EXPLORATIONS WITH OPTICALLY ACTIVE, CAGE-ANNULATED CROWN ETHERS

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A variety of optically active macrocyclic crown ethers that serve as "host" systems that are capable of differentiating between enantiomeric "guest" molecules during host-guest complexation have been prepared via incorporation of chiral elements into the crown ring skeleton. The ability of these crown ethers to recognize the enantiomers of guest salts, i.e., (±) α-methyl benzylamine and to transport them enantioselectively in W-tube transport experiments were studied.

The ability of these crown ethers to perform as chiral catalysts in an enantioselective Michael addition was studied. The extent of asymmetric induction, expressed in terms of the enantiomeric excess (%*ee*), was monitored by measuring the optical rotation of the product and comparing to the literature value.

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CHAPTER I: INTRODUCTION

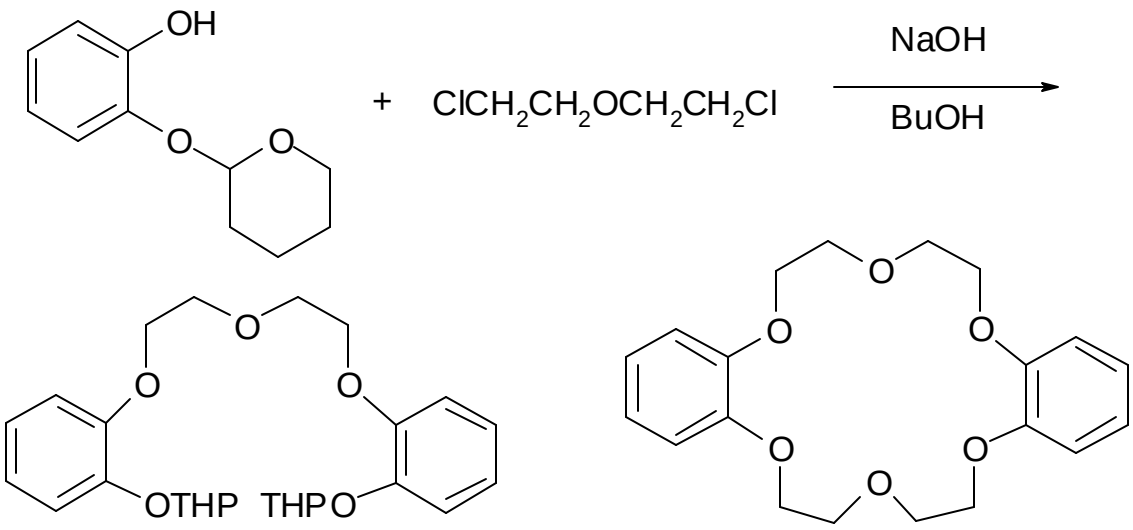
Crown ether chemistry is generally considered to begin when Pedersen's first paper appeared in 1967.[1] Pedersen not only prepared many examples of such compounds, but also he clearly recognized their potential as complexant as well. The term "crown ether" was first suggested by Pedersen and was subsequently widely adopted.

In July 1962, C.J. Pedersen isolated an unusual crystalline by-product from a reaction mixture and later carefully studied its interesting properties.[2] In order to prepare bis[(2-*o*-hydroxyphenoxy) ethyl ether **1**, Pedersen reacted a monoprotected catechol with 2-chloroethyl ether. The intended reaction sequence is shown in Scheme 1.1.

After sequential Williamson reactions occurred, it was Pedersen's intention to cleave the THP ethers, thereby affording **1**. Actually, he was able to isolate **1,** but he also obtained a small amount of fluffy white crystals, which melted *ca*. 164°C. Although the IR spectrum of the white crystals showed no hydroxyl absorption, this material nevertheless appeared to interact with alkali metal cations. We now know that the compound isolated by Pedersen was dibenzo-18-crown-6 (**2)**. In addition, he observed that **2** can form stable complexes with alkali metal cations.

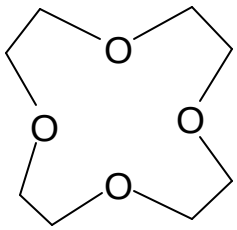
Pedersen had intended for compound **1** to be a phenolic complexing agent for alkali metal cations, but he was surprised when his side-product **2** showed favorable complexing behavior. Moreover, the alkali metal complexes displayed unexpectedly high solubility in organic solvents.

Scheme 1.1



1 **2**

Actually, some examples of macrocyclic polyethers had been reported in the chemical literature prior to the time of Pederson's unexpected discovery. 12-crown-4 (**3**) was produced via cyclooligomerization of ethylene oxide, but unfortunately, it was only deemed "valuable as a high boiling neutral solvent"[3] at that time.



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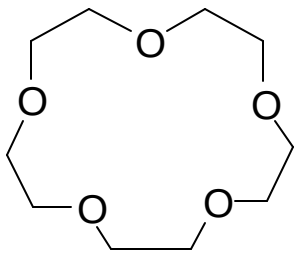
CLASSIFICATION OF CROWN COMPOUNDS

As in any field, new structures need new names. The field of crown ether chemistry contains its own jargon, which is clarified below.

Crown Ethers

The term "crown" generally refers to marocyclic polyethers[4] that contain the ethyleneoxy unit as the fundamental repeating structure. That the basic repeating unit is ethyleneoxy rather than methyleneoxy or propyleneoxy is not an accident when every third atom is oxygen, binding to cations is most effective. Moreover, unfavorable conformational interactions are reduced in this situation relative to the carbon analogs. In fact, these interactions could be reduced even further by using repeating methyleneoxy units, but the hydrolytic stability of such species generally is inferior to their crown ethers, albeit with some notable exceptions.[5]

The terminology suggested by Pedersen[1] for simple crown ethers contains two numbers. The first number indicates the total number of atoms in the macrocycle. The second number indicates how many heteroatoms are present in the ring. For instance, compound **4** as shown below, contains fifteen atoms in the ring, five of which are oxygen. Hence the commonly accepted trivial name for this compound is "15-crown-5".

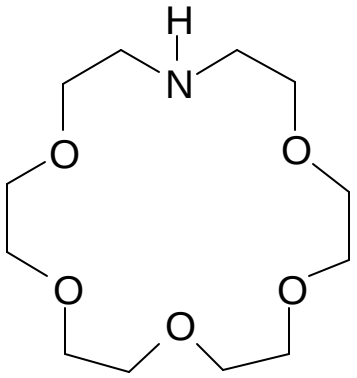


4

Generally, the term “crown ether” refers specifically to those medium sized or macrocyclic systems that possess only one ring and that contain only oxygen heteroatoms in the ring.

Azacrown

This terminology is an extension of the nonsystematic nomenclature described above. Both “amino-crown” and “azacrown” connote the presence of a nitrogen atom in place of oxygen in the macroring structure, however, the latter term is used more frequently. The structures below correspond to monoaza-18-crown-6 (**5)** and 1,10-diaza-18-crown-6 (**6**). Inorganic chemists generally refer to polyaza-crowns as "cyclens”.



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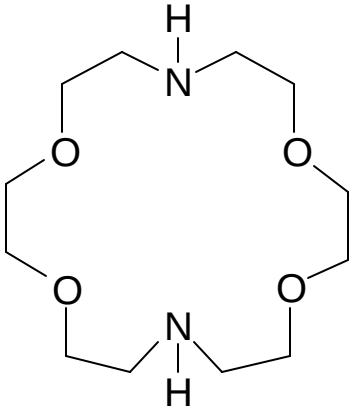
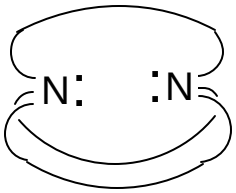


6

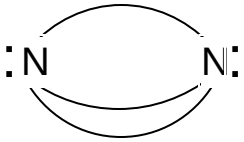
In-Out Bicyclic Amines

This class of compounds was created by Simmons and Park[6,7]at the same time that Lehn and coworkers were preparing the first cryptands (defined below). These compounds are macrobicyclic structures in which both rings contain two tertiary nitrogen atoms. Compounds **7** and **8** are illustrated below in their “in-in” and “out-out” forms.

These compounds possess the interesting framework of the cryptands, however, they lack the possibility of heteroatom cation-binding, which renders them less relevant to the present discussion.



“in-in”
7

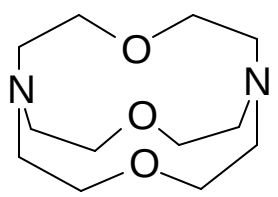


“out-out”
8

Cryptands and Cryptates

This group of compounds was first introduced by Lehn and co-workers.[8] They are macrobi, macrotri, or macropolycyclic compounds that are similar to the "in-out" amines illustrated above but which possess crown-like bridges throughout. These compounds have the ability not only to complex cations but also to encapsulate or entomb them, so the term “cryptand” was suggested.[9] Complexes of cryptands are referred to as" cryptates".

For the purposes of nomenclature, simple cryptands are assumed to be macrobicyclic, and nitrogen is assumed to be the bridgehead atom. Various cryptands are named by assigning numbers according to the number of heteroatoms in each ethylenoxy chain. The two cryptands shown below are designated [1.1.1]-cryptand (**9**) and [2.2.1]-cryptand (**10**), respectively.



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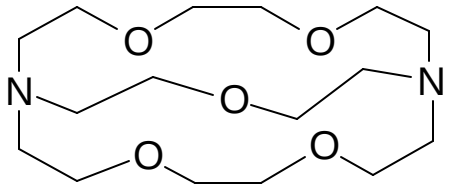

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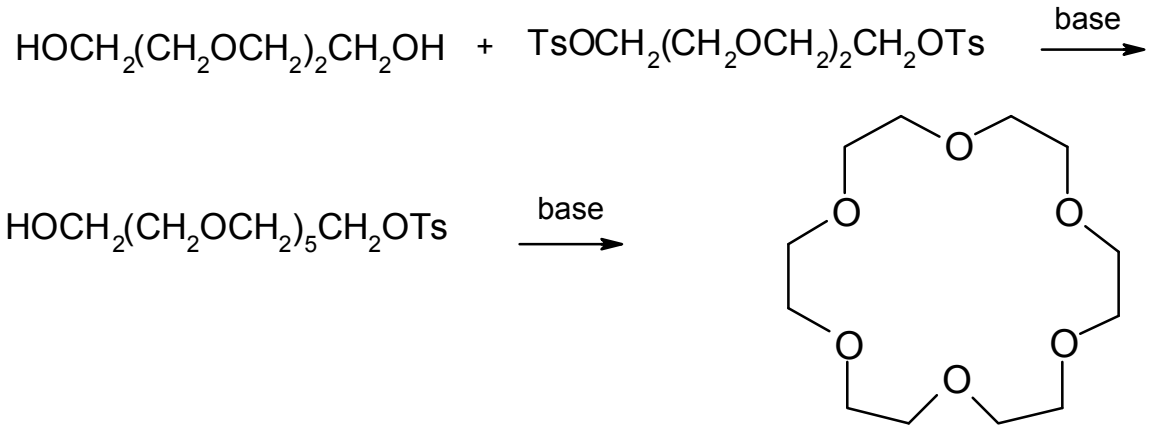
Synthesis of Macrocyclic Polyethers and the Template Effect

It has been accepted for many years that large rings must be prepared under high dilution conditions so that the probability of intramolecular cyclization exceeds the probability of linear polymer formation.[10] Nevertheless, many macrocyclic polyether syntheses have been reported that do not require high dilution conditions.[1] The success of these large-ring intramolecular S_N2 reactions is generally attributed to the operation of a template effect that accompanies crown ether synthesis.

The Willamson ether synthesis is commonly employed to prepare macrocyclic polyethers. This reaction is well understood, several examples of the Williamson synthesis appear in the literature.[11]Although the simplest example of such a reaction would involve a ?-haloethylene glycol oligomer which undergoes intramolecular cyclization, it is more common for two new bonds to be formed during a crown syntheses.

An early example of the formation of a crown by a "double-Williamson" synthesis can be found in Dale's[12] synthesis of 18-crown-6 (**11**, Scheme 1.2)**.**

Scheme 1.2



11

The first C-O bond formation is not strongly affected by the presence of a templating cation. However, in the second step, either the presence of a template or high dilution is required. The template can be provided by an alkali metal cation, for which the long polyether chain has a certain affinity. Presumably, the cation is ion-paired with the alkoxide anion, and the remainder of the chain becomes associated with the templating cation. Note that this arrangement corresponds to Ugelstad's "self-solvating" bases,[13] as illustrated in Scheme 1.3.

Scheme 1.3

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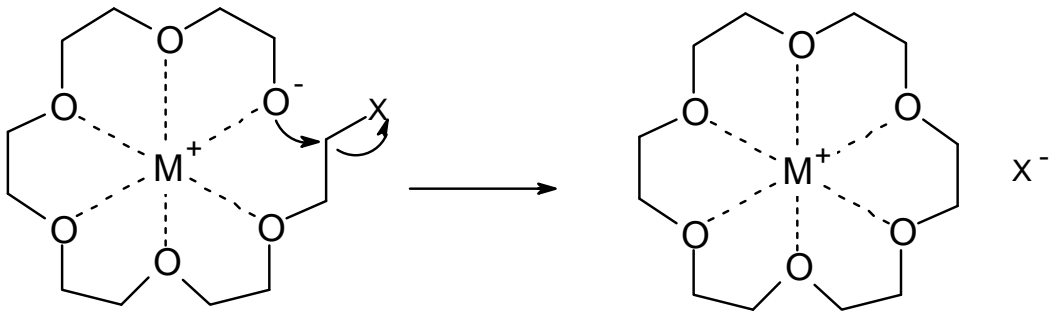


Since the ligand-template interaction occurs in such a way that the two ends of the molecule are maintained in close mutual proximity, the reaction can be performed at much higher concentrations than otherwise could be possible. The evidence for the operation of such a "template effect" is considered below.

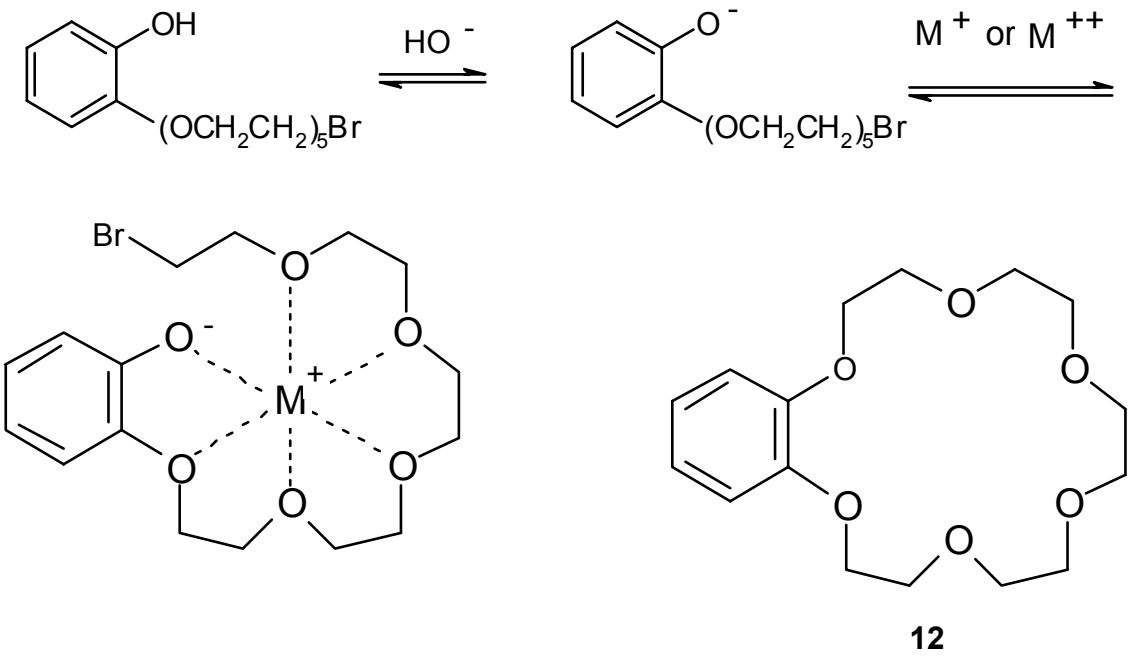
In 1972, Greene made the first suggestion of a "template effect" in the literature.[14] This concept is illustrated in Scheme 1.3. In his paper, Greene presented evidence to support this concept. First, he noted that when the final concentration of 18-crown-6 in a reaction mixture was increased from 0.04 M to 0.09 M, the yield of crown dropped only slightly (84% to 75%). In a competition experiment, equal amounts of 18-crown-6 and 21-crown-7 were formed when one molar equivalent each of a mixture of triethylene glycol and tetraethylene glycol was allowed to compete for reaction with triethylene glycol ditosylate in the presence of KO-*t*-Bu/THF.

Equal amounts of the two crown ethers also were formed when Bu_4NOH used as a base, but both the reaction rate and the yield of crown ethers were reduced considerably. Greene noted that such a template effect actually involves a binding interaction between the open-chain intermediate and the templating cation. It is true that these interactions are weak relative to crown-cation interactions, but evidence for such interactions has been reported.[15]

Mandolini and Masci[16] also studied the template effect. They tried to synthesize benzo 18-crown-6 (**12**) by cyclizing the same starting materials in the presence of various hydroxide bases (see Scheme 1.4). A "size-fit" relationship between the templating cation

and the polyether moiety can be inferred via analysis of kinetic data obtained for individual experiments.

Scheme 1.4



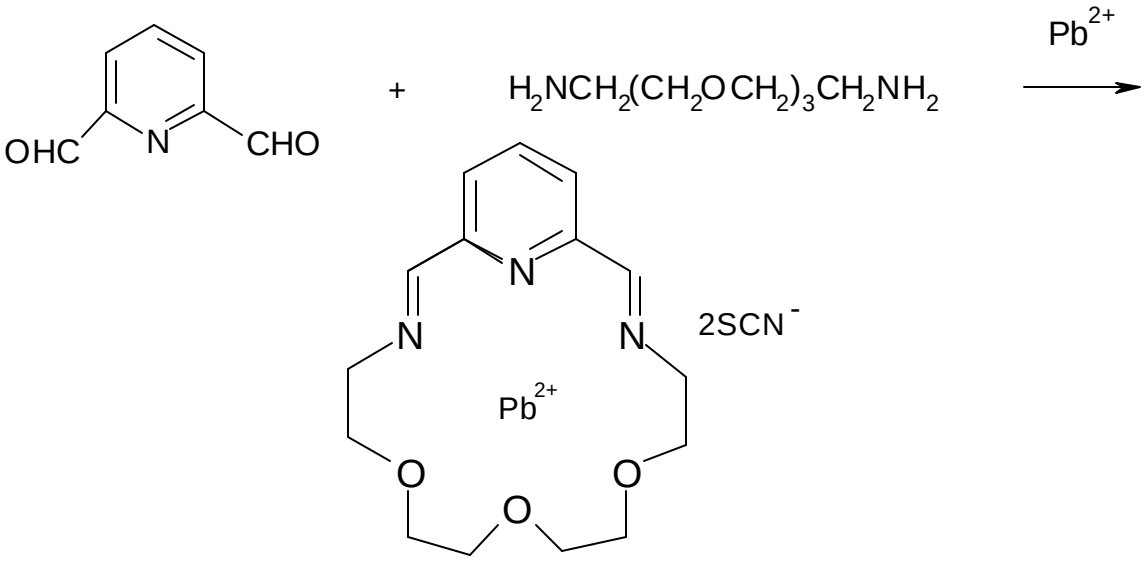
12

Mandolini and Masci[16] also found that tetraethylammonium hydroxide possesses an appropriate basicity to facilitate reaction, but the size of the $(nBu)_4N^+$ cation is too large to template the potential ring system into a suitable conformation for intramolecular cyclization. Lithium cation (from LiOH) also was found to be inefficient, because Li^+ cation is too small to coordinate with the heteroatoms in the chain. Instead, Na^+ and K^+ ions were found to be the most effective templating agents in this system. Such empirical data has been generalized to permit correlation of optimal coordinating cation template with desired ring size.[17]

The role of template effect in some situations can be dramatic. “Resinous gums”

(assumed to be polymeric condensation products) were formed in the reaction between 1,11-diamino-3,6,9-trioxaundecane and pyridine-2,6-dicarboxaldehyde. The desired macrocycle was obtained in good yield when the reaction was templated with $Pb(SCN)_2$ (Scheme 1.5).[18]

Scheme 1.5



13

Complexation of Crown Ethers

Pedersen's papers on crown ethers[1] described for the first time the synthesis of 33 crown ethers and their complexation with metal cations and ammonium salts. Subsequently, the design and synthesis of crown ethers as well as the study of their potential complexation ability with a variety of guests have become an important and rapidly growing field of host-guest chemistry. Molecules or atoms which may be cationic,[19] anionic,[20,21] or neutral[21] can serve as guests. Actually, crown ethers form

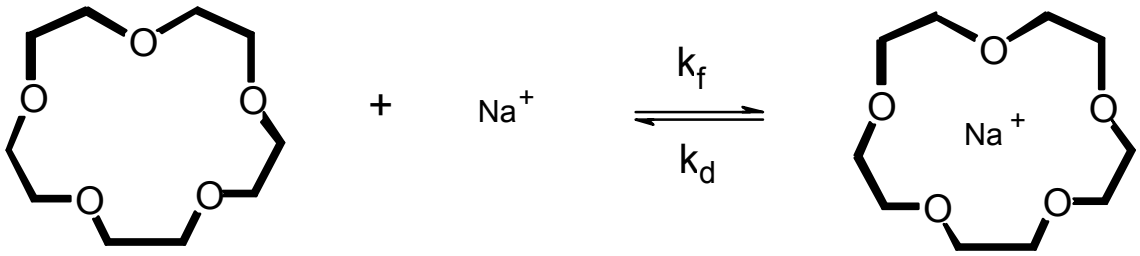
complexes with a variety of substrate species including (i) alkali metal (e.g., K^+), alkaline earth metal (e.g., Ba^{2+}), as well as the harder transition metal and post-transition metal cations,[22,23] (ii) nonmetal inorganic cations[24,25] such as NH_4^+, $H_2NNH_3^+$, H_3O^+, and $HONH_3^+$, (iii) neutral inorganic complexes[26] such as $F_3B{:}NH_3$ and $H_3B{:}NH_3$, (iv) transition metal complexes[27] that contain NH, OH, and CH acidic ligands (e.g., NH_3, H_2O, and CH_3CN), (v) organic cations[28,29] such as PhN_2^+, $MeNH_3^+$, $PhCH_2NH_3^+$, and neutral organic molecules[30,31] that contain polar N-H (e.g., $PhNHNH_2$) and C-H (e.g.,CH_3NO_2) bonds.

The noncovalent bonds that hold molecular complexes together are primarily electrostatic in nature. They include the following interactions: pole-pole, pole-dipole, dipole-dipole, dipole-induced dipole, and induced dipole-induced-dipole, that is, dispersion forces of the van der Waals-London type. Molecular complexes that involve cationic species possess considerable stability (binding free energies = 5-15 kcal mol^{-1} depending upon the nature of the solvent). A template effect that involves a metal cation often accompanies synthesis of 18-crown-6 and other crown ether derivatives.

Molecular complexes that involves neutral species are very much less stable (binding free energies = 0.5-5.0 kcal mol^{-1}, depending upon the nature of the solvent). Apolar solvents (e.g., CH_2Cl_2 and $CHCl_3$) favor complexation. Polar solvents (e.g., MeOH and H_2O) often promote partial dissociation of molecular complexes and thereby disfavor complexation.

Complexation of hosts with a variety of guests involves equilibrium reactions. As an example, complexation of Na^+ by 15-crown-5 is shown in Scheme 1.6. Here, K_f and K_d are the rate constants for complexation and dissociation, respectively.

Scheme 1.6



The stability constant (K_s) is the equilibrium constant for this reaction. It indicates the stability of the resulting complex in the solution and can be expressed by the following equation:

$$K_s = k_f / k_d = [\text{15-crown-5: } Na^+] / [\text{15-crown-5}]\cdot[Na^+]$$

The design of host systems that bind selectively with one guest is an important area in the field of host-guest chemistry. Many factors can influence the selectivity of host molecules. For instances, the size-fit between the cation and marcrocycle cavity dimensions, conformational flexibility of macrocycles, shape and topology of macrocycles, and number, type, and arrangement of donor atoms in the ring.

The "Size-Fit Principle"[33] suggests that the most stable complexes result when the diameter of the metal cation roughly matches the hole diameter of the crown ether. In such case, the cation fit is particularly good, and the resulting stability constants (K_s) are generally highest. The ionic crystal radii of alkali metal cations and the cavity sizes for

crown ethers that have been obtained from X-ray crystallography are shown in Table 1.1[32] and Table 1.2,[33] respectively. By comparing the data in these two tables, it can be anticipated that K^+ fits inside the cavity of 18-crown-6, whereas Li^+ and Na^+ fit inside the cavity of 12-crown-4 and 15-crown-5, respectively. These expectations have been confirmed experimentally.

Table 1.1. Cation sizes from X-ray crystallographic data.[32]

Cation	Li^+	Mg^{++}	Na^+	Ca^{++}	Sr^{++}	K^+	Rb^+	Ba^{++}	Cs^+
Diameter(Å)	1.20	1.30	1.90	1.98	2.26	2.66	2.96	2.70	3.38

Table 1.2. X-ray data of cavity size for several crown ethers.[33]

Ligand	12-crown-4	15-crown-5	18-crown-6	21-crown-7
Diameter(Å)	1.2	1.7-2.2	2.6-3.2	3.4-4.3

Heteroatom selection is another important consideration. A useful first step is to match the guest to a host heteroatom based on Pearson's[34] hard/soft acid and base principle. Soft acids are expected to coordinate well with soft bases, while hard acids are expected to coordinate well with hard base (see Table1.3).[34]

Correlations between certain guest cations and heteroatoms have been established in macrocyclic polyether systems. Crown ethers have oxygen atoms which are "hard base" moieties as coordinating sites, coordinate well with hard acid guests. There is also an effect on ligand selectivity when additional oxygen atoms are included as donor sites.

Table 1.3 Classification of acids and bases according to the Pearson's HSAB principle.[34]

Acids	
Hard	Soft
H^+, Li^+, Na^+, K^+ Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+} Al^{3+}, Sc^{3+}, Ga^{3+}, In^{3+}, La^{3+} Gd^{3+}, Lu^{3+}, Cr^{3+}, Co^{3+}, Fe^{3+}, As^{3+} Si^{4+}, Ti^{4+}, Zr^{4+}, Hf^{4+}, Th^{4+}, U^{4+} Pu^{4+}, Ce^{4+}, WO^{4+}, Sn^{4+} UO^{2+}, VO^{2+}, MoO^{3+}	Cu^+, Ag^+, Au^+, Tl^+, Hg^+ Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+} $CH_3{}^+Hg$, $Co(CN)_5{}^{2-}$, Pt^{4+} Te^{4+}, Br^+, I^+
Bases	
Hard	Soft
H_2O, OH^-, F^-, $CH_3CO_2{}^-$, $PO_4{}^{3-}$ $SO_4{}^{2-}$, Cl^-, $CO_3{}^{2-}$, $ClO_4{}^-$, $NO_3{}^-$ ROH, RO^-, R_2O, NH_3, RNH_2 NH_2NH_2	R_2S, RSH, RS^-, I^-, SCN^- $S_2O_3{}^{2-}$, R_3P, R_2As, $(RO)_3P$ CN^-, RNC, CO, C_2H_4, H^-

The "Preorganization Principle"[35] along with the results of molecular mechanics calculations has been used to identify host systems that are able to recognize guest species with high selectivity. The design of preorganized hosts provides a significant challenge to organic chemists. The Preorganization Principle states that "a host is said to be preorganized if its bound and unbound conformations closely resemble one another".[35] The Preorganization Principle[35] predicts that the logK of host-guest complex formation will be increased dramatically if both the host and guest are well-structured for binding and require little solvation prior complexation. The majority of preorganized macrocycles such as spherands, cryptahemispherands, calixarenes, and small cryptands form very

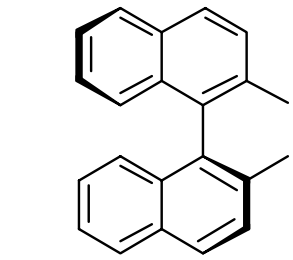
stable complexes with targeted guests and display significant selectivity in their ability to bind to specific guests.

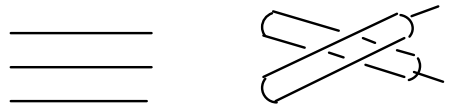
Introduction of Chiral Crown Ethers

Molecular recognition[36] is the process by which a ligand (molecular receptor) selects and binds a specific substrate via a structurally well-defined pattern of intermolecular forces. Enantiomeric recognition,[37] a special case of molecular recognition, involves discrimination between enantiomers of a guest by a chiral host.

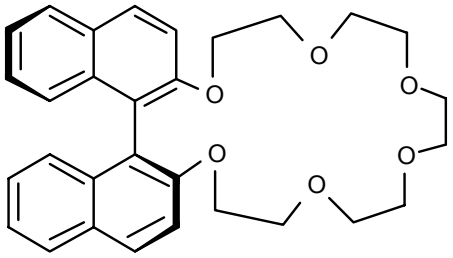
In 1973, Cram[38] described the first chiral crown ethers to exhibit chiral recognition towards enantiomeric substrates. They were prepared from optically pure 2,2'-dihydroxy 1,1'-binaphthyl (**14**), which can be obtained via optical resolution by using any of a number of different methods.[39] The isolation of optically pure enantiomers of this atropisomeric diol reflects its C_2 axis of chirality that results via hindered rotation around its naphthalene-naphthalene bond. The structures of both binaphthyl-20-crown-6 (**15**) and bisbinaphthyl-22-crown-6 (**16**) are similar to that of 18-crown-6. However, the bismethylenedioxy repeating unit is separated by binaphthyl residues, consequently some of the aliphatic oxygen atoms in the resulting crown ether are replaced by less basic aryl oxygen atoms .

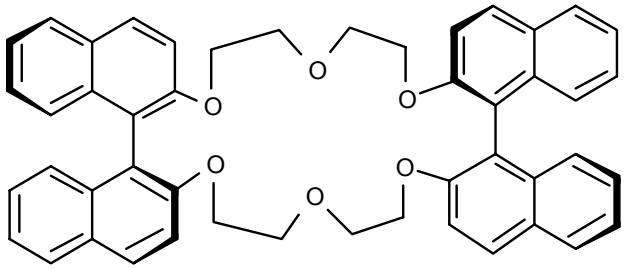
Scheme 1.7





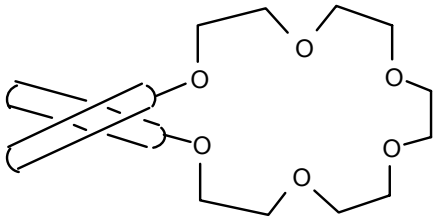
(S)-14

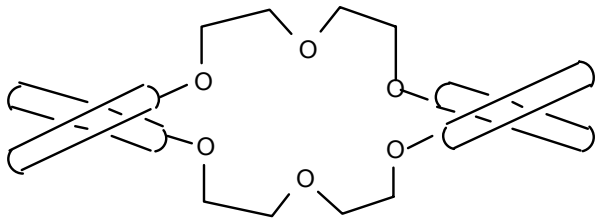




(S)-15

(S,S)-16



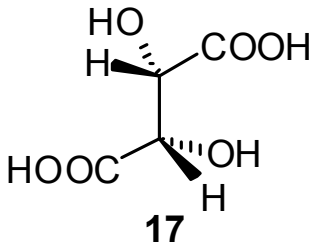


The 2, 2-dihydroxy-1, 1-binaphthyl moiety presents a steric and chiral barrier in **14** toward an approaching guest molecule or ion. In host systems, the two naphthalene rings occupy different planes, each of which is roughly perpendicular to the plane of the cyclic ether ring. One of the naphthalene rings forms a wall that extends along the side of and outward from one face of the cyclic ether, whereas the other naphthalene ring provides a wall along the side of and outward from the opposite face of the cyclic ether. Thus, enantiomeric discrimination is achieved via atropisomerism caused by hindered rotation of the binaphthyl units in the system. Thus, for example, chloroform solution of chiral receptor molecule (**16**) extracts twice as much of the (*R*)-enantiomer as the (*S*)-enantiomer from(*R, S*)-$PhCHMeNH_3PF_6$ dissolved in a 2.5 M aqueous solution of $NaPF_6$ at -14 °C.[40]

A large number of chiral crown ethers have been prepared by numerous groups. Scientists have subdivided this mass of compounds into three principal groups: (i) Cram's chiral binaphthyl systems, (ii) chiral crown ethers that contain a chiral tartaric acid derived moiety, and (iii) crown ethers that incorporate chiral derivatives of monosaccharides.

Crowns that Incorporate the Tartaric acid Subunit

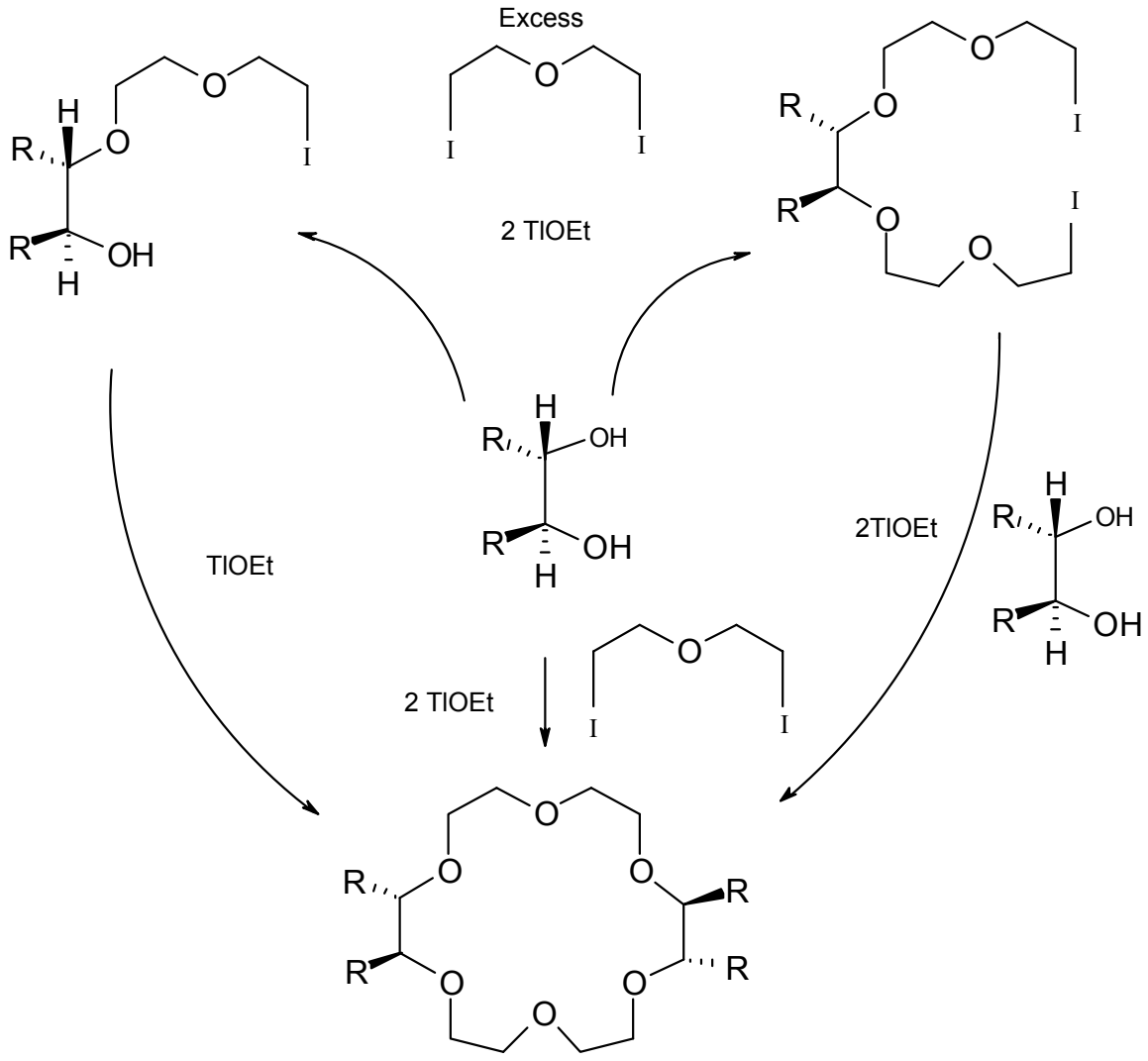
Lehn and co-workers[41] identified **L**-tartaric acid (**17**) as a suitable precursor that can be used to synthesize chiral 18-crown-6 derivatives. Compound **17** contains an asymmetrically functionalized ethylene glycol unit of known absolute configuration, and it is also readily available in enantiomerically pure form.



17

A one-step synthesis of a bistartaro-18-crown-6 derivative **L**, **L-18** has been designed (Scheme 1.8).[42] This synthesis route relies upon alkylation of the dithallium alcoholate of the bis(*N*,*N*-dimethylamide) of L-tartaric acid with the appropriate diiodide, i.e., 1,5-diiodo-3-oxapentane. This procedure affords the same yield (20%) of **L**, **L-18** as the alternative two-step route shown in Scheme 1.8.

Scheme 1.8



L, L-18

Although the crown ethers that incorporate **17** as a subunit are quite numerous, most are prepared by using essentially the same methods. The nucleophiles are usually aliphatic alcohols, and NaH is generally the base of choice. Electrophiles may be either halides or tosylates.

Crowns that Incorporate Sugar Subunits

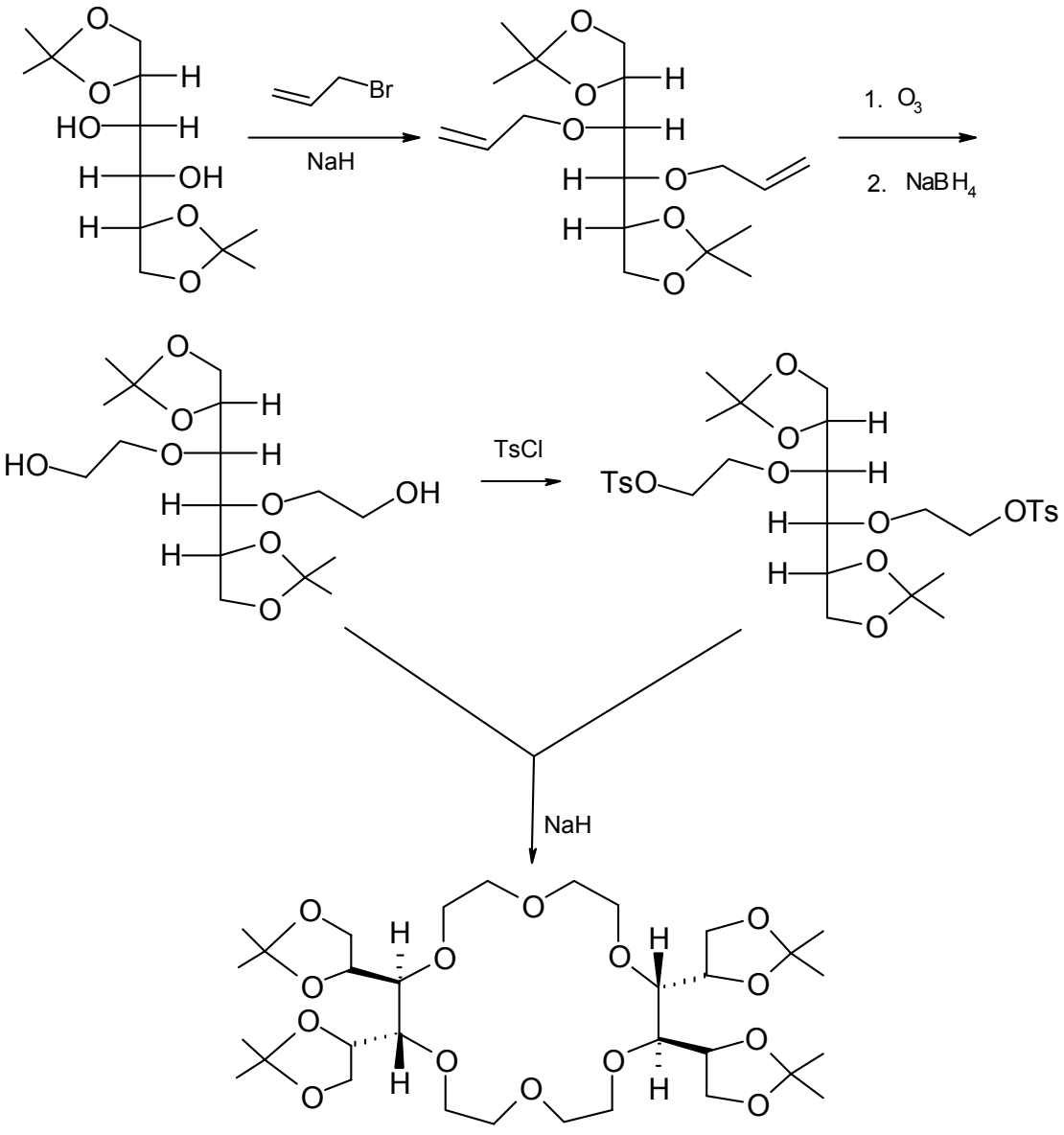
Several compounds have been prepared that contain a chiral sugar-derived subunit.[43-45] Much of this work has been reported by Stoddart and coworkers, who have pioneered this field. Their goal was to prepare a chiral receptor for ammonium ions, which could be utilized in enzyme model studies, just as similar compounds prepared by Cram's group have been employed for this purpose.

Most of the cyclizations of aliphatic crown ethers reported in the literature have been performed by using NaH or KH as base, the former being more common. Solvents that have been used to prepare sugar-based crown ethers include THF, DMF and DMSO. In the first paper to report the incorporation of a sugar unit (mannitol) into the crown ether, DMSO was solvent of choice.[46] As usual, diethylene glycol ditosylate was used as electrophile in this synthesis.[46]

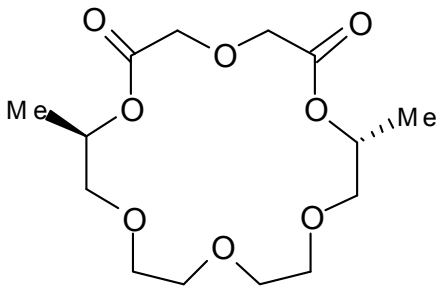
An interesting feature of the synthesis is the use of allyl as a two-carbon extension unit. This approach has been used for the stereospecific synthesis of dicyclohexano-18-crown-6. In the present case, mannitol bis-acetonide was converted into the corresponding allyl ether, which subsequently was ozonized (reductive workup) to afford the corresponding bis-ethyleneoxy derivative. The latter two groups were converted to

the corresponding tosylate, which then was allowed to react with its precursor to afford the chiral crown ether. The entire process is summarized in Scheme 1.9.

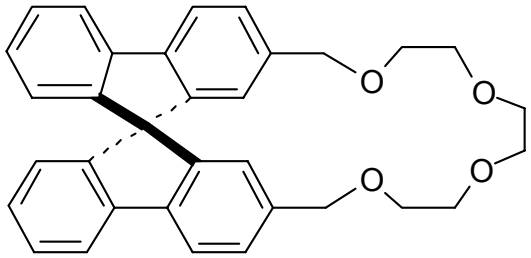
Scheme 1.9



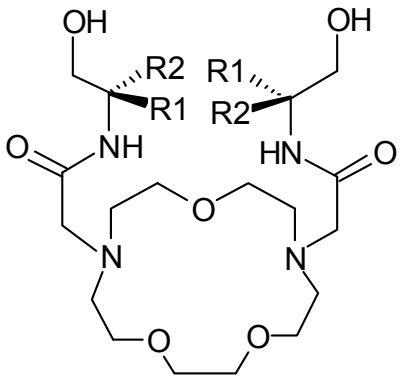
Chiral crown ethers also can be prepared from other sources: (i) Compound **19** has been synthesized from precursors derived from lactic acid;[47,48] (ii) Compound **20** has been prepared from 9,9'-spirobifluorene derivatives;[49,50] (iii) Compound **21** has been prepared from α-amino acid derivatives.[51]



19



20

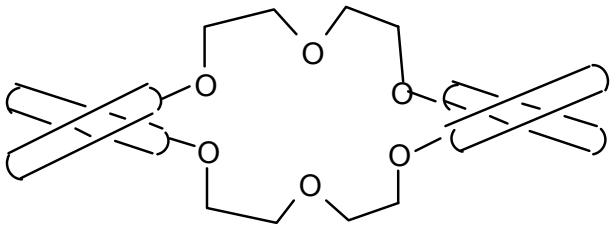


21

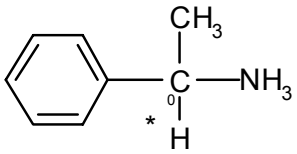
Cram and co-workers first studied enantiomeric recognition of primary ammonium salts by using binaphthyl chiral crown ethers. They performed optical resolution of racemic α-methyl benzylamine **22**) by using (-)-(*S, S*)-bis(binaptho-22-crown-6) (**16**) via simple $CHCl_3$-H_2O extraction.[40] When **16** and **22** in $CHCl_3$ and H_2O were shaken in the presence of $NaPF_6$, the optical rotation of **22** bound by **16** to form a complex in the $CHCl_3$ layer was [α] = + 9.41 (CHCl3). The result indicates that the bound stereoisomer was (+)-(*R*)-**22**, with an optical purity of 27%, which suggested that the host, (-)-(*S, S*)-

16, forms a more stable complex with (+)-(*R*)-**22** than with (-)-(*S*)-**22**. The possible conformations of these diastereomeric complexes are shown in Scheme 1.10. In each case, the bulky benzyl group is situated above the widest space in the cavity. Examination of CPK models[40] of the various complexes also indicates that the steric relationships between (*S, S*)-**16** and (*R*)-**22** are more compatible than those between(*S, S*)-**16** and (*S*)-**22**.

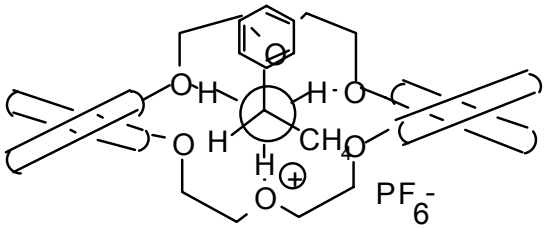
Scheme 1.10



(-)-(S,S)-16

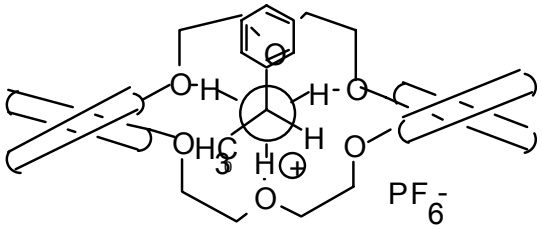


22



(-)-(S,S)-16 (S)-22

Sterically unfavorable



(-)-(S,S)-16 (R)-22

Sterically favorable

NMR sectroscopy, calorimetric titration, molecular mechanics calculations, liquid-liquid extraction, chromatography, X-ray crystallography, and electrochemical methods all have been used as techniques to evaluate the extent of enantiomeric recognition.

Binding between a host and enatiomeric ammonium guest can be affected by hydrogen bonding, Van der waals forces, short-range repulsions, intermolecular interactions, electronic effect, etc.

It is well known that among the various binding types, hydrogen bonding is an important stabilizing force that promotes complex formation between the macrocyclic receptor and the substrate. Cram and coworkers[52] resolved racemic amino ester and primary ammonium salts by stereoselective passive transport of their corresponding HCl, HBr, or HPF_6 salts from one aqueous phase to another through a $CHCl_3$ membrane. Investigation of optically selective transport generally is performed by using a U-tube resolving machine and or a W-tube resolving machine (Figure1.1[53] and Figure1.2,[53] respectively).

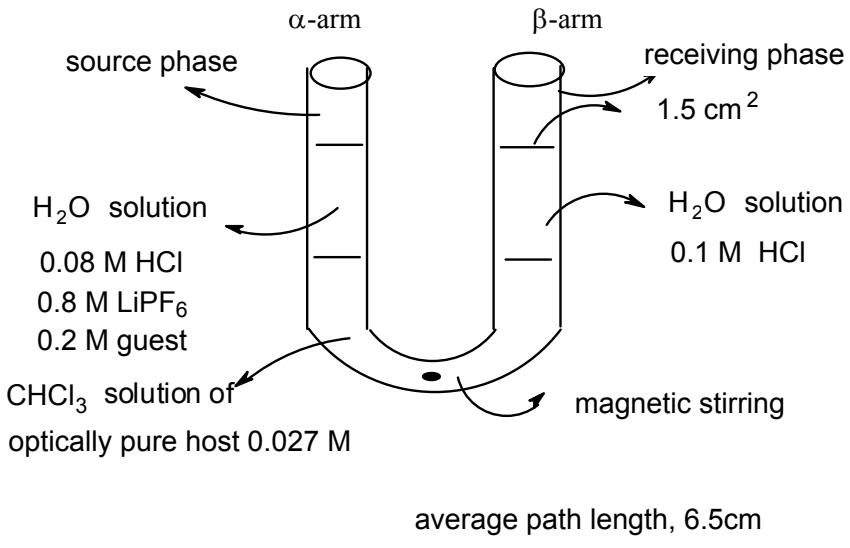


Figure 1.1 U-tube resolving machine.[53]

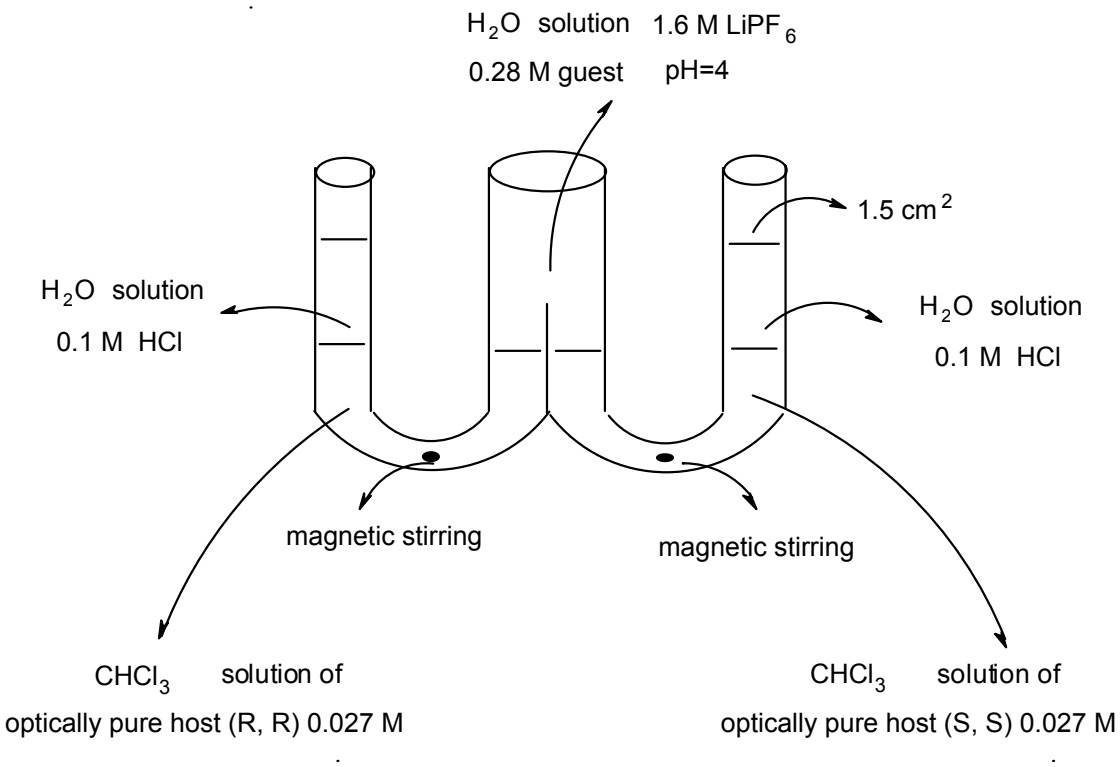


Figure 1.2 W-tube resolving machine.[53]

Applications of Chiral Crown Ethers

Shortly after Pedersen's papers that described the 33 crown ethers[1] for the first time, scientists have found that crown ethers have application to many fields. Chiral crown ethers have been used to achieve chiral compounds by several methods.

One of the most successful applications of chiral crown ethers has impacted the field of organic synthesis. An example in this regard is provided by phase-transfer catalysis (PTC), which relies typically on a simple reaction procedure, mild conditions, inexpensive and safe reagents and solvents. PTC has been used to facilitate reaction scale-up.[54] In addition, the use of PTC for the preparation of chiral, non-racemic compounds from prochiral substrates by using chiral catalysts is becoming an important area in catalysis.[55]

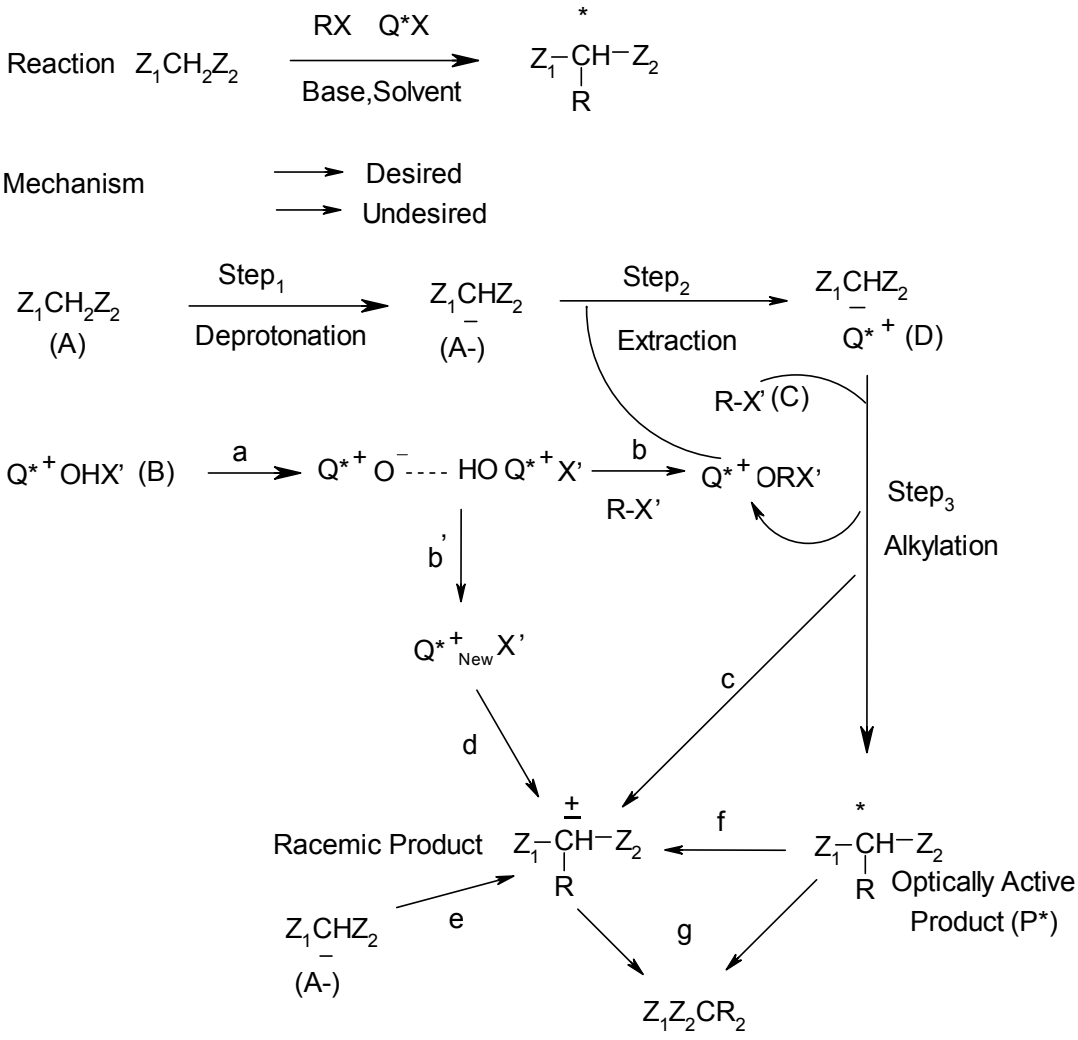
The development of improved catalytic asymmetric reactions[56] to form carbon-carbon bonds is a challenging problem in organic synthesis. Although many crown ethers have been successfully applied in catalytic asymmetric synthesis,[57] chiral recognition at the transition states that lead to asymmetric induction is not as well understood as the corresponding ground state process. Thus, the development of easily accessible chiral crown ethers as an efficient class of chiral catalysts is desirable both for practical uses and to promote improved understanding of the transition state process that lead to high level of chiral recognition in host-guest complexes.

A mechanistic scheme for monoalkylation of active methylene compounds,[58] shown in Scheme 1.11, can be used to explain the variables common to many of the systems studied. This process requires three main steps: (i) base promoted deprotonation of the

active methylene compound, which generally occurs at the interface between the two layers (liquid-liquid (L/L) or solid-liquid (S/L)); (ii) ion-exchange of the anion (A^-) with the cation of the chiral quaternary ammonium compound (quat) to form a lipophilic ion-pair (D), which then either reacts at the interface (step 3) or is extracted into the bulk organic phase; (iii) creation of the new chiral center in product P^* by alkylation of the ion-pair (D) with concomitant regeneration of catalyst.

Several side reactions can occur in competition with formation of the optically active product: (i) alkylation of the "wrong" ion-pair that lead to the enatiomer of the target product (step c); (ii) side-reactions of either the starting substrate or the reaction product [racemization (step f) and or dialkylation (step g) following product formation as well as the hydrolyses reactions]; (iii) interfacial alkylation (step e) of substrate anion (A^-) in the absence of the quat cation, which necessarily yields racemic product; (iv) reaction of the chiral quat (B) to form a new organic compound , which might function either as the reactive catalyst species (step b) or as a compound (step b') that either is an ineffective catalyst or leads to racemic product.

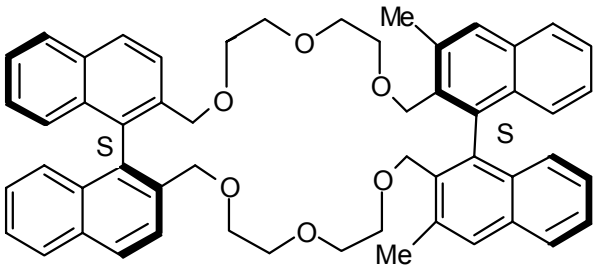
Scheme 1.11


Reaction
RX Q*X
Base,Solvent
Mechanism
Desired
Undesired
Step1
Deprotonation
(A)
(A-)
Step2
Extraction
(D)
R-X' (C)
(B)
a
b
R-X'
Step3
Alkylation
b'
New
c
d
e
f
g
Racemic Product
Optically Active
Product (P*)

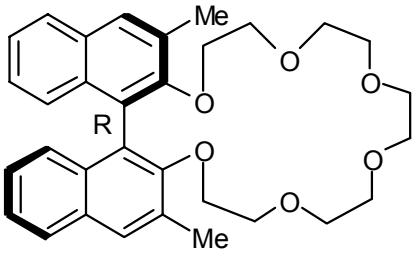
Crown ethers have shown impressive enantioselectivities in Michael additions. Scheme 1.12 includes several chiral crown ethers that have been used as chiral catalysts in Michael additions.

Scheme 1.12

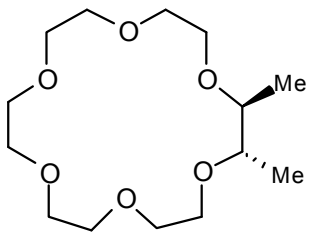
Michael addition reaction



(Michael, 99%ee)



(Michael, 83%)



(Michael, 79%)

Application of chiral crown ethers in chromatography

Chiral stationary phases (CSPs) based on chiral crown ethers have been employed widely for enantioselective separation of primary amines by liquid chromatography. In the late 1970s, Cram and co-workers[59] utilized bis-(1,1'-binaphthyl)-22-crown-6 that had been immobilized on polystyrene or silica gel to obtain CSPs that proved capable of optical resolution of the enantiomers of ?-amino acids and their derivatives. Shinbo and co-worker[60] dynamically coated chiral crown ethers based on disubstituted 1.1'-binaphthyl-20-crown-6 on octadecyl silica gel. Dynamically coated CROW-NPAK CR[61] columns from Daicel Chemical Industries have been widely used for enantioselective resolution of racemic primary amines.

Figure **1.3** shows the covalently bonded CSPs based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid that have been used for resolution of primary amines. This system was first applied by Hyun and co-workers.[62]

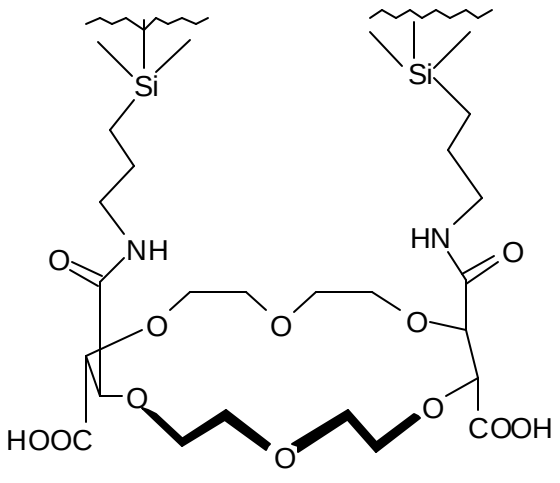


Figure 1.3 Chiral crown ether stationary phase.[62]

CHAPTER II

SYNTHESIS OF OPTICALLY ACTIVE, CAGE-ANNULATED CROWN ETHERS: POTENTIAL NEW AGENTS FOR ENANTIOSELECTIVE RECOGNITION OF CHIRAL AMMONIUM SALTS

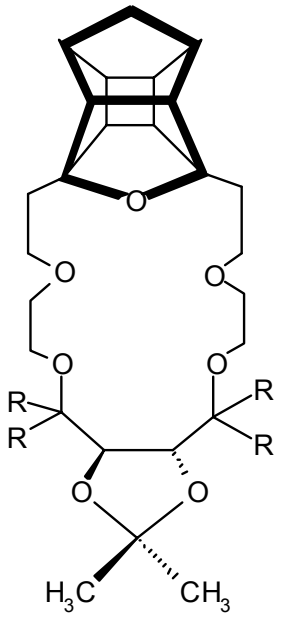
In 1973, Cram and coworkers[38] for the first time prepared chiral crown ethers that contain binaphthyl chiral subunits. Those crown ethers exhibited high enantiomer-selectivity toward complexation with chiral organic ammonium salts and amino acids salts. Since that time, the design and synthesis of chiral crown ethers that possess chiral recognition ability carry great potential for the analysis and separation of enantiomers have become an important and rapidly growing field of host-guest chemistry.

Our laboratory has also been interested in the chiral recognition ability of crown ethers toward chiral amines and organic ammonium salts, and we have synthesized a series of optically active crown ethers.[63] The advantage of crown ethers constructed by using a synthetic chiral building block is that the chiral cavity can be modified readily, thereby resulting in the improved enantiomeric selectivity.

Recently, our group's continuing interest prompted us to examine the enantiomer recognition behavior of chiral crown ethers that incorporate tartaric acid derivatives as chiral subunits. As can be seen in Scheme 2.1, these crown ethers also incorporate a cage moiety into the chiral macrocycles. This structural feature reduces conformational flexibility of the crown ether by introducing a measure of rigidity into the crown ether backbone. Further more, the cage moiety has been shown to influence the ability of cage-annulated crown ethers to behave as complexing ligands by helping to define the size and

shape of the host cavity. Finally, the cage moiety serves as a lipophilic component, thereby improving the solubility of cage containing crown ethers in nonpolar solvents relative to that of the corresponding noncage-containing systems.

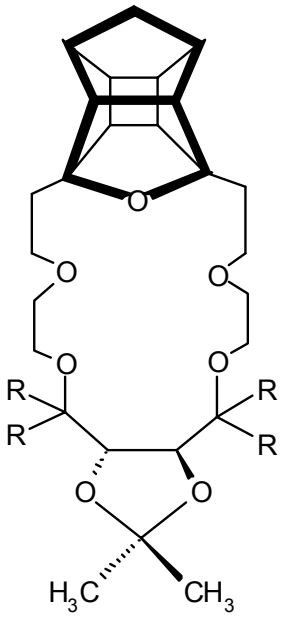
Scheme 2.1



(***S,S***)**-5a**

(***R,R***)**-6a**

(***R,R***)**-7a**



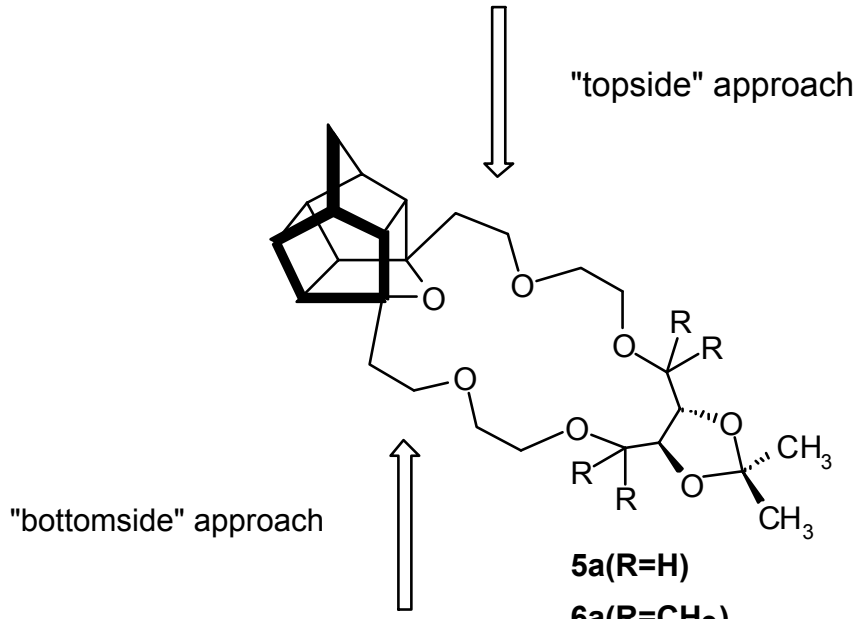
(***R,R***)**-5b (** R= H**)**

(***S,S***)**-6b (** R=CH_3)

(***S,S***)**-7b (**R=Ph**)**

It is also interesting to note that the starting material, i.e., cage–ditosylate (**1**) possess C_s symmetry, whereas incorporation of the tartaric acid derivatives into **1** affords **5a-7a** with concomitant loss of symmetry. As a result, host molecules **5a-7a** will have two different sites of complexation with the incoming guest molecules, i.e., approach of the guest may occur toward either the "top" or "bottom" face, as shown in Scheme 2.2.

Scheme2.2



5a(R=H)

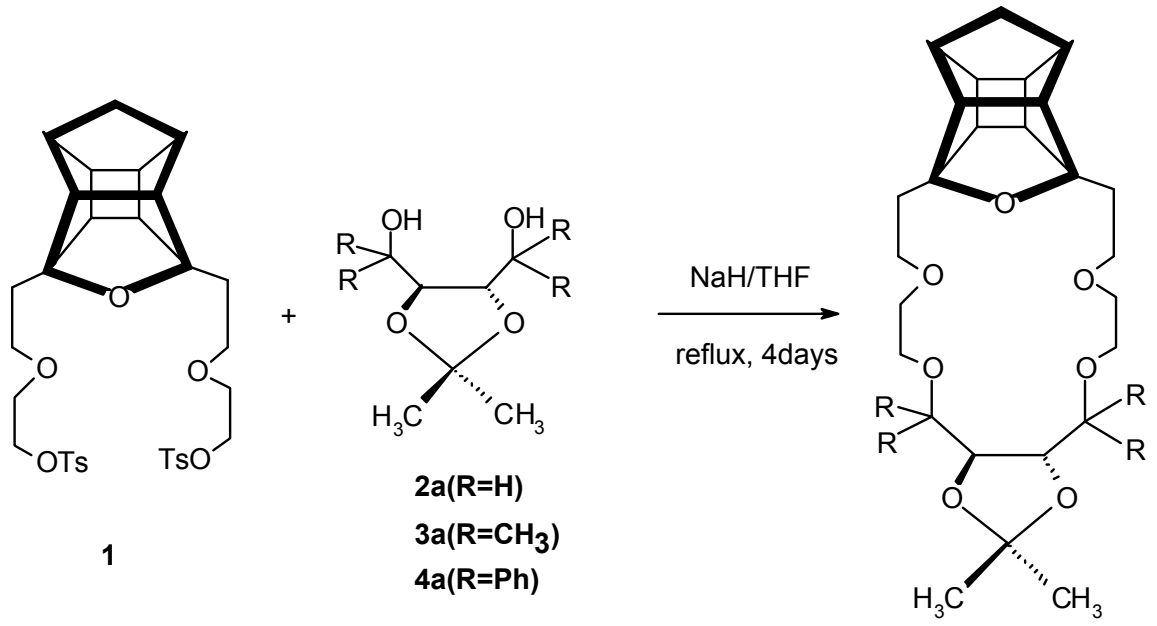
6a(R=CH_3)

7a(R=Ph)

Results and Discussions

I. Synthesis of novel cage-functionalized crown ethers that contain tartaric acid-derived chiral centers.

Scheme 2.3



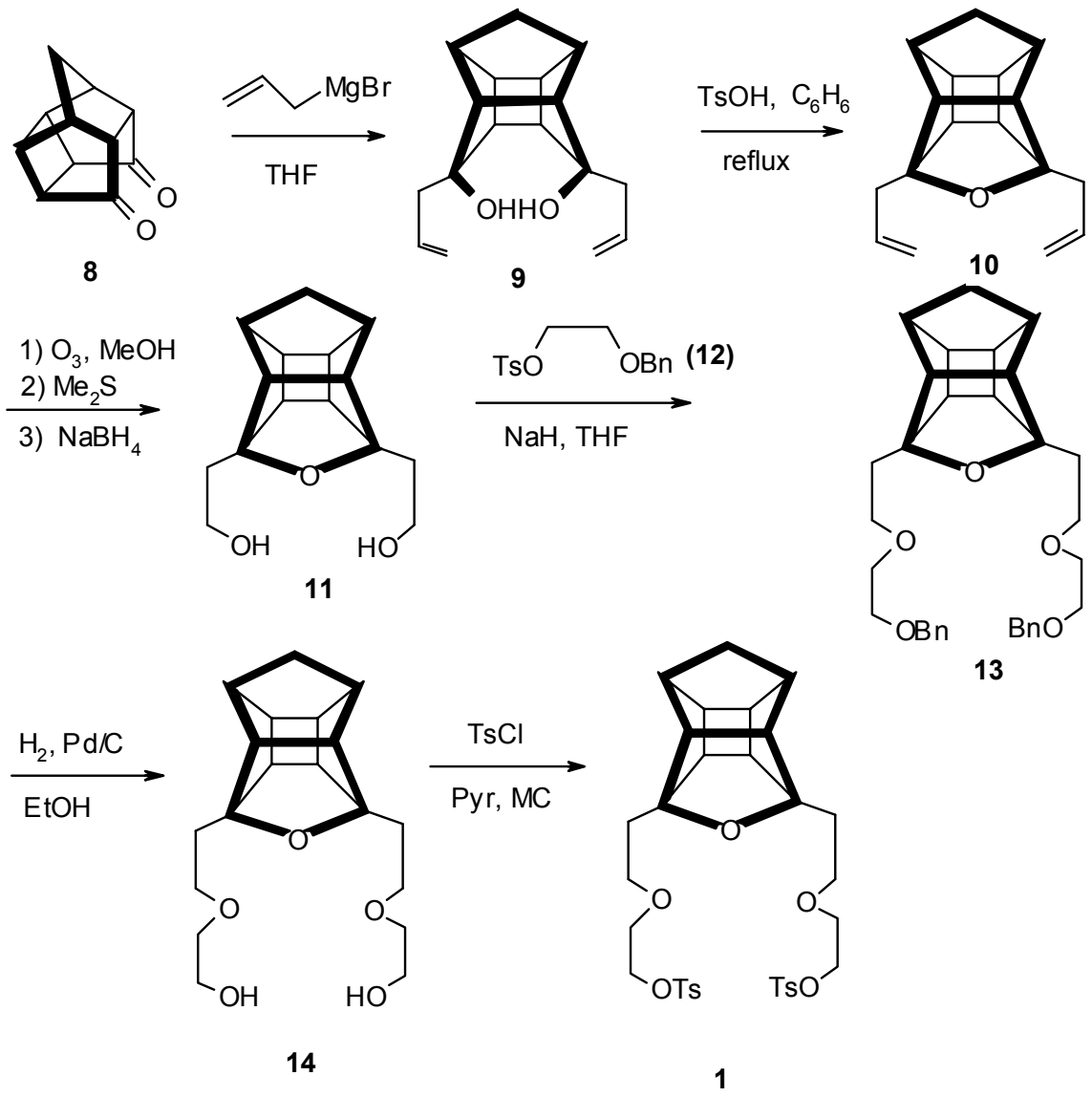
1

2a(R=H)
3a(R=CH_3)
4a(R=Ph)

5a(R=H)
6a(R=CH_3)
7a(R=Ph)

The approach employed to prepare the new chiral, cage-annulated crown ethers, i.e. **5a-7a**, is shown in Scheme 2.3. Therein, we can see that these compounds can be prepared by joining the top part (**1**) to the bottom parts (**2a-4a**). For starting material **1**,[64] relevant procedures in this purpose are shown in Scheme 2.4.

Scheme 2.4



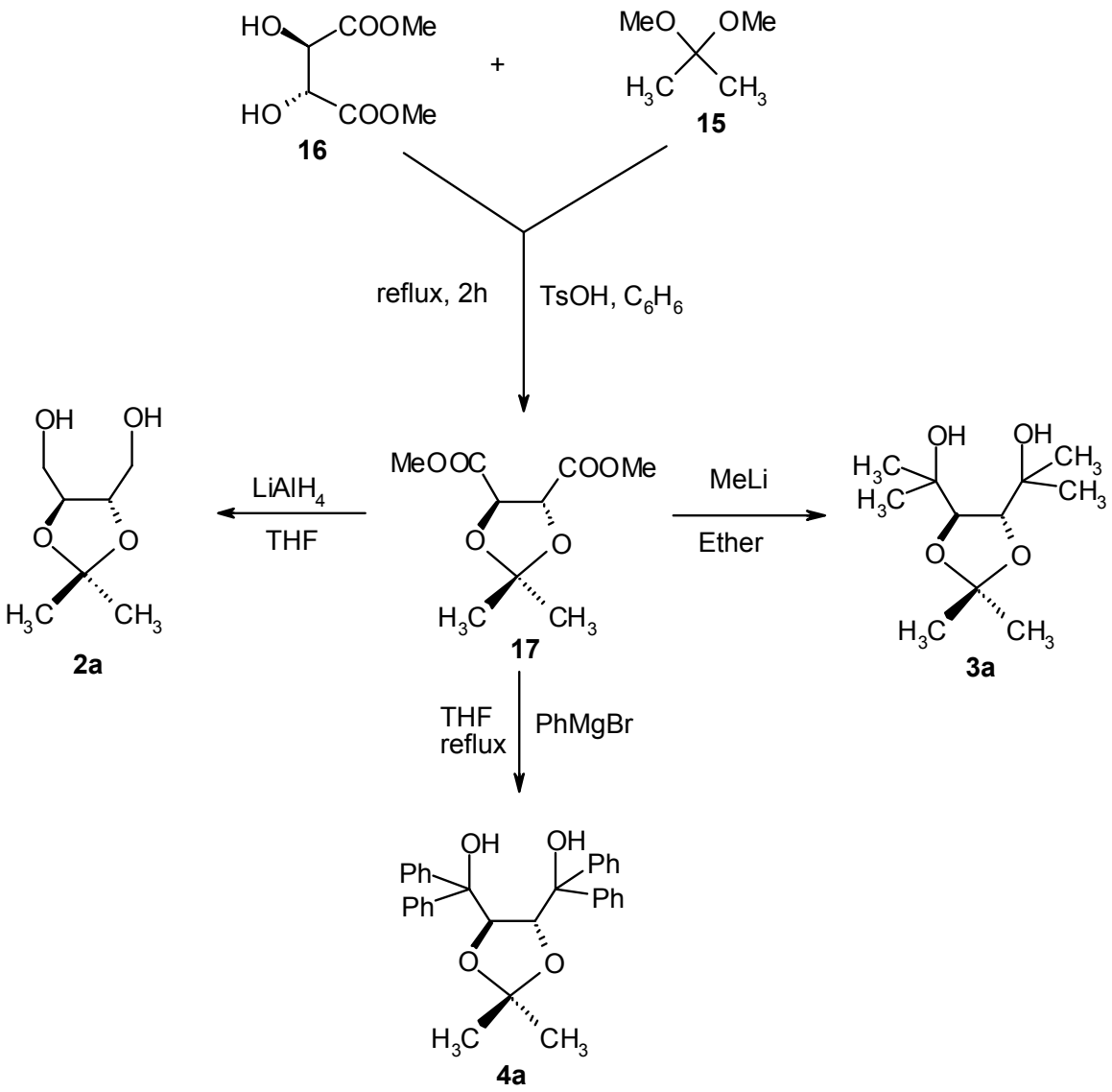
After PCU-8,11-dione (**8**) was allowed to react with excess allylmagnessium bromide, the corresponding *endo*-8,*endo*-11 diol, **9**, was obtained in 52% yield. Dehydration of **9** in a Dean-Stark apparatus, performed in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH), afforded the corresponding hexacyclic ether

10, in 62% yield. Ozonolysis of **10** followed by a reductive workup produced the corresponding diol, **11**, in 91% yield. After base promoted reaction of **11** with 1-benzyloxy-2-tosyloxyethane (**12**), the *O*-benzyl-protected ligand (**13**) was produced in 44% yield. Subsequent bis(de-*O*-benzylation) of **13** produced **14** in 90% yield. Finally, base promoted reaction of **14** with TsCl afforded the corresponding cage ditosylate, **1**, in 85% yield.

The starting materials **2a-5a**, which were prepared from optically active (+)-dimethyl-L-tartrate, provide the source of optical activity in the crown ethers of interest. Relevant produces in this regard are shown in Scheme 2.5.

By using 2, 2-dimethoxypropane (**15**) to protect the two alcohol OH groups in dimethyl-L-tartrate (**16**), compound **17**[65] was obtained in 92% yield. Lithium aluminum hydride promoted reduction of diester (**17**) to 2, 3-*O*-ispropylidere-D-threitol (**2a**)[65] in 70% yield. By using MeLi, four methyl groups could be introduced into **17**, thereby affording **3a**[66] in 85% yield. Reaction of **17** with PhMgBr in THF gave **4a**[67] in 69% yield.

Scheme 2.5


HO
COOMe
HO
COOMe
16
+
MeO
OMe
H3C
CH3
15
reflux, 2h
TsOH, C6H6
LiAlH4
THF
MeOOC
COOMe
MeLi
Ether
OH
OH
H3C
CH3
2a
17
3a
THF
reflux
PhMgBr
Ph
Ph
4a

By using (-)-dimethyl-D-tartrate and following the same procedures as that shown in Scheme 2.5, compounds **2b-4b** could be prepared (see Scheme 2.6). The structures of **2a-4a** and **2b-4b** were confirmed via analysis of their respective of ^{1}H NMR and ^{13}C NMR spectra (see the Experimental Section). In addition, the X-ray crystal structure of **3a** has been obtained; the corresponding X-ray structure drawing is shown in Figure 2.1.[68]

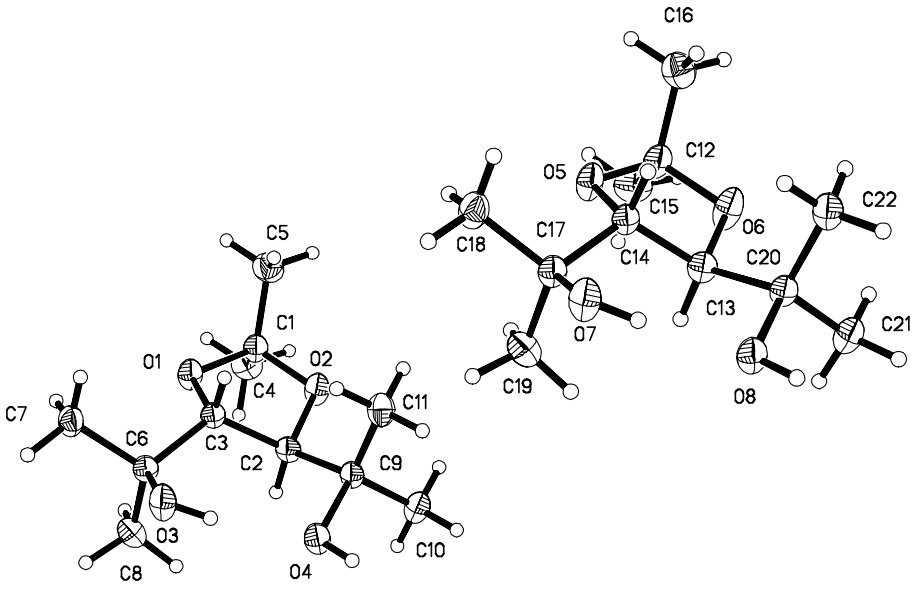
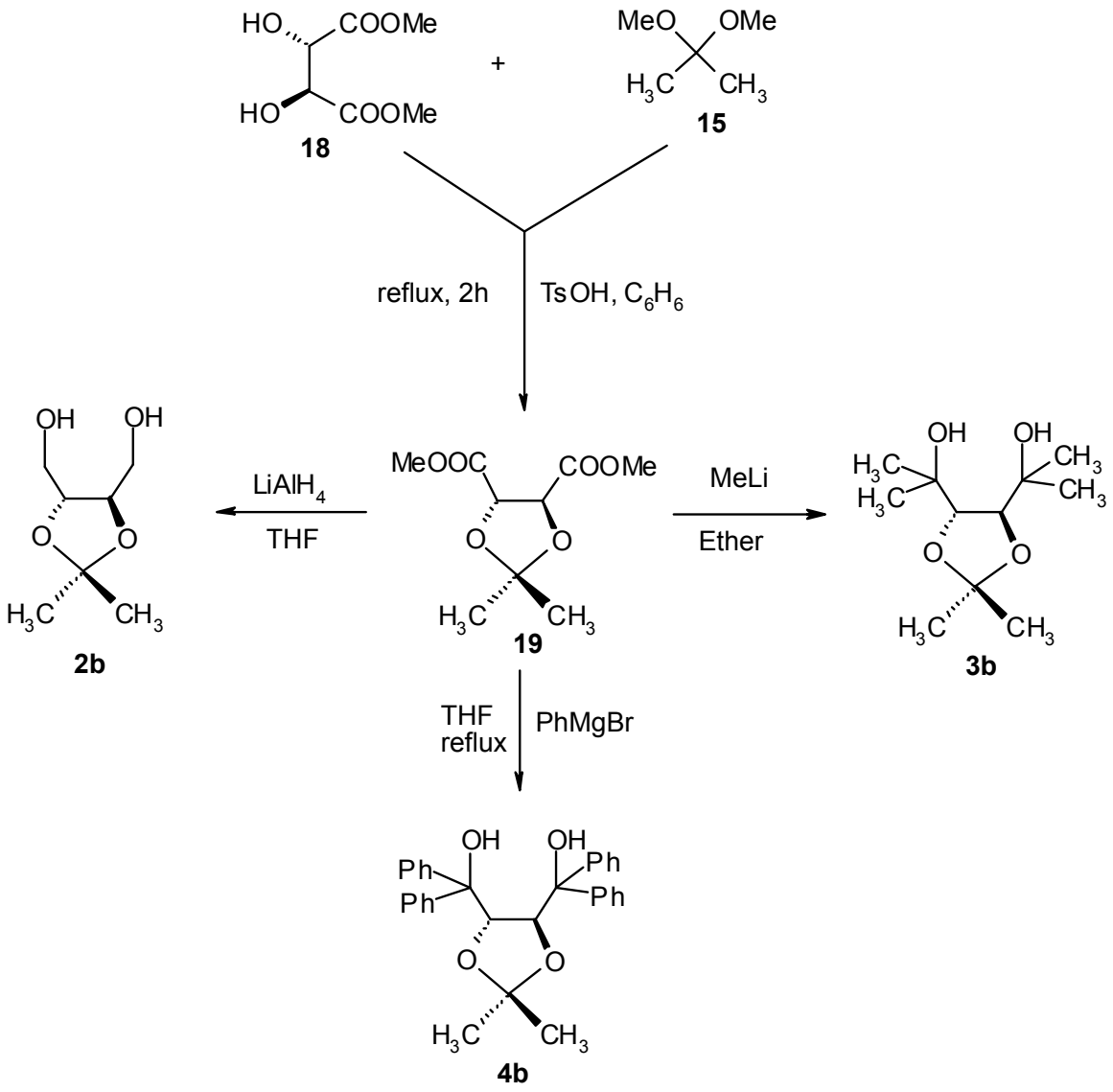


Figure 2.1 X-ray structure drawing of **3a**. Two molecules present in the unit cell are shown.[68]

Scheme 2.6



Thereby, the novel cage-functionalized crown ethers **5b-7b** were prepared by following procedure analogous to that shown as Scheme 2.3 (see Scheme 2.7). The structures of **5a-7a** and **5b-7b** were confirmed via analysis of their respective of ^{1}H and ^{13}C NMR spectra and via high-resolution mass spectral (HRMS) analysis (see the

Experimental Section). In addition, the X-ray crystal structure of **7a** has been obtained. The corresponding X-ray structure drawing is shown in Figure 2.2.[69]

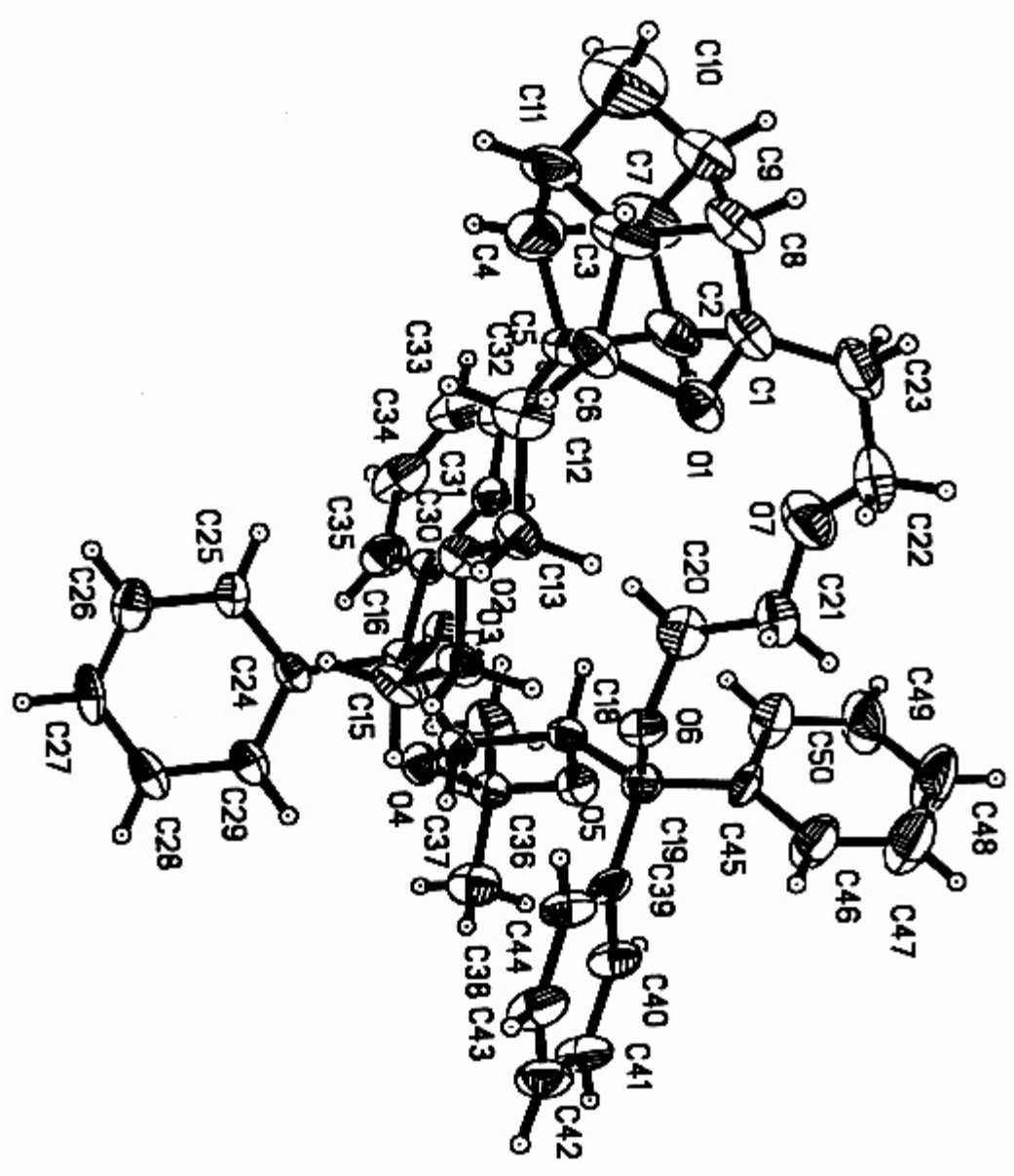
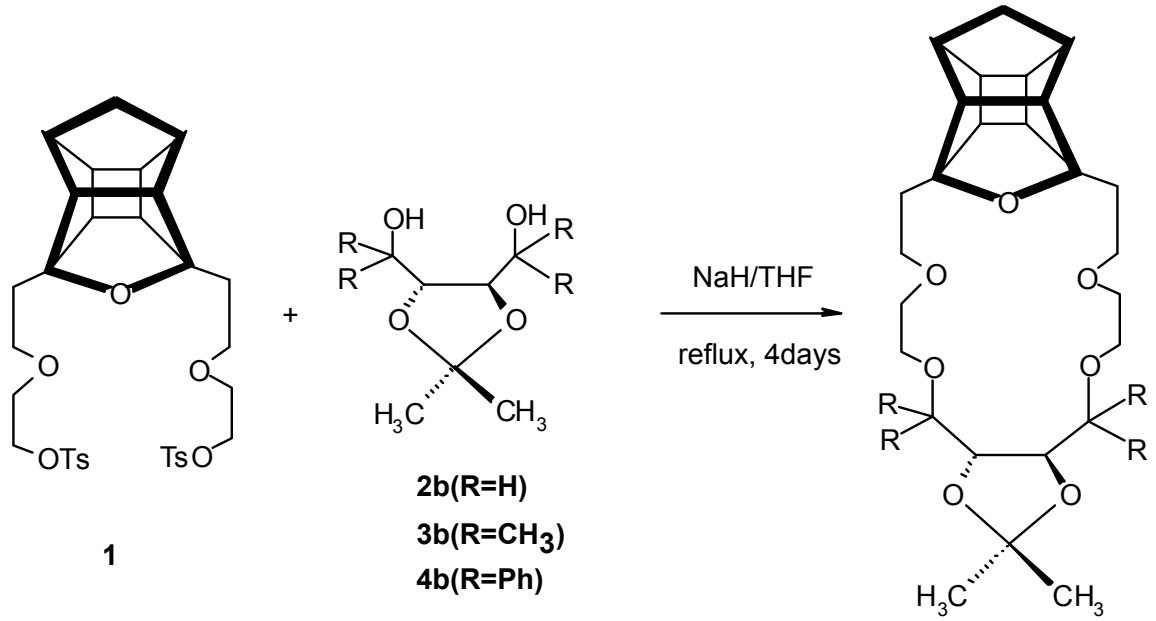


Figure 2.2 X-ray structure drawing of **7a**.[69]

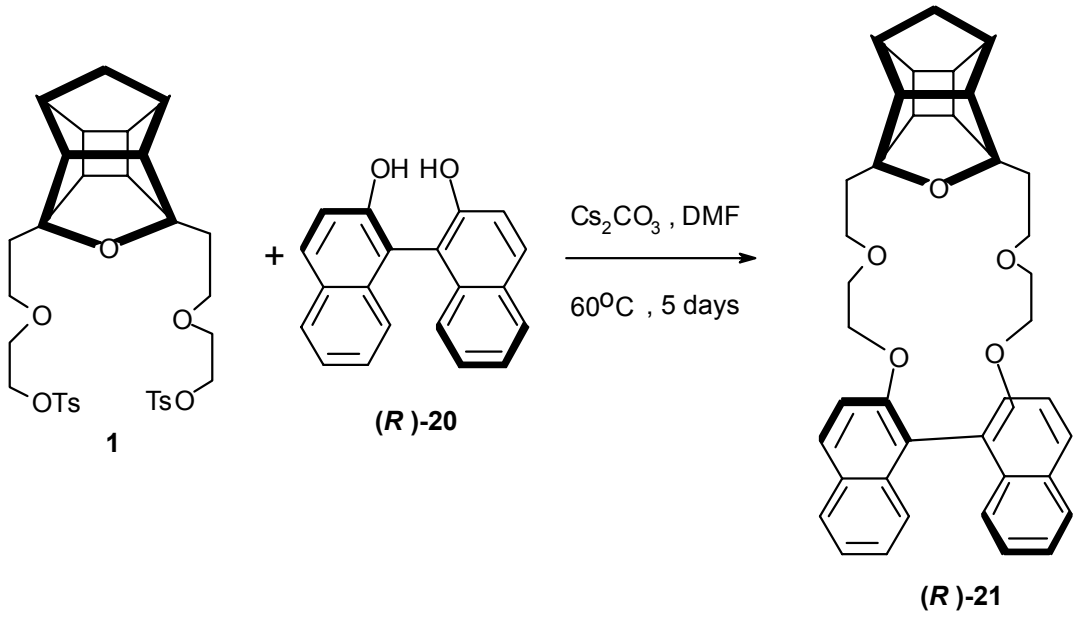
Scheme 2.7

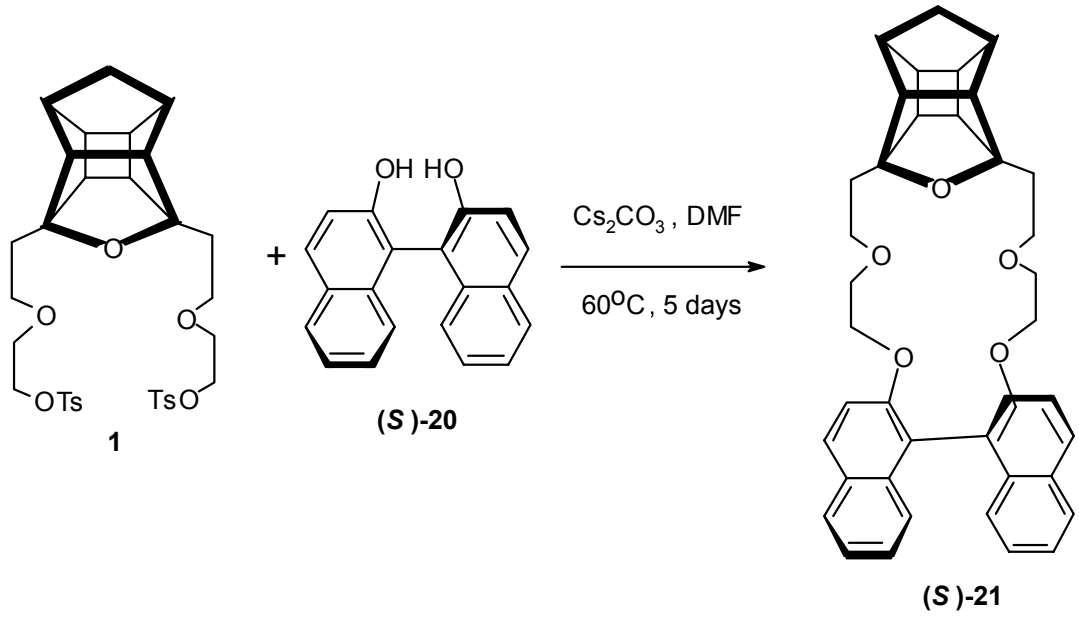


II. Synthesis of novel cage-functionalized crown ethers that contain binaphthyl-derived chiral centers.

Axially dissymmetric 1,1'-binaphthyl-2,2'-diol (*R*)-**20** and (*S*)-**20** were used as chiral components to prepare cage-functionalized chial crown ethers (*R*)-**21**[70] and (*S*)-**21.** The synthetic procedure employed for this purpose is shown in Scheme 2.8. The chiral hosts were thereby obtained in 64% yield via Cs^+-templated reaction of cage ditosylate **1** with (*R*)-**20** or (*S*)-**20**.

Scheme 2.8


OH HO
Cs_2CO_3 , DMF
60^oC , 5 days
OTs
TsO
1
(*R*)-20
(*R*)-21


OH HO
Cs_2CO_3 , DMF
60^oC , 5 days
OTs
TsO
1
(*S*)-20
(*S*)-21

The structures of (*R*)-**21** and (*S*)-**21** were confirmed via analysis of their respective of ^{1}H and ^{13}C NMR spectra and via HRMS analysis (see the Experimental Section). In addition, the X-ray crystal structure of (*S*)-**21** has been obtained. The corresponding X-ray structure drawing is shown in Figure 2.3.[71]

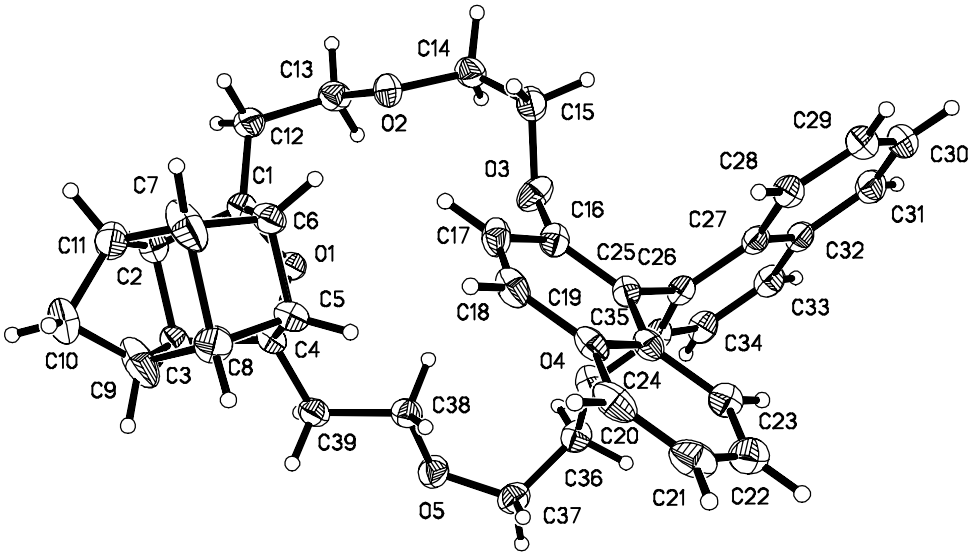


Figure 2.3. X-ray structure drawing of (*S*)-**21**.[71]

III. Transport experiment in a w-tube.

In order to test the enantiomeric recognition capability of cage functionalized chiral crown ethers **5a, 5b, 6a, 6b, 7a,** and **7b** toward enantioselective transport of (±) α-methyl benzylamine (**22)**, a series W-tube (see Figure 2.4) transport experiments[53] were performed. The results thereby obtained are shown in Tables 2.1, 2.2 and 2.3,

respectively. The W-tube transport experiments were performed in 72 hours. As can be seen from these results, hosts **5a** and **5b** display greater enantioselectivity toward (±) α-methyl benzylamine (**22**) than do hosts **6a** and **6b**. Hosts **6a** and **6b** proved to be more effective in this regard than hosts **7a** and **7b**.

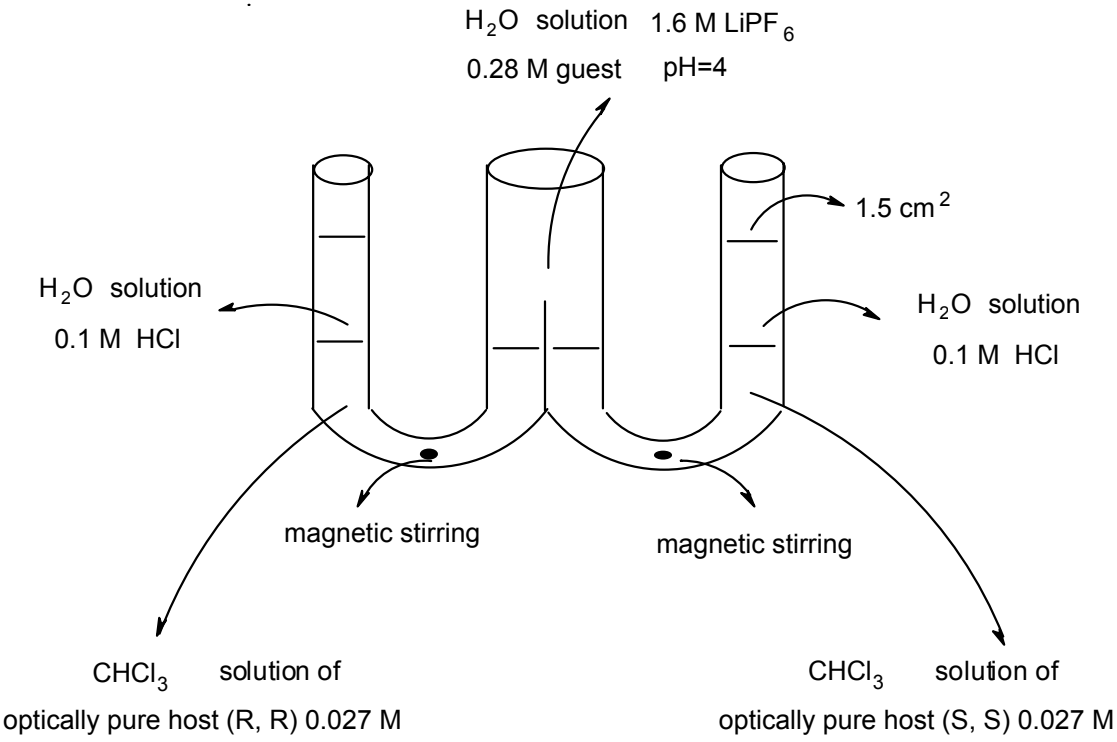


Figure 2.4 W-tube resolving machine.[53]

As can be seen from the result shown in Table 2.1 (run 2), host **5a** transported 11.2% of guest (±) α-methyl benzylamine after 24h with 91% enantiomeric purity by complexing preferentially with (*S*)-**22**. Similarly, host **5b** transported 11.1% of guest (±)

α-methyl benzylamine with 91% enantiomeric purity by complexing preferentially with (*R*)-**22**.

After 48h, 19% of guest (**22)** was transported with 90% enantiomeric purity by **5a**; the *S*-guest enantiomer was transported preferentially by host **5a**. Similarly, 18% of guest (**22**) was transported with 90% enantiomeric purity by **5b**; the *R*-guest enantiomer was transported preferentially by host **5b**.

After 72h, 24% of guest (**22**) was transported with 90% enantiomeric purity by **5a**; the *S*-guest enantiomer was transported preferentially by host **5a**. Similarly, 25% of guest (**22**) was tansported with 90% enantiomeric purity by **5b**; the *R*-guest enantiomer was transported preferentially by host **5b**.

In control studies (run 1), the hosts were absent from the $CHCl_3$ layers in order to test the guest transported by the $CHCl_3$ medium. After 24 h, only *ca.* 2 mg (0.2%) of guest (±)-**22** were obtained in each of the receiving phases.

Table 2.1. Results of W-tube transport experiments obtained by using 0.027 M Hosts (**5a** and **5b**, run 2) and control studies (run 1).

host	guest	time (h)	%transferred	configuration of dominant enantiomer	enantiomeric purify (%)
---	**22**	24	0.2	---	---
---	**22**	24	0.2	---	---
(*S,S*)-**5a**	**22**	24	11.1	*S*	91
(*R,R*)-**5b**	**22**	24	11.2	*R*	91
(*S,S*)-**7a**	**22**	48	18.5	*S*	90
(*R,R*)-**7b**	**22**	48	18.6	*R*	90
(*S,S*)-**7a**	**22**	72	24.4	*S*	90
(*R,R*)-**7b**	**22**	72	24.6	*R*	90

Table 2.2. Results of W-tube transport experiments obtained by using 0.027 M Hosts (**6a** and **6b**, run 3).

host	guest	time (h)	%transferred	configuration of dominant enantiomer	enantiomeric purify (%)
(*R,R*)-**6a**	**22**	24	8.6	*S*	87
(*S,S*)-**6b**	**22**	24	8.4	*R*	86
(*R,R*)-**6a**	**22**	48	14.3	*S*	88
(*S,S*)-**6b**	**22**	48	14.3	*R*	87
(*R,R*)-**6a**	**22**	72	18.8	*S*	85
(*S,S*)-**6b**	**22**	72	18.9	*R*	85

Table 2.3. Results of W-tube transport experiments obtained by using 0.027 M Hosts (**7a** and **7b**, run 4).

enantiomeric host	guest	time (h)	%transferred	configuration of dominant enantiomer	purify (%)
(*R,R*)-**7a**	**22**	24	4.1	*S*	61
(*S,S*)-**7b**	**22**	24	4.2	*R*	61
(*R,R*)-**7a**	**22**	48	6.8	*S*	60
(*S,S*)-**7b**	**22**	48	6.9	*R*	60
(*R,R*)-**7a**	**22**	72	8.7	*S*	60
(*S,S*)-**7b**	**22**	72	8.8	*R*	60

W-tube transport experiments were also performed to test the ability of the two cage functionalized binaphthyl-derived chiral crown ethers, i.e., (*R*)-**21** and (*S*)-**21**, to perform enantioselective transport of the enantiomers of (±) α-methyl benzylamine (**22)**. As can be seen from the data in Table 2.4, host (*R*)-**21** transported 3.6% of guest (±) α-methyl benzylamine after 24 h with 77% enantiomeric purity; guest (*S*)-**22** was transported preferentially by host (*R*)-**21**. Similarly, host (*S*)-**21** transported 3.7% of guest (±) α-methyl benzylamine after 24 h with 76% enantiomeric purity; guest (*R*)-**22** was transported preferentially by host (*S*)-**21**.

After 48 h, 6.1% of guest **22** was transported by (*R*)-**21** with 75% enantiomeric purity; guest (*S*)-**22** was transported preferentially by host (*R*)-**21**. Similarly, 6.2% of

guest **22** was transported by (*S*)-**21** with 75% enantiomeric purity; guest (*R*)-**22** was transported preferentially by host (*S*)-**21**.

After 72 h, 7.5% of guest **22** was transported by (*R*)-**21** with 74% enantiomeric purity; guest (*S*)-**22** was transported preferentially by host (*R*)-**21**. Similarly, 7.6% of guest **22** was transported by (*S*)-**21** with 75% enantiomeric purity; guest (*R*)-**22** was transported preferentially by host (*S*)-**21**.

Table 2.4. Results of W-tube transport experiments obtained by using 0.027 M Hosts ((*R*)-**21** and (*S*)-**21**, run 5).

host	guest	time (h)	%transferred	configuration of dominant enantiomer	enantiomeric purify (%)
(*R*)-**21**	**22**	24	3.6	*S*	77
(*S*)-**21**	**22**	24	3.7	*R*	76
(*R*)-**21**	**22**	48	6.1	*S*	75
(*S*)-**21**	**22**	48	6.2	*R*	75
(*R*)-**21**	**22**	72	7.5	*S*	74
(*S*)-**21**	**22**	72	7.6	*R*	75

Summary and Conclusions

Enantiomerically pure cage-functionalized crown ethers **5a-7a**, **5b-7b** and **21** have been prepared. A 1,1'-bi-2-napthol moiety serves as the source of chirality in **21**, while the corresponding chiral moieties in **5a-7a** and **5b-7b** are derived from optically active tartaric acids.

The ability of **5a-7a** and **5b-7b** to recognize the enantiomers of guest salts, i.e., (±) α-methyl benzylamine (**22**) and to transport them enantioselectively in W-tube transport experiments were studied. Hosts **5a** and **5b** display a higher enantioselectivity toward (±) α-methyl benzylamine (**22**) than do hosts **6a** and **6b**. Hosts **6a** and **6b** were more effective in this regard than hosts **7a** and **7b**. As can be seen from the structures of host molecules **5a-7a** and **5b-7b**, the primary difference among them is the presence of substituent groups, i.e., H, CH_3, or Ph in the chiral building blocks. The unsubstituted host systems (i.e., R=H) afforded the best results in the W-tube transport experiments, whereas the largest substituted group (i.e., R=Ph) in the host system proved to have a deleterious effect upon host enantio-selectivity.

W-tube transport experiments were also performed to test the enantiomeric recognition ability of the two cage functionalized binaphthol-derived chiral crown ethers, i.e., (*R*)-**21** and (*S*)-**21**, toward enantioselective transport of enantiomers of (±) α-methyl benzylamine (**22)**.As can be seen from the data in Tables 2.1-2.4, after 48 h or 72 h, the enantioselective transport results are almost same as that after 24 h. Thus, unlike U-tube

transport experiments,[53] the enantioselectivities as measured via W-tube transport experiments are not time-dependent.

Experimental Section

Melting points are uncorrected. All UV readings were recorded by using a Hewlett-Packard Model 84524 Diode Array UV-visible spectrophotometer. Optical rotations were taken on a Perkin-Elmer 241 polarimeter. High-resolution mass spectral data reported herein were obtained by Professor Jennifer S. Brodbelt at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin by using a ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ. Host ligand that possessed maximum optical rotation was used unless otherwise noted. Prior to reuse, the host was purified by chromatography to remove small amounts of accrued oxidation products. Spectroscopic grade $CHCl_3$ was washed with water to remove EtOH.

***exo*-8-*exo*-11-Diallylpentacyclo[5.4.0.0^{2,6}.0^{3,10}0^{5,9}]undecane-*endo*-8-*endo*-11-diol (9).** A slurry of activated Mg (15.0 g, 0.617 mol) in dry Et_2O (125 mL) under argon was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added dropwise with stirring a solution of freshly distilled allyl bromide (25 mL, 36 g, 0.30 mol) in dry Et_2O (175 mL) at such a rate (*ca*. 4 h) that the interal temperature did not rise above 5°C. After the addition of allyl bromide had been completed, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to

ambient temperature under stirring during 17 h. The reaction mixture then was refluxed during 2 h. The resulting Grignard solution was transferred under argon into another flask. Ether was removed *in vacuo*, and was replaced by dry THF (200 mL). The resulting solution was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added slowly with stirring a solution of **8**[72] (8.5 g, 49 mmol) in dry THF (50 mL). After the addition had been completed, the ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring under argon during 20 h. The reaction mixture was cooled once again to 0°C, and the reaction was quenched via careful addition of saturated aqueous NH_4Cl (50 mL). The layers were separated, and the aqueous solution was extracted with EtOAc (3 × 70mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from hexane, thereby affording **9** (6.6 g, 52%) as a colorless microcrystalline solid: mp 82-83°C, IR (KBr) 3169 (s), 2976 (s), 1693 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.03 (*A*B, J_{AB} = 10.6 Hz, 1 H), 1.46 (A*B*, J_{AB} = 10.6 Hz, 1 H), 1.89-2.19 (m, 6 H), 2.22-2.52 (m, 6 H), 4.89-5.08 (m, 4 H), 5.73-6.00 (m, 2H), 6..91 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 33.6 (t), 39.7 (d), 42.6 (d), 43.8 (d), 43.8 (t), 48.8 (d), 77.0 (s), 117.0 (t), 133.6 (d); Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C 79.14; H, 8.42.

3,5-Dially-4-oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodcane (10). To a solution of **9** (6 g, 232 mmol) in benzene (120 mL) was added TsOH (350 mg, 1.8 mmol, catalytic amount), and the resulting mixture was refluxed in a Dean-Stark apparatus with periodic removed of water during 36 h. Additional TsOH (360 mg) was added at 12 h intervals.

The reaction mixture was allowed to cool gradually to ambient temperature and then was washed sequentially with 10% aqueous $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL). The layers were separated, and the organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 5% EtOAc-hexane. Pure **10** (3.4 g, 62%) was thereby ontained as colorless oil; IR (film) 3075 (m), 2965 (s), 1640 (m), 997 (s) 910 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.46 (*A*B, J_{AB} = 10.2 Hz, 1 H), 1.82 (A*B*, J_{AB} = 10.2 Hz, 1 H), 2.35 (br s, 2 H), 2.45-2.65 (m, 10 H), 4.96-5.18 (m, 4 H), 5.67-5.90 (m, 2 H), 6.91 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 37.3 (t), 41.7 (d), 43.1 (t), 44.3 (d), 47.6 (d), 58.4 (d), 94.0 (s), 116.5 (t), 134.2 (d); Exact mass (CI HRMS) Calcd for $C_{17}H_{20}O_1$: $[M_r + H]^+$*m/z* 241.1592. Found: $[M_r + H]^+$*m/z* 241.1601.

3,5-[2,2–Bis(hydroxyethyl)]-4-oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]-dodecane (11). A two-neck round bottom flask equipped with a bubbler and a magnetic stirrer was charged with a solution of **10** (5.95 g, 24.8 mmol) in freshly dried MeOH (220 mL), and the reaction vessel was cooled to -78 °C via immersion in an external dry ice-acetone cold bath. Ozone was bubbled through this solution until a blue color persisted (*ca*. 1 h), at which time the ozone source was disconnected from the reaction flask. Argon was bubbled through the cold reaction mixture to purge excess ozone, and this was followed by dropwise addition of Me_2S (5 mL, 68 mmol) with stirring to the cold (-78 °C) reaction mixture. After the addition of Me_2S had been completed, the external cold bath was removed, and the resulting mixture was allowed to warm gradually to ambient temperature while stirring during 2 h. The reaction mixture was cooled to 0 °C via

application of external ice-water bath, and $NaBH_4$ (2.0 g, 53 mmol, excess) was added portionwise to the reaction mixture at such a rate that the internal temperature did not exceed 5°C. After all the $NaBH_4$ had been added, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 4 h. Concentrated aqueous HCl was added dropwise to adjust the Ph to *ca*. 5; then solid $NaHCO_3$ (2.0 g, 24 mmol) and solid NaCl (5.0 g, 86 mmol) were added sequentially to the reaction mixture. The resulting mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was extracted sequentially with $CHCl_3$ (2 × 75 mL) and EtOAc (2 × 75 mL). The combined organic layers were washed sequentially with water (75 mL), and brine (75 mL), dried ($MgSO_4$) and filtered, and the filtrate was concentrated in *vacuo*. The residue was purified via column chromatography on silica gel by eluting with 30% EtOAc-hexane. Pure **11** (5.6 g, 91%) was thereby obtained as a colorless microcrystalline solid: mp 153-153.5 °C. IR (nujol) 3320 (m), 2980 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.53 (*A*B, J_{AB} = 10.5 Hz, 1 H), 1.88 (A*B*, J_{AB} = 10.5 Hz, 1 H), 2.01 (t, *J*= 6.2 Hz, 4 H), 2.32-2.47 (m, 4 H), 2.52-2.68 (m, 6 H), 3.75 (t, *J* = 6.2 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 34.6 (t), 41.4 (d), 43.5 (t), 44.1 (d), 47.7 (d), 58.8 (d), 60.1 (t), 96.0 (s); Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.65; H, 8.06.

3,5-Bis[2-(2'-benzyloxyethoxy)ethyl-4-oxahexacyclo[5.4.1.$0^{2,6}0^{3,10}0^{5,9}.0^{8,11}$]dodecane (13). A suspension of NaH (60% suspension in minernal oil, 660 mg, 16.4 mmol) in dry THF (10 mL) under argon was cooled to 0°C via application of an external ice-water bath. To this cooled solution was

added dropwise with stirring a solution of **11** (1.85 g, 7.45 mmol) in THF (10 mL). The resulting white suspension was stirred at 0 °C during 10 minutes, at which time external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 2 h. The reaction mixture again was cooled to 0 °C via application of an external ice-water bath, and to the cooled reaction mixture was added dropwise with stirring a solution of 1-(benzyoxy)-2-(*p*-toluensulfonyloxy) ethane (5.02 g, 16.4 mmol) in THF (10 mL). The resulting suspension was stirred at 0 °C for 10 minutes, at which time the external cold bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring at that temperature during 2 days. The reaction mixture was concentrated *in vacuo*, and ice-water (5 mL) was added to the residue. The resulting aqueous suspension was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc-hexane. Pure **13** (1.7 g, 44%) was thereby obtained as a colorless, viscous oil. IR (film) 2951 (s), 2870 (s), 1450 (m), 1111 (vs), 736 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.45 (*A*B, J_{AB} = 10.3 Hz, 1 H), 1.82 (A*B*, J_{AB} = 10.3 Hz, 1 H), 2.10 (t, *J* = 7.14 Hz, 4 H), 2.36 (br s, 2 H), 2.48-2.52 (m, 6 H), 3.51-3.59 (m, 12 H) 4.55 (s, 4 H), 7.27-7.34 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 32.6 (t), 41.8 (d), 43.5 (t), 44.5 (d), 48.7 (d), 58.8 (d), 68.1 (t), 69.5 (t), 70.2 (t), 73.2(t), 94.4 (s), 127.6 (d), 127.7 (d), 138.3 (s); Anal. Calcd for $C_{33}H_{40}O_5$: C, 76.71; H, 7.80. Found: C 76.48; H, 7.70.

3,5-Bis[2-(2'-hydroxyethoxy)ethyl-4-oxahexacyclo[5.4.1.$0^{2,6}$$0^{3,10}$$0^{5,9}$.$0^{8,11}$]dodecane (14). To a solution of **13** (1.70 g, 3.29 mmol) in EtOH (50 mL) was added 10% Pd-C

(180 mg, catalytic amount), and the resulting mixture was hydrogenated by using H_2 (g) (58 psi) on a Parr shaker apparatus for 24 h. The reaction mixture was filtered through a bed of Celite® to remove spent catalyst. The filtrate was concentrated in *vacuo*, thereby affording **14** (990 mg, 90%), as a colorless, viscous oil; IR (film) 3416 (s), 2945 (s), 2864 (s), 1367 (w), 1128 (s), 1066 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.45 (*A*B, J_{AB} = 10.4 Hz, 1 H), 1.80 (A*B*, J_{AB} = 10.4 Hz, 1 H), 2.00 (t, *J* = 6.6 Hz, 4 H), 2.32 (br s, 2 H), 2.40-2.52 (m, 6 H), 3.04 (s, 1 H, peak disappears when NMR sample is shaken with D_2O), 3.41-3.61 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 32.2 (t), 41.5 (d), 43.5 (t), 44.2 (d), 48.1 (d), 58.5 (d), 61.4 (t), 67.8 (t), 71.7 (t), 94.7 (s); Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.60; H, 8.23.

3,5-Bis[2-(2'-*p*-toluenesulfonyloxyethoxy)ethyl]-4-oxahexacyclo-[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane (1).[64] A solution of *p*-TsCl (0.697 g, 3.66 mmol) in dry pyridine (6 mL) was placed in a round-bottom flask that previously had been flushed thoroughly with dry argon. This solution was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added dropwise with stirring a solution of **14** (410 mg, 1.22 mmol) in dry CH_2Cl_2 (10 mL) during 15 minutes. After the addition of **14** had been completed, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring overnight. The reaction mixture was poured into ice-water (150 mL), and the resulting aqueous suspension was extracted with CH_2Cl_2 (200 mL). The organic layer was washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 50%

EtOAc-hexane. Compound **1** (550 mg, 70%) was thereby obtained as colorless, viscous oil; IR (film) 2958 (s), 2872 (m), 1356 (s), 1178 (vs), 1024 (m), 927 (s), 665 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.45 (*A*B, J_{AB} = 10.4 Hz, 1 H), 1.80 (A*B*, J_{AB} = 10.4 Hz, 1 H), 1.97 (t, *J* = 7.0 Hz, 4 H), 2.30 (br s, 2 H), 2.42 (s, 10 H), 2.49-2.58 (m, 2 H), 3.45(t, *J* = 7.0 Hz, 4 H), 3.57(t, *J* = 4.8 Hz, 4 H), 4.11 (t, *J* = 4.8 Hz, 4 H), 7.31 (*A*B, J_{AB} = 8.2 Hz, 2 H), 7.77 (A*B*, J_{AB} = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.6 (q), 32.6 (t), 41.7 (d), 43.4 (t), 44.4 (d), 48.3 (d), 58.2 (d), 68.1 (t), 68.4 (t), 69.2 (t), 94.2 (s), 127.9 (d), 129.8(d), 133.0 (s), 144.7(s); Anal. Calcd for $C_{33}H_{40}O_9S_2$: C, 61.47; H, 6.25. Found: C, 61.62; H, 6.08.

Dimethyl 2, 3-*O*-isopropylidene-L-tartrate (17).[65] To a solution of dimethyl L-tartrate (19.3 g, 93.6 mmol) in dry benzene (45 mL) under argon with stirring was added 2,2-dimethoxypropane (11.71 g, 112.43 mmol) and TsOH (50 mg, catalytic amount). The resulting solution was refluxed during 10 h while the benzene-methanol azeotrope (b.p. 58°C) was slowly removed via distillation. Solvent and unreacted 2,2-dimethoxypropane then were removed *in vacuo*, and the product was distilled, thereby affording **17** as yellow oil (21.0 g, 92%). IR (film) 2993 (w), 2957 (w), 1761 (s), 1438 (m), 1383 (m), 1212 (s), 1111 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.44 (s, 6 H), 3.76 (s, 6 H), 4.71 (br s, 2 H). ^{13}C NMR ($CDCl_3$) δ 26.7 (q, 2 C), 53.3 (d, 2 C), 77.5 (q, 2 C), 114.3 (s), 170.5 (s, 2 C).

Dimethyl 2,3-*O*-isopropylidene-D-tartrate (19). Compound **19** was prepared by application of the same procedure as that which was used to prepare **17** and by using dimethyl D-tartrate as the starting material. The ^1H NMR spectra of the material thereby obtained was essentially identical with the corresponding spectra obtained above for **17** as yellow oil (19.0 g, 90%)**.** IR (film) 2993 (w), 2957 (w), 1761 (s), 1438 (m), 1383 (m),

1212 (s), 1111 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.44 (s, 6 H), 3.76 (s, 6 H), 4.71 (br s, 2 H). ^{13}C NMR ($CDCl_3$) δ 26.7 (q, 2 C), 53.3 (d, 2 C), 77.5 (q, 2 C), 114.3 (s), 170.5 (s, 2 C).

2, 3-*O*-ispropylidene-L-threitol (2a).[65] A slurry of $LiAlH_4$ (2.16 g, 56.9 mmol) in dry THF (120 mL) was cooled to O °C via application of an external ice-water bath. To this cooled slurry was added dropwise with stirring a solution of the diester **17** (7 g, 28.5 mmol) in THF (20 mL) over 30 minutes. After all of the reducing agent had been added, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 3h. The reaction mixture then was refluxed during 16 h. The reaction mixture was cooled once again to 0 °C and saturated aqueous Na_2SO_4 (15 mL) was added dropwise to the cooled reaction mixture. The external ice-water bath was removed and the reaction mixture was allowed to warm gradually to ambient temperature. The resulting white slurry was filtered through a pad of Celite and the residue was washed with EtOAc (50 mL). The organic extract was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc-hexanes, thereby affording pure **2a** (4.1 g, 70%) as a colorless oil; IR (film) 3411 (s), 2987 (s), 2931 (s), 2867 (s), 1461 (m), 1385 (s), 1212 (s), 1051 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.42 (s, 6 H), 2.41 (br s, 2 H), 3.67 (dd(*A*B), J_{AB} = 11.8 Hz, J_1 = 2.6 Hz, J_2 = 1.5 Hz, 2 H), 3.77 (dd(A*B*), J_{AB} = 11.8 Hz, J_1 = 2.6 Hz, J_2 = 1.5 Hz, 2 H) 3.99 (ddd, J = 4.0 Hz, J_1 = 2.5 Hz, J_2 = 1.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.6 (q), 27.0 (q), 62.1 (t), 78.1 (d), 109.3 (s).

2, 3-*O*-ispropylidene-D-threitol (2b). Compound **2b** (3.1 g, 71%) was prepared by application of the same procedure that was used to prepare **2a** and by using **19** as starting

material. The ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical with the corresponding spectra obtained above for **2a** as a colorless oil**.** IR (film) 3411 (s), 2987 (s), 2931 (s), 2867 (s), 1461 (m), 1385 (s), 1212 (s), 1051 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 6 H), 2.41 (br s, 2 H), 3.67 (dd(*A*B), J_{AB} = 11.8 Hz, J_1 = 2.6 Hz, J_2 = 1.5 Hz, 2 H), 3.77 (dd(A*B*), J_{AB} = 11.8 Hz, J_1 = 2.6 Hz, J_2 = 1.5 Hz, 2 H) 3.99 (ddd, J = 4.0 Hz, J_1 = 2.5 Hz, J_2 = 1.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.6 (q), 27.0 (q), 62.1 (t), 78.1 (d), 109.3 (s).

(4*R*, 5*R*)-2, 2-Dimethyl-4, 5-bis(1-hydroxy-1-methylethyl)-1, 3-dioxolane(3a).[66] A solution of MeLi (ca. 1.5 M in Et_2O, 81.3 mL, 120 mmol) was cooled to O °C via application of an external ice-water bath. To this cooled solution was added dropwise with vigorously stirring a solution of **17** (2.5 g, 10.16 mmol) in dry Et_2O (30 mL) over 30 minutes. After all of **17** had been added, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature. Then after stirring overnight at room temperature, the mixture was treated with excess of saturated aq.NH_4Cl solution (pH was adjusted to 6.5-7 via dropwise adding 0.5 M aqueous HCl) and stirred for 1 h. The ether layer was separated, aqueous phase was extracted with ether (2 × 50 mL) and combined ether extract was washed with brine and dried ($MgSO_4$). The solvent was evaporated and the crude product was recrystallized using EtOAc-hexanes to afford pure **3a** (2.2g, 85%) as a colorless solid: mp 152-154 °C. IR (KBr) 3214 (s), 2976 (w), 1179 (m), 1063 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 6 H), 1.28 (s, 6 H), 1.33 (s, 6 H), 3.69 (s, 2 H), 4.08 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.6 (q), 27.3 (q, 2C), 29.1 (q), 70.4 (s), 82.7 (d), 107.6 (s).

(4*S*, 5*S*)-2, 2-Dimethyl-4, 5-bis(1-hydroxy-1-methylethyl)-1, 3-dioxolane(3b). Compound **3b** was prepared by application of the same procedure that was used to prepare **3a** and by using **19** as starting material. The ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical with the corresponding spectra obtained above for **3a.** IR (KBr) 3214 (s), 2976 (w), 1179 (m), 1063 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 6 H), 1.28 (s, 6 H), 1.33 (s, 6 H), 3.69 (s, 2 H), 4.08 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.6 (q), 27.3 (q, 2C), 29.1 (q), 70.4 (s), 82.7 (d), 107.6 (s).

(4*R*, 5*R*)-2, 2-dimethyl-a, a, a', a'-tetraphenyl-1, 3-dioxolane-4, 5-dimethanol (4a).[67] A slurry of activated Mg (3.7 g, 152 mmol) in dry THF (100 mL) under argon was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added dropwise with stirring a solution of bromobenzene (12.8 mL, 122 mmol) in dry THF (30 mL) at such a rate (*ca*. 3 h) that the internal temperature did not rise above 5 °C. After the addition has been completed, the mixture was stirred at ambient temperature during 3 h until almost all Mg was dissolved. A solution of **17** (2.5 g, 10.16 mmol) in dry THF (35 mL) was added dropwise to the reaction mixture with stirring during 30 minutes, at which time the resulting mixture was stirred at ambient temperature during 2 h and refluxed during 2 h. After that time, the reaction mixture was cooled gradually to ambient temperature and kept at this temperature with stirring during 12 h. After cooling to 0 °C, the reaction mixture was quenched via careful dropwise addition of saturated aqueous NH_4Cl (20 mL) with stirring. The resulting mixture was stirred at ambient temperature during 2 h. The layers then were separated, and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine

(2 × 25 mL) and dried with $MgSO_4$ and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc-hexanes, thereby affording pure **4a** (2.4 g, 69%) as a colorless solid: 195-197 °C. IR (KBr) 3291 (s), 3059 (w), 2987 (w), 1493 (m), 1447 (m) 1217 (m), 1046 (m), 758 (s), 699 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.05 (s, 6 H), 3.67 (br s, 2 H), 4.61 (s, 2 H), 7.20-7.63 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 27.1 (q), 78.2 (s), 81.0 (d), 109.5 (s), 127.2 (d), 127.3 (d), 127.6 (d, 2 C), 128.1 (d) 128.6 (d), 142.7 (s), 145.9 (s).

(4*S*, 5*S*)-2,2-dimethyl-a, a, a', a'-tetraphenyl-1, 3-dioxolane-4, 5-dimethanol (4b). Compound **4b** was prepared by application of the same procedure that was used to prepare **4a** by using **19** as the starting material. The ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical with the corresponding spectra obtained above for **4a.** IR (KBr) 3291 (s), 3059 (w), 2987 (w), 1493 (m), 1447 (m) 1217 (m), 1046 (m), 758 (s), 699 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.05 (s, 6 H), 3.67 (br s, 2 H), 4.61 (s, 2 H), 7.20-7.63 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 27.1 (q), 78.2 (s), 81.0 (d), 109.5 (s), 127.2 (d), 127.3 (d), 127.6 (d, 2 C), 128.1 (d) 128.6 (d), 142.7 (s), 145.9 (s).

***Cage-functionalized chiral crown ether* (*S,S*)-5a**

Reaction of 1 with (*S,S*)-2a: A suspension of NaH (60% suspension in minernal oil, 76 mg, 1.59 mmol) in dry THF (10 mL) under nitrogen was cooled to 0 °C via application of an external ice-water bath. To this cooled suspension was added dropwise with stirring a solution of (*S,S*)-**2a** (70 mg, 0.42 mmol) in dry THF (8 mL) under argon, and the resulting mixture was stirred at 0 °C under argon during 1 h. The external ice-water bath then was removed, and the reaction mixture was allowed to warm gradually to

ambient temperature while stirring during 1 h. To the resulting mixture was added dropwise with stirring a solution of **1** (259 mg, 0.40 mmol) in dry THF (5 mL). After the addition of **1** had been completed, the reaction mixture was refluxed during 4 days, at which time the reaction was quenched via addition of cold water (15 mL). The resulting aqueous suspension was extracted with EtOAc (60 mL), and the organic layer was washed sequentially with water (40 mL) and with brine (40 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc-hexane. Pure (*S,S*)-**5a** [110 mg, 61%, $[\alpha]_D$ = +9.4 (*c* 1.5, $CHCl_3$)] was thereby obtained as a colorless oil; IR (neat) 2941 (s), 2858 (s), 1448 (w), 1250 (m), 1116cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.40 (s,6 H),1.48(*A*B, J_{AB} = 11.9 Hz,1 H), 1.83 (A*B*, J_{AB} = 11.9 Hz,1 H), 1.96-2.06 (m,4 H), 2.37 (br s, 2 H), 2.56-2.63 (m, 6 H), 3.56-3.71 (m,16 H), 3.95-3.99 (m,2 H); ^{13}C NMR($CDCl_3$) δ 26.9 (q, 2 C), 32.4 (t, 2 C), 41.4 (d,2 C),43.4 (t), 43.9 (d,2 C), 47.9 (d), 48.0 (d), 58.9 (d), 58.9 (d), 68.2 (t,2 C), 70.1 (t, 2 C), 71.9 (t, 2 C), 72.0 (t, 2 C),77.4 (d,2 C), 94.3 (s,2 C),109.4 (s). Exact mass (CI-HRMS) $[M_r + H]^+$ Calcd for $C_{26}H_{38}O_7$: *m/z* 463.2696, Found: *m/z* 463.2700.

***Cage-functionalized chiral crown ether* (*R,R*)-5b**

Reaction of 1 with (*R,R*)-2b: Application of the foregoing procedure to the reaction of **1** with (*R,R*)-**2b** followed by column chromatographic purification of the crude reaction product according to the procedure given above, afforded pure (*R,R*)-**5b** [120 mg, 63%, $[\alpha]_D$ = -9.4° (*c* 1.5, $CHCl_3$)] as a colorless oil. The IR, ^{1}H NMR, and ^{13}C

NMR spectra of the material thereby obtained were essentially identical with the corresponding spectra obtained above for (*S,S*)-**5a**. IR (neat) 2941 (s), 2858 (s), 1448 (w), 1250 (m), 1116cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.40 (s,6 H),1.48(*A*B, $J_{\mathbf{AB}}$ = 11.9 Hz,1 H), 1.83 (A*B*, $J_{\mathbf{AB}}$ = 11.9 Hz,1 H), 1.96-2.06 (m,4 H), 2.37 (br s, 2 H), 2.56-2.63 (m, 6 H), 3.56-3.71 (m, 16 H), 3.95-3.99 (m, 2 H); ^{13}C NMR($CDCl_3$) δ 26.9 (q, 2 C), 32.4 (t, 2 C), 41.4 (d, 2 C),43.4 (t), 43.9 (d, 2 C), 47.9 (d), 48.0 (d), 58.9 (d), 58.9 (d), 68.2 (t,2 C), 70.1 (t, 2 C), 71.9 (t, 2 C), 72.0 (t, 2 C),77.4 (d, 2 C), 94.3 (s, 2 C),109.4 (s). Exact mass (CI-HRMS) [M_{r} + H]$^{+}$ Calcd for $C_{26}H_{38}O_7$: *m/z* 463.2696, Found: *m/z* 463.2700.

***Cage-functionalized chiral crown ether* (*R,R*)-6a**

Reaction of 1 with (*R,R*)-3a. A suspension of NaH (60% suspension in minernal oil, 72 mg, 1.48 mmol) in dry THF (10 mL) under nitrogen was cooled to 0 °C via application of an external ice-water bath. To this cooled suspension was added dropwise with stirring a solution of (*R,R*)-**3a** (105 mg, 0.49 mmol) in dry THF (8 mL) under argon, and the resulting mixture was stirred at 0 °C under argon during 1 h. The external ice-water bath then was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 1 h. To the resulting mixture was added dropwise with stirring a solution of **1** (318 mg, 0.49 mmol) in dry THF (5 mL). After the addition of **1** had been completed, the reaction mixture was refluxed during 4 days, at which time the reaction was quenched via careful dropwise addition of cold water (15 mL). The resulting aqueous suspension was extracted with EtOAc (60 mL), and the organic layer was washed sequentially with water (40 mL) and with brine (40 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*.

The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc-hexane. Pure (*R,R*)-**6a** [174 mg, 64%, $[\alpha]_D$ = +11.2° (*c* 1.6, $CHCl_3$] was thereby obtained as a colorless microcrystalline solid: mp 136-138 °C; IR (neat) 2933 (w), 2854 (m), 1479 (m), 1365 (s), 1238 (m), 1030 (m), 979 (w), 852 (s), 725 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.18 (s, 6 H), 1.21 (s, 3 H), 1.22 (s, 3 H), 1.45-1.51 (s, 6 H), 1.83 (*A*B, J_{AB} = 8.0 Hz, 1 H), 1.95-2.02 (m, 5 H), 2.35-2.80 (m, 8 H), 3.40-3.89 (m, 12 H), 4.12 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.2 (q, 2 C), 22.8 (q, 2 C), 28.3 (q, 2 C), 32.6 (t, 2 C) 41.4 (d), 41.5 (d), 43.5 (t), 43.9 (d), 44.0 (d), 47.8 (d), 48.3 (d), 58.5 (d), 58.9 (d), 62.4 (t), 62.6 (t), 68.1 (t), 68.2 (t), 70.3 (t, 2 C), 75.9 (t, 2 C), 84.6 (d, 2 C), 94.5 (s, 2 C), 110.6 (s). Exact mass (CI-HRMS) $[M_r + H]^+$ Calcd for $C_{30}H_{46}O_7$: *m/z* 519.3322, Found: *m/z* 519.3329.

***Cage-functionalized chiral crown ether* (*S,S*)-6b**

Reaction of 1 with (*S,S*)-3b. Application of the foregoing procedure to the reaction of **1** with (*S,S*)-**3b** followed by column chromatographic purification of the crude reaction product according to the procedure given above, afforded pure (*S,S*)-**6b** [160mg, 65%, $[\alpha]_D$ = -11.2° (*c* 1.6, $CHCl_3$)] as a colorless microcrystalline solid: mp 136-138 °C. The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical with the corresponding spectra obtained above for (*R,R*)-**6a**. IR (neat) 2933 (w), 2854 (m), 1479 (m), 1365 (s), 1238 (m), 1030 (m), 979 (w), 852 (s), 725 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.18 (s, 6 H), 1.21 (s, 3 H), 1.22 (s, 3 H), 1.45-1.51 (s, 6 H), 1.83 (*A*B, J_{AB} = 8.0 Hz, 1 H), 1.95-2.02 (m, 5 H), 2.35-2.80 (m, 8 H), 3.40-3.89 (m, 12 H), 4.12 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.2 (q, 2 C), 22.8 (q, 2 C), 28.3 (q, 2 C), 32.6 (t, 2 C) 41.4

(d), 41.5 (d), 43.5 (t), 43.9 (d), 44.0 (d), 47.8 (d), 48.3 (d), 58.5 (d), 58.9 (d), 62.4 (t), 62.6 (t), 68.1 (t), 68.2 (t), 70.3 (t, 2 C), 75.9 (t, 2 C), 84.6 (d, 2 C), 94.5 (s, 2 C), 110.6 (s). Exact mass (CI-HRMS) $[M_r + H]^+$ Calcd for $C_{30}H_{46}O_7$: *m/z* 519.3322, Found: *m/z* 519.3329.

***Cage-functionalized chiral crown ether* (*R,R*)-7a**

Reaction of 1 with (*R,R*)-4a: A suspension of NaH (60% suspension in minernal oil, 76 mg,1.59 mmol) in dry THF (10 mL) under argon was cooled to 0 ^oC via application of an external ice-water bath. To this cooled suspension was added dropwise with stirring under argon a solution of (*R,R*)-**4a** (280 mg, 0.6 mmol) in THF (10 mL) during 45 minutes. The external ice-water bath then was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 1h. At that time, a solution of **1** (389 mg, 0.6 mmol) in dry THF (10 mL) was added dropwise with stirring to the reaction mixture was refluxed under argon during 5 days. The reaction mixture then was cooled to 0 ^oC via application of an external ice-water bath, and the cooled reaction mixture subsequently was quenched via careful, dropwise addition of water (4 mL). The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (60 mL). The resulting solution was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue thereby obtained was purified via column chromatography on silica gel by eluting with 15% EtOAc in hexane. Pure (*R,R*)-**7a**. [285 mg, 62%, $[\alpha]_D$=+21.1° (*c* 1.1 $CHCl_3$)] was thereby obtained as a colorless microcrystalline solid : mp 179-180.5 °C; IR(film) 2926 (s),1580 (m), 1456 (s), 1366 (m), 1260 (m), 1070 (s), 736 (s), 720 cm^{-1}(m); ^1H NMR ($CDCl_3$) δ 1.05 (s,6

H),1.55(*A*B, J_{AB} = 8.6 Hz,1 H), 1.83-2.10 (m, 5 H), 2.38-2.86 (m, 8 H), 3.28-3.49 (m, 6 H), 3.50-3.68 (m, 2 H), 3.72 (t, *J* = 6.6 Hz, 4 H), 4.75 (s, 2 H) 7.20-7.48 (m, 20 H); ^{13}C NMR(CDCl3) δ 27.9 (q, 2 C), 32.4 (t, 2 C), 41.5 (d, 2 C),43.6 (t), 43.9 (d, 2 C), 48.6 (d), 48.8 (d), 59.4 (d), 59.6 (d), 64.2 (t, 2 C), 68.6 (t, 2 C), 70.4 (t, 2 C), 79.4 (d, 2 C), 83.9 (s), 84.0 (s), 94.3 (s, 2 C), 107.2 (s), 126.6 (d, 4 C), 126.7 (d, 4 C), 126.9 (d, 2 C), 127.3 (d, 2 C), 129.2 (d, 2 C), 129.3 (d, 2 C), 129.6 (d, 4 C), 142.3 (s, 2 C), 143.5 (s, 2 C).Exact mass (CI HRMS) Calcd for $C_{50}H_{54}O_7$: *m/z* 767.3948, Found: *m/z* 767.3942.

***Cage-functionalized chiral crown ether* (*S,S*)-7b**

. **Reaction of 1 with (*S,S*)-4b:** Application of the foregoing procedure to the reaction of **1** with (*S,S*)-**4b** followed by column chromatographic purification of the crude reaction product according to the procedure given above, afforded pure (*S,S*)-**7b** [270mg, 65%, $[\alpha]_D$ = -21.1° (*c* 1.1 $CHCl_3$)] was thereby obtained as a colorless microcrystalline solid: mp 179-180.5 °C. The IR, ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical with the corresponding spectra obtained above for (*R,R*)-**7a**. IR(film) 2926 (s),1580 (m), 1456 (s), 1366 (m), 1260 (m), 1070 (s), 736 (s), 720 cm^{-1}(m); ^{1}H NMR ($CDCl_3$) δ 1.05 (s,6 H),1.55(*A*B, J_{AB} = 8.6 Hz,1 H), 1.83-2.10 (m, 5 H), 2.38-2.86 (m, 8 H), 3.28-3.49 (m, 6 H), 3.50-3.68 (m, 2 H), 3.72 (t, *J* = 6.6 Hz, 4 H), 4.75 (s, 2 H) 7.20-7.48 (m, 20 H); ^{13}C NMR(CDCl3) δ 27.9 (q, 2 C), 32.4 (t, 2 C), 41.5 (d, 2 C),43.6 (t), 43.9 (d, 2 C), 48.6 (d), 48.8 (d), 59.4 (d), 59.6 (d), 64.2 (t, 2 C), 68.6 (t, 2 C), 70.4 (t, 2 C), 79.4 (d, 2 C), 83.9 (s), 84.0 (s), 94.3 (s, 2 C), 107.2 (s), 126.6 (d, 4 C), 126.7 (d, 4 C), 126.9 (d, 2 C), 127.3 (d, 2 C), 129.2 (d, 2 C), 129.3 (d, 2 C),

129.6 (d, 4 C), 142.3 (s, 2 C), 143.5 (s, 2 C).Exact mass (CI HRMS) Calcd for $C_{50}H_{54}O_7$: *m/z* 767.3948, Found: *m/z* 767.3942.

***Cage-functionalized chiral crown ether* (*S*)-21**

Reaction of 1 with (*S*)-(-)-1,1'-Binaphthol [(*S*)-20]. A suspension of Cs_2CO_3 (1.27 g, 3.90 mmol) in DMF (90 mL) was heated to 60 °C. To this warm solution was added dropwise with stirring a solution of **1** (1.11 g, 1.71 mmol) and (*S*)-(-)-1,1'-binaphthol [(*S*)-**20**, 503 mg, 1.74 mmol] in DMF (30 mL) during 8 h, and the resulting mixture was stirred at 60 °C during 4.5 days. The reaction mixture was allowed to cool gradually to ambient temperature, at which time water (150 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed sequentially with water (2 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via colume chromatography on silica gel by eluting with 10% EtOAc-hexane. Pure (*S*)-**21** [334 mg, 33%, $[\alpha]_D$ = -54.0° (*c* 0.2, $CHCl_3$] was thereby obtained as a colorless micrcrocrystalline solid: mp 171.5-172.5 °C; IR (film): 2959 (s), 2947 (s), 2936 (s), 2859 (m), 1618 (w), 1591 (m), 1508 (m), 1472 (m), 1325 (m), 1265 (s), 1242 (s), 1223 (s), 1134 (s), 1090 (s), 806 (s), 739 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.49 (*A*B, J_{AB} = 10.4 Hz, 1 H), 1.78 - 1.95 (m, 5 H), 2.31-2.35 (m, 4 H), 2.51-2.55 (m, 4 H), 3.25-3.42 (m, 4 H), 3.52-3.64 (m, 4 H), 3.87-3.97 (m, 2 H), 4.09-4.21 (m, 2 H), 7.10-7.36 (m, 6 H), 7.45 (d, *J* = 9.1 Hz, 2 H), 7.84 - 7.96 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 32.4 (t), 41.3 (d), 41.4 (d), 43.5 (t, 2 C), 43.8 (t), 43.9 (d, 2 C), 48.1 (d), 48.4 (d), 58.6 (d), 59.1 (d), 68.4 (t,

2 C), 69.9 (t), 70.0 (t), 70.5 (t), 70.6 (t), 94.3 (s, 2 C), 117.0 (d), 117.1 (d), 120.9 (s, 2 C), 123.7 (d, 2 C), 125.4 (d, 2 C), 126.2 (d, 2 C), 127.8 (d, 2 C), 129.2 (d, 2 C), 129.5 (s, 2 C), 134.1 (s, 2 C), 154.7 (s, 2 C). Exact mass (CI-HRMS) $[M_r + H]^+$ Calcd for $C_{39}H_{38}O_5$: *m/z* 587.2795, Found: *m/z* 587.2802. Anal. Calcd for $C_{39}H_{38}O_5$: C, 79.84; H, 6.53. Found: C, 80.09; H, 6.53. The structure of (*S*)-**21** was determined unequivocally via application of X-ray crystallographic techniques (*vide infra*).

***Cage-functionalized chiral crown ether* (*R*)-21**[68]

Reaction of 1 with (*R*)-(+)-1,1'-Binaphthol[(*R*)-20]. Application of the foregoing procedure to the reaction of **1** (1.24 g, 1.93 mmol) in DMF (140 mL) with (*R*)-(+)-1,1'-binaphthol ((*R*)-**20**, 521 mg, 1.80 mmol), performed in the presence of Cs_2CO_3 (4.21 g, 12.9 mmol) and followed by column chromatographic purification of the crude reaction product according to the procedure given above, afforded pure (*R*)-**21** [323 mg, 31%, $[\alpha]_D$ = +54.0° (*c* = 0.2, $CHCl_3$)] as a colorless microcrystalline solid: mp 173.5-174.3 °C. The IR, ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical with the corresponding spectra obtained above for (*S*)-**21**. ; IR (film): 2959 (s), 2947 (s), 2936 (s), 2859 (m), 1618 (w), 1591 (m), 1508 (m), 1472 (m), 1325 (m), 1265 (s), 1242 (s), 1223 (s), 1134 (s), 1090 (s), 806 (s), 739 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.49 (*A*B, J_{AB} = 10.4 Hz, 1 H), 1.78 - 1.95 (m, 5 H), 2.31-2.35 (m, 4 H), 2.51-2.55 (m, 4 H), 3.25-3.42 (m, 4 H), 3.52-3.64 (m, 4 H), 3.87-3.97 (m, 2 H), 4.09-4.21 (m, 2 H), 7.10-7.36 (m, 6 H), 7.45 (d, *J* = 9.1 Hz, 2 H), 7.84 - 7.96 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 32.4 (t), 41.3 (d), 41.4 (d), 43.5 (t, 2 C), 43.8 (t), 43.9 (d, 2 C), 48.1 (d), 48.4 (d), 58.6 (d), 59.1 (d), 68.4 (t, 2 C), 69.9 (t), 70.0 (t), 70.5 (t), 70.6 (t), 94.3 (s, 2 C), 117.0

(d), 117.1 (d), 120.9 (s, 2 C), 123.7 (d, 2 C), 125.4 (d, 2 C), 126.2 (d, 2 C), 127.8 (d, 2 C), 129.2 (d, 2 C), 129.5 (s, 2 C), 134.1 (s, 2 C), 154.7 (s, 2 C). Exact mass (CI HRMS) Calcd for $C_{39}H_{38}O_5$: M_r^+ *m/z* 587.2798. Found: M_r^+ *m/z* 587.2763. Anal. Calcd for $C_{39}H_{38}O_5$: C, 79.84; H, 6.53. Found: C, 80.08; H, 6.78.

W-Tube Transport Experiments

(±)-α-Methylbenzylammonium chloride (**22**) was prepared by bubbling dry HCl gas through a solution of α-methylbenzylamine (4.0 g, 33 mmol) in dry Et_2O (30 mL). The precipitated salt thereby obtained was isolated by suction filtration and subsequently was purified via recrystallization from MeOH to afford pure **22** (3.0 g, 58%): mp 154-155 °C. A 2.4 M solution of $LiPF_6$ in D_2O was prepared[73] by dropwise addition of precooled (0 °C) D_2O (7.0 mL, 350 mmol) to $LiPF_6$ (9.4 g, 62 mmol) under inert atmosphere in a dry box. The addition of D_2O was performed at a rate such that the temperature of the aqueous solution never rose above 10 °C. After the addition of reagents had been completed, the pH of the resulting solution was adjusted to 4.0 via careful, dropwise addition of a saturated solution of LiOD in D_2O. Then, D_2O was added to adjust the final volume of this solution to 25 mL. The resulting solution was maintained at 0 °C via application of an external ice-water bath.

The W-tube apparatus employed in this study has been described elsewhere.[69] The total volume of the W-tube was 60 mL. The two arms were constructed of glass, 1.3 cm i.d. When loaded, the average $CHCl_3$ path was 9.0 cm. All four H_2O-$CHCl_3$ interfaces possessed an area of 1.3 cm^2.

The apparatus was maintained at 24 ±1 °C. The two source phases occupied the right and left arm of the W-tube. Into the right arm was introduced a 0.027 M solution of (*R*)-host in $CHCl_3$ (10 mL); a similar quantity of (*S*)-host was placed in the left arm of the W-tube. The solution in each arm of the apparatus was stirred magnetically. The two arms were separated by a glass barrier that extended upward into a central reservoir *ca.* 2 cm above the levels of the two $CHCl_3$ solutions. The glass barrier prevented the two $CHCl_3$ layers from coming into mutual contact. Into the central reservoir was placed 15 mL of 1.6 M aqueous $LiPF_6$ and 0.28 M (±)-**22** that had been adjusted to pH 4 (*vide supra*). As receiving phases, 5 mL of 0.1 M HCl was introduced into the left and right arms of the W-tube above each $CHCl_3$ phase, respectively. At time t = 0, magnetic stirring of the organic layer in each arm of the apparatus was initiated, with the stirring rates maintained as nearly equal as possible. Considerable care was expended to avoid creating turbulance that might cause frothing of the $CHCl_3$ layer.

Transport Experiment 1 (control experiment). In this experiment, no host was present in either $CHCl_3$ layer. After 24 h, the aqueous receiving phases were removed individually via pipette. Water (5 mL) was added to the left and to the right arms of the apparatus; then, in each case, the water was withdrawn via pipette and was added to each receiving phase, respectively. The combined aqueous solutions each were rendered basic via addition of excess 3% aqueous NH_4OH. The resulting mixtures were extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrates were concentrated *in vacuo*. In each case, *ca.* 2 mg of (±)-**22** was

obtained, thereby indicating that this quantity of racemic guest amine had been transported through the $CHCl_3$ membrane in the absence of any added host.

Transport Experiment 2. Into the right arm of the W-tube apparatus was placed 10 mL of a 0.027 M solution that contained 125 mg of host, (*R,R*)-**5b**, in $CHCl_3$; a similar quantity of (*S,S*)-**5a** was placed in the left arm of the apparatus. The source phase was prepared by placing 10 mL of 2.4 M aqueous $LiPF_6$ and (±)-**22** (667 mg, 4.2 mmol) into a small beaker. This mixture was diluted with water to 15 mL, the pH of the solution was adjusted to pH 4 (*vide supra*), and the resulting aqueous solution was introduced into the central reservoir in the W-tube apparatus. As receiving phases, 5 mL of 0.1 M HCl was introduced into the left and right arms of the W-tube above each $CHCl_3$ phase, respectively. The resulting two-phase systems were stirred magnetically during 24 h, at which time the aqueous receiving phases were removed individually via pipette. Water (5 mL) was added to the left and to the right arms of the apparatus; then, in each case, the water was withdrawn via pipette and was added to each receiving phase, respectively. The combined aqueous solutions each were rendered basic via addition of excess 3% aqueous NH_4OH. The resulting mixtures were extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrates were concentrated *in vacuo*. It was found that (*R*)-(+)-**22** (57.1 mg, 11.2%, $[\alpha]_D$ +39.5°, optical purity 90.5%, 81% *ee*) had been transported by (*R,R*)-**5b** into the left-arm receiving phase, whereas (*S*)-(-)-**22** (56.8 mg, 11.%, $[\alpha]_D$ -39.8°, optical purity 91%, 82% *ee*) had been transported by (*S,S*)-**5a** into the right-arm receiving phase.

By following the same procedure as described above, the resulting two-phase systems were stirred magnetically during 48 h. It was found that (*R*)-(+)-**22** (94.6 mg, 18.6%, $[\alpha]_D$ +39.2°, optical purity 90%, 80% *ee*) had been transported by (*R,R*)-**5b** into the left-arm receiving phase, whereas (*S*)-(-)-**22** (94.2 mg, 19%, $[\alpha]_D$ -39.4°, optical purity 90%, 80% *ee*) had been transported by *(S,S)*-**5a** into the right-arm receiving phase.

By following the same procedure as described above, the resulting two-phase systems were stirred magnetically during 72 h. It was found that (*R*)-(+)-**22** (124.8mg, 25%, $[\alpha]_D$ +39.1°, optical purity 90%, 80% *ee*) had been transported by (*R,R*)-**5b** into the left-arm receiving phase, whereas (*S*)-(-)-**22** (124.3 mg, 24%, $[\alpha]_D$ -39.3°, optical purity 90%, 80% *ee*) had been transported by (*S,S*)-**5a** into the right-arm receiving phase.

Transport Experiment 3. Into the right arm of the W-tube apparatus was placed 10 mL of a 0.027 M solution that contained 140 mg of host, (*R,R*)-**6a,** in $CHCl_3$; a similar quantity of (*S,S*)-**6b** was placed in the left arm of the apparatus. The source phase was prepared by placing 10 mL of 2.4 M aqueous $LiPF_6$ and (±)-**22** (667 mg, 4.2 mmol) into a small beaker. This mixture was diluted with water to 15 mL, the pH of the solution was adjusted to pH 4 (*vide supra*), and the resulting aqueous solution was introduced into the central reservoir in the W-tube apparatus. As receiving phases, 5 mL of 0.1 M HCl was introduced into the left and right arms of the W-tube above each $CHCl_3$ phase, respectively. The resulting two-phase systems were stirred magnetically during 24 h, at which time the aqueous receiving phases were removed individually via pipette. Water (5 mL) was added to the left and to the right arms of the apparatus; then, in each case, the

water was withdrawn via pipette and was added to each receiving phase, respectively. The combined aqueous solutions each were rendered basic via addition of excess 3% aqueous NH_4OH. The resulting mixtures were extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrates were concentrated *in vacuo*. It was found that (*R*)-(+)-**22** (42.8 mg, 8.4%, $[\alpha]_D$ +37.5°, optical purity 86%, 72% *ee*) had been transported by (*S,S*)-**6b** into the left-arm receiving phase, whereas (*S*)-(-)-**22** (43.7 mg, 8.6%, $[\alpha]_D$ -38.2°, optical purity 87%, 75% *ee*) had been transported by (*R,R*)-**6a** into the right-arm receiving phase.

By following the same procedure as described above, the resulting two-phase systems were stirred magnetically during 48 h. It was found that (*R*)-(+)-**22** (72.7 mg, 14%, $[\alpha]_D$ +37.9°, optical purity 87%, 73% *ee*) had been transported by (*S,S*)-**6b** into the left-arm receiving phase, whereas (*S*)-(-)-**22** (73.0 mg, 14%, $[\alpha]_D$ -38.4°, optical purity 88%, 76% *ee*) had been transported by (*R,R*)-**6a** into the right-arm receiving phase.

By following the same procedure as described above, the resulting two-phase systems were stirred magnetically during 72 h. It was found that (*R*)-(+)-**22** (96.0 mg, 18.9%, $[\alpha]_D$ +37.1°, optical purity 85%, 70% *ee*) had been transported by (*S,S*)-**6b** into the left-arm receiving phase, whereas (*S*)-(-)-**22** (96 mg, 19%, $[\alpha]_D$ -37.0°, optical purity 85%, 69% *ee*) had been transported by (*R,R*)-**6a** into the right-arm receiving phase.

Transport Experiment 4. Into the right arm of the W-tube apparatus was placed 10 mL of a 0.027 M solution that contained 207 mg of host, (*R,R*)-**7a**, in $CHCl_3$; a similar quantity of (*S,S*)-**7b** was placed in the left arm of the apparatus. The source phase was prepared by

placing 10 mL of 2.4 M aqueous $LiPF_6$ and (±)-**22** (667 mg, 4.2 mmol) into a small beaker. This mixture was diluted with water to 15 mL, the pH of the solution was adjusted to pH 4 (*vide supra*), and the resulting aqueous solution was introduced into the central reservoir in the W-tube apparatus. As receiving phases, 5 mL of 0.1 M HCl was introduced into the left and right arms of the W-tube above each $CHCl_3$ phase, respectively. The resulting two-phase systems were stirred magnetically during 24 h, at which time the aqueous receiving phases were removed individually via pipette. Water (5 mL) was added to the left and to the right arms of the apparatus; then, in each case, the water was withdrawn via pipette and was added to each receiving phase, respectively. The combined aqueous solutions each were rendered basic via addition of excess 3% aqueous NH_4OH. The resulting mixtures were extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrates were concentrated *in vacuo*. It was found that (*R*)-(+)-**22** (21 mg, 4.1%, $[\alpha]_D$ +26.6°, optical purity 61%, 22% *ee*) had been transported by (*S,S*)-**7b** into the left-arm receiving phase, whereas (*S*)-(-)-**22** (21 mg, 4.1%, $[\alpha]_D$ -26.8°, optical purity 61%, 23% *ee*) had been transported by (*R,R*)-**7a** into the right-arm receiving phase.

By following the same procedure as described above, the resulting two-phase systems were stirred magnetically during 48 h. It was found that (*R*)-(+)-**22** (35 mg, 6.9%, $[\alpha]_D$ +26.2°, optical purity 60%, 20% *ee*) had been transported by (*S,S*)-**7b** into the left-arm receiving phase, whereas (*S*)-(-)-**22** (35 mg, 6.9%, $[\alpha]_D$ -26.3°, optical purity 60%, 20% *ee*) had been transported by (*R,R*)-**7a** into the right-arm receiving phase.

By following the same procedure as described above, the resulting two-phase systems were stirred magnetically during 72 h. It was found that (*R*)-(+)-**22** (45 mg, 8.8%, $[\alpha]_D$ +26.0°, optical purity 60%, 19% *ee*) had been transported by (*S,S*)-**7b** into the left-arm receiving phase, whereas (*S*)-(-)-**22** (44 mg, 8.7%, $[\alpha]_D$ -26.2°, optical purity 60%, 20% *ee*) had been transported by (*R,R*)-**7a** into the right-arm receiving phase.

Transport Experiment 5. Into the right arm of the W-tube apparatus was placed 10 mL of a 0.027 M solution that contained 158 mg of host, (*R*)-**21**, in $CHCl_3$; a similar quantity of (*S*)-**21** was placed in the left arm of the apparatus. The source phase was prepared by placing 10 mL of 2.4 M aqueous $LiPF_6$ and (±)-**22** (667 mg, 4.2 mmol) into a small beaker. This mixture was diluted with water to 15 mL, the pH of the solution was adjusted to pH 4 (*vide supra*), and the resulting aqueous solution was introduced into the central reservoir in the W-tube apparatus. As receiving phases, 5 mL of 0.1 M HCl was introduced into the left and right arms of the W-tube above each $CHCl_3$ phase, respectively. The resulting two-phase systems were stirred magnetically during 24 h, at which time the aqueous receiving phases were removed individually via pipette. Water (5 mL) was added to the left and to the right arms of the apparatus; then, in each case, the water was withdrawn via pipette and was added to each receiving phase, respectively. The combined aqueous solutions each were rendered basic via addition of excess 3% aqueous NH_4OH. The resulting mixtures were extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. It was found that (*R*)-(+)-**22** (19 mg, 3.7%, $[\alpha]_D$ +33.4°, optical

purity 76%, 53% *ee*) had been transported by (*S*)-**21** into the left-arm receiving phase, whereas (*S*)-(-)-**22** (19 mg, 3.6%, $[\alpha]_D$ -33.5°, optical purity 77%, 53% *ee*) had been transported by (*R*)-**21** into the right-arm receiving phase.

By following the same procedure as described above, the resulting two-phase systems were stirred magnetically during 48 h. It was found that (*R*)-(+)-**22** (32 mg, 6.2%, $[\alpha]_D$ +32.8°, optical purity 75%, 50% *ee*) had been transported by (*S*)-**21** into the left-arm receiving phase, whereas (*S*)-(-)-**22** (31 mg, 6.1%, $[\alpha]_D$ -32.9°, optical purity 75%, 51% *ee*) had been transported by (*R*)-**21** into the right-arm receiving phase.

By following the same procedure as described above, the resulting two-phase systems were stirred magnetically during 72 h. It was found that (*R*)-(+)-**22** (39 mg, 7.6%, $[\alpha]_D$ +32.7°, optical purity 75%, 49% *ee*) had been transported by (*S*)-**21** into the left-arm receiving phase, whereas (*S*)-(-)-**22** (39 mg, 7.5%, $[\alpha]_D$ -32.5°, optical purity 74%, 48% *ee*) had been transported by (*R*)-**21** into the right-arm receiving phase.

CHAPTER III

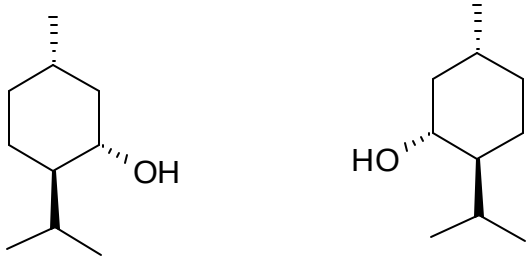
ASYMMETRIC MICHAEL ADDITION BY CAGE-ANNULATED CHIRAL CROWN ETHERS

INTRODUCTION

Synthesizing single-enantiomer compounds is of special interest to organic chemists, especially to medicinal chemists. Although some compounds of this type can be obtained from the "chiral pool" of natural products, the isolation and purification of compounds of this type frequently is labor- and time- intensive.

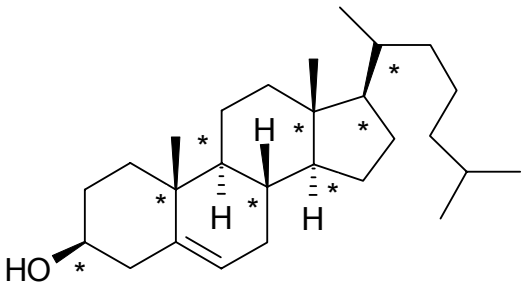
Normally, it is much easier to prepare racemates than to synthesize single-enantiomerically pure compounds. However, generally only one of the two enantiomers displays biological activity,[74] which is the key factor for the pharmaceutical applications. For example, **1** and **2** are enantiomers, but only **1** (peppermint)[74] has biological activity.

Scheme 3.1



1 **2**

In addition, some compounds have several asymmetric centers. For example, cholesterol (**3**)[75] has eight asymmetric centers. If the chirality of any one of the asymmetric centers is changed, the potential biological activity resulting compound will be altered.



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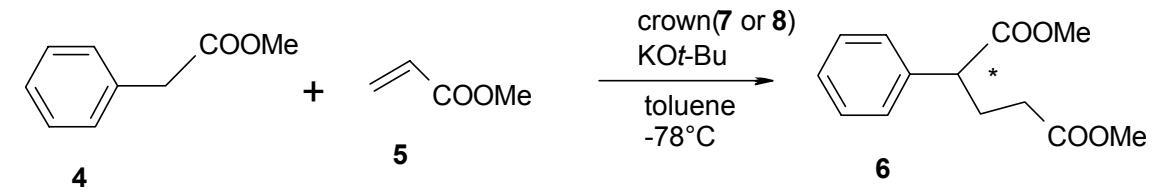
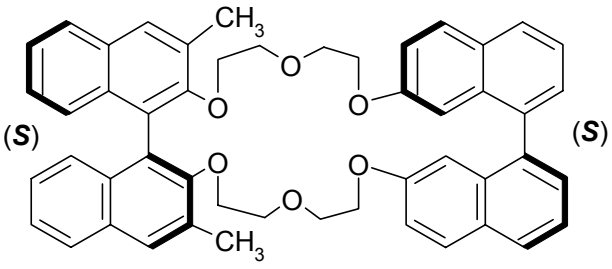
Thus, enantioselective synthesis presents an important challenge to synthetic organic chemists. Several synthetic methods have been developed in an effort to foster enantioselectivity. An example in this regard is provided by phase-transfer catalysis (PTC), which relies typically on simple reaction procedures and mild conditions, and employs relatively inexpensive and safe reagents and solvents. The use of optically active phase transfer catalysts for the preparation of chiral, non-racemic compounds from prochiral substrates is becoming an important area in catalysis.[55]

A number of compounds, including chiral crown ethers, have been used as chiral catalysts in phase-transfer reactions.[76] In 1981, Cram and coworkers[77] for the first time reported several chiral crown ethers that function as catalysts in phase-transfer reactions (see Scheme 3.2).

Scheme 3.2



4 5 6



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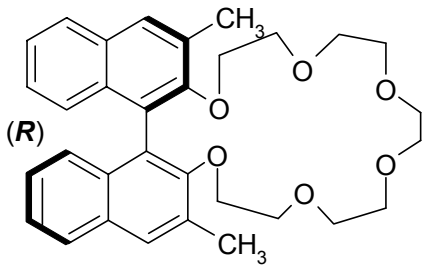

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The model reaction selected for testing the catalytic activity of chiral crown ethers was the Michael addition of methyl phenylacetate (**4**) to methyl acrylate (**5**), in the presence of catalytic quantities of the crown ether. Potassium *t*-butoxide was used as a base, and the reactions were carried out at -78 °C in toluene. The reagents were used in the following ratios: methyl phenylacetate : methyl acrylate : KO-*t*-Bu : crown ether = 2:1: 0.5:0.1. The extent of asymmetric induction, expressed in terms of the enantiomeric excess (%ee), was monitored by measuring the optical rotation of the product. Table 3.1 list the results obtained when Cram's crown ethers (**7** and **8**) were used as the chiral catalysts.[56]

Table 3.1. Results obtained by using Cram's crown ethers (**7** and **8**) as chiral catalysts in the Michael addition reaction.[77]

catalyst	time (h)	yield (%)	configuration of dominant enantiomer	enantiomeric excess (%)
(*S,S*)-**8**	5	80	*S*	65
(*R*)-**9**	4	90	*S*	83

Although several chiral crown ethers have been synthesized and their chiral recognition abilities have been investigated, only a few of these compounds have been applied successfully to catalytic asymmetric synthesis. Also, the nature of the transition states that lead to asymmetric induction is not well understood. Several mechanism have been proposed by different groups, as an example, the mechanism proposed by Tõke and coworkers[77] is shown in Figure 3.1.

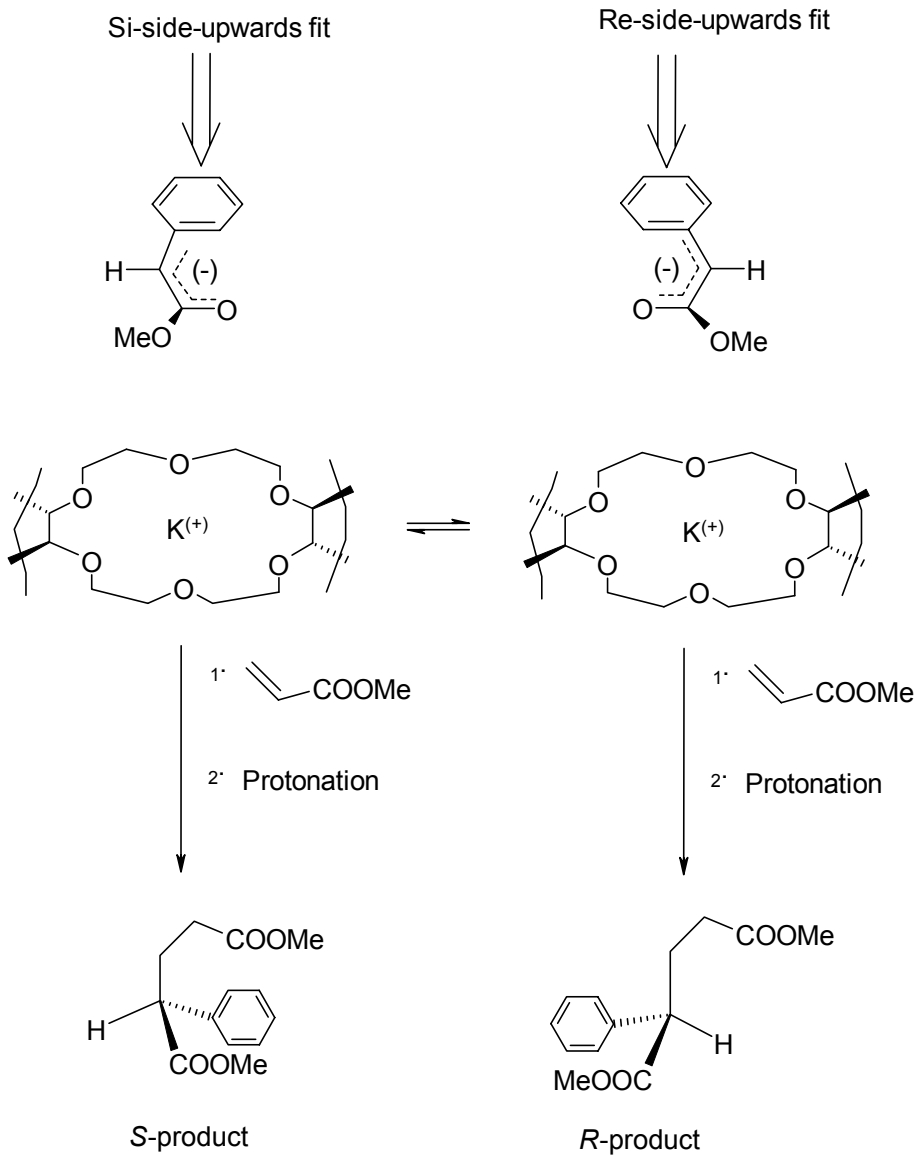


Figure 3.1 Mechanism proposed by Tõke and coworkers for asymmetric Michael addition.[77]

In order to explain the stereochemical outcome of this reaction, it has been suggested that an equilibrium exists between ion pair complexes formed via interaction among the Z-enolate[78] – metal ion – crown ether. The course of the reaction is believed to be controlled by the relative stability of these complexes.

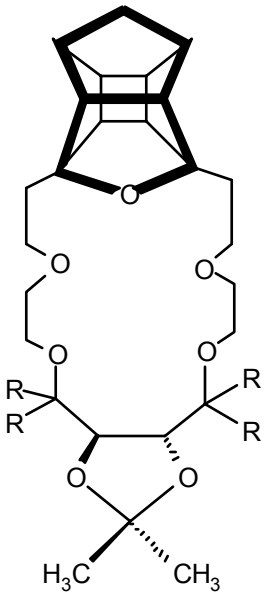
In this equilibrium, it is suggested one side fit of the Z-enolate is preferred. Then after the anion has been trapped by acrylate, one product enantiomer will be produced preferentially over the other.

As a part of our continuing interests in host-guest chemistry, we have synthesized a series of optically active crown ethers by using synthetic chiral building blocks, and the chiral recognition ability of resulting crown ethers toward primary ammonium ions were studied (see Chapter II). We have shown previously that the incorporation of a cage moiety in to the host system can influence its complexation properties.[64] Thus, incorporation of a rigid cage moiety into the host system, which was used as the chiral catalysts in the asymmetric Michael addition reactions, was of particular interest to our study. We now report our observations on asymmetric Michael addition reactions obtained by using our cage-functionalized crown ethers as chiral catalysts.

Results and Discussions

In our initial study, a series of chiral crown ethers were prepared, and the chiral recognition abilities of these chiral crown ethers toward racemic primary ammonium ions were studied. Scheme 3.3 shows the structures of these "host" systems and the synthetic procedures of these chiral crown ethers were described in details in Chapter II.

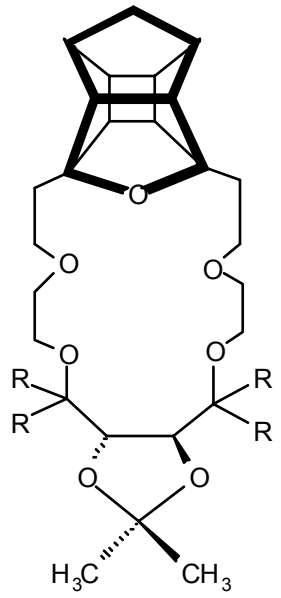
Scheme 3.3



(*S,S*) **-10**

(*R,R*) **-11**

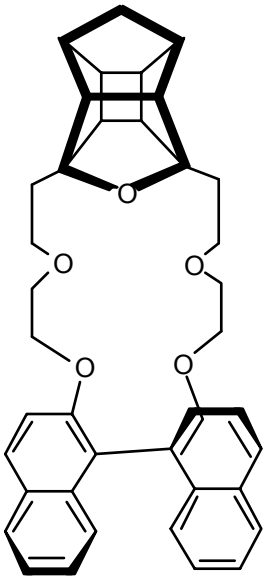
(*R,R*) **-12**



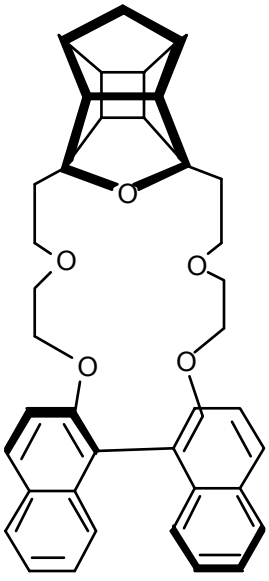
(*R,R*) **-10 (** R= H**)**

(*S,S*) **-11 (** R=CH3)

(*S,S*) **-12** (R=Ph**)**



(*S*)-**13**



(*R*)-**13**

In this phase-transfer catalysis (PTC) study, enantioselective Michael addition of methyl phenylacetate (**4**) to methyl acrylate (**5**) was investigated as the model reaction (see Scheme 3.4). "Host" molecules (*R,R*)-**10**, (*S,S*)-**11**, (*R,R*)-**11**, (*S,S*)-**12** and (*S*)-**13** were selected as the chiral catalysts in this study. The reaction was carried out at -78 °C in toluene by using KO-*t*-Bu as base to promote Michael addition. The extent of asymmetric induction, expressed in terms of the enantiomeric excess (%ee), was monitored by measuring the optical rotation of the product ester and comparing to the literature value.[77] The results of the experiments are presented in Table 3.2

Scheme 3.4

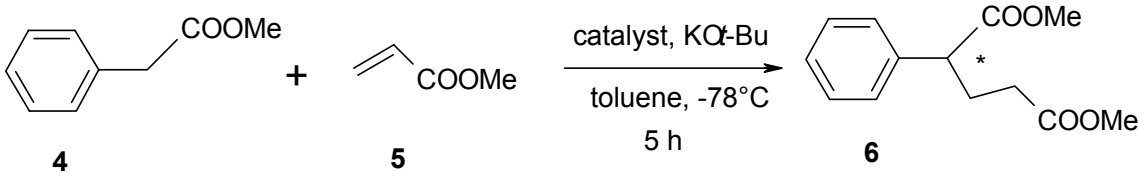


Table 3.2. Results of cage-annulated chiral crown ethers used as chiral catalysts in the Michael addition reaction.

catalyst	time (h)	yield (%)	configuration of dominant enantiomer	enantiomeric excess (%)
(*R,R*)-**10**	5	93	*R*	71
(*S,S*)-**11**	5	95	*R*	87
(*R,R*)-**11**	5	93	*S*	85
(*S,S*)-**12**	5	92	*R*	49
(*S*)-**13**	5	89	*R*	61

As can be seen from the data shown in Table 3.2, host molecules (*S*,*S*)-**11** and (*R*,*R*)-**11** afforded the best results. When host (*S*,*S*)-**11** is employed as the chiral catalyst, the chemical yield of product **6** is 95%, the product is formed with 87%ee and the configuration of the dominant product enantiomer is *R*. When host (*R*,*R*)-**11** is used as the chiral catalyst, the chemical yield of product **6** is 93%, the product is formed with 85%ee and the configuration of the dominant product enantiomer is *S*.

Summary and Conclusions

A series of enantiomerically pure cage-annulated crown ethers **10**-**13** have been prepared. The ability of these crown ethers to perform as chiral catalysts in an enantioselective Michael addition was studied.

In the Michael addition reaction, all of the chiral crown ethers used as phase transfer catalysts afforded the desired product, **6,** in good chemical yield (i.e., >90%). It also can be seen from the data in Table 3.2 that all the catalysts produce **6** enantioselectively, catalyst **11** proved to be particularly effective in this regard.

The use of (*R*,*R*)-**11** as chiral catalyst in the Michael addition reaction results in asymmetric induction, thereby leading to product **6** with 85%ee; the configuration of the dominant product enantiomer is *S*. Similarly, the use of (*S*,*S*)-**11** for this purpose affords **6** with 87%ee; the configuration of the dominant product enantiomer is *R*. Typically, one enantiomerically pure catalyst provides one enantiomer of the product in excess, whereas the other enantiomerically pure catalyst affords principally the product enantiomer of opposite chirality. Thus, by a simple choice of catalyst, it is possible to prepare either of the two enantiomeric products at will.

Experimental Section

Melting points are uncorrected. All UV readings were recorded by using a Hewlett-Packard Model 84524 Diode Array UV-visible spectrophotometer. Optical rotations were taken on a Perkin-Elmer 241 polarimeter. High-resolution mass spectral data reported herein were obtained by Professor Jennifer S. Brodbelt at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin by using a ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ. Host ligand that possessed maximum optical rotation was used unless otherwise noted. Prior to reuse, the host was purified by chromatography to remove small amounts of impurities. Spectroscopic grade $CHCl_3$ was washed with water to remove EtOH and trace quantities of HCl.

Chiral crown ether (*R*,*R*)-10 used as catalyst in Michael addition reaction. A suspension of powered KO-*t*-Bu (120 mg, 1.1 mmol) in dry toluene (5 mL) under argon was cooled to -78 ºC via immersion in an external dry ice-acetone cold bath. To this cooled solution was added dropwise with stirring a solution of methyl phenylacetate (660 mg, 4.4 mmol) and (*R*,*R*)-**10** (100 mg, 0.22 mmol) in dry toluene (10 mL) during 15 minutes. After the addition of reagent had been completed, the reaction mixture was stirred under argon at -78 °C during 15 minutes. After that time, a solution of methyl acrylate (190 mg, 2.2 mmol) in dry toluene (10 mL) was added dropwise with stirring to the reaction mixture during 30 minutes, and the resulting mixture was maintained at -78

ºC while stirring during 4 h. The reaction mixture then was poured into saturated aqueous NH_4Cl (30 mL), and the resulting aqueous suspension was extracted with toluene (2 × 30 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 15% EtOAc-hexane. Pure **6** [480 mg, 93%, $[\alpha]_D$ = -62.9° (*c* 5. EtOH), 71%ee] was thereby obtained as a colorless oil; IR (film) 3029 (w), 2952 (m), 1731 (s), 1437 (s), 1233 (s), 737 (w), 700 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.46-1.48 (m, 2 H), 3.63-3.65 (m, 2 H), 3.66 (s, 3 H), 3.68-3.69 (m, 1 H), 3.72 (s, 3 H) 7.25-7.42 (m, 5 H); ^{13}C NMR($CDCl_3$) δ 28.8 (t), 32.2 (t), 50.9 (d), 52.1 (q), 52.5 (q), 127.9 (d), 128.4 (d, 2 C), 129.3 (d, 2 C), 139.9 (s), 173.3 (s), 174.2 (s).

Chiral crown ether (*S*,*S*)-11 used as catalyst in Michael addition reaction. A suspension of powered KO-*t*-Bu (110 mg, 0.95 mmol) in dry toluene (5 mL) under argon was cooled to -78 ºC via immersion in an external dry ice-acetone cold bath. To this cooled solution was added dropwise with stirring a solution of methyl phenylacetate (570 mg, 3.8 mmol) and (*S*,*S*)-**11** (100 mg, 0.19 mmol) in dry toluene (10 mL) during 15 minutes. After the addition of reagent had been completed, the reaction mixture was stirred under argon at -78 °C during15 minutes. After that time, a solution of methyl acrylate (160 mg, 1.9 mmol) in dry toluene (10 mL) was added dropwise with stirring to the reaction mixture during 30 minutes, and the resulting mixture was maintained at -78 ºC while stirring during 4 h. The reaction mixture then was poured into saturated aqueous NH_4Cl (30 mL), and the resulting aqueous suspension was extracted with toluene (2 × 30 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and

filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 15% EtOAc-hexane. Pure **6** [420 mg, 95%, $[\alpha]_D$ = -77.2° (*c* 5. EtOH), 87%ee] was thereby obtained as a colorless oil; IR (film) 3029 (w), 2952 (m), 1731 (s), 1437 (s), 1233 (s), 737 (w), 700 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.46-1.48 (m, 2 H), 3.63-3.65 (m, 2 H), 3.66 (s, 3 H), 3.68-3.69 (m, 1 H), 3.72 (s, 3 H) 7.25-7.42 (m, 5 H); ^{13}C NMR($CDCl_3$) δ 28.8 (t), 32.2 (t), 50.9 (d), 52.1 (q), 52.5 (q), 127.9 (d), 128.4 (d, 2 C), 129.3 (d, 2 C), 139.9 (s), 173.3 (s), 174.2 (s).

Chiral crown ether (*R*,*R*)-11 used as catalyst in Michael addition reaction. A suspension of powered KO-*t*-Bu (110 mg, 0.95 mmol) in dry toluene (5 mL) under argon was cooled to -78 ºC via immersion in an external dry ice-acetone cold bath. To this cooled solution was added dropwise with stirring a solution of methyl phenylacetate (570 mg, 3.8 mmol) and (*R*,*R*)**-11** (100 mg, 0.19 mmol) in dry toluene (10 mL) during 15 minutes. After the addition of reagent had been completed, the reaction mixture was stirred under argon at -78 °C during15 minutes. After that time, a solution of methyl acrylate (160 mg, 1.9 mmol) in dry toluene (10 mL) was added dropwise with stirring to the reaction mixture during 30 minutes, and the resulting mixture was maintained at -78 ºC while stirring during 4 h. The reaction mixture then was poured into saturated aqueous NH_4Cl (30 mL), and the resulting aqueous suspension was extracted with toluene (2 × 30 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 15% EtOAc-hexane. Pure **6** [410 mg, 93%, $[\alpha]_D$ = + 75.6° (*c* 5. EtOH), 85%ee] was thereby obtained as a colorless oil; IR (film)

3029 (w), 2952 (m), 1731 (s), 1437 (s), 1233 (s), 737 (w), 700 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.46-1.48 (m, 2 H), 3.63-3.65 (m, 2 H), 3.66 (s, 3 H), 3.68-3.69 (m, 1 H), 3.72 (s, 3 H) 7.25-7.42 (m, 5 H); ^{13}C NMR($CDCl_3$) δ 28.8 (t), 32.2 (t), 50.9 (d), 52.1 (q), 52.5 (q), 127.9 (d), 128.4 (d, 2 C), 129.3 (d, 2 C), 139.9 (s), 173.3 (s), 174.2 (s).

Chiral crown ether (*S*,*S*)-12 used as catalyst in Michael addition reaction. A suspension of powered KO-*t*-Bu (73 mg, 0.65 mmol) in dry toluene (5 mL) under argon was cooled to -78 ºC via immersion in an external dry ice-acetone cold bath. To this cooled solution was added dropwise with stirring a solution of methyl phenylacetate (390 mg, 2.6 mmol) and (*S*,*S*)-**12** (100 mg, 0.13 mmol) in dry toluene (10 mL) during 15 minutes. After the addition of reagent had been completed, the reaction mixture was stirred under argon at -78 °C during15 minutes. After that time, a solution of methyl acrylate (112 mg, 1.3 mmol) in dry toluene (10 mL) was added dropwise with stirring to the reaction mixture during 30 minutes, and the resulting mixture was maintained at -78 ºC while stirring during 4 h. The reaction mixture then was poured into saturated aqueous NH_4Cl (30 mL), and the resulting aqueous suspension was extracted with toluene (2 × 30 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 15% EtOAc-hexane. Pure **6** [280 mg, 92%, $[\alpha]_D$ = -43.5° (*c* 5. EtOH), 49%ee] was thereby obtained as a colorless oil; IR (film) 3029 (w), 2952 (m), 1731 (s), 1437 (s), 1233 (s), 737 (w), 700 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.46-1.48 (m, 2 H), 3.63-3.65 (m, 2 H), 3.66 (s, 3 H), 3.68-3.69 (m, 1 H), 3.72 (s, 3 H)

7.25-7.42 (m, 5 H); ^{13}C NMR($CDCl_3$) δ 28.8 (t), 32.2 (t), 50.9 (d), 52.1 (q), 52.5 (q), 127.9 (d), 128.4 (d, 2 C), 129.3 (d, 2 C), 139.9 (s), 173.3 (s), 174.2 (s).

Chiral crown ether (*S*)-13 used as catalyst in Michael addition reaction. A suspension of powered KO-*t*-Bu (95 mg, 0.85 mmol) in dry toluene (5 mL) under argon was cooled to -78 ºC via immersion in an external dry ice-acetone cold bath. To this cooled solution was added dropwise with stirring a solution of methyl phenylacetate (510 mg, 3.4 mmol) and (*S*)**-13** (100 mg, 0.17 mmol) in dry toluene (10 mL) during 15 minutes. After the addition of reagent had been completed, the reaction mixture was stirred under argon at -78 °C during15 minutes. After that time, a solution of methyl acrylate (146 mg, 1.7 mmol) in dry toluene (10 mL) was added dropwise with stirring to the reaction mixture during 30 minutes, and the resulting mixture was maintained at -78 ºC while stirring during 4 h. The reaction mixture then was poured into saturated aqueous NH_4Cl (30 mL), and the resulting aqueous suspension was extracted with toluene (2 × 30 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 15% EtOAc-hexane. Pure **6** [360 mg, 89%, $[\alpha]_D$ = -54.2° (*c* 5. EtOH), 61%ee] was thereby obtained as a colorless oil; IR (film) 3029 (w), 2952 (m), 1731 (s), 1437 (s), 1233 (s), 737 (w), 700 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.46-1.48 (m, 2 H), 3.63-3.65 (m, 2 H), 3.66 (s, 3 H), 3.68-3.69 (m, 1 H), 3.72 (s, 3 H) 7.25-7.42 (m, 5 H); ^{13}C NMR($CDCl_3$) δ 28.8 (t), 32.2 (t), 50.9 (d), 52.1 (q), 52.5 (q), 127.9 (d), 128.4 (d, 2 C), 129.3 (d, 2 C), 139.9 (s), 173.3 (s), 174.2 (s).

1. Pedersen, C. J. *J. Amer. Chem. Soc*. **1967**, *89*, 7017-7026.
2. Hiroaka, M. *Crown Compounds and Their Characteristics* Elsevier Scientific Publishing Company: New York, NY. 1982, 1-3.
3. Stewart, D. G.; Wadden, D. Y.; Barrows, E. T. Brit. Patent 785, 229: 1957. *(C.A. 52, 5038h)*.
4. (a) Pedersen, C. J. in *Synthetic Multidentate Macrocyclic Compounds,* Izatt, R. M., Christensen, J. J., Eds.; Academic Press: New York, 1978. (b) Bradshaw, J. S. in *Synthetic Multidentate Macrocyclic Compounds,* Izatt, R. M., Christensen, J. J., Eds.; Academic Press: New York, 1978.
5. Gold, V.; Sghibartz, C. M. *J. Chem. Soc., Chem. Commun*. **1978**, 507-508.
6. Park, C. H.; Simmons, H. E. *J. Am. Chem. Soc*. **1968**, *90*, 2429-2431.
7. Simmons, H. E.; Park, C. H. *J. Am. Chem. Soc*. **1968**, *90*, 2428-2429.
8. Lehn, J. M. *Acc. Chem. Res*. **1978**, *11*, 49 and references therein.
9. Dietrich, B.; Lehn, J. M.; Sauvage, J. P. *Tetrahedron Letters*, **1969**, 2885-2889.
10. Eliel, E. L.; *Stereochemistry of Carbon Compounds*. McGraw Hill, New York, 1962, p. 198.
11. Furniss, B. S.; Hannafotd, A. J.; Smith, P. W. G.; Tachell, A. R. *Vogel's Textbook of Practical Organic Chemistry* Longman: New York. 1989, p. 583.
12. Dale, J.; Kristiansen, P. O. *J. Chem. Soc., Chem. Commun*. **1971**, 670-671.
13. Ugelstad, J.; Mork, P. C.; Jensen, B. *Acta Chem. Scand*. **1963**, *17*, 1455.
14. Greene, R. N. *Tetrahedron Letters*, **1972**, *13*, 1793-1796.
15. Chan, L. L.; Wong, K. H.; Smid, J. *J. Am. Chem. Soc*, **1970**, *92*, 1955-1963.

16. Mandolini, L.; Masci, B. *J. Am. Chem. Soc*. **1977**, *99*, 7709-7710.

17. GoKel, G. W.; Korzeniowski, S. H. *Macrocyclic Polyether Syntheses* Springer Verlag: New York, 1982, p. 14.

18. Fenton, D. E.; Cook, D. H.; Nowell, I. W. *J. Chem. Soc., Chem. Commun*. **1977**, 274-275.

19. Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J.; Sen, D. *Chem. Rev*. **1985**, *85*, 271-339.

20. Schmidtchen, F. P.; Berger, M. *Chem. Rev*. **1997**, *97*, 1609-1646.

21. Vögtle, F.; Sieger, H.; Müller, W. M. *Top. Curr. Chem*. **1981**, *98*, 107-161.

22. Truter, M. R.; Pederson, C. J. *Endeavour*.**1971**, *30*, 142.

23. Lehn, J. M. *Structure and Bonding*. **1973**, *16*, 1.

24. Pedersen, C. J. *J. Amer. Chem. Soc*. **1967**, *89*, 2495-2496.

25. Trueblood, K. N.; Knobler, C. B.; Lawrence, D. S.; Stevens, R.V. *J. Am. Chem. Soc.* **1982**, *104*, 1355-1362.

26. (a) Colquhoun, H. M.; Jones, G.; Maud, J. M.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc*. **1984**, 63. (b) Alston, D. R.; Stoddart, J. F.; Wolsteholme, J. B.: Allwood, B. L.; Williams, D. J. *Tetrahedron,* **1985**, *41*, 2923-2926.

27. (a) Colquhoun, H. M.; Lewis, D. F.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc*. **1983**, 607. (b) Colquhoun, H. M.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int*. *Ed. Engl*. **1986**, *25*, 487-491.

28. Kyba, E. P.; Helgeson, R. C., Madan, K.; Gokel, G. W.; Tarnowski, T. L. Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc*. **1977**, *99*, 2564-2571.

29. Allwood, B. L.; Colquhoun, H. M.; Crosby, J.; Pears, D. A.; Stoddart, J. F.; Williams, D .J. *Angew. Chem., Int*. *Ed. Engl*. **1984**, *23*, 824-826.

30. Pedersen, C. J. *J. Org. Chem.* **1971**, 36, 1690-1693.

31. de Boer, J. A. A.; Reinhoudt, D. N.; Harakema, S.; Hummel, G. J.; de Jong, F. *J. Am. Chem. Soc*. **1982**, *104*, 4073-4076.

32. Shannon, R. D.; Trewitt, C. T. *Acta Crystallogr*, *Sect. B*, **1969**, *25*, 925-928.

33. (a) Christensen, J. J.; Eatough, D. J.; Izatt, R. M. *Chem. Rev*. **1974**, *74*, 351-384. (b) Newcome, G. R.; Sauer, J. M.; Roper, J. M.; Hager, D. D. *Chem. Rev*. **1977**, *77*, 513-597.

34. Hancock, R. D.; Martell, A. E. *Chem. Rev*. **1989**, *89*, 1875-1917.

35. (a) Cram. D. J.; Ho, S. P. *J. Am. Chem. Soc***. 1986**, *108*, 2998-3005. (b) Cram, D. J.; Lehn, G. M. *J. Am. Chem. Soc*. **1985**, *107*, 3657-3668.

36. Lehn, J. M. *Angew. Chem*., *Int. Ed. Engl*. **1988**, *27*, 89-112.

37. (a) Webb, T. H.; Wilcox, C. S. *Chem. Soc. Rev*. **1993**, *22*, 383-395. (b) Prelog, V.; Kovacevic, M; Egli, M, *Angew. Chem*., *Int. Ed. Engl*. **1989**, 28, 1147-1152. (c) Cram, J. M. *Science.***1974**, *183*, 803-809. (d) Cram, D. J. *Science.* **1988**, *240*, 760-767.

38. Kyba, E. P.; Siegel, M. G.; Sousa, L. R.; Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2691-2692.

39. (a) Jacques, J.; Fouquecy, C.; Viterbo, R. *Tetrahedron lett*. **1971**, *12*, 4617-4620. (b) Pirkle, W. H.; Schreiner, J. L. *J. Org. Chem*. **1981**, *46*, 4988-4991.

40. Girodeau, J. M.; Lehn, J. M.; Sauvage, J. P. *Angew. Chem*., *Int. Ed. Engl*. **1975**, *14*, 764-765.

41. Behr, J. P.; Girodeau, J. M.; Hayward, R. C.; Lehn, J. M.; Sauvage, J. P. *Helv. Chim. Acta*, **1980**, *63*, 2096-2111.

42. Kalinowski, H. O.; Seebach, D.; Crass, G. *Angew. Chem., Int. Ed. Engl*. **1975**, *14*, 762-764.

43. Andrews, D. G.; Ashton, P. R.; Laidler, D. A.; Stoddart, J. F.; Wolstenholme, J. B. *Tetrahedron Letters*, **1979**, *20*, 2629-2632.

44. Coxon, A. C.; Laidler, D. A.; Pettman, R. B.; Stoddart, J. F. *J. Am. Chem. Soc*. **1978**, *100*, 8260-8262.

45. Curtis, W. D.; Laidler, D. A.; Stoddart, J. F.; Jones, G. H. *J. Chem. Soc., Perkin Trans. I*, *1977*, 1756-1769.

46. Curtis, W. D.; Laidler, D. A.; Stoddart, J. F.; Jones, G. H. *J. Chem. Soc., Commun*, *1975*, 833-885.

47. Mack, M. P.; Hendrixon, R. R.; Palmer, R. A.; Chirardelli, R. G. *J. Am. Chem. Soc*. **1976**, *98*, 7830-7832.

48. Mack, M. P.; Hendrixon, R. R.; Palmer, R. A.; Chirardelli, R. G. *J. Org. Chem*. **1983**, *48*, 2029-2035.

49. Prelog, V. *Pure Appl. Chem*. **1978**, *50B*, 93-106.

50. Prelog, V.; Bedekovic, D. *Helv. Chim. Acta,* **1979**, *62*, 2285-2301.

51. Žinić, M.; Bosnić-Kasnar, B.; Kolbah, D. *Tetrahedron Lett*. **1980**, *21*, 1365-1368.

52. Peacock, S. C.; Domeier, L. A.; Gaeta, F. C. A.; Helgeson, R. C.; Timko, J. M.; Cram. D. J. *J. Am. Chem. Soc*. **1978**, *100*, 8190-8202.

53. Newcomb, M.; Toner, J. L.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc*. **1979**, *101*, 4941-4947.

54. (a) Brandstrom, A. *P. Org. Chem*. **1977**, *15*, 267-330. (b) Freedman, H. H. *Pure Appl. Chem*. **1986**, *58*, 857-868.

55. (a) Manual, A. L.; Mamual, M. L.; Soledad, P. *Tetrahedron Letters*. **1986**, *27*, 3551-3554. (b) Ebrahim, S.; Wills, M. *Tetrahedron: Asymmetry.* **1997**, *8*, 3163-3173.

56. Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc. Chem., Commun*. **1981**, 625-628.

57. Manual, A. L.; Barbero, J. J.; Mamual, M. L.; Soledad, P. *Tetrahedron*. **1988**, *44*, 1535-1543.

58. (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc*. **1989**, *111*, 2353-2355. (b) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron.* **1994**, *50*, 4507-4518.

59. (a) Sousa, L. R.; Sogah, G. D. Y.; Hoffman, D. H.; Cram, D. J. *J. Am. Chem. Soc*. **1978**, *100*, 4569-4576. (b) Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc*. **1979**, *101*, 3035-3042.

60. Shino, T; Yamaguchi, T; Nishimura, K; Sugiura, M. *J. Chromatogr*. **1987**, *405*, 145-153.

61. Lee, W; Hong, C. Y. *J. Chromatogr*. **2000**, *810*, 113-120.

62. Hyun, M. H.; Jin, J. S; Lee, W. *J. Chromatogr*. **1998**, *822*, 155-161.

63. Marchand, A. P.; Takhi, M.; Kumar, V. S.; Krishnudu, K.; Ganguly, B. *ARKIVOC* URL: http:// www.arkat-usa.org/ark/journal/Volume2/part3/Pihlaja/KP-159A/KP-159A.pdf, **2001**, 2 (iii), 13-21.

64. (a) Marchand, A. P.; Chong, H.-S.; Alihodžic, S.; Watson, W. H.; Bodige, S. G. *Tetrahedron.* **1999**, *55*, 9687-9696. (b) Marchand, A. P.; Chong, H.-S. *Tetrahedron.* **1999**, *55*, 9697-9706.

65. Carmack, M.; Kelley, C. J. *J. Org. Chem*. **1968**, *33*, 2171-2173.

66. Matteson, D. S.; Beedle, E. C.; Kandil, A. A. *J. Org. Chem.* **1987**, *52*, 5034-5036.

67. Toda, F; Tanaka, K. *Tetrahedron Lett*. **1988**, *29*, 551-554.

68. Watson, W. H.; Ejsmont, K. *Department of Chemistry, Texas Christian University*. ***In Press***

69. Watson, W.H.; Ejsmont, K. *Department of Chemistry, Texas Christian University*. ***In Press***

70. Marchand, A. P.; Chong, H.-S.; Ganguly, B. *Tetrahedron: Asymmetry* **1999**, *10,* 4695-4700.

71. Watson, W.H.; Ejsmont, K. *Department of Chemistry, Texas Christian University*. ***In Press***

72. Marchand, A. P.; Allen, R. W. *J. Org. Chem*. **1974**, 39, 1596.

73. (a) Kyba, E. P.; Timko, J. M.; Kaplan, L. J.; de Jong, F.; Gokel, G. W.; Cram, D. J. *J. Am. Chem. Soc.* **1978**, *100,* 4555-4568. (b) Horvath, V.; Takacs, T.; Horvai, G.; Huszthy, P.; Bradshaw, J. S.; Izatt, R. M. *Anal. Lett.* **1997**, *30*, 1591.

74. Tassou, C. C.; Drosinos, E. H.; Nychas, G. J. *J. Appl. Bacter*. **1995**, *78*, 593-600.

75. Dnistrian, A. M.; Schwartz, M. K.; Greenberg, E. J.; Smith, C. A.; Schwartz, D. C. *Int. J. Clin. Chem.* **1993**, *223*, 43-52.

76. O'Donnell, M. J. in *Catalytic Asymmetric Synthesis: Asymmetric Phase Transfer Reactions*, Ojima, I. Ed., VCH: Publishers, New York, *8*., 1993, p. 727-755.

77. László, T.; Péter, B.; György, M. K.; Melinda, A.; László, F. *Tetrahedron*, **1998**, *54*, 213-222.

78. Brunet, E.; Poveda, A. M.; Rabasco, D.; Oreja, E.; Font, L. M.; Batra, M. S.; Rodriges-Ubis, J. C. *Tetrahedron: Asymmetry*. **1994**, *5*, 935-948.