$C_{10}H_7N_3O_5 \cdot 0.75H_2O$: C, 45.72; H, 3.26; N, 15.98. Found: C, 45.81; H, 3.04; N, 15.77.

6-(Methylamino)-8-(methylimino)quinazoline-2,4,5-(1*H*,3*H*)-trione (3). Addition of 0.19 g (0.76 mmol) of 1 to 5 mL of 40% aqueous monomethylamine was followed by heating at reflux for 15 min. After the reaction mixture was chilled for 1 h, the red product was filtered off and washed with water and then methanol. Recrystallization from 4 N HCl afforded fibrous red crystals: 0.10 g (56%); mp 220–250 °C with evolution of gas; TLC [butanol–acetic acid–H_2O (5:3:2)] on silica gel, R_f 0.22 as a red spot; ^1H NMR (trifluoroacetic acid-d_1 with 1 drop of D_2O against Me_4Si) δ 6.00 (1 H, s, 7-H), 3.44 and 3.37 (6 H, two s, aminomethyl and iminomethyl, no assignments made); ^{13}C NMR (trifluoroacetic acid-d_1 with 1 drop of D_2O, against Me_4Si) δ 158.8, 145.8, 138.0, 137.2, 136.6, 136.1, 90.2, 72.1 (no assignments made), 16.1 and 14.7 (methyl groups); MS (EI mode) m/e 234 (M^+), 203 ($M^+ - CO$), 190 ($M^+ - HN{=}C{=}O$), 178 ($M^+ - HC{\equiv}CNHCH_3$); IR (KBr) 3232, 1641, 1635, 1596, 1525, 1499, 1464, 1413 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_4O_3 \cdot 1.25H_2O$: C, 46.78; H, 4.90; N, 21.81. Found: C, 46.75; H, 4.44; N, 21.44.

8-(Phenylimino)-6-acetamidoquinazoline-2,4,5-(1*H*,3*H*)-trione (11). A mixture consisting of 200 mg (0.80 mmol) of 1, 2.0 g of aniline, and 10 mL of DMF was heated at reflux for 2 min. Upon cooling to room temperature, the volume of the reaction mixture was diluted to 50 mL with water. After chilling for 12 h, this mixture yielded red crystals that were filtered and recrystallized from ethanol: yield of copper-colored flakes 51.5 mg (20%); dec pt >250 °C; TLC [butanol–acetic acid–H_2O (5:2:3)] on silica gel, R_f 0.51; ^1H NMR (Me_2SO-d_6) δ 11.18 and 9.57 (3 H, two br s, N(1)-H, N(3)-H, and amide NH, no assignments made), 7.86 (1 H, s, 7-H), 7.56–6.95 (5 H, complex m, phenyl), 2.11 (3 H, s, methyl of 6-acetamido group); IR (KBr) 3445, 3312, 1733, 1696, 1493, 1396 cm^{-1}; MS (EI mode) m/e 324 (M^+), 282 ($M^+ - HN{=}C{=}O$). Anal. Calcd for $C_{16}H_{12}N_4O_4 \cdot 2.5H_2O$: C, 52.03; H, 4.64; N, 15.16. Found: C, 51.94; H, 3.19; N, 15.02. The percentage of hydrogen is seen to deviate widely.

6-Amino-7-bromoquinazoline-2,4,5,8-(1*H*,3*H*)-tetrone (10). A mixture of 0.107 g (0.43 mmol) of 1 and 1.0 mL of bromine in 20 mL of acetic acid was heated at reflux for 5 min. Upon cooling of the reaction to room temperature, the purple precipitate was filtered off and washed with diethyl ether: yield of **10** as an analytically pure purple microcrystalline solid 0.10 g (87%); mp dec pt >300 °C; TLC [butanol–acetic acid–H_2O (5:2:3)] on silica gel, R_f 0.51; IR (KBr) 3174, 1754, 1710, 1591, 1502, 1387 cm^{-1}; MS (EI mode) m/e 287 ($M^+ + 2$), 244 ($M^+ + 2 - O{=}C{=}NH$), 206 ($M^+ - HBr$). Anal. Calcd for $C_8H_4BrN_3O_4$: C, 33.58; H, 1.40; N, 14.67. Found: C, 33.50; H, 1.40; N, 14.57. pK_a for N(1) proton dissociation is 5.62 ± 0.08. UV data λ_{max}, nm (ϵ): (**10**) 286 (1×10^4), 326 (1.66×10^4), 508 (1200), (**10**$^-$) 274 (1.3×10^4), 350 (2.3×10^4), 480 (690).

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Proton-Ionizable Crown Compounds. 2. Synthesis, Complexation Properties, and Structural Studies of Macrocyclic Polyether–Diester Ligands Containing a 4-Hydroxypyridine Subcyclic Unit‖

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A series of macrocyclic polyether–diester ligands containing a proton-ionizable 4-hydroxypyridine subcyclic unit has been prepared. These new macrocyclic ligands form stable complexes with both alkylammonium perchlorate salts and with alkylamines. The crystal structure for one of these complexes with an alkylamine shows that the hydroxy proton has been donated to the amine with the resultant formation of a 4-pyridone unit. Chiral dimethyl- and diphenyl-substituted macrocycles containing the 4-hydroxypyridine subcyclic unit exhibit chiral recognition for the enantiomers of 2-(1-naphthyl)ethylamine and their hydrogen perchlorate salts.

We are interested in the design of host macrocycles which show selectivity toward guest molecules and ions, especially those with enantiomeric properties. An important aspect of such design is the creation of host molecules capable of exchanging protons on the host for the guest ions of interest at membrane interfaces. Such capability could lead to the design of selectivity into an appropriate membrane system making continuous proton-coupled ion transport possible. The feasibility of proton-coupled transport of alkali metal cations by calixarenes has been shown,[1] and selectivity for Cs^+ over other alkali cations in mixtures of these has been demonstrated.[2]

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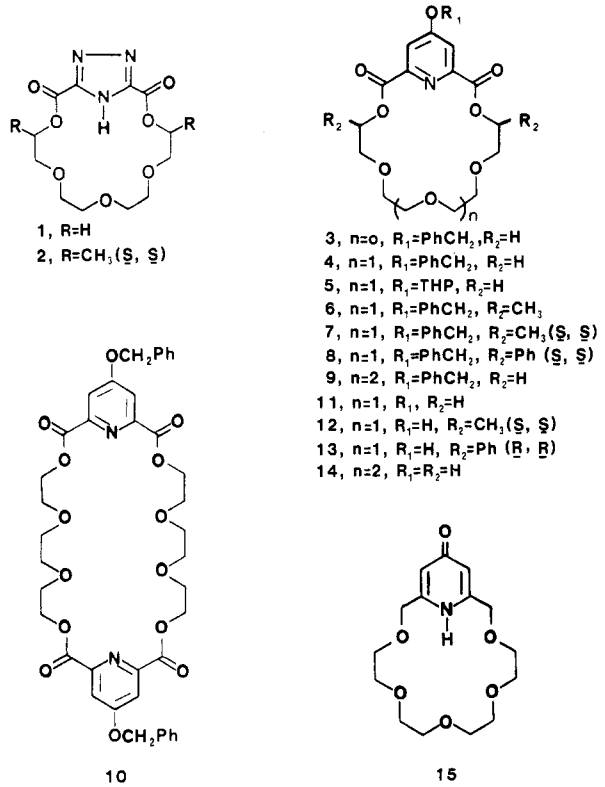


Figure 1. Structures of compounds.

We have prepared two new classes of proton-ionizable macrocycles based on the cyclic polyether structure in which the ionizable function is part of the macrocyclic ring. The synthesis, complexation properties, and structural studies of diester macrocycles from one of these classes which contains a proton-ionizable triazole subcyclic unit was reported recently by us[3] (see compounds 1 and 2, Figure 1). The work of others which involves proton-ionizable crown compounds has been reviewed by us.[3] The triazole-containing macrocycles complexed with amines in a manner that involved the transfer of the proton of the triazole ring to the amine. In fact, the complex of 1 with benzylamine was kinetically more stable than its complex with benzylammonium perchlorate.[3]

We now report the synthesis, some complexation reactions, and structural properties of a second class of diester crown compounds containing a proton-ionizable 4-hydroxypyridine subcyclic unit (compounds **11–14**, Figure 1). A preliminary publication describing compound **11** and its properties as compared to ligand **15**, the non-ester analogue of **11**, has been published.[4] These new proton-ionizable ligands form stable complexes with both alkylamines and alkylammonium salts. The crystal structure of compound **11** shows the 4-hydroxypyridine structure which is unusual since 4-hydroxypyridine compounds in general have a 4-pyridone structure. The crystal structure of an amine complex shows that the proton has been transferred to the amine resulting in a 4-pyridone structure. The crystal structure also shows an uncomplexed ligand to be present in the 4-hydroxypyridine form. Compounds **12** and **13** exhibit chiral recognition for the enantiomers of 2-(1-naphthyl)ethylamine and their hydrogen perchlorate salts.

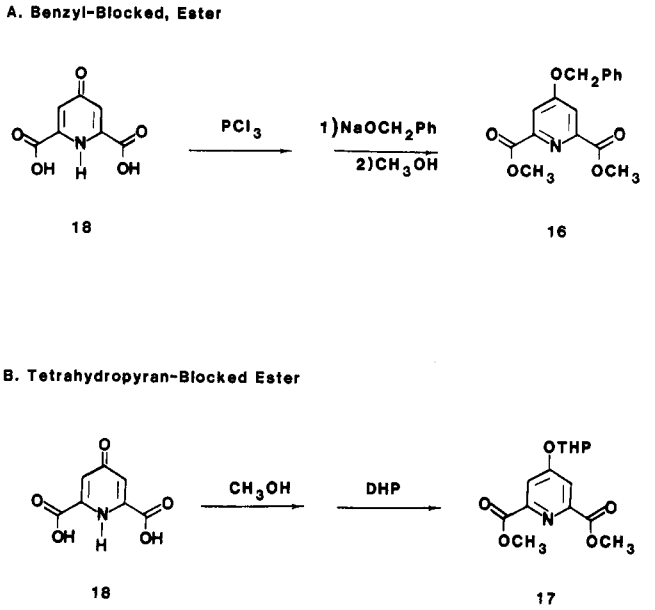
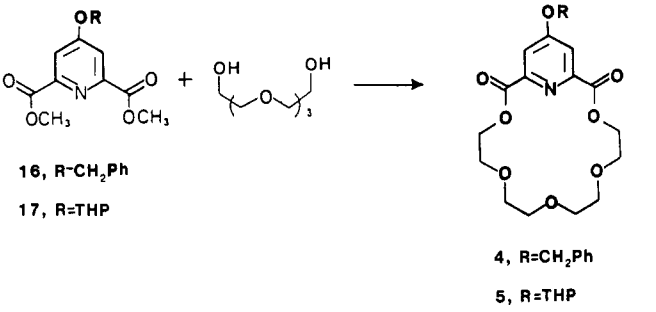


Figure 2. Preparation of starting diester compounds.

Results and Discussion

Compounds **3–10** (Figure 1) were prepared by the reaction of dimethyl 4-(benzyloxy)-2,6-pyridinedicarboxylate (**16**) or its tetrahydropyranyl-blocked analogue (**17**) with the appropriate glycol in benzene using an alkali metal methoxide as the catalyst. The reaction was driven to



completion by removal of the methanol by its absorption into molecular sieves. Product yields ranged from 5% to 57% for this reaction. The benzyl-blocked crowns were then reduced to the 4-hydroxypyridine-containing crowns **11**, **12**, and **14** in a Parr hydrogenator with palladium on carbon as a catalyst. Yields ranged from 30% to 78%. Crown **11** was also prepared by hydrolyzing THP-blocked macrocycle **5**. Chiral crown **13** was prepared from THP-blocked ester **17** as above, but the THP-blocked crown was hydrolyzed immediately to form **13**. The structures proposed for the macrocyclic compounds are consistent with data obtained from IR and ^{1}H NMR spectra, combustion analyses, and molecular weight and crystal structure determinations.

The starting dimethyl 4-(benzyloxy)-2,6-pyridinedicarboxylate (**16**) was prepared as shown in Figure 2A from commercially available chelidamic acid (**18**).[5,6] Dimethyl 4-[(tetrahydro-2-pyranyl)oxy]-2,6-pyridinedicarboxylate (**17**) was also prepared from acid **18** as shown in Figure 2B.

The new macrocyclic compounds formed complexes with various guest species. The benzyl-blocked ligands **4** and **7** formed complexes with alkylammonium salts while the

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Table I. Carbon–Carbon Bond Lengths on the Pyridine Unit

	CA2–CA3	CA3–CA4	CA4–CA5	CA5–C18	CA4–OA4
11 (Figure 3)	1.380 (3)	1.393 (4)	1.386 (3)	1.372 (3)	1.336 (3)
methyl derivative of 11 ($R_1 = CH_3$) (Figure 4)	1.381 (3)	1.380 (4)	1.389 (4)	1.376 (3)	1.351 (3)
benzylamine complex of 11 (Figure 6)					
uncomplexed	1.376 (7)	1.382 (9)	1.389 (9)	1.389 (7)	1.339 (7)
complexed	1.383 (9)	1.406 (11)	1.413 (10)	1.375 (8)	1.289 (9)
benzylammonium perchlorate complex of 11 (Figure 5)	1.379 (8)	1.379 (10)	1.354 (10)	1.395 (9)	1.359 (8)
15 (ref 4)	1.352 (3)	1.432 (3)	1.441 (3)	1.350 (3)	1.261 (3)

[a] Because there are two ligand units in the benzylamine complex, the atoms of the pyridine unit in the complexed molecule are labeled C22, CA23, CA24, OAC4, CA25, and C38 in the atom list.

ligands containing 4-hydroxypyridine moieties **11–13** formed complexes with both alkylamines and alkylammonium salts. The 18-membered ring ligands containing the 4-hydroxypyridine unit (**11–13**) also formed monohydrates.

The pK_1 and pK_2 values (valid in H_2O) for the consecutive removal of protons from the H_2L^+ form of **11** as determined by a calorimetric titration technique are estimated to be 1.70 and 8.49, respectively. These numbers differ appreciably from the pK_1 and pK_2 values for the parent 4-hydroxypyridine ($pK_1 = 3.27$ and $pK_2 = 11.09$)[7] and 4-pyridone ligand **15** ($pK_1 = 3.10$ and $pK_2 = 10.98$).[4] The significant difference between the pK_n values of **11** and **15** together with the fact that the pK_n values for **15** are similar to those for 4-pyridone suggests that compound **11** contains the 4-hydroxypyridine structure. Indeed, the reported X-ray structure of **15** was shown to contain the 4-pyridone unit[4] while the X-ray structures reported here for the hydrate of **11** and the alkylammonium salt complex of **11** show a 4-hydroxypyridine unit. These latter data were obtained to clarify the structure of the pyridine ring of **11** in the indicated complexes.

Four crystal structures were determined in order to establish whether 4-hydroxypyridine or 4-pyridone was present in **11** and to determine the type of complexation that occurs between **11** and an amine and an organic ammonium salt. The experimental details as well as a discussion of the X-ray structure solutions are given in the Experimental Section. Computer drawings of the four structures are shown in Figures 3–6. The pertinent structural features are summarized here.

In Figure 3, it is seen that the hydrogen atom HOA4 is bonded to OA4 which establishes that the six-membered ring of **11**·H_2O exists as a 4-hydroxypyridine. This structural assignment was verified by the X-ray study of the benzyl amine complex of **11** (Figure 4). This structure is particularly informative as the asymmetric unit contains the complex of **11** and also an uncomplexed ligand. The presence of the hydrogen atom, HOA4, in the uncomplexed molecule confirms the presence of a 4-hydroxypyridine subunit. However, in the complex there was no hydrogen on OA24 and the six-atom ring is present as a 4-pyridone with a hydrogen being donated to the nitrogen of the amine. This will be discussed below. The hydrogen atom on OA4 in the benzylammonium perchlorate complex of **11** could not be located (Figure 5). This was likely due to the fact that the disorder of the ClO_4^- affected the intensity data significantly. However, a pyridine subunit was present in this molecule. Aside from the presence of the hydroxy hydrogen, a pyridine can be distinguished from a pyridone by the presence of a longer C–O interatomic distance (ca. 1.35 Å for a hydroxy group vs. ca. 1.25 Å for a carbonyl in the pyridone) and by the presence of

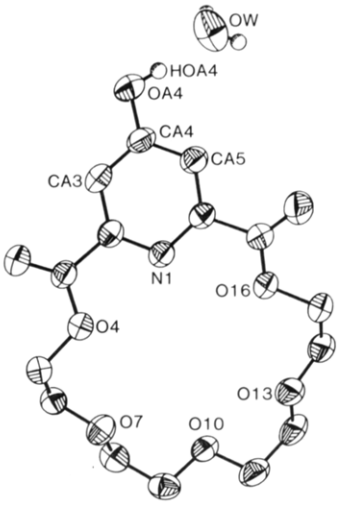

Figure 3. Computer drawing of **11**·H_2O. All hydrogen atoms except for HOA4 and the water hydrogen atoms are omitted for clarity.

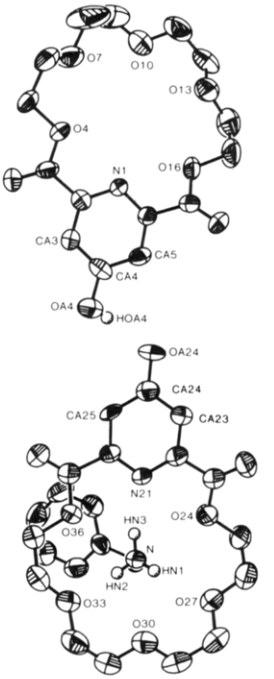

Figure 4. Computer drawing of the asymmetric unit of the phenylamine complex of **11**. All hydrogen atoms except HOA4 are omitted for clarity. The methene chlorides were omitted for the same reason.

equal C–C bond lengths in the pyridine as opposed to the presence of both double and single bonds in a pyridone. The C–C and C–O bond lengths in the six-membered subunit in all the structures studied are listed in Table I. The structure of the methyl derivative of **11** (Figure 6) was determined to establish definitive bond lengths for a

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Table II. Hydrogen Bond Data

molecule	X–H···A	X–A, Å	H···A, Å	X–H···A, deg
11	OA4 HOA4 OW	2.581 (5)	1.71 (3)	172 (3)
	OW HOW1 O13[a]	2.934 (4)	2.22 (4)	152.4
benzylamine complex of **11** (Figure 6)	N HN3 N21	2.911 (7)	2.02 (4)	169 (4)
	N HN1 O27	2.888 (7)	2.18 (5)	144 (5)
	N HN2 O33	2.872 (7)	2.01 (4)	175 (4)
	OA4 HOA4 OA24[a]	2.501 (7)	1.87 (4)	158 (4)
benzylammonium complex of **11** (Figure 6)	N H3N N1	2.892 (7)	1.83 (7)	172 (5)
	N H1N O7	2.933 (8)	2.24 (5)	170 (5)
	N H2N O13	2.853 (7)	1.99 (5)	173 (5)
	OA4 HOA4 OCl3	2.92 (1)	1.96 (1)	155 (5)

[a] A belongs to a symmetry related molecule.

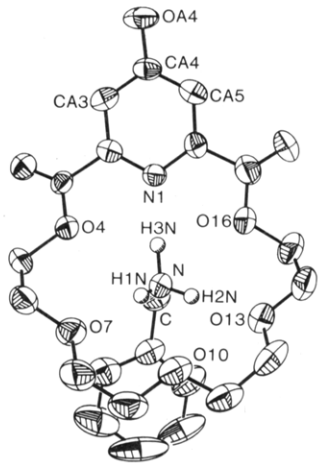

Figure 5. Computer drawing of the phenylammonium perchlorate complex of **11**. The perchlorate ion and all hydrogen atoms are omitted for clarity.

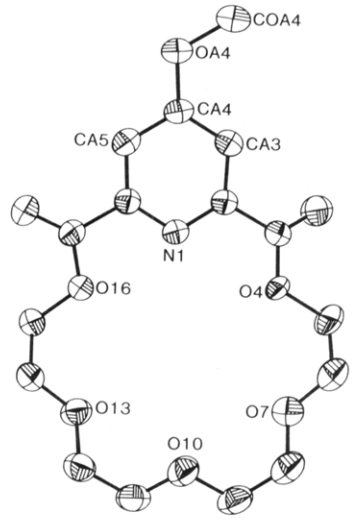

Figure 6. Computer drawing of the methyl derivative. All hydrogen atoms are omitted for clarity.

pyridine and these data are included in Table I. The data for **15**,[4] which was known to contain a pyridone, are also included in the table for comparison. Note that **11** has nearly equal C–C bond lengths and a long C–O (CA4–OA4) length in the pyridine unit while **15** has both short and long C–C bond lengths and a short C–O length. The benzylamine complex of **11** has units with each of these two types of C–C and C–O bond lengths. These results clearly show the 4-pyridone unit for **15** and a 4-hydroxypyridine unit for **11**. The complex of **11** and benzylamine has both of these types of six-membered rings.

The structures of **11**·H_2O and the methyl derivative of **11** ($R_1 = CH_3$) are similar (see Figures 3 and 6). The lattice parameters (Table V, supplementary material) are also similar but the compounds are not isostructural. The major difference between the two compounds is the presence of the water of hydration in the solid-state structure of **11**. The water is hydrogen bonded to the hydroxy group (OA4–HOA4···OW) and also to O13 of a symmetery related **11** (OW–HOW1···O13′). The hydrogen bond data are summarized in Table II. It is interesting to note that in the hydrate of compound **1** the water molecule is located in the cavity of the ring[3] while in the hydrate of **11** the water is outside the cavity.

The complexes of **11** with benzylamine (Figure 4) and benzylammonium perchlorate (Figure 5) involve similar host–guest coordination. In each case, the nitrogen of the guest interacts with the host through three hydrogen bonds. The acceptor atoms in the ligand are N21, O27, and O33 in the benzylamine complex (Figure 4) and N1, O7, and O13 in the benzylammonium perchlorate complex (Figure 5). Hydrogen bond data are listed in Table II for the two complexes. These data indicate that the nitrogen of benzylamine is basic enough to remove the hydroxy hydrogen in order to form a third hydrogen bond from N of the benzylamine to N21. This is analogous to the removal of a hydrogen atom from a crown ligand by an amine reported for a triazolo 18-crown-6 complex.[3] As discussed earlier the asymmetric unit of the benzylamine complex contains both a complexed and an uncomplexed ligand. The two molecules are linked together by a strong hydrogen bond (OA4···OA24, 2.501 (7) Å, see Table II). The presence of this interaction may account for the rather long CA24–OA24 double bond distance (1.289 (9) Å) and the fact that the differences between the single and double carbon–carbon bond lengths in the pyridone subunit in the complexed molecule are not as pronounced as they are in **15**.

Complexes of **4**, **7**, and **11**–**13** with organic ammonium cations and complexes of **11**–**13** with organic amines gave ^{1}H NMR spectra with temperature-dependent characteristics.[5,8] Free energy of activation ($\Delta G_c^{\ddagger}$) values were determined for these complexes and are listed in Table III. The $\Delta G_c^{\ddagger}$ values show that the 4-hydroxypyridine ligands (**11**–**13**) form kinetically more stable complexes with the organic ammonium salts ($\Delta G_c^{\ddagger}$ = 14.1 kcal/mol for the complex of **11** with benzylammonium perchlorate) than they do with the corresponding organic amines ($\Delta G_c^{\ddagger}$ = 12.3 kcal/mol for the complex of **11** with benzylamine). These results are different from those found for the complexes of proton-ionizable ligand **1**, which contains the triazole subcyclic unit. Ligand **1** formed a kinetically more stable complex with benzylamine (14.0 kcal/mol) than it

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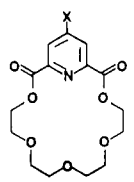
Table III. Free Energies of Activation ($\Delta G_c^{\ddagger}$, kcal/mol) in CD_2Cl_2[a] for the Interaction of New Ligands with Alkylammonium Salts and Amines

ligand	value	$BnzNH_3ClO_4$[b]	(S)-NapEt-NH_3ClO_4[b]	(R)-NapEt-NH_3ClO_4[b]
4	T_c, °C	25		
	$\Delta G_c^{\ddagger}$	13.6		
(S,S)-7	T_c, °C		7	31
	$\Delta G_c^{\ddagger}$		13.1	14.5
11	T_c, °C	35		
	$\Delta G_c^{\ddagger}$	14.1		
(S,S)-12	T_c, °C	6	−8	32
	$\Delta G_c^{\ddagger}$	14.2	13.4	14.5
(R,R)-13	T_c, °C	23	27	−1
	$\Delta G_c^{\ddagger}$	13.7	13.7	13.4

ligand	value	$BnzNH_2$	(S)-Nap-$EtNH_2$	(R)-Nap-$EtNH_2$
11	T_c, °C	−10		
	$\Delta G_c^{\ddagger}$	12.3		
(S,S)-12	T_c, °C	−52	−71	−46
	$\Delta G_c^{\ddagger}$	11.0	10.3	11.0
(R,R)-13	T_c, °C	−26	−32	−60
	$\Delta G_c^{\ddagger}$	11.4	11.3	10.3

[a] Varian SC-300 spectrometer was used to record all ^1H NMR spectra. T_c = coalescence temperature. $\Delta G_c^{\ddagger}$ values are ±0.2. The ester CH_2 or CH was the ^1H NMR probe for all compounds except 12 where the CH_3 peaks were the probe. [b] $BnzNH_3ClO_4$ = benzylammonium perchlorate, Nap$EtNH_3ClO_4$ = the hydrogen perchlorate salt of α-(1-naphthyl)ethylamine.

Table IV. Comparison of $\Delta G_c^{\ddagger}$ (kcal/mol) and T_c Values for the Interaction of Various 4-Substituted-Pyridino Crown Compounds with $BnzNH_3ClO_4$



	X				
	Cl[a]	H[a]	OCH_3[a]	OBnz	OH
T_c	0	10	25	25	35
$\Delta G_c^{\ddagger}$	12.5	13.0	13.7	13.6	14.1

[a] Reference 5.

did with benzylammonium perchlorate (10.4 kcal/mol).[3] We have shown that electron-donating groups substituted in the 4-position of the pyridino crown compounds greatly enhance the complexing abilities of these crown compounds with benzylammonium perchlorate.[5,8] The $\Delta G_c^{\ddagger}$ values in Table IV are seen to increase by ca. 0.5 kcal/mol as the 4-substituent is changed consecutively in the series chlorine, hydrogen, alkoxy, hydroxy. These results are consistent with the relative electron-donating properties of the substituent with the hydroxy group being the best electron donor.

An explanation for the fact that complexes of the 4-hydroxypyridine ligands with amines are kinetically less stable than those with ammonium salts is not so straightforward. In the case of complexes of 1 with amines, the resulting complex has a negative charge in the triazole ring which would be close to the ammonium cation, thus enhancing the stability of the complex. On the other hand, complexes of 11 with amines would have a negative charge on a 4-oxygen-substituted pyridine which would have the charge delocalized into a larger volume. Further work is needed to determine the possible importance of these effects in causing the differences in the stabilities for the two systems.

Chiral recognition by (S,S)-7 for the enantiomers of $NapEtNH_3ClO_4$ and (S,S)-12 and (R,R)-13 for both the enantiomers of $NapEtNH_3ClO_4$ and $NapEtNH_2$ is shown by the data in Table III. The S,S ligands formed kinetically more stable complexes with the R form of the amine or ammonium salt as was the case for other S,S-pyridino diester crowns.[8,9] Ligand (R,R)-13 formed more stable complexes with the S form of the amine or salt as did the unsubstituted R,R-pyridino crown.[8] The degree of chiral recognition does not seem to depend on the size of the substituent. Dimethyl-substituted ligands 7 and 12 show greater chiral recognition for the R form of the ammonium salt (1.4 and 1.1 kcal/mol difference, respectively) than diphenyl-substituted ligand 13 does for the S ammonium salt (0.3 kcal/mol difference). The fact that ligands 12 and 13 exhibited chiral recognition for the enantiomers of $NapEtNH_2$ is important. These are the first synthetic proton-ionizable ligands to show chiral recognition for organic amines. The ease of preparation of these compounds offers promise that they could find use in the resolution of optically active organic amines and amino acids.

Experimental Section

IR spectra were obtained on a Beckman Acculab 2 spectrophotometer. The proton NMR spectra were obtained on a JEOL FX-90Q spectrometer. All temperature-dependent ^1H NMR were obtained on a Varian SC-300 spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Molecular weights were obtained by osmometry on a Hitachi Perkin-Elmer Model 115 molecular weight apparatus. Optical rotations were determined 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 commercial sources where available. The following compounds were prepared by literature methods: (2S,12S)-4,7,10-trioxatridecane-2,12-diol,[10] 4,7,10-trioxatridecane-2,12-diol,[11] and (R,R)-(−)-1,11-diphenyl-3,6,9-trioxaundecane-1,11-diol by the same method as the corresponding S,S isomer.[9] All other starting materials were prepared according to the following procedures.

Dimethyl 4-(Benzyloxy)-2,6-pyridinedicarboxylate (16) (see Figure 2A). 4-Chloro-2,6-pyridinedicarbonyl chloride[5] (75.6 g, 0.32 mol) was added slowly to 3.5 equiv of sodium benzyl oxide in an excess of benzyl alcohol. The resulting mixture was stirred at 70 °C until a ^1H NMR analysis showed that the acid chloride had reacted (about 12 h). The reaction was then neutralized with acetic acid and the product was extracted with chloroform. The chloroform and excess benzyl alcohol were removed to yield a viscous oil. Methanol (500 mL) was added and the solution was cooled to −10 °C to yield 72.6 g (50.0%) of dibenzyl 4-(benzyloxy)-2,6-pyridinedicarboxylate as white crystals, mp 85–85.5 °C.

The dibenzyl ester (72.6 g, 0.16 mol) was added to 500 mL of anhydrous methanol containing 2 drops of cesium methoxide as a catalyst. The mixture was refluxed several minutes until it became clear. The reaction was then cooled to −10 °C to yield a crude white solid. The solid dimethyl ester 16 was recrystallized in base-free methanol to yield 34.9 g (72.4%) of white plates: mp 112–113 °C; IR (KBr) 1700, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 6 H, OCH_3), 5.16 (s, 2 H, OCH_2), 7.32 (s, 5 H), 7.80 (s, 2 H). Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02. Found: C, 63.63; H, 5.11.

Dimethyl 4-[(Tetrahydro-2-pyranyl)oxy]-2,6-pyridinedicarboxylate (17) (see Figure 2B). Chelidamic acid monohydrate (97%, 52.0 g, 0.275 mol) and a catalytic amount of sulfuric acid (10 mL) were dissolved in 700 mL of methanol and the mixture was refluxed for 20 h. After it was cooled to room temperature, the reaction mixture was neutralized with aqueous sodium carbonate solution and then acidified by concentrated hydrochloric

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acid. Water was added and the resulting mixture was extracted with dichloromethane to give a yellow solid. Crude dimethyl chelidamate was recrystallized from methanol: 31.7 g (55%); mp 169–169.5 °C (lit. mp 165 °C for the monohydrate);[12] IR (KBr) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.00 (s, 6 H, OCH_3), 7.52 (s, 2 H), 9.18 (br s, 1 H, OH). Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30. Found: C, 51.00; H, 4.37.

A mixture of dimethyl chelidamate (14.0 g, 0.0663 mol), 2,3-dihydropyrane (23.0 g, 0.273 mol), and pyridinium *p*-toluenesulfonate (PPTS)[13] (1.70 g, 6.76×10^{-3} mol) in 200 mL of dichloromethane was stirred for 16 h at room temperature. The reaction mixture was washed twice with 50-mL portions of 5% brine and then with 50 mL of water and dried over anhydrous sodium sulfate. The dichloromethane was evaporated to give a yellowish solid (19.7 g). The crude product was recrystallized from acetone to give **17** as white crystals: 15.95 g (81%); mp 120–121.5 °C; IR (KBr) 1710, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48–2.08 (m, 6 H), 3.50–3.84 (m, 2 H), 4.01 (s, 6 H), 5.69 (s, 1 H), 7.95 (s, 2 H). Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80. Found: C, 56.88; H, 5.95.

General Procedure for the Synthesis of Macrocyclic Compounds. The appropriate diester and glycol were combined in 300 mL of benzene in a flask equipped with a Soxhlet extraction apparatus. Molecular sieves (4 Å) were placed in the extraction thimble and the solution was refluxed through the Soxhlet for 12 h and then 5 drops of cesium methoxide catalyst were added. The reaction mixture was refluxed until the reaction was complete (TLC). Fresh molecular sieves were added as needed. Acetic acid was then added to neutralize the base and the benzene was removed under reduced pressure. Specific details are given for each compound.

16-(Benzyloxy)-3,6,9,12-tetraoxa-18-azabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione (3) and 16,33-Bis(benzyloxy)-3,6,9,12,20,23,26,29-octaoxa-35,36-diazatricyclo[29.3.1.^{14,18}]hexatriconta-1(35),14(36),15,17,31,33-hexaene-2,13,19,30-tetraone (10). The benzyl-blocked ester **16** (7.05 g, 0.023 mol) and 3.52 g (0.023 mol) of triethylene glycol were used. The reaction was refluxed for 3 days. The resulting crude oil was placed in a test tube and extracted with heptane on a continuous extractor. After a few hours, the heptane was removed and replaced with fresh heptane. The first batch of heptane was evaporated to give a white solid. The solid was recrystallized from acidified methanol to yield compound **3**: 0.5 g (5.4%); mp 139–140 °C; IR (KBr) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (m, 8 H, OCH_2), 4.44 (m, 4 H, $COOCH_2$), 5.20 (s, 2 H, $PhCH_2$), 7.40 (s, 5 H), 7.76 (s, 2 H). Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; mol wt, 387.3. Found: C, 61.91; H, 5.45; mol wt 369.8.

The extraction was then continued for 3 days. The second batch of heptane was evaporated, yielding compound **10** as a waxy solid: 1.48 g (8.3%); mp 158–168 °C; IR (film) 1720, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.3–3.9 (m, 16 H, OCH_2), 4.40 (m, 8 H, $COOCH_2$), 5.12 (s, 4 H, $PhCH_2$), 7.35 (s, 10 H), 7.72 (s, 4 H). Anal. Calcd for $C_{40}H_{42}N_2O_{14}$: C, 62.01; H, 5.46; mol wt, 774.8. Found: C, 61.91; H, 5.56; mol wt, 760.8.

19-(Benzyloxy)-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (4). The benzyl-blocked ester **16** (10.0 g, 0.033 mol) and 6.45 g (0.033 mol) of tetraethylene glycol were used. The reaction proceeded for 2 days, and the resulting oil was extracted from hexane for 15 h. The hexane was cooled to yield a white solid: 7.5 g (52.7%); mp 107–108.5 °C; IR (KBr) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 8 H, OCH_2), 3.90 (m, 4 H, OCH_2), 4.52 (m, 4 H, $COOCH_2$), 5.22 (s, 2 H, $PhCH_2$), 7.42 (s, 5 H), 7.92 (s, 2 H). Anal. Calcd for $C_{22}H_{25}NO_8$: C, 61.25; H, 5.84; mol wt, 431.4. Found: C, 61.13; H, 5.89; mol wt, 443.8.

19-[(Tetrahydro-2-pyranyl)oxy]-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (5). The tetrahydropyranyl-blocked ester **17** (6.22 g, 0.0211 mol) and tetraethylene glycol (4.09 g, 0.0211 mol) were used. The reaction proceeded for 4 days to give a slightly yellow solid. The crude product was recrystallized from acetone/hexane to give white crystals: 5.09 g (56.7%); mp 115.5–116.5 °C; IR (KBr) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48–2.08 (m, 6 H), 3.50–4.04 (m, 14 H, OCH_2), 4.42–4.64 (m, 4 H, $COOCH_2$), 5.67 (s, 1 H), 7.95 (s, 2 H). Anal. Calcd for $C_{20}H_{27}NO_9$: C, 56.46; H, 6.40; mol wt, 425.4. Found: C, 56.20; H, 6.28; mol wt, 414.

19-(Benzyloxy)-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (6). Benzyl-blocked ester **16** (5.0 g, 0.017 mol) and racemic 4,7,10-trioxatridecane-2,12-diol (3.69 g, 0.017 mol) were reacted for 5 days. The product was extracted with hot hexane to yield white crystals: 2.1 g (28.4%); mp 111–113 °C; IR (KBr) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (d, 6 H, CH_3), 3.65 (m, 12 H, OCH_2), 5.16 (s and m, 4 H, $PhCH_2$ and COOCH), 7.32 (s, 5 H), 7.80 (s, 2 H). Anal. Calcd for $C_{24}H_{29}NO_8$: C, 62.73; H, 6.36; mol wt, 459.5. Found: C, 62.47; H, 6.48; mol wt, 452.

19-(Benzyloxy)-(4*S*,14*S*)-(+)-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (7). Benzyl-blocked ester **16** (5.0 g, 0.017 mol) was reacted with 3.69 g (0.017 mol) of (2*S*,12*S*)-4,7,10-trioxatridecane-2,12-diol for 6 days. The product was extracted with hot hexane to yield a white solid: 2.72 g (34.8%); mp 98–99 °C; $[\alpha]^{25}_D$ +2.07° (*c* 0.97, $CHCl_3$); IR (KBr) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (d, 6 H, CH_3), 3.40–3.85 (m, 8 H, OCH_2), 3.96 (m, 4 H, OCH_2), 5.22 (s and m, 4 H, $PhCH_2$ and COOCH), 7.42 (s, 5 H), 7.84 (s, 2 H). Anal. Calcd for $C_{24}H_{29}NO_8$: C, 62.73; H, 6.36; mol wt, 459.5. Found: C, 62.59; H, 6.45; mol wt, 481.8.

19-(Benzyloxy)-(4*S*,14*S*)-(−)-4,14-diphenyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (8). Benzyl-blocked ester **16** (3.91 g, 0.013 mol) and 4.50 g (0.013 mol) of (*S,S*)-(+)-1,11-diphenyl-3,6,9-trioxaunndecane-1,11-diol[9] were used. The reaction proceeded for 10 days, and the product was extracted with hot hexane. The product was further purified by column chromatography and recrystallized from hexane to yield a white solid: 0.61 g (8.2%); mp 88–89 °C; $[\alpha]_D$ −0.512° (*c* 1.02, $CHCl_3$); IR (KBr) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.4–4.1 (m, 12 H, OCH_2), 5.16 (s, 2 H, $PhCH_2$), 6.10 (m, 2 H, COOCH), 7.35 (m, 15 H), 7.72 (s, 2 H). Anal. Calcd for $C_{34}H_{33}NO_8$: C, 69.97; H, 5.70; mol wt, 583.6. Found: C, 69.40; H, 5.89; mol wt, 587.

22-(Benzyloxy)-3,6,9,12,15,18-hexaoxa-24-azabicyclo[18.3.1]tetracosa-1(24),20,22-triene-2,19-dione (9). Benzyl-blocked ester **16** (5.0 g, 0.017 mol) was reacted with 4.78 g (0.017 mol) of pentaethylene glycol for 7 days. The product was extracted using hot hexane to yield a white solid: 1.70 g (21.5%); mp 91–92 °C; IR (KBr) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66 (s, 4 H, OCH_2), 3.6–3.8 (m, 4 H, OCH_2), 3.78 (s, 4 H, OCH_2), 3.92 (m, 4 H, OCH_2), 4.52 (m, 4 H, $COOCH_2$), 5.22 (s, 2 H, $PhCH_2$), 7.42 (s, 5 H), 7.88 (s, 2 H). Anal. Calcd for $C_{24}H_{29}NO_9$: C, 60.62; H, 6.15; mol wt, 475.5. Found: C, 60.63; H, 6.21; mol wt, 462.2.

General Procedure for the Reduction of the Benzyloxy Crown Compounds. The benzyloxy crown compound was added to about 200 mL of isopropyl alcohol with a catalytic amount of 10% palladium on carbon. The crown was reduced in a Parr hydrogenator with 50 psi of hydrogen. The solvent was removed and the product was recrystallized from anhydrous, base-free methanol. Specific details are given for each compound.

19-Hydroxy-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (11). Compound **4** (3.0 g, 0.007 mol) and 300 mg of 10% palladium on carbon were used. Reduction was complete in 3 h yielding a white solid: 1.82 g (76.2%); mp 142–143 °C; IR (KBr) 1715 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 3.90 (s, 8 H, OCH_2), 3.94 (m, 4 H, OCH_2), 4.74 (m, 4 H, $COOCH_2$), 7.46 (s, 2 H). Anal. Calcd for $C_{15}H_{19}NO_8 \cdot H_2O$: C, 50.14; H, 5.89. Found: C, 50.01; H, 5.98.

Compound **11** was also prepared by stirring a mixture of 1.08 g (2.54×10^{-3} mol) of **5** and 65 mg (2.59×10^{-4} mol) of PPTS in 20 mL of ethanol for 3 h at 55–60 °C. The mixture was concentrated to give a slightly yellow oil. The crude product was recrystallized from methanol to give compound **11** as a monohydrate: 632 mg (69%); mp 143–144 °C. The IR and ^1H NMR spectra were identical with those reported above.

19-Hydroxy-(4*S*,14*S*)-(−)-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (12). Compound **7** (0.45 g, 0.001 mol) and 120 mg of 10% palladium on carbon were reacted for 1 h. The product was a white solid: 0.11 g (29.8%); mp 95–97 °C; $[\alpha]^{25}_D$ −18.3° (*c* 0.88, $CHCl_3$); IR (KBr) 1720 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 1.32 (d,

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6 H, CH_3), 3.4–3.8 (m and s, 12 H, OCH_2), 5.24 (m, 2 H, COOCH), 7.18 (s, 2 H). Anal. Calcd for $C_{17}H_{23}NO_8 \cdot H_2O$: C, 52.71; H, 6.50. Found: C, 52.83; H, 6.59.

19-Hydroxy-(4*R*,14*R*)-(−)-4,14-diphenyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (13). Tetrahydropyranyl-blocked ester 17 (3.47 g, 1.17×10^{-2} mol) and 4.07 g (1.17×10^{-2} mol) of (2*R*,12*R*)-4,7,10-trioxatridecane-2,12-diol were reacted as above to 19-[(tetrahydro-2-pyranyl)oxy]-3,6,9,12,15-pentaoxa-21-azobicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione. 19-[(tetrahydro-2-pyranyloxy]-3,6,9,12,15-pentaoxa-21-azobicyclo[15.3.1]heneicosa-1-(21),17,19-triene-2,16-dione. The reaction mixture was separated by GPC (Bio-Beads S-X2) into 10 fractions. The fraction containing the tetrahydropyranyl-blocked compound (1.4 g) was dissolved in 20 mL of ethanol, PPTS (60 mg) was added, and the solution was stirred for 2 h at 50–60 °C. After evaporating the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$). The product was recrystallized from acetone/hexane to give 185 mg (3.1%) of a white solid: mp 119–122 °C; $[\alpha]^{25}_D$ −38.9° (*c* 0.314, $CHCl_3$); IR (KBr) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.4–4.1 (m, 15 H), 6.08 (t, J = 4.7 Hz, 2 H), 7.08 (s, 2 H), 7.35 (s, 10 H). Anal. Calcd for $C_{27}H_{27}NO_8 \cdot H_2O$: C, 63.40; H, 5.71; mol wt, 511.5. Found: C, 63.43; H, 5.53; mol wt, 478.

22-Hydroxy-3,6,9,12,15,18-hexaoxa-24-azabicyclo[18.3.1]-tetracosa-1(24),20,22-triene-2,19-dione (14). Compound 9 (0.4 g, 0.0008 mol) was reduced with 50 mg of palladium on carbon for 5 h. The product was an off-white solid: 0.24 g (77.6%); mp 85–89 °C; IR (KBr) 1720 and 3550 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 3.64 (s, 4 H, OCH_2), 3.70 (s, 4 H, OCH_2), 3.7 (m, 4 H, OCH_2), 3.88 (m, 4 H, OCH_2), 4.56 (m, 4 H, $COOCH_2$), 7.24 (s, 2 H). Anal. Calcd for $C_{17}H_{23}NO_9 \cdot H_2O$: C, 50.62; H, 6.25. Found: C, 51.29; H, 6.37.

General Procedure for the Preparation of Complexes with Macrocyclic Ligands. Two methods were employed to form the macrocyclic complexes. Method A was used with the amine complexes of compound 12, and method B was used with the ammonium salt complexes of compounds 7, 12, and 13. Three amines and their hydrogen perchlorate salts were used: benzylamine, (*R*)-α-(1-naphthyl)ethylamine and (*S*)-α-(1-naphthyl)-ethylamine.

Method A. Equimolar solutions of 12 and the amine in chloroform-d_1 (0.500 mL) were mixed in an NMR tube. A ^1H NMR spectrum was taken and the integration was checked to see if the crown to amine ratio was 1:1. If not, the solution of amine or crown was added until ^1H NMR spectrum showed that the two compounds were present in equimolar amounts. The solvent was then removed.

Method B. Equimolar amounts of the macrocycle and the amine salts were weighed to an accuracy of 0.1 mg and added together.

The Complex of 11 with Benzylamine. Compound 11 (384 mg, 1.07×10^{-3} mol) and benzylamine (229 mg, 2.14×10^{-3} mol) were dissolved in dichloromethane. Toluene was added to the solution and the dichloromethane was slowly evaporated to give a slightly yellow solid. The solid was twice recrystallized from dichloromethane–toluene to give 122 mg (12%) of white crystals used for an X-ray study: mp 180.5–181.5 °C; IR (KBr) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.4–3.9 (m, 29 H), 4.28–4.56 (m, 8 H), 5.30 (s, 4 H, CH_2Cl_2), 7.0–7.4 (m, 5 H), 7.58 (s, 4 H), 7.8 (br, 1 H). Anal. Calcd for $C_{37}H_{47}N_3O_{16} \cdot 2.2CH_2Cl_2$: C, 48.21; H, 5.30. Found: C, 48.20; H, 5.49.

The Complex of 11 with Benzylammonium Perchlorate. Compound 11 (121.5 mg, 3.38×10^{-4} mol) and benzylammonium perchlorate (70.2 mg, 3.38×10^{-4} mol) were combined in dichloromethane–toluene. The product was recrystallized to give 116 mg (63%) of white needles: mp 206–207 °C; IR (KBr) 1730 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.1–3.88 (m, 15 H), 4.11 (s, 2 H, $C_6H_5CH_2$), 4.28–4.56 (m, 4 H), 7.41 (s, 5 H), 7.62 (s, 2 H), 8.1 (br, 1 H). Anal. Calcd for $C_{22}H_{29}N_2O_{12}Cl$: C, 48.14; H, 5.33. Found: C, 47.96; H, 5.18.

X-ray Determination. Single crystals suitable for X-ray structural studies were prepared in our laboratory. Data for unit cell determinations and also for the structural studies were collected utilizing a Nicolet R3 autodiffractometer with graphite monochromated Cu radiation (λ = 1.541 82 Å). Lattice parameters for each structure were determined by a least-squares technique involving centered 2θ values. The space groups for the four crystals were determined by examining systematic extinction data and intensity statistics. Single crystal data were obtained by using a θ–2θ variable scan rate technique. Three standard reflections were measured at 100-reflection intervals. The only compound that showed a significant and systematic change in the standard intensities was the benzylamine complex of 11. The drop in intensity was likely caused by the loss of solvent molecules (CH_2Cl_2) from the crystal. The composition based on a density measurement indicated there were 2.6 solvent molecules for each $2(C_{15}H_{19}NO_8) \cdot C_7H_9N$ unit while chemical analysis showed there were 2.2 CH_2Cl_2 molecules for the same unit. This difference in composition can be explained by the length of storage of the crystals before analysis. In support of this proposition, it was found that the intensities of the standard reflections continued to drop for several days after data collection was completed. Data with $I < 2\sigma(I)$ were considered unobserved. The crystal data are summarized in Table V in the supplementary material. Trial models for the four structures were obtained by using direct methods and the structures were refined by using a cascading least-squares technique. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms that were involved in hydrogen bonds or bonded to the oxygen of the pyridine moiety were refined isotropically. Positions for all other hydrogens were calculated on the basis of stereochemical considerations and were allowed to ride on the carbon atoms to which they were bonded during the refinement process. The ClO_4^- in the benzylammonium perchlorate complex which was disordered was refined as a tetrahedral rigid body. The rather large thermal motion of some of the ring atoms of the polyether molecules indicated some disorder (i.e., O4 and C5 of the methyl derivative of 11), but inasmuch as it was not very relevant to the study it was not resolved. The final difference map of each compound did not contain any unexpected peaks. All crystallographic calculations were performed by using the SHELXTL[14] crystallography package, which is part of the Nicolet R3 system.

Determination of $\Delta G^{\ddagger}$ Values. The $\Delta G^{\ddagger}$ values for the complexes of compounds 7 and 11–13 were obtained by using the following experimental sequence. First, a ^1H NMR spectrum of the complex (about 10 mg) in dichloromethane-d_2 was obtained. Next, the probe temperature was lowered until one or more sets of peaks separated. Successive ^1H NMR spectra were taken while the temperature was raised to about 20 °C above the temperature at which the peaks coalesced. The $\Delta G^{\ddagger}$ values were calculated from the $\Delta\nu$ and T_c values by the procedure of Sutherland[15] and are shown in Table III.

Determination of pK_1^H, pK_2^H, and ΔH_n^H Values. Values of pK_n^H and related ΔH_n^H for the consecutive ionization of protons from the protonated form of compound 11 (H_2L^+) were determined in water solvent for reactions 1 and 2 by using a TRONAC

$$H_2L^+ = HL + H^+ \quad (1)$$

$$HL = L^- + H^+ \quad (2)$$

450 isoperibol calorimeter. A 0.005 M solution of 11 was titrated with either a standard lithium hydroxide solution or with a standard aqueous HCl solution, depending on which pK^H value was to be determined. The data were analyzed by using a nonlinear least-squares minimization program, EQDH. The values obtained were pK_1^H = 8.49 (ΔH_1^H = 4.46 kcal/mol, ΔS_1^H = −23.76 cal/(deg mol)) and pH_2^H = 1.70 (ΔH_2^H = 0.35 kcal/mol, ΔS_2^H = −6.58 cal/(deg mol)). These values are considered to be approximate because only one run was made due to limited availability and instability of compound 11.

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Supplementary Material Available: Table of crystal and experimental data for X-ray structural studies (Table V), tables of positional and thermal parameters of the atoms of $11 \cdot H_2O$, methylsubstituted 11, [benzylamine complex of 11]$\cdot 2.6CH_2Cl_2$, and [benzylammonium complex of 11] + ClO_4^- (Tables VI, VII, VIII, and IX, respectively), and tables of selected bond lengths and angles of those compounds (Tables X, XI, XII, and XIII, respectively) (13 pages). Ordering information is given on any current masthead page.

(*E*)-1-Bromo-3,3-diethoxy-1-propene (Diethyl Acetal of 3-Bromoacrolein). A Versatile Synthon for the Synthesis of Furans, Butenolides, and (*Z*)-Allyl Alcohols

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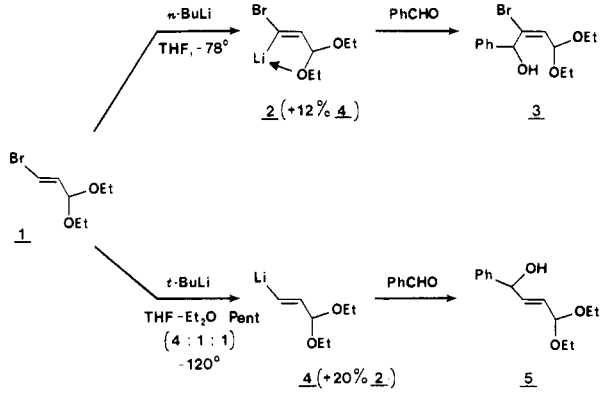
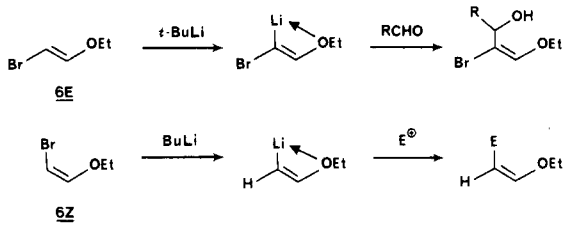
A convenient preparation of the title compound allowed a study in which the α-lithio-α-bromovinyl acetal **2** could be evaluated as a precursor to furans, butenolides, and (*Z*)-allyl alcohols. Reaction of the lithio derivative with aldehydes, ketones, and alkyl halides took place in a convenient manner. The bromine was either transformed at a later stage to an alkyl group or reduced to hydrogen with tin hydrides. The carbonyl adducts of **2** could be transformed, on mild hydrolysis, to butenolides or 2,3-disubstituted furans. An interesting solvent system (1:1:1 THF–Et_2O–pentane) allowed vinyl proton abstraction and halogen–metal exchange to take place in one pot.

During the course of our synthetic work on the total synthesis of (±)-maytansine and (–)-maysine,[1] we utilized an interesting version of 3-bromoacrolein, namely the diethyl acetal **1**, which, although prepared earlier,[2] was difficult to reproduce on multigram scale. We were successful in preparing this compound on 20-g scale[1] and now report our findings wherein **1** can serve as a useful precursor to furans, butenolides, and (*Z*)-allyl alcohols. These compounds have attracted considerable attention[3] in recent years due to their presence in a number of naturally occurring materials.



When the bromo acetal **1** was treated with *n*-butyllithium in THF (–78 °C), followed by the addition of benzaldehyde after 5 min, the bromoallylic alcohol **3** was obtained accompanied by 12% of the debromoallylic alcohol **5**. The bromo alcohol **3** was isolated in 60–65% yield after chromatography. On the other hand, when **1** was treated with 2.3 equiv of *tert*-butyllithium[4] in Trapps solvent[5] at –120 °C and benzaldehyde added, the debromoallylic alcohol **5** was isolated (61%) accompanied by 20% of the bromo alcohol **3**. Thus, at lower temperatures halogen–metal exchange was the predominant process, whereas with the less encumbered base (*n*-BuLi) at higher temperature, proton abstraction became the major event.[4] Halogen–metal exchange (**1** → **4**) has been observed on numerous occasions[6] while deprotonation of α-halovinyl compounds (**1** → **2**) affording α-lithio-α-halovinyl derivatives has been examined less frequently. Schlosser has shown[7] that the (*E*)-bromovinyl ether **6E** is deprotonated with strong base affording the bromovinyl adducts on addition to carbonyls. On the other hand, the (*Z*)-



bromovinyl ether **6Z** undergoes the expected halogen–lithium exchange with high stereoselectivity. More recently, Smithers[8] reported the behavior of the 1,1-dibromovinyl ether **7** and showed that the α-lithio-α-bromo derivative **8** could be formed and induced to react with

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