Recognition by New Symmetrically Substituted Chiral Diphenyl- and Di-*tert*-butylpyridino-18-crown-6 and Asymmetrically Substituted Chiral Dimethylpyridino-18-crown-6 Ligands of the Enantiomers of Various Organic Ammonium Perchlorates

Peter Huszthy,† Jerald S. Bradshaw,* Cheng Y. Zhu, and Reed M. Izatt

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

Shneior Lifson

Department of Chemical Physics, Weizmann Institute of Science, Rehovot 76100, Israel

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Three new chiral pyridino-18-crown-6 ligands have been prepared. These ligands contain either two phenyl, two *tert*-butyl, or two methyl substituents on chiral macroring carbon atoms. The chiral di-*tert*-butyl-substituted diester crown analogue was also prepared. The starting chiral di-*tert*-butyl-substituted tetraethylene glycol needed to prepare the two di-*tert*-butyl-substituted crowns was obtained from chiral *tert*-butyl-1,2-ethanediol, which was resolved from its bis(hydrogen phthalate) brucine salt. A high degree of chiral recognition in CD_2Cl_2 of the enantiomers of [α-(1-naphthyl)ethyl]ammonium perchlorate (NapEt) was shown by the diphenyl- and di-*tert*-butyl-substituted crowns as measured by differences in the free energy of activation (ΔG_c^*) values determined by temperature-dependent ^1H NMR spectroscopy. The diphenyl- and di-*tert*-butyl-substituted crowns also exhibited high chiral recognition for the enantiomers of NapEt and other chiral organic ammonium salts in methanol and methanol–chloroform mixtures as shown by a large difference in the log K values determined by a direct ^1H NMR technique.

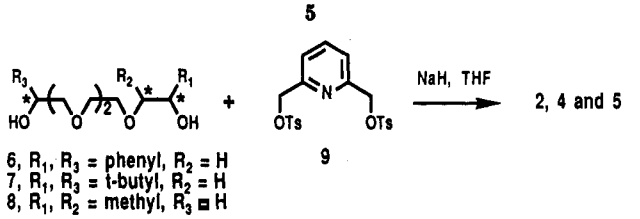
Introduction

The design, synthesis, and use of macrocycles capable of selective recognition of other molecules is of great interest in a variety of fields.[1-3] Remarkable recognition behavior between hosts and guests occurs in many chemical interactions including those involving enzymes, antibodies, antigens, and stereoselective catalysts. There has been much interest in designing certain information into macrocyclic hosts, which enables these hosts to recognize specific guests. A brief review of recent work by us and others[4] includes the enantiomeric recognition of organic amines and ammonium salts by chiral macrocyclic ligands. Our interest has been focused on identifying and quantitating the parameters that are involved in the recognition process in these chiral systems.

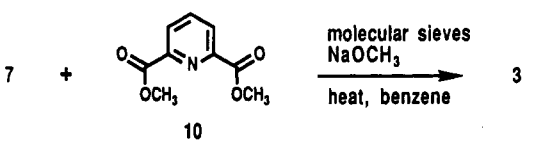
Our interest in enantiomeric recognition has focused on the interaction of chiral crowns containing pyridine units with organic ammonium salts.[4-7] These interactions were chosen because they show appreciable enantiomeric recognition in certain cases. Thus, they present the possibility of a systematic study of how the extent of enantiomeric recognition varies with crown substituent, guest type, and solvent. The results of such a study could lead to the ability to design specific information into hosts, which would allow them to have superior recognition for one guest enantiomer over another.

The pyridino-crowns form strong complexes with certain organic ammonium salts.[5,8] The pyridino-crowns with two methyl or two phenyl groups substituted on chiral ring carbon atoms have been shown to have recognition in chloroform and methanol/chloroform mixtures for the enantiomers of [α-(1-naphthyl)ethyl]ammonium perchlorate (NapEt) and the methyl ester of phenylalaninium perchlorate as determined both by a temperature-dependent ^1H NMR technique in CD_2Cl_2 and titration calorimetry in CH_3OH.[5,6] The degree of chiral recognition measured as the difference in free energy of activation values ($\Delta\Delta G_c^*$) determined by a ^1H NMR technique for the association of chiral dimethyl-, diphenyl- and di-*sec*-butyl-substituted crowns with NapEt perchlorate was compared with similar data obtained from calculations using empirical energy functions.[4] The calculated and observed $\Delta\Delta G_c^*$ values were similar for the systems studied

Scheme I. Preparation of Chiral Pyridino-crowns 2, 4, and 5



Scheme II. Preparation of Chiral Pyridinodicarbonyl-crown 3



(1) Potvin, P. G.; Lehn, J.-M. Design of Cation and Anion Receptors, Catalysts and Carriers. In *Synthesis of Macrocycles: The Design of Selective Complexing Agents*; Izatt, R. M, Christensen, J. J., Eds.; Wiley-Interscience: New York, 1987; pp 167-239.

(2) Stoddart, J. F. Synthetic Chiral Receptor Molecules from Natural Products. In *Progress in Macrocyclic Chemistry*; Izatt, R. M., Christensen, J. J., Eds.; Wiley-Interscience: New York, 1981; Vol. 2, pp 173-250.

(3) Stoddart, J. F. Chiral Crown Ethers. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley-Interscience: New York, 1988; Vol. 17, pp 207-288.

(4) 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.

(5) Davidson, R. B.; Bradshaw, J. S.; Jones, B. A.; Dalley, N. K.; Christensen, J. J.; Izatt, R. M.; Morin, F. G.; Grant, D. M. *J. Org. Chem.*, **1984**, *49*, 353.

(6) Bradshaw, J. S.; Thompson, P. K.; Izatt, R. M.; Morin, F. G.; Grant, D. M. *J. Heterocyclic Chem.* **1984**, *21*, 897.

(7) Bradshaw, J. S.; Colter, M. L.; Nakatsuji, Y.; Spencer, N. O.; Brown, M. F.; Izatt, R. M.; Arena, G.; Tse, P.-K.; Wilson, B. E.; Lamb, J. D.; Dalley, N. K.; Morin, F. G.; Grant, D. M. *J. Org. Chem.* **1985**, *50*, 4865.

(8) Bradshaw, J. S.; Maas, G. E.; Lamb, J. D.; Izatt, R. M.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 467.

† Permanent address: Institute of Organic Chemistry, Technical University, Budapest, Hungary.

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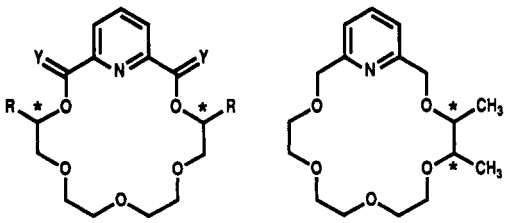


1, Y = O, R = phenyl
2, Y = H_2, R = phenyl
3, Y = O, R = t-butyl
4, Y = H_2, R = t-butyl

5

Figure 1. Chiral diphenyl-, di-*tert*-butyl-, and dimethylpyridino-18-crown-6 ligands.

except for compound 1 (see Figure 1) and for the chiral di-*sec*-butylpyridino-18-crown-6. Calculations of $\Delta\Delta G_c^*$ values for the association of various chiral dialkyl-substituted pyridino-crowns with chiral NapEt predicted that enantiomeric recognition by di-*tert*-butyl-substituted crowns **3** and **4** should be much higher than that for these crowns substituted with less hindering substituents.[4]

This paper describes the synthesis of chiral di-*tert*-butylpyridino-crowns **3** and **4**. Since chiral crown **1** exhibited excellent chiral recognition for the enantiomers of NapEt,[4] chiral diphenyl-substituted macrocycle **2** was also prepared. Koga and co-workers reported that 2(*S*),3(*S*)-dimethyl-18-crown-6 exhibited high asymmetric induction as a catalyst for an asymmetric Michael addition reaction.[9] Accordingly, chiral dimethylpyridino-18-crown-6 (**5**) was prepared. The enantiomeric recognition of NapEt by these new chiral macrocycles as determined by temperature-dependent ^{1}H NMR measurements and by a direct ^{1}H NMR determination of log *K* values[10] is also reported.

Results and Discussion

New macrocycles **2–5** were prepared as shown in Schemes I and II. The yields for the Williamson ether type cyclizations shown in Scheme I were in the 30–70% range, while the cyclic transesterification reaction[6,11] gave a 15% yield of **3**. 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 dialkyl-substituted tetraethylene glycols needed for the preparation of the chiral macrocycles were obtained as shown in Scheme III. Compound **6** was prepared in a higher yield by a different method (see Scheme IIIA) than that reported previously.[6] (*S*)-(+)-**14a** needed for **7** (Scheme IIIB) was prepared by the resolution of racemic **14**. Compound **14** was reacted with phthalic anhydride followed by salt formation with (−)-brucine. The (*S*)-(+)-**14** bis(hydrogenphthalate) (−)-brucine salt was recrystallized several times until there was no change in its optical rotation and melting point. This salt was treated first with cold aqueous sodium hydroxide to remove (−)-brucine followed by prolonged treatment with an excess of aqueous sodium hydroxide (saponification) to give (*S*)-(+)-**14a**. Partially resolved (*R*)-(−)-**14b** was isolated in a like manner from the mother liquors. The enantiomeric excess of **14a** was 97+% as determined by supercritical fluid chromatography (SFC) on a new chiral 1,2-diamidocyclohexane–oligosiloxane copolymer.[12] This process to resolve *tert*-butyl-1,2-ethanediol is more time consuming than the reported yeast-catalyzed reductive formation of optically active *tert*-butyl-1,2-ethanediol from 3,3,3-trimethyl-1-hydroxyacetone.[13] The yeast reduction process, in our hands, also produced (*R*)-(−)-**14b** as confirmed by SFC.[12] However, other products that could not be separated from **14b** also formed in our yeast reduction reaction. Tosylation followed by reaction with dihydropyran gave (*S*)-(+)-2-*tert*-butyl-2-(tetrahydropyranoxy)-ethyl tosylate (**16a**), which was needed to prepare **7** (see Scheme IIIB).

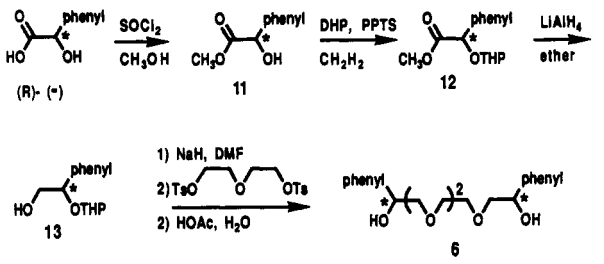
The preparation of chiral dimethyl-substituted **8** (Scheme IIIC) was started by the monotritylation of triethylene glycol to give **17**. Compound **17** was tosylated to obtain the α-trityl-ω-tosylate derivative of triethylene glycol **18**. Compound **18** was reacted with monobenzylated 2(*R*),3(*R*)-butanediol **19**[4] to form the α-trityl-ω-benzyl-protected tetraethylene glycol **20**. Deprotection of **20** gave the chiral dimethyltetraethylene glycol **8**.

Elemental analyses for the chiral tetraethylene glycols **6–8** were not obtained. However, good analyses were obtained for the macrocycles prepared from these glycols.

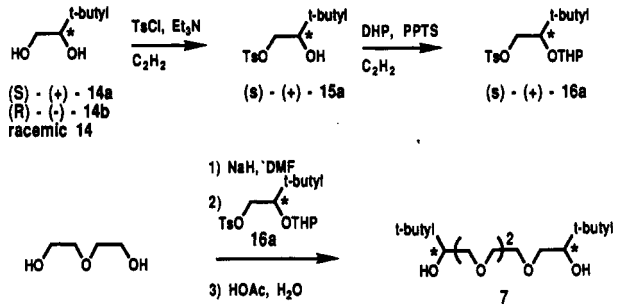
Complexation of the enantiomeric forms of NapEt by ligands **2–5** has been studied by the temperature-de-

Scheme III. Preparation of Chiral Tetraethylene Glycol Starting Materials

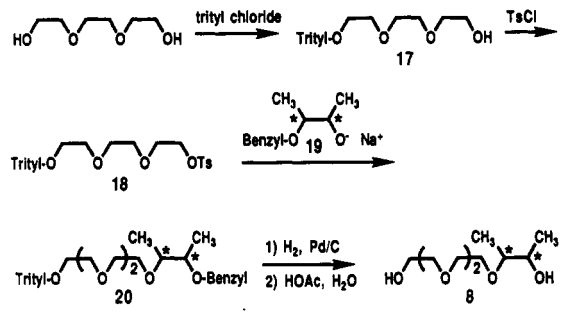
A. Diphenyl glycol 6



B. Di-t-butyl Glycol 7



C. Dimethyl glycol



(9) Aoki, S.; Sasaki, S.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 7229.
(10) Zhu, C. Y.; Bradshaw, J. S.; Oscarson, J. L.; Izatt, R. M. *J. Incl. Phenom.*, in press.
(11) Bradshaw, J. S.; Jones, B. A.; Nielson, R. A.; Spencer, N. O.; Thompson, P. K. *J. Heterocyclic Chem.* **1983**, *20*, 957.
(12) Rossiter, B. E.; Petersson, P., Johnson, D. F.; Eguchi, M.; Bradshaw, J. S.; Markides, K. E.; Lee, M. L. *Tetrahedron Lett.*, in press.
(13) Guette, J. P.; Spasky, N. *Bull. Soc. Chim. Fr.* **1972**, *11*, 4217.

Table I. Free Energies of Activation (ΔG_c^*) Values (kcal/mol) in CD_2Cl_2[a] for the Interaction of Chiral Macrocyclic Ligands with the Enantiomers of [α-(1-Naphthyl)ethyl]ammonium Perchlorate (NapEt)

ligand	value[a]	(R)-NapEt	(S)-NapEt
(S,S)-1[b]	T_c	11	-35
	(ΔG_c^*)	13.3	12.0
(R,R)-2	T_c	6	-34
	(ΔG_c^*)	14.2	11.4
(S,S)-3	T_c	-54	<-90
	(ΔG_c^*)	10.3	<8.5
(S,S)-4	T_c	-38	-95
	(Δ_{Gc}^*)	11.3	8.8
(S,S)-5	T_c	28	30
	(ΔG_c^*)	14.9	14.6

[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 the complexes of 2 and 5 and the CH_3 groups of *tert*-butyl for 3 and 4. T_c = coalescence temperature (°C). ΔG_c^* values were ±0.2. [b] Data taken from ref 4.

pendent ^1H NMR technique[4-7,14,15] and by determining the log K values for the association of the chiral ligand and the salt enantiomer by a direct ^1H NMR technique.[10] The peaks in the ^1H NMR spectra of the complexes attributable to the hydrogens on the carbon next to the pyridine ring for **2** and **5** or the *tert*-butyl hydrogens for **3** and **4** separated into two peaks of equal intensities at low temperature. The kinetic parameters for the dissociation of these complexes were then calculated as reported.[4,14,15] Table I shows the coalescence temperature (T_c) and ΔG_c^* values for the dissociation of the complexes of **1** (for comparison purposes)[4] and **2-5** with the *R* and *S* forms of NapEt.

The data in Table I show that these chiral ligands exhibit enantiomeric recognition for the chiral forms of NapEt. Chiral ligands **2**, **3**, and **4** formed kinetically stronger complexes with one enantiomer of NapEt over the other form by 2.8, more than 1.8, and 2.5 kcal/mol, respectively. These observed $\Delta\Delta G_c^*$ values are greater than any other measured values for similar systems.[4] Thus, as predicted,[4] the large *tert*-butyl and phenyl substituents provide sufficient steric hindrance that one of the enantiomeric guests is recognized over the other by a large factor. It is important to note that the observed $\Delta\Delta G_c^*$ value for the complexes of **4** and the enantiomers of NapEt (2.5 kcal/mol) is very close to the calculated value of 2.2 kcal/mol as determined from empirical energy functions.[4]

The computer-generated stereoviews of the (*S,S*)-**1** and (*S,S*)-**2** complexes with (*R*)- and (*S*)-NapEt are shown in Figures 2 and 3, respectively. These stereoviews represent the calculated structures of the most stable conformations of the respective complexes. As was observed previously in similar calculated stereoviews of the (*S,S*)-**4** complexes with (*R*)- and (*S*)-NapEt,[4] in the (*S,S*)-**1**- and (*S,S*)-**2**-*R* salts, the naphthalene of the guest is contacting the host pyridine and is away from the large host phenyl substituents on the same side of the complexes (stereoviews A in Figures 2 and 3). On the other hand, in the (*S,S*)-**1**- and (*S,S*)-**2**-*S* salts, the naphthalene of the guest is extremely close to the large host phenyl substituents, which creates distortions in the complexes. Thus, these stereoviews show the steric parameters that cause the recognition by *S,S* hosts for the *R* salts as shown by the $\Delta\Delta G_c^*$ values in Table I. The computer-calculated $\Delta\Delta G_c^*$ value of 1.4 kcal/mol for the complexes of **2** with *R* and *S* forms of NapEt is not significantly different from the observed value of 2.8 shown in Table I.

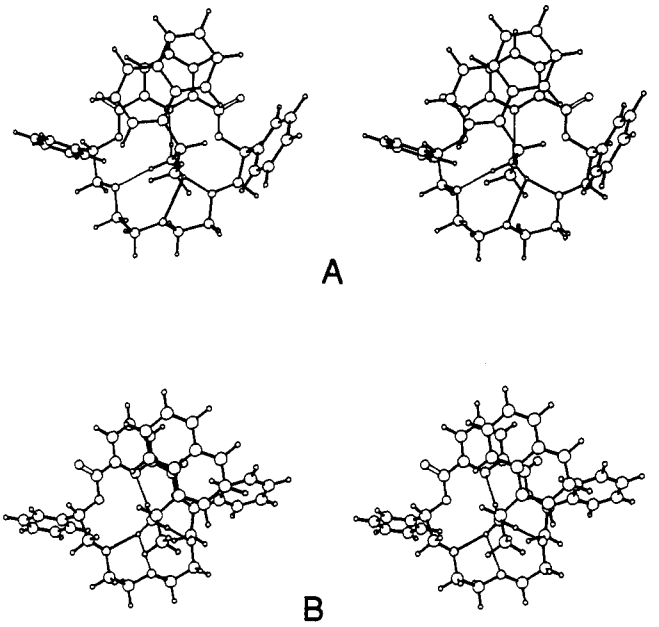


Figure 2. Computer-generated stereoviews obtained from force field calculations of the complexes of (*S,S*)-**1** with (*R*)-[α-(1-naphthyl)ethyl]ammonium perchlorate (stereoviews A) and with the *S* perchlorate (stereoviews B).

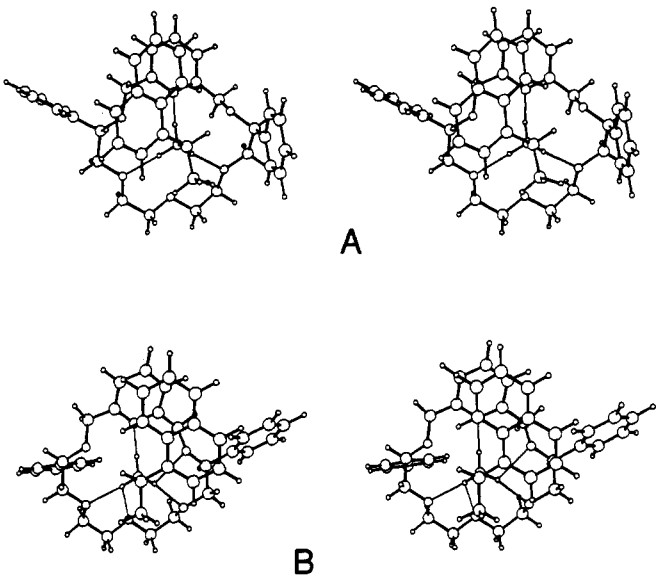


Figure 3. Computer-generated stereoviews obtained from force field calculations of the complexes of (*S,S*)-**2** with (*R*)-[α-(1-naphthyl)ethyl]ammonium perchlorate (stereoviews A) and with the *S* perchlorate (stereoviews B).

Complexation of the enantiomeric forms of NapEt by chiral ligands **1-5** was also studied by determining the log K values in $CD_3OD/CDCl_3$ mixtures or in CD_3OD using a direct ^1H NMR technique.[10] Table II lists the log K values for these interactions. It is evident from the data in Table II that the phenyl- and *tert*-butyl-substituted macrocycles (**1** and **4**) provide excellent chiral recognition for the enantiomers of various chiral organic ammonium salts. The difference in log K values for the interactions of (*S,S*)-**1** and (*S,S*)-**4** for the *R* and *S* forms of NapEt (>0.85 and 0.71) are the highest yet observed for these types of interactions.[4,5] Thus, the superior chiral recognition by the chiral diphenyl- and di-*tert*-butyl crowns predicted by empirical energy functions[4] has been shown by both the temperature-dependent ^1H NMR technique

(14) Sutherland, I. O. *Annu. Rep. NMR Spectrosc.* **1971**, *4*, 71.
(15) Baxter, S. L.; Bradshaw, J. S. *J. Heterocyclic Chem.* **1981**, *18*, 233.

Table II. log K Values[a] for Interactions of Chiral Ligands with R and S Forms of Various Organic Perchlorate Salts at 25 °C

	log K values (solvent)[c]				
salt[b]	(S,S)-1	(R,R)-2	(S,S)-3	(S,S)-4	(R,R)-5
(R)-A	2.15 (70 M/30 C)	2.92 (100 M)	(10 M/90 C)[d]	1.33 (10 M/90 C)	3.00 (100 M)
(S)-A	<1.30 (70 M/30 C)	3.10 (100 M)	(10 M/90 C)[d]	0.62 (10 M/90 C)	2.94 (100 M)
(R)-B	2.62[e] (50 M/50 C)	2.91 (100 M)			
(S)-B	2.06[e] (50 M/50 C)	3.05 (100 M)			
(R)-C	2.24[e] (50 M/50 C)				
(S)-C	2.95[e] (50 M/50 C)				
(R)-D	2.18 (50 M/50 C)				
(S)-D	1.76 (50 M/50 C)				
(R)-E	1.60 (50 M/50 C)				
(S)-E	1.28 (50 M/50 C)				

[a] log K values were determined by a direct ^{1}H NMR procedure as described fully in ref 10. [b] The salts are the following: A, the hydrogen perchlorate salt of [α-(1-naphthyl)ethyl]amine; B, the hydrogen perchlorate salt of (α-phenylethyl)amine; C, the hydrogen perchlorate salt of 2-amino-2-phenylethanol; D, the hydrogen perchlorate salt of 2-amino-3-phenyl-1-propanol; E, the hydrogen perchlorate salt of methyl phenylalaninate. [c] Solvents are given as volume percentages of CD_3OD (M) and $CDCl_3$ (C). [d] log K value was low so that accurate measurements could not be made. [e] Observation done at 20 °C.

(Table I) and the direct ^{1}H NMR-derived log K values (Table II).

It is interesting that (R,R)-2 and (S,S)-3 exhibit little or no recognition for the R and S forms of NapEt in CD_3OD or $CD_3OD/CDCl_3$ mixture (Table II). In the case of interactions of (R)- and (S)-NapEt (and also of (R)- and (S)-(α-phenylethyl)ammonium perchlorate) with (R,R)-2, the reactions were studied in CD_3OD since the interactions in less polar solvents would be so large that it would be difficult to get accurate data by the direct ^{1}H NMR method. The interaction of (S,S)-3 with NapEt is so weak that differences in log K values could not be measured.

Considerable chiral recognition was observed in the interaction of (S,S)-1 with the enantiomers of other chiral organic ammonium salts (Table II). Thus, the Δ log K values for the interaction of (S,S)-1 with the R and S forms of hydrogen perchlorate salts of (α-phenylethyl)amine, 2-amino-2-phenylethanol, 2-amino-3-phenyl-1-propanol, and methyl phenylalaninate were between 0.32 and 0.71. In every case, the (S,S)-1–R salt complex was the most stable except for the (S,S)-1–hydrogen perchlorate salts of 2-amino-2-phenylethanol complexes where the (S,S)-1–S salt formed the most stable complex.

There are many interesting stability relationships that cannot be explained. The fact that the (S,S)-1–(S)-hydrogen perchlorate salt of 2-amino-2-phenylethanol is the most stable complex, as mentioned in the previous paragraph, cannot be explained. Also, the fact that the (R,R)-2–(R)-NapEt forms the kinetically most stable product (Table I) cannot be explained. This (R,R)-2–NapEt complex system is the first time that any chiral (S,S)- or (R,R)-pyridino-18-crown-6 has formed a kinetically more stable complex with NapEt of the same configuration. These interesting paradoxes show that more studies need to be done in order to understand these interesting interactions.

Experimental Section

The ^{1}H NMR spectra were obtained at 200-MHz in $CDCl_3$ unless otherwise indicated. Melting points are uncorrected. The hydrogen perchlorate salts of the chiral amines were prepared as reported.[5] 2,6-Pyridinedimethyl ditosylate (9) was prepared as reported.[4] 2,6-Pyridinedicarbonyl dichloride, (±)-3,3-dimethyl-1,2-butanediol (14) (distilled twice under reduced pressure before use), brucine dihydrate, phthalic anhydride, (R)-(−)-mandelic acid, dihydropyran, tosyl chloride, and diethylene and triethylene glycol were purchased from Aldrich Chemical Co. Diethylene glycol ditosylate was prepared in a 90% yield from diethylene glycol and tosyl chloride in tetrahydrofuran (THF) with powdered KOH as the base as reported for analogous compounds.[4] Dimethyl 2,6-pyridinedicarboxylate was prepared from 2,6-pyridinedicarbonyl dichloride and methanol and recrystallized from water.

Preparation of (R)-(−)-Methyl Mandelate (11; Scheme IIIA). To a stirred solution of 30 g (0.20 mol) of (R)-(−)-mandelic acid in 360 mL of dry and pure methanol was slowly added 16.0 mL (26.1 g, 0.22 mol) of thionyl chloride at −10 °C. The mixture was stirred at −10 °C for 10 min and then at room temperature for 4 h. After evaporation of the solvent, the residue was dissolved in a mixture of 150 g of ice, 150 mL of water, and 500 mL of ether. The mixture was shaken and separated. The organic phase was washed with saturated brine, dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure to give 32.12 g (98%) of 11: mp 55–56 °C; $[\alpha]^{20}_D$ −144.9° (c = 1.133, methanol) lit.[16] for the S-(+) isomer, mp 55–56 °C; $[\alpha]^{27}_D$ +144°;[16] IR(KBr) 3442, 1744 cm^{-1}; ^{1}H NMR δ 3.58 (1 H, broad s, disappeared in D_2O), 3.73 (3 H, s), 5.16 (1 H, s), 7.27–7.47 (5 H, m).

(R)-(−)-Methyl 2-Phenyl-2-(tetrahydropyranyloxy)acetate (12). To a mixture of 10.9 g (0.066 mol) of 11 and 25.2 mL (23.2 g, 0.28 mol) of dihydropyran in 260 mL of pure and dry CH_2Cl_2 at 0 °C and under Ar was added 1.9 g of pyridinium p-toluenesulfonate (PPTS) catalyst, and the reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 2 h. The mixture was washed three times with 100-mL portions of ice-cold water, dried ($MgSO_4$), and filtered, and the solvent was evaporated under reduced pressure. The residue (16.42 g, 100%), a colorless oil, was used in the next step without further purification: $[\alpha]^{20}_D$ −70.2° (c = 1.978, benzene); IR (neat) 1752 cm^{-1}; ^{1}H NMR δ 1.36–2.0 (6 H, m), 3.40–3.53 and 3.8–4.03 (2 H, m), 3.7 (3 H, s), 4.55 and 4.85 (1 H, t), 5.22 and 5.32 (1 H, s), 7.25–7.52 (5 H, m).

(R)-(−)-2-Phenyl-2-(tetrahydropyranyloxy)ethanol (13). A solution of 16.4 g (0.066 mol) of 12 in 320 mL of dry ether was added dropwise to a stirred suspension of 7.4 g (0.019 mol) of $LiAlH_4$ and 190 mL of ether at 0 °C under Ar over 45 min. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h, and then it was refluxed for 3 h. The mixture was cooled in an ice bath, and 7.5 mL of saturated NH_4Cl solution, 7.5 mL of 10% aqueous NaOH, and 7.5 mL of water were added consecutively. After the addition, the mixture was stirred at 0 °C for 10 min and at room temperature overnight. The white precipitate was filtered and washed with ether. The filtrate and washing were combined, dried ($MgSO_4$), and filtered, and the solvent was evaporated under reduced pressure. The residue (14.45 g, 99%) was purified by column chromatography on silica gel with THF/toluene (1/10) as eluent to give 13.6 g (93%) of 13 as two diasteromers $[\alpha]^{20}_D$ −72.4° (c = 2.52, benzene); IR (neat) 3432 cm^{-1}; ^{1}H NMR δ 1.37–1.98 (6 H, m), 2.4 and 3.12 (1 H, t and q, disappeared in D_2O), 3.2–3.33, 3.46–3.79, and 3.92–4.08 (4 H, m), 4.51 and 4.91 (1 H, t), 4.7 and 4.8 (1 H, t and q), 7.18–7.42 (5 H, m).

(R,R)-(−)-1,11-Diphenyl-3,6,9-trioxaundecane-1,11-diol (6). To a stirred suspension of 2.8 g (93 mmol) of NaH (80% dispersion

(16) Kameyama, M.; Kamigata, N.; Kobayashi, M. J. Org. Chem. 1987, 52, 3312.

in mineral oil) in 15 mL of dry dimethylformamide (DMF) was added dropwise under Ar at 0 °C 14.6 g (65.7 mmol) of 13 dissolved in 50 mL of DMF. After being stirred at 0 °C for 10 min and at room temperature for 10 min, the reaction mixture was stirred at 80 °C for 1.5 h. The mixture was cooled to 0 °C, and 12.43 g (30 mmol) of diethylene glycol ditosylate dissolved in 40 mL of DMF was added dropwise. After being stirred at 0 °C for 10 min and at room temperature for 10 min, the reaction mixture was stirred at 80 °C for 40 h. After the solvent was evaporated under reduced pressure, the residue was dissolved in a mixture of 50 mL of ice water and 400 mL of CH_2Cl_2. The phases were mixed well and separated. The aqueous phase (pH > 12) was shaken twice with 100-mL portions of methylene chloride. The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure. A solution of 13.5 mL of distilled water and 122 mL of glacial acetic acid was added to the crude product, and the resulting mixture was stirred at 90 °C for 3 h. After the solvent was evaporated under reduced pressure, the residue was dissolved in toluene and evaporated. The residue was purified on a silica gel column using ethyl acetate/hexane (1/1 and 2/1) as eluents to give 7.8 g (75%) of **6** as an oil: $[\alpha]^{20}_D$ −90.07° (*c* = 1.511, $CHCl_3$) (lit.[6] for the crude product of the *S,S*-(+) isomer, $[\alpha]^{25}_D$ +74.1°); IR (neat) 3431 cm^{-1}; ^1H NMR δ 3.37–3.8 (12 H, m), 4.57 (2 H, broad s, disappeared in D_2O), 4.87–4.99 (2 H, m), 7.18–7.43 (10 H, m); MS *m/e* 347 ($M^+ + 1$).

Resolution of (±)-3,3-Dimethyl-1,2-butanediol (14). To a mixture of 56.7 g (0.48 mol) of **14** and 142.2 g (0.96 mol) of phthalic anhydride was added 77.6 mL (75.94 g, 0.96 mol) of pyridine. The resulting mixture was stirred under Ar at 95 °C for 4 h then allowed to stand at room temperature overnight. The viscous material was dissolved in 1600 mL of ether. Ice (200 g) and then a mixture of 100 mL of concentrated HCl and 200 g of ice were added to the ethereal solution. The mixture was shaken and separated. The aqueous phase was washed with 500 mL of ether. The combined organic phases were washed with 1000 mL of water and then with saturated brine. The organic layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure. The residue was titurated with 1400 mL of hexane when a white crystalline material formed. The mixture was filtered to give 195 g (98%) of (±)-1,2-bis(*o*-carboxybenzoyloxy)-3,3-dimethylbutane: mp 168–170 °C; IR (KBr) 3650–2200 (broad), 1729 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.0 (9 H, s), 2.7–4.0 (2 H, b s, disappeared in D_2O), $-CH_2CH-$ gives an AMX pattern δ_A 4.32 (1 H, q), δ_M 4.65 (1 H, q), δ_X 5.18 (1 H, q), J_{AM} = 20 Hz, J_{AX} = 12 Hz, J_{MX} = 5 Hz, 7.51–7.8 (8 H, m). The product (mp 168–170 °C) was used for the next step. Pure material (mp 176–178 °C) was obtained after recrystallization from hot acetone.

To a stirred mixture of 265 g (0.62 mol) of (−)-brucine dihydrate and 4000 mL of acetone was added 213 g (0.51 mol) of the (±)-diester at room temperature. In a short time, a clear solution formed, but after 10 min a white precipitate appeared. The reaction mixture was stirred for 32 h at room temperature, and the crystals were filtered and washed with acetone. (From this first mother liquor and washing (*R*)-(−)-3,3-dimethyl-1,2-butanediol (**14b**) with 42% ee could be obtained.) The crude monobrucine salt (249 g) was then recrystallized five times from 1,2-dichloroethane/acetone in the following way: the salt was dissolved in hot 1,2-dichloroethane (4.2 mL/g), and to this solution while stirring was added hot acetone (30.5 mL/g). After being mixed well, this solution was poured immediately into an Erlenmeyer flask, corked, and left standing at room temperature for 6 days. After five recrystallizations, the monobrucine diastereomeric salt was filtered and air dried to give 84.5 g (41%) of solid: mp 177–179 °C; $[\alpha]^{20}_D$ −3.06° (*c* = 1.698, chloroform). Anal. Calcd for $C_{45}H_{48}N_2O_{12}$: C, 66.82; H, 5.98. Found: C, 66.77; H, 5.83. In the ^1H NMR spectrum, the ratio of the brucine OCH_3 protons and the *tert*-butyl protons confirmed the 1:1 adduct.

The previous salt ($[\alpha]^{20}_D$ −3.06°; 84 g, 0.10 mol) was dissolved in 550 mL of $CHCl_3$. To this solution was added 100 mL of distilled water, 50 g of ice, and 11.25 g (0.28 mol) of NaOH dissolved in 200 mL of ice-cold water, consecutively. The mixture was mixed vigorously for 4 min, and the phases were separated. The aqueous phase was washed twice with 100-mL portions of $CHCl_3$ The combined $CHCl_3$ solutions were dried ($MgSO_4$), filtered, and evaporated to give 43.9 g (98%) of recovered brucine dihydrate. The aqueous solution was concentrated to 50 mL under reduced pressure, and then 8.32 g (0.21 mol) of NaOH dissolved in 50 mL of ice-cold water was added. The mixture was stirred at 0 °C for 10 min and then at room temperature for 3 days. The solution was shaken with one 300-mL portion and three 100-mL portions of ethyl acetate. The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by distillation under reduced pressure to give 10.9 g (89%) of **14a**: bp 109–110 °C (15 mm); mp 39–40 °C; $[\alpha]^{20}_D$ +25.64° (*c* = 0.715, $CHCl_3$) (lit.[17] $[\alpha]^{20}_D$ +24.4° and, for the *R*-(−) isomer, −28.1°[13]). The % ee was determined to be 98% by SFC analysis.[12] We and others[17] observed sizeable fluctuations of specific rotation depending on concentration. After two recrystallizations from 1,2-dichloroethane/acetone, we obtained a monobrucine diastereomeric salt in 68% yield: mp 167–169 °C; $[\alpha]^{20}_D$ −3.62° (*c* = 1.629, chloroform). From this salt, we obtained (*S*)-(+)-3,3-dimethyl-1,2-butanediol (**14a**): 89% yield; $[\alpha]^{20}_D$ +22.91° (*c* = 0.681, $CHCl_3$) (85% ee by the SFC method).[12] This compound was recrystallized from hexane to give a 55% yield of **14a**: $[\alpha]^{20}_D$ +25.88° (*c* = 0.769, $CHCl_3$) (100% ee by the SFC method);[12] mp 41–42 °C; IR (neat) 3408 cm^{-1}; ^1H NMR δ 0.9 (9 H, s), 3.12–3.52 (4 H, m), 3.62–3.80 (1 H, m). From the mother liquor, 34% of **14a** diol was obtained with $[\alpha]^{20}_D$ +16.99° (*c* = 0.730, chloroform) (67.5% ee by the SFC method).[12] From the monobrucine salt recovered from the acetone solution and washing (see the previous text), the partially resolved *R*-(−) diol **14b** was also obtained. After distillation of the product under reduced pressure (bp 108–109 °C (15 mm)), **14b** was obtained in a 77% yield: $[\alpha]^{20}_D$ −10.84° (*c* = 0.664, $CHCl_3$) (42% ee by the SFC method).[12]

(*S*)-(+)-1-(Tosyloxy)-3,3-dimethyl-2-butanol (15a; Scheme IIIB). Tosyl chloride (16.1 g, 85.6 mmol; recrystallized from hot hexane) dissolved in 60 mL of CH_2Cl_2 was slowly added over an 80-min period to a mixture of 10.11 g (85.56 mmol) of (*S*)-(+)-**14a** and 14.46 mL (103.95 mmol) of triethylamine in 36 mL of CH_2Cl_2 at −16 °C. The reaction mixture was stirred at −16 °C for 30 min, the cooling bath was removed, and the mixture was stirred at room temperature for 80 h. After the reaction was complete, 300 mL of CH_2Cl_2 was added to the reaction mixture and it was washed with 200 mL each of ice-cold water, 10% aqueous HCl, water, saturated aqueous $NaHCO_3$, and water. The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was recrystallized from disopropyl ether/hexane to give 13.4 g (83%) of (*S*)-(+)-**15a**: mp 45–46 °C (lit.[13] mp for the *R*-(−) isomer 40 °C); $[\alpha]^{25}_D$ +27.42° (*c* = 1.098, benzene); IR (KBr) 3546, 1352, 1172 cm^{-1}; ^1H NMR δ 0.87 (9 H, s), 2.14 (1 H, b d), 2.44 (3 H, s), $-CH_2CH-$ gives an AMX pattern δ_A 3.5 (1 H, q), δ_M 3.91 (1 H, q), δ_X 4.21 (1 H, q), J_{AM} = 16 Hz, J_{MX} = 12 Hz, J_{AX} = 5 Hz; 7.33 (2 H, d), 7.78 (2H, d) (the latter two doublets gave an AA'BB' spin system with *J* = 12 Hz).

(*S*)-(+)-3,3-Dimethyl-2-(tetrahydropyranyloxy)butyl *p*-Toluenesulfonate (16a). To a stirred mixture of 10.25 g (37.63 mmol) of **15a** and 6.87 mL (6.37 g, 75.26 mmol) of dihydropyran in 150 mL of dry CH_2Cl_2 was added under Ar at 0 °C 0.8 g of PPTS catalyst, and the reaction mixture was stirred at 0 °C for 4 h and then at room temperature for 14 h. The reaction mixture was poured into a separatory funnel, and the flask was rinsed with 150 mL of CH_2Cl_2. The combined organic phase was washed with a mixture of 100 g of ice and 100 mL of water, then ice-cold saturated $NaHCO_3$, and ice-cold water. The organic phase was dried ($MgSO_4$) and filtered, and the solvent was evaporated. The residue was dissolved in dry benzene, and the benzene was evaporated under reduced pressure to give 13.4 g (100%) of **16a** as a mixture of two diastereoisomers: $[\alpha]^{20}_D$ +2.12° (*c* = 6.508, benzene); IR (neat) 1364, 1177, 1077, 1033, 904 cm^{-1}; ^1H NMR δ 0.85 and 0.9 (9 H, s), 2.43 and 2.45 (3 H, s), 3.25–3.55 (2 H, m), 3.72–4.03 (2 H, m), 4.11–4.3 (1 H, m), 4.52 and 4.63 (1 H, t, *J* = 6 Hz), 7.27–7.42 (2 H, m), 7.72–7.87 (2 H, m). This material was used in the next step without further purification.

(*S,S*)-(+)-1,11-Di-*tert*-butyl-3,6,9-trioxaundecane-1,11-diol (7). To a stirred mixture of 1.53 g (51 mmol) of NaH (80% dispersion in mineral oil) and 100 mL of dry DMF was added dropwise under Ar at room temperature 1.91 g (18 mmol) of

(17) Ko, K.-Y.; Frazee, W. J.; Eliel, E. L. *Tetrahedron* **1984**, *40*, 1333.

diethylene glycol dissolved in 35 mL of DMF. After addition of the glycol, the reaction mixture was stirred at room temperature for 1 h and then at 80 °C for 2 h. The mixture was cooled to 0 °C, and 13.0 g (36.5 mmol) of **16a** dissolved in 45 mL of dry DMF was added dropwise. After the mixture was stirred at 0 °C for 10 min and at room temperature for 30 min, it was stirred at 90 °C for 40 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in 50 g of ice and 350 mL of CH_2Cl_2. The phases were mixed and separated. The aqueous phase (pH ≥ 12) was washed twice with 100-mL portions of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue (7.0 g) was dissolved in 7 mL of distilled water and 63 mL of glacial acetic acid. The mixture was stirred at 90 °C for 4 h. The solvent was evaporated under reduced pressure. The residue was dissolved in 40 mL of toluene, and the solvent was evaporated. This residue was purified on a silica gel column with ethyl acetate/toluene (1/2) as eluent to give 2.03 g (37%) of **7**: $[\alpha]^{20}_D$ +38.0° (c = 2.084, benzene); IR (neat) 3468, 1125 cm^{-1}; ^1H NMR δ 0.93 (18 H, s), 3.23–3.52 (6 H, m), 3.53–3.76 (10 H, m); MS m/e 307 ($M^+ + 1$).

10,10,10-Triphenyl-3,6,9-trioxadecanol (17; Scheme IIIC). To a solution of 33.93 g (0.23 mol) of triethylene glycol and 80 mL of dry pyridine was added dropwise 12.6 g (0.0452 mol) of trityl chloride dissolved in 50 mL of pyridine at 0 °C under Ar. After addition, the mixture was stirred at 0 °C for 3 h and then at room temperature for 14 h. After the reaction was complete, the solvent was evaporated under reduced pressure. The residue was triturated twice with 400 mL of ice-cold water and the water was decanted. The residue was then dissolved in 400 mL of ether, and the solution was washed with 400 mL of ice-cold water and with 200 mL of saturated brine. The organic phase was dried ($MgSO_4$) and filtered, and the solvent was evaporated. The residue was purified on a silica gel column with toluene and then ethyl acetate/toluene (1/3) as eluents to give 14.74 g (83%) of **17**: IR (neat) 3442, 3085, 3057, 3030, 1596, 1490 cm^{-1}; ^1H NMR δ 2.9 (1 H, t, disappeared in D_2O), 3.25 (2 H, t), 3.58 (2 H, t, J = 7 Hz), 3.6–3.8 (8 H, m), 7.12–7.37 (9 H, m), 7.37–7.56 (6 H, m).

10,10,10-Triphenyl-3,6,9-trioxadecyl *p*-Toluenesulfonate (18). To a vigorously stirred mixture of 12.17 g (31 mmol) of **17** and 4.1 g (62 mmol, 85%) of finely powdered KOH in 100 mL of THF was added dropwise at 0 °C under Ar 7.45 g (39 mmol) of tosyl chloride dissolved in 75 mL of THF. The reaction mixture was stirred at 0 °C for 3 h and then at room temperature for 7 h. When the reaction was complete, the solvent was evaporated under reduced pressure. CH_2Cl_2 (300 mL) and 150 g of ice were added to the residue, and the phases were mixed thoroughly. The aqueous phase was washed with 100 mL of CH_2Cl_2. The combined organic phases were washed with 200 mL of water, dried ($MgSO_4$), and filtered, and the solvent was evaporated under reduced pressure to give 16.61 g (98%) of crude **18**: IR (neat) 3085, 3057, 3032, 1597, 1490, 1360, 1177 cm^{-1}; ^1H NMR δ 2.38 (3 H, s), 3.21 (2 H, t, J = 6 Hz), 3.51–3.78 (8 H, m), 4.15 (2 H, t, J = 6 Hz), 7.14–7.37 (11 H, m), 7.37–7.52 (6 H, m), 7.75 (2 H, d, J = 12 Hz). This material was used in the next step without further purification.

3(*R*),4(*R*)-Dimethyl-1,15,15,15-tetraphenyl-2,5,8,11,14-pentaoxadodecane (20). To a stirred mixture of 1.25 g (41.7 mmol) of NaH (80% suspension in mineral oil) and 10 mL of DMF was added dropwise 5.35 g (29.7 mmol) of 3(*R*)-(benzyloxy)-2-(*R*)-butanol (**19**)[4] dissolved in 30 mL of DMF at room temperature under Ar. The mixture was stirred at room temperature for 10 min then at 85 °C for 2 h. The mixture was cooled to 0 °C, and 16.24 g (29.7 mmol) of **18** dissolved in 60 mL of DMF was added dropwise. The reaction mixture was stirred at 0 °C for 10 min, at room temperature for 10 min, and then at 85 °C for 2 days. When the reaction was complete, the solvent was evaporated under reduced pressure. Ice (60 g) and 400 mL of CH_2Cl_2 were added to the residue. The mixture was shaken, and the phases were separated. The aqueous phase (pH ≥ 12) was washed with 100 mL of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue (16.4 g, 99.5%) was purified on a silica gel column with ethyl acetate/hexane (1/8 then 1/4) as eluents to give 8.7 g (53%) of **20**: IR (neat) 3086, 3060, 3030, 1597, 1491, 1094 cm^{-1}; ^1H NMR δ 1.08–1.2 (6 H, m), 3.18–3.37 (2 H, m), 3.48–3.72 (12 H, m), 4.38–4.71 (2 H, m), 7.13–7.52 (20 H, m).

(10*R*,11*R*)-(−)-10-Methyl-3,6,9-trioxa-1,11-dodecanediol (8). Compound **20** (6.96 g, 12.55 mmol) and 1.0 g of activated C (Norit A) was stirred in 100 mL of absolute ethanol for 2 h. The C was filtered, and the clear filtrate was added to 1.0 g of prehydrogenated 10% Pd/C catalyst in 50 mL of ethanol. The hydrogenation was carried out at room temperature under an atmospheric pressure of H_2 for 4 days. The catalyst was filtered and washed with ethanol, and the solvent was evaporated under reduced pressure. Because the TLC analysis of the product showed that the Ph_3C–O bond remained intact during the hydrogenation, the product was stirred in a mixture of 54 mL of glacial acetic acid and 6 mL of water at 90 °C for 4 h. After the reaction was complete, the solvent was evaporated under reduced pressure. The residue was triturated with distilled water (60 mL), and then the trityl alcohol was filtered and washed twice with 15 mL of water. The aqueous filtrate and washings were combined, and the solvent was evaporated under reduced pressure. Dioxane was added and evaporated. Toluene was added and evaporated. The residue was purified by distillation under reduced pressure to give 1.95 g (70%) of **8**: bp 110–112 °C (0.2 mm); $[\alpha]^{20}_D$ −30.5° (c = 1.495, benzene); IR (neat) 3440, 1105 cm^{-1}; ^1H NMR δ 1.08 (6 H, d, J = 7 Hz), 3.1–3.18 (1 H, m), 3.4–3.8 (15 H, m), 3.82–3.95 (1 H, m), 4.52 (1 H, s broad).

General Procedure for Preparing Crowns 2, 4, and 5 (Scheme I). To a stirred mixture of 0.62 g (20.7 mmol) of NaH (80% dispersion in mineral oil) and 10 mL of THF (distilled under Ar from $LiAlH_4$) was added dropwise under Ar 7.38 mmol of the appropriate diol (**6**, **7**, or **8**) dissolved in 70 mL of THF at room temperature. After addition, the mixture was stirred at room temperature for 10 min then refluxed for 2.5 h. The reaction mixture was cooled to 0 °C, and 3.30 g (7.38 mmol) of ditosylate **9**[4] dissolved in 70 mL of THF was added dropwise. After addition, the reaction mixture was stirred at 0 °C for 3 h and then at room temperature for 3 days. When the reaction was complete, the solvent was evaporated under reduced pressure. The residue was thoroughly mixed with 20 g of ice and 150 mL of CH_2Cl_2, and the phases were separated. The aqueous phase (pH ≥ 12) was washed twice with 100-mL portions of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered and the solvent was evaporated. The residue was purified and characterized as described in the following text for each individual crown.

(4*R*,14*R*)-(−)-4,14-Diphenyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (2). Crown **2** was prepared as described previously using 2.56 g (7.38 mmol) of **6**. The crude product was purified by chromatography first on neutral alumina with ethanol/toluene (1/140 followed by 1/70), then on silica gel with methanol/acetonitrile/toluene (4/1/1). The resulting white solid was recrystallized from isopropyl ether to give 1.19 g (36%) of **2** as white crystals: mp 66–67 °C; $[\alpha]^{20}_D$ −128.9° (c = 0.34, benzene); ^1H NMR δ 3.5–3.85 (12 H, m), 4.02–4.85 (6 H, m), 7.13 (2 H, d, J = 10 Hz), 7.19–7.45 (10 H, m), 7.59 (1 H, t, J = 10 Hz); MS m/e 449 (M^+). Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95. Found: C, 72.13; H, 7.00.

(4*S*,14*S*)-(+)-4,14-Di-*tert*-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (4). Crown **4** was prepared as described previously using 2.26 g (7.38 mmol) of **7**. The crude product was purified by chromatography on silica gel (THF/toluene (1/8)) to give 2.19 g (73%) of **4** as a clear oil: $[\alpha]^{25}_D$ −15.09° (c = 0.424, benzene); ^1H NMR δ 0.95 (18 H, s), 3.19–3.74 (14 H, m), the benzylic $-CH_2-$ gives an AB quartet, δ_A 4.82, δ_B 4.92, J_{AB} = 14 Hz (4 H), 7.32 (2 H, d), 7.66 (1 H, t, J = 10 Hz); MS m/e 409 (M^+). Anal. Calcd for $C_{23}H_{39}NO_5$: C, 67.45; H, 9.60. Found: C 67.45; H, 9.42.

(4*R*,5*R*)-(−)-4,5-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (5). Crown **5** was prepared as described previously using 1.64 g (7.38 mmol) of **8**. The crude product was purified by chromatography on neutral alumina (ethanol/toluene (1/80)) to give 1.04 g (43%) of **5** as a clear oil; $[\alpha]^{25}_D$ −24.45° (c = 1.648, benzene); ^1H NMR δ 0.97 (3 H, d), 1.05 (3 H, d, J = 7 Hz), 3.3–3.77 (14 H, m), 4.65 (2 H, s), the benzylic $-CH_2-$ gives an AB quartet, δ_A 4.69, δ_B 4.79, J_{AB} = 16 Hz, 7.15 (1 H, d), 7.25 (1 H, d), 7.6 (1 H, t, J = 12 Hz); MS m/e 425 (M^+). Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36. Found: C, 62.48; H, 8.41.

(4*S*,14*S*)-(+)-4,14-Di-*tert*-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (3;

Scheme II). Crown **3** was prepared with some modifications by the method developed by Bradshaw and co-workers for obtaining similar crowns.[6,11] A mixture of 401 mg (1.31 mmol) of **7**, 256 mg (1.31 mmol) of dimethyl 2,6-pyridinedicarboxylate, and 35 mg (0.65 mmol) of $NaOCH_3$ was combined with 120 mL of dry benzene in a flask equipped with a Soxhlet apparatus. Molecular sieves (4 Å, 10 g) were placed in the extraction thimble, and the mixture was refluxed through the Soxhlet for 32 h. Because the TLC (THF/isopropyl ether (1/8)) showed that the diester was consumed but not the diol, another 100 mg (0.51 mmol) of diester was added and the mixture was refluxed for another 24 h. The cold mixture was acidified with 0.2 mL of glacial acetic acid, and the solvent was removed under reduced pressure. Ice (10 g) and 50 mL of CH_2Cl_2 were added to the residue, the resulting mixture was shaken, and the phases were separated. The organic phase was dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (THF/toluene (1/8)). The resulting solid was recrystallized from hexane to give 85 mg (15%) of white crystals: mp 96-97 °C; $[\alpha]^{25}_D$ -24.33° (c = 0.825, benzene); ^1H NMR δ 1.05 (18 H, s), 3.38-3.87 (12 H, m), 5.2 (2 H, t, J = 8 Hz), 7.95 (1 H, t), 8.12 (2 H, d, J = 10 Hz); MS m/e 437 (M^+). Anal. Calcd for $C_{23}H_{35}NO_7$: C, 63.14; H, 8.06. Found: C, 63.18; H, 8.13.

Determination of ΔG_c^* Values. ΔG_c^* values listed in Table I were determined as reported.[5-8,15]

Determination of log K Values by the Direct ^1H NMR Method. The log K values listed in Table II were determined as reported.[10] A sample containing a few milligrams of macrocycle in a known volume of solvent was first loaded into the probe, and a spectrum was taken. The sample was then unloaded, added to the sample tube with a small amount of the ammonium salt, and reloaded into the probe, and another spectrum was taken. This process was repeated until no significant change was observed in successive ^1H NMR spectra. Usually 8-12 spectra were taken for each log K determination. The crown ether concentrations were ~0.01-0.015 M and the ammonium salt concentrations varied from 0.0 M to ~0.06 M for each of the experiments. In such experiment, an accurately weighed quantity of the crown ether was dissolved in a known volume of solvent at 25.0 °C. The analytical balance used was calibrated for accuracy using a standard weight from the National Institute of Standards and Technology. The salt concentrations were calculated on the basis of the integral ratio of a particular ammonium salt signal to a particular crown ether signal in the spectra. In order to obtain a quantitative integration, the time delay between the two pulses for each NMR acquisition was set long enough to allow sufficient relaxation of the signals of interest. The log K values were then calculated from the differences in chemical shift values as reported.[10]

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Supplementary Material Available: ^1H NMR spectra for compounds **6-8**, **11-18**, and **20** (12 pages). Ordering information is given on any current masthead page.

Base-Catalyzed Alkylation of 2-Naphthol with Glyoxal

Taketoshi Kito,* Kohji Yoshinaga, Makoto Yamaye,[1] and Hoyou Mizobe

Department of Chemistry, Kyushu Institute of Technology, Sensui-cho, Tobata-ku, Kitakyushu-shi 804, Japan

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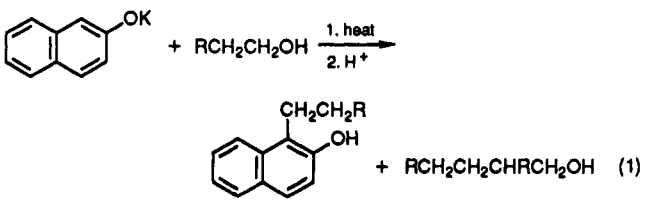
Alkylation of potassium 2-naphthyl oxide with glyoxal in aqueous media formed 1,2-dihydronaphtho[2,1-*b*]furan-1,2-diol (**1**). Without isolation of **1**, acidification of this reaction mixture with aqueous HCl led to three products, i.e., the lactone of (2-hydroxy-1-naphthyl)acetic acid (**2**), the hemiacetal of bis(2-hydroxy-1-naphthyl)acetaldehyde (**3**), and the corresponding acetal (**4**). Mutual interconversions of **1** and these three products revealed the reaction pathway and the mechanisms of formation of the lactone and the acetal.

Introduction

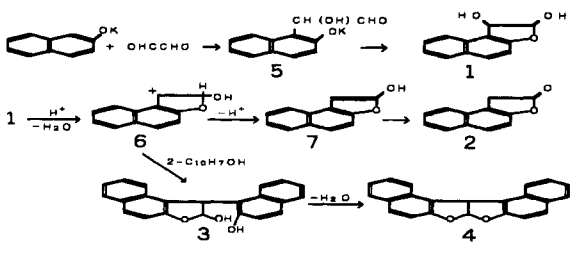
We have reported the base-catalyzed reaction of 2-naphthol with a primary alcohol (e.g., 1-butanol) to form 1-alkyl-2-naphthols and 2-alkyl-substituted alkanols.[2]



Use of benzyl alcohol as the primary alcohol produces only 1-benzyl-2-naphthol. Based on the isolation of three precursors for this reaction, we proposed an aldehyde mechanism, i.e., benzaldehyde as the key intermediate to initiate the reaction.[3] In an extension of our project to the use of dialdehydes, we here report the base-catalyzed alkylation of 2-naphthol with glyoxal.

The reaction of either phenols or naphthols with glyoxal has been reported by several investigators, including

Scheme I



Dischendorfer,[4] McGowan, Anderson, and Walker,[5] and Coxworth.[6] Although there had been discrepancies in structural analyses for the condensation products, Coxworth finally characterized them as the acetal type, rather than the ether type, by means of ^1H NMR spectroscopy.[6] For example, the reaction of glyoxal with 2-naphthol in acidic media gave 7a,14c-dihydronaphtho[2,1-*b*]naphtho-[2′,1′:5,6]furo[3,2-*d*]furan (**4**).[6]

Recently, Maravigna synthesized thermally stable polymers containing the furofuran skeleton by condensa-

(1) Faculty of Engineering, Kyushu Kyoritsu University.
(2) Kito, T.; Ota, K. *J. Org. Chem.* **1977**, *42*, 2020.
(3) Kito, T.; Yoshinaga, K.; Ohkami, S.; Ikeda, K.; Yamaye, M. *J. Org. Chem.* **1985**, *50*, 4628.
(4) Dischendorfer, O. *Monatsh.* **1940**, *73*, 45.
(5) McGowan, J. C.; Anderson, J. M.; Walker, N. C. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 597.
(6) Coxworth, E. C. M. *Can. J. Chem.* **1967**, *45*, 1778.

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