Crown Cation Complex Effects. 20. Syntheses and Cation Binding Properties of Carbon-Pivot Lariat Ethers[1]

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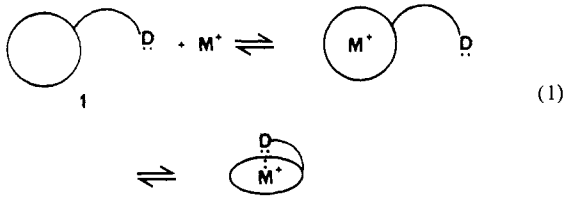
Abstract: In an effort to devise synthetic cation binders that will mimic the behavior of naturally occurring ionophores such as valinomycin, we have prepared approximately 30 macrocylic (crown) polyethers bearing flexible side chains attached to the macro ring at carbon. In many of these "carbon-pivot" compounds, the side chain contains one or more neutral donor groups that, if in a suitable geometrical arrangement, may provide additional solvation to the macro-ring-bound cation. Although such donors often enhanced the cation binding ability, overall, the increases in stability constants were modest. The physical resemblance and concept of "roping and tying" the cation suggest the name "lariat ethers". Syntheses of these molecules and binding by them of Na^+ and K^+ cations are reported and conclusions drawn about the structural requirements and cation binding efficacy of these materials.

Two observations concerning the naturally occurring cyclic antibiotic ionophore valinomycin[2] are quite striking: First, although it is a 36-membered-ring depsipeptide, it is selective for potassium cation.[3] In crown ether chemistry, one expects an 18-membered ring to be selective for potassium and other ring sizes to favor cations of radii similar to the macrocycle's "hole".[4] Second, the complex formed between valinomycin and K^+ is three-dimensional, i.e., the ligand wraps around the cation tennis-ball-seam fashion.[5] Nevertheless, the kinetics[6] for this three-dimensional, cryptand-like behavior occurs much more rapidly than does the corresponding reaction between K^+ and [2.2.2]cryptand, the latter also being a three-dimensional cation binder.[7]

In light of these two observations, it occurred to us that in the development of synthetic models for naturally occurring ionophores, it might be useful to incorporate these two properties. We therefore undertook the design and synthesis of a group of macrocyclic polyethers replete with one or more donor groups appended to the macroring as part of a flexible arm. It was thought that the macroring would envelop the cation in the fashion normally associated with crown ether binding and the donor groups attached to the flexible side arm would further solvate the bound cation. This ability of such molecules to "rope and tie" the cation as a lasso is used to bind an animal suggested the name "lariat ethers".[8] The generalized structure is illustrated (**1**), and the kinetic concept is shown in eq 1.



(1)

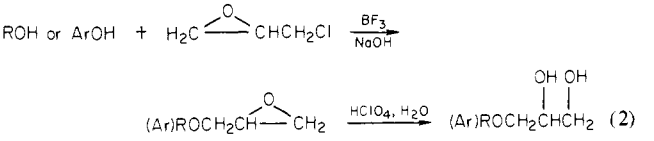
Equation 1 is meant only to illustrate the notion and is undoubtedly oversimplified. Furthermore, we have not as yet made accurate determinations of any of the rate constants. Nonetheless, we have obtained some information on the dynamics of these systems and this is presented elsewhere.[9]

Results and Discussion

Synthesis. During the initial studies, two decisions were required. First, an appropriate "pivot" unit had to be selected. This unit would be incorporated in the crown and would also serve as a binding point for the side arm. Second, various donor groups (D: in eq 1) were considered. Since it was hoped that such compounds might also be utilized in phase-transfer catalytic processes wherein the side arm is part of a tether between macroring and a polymer, it was necessary to make the pivot molecule as inexpensive as possible. Glycerol therefore seemed a logical choice.

The glycerol unit could be incorporated in either of two obvious ways. Primary and secondary hydroxyls could be used as nucleophiles for formation of the ring, leaving a remaining primary hydroxyl for attachment of the side arm and donor group. Thus, a standard ethylenoxy unit could be incorporated into the ring, and a hydroxymethyl group would be available for side arm modification. Alternatively, the glycerol unit may be incorporated into the macroring through both of the primary hydroxyls and the side arm attached via the secondary hydroxyl. The latter situation would result in a crown having a three-carbon unit as part of the ring, and such structures are subject to greater conformational problems than are the ethylenoxy unit.[10] The former situation was therefore judged most suitable for the first studies.

A number of side arms can be incorporated quite readily. Priority was given to side arms having ethylenoxy side chain units so that the complexes would have as high a symmetry as possible. Methoxyethanol, methoxyethoxyethanol, and congeners as well as substituted phenols were chosen. The necessary precursor unit was prepared by treating either the alcohol or phenol with epichlorohydrin.[11] In the case of alcohol precursors, the chlorohydrin was isolated and then treated with 50% NaOH to give the glycidyl ether. In the case of phenolic precursors, the conversion to the glycidyl ether could be accomplished in a single step. Hydrolysis with dilute perchloric acid afforded the diol, as illustrated in eq 2.



(2)

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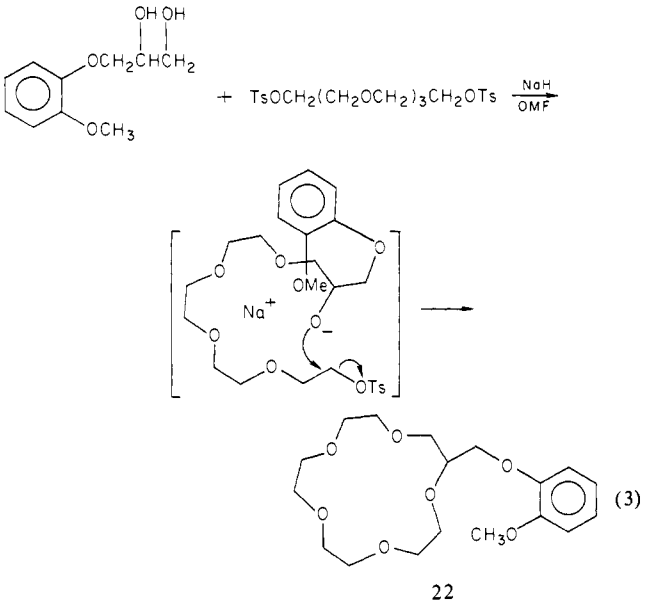
Treatment of the diol with either tetraethyleneglycol ditosylate or dimesylate (1.0 equiv) and NaH (2.2 equiv) in THF afforded the 15-crown-5 derivatives in approximately 30–70% yield after chromatography (Al_2O_3). The yields did not depend appreciably on the leaving group, but workup was occasionally simplified when the dimesylate was used (see Experimental Section).

One of the basic compounds for the formation of several lariat ether derivatives is hydroxymethyl-15-crown-5 (**3**). This compound has been reported previously by Montanari and Tundo, who prepare it from the corresponding *tert*-butyl ether (**8**).[12] Our own approach was to prepare the benzyl ether (**21**) and hydrogenolyze over Pd/C catalyst. A similar procedure has been reported by Czech.[13] Since **21** was required as an intermediate in the synthesis of inter alia **9–13**, it was prepared a number of times. Although we obtained a yield of 62% in one reaction, 38% was typical. Hydrogenolysis of most benzyl ethers we have prepared proceeded in essentially quantitative yield. Occasionally, cleavage was less effective than desired, and the expedient of adding a small amount of concentrated HCl proved efficacious.

Yields were not appreciably altered by the presence of an aliphatic rather than an aromatic side arm (alcohol vs. phenol precursor), but the presence of a donor group at a distance from the crown's hole suitable for a secondary interaction was important. It was postulated by Greene[14] that a template effect was responsible for the high yields observed in these ring-formation reactions. Evidence for the template effect has accumulated,[15] although there have also been skeptics of this theory.[16] In any event, in molecules designed with side arms capable of secondary binding through donors groups in them, one might anticipate that yields would be high (more organization in the transition state leading to cycle) when such donor groups are present in contrast to the situation prevailing in their absence. An example of this is shown in eq 3 in which the cyclization to yield 2-((2-methoxyphenoxy)methyl)-15-crown-5 (**22**) is illustrated. When the 2-methoxy group is present, the cycle is formed in about 70% yield, whereas in its absence (**20**), or when the methoxy group is in the 3- (meta, **23**) or 4- (para, **24**) position, yields are lower (see Table I). The yield reported for the cyclization of 15-crown-5 (**1**), the parent system, is 29%.[17]



(3)

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Binding Studies. Because of our interest in phase-transfer catalysis (ptc) and the hope that these molecules might be of utility in that application, we examined the cation binding of the lariat ethers in a system that has many of the properties of ptc, namely the dichloromethane–water system. Binding was assessed by the picrate extraction technique[19] in which the cation is transported from water to CH_2Cl_2 by the crown. The yellow picrate anion accompanies the crown complexed cation, and the extent of extraction can be assessed colorimetrically. The resulting binding "constants" are actually the percent of metal picrate that partitions from the aqueous to the organic phase due to the crown's influence. Such measurements are of value primarily for comparative purposes since they do not represent a true homogeneous equilibrium binding situation. Binding data of this and the type described below may be found in the table. It should also be noted that the cation binding ability of these ligands as expressed in extraction constants also reflects differences in lipophilicity. This is not a variable in the homogeneous stability constants since no partitioning between two immiscible solvents is involved.

A more appropriate measure of a ligand's binding ability may be obtained by measuring its equilibrium binding (or stability) constant, K_s (eq 4). We have done this for a number of compounds using an electrochemical technique.[19] The conductivity of a salt solution is measured before and after addition of the ligand, and the association constant is calculated from the voltage (conductivity) difference.[19a] The stability constants were determined in polar solvents, primarily 90% MeOH or anhydrous MeOH. The stability constants for simple crowns are largest in the least polar solvents and decrease with increasing solvent polarity. In fact, we have recently shown that log K_s for the reaction between either 15-crown-5 or 18-crown-6 and Na^+ increases almost linearly as the weight percent of H_2O in MeOH is decreased.[20] Although binding constants would be much higher in nonpolar solvents like $CHCl_3$ and differences would be more dramatic, our interest in the potential biological activity of these compounds suggested that the use of a medium as close to water as practical would be efficacious.

$$\text{ligand} + M^+ \overset{K_s}{\rightleftharpoons} [\text{ligand-M}]^+ \qquad (4)$$

Several facts about the effect of side chains in these systems emerge from a perusal of the data shown in Table I. First, it appears that placement on the macroring of an arm that is sterically incapable of donation to a ring-bound cation generally reduces, rather than enhances, binding. This is most apparent in the extraction constants where differences in binding tend to be magnified relative to stability constants determined in polar solution.[8] Thus, extraction of sodium picrate by **2**, **3**, **4**, **11**, and **20** is inferior to that of 15-crown-5 (**1**). As the lipophilicity of the side chain increases, however, irrespective of the availability of donor groups thereupon, the extraction constants rise. As noted above, this is due, in part, to the partition aspect of extraction constants. The extraction constant for 2-(2-butoxymethyl)-15-crown-5 (**7**, 10.3%) is higher than the constant for 2-(methoxymethyl)-15-crown-5 (**4**, 5.1%) or 15-crown-5 (**1**, 7.6%).

Both extraction and stability constants for ester derivatives of **3** are diminished relative to 15-crown-5. In this case, there is presumably an unfavorable steric interaction between cation and side chain, as seen for both alkyl and simple alkoxy derivatives. The potential advantage of the carbonyl group is apparently negated by the conformational preference of the C–O–CO– unit to be *E* rather than *Z*.[21]

As noted above, binding differences tend to be magnified in the nonpolar solutions relative to polar ones.[8b] Even so, it appears that the stability constants for nearly all of the carbon-pivot lariat ethers are disappointingly small. We feel that this is probably due to hydrogen bonding of the side chain heteroatoms by the

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(13) Czech, B. *Tetrahedron Lett.* **1980**, *21*, 4197.
(14) Greene, R. N. *Tetrahedron Lett.* **1972**, 1793.
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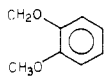
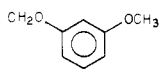
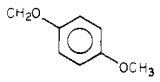
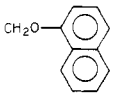
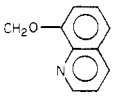
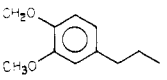
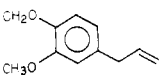
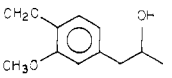
(20) Dishong, D. M.; Gokel, G. W. *J. Org. Chem.* **1982**, *47*, 147.
(21) (a) Gandour, R. D. *Bioorg. Chem.* **1981**, *10*, 169. (b) Patai, S., Ed. "Chemistry of the Ester Group Supplement E"; Wiley: New York, 1980.

Table I. Complexation Behavior of Carbon-Pivot Lariat Ethers

no.	side arm[a]	yield,[b] %	extraction const[c] % Na^+	extraction const[c] % K^+	log K_s Na^+ [d] 90% MeOH	log K_s Na^+ [d] MeOH	log K_s K^+ [d] 90% MeOH	log K_s K^+ [d] MeOH
1	H	29	7.6	5.7	2.97	3.27	3.18	3.60
2	CH_2CH_3	49	nd[e]	nd	2.70	nd	nd	nd
3	CH_2OH	93	2.7	4.4	2.70	2.94	2.93	3.09
4	CH_2OCH_3	23	5.1	3.3	2.81	3.03	2.78	3.27
5	$CH_2OCH_2CH{=}CH_2$	34	7.0	4.4	2.73	nd	2.73	nd
6	$CH_2O(CH_2)_2CH_3$	82	4.3	1.3	2.84	nd	nd	nd
7	$CH_2O(CH_2)_3CH_3$	64	10.3	10.1	nd	nd	nd	nd
8	$CH_2OC(CH_3)_3$	46	3.8	4.5	2.81	nd	nd	nd
9	$CH_2OSi(CH_3)_3$	68	7.3	8.2	nd	nd	nd	nd
10	$CH_2O(CH_2)_{15}CH_3$	84	nd	nd	nd	nd	nd	nd
11	CH_2OOCCH_3	68	3.6	5.4	2.36	nd	nd	nd
12	$CH_2OOC(CH_2)_2CH_3$	62	3.9	4.5	nd	nd	nd	nd
13	$CH_2OOC(CH_2)_{14}CH_3$	32	3.1	3.2	nd	nd	nd	nd
14	$CH_2OCH_2CH_2OCH_3$	61	18.0	13.7	2.83	3.01	2.97	3.20
15	$CH_2OCH_2CH_2OBu$	55	11.2	10.9	2.94	3.09	nd	3.37
16	$CH_2OCH_2CH(OH)CH_3$	94	10.0	5.1	2.75	3.14	nd	nd
17	$CH_2O(CH_2CH_2O)_2CH_3$	48	15.7	24.4	2.94	3.13	3.21	3.50
18	$CH_2O(CH_2CH_2O)_3H$	94	15.3	26.5	2.80	3.04	nd	3.45
19	$CH_2O(CH_2CH_2O)_3CH_3$	70	15.7	32.1	2.94	3.09	nd	3.52
20	CH_2OPh	34	4.0	4.3	2.51	nd	nd	nd
21	CH_2OCH_2Ph	36	7.9	5.8	2.74	nd	nd	nd
22		70	15.7	10.2	2.97	3.24	3.11	3.47
23		57	nd	nd	2.57	2.89	2.86	nd
24		29	6.4	10.7	2.56	nd	2.73	nd
25		31	nd	nd	2.74	nd	nd	nd
26		57	nd	nd	3.39	3.72	3.19	nd
27	CH_2OOCPh	80	4.6	6.5	nd	nd	nd	nd
28	$CH_2OOCC_6H_4OCH_3$-4	74	nd	nd	nd	nd	nd	nd
29	$CH_2OOCC_6H_4NO_2$-4	78	nd	nd	nd	nd	nd	nd
30		99	24.3	17.6	2.94	nd	nd	nd
31		62	15.7	10.2	2.86	nd	3.20	nd
32		97	14.2	12.8	2.93	nd	3.29	nd

[a] Indicates residue attached to the 2-position of 15-crown-5. [b] Yield is for the step leading to the indicated product and not necessarily for the cyclization step, see Experimental Section for details. [c] See text and ref 19. [d] See Experimental Section and ref 8b. [e] nd, not determined.

solvent, reducing the effectiveness of donation from the side arm to the ring-bound cation and to the relative lack of flexibility in these structures. Where the heteroatom donor group on the side arm is held in proximity to the ring and the degrees of freedom for that side arm are minimized as in the case of **26**, better binding is observed (log K_s = 3.39 for **26** vs. 2.97 for **1**).

Another interesting aspect of the binding is that both extraction and stability constants are greater for potassium than for sodium cations when more than one potential donor group is available in the side arm. A comparison of **14** with **17** demonstrates this clearly. The single donor atom in **14** (the first is sterically inaccessible to the ring-bound cation) provides an environment that favors sodium. Potassium is favored by **17**, which can center two donor atoms over the ring-bound species. Implicit in this is that K^+ probably "perches" on the macroring whereas Na^+ "nests" in it. This behavior for multidonor ionophores parallels the behavior of the highly flexible naturally occurring systems like yalinomycin,[5,22] nonactin,[23] or monensin.[24]

Biological Activity. We have noted above that an important motivation in the design of lariat ethers was to develop molecules that would prove biologically active. The design was based primarily on observations concerning natural ionophores and on kinetic assumptions that remain to be confirmed. Nevertheless, many of the molecules reported here are active in certain test systems. Many, if not most, of the compounds illustrated in the

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(23) Kilbourn, B. T.; Dunitz, J. D.; Pioda, L. A. R.; Simon, W. *J. Mol. Biol.* **1967**, *30*, 559.
(24) Pinkerton, M.; Steinrauf, L. K. *J. Mol. Biol.* **1970**, *49*, 533.

table have proved active in tracheal smooth muscle systems.[25] Whether the activity is due to ionophoric activity or to a coincidental shape relationship to some receptor is not currently known. Neither is it currently clear whether the molecules are acting in the membrane (lipid) or in the essentially aqueous cytosol of the cell. The enhanced "binding" as measured in the picrate extraction technique may mean that these molecules could be effective in transferring a cation from aqueous to lipid phases but are poor binders at large in the cell. Such questions are obviously important areas for future investigation.

Summary

The molecules called lariat ethers are designed in analogy to naturally occurring ionophores to have cation binding macrorings (crown ether moeities) and Lewis basic donor groups on a flexible side arm attached to the ring. Such an arrangement should offer a cation three-dimensional solvation. From the data presented here, it is clear that the donor group(s) must be at a distance suitable for an approximately apical interaction with the ring-bound cation. In the carbon-pivot systems described here, the presence of any side chain appears to decrease (relative to 15-crown-5) the strength of binding between ligand and cation, but binding enhancement is observed when the donor group geometry is appropriate. The effect of solvent competition on the binding is clearly very important for these systems since binding enhancements are observed almost exclusively for the two-phase rather than the homogeneous solvent system. In the latter case, of course, the more polar solvent appears to compete more effectively with the ligand for the cation. Most of the molecules reported here are, indeed, biologically active, but the mechanism of their action is not yet known.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 281 spectrophotometer as neat samples unless otherwise specified and are calibrated against the 1601-cm^{-1} band of polystyrene. ^1H NMR spectra were recorded on a Varian EM 360 spectrometer as ca. 15 wt % solutions in $CDCl_3$ unless otherwise specified. The chemical shifts are reported in parts per million (δ) downfield from internal Me_4Si. Gas chromatographic analyses were conducted on a Varian Associates Model 920 analytical gas chromatograph equipped with a thermal conductivity detector and a 5 ft × 0.25 in. 1.5% OV-101 column on 100/120 mesh Chromosorb G. Helium was used as the carrier gas, and the flow rate was ca. 60 mL/min. Combustion analyses for C, H, and N were performed by Franz Kasler, Ph.D., of the University of Maryland.

All reagents were the best grade commercially available and were used without further purification unless otherwise specified. THF was distilled over $LiAlH_4$ under a dry N_2 atmosphere immediately before use. DMF was dried by distilling over CaH_2 prior to use. All other solvents used were reagent grade and were not purified further. 15-Crown-5 was purchased from Aldrich Chemical Co. and was distilled prior to use.

General Procedure for the Preparation of Lariat Ethers with Aliphatic Side Arms. Procedure A. The appropriate alcohol (4 equiv) and 5% $BF_3{\cdot}Et_2O$ (0.01 equiv) were mixed in a three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel. The temperature was maintained at ca. 80 °C with an oil bath. Epichlorohydrin (1 equiv) was added to the reaction flask over a 1–2-h period via the dropping funnel. After addition was complete, the mixture was stirred for an additional 15–20 h. The reaction mixture was then cooled to room temperature and diluted with water. The solution was exhaustively extracted with CH_2Cl_2. The combined extracts were washed with brine and dried (Na_2SO_4). The CH_2Cl_2 was removed by evaporation in vacuo. The crude halohydrin was vacuum distilled through a 10-cm Vigreux column.

The purified halohydrin (1 equiv) was placed in a three-necked, round-bottomed flask equipped with a mechanical stirrer, a N_2 inlet, and a dropping funnel. The contents of the reaction vessel were cooled to ca. 5 °C in an ice bath. NaOH (50% aqueous, 1.25 equiv) was added (dropwise) over a 1-h period. When the reaction was complete (TLC), water was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with H_2O until neutral, then washed with brine, and dried (Na_2SO_4). The solvent was removed by evaporation in vacuo. If necessary, the product, a glycidyl ether, was purified by vacuum distillation.

Hydrolysis of the glycidyl ether was accomplished in a three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, and a thermometer. The glycidyl ether (1 equiv), H_2O (ca. 50 equiv), and 72% $HClO_4$ (0.01 equiv) were mixed together in the reaction vessel and were stirred at ca. 80 °C overnight. The mixture was then cooled, neutralized (5% Na_2CO_3), and the water evaporated in vacuo. The crude 3-substituted-1,2-propanediol was purified by either recrystallization or vacuum distillation (10-cm Vigreux column).

Cyclization was accomplished as follows. A three-necked, round-bottomed flask was equipped with a mechanical stirrer, reflux condenser, addition funnel, and N_2 purge. The flask was charged with NaH (50% in oil, 10.56 g, 0.22 mol) that was washed with hexanes (3 × 100 mL) and then suspended in THF (400 mL, vigorous stirring). The mixture was heated to reflux. The 3-substituted-1,2-propanediol (0.10 mol) was dissolved in THF (100 mL) along with tetraethylene glycol ditosylate (TEGTs) (50.2 g, 0.10 mol) or tetraethylene glycol dimesylate (TEGMs) (35.0 g, 0.10 mol). This solution was added dropwise over 2–3 h, stirred vigorously for 24 h at reflux, allowed to cool, and then filtered. The THF was stripped away on a rotary evaporator. [NB, if TEGMs was used, the NaOMs was too fine to be removed by suction filtration. In this case, the solvent was evaporated in vacuo and the residue taken up in H_2O (300 mL)]. The aqueous mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic phases were dried (Na_2SO_4) and filtered. The CH_2Cl_2 was evaporated.) The crude product mixture was chromatographed over alumina with 0–10% (v/v) 2-propanol/hexanes as eluent. The purified products were obtained as colorless to pale yellow oils. Some compounds were further purified by Kugelrohr distillation.

General Procedure for the Preparation of Lariat Ethers with Aromatic Side Arms, Procedure B. The appropriate phenol (1 equiv) and epichlorohydrin (4 equiv) were heated together to ca. 80 °C in a three-necked, round-bottomed flask equipped with mechanical stirrer, reflux condenser, and dropping funnel. The funnel was charged with NaOH (50% aqueous, 1.05 equiv). The base was then added to the reaction flask over a 1–2-h period. The mixture was stirred for an additional 2 h, cooled, and water added to dissolve the salts. The phases were separated, and the organic layer was washed with 10% NaOH and brine and dried. Residual epichlorohydrin was removed by rotary evaporation, and the crude glycidyl ether was vacuum distilled (10-cm Vigreux column).

Hydrolysis of the aromatic glycidyl ethers and subsequent cyclization of the 3-substituted-1,2-propanediols were accomplished as described in Procedure A.

2-(((Tosyl)oxy)methyl)-15-crown-5. A 10-mL flask was equipped with a 10-mL addition funnel and a stir bar, and *p*-TsCl (0.76 g, 4.0 mmol) and pyridine (1.0 mL) were added. The mixture was stirred and cooled (ice bath). 2-(Hydroxymethyl)-15-crown-5 (see below, **3**, 1.00 g, 4.0 mmol) in pyridine (1 mL) was added over 5 min, and the mixture was stirred for 1 h. The mixture was poured into H_2O (10 mL) and extracted (CH_2Cl_2, 3 × 15 mL). The combined extracts were washed with ice-cold 6 N HCl (3 × 10 mL) and brine (10 mL) and dried (Na_2SO_4). 2-(((Tosyl)oxy)methyl)-15-crown-5 was isolated (87%) as a pale yellow oil: ^1H NMR δ 2.45 (s, 3 H), 3.64 (m, 19 H), 4.15 (m, 2 H), 7.7 (q, 4 H).

2-Ethyl-15-crown-5 (2). Compound **2** was prepared from the above tosylate (1.4 g, 3.5 mmol) and dimethyl copper lithium (7.0 mmol) by using the method of Johnson and Dutra.[26] Pure **2** was obtained (49%) as a pale yellow oil after column chromatography on alumina (15 g, 0–2% 2-PrOH/hexanes): ^1H NMR δ 0.96 (t, 3 H), 1.5 (m, 2 H), 3.7 (m, 19 H); IR (cm^{-1}) 2880, 1460, 1350, 1295, 1250, 1130, 1040, 990, 940, 850. Anal. Calcd for $C_{12}H_{24}O_5$: C, 58.04; H, 9.74. Found: C, 57.63; H, 9.53.

2-(Hydroxymethyl)-15-crown-5 (3). A 500-mL Parr bottle was charged with 2-((benzyloxy)methyl)-15-crown-5 (see below, **21**, 12.4 g, 0.036 mol), EtOH (absolute, 100 mL), and 10% Pd/C catalyst (200 mg). The reaction mixture was shaken for 24 h at 25 °C under H_2 (60 psi), then filtered through a bed of Celite in a Buchner funnel, and the solvent evaporated to afford 8.8 g of crude **3**. The residue was distilled (Kugelrohr) to yield 8.4 g (93%) of analytically pure **3**: ^1H NMR δ 2.6 (br t, 1 H), 3.63 (br s, 21 H); IR (cm^{-1}) 3500–3100 (s), 3000–2800 (s), 1450, 1350, 1290, 1250, 1150–1020 (s), 980, 940, 840. Anal. Calcd for $C_{11}H_{22}O_6$: C, 52.78; H, 8.86. Found: C, 52.85; H, 8.90.

2-(Methoxymethyl)-15-crown-5 (4). Compound **4** was prepared according to procedure A from 1-chloro-3-methoxypropan-2-ol derived in turn from MeOH (128 g, 4 mol). The crude halohydrin was purified by vacuum distillation (10-cm Vigreux): yield, 77 g (62%); bp 81–85 °C (25 torr) [lit.[27] bp 79–79.3 °C (23 torr)]; ^1H NMR δ 2.93 (d, 1 H), 3.37

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(s, 3 H), 3.4–4.1 (m, 5 H). 3-Methoxypropylene 1,2-oxide was prepared from the above halohydrin (50 g, 0.40 mol) and purified by distillation (10-cm Vigreux) to yield the pure oxirane: 31 g (88%); as a colorless liquid, bp 105–107 °C (760 torr) [lit.[10] bp 110.5 °C (760 torr)]; ^{1}H NMR δ 2.63 (m, 2 H), 3.13 (m, 1 H), 3.30 (s, 3 H), 3.60 (m, 2 H). Hydrolysis of the epoxide (29.3 g, 0.33 mol) gave (after vacuum distillation) 3-methoxy-1,2-propanediol: as a colorless oil, 29.2 g (83%); bp 115–119 °C (25 torr) [lit.[10] bp 73–75 °C (0.3 torr)]; ^{1}H NMR δ 3.38 (s, 3 H), 3.4–4.1 (m, 7 H). Compound **4** was prepared from 3-methoxy-1,2-propanediol (10.6 g, 0.10) and TEGTs. The crude product was chromatographed (alumina, 0–4% 2-PrOH/ligroin) to give pure **4**: 6.04 g (23%) ^{1}H NMR δ 3.46 (s, 3 H), 3.76 (br s, 21 H); IR (cm^{-1}) 2860, 1445, 1350, 1290, 1250, 1195, 1120 (s), 975, 930, 840. Anal. Calcd for $C_{12}H_{24}O_6$: C, 54.53, H, 9.15. Found: C, 54.70; H, 9.38.

2-(((Allyl)oxy)methyl)-15-crown-5 (5). Compound **5** was prepared according to procedure A by using commercial (Aldrich) allyl glycidyl ether (500 g, 4.38 mol) that was hydrolyzed to 3-(allyl)oxy-1,2-propanediol. Pure diol (498 g, 86%) was obtained after distillation; bp 76–83 °C (0.04 torr) [lit.[10] bp 111–114 °C (3.0 torr)]; the NMR[28] and IR[29] spectra were identical with those reported. Crown **5** was prepared from 3-(allyl)oxy-1,2-propanediol (54.1 g, 0.41 mol) and TEGTs (206 g, 0.41 mol). The crude product (96 g) was extracted exhaustively (hexanes) to afford a pale yellow oil (66 g), which was vacuum distilled to give **5**: 40 g (34%); bp 134–140 °C (0.05 torr); ^{1}H NMR (CCl_4) δ 3.53 (br s, 21 H), 3.8–4.0 (d, 2 H), 4.9–5.3 (m, 2 H), 5.5–6.1 (m, 1 H); IR (cm^{-1}) 3080, 2860 (s), 1450, 1350, 1295, 1250, 1130 (s), 980, 930. Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 57.63; H, 9.30.

2-(*n*-Propoxymethyl)-15-crown-5 (6). Hydrogenation of **5** (1.45 g, 5.0 mmol) in absolute EtOH (50 mL) and 10% Pd/C (0.5 g) for 6 h at 25 °C afforded **6** (1.2 g, 82%) as a colorless oil: ^{1}H NMR (CCl_4) δ 0.7–1.1 (t, 3 H), 1.1–1.7 (m, 2 H), 3.55 (br s, 23 H); IR (cm^{-1}) 2950–2850 (s), 1460, 1350, 1290, 1240, 1120 (s), 980, 940. Anal. Calcd for $C_{14}H_{28}O_6$: C, 57.51; H, 9.65. Found: C, 57.73; H, 9.90.

2-(*n*-Butoxymethyl)-15-crown-5 (7). A 10-mL flask was charged with **3** (0.63 g, 2.5 mmol), *n*-BuBr (0.34 g, 2.5 mmol), 50% aqueous NaOH (2.0 g), and CH_2Cl_2 (1 mL). The mixture was stirred overnight at 25 °C and poured into CH_2Cl_2 (25 mL). The phases were separated, and the organic layer was washed with ice–water (3 × 20 mL), dried (Na_2SO_4), filtered, and reduced in vacuo to yield pure **6**: 0.50 g (64%); ^{1}H NMR δ 0.7–1.9 (m, 7 H), 3.53 (br s, 23 H); IR (cm^{-1}) 2950–2850 (s), 1450, 1350, 1290, 1240, 1120 (s), 980, 940, 840. Anal. Calcd for $C_{15}H_{30}O_6$: C, 58.80; H, 9.87. Found: C, 58.70; H, 10.11.

2-(*tert*-Butoxymethyl)-15-crown-5 (8). Compound **8** was prepared according to procedure A except that hydrolysis of the glycidyl ether was modified. 1-Chloro-3-*tert*-butoxypropan-2-ol was prepared from *tert*-butyl alcohol (296 g, 4.0 mol). The product (pure by GC and NMR) was used without further purification: 142 g (85%); ^{1}H NMR δ 1.17 (s, 9 H), 2.67 (d, 1 H), 3.4–4.0 (m, 5 H). 3-*tert*-Butoxypropylene 1,2-oxide, prepared from the above halohydrin (124 g, 0.75 mol), was vacuum distilled to give the pure epoxide as a colorless oil: 67 g (70%); bp 66–67 °C (25 torr) [lit.[11] bp 152 °C (760 torr)]; ^{1}H NMR δ 1.17 (s, 9 H), 2.7 (m, 2 H), 3.13 (m, 1 H), 3.50 (m, 2 H). Hydrolysis of the epoxide (47 g, 0.36 mol) was accomplished as described in ref 12: 42 g (79%) bp 124–130 °C (25 torr) [lit.[12] bp 115–117 °C (16 torr)]. Compound **8** was prepared from the diol (14.8 g, 0.10 mol) and TEGTs (50.2 g, 0.10 mol). Chromatography of crude **8** (29.2 g) on alumina (400 g, 0–2% 2-PrOH/hexanes) afforded pure **8** as a colorless oil: 14 g (46%); ^{1}H NMR δ 1.12 (s, 9 H), 3.73 (br s, 21 H); IR (cm^{-1}) 2960, 2860, 1615, 1460, 1385, 1360, 1290, 1250, 1190, 1130 (s), 980, 935, 875, 840, 750. Anal. Calcd for $C_{15}H_{30}O_6$: C, 58.80; H, 9.87. Found: C, 58.70; H, 10.11.

2-(((Trimethylsilyl)oxy)methyl)-15-crown-5 (9). A 50-mL, three-necked flask was charged with **3** (1.25 g, 5.0 mmol), THF (30 mL), and Et_3N (0.71 g, 7.0 mmol). The mixture was stirred and cooled to ca. 5 °C, and Me_3SiCl (0.65 g, 6.0 mmol) diluted with THF (3 mL) was added over 5 min. The mixture was stirred overnight at room temperature, filtered, and reduced to minimum volume. The residue (1.5 g) was dissolved in CH_2Cl_2 (50 mL), filtered (alumina), and reduced in vacuo to afford pure **9** (1.1 g, 68%); ^{1}H NMR (CCl_4/CH_2Cl_2 std) δ 0.05 (s, 9 H), 3.45 (br s, 21 H), IR (cm^{-1}) 2950–2850 (s), 1450, 1350, 1290, 1250 (s), 1130 (s), 940, 870 (s), 840 (s), 745. Anal. Calcd for $C_{14}H_{30}O_6Si$: C, 52.14; H, 9.38. Found: C, 52.01; H, 9.67.

2-(((*n*-Hexadecyl)oxy)methyl)-15-crown-5 (10). A 10-mL flask was charged with **3** (0.63 g, 2.5 mmol), *n*-hexadecyl bromide (0.67 g, 2.5 mmol), 50% NaOH (2 g, 25 mmol), and CH_2Cl_2 (1 mL). The mixture was stirred overnight at room temperature and then poured into CH_2Cl_2 (25 mL). The phases were separated, and the organic layer was washed with ice–water (3 × 20 mL), dried (Na_2SO_4), filtered, and reduced in vacuo to afford **10** as a colorless oil: 1.0 g (84%); ^{1}H NMR δ 0.7–1.1 (m, 3 H), 1.25 (br s, 28 H), 3.55 (br s, 23 H); IR (heat) (cm^{-1}) 2920 (s), 2840 (s), 1460, 1350, 1290, 1250, 1130 (s), 980, 940. Anal. Calcd for $C_{27}H_{54}O_6$: C, 68.31; H, 11.47. Found: C, 68.11; H, 11.55.

General Procedure for the Preparation of Esters of 3, Procedure C. A 50-mL, three-necked flask was charged with **3**, (1.25 g, 5.0 mmol), CH_2Cl_2 (35 mL), and pyridine (2.0 mL, 25 mmol). The mixture was stirred and cooled (ca. 5 °C). Esterification was accomplished by dropwise addition of the appropriate acyl chloride (5.0 mmol) diluted with CH_2Cl_2 (3 mL). The reaction mixture was stirred overnight at room temperature, then transferred to a 60-mL separatory funnel, and washed with 1 N HCl (3 × 15 mL), 5% Na_2CO_3 (1 × 15 mL), and ice–water. It was then dried (Na_2SO_4), filtered, and reduced in vacuo to afford the pure ester.

2-(Acetoxymethyl)-15-crown-5 (11). Compound **11** from **3** and AcCl (0.39 g) as described in procedure C was isolated as a colorless oil: 1.0 g (68%); ^{1}H NMR δ 2.10 (s, 3 H), 3.63 (br s, 19 H), 4.07 (d, 2 H); IR (cm^{-1}) 2980–2840 (s), 1745 (s), 1450, 1370, 1240 (s), 1130 (s), 1045, 980, 940, 840. Anal. Calcd for $C_{13}H_{24}O_7$: C, 53.41; H, 8.27. Found: C, 53.70; H, 8.53.

(15-Crown-5)methyl Butanoate (12). Compound **12**, prepared from **3** and PrCOCl (0.53 g) as described in procedure C, was isolated as a colorless oil: 1.0 g (62%); ^{1}H NMR δ 1.0 (t, 3 H), 1.3–2.0 (m 2 H), 2.35 (t, 2 H), 3.63 (br s, 19 H), 4.2 (m, 2 H); IR (cm^{-1}) 2980–2850 (s), 1740 (s), 1460, 1350, 1300, 1250, 1180, 1130 (s), 940. Anal. Calcd for $C_{15}H_{28}O_7$: C, 56.23; H, 8.81. Found: C, 56.50; H, 9.10.

(15-Crown-5)methyl Hexadecanoate (13), Compound**13**, prepared from **3** and hexadecanoyl chloride (1.37 g) (procedure C), was obtained after chromatography (Al_2O_3) as an analytically pure oil that converted to a waxy white solid on standing: 0.8 g (32%); mp 23–24 °C; ^{1}H NMR δ 0.7–1.8 (m, 29 H), 2.1–2.5 (m, 2 H), 3.63 (br s, 19 H), 4.1–4.25 (m, 2 H); IR (cm^{-1}) 2920 (s), 2840 (s), 1735 (s), 1460, 1350, 1290, 1250, 1130 (s), 980, 940. Anal. Calcd for $C_{27}H_{52}O_7$: C, 66.36; H, 10.73. Found: C, 66.32; H, 11.08.

2-((2-Methoxyethoxy)methyl)-15-crown-5 (14). Compound **14** was prepared as described in procedure A. 1-Chloro-3-(2-methoxyethoxy)-propan-2-ol was prepared from 2-methoxyethanol (243 g, 3.2 mol). The crude chlorohydrin (122 g, 73%) was sufficiently pure (GC, NMR) for further use; ^{1}H NMR 3.40 (s, 3 H), 3.45–4.20 (m, 10 H). 3-(2-Methoxyethoxy)propylene 1,2-oxide was prepared from the halohydrin (120 g, 0.71 mol). The epoxide was purified by distillation (10-cm Vigreux): 58 g (62%); bp 97–98 °C (25 torr) [lit.[30] bp 80–81 °C (13 torr)]; ^{1}H NMR δ 2.6–2.9 (m, 2 H), 3.20 (m, 1 H), 3.40 (s, 3 H), 3.45–4.0 (m, 6 H). Hydrolysis of this epoxide (52 g, 0.39 mol) afforded after distillation 3-(2-methoxyethoxy)-1,2-propanediol: 22.8 g, (39%); bp 155–157 °C (25 torr); ^{1}H NMR δ 3.40 (s, 3 H), 3.45–4.1 (m, 11 H); IR (cm^{-1}) 3400 (OH). Compound **14** was prepared from the preceding diol (15.0 g, 0.10 mol) and TEGTs. Crude **14** (32 g) was chromatographed (Al_2O_3, 300 g, 0–4% 2-PrOH/hexanes) to afford a pale yellow oil. A 2-g sample was further purified (Kugelrohr): 18.7 g (61%); bp 150–155 °C (0.15 torr); ^{1}H NMR δ 3.33 (s, 3 H), 3.56 (br s, 25 H); IR (cm^{-1}) 2880, 1505, 1450, 1355, 1290, 1250, 1195, 1120 (s), 1030, 980, 935, 870, 845. Anal. Calcd for $C_{14}H_{28}O_7$: C, 54.53; H, 9.15. Found: C, 54.54; H, 9.28.

2-((2-*n*-Butoxyethoxy)methyl)-15-crown-5 (15). Compound **15** was prepared as described in procedure A. Crude 1-chloro-3-(2-*n*-butoxyethoxy)propan-2-ol (prepared from 2-*n*-butoxyethanol, 473 g, 4.0 mol) was sufficiently pure (GC, >95% NMR) for further use: 174 g (83%); ^{1}H NMR δ 0.93 (t, 3 H), 1.2–1.9 (m, 4 H), 3.1–4.1 (m, 12 H). 3-(2-*n*-Butoxyethoxy)propylene 1,2-oxide was prepared from the above halohydrin (158 g, 0.75 mol): 96 g (73%); bp 113–114 °C (25 torr) [lit.[30] bp 90–93 °C (14 torr)]; ^{1}H NMR δ 0.93 (t, 3 H), 1.1–1.9 (m, 4 H), 2.5–2.9 (m, 2 H), 3.2 (m, 1 H), 3.3–3.9 (m, 8 H). Hydrolysis of this epoxide (93 g, 0.53 mol) gave 3-(2-*n*-butoxyethoxy)-1,2-propanediol. This diol was sufficiently pure (GC, NMR) for further use: 84.5 g (83%); ^{1}H NMR δ 0.93 (t, 3 H), 1.1–1.8 (m, 4 H), 3.3–4.0 (m, 13 H). Compound **15**, prepared from the preceding diol (19.2 g, 0.10 mol) and TEGTs, was obtained after chromatography (Al_2O_3, 300 g, 0–2% 2-PrOH/hexanes) as a colorless oil: 19.1 g (55%); ^{1}H NMR δ 0.93 (t, 3 H), 1.3–1.7 (m, 4 H), 3.5–3.9 (m, 27 H); IR (cm^{-1}) 2860, 1450, 1350, 1290, 1250, 1120 (s), 1040, 980, 935, 840. Anal. Calcd for $C_{17}H_{34}O_7$: C, 58.26; H, 9.78. Found: C, 58.40; H, 10.07.

2-((2-Hydroxypropoxy)methyl)-15-crown-5 (16). Compound **16** was prepared from 2-(((allyl)oxy)methyl)-15-crown-5 (**5**) by the oxymercuration–demercuration method of Brown et al:[31] 1.45 g (94%); ^{1}H

(28) "Sadtler Standard NMR Spectra"; Sadtler Research Laboratories: Philadelphia, 1972; NMR 13081.
(29) "Sadlter Standard Grating Spectra"; Sadtler Research Laboratories: Philadelphia 1966; IR 686.
(30) Novak, J. *Collect. Czech. Chem. Commun.* **1967**, *32*, 3794.
(31) Brown, H. C.; Lynch, J. G.; Hammer, W. J.; Lin, L. C. *J. Org. Chem.* **1979**, *44*, 1910.

NMR δ 1.1–1.2 (d, 3 H), 2.9 (br s, 1 H) 3.63 (br s, 24 H); IR (cm^{-1}) 3400–3200 (s), 2960–2840 (s), 1450, 1300, 1250, 1150–1050 (s), 1030, 950, 850. Anal. Calcd for $C_{14}H_{28}O_7$: C, 54.53; H, 9.15. Found: C, 54.27; H, 9.42.

2-((2-(2-Methoxyethoxy)ethoxy)methyl)-15-crown-5 (17). Compound **17** was prepared as described in procedure A. 1-Chloro-3-((2-(2-methoxyethoxy)ethoxy)methyl)propan-2-ol was prepared from diethylene glycol monomethyl ether (480 g, 4.0 mol). The halohydrin was obtained as a colorless oil: 119 g (56%); bp 96–100 °C (0.7 torr); ^1H NMR δ 3.37 (s, 3 H), 3.45–4.1 (m, 14 H). 3-(2-(2-Methoxyethoxy)ethoxy)propylene 1,2-oxide was prepared from the above halohydrin (106 g, 0.50 mol): 85 g (97%); ^1H NMR δ 2.67 (m, 2 H), 3.2 (m, 1 H), 314 (s, 3 H), 3.5–3.8 (m, 10 H). Hydrolysis of this epoxide gave 3-(2-(2-methoxyethoxy)ethoxy)-1,2-propanediol: 64 g (73%); 110–115 °C (0.05 torr); ^1H NMR δ 3.2 (t, 1 H), 3.37 (s, 3 H), 3.4–4.0 (m, 14 H). Compound **17** (34 g) was prepared from the preceding diol (19.4 g; 0.10 mol) and TEGTs and was isolated after chromatography (Al_2O_3) as a pale yellow oil: 16.9 g (48%); ^1H NMR δ 3.33 (s, 3 H), 3.7 (br s, 29 H); IR (cm^{-1}) 2860, 1900, 1615, 1450, 1350, 1290, 1245, 1195, 1120 (s), 1040, 980, 935, 870, 840. Anal. Calcd for $C_{16}H_{32}O_8$: C, 54.53; H, 9.15. Found: C, 54.40; H, 9.42.

2-((2-(2-(2-Hydroxyethoxy)ethoxy)ethoxy)methyl)-15-crown-5 (18). A 50-mL, three-necked flask was charged with NaH (50% in oil, 0.24 g, 5.0 mol) and THF (10 mL) to which **3** (1.25 g, 5.0 mol) in THF (5 mL) was added dropwise. After 20 min, 2-(2-(2-(benzyloxy)ethoxy)-ethoxy)ethyl *p*-toluenesulfonate (1.97 g) in THF (5 mL) was added to the flask in a stream and the mixture stirred for 2 h at ambient temperature, filtered, and reduced in volume. The crude amber oil (2.1 g) was column chromatographed (Al_2O_3, 20 g) to give pure benzyl-protected **18** as a colorless oil: 1.6 g (68%); ^1H NMR δ 3.66 (br s, 33 H), 4.53 (s, 2 H), 7.32 (s, 5 H); IR (cm^{-1}) 3080, 3060, 3030, 2860, 1900, 1620, 1450, 1350, 1290, 1250, 1200, 1110 (s), 1035, 980, 935, 870, 845, 735, 695. Anal. Calcd for $C_{24}H_{40}O_9$; C, 61.00, H, 8.53. Found: C, 61.28; H, 8.77. Benzyl-protected **18** (4.0 g, 8.5 mol) was hydrogenolyzed (Parr bottle, EtOH, 75 mL of 10% Pd/C, 0.1 g). After 23 h under H_2 (60 psi) at ambient temperature, the mixture was filtered and stripped of solvent to give **18** as a nearly colorless oil: 3.04 g (94%); ^1H NMR δ 2.83 (t, 1 H), 3.69 (m, 33 H); IR (cm^{-1}) 3300, 2850, 1450, 1350, 1290, 1245, 1110, 1030, 930, 845. Anal. Calcd for $C_{17}H_{34}O_9$: C, 53.39; H, 8.96. Found: C, 53.36; H, 9.20.

2-((2-(2-(2-Methoxyethoxy)ethoxy)ethoxy)methyl)-15-crown-5 (19). A 50-mL, three-necked flask was charged with NaH (50% in oil, 0.13 g, 2.7 mmol) and washed with hexanes (3 × 15 mL) followed by THF (15 mL), and then **18** (1.00 g, 2.6 mmol) in THF (5 mL) was added to the reaction flask over a 5-min period. The mixture was stirred for 20 min. Dimethyl sulfate (0.33 g, 2.6 mmol) was added in one portion. The mixture was stirred for 1 h, then filtered, and stripped of solvent. Chromatography (Al_2O_3, 20 g) of the crude amber oil (1.00 g) afforded **19** as a colorless oil: 0.72 g (70%); ^1H NMR δ 3.37 (s, 3 H), 3.68 (m, 33 H); IR (cm^{-1}) 2860, 1445, 1350, 1290, 1245, 1195, 1120 (s), 1030, 980, 940, 845, 725. Anal. Calcd for $C_{18}H_{36}O_9$: C, 54.53; H, 9.15. Found: C, 54.25; H, 9.40.

2-((Phenoxy)methyl)-15-crown-5 (20). Compound **20** was prepared as described in procedure B. 3-Phenoxypropylene 1,2-oxide was prepared from phenol (212 g, 2.25 mol) and obtained as a colorless oil: 213 g (63%); bp 123–124 °C (25 torr) [lit.[11] bp 243 °C (760 torr)]; ^1H NMR δ 2.66 (m, 2 H), 3.2 (m, 1 H), 3.77 (m, 2 H), 6.8–7.4 (m, 5 H). This epoxide (213 g, 1.42 mol) was hydrolyzed to give 3-phenoxy-1,2-propanediol. The crude diol was vacuum distilled; the pure product solidified on standing: 187 g (78%); bp 127 °C (0.02 torr); mp 56–57 °C (lit.[11] mp 56 °C); ^1H NMR δ 3.40 (d, 2 H, –OH), 3.7 (br s, 2 H), 3.9 (br s, 3 H). Compound **20**, prepared from 3-phenoxy-1,2-propanediol (16.8 g, 0.10 mol) and TEGTs was obtained after chromatography as a yellow oil: 10.44 g (34%); ^1H NMR δ 3.7 (br s, 19 H), 3.78 (d, 2 H), 6.5–7.1 (m, 5 H); IR (cm^{-1}) 3060, 3040, 2870, 1940, 1840, 1770, 1595, 1495, 1455, 1350, 1290, 1245, 1120 (s), 1040, 980, 935, 875, 845, 810, 755, 690. Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.55; H, 8.23.

2-((Benzyloxy)methyl)-15-crown-5 (21). Compound **21** was prepared as described in procedure A except that equimolar amounts of benzyl alcohol (324 g, 3.0 mol) and epichlorohydrin (278 g, 3.0 mol) were used. The crude product was vacuum distilled (25-cm Vigreux): 353 g (58%); bp 95–120 °C (0.03 torr) [lit.[32] bp 104 °C (0.01 torr)]; ^1H NMR δ (CCl_4) 3.05 (br s, 1 H), 3.3–3.5 (d, 4 H), 3.6–4.0 (m, 1 H), 4.45 (s, 2 H), 7.15 (s, 5 H). 3-(Benzyloxy)propylene 1,2-oxide was prepared from the above halohydrin (353 g, 1.76 mol). The product was pure by GC and NMR and was used directly: 263 g (92%); ^1H NMR δ 2.3–2.75 (m, 2 H), 2.8–3.3 (m, 1 H), 3.3–3.75 (m, 2 H), 4.47 (s, 2 H), 7.15 (s, 5 H). The epoxide (262 g, 1.6 mol) was hydrolyzed to 3-(benzyloxy)-1,2-propanediol, which, after distillation, afforded the pure diol: 264 g (90%); bp 127–136 °C (0.04 torr) [lit.[11] bp 142–146 °C (0.6 torr)]; ^1H NMR δ 2.8–4.0 (m, 7 H), 4.50 (s, 2 H), 7.25 (s, 5 H). Compound **21** was obtained from 3-(benzyloxy)-1,2-propanediol (18.2 g, 0.10 mol) and TEGTs (50.2 g, 0.10 mol) after chromatography as a yellow oil (18.0), which was further purified by distillation (Kugelrohr): 12.4 g (36%); bp 164–166 °C (0.02 torr); ^1H NMR δ 4.5 (s, 2 H), 7.25 (s, 5 H); IR (cm^{-1}) 3060, 3030, 2980–2800, 1450, 1350, 1250, 1200, 1150–1060 (s), 970, 940, 845, 735, 700. Anal. Calcd for $C_{18}H_{28}O_6$: C 63.51; H, 8.29. Found: C, 63.59; H, 8.40.

2-((2-Methoxyphenoxy)methyl)-15-crown-5 (22). Compound **22** was prepared as described in procedure B. 3-(2-Methoxyphenoxy)propylene 1,2-oxide was obtained from guaiacol (113 g, 0.91 mol) as a colorless oil: 130 g (80%); bp 106–107 °C (0.02 torr) [lit.[33] bp 123–125 °C (2 torr)]; ^1H NMR δ 2.6–3.0 (m, 2 H), 3.2–3.5 (m, 1 H), 3.80 (s, 3 H), 3.9–4.4 (m, 2 H), 6.83 (s, 4 H). This epoxide (126 g, 0.70 mol) was hydrolyzed to give, after crystallization from 1:1 Me_2CO:hexane, 3-(2-methoxyphenoxy)-1,2-propanediol as a white solid: 110 g (80%); mp 78.5–80 °C (lit.[34] mp 78.5–79.5 °C; ^1H NMR δ 3.2 (br s, 1 H), 3.7 (s, 6 H), 4.0 (s, 3 H), 6.78 (s, 4 H). Compound **22** was obtained from the preceding diol (19.8 g, 0.10 mol) and TEGTS after chromatography (Al_2O_3, 300 g) as a pale yellow oil: 12.4 g (70%); ^1H NMR δ 3.6–4.3 (m, 24 h), 6.82 (s, 4 H); IR (cm^{-1}) 3060, 2870, 1595, 1505, 1455, 1355, 1330, 1290, 1255, 1235, 1180, 1120 (s), 980, 940, 870, 760, 740. Anal. Calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92. Found: C, 60.48; H, 8.20.

2-((3-Methoxyphenoxy)methyl)-15-crown-5 (23). Compound **23** was prepared as described in procedure B. 3-(3-Methoxyphenoxy)propylene 1,2-oxide prepared from 3-methoxyphenol (34.1 g, 0.25 mol) was obtained as a colorless oil: 36.1 g (80%); bp 99–100 °C (0.1 torr) [lit.[35] bp 155 °C (13 torr)]; ^1H NMR δ 2.5–2.9 (m, 2 H), 3.0–3.3 (m, 1 H), 3.69 (s, 3 H), 3.8–4.2 (m, 2 H), 6.2–6.5 (m, 3 H), 6.8–7.2 (m, 1 H). This epoxide (36.0 g, 0.20 mol) was hydrolyzed to 3-(3-methoxyphenoxy)-1,2-propanediol, obtained as a white solid after crystallization from Me_2CO/hexane (1:1 v/v): 29.9 g (76%); mp 73–74 °C (lit.[34] 73–73.5 °C); ^1H NMR δ 2.8–3.1 (t, 1 H), 3.3–3.4 (d, 1 H), 3.70 (s, 5 H), 4.0 (s, 3 H), 6.3–6.6 (m, 3 H), 6.9–7.3 (m, 1 H). Ether **23**, prepared from the preceding diol (19.8 g, 0.10 mol) and TEGTs, was obtained as a colorless oil after column chromatography (Al_2O_3, 400 g): 20.3 g (57%); ^1H NMR δ 3.5–4.0 (m, 24 H), 6.4–6.6 (m, 3 H), 6.9–7.3 (m, 1 H); IR (cm^{-1}) 3060, 2860, 1590, 1490, 1440, 1350, 1280, 1260, 1200, 1120 (s), 1040, 980, 940, 840, 760, 680, 660. Anal. Calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92. Found: C, 60.39; H, 8.20.

2-((4-Methoxyphenoxy)methyl)-15-crown-5 (24). Compound **24** was prepared as described in procedure B. 3-(4-Methoxyphenoxy)propylene 1,2-oxide was prepared from 4-methoxyphenol (124 g, 1.0 mol) and was used without further purification: 163 g (83%); mp 40–42 °C (lit.[36] mp 46–47 °C); ^1H NMR δ 2.6–3.0 (m, 2 H), 3.1–3.4 (m, 1 H), 3.67 (s, 3 H), 3.9–4.3 (m, 2 H), 6.78 (s, 4 H). This epoxide (160 g, 0.82 mol) was hydrolyzed to give 3-(4-methoxyphenoxy)-1,2-propanediol. The crude diol (mp 67–68 °C) was recrystallized from hexane to give the product as a white solid: 142 g (81%); mp 80–81 °C (lit.[34] mp 80.5–81.5 °C); ^1H NMR δ 3.0–3.2 (t, 1 H), 3.4–3.6 (d, 1 H), 3.6–4.2 (m, 8 H), 6.76 (s, 4 H). Ether **24**, prepared from the preceding diol (19.8 g, 0.10 mol) and TEGTs, was obtained after chromatography (Al_2O_3, 300 g) as a pale yellow oil: 10.1 g (29%); ^1H NMR δ 3.5–4.2 (m, 24 H), 6.77 (s, 4 H); IR (cm^{-1}) 3040, 1615, 1590, 1510, 1465, 1350, 1290, 1230, 1175, 1120 (s), 1035, 980, 940, 825, 745. Anal. Calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92. Found: C, 60.45; H, 8.11.

2-(((1-Naphthyl)oxy)methyl)-15-crown-5 (25). Compound **25** was prepared as described in procedure B. 3-((1-Naphthyl)oxy)propylene 1,2-oxide was prepared from 1-naphthol (36.0 g, 0.25 mol): 46.2 g (92%); ^1H NMR δ 2.5–2.9 (m, 2 H), 3.0–3.3 (m, 1 H), 3.8–4.2 (m, 2 H), 6.8 (m, 1 H), 7.2–8.0 (m, 5 H), 8.2 (m, 1 H). This epoxide was hydrolyzed to give, after crystallization from CCl_4, 3-((naphthyl)oxy)-1,2-propanediol as a white solid: 23.3 g (46%); mp 93–94 °C (lit.[37] 96–97 °C); ^1H NMR δ 2.3–2.7 (t, 1 H), 2.9–3.1 (d, 1 H), 3.7–4.0 (m, 2 H), 4.2 (s, 3 H), 6.7–6.9 (m, 1 H), 7.2–8.0 (m, 5 H), 8.1–8.3 (m, 1 H). The preceding diol (10.9 g, 0.05 mol) was treated with TEGTs (25.1 g, 0.05

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mol) to give **25** as a pale yellow oil after chromatography (Al_2O_3, 300 g): 5.8 g (31%); ^1H NMR δ 3.6–4.2 (m, 21 H), 6.8 (m, 1 H), 7.4 (m, 4 H), 7.8 (m, 1 H), 8.2 (m, 1 H); IR (cm^{-1}) 3050, 2860, 1720, 1630, 1600, 1580, 1510, 1460, 1400, 1355, 1270, 1245, 1180, 1130 (s), 1100, 1020, 985, 935, 845, 795, 775, 740, 660. Anal. Calcd for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 66.97; H, 7.71.

2-(((8-Quinolinyl)oxy)methyl)-15-crown-5 (26). A 1-L, three-necked flask was charged with KO-*t*-Bu (33.7 g, 0.30 mol), THF (300 mL), and 8-hydroxyquinoline, which was added in several portions. After 30 min at reflux, 3-chloro-1,2-propanediol (33.2 g, 0.30 mol) in THF (75 mL) was added over a 1-h period. Stirring at reflux was continued overnight. The mixture was filtered. After washing the solid with H_2O, 3-((8-quinolinyl)oxy)-1,2-propanediol was obtained as a light pink crystalline solid: 26.3 g (40%); mp 190–192 °C; ^1H δ (Me_2SO-d_6) 2.5 (m, 1 H), 3.3–3.8 (m, 6 H), 7.0–7.7 (m, 4 H), 8.4 (m, 1 H), 8.9 (m, 1 H). A 500-mL, three-necked flask was charged with DMF (200 mL) and NaH (5.04 g, 0.105 mol). 3-((8-Quinolinyl)oxy)-1,2-propanediol was added in several portions under an N_2 purge. After 20 min, TEGTs (25.1 g, 0.05 mol) in THF (50 mL) was added in a stream. The mixture was stirred for 24 h, filtered, and stripped of solvent, and the crude product was chromatographed (Al_2O_3, 300 g) to afford **26** as a viscous oil: 10.7 g (57%); ^1H NMR δ 3.7–4.3 (m, 21 H), 7.1–7.6 (m, 4 H), 8.1 (m, 1 H), 9.0 (m, 1 H); IR (cm^{-1}) 3060, 3040, 2880, 1950, 1615, 1595, 1570, 1500, 1470, 1425, 1380, 1355, 1320, 1265, 1185, 1110 (s), 990, 940, 820, 790, 750, 730, 705, 640. Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.65; H, 7.21; N, 3.71. Found: C, 63.60; H, 7.50; N, 3.50.

(15-Crown-5)methyl Benzoate (27). Compound **27** was prepared as described in procedure C from benzoyl chloride (0.70 g). Pure **27** was isolated as a colorless oil: 1.4 g (80%); ^1H NMR δ 3.52 (br s, 19 H), 4.1–4.4 (m, 2 H), 7.3–7.6 (m, 3 H), 7.8–8.1 (m, 2 H); IR (cm^{-1}) 2950–2860 (s), 1790, 1720 (s), 1600, 1585, 1450, 1350, 1315, 1275 (s), 685, 670. Anal. Calcd for $C_{18}H_{26}O_7$: C, 61.00; H, 7.40. Found: C, 61.09; H, 7.62.

(15-Crown-5)methyl 4-Methoxybenzoate (28). Compound **28** was prepared as described in procedure C from 4-methoxybenzoyl chloride on an 8.0-mmol scale. Pure **28** was isolated as a colorless oil: 2.3 g (74%); ^1H NMR δ 3.68 (s, 19 H), 3.85 (s, 3 H), 4.3–4.5 (m, 2 H), 6.9 (d, 2 H), 8.1 (d, 2 H); IR (cm^{-1}) 2940–2840 (s), 1710 (s), 1600 (s), 1505, 1450, 1350, 1250 (s), 1165, 1110 (s), 1020, 980, 930, 840, 760, 690. Anal. Calcd for $C_{19}H_{28}O_8$: C, 59.36; H, 7.34. Found: C, 59.57; H, 7.51.

(15-Crown-5)methyl 4-Nitrobenzoate (29). Compound **29** was prepared as described in procedure C from 4-nitrobenzoyl chloride on an 8-mmol scale. Pure **29** was obtained as a yellow oil: 2.5 g (78%); ^1H NMR δ 3.63 (s, 19 H), 4.3–4.6 (m, 2 H), 8.15 (s, 4 H); IR (cm^{-1}) 3110, 3070, 3050, 2960–2820 (s), 1720 (s), 1600, 1520 (s), 1445, 1345, 1270 (s), 1110 (s), 1010, 980, 930, 870, 830, 775, 710 (s). Anal. Calcd for $C_{18}H_{25}NO_9$: C, 54.13; H, 6.31; N, 3.50. Found: C, 54.10; H, 6.60; N, 3.20.

Preparation of 2-((2-Methoxy-4-propylphenoxy)methyl)-15-crown-5 (30). Hydrogenation of **31** (see below, 5.00 g, 12.5 mmol) in absolute EtOH (200 mL) with 10% Pd/C catalyst (0.25 g) afforded **30** as an analytically pure oil: 4.98 g (99%); ^1H NMR δ 0.90 (t, 3 H), 1.3–1.8 (m, 2 H), 2.3–2.6 (t, 2 H), 3.4–4.1 (m, 24 H), 6.5–6.9 (m, 3 H); IR (cm^{-1}) 3040, 2960, 2930, 2870, 1605, 1590, 1515, 1465, 1450, 1420, 1350, 1260, 1235, 1190, 1130 (s), 1030, 985, 935, 845, 800. Anal. Calcd for $C_{21}H_{34}O_7$: C, 63.29; H, 8.60. Found: C, 63.42; H, 8.85.

2-((4-Allyl-2-methoxyphenoxy)methyl)-15-crown-5 (31). Compound **31** was prepared as described in procedure B. 3-(4-Allyl-2-methoxyphenoxy)propylene 1,2-oxide was prepared from eugenol (328 g, 2.0 mol): 341 g (78%); bp 132–134 °C (0.15 torr) [lit.[38] bp 148–152 °C (0.005 torr)]; ^1H NMR δ 2.6–2.9 (m, 2 H), 3.2–3.5 (d, 3 H), 3.83 (s, 3 H), 3.9–4.3 (m, 2 H), 4.7–5.3 (d, 2 H), 5.6–6.3 (m, 1 H), 6.5–6.9 (m, 3 H). This glycidyl ether was hydrolyzed (340 g, 1.54 mol) to give 3-(4-allyl-2-methoxyphenoxy)-1,2-propanediol. The diol was recrystallized from C_6H_6: 355 g (97%); mp 77–79 °C (lit.[39] mp 79 °C); ^1H NMR δ 2.9–3.2 (t, 1 H), 3.2–3.5 (d, 2 H), 3.6–4.3 (d, 6 H), 4.8–5.3 (d, 2 H), 5.6–6.3 (m, 1 H), 6.5–7.0 (m, 3 H). This diol (119 g, 0.50 mol) was treated with TEGTs (251 g, 0.50 mol) to give **31** after chromatography (Al_2O_3, 600 g) as a pale yellow oil: 124 g (62%); ^1H NMR δ (CCl_4) 3.3 (d, 2 H), 3.7 (s, 19 H), 3.80 (s, 3 H), 3.9 (d, 2 H), 5.0 (d, 2 H), 5.6–6.3 (m, 1 H), 6.5–7.0 (m, 3 H); IR (cm^{-1}) 3060, 3000, 2865, 1635, 1600, 1585, 1510, 1465, 1450, 1420, 1345, 1260, 1230, 1130 (s), 990, 930, 850, 800, 745. Anal. Calcd for $C_{21}H_{32}O_7$: C, 63.62; H, 8.14. Found: C, 63.40; H, 8.13.

2((4-(2-Hydroxypropyl)-2-methoxyphenoxy)methyl)-15-crown-5 (32). Compound **32** was prepared from 2-((4-allyl-2-methoxyphenoxy)-methyl)-15-crown-5 (**31**, 1.00 g, 2.5 mmol) by the oxymercuration–demercuration method of Brown et al.[31] The product was obtained as a colorless oil: 1.0 g (97%); ^1H NMR δ 2.6 (d, 3 H), 1.7–1.9 (s, 1 H), 2.6–2.8 (m, 2 H), 3.5–4.2 (m, 25 H), 6.6–7.0 (m, 3 H); IR (cm^{-1}) 3440, 3060, 2880, 1720, 1590, 1515, 1460, 1420, 1350, 1260, 1240, 1120 (s), 1030, 940, 850, 800, 740. Anal. Calcd for $C_{21}H_{34}O_8$: C, 60.85; H, 8.27. Found: C, 60.95; H, 8.50.

Method for Determining Extraction Constants. "Extraction constants" were determined by partitioning picrate salts (7×10^{-5} M) between water and CH_2Cl_2 in the presence of ligand (7×10^{-5} M); picrate ion concentration in the organic layer was determined by UV–VIS spectroscopy as described by Frensdorff.[40]

Determination of Stability Constants. Binding or stability constants for **1-32** were determined potentiometrically by a modification of the Frensdorff method.[41] The emf was measured with an Orion Research Model 701A digital Ionalyzer that has a sensitivity of ±0.1 mV. A Corning sodium ion specific electrode (cat. no. 476210) was used to obtain sodium ion binding constants, and a Corning monovalent cation electrode (cat. no. 476220) was used to ascertain potassium ion binding constants. The reference electrode was Ag/AgCl (Corning 476029). All measurements were conducted in a water-free glove box under an atmosphere of nitrogen. The binding constants were determined at 25.0 ± 1.0 °C. Constant temperature was maintained with a bath of circulating di-*n*-butyl phthalate.

Each binding constant was determined by the following procedure. Stock solutions of 2.00×10^{-3} M NaCl and 2.00×10^{-3} M KCl (Fisher, A.C.S. Certified) in anhydrous MeOH (Baker reagent) were prepared. Samples of the ligands in anhydrous MeOH (ca. 6.00×10^{-3} M to 7.00×10^{-3} M) were also prepared. The activity of Na^+ and K^+ in the absence of complexing agents was measured in a solution prepared by mixing 10.0 mL of the stock salt solution and 10.0 mL of MeOH. The emf reading was taken after stirring the solution (magnetically for 5 min) and then allowing it to become quiescent for 1 min. The emfs of the salt–crown mixtures were similarly obtained from solutions prepared by mixing 10.0 mL of the stock salt solution and 10.0 mL of a crown ether MeOH solution. The emfs of the salt and the salt–crown solutions were measured alternatively, and each run consisted of at least three measurements of each solution. The emf values of each solution were averaged, and these averaged values were used to calculate the binding constants as described by Frensdorff.[41] The error in such measurements has been placed at ±10%.

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Registry No. 1, 33100-27-5; **2**, 75507-15-2; **3**, 75507-25-4; **4**, 76719-73-8; **5**, 68167-86-2; **6**, 84130-85-8; **7**, 75507-18-5; **8**, 76719-77-2; **9**, 84130-86-9; **10**, 84130-87-0; **11**, 76719-74-9; **12**, 84130-88-1; **13**, 84130-89-2; **14**, 76719-78-3; **15**, 76719-79-4; **16**, 79036-71-8; **17**, 76726-87-9; **18**, 84130-90-5; **19**, 84130-91-6; **20**, 75507-16-3; **21**, 75507-17-4; **22**, 76719-75-0; **23**, 84130-92-7; **24**, 76719-76-1; **25**, 84130-93-8; **26**, 84130-94-9; **27**, 84130-95-0; **28**, 84130-96-1; **29**, 84130-97-2; **30**, 84130-98-3; **31**, 84130-99-4; **32**, 79036-70-7; 2-((tosyloxy)methyl)-15-crown-5, 84131-00-0; 1-chloro-3-methoxypropan-2-ol, 4151-97-7; 3-methoxypropylene 1,2-oxide, 930-37-0; 3-methoxy-1,2-propanediol, 623-39-2; tetraethylene glycol ditosylate, 37860-51-8; allyl glycidyl ether, 106-92-3; 3-allyloxy-1,2-propanediol, 123-34-2; 1-chloro-3-*tert*-butoxypropan-2-ol, 22576-65-4; 3-*tert*-butoxypropylene 1,2-oxide, 7665-72-7; 3-*tert*-butoxy-1,2-propanediol, 74338-98-0; *n*-hexadecyl bromide, 112-82-3; butyryl chloride, 141-75-3; hexadecanoyl chloride, 112-67-4; 1-chloro-3-(2-methoxyethoxy)propan-2-ol, 18371-79-4; 3-(2-methoxyethoxy)propylene 1,2-oxide, 13483-49-3; 3-(2-methoxyethoxy)-1,2-propanediol, 84131-01-1; 1-chloro-3-(2-*n*-butoxyethoxy)-propan-2-ol, 16514-14-0; 2-*n*-butoxyethanol, 111-76-2; 3-(2-*n*-butoxyethoxy)propylene 1,2-oxide, 13483-47-1; 3-(2-*n*-butoxyethoxy)-1,2-propanediol, 20248-81-1; epichlorohydrin, 106-89-8; 2-methoxyethanol, 109-86-4; 1-chloro-3-((2-(2-methoxyethoxy)ethoxy)methyl)propan-2-ol, 84131-02-2; diethylene glycol monomethyl ether, 111-77-3; 3-(2-(2-methoxyethoxy)ethoxy)propylene 1,2-oxide, 71712-93-1; 3-(2-(2-methoxyethoxy)ethoxy)-1,2-propanediol, 84131-03-3; 2-(2-(2-(benzyloxy)-ethoxy)ethoxy)ethyl *p*-toluenesulfonate, 84131-04-4; 2-((2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethoxy)methyl)-15-crown-5, 84131-05-5; 3-phenoxypropylene 1,2-oxide, 122-60-1; phenol, 108-95-2; 3-phenoxy-1,2-propanediol, 538-43-2; benzyl alcohol, 100-51-6; 1-chloro-3-(benzyloxy)propan-2-ol, 13991-52-1; 3-(benzyloxy)propylene 1,2-oxide, 2930-05-4; 3-(benzyloxy)-1,2-propanediol, 4799-67-1; 3-(2-methoxyphenoxy)propylene 1,2-oxide, 2210-74-4; guaiacol, 90-05-1; 3-(2-meth-

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oxyphenoxy)-1,2-propanediol, 93-14-1; 3-(3-methoxyphenoxy)propylene 1,2-oxide, 2210-75-5; 3-methoxyphenol, 150-19-6; 3-(3-methoxyphenoxy)-1,2-propanediol, 17131-51-0; 3-(4-methoxyphenoxy)propylene 1,2-oxide, 2211-94-1; 4-methoxyphenol, 150-76-5; 3-(4-methoxyphenoxy)-1,2-propanediol, 17131-52-1; 3-((1-naphthyl)oxy)propylene 1,2-oxide, 2461-42-9; 1-naphthol, 90-15-3; 3-((1-naphthyl)oxy)-1,2-propanediol, 36112-95-5; 8-hydroxyquinoline, 148-24-3; 3-chloro-1,2-propanediol, 96-24-2; 3-((8-quinolinyl)oxy)-1,2-propanediol, 56469-01-3; benzoyl chloride, 98-88-4; 4-methoxybenzoyl chloride, 100-07-2; 4-nitrobenzyl chloride, 122-04-3; 3-(4-allyl-2-methoxyphenoxy)propylene 1,2-oxide, 36014-34-3; eugenol, 97-53-0; 3-(4-allyl-2-methoxyphenoxy)-1,2-propanediol, 398-58-3; Na^+, 17341-25-2; K^+, 24203-36-9.

Total Synthesis of the Hypocholesterolemic Agent Compactin

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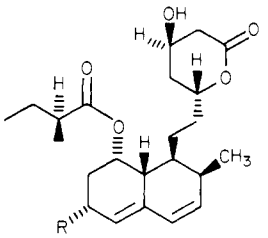
Abstract: A total synthesis of (+)-compactin (ML-236B) (**1a**), a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, is presented. The key chiral hexahydronaphthalene intermediate, **3**, was efficiently synthesized in 70% overall yield from the optically active diol (−)-**6**. In turn, (−)-**6** was obtained via microbiological reduction of the racemic dione (±)-**5**. (+)-Compactin (**1a**) was prepared in 14 steps from **3** in 0.8% yield.

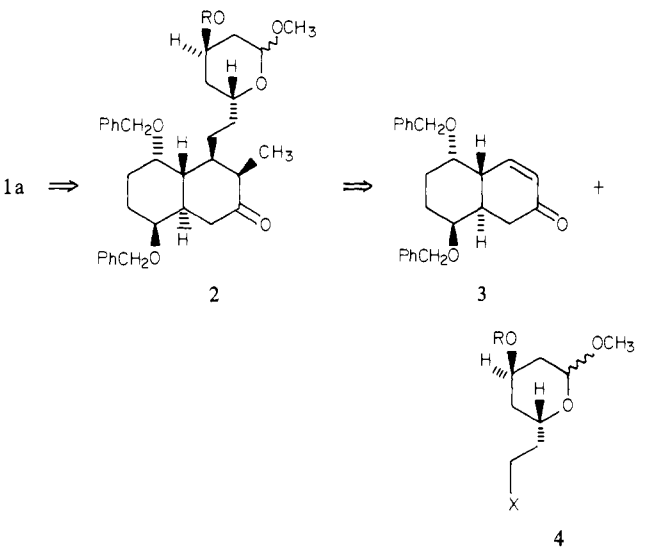
In 1976, an important new class of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors was discovered. The first member of this family, compactin (**1a**), was isolated from



1a, R = H
1b, R = CH_3

Penicillium brevicompactum[1] by the Beecham group as an antifungal metabolite. Later, this same metabolite, designated as ML-236B,[2] and other derivatives were isolated from *Penicillium citrinum* by the Sankyo group as hypocholesterolemic agents. Subsequently, Monacolin K[3] (**1b**) or Mevinolin[4] was discovered by two independent groups from cultures of *Monascus ruber* and *Aspergillus terreus*, respectively. All of these compounds are potent competitive inhibitors of HMG-CoA reductase,[2-5] the rate-limiting enzyme in cholesterol biosynthesis,[6] with **1b** being the most potent. However, the pharmacology of **1a** is the most extensively studied. Compactin effectively reduced plasma cholesterol levels in a number of animal species including dogs,[7a] monkeys,[7b] and humans.[7c] Further, it has been investigated

Scheme I



clinically as a hypocholesteremic drug with encouraging results. It can selectively reduce the low-density lipoprotein (LDL) without affecting the desirable high-density lipoprotein (HDL).[8] On the other hand, it is possible that these compounds will produce unexpected side effects and that new chemical variants will have to be developed to further enhance the therapeutic efficacy.

Compactin is a challenging synthetic target owing to the presence of seven asymmetric centers, a high degree of functionalization, and the highly sensitive β-hydroxy-δ-lactone, which is essential for biological activity. In recent years, extensive synthetic studies have resulted in the syntheses of the hexahydronaphthalene nucleus,[9] the lactone moiety,[10] and the simpler

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