STABLE NORCARADIENES: A NEW APPROACH TO THE TOTAL SYNTHESIS OF KAURENOID DITERPENES

A Thesis Submitted for the Degree of Doctor of Philosophy of

The Australian National University

Research School of Chemistry

by

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DECLARATION

This thesis contains no material previously submitted for a degree in any other University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

Jonathan Charles Morris
I have tried to write this succinctly without allowing too much emotion to cloud my account of the events and so I would like to end by simply screaming, 

"Waaaaaaaaaaaaaaaawaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaarrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr
I would like to thank Professor Lew Mander for his supervision of the work presented in this thesis. His friendship and support both inside and outside the lab have been very much appreciated. I am thankful for the time that I have been able to spend in his research group. I would also like to take the opportunity to thank Stephanie Mander for her kindness and friendship over the last three years.

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Grateful acknowledgement is made of the support provided by an Australian Postgraduate Research (Award Higher Level).

Finally, to my darling wife, Joanna, thank you for your unfailing support and understanding over the last three years. Your love and devotion has meant a great deal to me during this time.
ABSTRACT

This thesis describes a new approach to the synthesis of the kaurenoid diterpenes. In the first chapter, an overview of the strategies used for the synthesis of these compounds is provided. A [4+2] cycloaddition of a suitable dienophile to a vinyl norcaradiene was proposed as a feasible alternative approach which should provide the kaurenoid diterpenes in a rapid, stereocontrolled manner.

The synthesis of the norcaradienes by an intramolecular cyclopropanation process was explored in Chapter Two. It was found that rhodium (II) catalysts gave variable yields, mainly due to the competing C-H insertion process. On the other hand, copper (II) catalysts gave consistent yields. The norcaradienes displayed a sensitivity to acid, which limited their utility as synthons.

The results obtained in Chapter Three have demonstrated that the synthetic plan proposed in Chapter One has significant merit. A rapid stereocontrolled assembly of advanced intermediates for the synthesis of kaurenoid diterpenes has been achieved using Diels-Alder methodology.

Investigations in Chapter Four have established the potential of the Sharpless asymmetric dihydroxylation as a feasible approach to optically active functionalised tetrahydronaphthoic acids, which are potential precursors for the enantioselective synthesis kaurenoid diterpenes.

The future potential of the work described in this thesis is briefly discussed in Chapter Five.
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6.4 Chapter Four Experimental

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# ABBREVIATIONS

The following abbreviations have been used throughout this thesis:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>Acetylacetonate</td>
</tr>
<tr>
<td>AD</td>
<td>Asymmetric Dihydroxylation</td>
</tr>
<tr>
<td>APT</td>
<td>Attached Proton Test</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
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<tr>
<td>Bu</td>
<td>Butyl</td>
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<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>cap</td>
<td>Caprolactam</td>
</tr>
<tr>
<td>CD</td>
<td>Circular Dichroic</td>
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<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DHQ</td>
<td>Dihydroquinine</td>
</tr>
<tr>
<td>DHQD</td>
<td>Dihydroquinidine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(Dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
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<tr>
<td>DQFCOSY</td>
<td>Double Quantum Filtered Correlation Spectroscopy</td>
</tr>
<tr>
<td>E</td>
<td>entgegen</td>
</tr>
<tr>
<td>EI</td>
<td>Electron Impact</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>GA</td>
<td>Gibberellic Acid</td>
</tr>
<tr>
<td>HETCOR</td>
<td>Heteronuclear Correlation Spectroscopy</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>Im</td>
<td>Imidazole</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
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<tr>
<td>Abbreviation</td>
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<tr>
<td>mand</td>
<td>Mandelate</td>
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<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MEM</td>
<td>Methoxymethyl</td>
</tr>
<tr>
<td>MHz</td>
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</tr>
<tr>
<td>MOM</td>
<td>β-Methoxyethoxymethyl</td>
</tr>
<tr>
<td>MPLC</td>
<td>Medium Pressure Liquid Chromatography</td>
</tr>
<tr>
<td>MTPA</td>
<td>Methoxy-α-trifluoromethylphenyl</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>2D NMR</td>
<td>Two Dimensional Nuclear Magnetic Resonance Spectroscopy</td>
</tr>
<tr>
<td>nOe</td>
<td>Nuclear Overhauser Experiment</td>
</tr>
<tr>
<td>ORD</td>
<td>Optical Rotatory Dispersion</td>
</tr>
<tr>
<td>OTf</td>
<td>Triflate</td>
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<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
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<td>Phthalazine</td>
</tr>
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<td>pfb</td>
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</tr>
<tr>
<td>ppm</td>
<td>Parts per Million</td>
</tr>
<tr>
<td>psNOESY</td>
<td>Phase Sensitive Nuclear Overhauser Spectroscopy</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>thexyl</td>
<td>2-(2,3-Dimethylbutyl)</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>Tetrahydropyranil</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TPA</td>
<td>Triphenylacetate</td>
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<td>Z</td>
<td>zusammen</td>
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CHAPTER ONE

INTRODUCTION

The laurenoid diterpenes constitute a large class of tetracyclic 20-carbon molecule isolated from plants, micro-organisms and marine organisms. They are characterized by a trans-cyclohexane ring and a bicyclo[2.2.1]heptane CD-ring system, as illustrated by the parent compound ent-laurenone 1. Many of these diterpenes, notably those that are highly functionalized, and closely related structural variants like the gibberellins, possess interesting biological activities, e.g. antitumour, anti-HIV and antimicrobial activity, plant regulatory activity, and others.

The gibberellins and antheridialones are structurally similar to the laurenones with the major difference being the five-membered B-ring. The gibberellins are biosynthetically derived from ent-laurenone and can be divided into two groups: the C19 tetracyclic lactones (e.g. gibberellic acid 2) and those containing a C15 tetracyclic skeleton (e.g. gibberellin A1 3). The antheridialones are a recently discovered class of compounds, differing from the gibberellins only in the bridging D-ring, which can be present as part of a bicyclo[2.2.2] (e.g. antheridial acid 4) or a cyclopentyl-containing CD-ring system (e.g. 1-hydropyr-9,15-cyclogibberellin 5).
1.1 INTRODUCTION

The kaurenoid diterpenes constitute a large class of tetracyclic 20-carbon molecules isolated from plants, micro-organisms and marine organisms.\(^1\) They are characterised by a \textit{trans-anti-cis} carbon skeleton and a bicyclo[3.2.1]octane CD-ring system, as illustrated by the parent compound \textit{ent}-kaurene 1. Many of these diterpenes, notably those that are highly functionalised, and closely related structural variants like the gibberellins, possess interesting biological activities, \textit{e.g.} antitumour,\(^2\) anti-HIV\(^3\) and antibacterial activity,\(^4\) plant regulatory activity,\(^5\) and animal toxicity.\(^6\)

![Structure of ent-kaurene](image)

The gibberellins and antheridiogens are structurally similar to the kaurenes, with the major difference being the five-membered B-ring. The gibberellins are biosynthetically derived from \textit{ent}-kaurene\(^7\) and can be divided into two groups: the C19 pentacyclic lactones (\textit{e.g.} gibberellic acid 2) and those containing a C20 tetracyclic skeleton (\textit{e.g.} gibberellin A\(_{12}\) 3). The antheridiogens are a recently discovered class of compounds, differing from the gibberellins only in the bridging D-ring, which can be present as part of a bicyclo[2.2.2] (\textit{e.g.} antheridic acid 4) or a cyclopropyl-containing CD-ring system (\textit{e.g.} 1-hydroxy-9,15-cyclogibberellin 5).\(^8\)

\(^*\) Apart from the structures in Chapter Five, all the structures represented are racemates, but for convenience only one enantiomer has been drawn.
The structural complexity and biological significance of the kaurenoid diterpenes have long fascinated synthetic organic chemists. For instance, molecules such as gibberellic acid 2, with its highly functionalised nature and propensity for rearrangement, have constituted appealing, but formidable synthetic challenges. A great deal of work has been directed towards the total synthesis of these molecules, representing much creative endeavour. This work has been recently reviewed and a selection of syntheses which demonstrate the range of different approaches is provided in the next section.
1.2 STRATEGIES AND METHODS FOR THE SYNTHESIS OF KAURENOID DITERPENES

One of the major synthetic challenges in constructing these molecules is the establishment of the correct stereochemistry at the ring junctions, i.e. the trans stereochemistry of the AB-ring junction, the cis stereochemistry of the CD-ring junction and the anti relationship between substituents at C-9 and C-10.

1.2.1 ABC + D Approaches

The more popular strategies for the total synthesis of kaurenoids and gibberellins have involved the addition of the D-ring to a suitably functionalised ABC ring system. The syntheses of the ABC ring systems have followed two different approaches: either AC+B or BC+A, with the former the more common. Examples of successful targets include ent-kaurene, gibberellic acid, gibberellin A12, antheridic acid, phyllocladene, atisirene, kaurenoic acid, ent-kaurenediol, hibaene, steviol and gibberellin A15.
While these strategies do appear attractive, many approaches have never been completed and the majority of those that have, are not efficient. Generally, construction of the ABC tricyclic system with appropriate stereochemistry occurs in a relatively efficient and selective manner, but the manipulation of functionality and the formation of the D-ring can be lengthy, and often lacks selectivity.

Ireland and co-workers\textsuperscript{10} synthesised ent-kaurene 1 utilising the AC+B+D method of ring assembly, the key steps of which are outlined in Scheme 1.1. The major problems with this route were that cyclisation of the alcohol 13 to form the trans-fused AB-ring junction was not stereoselective, the synthesis of the aldehyde 14 was lengthy; and the hydroboration/oxidation process gave the desired C-14 ketone 15 in only 26\% yield, admixed with the C-13 isomer (42\% yield). Aldehyde 14, to which a more efficient synthetic route was reported later,\textsuperscript{15c} was also used for the syntheses of atisirene\textsuperscript{10b,15c} phyllocladene,\textsuperscript{15b,15c} and hibaene.\textsuperscript{18}

\textbf{Scheme 1.1}

An alternative BC+A+D approach has been used by Mori and Matsui\textsuperscript{16} in the synthesis of kaurenoic acid 8 and by Fujita and Ochiai\textsuperscript{17} in a synthesis of ent-
kaurenediol 9. Fujita's synthesis of ent-kaurenediol is a classic illustration of the problems encountered in the construction of functionalised kaurenoids (Scheme 1.2). The ABC ring system was efficiently synthesised with the key step being the regiocontrolled formation of the $\beta,\gamma$-unsaturated ketone 16, utilising a Birch reduction of the anisole moiety. However, the transformation of alkene 17 to the 11-hydroxy derivative 18 was not stereoselective and the entire sequence therefore required a large number of oxidations and reductions before the target was obtained.

**Scheme 1.2**

In the synthesis of kaurenoids using this ABC+D approach, the D-ring is added to an appropriately functionalised hydrophenanthrene. For the gibberellins, the equivalent hydrofluorene based approach has been used, albeit with only one successful approach, that of Mander and coworkers\textsuperscript{11} in a formal total synthesis of gibberellic acid 2 (Scheme 1.3). The D-ring was installed using the very efficient acid-catalysed cyclisation of a diazoketone. Following the
pioneering work of Loewenthal on a similar system, the tetracycle was carboxylated to afford the 6α-acid 19. The 6α stereochemistry, presumably formed as a consequence of stereoelectronic control, ensured that both hydrogenation of the Δ9(11)-ene bond and alkylation at C4 occurred on the upper face as desired. This synthesis is an interesting example of how fine the balance between success and failure can be. If the initial carboxylation of C6 had afforded the thermodynamically more stable 6β-ester, the entire synthesis would have failed due to the lack of stereocontrol in the subsequent hydrogenation and alkylation steps.

Scheme 1.3

The synthesis of antheridic acid 4 by Corey and Myers is the only other ABC+D approach which successfully overcomes the problems of length and selectivity (Scheme 1.4). Obviously, the fact that a bicyclo[2.2.2] ring system is desired, rather than the standard bicyclo[3.2.1]octane, is a factor in this success.
The methodology of Loewenthal\textsuperscript{21} was again used to generate a suitably substituted A-ring in the AC bicyclic compound. The B-ring was attached \textit{via} a stereocontrolled intramolecular cyclopropanation reaction utilising diazoacetate 20, followed by a vinyl-cyclopropane rearrangement.\textsuperscript{14} The D-ring was attached using a Diels-Alder reaction, and further functional group manipulation over a number of steps afforded antheridic acid 4.

\textbf{Scheme 1.4}

More efficient approaches have involved the addition of the A-ring to a suitably functionalised BCD tricyclic intermediate, particularly in the case of the gibberellins.\textsuperscript{8} Surprisingly, the synthesis of \textit{ent}-kaurene 1 by Masamune\textsuperscript{22} is the only example of this approach in the synthesis of kaurenoids.
(Scheme 1.5). His approach involved ipso-alkylation of the aromatic moiety of a
diastereomeric mixture of bromohydrin ethers 21 by treatment with base. Unfortunately, only one of these bromohydrin diastereoisomers cyclised to give
the dieneone 22, in a 30% overall yield, due to severe nonbonding interactions in the transition state which would be required for the other diastereoisomer. The dieneone was elaborated to the β-keto ester 23, and a Robinson annelation sequence completed the formation of the kaurene skeleton 24. The trans-AB ring junction was established efficiently from this material and after some functional group manipulation, ent-kaurene was obtained.

Scheme 1.5

Masamune's approach to the D-ring inspired Mander and coworkers\textsuperscript{23} to utilise an intramolecular ipso-alkylation of a hydronaphthalene derivative via a protonated diazoacetyl moiety. This was used in Mander's first synthesis\textsuperscript{24} of gibberellic acid 2 (Scheme 1.6). An efficient cyclisation was achieved, since the reactive intermediate was sp\textsuperscript{2}-hybridised at pro-C(16), which avoided the problem encountered by Masamune. The resultant dienedione 25 was converted to the BCD ring system 26 by a Wolff ring contraction, after the
The direct formation of an α-diazocyclohexanone moiety. The desired cis-CD ring junction 27 was obtained utilising a hydroboration reaction in which the 6α-ester moiety shielded the bottom face and ensured stereoselectivity.

Scheme 1.6

Addition of nucleophiles to pro-C(10) in the subsequent enone 28 was stereoselective due to the convex shape of the molecule, although most reagents caused epimerisation at pro-C(9). The trans-AB ring junction was obtained by the ester-based intramolecular Michael reaction and the synthesis of 2 completed by the use of a previously developed aldol process, although the
elaboration of the allyl moiety meant that this synthesis was not as efficient as initially envisaged.

The first total synthesis of gibberellic acid was achieved by the Corey group\textsuperscript{26} and also involved a BCD+A approach (Scheme 1.7). The key step in this synthesis was the employment of an intramolecular Diels-Alder reaction to complete the A-ring. The precursor 30 to this reaction was available in 24 steps starting from anisole and involved the annelation of the D-ring by pinacol reduction of the ketoaldehyde 29. The pentacycle 31 was obtained by heating the ester at 160°C in benzene and due to the intramolecular nature of the reaction, the correct relative stereochemistry at C5 was obtained. The resultant convexity of the upper face of the A and B rings meant that C-methylation at C4 occurred in the correct stereochemical manner. More efficient approaches to 30 have been reported by Corey\textsuperscript{27}, Stork\textsuperscript{28} and recently by Barco.\textsuperscript{29}

Both of these syntheses of gibberellic acid are reasonably efficient, but the cost of introducing extra functionality early in the synthesis would be prohibitive,
thus precluding the adaptation of these approaches to the synthesis of some of the rarer and more complex gibberellins

### 1.2.3 Multibond Forming Approaches

Thus far, it can be seen that the syntheses of these diterpenes are lengthy and often inefficient and it would appear that this is primarily due to the number of steps that require sequential additions of relatively small synthons. An attractive way to overcome this limitation would be to utilise reactions where more than one C-C bond is formed. There have been several syntheses of kaurenoid diterpenes which utilise this concept, with varying degrees of success.

The earliest reported case of this type of approach was the synthesis of the hibane derivative 34 by Kametani and coworkers. Carbinol 34 differs from the kaurene structure in that the D-ring has the opposite relative configuration (i.e. trans/anti/trans). The approach involves the use of an o-quinonemethide cycloaddition and the key steps are summarised in Scheme 1.8. It allows for the rapid and efficient synthesis of the tetracyclic skeleton 32, but a lengthy series of reactions were required to elaborate the A-ring, which involved an Eschenmoser cleavage of the A-ring to afford the alkyne 33, followed by reconstitution of the ring and the introduction of three methyl groups.
This area of work has been revisited recently by Malacria and coworkers.\textsuperscript{31} They utilised a sequence of consecutive [3+2], [2+2+2] and [4+2] cycloaddition reactions, with the last reaction being the same \(\alpha\)-quinonemethide approach of Kametani\textsuperscript{30} (Scheme 1.9). This enabled the rapid assembly of a tetracyclic system, but it was found that only the phyllocladene stereochemistry could be obtained efficiently. It was found that by changing the substituents \(X\), \(R\) and \(R'\), the ratio of the two products could be varied, but the phyllocladene-type skeleton was always predominant. The presence of the aromatic A-ring does not augur well for a satisfactory synthesis of phyllocladene, let alone kaurenoid diterpenes.
Atractyligenin 39, the aglycone of the potent toxin atractyloside, has been synthesised by Corey and coworkers\textsuperscript{32} in an elegant and interesting synthesis (Scheme 1.10). A novel approach was utilised to construct the skeleton, involving an AC ring precursor 35. The B- and D-rings are formed simultaneously from the cyclopropyl carbinol 37, which can be obtained from the diazoester 36 in a two step process. While this double ring formation occurred both stereoselectively and regioselectively, there are, in total, a large number of steps required to obtain the key substrate 38 and then to elaborate to the natural product.
DeClercq's 16-step synthesis\textsuperscript{33} of GA\textsubscript{5} 43 represents the most direct approach to a gibberellin, while a later modification\textsuperscript{34} has the potential to be used in kaurene synthesis with the alternative synthesis of a six-membered B ring (Scheme 1.11). In both syntheses, a CD bicyclic precursor was rapidly obtained from 3-methoxybenzoic acid 40. The key process was the intramolecular Diels-Alder reaction of a furan with an appropriately substituted dienophile, generating the A and B rings in one step (for the original synthesis, pathway a, while pathway b is followed in the later synthesis). It was found that the maximum yield and highest endo selectivity was obtained when this reaction was performed in aqueous solution and in the presence of \( \beta \)-cyclodextrin. The Diels-Alder adducts 41 and 42 contained enough suitable functionality for elaboration to the natural product in a minimal number of steps, thus ensuring an efficient overall process in both cases.
Perhaps the most striking of the multibond forming processes is that of Overman and coworkers\textsuperscript{35} in their syntheses of scopadulcic acids A and B, \textsuperscript{46} and \textsuperscript{47} respectively. Both involve a palladium-polyene cyclisation of a suitably functionalised 5-methylene cycloheptene which forms the BCD tricyclic system. The first generation synthesis was that of scopadulcic acid B and involved the use of an aryl iodide derivative \textsuperscript{44} which afforded the tetracycle in one step.\textsuperscript{35a} However, the elaboration of the aromatic A-ring was laborious and indirect, as has already been seen with other approaches in this section. The second generation synthesis addressed this problem by using vinylic iodide precursor \textsuperscript{45}, which allowed a more direct elaboration from an acyclic precursor to afford scopadulcic acid A.\textsuperscript{35b} Complete stereocontrol in the bis-Heck cyclisation was obtained using this approach.
Although there are now numerous documented syntheses of these diterpenes, many unfortunately fail to meet even modest levels of efficiency and/or...
flexibility. This has resulted in inefficient and protracted syntheses for most compounds, even the relatively simple parent structure ent-kaurene 1.

Furthermore, the procedures generally do not allow for the introduction of additional functionality into the B and C-rings, which may be a requirement for biological activity. This has led to the use of partial synthesis to provide access to highly functionalised derivatives, especially in the area of gibberellins and antheridiogens. However, as the complexity of these compounds increase so do the number of synthetic steps. Indeed, some partial syntheses exceed twenty steps and can be even longer than some of the more efficient total syntheses.

While the last synthesis in Section 1.2.3 does not appear applicable to the synthesis of the kaurenes or its structural variants, it does serve to illustrate that rapid and efficient syntheses of polycyclic molecules can be possible when a multibond forming process is utilised, particularly if suitable functionality is in place so that the degree of subsequent manipulation to obtain the desired product is minimised.
1.3 A NEW APPROACH TO THE TOTAL SYNTHESIS OF KAURENOID DITERPENES

Benzenoid synthons afford a rich and diverse array of options for the synthesis of complex polycyclic structures. They possess great potential utility, since such synthons must intrinsically provide a minimum of six carbons, with the aryl ring an excellent source of latent functionality. Oxidative and reductive processes, especially the Birch reduction, have proven extremely useful in the elaboration of such benzenoid synthons. However, the more powerful protocols have involved carbon-carbon bond formation at substituted positions on the aryl ring with concomitant dearomatisation.

The intramolecular 1,3-photocycloaddition reaction is a compelling example of such a process. Several impressive short syntheses of complex polycyclic natural products have been achieved incorporating this methodology. For example, the synthesis of silphinene 48 has been completed in several laboratories in 10-20 steps, but Wender's process achieved the target in a total of four (Scheme 1.13).

Scheme 1.13

```
1. LiO / ~-
2. NH₃, NH₄Cl, Li
   87%

1:1

Li/MeNH₂
63%

48
```
Some of the syntheses in the earlier section illustrate just how powerful the creative utilisation of benzenoid synthons can be. Despite this, the full potential of aryl synthons has not been realised and definitely warrants further investigation. In a search for more effective strategies, we speculated on the suitability of the norcaradienes, as they represent a prime example of under-utilised and potentially flexible synthons. While the electrocyclic rearrangement of norcaradienes to form seven-membered rings has proven to be quite popular (Figure 1.1) and a few representative examples of such syntheses are presented below, there have been no reports on the use of isolable norcaradienes in synthesis.

Figure 1.1: The equilibrium between norcaradiene and cycloheptatriene.

An elegant exploitation of the norcaradiene to cycloheptatriene rearrangement may be seen in the first total synthesis of colchicine 50 reported by Eschenmoser and coworkers\(^{40}\) (Scheme 1.14). Interestingly, as further evidence for the structural assignment, the cycloheptatriene 49 was hydrolysed to the diacid, which was dehydrated with acetic anhydride to form the stable norcaradiene 51. The cycloheptatriene 52 is destabilised by the geometric constraints provided by the attached five-membered ring and consequently, only the norcaradiene structure is observed.
Recently, Banwell and Lambert\textsuperscript{41} also exploited the rearrangement in their fully regiocontrolled total synthesis of desacetamidoisocolchicine \textit{53}, an advanced intermediate in the Eschenmoser synthesis of colchicine (Scheme 1.15). They used the cyclopropyl functionality to maintain regiochemical integrity throughout the reaction sequence leading to the troponoid \textit{53}. 

\textbf{Scheme 1.14}
McKervey and coworkers observed an equilibrium of valence tautomers during the rhodium(II)-catalysed intramolecular cyclopropanation reaction of diazoketone 54. A rapid equilibrium between the tricyclic norcaradiene 55 and the bicyclic trienone 56 was observed by $^1$H NMR spectroscopy, with the former being the dominant component (Scheme 1.16). The mixture was carried on to afford an advanced confertin intermediate 57 in six steps and 20% overall yield, constituting a formal synthesis of (+)-confertin 58, since Quinkert and coworkers had previously obtained the natural product from this precursor.
Due to much conjecture over the relationship between norcaradienes and cycloheptatrienes in the 1960s, there has been some interest in the synthesis of stable norcaradienes. It was revealed that these compounds could be isolated if; (a) there were two electron-withdrawing groups on the cyclopropyl moiety, (b) one of the two double bonds of the norcaradiene was included in an aromatic ring, or (c) the ring junction carbons were bridged with an additional ring, which rendered the cycloheptatriene (e.g. 59) less stable than the norcaradiene tautomer (e.g. 60) (Scheme 1.17). In the final case, however, it was discovered that a six-membered bridging ring was not able to significantly destabilise the cycloheptatriene 61, which was the only product observed.
Surprisingly, although examples of stable, isolable norcaradienes have been known for approximately thirty years, there have been no reports of their use as benzenoid-derived synthons, apart from the above mentioned use as cycloheptatriene equivalents. In spite of this, they are readily prepared and appear to be attractive synthons, due to the wealth of transformations available for the cyclopropane ring.  

In a continuing quest for new ways of utilising benzenoid synthons, it was decided to examine the transition-metal catalysed intramolecular cyclopropanation reaction of the aromatic ring in tetrahydronaphthyl diazomethyl ketones such as 62, in the expectation that tetracyclic stable norcaradienes (e.g. 63) would be obtained and could then be utilised as synthetic intermediates (Scheme 1.18). Geometric constraints would surely render these norcaradienes energetically more favourable than the tautomeric cycloheptatrienes (e.g. 64).

![Scheme 1.18](image)

If this was successful, we could envisage the following synthetic plan as a feasible approach to the total synthesis of kaurenoid diterpenes. The [4+2] cycloaddition of an appropriate dienophile (e.g. methyl acrylate) to a vinyl norcaradiene 65 would afford adduct 66 as the preferred product if the following assumptions held: (a) the more exposed vinyl cyclohexene moiety would function as the operational diene, (b) the preferred regiochemistry would favour an 'ortho' adduct, (c) endo adducts would be kinetically favoured...
over the exo isomers and (d) the upper face of the triene would be effectively shielded by the pro-15 hydrogen atom attached to the cyclopropyl ring, thereby favouring transition state A over B (Figure 1.2).

**Figure 1.2:** Two possible endo-transition states for the [4+2] cycloaddition of vinyl norcaradiene 65 and methyl acrylate.

The cyclopropane moiety serves two functions – controlling the stereochemistry of the Diels-Alder reaction and affording access to both of the desired CD ring systems depending on which bond of the cyclopropane is broken subsequently. For most targets, the introduction of a extra methyl group at C4 would be necessary, but the correct stereochemistry should follow from the correct configuration of C5 as has been previously shown.11,26,47
Clearly, this approach would allow access to either kaurene or gibberellin skeletons, but would also have the potential to generate bicyclo[2.2.2] ring systems as well. It achieves the rapid assembly of the skeleton in a minimal number of steps, but is also compatible with the early introduction of C-ring substituents, which would be especially advantageous if it could be achieved as an integral part of an enantioselective route. The central issue in such a synthesis is the formation of the desired stereochemical relationship between the D-ring and the AB ring junction, as once this stereochemistry is set, the relative stereochemistry of the other stereocentres should follow.
CHAPTER TWO

SYNTHESIS AND CHEMISTRY OF STABLE NORCARADIENES

Table 2.1: The Rh(III) Catalyzed Reaction of Dicyanocycloheptatriene (92) (Scheme 2.1)

<table>
<thead>
<tr>
<th>Compound</th>
<th>63</th>
<th>67</th>
<th>68</th>
<th>69</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Yield*</td>
<td>41 (39)</td>
<td>46 (40)</td>
<td>74</td>
<td>64</td>
</tr>
</tbody>
</table>

*Yields are based on $^1$H NMR spectra of crude reaction mixture yields in parentheses; in situ isolation of isolated compounds following sodium pentoxide liquid chromatography on silica. Isolated quantities were isolated in some cases but never in appreciable quantities in absence of chromatography.

The author gratefully acknowledges the contributions of Dori Den Rodgers and Reuel Bell who undertook the initial studies on the rhodium (III)-catalyzed reaction of tetracyanoethylene disuccinimide (TCE-DSI) images.
2.1 INITIAL INVESTIGATIONS INTO THE FORMATION OF STABLE NORCARADIENES

The transition metal catalysed cyclopropanation of aromatic ring systems to afford cycloheptatrienes from suitably substituted diazoketones is a well-established procedure. Copper catalysis gives moderate to good yields, but the advent of rhodium (II) carboxylates as catalysts has enabled the reaction to proceed in essentially quantitative yields in many cases.

The diazoketone $62^{51}$ in dichloromethane was added via syringe pump to a solution of rhodium (II) acetate (2 mole %) in dichloromethane at reflux. Four compounds were produced in the ratio of 41:46:7:6 according to $^1$H NMR analysis of the crude reaction product (Scheme 2.1 and Table 2.1).

**Table 2.1: The Rh$_2$(OAc)$_4$ Catalysed Reaction of Diazoketone 62 (Scheme 2.1)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>63</th>
<th>67</th>
<th>68</th>
<th>69</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Yield$^a$</td>
<td>41 (39)</td>
<td>46 (41)</td>
<td>7 (-)$^b$</td>
<td>6 (-)$^b$</td>
</tr>
</tbody>
</table>

$^a$ Yields are based on $^1$H NMR spectra of total reaction mixtures: yields in parentheses are those of isolated compounds following medium pressure liquid chromatography on silica.

$^b$ Small quantities were isolated in some runs, but never in appreciable quantities to allow characterisation.

* The author gratefully acknowledges the contributions of Drs Dan Rodgers and Russell Bell who undertook the initial studies on the rhodium (II)-catalysed cyclopropanation of tetrahydronaphthyl diazomethyl ketones.
Initial attempts to chromatograph the mixture on silica resulted in loss of material and poor separation. However, medium pressure liquid chromatography (MPLC) proved to be an excellent option, rapidly allowing the isolation of the two major compounds 63 and 67 in 39% and 41% yield, respectively.

The spectroscopic data for 63 seemed to suggest that the desired norcaradiene had been obtained, as opposed to the ring expanded cycloheptatriene 64. The carbonyl absorption frequency at 1710 cm\(^{-1}\) was consistent with the norcaradiene structure, as the corresponding literature values\(^{52}\) for cyclopropyl conjugated ketones were in the range of 1685 - 1740 cm\(^{-1}\). However, subsequent analysis by \(^{13}\)C NMR spectroscopy eliminated the possibility of a cycloheptatriene product. There were seven resonances in the aliphatic region and the attached proton technique (APT) enabled these signals to be assigned to two quaternary, three methylene and two methine carbons. Obviously, the corresponding spectrum for the cycloheptatriene would have been markedly different. The olefinic region contained four resonances that were assigned as methine carbons. The resonances at 48.1 (C), 45.0 (C) and 32.6 (CH) ppm were assigned to the cyclopropane ring system and correlated well with data from intermediates in the synthesis of 9,15-cyclogibberellins (Figure 2.1).\(^{53}\) A singlet at 0.59 ppm in the \(^1\)H NMR spectrum can presumably be only that from the single cyclopropyl proton.

![Figure 2.1: A 9,15-cyclogibberellin derivative, with selected \(^{13}\)C NMR data.](image-url)
The other major product 67 was presumed to be the result of C-H insertion by the metal carbenoid, known to be a facile process under catalytic conditions using rhodium catalysts (Figure 2.2). This compound has been prepared previously by Kitahonki and coworkers, although the reported spectroscopic data were incomplete. The IR absorption at 1740 cm\(^{-1}\) was typical for a cyclopentanone, while the \(^{13}\)C APT NMR spectrum revealed an intact aromatic ring together with three aliphatic methylene and two methine carbons. As most of the signals in the \(^1\)H spectrum were well separated, it was possible to assign all of the protons. The multiplet at \(\delta\) 3.37 was attributed to H5 and equivalent signals proved to be invaluable in the \(^1\)H NMR analysis of the reaction mixtures of later examples.

\[\text{Figure 2.2: The numbering scheme for cyclopentanone 67.}\]

The low abundance of the remaining two compounds (68 and 69) precluded their isolation and characterisation. Byproducts of this type became more important in related compounds and their formation and structural elucidation will be discussed in sections 2.2.3 and 2.3.3.
2.2 INVESTIGATIONS INTO THE SCOPE OF THE REACTION

Despite the disappointing yield of the norcaradiene 63, the absence of the rearranged cycloheptatriene 64 encouraged us to explore the scope of the reaction by adding electron donating substituents to the aromatic ring. It was expected that the increased electron density of the aromatic ring would afford higher yields of norcaradienes.

2.2.1 Cyclopropanation of methoxy-substituted diazoketones

The methoxy-substituted diazoketones were easily prepared from their respective carboxylic acids via the acyl chloride. The general procedure and spectroscopic data of the resulting diazoketones are presented in the experimental section. The diazoketones were decomposed in a similar manner to that of diazoketone 62, with the desired norcaradiene products formed in variable yields ranging from 21-71% (Scheme 2.2 and Table 2.2). Not surprisingly, the methoxy-substituted norcaradienes were more susceptible to hydrolysis, especially in the presence of silica gel, and required very careful handling. Indeed, the norcaradiene 77 (from the 7-methoxy series) rearranged instantly upon exposure to silica gel to form the trienone 82. The structural elucidation of similar compounds will be discussed in section 2.5.2.1.

There does appear to be an enhanced yield of norcaradienes, associated with the higher electron densities resulting from methoxy substitution, except in the
case of the 8-methoxy compound. The low yield for this compound will be discussed further in section 2.3. The 71% isolated yield for the 6-methoxy substrate 73 was very encouraging. Generally speaking, lower yields of the norcaradienes appear to correspond to increased yields of C-H insertion products, which is particularly noticeable from comparison of the 7-methoxy and 8-methoxy cases. In order to optimise the yields of norcaradienes, a better understanding of the C-H insertion process was sought.

Scheme 2.2

![Scheme 2.2](image)

**Table 2.2:** Results from the rhodium (II) acetate catalysed reactions of tetrahydronaphthyl diazoketones (Scheme 2.2)

<table>
<thead>
<tr>
<th>[A]a</th>
<th>R =</th>
<th>[B]</th>
<th>% Yieldb</th>
<th>[C]</th>
<th>% Yieldb</th>
</tr>
</thead>
<tbody>
<tr>
<td>[62] 5-OMe</td>
<td>63</td>
<td>41 (39)</td>
<td>67</td>
<td>46 (41)</td>
<td></td>
</tr>
<tr>
<td>[70] 6-OMe</td>
<td>71</td>
<td>45 (41)</td>
<td>20</td>
<td>67 (71)</td>
<td></td>
</tr>
<tr>
<td>[73] 7-OMe</td>
<td>74</td>
<td>51 (0)c</td>
<td>81</td>
<td>49 (44)</td>
<td></td>
</tr>
<tr>
<td>[76] 8-OMe</td>
<td>77</td>
<td>24 (21)</td>
<td>80</td>
<td>57 (56)</td>
<td></td>
</tr>
</tbody>
</table>

a All reactions carried out with 2 mole % of catalyst in dichloromethane at reflux.
b Yields are based on 1H NMR spectra of total reaction mixtures: yields in parentheses are those of isolated compounds following medium pressure liquid chromatography on silica.
c The norcaradiene rearranged on silica to afford the enone 82 in 46% isolated yield.
2.2.2 The Mechanism of C-H Insertion

There has been much debate over the mechanism of rhodium (II)-catalysed C-H insertion.\textsuperscript{57} It has been agreed that the reaction occurs \textit{via} a highly electrophilic metal carbenoid intermediate, for which two resonance contributing structures (83 and 84) can be drawn (Figure 2.3). Due to the highly electrophilic nature of these metal carbenes, Doyle has suggested that they should be viewed as metal-stabilised carbocations (83), with electron donation through the dirhodium framework providing stability.\textsuperscript{50,58,59}

![Figure 2.3: Resonance structures depicting the rhodium carbene intermediate.](image)

Taber's group have published numerous examples of the versatility of the rhodium-catalysed C-H insertion reaction to form five-membered carbocyclic rings.\textsuperscript{60-62} A series of competitive intramolecular C-H insertion reactions established that the observed order of reactivity of C-H bonds is methine $>$ methylene $>>$ primary, with the additional observation that benzylic and allylic methylenes were less reactive than aliphatic methylenes.\textsuperscript{62} These results led to a suggestion that the reaction proceeds by complexation of a coordinatively unsaturated rhodium carbene complex to the electron density in the C-H bond. As a result, Taber and Ruckle\textsuperscript{62} proposed that the phenyl substituent, being inductively electron withdrawing in nature, must deactivate the benzylic methylene. However, recent examples by Ceccherelli and coworkers have shown that allylic C-H insertion is greatly favoured over non-allylic methylene insertion.\textsuperscript{63} As noted by Doyle, it is surprising that allylic and benzylic
methylenes would be less reactive in what is essentially an electrophilic transformation. 58

Doyle and coworkers 54,58,59 have proposed a mechanism based on the experimental observations that C-H insertion occurs with retention of configuration at the centre undergoing insertion, 60 and that the ligands on the rhodium framework remain intact during insertion, as evidenced by the high degree of enantioselectivity when using chiral rhodium catalysts. 64-66 It is suggested that C-H insertion occurs by the interaction of the p-orbital on the carbenic carbon with the σ orbital of the C-H bond (Figure 2.4). Thus, this overlap initiates a process in which C-C and C-H bond formation with the carbene carbon proceeds as the ligated metal dissociates. Doyle 59 has developed a model which accounts for the diastereoselectivity of the various C-H insertion reactions, thereby enabling the results with regard to benzylic and allylic methylenes to be explained by conformational effects, as opposed to electronic effects postulated by Taber and Ruckle.

Figure 2.4: A mechanistic depiction of the C-H insertion process. 54,58,59

Stork and Nakatani 67 have observed that an ester substituent drastically deactivates both alpha and beta methylenes towards C-H insertion, such that when this insertion was the only available pathway for five-membered ring formation, the carbene dimer 85 was the only isolable product (Scheme 2.3). While Doyle’s model rationalises these results purely on steric grounds, it was acknowledged that electronic destabilisation can be a factor in the C-H insertion. 54
Conversely, electron donating groups should activate C-H bonds to insertion. Adams and coworkers have achieved extraordinary regiocontrol using this principle, culminating in the synthesis of a number of natural products.68

2.2.3 Testing the Hypothesis

The activation of the aromatic ring system by electron-donating groups does seem to provide an acceptable explanation of the results obtained in the case of the methoxy-substituted diazoketones. While methoxy substituents do appear to afford higher yields of cyclopropanation products, due to their electronic stabilising effects, they also promote C-H insertion at the benzylic positions. When such favourable electronic factors coincide with the formation of a five-membered ring, insertion could be expected to become a more dominant pathway and this would appear to be exactly the case for the 7-methoxy analogue. The 6-methoxy substituent activates the benzylic position that would afford a four membered ring after C-H insertion, and as this is not favoured, cyclopropanation is still the dominant pathway. This rationale makes the 8-methoxy substrate all the more perplexing, as it should produce comparable results to the 6-methoxy series, based on the above argument.
To test the hypothesis of activation by methoxy groups further, the same substrates were treated with rhodium (II) triphenylacetate [Rh$_2$(TPA)$_4$], which has been reported to be a highly selective catalyst for C-H insertion processes.$^{69}$ In this case, the amount of cyclopropanation should be diminished and should allow more definite conclusions to be drawn from the influence of the methoxy substituent upon C-H insertion.

These reactions were performed in a similar manner (Scheme 2.4) to those above and the results are presented in Table 2.3. The yields of the cyclopentanone insertion products [C] increased in all cases, with a resultant decrease in cyclopropanation. The activating role of the methoxy group can be seen from the results for the 6-methoxy and 7-methoxy substrates. The cyclopentanone was almost exclusively formed in the 7-methoxy series, while the amount of C-H insertion for the 6-methoxy compound 73 was actually lower than that obtained for the parent system 62. In this case, it would appear that cyclopropanation of the aromatic ring was definitely preferred over the formation of a more strained cyclobutanone insertion product.

Interestingly, no cyclopropanation was observed for the 8-methoxy compound, but the cyclobutanone 87 was obtained in a 17% yield. The initial structural proof came from the IR carbonyl absorption of 1775 cm$^{-1}$, which was consistent with a cyclobutanone ring system.$^{70,71}$ Insertion into the benzylic methylenes was apparent from the chemical shifts of the two methylene carbons (21.6 and 27.6 ppm) remaining in that portion of the $^{13}$C NMR spectrum of 87. The resonance at 21.6 ppm was comparable to the chemical shift of C3 in the diazoketone. The resonances at 57.9, 53.9 and 21.7 ppm were assigned to C2a, C1 and C8b respectively. The $^1$H NMR spectrum was very complex, but using the $^1$H-$^1$H-double quantum filtered correlation spectroscopy technique (DQFCOSY), all of the protons could be assigned. Strong evidence for the proposed structure was provided by the observation that there were only three
cross-peaks for H8b, as would be expected. The alternative cyclobutanone would be expected to have five such cross peaks for the equivalent proton.

Scheme 2.4

![Image of Scheme 2.4]

Table 2.3: Results from the Rh2(TPA)4 catalysed reactions of tetrahydronaphthyl diazoketones (Scheme 2.4).

<table>
<thead>
<tr>
<th>[A]a</th>
<th>R=</th>
<th>[B]</th>
<th>% Yieldb</th>
<th>[C]</th>
<th>% Yieldb</th>
<th>[D]</th>
<th>% Yieldb</th>
</tr>
</thead>
<tbody>
<tr>
<td>[70]</td>
<td>5-0Me</td>
<td>[71]</td>
<td>41 (32)</td>
<td>[72]</td>
<td>50 (45)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[73]</td>
<td>6-0Me</td>
<td>[74]</td>
<td>52 (51)</td>
<td>[75]</td>
<td>45 (38)</td>
<td>[86]</td>
<td>5 (4)</td>
</tr>
<tr>
<td>[76]</td>
<td>7-0Me</td>
<td>[77]</td>
<td>10 (0)c</td>
<td>[78]</td>
<td>89 (81)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[79]</td>
<td>8-0Me</td>
<td>[80]</td>
<td>0</td>
<td>[81]</td>
<td>73 (70)</td>
<td>[87]</td>
<td>23 (17)</td>
</tr>
</tbody>
</table>

a All reactions carried out with 2 mole % of catalyst in dichloromethane at reflux.
b Yields are based on 1H NMR spectra of total reaction mixtures: yields in parentheses are those of isolated compounds following medium pressure liquid chromatography on silica.
c The norcaradiene rearranged on silica to afford the enone 82 in 5% yield.

In summary, it has been shown that the synthesis and isolation of the stable norcaradienes is possible. Moreover, their isolated yields could be enhanced by increasing the electron density in the aromatic ring by the use of methoxy substituents, although this also promoted C-H insertion at benzylic positions, which in some cases resulted in lower yields for the cyclopropanation. The reactivity of the 8-methoxy diazoketone 79 does not fit this pattern and investigations into why this is so will be discussed in the next section.
SECTION 2.3: INVESTIGATIONS INTO THE LOW YIELDS OF THE 8-METHOXY NORCARADIENE 80

As mentioned earlier, the anomalous results obtained for the 8-methoxy substrate 79 (Scheme 2.5) were very perplexing, as they were expected to be comparable to those of the 6-methoxy compound. This was very disappointing as the 8-methoxy substitution is a key element in the proposed synthetic plan discussed in Chapter One.

![Scheme 2.5](image)

The low yield was not readily explained, unless one invoked steric inhibition by the *peri* substituent. The fact that the amount of cyclopropanation had decreased as an apparent consequence of forming a larger proportion of the cyclopentanone 81, was believed to be significant, especially since the 8-methoxy substituent should favour the formation of the cyclobutanone 87. It could be possible that the methoxy group is bulky enough to push the rhodium complex away from the aromatic ring and in closer proximity to the benzylic methylene at C4, so that C-H insertion occurs due to a conformational effect rather than any electronic factors.
2.3.1 The Use of a Hydroxy Group

To test this proposal, it was decided to use the 8-hydroxy diazoketone 92, and observe the ratio of products. The hydroxy group is obviously not as sterically demanding and accordingly, the yield of cyclopropanation should be higher, if steric inhibition is indeed a factor. To ensure that any changes were not merely due to the different substituent, the 6-hydroxy diazoketone 88 was also investigated.

It came as no surprise that in both cases, the initial cyclopropanation products were too unstable to be isolated, with the dienediones being obtained instead (Scheme 2.6 and Table 2.4). Both of the dienediones 89 and 93 have been previously synthesised and their identities were confirmed by comparison with authentic samples.

Again, there was a difference between the 6- and 8-substituted substrates. Although the amount of cyclopropanation for the 8-hydroxy isomer 92 had increased, it was still appreciably below that of the 6-substituted isomer. This seemed to suggest that steric factors could explain the lower yields for the cyclopropanation. Obviously though, the phenol group has some steric demand, so it could still perturb the system to some extent.

Interestingly, the yield of cyclopropanated product 89 had decreased for the 6-hydroxy substrate with respect to that of the 6-methoxy substrate (72% isolated). The hydroxy substituent is substantially more electron donating than a methoxy group and as a consequence should activate C-H insertion at the para benzylic position to a much greater extent. Surprisingly, no cyclobutanone was observed in the product mixture of the reaction. The 1,2-dihydronaphthalene 91 was a new product and constituted a significant proportion of the reaction mixture. Unfortunately, the alkene could not be
isolated in pure form, due to the scale of the reaction. The additional olefinic signals of the 1,2-dihydronaphthalene in the ¹H NMR spectrum (5.90 and 6.65 ppm) were very characteristic and helped to confirm the structure. The formation of this alkene was very unusual and obviously would not arise from a direct C-H insertion process, but possibly from the elimination of ketene. The formation of this unusual product will be discussed later in section 2.3.3.

Scheme 2.6

![Scheme 2.6](image)

**Table 2.4:** Results from the Rh₂(OAc)₄ catalysed reactions of hydroxy-substituted tetrahydronaphthyl diazoketones (Scheme 2.6).

<table>
<thead>
<tr>
<th>Substrateᵃ</th>
<th>% Yieldᵇ</th>
<th>% Yieldᵇ</th>
<th>% Yieldᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>[88]</td>
<td>[89] 61 (55)</td>
<td>[90] 25</td>
<td>[91] 14</td>
</tr>
<tr>
<td>[92]</td>
<td>[93] 39 (35)</td>
<td>[94] 45</td>
<td>[95] 16</td>
</tr>
</tbody>
</table>

ᵃAll reactions carried out with 2 mole % of catalyst in dichloromethane at reflux.
ᵇYields are based on ¹H NMR spectra of total reaction mixtures: yields in parentheses are those of isolated compounds following medium pressure liquid chromatography on silica.
A similar amount of alkene 95 was observed for the 8-hydroxy substrate 92, with the remaining material being the cyclopentanone 94. The amount of 94 had decreased relative to the 8-methoxy substrate, but still remained the major product. This lends support to the argument that for the 8-substituted diazoketones, the metal carbene complex is being pushed away from the aromatic moiety, towards the benzylic hydrogens. Nevertheless, we were troubled that inspection of molecular models seemed to suggest that the 8-methoxy or hydroxy substituents were not close enough to have a steric effect. However, it was noticed that if a late, product-like transition state was considered for the cyclopropanation, the 8-substituent was eclipsed with the β-hydrogen of the C1 methylene (cf. 79), while it was in a staggered conformation when looking at the C-H insertion transition state. This difference may be sufficient to alter the balance in the competing reactions.

2.3.2 The Use Of Dimethoxy Substituents

To explore the impact of the 8-substituents further, the 6,8-dimethoxy diazoketone 96 was examined to determine whether the electronic effect of the 6-methoxy substituent would override the presumed steric effect of the 8-methoxy substituent. The 6,8-dimethoxy diazoketone 96 was readily available, as it had been used in a synthesis of 15-desoxyeffusin.74,75 The 6,7-dimethoxy substrate 10075 was also investigated for comparative purposes.

Under the conditions discussed earlier, the 6,7-dimethoxy substrate 100 afforded only two products, the norcaradiene 101 and the cyclopentanone 102,
in a ratio of 66:33 as determined by $^1$H NMR analysis (Scheme 2.7 and Table 2.5). This ratio fell in between the results obtained for each individual monomethoxy compound (cf. Table 2.2).

Scheme 2.7

Table 2.5: Results from the Rh$_2$(OAc)$_4$ catalysed reactions of dimethoxy-substituted tetrahydronaphthyl diazoketones (Scheme 2.7).

<table>
<thead>
<tr>
<th>Substrate$^a$</th>
<th>% Yield$^b$</th>
<th>% Yield$^b$</th>
<th>% Yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[96]</td>
<td>[97] 39 (0)$^c$</td>
<td>[98] 32 (30)</td>
<td>[99] 23 (20)</td>
</tr>
<tr>
<td>[100]</td>
<td>[101] 66 (0)$^c$</td>
<td>[102] 33 (31)</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ All reactions carried out with 2 mole % of catalyst in dichloromethane at reflux.

$^b$ Yields are based on $^1$H NMR spectra of total reaction mixtures: yields in parentheses are those of isolated compounds following medium pressure liquid chromatography on silica.

$^c$ The norcaradienes 97 and 101, rearranged on silica to afford the dienedione 103 (38% isolated yield) and the enone 104 (64% isolated yield) respectively.

In the course of purification, the norcaradiene 101 rearranged instantaneously on silica and the known enone 104 was isolated in 64% yield.$^7$ The formation of similar types of compound will be discussed in section 2.5.2.1.
The 6,8-dimethoxy substrate 96 afforded a 39% yield of the norcaradiene 97, which similarly rearranged upon chromatography on silica to afford the known dienedione 103. This isolated product was in contrast to the trienones obtained from the rearrangement of the 6,7-dimethoxy and 7-methoxy norcaradienes 101 and 77. In some reactions, an initial rearrangement product 106 was obtained, which slowly converted to the isolated dienedione 103 (Scheme 2.8).

Scheme 2.8

The $^1$H NMR spectrum of this initial product had a triplet at 5.1 ppm, which was assigned to the new olefinic proton, and a two proton singlet at 4.94 ppm ascribed to the enol ether protons. Compound 106 must presumably arise from the cation 105, which is stabilised by both methoxy groups and accordingly the
series of sigmatropic shifts after cyclopropane ring cleavage, which give rise to
the rearranged trienones (see section 2.5.2.1) would be disfavored in this case.

The most striking aspect of this reaction was the amount of alkene 99 formed.
Egli reported the synthesis of this compound from the corresponding 1-tetralone, but without full spectroscopic data. Analysis of the $^1$H NMR spectrum showed two doublets of triplets at $\delta$ 5.90 and $\delta$ 6.75, which are typical values for 1,2-dihydronaphthalenes, while the $^{13}$C NMR spectrum clearly exhibited resonances corresponding to the two olefinic methine and two aliphatic methylene carbons.

The formation of alkene 99 in the diazodecomposition of 6,8-dimethoxy diazoketone 97 was a major complication, as it now meant three reactions were in competition with one another. Since, it was not seen in the 6,7-dimethoxy diazodecomposition reaction, any comparison of the two reactions would be essentially invalid. In the case of the hydroxy-substituted substrates 88 and 92, the amount of alkene formation was virtually the same, such that a comparison of the amounts of cyclopropanation still had some merit.

The 6,8-dimethoxy substrate was important in that it allowed isolation and characterisation of the alkene 99, and an investigation into the source of this unusual product is presented in the next section.

2.3.3 The Origin of the Alkene

The alkene byproduct had previously been seen in the monomethoxy series (Section 2.2), but not in isolable yields. As small amounts of the cyclobutanones were also observed as byproducts in these reactions, it seemed advisable to check that the cyclobutanone had not decomposed with the elimination of ketene, to yield the alkene. To do this, the purified 8-methoxy cyclobutanone 87
was resubjected to the cyclopropanation reaction conditions, but was recovered unchanged.

Due to results obtained from an investigation of the stereoelectronic effects of C-H insertion, Adams and Spero\textsuperscript{73} discussed Taber's proposal\textsuperscript{57,62} of the possibility of hydrogen transfer to rhodium, followed by reductive elimination and C-C bond formation. They postulated that hydrogen could be transferred as hydride to the rhodium, and replaced the hydrogen with deuterium in their substrate, in the hope of observing a kinetic isotope effect. The failure to do so was interpreted as an implication that the hydride transfer was not the rate determining step.

In Doyle's mechanism, the implication was that the overlap of the two orbitals and resultant bond formation was a concerted, synchronous process. The alkene formation in our systems indicated that there may be exceptions to this. It is believed that hydride transfer does occur, but with sufficient activation, may not necessarily be concerted with C-C bond formation, especially where cyclobutanone formation would be involved. Under these circumstances, fragmentation with loss of ketene might become a competitive pathway as postulated in Scheme 2.9.

\textbf{Scheme 2.9}
In order to obtain evidence for the proposed formation of ketene, the diazo-decomposition of the 6,8-dimethoxy diazoketone 96 was repeated, but with apparatus designed to distill the solvent quickly into a sample of p-toluidine 107. The acetamide derivative 108 was isolated in 70% of the theoretical amount, based on the alkene, using this procedure (Scheme 2.10), which was obviously strong evidence for the proposal of ketene elimination.

Scheme 2.10

In a related piece of work carried out within our research group, it was found that in the cyclopropanation of the gibberellin derivative 109, 20% of the crude reaction mixture consisted of the unusual enol ether 110 (Scheme 2.11). It was proposed in this case that the hydride was transferred to the carbenoid, but as elimination was not a feasible process in this case, the positive charge was attacked by the oxygen of the carbonyl, with resultant elimination of the rhodium to afford the observed compound 110.

Further experiments could be designed to confirm these results, but it was felt that this was too far outside the scope of the current investigation. Indeed, it did not appear that further investigations into the low yield of cyclopropanation for the 8-methoxy substrate would lead to significantly improved yields. In conclusion, some evidence exists suggesting that the yields of cyclopropanation for the 8-methoxy substrate were lower due to steric inhibition by the peri methoxy group, but unfortunately, further analysis was complicated by the formation of an unwanted byproduct. Interestingly, the
formation of this alkene provided further insight into the mechanism of rhodium-catalysed C-H insertion processes.

As the point of this investigation was to establish the viability of stable s-tetrahydronorcaradienes as benzylidene cyclopropanes in the yield of the cyclopropanation were required, especially for the 8-methoxy substrate since it was felt that the following would be (a) achieving this and (b) investigating a range of different catalysts.

Scheme 2.11

As the main objective of this paper was to prepare the C4 hydroxy group as a carbonyl, it was therefore decided to replace these benzylidene hydroxyl groups with methylene hydrogens that were prepared for a series of experiments.

Scheme 2.12

Accordingly, the diastereomeric mixture of dicyclopentanone 111 and 8-methoxy-4-ene dicyclopentane 112 were investigated (Scheme 2.12).
2.4 INCREASING THE YIELD OF THE NORCARADIENES

As the point of this investigation was to establish the viability of stable norcaradienes as benzenoid synthons, improvements to the yield of the cyclopropanation were required, especially for the 8-methoxy substrate, since it was felt to be important in the context of the proposed total synthesis. It was felt that there were two ways of achieving this: (a) substitution of the tetrahydro ring so as to remove the hydrogens that were available for insertion reactions and (b) investigation of a range of different catalysts.

2.4.1 Investigations into the substitution of the tetrahydro ring

2.4.1.1 Use of Tetralone Diazoketones

As C-H insertion into the benzylic position at C4 was the major side-reaction, it was decided to remove these benzylic hydrogens altogether. The replacement of the C4 methylene group with a carbonyl group appeared to be a most attractive way of doing so, as it could allow later functionalisation of the C11 and C12 positions of kaurenoid diterpenes. Accordingly, the diazo-decomposition of diazoketone 111 and 8-methoxy-4-keto diazoketone 113 were investigated (Scheme 2.12).

![Scheme 2.12](image-url)

**Scheme 2.12**

111 R=H
113 R=OMe
112 R=H
114 R=OMe
To our dismay, the 4-keto diazoketone 111 afforded only an 18% yield of the norcaradiene 112 upon treatment with Rh$_2$(OAc)$_4$ under the same conditions used previously (Table 2.6). The remainder of the reaction mixture was not characterised. McKervey and coworkers$^{42,79}$ have noted that rhodium S-(+)-mandelate [Rh$_2$(mand)$_4$] afforded higher yields when cyclopropanating some benzene derivatives. This was also the case for substrate 111, with an isolated yield of 60% of norcaradiene 112 being obtained upon treatment with Rh$_2$(mand)$_4$ in dichloromethane at reflux. The 8-methoxy substituted diazoketone 113 afforded a similar isolated yield (59%), using identical conditions.

### Table 2.6: Results from the Rh(II) catalysed reactions of 4-keto-substituted tetrahydronaphthyl diazoketones (Scheme 2.12).

<table>
<thead>
<tr>
<th>Substrate$^a$</th>
<th>Catalyst</th>
<th>Product</th>
<th>Yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>111</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>[112]</td>
<td>18</td>
</tr>
<tr>
<td>111</td>
<td>Rh$_2$(mand)$_4$</td>
<td>[112]</td>
<td>65 (60)</td>
</tr>
<tr>
<td>113</td>
<td>Rh$_2$(mand)$_4$</td>
<td>[114]</td>
<td>62 (59)</td>
</tr>
</tbody>
</table>

$a$ All reactions carried out with 2 mole % of catalyst in dichloromethane at reflux.  
$b$ Yields are based on $^1$H NMR spectra of total reaction mixtures: yields in parentheses are those of isolated compounds following medium pressure liquid chromatography on silica.

The spectroscopic data of both norcaradienes 112 and 114 were consistent with the norcaradienes discussed previously. Interestingly, no traces of any products arising from ketene elimination were observed. These results were very pleasing, especially for the 8-methoxy substrate, as the yield had essentially tripled.
2.4.1.2 Introduction of an alpha substituent

A more commonly found substitution pattern in the kaurenoid diterpenes is hydroxylation at C13, and being a bridgehead alcohol, would be extremely difficult to establish at a later stage. The α-trichloroacetoxy diazoketone 115 was used in the Mander gibberellin synthesis to produce dienedione 116 (Scheme 2.13). However, when this compound was treated with Rh$_2$(OAc)$_4$, a complex mixture was obtained and this was attributed to the metal carbenoid reacting with the carbonyl group of the trichloroacetate, an example of the well-known carbonyl ylide reaction.54

![Scheme 2.13](attachment:image.png)

Thus, a protecting group that was not susceptible to such metal carbenoid reactions was required. A silyl protecting group appeared to be the most promising, as many other protecting groups have hydrogens available for rhodium carbenoid C-H insertion.

The hydroxy acid 117 was silylated using t-butyldimethylsilyl chloride (TBDMSCl) and imidazole to afford the α-silyloxy silyl ester 118 quantitatively (Scheme 2.14). Hydrolysis of the ester, based on a procedure described by Morton and Thompson,80 afforded the acid 119 in 55% yield. The diazoketone 120 was obtained in 70% yield via the acyl chloride. It has been reported81 that acid chlorides can be obtained directly from t-butyldimethylsilyl esters upon
treatment with oxalyl chloride and DMF, however much lower yields of the diazoketone were observed under these conditions.

Scheme 2.14

Exposure of the diazoketone 120 to rhodium acetate afforded a three component mixture of norcaradiene 121, cyclopentanone 122 and cyclobutanone 123 in the ratio of 52:18:25 (Scheme 2.15). All attempts to obtain pure materials failed, although some enrichment was possible and accordingly, only NMR data for 121 and 123 can be presented. The data were consistent with that obtained previously for both classes of compounds, with the $^{13}$C NMR data proving to be particularly useful.

Scheme 2.15
The yield of cyclopropanation had essentially doubled upon substitution of the alpha hydrogen by an OTBDMS group. While the reasons for this were not readily apparent, it was a very gratifying result.

2.4.2 Investigations into the use of different catalysts

2.4.2.1 Rhodium catalysts

In recent years, much attention has focused on regiochemical control in rhodium (II) catalysed diazodecomposition reactions. While some success has been obtained by altering substituents on the carbene, more notable results have been acquired with the use of different ligands on the catalyst. Of this latter work, the most dramatic results were obtained by Doyle, Padwa and coworkers, as they found that decreased electron withdrawal by the ligands on rhodium lowered the reactivity of the catalyst, but increased selectivity. In a competition experiment, the use of a strongly electron-withdrawing ligand, perfluorobutyrate, resulted in preferential formation of the tertiary insertion product 125, while rhodium (II) caprolactam [Rh₂(cap)₄] afforded cyclopropane 126 exclusively for the same substrate 124 (Scheme 2.16).

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>125:126</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh₂(OAc)₄</td>
<td>56:44</td>
</tr>
<tr>
<td>Rh₂(cap)₄</td>
<td>0:100</td>
</tr>
<tr>
<td>Rh₂(pfb)₄</td>
<td>100:0</td>
</tr>
</tbody>
</table>
Rhodium acetate was found to afford a 56:44 mixture, which is approximately halfway between the other results. This distribution was consistent with the difference in electrophilicity of the catalysts and further examples were presented that confirmed this trend.

Although the use of Rh\textsubscript{2}(cap)\textsubscript{4} resulted in cyclopropanation being favoured over C-H insertion in the class of compounds described above, it favoured C-H insertion (e.g. 129) over cyclopropanation of an aromatic moiety (e.g. 128) in the case of aryl diazoamides (e.g. 127) (Scheme 2.17).\textsuperscript{83} These disparate results did not allow a confident prediction for their use on the tetrahydronaphthyl diazoketones discussed earlier.

**Scheme 2.17**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>128:129</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh\textsubscript{2}(OAc)\textsubscript{4}</td>
<td>68:32</td>
</tr>
<tr>
<td>Rh\textsubscript{2}(cap)\textsubscript{4}</td>
<td>3:97</td>
</tr>
<tr>
<td>Rh\textsubscript{2}(pfb)\textsubscript{4}</td>
<td>95:5</td>
</tr>
</tbody>
</table>

Unfortunately, it was found that Rh\textsubscript{2}(cap)\textsubscript{4} afforded lower yields of norcaradienes in all cases examined, together with increased C-H insertion (Scheme 2.18 and Table 2.7). Interestingly, no norcaradiene resulting from the 8-methoxy diazoketone 79 was observed. In the case of the aryl diazoamides, the results with rhodium (II) perfluorobutyrinate [Rh\textsubscript{2}(pfb)\textsubscript{4}] were found to be complementary, favouring cyclopropanation of the aromatic ring. However, in
the two tetrahydronaphthyl diazomethyl ketones examined, only increased C-H insertion was observed.

Scheme 2.18

Table 2.7: $^1$H NMR yields of rhodium (II) caprolactam and perfluorobutyrate catalysed reactions of tetrahydronaphthyl ketones (Scheme 2.18)*

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Substrate (R =)</th>
<th>[A] % Yield of A</th>
<th>[B] % Yield of B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh$_2$(cap)$_4$</td>
<td>H, 62</td>
<td>[63] 11</td>
<td>[66] 70</td>
</tr>
<tr>
<td>&quot;</td>
<td>5-0Me, 70</td>
<td>[71] 10</td>
<td>[72] 65</td>
</tr>
<tr>
<td>&quot;</td>
<td>6-0Me, 73</td>
<td>[74] 55</td>
<td>[75] 29</td>
</tr>
<tr>
<td>&quot;</td>
<td>7-0Me, 76</td>
<td>[77] 21</td>
<td>[78] 76</td>
</tr>
<tr>
<td>&quot;</td>
<td>8-0Me, 79</td>
<td>[80] 0</td>
<td>[81] 70</td>
</tr>
<tr>
<td>Rh$_2$(pfb)$_4$</td>
<td>6-0Me, 73</td>
<td>[74] 17</td>
<td>[75] 76</td>
</tr>
<tr>
<td>&quot;</td>
<td>7-0Me, 76</td>
<td>[77] 19</td>
<td>[78] 70</td>
</tr>
</tbody>
</table>

The failure of these catalysts was a great disappointment, especially when in related model studies of a troponoid diterpene, harringtonolide, it was found that Rh$_2$(cap)$_4$ dramatically increased the yield of the cycloheptatriene 130 (Scheme 2.19).$^{85}$

* Rh$_2$(cap)$_4$ and Rh$_2$(pfb)$_4$ were generously provided by Professor Michael Doyle of Trinity University, San Antonio.
As seen in section 2.4.1.1, Rh$_2$(mand)$_4$ can be used to increase the yield of cyclopropanation in the tetralone series. Unfortunately, its use in the tetralin series was not as successful, with lower yields for all cases when compared to Rh$_2$(OAc)$_4$ (cf. Section 2.2) (Scheme 2.18 and Table 2.8).

Table 2.8: $^1$H NMR yields of rhodium (II) mandelate catalysed reactions of tetrahydronaphthyl diazoketones (Scheme 2.18)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>[A] % Yield</th>
<th>[B] % Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-OMe, 73</td>
<td>[74] 50</td>
<td>[75] 33</td>
</tr>
<tr>
<td>7-OMe, 76</td>
<td>[77] 44</td>
<td>[78] 51</td>
</tr>
<tr>
<td>8-OMe, 79</td>
<td>[80] 21</td>
<td>[81] 38</td>
</tr>
</tbody>
</table>

2.4.2.2 Copper Catalysts

Copper catalysts have been used with moderate success in the cyclopropanation of alkenes and aromatic rings$^{49}$ and so it should be possible to improve the amount of cyclopropanation for some of our substrates by utilising these catalysts. Of the wide range of catalysts investigated using diazoketone 79 as the substrate, copper (II) acetylacetonate$^{48,86}$ in 1,2-dichloroethane at reflux was the system that afforded the highest yield of
norcaradiene 80 (65% after chromatography), essentially a three-fold increase in yield when compared to the Rh$_2$(OAc)$_4$ result (21%) (Table 2.9).

![norcaradiene](image)

Table 2.9: $^1$H NMR yields of copper-catalysed reactions of diazoketone 79

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>% Yield of Cyclopropanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CuCl,P(OMe)$_3$</td>
<td>20</td>
</tr>
<tr>
<td>Cu(OTf)$_2$</td>
<td>11</td>
</tr>
<tr>
<td>Cu bronze</td>
<td>20</td>
</tr>
<tr>
<td>CuI</td>
<td>35</td>
</tr>
<tr>
<td>CuCl</td>
<td>29</td>
</tr>
<tr>
<td>Cu($t$-butylsalicylimidato)$_2$</td>
<td>32</td>
</tr>
<tr>
<td>Cu(acetylacetonate)$_2$</td>
<td>66</td>
</tr>
</tbody>
</table>

It was found that this catalyst gave consistent isolated yields (55-65%) of all norcaradienes, irrespective of the substrate, with only small amounts of the cyclopentanones observed (Scheme 2.20 and Table 2.10). Thus, it would appear that for the synthesis of the norcaradienes, copper (II) acetylacetonate [Cu(acac)$_2$] was the catalyst of choice, except in the case of the 6-methoxy substrate 73, where Rh$_2$(OAc)$_4$ remained superior.
2.4.3 Conclusions

The transition-metal catalysed intramolecular cyclopropanation of the aromatic ring in tetrahydronaphthyl diazomethyl ketones, has been shown to be a viable method for the synthesis of stable tetracyclic norcaradienes. It was found that the use of copper (II) catalysts afforded consistent yields regardless of the substrate, while rhodium catalysis could only provide variable yields due to competing C-H insertion processes.
2.5 SOME CHEMISTRY OF THE NORCARADIENES

As the synthesis of the norcaradienes was now a viable process, attention was turned to the chemistry of these compounds. There appeared to be two ways to utilise these compounds: (a) acid cleavage of the cyclopropane ring to generate the bicyclo[3.2.1] and [2.2.2] ring systems respectively, and (b) selective hydrolysis of the enol ether so that the cyclopropane remained intact. In the following work, the majority of the reactions were performed on the most accessible norcaradiene 74.

2.5.1 Hydrolytic Cyclopropane Ring Cleavage

Treatment of the norcaradiene 74 with aqueous 3M hydrochloric acid in acetone afforded the dienedione 89 in 91% yield after chromatography (65% overall yield starting from the diazoketone 73) (Scheme 2.21). This dienedione was obtained directly upon cyclopropanation of the hydroxy diazoketone 88 in a yield of 55% (Section 2.3.1), but was originally synthesised by Mander and coworkers\(^\text{51}\) during a study of the ipso-alkylation of benzenoid moieties in tetrahydronaphthyl diazomethyl ketones.
After exposure of diazoketone 73 to trifluoroacetic acid, Mander and coworkers obtained the dienedione 89 in 86% yield. The cyclopropanation-hydrolysis procedure was less satisfactory than the direct method in this case, but a significant improvement was seen when attention was turned to the hydrolysis of norcaradiene 77. In the analogous system, Mander and coworkers had obtained only a 48% yield of the desired bicyclo[2.2.2] ring system 132 when the hydroxy diazoketone 131 was treated with trifluoroacetic acid (Scheme 2.22).

**Scheme 2.22**

As reported in Section 2.4.2.2, the cyclopropanation of diazoketone 76 with Cu(acac)₂ gave the desired norcaradiene 77 in 65% yield by ¹H NMR analysis. All attempts to chromatograph the crude product resulted in rearrangement (cf. Section 2.2.1). If the crude material from the cyclopropanation was instead treated with 3M HCl/acetone, dienedione 132 was obtained in an excellent yield (73% over the two steps) (Scheme 2.23).

**Scheme 2.23**
The high yield for the combined process is particularly interesting and indicates that the cyclopropanation with copper catalysis must be occurring in approximately 80% yield, based on the 91% yield for the hydrolysis of norcaradiene 74. Thus, it appears that the cyclopropanation-hydrolysis method can provide a significant advantage over the acid-catalysed ipso-alkylation of the benzene moieties of the methoxy-substituted diazoketones.

2.5.2 Selective Enol Ether Hydrolysis

2.5.2.1 Attempted acid cleavage of norcaradiene 74

Having shown that cyclopropyl ring cleavage with aqueous acid was a useful process, it was decided to investigate the alternative enol ether hydrolysis with the intention of leaving the cyclopropane ring intact. Unfortunately, this proved to be impossible. The use of weaker acids (acetic acid, oxalic acid) resulted in a mixture of two compounds, with dienedione 89 still predominating, but none of the desired enedione was observed. The use of mercury (II) nitrate in aqueous acetonitrile resulted in a similar mixture, even though this reagent is mild enough to hydrolyse enol ethers selectively in the presence of ethylene ketals.\(^\text{11}\)

In the course of investigating the stability of the norcaradienes to Lewis acid catalysts, it was discovered that the use of 5M LiClO\(_4\) in ether\(^\text{87}\) resulted in the rapid conversion of norcaradiene 74 to trienone 133 in 95% yield (Scheme 2.24).

The IR spectrum of compound 133 was consistent with examples of similar compounds characterised by Mander and coworkers.\(^\text{75,88}\) The \(^{13}\text{C}\) NMR spectrum was particularly useful and indicated that there were only three aliphatic methylene carbons (23.9, 37.5 and 48.1 ppm), one aliphatic methine carbon (52.4 ppm) and one aliphatic quaternary carbon (48.6 ppm). Of the six
olefinic resonances, those at 142.4 and 161.2 ppm, combined with the shift of the carbonyl group (201.9 ppm), were diagnostic indicators for the presence of an \(\alpha,\beta\)-unsaturated ketone. The characteristic peak in the \(^1\)H NMR spectrum was the singlet at \(\delta 5.67\), which was assigned to H9.

Comparison of the data for this compound to the \(^1\)H NMR spectra of the crude mixtures of the above hydrolysis reactions, revealed that the trienone 133 was the second component in these mixtures. Similar compounds were observed in Sections 2.2.1 and 2.3.2 and their spectroscopic data are presented in the experimental section. Presumably, these compounds arise from the initial fragmentation of the cyclopropane ring, followed by a 1,2-sigmatropic shift (Scheme 2.24).\(^{75,88}\) Interestingly, these compounds have essentially the CD-ring system of the scopadulcic acids\(^{35,89}\) (cf. Chapter One) and perhaps the 7-methyl homologues could be potential intermediates in a total synthesis of these compounds.
2.5.2.2 Attempted hydrolysis of methylenated norcaradienes

From the above work, it was apparent that selective hydrolysis of the enol ether was not possible. The presence of the carbonyl group was presumed to be an important factor, with its capacity to act as an 'electron sink'. By removing this functionality, it might still be possible to carry out the desired hydrolysis. The best way to achieve this was believed to be methylation of the ketone. Wittig methylation was unsuccessful, however, and the sensitivity of the norcaradienes to acid proved a major stumbling block for other procedures. The Lombardo-Oshima titanium methylation$^{90}$ and the zirconium alternative to the Lombardo reaction,$^{91}$ resulted in rapid decomposition of the norcaradiene, with no identifiable products isolated.

The Peterson methylation$^{92}$ involves the use of trimethylsilylmethyl lithium to form a β-hydroxy silane, which can be collapsed to the olefin using either acid or base. The norcaradiene 74 reacted rapidly with the lithium reagent to afford the expected β-hydroxy silane 134 in 96% yield (Scheme 2.25). The spectroscopic data of the product were similar to that observed for the starting material, except that the ketone resonance in the $^{13}$C NMR spectrum had been replaced with a signal for C4 at 81.5 ppm, as well as the appropriate signals for a CH$_2$TMS moiety.

Scheme 2.25
Attempts to collapse this adduct to olefin 135 proved to be futile, with either starting material returned unchanged, or complete decomposition the only result. Peterson\textsuperscript{92} reported that the addition of potassium hydride can promote elimination, but even after 24 h in the presence of KH in THF at reflux, the adduct was unchanged. Cohen and coworkers\textsuperscript{93} have reported that diglyme solutions work effectively for these reactions if THF proved to be an unsatisfactory solvent. However, decomposition of the adduct was the only result upon exposure to this system. Other procedures attempted were thionyl chloride\textsuperscript{94} and mesyl chloride/triethylamine\textsuperscript{95} and while these appeared similarly unsuccessful, the starting material could not be recovered after work-up, presumably due to decomposition upon exposure to these reagents.

Thus, it would appear that the acid sensitivity of the norcaradienes precludes effective attempts to methylenate the ketone functionality.

2.5.2.3 Enol ether removal via ring contraction

For some synthetic targets, the Wohl ring contraction method\textsuperscript{96} appeared to offer an attractive way of overcoming the problems encountered in the previous sections. This reaction involves the addition of an arene sulfonyl azide to enol ethers of cyclic ketones to form $\Delta^2$-triazolines 136 (Scheme 2.26). Due to the strong electron-withdrawing substituent on the azide, the triazoline is unstable and loses nitrogen readily to afford the ring-contracted imidate ester 137, hydrolysis of which affords carboxylic ester 138.
Application of this method to the norcaradienes would allow removal of the enol ether functionality in one step, yielding a cyclopentene carboxylic acid (cf. 139), which could provide promising intermediates for the synthesis of gibberellins and antheridiogens (Scheme 2.27).

However, the thermal reaction of the norcaradiene 74 and p-bromophenylsulfonyl azide in acetonitrile did not proceed, even after 48 h in acetonitrile at reflux. Goldsmith and Soria\textsuperscript{97} have reported that the use of ultrasound can greatly accelerate the rate of these reactions, but again, no reaction was observed after 24 h. Dauben and Bunce have utilised high pressure to accelerate this reaction, even for silyl enol ethers which are less reactive than methyl enol ethers.\textsuperscript{98,99} Exposure of the norcaradiene to 10 kbar of pressure at 40°C for 24 h finally induced a reaction, but unfortunately, the product was not the desired ring-contracted product 139, rather the rearranged trienone 133 observed previously in this section.\textsuperscript*  

\* The high pressure reaction was kindly performed by Dipl. Chem. Frank Graupner of Georg-August University, Göttingen.
2.5.3 Conclusions

Not surprisingly, the norcaradienes are acid-sensitive and reveal a propensity for rearrangement which limits the options for future elaboration. Pleasingly, access to some unusual ring systems was possible and the cyclopropanation-hydrolysis of the methoxy-substituted diazoketones complements existing methods. This procedure clearly exhibits potential for the synthesis of a wide range of tetracyclic diterpenes. If the norcaradienes are to be exploited as cyclopropyl-containing synthons, a method of deactivating the system needs to be found. One example of how to achieve this will be discussed in the following chapter.
CHAPTER THREE

A DIELS-ALDER APPROACH TO THE TOTAL SYNTHESIS OF KAURENOID DITERPENES
3.1 INTRODUCTION

In the preceding chapter, it was demonstrated that the transition metal catalysed intramolecular cyclopropanation reaction of tetrahydronaphthyl diazomethyl ketones afforded stable, isolable norcaradienes. In this chapter, a procedure for the addition of a suitably substituted A ring to a product of this type will be described, thereby allowing the rapid assembly of advanced intermediates for the synthesis of tetra- and pentacyclic kaurenoid diterpenes.

There are two major criteria for consideration in the design of a synthesis of kaurenoid diterpenes. First, it should be flexible and amenable to early functionalisation of the carbon skeleton, so that a wide range of compounds may be accessed. As discussed in Chapter 1, there are a number of syntheses involving elegant work to obtain the ABC ring system with the appropriate stereochemistry, but the introduction of C ring substituents and the formation of the D-ring is often lengthy and lacking in selectivity.

The other criterion is the establishment of the desired stereochemical relationship between the D ring and the AB ring fusion (i.e. H5 should be syn to C15). This difficulty is highlighted by the experience of Mander and Pyne, who obtained mainly the anti product 141 from the intramolecular Michael addition of dienedione 140 (Scheme 3.1). This proved contrary to the expectation that the top face of the molecule would be shielded by the ethano bridge, and that addition to the α face would therefore be favoured. This meant that, at a later stage, the CD ring system would require manipulation in order to obtain the correct stereochemical relationship, thus greatly reducing the overall efficiency of the scheme.
As discussed in Chapter One, the [4+2] cycloaddition of an appropriate dienophile, such as methyl acrylate, to a vinyl norcaradiene (cf. 65) appeared to be an attractive approach for the synthesis of the kaurenoid diterpenes (Scheme 3.2). The cyclopropane moiety would be expected to control the relative stereochemistry between H5 and H15 by shielding the top face of the molecule and so favour addition anti to the cyclopropane, affording adduct 66. The fusion of the cyclopropane also means that the ring system has a concave face, which should prevent the Diels-Alder reaction occurring with the endocyclic diene.

It was decided to utilise the methoxy vinyl norcaradiene 142 in the synthesis, as it was felt that the simple vinyl norcaradiene 65 might not provide the desired level of control of the regiochemistry in the course of the Diels-Alder reaction. This would mean that the use of nonsymmetrical dienophiles, such as the synthetically useful acrylate esters, would be
precluded as the carboxy group would not be in the desired position. In addition, the reactivity of the diene should also be enhanced by the methoxy substituent.

![Chemical Structure](image)

The most important reason for the presence of the methoxy substituent, however, is the provision of suitable functionality in the B-ring of the kaurenoid skeleton to ensure a flexible synthesis. For example, this enables the subsequent ring contraction of the resultant six-membered ring to the five-membered ring of the gibberellins and antheridiogens, as well as providing access to the B-ring substituted kaurenes.
3.2 ATTEMPTED FORMATION OF THE VINYL DIAZOKETONE 147

5-Formyl-8-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid 144 has been synthesised\textsuperscript{100} in this research group previously and is available in large quantities from 1,6-dimethoxynaphthalene 143 in three steps (Scheme 3.3). The aldehyde was methylenated in 81% yield using methylene triphenylphosphorane in THF to afford acid 145.

![Scheme 3.3](image)

The most widely used procedure\textsuperscript{101} for the synthesis of diazoketones from carboxylic acids is the preparation of the acyl chloride and subsequent reaction with diazomethane (Scheme 3.4). The major advantage of this procedure is that even sterically hindered acid chlorides will react with diazomethane.

![Scheme 3.4](image)

Treatment of acid 145 with oxalyl chloride and a catalytic amount of DMF in dichloromethane, afforded an acid chloride with 100% recovery of mass. Addition to an ethereal solution of diazomethane, however, did not produce the desired diazoketone 147 (Scheme 3.5). From the $^1$H NMR spectrum of the reaction mixture, it was apparent that a diazoketone had
been formed, but that the vinyl group had been destroyed. The broadness of most resonances indicated that some sort of polymerisation had occurred. Careful re-examination of the acid chloride step indicated that the 'polymerisation' had occurred at this stage, presumably from attack of either oxalyl chloride or HCl generated from the acid chloride formation upon the vinyl group.

Scheme 3.5

Similar problems with acid-sensitive substrates have been overcome using pyridine salts of carboxylic acids. In this case, the addition of pyridine did not prevent the 'polymerisation' occurring and a similar product mixture was obtained. An attempt to generate acid chloride via treatment of the acid with carbon tetrachloride and triphenylphosphine was not successful, with starting material being recovered unchanged.
3.3 ATTEMPTED METHYLENATION OF FORMYL NORCARADIENE 149

As vinyl acid chloride 146 could not be generated successfully, it was decided to investigate the synthesis of the aldehyde diazoketone 148. It was felt that the norcaradiene 149 obtained from this substrate could be converted to either of the vinyl norcaradienes 150 or 151 via the Peterson reaction. (Scheme 3.6) Although the adduct from the Peterson reaction of the 6-methoxy norcaradiene 74 could not be collapsed (cf. Section 2.5.2.2), it was felt that the elimination of the adduct arising from attack of the Peterson reagent on the formyl group would occur, resulting in the formation of the desired vinyl norcaradiene system. As long as this occurred cleanly, we were unconcerned over what form the functionality at C4 took.

Scheme 3.6

3.3.1 The Synthesis of the Norcaradiene 149

Treatment of the acid 144 with oxalyl chloride and a catalytic amount of DMF in dichloromethane resulted in a single compound, with $^1$H and $^{13}$C NMR spectroscopy revealing the disappearance of the aldehyde
functionality. The presence of an acid chloride moiety was confirmed by the absorption at 1790 cm\(^{-1}\) in the infrared spectrum. The \(^1\)H spectrum was essentially the same as that of the acid, with the exception of a singlet resonating at 6.91 ppm in lieu of the aldehyde proton, while the \(^13\)C APT spectrum revealed a methine resonance at 69.6 ppm.

When the acid chloride was treated with dry methanol, the only product obtained was tentatively assigned as the dimethoxy acetal 153, in view of the two methoxy signals at 3.4 ppm in the \(^1\)H NMR spectrum. The reactivity of the new functionality, combined with the abovementioned unusual shifts in the NMR spectra, which were similar to those found in spectra of dichloromethyl benzene, led to the proposal of the structure 152 for the acid chloride (Scheme 3.7).

![Scheme 3.7](image)

Similar compounds have been reported by Newman and Sujeeth\(^{104}\) upon treatment of aromatic aldehydes with thionyl chloride and DMF. When DMF is added to thionyl chloride (or oxalyl chloride, phosphorous pentachloride or phosgene) in cold dichloromethane, the complex 154 is believed to be formed (Scheme 3.8).\(^{105}\) Upon heating, sulfur dioxide is expelled to produce the Vilsmeier reagent 155.\(^{106}\) It is proposed that the complex 154 attacks the carbonyl oxygen at the cationic oxygen to form the adduct 156. Rearrangement with concomitant loss of sulfur dioxide and DMF, gives the chloromethylphenyl cation which reacts with the chloride anion to afford the observed dichloride.
The dichloromethyl acyl chloride 152 was treated with diazomethane at -20°C to afford diazoketone 157 in quantitative yield (Scheme 3.9). The characteristic diazoketone IR absorption at 2105 cm⁻¹ provided straightforward evidence of the transformation. Attempts to purify the diazoketone on silica gel resulted in collapse of the dichloromethyl group to the aldehyde, with the HCl generated reacting with the diazoketone moiety to give chloromethyl ketone 158, as the only isolable product. The structure was proposed due to the appearance of signals for the newly generated methylene group at δ 4.29 in the ¹H NMR spectrum and the ¹³C NMR resonance at 42.9 ppm, which was deduced as belonging to a methylene carbon from the APT pulse sequence.

In some cases of the diazoketone generation, the presence of the aldehyde diazoketone 148 was observed in the ¹H NMR spectrum. This was attributed to the presence of water, which would hydrolyse the dichloromethyl moiety.
When one reaction was allowed to stir for 72 h at room temperature with 20 equivalents of diazomethane, the aldehyde diazoketone 148 became the major product. However, the longer the reaction was left, the more chloroketone 158 was formed. These problems were essentially overcome if the crude reaction product was dissolved in wet tetrahydrofuran with several equivalents of triethylamine present to remove the HCl produced. The dichloromethyl group slowly collapsed to afford formyl diazoketone 148 in 63% yield after chromatography, with chloroketone 158 obtained in 12% yield.

The presence of the diazoketone moiety was again confirmed by the infrared absorption at 2105 cm⁻¹ and the broad signal at 5.45 ppm in the ¹H NMR spectrum. The broadness of the proton attached to the diazoketone moiety has been ascribed to free rotation about the C-C bond being hindered as a result of the interaction of the π-electrons on the α-carbon with the π-system of the carbonyl group, which means that the diazoketone exists as an equilibrium mixture of cis and trans rotamers.
The diazoketone 148 was treated with catalytic Cu(acac)_2 in dry 1,2-dichloroethane at reflux, to give the formyl norcaradiene 149 in 65% yield (Scheme 3.10). As the structural elucidation of the norcaradienes was presented in the preceding chapter, it is sufficient to say that all spectroscopic data were consistent with previous results and the presence of the aldehyde function was apparent from NMR spectra.

![Scheme 3.10]

3.3.2 Attempted Methylenation of the Norcaradiene 149

Attempts to methylenate norcaradiene 149 were initially fruitless, as the Wittig reaction, Lombardo-Oshima reaction,^90^ and zirconium cyclopentadiene dichloride alternative to the Lombardo-Oshima reaction,^91^ all resulted in rapid decomposition of the substrate.

In Chapter 2.5.2.2, trimethylsilylmethyl lithium (TMSCH$_2$Li) was shown to add rapidly to cyclopropyl ketone 74, but the resultant adduct proved resistant to attempts to collapse it to the olefin. In the case of norcaradiene 149, this was not important as long as the conjugated triene system could be obtained, since the Diels-Alder reaction should not be adversely affected by the presence of the β-hydroxysilane. Indeed, it was felt that the Peterson adduct could actually help stabilise the norcaradiene by reducing its susceptibility to acid.
In the event, addition of 3 equivalents of TMSCH$_2$Li to norcaradiene 149 at 0°C resulted in the formation of two major compounds, one of which was identified as the triene 151 from the typical $^1$H NMR resonances of terminal double bonds (Scheme 3.11). The remaining product proved to be the initial bisadduct 159. The presence of the bisadduct was not considered problematical as it was hoped this would collapse easily to afford olefin 151 after treatment with a base. Addition of potassium hydride in THF to the reaction mixture and stirring overnight, afforded 151 (12% isolated yield) and a new compound (9% isolated yield), both of which were unstable and characterised by $^1$H NMR spectroscopy only. For the new compound, the presence of $^1$H NMR signals for two distinct TMS groups and a triplet at 6.05 ppm were considered diagnostic for the allyl silane 160, which must have arisen from the formal elimination of methanol. Re-examination of the reaction mixture, before potassium hydride was added, revealed that this compound was present and consisted of 5% of the material.

Scheme 3.11

![Scheme 3.11](image-url)
There have been a number of reports\textsuperscript{108} describing the dehydration of Peterson adducts, rather than the expected $\beta$-hydroxysilane elimination, and for the case studied, dehydration would be promoted by the methoxy group. The overall yield of these products was only 21\%, and as a consequence, the approach was discarded as not being synthetically viable.
3.4 The Use of a Deactivated Styrene Derivative

Although the methylation reaction was not successful, the work in this area helped clarify the reason for the 'polymerisation' of the vinyl acid 145 upon treatment with oxalyl chloride (Section 3.2). Obviously, deactivation of the double bond is necessary for the acid chloride approach to become viable with the simplest solution being the attachment of an electron-withdrawing substituent. The nitrile group appeared particularly attractive as it could be discriminated from the ester groups in the Diels-Alder adduct at a later stage. For example, Watt and coworkers\textsuperscript{109} have found that nitriles 161 can be converted into ketones 163, via hydroperoxy nitriles 162 (Scheme 3.12), which would allow for straightforward functionalisation of the A-ring, an obviously attractive feature for the synthesis.

\begin{center}
\textbf{Scheme 3.12}
\end{center}

\[
\begin{align*}
\text{CN} & \text{Li(N} \text{Pr}_2 \text{Et)} \quad \text{HOO} & \text{CN} \\
R & \text{-78°C; O}_2 & R' \\
161 & \text{SnCl}_2 & \text{163}
\end{align*}
\]

3.4.1 Synthesis of the cyanovinyl norcaradiene 167

The cyanovinyl acid was obtained as a mixture of E and Z isomers (163 and 164) from the formyl acid 144 in 90\% yield using a Wadsworth-Evans reaction\textsuperscript{110} (Scheme 3.13). The Z-isomer 165 was not expected to react under the Diels-Alder conditions,\textsuperscript{111} and so it was pleasing to find that the E:Z ratio was 3:1 as others have reported the formation of lower proportions of the desired E-isomers.\textsuperscript{112} The desired E isomer 164 was easily separated from the Z-isomer by recrystallisation from methanol. The large \textit{trans} coupling (\(J = 16.4\) Hz) of the alkene protons was compelling evidence for the stereochemistry of the double bond, while the IR absorption at 2225 cm\textsuperscript{-1} and
the $^{13}$C NMR resonance at 118.8 ppm, confirmed that the nitrile group was present.

Attempts to isomerise the mixture of methyl esters prepared by the reaction of the acids 164 and 165 with methyl iodide and potassium carbonate, to enhance the proportion of the $E$-isomer further were very disappointing. The use of iodine/$H^+$, thiophenoxide radicals, and iodine with tungsten lamp irradiation failed to effect any change. Remarkably, the use of a mercury lamp with iodine resulted in a change of ratio of $E:Z$ of 3:1 to 1:3. It was also observed that prolonged exposure to light slowly isomerised the $E$ isomer.

When the $E$-cyanovinyl acid 164 was added to oxalyl chloride and a catalytic quantity of DMF in dichloromethane, a smooth reaction took place (Scheme 3.14). Treatment of the crude product with an ethereal solution of diazomethane gave the diazoketone 166 as a yellow crystalline solid in 71% yield. The IR absorption at 2120 cm$^{-1}$ confirmed the presence of the diazoketone. Cyclopropanation, under the same conditions as those used for the formyl diazoketone 148, gave the trans-cyanovinyl norcaradiene 167 in 60% yield. This norcaradiene was similar to those discussed in Section 3.3.1.
3.4.2 Investigation into the Diels-Alder Reaction

In the ensuing Diels-Alder reaction, substitution by the cyano group would possibly give the 'wrong' regioisomer if methyl acrylate was used, if indeed, it reacted at all, since electron-withdrawing substituents on the diene slow the Diels-Alder reaction down. Consequently, it was decided to investigate the reaction of norcaradiene 167 with maleic anhydride. The norcaradiene 167 and maleic anhydride (carefully sublimed to remove any traces of maleic acid) were dissolved in benzene and the solution heated to 80°C (Scheme 3.15). After several hours, a white solid began to precipitate from the reaction mixture. TLC analysis indicated that the starting material was still present but that the solid was a new product of lower Rf. After 48 hours at 80°C, the starting material had been totally consumed. Isolation and recrystallisation of the residue from acetone afforded an extremely insoluble white solid in 88% yield, with ¹H NMR spectroscopy indicating the presence of a single diastereoisomer of adduct 168.

The ¹H NMR spectra indicated that the Diels-Alder reaction had occurred as desired at the terminal portion of the triene system, as the terminal vinyl group had disappeared and the enol ether moiety was still present. The assignment of the NMR spectra was assisted by comparisons with 175 prepared subsequently (Section 3.6).
Essentially the only differences in the $^1$H NMR were the positions of the anhydride ring junction protons (H7 and H8) and the proton adjacent to the nitrile (H9). The resonances for the ring junction protons were at 3.94 and 4.20 ppm respectively, while the resonance for H9 was at 4.05 ppm. Both the ring junction protons were observed as doublets of doublets, with the higher field signal having coupling constants of 6.8 and 9.3 Hz and the lower field signal coupling constants of 5.3 and 9.3 Hz. Homodecoupling experiments determined that the lower field signal was coupled to the multiplet at 4.05 ppm, which had been previously assigned to the proton alpha to the nitrile. Thus, the signals at 4.20 and 3.94 ppm were H8 and H7 respectively. The small vicinal coupling constant between H8 and H9 suggested that these hydrogens were on the same side of the molecule (i.e. cis), with the obvious conclusion that the endo adduct had been formed.

When attention was turned to determining the relative stereochemistry between H6a and H4a so as to confirm that the Diels-Alder reaction had occurred anti to the cyclopropane ring, it was found that the adduct had decomposed. As the work in forthcoming sections began to show promise, this area of study was not pursued further.
3.5 THE USE OF MIXED CARBONIC ANHYDRIDES

The only other viable direct synthesis of diazoketones from carboxylic acids involves the use of mixed carbonic anhydrides. The acid is treated with an alkyl chloroformate in the presence of triethylamine, to form the carbonic anhydride, which generally can be isolated and in some cases purified. The anhydride is treated with an ethereal solution of diazomethane to afford the diazoketone (Figure 3.1). The main disadvantage is the sensitivity of the anhydrides to steric effects, which was the reason why the reaction was not initially investigated. Primary anhydrides react at a reasonable rate, but secondary and tertiary ones proceed much more slowly.

$$\text{R-CO}_2\text{H} \xrightarrow{\text{R'-COCl}} \text{R-CO}_2\text{CO}_2\text{R'} \xrightarrow{\text{CH}_2\text{N}_2} \text{R-COCHN}_2$$

**Figure 3.1:** The synthesis of diazoketones *via* the mixed carbonic anhydrides (R' = alkyl).

Initial attempts to synthesise the vinyl carbonic anhydride 169 were disappointing. The acid 145 was dissolved in ether and cooled to 0°C, before the successive addition of triethylamine and ethyl chloroformate (Scheme 3.16). This procedure often afforded the anhydride 169 contaminated with 30-40% of the corresponding ester 170 and small quantities of the symmetrical anhydride 171.
It has been reported that carboxylic carbonic anhydrides can decompose in two ways to afford; (a) the carboxylic ester and carbon dioxide or (b) the symmetrical acid anhydride, carbon dioxide and the alkyl carbonate (Scheme 3.17).\textsuperscript{117b,118} Kim and coworkers\textsuperscript{119} have exploited these pathways to obtain efficient conversion of anhydrides to esters by using 4-(dimethylamino)pyridine (DMAP). It has been observed that tertiary amines have a catalytic effect, which lowers the temperature of decomposition.
It has been proposed that these modes of decomposition proceed by an ionic chain reaction involving alkoxide as the chain carrier.\textsuperscript{118b,120} The alkoxide could be generated by attack of a nucleophile on the mixed anhydride.

It was reasoned that by adding ethyl chloroformate to acid 145, the newly formed carbonic anhydride 169 could be attacked by carboxylate anion to form the symmetrical anhydride 171 and ethyl carbonate anion, which is known to decarboxylate producing CO\textsubscript{2} and ethoxide ion. The ethoxide would attack the mixed carbonic anhydride to yield the ethyl ester 170 as summarised in Scheme 3.17.

After much experimentation, it was found that the best results were obtained when the acid 145 was added very slowly to a solution of ethyl chloroformate (carefully purified and distilled) and triethylamine in ether at 0°C (Scheme 3.18). In this fashion, the anhydride 169 was obtained in 100% purity, with no trace of the ethyl ester 170 or the symmetrical anhydride 171. Standard treatment with an ethereal solution of diazomethane at 0°C for several hours produced no substantial quantity of diazoketone 147 until the solution was allowed to warm to room temperature. If the reaction was allowed to stir overnight at room temperature, a new spot on the baseline of the TLC slide began to form and this greatly affected the yield of the diazoketone. Thus, the best conditions were found to be stirring the reaction mixture at room temperature for 4.5 hours, which resulted in a yield of 51% after chromatography.

\textbf{Scheme 3.18}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {COOH} ;
\node (b) at (1.5,0) {\textcolor{red}{\textsuperscript{145}}} ;
\node (c) at (3,0) {\textcolor{red}{\textsuperscript{169}}} ;
\node (d) at (4.5,0) {\textcolor{red}{\textsuperscript{147}}} ;
\draw[->] (a) -- (b) node[midway, above] {EtCO\textsubscript{2}Cl} ;
\draw[->] (b) -- (c) node[midway, above] {NET\textsubscript{3}/0°C} ;
\draw[->] (c) -- (d) node[midway, above] {CH\textsubscript{2}N\textsubscript{2}} ;
\end{tikzpicture}
\end{center}

68% yield based on recovered starting material
Some of the anhydride 169 remained unchanged at this stage and the above chromatography of the crude reaction mixture facilitated hydrolysis and, therefore, recovery of the starting material 145 (18%). Thus, conversion to the diazoketone 147 was 68%, based upon recovered starting material, which was recyclable.

Of concern was the consumption of the diazoketone 147, upon exposure to diazomethane for any longer period than 5 hours. The polar compound mentioned above was isolated and from the $^1$H NMR analysis, it could be seen that the tetrahydro portion of the starting material was unchanged (indeed, that there was a diazoketone moiety present). However, the vinylic double bond was absent and the region from 4.30-6.75 ppm was markedly different to that of the starting material, as well as two new signals in the aliphatic region. The complexity of the spectrum, coupled with the observation that in the $^{13}$C NMR spectrum of almost two sets of each peak, led to the belief that a mixture of diastereoisomers had been isolated.

It was surmised that the styrene double bond was being attacked by diazomethane, an excellent 1,3-dipolarophile. Kadaba and Colturi observed that diazomethane will react with substituted styrenes to afford 1-pyrazolines (e.g. 173) (Scheme 3.19). While the regiochemistry of this reaction appears surprising, it can be readily explained by frontier orbital theory. It was noted that $p$-methoxystyrene 172 was unusually susceptible to this type of attack and this was explained in terms of an electron-withdrawing inductive effect predominating over an electron-releasing resonance effect.
When p-methoxystyrene was stirred in a solution of ethereal diazomethane overnight at room temperature, the formation of a baseline product on the TLC slide was observed, exactly like the vinyl diazoketone situation. The chemical shifts in the $^1$H NMR spectrum were essentially the same as that observed in the vinyl diazoketone case, except that each signal was far less complex. Obviously, in this model case it is not possible to have diastereoisomers. This comparison indicated that the byproduct in the vinyl diazoketone formation was a diastereomeric mixture of 1-pyrazolines 174.

Irrespective of the above problems, a procedure was now in place to obtain the diazoketone 147 in reasonable quantities.
3.6 DIELS-ALDER REACTIONS OF NORCARADIENE 142

Treatment of the diazoketone 147 under the same cyclopropanation conditions, as for diazoketone 148, gave the norcaradiene 142 as an oil in 53% yield, which was lower than the other cyclopropanation reactions but probably reflects the instability of the triene system (Scheme 3.20).

Scheme 3.20

This compound was extremely labile and even storage in the freezer under a nitrogen atmosphere could not prevent decomposition. In sharp contrast, the formyl and cyanovinyl norcaradienes 149 and 167 were quite stable upon storage.

3.6.1 The Diels-Alder Reaction Between Norcaradiene 142 and Maleic Anhydride.

The Diels-Alder reaction of norcaradiene 142 and maleic anhydride was first investigated, as it was not certain that methyl acrylate would prove to be a sufficiently reactive dienophile. Treatment of the vinyl norcaradiene in benzene at 80°C with freshly sublimed maleic anhydride resulted in the formation of a single new compound after a reaction time of 4 hours. Isolation and chromatography of the crude product produced a white solid in 79% yield, with 1H NMR spectroscopy indicating the presence of a single diastereoisomer of adduct 175 (Scheme 3.21).
A doublet at δ 1.78 (J = 12.0 Hz) was assigned as H11α, based on comparisons with the data of the 9,15-cyclogibberellins,53 while another doublet at δ 1.74 (J = 2.0 Hz) was assumed to be the resonance for the cyclopropyl proton H4a since it was at quite high field and exhibited a small 4-bond coupling. The multiplet at δ 2.98 was tentatively assigned to H6a because of the complexity of the coupling. The doublet at δ 4.58 and the methoxy signal at δ 3.68 provided evidence for an intact enol ether moiety, with confirmation obtained from the 13C NMR resonances at 89.1 ppm (C6) and 153.0 ppm (C5). This spectrum also revealed the presence of the anhydride (170.2 and 173.9 ppm) and cyclopropane moieties (34.3, 36.8, and 40.2 ppm). The infrared absorptions at 1850 and 1780 cm⁻¹ confirmed the presence of the anhydride, while the carbonyl absorption at 1720 cm⁻¹ corresponded to a cyclopropyl conjugated ketone.52 Interestingly, in the mass spectrum the base peak was m/z 228, which occurs by the loss of maleic anhydride through a retro-Diels-Alder process.

In terms of the regiochemistry, the presence of the enol ether, the olefinic H10 proton (δ 6.18) and the absence of resonances for the terminal vinyl group, indicated that the Diels-Alder reaction had indeed occurred with the more exposed terminal diene. As the gross structure of the adduct 175 was now established, it was important to determine the stereochemistry of the molecule, particularly with regard to the relationship between the AB ring
junction and the cyclopropane ring. To do so, it was first necessary to assign as many of the proton signals as possible in the $^1$H NMR spectrum.

From the double-quantum filtered $^1$H-$^1$H correlation spectroscopy experiment (DQFCOSY), it was possible to confirm the assignment of the cyclopropyl proton (Figure 3.2).

The previously assigned H11α had only one strong crosspeak to a multiplet at $\delta$ 2.76, which was obviously the geminal proton H11β. This signal, in turn, had a crosspeak to the multiplet at $\delta$ 2.24, which must therefore be H3. Apart from the expected moderately strong couplings to both of the H2 protons, H3 had a small crosspeak to the signal for the cyclopropyl proton (H4a, $\delta$ 1.74), which explains the small coupling constant displayed in the 1D experiment. This small W-coupling has been observed in several 9,15-cyclogibberellin derivatives.

The olefinic signal (H10) at $\delta$ 6.18 provided a convenient starting point for the assignment of the A ring protons. As anticipated, this proton exhibited coupling to two protons (δ 2.92 and δ 2.22) which were obviously those of H9. These signals were coupled to one another and to a signal at δ 3.44, which was assigned as H8. Unfortunately, none of this information allows the assignment of exact stereochemistry to the H9 protons. The above-mentioned H8 proton has a cross peak with a multiplet at $\delta$ 3.37 and accordingly, this was attributed to H7. As there was a crosspeak from the signal for H7 to the complex multiplet at δ 2.98, the original assignment of H6a was confirmed. The H6a resonance had two other cross peaks, the expected one to the enol ether proton and an allylic coupling to the H10 proton.
Figure 3.2: $^1$H-$^1$H DQFCOSY NMR spectrum of adduct 175 (300 MHz, CDC$_3$).
With essentially every proton assigned, attention was turned to the determination of relative stereochemistry. The one-dimensional nuclear Overhauser experiment (nOe) could not be used due to the proximity of some of the signals to one another. The alternative phase-sensitive two-dimensional nOe experiment (psNOESY) has the advantage that all nOe interactions of the whole molecule are simultaneously observed, necessitating only one NMR experiment.\textsuperscript{122,124} In a psNOESY spectrum, the weaker crosspeaks show the proximity in space of protons that are not geminal to one another and proved to be a superb experiment for the assignment of the relative stereochemistry of the maleic anhydride adduct 175 (Figure 3.3).

Obviously, the most important crosspeak is that between H4a and H6a, as it confirmed that the Diels-Alder reaction had occurred \textit{anti} to the cyclopropyl ring system, thereby establishing the correct relationship between the AB ring junction and the D ring. The \textit{syn} Diels-Alder adduct would have H6a \textit{anti} to the cyclopropyl proton, where no nOe interactions would be observable. A reasonably strong nOe between H6a and H7, together with the weaker one between H6a and H8, provided strong evidence for the \textit{anti} relationship of the anhydride moiety to H6a. Therefore, from these nOe interactions it can be determined that the Diels-Alder reaction had occurred exactly as predicted in the outline of the synthetic plan. That is, \textit{anti} to the cyclopropane ring in the \textit{endo} orientation as represented below.
Some of the crosspeaks indicated an averaged conformation for the A ring, which can change from twist chair to boat conformation on the NMR time scale. For instance, the crosspeak between H9α and one of the H9 multiplets (δ 2.20) could only be observed if the molecule is in the boat conformation, while the critical NOE between the pyrrolidine proton only appears possible in the twist chair conformation (δ 3.4).

Figure 3.3: An expansion of the psNOESY NMR spectrum (300MHz, CDCl₃) for adduct 175.
Some of the crosspeaks indicated an averaged conformation for the A ring, which can change from twist chair to boat conformations on the NMR time scale. For instance, the crosspeak between H6a and one of the H9 multiplets (δ 2.22), could only be observed when the A ring is in the boat conformation, while the critical nOe between H6a and the cyclopropyl proton only appears possible in the twist chair conformer (Figure 3.4).

![Figure 3.4: A depiction of the two A-ring conformers for the adduct 175.](image)

Shortly after the above stereochemical determination was completed, a suitable single crystal was obtained for X-ray crystallographic examination. As can be seen in Figure 3.5, the stereochemical assignment from the psNOESY experiment was confirmed. Interestingly, the Diels-Alder adduct 175 crystallised as a racemic conglomerate and from the space group and the inspection of the unit cell, only one enantiomer was present in the crystal. The structures in this thesis have been drawn as the enantiomer that corresponds to that of ent-kaurene. The crystal selected for X-ray analysis has the antipodal configuration.
3.6.2. The Use of Methyl Acrylate as an Alkylating Agent

Having now established that the Diels-Alder reaction between the norcaradiene 142 and acrylate is an effective method of introducing two substituents at C4, and methyl acrylate would enable the subsequent introduction of functionality alpha to the double bond, the disadvantage with maleic anhydride was the introduction of an extra carbon in a position where it was not required, and accordingly it would have had to be removed at a later stage in the synthetic scheme.

The reaction between norcaradiene 142 and methyl acrylate is shown as follows:

![Diagram of the reaction between norcaradiene 142 and methyl acrylate](image)

The NMR spectra of the major component showed some similarity with that of the maleic anhydride adduct 175, although the absence of the extra carboxyl group and the corresponding presence of a methyl group had

Figure 3.5: X-Ray Crystal Structure of Diels-Alder adduct 175.
3.6.2: The Use of Methyl Acrylate as a Dienophile

Having now established that the Diels-Alder reaction between the norcaradiene 142 and maleic anhydride had gone exactly as planned, attention was turned to the use of methyl acrylate as the dienophile, as it should prove synthetically more useful. The majority of kaurenoid diterpenes possess two substituents at C4, and so methyl acrylate would enable the subsequent introduction of functionality alpha to the ester function. The disadvantage with maleic anhydride was the introduction of an extra carbon in a position where it was not required, and accordingly it would have to be removed at a later stage in the synthetic stage.

The reaction between norcaradiene 142 and methyl acrylate in benzene at reflux was complete in 24 h. Chromatography of the crude reaction product afforded an inseparable mixture of diastereoisomers 176 in 56% yield (Scheme 3.22). Integration of the $^1$H NMR resonances for the olefinic and enol ether protons established the ratio of diastereoisomers to be 71:17:12.

Scheme 3.22

The $^1$H NMR spectrum of the major component showed some similarities with that of the maleic anhydride adduct 175, although the absence of the extra carboxyl group and the corresponding presence of a methylene group, meant that the some of the previously well-separated resonances had
moved to higher field and merged with the aliphatic signals in the spectrum. By performing the cyclopropanation and Diels-Alder reactions in 'one-pot', the yield over both steps increased to 51%, a major improvement over the combined yield of 30% for the two distinct reactions (Scheme 3.23).

As some of the nOe interactions that were needed to assign the relative stereochemistry would be relatively weak, it was thought unwise to perform the two-dimensional NMR experiments on the diastereomeric mixture, as there would be the distinct possibility of misinterpretation of the signals. Unfortunately, all attempts to separate the diastereoisomers were unsuccessful (recrystallisation, high-pressure liquid chromatography and MPLC) and in the process, it was discovered that the mixture was susceptible to decomposition over a relatively short period of time if left in solution. This indicated that the stereochemical determination via 2D NMR methods would probably be unsuccessful, due to the possibility of decomposition during the often lengthy acquisition times.

Hydrolysis of the crude reaction product 176 afforded a diastereoisomeric mixture of diones 177, which proved to be quite stable. This three step sequence starting from diazoketone 147 involved no chromatography of the intermediates and proceeded in a greatly improved overall yield of 63% (Scheme 3.24). In a related system discussed in the following section, a
similar hydrolysis gave an 83% yield, implying that the cyclopropanation/Diels-Alder process in this case must be occurring in an efficient manner. Examination of the olefinic region of the $^1$H NMR spectrum of the reaction product revealed four signals ($\delta$ 5.75, 5.80, 6.02, 6.08) in the ratio of 60:11:18:10, in contrast to the three diastereoisomers observed in the initial Diels-Alder reaction. Presumably, in the latter case, the appropriate $^1$H NMR resonance for the fourth isomer was undetectable under that of the major isomer, such that the determined ratio of 71:17:12 should be 60:11:17:12.

Scheme 3.24

Fortunately, the major diastereoisomer 178 of the hydrolysis mixture was obtained in high purity after two recrystallisations from ether/hexane. The $^1$H NMR spectrum was significantly different from the enol ether, with only four readily assignable signals [$\delta$ 5.77 (H10), 3.69 (CO$_2$Me), 2.90 (H4a), 1.69 (H11a)]. The remaining resonances ranged from 1.4-2.8 ppm and generally overlapped with one another. The $^{13}$C NMR spectrum confirmed the presence of the cyclopropane ring (29.2, 45.2 and 48.0 ppm), the ester functionality (51.8 and 173.5 ppm) and the two carbonyl groups (203.7 and 210.9 ppm).

The overlapping signals in the above $^1$H NMR spectrum proved to be a major stumbling block with regard to the 2D NMR work. Indeed, even
when the spectra (DQFCOSY, psNOESY) were run at 500 MHz, there was little prospect of assignment. Although four signals had been previously assigned and from these some of the surrounding protons identified, the overlapping of remaining signals meant that it was difficult to assign the majority of the protons with any confidence. In particular, with the psNOESY spectrum, it was difficult to establish the stereochemistry of the molecule, since the removal of the enol ether moiety produced a B-ring with much greater flexibility and the two conformationally mobile rings gave rise to many different nOe interactions. The complexity of the 2D NMR spectra precluded any unambiguous assignment of the relative stereochemistry. The 2D spectra are presented in figures 3.6 and 3.7.

As the reaction of the norcaradiene with maleic anhydride was completely stereoselective resulting in H6a being syn to the cyclopropyl ring, it could be assumed the methyl acrylate reaction should produce a similar result, and that the major product would have the correct stereochemistry. With regard to stereochemistry of the ester moiety, it was felt that it must result from endo addition of the dienophile anti to the cyclopropane ring, as for the maleic anhydride reaction. This was supported by the observation that treatment of the pure diastereoisomer 178 with 0.2M sodium methoxide for 72 h, produced a 95:5 mixture, in which the minor compound was unchanged starting material (Scheme 3.25).

![Scheme 3.25](image-url)
Figure 3.6: An expansion of the $^1$H-$^1$H DQFCOSY NMR spectrum (500 MHz, CDCl$_3$) of adduct 178.
The new product exhibited the same class of product as the diene isomer in the \(\text{H} \text{NMR}\) spectrum as one of the diastereoisomers in the original mixture. This suggested a belief that kinetic and thermodynamic product \(179\) was obtained, since it is equilibrated to produce the thermodynamic \(\alpha\) product \(179\) in context of the total synthesis. The stereochemistry at \(\text{C}7\) was not important, as literature reports indicate that \(\text{C}6\)-methylation occurs in the desired fashion if the stereochemistry at \(\text{C}6\) is correct (i.e. S to the D-ring).

There does exist the possibility for incorporation of the wrong diene isomer, but based on the literature, work could be performed in the diene to ensure the correct diastereoisomer. The correct diastereoisomer of the \(\alpha\)-adduct \(178\) was confirmed by NMR and mass spectrometry, and it was found to be the major isomer.

Figure 3.7: An expansion of the psNOESY NMR spectrum (500MHz, CDCl\(_3\)) for adduct 178.
The new product exhibited the same chemical shift for the olefinic proton in the $^1$H NMR spectrum as one of the minor diastereoisomers in the original mixture. This epimerisation supported the belief that kinetic endo isomer 178 was obtained, since it could be equilibrated to produce the thermodynamic exo product 179. In the context of the total synthesis, the stereochemistry at C7 was not important, as literature reports indicate that C-methylation occurs in the desired fashion if the stereochemistry at C6a was correct (i.e. syn to the D-ring).

There does exist the possibility for the formation of the wrong regioisomer, but based on work discussed in the next section where citraconic anhydride was used as the dienophile, it was felt that this was unlikely to be the case for the major isomer.

To summarise this reaction, four diastereoisomers were obtained from the Diels-Alder reaction in the ratio of 60:11:17:12, where the first two compounds are believed to be the result of anti addition and are endo and exo adducts respectively. The remaining isomers were presumed to be the adducts resulting from syn addition, although it cannot be discounted that they may be regioisomers where the ester group is at C8.

### 3.6.3 Investigations into the Use of Substituted Dienophiles

As mentioned in the previous section, there are excellent precedents for the introduction of the extra functionality at C7 of the Diels-Alder adducts in the correct stereochemical manner, so as to establish the correct C4 configuration of the kaurenoid diterpenes. Provided that a suitable dienophile could be harnessed, however, [4+2] cycloaddition had the potential to provide a more direct synthesis of such compounds. It must be noted that the endo isomer must be obtained in order to obtain the correct stereochemistry.
Methyl methacrylate proved, not surprisingly, to be totally unreactive. After 72 h in benzene at reflux, no trace of any Diels-Alder adducts 180 were detected (Scheme 3.26). Attempts to induce a reaction using longer reaction times resulted in complete decomposition of the starting material.

**Scheme 3.26**

On the other hand, the electronically activated citraconic anhydride reacted readily with norcaradiene 142, affording a 93:7 mixture of diastereoisomers 181 after 9 hours in benzene at reflux in a yield of 76% (Scheme 3.27). The 'one-pot' process starting from diazoketone 147 again gave a greatly improved overall yield, in this case 68%. Separation of the two diastereoisomers was not possible, although a number of methods were attempted.

**Scheme 3.27**
Not surprisingly, the $^1$H NMR spectrum of the major component was similar to that of the maleic anhydride adduct, with the additional signal for the newly introduced methyl group at $\delta$ 1.57. The only differences were the positions of H6a and H8. In the maleic anhydride adduct 175, the signals for these two protons were at $\delta$ 2.98 and $\delta$ 3.44 respectively, while for the citraconic anhydride adduct they were found at $\delta$ 2.66 and $\delta$ 3.02. The differences in these chemical shifts were found to be quite important once the psNOESY spectrum had been recorded.

Of the three nOes seen for the methyl group, the most important were those to H6a and H8 (Figure 3.8). These indicated that H6a was anti to the anhydride moiety and accordingly, an endo adduct had been obtained. The most startling aspect of the psNOESY spectrum was the absence of the crucial nOe interaction between H6a and H4a, which had been seen in the spectrum of the maleic anhydride adduct.

While the obvious conclusion was that the Diels-Alder reaction had occurred syn to the cyclopropane ring with an endo orientation, this was considered highly unlikely, especially in light of the facial selectivity of the maleic anhydride example. The observation of a small nOe interaction between H9$\beta$ and H6a, as well as moderate one between H8 and H9$\alpha$, provided an alternative explanation as these interactions could only be possible if the A-ring was in a boat conformation.
Figure 3.8: An expansion of the psNOESY NMR spectrum (300MHz, CDCl₃) for adduct 181.
It would appear that the citraconic anhydride adduct 181 exists exclusively in this conformation when in deuteriochloroform. Examination of molecular models indicated that H4a and H6a were well separated in space so that a nOe interaction would be unlikely (Figure 3.9). Such an interaction would only be possible in the alternative twist-chair conformation.

Fortuitously, it was found that only the alternative twist-chair conformer was observed when the $^1$H NMR spectrum was recorded in d$_6$-acetone. The similarity of this spectrum to that of maleic anhydride was remarkable, with H6a and H8 at $\delta$ 2.78 and $\delta$ 3.30 (cf. $\delta$ 2.98 and $\delta$ 3.44 in compound 175). As mentioned previously, the shifts in CDCl$_3$ were $\delta$ 2.66 and $\delta$ 3.02 respectively. The cyclopropyl proton H4a had shifted to $\delta$ 1.59, which was unfortunate as the methyl group resonated at $\delta$ 1.60. It was most important to establish the respective stereochemical relationship between H4a, H6a and the methyl group and as such, the overlapping chemical shifts of H4a and the methyl group would give corresponding nOe interactions, which meant that it could be difficult to determine if the response was due to both signals or to only one.

It was only possible to discern these interactions when the psNOESY spectrum was recorded at 500 MHz, with the stronger interaction a result of proximity of the methyl group to H6a (Figure 3.10).
Figure 3.10: An expansion of the psNOESY NMR spectrum (500MHz, acetone) for adduct 181.
Therefore, the cyclopropane ring was *syn* to H6a and the methyl group as had been expected. The nOe interactions between H8 and H6a, and H8 and H9β, provided further evidence for the twist-chair conformer.

So, in conclusion, the Diels-Alder reaction of citraconic anhydride and norcaradiene afforded a 93:7 ratio of diastereoisomers. It was found that the major component exists in two conformations, which are solvent dependent. Phase-sensitive NOESY experiments on each conformer established that the major diastereoisomer results from the Diels-Alder reaction occurring *anti* to the cyclopropane ring in an *endo* orientation. Thus, the relative stereochemistry of the major diastereoisomer was as depicted below. Therefore, the correct configuration at C4 and C5 in kaurenoid diterpenes has been established in this Diels-Alder process, which is potentially a more direct approach to most of the target diterpenes.

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\text{OMe}
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181
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CHAPTER FOUR

AN INVESTIGATION INTO THE ENANTIOSELECTIVE SYNTHESIS
OF FUNCTIONALISED TETRAHYDRO-2-NAPHTHOIC ACIDS

Due to an enormous amount of work over the last few decades, there are a large number of approaches for the synthesis of optically active materials. These methods, those involving catalytic systems are obviously the most desirable. In the context of the aforementioned route, Noyori’s asymmetric hydrogenation and Sharpless’ asymmetric dihydroxylation (AD) would appear to be particularly useful. One of the aims in designing the proposed total synthesis of curcumin dipropionate, was to ensure flexibility so that a wide range of compounds could be accessed by the same asymmetric. Asymmetric hydrogenation appeared to be suitable only for preparing the optically active tetrahydro-2-naphtoic acid. Accordingly, it was decided to investigate the Sharpless asymmetric dihydroxylation reaction as a means of producing sufficiently functionalised optically-active 1,2,3,4-tetrahydro-2-naphthoic acids.
4.1 INTRODUCTION

Having established a feasible approach to attach a suitably substituted A ring to a norcaradiene intermediate, our attention was focused on the development of an enantioselective synthesis. Since each step in the synthesis is essentially stereoselective, the key to an enantioselective synthesis is controlling the stereochemistry at C2 of the 1,2,3,4-tetrahydro-2-naphthoic acid precursor 181.

Due to an enormous amount of work over the last few decades, there are a large number of approaches for the synthesis of optically active materials.\textsuperscript{126,127} Of these methods, those involving catalytic systems are obviously the most desirable. In the context of the aforementioned route, Noyori's asymmetric hydrogenation and Sharpless' asymmetric dihydroxylation (AD) would appear to be particularly useful.\textsuperscript{127}

One of the aims, in designing the proposed total synthesis of kaurenoid diterpenes, was to ensure flexibility, so that a wide range of compounds could be accessed by the same approach. Asymmetric hydrogenation appeared to be suitable only for preparing the optically active tetrahydro acid 182. Accordingly, it was decided to investigate the Sharpless asymmetric dihydroxylation reaction as a means of producing suitably functionalised optically active 1,2,3,4-tetrahydro-2-naphthoic acids.

The first asymmetric dihydroxylation reaction was reported by Hentges and Sharpless,\textsuperscript{128} who found that osmylation of olefins in the presence of stoichiometric quantities of cinchona alkaloid derivatives afforded optically
active diols. The transition to a catalytic asymmetric dihydroxylation occurred in 1987 when Sharpless and coworkers found that N-methylmorpholine-N-oxide could be used as a cooxidant.\textsuperscript{129} Initially, chiral ligands based on the cinchona alkaloids were used (Figure 4.1), but since that time, a number of modifications of reaction conditions and chiral ligands have occurred, significantly improving the enantioselectivity over a broad range of olefinic substrates.

![Dihydroquinidine (DHQD)](image1.png) ![Dihydroquinine (DHQ)](image2.png)

**Figure 4.1:** The Cinchona Alkaloids

The asymmetric complex formed by osmium tetroxide, chiral ligand, and the olefinic substrate delivers two oxygen atoms to a designated face of the olefin, depending on which antipode of the ligand is used. A mnemonic has been designed, showing olefin orientation and facial selectivity (Figure 4.2), with the shaded areas used to represent the putative asymmetric protuberances on the oxygen-donating surfaces.\textsuperscript{130,131} The olefin is oriented to fit the size constraints, where \( R_L \) equals the largest substituent, \( R_M \) equals the medium-sized substituent, and \( R_S \) equals the smallest substituent other than hydrogen. Delivery of the oxygen atoms will be to the upper face (designated \( \beta \)) if a dihydroquinidinidine (DHQD) derived chiral auxiliary is used, and to the lower face (\( \alpha \)) for dihydroquinine (DHQ) derived auxiliaries. The mnemonic is empirical and is based on the enantioselectivities observed on a range of olefins. The absolute configuration can be assigned and thus, prediction of the enantioselectivity for a new dihydroxylation substrate is possible. However,
Sharpless and Johnson\textsuperscript{132} warn that the mnemonic is only suggestive of new diol configurations and so, the predictions should be carried out with a degree of caution.

![Diagram of the Sharpless mnemonic](image)

**Figure 4.2: The Sharpless mnemonic\textsuperscript{131}**

The Sharpless AD has been transformed in the last few years with the discovery of the biscinchona phthalazine ligands, $\text{[DHQD]}_2\text{-PHAL}$ \textsuperscript{183} and $\text{[DHQ]}_2\text{-PHAL}$ \textsuperscript{184} (Figure 4.3), which provide unprecedented enantiomeric excesses, and the observation that osmate ester hydrolysis is accelerated by organic sulfonamides.\textsuperscript{131} This has meant that a large range of olefins are now amenable to AD, but more importantly, at a reasonable rate and with high enantioselectivity. Only trace quantities of the expensive alkaloid ligand and osmium tetroxide are required and these dihydroxylation systems are now commercially available from the Aldrich Chemical Company.

![Diagram of the phthalazine ligands](image)

**Figure 4.3: The phthalazine ligands 183 and 184**
In order to produce functionalised tetrahydronaphthoic acids, the choice of substrate for the AD comes down to two possibilities: 8-methoxy-3,4-dihydro-2-naphthoic acid 185 or 8-methoxy-1,4-dihydro-2-naphthoic acid 186.

In an efficient enantioselective synthesis of anthracycline antibiotics, Tomioka and coworkers 133 have carried out a stoichiometric AD, using a chiral diamine, on methyl 5,8-dimethoxy-3,4-dihydro-2-naphthoate 187 and obtained a 85% enantiomeric excess of the diol 188 (Scheme 4.1).

The desired 8-methoxy isomer 185 should give a similar result and there exists the possibility that the catalytic AD could give a higher enantiomeric excess in this case. A major disadvantage of the 3,4-dihydro substrate is that the secondary hydroxyl substituent is introduced at what will be the 14-position in
kaurenoid diterpenes (Figure 4.4). Although C14 hydroxylation is known in kaurenes, it is unprecedented in the gibberellin family.\(^1\) Clearly, introduction of the 14-hydroxy substituent does not, therefore, fully meet the goal of a total synthesis possessing flexibility.

![Figure 4.4: The positions of C12 and C14 in a kaurene skeleton.](image)

Dihydroxylation of the analogous 1,4-dihydro substrate 186 would eventually afford a hydroxyl group at C12 (Figure 4.4), a position that is often found to be functionalised in kaurenoid diterpenes and gibberellins. Some complex chemistry has been required to introduce a hydroxyl group at this position in other syntheses. In the partial syntheses of several putative gibberellins, a transannular oxidation was used to introduce the 12\(\beta\) hydroxyl group, using a bromohydrin derived from a 16,17-olefinic precursor (Scheme 4.2).\(^{134,135}\)

**Scheme 4.2**

![Scheme 4.2: Steps of the reaction](image)
The 16,17-double bond was also utilised to direct the hydroboration of an 11,12-ene (Scheme 4.3) and afford a 12,17-diol in 76% yield.\textsuperscript{123} This was the key step in a 20 step synthesis of 3α,12β-dihydroxy-9,15-cyclo-GA\textsubscript{9}, which is possibly the structure of a new antheridiogen from \textit{Anemia phyllitidis}.

Clearly, early introduction of the 12-hydroxy functionality would be advantageous, providing access to a number of interesting natural products. Accordingly, the Sharpless AD was investigated using 8-methoxy-1,4-dihydro-2-naphthoic acid \textsuperscript{186} as the substrate.
4.2 THE SYNTHESIS OF 8-METHOXY-1,4-DIHYDRO-2-NAPHTHOIC ACID 186

4.2.1 Literature Methods For Making 1,4-Dihydro-2-naphthoic acids

The synthesis of 1,4-dihydro-2-naphthoic acid 190 has been achieved in a number of ways, although only two of these provide synthetically useful quantities.136-139 The first method was the reduction of 2-naphthoic acid 189 by 3% sodium amalgam in aqueous alkaline solution, which was originally performed by Baeyer and Besemfelder in 1891 (Scheme 4.4).136 Later work confirmed that the 1,4-isomer was the major product (60%) if the reaction was performed in hot aqueous alkaline solution and could be separated from the unwanted 1,2-isomer 191 by fractional precipitation.140,141

Scheme 4.4

The Birch reduction of 2-naphthoic acids results in the preferential reduction of the carboxyl-bearing ring37 and forms the basis of the alternative approach to the 1,4-dihydro acids. When five equivalents of metal and an alcohol are used, the tetrahydro acids 192 are formed in 90% yield.37,139 Slobbe found that in the absence of an alcohol, limited quantities of metal (ca 3 equivalents) can limit the reduction to the dihydro stage.142 When methyl iodide was used as the quenching agent, the 1,2-dihydro alkylated acid 193 was obtained as the major product (74%) together with over-reduced material (16%).
Subba Rao and coworkers\textsuperscript{139,143} confirmed this result, but used solid ammonium chloride as the quenching agent, to obtain the 1,4-dihydro acid 190 as the major product (75\% yield). Anhydrous ferric chloride has been employed\textsuperscript{144} previously to limit the reduction of polycyclic aromatics and when it was used in the Birch reduction of 2-naphthoic acid, the 1,4-isomer 190 was isolated in 75\% yield, being the only compound produced (Scheme 4.5).

The reduction of aromatic carbonyl compounds normally occurs by a 1,4-pathway but in the case of 2-naphthoic acids, it is believed that as a consequence of the energetic advantage in preserving aromaticity in the second ring, the alternative \textit{ortho} protonation at C1 occurs (Scheme 4.6).\textsuperscript{37} This dienediolate 194 is stable to further reduction because of its charge, but in the presence of a proton source (\textit{e.g.} EtOH) protonation and further reduction becomes possible.\textsuperscript{142}
Harvey and Urberg\textsuperscript{144} investigated the influence of ferrous salts on the reduction of the polycyclic aromatic hydrocarbons. They discovered an iron-catalysed consumption of lithium upon interaction with ammonia once the initial protonation has occurred, which consumes any excess lithium. The Subba Rao method was chosen as a starting point due to its simplicity and selectivity.

4.2.2 Synthesis of 8-methoxy-2-naphthoic acid 199

Although 8-methoxy-2-naphthoic acid 199 has been made in a number of ways the majority of these methods are not synthetically useful\textsuperscript{145-149}. Jacques hydrolysed 8-methoxy-2-naphthonitrile 198 with 36\% aqueous sodium hydroxide solution in 2-methoxyethanol, in excellent yield\textsuperscript{145}. However, the naphthonitrile precursor was synthesised from the corresponding naphthylamine 197, which itself is available\textsuperscript{149,150} in four steps from 2-naphthylamine 195 (Scheme 4.7), an overall sequence which is not synthetically viable. Indeed, the first step involves the sulfonation of 2-naphthylamine and affords two compounds, the minor compound being the desired 2-aminonaphthyl-8-sulfonic acid 196. As the majority of the alternative syntheses\textsuperscript{146-149} proceed via 196, it was felt that a more efficient approach should be developed.
The 3,4-dihydronaphthonitrile 200 has been used\textsuperscript{72} to synthesise 8-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid 201, which was an intermediate in the total synthesis of gibberellin A\textsubscript{4} by Mander and coworkers.\textsuperscript{151} The nitrile is available from 1,7-dimethoxynaphthalene in three steps, in an approximate overall yield of 60\% (Scheme 4.8).

Aromatisation of the nitrile 200 proved to be quite difficult.\textsuperscript{152} Treatment with palladium-on-carbon in xylene at reflux, resulted in a reaction, but aside from the desired product 198 (60\%), there was an impurity which accounted for 40\%
of the material. When the nitrile was treated with p-chloranil in chlorobenzene at reflux, only 20% conversion to the naphthonitrile was observed.

The dehydrogenation was successfully completed using 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ) in chlorobenzene at reflux, producing the naphthonitrile in 90% yield after chromatography. Hydrolysis, using Jacques' method, gave the desired 8-methoxy-2-naphthoic acid 199 in 80% yield and in 43% overall yield from 1,7-dimethoxynaphthalene (Scheme 4.9).

### Scheme 4.9

\[
\begin{align*}
\text{OMe} & \quad \text{DDQ} \quad 90\% \\
200 & \quad \text{CN} \\
\text{OMe} & \quad \text{CN} \\
198 & \quad \text{NaOH} \quad 80\% \\
\text{OMe} & \quad \text{CO}_2\text{H} \\
199 &
\end{align*}
\]

#### 4.2.3 Birch Reductions Using Ferric Chloride

The Birch reduction of 8-methoxy-2-naphthoic acid 199 using the conditions outlined by Subba Rao was extremely disappointing. An inseparable mixture of four compounds was obtained, with the three major products being the 1,2-dihydro isomer 202, the over-reduced tetrahydro acid 201, and starting material. Only a trace of the desired 1,4-dihydro isomer 186 could be observed in the ^1H NMR spectrum.
Assuming that the substrate was the problem, the reduction of 6-methoxy-2-naphthoic acid was attempted following the literature procedure. Although the reported conditions (5 equivalents of lithium, 5% anhydrous ferric chloride, ammonia and THF with a quench of solid ammonium chloride) were used, a similar complex mixture to that above was obtained.

Quenching with solid ammonium chloride is a difficult procedure, as it is hard to add all of the reagent in one portion. Slobbe\textsuperscript{142} noted that quenching with ammonium chloride gave a consistently larger proportion of over-reduction compared to methyl iodide, as well as unchanged starting material. The use of ethanol as the quenching agent in the reduction of 8-methoxy-2-naphthoic acid\textsuperscript{199}, resulted in no change to this ratio, so the problem is obviously not the result of incomplete quenching.

The presence of large quantities of the over-reduced product seemed to suggest that the intermediate protonated product was being quenched as the reaction was occurring. As no alcohol was present in the reduction and care was taken to prevent any moisture entering the reaction mixture, it was unclear how this indiscriminate quenching had occurred. When ammonia is added to the carboxylic acid in THF, the ammonium salt is formed as a white precipitate, which does not dissolve until lithium is added.\textsuperscript{37} The ammonium ions formed in this way are presumably the source of the quenching. This hypothesis was tested by substituting the potassium salt.\textsuperscript{153}

The easiest way to make the salt was to use a ‘one-pot’ procedure, where the acid\textsuperscript{199} was dissolved in the amount of THF needed for the Birch reduction and treated with potassium hydride, which led to immediate hydrogen gas evolution. After one hour at room temperature, a thick white suspension had formed. The anhydrous ferric chloride was added and the predried ammonia distilled into the flask. The solution became clear upon addition of the
ammonia, following which, the lithium was added over a period of 45 minutes. Upon complete addition, the reaction mixture was quenched with dry ethanol, leading to the isolation of two compounds in a 70:30 ratio. These proved to be the desired 1,4-dihydro acid 186 and the 1,2-dihydro acid 202, with the 1,4-isomer predominating (Scheme 4.10). Recrystallisation of the crude product gave the 1,4-isomer 186 in 50% yield.

Scheme 4.10

![Reaction Scheme](image)

The $^1$H NMR spectrum of the 1,4-dihydro acid 186, in d$_6$-acetone, showed the presence of two strongly coupled multiplets at 3.57 and 3.74 ppm as well as a multiplet at 7.25 ppm, which were assigned to the two CH$_2$ groups and the olefinic hydrogen at C3, respectively. The $^{13}$C NMR spectrum confirmed this assignment as there were resonances at 131.9 and 134.7 ppm for the olefinic carbons. In addition, the resonance at 165.8 ppm was indicative of an $\alpha,\beta$-unsaturated carboxylic acid.

In this experiment, the ammonia had been allowed to evaporate over approximately 2 h. It was discovered that the slower the evaporation after ethanol was added, the higher the proportion of the 1,4-dihydro compound in the reaction product. To illustrate, an evaporation time of 5 h gave a 92:8 ratio of 1,4- to 1,2-dihydro acids. This crude mixture was recrystallised to afford the 1,4-dihydro acid in a yield of 80%, but this should be higher as the remaining material from the mother liquor could not be separated from the 1,2-dihydro...
isomer. Longer evaporation times than this did not change the 92:8 ratio significantly, but did result in the formation of the naphthoic acid, presumably from aerial oxidation.

Interestingly, if the quench with ethanol is omitted and the reaction mixture worked up in the usual manner, the 1,2-dihydro acid 202 was isolated as the major product (64% yield). The $^1$H NMR signals for the 1,2-dihydro naphthalene moiety were very diagnostic, as were the $^{13}$C NMR data. The $^{13}$C NMR spectrum had only two resonances in the aliphatic region and these signals were assigned to the two methylenes. In the same paper that the synthesis of the 1,4-dihydro acids is reported, Subba Rao looked at the reductive methylation of naphthoic acids using similar conditions, except that the quenching agent was methyl iodide.\textsuperscript{139} In these cases, 2-methyl-1,2-dihydro-2-naphthoic acids (for example, 203) were the only compounds isolated. As an explanation, it was proposed that the protonation step was effected by thermodynamic control while the methylation was governed by kinetic control.

\begin{center}
\includegraphics[width=0.2\textwidth]{203}
\end{center}

Obviously, the results obtained with ethanol quenching suggest that this is not so. The 1,2-dihydro isomer 202 was formed when the reaction was quenched, regardless of the quenching agent, but isomerises upon addition of ethanol. Ethoxide anion must therefore be generated after quenching and it is a sufficiently strong base to abstract the hydrogen alpha to the carboxylic acid. The 1,4-dihydro acids (cf. 190) are reported to be the more stable of the two compounds, so that given time, the equilibrium will favour the thermodynamically more stable product.\textsuperscript{136,140} Thus, the thermodynamic
product does indeed result from protonation, but not directly as suggested by Subba Rao and coworkers.

To summarise, the Birch reduction using ferric chloride does afford the 1,4-dihydro acid 186 in 80% yield, providing the carboxylate salt is used and the reaction mixture is quenched with ethanol and allowed to equilibrate before standard workup conditions are employed.
4.3 SHARPLESS ASYMMETRIC DIHYDROXYLATION OF METHYL 1,4-DIHYDRO-2-NAPHTHOATE 204

The 1,4-dihydro acid 186 was treated with an ethereal solution of diazomethane and the methyl ester 204 was isolated in 95% purity in approximately 90% yield (Scheme 4.11). The aromatised ester 205 was an inseparable contaminant (5%). Not surprisingly, compound 204 was susceptible to oxidation and had to be used relatively quickly in the AD reaction which followed.

Scheme 4.11

Both antipodes of the kaurene\(^1\) are found in nature with \(\text{ent-kaurene 1}\) demonstrated to be the biosynthetic precursor of the gibberellins.\(^7\) Accordingly, it was decided to pursue the absolute configuration of \(\text{ent-kaurene}\). After examining the previously discussed mnemonic for the AD reaction, it was concluded that use of the \((\text{DHQ})_2\)-PHAL ligand 184 should give the desired enantiomer corresponding to the \(\text{ent-kaurene absolute configuration}\).

Figure 4.5: The two antipodes of kaurene.
The 1,4-dihydro methyl ester 204 was added to a rapidly stirred mixture of AD mix α, one of two commercially available preparations of the Sharpless recipe\textsuperscript{131} (0.2 mole \% osmium, 1 mole \% ligand) in t-butanol and water at 0°C. Methanesulfonamide (one equivalent) was added as an accelerator and the resultant heterogeneous slurry was vigorously stirred at 0°C for 24 hours. At this point, very little reaction had occurred, so the mixture was warmed to room temperature. However, after 48 h at room temperature, the reaction was estimated to be only 20\% complete.

In the case of sluggish reactions, Sharpless\textsuperscript{154} has advocated the use of a modified mixture where the amount of osmium was increased to 1 mole \% and the ligand to 5 mole \%. In a more recent review,\textsuperscript{132} it was suggested that the ligand loading could be dropped to 1 or 2 mole \% without any compensatory loss in the reaction rate or enantiomeric excess. It was decided to use the mixture containing 1 mole \% osmium and 2 mole \% ligand as the literature indicated that slightly higher enantiomeric excesses were obtained, than with the 1 mole \% mixture.

Under these conditions, the reaction was complete after 5 h at 0°C (Scheme 4.12). TLC analysis showed a new baseline spot with only a trace of a higher running material, which was the methyl 8-methoxy-2-naphthoate 205 carried through from the earlier esterification. This impurity was easily removed by chromatography and the diol 206 was isolated in 85\% yield. The recyclable ligand remains on the column while eluting with ethyl acetate/hexane mixtures, but can be easily removed upon elution with methanol.
The \textsuperscript{1}H NMR spectrum of 206 revealed the presence of a doublet of doublets at 4.26 ppm, which was assigned to the methine hydrogen H3. One of the hydroxylic protons was observed as a broad singlet at 3.38 ppm. Unfortunately, the rest of the aliphatic signals were overlapped, so that no other assignments were possible. The \textsuperscript{13}C NMR spectrum exhibited resonances at 69.9 and 76.1 ppm, which were assigned as C3 and C2 respectively, using the attached proton technique (APT) to determine their multiplicity.

For comparative purposes, the racemate was obtained by carrying out the identical reaction, in the absence of ligand, to afford the diol rac-206 in 89\% yield. This reaction was appreciably slower, taking 18 h at room temperature.

The enantiomeric excess of the AD was determined by preparing the mono-\(\alpha\)-methoxy-\(\alpha\)-trifluoromethylphenyl acetate (mono-MTPA ester) and recording the \textsuperscript{19}F NMR spectrum.\textsuperscript{155} This derivative proved difficult to synthesise, with a large excess of the Mosher acid chloride\textsuperscript{155} (MTPA-Cl) required to ensure a complete reaction. The \textsuperscript{19}F NMR spectrum was recorded in deuteriochloroform and an 83\% enantiomeric excess was calculated. This result was disappointing, as it was hoped that an enantiomeric excess of greater than 90\% would be attained, based on Sharpless' observations.
4.4 DETERMINATION OF THE ABSOLUTE CONFIGURATION OF THE DIOL 206

One recrystallisation of the diol 206 from ethyl acetate/hexane gave material which was optically pure, as determined by Mosher ester analysis. Having the material in an optically pure form, it was felt that the absolute configuration of the diol 206 should be determined before any attempts to improve the enantiomeric excess were made. Indeed, if the (DHQ)2-PHAL ligand 184 was producing the wrong enantiomer, substitution of the ligand for (DHQD)2-PHAL 183 should correct things. In changing to this ligand, there would be the distinct possibility of a slight increase in the ee due to the observed phenomenon of consistently higher enantiomeric excesses (2-10%) using (DHQD)2-PHAL.132

4.4.1 The Modified Mosher Method For Determining Absolute Configurations

The most secure way of determining the absolute configuration of a compound is to incorporate a chiral auxiliary and obtain an X-ray crystal structure of the diastereoisomer. Suitable crystals of the (R)- and (S)-Mosher esters of diol 206 could not be obtained, despite numerous efforts to grow a suitable crystal. The use of other chiral auxiliaries was similarly unsuccessful.

There are several chemical methods that have been used to determine the absolute configuration, and of these, the method of Mosher has been the most frequently used.155 This involves the use of MTPA derivatives of chiral secondary alcohols. Variations using O-methyl mandelates and MTPA esters have also been reported.156,157
Popular modifications of the original Mosher method utilise the difference in steric bulk of the substituents on the \( \beta \) and \( \beta' \)-carbons, which leads to chemical shift differences between the two CF\(_3\) (\(^{19}\text{F}\)) or OMe (\(^{1}\text{H}\)) substituents.\(^{155b,158}\) Kakisawa\(^{159}\) has utilised the power of high-field FT NMR techniques to extend the range of the original method by allowing examination of the chemical shift differences of as many protons as can be assigned. The principal advantage of this method is that more than two data points are involved, so that a more accurate result can be obtained. Indeed, Kakisawa and coworkers compared their method against the \(^{19}\text{F}\) NMR method, and found that only 40% of the results obtained by the fluorine method were correct.\(^{159}\)

The Mosher method and subsequent variations are based on the proposal that in solution, the carbinyl proton, the carbonyl and the trifluoromethyl substituent are located in the same plane. This has been termed the ideal configuration and is depicted in Figure 4.6. Evidence for this arrangement comes from X-ray studies\(^{160,161}\) and infrared spectroscopy.\(^{162}\) In addition, the carbonyl and the trifluoromethyl substituent have a syn relationship, which was suggested by optical rotatory dispersion (ORD) and circular dichroic (CD) studies.\(^{163}\) These indicated that the syn conformation accounted for the chiroptical observations, although it was not necessarily the major conformation.

![Figure 4.6](image)

**Figure 4.6:** Depiction of the ideal conformation of Mosher esters as proposed by Mosher.\(^{155a}\)
The first step in the Mosher method is the formation of the diastereoisomeric (R)- and (S)-MTPA esters of the chiral secondary alcohol, followed by analysis of the individual $^1$H NMR spectra. Due to the diamagnetic effect of the benzene ring, $^1$H NMR signals of the R$_1$ group in the (R)-MTPA ester appear upfield, relative to those in the (S)-MTPA ester. The opposite relationship is seen for the $^1$H NMR signals of the R$_2$ group. Therefore, in defining $\Delta\delta = \delta_S - \delta_R$, protons on the right side of the MTPA plane must have positive values ($\Delta\delta > 0$) and protons on the left side of the plane must have negative values ($\Delta\delta < 0$), as illustrated in Figure 4.7.\textsuperscript{159}

![Figure 4.7: The model\textsuperscript{159} used for the determination of absolute configuration of secondary alcohols.](image)

The modified procedure of Kakisawa\textsuperscript{159} involves (a) assignment of as many proton signals as possible to each of the (R)- and (S)-MTPA esters; (b) calculation of $\Delta\delta$ values for these protons; (c) placing protons with positive $\Delta\delta$ values on the right side and those with negative $\Delta\delta$ values on the left side of the MTPA plane; and (d) construction of a molecular model and confirmation that all assigned protons with positive and negative $\Delta\delta$ values are actually found on the right and left sides of the MTPA plane respectively. In addition, the absolute values of $\Delta\delta$ must be inversely proportional to the distance from the MTPA moiety. When all conditions are satisfied, the correct absolute configuration of the molecule will be represented. If the $\Delta\delta$ values are irregularly arranged around the molecule, the data cannot be used to determine the absolute configuration.\textsuperscript{159}
4.4.2 Determination of the Absolute Configuration of the Diol

The synthesis of the (R)- and (S)-MTPA esters of the recrystallised diol 206 proved to be quite difficult, as noted in Section 4.3. In this case, however, complete reaction was not crucial (unlike the enantiomeric excess determination) and the yields, after chromatography, for the (R)- and (S)-MTPA esters 207 and 208 respectively, were 47% and 53%, with some starting material recovered in both cases. The $^1$H NMR data of the tetrahydro ring system for each diastereoisomer is presented in Table 4.1.

![Diastereoisomers 207 and 208](image)

**Table 4.1: $^1$H NMR spectral data for the (R)- and (S)-MTPA esters (207 and 208) of optically pure diol 206**

<table>
<thead>
<tr>
<th>$^1$H Signals</th>
<th>$\delta_S$ (ppm)</th>
<th>$\delta_R$ (ppm)</th>
<th>$\Delta\delta$ (ppm)</th>
<th>$\Delta\delta$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>3.14</td>
<td>3.11</td>
<td>+0.03</td>
<td>+9</td>
</tr>
<tr>
<td>H4(\alpha)</td>
<td>3.15</td>
<td>3.27</td>
<td>-0.12</td>
<td>-36</td>
</tr>
<tr>
<td>H4(\beta)</td>
<td>3.23</td>
<td>3.32</td>
<td>-0.09</td>
<td>-27</td>
</tr>
<tr>
<td>CO$_2$Me</td>
<td>3.78</td>
<td>3.63</td>
<td>+0.15</td>
<td>+45</td>
</tr>
<tr>
<td>H3</td>
<td>5.60</td>
<td>5.54</td>
<td>+0.06</td>
<td>+18</td>
</tr>
</tbody>
</table>

The Newman projection of each diastereoisomer, using the absolute configuration predicted by the Sharpless mnemonic, clearly indicates why the shifts occur (Figure 4.8).
It can be seen that the methine of C3 has a positive $\Delta \delta$ value and according to Mosher's proposal, if it is in the ideal conformation, this value should be zero. Kakisawa and coworkers$^{159}$ have observed this in some of the compounds studied, particularly those that have nonequivalent $\beta$-carbons and it is proposed that the steric compression from these is not equal and results in some distortion of the conformation(s) of either of the (R)- and (S)-MTPA compounds. It was suggested that if there is a slight deviation from the ideal conformation, the methine would be anisotropically affected more by the carbonyl group than by the phenyl group. In the case of compounds 207 and 208, the MTPA ester moiety is flanked by secondary and quaternary $\beta$-carbons respectively. The abovementioned deviation of the methine signal from the ideal conformation is in line with the values obtained by Kakisawa.$^{159}$

When the Kakisawa procedure was followed to completion, the absolute configuration at C3 was determined to be $S$. As the dihydroxylation is stereospecific, this means that the absolute stereochemistry at C2 must be $R$. Reassuringly, the absolute configuration matches that predicted by the Sharpless mnemonic.
4.5 IMPROVEMENTS TO THE ENANTIOMERIC EXCESS IN THE AD

To qualify for the term 'enantioselective synthesis', the enantiomeric excess is expected to be greater than 90%, and so the 83% ee obtained for the methyl ester 202 in the AD was a disappointing result, particularly as several of Sharpless' results suggested that the enantiomeric excess should be excellent (Table 4.2). For example, when ethyl cinnamate 209 is dihydroxylated, the enantiomeric excess was 95% when (DHQ)₂-PHAL was used, while for a similar compound to the substrate being investigated, 1-acetyl-1-cyclohexene 210, the enantiomeric excess was 98% using (DHQD)₂-PHAL as the chiral ligand. 164

Table 4.2: Examples of the enantiomeric excesses obtained upon asymmetric dihydroxylation

<table>
<thead>
<tr>
<th>Olefin</th>
<th>(DHQD)₂-PHAL</th>
<th>(DHQ)₂-PHAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂Et</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>209</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>98</td>
<td>not determined</td>
</tr>
<tr>
<td>210</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>211</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>75-80</td>
<td>not determined</td>
</tr>
<tr>
<td>212</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1-Phenyl-1-cyclohexene 211 also affords extremely high enantiomeric excesses: 99% ee with (DHQD)$_2$-PHAL and 97% ee for (DHQ)$_2$-PHAL.$^{131}$ This is in sharp contrast to the analogous 1-methyl-1-cyclohexene 212 which gave an enantiomeric excess of approximately 75-80% using (DHQD)$_2$-PHAL.$^{165}$

In a recent paper, Sharpless and coworkers$^{166}$ investigated the kinetics of the AD. It was found that (DHQD)$_2$-PHAL gave exceptionally high rate constants with aromatic substrates. This was attributed to the presence of a 'binding pocket', set up by the aromatic ring systems of the ligand, which enabled especially good transition-state stabilisation for aromatic olefins within the pocket. These results led them to a revision of the mnemonic. Previously, the southwest quadrant had been represented as a sterically neutral area, but is now viewed as an attractive area, especially well suited to accommodate flat aromatic substituents. The revised mnemonic now offers an explanation for the difference in outcomes for compounds 211 and 212.

With the above results in mind, the benzyl and the diphenylmethyl esters, 213 and 214, were investigated to see if any worthwhile improvements in the enantiomeric excess could be obtained from the AD.

Initial attempts to make the benzyl ester 213 by the classical method of benzyl bromide and potassium carbonate proved to be unsatisfactory.$^{167}$ The long reaction time required meant that aromatisation, a minor problem in the formation of the methyl ester, became a major issue under these conditions. Even catalytic phase-transfer conditions failed to prevent appreciable aromatisation. However, it was discovered that the benzyl ester 213 was rapidly formed, with only minor aromatisation, when the preformed acyl imidazole was treated with benzyl alcohol in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 4.13). This procedure was a variant of that used by Ohta and coworkers$^{168}$ in their synthesis of t-butyl
esters. The desired benzyl ester 213 was isolated in 90% purity in approximately 83% yield. The aromatised benzyl naphthoate 215 was the contaminant and could not be removed from the dihydro ester.

Due to the insolubility of the benzyl ester 213 in the solvent system for the dihydroxylation, toluene was added to the reaction mixture, which appreciably lowered the rate of the reaction, as has been mentioned by Sharpless and coworkers. The benzyl ester diol rac-216 was isolated in 74% yield, after chromatography (an 82% yield, if the contamination of the aromatic impurity from the esterification was taken into consideration) (Scheme 4.14). When the 2 mole % (DHQ)$_2$-PHAL/1 mole % osmium AD mixture was used, a 92% enantiomeric excess was obtained for diol 216 (determined in exactly the same manner as that for diol 206). This was a very pleasing result, especially as the diol 216 could be obtained in optical purity upon one recrystallisation from ether.
Although the AD furnished material now satisfactorily above the 90% ee mark, the diphenylmethyl ester 214 was synthesised to see if the enantiomeric excess could be further increased. The esterification method was similar to that of the benzyl ester, although the use of diphenylmethyl alcohol required the reaction mixture to be heated to reflux for complete reaction. The desired ester 214 was isolated in 70% purity in approximately 50% yield, with the aromatised diphenylmethyl naphthoate 217 an inseparable contaminant (Scheme 4.15).

In the AD, the diphenylmethyl ester 214 did not react under the same conditions as those of the benzyl and methyl esters, with all attempts to dihydroxylate the material failing. Presumably, the ester group is too bulky to allow the osmium complex to reach the alkene bond.
4.6 CONCLUSIONS

In this Chapter, details of an investigation into the Sharpless asymmetric dihydroxylation of 1,4-dihydro-2-naphthoic esters have been presented. It was found that the literature procedure for the synthesis of 1,4-dihydronaphthoic acids was not reproducible, but with several modifications, the acid 186 could be obtained in excellent yields. The AD of the methyl ester of 8-methoxy-1,4-dihydro-2-naphthoic acid 204 gave the diol 206 in 83% enantiomeric excess, a result lower than had been expected. Based on the observation that flat aromatic olefins appear to be ideal substrates for the AD, the benzyl ester 213 was synthesised, and in the AD, this substrate furnished the diol 216 in 92% ee. The use of the diphenylmethyl ester 214 in the same sequence was unsuccessful. Thus, the Sharpless AD of 1,4-dihydro-2-naphthoate esters can give excellent enantiomeric excesses after ester group optimisation. The 2,3-dihydroxytetrahydro-2-naphthoate products should be amenable to further elaboration and thus, afford substituted optically active norcaradienes, which may, in the future, be utilised in the synthetic scheme developed in Chapter 3.
CHAPTER FIVE

CONCLUSIONS AND FUTURE WORK

In a discussion on synthetic design, Wender and Miller have emphasized that by choosing chemical processes that allow for a greater increase in complexity relative to the target, a shorter synthesis should necessarily be obtained, provided that all required substrates are readily available. Clearly, the most attractive means of achieving this increase in complexity per synthetic operation would be to use a reaction that involves multibond formation, but these types of processes are often not readily available. Wender and Miller noted that an alternative was to use a combination of two or more reactions for the formation of one or two bonds. This type of approach is becoming increasingly popular as evidenced by the predominance of serial, cascade and/or random processes.

The cyclopropanation/Diels-Alder process described in the preceding sections is clearly an example of the advantages of this latter approach.

It was established that the norcaradienes could be synthesized by the transition-metal catalysed intramolecular cyclopropanation reaction of substituted tetrahydroazulene homologues. While the yields were variable when rhodium catalysts were used, it was found that significant yields of the norcaradienes were achieved when copper catalysts were employed as the catalyst. The norcaradienes displayed a sensitivity to acid, which limited their utility as synthons.

The results obtained in Chapter Three have demonstrated that the synthetic plan proposed in Chapter One has significant merit. A facile stereocinetically controlled assembly of advanced intermediates for the synthesis of ketoneoid dienes has been achieved. The vinyl norcaradiene 343 has proven to be an excellent diene in the Diels-Alder reaction with various dienophiles (Scheme 5.1). As predicted, the cyclopropane moiety shielded the top face of the molecule and so favored addition of dienophiles with the cyclopropane. In the case of the enolyl chloride dienophile, this has resulted...
In a discussion on synthetic design, Wender and Miller\textsuperscript{169} have emphasised that by choosing chemical processes that allow for a greater increase in complexity relative to the target, a shorter synthesis should necessarily be obtained, provided that all necessary materials are readily available. Clearly, the most attractive means of achieving this increase in complexity per synthetic operation would be to use a reaction that involves multibond formation, but these types of processes are often not readily available. Wender and Miller\textsuperscript{169} noted that an alternative was to use a combination of two or more sequential reactions that each allow for the formation of one or two bonds. This type of approach is becoming increasingly popular as evidenced by the preponderance of serial, cascade and/or tandem processes.\textsuperscript{170} The cyclopropanation/Diels-Alder process described in the preceding sections is clearly an example of the advantages of this latter approach.

It was established that the norcaradienes could be synthesised by the transition-metal catalysed intramolecular cyclopropanation reaction of substituted tetrahydronaphthyl diazomethyl ketones. While the yields were variable when rhodium catalysts were used, it was found that consistent yields of the norcaradienes were achieved when copper (II) acetylacetonate was employed as the catalyst. The norcaradienes displayed a sensitivity to acid, which limited their utility as synthons.

The results obtained in Chapter Three have demonstrated that the synthetic plan proposed in Chapter One has significant merit. A rapid stereocontrolled assembly of advanced intermediates for the synthesis of kaurenoid diterpenes has been achieved. The vinyl norcaradiene 142 has proven to be an excellent diene in the Diels-Alder reaction with various dienophiles (Scheme 5.1). As predicted, the cyclopropane moiety shielded the top face of the molecule and so favoured addition of dienophiles anti to the cyclopropane. In the case of the anhydride dienophiles, this has resulted
in excellent stereoselectivity. It was found that the yields improved appreciably when the cyclopropanation and Diels-Alder reaction were performed in 'one-pot'.

Scheme 5.1

In this sequence of two reactions, the synthesis of a pentacyclic intermediate has been achieved, starting from a bicyclic precursor, and in the process, formed four C-C bonds and three rings, as well as the introduction of five stereogenic centres with the correct relative stereochemistry (although not all of these bonds are necessarily required for the final target molecule). It is interesting to note that the Diels-Alder products are available in seven steps from a commercially available starting material and in this sequence, six of these steps are C-C bond forming processes.

The preference for the endo orientation of the dienophile has allowed the use of citraconic anhydride, which means that the C4 configuration in the kaurenoid diterpenes can be established concurrently with the stereochemistry at C5. The citraconic anhydride adduct 181 would appear to have great potential in the synthesis of gibberellins and antheridiogens.
To complete the synthesis, the A-ring must be elaborated, the B-ring contracted to give the five-membered ring, and depending on the desired CD ring system, the cyclopropane ring cleaved. Of these, the ring contraction and the cleavage of the cyclopropane moiety have some literature precedent. DeClercq's second synthesis of GA5 utilised a phase-transfer diazo transfer/ring contraction process, originally established by Mander and coworkers, with great success. The research groups of Tahara [equation (a) in Scheme 5.2] and Mander [equation (b) in Scheme 5.2] have reported work on the cleavage of cyclopropyl ketones, with the bicyclo[3.2.1]octane ring system predominating. The double bond at C10-C10a of 181 would be expected to allow even greater selectivity in such a process.

Scheme 5.2

The main obstacle to achieving the synthesis of the kaurenes is the introduction of the C-20 methyl group (Figure 5.1). A secure approach is the intramolecular cyclopropanation reaction of a diazoketone, which has been used with much success in the synthesis of C-20 gibberellins [approach (a)]. More direct processes could possibly involve either palladium-assisted allylic substitution [approach (b)] or hydroxy-directed Simmons-Smith cyclopropanation [approach (c)]. The starting materials for these
reactions should be readily available from the enone 182, which itself should be available from an allylic oxidation.

Figure 5.1: Proposed methods for the introduction of the C-20 methyl group in kaurenes [R = Me/H; R' = CO₂Me/anhydride; R'' = H/anhydride].

The other advantage of the enone 182 is that it should facilitate removal of the extraneous carboxy group from the anhydride moiety. Alternatively, the carboxy group could be used to introduce functionality at C3 of the kaurenoid diterpenes.

The above ideas, coupled with the development of an enantioselective route to functionalised tetrahydronaphthoic acids, would seem to indicate that a rapid, efficient synthesis of optically active kaurenoid diterpenes is possible using the cyclopropanation/Diels-Alder approach.
6.1 GENERAL EXPERIMENTAL

Melting points were recorded on a Reichert hot-stage and are uncorrected.

Microanalyses were carried out by the Australian National University
Analytical Services Unit, Canberra.

Low resolution EI mass spectra (70 eV) and high resolution accurate mass measurements were recorded on a VG Micromass 7070F double focusing mass spectrometer. The molecular ion (M+)'s present, significantly high mass ions and the more important fragment ions are reported. Data are presented in the following order: m/z value, relative intensity as a percentage of the base peak.

Infrared spectra (V_{max}) were recorded on a Perkin-Elmer 683 infrared spectrophotometer in 0.25 mm NaCl solution cells using "Spectrograde" chlormform (unless otherwise stated).

All optical rotations (\[\alpha\]D) were measured on a Perkin-Elmer 341 polarimeter in spectroscopic grade chlormform at 20°C.

\[\text{H}^1\text{NMR spectra were recorded on the following instruments: Varian}\]
\[\text{Gemini 300 at 300 MHz, Varian VX200 at 300 MHz and Varian VX300 at}\]
\[500 MHz.}\]
\[\text{C}\]\[\text{H}\]\[\text{NMR spectra were recorded on the following instruments:}\]
\[\text{Varian Gemini 300 at 75.5 MHz and Varian VX200 at 79.4 MHz.}\]

Chemical shifts are reported as \[\delta\] values in parts per million (ppm). Trimethylsilane (TMS) was used as the nominal standard for all recorded NMR spectra. For proton spectra recorded in chlormform, the residual peak of CHCl_3 was used as the internal reference (7.26 ppm) while the central peak of CDCl_3 (77.6 ppm) was used as the reference for carbon spectra. In cases where dimethyl


CHAPTER SIX

EXPERIMENTAL
6.1 GENERAL EXPERIMENTAL

Melting points were recorded on a Reichert hot-stage and are uncorrected. Microanalyses were carried out by the Australian National University Analytical Services Unit, Canberra.

Low resolution EI mass spectra (70 eV) and high resolution accurate mass measurements were recorded on a VG Micromass 7070F double focussing mass spectrometer. The molecular ion (M⁺), if present, significantly high mass ions and the more intense low mass ions are reported. Data are presented in the following order: m/z value; relative intensity as a percentage of the base peak.

Infrared spectra (νmax) were recorded on a Perkin-Elmer 683 Infrared spectrophotometer in 0.25 mm NaCl solution cells using "Spectrograde" chloroform (unless otherwise stated).

All optical rotations ([α]D20) were measured on a Perkin-Elmer 341 polarimeter in spectroscopic grade chloroform at 20°C.

1H NMR spectra were recorded on the following instruments: Varian Gemini 300 at 300 MHz, Varian VXR300 at 300 MHz and Varian VXR500 at 500 MHz. 13C NMR spectra were recorded on the following instruments: Varian Gemini 300 at 75.5 MHz and Varian VXR300 at 75.4 MHz. Chemical shifts are reported as δ values in parts per million (ppm). Tetramethylsilane (TMS) was used as the nominal standard for all recorded NMR spectra. For proton spectra recorded in chloroform, the residual peak of CHCl₃ was used as the internal reference (7.26 ppm) while the central peak of CDCl₃ (77.0 ppm) was used as the reference for carbon spectra. In cases where dimethyl sulfoxide was used as solvent, proton spectra were referenced against
residual d5-DMSO (2.50 ppm) and carbon spectra relative to the central peak of the d6-DMSO heptet (39.5 ppm). Proton spectra recorded in acetone were referenced against residual d5-acetone (2.05 ppm) while carbon spectra were referenced relative to the d6-acetone carbonyl singlet (204.1 ppm). Data are recorded as follows: chemical shift (δ), multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, dd: doublet of doublets, etc: br indicates some degree of broadening in the signal), coupling constant(s) (Hz), integrated intensity (for proton spectra) and assignment (first order analyses of spectra were attempted where possible and, consequently, chemical shifts and coupling constants for multiplets may only be approximate). Distortionless enhancement by polarisation transfer (DEPT) and the attached proton test (APT) were used in the assignment of carbon spectra.122

Two dimensional NMR experiments were carried out using the following instruments: Varian VXR300 and Varian VXR500. The pulse sequences used were homonuclear (1H/1H) correlation spectroscopy (COSY), double quantum filtered homonuclear (1H/1H) correlation spectroscopy (DQFCOSY), heteronuclear (1H/13C) correlation spectroscopy (HETCOR) and phase sensitive Nuclear Overhauser and exchange spectroscopy (PS-1H/1H-NOESY).122

Analytical thin layer chromatography (TLC) was conducted on micro-slides coated with Merck Kieselgel KG60F-254. The developed plates were visualised under shortwave ultraviolet light and stained with 13% (w/v) vanillin in concentrated sulfuric acid at 180°C. Flash chromatography was conducted according to the method of Still and coworkers177 using Merck Kieselgel 60 as the adsorbent and analytical reagent (AR) grade solvents as indicated. Medium pressure liquid chromatography (MPLC) was conducted using a CfG Prominent Duramat® pump, a Waters Associate Differential
Refractometer R40 diffractometer and Merck Lobar® Fertigsäule Größe LiChroprep® Si60 (40 - 63 µm) columns.

Solvents and reagents used in reactions were purified according to well-established procedures. Tetrahydrofuran (THF), diethyl ether (ether) and benzene were purified by distillation from sodium benzophenone ketyl. Methanol was purified by distillation from magnesium methoxide. N,N-Dimethylformamide (DMF) was dried by the method of Burfield and Smithers. Dichloromethane, 1,2-dichloroethane and triethylamine were distilled from calcium hydride. Ethanol-free ethereal diazomethane was prepared from Diazald® (N-methyl-N-nitroso-p-toluenesulfonamide) purchased from Aldrich. Rhodium (II) acetate [Rh₂(OAc)₄], copper (II) trifluoromethanesulfonate [Cu(OTf)₂] and copper bronze were purchased from the Aldrich Chemical Company and were used as supplied. Rhodium (II) caprolactam [Rh₂(cap)₄] and rhodium (II) perfluorobutyrate [Rh₂(pfb)₄] were kindly supplied by Professor Michael Doyle of Trinity University. The following catalysts were prepared by literature procedures: copper (I) chloride, copper (I) iodide, copper (II) (t-butylsalicylimidato)₂ [Cu(TBS)₂], rhodium (II) [S-(+)-mandelate] [Rh₂(mand)₄], rhodium (II) triphenylacetate [Rh₂(TPA)₄], copper (II) acetylacetonate [Cu(acac)₂] and copper (I) chloride trimethyl phosphite [CuCl·P(OMe)₃].

Unless otherwise stated, all reactions were performed under a dry nitrogen atmosphere. Reaction temperatures refer to the external bath temperature. All organic extracts were dried with anhydrous sodium sulfate. After filtration of solutions from drying reagents, the bulk of the solvent was removed on a Büchi rotatory evaporator. The last traces of solvent were removed under high vacuum.
NOTES ON NOMENCLATURE

The nomenclature system used in this dissertation conforms to the indexing policies of the Chemical Abstracts Service (CA Index Guide, Appendix IV), which are generally in accordance with the rules published by the International Union of Pure and Applied Chemistry (IUPAC). The base structures for the compounds named are presented below.

- Naphthalene
- 1H-3,4b-methanocycloprop[1,2:1,3]dibenzene
- 5,8-methano-1H-benzocycloheptene
- Cyclobuta[a]naphthalene
- 4a,7-methano-4aH-benzocycloheptene
- 2H-2,4a-ethanonaphthalene
- 1H-3,4b-methanobenzo[1,3]cycloprop[1,2-a]naphthalene
NOTE: The author gratefully acknowledges the contributions of Drs Dan Rogers and Russell Bell for their initial work in this area. All chromatography and characterisation was performed by the author. The high pressure reaction of norcaradiene 74 with \( p \)-bromobenzenesulfonyl azide was kindly performed by Dipl. Chem. Frank Graupner of Georg-August University, Göttingen.

6.2.1 Preparation Of The Carboxylic Acids

The following carboxylic acids were prepared by literature procedures; 1,2,3,4-tetrahydro-2-naphthoic acid,\(^{187}\) 5-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid,\(^{72}\) 6-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid,\(^{188}\) 7-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid,\(^{188,189}\) 8-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid,\(^{72}\) 4-keto-1,2,3,4-tetrahydro-2-naphthoic acid,\(^{78}\) 4-keto-8-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid,\(^{190}\) 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic acid,\(^{191}\) 6,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic acid,\(^{74,90}\) 6-hydroxy-1,2,3,4-tetrahydro-2-naphthoic acid,\(^{188}\) 8-hydroxy-1,2,3,4-tetrahydro-2-naphthoic acid.\(^{90}\)

(2RS)-2-t-Butyldimethylsilyloxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid 119
t-Butyldimethylsilyl chloride (700 mg, 2.5 eq.) was added in one portion to a stirred solution of 2-hydroxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid (410 mg, 1.85 mmol) and imidazole (620 mg, 5 eq.) in DMF (2 ml). The solution was stirred at room temperature for 10 mins and poured into water. The solution was extracted with ether (x 3). The organic extracts were washed with water and brine. Evaporation of the solvent in vacuo gave an oil. Chromatography, using 10% ethyl acetate/hexane as the eluent gave (2RS)-t-butyldimethylsilyl 2-t-butyldimethylsilyloxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthoate as an oil, which solidified (830 mg, 100%), m.p. 58-60°C.

IR (CHCl₃) 2930, 2890, 2850, 1720, 1585 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ -0.06 (s, 3H, SiCH₃), 0.16 (s, 3H, SiCH₃), 0.27 (s, 3H, SiCH₃), 0.31 (s, 3H, SiCH₃), 0.75 (s, 9H, SiC(CH₃)₃), 0.92 (s, 9H, SiC(CH₃)₃), 2.02 (m, 2H, H3), 2.75 (dt, J = 5.5, 11.6 Hz, 1H, H4), 2.93 (d, J = 17.6 Hz, 1H, H1), 3.05 (m, 1H, H4), 3.14 (d, J = 17.6 Hz, 1H, H1), 3.82 (s, 3H, OMe), 6.66 (d, J = 8.2 Hz, 1H, H7), 2.05 (s, 3H, SiCH₃), 17.6 (SiC(CH₃)₃), 18.4 (SiC(CH₃)₃), 25.5 (SiC(CH₃)₃), 25.7 (SiC(CH₃)₃), 25.8 (C3), 33.0 (C1 or C4), 33.3 (C4 or C1), 55.2 (OMe), 75.9 (C2), 106.9 (C7), 120.6 (C6), 122.9 (C4a), 126.0 (C5), 136.5 (C8a), 157.3 (C8), 175.2 (CO₂TBDMS).

MS (EI) m/z 393 (M⁺ - C₄H₉, 6%), 365 (5), 291 (3), 233 (4), 147 (43), 73 (100).

Analysis calc'd for C₂₄H₄₂Si₂O₄: C 63.95; H 9.39; found: C 63.67; H 9.80.

The ester (810 mg) was added to a solution of methanol (25 ml), tetrahydrofuran (8 ml) and aqueous potassium carbonate (0.7 M, 8 ml) at room temperature. The solution was stirred for 8 h, diluted with water and acidified carefully to pH 4 with 1M aqueous potassium hydrogen sulfate. The suspension was extracted with ethyl acetate (x 3). The organic extracts were washed with water and brine. Removal of the solvent gave the acid
119 as an oil (100%). Chromatography, using 25% ethyl acetate/hexane, gave 119 as an oil, which slowly crystallised as needles (341 mg, 55%),
m.p. 124-126°C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ -0.06 (s, 3H, SiCH$_3$), 0.17 (s, 3H, SiCH$_3$), 0.83 (s, 9H, SiC(CH$_3$_3)$_3$), 2.12 (m, 1H, H3), 2.82 (m, 1H, H3), 2.90-3.15 (m, 2H, H4 x 2), 3.10 (AB system, $\delta_A = 3.08$, $\delta_B = 3.12$, $J_{AB} = 17.6$ Hz, 2H, H1 x 2), 3.83 (s, 3H, OMe), 6.69 (d, $J = 8.2$ Hz, 1H, H7), 6.74 (d, $J = 7.6$ Hz, 1H, H8), 7.10 (dd, $J = 7.6$, 8.2 Hz, 1H, H6).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ -3.7 (SiCH$_3$), -3.2 (SiCH$_3$), 18.3 (SiC(CH$_3$_3)$_3$), 25.3 (C3), 25.6 (SiC(CH$_3$_3)$_3$), 32.7 (C1 or C4), 32.8 (C4 or C1), 55.3 (OMe), 75.3 (C2), 107.0 (C7), 120.7 (C6), 122.1 (C4a), 126.2 (C5), 136.4 (C8a), 157.3 (C8), 180.6 (CO$_2$H).

MS (El) m/z 279 (M$^+ - C_4H_9$, 28%), 251 (24), 235 (38), 159 (48), 75 (100).

HRMS (El) m/z calc'd for M$^+ - C_4H_9$: C$_{14}H_{19}$SiO$_4$: 279.1053, found 279.1052.

### 6.2.2 Preparation of the Diazoketones

All of the diazoketones were prepared from the corresponding carboxylic acids using the general procedure outlined below.

The carboxylic acid (1 mmole) in dry dichloromethane (10 ml) was added dropwise to oxalyl chloride (2 ml) under a N$_2$ atmosphere. One drop of dry DMF was added (evolution of gas) and the yellow solution was stirred for 14 h. The volatile components were removed in vacuo and dry benzene was added. The benzene was removed in vacuo and the procedure repeated twice more to yield the acid chloride (100% recovery) as a yellow oil. After 1 h on high vacuum the acid chloride was dissolved in dichloromethane (10
ml) and added to fresh ethereal diazomethane (0.4 M, 5 equivs) at -20°C (methanol/ice bath) under nitrogen. The bright yellow solution was stirred for 15 h and filtered through celite in a well-ventilated fumehood. The solvent was removed \textit{in vacuo} to afford a yellow oil. This was purified on silica, using ethyl acetate/hexane mixtures as the eluent, to give the \textit{diazoketone} (70-85\% yield) as a yellow crystalline solid.

a) \textit{(2RS)-Diazomethyl 1,2,3,4-tetrahydro-2-naphthyl ketone 6,}

m.p. 41-43°C (lit\textsuperscript{51} m.p. 40-43°C).

\textbf{1H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 1.90 (m, 1H, H3), 2.15 (m, 1H, H3), 2.70 (m, 1H, H2), 2.80-3.10 (m, 4H, H4 and H1), 5.40 (br s, 1H, COCHN\textsubscript{2}), 7.15 (m, 4H, H5, H6, H7 and H8).

b) \textit{(2RS)-Diazomethyl 5-methoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 7,}

a small sample was recrystallised from ether/hexane to afford 7 as yellow rods, m.p. 62-64°C.

\textbf{IR} (CHCl\textsubscript{3}) 2950, 2100, 1640, 1585 cm\textsuperscript{-1}.

\textbf{1H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 1.80 (m, 1H, H3), 2.15 (m, 1H, H3), 2.50-2.70 (m, 2H, H1 and H2), 2.85-3.10 (m, 3H, H1 and H4 x 2), 3.82 (s, 3H, OMe), 5.39 (br s, 1H, COCHN\textsubscript{2}), 6.68 (d, \(J = 8.1\) Hz, 1H, H6), 6.74 (d, \(J = 7.8\) Hz, 1H, H8), 7.12 (dd, \(J = 7.8, 8.1\) Hz, 1H, H7).

\textbf{13C NMR} (75 MHz, CDCl\textsubscript{3}) \(\delta\) 22.7 (C3), 25.8 (C1 or C4), 31.7 (C4 or C1), 45.2 (C2), 53.7 (COCHN\textsubscript{2}), 55.1 (OMe), 107.0 (C6), 121.1 (C7), 121.4 (C4a), 126.1 (C8), 136.2 (C8a), 157.0 (C5), 197.4 (COCHN\textsubscript{2}).

\textbf{MS} (EI) \(m/z\) 230 (M\textsuperscript{+}, 1\%), 202 (54), 174 (30), 159 (100), 146 (53), 134 (37), 128 (38), 115 (81), 104 (90), 91 (79), 77 (45), 65 (44).

\textbf{Analysis} calc'd for C\textsubscript{13}H\textsubscript{14}N\textsubscript{2}O\textsubscript{2}: C 67.81; H 6.13; N 12.17; found: C 68.01; H 6.35; N, 11.90.
c) (2RS)-Diazomethyl 6-methoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 73, m.p. 51-53°C (lit51 m.p. 51-53°C).

\(^1\)H NMR (300 MHz, CDCl\(_3\) \(\delta\) 1.85 (m, 1H, H3), 2.08 (m, 1H, H3), 2.62 (m, 1H, H2), 2.70-3.00 (m, 4H, H4 x 2 and H1 x 2), 3.78 (s, 3H, OMe), 5.40 (br s, 1H, COCHN\(_2\)), 6.62 (d, \(J = 2.6\) Hz, 1H, H5), 6.71 (dd, \(J = 2.6, 8.7\) Hz, 1H, H7), 7.00 (d, \(J = 8.7\) Hz, 1H, H8).

d) (2RS)-Diazomethyl 7-methoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 76, a small sample was recrystallised from pentane to afford 76 as yellow prisms, m.p. 35-37°C.

IR (CHCl\(_3\)) 2970, 2105, 1640, 1610 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CDCl\(_3\) \(\delta\) 1.83 (m, 1H, H3), 2.10 (m, 1H, H3), 2.65 (m, 1H, H2), 2.70-3.10 (m, 4H, H4 x 2 and H1 x 2), 3.78 (s, 3H, OMe), 5.37 (br s, 1H, COCHN\(_2\)), 6.64 (d, \(J = 2.6\) Hz, 1H, H8), 6.71 (dd, \(J = 2.6, 8.4\) Hz, 1H, H6), 7.00 (d, \(J = 8.4\) Hz, 1H, H5).

\(^1\)C NMR (75 MHz, CDCl\(_3\) \(\delta\) 26.2 (C3), 27.5 (C1 or C4), 31.6 (C4 or C1), 45.3 (C2), 53.6 (COCHN\(_2\)), 54.9 (OMe), 112.0 (C6 or C8), 113.2 (C8 or C6), 127.4 (C4a), 129.4 (C5), 135.7 (C8a), 157.3 (C7), 197.2 (COCHN\(_2\)).

MS (EI) \(m/z\) 230 (M\(^+\), 1%), 202 (46), 174 (36), 159 (100), 146 (45), 134 (58), 115 (48), 104 (27), 91 (66), 77 (38), 65 (33), 51 (45).

Analysis calc'd for C\(_{13}\)H\(_{14}\)N\(_2\)O\(_2\): C 67.81; H 6.13; N 12.17; found: C 67.96; H 6.37; N, 12.44.

e) (2RS)-Diazomethyl 8-methoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 79, m.p. 73-74°C (lit\(^{23,72}\) m.p. 73-74°C).

\(^1\)H NMR (300 MHz, CDCl\(_3\) \(\delta\) 1.90 (m, 1H, H3), 2.15 (m, 1H, H3), 2.70 (m, 1H, H2), 2.80-3.10 (m, 4H, H4 x 2 and H1 x 2), 5.40 (br s, 1H, COCHN\(_2\)), 6.69 (d, \(J = 7.8\) Hz, 1H, H7), 6.72 (d, \(J = 7.8\) Hz, 1H, H5), 7.11 (t, \(J = 7.8\) Hz, 1H, H6).

f) (2RS)-Diazomethyl 6-hydroxy-1,2,3,4-tetrahydro-2-naphthyl ketone 88,
m.p. 127-130°C (dec) [lit51 m.p. 127-130°C (dec)].

\[ \text{H NMR (300 MHz, CDCl}_3 \text{)} \delta 1.82 (m, 1H, H3), 2.09 (m, 1H, H3), 2.62 (m, 1H, H2), 2.77-2.90 (m, 4H, H1 x 2 and H4 x 2), 5.12 (br s, 1H, OH), 5.35 (br s, 1H, COCHN\text{2}), 6.57 (d, J = 2.5 Hz, 1H, H5), 6.62 (dd, J = 2.5, 8.2 Hz, 1H, H7), 6.95 (d, J = 8.2 Hz, 1H, H8).

\]

\[ g) (2RS)-Diazomethyl 8-hydroxy-1,2,3,4-tetrahydro-2-naphthyl ketone 92, m.p. 140-142°C (dec) [lit] m.p. 141-42°C (dec)].

\[ \text{H NMR (300 MHz, CDCl}_3 \text{)} \delta 1.80 (m, 1H, H3), 2.10 (m, 1H, H3), 2.60-3.05 (m, 5H, H1 x 2, H4 x 2 and H2), 5.20 (br s, 1H, OH), 5.40 (br s, 1H, COCHN\text{2}), 6.60 (d, J = 8.7 Hz, 1H, H5), 6.68 (d, J = 8.7 Hz, 1H, H7), 7.00 (t, J = 8.7 Hz, 1H, H6).

\]

\[ h) (2RS)-Diazomethyl 6,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 96, m.p. 83-85°C (dec) [lit74,88 m.p. 84-85°C (dec)].

\[ \text{H NMR (300 MHz, CDCl}_3 \text{)} \delta 1.80 (m, 1H, H3), 2.10 (m, 1H, H3), 2.60 (m, 2H, H1 and H2), 2.70-3.00 (m, 3H, H1 and H4 x 2), 3.78 (s, 3H, OMe), 3.80 (s, 3H, OMe), 5.38 (br s, 1H, COCHN\text{2}), 6.25 (d, J = 1.6 Hz, 1H, H7), 6.30 (d, J = 1.6 Hz, 1H, H5).

\]

\[ i) (2RS)-Diazomethyl 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 100, m.p. 93-95°C (dec) [lit75 m.p. 92-95°C (dec)].

\[ \text{H NMR (300 MHz, CDCl}_3 \text{)} \delta 1.80 (m, 1H, H3), 2.08 (m, 1H, H3), 2.63 (m, 2H, H1 and H2), 2.75-3.00 (m, 3H, H1, H4 x 2), 3.84 (s, 6H, OMe x 2), 5.36 (br s, 1H, COCHN\text{2}), 6.58 (s, 2H, H5 and H8).

\]

\[ j) (2RS)-Diazomethyl 4-keto-1,2,3,4-tetrahydro-2-naphthyl ketone 111, m.p. 88-90°C (lit78 m.p. 87-89°C).

\]
1H NMR (300 MHz, CDCl₃) δ 2.80 (m, 2H, H3 x 2), 3.00-3.30 (m, 3H, H2 and H1 x 2), 5.50 (br s, 1H, COCHN₂), 7.26 (d, J = 7.4 Hz, 1H, H8), 7.31 (t, J = 7.4 Hz, 1H, H6), 7.50 (t, J = 7.4 Hz, 1H, H7), 7.98 (d, J = 7.4 Hz, 1H, H5).

k) (2RS)-Diazomethyl 4-keto-8-methoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 113, a small sample was recrystallised from ether/hexane to afford 113 as yellow prisms,

m.p. 100-102°C.

IR (CHCl₃) 2950, 2105, 1685, 1640 cm⁻¹.

1H NMR (300 MHz, CDCl₃) δ 2.70-2.95 (m, 3H, H1 and H3 x 2), 3.05 (m, 1H, H2), 3.27 (dd, J = 3.8, 17.0 Hz, 1H, H1), 3.86 (s, 3H, OMe), 5.45 (br s, 1H, COCHN₂), 7.04 (d, J = 7.9 Hz, 1H, H7), 7.29 (t, J = 7.9 Hz, 1H, H6), 7.63 (d, J = 7.9 Hz, 1H, H5).

13C NMR (75 MHz, CDCl₃) δ 25.7 (C1), 40.4 (C3), 44.9 (C2), 54.4 (COCHN₂), 55.7 (OMe), 114.8 (C7), 127.3 (C5), 127.4 (C8a), 156.7 (C8), 194.2 (C4), 196.5 (COCHN₂).

MS (EI) m/z 244(M⁺, 3%), 216 (50), 174 (100), 161 (67), 131 (28), 115 (20), 90 (70).

HRMS (EI) m/z calc'd for M⁺ - N₂, C₁₃H₁₂O₃: 216.0786, found 216.0787.

l) (2RS)-Diazomethyl 2-t-butyldimethylsilyloxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 120, isolated as a yellow oil,

IR (CHCl₃) 2930, 2100, 1720, 1585 cm⁻¹.

1H NMR (300 MHz, CDCl₃) δ -0.32 (s, 3H, SiCH₃), 0.12 (s, 3 H, SiCH₃), 0.86 (s, 9H, Si[C(CH₃)₃]), 1.88 (m, 2H, H3), 2.76 (dt, J = 4.9, 12.0 Hz, 1H, H4), 2.86 (d, J = 18.2 Hz, 1H, H1), 3.00 (m, 1H, H4), 3.32 (d, J = 18.2 Hz, 1H, H1), 3.81 (s, 3H, OMe), 5.84 (br s, 1H, COCHN₂), 6.66 (d, J = 7.9 Hz, 1H, H7), 6.68 (d, J = 7.9 Hz, 1H, H6), 7.10 (t, J = 7.9 Hz, 1H, H5).

13C NMR (75 MHz, CDCl₃) δ -3.7 (CH₃Si), -2.9 (CH₃Si), 18.3 (C-Si), 25.4 (C3), 25.9 ([CH₃]₃C-Si), 31.5 (C1 or C4), 33.6 (C4 or C1), 52.1 (COCHN₂), 55.2 (OMe),
79.6 (C2), 107.0 (C7), 120.5 (C6), 122.9 (C8a), 126.1 (C5), 136.4 (C4a), 157.3 (C8), 199.4 (COCHN2).

**MS** (EI) m/z 332 (M+ - N2, 2%), 318 (3), 303 (3), 291 (61), 275 (59), 247 (94), 228 (31), 159 (30), 115 (24), 73 (100), 59 (18).

**HRMS** (EI) m/z calc'd for M+ - N2, C19H28SiO3: 332.1808, found 332.1808.

### 6.2.3 CYCLOPROPANATIONS

#### General Procedure

The diazoketone (1 mmole), in dry dichloromethane [for Rh (II) reactions] or 1,2-dichloroethane [for Cu (II) reactions], was added via a syringe pump at a rate of 0.15 ml/min to a solution of the catalyst (2 mole %) in dichloromethane or 1,2-dichloroethane at reflux. Upon addition, the solution was refluxed for 5 min and the solvent removed *in vacuo* (no heating). The residue was dissolved in CDCl3 and the 1H NMR spectrum was recorded. The ratio of products was determined by comparison of the olefinic protons to the aromatic protons. The green oil was chromatographed using MPLC with ethyl acetate/hexane mixtures as eluants to afford the products.

The results are tabulated for each catalyst used, with the 1H NMR yield first and the isolated yield in parentheses.
i) Reactions of (2RS)-Diazomethyl 1,2,3,4-tetrahydro-2-naphthyl ketone 62

The reaction mixture was purified by MPLC (10% ethyl acetate/hexane). In order of elution;

1) (5RS,8RS)-5,6,8,9-Tetrahydro-5,8-methano-7H-benzocyclohepten-7-one 67, as a clear oil. This compound has been reported in the literature but the $^1$H NMR spectrum was run at 60MHz and poorly tabulated. A complete set of data was obtained,

$^1$H NMR (300 MHz, CDCl$_3$) δ 2.16 (ddd, J = 1.0, 2.9, 11.4 Hz, H$_1$O), 2.33 (dd, J = 3.3, 17.6 Hz, H$_1$H$_6$), 2.34 (m, obscured, 1H, H10), 2.54 (dd, J = 6.7, 17.6 Hz, 1H, H6), 2.77 (m, 1H, H8), 2.96 (d, J = 17.0 Hz, H9a), 3.15 (dd, J = 5.7, 17.0 Hz, 1H, H9b), 4.45 (m, 1H, H5), 7.00-7.20 (m, 4H, H1, H2, H3 and H4).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 33.6 (CH$_2$), 34.0 (CH$_2$), 38.1 (C6), 45.2 (C8), 49.8 (C5), 126.2 (CH), 126.9 (CH), 127.1 (CH), 129.1 (CH), 132.5 (C9a), 142.7 (C4a), 221.1 (C7).

MS (EI) m/z 172 (M+, 74%), 154 (5), 144 (8), 129 (100), 115 (53), 91 (11), 77 (10), 63 (15), 51 (16).

HRMS (EI) m/z calc'd for C$_{12}$H$_{12}$O: 172.0888, found 172.0892.
2) (3RS,4aSR,4bRS,10bRS)-2,3-Dihydro-1H-3,4b-methanocycloprop[1,2:1,3]dibenzene-4(4aH)-one 63, a small sample was sublimed at 50°C at 0.01 mm Hg to afford 66 as a white solid, m.p. 73-75°C.

IR (CHCl₃) 2940, 1710 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ 0.58 (s, 1H, H₄a), 1.86 (m, 2H, H₂ x 2), 1.96 (d, J = 11.9 Hz, 1H, H₉a), 2.08 (m, 1H, H₁a), 2.20-2.40 (m, 2H, H₃ and H₁P), 2.52 (m, 1H, H₉β), 6.02 (m, 3H, H₅, H₆, and H₇), 6.23 (m, 1H, H₈).

¹³C NMR (75 MHz, CDCl₃) δ 22.6 (C₁), 27.5 (C₂), 30.9 (C₉), 32.6 (C₄a), 42.1 (C₃), 45.0 (C₄b or C₈a), 48.1 (C₈a or C₄b), 122.3 (CH), 122.6 (CH), 129.6 (CH), 131.0 (CH), 216.9 (C₄).

MS (El) m/z 172 (M⁺, 24%), 144 (19), 129 (100), 116 (97), 103 (60), 91 (14), 77 (39), 63 (33), 51 (44).

HRMS (El) m/z calc’d for C₁₂H₁₂O: 172.0888, found 172.0887.

Analysis calc’d for C₁₂H₁₂O: C, 83.69; H, 7.02; found: C, 83.71; H, 7.38.

ii) Reactions of (2RS)-Diazomethyl 5-methoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 70

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The reaction mixture was purified by MPLC (15% ethyl acetate/hexane). In order of elution;

1) (5RS,8RS)-4-Methoxy-5,6,8,9-tetrahydro-5,8-methano-7H-benzocyclohepten-7-one 72, a small sample was recrystallised from ether/pentane to give 73 as a white amorphous solid, m.p. 51.5-53°C.

IR (CHCl3) 2960, 1740, 1580 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ 2.05 (ddd, J = 1.0, 2.1, 11.7 Hz, 1H, H10), 2.27 (dd, J = 3.4, 17.6 Hz, 1H, H6), 2.32 (m, obscured, 1H, H10), 2.50 (dd, J = 6.6, 17.6 Hz, 1H, H6), 2.74 (m, 1H, H8), 2.94 (d, J = 17.5 Hz, H9α), 3.15 (dd, J = 5.5, 17.5 Hz, 1H, H9β), 3.83 (s, 3H, OMe), 3.96 (m, 1H, H5), 6.69 (d, J = 7.8 Hz, 2H, H1 and H3), 7.12 (t, J = 7.8 Hz, 1H, H2).

¹³C NMR (75 MHz, CDCl₃) δ 30.0 (CH₂), 33.4 (CH₂), 34.2 (CH₂), 45.1 (C8), 49.0 (C5), 55.4 (OMe), 107.7 (C3), 121.3 (C2 or C1), 127.1 (C1 or C2), 131.4 (C9a), 133.9 (C4a), 155.3 (C4), 221.8 (C7).

MS (EI) m/z 202 (M⁺, 92%), 187 (4), 174 (6), 159 (100), 144 (42), 129 (41), 115 (83), 103 (12), 91 (29), 77 (31), 63 (40), 51 (47).

HRMS (EI) m/z calc'd for C₁₃H₁₄O₂: 202.0994, found 202.0100.

Analysis calc'd for C₁₃H₁₄O₂: C, 77.20; H, 6.98; found: C, 77.02; H, 7.09.

2) (3RS,4aSR,4bRS,10bRS)-8-Methoxy-2,3-dihydro-1H-3,4b-methanocyclop[1,2;1,3]dibenzene-4(4aH)-one 71, an attempt to sublime a small sample resulted in decomposition of the compound, m.p. 45-47°C.

IR (CHCl₃) 2970, 1710 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ 0.84 (d, J = 1.6 Hz, 1H, H4a), 1.80 (m, 2H, 2 x H2), 1.95 (d, J = 11.8 Hz, 1H, H9α), 2.00 (m, 1H, H1α), 2.24 (m, 1H, H3), 2.47 (m, 1H, H9β), 2.57 (m, 1H, H1β), 3.60 (s, 3H, OMe), 5.10 (d, J = 6.8 Hz, 1H, H7), 5.78 (d, J = 9.1 Hz, 1H, H6), 5.96 (dd, J = 6.8, 9.1 Hz, 1H, H5).
$^{13}$C NMR (75 MHz, CDCl$_3$) δ 17.6 (C1), 27.1 (C2), 30.5 (C9), 32.6 (C4a), 41.6 (C3), 45.3 (C4b or C8a), 46.4 (C8a or C4b), 55.2 (OMe), 93.1 (C7), 120.8 (C6), 122.9 (C5), 160.1 (C8), 216.4 (C4).

**MS** (EI) m/z 202 (M+, 98%), 174 (26), 159 (100), 146 (86), 131 (38), 115 (68), 103 (69), 91 (43), 77 (67), 63 (50), 51 (77).

**HRMS** (EI) m/z calc’d for C$_{13}$H$_{14}$O$_2$: 202.0994, found 202.0994.

### iii) Reactions of (2RS)-Diazomethyl 6-methoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 73

![Chemical structure of 73, 74, 75, and 86](image)

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The reaction mixture was purified by MPLC (15% ethyl acetate/hexane). The cyclobutanone 86 was only characterised by $^1$H NMR due to the small amount isolated. In order of elution:

1) (2aRS,8bRS)-6-Methoxy-1,2,2a,8b,3,4-hexahydrocyclobuta[a]naphthalen-2-one 86, isolated as a clear oil,
\( ^1\text{H NMR} \) (300 MHz, CDCl$_3$) \( \delta \) 1.705 (m, 1H, H3\( \beta \)), 2.06 (m, 1H, H3\( \alpha \)), 2.65 (m, 2H, H4 x 2), 2.79 (m, 1H, H1\( \alpha \)), 3.52 (m, 1H, H1\( \beta \)), 3.69 (m, 1H, H2a), 3.85 (s, 3H, OMe), 3.87 (obscured, m, 1H, H8b), 6.64 (d, \( J = 2.3 \text{ Hz} \), 1H, H4), 6.74 (dd, \( J = 2.3, 8.4 \text{ Hz} \), 1H, H2), 6.99 (d, \( J = 8.4 \text{ Hz} \), 1H, H1).

2) (5RS,8RS)-3-Methoxy-5,6,8,9-tetrahydro-5,8-methano-7H-benzocyclohepten-7-one 75, isolated as a clear oil which slowly crystallised on standing, m.p. 54-56°C.

IR (CHCl$_3$) 2960, 1740, 1610, 1505 cm$^{-1}$.

\( ^1\text{H NMR} \) (300 MHz, CDCl$_3$) \( \delta \) 2.15 (dd, \( J = 3.3, 11.6 \text{ Hz} \), 1H, H10), 2.32 (dd, \( J = 3.4, 17.8 \text{ Hz} \), 1H, H6), 2.33 (m, obscured, 1H, H10), 2.52 (dd, \( J = 6.4, 17.8 \text{ Hz} \), 1H, H6), 2.74 (m, 1H, H8), 2.90 (d, \( J = 17.5 \text{ Hz} \), H9\( \alpha \)), 3.07 (dd, \( J = 5.5, 16.5 \text{ Hz} \), 1H, H9\( \beta \)), 3.37 (m, 1H, H5), 3.78 (s, 3H, OMe), 6.00 (d, \( J = 2.6 \text{ Hz} \), 1H, H4), 6.71 (dd, \( J = 2.6, 8.5 \text{ Hz} \), 1H, H2), 6.98 (d, \( J = 8.5 \text{ Hz} \), 1H, H1).

\( ^{13}\text{C NMR} \) (75 MHz, CDCl$_3$) \( \delta \) 33.3 (CH$_2$), 33.6 (CH$_2$), 38.5 (C6), 45.3 (C8), 49.6 (C5), 55.2 (OMe), 112.3 (C4 or C2), 112.5 (C2 or C4), 124.2 (C9a), 130.2 (C1), 143.9 (C4a), 157.8 (C3), 221.2 (C7).

MS (EI) \( \text{m/z} \) 202 (M$^+$, 100%), 187 (5), 174 (9), 159 (59), 144 (28), 128 (30), 115 (65), 103 (15), 91 (29), 77 (27), 63 (33), 51 (43).

Analysis calc’d for C$_{13}$H$_{14}$O$_2$: C, 77.20; H, 6.98; found: C, 77.05; H, 7.19.

3) (3RS,4aSR,4bRS,10bRS)-7-Methoxy-2,3-dihydro-1H-3,4b-methanocycloprop[1,2:1,3]dibenzene-4(4aH)-one 74, a small sample was sublimed at 72°C at 0.1 mm Hg to give 74 as fine needles, m.p. 69-71°C.

IR (CHCl$_3$) 2950, 1710, 1650, 1580 cm$^{-1}$.

\( ^1\text{H NMR} \) (300 MHz, CDCl$_3$) \( \delta \) 0.68 (d, \( J = 1.6 \text{ Hz} \), 1H, H4a), 1.80 (m, 2H, H2), 1.90 (d, \( J = 11.8 \text{ Hz} \), 1H, H9\( \alpha \)), 2.10 (m, 1H, H1\( \alpha \)), 2.20-2.40 (m, 2H, H3 and H1\( \beta \)), 2.44 (m, 1H, H9\( \beta \)), 3.52 (s, 3H, OMe), 4.95 (d, \( J = 1.8 \text{ Hz} \), 1H, H8), 5.78 (dd, \( J = 1.8, 9.7 \text{ Hz} \), 1H, H6), 5.96 (d, \( J = 9.7 \text{ Hz} \), 1H, H5).
\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 23.7 (C1), 27.1 (C2), 32.4 (C9), 33.4 (C4a), 42.2 (C3), 42.7 (C4b or C8a), 47.1 (C8a or C4b), 54.5 (OMe), 100.0 (C8), 122.0 (C6), 131.9 (C5), 153.6 (C7), 216.0 (C4).

MS (EI) \(m/z\) 202 (M\(^+\), 60%), 187 (6), 174 (29), 159 (71), 146 (57), 133 (100), 115 (39), 103 (31), 91 (35), 77 (50), 63 (38), 51 (68).

HRMS (EI) \(m/z\) calc'd for C\(_{13}\)H\(_{14}\)O\(_2\): 202.0994, found 202.0994.

Analysis calc'd for C\(_{13}\)H\(_{14}\)O\(_2\): C, 77.20; H, 6.98; found: C, 76.88; H, 7.09.

iv) Reactions of (2RS)-Diazomethyl 7-methoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 77

From the \(^1\)H NMR spectrum the norcaradiene 77 was present but attempts to purify it resulted in instantaneous rearrangement to the enone 82. The NMR spectra of the norcaradiene are presented below followed by the products obtained after MPLC (15% ethyl acetate/hexane);
1) (3RS,4aSR,4bRS,10bRS)-6-methoxy-2,3-dihydro-1H-3,4b-methanocycloprop[1,2;1,3]dibenzene-4(4aH)-one 77,

**1H NMR** (300 MHz, CDCl₃) δ 0.66 (s, 1H, H₄a), 1.84 (m, 2H, H₂), 1.97 (d, J = 11.7 Hz, 1H, H₉α), 2.05 (m, 1H, H₁α), 2.25-2.42 (m, 2H, H₃ and H₁ß), 2.45 (m, 1H, H₉ß), 3.57 (s, 3H, OMe), 5.13 (d, J = 2.1 Hz, 1H, H₅), 5.85 (dd, J = 2.1, 9.9 Hz, 1H, H₇), 6.04 (d, J = 9.9 Hz, 1H, H₈).

**13C NMR** (75 MHz, CDCl₃) δ 23.7 (C₁), 27.1 (C₂), 32.4 (C₉), 33.4 (C₄a), 42.2 (C₃), 42.7 (C₄b or C₈a), 47.1 (C₈a or C₄b), 54.5 (OMe), 100.0 (C₈), 122.0 (C₆), 131.9 (C₅), 153.6 (C₇), 216.0 (C₄).

2) (5RS,8RS)-2-Methoxy-5,6,8,9-tetrahydro-5,8-methano-7H-benzocyclohepten-7-one 78, isolated as a clear oil which slowly crystallised on standing, m.p. 54-55°C.

**IR** (CHCl₃) 2960, 1740, 1610, 1500 cm⁻¹.

**1H NMR** (300 MHz, CDCl₃) δ 2.14 (dd, J = 3.2, 11.6 Hz, 1H, H₁₀), 2.26-2.35 (m, 2H, H₆ and H₁₀), 2.51 (dd, J = 6.0, 17.6 Hz, 1H, H₆), 2.74 (m, 1H, H₈), 2.93 (d, J = 17.2 Hz, H₉α), 3.13 (dd, J = 5.6, 17.2 Hz, 1H, H₉ß), 3.41 (m, 1H, H₅), 3.78 (s, 3H, OMe), 6.61 (d, J = 2.3 Hz, 1H, H₁), 6.68 (dd, J = 2.3, 8.5 Hz, 1H, H₃), 6.98 (d, J = 8.5 Hz, 1H, H₄).

**13C NMR** (75 MHz, CDCl₃) δ 34.0 (CH₂), 34.3 (CH₂), 37.4 (C₆), 45.1 (C₈), 49.9 (C₅), 55.2 (OMe), 112.1 (C₁ or C₃), 113.9 (C₃ or C₁), 128.0 (C₄), 133.7 (C₄a or C₉a), 135.0 (C₉a or C₄a), 158.5 (C₂), 221.4 (C₇).

**MS** (EI) m/z 202 (M⁺, 56%), 187 (2), 174 (3), 159 (100), 144 (31), 128 (17), 115 (28), 91 (13), 77 (12), 63 (14), 51 (18).

**HRMS** (EI) m/z calc'd for C₁₃H₁₄O₂: 202.0994, found 202.0994.

**Analysis** calc'd for C₁₃H₁₄O₂: C, 77.20; H, 6.98; found: C, 77.47; H, 7.27.

3) (4aRS,7SR)-3-Methoxy-5,6-dihydro-4a,7-methano-4aH-benzocyclohepten-8(7H)-one 82, isolated as a yellow gel,

**IR** (CHCl₃) 2950, 1670, 1565 cm⁻¹.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.50 (m, 1H, H10), 1.75-1.95 (m, 4H, H5 x 2 and H6 x 2), 2.28 (m, 1H, H10), 3.08 (m, 1H, H7), 3.61 (s, 3H, OMe), 4.87 (d, $J = 1.7$ Hz, 1H, H3), 5.82 (s, 1H, H9), 6.21 (dd, $J = 1.7$, 9.5 Hz, 1H, H2), 6.29 (d, $J = 9.5$ Hz, 1H, H1).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 23.2 (CH$_2$), 38.5 (CH$_2$), 48.1 (C4a), 49.7 (C10), 52.4 (C7), 54.5 (OMe), 105.1 (C4), 123.6 (C9), 126.1 (C2), 130.8 (C1), 151.9 (C9a), 164.3 (C3), 203.0 (C8).

MS (EI) m/z 202 (M$^+$, 6%), 188 (47), 160 (27), 147 (74), 132 (17), 117 (41), 91 (86), 77 (46), 65 (52), 51 (100).

HRMS (EI) m/z calc'd for C$_{13}$H$_{14}$O$_2$: 202.0994, found 202.0994.

v) Reactions of (2RS)-Diazomethyl 8-methoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 79

$$\begin{align*}
\text{COCH}_2 & \rightarrow \text{O} \\
\text{79} & \rightarrow \text{80} + \text{81} + \text{87}
\end{align*}$$

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The reaction mixture was purified by MPLC (15% ethyl acetate/hexane). In order of elution;

1) (2aRS,8bRS)-8-Methoxy-1,2,2a,8b,3,4-hexahydrocyclobuta[a]naphthalen-2-one 87, isolated as a clear oil,

IR (CHCl₃) 2950, 1775, 1585, 1470 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ 1.75 (m, 1H, H₃P), 2.10 (m, 1H, H₃α), 2.68 (m, 2H, H₄ x 2), 2.75 (m, 1H, H₁α), 3.59 (m, 1H, H₁β), 3.72 (m, 1H, H₂a), 3.84 (s, 3H, OMe), 3.86 (obscured, m, 1H, H₈b), 6.76 (d, J = 7.9 Hz, 2H, H₅ and H₇), 7.15 (t, J = 7.9 Hz, 1H, H₆).

¹³C NMR (75 MHz, CDCl₃) δ 21.6 (C₃), 21.7 (C₈b), 27.6 (C₄), 53.9 (C₁), 55.4 (OMe), 57.9 (C₂a), 108.0 (C₇), 121.1 (C₆), 126.6 (C₈a), 127.8 (C₅), 138.3 (C₄a), 157.6 (C₈), 213.4 (C₂).

MS (EI) m/z 202 (M⁺, 2%), 160 (100), 145 (20), 129 (21), 115 (29), 91 (15), 77 (12), 63 (13), 51 (16).

HRMS (EI) m/z calc’d for C₁₃H₁₄O₂: 202.0994, found 202.0994.

Analysis calc’d for C₁₃H₁₄O₂: C, 77.20; H, 6.98; found: C, 77.10; H, 7.91.

2) (5RS,8RS)-1-Methoxy-5,6,8,9-tetrahydro-5,8-methano-7H-benzocyclohepten-7-one 81, isolated as a clear oil,

IR (CHCl₃) 2960, 1740, 1585, 1470 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ 2.14 (dd, J = 3.2, 11.6 Hz, 1H, H₁₀), 2.26-2.35 (m, 2H, H₆ and H₁₀), 2.51 (dd, J = 6.0, 17.6 Hz, 1H, H₆), 2.74 (m, 1H, H₈), 2.93 (d, J = 17.2 Hz, 1H, H₉α), 3.13 (dd, J = 5.6, 17.2 Hz, 1H, H₉β), 3.41 (m, 1H, H₅), 3.78 (s, 3H, OMe), 6.61 (d, J = 2.3 Hz, 1H, H₁), 6.68 (dd, J = 2.3, 8.5 Hz, 1H, H₃), 6.98 (d, J = 8.5 Hz, 1H, H₄).

¹³C NMR (75 MHz, CDCl₃) δ 29.6 (CH₂), 33.4 (CH₂), 38.0 (C₆), 44.9 (C₈), 49.5 (C₅), 55.1 (OMe), 108.2 (C₂), 119.3 (C₃), 121.0 (C₄), 133.7 (C₄a or C₉a), 135.0 (C₉a or C₄a), 158.5 (C₁), 221.4 (C₇).
**MS** (EI) m/z 202 (M+, 100%), 187 (5), 174 (8), 159 (75), 144 (40), 128 (40), 115 (85), 103 (16), 91 (32), 77 (32), 63 (34), 51 (48).

**HRMS** (EI) m/z calc'd for C_{13}H_{14}O_2: 202.0994, found 202.0994.

3) (3RS,4aSR,4bRS,10bRS)-5-Methoxy-2,3-dihydro-1H-3,4b-methanocycloprop[1,2:1,3]dibenzene-4(4aH)-one 80, a small sample was sublimed at 55°C at 0.01 mm Hg to afford 81 as white prisms, m.p. 95-97°C.

**IR** (CHCl₃) 2950, 1715, 1560 cm⁻¹.

**¹H NMR** (300 MHz, CDCl₃) δ 0.80 (d, J = 1.6 Hz, 1H, H₄a), 1.83 (d, J = 22.3 Hz, 1H, H₉α), 1.90 (m, 2H, H₂ x 2), 2.11 (m, 1H, H₁α), 2.28 (m, 1H, H₁β), 2.30 (m, 1H, H₃), 2.81 (m, 1H, H₉β), 3.68 (s, 3H, OMe), 5.11 (d, J = 7.0 Hz, 1H, H₆), 5.62 (d, J = 9.4 Hz, 1H, H₈), 5.92 (dd, J = 7.0, 9.9 Hz, 1H, H₇).

**¹³C NMR** (75 MHz, CDCl₃) δ 22.3 (Cl), 27.4 (C₂), 28.0 (C₉), 30.9 (C₄a), 41.6 (C₃), 43.6 (C₄b or C₈a), 48.4 (C₈a or C₄b), 55.5 (OMe), 91.9 (C₆), 122.0 (C₇ or C₈), 122.6 (C₈ or C₇), 158.5 (C₅), 217.0 (C₄).

**MS** (EI) m/z 202 (M⁺, 82%), 187 (7), 174 (25), 159 (100), 146 (91), 133 (83), 115 (79), 103 (77), 91 (47), 77 (70), 63 (50), 51 (70).

**Analysis** calc'd for C_{13}H_{14}O_2: C, 77.20; H, 6.98; found: C, 76.85; H, 7.17.

vi) Reactions of (2RS)-Diazomethyl 6-hydroxy-1,2,3,4-tetrahydro-2-naphthyl ketone 88

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<td>Rh₂(OAc)₄</td>
<td>61 (55)</td>
<td>25</td>
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Although the reaction mixture was purified by MPLC (50% ethyl acetate/hexane), the only isolable product was the dienedione 89 due to the scale of the reaction. The cyclopentanone 90 was identified by the $^1$H NMR signal at 3.35 ppm and the alkene 91 by the $^1$H NMR signals at 5.90 and 6.65 ppm.

(4aRS,7SR)-8,9-Dihydro-4a,7-methano-4aH-benzocyclohepten-2(7H),6(5H)-one 89 was isolated as a crystalline solid, m.p. 113-115°C (lit. m.p. 113-115°C).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.66-1.80 (m, 2H, H2), 2.10 (m, 1H, H1), 2.28 (dd, J = 3.3, 18.3 Hz, 1H, H9α), 2.34 (m, 1H, H1), 2.49 (d, J = 18.3 Hz, 1H, H9β), 2.51 (m, 1H, H4), 2.61 (dd, J = 6.6, 15.9 Hz, 1H, H4), 2.75 (m, 1H, H3), 6.14 (d, J = 1.9 Hz, 1H, H5), 6.36 (dd, J = 1.9, 9.9 Hz, 1H, H6), 6.81 (d, J = 9.9 Hz, 1H, H8).

vii) Reactions of (2RS)-Diazomethyl 8-hydroxy-1,2,3,4-tetrahydro-2-naphthyl ketone 92

\[
\begin{array}{c}
\text{COCHN}_2 \\
\text{OH}
\end{array} \rightarrow \begin{array}{c}
\text{CO} \\
\text{O}
\end{array} + \begin{array}{c}
\text{CO} \\
\text{O}
\end{array} + \begin{array}{c}
\text{OH} \\
\text{OH}
\end{array}
\]

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<td>39 (35)</td>
<td>45</td>
<td>16</td>
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Although the reaction mixture was purified by MPLC (50% ethyl acetate/hexane), the only isolable product was the dienedione 93 due to the scale of the reaction. The cyclopentanone 94 was identified by the $^1$H NMR signal at 3.42 ppm and the alkene 95 by the $^1$H NMR signals at 5.60 and 5.85 ppm.
(4aRS,7RS)-8,9-Dihydro-4a,7-methano-4aH-benzocyclohepten-4(7H),6(5H)-one 93 was isolated as a crystalline solid, m.p. 57-59°C (lit72 m.p. 57-58°C).

1H NMR (300 MHz, CDCl3) δ 1.50-1.90 (m, 3H, H2 and H4), 2.10 (m, 1H, H1), 2.25 (dd, J = 5.1, 15.2 Hz, 1H, H9α), 2.41 (m, 1H, H1), 2.56 (dd, J = 5.1, 10.2 Hz, 1H, H9β), 2.80 (m, 1H, H3), 3.02 (d, J = 15.2 Hz, 1H, H4), 6.10 (d, J = 5.1 Hz, 1H, H5), 6.15 (d, J = 9.7 Hz, 1H, H6), 7.12 (dd, J = 5.1, 9.7 Hz, 1H, H7).

viii) Reactions of (2RS)-Diazomethyl 6,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 96

\[
\begin{array}{ccc}
\text{MeO} & \text{COCHN}_2 & \text{MeO} \\
\text{MeO} & \text{MeO} & \text{MeO} \\
96 & + & 97, 98, 99 \\
\end{array}
\]

\[
\begin{array}{ccc}
\text{MeO} & \text{OMe} & \text{MeO} \\
\text{MeO} & \text{OMe} & \text{MeO} \\
97 & + & 98, 99 \\
\end{array}
\]

\[
\begin{array}{ccc}
\text{MeO} & \text{OMe} & \text{MeO} \\
\text{MeO} & \text{OMe} & \text{MeO} \\
103 & + & 106 \\
\end{array}
\]

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<td>39 (0)</td>
<td>32 (30)</td>
<td>23 (20)</td>
<td>0 (38)</td>
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From the 1H NMR spectrum, the norcaradiene 97 was present but attempts to purify it resulted in an instantaneous rearrangement to the dienenone 103. The 1H NMR spectrum of norcaradiene is presented below and the products after MPLC (25% ethyl acetate/hexane) in order of elution;
1) (3RS,4aSR,4bRS,10bRS)-5,7-Dimethoxy-2,3-dihydro-1H-3,4b-methanocycloprop[1,2:1,3]dibenzen-4(4aH)-one 97.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.90 (s, 1H, H4a), 1.70-2.30 (m, 7H, H1 x 2, H2 x 2, H9 x 2 and H3), 3.53 (s, 3H, OMe), 3.65 (s, 3H, OMe), 4.65 (s, 1H, H6), 4.95 (s, 1H, H8).

2) 5,7-Dimethoxy-1,2-dihydronaphthalene 99, isolated as a clear oil. This compound has been reported in the literature$^76$ but the $^1$H NMR spectrum was run at 60MHz and poorly tabulated. Complete data was therefore obtained,

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.26 (m, 1H, H2), 2.73 (t, $J = 8.2$ Hz, 1H, H1), 3.81 (s, 3H, OMe), 5.90 (dt, $J = 4.4$, 9.6 Hz, 1H, H3), 6.31 (s, 2H, H6 and H8), 6.75 (dt, $J = 1.8$, 9.6 Hz, 1H, H4).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 22.8 (C1), 28.5 (C2), 55.3 (OMe), 55.5 (OMe), 96.3 (C4), 104.8 (C3), 121.2 (C8 or C6), 124.8 (C8a), 138.1 (C4a), 155.8 (C5), 159.1 (C7).

MS (EI) m/z 190 (M$^+$, 100%), 175 (40), 159 (20), 147 (15), 115 (28), 103 (10), 91 (9), 77 (46), 77 (8), 63 (3), 51 (3).

3) (5RS,8RS)-1,3-Dimethoxy-5,6,8,9-tetrahydro-5,8-methano-7H-benzocyclohepten-7-one 98, isolated as a clear oil,

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.10 (dd, $J = 3.0$, 11.6 Hz, 1H, H10), 2.25 (m, obscured, 1H, H10), 2.32 (dd, $J = 3.3$, 17.6 Hz, 1H, H6), 2.50 (dd, $J = 6.0$, 17.6 Hz, 1H, H6), 2.70-2.90 (m, 3H, H8 and H9 x 2), 3.35 (m, 1H, H5), 3.78 (s, 3H, OMe), 3.80 (s, 3H, OMe), 6.22 (d, $J = 1.5$ Hz, 1H, H2), 6.30 (d, $J = 1.5$ Hz, 1H, H4).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 29.1 (CH$_2$), 33.5 (CH$_2$), 38.5 (CH$_2$), 44.9 (C8), 49.4 (C5), 55.2 (OMe), 55.3 (OMe), 96.4 (C2), 103.1 (C4), 113.1 (C9a), 144.5 (C4a), 158.5 (C1 or C3), 159.1 (C3 or C1), 221.2 (C7).

MS (EI) m/z 232 (M$^+$, 100%), 191 (82), 175 (23), 159 (17), 128 (20), 115 (65), 103 (29), 91 (39), 77 (46), 63 (33), 51 (47).

HRMS (EI) m/z calc'd for C$_{14}$H$_{16}$O$_3$: 232.1099, found 232.1100.
4) (4aRS,7SR)-4-Methoxy-8,9-dihydro-4a,7-methano-4aH-benzocyclohepten-2(7H),6(5H)-dione 103, isolated as pale yellow crystals, m.p. 180-182°C (lit. m.p. 181-182°C).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.72 (dd, J = 3.4, 11.6 Hz, 1H, H2), 1.77 (m, 1H, H2), 2.08 (m, 1H, H3), 2.19 (dd, J = 3.0, 19.0 Hz, 1H, H9), 2.40 - 2.80 (m, 4H, H1 x 2 and H4 x 2), 2.94 (d, J = 19.0 Hz, 1H, H9), 3.77 (s, 3H, OMe), 5.67 (d, J = 1.5 Hz, 1H, H3), 6.03 (d, J = 1.5 Hz, 1H, H8).

5) In some runs, compound 106 was observed by $^1$H NMR spectroscopy, (4aRS,7SR)-2,4-Dimethoxy-7,8-dihydro-4a,7-methano-4aH-benzocyclohepten-6(5H)-one 106,

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.00 (m, 1H), 2.25 (m, 1H), 2.45 (d, J = 17.6 Hz, 1H), 2.50-2.80 (m, 4H), 3.60 (s, 3H, OMe), 3.62 (s, 3H, OMe), 4.93 (br s, 2H, H1 and H3), 5.10 (br t, 1H, H9).

ix) Reactions of (2RS)-Diazomethyl 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 100

![Chemical structure]

<table>
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<td>66 (0)</td>
<td>33 (31)</td>
<td>0 (64)</td>
</tr>
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</table>

From the $^1$H NMR spectrum, the norcaradiene 101 was present but attempts to purify it resulted in instantaneous rearrangement to the enone 104. The
The H NMR spectrum of the norcaradiene is presented below followed by the products after MPLC (25% ethyl acetate/hexane) in order of elution;

1) \((3RS,4aSR,4bRS,10bRS)-6,7\text{-Dimethoxy-2,3-dihydro-1H-3,4b-methanocyclopenta[1,2:1,3]dibenzene-4(4aH)-one}\) 101,

**1H NMR** (300 MHz, CDCl3) \(\delta\)
- 0.72 (s, 1H, H4a),
- 1.75-1.85 (m, 2H, H2),
- 1.92 (d, \(J = 11.8\) Hz, 1H, H9a),
- 2.00 - 2.40 (m, 4H, H1 x 2, H9b and H3),
- 3.58 (s, 3H, OMe),
- 3.63 (s, 3H, OMe),
- 5.05 (s, 1H, H5),
- 5.20 (s, 1H, H8).

2) \((5RS,8RS)-2,3\text{-Dimethoxy-5,6,8,9-tetrahydro-5,8-methano-7H-benzocyclohepten-7-one}\) 102, a small sample was recrystallised from ether/pentane to give 102 as a white amorphous solid,

**m.p.** 125-126°C.

**IR** (CHCl3) 2960, 1740, 1610, 1515 cm⁻¹.

**1H NMR** (300 MHz, CDCl3) \(\delta\)
- 2.15 (dd, \(J = 3.0, 11.6\) Hz, 1H, H10),
- 2.30 (dd, \(J = 3.3, 17.6\) Hz, 1H, H6),
- 2.32 (m, obscured, 1H, H10),
- 2.51 (dd, \(J = 6.0, 17.6\) Hz, 1H, H6),
- 2.74 (m, 1H, H8),
- 2.88 (d, \(J = 17.0\) Hz, 1H, H9a),
- 3.09 (dd, \(J = 5.7, 17.0\) Hz, 1H, H9b),
- 3.35 (m, 1H, H5),
- 3.63 (s, 3H, OMe),
- 3.66 (s, 3H, OMe),
- 6.56 (s, 2H, H1 and H4).

**13C NMR** (75 MHz, CDCl3) \(\delta\)
- 33.8 (CH2),
- 34.1 (CH2),
- 37.8 (CH2),
- 45.2 (C8),
- 49.9 (C5),
- 55.7 (OMe),
- 55.9 (OMe),
- 110.2 (C4 or C1),
- 111.9 (C1 or C4),
- 124.6 (C9a),
- 134.9 (C4a),
- 147.3 (C2 or C3),
- 147.9 (C3 or C2),
- 221.4 (C7).

**MS** (El) \(m/z\)
- 232 (M⁺, 100\%),
- 217 (7),
- 189 (71),
- 175 (18),
- 158 (14),
- 128 (18),
- 115 (43),
- 103 (26),
- 91 (28),
- 77 (31),
- 63 (22),
- 51 (34).

**HRMS** (El) \(m/z\) calc'd for C\(_{14}\)H\(_{16}\)O\(_3\): 232.1099, found 232.1099.

**Analysis** calc'd for C\(_{14}\)H\(_{16}\)O\(_3\): C, 72.39; H, 6.94; found: C, 72.05; H, 7.30.

3) \((4aRS,7SR)-2,3\text{-Dimethoxy-5,6-dihydro-4a,7-methano-4aH-benzocyclohepten-8(7H)-one}\) 104, isolated as a yellow gel, which was identical to an authentic sample,\(^\text{75}\)
1H NMR (300 MHz, CDCl₃) δ 1.55 (m, 1H, H10), 1.70-1.95 (m, 4H, H5 x 2 and H6 x 2), 2.23 (m, 1H, H10), 3.08 (m, 1H, H7), 3.68 (s, 3H, OMe), 3.82 (s, 3H, OMe), 5.02 (s, 1H, H1), 5.55 (s, 1H, H4), 5.82 (s, 1H, H9).

x) Reactions of (2RS)-Diazomethyl 4-keto-1,2,3,4-tetrahydro-2-naphthyl ketone 111

The reaction mixture was purified by MPLC (35% ethyl acetate/hexane) to afford (3RS,4aSR,4bRS,10bRS)-2,3-dihydro-1H,3,4b-methanocyclopropa-
[1,2:1,3]dibenzen-1,4(4aH)-dione 112 as a clear oil.

IR (CHCl₃) 3060, 2950, 1740, 1710, 1420 cm⁻¹.

1H NMR (300 MHz, CDCl₃) δ 1.04 (s, 1H, H4a), 2.14 (d, J = 12.5 Hz, 1H, H9α), 2.45 (dd, J = 1.1, 15.7 Hz, 1H, H9β), 2.60 (m, 2H, H2 x 2), 2.82 (m, 1H, H3), 6.20-6.30 (m, 3H, H5, H6 and H7), 6.70 (m, 1H, H8).

13C NMR (75 MHz, CDCl₃) δ 31.1 (C4a), 33.1 (C9), 39.0 (C3), 41.4 (C2), 45.1 (C4b), 55.6 (C8a), 122.5 (CH), 123.4 (CH), 124.2 (CH), 126.2 (CH), 200.0 (C1), 211.3 (C4).

MS (EI) m/z 186 (M⁺, 85%), 168 (9), 157 (17), 141 (38), 129 (80), 115 (100), 104 (24), 89 (32), 77 (35), 63 (52), 51 (64).

HRMS (EI) m/z calc'd for C₁₂H₁₀O₂: 186.0673, found 186.0681.
xi) Reactions of (2RS)-Diazomethyl 4-keto-8-methoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 113

\[
\begin{align*}
\text{O} & \quad \text{COCHN}_2 \\
\text{OMe} & \quad \text{O}
\end{align*}
\]

The crude reaction mixture was purified by MPLC (35% ethyl acetate/hexane) to afford \( (3R,4aS,4bS,10bR)-5\text{-methoxy-2,3-dihydro-1H-3,4b-methanocyclopropa[1,2:1,3]dibenzene-1,4(4aH)-dione 114} \) as a clear oil, IR (CHCl\(_3\)) 2940, 1730, 1710, 1645, 1560 cm\(^{-1}\).

\( ^1H \text{NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 1.18 (s, 1H, H4a), 1.98 (d, \( J = 12.7 \) Hz, 1H, H9\( \alpha \)), 2.42 (m, 1H, H9\( \beta \)), 2.58 (m, 2H, H2 x 2), 3.06 (m, 1H, H3), 3.71 (s, 3H, OMe), 5.25 (d, \( J = 6.6 \) Hz, 1H, H6), 6.12 (d, \( J = 9.4 \) Hz, 1H, H8), 6.18 (dd, \( J = 6.6, 9.4 \) Hz, 1H, H7).

\( ^{13}C \text{NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 29.2 (C4a), 31.3 (C9), 38.8 (C3), 41.4 (C2), 44.2 (C4b), 55.9 (OMe), 56.3 (C8a), 93.5 (C6), 113.7 (C7), 123.9 (C8), 155.5 (C5), 200.4 (C1), 211.6 (C4).

\( \text{MS (EI)} \) \( m/z \) 216 (M\(^+\), 39\%), 187 (18), 171 (10), 159 (29), 145 (41), 129 (31), 115 (79), 103 (38), 91 (55), 77 (67), 63 (77), 51 (100).

\( \text{HRMS (EI)} \) \( m/z \) calc'd for C\(_{13}\)H\(_{12}\)O\(_3\): 216.0787, found 216.0786.
xii) Reactions of (2RS)-Diazomethyl 2-t-butyldimethylsilyloxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthyl ketone 120

\[
\text{OTBDMS} \quad \text{COCHN}_2 \quad \text{OTBDMS} \quad \text{OTBDMS} \quad 0
\]

\[
\text{OMe} \quad \text{OMe} \quad 120 \quad 121 \quad 122 \quad 123
\]

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<td>Cu(acac)_2</td>
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Repeated chromatography, using MPLC (10% ethyl acetate/hexane), failed to yield pure material for any of the compounds. Accordingly, only NMR data for the norcaradiene 121 and the cyclobutanone 123 can be given,

1) (2aRS,8bRS)-2a-t-Butyldimethylsilyloxy-8-methoxy-1,2,2a,8b,3,4-hexahydrocyclobuta[a] naphthalen-2-one 123,

\( ^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 0.09 (SiCl\(_3\)), 0.19 (SiCH\(_3\)), 0.86 (SiC[CH\(_3\)]\(_3\)), 1.83 (ddd, \( J = 4.0, 14.1, 19.4 \) Hz, 1H, H3), 1.94 (dt, \( J = 3.5, 9.4 \) Hz, 1H, H3), 2.56-2.70 (m, 2H), 2.92 (m, 1H), 3.20-3.42 (m, 2H), 3.84 (s, 3H, OMe), 6.75 (d, \( J = 7.7 \) Hz, 1H, H7), 6.80 (d, \( J = 8.2 \) Hz, 1H, H6), 7.17 (dd, \( J = 7.7, 8.2 \) Hz, 1H, H5).

\( ^13\text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) -3.2 (2 \( x \) SiCH\(_3\)), 18.1 (SiC[CH\(_3\)]\(_3\)), 24.5 (C3), 25.7 (SiC[CH\(_3\)]\(_3\)), 29.4 (C4), 33.9 (C8b), 46.6 (C1), 55.3 (OMe), 88.3 (C2a), 107.8 (C7), 120.5 (C6), 125.1 (C4a), 126.9 (C5), 138.4 (C8a), 157.7 (C8), 210.2 (C2).

2) (3RS,4aSR,4bRS,10bRS)-3-t-Butyldimethylsilyloxy-5-methoxy-2,3-dihydro-1H-3,4b-methanocycloprop[1,2:1,3]dibenzene-4(4aH)-one 121,

\( ^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 0.11 (SiCH\(_3\)), 0.14 (SiCH\(_3\)), 0.48 (s, 1H, H4a), 0.87 (SiC[CH\(_3\)]\(_3\)), 1.83 (m, 1H, H2), 2.00 (d, \( J = 11.6 \) Hz, 1H, H9\( \alpha \)), 2.25 (m, 1H, H1),
2.36 (m, 1H, H1), 2.79 (d, J = 11.6 Hz, H9β), 2.92 (m, 1H, H2), 3.66 (s, 3H, OMe), 5.09 (d, J = 6.9 Hz, 1H, H6), 5.62 (d, J = 9.3 Hz, 1H, H7), 5.97 (dd, J = 6.9, 9.3 Hz, 1H, H8).

13C NMR (75 MHz, CDCl3) δ -2.5 (2 x SiCH3), 18.2 (SiC[CH3]3), 24.9 (C1), 25.8 (SiC[CH3]3), 26.1 (C4a), 35.2 (C2), 35.9 (C9), 41.7 (C8a), 47.7 (C4b), 55.6 (OMe), 78.2 (C3), 91.9 (C6), 121.4 (C8 or C7), 123.0 (C7 or C8), 158.5 (C5), 212.9 (C4).

6.2.4 Trapping Of Ketene

The apparatus was set up so that solvent could be distilled off throughout the addition of the diazoketone. The receiver flask of the distillation apparatus contained p-toluidine 107 (60 mg). The diazoketone 96 (75 mg, 0.289 mmole) in dichloromethane (4 ml) was added via a syringe pump at a rate of 0.15 ml/min to a solution of rhodium acetate (2 mg) in dichloromethane (2 ml) at reflux. Upon addition the distillation was continued for 5 min. The reaction mixture was evaporated in vacuo to afford a green oil which was identical in composition to that of experiment 5.2.3.viii. The distillate was diluted with dichloromethane and washed with 3M HCl solution. The aqueous solution was back-extracted twice. The combined organic extracts were washed with water and brine. Evaporation of the solvent in vacuo gave 4'-methylacetanilide 108 (6 mg, 70% of the theoretical amount based on alkene) as a crystalline solid which was identical to an authentic sample, m.p. 151-153°C (lit m.p. 153°C).
1H NMR (300 MHz, CDCl₃) δ 2.16 (s, 3H), 2.31 (s, 3H), 7.11 (d, J = 8.4 Hz, 1H, H2), 7.37 (d, J = 8.4 Hz, 1H, H3).

6.2.5 Chemistry of the Norcaradienes

Hydrolysis of the 6-methoxy norcaradiene 74

The enol ether 74 (50 mg, 0.248 mmols) was dissolved in acetone (5 ml) and water (0.5 ml). Aqueous HCl solution (30%, 0.5 ml) was added to the solution, which turned yellow instantly. The solution was stirred at room temperature for 5 min and diluted with water. The solution was extracted with ethyl acetate (x 3) and washed with water and brine respectively. Evaporation of the solvent in vacuo gave a brown oil which was purified by chromatography on silica, using 50% ethyl acetate/hexane as the eluent, to give the dienedione 89 as a colourless solid (19mg, 91%). This was identical to an authentic sample. The spectroscopic data has been presented in section 5.2.v.

Cyclopropanation/Hydrolysis of 7-methoxy diazoketone 76

The norcaradiene 74 (10 mg) was dissolved in 3 M HCl (1 ml) under nitrogen and the solution was stirred at room temperature for 10 min. The solution was diluted with water and washed with water and brine. The solvent was removed in vacuo to afford a green solid 132 which was identical to an authentic sample. The spectroscopic data has been presented in section 5.2.v.
The diazoketone 76 (20 mg, 0.087 mmoles) in dry 1,2-dichloroethane (2 ml) was added over 2 min, by syringe, to a solution of Cu(acac)$_2$ (1 mg) in 1,2-dichloroethane (2 ml) at reflux. Upon addition, the solution was refluxed for a further 5 min. The solvent was evaporated to afford a green oil, which was immediately dissolved in acetone (3 ml) and 30% HCl solution (0.5 ml) added. After 5 min at room temperature, the yellow solution was diluted with water and extracted with dichloromethane (x 3). The dichloromethane extracts were washed with water and brine and the solvent was removed in vacuo to afford a green oil. Chromatography on silica, using 50% ethyl acetate/hexane, gave the impure dienedione. Sublimation at 120°C/0.01 mm Hg gave 2H-2,4a-ethanonaphthalen-3(4H),7(1H)-dione 132 as white crystals (12 mg, 73%) which was identical to an authentic sample,$^{188,189}$ m.p. 112-114°C (lit (Beames, 1972), (Beames, 1971), m.p. 113-114°C).

$^1$H NMR (300 MHz, CDCl$_3$) δ 1.60-1.94 (m, 4H, H$_9$ x 2, H$_4$ and H$_{10}$), 2.09 (br d, J = 11.7 Hz, 1H, H$_4$), 2.35 (m, 1H, H$_{10}$), 2.52 (d, J = 15.9 Hz, 1H, H$_1$), 2.92 (d, J = 15.9 Hz, 1H, H$_1$), 3.02 (br t, J = 6.3 Hz, 1H, H$_3$), 6.02 (s, 1H, H$_S$), 6.23 (d, J = 9.8 Hz, 1H, H$_7$), 7.04 (d, J = 9.8 Hz, 1H, H$_8$).

Rearrangement of Norcaradiene 74 Using 5M LiClO$_4$ in Ether

The norcaradiene 74 (12 mg, 0.474 mmoles) was dissolved in 5 M LiClO$_4$ in ether (1 ml) under a nitrogen atmosphere. The clear solution was stirred at room temperature for 1 h, in which time the solution became red. The solution was diluted with ether and washed with water and brine. The solvent was removed in vacuo to afford an orange oil. Chromatography on
silica gel using 50% ethyl acetate/hexane as eluent gave 4aRS,7RS)-2-methoxy-5,6-dihydro-4a,7-methano-4aH-benzocyclohepten-8(7H)-one 133, as an orange gel (11 mg, 95%).

IR (CHCl₃) 2970, 1730, 1640, 1575 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ 1.55 (m, 1H, H10), 1.70-1.83 (m, 2H, H5), 1.85-1.95 (m, 2H, H6), 2.22 (m, 1H, H10), 3.05 (m, 1H, H7), 3.76 (s, 3H, OMe), 5.49 (d, J = 2.0 Hz, 1H, H1), 5.67 (s, 1H, H9), 5.75 (dd, J = 1.0, 8.7 Hz, 1H, H3), 6.00 (d, J = 8.7 Hz, 1H, H4).

¹³C NMR (75 MHz, CDCl₃) δ 23.9 (CH₂), 37.5 (CH₂), 48.1 (CH₂), 48.6 (C₄a), 52.4 (C₇), 55.4 (OMe), 96.1 (C₁), 118.5 (C₃ or C₄), 121.9 (C₄ or C₃), 142.4 (C₉), 161.2 (C₉a), 167.7 (C₂), 201.9 (C₈).

MS (El) m/z 202 (M⁺, 57%), 174 (17), 161 (96), 146 (45), 133 (100), 115 (36), 103 (44), 91 (28), 77 (60), 76 (40), 51 (55).

HRMS (El) m/z calc’d for C₁₃H₁₄O₂: 202.0994, found 202.0994.

Analysis calc’d for C₁₃H₁₄O₂: C, 77.20; H, 6.98; found: C, 77.48; H, 7.08.

Peterson reaction on the 6-methoxy norcaradiene 74

Trimethylsilylmethyl lithium in pentane (1M, 200µL) was added via syringe to a solution of the norcaradiene 74 (21 mg, 0.104 mmoles) in dry THF (3 ml) at 0°C. The solution was stirred at 0°C for 30 min and at room temperature for 2 h. The reaction was quenched by the addition of saturated ammonium chloride solution and extracted with ether (x 3). The extracts were washed with brine and the solvent removed to give a yellow oil. Chromatography, using 10% ethyl acetate/hexane, gave (3RS,4aSR,4bRS, 10bRS)-4-hydroxy-4-
trimethylsilylmethyl-7-methoxy-2,3,4,4a-tetrahydro-1H-3,4b-methanocyclo-
prop[1,2:1,3]dibenzenes 64 as a clear oil (29 mg, 96%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.08 (s, 9H, Si(CH$_3$)$_3$), 0.44 (s, 1H, H4a), 1.11 (s, 2H, CH$_2$TMS), 1.30 (m, 1H, H1), 1.72 (d, $J$ = 12.7 Hz, 1H, H9a), 1.82-2.04 (m, 3H, H3 and H2), 2.24-2.46 (m, 2H, H9B and H1'), 3.55 (s, 3H, OMe), 5.01 (d, $J$ = 1.0 Hz, 1H, H8), 5.75 (dd, $J$ = 1.0, 8.7 Hz, 1H, H6), 6.00 (d, $J$ = 8.7 Hz, 1H, H5).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 0.52 (Si(CH$_3$)$_3$), 22.8 (CH$_2$), 23.2 (CH$_2$), 28.5 (CH$_2$), 34.8 (CH$_2$), 37.1 (C4a), 42.3 (C3), 53.5 (C8a or C8b), 54.1 (C8a or C8b), 54.4 (OMe), 81.5 (C4), 101.0 (C8), 116.2 (C6), 128.4 (C5), 153.0 (C7).

MS (EI) m/z 290 (M$^+$, 10%), 229 (10), 203 (18), 175 (23), 147 (17), 115 (27), 86 (67), 84 (94), 75 (79), 73 (100), 49 (70).

Attempted Ring Contraction of the 6-methoxy norcaradiene 74

![Reaction Diagram]

a) Thermal Reaction

The norcaradiene 74 and p-bromobenzenesulfonyl azide in CH$_3$CN were heated at 80°C for 48 h. There was no reaction as determined by TLC and $^1$H NMR analysis.

b) Sonication

The enol ether 74 and p-bromobenzenesulfonyl azide in CH$_3$CN were sonicated for 24 h. TLC and NMR analysis revealed that no reaction had occurred.
c) **High Pressure**

The enol ether 74 (50 mg, 0.25 mmol) and \( p \)-bromobenzenesulfonyl azide (73.5 mg, 0.25 mmole) in 2:1 CH\(_3\)CN/CH\(_2\)Cl\(_2\) (4 ml) were subjected to 10 kbar of pressure for 24 h at 40°C using a Fa Andreas Hoefer, Muhlheim high pressure apparatus. The solvent was removed *in vacuo* and the residue chromatographed using 50% ethyl acetate/hexane as eluent to afford trienone 133 (*cf.* rearrangement of norcaradiene 74 with 5M LiClO\(_4\)/Et\(_2\)O).

A solution of the acid 446 (2 g, 3.33 mmole) in dichloromethane (150 ml) was added dropwise to a solution of oxalyl chloride (5 ml) and dichloromethane (15 ml) at room temperature under a nitrogen atmosphere. One drop of dry DMP was added (evolution of gas) and the resultant solution stirred for 14 h. The volatile components were removed *in vacuo* and the procedure repeated twice more to afford the dichloromethyl acid chloride 132 as a yellow oil (100%).

\( ^2\)H NMR (300 MHz, CDCl\(_3\)) δ 2.80 (m, 1H, HD), 2.42 (m, 1H, HD), 2.29-3.00 (br, 2H, H\(_2\) and H\(_1\)), 3.00-3.50 (m, 3H, H\(_1\), H\(_4\) < 2), 3.88 (s, 3H, OMe), 6.41 (d, \( J = 8.7 \) Hz, A), 6.91 (s, 1H, CHCl\(_3\))

\( ^13\)C NMR (75 MHz, CDCl\(_3\)) δ 124.1 (CH\(_3\)), 124.9 (CH\(_2\)), 123.7 (2CH), 36.3 (2CH), 45.4 (OMe), 67.4 (CHCl\(_3\)), 169.3 (C\(_7\)), 126.3 (C\(_8\)), 126.3 (C\(_9\)), 125.6 (C\(_10\)), 132.7 (C\(_2\)), 158.0 (C\(_3\)), 176.4 (COCl).

After 1 h on high vacuum, to remove any traces of HCl, the oil was dissolved in dichloromethane (100 ml) and added dropwise to a fresh solution of diazomethane (0.4 M, 5 equiv) at -20°C under nitrogen. After stirring for 25
6.3 CHAPTER THREE EXPERIMENTAL

6.3.1 Formyl Norcaradiene Approach

(2RS)-Diazomethyl 5-formyl-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl ketone 148.

A solution of the acid 144 (2 g, 8.55 mmole) in dichloromethane (150 ml) was added dropwise to a solution of oxalyl chloride (5 ml) and dichloromethane (15 ml) at room temperature under a nitrogen atmosphere. One drop of dry DMF was added (evolution of gas) and the resultant solution stirred for 14 h. The volatile components were removed in vacuo and the procedure repeated twice more to afford the dichloromethyl acid chloride 152 as a yellow oil (100%), IR (CHCl₃) 2950, 1790, 1590, 1480 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ 2.00 (m, 1H, H₃), 2.42 (m, 1H, H₃), 2.79-3.00 (m, 2H, H₂ and H₁), 3.05-3.30 (m, 3H, H₁, H₄ x 2), 3.88 (s, 3H, OMe), 6.81 (d, J = 8.7 Hz, 1H, H₇), 6.91 (s, 1H, CHCl₂), 7.69 (d, J = 8.7 Hz, 1H, H₆).

¹³C NMR (75 MHz, CDCl₃) δ 24.4 (CH₂), 24.9 (CH₂), 25.9 (CH₂), 30.5 (C₂), 55.4 (OMe), 69.6 (CHCl₂), 107.5 (C₇), 122.8 (C₈a), 126.3 (C₆), 129.6 (C₄a), 132.7 (C₅), 158.0 (C₈), 176.4 (COCl).

After 1 h on high vacuum, to remove any traces of HCl, the oil was dissolved in dichloromethane (100 ml) and added dropwise to fresh ethereal diazomethane (0.4 M, 5 equiv) at -20°C under nitrogen. After stirring for 15
h the yellow solution was filtered through celite in a well-ventilated fume hood. The solvent was removed in vacuo to afford the dichloromethyl diazoketone 157 as an orange oil (100%),

**IR** (CHCl3) 2970, 2105, 1640 cm⁻¹.

**1H NMR** (300 MHz, CDCl3) δ 1.80 (m, 1H, H3), 2.15 (m, 1H, H3), 2.60 (m, 1H, H2), 2.55-3.15 (m, 4H, H1 and H4), 3.82 (s, 3H, OMe), 5.42 (br s, 1H, COCHN2), 6.76 (d, J = 8.7 Hz, 1H, H7), 6.90 (s, 1H, CHCl2), 7.66 (d, J = 8.7 Hz, 1H, H6).

**13C NMR** (75 MHz, CDCl3) δ 24.9 (2 x CH2), 25.9 (CH2), 44.2 (C2), 53.8 (COCHN2), 55.2 (OMe), 69.6 (CHCl2), 107.3 (C7), 124.2 (C8a), 125.9 (C6), 129.7 (C4a), 133.3 (C5), 158.1 (C8), 197.0 (COCHN2).

The oil was dissolved in THF (65 ml), triethylamine (6 ml) and water (1.5 ml) and the resultant solution was stirred for 16 h. The majority of the THF was removed in vacuo and the residue dissolved in dichloromethane. The solution was washed with water and brine. Evaporation of the solvent gave an orange oil, which was chromatographed on silica gel, using 50% ethyl acetate/hexane as eluent, to give in order of elution,

1) (2RS)-2-chloromethyl-5-formyl-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl ketone 158, as a white solid (265 mg, 12%), a small sample was recrystallised from ether to give 158 as white needles, m.p. 145-147°C.

**1H NMR** (300 MHz, CDCl3) δ 1.75 (m, 1H, H3), 2.20 (m, 1H, H3), 2.70 (dd, J=12.0, 18.2 Hz, 1H, H1), 2.95-3.20 (m, 3H, H1, H2 and H4), 3.54 (dt, J = 4.6, 13.7 Hz, 1H, H4), 3.92 (s, 3H, OMe), 4.29 (d, J = 1.3 Hz, 2H, COCH2Cl), 6.85 (d, J = 8.7 Hz, 1H, H7), 7.68 (d, J = 8.7 Hz, 1H, H6), 10.04 (s, 1H, CHO).

**13C NMR** (75 MHz, CDCl3) δ 24.6 (CH2), 25.2 (CH2), 26.3 (CH2), 42.9 (CH2Cl), 47.2 (C2), 55.6 (OMe), 106.9 (C7), 124.8 (C8a), 127.1 (C4a), 134.9 (C6), 139.6 (C5), 161.5 (C8), 191.9 (CHO), 204.4 (COCH2Cl).
**MS(EI) m/z**266 (M⁺, 25%), 230 (15), 217 (27), 189 (98), 187 (100), 161 (41), 144 (31), 128 (36), 115 (72), 91 (70), 77 (50), 63 (30), 51 (46).

**HRMS m/z**calc'd for C₁₄H₁₅NO₃Cl: 266.0709, found 266.0710.

2) the title compound 148 as yellow crystals (1.39 g, 63%). A small sample was recrystallised from ether to give 148 as yellow prisms, m.p. 126-128°C.

**IR** (CHCl₃) 2950, 2105, 1690, 1640, 1580, 1370 cm⁻¹.

**¹H NMR** (300 MHz, CDCl₃) δ 1.70 (m, 1H, H₃), 2.10 (m, 1H, H₃), 2.53 (m, 1H, H₂), 2.62 (dd, J=10.4, 17.5 Hz, 1H, H₁), 2.91 (dd, J = 4.8, 17.5 Hz, 1H, H₁), 2.95 (dd, J = 5.5, 10.8 Hz, 1H, H₄), 3.48 (dt, J = 4.8, 18.4 Hz, 1H, H₄), 3.84 (s, 3H, OMe), 5.45 (br s, 1H, COCHN₂), 6.76 (d, J = 8.7 Hz, 1H, H₇), 7.59 (d, J = 8.7 Hz, 1H, H₆), 9.96 (s, 1H, CHO).

**¹³C NMR** (75 MHz, CDCl₃) δ 25.0 (CH₂), 25.6 (CH₂), 26.1 (CH₂), 43.9 (C₂), 53.7 (COCHN₂), 55.4 (OMe), 106.7 (C₇), 125.0 (C₈a), 126.8 (C₄a), 134.3 (C₆), 139.6 (C₅), 161.3 (C₈), 191.6 (CHO), 197.1 (COCHN₂).

**MS(EI) m/z**230 (M⁺ - N₂, 51%), 202 (45), 187 (55), 175 (36), 159 (35), 144 (39), 128 (52), 115 (100), 91 (87), 77 (67), 63 (56), 51 (83).

**Analysis** calc'd for C₁₄H₁₄N₂O₃: C, 65.11; H, 5.46; N, 10.83; found: C, 64.88; H, 5.24; N, 10.60.

(3RS,4aSR,4bRS,10bRS)-8-Formyl-5-methoxy-2,3-dihydro-1H-3,4b-methano cyclopropa[1,2:1,3]dibenzenemethano-4(4aH)-one 149
The diazoketone 148 (45 mg, 0.174 mmoles) in dry 1,2-dichloroethane (4 ml) was added to a solution of Cu(acac)$_2$ (0.9 mg, 2 mole %) in 1,2-dichloroethane (2 ml), at reflux, at a rate of 0.35 ml/min using a syringe pump. Upon addition, the solution was refluxed for 5 min. To remove the copper residues, the solution was filtered through a small plug of silica gel using 25% ethyl acetate/1,2-dichloroethane as the eluent to afford the impure norcaradiene as a yellow oil. The oil was purified using MPLC with 15% ethyl acetate/1,2-dichloroethane as eluent to give the formyl norcaradiene 149 as a yellow solid (27 mg, 65%). A small sample was sublimed at 100°C at 0.01 mm Hg to give 149 as yellow needles, m.p. 151-153°C.

IR (CHCl$_3$) 2950, 1725, 1665, 1535 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.92 (s, 1H, H4a), 1.80 (m, 2H, H2 x 2), 1.82 (d, J=12.3 Hz, 1H, H9$\alpha$), 1.98 (m, 1H, H1$\alpha$), 2.29 (m, 1H, H3), 2.77 (m, 1H, H9$\beta$), 3.49 (m, 1H, H1$\beta$), 3.66 (s, 3H, OMe), 3.81 (s, 3H, OMe), 5.36 (d, J=7.4 Hz, 1H, H6), 6.82 (d, J=7.4 Hz, 1H, H7), 9.38 (br s, 1H, CHO).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 18.2 (C1), 27.2 (C2), 27.7 (C9), 31.0 (C4a), 41.2 (C3), 42.4 (C4b), 44.7 (C8a), 56.6 (OMe), 92.6 (C6), 130.9 (C8), 145.0 (C7), 167.3 (C5), 191.0 (CHO), 214.9 (C4).

MS (EI) m/z 230 (M$^+$, 99%), 202 (71), 187(52), 174 (65), 161 (100), 146 (41), 131 (54), 115 (86), 103 (59), 91 (42), 77 (69), 63 (57), 51 (75).

HRMS m/z calc'd for C$_{14}$H$_{14}$O$_3$: 230.0943, found 230.0942.

Analysis calc'd for C$_{15}$H$_{16}$O$_2$: C, 73.03; H, 6.13; found: C, 73.35; H, 6.18.

Peterson reaction of formyl norcaradiene and attempted collapse
Trimethylsilylmethyl lithium in pentane (1M, 1 ml) was added by syringe to an ice-cold solution of the cyclopropyl ketone 149 (63 mg, 0.274 mmoles) in dry THF (10 ml) under a nitrogen atmosphere. The solution was warmed to room temperature after 2 h. TLC analysis indicated that the starting material had been consumed and two new spots had appeared (in 10% ethyl acetate/hexane the two spots were at $R_f$ 0.5 and 0.8). Potassium hydride (42 mg) was added and the suspension was stirred at room temperature for 18 h. The compound at $R_f$ 0.5 had been replaced with a spot at $R_f$ 0.3. Filtration through a very small plug of silica (to remove the potassium hydride) gave the mixture of compounds as a orange oil (60 mg). Chromatography on silica, using 10% ethyl acetate/hexane, gave in order of elution:

1) (3RS,4RS,4aSR,4bRS,10bRS)-4-hydroxy-5-methoxy-4-trimethylsilylmethyl-8-vinyl-2,3,4,4a-tetrahydro-1H-3,4b-methanocyclopropa[1,2:1,3]dibenzene 151 (10 mg, 12%). The compound was unstable and only the $^1$H NMR spectrum was recorded.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.08 (s, 9H, TMS), 0.52 (s, 1H, H4a), 1.00-1.45 (m, 4H, CH$_2$TMS and H2 x 2), 1.12 (d, $J = 9.8$ Hz, 1H, H9$\alpha$), 1.70-2.00 (m, 2H, H1$\alpha$ and H3), 2.40-2.55 (m, 2H, H1$\beta$ and H9$\beta$), 3.62 (s, 3H, OMe), 4.90 (d, $J = 6.1$ Hz, 1H, H6), 4.95 (dd, $J = 1.0, 9.1$ Hz, 1H, CH=CH$_2$), 5.35 (dd, $J = 1.0, 15.2$ Hz, 1H, CH=CH$_2$), 5.92 (d, $J = 6.1$ Hz, 1H, H7), 6.41 (dd, $J = 9.1, 15.2$ Hz, 1H, CH=CH$_2$).

2) (3RS,4RS,4aSR,4bRS,10bRS)-8-(trimethylsilylethylidene)-4-hydroxy-5-methoxy-4-trimethylsilylmethyl-2,3,4,4a-tetrahydro-1H-3,4b-methanocyclopropa[1,2:1,3]dibenzene-5-one 160 (9 mg, 9%). The compound was unstable and only the $^1$H NMR spectrum was recorded.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.02 (s, 6H, TMS), 0.08 (s, 12 H, TMS), 1.05 (AB system, $\delta_A = 1.02$, $\delta_B = 1.08$, $J_{AB} = 12.0$ Hz, 2H, CH$_2$TMS), 1.25 (s, 2H, CH$_2$TMS), 1.40-2.10 (m, 6H, H1 x 2, H2 x 2, H3 and H4a), 2.50 (m, 2H, H9$\beta$ and
H1β), 5.78 (d, J = 1.0, 9.7 Hz, 1H, H7), 6.05 (dt, J = 1.0, 7.6 Hz, 1H, H10), 7.00 (d, J = 9.7 Hz, 1H, H6).

6.3.2 Use of a Deactivated Styrene Derivative

(2RS)-Trans and cis 5-(cyanovinyl)-8-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid (164 and 165).

Diethyl cyanomethylphosphonate (3.2 ml, 4 equiv) in dry THF (15 ml) was added dropwise to sodium hydride (765 mg) under a nitrogen atmosphere at 0°C. The suspension was stirred for 5 min and the aldehyde 144 (1.5 g, 6.4 mmoles) in THF (40 ml) was added rapidly from a dropping funnel. After stirring at 0°C for 1 h the solution was warmed to room temperature and stirred for 2 h. The reaction was quenched with water and acidified to pH 1 with concentrated hydrochloric acid. The aqueous solution was extracted with ethyl acetate and the combined organic extracts were washed with water and brine. The solvent was removed in vacuo to give a brown solid which was purified by column chromatography using 1% CH2Cl2/50% ethyl acetate/49% hexane as eluent to give the mixture of acids 164 and 165 as a cream solid (1.48 g, 90%). 1H NMR spectroscopy revealed that there was a 3:1 mixture of trans to cis isomers. Two recrystallisations of the mixture with methanol gave the trans acid 164 as pale yellow prisms (1.02 g, 62%), m.p. 189-191°C.

IR (CHCl3) 3000, 2225, 1750, 1710, 1590 cm⁻¹.
$^1H$ NMR (300 MHz, d$_6$-acetone) $\delta$ 1.85 (m, 1H, H3), 2.28 (m, 1H, H3), 2.63-2.85 (m, 3H, H2, H1 and H4), 2.96 (dt, J = 5.0, 17.6 Hz, 1H, H4), 3.08 (m, 1H, H1), 3.84 (s, 3H, OMe), 5.66 (d, J = 16.4 Hz, 1H, CH=CHCN), 6.71 (d, J = 8.6 Hz, 1H, H7), 7.36 (d, J = 8.6 Hz, 1H, H6), 7.62 (d, J = 16.4 Hz, 1H, CH=CHCN).

$^{13}C$ NMR (75 MHz, d$_6$-acetone) $\delta$ 24.8 (CH$_2$), 25.6 (CH$_2$), 25.8 (CH$_2$), 38.3 (C2), 55.4 (OMe), 94.5 (CH=CHCN), 107.5 (C7), 118.8 (CN), 124.6 (C8a or C4a), 124.7 (C6), 124.8 (C4a or C8a), 136.0 (C5), 147.8 (CH=CHCN), 159.5 (C8), 179.1 (CO$_2$H).

MS (EI) m/z 257 (M$^+$, 32%), 210 (59), 195 (59), 180 (100), 167 (22), 153 (23), 140 (42), 128 (40), 115 (91), 102 (18), 84 (71), 77 (44), 63 (60), 51 (65).

Analysis calc'd for C$_{15}$H$_{15}$N$_2$O$_3$: C, 70.02; H, 5.88; N, 5.44; found: C, 70.17; H, 6.16; N, 5.12.

Concentration of the mother liquor gave the cis acid 165 as white prisms (0.43 g, 26%), m.p. 196-198°C.

IR (CHCl$_3$) 3000, 2225, 1750, 1710, 1590 cm$^{-1}$.

$^1H$ NMR (300 MHz, d$_6$-acetone) $\delta$ 1.82 (m, 1H, H3), 2.28 (m, 1H, H3), 2.66-2.85 (m, 3H, H2, H1 and H4), 2.86 (dt, J = 5.0, 17.6 Hz, 1H, H4), 3.04 (m, 1H, H1), 3.85 (s, 3H, OMe), 5.48 (d, J = 12.0 Hz, 1H, CH=CHCN), 6.91 (d, J = 8.7 Hz, 1H, H7), 7.40 (d, J = 8.7 Hz, 1H, H6), 7.76 (d, J = 12.0 Hz, 1H, CH=CHCN).

$^{13}C$ NMR (75 MHz, d$_6$-acetone) $\delta$ 26.3 (CH$_2$), 27.1 (CH$_2$), 27.3 (CH$_2$), 39.6 (C2), 56.5 (OMe), 95.9 (CH=CHCN), 108.4 (C7), 118.9 (CN), 125.9 (C8a or C4a), 126.5 (C4a or C8a), 127.9 (C6), 137.7 (C5), 148.2 (CH=CHCN), 160.3 (C8), 177.4 (CO$_2$H).

MS (EI) m/z 257 (M$^+$, 80%), 226 (17), 210 (94), 195 (69), 180 (100), 153 (28), 140 (30), 127 (27), 115 (63), 77 (37), 63 (41), 51 (43).

HRMS m/z calc'd for C$_{15}$H$_{15}$N$_2$O$_3$: 257.1052, found 257.1053.
(2RS)-Methyl trans and cis 5-(cyanovinyl)-8-methoxy-1,2,3,4-tetrahydro-2-naphthoate.

The crude reaction mixture of the previous experiment 164/165 (3.84 g, 3:1 trans to cis) was added to a mixture of K$_2$CO$_3$ (5.2 g) and MeI (2.5 ml) in DMF (20 ml). The resultant suspension was stirred for 13 h at room temperature under a nitrogen atmosphere. The reaction was poured into water and extracted with ethyl acetate. The organic extracts were washed with water and brine. The solvent was removed in vacuo to give the methyl ester as a oily solid. Column chromatography using silica gel, with 25% ethyl acetate/hexane as eluent, gave (2RS)-methyl trans and cis 5-(cyanovinyl)-8-methoxy-1,2,3,4-tetrahydro-2-naphthoate as a white solid (3.58 g, 88% over two steps) in a trans/cis ratio of 3:1, m.p. 75-79°C.

IR (CHCl$_3$) 2960, 2210, 1770, 1590 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.81 (m, 1H, H3), 2.22 (m, 1H, H3), 2.58-3.14 (m, 5H, H2, H1 x 2 and H4 x 2), 3.73 (s, 6H, OMe), 3.85 (s, 3H, OMe), 3.86 (s, 3H, OMe), 5.38 (d, J = 11.7 Hz, 1H, cis-CH=CHCN), 5.66 (d, J = 16.4 Hz, 1H, trans-CH=CH$_2$), 6.71 (d, J = 8.5 Hz, 1H, trans-H7), 6.77 (d, J = 7.5 Hz, cis-H7), 7.32 (d, J = 7.5 Hz, 1H, cis-H6), 7.35 (d, J = 8.5 Hz, 1H, trans-H6), 7.61 (d, J = 16.4 Hz, 1H, trans-CH=CHCN), 7.85 (d, J = 12.0 Hz, 1H, cis-CH=CHCN).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 24.9 (2 x CH$_2$), 25.7 (2 x CH$_2$), 25.9 (CH$_2$), 26.1 (CH$_2$), 38.5 (C2), 38.6 (C2), 51.8 (2 x OMe), 55.3 (2 x OMe), 94.5 (2 x CH=CHCN), 107.1 (C7), 107.5 (C7), 117.7 (CN), 118.8 (CN), 124.4 (C8a or C4a), 124.7 (C6), 124.8 (C4a or C8a), 124.9 (C4a or C8a), 126.7 (C6), 136.0 (C5), 136.1 (C5), 146.8
(CH=CHCN), 147.7 (CH=CHCN), 158.9 (C8), 159.4 (C8), 175.5 (CO₂Me), 175.6 (CO₂Me).

**MS(EI)** \( m/z 271 \) (M⁺, 21%), 240 (8), 210 (98), 195 (53), 180 (100), 167 (20), 153 (24), 140 (30), 127 (32), 115 (19), 77 (49), 51 (64).

**HRMS** \( m/z \) calc'd for C₁₆H₁₇N₀₃: 271.1208, found 271.1209.

### Isomerisation of the Nitrile double bond

The methyl ester (3:1 \textit{trans}/\textit{cis} ratio; 12 mg, 0.443 mmoles) and a small crystal of iodine were dissolved in a mixture of hexane (3 ml) and dichloromethane (1 ml) and irradiated with a 450 W mercury lamp for 3 h. The solution was washed with 0.2M Na₂S₂O₅ solution to remove the iodine and evaporated \textit{in vacuo} to afford a white solid which, from \( ^1 \text{H} \) spectroscopy, was a 35:65 \textit{trans} to \textit{cis} mixture.

\( (2RS)-\text{Trans-Diazomethyl} \ 5-(\text{cyanomethyl})-8\text{-methoxy-1,2,3,4-tetrahydro naphthalen-2-yl ketone} \ 166. \)

A solution of the acid 164 (1.02 g, 3.97 mmole) in dichloromethane (20 ml) was added dropwise to a solution of oxalyl chloride (5 ml) and dichloromethane (5 ml) at room temperature under a nitrogen atmosphere. One drop of dry DMF was added (evolution of gas) and the resultant solution stirred for 14 h. The volatile components were removed \textit{in vacuo} and the procedure repeated twice more to afford the acid chloride as a orange solid. After 1 h on high vacuum, to remove any traces of HCl, the oil was dissolved in dichloromethane (30 ml) and added to fresh ethereal
diazomethane (0.4 M, 5 h) at -20°C (methanol/ice bath) under nitrogen. After stirring for 15 h the yellow solution was filtered through celite in a well-ventilated fumehood. Evaporation of the solvent in vacuo gave an orange oil, which was chromatographed on silica gel using 50% ethyl acetate/5% 1,2-dichloroethane/45% hexane as eluent to give the *diazoketone* 166 as yellow crystals (796 mg, 71%). A small sample was recrystallised from ether to give 166 as yellow needles.

**m.p.** 139-141°C.

**IR** (CHCl₃) 2950, 2225, 2120, 1645, 1590 cm⁻¹.

**¹H NMR** (300 MHz, CDCl₃) δ 1.82 (m, 1H, H₃), 2.15 (m, 1H, H₃), 2.55 (m, 1H, H₂), 2.60-2.80 (m, 2H, H₄ x 2), 2.93 (m, 2H, H₁ x 2), 3.84 (s, 3H, OMe), 5.42 (br s, 1H, COCHN₂), 5.66 (d, J = 16.4 Hz, 1H, CH=CHCN), 6.71 (d, J = 8.8 Hz, 1H, H₇), 7.35 (d, J = 8.8 Hz, 1H, H₆), 7.60 (d, J = 16.4 Hz, 1H, CH=CHCN).

**¹³C NMR** (75 MHz, CDCl₃) δ 25.1 (CH₂), 25.9 (CH₂), 26.0 (CH₂), 44.2 (C₂), 53.9 (COCHN₂), 55.4 (OMe), 94.5 (CH=CHCN), 107.5 (C₇), 118.8 (CN), 124.7 (C₆), 124.7 (C₈a and C₄a), 136.0 (C₅), 147.7 (CH=CHCN), 159.4 (C₈), 196.9 (COCHN₂).

**MS(EI) m/z** 281 (M⁺, 2%), 253 (45), 210 (85), 195 (42), 155 (75), 140 (67), 128 (51), 115 (100), 77 (48), 63 (66), 51 (73).

**HRMS m/z** calc'd for C₁₆H₁₅N₃O₂: 281.1164, found 281.1165.

**Analysis** calc'd for C₁₆H₁₅N₃O₂: C, 68.31; H, 5.37; N, 14.94; found: C, 67.97; H, 5.42; N, 14.71.

(3RS,4aSR,4bRS,10bRS)-Trans 8-cyanomethyl-5-methoxy-2,3,4,4a-tetrahydro-1H-3,4b-methanocyclo propa[1,2:1,3]dibenzene-4-one 167.
The diazoketone 166 (796 mg, 2.83 mmoles) in dry 1,2-dichloroethane (20 ml) was added to a solution of Cu(acac)$_2$ (7 mg, 2 mole %) in 1,2-dichloroethane (20 ml), at reflux, at a rate of 0.15 ml/min using a syringe pump. Upon addition the solution was refluxed for 5 min. To remove the copper residues the solution was filtered through a small plug of silica gel using 50% ethyl acetate/1,2-dichloroethane as the eluent to afford the impure norcaradiene as a yellow oil. The oil was purified using MPLC with 30% ethyl acetate/65% hexane/5% 1,2-dichloroethane as eluent to give the cyano norcaradiene 167 as a yellow solid (430 mg, 60%). A small sample was recrystallised from ether to give 167 as pale yellow needles, m.p. 130-132°C.

IR (CHCl$_3$) 2950, 2220, 1720, 1540 cm$^{-1}$.

$^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.95 (d, J = 1.6 Hz, 1H, H4a), 1.81 (d, J = 12.4 Hz, 1H, H9a), 1.80-2.05 (m, 3H, H2 x 2, H1α), 2.30 (m, 1H, H3), 2.53 (m, 1H, H1β), 2.79 (m, 1H, H9β), 3.73 (s, 3H, OMe), 5.19 (d, J = 7.2 Hz, 1H, H6), 5.44 (d, J = 16.4 Hz, 1H, CH=CHCN), 6.35 (d, J = 7.2 Hz, 1H, H5), 7.09 (d, J = 16.4 Hz, 1H, CH=CHCN).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 19.3 (C1), 27.2 (C2), 27.5 (C9), 29.6 (C4a), 40.7 (C3), 42.0 (C4b or 8a), 44.2 (C8a or 4b), 56.1 (OMe), 92.6 (C6), 93.2 (CH=CHCN), 118.8 (CN), 127.0 (C8), 128.4 (C7), 148.2 (CH=CHCN), 162.6 (C5), 214.9 (C4).

MS (EI) m/z 253 (M+, 100%), 202 (71), 187(52), 174 (65), 161 (100), 146 (41), 131 (54), 115 (86), 103 (59), 91 (42), 77 (69), 63 (57), 51 (75).

Analysis calc'd for C$_{16}$H$_{15}$N$\text{O}_2$: C, 75.87; H, 5.97; N, 5.53 found: C, 75.61; H, 5.96; N, 5.72.
(3RS,4aSR,4bRS,6aSR,7RS,8SR,9SR,10bRS)-9-Cyano-5-methoxy-2,3,6a,7,8,9-hexahydro-1H-3,4b-methanobenzo-[1,3]-cyclopropa[1,2-a]naphthalene-4(4aH)-one-7,8-dicarboxylic anhydride 168

1H NMR (300 MHz, d6-acetone) δ 1.81 (s, 1H, H4a), 1.90 (d, J = 12.3 Hz, 1H, H11α), 1.90-2.10 (m, 3H, H2 x 2 and H1α), 2.25 (m, 1H, H3), 2.69 (m, 1H, H1β), 2.78 (m, 1H, H11β), 3.35 (m, 1H, H6a), 3.78 (s, 3H, OMe), 3.94 (dd, J = 6.8, 9.3 Hz, 1H, H7), 4.05 (m, 1H, H9), 4.20 (dd, J = 5.3, 9.3 Hz, 1H, H8), 4.89 (d, J = 3.3 Hz, 1H, H6), 6.39 (m, 1H, H10).

13C NMR (75 MHz, d6-acetone) δ 18.0 (C1), 25.1 (C4a), 25.8 (C2), 26.1 (C9), 33.1 (C6a), 35.0 (C4b or C10b), 37.9 (C10b or C4b), 39.6 (C7), 42.1 (C8), 42.8 (C3), 44.7 (C9), 53.3 (OMe), 88.2 (C6), 117.0 (CN), 119.7 (C10), 139.4 (C10a), 151.3 (C5), 168.3 (C12 or C13), 169.6 (C13 or C12) 208.5 (C4).

The norcaradiene 167 (300 mg, 1.19 mmoles) and freshly sublimed maleic anhydride (250 mg, 2.6 equiv) were dissolved in dry benzene (30 ml). The solution was heated at 80°C for 48 h, in which time a white solid precipitated from the reaction mixture. TLC analysis indicated that all of the starting material had been consumed. The solvent was removed on the rotatory evaporator to afford a yellow solid (450 mg, >100%). 1H NMR spectroscopy revealed that only one diastereoisomer had been formed. The solid was recrystallised from acetone to afford the adduct 168 as fine white needles (365 mg, 88%), m.p. 168-170°C.
MS (EI) m/z 351 (M+, 28%), 323 (10), 278 (17), 253 (88), 236 (34), 222 (25), 210 (28), 197 (30), 166 (43), 153 (30), 140 (40), 127 (30), 115 (34), 89 (31), 77 (49), 63 (47), 55 (100), 51 (56).

HRMS m/z calc’d for C_{20}H_{17}N_{05}: 351.1108, found 351.1111.

6.3.3 Vinyl Norcaradiene Series

(2RS)-8-Methoxy-5-vinyl-1,2,3,4-tetrahydro-2-naphthoic acid 145.

A solution of methylenetriphenylphosphorane in THF (0.54 M; prepared from methyl triphenylphosphonium bromide and sodium hydride in THF) was cannulated into a solution of the aldehyde 144 (2.0 g, 8.62 mmole) in THF (100 ml) until the yellow colour persisted and TLC analysis indicated that no starting material remained. The reaction mixture was quenched with water and acidified to pH 1 with concentrated HCl to give a white precipitate. The aqueous layer was extracted with ethyl acetate (x 3). The organic extracts were washed with water and brine. Evaporation of the solvent in vacuo gave an orange oil which was purified by chromatography on silica gel using 50% ethyl acetate/hexane as eluent to afford the vinyl acid 145 as white crystals (1.6 g, 81%). A small sample was recrystallised from ether to give 145 as small white prisms,
m.p. 179-181°C.

1H NMR (300 MHz, CDCl3) δ 1.82 (m, 1H, H3), 2.25 (m, 1H, H3), 2.65-2.80 (m, 3H, H2, H1 and H4), 2.96 (dt, J = 4.6, 15.9 Hz, 1H, H4), 3.14 (m, 1H, H1), 3.83 (s, 3H, OMe), 5.19 (dd, J = 1.5, 10.9 Hz, 1H, CH=CH2), 5.51 (dd, J = 1.5, 17.4 Hz, 1H,
CH=CH₂), 6.71 (d, J = 8.5 Hz, 1H, H7), 6.86 (dd, J = 10.9, 17.4 Hz, 1H, CH=CH₂),
7.54 (d, J = 8.5 Hz, 1H, H6).

**1³C NMR** (75 MHz, CDCl₃) δ 25.1 (CH₂), 25.7 (CH₂), 26.1 (CH₂), 38.9 (C₂), 55.3
(OMe), 107.2 (C₇), 113.9 (CH=CH₂), 123.5 (C₈a), 123.7 (CH=CH₂), 129.4 (C₄a),
134.2 (C₅), 134.3 (C₆), 156.9 (C₈), 181.7 (CO₂H).

**MS** (EI) m/z 232 (M⁺, 100%), 217 (13), 187 (75), 171 (46), 155 (43), 128 (39), 115
(49), 91 (23), 77 (24), 63 (21), 51 (27).

**Analysis** calc’d for C₁₄H₁₆O₃: C, 72.39; H, 6.94; found: C, 72.48; H, 7.25.

(2RS)-Diazomethyl 8-methoxy-5-vinyl-1,2,3,4-tetrahydronaphthalen-2-yl
ketone 147.

\[
\text{OMe} \quad 145 \quad \xrightarrow{\text{EtO₂Cl}} \quad \xrightarrow{\text{NEt₃}} \quad \text{OMe} \quad 169 \quad \xrightarrow{\text{CH₂N₂}} \quad \text{OMe} \quad 147
\]

A solution of the vinyl acid 145 (70 mg, 0.30 mmoles) in dry ether (20 ml)
was added slowly to an ice-cold solution of ethyl chloroformate (50 µL, 2
equiv) and triethylamine (225 mL, 5 equiv) in dry ether (10 ml). The
solution was stirred for 2 h at 0°C, diluted with ether and washed with water
and brine. Removal of the solvent in vacuo gave the (2RS)-ethylcarbonyl 8-
methoxy-5-vinyl-1,2,3,4-tetrahydro-2-naphthoate 169 as a clear oil,
**IR** (CHCl₃) 2985, 1825, 1760, 1600, 1480 cm⁻¹.

**¹H NMR** (300 MHz, CDCl₃) δ 1.40 (t, J = 7.1 Hz, 3H, CH₂CH₃), 1.83 (m, 1H,
H₃), 2.30 (m, 1H, H₃), 2.65-2.82 (m, 3H, H₂, H₁ and H₄), 2.94 (m, 1H, H₄), 3.18
(dd, J = 4.0, 16.5 Hz, 1H, H₁), 3.82 (s, 3H, OMe), 4.34 (q, J = 7.1 Hz, 2H,
CH₂CH₃), 5.18 (dd, J = 1.5, 10.9 Hz, 1H, CH=CH₂), 5.51 (dd, J = 1.5, 17.4 Hz, 1H,
CH=CH₂), 6.70 (d, J = 8.7 Hz, 1H, H₇), 6.83 (dd, J = 10.9, 17.4 Hz, 1H, CH=CH₂),
7.32 (d, J = 8.7 Hz, 1H, H₆).
**13C NMR** (75 MHz, CDCl₃) δ 13.9 (CH₃), 24.9 (CH₂), 25.5 (CH₂), 26.0 (CH₂), 39.4 (C₂), 55.3 (OMe), 55.9 (OMe), 65.7 (OCH₂), 107.4 (C₇), 114.0 (CH=CH₂), 122.8 (C₈a), 124.1 (CH=CH₂), 129.4 (C₄a), 133.9 (C₅), 134.1 (C₆), 149.3 (CO₂CO₂Et), 156.9 (C₈), 170.0 (CO₂CO₂Et).

**MS** (EI) m/z 304 (M⁺, 57%), 260 (13), 231 (14), 215 (24), 186 (100), 171 (65), 155 (28), 128 (27), 115 (22).

**HRMS** m/z calc'd for C₁₇H₂₀O₅: 304.1309, found 304.1311.

After 30 min on high vacuum, the crude anhydride was dissolved in dichloromethane (20 ml) and added dropwise to fresh ethereal diazomethane (0.4 M, 10 equiv) at 0°C. The yellow solution was stirred at 0°C for 30 min and 4.5 h at room temperature. The solvent was removed *in vacuo* to afford the crude diazoketone as an orange oil. Chromatography on silica gel, using 25% ethyl acetate/hexane, gave in order of elution,

1) the *diazoketone* **147** as a yellow solid (39 mg, 51%; the net yield was 68% based on recovered starting material). A small sample was recrystallised from ether to give **147** as fine yellow needles, m.p. 106-107°C.

**IR** (CHCl₃) 2950, 2115, 1645, 1600 cm⁻¹.

**1H NMR** (300 MHz, CDCl₃) δ 1.80 (m, 1H, H₃), 2.12 (m, 1H, H₃), 2.55 (m, 1H, H₂), 2.55-2.72 (m, 2H, H₁ and H₄), 2.95 (dd, J = 3.4, 5.0 Hz, 1H, H₄), 3.02 (dd, J = 3.8, 17.6 Hz, 1H, H₁), 3.83 (s, 3H, OMe), 5.20 (dd, J = 1.6, 11.0 Hz, 1H, CH=CH₂), 5.41 (br s, 1H, COCHN₂), 5.52 (dd, J = 1.6, 17.2 Hz, 1H, CH=CH₂), 6.70 (d, J = 8.6 Hz, 1H, H₇), 6.86 (dd, J = 11.0, 17.2 Hz, 1H, CH=CH₂), 7.34 (d, J = 8.6 Hz, 1H, H₆).

**13C NMR** (75 MHz, CDCl₃) δ 25.4 (CH₂), 26.1 (CH₂), 26.3 (CH₂), 44.7 (C₂), 53.7 (COCHN₂), 55.3 (OMe), 107.2 (C₇), 113.7 (CH=CH₂), 123.6 (C₈a), 123.8 (CH=CH₂), 129.3 (C₄a), 134.1 (C₆), 134.3 (C₅), 156.8 (C₈), 197.6 (COCHN₂).
MS (EI) m/z 256 (M+, 9%), 228 (37), 197 (36), 185 (45), 171 (40), 141 (36), 129(65), 115 (100), 91 (41), 77 (34), 63 (32), 51 (45).

HRMS m/z calc'd for C\textsubscript{15}H\textsubscript{16}N\textsubscript{2}O\textsubscript{2}: 256.1212, found 256.1211.

Analysis calc'd for C\textsubscript{15}H\textsubscript{16}N\textsubscript{2}O\textsubscript{2}: C, 70.29; H, 6.29; N, 10.93; found: C, 70.34; H, 6.41; N, 10.82.

and 2) the starting material 145 (18 mg).

Isolation of the 1,3-dipolar cycloaddition adduct 174 from the diazoketone formation.

![Chemical structure diagram]

The reaction to form 147 was repeated, except that the reaction mixture was allowed to stir for 18 h at room temperature. The solvent was removed and the residue chromatographed, using 25% ethyl acetate/hexane to remove the diazoketone 147 (35%), and 50% ethyl acetate/hexane to obtain (2RS,5'SR)-diazomethyl 5--3'-1'-pyrazolinyl)-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl ketone 174 as yellow crystals (21%). From the NMR data it was evident that there was a mixture of diastereoisomers,

\textbf{1H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 1.35 (m, 1H, H4'), 1.85 (m, 1H, H3), 2.10-2.30 (m, 2H, H3 and H4'), 2.55 (m, 1H, H2), 2.50-2.80 (m, 3H, H1, H2 and H3), 2.90-3.10 (m, 2H, H4), 3.15 (m, 1H, H1'), 3.83 (s, 3H, OMe), 4.36 (m, 1H, H3'), 4.76 (m, 1H, H5'), 5.42 (br s, 1H, COCHN\textsubscript{2}), 5.50 (m, 1H, H5'), 6.58-6.75 (m, 2H, H6 and H7).

\textbf{13C NMR} (75 MHz, CDCl\textsubscript{3}) \(\delta\) 25.40 (CH\textsubscript{2}), 25.45 (CH\textsubscript{2}), 25.52 (CH\textsubscript{2}), 25.64 (CH\textsubscript{2}), 25.80 (CH\textsubscript{2}), 26.19 (CH\textsubscript{2}), 26.30 (CH\textsubscript{2}), 26.40 (CH\textsubscript{2}), 44.6/44.8 (C2),
53.8/53.9 (COCHN\(_2\)), 55.3 (OMe), 76.4/76.5 (CH), 86.6/86.8 (CH), 107.2/107.3 (C7), 123.8/124.5 (C8a), 129.4/129.6 (C4a), 134.5 (C6), 156.7 (C8), 197.4 (COCHN\(_2\)).

\(3RS,4aSR,4bRS,10bRS\)-5-Methoxy-8-vinyl-2,3-dihydro-1H-3,4b-methano cyclopropa[1,2:1,3]dibenzene-4(4aH)-one 142

The diazoketone 147 (276 mg, 1.08 mmoles) in dry 1,2-dichloroethane (20 ml) was added to a solution of Cu(acac)_2 (6 mg, 2 mole \%) in 1,2-dichloroethane at reflux, at a rate of 0.35 ml/min using a syringe pump. Upon addition the solution was refluxed for 5 min. To remove the copper residues the solution was filtered through a small plug of silica gel using 50\% ethyl acetate/hexane as the eluent to afford the impure norcaradiene as a yellow oil. The oil was purified using MPLC with 25\% ethyl acetate/hexane as eluent to give the vinyl norcaradiene 142 as a clear oil (131 mg, 53\%).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.91 (d, \(J = 1.6\) Hz, H4a), 1.70-1.90 (m, 2H, H2 x 2), 1.82 (d, \(J = 12.3\) Hz, 1H, H9\(\alpha\)), 1.98 (m, 1H, H1\(\alpha\)), 2.29 (m, 1H, H3), 2.77 (m, 1H, H1\(\beta\)), 3.49 (m, 1H, H9\(\beta\)), 3.66 (s, 3H, OMe), 5.01 (dd, \(J = 1.5, 11.8\) Hz, 1H, CH=CH\(_2\)), 5.09 (d, \(J = 7.2\) Hz, 1H, H6), 5.34 (dd, \(J = 1.5, 17.3\) Hz, 1H, CH=CH\(_2\)), 6.06 (dd, \(J = 1, 7.2\) Hz, 1H, H7), 6.42 (ddd, \(J = 1.0, 11.8, 17.3\) Hz, 1H, CH=CH\(_2\)).

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 19.7 (C1), 27.6 (C2), 27.7 (C9), 30.5 (C4a), 41.1 (C3), 42.7 (C4b), 46.5 (C8a), 55.5 (OMe), 92.3 (C6), 113.0 (CH=CH\(_2\)), 120.5 (CH=CH\(_2\)), 131.1 (C8), 134.8 (C7), 158.5 (C5), 216.5 (C4).
MS (EI) m/z 228 (M+, 8%), 200 (2), 172 (4), 159 (9), 141 (4), 115 (10), 84 (100), 77 (14), 57 (32), 51 (73).

Analysis calc'd for C_{15}H_{16}O_2: C, 78.92; H, 7.06; found: C, 78.80; H, 7.44.

(3RS,4aSR,4bRS,6aSR,7RS,8RS,10bRS)-5-Methoxy-2,3,6a,7,8,9-hexahydro-1H-3,4b-methanobenzo-[1,3]-cyclopropa[1,2-a]naphthalene-4(4aH)-one-7,8-dicarboxylic anhydride 175

The norcaradiene 142 (15 mg, 0.658 µmoles) and freshly sublimed maleic anhydride (13 mg, 2 equiv) in dry benzene (4 ml) were heated at 80°C for 4 h. The solvent was removed in vacuo. Only one diastereoisomer could be detected by $^1$H NMR spectroscopy. The white solid was purified by MPLC, using 50% ethyl acetate/hexane as the eluent, to afford the Diels-Alder adduct 175 as a white solid (17 mg, 79%). A sample was recrystallised from ether to give 175 as white needles, m.p. 220-222°C.

IR (CHCl$_3$) 2970, 1850, 1780, 1720 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) δ 1.74 (d, J = 2.0 Hz, 1H, H$_4$a), 1.78 (d, J = 12.0 Hz, 1H, H$_{11}$α), 1.84-2.00 (m, 3H, H$_1$α and H$_2$ x 2), 2.22 (m, 1H, H$_9$β), 2.24 (m, 1H, H$_3$), 2.42 (m, 1H, H$_1$β), 2.76 (m, 1H, H$_{11}$β), 2.92 (m, 1H, H$_9$α), 2.98 (m, 1H, H$_6$a), 3.37 (m, 1H, H$_7$), 3.44 (m, 1H, H$_8$), 3.68 (s, 3H, OMe), 4.58 (d, J = 4.6 Hz, 1H, H$_6$), 6.18 (m, 1H, H$_{10}$).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 19.7 (C1), 24.9 (C2), 27.5 (C11), 27.7 (C9), 34.3 (C4a), 36.8 (C4b or C10b), 40.2 (C10b or C4b), 40.4 (C3), 41.1 (C7), 45.1 (C6a), 46.4
(C8), 55.0 (OMe), 89.1 (C6), 123.5 (C10), 138.1 (C10a), 153.0 (C5), 170.2 (C12 or C13), 173.9 (C13 or C12), 212.3 (C4).

**MS** (EI) $m/z$ 326 (M+, 14%), 298 (6), 253 (13), 228 (100), 200 (21), 185 (28), 172 (27), 158 (40), 141 (24), 128 (30), 115 (38), 91 (30), 84 (100), 77 (27), 55 (41), 51 (25).

**HRMS** $m/z$ calc'd for C$_{19}$H$_{18}$O$_5$: 326.1154, found 326.1154.

**Investigations into the Diels-Alder reaction of Norcaradiene 142 Using Methyl Acrylate as the Dienophile**

a) **Diels-Alder Reaction**

The norcaradiene 142 (26 mg, 0.114 mmole) and freshly distilled methyl acrylate (0.3 ml) in dry benzene (3 ml) were heated at 80°C for 24 h. The solvent was removed *in vacuo* and a $^1$H NMR spectrum recorded to show that three diastereoisomers were present in a 71:17:12 ratio. The white solid was purified by MPLC, using 20% ethyl acetate/hexane as the eluent, to afford the Diels-Alder adducts 176 as a white solid (20 mg, 56%). Attempts to separate the diastereoisomers resulted in their decomposition. The ratio was determined by integration of the olefinic proton (H10) and the enol ether proton (H6) resonances in the $^1$H NMR spectrum. The chemical shifts for these protons for each diastereoisomer are: A ($\delta$ 5.62, 4.22); B ($\delta$, 5.89, 4.42); C ($\delta$ 5.79, 4.18). The spectroscopic data for the major isomer are presented below,
**1H NMR** (500 MHz, CDCl3) δ 1.60-2.00 (m, 4H), 1.82 (d, J = 12.0 Hz, 1H, H1α), 2.05-2.35 (m, 5H), 2.50 (s, 1H, H4a), 2.63 (m, 1H, H11β), 2.84 (m, 1H), 2.90 (m, 1H, H6a), 3.48 (s, 3H, OMe), 3.67 (s, 3H, OMe), 4.22 (m, 1H, H6), 5.62 (m, 1H, H10).

**13C NMR** (75 MHz, CDCl3) δ 18.8 (CH2), 22.2 (CH2), 24.5 (CH2), 27.7 (CH2), 27.9 (CH2), 32.7 (CH), 39.4 (C), 41.4 (CH), 43.5 (C), 43.8 (CH), 54.9 (OMe), 91.4 (H6), 121.4 (ClO), 133.7 (ClOa), 153.5 (C5), 174.2 (CO2Me), 213.4 (C4)

**MS** (EI) m/z 314 (M⁺, 47%), 255 (38), 141 (31), 128 (43), 115 (46), 91 (43), 71 (100), 58 (91).

b) **One Pot Cyclopropanation/Diels-Alder Reaction**

The diazoketone 147 (32 mg, 0.125 mmole) in dry 1,2-dichloroethane (2 ml) was added at a rate of 0.15 ml/min to a solution of Cu(acac)₂ (0.75 mg, 2 mole %) in dry 1,2-dichloroethane (2 ml) at reflux. Upon addition, methyl acrylate (4 drops) was added to the reaction mixture and the solution heated at 80°C for a further 21 h. The solvent was removed in vacuo and the residue chromatographed on silica gel, using 25% ethyl acetate/hexane as the eluent, to afford the same 71:17:12 mixture of diastereoisomers 176 as a white solid (20 mg, 51% for the two steps).
c) One Pot Cyclopropanation/Diels-Alder/Hydrolysis

(3RS,4aSR,4bRS,6aSR,7RS,10bRS)- Methyl 2,3,6a,7,8,9-hexahydro-1H-3,4b-methanobenzo-[1,3]-cyclopropa[1,2-a]naphthalene-4(4aH),5(6H)-dione-7-carboxylate 177

The diazoketone 147 (77 mg, 0.301 mmoles) in dry 1,2-dichloroethane (4 ml) was added, at a rate of 0.15 ml/min, to a solution of Cu(acac)₂ (1 mg, 2 mole %) in dry 1,2-dichloroethane (2 ml) at reflux. Upon addition, methyl acrylate (5 drops) was added to the reaction mixture and the solution heated at 80°C for a further 21 h. The solvent was removed in vacuo to afford a green/yellow oil, which was dissolved in acetone (5 ml). Upon addition of 2 M HCl (10 drops) the solution turned an orange colour. After 5 min the solution was diluted with water and extracted with ethyl acetate (x 3). After washing with water and brine, the solvent was removed in vacuo to give an orange oil. The residue was purified by MPLC, using 25% ethyl acetate/hexane as the eluent, to afford the mixture of diastereoisomers 177 as a white solid (57 mg, 63% for the three steps). ¹H NMR spectroscopy revealed that there was a ratio of 60:11:18:10. Two recrystallisations from ether/hexane gave the major adduct 178 as white needles, m.p. 149-151°C.

IR (CHCl₃) 2950, 1725, 1685 cm⁻¹.
\textbf{1H NMR} (300 MHz, CDCl\textsubscript{3}) $\delta$ 1.48-1.62 (m, 2H), 1.69 (d, $J$ = 12.7 Hz, 1H, H\textsubscript{11a}), 1.85-2.35 (m, 8H), 2.65-2.82 (m, 3H), 3.00 (d, $J$ = 1.4 Hz, 1H, H\textsubscript{4a}), 3.69 (s, 3H, OMe), 5.77 (m, 1H, H\textsubscript{10}).

\textbf{13C NMR} (75 MHz, CDCl\textsubscript{3}) $\delta$ 18.6 (CH\textsubscript{2}), 19.2 (CH\textsubscript{2}), 25.1 (CH\textsubscript{2}), 26.7 (CH\textsubscript{2}), 27.5 (CH\textsubscript{2}), 29.2 (C\textsubscript{4a}), 40.2 (CH\textsubscript{2}), 40.7 (CH), 40.9 (CH), 42.8 (CH), 45.2 (C\textsubscript{4b} or C\textsubscript{10b}), 48.0 (C\textsubscript{10b} or 4b), 51.8 (OMe), 123.2 (C\textsubscript{10}), 133.9 (C\textsubscript{10a}), 173.5 (CO\textsubscript{2}Me), 203.7 (C5), 210.9 (C3).

\textbf{MS} (El) $m/z$ 300 (M\textsuperscript{+}, 100\%), 241 (52), 213 (25), 185 (16), 128 (16), 73 (62), 59 (19).

\textbf{HRMS} $m/z$ calc'd for C\textsubscript{18}H\textsubscript{20}O\textsubscript{4}: 300.1362, found 300.1363.

**Epimerisation of the major adduct**

The adduct 178 (90\% diastereomeric purity) in 0.3M sodium methoxide (5 ml; prepared by adding 35 mg of sodium metal to dry methanol [5 ml]) was stirred at room temperature for 70 h under nitrogen. Water was added to quench the reaction and the aqueous solution was extracted with ethyl acetate (x 3). The organic extracts were washed with water and brine. The solvent was removed \textit{in vacuo} to afford a white solid (95\% recovery). \textbf{1H NMR} spectroscopy revealed that 178 was the minor product in a 10:1 mixture. The \textbf{1H NMR} signals of the major product 179 corresponded to the second diastereoisomer in the reaction mixture from the preceding experiment,
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.60-1.75 (m, 2H), 1.88 (d, J = 12.7 Hz, 1H, H11\(a\)), 1.90-2.45 (m, 9H), 2.65-2.83 (m, 3H), 2.86 (s, 1H, H4a), 3.74 (s, 3H, OMe), 5.82 (m, 1H, H10).

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 18.6 (CH\(_2\)), 24.8 (CH\(_2\)), 25.1 (CH\(_2\)), 26.8 (CH\(_2\)), 27.9 (CH\(_2\)), 29.7 (CH\(_2\)), 31.0 (C4a), 40.3 (CH), 40.8 (CH), 45.4 (C4b or C10b), 46.9 (C10b or 4b), 47.7 (CH), 52.1 (OMe), 122.8 (C10), 132.7 (C10a), 174.9 (CO\(_2\)Me), 203.4 (C5), 210.8 (C3).

3RS,4aSR,4bRS,6aSR,7RS,8RS,10bRS-5-Methoxy-7-methyl-2,3,6a,7,8,9-hexahydro-1H-3,4b-methanobenzo-[1,3]-cyclopropa[1,2-a]naphthalene-4(4aH)-one-7,8-dicarboxylic anhydride 181

a) Diels-Alder Reaction

The norcaradiene 142 (15 mg, 0.658 \(\mu\)moles) and freshly distilled citraconic anhydride (0.1 ml, 20 \(\mu\)l) in dry benzene (4 ml) were heated at 80°C for 9 h. The solvent was removed \textit{in vacuo} and a \(^1\)H NMR spectrum recorded to show that two diastereoisomers were present in a 93:7 ratio. The white solid was purified by MPLC, using 50\% ethyl acetate/hexane as the eluent, to afford the \textit{Diels-Alder adduct} 181 as a white solid (17 mg, 76\%). A sample was recrystallised from ether to give 181 as white irregular prisms. The two diastereoisomers could not be separated and only data for the major isomer is reported.

m.p. 193-199°C.
IR (CHCl₃) 2970, 1850, 1780, 1720 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ 1.57 (s, 3H, Me), 1.69 (d, J = 1.5 Hz, 1H, H₄₈), 1.75 (d, J = 12.3 Hz, 1H, H₁₁α), 1.82-1.96 (m, 3H, H₁α and H₂), 2.15-2.28 (m, 2H, H₃ and H₉β), 2.38 (m, 1H, H₁β), 2.66 (m, 1H, H₆₆a), 2.73 (m, 1H, H₁₁β), 2.90 (m, 1H, H₉α), 3.02 (dd, J = 2.2, 5.8 Hz, 1H, H₈), 3.67 (s, 3H, OMe), 4.68 (d, J = 3.0 Hz, 1H, H₆), 6.24 (m, 1H, H₁₀).

¹H NMR (500 MHz, d₆-acetone) δ 1.59 (d, J = 1.5 Hz, 1H, H₄₈a), 1.60 (s, 3H, Me), 1.71 (d, J = 12.1 Hz, 1H, H₁₁α), 1.74-1.90 (m, 3H, H₁α and H₂), 2.03 (m, 1H, H₃), 2.31 (m, 1H, H₉β), 2.44 (m, 1H, H₁β), 2.63 (m, 1H, H₁₁β), 2.75 (m, 1H, H₉α), 2.78 (m, 1H, H₆₆a), 3.30 (dd, J = 2.3, 5.5 Hz, 1H, H₈), 3.64 (s, 3H, OMe), 4.84 (d, J = 3.3 Hz, 1H, H₆), 6.31 (m, 1H, H₁₀).

¹³C NMR (75 MHz, CDCl₃) δ 20.3 (C₁), 22.2 (Me), 24.0 (C₂), 27.4 (C₉ or C₁₁), 27.6 (C₁₁ or C₉), 36.8 (C₄b or C₁₀b), 40.0 (C₁₀b or C₄b), 41.0 (C₄a), 41.2 (C₃), 45.1 (C₆₆a), 49.1 (C₈), 50.9 (C₇), 54.8 (OMe), 86.6 (C₆), 125.6 (C₁₀), 137.8 (C₁₀a), 153.6 (C₅), 172.8 (C₁₂ or C₁₃), 173.3 (C₁₃ or C₁₂), 212.2 (C₄).

MS (EI) m/z 340 (M⁺, 10%), 298(6), 228 (100), 200 (26), 185 (35), 172 (33), 159 (35), 158 (37), 128 (22), 115 (18).

HRMS m/z calc'd for C₂₀H₂₀O₅: 340.1311, found 340.1311.

Analysis calc'd for C₂₀H₂₀O₅: C, 70.58; H, 5.92; found: C, 70.25; H, 6.33.

b) One Pot Cyclopropanation/Diels-Alder Reaction

The diazoketone 147 (39 mg, 0.152 mmoles) in dry 1,2-dichloroethane (4 ml) was added at a rate of 0.15 ml/min to a solution of Cu(acac)₂ (0.75 mg, 2
mole %) in dry 1,2-dichloroethane (3 ml) at reflux. Upon addition, citraconic anhydride (2 drops) was added to the reaction mixture and the solution heated at 80°F for a further 6 h. The solvent was removed in vacuo and the residue chromatographed, using 50% ethyl acetate/hexane as the eluent, to afford the 93:7 mixture of diastereoisomers 181 as a white solid (35 mg, 68% for the 2 steps).
6.4 CHAPTER FOUR EXPERIMENTAL

6.4.1 Synthesis of 8-Methoxy-2-naphthoic acid 200

8-Methoxy-2-naphthonitrile 198

A solution of 1,2-dihydro-8-methoxy-2-naphthonitrile 200 (7.49 g, 0.041 moles) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (9.8 g, 1.04 equiv) in dry chlorobenzene (100 ml) were refluxed for 2 h. After cooling the solution, the solution was filtered through alumina, using dichloromethane as the eluent, to give the naphthonitrile 198 as cream needles (6.7 g, 90%), m.p. 72-74°C. (lit 145 m.p. 73-73.5°C).

$^1$H NMR (300 MHz, CDCl$_3$) δ 3.75 (s, 3H, OMe), 6.63 (d, J = 8.4 Hz, 1H, H3), 7.17 (d, J = 8.4 Hz, 1H, H4), 7.23 (d, J = 7.9 Hz, 1H, H7), 7.31 (d, J = 7.9 Hz, 1H, H5), 7.56 (dd, J = 7.9 Hz, 1H, H6), 8.36 (s, 1H, H1).

8-Methoxy-2-naphthoic acid 199

The nitrile was hydrolysed according to the method of Jacques 145 to afford the acid 199 as a white solid in 80% yield, m.p. 233-234°C (lit 145 m.p. 234°C).

$^1$H NMR (300 MHz, CDCl$_3$) δ 3.96 (s, 3H, OMe), 6.90 (d, J = 8.4 Hz, 1H, H3), 7.40-7.55 (m, 2H, H4 and H7), 7.82 (t, J = 7.9 Hz, 1H, H6), 7.95 (d, J = 7.9 Hz, 1H, H5), 8.83 (s, 1H, H1).
6.4.2 Birch Reductions Using Ferric Chloride

1,4-dihydro-8-methoxy-2-naphthoic acid 186

Dry THF (17 ml) was added to a mixture of the acid 199 (1.01 g, 5.0 mmoles) and potassium hydride (200 mg, 1 equiv) under nitrogen. Hydrogen was immediately evolved. After 1 h, anhydrous ferric chloride (50 mg, 5 % by weight) was added to the thick white suspension. Ammonia (predried with sodium, 100 ml) was distilled into the flask, which had been cooled to -78°C (acetone/dry ice). Upon completion of the distillation, the bath was removed and small pieces of lithium wire (263 mg, 7.5 equiv) were added over a period of 45 min at -33°C. The solution was stirred at -33°C for 10 mins after addition of the lithium and dry ethanol (2.5 ml) was added dropwise. The ammonia was allowed to evaporate over a period of 5 h using a slow stream of nitrogen. The residue was dissolved in water and this was acidified to pH 1 with concentrated hydrochloric acid. The suspension was extracted with ethyl acetate (x 3). After washing with water and brine the solvent was removed in vacuo to afford a white solid. 1H NMR spectroscopy revealed that there was a 92:8 mixture of the 1,4-dihydro acid 186 and 1,2-dihydro acid 202. Recrystallisation of the mixture using ethyl acetate gave the 1,4-dihydro acid 186 as white prisms (820 mg, 80%), m.p. 204-206°C.

1H NMR (300 MHz, d6-acetone) δ 3.57 (m, 2H, H1 x 2), 3.74 (m, 2H, H4 x 2), 3.96 (s, 3H, OMe), 6.88 (d, J = 7.7 Hz, 1H, H7), 6.92 (d, J = 8.2 Hz, 1H, H5), 7.25 (m, 1H, H3), 7.27 (dd, J = 7.7, 8.2 Hz, 1H, H6).
\( ^{13} \text{C NMR} \) (75 MHz, d6-acetone) \( \delta \) 22.2 (C1), 29.1 (C4), 53.5 (OMe), 106.2 (C7), 118.8 (C6), 120.8 (C4a), 125.6 (C5), 126.8 (C8a), 131.9 (C2), 134.7 (C3), 155.8 (C8), 165.8 (CO\(_2\)H).

MS (EI) \( m/z \) 204(M+, 63\%), 159 (100), 144 (56), 127 (38), 115 (52), 63 (20), 51 (19).

Analysis calc'd for C\(_{12}\)H\(_{12}\)O\(_3\): C, 70.58; H 5.92; found: C, 70.44; H 5.82.

(2RS)-1,2-dihydro-8-methoxy-2-naphthoic acid 202

The same procedure as the previous experiment was followed except that ethanol was not added. The ammonia was allowed to evaporate and the residue quenched with water. After the usual workup, the solvent was removed \textit{in vacuo} to afford a white solid. \( ^1 \text{H NMR} \) spectroscopy revealed that there was a 80:20 mixture of the 1,2-dihydro acid 202 and 1,4-dihydro acid 186. The 1,4-dihydro acid 186 was removed by recrystallisation to afford the 1,2-dihydro acid 202 as a white solid (64\%).

\( ^1 \text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 2.90 (dd, \( J = 7.8, 17.6 \) Hz, 1H, H1), 3.23 (dd, \( J = 7.8, 17.6 \) Hz, 1H, H1), 3.45 (m, 1H, H2), 3.80 (s, 3H, OMe), 6.07 (dd, \( J = 2.2, 8.4 \) Hz, 1H, H3), 6.50 (dd, \( J = 1.2, 8.4 \) Hz, 1H, H4), 6.68 (d, \( J = 7.9 \) Hz, 1H, H7), 6.75 (d, \( J = 7.9 \) Hz, 1H, H5), 7.13 (t, \( J = 7.9 \) Hz, 1H, H6).

\( ^{13} \text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 22.2 (C1), 39.7 (C2), 55.4 (OMe), 110.2 (C7), 119.2 (C6), 121.0 (C4a), 124.7 (C3), 127.1 (C4), 129.0 (C5), 133.7 (C8a), 156.2 (C8), 180.5 (CO\(_2\)H).
6.4.3 Dihydroxylation of the 1,4-Dihydro Methyl Ester 204

Methyl 1,4-dihydro-8-methoxy-2-naphthoate 204

The acid 186 (191 mg, 0.94 mmoles) in methanol (35 ml) was treated with ethereal diazomethane until the solution remained yellow and TLC analysis revealed that no starting material remained. After addition of one drop of glacial acetic acid, to destroy the excess diazomethane, the solvent was removed \textit{in vacuo} to afford an oily residue. Chromatography, using 10\% ethyl acetate/hexane, gave the \textit{methyl ester} 204 as an oil in 95\% purity (194 mg, 90\%). The contaminant was methyl 8-methoxy-2-naphthoate 205 (5\%).

\textbf{1H NMR} (300 MHz, CDCl$_3$) $\delta$ 3.53 (m, 2H, H1 x 2), 3.62 (m, 2H, H4 x 2), 3.82 (s, 3H, OMe), 3.86 (s, 3H, OMe), 6.73 (d, J = 8.0 Hz, 1H, H7), 6.76 (d, J = 7.5 Hz, 1H, H5), 7.15 (m, 1H, H3), 7.17 (dd, J = 7.5, 8.0 Hz, 1H, H6).

\textbf{13C NMR} (75 MHz, CDCl$_3$) $\delta$ 23.6 (C1), 30.8 (C4), 51.7 (CO$_2$Me), 55.2 (OMe), 107.4 (C7), 120.0 (C6), 122.4 (C4a), 126.8 (C5), 128.0 (C8a), 133.0 (C2), 136.1 (C3), 157.1 (C8), 167.4 (CO$_2$Me).

\textbf{MS} (EI) m/z 218(M$^+$, 51\%), 159 (100), 144 (61), 127 (31), 115 (56).

\textbf{HRMS} (EI) m/z calc'd for M$^+$, C$_{13}$H$_{14}$O$_3$: 218.0943, found 218.0942.

Preparation of a 1 mol \% Osmium: 2 mol \% (DHQ)$_2$-PHAL Asymmetric Dihydroxylation Mixture (2 mol \% AD mix $\alpha$)

Potassium ferricyanide (1667 mg, 3 equiv), anhydrous potassium carbonate (697 mg, 3 equiv), (DHQ)$_2$-PHAL (26.5 mg, 0.2 equiv) and potassium osmate dihydrate (6.3 mg, 0.1 equiv) were vigorously mixed in a round bottom flask,
using two magnetic stirrer bars to grind the mixture. After 1 h a fine orange powder was formed. The powder was stored away from light and moisture.

Methyl (2RS,3SR)-2,3-dihydroxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthoate rac-206

Potassium ferricyanide (136 mg, 3 equiv), anhydrous potassium carbonate (57 mg, 3 equiv), potassium osmate dihydrate (0.5 mg, 0.1 equiv), and methanesulfonamide (12 mg, 1 equiv) were added to a mixture of t-butanol (1.35 ml) and water (1.35 ml) at room temperature. Once all the solids had dissolved the mixture was cooled to 0°C for 10 min. The ester 204 (30 mg, 0.14 mmoles) was added in one portion to the heterogeneous slurry. The cooling bath was removed and the mixture stirred vigorously for 18 h. Solid sodium sulfate was added and the mixture stirred for 1 h. After dilution with water, ethyl acetate was added. Upon separation of the layers, the aqueous layer was further extracted with the organic solvent (x 2). The combined organic layers were washed with 2N KOH and brine, to remove the methanesulfonamide, and the solvent removed in vacuo. Chromatography on silica, using 25% ethyl acetate/hexane to remove the unreacted naphthoate contaminant and 50% ethyl acetate/hexane to elute the diol rac-206 as a white solid (30 mg, 89%). A small sample was recrystallised from ethyl acetate/hexane to give rac-206 as prismatic needles, m.p. 149-151°C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.94-3.16 (m, 4H, H$_1$ x 2 and H$_4$ x 2), 3.38 (br s, 1H, OH), 3.79 (s, 3H, OMe). 3.88 (s, 3H, OMe), 4.26 (dd, $J = 6.4, 10.6$ Hz, 1H, H$_3$), 6.68 (d, $J = 7.9$ Hz, 1H, H$_7$), 6.73 (d, $J = 7.9$ Hz, 1H, H$_5$), 7.14 (t, $J = 7.9$ Hz, 1H, H$_6$).
13C NMR (75 MHz, CDCl3) δ 33.9 (C1 or C4), 34.1 (C4 or C1), 53.3 (OMe), 55.2 (OMe), 69.9 (C3), 76.1 (C2), 107.4 (C7), 120.5 (C4a), 120.9 (C6), 127.0 (C5), 134.9 (C8a), 157.2 (C8), 176.1 (CO₂Me).

MS (EI) m/z 252 (M⁺, 6%), 234 (16), 175 (100), 147 (41), 91 (37), 77 (26).

HRMS (EI) m/z calc'd for M⁺, C₁₃H₁₆O₅: 252.0998, found 252.0998.

Analysis calc'd for C₁₃H₁₆O₅: C, 61.90; H 6.39; found: C, 61.73; H 6.72.

Methyl (2R,3S)-2,3-dihydroxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthoate 206

\[
\text{OMe} \quad \overset{2 \text{ mol}/\text{o} (\text{DHQ})_2 \text{PHAL}}{\text{CH₃SO₂NH₂}} \quad \overset{1 \text{ mol}/\text{o} \text{K₂O₃O₃(OH)}_₄}{\text{t-BuOH/H₂O}} \quad \overset{4°C}{\text{K₃Fe(CN)}_₄ \text{K₂CO₃}} \quad \text{OMe} \\
204 \quad \overset{206}{\text{OH}} \quad \overset{\text{OH}}{\text{CO₂Me}}
\]

The 2 mole % AD mix α (162.5 mg) was added to a rapidly stirred solution of t-butanol (1.15 ml), water (1.15 ml), and methanesulfonamide (11 mg) at room temperature. After stirring for 5 min, the solution was cooled to 0°C and stirred until a thick orange-yellow slurry resulted (ca. 10 min). The ester 204 (25 mg, 0.115 mmoles) was added in one portion and the heterogeneous slurry was stirred vigorously for 5 h at 4°C. Solid sodium sulfite (ca. 150 mg) was added at room temperature and the mixture stirred for 1 h. After dilution with water, ethyl acetate was added. Upon separation of the layers, the aqueous layer was further extracted with the organic solvent (x 2). The combined organic layers were washed with 2N KOH and brine, to remove the methanesulfonamide, and the solvent removed in vacuo. Chromatography on silica, using 25% ethyl acetate/hexane to remove the unreacted naphthoate contaminant 205 and 50% ethyl acetate/hexane to elute the diol 206 as a white solid (24 mg, 85%) which was identical to the racemic material prepared above, \([\alpha]^{20}_D +18.0°\) (c = 1.50, CHCl₃). The enantiomeric excess was determined to be 83%, using 19F NMR analysis of the mono-Mosher ester.

A sample was recrystallised from ethyl acetate/hexane to afford white needles,
[\alpha]_D^{20} +22.2° (c = 0.85, CHCl_3). Further recrystallisations did not change the optical rotation.

**Methyl (2R,3S,2'R)-2-hydroxy-3-[2'-methoxy-2'-(trifluoromethyl)phenylacetyl]oxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthoate 207**

A solution of the recrystallised methyl ester diol 206 (4 mg, 16.1 µmoles), triethylamine (6.7 µL, 3 equiv) and dimethylaminopyridine (DMAP) (1.5 mg) in dry dichloromethane (1 ml) was added to (S)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) (synthesised from [R]-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) using the method of Ward\(^{155c}\) (5.2 mg, 1.2 equiv) under nitrogen at room temperature. The reaction was stirred for 24 h and the solvent removed *in vacuo* to afford a mixture of the ester and starting material. Chromatography of the crude material, using 25% ethyl acetate/hexane, gave the Mosher ester 207 as a clear oil (3.5 mg, 47%).

**\(^1\)H NMR** (300 MHz, CDCl_3) δ 3.11 (AB system, δ_A = 3.09, δ_B = 3.13, J_AB = 18.2 Hz, 2H, H1 x 2), 3.27 (dd, J = 11.4, 15.1 Hz, 1H, H4α), 3.32 (dd, J = 6.0 Hz, 15.1 Hz, 1H, H4β), 3.38 (br s, 1H, OH), 3.55 (s, 3H, OMe), 3.63 (s, 3H, CO_2Me), 3.80 (s, 3H, OMe), 5.54 (dd, J = 6.0, 11.4 Hz, 1H, H3), 6.70 (d, J = 8.2 Hz, 1H, H7), 6.73 (d, J = 7.8 Hz, 1H, H5), 7.16 (dd, J = 7.8, 8.2 Hz, 1H, H6), 7.41-7.55 (m, 5H, C_6H_5).
Methyl (2R,3S,2'S)-2-hydroxy-3-[2'-methoxy-2'-(trifluoromethyl)phenylacetyl]oxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthoate 208

\[
\text{R-MTPA-CI} \xrightarrow{\text{NEt}_3/DMAP}} \text{CHCl}_2
\]

The same procedure was used, as the previous reaction, except that the Mosher's acid chloride was derived from (S)-MTPA. The ester 208, after chromatography, was obtained as a clear oil (4.0 mg, 53%).

\(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 3.14 (AB system, \(\delta_A = 3.09, \delta_B = 3.13, J_{AB} = 18.2\) Hz, 2H, H1 x 2), 3.15 (partially obscured, 1H, H4\(\alpha\)), 3.23 (dd, \(J = 6.0\) Hz, 15.1 Hz, 1H, H4\(\beta\)), 3.34 (br s, 1H, OH), 3.50 (s, 3H, OMe), 3.78 (s, 3H, CO\textsubscript{2}Me), 3.80 (s, 3H, OMe), 5.60 (dd, \(J = 6.0, 11.0\) Hz, 1H, H3), 6.70 (d, \(J = 8.1\) Hz, 1H, H7), 6.72 (d, \(J = 7.2\) Hz, 1H, H5), 7.15 (dd, \(J = 7.2, 8.1\) Hz, 1H, H6), 7.36-7.52 (m, 5H, -C\textsubscript{6}H\textsubscript{5}).

6.4.4 Dihydroxylation of Benzyl-type Esters

Benzyl 1,4-dihydro-8-methoxy-2-naphthoate 213

\[
\text{1. N,N-dimidazole carbonyl} \xrightarrow{\text{PhCH}_2OH/DBU}} \text{HBn}
\]

The acid 186 (110 mg, 0.54 mmole) was added in one portion to a solution of N,N-dimidazole carbonyl (150 mg, 2 equiv) in dichloromethane (10 ml) at room temperature. Gas was evolved and the resultant solution was stirred for 30 min. Freshly distilled benzyl alcohol (59 µl) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (84 µl) were added successively and the solution stirred at room temperature for 2 h. The reaction mixture was diluted with dichloromethane and washed with 1 M HCl solution, water, 10% sodium carbonate solution, and
brine. Evaporation of the solvent gave a white solid. Chromatography, using 10% ethyl acetate/hexane, gave the benzyl ester 213 as a white solid in 90% purity (146 mg, 83%). The contaminant was benzyl 8-methoxy-2-naphthoate 215 (10%).

\[ ^{1}H\text{ NMR (300 MHz, CDCl}_{3}\text{)} \delta 3.53-3.70 (m, 4H, H1 x 2 and H4 x 2), 3.85 (s, 3H, OMe), 5.28 (s, 2H, CH}_{2}Bn), 6.73 (d, J = 8.2 Hz, 1H, H7), 6.76 (d, J = 7.7 Hz, 1H, H5), 7.17 (dd, J = 7.7, 8.2 Hz, 1H, H6), 7.20 (m, 1H, H3), 7.30-7.50 (m, 5H, CH}_{2}C_{6}H_{5}). \]

\[ ^{13}C\text{ NMR (75 MHz, CDCl}_{3}\text{)} \delta 23.6 (C1), 30.8 (C4), 55.2 (OMe), 66.2 (CH}_{2}), 107.4 (C7), 120.0 (C6), 122.4 (C4a), 126.8 (C5), 128.1 (2 x CH, CH}_{2}C_{6}H_{5}), 128.5 (2 x CH, CH}_{2}C_{6}H_{5}), 133.0 (C8a), 136.3 (C2), 136.4 (C3), 157.1 (C8), 166.7 (CO_{2}Bn). \]

\[ \text{MS (El) } m/z 218(M^+, 51\%), 159 (100), 144 (61), 127 (31), 115 (56). \]

Benzyl (2RS,3SR)-2,3-dihydroxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthoate rac-216

The benzyl ester 213 was dihydroxylated using the method detailed for the methyl ester except that due to the insolubility of the ester in the solvent system toluene was added to the reaction mixture. The ratio of t-butanol, water, and toluene was 16.7:16.7:2. The reaction was complete after 20 h. Chromatography on silica, using the same solvent systems as for the methyl ester series, gave the benzyl ester diol rac-216 as a white solid (74%). A small sample was recrystallised from ether to afford rac-216 as fine white needles, m.p. 145-147°C.

\[ ^{1}H\text{ NMR (300 MHz, CDCl}_{3}\text{)} \delta 3.14-3.20 (m, 4H, H1 x 2 and H4 x 2), 3.52 (br s, 1H, OH), 3.79 (s, 3H, OMe), 4.31 (dd, J = 6.5, 10.2 Hz, 1H, H3), 5.31 (AB system, \delta_{A} = 5.28, \delta_{B} = 5.34, J_{AB} = 12.3 Hz, 2H, CH}_{2}Ph), 6.68 (d, J = 8.1 Hz, 1H, H7), 6.71 \]
(d, J = 7.7 Hz, 1H, H5), 7.14 (dd, J = 7.7, 8.1 Hz, 1H, H6), 7.20-7.30 (m, 5H, CH₂C₆H₅).

¹³C NMR (75 MHz, CDCl₃) δ 34.0 (C1 or C4), 34.1 (C4 or C1), 55.2 (OMe), 68.0 (CH₂), 69.9 (C3), 76.1 (C2), 107.5 (C7), 120.5 (C4a), 120.9 (C6), 127.0 (C5), 128.0 (CH), 128.5 (CH), 128.6 (CH), 134.8 (C), 135.0 (C8a), 157.2 (C8), 175.6 (CO₂Bn).

MS (EI) m/z 328 (M⁺, 5%), 310 (7), 220 (120), 176 (80), 148 (40), 91 (100).

Analysis calc'd for C₁₉H₂₀O₅: C, 69.50; H 6.14; found: C, 69.24; H 6.06.

Benzyl (2R,3S)-2,3-dihydroxy-8-methoxy-1,2,3,4-tetrahydro-2-naphthoate 216

![Chemical structure](image)

The benzyl ester 213 was asymmetrically dihydroxylated in a similar manner to the methyl ester series except that toluene was added to solubilise the ester. The reaction was complete after 18 h at 4°C. The diol 216 was obtained in 74% yield, using the same workup and chromatography conditions. [α]D²⁰ +2.1° (c = 1.30, CHCl₃). The enantiomeric excess was determined to be 92%, using ¹⁹F NMR analysis on the mono-Mosher ester.

A sample was recrystallised from ether to afford white needles, [α]D²⁰ +2.4° (c = 1.60, CHCl₃). Further recrystallisations did not change the optical rotation.

Diphenylmethyl 1,4-dihydro-8-methoxy-2-naphthoate 214

![Chemical structure](image)
The diphenylmethyl ester 214 was synthesised in a identical fashion to that of the benzyl ester 213 except that diphenylmethyl alcohol was used and the solution was refluxed for 15 min after the addition of the alcohol and DBU. Chromatography, using 10% ethyl acetate/hexane, gave the diphenylmethyl ester 214 (50%) which was contaminated with 30% diphenylmethyl 8-methoxy-1,2,3,4-tetrahydro-2-naphthoate 217. A small sample was purified by MPLC, using 5% ethyl acetate/hexane, to give 214 as a white solid,

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.53-3.70 (m, 4H, H1 x 2 and H4 x 2), 3.85 (s, 3H, OMe), 6.73 (d, $J = 7.7$ Hz, 1H, H7), 6.77 (d, $J = 7.7$ Hz, 1H, H5), 7.05 (s, 1H, CHPh$_2$), 7.17 (t, $J = 7.7$ Hz, 1H, H6), 7.30-7.50 (m, 11H, H3 and CH[C$_6$H$_5$]$_2$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 23.4 (C1), 30.8 (C4), 55.1 (OMe), 76.7 (CHPh$_2$), 107.3 (C7), 119.9 (C6), 122.3 (C4a), 126.7 (C5), 126.8 (CH), 127.0 (2 x CH, CH[C$_6$H$_5$]$_2$), 127.7 (CH), 128.1 (CH), 128.2 (CH), 128.4 (2 x CH, CH$_2$C$_6$H$_5$), 132.9 (C8a), 136.5 (C), 136.6 (C2), 140.4 (C3), 156.9 (C8), 165.6 (CO$_2$CHPh$_2$).

MS (EI) m/z 370(M$^+$, 1%), 324 (0.4), 202 (14), 167 (100), 159 (18), 115 (10), 77 (8).

HRMS (EI) m/z calc'd for M$^+$, C$_{25}$H$_{22}$O$_3$: 370.1569, found 370.1568.
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77. D. Owen, unpublished work.
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165. K. B. Sharpless, personal communication.


APPENDIX

Crystal Data
Compound 175, C_{25}H_{14}O_8, M = 426.35, orthorhombic space group P2_12_12_1 (no. 19), a = 8.7248(2), b = 10.1058(8), c = 32.043(3) Å, V = 3148.95(10) Å³, Z = 4, D_x = 1.547 g/cm³. Colourless needles. Crystal dimensions 0.54 x 0.18 x 0.04 mm, µ(Cu Kα) = 9.29 cm⁻¹.

Data Collection and Processing
Compound 175. Intensities were recorded for 2731 unique reflections by an a/2θ scan, scan width 0.5°, 0.50sec/0°, scan rate 4°/min in a Rigaku-Rigaku AFC6S diffractometer at 298 K with Cu Kα radiation. Intensity data were corrected for Lorentz and polarization factors and for absorption.

Structure Analysis and Refinement
Compound 175. The structure was solved by direct methods with SHELXS-97 and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms could not be refined satisfactorily and were included in calculated positions. The final cycle of full-matrix least-squares refinement was based on 1741 observed reflections (I > 2σ(I)) and 35 variable parameters and converged with unweighted and weighted agreement factors of R = 0.045 and R_w = 0.043. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.41 and -0.19 e Å⁻³, respectively.
Data from Single-Crystal X-Ray Diffraction Analysis of Compound 175.

Crystal Data

Compound 175. C\textsubscript{19}H\textsubscript{18}O\textsubscript{5}, M = 326.35, orthorhombic space group P\textsubscript{2}1\textsubscript{2}1\textsubscript{2}1 (#19), a = 9.786(2), b = 10.106(3), c = 32.043(3) Å, V = 3.168.9(10) Å\textsuperscript{3}, λ = 1.54178 Å, Z = 8, D\textsubscript{c} = 1.368 g/cm\textsuperscript{3}. Colourless needles. Crystal dimensions 0.24 x 0.10 x 0.04 mm, μ(Cu-K\textsubscript{α}) = 8.20 cm\textsuperscript{-1}.

Data Collection and Processing

Compound 175. Intensities were recorded for 2731 unique reflections by an ω-2θ scan, scan width 0.84° + 0.30tanθ°, scan rate 4°/min (in ω), 2θ\textsubscript{max} = 102.2° on a Rigaku-AFC6R diffractometer at 23.0 °C with Cu-K\textsubscript{α} radiation. Intensity data were corrected for Lorentz and polarisation factors and for absorption.

Structure Analysis and Refinement

Compound 175. The structure was solved by direct methods with SHELXS-86 and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms could not be refined satisfactorily and were included in calculated positions. The final cycle of full-matrix least-squares refinement was based on 1741 observed reflections (I > 3.00σ(I)) and 434 variable parameters and converged with unweighted and weighted agreement factors of R = 0.049 and R\textsubscript{w} = 0.043. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.19 and -0.16 e Å\textsuperscript{-3}, respectively.
The full set of data including bond lengths and valence angles for the non-hydrogen atoms, anisotropic thermal parameters and atomic parameters, together with their estimated standard deviations, have been deposited at Cambridge Crystallographic Data Centre.