Enantiomeric Recognition of Organic Ammonium Salts by Chiral Dialkyl-, Dialkenyl-, and Tetramethyl-Substituted Pyridino-18-crown-6 and Tetramethyl-Substituted Bis-pyridino-18-crown-6 Ligands: Comparison of Temperature-Dependent ^{1}H NMR and Empirical Force Field Techniques[1]

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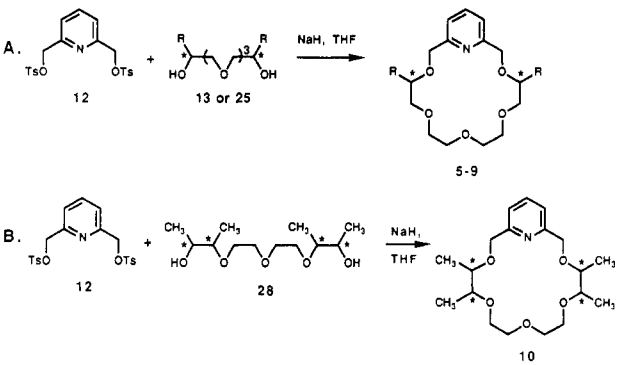
Six new chiral pyridino-18-crown-6 and one chiral bis-pyridino-18-crown-6 ligands have been prepared. The pyridino-crowns contain either two isopropyl, two isobutyl, two (*S*)-*sec*-butyl, two benzyl, two 3-butenyl, or four methyl substituents on chiral macroring carbon atoms. The starting chiral dialkyl-substituted tetraethylene glycols needed for the preparation of the chiral dialkyl-crowns were prepared starting from the appropriate amino acid. The bis(3-butenyl-substituted) tetraethylene glycol was prepared from D-mannitol. The chiral tetramethyl-substituted tetraethylene glycol needed to prepare the chiral tetramethyl-substituted pyridino-18-crown-6 was prepared from monobenzyl-blocked (2*R*,3*R*)-2,3-butanediol. Chiral tetramethyl-bis-pyridino-18-crown-6 was prepared by the cyclization of 2 mol of (2*R*,3*R*)-2,3-butanediol with 2,6-bis[(tosyloxy)methyl]pyridine. Energy of activation ($\Delta G_c^{\ddagger}$) values determined by the temperature-dependent ^{1}H NMR spectroscopy technique indicated that these chiral ligands exhibited chiral recognition for the enantiomers of various organic ammonium salts. Differences in $\Delta G_c^{\ddagger}$ values ($\Delta\Delta G_c^{\ddagger}$) were compared in several cases with the corresponding energy differences calculated from empirical energy functions. The observed and calculated $\Delta\Delta G_c^{\ddagger}$ values were in good agreement in most cases. An X-ray analysis of a crystal of the tetramethyl-bis-pyridino-18-crown-6 ligand (11) shows that the two pyridine rings are bent out of the plane of the four oxygen atoms.

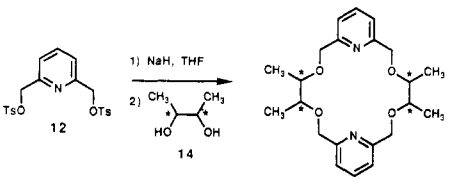
Introduction

The successful design, synthesis, and use of molecules capable of the selective recognition of other species is of great interest to workers in catalysis, separations, enzyme functions, and other areas involving molecular recognition. The careful characterization of such synthetic systems could lead to a much improved understanding of natural systems. One area of recent interest is the enantiomeric recognition of organic amines by chiral macrocyclic ligands. Several research groups have carried out work involving these host–guest systems. Cram and his co-workers have reported chiral recognition of organic amines by a solvent extraction technique,[2-4] transport of amines through liquid membranes,[5] and partial resolution using chromatography of an amino acid on a silica gel or polystyrene bound chiral host material.[6] Lehn and his co-workers have studied reactivity differences when certain *p*-nitrophenyl esters were thiolyzed while complexed with chiral host molecules.[7] These researchers have studied many different molecular receptors.[8,9] Other research groups including our own have observed enantiomeric recognition of organic ammonium salts by chiral crowns derived from simple sugar molecules,[10,11] by chiral diaza-crowns,[12] by chiral crowns containing pyridine and triazole subcyclic units using the temperature-dependent ^{1}H NMR spectroscopy technique,[13-16] and by chiral pyridino-crowns using titration ca-

Scheme I. Preparation of Chiral Dialkyl-, Di-3-butenyl-, and Tetramethyl-crowns



Scheme II. Preparation of Chiral Tetramethyl-bis-pyridino-18-crown-6



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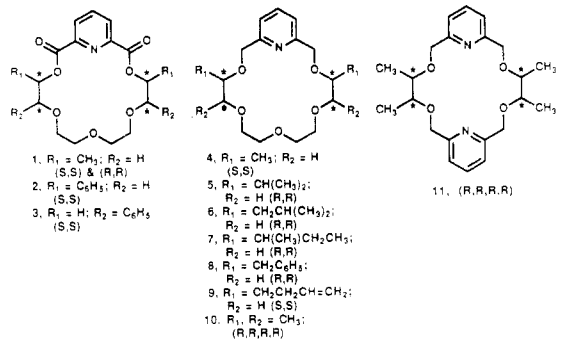

Figure 1. Chiral pyridino-18-crown-6 ligands.

lorimetry.[13] We have shown[13,17] that the pyridino-crowns form strong complexes with protonated organic amines. For example, chiral ligands **1**, **2**, and **4**, with methyl and phenyl substituents, exhibited recognition for the enantiomers of [α-(1-naphthyl)ethyl]ammonium perchlorate and the methyl ester of phenylalaninium perchlorate.[13,14] An excellent review of chiral crown ethers and their interactions with organic ammonium salts has been published.[18]

The present paper describes the synthesis of new chiral pyridino-crown compounds, each containing pairs of the following substituents: isopropyl (**5**, Figure 1), isobutyl (**6**), *sec*-butyl (**7**), benzyl (**8**), and 3-butenyl (**9**). The preparations of chiral tetramethyl-substituted pyridino-18-crown-6 (**10**) and bis-pyridino-18-crown-6 (**11**) ligands are also reported. The interactions of several of the new chiral crowns with certain organic ammonium salts are characterized using measured free energy of activation ($\Delta G_c^{\ddagger}$) values. The degree of chiral recognition measured as the $\Delta\Delta G_c^{\ddagger}$ value is correlated with similar data obtained from calculations using empirical energy functions.[19-23] Finally, an X-ray crystallographic study of **11** is reported.

Results and Discussion

New chiral macrocycles **5**–**11** (Figure 1) were prepared as shown in Schemes I and II. The yields for the 1:1 cyclization reactions (Scheme I) were in the 38–55% range. The yield for the 2:2 product (Scheme II) was only 15%. The structures proposed for these new macrocycles are consistent with data obtained from ^{1}H NMR, MS, and IR spectra and elemental analyses.

The chiral alkyl-substituted tetraethylene glycols needed for the preparation of the macrocycles were obtained as shown in Scheme III. Compounds **13** (R = isopropyl, isobutyl, (*S*)-*sec*-butyl, and benzyl) were all prepared from the corresponding amino acids (Scheme IIIA). The conversion of the amino acid to epoxide **17** was carried out by using the method of Koppenhoefer and Schurig.[24,25] Our epoxides **17** where R was isopropyl, isobutyl, and (*S*)-*sec*-butyl had nearly the same optical rotation as that reported.[25] The reaction of epoxide **17** with diethylene glycol and a catalytic amount of sodium was carried out as reported for the preparation of the chiral dimethyltetraethylene glycol.[26,27] In the preparation of the dimethyltetraethylene glycol, it was shown that a small amount (5–10%) of the product contained a methyl group on the second carbon from one of the hydroxy groups resulting from attack of the alkoxide ion on the most substituted carbon of the epoxide.[27,28] In the case of **13** (R = isopropyl, isobutyl, (*S*)-*sec*-butyl, and benzyl), the amount of the positional isomer should be smaller since the R group of **17** is much larger than methyl.

The chiral bis(3-butenyl-substituted)tetraethylene glycol **25** needed to prepare **9** was prepared from D-mannitol as shown in Scheme IIIB. Compound **19** was prepared as reported.[29] Tosylate **20** was prepared in an 85% yield

Scheme III. Preparation of Chiral Glycols

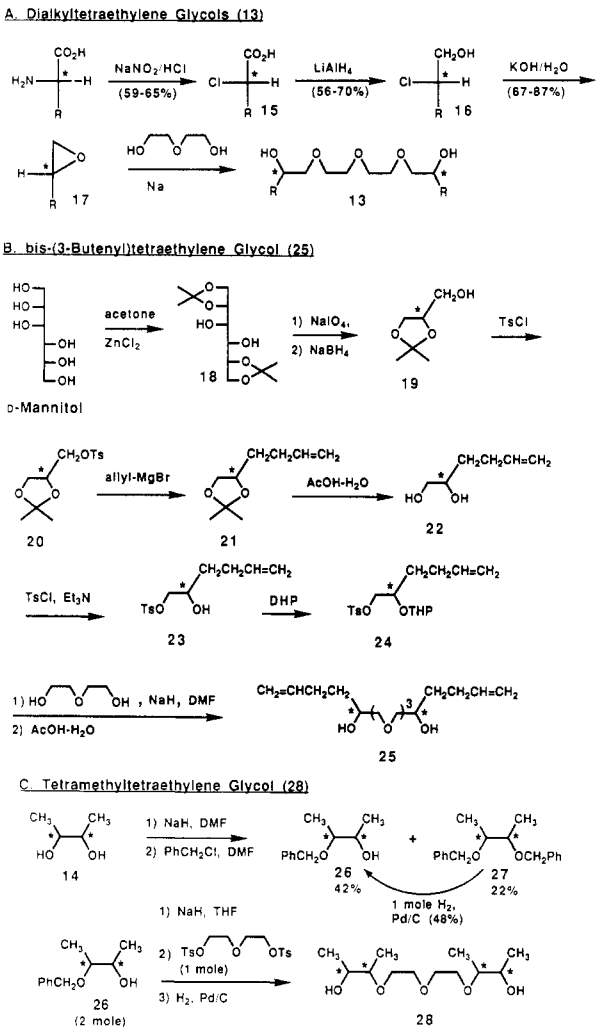

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Table I. Free Energies of Activation, $\Delta G_c^{\ddagger}$ Values (kcal/mol), in CD_2Cl_2[a] for the Interaction of Chiral Macrocyclic Ligands with Chiral Alkylammonium Salts

ligand	value[a]	(*R*)-A[b]	(*S*)-A[b]	(*R*)-B[b]	(*S*)-B[b]	(*R*)-C[b]	(*S*)-C[b]	(*R*)-D[b]	(*S*)-D[b]
(*S,S*)-**1**[c]	T_c	12	−19			−25	−36		
	$\Delta G_c^{\ddagger}$	13.4	12.3			12.1	11.8		
(*S,S*)-**2**[d]	T_c	11	−35			−21	−45		
	$\Delta G_c^{\ddagger}$	13.3	12.0			11.9	10.8		
(*S,S*)-,**3**[c]	T_c					−33	−28		
	$\Delta G_c^{\ddagger}$					11.5	11.6		
(*S,S*)-**4**[c]	T_c	−56	−86			−40	−73		
	$\Delta G_c^{\ddagger}$	10.3	8.7			11.3	10.0		
(*R,R*)-**7**	T_c	−20	5	−50	−15	−42	−48	−30	−39
	$\Delta G_c^{\ddagger}$	12.5	13.3	10.8	12.1	11.3	10.9	12.6	11.0
(*S,S*)-**9**	T_c	29	10						
	$\Delta G_c^{\ddagger}$	14.2	13.3						
(*R,R,R,R*)-**10**	T_c	3	27	−21	25				
	$\Delta G_c^{\ddagger}$	13.4	14.3	12.1	14.3				
(*R,R,R,R*)-**11**	T_c	−52	−43	−38	−46				
	$\Delta G_c^{\ddagger}$	10.5	11.2	11.2	10.6				

[a] A Varian Gemini-200 spectrometer was used to record all ^1H NMR spectra. Equimolar amounts of ligand and salt were dissolved in CD_2Cl_2. The hydrogens on the CH_2 next to the pyridine ring were used as the ^1H NMR probe for all complexes of **7** and **9** and the methyl hydrogen atoms for **10** and **11**. T_c = coalescence temperature (°C). $\Delta G_c^{\ddagger}$ values were ±0.2. [b] A = the hydrogen perchlorate salt of (*R*)- or (*S*)-α-(1-naphthyl)ethylamine; B = hydrogen perchlorate salt of (*R*)- or (*S*)-α-phenylethylamine; C = the hydrogen perchlorate salt of methyl phenylalaninate; D = the hydrogen perchlorate salt of (*R*)- or (*S*)-2-amino-2-phenylethanol. [c] Data for **1**, **3**, and **4** are taken from ref 13. [d] Data for **2** were 13 and 12.3 kcal/mol in ref 14. The measurements were repeated on the Gemini-200 to give the values shown.

using powdered potassium hydroxide as the base in THF. The 2,6-bis[(tosyloxy)methyl]pyridine (**12**) needed for all cyclization reactions was prepared in the same manner to give a 91% yield, much higher than that reported for this material.[30] Tosylate **20** reacted readily with allyl Grignard to give 3-butenyl-substituted **21**. After removal of the blocking group, **22** was first tosylated at the primary hydroxy group and then the secondary hydroxy group was blocked with dihydropyran to give **24**. This latter compound was reacted with diethylene glycol and then deblocked to give **25**.

(*R,R,R,R*)-Tetramethyl-substituted tetraethylene glycol **28** needed to prepare **10** was made as shown in Scheme IIIC from commercially available (*R,R*)-2,3-butanediol (**14**). The first step was the reaction of **14** with benzyl chloride to block one of the hydroxy groups. In addition to monoblocked glycol **26**, some diblocked **27** also was isolated. This latter material was reacted with 1 equiv of hydrogen using a palladium on carbon catalyst to give additional monoblocked **26**. After the reaction of 1 mol of diethylene glycol ditosylate with 2 mol of the monosodium salt of **26** followed by reduction, glycol **28** was obtained.

Elemental analyses for compounds **13**, **25**, and **28** were not obtained. However, good analyses were obtained for all macrocycles prepared from these glycols.

Complexation of the enantiomeric forms of various organic ammonium salts by some of these ligands has been studied by the temperature-dependent ^1H NMR technique.[13-16,31,32] At low temperatures, the peaks in the ^1H NMR spectra of the complexes attributable to the hydrogen atoms on the CH_2 groups attached to the pyridine rings (centered at about δ 4.5), or the methyl hydrogens in the case of **10** and **11**, separated into two peaks of equal intensities. The low temperature peak separations were 40–140 Hz. At high temperatures, the appearance of a single peak is caused by a fast intermolecular or intramolecular face-to-face guest exchange. The kinetic parameters for the dissociation of these complexes were calculated as reported.[10,17,31,32] Table I shows the coalescence temperatures (T_c) and $\Delta G_c^{\ddagger}$ for the dissociation of the complexes of **1–4**, **7**, and **9–11** with various chiral organic ammonium salts. The majority of the data are for complexes of these chiral ligands with the hydrogen perchlorate salts of (*R*)- and (*S*)-α-(1-naphthyl)ethylamine (A).

It is evident from the differences in the $\Delta G_c^{\ddagger}$ values in Table I that these chiral ligands exhibit enantiomeric recognition for chiral forms of various organic ammonium salts. All the *S,S* ligands formed kinetically more stable complexes with the *R* than with the *S* form of A. As expected, complexes of the *R,R* and *R,R,R,R* ligands with the *S* form of A were more stable kinetically than those with the *R* form. The degree of recognition was similar in all ligand–A complexes as shown by the $\Delta\Delta G_c^{\ddagger}$ values being 0.7 to 0.9 kcal/mol except for **1**, **2**, and **4** where $\Delta\Delta G_c^{\ddagger}$ values were 1.1, 1.3, and 1.6 kcal/mol, respectively. An X-ray crystal study of the complexes of (*S,S*)-**1** with both (*R*)- and (*S*)-A showed that the methyl groups on the chiral carbons of (*S,S*)-**1** interact sterically with one of the naphthylene hydrogens of A in the (*S,S*)-**1**-(*R*)-A complex.[13] We had hoped that larger alkyl groups attached to the chiral centers, such as the *sec*-butyl groups of **7**, would cause even greater enantiomeric recognition. This was not the case. It is possible that the larger substituents cause steric interactions in both sets of complexes.

The reasons for the observed enantiomeric recognition by these ligands for the other chiral salts are not so clear. Ligand **10** showed excellent recognition of the *S* form of the hydrogen perchlorate salt of α-phenylethylamine (B) over the *R* form by 2.2 kcal/mol. Even though high recognition values were not evident for the complexes of **7** with the enantiomers of A, ligand **7** did show good recognition for the *R* form of the hydrogen perchlorate salt of 2-amino-2-phenylethanol (D) over the *S* form by 1.6 kcal/mol.

In Table II, values for the difference in $\Delta G_c^{\ddagger}$ ($\Delta\Delta G_c^{\ddagger}$) for the interaction of various chiral ligands with the hydrogen perchlorate salt of α-(1-naphthyl)ethylamine (A) as observed by the temperature-dependent ^1H NMR technique are compared with those calculated from the conformational equilibrium energies of the complexes.[19,20] These calculated energies included those for the ion–ligand interactions and the strain energy of the ligands that are the main components of $\Delta G_c^{\ddagger}$. They are therefore the main contributors to $\Delta\Delta G_c^{\ddagger}$. The other components that are temperature or solvent dependent are smaller and not much different for the *R* and *S* complex and therefore are

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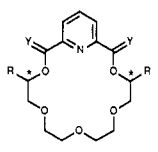
Table II. Differences in Free Energies of Activation ($\Delta\Delta G_c^{\ddagger}$, kcal/mol) [$\Delta G_c^{\ddagger}(R) - \Delta G_c^{\ddagger}(S)$] for the Interaction of Various Chiral Macrocyclic Ligands with (*R*)- and (*S*)-[α-(1-Naphthyl)ethyl]ammonium Perchlorate (A in Table I) As Determined Experimentally (NMR) and As Calculated from Empirical Energy Functions[a]

ligand	$\Delta\Delta G_c^{\ddagger}$ obsd	$\Delta\Delta G_c^{\ddagger}$ calcd
(*S*,*S*)-**1**	1.1[b]	0.7
(*S*,*S*)-**2**	1.3	2.5
(*S*,*S*)-**3**	0.1[b]	0.1
(*S*,*S*)-**4**	1.6[b]	1.7
(*R*,*R*)-**7**	0.8	1.7
(*R*,*R*,*R*,*R*)-**10**	0.9	0.9
I[c] R = *tert*-butyl (Y = O)		2.5
I,[c] R = *tert*-butyl (Y = H_2)		2.2
I,[c] R = $(CH_2)_3$Ph (Y = O)		1.5
I,[c] R = $(CH_2)_4$Ph (Y = O)		1.6
I,[c] R = $(CH_2)_4$Ph (Y = H_2)		1.1
I,[c] R = $(CH_2)_3$(1-Nap) (Y = O)		1.5
I,[c] R = $(CH_2)_4$(1-Nap) (Y = O)		1.2
I,[c] R = CH_2OPh (Y = O)		0.6
I,[c] R = CH_2OPh (Y = H_2)		1.3
I,[c] R = CH_2O(1-Nap) (Y = O)		1.1
I,[c] R = CH_2O(2-Nap) (Y = O)		0.7
I,[c] R = CH_2O(1-Nap) (Y = H_2)		0.8
I,[c] R = CH_2O(2-Nap) (Y = H_2)		1.4

[a] Empirical calculations as reported in ref 19 and 20. [b] Data from ref 13. [c] Structure I is given below.



mostly cancelled out in the calculated $\Delta\Delta G_c^{\ddagger}$ values.[19,20] Consequently, the calculated energy difference represents approximately the $\Delta\Delta G_c^{\ddagger}$ value.

The calculated values of these interaction energies are based on the empirical functions of bond lengths, bond angles, torsional angles, and interatomic Coulombic and Lennard–Jones interactions. The calculations were performed by the empirical force field method that has been described in ref 19 and 20. The reliability of this method in making theoretical predictions that were borne out by experiment has been checked and confirmed in many instances.[19,20] More recently, this method has been used in the discovery of a hydration pattern in enniatin crystals that escaped detection by X-ray diffraction analysis[21] and in the design of biomimetic ferric ion carriers.[22] The empirical force field method yields equilibrium conformations for which the total energy is at a local minimum and determines their corresponding energies. In the present macrocyclic molecules and their ion complexes, the number of such local low-energy minima is limited because the macrocyclic "conformational space" is restricted by the conditions of ring closure. A thorough scan of the conformational space produced all low energy minima of both enantiomers, including the most stable *R* and *S* conformations, whose energy difference is given in the last column of Table II.

The computer-calculated $\Delta\Delta G_c^{\ddagger}$ values for the complexes of ligands **1**, **3**, **4**, and **10** with A were about the same as those observed by the ^1H NMR method. The calculated $\Delta\Delta G_c^{\ddagger}$ values for the complexes of **2** and **7** were significantly higher than the observed values. On the basis of this significant, though less than thorough, agreement between the observed and calculated values of $\Delta\Delta G_c^{\ddagger}$ for some of these complexes, the force field calculations were further extended to many other variants of the same family of molecules (structure I in Table II). The results are included in Table II. They were used to estimate the expected capacity of these variants for enantiomeric recognition and helped to choose which variants should be synthesized and which should not. Thus, the variant I, *R* = *tert*-butyl, is predicted to yield high enantiomeric recognition and is currently being prepared in our laboratory. Other variants were shown to be less promising and are not being prepared. For example, it was thought that perhaps the naphthalene group of the ammonium salt could be sandwiched between the pyridine of the crown and a naphthyl or phenyl group at the end of a chain attached to the macrocycle ring. After several calculations with R = $(CH_2)_n$-naphthyl and $(CH_2)n$-phenyl with *n* values of 3 and 4 (see Table II), the idea was rejected because the calculated $\Delta\Delta G_c^{\ddagger}$ values were never more than about 1.5. These calculated values were not significantly different from the values for already prepared **4**, **7**, and **10**, so compounds I (Table II) where R = $(CH_2)_n$-naphthyl or $(CH_2)_n$-phenyl will not be prepared.

The computer-generated stereoviews of the ligand–ion complexes complemented the calculated $\Delta\Delta G_c^{\ddagger}$ values by exposing visually the nature of the ion–ligand interactions and the source of the enantiomeric recognition. Figure 2 represents stereoviews of the two diastereoisomeric ion complexes with ligand I (*R* = *tert*-butyl) each viewed from two perpendicular directions. It is seen that for the *R* enantiomer, the *tert*-butyl substituent contacts the methyl part of the salt, the naphthyl substituent of the salt contacts the pyridine, and the three NH bonds are properly oriented toward their respective ligating groups, thus optimizing the salt–ligand electrostatic interaction. The *S* enantiomeric salt appears to be less favorably bound to the ligand. The naphthyl substituent of the salt repels the *tert*-butyl substituent of the ligand, thus introducing distortion and strain in the complex, and the NH bonds are not well oriented toward their respective ligating group, thus weakening the salt–ligand interaction.

Similar analyses of the computer-generated stereoviews of the other complexes listed in Table II revealed a common pattern, namely, that the *R* ion is favorably interacting with the neighbor R substituent on the *S*,*S* ligand, while the *S* ion has the naphthyl group too close to the R group of the *S*,*S*, ligand, and therefore interacts unfavorably. The specific details of these interactions varied widely from complex to complex. The reason for this diversity is that the macrocyclic backbone possesses several, though few, conformations of low energy, and the interaction of the ligating ion with the R group may affect their relative stability. Furthermore, this flexibility may explain why enantiomeric recognition of most of these variants is confined within the narrow range of less than about 1.6 kcal/mol of $\Delta\Delta G_c^{\ddagger}$ values. Whenever the enantiomeric recognition with respect to any given conformation is too large, the unfavored ionic enantiomer may prefer to adopt another formation of higher stability.

The structure of macrocycle **11** has been determined by an X-ray crystallographic procedure. Atomic parameters of the non-hydrogen atoms are listed in Table III. Computer drawings of the structure of **11** are shown in Figures 3 and 4. While the structural formula of the ligand allows for symmetry including a 2-fold axis, the conformation of the molecule in the solid state does not contain any such symmetry. This is apparent in Figure 3, which is a view looking down on the plane of the molecule. The presence of the two aromatic pyridine groups causes the molecule to be rather rigid and strained. The torsion angles do not have the usual low energy values of 60° for O–C–C–C

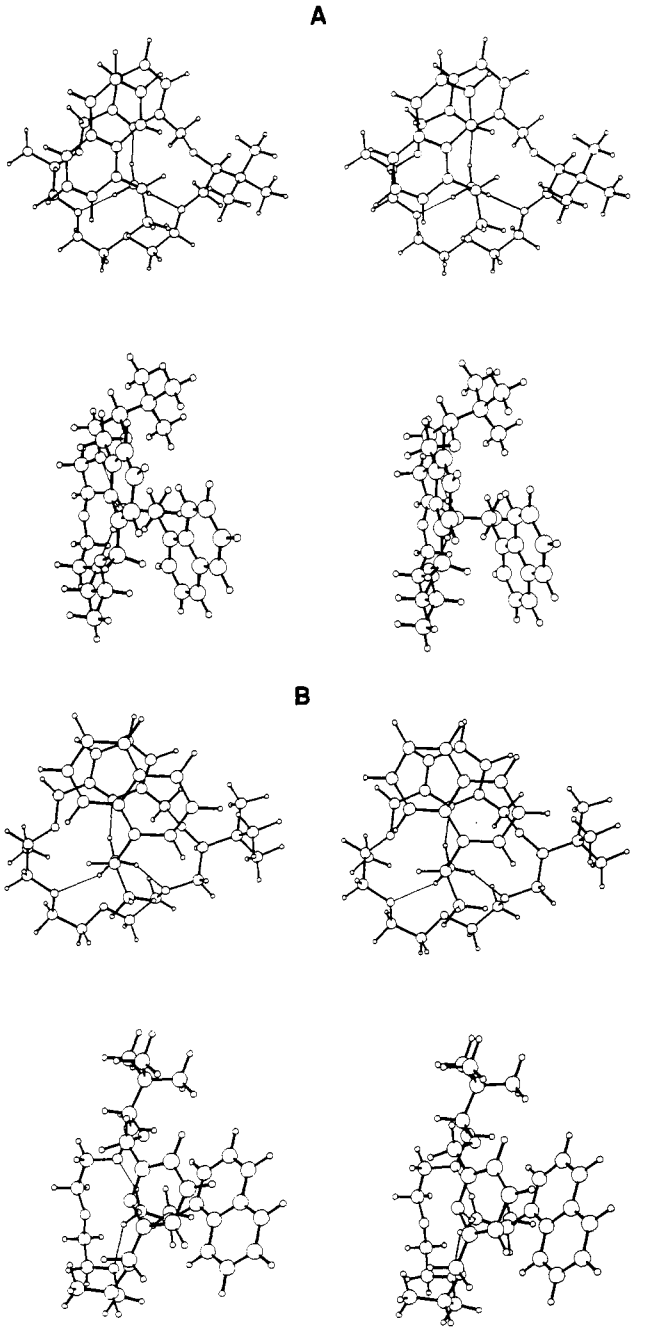


Figure 2. Computer-generated stereoviews obtained from force field calculations of the complexes of the proposed (*S,S*)-di-*tert*-butyl-substituted pyridino-18-crown-6 with (*R*)-[α-(1-naphthyl)ethyl]ammonium perchlorate (stereoviews A) and with the (*S*)-perchlorate (stereoviews B).

angles and 180° for C–O–C–C. The torsion angles are listed in Table IV. The deviation of donor atoms from the least-squares plane calculated for the four oxygen atoms are N1 +0.197 Å, O8 +0.862 Å, O11 −0.860 Å, N18 −0.157 Å, O20 +0.570 Å, and O28 −0.057 Å. The bond lengths in the ring molecule are normal. The average C–O bond is 1.42 (3) Å and the average C–C bond is 1.50 (1) Å. A side view of this molecule (Figure 4) shows the degree to which the two pyridine rings are bent out of the plane of the four oxygen atoms.

Experimental Section

Infrared (IR) spectra were obtained on Matson Sirius FTIR or Perkin-Elmer 1600 FTIR spectrometers. The proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on JEOL FX-90Q or Varian Gemini 200 spectrometers using deuteriochloroform ($CDCl_3$) unless otherwise indicated. The temperature-dependent ^{1}H NMR spectral studies were carried out on the

Table III. Positional (×10^4) and Isotropic Thermal (×10^3) Parameters of Non-Hydrogen Atoms of 11 with Esd Values in Parentheses

atom	*x*	*y*	*z*	*U* (Å^2)
N1	671 (8)	11986	2199 (7)	53 (3)
C2	503 (10)	13124 (22)	2988 (9)	52 (4)
C3	648 (10)	15313 (26)	2985 (9)	57 (4)
C4	996 (9)	16292 (26)	2177 (8)	58 (4)
C5	1163 (10)	15166 (27)	1366 (10)	64 (4)
C6	971 (10)	12950 (22)	1417 (9)	46 (3)
C7	1196 (12)	11566 (29)	569 (10)	77 (4)
O8	1900 (7)	12418 (18)	−69 (7)	73 (3)
C9	1976 (11)	11260 (26)	−962 (9)	67 (4)
C9M	1881 (13)	128850 (30)	−1755 (12)	96 (6)
C10	3035 (11)	10037 (27)	−958 (9)	63 (4)
C10M	3057 (13)	8609 (30)	−1845 (11)	91 (5)
O11	3153 (7)	8671 (18)	−113 (6)	71 (3)
C12	3984 (11)	9308 (28)	560 (9)	69 (4)
C13	4049 (10)	7954 (23)	1427 (9)	50 (3)
C14	3871 (10)	5745 (23)	1372 (9)	61 (4)
C15	4010 (11)	4595 (30)	2175 (10)	71 (5)
C16	4315 (10)	5561 (24)	3033 (9)	58 (4)
C17	4472 (10)	7717 (23)	3042 (9)	52 (3)
N18	4355 (8)	8877 (20)	2250 (7)	54 (3)
C19	4766 (10)	8923 (25)	3962 (8)	57 (4)
O20	3896 (6)	10280 (18)	4234 (5)	55 (2)
C21	2825 (10)	9367 (23)	4272 (8)	51 (3)
C21M	2796 (13)	7649 (30)	5041 (11)	94 (6)
C22	2039 (9)	11124 (22)	4421 (8)	50 (4)
C22M	2079 (11)	12006 (29)	5454 (9)	74 (4)
O23	978 (6)	10355 (17)	4160 (5)	53 (2)
C24	184 (10)	11899 (26)	3834 (8)	60 (4)

Table IV. Ring Torsion Angles (deg) of 11 with Esd Values in Parentheses

N1–C6–C7–O8	−155 (1)
C6–C7–O8–C9	−170 (1)
C7–O8–C9–C10	−105 (1)
O8–C9–C10–O11	55 (2)
C9–C10–O11–C12	−111 (1)
C10–O11–C12–C13	177 (1)
O11–C12–C13–N18	−147 (1)
C12—C13–N18–C17	−177 (1)
C13–N18–C17–C19	−177 (1)
N18–C17–C19–O20	67 (1)
C17–C19–O20–C21	51 (1)
C19–O20–C21–C22	−172 (1)
O20–C21–C22–O23	162 (1)
C21–C22–O23–C24	−153 (1)
C22–O23–C24–C2	58 (1)
O23–C24–C2–N1	60 (2)
C24–C2–N1–C6	−179 (1)
C2–N1–C6–C7	177 (1)

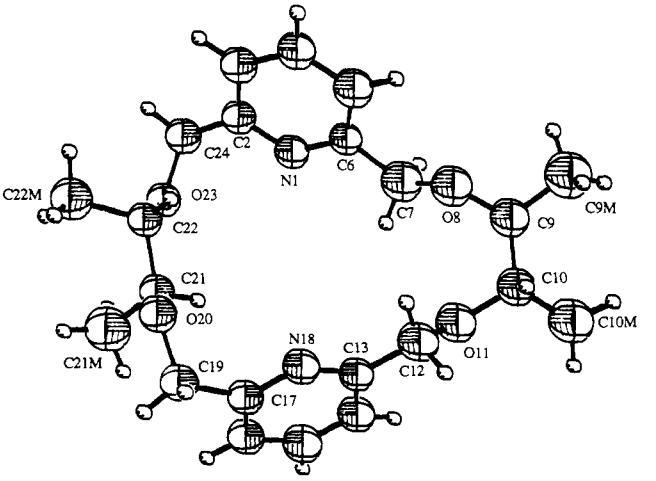


Figure 3. Stereoview obtained from X-ray data of 11 looking down on the molecule.

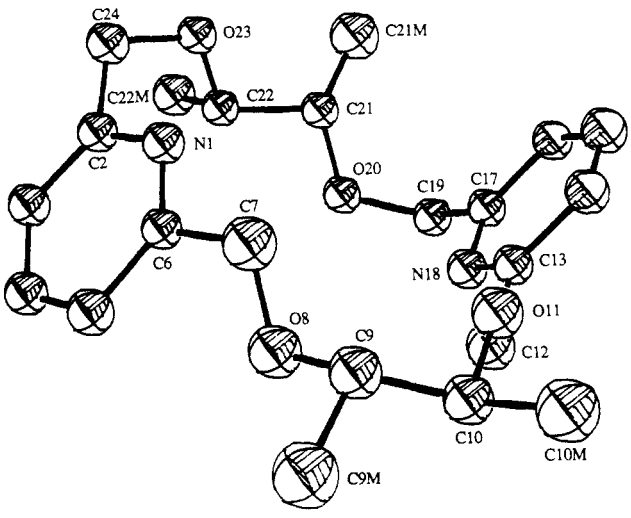


Figure 4. Side view obtained from X-ray data of **11** showing the relationship of the two pyridine rings.

Gemini 200 spectrometer. The crystal structural determination was done on a Nicolet R3 autodiffractometer. Molecular weights were determined by the electron impact method on a Finnegan 8430 high resolution mass spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Optical rotations were taken on a Perkin-Elmer 241 polarimeter. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. The hydrogen perchlorate salts of the chiral amines used in the study were prepared as reported.[13]

Preparation of (2*R*)-1,2-Epoxyalkanes 17 (Scheme IIIA).[24,25] The optically active 1,2-epoxyalkanes were prepared by the method of Koppenhoeffer and Schurig[24,25] as shown in Scheme IIIA. The intermediate product yields, boiling points, and optical rotations, with literature values[24,25] for the rotations given in parentheses, are as follows: **15** (R = isopropyl), 63%, 106 °C/12 mm, $[\alpha]_D$ -0.91° (-1.44°); **15** (R = isobutyl), 69%, 113–116 °C/10 mm, $[\alpha]_D$ -31.36° (-31.73°); **15** (R = *sec*-butyl), 61%, 115–118 °C/15 mm, $[\alpha]_D$ -4.62° (-4.78°); **15** (R = benzyl), 62%, 129 °C/1 mm, α_D +6.12° (neat), ^{1}H NMR δ 11.65 (b, 1 H), 7.3 (m, 5 H), 4.5 (t, 1 H), 3.28 (dq, 2 H); **16** (R = isopropyl), 72%, 64–66 °C/12 mm, $[\alpha]_D$ +3.1 (+3.6); **16** (R = isobutyl), 70%, 74–76 °C/15 mm, $[\alpha]_D$ -47.34° (-48.8°); **16** (R = *sec*-butyl), 81%, 79 °C/12 mm, $[\alpha]_D$ -7.60° (-7.6°); **16** (R = benzyl), 76%, 129 °C/10 mm, $[\alpha]_D$ -19.81° (*c* = 0.135, chloroform), ^{1}H NMR δ 7.28 (m, 5 H), 4.2 (m, 1 H), 3.8 (m, 1 H), 3.7 (m, 1 H), 3.08 (m, 2 H), 2.07 (t, 1 H); **17** (R = isopropyl), 62%, 82 °C/730 mm, $[\alpha]_D$ -4.54° (-4.46°); **17** (R = isobutyl), 82%, 108 °C/730 mm, $[\alpha]_D$ +19.67° (+20.47°); **17** (R = *sec*-butyl), 85%, 109 °C/726 mm, $[\alpha]_D$ +14.36° (+14.4°); **17** (R = benzyl). A column was packed with an estimated 300 mL of Amberlite IRA 400 (OH) ion-exchange resin and washed with several column volumes of methanol. A solution of 35 g (0.20 mol) of **16** (R = benzyl) in 200 mL of methanol was run through the column and collected at a rate of 60 drops/min. If the effluent contained starting material (by GC), the solution was evaporated and run through the column a second time. The column was used until the ratio of hydroxide to substrate was equal to ≈5 mequiv/mequiv of substrate, then a new column was used. This procedure was repeated several times using 4.36 g (0.024 mol), 6.15 g (0.036 mol), 2.13 g (0.012 mol), 10.6 g (0.062 mol), and 24 g (0.14 mol) of **16** (R = benzyl) to obtain a total of 51.56 g (81%) of a clear oil: bp 93 °C/35 mm; ^{1}H NMR δ 7.26 (m, 5 H), 3.15 (m, 1 H), 2.87 (m, 2 H), 2.78 (m, 1 H), 2.54 (q, 1 H); IR (neat) 3028, 2991, 2917, 1605, 1496, 1454, 1404, 1258, 1030, 967, 933, 846, 817, 736, 700 cm^{-1}; $[\alpha]_D$ +19.19° (neat) (lit. value for the *S* form of unidentified purity was -10.01°).[33]

Preparation of 2,12-Disubstituted Tetraethylene Glycols 13 (Scheme IIIA). Diethylene glycol and a catalytic amount of sodium metal were placed in an oven-dried 250-mL, three-necked round-bottom flask equipped with a 125-mL addition funnel, nitrogen inlet, magnetic stirring bar, and a dry ice/isopropyl alcohol or acetone condenser. This mixture was heated to between 90 °C and 100 °C and the sodium allowed to dissolve. Two equivalents plus 10% of the epoxide **17** were added over a period of 1.5 h. The mixture was then stirred for 22 h at 100 °C. The reaction mixture was allowed to cool to room temperature and sodium bicarbonate was added to neutralize the base. Ethyl ether (100 mL) was added to the cooled mixture and the solution was extracted with 150 mL of a 10% brine solution. The brine solution was then washed with two 200-mL portions of ether. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and evaporated to leave a yellow oil. The oil was then distilled under vacuum to obtain the pure product. Specific details for each glycol are as follows.

(3*R*,13*R*)-2,14-Dimethyl-5,8,11-trioxapentadecane-3,13-diol (13, R = Isopropyl). Compound **13** (R = isopropyl) was prepared as described above using 27.29 g (0.32 mol) of **17** (R = isopropyl), 16.36 g (0.15 mol) of diethylene glycol, and 0.48 g (0.02 mol) of sodium metal. The light yellow oil obtained as the crude product was distilled to give 26.79 g (62%) of the product as a colorless oil: bp 118 °C/0.05 mm; ^{1}H NMR δ 3.68 (d, 2 H), 3.63 (m, 10 H), 3.49 (m, 2 H), 3.35 (q, 2 H), 1.66 (m, 2 H), 0.95 (d, 6 H), 0.89 (d, 6 H); $[\alpha]_D$ -27.99° (*c* = 0.103, chloroform); MS, *m/e* 278 (M$^+$).

(4*R*,14*R*)-2,16-Dimethyl-6,9,12-trioxaheptadecane-4,14-diol (13, R = Isobutyl). Compound **13** (R = isobutyl) was prepared as described above using 54.7 g (0.54 mol) of **17** (R = isobutyl), 27.33 g (0.26 mol) of diethylene glycol, and 0.8 g (0.035 mol) of sodium metal. A light yellow oil was obtained as the crude product, which was distilled to give 32.50 g (41%) of the product as a colorless oil: bp 113–138 °C/0.05 mm; ^{1}H NMR δ 3.82 (m, 4 H), 3.64 (s, 8 H), 3.52 (d, 1 H), 3.51 (d, 1 H), 3.25 (q, 2 H), 1.78 (m, 2 H), 1.38 (m, 2 H), 1.06 (m, 2 H), 0.90 (d, 6 H), 0.86 (d, 6 H); $[\alpha]_D$ -8.79° (*c* = 0.103, chloroform); MS, *m/e* 307 (M$^+$).

(3*S*,4*R*,14*R*,15*S*)-3,15-Dimethyl-6,9,12-trioxaheptadecane-4,14-diol (13, R = *sec*-Butyl). Glycol **13** (R = *sec*-butyl) was prepared as described above using 53.20 g (0.53 mol) of **17** (R = *sec*-butyl), 26.83 g (0.25 mol) of diethylene glycol, and 0.75 g (0.03 mol) of sodium metal. The light yellow oil was distilled to give 57.25 g (74%) of the product as a colorless oil: bp 114–137 °C/0.05 mm; ^{1}H NMR δ 3.58 (m, 2 H), 3.45 (m, 2 H), 3.33 (m, 2 H), 1.38 (m, 4 H), 1.07 (m, 2 H), 0.82 (m, 12 H); $[\alpha]_D$ -30.09° (*c* = 0.101, chloroform); MS, *m/e* 307 (M$^+$).

(2*R*,12*R*)-1,13-Diphenyl-4,7,10-trioxatridecane-2,12-diol (13, R = Benzyl). Glycol **13** (R = benzyl) was prepared as described above using 50.1 g (0.37 mol) of **17** (R = benzyl), 18.83 g (0.18 mol) of diethylene glycol, and 0.55 g of sodium metal. The resulting yellow oil (63.86 g) was chromatographed using preparative HPLC (ethyl acetate/hexane 1/1). The peak that contained the majority of the material was Kugelrohr distilled (185–200 °C/0.15 mm) to give 30.7 g (42%) of a clear viscous oil: ^{1}H NMR δ 7.21 (m, 10 H), 3.99 (m, 4 H), 3.62 (s, 8 H), 3.50 (dd, 2 H), 3.2 (dd, 2 H), 2.79 (dq, 4 H); $[\alpha]_D$ -7.57° (*c* = 0.20, chloroform); MS, *m/e* 375 (M$^+$).

(2*S*)-Glycerol 1,2-Acetonide (19) (Scheme IIIB). Compound **19** was synthesized from D-mannitol by the procedure of Eibl.[29] The pH of the reaction mixture of **18** with sodium periodate was kept at a pH of 6 or greater using lithium hydroxide. The product (46%) was a liquid: bp 34 °C/0.1 mm; $[\alpha]_D$ +14.9° (neat) (lit.[29] +15.2°).

(2*R*)-3-(Tosyloxy)-1,2-propanediol Acetonide (20) (Scheme IIIB). To 55.55 g (0.42 mol) of **19** in 350 mL of dry THF was added 38 g (0.6 mol) of powdered potassium hydroxide. The mixture was stirred and cooled to 0 °C. Tosyl chloride (recrystallized from hexane) (91.5 g, 0.48 mol) in 300 mL of dry THF was slowly added to the above, stirred mixture at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 5 h and at room temperature for 12 h. The solid was filtered and the residue washed with 50 mL of THF. The filtrate and wash were evaporated under reduced pressure and the residue was recrystallized from ether–petroleum ether to give 102 g (85%) of **20**: mp 28–30 °C; $[\alpha]_D$ -4.8° (*c* = 13, ethanol) (lit. -4.6°[34] and -4.5°[35]). Com-

(33) Hiraro, T.; Inoue, S.; Tsurata, T. *Makromol. Chem.* **1976**, *177*, 3245.

(34) Baer, E.; Fisher, O. L. *J. Am. Chem. Soc.* **1948**, *70*, 609.

pound **20** exhibited the same ^1H NMR spectrum as that reported.[35]

(*S*)-4-(3-Butenyl)-2,2-dimethyl-1,3-dioxolane (21) (Scheme IIIB). A solution of 70 g (0.25 mol) of **20** in 270 mL of dry benzene was slowly added to 270 mL of a stirred 1.0 M ethereal solution of allylmagnesium bromide (prepared from allyl bromide and magnesium) at 0 °C under an argon atmosphere. A lithium copper chloride (Li_2CuCl_4) catalyst (10 mL in THF) was added and the reaction mixture was stirred for 30 min at 0 °C and for 22 h at room temperature. The solid was filtered and the residue washed 3 times with 40-mL portions of benzene. The filtrate and washes were extracted with 400 mL of saturated aqueous ammonium chloride solution. The aqueous phase was washed with 100 mL of benzene and the combined organic phases were dried over anhydrous magnesium sulfate. The mixture was filtered, the solvent was evaporated under reduced pressure, and the residue was distilled to give 26.6 g (68%) of liquid **21**: bp 60–61 °C/9 mm; $[\alpha]_D$ +16.04 (c = 11.5, benzene); ^1H NMR δ 5.85–5.61 (m, 1 H), 5.05–4.82 (m, 2 H), 4.11–3.90 (m, 2 H), 3.52–3.36 (m, 1 H), 2.25–1.88 (m, 2 H), 1.78–1.40 (m, 2 H), 1.33 (s, 3 H), 1.28 (s, 3 H); IR (neat) 3100, 2995, 2950, 2875, 1640, 1460, 1375, 1360, 1250, 1220, 1070, 1000, 920, 860, 810 cm^{-1}.

(*S*)-5-Hexene-1,2-diol (22) (Scheme IIIB). Compound **21** (24.0 g, 0.15 mol) was stirred with a mixture of 120 mL of glacial acetic acid and 13.2 mL of distilled water at 80 °C for 50 min. The mixture was evaporated under reduced pressure. The residue was dissolved in 50 mL of dry dioxane and the dioxane was evaporated under reduced pressure. This process was repeated using 60 mL of toluene to remove the last traces of water and acetic acid. The residue was distilled to give 15.6 g (87%) of **22**: bp 72 °C/0.16 mm; $[\alpha]_D$ −19.04° (c = 10.0, ethanol); ^1H NMR δ 5.90–5.62 (m, 1 H), 5.1–4.85 (m, 2 H), 4.30 (bs, 2 H, disappeared in D_2O), 3.75–3.47 (m, 2 H), 3.43–3.20 (m, 1 H), 2.3–1.9 (m, 2 H), 1.65–1.30 (m, 2 H); IR (neat) 3400 (br), 3100, 2995, 2950, 2870, 1640, 1460, 1420, 1100, 1050, 1000, 910, 870, 800 cm^{-1}.

(*S*)-1-(Tosyloxy)-5-hexen-2-ol (23) (Scheme IIIB). To a stirred mixture of 14.8 g (0.13 mol) of **22**, 90 mL of dry methylene chloride, and 19.6 mL (14.23 g, 0.14 mol) of triethylamine at 0 °C was slowly added 24.3 g (0.13 mol) of tosyl chloride dissolved in 90 mL of dry methylene chloride. The resulting mixture was stirred at 0 °C for 5 h and at room temperature for 42 h. The solvents were evaporated under reduced pressure and the residue was triturated with dry ether. The solid triethylammonium chloride was filtered and the salt was washed with 25 mL of dry ether. The filtrate and ether wash were combined and evaporated. The residue was chromatographed on silica gel using toluene and then ethyl acetate/toluene 1/20, then 1/15 as eluants to give 22.7 g (66%) of **23** as an oil: $[\alpha]_D$ +3.99° (c = 13.2, benzene); ^1H NMR δ 7.80 (d, 2 H), 7.35 (d, 2 H), 5.88–5.62 (m, 1 H), 5.08–4.89 (m, 2 H), 4.11–3.74 (m, 3 H), 2.58 (bs, 1 H, disappeared in D_2O), 2.43 (s, 3 H), 2.28–1.92 (m, 2 H), 1.63–1.39 (m, 2 H); IR (neat) 3450 (br), 3100, 3040, 2995, 2950, 2920, 2855, 1640, 1600, 1500, 1460, 1360, 1190, 1180, 1100, 970, 940, 830, 810, 790, 670 cm^{-1}.

(*S*)-1-(Tosyloxy)-2-(tetrahydropyranyloxy)-5-hexene (24) (Scheme IIIB). A mixture of 17.1 g (63 mmol) of **23**, 22.4 g (270 mmol) of 3,4-dihydro-2*H*-pyran (DHP), 280 mL of dry methylene chloride, and 1.8 g of pyridinium tosylate (PPTS) catalyst was stirred at room temperature for 18 h. The mixture was extracted twice with 160-mL portions of water and the organic layer was dried over anhydrous magnesium sulfate. The material was filtered and the solvent and excess DHP were evaporated under reduced pressure. The residue was chromatographed on silica gel using toluene to give 21.0 g (94%) of **24** as an oil: $[\alpha]_D$ −12.04° (c = 11.6, benzene); ^1H NMR δ 7.82 (d, 2 H), 7.36 (d, 2 H), 5.9–5.6 (m, 1 H), 5.1–4.88 (m, 2 H), 4.65–4.58 (m, 1 H), 4.21–3.65 (m, 5 H), 2.44 (s, 3 H), 2.25–1.92 (m, 2 H), 1.9–1.35 (m, 8 H); IR (neat) 3100, 3040, 2995, 2950, 2930, 2900, 2880, 1640, 1600, 1500, 1470, 1450, 1360, 1200, 1180, 1040, 1020, 990, 900, 860, 830, 770, 680 cm^{-1}.

(5*S*,15*S*)-7,10,13-Trioxa-1,18-nonadecadiene-5,15-diol (25) (Scheme IIIB). Diethylene glycol (3.18 g, 30 mmol) in 30 mL of DMF was added dropwise to a stirred mixture of 2.4 g (80 mmol) of sodium hydride (80% dispersion in mineral oil) in 20 mL of dry DMF at 0 °C under an argon atmosphere. The mixture was stirred at 0 °C for 10 min, then at room temperature for 30 min, and at 80 °C for 1 h. The mixture was cooled to room temperature and 23.0 g (65 mmol) of **24** in 60 mL of DMF was added dropwise to it. The resulting mixture was stirred at room temperature for 30 min and then at 80 °C for 1 day. The solvent was then evaporated under vacuum and the residue was added to a mixture of 250 mL of saturated aqueous sodium bicarbonate and 250 mL of ethyl acetate. The phases were mixed and separated. The aqueous phase was extracted twice with 100-mL portions of ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was evaporated. This crude THP-blocked tetraethylene glycol product (12.2 g) was stirred in a mixture of 80 mL of glacial acetic acid and 9 mL of distilled water at 80 °C for 1 h. The solvents were removed under vacuum (70 °C/0.1 mm) and the residue was chromatographed on silica gel (ethyl acetate/toluene 1/1 and 3/1) to give 7.08 g (78%) of **25** as an oil: $[\alpha]_D$ +17.48° (c = 14, benzene); ^1H NMR δ 5.9–5.64 (m, 2 H), 5.08–4.85 (m, 4 H), 4.02 (bs, 2 H, disappeared in D_2O), 3.88–3.2 (m, 14 H), 2.3–1.94 (m, 4 H), 1.62–1.26 (m, 4 H); IR (neat) 3420 (br), 3100, 3030, 2995, 2940, 2870, 1640, 1470, 1420, 1360, 1120, 1000, 910 cm^{-1}.

(2*R*,3*R*,11*R*,12*R*)-3,11-Dimethyl-4,7,10-trioxatridecane-2,12-diol (28) (Scheme IIIC). To a suspension of 100 mL of dry DMF and 12.0 g (0.4 mol) of sodium hydride (80% dispersion in mineral oil) was added 29.0 g (0.32 mol) of **14** dissolved in 250 mL of dry DMF at room temperature. Following the addition, the mixture was stirred at 80 °C for 80 min. After cooling to room temperature, 40.5 g (0.32 mol) of benzyl chloride dissolved in 150 mL of dry DMF were added to the stirred mixture over a 1-h period. The reaction was then stirred at 70 °C for 15 h. The solvent was evaporated under reduced pressure and the residue was mixed with ice (200 g) and ethyl acetate (300 mL). The pH was adjusted to 7. The two phases were separated and the aqueous phase was washed with two 100-mL portions of ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography on silica gel using hexane followed by ethyl acetate/hexane 1/8 as eluants to give 23.4 g of **26** (42%), bp 68–70 °C/0.065 mm. Compound **27** (bp 118–122 °C/0.065 mm) was also isolated from the reaction mixture in a 22% yield. This material was reduced to **26** in a 48% yield using 1 mol of hydrogen with a platinum catalyst.

To a slurry of 4.43 g (0.15 mol) of sodium hydride (80% in mineral oil) and 20 mL of dry THF was added dropwise 22.1 g (0.12 mol) of **26** in 80 mL of dry THF at room temperature. After being stirred for 10 min, the mixture was refluxed for 1 h. The reaction mixture was then cooled to 0 °C in an ice bath and 24.0 g (0.058 mol) of diethylene glycol ditosylate (prepared as above for **20** from diethylene glycol to give a 90% yield, mp 90 °C) dissolved in 100 mL of dry THF was added dropwise. After 30 min at 0 °C, the reaction mixture was stirred at room temperature for 3 days. The solvent was then evaporated under vacuum and the residue added to a mixture of 100 g of ice, 100 mL of water, and 300 mL of ethyl acetate. The aqueous phase was then washed with two 100-mL portions of ethyl acetate. The combined organic phases were then washed with 100 mL of saturated brine solution, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The unreacted **26** was removed by distillation (68–70 °C/0.065 mm) and the residue was purified by column chromatography on silica gel using hexane followed by acetone/hexane 1/7 as eluants to give 15.7 g (63%) of the bis(benzyl-blocked) **28**. This latter material (9.8 g, 0.023 mol) was stirred with 1.5 g of activated charcoal and 110 mL of ethanol for 1 h and filtered. The resulting solution was added to 1.0 g of 10% Pd–C and the slurry was stirred at room temperature under H_2 at atmospheric pressure until the theoretical volume of H_2 was consumed (1.1 L, 0.046 mol). The catalyst was filtered and washed with ethanol and the solvent was evaporated. The residue was distilled under vacuum to give 5.4 g (95%) of **28**: bp 110–112 °C/0.2 mm; ^1H NMR δ 4.4 (b, 2 H), 3.7–3.8 (m, 2 H), 3.5–3.7 (m, 8 H), 3.1–3.3 (m, 2 H), 1.15 (d, 6 H), 1.11 (d, 6 H); $[\alpha]_D$ −42.9° (c = 21.7, ethanol).

2,6-Bis[(tosyloxy)methyl]pyridine (12). This starting material was prepared as above for **20** from 2,6-pyridinedimethanol.

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The yield was 91%, mp 121–122 °C (lit.[30] mp 121–122 °C).

General Procedure for the Preparation of the Chiral Monopyridino-Crowns (Scheme I). In an oven-dried 2-L three-necked round-bottom flask equipped with an addition funnel, nitrogen inlet, and stirring bar were placed 250 mL of dry THF and sodium hydride (80% dispersion in mineral oil). The optically active glycol dissolved in 300 mL of THF was added over a period of 1 h with the addition beginning at room temperature and the flask slowly heated to reflux temperature during the addition. The solvent was allowed to reflux a total of 1 h and the reaction mixture was cooled to room temperature and finally to −75 °C. Compound **12** dissolved in 300 mL of dry THF was then added over a 2-h period. The reaction mixture was stirred for 30 min at −78 °C and then allowed to slowly warm to room temperature. The mixture was stirred at room temperature for 2 days. When the reaction was complete as determined by TLC, the mixture was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in methylene chloride and washed with water. The aqueous phase was then washed twice wth 100-mL portions of methylene chloride. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was decolorized using charcoal in an ethanol/toluene 1/5 mixture. This usually produced a light orange oil upon evaporation of the solvent. The material could be further purified using neutral alumina column chromatography (ethanol/toluene 1/100) or using a C_{18} reverse-phase HPLC column (methanol/water 95/5).

(4*R*,14*R*)-4,14-Diisopropyl-3,6,9,12,15-pentoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (5). Crown **5** was prepared as described above using 2.75 g of sodium hydride, 6.96 g (0.025 mol) of **13** (R = isopropyl), and 10.84 g (0.025 mol) of **12**. The product was purified by preparative HPLC (methanol/H_2O 87/13) to give 5.23 g (55%) of a yellow oil: ^{1}H NMR δ 7.65 (t, 1 H), 7.28 (d, 2 H), 4.82 (dd, 4 H), 3.6 (m, 12 H), 3.40 (q, 2 H), 1.87 (m, 2 H), 0.98 (d, 6 H), 0.95 (d, 6 H); $[\alpha]_D$ −4.48° (*c* = 0.101, chloroform); MS, *m/e* 382 (M^+). Anal. Calcd for $C_{21}H_{35}NO_5$: C, 66.11; H, 9.25. Found: C, 66.24; H, 9.17.

(4*R*,14*R*)-4,14-Diisobutyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (6). Crown **6** was synthesized as described above using 2.75 g of sodium hydride, 9.19 g (0.03 mol) of **13** (R = isobutyl), and 13.01 g (0.03 mol) of **12**. The product was purified by preparative HPLC (methanol/water 87/13) to give 5.25 g (43%) of a slightly yellow oil: ^{1}H NMR δ 7.65 (t, 1 H), 7.28 (d, 2 H), 4.83 (dd, 4 H), 3.5–3.7 (m, 14 H), 1.77 (m, 2 H), 1.51 (m, 2 H), 1.2 (m, 2 H), 0.90 (t, 12 H); $[\alpha]_D$ +2.97° (*c* = 0.204, chloroform); MS, *m/e* 409 (M^+). Anal. Calcd for $C_{23}H_{39}NO_5$: C, 67.45; H, 9.59. Found: C, 67.29; H, 9.33.

(4*R*,14*R*)-4,14-Di-[(*S*)-*sec*-butyl]-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (7). Crown **7** was prepared as described above using 2.9 g of sodium hydride, 9.25 g (0.03 mol) of **13** (R = *sec*-butyl), and 13.04 g (0.03 mol) of **12**. The product was purified by both chromatography and preparative HPLC (methanol/water 87/13) to give 6.38 g (52%) of a yellow oil: ^{1}H NMR δ 7.65 (t, 1 H), 7.28 (d, 2 H), 4.82 (dd, 4 H), 3.6–3.47 (m, 14 H), 1.58 (m, 4 H), 1.20 (m, 2 H), 0.94 (d, 6 H), 0.91 (d, 6 H); $[\alpha]_D$ −10.84° (*c* = 0.138, chloroform); MS, *m/e* 410 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{39}NO_5$: C, 67.45; H, 9.59. Found: C, 67.37; H, 9.39.

(4*R*,14*R*)-4,14-Dibenzyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (8). Crown **8** was prepared as described above using 2.9 g of sodium hydride, 7.50 g (0.02 mol) of **13** (R = benzyl), and 8.96 g (0.02 mol) of **12**. A bright yellow oil was obtained after chromatography. Final purification was achieved by preparative HPLC (methanol/water 4/1) to give 3.65 g (38%) of a yellow oil: ^{1}H NMR δ 7.5 (t, 1 H), 7.24 (s, 10 H), 7.05 (t, 2 H); 4.68 (m, 4 H), 3.82 (m, 2 H), 3.50 (m, 12 H), 2.82 (m, 4 H); $[\alpha]_D$ −4.46° (*c* = 0.20, chloroform); MS, *m/e* 477 (M^+). Anal. Calcd for $C_{29}H_{35}NO_5$: C, 72.93; H, 7.38. Found: C, 72.92; H, 7.27.

(4*S*,14*S*)-4,14-Di-(3-butenyl)-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (9). Macrocycle **9** was prepared as reported above using 0.65 g of sodium hydride, 2.31 g (7.6 mmol) of **25**, and 3.58 g (8 mmol) of **12**. The crude product was purified by chromatography on neutral alumina (ethanol/toluene 1/150) to give 1.58 g (51%) of **9** as a clear oil: ^{1}H NMR δ 7.6 (t, 1 H), 7.2 (d, 2 H), 5.88–5.63 (m, 2 H), 5.06–4.85 (m, 4 H), 4.84–4.68 (m, 4 H), 3.7–3.35 (m, 14 H), 2.3–1.96 (m, 4 H), 1.7–1.38 (m, 4 H); $[\alpha]_D$ −14.82 (*c* = 11.8, benzene); $[\alpha]_D$ +18.17° (*c* = 12.5, ethanol); MS, *m/e* 405 (M^+). Anal. Calcd for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.45. Found: C, 68.15; H, 8.61; N, 3.43.

(4*R*,5*R*,13*R*,14*R*)-4,5,13,14-Tetramethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (10). Compound **10** was synthesized following the general procedure using 0.65 g of sodium hydride, 1.91 g (7.63 mmol) of **28**, and 3.58 g (8 mmol) of **12**. The crude material was purified by column chromatography using neutral alumina (ethanol/toluene 1/100) to give 1.27 g (47%) of **10** as a clear oil: ^{1}H NMR δ 7.7 (t, 1 H), 7.3 (d, 2 H), 4.8 (dd, 4 H), 3.4–3.7 (m, 12 H), 1.18 (d, 6 H), 1.1 (d, 6 H); $[\alpha]_D$ −43.3° (*c* = 8, ethanol); MS, *m/e* 353 (M^+). Anal. Calcd for $C_{19}H_{31}NO_5$: C, 64.56; H, 8.84. Found: C, 64.52; H, 8.89.

(4*R*,5*R*,15*R*,16*R*)-4,5,15,16-Tetramethyl-3,6,14,17-tetraoxa-23,24-diazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8,10,12(24),19,21-hexaene (11) (Scheme II). (2*R*,3*R*)-2,3-Butanediol (2.02 g, 22.4 mmol) dissolved in 90 mL of dry THF was added dropwise to a stirred mixture of 1.8 g (60 mmol) of sodium hydride (80% suspension in mineral oil) and 30 mL of dry THF at room temperature and under an atmosphere of argon. This mixture was stirred at room temperature for 20 min and then at reflux temperature for 1 h. The stirred mixture was cooled to 0 °C and 10 g (22.4 mmol) of **12** was added in one portion. The resulting mixture was stirred at 0 °C for 10 min and at room temperature for 30 min and refluxed for 20 h. The solution was then cooled and evaporated under reduced pressure and the residue was added to a mixture of 80 mL each of methylene chloride and water. The phases were mixed and separated. The aqueous phase was extracted twice with 30-mL portions of methylene chloride. The combined organic phases were dried over anhydrous magnesium sulfate. The filtered solution was evaporated under reduced pressure and the residue was chromatographed on silica gel using toluene and then THF/toluene 1/4 as eluants. The resulting solid was recrystallized from heptane to give 0.64 g (15%) of **11**: mp 100–101 °C; $[\alpha]_D$ −35.41 (*c* = 4.61, benzene); ^{1}H NMR δ 7.65 (t, 2 H), 7.25 (d, 4 H), 4.78–4.52 (diastereotopic AB, 8 H), 3.72–3.54 (m, 4 H), 1.17 (d, 12 H); MS, *m/e* 386 (M^+). Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82. Found: C, 68.37; H, 7.88.

Procedure Used for the Calculation of $\Delta\Delta G_c^{\ddagger}$ from Empirical Functions. The search for the energy of the most stable conformation of the ligand molecule was performed by scanning the whole conformational space of the molecule. All torsional angles of the backbone of the molecule were varied, subject to the restriction that the backbone must form a closed ring. In the initial scanning process, the conformational energy was estimated without minimization. This procedure was sufficient, however, to choose scores of candidate conformations that were used as initial data for seeking conformations of minimum energy. Minimization was performed by a quadratically convergent minimization algorithm. Many conformations of local minimum energy were found, but most of them had very high energies. By Boltzman's distribution law, they had a very low probability of occurrence and were therefore ignored. Few conformations were within the range of 5 kcal/mol above the most stable conformation. These were used as initial conformations for complexation with each of the two ionic enantiomers. The minimal energies of these complexes were derived, and the lowest one for each of the two enantiomeric ions was taken to represent $\Delta G_c^{\ddagger}$ of that ionic complex. Their difference is given as $\Delta\Delta G_c^{\ddagger}$ in Table II. It should be emphasized that the calculated conformations of the *R* ion complex and the *S* ion complex were always different. This was not only because the equilibrium conformations of the free ligands were affected by the *S* and *R* ionic enantiomers differently, but also because the lowest energy conformation of an ion complex was not necessarily derived from the lowest energy conformation of the free ligand. In some cases the most stable *R* ion complex and the *S* ion complex were derived from different free-ligand conformations.

In principle, our calculated estimate of $\Delta G_c^{\ddagger}$ could be improved by taking into account the metastable conformations as well as the most stable one in a statistical mechanical derivation of $\Delta G_c^{\ddagger}$. However, experience has shown that the contribution of the metastable states was small and that furthermore it affected similarly both ion complexes. It had consequently an insignificant

Table V. Crystal and Experimental Data for 11

formula	$C_{22}H_{30}N_2O_4$
formula weight	386.6
$F(000)$	416
crystal size, mm	0.05 × 0.15 × 0.60
Space group	$P2_1$
a, Å	12.204 (5)
b, Å	6.320 (3)
c, Å	13.895 (8)
β, deg	93.26 (4)
V, Å^3	1070.0 (9)
Z	2
d_{calcd}, g cm^{-3}	1.20
μ, cm^{-1}	0.77
sin θ/λ	0.55
total data	1658
obsd data	901
unobsd data	757
R_m	0.02
R	0.078
no. of parameters refined	124
goodness of fit	1.29

effect on the $\Delta\Delta G_c^*$ and was therefore ignored.

X-ray Structural Determination of 11. Crystals of compound 11 were often twinned and those that were not grew as very thin needles so a crystal suitable for an X-ray structural study was difficult to find. After several attempts, a crystal with dimension of 0.05 mm × 0.15 mm × 0.60 mm was chosen for the study. Even this crystal was not totally suitable as very few reflections above a 2θ limit of 40° were observed. Data were collected to a sin θ/λ limit of 0.55 (2θ = 46°). Some data between 2θ values of 46 and 50 were measured but none were greater than $3\sigma(I)$.

Lattice parameters and the orientation matrix were obtained by using a least-squares procedure involving 22 centered reflections 7° < 2θ < 22°. These data as well as single-crystal data were obtained on a Nicolet R3 automated diffractometer which used monochromated Mo Kα radiation (λ = 0.71073 Å). Crystal data and experimental conditions are summarized in Table V. Single-crystal data were measured by using θ-2θ scans with a variable scan rate (2.93 to 29.3°/min) and backgrounds on each side of the peak were measured so that the total time used to measure the background was equal to the scan time. A total of 901 observed unique data were obtained ($F > 4\sigma(F)$).

The structure was solved by using direct methods. All nonhydrogen atoms were located in the E map. Positions for all hydrogens were calculated on the basis of known stereochemical conditions. All hydrogens were allowed to ride on neighboring atoms and the thermal parameters of the hydrogen atoms were not refined. Because of the relatively few observed data and the large number of possible parameters only an isotropic refinement was used. The structure was refined to an R value of 0.078. With these conditions the observation/parameter ratio was about 7.2. Unit weights were used in the refinement. All programs used in the structure solution, refinement, and display are included in the SHELXTL program package.[36] Atomic scattering factors were obtained from ref 37.

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Supplementary Material Available: Tables containing hydrogen atom atomic parameters and bond lengths and angles for 11 and ^{1}H NMR spectra for compounds **15** (R = benzyl), **16** (R = benzyl), **17** (R = benzyl), **13** (R = benzyl, R = isopropyl, R = isobutyl, R = *sec*-butyl), **21-25**, and **28** (17 pages); table of observed and calculated structure factors for 11 (6 pages). Ordering information is given on any current masthead page.

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The Asymmetric Synthesis of 2,2-Dialkyl Carboxylic Esters and 2,2-Disubstituted Dihydronaphthalenes

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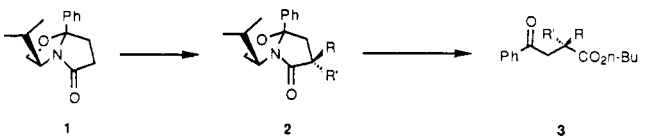
The bicyclic lactams derived from (*S*)-valinol and 3-benzoylpropionic acid or levulinic acid are useful chiral precursors to the title compounds. Metalation of bicyclic lactams **1** or **4** and alkylation followed by acidic hydrolysis leads to racemic 2-alkyl carboxylic acids. However, sequential metalation-alkylation to 2,2-dialkyl bicyclic lactams **2** and **5** furnishes these systems with good diastereoselectivity. Treatment of **5** with triflic acid causes a facile rearrangement to the oxazolines **7** and hydrolysis leads to the carboxylic esters. Under certain conditions, hydrolysis leads directly to naphthalenes **11**.

Several years ago we reported that the bicyclic lactams **1** were very useful precursors to chiral, nonracemic 2,2-dialkyl carboxylic esters **3** prepared in very high enantiomeric excess.[1] These initial studies on this versatile template required that the two α-protons in **1** were sequentially removed and alkylated with two different electrophiles to furnish **2** followed by hydrolysis in acidic 1-butanol. The method was found to be quite suitable for a number of 2,2-dialkyl carboxylic esters. Subsequent to that preliminary report we have shown in a number of other instances that the bicyclic lactams are indeed highly useful for the efficient asymmetric synthesis of geminally substituted chiral cyclopentenones,[2] cyclohexenones,[3] and a number of naturally occurring substances.[4]



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