New Pyridino-18-crown-6 Ligands Containing Two Methyl, Two *tert*-Butyl, or Two Allyl Substituents on Chiral Positions Next to the Pyridine Ring

Yoichi Habata,† Jerald S. Bradshaw,* J. Jolene Young, Steven L. Castle, Peter Huszthy,‡ Tongjin Pyo,§ Milton L. Lee, and Reed M. Izatt

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602

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Chiral 2,16-diallyl-, 2,16-dimethyl-, and 2,16-di-*tert*-butylpyridino-18-crown-6 ligands have been prepared by treating the appropriate chiral α,α′-disubstituted pyridinedimethanol with tetraethylene glycol ditosylate in the presence of base. In these reactions, chiral 2:2 dimers (dipyridino-36-crown-12 derivatives) were also obtained. The log *K* values for the interaction of these chiral ligands with the enantiomers of (α-phenylethyl)ammonium perchlorate (PhEt) and (α-(1-naphthyl)ethyl)-ammonium perchlorate (NapEt) were measured using an ^{1}H NMR titration method in a $CDCl_3$/CD_3OD (1/1) solvent mixture. The log *K* values indicate that these chiral pyridino-18-crown-6 ligands have high complexing abilities and some enantiomeric recognition for the chiral organic ammonium perchlorates. The ^{1}H NMR titration experiments also show that the phenyl ring of the guest PhEt is approximately parallel to the pyridine ring in the chiral diallyl- and dimethyl-substituted ligand complexes with chiral PhEt and the phenyl ring is perpendicular to the pyridine ring in the chiral di-*tert*-butyl-substituted ligand complex with PhEt. These results were supported by MM2 calculations.

Introduction

Since the pioneering work of Cram and his co-workers on chiral crown ethers based on the "naphthalene wall",[1] enantiomeric recognition of optically active amino acids and organic ammonium ions by chiral crowns and their analogues has received much attention.[2] In order to develop qualitative and quantitative relationships between molecular structural features of chiral crown ether hosts and chiral organic ammonium ion guests, we have prepared a series of chiral crown ethers, aza-crown ethers, and crown ether diesters having pyridine, triazole, and pyrimidine subcyclic units.[3−14] Thermodynamic and kinetic parameters for chiral host−chiral guest interactions have been determined using ^{1}H NMR spectroscopy, titration calorimetry, and Fourier transform ion cyclotron resonance mass spectrometry techniques.[4,7,8,10−12,14,15−18] To expand our research on the chiral host−chiral guest interactions by the pyridino-crown ethers, we have prepared new pyridino-18-crown-6 ligands containing substituents on chiral positions next to the pyridine ring (in positions 2 and 16). Computer and CPK modeling shows that introduction of allyl or alkyl groups at the 2- and 16-positions in pyridino-18-crown-6 should give an effective chiral barrier in the crown ring and should increase the rigidity around the chiral barrier.[19] The increased rigidity may prevent a "splaying motion"[20] in the molecule, which would greatly reduce enantiomeric recognition. Therefore, it is expected that the 2,16-disubstituted pyridino-18-crown-6 derivatives would exhibit increased enantiomeric recognition for chiral organic ammonium ions. Li et al. reported that chiral 2,16-dimethyl-substituted triazolo-18-crown-6 having cholesteryl or *n*-dodecyl groups as lipophilic side arms exhibited high chiral recognition for the enantiomers of several organic ammonium ions.[21] Those results also support our supposition.

† Permanent address: Department of Chemistry, Faculty of Science, Toho University, Funabashi, Chiba 274, Japan.
‡ Permanent address: Institute of Organic Chemistry, Technical University, Budapest, Hungary.
§ Permanent address: Department of Chemistry, Kaugwen University, Chugweon, Korea.
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(1) Kyba, E. B.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2692.
(2) Wang, T.-M.; Bradshaw, J. S.; Izatt, R. M. *J. Heterocycl. Chem.* **1994**, *31*, 1097 and references cited therein.
(3) Jones, B. A.; Bradshaw, J. S.; Brown, P. R.; Christensen, J. J.; Izatt, R. M. *J. Org. Chem.* **1983**, *48*, 2635.
(4) Davidson, R. B.; Bradshaw, J. S.; Jones, B. A.; Dalley, N. K.; Christensen, J. J.; Izatt, R. M. *J. Org. Chem.* **1984**, *49*, 353.
(5) McDaniel, C. W.; Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M.; Savage, P. B.; Tarbet, B. J.; Bruening, R. L. *J. Heterocycl. Chem.* **1989**, *26*, 413.
(6) Bradshaw, J. S.; McDaniel, C. W.; Krakowiak, K. E.; Izatt, R. M. *J. Heterocycl. Chem.* **1990**, *27*, 1477.
(7) Bradshaw, J. S.; Huszthy, P.; McDaniel, C. W.; Zhu, C. Y.; Dalley, N. K.; Izatt, R. M.; Lifson, S. *J. Org. Chem.* **1990**, *55*, 3129.
(8) Huszthy, P.; Bradshaw, J. S.; Zhu, C. Y.; Izatt, R. M.; Lifson, S. *J. Org. Chem.* **1991**, *56*, 3330.
(9) Bradshaw, J. S.; Krakowiak, K. E.; Huszthy, P.; Izatt, R. M. *J. Heterocycl. Chem.* **1991**, *28*, 773.
(10) Huszthy, P.; Oue, M.; Bradshaw, J. S.; Zhu, C. Y.; Wang, T.-M.; Dalley, N. K.; Curtis, J. C.; Izatt, R. M. *J. Org. Chem.* **1992**, *57*, 5383.
(11) Chu, I.; Dearden, D. V.; Bradshaw, J. S.; Huszthy, P.; Izatt, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 4318.
(12) Izatt, R. M.; Zhu, C. Y.; Huszthy, P.; Bradshaw, J. S. In *Enantiomeric Recognition in Macrocycle−Primary Ammonium Cation Systems in Crown Ethers, Toward Future Applications*; Cooper, S. R., Ed.; VCH: New York, 1992; p 207.
(13) Redd, J. T.; Bradshaw, J. S.; Huszthy, P.; Izatt, R. M. *J. Heterocycl. Chem.* **1994**, *31*, 1047.
(14) Bradshaw, J. S.; Huszthy, P.; Redd, J. T.; Zhang, X. X.; Wang, T.-M.; Hathaway, J. K.; Young, J.; Izatt, R. M. *Pure Appl. Chem.* **1995**, *67*, 691.
(15) Bradshaw, J. S.; Huszthy, P.; McDaniel, C. W.; Oue, M.; Zhu, C. Y.; Izatt, R. M.; Lifson, S. *J. Coord. Chem. Sect. B* **1992**, *27*, 157.
(16) Izatt, R. M.; Wang, T.-M.; Huszthy, P.; Hathaway, J. K.; Zhang, X. X.; Curtis, J. C.; Bradshaw, J. S.; Zhu, C. Y. *J. Inclusion Phenom.* **1994**, *17*, 157.
(17) Zhu, C. Y.; Bradshaw, J. S.; Oscarson, J. L.; Izatt, R. M. *J. Inclusion Phenom.* **1992**, *12*, 275.
(18) Wang, T.-M.; Bradshaw, J. S.; Curtis, J. C.; Huszthy, P.; Izatt, R. M. *J. Inclusion Phenom.* **1993**, *13*, 113.
(19) CAChe ver. 3.7 was used for computer modeling. MM2 parameters were used for optimization.
(20) Goldberg, I. *J. Am. Chem. Soc.* **1977**, *99*, 6049.
(21) Li, Y.; Echegoyen, L.; Martinez-Diaz, M. V.; Mendoza, J.; Torres, T. *J. Org. Chem.* **1991**, *56*, 4196.

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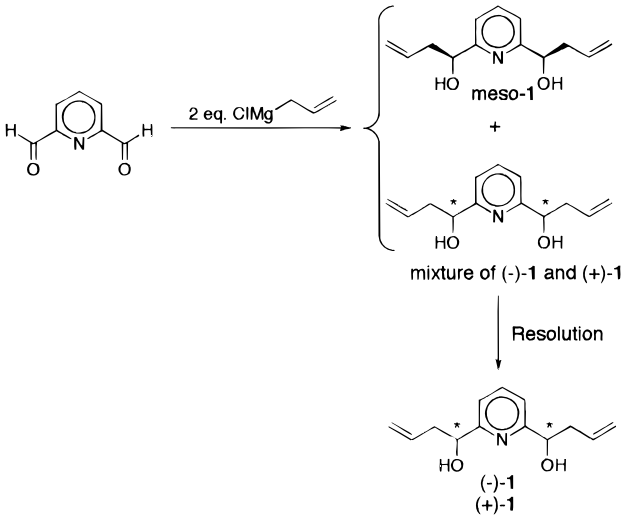
Scheme 1. Preparation of *meso*-, (−)-, and (+)-α,α′-Diallyl-2,6-pyridinedimethanol



This paper describes the synthesis of meso and chiral 2,16-diallyl-, 2,16-dimethyl-, and 2,16-di-*tert*-butyl-substituted pyridino-18-crown-6 ligands. We also isolated meso and chiral 2:2 dimers (the dipyridino-36-crown-12 ligands) for the first time. The log *K* values for the interaction of these chiral ligands with chiral (α-phenylethyl)ammonium perchlorate (PhEt) and (α-(1-naphthyl)-ethyl)ammonium perchlorate (NapEt) determined by an ^{1}H NMR titration method are also reported.

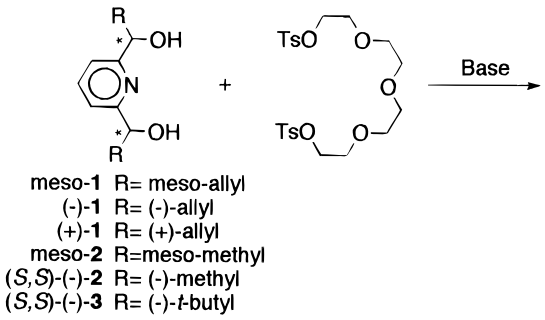
Results and Discussion

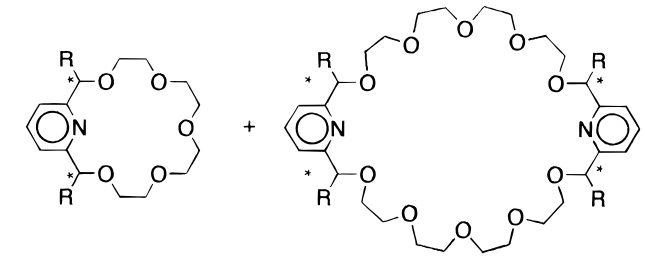
Synthesis and Structure. α,α′-Diallyl-2,6-pyridinedimethanol (*meso*-, (−)-, and (+)-**1**) were prepared by the Grignard reaction of 2,6-pyridinedicarboxaldehyde and allylmagnesium chloride (Scheme 1). *meso*-**1** and (±)-**1** were separated on a silica gel column using C_6H_{14}/EtOAc: 4/1 as eluent to give 24% yield of (±)-**1** and 20% of *meso*-**1**. Resolution of (−)-**1** and (+)-**1** from the racemic mixture was carried out using a Regis−Pirkle HPLC column to give optically pure (−)-**1** (92.8% ee, 46% yield) and (+)-**1** (99% ee, 17% yield). The structures of *meso*-**1**, (−)-**1**, and (+)-**1** were confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS. Chiral α,α′-dimethyl- and di-*tert*-butyl-2,6-pyridinedimethanols (*meso*-**2**, (*S*,*S*)-(−)-**2**,[22] and (*S*,*S*)-(−)-**3**[23,24]) were prepared and resolved according to the procedures described in the literature.

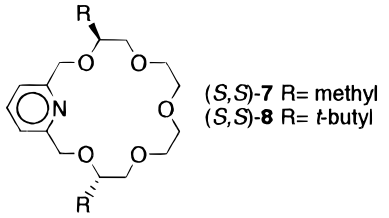
Using these chiral α,α′-disubstituted pyridinedimethanols, new chiral macrocycles were prepared as shown in Scheme 2. The reactions of diallyl- and dimethyl-substituted pyridinedimethanols with tetraethylene glycol ditosylate in the presence of base gave not only pyridino-18-crown-6 derivatives (**4a** and **5a**) but also the 2:2 dimers (dipyridino-36-crown-12 derivatives **4b** and **5b**). However, when di-*tert*-butylpyridinedimethanol (*S*,*S*)-(−)-**3** was used, only monomer (*S*,*S*)-(−)-**6a** was isolated.

The structures of *meso*-, (−)-, and (+)-**4a** and -**5a** and *meso*-**4b** (the 2:2 dimer) were confirmed by ^{1}H NMR, ^{13}C

Scheme 2. Preparation of *meso* and Chiral Pyridino-18-crown-6 and Dipyridino-36-crown-12 Ligands







NMR, and HRMS analyses (the elemental composition of (−)- and (+)-**4b** and (*S*,*S*)-(−)-**6a** were confirmed by elemental analyses instead of HRMS). In all cases, *meso*, (−), and (+) derivatives exhibited the same ^{1}H and ^{13}C NMR spectra in $CDCl_3$. When the ^{1}H NMR spectra of *meso*-**4a** and the chiral forms of **4a** were measured in benzene-d_6, there were no chemical shift changes in the allyl protons, although a small change for the methylene protons of the crown ring was observed. On the other hand, the spectra of the 1:1 and 2:2 macrocycles exhibited significant differences. The differences in the ^{1}H NMR spectra of *meso*-, (−)-, and (+)-**4a** and their dimers (*meso*-, (−)-, and (+)-**4b**) (^{1}H NMR spectra of *meso*-**4a** and *meso*-**4b** are shown in Figure 1 as a typical example) are as follows: (i) a doublet at $\delta = 7.34$ for the protons at the 3-position in the pyridine ring of all **4a** ligands appears at a higher field ($\delta = 7.18$) in the spectrum of all **4b** ligands, (ii) a multiplet for the $-CH_2CH_2O-$ units in all **4b** ligands is less complex than that of all **4a** ligands, and (iii) although the signal for the allyl protons at $\delta =$ 2.57 for all **4a** ligands splits into a triplet, that of all **4b** ligands splits into an octet. Figure 2 shows the calculated splitting patterns of the allyl moieties of all **4a** and **4b** ligands, which are presumed to have AB(M)XYZ(H_A and H_B protons are isochronous) and AB(M)XYZ patterns, respectively. If the above assumptions are correct, when the H_M proton is decoupled, signals for the allyl protons

(22) Bailey, D.; O'Hagen, D.; Dyer, U.; Lamont, R. B. *Tetrahedron: Asymmetry* **1993**, *4*, 1255. The authors reported that (−)-α,α′-dimethylpyridinedimethanol was the (*S*,*S*)-form.

(23) Hawkins, J. M.; Dewan, J. C.; Sharpless, K. B. *Inorg. Chem.* **1986**, *25*, 1501. The authors reported that (+)-α,α′-di-*tert*-butylpyridinedimethanol was the (*R*,*R*)-form.

(24) Hawkins, J. M. Ph.D. Thesis, MIT, 1986, p 89.

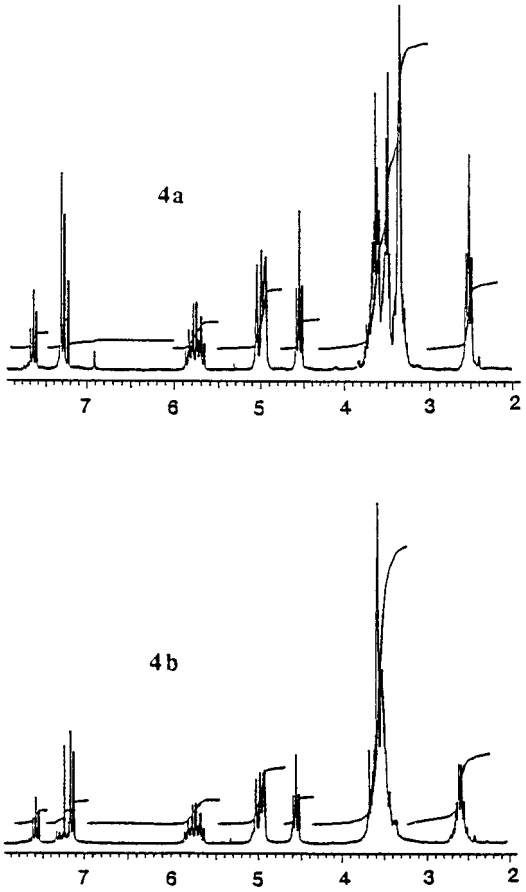


Figure 1. ^{1}H NMR spectra of *meso*-**4a** and *meso*-**4b** in $CDCl_3$.

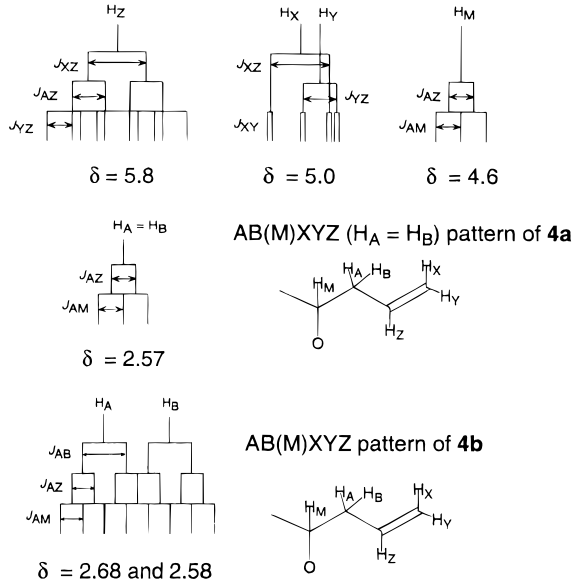


Figure 2. Splitting patterns of allyl moiety protons of **4a** and **4b**.

at $\delta = 2.57$ (H_A and H_B) in all **4a** and **4b** ligands should be changed to a doublet and a heptet, respectively. Figure 3 shows the spectral change in the allyl proton splitting before and after irradiation to the H_M protons. As we expected, when irradiated, a doublet in all **4a** spectra and a heptet in all **4b** spectra were observed. Computer modeling indicates that the macroring is twisted, and therefore, the allyl substituents in all **4b** ligands are in a more crowded space than those in all **4a**

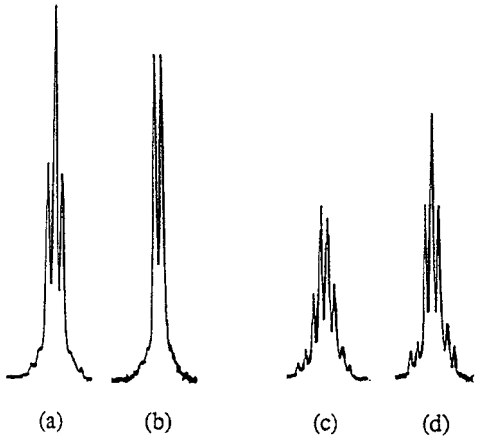


Figure 3. H_A and H_B proton signals of **4a** and **4b**. **4a**: before (a) and after (b) irradiation to H_M protons. **4b**: before (c) and after (d) irradiation to H_M protons.

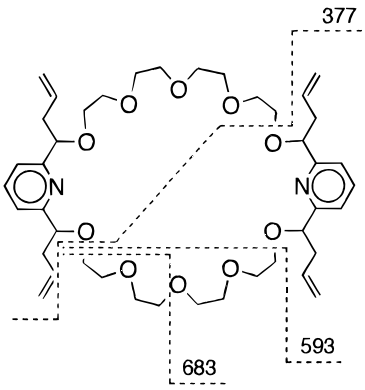


Figure 4. Postulated cleavage patterns of **4b**.

ligands. Thus, the more complicated splitting pattern in 2:2 dimer **4b** is due to a slow rotation rate of the allyl moiety in the NMR time scale.

The ^{13}C NMR spectra reflect the carbon skeletons of molecules. In the ^{13}C NMR spectra of all **4a** ligands and all **4b** ligands, the chemical shift of the corresponding carbons in each structure appears at almost the same positions (see the Experimental Section). The exceptions are as follows: (i) signals for carbons at position 3 on the pyridine ring in all **4b** ligands (120.8 ppm) appear at a lower field by 1 ppm than those of all **4a** ligands (119.8 ppm), and (ii) although there are four signals for the $-CH_2CH_2O-$ carbons at 71.2, 70.8, 70.7, and 69.1 ppm for all **4a** ligands, only three signals at 70.8 (intense signal), 70.7, and 68.6 ppm appear in the spectra of all **4b** ligands. The more flexible ethylenoxy units of the dimer (**4b**) should provide a more simplified ^{13}C NMR spectral pattern.

In the EI mass spectra for the *meso* and chiral forms of **4b**, fragment ion peaks at 754 (observed only for *meso*-**4b**), 377 and 336 are assigned for $[M]^+$, $[M/2]^+$, and $[M/2 - CH_2CH{=}CH_2]^+$, respectively. Although a parent ion peak arising from M^+ is usually observed in a FAB mass spectrum, only fragment ion peaks could be observed for (−)- and (+)-**4b**. The fragment ion peaks at 706 (683 + Na^+), 684 (683 + 1), 616 (593 + Na^+), 594 (593 + 1), 400 (377 + Na^+), and 378 (377 + 1) could be reasonably assigned to the species shown in Figure 4. In all FAB mass spectra of *meso*-, (−)- and (+)-**4b**, the fragment ion at 594 (593 + 1 in Figure 4) is the base peak. This observation suggests that the fragment ion at 594 is

Table 1. Log *K* Values for the Complexation of Chiral Macrocyclic Compounds with (*R*)- and (*S*)-Forms of (α-Phenylethyl)ammonium Perchlorate (PhEt) and (α-(1-Naphthyl)ethyl)ammonium Perchlorate (NapEt) in $CDCl_3/CD_3OD$ (1/1) Solution

compd	sub-stituent	log *K* values			
		(*S*)-PhEt	(*R*)-PhEt	(*S*)-NapEt	(*R*)-NapEt
meso-**4a**	allyl	3.67[a]			
(−)-**4a**	allyl	3.62[a]	3.84[a]	3.84	3.92
meso-**5a**	methyl	3.74			
(*S*,*S*)-(−)-**5a**	methyl	3.69	3.45		
(*S*,*S*)-(−)-**6a**	*t*-butyl	2.25	1.91	*b*	*b*
meso-**4b**	allyl	*c*			
(−)-**4b**	allyl	*c*			
(+)-**4b**	allyl	*c*			
(*S*,*S*)-**7**	methyl	3.29[d]	3.62[d]	3.42[d]	3.96[d]
(*S*,*S*)-**8**	*t*-butyl			0.62[d]	1.33[d]

[a] At 26 °C. All others at 25 °C. [b] Values could not be determined because of overlap between the signals corresponding to the pyridine and naphthalene rings. [c] Did not show complexation. [d] Reference 2.

formed directly from **4b** or from the fragment ion at 684 (683 + 1 in Figure 4). These EI and FAB mass spectral data strongly suggest that *meso* and chiral forms of **4b** are the 2:2 dimer. The mass spectral experiments also suggest that the 2:2 dimers (−)- and (+)-**4b** are readily cleaved under EI and FAB mass spectral conditions. Although two diastereomeric forms (*syn* and *anti*) in *meso*-**4b** are possible, they could not be separated. The structures of the other 2:2 dimers were confirmed in the same manner.

Enantiomeric Recognition of Chiral Ammonium Perchlorates. Enantiomeric recognition of PhEt and NapEt with the chiral 2,16-disubstituted pyridino-18-crown-6 ligands and dimers in a $CDCl_3/CD_3OD$ (1/1) solvent mixture has been evaluated using the ^{1}H NMR titration method[2,16] (Table 1). Unfortunately, these chiral ligands did not exhibit good chiral recognition toward the enantiomers of PhEt. (−)-**4a**, having two allyl groups, favored the (*R*)-form of PhEt and NapEt over the (*S*)-forms by 0.22 and 0.08 log *K* units, respectively, while (*S*,*S*)-(−)-**5a** and (*S*,*S*)-(−)-**6a**, having two methyl and two *tert*-butyl groups as chiral barriers, formed more stable complexes with (*S*)-PhEt than (*R*)-PhEt (Δ log ***K*** of (*S*,*S*)-(−)-**5a** and (*S*,*S*)-(−)-**6a** complexes were 0.24 and 0.34, respectively). In previous systems where the alkyl groups were attached to chiral carbon positions three atoms removed from the pyridine ring, the (*S*,*S*)-ligands formed stronger complexes with the (*R*)-forms of the ammonium salts (Table 1, (*S*,*S*)-**7** and (*S*,*S*)-**8**).[16] It is important to note that the spatial arrangement of the similar groups in (*S*,*S*)-(−)-**5a** and (*S*,*S*)-(−)-**6a** are the same as in the (*R*,*R*)-forms of **7** and **8**. The ^{1}H NMR spectra for the (*S*,*S*)-(−)-**6a** complexes with (*R*)- and (*S*)-NapEt were very complicated because of the overlap of signals from the pyridine and naphthalene rings. This prevented a determination of log *K* values.

Figure 5 shows the results of the computer modeling of (*S*,*S*)-**4a**−(*R*)-PhEt, (*S*,*S*)-**5a**−(*S*)-PhEt and (*S*,*S*)-**6a**−(*S*)-PhEt systems.[19] The models show that the crown rings are twisted with the ethylenoxy groups forced in a direction opposite from the substituent. This forms a chiral wall or barrier on the side of the macroring opposite to the substituent. When the substituents are effective chiral barriers such as methyl and *tert*-butyl groups, the hosts recognize the guests by the chiral substituent barriers (Figure 6). On the other hand, when the substituent is an ineffective barrier such as the allyl group, which can rotate away from the cavity, the ethylenoxy wall in the crown ring acts as the chiral barrier. Thus, (*S*,*S*)-**4a** may exhibit recognition toward the opposite guest enantiomers than do ligands (*S*,*S*)-(−)-**5a** and (*S*,*S*)-(−)-**6a**. The dimers did not interact with the ammonium salts because the large and flexible rings do not allow the formation of tripod-type hydrogen bonds with the ammonium salts.

The ^{1}H NMR titration experiments for log *K* measurements also offered some information on the structures of the complexes. When (*S*)- and (*R*)-PhEt were added to the crown ethers, the signals for the protons in position 4 of the pyridine ring shifted to a higher field for (−)-**4a** and (*S*,*S*)-(−)-**5a** and a lower field for (*S*,*S*)-(−)-**6a**. These differences in the chemical shifts can be explained by the ring current effects of the phenyl ring of PhEt. When the pyridine ring of the crown ether is placed in the shielding zone of the phenyl ring of the guest (the pyridine ring is parallel to the phenyl ring), the signals for the pyridine ring protons shift to a higher field. On the other hand, when the pyridine ring is placed in the deshielding zone of the phenyl ring (the pyridine ring is perpendicular to the phenyl ring), the signals for the pyridine ring protons shift to a lower field. Therefore, the ^{1}H NMR spectral data suggest that the aromatic rings of the host and guest may be overlapped parallel in (−)-**4a**−(*R*)-PhEt and (*S*,*S*)-(−)-**5a**−(*S*)-PhEt systems and perpendicular in (*S*,*S*)-(−)-**6a**−(*S*)-PhEt system. We suspect that the large *tert*-butyl substituent is not allowing the two aromatic rings to become parallel in the (*S*,*S*)-**6a**−(*S*)-PhEt complex. Figure 5 shows the molecular model with the phenyl ring of PhEt parallel to the pyridine ring in the (*S*,*S*)-**4a**−(*R*)-PhEt and (*S*,*S*)-**5a**−(*S*)-PhEt systems and the phenyl ring perpendicular to the pyridine ring in the (*S*,*S*)-**6a**−(*S*)-PhEt system. MM2 calculations support the presumed structures of (−)-**4a**−(*R*)-PhEt, (*S*,*S*)-(−)-**5a**−(*S*)-PhEt and (*S*,*S*)-(−)-**6a**−(*S*)-PhEt complexes.

Experimental Section

Materials and Apparatus. *meso*-, (−)-, and (+)-2,6-di-*tert*-butyl- and 2,6-dimethyl-substituted pyridinedimethanol were prepared as reported.[22,24] The ^{1}H and ^{13}C NMR spectra were obtained at 200 and 50 MHz, respectively. The ^{1}H NMR spectra for calculation of log *K* values were obtained at 500 MHz.

Synthesis and Resolution of α,α′-Diallyl-2,6-pyridinedimethanol (*meso*-1, (−)-1, and (+)-1). A solution of 2,6-pyridinedicarboxaldehyde (2.83 g, 20.9 mmol) in dry THF (75 mL) was added dropwise over a period of 30 min to a 2.0 M solution of allylmagnesium chloride in THF (22 mL, 44.0 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 2 h. The reaction mixture was then quenched by the addition of 50 mL of water. The organic and aqueous layers were separated, and the aqueous layer was extracted with ether (75 mL × 3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was eluted from a silica gel column with 4/1 hexane/ethyl acetate to give 1.11 g (24%) of the (±)-diol (mixture of (−)-**1** and (+)-**1**) and 0.90 g (20%) of the *meso*-diol (*meso*-**1**). *meso*-**1** was an oily white solid: ^{1}H NMR ($CDCl_3$) δ 7.70 (t, J = 7.7 Hz, 1H), 7.23 (d, J = 7.7 Hz, 2H), 3.61 (broad s, 2H), the allyl moiety showed an AB(M)XYZ pattern; δH_A 2.66 (quin, 2H), δH_B 2.49 (quin, 2H), δ_M 4.83 (dd, 2H), δH_Z 5.82 (m, 2H), δH_X 5.12 (q, 2H), δH_Y 5.11 (q, 2H), J_{AB}(gem) = 13.7 Hz, J_{AB} = J_{AM} = 6.0 Hz, J_{XZ}(*trans*) = 15.5 Hz, J_{YZ}(*cis*) = 11.9 Hz; ^{13}C NMR ($CDCl_3$) δ 162.6, 137.6, 134.2, 119.3, 118.5, 72.6, 43.0; HRMS calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1241.

A mixture of the (±)-diol (1.10 g, 5.02 mmol), 4-(dimethylamino)pyridine (0.219 g, 5.02 mmol), triethylamine (200 mL),

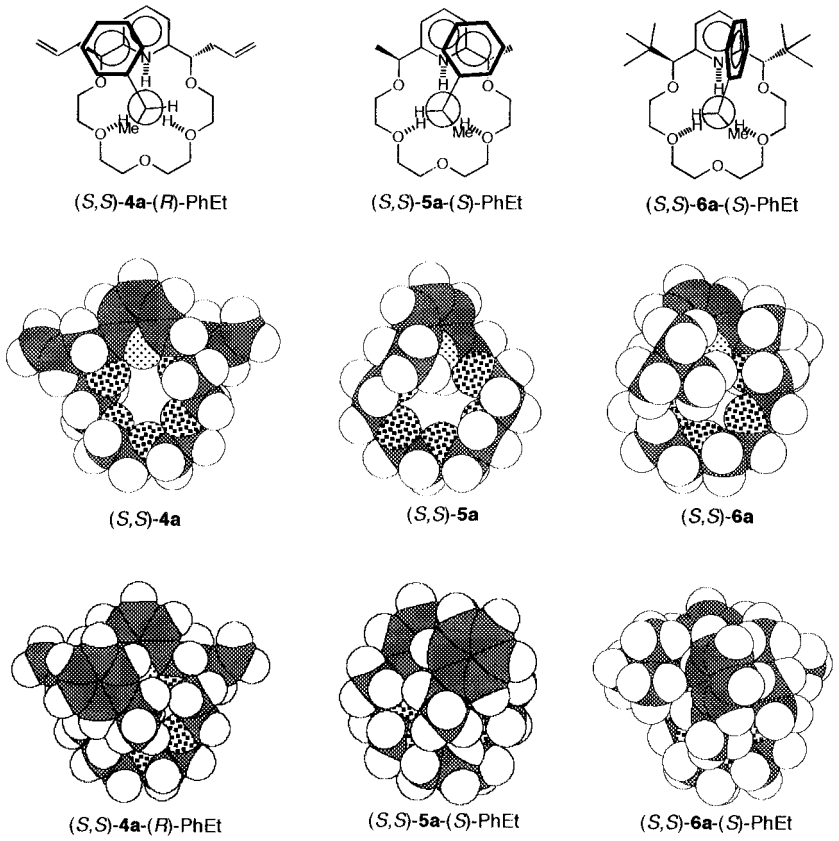


Figure 5. One of the lowest energy structures of (*S*,*S*)-**4a**, (*S*,*S*)-**5a**, (*S*,*S*)-**6a**, (*S*,*S*)-**4a**−(*R*)-PhEt, (*S*,*S*)-**5a**−(*S*)-PhEt, and (*S*,*S*)-**6a**−(*S*)-PhEt.

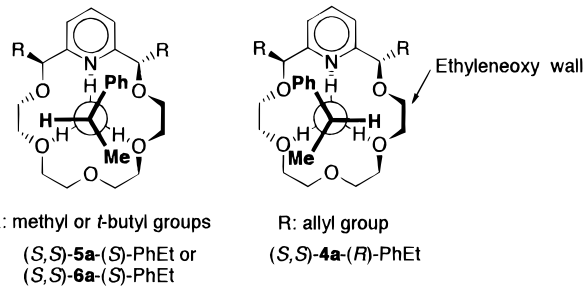


Figure 6. Schematic drawing of the chiral pyridino-18-crown-6 ligand−enantiomeric PhEt complexes.

and acetic anhydride (100 mL) was stirred at rt under Ar for 1.5 h. The mixture was then concentrated under reduced pressure and eluted from a silica gel column with hexane/ethylacetate: 4/1 to give 1.35 g of the racemic diacetate. The diacetate was dissolved in 13.5 mL of 25% $CHCl_3$ and 1% *i*-C_3H_7OH and injected onto a Regis−Pirkle-type 1-A semi-preparative chiral HPLC (25 cm × 10 mm i.d.) column. Repeated injections of 20 μL each and elution with 1% *i*-C_3H_7-OH in hexane (flow rate 3 mL/min) gave 0.280 g of the first eluted enantiomer (retention time = 20.6 min) and 0.490 g of the second eluted enantiomer (retention time = 21.5 min). The enantiomers were stirred in K_2CO_3-saturated CH_3OH (140 mL for the first enantiomer and 225 mL for the second) for 1 h, and the CH_3OH was removed under reduced pressure. The residue was dissolved in H_2O (40 mL for the first enantiomer and 50 mL for the second) and extracted with ether (75 mL × 4 for the first enantiomer and 100 mL × 4 for the second enantiomer). The dried ($MgSO_4$) ether extracts were concentrated under reduced pressure to give 0.175 g of diol (+)-**1** (99% ee by HPLC) derived from the first eluted enantiomer and 0.354 g of diol (−)-**1** (92.8% ee by HPLC) derived from the second eluted enantiomer. This represents a 16% yield of the (+)-**1**, a 32% yield of the (−)-**1**, and a 48% yield for the entire resolution process. (+)-**1** solidified on standing in the refrigerator: mp 49−51 °C; $[\alpha]^{25}_D = +102°$ (c = 0.85, C_2H_5-OH); HRMS calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1240. (−)-**1** solidified on standing in the refrigerator: mp 48−50 °C; $[\alpha]^{25}_D = -81.1°$ (c = 0.90, C_2H_5OH); HRMS calcd for $C_{13}H_{17}$-NO_2 219.1259, found 219.1239. The ^1H and ^{13}C NMR spectral data for (−)-**1** and (+)-**1** were the same as that of the *meso*-isomer reported above.

Preparation of *meso*-2,16-Diallyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (4a) and *meso*-2,16,22,36-Tetraallyl-3,6,9,12,15,23,26,29,32,35-decaoxa-41,42-diazatricyclo[36.3.1.1^{17,21}]dotetraconta-1(41),17,19,21,37,39-hexaene (4b) (Scheme 2). *meso*-Diallyl-substituted pyridino-crown ethers were prepared using two procedures as follows: (i) K (0.12 g, 3.05 mmol) was added to 25 mL of *t*-BuOH under Ar. The solution was heated to 70 °C for 40 min and then cooled to rt. *meso*-α,α′-Diallylpyridinedimethanol (*meso*-**1**) (0.20 g, 0.91 mmol) in *t*-BuOH (20 mL) was added dropwise, and the mixture was stirred for 2 h at 70 °C. After the solution was cooled to rt, tetraethylene glycol ditosylate (0.528 g, 1.05 mmol) in 20 mL of dry THF was added dropwise over the period of 20 min. The mixture was stirred for 6 days at rt and then at 100 °C for 1 h. After the reaction mixture was cooled, 25 mL of CH_2Cl_2 and 20 mL of distilled H_2O were added. The CH_2Cl_2 layer was separated, and the H_2O layer was extracted with CH_2Cl_2 (20 mL × 2). The CH_2Cl_2 solutions were combined and evaporated under reduced pressure. The residual oil was chromatographed on alumina using 100/1 toluene/ethanol as eluent. The second fraction was further purified by gel permeation (Sephadex LH-20 with C_2H_5OH as eluent) to give 0.022 g of *meso*-**4a** (6%) and 0.020 g of the dimer *meso*-**4b** (6%) as oils.

(ii) *meso*-**1** (0.070 g, 0.32 mmol) in *t*-BuOH (10 mL) was added dropwise to 10 mL of *t*-BuOH containing K (0.039 g, 1.0 mmol) under Ar. After the solution was stirred for 16 h at rt, tetraethylene glycol ditosylate (0.194 g, 0.39 mmol) in 7 mL of dry THF was added dropwise over a period of 15 min. The mixture was stirred for 6 days at rt. Although the spot

for the ditosylate disappeared in alumina TLC, the spot for the diol did not. K (0.033 g, 0.85 mmol) and ditosylate (0.150 g, 0.30 mmol) were further added, and stirring was continued for 28 h at rt. The spot for the diol disappeared, and therefore, the reaction mixture was evaporated under reduced pressure at rt. The residual solid was dissolved in $C_6H_5CH_3$ and separated on an alumina column ($C_6H_5CH_3/C_2H_5OH$: 300/1). The second fraction was further purified by gel permeation to give 0.039 g of *meso*-**4a** (33%) as an oil. Under these reaction conditions, the dimer *meso*-**4b** could not be obtained. *meso*-**4a** exhibited the following properties: ^{1}H NMR ($CDCl_3$) δ 7.70 (t, J = 7.7 Hz, 1H), 7.34 (d, J = 7.7 Hz, 2H), 4.60 (dd, J = 7.1 Hz, 2H, H_M), 3.83−3.30 (m, 16H). The allyl moiety of *meso*-**4a** showed an AB(M)XYZ pattern (H_A and H_B protons are isochronous): δH_A 2.57 (dd, 4H), δH_Z 5.81 (m, 2H), δH_X 5.04 (q, 2H), δH_Y 5.01 (q, 2H), $J_{AM} = J_{AZ}$ = 7.1 Hz, J_{XZ}(*trans*) = 16.9 Hz, J_{YZ}(*cis*) = 9.9 Hz, J_{XY}(*gem*) = 2.1 Hz; ^{13}C NMR ($CDCl_3$) δ 161.2, 137.0, 134.7, 119.8, 117.3, 83.6, 71.2, 70.8, 70.7, 69.1, 41.0; HRMS calcd for $C_{21}H_{31}NO_5$ 378.2289 found 378.2280. *meso*-**4b** (from i) exhibited the following properties: ^{1}H NMR ($CDCl_3$) δ 7.62 (t, J = 7.7 Hz, 2H), 7.18 (d, J = 7.7 Hz, 4H), 4.59 (dd, J = 6.7 Hz, 4H, H_M), 3.68−3.38 (m, 32H). The allyl moiety of *meso*-**4b** showed an AB(M)XYZ pattern: δH_A 2.68 (quin, 4H), δH_B 2.58 (quin, 4H), δH_Z 5.77 (m, 4H), δH_X 5.01 (q, 4H), δH_Y 4.98 (q, 4H), J_{AB}(*gem*) = 14.1 Hz, $J_{AZ} = J_{AM}$ = 6.7 Hz, J_{XZ}(*trans*) = 17.1 Hz, J_{YZ}(*cis*) = 10.2 Hz, J_{XY}(*gem*) = 1.5 Hz; ^{13}C NMR ($CDCl_3$) δ 161.1, 136.4, 134.8, 120.8, 117.1, 82.8, 70.8, 70.7, 68.6, 40.7; EI-MS 160 (100), 336 (22), 377 (M^+/2, 4), 754 (M^+, 0.5); FAB-MS 378 (5), 400 (377 + Na^+, 16), 486 (49), 508 (485 + Na^+, 26), 594 (100), 616 (593 + Na^+, 81), 684 (18), 706 (683 + Na^+, 5); HRMS calcd for $C_{42}H_{62}N_2O_{10}$ 777.4298, found 777.4302.

Preparation of (−)-2,16-Diallyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (4a) and (−)-2,16,22,36-Tetraallyl-3,6,9,12,15,23,26,29,32,35-decaoxa-41,42-diazatricyclo[36.3.1.1^{17,21}]dotetraconta-1(41),17,19,21,37,39-hexaene (4b) (Scheme 2). The reaction of (−)-diol **1** with tetraethylene glycol ditosylate was carried out using method ii described above using 0.098 g of the (−)-diol **1** to give 0.025 g of (−)-**4a** (15%) and 0.041 g of (−)-**4b** (24%) as oils. (−)-**4a** gave the following properties: $[\alpha]^{25}_D = -2.4°$ (c = 1.0, $CHCl_3$); HRMS calcd for $C_{21}H_{31}NO_5$ 378.2289, found 378.2283. (−)-**4b** gave the following properties: $[\alpha]^{25}_D = -48°$ (c = 0.55, $CHCl_3$); EI-MS 160 (100), 336 (80), 377 (M^+/2, 20); FAB-MS 378 (4), 400 (377 + Na^+, 7), 486 (54), 508 (485 + Na^+, 7), 594 (100), 616 (593 + Na^+, 24), 684 (25), 706 (683 + Na^+, 3). Anal. Calcd for $C_{42}H_{62}N_2O_{10}$: C, 66.82; H, 8.28. Found: C, 66.68; H, 8.23. The ^{1}H and ^{13}C NMR spectra of (−)-**4a** and (−)-**4b** were the same as those of the *meso*-compounds.

Preparation of (+)-2,16-Diallyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (4a) and (+)-2,16,22,36-Tetraallyl-3,6,9,12,15,23,26,29,32,35-decaoxa-41,42-diazatricyclo[36.3.1.1^{17,21}]dotetraconta-1(41),17,19,21,37,39-hexaene (4b) (Scheme 2). The reaction of (+)-diol **1** with tetraethylene glycol ditosylate was carried out using method ii described above using 0.078 g of (+)-diol **1** to give 0.020 g of (+)-**4a** (15%) and 0.011 g of (+)-**4b** (8%) as oils. (+)-**4a** exhibited the following properties: $[\alpha]^{25}_D = +2.2°$ (c = 1.0, $CHCl_3$); HRMS calcd for $C_{21}H_{31}NO_5$ 378.2289, found 378.2283. (+)-**4b** exhibited the following properties: $[\alpha]^{25}_D = +44°$ (c = 0.66, $CHCl_3$); EI-MS: 160 (100), 336 (59), 377 (M^+/2, 11); FAB-MS: 378 (5), 400 (377 + Na^+, 16), 486 (41), 508 (485 + Na^+, 27), 594 (100), 616 (593 + Na^+, 52), 684 (10), 706 (683 + Na^+, 4). Anal. Calcd for $C_{42}H_{62}N_2O_{10}$: C, 66.82; H, 8.28. Found: C, 66.77; H, 8.20. The ^{1}H and ^{13}C NMR spectra of (+)-**4a** and (+)-**4b** were the same as those of the *meso*-compounds.

Preparation of (*S*,*S*)-(−)-2,16-Di-*tert*-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (6a) (Scheme 2). A suspension of NaH (80% in mineral oil, 0.14 g, 4.67 mmol) in dioxane (25 mL, dried over molecular sieves) was stirred at rt under Ar. To this suspension was added a solution of the (*S*,*S*)-(−)-**3** (0.190 g, 0.756 mmol) in dioxane (60 mL). The mixture was heated to 70 °C and stirred for 3 h, after which time a solution of tetraethylene glycol ditosylate (0.45 g, 0.895 mmol) in dioxane (30 mL) was added dropwise over a period of 30 min. The reaction mixture was stirred at 70 °C for 6 days, after which time the reaction was quenched by the addition of 40 mL of distilled H_2O. The mixture was concentrated under reduced pressure, and the residue was dissolved in an ether/water mixture. The organic layer was removed, and the aqueous layer was extracted with ether (50 mL × 5). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give 0.26 g of an oil. This oil was eluted from an alumina column with 100/1 $C_6H_5CH_3/C_2H_5OH$ to give 0.14 g of crude product. This material was eluted from a silica gel column with $C_6H_5CH_3$ and then with 100/1 $C_6H_5CH_3/C_2H_5OH$ to give 0.0501 g of (*S*,*S*)-(−)-**6a** (16%) as an oily white solid: $[\alpha]^{25}_D = -28.8°$ (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.58 (t, J = 7.7 Hz, 1H), 7.12 (d, J = 7.7 Hz, 2H), 4.21 (s, 2H), 3.75−3.40 (m, 16H), 0.92 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 164.2, 134.6, 122.0, 77.7, 71.0, 70.7, 70.6, 69.4, 29.7, 26.5; EI-MS 353 ($M^+ - C_4H_9$, 100), 409 (M^+, 6); FAB-MS 432 ($M + Na^+$, 100). Anal. Calcd for $C_{23}H_{39}NO_5$: C, 67.45; H, 9.60. Found: C, 67.29; H, 9.36.

Preparation of *meso*-2,16-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (5a) (Scheme 2). *meso*-α,α′-Dimethylpyridinedimethanol (*meso*-**2**) was treated with tetraethylene glycol ditosylate in a similar manner as above for the synthesis of (*S*,*S*)-(−)-**6a**. After the reaction mixture was treated in the usual manner, the residual oil was separated and purified on an alumina column ($C_6H_5CH_3/C_2H_5OH$ 300/1) and then subjected to gel permeation (Sephadex-LH20 with C_2H_5OH as the eluent). Macrocycle *meso*-**5a** was obtained in 4.8% yield as an oil: ^{1}H NMR δ ($CDCl_3$) 7.73 (t, J = 7.7 Hz, 1H), 7.36 (d, J = 7.7 Hz, 2H), 4.69 (q, J = 6.6 Hz, 2H), 3.73−3.38 (m, 16H), 1.50 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 162.2, 137.2, 119.0, 79.5, 70.8, 70.6, 70.4, 68.1, 21.9; HRMS calcd for $C_{17}H_{27}NO_5$ 326.1967, found 326.1977.

Preparation of (*S*,*S*)-(−)-2,16-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (5a) and (*S*,*S*,*S*,*S*)-2,16,22,36-Tetramethyl-3,6,9,12,15,23,26,29,32,35-decaoxa-41,42-diazatricyclo[36.3.1.1^{17,21}]-dotetraconta-1(41),17,19,21,37,39-hexaene (5b) (Scheme 2). (*S*,*S*)-(−)-α,α′-Dimethylpyridinedimethanol was reacted, and the products were purified as above for the preparation of (*S*,*S*)-(−)-**6a** to give (*S*,*S*)-(−)-**5a** and (*S*,*S*,*S*,*S*)-**5b** as oils in 1.5% and 0.4% yields, respectively. (*S*,*S*)-(−)-**5a** exhibited the following properties: $[\alpha]^{25}_D = -2.2°$ (c = 1.0, $CHCl_3$); HRMS calcd for $C_{17}H_{27}NO_5$ 326.1967, found 326.1975. The ^{1}H and ^{13}C NMR spectra of (*S*,*S*)-(−)-**5a** were the same as those of *meso*-**5a**. (*S*,*S*,*S*,*S*)-**5b** exhibited the following properties: ^{1}H NMR δ ($CDCl_3$) 7.64 (t, J = 7.7 Hz, 2H), 7.20 (d, J = 7.7 Hz, 4H), 4.69 (q, J = 6.5 Hz, 4H), 3.74−3.48 (m, 32H), 1.51 (d, J = 6.5 Hz, 12H); ^{13}C NMR ($CDCl_3$) δ 162.2, 136.7, 119.8, 78.8, 70.6, 70.5, 67.7, 22.0; FAB-MS 326 (M^+/2 + 1 100), 348 (325 + Na^+, 55), 364 (M^+/2 + CH_2 + Na^+ 11), 378 (M^+/2 + CH_2CH_2 + Na^+, 3), 386 (M^+/2 + OCH_2CH_2O, 1.2), 503 ($M^+ - O(CH_2CH_2O)_3$, <0.5), 547 ($M^+ - O(CH_2CH_2O)_2$, <0.5), 675 ($M^+ + Na^+$, 0.8). The optical rotation of (*S*,*S*,*S*,*S*)-**5b** could not be measured because there was not enough compound.

Determination of log *K* Values. The log K values were determined by the ^{1}H NMR titration method as reported.[2,16]

Acknowledgment. This work was supported by the Office of Naval Research.

Supporting Information Available: ^{1}H NMR spectra for *meso*-, (+)-, and (−)-**1**, *meso*-, (+)-, and (−)-**4a** and -**4b**, and (*S*,*S*)-(−)-**6a** and ^{13}C NMR spectra for *meso*-**5a**, (*S*,*S*)-(−)-**5a**, and (*S*,*S*,*S*,*S*)-**5b** (13 pages). This material is contained in 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.

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