combined organic phases were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the crude product was purified by column chromatography, first on silica gel with tetrahydrofuran/toluene: 1/8 as eluent, and then on neutral alumina using ethanol/toluene 1/33 as eluent to give 0.22 g (19%) of **10** as a light brown oil; ir (neat): 3318, 3060, 3048, 2931, 2860, 1652, 1407, 1366, 1184, 1112 cm^{-1}; ^1H nmr: δ 2.62 (s, 3 H), 3.15 (m, 4 H), 3.45-4.00 (bm, 15 H), 4.50 (m, 2 H), 7.37 (m, 10 H), 8.4 (dd, 2 H); ms: (low voltage), m/z 548 (M^+), 457 (base peak).

Anal. Calcd. for $C_{30}H_{36}N_4O_6$: C, 65.68; H, 6.61. Found: C, 65.40; H, 6.75.

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