The design and synthesis of biphenol derived host molecules.

Nicola Jane. Fransen

University of Windsor

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The Design and Synthesis
Of Biphenol Derived Host Molecules.

by

Nicola Jane Fransen

A Thesis Submitted
to the Faculty of Graduate Studies and Research through the
Department of Chemistry and Biochemistry in Partial Fulfillment of the
Requirements for the Degree of Master of Science at the
University of Windsor

Windsor, Ontario, Canada
1996
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“The artist finds greater pleasure in painting than in having completed the picture.”

Seneca
Abstract

The study of host-guest chemistry is an important new area of scientific investigation. Host molecules were designed using a rigid biphenol framework, convergent binding groups and rigid spacers capable of \( \pi \)-stacking. The syntheses of several of such host molecules, such as 47 and 50 containing alkyne spacers and 89 and 90 containing an aryl spacer, were completed. The synthetic pathways that lead to the formation of these macrocycles will be discussed.
Dedication

To Johnny,
For all he has done.
Acknowledgements

I would like to first thank my supervisor, Philip Dutton, for his guidance, encouragement and financial support. His assistance during my program will always be fondly remembered.

I would like to also thank, those fellow lab mates I have worked with in the last few years, including John Fransen, Joe Bencsik, Mike Weller, Paul Kennedy, and Christine Drouillard. They have all helped make my schooling quite enjoyable. Also, thanks should be given to other members of the department, particularly, Dr. John McIntosh and Dr. Jim Green, who have both been great sources of knowledge and assistance. I have had the distinctive pleasure of working with Anne Charlton, Michael Siwes, Steve Trepanier, Kevin McKay, Jay Kiser, Rick Mastronardi, Ed Brnardic and Jeff Baldwin and they have all made my stay amusing and enlightening, to say the least. My friendship with these individuals has not only enriched my chemistry knowledge, but has also taught me about vampires, hunting, politics, bikinis and fruitcakes.

My family deserves great thanks for always supporting me in my studies. My mum and dad, Anne and Jim, have been constant sources of encouragement, have always had great pride and confidence in my abilities and will always be loved greatly. My brother, Mike, is the role model of the ideal student and I thank him for being a worthy inspiration. Most importantly, I would like to thank my wonderful husband, John, for being supportive, encouraging and a great friend. I love him dearly and cannot thank him enough for all that he has done for me.
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<th>Description</th>
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<tr>
<td>br</td>
<td>broad (IR)</td>
</tr>
<tr>
<td>n-BuLi</td>
<td><em>normal</em>-butyl lithium</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift, delta scale</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>wavenumbers</td>
</tr>
<tr>
<td>CPK</td>
<td>Corey-Pauling-Koltun</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarization transfer</td>
</tr>
<tr>
<td>DHP</td>
<td>dihydropyran</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td><em>N,N</em>-dimethylformamide</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>eq</td>
<td>equivalents (molar)</td>
</tr>
<tr>
<td>g</td>
<td>grams</td>
</tr>
<tr>
<td>h</td>
<td>hours</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>K</td>
<td>kelvin</td>
</tr>
<tr>
<td>λ</td>
<td>wavelength</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<td>--------------</td>
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<tr>
<td>LG</td>
<td>leaving group</td>
</tr>
<tr>
<td>LSIMS</td>
<td>liquid secondary ion mass spectroscopy</td>
</tr>
<tr>
<td>m</td>
<td>medium (IR), multiplet (NMR)</td>
</tr>
<tr>
<td>M</td>
<td>molarity, (moles/L)</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz ($10^6$ s$^{-1}$)</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>mm</td>
<td>millimetre</td>
</tr>
<tr>
<td>mmHg</td>
<td>millimetres of mercury</td>
</tr>
<tr>
<td>mL</td>
<td>millilitres</td>
</tr>
<tr>
<td>μL</td>
<td>microlitres</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>nm</td>
<td>nanometres</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR)</td>
</tr>
<tr>
<td>s</td>
<td>strong (IR), singlet (NMR)</td>
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<tr>
<td>t</td>
<td>triplet (NMR)</td>
</tr>
<tr>
<td>TBDMS</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>TDSCI</td>
<td>thexyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyranyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>Tr</td>
<td>trityl (triphenylmethyl)</td>
</tr>
<tr>
<td>Ts</td>
<td>tosylate (p-toluenesulfonate)</td>
</tr>
<tr>
<td>w</td>
<td>weak (IR)</td>
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</table>
Chapter One

Introduction

1.1 Introduction

Host-guest chemistry refers to the study of two or more molecules coming together to form a non-covalent complex.\textsuperscript{1} This area is a subset of supramolecular chemistry which is a broad sphere of chemistry encompassing areas such as clathrate inclusion compounds, directed crystal formation, micelles, molecular devices and other phenomena dealing with intermolecular interactions.\textsuperscript{2} With interest in molecular recognition being expressed by organic, inorganic and bio-organic chemists, a new area in chemical studies began in which the focus changed from the study of the covalent bond to the exploration of the non-covalent bond.

The design of host molecules and the study of their intermolecular interactions with various guests is an important area in this discipline. With studies focusing on the factors affecting the effective complexation between host and guest, host molecules have progressed from simple polyethers to complex preorganized molecules. These complexes are held together by hydrogen bonds, ion-dipole interactions, $\pi$-acid to $\pi$-base interactions, van der Waals forces, and hydrophobic interactions.\textsuperscript{3}

Although this is a relatively new field of study, it has received much attention in both the organic and inorganic disciplines. In 1987, three researchers in this field, Charles J. Pedersen, Jean-Marie Lehn and Donald J. Cram,
were awarded the Nobel Prize for their work.\textsuperscript{3-5} The design and study of innovative host molecules are interesting fields of study and current research into this area will be reviewed.

Research in this field began with the chance synthesis of 1, dibenzo-18-crown-6 by Pedersen in 1967.\textsuperscript{6} While attempting to synthesize a related compound from catechol and 1,2-dichloroethane, solid crystals were found which proved to be 1. It was known that ethers could form coordination complexes with a variety of compounds by using the unshared pair of electrons from the oxygen atom.\textsuperscript{7} Pedersen noted that the presence of the six oxygen atoms, presenting a field of high electron density within the ring,\textsuperscript{7} made the compound useful for the binding of cations.\textsuperscript{4} Corey-Pauling-Koltun (CPK) modeling and binding studies showed that the molecule was indeed well suited for the binding of a potassium cation within the cavity. The work was expanded to include the study of different sized rings, ranging from 12 to 60 atoms, and the incorporation of different donor atoms. Due to the three dimensional shape of these novel molecules and their

![Figure 1. Pedersen's Dibenzo-18-crown-6.\textsuperscript{4}](image-url)
"capping" appearance in complexes, they became known as "crown ethers". As a result of the attention drawn by this early work, the field of the host-guest chemistry began.4,8

Based on the work of Pedersen, Lehn extended the complexation of the crown ether and guest to the encapsulation of cations by more three dimensional molecules.5 By incorporating a nitrogen into the polyether backbone, a bicyclic host molecule was created (Figure 2). This family of host molecules, known as the cryptands, was designed with different sized chains and various donor groups to be more effective in the binding of cationic guests.

![Figure 2. Lehn's [2,2,2] Cryptand.](image)

The concept of a host binding to a guest molecule was taken a step further by Cram who envisioned a three dimensional host molecule that would possess a chiral cavity.3 By changing the shape of the cavity, the host molecule was used to bind chiral guests. Thus, Cram and his colleagues have shown that one enantiomer of a racemic mixture of chiral amines was selectively bound by chiral hosts, such as 3. The chiral hosts were designed by the incorporation of a binaphthyl unit into the crown ether structure (Figure 3). The hosts were found
to complex different isomers to different extents and therefore the area of chiral macrocyclic chemistry began.\textsuperscript{3,9}

![Diagram](image)

Figure 3. Cram's Chiral Crown Ether.\textsuperscript{3}
1.2 Naturally Occurring Macrocycles

Host-guest chemistry has its roots in nature since macrocyclic ligands are involved in a number of biological systems.\textsuperscript{1,10-12} The interactions of enzymes with substrates, drug action, and immunological response are all dependent on specific, non-covalent recognition between molecules. Many naturally occurring complexes can be found such as chlorophyll, hemoglobin, and vitamin B\textsubscript{12}.\textsuperscript{9} The complex of iron within the porphyrin ring of hemoglobin, as shown in Figure 4, illustrates the importance of the interaction between organic hosts and biologically important ions in nature. Studies of the recognition in designed supramolecular complexes may provide molecular level answers to important open questions in the biological sciences.\textsuperscript{13} Organic chemists are able to synthesize non-natural hosts that can perform molecular recognition and provide a simple model for the complex interactions of biochemical processes.\textsuperscript{1}

![Figure 4. Iron Complexed within Porphyrin Ring of Hemoglobin.\textsuperscript{13}](image-url)
Ionophoric antibiotics are ideal host molecules capable of recognizing and non-covalently binding specific alkali metal substrates. The antibiotic valinomycin, illustrated in Figure 5, possesses both amide and ester linkages. This yields a three dimensional structure that creates a hydrophilic interior environment and a lipophilic exterior: a characteristic that is common with many host molecules.\textsuperscript{1,14} This molecule can solubilize alkali metal salts and transport them across the membrane.

![Figure 5. Macrocyclic Antibiotic, Valinomycin as a Complex with Potassium Ion.\textsuperscript{1}]

Enzymes also illustrate the importance of molecular recognition in nature. Since the first step in enzymatic catalysis is the formation of a highly selective molecular complex that orients the reactants and catalysts, and the last step is the decomplexation of that complex, it is obvious that molecular recognition is very important in biochemistry.\textsuperscript{9,15} In addition, enzymes possess asymmetric active sites and are often able to distinguish between two closely related guest molecules differing at only one chiral center.
A future goal of this discipline would be the design of molecular complexes that would be able to promote enzyme-like rate enhancements of one specific enantiomer of a molecule. On a more general level, the study of different factors of complexation with specific and simple cases can permit determination of their effects and help with the understanding of properties of more complex natural products.²

Biochemical phenomena have definitely provided inspiration for much of the current work in chemical molecular recognition.¹³ These investigations can generate a greater understanding of weak, non-covalent interactions in different complexes. The knowledge gained through this field also has applications in metal ion discrimination, analytical uses, development of new synthetic organic techniques and the possibility of enantiomeric purification.¹⁸ Far reaching goals may include efficient homogeneous solution catalysts and electronic devices for information storage.¹
1.3 Complexation of Ionic Guests by Host Molecules

The discipline of host guest chemistry was initiated with the work of Pederson who found that polyether compounds, (for example Figure 6), were very effective in binding metal cations.\(^6\) It was shown that the size of the macrocycle would effect the ability to complex cations of different sizes. Simple attraction of positive and negative charges accounts for much of the binding between the neutral host and charged guest.\(^9\) The incorporation of donor heteroatoms into the cyclic backbone of the macrocycle allows for effective complexation with electron deficient guests through ion-dipole interactions. The type of donor atom present in the ring affects the complexation: nitrogen, sulfur, and phosphorus tend to bind transition metals and oxygen heteroatoms tend to bind alkali and alkali earth ions.\(^14\) Very stable complexes can be formed when host and guest are matched to one another with respect to charge type and size.\(^9\)

![Figure 6. Crown Ether Complex of Potassium Ion.\(^6\)](image)

The three dimensional structure of the host creates an environment that tends to be more hydrophilic in their inner sphere and lipophilic on their outer sphere and therefore, this creates an ideal host for complexation and
lipophilization of alkali metal cations. Since the crown ethers and related molecules often are polar, symmetrical and readily soluble in many solvents, they have great synthetic and practical value.

Several macrocycles have been synthesized which are able to bind anions. Since anionic substrates participate in approximately 70% of all enzymatic reactions, the study of anion complexation by synthetic organic receptors has become a major area of molecular recognition. In general, the cavity of the macrocycle must be larger than those for cation binding, and the heteroatoms involved in the binding must have polarity opposite to that of the crown ethers.

Much of the work done in this area was performed by Lehn and coworkers and is illustrated with an example in Figure 7. Protonation of the six secondary amines yields macrobicyclic hexa-ammonium ions which are able to form complexes with a variety of anionic substrates in solution. It is thought that small anions form inclusion complexes with full cavity incorporation whereas large

![Figure 7. Host Molecule Capable of Binding Anions.](image)
anions, like $\text{SO}_4^{2-}$, bind outside the cavity through hydrogen bonding to the $\text{NH}_2^+$ sites.

The majority of cyclophane receptors have been prepared with the aim of binding ionic guests by utilizing frameworks which organize a converging array of oxygen, sulfur, nitrogen or other donor centers. Such ionic guests, which were complexed in these systems, include metals and ammonium salts. The key binding force is the interaction between the crown-like array of donor centers and the ion. Some elegant examples are shown in Figure 8 and include a lariat ether, 8,$^{17-19}$ an aromatic spherand, 9,$^{20,21}$ and a calix[4]resorcinarene, 10.$^{22-26}$

![Figure 8. Macrocycles Capable of Binding Cations.$^{17,20,23}$](Image)

8

9

10

$R = (\text{CH}_2)^{10}\text{CH}_3$
1.4 Complexation of Non-Ionic Guests by Host Molecules.

Synthetic host molecules have been shown to be very effective in the complexation of charged molecules. A more challenging task is to recognize and bind neutral organic molecules since the attractive forces involved in complexation are less well understood. Although cyclic ethers are useful in binding ions, additional units are required if hosts are to have more shape and additional types of binding sites. Early advances in binding organic compounds involved the cyclodextrins, Figure 9, which provide hydrophobic binding sites for a variety of relatively small organic molecules.

These host molecules are made up of 6, 7, or 8 glucose units linked head to tail in a large ring. The molecules are in the shape of hollow truncated cones with the primary hydroxy groups projecting from the narrow rim of the cone and the secondary hydroxy groups from the wide rim as represented by 12. All of these compounds are soluble in water with the inside of the cone being less polar than the outside, therefore, organic molecules readily fill the cavity. In 1975, Siegel and Breslow reported that aromatic compounds such as toluene and anisole are bound by the cyclodextrins. Cyclodextrins have been made which mimic some enzyme functions. The lipophilic cavity binds the lipophilic portion of the substrate. Functionalization of the hydroxyl group at the top or the bottom of the cone has allowed catalytic sites to be incorporated into the host. Since the cyclodextrins can be formed in different sizes, they are able to complex many different guests and have been widely used industrially.
Figure 9. Cyclodextrin Molecule - Structure and Schematic Representation.$^{15}$

The cyclodextrins are natural products with lipophilic interiors and hydrophilic exteriors and their complexes are limited to aqueous solutions. Modifications of cyclodextrins have been performed to only a limited extent. The goal has thus become the synthesis of unique macrocycles which have hydrophobic interior cavities and with which complexation could occur in a variety of media. Since the hosts are synthetic, much complementarity between host and guest can be built into the molecule.$^{9}$

The goal of host guest chemistry lies in the design of novel molecules capable of complexing a very specific substrate molecule. A complementary stereoelectronic arrangement of binding sites between host and guest will lead to effective complexation. By incorporating multiple binding sites into the complex, this structural organization will lead to high binding selectivity. Hosts that must
reorganize their structures to complex a guest will not be as effective as those preorganized for binding during synthesis.\textsuperscript{3}

The first unambiguous evidence for the stoichiometric inclusion of an apolar guest into the cavity of a synthetic cyclophane host in the aqueous state was provided by Koga in 1980.\textsuperscript{13,28} In a dilute hydrochloric acid solution, the tetraprotonated 13 and 2,7-naphthalenediol form a 1:1 complex. Specific and individual complexation-induced changes in the proton chemical shifts of both binding partners were observed in the spectrum of a solution of host and guest. This work established \textsuperscript{1}H NMR spectroscopy as the method of choice in the study of cyclophane complexation in solution.\textsuperscript{13} The work begun by Koga initiated a vigorous development of cyclophanes that would bind organic molecules in aqueous solution.\textsuperscript{29}

Figure 10. Koga's Cyclophane - First Host Molecule for an Organic Guest in Aqueous Solution.\textsuperscript{29}

The binding of non-ionic guests by host molecules in organic solutions has received much attention. Complexes of crown ethers and small neutral
molecules possessing C-H, N-H or O-H acidic functionalities were formed in a variety of different non-aqueous solutions. For example, complexes with acetonitrile, nitromethane, aromatic amines, phenols, and alcohols have been characterized in the solid state. The major components in these host-guest relationships was the hydrogen bonding between guest and host as well as dipole-dipole and van der Waals' forces. To increase the effectiveness of the binding of neutral molecules, additional recognition sites were built into the host molecules.

Reinhoudt and coworkers found that the incorporation of a carboxylate group into a polyether binding site of a large macrocycle would complex a molecule of water or urea. Figure 11 shows an example of such a molecule. When the molecule was complexed with a guest, an increase in the pKa was shown to exist as a result of the intramolecular hydrogen bonding. The acidic proton does not dissociate but rather assists in the complexation of the guest.

![Carboxylate Containing Macrocycle](image)

Figure 11. Carboxylate Containing Macrocycle.
In a similar host molecule, convergent phenol groups were shown to stabilize small organic molecules, such as urea. As seen in Figure 12, the guest, being completely encapsulated within the macrocyclic cavity, acts as a donor in the hydrogen bonding to the three ether oxygens and to one phenolic oxygen. Furthermore, a strong hydrogen bond is formed from the other phenolic oxygen to the carbonyl.

![Crystal Structure of Host With Convergent Binding Sites](image)

Figure 12. Crystal Structure of Host With Convergent Binding Sites.

The development of synthetic molecular receptors with organized hydrogen bonding sites for the binding of neutral molecules began in earnest in the mid 1980's. Rebek\textsuperscript{31,32} pioneered a new area of research with the design of cleft type receptors aligned with converging functional groups for hydrogen bonding neutral molecules. The use of Kemp's triacid, 16, introduced a triaxial conformation of three carboxyls and forced a U-shape between any two spacers involved (Figure 13).\textsuperscript{32} When a large spacer was used, as in Figure 14, a similar macrocycle could be formed which could complex a small aromatic amine
within the rigidly formed cavity. Although non-macrocyclic, these molecules showed how effectively hydrogen bonds could be used in the recognition of guests.\textsuperscript{32}

Host molecules with concave functionality were designed to have high specificity for guest molecules. There was a shift of attention from the macrocyclic polyethers to synthetic receptors in a variety of different shapes and sizes.\textsuperscript{32} Whillock prepared hosts, such as 20, that were preorganized for binding guests via a pyridine nitrogen oriented towards a rigidly defined cavity binding site. This molecule would allow favourable hydrogen-bonding interaction with hydrogen donor centers of encapsulated guests in non-aqueous media.\textsuperscript{33} The binding specificity of a guest, such as $p$-nitrophenol, is determined by the
complementarity of the guest to the cavity and by the hydrogen bond strength. The basicity of the pyridine nitrogen and the rigidity of the host molecule were varied in a series of host molecules to help determine the factors affecting complexation.\textsuperscript{33-35}

\begin{center}
\includegraphics[width=0.5\textwidth]{fig15.png}
\end{center}

\textbf{Figure 15. Whitlock's Tricycle.}\textsuperscript{33}

Vögtle prepared compounds such as 21 which were modeled after a macrobicyclic enterobactin known to bind Fe(III) strongly.\textsuperscript{36} These tris(bipyridine) macrobicyclic compounds were found to complex trihydroxy benzenes with high selectivity. The necessary complementarity between host and guest is illustrated by the fact that 1,3,5-trihydroxy benzenes were complexed effectively but the 1,2,3-isomer was not bound.\textsuperscript{37} The multiple hydrogen bonding between the phenolic hydroxy groups and the bipyridine acceptor as well as van der Waals interactions account for this stable complex formation.
Figure 16. Vögtle's Molecule.\textsuperscript{37}

Nucleotide recognition has received much attention in current studies since the biological process of recognition is crucially important. As hydrogen bonding is primarily responsible for the molecular recognition between the subunits, (Figure 17) this area is lucrative for exploration. To mimic the multi-point hydrogen-bonding recognition of the nucleotides and their receptors, synthetic hosts have been designed.\textsuperscript{38}

The host 26 was designed to bind thymine nucleotides, 22, through three hydrogen bonds produced by the incorporation of 2,6-diaminopyridine and $\pi-\pi$...
Figure 17. Hydrogen Bonding found in Base Pairs of Nucleotides.

stacking interactions between the naphthalene and thymine rings.\textsuperscript{39,40} The free host molecule has been analyzed by X-ray crystallography and was found to have an open conformation. Upon complexation with a guest such as 1-butylthymine, the solid state structure changes dramatically. The naphthalene unit lies planar to the guest and the three hydrogen bonds are holding the guest in a 1:1 complex. A schematic representation of the interaction between host and guest is given in Figure 18.\textsuperscript{38} The changing of the configuration of the molecule upon complexation with a guest has been described as an induced fit model and requires some flexibility in the host to obtain maximum favourable binding interactions. Hamilton\textsuperscript{39,41,42} has created a series of similar host molecules to explore the effects of different rigid sub-units as well as the effect of changing the basicity of the pyridine nitrogen.
Figure 18. Hamilton’s Host and the Interaction with a Guest.

The binding of host to guest in many systems is partially effected through the π–π stacking interactions. These interactions can be face-to-face or face-to-edge (Figure 19) depending on the electrostatics of the two aromatic molecules. In the edge-to-face interactions, the positively polarized hydrogen atoms on one ring attract the negatively polarized region of the second in a perpendicular fashion. In a face-to-face stacking mode, positive regions on one ring align with negative regions on the other ring in a parallel fashion. Both types of interactions are found in the stabilization of proteins. By varying the types of guest molecules involved in the interaction with the host, both types of aromatic interactions can be seen. Complexes such as 27 are an example of face-to-face stacking.

Figure 19. Types of π–π Interactions.
Hamilton also explored the complexation of other guest molecules.\textsuperscript{42,43} The goal in the design of these molecules was to incorporate several inwardly facing hydrogen bonding groups into a cavity of defined geometry. This design should lead to strong and selective binding to those guests showing complementary shape, size, and hydrogen bonding characteristics. The guest molecules used in this series of studies were derived from barbituric acid which are biologically important molecules.\textsuperscript{42} To create many possible hydrogen-bonding possibilities, two units of 2,6-diaminopyridine were incorporated. \textsuperscript{1}H NMR was used to analyze the complexation with a variety of guests. Figure 20 shows a hexa-hydrogen bonded complexes with a barbital derivative.\textsuperscript{42} The complementarity between the host and guest is easily seen in the diagram.\textsuperscript{43}

![Chemical Structure](image)

Figure 20. Hamilton's Receptor for Barbiturate Derivatives.\textsuperscript{42,43}
Hamilton has thus shown that the careful positioning of inwardly facing hydrogen bonding groups into a semi-rigid receptor can lead to a strong complexation of substrates.

Host guest chemistry has developed to the point of creating specifically designed hosts capable of complexing specific guest molecules. With the use of convergent functional groups introduced into a rigid framework strong associations between host and guest can be formed.
1.5 Biphenyl and Binaphthyl Derived Host Molecules

In the design of host molecules, the incorporation of a binaphthol, 30, or a biphenol, 29, unit has proven to be successful in creating useful molecules. These two foundation molecules are shown in Figure 21 and are similar in that both contain two aryl moieties separated by a single carbon-carbon bond. However, the presence of the steric hindrances within the biphenol molecule prevents the free rotation of this carbon-carbon bond at ambient temperature, while the steric hindrances within the binaphthol molecule prevents this free rotation altogether.

![Figure 21. Biphenol and Binaphthol Moieties Used in Host Molecules.](image)

The structures of these molecules make them ideally suited for host molecules designed to have convergent functional groups. The oxygens are a similar distance apart as compared to those found in the crown ether molecules. Partial rotation about the aryl-aryl bond is possible allowing for O-O distance to change from the distance observed in ethylene glycol to that observed in propylene glycol thus accommodating different guests. Also, when introduced into a host, the free hydroxyl groups could provide convergent binding sites.
allowing hydrogen-bonding interactions. Both binaphthyls and biphenyls have been used as components of synthetic hosts.

The binaphthyl series of host molecules have been widely studied and are interesting since the binaphthyls are chiral and therefore provide a chiral environment for binding. Cram investigated complexation of optically active ammonium salts by enantiomerically pure binaphthyl derivatives and found they could separate racemic mixtures.\(^2,^9\) Chiral recognition of a guest requires the presence of a suitable cavity; for there to be good chiral discrimination, only one of the two enantiomers in a racemic mixture should be complexed strongly by the macrocycle.\(^2\)

![Figure 22. Binaphthyl Crown Ether Molecule.](image)

When the rigid binaphthyl unit is incorporated into a cyclic ether, the two naphthalene rings occupy different planes each of which is perpendicular to the best plane of the cyclic ether.\(^9\) One of the naphthalene rings forms a wall that extends along the side of, and outward from, one face of the cyclic ether. The other ring provides a wall along the side of and outward from the opposite face of
the cyclic ether. The result is an asymmetric cavity the cross section of which is shaped like a pair of pliers, as illustrated in Figure 22.

Side chains attached at the 3-positions extend along the side of the cyclic ethers. As seen in Figure 23, the side chain terminates in a carboxyl group whose derived anion can rest centered just below the hole of the macrocycle. When the host cyclic ether was prepared in an optically pure state and absorbed onto silica gel, total optical resolution was realized between a racemic mixture of \( \alpha \)-phenylethylamine salts.

![Figure 23. Binaphthyl Derived Hosts With Side-Arm.](image)

Biphenol moieties have been used in the synthesis of hosts by Pierre. Molecules such as 34 were prepared from biphenol and contain a nitrogen functionality in the chain. The imine allows complexation through the lone pair of electrons of nitrogen. The compounds were made using different diamines and a covalent boron template. The hydrophobic exterior and hydrophilic interior allows for the complexation of small, polar guests. Different lengths of spacers have
been used to increase the size of the cavity. Pierre was able to incorporate biphenol moieties into a host molecule such that the host possesses multiple convergent binding sites.\textsuperscript{45}

Figure 24. Pierre's Biphenol Derived Macrocycle.\textsuperscript{45}
1.6 Goal of Project

The design of host molecules for the purpose of binding organic guests is an interesting field of study. It was the goal of this project to incorporate various factors into the design of host molecules. As means of binding guest molecules, dipole-dipole, hydrogen-bonding and \( \pi \)-stacking interactions have all been used in various host molecules. The purpose of this project was to develop hosts that would incorporate all of these features into a well-defined host as represented in Figure 25. The host molecule would have a rigid outer backbone derived from two bipheno1 units and would contain convergent hydroxyl groups capable of hydrogen bonding to guests. The introduction of rigid spacers groups would serve to keep the opposite hydroxyl groups from intramolecularly bonding to each other as well as allowing for \( \pi \)-stacking interactions that would help bind aromatic hosts. Preorganization of the host molecule to bind aromatic guests which possess polar groups should increase the hosts’ ability to bind guests.\(^{15} \) The synthesis of such host molecules was the goal of this thesis. The results of this investigation will be discussed.

Figure 25. Representative Host Molecules and Interaction with a Guest.
Chapter Two

Results and Discussion

2.1 Introduction

The goal of this project was to design host molecules that were capable of binding polar, aromatic guest molecules. The complexation of such guests would occur primarily by hydrogen bonding and π-stacking interactions with the host. The general form of the molecule is shown in Figure 26. By preorganizing the host's structure to fit the desired guests and by limiting the flexibility of the host, effective complexation should occur. Two biphenol groups were to be used for the backbone of the molecules as they contain phenol groups that would be capable of forming hydrogen bonds to potential guests. The oxygens of the biphenol moieties are ideal distances apart for complexation purposes. The biphenol backbones were to be separated by spacer groups, Y. These spacers

![Diagram of molecular structure]

Figure 26. Synthetic Goal of Project.
would be rigid in nature and would prevent the hydroxyl groups from intramolecular binding which would inhibit binding potential. The spacers would ideally have π-stacking abilities that would help to bind aromatic guests into the cavity.

This chapter will detail the synthesis of the biphenol portion of the molecule, synthesis of two macrocycles with alkyne spacers, 47 and 50, attempted stepwise synthesis of a macrocycle with an aromatic spacers and the one-pot synthesis of two macrocycles which contain aromatic spacers, 89 and 90.
2.2 Synthesis of Biphenyl Moiety of Host Molecules.

The host molecules were designed to contain a biphenol functionality.\textsuperscript{44} This moiety would introduce a rigid backbone to the macrocycle as well as provide convergent hydroxyl groups that could be used in the complexation of various guests. The initial steps in the synthesis of the biphenol derived portion of the molecule are shown in Figure 27. Biphenol was allylated using the Williamson ether synthesis\textsuperscript{44-47} to produce 37 in 80% yield. A [3+3] Claisen rearrangement\textsuperscript{45,46,48,49} was used to rearrange the allyl groups from the phenol positions to the 3,3'-positions in 89% yield. These allyl groups were now in the position required for the host molecule 36.

![Chemical structure](image)

**Figure 27. Synthesis of Biphenol Portion of Host Molecule, 38.**

Since the Williamson ether synthesis was to be used in later steps, the phenol groups were protected as the methyl ethers.\textsuperscript{7,47,50} Methyl ethers were chosen as they were easy to introduce and could be removed with boron tribromide without disrupting other ether linkages that would be present in the
molecule. This was done via proton abstraction with sodium hydride and subsequent methylation with dimethyl sulfate in 91% yield (Figure 23).

![Chemical structures](image)

**Figure 28. Protection of the Phenol Groups.**

The double bond in 39 was in a position which may have led to isomerization into conjugation with the aromatic ring. As this was not desired, purposeful isomerization was done in order to characterize that product. This transformation did not occur under conditions of concentrated acid (HCl) or base (KOH). When stirred with potassium t-butoxide in DMSO overnight, the

![Chemical structures](image)

**Figure 29. Isomerization of Double Bonds of 39.**
isomerization did occur to produce 40. Only the trans double bond was seen as evidenced by both proton NMR and IR analysis. No compound 40 was seen to contaminate the compound 39.

Functionalization of the allyl group of 39 was performed using ozonolysis with a reductive workup51,52 to the alcohol to produce 41 in 87% yield (Figure 30). The alcohol was made directly from the ozonide since attempts to isolate the aldehyde intermediate were unsuccessful.

![Chemical Structures](image)

Figure 30. Functionalization of Alkene Portion of 39.

The alcohol, 41, would serve as the basis molecule to be incorporated into the desired host molecules. It was obtained from the biphenol in four steps in an overall yield of 69%. The $^1$H NMR spectra showed all the expected peaks such as a D$_2$O exchangeable signal, a methyl singlet at 3.4 ppm, as well as two triplets with $J= 6.4$ Hz. The IR spectra clearly showed an alcohol functionality and high resolution mass spectrometry confirmed the formula of the molecule.

With the alcohol functionality present in 41, the incorporation of spacer groups to produce a macrocycle, such as 36, could be performed using standard
ether synthesis conditions. In macrocyclic chemistry, it is believed that a stepwise synthesis is generally favourable over a multi-component, one pot synthesis. Two types of cyclization reactions are shown in Figure 31. In the first, which is a two component cyclization reaction, an intermolecular condensation must occur followed by an intramolecular cyclization. The second example shows a four component system in which many reactions must take place in order for the cyclization to take place. Entropically, the reaction scheme A, is favoured as a synthetic pathway and therefore, would be attempted in the synthesis of biphenol derived host molecules. Thus, with 41, the spacers will be added, and then the ring closed.

Figure 31. Methods of Macrocyclization.
2.3 Synthesis of Host Molecules with Alkynyl Spacer Groups.

With the backbone molecule containing the biphenol portion synthesized, it was now necessary to functionalize the alcohol. This was done using the Williamson ether synthesis using the diol, 41, a base and a bromide. Propargyl bromide was chosen as two terminal acetylene groups would be introduced. Acetylene groups have been shown to couple under very mild conditions to form conjugated acetylenes.$^{54,55}$

The synthesis proceeded with the diol being converted to the dianion by sodium hydride. This anion was then reacted with the electrophilic propargyl bromide, as shown in Figure 32.

![Figure 32. Propargylation of 40.](image)

Although the compound, 42, was made, as proven by the NMR and IR, the 9.6 % yield was disappointingly low. The reason for this very low yield may be the result of the bromide of propargyl bromide not being a very good leaving group as compared to benzyl or allyl bromide. The mechanisms of attack for the nucleophilic substitution reaction with the propargyl electrophile proceeds
primarily through a $S_N2'$, while the nucleophilic substitution reaction of a benzyl or allyl electrophile would follow the $S_N2$ mechanism (Figure 33). The propargyl electrophile would therefore result in the formation of an allene product. Although no evidence of an allene was found in the products upon purification, this competing reaction could explain the lowering yields.

![Reaction Mechanisms](image)

Figure 33. $S_N2$ versus $S_N2'$ Mechanisms with Attack on Propargyl Bromide.

In an attempt to improve the yield of 42, the use of the cobalt complex of propargyl alcohol was employed (Figure 34). The cobalt complex, 44, was formed by refluxing $\text{Co}_2(\text{CO})_8$ and propargyl alcohol. The cation of the cobalt complex, 45, was then prepared in situ by reacting it with tosic acid. The carbocation was formed by the loss of water which was removed with 4Å molecular sieves. The cobalt cation is relatively stable, but should be active enough to react with an electron rich alcohol, such as 41, to give the desired product. In addition, the $S_N2'$ mechanism does not occur with cobalt propargylated cations. Unfortunately, this reaction was unsuccessful and
yielded only starting materials. Perhaps the alcohol, 41, was not nucleophilic enough or was too bulky to attack the cationic propargyl complex.

\[
\text{HO} \quad \begin{array}{c} \text{Co}_2(\text{CO})_8 \\ \text{THF} \end{array} \quad \text{HO} \quad \begin{array}{c} \text{Co}_2(\text{CO})_6 \\ \text{H}^+ \end{array} \quad \begin{array}{c} \text{Co}_2(\text{CO})_6 \end{array}
\]

43 44 45

Figure 34. Synthesis of Propargyl Alcohol Di-Cobalt Hexacarbonyl Complex.

\[
\begin{array}{ccc}
\text{HO} & \begin{array}{c} \text{Co}_2(\text{CO})_6 \\
\text{THF} \\
0.5 \text{ Eq. 41} \end{array} & \begin{array}{c} \text{TsOH} \\
\end{array} & \begin{array}{c} \text{O} \\
\end{array} \\
\text{O} & \begin{array}{c} \text{Co}_2(\text{CO})_6 \\
\text{O} \\
\end{array} & \begin{array}{c} \text{Co}_2(\text{CO})_6 \\
\text{O} \\
\end{array} \\
\text{H} & \begin{array}{c} \text{O} \\
\end{array} & \begin{array}{c} \text{O} \\
\end{array} \\
\end{array}
\]

44 46

Figure 35. Attempted Reaction of Di-Cobalt Hexacarbonyl Complex with 41.

Thus, the yield of the initial reaction in the formation of 42 could not be improved from the 9.6% yield. Using 42 produced as in Figure 32, a Glaser coupling reaction\textsuperscript{54,55,59-61} was carried out (Figure 36). Using stoichiometric amounts of cupric salts under an atmosphere of oxygen as an oxidizing agent, the coupling reaction was attempted to join two equivalents of compound 42 to produce a macrocycle of the form 36. Instead of two molecules coupling to each other, the terminal alkynes self coupled to form a small cyclophane ring (Figure
37), as was determined by mass spectroscopy.\textsuperscript{54,55} Compound 47 was produced as a small macrocycle in 26 % yield that, although it was not the desired product, was interesting in itself and could be useful in further binding studies for other types of guest molecules.

\begin{equation}
2 \quad R \equiv \quad H \xrightarrow{\text{Glaser Conditions}} \quad R \equiv \quad \equiv \quad R
\end{equation}

Figure 36. The Glaser Coupling Reaction.\textsuperscript{54}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure37.png}
\caption{Initial Attempts at Cyclization of the Propargylated Diol.}
\end{figure}

This macrocycle, 47, was characterized by \textsuperscript{1}H NMR which was found to be similar to that of 42 except the terminal acetylene protons were absent and there was subsequently no coupling seen in the nearby methylenes. \textsuperscript{13}C and IR spectra were as to be expected. Analysis of the molecule was dependent on mass spectrometry which showed a molecular ion at 376 gmo\textsuperscript{l} and high resolution analysis which showed an exact molecular weight of 376.1683 gmo\textsuperscript{l}.
The intramolecular cavity of 47 appears not to be large enough for the complexation of aromatic guests, thus it was attempted to synthesize a host in which the terminal acetylenes coupled intermolecularly and not intramolecularly.

In order to prevent the self-condensation, the Cadiot-Chodkiewicz coupling reaction was used.61 A terminal acetylene reacts with a 1-bromo-acetylene in the presence of a cuprous salt catalyst and an amine (Figure 38). Generally, this coupling reaction can be used for asymmetrical diyne synthesis, but in this case it would be used to prevent ring closure on itself.61

\[
\begin{array}{c}
\text{R} - \equiv - \text{H} + \quad \text{R'} - \equiv - \text{Br} \\
\text{Cadiot} \\
\text{Chodkiewicz} \\
\text{Conditions} \\
\rightarrow \quad \text{R} - \equiv - \equiv - \equiv - \text{R'}
\end{array}
\]

Figure 38. Cadiot-Chodkiewicz Coupling.61

The terminal acetylene, 42, was to be brominated to produce the alkyne necessary for this coupling reaction. Sodium hydride (pKa = 35) was chosen as the base to abstract the acetylene proton (pKa = 25) and bromine would be used to brominate the acetylide anion.15(Figure 39) Under these conditions, the acetylenic proton appeared not to have been removed, but rather bromination across the alkyne to form the alkene had occurred. The highly activated aromatic ring was also brominated to produce 48. The three electron donating substituents on the aromatic ring create a very electron rich system that favours the electrophilic addition of bromine.
Bromination thus had to be performed using a different set of conditions. A more reactive base (n-BuLi) and F₂BrCCBrF₂ as the bromine source were used in hopes of preventing bromination across the double bond or onto the aromatic ring (Figure 40). The brominated alkyne, 49, was prepared in 93% yield and the ¹H NMR spectrum was very similar to that of 42 except for the missing acetylene signal and the absence of splitting in the methylene signal.
Cadiot-Chodkiewicz coupling\textsuperscript{61} proceeded by dissolving the cuprous chloride catalyst in aqueous ethylamine. (Figure 41) A catalytic amount of reducing agent, hydroxylamine hydrochloride, was added to keep the copper in the cuprous state. The acetylenic compound, 42, was added, followed by 49 and a conjugated diyne, 50, was produced as the desired macrocycle in 25\% yield.

\begin{center}
\includegraphics[width=\textwidth]{figure41.png}
\end{center}

Figure 41. Cyclization of Propargylated Diol.

This macrocycle, 50, contained all the prerequisites for the desired host. The methoxy groups were oriented towards the center of the cavity and are preorganized for the binding of polar guests. The dialkynie spacers are rigid enough to create a large sized cavity and may also aid in the binding of aromatic guests through $\pi-\pi$ interactions. This macrocycle was characterized by $^1$H NMR and proved to be very similar to its smaller counterpart, 47, as illustrated in Table 1. The methylene signal adjacent to the alkyne was found at 4.21 ppm in the small macrocycle 47 and at 4.22 ppm in the larger ring, 50. Other spectral features of the $^{13}$C NMR and IR were very similar. Mass spectrometry was the
important spectral analysis used in the identification process as it illustrated a $M^+$ peak at 754 g mol$^{-1}$.

Table 1. $^1$H NMR Analysis of 47 and 50 (ppm)

<table>
<thead>
<tr>
<th>functional group</th>
<th>Compound 47 (ppm)</th>
<th>Compound 50 (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aromatic-H</td>
<td>7.20 (m)</td>
<td>7.18 (m)</td>
</tr>
<tr>
<td>ArCH$_2$CH$_2$O</td>
<td>3.36 (t)</td>
<td>3.39 (t)</td>
</tr>
<tr>
<td>ArCH$_2$CH$_2$O</td>
<td>3.76 (t)</td>
<td>3.76 (t)</td>
</tr>
<tr>
<td>ArOCH$_3$</td>
<td>2.98 (s)</td>
<td>2.98 (s)</td>
</tr>
<tr>
<td>OCH$_2$C=C</td>
<td>4.21 (s)</td>
<td>4.22 (s)</td>
</tr>
</tbody>
</table>
2.4 Attempted Stepwise Synthesis of Macrocycles
With Aryl Spacer Groups.

Another macrocyclic compound containing an aromatic spacer group was envisioned such that the two spacers would be rigid and would provide \( \pi \)-stacking capabilities. The opposite aryl groups would provide \( \pi \)-stacking possibilities that could increase the binding potential of a guest molecule. Many synthetic paths were explored to synthesize this molecule in a stepwise manner. Initial attempts are discussed in the following section.

The diol, 41, containing the biphenyl moiety could be functionalized with the necessary aryl groups using 4-bromobenzyl bromide. This reaction would leave an aryl bromide for further functionalization (Figure 42). The alkoxide was formed with sodium hydride, followed by bromide addition to produce 51 in excellent yield (92 %). As benzyl bromide is a good electrophile, this high yield

![Chemical Structures]

Figure 42. Synthesis of Bromobenzylated Compound, 51.
was expected. The resulting dibromide, 51, was distinguished by the additional $^1$H NMR signals of a methylene singlet at 4.48 ppm and a $\rho$-substituted aromatic ring at 7.4 ppm as well as by the disappearance of the D$_2$O exchangeable alcohol signal.

Functionalization of the resulting dibromide, 51, proved to be difficult. The first technique that was applied was one of the most common reactions in organic synthesis, the Grignard reaction. The digrignard was expected to react with formaldehyde to give a bis(benzylic alcohol) compound, as shown in Figure 43.

![Diagram](image)

**Figure 43. Attempted Grignard Reaction of 51.**

The reaction was attempted using standard Grignard conditions (Mg turnings, Et$_2$O) and dry formaldehyde as an electrophile but no product was obtained. As the bromide starting material was recovered under these conditions and the magnesium did not appear to be react, it was concluded that the problem was in the formation of the Grignard reagent. More rigorous conditions were applied including: Mg° powder, Rieke activated magnesium$^{62-64}$ and initiators,
iodine and C\textsubscript{2}H\textsubscript{4}Br\textsubscript{2}, as summarized in Table 2. Under all of these conditions, the reaction failed to yield any product, yielding only starting material.

**Table 2. Grignard Conditions Used With 51**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Initiator</th>
<th>Magnesium Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et\textsubscript{2}O</td>
<td>iodine</td>
<td>turnings</td>
</tr>
<tr>
<td>THF</td>
<td>iodine</td>
<td>turnings</td>
</tr>
<tr>
<td>THF</td>
<td>dibromoethane</td>
<td>turnings</td>
</tr>
<tr>
<td>THF</td>
<td>iodine</td>
<td>powder</td>
</tr>
<tr>
<td>Et\textsubscript{2}O</td>
<td>iodine</td>
<td>powder (sonicated)</td>
</tr>
<tr>
<td>THF</td>
<td></td>
<td>Rieke activated metal</td>
</tr>
</tbody>
</table>

Since Grignard conditions appeared not to be useful in the functionalization of the dibromide, metal halogen exchange was attempted. Organolithium compounds are widely used as reagents for organic synthesis and can readily be reacted with aryl halides to form a very reactive nucleophile.\textsuperscript{15} Using \textit{n}-BuLi, attempts were made to replace the bromide with a lithium atom which could then be reacted with the formal cation equivalent, DMF to produce the di-aldehyde, 53 (Figure 44).

This reaction too proved to be unsuccessful. Unlike with the Grignard conditions, the starting material was not recovered using \textit{n}-BuLi. The \textit{n}-BuLi (pKa = 50)\textsuperscript{16} may have been acting as a base and abstracting one or more of the
many benzylic protons (pKa = 40)\textsuperscript{15} and thus leading to a mixture of many unidentified products.

![Chemical structures](image)

Figure 44. Attempted Functionalization of 51 Using n-BuLi.

Nevertheless, another reaction of with 51 was performed in hopes of functionalizing the di-bromide. The formation of a dimethyl ester was performed by using a cobalt catalyzed carboxylation\textsuperscript{65-67} (Figure 45). A cobalt based catalyst, CH\textsubscript{3}OOCCCH\textsubscript{2}Co(CO)\textsubscript{4} was generated 'in situ' by the reaction of Co(CO)\textsubscript{4}\textsuperscript{-} and the \(\alpha\)-haloester, ClCH\textsubscript{2}COOCH\textsubscript{3}. The reaction was carried out under a carbon monoxide atmosphere and in the presence of methanol as a solvent\textsuperscript{65,66}.

The diester, 54, was formed in poor yields (10\%) and required a large amount of cobalt octacarbonyl, which should have been required in only catalytic amounts\textsuperscript{67}. It was then concluded that this was not a useful reaction for the
Figure 45. Carbonylation of Dibromide 51.

functionalization of 51. As the Grignard, n-BuLi and cobalt conditions had all been very disappointing, it was thought that the bromine atoms must not be easily accessible to the reagents. An alternate pathway for the introduction of the aryl spacer group had to be designed.

As the functionalization of the aryl group was difficult to perform after it was inserted into the molecule, the design of a spacer similar to that shown below in Figure 46 was attempted. Such a molecule would contain a benzyl halide leaving group as well as a protected benzyl alcohol. This protecting group would prevent the nucleophile from reacting with the alcohol while admitting attack at the leaving group.

Figure 46. Synthetic Goal for Stepwise Synthesis of Macrocycle.
This spacer group molecule could be incorporated into the host molecule as shown in Figure 47. The biphenol moiety, 41, could perform a nucleophilic substitution at the benzyl leaving group position on the spacer molecule, 55. The

Figure 47. Scheme for Incorporation of Spacer, 55.
protecting groups of 56 would then be removed to reveal the di-alcohol, 57, that would itself be converted to a di-leaving group, 58. The macrocycle could then be formed by a reaction of another equivalent of biphenol molecule, 41, using basic conditions under high dilution. With this synthetic scheme, there are several conditions that must be considered. The spacer molecule represented in Figure 46 had to be synthesized with a protecting group that would be stable to the nucleophilic substitution of Step 1, Figure 47. Also, cleavage of the protecting group must be achieved without disrupting the rest of the molecule. As molecule 56 contains many ether linkages, use of protecting groups such as methyl ethers, or benzyl ethers would be inappropriate. In addition, protecting groups that require harsh conditions for removal could not be used. With these considerations in mind, attempts were made at the synthesis of 55.

It was expected that 55 could be synthesized starting from p-methyl benzyl alcohol. The leaving group could be introduced by using NBS under radical conditions to brominate in the α-position of the methyl group (Figure 48). Using standard conditions, this reaction failed as was evidenced by the crude $^1$H NMR

![Figure 48. Attempted Bromination of p-Methyl Benzyl Alcohol.](image-url)
showing many products, including some bromination on the α-position of the benzyl alcohol.

It was thought that perhaps the presence of the alcohol functionality of 60 was interfering with the reaction or that polymerization would occur when molecule 61 was formed. This is illustrated in Figure 49.

![Figure 49. Proposed Polymerization of α-Bromo-α'-Hydroxy-p-Dimethyl benzene.](image)

A similar reaction was performed using p-tolualdehyde, 63, as the substrate, but this too failed, yielding no discernible products. (Figure 50)

![Figure 50. Attempted Bromination of p-Methyl Benzaldehyde.](image)

Thus, to produce the desired spacer group, it was thought that the alcohol, 60, or aldehyde, 63, should be protected first and then the bromination reaction performed and this would lead to a synthetic equivalent of 55. (Figure 51)
Thus, the alcohol, 60, was protected with a variety of groups including THP,\textsuperscript{50,69} 67, dimethyl thexyl silyl,\textsuperscript{50} 69, trityl,\textsuperscript{50} 71, and acetates\textsuperscript{50,} 73 (Figure 52).
In a similar synthetic scheme, \( p \)-tolualdehyde was protected as the acetal \(^{50}\)(Figure 53). Subsequent bromination of the methyl group was attempted and in all cases failed to yield the desired products. Generally, the crude product mixture contained a mixture of unidentifiable products and often the protecting group was removed by the bromination conditions.

![Chemical Structures](image)

Figure 53. Attempted Bromination of Acetal Protected \( p \)-Methyl Benzaldehyde.

As all the above attempts at bromination using NBS failed, another synthetic route was developed. It was believed that a similar spacer group to \( 55 \) could be synthesized by the difunctionalization of \( p \)-bromotolualdehyde.\(^{50}\) (Figure 54) To do so, the para substituted aldehyde was reduced to the corresponding \( p \)-substituted alcohol, \( 78 \), using lithium aluminum hydride in 76% yield. The alcohol was then protected as the dimethyl thexyl silyl ether, \( 79 \), in 87% yield using dimethyl thexyl silyl chloride.\(^{50}\) This protecting group was chosen as it is stable to Grignard conditions and the conditions of its subsequent removal, as in Figure 47, Step 2, will not affect other functional groups in the molecule.\(^{50}\)
Figure 54. Synthesis of \( \rho \)-Bromobenzyl Alcohol Protected with a Silyl Group.

To synthesize the benzylic alcohol, attempts were made to produce the Grignard reagent of the bromide 79 followed by its reaction with formaldehyde. Unfortunately, this reaction would not work, the Grignard reagent was not made and thus the pathway was abandoned for a different one.

Figure 55. Attempted Grignard of 79.

Another attempt was made at the synthesis of this aryl spacer group, 55, starting from dimethyl terephthalic acid. The di-ester has two equivalent groups in the para positions. The di-ester was reduced to the dialcohol, 82, in good yield (98%).
Figure 56. Synthesis of Benzene Dimethanol.

To produce a compound of the form 55 it would be necessary to mono-protect one of the two benzyl alcohol groups and to convert the other to a leaving group. In deciding which group to introduce first, (Figure 57) it was thought that incorporating the leaving group first may lead to unwanted products during the

Figure 57. Reasoning for the Choice of Synthetic Paths.
second step of adding the protecting group under basic conditions. Conversely, the introduction of the protecting group first should not hinder the incorporation of the leaving group under standard conditions.

In the protection of the diol, 82, it was expected that a statistical distribution of the non-protected, mono-protected and diprotected alcohols would be formed in the ratio of 1:2:1 respectively and from this mixture, the monoprotected alcohol could be isolated. (Figure 58) Again, the protecting group chosen was a dimethyl thexyl silyl ether because of its easy introduction and non-disruptive removal. When the reaction was performed, it was found that the products consisted mostly of the non-silylated, 82, and di-silylated form, 84, with the mono-protected alcohol, 83, produced in only small amounts. Due to the poor solubility of the diol, 82, in the reaction solvent, it was concluded that the protection of one of the alcohols with a silyl group increases its solubility and thus makes it more likely to react further. Thus, it was difficult to isolate a monofunctionalized benzene-dimethanol compound and consequently this pathway was also abandoned.

![Figure 58. Attempted Mono-Protection of Benzene Dimethanol.](image-url)
Figure 59. Products of Attempted Mono-Protection of Benzene Dimethanol.

The stepwise synthesis of a host molecule was subsequently attempted through the use of α-bromo-p-toluic acid, 85. The rationale for using this molecule is that it has a good leaving group (bromide) and has an acid functionality that can later be changed into a leaving group at the α-position. A commercially available compound, 85, was purchased as it was of the same form as 55. The benzyl bromide is a good leaving group and the acid functionality could be reduced to an alcohol once incorporated into the molecule. (Figure 47)

Figure 60. α-Bromo-p-toluic Acid.
As this molecule was to be reacted with a nucleophile, there was concern about the competition between attack at the benzyl bromide site and attack at the carbonyl as well as the possible attack of the acid on another molecule of 85 as illustrated in Figure 61.

![Chemical structure](image)

Figure 61. Synthetic Considerations in the Use of 85.

These problems were alleviated with the protection of the acid as the sodium salt (Figure 62). It was thought that the carboxylate ion was not susceptible to nucleophilic attack at the carbonyl and would not be nucleophilic enough to attack the benzyl position of an addition molecule.

![Chemical structure](image)

Figure 62. Protection of the Acid, 85, as the Sodium Salt, 86.
The incorporation of this molecule into the biphenol framework was effected by mixing the salt, 86, NaH and 41 and then heating to reflux overnight. The diacid was produced in unreasonably low yields as shown in Figure 63. The diacid, 87, was very polar and difficult to purify from the crude mixture.

Figure 63. Attempted Incorporation of the Aryl Spacer into Molecule.

The stepwise synthetic route towards a macrocycle seemed not to be useful in the synthesis of a large host molecule. A new route was then designed.
2.5 One Pot Synthesis of A Macrocyle with an Aryl Spacer Group.

One pot reaction systems are not favoured entropically. There are many reaction which have to occur together in order for the desired products to be obtained. Nevertheless, after the failure of several stepwise synthetic routes, a one pot synthesis of the desired macrocycle was attempted as illustrated in Figure 64.

\[
\begin{align*}
41 & \xrightarrow{1. NaH} \quad 88 \\
& \xrightarrow{2.} \quad 89
\end{align*}
\]

Figure 64. One Pot Synthesis of 86

In order to successfully make 89, four \(S_{N2}\) reactions had to occur, combining two molecules of 41 and two molecules of 88. The desired macrocyle was isolated from the crude reaction mixture in a low 2% yield. It was characterized by \(^1\)H NMR which produced a signal for the methylene group next to the newly incorporated spacer as a singlet and the other two methylene signals
are triplets coupled to each other with \( J = 7.1 \) Hz. Analysis of the \( ^{13}\text{C} \) and IR spectra show all of the expected signals. Final determination of the composition of the product, \( \text{89} \), was obtained from mass spectrometry which showed a M'1 signal at 809 g mol\(^{-1}\).

The host molecule, \( \text{89} \), was similar to macrocycle \( \text{50} \) in that it too was preorganized for the binding of guest molecules. The biphenyl moieties and the aryl spacer molecules create a well defined cavity into which the methoxy groups converge. The ether linkages provide dipole interactions to assist in the binding of polar guests. The aryl spacers are also positioned in such a way as to allow potential \( \pi \)-stacking interactions to occur with possible aromatic guests.

Although the desired macrocycle was obtained from the reaction, it was not the predominant product. Not surprisingly, the product of a cyclization reaction involving one molecule of \( \text{41} \) and one molecule of \( \text{88} \) was the primary product with a yield of 21%. This smaller cyclic molecule, \( \text{90} \), which was isolated as a white solid is shown below.

![Diagram of molecule 90](image)

Figure 65. Small Macrocyle, \( \text{90} \), Isolated from Cyclization Reaction.
This small macrocycle was characterized by $^1$H NMR analysis which seemed to indicate a very strained ring in which little flexibility existed as the methylene protons in the ring gave a very complex splitting pattern. A comparison of the $^1$H NMR spectra for compounds 89 and 90 is given in Table 3. Analysis of $^{13}$C and IR showed all of the expected signals and mass spectroscopy was used to identify the compound with a $M^+$ of 404 and molecular formula of C$_{26}$H$_{26}$O$_4$. Although this molecule was not the desired product, it is nonetheless an interesting cyclophane which may have use in future binding studies using different types of guest molecules.

Table 3. $^1$H NMR Analysis of 89 and 90 (ppm).

<table>
<thead>
<tr>
<th>functional group</th>
<th>Compound 89</th>
<th>Compound 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>aromatic-H</td>
<td>7.18 (m)</td>
<td>7.19 (m)</td>
</tr>
<tr>
<td>ArCH$_2$CH$_2$O</td>
<td>2.99 (t)</td>
<td>3.39 (m) &amp; 2.48 (m)</td>
</tr>
<tr>
<td>ArCH$_2$CH$_2$O</td>
<td>3.68 (t)</td>
<td>3.91 (m) &amp; 3.73 (m)</td>
</tr>
<tr>
<td>ArOCH$_3$</td>
<td>3.26 (s)</td>
<td>3.14 (s)</td>
</tr>
<tr>
<td>ArCH$_2$O</td>
<td>4.49 (s)</td>
<td>4.86 &amp; 4.21 (AB)</td>
</tr>
</tbody>
</table>
2.6 Future Work in this Area.

With the synthesis of the host molecules 50 and 89 complete, a study of their effectiveness in binding guest molecules will be completed. The host molecules were preorganized to specifically bind guests which are aromatic in nature and contain para substituted polar groups. Examples of the possible host molecules which will be studied are shown below in Figure 66. Analysis of the effectiveness of complexation will be determined by analysis of complexation induced NMR spectral changes.

![Molecules 91-96](image)

Figure 66. Possible Guest Molecules.

Research in this field will also be expanded to include the study of other similar hosts and their abilities to bind guest molecules. By varying the nature of the spacer moiety, the size of the rigid cavity can be changed to accommodate
different guests. Some possible examples of biphenyl derived host molecules which could be synthesized are shown below in Figure 67.

Figure 67. Possible Future Biphenol Derived Macrocylices.
Conclusion

The object of this project was to synthesize a variety of host molecules which would be capable of binding organic guest molecules. The macrocycles were designed to contain biphenol moieties as a backbone, ether linkages for complexation and rigid spacer groups to both define the cavity and to introduce π-stacking capabilities for the interaction with future guest molecules. Using alkynyl spacer groups, which were introduced by propargyl bromide, a small and large macrocycle were synthesized by a stepwise procedure. These compounds are illustrated in Figure 68.

Figure 68. Host Molecules Synthesized with Alkynyl Spacers.
Another pair of macrocycles were synthesized using a one-pot reaction system. The spacer group was an aryl moiety which was introduced through the use of α,α'-dibromo-m-xylene and produced both compounds 89 and 90.

Figure 69. Host Molecules Synthesized with Aryl Spacers.

Host molecules 50 and 87 are preorganized for the complexation of aromatic guests containing polar substituents. The future work in this area is
directed to the study of the effectiveness of complexation with a variety of different hosts using extensive $^1$H NMR analysis. Also, the design of the host molecules can be extended to include a wide range of similar hosts which would contain different spacer molecules and would therefore exhibit different or more specific binding abilities.
Chapter Three

Experimental

General Procedures

Nuclear magnetic resonance spectra were run on a Bruker AC300 Spectrometer at 300.1 MHz for $^1$H, and at 75.5 MHz for $^{13}$C and DEPT pulse sequencing. DEPT experiments are noted by the multiplicity in brackets within the $^{13}$C data. D$_2$O exchangeable protons are noted as "D$_2$O ex" in the $^1$H data. The chemical shifts are reported in parts per million with the solvent signals used as the standards relative to Me$_4$Si. Fourier Transform Infrared were run on a Nicolet 5DX Spectrometer or on a Bomem Michelson 100 Spectrometer. Elemental analysis was performed by Guelph Chemical Laboratories, Guelph, Ontario. Liquid and oil samples were performed as neat films on potassium bromide plates and solid samples run as pellets in potassium bromide. The melting points were determined on a Fisher-Johns hot plate melting point apparatus and are not corrected. High resolution mass spectrometry was performed on a Kratos Profile mass spectrometer and are within 5 ppm of the expected value. Ozone was produced using a Polymetrics Laboratory Ozonator Model T-816. Column chromatography was performed using silica gel 60 (70-230) mesh or silica gel 60 (230-400) and thin layer chromatography was performed using 0.2 mm silica gel on aluminum plates with 254 nm indicator. Reagents were used as purchased with the exception of tetrahydrofuran (THF) and diethyl ether (Et$_2$O) which were distilled from potassium and benzophenone,
and methylene chloride which was distilled from calcium hydride under a dry nitrogen gas atmosphere. The phrase “conventional workup” refers to the extraction of the reaction product with diethyl ether or methylene chloride, drying of the organic extract over MgSO₄, followed by filtration and subsequent evaporation to dryness under reduced pressure to afford the crude product. All reactions were carried out under a dry nitrogen gas atmosphere unless otherwise noted.

**Synthesis of 2,2'-bis-allyloxy-1,1'-biphenyl (37).**

\[ \text{O} \begin{array}{c} \text{O} \\ \text{O} \end{array} \]

Sodium hydride (27.65 g of 60% dispersion in oil, 960 mmol) was washed with pentane (3 x 10 mL) and dried under an inert atmosphere in a 3-neck, 2.0 L round bottom flask. Dry DMF (1.0 L) was added via canula followed by biphenol, 29, (74.48 g, 400 mmol) dissolved in 200 mL of DMF. Hydrogen gas was evolved. The reaction was allowed to stir for half an hour at room temperature. Allyl bromide (83.10 mL, 960 mmol) was added by syringe over a period of a half an hour. The reaction was heated to reflux for 24 h and then cooled to room temperature. A conventional workup was performed and the crude oil was purified by column chromatography with a solvent mixture of 9:1 petroleum
ether:ethyl acetate to obtain a thick, yellow oil (102.31 g, 380 mmol, 98%, Rf = 0.65, 9:1 petroleum ether:ethyl acetate).

IR (cm⁻¹) : 3067 (m), 3018 (m), 2988 (m), 2861 (m), 1644 (m), 1593 (m), 1480 (m), 1444 (s), 1262 (s), 1123 (m), 754 (s).

¹H NMR (CDCl₃) : 7.14 (m, 4H), 5.94 (m, 1H), 5.29 (dd, 1H, 17.1 Hz, 1.2 Hz), 5.18 (dd, 1H, 11.2 Hz, 1.2 Hz), 4.55 (d, 2H, 4.6 Hz).

¹³C NMR (CDCl₃) : 156.0 (s), 133.5 (d), 131.4 (d), 128.3 (s), 128.3 (d), 120.4 (d), 116.2 (t), 112.3 (d), 68.8 (t).

Low Resolution Mass Spectrometry (m/z) : 266 (M⁺), 225, 197, 184, 168.

High Resolution Mass Spectrometry : calculated for C₁₈H₁₈O₂, 266.1307 g mol⁻¹; found 266.1300 g mol⁻¹.

Synthesis of 3,3'-bis-allyl-2,2'-dihydroxy-1,1'-biphenyl (38). ⁴⁵,⁴⁶,⁴⁸,⁴⁹

![Synthesis of 3,3'-bis-allyl-2,2'-dihydroxy-1,1'-biphenyl (38).](image)

Compound 37 (106.23 g, 390 mmol) in decalin (800 mL) was added to a 3-neck, 2.0 L round bottomed flask, as a solution under a N₂ atmosphere. The reaction was heated to reflux for 120 h. The solution was cooled to room temperature and a majority of the decalin removed by vacuum distillation (45°C, 4.0 mmHg). The remaining decalin was removed and purification was effected
using column chromatography on silica gel with 5:1 petroleum ether:ethyl acetate.
The desired product was obtained as a yellow oil (92.91 g, 351 mmol, 89%, Rf =
0.60, 5:1 petroleum ether: ethyl acetate).

IR (cm⁻¹) : 3533 (s br), 3073 (m), 2927 (m), 1644 (m), 1450 (m), 1222 (s),
1198 (s), 750 (m).

¹H NMR (CDCl₃) : 7.10 (m, 3H), 6.04 (m, 1H), 5.41 (s, D₂O ex, 1H), 5.13
(m, 2H), 3.47 (d, 2H, 6.5 Hz).

¹³C NMR (CDCl₃) : 151.2 (s), 135.5 (d), 130.5 (d), 129.2 (d), 127.3 (s),
123.3 (s), 121.2 (d), 116.2 (t), 34.8 (t).

Low Resolution Mass Spectrometry (m/z) : 266 (M⁺), 225, 184, 104, 57.

High Resolution Mass Spectrometry : calculated for C₁₈H₁₆O₂,
266.1307 gmol⁻¹; found 266.1315 gmol⁻¹.

Synthesis of 3,3'-bis-allyl-2,2'-dimethoxy-1,1'-biphenyl (39). ⁷,⁴⁷,⁵⁰

Sodium hydride (13.96 g of 80% dispersion in oil, 480 mmol) was washed
with hexane (3 x 10 mL) and dried under an inert atmosphere in a 3-neck, 2.0L
round bottom flask. Dry THF (1.5 L) was added via syringe, followed by 38
(53.79 g, 200 mmol), upon which hydrogen gas was evolved. The reaction was
allowed to stir for half an hour at 0°C. Dimethyl sulfate (45.42 mL, 480 mmol) was added by syringe over a period of a half an hour. The reaction was heated to reflux for 24 h and then cooled to room temperature. A conventional workup was performed and the crude oil was purified by column chromatography using a 9:1 petroleum ether:ethyl acetate solvent mixture to produce a dark yellow oil (53.52 g, 182 mmol, 91%, $R_f = 0.70$, 9:1 petroleum ether:ethyl acetate).

IR (cm$^{-1}$) : 3074 (m), 2978 (m), 2935 (s), 1640 (m), 1458 (s), 1222 (s), 788 (s).

$^1$H NMR (CDCl$_3$) : 7.15 (m, 3H), 6.02 (m, 1H), 5.10 (m, 2H), 3.49 (d, 2H, 6.3 Hz), 3.37 (s, 3H).

$^{13}$C NMR (CDCl$_3$) : 155.8 (s), 137.4 (d), 133.1 (s), 132.1 (s), 129.2 (d), 129.2 (d), 123.7 (d), 115.6 (t), 60.5 (q), 34.2 (t).

Low Resolution Mass Spectrometry (m/z) : 294 (M$^+$), 279, 238, 222, 57.

High Resolution Mass Spectrometry : calculated for C$_{29}$H$_{22}$O$_2$, 294.1619 gmol$^{-1}$; found 294.1606 gmol$^{-1}$.

*Synthesis of 3,3'-bis-(propyl-2-ene)-2,2'-dimethoxy-1,1'-biphenyl (40)*$^{51,52}$

Methylated compound, 39, (0.59 g, 2.0 mmol) and potassium t-butoxide (0.89 g, 8.0 mmol) were added to a round bottom flask. Dimethyl sulfoxide
(35 mL) was added and the reaction stirred for 24 h at room temperature under a nitrogen atmosphere. A saturated NaCl solution (25 mL) and diethyl ether (25mL) were added and a conventional workup was performed. The product was purified by column chromatography using a 19:1 petroleum ether:diethyl ether solvent mixture to produce a white solid. (0.39 g, 1.34 mmol, 67 %, Rf = 0.75, 19:1 petroleum:ether diethyl ether).

IR (cm⁻¹) : 3039 (m), 2956 (m), 2927 (m), 1641 (m), 1585 (m), 1453 (s), 1222 (m), 788 (m), 762 (m).

¹H NMR (CDCl₃) : 7.18 (m, 3H), 6.74 (d, 1H, 16.2 Hz), 6.28 (dq, 1H, 16.2 Hz, 7.1 Hz); 3.42 (s, 3H), 1.90 (d, 3H, 7.1 Hz).

¹³C NMR (CDCl₃) : 154.6 (s), 132.4 (s), 131.4 (s), 129.8 (d), 126.8 (d), 125.7 (d), 125.6 (d), 123.6 (d), 60.8 (q), 18.8 (q).

Low Resolution Mass Spectrometry (m/z) : 294 (M⁺), 237, 165, 81, 55.

High Resolution Mass Spectrometry : calculated for C₂₀H₂₂O₂, 294.1620 gmol⁻¹, found 294.1630 gmol⁻¹.

Melting Point : 94 - 97°C.

Elemental Analysis : calculated for C₂₀H₂₂O₂ : 81.59 %C, 7.54 %H, found 80.59 %C, 7.63 % H.
Synthesis of 3,3'-bis-(2-hydroxy ethyl)-2,2'-dimethoxy-1,1'-biphenyl (41). 51,52

![Chemical Structure]

To a 3-neck, 250 mL round bottom flask equipped with a condenser and a gas inlet, 39, (2.97 g, 10 mmol) was added. Chloroform (150 mL) was added and the solution was cooled to -25°C in a dry ice/carbon tetrachloride bath. Ozone was bubbled through the solution at a rate of 0.12 g of ozone per minute for approximately 10 min. A solution of NaBH₄ (6.00 g, 160 mmol) in 30 mL of 4:1 ethanol:water was added and the solution was stirred at reflux for 24 h. The reaction was cooled to room temperature, water (50 mL) was added, and a conventional workup was performed. The product was purified by column chromatography using diethyl ether as a solvent to produce a light yellow solid (2.63 g, 8.7 mmol, 87%, Rᵢ = 0.35, diethyl ether).

IR (cm⁻¹) : 3419 (s br), 3064 (m), 2960 (m), 2930 (m), 1646 (m), 1454 (m), 1259 (m), 1059 (m), 803 (m).

¹H NMR (CDCl₃) : 7.18 (m, 3H), 3.90 (t, 2H, 6.4 Hz), 3.40 (s, 3H), 2.98 (t, 2H, 6.4 Hz), 1.91 (s, D₂O ex, 1H).

¹³C NMR (CDCl₃) : 156.1 (s), 131.9 (s), 130.3 (s), 130.2 (d), 130.2 (d), 123.8 (d), 63.3 (t), 60.5 (t), 33.9 (q).

Low Resolution Mass Spectrometry (m/z) : 302 (M⁺), 239, 195, 104, 91.
High Resolution Mass Spectrometry: calculated for $\text{C}_{16}\text{H}_{22}\text{O}_4$, 302.1518 g mol$^{-1}$, found 302.1506 g mol$^{-1}$.

Melting Point: 80 - 83°C.

Elemental Analysis: calculated for $\text{C}_{16}\text{H}_{22}\text{O}_4$: 71.49 %C, 7.34 %H, found 70.47 %C, 7.36 %H.

**Synthesis of 3,3′-bis-(3″-oxyhex-5″-ynyl)-2,2′-dimethoxy-1,1′-biphenyl (42).**

Sodium hydride (0.38 g of 60% in oil, 9.4 mmol) was washed with hexane (3 x 2 mL) and dried under an inert atmosphere in a 3-neck, 100 mL round bottom flask. Dry THF (50 mL) was added via syringe followed by 41 (1.18 g, 3.9 mmol). The reaction was allowed to stir for half an hour at 0°C. Propargyl bromide (1.05 mL, 9.4 mmol) was then added by syringe over ten minutes. The reaction was then heated to reflux for 24 h. The reaction was cooled to room temperature and a conventional workup was performed. The crude oil was purified by column chromatography using a 9:1 petroleum ether:ethyl acetate solvent mixture to produce a dark yellow oil (0.20 g, 0.37 mmol, 9.6 %, $R_f = 0.8$, 9:1 petroleum ether:ethyl acetate).
IR (cm\(^{-1}\)) : 3284 (s), 3057 (m), 2933 (s), 2857 (s), 2114 (m), 1719 (m),
1586 (w), 1464 (m), 1456 (s), 1094 (s), 766 (m).
\(^{1}\)H NMR (CDCl\(_3\)) : 7.20 (m, 3H), 4.16 (d, 2H, 2.4 Hz), 3.78 (t, 2H,
7.2 Hz), 3.37 (s, 3H), 3.00 (t, 2H, 7.2 Hz), 2.40 (t, 1H, 2.4 Hz).
\(^{13}\)C NMR (CDCl\(_3\)) : 156.2 (s), 132.1 (s), 131.7(s), 130.0 (d), 130.0 (d),
123.5 (d), 79.9 (d), 74.2(s), 70.3 (t), 60.8 (q), 58.1 (t), 30.4(t).
Low Resolution Mass Spectrometry (m/z) : 378 (M\(^+\)), 309, 153, 107, 77.
High Resolution Mass Spectrometry : calculated for C\(_{24}\)H\(_{25}\)O\(_4\),
378.1824 gmol\(^{-1}\), found 378.1831 gmol\(^{-1}\).
Elemental Analysis : calculated for C\(_{24}\)H\(_{25}\)O\(_4\) : 76.17 %C, 6.92 %H,
found 75.00 %C, 7.08 % H.

**Synthesis of propargyl alcohol dicobalt hexacarbonyl (44),** \(^{56,70}\)

\[
\begin{array}{c}
\text{HO} \\
\text{C}_{24}\text{H}_{25}\text{O}_{4}
\end{array}
\]

Solid C\(_2\)(CO)\(_8\) (0.62 g, 2.0 mmol) was added to a 50 mL round bottom flask. Dry diethyl ether (25 mL) was added by syringe and the reaction cooled to -78°C. Propargyl alcohol (0.12 mL, 2.0 mmol) was added. The reaction was stirred at -78°C for 2 h and allowed to warm slowly to room temperature. The reaction was stirred for 24 h and then was filtered through Hyflow. The burgundy oil was purified by column chromatography using a 9:1 petroleum ether:diethyl ether solvent mixture to produce a burgundy solid which was stored until
subsequent usage in the refrigerator to prevent decomplexation. (0.53 g, 1.6 mmol, 78 %, \( R_f = 0.80 \), (9:1 petroleum ether:diethyl ether).

\[
\text{IR (cm}^{-1}) : 3266 (m), 2096 (m), 2062 (s), 2050 (s), 2023 (s), 1023 (w),
987 (w), 518 (m), 494 (m).
\]

\[
\text{\(^1\text{H NMR (CDCl}_3\) : 6.05 (s, 1H), 4.78 (d, 2H, 6.2 Hz), 1.83 (t, 1H, 6.2 Hz).}
\]

\[
\text{\(^{13}\text{C NMR (CDCl}_3\) : 215.5, 96.8, 71.3, 63.5.}
\]

\[
\text{Low Resolution Mass Spectrometry (m/z) : 342 (M^+, 314, 286, 258, 230, 202, 174, 55.}
\]

\[
\text{High Resolution Mass Spectrometry : calculated for C}_{25}\text{H}_{40}\text{O}_7\text{Co}_2, 341.8621 \text{g mol}^{-1}, \text{found 341.8632 g mol}^{-1}.
\]

\[
\text{Melting Point : 37 - 41°C.}
\]

**Attempted reaction of \textbf{41} with propargyl alcohol-dicobalt hexacarbonyl.\textsuperscript{56-58}**

Propargyl alcohol-cobalt complex, \textbf{44}, (0.16 g, 0.47 mmol) and THF (30 mL) were added to a 50 mL, 3 necked, round bottom flask. Tosic acid (100 mg) and dried 4Å molecular sieves were added and the reaction stirred at 0°C for 1 h. The dialcohol, \textbf{41}, (0.071, 0.23 mmol) was added and the reaction stirred for an additional 5 h at 0°C. The reaction mixture was allowed to warm to room temperature and was then stirred for 20 h. The progress of the reaction was monitored by TLC which indicated that starting material still remained. The reaction was heated to reflux for 24 h, the reaction was cooled to room temperature, and a conventional workup was performed to produce a red solid.
This was not the desired product as only a mixture of starting materials remained as evidenced by $^1$H NMR analysis.

**Synthesis of 3,10-dioxa-14,20-dimethoxy-6,8-diyne-[0,12]-metacyclopheane (47)**

Dialkyne, 42, (0.05 g, 0.10 mmol), CuCl (1.57 g, 15 mmol), and CuCl$_2$ (0.32 g, 2.4 mmol) were added to a 100 mL round bottom flask with DMF (50 mL). This mixture was stirred in the flask while open to the atmosphere for 3 days. DMF was removed under reduced pressure. Water (15 mL) and diethyl ether (10 mL) were added and a conventional workup was performed. The crude oil was purified by preparatory thin layer chromatography using a 9:1 petroleum ether:ethyl acetate solvent mixture to produce a dark yellow oil (0.01 g, 0.03 mmol, 26 %, R$_f$=0.65, 10:1 petroleum ether:ethyl acetate).

IR (cm$^{-1}$) : 3056 (m), 2953 (s), 2924 (s), 2853 (s), 2155 (w), 1714 (s), 1651 (m), 1462 (s), 1455 (s), 1010 (m), 737 (m).

$^1$H NMR (CDCl$_3$) : 7.20 (m, 3H), 4.21 (s, 2H), 3.76 (t, 2H, 6.9 Hz), 3.36 (s, 3H), 2.98 (t, 2H, 6.9 Hz).

$^{13}$C NMR (CDCl$_3$) : 156.3 (s), 132.1 (s), 131.6 (s), 130.2 (d), 130.1 (d), 123.6 (d), 75.5 (s), 70.4 (t), 70.3 (s), 60.7 (q), 58.6 (t), 30.7 (t).
Low Resolution Mass Spectrometry (m/z): 376 (M'), 330, 302, 239, 195.

High Resolution Mass Spectrometry: calculated for C_{24}H_{24}O_{4},
376.1675 g mol\(^{-1}\), found 376.1683 g mol\(^{-1}\).

Synthesis of 5,5'-dibromo-3,3'-bis-(Z-3-oxy-5,6-dibromo-hex-5-enyl)-2,2'-dimethoxy-1,1'-biphenyl (48).

Sodium hydride (7 mg of 60% dispersion in oil, 0.17 mmol) was washed with hexane (2 x 2 mL) and dried under an inert atmosphere in a 3-neck, 50 mL round bottom flask. Dry THF (10 mL) was added via syringe followed by 42, (0.03 g, 0.08 mmol) dissolved in dry THF (10 mL). The reaction was allowed to stir for half an hour at -78\(^\circ\)C. Bromine (8.7 µL, 0.20 mmol) was then added by syringe over a period of ten minutes. The reaction was allowed to stir for one hour and then warmed to room temperature. Water (15 mL) and diethyl ether (15 mL) were added and a conventional workup was performed. The crude oil was purified by column chromatography using a 9:1 petroleum ether:ethyl acetate solvent mixture to produce a light yellow oil (45 mg, 0.05 mmol, 29 %, R_f=0.85, 9:1 petroleum ether:ethyl acetate).
IR (cm⁻¹) : 3078 (m), 2930 (s), 2863 (s), 1603 (w), 1567 (m), 1468 (s), 1455 (m), 1101 (s), 796 (s).

¹H NMR (CDCl₃) : 7.44 (d, 1H, 2.4 Hz), 7.33 (d, 1H, 2.4 Hz), 6.65 (s, 1H), 4.37 (s, 2H), 3.68 (t, 2H, 6.7 Hz), 3.39 (s, 3H), 2.96 (d, 2H, 6.7 ;Hz).

¹³C NMR (CDCl₃) : 155.3 (s), 134.4 (s), 133.3 (d), 132.3 (s), 132.2 (d), 123.1 (s), 116.3 (s), 105.9 (d), 70.8 (t), 69.7 (t), 60.9 (q), 30.2 (t).

Low Resolution Mass Spectrometry (LSIMS) (m/z) : 855 (M+1), 641, 286, 133, 77.

Synthesis of 3,3'-bis-(3''-oxy-6''-bromo-hex-5''-ynyl)-2,2'-dimethoxy-1,1'-biphenyl (49).

A solution of 42 (0.10 g, 0.26 mmol) in THF (30 mL) was added to a 50 mL round bottom flask and cooled to -78°C. BuLi (0.25 mL of 2.5 M, 0.63 mmol) was added and the reaction was stirred for 1 h. Dibromotetrafluoroethane (0.070 mL, 0.63 mmol) was then added and the reaction stirred for 1 h at -78°C and then warmed to room temperature. The reaction was stirred overnight and a conventional workup was performed to yield a crude yellow oil which produced
only one spot on TLC and was used without further purification. (130 mg, 0.24 mmol, 93%, Rf=0.9, 8:2 petroleum ether:ethyl acetate).

IR (cm$^{-1}$) : 3057 (m), 2932 (s), 2858 (s), 2212 (m), 1713 (m), 1587 (m), 1469 (s), 1454 (m), 1087 (m), 764 (m).

$^1$H NMR (CDCl$_3$) : 7.15 (m, 3H), 4.19 (s, 2H), 3.76 (t, 2H, 7.2 Hz), 3.37 (s, 3H), 2.99 (t, 2H, 7.2 Hz).

$^{13}$C NMR (CDCl$_3$) : 156.2 (s), 132.0 (s), 131.6 (s), 130.0 (d), 130.0 (d), 123.6 (d), 76.0 (s), 70.4 (t), 60.8 (q), 59.0 (t), 45.8 (s), 30.4 (t).

Low Resolution Mass Spectrometry (LSIMS) (m/z) : 536 (M$^+$), 401, 253, 133, 71.

Synthesis of Macrocycle 2 (50)$^{61}$

MeOH (20 mL), NH$_2$OH·HCl (13 mg), H$_2$O (10 mL), n-BuNH$_2$ (5 mL) and CuCl (2 mg) were added to a 50 mL round bottom flask. The O$_2$ was removed by bubbling through a steady stream of N$_2$. Compound 42 (50 mg, 0.13 mmol) was dissolved in MeOH and added to the reaction flask. The di-bromoalkyne 49 (71 mg, 0.13 mmol) was dissolved in 1:1 Et$_2$O : MeOH and added to the reaction flask over one hour by syringe pump. The reaction was stirred overnight under a
N₂ atmosphere and then a conventional workup was performed. The crude oil was purified by column chromatography using a 9:1 petroleum ether : ether solvent system to produce the product as a dark yellow oil. (23 mg, 0.03 mmol, 25 %, Rf=0.60, 9:1 petroleum ether:ethyl acetate).

IR (cm⁻¹) : 3058 (w), 2926 (s), 2851 (s), 2248 (w), 1723 (w), 1587 (m), 1469 (m), 1455 (m), 1221 (m), 1090 (m), 764 (w).

¹H NMR (CDCl₃) : 7.18 (m, 3H), 4.22 (s, 2H), 3.76 (t, 2H, 7.0 Hz), 3.39 (s, 3H), 2.98 (t, 2H, 7.0 Hz).

¹³C NMR (CDCl₃) : 158.3 (s), 132.1 (s), 131.5 (s), 130.2 (d), 130.0 (d), 123.5 (d), 77.2 (s), 75.4 (s), 70.4 (t), 60.6 (q), 58.5 (t), 30.6 (t).

Low Resolution Mass Spectrometry (LSIMS) : 753 (M⁺1), 403, 307, 154, 171.

**Synthesis of 3,3'-bis-(3''-oxy-4''-(p-bromo-phenyl)-butyl)-2,2'-dimethoxy-1,1'-biphenyl (51).**

![Chemical structure](image)

Sodium hydride (0.11 g of 60% dispersion in oil, 4.4 mmol) was washed with hexane (3 x 5 mL) and dried under an inert atmosphere in a 3-neck, 100 mL round bottom flask. Dry THF (60 mL) was added via syringe followed by 41 (0.60
g, 2.0 mmol) dissolved in THF. The reaction was allowed to stir for half an hour at 0°C. 4-Bromobenzyl bromide (0.99 g, 4.0 mmol) was added by syringe over half an hour and the reaction was then heated to reflux for 24 h. The reaction was cooled to room temperature, water (40 mL) and diethyl ether (40 mL) were added, and a conventional workup was performed. The crude light yellow oil was used as obtained without further purification since it produced only one spot on TLC. (1.19 g, 18.5 mmol, 92% Rf=0.75, 9:1 petroleum ether:ethyl acetate).

IR (cm⁻¹) : 3057 (m), 3025 (m), 2932 (s), 2860 (s), 1721 (m), 1591 (m), 1485 (s), 1454 (m), 1415 (s), 1219 (m) 802 (m), 478 (m).

¹H NMR (CDCl₃) : 7.19 (m, 7H), 4.48 (s, 2H), 3.71 (t, 2H, 6.9 Hz), 3.32 (s, 3H), 3.01 (t, 2H, 6.9 Hz).

¹³C NMR (CDCl₃) : 156.2 (s), 137.6 (s), 132.0 (s), 131.9 (s), 131.4 (d), 130.2 (d), 129.9 (d), 129.2 (2), 123.5 (d), 121.3 (s), 72.1 (t), 70.7 (t), 60.6 (q), 30.7 (t).

Low Resolution Mass Spectrometry (m/z) : 638 (M⁺), 640 (M⁺2), 642 (M⁺4), 472, 386, 302, 55.

High Resolution Mass Spectrometry : calculated for C₃₂H₃₂O₄Br₂, 640.0648 gmol⁻¹, found 640.0657 gmol⁻¹.

Elemental Analysis : calculated for C₃₂H₃₂O₄Br₂ : 60.18 %C, 5.05 %H, found 59.64 %C, 5.02 % H.
General Procedure for the Grignard reaction of 51\textsuperscript{15,62-64}

The general procedure used for the attempted formation of the Grignard reagent with 51 and subsequent reaction with an electrophile is shown below. Conditions that were used are summarized in Table 2.

Magnesium (2.2 eq.) was weighed into a 3 neck, round bottom flask. Dry solvent was added by syringe. Compound 51 (1 eq) was added to the reaction flask dissolved in 10 mL of dry diethyl ether. An initiator was added and the reaction heated to reflux for 3-4 h. The reaction was cooled to room temperature and paraformaldehyde (6.6 eq), which had been previously dried over P$_2$O$_5$\textsuperscript{71} was added with a solid addition funnel. The reaction was heated to reflux for 24 h. The reaction was cooled to room temperature, 10% HCl was added to dissolve the magnesium and a conventional workup was performed. The reaction yielded only the starting material, 51, in all cases.

Attempted metal halogen exchange reaction with 51

To an oven dried 3-neck round bottom flask, a solution of 51 (1 eq) in THF (30 mL) was added and the solution cooled to -78°C. BuLi (2.4 eq) was then added by syringe and the solution stirred for half an hour. DMF (2.4 eq) was added by syringe and the reaction allowed to warm to room temperature where it was stirred for 2 h. A conventional aqueous workup followed but no desired product was obtained as evidenced by $^1$H NMR analysis.
Synthesis of 3,3'-bis-(2-(4-carboxethoxybenzyloxy)ethyl)-2,2'-dimethoxy-1,1'-biphenyl (54).\textsuperscript{65-67}

To a 50 mL 3 neck round bottom flask, 51 (0.16 g, 0.25 mmol), Co\textsubscript{2}(CO)\textsubscript{8} (0.10 g, 0.04 mmol), ClCH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{3} (10 mL, 0.12 \mu mol), K\textsubscript{2}CO\textsubscript{3} (0.56 g, 4 mmol) and methanol (30 mL) were added. The reaction was heated to reflux for 4 days under a CO atmosphere. The solution turned a light purple colour. The reaction was cooled to room temperature and filtered to remove any remaining transition metal compounds. The solvent was evaporated under reduced pressure and the crude oil was purified by column chromatography using a 9:1 petroleum ether:ethyl acetate solvent mixture to produce a dark yellow oil (31 mg, 0.05 mmol, 10 \%, R\textsubscript{f} = 0.5, 9:1 petroleum ether:ethyl acetate).

IR (cm\textsuperscript{-1}) : 3058 (m), 2929 (s), 2856 (s), 1722 (s), 1613 (m), 1591 (m), 1485 (m), 1454 (m), 1278 (s), 1105 (s), 757 (m), 704 (w).

\textsuperscript{1}H NMR (CDCl\textsubscript{3}) : 7.62 (AA'BB', 4H), 7.17 (m, 3H), 4.59 (s, 2H), 3.89 (s, 3H), 3.73 (t, 2H, 7.1 Hz), 3.31 (s, 3H), 3.03 (t, 2H, 7.1 Hz).
$^{13}$C NMR (CDCl$_3$): 156.3 (s), 143.9 (s), 131.9 (s), 131.5 (s), 130.3 (d), 130.1 (d), 129.7 (d), 129.3 (s), 127.2 (d), 123.6 (d), 72.3 (t), 71.1 (t), 60.7 (q), 52.2 (q), 30.8 (t).


Elemental Analysis: calculated for C$_{36}$H$_{38}$O$_6$: 72.21 %C, 6.40 %H, found 72.22 %C, 6.40 % H.

**General procedure for bromination**

The substrate (1.0 eq) was dissolved in carbon tetrachloride or benzene. N-bromosuccinimide (1.1 eq) and a catalytic amount of benzoyl peroxide (0.01 eq) were added. The reaction was heated to reflux overnight, cooled to room temperature and filtered to remove succinimide. The solvent was removed under reduced pressure and the product dried.

Bromination was attempted on the following compounds:

- $p$-methylbenzyl alcohol
- $p$-methylbenzaldehyde
- 2-(4-methylbenzyloxy)tetrahydopyran
- 2-(4-methyl)-phenyl-1,3-dioxane.
- 4-methyl-benzyloxy-dimethylthexyl silane
- 4-methyl-benzyloxy-triphenyl methane
- 4-methyl-benzyloxy-acetate
The products were analyzed by NMR techniques. A methylene signal for the product was expected at approximately 4.6 ppm indicative of a BrCH₂Ar. All these reactions failed and in many cases the product no longer contained the protecting group of the starting material.

Synthesis of 2-(4-methylbenzyloxy)tetrahydropyran (67)₅₀,₆₉

\[ \text{Chemical Structure} \]

*p*-Methyl benzyl alcohol, 60, (1.22 g, 10 mmol) was added to a 3-neck round bottom flask followed by dihydropyran (1.19 mL, 13 mmol) and hydrochloric acid (0.1 mL). The reaction was stirred at room temperature for 2 h. The pH of the solution was adjusted to 7 with saturated NaHCO₃. Diethyl ether (20 mL) was added and a conventional workup was performed. The product was obtained as a clear oil after distillation under reduced pressure (60°C, 2 mmHg). (1.27 g, 6.2 mmol, 62%, Rᵣ=0.70, 4:1 petroleum ether:ethyl acetate).

IR (cm⁻¹) : 3036 (m), 2942 (s), 2869 (s), 1722 (m), 1612 (m), 1516 (m), 1453 (m), 1033 (m), 950 (m).

¹H NMR (CDCl₃) : 7.21 (AA'BB', 4H), 4.75 (1/2 of AB, 1H, 11.8 Hz), 4.71 (t, 1H, 3.4 Hz), 4.47 (1/2 of AB, 1H, 11.8 Hz), 3.94 (m, 1H), 3.57 (m, 1H), 2.35 (s, 3H), 1.82 (m, 6H).

¹³C NMR (CDCl₃) : 137.3 (s), 135.4 (s), 129.2 (d), 128.1 (d), 97.7 (d), 68.8 (t), 62.2 (t), 30.7 (t), 25.6 (t), 21.3 (q), 19.5 (t).
Low Resolution Mass Spectrometry (m/z): 206 (M⁺), 122, 105, 91, 84.

High Resolution Mass Spectrometry: Calculated for C_{13}H_{18}O_{2},
206.1307 gmol⁻¹, found 206.1306 gmol⁻¹.

Synthesis of 4-methyl-benzylxy-dimethylthexyl silane (69)⁵⁰

![Chemical Structure Image]

p-Methyl benzy alcohol, 60, (1.22 g, 10 mmol) and imidazole (1.36 g, 20 mmol) were weighed into a 3-neck round bottom flask. Dry dimethylformamide (30 mL) was then added. The reaction was stirred at room temperature for one half hour. Dimethyl thexyl silyl triflate (2.56 mL, 10 mmol) was added and the reaction was stirred for 24 h. Water (40 mL) and diethyl ether (40 mL) were added and a conventional workup was performed. The product was a light yellow oil which produced only one spot on TLC and was used without further purification. (2.27 g, 8.6 mmol, 86%, Rf=0.90, 19:1 petroleum ether:ethyl acetate).

IR (cm⁻¹): 3096 (m), 3049 (m), 2957 (s) 2866 (s), 1611 (w), 1515 (m), 1462 (m), 1253 (s), 1087 (s), 830 (s).

¹H NMR (CDCl₃): 7.17 (AA'BB', 4 H), 4.69 (s, 2H), 2.34 (s, 3H), 1.70 (m, 1 H), 0.91 (m, 12 H), 0.13 (s, 6 H).

¹³C NMR (CDCl₃): 136.8 (s), 134.6 (s), 127.2 (d), 124.4 (d), 63.0 (t), 32.6 (q), 23.6 (s), 19.4 (d), 18.7 (q), 16.9 (q), -4.9 (q).

Low Resolution Mass Spectrometry (m/z): 264 (M⁺), 179, 149, 105, 75.
High Resolution Mass Spectrometry: Calculated for C_{15}H_{28}OSi, 264.1909 g mol^{-1}, found 264.1904 g mol^{-1}.

Synthesis of \((4\text{-methylbenzyloxy})\text{triphenylmethane (71)}^{50,72}\)

\[
\text{\begin{tikzpicture}
  \node[anchor=north east] at (0,0) {\includegraphics[width=0.2\textwidth]{molecule.png}};
\end{tikzpicture}}
\]

\(\rho\)-Methyl benzyl alcohol, 60, (1.22 g, 10 mmol) and dimethyl formamide (50 mL) were added to a 3 neck round bottom flask. Trityl chloride (3.06 g, 11 mmol), 4-dimethylaminopyridine (0.05g, 0.4 mmol) and triethyl amine (2.09 mL, 15 mmol) were then added. The reaction was stirred overnight under a nitrogen atmosphere. Water (40 mL) and diethyl ether (40 mL) were added and a conventional workup was performed. The crude compound was purified by column chromatography using petroleum ether as solvent to obtain a white solid (1.89 g, 5.2 mmol, 52%, \(R_t = 0.90\) petroleum ether).

\begin{itemize}
  \item IR (cm\(^{-1}\)) : 3049 (m), 2855 (m), 1629 (w), 1515 (w), 1446 (m), 1088 (m), 705 (m), 693 (m), 629 (m).
  \item \(^1\)H NMR (CDCl\(_3\)) : 7.45 (m, 19H), 4.34 (s, 2H), 2.51 (s, 3H).
  \item \(^{13}\)C NMR (CDCl\(_3\)) : 144.5 (s), 137.0 (s), 136.4 (s), 129.3 (s), 129.1 (s), 128.1, (s), 127.4 (d), 127.3 (d), 87.3 (s), 66.0 (t), 21.5 (q).
\end{itemize}

High Resolution Mass Spectrometry: Calculated for C\(_{27}\)H\(_{24}\)O, 364.1827 g mol\(^{-1}\), found 364.1831 g mol\(^{-1}\).

Melting Point: 112 - 115°C.
Synthesis of 4-methyl benzyl acetate (73)\(^{50,73}\)

\[
\begin{array}{c}
\text{O} \\
\text{C} \\
\text{O}
\end{array}
\]

\(p\)-Methylbenzyl alcohol, 60, (1.22 g, 10 mmol) and acetic anhydride (50 mL) were added to a 3-neck round bottom flask. Hydrochloric acid (5 drops) was then added and the reaction heated to reflux overnight. The reaction was cooled to room temperature, ice water (25 mL) and saturated \(\text{NaHCO}_3\) (200 mL) were added and a conventional workup was performed. The crude yellow oil produced only one spot on TLC and was used without further purification. (1.05 g, 6.40 mmol, 64 %, \(R_f = 0.35\), 9:1 petroleum ether:ethyl acetate).

IR (cm\(^{-1}\)) : 3027 (m), 2953 (m), 1741 (s), 1615 (m), 1518 (m), 1453 (m), 1229 (s), 1021 (m), 805 (m), 559 (m).

\(^1\text{H NMR (CDCl}_3\) : 7.20 (AA'BB', 4H), 5.06 (s, 2H), 2.34 (s, 3H), 2.10 (s, 3H).

\(^13\text{C NMR (CDCl}_3\) : 171.0 (s), 138.2 (s), 133.0 (s), 129.4 (d), 128.5 (d), 66.3 (t), 21.3 (q), 21.1 (q).

Low Resolution Mass Spectrometry (m/z) : 164(M\(^+\)), 122, 105, 91, 77.

High Resolution Mass Spectrometry : Calculated for \(\text{C}_{10}\text{H}_{12}\text{O}_2\), 164.8885 g\(\text{mol}^{-1}\), found 164.0837 g\(\text{mol}^{-1}\).
Synthesis of 2-(4-methylphenyl)-1,3-dioxane (75)\textsuperscript{50}

\[
\begin{align*}
\text{IR} (\text{cm}^{-1}) & : 3016 (\text{m}), 2963 (\text{s}), 2852 (\text{s}), 1714 (\text{m}), 1611 (\text{m}), 1518 (\text{m}), 1468 (\text{m}), 1103 (\text{m}), 989 (\text{m}), 810 (\text{m}). \\
\text{H NMR (CDCl}_3\text{)} & : 7.25 (AA'BB', 4\text{H}), 5.46 (\text{s, 1H}), 4.23 (\text{m, 2H}), 3.96 (\text{m, 2H}), 2.38 (\text{m, 1H}), 2.32 (\text{s, 3H}), 2.21 (\text{m, 1H}). \\
\text{C NMR (CDCl}_3\text{)} & : 138.5 (\text{s}), 135.9 (\text{s}), 128.9 (\text{d}), 125.9 (\text{d}), 101.7 (\text{d}), 67.4 (\text{t}), 25.8 (\text{t}), 21.3 (\text{q}). \\
\text{Low Resolution Mass Spectrometry (m/z)} & : 178 (\text{M}^+) , 177, 119, 84. \\
\text{High Resolution Mass Spectrometry} & : \text{Calculated for } C_{11}H_{14}O_2, 178.0994 \text{ g mol}^{-1}, \text{found } 178.1001 \text{ g mol}^{-1}. 
\end{align*}
\]
Synthesis of 4-bromobenzylalcohol (78).

\[
\text{Br} \quad \text{OH}
\]

Lithium aluminum hydride (0.75 g, 20 mmol) was added to a dry 100 mL, 3 neck, round bottom flask under a N₂ atmosphere. Dry tetrahydrofuran (60 mL) was added by syringe followed by p-bromobenzaldehyde, 77, (3.60 g, 20 mmol) as a solution in tetrahydrofuran (10 mL). The reaction was heated to reflux overnight and was then cooled to room temperature. Water (10 mL) and diethyl ether (50 mL) were added and a conventional workup was performed. The product was a white solid. (2.82 g, 15.2 mmol, 76 %, Rf=0.2, ethyl acetate).

IR (cm⁻¹) : 3406 (s), 3049 (m), 2945 (m), 1590 (m), 1483 (m), 1009 (m), 826 (m), 792 (m).

¹H NMR (CDCl₃) : 7.33 (AA'BB', 4H), 4.60 (s, 2H), 2.02 (s, D₂O ex, 1H).

¹³C NMR (CDCl₃) : 139.7 (s), 131.8 (d), 128.6 (d), 121.4 (s), 64.6 (t).

Low Resolution Mass Spectrometry (m/z) : 185 (M⁺), 187 (M⁺2), 107, 97, 85, 77, 59.

High Resolution Mass Spectrometry : Calculated for C₇H₇OBr,

185.9680 g mol⁻¹, found 185.9685 g mol⁻¹.

Melting Point : 68 - 73°C.
Synthesis of 4-bromobenzyl(dimethylthethyl)silane (79)^50

\[
p-	ext{Bromobenzyl alcohol, 78, (0.37 g, 2 mmol) and imidazole (0.27 g, 4.0 mmol) were weighed into a 3-neck round bottom flask. Dry dimethylformamide (30 mL) was then added. The mixture was stirred at room temperature for half an hour. Dimethylthethylsilyl triflate (0.51 mL, 2.0 mmol) was then added and stirring was continued for 24 h. Water (40 mL) and diethyl ether (40 mL) were added and a conventional workup was performed. The product was a clear oil which produced only one spot on TLC and was used without further purification. (0.57 g, 1.74 mmol, 87%, Rf=0.85, 4:1 petroleum ether:ethyl acetate).}
\]

IR (cm\(^{-1}\)) : 3013 (m), 2957 (s), 2866 (s), 1593 (m), 1463 (m), 1377 (m), 1252 (m), 1098 (s), 831 (s).

\(^1\)H NMR (CDCl\(_3\)) : 7.44 (AA'BB', 4H), 4.65 (s, 2H), 1.65 (m, 1H), 0.90 (m, 12H), 0.13 (m, 6H).

\(^13\)C NMR (CDCl\(_3\)) : 140.6 (s), 131.3 (d), 127.8 (d), 120.6 (s), 64.2 (t), 34.3 (d), 25.3 (s), 20.5 (q), 18.6(q), -3.3 (q).

Low Resolution Mass Spectrometry (m/z) : 328 (M\(^+\)), 330 (M\(^+\)2), 243, 165, 91, 84.

High Resolution Mass Spectrometry : Calculated for C\(_{15}\)H\(_{25}\)OSiBr, 328.0858 g mol\(^{-1}\), found 328.0868 g mol\(^{-1}\).
Attempted Grignard of 79

Magnesium (1.2 eq) was weighed into a 100 mL 3 neck, round bottom flask followed by dry ether (50 mL) was added by syringe. 79 (1.0 eq) was dissolved in 10 mL of dry diethyl ether and was added to the reaction flask. Iodine was added and the reaction was heated to reflux for 2-3 h. The reaction was cooled to room temperature and paraformaldehyde, which had been previously dried with P2O5,71 was added with a solid addition funnel under a N2 atmosphere. The reaction was heated to reflux for 24 h then was cooled to room temperature. The remaining magnesium was dissolved by the addition of 10% HCl and a conventional workup was performed. Only starting material was obtained.

Synthesis of 1,4-benzene dimethanol (82).

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{ } & \\
\text{ } & \\
\text{ } & \\
\text{ } & \\
\end{align*}
\]

Lithium aluminum hydride (7.00 g, 200 mmol) was added to a 500 mL 3-neck round bottom flask. Dry tetrahydrofuran (250 mL) was added. Benzene di-methyl ester, 81, (9.76 g, 50.0 mmol) was added by solid addition funnel and the reaction heated to reflux overnight. The reaction was cooled to room temperature. Excess lithium aluminum hydride was consumed with water (20 mL), the aqueous layer acidified with HCl, and a conventional workup was performed. The crude solid was purified by column chromatography with a
solvent mixture of 19:1 petroleum ether:diethyl ether to produce a light yellow solid (6.78 g, 49.0 mmol, 98 %, R_f = 0.1, ethyl acetate).

IR (cm\(^{-1}\)) : 3540 (br), 3123 (m), 2850 (m), 1418 (s), 1375 (m), 1222 (m), 1015 (s), 823 (m).

\(^1\)H NMR (CDCl\(_3\)) : 7.34 (m, 4H), 4.68 (s, 4H), 1.62 (s, br, D\(_2\)O ex., 2H).

\(^13\)C NMR (CDCl\(_3\)) : 140.8 (s), 127.3 (d), 65.2 (t).

Low Resolution Mass Spectrometry (m/z) : 138 (M\(^+\)), 120, 107, 91, 79.

High Resolution Mass Spectrometry : Calculated for C\(_8\)H\(_{10}\)O\(_2\), 138.0681 gmol\(^{-1}\), found 138.0681 gmol\(^{-1}\).

**Synthesis of 4-methanolbenzyloxydimethylthexyl silane (83).**

\[
\text{HO} \quad \text{O} \quad \text{Si} \\
\downarrow \\
\text{p-Benzenedimethanol, 82, (0.28 g, 2.0 mmol) and imidazole (0.27 g, 4.0 mmol) were weighed into a 3-neck round bottom flask. Dry dimethylformamide (50 mL) was then added. The reaction was stirred at room temperature for one half hour. Dimethyl thexyl silyl triflate (0.51 mL, 2.0 mmol) was added and the reaction was stirred for 24 h. Water (40 mL) and diethyl ether (40 mL) were added and a conventional workup was performed. The crude mixture was purified by column chromatography with a 3:17 diethyl ether : petroleum ether solvent sysytem to produce the product as a light yellow oil. (0.08 g, 0.28 mmol, 14 %, R_f=0.95, 3:17 diethyl ether : petroleum ether).} 
\]
IR (cm⁻¹) : 3345 (br, s), 3053 (w), 3018 (m), 2957 (s), 2866 (s), 1614 (w), 1514 (m), 1462 (m), 1377 (m), 1088 (s), 778 (m).

¹H NMR (CDCl₃) : 7.29 (m, 4H), 4.71 (s, 2H), 4.62 (s, 2H), 1.98 (br s, 1H), 1.67 (m, 1H), 0.91 (m, 12H), 0.12 (m, 6H).

¹³C NMR (CDCl₃) : 141.0 (s), 139.4 (s), 126.9 (d), 126.2 (d), 65.2 (t), 64.5 (t), 34.2 (d), 25.2 (s), 20.3 (q), 18.5 (q), -3.3 (q).

Low Resolution Mass Spectrometry (m/z) : 280 (M⁺), 263, 195, 121, 91, 75.

High Resolution Mass Spectrometry : Calculated for C₁₈H₂₆O₂Si, 280.1859 gmol⁻¹, found 280.1846 gmol⁻¹.

**Synthesis of 3,3'-bis-(2-(4-carboxybenzyl)oxy)ethyl)-2,2'-dimethoxy-1,1'-biphenyl (87).**

Sodium hydride (0.18 g of 60% dispersion in oil, 4.4 mmol) was washed with hexane (3 x 3 mL) and dried under an inert atmosphere in a 3-neck, 100 mL
round bottom flask. Dry THF (20 mL) was added and the flask was cooled to 0°C. A solution of α-bromo-p-toluic acid, 85, (0.45 g, 2.1 mmol) in THF (10 mL) was added and the solution stirred for 30 min. A solution of 41 (0.30 g, 1.0 mmol) in THF (10 mL) was added and the reaction stirred at 0°C for 30 minutes. The reaction was heated to reflux for 24 h, cooled to room temperature, acidified with HCl and a conventional workup was performed to yield the crude product. The product was purified by column chromatography using ethyl acetate as the solvent. (0.057 g, 0.10 mmol, 10 %, Rf=0.2, ethyl acetate).

IR (cm⁻¹) : 3500-3400 (br), 3075 (m), 2861 (s), 1678 (s), 1612 (m), 1577 (m), 1454 (m), 1291 (s), 1094 (s), 757 (m), 546 (w).

¹H NMR (CDCl₃) : 12.85 (s, 1H, D₂O ex.), 7.64 (AA'BB', 4 H), 7.18 (m, 3H), 4.59 (s, 2H), 3.71 (t, 2H, 6.9 Hz), 3.29 (s, 3 H), 2.95 (t, 2H, 6.9 Hz).

¹³C NMR (d6-DMSO) : 167.2 (s), 155.8 (s), 143.8 (s), 131.8 (s), 131.7 (s), 131.5 (s), 129.7 (d), 129.4 (d), 129.3 (d), 127.1 (d), 123.3 (d), 71.2 (t), 70.2 (t), 60.1 (q), 30.1 (t).

Low Resolution Mass Spectrometry (LSIMS) (m/z) : 571 (M⁺1), 491, 460, 391, 273.

Melting Point : 175-177 °C
Synthesis of Macrocycle 3 (89) and Macrocycle 4 (90).

Sodium hydride (80 mg of 60% dispersion in oil, 2.0 mmol) was washed with hexane (2 x 5 mL) and dried under an inert atmosphere in a 3-neck, 100 mL round bottom flask. Dry THF (50 mL) was added via syringe followed by 41 (0.302 g, 1.0 mmol) dissolved in THF. The reaction was allowed to stir for half an hour at 0°C. α,α'-dibromo-m-xylene, 88, (0.262 g, 1.0 mmol) was added by syringe over half an hour and the reaction was then heated to reflux for 24 h. The reaction was cooled to room temperature, water (30 mL) and diethyl ether (30 mL) were added, and a conventional workup was performed. The crude yellow oil was purified by column chromatography using 4:1 petroleum ether : ether as the solvent. (15 mg, 0.02 mmol, 2%, Rf=0.2, 4:1 petroleum ether : ether).

IR (cm⁻¹): 3056 (w), 3026 (w), 2957 (s), 2929 (s), 2855 (s), 1681 (m), 1589 (w), 1468 (m), 1454 (m), 1221 (s), 1087 (s), 763 (m).
\(^1\)H NMR (CDCl\(_3\)) : 7.18 (m, 10H), 4.49 (s, 4H), 3.68 (t, 4H, 7.1 Hz), 3.26 (s, 6H), 2.99 (t, 4H, 7.1 Hz).

\(^{13}\)C NMR (CDCl\(_3\)) : 157.3 (s), 138.7 (s), 132.1 (s), 130.3 (s), 130.0 (d), 128.4 (d), 126.9 (d), 126.8 (d), 125.1 (d), 123.6 (d), 72.8 (t), 70.6 (t), 60.7 (q), 30.9 (t).

Low Resolution Mass Spectrometry (m/z) : 809 (M\(^+\)), 525, 307, 154, 105.

![Chemical Structure](image)

From the above reaction, 90 was isolated by column chromatography using 4:1 petroleum ether : ether as the solvent and subsequent recrystallization from diethyl ether. (85 mg, 0.21 mmol, 21 %, R\(_f\)=0.24, 4:1 petroleum ether:ether).

IR (cm\(^{-1}\)) : 3051 (m), 2924 (m), 2861 (m), 1570 (m), 1474 (s), 1438 (m), 1389 (m), 1220 (s), 1081 (s), 752 (m).

\(^1\)H NMR (CDCl\(_3\)) : 7.19 (m, 10 H), 4.86 (1/2 of AB, 2H, 10.1 Hz), 4.21 (1/2 of AB, 2H, 10.1 Hz), 3.91 (m, 2H), 3.75 (m, 2H), 3.39 (m, 2H), 3.14 (s, 6H), 2.48 (d of t, 2H, 4.2 Hz, 13.5 Hz).

\(^{13}\)C NMR (CDCl\(_3\)) : 157.8 (s), 138.6 (s), 133.0 (s), 132.1 (s), 130.2 (d), 129.9 (d), 129.1 (d), 127.6 (d), 127.4 (d), 123.0 (d), 71.7 (t), 71.3 (t), 60.1 (q), 30.3 (t).
Low Resolution Mass Spectrometry (m/z) : 405 (M⁺), 285, 253, 149, 105, 69.

High Resolution Mass Spectrometry : Calculated for C₂₈H₂₆O₄, 404.1988 g mol⁻¹, found 404.2001 g mol⁻¹.

Melting Point : 144 -146 °C.

Elemental Analysis : calculated for C₂₈H₂₆O₄ : 77.19 % C, 6.98 % H, found 77.06 % C, 7.00 % H.
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**Awards**

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<td>Fr. Armstrong Memorial Award</td>
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Presentations and Publications

Fransen, N. J., Dutton, P. J. 1995 *Synthesis of Biphenol Derived Host Molecules* at 78th Canadian Chemical Conference, University of Guelph, Guelph, Ontario, Canada.