The Synthesis of Some Novel Molecular Clefts

A Thesis submitted for the degree of

Doctor of Philosophy

of The Australian National University

by

Jo-Anne Michelle Rasmussen

April, 2002

Research School of Chemistry
Canberra, Australia
Sam could not see the course immediately above him, where it was lowest, for a steep slope went up from where he stood; but he guessed that if he could only struggle on just a little way further up, they would strike his path. A gleam of hope returned to him. They might conquer the mountain yet.

In all that ruin of the world for the moment he felt only joy, great joy. The burden was gone....he was free....For the Quest is achieved, and now all is over.

Book VI
The Lord of the Rings
J. R. R. Tolkien.
Declaration

I declare that the material presented in this thesis represents the result of original work carried out by me and has not been submitted for examination for any other degree. This thesis is less than 100,000 words in length. Wherever possible, established methodologies have been acknowledged by citation of the original publications from which they derive.

Jo-Anne Rasmussen

April, 2002
Acknowledgments

Firstly, I would like to thank my supervisor, Professor Martin Banwell, for his guidance and supervision throughout my PhD.

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My most heartfelt appreciation goes to Scott Stewart, who has encouraged and supported me throughout my PhD and without whom my life is not complete. I thank you for sharing with me your love and passion for life.
Abstract

The work detailed in this thesis was concerned with the synthesis of various novel molecular clefts.

The introductory chapter (Chapter 1) outlines the recent work in the area of supramolecular chemistry and in particular, in the field of molecular clefts. As incorporation of phenanthroline and catechol ligands into the target molecular clefts was envisaged, a short introduction as to the use of such compounds as binding agents has also been included. Furthermore, as the basis for this project was founded in previous research carried out within these laboratories, a brief description of such work is also provided. The final section of Chapter 1 describes the aims of the author’s research in terms of the strategy devised for the synthesis of molecular clefts, as well as potential applications of such compounds.

Chapter 2 details the work carried out in applying a capricious reaction of gem-dibromocyclopropanes with organolithium compounds so as to form cyclopropylidene dimers required for the preparation of the first class of targeted molecular clefts. The attempted electrocyclic ring opening of the same gem-dibromocyclopropanes to form cycloheptenes capable of elaboration to the second class of targeted molecular clefts is also described.

Chapter 3 details the pursuit of alternate routes to seven-membered ring containing compounds by a variety of methods and culminating in the successful synthesis of a benzosuberone 172 via a double alkylation process.

The titanium mediated coupling reactions of benzosuberone 172 are detailed in Chapter 4. This coupling was followed by various functionalisation regimes including the formation of tetracarbonyl compounds capable of engaging in Schiff base
condensation reactions to afford bisphenanthroline containing molecular clefts with metal binding capabilities. Chapter 5 outlines the attempts to synthesise related clefts incorporating five-membered rings and possessing smaller 'bite angles' between the two arms of the cleft.

Chapter 6 describes the study of the uncatalysed hydrogen transfer reaction between 1,4-cyclohexadiene (148) and various ortho- and para-quinones at both atmospheric and high pressure (19 kbar).

The final chapter (Chapter 7) provides the experimental detail to support the claims made in the preceding five chapters.
The following abbreviations have been used throughout this thesis:

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<th>Meaning</th>
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<tr>
<td>Ac</td>
<td>acetate</td>
</tr>
<tr>
<td>ADEP</td>
<td>Anisotropic Displacement Ellipsoid Plot</td>
</tr>
<tr>
<td>app</td>
<td>apparent ((^1)H NMR spectroscopy)</td>
</tr>
<tr>
<td>APT</td>
<td>Attached Proton Test ((^13)C NMR spectroscopy)</td>
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<tr>
<td>aq.</td>
<td>aqueous</td>
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<tr>
<td>atm</td>
<td>atmosphere</td>
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<td>b.p.</td>
<td>boiling point</td>
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<tr>
<td>Bu</td>
<td>butyl</td>
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<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>c</td>
<td>concentration (g/100 mL)</td>
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<tr>
<td>ca.</td>
<td>circa (approximately)</td>
</tr>
<tr>
<td>cat.</td>
<td>catalyst</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical Ionisation (Mass Spectrometry)</td>
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<tr>
<td>conc.</td>
<td>concentrated</td>
</tr>
<tr>
<td>18-C-6</td>
<td>18-crown-6 (a crown ether)</td>
</tr>
<tr>
<td>8</td>
<td>chemical shift (parts per million)</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DMAD</td>
<td>dimethyl acetylenedicarboxylate</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>E$_{1/2}$</td>
<td>reduction potential</td>
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<tr>
<td><em>e.g.</em></td>
<td><em>exempli gratia</em> (for example)</td>
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<tr>
<td>EI</td>
<td>Electron Impact (Mass Spectrometry)</td>
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<td>eq</td>
<td>equivalents</td>
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<tr>
<td>Et</td>
<td>ethyl</td>
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<tr>
<td><em>et al.</em></td>
<td><em>et alia</em> (and others)</td>
</tr>
<tr>
<td><em>etc.</em></td>
<td><em>et cetera</em> (and so on)</td>
</tr>
<tr>
<td>ether</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>eV</td>
<td>electron volt</td>
</tr>
<tr>
<td>FAB</td>
<td>fast atom bombardment</td>
</tr>
<tr>
<td>GC</td>
<td>Gas Chromatography/Chromatogram</td>
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<td>GCMS</td>
<td>Gas Chromatography/Mass Spectrometry</td>
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<tr>
<td>h</td>
<td>hour(s)</td>
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<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
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<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry/Spectrum</td>
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<tr>
<td>Hz</td>
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<tr>
<td>i.d.</td>
<td>internal diameter</td>
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<tr>
<td><em>i.e.</em></td>
<td><em>id est</em> (that is)</td>
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<tr>
<td>IR</td>
<td>infrared</td>
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<tr>
<td><em>J</em></td>
<td>coupling constant (Hz)</td>
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<td>lit.</td>
<td>literature</td>
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<tr>
<td>kbar</td>
<td>kilobar (pressure)</td>
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<td>M$^+$</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>Me</td>
<td>methyl</td>
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<tr>
<td>MHz</td>
<td>megahertz</td>
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<tr>
<td>mg</td>
<td>milligram(s)</td>
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<td>min</td>
<td>minute(s)</td>
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<td>millilitre(s)</td>
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<td>mol</td>
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<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point (°C)</td>
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<tr>
<td>MS</td>
<td>Mass Spectrometry/Spectrum</td>
</tr>
<tr>
<td>m/z</td>
<td>mass-to-charge ratio (Mass Spectrometry)</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>V&lt;sub&gt;max&lt;/sub&gt;</td>
<td>infrared absorption maxima (cm&lt;sup&gt;-1&lt;/sup&gt;)</td>
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<tr>
<td>ORTEP</td>
<td>Oak Ridge Thermal Ellipsoid Plot</td>
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<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>petrol</td>
<td>petroleum spirits with 40-60 °C boiling range</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
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<td>ppm</td>
<td>parts per million</td>
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<td>quant.</td>
<td>quantitative</td>
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<td>®</td>
<td>registered trademark</td>
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<tr>
<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>retardation factor</td>
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<tr>
<td>R&lt;sub&gt;t&lt;/sub&gt;</td>
<td>retention time</td>
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<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>sec</td>
<td>second(s)</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>TBAP</td>
<td>tetra-\textit{n}-butylammonium perchlorate</td>
</tr>
<tr>
<td>TEAI</td>
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<td>benzyltriethylammonium chloride</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
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<td>THF</td>
<td>tetrahydrofuran</td>
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<td>thin layer chromatography</td>
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<tr>
<td>TM</td>
<td>trademark</td>
</tr>
<tr>
<td>\textit{p}-TsOH</td>
<td>\textit{para}-toluenesulfonic acid</td>
</tr>
<tr>
<td>SCE</td>
<td>standard calomel electrode</td>
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<tr>
<td>sm</td>
<td>starting material</td>
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<td>UV</td>
<td>ultraviolet</td>
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<td>V</td>
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<td>\textit{via}</td>
<td>by way of</td>
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<td>A.1.7</td>
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1.1 Overview

Supramolecular chemistry is now at the forefront of modern science and has contributed enormously to our current knowledge of the behaviour of the non-covalent bond. The fundamental elements of this scientific domain have existed in nature since the dawn of time, involving elaborate biological systems that perform every task essential to maintaining life on earth. For generations scientists have attempted to explore these systems and by identifying key biochemical pathways, have gained valuable knowledge about the types of interactions involved including the binding capabilities of enzymes. In the laboratory, the synthesis of some of these complicated systems has been achieved using classical chemical techniques. An alternative approach is to build such ‘supermolecules’ from molecular building blocks via self-assembly and by exploiting non-covalent interactions.
The term "supramolecular chemistry" was first popularised by Lehn\textsuperscript{2a-d} in the mid-to-late 1970's, although the concepts behind this term certainly predate the phrase. So, what is supramolecular chemistry? The most quoted answer is "chemistry beyond the molecule",\textsuperscript{2e} which is clearly an extremely broad and rather vague term. Nevertheless, it can be said that supramolecular chemistry uses the practical synthetic methods of both organic and inorganic chemistry to construct the individual components of the target supramolecular system. Coordination chemistry, intermolecular interactions, molecular recognition and functional group complementarity are exploited for the assembly of these components so as to create the target 'supermolecules'. The principles of physical chemistry are then employed in investigating the properties of such assemblies. Finally, supramolecular chemistry reaches into the realms of biochemistry, biology and materials science in finding applications for these supramolecular arrays.\textsuperscript{3}

Perhaps the earliest examples of supramolecular structures derive from the inorganic/organic chemistry interface. Coordination complexes that involve 'intermolecular' interactions to bind metals into 'host' molecules, such as ferrocene (1),\textsuperscript{4} the bis(phen)palladium complex 2\textsuperscript{5} or the cobalt cage complex 3\textsuperscript{6} (Figure 1.1) provide excellent examples of such supermolecules.

\begin{figure}[h]
  \centering
  \includegraphics[width=\textwidth]{figures/figure1.png}
  \caption{Examples of coordination complexes that involve 'intermolecular' interactions.}
\end{figure}
One particularly important aspect of supramolecular chemistry is the matter of host-guest interactions. The 'host' or an assembly of small molecules that comprise the 'host' usually displays some degree of preorganisation which often manifests itself as a cavity or cleft that is used, in a rather specific manner, for binding the 'guest'. The 'guest' has complementary functionality to that at the binding site of the 'host' and associates through intermolecular interactions. Such notions are elaborated upon in the following discussion.

The fortuitous discovery, by Pedersen in 1967,\(^7\) of the crown ethers signalled the beginning of modern day supramolecular chemistry involving organic compounds. Thus, by combining catechol (4) with bis(2-chloroethyl) ether (5) in the presence of sodium hydroxide (Scheme 1.1) Pedersen was able to isolate small amounts of the dibenzo[18]crown-6 (6) incorporating sodium. His observation that the sodium ion had "fallen into the hole" of the crown led to the development of one of the most widely used families of host compounds, namely the crown ethers.

![Scheme 1.1](image_url)

**Scheme 1.1**

*Reagents and Conditions:* (i) NaOH, n-BuOH.

As a consequence, metal binding within a cavity became a popular topic of study, and two other groups also engaged in pioneering work in this field. Thus, Lehn's group concentrated on the cryptates (7)\(^1\) while Cram's group investigated the spherand family
of compounds (8)\(^8\) (Figure 1.2). The culmination of work in this area was the awarding of the 1987 Nobel Prize for Chemistry to Pedersen,\(^9\) Lehn\(^2\) and Cram.\(^8\)

![Figure 1.2](image)

**Figure 1.2** Lehn's cryptate 7 (lithium complex) and Cram's spherand 8 (sodium complex). Note: structures not drawn to the same scale.

Today, there is a large number of research groups operating within the realm of supramolecular chemistry thereby producing a diverse array of remarkable structures, many of which have become well known in the literature. Numerous publications report on the assembly of sophisticated systems from various new classes of compounds that have been synthesised.\(^10\) The naming of such entities often exploits an aesthetic parallel rather than accurately representing the chemical functionality present. Some of the more popular building blocks and nomenclature are highlighted by the structures 9-16\(^11\) shown in Figure 1.3. The synthesis of these building blocks is often non-trivial, however once accessible they are frequently used for the assembly of even larger supramolecular arrays.
Figure 1.3 Contemporary examples of supramolecular species: porphyrin rotaxane 9; catenane 10; calixarene 11; carcerand 12; cyclophane 13; dendrimer 14, cyclodextrin 15 and modified cyclodextrin dimer 16.11
The elaboration of these building blocks into supramolecular assemblies has led to arrays which possess interesting properties including, for example:

(a) enzyme mimics\textsuperscript{12} and inhibitors that exploit the selective binding and sometimes transportation of a complementary guest;

(b) molecular wires and nanoelectronic components\textsuperscript{13} designed such that single molecules or small groups of molecules are potentially capable of use in computer circuitry;

(c) electron and energy transfer systems\textsuperscript{14} capable of use in molecular photovoltaic systems or artificial photosynthesis, \textit{e.g.} compound \textbf{17} (Figure 1.4);

(d) molecular-level devices and machines\textsuperscript{15} that use molecular recognition and switching controlled by electrons, protons or metal ions (Figure 1.5);

(e) luminescent logic and sensing systems\textsuperscript{13} where light-powered molecular-level devices generate specific outputs;

(f) arrays for use in nanochemistry\textsuperscript{16} where the assembly of optimal target molecules provides an insight into structure and function at a single-molecule level;

(g) encapsulation complexes\textsuperscript{17} which take advantage of intermolecular binding to probe chiral recognition and catalysis, \textit{e.g.} compound \textbf{18} (Figure 1.6);

(h) designer materials,\textsuperscript{13} such as polymers, held together by intermolecular bonds;

(i) architectural curiosities where different topological and aesthetic designs are synthesised, which may or may not have interesting and/or useful properties.

As illustrated, the diversity of supramolecular chemistry is extensive and this short introduction only touches upon this relatively young and very fertile field.
Figure 1.4 Electron and energy transfer device.\textsuperscript{14}

Figure 1.5 Molecular level switch incorporating a catenane.\textsuperscript{15}

Figure 1.6 Sample of an encapsulation complex featuring host-guest interactions based on Reinholdt’s clathration by calix[4]arenes.\textsuperscript{17}
1.2 Recent Examples of Supramolecular Clefts and Their Host-Guest Properties

The particular class of supramolecular compounds that will be discussed in detail in this thesis is that of molecular clefts. Structures belonging to this class usually possess a C- or U-shaped cavity thus providing a concave region for the binding of guests. Such systems commonly contain convergent functional groups which enable the sequestering of small molecules that have complementary functionality, size and/or shape to that of the binding site of the cleft. The creation of such clefts often involves the synthesis of a preorganised, rigid scaffold to which the binding portion(s) of the molecule can be attached. More specifically, a C- or U-shape should be the preferred conformation of the cleft, the integrity of which is maintained throughout the necessary association steps leading to incorporation of the guest. Other names have arisen for these types of U-shaped compounds including molecular 'tweezers' and molecular 'clips'. Presently, it is up to individual groups as to which term(s) they prefer. However, throughout this thesis all three names will be used interchangeably in referring to the generic C- or U-shaped cavity.

The term 'molecular cleft' dates back to Rebek's 1985 paper in which he describes the synthesis of "structures featuring a molecular cleft" where "carboxyl derivatives converge to provide receptors for molecules." Thus, at this time Rebek showed (Scheme 1.2) that condensation of the triacid (Kemp's triacid) with the appropriate spacer [either m-xylidene diamine or acridine yellow] gave high yields of the corresponding clefts and . The two convergent carboxylic acid moieties within the products enable hydrogen bonding interactions with guest molecules, whilst π-stacking between the spacer group and the aromatic guests also occurs thus providing further stabilisation of the host-guest complex.
As shown in Figure 1.7, the U-shape of the related cleft 24,18 is rigidly maintained by virtue of the methyl substituents on the triacid residue 19 (which prevent epimerisation) while the methyl groups of the aromatic spacer inhibit rotation about the C-N bonds and thus maintain the syn-orientation of the triacid 'arms' of these clefts. Guests including pyrazine, diketopiperazines, phenols (25) (Figure 1.7), diols, diamines and aminoalcohols, were found to be of complementary geometry and possessing functionality that allows for binding within the cavity of such molecular clefts.

Figure 1.7 Rebek’s cleft 24 binding phenol (25).\(^5\)

\(^5\) The numbering scheme used for host-guest complexes reported in this thesis derives from the numbers of the component parts. Thus, the complex shown in Figure 1.7 comprises host 24 (black) and guest 25 (in red) and is therefore numbered 24.25. Key interactions are shown in blue.
Since this initial work, the Rebek group has reported the preparation of a large number of molecular clefts incorporating different binding sites and spacers. Another example, 26, has both a larger spacer group as well as a deeper cavity when compared to the original systems (Figure 1.7) and, as such, is capable of binding larger guests, e.g. phenazine (27) (Figure 1.8). In addition, the convergent functional groups within cleft 26 are capable of undergoing irreversible intramolecular acyl transfer, in this case from oxygen to nitrogen, to give compound 28 (Scheme 1.3). The high yield observed for this reaction is attributed to the close proximity of the reacting centres which results from their positioning on the rigid scaffold. The significance of this situation is that such scaffolds could allow acidic and basic functions to be isolated from each other and yet participate in the concerted catalysis of a reaction involving a substrate constrained between them.

![Figure 1.8](image_url)

**Figure 1.8** Extended cleft 26 binding phenazine (27).

![Scheme 1.3](image_url)

**Scheme 1.3**

Reagents and Conditions: (i) Et$_3$N, CDCl$_3$, ~23 °C.
In very recent work, Rebek has formed, in effect, a number of 'double-cleft' species that can encapsulate several guests within the resulting cavity. These systems have been termed the tennis ball 29\(^{22}\) (Figure 1.9), softball 30\(^{23}\) (Figure 1.10) and football complexes.\(^{24}\) Within the cavity of the softball, 30, which is an extended version of the tennis ball, 29, Rebek\(^{13,24}\) has catalysed Diels-Alder reactions including those between \textit{para}-benzoquinone (31) and dimethylthiophene dioxide (32) (Figure 1.10). Once adduct 33 has formed, it is no longer capable of effective binding within the cavity and is thus replaced by new reactant molecules thereby perpetuating the catalytic cycle.\(^{13}\)

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.9.png}
\caption{Rebek's tennis ball cleft 29.\textsuperscript{22}}
\end{figure}
Figure 1.10 Catalytic Diels-Alder cycle between \textit{para}-benzoquinone (31) and dimethylthiophene dioxide (32) in a softball capsule.\textsuperscript{13}

Many other clefs have now been synthesised in which convergent functionality is incorporated on the inner walls of a cavity. Closely related to Rebek’s work, Kohmoto\textsuperscript{25} has used a cholic acid moiety to construct the sides of cleft 34 (Figure 1.11). Whilst free rotation occurs about the C-N bonds of 34 at ambient temperatures, upon addition of the relevant guest, such as naphthalene-2,6-dimethanol (35), the molecule assumes, in an exclusive fashion, the illustrated U-shaped conformation.
34.35

**Figure 1.11** Kohmoto's cholic acid cleft 34 binding guest 35.25

Deslongchamps26 has designed a cleft for the recognition of adenine and its derivatives and this too has convergent functional groups, based on hydroxyimides, which are held in the proper orientation by a carbazole spacer. The resulting cleft 36 associates strongly in a 1:1 host-guest complex with 9-N-ethyladenine (37) as shown in Figure 1.12.

36.37

**Figure 1.12** Deslongchamps cleft 36 incorporating adenine derivative 37.26

Mizutani27 has utilised a tetraol framework for his synthesis of host 38 which exhibits "controlled flexibility" and thereby complexes 1,4-dioxane in solution (Figure 1.13). In a related vein, Sawada28 has prepared the cleft 39 which he terms molecular tweezers, incorporating a metacyclophane with four methoxy groups facing one another. This system has been shown to selectively bind silver ions.
Warrener\cite{29} has reported the 'modular' synthesis of clefts by attaching, via a 1,3-dipolar cycloadition reaction, the 'wall molecules' \textit{40} and \textit{41} to a preformed base \textit{42}, such that the functionality within the cavity of the resulting cleft can be manipulated. For example, as shown in Scheme 1.4, cleft \textit{43} has a crown ether on only one side of the cavity, thus emphasising that unsymmetrical clefts can also be made. Such modular design should allow for the synthesis of a cleft that can easily be 'diversified' through simple chemistry and in either a symmetrical or unsymmetrical fashion.

\textit{Scheme 1.4}

\textit{Reagents and Conditions:} (i) 14 kbar, CH$_2$Cl$_2$. 

\textbf{Figure 1.13} Mizutani's tetraol cleft \textit{38}\textsuperscript{27} and Sawada's metacyclophane \textit{39}\textsuperscript{28}.

\begin{center}
\includegraphics[width=0.8\textwidth]{figure113.png}
\end{center}
In a recent paper, Klärner\textsuperscript{30} described the use of NMR techniques to probe the interactions between tweezer molecule 44 (Figure 1.14) and the electron-deficient guest 1,4-dicyanobenzene (45). The concave topology of compound 44 enables the guest molecule to be bound by multiple $\pi$-stacking interactions thus illustrating the importance of both geometric and electronic features in the binding of guest molecules.

![Figure 1.14](image)

**Figure 1.14** Klärner's molecular tweezer 44 binding 1,4-dicyanobenzene (45).\textsuperscript{30}

Another example of molecular tweezers is shown in Figure 1.15 and comes from the Schrader\textsuperscript{31} laboratories. In this species the receptor molecule, 46, is a remarkably simple bisphosphonate that selectively complexes arginine substructures such as methylguanidine (47). It is envisaged that these systems may be used as an enzyme mimic to cleave proteins at the peptidic bond immediately after arginine.

![Figure 1.15](image)

**Figure 1.15** Schrader's cleft 46 binding methylguanidine (47).\textsuperscript{31}
Based on structural analogies with Tröger's base (48), Harding\textsuperscript{32} has synthesised the versatile and chiral carbocyclic cleft molecule 49 (Figure 1.16). This provides a V-shaped cavity that can be 'fine-tuned' by various functionalisation regimes, involving manipulation of either the bromine or carbonyl units, so as to establish recognition of a range of chiral substrates/guests. Similar V-shaped clefts have been reported by Gates,\textsuperscript{33} including the bisthioester derivative 50 in which the cavity walls have been extended, relative to congener 49, \textit{via} naphthalene moieties.

![Figure 1.16 Tröger's base 48; Harding's derivative 49\textsuperscript{32} and Gates' derivative 50\textsuperscript{33}](image)

In a slightly different approach, Bell\textsuperscript{34} has designed a system of fused carbocyclic and heterocyclic rings that form a planar and rigid cavity capable of binding metal ions (Figure 1.17). These compounds are termed 'heptacyclic terpyridyl' clefts (51) and derivatives there-of, such as 52,\textsuperscript{35} have also been found to bind small molecules such as urea (53). Thus, by virtue of the hydrogen bonding interactions between the cleft and urea (53), solubilisation of the latter in relatively non-polar organic solvents can be accomplished. This capacity is of some significance in clinical chemistry. Also aiding in the solubility of these complexes are the appended butyl chains associated with clefts 51, 52 and 54. It can be seen from Figure 1.17 that cleft 52 binds only four sites on the urea molecule (53). In contrast, a second generation and superior cleft, 54,\textsuperscript{35} has all six possible sites catered for and thus, selectivity for urea (53) over, for example, \textit{N}-alkyl ureas is dramatically increased.
Molecular clips based on diphenylglycouril 55,36 and more recently, dimethylpropanediurea 5637 (Figure 1.17) have emerged from Nolte's research group. The latter cleft is the deeper and furthermore, the carbonyl oxygen atoms are closer together. Both clefts show an affinity for dihydroxybenzenes such as resorcinol (57) (Figure 1.18) and complex these species by exploiting hydrogen bonding between the hydroxy groups of the guest and the urea carbonyl groups of the host. Further stabilisation is provided by the \( \pi-\pi \) interactions between the aromatic guest molecule and the inner walls of the cavity.
Figure 1.18 Nolte's diphenylglycouril cleft 55 and dimethylpropanediurea cleft 56 showing their affinity for resorcinol (57).

From this small cross-section of the contemporary literature it is clear that molecular clefts can be assembled from a variety of molecular components. The fundamental chemical concepts behind their construction are entrenched in classical synthetic chemistry, however the tasks that these species are designed for bring a renewed value to such chemistry. On the basis of the foregoing, from simple metal binding to complex enzyme mimicry, molecular clefts are expanding the boundaries of supramolecular chemistry.
1.3 Recent Examples of Phenanthroline and Catechol Derivatives Used as Ligands

Molecular clefts often take advantage of the binding capabilities of common ligands to enable them to incorporate specific types of guest. Two ligands often chosen because of their abilities to bind a range of guests are 1,10-phenanthroline (58) and catechol (4). The following discussion is a brief outline of the derivatives of ligands 58 and 4 that have or could be incorporated into a molecular cleft and thereby used to bind a guest molecule or metal species. These ligands have been selected for discussion at this point because they represent the ones exploited in the author's work as described later in this thesis.

1.3.1 Phenanthroline Derivatives

In recent years, the synthesis of molecular clefts capable of engaging in multiple hydrogen bonding interactions has been described (Figure 1.19). Hamilton\textsuperscript{38} and coworkers have utilised the multiple hydrogen bonding interactions within molecular clefts such as compound 59 to bind guests of the barbiturate family (60). Related clefts, \textit{e.g.} 61,\textsuperscript{38} have been designed to bind dicarboxylic acids such as hexanedioic acid (62). Such nitrogen rich clefts incorporate multiple sites for guest binding by exploiting the hydrogen bonding interactions between amines and carbonyl groups. This presence of multiple nitrogens is a regular feature in Hamilton's clefts and one that has been employed in the synthesis of the systems described in this thesis.
In a 1995 paper, Hamilton described the synthesis of a "chromogenic receptor for the recognition of dicarboxylic acids" where the receptor or cleft $63$ (Scheme 1.5) is prepared from readily available $1,10$-phenanthroline ($58$). Thus, this latter compound was reacted, using the Sauvage method with phenyllithium and manganese dioxide to give the phenyl derivative $64$. Compound $64$ was then subjected to reaction with another lithio-species (prepared in situ), again in the presence of manganese dioxide, to give the unsymmetrical phenanthroline derivative $65$ capable of being monofunctionalised. Conversion of compound $65$ into the dibromomethyl derivative $66$ was achieved using $N$-bromosuccinimide. Transformation of compound $66$ into the corresponding aldehyde $67$, then enabled access to the acid $68$ via reaction with tetrabutylammonium permanganate ($TBA^+\text{MnO}_4^-$). The required additional nitrogen functionality was introduced via conversion of compound $68$ to the acid chloride and reaction of this with $2$-amino-$6$-picoline to furnish compound $63$. This cleft binds dicarboxylic acids, such as $69$, very effectively (Scheme 1.5). As shown in Scheme 1.6, cleft $70$, in which both arms have been functionalised symmetrically, was synthesised using similar chemistry to that just described, again commencing from $1,10$-phenanthroline ($58$) and going through the intermediate aldehyde $71$ and the acid $72$.  

Figure 1.19 Hamilton's clefts: $59$ binding a barbiturate derivative ($60$) and $61$ binding a dicarboxylic acid ($62$).
Scheme 1.5

Reagents and Conditions: (i) PhLi, MnO₂, Et₂O; (ii) p-MePhl, Et₂O, t-BuLi, toluene, MnO₂; (iii) 2.1 eq NBS, benzoyl peroxide, CCl₄; (iv) NaOH, EtCO₂H, then 2 M NaOH, THF; (v) TBA⁺MnO₄⁻, pyridine, THF; (vi) oxalyl chloride, 2-amino-6-picoline, CH₂Cl₂; (vii) glutaric acid (69), CDCl₃.

Scheme 1.6

Reagents and Conditions: (i) TBA⁺MnO₄⁻, pyridine, THF; (ii) 2-amino-6-picoline, oxalyl chloride, CH₂Cl₂.
The preceding discussion is relevant to the work detailed within this thesis, as it was envisaged that similar types of functionalisation could be employed once phenanthroline moieties had been attached to the scaffold associated with the author's target clefts, thus enabling binding of guests at the 'tips' of such systems. Such notions will be elaborated upon later in this chapter.

As seen in Scheme 1.7, the 1,10-phenanthroline portion of cleft 70 binds to copper(II) to form a 2:1 complex.\textsuperscript{39} A range of dicarboxylic acids were then added to a chloroform solution of these orange-coloured receptors. The resulting complex with acid 69 shows large shifts in the visible absorption bands as evidenced by a colour change from orange to red. This chromogenicity was found to be guest dependent and due to a conformational change in the receptors resulting from the hydrogen bonding interactions with each different dicarboxylic acid. It is thus envisaged that this type of system could serve as a basis for a chemoselective sensor for biologically important dicarboxylic acids such as glutaric acid (69) (Scheme 1.7).

![Scheme 1.7](image-url)

*Reagents and Conditions:* (i) Cu(CH\textsubscript{3}CN\textsubscript{4})\textsuperscript{4+BF\textsubscript{4}⁻}, MeCN/CH\textsubscript{2}Cl\textsubscript{2}; (ii) CHCl\textsubscript{3}.
As highlighted in Scheme 1.7, the 1,10-phenanthroline group can be used to position two coordinating 'arms' in a convergent arrangement. These arms can be attached to a single side of the phenanthroline moiety or to both sides, in either a symmetrical or unsymmetrical manner, respectively. A plethora of derivatives can be made from 1,10-phenanthroline (58) and their most common use is as ligands in the study of coordination complexes.41 Some examples are shown in Figure 1.20, illustrating the types of moieties that have been attached at the 2- and/or 9-positions of the 1,10-phenanthroline framework. Of particular interest are those that contain binding sites similar to the multiple nitrogen environments evident in Hamilton's ligands. Two other readily accessible 2,9-disubstituted derivatives of 1,10-phenanthroline (58) that are often used as starting materials for the synthesis of the afore-mentioned systems are 2,9-dimethyl-1,10-phenanthroline (73) and 2,9-dichloro-1,10-phenanthroline (74).

\[ \text{Me} \quad \text{Me} \quad \text{Cl} \quad \text{Cl} \]

73 74

In Figure 1.20, the first example 75,42 is an unsymmetrical terdentate ligand which complexes through π-stacking and steric effects to ruthenium(II) in a pentaazo-coordinated (N5) fashion. Amine 76,43 also known as 'clip-phen', is used as an artificial nuclease when bound to copper(II), and exhibits good DNA cleavage properties. The phenanthroline 77,44 when bound to zinc(II), has been used as a model for the NADH-alcohol dehydrogenase coenzyme-enzyme couple. The propeller shaped molecule 78,45 which was synthesised by a triple condensation method, has the three bidentate chelating sites orientated such that they can interact in a cooperative fashion above or below the plane of the central benzene ring. This compound also highlights the value of the Friedländer synthesis in preparing phenanthroline derivatives.
Figure 1.20 Examples of 2-substituted and 2,9-disubstituted derivatives of 1,10-phenanthroline (58) used in supramolecular chemistry.
Bishydrazine 79\textsuperscript{46} is a tetradentate ligand with good affinity for nickel(II) as well as a range of other metals. Compound 80\textsuperscript{47} is an example of an N-heterocyclic ligand that may be capable of binding to DNA through intercalation. On the other hand, the symmetrically 'strapped' derivative 81\textsuperscript{46} is known to specifically bind zinc(II). Bisamide 82\textsuperscript{48} is a precursor to a metallic catalyst and is derived from the parent 2,9-dimethyl-1,10-phenanthroline (73). Compound 83\textsuperscript{49} is a precursor to a potential artificial enzyme (esterase) which incorporates a β-cyclodextrin at the terminal amine group, while congener 84\textsuperscript{50} has two ether tethers and is derived from the 2,9-dichloro-1,10-phenanthroline (74), and its hydrochloride salt is used to intercalate with DNA. Tweezer 85\textsuperscript{51} complexes to chromium via the arene units and to copper at the 1,10-phenanthroline moiety. Compound 86\textsuperscript{52} has been synthesised as a molecular wire for the storage and transfer of information through electron transfer. Changing the coordination geometry of the phenanthroline base to metals has been achieved via the chiral phenanthroline 87\textsuperscript{53} which also displays catalytic properties.

As mentioned earlier (page 20), Sauvage\textsuperscript{40} has devised a synthetic strategy for the direct attachment of aryl substituents to the 2- and 9- positions of phenanthroline using the appropriate lithio-species. Thus, compound 88\textsuperscript{40} has been synthesised by this means and the derived macrocyclic ether 89\textsuperscript{54} has been further elaborated so as to incorporate a crown ether-type component after initial aryl attachment. These two ligands have been complexed to copper(I) to produce Sauvage's catenanes. Porphyrin 90,\textsuperscript{55} also synthesised by this methodology, has been used to make rotaxanes while bisphenol 91\textsuperscript{56} complexes copper(I) to, eventually, produce trefoil knots. Sauvage's methodology has been used to generate compound 92\textsuperscript{57} which selectively binds zinc(II) over nickel(II), copper(II) and iron(II) due to the preferred binding geometry of the cleft. This selectivity can be exploited in the hydrometallurgical recovery of zinc.
Tetraol 93,58 again synthesised using the Sauvage method, exhibits bimetallic complexation involving nickel(I)-nickel(I) and nickel(I)-copper(I) combinations. This latter complex could catalyse oxidations, polymerisations and aminations.

The extended phenanthroline derivatives 9459 and 9560 not only form luminescent complexes with rhenium(II) but also bind to DNA in an intercalative manner and could thus be used as DNA sensors. Finally, compound 9661 is an extended planar ligand that has been synthesised from 2,9-dichloro-1,10-phenanthroline (74) and photolysis of the ruthenium(II) complex results in rapid electron transfer and charge separation.

Phenanthroline ligands have been coordinated to a variety of metals and the resulting complexes can assume a range of different geometries. For example, in Sauvage's catenanes, rotaxanes and trefoil knots (involving phenanthroline derivatives 88,40 89,54 9055 and 9156) the participating complexes are stable pseudotetrahedral copper(I) bischelates, while compound 7946 forms a pseudooctahedral complex with nickel(II). Furthermore, phenanthroline derivatives can act as bi-, tri-, tetra- and, in some cases, hexa-dentate ligands for a variety of metals including nickel, copper, zinc, silver, cadmium, iron, mercury and rhenium.

As highlighted through the examples given above, phenanthroline derivatives62 are extremely versatile systems that represent excellent ligands for attachment to preformed U-shaped molecules not only to extend the depth of the cavity but to also enhance the complexation and self-assembling properties of such clefts. The ensuing chapters outline work undertaken by the author directed towards achieving this goal.
1.3.2 Catechol Derivatives

Another important ligand in supramolecular chemistry is catechol (4) because, like 1,10-phenanthroline (58), it is also known to complex to a wide range of metal ions. Thus, derivatives of catechol make excellent scaffolds for metal complexation as highlighted by the examples provided in Figure 1.21. For example, boron(III) is known to bind to catechol (4), as evident in the commercially available catecholborane (97).\textsuperscript{63} In the case of complex 98,\textsuperscript{64} the boron is initially complexed to form a preorganised cavity bearing one negative charge, a situation which facilitates the uptake of various alkali metal cations (potassium being favoured) by virtue of generating a neutral species. As highlighted in complex 99, boron(III) can also coordinate with catechols so as to attain tetrahedral geometry.\textsuperscript{65} In the copper(II) complex 100,\textsuperscript{66} square planar geometry about the metalloid centre is observed, while in the nickel(II) complex 101\textsuperscript{67} the metal is located in a distorted octahedral environment comprising two catechol ligands in the equatorial plane and two axially orientated water molecules. The oxovanadium(IV) derivative 102\textsuperscript{68} has the metal adopting a square pyramidal geometry with the bidentate catecholamides in the equatorial plane and the oxo group at the apex. The catechol residues of complex 103\textsuperscript{69} are bound to a polymer support and then treated with methylarsonic acid to give the arsenic(V) catecholates shown. More exotic metals including niobium(V) and tantalum(V) can be bound by catechol as shown in complex 104.\textsuperscript{70} Gallium(III) has also been used to form catechol complexes and in the case of 105,\textsuperscript{71} three such ligands are involved in forming the observed dinuclear gallium(III) catecholamide triple helices (105\textsubscript{3}.Ga\textsubscript{2}).

Incorporation of catechols within a cleft-like framework could lead to a variety of unusual architectures involving monomeric, dimeric or tetrameric assemblies. The following chapters outline the author’s various attempts at assembling such arrays.
Figure 1.21 Examples of catechol complexes with a variety of metals.
1.4 Summary of Previously Reported Work on Molecular Clefts Based on Cyclopropylidene Dimers

The studies detailed in the following chapters of this thesis have evolved from previous work undertaken within the Banwell group by Dr Justine Walter. Walter exploited the methyllithium promoted coupling of gem-dibromocyclopropanes such as 106 in order to synthesise (Scheme 1.8) the syn- and anti-species, 107 and 108 which were obtained in 51% and 30% yield, respectively. The double bond associated with the syn-compound was subsequently cyclopropanated to give, after other functional group manipulations, the U-shaped cavity or cleft-like molecule 109. Congeners 110 and 111 were synthesised in a similar manner. Each of compounds 107 and 109-111 have convergent functionality on the interior 'walls' of the cleft thus making them potential hosts for complementary guest molecules.

Scheme 1.8

Reagents and Conditions: (i) MeLi, Et2O, -78 °C.
By manipulating the double bond via, for example, dichlorocarbene addition, at
the base or the 'hinge' of such systems the 'bite' angle of the resulting clefts, and
therefore the 'trans-cavity' distance, can be changed significantly. For example, as
determined by X-ray analyses, in cleft 107 this distance is 9.3 Å and in the related
dichlorocarbene adduct 109 it is reduced to ~5 Å (Figure 1.22).

![Figure 1.22](image)

**Figure 1.22** Difference in 'trans-cavity' distances between cleft molecules 107 and 109.

A possible pathway by which the pivotal coupling of gem-dibromocyclopropanes could occur is shown in Scheme 1.9. Thus, it is believed
that the starting dibromide, *e.g.* 112, undergoes a metal-for-halogen exchange to give
the corresponding organolithium 113. Two of these latter species are then thought to
combine with accompanying loss of LiBr, to give the intermediate 114. This α-
brominated lithio compound then loses another molecule of LiBr to yield the syn- and
anti-cyclopropylidene dimers 115 and 116, respectively. Often, such compounds are
not the sole products of the reaction as the methyl bromide byproduct arising from the
initial metal-for-halogen exchange reaction can trap the lithio species 113 to give the
methyl substituted system 117. Typically these coupling reactions are carried out at <
100 °C, since at higher temperatures, loss of lithium bromide from 113 results in
formation of the highly reactive cyclopropylidene 118, which can undergo various C-H
insertion reactions to give, via intramolecular processes, hydrocarbons such as 119 and 120 or, via intermolecular reactions, the solvent insertion product 121. By careful manipulation of the reaction conditions Walter was able to suppress such side reactions and thereby establish a workable synthesis of a useful range of cyclopropylidene adducts including the syn- and anti-systems 107 and 108 (Scheme 1.8).

**Scheme 1.9** Proposed pathway for the formation of compounds 115 and 116 as well as certain common intermediates.

In the case of syn-adduct 107 (Scheme 1.10), this was subjected to a dichlorocarbene addition reaction so as to functionalise the double bond and thus give
compound 122 (90% yield). Deprotection of bisacetonide 122 using aqueous acetic acid yielded the tetraol 123 (10% yield), which was characterised as the previously described tetraacetate 109 (Figure 1.22). Using FABMS techniques it was established that compound 123 can accept D-ribose (124) as a guest molecule and does so because in its pyranose form this aldopentose (124) possesses three cis-related hydroxy groups that can engage in hydrogen bonding interactions with the four converging hydroxyls of the host.74 Thus, as judged by mass spectral analysis, cleft 123 forms a 1:1:1 complex with D-ribose (124) and sodium ion (Na⁺). Similar experiments indicate that analogous 1:1:1 complexes are also formed between cleft 123, sodium ion and D-fructose, D-xylose and D-glucose as well,74 although in competitive experiments, selectivity for D-ribose (124) is observed.

\[
\begin{align*}
\text{i} & \quad \text{Cl} \quad \text{Cl} \\
\text{107} & \quad \text{122} \\
\text{ii} & \quad \text{Cl} \quad \text{Cl} \\
\text{109} & \quad \text{123.124} \\
\text{iii} & \quad \text{AcO} \quad \text{AcO} \quad \text{OAc} \quad \text{OAc} \\
\text{iv, v} & \quad \text{HO} \quad \text{OH} \quad \text{OH} \quad \text{OH}
\end{align*}
\]

**Scheme 1.10**

*Reagents and Conditions:* (i) NaOH (50% aq.), CHCl₃, TEBAC, 0 °C → rt, 4 h; (ii) AcOH (60% aq.), 80 °C, 48 h; (iii) Ac₂O, DMAP, pyridine, rt, 24 h; (iv) KOH, MeOH, CHCl₃, 15 min; (v) D-ribose (124), CDCl₃.
The synthesis of cleft 110 followed a similar pathway (Scheme 1.11) to that employed in gaining access to congener 122 (Scheme 1.8). Thus, compound 125 was coupled using methyllithium to give compound 126 (7% yield), which was subjected to dichlorocarbene addition reaction conditions thus providing cyclopropane 110 in 74% yield. The same methodology was used in converting compound 127 into cyclopropylidene dimer 128 (11% yield), which was subsequently functionalised to obtain cleft 111 (91% yield).

![Scheme 1.11](image)

*Reagents and Conditions:* (i) MeLi, Et₂O, -78 °C (ii) NaOH (50% aq.), CHCl₃, TEBAC, 0 °C → rt, 4 h.

In an interesting series of transformations, compound 111 was subjected to oxidative demethylation with silver(II) oxide in a mixture of 6 M aqueous nitric acid and 1,4-dioxane to produce the bis-para-benzoquinone species 129, as a bright yellow solid in quantitative yield (Scheme 1.12). Walter observed that after exposure to sunlight for six days cleft 129 was converted into the photoadduct 130²⁵ (68% yield). The [2πs+2πs] photoaddition reaction involved is facilitated by the close proximity of the arms of the cleft which are held in a U-shaped arrangement by virtue of the presence
Chapter 1

of the gem-dichlorocyclopropane moiety and other components of the σ-framework. Compound 130 was fully characterised, including by single crystal X-ray analysis\(^\text{75}\) (Figure 1.23). This compound was then exposed to sunlight for 6 weeks, producing the bisphotoadduct 131 (Scheme 1.12), in quantitative yield. In this reaction the remaining two double bonds in 130 have undergone another \([2\pi+2\pi]\) photoaddition. Alternatively, by using a 300 W tungsten lamp to irradiate substrate 129 for one hour, a 3:1 mixture of photoadducts 130 and 131 was obtained. Thus, two caged-molecules, 130 with a large cavity and 131 with two smaller cavities, were produced in a straightforward and efficient manner. It is worth noting at this point, that compound 131 represents a potential precursor to tetraol 132, a derivative of the thus far elusive hexaprismane\(^\text{a}\) structure 133 (Scheme 1.12).\(^\text{76}\)

![Scheme 1.12](image)

Reagents and Conditions: (i) Ag\(_2\)O, 1,4-dioxane, 6 M HNO\(_3\); (ii) sunlight, CDCl\(_3\), rt, 6 days; (iii) sunlight, CDCl\(_3\), rt, 6 weeks; (iv) pinacolic coupling.

\(^\text{a}\) Hexaprismane (133) is of interest because it is predicted to be a highly strained molecule and thermal cycloreversion to two benzene molecules should be a symmetry allowed process under thermal conditions. Thus, hexaprismane (133) is predicted to have little, if any, kinetic stability. Despite many attempts at their preparation, hexaprismane (133) and its derivatives remain unknown.\(^\text{76}\)
1.5 Research Aims

The objective of the research work detailed in the following chapters was to synthesise various compounds that possess a U-shaped cavity or cleft to which are attached, at the outer ends of their arms, potentially coordinating groups such as 1,10-phenanthrolines and catechols. As illustrated in Section 1.2, whilst there is an abundance of methods available for the construction of molecular clefts the initial basis of this project was the work previously carried out by Dr Justine Walter\textsuperscript{72} (Section 1.4). Ultimately the desired compounds would incorporate a 'hinge' at the apex of the cleft that could be manipulated so as to provide the optimal angle of 'bite' for cooperative interactions of the appended ligands (Figure 1.24). It was envisaged that the clefts so constructed would engage in complexation through intermolecular interactions, including hydrogen bonding and $\pi$-stacking, to form a range of supramolecular assemblies incorporating various substrates and metals. Some of the anticipated
functional properties of such clefts will be discussed after a description of the details regarding their formation.

![Diagram of molecular clefts](image)

**Figure 1.24** Schematic of target molecular clefts.

The upper portion of the cleft was to incorporate a cyclopropyldene dimer obtained through the chemistry outlined in the preceding section (Section 1.4). For the pivotal Schiff base condensation to occur, a diketone residue was required at the 'tips' of each arm of the cleft. To these ends it was envisaged, for example, that Walter's tetraol 123 could be elaborated into such a compound through simple oxidation techniques to give tetraketone 134 (Scheme 1.13), which should then participate in Schiff base condensation with the known 5,6-diamino-1,10-phenanthroline 135. The successful implementation of such chemistry would create cleft 136, with extended arms comprised of aromatic surfaces and functionalised tips that might serve useful purposes as enunciated later in this chapter.
An extension of the foregoing ideas is shown in Scheme 1.14 and was to involve formation of gem-dibromocyclopropane 137 and its conversion into the syn-adduct 138. The dichlorocarbene adduct 139, of the latter compound, would then be subject to de-isopropylation conditions developed in these laboratories to form the biscaltehol 140. This last compound is not only of interest in its own right but also because it should be capable of conversion into the bis-ortho-benzoquinone 141, an isomer of the interesting bis-para-benzoquinone 129, prepared by Walter. Compound 141 might be expected to engage in a two-fold Schiff base condensation with diamine 135 so as to form the bis-1,10-phenanthroline derivative 142.
As noted above, each of compounds 140, 141 and 142 are of considerable interest. Thus, the first should exhibit some of the characteristics of the catechols mentioned in Section 1.3.2 and bind to various metal species to afford a range of monomers, dimers and polymers of differing geometries. Further, and in keeping with Walter's work\textsuperscript{75} (Scheme 1.12), it was anticipated that compound 141 (Scheme 1.15) could, by virtue of the proximity of the relevant chromophores, engage in a $[2\pi_s+2\pi_s]$
cycloaddition reaction followed by a [3,3]-sigmatropic shift (or direct [4\(\pi\)+4\(\pi\)]
cycloaddition reaction), to give the photoadduct 143. Alternatively, compound 141
could also undergo two photochemically promoted [2\(\pi\)+2\(\pi\)] cycloaddition reactions to
give cage molecule 144. Unlike, Walter's compound 129, where the initial photoadduct
130 underwent a further [2\(\pi\)+2\(\pi\)] cycloaddition reaction, compound 143 may be
photochemically inactive and therefore unlikely to give adduct 144 directly. The two
caged compounds 143 and 144, however formed, have all four carbonyls emanating
from a common base and pointing in the same direction, a structural motif that is
important in supramolecular chemistry.

Scheme 1.15

It should be noted that, for convenience, compounds 138-142 have all been
represented as planar molecules. It is anticipated that they will, in reality, exist in U-
shaped conformations as depicted in the Chem3D™ representation of 142 (Figure 1.25).
As mentioned previously, the size of the cavity involved will depend upon the type of functionality present at the hinge of the cleft, as well as the phenanthroline derivative chosen for the tips of the cleft.

![Figure 1.25 Likely shape of cleft 141 generated using Chem3D™.](image)

Elaboration of the phenanthroline residues present in compound 142 could involve incorporation of Hamilton-type ligands to give, for example, 145 (Scheme 1.16). This latter cleft might then complex two dicarboxylic acids, such as maleic acid (146) (Scheme 1.16), one on each arm of the cleft, so that they would be held in close proximity. Once the distance is optimised, the two unsaturated diacids could then react in an intermolecular $[2\pi+2\pi]$ and photochemically promoted cycloaddition process to produce a photoadduct 147 that would then be 'incompatible' with the host (due to the puckered nature of the product cyclobutane ring) and fall away from the cavity, thereby freeing the cleft for participation in the next catalytic cycle. As such, this system would compare to Rebek's softball capsule\(^1\) (Figure 1.10) which allows the catalytic Diels-Alder reaction to occur. Catalysts for $[2\pi+2\pi]$ photocycloaddition reactions are rare, with the most obvious example being copper(I) trifluoromethanesulfonate.\(^7\) It has been shown that photodimerisations require the precoordination of both C=C bonds with the copper(I) catalyst. Another advantage of the precoordination of cleft 145 with diacid 146 is that the photocycloaddition product 147 should have all of the carboxylic acids on the same side of the molecule, \textit{i.e.} an all \textit{cis}-arrangement about the central cyclobutane ring, thus creating another cleft-like molecule (Scheme 1.16). In principle,
cleft 145 could also incorporate chiral moieties such that enantioselective formation of chiral products from achiral precursors might be possible.

The foregoing discussion should serve to highlight the supramolecular potential of compounds such as 140, 141, 142 and 145. The following chapters detail the author's efforts to prepare these and related compounds as a prelude to examining some of their properties.

Scheme 1.16
1.6 References


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Chapter 2. Approaches Towards the Synthesis of New Molecular Clefts Based on gem-Dibromocyclopropanes

2.1 Overview

This chapter details attempts to prepare the targeted molecular clefts 134 and 140 from their appropriate gem-dibromocyclopropyl precursors. As alluded to earlier, the derived cyclopropylidene adducts were to be elaborated so as to incorporate the required tetracarbonyl and biscatechol functionality, respectively. The methodology that was utilised in attempts to achieve such ends is described below.
2.2 Approaches Towards the Synthesis of New Molecular Clefts Using gem-Dibromocyclopropanes

2.2.1 Synthesis Based Upon Established gem-Dibromocyclopropane Methodology

In connection with approaches to target tetraketone 134 precursor 123, previously described by Walter, was required. Consequently, the Walter synthesis, as outlined in Scheme 2.1, was repeated. Following work first reported by Lambert et al.,\textsuperscript{1} controlled dibromocarbene addition to commercially available 1,4-cyclohexadiene (148) provided adduct 149 in 53% yield. This latter compound was then converted into the hydroxyacetate 150 (98% yield) \textit{via} a Woodward-Prévost\textsuperscript{2} reaction (employing silver acetate, iodine and aqueous acetic acid).\textsuperscript{2} The acetate group in the latter compound was then removed using methanolic sodium hydroxide affording the cis-1,2-diol 151 in quantitative yield. Acetonide protection of the latter moiety using 2,2-dimethoxypropane in the presence of \textit{para}-toluenesulfonic acid and acetone then provided compound 106 (86% yield). The spectral data derived from all of the above-mentioned products were identical, in all respects, with those reported previously.\textsuperscript{1}

\textsuperscript{2} This reaction results in nett \textit{syn}-addition of the diol moiety to the more hindered face of the alkene. For discussion of the mechanism of this reaction see reference 2.
Scheme 2.1

Reagents and Conditions: (i) CHBr₃, NaOH (50% aq.), TEBAC, 0 °C → rt, 24 h; (ii) AgOAc, I₂, AcOH, H₂O, rt, 48 h; (iii) NaOH, MeOH, rt, 6 h; (iv) 2,2-dimethoxypropane, acetone, p-TsOH, rt, 2 h; (v) MeLi or PhLi, Et₂O, -80 °C, 4 h; (vi) NaOH (50% aq.), TEBAC, CHCl₃, 0 °C → rt, 3 h; (vii) CH₃CO₂H, 80 °C, 48 h; (viii) (CF₃CO)₂O, DMSO, CH₂Cl₂, -60 °C, 1.5 h.
The previously reported alkyllithium mediated coupling of gem-dibromocyclopropane 106 was repeated by this author using methyllithium to give the expected alkene species 107 and 108 (15% and 12% yield respectively), along with the methyl substituted cyclopropane 152 (R=Me) (10% yield). When phenyllithium was used for this reaction, the two alkenes 107 and 108 were again isolated (19% and 15% yield respectively) but were now accompanied by the phenyl cyclopropane derivative 153 (R=Ph) (29% yield). The phenyl derivative 153 was isolated as a single diastereomer, however the stereochemistry at C5 was not determined. The $^1$H NMR spectrum of compound 153 shows a multiplet at $\delta$ 7.25-7.46 corresponding to the signals from the phenyl protons. The signal due to the two equivalent methine protons attached to the cyclopropane ring appears at $\delta$ 4.33-4.38 and that corresponding to the methine adjacent to the acetonide oxygens appears at $\delta$ 2.52-2.60. The $^{13}$C NMR spectrum shows the expected eleven resonances with that due to the quaternary carbon of the acetonide group appearing at $\delta$ 108.7. Mass spectral and elemental analysis establish the molecular formula of compound 153 as $\text{C}_{16}\text{H}_{19}\text{BrO}_{2}$.

Although combined yields of alkenes 107 and 108 of 81% have been reported, the outcomes of these reactions are, in fact, extremely variable as observed by this author and through the work of others, thus suggesting that the required coupling process is a fickle one. Ultimately the reaction mixtures were subjected to semi-preparative HPLC in order to separate the 'monomeric' compounds from the coupled species 107 (15% yield) and 108 (11% yield). The shape of the anti-alkene 108, precludes its use in making U-shaped clefts so no further reactions were undertaken with this material. In contrast, the syn-adduct 107 was elaborated, via a dichlorocarbene addition reaction, to compound 122 (90% yield). Deprotection of the latter species using aqueous acetic acid then gave the target tetraol 123 in 98% yield.
It was now necessary to oxidise all four hydroxyls within tetraol 123 such that a Schiff base condensation on the derived tetraketone could be examined. Oxidation of tetraol 123 proved quite difficult to achieve on a preparative scale. Application of modified Swern conditions (trifluoroacetic anhydride, dimethylsulfoxide, dichloromethane)\(^4\) (Scheme 2.1) to tetraol 123, resulted in a complex and dark yellow coloured product mixture and the presence of the bisdiketone 134 could be detected by mass spectrometric methods. All attempts to isolate and purify this material were, unfortunately, unsuccessful. As a result of the difficulties encountered in both the initial coupling of gem-dibromocyclopropane 106 and the oxidation of tetraol 123 an alternative strategy for accessing suitably functionalised coupled products was formulated. Details associated with this approach are described in the following section.

### 2.2.2 Synthesis and Reaction of gem-Dibromocyclopropane 137

In light of the difficulties outlined in the preceding section, the implementation of the proposals detailed in Section 1.14 of Chapter 1 became the next objective of the author's work. Efforts along these lines required access to gem-dibromocyclopropane 137 where the pivotal catechol residue was protected as a bisisopropyl ether. This protecting group was chosen because of the facility with which it could be removed.\(^5\) A further motivation for targeting compound 137 stemmed from earlier reports\(^6\) that subjecting congeners 154 and 155 to the alkyllithium mediated coupling reaction had been unsuccessful and at least in part, because of the insolubility of these compounds at the low temperatures (-100 °C) required. It was expected that the increased lipophilic character of compound 137 (due to the presence of the isopropyl groups) should assist in its solubilisation at low temperatures.
The synthesis of compound 137 (Scheme 2.2) began with the protection of commercially available 2,3-dihydroxynaphthalene (156) as its bisisopropyl ether. Thus, compound 156 was treated with 2-bromopropane and potassium carbonate in N,N-dimethylformamide and in this way target bisether 157 was obtained in 97% yield. Distinctive signals associated with the isopropyl group were observed in the $^1$H NMR spectrum: at $\delta$ 4.62 (sep, $J = 6.1$ Hz) for the methine proton and at $\delta$ 1.42 (d, $J = 6.1$ Hz) for the methyl group protons. The 70 eV electron impact mass spectrum exhibited the expected molecular ion as well as fragment ions resulting from successive loss of CH$_2$CHCH$_3$ (42 mass units) from each of the isopropoxy groups. Such distinctive spectral characteristics were also observed for all of the other compounds reported herein which incorporate isopropoxy groups.

The protected catechol 157 was subjected to Birch reduction, using sodium metal in liquid ammonia, to give the air sensitive dihydronaphthalene derivative 158 in quantitative yield. Phase transfer catalysed addition of dibromocarbene to the latter compound produced the gem-dibromocyclopropane compound 137 as a white crystalline solid, albeit in only 24% yield. The $^1$H NMR spectrum of compound 137 shows a distinctive two-proton resonance at $\delta$ 3.17 for the two equivalent methine protons at C1a and C7a. In the $^{13}$C NMR spectrum (Figure 2.1) the signal corresponding to the gem-dibromocyclopropyl carbon appears at $\delta$ 39.0, while in the 70 eV EI mass spectrum, a cluster of molecular ions was observed at $m/z$ 420, 418 and 416 and in the 1:2:1 ratio, expected for a dibrominated compound. High resolution mass
spectrometry and elemental analysis confirmed the expected molecular formula, C_{17}H_{22}Br_{2}O_{2}.

Attempts at coupling the *gem*-dibromocyclopropane 137 to form the *syn*-adduct 159, were undertaken using methyllithium, phenyllithium and *n*-butyllithium. However all were unsuccessful with only starting material 137 isolated from the reaction mixtures.

\[ \text{HO} \quad \text{HO} \]

156

\[ \rightarrow \]

157

\[ \rightarrow \]

158

\[ \rightarrow \]

159

Scheme 2.2

*Reagents and Conditions:* (i) K_{2}CO_{3}, DMF, 2-bromopropane, 100 °C, 3 h; (ii) Na, *t*-BuOH, THF, NH_{3}, -78 °C, 2 h; (iii) NaOH (50% aq.), CHBr_{3}, TEBAC, 0 °C → rt, 24 h; (iv) MeLi or PhLi or *n*-BuLi, Et_{2}O, -80 °C.

As the alkyl lithium mediated coupling reactions of the three *gem*-dibromocyclopropanes 154, 155 and 137 were found to be highly capricious, yielding only small amounts, if any, of the required alkenes, the preparation of molecular clefts *via* an alternate synthetic pathway which avoided this problematic conversion was investigated. Such alternate pathways were designed to exploit the ready availability of these *gem*-dibromocyclopropanes and are described in the next section.
Figure 2.1 75.4 MHz $^{13}$C NMR spectrum of *gem*-dibromocyclopropane 137.
(Spectrum recorded in CDCl$_3$)
2.3 An Alternative Approach to the Synthesis of Molecular Clefts Based on gem-Dibromocyclopropanes

For the reasons just mentioned, it was decided to utilise the gem-dibromocyclopropane 137 already in hand in an alternate approach to the coupled alkenes. In particular, it was thought that ring expansion of the cyclopropyl moiety within substrate 137 could be exploited in providing a compound such as 160 (Scheme 2.3), which might then be manipulated via a homocoupling and various other functional group interconversions to produce cleft-like systems.

The critical first step in implementing such a strategy is the electrocyclic ring opening of a gem-dibromocyclopropane to form a π-allyl cation that is then captured by a nucleophile, such as the bromide ion involved in the initial ionisation process, to give products of the general type 160. Once the ring opening had been effected, removal of the 'R' group would follow to give the desired cycloheptenylbromide 161. The metal mediated homocoupling of this latter compound followed by 1,4-reduction of the resulting diene would then furnish adduct 162. From this point, the reaction sequence parallels that described previously (Scheme 1.14). Thus, subjection of compound 162 to functionalisation at the alkenyl hinge, through carbene addition, could afford adduct 163. Deprotection of 163 would lead to biscatechol 164 which would in turn, be subject to an oxidation reaction to yield bis-ortho-benzoquinone 165. Ultimately Schiff base condensation of compound 165 with a 1,10-phenanthroline derivative (e.g. 135) could furnish cleft molecule 166, which bears a strong resemblance to the originally targeted system 142. Such a cleft would still maintain the desirable features outlined in Section 1.5, that is, a hinge capable of incorporating varying functionality; arms which can be easily manipulated and the phenanthroline group at the 'tips' of the cleft also capable of functionalisation.
Scheme 2.3
2.3.1 Efforts Directed Towards the Ring Expansion of *gem*-Dibromocyclopropane 137

The pathway by which electrocyclic ring opening of the cyclopropyl cation derived *via* ionisation of ring-fused *gem*-dibromocyclopropanes occurs is illustrated in Scheme 2.4 using the 'parent' system 167. According to the Woodward-Hoffmann-de Puy rule, the ring opening of cyclopropyl cations to allyl cations should proceed in a disrotatory manner in order to fulfil the requirements of the principles of conservation of orbital symmetry. Further, the cleavage of the C1 - C6 bond in 167 (Scheme 2.4) is concerted with the loss of the *endo*-oriented leaving group (Br⁻) at C7. The resulting allyl cation (168) is then attacked by a nucleophile to give the product 169. The ring opening reaction is facilitated by silver ions *via* an increase in the rate of ionisation of the carbon-halogen bond. The counter-ion (X⁻) associated with the original silver salt can trap the allyl cation (168), or a deliberately added nucleophile, NuH, can also act as the trapping agent. Under thermal conditions, and in the absence of silver salts or added nucleophiles, the ring expanded isomer 170, of the original substrate is observed.
In keeping with such ideas and in an effort to effect the electrocyclic ring opening of compound 137 (Scheme 2.5) the reaction conditions outlined in Table 2.1 were examined.

![Diagram of compounds 137 and 160]

**Scheme 2.5**

<table>
<thead>
<tr>
<th>Entry #</th>
<th>Reaction Conditions</th>
<th>Expected Product</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>160 °C, 3 h</td>
<td>( R' = \text{Br} )</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>AgNO(_3), MeOH, 80 °C, 5 h</td>
<td>( R' = \text{OMe} )</td>
<td>starting material recovered</td>
</tr>
<tr>
<td>3</td>
<td>AgNO(_3), THF, Et(_3)SiH, 80 °C, 4 h</td>
<td>( R' = \text{H} )</td>
<td>starting material recovered</td>
</tr>
<tr>
<td>4</td>
<td>AgNO(_3), t-BuOH, Et(_3)SiH, 100 °C, 5 h</td>
<td>( R' = \text{H} )</td>
<td>starting material recovered</td>
</tr>
<tr>
<td>5</td>
<td>AgNO(_3), 1,4-dioxan, Et(_3)SiH, 120°C, 15 h</td>
<td>( R' = \text{H} )</td>
<td>starting material recovered</td>
</tr>
<tr>
<td>6</td>
<td>AgOAc, MeCO(_2)H, 80 °C, 3 h</td>
<td>( R' = \text{OAc} )</td>
<td>starting material recovered</td>
</tr>
<tr>
<td>7</td>
<td>AgNO(_3), NaOAc, MeCO(_2)H, 120 °C, 16 h</td>
<td>( R' = \text{OAc} )</td>
<td>starting material recovered</td>
</tr>
<tr>
<td>8</td>
<td>AgOAc, t-BuOH, 100 °C, 16 h</td>
<td>( R' = \text{OAc} )</td>
<td>starting material recovered</td>
</tr>
<tr>
<td>9</td>
<td>Rh/Al(_2)O(_3), EtOH, H(_2), 16 h</td>
<td>( R' = \text{H} )</td>
<td>decomposition</td>
</tr>
<tr>
<td>10</td>
<td>AgOTs, MeCN, 100 °C, 16 h</td>
<td>( R' = \text{OTs} )</td>
<td>starting material recovered</td>
</tr>
</tbody>
</table>

**Table 2.1 Conditions Examined in Attempting to Effect the Ring Opening of gem-Dibromocyclopropane 137 with Incorporation of \( R' \) as Shown in Scheme 2.5.**
Initially, a neat sample of dibromide 137 was heated at 160 °C (Table 2.1 Entry 1), however only decomposition of the starting material was observed. The silver(I) mediated ring opening of compound 137 was then examined (Table 2.1 Entries 2-10) involving various counter-ions in the attempted trapping of the anticipated allyl cation. Unfortunately all of these reactions were unsuccessful and starting material was isolated in most cases.

In a slightly different approach to the ring opening of *gem*-dibromocyclopropane 137, the hoped for allyl cation was to be deprotonated by added base (rather than captured with a nucleophile) to give diene 171 (Scheme 2.6). Selective reduction of the non-brominated double bond within the latter should be possible and thus provide the target homocoupling substrate 161.\(^\text{11}\)

![Scheme 2.6](image)

**Table 2.2 Conditions Examined in Attempting to Effect the Ring Opening of *gem*-Dibromocyclopropane 137 as Shown in Scheme 2.6.**

<table>
<thead>
<tr>
<th>Entry #</th>
<th>Reaction Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pyridine, 100 °C, 2 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>Quinoline, 200 °C, 20 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>Quinoline, AgNO₃, 200 °C, 24 h</td>
<td>starting material recovered</td>
</tr>
<tr>
<td>4</td>
<td>DBU, toluene, 130 °C, 2 d</td>
<td>starting material recovered</td>
</tr>
<tr>
<td>5</td>
<td>AgNO₃, TFA, rt, 16 h</td>
<td>starting material recovered</td>
</tr>
<tr>
<td>6</td>
<td>AgOCOCF₃, TFA, rt, 16 h</td>
<td>starting material recovered</td>
</tr>
<tr>
<td>7</td>
<td>AgNO₃, CH₃CN, 100 °C, 16 h</td>
<td>starting material recovered</td>
</tr>
</tbody>
</table>
In the event, however, all attempts (see Table 2.2) to effect the conversion from 137 to 171 were unsuccessful even when elevated temperatures (Entry 1 and 2) or silver(I) triflate (Entry 6) were employed. This lack of reactivity towards the electrocyclic ring opening was unexpected as evidence from the literature\textsuperscript{9} indicates that systems like 137, should readily undergo such reactions.

Due to the difficulties encountered in attempting to effect ring expansion of the \textit{gem}-dibromocyclopropane 137, other methods of achieving the pivotal alkene 162 were pursued and with greater success. Details are provided in the next chapter.
2.4 References


(6) Banwell, M. G.; Longmore, R. W. unpublished observations.


3.1 Overview

Based on the analyses defined in the latter part of the preceding chapter, the new 'coupling substrates' required in forming the newly targeted molecular clefts such as compound 164, were benzosuberones, *e.g.* 172. Further, related clefts could also be obtained from other compounds incorporating odd-sized rings (*e.g.* containing 3, 5, 7 or 9 membered rings) including indan-2-one 173. Such compounds would be subject to McMurry coupling reactions in order to provide the required alkenes for cleft formation.

As the previous attempts to synthesise a seven-membered precursor by ring expansion of *gem*-dibromocyclopropane 137 were unsuccessful, the new strategy was to involve construction of the requisite seven- or five-membered ring through an appropriate cyclisation procedure. This chapter outlines the methods examined in preparing the seven-membered compound 172.
3.2 Methods Available for Construction of Benzosuberone 172

A particularly relevant procedure for constructing compound 172 appeared to be one involving the Dieckmann condensation reaction. Dran\(^1\) has used this process to effect the conversion of diester 174 (Scheme 3.1) into β-ketoester 175 (65\% yield) incorporating a seven-membered ring. Bases such as sodium hydride and sodium methoxide are useful reagents for effecting such conversions which are driven to completion by virtue of the formation of a highly stabilised enolate anion, namely the conjugate base of the final product.\(^2\)

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me}
\end{array}
\xrightarrow{\text{i}}
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me}
\end{array}
\]

\textbf{Scheme 3.1}

\textit{Reagents and Conditions}: (i) NaOMe, xylene, reflux, 36 h.

Another relevant cyclisation reaction has been reported by Reid and Schwenecke\(^3\) who used sodium hydroxide to effect the condensation of the dialdehyde 176 with 2-
butanone and subsequent cyclisation then dehydration to give the benzotropone 177 in 59% yield (Scheme 3.2). The latter conversion can be regarded as involving a 'double-barrelled' aldol condensation reaction.

![Scheme 3.2](image)

_Scheme 3.2_

*Reagents and Conditions:* (i) MeCOCH₂Me, NaOH, MeOH.

In a related vein, McChesney⁴ has used an intramolecular aldol reaction, as shown in Scheme 3.3, to effect cyclisation of compound 178 with subsequent loss of water so as to form dihydrobenzocycloheptene 179.

![Scheme 3.3](image)

_Scheme 3.3_

*Reagents and Conditions:* (i) KHSO₄, C₆H₆, 6 h.

Another pertinent cyclisation process exploits dianion 180 (Scheme 3.4), which is generated in a stepwise approach via the mono-anion (in red) from methyl acetoacetate using sodium hydride then a strong lithium base. Weiler and Huckin⁵ investigated the reaction of this dianion 180 with dihaloalkanes and found that after the initial alkylation,
cyclisation occurs via intermediate 181 to give the product 182 in good yield (68%) provided that an excess of dianion 180 is avoided and the reaction is run under dilute conditions. Again the driving force for this reaction is the formation of a highly stabilised enolate anion, the conjugate base of β-ketoester 182 in this case.

![Diagram of cyclisation reaction]

**Scheme 3.4**

*Reagents and Conditions:* (i) Br(CH₂)₃Br, THF, 10 min.

The following sections detail attempts to implement such cyclisation procedures in an effort to synthesise seven-membered ring containing compounds as required in target 172.

### 3.3 Dieckmann Condensation Method

In order to implement a cyclisation process similar to that reported by Dran,¹ (Scheme 3.1) the relevant diester 183 was synthesised from catechol (4) by the pathway shown in Scheme 3.5. Thus, protection of catechol 4 as the bisisopropyl ether, using standard techniques,⁶ afforded compound 184 in 98% yield. This compound exhibited the diagnostic signals, as previously described (page 54), for the isopropyl moiety in the ¹H NMR, ¹³C NMR and mass spectra.
Compound 184 was subjected to a silver(I) promoted iodination reaction to give the diiodo derivative 185 in 92% yield. The latter material was immediately subjected to a double-barrelled Heck reaction with methyl acrylate to give the corresponding bisacrylate 186 in quantitative yield. Hydrogenation of the double bonds in 186, in the presence of palladium on activated carbon, afforded the required diester 183, also in a quantitative yield. This last conversion was confirmed by $^1$H NMR spectroscopic analysis, where the signals associated with the alkenic protons in 186, a doublet at $\delta$ 6.23 ($J = 15.7$ Hz) and also at $\delta$ 8.00 ($J = 15.7$ Hz) (Figure 3.1), have disappeared in the spectrum of the product 183 (Figure 3.2). In this spectrum signals are now observed at $\delta$ 2.55 and $\delta$ 2.85 (2 x triplets, $J = 7.5$ Hz) and which are attributed to the newly introduced methylene groups.

Reagents and Conditions: (i) K$_2$CO$_3$, DMF, 2-bromopropane, 100 °C, 8 h; (ii) I$_2$, AgOAc, CHCl$_3$, 12 h; (iii) methyl acrylate, Pd(OAc)$_2$, K$_2$CO$_3$, n-Bu$_4$NBr, DMF, 120 °C, 48 h; (iv) Pd/C, H$_2$, THF, 12 h.
Figure 3.1 300 MHz $^1$H NMR spectrum of bisacrylate 186.
(Spectrum recorded in CDCl$_3$)
Figure 3.2 300 MHz $^1$H NMR spectrum of diester 183.
(Spectrum recorded in CDCl$_3$)
Compound 183 was now suitably functionalised for a Dieckmann ester condensation to occur and several conditions were examined in attempts to produce the anticipated cyclisation product 187 (Scheme 3.6). These included the use of a variety of sodium and potassium bases in differing solvents, at several pressures and with the addition of many catalysts. However, none of the sets of conditions examined afforded the required compound 187. As a consequence, an alternative route to this type of benzosuberone was sought.

![Chemical structures](image)

Scheme 3.6

3.4 Double-Barrelled Aldol Condensation Method

The next strategy to be examined was based on the work by Reid and Schwenecke\(^3\) as described earlier and summarised in Scheme 3.2. To such ends, it was envisaged that introduction of a second aldehyde moiety into piperonal (188)* would give the dialdehyde 189. The latter compound was expected to undergo an intermolecular aldol condensation reaction with acetone and a subsequent intramolecular version of the same process to yield benzotropone 190 (Scheme 3.7).

* Piperonal was chosen during preliminary investigations of this approach because of its ready availability in large quantity.
Hydrogenation of the double bonds in the seven-membered ring of 190 would then lead to a possible substrate 191, for the pivotal McMurry coupling reaction. Ultimately, the methylene protecting group would be replaced with the bisisopropoxy system, as relatively mild methods for removal of the latter have been developed.

Piperonal (188) was reacted with 1-dichloromethoxy-butane, which acts as a synthetic equivalent of +CHO, in the presence of tin(IV) chloride. The desired dialdehyde 189 was not isolated, rather, trace amounts of compounds 192 (4% yield) and 193 (2% yield) were obtained as the only isolable products of reaction (Scheme 3.8).
In the $^1$H NMR spectrum of compound 192, the signal due to the methine proton of the dichloromethyl moiety appears at δ 7.17 while the signal due to the aldehyde proton resonates at δ 9.94. The mass spectrum of compound 192 shows three molecular ions at $m/z$ 232, 234 and 236 and in a ratio of 100:60:10 expected for a dichloro-containing compound.

Coproduct 193 was also fully characterised by standard spectroscopic methods as well as by single crystal X-ray analysis (Figure 3.3). In an overall sense, the aldehyde and dichloromethyl groups within this product appear to have been transposed relative to the starting aldehyde 188. In terms of origins, compound 193 could be the product of (i) dichloromethylation of benzo[1,3]dioxole-4-carbaldehyde (isopiperonal) present as an impurity in the starting piperonal (188); (ii) a tin(IV) chloride catalysed isomerisation of an initially formed mono(dichloromethyl) product or (iii) the product of selective hydrolysis of the bis(dichloromethyl) compound to the observed monoaldehyde. However, as the yield of product 193 was very low and determination of the origins of this product being beyond the scope of this thesis such matters were not pursued.
Figure 3.3 ADEP\textsuperscript{9} derived from a single crystal X-ray analysis of compound 193.
While compound 192 could be considered a synthetic equivalent to the dialdehyde 189, the low yields of this material precluded extensive pursuit of such possibilities. Nevertheless, it was observed that when compound 192 was treated with sodium hydroxide and acetone in methanol the originally desired dialdehyde 189 was formed (Scheme 3.9) and the data obtained for this compound were identical, in all respects, with those reported in the literature. However, no products (e.g. 190) arising from double-barrelled aldol condensation of this aldehyde with the added acetone were observed. Clearly then, this process did not generate the required cyclisation product. As a result alternate methods for constructing the target seven-membered ring were investigated.

Scheme 3.9

Reagents and Conditions: (i) acetone, NaOH, MeOH, 2 h.
3.5 The Dianion Method

In principle, commercially available veratrole (194)\(^{\text{a}}\) could be subject to a bis(chloromethylation) step to yield compound 195 (Scheme 3.10) which should be amenable to annulation using the dianion of methyl acetoacetate 180 so as to give a seven-membered ring containing compound 196.

\[ \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \]
\[ \text{194} \quad \xrightarrow{\text{i}} \quad \text{MeO} \quad \text{MeO} \quad \text{Cl} \quad \text{Cl} \]
\[ \text{195} \]

Scheme 3.10

Reagents and Conditions: (i) 1,4-dioxane, HCl, HCHO (35% aq.), 0 °C → rt, 3 h.

The bis(chloromethyl) compound 195 required to test this proposal was synthesised via known chemistry,\(^{11}\) albeit in low yields (28%). As previously noted, a dilute solution of the dianion is reportedly\(^{5}\) required to facilitate formation of cyclised products, therefore the veratrole derivative 195 was subjected to the relevant conditions involving a \(\sim 0.4\) M solution of the preformed dianion of methyl acetoacetate 180 in tetrahydrofuran. Several different reaction conditions were examined in order to effect this cyclisation including the application of various temperatures, solvents, pressures and catalysts. Formation of a cyclised product, \(i.e.\) a benzosuberone, was not achieved under any of these conditions.

\(^{a}\) Veratrole was chosen during preliminary investigations of this approach because of its ready availability in large quantity.
The only reaction conditions under which a compound other than starting material was isolated involved the original set proposed by Weiler,\(^5\) and involved a two step dianion production with sodium hydride followed by \(n\)-butyllithium (Scheme 3.11). The isolated compound was the \(\beta\)-keto ester 197 (86\% yield) which suggests that the dianion 180 was in fact formed prior to reaction with 195, however the desired cyclisation reaction did not take place because hydrolysis of the remaining benzylic chloride residue occurs instead. Nevertheless, compound 195 could still afford the target compound 196. Following a lead from the literature,\(^4\) alcohol 197 was efficiently converted into the corresponding aldehyde 198 (97\% yield) using pyridinium chlorochromate as oxidant. The latter compound failed to engage, under a range of conditions, in the desired intramolecular aldol condensation reaction so as to afford target 199.

![Scheme 3.11](image)

*Reagents and Conditions:* (i) MeCOCH\(_2\)CO\(_2\)Me, NaH (50\%), \(n\)-BuLi, THF, 0 °C \(\rightarrow\) rt, 35 min; (ii) PCC, CH\(_2\)Cl\(_2\), rt, 2 h; (iii) KHSO\(_4\), C\(_6\)H\(_6\), reflux, 6 h or \(p\)-TsOH, toluene, reflux, 7 h.
The difficulties encountered to this point were finally overcome using the two-fold alkylation strategy described in the following section.

3.6 Successful Synthesis of Benzosuberone 172

The reaction sequence shown in Scheme 3.12 outlines the successful synthesis of target 172. The previously described bisisopropyl ether 184 was subjected to standard bis(chloromethylation) conditions11 to afford compound 200. Significantly improved yields were obtained in this conversion when the solvent was changed from the reported solvent 1,4-dioxane (24% yield) to 1,2-dimethoxyethane (78% yield).

In the $^1$H NMR spectrum of compound 200 the resonance due to the four equivalent methylene protons appears as a singlet at $\delta$ 4.67 and in the $^{13}$C NMR spectrum the signal for the carbon of this same group appears at $\delta$ 44.0, as expected for a benzylic chloromethyl moiety. The $^1$H NMR spectrum also exhibits a singlet at $\delta$ 6.91, arising from the two equivalent aromatic protons, thus providing further support for the presence of a plane of symmetry in this molecule. The mass spectrum of compound 200 shows three molecular ions at $m/z$ 290, 292 and 294 in a ratio of 100:60:10 consistent with the presence of two chlorines.
Scheme 3.12

Reagents and Conditions: (i) HCHO (35% aq.), HCl, DME; $0\degree C\rightarrow rt$, 16 h; (ii) $n$-Bu$_4$NBr, (CH$_2$CO$_2$Me)$_2$CO, NaHCO$_3$ (5% aq.), CH$_2$Cl$_2$, 12 h; (iii) H$_2$SO$_4$ (15% aq.), reflux, 48 h.

Initial attempts to effect reaction of dichloro compound 200 with dianion 180 using Weiler's$^5$ alkylation conditions only lead to complex mixtures of products and recovery of small portions of starting material. Successful alkylation followed by cyclisation was, however, achieved following Tashiro's conditions$^1$ (a two phase system comprising dimethyl-1,3-acetone dicarboxylate, tetra-$n$-butylammonium bromide, 5% aqueous sodium hydrogen carbonate and dichloromethane) to give target 201 in good yield (Scheme 3.12) and as a mixture of diastereoisomers (as judged by $^1$H NMR analysis). These products were not separated from one another but immediately subjected to a two-fold decarboxylation reaction using 10% sulphuric acid (Scheme 3.12).$^4$ The $^1$H NMR spectrum of the, by now, long sought after product 172 (Figure 3.4), which was obtained in
88% yield, exhibited the expected signals which correspond to the isopropoxy protons [δ 1.33 (methyl) and δ 4.45 (methine)], the aromatic protons (δ 6.78) and the two sets of methylene protons associated with the seven-membered ring (δ 2.57-2.61 and δ 2.79-2.83). Moreover, due to the symmetry elements associated with ketone 172, there are only eight signals in the $^{13}$C NMR spectrum (Figure 3.5), with the resonance due to the carbonyl carbon appearing at δ 212.3. The infrared spectrum also supports the assigned structure with the appearance of a band at 1701 cm$^{-1}$, as expected for a ketone carbonyl incorporated in a seven-membered ring.

With benzosuberone 172 in hand, the next step in the reaction sequence was its subjection to a McMurry coupling reaction so as to form the pivotal precursor to the target molecular clefts. Details associated with such work are discussed in the ensuing chapter.
Figure 3.4 300 MHz $^1$H NMR spectrum of benzosuberone 172.
(Spectrum recorded in CDCl$_3$)
Figure 3.5 75.4 MHz APT $^{13}$C NMR spectrum of benzosuberone 172.
(Spectrum recorded in CDCl$_3$)
3.7 References

(7) Lansky, A.; Reiser, O.; de Meijere, A. Synlett 1990, 405.
Chapter 4. Towards the Synthesis of Molecular Clefts Based on Benzosuberone 172

4.1 Overview

In the preceding chapter the successful synthesis of benzosuberone 172 from commercially available catechol (4) (Scheme 3.12) was detailed. Following this success, the conversion of compound 172 via a McMurry or pinacol coupling reaction, was pursued with a view to elaboration of the resulting alkene or diol to the target molecular clefts, such as 166. This chapter details efforts to implement such objectives.

\[ \text{172} \]

\[ \text{166} \]
4.2 Reductive Coupling Reactions of Benzosuberone

4.2.1 McMurry Coupling Reaction

The reductive coupling of carbonyl compounds to form 'dimeric' products is well known and one particularly popular method for achieving this is the McMurry coupling or cross coupling of ketones (203) to form olefins (204). Such conversions are mediated by various low valent titanium species (Scheme 4.1). McMurry reported this set of reaction conditions in 1974 and now has his name inextricably attached to them, although Mukaiyama and Tyrlik also discovered the same sorts of conversions and independently published their results a year earlier.

\[
\begin{align*}
2 \times \text{R} \quad \text{O} \quad \text{R} & \xrightarrow{\text{low valent Ti}} \quad \text{R} \quad \text{R} \quad \text{R} \quad \text{R} \\
\end{align*}
\]

Scheme 4.1

McMurry’s coupling reagent was originally prepared by reduction of titanium(III) chloride with lithium aluminium hydride in tetrahydrofuran. Mukaiyama, on the other hand, prepared his system from titanium(IV) chloride and zinc, while Tyrlik’s system was generated from titanium(III) chloride and magnesium. In 1990 Carroll and Taylor reported the formation of olefins via reductive coupling of carbonyl compounds with titanium(IV) chloride and a magnesium amalgam. Due to the heterogeneous nature of the medium, yields observed in these reactions vary tremendously (3-99%) and depend mainly on the purity of the titanium species and the activation method employed.
The proposed mechanism\(^1,2,5\) (Scheme 4.2) for the formation of the olefins from the corresponding ketone(s) is similar to most other metal mediated reductions, although the strong titanium-oxygen bond in the initial product greatly facilitates the coupling process. It is thought that the initially formed pinacolate 205 binds to the surface of a small, zero-valent titanium particle. In order for the coupling to take place the oxyanions of the two independent molecules must be able to reach the same surface (but not necessarily the same titanium atom),\(^\ast\) as shown in structure 206. The coupling process to give species 207 occurs at the titanium surface and is followed by stepwise cleavage of the carbon-oxygen bonds in 207 to give 208, then alkene 204. An oxide-coated titanium surface is the other product of this process.

\[ \text{Scheme 4.2} \quad \text{Proposed mechanism for the McMurry coupling reaction to form olefins involving low valent titanium.}^5 \]

\(^\ast\) McMurry’s experiments eliminated the operation of other pathways involving a discrete cyclic or acyclic dioxy titanium species.\(^5a\)
After exploring the various modifications of the McMurry coupling reaction, target alkene 209 (98% yield) (Scheme 4.3) was eventually produced from benzosuberone 172 using the Mukaiyama system comprising titanium(IV) chloride and zinc powder.

![Scheme 4.3](image)

Reagents and Conditions: (i) TiCl₄, DME, Zn, reflux, 48 h.

In the ¹H NMR spectrum of alkene 209 (Figure 4.1) the signals corresponding to the methylene protons of the seven-membered ring have now shifted upfield, to δ 2.62-2.66 and δ 2.38-2.42, as compared to those in the analogous spectrum of precursor 172 (Figure 3.4). In the ¹³C NMR spectrum of alkene 209 (Figure 4.2) the signal at δ 212.3 due to the carbonyl carbon present in the starting material (Figure 3.5) has disappeared and a new resonance at δ 136.1, corresponding to the alkenyl carbons, is observed. The resonances attributed to the aromatic carbons appear at δ 147.3, δ 134.6 and δ 120.9, while the signals corresponding to the methylene carbons of the seven-membered ring appear at δ 36.3 and δ 32.2. In the infrared spectrum, the distinctive carbonyl stretching band observed at 1701 cm⁻¹ for the starting material 172 has now disappeared. In the mass spectrum of alkene 209 the molecular ion m/z 520 is present and accompanied by fragment ions resulting from successive loss of CH₂CHCH₃ (42 mass units) from the four isopropyl moieties. Such data clearly indicates that successful reductive coupling of benzosuberone 172 has occurred.
Figure 4.1 300 MHz $^1$H NMR spectrum of McMurry coupling product 209.
(Spectrum recorded in CDCl$_3$)
Figure 4.2 75.4 MHz APT $^{13}$C NMR spectrum of McMurry coupling product 209. (Spectrum recorded in CDCl$_3$)
As noted, the yields observed in the McMurry coupling process can be highly variable and the afore-mentioned reaction is no exception. One byproduct, consistently isolated from this reaction was the corresponding 1,2-diol or pinacol which can also be used in the synthesis of molecular clefts and as such will now be discussed.

4.2.2 Pinacol Coupling Reaction

The pinacol coupling of ketones (203) to give the corresponding 1,2-diol (210) (Scheme 4.4) can be achieved under the McMurry conditions.\(^6\) Indeed pinacols are, for all intents and purposes, intermediates in the McMurry coupling and by manipulating the reaction conditions either the pinacol or olefin can be obtained on an exclusive basis. This is typically achieved by controlling the temperature at which the reaction is carried out. Thus, at low temperatures the pinacol can be obtained, while at higher temperatures, often involving reflux conditions, alkene production is observed. Mixtures of both the pinacol and the olefin are isolated, however yields still vary greatly.

\[
\begin{align*}
2 \times \text{R} & \xrightarrow{\text{O}} \text{R} & \text{low valent Ti} & \xrightarrow{\text{HO}} \text{R} & \text{R} \\
\text{203} & & & \text{210}
\end{align*}
\]

Scheme 4.4

Surprisingly, good yields of pinacol 211 (64\%) (Scheme 4.5) were obtained in refluxing tetrahydrofuran, conditions which usually favour the formation of the corresponding olefin 209. Consistent yields of the pinacol 211 (78\%) could be obtained by using the Carroll-Taylor\(^4\) conditions (magnesium amalgam, titanium(IV) chloride) (Scheme 4.5), at a temperature of 0 °C.
In the $^1$H NMR spectrum of pinacol 211, the non-equivalence of the methylene protons gives rise to the four signals at $\delta$ 3.10 (triplet, $J = 13.2$ Hz), $\delta$ 2.34-2.41, $\delta$ 1.95-2.04 and $\delta$ 1.45 (doublet of doublets, $J = 6.1$ and 1.5 Hz). The $^{13}$C NMR spectrum shows no trace of a peak due to a carbonyl or olefinic carbon but there is a signal attributable to an oxygenated sp$^3$-carbon at $\delta$ 78.6 as would be expected for structure 211. The infrared spectrum of compound 211 shows no absorption due to a carbonyl chromophore but a broad band centred at 3480 cm$^{-1}$ is observed as would be expected for a diol. The 70 eV electron impact mass spectrum also supports the proposed structure of 211 with a molecular ion being observed at $m/z$ 554. The fragment ions appearing at $m/z$ 536 and 518 are attributed to successive losses of two molecules of water.

The cleft molecules 209 and 211 were synthesised in sufficient quantities to enable studies of their functionalisation at the double bond (in the former case) and at the diol (in the latter case). Such functionalisation should provide clefts with rather different 'trans-cavity' distances in terms of the degree of convergence of the two arms of each cleft.
4.3 Cyclofunctionalisation at the 'Hinges' of Compounds 209 and 211

Following the work described in earlier sections of this thesis, the double bond of alkene 209 was subjected to a phase transfer type dichlorocarbene addition reaction so as to furnish adduct 212 in quantitative yield (Scheme 4.6).

![Scheme 4.6](image)

**Scheme 4.6**

*Reagents and Conditions: (i) NaOH (50% aq.), TEBAC, CHCl₃, 0 °C → rt, 13 h.*

In the $^1$H NMR spectrum of compound 212, the signals due to the methylene protons associated with the seven-membered rings are now split into three distinct envelopes which appear at $\delta$ 2.87-2.90, $\delta$ 2.57-2.65 and $\delta$ 1.85-1.98. In the $^{13}$C NMR spectrum of cyclopropane 212 no signal due to an sp$^2$-hybridised carbon of an alkene is seen, rather a signal at $\delta$ 78.2, which corresponds to the quaternary carbon bearing the chlorine atoms, is observed. The mass spectrum shows the anticipated molecular ions at m/z 602, 604 and 606 and in a ratio of 100:60:10 as expected for a dichlorinated compound.

The diol moiety within pinacol 211 could be protected as the corresponding acetonide using standard conditions$^7$ and in this way gave the cleft 213, although in a rather disappointing 28% yield (Scheme 4.7). The $^1$H NMR spectrum of this product shows signals due to the methylene protons at $\delta$ 3.12-3.20, $\delta$ 2.39-2.47 and $\delta$ 2.12-2.18 and a singlet corresponding to the equivalent methyl group protons of the acetonide appears at $\delta$
1.52. In the $^{13}$C NMR spectrum ten signals are observed with that due to the quaternary carbon of the acetonide moiety appearing at $\delta$ 106.5, while the resonance arising from the quaternary carbons attached to the oxygen appears at $\delta$ 86.7. In the infrared spectrum of acetonide 213, the dominating -OH stretching band of the precursor 211 is absent.

![Scheme 4.7](image)

**Scheme 4.7**

*Reagents and Conditions:* (i) acetone, $p$-TsOH, 2,2-dimethoxypropane, rt, 2 h then NaOH (10% aq.); (ii) (CCl$_3$O)$_2$CO, pyridine, CH$_2$Cl$_2$, -70 °C → rt, 20 h.

The pinacol 211 was also protected, following Burk's procedure,$^8$ as the cyclic carbonate to give a third cleft molecule 214 in 67% yield (Scheme 4.7). The carbonate protecting group was chosen as it is relatively stable under both acidic and basic conditions,$^9$ such that the necessary removal of the isopropyl groups later in the synthesis may not prove as problematic as might be the case with the acetonide 213.

In the $^1$H NMR spectrum of cyclic carbonate 214 (Figure 4.3) there is a signal at $\delta$ 6.66 corresponding to the aromatic protons. The resonances due to the methylene protons of the seven-membered ring appear at $\delta$ 3.08-3.17, $\delta$ 2.50 (doublet of doublets, $J = 14.7$ and 6.3 Hz), $\delta$ 2.21-2.28 and $\delta$ 1.40-1.49. These resonances are in similar positions to those of
the acetonide 213, where the protons adjacent to the oxygen functionality in both compounds are significantly deshielded and therefore shifted downfield in the spectrum. By comparison, in the analogous spectrum of gem-dichlorocyclopropane 212 all the resonances due to the methylene protons appear in the region between $\delta$ 1.90-2.90. In the $^{13}$C NMR spectrum of compound 214 (Figure 4.4), the signal due to the carbonyl carbon of the cyclic carbonate moiety appears at $\delta$ 153.8 while the two equivalent quaternary carbons at the hinge of the cleft gives rise to a signal at $\delta$ 90.3. The equivalent signal in the spectrum of acetonide 213 appears at $\delta$ 86.7. In the infrared spectrum of compound 214 the band observed at 1799 cm$^{-1}$ is assigned to stretching of the carbonate carbonyl moiety.

The structure of compound 214 was confirmed by single crystal X-ray analysis and the derived ADEP (Figure 4.5) serves to highlight the cleft-like nature of this compound. Interestingly, there are two crystallographically independent molecules per asymmetric unit. The carbonate group is clearly visible at the hinge of the cleft and the two arms are twisted about the hinge, while the isopropoxy groups are at the terminus. The intramolecular 'trans-cavity' distance from oxygen to oxygen within each of the two crystallographically independent molecules of the crystal of compound 214 is ~12 Å.

Three cleft molecules 212, 213 and 214 were now in hand. In order to further extend and incorporate, using Schiff base condensation chemistry, a phenanthroline moiety within the arms of these clefts, the isopropyl protecting groups needed to be removed so as to produce the corresponding biscatechols. Of course, as foreshadowed in earlier sections of this thesis, the biscatechols themselves are of interest as potential supramolecular building blocks. The preparation of such compounds and a description of some of their spectral and chemical properties is presented in the following sections.
Figure 4.3 300 MHz $^1$H NMR spectrum of cyclic carbonate 214.
(Spectrum recorded in CDCl$_3$)
Figure 4.4 75.4 MHz $^{13}$C NMR spectrum of cyclic carbonate 214.
(Spectrum recorded in CDCl$_3$)
Figure 4.5  ADEP derived from a single crystal X-ray analysis of cyclic carbonate 214.
4.4 Synthesis of Biscatechols 215 and 216

4.4.1 Deprotection of Precursor Tetraisopropyl Ethers 212 and 214

As noted in the preceding section, four-fold deisopropylation of compounds 212, 213 and 214 was now required in order to obtain the corresponding functionalised cleft molecules each incorporating two free catechol residues. A relatively mild method for the removal of the isopropyl groups was recently established in these laboratories. Thus, aluminium(III) chloride was found to cleave isopropyl aryl ethers in the presence of other sensitive functional groups, to yield the corresponding phenol in very good yields (>95%). Unfortunately, substrates 212 and 214 failed to react under such conditions and only starting material was recovered. In contrast, when compound 213 was subjected to these conditions removal of the isopropyl groups was successful, however as predicted, the acetonide moiety was also removed. This outcome was disappointing since previous workers had not experienced difficulties in deprotecting similarly functionalised compounds.

The deprotection problems mentioned above were overcome by using more traditional methods for the removal of isopropyl groups, that is by employing the aggressive reagent boron(III) chloride. Thus, when compounds 212 and 214 were each treated with boron(III) chloride in dichloromethane at 0 °C biscatechols 215 and 216, respectively, were produced in quantitative yield (Scheme 4.8).
The $^1$H NMR spectrum of compound 215, recorded in $d_4$-methanol, showed no signals consistent with an isopropyl moiety. The signal due to the four equivalent aromatic protons appears as a singlet at $\delta$ 6.53 while the resonances due to the methylene protons appear at $\delta$ 2.78-2.82 (4H), $\delta$ 2.50-2.57 (4H) and $\delta$ 1.87 (8H). Due to exchange with the deuterated solvent, signals arising from the catechol –OH groups were not observed. The $^{13}$C NMR spectrum shows the expected seven signals with that due to the dichlorinated quaternary carbon of the cyclopropane ring appearing at $\delta$ 79.3. The infrared spectrum shows a very broad band at 3320 cm$^{-1}$ corresponding to -OH stretching of the hydroxyls associated with the biscatechol. Confirmation of the structure of 215 was achieved via a single crystal X-ray analysis. The ADEP (Figure 4.6) generated from this study shows that the cleft is very broad, although interestingly, in the solid state compound 215 forms layers connected by hydrogen bonds between independent molecules (Figure 4.7). Both seven-membered rings adopt highly stable chair-like conformations. The 'trans-cavity' distance is slightly larger for cleft 215 (13 Å) than for cleft 214 (12 Å).
Figure 4.6 ADEP derived from a single crystal X-ray analysis of *gem*-dichlorocyclopropane 215, showing intramolecular hydrogen bonding.
Figure 4.7 ADEP derived from a single crystal X-ray analysis of *gem*-dichlorocyclopropane 215 viewed down the b-axis, showing intermolecular hydrogen bonding.
As for biscatechol 215, the $^1$H NMR spectrum of congener 216 (in d$_4$-methanol) was devoid of signals due to isopropyl groups and only signals due to aromatic protons (at $\delta$ 6.54) and the methylene protons [at $\delta$ 2.90-2.99, $\delta$ 2.39-2.46, $\delta$ 2.10-2.17 and $\delta$ 1.31 (triplet, $J$ = 13.4 Hz)] were observed. Seven signals appear in the $^{13}$C NMR spectrum of compound 216 with that due to the carbonyl carbon appearing at $\delta$ 158.5.

For the purposes of comparison, the $^1$H NMR and $^{13}$C NMR spectral data of compounds 212, 214, 215 and 216 have been collated and are shown in Table 4.1. From these data it can clearly be seen that the isopropyl groups have been removed in the latter pair of compounds.

It is obvious that the two biscatechol 215 and 216 were in hand and as such, studies on their capacity to participate in the anticipated complexation processes could begin. The following section details the work associated with these studies.
Table 4.1 Comparison of $^1$H NMR$^a$ and $^{13}$C NMR$^b$ spectral data for compounds 212, 214, 215 and 216.

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<td>153.8</td>
<td>158.5</td>
</tr>
</tbody>
</table>

$^a$ $^1$H NMR data recorded at 300 MHz, in CDCl$_3$ for 212 and 214 and CD$_3$OD for 215 and 216.

$^b$ $^{13}$C NMR data recorded at 75.4 MHz, in CDCl$_3$ for 212 and 214 and CD$_3$OD for 215 and 216.
4.4.2 Efforts to Exploit Cleft 216: Attempted Assembly of Supramolecular Structures

As outlined in Section 1.3.2, catechols are known to chelate metals and form a diverse range of complexes. On this basis biscatechol 216 was reacted with a variety of metals to investigate its binding affinities and capacities to adopt various coordination geometries. Theoretically, this cleft molecule 216 could complex with a single metal atom to form a complex of the type 216.M (Scheme 4.9) or with two metal atoms to give a dimer such as 216$_2$.M$_2$. Of course, polymer formation is another process that cannot be overlooked. Some capacity to exclude such possibilities would involve controlling the concentration of one or both of the relevant reactants. The metals employed in these investigations were nickel(II), copper(II), boron(III) and vanadium(VI).\textsuperscript{12} The reactions were carried out using literature procedures\textsuperscript{12} which involved the careful addition of the relevant metal salt to a solution of the biscatechol 216 in methanol. Such mixing was followed by addition of a base, such as sodium hydroxide, potassium hydroxide or pyridine so as to facilitate formation of more highly coordinating phenoxyanions. Unfortunately, all such reactions yielded insoluble solids that could not be characterised.

Potential problems associated with these reactions arise from the large 'trans-cavity' distance associated with biscatechol 216 which may be too wide for intramolecular complexation, as required in the formation of 216.M. As a consequence polymers could be formed rather readily and such products may account for the insoluble materials observed.
Another reaction of biscatechol 216 that was investigated employed 1,2,4,5-tetra(bromomethyl)benzene (217) in an effort to 'cap' the cleft in a manner related to the literature processes shown in Scheme 4.10.\textsuperscript{13} Tetraphenol 218 has been shown to react with compound 217 to give the macrocyclic compound 219. Similarly, for the calixarene 220, reaction with 217 in the presence of cesium carbonate gives the capped compound 221 (Scheme 4.10). However, when this type of reaction was attempted with biscatechol 216 no caged compound 222 was isolated (Scheme 4.11). This outcome may once again reflect the large 'trans-cavity' distance within compound 216.
Scheme 4.10

Reagents and Conditions: (i) MeCN, K₂CO₃, reflux, 3 d; (ii) MeCN, Cs₂CO₃, reflux, 16 h.

Scheme 4.11

Reagents and Conditions: (i) MeCN, Cs₂CO₃, 3 d.
4.5 Synthesis of Tetraketone Building Blocks

In order for the above-mentioned types of clefts to engage in Schiff base condensations, biscatechols 215 and 216 must first be converted into the corresponding ortho-quinonoid compounds. Oxidation of quinols to the corresponding quinones has been achieved using a wide range of reagents including (diacetoxyiodo)benzene. Indeed, this reagent effects the conversion of catechols into ortho-benzoquinones in generally excellent yield (91-99% yield). In the event, treatment of biscatechols 215 and 216 with this reagent yielded the anticipated bis-ortho-benzoquinones, 223 and 224, respectively, in quantitative yields (Scheme 4.12). Due to the sensitivity of these compounds, purification was not possible. Nevertheless, examination of the ¹H NMR spectra of the crude product mixtures suggested that these compounds were being formed. The resonance due to the 'aromatic' protons appeared at ~δ 6.2 as compared with a chemical shift of ~δ 6.5 observed for the biscatechol precursors. Further, in the infrared spectra of the crude reaction mixture a strong quinonoid carbonyl stretching band was observed at ~1660 cm⁻¹.

![Scheme 4.12](image)

Reagents and Conditions: (i) PhI(OAc)₂, MeOH, rt, 0.5 h.
On this basis crude samples of the oxidation product derived from compound 216 were treated with 5,6-diamino-1,10-phenanthroline (135) both in the presence of the solvent, methanol and under solvent free conditions (Scheme 4.13). Unfortunately, no useful outcome was obtained under such conditions and the bis-ortho-benzoquinone rapidly decomposed, perhaps because of Michael addition of the bisamine to quinone. In order to eliminate the possibility of such undesirable side reactions taking place, attempts were made to engage the bis-ortho-benzoquinone in Diels-Alder reactions to generate adducts containing deconjugated α-dicarbonyl units which would only be capable of participating in Schiff base condensation reactions.

So called domino Diels-Alder reactions have been observed between a suitable bisdiene such as 226 and dimethyl acetylenedicarboxylate (DMAD, 227) (Scheme 4.14).15 The products isolated from this reaction were a 1:1 mixture of compounds 228 and 229, in which the newly formed single bond (shown in red) has been inserted between the two cyclopentadiene residues.15a,b The initial Diels-Alder reaction is intermolecular and the subsequent cycloaddition reaction an intramolecular variant.
Attempts to implement this procedure by reacting bis-ortho-benzoquinone 224 with DMAD in an effort to produce adduct 230 (Scheme 4.15) were unsuccessful. This reaction was also carried out at elevated pressures (19 kbar) but to no avail. Such outcomes are most likely due to the electronic incompatibilities of the diene and dienophile partners.

A related tandem Diels-Alder reaction with the electronically more appropriate bisdienophile 1,4-cyclohexadiene (148) was also attempted at high pressure (19 kbar) in an effort to generate compound 231 (geometry at cyclohexane stereocentres not defined) (Scheme 4.16). This reaction was not successful, however it was noticed that the
biscatechol 216 had been generated, presumably via high pressure promoted hydrogen transfer from the diene to the bis-ortho-benzoquinone 224.

![Scheme 4.16](image)

Reagents and Conditions: (i) 19 kbar, CH\(_2\)Cl\(_2\), 4 h.

In contrast to the foregoing, a cycloaddition reaction between cyclopentene (232) and bis-ortho-benzoquinone 224 was achieved at high pressure (19 kbar) to yield a mixture of what is tentatively assigned as the (bis)Diels-Alder adduct 233 and its two other possible diastereoisomers (see below) in 10% combined yield (Scheme 4.17). The same reaction was also attempted at atmospheric pressure, however no characterisable products were isolated.

\(\Sigma\) This observation led to an investigation into the reaction of 1,4-cyclohexadiene (148) with a variety of quinonoid compounds at high pressure (19 kbar). The outcomes and significance of such studies are described in Chapter 6.
Reagents and Conditions: (i) 19 kbar, CH₂Cl₂, acetone, 4 h.

The Diels-Alder adduct 233 shown in Scheme 4.17 is just one of three possible diastereomers that could arise from this reaction. In compound 233, the five-membered rings are orientated in an anti-relationship and have been attached to the original bisquinonoid scaffold in two distinct Diels-Alder reactions. One of these reactions involves the endo-transition state and the other the exo-transition state, hence this adduct is described as the endo-exo product. Based on this analysis, the two other possible products are the more symmetrical exo-exo and endo-endo adducts 234 and 235, respectively. Spectroscopic analysis of the reaction mixture suggested that all three of these compounds, that is 233-235, had been formed and they proved impossible to separate from one another by normal chromatographic methods.
Chapter 4

The $^1$H NMR spectrum of the material presumed to contain a mixture of compounds 233-235 showed a complex set of peaks in the region $\delta$ 1.0-2.9 and a multiplet at $\delta$ 3.19-3.21 which is assigned to the bridgehead protons flanked by the carbonyl and alkene moieties. In the $^{13}$C NMR spectrum (Figure 4.8, for expansions of this spectrum see Appendix A.1.4), most signals are either doubled up or tripled up. The signals due to the carbonyls of the diketone moiety appear at $\delta$ 190.5 and $\delta$ 190.6 while the resonances due to the carbonyl carbon are observed at $\delta$ 152.6 and $\delta$ 152.8. The signals corresponding to the double bond carbons can be seen at $\delta$ 139.2, $\delta$ 139.5 and $\delta$ 139.9 while those due to the oxygenated sp$^3$-hybridised carbon appear at $\delta$ 89.7, $\delta$ 90.1 and $\delta$ 90.2. The signal corresponding to the bridgehead protons adjacent to the double bond appear at $\delta$ 60.1, $\delta$ 60.3 and $\delta$ 60.4, while the other bridgehead protons appear at $\delta$ 42.1, $\delta$ 42.3 and $\delta$ 42.4. The remaining methylene carbons give rise to signals at $\delta$ 27.5, $\delta$ 27.6, $\delta$ 29.6, $\delta$ 30.5, $\delta$ 30.6, $\delta$ 31.5, $\delta$ 31.6 and $\delta$ 31.7.\footnote{Strictly speaking these $^1$H and $^{13}$C NMR data do not exclude the possibility that the 'mixture' is, in fact, comprised of just the unsymmetrical adduct 233 and only one of the isomers 234 or 235. However, since the endo-exo compound 233 must be present in the reaction mixture, it is hard to explain why there should be selective formation of 234 over 235 or vice versa.} The infrared spectrum of the mixture still shows two carbonyl stretching bands at 1797 cm$^{-1}$ (carbonate) and 1728 cm$^{-1}$ (diketone). The 70 eV mass spectrum shows a molecular ion at $m/z$ 544 and the molecular formula was confirmed by high resolution mass spectrometry ($C_{33}H_{36}O_7$).
Figure 4.8 75.4 MHz $^{13}$C NMR spectrum of the mixture of Diels-Alder adducts 233, 234 and 235.
(Spectrum recorded in CDCl$_3$) (For expansions see Appendix A.1.4)
It was now time to subject these compounds to the pivotal Schiff base condensation in order to generate molecular clefts possessing 1,10-phenanthroline residues at the terminus of each arm. Details of efforts along these lines are provided in the subsequent section.

4.6 Synthesis of an Extended Molecular Cleft via Schiff Base Condensation

4.6.1 Synthesis of Phenanthroline Ligands

In Section 1.3.1 a brief introduction was given to the diverse range of ligands that could be synthesised from 1,10-phenanthroline (58) and also the wide variety of functions these ligands have. It was envisaged that 1,10-phenanthroline would make a good ligand to attach to the arms of cleft molecules such as 233-235, not only to extend the depth of the cavity but also to confer potential functional properties to the resulting conjugate. To these ends various 1,10-phenanthroline derivatives such as the 5,6-diamino compound 135 and dione 236 were synthesised. These compounds were prepared from 1,10-phenanthroline (58) following literature procedures, however this synthesis proved capricious. Nevertheless the spectral data derived from each of these compounds were identical, in all respects, with those reported in the literature.
5,6-Diamino-1,10-phenanthroline (135) was initially targeted for synthesis as this has been shown to readily undergo Schiff base condensation with a variety of diketones.\(^{17}\) 1,10-Phenanthroline-5,6-dione (236) was also synthesised so that a deeper cleft could be made through initial Schiff base condensation with 1,2,4,5-tetraminobenzene (237) to give the extended ligand 238 (Scheme 4.18).\(^{18}\) The latter compound could then undergo a second double-barrelled Schiff base condensation with cleft molecules such as tetraketone 233 to give a series of related systems with much deeper cavities. Unfortunately, the extended ligand 238 could not be isolated from the relevant reaction mixtures and so the focus of the remaining work described here was on exploiting the 5,6-diamino derivative 135.

Scheme 4.18

4.6.2 Schiff Base Condensation of Clefts 233, 234 and 235 with Ligand 135

There are numerous procedures reported in the literature for effecting Schiff base condensation reactions,\(^{17,18}\) however the most successful with regard to the reaction of the mixture of compounds 233-235 with diamine 135, involved the application of acetic acid\(^{20}\) in refluxing ethanol (Scheme 4.19).
Scheme 4.19

Reagents and Conditions: (i) EtOH, AcOH, reflux, 16 h.

The presence of the anticipated Schiff base product 239 was detected by FAB mass spectral analysis, which revealed the expected molecular ion at m/z 893 (M+H)+. However, all attempts at purifying this component of the crude reaction mixture were unsuccessful. Given that a mixture of compounds 233, 234 and 235 was subjected to these conditions the corresponding mixture of adducts of 239 should be obtained as well. The 1H NMR spectrum of the crude mixture shows peaks in the region of δ 7.0-9.0 (~12H) that could correspond to the phenanthroline moiety of the cleft, while a broad set of peaks in the δ 1.0-3.0 region (~36H) may be due to the protons associated with the upper portion of the cleft.

Various chromatographic and other manipulations of the crude reaction mixture provided small samples of solid materials that could be recrystallised and were then subjected to single crystal X-ray analysis. Whilst such processes did not lead to clean samples of any of the diastereoisomers associated with cleft 239, several interesting compounds were isolated. Thus, the crystalline phenanthroline derivatives 240 and 241 were obtained and details of the resulting X-ray analyses are provided in Figures 4.9 and 4.10 (respectively) as well as Appendix A.1.5 and A.1.6.
Figure 4.9 ORTEP derived from a single crystal X-ray analysis of phenanthroline derivative 240.
Figure 4.10 Perspective diagram derived from a single crystal X-ray analysis of phenanthroline derivative 241.
Compound 240 is presumably formed via Schiff base condensation of 5,6-diamino-1,10-phenanthroline (135) with 5,6-dione 236 (Scheme 4.20) the latter probably being present in trace amounts and generated during the preparation of the 5-nitro-1,10-phenanthroline (242) precursor to 135. Compound 240 has been synthesised previously\textsuperscript{21} (and is used as a ligand in organometallic chemistry), although the X-ray crystal structure has not been reported. Bislactam 241 is probably formed by condensation of compound 135 and diacid 243 (Scheme 4.20) with the latter being formed by oxidative cleavage of 1,10-phenanthroline (58), presumably in the initial step shown in Scheme 4.20 (and carried through the reaction sequence leading to bislactam 241).\textsuperscript{22}

As the Schiff base condensation reaction shown in Scheme 4.19 was carried out on a small scale (5 mg of a mixture of compounds 233, 234 and 235 used), the isolation of compounds 240 and 241, as single crystals, certainly does not represent the complete spectrum of products obtained from the reaction mixture. Clearly, future work must be directed towards the large scale production of compounds 233-235, their purification and their independent subjection to Schiff base type condensation with pure samples of 5,6-diamino-1,10-phenanthroline (135).
Scheme 4.20

Reagents and Conditions: (i) HNO₃, H₂SO₄, reflux, 1 h; (ii) NH₂OH·HCl, KOH, EtOH, 50 °C, 1 h; (iii) 10% Pd/C, NH₂NH₂·xH₂O, EtOH, 65 °C, 1 h; (iv) compound 236, EtOH, AcOH, reflux, 16 h; (v) compound 243, EtOH, AcOH, reflux, 16 h.
4.7 Summary and Future Objectives

This chapter has detailed the synthesis of some novel molecular clefts, namely the *gem*-dichlorocyclopropanated biscatechol 215, the cyclic carbonate based biscatechol 216 and the Diels-Alder adducts 233, 234 and 235. The synthesis of these clefts began with the commercially available catechol (4) that served as the starting material for a series of now reliable manipulations to ultimately generate benzosuberone 172. This last compound was then subjected to McMurry and pinacolic coupling reactions, each using low valent titanium species to furnish the two coupled products 209 and 211. Further elaboration at the hinge of each of these molecules via a dichlorocarbene addition to alkene 209 and cyclic carbonate formation from the diol in 211, then produced compounds 215 and 216, respectively. Removal of the isopropyl moieties with boron(III) chloride followed by oxidation with (diacetoxyiodo)benzene led to compounds 223 and 224, respectively. High pressure promoted Diels-Alder reaction with cyclopentene was carried out on cleft 224 to yield the mixture of adducts 233, 234 and 235. Finally, this mixture of clefts was further elaborated through a Schiff base condensation with 5,6-diamino-1,10-phenanthroline (135) to give trace amounts of a mixture of extended phenanthroline clefts 239.

Continuation of this project should focus, in the first instance, on the isolation and rigorous characterisation of compound 239. Complexation studies on this Schiff base condensation product, so as to determine the types of complexes capable of being formed, could then be undertaken. In principle, a range of interesting mono-, di- and/or poly-meric species (see Figure 4.11 for some possibilities) could be generated. The synthesis of various organometallic species should also be investigated as well as the possible complexation of organic molecules that take advantage of the π-stacking ability of the aromatic moieties within cleft 239 (Figure 4.11).
Another avenue to be explored is the functionalisation of the cleft 239, using Sauvage’s methodology, so as to give a range of derivatives, such as 244, incorporating the Hamilton type ligands (Scheme 4.21). The complexation properties of these extended clefts could then be investigated in order to establish if the proposed catalysis (Section 1.5) of photochemical reactions between bound dicarboxylic acids could actually be realised.
4.8 References


(6) Hassner, A.; Stumer, C. *Organic Synthesis Based on Name Reactions and Unnamed Reactions*, Elsevier Science Ltd, New York, **1994**.


Chapter 5. Synthesis of Molecular Clefts Based Upon Indan-2-one 173

5.1 Overview

As mentioned previously, compounds containing odd-sized carbocyclic rings especially those incorporating five or seven carbons, represent useful building blocks for the assembly of molecular clefts. This chapter outlines the synthesis of a five-membered ring system, namely indan-2-one 173, from catechol (4). Reductive homocoupling of this species afforded a compound expected to have a small enough cleft such that some interaction between the residues at the tips of the two arms of this system should be possible and thereby initiate chemical transformations similar to those observed by Walter for bis-para-benzoquinone 129 (Section 1.4).\textsuperscript{1}
5.2 Synthesis of Indan-2-one 173

Initially it was considered that the target indan-2-one 173 could be synthesised in a similar manner to that used in the preparation of the seven-membered analogue 172. Thus, using the common intermediate 200 (Scheme 5.1), it was thought insertion via the iron(II) complex 245, of carbon monoxide would deliver the target system 173.

![Scheme 5.1](image)

Literature precedent\(^2\) for this type of reaction exists, as evidenced by the observation that sequential treatment of the iron(III) complex 246 of bis(bromomethyl) 247 with Fe\(_2\)(CO)\(_9\) then cerium(IV) or aluminium(III) chloride produces indan-2-one (248) in 90% yield (Scheme 5.2). This type of conversion most likely involves addition of carbon monoxide to the starting complex 246 followed by ring closure to give the product 248.
All attempts to apply literature methods for the formation of the iron(III) complex 245 (Scheme 5.1) from precursor 200 were unsuccessful, perhaps due to the competing binding of iron(III) to the ether oxygens of the protected catechol moiety.

A revised strategy for obtaining indan-2-one 173 was devised, again beginning with catechol (4) (Scheme 5.3). Thus, the previously prepared bisisopropyl ether 1843 was subjected to a silver(I) mediated monoiodination reaction to give iodo derivative 249 in quantitative yield. The $^1$H NMR spectrum of compound 249 showed a doublet at $\delta$ 6.64 ($J = 8.9$ Hz) which is as expected for the aromatic proton at C6. The signals due to the two remaining aromatic protons, which are adjacent to the iodine, appear as a multiplet at $\sim \delta$ 7.18. In the 70 eV mass spectrum the expected molecular ion is observed at $m/z$ 320, while the high resolution mass spectrum confirms the molecular formula, $C_{12}H_{17}I_{2}O_2$.  

Scheme 5.2

Reagents and Conditions: (i) $Fe_2$(CO)$_9$ or $Na_2Fe$(CO)$_4$ (ii) $AlCl_3$, $C_6H_6$, rt, 2 h.
Reagents and Conditions: (i) 2-bromopropane, K$_2$CO$_3$, DMF, 100 °C, 8 h; (ii) I$_2$, AgOAc, CHCl$_3$, rt, 10 h; (iii) allylmagnesium chloride, Pd(PPh$_3$)$_4$, THF, reflux, 1 h; (iv) AcOH, t-BuOH, NaIO$_4$, KMnO$_4$, H$_2$O, 0 °C, 1 h; (v) oxalyl chloride, pyridine, C$_6$H$_6$, rt, 0.5 h; (vi) CH$_2$N$_2$, C$_6$H$_6$, 0 °C → rt, 20 h; (vii) Rh$_2$(OAc)$_4$, CH$_2$Cl$_2$, rt, 15 mins.

Compound 249 was reacted with allylmagnesium chloride and tetrakis(triphenylphosphine)palladium(0) [Pd(PPh$_3$)$_4$] to give the expected cross coupling product, namely alkene 250 in quantitative yield. In the $^1$H NMR spectrum of compound 250, the signals corresponding to the vinylic protons appear as multiplets at δ 5.90-5.99 (methine proton) and δ 5.03-5.09 (methylene protons). The signal due to the benzylic protons appears as a doublet at δ 3.30 ($J = 6.6$ Hz). The aromatic protons give rise to a complex set of signals in the range δ 6.68-6.85. The usual isopropoxy resonances are observed at δ 4.38-4.49 (multiplet), δ 1.32 and δ 1.31 (2 x doublets, $J = 6.1$ Hz, 6H each).
In the next step of the reaction sequence alkene 250 was subjected to a modified Lemieux-von Rudloff oxidation4 (NaIO4, KMnO4) in the presence of acetic acid.5 Acetic acid was added to buffer the reaction mixture and thereby slow migration of the double bond into conjugation with the aromatic ring, a situation which would lead to the benzoic acid rather than the desired aryl acetic acid 251. Under such conditions, target 251 was afforded in 86% yield and all the derived spectral data were consistent with the assigned structure. The signal at δ 3.55 (singlet) in the 1H NMR spectrum, arises from the benzylic methylene protons while that observed at δ 40.5 in the 13C NMR spectrum is assigned to the associated carbon and suggests that the assigned structure 251 is correct.

Chatterjee6 had used the dimethoxy derivative 254, of compound 251, in his synthesis of (±)-norcoralydine, whereby conversion of the former aryl acetic acid (Scheme 5.4) into the corresponding diazoketone 255 was followed by treatment with trifluoroacetic acid to effect cyclisation so as to form indan-2-one 256 in 70% yield.

![Scheme 5.4](image)

Reagents and Conditions: (i) (COCl)2, C6H6 then CH2N2, Et2O, (C2H5)3N; (ii) CF3CO2H

To the same ends, acid 251 was converted into the corresponding acid chloride 252 using oxalyl chloride and pyridine (98% yield) (Scheme 5.3). This latter compound was immediately subjected to reaction with diazomethane (CAUTION: explosive!), following the Mander procedure,7 to give the diazoketone 253 (98% yield) as a bright orange oil. In
the $^1$H NMR spectrum of compound 253 the signal due to the methine proton adjacent to the diazo moiety appears as a singlet at $\delta$ 5.11, while the signal corresponding to the benzylic methylene protons appears as a singlet at $\delta$ 3.52. In the $^{13}$C NMR spectrum the signal due to the C-N$_2$ carbon appears at $\delta$ 54.9 while that for the benzylic methylene is observed at $\delta$ 47.8. In the infrared spectrum an absorption band indicative of a diazo compound was observed at 2103 cm$^{-1}$.

As the diazoketone 253 was in hand, several methods for effecting its cyclisation to indan-2-one 173 were examined, including those developed by Chatterjee$^6$ and using trifluoroacetic acid. Eventually, the readily available rhodium(II) acetate dimer$^8$ [Rh$_2$(OAc)$_4$] proved the most effective agent for carrying out the desired cyclisation and indan-2-one 173 was obtained in quantitative yield (Scheme 5.3). The $^1$H NMR spectrum of the indan-2-one 173 shows the expected four signals with that due to the methylene protons of the five-membered ring appearing as a singlet at $\delta$ 3.49. In the $^{13}$C NMR spectrum seven signals were observed with that due to the carbonyl carbon appearing at $\delta$ 215.8. The infrared spectrum showed a band at 1750 cm$^{-1}$, which is characteristic of the stretching frequency of the carbonyl moiety in a cyclopentanone.

With compound 173 now available, its reductive coupling to give the corresponding alkene and pinacol was pursued. Details are provided in the following section.
5.3 Pinacol Coupling of Indan-2-one 173

5.3.1 Titanium Mediated Reactions

Several methods for coupling indan-2-one 173 were examined and such studies began with the titanium(IV) mediated McMurry and pinacol coupling reactions. No McMurry type olefins were observed in any of the reaction mixtures, however the pinacol 257 (Scheme 5.5) was isolated from the titanium(IV) and magnesium amalgam mediated reaction.\(^9\) As in the case of the reaction involving benzosuberone 172 (Section 4.2), the yield of this reaction was extremely variable (6-32% yield).

\[ \text{Scheme 5.5} \]

Reagents and Conditions: (i) Mg, HgCl\(_2\), TiCl\(_4\), THF, 0 °C, 16 h or (ii) Sml\(_2\), THF, reflux, 16 h.

In the \(^1\)H NMR spectrum of pinacol 257, which was obtained as a yellow oil, the signal due to the methylene protons of the five-membered ring is split into two sets of doublet of doublets which appear at \(\delta\) 3.16 \((J = 16.0\) and 6.0 Hz) and \(\delta\) 2.81 \((J = 16.0\) and 3.1 Hz).\(^8\) Seven signals were observed in the \(^{13}\)C NMR spectrum of compound 257.

\(^8\) The non-equivalence of these smaller couplings, while surprising, is real and, at the present, no satisfactory explanation can be advanced to account for this.
including diagnostic ones at δ 73.7 (corresponding to the quaternary carbon possessing attached hydroxyls) and δ 42.6 (corresponding to the sp²-hybridised carbons in the five-membered rings). The infrared spectrum showed a band at 3451 cm⁻¹, which corresponds to the stretching frequency of an alcohol moiety.

Due to the fickle nature of these low valent titanium mediated couplings, alternative methods for obtaining pinacol 257 were examined.

5.3.2 Samarium(II) Mediated Reactions

There is abundant literature on the samarium(II) mediated pinacolic coupling of ketones¹⁰ although it is clear that the presence of a proton source should be avoided since this tends to produce the simple alcohol reduction product in preference to the pinacol. Application of the appropriate reaction conditions to indan-2-one 173 (Scheme 5.5) produced the desired pinacol 257 and in 40% yield. The material obtained by this means was identical in all respects, with the samples obtained earlier. Again the yield (18-40% yield) was variable and depended on the purity of the samarium(II) being used. Freshly prepared samarium(II) iodide⁹ is recommended to achieve the best possible yields.

⁹ Samarium(II) iodide was prepared following literature procedures¹⁰ from either the samarium powder or ingots of samarium metal and diiodoethane (freshly washed and dried). Solutions of samarium(II) iodide are light sensitive as well as extremely oxygen sensitive so these were stored under an argon or nitrogen atmosphere. All reactions were carried out under an atmosphere of nitrogen and all glassware was rigorously dried.
5.4 The Synthesis of a Novel Molecular Cleft Containing Five-Membered Rings

As in the seven-membered series, the pinacol 257 was initially protected as the corresponding cyclic carbonate 258 and triphosgene\(^\text{11}\) was again the preferred reagent for effecting the conversion. By such means, the cyclic carbonate 258 was afforded in 82% yield (Scheme 5.6).

![Scheme 5.6](image)

**Scheme 5.6**

*Reagents and Conditions: (i) (CCl\(_3\))\(_2\)CO, pyridine, CH\(_2\)Cl\(_2\), -70 °C → rt, 16 h.*

In the \(^1\)H NMR spectrum of carbonate 258, the signals due to the methylene protons of the five-membered ring appear at δ 3.08 (doublet of doublets, \(J = 17.1\) and 2.8 Hz) and δ 3.31 (doublet of doublets, \(J = 17.1\) and 6.3 Hz)\(^3\) as compared with δ 2.81 and δ 3.16 for the equivalent protons in precursor 257. In the \(^{13}\)C NMR spectrum (Figure 5.1), the signal corresponding to the carbonate carbon appears at δ 150.4 and in the infrared spectrum the absorption band corresponding to the stretching frequency of the cyclic carbonate carbonyl moiety appears at 1773 cm\(^{-1}\).

\(^3\) The non-equivalence of these smaller couplings, while surprising, is real and, at the present, no satisfactory explanation can be advanced to account for this.
**Figure 5.1** 75.4 MHz $^{13}$C NMR spectrum of cyclic carbonate 258. (Spectrum recorded in CDCl$_3$)
Due to the success achieved in the analogous seven-membered series (Scheme 4.9), a cleavage of the isopropyl moieties within compound 258 was attempted using boron(III) chloride (Scheme 5.7). The targeted bisatechol 259 was not isolated, rather, a complex mixture of products was obtained. In the $^1$H NMR spectrum of the crude reaction mixture a signal at $\delta 6.72$ is attributed to the aromatic protons, while resonances at $\delta 3.32-3.37$ and $\delta 2.94-3.00$ suggest that the methylene protons of the five-membered ring are still intact. However, the $^{13}$C NMR and infrared spectra of the same material suggest the carbonate group has also been cleaved under these reaction conditions. This unexpected and disappointing outcome prevented any further investigations in this area during the term of the author's PhD studies.

Due to this problem in the latter stages of the synthesis a functional molecular cleft containing a five-membered ring was not achieved. The following section suggests future work which might address these problems.
5.5 Future Objectives

As noted in the preceding section, only the isopropyl protected and five-membered ring containing cleft molecule 258 could be obtained in the time available to the author. The selective deprotection of this compound to produce the biscaltehol 259 should be achievable under milder conditions that, once found, would deliver a highly interesting cleft molecule. If such conditions cannot be found, then use of another protecting group at the hinge of the cleft could be employed. Introduction of a different moiety at the hinge would also enable the investigation of the difference, if any, between the 'trans-cavity' distances of such species. A possible protecting group could be the di-tert-butylsilylene group\textsuperscript{12} as shown in structure 260 (Figure 5.2), which is usually only cleaved in the presence of fluoride ions and therefore should be stable to boron(III) species required for the removal of the isopropyl groups. Figure 5.2 highlights the capacity of compounds such as 259 and 260 to adopt cleft like shapes which should encourage future work in this area.

![Figure 5.2 Proposed Chem 3D™ representations of compounds 259 and 260.](image-url)
Once this protecting group dilemma has been resolved oxidation of biscatechols such as 259 to the corresponding bis-ortho-benzoquinone 261 (Scheme 5.8) can be undertaken. Studies could then be carried out to determine if compound 261 will engage in intramolecular \([2\pi+2\pi]\) photocycloaddition and [3,3]-sigmatropic reaction sequences to afford tetraketone 262, which represents an ideal scaffold for two-fold Schiff base condensation reactions of the type portrayed in Scheme 5.8.

Scheme 5.8
5.6 References


6.1 Overview

The studies described in this chapter evolved from the observation that a high pressure promoted reaction between 1,4-cyclohexadiene (148) and bis-ortho-benzoquinone 224 produced the biscatechol 216 instead of the desired tandem Diels-Alder adduct 231 (Scheme 6.1). Due to the potential synthetic utility of this type of process, several other compounds were reacted with 1,4-cyclohexadiene (148) in order to examine the scope and limitations, as well as the mechanism, of this uncatalysed hydrogen transfer process.¹
**Scheme 6.1**

Reagents and Conditions: (i) 8.8 eq 1,4-cyclohexadiene (148), CH$_2$Cl$_2$, acetone, 19 kbar, 4 h.

**6.2 Introductory Comments**

Hydrogen transfer processes play an important role in coal liquefaction and are probably also significant transformations in certain biochemical dehydrogenations.$^1$ Most of the relevant reactions described in the literature use catalysts to effect this transfer and operate under either homogeneous or (more commonly) heterogeneous conditions.$^2$ Common catalysts include palladium on carbon, Raney nickel, palladium black and iron(III) chloride,$^2$ as well as some organic compounds such as porphyrins and phthalocyanine.$^3$ Typically these reactions are undertaken in solvents such as toluene, benzene and 1,4-dioxane which exert a minimal interaction with the catalyst and do not
therefore, deactivate it. Several uncatalysed hydrogen transfer processes are known, however these generally require the use of very high temperatures (80-300 °C) and thus limit the type of substrates capable of participating. A recent review\(^{1b}\) of these types of thermally promoted reactions highlights the use of 9,10-dihydroanthracene (264) as a hydrogen donor to alkenes such as 265 which is typical of the sort of acceptor molecule involved. The products of this process are anthracene (266) and arylalkane 267 (Scheme 6.2).

![Scheme 6.2](image)

**Scheme 6.2**

*Reagents and Conditions:* (i) diphenyl ether, 280-320 °C.

Quinones such as para-benzoquinone (31) can also accept hydrogen from various dihydroaromatics [e.g. 1,4-dihydronaphthalene (268)] and their heteroatom counterparts to produce the corresponding hydroquinone (e.g. 269) (Scheme 6.3).\(^1\)

![Scheme 6.3](image)

**Scheme 6.3**

*Reagents and Conditions:* (i) anisole, 130 °C
Another example is the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (270) for effecting dehydrogenation of both simple and complex hydroaromatic carbocyclic compounds as illustrated by the conversion of 1,2,3,4-tetrahydronaphthalene (271) into naphthalene (272) (78% yield) (Scheme 6.4).\textsuperscript{4a} The ability of DDQ to effect such dehydrogenations in the presence of other potentially oxidisable functional groups such as alcohols and phenols serves to highlight the utility of such high potential quinones in chemical synthesis. Chloranil (273) represents a further example of a powerful quinone capable of engaging (as acceptor) in this type of hydrogen transfer.\textsuperscript{4b} One of the key features associated with the two conversions just described as well as related ones, is that the focus is often on the aromatisation of the donor molecule and not on the accompanying reduction of the acceptor compound. In contrast, the work described in this chapter was more focussed on the fate of the acceptor quinone rather than the dihydroaromatic donor.

\begin{center}
\begin{tikzpicture}
\node[anchor=west] (a) at (0,0) {271};
\node[anchor=west] (b) at (2,0) {270 R=CN};
\node[anchor=west] (c) at (4,0) {273 R=Cl};
\node[anchor=west] (d) at (6,0) {272};
\node[anchor=west] (e) at (2,1) {\textcolor{red}{X}};
\draw (a) -- (b);
\draw (b) -- (c);
\draw (c) -- (d);
\end{tikzpicture}
\end{center}

\textit{Scheme 6.4}

\textit{Reagents and Conditions:} (i) \textcolor{red}{C}_6\textcolor{red}{H}_6, 80 \textdegree{}C, 5 h.

1,4-Cyclohexadiene (148) is a good hydrogen donor and has been used extensively in the presence of various catalysts to effect hydrogen transfer reactions. Further, the same compound has also been used in an uncatalysed hydrogen transfer reaction with \textit{para-}
benzoquinone (31) and it was reported that the dehydrogenation of diene 148 readily took place at 80 °C with complete conversion to benzene and 1,4-hydroquinol being observed after 24 hours.\textsuperscript{1c} There appear to be no reports in the literature suggesting that this donor has ever been used in an uncatalysed reaction at room temperature, or at elevated pressures. In view of this situation, and the potential utility of an uncatalysed hydrogen transfer reaction that can take place at room temperature, the results of a study of the reaction between 1,4-cyclohexadiene (148) (donor) and various quinone acceptors under such conditions are presented here.

6.3  \textbf{Reactions of Various Quinones with 1,4-Cyclohexadiene (148) at 19 kbar}

As described earlier, the reaction between 1,4-cyclohexadiene (148) and bis-ortho-benzoquinone 224 (Scheme 6.1) was carried out at 19 kbar in a dichloromethane/acetone (5:1) solvent mixture. The originally targeted tandem Diels-Alder product 231 was not observed, instead biscatechol 216 was formed. It appeared that a high pressure promoted and uncatalysed hydrogen transfer reaction had taken place and this led to an investigation of the capacity of 1,4-cyclohexadiene (148) to engage in the same way with other acceptor molecules, especially quinones.

The results of this investigation are summarised in Table 6.1. All reactions were allowed to run for four hours then concentrated without heating under reduced pressure to afford a residue which was then analysed by \textsuperscript{1}H NMR spectroscopy. All of the potential hydrogen acceptor compounds were commercially available, except 1,10-phenanthroline-5,6-dione (236) which was prepared via known procedures.\textsuperscript{5}
Table 6.1 Outcomes of Uncatalysed Hydrogen Transfer Reactions from 1,4-Cyclohexadiene (148) to Various Acceptor Molecules Conducted at 19 kbar

<table>
<thead>
<tr>
<th>Entry #</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield / % Conversion</th>
<th>Conditions(^a)</th>
<th>(-E_{1/2}) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="274" /></td>
<td>no reaction</td>
<td>-</td>
<td>I</td>
<td>1.27, 1.74(^c)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="275" /></td>
<td>no reaction</td>
<td>-</td>
<td>I</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="276" /></td>
<td>no reaction</td>
<td>-</td>
<td>I</td>
<td>1.27, 2.10(^d)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="277" /></td>
<td>no reaction</td>
<td>-</td>
<td>I</td>
<td>1.04, 1.76(^e)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="278" /></td>
<td><img src="image" alt="279" /></td>
<td>96% / 100%</td>
<td>I, III</td>
<td>0.20, 0.67(^f)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>96% / 100%</td>
<td></td>
<td>0.0478</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="280" /></td>
<td>no reaction</td>
<td>-</td>
<td>I</td>
<td>0.31, 0.96(^f)</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="280" /></td>
<td><img src="image" alt="281" /></td>
<td>100% / 50%</td>
<td>II</td>
<td>0.31, 0.96(^f)</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="31" /></td>
<td><img src="image" alt="269" /></td>
<td>89% / 66%</td>
<td>I, II</td>
<td>0.15, 0.81(^f)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>96% / 100%</td>
<td></td>
<td>0.92(^h)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.40, 1.24(^i)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.52(^j)</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="282" /></td>
<td>no reaction</td>
<td>-</td>
<td>I, II</td>
<td>0.55, 1.17(^f)</td>
</tr>
<tr>
<td>Entry #</td>
<td>Starting Material</td>
<td>Product</td>
<td>Yield / % Conversion</td>
<td>Conditions&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(-E_{1/2})&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>---------</td>
<td>------------------</td>
<td>---------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>10</td>
<td><img src="283" alt="Image" /></td>
<td>no reaction</td>
<td>-</td>
<td>I,II</td>
<td>0.25&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td><img src="284" alt="Image" /></td>
<td><img src="285" alt="Image" /></td>
<td>90% / 100%</td>
<td>I</td>
<td>0.30, 0.76&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td><img src="236" alt="Image" /></td>
<td><img src="286" alt="Image" /> + SM</td>
<td>80% / 50%</td>
<td>I</td>
<td>0.45, 1.25&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td><img src="287" alt="Image" /></td>
<td><img src="288" alt="Image" /> + SM</td>
<td>89% / 50% / 89% / 50%</td>
<td>I, II</td>
<td>0.84&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>14</td>
<td><img src="278" alt="Image" /></td>
<td><img src="290" alt="Image" /></td>
<td>91%</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td><img src="31" alt="Image" /></td>
<td><img src="291" alt="Image" /></td>
<td>81%</td>
<td>IV</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Reagents and Conditions: (I) 8.8 eq 1,4-cyclohexadiene (148), CH<sub>2</sub>Cl<sub>2</sub>, 19 kbar, 4 h; (II) 60 eq 1,4-cyclohexadiene (148), CH<sub>2</sub>Cl<sub>2</sub>, 19 kbar, 4 h; (III) 8.8 eq 1,4-cyclohexadiene (148), CH<sub>2</sub>Cl<sub>2</sub>, vitamin E, 19 kbar, 4 h; (IV) 8.8 eq 1,3-cyclohexadiene (289), CH<sub>2</sub>Cl<sub>2</sub>, 19 kbar, 4 h.

<sup>b</sup> Polarographic data for reduction of quinones listed as: solvent, supporting electrolyte (0.1 M), reference electrode, temperature (°C). Halfwave potentials are given in volts (V).<sup>5</sup>

<sup>c</sup> DMF, TEAI, Hg pool, 25 °C.
<sup>d</sup> DMF, TBAP, Ag-AgCl, 19 °C.
<sup>e</sup> DMSO, TBAP, SCE, 25 °C.
<sup>f</sup> DMF, TEAP, Ag-AgCl, 19 °C.
<sup>g</sup> DMF, TBAF, SCE, 22 °C.
<sup>h</sup> DMF, TBAP, Hg pool, 25 °C.
<sup>i</sup> DMSO, TEAP, SCE, 25 °C.
<sup>j</sup> MeCN, TEAP, SCE, 25 °C.
<sup>k</sup> MeCN, TBAP, SCE, 25 °C.
Alkenes 274 and 275 (Entry 1 and 2) are known to undergo metal catalysed hydrogenation under conventional conditions. However upon reaction at 19 kbar with just diene 148, no products were isolated and only starting material was recovered. Diketones 276 and 277 (Entry 3 and 4) were chosen to determine if the reactions described here were restricted to quinonoid compounds. The lack of any reaction of these substrates tends to support such a conclusion. So, in contrast to the foregoing results, ortho-naphthoquinone (278) (Entry 5) reacted with diene 148 to give the corresponding catechol 279 which was isolated in quantitative yield. The spectral data derived from this material were identical with those reported in the literature. Gas chromatographic analysis of such reaction mixtures before and after subjection to 19 kbar was used to establish that benzene was being formed as a stoichiometric coproduct in these processes. A reaction in which vitamin E (Entry 5, conditions III), an organic soluble radical scavenger, was added was also undertaken. Given the lack of influence of the additive on the outcome of the reaction, a free radical pathway is probably not operative.

The reactions were sometimes sensitive to the molar excess of 1,4-cylohexadiene (148) used. Thus para-naphthoquinone (280) (Entry 6) was also subjected to the high pressure conditions with 8.8 equivalents of 148 but no reaction was observed. In contrast, when 60 equivalents of diene 148 were used, a 1:1 mixture of 280 and the corresponding hydroquinone 281 was produced (Entry 7). This result establishes that para-quinones do engage in hydrogen transfer but seemingly at a much slower rate than their ortho-quinonoid counterparts. When para-benzoquinone (31) (Entry 8) was subjected to reaction with 8.8 equivalents of diene 148, a 1:1.4 mixture of quinone 31 and hydroquinone 269 was obtained. However, when 60 equivalents of 148 were used, complete conversion to the hydroquinone 269 was achieved and in quantitative yield. 9,10-Anthraquinone (282)
(Entry 9) was also subjected to reaction with 8.8 and 60 equivalents of 148 but in each case only starting material was recovered.

These outcomes correlate with the reduction potentials (-E_{1/2}) of *para*-quinones 31, 280 and 282 which are 0.15, 0.31 and 0.55 V, respectively. Thus, compound 272 has the lowest reduction potential and was, not surprisingly, the most reactive under these conditions. *para*-Naphthoquinone 280 has a reduction potential of 0.31 V and is less reactive, however compound 280 does show some reactivity at higher concentrations of 148. On the other hand 9,10-anthraquinone (282) which has the highest potential did not react at all. Surprisingly, 2-hydroxy-1,4-naphthoquinone (283) (Entry 10), which has a reduction potential of 0.225 V [smaller than that of the reactive *para*-benzoquinone (280) (-E_{1/2} = 0.31 V)] also failed to react. This outcome may reflect solubility problems at the high pressures involved rather than any inherent lack of reactivity of substrate 283.

In order to further test the proposed relationship between reduction potential and reactivity, various *para*-quinones were compared to their *ortho*-quinonoid counterparts. For example the reduction potential of *ortho*-naphthoquinone 278 is 0.20 V, while that for *para*-naphthoquinone 280 is 0.31 V, consistent with the observation that the former compound is more reactive than the latter in its reaction with diene 148 (compare entries 5 and 7). As expected, analogous comparison of the reactions of 9,10-phenanthrenequinone 284 (0.30 V) and 9,10-anthraquinone (282) (0.55 V) also reveals this correlation (Entries 11 and 9). The lack of reactivity of ethyl cinnamate 274 (Entry 1), camphorquinone 276 (Entry 3) and benzil 277 (Entry 4) is not surprising in light of their high reduction potentials.

When 1,10-phenanthroline-5,6-dione (236) (Entry 12) was subjected to reaction with diene 148 at 19 kbar, a 1:1 mixture of the 5,6-dihydroxy-1,10-phenanthroline (286)
and the starting material 236 was obtained. Product 286 proved difficult to handle being insoluble in conventional organic solvents and only partially soluble in d$_6$-dimethyl sulfoxide and then only on heating. The $^1$H NMR spectral data recorded in this solvent did however correspond to those reported in the literature.$^5$ The reduction potential for compound 236 is 0.445 V which is slightly lower than $para$-benzoquinone (31) (0.52 V)$^1$ therefore it is expected that the two would display similar reactivity which is indeed the case. The strained quinone 287 (Entry 13) was also reacted with 8.8 and 60 equivalents of 148 and produced small amounts of the adduct 288 although only at low conversions (~17%). The 1,8-naphthalic anhydride 288 is a well known$^9$ oxidation product of acenaphthene and acenaphthaquinone (287) and probably results from the presence of oxygen in the reaction mixture and/or exposure of the compound to oxygen during the various manipulations involved in analysing the reaction mixture. The lack of products arising from hydrogen transfer is probably due to the high reduction potential of this compound 287 [0.84 V vs. 0.47 V for $ortho$-quinone (278)].$^6$

To identify if the afore-mentioned reactions between diene (148) and the quinones listed above were particular to this donor, $ortho$-quinone 278 was subjected to a high pressure reaction with 1,3-cyclohexadiene (289) (Entry 14) and product 290 was thereby obtained. This latter compound, which was fully characterised by normal spectroscopic and X-ray crystallographic methods (Figure 6.1), almost certainly arises $via$ an initial Diels-Alder reaction between the reactants 289 and 278. The resulting adduct then aromatises through keto-to-enol tautomerisation processes, and the resulting hydroquinone is then oxidised to the observed quinone 290. Similarly, when the $para$-quinone 31 was subjected to the same conditions (Entry 15) the now expected Diels-Alder adduct 291 was obtained in 81% yield. The spectroscopic data derived from this compound were identical with those
reported previously.\textsuperscript{10} Such results suggest that the uncatalysed hydrogen transfer processes detailed above will, not surprisingly, only succeed if non-conjugated dihydroaromatics such as 1,4-cyclohexadiene (148) are employed as hydrogen donors.
Figure 6.1 ADEP derived from a single crystal X-ray analysis of rearomatised Diels-Alder adduct 290 from the reaction of 1,2-naphthoquinone (278) and 1,3-cyclohexadiene (289) at 19 kbar.
6.4 Reactions of Various Quinones with 1,4-Cyclohexadiene (148) at 1 Bar (One Atmosphere)

As mentioned previously, Braude and Linstead\textsuperscript{1b} examined the reaction of 1,4-cyclohexadiene (148) with \textit{para}-benzoquinone (31) at 80 °C. Hydrogen transfer was observed at this temperature and it was concluded that "migration is normally limited to high temperature ranges since the energy of activation will usually be of the same order as the dissociation energy of at least one of the X-H bonds concerned."\textsuperscript{1b} This observation may account for the fact that there are no reports of investigations of the equivalent uncatalysed hydrogen transfer reaction at room temperature. Given the observations described in the preceding section, however, an investigation of the reaction of various quinonoid compounds with 1,4-cyclohexadiene (148) at 1 bar and room temperature had to be undertaken in order to assess the impact of pressure of the above-mentioned type of hydrogen transfer processes. The results of such an investigation are summarised in Table 6.2. Aliquots of the reaction mixtures were withdrawn at 24, 48 and 72 hour intervals and analysed by \textsuperscript{1}H NMR spectroscopy.

The reaction of \textit{ortho}-quinone 278 (Entry 1) with 148 at 1 bar and room temperature produced the catechol 279 and after 48 hours a 1:1 mixture of starting material and product was observed. After 72 hours a 1:2 mixture of 278 and 279 was obtained as judged by \textsuperscript{1}H NMR spectroscopic analysis (Figure 6.2). When compound 278 was reacted with 1,3-cyclohexadiene (289) (Entry 2) under the same conditions no products were isolated. This leads to the conclusion that the reaction involving 1,4-cyclohexadiene (148) and 278 is facile and proceeds under very mild conditions. The \textit{ortho}-quinone 278 was treated with 1, 2 and 4.4 equivalents of diene 148 and given the likely bimolecularity of the reaction, the
Table 6.2 Outcomes of Uncatalysed Hydrogen Transfer Reactions from 1,4-Cyclohexadiene (148) to Various Acceptor Molecules Conducted at 1 Bar (Atmospheric Pressure) and Room Temperature

<table>
<thead>
<tr>
<th>Entry #</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield / % Conversion&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="278" /></td>
<td><img src="image" alt="279" /> + SM</td>
<td>96% / 66%&lt;sup&gt;a&lt;/sup&gt; no reaction&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="280" /></td>
<td>no reaction&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="278" /> <img src="image" alt="280" /></td>
<td><img src="image" alt="279" /> + 278 + 280</td>
<td>98%&lt;sup&gt;a&lt;/sup&gt; 98%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="283" /></td>
<td>no reaction&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="31" /> <img src="image" alt="269" /></td>
<td><img src="image" alt="269" /></td>
<td>89% / 26%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="282" /></td>
<td>no reaction&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="284" /></td>
<td>no reaction&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="236" /> <img src="image" alt="287" /></td>
<td><img src="image" alt="287" /> + SM</td>
<td>89% / 61%</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="288" /> <img src="image" alt="288" /></td>
<td><img src="image" alt="288" /> + SM</td>
<td>89% / 61%</td>
</tr>
</tbody>
</table>

<sup>a</sup> 8.8 eq 1,4-cyclohexadiene (148), CH<sub>2</sub>Cl<sub>2</sub>, 1 atm, 72 h.
<sup>b</sup> 8.8 eq 1,3-cyclohexadiene (289), CH<sub>2</sub>Cl<sub>2</sub>, 1 atm, 72 h.
<sup>c</sup> 60 eq 1,4-cyclohexadiene (148), CH<sub>2</sub>Cl<sub>2</sub>, 1 atm, 72 h.
<sup>d</sup> Yields and % conversion ratios are taken after 72 h.
Figure 6.2 300 MHz $^1$H NMR spectra of ortho-quinone 278 and mixtures derived from its reaction with 1,4-cyclohexadiene (148). (Spectra recorded in $d_6$-acetone.) Top spectrum shows the starting material 278. Middle spectrum shows the reaction mixture after 48 hours (1:1 mixture of 278 and hydroquinone 279) and bottom spectrum shows the reaction mixture after 72 hours (1:2 mixture of 278 and hydroquinone 279).
hydrogen transfer process was much slower when low concentrations of the donor compound were employed. The para-quinone 280 (Entry 3) failed to react with diene 148 so it was not surprising that in various competition experiments (see Entry 3) involving 1:1 mixtures of this substrate and the ortho-quinonoid isomer 278, that the latter compound reacted while the former did not. This shows that an ortho-quinone is likely to be selectively reduced in the presence of a para-isomer, which has the potential for development as a useful technique in quinone chemistry.

The hydroxy substituted para-naphthoquinone 283 (Entry 5) was also treated with diene 148 at one atmosphere and as was the case with the equivalent high pressure experiment only starting material was recovered. This outcome may be due, in part, to the insoluble nature of substrate 283. The para-benzoquinone (31) was reactive towards diene 148 at one atmosphere and after 24 hours a 7:1 mixture of the substrate and hydroquinone (269) was observed. After 48 hours a 3.5:1 mixture of 31 and 269 was obtained and finally. After 72 hours a 2.9:1 mixture of starting material and product was isolated. This result shows that para-quinones are capable of engaging in hydrogen transfer at one atmosphere although not as readily as the ortho-quinonoid congeners. Only starting material was recovered when 9,10-anthraquinone (282) (Entry 6) or ortho-quinones 284 (Entry 7) and 236 (Entry 8) were reacted with 148. In contrast, the latter two compounds reacted with 148 at 19 kbar which suggests that high pressure does promote the hydrogen transfer process in certain cases. The strained quinone 287 (Entry 9) was also treated with diene 148 at one atmosphere but after 72 hours only a mixture of the oxidative degradation product 288 and starting material was observed.
6.5 Conclusions and Future Objectives

From the preliminary studies detailed above it has been shown that an uncatalysed hydrogen transfer occurs between 1,4-cyclohexadiene (148) and certain quinonoid compounds. It is clear that the ortho-quinones generally react more rapidly than their para-quinonoid counterparts. Further, some reactions occur at room temperature and one atmosphere while others require higher pressures and of course, some quinones do not react at all under either set of conditions. The reduction potentials of the quinone substrates have been shown to correlate with their reactivity.\footnote{1,6} As mentioned earlier, previous studies in this area had suggested that high temperatures were necessary to overcome the energy of activation of the reaction,\footnote{1} however, the work detailed in this chapter reveals that this is not necessarily so.

The mechanism for the hydrogen transfer reaction detailed here remains uncertain, although the two-step and ionic process proposed in Scheme 6.5 would appear to be a reasonable one.\footnote{1} As such, one hydrogen atom with its electron pair is transferred to the quinone 292 to form the conjugate acid 293 of the dehydrogenation product and the quinol anion 294 (Scheme 6.5). This first and slow step would then be followed by a rapid proton transfer to give the final products, namely catechol (4) and benzene. The greater reactivity of the ortho-quinones versus the para-quinones can be explained by the ability of both carbonyl groups in the former class of compounds to participate in the removal of the hydride ion in the proposed rate determining step. The resulting quinone anion will be further stabilised by intramolecular hydrogen bonding. Of course, the reaction is driven, in the main, by the gain in resonance stabilisation energy that accompanies aromatisation of the 1,4-cyclohexadiene (148).
Scheme 6.5 Proposed mechanism for the uncatalysed hydrogen transfer between 1,4-cyclohexadiene (148) and quinones.

Future investigations in this area will be concerned with exploiting this simple and rather effective uncatalysed hydrogen transfer reaction in the synthesis of various quinonoid natural products.
6.6 References


7.1 General Protocols

Analytical thin layer chromatography (TLC) was performed on glass-backed 0.2 mm thick silica gel 60 F$_{254}$ plates as supplied by Merck. Visualisation of eluted plates was through use of a 254 nm UV lamp and/or by treatment with a suitable reagent dip followed by heating. The reagent dips used included phosphomolybdic acid:ceric sulfate:sulfuric acid (conc.):water (37.5 g:7.5 g:37.5 g:720 mL); anisaldehyde:sulfuric acid (conc.):ethanol (2 mL:5 mL:93 mL) and 2,4-dinitrophenylhydrazine:sulfuric acid (conc.):water:ethanol (12 g:60 mL:80 mL:200 mL).
Flash chromatography was performed according to the method of Still et al. using the analytical grade solvents indicated and silica gel 60 (0.040-0.0063 mm) as supplied by Merck.

Gas Chromatographic (GC) analysis was carried out using a Varian 3400 Gas Chromatograph fitted with a SGE BPX5 capillary column [25 m long x 0.22 mm wide (i.d.) and 25 micron coat]. The eluted fractions were detected using a flame ionisation detector operating at 300 °C while helium was employed as the carrier gas (flow rate ca. 35 cm/sec). Specific temperature programs are detailed for each individual analysis.

High Performance Liquid Chromatography (HPLC) was conducted on a Waters µ-Porasil™ semi-preparative silica column (7.8 x 300 mm) connected to an ISCO Model 2350 pump and using the HPLC grade solvents indicated. The peaks were detected using an ERMA ERC-7512 refractive index detector connected to a Spectra-Physics SP4270 reporting integrator.

Reactions employing air and/or moisture sensitive reagents and intermediates were carried out under an atmosphere of nitrogen. In all cases the glassware was flame dried then cooled, under an atmosphere of nitrogen, prior to the addition of the solvents, starting materials and reagents. When reactions were conducted at, or below 0 °C, the internal temperature was monitored using an alcohol thermometer. ACE™ Pressure Tubes were used for reactions that required heating in a closed system.

Starting materials and reagents were generally available from the Aldrich, Merck, or Lancaster Chemical Companies and were used as supplied or purified further according to the methods defined by Perrin and Armarego.2 Drying agents and other inorganic salts were purchased from AJAX, BDH or Unilab Chemical Companies. Reaction solvents were also purified according to the methods defined by Perrin and Armarego.2 Thus,
tetrahydrofuran (THF), 1,2-dimethoxyethane (DME) and diethyl ether (ether) were distilled from sodium benzophenone ketyl. Methanol and ethanol were distilled from their respective magnesium alkoxide salts. Benzene, toluene, dichloromethane (CH₂Cl₂), hexane and N,N-dimethylformamide (DMF) were distilled from calcium hydride. Pyridine and triethylamine were distilled from potassium hydroxide pellets. Sodium and potassium hydrides (dispersions in mineral oil) were washed several times with hexane and dried under reduced pressure before being used. Petrol refers to that petroleum fraction with a boiling range of 40-60 °C and was used as supplied.

High pressure reactions were carried out in a 20 kbar high pressure reactor purchased from PSIKA Pressure Systems Ltd. Reaction samples were placed in teflon reaction chambers constructed within the Research School of Chemistry and consisting, in part, of a hollow teflon cylindrical base (24 mm in diameter and 2 mm wall thickness). After filling these chambers they were fitted with a solid teflon plunger incorporating two rubber O-rings. Reactions were carried out in a 17:3 v/v castor oil/methanol mix at 19 kbar. Specific reaction times are detailed for each individual case.

Melting points were measured on a Reichart hot-stage microscope apparatus and are uncorrected.

Proton (¹H) and carbon (¹³C) nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini 300 or a Varian Mercury 300 spectrometer, operating at 300 MHz for proton and 75.4 MHz for carbon. Chemical shifts are recorded as δ values in parts per million (ppm). For ¹H NMR spectra recorded in CDCl₃, the peak due to residual CHCl₃ (7.26 ppm) was used as the internal reference, while the central peak (δ 77.0) of the CDCl₃ triplet was used as the internal reference for ¹³C NMR spectra. In cases where (CD₃)₂SO was used as solvent, ¹H NMR spectra were referenced against the central peak
(δ 2.49) of the pentet due to (CHD₂)(CD₃)SO and ¹³C NMR spectra referenced against the central peak of the (CD₃)₂SO heptet (δ 38.5). When CD₃OD was used as solvent, the ¹H NMR spectra were referenced against the central peak of the residual CHD₂OD pentet (δ 3.30) and the ¹³C NMR spectra against the central peak of the CD₃OD heptet (δ 49.0). For spectra recorded in (CD₃)₂CO, the central peak (δ 2.17) of the pentet due to the residual (CHD₂)(CD₃)CO was used for ¹H NMR spectral calibration and the ¹³C NMR spectra were referenced relative to the (CD₃)₂CO heptet (δ 30.2). When D₂O was used, ¹H NMR spectra were referenced against the singlet (δ 4.8) due to the residual H₂O. ¹H NMR spectral data were recorded as follows: chemical shift (δ in ppm), multiplicity and coupling constant(s) J (Hz) where multiplicity is defined as (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sep = septet, m = multiplet, dd = doublet of doublets, br = broad, or combinations of the above). ¹³C NMR spectral data were recorded as follows: chemical shift (δ), and protonicity where the latter is defined as: C = quaternary; CH = methine; CH₂ = methylene; CH₃ = methyl. The assignment of individual signals observed within various ¹³C NMR spectra were often assisted by conducting an attached proton test (APT) experiment.

Infrared spectra (v max) were recorded on a Perkin-Elmer Spectrum One Instrument. Samples were analysed as KBr disks (for solids) or as thin films on KBr plates (for oils). Absorption maxima (v max) are recorded in wavenumbers (cm⁻¹).

Low and high resolution mass spectra were recorded on a VG Fisons AutoSpec three sector (E/B/E) double-focussing mass spectrometer, using positive-ion electron impact techniques at the voltages indicated or on a VG ZAB-2SEQ hybrid sector instrument using a LSIMS source. Mass spectral data are listed as: mass-to-charge ratio
(m/z) then in brackets, assignment (where possible) followed by intensity relative to the base peak.

Elemental analysis were performed by the Australian National University Microanalytical Services Unit located in the Research School of Chemistry, Canberra, ACT, Australia.

Single crystal X-ray diffraction data were collected on either a Nonius Kappa CCD or Rigako AFC 6R instrument. Data collection, structure solution and refinement were undertaken by staff of the Australian National University Crystallography Unit located in the Research School of Chemistry, Canberra, ACT, Australia. Full structure reports are provided in Appendix 1.
7.2 Experimental Details Associated with Work Described in Chapter 2

\(1\alpha,6\alpha\)-7,7-Dibromobicyclo[4.1.0]hept-3-ene (149)

Aqueous sodium hydroxide (100 mL of 50% w/v aqueous solution) was added, in one portion, to a magnetically stirred solution of 1,4-cyclohexadiene (148) (29.7 mL, 0.31 mol), bromoform (135 mL, 1.55 mol) and benzyltriethylammonium chloride (500 mg, 0.002 mol) in benzene (100 mL) maintained at 0 °C. Stirring was continued for 1 h at 0 °C, then the mixture was allowed to stand at room temperature for 24 h, then diluted with water (1 x 200 mL) and extracted with petrol (3 x 100 mL). The combined organic fractions were dried (\(\text{MgSO}_4\)), filtered and concentrated under reduced pressure to afford a pale, yellow oil. Distillation of this material afforded the title compound 149\(^3\) (40.4 g, 52%) as a clear, colourless oil, b.p. 110 °C/10 mm Hg (lit.\(^3\) b.p. 54 °C/0.3 mm Hg). The spectral data derived from this material were identical, in all respects, with those reported in the literature.\(^3\)

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 5.51 (s, 2H), 2.51-2.41 (m, 2H), 2.12-2.07 (m, 2H), 1.93-1.90 (m, 2H).
Finely ground iodine (2.91 g, 11.4 mmol) was added, in small portions over 30 mins, to a magnetically stirred solution of the alkene 149 (2.63 g, 10.4 mmol) and silver acetate (3.50 g, 20.9 mmol) in acetic acid (46 mL) maintained at room temperature. Water (195 µL) was then added, in one portion, and the resulting solution stirred at room temperature for 48 h, then filtered through a pad of Celite®. The filtrate was washed with water (1 x 100 mL), NaHCO₃ (saturated aqueous solution), until the washings remained alkaline, then Na₂S₂O₅ (1 x 50 mL of a 20% aqueous solution) and water (1 x 100 mL). The combined organic fractions were dried (MgSO₄), filtered and concentrated under reduced pressure to yield diol monoacetate 150³ (3.36 g, 98%) as a colourless, crystalline solid, m.p. 80-82 °C (lit.³ m.p. 82-83 °C). The spectral data derived from this material were identical, in all respects, with those reported in the literature.³

¹H NMR (300 MHz, CDCl₃) δ 4.83-4.78 (m, 1H), 3.82-3.77 (m, 1H), 2.45-2.36 (m, 2H), 2.07 (s, 3H), 1.91-1.69 (m, 5H).
Sodium hydroxide (0.78 g, 19.5 mmol) was added slowly to a magnetically stirred solution of acetate 150 (3.00 g, 9.14 mmol) in methanol (70 mL) maintained at room temperature. Stirring was continued for 6 h then HCl (80 mL of a 2 M aqueous solution) was added and the resulting mixture extracted with CH$_2$Cl$_2$ (3 x 100 mL). The combined organic extracts were then dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford a yellow solid, which was recrystallised (1:1 v/v CHCl$_3$/hexane) to yield the diol 151$^3$ (2.58 g, 100%) as colourless needles, m.p. 102-103 °C (lit.$^3$ m.p. 103-103.5 °C). The spectral data derived from this material were identical, in all respects, with those reported in the literature.$^3$

$^1$H NMR (300 MHz, CDCl$_3$) δ 3.71-3.66 (m, 2H), 2.47-2.36 (m, 2H), 1.98 (s, 2H), 1.90-1.84 (m, 2H), 1.70-1.61 (m, 2H).
(1α,2α,5α,6αα,5,5-Dibromo-1a,2,2a,5a,6,6a-hexahydro-2,2-dimethyl-4H-
cyclopropa[f]-1,3-benzodioxole (106)

\[
\begin{array}{c}
\text{151} \\
\text{106}
\end{array}
\]

\text{para-Toluenesulfonic acid (100 mg, 0.52 mmol) was added, in one portion, to a}
\text{magnetically stirred solution of diol 151 (2.00 g, 6.99 mmol) in 2,2-dimethoxypropane (10}
\text{mL, 81.0 mmol) and acetone (3 mL) maintained at room temperature under an atmosphere}
\text{of nitrogen. Stirring was continued for 24 h at which point NaOH (10 mL of a 10%}
\text{aqueous solution) was added to the reaction mixture and stirring continued for a further 10}
\text{min. Brine (10 mL) was then added and the resulting mixture extracted with ethyl acetate}
\text{(3 x 10 mL) then dried (MgSO}_4\text{), filtered and concentrated under reduced pressure to afford}
\text{the title compound 106}^4\text{ (1.97 g, 100%) as a colourless, crystalline solid, m.p. 110-111 °C}
\text{(lit.}^4\text{ m.p. 109-109.5 °C). The spectral data derived from this material were identical, in all}
\text{respects, with those reported in the literature.}^4

\text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3\text{) δ 4.28-4.24 (m, 2H), 2.58-2.48 (m, 2H), 1.69-1.63 (m, 2H),}
\text{1.44 (s, 3H), 1.33 (s, 3H), 1.09-1.01 (m, 2H).}
Chapter 7

Reaction of *gem*-Dibromocyclopropane 106 with Organolithium Species.


Method A: Methylithium

Methylithium (2.90 mL of a 1.4 M solution in ether, 4.05 mmol) was added slowly to a magnetically stirred solution of *gem*-dibromocyclopropane 106 (600 mg, 1.84 mmol) in ether (6 mL) maintained at -80 °C (ethyl acetate/liquid nitrogen slurry) under an atmosphere of nitrogen. The resulting mixture was stirred at -80 °C for 4 h and room temperature for 5 h before being diluted with water (5 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to yield a colourless, crystalline solid. Subjection of this material to semi-preparative HPLC (1:9 v/v ethyl acetate/hexane elution, flow rate 10 mL/min) provided three fractions, A, B and C.
Concentration of fraction A (R_t = 16.4 min) gave (1α,2α,5α,6α)-5-bromo-5-methyl-1a,2a,5a,6a-hexahydro-2,2-dimethyl-4H-cyclopropa[f]-1,3-benzodioxole (152)\(^4\) (30.0 mg, 10%) as a colourless, crystalline solid, m.p. 58-60 °C (lit.\(^4\) m.p. 63-68 °C). The spectral data derived from this material were identical, in all respects, with those reported in the literature.\(^4\)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 4.32-4.27 (m, 2H), 2.40-2.33 (m, 2H), 1.82 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H), 1.24-1.13 (m, 2H), 0.79-0.73 (m, 2H).

Concentration of fraction B (R_t = 22.3 min) gave [3α,4α,Z(3αR*,4αS*,5αR*,6αS*)]-5-{3'a,4',4'a,5',5'a,6',6'a-hexahydro-2',2'-dimethyl-5'H-cyclopropa[f]-1',3'-benzodioxol-5'-ylidene}-3a,4,4a,5,5a,6a-hexahydro-2,2-dimethyl-5H-cyclopropa[f]-1,3-benzodioxole (107)\(^4\) (45.0 mg, 15%) as a colourless, crystalline solid, m.p. 155-157 °C (lit.\(^4\) m.p. 151-155 °C). The spectral data derived from this material were identical, in all respects, with those reported in the literature.\(^4\)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 4.32-4.27 (m, 4H), 2.55-2.46 (m, 4H), 1.49 (t, J = 5.1 Hz, 4H), 1.42 (s, 6H), 1.34 (s, 6H), 0.99-0.94 (m, 4H).

Concentration of fraction C (R_t = 27.4 min) gave [3α,4α,5E(3αR*,4αR*,5αS*,6αS*)]-5-{3'a,4',4'a,5',5'a,6',6'a-hexahydro-2',2'-dimethyl-5'H-cyclopropa[f]-1',3'-benzodioxol-5'-ylidene}-3a,4,4a,5,5a,6a-hexahydro-2,2-dimethyl-5H-cyclopropa[f]-1,3-benzodioxole (108)\(^4\) (36.0 mg, 12%) as a colourless, crystalline solid, m.p. 210-212 °C (lit.\(^4\) m.p. 211-212 °C). The spectral data derived from this material were identical, in all respects, with those reported in the literature.\(^4\)
\textbf{Chapter 7}

\textbf{1H NMR} (300 MHz, CDCl$_3$) $\delta$ 4.30-4.26 (m, 4H), 2.43-2.37 (m, 4H), 1.47-1.46 (m, 4H), 1.33 (s, 6H), 1.31 (s, 6H), 1.18-1.13 (m, 4H).

\textbf{Method B: Phenyllithium/CuCl$_2$}

Phenyllithium (0.75 mL of a 1.8 M solution in ether, 1.36 mmol) was added slowly to a magnetically stirred solution of the acetonide 106 (200 mg, 0.61 mmol) and copper(II) chloride (17.0 mg, 0.12 mmol) in ether (2 mL) maintained at -80 °C under an atmosphere of nitrogen. The resulting mixture was stirred at -80 °C for 4 h and room temperature for 5 h before being diluted with water (5 mL) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure to yield a yellow oil. Subjection of this material to HPLC (1:19 v/v ethyl acetate/hexane elution, flow rate 2 mL/min) provided three fractions, A, B and C.

Concentration of fraction A ($R_t = 17.1$ min) gave (1\textalpha\textalpha,2\textalpha\textalpha,5\textalpha\textalpha,6\textalpha\textalpha)-5-bromo-2,2-dimethyl-1\textalpha,2\textalpha,5\textalpha,6\textalpha-hexahydro-5-phenyl-4H-cyclopropa[f]-1,3-benzodioxole (153) (30.0 mg, 29%) as a colourless crystalline solid, m.p. 125-127 °C.

\textbf{1H NMR} (300 MHz, CDCl$_3$) $\delta$ 7.46-7.25 (m, 5H), 4.38-4.33 (m, 2H), 2.60-2.53 (m, 2H), 1.50 (s, 3H), 1.45-1.40 (m, 2H), 1.38 (s, 3H), 1.34-1.27 (m, 2H).

\textbf{13C NMR} (75.4 MHz, CDCl$_3$) $\delta$ 145.5 (C), 129.4 (2 x CH), 129.1 (2 x CH), 128.6 (CH), 108.8 (C), 74.3 (2 x CH), 53.3 (C), 28.8 (2 x CH$_2$), 27.7 (CH$_3$), 24.8 (CH$_3$), 21.8 (2 x CH).

\textbf{Infrared Spectrum} (KBr) $\nu_{\text{max}}$ 2980, 2904, 1459, 1376, 1261, 1210, 1165, 1064, 1052, 898, 753, 696, 624, 518 cm$^{-1}$. 
**Mass Spectrum** (70 eV) m/z 324 (1), 322 (M⁺; 2%), 309 (40), 307 [(M-H₃C⁻)⁺, 44%] 266 (55), 264 (55), 185 (100), 167 (76), 129 (97), 91 (21), 77 (10).

**HRMS** C₁₆H₁₉BrO₂ requires: M⁺, 324.0547 Found: M⁺, 324.0547.

**Elemental Analysis** C₁₆H₁₉BrO₂ requires: C, 59.46; H, 5.92; Br, 24.72. Found: C, 59.46; H, 5.92; Br, 24.60%.

Concentration of fraction B (Rₜ = 28.8 min) gave syn-cyclopropylidene dimer 107 (20 mg, 19%), as a colourless, crystalline solid, m.p. 155-157 °C. This material was identical, in all respects, to that prepared *via* method A.

Concentration of fraction C (Rₜ = 38.3 min) gave anti-cyclopropylidene dimer 108 (15 mg, 15%), as a colourless, crystalline solid, m.p. 210-212 °C. This material was identical, in all respects, to that prepared *via* method A.

(3aR,4aS,5aR,6aS,3"aS,4"aR,5"aS,6"aR)-3',3'-Dichloro-3a,4,4a,5a,6,6a,3"a,4", 4"a,5"a,6",6"a-dodecahydro-2,2,2",2"-tetramethyldispiro[5H-cyclopropa[f]-1",3"-benzodioxole-5,1'-cyclopropane-2',5"-5H-cyclopropa[f]-1,3-benzodioxole] (122)
Sodium hydroxide (5.88 mL of a 50% aqueous solution) was added, in one portion, to a magnetically stirred solution of syn-cyclopropylidene dimer 107 (72.0 mg, 0.22 mmol) and benzyltrihyamine chloride (14.9 mg, 0.06 mmol) in CHCl₃ (1.5 mL) maintained at 0 °C. The resulting mixture was stirred vigorously at 0 °C for 1 h and then at room temperature for 3 h. The reaction mixture was then diluted with water (2 mL) and extracted with petrol (3 x 5 mL). The combined organic phases were then dried (MgSO₄), filtered and concentrated under reduced pressure to yield tricyclane 122 (80.9 mg, 90%) as a colourless, crystalline solid, m.p. 215-217 °C (lit. m.p. 217-218 °C). The spectral data derived from this material were identical, in all respects, with those reported in the literature.

\(^1\)H NMR (300 MHz, CDCl₃) δ 4.30-4.26 (m, 4H), 2.55-2.46 (m, 4H), 1.69-1.58 (m, 4H), 1.37 (s, 6H), 1.33 (s, 6H), 1.09-1.01 (m, 4H).

(1aR,3S,4R,5aS,1"aS,3"R,4"S,5"aR)-3',3''-Dichlorodispiro{bicyclo [4.1.0]heptane-7,1'-cyclopropane-2'',7''-bicyclo[4.1.0]heptane}-3,3'',4,4''-tetraol tetraacetate (109)
The bisacetonide 122 (80.0 mg, 0.19 mmol) was suspended in acetic acid (70 mL of a 60% aqueous solution) and heated at 80 °C for 48 h. The cooled reaction mixture was concentrated under reduced pressure to give tetraol 123 (63.0 mg, 98%) as a colourless solid. This material was immediately acetylated for the purposes of purification and characterisation. Thus, tetraol 123 was added to a magnetically stirred solution of acetic anhydride (0.68 mL, 7.26 mmol), pyridine (1.37 mL, 16.9 mmol) and 4-(N,N-dimethylamino)pyridine (trace) in CH₂Cl₂ (24 mL) maintained at room temperature under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature for 24 h then diluted with water (20 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were washed with HCl (1 x 50 mL of a 2 M aqueous solution), NaHCO₃ (1 x 30 mL of a saturated aqueous solution) and water (1 x 30 mL), then dried (MgSO₄), filtered and concentrated under reduced pressure to afford the tetraacetate 109 (59.1 mg, 62%) as a colourless, crystalline solid, m.p. 220-223 °C (lit. m.p. 224-225 °C). The spectral data derived from this material were identical, in all respects, with those reported in the literature.

\[^1\text{H NMR} (300 \text{ MHz, CDCl}_3) \delta 5.23-5.15 (m, 4H), 2.46-2.38 (m, 4H), 2.05 (s, 12H), 1.82-1.69 (m, 8H).\]
(1αR,3S,4R,5aS,1"αR,3"βS,4"βR,5"αS)-3',3'-Dichlorodispiro[bicyclo[4.1.0]heptane-7,1'-cyclopropane-2",7"-bicyclo[4.1.0]heptane]-3,3",4,4"-tetraol (123)

The tetraacetate 109 (21.3 mg, 0.04 mmol) was dissolved in a minimum volume of CHCl₃ then diluted six-fold with methanol. Potassium hydroxide (2 pellets) was added and the ensuing mixture stirred at room temperature for 15 min, then diluted with water (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure to afford the tetraol 123 (13.8 mg, 97%) as a colourless, crystalline solid, m.p. 180-182 °C.

Due to its insoluble nature, compound 123 was not subject to any spectroscopic characterisation.
Attempted Formation of \((1aR,3S,4R,5aS,1''aR,3''S,4''R,5''aS)-3',3'\text{-}\)Dichlorodispiro\{bicyclo[4.1.0]heptane\}1',7'-cyclopropane-2'',7''-bicyclo[4.1.0]heptane\}3,3'',4,4''-tetraone (134)

\[
\begin{array}{c}
\text{Cl} \quad \text{Cl} \\
\text{HO} \quad \text{OH} \\
123 \\
\end{array}
\quad
\begin{array}{c}
\text{Cl} \quad \text{Cl} \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{O} \\
134 \\
\end{array}
\]

Trifluoroacetic anhydride (12.1 µL, 85.6 µmol) was added, dropwise, to a magnetically stirred solution of DMSO (6.70 µL, 94.7 µmol) in CH\(_2\)Cl\(_2\) (200 µL) maintained at -60 °C under an atmosphere of nitrogen. Stirring was continued at this temperature for 10 min, after which time a solution of the tetraol 123 (5 mg, 14.9 µmol) in DMSO/CH\(_2\)Cl\(_2\) (10 µL of a 1:1 solution) was added dropwise. The ensuing mixture was stirred at -60 °C for 1.5 h then warmed to 5 °C, poured into HCl (1 mL of a 2 M aqueous solution) and extracted with CH\(_2\)Cl\(_2\) (3 x 2 mL). The combined organic extracts were washed with water (1 x 2 mL), then dried (MgSO\(_4\)), filtered and concentrated under reduced pressure to yield a bright yellow oil (2 mg). Whilst mass spectral analysis suggested the presence of trace amounts of tetraone 134, (expected M\(^+\) observed at \(m/z\) 318, 316 and 314) this material could not be isolated from the crude reaction mixture.
2,3-Bis(1-methylethoxy)naphthalene (157)

2-Bromopropane (14.7 mL, 156 mmol) was added, in one portion, to a magnetically stirred solution of 2,3-dihydroxynaphthalene (156) (10.0 g, 62.4 mmol) and K₂CO₃ (21.6 g, 219 mmol) in DMF (100 mL) maintained at room temperature under an atmosphere of nitrogen. The resulting mixture was maintained at 100 °C for 3 h and room temperature for 4 days, before being diluted with water (200 mL) and extracted with ether (2 x 200 mL). The combined organic layers were washed with water (1 x 100 mL), then dried (MgSO₄), filtered and concentrated under reduced pressure to afford a colourless solid. Recrystallisation (petrol) of this material gave the title compound 157 (15.5 g, 97%) as colourless prisms, m.p. 53-54 °C.

**¹H NMR** (300 MHz, CDCl₃) δ 7.68-7.64 (m, 2H), 7.33-7.29 (m, 2H), 7.20 (s, 2H), 4.62 (sep, J = 6.1 Hz, 2H), 1.42 (d, J = 6.1 Hz, 12 H).

**¹³C NMR** (75.4 MHz, CDCl₃) δ 149.2 (2 x C), 129.6 (2 x C), 126.3 (2 x CH), 124.0 (2 x CH), 112.3 (2 x CH), 71.9 (2 x CH), 22.1 (4 x CH₃).

**Infrared Spectrum** (KBr) νₘₐₓ 2980, 1622, 1597, 1479, 1373, 1254, 1168, 1111, 941, 859, 750 cm⁻¹.

**Mass Spectrum** (70 eV) m/z 244 (M⁺, 15%), 202 [(M-CH₂CHCH₃)⁺, 10%] 160 [(M-
2xCH₂CHCH₃⁺, 100%], 131 (50), 114 (43), 102 (25), 77 (7).

**HRMS** C₁₆H₂₀O₂ requires: M⁺, 244.1463. Found: M⁺, 244.1462.

**Elemental Analysis** C₁₆H₂₀O₂ requires: C, 78.65; H, 8.25. Found: C, 78.64; H, 8.09%.

**6,7-Bis(1-methylethoxy)-1,4-dihydrophanthlene (158)**

![Chemical structure](image)

Sodium metal (6.00 g, 254 mmol) was added, in small pieces, to a magnetically stirred solution of 2,3-bis(1-methylethoxy)naphthalene (157) (15.0 g, 61.5 mmol), tert-butanol (11.7 mL, 123 mmol) and THF (100 mL) in ammonia (200 mL) maintained at -78 °C under an atmosphere of nitrogen. The resulting blue mixture was stirred at -78 °C for 2 h, after which time it was quenched with sufficient solid NH₄Cl, to render the reaction mixture permanently colourless. The reaction vessel was flushed with a stream of nitrogen so as to remove excess ammonia and the residue thus obtained was diluted with ice-cold water (100 mL, CAUTION!) and extracted with ether (2 x 100 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash chromatography (4:1 v/v CH₂Cl₂/petrol elution) and concentration of the appropriate fractions (Rf = 0.6) afforded the *dihydro-compound* 158 (15.0 g, 99%) as a clear, yellow oil.
\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 6.67 (s, 2H), 5.89 (s, 2H), 4.42 (sep, \(J = 6.1\) Hz, 2H), 3.30 (d, \(J = 1.1\) Hz, 4H), 1.32 (d, \(J = 6.1\) Hz, 12H).

\(^{13}\text{C NMR}\) (75.4 MHz, CDCl\(_3\)) \(\delta\) 147.4 (2 \(\times\) C), 127.1 (2 \(\times\) C), 124.6 (2 \(\times\) CH), 110.1 (2 \(\times\) CH), 72.2 (2 \(\times\) CH), 29.2 (2 \(\times\) CH\(_2\)), 22.3 (4 \(\times\) CH\(_3\)).

**Infrared Spectrum** (KBr) \(v_{\text{max}}\) 3450, 2975, 1599, 1505, 1382, 1371, 1255, 1109 cm\(^{-1}\).

**Mass Spectrum** (70 eV) \(m/z\) 246 (M\(^+\), 60\%), 204 [(M-CH\(_2\)CHCH\(_3\))\(^+\), 20\%], 162 [(M-2xCH\(_2\)CHCH\(_3\))\(^+\), 100\%], 144 (20), 131 (15), 115 (30).

**HRMS** \(\text{C}_{16}\text{H}_{22}\text{O}_2\) requires: M\(^+\) 246.1619. Found: M\(^+\), 246.1622.

\((1a\alpha,7a\alpha)-4,5\text{-Bis(1-methylethoxy)-1,1-dibromo-1a,2,7,7a-tetrahydro-1H-}\)

cyclopropa[b] naphthalene (137)

![Chemical Structure](image)

Sodium hydroxide (1.31 mL of a 50\% aqueous solution) was added, in one portion, to a magnetically stirred solution of compound 158 (1.10 g, 4.50 mmol) and benzyltriethylammonium chloride (20.0 mg, 0.09 mmol) in bromoform (1.94 mL, 22.5 mmol) maintained at 0 °C under an atmosphere of nitrogen. The resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 24 h before being diluted with water.
(2 mL) and extracted with petrol (3 x 5 mL). The combined organic fractions were dried (MgSO₄), filtered and concentrated under reduced pressure to give a colourless solid. This material was immediately passed through a short pad of silica (1:9 v/v ethyl acetate/petrol elution) and concentration of the appropriate fractions (R_f = 0.6) afforded a colourless solid which was recrystallised (petrol) to give the title compound 137 (454 mg, 24%) as a colourless powder, m.p. 77 °C.

^1H NMR (300 MHz, CDCl₃) δ 6.63 (s, 2H), 4.40 (sep, J = 6.0 Hz, 2H), 3.21-3.13 (m, 2H), 2.65 (d, J = 17.5 Hz, 2H), 2.12-2.09 (m, 2H), 1.30 (d, J = 6.0 Hz, 12H).

^13C NMR (75.4 MHz, CDCl₃) δ 147.4 (2 x C), 126.2 (2 x C), 118.0 (2 x CH), 72.3 (2 x CH), 39.0 (C), 27.8 (2 x CH), 26.3 (2 x CH₂), 22.3 (4 x CH₃).

Infrared Spectrum (KBr) v_max 2923, 2852, 1507, 1251, 1111, 956, 729 cm⁻¹.

Mass Spectrum (70 eV) m/z 420 (41), 418 (71), 416 (M⁺, 43%), 378 (17), 376 (35), 374 [(M-CH₂CHCH₃)⁺, 18%] 336 (40), 334 (71), 332 [(M-2xCH₂CHCH₃)⁺, 43%], 255 (57), 253 [(M-(2xCH₂CHCH₃)Br)⁺, 63%], 174 [(M-(2xCH₂CHCH₃)Br₂)⁺, 100%], 161 (85), 128 (27), 115 (40).


Elemental Analysis C₁₇H₂₂O₂Br₂ requires: C, 48.83; H, 5.30; Br, 38.22. Found: C, 48.72; H, 5.30; Br, 38.02%.
2-Bromopropane (25.5 mL, 0.27 mol) was added, in one portion, to a magnetically stirred mixture of catechol (4) (10.0 g, 0.09 mol) and K$_2$CO$_3$ (31.5 g, 0.32 mol) in DMF (100 mL) maintained at room temperature under an atmosphere of nitrogen. The resulting mixture was heated at 100 °C for 8 h, then diluted with water (100 mL) and extracted with ether (2 x 100 mL). The combined organic fractions were dried (MgSO$_4$), filtered and concentrated under reduced pressure to yield a yellow oil. A solution of this material was passed through a pad of silica (1:19 v/v ethyl acetate/petrol elution) affording, after concentration of the filtrate, the title compound 184 (17.3 g, 98%) as a pale, yellow oil.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.96-6.93 (m, 4H), 4.50 (sep, $J = 6.0$ Hz, 2H), 1.37 (d, $J = 6.0$ Hz, 12H).

$^{13}$C NMR (75.4 MHz, CDCl$_3$) $\delta$ 149.8 (2 x C), 122.4 (2 x C), 119.0 (2 x CH), 72.7 (2 x CH), 22.8 (4 x CH$_3$).
Infrared Spectrum (KBr) \( \nu_{\text{max}} \) 2975, 1592, 1494, 1382, 1255, 1209, 1120, 958, 743 cm\(^{-1}\).

**Mass Spectrum** (70 eV) \( m/z \) 194 (M\(^+\), 37%), 152 [(M-CH\(_2\)CH\(_3\))\(^+\), 15%], 110 [(M-2xCH\(_2\)CHCH\(_3\))\(^+\), 100%].

**HRMS** C\(_{12}\)H\(_{18}\)O\(_2\) requires: M\(^+\), 194.1306. Found: M\(^+\), 194.1307.

**Elemental Analysis** C\(_{12}\)H\(_{18}\)O\(_2\) requires: C, 74.19; H, 9.34. Found: C, 74.22; H, 9.31%.

**4,5-Bis(1-methylethoxy)-1,2-diiodobenzene (185)**

\[
\text{O} \quad \text{I}\_2, \text{CHCl}_3 \\
\text{AgOAc} \\
\text{O} \quad \text{I} \quad \text{O}
\]

A solution of molecular iodine (3.29 g, 12.8 mmol) in CHCl\(_3\) (150 mL) was added, dropwise, to a magnetically stirred mixture of 1,2-bis(1-methylethoxy)benzene (184) (1.00 g, 5.20 mmol) and silver acetate (2.15 g, 12.9 mmol) in CHCl\(_3\) (15 mL) maintained at room temperature under an atmosphere of nitrogen. Stirring was continued for 12 h then the silver salts were removed by filtration and the filtrate was washed with water (2 x 50 mL), Na\(_2\)S\(_2\)O\(_5\) (1 x 100 mL of a 20% aqueous solution) and brine (1 x 50 mL), before being dried (MgSO\(_4\)), filtered and concentrated under reduced pressure to yield the **title compound** 185 (2.10 g, 92%) as a pale, yellow oil.
\(^{1}\text{H} \text{NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 7.31 (s, 2H), 4.40 (sep, \(J = 6.1\) Hz, 2H), 1.30 (d, \(J = 6.1\) Hz, 12H).

\(^{13}\text{C} \text{NMR}\) (75.4 MHz, CDCl\(_3\)) \(\delta\) 149.5 (2 x C), 127.6 (2 x CH), 96.8 (2 x C), 72.6 (2 x CH), 22.0 (4 x CH\(_3\)).

**Infrared Spectrum** (KBr) \(v_{\text{max}}\) 2975, 1471, 1383, 1246, 1184, 1107, 939, 881, 638 cm\(^{-1}\).

**Mass Spectrum** (70 eV) \(m/z\) 446 (M\(^{+}\), 52%), 404 [(M-CH\(_2\)CH\(_3\))\(^{+}\), 31%], 362 [(M-2xCH\(_2\)CH\(_3\))\(^{+}\), 100%], 333 (20), 235 [(M-(2xCH\(_2\)CH\(_3\))I)\(^{+}\), 35%], 108 (26%).

**HRMS** \(\text{C}_{12}\text{H}_{16}\text{I}_{2}\text{O}_{2}\) requires: M\(^{+}\), 445.9239. Found: M\(^{+}\), 445.9242.

3,3'-(4,5-Bis(1-methylethoxy)-1,2-phenylene)-2-propenoic acid Bismethyl ester (186)

![Chemical structure](image)

Methyl acrylate (0.67 mL, 7.52 mmol) was added to a magnetically stirred mixture of the diiodo-compound 185 (1.00 g, 2.24 mmol), palladium(II) acetate (143 mg, 0.64 mmol), K\(_2\)CO\(_3\) (1.04 g, 7.52 mmol) and tetra-\(n\)-butylammonium bromide (1.03 g, 3.19 mmol) in DMF (25 mL) maintained at room temperature under an atmosphere of nitrogen in a sealed tube. The reaction mixture was heated at 120 °C for 48 h, then cooled and diluted with CH\(_2\)Cl\(_2\) (25 mL) and the resulting solution filtered through a pad of Celite\textsuperscript{®}. The filtrate
was washed with water (2 x 25 mL) and the combined organic phases were then dried (MgSO₄), filtered and concentrated under reduced pressure to yield a yellow solid. This material was passed through a pad of silica (1:9 v/v ethyl acetate/petrol elution) to yield the title product 186 (0.80 g, 98%) as a yellow, crystalline solid, m.p. 66-68 °C.

**1H NMR** (300 MHz, CDCl₃) δ 8.00 (d, J = 15.7 Hz, 2 H), 7.07 (s, 2H), 6.23 (d, J = 6.1 Hz, 2H), 4.55 (sep, J = 6.1 Hz, 2H), 3.82 (s, 6H), 1.37 (d, J = 6.1 Hz, 12H).

**13C NMR** (75.4 MHz, CDCl₃) δ 166.9 (2 x C), 150.6 (2 x C), 140.8 (2 x CH), 127.8 (2 x C), 119.1 (2 x CH), 114.8 (2 x CH), 72.2 (2 x CH), 51.8 (2 x CH₃), 22.2 (4 x CH₃).

**Infrared Spectrum** (KBr) νₘₐₓ 2977, 1718, 1631, 1590, 1501, 1271, 1167, 1103 cm⁻¹.

**Mass Spectrum** (70 eV) m/z 362 (M⁺, 35%), 331 (10), 288 (7), 261 (15), 229 (15), 218 (100), 187 (76), 160 (35).


**Elemental Analysis** C₂₀H₂₆O₆ requires: C, 66.28; H, 7.23. Found: C, 66.48; H, 6.88%.

**4,5-Bis(1-methylethoxy)-1,2-benzenedipropanoic acid Bismethyl ester (183)**

\[
\begin{align*}
\text{O} & \quad \text{CO₂Me} \\
\text{O} & \quad \text{CO₂Me} \\
\end{align*}
\]

186 \[\xrightarrow{\text{PO/C}}\]

\[
\begin{align*}
\text{O} & \quad \text{CO₂Me} \\
\text{O} & \quad \text{CO₂Me} \\
\end{align*}
\]

183
Palladium on activated carbon (0.15 g of a 10% w/w dispersion) was added to a magnetically stirred solution of the bisalkene 186 (2.40 g, 6.60 mmol) in THF (70 mL) maintained at room temperature. This suspension was placed under an atmosphere of hydrogen (760 mm Hg) and stirring continued for 12 h. The resulting black mixture was filtered through a pad of Celite® and the filtrate concentrated under reduced pressure to afford the product 183 (2.30 g, 95%) as a pale, yellow oil.

$^1\text{H NMR}$ (300 MHz, CDCl$_3$) $\delta$ 6.69 (s, 2H), 4.40 (sep, $J = 6.1$ Hz, 2H), 3.66 (s, 6H), 2.85 (t, $J = 7.9$ Hz, 4H), 2.55 (t, $J = 7.9$ Hz, 4H), 1.28 (d, $J = 6.1$ Hz, 12H).

$^{13}\text{C NMR}$ (75.4 MHz, CDCl$_3$) $\delta$ 173.9 (2 x C), 148.0 (2 x C), 131.9 (2 x C), 119.7 (2 x CH), 72.7 (2 x CH), 52.2 (2 x CH$_3$), 35.9 (2 x CH$_2$), 27.7 (2 x CH$_2$), 22.8 (4 x CH$_3$).

Infrared Spectrum (KBr) $\nu_{\text{max}}$ 2975, 1738, 1507, 1282, 1195, 1112 cm$^{-1}$.

Mass Spectrum (70 eV) m/z 366 (M+, 96%), 324 [(M-CH$_2$CHCH$_3$)+, 17%], 282 [(M-2xCH$_2$CHCH$_3$)+, 100%], 250 (36), 222 (67), 209 (38), 190 (58), 149 (40), 91 (14).

HRMS C$_{20}$H$_{30}$O$_6$ requires: M+, 366.2042. Found: M+, 366.2043.

Elemental Analysis C$_{20}$H$_{30}$O$_6$ requires: C, 65.55; H, 8.25. Found: C, 65.72; H, 8.50%.
6-(Dichloromethyl)-1,3-benzodioxole-5-carboxaldehyde (192) and 6-(Dichloromethyl)-1,3-benzodioxole-4-carboxaldehyde (193)

1-Dichloromethoxy-butane (5.15 g, 33.0 mmol) was added dropwise to a magnetically stirred solution of piperonal (188) (1.00 g, 6.60 mmol) and tin(IV) chloride (3.85 mL, 33.0 mmol) in CH₂Cl₂ (25 mL) maintained at 0 °C under an atmosphere of nitrogen. The cooling bath was removed from the now purple solution which was stirred for a further 2 h at room temperature then poured into ice water (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic fractions were washed with water (1 x 100 mL) then dried (MgSO₄), filtered and concentrated under reduced pressure to yield a yellow solid. Subjection of this material to flash chromatography (3:2 v/v CH₂Cl₂/petrol elution) produced two major fractions, A and B.

Concentration of fraction A (Rf = 0.5) gave 6-(dichloromethyl)-1,3-benzodioxole-5-carboxaldehyde (192) (50 mg, 4%) as a yellow solid, m.p. 72-74 °C.

¹H NMR (300 MHz, CDCl₃) δ 9.94 (s, 1H), 7.97 (s, 1H), 7.50 (s, 1H), 7.16 (s, 1H), 6.12 (s, 2H).

¹³C NMR (75.4 MHz, CDCl₃) δ 189.9 (C), 152.3 (C), 148.9 (C), 137.8 (C), 125.5 (C), 112.0 (CH), 108.9 (CH), 102.8 (CH), 66.5 (CH₂).
Infrared Spectrum (KBr) $v_{\text{max}}$ 2915, 1694, 1611, 1506, 1487, 1374, 1280, 1262, 1037, 931, 797, 754, 715 cm$^{-1}$.

Mass Spectrum (70 eV) $m/z$ 236 (10), 234 (36), 232 (M$^+$, 45%), 199 (50), 197 [(M-Cl$^+$)+,100], 169 (46), 133 (33), 111 (24), 75 (44).


Concentration of fraction B ($R_f = 0.4$) gave 6-dichloromethyl-1,3-benzodioxole-4-carboxaldehyde (193) (20 mg, 2%) as a yellow solid, m.p. 114-116 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 10.12 (s, 1H), 7.36 (d, $J = 1.8$ Hz, 1H), 7.32 (d, $J = 1.8$ Hz, 1H), 6.66 (s, 1H), 6.19 (s, 2H).

$^{13}$C NMR (75.4 MHz, CDCl$_3$) $\delta$ 186.9 (C), 151.1 (C), 150.1 (C), 134.9 (C), 118.4 (CH), 117.9 (C), 111.4 (CH), 103.8 (CH), 71.2 (CH$_2$).

Infrared Spectrum (KBr) $v_{\text{max}}$ 2913, 1691, 1635, 1472, 1448, 1267, 1052, 926, 735 cm$^{-1}$.

Mass Spectrum (70 eV) $m/z$ 236 (5), 234 (21), 232 (M$^+$, 31%), 199 (60), 197 [(M-Cl$^+$)+, 100%], 167 (16), 111 (12), 75 (40).


X-ray Crystallographic Analysis See Appendix 1; A.1.1.

The poor mass balance associated with this reaction is due to the decomposition of starting material 188 under the harsh conditions employed.
Sodium hydroxide (80 \( \mu \)L of a 20% w/v methanolic solution) was added, in one portion, to a magnetically stirred solution of the compound 192 (50 mg, 0.22 mmol) and acetone (20 \( \mu \)L, 0.25 mmol) in cold methanol (100 \( \mu \)L). Stirring was continued for 0.2 h then the mixture was left to stand for 3 days. The solid thus obtained was removed by filtration and then washed with CHCl₃ (3 x 10 mL). The combined filtrates were concentrated under reduced pressure to yield the title compound 189 (24.5 mg, 62%) as a colourless solid, m.p. 143-145 °C (lit. 147 °C). The spectral data derived from this material were identical, in all respects, with those reported in the literature.\(^5\)

\(^{1}\text{H NMR}\) (300 MHz, CDCl₃) \( \delta \) 10.47 (s, 2H), 7.40 (s, 2H), 6.17 (s, 2H).

1,2-Bis(chloromethyl)-4,5-dimethoxybenzene (195)

\[ \text{MeO} \] \[ \text{MeO} \] \[ \text{MeO} \] \[ \text{MeO} \] \[ \text{CH₃O, 1,4-dioxane} \] \[ \text{HCl (concentrated)} \] \[ \text{HCl (gas)} \] \[ \text{MeO} \] \[ \text{MeO} \] \[ \text{Cl} \] \[ \text{Cl} \] \[ 194 \] \[ 195 \]
Formaldehyde (3 mL of a 35% aqueous solution) was added, in one portion, to a magnetically stirred solution of veratrole (194) (3.87 mL, 30.4 mmol) and HCl (4 mL of a conc. solution) in 1,4-dioxane (25 mL) maintained at 0 °C under an atmosphere of HCl. Stirring was continued for 0.75 h, then a second aliquot of formaldehyde (3 mL of a 35% aqueous solution) was added, in one portion. After 2 h the ice bath was removed and the mixture left to stand at room temperature for 16 h. Water (50 mL) was then added to the reaction mixture which was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to yield a colourless solid. This material was passed through a pad of silica (3:2 v/v CH₂Cl₂/petrol elution) to give the bis(chloromethylated) product 195 (2.00 g, 28%) as a colourless solid, m.p. 74-76 °C (lit. m.p. 76-78 °C). The spectral data derived from this material were identical, in all respects, with those reported in the literature.

¹H NMR (300 MHz, CDCl₃) δ 6.87 (s, 2H), 4.71 (s, 4H), 3.91 (s, 6H).

5-(3,4-Dimethoxy-6-hydroxymethylphenyl)-2-oxo-pentanoic acid Methyl ester (197)

Methyl acetoacetate (27 μL, 0.25 mmol) was added, dropwise, to a magnetically stirred mixture of sodium hydride (50.0 mg, 0.21 mmol) in THF (630 μL) maintained at 0 °C
under an atmosphere of nitrogen. The resulting colourless solution was stirred at 0 °C for 10 min, then \textit{n}-butyllithium (106 µL of a 1.6 M solution in THF, 0.27 mmol) was added dropwise and the reaction mixture stirred at 0 °C for a further 10 min. The ensuing solution was then added, dropwise, to a magnetically stirred solution of the bis(chloromethyl) compound 195 (50.0 mg, 0.21 mmol) in THF (150 µL) maintained at 0 °C under an atmosphere of nitrogen. The resulting mixture was stirred at 0 °C for 10 min, then at room temperature for 15 min, after which time the solution was diluted with water (2 mL) and extracted with ether (3 x 2 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure to yield the \textit{title compound} 197 (50 mg, 81%) as a clear, colourless oil.

\textbf{1H NMR} (300 MHz, CDCl₃) δ 6.75 (s, 1H), 5.75 (s, 1H), 3.87 (s, 6H), 3.70 (s, 3H), 3.62-3.43 (m, 2H), 3.16-3.05 (m, 2H), 2.85 (s, 2H), 2.63-2.60 (m, 2H).

\textbf{13C NMR} (75.4 MHz, CDCl₃) δ 206.2 (C), 169.9 (C), 147.8 (C), 147.5 (C), 132.3 (C), 129.1 (C), 113.5 (CH), 112.4 (CH), 59.4 (CH₃), 56.1 (CH₃), 56.0 (CH₃), 52.2 (CH₂), 44.1 (CH₂), 33.1 (CH₂), 30.4 (CH₂).

\textbf{Infrared Spectrum} (KBr) νₜₘₐₓ 3389, 2953, 1743, 1703, 1517, 1453, 1267, 1232, 1141, 1111 cm⁻¹.

\textbf{Mass Spectrum} (70 eV) m/z 278 [(M-H₂O)⁺, 95%], 266 (37), 246 (41), 219 (35), 177 (42), 151 (100).

\textbf{HRMS} C₁₅H₁₈O₅ requires: (M-H₂O)⁺, 278.1154. Found: (M-H₂O)⁺, 278.1151.
5-(4,5-Dimethoxy-2-formylphenyl)-2-oxo-pentanoic acid Methyl ester (198)

Pyridinium chlorochromate (48.0 mg, 0.22 mmol) was added to a magnetically stirred solution of alcohol 197 (50.0 mg, 0.17 mmol) in CH$_2$Cl$_2$ (0.5 mL) maintained at room temperature under an atmosphere of nitrogen. Stirring was continued for 2 h, then ether (2 mL) was added to the reaction mixture which was then filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure to give the aldehyde 198 (48.0 mg, 96%) as a clear, colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.81 (s, 1H), 7.21 (s, 1H), 6.58 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.85-3.81 (m, 2H), 3.68 (s, 3H), 3.46-3.42 (m, 2H), 2.80-2.75 (m, 2H).

Infrared Spectrum (KBr) $\nu_{max}$ 2930, 2852, 1745, 1715, 1607, 1518, 1262, 1101, 1024 cm$^{-1}$.

Due to the sensitivity of compound 198 it was not subject to any further spectroscopic characterisation.
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1,2-Bis(chloromethyl)-4,5-bis(1-methylethoxy)benzene (200)

Formaldehyde (5 mL of a 35% aqueous solution) was added, in one portion, to a magnetically stirred solution of compound 184 (10.0 g, 51.5 mmol) and HCl (6.7 mL of a 37% w/w aqueous solution) in DME (50 mL) maintained at 0 °C under an atmosphere of HCl. Stirring was continued for 0.75 h, then a second aliquot of formaldehyde (5 mL of a 35% aqueous solution) was added, in one portion, and stirring was continued for 2 h. After this time the ice bath was removed and the solution was stirred at room temperature for 16 h. Water (50 mL) was then added and the mixture extracted with CH₂Cl₂ (3 x 50 mL), dried (MgSO₄), filtered and concentrated under reduced pressure to yield a colourless solid. This material was passed through a pad of silica (3:2 v/v CH₂Cl₂/petrol elution) and concentration of the appropriate fractions (Rf = 0.4) then gave the title compound 200 (11.6 g, 78%) as colourless prisms, m.p. 69-70 °C.

¹H NMR (300 MHz, CDCl₃) δ 6.91 (s, 2H), 4.67 (s, 4H), 4.49 (sep, J = 6.0 Hz, 2H), 1.34 (d, J = 6.0 Hz, 12 H).

¹³C NMR (75.4 MHz, CDCl₃) δ 150.0 (2 x C), 129.9 (2 x C), 120.3 (2 x CH), 72.9 (2 x CH), 44.0 (2 x CH₂), 22.8 (4 x CH₃).
**Infrared Spectrum** (KBr) $v_{\text{max}}$ 2980, 1600, 1518, 1379, 1282, 1256, 1220, 1138, 1096, 928, 682 cm$^{-1}$.

**Mass Spectrum** (70 eV) $m/z$ 294 (6), 292 (25), 290 (M$^+$, 31%), 252 (3), 250 (10), 248 [(M-CH$_2$CHCH$_3$)$^+$, 15%], 210 (17), 208 (47), 206 [(M-2xCH$_2$CHCH$_3$)$^+$, 62%], 173 (45), 171 [(M-(2xCH$_2$CHCH$_3$)Cl$^+$), 100%], 136 [(M-(2xCH$_2$CHCH$_3$)Cl$_2$)$^+$, 30%].

**HRMS** C$_{14}$H$_{20}$Cl$_2$O$_2$ requires: M$^+$, 290.0840. Found: M$^+$; 290.0838.

**Elemental Analysis** C$_{14}$H$_{20}$Cl$_2$O$_2$ requires: C, 57.74; H, 6.92; Cl, 24.35. Found: C, 58.01; H, 6.63; Cl, 24.60%.

2,3-Bis(1-methylethoxy)-7-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene-6,8-dicarboxylic acid Dimethyl ester (201)

Dimethyl-1,3-acetonedicarboxylate (16.5 mL, 112 mmol) in CH$_2$Cl$_2$ (60 mL) was added, in one portion, to a magnetically stirred solution of the bis(chloromethyl) compound 200 (12.0 g, 41.3 mmol), tetra-$n$-butylammonium bromide (7.41 g, 23.0 mmol) and NaHCO$_3$ (500 mL of a 5% aqueous solution) in CH$_2$Cl$_2$ (60 mL) maintained at room temperature under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature for 12 h
then diluted with water (100 mL) and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated under reduced pressure to yield a yellow oil which was immediately subjected to the next step in the reaction sequence (see below).

**2,3-Bis(1-methylethoxy)-5,6,8,9-tetrahydro-7H-benzocyclohepten-7-one (172)**

![Chemical structure](image)

Sulfuric acid (500 mL of a 15% aqueous solution) was added to the yellow oil derived from the previous reaction and the resulting solution heated at reflux for 48 h. The cooled reaction mixture was then treated with water (100 mL) followed by solid NaCl and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with NaHCO₃ (1 x 150 mL of a saturated aqueous solution) and brine (1 x 150 mL), then dried (MgSO₄), filtered and concentrated under reduced pressure to yield a yellow solid. Subjection of this material to flash chromatography (1:4 v/v ethyl acetate/petrol elution) and concentration of the appropriate fractions (Rf = 0.7) afforded the title compound **172** (10.0 g, 88%) as a pale yellow solid, m.p. 44-46 °C.
\( ^1H \text{NMR} \) (300 MHz, CDCl\textsubscript{3}) \( \delta \) 6.79 (s, 2H), 4.45 (sep, \( J = 6.0 \) Hz, 2H), 2.83-2.79 (m, 4H), 2.61-2.57 (m, 4H), 1.33 (d, \( J = 6.0 \) Hz, 12H).

\( ^13C \text{NMR} \) (75.4 MHz, CDCl\textsubscript{3}) \( \delta \) 212.3 (C), 148.3 (2 x C), 134.4 (2 x C), 120.2 (2 x CH), 73.0 (2 x CH\textsubscript{2}), 45.4 (2 x CH\textsubscript{2}), 30.8 (2 x CH\textsubscript{2}), 22.9 (4 x CH\textsubscript{3}).

**Infrared Spectrum** (KBr) \( \nu_{\text{max}} \) 2974, 1701, 1506, 1280, 1111, 949 cm\(^{-1}\).

**Mass Spectrum** (70 eV) \( m/z \) 276 (M\(^+\), 47\%), 234 [(M-CH\textsubscript{2}CHCH\textsubscript{3})\(^+\), 17\%], 192 [(M-2xCH\textsubscript{2}CHCH\textsubscript{3})\(^+\), 100\%], 164 (30), 149 (28), 136 (18), 91 (16), 77 (12).

**HRMS** \( \text{C}_{17}\text{H}_{24}\text{O}_3 \) requires: M\(^+\), 276.1725. Found: M\(^+\), 276.1722.

**Elemental Analysis** \( \text{C}_{17}\text{H}_{24}\text{O}_3 \) requires: C, 73.88; H, 8.75. Found: C, 73.64; H, 8.51\%.
Chapter 7

7.4 Experimental Details Associated with Work Described in Chapter 4

2,3,2',3'-Tetra(1-methylethoxy)-5,6,8,9,5',6',8',9'-octahydro-[7,7']bibenzocycloheptenylidene (209)

Titanium(IV) chloride (0.59 mL, 5.43 mmol) was added, in one portion, to a magnetically stirred solution of compound 172 (1.00 g, 3.62 mmol) in DME (25 mL) maintained at -10 °C under an atmosphere of nitrogen. Zinc powder (0.71 g) suspended in DME (20 mL) was then added, in small portions, and the resulting mixture heated at reflux for 48 h. The cooled reaction mixture was then treated with K₂CO₃ (25 mL of a 10% aqueous solution) and the ensuing mixture extracted with ether (3 x 50 mL), dried (MgSO₄), filtered and concentrated under reduced pressure to yield a colourless solid. Subjection of this material to flash chromatography (1:9 v/v ethyl acetate/petrol elution) and concentration of the appropriate fractions (Rf = 0.6) yielded the alkene 209 (924 mg, 98%) as a colourless, crystalline solid, m.p. 152-154 °C.
$^1$H NMR (300 MHz, CDCl$_3$) δ 6.66 (s, 4H), 4.39 (sep, $J = 6.1$ Hz, 4H), 2.66-2.63 (m, 8H), 2.42-2.38 (m, 8H), 1.28 (d, $J = 6.1$ Hz, 24H).

$^{13}$C NMR (75.4 MHz, CDCl$_3$) δ 147.3 (4 x C), 136.1 (2 x C), 134.6 (4 x C), 120.8 (4 x CH), 72.9 (4 x CH), 36.3 (4 x CH$_2$), 32.2 (4 x CH$_2$), 22.9 (8 x CH$_3$).

**Infrared Spectrum** (KBr) $\nu_{\text{max}}$ 2975, 2919, 1510, 1200, 1113, 1100, 962 cm$^{-1}$.

**Mass Spectrum** (70 eV) m/z 520 (M$^+$, 100%), 478 [(M-CH$_2$CHCH$_3$)$^+$, 20%], 436 [(M-2xCH$_2$CHCH$_3$)$^+$, 10%], 394 [(M-3xCH$_2$CHCH$_3$)$^+$, 12%], 352 [(M-4xCH$_2$CHCH$_3$)$^+$, 20%], 175 (43), 149 (45), 137 (40).

**HRMS** C$_{34}$H$_{48}$O$_4$ requires: M$^+$, 520.3552. Found: M$^+$, 520.3552.

**Elemental Analysis** C$_{34}$H$_{48}$O$_4$ requires: C, 78.42; H, 9.29. Found: C, 78.59; H, 9.21%.

2,3,2',3'-Tetra(1-methylethoxy)-5,6,8,9,5',6',8',9'-octahydro-[7,7']bibenzocycloheptenyldiene (209) and 2,3,2',3'-Tetra(1-methylethoxy)-5,6,8,9,5',6',8',9'-octahydro-[7,7']bibenzocycloheptenyl-7,7'-diol (211)
Method A. Titanium(IV) chloride/Zinc

A mixture of benzosuberone 172 (500 mg, 1.81 mmol) and pyridine (129 µL) in THF (500 µL) was added slowly to a magnetically stirred solution of titanium (IV) chloride (213 µL, 1.94 mmol) and zinc powder (258 mg, 3.95 mmol) in THF (5 mL) maintained at 0 °C under an atmosphere of nitrogen. The resulting mixture was heated at reflux for 20 h, then the cooled solution was treated with K₂CO₃ (20 mL of a 10% saturated aqueous solution) and extracted with ether (3 x 20 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford a yellow oil. This material was passed through a pad of silica (1:9 v/v ethyl acetate/petrol then neat ethyl acetate elution) to yield two fractions, A and B.

Concentration of fraction A (Rf = 0.6) afforded the alkene 209 (55.0 mg, 12%) as a colourless, crystalline solid, which was identical, in all respects, with the material obtained previously.

Concentration of fraction B (Rf = 0.1) yielded the pinacol 211 (300 mg, 64%) as a colourless, crystalline solid, m.p. 49-51 °C.

\[ ^1H \text{NMR} \quad (300 \text{ MHz, CDCl}_3) \delta \ 6.65 \ (s, 4H), \ 4.38 \ (\text{sep, } J = 6.1 \text{ Hz, } 4H), \ 3.10 \ (t, J = 13.2 \text{ Hz, } 4H), \ 2.41-2.34 \ (m, 4H), \ 2.04-1.95 \ (m, 6H), \ 1.45 \ (t, J = 12.8 \text{ Hz, } 4H), \ 1.29 \ (dd, J = 6.1 \text{ and } 1.5 \text{ Hz, } 24H). \]

\[ ^{13}C \text{NMR} \quad (300 \text{ MHz, CDCl}_3) \delta \ 146.9 \ (4 \times C), \ 136.2 \ (4 \times C), \ 119.3 \ (4 \times CH), \ 78.6 \ (2 \times C), \ 72.4 \ (4 \times CH), \ 33.1 \ (4 \times CH_2), \ 28.8 \ (4 \times CH_2), \ 22.4 \ (8 \times CH_3). \]
**Infrared Spectrum** (KBr) $v_{\text{max}}$ 3479, 2973, 2931, 1505, 1381, 1289, 1193, 1111, 959, 915, 733 cm$^{-1}$.

**Mass Spectrum** (70 eV) $m/z$ 554 (M$^+$, 2%), 536 (3), 518 (2), 394 (20), 336 (31), 278 (61), 234 (27), 194 (100), 176 (96), 156 (55).

**HRMS** $C_{35}H_{50}O_6$ requires: M$^+$, 554.3607. Found: M$^+$, 554.3601.

**Elemental Analysis** $C_{35}H_{50}O_6\cdot H_2O$ requires: C, 71.29; H, 9.15. Found: C, 70.88; H, 8.95%.

**Method B. Titanium(IV) chloride/Amalgamated Magnesium**

Magnesium powder (263.9 mg, 10.9 mmol) was added, in one portion, to a magnetically stirred solution of mercury(II) chloride (78.2 mg, 289.6 mmol) in THF (1 mL) maintained at room temperature under an atmosphere of nitrogen. Stirring was continued for 0.5 h, then the supernatant liquid was withdrawn and the amalgam washed with THF (3 x 2 mL). THF (2 mL) was added and the mixture cooled to $-$10 °C, then titanium(IV) chloride (590 µL, 5.43 mmol) was added dropwise, followed by a solution of benzosuberone 172 (1.00 g, 3.62 mmol) in THF (1.5 mL). The resulting mixture was stirred at 0 °C for 16 h and then treated with $K_2CO_3$ (5 mL of a saturated aqueous solution) and extracted with ether (2 x 5 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield pinacol 211 (780 mg, 78%) as a colourless, crystalline solid, which was identical, in all respects, with that obtained previously.
Sodium hydroxide (1.2 mL of a 50% aqueous solution) was added, in one portion, to a magnetically stirred solution of the alkene 209 (100 mg, 0.19 mmol) and benzyltriethylammonium chloride (12.8 mg, 0.06 mmol) in CHCl₃ (5 mL) maintained at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 12 h, after which time water (5 mL) was added and the mixture extracted with petrol (3 x 50 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated under reduced pressure to yield the title gem-dichlorocyclopropane 212 (112 mg, 98%) as a pale yellow oil.

**1H NMR** (300 MHz, CDCl₃) δ 6.66 (s, 4H), 4.40 (sep, J = 6.1 Hz, 4H), 2.90-2.87 (m, 4H), 2.65-2.57 (m, 4H), 1.98-1.85 (m, 8H), 1.29 (d, J = 6.1 Hz, 24H).

**13C NMR** (75.4 MHz, CDCl₃) δ 146.8 (4 x C), 135.1 (4 x C), 119.7 (4 x CH), 77.8 (C), 72.4 (4 x CH), 39.6 (2 x C), 32.4 (4 x CH₂), 31.5 (4 x CH₂), 22.4 (8 x CH₃).

**Infrared Spectrum** (KBr) νmax 2974, 2928, 1505, 1381, 1287, 1194, 1111, 941 cm⁻¹.

**Mass Spectrum** (70 eV) m/z 606 (10), 604 (60), 602 (M⁺, 80%), 568 (12), 566 [(M-Cl⁺), 40%], 532 [(M-Cl₂)⁺, 20%], 439 (10), 362 (10), 217 (40), 149 (50), 137 (100).
**HRMS** \( C_{35}H_{48}^{37}\text{Cl}_2\text{O}_4 \) requires: \( M^+ \), 606.2870. Found: \( M^+ \), 606.2870.

4',4'-Dimethyl-3',5'-dioxa-5,5'',6,6'',8,8'',9,9''-octahydro-2,2'',3,3''-tetra(1-methylethoxy)-dispiro[7H-benzocycloheptene-7,1'-cyclopentane-2',7''-7''H-benzocycloheptene] (213)

Acetone (100 µL) was added, in one portion, to a magnetically stirred solution of pinacol 211 (100 mg, 0.18 mmol) and para-toluenesulfonic acid (3.00 mg, 0.02 mmol) in 2,2-dimethoxypropane (350 µL) maintained at room temperature under an atmosphere of nitrogen. Stirring was continued for 2 h, then sodium hydroxide (250 µL of a 10% aqueous solution) was added and the resulting solution stirred for a further 10 min then diluted with water (2 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated under reduced pressure to give the **acetonide** 213 (30.0 mg, 28%) as a yellow oil.

**\(^1\text{H NMR}**** (300 MHz, CDCl₃) \( \delta \) 6.66 (s, 4H), 4.40 (sep, \( J = 6.1 \text{ Hz}, 4\text{H} \)), 3.21-3.12 (m, 4H), 2.47-2.39 (m, 4H), 2.18-2.11 (m, 4H), 1.52 (s, 6H), 1.30 (d, \( J = 5.1 \text{ Hz}, 24\text{H} \)), 1.29-1.20 (m, 4H).
\(^{13}\text{C}\) NMR (75.4 MHz, CDCl\(_3\)) \(\delta\) 146.7 (4 x C), 136.2 (4 x C), 119.3 (4 x CH), 106.5 (C), 86.7 (2 x C), 72.3 (4 x CH), 33.9 (4 x CH\(_2\)), 30.0 (2 x CH\(_3\)), 29.2 (4 x CH\(_2\)), 22.3 (8 x CH\(_3\)).

Infrared Spectrum (KBr) \(v_{\text{max}}\) 2973, 2932, 1505, 1379, 1291, 1229, 1112, 1073, 967, 917, 733 cm\(^{-1}\).

Mass Spectrum (70 eV) \(m/z\) 594 (M\(^+\), 100%), 582 (25), 579 [(M-CH\(_3\))\(^+\), 2%], 552 [(M-CH\(_2\)CHCH\(_3\))\(^+\), 4%].

HRMS \(C_{37}H_{54}O_6\) requires: M\(^+\), 594.3920. Found: M\(^+\), 594.3926.

3',5'-Dioxa-5,5",6,6"8,8",9,9"-octahydro-2,2",3,3"-tetra(1-methylethoxy)-dispiro[7H-benzocycloheptene-7,1'-cyclopentane-2',7"-7"H-benzocycloheptene]-4'-one (214)

A solution of triphosgene (164 mg, 0.55 mmol) in CH\(_2\)Cl\(_2\) (3 mL) was added, dropwise, to a magnetically stirred solution of pinacol 211 (620 mg, 1.11 mmol) and pyridine (538 \(\mu\)L, 6.66 mmol) in CH\(_2\)Cl\(_2\) (3 mL) maintained at -70 °C under an atmosphere of nitrogen. The resulting solution was warmed to room temperature over 20 h then treated with NH\(_4\)Cl (5 mL of a saturated aqueous solution) and extracted with CH\(_2\)Cl\(_2\) (3 x 5 mL). The combined organic extracts were washed with H\(_2\)SO\(_4\) (1 x 5 mL of a 15% aqueous solution), NaHCO\(_3\)
(1 x 5 mL of a saturated aqueous solution) and brine (1 x 5 mL) then dried (MgSO₄), filtered and concentrated under reduced pressure to yield the carbonate 214 (430 mg, 67%) as a colourless, crystalline solid, m.p. 192-196 °C.

**¹H NMR** (300 MHz, CDCl₃) δ 6.66 (s, 4H), 4.38 (sep, J = 6.1 Hz, 4H), 3.17-3.08 (m, 4H), 2.50 (dd, J = 14.7 and 6.3 Hz, 4H), 2.28-2.21 (m, 4H), 1.49-1.40 (m, 4H), 1.28 (d, J = 6.1 Hz, 24H).

**¹³C NMR** (75.4 MHz, CDCl₃) δ 153.8 (C), 147.2 (4 x C), 134.7 (4 x C), 119.3 (4 x CH), 90.3 (2 x C), 72.4 (4 x CH), 32.6 (4 x CH₂), 28.6 (4 x CH₂), 22.3 (8 x CH₃).

**Infrared Spectrum** (KBr) νₘₐₓ 2974, 1799, 1505, 1443, 1381, 1277, 1168, 1107, 1060, 1005, 917, 732 cm⁻¹.

**Mass Spectrum** (70 eV) m/z 580 (M⁺, 100%), 538 [(M-CH₂CHCH₃)+, 11%], 496 [(M-2xCH₂CHCH₃)+, 4%], 454 [(M-3xCH₂CHCH₃)+, 6%], 412 [(M-4xCH₂CHCH₃)+, 20%], 350 (12), 206 (40), 175 (26), 137 (20).

**HRMS** C₃₅H₄₈O₇ requires: M⁺, 580.3400. Found: M⁺, 580.3400.

**X-ray Crystallographic Analysis** See Appendix 1; A.1.2.
Boron(III) chloride (7 mL of a 1 M solution in CH$_2$Cl$_2$, 6.64 mmol) was added slowly to a magnetically stirred solution of compound 212 (500 mg, 0.83 mmol) in CH$_2$Cl$_2$ (22 mL) maintained at 0 °C under an atmosphere of nitrogen. Stirring was continued for 0.5 h then methanol (10 mL) was slowly added (CAUTION!) and the resulting solution was passed through a pad of silica (1:9 v/v ethyl acetate/petrol then neat methanol elution). The appropriate fractions were concentrated under reduced pressure to yield the tetraol 215 (353 mg, 98%) as a brown, crystalline solid, m.p. 174-176 °C.

$^1$H NMR (300 MHz, CD$_3$OD) δ 6.53 (s, 4H), 2.78-2.82 (m, 4H), 2.50-2.57 (m, 4H), 1.87 (br s, 8H) (4 x –OH proton resonances were not observed).

$^{13}$C NMR (75.4 MHz, CD$_3$OD) δ 143.6 (4 x C), 134.4 (4 x C), 117.3 (4 x CH), 79.3 (C), 41.2 (2 x C), 33.3 (4 x CH$_2$), 33.1 (4 x CH$_2$).

Infrared Spectrum (KBr) $\nu_{\text{max}}$ 3324, 2925, 1611, 1518, 1450, 1353, 1296, 1193, 1093, 1014 cm$^{-1}$.

Mass Spectrum (70 eV) $m/z$ 438 (1), 436 (2), 434 (M$^+$, 3%), 400 (3), 398 [(M-HCl)$^+$, 7%], 362 [(M-2HCl)$^+$, 2%], 243 (21), 175 (24), 149 (35), 136 (66) 123 (100).
HRMS C_{23}H_{23}ClO_4 requires: (M-HCl)^+, 398.1284. Found: (M-HCl)^+, 398.1284

X-ray Crystallographic Analysis  See Appendix 1, A.1.3.

3',5'-Dioxa-5.5",6,6",8,8",9,9"-octahydro-2,2",3,3"-tetrahydroxy-dispiro[7H-benzocycloheptene-7,1'-cyclopentane-2',7"-7"H-benzocycloheptene]-4'-one (216)

Boron(III) chloride (1 mL of a 1 M solution in CH_2Cl_2, 1.02 mmol) was added, in one portion, to a magnetically stirred solution of carbonate 214 (100 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) maintained at 0 °C under an atmosphere of nitrogen. Stirring was continued for 0.5 h, then methanol (10 mL) was slowly added (CAUTION!) and the resulting solution was passed through a pad of silica (1:9 v/v ethyl acetate/petrol then neat methanol elution). The appropriate fractions were concentrated under reduced pressure to yield tetraol 216 (68.6 mg, 98%) as a brown, crystalline solid, m.p. 163-165 °C.

^1H NMR (300 MHz, CD_3OD) δ 6.54 (s, 4H), 2.99-2.90 (m, 4H), 2.46-2.39 (m, 4H), 2.17-2.10 (m, 4H), 1.31 (t, J = 13.4 Hz, 4H) (4 x -OH proton resonances were not observed).

^13C NMR (75.4 MHz, CD_3OD) δ 158.5 (C), 146.9 (4 x C), 136.9 (4 x C), 119.9 (4 x CH), 95.0 (2 x C), 36.6 (4 x CH_2), 32.1 (4 x CH_2).
Infrared Spectrum (KBr) $v_{\text{max}}$ 3378, 2962, 1754, 1520, 1293, 1260, 1098, 1056, 1021, 801 cm$^{-1}$.

Mass Spectrum (70 eV) $m/z$ 412 (M$^+$, 100%), 368 (12), 350 (50), 213 (26), 201 (28), 175 (91), 149 (40), 137 (85), 123 (31).


Elemental Analysis $\text{C}_{23}\text{H}_{24}\text{O}_7\cdot\text{H}_2\text{O}$ requires: C, 64.18; H, 6.08. Found: C, 64.43; H, 6.08%.

3',3'-Dichloro-5,5",6,6",8,8",9,9"-octahydro-dispiro[7H-benzocycloheptene-7,1'-'cyclopropane-2',7"-7"H-benzocycloheptene]-2,2",3,3"-tetraone (223)

A solution of (diacetoxyiodo)benzene (148 mg, 0.46 mmol) in methanol (1.2 mL) was added, via cannula, to a magnetically stirred solution of the tetraol 215 (100 mg, 0.23 mmol) in methanol (5 mL) maintained at room temperature under an atmosphere of nitrogen. Stirring was continued for 0.5 h, then the solution was concentrated under reduced pressure to afford the bis-ortho-benzaquinone 223 (96.0 mg, 97%) as a yellow oil. Due to the sensitivity of compound 223, it was not subject to spectroscopic characterisation.
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3',5'-Dioxa-5',5'',6,6'',8,8'',9,9''-octahydro-dispiro[7H-benzocycloheptene-7,1'-'cyclopentane-2',7''-7''H-benzocycloheptene]-2,2'',3,3'',4'-pentaone (224)

A solution of (diacetoxyiodo)benzene (386 mg, 1.04 mmol) in methanol (2 mL) was added, via cannula, to a magnetically stirred solution of the tetraol 216 (214 mg, 0.52 mmol) in methanol (10 mL) maintained at room temperature under an atmosphere of nitrogen. Stirring was continued for 0.5 h, then the solvent was removed under reduced pressure to yield the bis-ortho-benzoquinone 224 (207 mg, 98%) as a yellow oil.

Due to the sensitivity of compound 224, it was not subject to spectroscopic characterisation.
Cyclopentene (232) (7 mL) was added, in one portion, to a teflon reaction chamber containing a solution of the bis-ortho-quinone 224 (211 mg, 0.52 mmol) in CH$_2$Cl$_2$/methanol (5 mL of a 4:1 v/v solution) maintained at room temperature under an atmosphere of nitrogen. The teflon reaction chamber was then sealed and pressurised at 19 kbar for 4 h. After depressurisation, the reaction mixture was concentrated under reduced pressure and the residue subjected to a preparative TLC plate (2:3 v/v ethyl acetate/petrol elution) and the appropriate band (R$_f$ = 0.3) was extracted with chloroform to give what is tentatively assigned as a 1:1:1 mixture of Diels-Alder adducts 233, 234 and 235 (27 mg, 10% combined yield) as a yellow glass. These diastereomers could not be separated from one another and were, therefore, characterised as the mixture.
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$^1$H NMR (300 MHz) $\delta$ 3.22-3.16 (m), 2.80-2.68 (m), 2.23-1.44 (m), 1.24-1.18 (m), 0.94-0.82 (m).

$^{13}$C NMR (75.4 MHz) $\delta$ 190.6 (C), 190.5 (C), 152.8 (C), 152.6 (C), 139.9 (C), 139.5 (C), 139.2 (C), 90.2 (C), 90.1 (C), 89.7 (C), 60.4 (CH), 60.3 (CH), 60.1 (CH), 42.4 (CH), 42.3 (CH), 42.1 (CH), 31.7 (CH$_2$), 31.6 (CH$_2$), 31.5 (CH$_2$), 30.6 (CH$_2$), 30.5 (2 x CH$_2$), 29.6 (2 x CH$_2$), 27.6 (2 x CH$_2$), 27.5 (2 x CH$_2$). (See Appendix A.1.4)

Infrared Spectrum (KBr) $v_{max}$ 3452, 2950, 1797, 1728, 1451, 1257, 1099, 1037 cm$^{-1}$.

Mass Spectrum (70 eV) $m/z$ 544 (M$^+$, 10%), 488 (100), 470 (40), 358 (80), 183 (86).

HRMS C$_{33}$H$_{36}$O$_7$ requires: M$^+$, 544.2461. Found: M$^+$, 544.2464.

Schiff Base Condensation Between 5,6-Diamino-1,10-phenanthroline (135) and the Mixture of Diels-Alder Adducts 233, 234 and 235

5,6-Diamino-1,10-phenanthroline (135) (10.5 mg, 0.05 mmol) was added, in one portion, to a magnetically stirred solution of the mixture of adducts 233, 234 and 235 (5.00 mg, 0.01
mmol) in ethanol (2 mL) maintained at room temperature under an atmosphere of nitrogen. Acetic acid (0.2 mL) was then added and the mixture heated at reflux for 16 h. The cooled reaction mixture was then treated with solid NaOH (2 pellets) and the ensuing mixture extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were washed with water (3 x 5 mL) and then concentrated under reduced pressure to yield a yellow oil. Subjection of this material to a preparative TLC plate (80:19:1 v/v/v CHCl₃/MeOH/aq. NH₃ elution) and extraction of the appropriate band (R_f = 0.3) with chloroform/methanol (1:1 v/v solution) gave a yellow oil (2.0 mg) and is believed to contain the Schiff base 239 as judged by mass spectral analysis.

Mass Spectrum (FAB) m/z 893 [(M+H)^+].

HRMS (FAB) C_{57}H_{49}N_{8}O_{3} requires: (M+H)^+, 893.3927. Found: (M+H)^+, 893.3952.
7.5 Experimental Details Associated with Work Described in Chapter 5

1,2-Bis(1-methylethoxy)-4-iodobenzene (249)

A solution of molecular iodine (9.78 g, 38.6 mmol) in CHCl₃ (500 mL) was added, dropwise, to a magnetically stirred mixture of compound 184 (5.00 g, 25.7 mmol) and silver acetate (6.43 g, 38.6 mmol) in CHCl₃ (100 mL) maintained at room temperature under an atmosphere of nitrogen. Stirring was continued for 10 h then the silver salts were removed by filtration and the filtrate washed with water (1 x 100 mL), Na₂S₂O₅ (1 x 100 mL of a saturated aqueous solution) and brine (1 x 100 mL). The combined organic phases were then dried (MgSO₄), filtered and concentrated under reduced pressure to yield the iodo compound 249 (8.20 g, 100%) as a yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.20-7.16 (m, 2H), 6.64 (d, J = 8.9 Hz, 1H), 4.45-4.40 (m, 2H), 1.32 (d, J = 6.2 Hz, 6H), 1.31 (d, J = 6.2 Hz, 6H).

¹³C NMR (75.4 MHz, CDCl₃) δ 149.9 (C), 148.9 (C), 130.4 (CH), 126.6 (CH), 119.8 (CH), 83.4 (C), 72.5 (CH), 72.3 (CH), 22.2 (4 x CH₃).

Infrared Spectrum (KBr) ν_max 2975, 2931, 1485, 1382, 1250, 1107, 954, 800 cm⁻¹.
Mass Spectrum (70 eV) m/z 320 (M⁺, 55%), 278 [(M-CH₂CHCH₃)⁺, 35%], 236 [(M-2xCH₂CHCH₃)⁺, 100%], 207 (20), 109 (35), 79 (24).

HRMS C₁₂H₁₇IO₂ requires: M⁺, 320.0273. Found: M⁺, 320.0269.

1,2-Bis(1-methylethoxy)-4-(2-propenyl)benzene (250)

Tetrakis(triphenylphosphine)palladium(0) (721 mg, 0.63 mmol) was added, in one portion, to a magnetically stirred solution of compound 249 (2.00 g, 6.25 mmol) in THF (2.00 mL) maintained at room temperature under an atmosphere of nitrogen. The reaction mixture was heated at reflux for 5 min then treated with allylmagnesium chloride (3.44 mL of a 2 M solution in THF, 6.87 mmol). After 1 h the cooled solution was filtered through a pad of Celite® and the filtrate concentrated under reduced pressure to afford an orange liquid. This material was passed through a pad of silica (3:2 v/v CH₂Cl₂/petrol elution) and concentration of the appropriate fractions (Rᵢ = 0.5) yielded compound 250 (1.46 g, 100%) as an orange liquid.

¹H NMR (300 MHz, CDCl₃) δ 6.85-6.68 (m, 3H), 5.99-5.90 (m, 1H), 5.09-5.03 (m, 2H), 4.49-4.38 (m, 2H), 3.30 (d, J = 6.6 Hz, 2H), 1.32 (d, J = 6.1 Hz, 6H), 1.31 (d, J = 6.6 Hz, 6H).
**13C NMR** (75.4 MHz, CDCl₃) δ 149.1 (C), 147.4 (C), 137.7 (CH), 133.7 (C), 121.5 (CH), 118.6 (CH), 115.5 (CH₂), 72.4 (2 x CH), 72.0 (CH), 39.7 (CH₂), 22.3 (4 x CH₃).

**Infrared Spectrum** (KBr) ν<sub>max</sub> 2974, 2930, 1503, 1381, 1264, 1109, 990, 911, 693 cm⁻¹.

**Mass Spectrum** (70 eV) m/z 234 (M⁺, 50%), 192 [(M-CH₂CHCH₃)+, 25%], 150 [(M-2xCH₂CHCH₃)+, 100%].

**HRMS** C₁₅H₂₂O₂ requires: M⁺, 234.1619. Found: M⁺, 234.1618.

**Elemental Analysis** C₁₅H₂₂O₂ requires: C, 75.88; H, 9.46. Found: C, 77.02; H, 9.20%.

### 3,4-Bis(1-methylethoxy)benzene acetic acid (251)

![Chemical structure](image)

Alkene **250** (1.66 g, 7.09 mmol) and acetic acid (88 mL) in tert-butanol (207 mL) were added, in one portion, to a magnetically stirred solution of potassium permanganate (1.12 g, 7.09 mmol) and sodium periodate (6.06 g, 28.4 mmol) in water (332 mL) maintained at 0 °C. Stirring was continued for 1 h then the reaction mixture was treated with sufficient solid Na₂SO₃ until the purple colour of the reaction mixture had been discharged. At this point, H₂SO₄ (50 mL of a 1 M aqueous solution) was added and the resulting yellow
solution was extracted with ether (3 x 200 mL). The combined organic fractions were dried (MgSO₄), filtered and concentrated under reduced pressure to give a yellow liquid. This material was passed through a pad of silica (1:4 v/v CH₂Cl₂/petrol then 3:2 v/v CH₂Cl₂/petrol elution) to give the acid 251 (1.53 g, 86%) as a pale, yellow oil.

**¹H NMR** (300 MHz, CDCl₃) δ 6.87-6.79 (m, 3H), 4.48-4.41 (m, 2H), 3.55 (s, 2H), 1.33 (d, J = 6.1 Hz, 6H), 1.32 (d, J = 6.1 Hz, 6H) (1 x −OH proton resonance was not observed).

**¹³C NMR** (75.4 MHz, CDCl₃) δ 178.0 (C), 148.9 (C), 148.3 (C), 126.5 (C), 122.4 (CH), 119.1 (CH), 117.9 (CH), 72.2 (CH), 72.1 (CH), 40.5 (CH₂), 22.2 (2 x CH₃), 22.1 (2 x CH₃).

**Infrared Spectrum** (KBr) ν max 2976, 1709, 1505, 1266, 1108, 944 cm⁻¹.

**Mass Spectrum** (70 eV) m/z 252 (M⁺, 25%), 210 [(M-CH₂CHCH₃)⁺, 5%], 168 [(M-2xCH₂CHCH₃)⁺, 100%], 123 (81), 77 (10).

**HRMS** C₁₄H₂₀O₄ requires: M⁺, 252.1361. Found: M⁺, 252.1360.

**Elemental Analysis** C₁₄H₂₀O₄ requires: C, 66.65; H, 7.99. Found: C, 66.65; H, 8.24%.

### 3,4-Bis(1-methylethoxy)benzyl diazomethyl ketone (253)

![Chemical structure of 3,4-Bis(1-methylethoxy)benzyl diazomethyl ketone (253)](image-url)
A solution of acid 251 (50.0 mg, 0.20 mmol) and pyridine (18 µL, 0.22 mmol) in benzene (250 µL) was added, dropwise, to a magnetically stirred solution of oxalyl chloride (30 µL, 0.33 mmol) in benzene (300 µL) maintained at room temperature under an atmosphere of nitrogen. Stirring was continued for 0.5 h then the solution was filtered and concentrated under reduced pressure. The residue was dissolved in benzene (500 µL) and cooled to 0 °C then diazomethane (2 mL of an ether solution) was added carefully and the ensuing solution was stirred at room temperature for 20 h. The resulting solution was diluted with CHCl₃ (5 mL) and concentrated under reduced pressure to yield a yellow oil. Subjection of this material to flash chromatography (1:4 v/v ethyl acetate/petrol elution) and concentration of the appropriate fractions (Rf = 0.4) afforded the diazoketone 253 (54.0 mg, 98%) as a bright yellow oil.

**1H NMR** (300 MHz, CDCl₃) δ 6.87-6.72 (m, 3H), 5.12 (s, 1H), 4.48-4.41 (m, 2H), 3.52 (s, 2H), 1.32 (d, J = 6.2 Hz, 12H).

**13C NMR** (75.4 MHz, CDCl₃) δ 193.6 (C), 149.4 (C), 148.6 (C), 128.1 (C), 122.8 (CH), 119.3 (CH), 118.5 (CH), 72.4 (2 x CH), 54.9 (CH), 47.8 (CH₂), 22.4 (4 x CH₃).

**Infrared Spectrum** (KBr) ν max 2976, 2931, 2103, 1638, 1505, 1357, 1264, 1136, 1108, 989, 949 cm⁻¹.

**Mass Spectrum** (70 eV) m/z 276 (M⁺, 11%), 248 [(M-N₂)⁺, 34%], 206 [(M-N₂CH₂CHCH₃)⁺, 7%], 164 [(M-N₂(2xCH₂CHCH₃))⁺, 70%], 136 (100), 123 (43).

**HRMS** C₁₅H₂₀N₂O₃ requires: M⁺, 276.1473. Found: M⁺, 276.1474.
A solution of diazoketone 253 (275 mg, 1.00 mmol) in CH₂Cl₂ (2 mL) was added, dropwise, to a magnetically stirred solution of rhodium(II) acetate dimer (0.10 mg, 0.0003 mmol) in CH₂Cl₂ (2 mL) maintained at room temperature under an atmosphere of nitrogen. Stirring was continued for 15 min then the mixture was filtered through Whatman® #1 filter paper and the filtrate concentrated under reduced pressure to yield the indan-2-one 173 (248 mg, 100%) as a yellow oil.

**1H NMR** (300 MHz, CDCl₃) δ 6.86 (s, 2H), 4.43 (sep, J = 6.1 Hz, 2H), 3.49 (s, 4H), 1.33 (d, J = 6.1 Hz, 12H).

**13C NMR** (75.4 MHz, CDCl₃) δ 215.8 (C), 148.8 (2 x C), 130.5 (2 x C), 114.9 (2 x CH), 72.5 (2 x CH), 44.1 (2 x CH₂), 22.3 (4 x CH₃).

**Infrared Spectrum** (KBr) ν max 2975, 2931, 1750, 1498, 1311, 1225, 1110, 1078 cm⁻¹.

**Mass Spectrum** (70 eV) m/z 248 (M⁺, 40%), 206 [(M-CH₂CHCH₃)⁺, 25%], 164 [(M-2xCH₂CHCH₃)⁺, 50%], 136 (100).

Method A. Titanium(IV) chloride/Amalgamated Magnesium

Magnesium powder (9.6 mg, 0.4 mmol) was added, in one portion, to a magnetically stirred solution of mercury(II) chloride (2.8 mg, 10.4 mmol) in THF (0.5 mL) maintained at room temperature under an atmosphere of nitrogen. Stirring was continued for 0.5 h then the supernatant liquid was withdrawn and the amalgam washed with THF (3 x 1 mL). THF (2 mL) was added and the mixture cooled to −10 °C, then titanium(IV) chloride (15 µL, 0.14 mmol) was added, dropwise, followed by a solution of indan-2-one 173 (34 mg, 0.13 mmol) in THF (0.5 mL). The resulting mixture was stirred at 0 °C for 16 h and then treated with K₂CO₃ (2 mL of a saturated aqueous solution) and extracted with ether (2 x 2 mL). The combined organic fractions were dried (MgSO₄), filtered and concentrated under reduced pressure to yield pinacol 257 (10 mg, 32%) as a yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 6.80 (s, 4H), 4.38 (sep, J = 6.1 Hz, 4H), 3.16 (dd, J = 16.0 and 6.0 Hz, 4H), 2.81 (dd, J = 16.0 and 3.1 Hz, 4H), 1.31 (d, J = 6.1 Hz, 24H) (2 x –OH proton resonances were not observed).

¹³C NMR (75.4 MHz, CDCl₃) δ 148.3 (4 x C), 133.5 (4 x C), 115.2 (4 x CH), 73.7 (2 x C),
72.5 (4 x CH), 42.6 (4 x CH₂), 22.4 (8 x CH₃).

**Infrared Spectrum** (KBr) $v_{\text{max}}$ 3451, 2974, 2930, 1740, 1608, 1494, 1309, 1262, 1110 cm⁻¹.

**Mass Spectrum** (70 eV) $m/z$ 498 (M⁺, 10%), 482 (30), 248 (35), 164 (60), 136 (100).

**HRMS** C₃₀H₄₂O₆ requires: M⁺, 498.2981. Found: M⁺, 498.2976.

**Method B. Samarium(II) Mediated Reaction**

A solution of indan-2-one 173 (50.0 mg, 0.20 mmol) in THF (5 mL) was added, dropwise, to a magnetically stirred solution of samarium(II) iodide (7 mL of a 0.1 M solution in THF, 0.72 mmol) maintained at room temperature under an atmosphere of nitrogen. The resulting solution was heated at reflux for 16 h then cooled, diluted with HCl (10 mL of a 0.1 M aqueous solution) and extracted with ether (3 x 10 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to yield a yellow oil. Subjection of this material to flash chromatography (1:4 v/v ethyl acetate/petrol elution) and concentration of the appropriate fractions ($R_f = 0.6$) afforded the pinacol 257 (20 mg, 40%) as a yellow oil, which was identical, in all respects, to that obtained previously.
3',5'-Dioxa-5,5"6,6"-tetra(1-methylethoxy)-dispiro[indan-2,1'-cyclopentane-2',1"-indan]-4'-one (258)

A solution of triphosgene (32.0 mg, 0.11 mmol) in CH₂Cl₂ (2 mL) was added, dropwise, to a magnetically stirred solution of pinacol 257 (35 mg, 0.07 mmol) and pyridine (33 µL, 0.41 mmol) in CH₂Cl₂ (0.5 mL) maintained at -70 °C under an atmosphere of nitrogen. The resulting solution was warmed to room temperature over 16 h then treated with NH₄Cl (5 mL of a saturated aqueous solution) and extracted with CH₂Cl₂ (3 x 5 mL). The combined organic phases were then dried (MgSO₄), filtered and concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash chromatography (1:9 v/v ethyl acetate/petrol elution) and concentration of the appropriate fractions (Rf = 0.5) afforded the carbonate 258 (30 mg, 81%) as a yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 6.79 (s, 4H), 4.40 (sep, J = 6.1 Hz, 4H), 3.31 (dd, J = 17.1 and 6.3 Hz, 4H), 3.08 (dd, J = 17.1 and 2.8 Hz, 4H), 1.32 (d, J = 6.0 Hz, 24H).

¹³C NMR (75.4 MHz, CDCl₃) δ 150.4 (C), 148.7 (4 x C), 131.9 (4 x C), 114.5 (4 x CH), 84.3 (2 x C), 72.5 (4 x CH), 39.2 (4 x CH₂), 22.4 (4 x CH₃), 22.3 (4 x CH₃).

Infrared Spectrum (KBr) νₘₐₓ 2974, 2918, 2849, 1773, 1494, 1153 cm⁻¹.
Mass Spectrum (70 eV) m/z 524 (M+, 20%), 482 [(M-CH₂CHCH₃)⁺, 4%], 440 [(M-2xCH₂CHCH₃)⁺, 2%], 398 [(M-3xCH₂CHCH₃)⁺, 4%], 356 [(M-4xCH₂CHCH₃)⁺, 30%], 326 (68), 314 (100), 285 (40), 269 (98), 224 (75), 148 (65), 91 (62).

7.6 Experimental Details Associated with Work Described in Chapter 6

General Procedure for Conducting High Pressure Promoted Hydrogen Transfer Reactions

1,4-Cyclohexadiene (148) was added, in one portion, to a teflon reaction chamber containing a solution of the substrate in CH₂Cl₂ and the appropriate cosolvent (1.8 mL combined volume) maintained at room temperature under an atmosphere of nitrogen. A teflon plunger fitted with O-rings was placed into the opening of the reaction chamber before the entire assembly was placed in the cavity of the High Pressure Reactor. The teflon reaction chamber was pressurised at 19 kbar for 4 h whilst being maintained at room temperature. After such time, the system was depressurised and the teflon plunger removed. The resulting mixture was concentrated under reduced pressure without heating.

\[\text{By placing a teflon sleeve over a part of the rubber O-rings and removing the sleeve once the plunger is in past the top of the cylindrical base most of the air/nitrogen can be expelled.}\]
1,2-Dihydroxynaphthalene (279)

![Reaction Diagram]

The high pressure promoted reaction between 1,2-naphthoquinone (278) (20 mg, 0.12 mmol) and 1,4-cyclohexadiene (148) (100 µL, 8.8 eq) in CH$_2$Cl$_2$ (1.5 mL) and acetone (300 µL), was carried out as described in the general procedure. After the reaction was complete the solvents were removed under reduced pressure to yield the title compound 279 (18.5 mg, 96%) as a brown, crystalline solid, m.p. 100-102 °C (lit. 101-103 °C). The spectral data derived from this material were identical, in all respects, with those reported in the literature.  

$^1$H NMR (300 MHz, CD$_3$OD) δ 8.04 (d, $J = 8.2$ Hz, 1H), 7.66 (d, $J = 7.9$ Hz, 1H), 7.33 (t, $J = 7.5$ Hz, 1H), 7.26-7.22 (m, 2H), 7.09 (d, $J = 8.8$ Hz, 1H) (2 x OH proton resonances were not observed).

GC analysis* was also carried out on the reaction mixture before and after exposure to 19 kbar of pressure. The amount of benzene ($R_f = 0.96$ min) present in the reaction sample had increased from ~0.003 M to ~0.011 M.

The above reaction was also performed in the presence of the organic soluble radical inhibitor vitamin E (20 µL) with no change in the result.

* The GC conditions consisted of a temperature ramp from 50-300 °C at 20 °C/min and held for 5 minutes. The detector was set at 250 °C.
The high pressure promoted reaction between 1,4-naphthoquinone (280) (20 mg, 0.12 mmol) and 1,4-cyclohexadiene (148) (680 µL, 60 eq) in CH₂Cl₂ (1.5 mL) and methanol (300 µL), was carried out as described in the general procedure. After the reaction was complete, the solvents were removed under reduced pressure to give a 1:1 mixture of 1,4-dihydroxynaphthalene (281) (9.5 mg, ~95% yield at ~50% conversion) and starting material 280 (9.5 mg, ~50% recovery).

The high pressure promoted reaction between para-benzoquinone (31) (100 mg, 0.90 mmol) and 1,4-cyclohexadiene (148) (750 µL, 8.8 eq) in CH₂Cl₂ (1.5 mL) and acetone (300 µL), was carried out as described in the general procedure. After the reaction was
complete the solvents were removed under reduced pressure to yield a 2:1 mixture of hydroquinone (269) (60 mg, ~89% yield at ~66% conversion) and starting material 31 (30 mg, ~33% recovery).

A second high pressure promoted reaction between para-benzoquinone (31) (20 mg, 0.18 mmol) and 1,4-cyclohexadiene (148) (1.02 mL, 60 eq) in CH₂Cl₂ (1.5 mL) and acetone (300 µL), was carried out as described in the general procedure. The solvent was removed under reduced pressure to yield hydroquinone (269) (19 mg, 96%), as a purple, crystalline solid, m.p. 173-175 °C (lit.7 172-175 °C). The spectral data derived from this material were identical, in all respects, with those reported in the literature.⁷

¹H NMR [300 MHz, (CD₃)₂CO] δ 6.63 (s) (2 x –OH proton resonances were not observed).

9,10-Dihydroxyphenanthrene (285)

The high pressure promoted reaction between phenanthrenequinone (284) (20 mg, 0.10 mmol) and 1,4-cyclohexadiene (148) (83 µL, 8.8 eq) in CH₂Cl₂ (1.5 mL) and acetone (300
µL) was carried out as described in the general procedure. After the reaction was complete the solvents were removed under reduced pressure to yield the hydroquinone 285 (19 mg, 90%) as a yellow, crystalline solid, m.p. 140-143 °C (lit.9 145 °C). The data derived from this material were identical, in all respects, with those reported in the literature.9

\[ \text{H NMR [300 MHz, (CD}_3\text{)}_2\text{CO]} \delta 8.07-8.00 (m, 4H), 7.67 (t, J = 7.2 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H) \] 

(2 x -OH proton resonances were not observed).

1,10-Phenanthroline-5,6-diol (286)

The high pressure promoted reaction between 1,10-phenanthroline-5,6-dione (236) (20 mg, 0.10 mmol) and 1,4-cyclohexadiene (148) (79 µL, 8.8 eq) in CH₂Cl₂ (1.5 mL) and CHCl₃ (300 µL), was carried out as described in the general procedure. After the reaction was complete the solvent was removed under reduced pressure to give a 1:1 mixture of 1,10-phenanthroline-5,6-diol (286) (8.5 mg, ~80% yield at ~50% conversion) and starting material 236 (8.5 mg, ~50% recovery).
1,8-Naphthalic Anhydride (288)

The high pressure promoted reaction between acenaphthenequinone (287) (20 mg, 0.11 mmol) and 1,4-cyclohexadiene (148) (92 µL, 8.8 eq) in CH₂Cl₂ (1.5 mL) and CHCl₃ (300 µL) was carried out as described in the general procedure. After the reaction was complete the solvent was removed under reduced pressure to yield a 1:5 mixture of anhydride 288 (3 mg, ~89% yield at ~17% conversion) and starting material 287 (15 mg, ~83% recovery).

A second high pressure promoted reaction between acenaphthenequinone (287) (20 mg, 0.11 mmol) and 1,4-cyclohexadiene (148) (790 µL, 60 eq) in CH₂Cl₂ (1.5 mL) and CHCl₃ (300 µL) was carried out as described in the general procedure. After the reaction was complete the solvent was removed by concentration under reduced pressure to give a 1:5 mixture of anhydride 288 (3 mg, ~89% yield at ~17% conversion) and starting material 287 (15 mg, ~83% recovery).
The high pressure promoted reaction between 1,2-naphthoquinone (278) (20 mg, 0.12 mmol) and 1,3-cyclohexadiene (289) (100 µL, 8.8 eq) in CH$_2$Cl$_2$ (1.5 mL) and acetone (300 µL) was carried out as described in the general procedure. The solvents were removed under reduced pressure to yield the title compound 290 (26 mg, 91%) as an orange, crystalline solid, m.p. 170-173 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.06-8.03 (m, 1H), 7.64-7.62 (m, 2H), 7.45-7.40 (m, 1H), 6.53-6.48 (m, 1H), 6.41-6.36 (m, 1H), 4.46-4.39 (m, 2H), 1.63-1.25 (m, 6H).

$^{13}$C NMR (75.4 MHz, CDCl$_3$) δ 180.7 (C), 175.4 (C), 158.3 (C), 140.3 (C), 135.6 (CH), 135.2 (CH), 132.9 (C), 131.6 (CH), 130.5 (C), 130.4 (CH), 129.2 (CH), 124.2 (CH), 36.5 (CH), 33.9 (CH), 25.1 (CH$_2$), 25.0 (CH$_2$).

Infrared Spectrum (KBr) $\nu_{\text{max}}$ 2944, 2874, 1693, 1650, 1587, 1266, 773, 723, 712 cm$^{-1}$.

Mass Spectrum (70 eV) $m/z$ 236 (M$^+$, 2%), 208 (20), 180 (100), 152 (30), 76 (18).

HRMS (FAB) C$_{16}$H$_{13}$O$_2$ requires: (M+H)$^+$, 237.0915. Found: (M+H)$^+$, 237.0915.

X-ray Crystallographic Analysis See Appendix 1, A.1.7.
The high pressure-promoted reaction between para-benzoquinone (31) (100 mg, 0.9 mmol) and 1,3-cyclohexadiene (289) (750 µL, 8.8 eq) in CH$_2$Cl$_2$ (1.5 mL) and acetone (300 µL), was carried out as described in the general procedure. After the reaction was complete the solvent was removed under reduced pressure to yield the Diels-Alder adduct 291 (160 mg, 81%) as a colourless, crystalline solid, m.p. 188-190 °C (lit. 196-198 °C). The spectral data derived from this material were identical, in all respects, with those reported in the literature.

$^1$H NMR (300 MHz, CDCl$_3$) δ 6.32 (dd, $J = 4.5$ and 3.1 Hz, 4H), 3.01-2.96 (m, 4H), 2.78 (s, 4H), 1.58-1.51 (m, 8H).
General Procedure for Conducting Hydrogen Transfer Reactions at One Atmosphere

1,4-Cyclohexadiene (148) was added, in one portion, to a solution of the substrate in CH$_2$Cl$_2$ and the appropriate cosolvent (1.8 mL combined volume) maintained at room temperature under an atmosphere of nitrogen. Stirring was continued for 72 h, after which time the reaction mixture was concentrated, without heating, under reduced pressure. Aliquots were removed from the reaction mixture at the 24, 48 and 72 h time points and the solvent removed under reduced pressure and the NMR spectra of the ensuing residues were recorded.

1,2-Dihydroxynaphthalene (279)

The reaction between 1,2-naphthoquinone (278) (20 mg, 0.12 mmol) and 1,4-cyclohexadiene (148) (100 µL, 8.8 eq) in CH$_2$Cl$_2$ (1.5 mL) and acetone (300 µL) was carried out as described in the general procedure. After the reaction was complete, the solvent was removed under reduced pressure to yield a 2:1 mixture of the catechol 279 (12 mg, ~96% yield at ~66% conversion) and starting material 278 (6 mg, ~33% recovery). Time dependent substrate/product distributions: 24 h, only starting material 278; 48 h, 1:1
Competition Experiment Involving 1,2-Naphthoquinone (278) and 1,4-Naphthoquinone (280)

The competitive experiment involving 1,2-naphthoquinone (278) (20 mg, 0.12 mmol), 1,4-naphthoquinone (280) (20 mg, 0.12 mmol) and 1,4-cyclohexadiene (148) (100 µL, 8.8 eq) in CH₂Cl₂ (1.5 mL) and acetone (300 µL) was carried out as described in the general procedure. After the reaction was complete the solvents were removed under reduced pressure to yield a 1:2:1 mixture of starting materials 278 and 280 as well as quinol 279 (19 mg, 98%). The data derived from these materials were identical, in all respects, with those obtained previously. Time dependent substrate/product distributions: 24 h, 1:1 starting materials 278:280; 72 h, 1:1:2 starting material 278:product 279:starting material 280.

A second reaction involving 1,2-naphthoquinone (278) (20 mg, 0.12 mmol) and 1,4-naphthoquinone (280) (20 mg, 0.12 mmol) and 1,4-cyclohexadiene (148) (680 µL, 60 eq) in CH₂Cl₂ (1.5 mL) and acetone (300 µL) was carried out as described in the general procedure. After the reaction was complete the solvents were removed under reduced pressure to yield a 1:1 mixture of starting materials 280 and quinol 279 (19 mg, 98%).
data derived from these materials were identical, in all respects, with those obtained previously. Time dependent substrate/product distributions: 24 h, 1:1:2 starting material 278:product 279:starting material 280; 72 h, 1:1 product 279:starting material 280.

**Hydroquinone (269)**

\[
\begin{align*}
\text{31} & \quad + \quad \text{148} \\
\text{CH}_2\text{Cl}_2 & \quad \text{acetone} \\
\text{1 atm} & \quad \rightarrow \\
\text{269} & \quad + \quad \text{31}
\end{align*}
\]

The reaction between *para*-benzoquinone (31) (20 mg, 0.18 mmol) and 1,4-cyclohexadiene (148) (150 µL, 8.8 eq) in CH\textsubscript{2}Cl\textsubscript{2} (1.5 mL) and acetone (300 µL) was carried out as described in the general procedure. After the reaction was complete the solvent was removed under reduced pressure to yield a 1:2.87 mixture of hydroquinone (269) (4.7 mg, ~89% yield at ~26% conversion) and starting material 31 (9.4 mg, ~74% recovery). Time dependent substrate/product distributions: 24 h, 7:1 starting material 31:product 269; 48 h, 3.5:1 starting material 31:product 269; 72 h, 2.9:1 starting material 31:product 269.
Chapter 7

1,8-Naphthalic Anhydride (288)

The reaction between acenaphthenequinone (287) (20 mg, 0.11 mmol) and 1,4-cyclohexadiene (148) (92 µL, 8.8 eq) in CH₂Cl₂ (1.5 mL) and CHCl₃ (300 µL) was carried out as described in the general procedure. After the reaction was complete the solvents were removed under reduced pressure to yield a 14:9 mixture of anhydride 288 (11 mg, ~89% yield at ~61% conversion) and starting material 287 (7 mg, ~39% recovery). Time dependent substrate/product distributions: 48 h, 5:3 starting material 287:product 288; 72 h, 9:14 starting material 287:product 288. The data derived from anhydride 288 was identical, in all respects, with those obtained in the literature.¹⁰

¹H NMR [300 MHz, (CD₃)₂SO] δ 8.51 (d, J = 7.6 Hz, 2H), 8.49 (d, J = 7.6 Hz, 2H), 7.90 (t, J = 7.6 Hz, 2H).
7.7 References


Appendices

A.1.1  X-Ray Structure Report for Compound 193  235
A.1.2  X-Ray Structure Report for Compound 214  236
A.1.3  X-Ray Structure Report for Compound 215  237
A.1.4  Partial $^{13}$C NMR Spectra of the Mixture of Diels-Alder Adducts 233, 234 and 235  238
A.1.5  X-Ray Structure Report for Compound 240  241
A.1.6  X-Ray Structure Report for Compound 241  242
A.1.7  X-Ray Structure Report for Compound 290  243
Appendix

A.1.1 X-Ray Structure Report for Compound 193

The relevant ADEP and crystallographic data for compound 193 are provided in PDF format on the CD found in the back cover of this thesis.

PDF files found on CD

A.1.1.1 Fully labelled ADEP derived from a single-crystal X-ray analysis of compound 193 (as above).

A.1.1.2 Unit cell for compound 193

A1.1.3 Full X-ray crystallographic report for compound 193: The crystal data are presented as provided by Dr. A. J. Edwards of the Australian National University.

PDF files can be viewed by either Mac or PC computers using Acrobat reader 4.0 which is free and available at http://www.adobe.com/products/acrobat/readstep2.html.
A.1.2 X-Ray Structure Report for Compound 214

The relevant ADEP and crystallographic data for compound 214 are provided in PDF format\(^v\) on the CD found in the back cover of this thesis.

\[\text{PDF files found on CD}\]

A.1.2.1 Fully labelled perspective diagram derived from a single-crystal X-ray analysis of compound 214 (molecule 1).

A.1.2.2 Fully labelled perspective diagram derived from compound 214 (molecule 2).

A.1.2.3 ADEP derived from compound 214 molecule 1.

A.1.2.4 ADEP derived from compound 214 molecule 1.

A.1.2.5 ADEP derived from compound 214 molecule 2.

A.1.2.6 ADEP derived from compound 214 molecule 2.

A.1.2.7 Unit cell for compound 214 as viewed down the a-axis.

A.1.2.8 Unit cell for compound 214 as viewed down the b-axis.

A.1.2.9 Unit cell for compound 214 as viewed down the c-axis.

A.1.2.10 Full X-ray crystallographic report for compound 214: The crystal data are presented as provided by Dr. A. J. Edwards of the Australian National University.

\(^v\) PDF files can be viewed by either Mac or PC computers using Acrobat reader 4.0 which is free and available at http://www.adobe.com/products/acrobat/readstep2.html.
A.1.3 X-Ray Structure Report for Compound 215

The relevant ADEP and crystallographic data for compound 215 are provided in PDF format\(^v\) on the CD found in the back cover of this thesis.

PDF files found on CD

A.1.3.1 Fully labelled ADEP derived from a single-crystal X-ray analysis of compound 215 (as above).

A.1.3.2 Unit cell for compound 215 as viewed down the b-axis, showing intermolecular hydrogen bonding.

A.1.3.3 Full X-ray crystallographic report for compound 215: The crystal data are presented as provided by Dr. A. J. Edwards of the Australian National University.

\(^v\) PDF files can be viewed by either Mac or PC computers using Acrobat reader 4.0 which is free and available at http://www.adobe.com/products/acrobat/readstep2.html.
A.1.4 Partial $^{13}$C NMR Spectra of the Mixture of Diels-Alder Adducts 233, 234 and 235

(Spectrum recorded in CDCl$_3$)
A.1.4.2 Partial 75.4 MHz $^{13}$C NMR spectrum of the mixture of Diels-Alder adducts 233, 234 and 235.
(Spectrum recorded in CDCl$_3$)
A.1.4.3 Partial 75.4 MHz $^{13}$C NMR spectrum of the mixture of Diels-Alder adducts 233, 234 and 235.

(Spectrum recorded in CDCl$_3$)
A.1.5 X-Ray Structure Report for Compound 240

The relevant ORTEP and crystallographic data for compound 240 are provided in PDF format\(^v\) on the CD found in the back cover of this thesis.

![Diagram](image)

PDF files found on CD

A.1.5.1 Fully labelled ORTEP derived from a single-crystal X-ray analysis of compound 240 (as above).

A.1.5.2 Full X-ray crystallographic report for compound 240: The crystal data are presented as provided by Dr. A. C. Willis of the Australian National University.

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\(^v\) PDF files can be viewed by either Mac or PC computers using Acrobat reader 4.0 which is free and available at http://www.adobe.com/products/acrobat/readstep2.html.
A.1.6 X-Ray Structure Report for Compound 241

The relevant ADEP and crystallographic data for compound 241 are provided in PDF format\(^v\) on the CD found in the back cover of this thesis.

PDF files found on CD

A.1.6.1 Fully labelled perspective diagram derived from a single-crystal X-ray analysis of compound 241 (as above).

A.1.6.2 Full X-ray crystallographic report for compound 241: The crystal data are presented as provided by Dr. A. J. Edwards of the Australian National University.

\(^v\) PDF files can be viewed by either Mac or PC computers using Acrobat reader 4.0 which is free and available at http://www.adobe.com/products/acrobat/readstep2.html.
A.1.7 X-Ray Structure Report for Compound 290

The relevant ADEP and crystallographic data for compound 290 are provided in PDF format on the CD found in the back cover of this thesis.

PDF files found on CD

A.1.7.1 Fully labelled ADEP derived from a single-crystal X-ray analysis of compound 290 (as above).

A.1.7.2 Full X-ray crystallographic report for compound 290: The crystal data are presented as provided by Dr. A. J. Edwards of the Australian National University.

PDF files can be viewed by either Mac or PC computers using Acrobat reader 4.0 which is free and available at http://www.adobe.com/products/acrobat/readstep2.html.