Host–Guest Complexation. 52. Bridged and Chiral Hemispherands[1]

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The synthesis, binding properties, and configurational stability of 10 new chiral hemispherand hosts containing the quaterphenyloxy framework are reported, as well as the crystal structures of free hosts **1**, **3**, **4**, and **10** (Chart I) and six complexes of **1**. Hosts **1** and **2**, although chiral and strong binders, are configurationally unstable due to the relatively low barriers to ring inversions of their $CH_3OC_6H_3$ and $EtOC_6H_3$ parts at ordinary working temperatures. Host **3** is configurationally stable due to the inability of the $PhCH_2OC_6H_3$ parts to undergo ring inversion. This host is a relatively poor binder in $CDCl_3$ at 25 °C of Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ picrates, in spite of the fact that its crystal structure shows it to be beautifully organized with all oxygens turned inward and all benzyls turned outward. Hosts **4–6** contain extra bridges in addition to the parent 18-membered macrorings. They are configurationally stable and are relatively strong binders. The presence of CH_3 groups in the four positions para to the quaterphenyloxy moiety in **5** produced an increase in binding compared to **4** without the CH_3 groups from 0.4 to 1.8 kcal mol^{-1} ($\Delta(-\Delta G°)$ values), depending on the guest. A crystal structure of **4** showed all of its oxygens' unshared electron pairs to be turned inward. Host **5** was obtained in an enantiomerically pure state. Hosts **5** and **6**, whose oxygen-bridging units are $CH_2CH_2CH_2$ and 1,2-$CH_2C_6H_4CH_2$, respectively, provided similar $-\Delta G°$ values for binding the eight cations. Host **7**, containing three chiral elements, was found to undergo ring inversion of its four $EtOC_6H_3$ groups at working temperatures, whereas **8**, containing four $C_6H_5CH_2OC_6H_3$ groups, was configurationally stable. As with **3**, the presence of the $C_6H_5CH_2OC_6H_3$ groups markedly depressed its binding properties. Without exception, peak binding for the 18-membered ring hosts (**1–8**) involved NaPic as guest. Hosts **9–12** all have 21-membered macrorings incorporating a quateraryloxy and either a *cis*-2,5-tetrahydrofuran or a 2,6-pyridine ring bridging unit to give seven heteroatom binding sites. The crystal structure of free **10** shows it is not highly preorganized for binding. Compounds **11** and **12** are diastereomers, which combine the chiral elements of the *cis*-2,5-tetrahydrofuran unit and an additional 1,2-$CH_2C_6H_4CH_2$ oxygen-bridging unit. Hosts **9**, **11**, and **12** show peak binding with KPic and **10** with CsPic. The highest $K_a(Na^+)/K_a(K^+)$ ratio (150) was observed for **7**, and the highest $K_a(K^+)/K_a(Na^+)$ ratio (2500) was observed for **8** (K_a are association constants, M^{-1}). These hemispherands are better binders of cations than the corands but poorer than the spherands, cryptands, or cryptahemispherands.

Introduction

Hemispherands have been defined as hosts, at least half of whose structure is preorganized into a binding conformation prior to complexation. One of the many possible families of hemispherands is conceptually derived by replacing one or more anisyl units of spherand[2] **13** by CH_2OCH_2 or other conformationally mobile ligating groups. Compound **14** provides a minimum number of anisyl units for them to be self-organizing.[3] Formal replacement of all the anisyl units of **13** by CH_2OCH_2 groups gives the parent corand **15**.[4] The observation that binding strength and selectivity decline in the order spherands > hemispherands > corands is accounted for by the principle of preorganization, which states that "the more highly hosts and guests are organized for binding and for low solvation *prior* to their complexation, the more stable will be their complexes".[2f,3]

A previous paper in this series[5] described the synthesis and binding properties of hemispherands having four contiguous anisyl units, as represented in generalized structure **16**. Hosts having this quateranisyl unit are chiral due to the disymmetric up–down–up–down arrangement of the four anisyl groups. These hosts are particularly attractive candidates for applications such as the enantioselective binding of chiral guests and the asymmetric catalysis of reactions of prochiral carbanions for these reasons: (1) When R = R′ and with proper choice of Z, hosts **16** have a C_2 axis which renders the two faces of the macrocycle equivalent. Alternatively, if either R or R′ is chosen to be a sterically bulky group, only one face of the macrocycle is accessible. (2) The structural rigidity and relatively strong binding free energies associated with these hosts are expected to minimize the formation of multiple diastereomeric complexes having similar energies. (3) Molecular model (CPK) examination and crystal structures reported in this paper reveal a high degree of chiral shape in the vicinity of the binding site in these hosts. (4) The binding properties of these hosts can be readily manipulated by variation in the groups R, R′, and Z.

For the potential of these chiral hosts to be realized, they must have sufficient configurational stability to permit the isolation and manipulation of pure enantiomers. In a previous study[5] we demonstrated that when R = R′ = CH_3, the quaterphenyl unit of hosts of type **16** undergoes rapid ring inversions at 25 °C. In the present work we report structural modifications that confer configurational stability on hosts of type **16** and their synthetic precursors as well as the preparation of an optically pure hemispherand host. We also demonstrate how these structural variations affect the binding properties of these hosts and report the results of a crystal structure survey of the complexes formed between a prototypical chiral host and several alkali-metal and alkylammonium ions.

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(5) Artz, S. P.; Cram, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 2160–2171.

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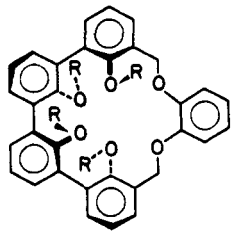
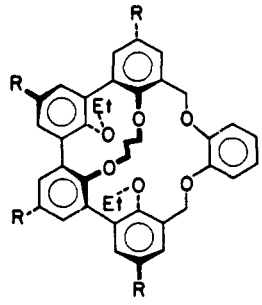
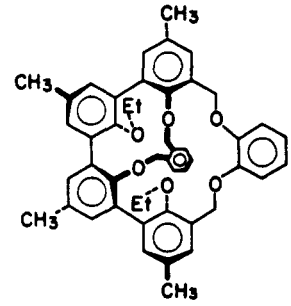
Chart I



1, R = CH_3
2, R = CH_3CH_2
3, R = $C_6H_5CH_2$



4, R = H
5, R = CH_3



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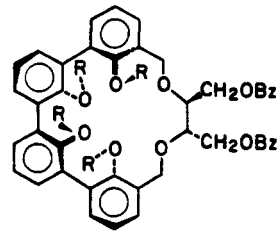
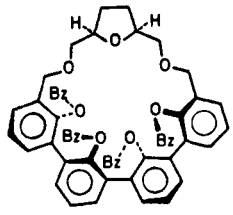


7, R = CH_3CH_2
8, R = $C_6H_5CH_2$



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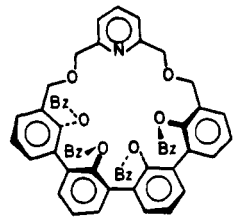

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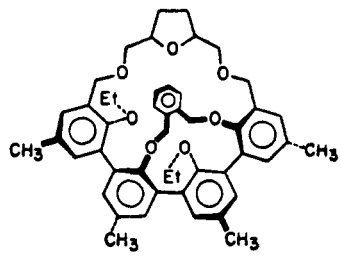
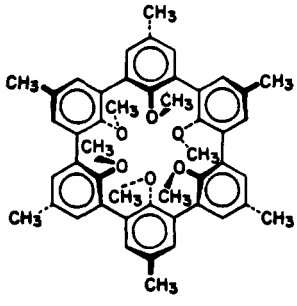


11, less polar isomer
12, more polar isomer



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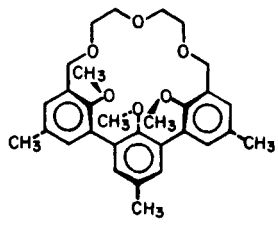

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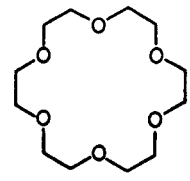

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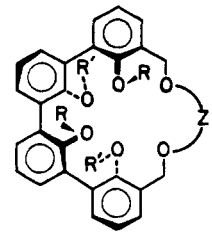

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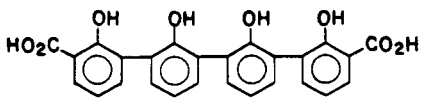

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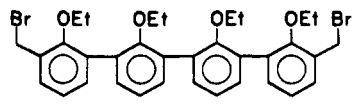

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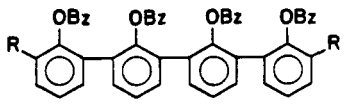
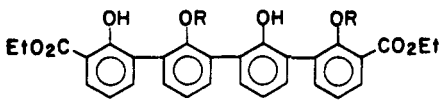


19, R = CO_2CH_2Ph; 20, R = CO_2H
21, R = CO_2Et; 22, R = CH_2OH
23, R = CH_2Br



24, R = Et
25, R = H

Results and Discussion

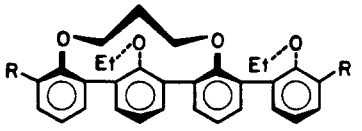
In the first section of this paper we describe the syntheses of hosts 3–12. In the second section, the configurational stability of the hosts and their synthetic precursors is described. Part three deals with the crystal structures of 1 and six of its complexes in which the guests are varied. The solution structure of 1 and its complexes are described in the fourth section. The fifth section describes the crystal structures of free hemispherands 3, 4, and 10. In the sixth section, the binding of 1–12 to the alkali-metal and ammonium picrates is correlated with the structures of the hosts and complexes.

Syntheses. Compounds 17 and 18 were prepared as described previously.[5] Alkylation of 17 with $C_6H_5CH_2Br$–K_2CO_3 in acetone at reflux gave the ester 19, which was

hydrolyzed and isolated as the diacid–tetraether **20** (62%). An attempted reduction of the two carboxyl groups of **20** with $(CH_2)_4O{\cdot}BH_3$ or $(CH_3)_2S{\cdot}BH_3$ led to partial cleavage of the benzyl ether groups. Therefore diacid **20** was esterified with Et_2SO_4–K_2CO_3 in acetone (100%), and the ester **21** produced was reduced with $LiAlH_4$ to the diol **22** (87%). This indirect route was preferable to direct reduction of diester **19** because the diacid **20** was easily purified by crystallization. Conversion of carefully dried diol **22** to dibromide **23** with PBr_3 went in 70% yield.

In initial attempts to prepare **24**, **17** was treated with 5 equiv of K_2CO_3 and 8 equiv of Et_2SO_4 in refluxing acetone to produce a 17% yield of **24** as well as **25** (34%). Although the desired **24** was once obtained in 83% yield (12 equiv each of K_2CO_3 and Et_2SO_4 in refluxing acetone), this heterogeneous reaction conducted repeatedly (45 runs) under a variety of conditions could not be reliably reproduced.

The two phenolic oxygens of **24** were bridged with $(TsOCH_2)_2CH_2$–Cs_2CO_3[6] in $(CH_3)_2NCHO$ under medium-dilution conditions to give **26** (47%). Reduction of **26** with $LiAlH_4$ gave **27** (69%), which on treatment with PBr_3 produced the desired dibromide **28** (68%).

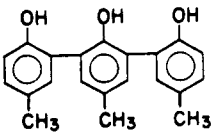


26, R = CO_2Et; **27**, R = CH_2OH

28, R = CH_2Br

Because of the uncertainties in the synthesis of key compound **24**, an alternative synthetic route into bridged quaterphenyl hemispherands was developed. Thus *p*-cresol was oxidatively trimerized via our previously described[7] procedure to give **29** (35%). The center phenolic hydroxyl was selectively ethylated (Et_2SO_4–K_2CO_3–$(CH_3)_2CO$) to produce **30** (53%), treatment of which with 1 equiv of Br_2 in $CHCl_3$[8] gave a 56% yield of **31** after chromatographic separation from the dibrominated side product and unreacted starting material. Reaction of the phenolic hydroxyls with CH_3OCH_2Br–NaH–tetrahydrofuran[9] gave **32** (97%), which was metalated with *n*-butyllithium,[10] and the organometallic produced was quenched with iodine to give **33** (96%).

Crystalline boronic acid **34** was prepared by ethylation of *p*-cresol with Et_2SO_4–K_2CO_3–$(CH_3)_2CO$[11] (86%) followed by ortho lithiation with *n*-butyllithium and quenching of the organometallic with trimethylborate[12] (74%). Palladium-catalyzed[13] cross coupling of iodide **33** with boronic acid **34** gave quaterphenyl **35** in 81% crystallized yield.



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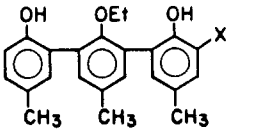
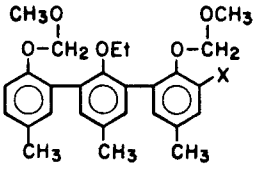
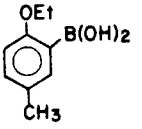


30, X = H; **31**, X = Br



32, X = Br; **33**, X = I



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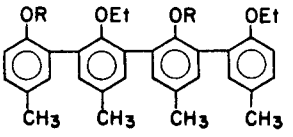
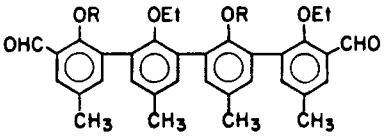
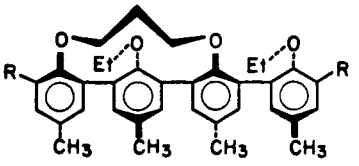


35, R = CH_2OCH_3; **36**, R = H

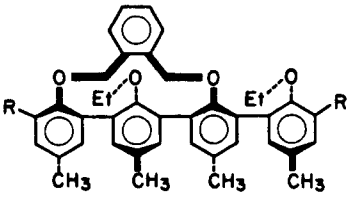


37, R = H; **38**, R = Et



39, R = CHO; **40**, R = CH_2OH

41, R = CH_2Br



42, R = CHO; **43**, R = CH_2OH

44, R = CH_2Br

The crystalline diphenol **36** was prepared by hydrolysis of **35** with hydrochloric acid in ethanol (95%). Treatment of diphenol **36** with hexamethylenetetraamine in refluxing CF_3CO_2H[14] for 2 weeks gave a 32% yield of the dialdehyde **37**. Running the reaction in CCl_3CO_2H at 90 °C increased the yield to 40% and gave a more easily purified product. The structural assignment of **37** was supported by the ^1H

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(12) (a) For a review of the synthesis and chemical properties of arylboronic acids, see: Lappert, M. F. *Chem. Rev.* **1956**, *56*, 959–1064. (b) The arylboronic acids used in this work were all air and moisture stable over a wide range of pH. Some tendency to form boronic anhydrides revealed itself if the compounds were treated with drying agents (magnesium sulfate) or subjected to a high vacuum for extended periods of time. Our experience suggests that this level of stability is typical of simple arylboronic acids. Heteroarylboronic acids, by contrast, are sometimes too hydrolytically labile to be useful in the Suzuki aryl–aryl coupling procedure.

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Table I. Dibromides and Diols Used To Produce Macrocycles and the Observed Yields

dibromide	diol	cycle	% yield
23	1,2-$(HO)_2C_6H_4$	**3**	41
28	1,2-$(HO)_2C_6H_4$	**4**	30
41	1,2-$(HO)_2C_6H_4$	**5**	35
44	1,2-$(HO)_2C_6H_4$	**6**	30
18	(*S,S*)-$(C_6H_5CH_2OCH_2CHOH)_2$	**7**	17
23	(*S,S*)-$(C_6H_5CH_2OCH_2CHOH)_2$	**8**	15
23	(*R,S*)-2,5-$(HOCH_2)_2(CH_2CH)_2O$	**9**	33
23	2,6-$(HOCH_2)_2C_5H_3N$	**10**	26
44	(*R,S*)-2,5-$(HOCH_2)_2(CH_2CH)_2O$	**11**[a]	3.5
44	(*R,S*)-2,5-$(HOCH_2)_2(CH_2CH)_2O$	**12**[a]	1.1

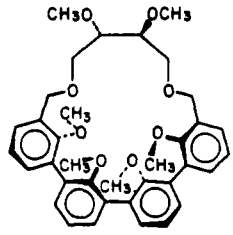
[a] Diastereomers, **11** being the less polar and **12** the more polar isomer (TLC).

NMR spectrum of its perethylation product **38**. The likelihood that the first formyl group substitutes ortho to the hydroxyl of **36** coupled with the 2-fold symmetry observed for derivative **38** rules out all isomeric structures.

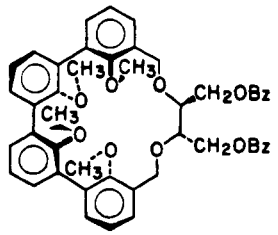
Bisphenol **37** was treated with $(TsOCH_2)_2CH_2$–Cs_2CO_3–$(CH_3)_2NCO$ to give bridged dialdehyde **39** (45%), reduction of which with $NaBH_4$–EtOH produced diol **40** (92%). Diol **40** after being carefully dried was treated with PBr_3 to give dibromide **41** (83%). Only the dextrorotatory form of **41** was fully characterized (see the next section). Similar reactions, except that 1,2-$(BrCH_2)_2C_6H_4$ was the bridging reagent, led from **37** to **42** (74%), to **43** (90%), to **44** (90%) (**44** was only partially characterized).

Formation of the macrocycles was accomplished by slow addition of a solution of the mixed diol and dibromide to a refluxing mixture of NaH–$(CH_2)_4O$. Table I lists the diols and dibromides used in these reactions leading to host compounds **3**–**12**. The yields varied from 1.1 to 41%, partly because of variation in the method and in the ease of isolation of the products. Many of the macrocycles could not be crystallized in less than a pure state and gave poor recovery upon chromatography on silica gel due to their scavenging and complexing with ions on the solid support (e.g., **11** and **12**). Purification by reverse-phase flash chromatography[15] was the final method of choice. Nonfractional filtration of the crude product mixture through hydrocarbon-capped silica gel with 3% (wt/vol) sodium bromide in 4:1 acetone/water (v/v) as the mobile phase was usually sufficient to obtain analytically pure host, H·NaBr. The hosts or their complexes often crystallized during concentration (rotary evaporation) of the column filtrates.

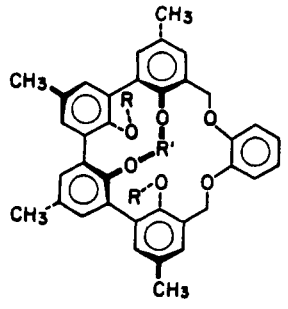
Configurational Stability of Hosts and Their Synthetic Precursors. An investigation into the configurational stability of hosts of type **16** having R = R′ = Me has been reported previously.[5] Dynamic ^1H NMR studies of 20-member ring host **45** revealed that the free energy barrier to configurational inversion of the quaterphenyl unit in this compound is greater than 21 kcal mol^{-1}. Host **1** gave two peaks of equal intensity on an analytical TAPA[16] HPLC column (retention time 5 min) but could not be resolved on a preparative scale using a cellulose column. Host **1** could be crystallized as its sodium mandelic acid complex but gave zero optical rotation after decomplexation (30 min). To determine whether the nonresolvability of **1** was due to a failure of the particular methods applied for resolution or due to configurational



45



46



47

lability, closely related host **46** was prepared. The two chiral centers of the (+)-tartaric acid derived bridging unit of **46** render the configurational inversion of the quaterphenyl unit in this compound an epimerization. In the event, host **46** crystallized as a single diastereomer. In solution, inversion of the quaterphenyl unit occurred rapidly at temperatures above −23 °C to give an 11:1 mixture of diastereomers.[5]

The inversion of configuration of the quaterphenyl unit in hosts **1**, **45**, andd **46** presumably occurs by successive passage of the methoxyl groups through the middle of the macrocycle.[17] In principle this process might be inhibited by using larger alkoxyl groups in place of methoxyl. In the current work host **7** was prepared to investigate this possibility. The ^1H NMR spectrum of free host **7** at 25 °C revealed the presence of only a single diastereomer. When a solution of this host was shaken with saturated aqueous sodium bromide solution, a 2.5:1 mixture of diastereomers was obtained. These results show that the energy barrier for an ethoxyl group to pass through the center of an 18-member ring is not sufficient to confer configurational stability of the quaterphenyl unit at 25 °C in the free host.

Formal replacement of the methoxyl groups of **46** with benzyloxyl groups gives host **8**. Host **8**, after purification by crystallization, consisted of a single diastereomer. This was shown by the observation of a single spot on thin-layer chromatography (silica gel), the observation of a single peak in its reverse-phase analytical HPLC trace, and its sharp melting point (139.0–142.0 °C.). Although its ^1H NMR spectrum was too complex to be useful for stereochemical studies, it is probably safe to assume that the quaterphenyl unit of this host is configurationally stable. Molecular model examination and the >21 kcal mol^{-1} free energy barrier to the stereochemical inversion in host **45** both suggest that passage of a benzyloxyl group through the middle of the 18-member ring would be a very slow process and would probably require the breaking of chemical bonds. The relatively weak binding exhibited by **8** compared to hosts **7** and **46** (see Table III) was initially attributed to selective formation (or selective isolation) of

(14) (a) Duff, J. C.; Bills, E. J. *J. Chem. Soc.* **1934**, 1305–1308. (b) Smith, W. E. *J. Org. Chem.* **1972**, *37*, 3972–3973. (c) We warmly thank Professor David N. Reinhoudt, whose research group demonstrated the utility of this reaction in a closely related system, and who provided the details of their procedure prior to publication.

(15) Kühler, T.; Lindsten, G. R. *J. Org. Chem.* **1983**, *48*, 3589–3591.

(16) Kim, Y. H.; Tishbee, A.; Gil-Av, E. *Chem. Commun.* **1981**, 75–76.

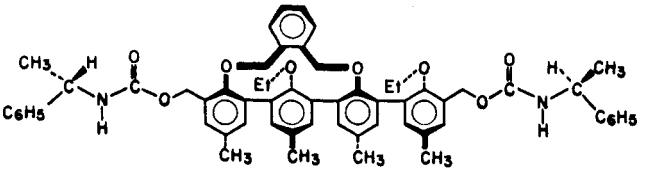
(17) An alternative mode of inversion, involving successive passage of the aryl carbons para to methoxyl through the 18-member ring, appears in molecular models to be a much higher energy process.

the weaker binder of the two noninterconverting diastereomers that might potentially be formed in the cyclization reaction. Binding studies that were later performed on host 3 suggested than another factor was responsible for the diminished binding (vide infra).

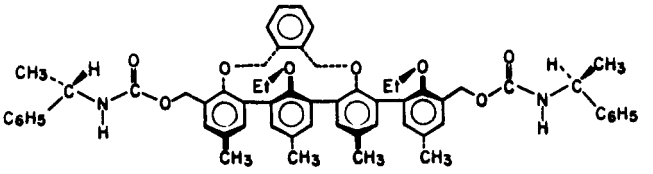
Because the ethoxyls of host 7 were not sufficiently bulky to render the quaterphenyl unit configurationally stable, further efforts to obtain optically active hosts made use of benzyloxy groups. Host 3 was alternately treated with 1.0 equiv of D-10-camphorsulfonic acid sodium salt, 1.0 equiv of L-(+)-mandelic acid sodium salt, 1.0 equiv of (+)-3-bromocamphor-8-sulfonic acid ammonium salt, 0.5 equiv of (−)-(α)-phenylethylammonium bromide, and 0.5 equiv of L-phenylalanine methyl ester hydrochloride. Attempts were made to selectively crystallize each of these complexes by slow evaporation of their solutions in 2:1 CH_2Cl_2–$CH_3C_6H_5$. In each case the free guest appeared to crystallize from solution, followed several days later by crystallization of the free host. The solids were collected by filtration and subjected to standard decomplexation procedures. In each case the optical rotation of the free host was zero at both 404 and 546 nm. The failure of these complexes to crystallize as complexes is in part due to the relatively weak binding exhibited by this host (see Table III). The relatively weak binding of this host (3) (and of host 8) is attributed to steric inhibition of contact ion pair formation based on the crystallographic investigations described in the next section. Because contact ion pair formation is an essential aspect of the mechanism by which hosts of this type were expected to induce asymmetry in the products of catalyzed reactions, no further attempts were made to resolve tetrabenzyloxy hemispherands.

An alternative approach to obtaining configurationally stable hemispherand hosts involves incorporation of a secondary bridge as in general structure 47. Such hosts are in principle configurationally stable if one of the following two conditions holds: (1) R is too large to pass through the macroring defined by three aryl rings and the secondary bridge R′. (2) Either R or R′ is too large to pass through the middle of the 18-member ring. One advantage of this approach is that if the first condition applies, classical resolution methods may be applied to synthetic precursors of the host compound, and we are no longer dependent on fortuitous crystallization of host–guest complexes with optically active counterions to obtain optically active hosts.

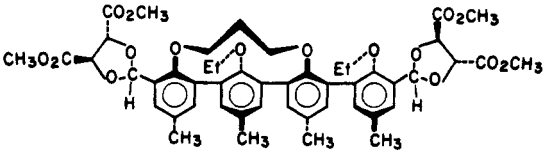
Compound 6 was the first host of this type that was sought in optically active form. The o-xylene bridging unit was chosen because it was hoped that its bulk would sterically hinder one face of the macrocycle and inhibit the formation of diastereomeric complexes arising from complexation on the two nonequivalent faces of the macrocycle. Treatment of synthetic intermediate 43 with 2 equiv of (S)-(−)-α-phenyethylisocyanate[18] in refluxing benzene gave two compounds having R_f values of 0.58 and 0.22 (silica gel, 35% EtOAc in CH_2Cl_2 by volume) in a ratio of 2.7:1. The FAB mass spectra of each of these two compounds gave an M + Na^+ peak corresponding to structure 48 as the nearly exclusive major peak above m/e 250.[19] The 500-MHz ^1H NMR spectrum of the higher R_f material was in accord with its structural assignment as a single diastereomer of 48. The ^1H NMR spectrum of the lower R_f material gave broad peaks. To the extent that this spectrum was interpretable, it was in accord with the production of the other diastereomer of 48. Thin-layer chromatographic analysis of the material having an R_f value of 0.22 after 3 weeks of storage in the solid state (foam) at 25 °C revealed that it had been almost completely converted into a material that cospotted with the aforementioned R_f 0.58 material. We conclude that the ethoxyl group of 48 can press through the middle of the 13-member ring formed by the o-xylene bridge. This hypothesis implies that synthetic intermediates 42–44 are not configurationally stable. On the basis of an assumption of a unimolecular process, a temperature of 25 °C, a time interval of 3 weeks, and an estimated conversion of 90%, the free energy barrier for the conversion of the R_f 0.22 material into the R_f 0.58 material was calculated to be ca. 25 kcal mol^{-1}. This is very similar to the inversion barrier of 26.5 kcal mol^{-1} observed for cyclotriveratrylene.[20] Molecular models (CPK) predict inversion barriers for cyclotriveratrylene and the quaterphenyl unit of 48, which are both high and roughly similar to one another.



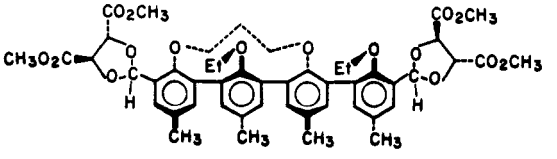
48a



48b



49a



49b

Although intermediates 42–44 appear not to be configurationally stable, host 6 should be. Stereochemical inversion of 6 requires not only that the ethoxyl group passes through the 13-member ring but also that the o-xylene group passes through the 18-membered ring as well. The successful separation and characterization of two noninterconverting diastereomers, hosts 11 and 12, demonstrate conclusively that at least one of these processes is very slow. Resolution of host 6 by crystallization of its complexes with chiral salts was not attempted because neither free 6 nor any of its complexes with achiral salts was ever induced to crystallize.

(18) Gschwend, H. W. *J. Am. Chem. Soc.* **1972**, *94*, 8430–8437.
(19) FAB mass spectra determined in m-nitrobenzyl alcohol as matrix give strong matrix-derived peaks below m/e 250.
(20) Collet, Andrē; Gabard, J. *J. Org. Chem.* **1980**, *45*, 5400–5401.
(21) Koenig, K. E.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1976**, *98*, 4018–4020.

Reaction of dialdehyde **39** with excess (+)-dimethyl-L-tartrate in the presence of catalytic *p*-toluenesulfonic acid gave the two diastereomeric bisacetals **49a** and **49b**. Separation of these isomers was facilitated by their widely varying physical properties. One isomer has an R_f value of 0.14 (silica gel, 4:1 CH_2Cl_2/EtOAc by volume) and mp 205.5–206.0 °C. The other isomer has an R_f value of 0.31 and is an oil. Usually the crystalline isomer was isolated from the crude reaction mixture by crystallization, and the noncrystalline isomer was isolated by medium-pressure chromatography of the mother liquor. No interconversion of these two isomers was observed by ^1H NMR when they were each dissolved (separately) in $C_6D_5NO_2$ and stored under nitrogen at 180 °C for 75 h. On the basis of the results of this experiment and on the assumption that a 5% interconversion of either isomer could have been detected by ^1H NMR, a lower limit of 40 kcal mol^{-1} was calculated for the free energy barrier to this process.

Removal of the chiral auxillary groups was accomplished with hydrochloric acid in refluxing ethanol. The overall chemical yield for both steps of the resolution process was 59% (summed weight of resolved enantiomers divided by weight of racemate). In one of several runs, the diastereomerically pure (^1H NMR, thin-layer chromatography) noncrystalline isomer of **49** gave rise to dialdehyde **39** of only 91% optical purity. Presumably the resolving agent contained some racemate. This partially racemic dialdehyde was carried on in three synthetic steps to macrocycle **5** of 93% optical purity (the optical rotation measured after a single crystallization of the macrocycle). When this material was crystallized from acetone/water three times, a 91% recovery of 100% optically pure material was obtained. The high efficiency of this optical enrichment process suggests that the melting point of resolved **5** may be higher than that of racemic material.

Crystal Structure Determinations of Host 1 and Its Complexes. Since host **1** is a prototype for the 18-membered ring compounds and since it and its complexes formed suitable crystals, the crystal structures of **1**, **1**·$LiClO_4$·H_2O, **1**·NaPic·H_2O, **1**·KSCN, **1**·RbPic, **1**·NH_4SCN, **1**·NH_4SCN·H_2O, and **1**·CH_3NH_3Pic were determined. Chart II contains stereoviews of the resulting structures.

Host **1**, with peak binding of ΔG = −12.8 kcal mol^{-1} (sodium), is among the strongest binders of the 23 quaterphenyl hemispherands described earlier.[5] Examination of CPK models[22] of **1** suggests that this host has only three important modes of conformation freedom: (1) Bond rotations in the $ArCH_2OC_6H_4OCH_2Ar$ portion of the molecule allow the angle between the plane of the catechol-derived ring and the best plane of the six host oxygens to vary between 0° and approximately 80°. When this angle is 0°, the electron pairs of the catechol oxygens point directly into the cavity of the host, giving a cavity that is complementary to Na^+. Rotation toward 80° causes the electron pairs of the catechol oxygens to point less directly inward, and the cavity appears more suitable for the formation of perching complexes with larger cations such as Rb^+. Conformations in which the benzyl methylenes occupy the cavity of the host appear strained and are unlikely to be significantly occupied at room temperature. (2) The aryl–oxygen bonds of the anisole units appear to be able to undergo a small degree of rotation without introduction of significant strain. Rotations of this type may serve to minimize unfavorable electron pair–electron pair interactions in the free host or to maximize electron pair–ion interactions in complexes of **1**. In models it is possible to insert one anisole methyl group into the cavity of the host without introducing excessive strain. (3) The aryl–aryl dihedral angles of the quaterphenyl unit can vary between values of approximately 45 and 90°. Increasing the values of the aryl–aryl dihedral angles enlarges the cavity diameter.

The crystal structure of **1** reveals that this host does not fill its own cavity in the absence of complexed guest. The catechol ring is rotated 77.9° out of the best plane of the six oxygens of the host. Molecular model examination suggests that this nearly perpendicular arrangement helps minimize unfavorable electron pair–electron pair interactions between the catechol oxygens and the oxygens of the quaterphenyl unit. The methoxyls of the quaterphenyl unit are also located in a manner that minimizes electron pair–electron pair interactions within the cavity of the host. Although the crystal structure of **1** fails to reveal any methyl groups turned into the cavity of the host, such a conformation may be partially occupied by **1** in solution. This is suggested by the lack of strain in such conformations in molecular models and by the superior binding properties[5] of host **2** relative to **1**. Molecular model examination suggests that turning an ethyl group into the cavity of **2** is more endothermic than turning a methyl group into the cavity of **1**.

In the stereoview of the crystal structure of **1**·$LiClO_4$, the ClO_4^- anion, which does not coordinate to the guest, is omitted. The Li^+ cation, which is too small to simultaneously contact all six oxygens of this relatively inflexible host, nests within the four oxygens of the quaterphenyl unit (Li–O distances 2.02–2.32 Å; standard[23] Li–O distance 2.16 Å). A water molecule simultaneously coordinates Li (Li–O distance 1.97 Å) and hydrogen bonds to the catechol oxygen at 4 o'clock (host oxygen–H distance 1.72 Å; the OHO angle is 156°). The remaining host oxygen at 2 o'clock coordinates Li^+ only weakly (Li–O distance 2.60 Å). The catechol ring lies at an angle of 48.2° to the best plane of the six host oxygens. Molecular model examination suggests that this angle is determined in part by the geometrical requirements for the water molecule to simultaneously coordinate Li^+ and hydrogen bond to the host. The aryl–aryl dihedral angles of the quaterphenyl unit decrease from an average value of 56.5° in the free host to an average value of 50.8° in **1**·$LiClO_4$.

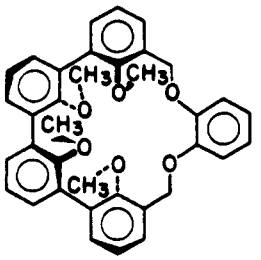
In the crystal structure of host **1**·NaPic, the picrate anion is not intimately involved in binding, and it is not shown in the stereoview in Chart II. Sodium ion is coordinated to all six oxygens of the host (Na–O distances 2.37–2.53 Å; standard[23] Na–O distance 2.52 Å) and to a water molecule (Na–O distance 2.35 Å). This water molecule is probably *not* hydrogen bonded to the host as all the host oxygens are coordinated to Na^+. The aryl–aryl dihedral angles of the quaterphenyl unit have an average value of 55.3° in this complex (56.5° in the free host). The catechol ring lies at an angle of 35.8° to the best plane of the six host oxygens. Molecular model examination suggests that the value of this latter angle reflects a compromise between maximizing the coordination of Na^+ by the catechol oxygens and minimizing steric hindrance to coordination of Na^+ by water. The Na^+ lies 0.47 Å out of the best plane of the host oxygens. Since the average deviation of the host oxygens themselves from this plane is 0.70 Å, this complex is well described as nesting.

Crystals of host **1**·KSCN obtained by slow evaporation of a solution of this complex in a mixture of CH_2Cl_2 and $(CH_2)_6$ contained two structurally similar but crystallographically distinct complexes. Only complex A is shown

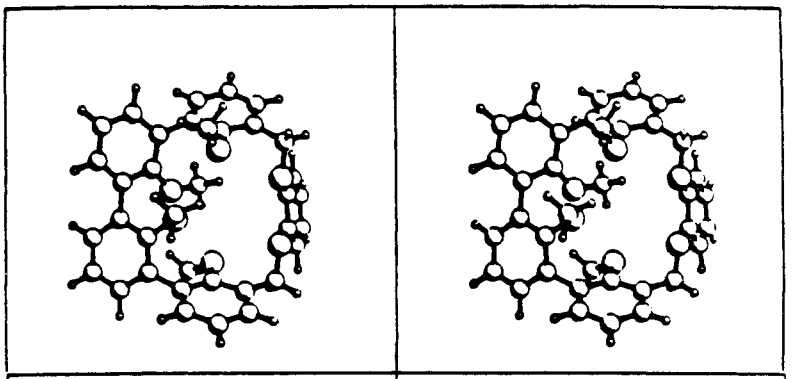
(22) Koltun, W. L. *Biopolymers* **1965**, *3*, 665–679.

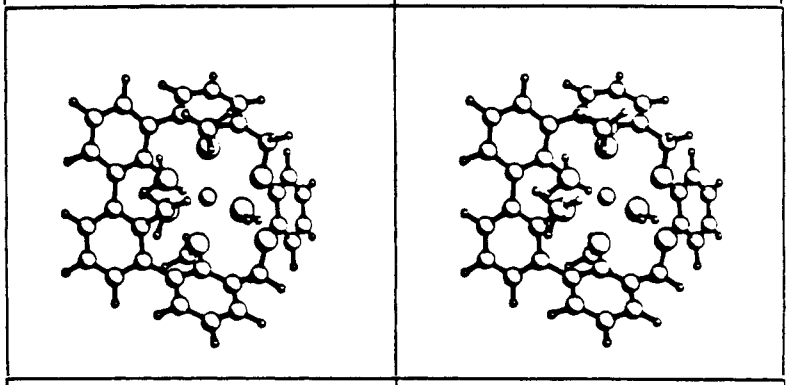
(23) (a) Shannon, R. D. *Acta Crystallogr., Sect. A* **1976**, *32*, 751–767. (b) *Handbook of Chemistry and Physics*, 57th ed.; CRC Press: Cleveland, OH, 1977; p D178.

Chart II. Crystal Structures of 1 and Its Complexes

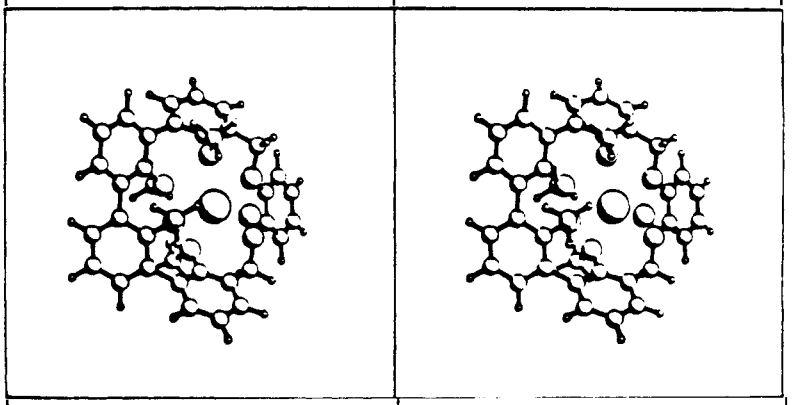


1

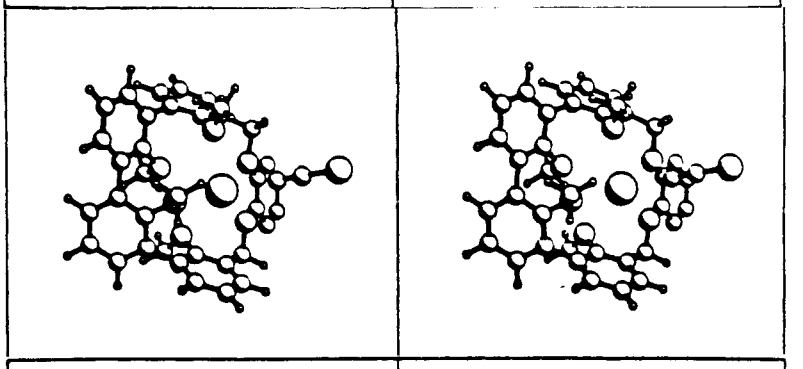




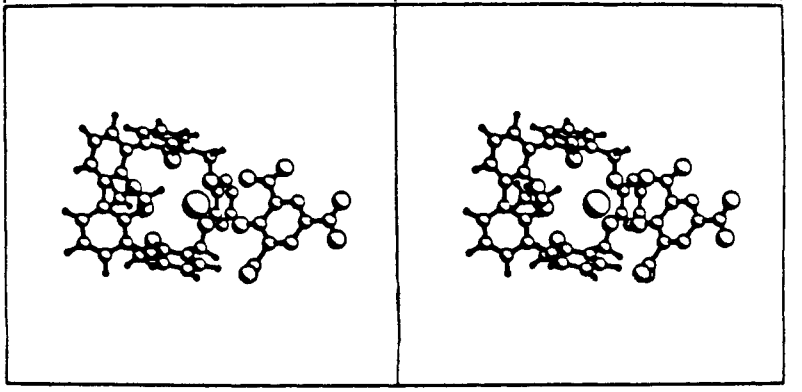
1 · Li^+ · H_2O



1 · Na^+ · H_2O

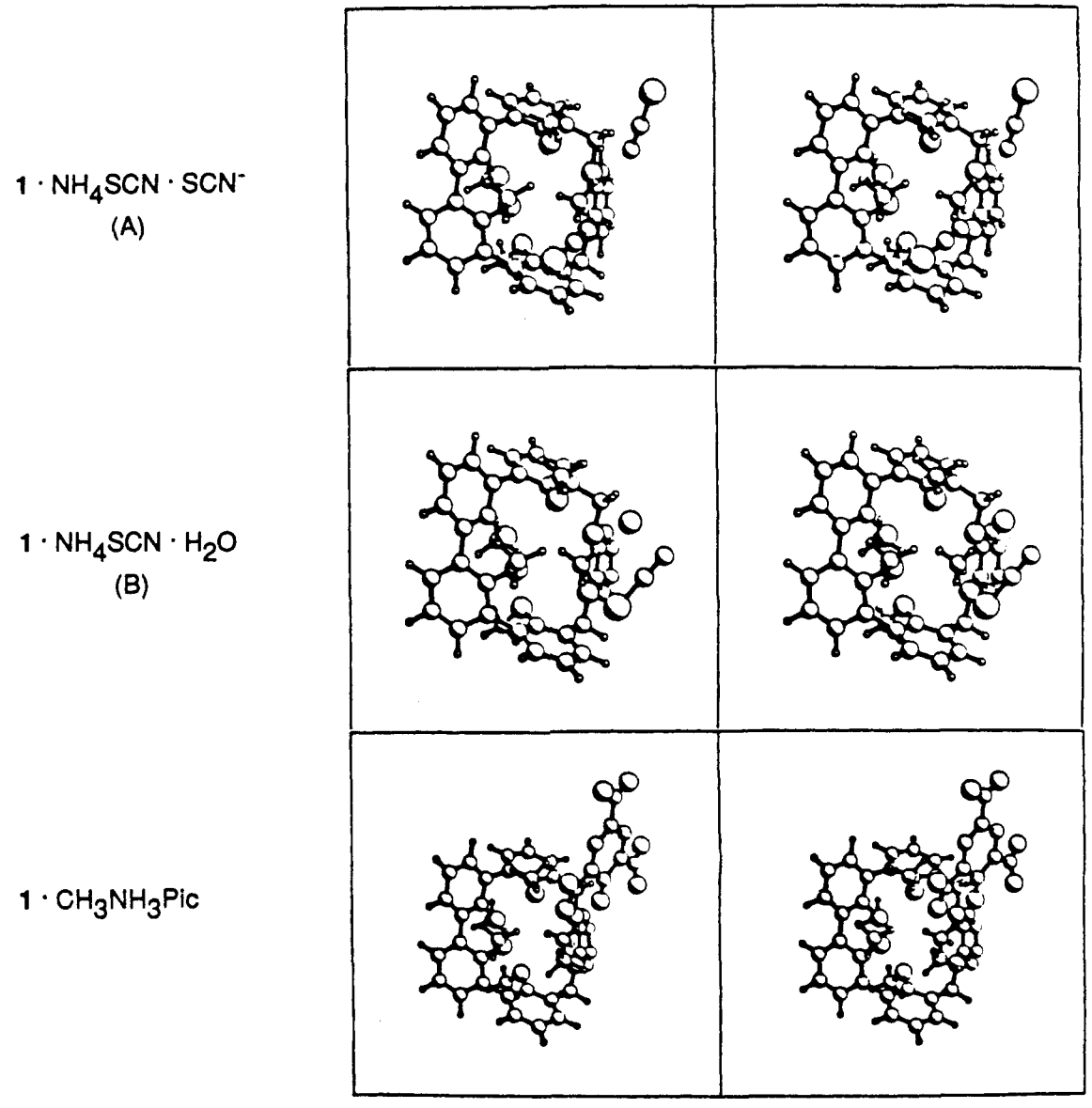


1 · KSCN



1 · RbPic

Chart II (*Continued*)



in Chart II. Contrary to expectations based on molecular model examination, complexes A and B are each better described as nesting rather than perching. In complex A the K^+ lies 1.00 Å out of the best plane of the six host oxygens. The average deviation of the host oxygens from this same plane is 0.69 Å. One anisole oxygen deviates from this plane by 1.21 Å on the same side of the plane as K^+. In complex B the K^+ lies 1.02 Å out of the best plane of the six host oxygens, and the average deviation of the six oxygens from this same plane is 0.66 Å. In each complex the K^+ ion is coordinated by all six oxygens of the host (complex A 2.58–2.99 Å; complex B 2.58–3.16 Å; standard[23] K–O distance 2.86 Å) and to the nitrogen of a thiocyanate counterion (complex A 2.70 Å; complex B 2.69 Å; standard[23] K–N distance 2.86 Å). The catechol ring lies at an angle to the best plane of the six host oxygens of 30.0° in complex A and 38.7° in complex B. The average of these two values is very similar to the value of this angle in the nesting complex 1·NaPic. The strain that results from insertion of the large potassium ion into the relatively small cavity of this host is reflected in the large quaterphenyl unit aryl–aryl dihedral angles in complexes A and B. The average value of these angles (averaged over both complexes) is 67.0°. This value is 10.5° greater than the average value of this parameter in free 1 and is the largest value of this parameter found in any of the complexes of 1 described in this paper.

A stereoview of the crystal structure of 1·RbPic is presented in Chart II. In contrast to the nesting arrangement observed in the complexes of 1 with the smaller ions, Rb^+ in 1·RbPic perches on one face of the macrocycle. Rubidium ion is displaced 1.97 Å from the best plane of the six host oxygens. The two nearest oxygens of the quaterphenyl unit are displaced from this same plane 1.42 (methoxyl oxygen at 8 o'clock) and 0.10 Å (methoxyl oxygen at 12 o'clock), respectively. The nearer anisole oxygens coordinate Rb^+ at distances of 2.91 and 2.93 Å (standard[23] Rb–O distance 2.92 Å) while the further anisole oxygens are essentially noncoordinating (Rb–O distances 4.11, 4.19 Å). The two catechol oxygens coordinate Rb^+ at distances of 2.89 and 2.92 Å. An interesting feature of this complex is the bidentate coordination of rubidium by the picrate counterion[24] (Rb–O distances: phenoxide oxygen, 2.77 Å; nitro oxygen, 3.21 Å). One nitro group of the picrate anion has rotated out of conjugation with the aromatic ring to reduce unfavorable steric interactions with

(24) Bidentate coordination of an alkali-metal cation by picrate anion has previously been observed in the crystal structure of valinomycin·NaPic: Steinrauf, L. K.; Hamilton, J. A.; Sabesan, M. N. *J. Am. Chem. Soc.* **1982**, *104*, 4085–4091.

Table II. Parameters Taken from Crystal Structures of Charts II and III[a]

compd	type complex	angle, deg: $(Ar-Ar)_4$ av dihedral	angle, deg: O_6 (best plane) and plane of 1,2-$C_6H_4O_2$	angle, deg: $C_6H_4O_2$ and $O_2 \cdot M^+$ planes of 1,2-$C_6H_4O_2$	dist of M^+ from O_6 best plane, Å
1		56.5	77.9		
1·$LiClO_4$	capsular	50.8	48.2	35.6	0.39
1·NaPic	nesting	55.3	35.8	20.3	0.47
1·KSCN (A)	nesting	67.2	30.0	4.2	1.00
1·KSCN (B)	nesting	66.9	38.7	14.0	1.02
1·RbPic	perching	65.7	43.7	7.5	1.97
1·NH_4SCN (A)	perching	61.5	50.2	3.4	2.07
1·NH_4SCN (B)	perching	61.1	39.6	6.6	1.85
1·CH_3NH_3Pic	perching	60.7	58.7	2.0	2.16
3 (A)		60.7	48.4		
3 (B)		62.9	46.6		
4		55.8	73.2		

[a] M^+ is the formally charged atom of the guest (metal ion or N^+ of ammonium).

the host anisole ring at six o'clock. An interesting question is whether the crystal structure of the potassium complex of 1 would have revealed a perching structure if a potentially bidentate counterion such as picrate had been used in place of thiocyanate.

When 1·NH_4SCN was recrystallized by slow evaporation of its solution in a mixture of CH_2Cl_2–EtOH, the resulting crystals contained two crystallographically distinct complexes, both pictured in Chart II. Complex A, 1·$NH_4SCN \cdot SCN^-$, is perching with the nitrogen atom of the guest lying 2.07 Å out of the best plane of the six host oxygens. Important interactions between host and guest include a hydrogen bond to the catechol oxygen at 4 o'clock (O–H distance 2.22 Å; N–H···O bond angle 160°) and a bifurcated hydrogen bond to the two nearest anisole oxygens of the quaterphenyl unit (O–H distances and NHO angles: 2.40 Å, 119°; 2.31 Å, 138°, respectively). The non-hydrogen-bonded catechol oxygen is close enough (2.94 Å) to have a significant stabilizing dipole–pole interaction with the nitrogen of the guest. The two non-hydrogen-bonded anisole oxygens are further away (>3.9 Å) and probably exert a minimal effect. The coordination sphere of the guest is completed by hydrogen bond formation to the nitrogens of two thiocyanate anions (H–NCS distances and NHN angles: 2.06 Å, 144°; 2.11 Å, 153°, respectively).

In complex B, 1·$NH_4SCN \cdot H_2O$, the ammonium ion binds to the host in qualitatively the same way. The guest nitrogen lies 1.85 Å out of the best plane of the six host oxygens. A hydrogen bond is formed to the catechol oxygen at 4 o'clock (O–H distance 1.98 Å; NHO angle 172°), and a bifurcated hydrogen bond is formed to the two anisole oxygens nearest the guest (O–H distances and NHO angles: 2.26 Å, 118°; 2.19 Å, 131°, respectively). The more nearly linear N–H–O arrangement of the nonbifurcated hydrogen bond in this complex, compared to the arrangement in complex A, results in part from a change in the angle between the plane of the catechol ring and the best plane of the six host oxygens from 50.2° in complex A to 39.6° in complex B. The catechol oxygen that is not involved in hydrogen bonding is located 2.88 Å from the nitrogen atom of the guest. The two thiocyanate nitrogens that served as external ligands for the ammonium ion in complex A are replaced by a water and a thiocyanate sulfur in complex B. The hydrogen bond to water is 1.95 Å in length, and the NHO angle is 172°; that to the thiocyanate sulfur is 2.51 Å long and has a NHS angle of 145°. The length of the hydrogen bond to sulfur reflects in part the larger covalent radius of this element. The thiocyanate anion in 1·$NH_4SCN \cdot H_2O$ is identical with the thiocyanate anion at 2 o'clock in the stereoview of 1·$NH_4SCN \cdot SCN^-$. Thus the thiocyanate anion forms a bridge between two crystallographically nonequivalent guests.

A stereoview of the crystal structure of host 1·CH_3NH_3Pic is shown in Chart II. The nitrogen of the guest perches 2.16 Å out of the best plane of the six host oxygens. As was observed in the crystal structures of 1·NH_4SCN, a bifurcated hydrogen bond is formed to the two nearest anisole oxygens of the quaterphenyl unit (O–H distances and NHO angles: 2.31 Å, 132°; 2.40 Å, 137°, respectively). The hydrogen bond to a single catechol oxygen observed in 1·NH_4SCN is replaced in 1·CH_3NH_3Pic by a hydrogen bond that is bifurcated between both catechol oxygens (O–H distances and NHO angles: 2.17 Å, 121°; 1.92 Å, 153°, respectively). The methyl group of the guest lies against the face of the anisole ring at 6 o'clock. The phenoxide oxygen of the picrate anion accepts a hydrogen bond from the nitrogen of the guest (O–H distance 1.92 Å; NHO angle 172°). A somewhat unusual feature of this complex is a weak hydrogen bond donated from the carbon[25] of methylammonium to a nitro oxygen of the picrate counterion (O–H distance 2.31 Å; CHO angle 133°).

These general conclusions apply to all the crystal structures of Chart II. All structures contain at least one water molecule or anion coordinated to the complexed guest. When the guests are Li^+, Rb^+, NH_4^+, and $CH_3NH_3^+$, the external ligand(s) apparently compensates for the guest's inability to fulfill its coordination requirements by simultaneously contacting all the binding sites of the host (size-noncomplimentarity). In the structures of the Na^+ and K^+ complexes, an external ligand (water or SCN^-) is coordinated to the guest in spite of the guest's ability to simultaneously contact all six oxygens of the host. Examination of molecular models suggests that in the absence of external ligands, optimized host–sodium and host–potassium complexes have an extremely uneven distribution of ligands over the surface of the metal ion. In these two complexes the function of the external ligand appears to be to compensate for the noncomplementarity of the symmetry properties of the host binding sites to those of the guest.[33]

Examination of the structural data in Table II allows several other generalizations to be made about the complexes of 1. In accord with predictions made by examination of molecular models, the average value of the aryl–aryl dihedral angles of the quaterphenyl unit varies with the size of the guest. Of all the complexes, the value

(25) (a) Berkovitch-Yellin, Z.; Leiserowitz, L. *Acta Crystallogr., Sect. B* **1984**, *40*, 159–165. (b) Greene, R. D. *Hydrogen Bonding by C–H Groups*; Wiley: New York, 1974. (c) de Boer, J. A. A.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J.; de Jong, F. *J. Am. Chem. Soc.* **1982**, *104*, 4073–4096.

of this parameter in 1·NaPic is most similar to the value observed in the free host. The dihedral angles decrease to allow the four anisole oxygens to converge on Li^+ in 1·$LiClO_4$ and increase to allow partial encapsulation of K^+ in 1·KSCN. In the perching complexes the average value of these angles is substantially greater than in the nesting Na^+ complex but somewhat less than in the nesting K^+ complex. Examination of molecular models suggests that large aryl–aryl dihedral angles direct the methoxyl unshared electron electron pairs more directly toward a perching guest than do smaller angles.

The angle of the catechol-derived ring to the best plane of the six host oxygens is largest for the free host 1 and smallest for the nesting complexes of Na^+ and K^+. This angle is the least disturbed in going from 1 (77.9°) to 1·CH_3NH_3Pic (48.2°) and 1·NH_4SCN (A, 50.2°), both of which are perching complexes. Examination of the angles between the $C_6H_4O_2$ and $O_2{\cdot}M^+$ planes of the 1,2-$C_6H_4O_2{\cdot}M^+$ moieties (M^+ is the metal ion or N^+ of ammonium ions) reveals (Table II) that except for 1·$LiClO_4$, 1·NaPic, and 1·K^+ (B), the catechol ring is orientated in a nearly optimum arrangement for interaction of its C–O dipoles with the positive charge of the guest. The very large value of this angle in 1·$LiClO_4$ is related to the fact that neither of the two catechol oxygens directly coordinates the lithium ion. The orientation of the catechol ring is apparently controlled by the hydrogen bonding requirements of the water molecule in this complex. In 1·NaPic, optimization of the orientation of the C–O dipoles is opposed by the steric requirements of a water molecule which is coordinating the nesting sodium ion.

This study provided several important pieces of information that are relevent to potential applications of chiral host compounds structurally related to 1: (1) All four of the alkali-metal ion complexes for which crystal structures were determined contained either water or a counterion coordinated to the metal ion. The formation of contact ion pairs between prochiral carbanions such as enolates and chiral corand–cation complexes is potentially useful for asymmetric catalysis.[26] (2) Examination of the crystal structures illustrated in Chart II suggests that the Na^+ and K^+ complexes of hosts closely related to 1 would provide more efficient transfer of chirality from host to reaction product than the use of Li^+, Rb^+, or Cs^+ complexes. (3) The relatively unstructured dipodal binding observed in the ammonium and methylammonium complexes of 1 suggests that 18-member macrocyclic hosts of this type are relatively poor candidates for enantioselective binding[27] of alkylammonium or amino acid guests.

Solution Structure of 1 and Its Complexes. Variable-temperature ^1H NMR studies coupled with molecular model examination support the supposition that the structures of these complexes in solution are similar to those revealed in the crystals. Molecular model examination suggests that the nesting complexes of 1 can achieve dynamic C_2 symmetry by a low-energy process involving dissociation of the external ligand (water or counterion), rotation about the benzyl C–O bonds of the host, and reassociation of the external ligand from the opposite face of the macrocycle. Perching complexes can achieve C_2 symmetry only by processes that transfer the guest ion from one face of the macrocycle to the other. Processes of this type, which are discussed below, are expected to be more energetically demanding than the process described for nesting complexes. In the event, all the complexes studied by ^1H NMR spectroscopy gave spectra at 300 K that were indicative of either static or dynamic C_2 symmetry. At lower temepratures, however, substantial differences were observed between the spectra of complexes having a nesting structure in the crystalline state and those having a perching structure in the crystalline state.

The 200-MHz ^1H NMR spectra of 1·NaPic in $CDCl_3$ revealed C_2 symmetry for this complex at temperatures ranging between 200 and 300 K. The 500-MHz spectrum of this complex at 180 K in CD_2Cl_2 also revealed C_2 symmetry. All these spectra were sharp and free of temperature-dependent broadening. These results are compatible with either of two structures for 1·NaPic in solution: a structure similar to that revealed in the crystal structure of 1·NaPic, having dynamic C_2 symmetry by virtue of the mechanism described above; a structure in which the sodium ion lacks external ligands and in which the catechol-derived aryl ring lies in the best plane of the six host oxygens. The latter type of complex would have static C_2 symmetry. Studies performed on host 3 (vide infra) strongly suggest that a structure of the latter variety would be higher in energy than a structure of the former.

The 500-MHz ^1H NMR spectrum of 1·RbPic in CD_2Cl_2 at 275 K was also compatible with a complex having dynamic C_2 symmetry on the ^1H NMR time scale. The inner and outer methoxyls of the quaterphenyl unit appeared in this spectrum as singlets at δ 2.58 and 3.15. As the temperature of the sample was lowered to 200 K, the peak at δ 2.58 broadened until it almost disappeared into the base line. As the temperature was lowered further to 180 K, this broad peak split into two broad peaks which sharpened with decreasing temperature. At 170 K, these peaks were sharp and had chemical shift values of δ 1.96 and 3.08, respectively. On the basis of a peak separation ($\Delta\nu$) of 560 Hz, a coalescence temperature (T_c) of 200 ± 5 K, and an assumption of a unimolecular process, the value of $\Delta G^{\ddagger}$ (200 K) was calculated[28] to be 8.7 ± 0.7 kcal mol^{-1} for the process leading to dynamic C_2 symmetry. The ease with which the dynamic C_2 symmetry of 1·RbPic could be frozen out on the ^1H NMR time scale supports the notion that this complex has a perching structure in solution as well as in the solid state.

For a perching complex such as 1·RbPic to achieve dynamic C_2 symmetry, a low-energy pathway must be available for transferring the guest from one face of the macrocycle to the other. One way in which this might occur would involve dissociation of the complex, followed by rotation about the benzyl C–O bonds of the host and recomplexation of the guest on the opposite face of the macrocycle. Examination of molecular models suggests that such a process requires the guest to move far enough away from the host binding site that its interaction with the host becomes negligible. Such a process would therefore be expected to result in complete scrambling of

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(27) (a) Timko, J. M.; Helgesson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 2828–2834. (b) Kyba, E. P.; Timko, J. M.; Kaplan, L. J.; deJong, F.; Gokel, G. W.; Cram, D. J. *Ibid.* **1978**, *100*, 4555–4568. (c) Sousa, L. R.; Sogah, G. D. Y.; Hoffman, D. H.; Cram, D. J. *Ibid.* **1978**, *100*, 4569–4576. (d) Peacock, S. C.; Domeier, L. A.; Gaeta, F. C. A.; Helgeson, R. C.; Timko, J. M.; Cram, D. J. *Ibid.* **1978**, *100*, 8190–8202. (e) Sogah, G. D. Y.; Cram, D. J. *Ibid.* **1979**, *101*, 3035–3042. (f) Newcomb, M.; Toner, J. L.; Helgeson, R. C.; Cram, D. J. *Ibid.* **1979**, *101*, 4941–4947. (g) Peacock, S. C.; Walba, D. M.; Gaeta, F. C. A.; Helgeson, R. C.; Cram, D. J. *Ibid.* **1980**, *102*, 2043–2052. (h) Lingenfelter, D. S.; Helgeson, R. C.; Cram, D. J. *J. Org. Chem.* **1981**, *46*, 393–406.

(28) Sandström, J. *Dynamic ^1H-NMR Spectroscopy*; Academic Press; New York, 1981; pp 81–84.

(29) Kost, D.; Carlson, E. H.; Raban, M. *Chem. Commun.* **1971**, 656–657.

host–guest pairs. A second mechanism by which a perching complex might achieve dynamic C_2 symmetry involves a "donut-hole" process in which the external ligand(s) of the guest dissociates, the guest passes through the middle of the macrocycle, and the external ligand(s) reassociates with the guest ion from the opposite face of the macrocycle. The first two steps of such a process might be concerted. This mechanism is suggested by the fact that 1·KSCN possesses a nesting structure in the crystalline state. The ionic radius of rubidium is only 0.15 Å greater than that of potassium.[23] A nesting complex might resemble either the transition state or a metastable intermediate in the donut-hole mechanism.

In an attempt to discriminate between the decomplexation/recomplexation mechanism and the donut-hole mechanism, the following experiment was performed: 3.5 equiv of free host 1 was added to a solution of 1·RbPic in CD_2Cl_2. At 200 K the 500-MHz ^1H NMR spectrum of this mixture revealed a sharp (outer) methoxyl peak at δ 2.93 for the free host and at δ 3.06 for the rubidium complex. The latter value is in good agreement with that obtained at this temperature in the absence of free host. Coalescence of these two peaks occurred at 230 K, and at 240 K these two peaks averaged into a single peak at δ 2.99. On the basis of a coalescence temperature of 230 ± 5 K, a frequency separation of 66 Hz, and an assumption of a unimolecular process, the method of Shanan-Atadi and Bar-Eli[30] was used to calculate $\Delta G^{\ddagger}$ (230 K) = 11.0 ± 0.7 kcal mol^{-1} for the dissociation of 1·RbPic in CD_2Cl_2. The assumption of a unimolecular mechanism for this process is supported by CPK molecular model examination, which suggests that a rubidium ion cannot simultaneously contact the binding sites of two different host molecules. The measured free energy barrier to dissociation of 1·RbPic in CD_2Cl_2 at 230 K is 2.3 kcal mol^{-1} greater than the previously measured value of the free energy barrier to the process by which this complex exhibits C_2 symmetry in the same solvent at 200 K. These experiments demonstrate that the dynamic C_2 symmetry observed for 1·RbPic at 300 K results at least in part from the migration of the rubidium ion from one face of the macrocycle to the other via a complexation/decomplexation mechanism. The data also strongly suggest but do not prove the existence of a second, lower energy, donut-hole mechanism. Our inability to draw firm conclusions about the existence of the latter mechanism arises from the relative imprecision of our $\Delta G^{\ddagger}$ measurements and from the fact that they were determined at different temperatures.

Variable-temperature 200-MHz ^1H NMR studies performed on 1·NH_4SCN in $CDCl_3$ gave results analogous to those obtained for 1·RbPic in the same solvent. The ^1H NMR spectrum of this complex at 300 K revealed methoxyl peaks at δ 2.73 and 3.34. The peak at δ 2.73 broadened as the temperature of the sample was lowered to 220 K and separated into two broad peaks below this temperature. At 204 K the higher field peak (of these latter two) was still somewhat broad and had a chemical shift of δ 2.22. The lower field peak was obscured by overlap with the methoxyl peak at δ 3.34 (which had also begun to broaden). On the basis of a coalescence temperature of 220 ± 10 K, a frequency separation of 225 ± 75 Hz, and an assumption of a unimolecular process, $\Delta G^{\ddagger}$ (220 K) for the process by which this complex exhibits dynamic C_2 symmetry was calculated to be 10.3 ± 1.4 kcal mol^{-1}. No experiments were performed to determine the nature of this process. The ease with which this C_2 symmetry could be frozen out on the ^1H NMR time scale supports the assignment of a perching structure for this complex in solution.

The methoxyl peak at δ 2.75 in the 200-MHz ^1H NMR spectrum of 1·CH_3NH_3Pic in $CDCl_3$ was observed to be substantially broadened even at 300 K. This observation, by analogy with the studies performed on 1·RbPic and 1·NH_4SCN and in contrast to the studies performed on 1·NaPic, supports the assignment of a perching structure for this complex in solution. No attempt was made to determine $\Delta G^{\ddagger}$ or the mechanism of the process leading to dynamic C_2 symmetry in this complex.

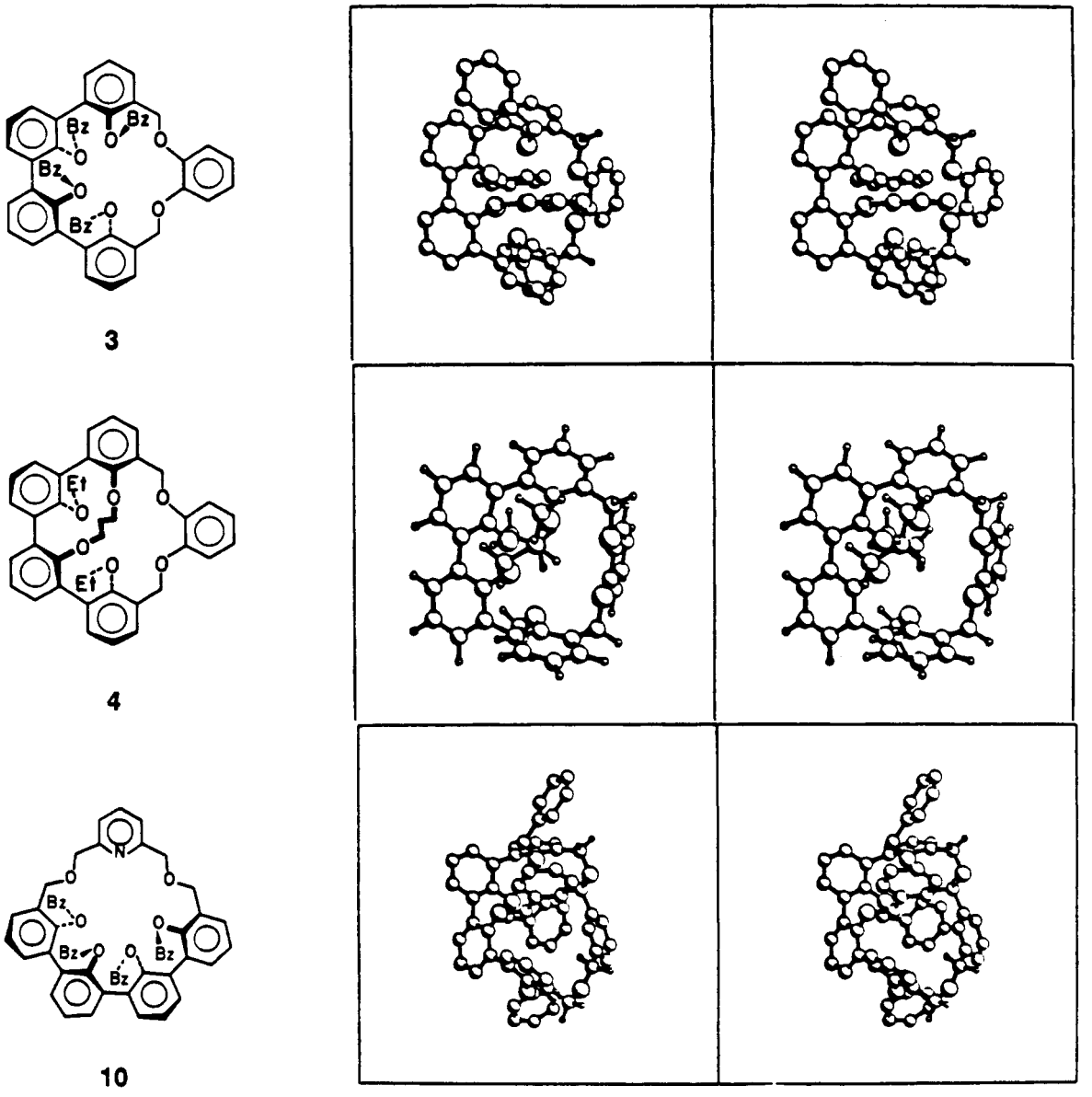
Crystal Structures of Hosts 3, 4, and 10. Crystals obtained by slow evaporation of a solution of host 3 in a mixture of CH_2Cl_2 and MeOH were found to contain two structurally similar but crystallographically distinct conformers of 3. Only conformer A is shown in Chart III. In accord with predictions made on the basis of molecular model examination, the average value of the aryl–aryl dihedral angles of the quaterphenyl unit increases slightly on going from free host 1 to free host 3 (Table II). This change is, however, only about one-half as great as the total variability in the value of this parameter among various complexes of 1. The catechol ring lies at an angle of 47.5° (average of the two crystal structures) to the best plane of the six host oxygens. Examination of molecular models and of the values observed for this angle in host 1 and its complexes suggests that this portion of the macrocycle is much more preorganized for binding in host 3 than in host 1. The greater preorganization of the catechol portion of the macrocycle in host 3 appears to be enforced by the steric bulk of the benzyl groups that overlie both faces of the macrocycle. The crystal structure of 3, the data in Table II, and molecular models all point to the conclusion that host 3 *is completely preorganized into its binding conformation prior to complexation.*

A stereoview of the crystal structure of host 4 is shown in Chart III. Host 4 is related to host 1 by formally replacing the two OCH_3 methyl groups on one face of the macrocycle with a trimethylene bridge and replacing the two remaining OCH_3 methyl groups with ethyl groups. The superior lithium-binding properties of host 4 as compared to host 1 (see the next section) can be explained by assuming that host 4 binds Li^+ in a manner similar to that observed in the crystal structure of 1·$LiClO_4$. Compression of the aryl–aryl dihedral angles of the quaterphenyl unit by the trimethylene bridge gives a cavity more complementary to Li^+ than that of 1. The average value of the aryl–aryl dihedral angles in 4, which is only 0.7° less than the average value of this parameter in 1, is somewhat misleading. The aryl–aryl dihedral angles of 4 that are encompassed by the trimethylene bridge have an average value of 47.2°. The average value for all three aryl–aryl dihedral angles of this host is raised to 55.8% by the single unencompassed aryl–aryl dihedral angle of 73.0°. Molecular model examination suggests that the value of this latter angle can vary freely with little change in the strain energy of the host. The particular value of this angle observed in the crystal structure of 4 may represent a relatively shallow energy minimum and/or the effects of crystal packing forces.

Chart III also contains a stereoview of the crystal structure of 10, which contains a 21-membered macrocyclic ring into which is incorporated a 2,6-disubstituted pyridine ring. Four benzyloxy groups attached to the quaterphenyl assembly along with the pyridine ring lend some degree of preorganization to this system, although not enough to prevent its cavity from being largely filled with three in-

(30) Shanan-Atadi, H.; Bar-Eli, K. H. *J. Phys. Chem.* **1970**, *74*, 961–963. The data presented in graphical form in this paper are presented in a more useful tabular form in ref 28.

Chart III. Crystal Structures of Free Hosts 3, 4, and 10



ward-turned CH_2 groups. The average dihedral angle for the $(Ar–Ar)_4$ moiety in **10** is 63°.

Correlation between Structure and Binding of These Hemispherands. The association constants (K_a, M^{-1}) and binding free energyes ($-\Delta G°$, kcal mol^{-1}) were determined at 25 °C by distributing Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ picrate salts between H_2O and $CDCl_3$ solutions of hosts **3–12**.[7,21,32] Table III records the results, including those K_a and $-\Delta G°$ values reported earlier for **1** and **2**.[5] These hemispherands are better general binders of cations than the corands but poorer than the spherands, cryptands, and the cryptahemispherands.[28]

Examination of Table III reveals that tetrabenzyloxy host **3** binds alkali-metal and alkylammonium ions much less strongly than the corresponding tetramethoxy and tetraethoxy hosts **1** and **2**. This result is surprising in light of the apparently greater degree of preorganization for binding observed in the crystal structure of **3** as compared to that of **1**. The unexpectedly low association constants observed for **3** were shown to represent equilibrium values in the cases of Li^+ and K^+ as guests. When the standard picrate extraction experiment was performed with vortexing times of 0.5–30 min, identical results were obtained independent of vortexing time. Rapid *decomplexation* of the NaBr complex of **3** was observed under two-phase conditions during its isolation procedure. The binding constants for host **3** (and all other new hosts reported in this paper) were calculated based on extraction experiments in which the two phases were vortexed together for at least 2 min.

Examination of the crystal structures of free host **3**, free hemispherand **1**, and the complexes of hemispherand **1** coupled with molecular model examination suggest the following explanation for the diminished binding ability of **3** relative to **1**. The six oxygens of host **3** or host **1** are by themselves able to satisfy the coordination requirements of alkali-metal and ammonium ions only poorly. Host **1** can compensate for this deficiency at the entropic cost of immobilizing a solvent molecule or counterion. In host **3**, coordination of the complexed guest by solvent or by the counterion is either impossible or very nearly so, due to the steric shielding of the occupied cavity by the four benzyl groups. Thus the relative binding abilities of hosts **3** and **1** reflect the opposing effects of greater preorganization of the host oxygens and poorer ion pairing or sol-

Table III. Association Constants and Binding Free Energies Calculated from Phase-Distribution Experiments of Picrate Salts in Water and Hosts in $CDCl_3$ at 25 °C

compd	cation	K_a, M^{-1}	$-\Delta G°$, kcal mol^{-1}	compd	cation	K_a, M^{-1}	$-\Delta G°$, kcal mol^{-1}
1	Li	1.7×10^5	7.1	7	Li	3.9×10^5	7.6
	Na	4.1×10^9	13.1		Na	1.7×10^9	12.6
	K	1.1×10^8	11.0		K	1.1×10^7	9.6
	Rb	6.7×10^6	9.3		Rb	1.0×10^6	8.2
	Cs	9.0×10^5	8.1		Cs	3.2×10^5	7.5
	NH_4	5.5×10^6	9.2		NH_4	1.3×10^6	8.3
	CH_3NH_3	6.9×10^4	6.6		CH_3NH_3	9.4×10^5	6.8
	$(CH_3)_3CNH_3$		<5.0		$(CH_3)_3CNH_3$	3.7×10^3	4.9
2	Li	1.6×10^5	7.1	8	Li		<7.0
	Na	1.6×10^9	12.5		Na	8.2×10^6	9.4
	K	4.2×10^8	11.8		K	4.2×10^5	7.7
	Rb	4.0×10^7	10.4		Rb	2.0×10^5	7.2
	Cs	3.4×10^6	8.9		Cs		<7.0
	NH_4	2.3×10^7	10.0		NH_4	7.6×10^4	6.7
	CH_3NH_3	2.0×10^5	7.2		CH_3NH_3		<6.0
	$(CH_3)_3CNH_3$		<5.0		$(CH_3)_3CNH_3$		<5.0
3	Li		<7.0	9	Li		<7.0
	Na	3.8×10^7	10.3		Na	1.6×10^5	7.1
	K	3.7×10^6	9.0		K	4.0×10^8	11.7
	Rb	5.5×10^5	7.8		Rb	2.8×10^8	11.5
	Cs	1.1×10^5	6.8		Cs	9.5×10^7	10.9
	NH_4	4.8×10^5	7.7		NH_4	8.8×10^7	10.8
	CH_3NH_3	3.8×10^4	6.2		CH_3NH_3	6.3×10^6	9.3
	$(CH_3)_3CNH_3$		<5.0		$(CH_3)_3CNH_3$		<5.0
4	Li	2.5×10^7	10.1	10	Li		<7.0
	Na	5.9×10^9	13.3		Na		<7.0
	K	1.4×10^9	12.5		K	3.8×10^6	9.0
	Rb	6.0×10^7	10.6		Rb	2.2×10^7	10.0
	Cs	1.4×10^6	8.4		Cs	9.9×10^6	9.5
	NH_4	2.1×10^7	10.0		NH_4	2.8×10^6	8.8
	CH_3NH_3	6.8×10^5	8.0		CH_3NH_3	4.0×10^5	7.6
	$(CH_3)_3CNH_3$	7.5×10^3	5.3		$(CH_3)_3CNH_3$		<5.0
5	Li	6.1×10^8	12.0	11	Li	4.4×10^8	11.8
	Na	6.3×10^{10}	14.7		Na	1.1×10^8	11.0
	K	3.3×10^9	13.0		K	1.6×10^{10}	13.9
	Rb	1.2×10^8	11.0		Rb	9.3×10^9	13.6
	Cs	5.2×10^6	9.2		Cs	8.5×10^8	12.2
	NH_4	1.1×10^8	11.0		NH_4	8.4×10^8	12.2
	CH_3NH_3	3.4×10^7	10.3		CH_3NH_3	2.3×10^8	11.4
	$(CH_3)_3CNH_3$	3.0×10^4	6.1		$(CH_3)_3CNH_3$	5.1×10^6	9.1
6	Li	9.8×10^7	10.9	12	Li	3.6×10^8	11.7
	Na	7.1×10^{10}	14.8		Na	2.2×10^8	11.4
	K	4.0×10^9	13.1		K	3.0×10^9	12.9
	Rb	6.9×10^7	10.7		Rb	5.9×10^9	13.3
	Cs	3.3×10^6	8.9		Cs	7.6×10^9	13.5
	NH_4	4.8×10^7	10.5		NH_4	5.4×10^8	11.9
	CH_3NH_3	1.7×10^6	8.5		CH_3NH_3	2.0×10^8	11.3
	$(CH_3)_3CNH_3$	6.7×10^3	5.2		$(CH_3)_3CNH_3$	1.2×10^7	9.7

vation of the host–guest complexes of **3** as compared to **1**.

An interesting comparison involves the binding properties of host **3** relative to those of spherand **13**. The crystal structures of free **13**, the sodium complex of **13**, and the lithium complex of **13** have been reported.[2] These structures reveal that **13** is completely organized into a binding conformation prior to complexation. Examination of the crystal structure of free **3** and of molecular models of its sodium and potassium complexes strongly implies that this is also true of host **3**. In both hosts a lipophilic barrier protects the binding site of the free host from solvation. These same barriers also prevent a bound guest from coordinating with solvent or contact ion pairing with anions. Both hosts have six oxygen ligating sites. Host **13** shows peak binding[3] for LiPic of $-\Delta G° > 23$ kcal mol^{-1}. Host **3** shows peak binding for NaPic of $-\Delta G° = 10.3$ kcal mol^{-1}. The >12.7 kcal mol^{-1} difference in peak binding free energy for these two hosts appears to be best attributed to the fact that **13** presents a complexed guest with an almost perfectly octahedral arrangement of ligating sites whereas the binding sites of **3** are organized into a much less symmetrical arrangement. This comparison suggests that the exceptionally strong binding of Li^+ and Na^+ exhibited by **13** arises not only from its superior degree of preorganization for binding compared to other hosts but also from the highly complementary relationship between its octahedral arrangement of binding sites and the spherical arrangement of binding sites presented by alkali-metal ion guests.

Host **5** differs from host **4** only in that **5** possesses a methyl group para to each oxygen of the quaterphenyl unit. Host **5** binds alkali-metal and ammonium ion guests 0.5–2.3 kcal mol^{-1} more strongly than host **4**. The overall stronger binding exhibited by **5** compared to **4** is probably best explained by the electron-releasing substituent effect of the methyl group.[31] In the crystal structures of the

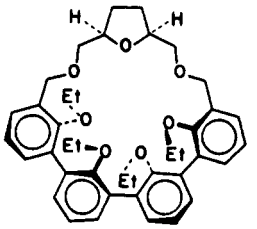
(31) For additional examples of this effect, see: (a) Cram, D. J.; Carmack, R. A.; deGrandpre, M. P.; Lein, G. M.; Goldberg, I.; Knobler, C. B.; Maverick, E. F.; Trueblood, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 7068–7073. (b) Doxsee, K. M.; Feigel, M.; Stewart, K. D.; Canary, J. W.; Knobler, C. B.; Cram, D. J. *Ibid.* **1987**, *109*, 3098–3107.

various complexes of 1 reported in this paper, the coordinating electron pairs of the anisole oxygens appear to be almost perfectly aligned for maximum resonance interaction with the aromatic ring. Electron release by the methyl group competes with that of the anisole oxygen for electron donation to the aromatic ring and thereby increases both the electron density on oxygen and the aromatic C–O dipole moment. This increase in the C–O dipole moment helps explain why the binding of the relatively hard Li^+ and Na^+ ions is enhanced by the addition of para methyl groups more than that of larger, softer cations such as potassium. The largest differential binding free energy between the two hosts is that for methylammonium ion (2.6 kcal mol^{-1}). In the crystal structure of $1{\cdot}CH_3NH_3Pic$ the electron-deficient methyl group of this guest lies against the face of one of the anisole rings.

Formal replacement of the trimethylene bridge of host 5 with an *o*-xylene bridge gives host 6. Unstrained molecular models can be made of host 6 in which the aryl ring of the *o*-xylene bridge is either lying over the center of one face of the macrocycle or folded back over the quaterphenyl unit. The ^1H NMR spectra of both free and complexed (NaI) 6 are compatible with either interconversion of these two conformers at a rate that is very fast on the ^1H NMR time scale or with a >97:3 predominance of one conformer. Examination of molecular models, calibrated to the observance/nonobservance of dynamic ^1H NMR phenomena in other systems, suggests that the former explanation is unlikely. The conformation of this host in both free and complexed states is assigned as that with the *o*-xylene ring lying over the face of the macrocycle based on the following evidence: (1) An aromatic multiplet is observed in the ^1H NMR spectrum of free host 6 at δ 6.38. Examination of a molecular model of the assigned conformation suggests that an aromatic proton of the xylene bridge (meta to methylene) is in the shielding cone of the catechol-derived ring. Examination of a model of the alternative conformation offers no explanation for this high-field shift. (2) Examination of Table III reveals that 6 binds both small ions (Li^+) and large ions (NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$) less strongly than 5. We presume that host 6 possesses the assigned conformation and that the modes of ion binding by hosts 6 and 5 are similar to those oberved in the crystal structures of complexes of 1. The external ligand (water or counterion) present in all the complexes of 1 must approach complexes of 6 from the face of the macrocycle that is opposite the *o*-xylene bridge. Bending of the catechol-derived ring out of the best plane of the six host oxygens and away from the external ligand (as was observed in complexes of 1) leads to unfavorable steric interactions between the catechol ring and the *o*-xylene bridge. These steric interactions increase in severity as the angle between the catechol ring and the best plane of the host oxygens increases. Examination of Tables II and III reveals that those ions for which an *o*-xylene bridge suppresses binding (compared to a trimethylene bridge) are those that are bound by 1 with an angle between the catechol ring and the best plane of the six host oxygens that is greater than 45°.

Comparison of the binding properties of tetramethoxy host 46, tetraethoxy host 7, and tetrabenzyloxy host 8 reveals roughly the same pattern of binding energies that were observed when the alkyloxy group was changed from methyl to ethyl to benzyl in the series of hosts 1–3. The methyl and ethyl compounds have similar binding properties, while those of the benzyl compound are much reduced. The decreased binding abilities of the benzyl compound 8 is attributed to the same cause (steric inhibition of solvation and ion pairing in the complex) to which the inferior binding properties of host 3 were attributed.

In contrast to the results just described, the presence of four benzyloxy groups in 21-member ring hosts 9 and 10 does not significantly diminish the binding abilities of these hosts relative to the corresponding tetramethoxy and tetraethoxy compounds. The greater conformational flexibility and the seven heteroatom binding sites of these larger hosts may lead to a mode of binding in which external ligands such as anions or water molecules are not employed. An alternative explanation, supported both by molecuolar model examination and by examination of the crystal structure of free host 10 (Chart III), is that in these larger ring hosts the benzyl groups are less constrained to lie over the face of the macrocycle and thus present less of a hindrance to external ligands. The latter hypothesis suggests that 9 and 10, unlike 8 and 3, might be useful as chiral catalysts. An additional reason for the preparation of host 9 was the observation that tetraethoxy host 50



50

binds K^+ selectively over Na^+ by 4.5 kcal mol^{-1} ($K_a(K^+)/K_a(Na^+)$ = 2000).[5] Molecular model examination suggests that host 50 binds Na^+ in a partially collapsed conformation in which the tetrahydrofuran ring has twisted out of the best plane of the host oxygens and one benzylic oxygen is turned out of the cavity. Molecular model examination further suggests that formation of a similar conformation in 9 might be inhibited by steric interactions between the benzyl groups and the tetrahydrofuran ring. In the event, the K^+ over Na^+ selectivity of 9 was found to be very similar to that of 50, with $\Delta(-\Delta G°)$ = 4.6 kcal mol^{-1}, or $K_a(K^+)/K_a(Na^+)$ = 2500.

An alternative approach to hosts having enhanced selectivity for K^+ over Na^+ involved examination of diastereomerically related hosts 11 and 12. We hoped that the *o*-xylene bridge of these hosts would inhibit formation of the collapsed conformation that was presumed for host 50 above. Of these isomeric hosts, 11 is the one having the greater R_f value on silica gel. The ^1H NMR spectra of these diastereomers are too complex to be useful for configurational assignment. Molecular model examination suggests that each of these hosts has stable conformations in which the *o*-xylene bridge either lies over the face of the macrocycle or folds back over the quaterphenyl unit. Interconversion between these two conformations appears to be sufficiently difficult that such a process should be slow on the ^1H NMR time scale. Examination of this prediction revealed that host 11 and its NaI complex each exist as a 2:1 mixture of slowly interconverting (^1H NMR time scale) conformers. It is not clear whether it is the same conformer that predominates in both the free and complexed host. The ^1H NMR spectra of 12 and its sodium iodide complex each revealed the presence of only a single conformer. The selectivity of these two hosts for potassium

(32) Helgeson, R. C.; Weisman, G. R.; Toner, J. L.; Tarnowski, T. L.; Chao, Y.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4928–4941.

(33) Gandour, R. D.; Fronczek, F. R.; Gatto, V. J.; Minganti, C.; Schultz, R. A.; White, B. D.; Arnold, K. A.; Mazzocchi, D.; Miller, S. R.; Gokel, G. W. *J. Am. Chem. Soc.* **1986**, *108*, 4078–4088.

over sodium is in each case slightly inferior to that of host **50**. The failure of this approach to making more potassium-selective hosts is probably due to compression of the aryl–aryl dihedral angles of the quaterphenyl unit by the *o*-xylene bridge, thus decreasing the cavity size and increasing the sodium binding ability.

Experimental Section

General Procedures. All procedures were performed under a dry N_2 atmosphere in glassware that was dried 3 h at 220 °C immediately before use. Diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium benzophenone ketyl before use. Amine solvents and bases were freshly distilled from CaH_2. Dimethylformamide (DMF) was stored 48 h over activated (24 h, 320 °C) 3-Å molecular sieves and degassed under high vacuum immediately before use. Benzene, toluene, and $(CH_3)_2NCH_2CH_2N(CH_3)_2$ were dried over activated 3-Å molecular sieves. Oil-free NaH was prepared by stirring a 50% dispersion of NaH in mineral oil with hexanes five times in a Büchner funnel (medium glass frit). *All synthesized compounds were dried under the conditions specified for their elemental analyses before use in analytical or further synthetic procedures.*

Melting points, 200-MHz ^1H NMR spectra, EI mass spectra, IR, and UV absorbance measurements were performed on commercial instruments described in previous publications.[5,8] Melting points are uncorrected. Proton NMR spectra were determined at 200 MHz unless otherwise specified. The FAB mass spectra were determined on a ZAB SE instrument using the matrices specified for individual compounds (NOBA refers to *m*-nitrobenzyl alcohol).

Silica gel (E. Merck, 63–200 μm) was used for preparative silica gel column chromatography. Silica gel thin-layer chromatography was performed with E. Merck aluminum-backed 0.2-mm silica 60 F_{254} plates. Alumina thin-layer chromatography was performed on E. Merck 0.2-mm neutral alumina 60 F_{254} plates. Gel permeation chromatography was performed on a 20 ft × 0.375 in. (o.d.) column packed with 200 g of 100-Å Styragel (Waters Associates) with CH_2Cl_2 as the mobile phase at flow rates of 3.8–4.1 mL/min and back pressures of 250–500 psi. Reverse-phase flash chromatography was performed on the support described by Kühler and Lindsten.[15] Reverse-phase thin-layer chromatography was performed on Whatman 0.2-mm $KC_{18}F$ octadecylsilane-bonded coated glass plates. Reverse-phase plates from other suppliers gave poorer correlation with the behavior of the aforementioned preparative support.

The following procedure was used to dry starting materials for specified moisture-sensitive reactions. The material to be dried was placed in the flask in which it was to be used. The volume of this flask was in all cases at least 75 mL/g of compound to be dried. Benzene (40 mL/g of compound) was added, and the flask was placed in a 120 °C oil bath. When about 90% of the benzene had evaporated, fresh benzene (40 mL/g of compound) was added. The solution was again evaporated to near dryness. After a third repetition of this process the flask was quickly removed from the oil bath and placed under a positive pressure of nitrogen (it is important not to introduce a flow of nitrogen *through* the flask at this point as benzene will condense in the outlet line and carry plasticizer back into the flask). After application of this procedure both the flask and its contents were suitable for use in moisture-sensitive procedures. The small amount of residual benzene did not interfere with any of the procedures described here.

2,2′2″,2‴-Tetrakis(phenylmethoxy)-[1,1′:3′,1″:3″,1‴-quaterphenyl]-3,3‴-dicarboxylic Acid (20). A mixture of 16.0 g (34.9 mmol) of **17**, 27.6 mL (232 mmol) of $C_6H_5CH_2Br$, 32.0 g (232 mmol) of K_2CO_3, and 750 mL of acetone was mechanically stirred at reflux temperature for 7 days. During this time 15 mL (126 mmol) of additional $C_6H_5CH_2Br$ was added every 24 h. The volume of the mixture was reduced in vacuo, and the residue was partitioned between CH_2Cl_2 and dilute hydrochloric acid (*vigorous gas evolution!*). The volume of the organic phase was reduced in vacuo, and the excess $C_6H_5CH_2Br$ was removed by vacuum distillation at 0.1 Torr. To the nonvolatile brown residue was added 400 mL of 95% EtOH, 80 mL of distilled water, and 20 g of NaOH. The mixture was refluxed for 8 h. The volume of the mixture was reduced in vacuo, and the residue was partitioned between Et_2O and dilute hydrochloric acid (aqueous phase acidic to litmus). The organic phase was washed with saturated aqueous NaCl solution and dried over $MgSO_4$. The mixture was filtered, and an equal volume of $(CH_2)_6$ was added to the filtrate. The volume of the solution was reduced in vacuo until an oily second phase appeared. A small amount of Et_2O was added to redissolve this second phase, and the mixture was allowed to stand for 12 h. This procedure yielded 17.8 g (62%) of **20** as an off-white solid which was collected by filtration; mp 138.5–140 °C; ^1H NMR ($CDCl_3$) δ 4.36 (s, inner OCH_2, 4 H), 4.57 (s, outer OCH_2, 4 H), 6.59 (d, J = 6.7 Hz, ArH, 4 H), 6.98–7.10 (m, ArH, 10 H), 7.23–7.39 (m, ArH, 10 H), 7.52–7.63 (m, ArH, 6 H), 8.17 (d of d, J = 7.8, 1.9 Hz, ArH ortho to carboxyl, 2 H); IR (KBr) 3600–2500, 1735, 1690, 1580, 1435, 1405, 1365, 1215, 1075, 980 cm^{-1}; MS (FAB, NOBA), m/e 841 ($M + Na^+$, 25%), 801 ($M^+ - OH$, 100%). Anal. Calcd for $C_{54}H_{42}O_8$ (sample dried 24 h at 10^{-5} Torr, 25° C): C, 79.20; H, 5.17. Found: C, 79.24; H, 5.28.

2,2′,2″,2‴-Tetrakis(phenylmethoxy)-[1,1′:3″,1‴:3‴,1⁗-quaterphenyl]-3,3‴-dimethanol (22). A stirred mixture of 13.4 g (16.4 mmol) of diacid **20**, 11.3 g (81.9 mmol) of K_2CO_3, 500 mL of acetone, and 6.4 mL (49.1 mmol) of Et_2SO_4 was refluxed for 15 h and then cooled to 25 °C. The excess Et_2SO_4 was destroyed by slow, careful addition of 100 mL of concentrated NH_4OH. After 1 h the volume was reduced by evaporation in vacuo. The residue was diluted with 300 mL of CH_2Cl_2 and cautiously acidified with 3 N hydrochloric acid (*gas evolution!*). The phases were separated, and the organic phase was washed with 3 N hydrochloric acid and dried ($MgSO_4$), and the solvent was removed in vacuo to give 14.4 g (100%) of diester **21** as an oil: R_f 0.40 (silica gel, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.32 (t, J = 7.2 Hz, CH_3 of ethyl, 6 H), 4.33 (s, inner OCH_2Ph, 4 H), 4.34 (q, J = 7.2 Hz, CH_2 of ethyl, 4 H), 4.71 (s, outer OCH_2Ph, 4H), 6.63 (d, J = 6.7 Hz, ArH, 4 H), 6.97–7.25 (m, ArH, 20 H), 7.48 (overlapping pair of d, J = 7.3, 7.3 Hz, ArH, 6 H), 7.79 (d of d, J = 7.8, 1.9 Hz, ArH ortho to carboethoxy, 2 H).

To a stirred suspension of 2.1 g (49.4 mmol) $LiAlH_4$ and 300 mL of Et_2O cooled in an ice bath was added dropwise (5 min) a solution of 14.4 g (16.4 mmol) of diester **21** in 200 mL of Et_2O. The mixture was stirred at 0 °C for an additional 40 min and then quenched by dropwise addition of 2 mL of distilled water. The mixture was filtered, and the filtrant was washed several times with Et_2O. The combined filtrate and washes were washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo. This procedure yielded 11.3 g (87% from **20**) of diol **22** as a yellow oil: R_f 0.65 (silica gel, 1:1 CH_2Cl_2/EtOAc); ^1H NMR ($CDCl_3$) δ 1.97 (t, J = 6.5 Hz, OH, 2 H), 4.39 (s, inner OCH_2Ph, 4 H), 4.54 (s, outer OCH_2Ph, 4 H), 4.64 (d, J = 6.5 Hz, CH_2 of hydroxymethyl, 4 H), 6.64 (d, J = 7.3 Hz, ArH, 4 H), 7.00–7.37 (m, ArH, 26 H), 7.52 (d, J = 7.5 Hz, ArH, 2 H); IR (neat) 3600–3100, 3060, 3020, 2920, 2860, 1440, 1410, 1360, 1210, 980 cm^{-1}; MS (FAB, NOBA), m/e 813 ($M + Na^+$, 8.4%). Anal. Calcd for $C_{54}H_{46}O_6$ (sample dried 24 h at 10^{-5} Torr, 25 °C): C, 82.00; H, 5.86. Found: C, 82.11; H, 5.86.

3,3‴-Bis(bromomethyl)-2,2′,2″,2‴-tetrakis(phenylmethoxy)-[1,1′:3′,1″:3″,1‴]-quaterphenyl (23). Azeotropic drying of 1.0 g (1.26 mmol) of diol **22** was performed in a 200-mL round-bottom flask according to the General Procedures (failure to carefully dry the diol led to greatly reduced yields). The diol was then dissolved in 100 mL of benzene, and 0.120 mL (1.26 mmol) of PBr_3 was added via syringe. The mixture was stirred 3 h at 25 °C and then quenched by addition of 50 mL of an aqueous saturated $NaHCO_3$ solution. The resulting emulsion was broken by adding 100 mL of Et_2O. The phases were separated, and the Et_2O layer was washed with brine and dried ($MgSO_4$). Solvent removal in vacuo gave an oil which was purified by eluting a CH_2Cl_2 solution of it through a 3-cm pad of silica gel in a 60-mL coarse fritted funnel. Evaporation of the filtrate gave 0.81 g (70%) of the dibromide **23** as an oil: R_f 0.28 (silica, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 4.38 (s, inner OCH_2Ph, 4 H), 4.59 (s, outer OCH_2Ph, 4 H), 4.65 (s, CH_2 of bromomethyl, 4 H), 6.63 (d, J = 6.5 Hz, ArH, 4 H), 7.00–7.28 (m, ArH, 20 H), 7.34 (d of d, J = 5.9, 2.1 Hz, 2 H), 7.42 (d of d, J = 7.5, 2.1 Hz, ArH, 2 H), 7.52 (d of d, J = 7.5, 1.6 Hz, ArH, 4 H); IR (neat) 3070, 3040, 2940, 2880, 1585, 1495, 1450, 1415, 1370, 1230, 1075, 990 cm^{-1}. Anal. Calcd for $C_{54}H_{44}Br_2O_4$ (sample dried 24 h at 10^{-5} Torr, 25 °C): C, 70.75; H, 4.84. Found: C, 70.84; H, 4.97.

Diethyl 2′,2‴-Diethoxy-2,2″-dihydroxy-[1,1′:3′,1″:3″,1‴-quaterphenyl]-3,3‴-dicarboxylate (24). A mixture of 6.00 g (13.1 mmol) of diacid **17**, 21.7 g (157 mmol) of K_2CO_3, 20.5 mL (157 mmol) of Et_2SO_4, and 250 mL of acetone was refluxed 70 h. Analysis of the reaction mixture by thin-layer chromatography at this point revealed two major products having R_f values of 0.72 and 0.64 (silica gel, 19:1 CH_2Cl_2/EtOAc). An additional 20 mL (153 mmol) of Et_2SO_4 was added. The mixture was refluxed an additional 5 days, at which point an identical chromatogram was obtained. The condenser was removed, and the bulk of the acetone evaporated. To the resulting mixture was added 250 mL of 2-butanone, and the mixture was refluxed 8 more days (10 mL (77 mmol) of Et_2SO_4 and 10 g (72 mmol) of K_2CO_3 were added on the third day). A third TLC of the reaction mixture was identical with the previous two. The volume of the mixture was reduced in vacuo. The residue was diluted with 300 mL of CH_2Cl_2 and carefully acidified with 3 N hydrochloric acid (*gas evolution!*). The phases were separated, the aqueous phase was washed with 100 mL of CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$). The solvent was removed in vacuo. The residue was chromatographed on 150 g of silica gel. The faster moving spot was eluted with 4:1 $CH_2Cl_2/(CH_2)_6$ and the slower spot with CH_2Cl_2. The fast-moving spot was isolated as 1.1 g (15%) of a white foam. The ^1H NMR and mass spectra of this material suggested that it was an isomer of **24**: R_f 0.72 (19:1 CH_2Cl_2/EtOAc); ^1H NMR ($CDCl_3$) δ 0.79 (t, J = 7.0 Hz, CH_3 of ethoxy, 6 H), 1.43 (t, J = 7.0 Hz, CH_3 of carboethoxy, 6 H), 3.49 (q, J = 7.0, CH_2 of ethoxy, 4 H), 4.43 (q, J = 7.0 Hz, CH_2 of carboethoxy, 4 H), 6.93 (t, J = 8.4 Hz, ArH, 4 H), 7.00–7.47 (m, ArH, 6 H), 7.59 (d of d, J = 7.7, 1.5 Hz, ArH, 2 H), 7.89 (d of d, J = 7.7, 2.0 Hz, ArH, 2 H), ca. 11.5 (folded-over s, OH); MS (EI, 70 eV), m/e 570 (M^+, 100%). The slow-moving spot, compound **24**, was isolated as 6.2 g (83%) of a white foam: R_f 0.64 (silica gel, 19:1 CH_2Cl_2/EtOAc); ^1H NMR ($CDCl_3$) δ 0.80 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 1.06 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 1.38 (t, J = 7.0 Hz, CH_3 of carboethoxy, 3 H), 1.42 (t, J = 7.0 Hz, CH_3 of carboethoxy, 3 H), 3.50 (q, J = 7.0 Hz, CH_2 of inner ethoxy, 2 H), 3.78 (q, J = 7.0 Hz, CH_2 of outer ethoxy, 2 H), 4.38 (q, J = 7.0 Hz, CH_2 of carboethoxy, 2 H), 4.42 (q, J = 7.0 Hz, CH_2 of carboethoxy, 2 H), 6.92 (t, J = 7.8 Hz, ArH, 1 H), 7.08 (t, J = 7.8 Hz, ArH, 1 H), 7.21 (t, J = 7.8 Hz, ArH, 1 H), 7.30–7.60 (m, ArH, 7 H), 7.80 (d, J = 7.8 Hz, ArH, 1 H), 7.92 (d, J = 7.8 Hz, ArH, 1 H), ca. 11.6 (folded-over s, OH); IR (neat) 3700–2900, 3000, 1715, 1675, 1620, 1480, 1390, 1380, 1325, 1290, 1250, 1160, 1090, 1030 cm^{-1}; MS (EI 16 eV), m/e 570 (M^+, 96%). Anal. Calcd for $C_{34}H_{34}O_8$ (sample dried 12 h at 10^{-1} Torr, 110 °C): C, 71.56; H, 6.00. Found: C, 71.57; H, 5.93. Isomeric structures compatible with the above data were eliminated by crystal-structure determination of macrocycle **4**, which was synthesized from **24** in four steps.

Attempts to reproduce the results described in this procedure were unsuccessful. In each case only perethylated product or inseparable mixtures were obtained.

18,14-Metheno-6*H*,14*H*-dibenzo[*f*,*m*][1,5]dioxacyclotetradecin-4-carboxylic Acid, 19-Ethoxy-10-[2-ethoxy-3-(ethoxycarbonyl)phenyl]-7,8-dihydro-, Ethyl Ester (26). A stirred mixture of 6.0 g (10.5 mmol) of diphenol **24**, 8.23 g (25.3 mmol) of Cs_2CO_3, 4.84 g (12.6 mmol) of $TsO(CH_2)_3OTs$, and 700 mL of DMF was heated to 75 °C over a period of 4 h. The mixture was stirred an additional 12 h, then the solvent was removed in vacuo (10^{-1} Torr), and the residue partitioned between 400 mL of Et_2O and 400 mL of distilled water. The aqueous phase was washed with 100 mL of Et_2O, and the combined organic extracts were washed with 100 mL of brine. The solution was dried ($MgSO_4$), and the solvent removed in vacuo. The product was chromatographed on 300 g of silica gel eluting with 1% EtOAc in CH_2Cl_2 until faster moving impurities were removed and then with a gradient of 2–5% EtOAc in CH_2Cl_2. This procedure gave 3.0 g (47%) of **26** as a white foam: R_f 0.14 (3% EtOAc in CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.74 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 1.09 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 1.33 (t, J = 7.0 Hz, CH_3 of carboethoxy, 3 H), 1.41 (t, J = 7.0 Hz, CH_3 of carboethoxy, 3 H), 1.51–1.74 (m, $CH_2CH_2CH_2$, 2 H), 3.29–3.40 (m, $CH_2CH_2CH_2$, 1 H), 3.46 (q, J = 7.0 Hz, CH_2 of inner ethoxy, 2 H), 3.50–3.57 (m, $CH_2CH_2CH_2$, 1 H), 3.71 (d of q, J = 14.0, 7.0 Hz, CH_2 of outer ethoxy), 1 H), 3.77–3.92 (m, CH_2 of outer ethoxy, $CH_2CH_2CH_2$, 2 H), 3.92–4.08 (m, $CH_2CH_2CH_2$, 1 H), 4.22–4.35 (d of q, J = 10.5, 7.0 Hz, CH_2 of carboethoxy, 2 H), 4.41 (q, J = 7.0 Hz, CH_2 of carboethoxy, 2 H), 7.20 (t, J = 7.5 Hz, ArH, 1 H), 7.18–7.52 (m, ArH, 7 H), 7.54–7.65 (d of d overlapping a second d of d, J = ca. 7.0, 2.0 Hz for each, ArH, 2 H), 7.69–7.80 (d of d overlapping a second d of d, J = ca. 7.0, 2.0 Hz for each, ArH, 2 H); IR ($CDCl_3$) 2975, 1710, 1465, 1440, 1380, 1290, 1215, 1145, 1100, 1080, 1025 cm^{-1}; MS (EI, 70 eV), m/e 610 (M^+, 100%). Anal. Calcd for $C_{37}H_{38}O_8$ (sample dried 12 h at 10^{-5} Torr, 110 °C): C, 72.77; H, 6.27. Found: C, 72.64; H, 6.25.

18,14-Metheno-6*H*,14*H*-dibenzo[*f*,*m*][1,5]dioxacyclotetradecin-4-methanol, 19-Ethoxy-10-[2-ethoxy-3-(hydroxymethyl)phenyl]-7,8-dihydro- (27). To a stirred solution of 1.68 g (2.75 mmol) of diester **26** in 150 mL of Et_2O was added 0.523 g (13.8 mmol) of $LiAlH_4$. The mixture was stirred for 18 h. The excess $LiAlH_4$ was decomposed by careful dropwise addition of water until gas evolution ceased. An additional 1.0 mL of water was added dropwise, and the mixture was filtered. The filtrant was washed three times with 30 mL of water-saturated Et_2O. The filtrate and washes were combined, and the solvent was removed in vacuo. The resulting white foam was chromatographed on 100 g of silica gel eluting with 3:2 CH_2Cl_2/EtOAc until the faster moving impurities were removed, then with 4:1 EtOAc/CH_2Cl_2. This procedure gave 1.00 g (69%) of **27** as a white foam: ^1H NMR ($CDCl_3$) δ 0.72 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 1.12 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 1.40–1.76 (m, $CH_2CH_2CH_2$, 2 H), 3.22–3.60 (m, $CH_2CH_2CH_2$, 3 H), 3.43 (q, J = 7.0 Hz, CH_2 of inner ethoxy, 2 H), 3.71 (q, J = 7.0 Hz, CH_2 of outer ethoxy, 2 H), 3.97–4.12 (m, $CH_2CH_2CH_2$, 1 H), 4.52 (d, J = 12.0 Hz, $ArCH_2O$, 1 H), 4.68 (d, J = 12.0 Hz, $ArCH_2O$, 1 H), 4.80 (d, J = 12.0 Hz, $ArCH_2O$, 1 H), 4.84 (d, J = 12.0 Hz, $ArCH_2O$, 1 H), 7.01–7.52 (m, ArH, 12 H); IR ($CDCl_3$) 3740–3650, 3640–3560, 2970, 2920, 2860, 1600, 1440, 1430, 1380, 1220, 1205, 1090, 1030 cm^{-1}; MS (EI, 70 eV), m/e 526 (M^+, 100%). Anal. Calcd for $C_{33}H_{34}O_6$ (sample dried 3 h at 10^{-1} Torr, 110 °C): C, 75.26; H, 6.51. Found: C, 75.37; H, 6.49.

18,14-Metheno-6*H*,14*H*-dibenzo[*f*,*m*][1,5]dioxacyclotetradecin, 4-(Bromomethyl)-10-[3-(bromomethyl)-2-ethoxyphenyl]-19-ethoxy-7,8-dihydro- (28). This compound was prepared by applying the procedure for preparation of dibromide **23** to 0.98 g (1.86 mmol) of diol **27**. Similar molar ratios of solvent and reagent were used. The only variation from this procedure was that the reaction time was only 1 h. The yield was 0.824 g (68%) of dibromide **28**, isolated as a white foam: R_f 0.50 (silica gel, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.73 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 1.16 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 1.42–1.85 (m, $CH_2CH_2CH_2$, 2 H), 3.37–3.70 (m, $CH_2CH_2CH_2$, 3 H), 3.40 (q, J = 7.0 Hz, CH_2 of inner ethoxy, 2 H), 3.78 (q, J = 7.0 Hz, CH_2 of outer ethoxy, 2 H), 4.10–4.29 (m, $CH_2CH_2CH_2$, 1 H), 4.38 (d, J = 9.1 Hz, $ArCH_2Br$, 1 H), 4.56 (d, J = 9.7 Hz, $ArCH_2Br$, 1 H), 4.75 (d, J = 9.1 Hz, $ArCH_2Br$, 1 H), 4.77 (d, J = 9.7 Hz, $ArCH_2Br$, 1 H), 7.03–7.51 (m, ArH, 12 H); MS (EI, 70 eV), 1:2:1 Br_2 isotope pattern centered at m/e 652 (M^+ + 2, 100%). Anal. Calcd for $C_{33}H_{32}Br_2O_4$ (sample dried 3 h at 10^{-1} Torr, 110 °C): C, 60.75; H, 4.94. Found: C, 60.88; H, 4.85.

2′-Ethoxy-5,5′,5″-trimethyl-[1,1′:3′,1″-terphenyl]-2,2″-diol (30). To a stirred 25 °C mixture of 50.0 g (156 mmol) of *p*-cresol trimer **29**, 22.7 g (164 mmol) of K_2CO_3, and 1.0 L of acetone was added after 1.5 h 22.6 mL (172 mmol) of Et_2SO_4 via syringe. After stirring for 6 days an additional 1.0 g (7.2 mmol) of K_2CO_3 and 2.0 mL (15.2 mmol) of Et_2SO_4 were added. The reaction mixture was stirred an additional 2 days and then quenched by slow, cautious addition of 100 mL of concentrated NH_4OH. After 0.5 h, the solvent was removed in vacuo and the residue was partitioned between CH_2Cl_2 and sufficient 3 N hydrochloric acid to make the aqueous phase acidic to litmus (*vigorous gas evolution!*). The organic phase was washed with 3 N hydrochloric acid and then with brine. It was then dried ($MgSO_4$) and the solvent was removed in vacuo. The product was isolated by chromatography on 2.5 kg of silica gel eluting with 0.5% EtOAc in CH_2Cl_2 until the faster moving impurities were removed and then with a gradient of increasing EtOAc concentration up to 5.0%. The resulting oil was dissolved in CH_2Cl_2, an equal volume of hexanes was added, and the volume of the mixture was reduced in vacuo until an oily second phase appeared. An amount of CH_2Cl_2 just sufficient to redissolve the oil was added, and the mixture was

allowed to stand 12 h. This procedure yielded 28.8 g (53%) of diol **30** as a white crystalline solid: mp 100.5–102.0 °C; R_f 0.45 (silica gel, 40:1 CH_2Cl_2/EtOAc); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.0 Hz, CH_3 of ethoxy, 3 H), 2.34 (s, outer $ArCH_3$, 6 H), 2.41 (s, inner $ArCH_3$, 3 H), 3.48 (q, J = 7.0 Hz, CH_2 of ethoxy, 2 H), 6.35 (s, OH, 2 H), 6.94 (d, J = 8.6 Hz, ArH ortho to hydroxyl, 2 H), 7.08–7.12 (m, ArH, 4 H), 7.19 (s, ArH, 2 H); IR ($CDCl_3$) 3600–3100, 3550, 3010, 2970, 2910, 2850, 1590, 1490, 1440, 1270, 1210, 1015 cm^{-1}; MS (EI, 70 eV), m/e 348 (M^+, 100%). Anal. Calcd for $C_{23}H_{24}O_3$ (sample dried 24 h at 10^{-5} Torr, 25 °C): C, 79.28; H, 6.94. Found: C, 79.31; H, 7.01.

3-Bromo-2′-ethoxy-5,5′,5″-trimethyl-[1,1′:3′,1″-terphenyl]-2,2″-diol (31). Diol **30**, 45.0 g (129 mmol), was dissolved in 800 mL of $CHCl_3$. The solution was cooled to −5 °C and vigorously agitated with a mechanical stirrer. A solution of 6.67 mL (129 mmol) of Br_2 in 200 mL of $CHCl_3$ was then added over 75 min. The mixture was allowed to warm to 25 °C over several hours and was then washed with distilled water. The organic phase was dried ($MgSO_4$), and the solvent was removed in vacuo. Examination of the mixture by TLC revealed the presence of three compounds having R_f values (silica gel, CH_2Cl_2) of 0.55, 0.32, and 0.15. The middle spot was later shown to correspond to the desired monobromination product **31**, and the slowest spot was shown to correspond to unreacted **30**. The mixture of products was chromatographed on 2.5 kg of silica gel eluting with 30% CH_2Cl_2 in hexanes until the fastest moving spot was completely removed from the column. The middle spot was then eluted with a gradient of increasing polarity up to 100% CH_2Cl_2. The slowest spot was eluted with 30% EtOAc in CH_2Cl_2. Monobrominated product **31** was isolated from this procedure as 31.0 g (56%) of a white foam: R_f 0.32 (silica gel, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.0 Hz, CH_3 of ethoxy, 3 H), 2.32 (s, $ArCH_3$, 3 H), 2.34 (s, $ArCH_3$, 3 H), 2.40 (s, $ArCH_3$, 3 H), 3.44 (q, J = 7.0 Hz, CH_2 of ethoxy, 2 H), 6.25 (s, OH, 1 H), 6.72 (s, OH, 1 H), 6.95, (d, J = 8.0 Hz, ArH ortho to hydroxyl, 1 H), 7.08–7.16 (m, ArH, 4 H), 7.21 (d, J = 1.6 Hz, ArH, 1 H), 7.35 (d, J = 1.6 Hz, ArH, 1 H); IR ($CDCl_3$) 3600–2700, 3520, 3020, 2975, 2920, 2860, 1760, 1590, 1570, 1510–1430, 1320, 1250–1160, 1020 cm^{-1}; MS (EI, 70 eV), m/e 428 (M^+ + 2, 100%), 426 (M^+, 98%). Anal. Calcd for $C_{23}H_{23}BrO_3$ (sample dried 24 h at 10^{-5} Torr, 25 °C): C, 64.64; H, 5.44. Found: C, 64.61; H, 5.46.

3-Bromo-2′-ethoxy-2,2″-bis(methoxymethoxy)-5,5′,5″-trimethyl-[1,1′:3′,1″]-terphenyl (32). To a stirred suspension of 10.5 g (439 mmol) of oil-free NaH in 1.0 L of THF was added dropwise over 30 min a solution of 62.5 g (146 mmol) of diol **31** in 1.5 L of THF. The mixture was stirred 1.5 h and then cooled to −5 °C. Addition of 29.8 mL (365 mmol) of $BrCH_2OCH_3$ was extended over 5 min. The temperature of the reaction was then allowed to rise to 25 °C over several hours. The excess NaH was destroyed by dropwise addition of absolute EtOH. The excess bromomethyl methyl ether was then destroyed by slow, cautious addition of 100 mL of concentrated NH_4OH. The solvent was removed in vacuo, and the residue was partitioned between Et_2O and water. The organic phase was washed with brine and dried ($MgSO_4$). Solvent removal in vacuo yielded 73.6 g (97%) of compound **32** as a yellow oil: R_f 0.67 (alumina, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.71 (t, J = 7.3 Hz, CH_3 of ethoxy, 3 H), 2.31 (overlapping s, $ArCH_3$, 6 H), 2.33 (s, $ArCH_3$, 3 H), 3.13 (s, OCH_3, 3 H), 3.35 (q, J = 7.3 Hz, CH_2 of ethoxy, 2 H), 3.37 (s, OCH_3, 3 H), 4.84 (s, OCH_2O, 2 H), 5.07 (s, OCH_2O, 2 H), 7.00–7.17 (m, ArH, 6 H), 7.38 (s, ArH, 1 H); IR (neat) 3100–2700, 1550, 1490, 1480–1410, 1220, 1190, 1145, 1070, 1000 cm^{-1}; MS (EI, 16 eV), m/e 514 (M^+, 0.7%), 440 ($M^+ - CH_3OCH_2OCH_3$, ^{81}Br, 95%), 438 ($M^+ - CH_3OCH_2OCH_3$, ^{79}Br, 100%). Anal. Calcd for $C_{27}H_{31}BrO_5$ (sample dried 24 h at 10^{-5} Torr, 60 °C): C, 62.95; H, 6.06. Found: C, 62.64; H, 6.07.

2′-Ethoxy-3-iodo-2,2″-bis(methoxymethoxy)-5,5′,5″-trimethyl-[1,1′:3′,1″]-terphenyl (33). Bromide **32**, 37.8 g (73.4 mmol), was dried for 24 h at 10^{-5} Torr and 60 °C. The vacuum was released to a positive pressure of nitrogen, and 500 mL of THF was added followed by 0.5 g of oil-free NaH. After stirring 30 min the mixture was cooled to −78 °C, and 32.8 mL of a 2.4 M solution (91.8 mmol) of n-butyllithium was added. The mixture was stirred an additional 10 min, and then a solution of 37.3 g (146 mmol) of I_2 in 150 mL of THF was added slowly until the iodine color persisted. The reaction was allowed to warm to 25 °C, and the excess I_2 was quenched by addition of a saturated aqueous sodium thiosulfate solution. The volume of the solution was reduced in vacuo and the nonvolatile residue was partitioned between CH_2Cl_2 and water. The organic phase was dried ($MgSO_4$), and the solvent removed in vacuo to give 39.8 g (96%) of iodide **33** as an orange oil: R_f 0.32 (silica gel, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.72 (t, J = 7.0 Hz, CH_3 of ethoxy, 3 H), 2.29 (s, $ArCH_3$, 3 H), 2.32 (s, $ArCH_3$, 3 H), 2.33 (s, $ArCH_3$, 3 H), 3.15 (s, OCH_3, 3 H), 3.36 (q, J = 7.0 Hz, CH_2 of ethoxy, 2 H), 3.38 (s, OCH_3, 3 H), 4.80 (s, OCH_2O, 2 H), 5.06 (s, OCH_2O, 2 H), 7.04–7.09 (m, ArH, 5 H), 7.18 (s, ArH, 1 H), 7.61 (d, J = 1.6 Hz, ArH ortho to I, 1 H); IR (neat) 3050–2750, 1755, 1595, 1545, 1495, 1480–1410, 1400–1380, 1280–1180, 1170–1120, 1070–900 cm^{-1}; MS (EI, 16 eV), m/e 562 (M^+, 0.3%), 486 ($M^+ - CH_3OCH_2OCH_3$, 100%). Anal. Calcd for $C_{27}H_{31}IO_5$ (sample dried 24 h at 10^{-5} Torr, 25 °C): C, 57.66; H, 5.56. Found: C, 57.96; H, 5.77.

2-Ethoxy-5-methylphenylboronic Acid (34). To a stirred mixture of 57.7 g (424 mmol) of p-methylphenetole,[11] 1.0 L of Et_2O, and 77.0 mL (510 mmol) of $(CH_3)_2NCH_2CH_2N(CH_3)_2$ was added 212 mL of 2.4 M (510 mmol) n-butyllithium over 5 min. A mild exotherm was observed, and the reaction was cooled in a 25 °C water bath. After 1.5 h the mixture was cooled to −78 °C and cannulated into a −78 °C solution of 227 mL (2.0 mol) trimethylborate in 300 mL of THF. Care was taken that the trimethylborate did not crystallize out of the THF solution. The mixture was allowed to warm to 25 °C over several hours, and 300 mL 3 N hydrochloric acid was added. After the mixture had stirred 6 h, 500 mL of distilled water was added, and the phases were separated. The organic phase was washed with 500 mL of 3 N aqueous NaOH solution. A precipitate formed which was removed by filtration. The filtrate was washed with an additional 500 mL of 3 N aqueous NaOH solution. The two basic aqueous phases and the precipitate were combined and acidified with 6 N hydrochloric acid. The resulting suspension was washed three times with Et_2O, and the combined organic phases were washed with brine. The solvent was removed in vacuo, and the crude oil dissolved in 400 mL of 95% EtOH. While the flask was swirled, water was added slowly until precipitation began. The solution was then cooled to −15 °C. This procedure yielded 66 g (74%) of boronic acid **34** as white needles: mp 92.0–94.0 °C (phase change, needles to polyhedra, 88.5–90.0 °C); ^1H NMR (DMSO-d_6) δ 1.36 (t, J = 7.0 Hz, CH_3 of ethoxy, 3 H), 2.23 (s, $ArCH_3$, 3 H), 4.06 (q, J = 7.0 Hz, CH_2 of ethoxy, 2 H), 6.85 (d, J = 8.6 Hz, ArH ortho to ethoxy, 1 H), 7.17 (d, J = 8.6 Hz, ArH para to boron, 1 H), 7.42 (s, ArH ortho to boron, 1 H), 7.62 (s, OH, 2 H); IR (solid film) 3650–3150, 3020, 2980, 2920, 1610, 1580, 1490, 1470, 1430–1370, 1370–1300, 1220, 1150, 1040 cm^{-1}; HR MS (EI, 70 eV) calcd for $C_9H_{13}O_3{}^{11}B$ 180.0958, found 180.0951 (M^+, 40%), calcd for $C_7H_7O_2{}^{11}B$ 134.0539, found 134.0542 ($M^+ - CH_3CH_2OH$, 100%).

2′,2‴-Diethoxy-2,2″-bis(methoxymethoxy)-5,5′,5″,5‴-tetramethyl-[1,1′:3′,1″:3″,1‴]-quaterphenyl (35). A mixture was prepared from 39.4 g (70.1 mmol) of iodide **33**, 15.2 g (84.1 mmol) of boronic acid **34**, 400 mL of benzene, 200 mL of 2 N sodium carbonate solution, 100 mL of 95% EtOH, and 100 mg (0.086 mmol) of $Pd(PPh_3)_4$. The mixture was refluxed for 24 h, and an additional 0.5 g (2.5 mmol) of boronic acid **34** and 50 mg (0.043 mmol) of $Pd(PPh_3)_4$ were added. After refluxing 18 h more, the mixture was allowed to cool and the phases were separated. The aqueous phase was washed with Et_2O, and the combined organic phases were washed successively with 3 N aqueous NaOH solution and brine. The solution was dried ($MgSO_4$), and the solvent was removed in vacuo. After several days a few small crystals formed in the crude brown oil. Pentane (100 mL) was added, and the flask was spun by attaching it to the neck of a rotary evaporator (no vacuum). After 5 h the three-phase mixture was entirely converted to off-white crystals and a dark orange mother liquor. The crystals were collected by filtration to yield 62.8 g (81%) of **35**: mp 92.0–93.0 °C; R_f 0.33 (silica gel, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.77 (t, J = 6.7 Hz, CH_3 of inner ethoxy, 3 H), 1.27 (t, J = 7.3 Hz, CH_3 of outer ethoxy, 3 H), 2.30 (s, $ArCH_3$, 3 H), 2.32 (s, $ArCH_3$, 3 H), 2.34 (overlapping s, $ArCH_3$, 6 H), 2.71 (s, inner OCH_3, 3 H), 3.39 (s, outer OCH_3, 3 H), 3.43 (q, J = 6.7 Hz, CH_2 of inner ethoxy, 2 H), 3.99 (q, J = 7.3 Hz, CH_2 of outer ethoxy, 2 H), 4.44 (s, inner OCH_2O, 2 H), 5.06 (s, outer OCH_2O, 2 H), 6.85 (d, J = 8.0 Hz, ArH, 1 H), 7.01–7.20 (m, ArH, 9 H);

IR (neat) 3040, 2990, 2935, 1500, 1440, 1385, 1230, 1150, 1040–950 cm^{-1}; MS (EI, 16 eV), *m/e* 570 (M^+, 0.4%), 494 ($M^+ - CH_3OCH_2OCH_3$, 100%). Anal. Calcd for $C_{36}H_{42}O_6$ (sample dried 24 h at 10^{-1} Torr, 80 °C): C, 75.76; H, 7.42. Found: C, 76.04; H, 7.35.

2′,2‴-Diethoxy-5,5′,5″,5‴-tetramethyl-[1,1′:3′,1‴]-quaterphenyl-2,2″-diol (36). To a homogeneous solution of 24.8 g (43.5 mmol) of quaterphenyl **35** in 50 mL of $CHCl_3$ was added 350 mL of absolute EtOH followed by 2.0 mL of concentrated hydrochloric acid. The mixture was stirred 24 h. The volume of the mixture was reduced in vacuo, with the temperature of the mixture not allowed to rise above 50 °C. (If the mixture is evaporated to near dryness above this temperature, decomposition occurs.) The residue was partitioned between CH_2Cl_2 and water. The organic phase was dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2, 95% EtOH was added, and the volume was reduced in vacuo. White crystals formed when the resulting solution had stood 12 h. This procedure gave 20.0 g (95%) of diol **36**: mp 131.5–133 °C; R_f 0.47 (silica gel, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.85 (t, *J* = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 1.32 (t, *J* = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 2.35–2.40 (overlapping s, $ArCH_3$, 12 H), 3.52 (q, *J* = 7.0 Hz, CH_2 of inner ethoxy, 2 H), 4.07 (q, *J* = 7.0 Hz, CH_2 of outer ethoxy, 2 H), 6.57 (s, OH, 1 H), 6.93–7.24 (m, ArH and OH, 10 H), 7.35 (s, ArH, 1 H); IR ($CDCl_3$) 3600–3100, 3010, 2970, 2910, 2850, 1590, 1495, 1470, 1440, 1390, 1220, 1025 cm^{-1}; MS (EI, 70 eV), *m/e* 482 (M^+, 100%). Calcd for $C_{32}H_{34}O_4$ (sample dried 5 h at 10^{-1} Torr, 110 °C): C, 79.64; H, 7.10. Found: C, 76.55; H, 7.07.

2′,2‴-Diethoxy-2,2‴-dihydroxy-5,5′,5″,5‴-tetramethyl-[1,1′:3′,1″:3″,1‴-quaterphenyl]-3,3‴-dicarbaldehyde (37). A mixture of 12.2 g (25.3 mmol) of diol **36**, 11.7 g (83.5 mmol) of hexamethylenetetraamine, and 500 g (3.07 mol) of Cl_3CCO_2H was heated to 85–90 °C for 36 h. The mixture was allowed to cool to 60 °C, and water was added just until the mixture turned cloudy (ca. 500 mL). After stirring 3 h (shorter stirring times reduced the yield), the mixture was slowly and cautiously poured into a vigorously stirred mixture of 500 mL of distilled water, 200 mL of Et_2O, and 400 g (4.76 mol) of $NaHCO_3$ in a 4.0-L beaker (*gas evolution*!). An additional 1.0 L of Et_2O was added, and the mixture was filtered through a medium glass frit. The phases were separated, and the aqueous phase was washed three times with Et_2O. The combined organic extracts were washed successively with a saturated aqueous $NaHCO_3$, 3 N hydrochloric acid, and brine. The solution was dried ($MgSO_4$), and the solvent was removed in vacuo. The nonvolatile residue was purified by elution through a 3-cm pad of silica gel in a 600-mL coarse-fritted glass funnel with 99:1 CH_2Cl_2/EtOAc. This procedure yielded 5.5 g (40%) of dialdehyde **37** as a yellow foam: R_f 0.58 (silica gel, 19:1 CH_2Cl_2/EtOAc); ^1H NMR ($CDCl_3$) δ 0.81 (t, *J* = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 1.10 (t, *J* = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 2.35 (s, $ArCH_3$, 3 H), 2.38 (s, $ArCH_3$, 3 H), 2.39 (s, $ArCH_3$, 3 H), 2.42 (s, $ArCH_3$, 3 H), 3.49 (q, *J* = 7.0 Hz, CH_2 of inner ethoxy, 2 H), 3.74 (q, *J* = 7.0 Hz, CH_2 of outer ethoxy, 2 H), 7.17 (s, ArH, 1 H), 7.20 (s, ArH, 1 H), 7.24 (overlapping s, ArH, 2 H), 7.37 (s, ArH, 1 H), 7.42 (overlapping s, ArH, 2 H), 7.47 (s, OH, 1 H), 7.65 (s, ArH, 1 H), 9.91 (s, CHO, 1 H), 10.46 (s, CHO, 1 H), 11.13 (s, OH, 1 H), the peaks at δ 7.47 and 11.13 were shifted in the presence of trace amounts of acid; IR (neat) 3700–2700, 3020, 2970, 2920, 2855, 1685, 1650, 1605, 1450, 1380, 1240–1200, 1030 cm^{-1}; MS (EI, 70 eV), *m/e* 538 (M^+, 100%) 492 ($M^+ - CH_3CH_2OH$, 44%). Anal. Calcd for $C_{34}H_{34}O_6$ (sample dried 3 h at 10^{-1} Torr, 180 °C): C, 75.82; H, 6.36. Found: C, 76.02; H, 6.42. A sample dried at 150 °C gave C and H values corresponding to a monohydrate.

15,11-Metheno-11*H*-tribenzo[*c*,*g*,*n*][1,6]dioxacyclopentadecin-7-carboxaldehyde, 22-Ethoxy-19-(2-ethoxy-3-formyl-5-methylphenyl)-5,21-dihydro-9,13,17-trimethyl- (42). A mixture of 4.0 g (74.3 mmol) of dialdehyde **37**, 2.35 g (89.2 mmol) of α,α′-dibromo-*o*-xylene, 3.70 g (267 mmol) of K_2CO_3, and 500 mL of acetone was refluxed 5 h, and then most of the acetone was evaporated. The residue was partitioned between 200 mL of water and 200 mL of Et_2O. The aqueous phase was washed with 100 mL of Et_2O, and the combined organic extracts were washed with brine. The solution was dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was chromatographed on 300 g of silica gel eluting with a gradient of 0.0–7.0% EtOAc in CH_2Cl_2. This procedure gave 3.5 g (74%) of compound **42** as a white foam: R_f 0.53 (silica gel, 19:1 CH_2Cl_2/EtOAc); ^1H NMR ($CDCl_3$) δ 0.77 (t, *J* = 6.8 Hz, CH_3 of inner ethoxy, 3 H), 1.26 (t, *J* = 6.8 Hz, CH_3 of outer ethoxy, 3 H), 2.33 (s, $ArCH_3$, 3 H), 2.40 (s, $ArCH_3$, 3 H), 2.43 (overlapping s, $ArCH_3$, 6 H), 3.42–3.58 (m, CH_2 of inner ethoxy, 2 H), 3.78–3.94 (m, CH_2 of outer ethoxy, 2 H), 4.29 (d, *J* = 8.7 Hz, $ArCH_2O$, 1 H), 4.32 (d, *J* = 10.7 Hz, $ArCH_2O$, 1 H), 4.84 (d, *J* = 10.7 Hz, $ArCH_2O$, 1 H), 5.33 (br d, *J* indeterminate, $ArCH_2O$, 1 H), 6.43 (d, *J* = 8.7 Hz, ArH, 1 H), 7.08–7.22 (m, ArH, 5 H), 7.24 (s, ArH, 1 H), 7.37 (s, ArH, 1 H), 7.51 (s, ArH, 1 H), 7.59 (s, ArH, 1 H), 7.69 (s, ArH, 1 H), 7.73 (s, ArH, 1 H), 10.39 (s, CHO, 1 H), 10.52 (s, CHO, 1 H); IR ($CDCl_3$) 2980, 2790, 1850, 1790, 1680, 1640, 1465, 1380, 1045 cm^{-1}; MS (EI, 70 eV), *m/e* 640 (M^+, 100%), 612 ($M^+ - CO$, 11%). Anal. Calcd for $C_{42}H_{40}O_6 \cdot {}^1/_2H_2O$ (sample dried 12 h at 10^{-1} Torr, 150 °C): C, 77.64; H, 6.36. Found: C, 77.81; H, 6.19.

15,11-Metheno-11*H*-tribenzo[*c*,*g*,*n*][1,6]dioxacyclopentadecin-7-methanol, 22-Ethoxy-19-(2-ethoxy-3-(hydroxymethyl)-5-methylphenyl)-5,21-dihydro-9,13,17-trimethyl- (43). A solution was prepared of 3.26 g (5.08 mmol) of dialdehyde **42** in 150 mL of methanol. After a few minutes the dialdehyde crystallized from the solution. Addition of 0.77 g (20.3 mmol) of $NaBH_4$ caused the dialdehyde to redissolve almost instantaneously. The mixture was stirred 24 h and then cautiously treated with 25 mL of 3 N hydrochloric acid. The mixture was stirred for 5 min, 50 mL of a saturated aqueous $NaHCO_3$ solution was added, and the mixture was stirred 30 min. The volume was reduced in vacuo, and the residue was partitioned between water and CH_2Cl_2. The aqueous phase was cautiously acidified with 3 N hydrochloric acid (*gas evolution*!) and washed with a second aliquot of CH_2Cl_2. The combined organic phases were dried by passage through filter paper, and the solvent was removed in vacuo. The residue was dissolved in 75 mL of CH_2Cl_2, and an equal volume of hexanes was added. Reduction of the volume of this solution in vacuo gave 2.95 g (90%) of white crystals of **43**: mp 142.5–145.0 °C; R_f 0.28 (silica gel, 3:1 EtOAc/CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.73 (t, *J* = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 1.13 (t, *J* = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 2.24 (s, OH, 2 H), 2.28 (s, $ArCH_3$, 3 H), 2.36 (s, $ArCH_3$, 3 H), 2.38 (s, $ArCH_3$, 3 H), 2.41 (s, $ArCH_3$, 3 H), 3.42 (br q, *J* = 7.0 Hz, CH_2 of inner ethoxy, 2 H), 3.66–3.78 (m, CH_2 of outer ethoxy, 2 H), 4.10 (d, *J* = 9.7 Hz, $ArCH_2O$, 1 H), 4.20 (d, *J* = 9.1 Hz, $ArCH_2O$, 1 H), 4.54 (d, *J* = 12.9 Hz, $ArCH_2O$, 1 H), 4.64 (d, 12.9 Hz, $ArCH_2O$, 1 H), 4.66 (d, *J* = 12.9 Hz, $ArCH_2O$, 1 H), 4.82 (d, *J* = 9.7 Hz, $ArCH_2O$, 1 H), 4.87 (d, *J* = 12.9 Hz, $ArCH_2O$, 1 H), 5.50 (br d, *J* indeterminate, $ArCH_2O$, 1 H), 6.37 (d, *J* = 7.0 Hz, ArH, 1 H), 7.05–7.21 (m, ArH, 10 H), 7.33 (s, ArH, 1 H); the following pairs of peaks were shown to be coupled by double-irradiation experiments: δ 4.10, 4.82; 4.20, 5950; IR ($CDCl_3$) 3700–3200, 3020, 2960, 2920, 2870, 1600, 1450, 1380, 1210, 1095, 1025 cm^{-1}; MS (EI, 70 eV), *m/e* 644 (M^+, 54%). Anal. Calcd for $C_{42}H_{44}O_6$ (sample dried 3 h at 10^{-1} Torr, 180 °C): C, 78.23; H, 6.88. Found: C, 78.12; H, 6.89. A sample dried at 150 °C gave C and H values corresponding to a hemihydrate.

Reaction of Racemic Diol 43 with (*S*)-(−)-Phenethyl Isocyanate. In a 25-mL round-bottom flask were combined 0.100 g (0.155 mmol) of diol **43**, 10 mL of benzene, 0.062 mL (0.621 mmol) of triethylamine, and 0.07 mL (ca. 0.31 mmol) of (*S*)-(−)-phenethyl isocyanate. The mixture was refluxed 24 h, and then an additional 0.07 mL (ca. 0.31 mmol) of (*S*)-(−)-phenethyl isocyanate was added. After refluxing an additional 24 h, analysis of the reaction mixture by TLC revealed the presence of two compounds having R_f values of 0.58 and 0.22 (silica gel, 35% EtOAc in CH_2Cl_2). The solvent was removed in vacuo. The residue was chromatographed on a 1-mm preparative-layer chromatography plate (E. Merck silica gel 60 F_{254}) eluting with 35% EtOAc in CH_2Cl_2. The bands corresponding to R_f 0.58 and 0.22 were scraped off the plate, and the compounds were freed from the silica gel support by washing with chloroform. The band at R_f 0.58 gave 0.073 g (50%) of a white solid tentatively identified as one of the stereoisomers of **48**: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.65 (t, *J* = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 0.98 (t, *J* = 6.8 Hz, CH_3 of outer ethoxy, 3 H), 1.31 (d, *J* = 6.8 Hz, CH_3 β to N, 3 H), 1.40 (d, partially obscured by impurity peak, *J* indetermined, CH_3 β to N, 3 H), 2.18 (s, $ArCH_3$, 3 H), 2.27 (s, $ArCH_3$, 3 H), 2.28 (s, $ArCH_3$, 3 H), 2.30 (s, $ArCH_3$, 3 H), 3.37 (br q, *J* = 6.8 Hz, CH_2 of inner ethoxy, 2 H), 4.03–4.23 (br m, CH_2 of outer ethoxy, 2 H), 4.55–5.22 (m, $ArCH_2O$, CH–N, and NH, 11 H), 6.34 (br s, NH,

1 H), 7.00 (d, J = 9.6 Hz, ArH, 4 H), 7.01–7.30 (m, ArH, 18 H); MS (FAB, NOBA), m/e 977 (M + K^+, 5%), 961 (M + Na^+, 100%). The band at R_f 0.22 gave 0.027 g (15%) of a white solid tentatively identified as the other stereoisomer of **48**: MS (FAB, NOBA), m/e 977 (M + K^+, 14%), 961 (M + Na^+, 94%).

18,14-Metheno-6*H*,14*H*-dibenzo[*f*,*m*][1,5]dioxacyclotetradecin-4-carboxaldehyde, 19-Ethoxy-10-[2-ethoxy-3-formyl-5-methylphenyl]-7,8-dihydro-2,12,16-trimethyl- (39), Racemic from Dialdehyde 37. A mixture of 5.50 g (10.2 mmol) of dialdehyde **37**, 10.0 g (3.06 mmol) of Cs_2CO_3, 4.7 g (12.2 mmol) of $TsO(CH_2)_3OTs$, and 800 mL of DMF was heated to 50 °C over a period of 3 h. After stirring at this temperature 5 h, the temperature of the mixture was raised to 60 °C. After an additional 2 h the solvent was removed in vacuo (0.2 Torr). The residue was partitioned between Et_2O and distilled water. The aqueous phase was washed with Et_2O, and the combined organic extracts were washed with brine. The solution was dried ($MgSO_4$), and the solvent was removed in vacuo. The nonvolatile residue was chromatographed on 250 g of silica gel eluting with a gradient of 0.00–0.75% EtOAc in CH_2Cl_2 until the product began to come off and then with 5.0% EtOAc in CH_2Cl_2. This procedure gave 2.67 g (45%) of racemic dialdehyde **39** as a yellow foam: R_f 0.38 (silica gel, 5% EtOAc in CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.77 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 1.15 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 1.45–1.80 (m, $CH_2CH_2CH_2$, 2 H), 2.34 (s, $ArCH_3$, 3 H), 2.42 (overlapping s, $ArCH_3$, 9 H), 3.35–3.57 (m, $CH_2CH_2CH_2$ and OCH_2 of inner ethoxy, 3 H), 3.58–3.67 (m, $CH_2CH_2CH_2$, 2 H), 3.72–3.90 (m, CH_2 of outer ethoxy, 2 H), 4.16–4.21 (m, $CH_2CH_2CH_2$, 1 H), 7.07 (s, ArH, 1 H), 7.11 (s, ArH, 1 H), 7.24 (overlapping s, ArH, 2 H), 7.52 (overlapping s, ArH, 2 H), 7.64 (overlapping s, ArH, 2 H), 10.36 (s, CHO, 1 H), 10.47 (s, CHO, 1 H); IR (neat) 3010, 2960, 2905, 2850, 1688, 1600, 1590, 1475, 1445, 1375, 1215, 1035 cm^{-1}; MS (EI, 70 eV), m/e 578 (M^+, 100%). Calcd for $C_{37}H_{38}O_6 \cdot H_2O$ (sample dried 3 h at 10^{-5} Torr, 180 °C): C, 74.47; H, 6.76. Found: C, 74.58; H, 6.62.

1,3-Dioxolane-4,5-dicarboxylic Acid, 2-[3-[10-[4,5-Bis(methoxycarbonyl)-1,3-dioxolan-2-yl]-19-ethoxy-7,8-dihydro-2,12,16-trimethyl-18,14-metheno-6*H*,14*H*-dibenzo[*f*,*m*][1,5]dioxacyclotetradecin-4-yl]-2-ethoxy-5-methylphenyl]-, Dimethyl Ester, Stereoisomers 49a and 49b. In a 1.0-L round-bottom flask were combined 2.90 g (5.02 mmol) of dialdehyde **39**, 5.54 g (31.1 mmol) of dimethyl L-tartrate, 100 mg (0.526 mmol) of *p*-toluenesulfonic acid monohydrate, and 500 mL of toluene. The flask was equipped with a 125-mL Soxhlet extractor that was loaded with ca. 25 g of activated 3-Å molecular sieves. The mixture was refluxed for 36 h at such a rate that a slow dropwise addition of toluene to the Soxhlet thimble was maintained. At the end of this period, analysis of the reaction mixture by TLC showed two major spots having R_f values of 0.31 and 0.14 (silica gel, 4:1 CH_2Cl_2/EtOAc). A very small amount of material having R_f values intermediate between these spots and starting material was also observed. Further refluxing increased the intensity of these spots with concomitant decrease in the reaction yield. The reaction mixture was cooled and diluted with Et_2O. It was washed with 200 mL of saturated aqueous $NaHCO_3$ solution, 200 mL of distilled water, and then 200 mL of brine. The solution was dried ($MgSO_4$), and the solvent was removed in vacuo. The nonvolatile residue was dissolved in 50 mL of CH_2Cl_2, and 100 mL of methanol was added. The volume of the solution was reduced in vacuo at 40 °C to 100 mL, and the resulting white crystals were collected by filtration. The solid was recrystallized two more times in the same manner. This material was found to correspond to the isomer having R_f 0.14. The mother liquors were combined, and the solvent was removed in vacuo. The resulting brown oil was purified on an 80 × 3 cm medium-pressure chromatography column. Elution with 10% EtOAc in $ClCH_2CH_2Cl$ gave 1.74 g (77% based on one enantiomer of **39**) of the diastereomer having R_f 0.31. Further elution of the column with a gradient of 10–60% EtOAc in $ClCH_2CH_2Cl$ yielded a small additional amount of the more polar diastereomer, which was crystallized twice from CH_2Cl_2/MeOH and combined with the previously crystallized material. The total yield of the more polar diastereomer was 2.68 g (60% based on one enantiomer of **39**). This crystalline solid had an unusually high tendency to develop a static charge and was difficult to handle without excessive loss of material. It was therefore dissolved in CH_2Cl_2 and evaporated to a foam before further use. The less polar diastereomer gave the following: R_f 0.31 (silica gel, 4:1 CH_2Cl_2/EtOAc); ^1H NMR ($CDCl_3$) δ 0.74 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 1.11 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 1.42–1.62 (m, $CH_2CH_2CH_2$, 2 H), 2.29 (s, $ArCH_3$, 3 H), 2.37 (overlapping s, $ArCH_3$, 6 H), 2.40 (s, $ArCH_3$, 3 H), 3.33–3.54 (m, OCH_2 of inner ethoxy, $CH_2CH_2CH_2$, 5 H), 3.62–3.79 (m, OCH_2 of outer ethoxy, 2 H), 3.82 (s, CO_2CH_3, 3 H), 3.86 (s, CO_2CH_3, 3 H), 3.87 (s, CO_2CH_3, 3 H), 3.88 (s, CO_2CH_3, 3 H), 4.05–4.25 (m, $CH_2CH_2CH_2$, 1 H), 4.84 (d, J = 3.7 Hz, CH α to carbonyl, 1 H), 4.89 (overlapping d, J = 3.7 Hz, CH α to carbonyl, 2 H), 4.99 (d, J = 3.7 Hz, CH α to carbonyl, 1 H), 6.46 (s, OCHArO, 1 H), 6.53 (s, OCHArO, 1 H), 7.01 (s, ArH, 1 H), 7.04 (s, ArH, 1 H), 7.16 (s, ArH, 1 H), 7.26 (s, ArH, 1 H), 7.32 (s, ArH, 1 H), 7.36 (s, ArH, 1 H), 7.50 (s, ArH, 1 H), 7.67 (s, ArH, 1 H); IR ($CDCl_3$) 3000–2820, 1750, 1450, 1435, 1380, 1220, 1205, 1100, 1040 cm^{-1}; MS (EI, 17 eV), m/e 898 (M^+, 100%); optical rotation (c = 5.1, CH_2Cl_2, 25 °C) $[\alpha]_{405}$ = +84.1°, $[\alpha]_{436}$ = +56.6°, $[\alpha]_{546}$ = +20.7°, $[\alpha]_{579}$ = +16.9°. Anal. Calcd for $C_{49}H_{54}O_{16}$ (sample dried 16 h at 10^{-5} Torr, 80 °C): C, 65.47; H, 6.06. Found: C, 65.25; H, 6.01. The more polar diastereomer gave the following: mp 205.5–206.0 °C; R_f 0.14 (silica gel, 4:1 CH_2Cl_2/EtOAc); ^1H NMR ($CDCl_3$) δ 0.74 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 1.14 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 1.45–1.69 (m, $CH_2CH_2CH_2$, 2 H), 2.30 (s, $ArCH_3$, 3 H), 2.36–2.39 (overlapping s, $ArCH_3$, 9 H), 3.32–3.55 (m, OCH_2 of inner ethoxy, $CH_2CH_2CH_2$, 5 H), 3.66–3.81 (m, OCH_2 of outer ethoxy, 2 H), 3.81 (s, CO_2CH_3, 3 H), 3.84 (s, CO_2CH_3, 3 H), 3.87 (overlapping s, CO_2CH_3, 6 H), 4.02–4.18 (m, $CH_2CH_2CH_2$, 1 H), 4.79 (d, J = 4.3 Hz, CH α to carbonyl, 1 H), 4.89 (d, J = 3.8 Hz, CH α to carbonyl, 1 H), 4.95–4.99 (m, CH α to carbonyl, 2 H), 6.42 (s, OCHArO, 1 H), 6.53 (s, OCHArO, 1 H), 6.98 (s, ArH, 1 H), 7.05 (s, ArH, 1 H), 7.17 (s, ArH, 1 H), 7.27 (s, ArH, 1 H), 7.29 (s, ArH, 1 H), 7.33 (s, ArH, 1 H), 7.47 (s, ArH, 1 H), 7.55 (s, ArH, 1 H); IR ($CDCl_3$) 3000–2850, 1755, 1480–1430, 1380, 1225, 1100 cm^{-1}; MS (EI, 70 eV), m/e 898 (M^+, 20%); optical rotation (c = 5.2, CH_2Cl_2, 25 °C) $[\alpha]_{405}$ = −123.4°, $[\alpha]_{436}$ = −89.7°, $[\alpha]_{546}$ = −41.0°, $[\alpha]_{579}$ = −34.1°, $[\alpha]_D$ = −32.1°. Anal. Calcd for $C_{49}H_{54}O_{16}$ (sample dried 16 h at 10^{-5} Torr, 80 °C): C, 65.47; H, 6.06. Found: C, 65.42; H, 6.12.

18,14-Metheno-6*H*,14*H*-dibenzo[*f*,*m*][1,5]dioxacyclotetradecin-4-carboxaldehyde, 19-Ethoxy-10-[2-ethoxy-3-formyl-5-methylphenyl]-7,8-dihydro-2,12,16-trimethyl- (39), Optically Active from Bistartrates 49a and 49b. To a suspension of 1.23 g (1.37 mmol) of the more polar diastereomer of **49** in 150 mL 95% EtOH was added 15 mL of distilled water and 4 mL of 3 N hydrochloric acid. The mixture was refluxed 2 h, and the volume was reduced to ca. 25 mL (not to dryness) in vacuo. After addition of 200 mL of CH_2Cl_2, the phases were separated. The organic phase was dried ($MgSO_4$), and the solvent removed in vacuo. The residue was filtered through a 3-cm pad of silica gel in a 60-mL coarse-fritted glass funnel eluting with 5% EtOAc in CH_2Cl_2. This procedure gave 0.713 g (90%) of (−)-**39** as a white foam whose spectroscopic properties were identical with the racemic material; optical rotation (c = 5.0, CH_2Cl_2, 25 °C) $[\alpha]_{436}$ = −34.5°, $[\alpha]_{546}$ = −37.0°, $[\alpha]_{579}$ = −33.2°, $[\alpha]_D$ = −31.4°. Anal. Calcd for $C_{37}H_{38}O_6$ (sample dried 3 h at 10^{-2} Torr, 170 °C): C, 76.79; H, 6.62. Found: C, 76.77; H, 6.75.

Application of the above procedure to the less polar diastereomer of **49** gave (+)-**39**. The spectroscopic properties of this material were identical with those of the racemate; optical rotation (c = 5.2, CH_2Cl_2, 25 °C) $[\alpha]_{436}$ = +30.2°, $[\alpha]_{546}$ = +30.6°, $[\alpha]_{579}$ = +27.7°, $[\alpha]_D$ = +27.3°. Anal. Calcd for $C_{37}H_{38}O_6$ (sample dried 3 h at 10^{-2} Torr, 170 °C): C, 76.79; H, 6.62. Found: C, 76.55; H, 6.72.

(−)-18,14-Metheno-6*H*,14*H*-dibenzo[*f*,*m*][1,5]dioxacyclotetradecin-4-methanol, 19-Ethoxy-10-[2-ethoxy-3-(hydroxymethyl)-5-methylphenyl]-7,8-dihydro-2,12,16-trimethyl- (40). To a solution of 0.820 g (1.42 mmol) of dialdehyde (−)-**39** in 50 mL of absolute EtOH was added 0.323 g (8.51 mmol) of sodium borohydride. The mixture was stirred 12 h. The excess $NaBH_4$ was destroyed by cautious dropwise addition of 3 N hydrochloric acid until gas evolution ceased. The solution was made basic by addition of 20 mL of saturated aqueous $NaHCO_3$ solution and stirred 3 h. The mixture was diluted by addition of 150 mL of CH_2Cl_2 and 70 mL of distilled water. The phases were separated, and the aqueous phase was washed three times with CH_2Cl_2. The

combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was chromatographed on 25 g of silica gel eluting with a gradient of 60–80% EtOAc in CH_2Cl_2. This procedure gave 0.758 g (92%) of diol (–)-**40** as a white foam: R_f 0.15 (silica gel, 1:1 EtOAc/CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.70 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 1.06 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 1.40–1.67 (m, $CH_2CH_2CH_2$, 2 H), 2.22 (s, $ArCH_3$, 3 H), 2.25–2.43 (overlapping s, $ArCH_3$, 9 H), 3.25–3.47 (m, $CH_2CH_2CH_2$ and OCH_2 of inner ethoxy, 5 H), 3.47–3.72 (m, OCH_2 of outer ethoxy, 2 H), 3.99–4.16 (m, $CH_2CH_2CH_2$, 1 H), 4.41 (d, J = 12.0 Hz, $ArCH_2O$, 1 H), 4.58 (d, J = 13.1 Hz, $ArCH_2O$, 1 H), 4.70 (d, J = 13.1 Hz, $ArCH_2O$, 1 H), 4.79 (d, J = 12.0 Hz, $ArCH_2O$, 1 H), 6.99–7.16 (overlapping s, ArH, 8 H); IR ($CDCl_3$) 3600–3100, 2960, 2910, 2860, 1480–1410, 1375, 1210, 1030 cm^{-1}; MS (EI, 70 eV), m/e 582 (M^+, 100%); optical rotation (c = 5.4, CH_3CN, 25 °C) $[\alpha]_{365}$ = –470°, $[\alpha]_{405}$ = –292.3°, $[\alpha]_{436}$ = –219.5°, $[\alpha]_{546}$ = –107.5°, $[\alpha]_{579}$ = –91.3°, $[\alpha]_D$ = –86.4°. Anal. Calcd for $C_{37}H_{42}O_6$ (sample dried 3 h at 10^{-1} Torr, 180 °C): C, 76.26; H, 7.26. Found: C, 76.22; H, 7.27.

Application of this procedure to dialdehyde (+)-**39** of 91% optical purity gave diol (+)-**40** of the same optical purity: optical rotation (c = 5.1, CH_3CN, 25 °C) $[\alpha]_{365}$ = +428°, $[\alpha]_{405}$ = +265.1°, $[\alpha]_{436}$ = +198.8°, $[\alpha]_{546}$ = +97.0°, $[\alpha]_{579}$ = +82.3°, $[\alpha]_D$ = +79.2°. Anal. Calcd for $C_{37}H_{42}O_6$ (sample dried 3 h at 10^{-1} Torr, 180 °C): C, 76.26; H, 7.26. Found: C, 76.32; H, 7.35.

(+)-18,14-Metheno-6*H*,14*H*-dibenzo[*f*,*m*][1,5]dioxacyclotetradecin, 4-(Bromomethyl)-10-[3-(bromomethyl)-2-ethoxy-5-methylphenyl]-19-ethoxy-7,8-dihydro-2,12,16-trimethyl-(41). Dibromide (+)-**41** was prepared by applying the procedure used to prepare dibromide **23** to 0.504 g (0.866 mmol) of diol (–)-**40**. Similar molar ratios of reagent and solvent were used. The yield was 0.512 g (83%) of (+)-**41** as a white foam: R_f 0.52 (silica gel, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.74 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 1.15 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 1.25–1.79 (m, $CH_2CH_2CH_2$, 2 H), 2.26 (s, $ArCH_3$, 3 H), 2.36 (s, $ArCH_3$, 3 H), 2.38 (overlapping s, $ArCH_3$, 6 H), 3.39 (q, J = 7.0 Hz, OCH_2 of inner ethoxy, 2 H), 3.39–3.60 (m, $CH_2CH_2CH_2$, 3 H), 3.76 (q, J = 7.0 Hz, OCH_2 of outer ethoxy, 2 H), 4.18–4.27 (m, $CH_2CH_2CH_2$, 1 H), 4.34 (d, J = 9.1 Hz, $ArCH_2Br$, 1 H), 4.52 (d, J = 9.1 Hz, $ArCH_2Br$, 1 H), 4.74 (overlapping d, J = 9.1 Hz, $ArCH_2Br$, 2 H), 7.06 (overlapping s, ArH, 2 H), 7.11–7.32 (overlapping s, ArH. 6 H); MS (EI, 70 eV) 1:2:1 Br_2 isotope pattern centered at m/e 708 (M^+ + 2, 100%); optical rotation (c = 4.3, CH_2Cl_2, 25 °C) $[\alpha]_{366}$ = +157.6°, $[\alpha]_{405}$ = +99.1°, $[\alpha]_{436}$ = +75.6°, $[\alpha]_{546}$ = +37.1°, $[\alpha]_{579}$ = +31.8°, $[\alpha]_D$ = +30.6°. Anal. Calcd for $C_{37}H_{40}Br_2O_4$ (sample dried 12 h at 10^{-1} Torr, 100 °C): C, 62.72; H, 5.69. Found: C, 62.41; H, 5.82.

The levorotary enantiomer (–)-**41** was prepared in like manner. It was not characterized but was instead used directly in the synthesis of macrocycle (–)-**5**.

General Procedure for the Preparation of Macrocycles 3–12. A three-neck 1.0-L round-bottom flask was equipped sequentially on the center neck with reflux-dilution thimble (30 mL capacity), condenser, and 500-mL Hershberg constant-addition funnel. The side necks were tightly stoppered. The addition funnel was then loaded with a solution of equimolar amounts of the dry diol and the azeotropically dried (General Procedure) dibromide in 250 mL of THF. The flask was loaded with excess (ca. 5 equiv) of NaH dispersion in mineral oil and 300 mL of THF. This suspension was heated to a vigorous reflux. The contents of the addition funnel were added to this suspension dropwise over a period of 24 h. The resulting mixture was refluxed an additional 18 h and cooled, and the excess NaH was destroyed by dropwise addition of absolute EtOH. The solvent was removed in vacuo, and the crude residue treated as described for the individual macrocycles.

(+)-(19*S*,20*S*)-19,20-Bis((phenylmethoxy)methyl)-27,28,29,30-tetraethoxy-18,21-dioxapentacyclo[21.3.1.1^{2,6}.1^{7,11}.1^{12,16}]triaconta-1(27),2,4,6(30),7,9,11(29),12,14,16(28),23,25-dodecaene (7). The reaction was run according to the general procedure above with 3.39 g (5.08 mmol) of dibromide **18**, 1.53 g, 5.08 mmol) of (*S*,*S*)-($C_6H_5CH_2OCH_2CHOH)_2$,[32] and 1.22 g (25.4 mmol) of 50% NaH dispersion in mineral oil. The crude residue was combined with the product of a similar reaction which had been run on a 1.59-mmol scale. It was partitioned between 300 mL of CH_2Cl_2 and 150 mL of distilled water. The organic phase was washed with 150 mL of distilled water four times. The solvent was removed in vacuo, and the residue was subjected to gel permeation chromatography. Fractions containing product were combined and chromatographed on 50 g of silica gel. The column was eluted with 6% MeOH in CH_2Cl_2 until the faster moving impurities were removed and then with 20% MeOH in CH_2Cl_2. Fractions containing only the spot at R_f 0.34 (silica gel, 9:1 CH_2Cl_2/CH_3OH) were combined and washed with 125 mL of distilled water four times. The solution was dried by passage through filter paper, and the solvent was removed in vacuo. This procedure gave 0.72 g (17%) of macrocycle **7** as a yellow foam: R_f 0.34 (silica gel, 9:1 CH_2Cl_2/CH_3OH); ^1H NMR ($CDCl_3$) δ 0.35 (t, J = 6.7 Hz, CH_3 of inner ethoxy, 6 H), 0.79 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 6 H), 2.70–2.92 and 2.92–3.17 (m, CH_2 of inner ethoxy, 4 H), 3.17–3.50 (m, CH_2 of outer ethoxy, 4 H), 3.72 (br d of d, J = 7.6, 1.6 Hz, OCH_2 adjacent to methine, 2 H), 3.95 (d, J = 7.6, OCH_2 adjacent to methine, 2 H), 4.23 (d, J = 1.6 Hz, OCH adjacent to methylene, 2 H), 4.42 (d, J = 11.5 Hz, $ArCH_2O$, 2 H), 4.45 (s, $ArCH_2O$, 4 H), 4.99 (d, J = 11.5 Hz, $ArCH_2O$, 2 H), 6.99–7.42 (m, ArH, 22 H). The following pairs of peaks were shown to be coupled by double irradiation experiments: (0.35, 2.92–3.17), (0.79, 3.17–3.50), (3.72, 3.95), (3.72, 4.23), (4.42, 4.99). No evidence for the existence of a second diastereomer was found in the ^1H NMR spectrum of the free host in $CDCl_3$, $(CD_3)_2CO$, or $Cl_2CDCDCl_2$; IR (thin film) 3065, 3035, 2980, 2930, 2870, 1585, 1445, 1380, 1230, 1090, 1030 cm^{-1}; MS (EI, 16 eV), m/e 808 (M^+, 6.0%); optical rotation (c = 3.9, $CHCl_3$, 25 °C) $[\alpha]_{365}$ = +221.5°, $[\alpha]_{405}$ = +120.6°, $[\alpha]_{436}$ = +86.4°, $[\alpha]_{546}$ = +40.1°, $[\alpha]_{579}$ = +33.4°, $[\alpha]_D$ = +32.3°. Anal. Calcd. for $C_{52}H_{56}O_8$ (sample dried 24 h at 10^{-5} Torr, 25 °C): C, 77.20; H, 6.98. Found: C, 77.12; H, 7.09.

A sample of host **7** was dissolved in CH_2Cl_2 and vigorously shaken with a saturated aqueous NaBr solution. The phases were separated. The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. The ^1H NMR spectrum of the resulting white foam in $CDCl_3$ revealed the formation of two diastereomeric complexes. The major diastereomer, which predominated by a factor of 2.5:1, appeared to be the same diastereomer that predominated in the free host. This diastereomer gave (in full) following: δ 0.35 (t, J = 7.3 Hz, CH_3 of inner ethoxy, 6 H), 0.79 (t, J = 7.3 Hz, CH_3 of outer ethoxy, 6 H), 2.73–2.94 and 2.95–3.13 (m, CH_2 of inner ethoxy, 4 H), 3.27–3.56 (m, CH_2 of outer ethoxy, 4 H), 3.72 (br d, J = 8.1 Hz, OCH_2 adjacent to methine, 2 H), 3.97 (d, J = 8.1 Hz, OCH_2 adjacent to methine, 2 H), 4.23 (br s, OCH adjacent to methylene, 2 H), 4.42 (d, J = 11.4 Hz, $ArCH_2O$, 2 H), 4.54 (s, $ArCH_2O$, 4 H), 4.98 (d, J = 11.4 Hz, $ArCH_2O$, 2 H), 6.99–7.58 (m, ArH, 22 H). The minor diastereomer gave (in part) the following: δ 0.31 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 6 H), 0.84 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 6 H), 4.09 (d, J = 6.0 Hz, OCH adjacent to methylene, 2 H), 4.34 (d, J = 10.5 Hz, $ArCH_2O$, 2 H), 4.58 (s, $ArCH_2O$, 4 H), 5.09 (d, J = 10.6 Hz, $ArCH_2O$, 2 H). The KBr complex of **7** gave a very similar ^1H NMR spectrum. The major difference was that the ratio of isomers was 3:1, with the same diastereomer predominating.

(20*R*,23*S*)-31,33,34,35-Tetrakis(phenylmethoxy)-18,25,32-trioxahexacyclo[25.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{20,23}]pentatriconta-1(31),2,4,6(35),7,9,11(34),12,14,16(33),27,29-dodecaene (9). The general procedure for macrocyclic ring closure was applied to 0.590 g (0.644 mmol) of dibromide **23** 0.085 g (0.644 mmol) of *cis*-tetrahydrofuran-2,5-dimethanol,[5] and 0.123 g (2.58 mmol) of 50% NaH dispersion in mineral oil. The crude product mixture was partitioned between 200 mL of CH_2Cl_2 and 200 mL of distilled water. The aqueous phase was washed with 100 mL of CH_2Cl_2, and the combined organic phases were washed with 100 mL of saturated aqueous KBr solution. The organic layer was dried ($MgSO_4$), and its volume was reduced to 2.0 mL. This solution was added dropwise to 20 mL of vigorously stirred hexanes. A viscous oil formed on the sides of the flask. The supernatant liquid was removed with a Pasteur pipet. The remaining thick oil was dissolved in 200 mL of CH_2Cl_2 and washed with 100 mL of distilled water three times. The solvent was removed in vacuo, and the residue was recrystallized from hot absolute EtOH to give 0.19 g (33%) of macrocycle **9** as a white solid: mp 183.0–185.0 °C; R_f 0.15 (silica gel, 7% MeOH in CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.28–1.55 (m, CH_2CH_2, 2 H), 1.64–1.93 (m, CH_2CH_2, 2 H), 3.00–3.15 (m, OCH or OCH_2, 1 H), 3.27–3.38 (m, OCH and OCH_2, 2 H), 3.72–4.14 (m, OCH, OCH_2, and $ArCH_2O$, 5 H), 4.15–4.71

(m, $ArCH_2O$, 10 H), 6.41–7.53 (m, ArH, 32 H); MS (FAB, 2-hydroxyethyl disulfide, trace of dimethylformamide), *m/e* 925 ($M + K^+$, 15%). Anal. Calcd for $C_{60}H_{54}O_7$ (sample dried 24 h at 10^{-5} Torr, 25 °C): C, 81.24; H, 6.14. Found: C, 81.33; H, 6.16.

32,34,35,36-Tetrakis(phenylmethoxy)-18,26-dioxa-33-azahexacyclo[26.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{20,24}]hexatriaconta-1(32),2,4,6(36),7,9,11(35),12,14,16(34),20,22,24(33),28,30-pentadecaene (10). The general procedure for macrocyclic ring closure was applied to 0.81 g (0.88 mmol) of dibromide **23**, 0.123 g (0.88 mmol) of pyridine-2,6-dimethanol, and 0.50 g (4.42 mmol) of 50% NaH dispersion in mineral oil. The crude residue was partitioned between 250 mL of CH_2Cl_2 and 250 mL of distilled ater. The solution was dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was preabsorbed onto 15-mL reverse-phase silica gel and flash chromatographed through an additional 70 mL of this support eluting with 2% (wt/vol) NaBr in 4:1 acetone/water. Fractions containing product were combined. Reduction of the volume in vacuo at 35 °C gave white crystals which were collected by filtration. This material was dissolved in 75 mL of CH_2Cl_2 and washed with 100 mL of distilled water four times. The solution was dried by passage through filter paper, and the solvent removed in vacuo. The residue was dissolved in 30 mL of acetone, and distilled water was added until the solution became slightly cloudy. Storing this solution 12 h at 25 °C gave 0.205 g (26%) of **10** as white polyhedral crystals; mp 149.5–150.5 °C; R_f 0.43 (silica gel, 9:1 CH_2Cl_2/MeOH); ^1H NMR ($(CD_3)_2CO$) δ 4.15 (d, J = 11.8 Hz, $ArCH_2O$, 2 H), 4.24 (d, J = 11.3 Hz, $ArCH_2O$, 2 H), 4.28 (s, $ArCH_2O$, 4 H), 4.33 (d, J = 11.8 Hz, $ArCH_2O$, 2 H), 4.43 (d, J = 11.3 Hz, $ArCH_2O$, 2 H), 4.48 (d, J = 13.0 Hz, $ArCH_2O$, 2 H), 4.65 (d, J = 13.0 Hz, $ArCH_2O$, 2 H), 6.59–6.78 (m, ArH, 7 H), 6.81–7.06 (m, ArH, 16 H), 7.19–7.27 (m, ArH, 11 H), 7.69 (t, J = 8.1 Hz, H of C-4 of pyridine ring, 1 H); MS (EI, 16 eV), *m/e* 893 (M^+, 10%), 802 ($M^+ - CH_2C_6H_5$, 11%), 786 ($M^+ - OCH_2C_6H_5$, 100%). Anal. Calcd. for $C_{61}H_{51}NO_6$ (sample dried 3 h at 10^{-1} Torr, 100 °C): C, 81.95; H, 5.75. Found: C, 81.80; H, 5.74.

(+)-(19*S*,20*S*)-19,20-Bis((phenylmethoxy)methyl)-27,28,29,30-tetrakis(phenylmethoxy)-18,21-dioxapentacyclo[21.3.1.1^{2,6}.1^{7,11}.1^{12,16}]triaconta-1(27),2,4,6(30),7,9,11(29),12,14,16(28),23,25-dodecaene (8). The general procedure for macrocyclic ring closure was applied to 1.39 g (1.52 mmol) of dibromide **23**, 0.458 g (1.52 mmol) of (*S,S*)-$(C_6H_5CH_2OCH_2CHOH)_2$,[32] and 0.73 g (15.2 mmol) of 50% NaH dispersion in mineral oil. The crude residue was diluted with 250 mL of CH_2Cl_2 and 250 mL of distilled water. It was acidified with 3 N hydrochloric acid, and the phases were separated. The organic phase was washed with brine and dried by passage through filter paper. The solvent was removed in vacuo. The residue was preabsorbed onto 15 mL of reverse-phase silica gel and flash chromatographed through an additional 70 mL of this support eluting with 3% (wt/vol) NaBr in 4:1 acetone/water. Fractions containing product were combined. The volume of the eluate was reduced by 30%, and the solution cooled to −10 °C. The white crystals that formed were collected by filtration. This material was dissolved in 200 mL CH_2Cl_2 and washed with 200 mL distilled water four times. The solution was dried by passage through filter paper, and the solvent removed in vacuo. The residue was dissolved in 50 mL of acetone, and distilled water was added until the solution became slightly cloudy. This solution stored for 12 h at −10 °C gave 0.247 g (15%) of macrocycle **8** as white crystals: mp 139.0–142.0 °C; R_f 0.41 (silica gel, 9:1 CH_2Cl_2/MeOH), 0.60 (reverse phase, 3% NaBr in 4:1 acetone/water); ^1H NMR ($CDCl_3$) δ 3.69 (br s, $ArCH_2O$, 4 H), 3.77 (d, J = 11.2 Hz, $ArCH_2O$, 2 H), 3.84 (d, J = 11.2 Hz, $ArCH_2O$, 2 H), 4.06 (br s, $ArCH_2O$, 4 H), 4.21–4.49 (m, $ArCH_2O$, 10 H) 6.41 (d, J = 7.3, ArH, 4 H), 6.55 (br d, J indeterminate, ArH, 4 H), 6.70–7.48 (m, ArH, 30 H), 7.53 (d, J = 7.3 Hz, ArH, 4 H); IR (thin film) 3060, 3030, 2930, 2880, 1585, 1450, 1435, 1370, 1210, 1085, 1015 cm^{-1}; MS (FAB, 2-hydroxyethyl disulfide, trace DMF), *m/e* 1079 ($M + Na^+$, 100%); optical rotation (c = 3.0, CH_2Cl_2, 25 °C) $[\alpha]_{365}$ = +418.9°, $[\alpha]_{405}$ = +250.3°, $[\alpha]_{436}$ = +184.1°, $[\alpha]_{546}$ = +85.4°, $[\alpha]_{579}$ = +72.5°, $[\alpha]_D$ = +69.2°. Anal. Calcd. for $C_{72}H_{64}O_8$ (sample dried 24 h at 10^{-5} Torr, 25 °C): C, 81.79; H, 6.10. Found: C, 81.85; H, 6.14.

29,30,31,32-Tetrakis(phenylmethoxy)-2*H*,23*H*-3,7:8,12:13,17:18,22-tetrametheno-1,24-benzodioxacyclohexacosin (3). The general procedure for macrocyclic ring closure was applied to 1.63 g (1.78 mmol) of dibromide **23**, 0.196 g (1.78 mmol) of catechol, and 0.52 g (10.8 mmol) of 50% NaH dispersion in mineral oil. The crude residue was diluted with 200 mL of CH_2Cl_2 and 200 mL of distilled water. The mixture was acidified with 3 N hydrochloric acid, and the phases were separated. The organic phase was dried by passage through filter paper. The solvent was removed in vacuo. The residue was preabsorbed onto 150 mL of reverse-phase silica gel and flash chromatographed through an additional 70 mL of this support eluting with 3% (wt/vol) NaBr in 8:3 acetone/water. Fractions containing product were combined. The volume of the eluate was reduced by 30% in vacuo at 35 °C. The resulting white crystals were collected by filtration. This material was dissolved in 250 mL of CH_2Cl_2 and washed with 200 mL of distilled water four times. The solution was dried by passage through filter paper, and the volume reduced in vacuo to 100 mL. The solution was diluted with 100 mL of MeOH, and the volume was again reduced in vacuo to 100 mL. The white precipitate that formed on standing was collected by filtration to give 0.63 g (41%) of macrocycle **3**: mp 187.0–187.5 °C; R_f 0.50 (silica gel, 9:1 CH_2Cl_2/MeOH), 0.25 (reverse phase, 3% NaBr in 8:3 acetone/water); ^1H NMR ($CDCl_3$) δ 3.72 (d, J = 12.3 Hz, $ArCH_2O$, 2 H), 3.91 (d, J = 9.7 Hz, $ArCH_2O$, 2 H), 3.98 (d, J = 9.7 Hz, $ArCH_2O$, 2 H), 4.19 (d, J = 12.3 Hz, $ArCH_2O$, 2 H), 4.44 (s, $ArCH_2O$, 4 H), 6.38 (d, J = 7.0, ArH, 4 H), 6.63 (t, J = 7.5 Hz, ArH, 4 H), 6.70–6.79 (m, ArH, 6 H), 6.85–7.09 (m, ArH, 16 H), 7.24 (t, J = 7.5 Hz, ArH, 2 H), 7.42 (d of d, J = 7.5, 2.2 Hz, ArH, 2 H), 7.51 (d of d, J = 7.5, 2.2 Hz, ArH, 2 H); MB (FAB, NOBA), *m/e* 887 ($M + Na^+$, 100%). Anal. Calcd for $C_{60}H_{48}O_6$ (sample dried 3 h at 10^{-1} Torr, 180 °C): C, 83.31; H, 5.71. Found: C, 83.34; H, 5.46.

21*H*-4,10[1′,3′]-Benzeno-22,26-metheno-6*H*,14*H*-tribenzo[*b*,*f*,*m*][1,4,8,12]tetraoxacycloeicosin, 27,29-Diethoxy-7,8-dihydro-, Stereoisomer 4. The general procedure for macrocyclic ring closure was applied to 0.483 g (0.740 mmol) of dibromide **28**, 0.0815 g (0.740 mmol) of catechol, and 0.141 g (2.94 mmol) of 50% NaH dispersion in mineral oil. The crude residue was diluted with 400 mL of CH_2Cl_2 and 400 mL of distilled water. It was acidified with 3 N hydrochloric acid, and the phases were separated. The organic phase was washed with 300 mL of distilled water four times. The solution was dried by passage through filter paper, and the solvent was removed in vacuo. The residue was subjected to gel permeation chromatography. Fractions containing product were combined, and the solvent removed in vacuo. The residue was preabsorbed on 15 mL of reverse-phase silica gel and flash chromatographed through an additional 70 mL of this support eluting with 3% (wt/vol) NaBr in 13:7 acetone/water. Fractions containing product were combined, and the volume was reduced 30% in vacuo. This solution was diluted with 150 mL of CH_2Cl_2, and the phases were separated. The organic phase was washed with 100 mL of distilled water four times. The solution was dried by passage through filter paper, and the solvent removed in vacuo. This procedure gave 0.132 g (30%) of macrocycle **4** as an off-white foam: mp 225.0–226.5 °C; R_f 0.21 (silica gel, 9:1 CH_2Cl_2/CH_3OH); ^1H NMR ($CDCl_3$) δ 0.24 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 0.83 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 1.17–1.45 (m, $CH_2CH_2CH_2$, 2 H), 2.38–2.52 (m, $CH_2CH_2CH_2$, 1 H), 2.77–3.21 (m, CH_2 of inner ethoxy plus $CH_2CH_2CH_2$, 4 H), 3.32–3.55 (m, $CH_2CH_2CH_2$, 1 H), 3.62–3.92 (m, CH_2 of outer ethoxy, 2 H), 4.80 (d, J = 10.2, $ArCH_2O$, 1 H), 4.98 (d, J = 12.3 Hz, $ArCH_2O$, 1 H), 5.36 (d, J = 12.3 Hz, $ArCH_2O$, 1 H), 5.54 (d, J = 10.2 Hz, $ArCH_2O$, 1 H), 6.68–7.53 (m, ArH, 16 H); MS (EI, 70 eV), *m/e* 600 (M^+, 100%). Anal. Calcd for $C_{39}H_{36}O_6 \cdot {}^1/_2H_2O$ (sample dried 6 h at 10^{-5} Torr, 150 °C): C, 76.83; H, 6.12. Found: C, 76.77; H, 6.27.

6*H*-15,24[1′,3′]-Benzeno-7,11-metheno-28*H*-tetrabenzo[*b*,*f*,*j*,*n*][1,4,8,13]tetraoxacycloheneicosin, 31,36-Diethoxy-17,22-dihydro-9,13,26,34-tetramethyl- (6). Dibromide **44** was formed from 0.80 g (1.24 mmol) of diol **43** according to the procedure for the preparation of dibromide **23**. Similar ratios of solvent and reagent were used. The only variation from this procedure was that CH_2Cl_2 was used instead of benzene as the reaction solvent. The yield of **44** was 0.857 g (90%), isolated as a yellow oil: R_f 0.27 (1:1 CH_2Cl_2/C_6H_{12}); ^1H NMR ($CDCl_3$) δ 0.78 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 1.13 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 2.24–2.37 (overlapping s, $ArCH_3$, 12 H), 3.45 (br q, J = 7.0 Hz, CH_2 of inner ethoxy, 2 H), 3.72 (q, J = 7.0 Hz, CH_2 of outer ethoxy, 2 H), 4.22 (br s, $ArCH_2O$ or $ArCH_2Br$, 2 H),

4.52–4.68 (m, $ArCH_2O$ and/or $ArCH_2Br$, 4 H), 4.84 (s, $ArCH_2O$ or $ArCH_2Br$, 2 H), 7.02–7.38 (m, ArH, 12 H); MS (EI, 16 eV), 1:2:1 Br_2 isotope pattern centered at m/e 770 ($M^+ + 2$, 24%). The general procedure for macrocyclic ring closure was applied to 0.857 g (1.11 mmol) of dibromide **44**, 0.122 g (1.11 mmol) of catechol, and 0.533 g (11.1 mmol) of 50% NaH dispersion in mineral oil. The crude residue was partitioned between 200 mL of CH_2Cl_2 and 200 mL of saturated aqueous NaBr solution. The solvent was removed in vacuo. The residue was chromatographed on 25 g of silica gel. The column was eluted with 4% MeOH in CH_2Cl_2 until the faster moving impurities were removed and then with a gradient of up to 8% MeOH. Fractions containing product were combined and washed with 200 mL of distilled water four times. The solution was dried by passage through filter paper, and the solvent removed in vacuo. This procedure gave 0.242 g (30%) of macrocycle **6** as a yellow foam: R_f 0.28 (silica gel, 9:1 CH_2Cl_2/CH_3OH); ^1H NMR ($CDCl_3$) δ 0.26 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 0.80 (t, J = 7.2 Hz, CH_3 of outer ethoxy, 3 H), 2.31 (s, $ArCH_3$, 3 H), 2.39 (s, $ArCH_3$, 3 H), 2.40 (s, $ArCH_3$, 3 H), 2.43 (s, $ArCH_3$, 3 H), 2.85–3.18 (m, CH_2 of inner ethoxy, 2 H), 3.30–3.52 (m, CH_2 of outer ethoxy, 2 H), 3.71 (d, J = 10.2, $ArCH_2O$, 1 H), 3.80 (d, J = 10.2 Hz, $ArCH_2O$, 1 H), 4.03 (d, J = 9.8 Hz, $ArCH_2O$, 1 H), 4.10 (d, J = 9.8 Hz, $ArCH_2O$, 1 H), 4.58 (d, J = 10.6 Hz, $ArCH_2O$, 1 H), 4.82 (d, J = 11.3 Hz, $ArCH_2O$, 1 H), 5.28 (d, J = 11.3 Hz, $ArCH_2O$, 1 H), 5.32 (d, J = 10.6 Hz, $ArCH_2O$, 1 H), 6.33–6.41 (m, ArH, 1 H), 6.69–6.94 (m, ArH, 6 H), 6.99 (s, ArH, 1 H), 7.02 (s, ArH, 1 H), 7.04 (s, ArH, 1 H), 7.17–7.30 (m, ArH, 6 H); MS (EI, 16 eV), m/e 718 (M^+, 16%). Anal. Calcd for $C_{48}H_{46}O_6$ (sample dried 6 h at 10^{-1} Torr, 80 °C): C, 80.20; H, 6.45. Found: C, 79.81; H, 6.79.

14*H*-1,23[1′,3′]-Benzeno-8,11-epoxy-15,19-metheno-5*H*-tribenzo[*c*,*g*,*k*][1,5,10,19]tetraoxacyclopentacosin, 33,38-Diethoxy-7,8,9,10,11,12,25,30-octahydro-3,17,21,36-tetramethyl-, Stereoisomers 11 and 12. Dibromide **44** was prepared and partially characterized as described in the procedure for the preparation of macrocycle **6**. The general procedure for macrocyclic ring closure was applied to 0.596 g (0.774 mmol) of dibromide **44**, 0.102 g (0.774 mmol) of *cis*-tetrahydrofuran-2,5-dimethanol,[5] and 0.37 g (7.74 mmol) of 50% NaH dispersion in mineral oil. The crude residue was diluted with 250 mL of CH_2Cl_2 and 150 mL of distilled water. It was acidified with 3 N hydrochloric acid, and the phases were separated. The solution was dried by passage through filter paper, and the solvent was removed in vacuo. The residue was preabsorbed onto 15 mL of reverse-phase silica gel and flash chromatographed over another 70 mL of this support eluting with 2.5% (wt/vol) KPF_6 in 3:1 acetone water. Fractions containing product were combined, and the volume of the solution was reduced 30% in vacuo. This solution was diluted with 300 mL of CH_2Cl_2, and the phases were separated. The solution was dried by passage through filter paper, and the solvent removed in vacuo. Analysis of this residue by regular-phase TLC revealed the presence of two spots having R_f values of 0.54 and 0.24 (silica gel, 9:1 CH_2Cl_2). These two compounds were separated by chromatography on 10 g of silica gel eluting with a gradient of 6–9% MeOH in CH_2Cl_2. Fractions corresponding to each product were combined and washed with 100 mL of distilled water four times. The two solutions were dried by passage through filter paper, and the solvent was removed in vacuo. The fractions corresponding to the higher R_f material yielded 0.014 g (3.5%) of a yellow oil (**11**). The fractions corresponding to the lower R_f material gave 0.021 g of a white foam. This latter material was dissolved in 0.5 mL of acetone, and water was added dropwise until the solution clouded. This solution after several days at −10 °C yielded 0.0065 g (1.1%) of **12** as white polyhedra. Characterization of **11**: R_f 0.54 (silica gel, 9:1 CH_2Cl_2/CH_3OH). The ^1H NMR of **11** in $(CD_3)_2CO$ was extremely complex owing to the presence of two slowly interconverting conformers in a ratio of approximately 2:1. The integrations in the following peak list are normalized to a single host molecule: δ 0.58 (t, J = 7 Hz, CH_3 of inner ethoxy, major conformer, 2 H), 0.75 (t, J = 7 Hz, CH_3 of inner ethoxy, minor conformer, 1 H), 1.01 (t, J = 7 Hz, CH_3 of outer ethoxy, major conformer, 2 H), 1.03 (t, J = 7 Hz, CH_3 of outer ethoxy, minor conformer, 1 H), 1.20–1.39 and 1.53–1.83 (m, CH_2 CH_2 of tetrahydrofuran ring, 4 H), 2.30 (s, $ArCH_3$, minor conformer, 1 H), 1.38 (s, $ArCH_3$, 3 H), 1.42 (overlapping s, $ArCH_3$, 8 H), 2.80–5.62 (m with major peaks at 3.01, 3.09, 3.15, 3.58, 3.87, 3.93, 3.99, 4.04, 4.12, 4.21, 4.28, 4.35, 4.55, 4.60, 5.07, and 5.13, aliphatic protons α to oxygen, 18 H), 6.26 (d, J = 8 Hz, ArH of *o*-xylyl, minor conformer, $^1/_3$ H), 6.43 (br d, J = 8 Hz, ArH of *o*-xylyl, major conformer, $^2/_3$ H, 1 H), 7.00–7.32 (m, ArH, 11 H); MS (EI, 70 eV), m/e 740 (M^+, 100%). Anal. Calcd for $C_{48}H_{52}O_7$ (sample dried 3 h at 10^{-1} Torr, 80 °C): C, 77.81; H, 7.07. Found: C, 77.72; H, 7.15.

When the ^1H NMR of **11** was determined in $(CD_3)_2CO$ in which excess NaI had been dissolved, a 2:1 mixture of conformers was again observed. The ^1H NMR spectrum of this mixture did not change during 24 h at 25 °C. It is not clear whether it is the same conformer that predominates. The integrations of the following peak list are normalized to a single complex: δ 0.65 (t, J = 7 Hz, CH_3 of inner ethoxy, minor conformer, 1 H), 0.71 (t, J = 7 Hz, CH_3 of inner ethoxy, major conformer, 2 H), 0.93 (t, J = 7 Hz, CH_3 of outer ethoxy, minor conformer, 1 H), 1.01 (t, J = 7 Hz, CH_3 of outer ethoxy, major conformer, 2 H), 1.24–1.39 and 1.54–1.71 (m, CH_2 CH_2 of tetrahydrofuran ring, 4 H), 2.43 (s, $ArCH_3$, 5 H), 1.50, 1.52, and 1.54 (overlapping s, $ArCH_3$, 7 H), 3.04–3.21 (m, OCH, 1 H), 3.41–3.58 (m, OCH_2 of inner ethoxy, OCH, 3 H), 3.61–3.77 (m, OCH_2 of outer ethoxy and CH_2O of tetrahydrofuran ring, 3 H), 3.86–4.12 (m, CH_2 of tetrahydrofuran ring, 3 H), 4.15–4.47 (m, $ArCH_2O$, 5 H), 4.47–4.62 (m, $ArCH_2O$, 1 H), 4.76 (d, J = 10 Hz, $ArCH_2O$, minor conformer, $^1/_3$ H), 4.82 (d, J = 10 Hz, $ArCH_2O$, $^2/_3$ H), 5.03–5.16 (m, $ArCH_2O$, 1 H), 5.97 (d, J = 8 Hz, ArH of *o*-xylyl, major conformer, $^2/_3$ H), 6.39 (d, J = 8 Hz, ArH of *o*-xylyl, minor conformer, $^1/_3$ H), 7.12–7.71 (m, ArH, 11 H).

Characterization of **12**: R_f 0.24 (silica gel, 9:1 CH_2Cl_2/MeOH); ^1H NMR ($(CD_3)_2CO$) δ 0.66 (t, J = 7 Hz, CH_3 of inner ethoxy, 3 H), 0.80 (t, J = 7 Hz, CH_3 of outer ethoxy, 3 H), 1.26–1.46 (m, CH_2CH_2 of tetrahydrofuran ring, 4 H), 2.42 (s, $ArCH_3$, 3 H), 2.47 (s, $ArCH_3$, 3 H), 2.53 (overlapping s, $ArCH_3$, 6 H), 3.25–3.58 and 3.61–3.75 (m, hydrogens of several carbons α to oxygen, 11 H), 3.98 (d, J = 9, $ArCH_2O$, 1 H), 4.02 (d, J = 9 Hz, $ArCH_2O$, 1 H), 4.14 (d, J = 9 Hz, $ArCH_2O$, 1 H), 4.21 (d, J = 10 Hz, $ArCH_2O$, 1 H), 4.47 (d, J = 10 Hz, $ArCH_2O$, 1 H), 4.73 (d, J = 10 Hz, $ArCH_2O$, 1 H), 5.26 (d, J = 10 Hz, $ArCH_2O$, 1 H), 5.96 (d, J = 8 Hz, ArH, 1 H), 7.08–7.51 (m, ArH, 10 H), 7.60 (d, J = 8 Hz, ArH, 1 H); MS (EI, 16 eV), m/e 740 (M^+, 100%). Anal. Calcd for $C_{48}H_{52}O_7$ (sample dried 3 h at 10^{-1} Torr, 180 °C): C, 77.81; H, 7.07. Found: C, 77.70; H, 6.98.

When excess NaI was added to a sample of **12** in $(CD_3)_2CO$, the following spectrum was obtained: ^1H NMR ($(CD_3)_2CO$) δ 0.59 (t, J = 7 Hz, CH_3 of inner ethoxy, 3 H), 0.82 (t, J = 7 Hz, CH_3 of outer ethoxy, 3 H), 1.10–1.31 (m, CH_2CH_2 of tetrahydrofuran ring, 4 H), 2.18 (s, $ArCH_3$, 3 H), 2.23 (s, $ArCH_3$, 3 H), 2.26 (overlapping s, $ArCH_3$, 6 H), 3.02–3.41 (m, hydrogens of several carbons α to oxygen, 11 H), 3.61 (d, J = 9, $ArCH_2O$, 1 H), 3.65 (d, J = 9 Hz, $ArCH_2O$, 1 H), 3.76 (d, J = 9 Hz, $ArCH_2O$, 1 H), 3.81 (d, J = 9 Hz, $ArCH_2O$, 1 H), 4.02 (d, J = 9 Hz, $ArCH_2O$, 1 H), 4.30 (d, J = 9 Hz, $ArCH_2O$, 1 H), 4.88 (d, J = 9 Hz, $ArCH_2O$, 1 H), 7.52 (t, J = 8 Hz, ArH, 1 H), 7.60–7.87 (m, ArH, 10 H), 7.94 (d, J = 8 Hz, ArH, 1 H).

(−)-21*H*-4,10[1′,3′]-Benzeno-22,26-metheno-6*H*,14*H*-tribenzo[*b*,*f*,*m*][1,4,8,12]tetraoxacycloeicosin, 27,29-Diethoxy-7,8-dihydro-2,12,24,32-tetramethyl-, Stereoisomer (−)-5. The general procedure for macrocyclic ring closure was applied to 0.512 g (0.723 mmol) of dibromide (+)-**41**, 0.0804 g (0.723 mmol) of catechol, and 0.17 g (3.6 mmol) of 50% NaH dispersion in mineral oil. The crude residue was diluted with 250 mL of CH_2Cl_2 and 100 mL of distilled water. The solution was dried by passage through filter paper, and the solvent removed in vacuo. The residue was preabsorbed on 15 mL of reverse-phase silica gel and flash-chromatographed through an additional 70 mL of this support. The eluent was a gradient starting with 3% (wt/vol) NaBr in 13:7 acetone/water and ending with 3% (wt/vol) NaBr in 4:1 acetone/water. Fractions containing product were combined, and the volume was reduced 30% in vacuo. This solution was diluted with 250 mL of CH_2Cl_2, and the phases were separated. The organic phase was washed with 200 mL of distilled water four times. The solution was dried by passage through filter paper, and the solvent removed in vacuo. The residue was dissolved in 50 mL of acetone, and 10 mL of distilled water was added. The volume of this solution was reduced in vacuo until a slight cloudiness appeared. This solution when stored 48 h at −10 °C

gave white needles which were collected by filtration. Recrystallization of this material two more times in the same manner gave 0.163 g (35%) of white needles of maximum rotation; mp 127.0–130.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.26 (t, J = 7.0 Hz, CH_3 of inner ethoxy, 3 H), 0.82 (t, J = 7.0 Hz, CH_3 of outer ethoxy, 3 H), 1.19–1.58 (m, $CH_2CH_2CH_2$, 2 H), 2.31 (s, $ArCH_3$, 3 H), 2.36 (s, $ArCH_3$, 3 H), 2.37 (s, $ArCH_3$, 3 H), 2.43 (s, $ArCH_3$, 3 H), 2.72–2.84 (m, $CH_2CH_2CH_2$, 1 H), 2.90–3.21 (m, CH_2 of inner ethoxy plus $CH_2CH_2CH_2$, 4 H), 3.28–3.59 (m, CH_2 of outer ethoxy, 2 H), 3.77–3.94 (m, $CH_2CH_2CH_2$, 1 H), 4.75 (d, J = 10.3, $ArCH_2O$, 1 H), 4.92 (d, J = 12.4 Hz, $ArCH_2O$, 1 H), 5.30 (d, J = 12.4 Hz, $ArCH_2O$, 1 H), 5.47 (d, J = 10.3 Hz, $ArCH_2O$, 1 H), 6.72–6.98 (m, catechol ArH, 3 H), 7.01–7.21 (m, ArH, 9 H); MS (EI, 70 eV), m/e 656 (M^+, 100%); optical rotation (c = 1.2, CH_2Cl_2, 25 °C) $[\alpha]_{365}$ = −5.15.8°, $[\alpha]_{405}$ = −351.5°, $[\alpha]_{436}$ = −273.3°, $[\alpha]_{546}$ = −143.6°, $[\alpha]_{579}$ = −121.8°, $[\alpha]_D$ = −116.8°. Anal. Calcd for $C_{43}H_{44}O_6$ (sample dried 3 h at 10^{-1} Torr, 80 °C): C, 78.63; H, 6.75. Found: C, 78.53; H, 6.75.

Application of this procedure to dibromide (−)-**41** of 92% optical purity gave macrocycle (+)-**5** of 96% optical purity. Two additional recrystallizations from acetone/water gave a 95% recovery of 100% optically pure (+)-**5**. This material was identical with the other enantiomer in all respects except for its direction of optical rotation: optical rotation (c = 1.0, CH_2Cl_2, 25 °C) $[\alpha]_{365}$ = +518.8°, $[\alpha]_{405}$ = +352.5°, $[\alpha]_{436}$ = +275.0°, $[\alpha]_{546}$ = +143.3°, $[\alpha]_{579}$ = +122.5°, $[\alpha]_D$ = +116.7°.

Preparation of Host–Guest Complexes and Crystal Structure Data. The $LiClO_4$ and NaPic complexes of **1** were prepared as follows: The host was dissolved in acetone, and 1.05 equiv of guest was added. After the mixture became homogenous (<10 min), the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and filtered through a glass wool plug in a Pasteur pipet to remove excess guest. The solvent was removed in vacuo. The KSCN, RbPic, NH_4SCN, and CH_3NH_3Pic complexes were prepared by a procedure that differed from that above only in that a MeOH solution of the guest was added to a $CHCl_3$ solution of the host. This procedure is advantageous in that both **1** and many of these salts are sparingly soluble in acetone.

Crystals suitable for X-ray structure determination were obtained by slow evaporation of a solution of ca. 25 mg of host (or complex) in approximately 1.5 mL of solvent. When mixed solvents were used, the ratio was approximately 1:1 (v/v). The most convenient and consistent method for obtaining a suitable rate of evaporation was to place this solution in a 3.0-mL vial whose cap contained one to three ca. 1-mm nail holes. The following solvents were used to obtain crystals for X-ray structure determination: free **1**, $CHCl_3$/MeOH; **1**·$LiClO_4$, $(CH_3)_2CO/CCl_4$; **1**·NaPic, $(CH_3)_2CO/C_6H_6$; **1**·KSCN, $CH_2Cl_2/(CH_2)_6$; **1**·RbPic, $(CH_3)_2CO$; **1**·NH_4SCN, CH_2Cl_2/absolute EtOH; **1**·(CH_3NH_3)Pic, $(CH_3)_2CO$/absolute EtOH; free **3**, CH_2Cl_2/MeOH; free **4**, $(CH_3)_2CO$/water.

All crystals were examined on automated diffractometers using Mo Kα radiation. All except compound **1** were measured at ambient temperature. All except compounds **1** and **1**·RbPic were measured on a modified Picker FACS-1 diffractometer. Heavy-atom methods were used to determine the structures of **1**·KSCN and **1**·RbPic. All other structures were determined by direct methods.

Compound **1** crystallizes in the monoclinic system $P2_1/c$. Unit-cell dimensions are as follows: a = 10.520 (1), b = 27.204 (4), c = 11.128 (2) Å, β = 118.38 (1)°, V = 2802 Å^3, Z = 4. The crystal was examined on a modified Syntex P$\bar{1}$ diffractometer at 118 K. The structure was determined by direct methods. Refinement of 403 parameters (3523 reflections with $I > 3\sigma(I)$) led to an agreement value, R, currently at 0.043.

Compound **1**·$LiClO_4$·H_2O crystallizes in the monoclinic system $P2_1/c$. Unit-cell dimensions are as follows: a = 13.279 (1), b = 10.8208 (9), c = 23.129 (2) Å, β = 94.641 (3)°, V = 3313 Å^3, Z = 4. The structure was determined by direct methods. Refinement of 275 parameters (2808 reflections with $I > 3\sigma(I)$) led to an agreement value, R, currently at 0.086.

Compound **1**·NaPic·H_2O crystallizes in the triclinic system P$\bar{1}$ with the following unit-cell dimensions: a = 11.2688 (8), b = 12.4839 (10), c = 15.268 (1) Å, α = 68.153 (2), β = 79.484 (2), γ = 84.178 (2)°, V = 1959 Å^3, Z = 2. Refinement of 322 parameters (3915 reflections with $I > 3\sigma(I)$) led to an agreement value, R, currently at 0.088.

Compound **1**·KSCN·CH_2Cl_2 crystallizes in the triclinic system P$\bar{1}$ with the following unit-cell dimensions: a = 12.940 (1), b = 11.2034 (9), c = 28.282 (2) Å, α = 84.309 (2), β = 83.762 (2), γ = 64.995 (2)°, V = 3688 Å^3, Z = 4. Block refinement of 217 + 202 + 45 parameters (4176 reflections with $I > 3\sigma(I)$) led to agreement value, R, currently at 0.094.

Compound **1**·RbPic was examined on a locally built Huber diffractometer. The compound crystallizes in the monoclinic system $C2/m$ with the following unit-cell dimensions: a = 33.848 (2), b = 15.2725 (9), c = 16.0084 (9) Å, β = 110.606 (2)°, V = 7746 Å^3, Z = 8. Refinement of 319 parameters (3281 reflections with $I > 3\sigma(I)$) led to an agreement value, R, currently at 0.061.

Compound **1**·NH_4SCN crystallizes in the triclinic system P$\bar{1}$ with the following unit-cell dimensions: a = 10.9454 (7), b = 18.513 1), c = 18.867 (1) Å, α = 66.192 (2), β = 76.040 (2), γ = 80.068 (2)°, V = 3382 Å^3, Z = 4. Block refinement of 197 + 256 parameters (3960 reflections with $I > 3\sigma(I)$) led to an agreement value, R, currently at 0.087.

Compound **1**·CH_3NH_3Pic crystallizes in the triclinic system P$\bar{1}$ with the following unit-cell dimensions: a = 11.2412 (7), b = 11.6179 (8), c = 15.6255 (1) Å, α = 88.602 (2), β = 87.366 (2), γ = 78.249 (2)°, V = 1996 Å^3, Z = 2. Refinement of 330 parameters (2755 reflections with $I > 3\sigma(I)$) led to agreement value, R, currently at 0.076.

Compound **3** crystallizes in the triclinic system P$\bar{1}$ with the following unit-cell dimensions: a = 10.693 (1), b = 20.052 (2), c = 22.186 (2) Å, α = 94.962 (3), β = 100.582 (3), γ = 95.255 (2)°, V = 4632 Å^3, Z = 4. Block refinement of 297 + 307 parametes (5612 reflections with $I > 3\sigma(I)$) led to an agreement value, R, currently at 0.132.

Compound **4** crystallizes in the monoclinic system $P2_1/n$ with the following unit-cell dimensions: a = 13.1716 (9), b = 17.809 (1), c = 13.516 (1) Å, β = 96.019 (3)°, V = 3155 Å^3, Z = 4. Refinement of 217 parameters (3106 reflections with $I > 3\sigma(I)$) led to an agreement value, R, currently at 0.080.

Compound **10** crystallizes in the triclinic system P$\bar{1}$ with a = 12.3592 (6), b = 12.5572 (6), c = 18.2683 (9) Å, α = 91.414 (1), β = 100.069 (1), γ = 119.761 (1)°, V = 2403 Å^3, Z = 2. Refinement of 260 parameters (4244 reflections with $I > 3\sigma(I)$) led to an agreement value, R, currently at 0.099.

Further crystallographic details will be published elsewhere.