prepared by the treatment of *o*-anisaldehyde with triethyl orthoformate in the presence of a catalytic amount of *p*-toluenesulfonic acid, was stirred at 80 °C for 3.5 h. The resulting precipitate was filtered, washed with ether, and recrystallized from CH_3CN to give **10**: yield 67% (280 mg); IR (KBr) 3020, 1605, 1545, 1485, 1465, 1315, 1260, 1170, 1035, 970, 770 cm^{-1}; ^1H NMR (CD_3CN) δ 1.74 (s, 6 H), 3.98 (s, 3 H), 3.99 (s, 3 H), 7.10 (t, J = 7.3 Hz, 1 H), 7.14 (d, J = 7.9 Hz, 1 H), 7.53 (d, J = 16.5 Hz, 1 H), 7.56–7.62 (m, 3 H), 7.64–7.71 (m, 2 H), 7.96 (dd, J = 1.2, 7.3 Hz, 1 H), 8.50 (d, J = 16.5 Hz, 1 H); ^{13}C NMR (CD_3CN) δ 26.57, 35.50, 53.51, 57.07, 113.31, 113.79, 115.88, 118.65, 122.28, 123.80, 130.31, 130.71, 131.48, 136.72, 142.92, 144.38, 150.28, 161.22, 183.94.

***N*-Acetylmonoaza-crown Ethers 11a–c (Exemplified with 11a).** To a CH_2Cl_2 solution (2.0 mL) of monoaza-15-crown-5 (55 mg, 0.25 mmol)[11] and finely ground K_2CO_3 (69 mg, 0.5 mmol) was added acetyl chloride (39 mg, 0.5 mmol) dropwise at 0 °C. After 2 h of stirring at rt, evaporation of the solvent was followed by extractive workup with CH_2Cl_2 gave **11a**.

11a: yield 90% (59 mg); oil; IR (neat) 2800, 1600, 1440, 1350, 1250, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (s, 3 H), 3.49–3.85 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 21.60, 47.66, 49.03, 69.15–71.53, 171.03.

11b: yield 88% (67 mg); oil; IR (neat) 2800, 1620, 1420, 1350, 1230, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3 H), 3.59–3.72 (m, 24 H); ^{13}C NMR ($CDCl_3$) δ 21.68, 46.71, 49.92, 69.47–70.92, 171.01.

11c: yield 90% (79 mg); oil; IR (neat) 2800, 1620, 1440, 1350, 1240, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3 H), 3.58–3.73 (m, 28 H); ^{13}C NMR ($CDCl_3$) δ 21.70, 46.36, 49.88, 69.43–70.99, 171.03.

Supplementary Material Available: Proton NMR spectra of all new compounds for which elemental analyses are not given (29 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

New Symmetrical Chiral Dibenzyl- and Diphenyl-Substituted Diamido-, Dithionoamido-, Diaza-, and Azapyridino-18-crown-6 Ligands

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Eleven new chiral macrocycles (**1–11**, see Figure 1) of the pyridino-18-crown-6 type have been prepared. Nine diazapyridino-crown ligands contain two amide (**1**, R = benzyl; **4**, R = phenyl), two *N*-methylamide (**7**, R = phenyl), two thionoamide (**2**, R = benzyl; **5**, R = phenyl), two *N*-methylthionoamide (**8**, R = phenyl), two amine (**3**, R = benzyl; **6**, R = phenyl), or two *N*-methylamine (**9**, R = phenyl) groups incorporated into the macroring. The appropriate chiral diamine was treated with dimethyl 2,6-pyridinedicarboxylate (or 2,6-pyridinedicarbonyl dichloride), *O,O'*-dimethyl 2,6-pyridinedicarbothioate, or 2,6-pyridinedimethyl ditosylate to prepare these materials. The macrocyclic diamides were also converted to the macrocyclic dithionoamides using Lawesson's reagent and the latter macrocycles were reduced to the diamines. A new symmetrically substituted dimethylazapyridino-18-crown-6 ligand (**10**) and its *N*-acetyl derivative **11** were also prepared. The interactions of some of the new chiral ligands with (*R*)- and (*S*)-[α-(1-naphthyl)ethyl]ammonium perchlorate were studied by ^1H NMR spectral techniques. The degree of enantiomeric recognition was determined by the difference of the free energy of activation values ($\Delta\Delta G^{\ddagger}$) and the difference in log K values for these interactions. The X-ray analyses of the dithionoamido ligands (**2**, **5**, and **8**) showed severe deviations of the S and N atoms from the plane of the pyridine ring, especially in the case of **8**. The optical rotation of **8** changed with time due to conformational changes. The relevant conformations of **8** are discussed in light of the X-ray crystallography, molecular mechanics, and ^1H NMR spectra.

Introduction

Enantiomeric recognition phenomena play an important role in a variety of physical, chemical, and biological processes. Examples include sensing, determination of concentrations, and separations of enantiomers; catalysis reactions; and incorporation of single enantiomeric forms of amino acids and sugars in biochemical pathways.

Our interest in enantiomeric recognition has focused on the interaction of chiral macrocycles with chiral organic ammonium salts.[1-5] Since Cram and his co-workers published their pioneering studies on the use of chiral macrocyclic ligands in enantiomeric recognition,[6] a great number of chiral macrocycles have been synthesized and studied. Most of this work has been reviewed.[4,5,7,8]

In the past decade, we have particularly been interested in the interactions of chiral macrocycles containing pyridine units with organic ammonium salts.[1-5] These crown ethers were chosen for study because they form strong complexes with organic ammonium salts[1] and they also show appreciable enantiomeric recognition in certain cases.[1-5] Thus, diester[1,2,5] (X = O, Y = O, R = alkyl, phenyl), dithiono ester[1] (X = O, Y = S, R = methyl), and

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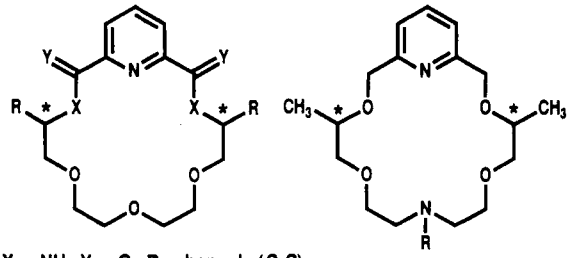

1, X = NH; Y = O; R = benzyl (*S,S*)
2, X = NH; Y ≡ S; R ≡ benzyl (*S,S*)
3, X ≡ NH; Y = H_2; R ≡ benzyl (*S,S*)
4, X ≡ NH; Y ≡ O; R ≡ phenyl (*S,S*)
5, X ≡ NH; Y ≡ S; R = phenyl (*S,S*)
6, X = NH; Y ≡ H_2; R ≡ phenyl (*S,S*)
7, X ≡ NCH_3; Y ≡ O; R = phenyl (*S,S*)
8, X ≡ NCH_3; Y ≡ S; R = phenyl (*S,S*)
9, X ≡ NCH_3; Y ≡ H_2; R = phenyl (*S,S*)

10, R ≡ H (*S,S*)
11, R = C(O)CH_3 (*S,S*)

Figure 1. Chiral diamido-, dithionoamido-, diaza, and azapyridino-18-crown-6 ligands.

non ester[1,4,5] (X = O, Y = H_2, R = alkyl, alkenyl, benzyl, phenyl) pyridino-18-crown-6 ligands (see Figure 1) have been studied.[8] In our efforts to identify, understand, and quantitate the factors responsible for enantiomeric recognition of selected chiral organic ammonium salts by chiral piridine-containing macrocycles, we have synthesized novel chiral hosts which possess desired stored information for recognizing guest enantiomers.[2-5] We have characterized the host–guest interactions for these chiral ligands by ^{1}H NMR spectroscopy,[1-5] calorimetric titration,[1] and X-ray crystallographic[1,3,4] and molecular mechanics (empirical force field)[4,5] procedures. Empirical force field calculations of enantiomeric selectivity in most cases correlated well with the observed differences in ΔG_c^* for chiral macrocycle–chiral organic ammonium salt interactions as determined by a temperature-dependent ^{1}H NMR technique.[4,5] Good agreement has also been found for log *K* (equilibrium constant for the above-mentioned host–guest interactions) values determined by calorimetric titration and those determined by a direct ^{1}H NMR titration technique.[9]

In a continuation of our effort to identify, understand, and quantitate the factors responsible for these host–guest interactions, we now have synthesized new diamido (**1**, **4**, **7**), dithionoamido (**2**, **5**, **8**), diaza (**3**, **6**, **9**), and monoaza (**10**) pyridino-18-crown-6 ligands. The acetyl derivative (**11**) of **10** was also prepared. **10** was prepared because amine groups of macrocycles can be used to chemically bond them to silica gel.[10-12] Chiral macrocycles chemically bound to silica gel are suitable for enantiomeric separations of chiral ammonium salts.[13]

Although the simple achiral di-*N*-tosyldiaza (X = *N*-Ts, Y = H_2, R = H, Figure 1)[14], diamido (X = NH, Y = O, R = H),[14] and the dibenzo analogue[15] of the latter have been prepared, their complexation properties with ammonium salts have not been studied. It is noteworthy to mention that chiral diamido diester[16] and dithionoamido diester[17] analogues of pyridino-18-crown-6 have also been prepared, but their complexation properties with ammonium salts likewise have not been studied. No diazapyridino-18-crown-6 ligands like **3**, **6**, and **9** have been reported, although the simple achiral diazapyridino-15-crown-5 is known.[18] On the other hand, enantiomeric recognition by chiral diaza-18-crown-6 macrocycles (not containing a pyridine unit) for the enantiomers of chiral organic ammonium salts have been extensively studied, and they exhibited selectivity in certain cases.[19-21]

Results and Discussion

New chiral macrocycles **1**–**11** (see Figure 1) were prepared as shown in Scheme I. Cyclization of diamines **14** and **15** with dimethyl 2,6-pyridinedicarboxylate in the presence of sodium tosylate gave the diamido-crowns **1** and **4** in yields of 29% and 25%, respectively (Scheme IA). Ligand **1** also was prepared in a yield of 23% in the absence of sodium tosylate. Diamines **14** and **15** were treated with *O,O'*-dimethyl 2,6-pyridinedicarbothioate in the presence of sodium tosylate to give **2** and **5** in yields of 28% and 8%, respectively. Cyclization of diamine **15** with 2,6-pyridinedicarbonyl dichloride gave **4** (Scheme IB) in a lower yield (16%) than the reaction with the diester, although the reaction of diacid dichlorides with diamines is usually an effective method for ring closure to form the macrocyclic diamides.[22-24] On the other hand, the high dilution reaction[25] of diamine **16** and the diacid dichloride at 0 °C gave *N,N'*-dimethyldiamido-crown **7** in a yield of 53%.

Pyridinodiamido-crowns **1**, **4**, and **7** were refluxed with Lawesson's reagent in toluene for 9 h to give dithionoamido-crowns **2** (88%), **5** (90%), and **8** (90%) (Scheme IC). Baxter and Bradshaw have shown that diester furano-18-crown-6 was transformed into the corresponding dithionoester furano-18-crown-6 in a good yield using Lawesson's reagent.[26] Lawesson's reagent also was used successfully by Kellogg and co-workers for the selective conversion of a diamidodiester crown into a dithioamido diester crown in a quantitative yield.[17] Dithionoamido-pyridino-crowns **2**, **5**, and **8** were reduced to diazapyridino-crowns **3** (32%), **6** (54%), and **9** (52%) by Raney nickel. We previously reported the reductive desulfurization of several dithionoester pyridino-crown ethers by Raney nickel in yields of 40–76%.[27] Diazapyridino-crowns **6** and **9** were also synthesized in different ways (Scheme IE and IF). Bistosylamide **17** was first cyclized with 2,6-pyridinedimethyl ditosylate in the presence of base to give

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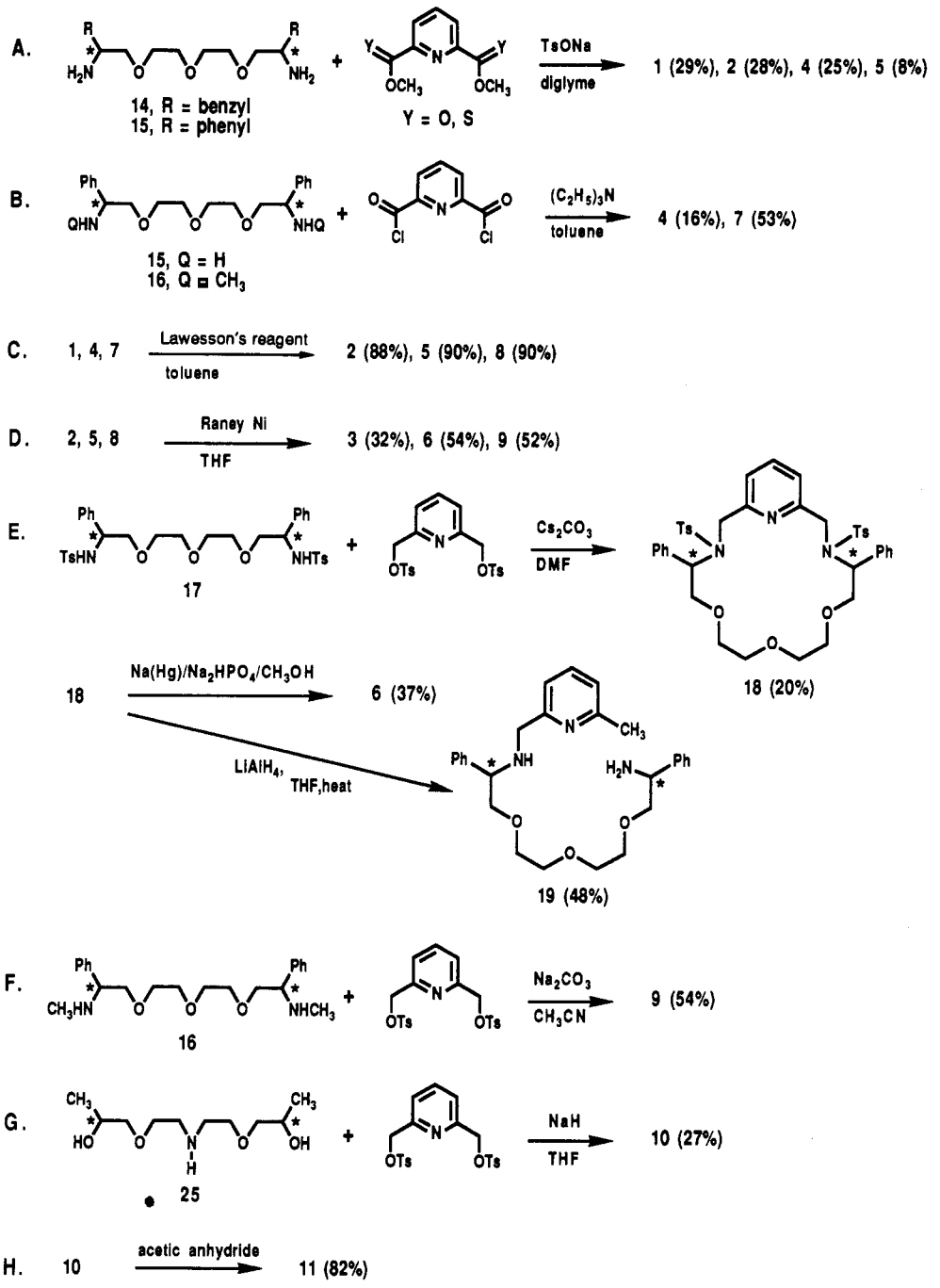
Scheme I. Preparation of New Chiral Pyridino-18-crown-6 Ligands



N,N'-ditosyldiaza-crown **18**. The latter crown was reduced to **6** by sodium amalgam in the presence of dibasic sodium phosphate in methanol as reported for similar compounds.[28,29] Our attempt to form **6** by reductive removal of the *N*-tosyl groups by $LiAlH_4$ in THF[30,31] was not successful since the macrocyclic ring opened to give product **19**. Similar reductive ring opening was observed by Newkome and Marston when they treated a pyridino-18-crown-6 derivative with $LiAlH_4$ in THF.[32] *N,N'*-Dimethyldiazapyridino-crown **9** was prepared in a yield of 54% by a one-step cyclization of *N,N'*-dimethyldiamine **16** with 2,6-pyridinedimethyl ditosylate (Scheme IF).

Chiral dimethylazapyridino-18-crown-6 (**10**) was prepared from the appropriate chiral azaglycol (**25**) in a 27% yield as described by us for the synthesis of several other chiral pyridino-crowns (Scheme IG).[4,5] Acetylation of **10** gave the *N*-acetylmonoaza-crown **11** in a good yield (Scheme IH).

The structures proposed for these new macrocycles (**1–11**) are consistent with data obtained from their ^1H NMR, MS, and IR spectra and elemental analyses (see the Experimental Section).

The chiral starting materials needed for the preparation of the chiral macrocycles **1–11** were obtained as shown in Scheme II. (*S*)-(+)-2-Phenylglycine was treated with formic acid and acetic anhydride to give formamide **12** (Scheme IIA). *N*-Methyl-2-phenyl-2-aminoethanol (**13**) was prepared by the reduction of compound **12**. Chiral diamines **14**, **15**, and **16** were prepared in yields of 58–85%

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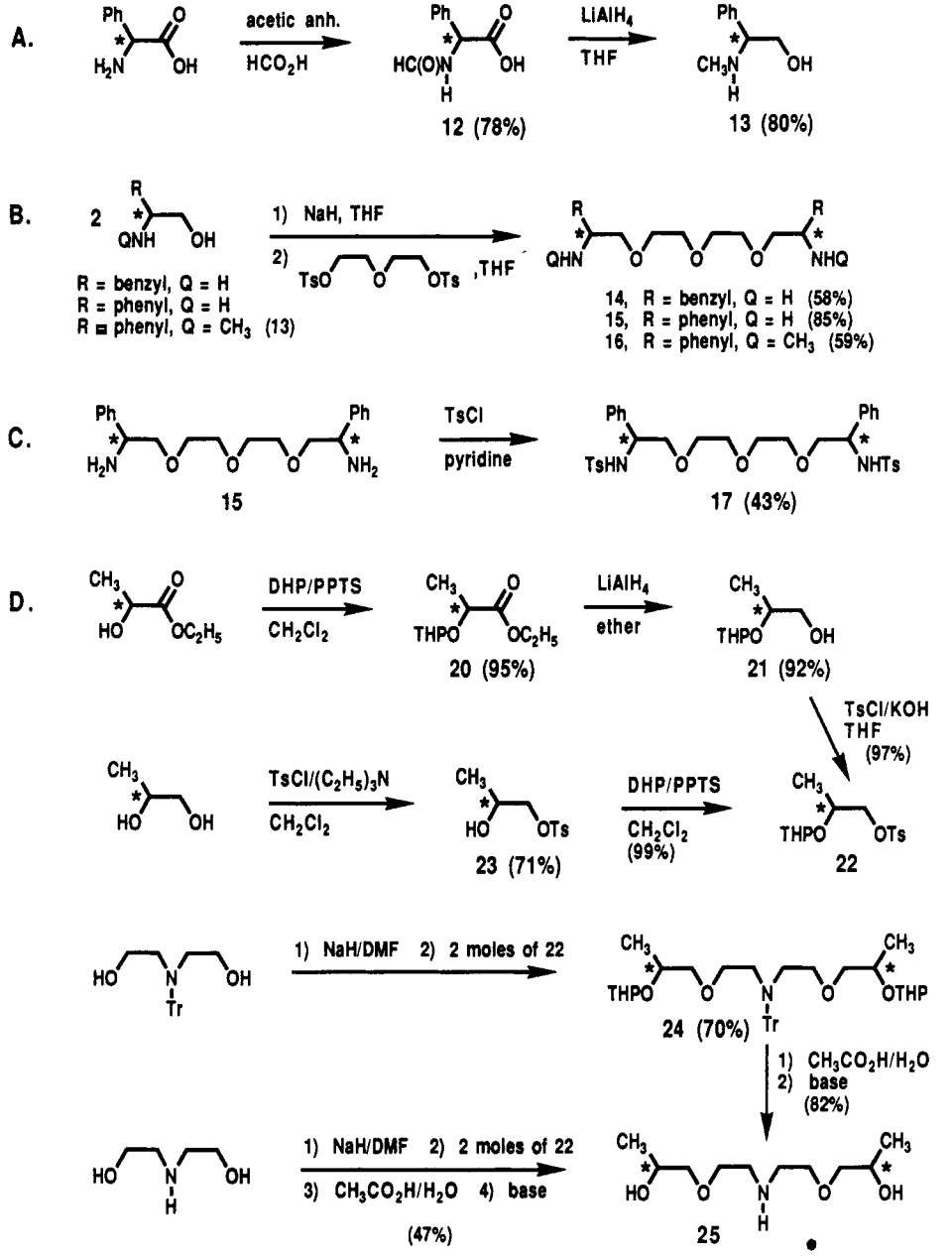
Scheme II. Preparation of Chiral Starting Materials



Note: Ts = tosyl; Tr = trityl; DHP = 3,4-dihydro-2*H*-pyran; PPTS = pyridinium tosylate; THP = tetrahydropyranyl

from (*S*)-2-benzyl-2-aminoethanol, (*S*)-2-phenyl-2-aminoethanol, and (*S*)-*N*-methyl-2-phenyl-2-aminoethanol (**13**), respectively, by treatment with diethylene glycol ditosylate in the presence of sodium hydride in THF (Scheme IIB).[20] Under these conditions, the alkoxide of the ethanolamine forms and acts as the nucleophile. Diamines **14** and **15** were difficult to purify not only by distillation but also by chromatography; however, the *N*,*N*′-dimethyldiamine **16** was easily purified by distillation under reduced pressure. α,ω-Bistosylamide **17** was obtained by tosylation of diamine **15** (Scheme IIC). This tosylation did not occur at 0 °C, but needed some heat as reported.[33,34]

The chiral dimethyl-substituted monoazatetraethylene glycol **25** was prepared as shown in Scheme IID. (*S*)-(−)-2-(Tetrahydropyranyloxy)propyl *p*-toluenesulfonate (**22**) was prepared in two ways. First, (*S*)-(−)-ethyl lactate was treated with 3,4-dihydro-2*H*-pyran (DHP) to give the THP-blocked ester **20**. Ester **20** was reduced to the THP-blocked propylene glycol **21** which was tosylated at the primary hydroxy group to give **22**. Second, (*S*)-(+)-1,2-propanediol was first tosylated at the primary position and then the secondary hydroxy group was protected with DHP to give **22**. Monoazatetraethylene glycol **25** was prepared from **22** by two synthetic routes. In the first route, the bis(sodium alkoxide) derivative of *N*-trityldiethanolamine was reacted with 2 mol of **22** to give *N*-trityl, *O*-THP-protected **24**. Compound **24** was deprotected with a water–acetic acid mixture to give chiral **25**. In the second route, the bisalkoxide derivative of diethanolamine (without the *N*-trityl group) was reacted with 2 mol of **22** to give the di-*O*-THP-protected precursor of **25** which was deprotected as mentioned above.

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Elemental analyses for the chiral diamine and glycol starting materials were not performed. However, good analyses were obtained for macrocycles 1–11 prepared from these starting materials.

Complexation of the enantiomeric forms of NapEt by some of the new ligands has been studied by the temperature-dependent ^1H NMR technique[1-5] and by determining the log K values for the association of the chiral ligand and the enantiomer salt by a direct ^1H NMR spectral method.[5,9] Table I contains the free energy of activation (ΔG_c^*) and log K values for the interaction of some of these new chiral ligands with the enantiomers of [α-(1-naphthyl)ethyl]ammonium perchlorate (NapEt). The data show that, in general, these chiral ligands exhibit only moderate or no recognition for the enantiomers of NapEt. The ΔG_c^* data show that ligands **7**, **8**, and **9** form stable complexes in CD_2Cl_2 with the R and S forms of NapEt but the resulting complexes each have about the same kinetic stability. This is in sharp contrast to complexation by the chiral diphenyl-substituted pyridino-18-crown-6 (Y = H_2, X = O, R = phenyl) and diester pyridino-18-crown-6 (Y = O, X = O, R = phenyl) ligands (see Figure 1) which exhibited considerable recognition of one form of NapEt over the other form in CD_2Cl_2 as determined by the temperature-dependent ^1H NMR method.[5] log K values in Table I do show that some of these ligands exhibit enantiomeric recognition in a mixture of 50% $CDCl_3$–50% CD_3OD or in CD_3NO_2. Dithionoamide (*S,S*)-**5** favored (*R*)-NapEt over (*S*)-NapEt by 0.37 log K unit. This recognition compares favorably with that obtained by the similar diphenyl-substituted crown (X = O, Y = O) ligand.[5] Ligand (*S,S*)-**8** also exhibited moderate recognition for (*R*)-NapEt in the 50% $CDCl_3$–50% CD_3OD mixture. Ligands (*S,S*)-**1** and (*S,S*)-**7** exhibit some recognition for one form of NapEt in CD_3NO_2. Thus, in some cases, these new chiral ligands show moderate enantiomeric recognition but they have inferior recognition properties as compared to the diphenyl- and di-*tert*-butyl-substituted pyridino-18-crown-6 and diester pyridino-18-crown-6 ligands (all have X = O).[5]

The data in Table I also show that log K values for macrocycle–ammonium salt interactions increase as the polarity of the solvent decreases. This is an expected trend for solvent effects in these types of interactions. It is also instructive to note that there is a significant decrease in log K values when an amide group is substituted for an ester in these systems. This is best observed by comparing the log K value of 0.7 (Table I) for the interaction of (*S,S*)-**4** with (*R*)-NapEt in a mixture of 50% $CDCl_3$–50% CD_3OD with a log K value of 2.15 for the same interaction of the comparable ester (X and Y = O, R = phenyl) in a mixture of 30% $CDCl_3$–70% CD_3OD.[5] The two solvent systems are slightly different but the latter solvent is more polar, which should decrease the log K value. This significant decrease in complexing ability for the diamido-crowns is probably a result of distorted macrorings that will be mentioned later. The diamino-crowns, on the other hand, form stronger complexes as shown by the log K value of 3.2 for the interaction of (*S,S*)-**9** with (*R*)-NapEt.

The structures of **2**, **5**, and **8** were determined by X-ray diffraction studies. The discussion of the experimental procedures used in these studies and tables of structure determination summaries, atomic parameters, and torsion angles are included in the supplementary material. The molecule of **5** contained a 2-fold axis. The unit cells of both **5** and **8** contain two chemically similar but crystallographically distinct molecules of **5** and **8**. Unfortunately, the amount of single-crystal data for each structure was not sufficient for a full anisotropic refinement, but by blocking atoms so that the number of parameters to be refined in each block was not so large, it was possible to refine most of the non-hydrogen atoms of the three structures anisotropically. Specifically, all non-hydrogen atoms of **2**, all non-hydrogen atoms of one molecule of **5**, and all non-hydrogen atoms of the macrocyclic ring, pyridine ring, and the sulfur atom of both molecules of **8** were refined anisotropically. One molecule of **5**, which was badly disordered, and the methyl and phenyl carbon atoms of the two molecules of **8** were refined isotropically. The resulting R values were for **2**, R = 0.057, R_W = 0.0645; for **5**, R = 0.097, R_W = 0.085; and for **8**, R = 0.079, and R_W = 0.043. Details of the blocking of parameters and the treatment of hydrogen atoms of the three structures are contained in the supplementary material.

Computer drawings of the three molecules are shown in Figures 2–4. Only one of the two molecules of **5** and **8** was included as the conformations of the pairs are similar.

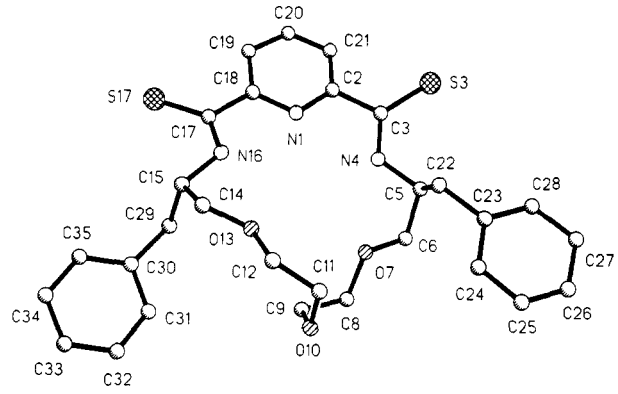

Figure 2. X-ray crystal structure of **2** drawn with SHLEXTL-PLUS.[39] Hydrogen atoms were omitted for clarity.

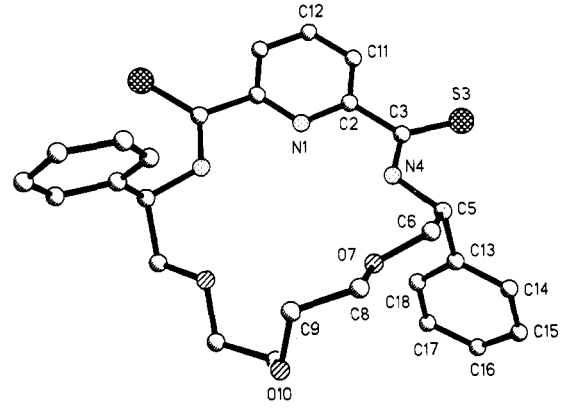

Figure 3. X-ray crystal structure of the unprimed molecule of **5** drawn with SHELXTL-PLUS.[39] The primed molecule and hydrogen atoms were omitted for clarity.

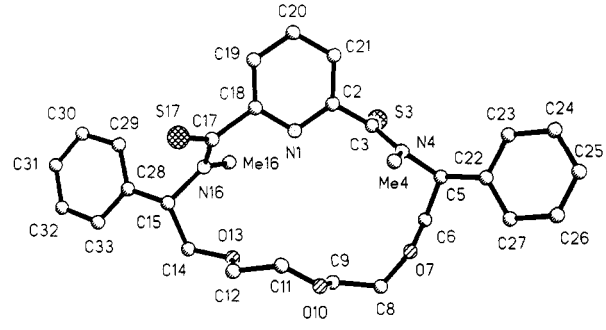

Figure 4. X-ray crystal structure of the unprimed molecule of **8** drawn with SHELXTL-PLUS.[39] The primed molecule and hydrogen atoms were omitted for clarity.

Table I. Free Energies of Activation (ΔG_c^*)[a] and log K Values[b] for the Interaction of Some Chiral Macrocyclic Ligands with the R and S Forms of [α-(1-Naphthyl)ethyl]ammonium Perchlorate (NapEt)

	ΔG_c^* values (kcal/mol)[c]		log K values at 20 °C			
ligand	(R)-NapEt	(S)-NapEt	(R)-NapEt[d]	(S)-NapEt[d]	(R)-NapEt[e]	(S)-NapEt[e]
(S,S)-1			g	g	0.8	1.00
(S,S)-4	f	f	0.7	g		
(S,S)-5			1.39	1.02		
(S,S)-7	11.3	11.2	g	g	2.75	2.55
(S,S)-8	>14.0	>13.9	0.7	0.5		
(S,S)-9	12.0	12.1	3.2	3.3	h	h

[a] A Varian VXR-500 spectrometer was used to record all ^{1}H NMR spectra for determination of both ΔG_c^* and log K values. The procedure for the determination of ΔG_c^* values was as described in refs 1–5. [b] log K values were determined by a direct ^{1}H NMR procedure as described in ref 9. [c] CD_2Cl_2 was used as a solvent. [d] 50%/50% (v/v) $CDCl_3$–CD_3OD mixture was used as a solvent. [e] CD_3NO_2 was used as solvent. [f] No splitting was observed in the ^{1}H NMR spectra. [g] log K value was so low that accurate measurements could not be made. [h] log K value was so high that accurate calculations could not be made.

Table II. Deviation of Nitrogen and Sulfur Atoms from the Plane of the Pyridine and Neighboring Carbon Atoms

molecule	deviation of S (Å)		deviation of N (Å)	
2	S3	0.46	N4	−0.39
	S17	−0.13	N16	0.21
5	S3	−0.20	N4	0.20
	S3′	−0.01	N4′	0.12
8	S3	−1.56	N4	1.02
	S17	1.16	N16	−0.90
	S3′	1.48	N4′	−0.99
	S17′	−1.21	N16′	1.02

These drawings clearly establish the structural formulas of the molecules and also show the conformation of each molecule. In all three molecules, the 18-member ring is severely strained and deviates from the expected conformation of 18-crown-6-type molecules. This is established by the torsion angles listed in the supplementary material. This strain is expected because of the presence of the aromatic pyridine ring in the macrocyclic ring and also the replacement of two of the oxygens of the ring by two nitrogens. As a result of these features, the carbon and oxygen atoms opposite the pyridine in the macrocyclic ring are disordered (see the thermal parameters for each structure in the supplementary materials). Perhaps the most interesting feature is the conformational change brought about by the presence of the methyl groups bonded to the nitrogens of the ether ring of 8. This effect is shown in the deviations of the S and N atoms from the plane of the pyridine ring. The deviations of the nitrogen and sulfur atoms from the plane calculated for the pyridine and neighboring carbon atoms bonded to the pyridine are shown in Table II.

Dithionoamide ligand 8 exhibited a time-dependent optical rotation. The first measurement, taken after 2 min of dissolution of the crystals (recrystallized from ethanol), was $[\alpha]^{22}_D$ +14.55° (c = 1.077, $CHCl_3$). The optical rotation of this solution increased gradually and after 30 min it was +106.0°, after 40 min +110.4°, after 60 min +112.2°, and after 90 min +112.3°. The optical rotation of the solution was then checked daily for 2 weeks, but no additional changes were observed. When 8 was recovered from the chloroform solution and recrystallized from ethanol, the resulting crystalline 8 had the same optical rotation and mp as the original solid. A change was also noted in the ^{1}H NMR spectrum of 8. The initial ^{1}H NMR spectrum of 8 in $CDCl_3$ was consistent with a compound having one conformation which is symmetric about the C_2 axis of symmetry. As early as 2 min after the crystals were dissolved, new peaks appeared which can be attributed to a second, less symmetrical conformer. After 40 min (about the time equilibrium was established), the ^{1}H NMR spectrum indicated the presence of a third conformer as well. The starting conformer predominates as shown in Figure 5, which shows the ^{1}H NMR spectra at 2 min, 40 min, and 2 weeks. The X-ray crystallographic study showed two conformers in the unit cell; however, they are very similar and could not be distinguished in solution by ^{1}H NMR spectroscopy. Neither contained a C_2 axis though Figure 4 shows a pseudo-2-fold axis passing through the nitrogen atom of the pyridine and the opposite oxygen atom on the macroring. The original conformer(s) in the crystal remains the dominant species (50–60%) in solution. The combination of the nonsymmetrical conformers accounts for about 50% of the total concentration as determined by integration of the peaks assigned to the

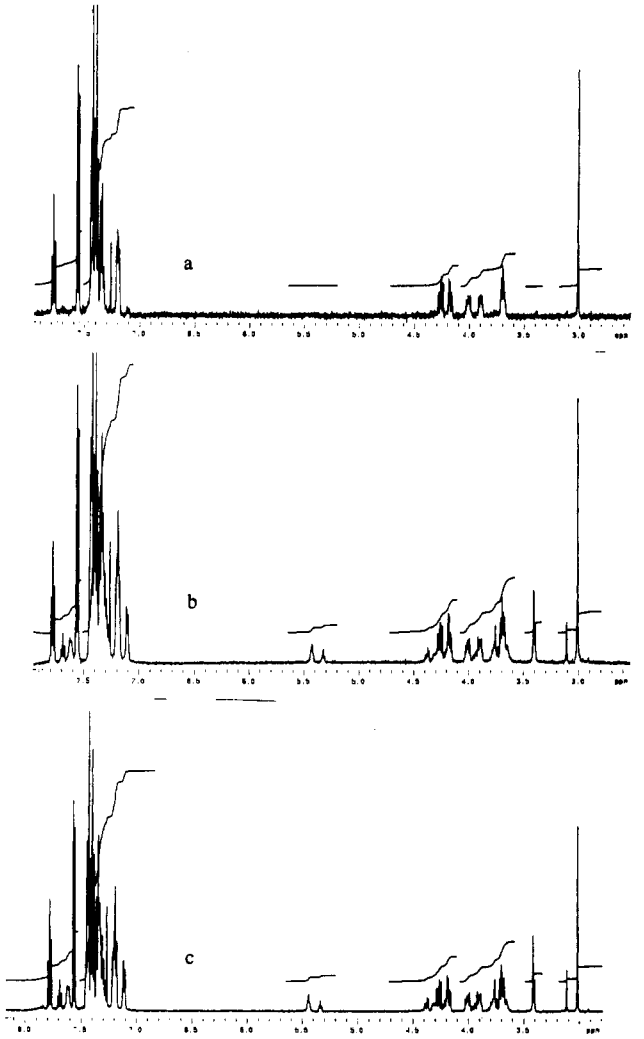

Figure 5. ^{1}H NMR spectra (500 MHz) of 8 in $CDCl_3$: (a) after less than 2 min; (b) after 40 min; (c) after 2 weeks.

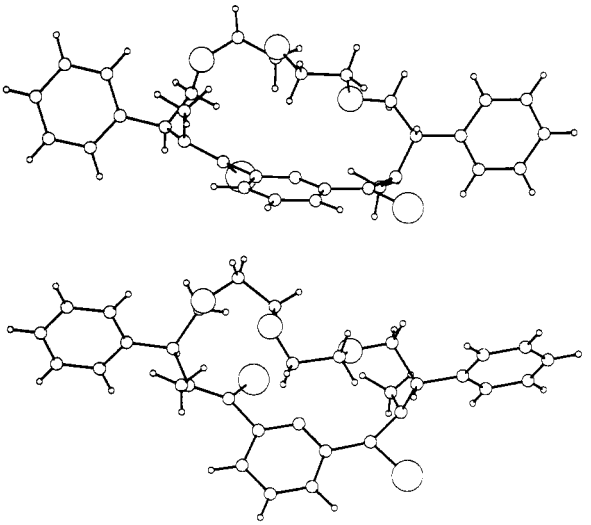

Figure 6. Force-field minimized structure of 8 using X-ray coordinates as the starting coordinates with the pyridine ring to the front (top) and the view normal to the pyridine ring (bottom).

benzylic C–H protons and 40% by integration of the *N*-methyl peaks. A minimum of three conformers is necessary to explain the three triplets observed for the pyridine hydrogen in position 4 (δ = 7.77, 7.69, and 7.85) and the four *N*-methyl peaks (δ = 3.00, 3.11, 3.40, and 3.42) observed at equilibrium. It is noteworthy that, similarly to the optical rotation results, there were no significant changes in the ^{1}H NMR spectrum after about 40 min (see Figure 5).

The optical rotation is a macroscopic measurement and is the result of isotropic motion averaging of all possible orientations of the chiral center. It is known that different conformers can have different optical rotations. In the case of compound 8, there are two identical chiral centers in each molecule. This means that the chiral centers isotropically tumble in pairs. In the symmetrical conformer, this pairwise tumbling would be expected to yield a different optical rotation than if the chiral centers were tumbling independently. Similarly, in the two nonsymmetrical conformers, the chiral centers tumble in pairs with distinctly different spatial relationships. The change in optical rotation with time can thus be attributed to the establishment of an equilibrium among three conformers.

The solid structure has two conformers varying only slightly. The C=S bonds are out of the plane of the pyridine ring and the planes of the phenyl rings are rotated about 90° from coplanarity with the neighboring C–H bonds (see Figure 4). Molecular modeling, using force field calculations, suggests that the C=S bonds would be coplanar with the pyridine ring when not in the solid state. This is the case for molecule 2 and 5 even in the solid state (see Table II). Performing a simple energy minimization, using the X-ray coordinates as the starting point, produces a conformation with that very characteristic (Figure 6). The methyl groups are out of the macrocycle "average" plane and are no longer anti to the sulfurs as they are in the solid (Figure 4). One phenyl ring is approximately coplanar with the adjacent C–H bond, deshielding this benzylic proton and shielding the neighboring macroring methylene protons. The other phenyl ring is not coplanar to the adjacent C–H bond and has the opposite shielding effect, causing chemical shift splitting.

The low energy conformation of 8, derived from a grid search using force-field calculations, can be seen in Figure 7. In this conformer, the C=S bonds are approximately coplanar with the pyridine ring. The methyl gruops are

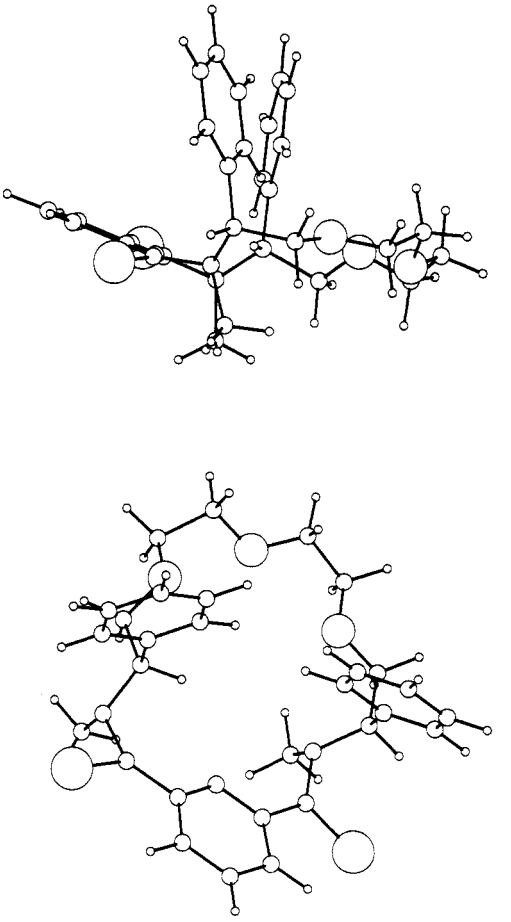

Figure 7. Low energy conformation of 8 from a grid search using force-field calculations with the pyridine ring to the left (top) and the pyridine ring to the front (bottom).

out of the plane of the macrocycle and are shielded by the C=S bonds and deshielded by the phenyl rings. The phenyl rings are approximately coplanar with the adjacent C–H bonds but are on the opposite side of the macroring from the neighboring macroring methylene protons. Thus, those methylene protons are too far removed from the benzene rings to be affected.

The equilibrium NMR spectrum of 8 requires the presence of at least three conformers to explain the chemical shifts. The major component is the conformer exhibiting C_2 symmetry, which is seen immediately upon dissolution of the crystals (conformer A) (Figure 4). The upfield movement (two triplets at δ = 5.34 and 5.46) of the chemical shift of the benzylic proton which occurs after a short time is consistent with the molecular modeling conformer seen in Figure 6 (conformer B) and would be caused by a rotation that brings the C=S bonds to coplanarity with the pyridine ring and the consequent movement of the benzylic protons from the deshielding to the shielding region of the C=S double bond. Although these protons are still deshielded by the phenyl rings, one phenyl ring is rotated as described above and the C_2 symmetry is lost. The presence of conformer B would also explain two of the methyl shifts seen at equilibrium (δ = 3.11 and 3.40). One of the methyl groups experiences an environment very similar (but not identical) to that in conformer A, while the other is substantially deshielded by rotation of its neighboring phenyl ring. The third methyl shift which is observed after several minutes must be attributed to the presnece of a third conformer. The molecular modeling conformer seen in Figure 7 (conformer C) is consistent with that third methyl shift (δ = 3.42) as

the environments of the methyl groups are identical in this conformer and there is substantial deshielding by the phenyl rings. The two small triplets from the hydrogen at position 4 on the pyridine ring (δ = 7.69 and 7.85) are also explained by the presence of conformers B and C, as is the additional doublet from the hydrogen at position 3 (δ = 7.60). The upfield triplet observed within a few minutes is consistent with conformer B. One C=S bond is rotated into close proximity with the proton at position 3 of the pyridine ring. This causes downfield movement of the chemical shift for the position 3 hydrogen due to deshielding by the C=S double bond and upfield movement of the chemical shift for the hydrogen at position 4, which is similar to the shielding which occurs at positions ortho to electron-withdrawing substituents on an aromatic ring. The other C=S bond is coplanar with the pyridine ring but is rotated away from the position 3 hydrogen and would thus not affect the pyridine ring protons. The position 4 hydrogen triplet at δ = 7.85 as well as the position 3 doublet at δ = 7.60 can be explained by conformer C. In this conformer both C=S bonds are coplanar with the pyridine ring and both are in close proximity to the position 3 hydrogen. The protons at position 3 experience the same deshielding, but now the position 4 hydrogen is also deshielded analogous to a proton ortho to two electron-withdrawing substituents.

Conformers A and B exhibit only small energy differences and therefore the equilibrium between them should be established rapidly. In the NMR spectra, the triplet at δ = 7.69 appears early on, as do the methyl shifts at δ = 3.11 and 3.42. Conformer C is markedly different from the other two conformers, which would indicate a higher energy barrier and thus a slower attainment of equilibrium. The triplet at δ = 7.85 ppm is only present much later in the study. No energies are reported as all modeling was performed in the gas phase at 0 K; therefore no solvent effects are included. All of the conformers are consistent with the NMR data but are not considered to be definitive. They are proposed only to suggest reasonable conformations and transitions that cause the time-dependent changes seen in the NMR spectra.

Experimental Section

The ^{1}H NMR spectra were obtained at either 200 or 500 MHz (for recognition studies) in $CDCl_3$ with TMS as the internal standard unless otherwise indicated. Melting points are uncorrected. Starting materials were used as purchased from Aldrich Chemical Co. unless otherwise noted. The hydrogen perchlorate salts of the chiral amines used in the study were prepared as reported.[1] Dimethyl 2,6-pyridinedicarboxylate,[5,35] *O,O'*-dimethyl 2,6-pyridinedicarbothioate,[27] 2,6-pyridinedimethyl ditosylate,[4] diethylene glycol ditosylate,[5] pyridinium *p*-toluenesulfonate (PPTS),[36] and *N*-(triphenylmethyl)diethanolamine[37] were prepared as reported.

(*S*)-(+)-2-(*N*-Formylamino)-2-phenylacetic Acid (12) (Scheme IIA). To a stirred solution of 25 g (0.165 mol) of (*S*)-(+)-2-amino-2-phenylacetic acid in 200 mL of 80% HCO_2H was added dropwise 106.3 mL of acetic anhydride at 0 °C. After the reaction mixture was stirred at 0 °C for 10 min and at rt for 4 h, it was treated with 70 mL of water. The solvent was removed under reduced pressure and the residue was recrystallized from water to give 23.90 g (78%) of **12** as crystals: mp 188–189 °C; $[\alpha]^{27}_D$ +198.05° (*c* = 0.41, THF); IR (KBr) 3346, 1701, 1619, 1518 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.37 (d, 1 H, *J* = 8 Hz), 7.27–7.43 (m, 5 H), 8.07 (s, 1 H), 8.91 (d, 1 H, *J* = 9 Hz, slowly disappeared in D_2O); MS *m/e* 179 (M^+).

(35) Ramsay, W. *Jahresber. Chem.* 1877, 436.
(36) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* 1977, *42*, 3772.
(37) Guttmann, S.; Pless, J. French Patent 1,521,092, 1968; *Chem. Abstr.* 1969, *71*, 12828e.

(*S*)-(+)-2-(*N*-Methylamino)-2-phenylethanol (13) (Scheme IIA). To a stirred suspension of 27.5 g (0.72 mol) of $LiAlH_4$ in 100 mL of dry and pure THF was added dropwise at 0 °C 16 g (0.089 mol) of **12** dissolved in 350 mL of THF. The reaction mixture was stirred at 0 °C for 30 min, at rt for 3 h, and at reflux temperature for 9 h. The reaction mixture was cooled to 0 °C and 50 mL of 15% aqueous NaOH was slowly added. After the mixture was stirred overnight at rt, the solid was filtered and washed with THF. The combined filtrate and washing solutions were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was distilled under reduced pressure to give 10.8 g (80%) of **13** as a clear oil: bp 90–92 °C/0.4 mmHg; $[\alpha]^{27}_D$ +85.6° (*c* = 1.03, $CHCl_3$); IR (neat) 3300, 1453, 1352 cm^{-1}; ^{1}H NMR δ 2.32 (s, 3 H), 2.68 (br s, 2 H, disappeared in D_2O), 3.51–3.78 (m, 3 H), 7.21–7.42 (m, 5 H).

(2*S*,12*S*)-(−)-2,12-Diamino-1,13-diphenyl-4,7,10-trioxatridecane (14) (Scheme IIB). Diamine **14** was prepared from (*S*)-(−)-2-amino-3-phenyl-1-propanol (11.75 g, 77.7 mmol) and diethylene glycol ditosylate (16.2 g; 39.1 mmol) as described in the literature.[20] The amine was purified by column chromatography on silica gel using concd. NH_4OH/C_2H_5OH (1/400) as eluent to give 8.45 g (58%) of **14** as a clear oil: $[\alpha]^{25}_D$ −6.41° (*c* = 2.95, benzene); IR (neat) 3373, 3300 cm^{-1}; ^{1}H NMR δ 1.33 (br s, 4 H, disappeared in D_2O), 2.41–2.81 (m, 4 H), 3.12–3.70 (m, 14 H), 7.08–7.33 (m, 10 H).

(1*S*,11*S*)-(+)-1,11-Diamino-1,11-diphenyl-3,6,9-trioxaundecane (15) (Scheme IIB). **15** was prepared in a similar manner[20] from (*S*)-(−)-2-amino-2-phenylethanol (10.0 g, 72.3 mmol) and diethylene glycol ditosylate (16.0 g, 38.6 mmol). Product **15** (9.71 g, 85%) was obtained as a light yellow oil: $[\alpha]^{27}_D$ +40.0° (*c* = 1.23, $CHCl_3$); IR (neat) 3371, 3301 cm^{-1}; ^{1}H NMR δ 1.80 (br s, 4 H, disappeared in D_2O), 3.30–3.68 (m, 12 H), 4.13–4.23 (m, 2 H), 7.18–7.40 (m, 10 H); MS *m/e* 344 (M^+).

(3*S*,13*S*)-(+)-3,13-Diphenyl-2,14-diaza-5,8,11-trioxapentadecane (16) (Scheme IIB). **16** was prepared in a similar manner[20] from (*S*)-(+)-2-(*N*-methylamino)-2-phenylethanol (**13**) (15.2 g, 100 mmol) and diethylene glycol ditosylate (20.7 g, 50 mmol). Product **16** (10.9 g, 59%) was a light yellow oil: $[\alpha]^{27}_D$ +74.31° (*c* = 1.02, $CHCl_3$); IR (neat) 3341 cm^{-1}; ^{1}H NMR δ 1.26 (br s, 2 H, disappeared in D_2O), 2.25 (s, 6 H), 3.38–3.85 (m, 14 H), 7.2–7.4 (m, 10 H); MS *m/e* 372 (M^+).

(1*S*,11*S*)-1,11-Bis(*p*-toluenesulfonamido)-1,11-diphenyl-3,6,9-trioxaundecane (17) (Scheme IIC). To a stirred solution of 12.9 g (68 mmol) of tosyl chloride in 30 mL of pyridine was added 12.5 g (34 mmol) of **15** in 30 mL of pyridine at 30 °C. After addition of **15**, the reaction mixture was stirred at 45 °C for 1 h and cooled to 0 °C. After ice was added to the reaction mixture, it was stirred overnight. The mixture was extracted three times with 100-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and filtered, and the volatile compounds were evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethanol/$CH_3CO_2C_2H_5$) (1/19) as eluent to give 10.2 g (43%) of **17** as a liquid: IR (neat) 3279, 3064, 3031, 1328, 1160 cm^{-1}; ^{1}H NMR δ 2.36 (s, 6 H), 3.27–3.77 (m, 12 H), 4.36–4.57 (m, 2 H), 6.96–7.70 (m, 20 H).

(*S*)-(−)-Ethyl 2-(Tetrahydropyranyloxy)propionate (20) (Scheme IID). To a stirred mixture of 152.3 g (1.3 mol) of (*S*)-(−)-ethyl lactate and 189 g (2.25 mol) of 3,4-dihydro-2*H*-pyran (DHP) in 500 mL of dry and pure CH_2Cl_2 was added at 0 °C and under Ar 8.0 g of PPTS catalyst. The resulting mixture was stirred under Ar at 0 °C for 3 h and then at rt for 20 h. After the reaction was completed, 800 mL of CH_2Cl_2 was added and the resulting solution was shaken three times with 500-mL portions of ice-cold water and once with saturated $NaHCO_3$. The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by fractional distillation under reduced pressure to give 249 g (95%) of **20** as a mixture of two diastreomers: bp 59–63 °C (0.25 mmHg); $[\alpha]^{20}_D$ −66.3° (*c* = 10.7, benzene); IR (neat) 1750 cm^{-1}; ^{1}H NMR δ 1.21 (t, 3 H, *J* = 6 Hz), 1.3 and 1.38 (d, 3 H, *J* = 7 Hz), 1.4–1.98 (m, 6 H), 3.35–3.55 and 3.75–4.0 (m, 2 H), 4.15 (q, 2 H, *J* = 6 Hz), 4.12 and 4.4 (q, 1 H, *J* = 7 Hz), 4.14–4.24 and 4.64–4.74 (m, 1 H).

(*S*)-(−)-2-(Tetrahydropyranyloxy)propanol (21) (Scheme IID). To a stirred suspension of 26.0 g (0.69 mol) of $LiAlH_4$ in 580 mL of dry and pure ether was added at 0 °C and under Ar a solution of 219 g (1.08 mol) of **20** in 350 mL of ether over a period

of 4 h. After the reaction mixture was stirred at 0 °C for 1 h and at rt for 1 h, it was refluxed for 20 h. After the reaction was completed, 500 mL of ether was added and the mixture was cooled to 0 °C. Saturated NH_4Cl (26 mL), 26 mL of 10% aqueous NaOH, and 26 mL of water were consecutively added very slowly to the well-stirred reaction mixture. After the mixture was stirred at 0 °C for 10 min and at rt for 10 min, it was refluxed for 8 h and left to stand overnight at rt. The white precipitate was filtered and the solid was washed with ether. The filtrate and washing were combined, dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue was purified by fractional distillation under reduced pressure to give 148 g (92%) of **21** as a mixture of two diastreomers: bp 61–71 °C (0.25 mmHg); $[\alpha]^{20}_D$ −1.58° (c = 10.7, benzene); IR (neat) 3434 cm^{-1}; ^1H NMR δ 0.99 and 1.08 (d, 3 H, J = 7 Hz), 1.3–1.82 (m, 6 H), 2.83 (t, 1 H, disappeared in D_2O), 3.22–3.55 (m, 2 H), 3.6–3.92 (m, 3 H), 4.36–4.48 and 4.60–4.66 (m, 1 H).

(*S*)-(−)-2-(Tetrahydropyranyloxy)propyl *p*-Toluenesulfonate (22) from 21 (Scheme IID). To a vigorously stirred suspension of 95 g (1.44 mol, 85%) of finely powdered KOH in 250 mL of THF were added at 0 °C and under Ar first 84.9 g (0.53 mol) of (*S*)-(−)-**21** dissolved in 300 mL of THF and then 163.0 g (0.85 mol) of TsCl dissolved in 550 mL of THF. The mixture was stirred at 0 °C for 3 h and then at rt for 24 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in a mixture of 1400 mL of CH_2Cl_2 and 400 g of ice. The mixture was shaken and the phases were separated. The aqueous phase was shaken with 300 mL of CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), and filtered, and the solvent was evaporated under reduced pressure to give 161.6 g (97%) of **22** as a mixture of two diastreomers. This material was used for the next step without further purification: $[\alpha]^{20}_D$ −5.78° (c = 6.67, benzene); IR (neat) 1361 and 1177 cm^{-1}; ^1H NMR δ 1.12 and 1.20 (d, 3 H, J = 7 Hz), 1.38–1.96 (m, 6 H), 2.45 (s, 3 H), 3.35–4.17 (m, 5 H), 4.58–4.72 (m, 1 H), 7.35 (d, 2 H, J = 10 Hz), 7.80 (d, 1 H, J = 10 Hz), 7.83 (d, 1 H, J = 10 Hz).

(*S*)-(+)-2-Hydroxypropyl *p*-Toluenesulfonate (23) (Scheme IID). To a stirred solution of 19.28 g (0.25 mol) of (*S*)-(+)-1,2-propanediol and 30.86 g (0.31 mol) of triethylamine in 100 mL of dry and pure CH_2Cl_2 at −20 °C under argon was added dropwise over a period of 4 h 48.23 g (0.25 mol) of TSCl (recrystallized from hot hexane) dissoved in 100 mL of CH_2Cl_2. The mixture was stirred at −20 °C for 3 h and then at rt for 40 h. After the reaction was completed, 300 mL of CH_2Cl_2 was added and the mixture was shaken successively with ice-cold water, 10% aqueous HCl, water, saturated $NaHCO_3$, and water. The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel using toluene and $CH_3CO_2C_2H_5$/toluene (1/5) as eluents to give 41.4 g (71%) of **23**: mp 34–35 °C (lit.[38] mp 31–32 °C); $[\alpha]^{20}_D$ +11.6° (c = 1.14, $CHCl_3$) (lit.[38] +12.2°); IR (neat) 3560, 3430, 1360, 1185 cm^{-1}; ^1H NMR δ 1.13 (d, 3 H, J = 7 Hz), 2.43 (s, 3 H), 3.03 (br s, 1 H, disappeared in D_2O), 3.78–4.09, (m, 3 H), 7.36 (d, 2 H, J = 10 Hz), 7.81 (d, 2 H, J = 10 Hz).

(*S*)-(−)-2-(Tetrahydropyranyloxy)propyl *p*-Toluenesulfonate (22) from 23 (Scheme IID). To a stirred solution of 14.42 g (62.62 mmol) of **23** and 11.03 g (131 mmol) of DHP in 250 mL of dry and pure CH_2Cl_2 was added 1.8 g of PPTS at 0 °C and under Ar. The reaction mixture was stirred at 0 °C for 3 h and then at rt for 16 h. After the reaction was completed, 150 mL of CH_2Cl_2 was added and the reaction mixture was shaken three times with 300 mL portions of ice-cold water and once with 300 mL of saturated $NaHCO_3$. The organic phase was dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure to give 19.5 g (99%) of **22** as a mixture of two diastreomers: $[\alpha]^{20}_D$ −5.16° (c = 6.53, benzene). This material had the same properties as that prepared from **21**.

(2*S*,12*S*)-(+)-7-Aza-4,10-dioxatridecane-2,12-diol (25) from *N*-Trityldiethanolamine (Scheme IID). To a stirred suspension of 3.78 g (0.126 mol, 80% dispersion in mineral oil) of NaH in 50 mL of dry and pure DMF was added dropwise at 0 °C under Ar 15.63 g (0.045 mol) of *N*-trityldiethanolamine dissolved in 80 mL of DMF. After addition, the reaction mixture was stirred at 0 °C for 10 min, at rt for 10 min, and then at 70 °C for 90 min. After cooling to 0 °C, 28.92 (0.092 mol) of **22** in 120 mL of DMF was added dropwise. After addition of **22**, the reaction mixture was stirred at 0 °C for 10 min, at rt for 10 min, and then at 70 °C for 86 h. After the reaction was completed, the solvent was evaporated to dryness at 0.05 mmHg. The residue was dissolved in a mixture of 400 mL of CH_2Cl_2, 100 g of ice, and 100 mL of water. The mixture was shaken well and the phases were separated. The aqueous phase was shaken twice with 200-mL portions of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using hexane and $CH_3CO_2C_2H_5$/hexane (1/6) as eluents to give 16.1 g (70%) of (2*S*,12*S*)-(−)-2,12-bis(tetrahydropyranyloxy)-7-trityl-7-aza-4,10-dioxatridecane (**24**) as an oil: $[\alpha]^{20}_D$ −2.33° (c = 4.86, benzene); IR (neat) 3090, 3040, 3010, 1590, 1510, 1490, 1120, 1040 cm^{-1}; ^1H NMR δ 1.10 and 1.18 (d, 6 H, J = 7 Hz), 1.38–1.95 (m, 12 H), 2.42–2.6 (m, 4 H), 3.22–3.68 (m, 10 H), 3.81–4.04 (m, 4 H), 4.65–4.83 (m, 2 H), 7.05–7.32 (m, 9 H), 7.44–7.57 (m, 6 H).

Compound **24** (15.35 g, 0.03 mol) was stirred with a mixture of 15 mL of water and 135 mL of glacial CH_3CO_2H at 90 °C for 3 h. After the reaction was completed, the excess reagent was evaporated under reduced pressure and the residue was triturated with 100 mL of water. The precipitated trityl alcohol was filtered and washed three times with 20-mL portions of water. The filtrate and washings were combined, and the aqueous solution was concentrated to 50 mL under reduced pressure. The aqueous solution was cooled to 0 °C and was acidified by concd HCl to pH ≤ 2. The aqueous phase was shaken three times with 50-mL portions of ether to remove impurities. The aqueous solution made alkaline with 30% NaOH at 0 °C (to pH ≥ 13). The solution was condensed to 20 mL and shaken with 100 mL of CH_2Cl_2 and three times with 20-mL portions of CH_2Cl_2. The combined organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by fractional distillation under reduced pressure to give 5.44 g (82%) of **25** as a viscous oil: bp 135–137 °C (0.1 mmHg); $[\alpha]^{20}_D$ +17.7° (c = 1.0, C_2H_5OH); IR (neat) 3396, 1117 cm^{-1}; ^1H NMR δ 1.09 (d, 6 H, J = 7 Hz), 2.82 (tr, 4 H, J = 6 Hz), 3.18–4.11 (m, 13 H); MS (CI) m/e 222 (M^+ + 1).

(2*S*,12*S*)-(+)-7-Aza-4,10-dioxatridecane-2,12-diol (25) from Diethanolamine (Scheme IID). To a stirred suspension of 23.0 g (0.767 mol, 80% dispession in mineral oil) of sodium hydride and 400 mL of DMF was added dropwise at rt and under Ar 36.48 g (0.347 mol) of diethanolamine in 400 mL of DMF. The reaction mixture was stirred at rt for 10 min and then at 85 °C for 2.5 h. The mixture was cooled to 0 °C and 219.2 g (0.697 mol) of **22** in 250 mL of DMF was added dropwise. After the mixture was stirred at 0 °C for 10 min and at rt for 1 h, it was stirred at 85 °C for 2 days. After the reaction was completed, the solvent was removed at 0.05 mmHg. The residue was dissolved in a mixture of 1.2 L of CH_2Cl_2, 150 g of ice, and 150 mL of water. The phases were shaken well and separated. The aqueous phase was shaken twice with 400-mL portions of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure to give 127 g of oil. The latter was stirred with a mixture of 100 mL of water and 900 mL of glacial CH_3CO_2H at 90 °C for 3 h. After the reaction was completed, the excess reagent was evaporated. Water (200 mL) was added to the residue and the mixture was acidified at 0 °C with concd HCl to pH ≤ 2. The aqueous solution was shaken three times with 300-mL portions of ether and then made alkaline with 30% NaOH at 0 °C. After the aqueous solution was concentrated to 120 mL, it was shaken once with 1500 mL of CH_2Cl_2 and three times with 400-mL portions of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by fractional distillation under reduced pressure to give 36.4 g (47%) of **25**: bp 134–136 °C (0.1 mmHg); $[\alpha]^{20}_D$ +16.96° (c = 1.463, C_2H_5OH). Compound **25** had the same IR and NMR spectra as that prepared from *N*-trityldiethanolamine above.

(4*S*,14*S*)-(−)-4,14-Dibenzyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (1) (Scheme IA). A mixture of 1.94 g (5.2 mmol) of (*S*,*S*-(−)-**14**, 1.01

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(39) Sheldrick, G. M. SHELXTL-PLUS, Siemens Analytical X-ray Instruments, Inc., Madison, WI, 1990.

g (5.2 mmol) of dimethyl 2,6-pyridinedicarboxylate, and 1.0 g (5.2 mmol) of NaOTs was stirred in 100 mL of dry and pure diglyme at 135 °C for 144 h under Ar. After the reaction was completed, the solvent was removed under reduced pressure. The residue was dissolved in a mixture of 150 mL of CH_2Cl_2, 30 g of ice, and 30 mL of water. The resulting mixture was shaken well and the phases were separated. The aqueous phase was shaken twice with 60-mL portions of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel using toluene and THF/toluene (1/8) as eluents to give 0.75 g (29%) of 1 as white crystals: mp 131–132 °C; $[\alpha]^{20}_D$ −160.8° (c = 0.854, benzene); IR (KBr) 3398, 3307, 1674, 1653, 1603, 1568, 1516, 1132 cm^{-1}; ^1H NMR δ 2.88–3.22 (m, 4 H), 3.37–4.06 (m, 12 H), 4.33–4.53 (m, 2 H), 7.12–7.48 (m, 10 H), 8.02 (t, 1 H, J = 10 Hz), 8.37 (d, 2 H, J = 10 Hz), 8.45 (d, 2 H, disappeared in D_2O, J = 14 Hz); MS m/e 503 (M^+). Anal. Calcd for $C_{29}H_{33}N_3O_5$: C, 69.17; H, 6.60. Found: C, 69.06; H, 6.65. This reaction was repeated in the absence of NaOTs to give 0.61 g (23%) of 1.

(4*S*,14*S*)-(−)-4,14-Dibenzyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dithione (2) from *O,O'*-Dimethyl 2,6-Pyridinedicarbothioate (Scheme IA). Compound 2 was prepared as described above for 1 starting from 1.96 g (5.26 mmol) of 14, 1.20 g (5.28 mmol) of *O,O'*-dimethyl 2,6-pyridinedicarbothioate, and 1.03 g (5.28 mmol) of NaOTs. The reaction was completed in 12 h at 135 °C. The crude product was purified by chromatography on silica gel using toluene and THF/toluene (1/40) as eluents to give 0.79 g (28%) of 2 as yellow crystals: mp 139–140 °C; $[\alpha]^{20}_D$ −193.9° (c = 0.639, benzene); IR (KBr) 3327, 3082, 3060, 3025, 1601, 1587, 1510, 1128 cm^{-1}; ^1H NMR δ 3.0 (t, 2 H, J = 14 Hz), 3.3 (d, 1 H, J = 6 Hz), 3.4 (d, 1 H, J = 6 Hz), 3.5 (d, 2 H, J = 14 Hz), 3.58–3.91 (m, 8 H), 4.2–4.4 (m, 2 H), 4.9–5.12 (m, 2 H), 7.08–7.56 (m, 10 H), 7.95 (t, 1 H, J = 10 Hz), 8.93 (d, 2 H, J = 10 Hz), 10.4 (d, 2 H, disappeared in D_2O, J = 12 Hz); MS m/e 535 (M^+). Anal. Calcd for $C_{29}H_{33}N_3O_3S_2$: C, 65.02; H, 6.21. Found: C, 65.04; H, 6.04.

(4*S*,14*S*)-(−)-4,14-Diphenyl-6,9,12-trioxa-3,5,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (4) from Dimethyl 2,6-Pyridinedicarboxylate (Scheme IA). Ligand 4 was prepared as described above for 1 starting from 1.72 g (5 mmol) of diamine 15, 0.98 g (5 mmol) of dimethyl 2,6-pyridinedicarboxylate, and 0.98 g (5 mmol) of NaOTs. The amide product was purified by chromatography on silica gel using toluene and THF/toluene (1/8) as eluents to give 0.59 g (25%) of 4 as white crystals: mp 180–181 °C (ethyl alcohol); $[\alpha]^{22}_D$ −192.1° (c = 1.12, $CHCl_3$); IR (KBr) 3462, 3260, 3060, 3024, 1664, 1533, 1494 cm^{-1}; ^1H NMR δ 3.4–4.08 (m, 12 H), 5.32–5.48 (m, 2 H), 7.19–7.53 (m, 10 H), 8.0 (tr, 1 H, J = 10 Hz) 8.35 (d, 2 H, J = 10 Hz), 8.97 (d, 2 H, J = 12 Hz, disappeared in D_2O); MS m/e 475 (M^+). Anal. Calcd for $C_{27}H_{29}N_3O_5$: C, 68.20; H, 6.15. Found: C, 67.94; H, 6.36.

(4*S*,14*S*)-(−)-4,14-Diphenyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dithione (5) from *O,O'*-Dimethyl 2,6-Pyridinedicarbothioate (Scheme IA). Ligand 5 was prepared as described above for 1 starting from 1.5 g (5 mmol) of diamine 15, 1.1 (5.6 mmol) of *O,O'*-dimethyl 2,6-pyridinedicarbothioate, and 0.97 g (5 mmol) of NaOTs. The crude product was purified by chromatography on silica gel using toluene and THF/toluene (1/32) as eluents to give 0.21 g (8%) of 5 as yellow crystals: mp 134–135 °C (C_2H_5OH); $[\alpha]^{25}_D$ −488.4° (c = 0.735, $CHCl_3$); IR (KBr) 3344, 3059, 3027, 1602, 1586, 1506, 1437, 1252, 1140, 1113, 1077 cm^{-1}; ^1H NMR δ 3.29–3.55 (m, 4 H), 3.58–3.85 (m, 4 H), 3.88–4.25 (m, 4 H), 5.92–6.02 (m, 2 H), 7.18–7.54 (m, 10 H), 7.93 (tr, 1 H, J = 10 Hz), 8.87 (d, 2 H, J = 10 Hz), 10.45 (d, 2 H, J = 12 Hz, disappeared in D_2O); MS m/e 507 (M^+). Anal. Calcd for $C_{27}H_{29}N_3O_3S_2$: C, 63.88; H, 5.76. Found: C, 63.80; H, 5.82.

(4*S*,14*S*)-(−)-4,14-Diphenyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (4) from 2,6-Pyridinedicarbonyl Dichloride (Scheme IB). Mixtures of 1.72 g (5 mmol) of diamine 15 and 1.4 mL (10 mmol) of triethylamine in 100 mL of pure and dry toluene and 1.02 g (5 mmol) of 2,6-pyridinedicarbonyl dichloride in 100 mL of pure and dry toluene were added simultaneously over a 5-h period to 500 mL of vigorously stirred pure and dry toluene at 0 °C. After the addition, the reaction mixture was stirred at rt for 1 day and then filtered. The filtrate was evaporated and the residue was purified by chromatography on silica gel using toluene and THF/toluene (1/8) as eluents to give 0.38 g (16%) of 4. Compound 4 prepared in this way had the same mp, optical rotation, and IR and ^1H NMR spectra as reported above.

(4*S*,14*S*)-(+)-3,15-Dimethyl-4,14-diphenyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (7) (Scheme IB). Compound 7 was prepared as described immediately above for 4 starting from 1.86 g (5 mmol) of 16, 1.4 mL (10 mmol) of triethylamine, and 1.02 g (5 mmol) of 2,6-pyridinedicarbonyl dichloride. The crude product was purified by chromatography on silica gel using toluene and THF/toluene (1/4) as eluents to give 1.34 g (53%) of 7 as white crystals: mp 77–79 °C; $[\alpha]^{27}_D$ +43.5° (c = 0.892, $CHCl_3$); IR (KBr) 1634 cm^{-1}; ^1H NMR δ 2.82–3.06 (m, 6 H), 3.58–4.36 (m, 12 H), 5.38–6.20 (m, 2 H), 7.08–8.00 (m, 13 H); MS m/e 503 (M^+). Anal. Calcd for $C_{29}H_{33}N_3O_5$: C, 69.17; H, 6.60. Found: C, 68.91; H, 6.74.

(4*S*,14*S*)-(−)-4,14-Dibenzyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dithione (2) from 1 (Scheme IC). Macrocycle 1 (1.01 g, 2 mmol) and 2.18 g (5.4 mmol) of Lawesson's reagent were stirred in 40 mL of pure and dry toluene at reflux temperature under Ar for 9 h. After the reaction was completed, the solvent was evaporated and the residue was purified by chromatography on silica gel using toluene and THF/toluene (1/40) as eluents to give 0.94 g (88%) of 2. All the physical properties of 2 prepared in this way were identical with those of 2 prepared above.

(4*S*,14*S*)-(−)-4,14-Diphenyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dithione (5) from 4 (Scheme IC). Compound 5 was prepared as described immediately above for 2 using 0.67 g (1.4 mmol) of 4 and 1.53 g (3.8 mmol) of Lawesson's reagent. The crude product was purified by chromatography on silica gel using toluene and THF/toluene (1/32) as eluents to give 0.64 g (90%) of 5. All the physical properties of 5 prepared in this way were identical to those of 5 prepared above.

(4*S*,14*S*)-(+)-3,15-Dimethyl-4,14-diphenyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dithione (8) (Scheme IC). Compound 8 was prepared as described immediately above for 2 and 5 using 0.55 g (1.1 mmol) of 7 and 1.21 g (3 mmol) of Lawesson's reagent. The crude product was purified by chromatography on silica gel using toluene and THF/toluene (1/28) as eluents to give 0.53 g (90%) of 8 as yellow crystals: mp 190–191 °C (C_2H_5OH); $[\alpha]^{22}_D$ (after 1.5 h) +112.3° (c = 1.077, $CHCl_3$) (see Results and Discussion section); IR (KBr) 1492, 1451, 1399, 1261, 1114 cm^{-1}; ^1H NMR (taken immediately after being dissolved in $CDCl_3$, see Figure 5) δ 3.0 (s, 6 H), 3.66–3.73 (m, 4 H), 3.84–4.04 (m, 4 H), 4.13–4.30 (m, 4 H), 7.17–7.23 (m, 2 H), 7.30–7.48 (m, 10 H), 7.58 (d, 2 H, J = 10 Hz), 7.77 (tr, 1 H, J = 10 Hz); MS (CI) m/e 536 ($M^+ + 1$). Anal. Calcd $C_{29}H_{33}N_3O_3S_2$: C, 65.02; H, 6.21. Found: C, 65.30: H, 6.10.

(4*S*,14*S*)-(+)-4,14-Dibenzyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (3) from 2 (Scheme ID). To a stirred suspension of 28 g of Raney nickel active catalyst in 60 mL of THF was added dropwise 1.09 g (2.03 mmol) of 2 in 60 mL of THF under Ar. The Raney nickel had previously been washed six times with distilled water, six times with CH_3OH, and six times with THF. After the reaction mixture was stirred at rt for 12 h, 30 mL of 30% aqueous NH_4OH/MeOH (1/9) was added and the mixture was stirred for another 30 min. The solution was decanted and the residue was stirred with THF/MeOH/30% aqueous NH_4OH (60/15/1.5) for 30 min. After decanting, the latter procedure was repeated once more. The solutions were combined and evaporated under reduced pressure. The residue was dissolved in 300 mL of CH_2Cl_2 and the solution was shaken with a mixture of 100 mL of 10% aqueous $Na_2S{\cdot}9H_2O$ and 10 mL of 30% aqueous NH_4OH for 10 min. The aqueous phase was shaken with two 50-mL portions of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified on silica gel using 30% aqueous NH_4OH/CH_3OH (1/400) as eluent to give 0.31 g (32%) of 3 as a very viscous oil: $[\alpha]^{20}_D$ +15.35° (c = 2.20, benzene); IR (neat) 3317, 3060, 3025, 1592, 1576, 1119 cm^{-1}; ^1H NMR δ 2.3–2.85 (m, 4 H), 2.85–3.21 (m,

4 H), 3.3 (t, 2 H, J = 12 Hz), 3.48–3.8 (m, 14 H), the diastereotopic methylene protons next to the pyridine ring give an AB pattern with δ_A = 3.91, δ_B = 3.99 (4 H, J_{AB} = 14 Hz), 7.02 (d, 2 H, J = 10 Hz), 7.10–7.39 (m, 10 H), 7.55 (t, 1 H, J = 10 Hz); MS (CI) m/e 476 $(M + 1)^+$. Anal. Calcd for $C_{29}H_{37}N_3O_3$: C, 73.23; H, 7.84. Found: C, 72.93; H, 7.68.

(4*S*,14*S*)-(+)-4,14-Diphenyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (6) from 5 (Scheme ID). Compound **6** was prepared as described above for **3** using 2.8 g of Raney nickel and 103 mg (0.20 mmol) of **5**. The crude product was purified by chromatography on silica gel using 30% aqueous NH_4OH/CH_3OH (1/400) as eluent to give 49 mg (54%) of **6** as a very viscous oil: $[\alpha]^{22}_D$ +54.21° (c = 0.939, $CHCl_3$); IR (neat) 3323, 3060, 3026, 1593, 1575, 1122 cm^{-1}; ^1H NMR δ 3.37 (br s, 2 H, disappeared in D_2O), 3.46–4.13 (m, 18 H), 6.85 (d, 2 H, J = 10 Hz), 7.20–7.52 (m, 11 H); MS (CI) M/e 448 $(M^+ + 1)$. Anal. Calcd for $C_{27}H_{33}N_3O_3$: C, 72.46; H, 7.43. Found: C, 72.34; H, 7.58.

(4*S*,14*S*)-(+)-3,15-Dimethyl-4,14-diphenyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (9) from 8 (Scheme ID). Compound **9** was prepared as described immediately above for **3** and **6** using 14 g of Raney nickel and 544 mg (1.02 mmol) of **8**. The crude product was purified by chromatography on silica gel using 30% aqueous NH_4OH/MeOH (1/150) as eluent to give 251 mg (52%) of **9** as a very viscous oil: $[\alpha]^{27}_D$ +57.8 (c = 0.638, $CHCl_3$); IR (neat) 3058, 3027, 1589, 1574, 1493 cm^{-1}; ^1H NMR δ 2.25 (s, 6 H), 3.48–4.12 (m, 18 H), 7.16–7.4 (m, 12 H), 7.63 (tr, 1 H, J = 10 Hz); MS (CI) m/e 476 $(M^+ + 1)$. Anal. Calcd for $C_{29}H_{37}N_3O_3$: C, 73.23; H, 7.84. Found: C, 73.12; H, 7.81.

(4*S*,14*S*)-(+)-4,14-Diphenyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (6) from 17 via 18 (Scheme IE). A mixture of 8.05 g (0.018 mol) of 2,6-pyridinedimethyl ditosylate, 11.71 g (0.081 mol) of *N,N'*-ditosyldiamine **17**, and 12.38 g (0.038 mol) of Cs_2CO_3 were stirred in 250 mL of DMF at 80 °C for 3 days. After the reaction was completed, the solvent was evaporated under reduced pressure, and the residue was dissolved in a mixture of 300 mL of CH_2Cl_2 and 200 mL of water. The phases were shaken well and separated. The aqueous phase was shaken twice with 100-mL portions of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel using THF/toluene (1/20) as eluent to give 2.77 g (20%) of **18** as white crystals: mp 84–86 °C; IR (KBr) 3061, 2870, 1596, 1576, 1456, 1338, 1159, 1090 cm^{-1}; ^1H NMR δ 2.42 (s, 6 H), 3.30–3.63 (m, 8 H), 4.00–4.22 (m, 4 H), the diastereotopic methylene protons next to the pyridine ring give an AB pattern with δ_A = 4.31, δ_B = 4.42 (4 H, J_{AB} = 18 Hz), 5.05 (tr, 2 H, J = 7 Hz), 7.00–7.55 (m, 17 H), 7.63 (d, 4 H, J = 10 Hz); MS (CI) m/e 756 $(M^+ + 1)$.

To a stirred suspension of 1.14 g (30 mmol) of $LiAlH_4$ in 100 mL of THF was added dropwise under Ar 2.27 g (3 mmol) of **18** dissolved in 50 mL of THF at reflux temperature. The reaction mixture was refluxed another day and cooled. Ethyl acetate (30 mL) and then 3 mL of H_2O were added to the reaction mixture and it was stirred a few hours. The precipitate was filtered and washed with $CHCl_3$. The filtrate and washing were evaporated, and the residue was purified by chromatography on silica gel using 30% aqueous NH_4OH/C_2H_5OH (1/400) as eluent to give 0.65 g (48%) of unwanted product (1*S*,11*S*)-(+)-1-amino-1,11-diphenyl-13-(6-methylpyridyl)-12-aza-3,6,9-trioxatridecane (**19**) as a very viscous oil: $[\alpha]^{27}_D$ +62.5° (c = 0.2, $CHCl_3$); IR (neat) 3382, 3328, 3060, 3027, 1591, 1570, 1104 cm^{-1}; ^1H NMR δ 2.25 (s, 3 H), 2.85 (br s, 3 H, disappeared in D_2O), 3.34–4.03 (m, 16 H), 7.01–7.66 (m, 13 H); MS m/e 449 (M^+). Anal. Calcd for $C_{27}H_{35}N_3O_3$: C, 72.13; H, 7.85. Found: C, 72.01; H, 7.89.

A mixture of 213 mg (0.282 mmol) of **18**, 160 mg (1.128 mmol) of finely powdered Na_2HPO_4, and 1.7 g of finely ground 6% sodium amalgam was stirred rapidly under Ar at rt for 2 h and then at gentle reflux for 4 h. After the reaction was completed, a mixture of 20 mL/4 mL/0.4 mL of THF/MeOH/30% aqueous NH_4OH was added to the reaction mixture at rt, and the mixture was stirred for 10 min and decanted. The latter procedure was repated two more times. The combined solutions were evaporated under reduced pressure and the residue was dissolved in 40 mL of CH_2Cl_2 and shaken with a mixture of 20 mL of 30% aqueous NH_4OH and 10% aqueous $Na_2S{\cdot}9H_2O$ (1/10) for 10 min. The aqueous phase was shaken twice with 10-mL portions of CH_2Cl_2. The combined organic solution was dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using 30% aqueous NH_4OH/CH_3OH (1/400) as eluent to give 47 mg (37%) of **6** which was identical in every respect to compound **6** prepared from **5**.

(4*S*,14*S*)-(+)-3,15-Dimethyl-4,14-diphenyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (9) from 16 (Scheme IF). To a well-stirred suspension of 10.6 g (0.1 mol) of Na_2CO_3 in 500 mL of CH_3CN were added solutions of 1.86 g (5 mmol) of diamine **16** in 60 mL of CH_3CN and 2.24 g (5 mmol) of 2,6-pyridinedimethyl ditosylate in 60 mL of CH_3CN simultaneously and dropwise over a 3-h period at rt. The reaction mixture was refluxed for 3 days and the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of 150 mL of CH_2Cl_2 and 100 mL of water, and the phases were shaken well and separated. The aqueous phase was shaken twice with 50-mL portions of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel using 30% aqueous NH_4OH/MeOH (1/150) as eluent to give 1.29 g (54%) of **9** which was identical in every aspect to compound **9** prepared from **8**.

(4*S*,14*S*)-(−)-4,14-Dimethyl-3,6,12,15-tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (10) (Scheme IG). To a stirred suspension of 2.91 g (97 mmol, 80% dispersion in mineral oil) of NaH in 80 mL of dry and pure THF was added dropwise 8.84 g (40 mmol) of **25** in 200 mL of THF under Ar at rt. The reaction mixture was stirred at rt for 10 min and then refluxed for 3 h. The mixture was cooled to 0 °C and 17.9 g (40 mmol) of 2,6-pyridinedimethyl ditosylate in 280 mL of THF was added dropwise. The reaction mixture was stirred at 0 °C for 10 min and then at rt for 96 h. After the reaction was completed, the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of 800 mL of CH_2Cl_2 and 80 g of ice. The mixture was shaken well and separated. The aqueous phase was shaken twice with 200-mL portions of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure. The residue was first purified on neutral alumina using toluene then C_2H_5OH/toluene (1/50) as eluents, followed by chromatography on silica gel using 30% aqueous NH_4OH/CH_3OH (1/400) as eluent to give 3.47 g (27%) of an oil: $[\alpha]^{20}_D$ −4.26° (c = 2.70, benzene); IR (neat) 3329, 3061, 1592, 1578, 1455, 1372, 1111 cm^{-1}; ^1H NMR δ 1.12 (d, 6 H, J = 7 Hz), 2.5 (br s, 1 H, disappeared in D_2O), 2.58–2.9 (m, 4 H), 3.29–3.63 (m, 8 H), 3.68–3.9 (m, 2 H); the methylene protons next to the pyridine ring give an AB pattern with δ_A = 4.77, δ_B = 4.82 (4 H, J = 14 Hz), 7.20 (d, 2 H, J = 12 Hz), 7.61 (t, 1 H, J = 12 Hz); MS (CI) m/e 325 $(M^+ + 1)$. Anal. Calcd for $C_{17}H_{28}N_2O_4$: C, 62.94; H, 8.70. Found: C, 62.76; H, 8.51.

(4*S*,14*S*)-(+)-4,14-Dimethyl-9-acetyl-3,6,12,15-tetraoxa-9,21-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (11) (Scheme IH). Crown **10** (0.45 g, 1.39 mmol) was refluxed with 10 mL of acetic anhydride for 3 min. After the reaction was completed, the excess reagent and acetic acid were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using diisopropyl ether and then CH_3OH/diisopropyl ether (1/6) as eluents to give 0.42 g (82%) of **11** as an oil: $[\alpha]^{20}_D$ +31.2° (c = 0.5, benzene); IR(neat) 1644, 1592, 1577, 1456, 1373, 1163 cm^{-1}; ^1H NMR δ 1.12 (d, 6 H, J = 7 Hz), 1.96 (s, 3 H), 3.03–3.58 (m, 12 H), 3.6–3.83 (m, 2 H), 4.48–4.9 (m, 4 H), 7.16 (d, 1 H, J = 12 Hz), 7.25 (d, 1 H, J = 12 Hz), 7.6 (t, 1 H, J = 12 Hz); MS m/e 366 (M^+). Anal. Calcd for $C_{19}H_{30}N_2O_5$: C, 62.27; H, 8.25. Found: C, 62.12; H, 8.13.

Determination of ΔG_c^* Values. ΔG_c^* values listed in Table I were determined as reported.[1-5]

Determination of log K Values. The log K values listed in Table I were determined by the direct ^1H NMR method as reported.[5,9]

X-ray Structural Determinations. Experimental details are in the supplementary material.

Molecular Modeling Studies. Molecular modeling was performed with force field calculations using the CHARMm (Polygen Corp) program. QUANTA (Polygen Corp) was used to

display and plot the conformations. Conformational searching was performed by systematically varying the torsional angles around all macrocycle bonds with energy minimization at each step.

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Supplementary Material Available: Experimental details for the X-ray structural studies, tables of X-ray structural data, and ^{1}H NMR spectra for compounds **12–18** and **20–25** (33 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Tetra-O-alkylated Calix[4]arenes in the 1,3-Alternate Conformation

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A general method has been developed for the preparation of tetra-*O*-alkylated calix[4]arenes in the 1,3-alternate conformation (**3a,c–e**) starting from *p-tert*-butylcalix[4]arenes **1a,b** using Cs_2CO_3 in DMF. The 1,3-alternate conformation was unequivocally proved by an X-ray structure determination of **3a**. The scope of the reaction was investigated starting from a series of diametrically di-*O*-alkylated calix[4]arenes **4a–e** having different substituents R_2 (*t*-Bu, CHO, NO_2, Br, CN) at the para positions of the phenolic rings. The reactions of **4a–d** (R_2 = *t*-Bu, CHO, NO_2, Br) yielded the corresponding tetra-*O*-alkylated calix[4]arenes in the 1,3-alternate conformation **5a–d** (51–73%). However, the dicyanocalix[4]arene **4e** gave the partial cone conformer **6** as the major reaction product.

Introduction

Calixarenes, which are phenol–formaldehyde cyclic oligomers, are receiving increasing attention in the field of supramolecular chemistry.[1,2] Calix[4]arenes (Chart I) can easily be (selectively)[3] functionalized both at the phenolic OH groups (lower rim) and, after removal of the *tert*-butyl groups, at the para positions of the phenol rings (upper rim).[4] Consequently they are now useful building blocks for molecules with different properties.[1,2] These properties are strongly influenced by the conformation of the calix[4]arene which is fixed after substitution with four bulky substituents (R > ethyl) at the phenolic oxygen atoms.[5] Therefore, control of the conformation during the alkylation is highly desirable. The calix[4]arene moiety can exist in four extreme conformations (Chart II) viz. the cone, the partial cone (paco), the 1,2-alternate, and the 1,3-alternate (1,3-alt) conformation. Methods have been developed to selectively prepare *O-alkylated* calix[4]arenes both in the cone and paco conformation.[6,7] The conformation in which a calix[4]arene is fixed upon derivatization depends on the temperature, the solvent, the base, the para substituents of the calixarene, and the reactivity of the electrophile. Recently we have reported an indirect way for the preparation of tetraethoxycalix[4]arene in the 1,2-alternate conformation.[8] The 1,3-alt conformers have been obtained only by *acylation*[9–11] or *aroylation*[10,12] of calix[4]arenes.

To the best of our knowledge only a few individual examples, including two metal complexes,[13,14] are known of isolated tetra-*O-alkylated* calix[4]arenes in the 1,3-alt conformation.[7,15–17] Recently, we[3a] and others[3c,6,7] found that in some cases the 1,3-alt could be detected in the reaction mixture of the tetraalkylation of calix[4]arenes. In this paper we describe the first preparative method for

Chart I

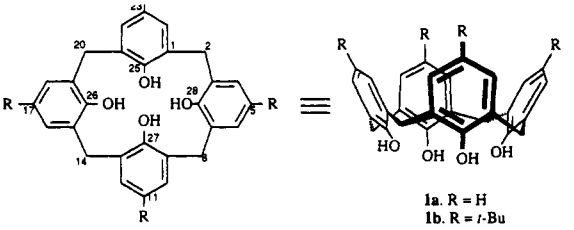
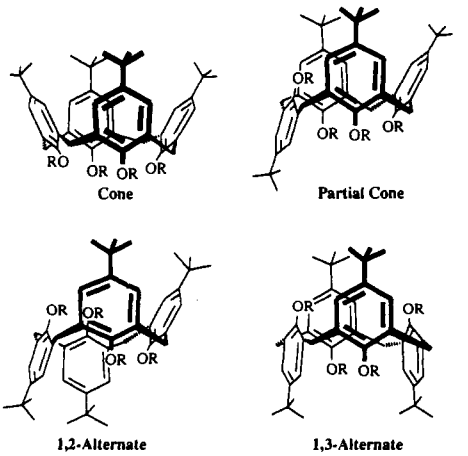


Chart II



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