SYNTHESIS AND HOST-GUEST INTERACTION OF CAGE-ANNULATED PODANDS, CROWN ETHERS, CRYPTANDS, CAVITANDS AND NON-CAGE-ANNULATED CRYPTANDS

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Symmetrical cage-annulated podands were synthesized via highly efficient synthetic strategies. Mechanisms to account for the key reaction steps in the syntheses are proposed; the proposed mechanisms receive support from the intermediates that have been isolated and characterized.

An unusual complexation-promoted elimination reaction was studied, and a mechanism is proposed to account for the course of this reaction. This unusual elimination may generalized to other rigid systems and thus may extend our understanding of the role played by the host molecules in “cation-capture, anion-activation” via complexation with guest molecules. Thus, host-guest interaction serves not only to activate the anion but also may activate the leaving groups that participate in the complexation.

Complexation-promoted elimination provides a convenient method to desymmetrize the cage while avoiding protection/deprotection steps. In addition, it offers a convenient method to prepare a chiral cage spacer by introducing 10 chiral centers into the host system in a single synthetic step.

Cage-annulated monocyclic hosts that contain a cage-butylenoxy spacer were synthesized. Comparison of their metal ion complexation behavior as revealed by the results of electrospray ionization mass spectrometry (ESI-MS), alkali metal picrate extraction, and pseudohydroxide extraction with those displayed by the corresponding
hosts that contain cage-ethylenoxy or cage-propylenoxy spacers reveals the effect of the length of the cage spacer upon the host-guest behavior.

A series of cage-annulated cryptands, cavitands and the corresponding non-cage-annulated model compounds have been synthesized. These host molecules display unusual behavior when examined by using ESI-MS techniques, i.e., they bind selectively to smaller alkali metal ions (i.e., Li$^+$ and Na$^+$), a result that deviates significantly from expectations based solely upon consideration of the size-fit principle. It seems likely that this behavior results from the effect of the host topology on host-guest behavior.

A series of non-cage-annulated cryptands also have been synthesized. These compounds can serve as starting materials for cavitand construction.
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CHAPTER 1 INTRODUCTION

1.1 A brief review of the history of crown ether chemistry

Pedersen’s discovery \(^{[1]}\) in 1967 signified the beginning of a brand new area of chemistry: crown ether chemistry, when he reported 48 cyclic polyethers derived from aromatic vicinal diols and subsequent hydrogenation. It is unlikely that Pedersen would have been honored as one of the three Nobel laureates in 1987, if his contribution were limited only to the synthesis of those structures. Since the first cyclic polyether structure 12-crown-4 was synthesized 10 years before his discovery, \(^{[2]}\) Pedersen’s most important contributions were: (i) that he showed, for the first time, the strong complexing ability of those structures toward metal ions, including alkali, alkaline earth and transition metal ions, and (ii) that he was the first person who tried to reveal the relationship between structure and complexation property, as evidenced by his later work. \(^{[3, 4, 77]}\)

![Figure 1. Some of Pedersen’s cyclic polyethers \(^{[1]}\)](image-url)
Shortly after Pedersen’s discovery, J. M. Lehn\textsuperscript{[5]} demonstrated that oxygen atoms can be replaced with nitrogen atoms; consequently, the two-dimensional monocyclic structures can be developed into three-dimensional bi- and tricyclic structures. Such three-dimensional structures display much stronger complexation ability and higher selectivity toward metal ions.\textsuperscript{[5,6]} Lehn’s work greatly extended the scope of crown ether chemistry and promoted further understanding of the relationship between structure and complexation property.

![Molecules](image)

**Figure 2.** Lehn’s molecules\textsuperscript{[5, 6]}

Cram\textsuperscript{[7, 8, 9]} pioneered the study of chiral crown ethers by introducing chiral binaphthyl moiety into the cyclic polyether backbone. Cram and coworkers synthesized the first chiral crown ethers according to the following scheme\textsuperscript{[7]} (see Figure 3):

Binaphthyl units provide a steric chiral barrier within the structure and render the resulting crown ethers capable of enantiomeric discrimination. Cram’s work made it possible for the first time to direct crown ether chemistry into the areas such as asymmetric synthesis\textsuperscript{[10, 11, 12]} and enzyme-mimicking.\textsuperscript{[13, 14, 15, 16]}
Figure 3. Synthesis of the first chiral crown ethers [7]

Based on the pioneering work of Pedersen, Lehn and Cram, the study of crown ether chemistry has led to important advances in the area of molecular recognition, which led subsequently to the establishment of new concepts such as host-guest chemistry [17] and supramolecular chemistry. [18]

1.2 Conventions of classification and nomenclature of macrocyclic polyethers

Systematic nomenclature (IUPAC) proves to be inconvenient for the nomenclature of cyclic polyethers. Vögtle and Weber [19,20] suggested the following non-systematic conventions for classification and nomenclature:

**Coronand:** Any medium sized macrocyclic system bearing only one ring and containing any heteroatom(s) (see 18-crown-6 in Figure 1 and 1,10-diaza-18-crown-6 in Figure 2).

**Crown ether:** Coronands containing only oxygen heteroatom(s) (see Figure 1).
**Potand:** Acyclic analogs of coronands or crown ethers (see Figure 4).

**Cryptand:** Bi or polycyclic compounds containing any heteroatom(s) (see Figure 1).

**Cryptate:** A complexes formed between a cryptand and a substrate (see Figure 4).

**Coronate:** A complexes formed between a coronand and a substrate (see Figure 4).

![Diagram of a podand, a coronate, and a cryptate]

**Figure 4.** Examples of a podand, a coronate and a cryptate

Pedersen [1] suggested the nomenclature for simple crown ethers, which involves two numbers: the first number indicates the total number of atoms in the ring, and the second number specifies the number of heteroatoms in the ring. The term “crown” is inserted between these two numbers to constitute the full name. Common examples includes e.g., 18-crown–6 and 15-crown-5 (see Figure 1). The term “crown” was suggested because of the fact that the macrocycle “crowned” the cations just as “a regal crown adorns the monarch’s brow”. [1]

The term azacrown is a logical extension, which indicates that at least one nitrogen atom is present in the ring. In practice, the nomenclature of azacrown ethers is a hybrid of systematic and non-systematic nomenclature. The basic frame for crown ether is adopted, and the position(s) of nitrogen atom(s) is specified, e.g., 1, 10-diaza-18-crown-6 (see Figure 2).
Lehn suggested the use of cryptands and cryptates, because the bicyclic and tricyclic macrocycles encapsulate cationic guests inside their cavity. Lehn assumed that nitrogen atoms are located at the bridgehead positions in his structures. Different cryptands are named by specifying the number of heteroatoms (usually oxygen atoms) in the ethylenoxy links, e.g., [2.2.2]-cryptand and [2.2.1]-cryptand (see Figure 2).

The term lariat ether was introduced by Gokel and coworkers. This class of macrocycles is usually monocyclic and has one or more pendent arms with donor atoms. The name presumes that the complexed cation is bound by both the macrocyclic ring and by the sidearm(s) in much the same fashion as a lasso binds an animal. Indeed, lariat ethers bind cations in a three dimensional style similar to cryptands.

![Diagram](image)

**Figure 5.** Binding fashion of lariat ethers: A lariat ether binds a guest cation first with its macroring with fast kinetics. Subsequent participation of side arms renders the complex three-dimensional. (Modified from ref. [22b])

Biscrown (see Figure 6) was first reported by Wong and his colleagues. It has two macrocyclic rings in its structure and can be viewed as a special type of lariat ethers. It binds to cations very effectively in a manner which is intermediate between that of
lariat ethers and cylindrical cryptands. It should be noted that both lariat ethers and cryptands can be N-pivot (see Figure 2) and C-pivot (see Figure 6).

The term “Spherand” or “cavitand” describes a three-dimensional, closed-shell structure. This kind of structure has not been accorded a convenient nomenclature. The first example was synthesized by Graft and Lehn (see Cavitand I in Figure 2). Because of difficulties attendant with their synthesis, there is only very limited number of such compounds in literature. In this review, such structure will be named “cavitand” whenever applicable.

\[\text{The first Bis-crown}\]

\[\text{A C-pivot cryptand}\]

1.3 Host-Guest chemistry and templating

Host-Guest Chemistry is an important concept. Although this term, first introduced by Cram in 1974, originated from crown ether chemistry, it is now applied in a much broader sense. A host can be any molecule which complexes, encapsulates or otherwise binds to a substrate. A guest can be whatever has been thus bound on,
encapsulated, and can be cationic, anionic or neutral molecules. The interaction between a host and a guest can be electrostatic and can involve hydrogen bonding or charge transfer interaction (cation-π interaction, or π-π stacking). The most important information the term “Host-Guest Chemistry” conveys is the complementarity between the host and the guest.

\[
\text{Ar} = 1,4\text{-phenylene, 2,5-naphthalene, or 4,4'}\text{-biphenylene}
\]

**Figure 7. An example of a Host-Guest complex**

Templating is another important concept in crown ether chemistry. It was first implied in Pedersen’s first discovery and explicitly proposed by Green in 1972.

Before the development of crown ether chemistry, macrocycles usually were synthesized by applying high dilution methods. Green found that when the concentration of reactants increased significantly, the yield of crown ether dropped only slightly, which indicated that the yield of crown ether is not concentration dependent. When Bu₄NOH was used in place of t-BuOK, the yield dropped considerably and the
yield of polycondensation product increased significantly. Green noted that there must be a kind of “templating effect” exerted by metal ions. He suggested that this effect might actually involve organization of open-chained ligands by cations via cation-dipole interaction, although such interaction is weaker than that which occurs between cyclic polyethers and cations. Green’s concept of templating can be illustrated approximately as in Figure 8.

Figure 8. Templating

K⁺ cation organizes the open-chained ligands in a fashion that promotes the subsequent intramolecular S_N2 reaction, and consequently favors the ring formation.
In addition to electrostatic interactions, $^{[33,34]} \pi-\pi$ stacking $^{[35]}$ and hydrogen bonding $^{[36-38]}$ also may serve as a force for templating. Figure 9 shows a templating process via $\pi-\pi$ stacking. Anionic $^{[39]}$ and neutral $^{[35]}$ species have also found to function effectively as templates.

Intermolecular templating processes, as illustrated in Figure 8, are most commonly employed to prepare macrocycles. Intramolecular templating can also occur when the substrate is properly functionalized (see Figure 10).

**Figure 9.** Templating of a neutral molecule via $\pi-\pi$ stacking $^{[35]}$

The strongest demand for templating occurs in the synthesis of catenanes, $^{[40, 41]}$ knots $^{[42]}$ and rotaxanes, $^{[43, 44]}$ which constitute more complicated class of macrocycles. Here, the demand for templating is so keen that in many cases stable and isolable intermediate complexes between the ligands and templates must be formed. Figure 11 shows an example of a templated synthesis of catenane that employs Cu (I) as the template. The intermediate complex was stable and could be isolated. $^{[45]}$
In general, all interactions that lead to the organization of the substrate (mostly open-chained ligands) can result in templating. All species that provide or induce such interactions can function as the template. The templating process frequently reflects the host-guest relation so extensively that the templating sites are maintained or “memorized” in the template-synthesized molecules, especially in the imprinting of polymers.\[46\]

It should be noted that the concept of templating was already developed by Bush and colleagues\[47-51\] before the advent of crown ether chemistry. As later verified in crown ether chemistry, they found that both kinetic and thermodynamic templating effects exist. This finding is important, because both types of effects can be used to advantage and can be rendered cooperative by carefully selecting reaction conditions when synthesizing macrocycles.
Figure 11. Templated synthesis of catenane\textsuperscript{[45]}
1.4 Synthesis of macrocyclic polyethers

It is convenient to discuss the synthesis of macrocyclic polyethers immediately after templating is covered, because synthetic efficiency depends mainly on the efficiency of the template. As mentioned previously, the host-guest relation already manifests itself in templated synthesis. Such relation is determined by the relative sizes of the target macrocycles and the templating species, i.e. “size-fit”, which will be discussed later.

The “size-fit relation” determines whether a species is the most efficient template for a specific macrocycle. In addition, the basicity of the base employed to effect cyclization is another important factor. Bowsher and Rest found that the yield of 12-crown-4 increased when NaH or LiOH was replaced by LiH. The former case, of course, reflects size-fit relation, but the latter case reflects the effect of basicity and indicates that the use of stronger base results higher yield of the desired cyclization product. Cook and colleagues employed NaOH as the base and LiClO₄ as the source of templating cation for this purpose. It is known that in general Li⁺, Na⁺, K⁺ and Cs⁺ were found among alkali metal ions to be the best templates to form 12-, 15-, 18- and 21-membered rings, respectively. Sr²⁺, and Ba²⁺ are the best cationic templates to use when forming 18-membered rings.

Pedersen proposed four principal methods for the synthesis of crown ethers, which were called the “V”, “W”, “X” and “Y” methods, respectively. These have been summarized by Bradshaw et al. as methods a, b, c, d and e in Figure 12. Method e is an extension of Pedersen’s method Y.
Figure 12. Synthetic methods for preparing crown ethers \[56\]

Dietrich \[57\] summarized fifteen possible cyclocondensation mechanisms that can be used to prepare cryptands, all of which have been realized in practice under different conditions. The various mechanisms are listed in Figure 13.

It should be noted that most of the mechanisms have been employed by using templated processes. Tripod coupling (mechanism C) and tripod capping (mechanism D) usually proceed with very low yield. \[58-60\] Franke and Vögtle \[58\] reported an astonishingly high yield (79%) of cryptand by using tripod coupling between a tosylamide salt and a mesylate. It was believed that the high yield resulted from the fact that the bulky tosyl
group retarded the intermolecular reaction. The intermediates in tripod capping are usually imines (i.e. Schiff base); subsequent reduction leads to the saturated cryptands.

![Figure 13. Schematic representations of possible cyclocondensation mechanisms](image)

Templating frequently is not necessary, because of the reduced flexibility of the imine (C=N) bonds. Based on this approach, tetrapod capping was employed successfully to make cryptands, as illustrated in Figure 14.
Intramolecular templating was used successfully by Annunziata, et.al \cite{62} in the synthesis of cryptands. A good example is illustrated in Figure 15. Compared to intermolecular-templated cyclization, intramolecular-templated synthesis requires a much higher degree of sophistication in molecular design.
Methods used to prepare azacrown ethers and lariat ethers are frequently a hybrid of those used for crown ether and cryptand synthesis, and will not be discussed here.

Okahara’s synthesis \cite{63, 64} of macrocyclic polyethers, shown in Figure 16 is a special synthetic method that often proves impractical, because intramolecular cyclization with a bifunctional starting material usually gives poor yield and the required starting material is not easily available. \cite{1} However, if designed carefully, this approach can afford the desired product in high yield. Okahara and his colleagues \cite{63} cleverly combine high dilution with templating effect; their method takes advantage of intramolecular cyclization over intermolecular cyclization. In this cases, \cite{64} high yields were obtained for 15-crown-5 (82%), 18-crown-6 (98%) and 21-crown-7 (80%) by slowly adding p-toluenesulfonyl chloride and the polyethylene glycol together in dioxane or diglyme solution into a suspension of powdered NaOH or KOH.
Figure 16. Okahara’s synthesis \[63\]

Okahara and coworkers \[65-67\] also extended this method to the synthesis of azacrown ethers by taking advantage of the difference of oxa (RO⁻) anion and neutral amine in nucleophilicity. They cleverly selected \(t\)-BuOK or \(t\)-BuONa as the base and thereby successfully avoided the extra steps that otherwise would be required to protect and deprotect the amino groups.

1.5 Structure and property relation in host-guest chemistry

In the early stage of crown ether chemistry, Pedersen \[1\] showed that crown ethers have stronger complexing ability and higher selectivity than the open-chained podand analogs. Subsequently, Lehn \[5\] showed that the three-dimensional cryptands are even stronger complexing agent and more specific than crown ethers. This kind of phenomena is called the “macrocyclic effect” and the “macrobicyclic effect”, respectively. \[68a-68c\]

These cyclization effects originate from the difference in structure among podands, crown ethers and cryptands, all of which possess different structural topologies. The topology, along with ring size determines the degree of preorganization of a specific structure for complexation.
1.5.1 Effect of Ligand topology and preorganization

Lehn \cite{69} classified polyether ligands into seven topologies, as in Figure 17.

![Figure 17. Ligand topology \cite{69}](image)

A: Acyclic podands
B: Macrocyclic crown ethers or azacrown ethers
C: Lariat ethers
D: Cryptands
E: Biscrowns
F: Spherands
G: Cylindrical polyethers
Among A to G, the structures of the various polyethers undergo important changes. The general trend is that the two-dimensional structure develops into a three-dimensional structure, wherein, for similar ring-size, the rigidity of the molecule increases. For example, rigidity increases along the series 18-crown-6, [2.2.2]-cryptand, cavitand I (see Figure 2). Increasing rigidity in this way restricts the ability of the ligand to undergo conformational reorganization. Thus more rigid ligands are more highly “preorganized”. Since the host must undergo conformational adjustment to provide a proper binding environment during the host-guest interaction, such an adjustment must be accompanied with concomitant expense of energy. Thus, preorganization of a ligand, which is associated with its topology, rigidity and solvation, becomes important. For a specific guest, the more highly preorganized ligand requires less conformational change and thus pays minimal energy cost for conformational adjustment.

Conformational adjustment includes two aspects: (i) desolvation and (ii) rearrangement of the atoms (including donor atoms) in the molecular backbone. Since the host-guest interaction is reciprocal, the preorganization of the guest, is also important. The guest also undergoes conformational adjustment \cite{17, 70} to complement the binding environment of the host. The effect of topology, preorganization and other factors such as solvation upon complexation and selectivity has been generalized as “preorganization principle” \cite{17, 70, 72} and “complementarity principle” \cite{72}.

The principle of preorganization \cite{72} states: “The more highly hosts and guests are organized for binding and low solvation prior to complexation, the more stable will be the complexes. Both host and guest participate in solvent interaction, so that
preorganization includes both enthalpic and entropic components.”. The principle of complementarity states “To complex, hosts must have binding sites that can simultaneously contact and attract the binding sites of guests without generating internal strains or nonbonded repulsions. This is the determinant of structural recognition.”.

Preorganization not only reduces the energy cost for conformational adjustment during complexation, but also arranges the donor atoms in closer mutual proximity. This in turn results in strong dipole-dipole interactions and steric resistance to solvation and thus elevates the overall energy of the system. Binding cations can effectively reduce the dipole-dipole repulsion inside the host molecule. Reduction in the degree of solvation results in a decreased energetic cost for desolvation. These two factors combine to further enhance the binding ability of preorganized host molecules.

The effect of topology and preorganization on host-guest interaction can be exemplified by the different binding kinetics and thermodynamics of crown ethers and cryptands. A good example presented by Gokel and coworkers, appears in Figure 18.

\[
\text{Host} + K^+ \xrightleftharpoons[k_D]{k_C} \text{Complex}
\]

- \(k_C\): Rate of complexation
- \(k_D\): Rate of decomposition
- \(K_S = k_C / k_D\): Stability constant of complex

**Figure 18. Kinetics and thermodynamics of complexation**

In aqueous solution, the \(k_C\), \(k_D\) and \(K_S\) values of 18-crown-6 and [2.2.2]-cryptand are listed in table 1.
Table 1. $k_C$, $k_D$ and $K_S$ values of 18-crown-6 and [2.2.2]-cryptand (73)

<table>
<thead>
<tr>
<th>Host</th>
<th>$k_C$ (M$^{-1}$s$^{-1}$)</th>
<th>$k_D$ (s$^{-1}$)</th>
<th>$K_S$ (M$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-crown-6</td>
<td>4.3 x 10$^8$</td>
<td>3.7 x 10$^6$</td>
<td>115</td>
</tr>
<tr>
<td>[2.2.2]-cryptand</td>
<td>7.5 x 10$^6$</td>
<td>38</td>
<td>2.0 x 10$^5$</td>
</tr>
</tbody>
</table>

Due to more flexibility, 18-crown-6 can easily adjust its conformation to bind potassium cation at much higher rate than does [2.2.2]-cryptand. However, due to its increased preorganization, [2.2.2]-cryptand “releases” its guest with greater difficulty than does 18-crown-6. The net result is that 18-crown-6 binds to potassium cation with faster kinetics and the resulting complex is thermodynamically less stable. By way of contrast, [2.2.2]-cryptand binds to potassium cation with slower kinetics, but the resulting complex is thermodynamically more stable.

Variations between kinetics and thermodynamics in binding has significant impact upon membrane transport, where rapid binding and reasonable stability is required in the source phase, and a rapid rate of release is required in the receiving phase. To transport properly, a carrier (host) must have a structure that can meet these required kinetic and thermodynamic criteria.

This consideration led to the design of lariat ethers in the late 1970s. (22) Lariat ethers bind cations faster with the macroring than do cryptands in the source phase. In addition, with the participation of the side arms, lariat ethers form more stable complex than do crown ethers in the source phase, but release cations faster than do cryptands in
the receiving phase because of the higher degree of flexibility associated with their topology (see Figure 5).

It should be noted that preorganization of a host is only meaningful with regard to a specific guest. A well-preorganized host doesn’t necessarily bind to all guests most strongly than a less-preorganized host, but it must bind to a certain guest most strongly. In this sense, preorganization is an ideal limit that is pursued when designing new hosts. Preorganization reflects and emphasizes selectivity, as revealed by strong complexation.

1.5.2 Size-fit and preorganization

Size-fit was first implied in Pedersen’s first discovery, \cite{1} and was explicitly proposed by him. \cite{74} The size-fit principle states that a host binds a guest most strongly if the diameter of the guest is close to, but no larger than, the ring or cavity size of the host. The most extensively studied examples are 15-crown-5 and 18-crown-6, which bind selectively to Na$^+$ and K$^+$ cation, respectively. The diameter of some cations and ring size of some hosts are listed in table 2 and table 3 respectively. As expected with size-fit principle, 15-crown-5, 18-crown-6, are most specific for Na$^+$ and K$^+$, respectively. [2.1.1]-cryptand, [2.2.1]-cryptand and [2.2.2]-cryptand bind Li$^+$, Na$^+$ and K$^+$ most strongly, respectively.

Size-fit is an empirical rule and is used as a rule-of-thumb. It is more applicable to cryptands than to crown ethers (see Tables 2, 3 and 4), and works well with alkali and alkaline earth metal cations. However, size-fit does not appear to play a comparably important role in binding to transition metal ions \cite{77a} and to lanthanides and actinides cations. \cite{78a, 78b} Other factors e.g., solvation, has strong impact on its applicability. For
example, although in many solvent systems 15-crown-5 binds most strongly to Na\(^+\) cation (see Table 5),\(^ {79}\) it binds most strongly to K\(^+\) in methanol solution (Figure 19).\(^ {80}\)

Table 2. IA and IIA metal cation diameters\(^ {1}\)

<table>
<thead>
<tr>
<th>Group I</th>
<th>Ionic diameter (Å)</th>
<th>Group II</th>
<th>Ionic diameter (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li(^+)</td>
<td>1.20</td>
<td>Mg(^{2+})</td>
<td>1.3</td>
</tr>
<tr>
<td>Na(^+)</td>
<td>1.90</td>
<td>Ca(^{2+})</td>
<td>1.98</td>
</tr>
<tr>
<td>K(^+)</td>
<td>2.66</td>
<td>Sr(^{2+})</td>
<td>2.26</td>
</tr>
<tr>
<td>Rb(^+)</td>
<td>2.96</td>
<td>Ba(^{2+})</td>
<td>2.70</td>
</tr>
<tr>
<td>Cs(^+)</td>
<td>3.34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3环尺寸的一些宿主

<table>
<thead>
<tr>
<th>Crown ethers</th>
<th>Cavity diameter(^ {75}) (Å)</th>
<th>Cryptands</th>
<th>Cavity diameter(^ {75}) (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-crown-4</td>
<td>1.2-1.5 [1.1.1]</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>15-crown-5</td>
<td>1.7-2.2 [2.1.1]</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>18-crown-6</td>
<td>2.6-3.2 [2.2.1]</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>21-crown-7</td>
<td>3.4-4.3 [2.2.2]</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[3.3.2]</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[3.3.3]</td>
<td>4.8</td>
<td></td>
</tr>
</tbody>
</table>
Table 4.  Size-fit in cation binding with cryptands as revealed by log K
(Modified from ref. [76])

<table>
<thead>
<tr>
<th>Cryptand</th>
<th>log K</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Li⁺</td>
</tr>
<tr>
<td>[1.1.1]</td>
<td>2.2</td>
</tr>
<tr>
<td>[2.1.1]</td>
<td>5.5</td>
</tr>
<tr>
<td>[2.2.1]</td>
<td>2.5</td>
</tr>
<tr>
<td>[2.2.2]</td>
<td>&lt;2</td>
</tr>
<tr>
<td>[3.2.2]</td>
<td>&lt;2</td>
</tr>
<tr>
<td>[3.3.2]</td>
<td>&lt;2</td>
</tr>
</tbody>
</table>

As a consequence of size-fit, large ring-size macrocycles often display “plateau effect” in cation binding,\(^{[52, 81-83]}\) whereby they are unable to differentiate among large cations e.g., K⁺, Rb⁺ and Cs⁺, but still able to discriminate against smaller cations, e.g., Li⁺ and Na⁺. On the other hand, small-ring size macrocycles behave as required by the preorganization principle and size-fit principle by displaying “peak selectivity”, as illustrated in Figure 20.\(^{[69, 84]}\)

The “Plateau Effect” can be understood in terms of preorganization. Larger macrocycles are less highly preorganized, and they have to undergo higher degree of conformational adjustment in order to provide a suitable binding environment, with concomitant expenditure of energy. Thus, the overall binding process becomes increasingly dependent upon the structure of the host and much less dependent upon the
guest. Consequently, the binding process fails to discriminate among the various guests; hence, larger macrocycles fails to display high binding selectivity toward larger cations. The difference in size between large macrocycles and small cations is too great; hence, the required conformational adjustment encounters a correspondingly high-energy barrier, thereby rendering large macrocycles still capable of differentiating among small cationic guests.

Table 5  Extraction equilibrium constants of 15-crown-5 with Na⁺ and K⁺  
(Modified from ref. [79])

<table>
<thead>
<tr>
<th>Solvent</th>
<th>log K Na⁺</th>
<th>log K K⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>dichloromethane</td>
<td>4.99±0.02</td>
<td>4.09±0.03</td>
</tr>
<tr>
<td>1, 2-dichloroethane</td>
<td>4.82±0.03</td>
<td>4.33±0.01</td>
</tr>
<tr>
<td>chlorobutane</td>
<td>5.09±0.01</td>
<td>3.46±0.03</td>
</tr>
<tr>
<td>benzene</td>
<td>5.05±0.01</td>
<td>2.96±0.03</td>
</tr>
<tr>
<td>toluene</td>
<td>5.14±0.01</td>
<td>2.99±0.04</td>
</tr>
<tr>
<td>m-xylene</td>
<td>5.18±0.03</td>
<td>2.89±0.02</td>
</tr>
<tr>
<td>chlorobenzene</td>
<td>5.63±0.01</td>
<td>3.84±0.03</td>
</tr>
<tr>
<td>bromobenzene</td>
<td>5.42±0.01</td>
<td>3.49±0.01</td>
</tr>
<tr>
<td>o-dichlorobenzene</td>
<td>5.45±0.01</td>
<td>4.36±0.04</td>
</tr>
<tr>
<td>chloroform</td>
<td>4.09±0.01</td>
<td>3.69±0.01</td>
</tr>
</tbody>
</table>
Figure 19. Solvent dependency of selectivity $^[80]$.

Figure 20. Peak selectivity $^[69]$.
In order to be useful, size-fit principle, just as the preorganization principle, must be used in a strict context. “Size-fit” refers to a situation where the host and guest interact with 1:1 stoichiometry. A size mismatch between a host and a guest does not necessarily mean that they fail to interact or that they don’t interact strongly. A small host may interact with a large guest with 2:1 stoichiometry, and this interaction may be quite strong. In fact, even a small podand can interact with guests that are far too large to “enclose” in 1:1 fashion. However, a small podand can interact with large guest in 3:1 fashion to form very stable complexes, which are termed as “open cryptands”.\[77b\]

1.5.3 Effect of substituent and lipophilicity

The effect of substituents was first observed by Pedersen.\[1\] Subsequently, many different moieties have been introduced into the macrocyclic backbone to modify the properties of the hosts, e.g., to increase rigidity and lipophilicity,\[85-100\] to introduce heteroatoms other than oxygen,\[101-105\] and to introduce chirality into the system.\[7-9\] The most common such moieties that frequently are introduced into the host backbone are various phenylene,\[99, 98\] pyridyl,\[101\] bipyridyl,\[102, 105\] phenanthryl,\[103\] biphenanthryl and binaphthyl,\[7-9, 104\] cage,\[85-88\] adamentanyl,\[85,86, 90\] and cubyl\[89\]. The effect of increased rigidity introduced by the incorporated moiety can be interpreted in terms of preorganization, as discussed previously. Introduction of chirality by incorporation of chiral moieties and the effect of donor atoms will be discussed later.

Lipophilicity affects host-guest behavior in several ways. In liquid-liquid extraction and liquid membrane transport, lipophilicity facilitates transport of the host-
guest complex from aqueous into organic phase due to the enhanced solubility of the complex in organic solvent. \[91, 92, 96\] In lipid membrane transport, the transport process is facilitated by the enhanced compatibility of the host-guest complex with the lipophilic membrane. \[108\] In addition to solubility or compatibility considerations, the lipophilic substituent shields the binding sites inside the host from external solvent attack. \[109\]

Lipophilicity affects selectivity significantly. This effect was demonstrated by Morf and Simmon \[110\] by comparing the selectivity of [2.2.2]-cryptand with two of its analogs that were rendered more lipophilic via incorporation of a benzene ring as illustrated in Figure 21. Morf and Simon \[110\] obtained the selectivity values of \(\text{Ba}^{2+}/\text{K}^+\), as listed in Table 6.

![Figure 21. Benzo-substituted analogs of [2.2.2]-cryptand](image)

<table>
<thead>
<tr>
<th>Hosts</th>
<th>[2.2.2]-crypt.</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{Ba}^{2+}/\text{K}^+)</td>
<td>260</td>
<td>60</td>
<td>1</td>
</tr>
</tbody>
</table>
The selectivity of $\text{Ba}^{2+}$ vs. $\text{K}^+$ decreases dramatically with increasing lipophilicity, although other factors such as the nature of donor atoms, ring-size and rigidity should also be considered.

1.5.4 Effect of donor atoms

Many donor atoms other than oxygen atoms have been introduced into the macrocyclic backbones; these donor atoms include nitrogen, sulfur, and selenium atoms. Heteroatoms affect host-guest interaction by influencing the preorganization of the macrocycles through their basicity, polarity, polarizability and size. For example, different donor atoms have different effect on the dipole-dipole repulsion and solvation properties of the macrocycles. Enhanced donor basicity is one of the factors responsible for the “macrocyclic effect”. However, interpretation of the effect of donor atom is not straightforward, because all the properties of donor atoms mentioned above must be considered, and those of the guest cations should also be taken into consideration.

In practice, the donor effect has been interpreted in terms of hard and soft acid and base (HSAB) theory. The softness of donor atoms decrease in the order of $\text{S} > \text{N} > \text{O}$; thus, sulfur in general is the best donor for transition metal ions, which usually are soft Lewis acids; oxygen is a hard Lewis base and is the best donor for alkali and alkaline earth metal ions, which are hard Lewis acids. Depending upon the structure of the host and the property of the guest, nitrogen can function as donor for both hard and soft metal ions.
In addition to its softness, sulfur is larger than nitrogen and oxygen and introduces stronger dipole-dipole repulsion into the system, thereby introducing stronger intramolecular strain \(^{[120a]}\) due to its larger size that reduces the dipole-dipole distance. Thus, in sulfur-containing macrocycles, the sulfur atoms turn to orient their lone electron pairs away from the center of the ring; \(^{[120b]}\) hence, compared to oxygen-containing macrocycles, sulfur-containing macrocycles requires additional energy for conformational adjustment during complexation. Unless the energy gain from complexation is sufficient to compensate for the energetic cost for conformational adjustment, sulfur-containing macrocycles usually do not form inclusion complex with alkali and alkaline earth metal ions, where the metal-sulfur interaction is weak due to the mismatch between hard acid and soft base. \(^{[119]}\) However, sulfur-containing macrocycles really form inclusion complexes with transition metal ions, where the strong metal–sulfur interaction can provide sufficient energy to compensate for the conformational adjustment. \(^{[120c]}\)

It is well established that phenolic oxygen atoms are less basic than alkoxy oxygen atoms, and thus are less effective as donors for complexation of alkali and alkaline earth metal cations. \(^{[1]}\) This accounts for the fact that introduction of rigid aryl moiety may not enhance the extent of host-guest interaction when a phenolic donor is introduced, despite the fact that the rigidity of the system is increased. \(^{[118]}\)

1.5.5 Effect of guest cation
As mentioned earlier, the size-fit principle works well with alkali and alkaline earth metal ions, but generally fails with transition metal ions, especially lanthanides and actinides. Alkali and alkaline earth metal ions contain no available d-orbitals and possess a simple spherical geometry that is easily accommodated by the host. However, most transition metal ions have unfilled d-orbitals; lanthanides and actinides even have unfilled f-orbitals. Both crystal field and ligand field theories dictate that these available d- or f-orbitals impose additional geometric requirements for complexation. Consequently, the importance of the role played by size-fit in determining the type and extent of host-guest interaction is reduced unless the geometric preference of metal ion is met.\(^{[121]}\)

The required coordination number of cationic guest also plays an important role in host-guest interactions.\(^{[110, 122, 123]}\) The preferred coordination number of some metal ions is listed in Table 7.

Coxon and colleagues\(^{[124]}\) presented an example showing the importance of coordination number in which the selectivity of \(\text{Ba}^{2+} / \text{K}^+\) with [2.2.2]-cryptand was compared against [2.2.C8]-cryptand (see Figure 22). The selectivity is exactly reversed when proceeding from [2.2.2]-cryptand to [2.2.C8]-cryptand; hence, Coxon et al. argued that the latter cryptand lacks sufficient donor atoms to saturate the preferred coordination number (8) of \(\text{Ba}^{2+}\). However, in this case, the two metal ions have different valence states; other factors, e.g., solvation, may also be important.

Dillon and coworkers\(^{[125]}\) studied the complexation properties of [2.2.2]-cryptands and [2.2.1]-cryptand \textit{vis-à-vis} their analogs [2.2.C8]-cryptand and [2.2.C5]-cryptand (see
Figure 22) with divalent metal cations. Their results indicated clearly that under the condition of approximate size-fit, [2.2.2]-cryptand and [2.2.1]-cryptand almost always display higher complexation ability. It should be noted that the regular cryptands and their analogs differ not only in the number of donor atoms, but also differ in other aspects due to differing degrees of dipole-dipole repulsion and degrees of solvation. These examples will be further analyzed when the effect of symmetry is discussed later.

Table 7. Coordination (hydration) numbers of IA and IIA metal ions [76]

<table>
<thead>
<tr>
<th>Cation</th>
<th>Li⁺</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Rb⁺</th>
<th>Cs⁺</th>
<th>Be²⁺</th>
<th>Mg²⁺</th>
<th>Ca²⁺</th>
<th>Sr²⁺</th>
<th>Ba²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

Solvation of the guest cations strongly affects the extent of host-guest interaction. Bushmann and coworkers [126] presented a good example in this respect. They studied the
complexation behavior of 18-crown-6 and [2.2.2]-cryptand in systems of varying water-chloroform ratios and found a strong dependence of complexation upon cation solvation. As already mentioned earlier, the effect of solvation is so strong that size-fit principle generally fails with lanthanides and actinides. \cite{78a, 78b}

1.5.6 Chiral macrocycles

Incorporation of chirality can be viewed as a special substituent effect from a synthetic point of view. Cram’s \cite{7} pioneering work triggered subsequent extensive study of chiral macrocycles. The principal method used to introduce chirality into macrocyclic system involves the incorporation of chiral moieties. These chiral moieties include biaryl (especially 1,1’-binaphthyl), \cite{7, 102-104, 127} monosaccharide derivatives, \cite{128-131} and tartaric acid-derived moieties. \cite{132, 133, 134} Some examples are presented in Figure 23 and Figure 24.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{chiral_crown_ether.png}
\caption{Chiral crown ethers derived from tartaric acid} \cite{133, 134}
\end{figure}
Chiral macrocycles have been used for recognition of chiral molecules, especially chiral ammonium salts. The source of enantiomeric discrimination is not straightforward. In general, in the three-point binding mode, the bulky groups of the host and guest will try to keep far away from each other (see Figure 25-1). In the complex \((15)\) formed between the host \((R, R)-5\) and \((S)\)-methyl phenylglycinate hydrochloride, examination of CPK molecular models predicts that the bulky groups of the guest salt all are able to keep away from the bulky phenyl groups of the host, and the resulting complex is relatively stable. In the complex \((16)\) formed between the same host and the \((R)\)-methyl phenylglycinate hydrochloride, not all the bulky groups of the guest salt can avoid the bulky phenyl groups of the host and the resulting complex is destabilized. Consequently, \((R, R)-5\) should recognize \((S)\)-methyl phenylglycinate hydrochloride selectively in presence of its enantiomer, \((R)\)-methyl phenylglycinate hydrochloride. This prediction has been verified experimentally. However, the existence of other interactions, e.g., \(\pi-\pi\) stacking precludes the use of this simple analysis.
On the other hand, the mechanism of enantiomeric discrimination may not be the same in solution as in the solid state. Such a situation is depicted in Figure 25-2. In the solid state, π-π stacking participates in the discrimination process, whereas in solution, solvation effect precludes π-π stacking.

![Figure 25-1. A chiral crown ether and its mechanism of chiral recognition](image)
1.6 Specially functionalized macrocycles and controlled binding

Specially functionalized macrocycles have been prepared which are ionizable (pH-switchable), photo-switchable, redox-switchable and thermally-switchable macrocycles. The functional group that is responsible for the special function of the macrocycle can be situated either in the macrocyclic backbone or in an attached sidearm. Two examples are illustrated in Figure 26 and Figure 27.

The inclusion of such special functionalities allow for controlled binding. The presence of a proton-ionizable group allows for pH control of binding. Proton-ionizable macrocycles advantageously minimize the dependence upon the counterion in liquid-liquid extraction and membrane transport while still maintaining the desired selectivity. Photo-switchable and redox-switchable macrocycles bear photo- or redox-sensitive groups, respectively. Their binding properties can be controlled via application of photo-irradiation or by an electrochemical mechanism. Figure 28 and 29 depict a photo controlled transport and a combined photo-, redox-, pH-, and thermally-controlled transport mechanism, respectively.
Figure 26. An ionizable crown ether \cite{141}

Figure 27. A Photo-switchable biscrown ether \cite{142}
**Figure 28.** A Photo controlled transport\(^{[142]}\)

**Figure 29.** A controlled transport with combined mechanism\(^{[145]}\)
1.7 Application of macrocycle

Crown ethers and other macrocycles found their practical values shortly after their invention.\cite{146, 147} So far, they have been widely employed in isotope separation,\cite{148} organic synthesis,\cite{149} biological reaction,\cite{150} environmental analysis,\cite{151} pharmaceutical industry,\cite{152} membrane transport,\cite{91, 92, 107, 108} and ion-selective electrodes.\cite{153} Additional applications of macrocycles include surfactants,\cite{154} antibiotic receptors,\cite{156} sensors,\cite{155} enzyme models,\cite{157} and catalysts.\cite{158} These applications are basically based upon the ability of macrocycles to capture cations and to activate anions with consequent enhancement of the basicity or nucleophilicity of the anion.\cite{159} The most important and practical current application of macrocyclic polyethers has been catalysis. In heterogeneous phase transfer catalysis, hydrophilic substrates are transported into organic phase (see Figure 30). In homogeneous catalysis, macrocycles enhance the solubility of the reactants in a given solvent system.\cite{160}

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {K$^+$ (crown) X$^-$ + R-Y \rightarrow R-Y \rightarrow K^+ (crown) Y$^-$};
  \node at (0,0) [circle, draw, thick, fill=white] {K$^+$ X$^-$ K$^+$ Y$^-$};
  \node at (0,0) [circle, draw, thick, fill=white] {Solid phase};

  \node at (-3,-2) {+ crown};
  \node at (3,-2) {- crown};

  \node at (-3,-3) {Organic phase};
\end{tikzpicture}
\end{center}

**Figure 30.** Solid-Liquid phase transfer catalysis with crown ethers \cite{161}
Chiral crown ethers catalyze asymmetric synthesis through substrate recognition and control of product stereochemistry. An example is shown in Figure 31.

\[
\begin{align*}
\text{Ph} & \quad \text{OMe} \\
\text{O} & \quad + \\
\text{OMe} & \quad \text{Ph} \\
\text{O} & \quad \text{O} \\
\text{KOBu}^+ & \quad \text{Chiral crown, Toluene, -70°C} \\
\text{OMe} & \quad \text{OMe} \\
\text{H} & \quad \text{OMe}
\end{align*}
\]

\text{Chiral crown} =

\begin{enumerate}
\item \textbf{Figure 31. Control of stereochemistry with chiral crown ethers} \cite{162}
\end{enumerate}

Macrocycles can be immobilized onto organic polymer backbone \cite{163} or onto silica \cite{164}. The resulting polymer-bound macrocycles can perform almost all of the functions of monomeric macrocycles, such as phase transfer catalysis, \cite{165} membrane transport, \cite{166} organic synthesis, \cite{167} and sensor-related application. \cite{168} The use of polymer-bound macrocycles facilitates recycling in extraction or catalysis and prevents macrocycles from being removed from the membrane during membrane transport. In particular, polymer-bound macrocycles have been employed successfully as the stationary phase in column chromatography for ion separation, \cite{169} and for chiral resolution. \cite{164, 170}
Combination of polymer chemistry with host-guest chemistry has led to the emergence of “imprinted polymer”, which involves a sophisticated application of supramolecular chemistry. First the monomer (usually non-cyclic) is complexed (or organized) with a specific cation (template). Subsequent polymerization (crosslinking) leads to the polymer that reserves or “memorizes” the cavity. The resulting polymer is then used to bind selectively to the cation, which serves as the template during the synthesis.\textsuperscript{[46]} This sequence of events is illustrated diagrammatically in Figure 32.

**Figure 32.** Representation of the imprinting of specific cavities in a cross-linked polymer by a template (T) with three different binding groups\textsuperscript{[46]}

1.8 Cryptands and cavitands
Cryptands and cavitands are the major part of my work. It is necessary and reasonable to “highlight” them in a separate section. Since principles that governs cation binding, e.g., preorganization principle, complementarity principle and size-fit principle, also apply, in fact, more suitably apply to cryptands and cavitands, cation binding with cryptands and cavitands will not be repeated except the shielding effect and symmetry effect which are also originated from the topology and preorganization of macrocycles. Concentration will be on anion recognition with cavitands and, especially cryptands.

1.8.1 Shielding and symmetry effect in cation binding.

The topology of cryptands and cavitands distinguish them from their monocyclic analogs. They encapsulate the guest in their three-dimensional cavity to form inclusion complex. The encapsulated species is shielded from external solvent attack, which confers additional stability to the complex. Cryptands even form complexes with lanthanides that display high kinetic stability in water, despite the fact that lanthanide and actinide complexes usually decompose in water. As a consequence of encapsulation, cation binding with cryptands and cavitands is less dependent on the counterion than are their monocyclic analogs. Such extremely strong shielding effects are best exemplified by the formation of alkalides, as shown in Figure 33. Encapsulation by [2.2.2]-cryptand effectively shields the sodium cation from interaction with sodium counter-anion. Cavitand I (Figure 2) forms the most stable Cs+ complex. The complex of Cavitand I with NH4+ is about 105 times more stable than the complex formed between 18-crown-6 and NH4+. 

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Symmetry is another important factor that influences binding in host-guest complexation. The effect of symmetry upon the binding properties of monocyclic polyethers is relatively unimportant, because monocyclic polyethers are much more flexible than cryptands and cavitands and can readily adjust their conformations during complexation. However, due to the higher degree of rigidity and preorganization present in cryptands and cavitands, symmetry becomes a significant factor in cation binding.

Previously (see Figure 22) the difference in binding ability between regular cryptands and their less structured analogs was interpreted by using available coordination numbers. But recently Izatt and colleagues\(^\text{\textsuperscript{177}}\) showed that symmetry plays an important role in determining the overall binding ability of cryptands. High symmetry cryptands usually show better complexation and selectivity properties. Thus, [2.2.2]-cryptand selects K\(^+\) over Na\(^+\) (K\(\text{K}_{\text{K}}\) / K\(\text{Na}_{\text{Na}}\) = 346). Although [2.2.1]-cryptand selects Na\(^+\) over K\(^+\), the selectivity is low (K\(\text{Na}_{\text{Na}}\) / K\(\text{K}_{\text{K}}\) = 26), probably due to the lower symmetry of [2.2.1]-cryptand \textit{vis-à-vis} that of [2.2.2]-cryptand.

Lehn and coworkers\(^\text{\textsuperscript{176}}\) compared cavitand I with its analog (see Figure 34) in which only one oxygen is replaced by a CH\(_2\) group in one bridge. For all cations tested, cavitand I shows much stronger complexation ability and much higher selectivity, especially in case of NH\(_4\)\(^+\) cation. Cavitand I and its analog possess very similar cavity
size and, in particular, both of them interact with NH$_4^+$ cation through four tetrahedrally-disposed N-H-N bonding. In this case, there is no problem with coordination number. The probable factor which is responsible for the difference in binding property may be the symmetry, although the additional oxygen donor in Cavitand I should also be taken into consideration.

![Analog of cavitand I](image)

**Figure 34. Analog of cavitand I**

### 1.8.2 Anion binding with cryptands and cavitands

Anion binding is still in its infancy compared to cation binding. However the demand for reliable anion binding has been increasing with respect to biological, chemical, and environmental concerns.

On the other hand, anion binding is more challenging than cation binding. There are two basic reasons for this: First, anions are larger than the isoelectronic cations (Table 8), indicating that electrostatic interaction is less effective. Secondly, most anions are not
simply spherical, as illustrated in Figure 35. Therefore, effective anion binding requires more elegant host molecular design.

<table>
<thead>
<tr>
<th>Cation</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Rb⁺</th>
<th>Cs⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radius (Å)</td>
<td>1.16</td>
<td>1.52</td>
<td>1.66</td>
<td>1.81</td>
</tr>
<tr>
<td>Anion</td>
<td>F⁻</td>
<td>Cl⁻</td>
<td>Br⁻</td>
<td>I⁻</td>
</tr>
<tr>
<td>Radius (Å)</td>
<td>1.19</td>
<td>1.67</td>
<td>1.82</td>
<td>2.06</td>
</tr>
</tbody>
</table>

Other factors such as solvation, lipophilicity also influences anion binding. More lipophilic anions are generally bound more strongly to lipophilic host binding sites. The relative lipophilicities of some anions are given in Figure 36.

Cryptands and cavitands take two major forms in anion binding: i.e., protonated state (protonated cryptands) and cryptated state (cryptates). Principles that governs cation binding, e.g., preorganization, complementarity and size-fit, all contribute to anion binding. The common structural feature of cryptands that have been most extensively employed for anion recognition is that they contain one or two tris(2-aminoethyl) amine(tren) residues. To facilitate the following discussion, the structures of the most important types of cryptands are illustrated in Figure 37.
Figure 35. Geometry of anions (modified from ref. [183])

Figure 36. Relative lipophilicities of some anions [183]
Figure 37. Cryptands for anion binding
Each tren residue (see Figure 37) provides three secondary amino groups that can interact with anionic guest *via* either protonation or coordination or as hydrogen bonding sites. This structural feature of tren residue is particularly important for anion binding with cryptates, as will be discussed in more detail *vide infra*.

1.8.2.1 Anion binding with protonated cryptands and cavitands

One important property of cryptands and cavitands is that their binding ability can be switched in solution by adjusting the pH of the medium. In this way, cavitand I has been successfully employed for cation, neutral molecule and anion binding, as illustrated in Figure 38. Park and Simmons first used protonated cryptands for anion binding in 1968. They synthesized a few macrobicyclic ammonium cages to bind halide ions effectively.

![Diagram](image)

*Figure 38* Switch of binding property of cavitand I

\[ \begin{align*}
\text{Cl}^– & = \text{Cl}\text{–} \\
\end{align*} \]
Lehn and colleagues \[^{[185]}\] were the first to use protonated cavitands for anion recognition. The tetraprotonated cavitand I binds to spherical anions via a combination of hydrogen bonding and electrostatic interaction in a tetrahedral geometry. Cavitand I is highly selective toward binding with Cl\(^-\) (see Figure 38). Their later work \[^{[186, 187]}\] clearly demonstrated the importance of size-fit and geometrical complementarity in anion binding. The smaller, hexaprotonated L1 ([L1H\(_6\)]\(^6+\)) has nearly a spherical cavity; it binds effectively with spherical halides with highest selectivity toward fluoride (see Figure 39). The larger hexaprotonated L2 ([L2H\(_6\)]\(^6+\)) is ellipsoidal and binds effectively to azide (see Figure 39). Both complexes have been isolated and characterized by application of single crystal X-ray crystallographic methods. \[^{[186, 187]}\]

![Figure 39. Anion inclusion complexes [L1H6F\(^-\)]\(^5+\) \[^{[186]}\] and [L2H6N3\(^-\)]\(^5+\) \[^{[187]}\] ](image)

Nelson and coworkers \[^{[188]}\] further demonstrated the significance of size-fit and ligand-anion complementarity. Protonated L4 selectively encapsulates the large, octahedral SiF\(_6^{2-}\) anion in the presence of high concentration of smaller tetrahedral BF\(_4^-\) anion. This occurs because of the complementarity of hydrogen-bond donor and acceptor
dispositions in the former, as demonstrated by the X-Ray crystal structure of the 1:1 host-guest complex. In addition, protonated L4 encapsulates tetrahedral perchlorate, which is larger than tetrafluoroborate. Small anions fail to form 1:1 inclusion complexes with [L4H₆]⁶⁺ due to size-mismatch; however they do form 2:1 inclusion complexes, in which one host encapsulates two anions such as NO₃⁻. L5 differs slightly from L4 in structure, but this slight difference renders L5 quite different from L4 toward anion binding, especially in cryptated state as will be discussed later.

1.8.2.2 Anion binding with cryptates

As mentioned earlier, the tren residue in the cryptand structure plays an important role in rendering the cryptands capable of anion recognition. Such a role becomes more important when the cryptates are employed to conduct anion recognition. The tren residue imposes a trigonal bipyrimidal geometry; the metal ion inside the cryptate contains a vacant axial orbit, the subsequent metal-anion interaction shows directionality.

Both mononuclear and binuclear cryptates have been employed for anion recognition, most successfully with dicopper cryptates. The cascade mechanism of anion binding with homo-binuclear cryptates is shown in Figure 40.

This mechanism implies that the most stable cryptates are the most effective anion complexants. Since dicopper complexes are the most stable cryptates, they generally have been proved to be the most successful anion receptors among all metal cryptates. The metal ions inside the cryptate cavity perform two basic functions. First, they preorganize the cryptand by coordinating with six donor atoms (three donor atoms in case of
monometallic cryptate). Secondly they provide coordinating sites for the incoming anionic guests.

Figure 40. Cascade mechanism\textsuperscript{[191]}

These properties confer different anion binding abilities upon cryptates as compared with protonated cryptands. Usually the energetic gain is much higher with cryptates than with protonated cryptands, due to the fact that coordination involves much stronger interaction than simple electrostatics, especially when dimetallic cryptates are employed.\textsuperscript{[191]} The complexed metal ions serve to increase selectivity by restricting the cavity size and geometry.

Nelson and colleagues\textsuperscript{[188]} compared the inclusion complex of ClO$_4^-$ in [L5H$_6$]$_{6+}$ ([L5H$_6$ClO$_4$]$^{5+}$) and that of OH$^-$ in [L5Cu(II)$_2$]$^{4+}$ ([L5Cu(II)$_2$OH]$^{3+}$). The cavity size in the former is 9.05 Å, while the later has a cavity size of only 8.05 Å. The smaller cavity size in the latter case appears to result from the helical conformation adopted by the cryptand. This apparently reflects the organizational role of metal ion Cu(II). They also found that while [L3H$_6$]$^{6+}$ fails to include linear N$_3^-$, cryptate [L3Cu(II)$_2$]$^{4+}$does.\textsuperscript{[192]} In the latter system the anion serves as coordinating ligand to the unsaturated metal centers and
bridges them. Figure 41 represents a cascade complex that was characterized via single crystal X-Ray structural analysis.

![Figure 41. A cascade complex of N₃⁻ with cryptate [L₄Cu(II)₂]⁴⁺](image)

Many anions of different geometry have been recognized successfully by using cryptates, especially dicopper cryptates. These anions include spherical halides, linear pseudohalides, (e.g., N₃⁻, CN⁻, NCO⁻, and SCN⁻), OH⁻, triangular planar anions (e.g., NO₃⁻, CO₃²⁻ and planar sulfonate dianions) and planar sulfonate dianions.

However, there appears to be no report of cryptate binding to tetrahedral and octahedral anions, e.g., ClO₄⁻ and SiF₆²⁻. This situation probably is associated with the facts that ClO₄⁻ and SiF₆²⁻ function as poor ligands toward transition metal ions, as judged by application of HSAB theory. In addition, the metal ions inside the cryptates restrict the molecular backbone to its ellipsoidal conformation, so that the cryptates are not able to
change their geometry or shape readily to accommodate tetrahedral and octahedral anions.

Flexibility significantly influences binding properties even in case of cryptates, which already are highly organized via coordination to the metal ions. The dicopper cryptate \([\text{L5Cu(II)₂}]^{4+}\) differs only slightly from \([\text{L3Cu(II)₂}]^{4+}\) and \([\text{L4Cu(II)₂}]^{4+}\) in structure, however, the former cryptate functions as a “universal” host for many anions of different size and geometry. The results of potentiometric studies \[^{[191]}\] showed that it effectively binds to spherical halides (see Figure 42), linear \(\text{N}_3^-\) and \(\text{NCO}^-\) and planar \(\text{HCO}_3^-\) anions due to its special flexibility, as defined by Fabbrizzi. \[^{[191]}\] However, \([\text{L4Cu(II)₂}]^{4+}\) fails to include monatomic anions. \[^{[191]}\] Crystalline \([\text{L3Cu(II)₂N}_3]^3+\) \[^{[192]}\] and \([\text{L4Cu(II)₂N}_3]^3+\) \[^{[193]}\] has been isolated and characterized, but so far there is no report to confirm the possible existence of crystalline \([\text{L5Cu(II)₂N}_3]^3+.\)

“Peak selectivity” \[^{[191]}\] also occurs in anion (halide) binding, which results from good correlation between anion (e.g., halide) diameter and the cavity size of the cryptate \([\text{L5Cu(II)₂}]^{4+}\).

![Figure 42. A flexible cryptate ([L5Cu(II)2]4+) binds spherical Br− \[^{[191]}\)](image-url)
Peak selectivity is illustrated by the plot shown in Figure 43 \(^{[191]}\).

![Graph showing selectivity in anion binding](image)

**Figure 43.** Peak selectivity in anion binding ([L5Cu(II)2X] \(^{3+}\), X = halides) \(^{[191]}\)

Interpretation of selectivity in anion binding is not as straightforward as in cation binding, because, as mentioned before, the shape and geometry of the guest anions play a significant role in determining the stability of the resulting host-guest complex. Fabbrizzi and colleagues \(^{[196]}\) investigated the inclusion behavior of [L4Cu(II)2] \(^{4+}\) with a series of multidentate anion via application of potentiometric titration methods. They thereby obtained the following data as listed in table 9.
Table 9. LogK values of anion binding with [L4Cu(II)]^{4+} \textsuperscript{[196]}

<table>
<thead>
<tr>
<th>LogK</th>
<th>4.78</th>
<th>4.60</th>
<th>2.95</th>
<th>3.26</th>
<th>3.32</th>
<th>2.97</th>
<th>4.56</th>
<th>2.70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anion</td>
<td>N\textsubscript{3}^{-}</td>
<td>NCO^{-}</td>
<td>NCS^{-}</td>
<td>SO\textsubscript{4}^{2-}</td>
<td>HCOO^{-}</td>
<td>CH\textsubscript{3}COO^{-}</td>
<td>HCO\textsubscript{3}^{-}</td>
<td>NO\textsubscript{3}^{-}</td>
</tr>
</tbody>
</table>

It is not surprising that [L4Cu(II)]^{4+} displays its highest avidity toward linear N\textsubscript{3}^{-} and NCO^{-}, due to the complementarity of their respective shapes with the ellipsoidal cavity of the cryptate, as noted previously. However, this cryptate shows poor avidity toward linear NCS^{-}, which should be preferred by [Cu(II)tren]^{2+} moiety. \textsuperscript{[201]} On the other hand, [L4Cu(II)]^{4+} shows surprisingly high affinity toward complexation of the nonlinear HCO\textsubscript{3}^{-}, which usually is not a good ligand for transition metal ions and whose triangular shape is not expected to fit especially well within the cryptate cavity.

Selectivity doesn’t appear to depend upon the charge of the anion. Fabbrizzi and colleagues \textsuperscript{[196]} concluded that the stability of the inclusion complex is not related to the intrinsic electron-donating tendency of the anion, but rather to its capacity to place two of its donor atoms in the fifth coordination site of each copper ion. They proposed the concept of “bite length” to account for the observed phenomena. Bite length is defined as the distance between the two proximate donor atoms of an anion, as illustrated in Figure 44 \textsuperscript{[196]}.

![Figure 44. Bite length \textsuperscript{[196]}](image-url)
A plot of logK value vs. the bite length shown in Figure 45 satisfactorily accounts for the observed selectivity. Linear $\text{N}_3^-$, and $\text{NCO}^-$ show highest avidity, because their bite lengths fit well the distance between the “fifth coordination sites” of the two copper ions (see Figure 41). Triangular $\text{HCO}_3^-$ also has a suitable bite length and is bound strongly; its structure was verified via single crystal X-Ray analysis. \[197\] The bite length of $\text{NCS}^-$ is too great to fit well, so it is bound weakly. Sulfate anion ($\text{SO}_4^{2-}$) is too large and also is bound poorly.

Another common structural feature among cryptands L3, L4 and L5 is that they all contain three aromatic rings in their molecular backbones. It is reasonable to expect that $\pi$-$\pi$ stacking and other interactions may occur, if the anionic guests possess a $\pi$ system. Nelson and coworkers \[202\] first observed $\pi$-$\pi$ stacking in anion binding with cryptates. The crystal structure of an imidazolate inclusion complex with cryptate $[\text{L4Cu(II)}_2]^{4+}$ clearly shows $\pi$-$\pi$ stacking with the imidazolate ring being sandwiched between two parallel benzene rings. This arrangement leads to unusual stacking distance (3.05 Å). The third benzene ring is almost perpendicular to the other three rings. One C-H bond of the third ring interacts with another benzene ring in an edge-to-face fashion to form unusual C-H–$\pi$ hydrogen bond. \[202\]

This behavior is not unique to imidazolate. Shortly after Nelson’s discovery, Fabbrizzi and colleagues \[194\] reported the crystal structure of $[\text{L4Ni(II)}_2\text{N}_3]^{3+}$ in which the azide anion is sandwiched in the complex in a similar fashion (see Figure 46).
Mononuclear cryptates also find application in anion binding, where lipophilicity of the anion exerts a significant influence upon the structure of the host-guest complex. Sarker and colleagues [200] observed that, hydrophilic cyanide remain partially outside the cavity in order to avoid interaction with the (hydrophobic) phenyl group (see Figure 47). By way of contrast, hydrophobic halides were completely encapsulated in the resulting host-guest complex. [200]

**Figure 45.** Peak selectivity as revealed with bite length [196]
In addition to copper cryptates, many other metal cryptates have been employed in anion binding. As mentioned earlier, those cryptates are not as stable as copper cryptates, and thus they are not as popular anion receptors as are copper cryptates. However, the use of copper cryptates suffers from a significant limitation as is the case with most other transition metal cryptates. They quench any proximate fluorophore either via electron transfer (eT) or via energy transfer (ET) mechanism. Therefore such hosts cannot be used as fluorosensor. However, zinc contains filled 3d orbitals, and it forms stable cryptates that are redox-inactive. Consequently zinc cryptates are not
involved in any eT and ET process and thus can be used as anion sensor via a fluorescence quenching mechanism. One such example was presented by Fabbrizzi and coworkers \cite{195} in which a zinc cryptate was used successfully as an anion sensor (see Figure 48).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure47.png}
\caption{Effect of lipophilicity on anion binding \cite{200}}
\end{figure}

It is rare that neutral cryptands are used directly for anion recognition. However, they can be used in this respect if a suitable functionality such as an amide group, is present in the structure. One excellent example in this regard was presented by Anslyn and coworkers. \cite{183b} The amide groups in the cryptand (shown in Figure 49) are arranged
in a trigonal prismatic array and thus are able to coordinate to the $\pi$-electron system of planar anions, such as $\text{AcO}^-$ and $\text{NO}_3^-$. The $\text{AcO}^-$ inclusion complexe was successfully isolated and subsequently was characterized via application of single crystal X-ray crystallographic methods.\textsuperscript{[183b]}

Figure 48. An example of zinc cryptate as anion sensor \textsuperscript{[195]}

Figure 49. A three-fold neutral cryptand recognizes trigonal planar nitrate \textsuperscript{[183b]}
CHAPTER 2 SYNTHESIS OF CAGE-ANNULATED LIGANDS

As discussed in chapter 1, incorporation of substituents is the dominant way to modify the structures of macrocycles and thereby to affect the overall preorganization of a given macrocyclic system. The cage moiety (see Figure 50) was first incorporated into crown ether systems by Dr. Marchand and his colleagues. [85, 88]

![Figure 50. The cage moiety and cage-annulated ligands](image)

The cage moiety offers several advantages compared to other moieties that frequently are incorporated into macrocycles:

(i) Effectively introduces lipophilicity into crown ether system and high synthetic efficiency. Eleven lipophilic saturated carbons can be introduced in a single synthetic step by employing cage-annulated ligands.

(ii) Effectively increases rigidity of the resulting host system. The cage moiety is much more rigid and bulky than other common moieties, e.g., phenyl, pyridyl moieties, and thus can affect the shape and size of the macrocyclic cavity.

(iii) The cage moiety does not affect the intrinsic properties of the donor atoms as do most bulky aromatic groups.
(iv) The cage moiety contains an oxygen atom that is more highly puckered and thus is potentially a more efficient donor than ordinary alkoxy oxygen donors. \(^{[85]}\)

(v) The cage potentially can be employed to introduce chirality into macrocyclic systems. The symmetry properties of the cage can be conveniently altered to produce ten new chiral centers.

The design and syntheses of new cage-annulated ligands and the related synthetic methods has been one of major objectives of the present study. Initially, the goal was to synthesize cage-annulated macrocycles that contain propylene-linking agents (see Figure 50, \(n = 3\)) and to compare their host-guest behavior with cage-annulated macrocycles that contain methylene (-CH\(_2\)-) or ethylene (-CH\(_2\)CH\(_2\)-) linking agents \(^{[87, 88]}\) (see Figure 50, \(n = 1\) or 2). This work has been extended to include efficient syntheses of cage-annulated podands that contain unsymmetrical ligands.

**RESULTS AND DISCUSSION**

2.1 Synthesis of symmetrical cage-annulated ligands

2.1.1 Modified syntheses of compound 2 and 3 and syntheses of compound 4 and 5

The first cage-annulated ligands were prepared according to the procedure illustrated in Figure 51. \(^{[85]}\) In this synthetic procedure, excess Grignard reagent was added to a solution of diketone (1); a 4:1 nucleophile-to-diketone (1) molar ratio was employed, which indicates the importance of the relative concentration of nucleophile.
The formation of a 1:1 adduct 5, as illustrated in Figure 52, occurs even at high (e.g., 4:1 or higher) nucleophile-to-diketone molar ratio, consequently leading to a yield of 2 as low as 59%. A molar ratio of 6:1 or even 8:1 was once employed in an effort to achieve a high yield. 

Figure 52. Equilibrium of the formation of the desired product and the byproduct
The formation of the byproduct 5 in Figure 52 is due to the rapid intramolecular addition of the *endo* hemiketal hydroxy group to the second ketone carbonyl group, which is in a very close proximity due to the restrictions imposed by the cage backbone. Once the byproduct is formed, excess nucleophile is needed in order to shift the equilibrium toward formation of the desired product. Synthetically, this turns out to be impractical. An examination of the reaction kinetics indicates that there are only two ways to increase the rate of nucleophilic addition, so that the intermolecular addition can compete with the intramolecular addition.

At constant substrate (i.e., diketone) concentration (see Experimental Section), the rate of nucleophilic addition, \( r \), can be related to the concentration of nucleophile [Nuc.] by the following expression:

\[
 r \propto \eta [\text{Nuc.}]
\]

Where \( \eta \) represents the intrinsic nucleophilicity of nucleophile.

Thus, the reaction rate is determined by two fundamental factors, i.e., \( \eta \) and [Nuc.]. A weak nucleophile leads to slow addition to the carbonyl group and consequently may produce a structure similar to the byproduct 5 as shown in Figure 52. This may preclude a synthetic approach that employs a nucleophile that is weaker than Grignard reagent (e.g., organozinc reagents).

Since the intrinsic nucleophilicity cannot be changed, the only way to increase the rate of intermolecular addition is to increase the molar ratio of the nucleophile to diketone. Two procedures may be employed to serve this purpose: (i) the use of large excess of Grignard regent, which is generally impractical, or (ii) the use of inverse
addition, i.e. the solution of 1 is added to the Grignard reagent rather than adding the Grignard reagent to the solution of 1. The second alternative procedure has proved to be very effective. By dropwise addition of the solution of 1 into Grignard reagent, the ratio of nucleophile to diketone is practically infinite at any given moment, consequently intermolecular addition competes very effectively with intramolecular addition, thereby affording a nearly quantitative yield of 2 at a nucleophile-to-diketone molar ratio of only 2.3:1 (1.15 equivalents of nucleophile, see Figure 53). The modified procedure is illustrated in Figure 53 (see the Experimental Section for details). The reduced usage of Grignard reagent also simplifies the workup procedure; thus 2 was obtained in 97% yield.

![Diagram](image-url)

**Figure 53.** Modified procedure for the synthesis of 2 and 3

A similar procedure has been employed to prepare 6 (see Figure 54); an excellent yield of the desired product was achieved by using this procedure.

Compound 3 and 7 were prepared by using similar procedures. In both cases, if the dehydration time is too short, i.e. 2-3 hours, the yield of the desired product was
relatively low.\textsuperscript{[85,204]} The difference in dehydration time needed for 3 from that is needed for 7 can be interpreted by resonance structures (Figure 55).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{synthesis.png}
\caption{Schematic representation of the syntheses of 6 and 7}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{dehydration.png}
\caption{Resonance structures during dehydration of 2}
\end{figure}

The resonance helps to stabilize the associated transition states; therefore, the rate of formation of 3 is greater than 7.

2.1.2 Synthesis of cage-annulated diol 9, 10 and 11

Compound 11 was prepared via hydroboration-oxidation, as depicted in Figure 57. Compound 10 was prepared previously via hydroboration-oxidation, as shown in Figure 51.\textsuperscript{[85]} Due to the fact that the commercial vinyl magnesium bromide is expensive
and difficult to handle, 10 now is prepared exclusively via ozonolysis as illustrated in Figure 56. Although 9 can be prepared in a similar way, the yield of 9 is much lower than that of 10.

Figure 56. Synthetic scheme for 9 and 10 [215]

Ozonolysis-sodium borohydride reduction is an excellent method that can be used to prepare 10, if (i) sodium carbonate is used and (ii) ozonolysis is kept at low temperature (< – 20°C). However, this reaction is sensitive to reaction conditions, e.g. substrate structure, moisture and temperature. The formation of byproducts (12 and 13) as
listed in Figure 58 will reduce the yield of the desired products 9 and 10, if the reaction condition is changed.

Byproduct monoacetal 12 was isolated and characterized by Dr. Boliang Deng [213] and monoester 13 was isolated in the present study. These two products were obtained under different reaction conditions. The former was isolated without the use of any base during ozonolysis.

![Figure 58. Byproducts from ozonolysis-sodium borohydride reduction](image)

Commercial methanol contains 0.5 - 1% water, and ozone flow also may contain moisture, despite the fact that ozone is dried by passage through calcium chloride drying tube. Usually ozonolysis is performed during 1-6 hours at –78°C depending upon the reaction scale. During this time, a significant amount of moisture is likely to be introduced along with the flow of ozone. Consequently water is inevitably present during ozonolysis. Depending upon the basicity of the system, HOO⁻ or HOOH must be produced when ozone is present, as shown in Figure 59.
O₃ + H₂O + B⁻ → HOO⁻ + BH + O₂

O₃ + H₂O → HOOH + O₂

**Figure 59. Generation of HOO⁻ or HOOH**

The *in-situ* generated HOOH or HOO⁻ along with other factors may be responsible for the formation of the monoacetal 12 and monoester 13. In the mechanism of ozonolysis, the first step is the formation of ozonide as illustrated in Figure 60.

**Figure 60. Formation of ozonide**

If no base is used, the mixture must be acidic according to the equation in Figure 59. The ozonide is not stable; it tends to undergo acid-catalyzed rearrangement to form aldehyde (14) and hemiacetalperoxide (15) as shown in Figure 61.\[^{206}\]
Both 14 and 15 can be converted to aldehyde and alcohol via subsequent reductions. However, 14 and 15 may also be converted to acetal by the action of catalytic amount of acid, according to the mechanisms depicted in Figure 62.
Depending upon the concentration of HOOH (which, in turn, depends on the concentration of moisture, according to Figure 59), 14 and 15 would be oxidized to ester (13) and acid (16), respectively during ozonolysis, according to Figure 63.

The mechanisms in Figure 62 and 63 indicate that under “neutral” (virtually acidic) condition, where no base is employed, the formation of byproduct 12 and other possible byproducts, e.g., 13 and 16 during ozonolysis, will reduce the overall yield of the desired product 10, because 12, 13 and 16 would remain intact in the subsequent Me₂S and NaBH₄ reductions. Consequently, 10 would be produced at reduced yield.

To convert 14 and 15 to acid or ester, high concentration of hydrogen peroxide must be present, since hydrogen peroxide is not a very strong oxidizing agent. Therefore,
under normal conditions where only low concentration of HOOH is present due to a low concentration of moisture, 13 and 16 may not be formed in significant amounts. However, low concentrations of hydrogen peroxide is sufficiently acidic to catalyze acetal formation. Therefore, experimentally only 12 was isolated. It is very likely that 12 is formed during ozonolysis rather than in the steps after ozonolysis.

Under basic conditions and low temperature (-78°C), there is no driving force for the ozonide to decompose in a way that is depicted in Figure 61. Other mechanisms, as

Figure 63. Formation of acid and ester during ozonolysis under acidic conditions
illustrated in Figure 64, are not very likely, because both HOO and CH$_3$OH are weak nucleophiles. Thus far, there is no experimental evidence to support these mechanisms. Therefore, essentially quantitative yield of 10 was afforded when ozonolysis was conducted at -78°C in the presence of sodium carbonate (see Experimental Section).

The formation of 13 was an accident. Ozonolysis was interrupted, and the reaction mixture was transferred and the reaction mixture was allowed to stand at ambient temperature during 12 hours, at which time the reaction was later resumed in the usual manner (see the Experimental Section). After the reaction, only 56% of 10 was obtained; surprisingly 15% of 13 was isolated. None of the mechanisms depicted in Figures 61-63 can account for the formation of significant amount of 13. It is likely that the formation of 13 is associated with the fact that the ozonized mixture was allowed to stand at ambient temperature during 12 hours.

Bailey and Erickson [206] reported that at elevated temperature (> -20°C), the initially formed ozonide undergoes a series of changes that lead to the formation of other intermediates that resist conversion to aldehydes when subject to subsequent reduction. Their argument can account for the resulting low yield obtained under acidic conditions, but it fails to account for the formation of 13 under basic conditions, since base was not employed during ozonolysis. Therefore it is very difficult to envision the mechanism by which 13 was formed. Two possible mechanisms that might be cited to account for the formation of 13 and also for the low yield of 10 are illustrated in Figure 65 [207] and Figure 66.
Figure 64. Two potential mechanisms of ozonide decomposition under basic conditions

Figure 65. Formation of ester and acid via hydride shift at elevated temperature
The O-O single bond of the ozonide is not very strong; at elevated temperature it may become polarized and subsequently initiate a 1,2-hydride shift toward electron-deficient oxygen, thereby leading to the formation of intermediates 13 and 16, or 14 and 16.

![Diagram]

Figure 66. Formation of acids and aldehydes via hydride shift at elevated temperature

Compound 3 was used to prepare 9 via ozonolysis-sodium borohydride reduction under a variety of reaction conditions. The system can be basic (Na₂CO₃) or acidic (no added base), and the solvent can be nucleophilic (MeOH) or non-nucleophilic (CH₂Cl₂); the overall yield of 9 is always low (30-40%). It is possible that the ozonide 17 (see Figure 68) formed from 3 is more strained than that formed from 7 (see Figure 60 and 59); and 17 should more readily undergo similar process (see Figure 61, 62, 63 and 64),
and these competing reactions consequently may reduce the yield of the desired alcohol 9.

Figure 67. Ozonide formed from 3 during ozonolysis

A solution of 3 was ozonized in CH₂Cl₂ when Na₂CO₃ was present. The ¹H NMR spectrum of the freshly ozonized reaction mixture shows two obvious absorptions at δ 8-9 and another one at δ 10-11, thereby suggesting that aldehyde or acids are formed in this reaction.

The above discussion suggests that for preparation of 9 from 3 via ozonolysis, a better synthetic procedure would be to conduct ozonolysis in CH₂Cl₂, which is nonnucleophilic. The reaction mixture first is treated with DMS (dimethyl sulfide) at a temperature below – 20°C and then is concentrated in vacuo at ambient temperature. The resulting residue is reduced with LiAlH₄ in dry THF in the usual manner.

2.1.3 Synthesis of cage-annulated ditosylates 18, 19 and 20.

The first cage-annulated ditosylate was synthesized by Dr. Marchand and colleagues. The synthetic scheme is shown in Figure 68.
An alternate synthetic method \cite{208} has been employed in the present research, which is very effective if the substrate is not water-sensitive and the solubility is not very low. This method is illustrated in Figure 69.

Figure 69. Synthesis of cage-annulated ditosylates

By using this procedure, \textbf{19} and \textbf{20} were obtained in excellent yields, but \textbf{18} was not the major product when this procedure was employed by using \textbf{9} as the substrate. The yield
of 18 could not be increased by using higher concentration of base and longer reaction time. The low yield of 18 and the formation of 21 reflect the effect of steric hindrance, which is exerted upon the methylene groups directly connected to the cage moiety. The importance of steric hindrance exerted by the cage moiety also can be observed by comparing the behavior of 18 and 19. Coupling 19 with 1,13-dibenzyl-1,7,13,19-tetraaza-24-crown-8 has been the primary method to make cage-annulated cryptands in the present study (vide infra). However, this procedure did not work when 18 was employed as one of the substrates for coupling.

2.1.4 Synthesis of cage-annulated diazide (22) and diamine (23)

Cage-annulated diamine was prepared according to the method shown in Figure 70. \(^{[209]}\) Ditosylate 20 was treated with NaN\(_3\) in DMF to afford a quantitative yield of pure diazide 22 without need for subsequent column chromatographic purification. Subsequent hydrogenolysis of 22 afforded a quantitative yield of diamine 23.

![Figure 70. Synthesis of cage-annulated diazide (19), diamine (20)](image-url)
2.1.5 Synthesis of cage-annulated dibromide (24)

Bromide is a good leaving group, and bromide-containing ligands are frequently employed to prepare crown ethers.\textsuperscript{[210]} Cage-annulated dibromide was prepared via anti-Marknikov addition of HBr to the C=C double bond in 7 as shown in Figure 71.\textsuperscript{[210,211]}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{synthesis_cage_annulated_dibromide}
\caption{Synthesis of cage-annulated dibromide}
\end{figure}

2.2 Synthesis of unsymmetrical cage-annulated ligands

2.2.1 An unusual complexation-promoted elimination

Extended cage-annulated ligands have been prepared primarily by using the procedure as shown in Figure 72.\textsuperscript{[212]}

Compound 27 and 28 can be used to prepare crown ethers by coupling with appropriate linking agents.\textsuperscript{[212]} But there is one problem: i.e. the intermediate 26 is usually obtained in low yield (44%).\textsuperscript{[212]} Presumably, the low yield of 26 is due to the competing elimination, which can occur in 25. An improved yield of 26 might be achieved if 10 and 25 are replaced by 19 and 29 as the starting materials in this reaction, as illustrated in Figure 73. Elimination is less likely to occur in 19 than in 25, since in 19 the leaving group (TsO) is connected to a primary carbon, an E1 mechanism is unlikely;
further more, since the methylene group directly connected to the cage moiety is sterically hindered (*vide supra*), both E2 and E1\textsubscript{cb} mechanisms are also unlikely to intervene.

![Figure 72. Synthesis of extended cage-annulated ligands](image)

Bn = PhCH\textsubscript{2}

Therefore, the following reaction was attempted (Figure 73):

![Figure 73. An unusual elimination](image)
Surprisingly, only 30, 31 and 3 were isolated, and under all reaction conditions tested, no 26 has ever been isolated! Since NaH is a strong base, it may cause 19 and any intermediates that might be generated during the reaction to undergo elimination. Therefore, the following reaction was conducted to investigate the effect of the basicity of NaH:

![Chemical structure](image)

**Figure 74. A suggested elimination reaction**

At both room temperature and at reflux, after three days, the above reaction failed to afford 3 or 31, and virtually all of the starting material 19 was recovered. Apparently, the basicity of NaH is not directly responsible for this unusual elimination.

To study the mechanism of this unusual elimination, some additional experiments were conducted. The results thereby obtained are listed in Table 10 and Table 11.

The following conclusions can be drawn *via* analyzing the results listed in Table 10 and Table 11:

(i) In all cases, 30 must be produced.
Table 10. Reaction results at room temperature

<table>
<thead>
<tr>
<th>Ratio* of 19:29:NaH</th>
<th>30</th>
<th>3</th>
<th>31</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1.1:3**</td>
<td>Present**</td>
<td>0*</td>
<td>Present**</td>
</tr>
<tr>
<td>1:3:5**</td>
<td>Present**</td>
<td>Present**</td>
<td>Present**</td>
</tr>
<tr>
<td>1:3:12***</td>
<td>27%***</td>
<td>13%***</td>
<td>3.5%***</td>
</tr>
</tbody>
</table>

* Equivalent ratio  ** Results of TLC analysis after 12 hours  *** Results after 72 hours

Table 11. Reaction results at reflux for 3 days

<table>
<thead>
<tr>
<th>Ratio* of 19:29:NaH</th>
<th>30</th>
<th>3</th>
<th>31</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1.1:3**</td>
<td>Present**</td>
<td>0**</td>
<td>Present**</td>
</tr>
<tr>
<td>1:2.2:6**</td>
<td>Present**</td>
<td>0**</td>
<td>0**</td>
</tr>
<tr>
<td>1:3:5</td>
<td>38%</td>
<td>20%</td>
<td>0</td>
</tr>
</tbody>
</table>

*Equivalent ratio  ** Results of TLC analysis

(ii) At room temperature, 31 always can be detected or isolated. It also can be detected under reflux condition when the concentration of BnOCH$_2$CH$_2$ONa is low. But
at high BnOCH$_2$CH$_2$ONa concentration at reflux temperature, 31 cannot be detected or isolated. Most likely, 31 is rapidly converted to either 3 or 30.

(iii) The formation of 3 totally depends on the concentration of BnOCH$_2$CH$_2$ONa. If the concentration of BnOCH$_2$CH$_2$ONa is low, it will not be generated, even at reflux or in the presence of a large amount of NaH. This result is in accordance with expectation (see Figure 74).

Therefore it seems clear that the unusual elimination is promoted by BnOCH$_2$CH$_2$ONa. However, in order to interpret the mechanism of this unusual elimination, three additional factors must be taken into consideration: (i) Compound 19 is a well-preorganized podand, and it may complex with metal ions. [77b] (ii) The activity of Na$^+$ is low when 29 is absent from the reaction, because NaH is not highly ionized, and dry THF is not a very strong ionizing solvent compared to DMF or DMSO. (iii) The activity of Na$^+$ is higher when 29 coexists with NaH, due to the fact that the ion pair Na$^+\cdot$OCH$_2$CH$_2$OBn must be generated. Therefore, it is reasonable to suggest two complexation modes in which Na$^+$ cation is coordinated to five oxygen donors.

![Figure 75. Two possible complexation modes](image)

83
In either complexation mode, Na⁺ cation polarizes (activates) the leaving group. Consequently, such activation may promote both substitution reaction and elimination, according to the scheme shown in Figure 76.

![Chemical Structures](image)

**Figure 76. Proposed mechanisms of an unusual elimination**

To distinguish between the two proposed mechanisms, two questions must be answered, i.e., which of 31 and 32 is the first formed intermediate? are they formed simultaneously? Although 32 has not been detected and isolated directly from the...
reaction mixture, it is still possible that 32 is the first-formed intermediate along the reaction coordinate if 32 eliminates so fast that it may not be detected or isolated under the reaction conditions.

To this end, compound 32 was prepared according to the following scheme as illustrated in Figure 77.

![Chemical reaction scheme](image)

**Figure 77.** An independent test on the elimination tendency of 32

When treated with NaH and 29, 32 undergoes elimination smoothly even at room temperature to afford 30, and, again, no 26 was isolated! But the elimination was not complete after 3 days at ambient temperature. This independent experiment precludes the possibility that 32 is an intermediate along the elimination pathway, because it could have been detected at ambient temperature if it were generated during elimination as depicted in Figure 73. Therefore, the elimination must follow the pathway where 31 is the intermediate. This independent experiment also can be used to support the complexation mode II, as suggested in Figure 75.
The significance of this unusual elimination includes two aspects: (i) It may also be extended to other rigid systems, e.g., the adamantane system, and thus may extend the understanding of the role that is played by the host molecules in “cation-capture, anion-activation” via complexation with guest molecules. Thus, complexation between host and guest molecules not only activates the anion, but also may activate the leaving groups that participate in the complexation; (ii) This elimination provides both a convenient method to break the left-right symmetry of the cage that avoids protection and deprotection and a convenient method to prepare chiral cage spacer that can introduce 10 chiral centers into the host system by one single synthetic step without changing the donor properties.

Dr. V. K. Gore suggested the following scheme to prepare 27, and this should be a very effective method if ozonolysis is conducted properly. Dr. Gore’s synthetic method is illustrated in Figure 78.

![Figure 78. Improved synthesis of 27](image-url)
2.2.2 Synthesis of unsymmetrical cage-annulated ligands

The cage moiety has intrinsic “top-bottom” dissymmetry (see Figure 50). Its “left-right” symmetry can be further broken to prepare unsymmetrical or chiral crown ethers. The “left-right” symmetry usually is broken by the methods similar to that which is illustrated in Figure 79, i.e. one side of the cage-annulated ligand is first protected while the other remains available for further modification. The need for protection and subsequent deprotection is inevitable; consequently the overall synthetic efficiency is reduced. This synthetic scheme is virtually a probability-controlled reaction, although the use of Ag₂O can increase the yield. [213]

![Chemical Reaction](image)

\[ \text{35, 59\%} \]

**Figure 79.** One method of breaking the left-right symmetry of the cage moiety

Since in compound 30 the left-right symmetry of the cage moiety has already been broken, it can be employed to prepare asymmetrically functionalized cage-annulated ligands. To this end, 30 offers several advantages: (i) One side already is protected. (ii) Compound 30 can be used to prepare both “arms” that contain one ethylene group on each side of the cage (i.e., -CH₂CH₂X and -CH₂CH₂Y; see structure I in Figure 80) via hydroboration-oxidation reaction, and “arms” that contain one methylene group on one
side and one ethylene group on the other side (i.e., -CH₂CH₂X, -CH₂X or -CH₂Y; see structure II in Figure 80) via ozonolysis-sodium borohydride reduction. This capability is useful, because structure II otherwise might be very difficult to prepare. Since it is already known that cage-annulated crown ethers that contain two methylene groups have different host-guest behavior from those that contain two ethylene groups, it is of considerable interest to study the complexation behavior of crown ethers that contain structure II.

![Figure 80. Cage-annulated ligands that lack left-right symmetry](image)

2.2.2.1 Synthesis and elimination of 32

Compound 32 was synthesized to test its tendency toward undergoing elimination. Since 32 is expected to be produced as an intermediate during the elimination reaction depicted in Figure 73 and 77. However, 32 never has been isolated in these unusual elimination reactions, as discussed previously. Compound 32 was synthesized from 33 by using the method illustrated in Figure 77.
Hydroboration-oxidization of 30 afforded 33 in nearly 80% yield; subsequent tosylation of 33 afforded 32 (55%). The lower yield of 32 vis-à-vis that of 19 may result from competing elimination, as illustrated in Figure 75 (mode II) and Figure 76. However, in aqueous phase, hydration reduces the tendency of Na⁺ cation to enter into complexation with ligands; consequently, the extent of complexation-promoted elimination is reduced, accordingly.

Pure 32 then was treated with NaH and 29 in dry THF. TLC analysis of the reaction mixture indicated that significant amount of 30 was produced after reaction had proceeded at ambient temperature during 12 hours. The elimination was complete after the reaction mixture had been refluxed with stirring during 48 hours. Compound 30 was isolated in nearly 70% yield; however, 26 was not isolated from this reaction.

2.2.2.2 Synthesis of 36 and 38

Compound 30 was subject to ozonolysis and subsequently was reduced according to the procedure illustrated in Figure 81. The reaction afforded a mixture of 36, 37 and 38. [214] Subsequent treatment of this product mixture with NaOMe-MeOH afforded a mixture of 36 and 38, which can be separated conveniently via elution chromatography.

The overall yield of 36 and 38 is somewhat low (ca. 50%) and is comparable to the yield of 9 that was obtained when 3 was employed to prepare 9 via ozonolysis.
Figure 81. Synthesis of 36 and 38
3.1 Synthesis and host-guest study of cage-annulated oxacrown ethers.

In the ethyleneoxy repeating unit (see 18-crown-6 in Figure 1) of crown ethers, every third atom is oxygen. In this situation, binding to guest ions or molecules is higher than that which would occur when heteroatoms are separated by additional intervening methylene groups. Hence, crown ethers that contain propyleneoxy repeating units are expected to be less efficient complexants than those, which contain ethyleneoxy repeating units.\[^{217}\] A primary research interest in host-guest chemistry at the University of North Texas has concentrated on macrocycles that contain a cage-annulated ethylene linking agent (see Figure 50, \(n = 2\)).\[^{85, 210, 211}\] Although these structures contain propyleneoxy repeating units, they nevertheless display high complexation capacity, probably due to the additional rigidity and lipophilicity that is introduced by the cage moiety and the increased electron-pair donating ability of the cage oxygen atom.\[^{85, 86, 88, 210, 211}\] To further study structure-property relationships in cage-annulated macrocycles, two new series of cage-annulated macrocycles have been developed that contain cage-annulated methyleneoxy (Figure 50, \(n = 1\)) and propyleneoxy (Figure 50, \(n = 3\)) repeating units, respectively.\[^{88}\]
RESULTS AND DISCUSSION

The cage-annulated propylenenox crown ethers were prepared according to the procedure in Figure 82. \(^{[85]}\)

![Synthesis of cage annulated oxacrown ethers](image)

**Figure 82.** Synthesis of cage annulated oxacrown ethers

Compound 11 was employed as the common starting material for all macrocycles. Compound 39 is an analog of 13-crown-5; its low yield probably reflects the fact that Na\(^+\) is not a good template in this case due to size mismatch. The yield of 40 is somewhat higher, due to the fact that it is an analog of 16-crown-4, which should have a diameter that is similar to that of 15-crown-5.

Compound 41 was employed as host in alkali metal complexation study. The results thereby obtained were compared with the corresponding results obtained by using 107 \(^{[251]}\) and 108 \(^{[85]}\) (see Figure 83) *vis-à-vis* 15-crown-5 (model compound). Similarly, the complexation behavior of compound 42 was compared with the corresponding results obtained by using 109 \(^{[251]}\) and 110 \(^{[251]}\) (see Figure 83) *vis-à-vis* 18-crown-6 as model.

Electrospray Ionization Mass Spectrometry (ESI-MS) \(^{[252]}\) and picrate extraction \(^{[252]}\)
methods were employed in these studies to assess host complexation ability. The test results are listed in Table 12. [88, 218]

![Figure 83. Model compounds for host-guest study](image)

It should be noted that \(107\) and \(109\) are the exact analogs of 15-crown-5 and 18-crown-6, respectively. Although \(107\) is more highly preorganized than 15-crown-5, the former host molecule displayed low avidity and selectivity toward alkali metal ions in alkali metal picrate extraction study. However, this host displays similar selectivity to that of 15-crown-5 in ESI-MS experiment. These results are not surprising, since, as already discussed in Chapter 1, a more highly preorganized host may not necessarily interact effectively with a specific guest.

Compound \(108\) shows slight selectivity toward \(K^+\) in the picrate extraction experiment. Compared with all its analogs, i.e. 15-crown-5, \(107\) and \(108, 41\) displays the lowest avidity toward almost all cations, but surprisingly, displays the highest selectivity toward \(K^+\) in both ESI-MS and alkali metal picrate extraction experiments. This result may reflect the fact that \(41\) contains two butyleneoxy units in structure, which are
responsible for the observed low avidity of this host toward alkali metal cations, as judged by the results of alkali metal picrate extraction experiments. However, the increased ring size of 41 (19 atoms in its molecular backbone), which is close to that of 18-crown-6, renders it selectivity toward K\(^+\). Thus, it appears that 41 binds selectively to K\(^+\), but with low avidity.

Compared to 18-crown-6, 109 shows similar avidity and selectivity in both picrate extraction and ESI-MS experiments. Consequently the presence of the cage moiety does not seem to affect the host-guest properties of 109 vis-à-vis 18-crown-6. Compared to other analogs, 42 generally displays the lowest avidity as an alkali metal cation complexant, which again reflects the effect of butyleneoxy units on complexation. In addition, in both picrate extraction and ESI-MS experiments 42 displays “Plateau Effect” due to its large ring size. Compound 110, whose ring size is intermediate between that of 109 and 42, displays high selectivity toward K\(^+\) and Rb\(^+\) with K\(^+\) > Rb\(^+\). 110 should be categorized as 20-crown-6, which is closer in ring size to 21-crown-7 (that selectively binds to Cs\(^+\)) than to 18-crown-6. The selectivity of 110 may reflect the fact that, due to the restriction of the bulky cage moiety, the flip of the ring is hindered and 110 turns out to be less flexible than 21-crown-7. Consequently, 110 displays selectivity toward K\(^+\) and Rb\(^+\), rather than toward Cs\(^+\). The lower avidity of 110 compared with 18-crown-6 is probably due to the two propyleneoxy units inside the crown ether ring.
Table 12. Results of host-guest tests via ESI-MS and picrate extraction

(Modified from references [88] and [218])

<table>
<thead>
<tr>
<th>Host</th>
<th>Li⁺</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Rb⁺</th>
<th>Cs⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-crown-5</td>
<td>1.3 ± 0.5</td>
<td>15.3 ± 0.4</td>
<td>6.7 ± 0.2</td>
<td>3.7 ± 0.4</td>
<td>± 0.3</td>
</tr>
<tr>
<td></td>
<td>(4)</td>
<td>(35)</td>
<td>(36)</td>
<td>(17)</td>
<td>(8)</td>
</tr>
<tr>
<td>107</td>
<td>BLD [c]</td>
<td>2.1 ± 0.2</td>
<td>1.6 ± 0.8</td>
<td>1.3 ± 0.9</td>
<td>0.4 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>(3)</td>
<td>(28)</td>
<td>(26)</td>
<td>(29)</td>
<td>(13)</td>
</tr>
<tr>
<td>108</td>
<td>2.8 ± 0.3 [d]</td>
<td>18.5 ± 1.0 [d]</td>
<td>29.0 ± 0.2 [d]</td>
<td>8.4 ± 1.3 [d]</td>
<td>BLD [c, d]</td>
</tr>
<tr>
<td>41</td>
<td>BLD [c]</td>
<td>BLD [c]</td>
<td>4.9 ± 0.5</td>
<td>0.9 ± 0.2</td>
<td>BLD [c]</td>
</tr>
<tr>
<td></td>
<td>(2)</td>
<td>(11)</td>
<td>(52)</td>
<td>(28)</td>
<td>(6)</td>
</tr>
<tr>
<td>18-crown-6</td>
<td>0.3 ± 0.3</td>
<td>5.3 ± 0.3</td>
<td>64.0 ± 0.4</td>
<td>57.8 ± 0.6</td>
<td>30.5 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>(1)</td>
<td>(6)</td>
<td>(60)</td>
<td>(24)</td>
<td>(8)</td>
</tr>
<tr>
<td>109</td>
<td>BLD [c]</td>
<td>11.3 ± 0.8</td>
<td>67.7 ± 0.2</td>
<td>60.0 ± 0.3</td>
<td>40.2 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>(0)</td>
<td>(6)</td>
<td>(68)</td>
<td>(22)</td>
<td>(3)</td>
</tr>
<tr>
<td>110</td>
<td>BLD [c]</td>
<td>0.07 ± 0.03</td>
<td>11.6 ± 0.1</td>
<td>7.8 ± 0.3</td>
<td>2.8 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>(0)</td>
<td>(13)</td>
<td>(58)</td>
<td>(20)</td>
<td>(9)</td>
</tr>
<tr>
<td>42</td>
<td>BLD [c]</td>
<td>BLD [c]</td>
<td>0.6 ± 0.3</td>
<td>0.2 ± 0.3</td>
<td>1.9 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>(4)</td>
<td>(11)</td>
<td>(24)</td>
<td>(30)</td>
<td>(31)</td>
</tr>
</tbody>
</table>

[a] Experimental conditions employed: 5mM host in CHCl₃ solvent (0.5 mL). Aqueous phase (0.5 mL) was 5.00 mM in alkali metal picrate. Averages and standard deviations are calculated for data obtained from three independent extraction experiments. [b] Data in parentheses taken from reference [218]. [c] BLD = Below limit of detection. [d] Data taken from reference [85].
The host-guest behavior displayed by 107, 108, 109, 110, 41 and 42 strongly suggests that, the ethylene linkages (see Figure 50, n = 2) provide the best overall selectivity and avidity among these macrocyclic polyethers.

It should be noted that the selectivity revealed by picrate extraction in Table 12 may not always match that revealed by ESI-MS due to different solvation of both the host and the guest. Additionally, the ESI-MS experiment does not reveal the intrinsic avidity of a host toward complexation with metal cations.

3.2 Synthesis of azacrown ethers and lariat ethers.

Azacrown ethers, including N-pivot lariat ethers, constitute another important classes of hosts. Many polyazacrown ethers are also used to prepare cryptands and cavitands. Protonated azacrown ethers can be employed for selective anion binding. Most azacrown ethers and lariat ethers were synthesized in the present study for use as starting material to prepare cryptands, as will be discussed in subsequent sections (vide infra).

RESULTS AND DISCUSSION

3.2.1 Synthesis of cage-annulated diazacrown ethers

Compound 44 was prepared according to the procedure shown in Figure 84. The starting material (i.e., 43) was conveniently prepared from the corresponding ditosylate via modification of a reported procedure. Base promoted coupling between 20 and 43 leads to diazacrown ether 44. Compound 48 was prepared similarly (see Figure 85).
Figure 84. Synthesis of 44

Figure 85. Synthesis of 48
In both cases, the yields were low, a result that reflects the effect of the butyleneoxy unit on complexation, as discussed previously (*vide supra*). In case of 44, the low yield may also reflect the size mismatch between K⁺ cation and the large cavity diameter of the crown ether (an analog of 22-crown-6); in case of 48, an insufficient number of donor atoms and the weaker electron-donating property of the phenoxy oxygen atoms may also be responsible (see Figure 8 in Chapter 1 for a representation of the templating process).

3.2.2 Synthesis and synergistic pseudo-hydroxide extraction test of 51

Compound 51 was prepared according to the procedure shown in Figure 86.

![Figure 86. Synthesis of 51](image)

This procedure afforded 50 in 21% yield. Here again, the butyleneoxy unit manifests its effect by imposing low product yield. Subsequent reduction of 50 with LiAlH₄ afforded 51 with good yield.
Compound 51 and its analogs, i.e. 111 and 112 (see Figure 87) were used to carry out synergistic pseudo-hydroxide extraction by Dr. Moyer and colleges in the Chemical Science Division, Oak Ridge National Laboratory.

![Figure 87. Compounds for synergistic pseudo-hydroxide extraction](Image)

Synergistic pseudo-hydroxide extraction is an approach to hydroxide separation, which employs a cation-exchange principle, as represented in Figure 88.

In synergistic pseudo-hydroxide extraction, a fluorinated alcohol (i.e. 113, see Figure 87), which is usually a weak acid and is in the organic phase together with crown ethers, undergoes proton exchange via deprotonation by aqueous hydroxide, e.g., NaOH, at elevated pH during the extraction process. The cation, e.g., Na⁺ cation, and the crown ether form a complex with the florinated alcoholate anion as the counterion, and the complex is extracted into organic phase, e.g., nitrobenzene. When the organic phase is treated with water after extraction, the complex decomposes due to hydrolysis of the alcoholate and subsequently releases sodium hydroxide.
Figure 88. Representation of synergistic pseudo-hydroxide extraction


The test results are shown in Figure 89. In Figure 89, the distribution behavior of \( \text{Na}^+ \) cation when each combination of crown ether and fluorinated alcohol (113) is used (\( D_{\text{Na, CE+113}} \), CE = crown ether) is compared with the corresponding behavior when each crown ether is used alone (\( D_{\text{Na, CE}} \)). The synergistic factor (s) is defined as the ratio of \( D_{\text{Na, CE+F}} / (D_{\text{Na, CE}}) \). [224]

The calculated synergistic factors are 24.5, 3.5 and 3.4 for compounds 111, 112, and 51 respectively, indicating that 111 has the strongest synergism. But a simple hypothetical model (see Figure 90) fails to interpret the different synergistic factors among compound 111, 112 and 51.
* Each plot shows the Na\(^+\) ion distribution ratios (D\(_{Na}\)) for a combination of 22 mM crown ethers 111, 112 or 51 with 44 mM fluorinated alcohol (113) vs D\(_{Na}\) for the corresponding crown ether used alone at 22 mM in nitrobenzene. Aqueous phase: 1 M NaX (X = ClO\(_4^-\), NO\(_3^-\), Br\(^-\), Cl\(^-\), F\(^-\), or OH\(^-\)). Equal phase volumes were gently agitated for 2 h at 25°C, and values of D\(_{Na}\) ([Na\(^+\)]\(_{org} \) / [Na\(^+\)]\(_{aq}\)) were determined by \(^{22}\)Na radiotracer techniques. Experimental uncertainty is approximately ± 5% unless otherwise indicated by error bars. Values of D\(_{Na,CE}\),113 and D\(_{Na,CE}\) for ClO\(_4^-\) and OH\(^-\) were corrected for slight extraction by 113 (D\(_{Na}\) was 1.0 ± (0.1) x 10\(^{-4}\) for NaClO\(_4\) and NaOH and < (1 x 10\(^{-5}\)) for all other sodium salts). Values of D\(_{Na}\) for NaF using receptor 112 and 51 were not obtained, owing to the formation of a third phase in the extraction system. Also should be noted that a stronger host molecule only moves the point up the diagonal line. It is the acidity of the hydroxy acid (113) that moves the point above the diagonal.

**Figure 89.** Results of synergistic pseudo-hydroxide extraction\(^{224}\)

ROH(org) + CE(org) + Na⁺ + OH⁻ $\rightleftharpoons$ RO⁻(org) + NaCE⁺(org) + H₂O(aq)

**Figure 90.** A simple model of synergistic pseudo-hydroxide extraction [224]


This model predicts “synergistic enhancement depends only on the properties of ion exchanger and thus is expected to be the same for all hosts”. [224] The different synergistic factors among compounds 111, 112, and 51 were explained by the possible ion-pair extraction that leads to a higher synergistic factor and the flexibility of the host that affect the complexation. [224]

The highest synergism of compound 111 may result from ion-pairing. [224] Compound 111, due to its cage-annulated methylene spacer, has higher degree of rigidity relative to 112 and 51; consequently, 111 encounters higher energy barrier than 112 and 51 to conduct conformational adjustment to encapsulate Na⁺ cation. Insufficient encapsulation of metal ion by the host enhances ion-pairing. [204, 224] Due to the existence of ion-pairing, 112, which displays the strongest overall extraction toward various salt in Figure 89, does not display the strongest synergism. [224] Compound 51 is highly flexible and consequently displays the lower overall extraction strength than 112. [224]

3.3 Synthesis of non-cage-annulated azacrown ethers and lariat ethers

**RESULTS AND DISCUSSION**

3.3.1 Synthesis of non-cage-annulated azacrown ethers 52, 55 and 56
Figure 91. Synthesis of \( N, N\)-Dibenzyl-1, 13-diaza-24-crown-8

Compound \( 52 \) was prepared by base promoted Coupling of \( 43 \) with its precursor ditosylate (see Figure 84) in the usual manner. \( 52 \) was afforded in 30% yield (Figure 91).

Compounds \( 55 \) and \( 56 \) were prepared according to the procedure shown in Figure 92. \(^{225}\) Both of these crown ethers are starting materials that were used to prepare cryptands, as will be discussed in the subsequent sections.

Intermediate \( 53 \) was prepared by treating \( 49 \) with a large excess of benzylamine at 160 °C. Since a large excess of benzylamine was employed, \( 53 \) thereby obtained is in high purity and can be used in the next reaction. Subsequent coupling of \( 49 \) and \( 53 \) afforded \( 54 \) in good yield. \(^{225}\)

Hydrogenolysis of \( 54 \) afforded \( 55 \) in quantitative yield, but reduction of \( 54 \) with \( \text{LiAlH}_4 \) afforded varying yields of \( 56 \).
3.3.2 Synthesis of lariats

Lariats 57 and 58 were intended for preparing cylindrical structures.\textsuperscript{[226]} They were prepared via similar procedures, as illustrated in Figure 93.

The use of excess halide promotes the formation of quaternary ammonium salt and consequently leads to low yield of the desired product. Indeed, 57 was obtained in low yield. However, when smaller quantities of halide were used, this procedure afforded 58 in 61\% yield (see the Experimental Section). Since this procedure avoids the use of protection and deprotection steps, 61\% is an acceptable yield.
3.4 Synthesis of cage-annulated cryptands and cavitands

Macrobicyclic and macropolycyclic ethers, e.g., cryptands, cavitands, \cite{5,6} have been proved to be more effective hosts than similar two-dimensional monocyclic analogs in terms of both complexation capacity and selectivity. \cite{5,6,76} An additional advantage inherent in these polyaza three-dimensional structures is that their binding properties can be varied among cation, anion and neutral molecule guests either by adjusting the pH of the media or by coordination to metal ions. \cite{176,178,181-193}

Considerable efforts have been made by researchers to modify the properties of these host structures by manipulating the size and shape of their molecular cavities and by changing the identity of the donor atoms in the macrocyclic system. \cite{85,174,227} In the present study, a series of cage-annulated cryptands, cavitand and their corresponding
model compounds were synthesized in an effort to further study the effect of cage-annulation \cite{86} upon host-guest behavior.

**RESULTS AND DISCUSSION**

![Reaction Scheme](image)

**Figure 94.** Synthesis of cage-annulated cryptands

Cryptands 59-62 (Figure 94) were prepared by reacting different combinations of 55 and 56 with 19 and 20. A "templating effect" on the yield of cryptands formed in these reactions could be observed in some cases, depending upon the choice of templating base employed (i.e., M\(_2\)CO\(_3\), M = Rb or Cs). Thus, the reaction of 19 with 56 afforded 59 in 61% yield when Rb\(_2\)CO\(_3\) was used as the templating base, whereas this same reaction, when performed in the presence of Cs\(_2\)CO\(_3\), produced 59 in 46% yield (see the Experimental Section). However, the corresponding reaction of 20 with 56 with either Rb\(_2\)CO\(_3\) or Cs\(_2\)CO\(_3\) afforded 60 in ca. 29% yield, thereby indicating the pronounced effect...
of the cage spacer on the yields. The nature of $N$-substituents does not appear to have a pronounced effect on the yield of products.

Subsequent hydrogenolysis of 59 and 61 afforded 63 and 64 in essentially quantitative yield.

![Chemical structures](image)

**Figure 95. Synthesis of cryptands with extended cage spacer**

Cryptands, i.e. 65, 66 and 67 were prepared according to the procedures illustrated in Figure 95 and 95. The results shown in Table 13 once again reflect the operation of “Templating effect”.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Template</th>
<th>Rb$^+$</th>
<th>Cs$^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td></td>
<td>...</td>
<td>4.7%</td>
</tr>
<tr>
<td>66</td>
<td></td>
<td>45%</td>
<td>Mess</td>
</tr>
</tbody>
</table>

Table 13. Template and yield

Compound 67 was prepared by hydrogenolysis of 66 in good yield.
Figure 96. Synthesis of cage-annulated cryptand 67

Cryptand 71 was prepared according to the procedure shown in Figure 97 in order to compare its complexation properties with those of other cryptands and also test the effect of $N$-substituent on complexation.

Figure 97. Synthesis of cage-annulated cryptand 71
In order to assess the effect of cage annulation upon the complexation behavior of the cage-annulated hosts, non-cage-annulated model compounds, i.e., 84 and 85 are necessary. The procedure employed for synthesizing 84 and 85 is shown in Figure 98.

![Reaction Scheme](image)

**Figure 98. Synthesis of model cryptands 84 and 85**

Cage annulated cavitand 86 was prepared by base promoted reaction of 63 with triethylene glycol ditosylate. The procedure is outlined in Figure 99.
3.5 Evaluation of host-guest behavior of cage-annulated cryptands and cavitands via alkali metal picrate extraction and electrospray ionization mass spectrometry (ESI-MS) methods

3.5.1 Alkali metal picrate extraction study of cage-annulated cryptands and cavitands

Picrate extraction was conducted according to the reported procedure. Since these cage-annulated cryptands each contains four basic nitrogen atoms, all extractions were conducted under elevated pH to avoid N-protonation. The extraction results obtained for of n = 2 hosts (see Figure 94, 96, 97 and 98) at pH 10.5 is listed in Table 14.

Surprisingly, totally “flat” behavior was obtained with all cryptands and cavitands, i.e., the extraction ability of each host toward all five alkali metal ions and ammonium cation is roughly the same. Analysis of the extraction data in Table 14 reveals that the relative bascity of the hosts corresponds to the relative avidity of these hosts, i.e., with the increasing basicity in the order: 57 < 56 < 63 < 84, 86, the percent extraction
increases in the same order: $57 < 56 < 63 < 84, 86$ (see Table 14). Although 86 contains only tertiary nitrogens, it still should be a very strong base in water.

Table 14. Picrate extraction at pH 10.5

<table>
<thead>
<tr>
<th>Host</th>
<th>Percentage of picrate extraction*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Li⁺</td>
</tr>
<tr>
<td>Li⁺</td>
<td>34.18</td>
</tr>
<tr>
<td>25.26</td>
<td>20.26</td>
</tr>
<tr>
<td>15.48</td>
<td>16.16</td>
</tr>
<tr>
<td>69.93**</td>
<td>69.8**</td>
</tr>
<tr>
<td>57.11</td>
<td>52.89</td>
</tr>
</tbody>
</table>

* Average from 3 independent tests. ** Original host solution contains 3% MeOH.
This conclusion follows by comparing 86 with cavitand I (see Figure 2 in Chapter 1). The latter is a very strong base with proton transfer values $\log K_1 = 10.57$, $\log K_2 = 8.01$, $\log K_3 = 6.73$, $\log K_4 = 4.06$; $^{[231, 232]}$ and this compound is much more basic than the common cryptands, i.e. [2.2.1]-, [2.2.2]-, [3.2.2]-, [3.3.2]- and [3.3.3]-cryptand. The first two logK values of cavitand I are comparable with the logK values of [2.1.1]-cryptand, which has a set of proton transfer values $\log K_1 = 10.64$, $\log K_2 = 7.85$ and is known to be a very strong base in water. $^{[231, 233]}$

Since 86 contains two propylene groups that usually enhance bascity $^{[231]}$, it should have similar bascity with cavitand I, if not more basic. Therefore, even at pH 10.5, the results in Table 14 still reflect the ion-pair (i.e., protonated host-picrate ion-pair) extraction. In fact, similar situation has already been reported. $^{[228]}

Table 15. Picrate extraction at pH 11.5-12.0

<table>
<thead>
<tr>
<th>Host</th>
<th>Percentage of picrate extraction*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Li$^+$</td>
</tr>
<tr>
<td><img src="image1" alt="Host" /></td>
<td>9.24</td>
</tr>
<tr>
<td><img src="image2" alt="Host" /></td>
<td>17.00</td>
</tr>
</tbody>
</table>

* Average from 3 independent tests.
Consequently, a medium of higher pH was required in order to test the selectivity of these hosts via picrate extraction. The results thereby obtained appear in Table 15. Once again, “flat” behavior is observed!

The results in Table 14 and 15 strongly suggest that these hosts are very sensitive to the pH of the medium, and they readily undergo protonation even at high pH. These results also suggest that pH 11-12, which is the regular condition for evaluating hosts that contain one or two basic nitrogen donors via alkali metal picrate extraction, \textsuperscript{[250]} is not suitable for hosts that contain more than two basic nitrogen donors.

Consequently, the pH value of the media was further increased to \textit{ca.} 13.0. The extraction results obtained for 63 at this pH appear in Table 16. Here it can be seen that at further elevated pH, the avidity of 63 is reduced dramatically. However, 63 apparently shows discrimination against larger Rb\textsuperscript{+} cation while it does not distinguish among smaller cations, i.e. Li\textsuperscript{+}, Na\textsuperscript{+} and K\textsuperscript{+}. This suggests that at pH 13 protonation is effectively retarded.

Table 16. Picrate extraction at pH 13.0

<table>
<thead>
<tr>
<th>Host</th>
<th>Percentage of picrate extraction*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Li\textsuperscript{+}</td>
</tr>
<tr>
<td></td>
<td>7.88</td>
</tr>
</tbody>
</table>

* Average from 3 independent tests. ** CsPicrate forms super-saturated solution.
However, the results in Table 16 is surprising, because usually the ring size of 63 is not appropriate in the case of Li$^+$ or Na$^+$ guest. In order to further study the host-guest behavior of the cage-annulated hosts, electrospray ionization mass spectrometry (ESI-MS) method has been employed. The use of ESI-MS avoids aqueous conditions and the results obtained via ESI-MS reflect direct competition among alkali cations at exactly the same conditions. Therefore, ESI-MS provides very reliable information about the selectivity of the host, but it does not reveal the corresponding avidity.

3.5.2 ESI-MS study of cage annulated cryptands and cavitands

ESI-MS study was carried out by Professor Jennifer S. Brodbelt and colleagues at the University of Texas, Austin. Conditions that were employed by professor Brodbelt are listed in Figure 100, Figure 101 and Table 17. By comparing the relative peak intensity of different alkali cation complexes in ESI-MS spectra (see Figure 100 and 100), the relative selectivities of the same host toward all five alkali metal cations can be determined. The relative selectivities thereby obtained are listed in Table 17.

Surprisingly, the results shown in Table 17 indicate that all hosts tested bind preferentially with smaller alkali cations, i.e. Li$^+$ and Na$^+$, with the exception that the cavitand 86 displays selectivity toward K$^+$. This observation is in accordance with the result listed in Table 16.

In addition, the results presented in Table 17 also contain some interesting features: (i) The selectivity toward Na$^+$ decreases with increasing rigidity of the host system. (ii) Within the same series ($n = 2$ or 3), the ratio of selectivity toward Li$^+$ over
1:3:3:3:3 C47: LiOH: NaOH: KOH: RbOH: CsCl

Conditions of ESI-MS: $5 \times 10^{-5}$ M solution of cryptand, $1.5 \times 10^{-4}$ M solution of LiOH, NaOH, KOH and RbOH, $1.5 \times 10^{-4}$ M solution of CsCl in MeOH, Total OH- concentration is $6 \times 10^{-4}$ M

Figure 100. ESI-MS spectra of 64 (C47 = 64)

1:3:3:3:3 C52: LiOH: NaOH: KOH: RbOH: CsCl

Conditions of ESI-MS: $5 \times 10^{-5}$ M solution of cryptand, $1.5 \times 10^{-4}$ M solution of LiOH, NaOH, KOH and RbOH, $1.5 \times 10^{-4}$ M solution of CsCl in MeOH, Total OH- concentration is $6 \times 10^{-4}$ M

Figure 101. ESI-MS spectra of 86 (C52 = 86)
Table 17. Evaluation of host-guest interaction by ESI-MS

<table>
<thead>
<tr>
<th>Host</th>
<th>Percent Signal Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Li⁺</td>
</tr>
<tr>
<td><img src="image1.png" alt="Host 1" /></td>
<td>34</td>
</tr>
<tr>
<td><img src="image2.png" alt="Host 2" /></td>
<td>34</td>
</tr>
<tr>
<td><img src="image3.png" alt="Host 3" /></td>
<td>38</td>
</tr>
<tr>
<td><img src="image4.png" alt="Host 4" /></td>
<td>29</td>
</tr>
<tr>
<td><img src="image5.png" alt="Host 5" /></td>
<td>28</td>
</tr>
<tr>
<td><img src="image6.png" alt="Host 6" /></td>
<td>20</td>
</tr>
</tbody>
</table>

**Conditions of ESI-MS:** 5 x 10⁻⁵ M solution of cryptand, 1.5 x 10⁻⁴ M solution of LiOH, NaOH, KOH and RbOH, 1.5 x 10⁻⁴ M solution of CsCl in MeOH, Total OH⁻ concentration is 6 x 10⁻⁴ M
that toward K$^+$ also decreases with increasing rigidity of the host system. (iii) Cage-annulated hosts display lower selectivity toward alkali metal cations compared to that shown by their non-cage-annulated analogs. This observation apparently conflicts with our previous results.\(^{[211,250]}\) (iv) The cryptands \((n = 2)\) display relatively higher selectivity toward Li$^+$, whereas, the cryptands \((n = 3)\) display relatively higher selectivity toward Na$^+$. Although compound 67 has a longer cage linkage as compared with compound 63, the former still displays preference for binding smaller alkali metal cations. The selectivity of compound 67 as revealed by ESI-MS is presented in Table 18.

<table>
<thead>
<tr>
<th>Host</th>
<th>Percent Signal Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Li$^+$</td>
</tr>
<tr>
<td>67</td>
<td>25</td>
</tr>
</tbody>
</table>

3.6 Synthesis of non-cage-annulated cryptands

RESULTS AND DISCUSSION
Cryptand 88 was prepared according to the procedure illustrated in Figure 102. The starting material 87 was prepared via a previously reported method. The base promoted reaction afforded 88 in 35% yield.

![Chemical structure](image1)

**Figure 102. Synthesis of pyridine-containing cryptand**

A similar cryptand 91 that contains a fluorobenzene moiety was prepared according to the following procedure (Figure 103):

![Chemical structure](image2)

**Figure 103. Synthesis of fluorine-containing cryptand**

The starting material 89 was prepared in a yield that is nearly twice of the reported yield by slightly modifying the original procedure (see the Experimental Section).
Cryptand 92 was prepared via base promoted reaction of 45 and 56. The low yield of 92 most likely results from poor templating. Experimentally, K⁺ and Rb⁺ have proved to be most effective in promoting coupling with 56. Cesium cation always appears to afford a low yield of the desired product (see Figure 94, 94 and Table 13).

![Figure 104. Synthesis of 92](image1)

Chiral cryptand 95 was prepared by base promoted reaction of 94 and 56. Chiral diol 93 was prepared from optically active (+)-diethyl L-tartrate. Tosylation of 93 under basic condition affored 94 as a colorless microcrystalline solid.

![Figure 105. Synthesis of 95](image2)
Cryptand 100 was prepared via base promoted reaction of 99 \cite{223} with 56 (see Figure 107).

Cryptand 101 was prepared in a similar manner as illustrated in Figure 108. In these two cases, the reasonably high yields were probably due to efficient templating.

![Figure 106. Synthesis of 100](image)

Cryptand 104 was prepared via base promoted reaction of 103 with 56, as illustrated in Figure 109. The low yield is likely due to the poor templating (cesium instead of rubidium as the template cation). The starting material 103 was prepared in a similar way as 99 was prepared.
3.7 Synthesis of a potential anion receptor

A potential anion receptor 97 was prepared by base promoted coupling of 56 and 96. Further investigation is needed to establish the identity of the “missing” counterion-anion X-. The X-ray structure drawing of 97 is shown in Figure 110.
Figure 110 X-Ray structure drawing of 97
EXPERIMENTAL SECTION

Melting points are uncorrected. 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, U. K.) that was operated in the chemical ionization mode. Elemental microanalysis were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

*exo*-8-*exo*-11-Divinylpentacyclo[5.4.0\(^{2,6,0}^{3,10,0}^{5,9}\)]undecane-*endo*-8-*endo*-11-diol (2). \[^{[85]}\] Commercial vinylmagnesium bromide suspension (750 mL of a 1 M solution in THF, 750 mmol) under argon was cooled to 0 °C via application of external ice-water bath. To this suspension was added dropwise with vigorous stirring a solution of 1 (56 g, 322 mole) in dry THF (500 mL) during 3 hours. After the addition of 1 had been completed, the mixture was allowed to warm to ambient temperature and then was stirred at that temperature during 24 hours. The reaction mixture then was cooled to 0°C via application of an external ice-water bath, and the reaction was quenched via dropwise addition of 5% aqueous HCl solution until a pH of ca. 5-6 was attained. The layers were separated, and the aqueous layer was extracted with 1:1 EtOAc-hexane (2 x 300 mL). The combined organic extracts were washed sequentially with water (2 x 500 mL) and saturated aqueous NaCl (500 mL). The organic layer was dried (Na\(_2\)SO\(_4\)) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via recrystallization from
hexane. Pure 2 (55 g) was thereby obtained as colorless microcrystalline solid: mp 66.5-67.3 °C. The mother liquor was concentrated in vacuo and the residue was purified via column chromatography on silica gel by eluting with 10% EtOAc-hexane. An additional quantity of pure 2 (17.1 g, total 97% yield) was thereby obtained. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.56 (AB, \(J_{AB} = 10.8\) Hz, 1 H), 1.93 (AB, \(J_{AB} = 10.8\) Hz, 1 H), 2.21 (br s, 2 H), 2.30-2.83 (m, 6 H), 5.00-5.23 (m, 4 H), 6.13-6.31 (dd, \(J_1 = 17.4\) Hz, \(J_2 = 10.8\) Hz, 2 H), 6.83 (s, 2 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 33.9 (t), 40.2 (d), 41.4 (d), 44.5 (d), 51.2 (d), 77.1 (s), 112.9 (t), 142.8 (d). The \(^1\)H and \(^{13}\)C NMR spectra of this material agree with the corresponding spectra reported previously for authentic 2.\(^{[85]}\)

3,5-Divinyl-4-oxahexacyclo[5.4.0\(^{2,6,9,11}\).0\(^{3,10}\).0\(^{5,8}\).0\(^{8,11}\)]dodecane (3).\(^{[85]}\) A solution of 2 (2.3 g, 10 mmol) and TsOH (200 mg, catalytic amount) in benzene (50 mL) was refluxed in a Dean-Stark apparatus. Additional (100 mg) TsOH was added at 12 h interval. The reaction was completed after 48 h as indicated by TLC analysis. To it was added K\(_2\)CO\(_3\) (600 mg) then was added with vigorous stirring. The mixture was washed sequentially with water (3 x 50 mL) and saturated NaCl (30 mL). The organic layer was dried (Na\(_2\)SO\(_4\)) 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 3 (2.05 g, 96%) was thereby obtained as colorless oil; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.56 (dt, \(J_1 = 10.5\) Hz, \(J_2 = 1.6\) Hz, 1 H), 1.93 (dt, \(J_1 = 10.5\) Hz, \(J_2 = 1.6\) Hz, 1 H), 2.49 (br s, 2 H), 2.69 (s, 6 H), 5.12-5.29 (m, 4 H), 6.13-6.31 (dd, \(J_1 = 17.6\) Hz, \(J_2 = 10.9\) Hz, 2 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 41.8 (d), 43.5 (t), 44.5 (d), 49.2 (d), 59.0 (d), 96.0 (s), 114.5 (t), 136.3
(d). The $^1$H and $^{13}$C NMR spectra of this material agree with the corresponding spectra reported previously for authentic 3.\textsuperscript{[85]}

\textit{exo-8-exo-11-Diallypentacyclo[5.4.0\textsuperscript{2,6}.0\textsuperscript{3,10}.0\textsuperscript{5,9}]undecane-endo-8-endo-11-diol} (6). A mechanically stirred suspension of freshly prepared allylmagnesium bromide (3000 mL of a 0.49 M solution in ethyl ether, excess) was cooled to 0 °C via application of external ice-water bath. To this suspension was added dropwise with vigorous stirring a solution of 1 (87 g, 0.5 mole) in dry THF (800 mL) at 0 °C during 3 h. After the addition of 1 had been completed, the ice-water bath was removed, the mixture was allowed to warm to ambient temperature and then was stirred at that temperature during 36 h. The reaction mixture was cooled to 0°C via application of an external ice-water bath, and the cooled reaction mixture was quenched via dropwise addition of 5% HCl chloride solution until a pH of ca. 5-6 had been attained. The layers were separated, and the aqueous layer was extracted with 1:1 EtOAc-hexane (3 x 500 mL). The combined extracts were washed sequentially with water (3 x 500 mL) and saturated aqueous NaCl (200 mL). The organic layer was dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated \textit{in vacuo}. The residue was purified via recrystallization from hexane, thereby affording pure 6 (106 g) as colorless microcrystalline solid: mp 82-83 °C. The mother liquor was concentrated \textit{in vacuo}, and the residue was purified via column chromatography on silica gel by eluting with 5% EtOAc-hexane. An additional quantity of pure 6 (22.9 g, total 100% yield) was thereby obtained. IR (KBr) 3169 (s), 2976 (s), 1639 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) $\delta$ 1.05 ($AB$, $J_{AB} = 10.8$ Hz, 1 H), 1.50 ($AB$, $J_{AB} = 10.8$ Hz, 1 H).
Hz, 1 H), 2.01-2.26 (m, 6 H), 2.30-2.59 (m, 6 H), 5.01-5.19 (m, 4 H), 5.21-5.30 (br s, 2 H), 5.79-6.03 (m, 2 H); $^{13}$C NMR (CDCl$_3$) δ 33.9 (t), 40.0 (d), 42.9 (d), 44.1 (d), 44.1 (t), 49.3 (d), 77.3 (s), 117.7 (t), 133.8 (d). Exact mass (CI-HRMS) $[M_{r} + H]^+$ Calcd for C$_{17}$H$_{22}$O$_2$: m/z 259.1698. Found: m/z 259.1699. Anal. Calcd. For C$_{17}$H$_{22}$O$_2$: C, 79.03, H, 8.58. Found: C, 79.14, H, 8.42.

**3,5-Diallyl-4-oxahexacyclo[5.4.02.6.03.10.05.9.08.11]dodecane (7)**. A solution of 6 (25.8 g, 100 mmol) and TsOH (1.5 g, catalytic amount) in benzene (500 mL) was refluxed in a Dean-Stark apparatus. Additional TsOH (200 mg) was added at 12 hour intervals. The reaction was completed after one week as indicated by TLC analysis. The reaction mixture was allowed to cool gradually to ambient temperature, and K$_2$CO$_3$ (5 g) then was added with vigorous stirring. The resulting mixture was washed sequentially with water (3 x 300 mL) and saturated aqueous NaCl (200 mL). The organic layer was dried (Na$_2$SO$_4$) 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 7 (23.5 g, 98%) was thereby obtained as colorless oil; IR (film) 3075 (m), 2965 (s), 1640 (m), 997 (s), 910 cm$^{-1}$ (s); $^1$H NMR (CDCl$_3$) δ 1.46 (AB, $J_{AB} = 10.2$ Hz, 1 H), 1.82 (AB, $J_{AB} = 10.2$ Hz, 1 H), 2.35 (br s, 2 H), 2.45-2.65 (m, 10 H), 4.96-5.15 (m, 4 H), 5.67-5.90 (m, 2 H); $^{13}$C NMR (CDCl$_3$) δ 37.5 (t), 41.7 (t), 43.3 (t), 44.5 (d), 47.8 (d), 58.6 (d), 95.1 (s), 116.9 (s), 134.4 (s). Exact mass (CI-HRMS) $[M_{r} + H]^+$ Calcd for C$_{17}$H$_{20}$O: m/z 241.1592. Found: m/z 241.1601.
3,5-[1',1''-Bis(hydroxymethyl)]-4-oxahexacyclo[5.4.0\(^2\),6\(^3\),10\(^4\),0\(^5\),9\(^6\),0\(^8\),11\(^7\)]dodecane (9). A mixture of 3 (2.12 g, 10 mmol) and Na\(_2\)CO\(_3\) (2 g) in MeOH (36 mL) was cooled to –78 °C via application of an external dry ice-acetone bath. Ozone was bubbled through this mixture until a sky blue color persisted, and the mixture then was purged with argon until the blue color disappeared. To this mixture was added Me\(_2\)S (3.5 mL, ca. 40 mmol, excess). The dry ice-acetone bath was removed, and the mixture was allowed to warm gradually to ambient temperature and was stirred at that temperature during an additional 2 h. The mixture was cooled to 0°C via application of an external ice-water bath. To this cooled mixture was added portionwise NaBH\(_4\) (1.5 g, ca. 40 mmol) during 1 h. After the addition of NaBH\(_4\) had been completed, the ice-water bath was removed and the mixture was allowed to warm gradually to ambient temperature and was stirred at that temperature during an additional 3 h. The reaction was cooled to 0 °C via application of an external ice-water bath and was quenched via dropwise addition of 18% aqueous HCl until a pH of ca. 5-6 had been attained. The mixture was concentrated on a rotary evaporator at a temperature that did not exceed 40 °C until the volume of the mixture had been reduced to ca. 20 mL. To the resulting mixture was added water (50 mL) followed by dropwise addition of 5% aqueous HCl until a pH of ca. 4-5 had been attained. The resulting mixture then was extracted with EtOAc (3 x 40 mL), and the combined extracts were washed sequentially with water (3 x 60 mL) and saturated aqueous NaCl (100 mL). The organic layer was dried (Na\(_2\)SO\(_4\)) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 80% EtOAc-hexane. Pure 9 (860 mg, 39%) was thereby obtained as colorless viscous oil;
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.51 (AB, \(J_{AB} = 10.5\) Hz, 1 H), 1.89 (AB, \(J_{AB} = 10.5\) Hz, 1 H), 2.40 (br s, 2 H), 2.55-2.99 (m, 6 H), 3.45 (AB, \(J_{AB} = 3.8\) Hz, 2 H), 3.73-3.91 (m, \(J = 3.2\) Hz, 4 H);
\(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 41.4 (d), 43.7 (t), 43.8 (d), 44.9 (d), 55.1 (d), 61.7 (t), 98.1 (s). The \(^1\)H and \(^{13}\)C NMR spectra of this material agree with the corresponding spectra reported previously for authentic 9. [88]

3,5-[2',2''-Bis(hydroxyethyl)]-4-oxahexacyclo[5.4.0.0\(^2,6\).0\(^3,10\).0\(^5,9\).0\(^8,11\)]dodecane (10): A mixture of 7 (24 g, 100 mmol) and Na\(_2\)CO\(_3\) (10 g) in MeOH (500 mL) was cooled to \(-78^\circ\)C via application of external dry ice-acetone bath. Ozone was bubbled through this mixture until a sky blue color persisted, and the mixture was purged with argon until the blue color disappeared. To this mixture was added Me\(_2\)S (35 mL, ca. 400 mmol, excessive). The external dry ice-acetone bath was then removed, and the mixture was allowed to warm gradually to ambient temperature and was stirred at that temperature during an additional 6 h. The mixture then was cooled to 0 \(^\circ\)C via application of an external ice-water bath. To this cooled mixture was added portionwise NaBH\(_4\) (15.5 g, ca. 400 mmol) during 3 h. After the addition of NaBH\(_4\) had been completed, the ice-water bath was removed and the mixture was allowed to warm gradually to ambient temperature and was stirred at that temperature overnight. The reaction mixture was cooled to 0 \(^\circ\)C via application of external ice-water bath and then was quenched via dropwise addition of 18% aqueous HCl until a pH of ca. 5-6 had been attained. The mixture was concentrated on a rotary evaporator at a temperature that did not exceed 40\(^\circ\)C until the volume of the mixture had been reduced to ca. 250 mL. To the resulting mixture was added water (250 mL) and followed by dropwise addition of 5% aqueous
HCl until a pH of ca. 4-5 had been attained. The mixture was then extracted with EtOAc (3 x 500 mL); the combined extracts were washed sequentially with water (3 x 500 mL) and saturated aqueous NaCl (300 mL). The organic layer was dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. Pure 10 (24.8 g, 100%) was thereby obtained as colorless microcrystalline solid: mp 153.6-155 °C; $^{[85]}$ $^1$H NMR (CDCl$_3$) $\delta$ 1.50 ($AB$, $J_{AB} = 10.4$ Hz, 1 H), 1.76 ($AB$, $J_{AB} = 10.4$ Hz, 1 H), 2.00 (t, $J = 6.16$ Hz, 4 H), 2.39 (br s, 2 H), 2.50-2.71 (m, 6 H), 2.89 (s, 2 H), 3.73 (t, $J = 6.1$ Hz, 4 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 34.2 (t), 41.3 (d), 43.4 (t), 44.0 (d), 47.6 (d), 58.1 (d), 59.8 (t), 96.1 (s). The $^1$H and $^{13}$C NMR spectra of this material agree with the corresponding spectra reported previously for authentic 10. $^{[85]}$

**Isolation of 13:** A mixture of 7 (48 g, 200 mmol) and K$_2$CO$_3$ (15 g) in MeOH (800 mL) was cooled to –78°C via application of external dry ice-acetone bath. Ozone was bubbled through this mixture. After the reaction had proceeded during 6 h, the expected sky blue color failed to appear. The mixture then was transferred in to a larger flask and an additional amount quantity of MeOH (500 mL) was added. The resulting mixture was purged with argon and was allowed to stand under argon at ambient temperature overnight. Ozonolysis then was resumed in a normal manner during an additional 6 h. However, the expected blue color still failed to appear. To this mixture was added Me$_2$S (75 mL, ca. 830 mmol, excess); the dry ice-acetone bath then was removed, and the mixture was allowed to warm gradually to ambient temperature and was stirred at that temperature during an additional 3 h. The mixture was cooled to 0 °C
via application of an external ice-water bath, and to this cooled mixture was added portionwise with stirring NaBH$_4$ (31 g, ca. 800 mmol) during 6 h. After the addition of NaBH$_4$ had been completed, the ice-water bath was removed, and the mixture was allowed to warm gradually to ambient temperature and was stirred at that temperature overnight. The reaction mixture was cooled to 0 °C via application of an external ice-water bath and was quenched by dropwise addition of 18% aqueous HCl until a pH of ca. 5-6 had been attained. The mixture was concentrated on a rotary evaporator at a temperature that did not exceed 40°C until the volume of the mixture had been reduced to ca. 500 mL. To the mixture was added water (500 mL) and followed by dropwise addition of 5% aqueous HCl until a pH of ca. 5-6 had been attained. The mixture was extracted with EtOAc (3 x 650 mL), and the combined extracts were washed sequentially with water (3 x 700 mL) and saturated aqueous NaCl (500 mL). The organic layer was dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 80% EtOAc-hexane. Pure 13 (8.3g, 15%) was thereby obtained as colorless oil. IR (film) 3450 (br, m), 2966 (s), 2866 (m), 1739 (vs), 1441 (m), 1196 (m), 1076 (m), 1001 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) $\delta$ 1.50 ($AB, J_{AB} = 10.5$ Hz, 1 H), 1.86 ($AB, J_{AB} = 10.5$ Hz, 1 H), 1.98 (m, 2 H), 2.38 (br s, 2 H), 2.53 (s, 1 H), 2.56-2.76 (m, 6 H), 2.80 (s, 2H), 3.65 (s, 3H), 3.73 (dt, $J_1 = 6.3$ Hz, $J_2 = 1.4$ Hz, 2 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 33.8 (t), 38.1 (t), 41.2 (d), 41.8 (d), 43.4 (t), 44.0 (d), 44.4 (d), 47.9 (d), 48.2 (d), 51.6 (q), 58.0 (d), 58.6 (d), 60.1 (t), 93.4 (s), 96.4(s), 170.9 (s). Exact mass (CI-HRMS) [M$_r$ + H]$^+$ Calcd for C$_{16}$H$_{20}$O$_4$: m/z 277.1440. Found: m/z 277.1434.
Continued elution of the chromatography column afforded pure 10 (27.8 g, 56%) as microcrystalline solid. $^1$H NMR (CDCl$_3$) $\delta$ 1.50 ($AB, J_{AB} = 10.4$ Hz, 1 H), 1.76 ($AB, J_{AB} = 10.4$ Hz, 1 H), 2.00 (t, $J = 6.16$ Hz, 4 H), 2.39 (br s, 2 H), 2.50-2.71 (m, 6 H), 2.89 (s, 2 H), 3.73 (t, $J = 6.1$ Hz, 4 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 34.2 (t), 41.3 (d), 43.4 (t), 44.0 (d), 47.6 (d), 58.1 (d), 59.8 (t), 96.1 (s). The $^1$H and $^{13}$C NMR spectra of this material agree with the corresponding spectra reported previously for authentic 10. [85]

3,5-[3',3''-Bis(hydroxypropyl)]-4-oxahexacyclo[5.4.0\[2,6\].0\[3,10\].0\[5,9\].0\[8,11\]]dodecane (11): A solution of 7 (4.8 g, 20 mmol) in dry THF (80 mL) was cooled to 0 °C via application of external ice-water bath under argon. To this solution was added dropwise with stirring commercial BH$_3$-THF complex (20 mL, 1M, 20 mmol) during 1 h. After the addition of BH$_3$-THF had been completed, the ice-water bath was removed and the mixture was allowed to warm gradually to ambient temperature and was stirred at that temperature during an additional 1.5 h. The mixture then was cooled to 0 °C via application of an external ice-water bath, and to the mixture was added sequentially aqueous NaOH (10 mL, 30%, 75 mmol) and 30% H$_2$O$_2$ (16.5 mL, 146 mmol, excess). The mixture then was heated at 40 °C during 0.5 h on a hot water bath and then was allowed to cool gradually to ambient temperature. The mixture was extracted with EtOAc (3 x 50 mL); the combined extracts were washed sequentially with water (2 x 100 mL) and saturated aqueous NaCl (100 mL). The mixture was dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 80% EtOAc-hexane. Pure 11 (3.6 g, 66%) was thereby
obtained as colorless viscous oil; IR (film) 3333 (s), 2947 (s), 1059 cm$^{-1}$ (s); $^1$H NMR (CDCl$_3$) $\delta$ 1.52 ($AB, J_{AB} = 10.4$ Hz, 1 H), 1.58-1.91 (m, 9 H), 2.35-2.65 (m, 8 H), 2.90 (br s, 2 H), 3.60 (t, $J = 5.7$ Hz, 4 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 28.5 (t), 29.4 (t), 41.3 (d), 43.3 (t), 44.2 (d), 47.5 (d), 58.3 (d), 62.8 (t), 96.1 (s). Exact mass (CI-HRMS) [M$_r$ + H]$^+$ Calcd for C$_{17}$H$_{24}$O$_3$: m/z 277.1804 Found: m/z 277.1809. Anal. Calcd. for C$_{17}$H$_{24}$O$_3$: C, 74.00, H, 8.80. Found: C, 73.87, H, 8.83.

**Tosylation of 9 (18) and isolation of 21:** A solution of 9 (300 mg, 1.36 mmol) in THF (15 mL) was cooled to 0°C via application of external ice-water bath. To this solution was added a solution of NaOH (2.5 g) in water (5 mL), and the mixture was stirred at that temperature during 0.5 h. To the mixture was added dropwise a solution of TsCl (0.78 g, 4.1 mmol) in THF (10 mL) during 15 minutes. After the addition of TsCl had been completed, the ice-water bath was removed, and the mixture was allowed to warm gradually to ambient temperature and was stirred during an additional 6 h. At that time TLC analysis of the reaction mixture indicated the absence of 9. To the mixture was added EtOAc (30 mL), and the resulting mixture was washed sequentially with water (2 x 20 mL) and saturated aqueous NaCl. The organic layer was dried (Na$_2$SO$_4$) 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. Pure 18 (150.8 mg, 21%) was thereby obtained as colorless viscous oil; IR (film) 2972 (w), 1597 (w), 1362 (s), 1176 (s), 1097 (w), 972 (s), 813 (s), 663 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) $\delta$ 1.50 ($AB, J_{AB} = 10.8$ Hz, 1 H), 1.86 ($AB, J_{AB} = 10.8$ Hz, 1 H), 2.43 (m, 8 H), 2.60 (s, 6 H), 4.21 (s, 4 H), 4.21 (s, 4 H), 4.21 (s, 4 H).
7.33 (AB, $J_{AB} = 8.2$ Hz, 4 H), 7.76 (AB, $J_{AB} = 8$ Hz, 4 H); $^{13}$C NMR (CDCl$_3$) δ 21.6 (q), 41.5 (d), 43.7 (t), 43.9 (d), 46.0 (d), 56.2 (d), 68.5 (t), 94.4 (s), 128.0 (d), 129.8 (d), 132.9 (s), 144.9 (s). Exact mass (CI-HRMS) [Mr + H]$^+$ Calcd for C$_{27}$H$_{28}$O$_7$S$_2$: m/z 529.1355. Found: m/z 529.1352.

Continued elution of the chromatography column with 70% EtOAc-hexane afforded pure 21 (300 mg, 59%) as colorless viscous oil; IR (film) 3455 (br, w), 3059 (w), 2963 (s), 2868 (m), 1566 9m), 1456 (m), 1366 9s), 1265 (m), 1176 (s), 1098 (m), 972 (s), 832 (m), 739 9s), 703 (m), 665 cm$^{-1}$ (m); $^1$H NMR: (CDCl$_3$) δ 1.51 (dt, $J_1 = 10.6$ Hz, $J_2 = 1.6$ Hz, 1 H), 1.80-1.93 (m, 2 H), 2.35-2.50 (m, 5 H), 2.51-2.60 (br s, 6 H), 3.71 (AB, $J_{AB} = 12.0$ Hz, 1 H), 3.80 (AB, $J_{AB} = 12.0$ Hz, 1 H), 4.26 (s, 2 H), 7.31 (AB, $J_{AB} = 8.2$ Hz, 2 H), 7.77 (dd, $J_1 = 8.2$ Hz, $J_2 = 1.8$ Hz, 2 H). $^{13}$C NMR (CDCl$_3$) δ 21.6 (q), 41.3 (d), 41.6 (d), 43.6 (t), 43.7 (d), 43.9 (d), 44.9 (d), 46.2 (d), 55.1 (d), 56.3 (d), 61.9 (t), 68.8 (t), 94.1 (s), 97.8 (s), 128.0 (d), 129.8 (d), 132.9 (s), 144.8 (s). Exact mass (CI-HRMS) [Mr + H]$^+$ Calcd for C$_{20}$H$_{22}$O$_5$S: m/z 375.1266. Found: m/z 375.1268.

**Synthesis of 19.** A solution of 10 (24.8 g, 100 mmol) in THF (100 mL) was cooled to 0 °C via application of an external ice-water bath. To this solution was added dropwise a solution of NaOH (40 g, 1 mole) in water (90 mL), and the mixture was stirred during 1.5 h. To the resulting mixture was added dropwise with stirring a solution of TsCl (41.9 g, 220 mmol) in THF (150 mL) during 2 h. After the addition of TsCl had been completed, the ice-water bath was removed; the mixture was allowed to warm gradually to ambient temperature and was stirred during an additional 3 h. At that time
TLC analysis of the reaction mixture indicated the absence of 10. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 90 mL). The combined organic layers were washed sequentially with water (2 x 200 mL) and saturated aqueous NaCl (150 mL). The organic layer was dried (Na$_2$SO$_4$) 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. Pure 19 (55.5 g, 100%) was thereby obtained as colorless viscous oil, which, upon standing at ambient temperature, solidified to afford colorless microcrystalline solid; $^1$H NMR (CDCl$_3$) $\delta$ 1.46 ($AB$, $J_{AB} = 10.5$ Hz, 1 H), 1.80 ($AB$, $J_{AB} = 10.5$ Hz, 1 H), 2.05 (t, $J = 7.0$ Hz, 4 H), 2.26-2.59 (m, 14 H), 4.05 (t, $J = 7.0$ Hz, 4 H), 7.31 ($AB$, $J_{AB} = 8.2$ Hz, 4 H), 7.77 ($AB$, $J_{AB} = 8.2$ Hz, 4 H). $^{13}$C NMR (CDCl$_3$) $\delta$ 21.6 (q), 31.7 (t), 41.5 (d), 43.5 (t), 44.1 (d), 48.2 (d), 58.7 (d), 67.6 (t), 93.6 (s), 127.8 (d), 129.8 (d), 133.1 (s), 144.7 (s). The $^1$H and $^{13}$C NMR spectra of this material agree with the corresponding spectra reported previously for authentic 19.$^{[86]}$

**Synthesis of 20.** A solution of 11 (13.8 g, 50 mmol) in THF (60 mL) was cooled down to 0 °C via application of an external ice-water bath. To this solution was added a solution of NaOH (20 g, 0.5 mole) in water (50 mL), and the resulting mixture was stirred during 1.5 h. To the mixture was added dropwise with stirring a solution of TsCl (21 g, 110 mmol) in THF (80 mL) during 2 hours. After the addition of TsCl had been completed, the ice-water bath was removed; the mixture was allowed to warm gradually to ambient temperature and was stirred during an additional 3 hours. At that time TLC analysis of the reaction mixture indicated the absence of 11. The layers were separated,
and the aqueous layer was extracted with EtOAc (2 x 60 mL). The combined organic layers were washed sequentially with water (2 x 150 mL) and saturated aqueous NaCl (100 mL). The organic layer was dried (Na₂SO₄) 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. Pure 20 (29.2 g, 100%) was thereby obtained as colorless viscous oil, which, upon standing at ambient temperature, solidified to afford colorless microcrystalline solid; mp 140.5-141.5 °C; IR (KBr) 2963 (s), 286 (w), 1593 cm⁻¹ (m); ¹H NMR (CDCl₃) δ 1.46 (AB, J_AB = 10.4 Hz, 1 H), 1.69 (m, 8 H), 1.80 (AB, J_AB = 10.4 Hz, 1 H), 2.25-2.59 (m, 14 H), 4.00 (m, 4 H), 7.31 (AB, J_AB = 8.4 Hz, 4 H), 7.75 (AB, J_AB = 8.4 Hz, 4 H); ¹³C NMR (CDCl₃) δ 21.6 (q), 25.0 (t), 28.4 (t), 41.5 (d), 43.4 (t), 44.2 (d), 47.6 (d), 58.5 (d), 70.8 (t), 95.3 (s), 127.8 (d), 129.8 (d), 133.1 (s), 144.7 (s). Exact mass (CI-HRMS) [M+H]+ Calcd for C₃₁H₃₆O₇S₂: m/z 585.1981. Found: m/z 585.1988. Anal. Calcd for C₃₁H₃₆O₇S₂: C, 63.68, H, 6.21. Found: C, 63.90, H, 6.45.

**3,5-[3’,3”-Bis(azidopropyl)]-4-oxahexacyclo[5.4.0²₆.0³₁₀.0⁵₈.0⁶₁₁]dodecane (22).** A mixture of 20 (2.93 g, 5 mmol) and NaN₃ (663 mg, 10.2 mmol) in DMF (30 mL) was heated at 90 °C under argon overnight. The reaction mixture was allowed to cool gradually to ambient temperature and then was poured into a mixture of ice-water (50 g). The resulting mixture was extracted with Et₂O (3 x 100 mL); the combined extracts were washed sequentially with water (3 x 300 mL) and saturated aqueous NaCl (100 mL). The organic layer was dried (Na₂SO₄) and filtered, and the filtrate was concentrated in vacuo. Pure 22 (1.63 g, 100%) was thereby obtained as colorless oil; IR (film) 2965 (s), 2863
(w), 2103 (vs), 1451 (w), 1350 (w), 1261 (m), 936 cm\(^{-1}\) (w); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.30-1.89 (m, 10 H), 2.20-2.66 (m, 8 H), 3.25 (t, \(J = 6.7\) Hz, 4 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 25.0 (t), 29.7 (t), 41.6 (d), 43.5 (t), 44.3 (d), 47.8 (d), 51.8 (t), 58.6 (d), 95.5 (s). \textit{Anal.} Calcd for C\(_{17}\)H\(_{22}\)N\(_6\)O: C, 62.50, H, 6.80. Found: C, 62.34, H, 6.70.

\textbf{3,5-[3',3''-Bis(aminopropyl)]-4-oxahexacyclo[5.4.0\textsuperscript{2,6}.0\textsuperscript{3,10}.0\textsuperscript{5,9}.0\textsuperscript{8,11}]dodecane} (23). A mixture of 22 (1.5 g, 4.6 mmol) and 10\% palladized charcoal (150 mg, catalytic amount) in MeOH (60 mL) was placed in a Parr shaker apparatus and was hydrogenated at 56 psi during 3 days. The reaction mixture was filtered to remove spent catalyst, and the filtrate was concentrated \textit{in vacuo}. The residue, 23 (1.26 g, 100\%) was obtained as colorless viscous oil; IR (film) 3360 (br, m), 2955 (s), 2863 (m), 1651 (m), 1573 (m), 1486 (m), 1327 (m), 1298 (m), 1132 (w), 928 cm\(^{-1}\) (w); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.30-1.91 (m, 14 H), 2.20-2.53 (m, 8 H), 2.60 (t, \(J = 6.9\) Hz, 4 H). \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 29.3 (t), 30.0 (t), 41.6 (d), 42.5 (t), 43.3 (t), 44.3 (d), 47.7 (d), 58.6 (d), 95.6 (s). Exact mass (CI-HRMS) \([M + H]^+\) Calcd for C\(_{17}\)H\(_{26}\)N\(_2\)O: \(m/z\) 275.2123. Found: \(m/z\) 275.2131.

\textbf{3,5-[3',3''-Bis(bromopropyl)]-4-oxahexacyclo[5.4.0\textsuperscript{2,6}.0\textsuperscript{3,10}.0\textsuperscript{5,9}.0\textsuperscript{8,11}]dodecane} (24). \cite{210,211} A mixture of of 5 (3 g, 12.5 mmol) and benzoyl peroxide (200 mg, catalytic amount) in hexane (50 mL) was cooled to 10 °C \textit{via} application of an external ice-water bath. To this mixture was bubbled gaseous HBr, which was generated by heating a solution of excessive bromine and tetralin, during 3h. \cite{204b,210,211} The reaction mixture was stirred during an additional 2 hours at 10 °C. The mixture was washed sequentially with
water (2 x 30 mL) and saturated aqueous NaHCO₃ (50 mL). The organic layer was dried (Na₂SO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with hexane. Pure 24 (1.7 g, 33%) was thereby obtained as colorless oil; IR (film) 2957 (s), 2859 (s), 1456(w), 1119(m), 735 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.50 (AB, J₂= 10.4 Hz, 1 H), 1.71-2.01 (m, 9 H), 2.31-2.63 (m, 8 H), 3.33-3.56 (t, J = 6.3 Hz, 4 H); ¹³C NMR (CDCl₃) δ 29.0 (t), 31.4 (t), 34.1 (t), 41.6 (d), 43.5 (t), 44.3 (d), 47.9(d), 58.6 (d), 95.3 (s). Exact mass (CI-HRMS) [M⁺ + H]⁺ Calcd for C₁₇H₂₂Br₂O: m/z 401.0116. Found: m/z 401.0100

**Synthesis of 30 and isolation of 31:** A solution of 19 (2.0 g, 3.6 mmol) and 29 (1.6 g, 10.9 mmol) in dry THF (125 mL) was cooled to 0 °C via application of an external ice-water bath. To this solution was added portionwise with stirring NaH (60% suspension in mineral oil, 1.7 g, 42.5 mmol) during 1 h. The ice-water bath was removed, and the mixture was allowed to warm gradually to ambient temperature and was stirred at that temperature until 19 had been completely consumed (ca. 3 days). The reaction then was quenched via dropwise addition of water (5 mL); the resulting mixture was dried (Na₂SO₄) 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 3 (154 mg, 13%) was thereby obtained as colorless oil; ¹H NMR (CDCl₃) δ 1.56 (dt, J₁ = 10.5 Hz, J₂ = 1.6 Hz, 1 H), 1.93 (dt, J₁=10.5 Hz, J₂ = 1.6 Hz, 1 H), 2.49 (br s, 2 H), 2.69 (s, 6 H), 5.12- 5.29 (m, 4 H), 6.13-6.31 (dd, J₁ = 17.6 Hz, J₂ = 10.9 Hz, 2 H); ¹³C NMR (CDCl₃) δ 41.8 (d), 43.5 (t), 44.5 (d), 49.2 (d), 59.0 (d), 96.0 (s), 114.5 (t), 136.3
(d) The $^1$H and $^{13}$C NMR spectra of this material agree with the corresponding spectra reported previously for authentic 3. [85]

Continued elution of the chromatography column afforded a mixture of 30 and 31, as indicated by analyzing the $^1$H and $^{13}$C NMR spectra of the eluate. This mixture was further purified via column chromatography on silica gel by eluting with 30% CH$_2$Cl$_2$-hexane. Pure 30 (356 mg, 27%) was thereby obtained as colorless oil; IR (film) 2959 (vs), 2860 (s), 1456 (w), 1101 (vs), 916 (m), 735 (m), 696 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) δ 1.52 (AB, $J_{AB} = 10.2$ Hz, 1 H), 1.89 (AB, $J_{AB} = 10.2$ Hz, 1 H), 2.16 (t, $J = 7.2$ Hz, 2 H), 2.39-2.71 (m, 8 H), 3.53-3.71 (m, 6 H), 4.57 (s, 2 H), 5.09-5.29 (m, 2 H), 6.19 (dd, $J_1 = 17.6$ Hz, $J_2 = 11.0$ Hz, 1 H), 7.22-7.39 (m, 5 H); $^{13}$C NMR (CDCl$_3$) δ 32.6 (t), 41.6 (d), 41.7 (d), 43.3 (t), 44.3 (d), 44.5 (d), 48.2 (d), 49.2 (d), 58.3 (d), 59.2 (d), 68.3 (t), 69.3 (t), 70.1 (t), 73.1 (t), 94.8 (s), 95.5 (s), 114.4 (t), 127.4 (d), 127.5 (d), 128.2 (d), 136.6 (d), 138.2 (s). Exact mass (CI-HRMS) $[M + H]^+$ Calcd for C$_{24}$H$_{28}$O$_3$: m/z 365.2117. Found: m/z 365.2119.

Continued elution of the chromatography column afforded pure 31 (48.6 mg, 3.5%) as colorless oil; IR (film) 2967 (s), 2866 (w), 1599 (w), 1960 (s), 1192 (sh s), 1176 (vs), 1096 (m), 959 (s), 932 (m), 818 (w), 772 (w) 663 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) δ 1.51 (AB, $J_{AB} = 10.52$ Hz, 1 H), 1.86 (AB, $J_{AB} = 10.52$ Hz, 1 H), 2.15 (t, $J = 6.98$ Hz, 2 H), 2.35-2.66 (m, 11 H), 4.13 (t, $J = 7.0$ Hz, 2 H), 5.06-5.20 (m, 2 H), 6.10 (dd, $J_1 = 17.6$ Hz, $J_2 = 10.8$ Hz, 1 H), 7.31 (AB, $J_{AB} = 8.2$ Hz, 2 H), 7.76 (AB, $J_{AB} = 8.2$ Hz, 2 H); $^{13}$C NMR (CDCl$_3$) δ 21.6 (q), 31.7 (t), 41.5 (d), 41.8 (d), 43.5 (t), 44.2 (d), 44.5 (d), 48.2 (d), 49.3 (d), 58.4 (d), 59.2 (d), 67.7 (t), 93.8 (s), 95.9 (s), 114.7 (t), 127.9 (d), 129.8 (d), 133.0 (s), 138.2 (s).
136.2 (d), 144.6 (s). Exact mass (CI-HRMS) [M\(_f\) + H]\(^+\) Calcd for C\(_{22}\)H\(_{24}\)O\(_4\)S\(_3\): m/z 385.1474. Found: m/z 385.1478.

**Synthesis of 32.** A solution of 33 (230 mg, 0.60 mmol) in THF (10 mL) was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added a solution of NaOH (200 mg, 5 mmol) in water (0.6 mL). The resulting mixture then was stirred for 0.5 h, at which time a solution of TsCl (171.8 mg, 0.90 mmol) in THF (5 mL) was added dropwise with stirring during 0.5 h. The external ice-water bath was removed, and the mixture was allowed to warm gradually to ambient temperature and was stirred at that temperature overnight. To this mixture was added EtOAc (25 mL), and the resulting mixture was washed sequentially with water (20 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried (Na\(_2\)SO\(_4\)) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica by eluting with 30% EtOAc-hexane. Pure 32 (179 mg, 55%) was thereby obtained as colorless oil; IR (film) 2969 (m), 2866 (w), 1653 (s), 1363 (w), 1176 (m), 1109 cm\(^{-1}\) (w); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.46 (AB, \(J_{AB} = 10.5\) Hz, 1 H), 1.82 (AB, \(J_{AB} = 10.5\) Hz, 1 H), 1.96-2.19 (m, 4 H), 2.26-2.61 (m, 11 H), 3.43-3.636 (m, 6 H), 4.13 (t, \(J = 7.0\) Hz, 2 H), 4.55 (s, 2 H), 7.20-7.39 (m, 7 H), 7.79 (AB, \(J_{AB} = 8.34\) Hz, 2 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 21.5 (q), 31.7 (t), 32.5 (t), 41.4 (d), 41.6 (d), 43.3 (t), 44.1 (d), 44.2 (d), 48.0 (d), 48.2 (d), 58.6 (d), 58.6 (d), 67.7 (t), 68.0 (t), 69.3 (t), 70.0 (t), 73.0 (t), 93.1 (s), 94.5 (s), 127.3 (d), 127.5 (d), 127.7 (d), 128.2 (d), 129.7 (d), 132.9 (s), 138.1 (s), 144.6 (s). Exact mass (CI-HRMS) [M\(_f\) + H]\(^+\) Calcd for C\(_{31}\)H\(_{38}\)O\(_6\)S\(_2\): m/z 537.2311. Found: m/z 537.2314.

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Elimination of 32: A solution of 32 (110 mg, 0.21 mmol) and 29 (36 mg, 0.24 mmol) in dry THF (10 mL) was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added NaH (60% dispersion in mineral oil, 30 mg, 0.75 mmol). The ice-water bath was removed and the mixture was allowed to warm gradually to ambient temperature. The reaction was monitored via TLC analysis, which indicated that the reaction was not completed after having proceeded during 24 h. The mixture then was refluxed during 48 h, at which time TLC indicated absence of 33. The reaction mixture was quenched via dropwise addition of water (20 mL), and the resulting mixture was extracted with EtOAc (2 x 30 mL). The combined extracts were washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL). The organic layer was dried (Na₂SO₄) 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 30 (52 mg, 69.6%) was thereby obtained as colorless oil. ¹H NMR (CDCl₃) δ 1.52 (AB, J_AB = 10.2 Hz, 1 H), 1.89 (AB, J_AB = 10.2 Hz, 1 H), 2.16 (t, J = 7.2 Hz, 2 H), 2.39-2.71 (m, 8 H), 3.53-3.71 (m, 6 H), 4.57 (s, 2 H), 5.09-5.29 (m, 2 H), 6.19 (dd, J₁ = 17.6 Hz, J₂ = 11.0 Hz, 1 H), 7.22-7.39 (m, 5 H); ¹³C NMR (CDCl₃) δ 32.6 (t), 41.6 (d), 41.7 (d), 43.3 (t), 44.3 (d), 44.5 (d), 48.2 (d), 49.2 (d), 58.3 d), 59.2 (d), 68.3 (t), 69.3 (t), 70.1 (t), 73.1 (t), 94.8 (s), 95.5 (s), 114.4 (t), 127.4 (d), 127.5 (d), 128.2 (d), 136.6 (d), 138.2 (s). ¹H and ¹³C NMR spectra of this material agree with the corresponding spectra reported previously for authentic 30.
Synthesis of 33. A solution of 30 (275 mg, 0.75 mmol) in dry THF (50 mL) was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added dropwise with stirring commercial BH$_3$-THF complex (1.5 mL, 1 M, 1.5mmol) during 15 minutes. The ice-water bath was removed, and the mixture was allowed to warm gradually to ambient temperature and was stirred under argon overnight. The mixture then was cooled to −78 °C via application of external dry ice-acetone bath, and a solution of NaOH (0.60 g, 15 mmol) in water (1.2 mL) was added. The mixture was stirred at −78 °C during 50 minutes, subsequently, was added dropwise with stirring a solution of H$_2$O$_2$ (1.7 mL, 30%, 15 mmol). The external dry ice-acetone bath was removed and the mixture was allowed to warm gradually to ambient temperature and was stirred during an additional 50 minutes. The mixture was heated at 50 °C until all of the precipitate had dissolved (ca. 0.5 h), at which time the reaction mixture was allowed to cool gradually to ambient temperature. The reaction mixture then was neutralized via dropwise addition of 9% aqueous HCl until a pH of ca. 5-6 had been attained. The mixture was extracted with EtOAc (3 x 60 mL); the combined extracts were washed sequentially with water (3 x 100 mL) and saturated aqueous NaCl (50 mL). The organic layer was dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 3% MeOH-CH$_2$Cl$_2$. Pure 33 (230 mg, 80%) was thereby obtained as colorless oil; IR (film) 3411 (br vs), 2969 (s), 2863 (m), 1723 (m), 1653 (s), 1455 (w), 1277 (m), 1109 cm$^{-1}$ (s); $^1$H NMR (CDCl$_3$) δ 1.26 (s, 1 H), 1.52 ($AB, J_{AB} = 10.44$ Hz, 1 H), 1.88 ($AB, J_{AB} = 10.44$ Hz, 1 H), 2.00 (m, 2 H), 2.11 (t, $J = 7.1$ Hz, 2 H), 2.51 (m, 8 H), 3.59 (m, 6 H), 3.78 (m, 2 H), 4.59
(s, 2 H), 7.35 (m, 5 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 32.5 (t), 33.7 (t), 41.3 (d), 41.7 (d), 43.4 (t), 43.9 (d), 44.4 (d), 47.7 (d), 48.0 (d), 58.3 (d), 58.5 (d), 60.2 (t), 68.2 (t), 69.3 (t), 70.2 (t), 73.2 (t), 95.3 (s), 96.2 (s), 127.5 (d), 127.7 (d), 128.3 (d), 138.2 (s). Exact mass (CI-HRMS) [M$+\text{H}]^+$ Calcd for C$_{24}$H$_{30}$O$_4$: m/z 383.2222. Found: m/z 383.2221.

**Synthesis of 35:** A solution of 10 (1.24 g, 5 mmol) in dry THF (36 mL) was cooled to 0 °C via application of an external ice-water bath. To this solution was added portionwise with stirring NaH (60% dispersion in mineral oil, 200 mg, 5.0 mmol) during 0.5 h. After the addition of NaH had been completed, the ice-water bath was removed and the resulting mixture was allowed to warm gradually to ambient temperature. The mixture then was heated to ca. 50 °C, and was added dropwise with stirring a solution of PhCH$_2$Br (940 mg, 5.5 mmol) in dry THF (10 mL) during 1 h. The resulting mixture then was heated at 50 °C during 6 h and then was allowed to cool gradually to ambient temperature. The reaction was quenched via dropwise addition of saturated aqueous NH$_4$Cl until a pH of ca. 6-7 had been attained. The mixture was extracted with EtOAc (3 x 50 mL); and the combined extracts were washed sequentially with water (2 x 100 mL) and saturated aqueous NaCl (100 mL). The organic layer was dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 70% EtOAc-hexane. Pure 35 (997 mg, 59%) was thereby obtained as colorless oil; $^1$H NMR (CDCl$_3$) $\delta$ 1.49 (AB, $J_{AB} = 10.4$ Hz, 1 H), 1.86 (m, $J = 10.4$ Hz, 1 H), 1.91-2.02 (m, $J = 5.9$ Hz, 2 H), 2.11 (t, $J = 6.9$ Hz, 2 H), 2.39 (br s, 2 H); 2.50-2.71 (m, 6 H), 3.56 (t, $J = 7.0$ Hz, 2 H), 3.75 (dt, $J_1 = 6.3$ Hz, $J_2 =$
1.5 Hz, 2 H), 4.56 (s, 2 H), 7.30 (m, 5 H); $^{13}$C NMR (CDCl$_3$) δ 32.6 (t), 33.8 (t), 41.3 (d), 41.7 (d), 43.4 (t), 43.9 (d), 44.4 (d), 47.8 (d), 48.0 (d), 58.5 (d), 58.5 (d), 60.2 (t), 67.5 (t), 72.9 (t), 95.4 (s), 96.2 (s), 127.5(d), 127.5 (d), 128.3 (d), 138.5 (s). Anal. Calcd for C$_{22}$H$_{26}$O$_3$: C, 78.06, H, 7.75. Found: C, 78.26, H, 7.69. [213b]

**Synthesis of 36 and 38:** A solution of 30 (869 mg, 2.4 mmol) in dry MeOH (86 mL) was cooled to –78 °C via application of external dry ice-acetone bath. Ozone was bubbled into the mixture until a blue color persisted. The mixture then was purged with argon at –78 °C until the blue color disappeared. To the resulting mixture was added Me$_2$S (1.2 mL, 15.6 mmol). The external dry ice-acetone bath was removed, and the mixture was allowed to warm gradually to ambient temperature and was stirred at that temperature during 1 h. The mixture was cooled to 0 °C via application of an external ice-water bath, and NaBH$_4$ (550 mg, 1.2 mmol) was added portionwise with stirring during 50 minutes. The external ice-water bath was removed and the mixture was allowed to warm gradually to ambient temperature and was stirred overnight. The mixture was cooled to 0 °C via application of an external ice-water bath and was quenched with 9% aqueous HCl until a pH of ca. 6 had been reached. The mixture was extracted with EtOAc (3 x 100mL); the combined extracts were washed sequentially with water (2 x 100 mL) and saturated aqueous NaCl (100mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 3% MeOH-CH$_2$Cl$_2$. A mixture of 36 and 37 (430 mg), as indicated via analysis of the $^1$H and $^{13}$C NMR spectra of the eluate, was thereby obtained.
Continued elution of the chromatography column afforded pure 38 (57.7 mg) as colorless oil; IR (film) 3406 (s), 2967 (s), 2869 (m), 1641 (w), 1299 (w), 1151 (s), 1059 (sh, m), 1033 (s), 883 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.49 (AB, J_AB = 10.5 Hz, 1 H), 1.85 (AB, J_AB = 10.4 Hz, 1 H), 2.03 (t, J = 6.2 Hz, 2 H), 2.36 (s, 2 H), 2.45-2.71 (m, 6 H), 3.13 (s, 2 H), 3.43-3.66 (m, 6 H), 3.76 (dd, J₁ = Hz, J₂ = Hz, 2 H); ¹³C NMR (CDCl₃) δ 32.2 (t), 41.3 (d), 41.6 (d), 43.5 (t), 43.8 (d), 44.1 (d), 44.9 (d), 48.1 (d), 55.1 (d), 58.5 (d), 61.3 (t), 61.8 (t), 67.9 (t), 71.7 (t), 95.6 (s), 97.2 (s). Exact mass (CI-HRMS) [Mᵣ + H]⁺ Calcd for C₁₆H₂₂O₄: m/z 279.1596. Found: m/z 279.1591.

The mixture of 36 and 37 was treated with excess NaOMe (500 mg, excess) in MeOH (30 mL) at ambient temperature overnight. The resulting mixture was purified via column chromatography on silica gel by eluting with 3% MeOH-CH₂Cl₂. Pure 36 was thereby obtained (180 mg, 21%) as colorless oil; IR (film): 3436 (br vs), 2969 (s), 2869 (m), 1649 (m), 1465 (w), 1113 (s), 1036 (m), 741 (m), 706 cm⁻¹ (s); ¹H NMR (CDCl₃) δ 1.49 (AB, J_AB = 10.5 Hz, 1 H), 1.85 (AB, J_AB = 10.5 Hz, 1 H), 2.11 (t, J = 7.1 Hz, 2 H), 2.26-2.71 (m, 9 H), 3.49-3.61 (m, 6 H), 3.79 (m, 2 H), 4.53 (s, 2 H), 7.23-7.35 (m, 5 H); ¹³C NMR (CDCl₃) δ 32.6 (t), 41.3 (d), 41.8 (d), 43.5(t), 43.9 (d), 44.3 (d), 45.1 (d), 48.2 (d), 55.4 (d), 58.5 (d), 62.1 (t), 68.2 (t), 69.3 (t), 70.1 (t), 73.1 (t), 95.3 (s), 96.5 (s), 127.5 (d), 127.6 (d), 128.3 (d), 138.2 (s). Exact mass (CI-HRMS) [Mᵣ + H]⁺ Calcd for C₂₃H₂₈O₄: m/z 369.2066. Found: m/z 369.2062.

Continued elution of the chromatography column afforded an additional quantity of 38 (141 mg, total 30% yield) as colorless oil. ¹H NMR (CDCl₃) δ 1.49 (AB, J_AB = 10.5
Hz, 1 H), 1.85 (AB, \( J_{AB} = 10.48 \) Hz, 1 H), 2.03 (t, \( J = 6.2 \) Hz, 2 H), 2.36 (s, 2 H), 2.45-2.71 (m, 6 H), 3.13 (s, 2 H), 3.43-3.66 (m, 6 H), 3.76 (dd, \( J_1 = \) Hz, \( J_2 = \) Hz, 2 H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 32.2 (t), 41.3 (d), 41.6 (d), 43.5 (t), 43.8 (d), 44.1 (d), 44.9 (d), 48.1 (d), 55.1 (d), 58.5 (d), 61.3 (t), 61.8 (t), 67.9 (t), 71.7 (t), 95.6 (s), 97.2 (s). The \(^1\)H and \(^{13}\)C NMR spectra of this material agree with the corresponding spectra reported previously for authentic 38.

Synthesis of 39. A solution of 11 (560 mg, ca. 2 mmol) in dry THF (40 mL) was cooled to 0 °C via application of an external ice-water bath. To this solution was added NaH (60% dispersion in mineral oil, 200 mg, 5 mmol, excess) portionwise with stirring during 0.5 h. The external ice-water bath was removed; the mixture was allowed to warm gradually to ambient temperature and subsequently was heated to 50 °C. To the resulting mixture was added dropwise with stirring a solution of ethylene glycol ditosylate (820 mg, 2.2 mmol) in dry THF (30 mL) during 2 h. The mixture then was heated at 50 °C during 48 h and subsequently was refluxed during 24 h. The reaction mixture was quenched with saturated aqueous NH\(_4\)Cl (3 mL). The resulting mixture was dried (Na\(_2\)SO\(_4\)) and filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (50 mL), and the resulting organic layer was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (20 mL), dried (Na\(_2\)SO\(_4\)) and then concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 30% EtOAc-hexane. Pure 36 (62 mg, 10%) was obtained as a pale yellow oil; IR (film) 2959 (vs), 2926 (sh, s), 2859 (m), 1456 (w), 1113 cm\(^{-1}\) (m); \(^1\)H NMR
Synthesis of 40. A solution of 11 (560 mg, ca. 2 mmol) in dry THF (40 mL) was cooled to 0 °C via application of an external ice-water bath. To this solution was added NaH (60% dispersion in mineral oil, 200 mg, 5 mmol, excess) portionwise with stirring during 0.5 h. The ice-water bath was removed, and the mixture was allowed to warm gradually to ambient temperature and subsequently was heated to 50 °C. To the resulting mixture was added dropwise a solution of diethylene glycol ditosylate (910 mg, 2.2 mmol) in dry THF (36 mL) during 2 h. The mixture then was heated at 50 °C for 48 h and subsequently refluxed for 24 h. The reaction mixture was quenched with saturated aqueous NH₄Cl (3 mL). The mixture was dried (Na₂SO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (50 mL) and was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (20 mL), dried (Na₂SO₄) and concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 30% EtOAc-hexane. Pure 40 was thereby obtained (303 mg, 43%) as colorless microcrystalline solid, m.p 96.3-96.9 °C; IR (KBr) 2966 (s), 2941 (sh, s), 2897 (s), 2865 (s), 1452 (m), 1354 (m), 1306 (m), 1152 (sh, s), 1136 (s), 1105 (s0, 1076 (m), 999 (m), 956 (m), 923 (m), 910 (w), 833 (w), 673 (w), 649 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.49 (AB, J_AB = 10.6 Hz, 1 H), 1.60-1.93 (m, 9 H), 2.28-2.66 (m, 8 H), 3.50-3.83 (m, 8 H); ¹³C NMR (CDCl₃) δ 25.8 (t), 29.3 (t), 41.8 (d), 43.5 (t), 44.5 (d), 47.8 (d), 58.7 (d), 70.7 (t), 95.7 (s). Exact mass (CI-HRMS) [M⁺ + H]⁺ Calcd for C₁₉H₂₆O₃: m/z 303.1960. Found: m/z 303.1958.
391 (m, 12 H); $^{13}$C NMR (CDCl$_3$): $\delta$ 26.4 (t), 27.6 (t), 41.3 (d), 43.5 (t), 43.9 (d), 47.4 (d), 58.2 (d), 70.1 (t), 72.3 (t), 72.5 (t), 95.3 (s). Exact mass (CI-HRMS) [$M_r + H]^+$ Calcd for C$_{21}$H$_{30}$O$_4$: $m/z$ 347.2222. Found: $m/z$ 347.2217.

**Synthesis of 41.** A solution of 11 (560 mg, *ca.* 2 mmol) in dry THF (40 mL) was cooled to 0 °C via application of an external ice-water bath. To this solution was added a mixture of NaH (60% suspension in mineral oil, 200 mg, 5 mmol, excess) and K$_2$CO$_3$ (510 mg, excess) portionwise with stirring during 0.5 h. The external ice-water bath was removed, and the mixture was allowed to warm gradually to ambient temperature and subsequently was heated to 50 °C. To the resulting mixture was added dropwise a solution of 1 g (2.2 mmol) triethylene glycol ditosylate in dry THF (30 mL) during 2 h. The mixture then was heated at 50 °C for 48 h and subsequently was refluxed during 24 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl (3 mL), dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc (50 mL) and was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (20 mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 30% EtOAc-hexane. Pure 41 (260 mg, 33%) was thereby obtained as colorless oil; IR (film) 2942 (s), 2863 (s), 1450 (w), 123 cm$^{-1}$ (s); $^1$H NMR (CDCl$_3$) $\delta$ 1.48 (AB, $J_{AB} = 10.5$ Hz, 1 H), 1.61-1.93 (m, 9 H), 2.29-2.71 (m, 8 H), 3.46-3.92 (m, 16 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 25.8 (t), 27.72 (t), 41.4 (d), 43.5 (t), 43.9 (d), 47.5 (d), 58.4 (d), 69.9 (t), 70.6 (t), 70.8 (t), 71.3 (t), 95.8 (s). Exact mass (CI-HRMS) [$M_r + H]^+$ Calcd for C$_{23}$H$_{34}$O$_5$: $m/z$ 391.2485. Found: $m/z$ 391.2480.
Synthesis of 42. A solution of 11 (560 mg, ca. 2 mmol) in dry THF (40 mL) was cooled to 0 °C via application of an external ice-water bath. To this solution was added a mixture of NaH (60% suspension in mineral oil, 200 mg, 5 mmol, excess) and K$_2$CO$_3$ portionwise with stirring during 0.5 h. The external ice-water bath was removed, and the mixture was allowed to warm gradually to ambient temperature and subsequently heated to 50 °C. To the resulting mixture was added dropwise a solution of tetraethylene glycol ditosylate (1.1 g 2.2 mmol) in dry THF (30 mL) during 2 h. The mixture then was heated at 50 °C for 48 h and subsequently was refluxed for 24 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl (3 mL). The mixture was dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (50 mL) and was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (20 mL), dried (Na$_2$SO$_4$) and was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 30% EtOAc-hexane. Pure 42 (200 mg, 23%) was thereby obtained as colorless oil; IR (film) 2963 (s), 2873 (s), 1452 (w), 1352 (m), 1298 (m), 1117 cm$^{-1}$ (s); $^1$H NMR (CDCl$_3$) δ 1.53 (AB, $J_{AB}$ = 10.3 Hz, 1 H), 1.55-1.83 (m, 9 H), 2.23-2.55 (m, 8 H), 3.39-3.66 (m, 20 H); $^{13}$C NMR (CDCl$_3$) δ 26.1 (t), 28.6 (t), 42.0 (d), 44.0 (t), 44.6 (d), 48.1 (d), 59.0 (d), 70.3 (t), 70.9 (t), 71.1 (t), 71.2 (t), 71.6 (t), 96.2 (s). Exact mass (CI-HRMS) [M$^+$ + H]$^+$ Calcd for C$_{25}$H$_{38}$O$_6$: m/z 435.2746. Found: m/z 435.2737.

Synthesis of 44. A mixture of 20 (1.17 g, 2 mmol), 43 (739 mg, 2 mmol) and K$_2$CO$_3$ (1.38 g, 10 mmol, excess) in dry CH$_3$CN (100 mL) was refluxed during 72 h. The
mixture then was allowed to cool to ambient temperature and filtered; the filtrate was concentrated in vacuo, and the resulting residue was dissolved in CHCl₃ (50 mL). The resulting solution was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL), dried (Na₂SO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with EtOAc. Pure 44 (355 mg, 29%) was thereby obtained as pale yellow oil; IR (film) 2959 (s), 2866 (s), 2808 (m), 1672 (m), 1452 (s), 736 (m), 700 cm⁻¹ (m); ¹H NMR (CDCl₃) δ 1.49 (AB, J_AB = 10.3 Hz, 1 H), 1.53-1.89 (m, J = 10.3 Hz, 9 H), 2.26-2.60 (m, 12 H), 2.69 (t, J = 6.0 Hz, 4 H), 3.45-3.73 (m, 16 H), 7.16-7.36 (m, 10 H); ¹³C NMR (CDCl₃) δ 23.1 (t), 29.8 (t), 41.5 (d), 43.4 (t), 44.19 (d), 47.7 (d), 52.9 (t), 54.6 (t), 58.5 (d), 59.9 (t), 69.4 (t), 70.5 (t), 70.7 (t), 96.8 (s), 126.8 (d), 128.1 (d), 129.9 (d), 139.6 (s). Exact mass (CI-HRMS) [M₊ H]⁺ Calcd for C₃₉H₅₂N₂O₄: m/z 613.4005. Found: m/z 613.4013.

Synthesis of 48. A mixture of 20 (1.17 g, 2 mmol), 45[222] (752 mg, 2 mmol) and K₂CO₃ (1.38 g, 10 mmol, excess) in dry CH₃CN (100 mL) was refluxed for 72 h. The mixture then was allowed to cool to ambient temperature and filtered; the filtrate was concentrated in vacuo, and the resulting residue was dissolved in CH₃CN (50 mL). The resulting solution was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL); dried (Na₂SO₄), and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with EtOAc. Pure 48 (262 mg, 21%) was thereby obtained as pale yellow oil; IR (film) 3028...
(w), 2955 (s), 2862 (s), 2798 (m), 1593 (m), 1501 (s), 1452 (s), 1356 (w), 1253 (s), 1026 (m), 739 (s), 698 cm$^{-1}$ (s); $^1$H NMR (CDCl$_3$) $\delta$ 1.49 ($AB$, $J_{AB}$ = 10.2 Hz, 1 H), 1.56-1.91 (m, $J$ = 10.2 Hz, 9 H), 2.26-2.73 (m, 12 H), 2.95 (t, $J$ = 6.4 Hz, 4 H), 3.79 (s, 4 H), 4.06 (t, $J$ = 6.4 Hz, 4 H), 6.71-4.91 (m, 4 H), 7.19-7.43 (10 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 23.7 (t), 29.6 (t), 41.9 (d), 44.0 (t), 44.4 (d), 48.3 (d), 53.1 (t), 55.2 (t), 59.0 (d), 60.3 (t) 68.5 (t), 96.5 (s), 116.3 (d), 122.1 (d), 127.3 (d), 128.6 (d), 129.3 (d), 140.6 (s), 150.2 (s). Exact mass (CI-HRMS) $[M_\text{r} + H]^+$ Calcd for C$_{39}$H$_{52}$N$_2$O$_4$: m/z 617.3743. Found: m/z 617.3748.

**Synthesis of 50.** A solution of 11 (1.66 g, 6.0 mmol) in dry THF (300 mL) was cooled to 0°C via application of an external ice-water bath. To this solution was added NaH (60% dispersion in mineral oil, 600 mg, 15 mmol, excess) portionwise with stirring during 1 h. The external ice-water bath was removed, and the mixture was allowed to warm gradually to ambient temperature. To the resulting mixture was added dropwise a solution of 49 (4.33 g, 6.6 mmol) in dry THF (50 mL) during 2 h. The mixture then was heated at 50°C during 72 h and subsequently was refluxed during 24 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl (5 mL), dried (Na$_2$SO$_4$), and filtered. The filtrate was concentrated in vacuo, and the resulting residue was dissolved in EtOAc (90 mL). The resulting solution was washed sequentially with water (2 x 50 mL) and saturated aqueous NaCl (50 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified via column chromatography on silica by eluting with EtOAc. Pure 50 (739 mg, 21%) was thereby obtained as pale yellow viscous oil; $^1$H NMR (CDCl$_3$) $\delta$
1.49 (AB, $J_{AB} = 10.3$ Hz, 1 H), 1.60-1.90 (m, $J = 10.3$ Hz, 9 H), 2.25-2.66 (m, 11 H), 3.35 (t, $J = 6.0$ Hz, 4 H), 3.41-3.86 (m, $J = 6.0$ Hz, 16 H), 7.24 (AB, $J_{AB} = 8.1$ Hz, 2 H), 7.68 (AB, $J_{AB} = 8.1$ Hz, 2 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.4 (q), 25.7 (t), 29.3 (t), 41.8 (d), 43.4 (t), 44.5 (d), 47.8 (d), 48.7 (t), 58.7 (d), 69.9 (t), 70.10 (t), 70.3 (t), 71.7 (t), 95.7 (s), 127.2 (d), 129.6 (d), 136.9 (s), 143.1 (s).

**Synthesis of 51.** A solution of 50 (700 mg, 1.19 mmol) in dry THF (50 mL) was cooled to 0 °C via application of an external ice-water bath. To this solution was added LiAlH$_4$ (95% dispersion in mineral oil, 200 mg, 4.76 mmol, excess) portionwise with stirring during 0.5 h. The external ice-water bath was removed, and the mixture was allowed to warm gradually to ambient temperature and subsequently was refluxed during 96 h. The reaction mixture was quenched with saturated aqueous Na$_2$SO$_4$ (5 mL) and filtered. The filtrate was concentrated in vacuo, and the resulting residue was dissolved in EtOAc (50 mL). The organic solution was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (50 mL), dried (Na$_2$SO$_4$), and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on alumina by eluting with 70% EtOAc-hexane. Pure 51 (409 mg, 80%) was thereby obtained as highly viscous brown oil; $^1$H NMR (CDCl$_3$) $\delta$ 1.49 (AB, $J_{AB} = 10.5$ Hz, 1 H), 1.60-1.89 (m, 9H), 2.28-2.59 (m, 8 H), 2.85 (t, $J = 6.0$ Hz, 4 H), 3.39-3.86 (m, $J = 6.0$ Hz, 17 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 25.3 (t), 27.8 (t), 41.4 (d), 43.5 (t), 43.9 (d), 47.5 (d), 49.0 (t), 58.3 (d), 69.2 (t), 69.7 (t), 70.2 (t), 71.1 (t), 95.8 (s).
**Synthesis of 52.** A mixture of tetraethylene glycol ditosylate (1.1g, 2.2 mmol), 43 (745 mg, 2 mmol) and K₂CO₃ (1.38 g, 10 mmol, excess) in dry CH₃CN (100 mL) was refluxed during 72 h. The mixture then was allowed to cool to ambient temperature and was filtered. The filtrate was concentrated *in vacuo*, and the resulting residue was dissolved in CHCl₃ (50 mL). The resulting solution was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL), dried (Na₂SO₄), concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel by eluting with EtOAc. Pure 52 (355 mg, 30%) was thereby obtained as pale yellow oil; IR (film) 2870 (s), 1699 (m), 1456 (m), 1126 (s), 736 (m), 700 cm⁻¹ (m); ¹H NMR (CDCl₃) δ 2.81 (t, J = 5.7 Hz, 8 H), 3.5-3.73 (m, 24 H), 7.19-7.39 (m, 10 H); ¹³C NMR (CDCl₃) δ 54.3 (t), 60.3 (t), 70.5 (t), 71.1 (t), 71.3 (t), 127.3 (d), 128.6 (d), 129.3 (d), 140.1 (s). Exact mass (CI-HRMS) [M⁺ + H]⁺ Calcd for C₃₀H₄₆N₂O₆: m/z 531.3434. Found: m/z 531.3392.

**Synthesis of Lairat ether 57.** A mixture of 55 (1.88 g, *ca.* 2.9 mmol), 2-bromoethanol (1.43 g, *ca.* 11.4 mmol, excess), NaI (200 mg, catalytic amount) and Na₂CO₃ (3.0 g, 28.6 mmol) in dry acetone (100 mL) was refluxed overnight. The mixture then was filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in CH₂Cl₂ (50 mL); the resulting solution was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL), dried (Na₂SO₄), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel by eluting with 0.1% Et₃N-EtOAc. Pure 57 (850 mg, 40%) was thereby obtained as highly viscous pale yellow oil; IR (film) 3406 (br, m), 3057 (w), 2953 (s),
2876 (s), 1666 (w), 1599 (m), 1451 (s), 1339 (s), 1157 (s), 1125 (s), 939 (s), 818 (s), 733 (s), 716 (s), 700 (s), 653 (s), 551 cm\(^{-1}\) (s); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.41 (s, 6 H), 2.63-2.85 (m, \(J_1 = 5.1\) Hz, \(J_2 = 5.5\) Hz, 12 H), 2.95 (br s, 2 H), 3.35 (t, \(J = 5.8\) Hz, 8 H), 3.43- 3.76 (m, \(J = 5.9\) Hz, 20 H), 7.31 (AB, \(J_{AB} = 8.3\) Hz, 4 H), 7.71 (AB, \(J_{AB} = 8.3\) Hz, 4 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 21.4 (q), 49.3 (t), 54.3 (t), 56.5 (t), 59.0 (t), 69.4 (t), 70.3 (t), 127.0 (d), 129.6 (d), 136.4 (s), 143.2 (s). Exact mass (CI-HRMS) \([M + H]^+\) Calcd for C\(_{34}\)H\(_{56}\)N\(_4\)O\(_{10}\)S\(_2\): m/z 745.3516. Found: m/z 745.3525.

**Synthesis of Lairat ether 58.** A mixture of 56 (700 mg, 1.33 mmol), 2-(2-chloroethoxy)ethanol (420 mg, 3.37 mmol), Na\(_2\)CO\(_3\) (1.41 g, 13.3 mmol) and NaI (150 mg, catalytic amount) in dry CH\(_3\)CN (50 mL) was refluxed for 3 days. The mixture then was filtered, and the filtrate was concentrated in vacuo. The resulting residue was dissolved in CH\(_2\)Cl\(_2\) (35 mL) and was washed sequentially with water (2 x 20 mL) and saturated aqueous NaCl (20 mL), dried (Na\(_2\)SO\(_4\)), and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 0.1% Et\(_3\)N-EtOAc. Pure 55 (571 mg, 61%) was thereby obtained as pale yellow oil; IR (film) 3368 (br m), 2949 (s), 2863 (s), 1568 (w), 1455 (m), 1329 (m), 1123 (s), 1059 (m), 733 (w), 700 cm\(^{-1}\) (w); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.66-2.93 (m, 20 H), 3.46-3.79 (m, 32 H), 4.00 (br s, 2 H), 7.21-7.39 (m, 10 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 53.8 (t), 54.5 (t), 55.3 (t), 59.9 (t), 61.7 (t), 69.1 (t), 69.2 (t), 69.8 (t), 72.5 (t), 126.8 (d), 128.1 (d), 128.9 (d), 139.3 (s). Anal. Calcd for C\(_{38}\)H\(_{64}\)N\(_4\)O\(_8\): C, 64.73, H, 9.16. Found: C, 64.45, H, 8.78.
Exact mass (CI-HRMS) \([M_f + H]^+\) Calcd for \(C_{38}H_{64}N_4O_8\): \(m/z\ 705.4802\). Found: \(m/z\ 705.4829\).

**Synthesis of 59.** To a solution of 19 (585 mg, 1.0 mmol) and 56 (528 mg, 1.0 mmol) in dry \(CH_3CN\) (120 mL) was added \(M_2CO_3\) (M = Rb, 2.31 g, 10 mmol; M = Cs, 3.26 g, 10 mmol), and the resulting mixture was refluxed during 5 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The filtrate was concentrated *in vacuo*, and the residue was dissolved in \(CHCl_3\) (50 mL). The resulting solution was washed sequentially with water (3 x 50 mL) and saturated aqueous NaCl (30 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 by eluting with 1% \(Et_3N-EtOAc\). Pure 59 (452 mg, 61% by using \(Rb_2CO_3\) as the templating base, 340 mg, 46% by using \(Cs_2CO_3\) as the templating base) was thereby obtained as a pale yellow, viscous oil; IR (film) 2953 (s), 2868 (s), 1451 (w), 1352 (s), 1118 (vs), 1061 (m), 729 (m), 696 cm\(^{-1}\) (m); \(^1H\) NMR (\(CDCl_3\)) \(\delta\ 1.52\ (AB, J_{AB} = 10.3\ Hz, 1\ H), 1.79-1.99\ (m, 5\ H), 2.36\ (br\ s, 2\ H), 2.58\ (s, 6\ H), 2.63-2.91\ (m, 20\ H), 3.43-3.63\ (m, 16\ H), 3.67\ (s, 4\ H), 7.19-7.37\ (m, 10\ H); \(^13C\) NMR (\(CDCl_3\)) \(\delta\ 29.7\ (t), 41.3\ (d), 43.6\ (t), 43.9\ (d), 47.9\ (d), 50.4\ (t), 54.1\ (t), 58.6\ (d), 59.8\ (t), 69.7\ (t), 70.0\ (t), 95.0\ (s), 126.8\ (d), 128.1\ (d), 128.8\ (d), 139.7\ (s).\) Exact mass (CI-HRMS) \([M_f + H]^+\) Calcd for \(C_{45}H_{64}N_4O_5\): \(m/z\ 741.4955\). Found: \(m/z\ 741.4964\). Anal. Calcd for \(C_{45}H_{64}N_4O_5\): C, 72.92, H, 8.71. Found: C, 72.77 H, 8.62.
Synthesis of 60. The procedure employed above to prepare 59 also was used to synthesize 60 by using 55 to replace 56 as the starting material. Pure 60 (Rb$_2$CO$_3$ as the templating base, 547 mg, 63%) was thereby obtained as a pale yellow, viscous semi-solid; IR (film) 3055 (w), 2959 (s), 2868 (s), 2816 (m), 1599 (w), 1452 (m), 1337 (s), 1304 (m), 1267 (m), 1157 (s), 1117 (s), 1090 (s), 1001 (m), 941 (w), 816 (m), 735 (s), 654 (m), 550 cm$^{-1}$ (s); $^1$H NMR (CDCl$_3$) $\delta$ 1.51 ($AB$, $J_{AB}$ = 10.3 Hz, 1 H), 1.73-2.05 (m, 5 H), 2.28-2.99 (m, 26 H), 3.17-3.79 (m, 24 H), 7.29 (m, 4 H), 7.69 ($AB$, $J_{AB}$ = 8.1 Hz, 4 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.1 (q), 30.2 (t), 41.7 (d), 43.9 (t), 44.2 (d), 48.2 (d), 50.1 (t), 51.5 (t), 54.6 (t), 54.7 (t), 58.8 (d), 70.6 (t), 70.8 (t), 95.2 (s), 129.6 (d), 138.1 (s), 138.2 (s), 142.6 (s). Exact mass (Cl-HRMS) [M$^+$ + H]$^+$ Calcd for C$_{45}$H$_{64}$N$_4$O$_9$S$_2$: m/z 869.4193. Found: m/z 869.4195.

Synthesis of 61. The procedure employed above to prepare 59 also was used to synthesize 61 by using 20 to replace 19 as the starting material. Pure 61 (215 mg, 28% by using Rb$_2$CO$_3$ as the templating base, 223 mg, 29% by using Cs$_2$CO$_3$ as the templating base) was thereby obtained as a pale yellow, viscous oil; IR (film) 2955 (s), 2861 (s), 1742 (w), 1452 (m), 1358 (m), 1123 (vs), 1063 (s), 735 (m), 698 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) $\delta$ 1.53 ($AB$, $J_{AB}$ = 10.3 Hz, 1 H), 1.56-1.85 (m, 8 H), 1.88 ($AB$, $J_{AB}$ = 10.3 Hz, 1 H), 2.33-2.69 (m, 12 H), 2.69-2.95 (m, 16 H), 3.42-3.66 (m, 16 H), 3.69 (s, 4 H), 7.20-7.42 (m, 10 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 23.8 (t), 29.2 (t), 41.4 (d), 43.6 (t), 43.9 (d), 47.6 (d), 54.0 (t), 54.7 (t), 54.9 (t), 58.5 (d), 60.2 (t), 69.3 (t), 70.2 (t), 96.1 (s), 126.8 (d), 128.1 (d),
128.8 (d), 139.7 (s). Exact mass (CI-HRMS) \([M + H]^+\) Calcd for C\(_{47}H_{68}N_4O_5\): \(m/z\) 769.5270. Found: \(m/z\) 769.5269.

**Synthesis of 62.** The procedure employed above to prepare 60 also was used to synthesize 62 by using 20 to replace 19 as the starting material. Pure 62 (242 mg, 27% by using Cs\(_2\)CO\(_3\) as the templating base) was thereby obtained as a yellow, viscous semi-solid; IR (film) 3054 (w), 2957 (s), 2863 (s), 2812 (m), 1599 (w), 1456 (m), 1339 (s), 1306 (s), 1267 (m), 1161 (s), 1119 (s), 1090 (s), 1003 (m), 943 (m), 816 (m), 733 (s), 654 (s), 550 cm\(^{-1}\) (s); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.49-1.79 (m, 9 H), 1.88 (\(AB, J_{AB} = 10.2\) Hz, 1 H), 2.30-2.85 (m, 26 H), 3.13-3.71 (m, 24 H), 7.26-7.35 (m, 4 H), 7.69(\(AB, J_{AB} = 8.1\) Hz, 4 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 21.4 (q), 23.3 (t), 29.0 (t), 41.4 (d), 43.5 (t), 43.9 (d), 47.6 (d), 49.7 (t), 54.1 (t), 54.3 (t), 54.8 (t), 58.4 (d), 69.2 (t), 70.5 (t), 96.1 (s), 127.1 (d), 129.6 (d), 138.4 (s), 143.2 (s). Exact mass (CI-HRMS) \([M + H]^+\) Calcd for C\(_{47}H_{64}N_4O_5\): \(m/z\) 897.4506. Found: \(m/z\) 897.4508.

**Synthesis of 63.** A mixture of 59 (370 mg, 0.5 mmol) and 10% palladized charcoal (150 mg, catalytic amount) in MeOH (60 mL) was placed in a Parr shaker apparatus and was hydrogenated at 56 psig during 4 days. The reaction mixture was filtered to remove spent catalyst, and the filtrate was concentrated \textit{in vacuo}. The residue, 63 (280 mg, 100%) was obtained as a pale yellow oil; IR (film) 3351 (br, s), 2944 (s), 2834 (s), 1449 (w), 1412 (w), 1269 (w), 1032 (vs), 739 cm\(^{-1}\) (s); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.44 (\(AB, J_{AB} = 10.2\) Hz, 1 H), 1.70-1.95 (m, 5 H), 2.39 (br s, 2 H), 2.42-3.01 (m, 28 H), 3.39-
3.76 (m, 16 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 29.3 (t), 41.2 (d), 43.5 (t), 43.8 (d), 47.9 (d), 49.28 (t), 49.34(t), 50.5 (t), 53.2 (t), 58.7 (d), 69.7 (t), 70.3 (t), 94.8 (s). Exact mass (CI-HRMS) $[M_r + H]^+$ Calcd for C$_{31}$H$_{52}$N$_4$O$_5$: m/z 561.4016. Found: m/z 561.4015.

**Synthesis of 64.** The procedure employed above to prepare 61 also was used to synthesize 64 by using 61 as the starting material. Pure 64 (471 mg, 100%) was thereby obtained as a colorless semisolid; IR (film) 3401 (br, s), 2967 (s), 2774 (m), 1635 (m), 1456 (m), 1366 (w), 1136 (s), 1065 cm$^{-1}$ (m); $^1$H NMR (CD$_3$OD): $\delta$ 1.58 ($AB$, $J_{AB}$ = 10.5 Hz, 1 H), 1.79-2.18 (m, 9 H), 2.41-2.79 (m, 8 H), 3.15-3.73 (m, 22 H), 3.77-4.15 (m, 16 H); $^{13}$C NMR (CD$_3$OD) $\delta$ 19.2 (t), 29.5 (t), 42.6 (d), 44.4 (t), 45.2 (d), 48.5 (d), 48.1 (t), 49.1 (t), 52.2 (t), 52.3 (t), 55.2 (t), 59.2 (d), 64.6 (t), 64.9 (t), 67.29 (t), 67.34 (t), 97.2 (s). Exact mass (CI-HRMS) $[M_r + H]^+$ Calcd for C$_{33}$H$_{56}$N$_4$O$_5$: m/z 589.4329. Found: m/z 589.4332.

**Synthesis of 65.** A mixture of 28 (644 mg, 1 mmol), 55 (656 mg, 1 mmol) and Cs$_2$CO$_3$ (3.25 g, 10 mmol) in dry CH$_3$CN (200 mL) was refluxed during 6 days. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in CH$_3$CN (50 mL) and the resulting solution was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 0.1% Et$_3$N-EtOAc. Pure 65 (46.5 mg, 4.7%) was thereby obtained as pale yellow oil; IR (film) 3057 (w), 2955 (s), 2863 (s), 1599 (w), 1452 (m), 1343 (s), 1306 (sh, m), 157
1159 (vs), 1119 (vs), 1010 (s), 816 (m), 735 (s), 716 (sh, w), 653 cm$^{-1}$ (m); $^1$H NMR: (CDCl$_3$) δ 1.50 ($AB$, $J_{AB} =10.1$ Hz, 1 H), 1.85 ($AB$, $J_{AB} = 10.1$ Hz, 1 H), 1.94-2.10 (m, 4 H), 2.29-2.88 (m, 26 H), 3.3 (t, $J = 5.9$ Hz, 8 H), 3.41-3.76 (m, 24 H), 7.28 ($AB$, $J_{AB} = 8.1$ Hz, 4 H), 7.67 ($AB$, $J_{AB} = 8.11$ Hz, 4 H); $^{13}$C NMR (CDCl$_3$) δ 21.4 (q), 32.3 (t), 41.5(d), 43.5 (t), 43.9 (d), 48.1 (d), 49.4 (t), 54.6 (t), 54.8 (t), 58.9 (d), 68.1 (t), 69.4 (t), 69.9 (t), 70.5 (t), 94.4 (s), 127.1 (d), 129.6 (d), 136.5 (s), 143.2 (s). Exact mass (CI-HRMS) [M$^+$ + H]$^+$ Calcd for C$_{49}$H$_{72}$N$_4$O$_{11}$S$_2$: m/z 957.471729. Found: m/z 957.4713.

**Synthesis of 66.** (i) Cs$^+$ Template: A mixture of 28 (644 mg, 1.0 mmol), 56 (528 mg, 1.0 mmol) and Cs$_2$CO$_3$ (3.25 g, 10 mmol, excess) in dry CH$_3$CN (200 mL) was refluxed during 6 days. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in CHCl$_3$ (50 mL) and the resulting solution was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL), and dried (Na$_2$SO$_4$), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel by eluting with 0.1% Et$_3$N-EtOAc. Nine fractions were collected, however, analysis of the $^1$H and $^{13}$C NMR spectra of each fraction failed to confirm the presence of 66. (ii) Rb$^+$ template: The reaction was repeated exactly with above procedures except that Cs$_2$CO$_3$ was replaced by Rb$_2$CO$_3$ (2.31 g, 10 mmol). The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in CHCl$_3$ (50 mL) and the resulting solution was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL), and dried (Na$_2$SO$_4$), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified
via column chromatography on silica gel by eluting with 0.1% Et₃N-EtOAc. Pure 66 (383 mg, 44.5%) was obtained as pale yellow oil; IR (film) 3059 (w), 3028 (w), 2974 (w), 2876 (w), 1451 (w), 1361 (vs), 1076 (sh m), 741 (w), 702 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.51 (AB, J_AB = 10.1 Hz, 1 H), 1.87 (AB, J_AB = 10.1 Hz, 1 H), 2.00-2.15 (m, 4 H), 2.36-2.68 (m, 8 H), 2.70-2.95 (m, 20 H), 3.44-3.79 (m, 28 H), 7.22-7.39 (m, 10 H); ¹³C NMR (CDCl₃) δ 32.5 (t), 41.6 (d), 43.5 (t), 44.1 (d), 48.2 (d), 53.9 (t), 54.9 (t), 55.2 (t), 59.0 (d), 60.0 (t), 68.1 (t), 69.6 (t), 70.0 (t), 94.4 (s), 126.8 (d), 128.1 (d), 128.8 (d), 139.6 (s). Exact mass (CI-HRMS) [M⁺ + H]⁺ Calcd for C₄₉H₇₂N₄O₇: m/z 829.5479. Found: m/z 829.5459.

Synthesis of 67. A mixture of 66 (363 mg 0.43 mmol) and 10% palladized charcoal (150 mg, catalytic amount) in MeOH (50 mL) was placed in a Parr shaker apparatus and was hydrogenated at 60 psi during 5 days. The mixture then was filtered, and the filtrate was concentrated and dried in vacuo. Pure 67 (273 mg, 91%) was thereby obtained as pale yellow viscous oil; IR (film) 3411 (br, m), 2948 (s), 2863 (s), 1571 (w), 1453 (w), 1107 cm⁻¹ (vs); ¹H NMR (C₆D₆) δ 1.43 (AB, J_AB = 10.2 Hz, 1 H), 1.81 (AB, J_AB = 10.2 Hz, 1 H), 2.03-2.16 (m, 4 H), 2.26 (br s, 2 H), 2.35-2.59 (m, 8 H), 2.60-2.89 (m, 20 H), 3.35-3.65 (m, 20 H), 3.71 (t, J = 6.4 Hz, 4 H); ¹³C NMR (C₆D₆) δ 33.1 (t), 41.9 (d), 43.8 (t), 44.4 (d), 48.9 (d), 49.8 (t), 55.3 (t), 55.8 (t), 59.5 (t), 68.4 (t), 70.1 (t), 70.4 (t), 70.8 (t), 94.6 (t). Exact mass (CI-HRMS) [M⁺ + H]⁺ Calcd for C₃₅H₆₀N₄O₇: m/z 649.4541. Found: m/z 649.4546.
**Synthesis of 68 and 69.** A mixture of 56 (1.06 g, 2.0 mmol), EtBr (2.2 mg, 2.0 mmol) and K$_2$CO$_3$ (1.38 g, 10 mmol) in dry CH$_3$CN (30 mL) was heated overnight with stirring at 50-60 °C. The resulting mixture was allowed to cool gradually to ambient temperature and then was filtered. The filtrate was concentrated in vacuo, and the residue was purified via column chromatography on alumina by eluting with EtOAc. Pure 68 (533 mg, 46%) was thereby obtained as a colorless oil; IR (film) 2963 (m), 2936 (m), 2864 (s), 1493 (w), 1352 (w), 1117 (vs), 1065 (s), 735 (m), 698 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) $\delta$ 1.02 (t, $J$ = 7.1 Hz, 6 H), 2.60-2.79 (m, 20 H), 3.49-3.61 (m, 16 H), 3.69 (s, 4 H), 7.19-7.39 (m, 10 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 12.0 (q), 49.3 (t), 53.6 (t), 53.8 (t), 69.8 (t), 126.8 (d), 128.1 (d), 128.8 (d), 139.7 (s). Exact mass (CI-HRMS) [M$_r$ + H]$^+$ Calcd for C$_{34}$H$_{36}$N$_4$O$_4$: m/z 585.4380. Found: m/z 585.4389.

Continued elution of the chromatography column afforded a second fraction from which pure 69 (332 mg, 30%) was obtained as a colorless oil; IR (film) 3335 (br, w), 2932 (m), 2861 (s), 1653 (w), 1452 (m), 1352 (w), 1117 (vs), 1063 (m), 735 cm$^{-1}$ (m) (m); $^1$H NMR (CDCl$_3$) $\delta$ 1.03 (t, $J$ = 7.0 Hz, 3 H), 1.99 (s, 1 H), 2.45-3.01 (m, 18 H), 3.36-3.93 (m, 20 H), 7.17-7.53 (m, 10 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 11.9 (q), 49.2 (t), 49.4 (t), 53.5 (t), 53.6 (t), 53.8 (t), 59.6 (t), 69.6 (t), 69.7 (t), 70.0 (t), 126.8 (d), 128.1 (d), 128.8 (d), 139.6 (s). Exact mass (CI-HRMS) [M$_r$ + H]$^+$ Calcd for C$_{32}$H$_{32}$N$_4$O$_4$: m/z 557.4067. Found: m/z 557.4071.

**Synthesis of 70.** A mixture of 69 (520 mg, 0.89 mmol) and 10% palladized charcoal (200 mg, catalytic amount) in MeOH (80 mL) was placed in a Parr shaker...
apparatus and was hydrogenated at 56 psig during 4 days. The reaction mixture was filtered to remove spent catalyst, and the filtrate was concentrated in vacuo. The residue, 70 (352 mg, 98%) was obtained as a pale yellow oil; IR (film) 3401 (br, m), 2967 (m), 2936 (m), 2874 (s), 1651 (w), 1454 (m), 1354 (w), 1113 (vs), 1072 cm\(^{-1}\) (m); \(^1\)H NMR (CDCl\(_3\)): \(\delta 0.96 \ (t, \ J = 7.1 \ Hz, \ 6 \ H), \ 2.55-2.82 \ (m, \ 20 \ H),\ 2.86 \ (br \ s, \ 2 \ H), \ 3.41-3.71(m, \ 16 \ H)\); \(^13\)C NMR (CDCl\(_3\)): \(\delta 11.8 \ (q), \ 48.8 \ (t), \ 49.0 \ (t), \ 53.4 \ (t), \ 69.5 \ (t), \ 70.0 \ (t). \) Exact mass (CI-HRMS) \([M_r + H]^+\) Calcd for C\(_{20}\)H\(_{44}\)N\(_4\)O\(_4\): \(m/z\) 405.3441. Found: \(m/z\) 405.3448.

**Synthesis of 71.** A mixture of 70 (330 mg, 0.82 mmol), 19 (454 mg, 0.82 mmol), and Rb\(_2\)CO\(_3\) (943 mg, 4.1 mmol) in dry CH\(_3\)CN (100 mL) was refluxed with stirring during 4 days. The mixture was allowed to cool gradually to ambient temperature and then was filtered. The residue was washed with CHCl\(_3\) (10 mL); the washings were combined with the filtrate, and the resulting mixture was concentrated in vacuo. The residue was dissolved in CHCl\(_3\) (50 mL), and was washed sequentially with water (3 x 50 mL) and saturated aqueous NaCl (30 mL), dried (Na\(_2\)SO\(_4\)) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on alumina by eluting with EtOAc. Pure 71 (248 mg, 49%) was thereby obtained as a colorless oil; IR (film) 2949 (s), 2835 (s), 1450 (w), 1269 (w), 1111 (w), 1026 (vs), 739 cm\(^{-1}\) (s); \(^1\)H NMR (CDCl\(_3\)): \(\delta 0.95 \ (t, \ J = 7.1 \ Hz, \ 6 \ H), \ 1.46 \ (AB, \ J_{AB} = 10.5 \ Hz, \ 1 \ H), \ 1.77-2.00 \ (m, \ 5 \ H), \ 2.22-2.53 \ (m, \ 32 \ H), \ 3.46-3.73 \ (m, \ 16 \ H)\); \(^13\)C NMR (CDCl\(_3\)): \(\delta 2.9 \ (q), \ 30.3 \ (t), \ 41.7 \ (d), \ 43.9 \ (t), \ 44.2 \ (d), \ 48.4 \ (d), \ 49.8 \ (t), \ 49.9 \ (t), \ 51.2 \ (t), \ 54.7 \ (t), \ 54.90\)
(t), 54.94 (t), 58.9 (d), 70.4 (t), 70.8 (t), 95.3 (s). Exact mass (CI-HRMS) \([M_r + H]^+\).
Calcd for C\(_{35}\)H\(_{60}\)N\(_4\)O\(_5\): \textit{m/z} 617.4642. Found: \textit{m/z} 617.4648.

**Synthesis of 72.** \[^{[236}, 237]\] A solution of 1,3-propanediol (7.6 g, 100 mmol), PhCH\(_2\)Br (20.57 g, 121 mmol) in dry THF (150 mL) was cooled to 0 °C \textit{via} application of an external ice-water bath. Sodium hydride (60% dispersion in mineral oil oil, 4.8 g, 120 mmol) was added portionwise with stirring during 1.5 h. After the addition of NaH had been completed, the reaction mixture was heated and stirred overnight at 50-60 °C. Subsequently, the reaction mixture was allowed to cool gradually to ambient temperature and then was cooled to 0 °C \textit{via} application of an external ice-water bath. To the cooled reaction mixture was added dropwise with stirring saturated aqueous NH\(_4\)Cl (ca. 3.5 mL) until evolution of gas had ceased. The resulting mixture was dried (Na\(_2\)SO\(_4\)) and filtered, and the filtrate was concentrated \textit{in vacuo}. The residue was purified \textit{via} column chromatography on silica gel by eluting with 15% acetone-hexane. Pure 72 (8.32 g, 50%) was thereby obtained as a colorless oil; IR (film) 3396 (br, s), 2945 (s), 2866 (s), 1456 (m), 1365 (m), 1096 (s), 1078 (s), 739 (s), 704 cm\(^{-1}\) (s); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.79-1.91 (m, 2 H), 2.68 (s, 1 H) 3.63 (t, \(J = 5.9\) Hz, 2 H), 3.75 (t, \(J = 5.9\) Hz, 2 H), 4.51 (s, 2 H), 7.26-7.41 (m, 5 H); \(^13\)C NMR (CDCl\(_3\)): \(\delta\) 32.1 (t), 61.3 (t), 69.0 (t), 73.1 (t), 127.5 (d), 127.6 (d), 128.3 (d), 138.0 (s). \[^{[236}, 237]\]

**Synthesis of 73.** \[^{[236}-238]\] A solution of 1,4-butanediol (9.0 g, 100 mmol), PhCH\(_2\)Br (20.57 g, 121 mmol) in dry THF (150 mL) was cooled to 0 °C \textit{via} application of an
external ice-water bath. Sodium hydride (60% dispersion in mineral oil oil, 4.8 g, 120 mmol) was added portionwise with stirring during 1.5 h. After the addition of NaH had been completed, the reaction mixture was heated and stirred overnight at 50-60 °C. Subsequently, the reaction mixture was allowed to cool gradually to ambient temperature and then was cooled to 0 °C via application of an external ice-water bath. To the cooled reaction mixture was added dropwise with stirring saturated aqueous NH₄Cl (ca. 3.5 mL) until evolution of gas had ceased. The resulting mixture was dried (Na₂SO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 15% acetone-hexane. Pure 73 (9.0 g, 50%) was thereby obtained as a colorless oil; IR (film) 3389 (br, s), 2937 (s), 2868 (s), 1725 (m), 1495 (m), 1454 (m), 1363 (m), 1279(m), 1101 (s), 1063 (s), 739 (s), 722 cm⁻¹ (s); ¹H NMR (CDCl₃) δ 1.61-1.79 (m, 4 H), 2.77 (br s, 1 H), 3.53 (t, J = 5.9 Hz, 1 H), 3.60 (t, J = 5.5 Hz, 2 H), 4.51 (s, 2 H), 7.23-7.42 (m, 5 H); ¹³C NMR (CDCl₃) δ 26.5 (t), 29.9 (t), 62.4 (t), 70.2 (t), 72.9 (t), 127.5 (d), 127.6 (d), 128.3 (d) 138.1 (s). [236-238]

Synthesis of 74. [239] A solution of 72 (4.16 g, 25.1 mmol) in THF (50 mL) was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added with stirring a solution of NaOH (5.01 g, 125 mmol) in water (10 mL), and the resulting mixture was stirred at 0 °C during 1 h. Subsequently, a solution of TsCl (5.73 g, 30.1 mmol) in THF (30 mL) was added dropwise with stirring to the cooled solution during 1 h. After the addition of TsCl had been completed, the external ice-water bath was removed, and the resulting mixture was allowed to warm gradually to ambient
temperature while stirring during 6 h. The reaction mixture was extracted with EtOAc (3 x 100 mL); the combined extracts were washed sequentially with water (200 mL) and saturated aqueous NaCl (100 mL), dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 8% acetone-hexane. Pure 74 (5.49 g, 69%) was thereby obtained as a colorless oil; IR (film) 3034 (w), 2965 (m), 2868 (s), 1601 (s), 1458 (s), 1362 (vs), 1179 (vs), 1101 (s), 951 (s), 819 (s), 743 (s), 704 (s), 667 (s), 580(s), 559 cm$^{-1}$ (s); $^1$H NMR (CDCl$_3$) $\delta$ 1.88-1.99 (m, 2 H), 2.41 (s, 3 H), 3.50(t, $J$ = 5.9 Hz, 2 H), 4.16 (t, $J$ = 6.2 Hz, 2 H), 4.39 (s, 2 H), 7.21-7.39 (m, 7 H), 7.79 (AB, $J_{AB}$ = 8.3 Hz, 2 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.5 (q), 29.3 (t), 65.57 (t), 67.62 (t), 72.9 (t), 127.4 (d), 127.5 (d), 127.8 (d), 128.3 (d), 129.7 (d), 133.0 (s), 138.0 (s), 144.6 (s). [239]

Synthesis of 75. [240] A solution of 73 (4.5 g, 25.1 mmol) in THF (50 mL) was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added with stirring a solution of NaOH (5.01 g, 125 mmol) in water (10 mL), and the resulting mixture was stirred at 0 °C during 1 h. Subsequently, a solution of TsCl (5.73 g, 30.1 mmol) in THF (30 mL) was added dropwise with stirring to the cooled solution during 1 h. After the addition of TsCl had been completed, the external ice-water bath was removed, and the resulting mixture was allowed to warm gradually to ambient temperature while stirring during 6 h. The reaction mixture was extracted with EtOAc (3 x 100 mL); the combined extracts were washed sequentially with water (200 mL) and saturated aqueous NaCl (100 mL), dried (Na$_2$SO$_4$) and filtered, and the filtrate was
concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 8% acetone-hexane. Pure 75 (6.92 g, 72%) was thereby obtained as a colorless oil; IR (film) 3063 (w), 2945 (m), 2862 (m), 1595 (m), 1499 (m), 1456 (m), 1363 (m), 1190 (s), 1180 (vs), 1121 (s), 1033 (m), 1011 (m), 818 (m), 704 (s), 579 (s), 563 cm\(^{-1}\) (s); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.57-1.83 (m, 4 H), 2.44 (s, 3 H), 3.43 (t, \(J = 6.0\) Hz, 2 H), 4.05 (t, \(J = 6.3\) Hz, 2 H), 4.46 (s, 2 H), 7.23-7.44 (m, 7 H), 7.78 (AB, \(J_{AB} = 8.4\) Hz, 2 H); \(^1^3\)C NMR (CDCl\(_3\)): \(\delta\) 21.6 (q), 25.6 (t), 25.8 (t), 69.2 (t), 70.4 (t), 72.8 (t), 127.5 (d), 127.8 (d), 128.3 (d), 129.8 (d), 133.1 (s), 138.3 (s), 144.6 (s).

**Synthesis of 76.** A solution of 72 (2.85 g, 17.2 mmol) and 74 (5.49 g, 17.2 mmol) in dry THF (50 mL) was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added portionwise with stirring NaH (60% suspension in mineral oil oil, 824 mg, 20.6 mmol) during 0.5 h. After the addition of NaH had been completed, the external ice-water bath was removed, and the reaction mixture was heated overnight with stirring at 50-60 °C. Subsequently, the reaction mixture was allowed to cool gradually to ambient temperature and then was cooled to 0 °C via application of an external ice-water bath. To the cooled reaction mixture was added dropwise with stirring saturated aqueous NH\(_4\)Cl (ca. 2 mL) until evolution of gas had ceased. The resulting mixture was dried (Na\(_2\)SO\(_4\)) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 3% acetone-hexane. Pure 76 (3.92 g, 73%) was thereby obtained as a colorless oil; IR (film) 3065 (w), 3032 (w), 2949 (m), 2924 (m), 2863 (s), 1740 (w), 1497 (w), 1454 (m), 1366
(m), 1103 (vs), 1023 (m), 737 (s), 698 cm\(^{-1}\) (s); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.80-1.93 (m, 4 H), 3.49-3.59 (m, 8 H), 7.22-7.35 (m, 10 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 30.1 (t), 67.3 (t), 72.9 (t), 127.4 (d), 127.5 (d), 128.2 (d), 138.5 (s). Exact mass (CI-HRMS) \([M + H]^+\) Calcd for C\(_{20}\)H\(_{26}\)O\(_3\): m/z 315.1960. Found: m/z 315.1958.

**Synthesis of 77.** A solution of 73 (3.1 g, 17.2 mmol) and 75 (5.7 g, 17.2 mmol) in dry THF (50 mL) was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added portionwise with stirring NaH (60% suspension in mineral oil, 824 mg, 20.6 mmol) during 0.5 h. After the addition of NaH had been completed, the external ice-water bath was removed, and the reaction mixture was heated overnight with stirring at 50-60 °C. Subsequently, the reaction mixture was allowed to cool gradually to ambient temperature and then was cooled to 0 °C via application of an external ice-water bath. To the cooled reaction mixture was added dropwise with stirring saturated aqueous NH\(_4\)Cl (ca. 2 mL) until evolution of gas had ceased. The resulting mixture was dried (Na\(_2\)SO\(_4\)) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 3% acetone-hexane. Pure 77 (5.0 g, 70%) was thereby obtained as a colorless oil; IR (film) 3036 (w), 2938 (m), 2859 (s), 1497 (w), 1454 (w), 1364 (w), 1208 (w), 1107 (vs), 1023 (w), 737 (s), 698 cm\(^{-1}\) (s); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.59-1.77 (m, 8 H), 3.41 (t, \(J = 6.1\) Hz, 4 H), 3.48 (t, \(J = 6.1\) Hz, 4H), 4.51 (s, 4 H), 7.23-7.39 (m, 10 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 26.5 (t), 70.1 (t), 70.5 (t), 72.8 (t), 127.4 (d), 127.6 (d), 128.3 (d), 138.6 (s). Exact mass (CI-HRMS) \([M + H]^+\) Calcd for C\(_{22}\)H\(_{30}\)O\(_3\): m/z 343.2273. Found: m/z 343.2281.
Synthesis of 78. [241-243] A mixture of 76 (3.90 g, 12.4 mmol) and 10% palladized charcoal (350 mg, catalytic amount) in MeOH (100 mL) was placed in a Parr shaker apparatus and was hydrogenated at 56 psig during 2 days. The reaction mixture was filtered to remove spent catalyst, and the filtrate was concentrated in vacuo. The residue, 78 (1.65 g, 99%) was obtained as a colorless oil; IR (film) 3371 (br, s), 2953 (s), 2886 (s), 1665 (m), 1439 (m), 1383 (m), 1127 (s), 1088 cm\(^{-1}\) (s); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.76-1.90 (m, 4 H), 3.45 (br s, 2 H), 3.60 (t, \(J = 5.9\) Hz, 4 H), 3.72 (t, \(J = 5.7\) Hz, 4 H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 32.0 (t), 60.5 (t), 69.1 (t). [241-243]

Synthesis of 79. [244-246] A mixture of 77 (4.1 g, 12.0 mmol) and 10% palladized charcoal (350 mg, catalytic amount) in MeOH (100 mL) was placed in a Parr shaker apparatus and was hydrogenated at 56 psig during 2 days. The reaction mixture was filtered to remove spent catalyst, and the filtrate was concentrated in vacuo. The residue, 79 (1.9 g, 98%) was obtained as a colorless oil; IR (film) 3380 (br, s), 2953 (s), 2878 (s), 1665 (w), 1462 (m), 1375 (m), 1123 (s), 1076 (s), 1015 (s), 976 cm\(^{-1}\) (m); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.51-1.70 (m, 8 H), 3.26 (br s, 2 H), 3.42 (t, \(J = 5.6\) Hz, 4 H), 3.56 (t, \(J = 5.8\) Hz, 4 H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 26.5 (t), 29.8 (t), 62.3 (t), 70.8 (t). [244-246]

Synthesis of 80. [241] A solution of 78 (1.60 g, 11.9 mmol) in THF (20 mL) was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added with stirring a solution of NaOH (5.0 g, 125 mmol) in water (10 mL), and the
resulting mixture was stirred at 0 °C during 1 h. Subsequently, a solution of TsCl (5.46 g, 28.7 mmol) in THF (30 mL) was added dropwise with stirring to the cooled solution during 1 h. After the addition of TsCl had been completed, the external ice-water bath was removed, and the resulting mixture was allowed warm gradually to ambient temperature while stirring during 6 h. The reaction mixture was extracted with EtOAc (100 mL); the organic layer was washed sequentially with water (2 x 50 mL) and saturated aqueous NaCl (50 mL), dried (Na₂SO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via fractional recrystallization from MeOH. Pure 80 (3.72 g, 71%) was thereby obtained as a colorless microcrystalline solid, mp 85-86 °C; IR (KBr) 2928 (w), 2903 (w), 2878 (w), 1597 (m), 1360 (s), 1190 (s), 1175 (vs), 1128 (s), 1101 (s), 951 (vs), 885 (m), 841 (s), 816 (s), 772 (s), 666 (vs), 581 (s), 558 cm⁻¹ (vs); ¹H NMR (CDCl₃) δ 1.71-1.85 (m, 4 H), 2.43 (s, 6 H), 3.31 (t, J = 6.0 Hz, 4 H), 4.04 (t, J = 6.2 Hz, 4 H), 7.32 (AB, J_AB = 8.2 Hz, 4 H), 7.75 (AB, J_AB = 8.2 Hz, 4 H); ¹³C NMR (CDCl₃) δ 21.6 (q), 29.2 (t), 66.2 (t), 67.5 (t), 127.5 (d), 127.8 (d), 129.8 (d), 133.0 (s), 144.7 (s). Exact mass (CI-HRMS) [M⁺ + H]⁺ Calcd for C₂₀H₂₆O₇S₂: m/z 443.1198. Found: m/z 443.1202.

**Synthesis of 81.** A solution of 79 (1.85 g, 11.4 mmol) in THF (20 mL) was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added with stirring a solution of NaOH (5.0 g, 125 mmol) in water (10 mL), and the resulting mixture was stirred at 0 °C during 1 h. Subsequently, a solution of TsCl (5.22 g, 27.4 mmol) in THF (30 mL) was added dropwise with stirring to the cooled solution
during 1 h. After the addition of TsCl had been completed, the external ice-water bath was removed, and the resulting mixture was allowed warm gradually to ambient temperature while stirring during 8 h. The reaction mixture was extracted with EtOAc (100 mL); the organic layer was washed sequentially with water (2 x 50 mL) and saturated aqueous NaCl (50 mL), dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated \textit{in vacuo}. The residue was purified via column chromatography by eluting with 20% EtOAc-hexane. Pure 81 (3.72 g, 71%) was thereby obtained as a colorless oil; IR (KBr) 2949 (s), 2942 (s), 2864 (s), 1600 (s), 1447 (m), 1356 (vs), 1192 (s), 1177 (m), 1099 (s), 943 (s), 818 (s), 789 (s), 735 (s), 665 (s), 577 (s), 556 cm\(^{-1}\) (s); $^1$H NMR (CDCl$_3$) $\delta$ 1.45-1.73 (m, 4 H), 2.42(s, 6 H), 3.28 (t, $J = 6.0$ Hz, 4 H), 4.00 (t, $J = 6.2$ Hz, 4 H), 7.31 ($AB$, $J_{AB}$ = 8.2 Hz, 4 H), 7.75 ($AB$, $J_{AB}$ = 8.2 Hz, 4 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.6 (q), 25.6 (t), 25.8 (t), 69.7 (t), 70.4 (t), 127.8 (d), 129.8 (d), 129.9 (d), 133.1 (s), 144.7 (s).

Exact mass (CI-HRMS) [M$_r$ + H]$^+$ Calcd for C$_{22}$H$_{30}$O$_7$S$_2$: $m/z$ 471.1511. Found: $m/z$ 471.1502.

**Synthesis of 82.** To a solution of 80 (442 mg, 1.0 mmol) and 56 (528 mg, 4.1 mmol) in dry CH$_3$CN (120 mL) was added Rb$_2$CO$_3$ (2.31 g, 10 mmol), and the resulting mixture was refluxed during 5 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The residue was washed with CHCl$_3$ (3 x 10 mL); the filtrate and CHCl$_3$ wash solutions were combined, and the resulting solution was concentrated \textit{in vacuo}. The residue was dissolved in CHCl$_3$ (50 mL); the resulting solution was washed sequentially with water (50 mL) and saturated aqueous NaCl (30
mL). The organic layer was dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography by eluting with 1% Et$_3$N-EtOAc. Pure 82 (247 mg, 40%) was thereby obtained as a pale yellow oil; IR (film) 3025 (w), 2942 (s), 2853 (s), 2807 (s), 1451 (m), 1352 (w), 1121 (s) 1061 (m), 735 (m), 698 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) $\delta$ 1.62-1.82 (m, 4 H), 2.41-2.70 (m, 12 H), 2.77 (t, $J = 6.2$ Hz, 8 H), 3.39-3.66 (m, 20 H), 3.70 (s, 4 H), 7.20-7.46 (m, 10 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 27.9 (t), 51.6 (t), 53.9 (t), 54.9 (t), 59.7 (t), 68.7 (t), 69.6 (t), 70.0 (t), 126.8 (d), 128.1 (d), 128.8 (d), 139.6 (s). Exact mass (CI-HRMS) [M$^+$ + H]$^+$ Calcd for C$_{36}$H$_{58}$N$_4$O$_5$: m/z 627.4485. Found: m/z 627.4475.

Synthesis of 83. The procedure employed above to prepare 82 also was used to synthesize 83 by starting with 81 (653 mg, 1 mmol) and 56 (528 mg, 1 mmol) as reactants. Pure 83 (143 mg, 22%) was thereby obtained as a pale yellow oil; IR (film) 3028 (w), 2944 (s), 2807 (m), 1452 (w), 1356 (w), 1119 (vs), 1063 (s), 735 (m), 698 cm$^{-1}$ (m); $^1$H NMR (C$_6$D$_6$) $\delta$ 1.59-1.81 (m, 8 H), 2.48 (t, $J = 6.6$ Hz, 4 H), 2.60-2.79 (m, 8 H), 2.83 (t, $J = 5.9$ Hz, 8 H), 3.36 (t, $J = 4.9$ Hz, 4 H), 3.42-3.73 (m, 20 H), 7.09-7.31 (m, 6 H), 7.36-7.46 (m, 4 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 25.6 (t), 27.8 (t), 54.7 (t), 55.5 (t), 55.8 (t), 60.7 (t), 70.4 (t), 70.6 (t), 70.7 (t), 127.0 (d), 128.4 (d), 129.1 (d), 140.8 (s). Exact mass (CI-HRMS) [M$^+$ + H]$^+$ Calcd for C$_{38}$H$_{62}$N$_4$O$_5$: m/z 655.4798. Found: m/z 655.4808.

Synthesis of 84. A mixture of 82 (500 mg, 0.80 mmol) and 10% palladized charcoal (150 mg, catalytic amount) in MeOH (80 mL) was placed in a Parr shaker
apparatus and was hydrogenated at 56 psig during 5 days. The reaction mixture was filtered to remove spent catalyst, and the filtrate was concentrated \textit{in vacuo}. The residue, \textbf{84} (357 mg, 100\%) was obtained as a pale yellow semi-solid; \textit{IR} (KBr) 3411 (br, s), 2922 (m), 2872 (m), 1653 (m), 1107 cm\(^{-1}\) (m); \textit{\(^1\)H NMR} (CD\(_2\)\(_3\)) \(\delta\) 1.69-1.83 (m, 4 H), 2.30 (br s, 2 H), 2.51-2.69 (m, 12 H), 2.74 (t, \(J = 5.1\) Hz, 8 H), 3.39 (t, \(J = 5.4\) Hz, 8 H), 3.50 (t, \(J = 5.1\) Hz, 8 H), 3.62 (t, \(J = 6.3\) Hz, 4 H); \textit{\(^13\)C NMR} (CD\(_2\)\(_3\)) \(\delta\) 28.9 (t), 49.9 (t), 52.2 (t), 55.2 (t), 68.8 (t), 70.0 (t), 71.0 (t). Exact mass (CI-HRMS) \([M + H]^+\) Calcd for C\(_{22}\)H\(_{46}\)N\(_4\)O\(_5\): \(m/z\) 447.3546. Found: \(m/z\) 447.3547.

\textbf{Synthesis of 85}. The procedure employed above to prepare \textbf{84} also was used to synthesize \textbf{85} by starting with \textbf{83} (327 mg, 0.50 mmol) as reactant. Pure \textbf{85} (216 mg, 91\%) was thereby obtained as a pale yellow oil; \textit{IR} (KBr) 3421 (br, s), 2936 (m), 2868 (m), 1653 (m), 1111 cm\(^{-1}\) (m); \textit{\(^1\)H NMR} (CD\(_3\)OD) \(\delta\) 1.16 (s, 2 H), 1.55 (m, 4 H), 1.85 (m, 4 H), 3.26-3.60 (m, 20 H), 3.63-4.03 (m, 2 H); \textit{\(^13\)C NMR} (CD\(_3\)OD) \(\delta\) 22.5 (t), 28.3 (t), 49.1 (t), 52.7 (t), 55.5 (t), 64.7 (t), 67.3 (t), 72.0 (t). Exact mass (CI-HRMS) \([M + H]^+\) Calcd for C\(_{24}\)H\(_{50}\)N\(_4\)O\(_5\): \(m/z\) 475.3859. Found: \(m/z\) 475.3863.

\textbf{Synthesis of 86}. A mixture of \textbf{63} (169 mg, 0.302 mmol), M\(_2\)CO\(_3\) (M = K, 417 mg, 3.02 mmol; M = Na, 319 mg, 3.01 mmol), and triethylene glycol ditosylate (138 mg, 0.302 mmol) in dry CH\(_3\)CN (60 mL) was refluxed with stirring during 5 days. The resulting mixture was allowed to cool gradually to ambient temperature and then was
filtered. The residue was washed with CHCl$_3$ (50 mL), and the combined filtrate and CHCl$_3$ washings were concentrated in vacuo. The residue was dissolved in CHCl$_3$ (50 mL); the resulting solution was washed sequentially with water (3 x 50 mL) and saturated aqueous NaCl (30 mL), dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on alumina by eluting with EtOAc. Pure 86 (94 mg, 46% with K$_2$CO$_3$ as the templating base; 60 mg, 30% with Na$_2$CO$_3$ as the templating base) was thereby obtained as a colorless oil; IR (film) 2955 (s), 2866 (s), 1657 (w), 1536 (w), 1119 (vs), 729 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) $\delta$ 1.48 ($AB, J_{AB} = 10.3$ Hz, 1 H), 1.75-1.95 (m, 5 H), 2.25-2.59 (m, 8 H), 2.69-2.90 (m, 24 H), 3.43-3.66 (m, 24 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 29.2 (t), 41.3 (d), 43.6 (t), 43.9 (d), 47.8 (d), 50.3 (t), 54.1 (t), 54.2 (t), 54.9 (t), 55.3 (t), 58.5 (d), 70.0 (t), 70.1 (t), 70.9 (t), 95.0 (s). Exact mass (CI-HRMS) [M$+$ + H]$^+$ Calcd for C$_{37}$H$_{62}$N$_4$O$_7$: m/z 675.4697. Found: m/z 675.4682.

Synthesis of 88. A mixture of 87 [247] (273 mg, 1.03 mmol), 56 (530 mg, 1 mmol) and K$_2$CO$_3$ (1.38 g, 10 mmol, excess) in dry CH$_3$CN (100 mL) was refluxed during 5 days. The mixture was filtered, and the filtrate was concentrated in vacuo. The resulting residue was dissolved in CHCl$_3$ (50 mL) and was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 1% Et$_3$N-EtOAc. Pure 88 (221 mg, 35%) was thereby obtained as viscous pale yellow oil; IR (film) 3061 (w), 3028 (w), 2939 (s), 2863 (s), 2808 (m), 1588 (m), 1576 (m), 1452 (s), 172
1358 (m), 1119 (s), 1059 (m), 735 (s), 698 cm\(^{-1}\) (s); \(^1\)H NMR (C\(_6\)D\(_6\)) \(\delta\) 2.55-2.72 (m, 8 H), 2.76-2.91 (m, 8 H), 3.30-3.53 (m, 20 H), 3.81-3.87 (s, 4 H), 6.73 (AB, \(J_{AB} = 8.00\) Hz, 2 H), 6.96-7.16 (m, 7H), 7.26 (d, 4H); \(^{13}\)C NMR (C\(_6\)D\(_6\)) \(\delta\) 54.7 (t), 55.4 (t), 60.6 (t), 61.6 (t), 70.5 (t), 70.6 (t), 121.1 (d), 127.0 (d), 128.4 (d), 129.0 (d), 135.8 (d), 140.8 (s), 160.2 (s).

Exact mass (CI-HRMS) \([M + H]^+\) Calcd for C\(_{37}\)H\(_{53}\)N\(_5\)O\(_4\): \(m/z\) 632.4176. Found: \(m/z\) 632.4186.

**Synthesis of 90.**\(^{[248]}\) A mixture of 86 (1.23 g, 10 mmol), N-bromosuccinimide (NBS) (3.56 g, 20 mmol) and benzoyl peroxide (150 mg) in dry CCl\(_4\) (50 mL) was purged with argon, which was dried via CaCl\(_2\) drying-tube, during 5 minutes. The mixture was refluxed during 16 h and then was allowed to cool gradually to ambient temperature. To the resulting mixture was added an additional quantity of benzoyl peroxide (50 mg), and the resulting mixture was heated during an additional 12 h. The mixture was allowed to cool gradually to ambient temperature and then was filtered and concentrated *in vacuo*. The residue was purified by recrystallization from hexane. Pure 90 (1.1 g) was thereby obtained as colorless microcrystalline solid. The mother liquor was further purified via column chromatography on silica gel by eluting with hexane, an additional quantity of 90 (276 mg, total yield 49%) was thereby obtained as colorless microcrystalline solid; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 4.50 (s, 4 H), 7.09 (t, \(J = 7.6\) Hz, 1 H), 7.34 (t, \(J = 7.3\) Hz, 2 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 25.2 (d, \(J = 20.6\) Hz), 124.6 (d, \(J = 18.2\) Hz), 125.7 (d, \(J = 59.6\) Hz), 131.7 (d, \(J = 13.4\) Hz), 158.47 (d, \(J = 1010.0\) Hz). The \(^1\)H and \(^{13}\)C NMR spectra of this material agree with the reported spectra for authentic 90.\(^{[248]}\)
**Synthesis of 91.** A mixture of **90** (297 mg, 1.05 mmol), **56** (528 mg, 1.00 mmol) and K₂CO₃ (1.38 g, 10 mmol, excess) in dry CH₃CN (100 mL) was refluxed during 5 days. The mixture was filtered, and the filtrate was concentrated in vacuo. The resulting residue was dissolved in CHCl₃ (50 mL), and the resulting solution was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL), dried (Na₂SO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 1% Et₃N-EtOAc. Pure **91** (247 mg, 38%) was thereby obtained as pale yellow, viscous oil; IR (film) 3059 (w), 3028 (w), 2939 (s), 2860 (s), 1495 (w), 1472 (s), 1452 (s), 1354 (m), 1276 (w), 1121 (vs), 1057 (s), 735 (s), 698 cm⁻¹ (s); ¹H NMR (C₆D₆) δ 2.49-2.91 (m, 16 H), 3.39-3.71 (m, 24 H), 6.79-6.90 (m, 1 H), 6.91-7.06 (m, J = 7.2 Hz, 2 H), 7.11-7.33 (m, 6 H), 7.36-7.49 (d, J = 7.2 Hz, 4 H); ¹³C NMR (C₆D₆) δ 54.40 (t), 55.9-56.0 (d, J = 27.5 Hz), 60.5 (t), 70.2 (t), 70.5 (t), 122.6-122.7 (d, J = 15.8 Hz), 126.9 (d), 127.2 (s), 128.4 (d), 129.1 (d), 131.4-131.5 (d, J = 20.2 Hz), 140.79 (s), 159.14-164.18 (d, J = 1008.8 Hz). Exact mass (CI-HRMS) [M₊H]⁺ Calcd for C₃₇H₅₃FN₄O₄: m/z 649.412910. Found: m/z 649.413473.

**Synthesis of 92.** A mixture of **45** (531.3 mg, 1.05 mmol), **56** (528 mg, 1.00 mmol) and Cs₂CO₃ (3.3 g, ca. 10 mmol, excess) in dry CH₃CN (100 mL) was refluxed during 5 days. The mixture was allowed to cool gradually to ambient temperature and filtered, and the filtrate was concentrated in vacuo. The resulting residue was dissolved in CHCl₃ (50 mL) and was washed sequentially with water (2 x 30 mL) and saturated
aqueous NaCl (30 mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel by eluting with 1% Et$_3$N-EtOAc. Pure 92 (105 mg, 15%) was thereby obtained as pale yellow viscous oil; IR (film) 3063 (w), 3030 (w), 2939 (s), 2868 (w), 1593 (m), 1503 (s), 1452 (s), 1358 (m), 1253 (s), 1223 (m), 1119 (s), 1053 (s), 735 (s), 700 cm$^{-1}$ (s); $^1$H NMR (C$_6$D$_6$) $\delta$ 2.72-2.96 (m, J = 5.7 Hz, 16 H), 3.09 (t, J = 5.7 Hz, 4 H), 3.40-3.66 (m, 20 H), 3.91-4.06 (t, J = 5.6, 4 H), 6.85 (m, 4 H), 7.10-7.29 (m, 6 H), 7.39(d, 4 J = 6.96 Hz, H); $^{13}$C NMR (C$_6$D$_6$) $\delta$ 54.6 (t), 54.9 (t), 55.5 (t), 60.5 (t), 69.1 (t), 70.65 (t), 115.3 (d), 121.6 (d), 127.0 (d), 128.4 (d), 140.7 (s), 150.3 (s). Exact mass (CI-HRMS) [M$_r$ + H]$^+$ Calcd for C$_{40}$H$_{58}$N$_4$O$_6$: m/z 691.4435. Found: m/z 691.4422.

**Synthesis of 94.** A solution of 93$^{[208, 249]}$ (2.00 g, 12.3 mmol) in THF (50 mL) was cooled to 0 °C *via* application of an external ice-water bath. To this solution was added dropwise with stirring a solution of NaOH (4.90 g, 123 mmol) in water (11 mL) during 0.5 h, and the resulting mixture was stirred at 0 °C during 1 h. To this mixture was added dropwise with stirring a solution of TsCl (5.15 g, 27 mmol, excess) in THF (25 mL) during 1 h. The external ice-water bath was removed; the mixture was allowed to warm gradually to ambient temperature and was stirred during an additional 2 h. The mixture then was washed with saturated aqueous NaCl (2 x 50 mL); the organic layer was dried (Na$_2$SO$_4$), filtered, and the filtrate was concentrated *in vacuo*. The residue was first purified *via* fractional crystallization, thereby affording pure 94 (3.5 g) as colorless microcrystalline solid. The mother liquor was further purified *via* column
chromatography on silica gel by eluting with 25% acetone-hexane, thereby affording an additional quantity of pure 94 (2.2 g, total yield 98%) as colorless microcrystalline crystal. $^1$H NMR (CDCl$_3$) $\delta$ 1.13 (s, 6 H), 1.83 (s, 6 H), 3.73-3.91 (m, 6 H), 6.72 (AB, $J_{AB}$ = 8.0 Hz, 4 H), 7.73 (AB, $J_{AB}$ = 8.0 Hz, 4 H). $^{13}$C NMR (CDCl$_3$) $\delta$ 21.1 (q), 26.74 (q), 68.6 (t), 75.3 (d), 110.5 (s), 128.2 (d), 129.9 (d), 133.6 (s), 144.7 (s). \[249b\] 

**Synthesis of 95.** A mixture of 56 (730 mg, 1.38 mmol), 94 (681 mg, 1.45 mmol) and Rb$_2$CO$_3$ (2.31 g, 10 mmol, excess) in dry CH$_3$CN (100 mL) was refluxed during 5 days. The mixture was allowed to cool gradually to ambient temperature and was filtered. The filtrate was concentrated in vacuo, and the resulting residue was dissolved in CHCl$_3$ (50 mL), and the resulting solution was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL), dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica by eluting with 1% Et$_3$N-EtOAc. Pure 95 (352 mg, 39%) was thereby obtained as slightly brown, viscous oil; IR (film) 3061 (w), 3028 (w), 2982 (s), 2936 (s) 2863 (s), 1705 (s), 1495 (m), 1452 (s), 1368 (s), 1256 (s), 1161 (s), 1123 (s), 1053 (s), 1028 (s), 735 (s), 698 (s); $^1$H NMR (C$_6$D$_6$) $\delta$ 1.51 (s, 6 H), 2.46-3.06 (m, 20 H), 3.23-3.68 (m, 22 H), 4.21(t, $J$ = 3.2 Hz, 2 H), 7.10-7.29 (m, 6 H), 7.31-7.41 (m, 4 H). $^{13}$C NMR (C$_6$D$_6$) $\delta$ 27.8 (q), 54.5 (t), 54.6 (t), 55.4 (t), 56.13 (t), 60.2 (t), 61.0 (t), 70.1 (t), 70.5 (t), 70.8 (t), 70.9 (t), 80.6 (d), 108.1 (s), 127.1 (d), 128.4 (d), 129.0 (d), 140.6 (s). Exact mass (CI-HRMS) [M$_r$ + H]$^+$ Calcd for C$_{37}$H$_{58}$N$_4$O$_6$: m/z 655.4435. Found: m/z 655.4441.
Synthesis of 97. A mixture of 96 (680 mg, 1.2 mmol), 56 (528 mg, 1.00 mmol) and Na$_2$CO$_3$ (1.06g, 10.00 mmol, excess) in dry CH$_3$CN (100 mL) was refluxed during 5 days. The mixture was allowed to cool gradually to ambient temperature and was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in CHCl$_3$ (50 mL) and was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL), dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in CH$_2$Cl$_2$ (30 mL). The solution was allowed to stand at ambient temperature for 0.5 h, during which time some precipitate had formed. The mixture was filtered, and the solid residue was washed with small amount of 30% CHCl$_3$-CH$_2$Cl$_2$ (5 mL) and then was dried in vacuo. Pure 97 (300 mg, 32%) was thereby obtained as colorless microcrystalline solid, mp 139-140 °C; IR (KBr) 3633 (w), 3435 (w), 3033 (w), 2871 (w), 1595 (w), 1478 (m), 1353 (s), 1172 (vs), 1120 (s), 1055 (s), 1011 (s), 934 (m), 822 (m), 733 (s), 681 (s), 612 (m), 569 (s), 546 cm$^{-1}$ (s); $^1$H NMR (CDCl$_3$) $\delta$ 2.21 (s, 3 H), 2.29 (s, 3 H), 2.50 (br s, 6 H), 2.80 (br s, 8 H), 3.16 (br s, 6 H), 3.31-3.53 (m, 8 H), 3.32-3.89 (m, 16 H), 7.02 ($AB$, J$_{AB}$ = 8.0 Hz, 2 H), 7.1-7.21 (m, 12 H), 7.50 ($AB$, J$_{AB}$ = 8.0 Hz, 2 H), 7.63 ($AB$, J$_{AB}$ = 8.1 Hz, 2 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.1 (q), 21.4 (q), 53.6 (t), 58.4 (t), 59.5 (t), 59.4 (t), 63.8 (t), 68.9 (t), 69.0 (t), 125.7 (d), 127.2 (d), 127.6 (d), 128.3 (d), 128.6 (d), 129.0 (d), 130.1 (d), 132.1 (s), 138.1 (s), 139.3 (s), 143.6 (s), 144.5 (s).

Synthesis of 100. A mixture of 99 (889 mg, 1.1 mmol), 56 (528 mg, 1 mmol) and Rb$_2$CO$_3$ (2.36 g, 10 mmol, excess) in dry CH$_3$CN (100 mL) was refluxed during 5 days. The mixture was allowed to cool gradually to ambient temperature and was filtered, and
the filtrate was concentrated in vacuo. The resulting residue was dissolved in CHCl₃ (50 mL), and the resulting solution was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL), dried (Na₂SO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica column by eluting with 1% Et₃N-EtOAc. Pure 100 (426 mg, 43%) was thereby obtained as pale brown, viscous oil; IR (film) 3060 (w), 3028 (w), 2928 (m), 1597 (w), 1452 (m), 1339 (s), 1155 (vs), 1119 (s), 1090 (s), 733 (s), 700 (m), 653 cm⁻¹ (m); ¹H NMR (CDCl₃) δ 2.18 (s, 6 H), 2.63-2.89 (m, 20 H), 3.19-3.29 (t, J = 6.7 Hz, 4 H), 3.29-3.40 (t, J = 5.5 Hz, 4 H), 3.41-3.62 (m, 20 H), 3.66 (s, 4 H), 7.2-7.4 (m, 14 H), 7.7 (AB, J₃₄ = 8.1 Hz, 4 H). ¹³C NMR (CDCl₃) δ 21.4 (q), 48.1 (t), 48.6 (t), 53.8 (t), 54.7 (t), 60.0 (t), 69.6 (t), 69.9 (t), 70.2 (t), 126.9 (d), 127.1 (d), 128.2 (d), 128.8 (d), 129.6 (d), 136.9 (s), 139.2 (s), 143.1 (s). Exact mass (CI-HRMS) [M₊H]⁺ Calcd for C₅₂H₇₆N₆O₉S₂: m/z 993.5193. Found: m/z 993.5187.

Synthesis of 101. A mixture of 49 (1.45 g, 2.20 mmol), 56 (1.05 g, 2.00 mmol) and Rb₂CO₃ (4.66 g, 20 mmol, excess) in CH₃CN was refluxed during 5 days. The mixture was allowed to cool gradually to ambient temperature and was filtered. The filtrate was concentrated in vacuo; the residue was dissolved in CHCl₃ (80 mL) and was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (50 mL), dried (Na₂SO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica by eluting with 1% Et₃N-EtOAc. Pure 101 (755 mg, 45%) was thereby obtained as pale brown, viscous oil; IR (film) 3061 (w), 3029
(w), 2933 (s), 2866 (s), 1605 (w), 1460 (m), 1348 (s), 1173 (s), 1123 (s), 1097 (s), 1050 (s), 739 (s), 706 (m), 656 (m), 553 cm\(^{-1}\) (s); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.43 (s, 3 H), 2.59-2.96 (m, 20 H), 3.35 (t, \(J = 5.8\) Hz, 4 H), 3.41-3.83 (m, 28 H), 7.30 (m, 12 H), 7.71 (AB, \(J_{AB} = 8.3\) Hz, 2 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 21.5 (q), 49.5 (t), 53.9 (t), 54.6 (t), 54.8 (t), 60.1 (t), 69.6 (t), 69.8 (t), 70.0 (t), 70.6 (t), 126.9 (d), 127.1 (d), 128.2 (d), 128.8 (d), 129.7 (d), 136.5 (s), 139.4 (s), 143.2 (s). Exact mass (CI-HRMS) \([M + H]^+\) Calcd for C\(_{45}\)H\(_{69}\)N\(_5\)O\(_8\)S: \(m/z\) 840.4945. Found: \(m/z\) 840.4938.

**Synthesis of 104.** A mixture of 103 (895 mg, 1.05 mmol), 56 (528 mg, 1.00 mmol) and Cs\(_2\)CO\(_3\) (3.25 g, 10 mmol, excess) in dry CH\(_3\)CN (100 mL) was refluxed during 7 days. The mixture was allowed to cool gradually to ambient temperature and was filtered. The filtrate was concentrated \(in\ \text{vacuo}\); the resulting residue was dissolved in CHCl\(_3\) (50 mL) and was washed sequentially with water (2 x 30 mL) and saturated aqueous NaCl (30 mL), dried (Na\(_2\)SO\(_4\)) and filtered, and the filtrate was concentrated \(in\ \text{vacuo}\). The residue was purified \(via\) column chromatography on silica by eluting with 1% Et\(_3\)N-EtOAc. Pure 104 (165 mg, 16%) was thereby obtained as pale brown viscous oil; IR (film) 3060 (w), 3028 (w), 2938 (m), 2865 (s), 1599 (w), 1495 (w), 1455 (w), 1343 (s), 1157 (s), 1119 (s), 1090 (m), 816 (w), 736 (w), 719 (w), 700 (w), 649 cm\(^{-1}\) (w); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.40 (s, 6 H), 2.69-2.91 (m, 20 H), 3.30-3.76 (m, 36 H), 7.19-7.43 (m, 14 H), 7.73 (AB, \(J_{AB} = 8.35\) Hz, 4 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 21.5 (q), 49.1 (t), 49.6 (t), 53.9 (t), 54.2 (t), 54.7 (t), 60.1 (t), 69.5 (t), 69.8 (t), 70.0 (t), 70.1 (t), 126.9 (d), 127.3 (d),
128.2 (d), 128.8 (d), 129.7 (d), 136.1 (s), 139.4 (s), 143.3 (s). Exact mass (CI-HRMS) 

\[ [M_r + H]^+ \text{ Calcd for C}_{45}\text{H}_{69}\text{N}_{5}\text{O}_{8}\text{S}: \text{ } m/z \text{ 1037.5456. Found: } m/z \text{ 1037.5452.} \]
REFERENCES AND FOOTNOTES


McMurray, T. J.; Raymond, K. N.; Smith, P. H. *Science* **1989**, 244, 938.


106. Sachleben, R. A.; Davis, M. C.; Bruce, J. J.; Ripple, E. S.; Driver, J. L.; Moyer,


   
   


1987, 4, 387; Chem. Abstr. 1987, 107, R175146g.


Commun. 1998, 971.


205. Mr. Zilin, Huang, Personal communication, 2000.


213. a) Dr. Boliang Deng, personal communication, **2000**.

b) Dr. Boliang Deng Characterized this compound.


251. Compound 107 was prepared by Dr. I.N.N., Namboothiri; Compounds 109 and 110 were prepared by Mr. Zilin Huang.

252. ESI-MS experiment was conducted by Dr. Brodbelt and her colleagues at University of Texas, Austin. Picrate extraction was conducted by Mr. Z. Huang.

253. The synthesis of 51 was a cooperation between Dr. Mohammad Tahki and the
author; compound 111 was synthesized by Dr. Satish Kumar and Mr. Zilin Huang; compound 112 was synthesized by Dr. Artie McKim and Dr. Kasireddy Krishnudu; compound 1,10-\(N,N\)-dibenzyl-1,10-dia-18-crown-6 was prepared by Dr. Artie McKim.