STUDIES TOWARDS THE TOTAL SYNTHESIS
OF HARRINGTONOLIDE

THIS THESIS IS PRESENTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

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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.

Daniel Harry Rogers
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This thesis describes studies towards the total synthesis of the biologically active diterpene harringtonolide. This complex secondary metabolite contains a structurally interesting tropone functionality and also possesses seven stereogenic centres, six of which are located on a single cyclohexane ring in the molecule. Formation of two of these centres was achieved by an intramolecular aldol reaction and, in the process, the fourth ring of the carbocyclic ring skeleton of harringtonolide was established. Before the aldol reaction, the seven and five membered rings were formed by a rhodium-induced intramolecular cyclopropanation/ring expansion process, by the attack of an $\alpha$-oxo-carbenoid moiety onto a benzene ring.

Chapter 1 delivers an account on the recent history of harringtonolide and briefly discusses its isolation, characterisation, possible biosynthesis and aspects concerning its biological activity. The chapter then proposes a strategy towards its total synthesis based on diazoketone chemistry, and takes into account previous work done in this area.

Chapter 2 describes the synthesis of the tricyclic tetrahydrophenanthrene intermediate 48, which contains a cis-fused ring junction, and how its shape was used to influence the creation of a third stereogenic center. The C-ring was then cleaved to provide the key tetrahydronaphthalene aldehyde 71.

Before embarking on the total synthesis of the natural product the cyclisation methodology was examined on relatively simple, but substrate-like, intermediates. The versatile bicyclic aldehyde 71 was found to be ideal for the synthesis of these model compounds. Chapter 3 discusses their synthesis, the subsequent cyclisation and probes the stability of the resulting cycloheptatriene adducts.

Having established the rhodium-cyclisation methodology it was now time to try it on the actual intermediate. However, it was necessary for the aldehyde functionality of the bicyclic
compound to be homologated first. This chemistry is entailed in the Chapter 4, which also describes the rhodium-carbenoid cyclisation of the homologated intermediate and further studies on model compounds.

Chapter 5 discusses the crucial intramolecular aldol reaction and the subsequent transformation of the resulting $\beta$-hydroxy ketone 69 into the key lactone alcohol 43. The oxidation of the cycloheptatriene moiety and a transannular oxidative ring closure are required to complete the synthesis. Chapter 6 proposes how these transformations might be achieved, and describes some model work in this area.
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<tbody>
<tr>
<td>APT</td>
<td>attach proton test</td>
</tr>
<tr>
<td>dppe</td>
<td>bis(diphenylphosphinyl) ethane</td>
</tr>
<tr>
<td>TBDMS</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>dimethylpyrazole</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarisation transfer</td>
</tr>
<tr>
<td>HETCOR</td>
<td>heteronuclear correlated spectrum</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrum</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>LTA</td>
<td>lead tetraacetate</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrum</td>
</tr>
<tr>
<td>NMMO</td>
<td>N-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Pyr.</td>
<td>pyridine</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>tlc</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-toluenesulphonic acid</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
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CHAPTER 1

INTRODUCTION

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1.1 Introduction

The principal objective of this thesis was to synthesise the biologically active plant growth inhibitor, harringtonolide 1.1,2 This diterpene has been isolated from Cephalotaxus sp. and shows promising antiviral and antitumor activity.2,3 Smaller quantities of a closely related compound, hainanolide 2, were isolated from the same source, but it shows relatively little biological activity.2

![Figure 1.1](image)

The [5,6,6,7] carbocyclic ring arrangement of 1 and 2 is unique in nature, and as such represents a new family of structurally novel secondary metabolites. Furthermore, these were the first naturally occurring tropone-containing compounds possessing a lactone moiety to be isolated.1 In light of these features, it is somewhat surprising that the syntheses of these natural products have received little attention since, coupled with their interesting biological properties, the complexity of their structures presents a considerable synthetic challenge.

Harringtonolide was first isolated from the yew, Cephalotaxus harringtonia, and its structure determined by X-ray crystallographic analysis1,4 and from spectroscopic data (nmr, ms and ir) by Buta, et al.1 The genus Cephalotaxus is a member of the plant family Taxaceae, which also includes the genus Taxus (collectively known as yew trees). The yews have been a rich source of a variety of structurally diverse and biologically potent diterpenes and, consequently, have generated considerable interest in pharmacology, botany and organic chemistry. Certainly the best known series of diterpenes from this source are the taxanes.
In particular, Taxol 3,5 isolated from the bark of the Pacific yew, shows considerable potential as an antitumour agent.6

![Figure 1.2](image)

With regard to the structure of harringtonolide, of particular interest is the presence of the cycloheptatrienone–or tropone moiety–since it is believed that this functionality holds the key to the biological activity of the compound (vide infra). The structurally interesting tropone moiety 4, more commonly as the 2-hydroxytropone 5 (or tropolone) skeleton, is incorporated into a large group of natural products from a broad range of biological sources.

![Figure 1.3](image)

Tropolones are quite prevalent in nature and account for more than 95% of the ca. 92 known troponoid natural products.7 They range in complexity from tropolone 5 itself8a (Pseudomonas plantarii),9 which shows broad-spectrum bactericidal activity,10 to more complex systems such as rubrulone 6 (from Staphylococcus echinoruber),11,12 a food colouring agent, and colchicine 713,14 (mainly from Colchicum sp.),15 which has been used extensively in the treatment of gout,16,17 and also has potential in the treatment of cancer.
In contrast, the parent tropones are relatively scarce. Apart from harringtonolide 1, and hainanolidol 2, nezukone 8 is the only other naturally occurring tropone to have been isolated to date. Nezukone, which has been synthesised in three laboratories,18-20 is found in *Thuja sp.*21 and seems to provide the parent plant with some measure of protection against fungal infection. In addition, a number of simple artificial troponoids have been synthesised, either for their theoretical interest8a-c or for their potential biological activity. For example, 9 shows remarkable antibacterial activity against a variety of gram negative and gram positive bacteria.10

1.2 History and Biological Activity of Harringtonolide

Over 15 years ago, it was discovered that extracts from *Cephalotaxus sinensis* were effective in the treatment of cancer in laboratory animals. Several years later, harringtonolide 1, along with a group of structurally unrelated alkaloids called cephalotaxines (e.g., 10-12, Figure 1.6), were identified as the principal agents most likely responsible for this activity.22
As part of a programme to find new plant growth regulators, Buta and his co-workers\(^1\) examined an ethanolic extract of the seeds from the North American yew, *C. harringtonia* (Forbes), and discovered that the growth of several species of plants were inhibited by application of this extract. From 2.5 kg of ground seeds (after exhaustive extraction with 2-propanol, further washing and purification), 30 mg of pure harringtonolide was obtained as pale yellow crystals. Application of the emulsified compound (10\(^{-3}\)M) to the axils of decapitated tobacco plants effected complete inhibition of bud growth for at least 14 days. Significant inhibition of the growth of bean plants was also observed upon application of low concentrations of harringtonolide in lanolin.

A year later, some Chinese workers\(^2\) reported the isolation of harringtonolide \(1\) from the bark of *C. hainanensis* (Li),\(^{23}\) a yew found predominantly in the Chinese province of Hainan. Extraction of 90 kg of the powdered bark with ethanol, followed by removal of cephalotaxines and other alkaloids with dilute HCl and further purification, provided 820 mg of pure harringtonolide which was called hainanolide. In addition, 140 mg of hainanolidol \(2\) was recovered. During a series of experiments to determine the structure of hainanolidol \(2\), the alcohol was converted to harringtonolide \(1\) via a transannular oxidative ether formation between C(15)-OH and C(5), using lead tetraacetate (LTA) in dry benzene at reflux (Scheme 1.1). Harringtonolide was obtained as one of two major products.\(^{24}\)
In addition to the work described above, Sun and co-workers also investigated the antitumour potential of harringtonolide and found it to be significantly active against sarcoma 180, Walker carcinosarcoma 256, Lewis lung carcinoma, L615 leukemia, P388 leukemia and L1210 leukemia.²

Further investigations were undertaken by Kang et al.³ to establish its potential antiviral activity. Using a plaque inhibition method in tissue culture for determining the effect of the tropone on a range of viruses, they discovered that harringtonolide has broad spectrum activity. In particular, it was found to be significantly active against three RNA viruses, namely influenza virus type A (WS), Newcastle disease virus and Japanese B encephalitis virus (A2), as well as the DNA virus, vaccinia virus.

Despite the interest surrounding the biological activity of harringtonolide and, indeed, the simpler tropones, there has been no reported speculation as to their mode of action in vivo. Presumably their biological activity is centered around the electrophilic tropone moiety with its ability to undergo 1,8-additions with nucleophiles (Scheme 1.2).

Perhaps inspired by harringtonolide’s potent biological activity and its therapeutic and commercial potential, Sun and his co-workers²⁵ undertook a search for a more common and widespread host yew for the purpose of providing larger amounts of harringtonolide. They
found that the bark of *C. fortunei*, which is located in three Chinese provinces, namely Ahui, Fujian and Zhejiang, also contained harringtonolide and, indeed, ir spectrophotometric measurements of extracts taken from trees in each province clearly indicated the presence of 1. Judging from the quantities of harringtonolide obtained from natural sources, however, it would seem unlikely that any viable commercial endeavour will eventuate. 26

1.3 Biosynthesis of Harringtonolide.

As mentioned above, yew trees contain a rich variety of diterpenes, which include the taxanes as well as harringtonolide. 27 A reasonably plausible biosynthetic route (Scheme 1.3) could therefore be postulated that branches from the pathway leading to the taxane ring system 28 and related structures.

Normally, the intermediate verticillol cation 14, which arises from ring closure of geranyl geranyl pyrophosphate 13, can undergo either a simple proton elimination to form verticillol 16, or a reductive ring closure \([C(2) \text{ to } C(7)]\) to form the taxane ring system 15. It is also possible to envisage that 14 could undergo a concerted [1,2]-hydride shift \{from C(10) to C(11)\} and [1,2]-methyl shift \{from C(15) to C(10)\}, respectively, followed by proton elimination to give 17. Subsequent cyclisation to 18, followed by i) a hydride shift to C(15) and an additional cyclisation, and ii) oxidative cleavage of the C(7)-methyl group, would lead to the C-19 harringtonolide ring skeleton 19.
Possible Biosynthetic Route Leading to the Harringtonolide Ring Structure

Scheme 1.3

1.4 Synthetic Strategies.

The simultaneous formation of the 7- and 5-membered carbocyclic ring system of harringtonolide, from an aromatic precursor, was considered to be the pivotal step in any proposed synthetic design. The most popular methods of synthesising tropones (or their precursors) usually involve the formation of an unstable norcaradiene by attack of carbenoids or other suitable species onto a benzenoid or reduced benzenoid ring, followed by rearrangement and consequent ring expansion. Some representative examples are shown in Schemes 1.4-1.6, below.
The procedure involving the carbenoid cyclopropanation/ring expansion cited in Scheme 1.4 was considered to be the most suitable for the synthetic plan, since an intramolecular cyclisation of this type would not only lead to the construction of the bicyclo[5.3.0]decane directly, but would also be expected to be significantly more regioselective than a similar intermolecular process. Other examples of the generation of the [5,7] ring systems in this
way have been reported (Scheme 1.7), the earlier work being done on aromatic diazoketones and esters in the presence of metal catalysts such as copper.\textsuperscript{31-35} The copper catalysts used for this process, however, generally led to low yields of the desired adduct.

![Scheme 1.7]

Cu powder, Cu-bronze, CuCl and the like were the first catalysts used routinely for the cyclopropagation of olefins with diazo compounds, as well as for other processes such as insertion reactions, dipolar additions and ylide generation.\textsuperscript{36} The dominant role of these heterogeneous catalysts has recently been challenged with the advent of powerful Group VIII metal catalysts such as rhodium acetate [Rh\textsubscript{2}(OAc)\textsubscript{4}] and palladium acetate, which have resulted in higher yields in the abovementioned metal-catalysed carbene transformations.\textsuperscript{37,38}

In a recent paper on transition metal-catalysed reactions of diazo compounds, Anciaux et al.\textsuperscript{39} screened a variety of metal catalysts and arrived at the conclusion that, in general, Rh(II) carboxylates were among the most efficient and versatile of all. In the same paper, the authors compared the relative efficiency of Pd, Cu and Rh catalysts for cyclopropanation on a variety of olefins by diazoesters, and found in all cases that Rh gave significantly
greater yields than Cu, and in most cases better yields than Pd. Since then, Rh(II) carboxylates have steadily become the catalysts of choice for most of these processes.

The carbenoid generated from the reaction of metals with diazo compounds is strongly electrophilic and thus usually reacts preferentially with electron-rich functional groups, such as double bonds and heteroatoms. Rhodium carbenoids react with most double bonds indiscriminately, except for strongly electron-deficient olefins (e.g., methyl maleate). Moreover, steric factors can also play a significant role in the selectivity of the reacting carbenoid if it is presented with more than one possible reaction site. Indeed, there is a delicate balance between this and the usually more important electronic considerations.

Carbenoid insertion reactions have also received considerable attention recently, because of their useful synthetic applications. Carbon-hydrogen bond insertion reactions are certainly the most common of this type, though there are other examples which include insertions into N-H, O-H and C-heteroatom bonds. Intramolecular C-H insertions to form 5-membered rings are certainly the most commonly reported. Examples of C-C and primary C-H (i.e., methyl) insertion by ketocarbenoids are very rare or non-existent, although Doyle et al. have noted that carbenoids from diazoesters will insert into the C-H bonds of methyl groups under certain conditions.

To illustrate the substrate preferences of rhodium-induced metal carbene transformations a number of relevant examples are provided in Schemes 1.8-1.12.
These and other examples seem to indicate a preference for attack on nucleophiles by the carbenoid in the following order: heteroatoms ($S^{48} > C=O^{49} > O^{50}$) ~ electron-rich aromatics and olefins (vinyl ethers > styrene) $^{39}$ > other olefins (cyclopentene > cyclohexene)
> 1-hexene) ~ C-H insertion (Ar-H$_{51}$ > CH > CH$_2$ > CH$_3^{44}$). In addition, there appears to be (for intramolecular reactions) a preference for forming 5-membered rings over 6-membered rings as would be expected on entropic grounds; the likelihood of forming larger rings greatly diminishes.$^{43}$ In actual fact, the entropy considerations are often the most important and formation of a 5-membered ring can override the preference for a more nucleophilic group if it results in the formation of a large (i.e., > 6 membered) ring (e.g., Schemes 1.9 and 1.12).

The culmination of all this technology no doubt enticed McKervey and co-workers$^{52}$ (1984) to explore the intramolecular cyclisation of diazoketones derived from dihydrocinnamic acids, using rhodium(II) acetate as the catalyst. The authors found in most of the cases studied (Scheme 1.13) that high yields of tetrahydroazulenones were observed. Interestingly, in the case of 22 the more sterically hindered site is cyclopropanated regioselectively, exemplifying the importance of electronic factors over steric concerns (vide ante).

![Scheme 1.13](image-url)
Following on from this work, Kennedy and McKervey\textsuperscript{53} later published the results of related studies outlining synthetic approaches toward confertin 31, where its 7- and 5-membered rings were derived from a rhodium-catalysed cyclisation. Their use of Rh(II) mandelate\textsuperscript{54} as a catalyst for the diazoketone decomposition was noteworthy, as its efficiency in the cyclisation was reported to be significantly greater than that of Rh(II) acetate.

\[
\text{Rh(II) mandelate} \rightarrow \text{CH}_2\text{Cl}_2, \text{reflux} \rightarrow \text{confertin 31}
\]

As illustrated in Scheme 1.14 (p.9), the mechanism for the rearrangement proceeds via a relatively unstable norcaradiene intermediate which undergoes a reversible electrocyclic rearrangement to the cycloheptatriene. It has been observed in some instances, however, especially when the intermediates are derived from \(\alpha\)-substituted diazoketones, that the energy difference between the two valence tautomers is not great, and the norcaradiene is a significant contributor to the equilibrium. As a case in point, Kennedy and McKervey reported that the cyclisation to form 30 from 27 gave a product which was determined by nmr spectral data to be best represented as a rapid equilibrium between the two tautomers 28 and 29, with the norcaradiene 28 being the major component.\textsuperscript{53} However, in most other cases, the equilibrium usually favours the 7-membered ring system, and the cycloheptatriene is the observed product.

1.5 Synthetic Approaches

Having decided on the diazoketone methodology for forming the [5,7] system, any proposed synthetic plan would require the following:
i) an intermediate containing a highly substituted aromatic ring that would be sufficient electron-rich to react selectively with the diazoketone residue, and then be readily converted to the tropone moiety,

ii) that the carbenoid generated from the diazoketone be suitably placed to react specifically with the required bond in the aromatic ring and,

iii) that the cyclisation reaction be late in the synthesis, since the resultant cycloheptatriene is expected to be relatively labile (especially to acid and oxygen55).

In a proposed retrosynthetic analysis of harringtonolide (Scheme 1.15), the first disconnection of the C(15)-O bond stemmed from the expectation that the C(5β)-alcohol 33 could undergo a transannular oxidative ring closure to C(15) (via 32, pathway A), in an analogous, but opposite manner to the conversion of hainanolidol 2 to harringtonolide (via 36, pathway C).24

Scheme 1.15
The synthesis of the alcohol 33 would be expected to be more straightforward and economical than the corresponding precursors from the other approaches (i.e., 35, 2 and 38) outlined in Scheme 1.15. Pathways B and D are more complicated because they require an oxygen function at C(10) or C(12) with an anti stereochemical relationship to a leaving group at C(12) and C(10), respectively. Pathway C, which would require the prior synthesis of hainanolidol 2, is problematical in that this approach not only requires the absence of an oxygen function at C(10), but also presents the difficulty of establishing the correct stereochemistry of the oxygen function at C(12).

Formation of the azulene ring system in the proposed intermediate 39 was planned from the rhodium-catalysed cyclisation of the diazoketone 40 (Scheme 1.16). The ensuing carbenoid would be expected to add to the aromatic ring to form the unstable norcaradiene intermediate 41, and subsequent ring expansion, followed by isomerisation of the Δ8 double bond with base, would then give the key intermediate cycloheptatriene 39.

The alcohol 33 could be expected to be formed by the diastereofacially controlled reduction of the C(10) carbonyl group in 39 from the less hindered convex (α) face, followed by oxidation of the cycloheptatriene ring to the tropone moiety (Scheme 1.17).
A crucial factor in this proposed synthetic route concerns the securing of the β-stereochemistry of the C(1) diazoketone side chain in 40 (Scheme 1.16). Examination of Dreiding models revealed that the carbenoid generated from the C(1α)-stereoisomer would not be able to reach the aromatic ring, and would be likely to react with another part of the molecule instead. The desired β-stereochemistry could presumably be obtained by way of a kinetically controlled quench in the preformed ester enolate of the proposed intermediate 44 (viz., 47, Scheme 1.18). Transformation of the ester group to the diazoketone residue using standard chemistry would then provide the desired intermediate 40. The lactone ester 44 could conceivably be derived from the β-ketoester 45 by reduction and subsequent lactonisation of the resulting β-hydroxy ester 46.

Scheme 1.17

Scheme 1.18
1.6 Synthetic Progress and Shortfalls

A plausible key building block in the synthetic design was therefore seen to be the tricyclic compound 48. The cis-fused phenanthrene ester 54, which is analogous to the one required, has been previously synthesised by O’Shea.\textsuperscript{56} From the bromo dienone 52, which was constructed using Birch reductive-alkylation chemistry, the phenanthrene was formed in modest yield through an intramolecular radical cyclisation process (Scheme 1.19).

A similar scheme for the synthesis of 48 above was planned and executed\textsuperscript{57} (Scheme 1.20), but with a few strategic modifications to the O’Shea approach. In order to construct the 1-alkyldihydrobenzoate intermediate 59 the synthesis of the aromatic alkylating fragment 58 was required. This was achieved in a six-step sequence starting from the readily available methoxyxylene 55. A considerable improvement in the efficiency of the cyclisation step was essential, and this was accomplished using an alternative acid catalysed cyclisation. As a consequence of the improved yields in the overall synthesis, particularly in the Birch alkylation and cyclisation steps, workable quantities (ca. 10 grams) of the tricyclic $\alpha,\beta$-unsaturated ketone could be obtained (see Chapter 2).
The four stages from 48 to the lactone 64 (Scheme 1.21), have been successfully completed by Russkamp\textsuperscript{58} (1986), albeit with considerable difficulties. In particular, the cuprate addition to the keto-enol mixture 60 and 61, and the subsequent reduction of the resulting mixture of 62 and 63 with sodium borohydride (NaBH\textsubscript{4}), gave relatively low yields. Moreover, to date, all attempts to enolise the ester with a variety of bases have failed. The difficulty in removing the C(10\beta)-proton can be readily appreciated by examination of Dreiding models, which indicate that any incoming base would be severely impeded due to steric hindrance.
Another possible option that was considered (Scheme 1.22) invoked the addition of a borane reducing agent to the olefin 67 and subsequent oxidative cleavage of the alkyl borane to form the \( \alpha \)-hydroxy compound 68. The reagent would be expected to attack from the less crowded convex (\( \alpha \)) face, thus providing the desired stereochemistry at C(5) and C(6). The current synthetic route to the unsaturated aldehyde 65, however, has proved to be longwinded and uneconomical.
1.7 Rethink: An Alternative Strategy.

At this point, an alternative approach to circumvent the problems encountered in the previous synthetic endeavours was desirable. Consequently, a modified synthesis from the convenient tricyclic enone 48 to the critical 10-hydroxy cycloheptatriene 66, was conceived (Scheme 1.24, next page). The new approach revolved around the expectation that the D-ring (Scheme 1.23) could be formed by an intramolecular aldol reaction (see Chapter 5).

In this remodelled strategy, the use of β-ketoesters such as 61 (Scheme 1.21) is avoided, and hence, the problems associated with their tendency to enolise. In addition, the diazoketone residue in 72 is relatively flexible and, accordingly, should be able to reach the aromatic ring. A further (and beneficial) consequence of this new scheme is that the
elaboration of the problematic stereochemistry at C(3a) [C(10) in lactone 44] can be delayed until a later stage in the synthesis.

![Scheme 1.24](image)

Central to this synthetic plan, therefore, is the aldol reaction from the aldehyde 70 to form the β-hydroxyketone 69, and the simultaneous generation of two new stereogenic centers. The potentially troublesome β-elimination of the newly formed β-hydroxyketone would have to be avoided. Also important is the proposed synthesis of the aldehyde 71, which would require an oxidative cleavage of the phenanthrene C-ring at an appropriate stage (see Chapter 2). Homologation of this presumably base-sensitive aldehyde† could be achieved directly using Wittig chemistry or by an extended process, such as Lombardo's alkylating procedure to give a methylenated intermediate which could be further elaborated to give the aldehyde 70 (see Chapter 4).

Another attractive aspect of this new approach is that it provides more immediate access to substrates suitable for model studies of the all-important rhodium-catalysed cyclisation. The

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† In order to preserve the stereochemistry at C(10) in 71, the conditions employed for the homologation step would have to be relatively mild, i.e. free of strong acids or bases.
manipulation of aldehyde 71 to compounds appropriate for the testing of the cyclisation reaction, as well as a discussion of the results, is described in detail in Chapters 3 and 4.

In conjunction with the above series, which incorporates an aromatic methyl group, a des-methyl sequence was also planned for model studies. The synthesis of this series would
a) provide a suitable intermediate that was more easily attainable (the sequence is 3-4 steps shorter without the aromatic methyl group), and
b) provide a significant quantity of material for studies at the leading edge. Furthermore, the possibility of using 73 as a true intermediate in the main synthetic sequence and introducing the methyl group at a later stage was also considered as an option (Scheme 1.25).

\[
\text{Scheme 1.25}
\]
CHAPTER 2

CONSTRUCTION OF THE BICYCLIC ALDEHYDE

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2.4 C-Ring Cleavage: Synthesis of the Bicyclic Aldehyde 33
2.5 Synthesis of the Des-methyl Analogue: A Useful Model Compound 36
2.1 Introduction

As was noted in Chapter 1, the tricyclic α,β-unsaturated ketone 48 is a key building block in the proposed synthesis of harringtonolide. The synthetic approach to 48 was based on similar designs toward other tricyclic compounds; the construction of the bicyclic precursor 76 using Birch reductive alkylation chemistry was considered to be central to the synthetic plan (Scheme 2.1). The synthesis of this alkylation product, its conversion to the tricyclic ketone 48 and ultimately the preparation of bicyclic aldehyde 71 are described in this chapter.

![Scheme 2.1](image)

In a final section of this chapter, the synthesis of the des-C(8)-methyl analogue of aldehyde 71 is detailed.

2.2 Synthesis of the Alkylating Fragment 58

In order to procure 76, it was first necessary to prepare the suitably substituted phenethyl iodide 58 in workable quantities and good overall yield. This was accomplished in a...
six-step sequence starting from the readily available 3,5-dimethylanisole 55 (48% overall yield).

Functionalisation of one of the methyl groups of the dimethylanisole was achieved by a radical bromination process, analogous to the synthesis of 56 recently published by Kunk et al. using N-bromosuccinimide in boiling CCl₄ (Scheme 2.2). The methoxyxylene, when subjected to these conditions in the presence of AIBN (a radical initiator) and tungsten lamps, proceeded smoothly to the desired benzyl bromide 56. In addition a ring-brominated by-product 77 and starting material were also recovered. Although the formation of 77 seemed unavoidable, its formation could be kept to a minimum by running the reaction under relatively dilute conditions with the careful exclusion of water and acid; if these precautions were not taken, ring-bromination occurred almost exclusively. Furthermore, the generation and maintenance of the radical chain was critical, and in this regard it was also important to eliminate oxygen from the system.

\[
\begin{align*}
\text{MeO} & \quad \text{NBS - AIBN} \\
55 & \quad \text{CCl}_4, \uparrow \downarrow \\
\text{MeO} & \quad \text{MeO} \\
56 & \quad \text{Br} \\
+ & \quad \text{Br}
\end{align*}
\]

\textbf{Scheme 2.2}

Relatively pure benzyl bromide could be isolated by distillation of the crude product. However, it was generally used directly in the subsequent reactions, after which the separation of the inert by-product 77 and starting material could be achieved more easily.

A one-carbon homologation of the side chain involving the displacement of the bromine atom with a suitable carbon nucleophile was executed using sodium cyanide in N-methyl-2-pyrrolidinone. Reaction of the bromide under these conditions led to the distillable nitrile 78 (Scheme 2.3) in good yield (91%). An absorption at 2250 cm⁻¹ in the ir spectrum corresponding to a C≡N triple-bond stretch and a resonance at δ117.7 in the ^13\text{C} nmr were clearly indicative of the presence of the nitrile functionality.
The nitrile was then hydrolysed to the corresponding acid 57. The impurities formed in the NBS reaction could be conveniently removed upon a single extraction with diethyl ether, prior to the acidification of the basic reaction mixture which led to the pure acid in essentially quantitative yield (based on pure starting material). Following this, the rapid and efficient reduction of 57 to the phenethyl alcohol was achieved using an excess of lithium aluminum hydride (LAH) in boiling ether. Careful work-up gave carbinol 79 in very good yield (94%).

The conversion of the alcohol functionality in 79 to a suitable leaving group, consequently transforming 79 into a useful alkylating agent for the Birch reduction, was achieved in a two-step process (Scheme 2.4). First, reaction of the alcohol with methanesulfonyl chloride in pyridine led to 80 in 91% yield. A strong absorption at 1360 cm\(^{-1}\) in the ir and the appearance of an extra methyl singlet at 82.86 in the \(^1H\) nmr spectrum was characteristic of the presence of the methanesulfonate residue. Displacement of the mesylate was easily facilitated with NaI in boiling acetone\(^66\) to give the iodide 58 (92%) which, due to a heavy atom effect by iodine, showed a large highfield shift of \(\Delta\delta65\) for C(8) in the \(^{13}C\) nmr spectrum.\(^67\) The crude, stable oil was used directly for the next experiment without further purification.
2.3 Construction of the Tricyclic Intermediate

The construction of polycarbocyclic ring systems using Birch reductive-alkylation methodology is well known and has been widely used in the synthesis of a variety of natural products.60,68 The highly nucleophilic nature of dihydrobenzoate dianions coupled with their ability to be alkylated regioselectively at the C(1)-position with an appropriate electrophile,69 make them ideally suited for the synthesis of 1-alkyl dihydrobenzoic acids.

When this methodology was applied to the system at hand, the resulting 1-alkyl dihydrobenzoic acid 76 was obtained in excellent yield (Scheme 2.5). Alkylation of the dianion, which was preformed by a dissolving metal reduction of benzoic acid [Li/NH3/THF, -78°C], with the iodide 58, afforded essentially pure 76 in 98% yield (based on the amount of benzoic acid used). The isochronism of the signals in the 1H and 13C nmr spectra corresponding to C(2)/C(6) and C(3)/C(5) indicated a plane of symmetry in the molecule.70 These data, in addition to a 2H signal observed for the H(4) protons, confirmed that the desired regiochemical outcome had been achieved.
With 76 in hand, the critical tricyclic compound 48 was synthesised in three stages. First, the acid was protected as the methyl ester 81 using freshly prepared ethereal diazomethane (100% yield). Oxidation of the diene to the dienone 59 gave a substrate suitable for cyclisation, which was achieved with acid catalysis.

The allylic oxidation of olefins to the corresponding α,β-unsaturated carbonyl compounds is a significant transformation in organic synthesis. A number of oxidants based on chromium have been reported to accomplish this process. Regrettably, the majority of these reagents, including sodium chromate in acetic acid/acetic anhydride or the more popular Collin's reagent [CrO₃.(pyr)₂], tend to give only moderate yields and/or the reaction rates are very slow. In addition, problems associated with handling, i.e. the stability of the reagent, difficulty in preparation and problems with work up have made their use less attractive for this procedure.

The reagent chromium trioxide combined with a dimethylpyrazole ligand (CrO₃.DMP), which was introduced by Salmond et al., has been used extensively for the oxidation of dienes to dienones. With its ease of preparation and dramatically improved reaction rates, it is now considered to be the preferred choice of reagent for this process. The ideal conditions for the oxidation of 81 to 59 were to use 8 equivalents of the reagent at -10°C, in CH₂Cl₂ [2h]. Work up of the reaction mixture required the breakdown of the excess organic of chromium complex to insoluble chromium(III) salts. This was conveniently accomplished by stirring with aqueous NaOH. Subsequent adsorption of the aqueous phase onto florisil, and filtration of the resulting flocculent mixture through silica gel, gave an easily manageable filtrate which contained the dienone (65% after chromatography) and recoverable dimethylpyrazole.

In contrast, the procedure outlined by Pearson et al., using t-butyl hydroperoxide and catalytic Cr(CO)₆ led to low yields of the desired product. Apart from the problems
associated with removal of the excessive peroxide on work up, an uncharacterised by-product was formed in significant amounts.

An acid-catalysed cyclisation of the dienone 59 to the tricyclic compound 48 would require a regioselective ring closure from C(8') to C(2)/C(6), in addition to the formation of a cis-fused ring system. This would result in the creation of two stereogenic centres. Acid-promoted cyclisations of compounds of this type strongly favour the formation of the cis-fused product especially when the substrate contains a bulky angular substituent at C(1). The corresponding methoxycarbonyl group in 59 would be expected to impede the approach of the aromatic ring as indicated in Figure 2.1. This would destabilise the transition state and, consequently, disfavour the formation of the trans compound. It is only when the angular group is small (i.e., H) and the adjacent carbon atoms possess substituents that hinder the attack of the aromatic ring from the top face that the trans compound is formed in significant amounts (e.g., Scheme 2.6).

![Figure 2.1](image_url)
A number of acid catalysts were investigated in the cyclisation of 59 to 48; namely PPA, BF₃.Et₂O⁷⁸ and TiCl₄. Of these, PPA was found to give the most favourable ratio of regioisomers. Treatment of the dienone with neat PPA at 35°C gave an 8:1 mixture of the desired enone and its regioisomer† 82 (90% overall yield). It is noteworthy that both regioisomers possess the desired cis-fused ring system and, indeed, no trans-isomers were detected. Low-field signals at δ6.97 and δ6.07 in ¹H nmr spectra as well as a strong absorption at 1685 cm⁻¹ in the ir indicated the presence of the α,β-unsaturated ketone moiety in 48. W-couplings between H(4b) and H(9α) (J = 1.5 Hz) and between H(7) and H(5α) (J = 0.9 Hz) provided further assistance in the structural assignment.

No regioselectivity was observed when TiCl₄ was used as the Lewis acid. The crude ¹H nmr showed roughly equal amounts of both regioisomers. On the other hand BF₃.Et₂O showed a strong selectivity for the undesired regioisomer⁵⁸ Based solely on steric considerations it would be reasonable to expect that 82 would be the major product formed. The bulk of the methoxy substituent is significantly less than that of the methyl group; consequently, peri-interactions with the pro-C(5) proton would tend to preclude the

† An attempt was made to recycle the undesired regioisomer with PPA at 65°C. Only starting material was recovered, indicating that the reaction was not appreciably reversible under these conditions.
formation of 48. In light of this observation it is not entirely clear why PPA gives predominantly the less thermodynamically favoured regioisomer. One reasonable explanation is that the highly polar PPA stabilises the transition state which possesses a greater dipole character and this would appear to be the one (83) that leads to 48 (Figure 2.2).79

![Figure 2.2](image)

Finally an X-ray crystallographic determination80 (Figure 2.3) of the major regioisomer confirmed the structure to be 48. A qualitative observation of the crystal structure, corroborated by the two W-couplings observed in the $^1$H nmr spectrum, indicates that the preferred conformation of the compound in solution is the same as that in the crystalline state.

![Figure 2.3](image)
2.4 C-Ring Cleavage: Synthesis of the Bicyclic Aldehyde

Based on the argument presented in Chapter 1, tricyclic enone 48 was expected to be a desirable intermediate in the synthesis because the convexity and rigidity of the molecule would assist in the preferential attack of the cuprate reagent (Figure 2.4) on the \( \alpha \)-face of the molecule. The propensity of such reagents to add axially should further reduce the likelihood of attack from the more crowded upper face.\(^ {81} \) The mechanism of 1,4-additions by cuprate reagents to \( \alpha,\beta \)-unsaturated ketones, recently postulated by Corey and Hannon,\(^ {82} \) also accounts for the high diastereoselectivity observed (Figure 2.5). This mechanism advocates the reversible formation of the dimethyl copper intermediates 85-88 (Figure 2.5). If this is the case, it is clear that the two possible conformations (i.e., 85 and 86) which arise from attack at the convex (\( \alpha \))-face would have considerably fewer steric interactions than those (i.e., 87 and 88) that arise from attack at the concave face.

![Figure 2.4](image-url)
Access to the bicyclic ring structure (vide ante) was gained by way of a C-ring cleavage of the hexahydrophenanthrene system. In order to secure regioselective control of the ring cleavage, it was considered appropriate to trap the enolate formed in the cuprate addition as the t-butyldimethylsilyl (TBDMS) enol ether. This was easily achieved by the addition of a premixed solution of TBDMS chloride, HMPA and the substrate in THF, to the freshly prepared cuprate. As expected, the α-C(8)-methyl compound was obtained exclusively (>95% ds) as the TBDMS enol ether 89 (91%). The 1H nmr spectrum showed a resonance at δ4.57 which corresponded to the olefinic proton H(7), as well as two vicinal couplings to H(4b) from H(5α) (6.8 Hz) and H(5β) (11.2 Hz). A homoallylic coupling of 1.5 Hz observed between H(8) and H(5β) is additional evidence for the assigned regiochemistry of the enol ether.
Scheme 2.8

The oxidative cleavage of alkyl enol ethers with ozone has been well documented. Methodology for the similar cleavage of TBDMS enol ethers, however, has not been forthcoming. The reasons became evident, as treatment of 89 with ozone under standard conditions \([i] \text{O}_3/\text{MeOH}, -78^\circ\text{C}, \text{ii} \text{Me}_2\text{S}\) gave an intractable oil.

An alternative two-step oxidation process was devised to achieve effectively the same result. Osmylation of 89, and subsequent oxidative cleavage of the resulting epimeric mixture of \(\alpha\)-ketols 90 and 91 with LTA (Scheme 2.9), led to the desired bicyclic system in the form of the aldehyde ester, 71.

Scheme 2.9

Thus, treatment of 89 with a catalytic amount of \(\text{OsO}_4\) in the presence of the co-oxidant, N-methylmorpholine N-oxide (NMMO), gave the \(\alpha\)-ketols as a 4:3 mixture of 90 and 91, respectively (79% overall yield). Interestingly, both compounds appear to have the hydroxy
substituent in an equatorial position where there is the highest probability of hydrogen bonding to the adjacent carbonyl group (Figure 2.6). Although the chair-like conformation adopted by the α-epimer 91 is undoubtedly more stable, the fact that 90 undergoes a conformational change to the skew-boat, evident by the two sets of diaxial couplings observed in the $^1$H nmr spectrum (Figure 2.6), suggests that hydrogen-bonding is sufficiently strong to override the increased non-bonded interactions encountered in the new conformation.

![Figure 2.6](image)

The α-ketols were rapidly and smoothly converted to the ester-aldehyde 71, using LTA in the presence of methanol. The observation of the aldehydic proton (H11) as a doublet at δ10.02 (δ202.7 in the $^{13}$C nmr spectrum) and the appearance of a methoxycarbonyl singlet at δ3.60 in the $^1$H nmr spectrum were indicative of the desired outcome. In addition to the aldehyde, however, the lactol 92 [$^1$H nmr doublet at δ4.93 (acetal H5); γ-lactone absorption at 1775 cm$^{-1}$ in the ir] was also isolated, the amount of which was mainly dependent on the purity of the LTA. Typically, the yield of the by-product varied from 0-15%. The procedure used [CH$_2$Cl$_2$/MeOH (3:2), r.t., 5 min] was a slight variation on that outlined by Hendrick and Anderson$^{86}$ which called for longer reaction times [MeOH/PhH, reflux, 3h]. Under their conditions, significantly more of 92 was observed. Furthermore, 71 transformed into 92 if it was left standing in the presence of traces of acid for a prolonged period.

2.5 Synthesis of the Des-methyl Analogue: A Useful Model Compound

As discussed in Chapter 1, the des-C(8)-methyl analogue of the aldehyde 71 was perceived to be a useful model compound. Starting from the commercially available acid 93, the
synthesis of 104 (Scheme 2.10) followed essentially the same route as its more elaborate cousin, but the fact that it was four steps shorter meant that larger amounts could be synthesised quickly, thereby facilitating exploratory chemistry. Indeed, the only variation (along with a corresponding improvement in yield) on the original scheme was the cyclisation of 99 to the tricyclic intermediate 100 using TiCl₄. Unlike its counterpart 59, treatment of 99 with this reagent at low temperature afforded the single regioisomer 100 in 90% yield. The success of this reaction is presumably due to the lack of steric interactions arising from the aromatic methyl group in 48.
CHAPTER 3

MODEL STUDIES ON THE RHODIUM CATALYSED CYCLISATION

3.1 Introduction

3.2 Choosing a Suitable Model Compound: The Spirolactone

3.3 Rhodium-Catalysed Cyclisation of the Diazoketone

Scheme 3.1
3.1 Introduction

The versatile aldehyde 71 was visualised as an intermediate that could be instrumental not only in exploration of the pathway toward the target compound, but also in conducting the initial model studies on the rhodium-catalysed cyclisation reaction. Before embarking upon a full-scale synthesis of the natural product, it was considered important to examine this methodology on a relatively simple model compound in order to establish the feasibility and facility of the reaction, as well as to probe the lability of the resulting adducts expected from the cyclisation. Subsequently, the transformation of the cyclised adduct to the tropone 108 could be examined, thereby providing valuable information about the chemistry of the benzazulenone system as well as reflecting the methodology required for the main synthetic approach (Scheme 3.1).

![Scheme 3.1]

3.2 Choosing A Suitable Model Compound: The Spirolactone

The bicyclic aldehyde 71 contains a carboxylate moiety (the C(1)-acetate residue) which, upon conversion to 106, would provide the diazoketone with the four-carbon backbone necessary for subsequent formation of the bicyclic [5,7] system. However, the aldehyde
functionality in 71 was considered to be too labile to withstand this process, so it was necessary to transform it to a system that could tolerate the subsequent chemistry. For this purpose the spirolactone 110 was chosen. Formation of the lactone moiety effectively ties back the C(2)-side chain and the C(2)-methoxycarbonyl group. This should confine the likelihood of attack by the proposed carbenoid onto the aromatic ring.

Reduction of the aldehyde with sodium cyanoborohydride [MeOH / HCl at pH 4] (Scheme 3.2) gave the alcohol 109 (67%) [ir: 1730 cm⁻¹ (esters); ¹H nmr 64.02 [H(11)] and 3.50 [H(11')]; ¹³C nmr 664.1 [C(11)]] which readily lactonised to the spirolactone 110 upon treatment with p-toluenesulfonic acid (PTSA) in boiling acetone. An absorption in the ir at 1765 cm⁻¹ indicated that formation of a γ-lactone had occurred. Furthermore, the low field shift of the C(5)-protons in the ¹H nmr spectrum in addition to the presence of ¹³C signals at 6178.4 [C(2)] and 670.7 [C(5)] and the disappearance of the methoxy signals (both ¹H and ¹³C) of the tertiary ester were clearly indicative of the formation of the lactone. The disadvantage of this reduction procedure was that under the acidic conditions of the reduction, the acetal 92 (Chapter 2) was also formed as a by-product (ca. 15%).

The spirolactone 110 could also be obtained by reduction of 71 with either sodium borohydride in methanol or zinc borohydride in diethyl ether / DMF. However, work up
in either case gave the 7-membered lactone 111 in conjunction with the desired lactone 110 in roughly equal amounts. Low field shifts of the C(8) protons (δ4.60 and 4.11) in the 1H nmr spectrum showed the presence of a lactone moiety and the lower energy carbonyl absorption (1730 cm⁻¹ as opposed to 1765 cm⁻¹ for the γ-lactone) indicated that it had a ring size greater than five. Although the components were separable by chromatography the mixture could be used directly for the subsequent hydrolysis.

When either pure 110 or the lactone mixture (110 and 111) was subjected to the hydrolytic conditions of sodium hydroxide in aqueous ethanol, tlc of the respective reaction mixtures indicated the presence of a single compound. However, even on careful acidification, the desired acid 112 was still accompanied by varying amounts of what appeared to be the 7-membered lactone acid 113. Fortunately, 112 (ir: 1765 cm⁻¹ (lactone), 1730 cm⁻¹ (acid), 13C nmr: δ178.1 [C(2)], δ70.7 [C(5)]) was found to be sparingly soluble in ether compared to 113, and on this basis the two could be separated and 113 recycled.

![Scheme 3.3](attachment:image)

The diazoketones synthesised in this thesis were prepared by one of two methods. The carboxylic acid (e.g., 112) was converted either to its acid chloride or to the corresponding methoxycarbonyl anhydride, and subsequent reaction with diazomethane led to the diazoketone.

By far the most widely used of these procedures in the literature is the one that proceeds via the acid chloride. The primary advantage to this method is that diazomethane reacts very rapidly with unhindered acid chlorides and at a reasonable rate with most hindered ones as well. A commonly observed by-product of this reaction, however, is the α-chloroketone.
116 which is formed as a result of the displacement of dinitrogen by chloride ion in the initially formed, highly reactive, alkylation product 115 (Scheme 3.4).92 This side reaction can essentially be avoided by using a combination of low temperatures (-20°C) and a large (ca. 10-fold) excess of diazomethane.93,94 The excessive diazomethane acts as a base to convert the diazonium compound 115 into the less reactive diazoketone 117 and the highly reactive diazonium methane which is produced in the process, is then trapped by the chloride ion. The generation of acid during the formation of acyl chlorides, however, generally precludes their use with acid-sensitive compounds. Although procedures do exist that avoid strongly acidic conditions (e.g., using the pyridine salt of the corresponding acid)91 these tend to be rather cumbersome95 and inadequate with functionalities which are especially acid sensitive (cf. § 4.4).

Scheme 3.4

A mild procedure that avoided the problems mentioned above involved the conversion of the carboxylic acid to the diazoketone via the mixed anhydride.96 In contrast with the acyl halides, however, only unhindered derivatives will react at a reasonable rate. Fortunately, all of the anhydrides synthesised were relatively unhindered and all reacted at satisfactory rates to afford the corresponding diazoketones in good yield. An added advantage of this procedure is that the intermediate anhydrides could be isolated and purified by recrystallisation.
Treatment of the acid 112 with methyl chloroformate in the presence of triethylamine (Scheme 3.5) cleanly afforded the crude anhydride 118 which showed a new methyl signal at δ 3.75 in the $^1$H nmr spectrum and at δ 56.1 in the $^{13}$C nmr spectrum. The crude anhydride (as a solution in a minimal amount of CH$_2$Cl$_2$) was then treated with freshly prepared ethereal diazomethane to give the diazoketone 119 in good yield. Signals at δ 192.8 [C(10')] and δ 54.1 [C(11')] in the $^{13}$C nmr spectrum and δ 5.14 [H(11')] in the $^1$H-nmr spectrum in addition to asymmetric and symmetric C=N=N stretching bands at 2100 and 1360 cm$^{-1}$ respectively, were indicative of the presence of the diazo group.

![Scheme 3.5](image)

The diazoketone could also be made via the acid chloride 120 by sequential treatment of the acid with oxalyl chloride followed by excess diazomethane at low temperature. However, these conditions resulted in low yields of the desired product. The acid 112 is not particularly acid-sensitive, but the low yield could be attributed to the poor solubility of the acid chloride in ether. In this regard, it is important not to add solid compounds to the diazomethane as this tends to promote the decomposition of the reagent.

A similar synthetic route was followed for the conversion of the aldehyde des-methyl analogue 121 to the diazoketone 126 (Scheme 3.6). Interestingly, only traces (ca. 5%) of
the 7-membered lactones 123 and 125 were formed in either the reduction of the aldehyde 121 [Zn(BH₄)₂] or the subsequent hydrolysis of the ester 122. Also of significance was the contrasting solubility of the intermediates compared to the aromatic methyl series. In particular, both the acid 124 and its corresponding acid chloride were found to be freely soluble in ether. Accordingly, the diazoketone 126 (ir: 2105 cm⁻¹ (C=N=N stretch), 1765 cm⁻¹ (lactone), ¹³C nmr: δ193.0 [C(10')], δ180.2 [C(2)]; ¹H nmr: δ5.28 [H(11')]) was easily made via the acid chloride.

![Scheme 3.6](image)

The ¹H and ¹³C nmr spectra of the diazoketones 119 and 126 were unusual in that significant broadening was detected in certain proton and carbon signals. This phenomenon was observed in all of the diazoketones that were synthesised and is discussed in Chapter 4.

### 3.3 Rhodium-Catalysed Cyclisation of the Diazoketone

With the diazoketone 119 in hand, the crucial testing of the cyclisation could be executed. MM2 molecular mechanics calculations performed on 119 indicated that the preferred ground state conformation would have the diazoketone side chain in a pseudo-equatorial position. However, it is possible that the carbenoid can attack the upper (β) face of the aromatic ring with equal facility through either conformer 128 or pseudo-axial conformer.
127 (Scheme 3.7). On the other hand, attack from the bottom (α) face would only be possible though the equatorial conformer 129. However, it could be anticipated that the relatively bulky methyl group would destabilise this transition state. Since α-keto-carbenoids rarely (if ever) insert into either C-C bonds or the C-H bond of methyl groups, and the rest of the molecule is effectively remote it seemed doubtful that the carbenoid generated from 119 would react with any other functional group in the molecule.

As anticipated, slow addition of the diazoketone 119 in CH₂Cl₂ to a catalytic amount of Rh(II) mandelate in boiling CH₂Cl₂ resulted in a remarkably clean reaction affording the cycloheptatriene 130 exclusively. The most striking evidence for the cyclisation was the appearance of olefinic signals in the ¹H nmr spectrum at δ5.79 and 5.54 corresponding to H(8) and H(6) and the disappearance of the aromatic signals associated with the aromatic precursor. Also significant were the higher field resonances of the C(9)-methyl, C(5) and C(4) protons. H(2α) at δ3.32 exhibited numerous splittings due to homoallylic couplings.
with the C(5) protons in addition to vicinal couplings with the C(2) protons, while H(9a) showed up as a very broad singlet. Signals at $\delta 215.1$, 104.3 and 53.0 in the $^{13}$C nmr spectrum corresponding to the carbonyl C(1), the olefin C(6) and the methine carbon C(9a) respectively, supported the structural assignment; absorptions at 1745 [C(1)] and 1760 cm$^{-1}$ ($\gamma$-lactone) in the ir spectrum clearly defined the respective carbonyl moieties.

In contrast, similar treatment of the des-methyl diazoketone 126 with Rh mandelate (Scheme 3.8) under the same reaction conditions led to a mixture of three products, namely, the expected benzazulenone 135, its H(9aa)-epimer 136 and the phenalene 137 resulting from apparent C-H insertion. The cycloheptatriene adducts were unstable to chromatography on silica gel and attempts to do so led to numerous uncharacterised compounds. The decomposition of the cycloheptatrienes is probably caused by the acidic nature of the gel and the presence of oxygen, the latter of which is known to be detrimental to such compounds.55 As a general illustration of the labile nature of these adducts, exposure of the C(9)-methyl cycloheptatriene 130 to the atmosphere overnight led to an intractable mixture.
For 135 the low field doublet of triplets at $\delta 6.00$ in the $^1$H nmr corresponding to H(8), showed a vicinal coupling with H(9) ($J = 9.9$ Hz) and further couplings with both H(9a) ($J = 2.0$ Hz) and H(6) ($J = 2.0$ Hz), while H(9) at $\delta 5.49$ showed a vicinal coupling with H(9a) ($J = 4.4$ Hz) in addition to the coupling with H(8). In all other respects, the remaining signals were similar to those observed for the C(9)-methyl homologue 130. The minor H(9αα) epimer 136 exhibited a complementary set of signals in its $^1$H nmr spectrum to that of 135.

The aromatic signals in the $^1$H nmr spectrum of 137 were analogous to those commonly observed for the aromatic C(8)-methyl compounds. Moreover, a diaxial relationship ($J = 13.1$ Hz) between H(9β) and H(9′α) and the absence of W couplings between H(7′α)
and H(9'α) and between H(4'α) and H(6'a) suggested the structure existed in a half-chair, half-chair conformation (see 137 in Scheme 3.13).

The formation of the α-epimer indicates that the carbenoid is able to attack from the bottom (α) face of the aromatic ring. This requires that the C(1) side chain adopts an equatorial position (i.e., 140) as depicted in Scheme 3.9. Apparently, the relatively small C(8')-proton does not destabilise the transition state associated with the formation of the cyclopropane intermediate as compared to the C(8')-methyl group of the corresponding homologue (cf. Scheme 3.7). On the other hand, the β-epimer 135 could arise by attack of the carbenoid on the top (β) face through either the axial conformer 138 or the equatorial conformer 139.

Scheme 3.9

Two conceivable mechanisms come to mind which explain the formation of the by-product 137. These involve

i) a direct insertion of the carbenoid into the aromatic C(8')-H bond, or
ii) an alternative ring opening of either norcaradiene 132, 133 to give a transient spiro intermediate (see Scheme 3.13) which then rearranges to give the phenalene compound 137.

Nakatani\textsuperscript{98} found that treatment of the diazoketone 141 with Rh\textsubscript{2}(OAc)\textsubscript{4} afforded a high yield of the 2-indanone 142 (Scheme 3.10). This result led him to conclude that the insertion of rhodium keto-carbenoids into aromatic C-H bonds\textsuperscript{99} is favoured over that of aliphatic ones. Therefore, it would not be unreasonable to expect that a similar insertion leading to the by-product 137 would be a rather facile process. However, all the relevant examples, both in the literature\textsuperscript{98,100} and from this laboratory (e.g., Scheme 3.11),\textsuperscript{101} have involved aromatic C-H insertions that led to 5-membered ring formation. In fact, intramolecular insertions of this type into benzene C-H bonds to form 6-membered rings appear to be unknown.

![Scheme 3.10](image)

There is considerable precedence for mechanism ii), also. McKervey and co-workers\textsuperscript{52} found that treatment of the cycloheptatriene 24 (cf. Scheme 1.13) with acid catalysed its conversion, via the minor norcaradiene 148, to the tetrahydronaphthalene 146 (Scheme 3.11).
The mechanism of this transformation implies the intermediacy of the spiro compound \( \text{150} \), which would be expected to rapidly rearrange via a \([1,2]\) shift of the more nucleophilic carbon-carbon bond (i.e., path \( a \)) ultimately leading to \( \text{146} \).

\[ \text{147} \rightarrow \text{148} \rightarrow \text{149} \rightarrow \text{146} \]

\[ \text{150} \rightarrow \text{151} \]

Scheme 3.12

A mechanism involving a spiro intermediate similar to that advocated in Scheme 3.12 could also account for the by-product \( \text{137} \). The rhodium mandelate could act as a Lewis acid to catalyse the reversible migration of the more nucleophilic "enolate" bond in the spiro intermediate \( \text{153} \) (Scheme 3.13) to \( \text{pro-C(6'\alpha)} \). Migration to this centre would occur in preference to \( \text{pro-C(3'\alpha)} \), since it allows the irreversible formation of an aromatic product.\(^\dagger\) Simple proton elimination would then give \( \text{137} \).

\[ \text{153} \rightarrow \text{151} \]

\(^\dagger\) Moreover, migration to \( \text{pro-C(6'\alpha)} \) would be preferred because it possesses greater localised cationic charge.
It is interesting to note that no similar apparent C-H insertion by-product was observed upon cyclisation of either of the other two des-methyl diazoketones subsequently synthesised (Chapter 4). Consequently, it is difficult to favour one mechanism over the other.

Conversion of the triene 130 to the $\alpha,\beta$-unsaturated ketone 157 was accomplished by adding DBU to the reaction mixture followed by an aqueous work-up. Interestingly, an intense purple colour developed upon the addition of the base, but diminished to a yellow colour after ca. 1 sec. Certainly the most obvious aspect of the $^1$H nmr spectrum was the replacement of the C(8) olefinic signal associated with 130 with two higher field signals at $\delta$2.97 and 2.09 corresponding to the new C(8) methylene protons. In addition, a noticeable low field shift of the C(9)-methyl protons, due to deshielding by the carbonyl group, was evident. Furthermore, a signal at $\delta$205.1 [C(1)] in the $^{13}$C nmr spectrum clearly characterised the presence of an $\alpha,\beta$-unsaturated ketone.
Similarly, treatment of the crude reaction mixture which contained 135 and 136 with DBU, led to a single cycloheptatrienone 156. This was then easily separated from the phenalene 137 by chromatography. Predictably, H(9) moved downfield to δ6.07 (from δ5.49 in 136), and a characteristic absorption at 1715 cm⁻¹ indicated the presence of the α,β-unsaturated ketone. Finally, a HETCOR nmr experiment corroborated the carbon-proton connectivities with those that had been assigned through normal ¹H and ¹³C nmr measurements.

There was a notable difference in the relative stabilities of the primary cyclisation products (e.g., 130) and the isomerised compounds (e.g., 157). The former had to be stored in an oxygen-free environment; but even at fairly low temperatures (ca. -5°C) substantial decomposition was observed over a period of two months or so. On the other hand, under the same storage conditions the isomerised material could be kept indefinitely without noticeable change. The C(9a)-proton in 130 would be expected to be highly activated and therefore readily reactive toward oxygen. In addition, under acidic conditions it would be expected that its isomeric norcaradiene, which is in equilibrium with 130, could rearrange further to give a complex mixture of products (cf. Scheme 3.12).
CHAPTER 4

APPLICATION OF THE CYCLISATION METHODOLOGY TO THE MAIN SYNTHETIC ROUTE

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4.1 Introduction

Homologation of the aldehyde 71 (Scheme 4.1) was necessary in order to complete the planned reconstruction of the D-ring to form 69 via an aldol reaction (see Chapters 1 and 5). To this end, a one-carbon extension of the C(2) side chain was investigated and successfully achieved by two different approaches. The more successful of these involved the use of Wittig chemistry. The desired homologated aldehyde could then, in principle, be liberated directly by treatment with acid, or maintained in a protected form as the acetal 160. This chemistry, as well as the ultimate preparation of the cycloheptatriene 162, is described in the latter part of this chapter. The synthesis of the corresponding des-C(9)-methyl analogue of 162 is also detailed.

![Scheme 4.1](image_url)

The second approach involved methylenation of the aldehyde using Lombardo's procedure. The reasons for the synthesis of the olefin 163 were two-fold. First, this stable intermediate could be used for continuing investigations of the rhodium cyclisation methodology (Scheme 4.2) which had been previously demonstrated on the spirolactone compounds (Chapter 3). Further examination was deemed worthwhile because the structure of 163 would more closely resemble the true intermediate that would be used in...
the main sequence. This chemistry, along with that of the des-methyl analogue, is depicted in the first part of this chapter. The second reason for the synthesis of the olefin was that its transformation to the homologated aldehyde 166 could theoretically be achieved by hydroboration and further oxidation. Moreover, the option of introducing an oxygen functionality at C(11) (e.g., to form 167) could be explored. The chemistry and implications of this oxidation are discussed in Chapter 6.

Scheme 4.2

4.2 Synthesis of the Olefinic Diazoketones

A method for methylenating the aldehyde 71 was required that would preserve the stereocenter at C(10). In this regard, Lombardo's procedure, which employs a mixture of TiCl4, CH2Br2 and Zn powder in THF, has been found to be especially useful for the methylenation of base-sensitive carbonyl compounds under essentially neutral conditions. For example, it has been used successfully on the base-sensitive intermediate 169, an intermediate used in the total synthesis of C19 gibberellins (Scheme 4.3). Attempts to achieve this one-carbon homologation with conventionally used ylides (e.g., Ph3P=CH2) led mainly to the C(8a)-epimer of the desired olefin 169.
In this case, although the yields were generally only moderate, the method was nevertheless found to be superior to conventional Wittig reagents for the alkylation of the C(2)-aldehyde residue (*vide infra*). Treatment of 71 (Scheme 4.4) with Lombardo's reagent gave a satisfactory yield (62%) of the desired olefin 163 in addition to numerous uncharacterised by-products. The replacement of the aldehyde signal in the $^1$H nmr spectrum with signals at $\delta 5.13$, $5.09$ [H(12, 12')], and a signal at $\delta 6.07$ [H(11)] which showed couplings to H(10) ($J = 8.9$ Hz), H(12$_{trans}$) ($J = 17.1$ Hz) and H(12$_{cis}$) ($J = 10.3$ Hz), indicated that the desired olefin had been obtained. The moderate yield obtained in this reaction is consistent with that reported by Lombardo during his attempts to methylenate aldehydes. Pinacol formation was cited as a major side reaction in this procedure.

The conversion of the olefin 163 to the diazoketone 164 was accomplished by a procedure analogous to that described for the formation of the spirolactone diazoketone 126 (Chapter 3). Hydrolysis of the ester 163 under basic conditions cleanly afforded the acid 171. Subsequent treatment of the acid with oxalyl chloride and alkylation of the resulting acid chloride with diazomethane gave the diazoketone 164 in good overall yield. A diagnostic absorption in its ir spectrum at 2100 cm$^{-1}$, as well as a characteristically broad signal at $\delta 4.87$ [H(11)] in the $^1$H nmr spectrum confirmed the presence of the diazoketone moiety. The preparation of 164 via the acid chloride was preferred over the anhydride method,
because the olefin intermediates were found to be both acid-stable and ether-soluble (cf. § 3.2).

\[ \text{MeO} \text{MeO} \text{CO}_2\text{Me} \]
\[ \text{MeO} \text{CO}_2\text{Me} \]

\[ \text{NaOH} / \text{H}_2\text{O} \]
\[ \text{EtOH, r.t.} \]

\[ \text{MeO} \text{2} \]
\[ \text{C EtOH, r.t.} \text{HO}_2\text{C} \]

\[ \text{i) } (\text{COCl})_2 \text{CH}_2\text{Cl}, 0\text{°C} \]
\[ \text{ii) } \text{CH}_2\text{N}_2 \text{Et}_2\text{O, } -20\text{°C} \]

\[ \text{Scheme 4.5} \]

Attempted methylenation of des-C(8)-methyl aldehyde 104 under normal 'salt-free' Wittig conditions \[ [(\text{Ph}_3\text{P}^+\text{CH}_3)\text{I}^-/\text{NaN(TMS)}_2, \text{-78°C to r.t.}] \]

led to a mixture of the desired olefin 172 in low yield (40%) together with the cyclopentanone 173 and other unidentified minor by-products, while 104 was easily converted to the olefin 172 (61%) using Lombardo's procedure (Scheme 4.6).

\[ \text{Scheme 4.6} \]

It is highly probable that 173 arose through condensation of the aldehyde enolate 174, which was formed under the basic reaction conditions (Scheme 4.7), with the C(9)-ester functionality. Attack on the transient aldehyde 175 by methoxide ion in a retro-aldol reaction (viz., 176) would eliminate methyl formate and, upon quenching of the enolate, ultimately lead to the cyclopentanone. H(3) gave rise to a doublet of quartets at δ2.70 in the
$^1$H nmr spectrum, showing a W-coupling with one of the C(1) methylene protons ($J = 1.3 \text{ Hz}$; assigned as H(1)), as well as a typical vicinal coupling with the C(3)-methyl group ($J = 7.4 \text{ Hz}$). H(9b) exhibited a W-coupling with H(4α) ($J = 1.3 \text{ Hz}$), in addition to vicinal couplings with H(1) and H(1') ($J = 9.7, 11.0 \text{ Hz}$). While these data clearly supported the structural assignment, the stereochemistry at C(3) could not be assigned with any certainty.

Eventually, conversion of the olefinic ester 172 to the corresponding diazoketone 178 (Scheme 4.8) was accomplished in a manner similar to that described for the C(8)-methyl series.
4.3 Cyclisation of the Olefinic Diazoketones

A high degree of chemoselectivity was achieved upon treatment of the olefinic diazoketone 164 with rhodium mandelate, affording the expected [5,7] cyclisation product 165 in 77% yield (ca. 90% of the crude product). Only a small amount (ca. 10%) of the cyclopropane 179, resulting from attack of the carbenoid onto the terminal olefin of the C(2) side chain, was also detected.

Scheme 4.9

By analogy with the lactone cycloheptatriene 130, the $^1$H nmr spectrum adduct 165 indicated the disappearance of the aromatic signals (around δ6.5) associated with the diazoketone 164, and the appearance of two additional signals at higher field {δ5.79 [H(8)] and δ5.60 [H(6)]}, as well as a broad singlet at δ2.76 [H(9a)] signifying that the cyclisation had occurred. On the other hand, the cyclopropane 179 showed the presence of high field signals in i) the $^1$H nmr spectrum at δ2.09, 1.38, 0.97 and 0.51, corresponding to the four cyclopropane protons H(10a), H(1a), H(1) and H(1'), respectively, and ii) the $^{13}$C nmr spectrum at δ25.2 [C(10a)], 16.1 [C(1a)] and 8.8 [C(1)]. Moreover, large diaxial couplings between H(8b) and H(9β) ($J = 12.8$) and between H(1a) and H(2) ($J = 11.3$ Hz), as well as a W-coupling between H(8b) and H(3α) ($J = 1.7$ Hz) indicated that the preferred conformation was that depicted in Figure 4.1.
The preferential attack of the carbenoid onto the aromatic ring can be mainly attributed to entropic effects, i.e., the formation of 5-membered rings is favoured over the formation of 7-membered rings.\textsuperscript{103,104} Moreover, the reaction of the carbenoid onto a rigid system such as the aromatic ring involves the loss of fewer degrees of freedom than attack onto a freely rotating species such as the terminal olefinic side chain. In this case, electronic factors may have a bearing the overall chemoselective outcome, but it is probably minor.

Similar treatment of the des-methyl olefinic diazoketone 178 with rhodium mandelate (Scheme 4.10) afforded a comparable ratio of the [5,7] cyclised adduct 180 and the cyclopropane 181, in addition to a small number (total ca. 5\%) of unidentified by-products. It is interesting to note that, contrary to the spirolactone model studies (cf. Chapter 3), no products arising from cyclopropanation on the lower (\alpha) face of the aromatic ring or C-H insertion were formed in any detectable (\textsuperscript{1}H nmr) amount.

Finally, addition of DBU to the reaction mixtures of the respective cycloheptatrienes 180 and 165 cleanly isomerised the $\Delta^8$ double bond into conjugation with the C(1)-carbonyl
group (Scheme 4.11). This was evident by examination of the ir spectrum of 183 which showed an \(\alpha,\beta\)-unsaturated ketone carbonyl stretch at 1700 cm\(^{-1}\). In addition, the replacement of the H(8) olefinic proton in the nmr spectrum with two methylene protons at \(\delta\)2.93 and 2.11 gave further support to the assigned structure.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{180 R = H} & \quad \text{182 R = H} \\
\text{165 R = Me} & \quad \text{183 R = Me}
\end{align*}
\]

Scheme 4.11

4.4 Homologation of Aldehyde 71 and Subsequent Conversion to the Diazoketone

The use of Wittig chemistry appeared to be the most obvious and direct way of homologating the aldehyde functionality of 71. This approach would involve the reaction between a carbonyl group and an alkoxymethyleneylide,\(^{105}\) previously generated by treatment of the corresponding Wittig salt with base. It was important to avoid enolisation of the aldehyde since this could lead to the formation of the C(8)-methyl cyclopentanone of 173 or, at a minimum, scramble the stereochemistry at C(10). Wittig reactions that employ the so-called "salt free" conditions (\textit{i.e.}, the use of a sodium or potassium base instead of lithium), have become popular in recent years.\(^{102}\) In particular, sodium hexamethyldisilazide [NaN(TMS)\(_2\)] has been used to improve the Z/E ratio.\(^{106}\) Although stereochemistry is not an issue in this case, the convenience of this reliable and commercially available (as a 1.0\(M\) solution in THF) base made its use attractive.
Reaction of 71 with an excess of the methoxymethylene ylide (Scheme 4.12), preformed from the treatment of very dry [Ph$_3$P+CH$_2$OMe]Cl$^-$ with sodium hexamethyldisilazide, afforded a 2:1 mixture of the (E)-methyleneol ether 158 and the (Z)-isomer 159 as well as varying amounts of the cyclopentanone 184. Although 184 was formed, the amounts were considerably smaller than those obtained from the methylene ylide described previously. In fact, when appropriate measures were taken to exclude moisture totally, the by-product could be almost completely suppressed. The appearance of an additional methoxy signal (158: 83.35 and 159: 83.36) and olefinic signals (158: 86.35 [H(12)], 4.99 [H(11)] and 159: 86.01 [H(12)], 4.63 [H(11)]) indicated the presence of the respective methyl enol ethers. Separation of the three components was rather tedious, and so the mixture was used directly for the next reaction, i.e., the conversion of the (E,Z)-methyl enol ether mixture to the dimethyl acetal 160 (Scheme 4.13).

This choice of protecting group stemmed from the expectation that it could be easily removed under relatively mild conditions at a later stage.$^{107-109}$ In particular, the selective cleavage of
the acetal over the methyl enol ether which would be present in the subsequently formed cycloheptatriene was highly desirable. Consequently, this tended to preclude the use of the conventional ethylene acetal as it seemed likely to possess stability comparable to that of the methyl enol ether. Other methods which involve the formation and removal of substituted acetals under relatively mild conditions have been reported,110 but their use would introduce additional stereogenic centre(s) which would tend to complicate spectral analysis.

Hence, the enol ethers 158 and 159, upon treatment with PTSA in the presence of methanol, were smoothly converted to the dimethyl acetal 160 (Scheme 4.13). The acetal, in contrast to the methyl enol ethers, was significantly more polar than the cyclopentanone 184 formed in the Wittig reaction and so the two components could be easily separated by chromatography. Associated with the introduction of the acetal group was the replacement of the olefinic protons from the methyl enol ethers with a low field doublet of doublets at δ4.46 [H(12)] (13C nmr: δ103.7), which showed vicinal couplings to the two new C(11) methylene protons (J = 8.1, 3.3 Hz).

\[ \text{MeO} \quad \text{MeO} \]
\[ \begin{array}{c}
\text{MeO} \\
\text{MeO2C} \\
\text{H} \\
\end{array} \quad \begin{array}{c}
\text{CO}_2\text{Me} \\
\text{OMe} \\
\text{OMe} \\
\end{array} \]
\[ \text{158} \quad 11-E \]
\[ \text{159} \quad 11-Z \]
\[ \text{MeO} \quad \text{MeO} \]
\[ \begin{array}{c}
\text{MeO} \\
\text{MeO2C} \\
\text{H} \\
\text{CO}_2\text{Me} \\
\text{OMe} \\
\text{OMe} \\
\end{array} \quad \begin{array}{c}
\text{OMe} \\
\text{OMe} \\
\text{OMe} \\
\text{160} \\
\end{array} \]

\[ \text{MeOH, } \uparrow \downarrow \text{ PTSA} \]

\[ \text{Scheme 4.13} \]

Hydrolysis of the ester (Scheme 4.14) was achieved under standard conditions without incident (cf. § 3.2). Subsequent conversion of the resulting acid to the diazoketone was not quite as straightforward, however. Treatment of the acid 185 under the conditions described for the conversion of the corresponding olefinic acid (cf. Scheme 4.5) to the diazoketone 161 gave a complex mixture of uncharacterised products. Presumably the acidic conditions of the oxalyl chloride reaction effected the cleavage of the acetal group. Further exposure of the resultant aldehyde to these conditions and subsequently to diazomethane no doubt resulted in the complex mixture.111 Fortunately, the alternative
method of diazoketone formation \( i.e., \) via the mixed anhydride 186 was available. 185 was converted to 186 by treatment with methyl chloroformate, and reaction of the resulting mixed anhydride with diazomethane led to a good overall yield (75%) of the diazoketone 161, which exhibited the usual features associated with the diazoketone moiety \( \{ ^1H \text{nmr: } \delta 4.99 \text{[H(11)]}; ^{13}C \text{nmr: } \delta 194.1 \text{[C(10)]}; \text{ir: } 2100 \text{cm}^{-1} \} \).

![Scheme 4.14](image)

Essentially identical conditions were employed for the conversion of the des-C(8)-methyl aldehyde 104 to the corresponding diazoketone 192 \( \{ ^1H \text{nmr: } \delta 5.03 \text{[H(11)]}; ^{13}C \text{nmr: } \delta 193.8 \text{[C(10)]}; \text{ir: } 2100 \text{cm}^{-1} \} \) (Scheme 4.15).
4.5 Overview of the Broadening Effect Associated with the Diazoketone Moiety

It is interesting to compare the six diazoketone compounds whose syntheses have been described, with respect to the broadening of some of the signals in the $^1H$ and $^{13}C$ nmr spectra. Figure 4.2 presents a summary of the nuclei which were noticeably broadened. It can be seen from these examples that the nuclei which do show broadening are localised around the diazoketone side chain and, in particular, around the diazo group itself. It would appear that the presence of the diazoketone moiety is therefore responsible for this effect since this phenomenon was not observed in any of the precursors leading up to these compounds.
Significant broadening of the methine protons in the $^1$H nmr spectra of both $\alpha$-diazoacetaldehyde and $\alpha$-diazoacetone (at ambient temperature) has been observed by Kaplan and Meloy.\textsuperscript{112} They proposed that free rotation about the C-C bond might be hindered through interaction of the $\pi$ electrons on the $\alpha$-carbon with the $\pi$ system of the carbonyl group. By performing variable temperature $^1$H nmr experiments, they managed to clearly show that the diazoketones exist as an equilibrium mixture of cis and trans forms. When the temperature was reduced to -18°C, the $^1$H nmr spectrum of $\alpha$-diazoacetaldehyde displayed a singlet corresponding to the methine proton in the predominant cis rotamer (i.e., carbonyl and diazo group in a cis relationship) at lower field to the minor trans rotamer, which existed as a doublet ($J = 7.5$ Hz). Conversely, the methine showed up as a sharp, time-average doublet ($J = 2.2$ Hz) when the temperature was increased to 71°C.

Variable-temperature $^1$H nmr experiments performed on diazoketones 126 and 161 showed similar results and, consequently, implied an analogous mechanism. At 22°C, significant
Figure 4.3
broadening was observed (e.g., see spectrum 1, Figure 4.3). When the temperature was raised by ca. 30°C, to 50°C (spectrum 3), it was clear that the broadening had almost completely disappeared. It is noteworthy that even at 30°C (spectrum 2) a noticeable sharpening of the signals was evident.

It is interesting to note that in examples 161, 164, 178 and 192 (Figure 4.2), only one of the methylene protons is broad while the other is a sharp doublet of doublets. In these cases, the chemical shift of the unbroadened partner is presumably uninfluenced by the different rotamers, which indicates that it is geometrically situated such that it 'sees' both rotamers similarly. Examination of the $^1$H nmr spectra of some other diazoketones (e.g., 193 and 194), suggests that the broadening effect is rather general, although not all diazoketone containing compounds show broadening. For example, H(20) in 195 shows up as a sharp singlet. Due to a significant increase in steric crowding around the diazoketone, this signal may in fact represent a single rotamer!

![Figure 4.4](image)

4.6 Cyclisation of the Diazoketone

Having established the feasibility of the rhodium-catalysed cyclisation, first on the relatively simple spirolactone model compounds (Chapter 3), and then on the more closely related olefinic compounds, it was now time to try the reaction on the true intermediate that would be used in the synthesis of the natural product. Treatment of the diazoketone 161 with
rhodium mandelate gave the expected cyclisation product 162 in conjunction with what appeared to be a 7-membered lactone 196 derived from carbenoid attack onto the C(2)-methoxycarbonyl group. 162 showed signals in the nmr spectra analogous to those for the cycloheptatrienes 165 and 130, indicating that cyclisation had occurred, i.e., two olefinic protons at δ5.77 and 5.56 corresponding to H(8) and H(6), as well as a methine proton at δ2.77 corresponding to H(9a). As expected, only the H(9αβ) epimer of 162 was formed, indicating that the C(8)-methyl group does indeed reduce the likelihood of attack of the carbenoid from the bottom (α) face (cf. § 3.3). The amount of the by-product 196 produced in the reaction seemed to depend on the scale of the reaction. In the exploratory runs, which utilised ca. 50 mg of diazoketone, virtually none of the by-product was detected by 1H nmr; on a larger scale (> 500 mg) 196 could account for up to 10% of the isolated material.

Carbenoids are known to attack the carbonyl oxygen of ester groups to form an oxonium ylide which can react further.49 Similar attack of the carbenoid generated from 161 (viz., 197) onto the C(2)-ester group would generate the ylide 198 which might be expected to undergo an intermolecular alkylation/dealkylation reaction with itself to give the methoxyvinyl lactone 196 (Scheme 4.17). High resolution mass spectra indicated the compound to be isomeric with the cyclised adduct 162. Moreover, the nmr data obtained for this compound also supported the assigned structure. The most significant features of the 13C nmr spectrum was the absence of any signals corresponding to the methoxy of a methoxycarbonyl function or a ketone carbonyl group, while a signal at higher field (δ175.0) signified the presence of an ester (or lactone) functionality [C(4)]. The methyl enol
ether moiety was indicated by the presence of a methoxy signal at δ3.41 (13C nmr: 859.6), and olefinic signals at δ5.97 [H(3)] in the 1H nmr spectrum, and at δ140.9 [C(3)] and 136.8 [C(2)] in the 13C nmr spectrum. One anomaly in this interpretation was the distinct lack of allylic coupling(s) between H(3) and either of the C(1) methylene protons in the 1H nmr. It would not be unreasonable to expect the adjacent C(2)-methoxy group to suppress the coupling between these protons, however. In most other respects the remaining parts of the structure were similar to that of 161.

Scheme 4.17

The entropy argument used to interpret the regiochemical outcome in the cyclisation of the olefinic diazoketone (cf. §4.3) can be invoked to explain this result as well. Judging from a number of relevant examples in the literature (compare ref. 46 and ref. 116, 117), the aromatic ring might be expected to be comparable to the ester with regard to their nucleophilicity and respective attraction for the carbenoid and so the difference would have to be attributed to those entropy factors described previously.

It was envisaged that the des-C(8)-methyl diazoketone 192 would behave in a manner similar to that of the olefinic diazoketone 178, rather than that of the corresponding spirolactone 126, which resulted in the formation of the apparent C-H insertion product in significant amounts upon treatment with the catalyst. This optimistic forecast was fairly critical with regard to the possibility of using the des-methyl cycloheptatriene as an alternative
intermediate in the total synthesis. Fortunately, treatment of the diazoketone 192 with rhodium mandelate led to the single [5,7] cyclised epimer 199, along with only minor unidentified by-products. Moreover, the by-product analogous to 196 above, was barely detectable (ca. 5%).

![Scheme 4.18](image)

Subsequently, addition of DBU to the reaction mixture from the rhodium cyclisation containing either 162 or 199 cleanly isomerised the double bond into conjugation with the carbonyl group. After work up, the respective cycloheptatrienes (for 201; $^1$H nmr: δ 5.13 [H(6)], 2.90 [H(8)] and 2.13 [H(8')]; ir: 1705 cm$^{-1}$) could be separated from the other minor components by chromatography.

![Scheme 4.19](image)
CHAPTER 5

THE ALDOL REACTION: ACCESS TO
THE TETRACYCLIC RING SYSTEM

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5.1 Introduction

With the tricyclic acetal \(201\) in hand, the crucial reconstruction of the D-ring was the next major transformation to be performed. Ring closure was expected to be accomplished by means of a base-catalysed intramolecular aldol reaction between the C(1) carbonyl enolate and the C(12) aldehyde of \(70\). It was considered especially important that the newly formed stereogenic centre at C(3a) of \(69\) possess the \(\alpha\)-stereochemistry as this would result in the required cis-fused ring junction seen in the natural product. Similarly, the stereogenic centre at C(3) would require the \(\alpha\)-stereochemistry, although this would not be quite as vital since the stereochemistry could probably be inverted at a later stage. Prior to the aldol reaction, however, careful and selective removal of the acetal protecting group was necessary to give the aldehyde \(70\). The chemistry of this step is encompassed in the first part of the chapter and is followed by a discussion of the subsequent aldol reaction. In the final part of the chapter the steps from the aldol product \(69\) to the critical lactone intermediate \(43\) are described.

Scheme 5.1
5.2 Cleavage of the Dimethyl Acetal

A method was needed for the efficient and selective removal of the dimethyl acetal protecting group from the cycloheptatriene 201 in the presence of the relatively labile methyl enol ether. It was envisaged that a reagent which promoted indiscriminate cleavage of both protecting groups (e.g., HCl/THF, H₂SO₄/acetone)¹¹⁸,¹¹⁹ might also cause the initially formed deprotected products to react further, resulting in a complex mixture. Although the Lewis acids iodotrimethylsilane and titanium tetrachloride have been shown to remove acetal protecting groups rapidly and efficiently at low temperatures,¹²⁰,¹²¹ their use (especially on a small scale) would be expected to produce varying quantities of acid which could be detrimental to both the starting material and the product(s).

Bromodimethylborane, on the other hand, has been noted to be very effective for removing acetal protecting groups under essentially neutral conditions.¹⁰⁸ Moreover, it has been found to remove acetals selectively in the presence of other sensitive functionalities, such as THP and TBDMS ethers, etc. Indeed, treatment of 201 with one equivalent of Me₂BBr in CH₂Cl₂ at -78°C selectively deprotected the dimethyl acetal in preference to the methyl enol ether. However, the reagent (or traces of acid) also effected isomerisation of the methyl enol ether double bond into conjugation with the C(1) carbonyl group, leading to the aldehyde tautomer 203 as the major product along with smaller amounts of the expected aldehyde 70, the dimethyl acetal tautomer 204 and recovered starting material.
In the aldehyde 70, signals at δ5.15 [H(6)] and δ3.72 [7-OMe] in the ¹H nmr spectrum indicated that the methyl enol ether was still intact, while the appearance of an aldehyde proton [H(12)] at δ9.72 and the disappearance of the dimethyl acetal signals (usually around δ3.5) provided clear evidence that deprotection had occurred chemoselectively.

Associated with the tautomeric aldehyde 203 was the lower field ¹H nmr shift of H(8) (Δδ0.22) as compared with H(6) in 70, as well as high field shifts of H(6) (Δδ0.2; H8 in 70) and H(2a) (Δδ0.4). Large differences lay in the signals of the ¹³C nmr spectra, which showed a low field shift of Δδ9.2 for C(7) which was now experiencing the electron withdrawing effect of the C(1) carbonyl group. In addition, C(5a) was now shielded as a consequence of conjugation to the electron-rich C(7)-methoxy group and, appropriately, exhibited a ca. 10 ppm shift to higher field.

It can be imagined that isomerisation of the enol ether double bond proceeds through a series of protonation/deprotonation steps via the oxonium cation 206, as depicted in Scheme 5.3.
An attempt was made to force the reaction to the tautomeric aldehyde 203 by subjecting the acetal to an excess of Me₂BBr, followed by an immediate quench. As expected, the addition of two equivalents of the reagent increased the amount of the aldehyde tautomer at the expense of the other previously observed products, but the ¹H nmr spectrum also indicated the formation of another minor compound. The addition of a further equivalent of Me₂BBr resulted in the formation of this new product as the major component. The presence of a lone methoxy signal in the ¹H nmr spectrum of the product suggested that both the acetal and the enol ether functionalities had undergone hydrolysis, while the lack of an aldehyde signal indicated that the product might have undergone the desired ring closure in an acid-catalysed aldol reaction (Scheme 5.2).

The formation of the desired aldol product would require the conversion of the C(2) methylene group in 201 to the C(3a) methine group in 205 (Scheme 5.2) and it was anticipated that this change would be clearly evident by inspection of the ¹³C nmr spectrum. However, examination of the ¹³C attached proton test (APT) spectrum of the product quickly revealed that there had been neither the required increase in the number of methine carbon signals nor a corresponding decrease in the number of methylene signals. In fact, it appeared that a methine carbon had been replaced by a quaternary carbon. A more thorough examination of the nmr spectra of the product led to the conclusion that the structure was that of an alternative aldol product, namely the unusual indenoazulene 207 (Figure 5.1).
A single olefinic signal at δ5.94 [H(10)] indicated that only one double bond was in conjugation with the C(9) carbonyl group, while the 13C nmr spectrum showed two relatively high field carbonyl signals at δ204.2 [C(1)] and 201.2 [C(9)] signifying that both carbonyl groups had double bonds conjugated to them. Further to this, the electron deficient C(11b) carbon atom was expected to be significantly deshielded by both enone moieties and was accordingly assigned to the unusually low field signal at δ180.5. This differed from the other, more electron-rich β-enone' C(11) carbon which was allocated to the signal at δ146.1. Also significant was the signal at δ3.04 [H(7α)] in the 1H nmr spectrum which exhibited large diaxial couplings with both H(8α) (J = 12.5 Hz) and H(7α) (J = 12.1 Hz) as well as smaller couplings with H(8β) (J = 7.5 Hz) and H(7β) (J = 6.6 Hz). As a consequence of these couplings, the structure was assigned the conformation depicted in Figure 5.1. Finally, the C(3α)-OH stereochemistry was tentatively assigned on the basis that the chemical shift of the OH proton was situated considerably downfield (δ4.26), which could be accounted for by hydrogen bonding with the C(1)-carbonyl group.

The reaction most likely proceeds via acetal cleavage concurrent with isomerisation of the methyl enol ether 208, followed by its subsequent cleavage to give the doubly deprotected enol product 209 (Scheme 5.4). The excess reagent or traces of acid could then catalyse a sequence of double bond migrations (viz. 209→211) and, ultimately, an aldol reaction with the aldehyde moiety to give 207.

Figure 5.1
It was clearly important, therefore, that the aldol reaction be performed prior to the cleavage of the methyl enol ether since the presence of the C(7) carbonyl tended to create other potential sites for the aldol cyclisation. Figure 5.2 illustrates that many of the protonated carbon atoms in the benzazulene ring system are potentially activated by at least one of the carbonyl groups of the cleaved adduct, as compared to that of the parent intact methyl enol ether, which has only two appreciably acidic sites.
An improved method for removing the acetal in 201 involved a transacetalation with acetone in the presence of a catalytic amount of the Grieco acid, lutidinium tosylate. However, even under these mild conditions, the tautomeric aldehyde 203 and acetal 204 were still formed in appreciable amounts and the desired aldehyde 70 was obtained in little over 50% yield.

![Scheme 5.5](image)

Gorla and Venanzi have been able to form the dimethylidioxolane 214 by a transketalisation from 213 to benzaldehyde using the catalyst [Pd(H2O)2(dppe)](CF3SO3)2 in excellent yield (Scheme 5.5). With this result in mind, it seemed reasonable to expect that the tranacetalation from the acetal in 201 to acetone could be achieved in a similar way. Remarkably, treatment of the acetal with a catalytic amount of [Pt(dppe)](CF3SO3)2 in dry acetone at ambient temperature afforded the aldehyde 70 in comparably good yield (75%), with only minor amounts of the corresponding tautomeric components 203 and 204 (Scheme 5.6). This procedure, which is a variation on the one reported, would appear to be an extremely mild and useful method for removing acetalcs and ketals in general.

![Scheme 5.6](image)
5.3 The Intramolecular Aldol Reaction of the Cycloheptatriene Aldehyde

Having attained the aldehyde 70, the system was now set up for the critical intramolecular aldol reaction necessary for the reconstruction of the D-ring. In addition to the ring closure, there was the question of obtaining the correct stereochemistry at the two new stereogenic centers created in the process. The generation of the pro-C(3αα)-H stereochemistry which would result in cis-fusion of the newly formed ring system was crucial, whereas the formation of the pro-C(3α)-OH stereochemistry was not essential, although highly desirable. The most important issue, however, was to avoid elimination of the initially formed β-hydroxyketone to the olefin.

In order to gain some insight into the likely stereochemical outcome of the aldol reaction, it was necessary to address the key issue as to whether the reaction would proceed under kinetic or thermodynamic control (i.e., whether or not it is reversible). If the aldolate was expected to form under kinetic control, the stereochemical relationship of the two newly formed asymmetric centres could probably be predicted with the Zimmerman-Traxler model, which rationalises the outcome in terms of transition state models on closed chair-like structures involving co-ordination between the two oxygen atoms and the metal centre (cf. Scheme 5.7). With the case at hand, only the (E)-enolate is possible. With this in mind, Dreiding models were examined in order to ascertain the possible transition state structures for the aldol reaction of 70, and it quickly became evident that, according to this model, the transition state resulting in the formation of 69 would have fewer steric interactions than those leading to the other possible isomer(s) (Scheme 5.7). It also became obvious from investigations of the models that the transition states leading to the formation of the two possible trans-fused isomers would be highly unlikely.
Reversible aldolisation, on the other hand, operates under thermodynamic control and so the outcome can be predicted on the basis of the relative stabilities of the four possible products. There are a number of factors that influence the rate of equilibration. First, equilibration of the two stereocentres can be much slower than the rate of reverse aldolisation, especially if the initial aldol (kinetic) reaction is highly stereoselective. As a case in point,\textsuperscript{126} the reaction between 219 and benzaldehyde (Scheme 5.8) gives an 80:1 mixture in favour of the thermodynamically less stable syn adduct, which essentially means that for every 80 reverse reactions (on average) only one anti adduct is formed.

\[ \text{Scheme 5.7} \]

Secondly, aldolates derived from relatively less basic enolates (e.g., ketones) are more likely to undergo reverse aldolisation (and hence syn-anti equilibration) than those derived from
strongly basic enolates (e.g., esters). Steric crowding in the product can also promote the reverse reaction.

With the case at hand, the enolate derived from the ketone would be relatively stable, and so it would be expected that an aldol reaction of this type would proceed under thermodynamic control. Moreover, reverse aldolisation would be enhanced by the use of a base where the metal counter-ion is sodium or potassium, since aldol products under these conditions are known to equilibrate at moderate rates even at low temperatures. Consequently, the stereochemical outcome should depend solely on the relative stabilities of the products. An examination of the four possible aldol products was therefore undertaken by way of MM2 calculations with support from Dreiding models. Based on these calculations (Figure 5.3), it became evident that both of the C(3αα)-H compounds 69 and 218, i.e., those with the cis-fused D-ring, would be favoured over the corresponding C(3αβ)-H, or trans-fused epimers 222 and 223. Surprisingly, the desired C(3αα)-H epimer 69, with the C(3α)-OH in the equatorial position, was predicted to be approximately 0.7 kcal mol\(^{-1}\) less stable than the corresponding C(3β)-OH epimer 218. Although the hydroxy group in 69 would experience a destabilising peri interaction with the in-plane C(4) carbonyl group, it has a better geometry for hydrogen bonding with the carbonyl group than the corresponding arrangement in 218. Clearly, this hydrogen bonding (which was not taken into account in the MM2 calculations) would have to be significant (\(>2\) kcal mol\(^{-1}\)) in order to shift the equilibrium back in favour of the equatorial C(3α)-OH epimer 69.†

Treatment of the aldehyde 70 with potassium carbonate and sodium bicarbonate buffer in methanol gave a ca. 6:1 mixture of isomers, as determined by the \(^1\)H nmr spectrum of the crude product. Examination of \(^13\)C nmr spectra quickly revealed that the major isomer (and most probably the minor compound as well) contained the requisite number of high field methine (4) and methylene (4) carbon atoms and this clearly defined the gross structure to be that of the desired aldol product.

†A ketone functionality was used to mimic the 10α-ester group, because the structural minimisation proceeded more smoothly.
Figure 5.3
MeO 85%, Me K₂CO₃, NaHCO₃, MeOH, r.t.

Scheme 5.9

With regard to the stereochemical outcome, it was established by ¹H nmr spectroscopy that the two components were a mixture of C(3)-OH epimers, both containing the desired cis-fused, or C(3αα)-H, stereochemistry (Scheme 5.9). Moreover, formation of the desired C(3α)-OH epimer 69 (85%) was favoured over the C(3β)-OH epimer 218 (15%).† Evidently, hydrogen bonding between the 3-OH group and the periplanar carbonyl group in 69 is sufficiently strong to override the destabilising strain noted above. Also important was the fact that no products arising from β-elimination of the hydroxy group were detected. This may be a consequence of the gentle conditions employed, or the fact that the C(3α) proton is at a bridgehead position and is constrained to a quasi-equatorial conformation in which overlap between the CH σ orbital and the πₜₜ is poor. Moreover, introduction of an sp² centre would confer considerable ring strain on the molecule.

The stereochemical relationships of the functional groups around the chair-like D-ring of 69 (Figure 5.4) were determined unambiguously by ¹H nmr spectroscopy. H(1) showed a large diaxial coupling (J = 12.4 Hz) with H(2α), which clearly demonstrated their antiperiplanar disposition. Similarly, H(3) exhibited large couplings with both H(3α) (J = 9.9 Hz) and H(2α) (J = 10.8 Hz). On the other hand, a coupling of 7.3 Hz between

† 218 could be re-equilibrated under the same reaction conditions to give a 6:1 mixture of 69 and 218.
H(3a) and H(10b) precluded the possibility of a \textit{trans}-fused ring junction, because this would require an antiperiplanar relationship (and hence a relatively large coupling) between these two protons. In all other respects, the remaining parts of the compound appeared essentially unchanged from its precursor. In contrast to 69, the C(3)-proton of the \(\beta\)-epimer 218 showed only minor couplings to H(2\(\alpha\)) \((J = 2.6 \text{ Hz})\), H(2\(\beta\)) \((J = 3.5 \text{ Hz})\) and H(3a) \((J = 5.3 \text{ Hz})\) [as well as an additional coupling to 3-OH (\(\delta 1.34\)) of \(J = 6.5 \text{ Hz}\)] which is consistent with this proton residing in the equatorial position. Furthermore, H(3) was shifted to lower field (\(\delta 4.36\)) by the deshielding effect of the carbonyl. Similarly, H(1) was noticeably deshielded (\(\Delta \delta 0.43\)) as a result of its close proximity to the axial 3-OH.

\[\text{Figure 5.4}\]

Finally, an X-ray crystallographic determination of the major aldol product confirmed the structure to be 69 (Figure 5.5).\(^{128}\) From a qualitative point of view, the crystal structure was identical to the structure generated by the MM2 programme in all respects.

\subsection*{5.4 Synthesis of the Lactone}

A number of options regarding the synthesis were considered at this stage (Scheme 5.10):

\begin{enumerate}
  \item[i)] the C(4) carbonyl could be reduced, thus forming the diol 202,
  \item[ii)] the C(3) carbinol could be induced to undergo an intramolecular lactonisation with the C(10a) methoxycarbonyl group giving the lactone 224, or
  \item[iii)] the cycloheptatriene could be oxidised to the tropone 225.
\end{enumerate}
Figure 5.5

An inspection of the 3-dimensional view of the isolated product 121 quickly revealed that the lower (6) face was dissymmetric between 2.111. As a consequence of the presence of the COOH carboxyl group, which was expected to result in a facile formation of the β-elimination 201, and amenable to reduction of the carbonyl group, it was transformed to the form of the ZnCl₂-methyl 121, at 0°C under stirring, as the main process. Although the reduction of the α,β unsaturated ketones was a potential problem across a
Scheme 5.10

Attempting to form the lactone immediately was thought to be a doubtful choice, because, under forcing conditions, an acid-catalysed elimination of the β-hydroxy group from the starting material or an analogous base-catalysed β-elimination of the acid functionality in the subsequently formed lactone were both potential problems. Similarly, the conditions forecast for the oxidation of the cycloheptatriene to the tropone could also result in elimination of the β-hydroxy group. Hence, the plan of attack addressed the first option, which was to reduce the carbonyl group to give the diol 202. Under mild reduction conditions, elimination of the C(3)-OH group would be unlikely (vide supra); furthermore, once the ketone is reduced, the C(3)-carbinol would be much less susceptible to elimination during the subsequent stages.

An inspection of the 3-dimensional shape of the aldol product 69 quickly revealed that the lower (α) face was distinctly convex (Scheme 5.11). As a consequence of this, reduction of the C(4) carbonyl group would be expected to result in the exclusive formation of the β-carbinol 202, since hydride delivery should occur from the α-face only. Indeed, reduction of the carbonyl group with sodium borohydride in the presence of CeCl₃ in methanol at 0°C¹²⁹ afforded the C(4β)-carbinol as the major product. Although 1,4-reduction of the α,β-unsaturated ketone was a potential problem, and can occur to a
significant extent with borohydride, any product arising from this side reaction was not
detected. This is probably a consequence of the highly substituted and hindered nature of
the olefin which would restrict access of the hydride to the C(5) center rather than the use of
CeCl₃. H(3a) exhibited a large coupling with H(3) ($J = 9.8$ Hz) and a smaller coupling with
H(10b) ($J = 7.0$ Hz) similar to that observed for 69, but an additional coupling with the
newly formed H(4) ($J = 6.8$ Hz) was also revealing. The appearance at low field ($\delta 3.20$)
of the C(3)-OH proton suggested that it was hydrogen-bonded to the oxygen of the C(4)-OH
group. For this to occur, the C(4)-OH must possess the $\beta$-stereochemistry.

Scheme 5.11

The intramolecular lactonisation between the C(3a)-OH and the C(10a) methoxycarbonyl
group proved to be rather difficult. A number of bases under varying conditions were tried
with little success. Eventually, a small amount of the lactone 43 was formed upon treatment
of the diol with potassium carbonate in boiling methanol under strictly anaerobic conditions.
In order to form the lactone, the D-ring must assume a boat conformation (Scheme 5.12),
but it was not anticipated that this should impede the ring closure. However, the required
breaking of the strong hydrogen bond between the two hydroxy groups no doubt
contributed to the resistance encountered in the lactonisation. Moreover, removal of the
C(4)-OH proton with base would give rise to an even stronger hydrogen bond.
Nevertheless, the lactone was easily separated from the starting material by chromatography,
and hence could be purified and characterised.
The disappearance of the methoxy group in the nmr spectra as well as the low field shift of H(1) (\(^{1}\text{H nmr: 84.85}; {^{13}\text{C nmr: 878.1}}\)) [formerly H(3)], provided clear evidence for the lactonisation and supported the earlier stereochemical assignment of the C(1\(\alpha\))-OH group [formerly C(3)]. The previously assigned stereochemistry at C(3\(\alpha\)) in 69 was also confirmed by inspection of the \(^{1}\text{H nmr spectrum of the lactone, which showed a W-coupling (}J = 1.5 \text{ Hz) between the pro-S H(12) and H(10\(\alpha\)).}^{\dagger}\) A further consequence of the lactonisation was that the pro-R H(12) (\(\delta 2.78\)) was considerably deshielded [compared to the pro-S H(12) at \(\delta 1.38\)] as a result of the close proximity of this proton to the C(10\(\beta\))-OH group. Finally, a large coupling between H(10\(\alpha\)) and H(10\(\beta\)) (\(J = 11.7 \text{ Hz}) indicated that the two protons were eclipsed and this is consistent with the boat conformation of the [2.2.2] bicyclic system.

\(\dagger\) This part of the investigation was carried out before obtaining the confirmatory X-ray structure for 69 and so it was noteworthy that this coupling would not be observed in any of the other isomeric aldol products.
CHAPTER 6

FUTURE DIRECTIONS

6.1 Introduction

6.2 Improving the Lactonisation Step

6.3 Conversion of the Cycloheptatriene to the Tropone Functionality

6.4 An Alternative Route to the Formation of Tetrahydrofuran Ring System

6.5 Harringtonolide as a Biologically Active Lead Compound: Analogues
6.1 Introduction

Two major transformations remain to be performed in order to complete the planned total synthesis of harringtonolide (Scheme 6.1). The first, and presumably the most difficult, is the oxidation of the cycloheptatriene moiety to the tropone (§ 6.3). This could be explored thoroughly on model compounds. The second transformation requires the transannular oxidation/ring closure to form the tetrahydrofuran ring and complete the synthesis.

![Scheme 6.1]

6.2 Improving the Lactonisation Step.

A remaining concern is the poor conversion of the diol to the lactone (see § 5.4, p.88). The yield of this reaction will certainly have to be improved in order to provide sufficient material to complete the final steps. As was discussed in the previous chapter, it was not the process of lactonisation that was inhibitingly slow; in fact the reaction had reached equilibrium after several hours. The reason why the equilibrium was tipped in favour of the diol was assumed to be due to the strong hydrogen bonding between the two carbinol groups. In order to alleviate this problem either the hydrogen bonding will have to be suppressed, or the reaction will have to be performed under non-equilibrating conditions. In the event that the ratio cannot be improved, the components can at least be separated and the diol recycled.
6.3 Conversion of the Cycloheptatriene to the Tropone Functionality.

It can be appreciated that the existing cycloheptatriene functionality and, in particular, the methyl enol ether in 43 would probably not tolerate the conditions forecast for the transannular oxidation/ring closure (lead tetraacetate oxidation). Consequently, it is important to perform the conversion of the cycloheptatriene to the tropone first. However, this conversion is not expected to be trivial. On the one hand, the allylic alcohol is expected to be highly prone to acid-catalysed elimination, while on the other, tropones are known to be relatively unstable, and once formed can undergo further reactions. Nevertheless, two oxidation methods are envisaged that could achieve the desired transformation: i) hydride abstraction to form an intermediate methoxytropylium cation (viz., 226), which could presumably be converted to the tropone 33, or ii) addition of a suitable leaving group via oxidation of the methyl enol ether (viz., 227), followed by elimination. Rather than attempt the cycloheptatriene oxidation on the limited quantity of the advanced intermediate, and run the risk of consuming this valuable material, it would be wiser to perform the exploratory chemistry on a more readily available substrate.

Scheme 6.2

For the purposes of testing the hydride abstraction procedure, the methoxycycloheptatriene 229 was chosen as a model substrate, since it is known that the tropylium cation can...
abstract hydride from a different cycloheptatriene molecule to form a new tropylium cationic species (Scheme 6.2). The equilibrium would be expected to favour the more stable cation, i.e., the methoxytropylium cation 230, which would closely resemble the corresponding cation of the proposed intermediate 226 (Scheme 6.2). In an experiment monitored by $^{13}$C nmr (acetonitrile-$d_3$), 229 was treated with an excess of tropylium tetrafluoroborate 228 which gave methoxytropylium cation 230, along with the reduction product, tropylene 231. After the reaction was complete, the addition of a small amount of water effected the rapid demethylation of this intermediate (no methoxy signals remained in the $^{13}$C nmr spectrum) to give what was presumably the hydroxytropylium cation 232, which is a protonated form of tropone 4.

**Scheme 6.3**

Trityl tetrafluoroborate is another well known hydride abstracting agent, and could also be utilised for the oxidation reaction. However, this procedure (as well as the tropylium cation chemistry) would be expected to generate some traces of acid which would be detrimental to the compound. Consequently, a buffer (e.g., a sterically hindered pyridine) would have to be employed in order to maintain the pH at fairly high level.
6.4 An Alternative Route to the Formation of the Tetrahydrofuran Ring System.

<table>
<thead>
<tr>
<th>R</th>
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<tr>
<td>β-OH</td>
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<tr>
<td>H</td>
<td>anti-OH</td>
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<tr>
<td>α-OH</td>
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<tr>
<td>β-OH</td>
<td>syn-OH</td>
<td>iv)</td>
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Figure 6.1

In Chapter 1, a retrosynthetic analysis of harringtonolide highlighted four possible approaches to the formation of the tetrahydrofuran ring system found in the natural product (Figure 6.1). These were:

i) a transannular oxidative ring closure from 10-OH to C(12), which was the principal approach targeted in this thesis,

ii) a similar ring closure in the reverse sense, i.e. from 12-OH to C(10), which has been accomplished previously by Sun et al.,

iii) an intramolecular displacement of an appropriate oxygen leaving group at C(10) by 12-OH, and

iv) a similar displacement of an appropriate leaving group at C(12) by 10-OH.

Securing a C(12)-OH oxygen functionality would provide other possible routes to the ether ring formation, negate the oxidative ring closure step in approach i), and avoid the problems associated with the acid-sensitive allylic alcohol in 43, since the conditions for the ring closure in approaches iii) and iv) would be expected to be relatively mild. To accommodate approaches ii) and iii), an oxygen functionality at C(12) with the correct relative stereochemistry is required. Hence a study was undertaken to explore ways of introducing this functionality into an earlier intermediate.
The more stereoselective of the procedures investigated involved the osmylation of the olefin 172 whose synthesis was described in Chapter 4 (Scheme 6.4). Treatment of the olefin with catalytic amount of OsO₄ in the presence of the co-oxidant NMMO provided an equal mixture of the γ-lactone 235 \[\text{\textsuperscript{13}C nmr: } \delta 83.1 \text{ [C(5)] and 61.1 [C(6)]} \text{; ir: } 1765 \text{ cm}^{-1} \text{ (γ-lactone)}\] and what was presumably the diol precursor 234 which, upon contact with silica gel, immediately formed 235 (85% yield). It would be reasonable to expect approach by the OsO₄ anti to the bulky substituent (R) (Figure 6.2) and this was consistent with the observed outcome\textsuperscript{132}. Nevertheless, it is rather surprising that no products arising from attack on the opposite (α) face could be detected from inspection of the \textsuperscript{1}H nmr spectrum.

The Conformation Which Minimises A(1,3)-Strain.

\textbf{Figure 6.2}
It is envisaged that either the diol 234 or the lactone 235 could be utilised in the preparation of the aldehyde 236, which would be a key intermediate in the alternative route. The proposed intermediate lactone 238, which could be expected to be synthesised by a similar route to the des-12-oxy lactone (43), would be nicely set up to undergo the ether ring closure (Scheme 6.5).

Scheme 6.5
6.5 Harringtonolide as a Biologically Active Lead Compound: Analogues.

Harringtonolide has been shown to be a potent antileukaemic and antiviral agent (Chapter 1). However, the prospects of obtaining sizeable quantities either synthetically or through natural sources, would not appear to be great. From a commercial point of view, simpler analogues of harringtonolide which possess comparable activity would be considerably more promising. Presumably, the tropone moiety is crucial to the activity and would have to be included in all of the proposed analogues. Ideally, a compound such as the simple benzazulene 239 which contains the A, B and C rings of the natural product, could be relatively easily synthesised and used in preliminary testing (Figure 6.3). Analogues that are more complicated variations on this theme could probably be made using the versatile synthetic route outlined in this thesis. Combined with the methodology for preparing tropones from cycloheptatrienes (§ 6.3), quite an array of analogue substrates could be conceived.

\[
\begin{align*}
\text{239} & \quad \text{240} \\
R = \text{H, Me, etc.}
\end{align*}
\]

Figure 6.3
EXPERIMENTAL
General Topics

i) Melting points were determined with a Reichert hot stage apparatus, and are uncorrected.

ii) Infrared spectra (IR) were recorded on a Perkin-Elmer 683 Infrared spectrophotometer in 0.25mm NaCl solution cells using "Spectrograde" chloroform as the solvent (unless otherwise stated). The following abbreviations are adopted: s (strong), m (medium), w (weak), br (broad), str (stretch), Ar (aromatic), asym (asymmetric), sym (symmetric), oop (out-of-plane).

iii) $^1$H NMR spectra were recorded on several instruments operating at either a) 300 MHz using a Varian XL300E, Varian VXR300S or Varian Gemini 300, or b) 500 MHz using a Varian XL500E. Samples were run in deuterochloroform (99.8% D) (unless indicated otherwise), using residual CHCl$_3$ as an internal standard ($\delta$ 7.26). Data are presented in the following order: chemical shift ($\delta$) relative to tetramethylsilane; multiplicity; relative proton integration; coupling constant $J$; assignment. The following abbreviations are adopted: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); dd (doublet of doublets), dt (doublet of triplets), etc.; (br) indicates a degree of broadening in a signal. First order analyses of spectra were attempted when possible and, consequently, chemical shifts and coupling constants for multiplets may only be approximate.

iv) $^{13}$C NMR spectra were recorded at 50.10 MHz using a JEOL JNM FX200 or, at 75.50 MHz using the 300 MHz instruments described above. Samples were run in deuterochloroform (99.8% D) (unless indicated otherwise), using CDCl$_3$ as an internal standard ($\delta$77.0). Chemical shifts ($\delta$) are reported relative to tetramethylsilane; assignments are based on multiplicities and chemical shifts. The assignments are made by a best fit approximation and so some assignments may be interchangeable. Multiplicities were determined from polarisation transfer techniques (DEPT) or from direct response to C-H couplings (APT).

v) Low resolution electron impact mass spectra (MS) were recorded at 70 e.v. on either a AEI MS 902 or VG-Micromass 7070F double focussing mass spectrometers. Data
are presented in the following order: \( m/z \) value; relative intensity as a percentage of the base peak. High resolution mass spectra (HRMS) were recorded on either of the above instruments using heptacosafluorotributylamine or perfluorokerosene as a reference.

vi) Microanalyses were performed by the Australian National University Analytical Services Unit, Canberra.

vii) Strain energy calculations were determined using the interactive molecular modelling program, called MODEL, which employs Allinger’s MM2 force field. Calculations were carried out on a DEC VAX 11/750 computer running VMS.

viii) Column chromatography was carried out using Merck Kieselgel 60 as the adsorbent generally using various ratios of ethyl acetate/pentane as the eluent. Analytical thin layer chromatography (TLC) was performed on micro-slides coated with Merck Kieselgel KG60F-254. The developed plates were visualised under shortwave ultraviolet light and then stained with 5% (w/v) vanillin in concentrated sulfuric acid at 180°C.

ix) Anhydrous solvents were prepared using standard procedures. In particular, THF and diethyl ether were distilled from the ketyl formed by the reaction of sodium with benzophenone.

x) Reaction temperatures refer to the external bath temperature.

xi) After filtration of solutions from drying reagents, the bulk of the solvent was removed on a Büchi rotary evaporator (water aspirator pressure). The last traces of solvent were then removed under high vacuum.

Notes on Nomenclature

The nomenclature system used in this dissertation conforms to the indexing policies of the Chemical Abstracts Service (CAS Index Guide, Appendix IV), which is generally in accordance with the rules published by the International Union of Pure and Applied Chemistry (IUPAC).
The synthetic route described below from the benzylbromide 55 up to, and including the TBDMS enol ether 89, was originally investigated by Dr W. F. Russkamp. Since a majority of the characterisations (i.e., all 300 MHz spectra, microanalyses and the X-ray analysis of 48, as well as numerous IR and MS measurements) and, in some cases, significant modifications and/or improvements to the procedures have been carried out by the Author, however, the details are included in this thesis. Similarly, the sequence in the des-methyl series from acid 93 up to and including enone 100 was originally outlined by Dr. J. Rheinheimer but the majority of the analyses were carried out by the Author.

2.1 Aromatic Methyl Series

1-Bromomethyl-3-methoxy-5-methylbenzene 56.

A catalytic amount (0.5 g) of AIBN was added to a mixture of 1-methoxy-3,5-dimethylbenzene 55 (27.2 g, 200 mmol; Rf = 0.82, 20% ethyl acetate in pentane), carefully dried N-bromosuccinimide (44.0 g, 247 mmol) and dry CCl₄ (350 mL) in a 1-L, 2-necked flask, fitted with a condenser and a nitrogen inlet. The mixture was irradiated with two 250 W tungsten lamps and heated at reflux until all of the NBS had been consumed (ca. 1 h).
The cooled reaction mixture was washed sequentially with 2M NaHSO₃ solution, water and brine, and the aqueous washings were back-extracted with CH₂Cl₂. The combined organic phases were filtered through phase-separation paper and dried further over anhydrous MgSO₄. Removal of solvent in vacuo afforded a pale yellow oil which was distilled under reduced pressure. The first fraction (3.8 g) was comprised mostly of starting material (ca. 70%) and the benzyl bromide 56 (ca. 30%), while the second fraction contained only 56 (28.8 g, 67%; bp 85-90°C/0.05 torr). Further purification by chromatography (20% ethyl acetate in pentane) and recrystallisation from ethyl acetate/pentane gave the product (Rf = 0.72) as white needles, mp 42-43°C.

\[\text{1}^1\text{H NMR (CDCl}_3, 300\text{ MHz), } \delta 6.77, 6.69, 6.64 (3 \times \text{s(br), } 3 \times 1\text{H, ArH}), 4.39 (\text{s, } 2\text{H, H7}), 3.78 (\text{s, } 3\text{H, 3-OMe}), 2.69 (\text{s(br), } 3\text{H, 5-Me}).\]

\[\text{13C NMR (CDCl}_3, 300\text{ MHz), } \delta 159.7 (\text{C3}), 139.8 (\text{C1}), 134.3 (\text{C5}), 122.6 (\text{C6}), 113.7 (\text{C2}), 112.0 (\text{C4}), 55.1 (3-\text{OMe}), 41.0 (\text{C7}), 21.4 (5-\text{Me}).\]

IR (film, cm\(^{-1}\)) 2960 (C-H str), 2840 (C-H str), 1598(s) (Ar C=C str), 1465 (Ar C=C str), 1300(s) (C-O str), 1155(s), 1065(s) (C-O str), 840 (C-H oop bend), 695(s) (C-H oop bend).

MS, m/z (relative intensity, %) 216 (M/++, 27.3), 214 (M+-1, 29.2), 136 (13), 135 (100), 91 (10).

ANALYSIS: Calcd for C₉H₁₁BrO: C, 50.26; H, 5.15; Br, 37.15.

Found: C, 50.05; H, 5.18; Br, 37.13.

The third fraction and residue was comprised mostly of 2-bromo-5-methoxy-1,3-dimethylbenzene 77 (ca. 20% of total; Rf = 0.60).
3-Methoxy-5-methylbenzeneacetonitrile 78.

Dried NaCN (6.86 g, 140 mmol) was added in one portion to a solution of the benzyl bromide 56 (15.1 g, 70.2 mmol) in dry N-methylpyrrolidinone (100 mL) at room temperature under a nitrogen atmosphere. The solution was left to stir overnight.

The reaction mixture was diluted with ether, washed sequentially with 2M HCl, water and brine, and the organic phase was then dried over MgSO₄. Evaporation of the solvent and distillation of the resulting pale yellow oil gave pure nitrile 78 (10.3 g, 91%; Rᵣ = 0.50, 17% ethyl acetate in pentane) as a colourless oil (bp 136-141°C/17 torr).

¹H NMR (CDCl₃, 300 MHz), δ 6.72 (s(br), 1H, H6), 6.66 (s(br), 2H, H2, H4), 3.78 (s, 3H, 3-OMe), 3.66 (s, 2H, H7), 2.32 (s(br), 3H, 5-Me).

¹³C NMR (CDCl₃, 300 MHz), δ 159.8 (C3), 140.0, 130.9 (C1, C5), 120.7 (C6), 117.7 (-CN), 113.9 (C2), 110.3 (C4), 54.9 (3-OMe), 23.0 (C7), 21.0 (5-Me).

IR (film, cm⁻¹) 2940 (C-H str), 2840 (C-H str), 2250 (C≡N str), 1600(s) (Ar C=C str), 1465(s) (Ar C=C str), 1330(s), 1290(s) (C-O str), 1070(s) (C-O str), 830 (C-H oop bend), 705 (C-H oop bend).

MS, m/z (relative intensity, %) 162 (M⁺+1, 11.1), 161 (M⁺, 100), 160 (13), 146 (33), 135 (12), 121 (16), 116 (15), 91 (34).

ANALYSIS: Calculated for C₁₀H₁₁NO: C, 74.51; H, 6.88

Found: C, 74.36; H, 6.84.
3-Methoxy-5-methylbenzeneacetic Acid 57.

An aqueous solution of 3M KOH (50 mL, 150 mmol) was added slowly to a stirred solution of the nitrile 78 (10.8 g, 67.0 mmol) in ethanol (100 mL) at room temperature and the resulting solution was heated at reflux for 11 h.

The reaction mixture was concentrated in vacuo, diluted with water and extracted with ether to remove non-aqueous impurities. The acidified aqueous phase (pH 2) was then extracted thoroughly with ether and the combined ether phases were washed successively with water and brine, and dried over MgSO4. Evaporation of solvent afforded essentially pure acid 57 (Rf = ca. 0.1, 17% ethyl acetate in pentane) as a pale yellow solid. Recrystallisation from ethyl acetate/pentane gave white needles (12.0 g, 99%), mp 86°C.

¹H NMR (CDCl₃, 300 MHz), δ 6.68 (s(br), 1H, H6), 6.64 (s(br), 2H, H2, H4), 3.76 (s, 3H, 3-OMe), 3.56 (s, 2H, H7), 2.29 (s(br), 3H, 5-Me)

¹³C NMR (CDCl₃, 300 MHz), δ 177.7 (-CO₂H), 159.5 (C3), 139.5, 134.3 (C1, C5), 122.5 (C6), 113.6, 111.9 (C2, C4), 54.9 (3-OMe), 40.9 (C7), 21.2 (5-Me).

IR (CHCl₃, cm⁻¹) 3700-2500(br,s) (O-H, C-H str), 1710(br) (C=O str), 1600(s) (Ar C=C str), 1460(s) (Ar C=C str), 1295(s) (C-O str), 1155 (C-O str), 1065(s) (C-O str).

MS, m/z (relative intensity, %) 180 (M⁺+1, 5.3), (M⁺, 48.9), 136 (17), 135 (100), 121 (14), 105 (18), 91 (37), 77 (22).
HRMS: Calcd for C_{10}H_{12}O_{3}: 180.0786. Found: 180.0802.

3-Methoxy-5-methylbenzeneethanol 79.

A solution of the acid 57 (30.0 g, 167 mmol) in dry diethyl ether (60 mL) was added dropwise, via a dropping funnel, to a stirred suspension of LiAlH₄ (6.8 g, 170 mmol) in dry ether (200 mL) under nitrogen. The reaction was maintained at a gentle reflux for a further 2-h.

The excess of hydride was carefully destroyed by the slow addition of saturated brine and then sufficient 2M HCl was added to dissolve completely all the remaining precipitate. The aqueous phase was extracted with ether and the combined organic phases were washed sequentially with water, saturated NaHCO₃ solution and brine, then dried over MgSO₄. Removal of solvent in vacuo afforded pure carbinol 79 (R_f = 0.35, 25% ethyl acetate in pentane) as a colourless oil (26.0 g, 94%).

H NMR (CDCl₃, 300 MHz), δ 6.65, 6.61, 6.51 (3 x s(br), 3 x 1H, ArH), 3.38 (t, 2H, \(^3J_{8,7} = 6.6\) Hz, H8), 3.78 (s, 3H, 3-0Me), 3.20-3.00 (s(br), 1H, 8-OH), 2.80 (t(br), \(^3J_{7,8} = 6.6\) Hz, H7), 2.32 (s(br), 3H, 5-Me).

C NMR (CDCl₃, 300 MHz), δ 159.7 (C3), 140.0, 139.7 (C1, C5), 122.3 (C6), 112.5, 111.7 (C2, C4) 63.4 (C8), 55.0 (3-0Me), 39.2 (C7), 21.4 (5-Me).

IR (CHCl₃, cm⁻¹) 3700-2800(br,s) (O-H str), 2940(s) (C-H str), 2840 (C-H str), 1598(s) (Ar C=C str), 1460(s) (Ar C=C str), 1290(s) (C-O str), 1150(s) (C-O str), 1070 (C-O str), 835 (C-H oop bend), 700 (C-H oop bend).
MS, m/z (relative intensity, %) 166 (M⁺, 61.3), 148 (6), 136 (50), 135 (100), 123 (24), 121 (19), 105 (33), 91 (33), 79 (16), 77 (16).

ANALYSIS: Calcd for C₁₀H₁₄O₂: C, 72.26; H, 8.49. Found: C, 72.15; H, 8.55.

3-Methoxy-5-methylbenzeneethanol Methanesulfonate 80.

A solution of the carbinol 79 (28.1 g, 169 mmol) in dry pyridine (200 mL) was cooled to -10°C under nitrogen and a solution of methanesulfonyl chloride (21.3 g, 186 mmol) in CH₂Cl₂ (20 mL), was added slowly over ca. 5 min. The resulting mixture was maintained at -10°C and stirred for a further 2 h.

Water (5 mL) was added slowly at -10°C and, after stirring at 0°C for 15 min, the reaction mixture was diluted with ether and washed with sufficient 2M HCl to remove the pyridine, then with saturated NaHCO₃ solution, and finally with brine. The organic phase was dried over MgSO₄ and solvent removed in vacuo to give the clean mesylate 80 (37.6 g, 91%; Rₐ = 0.38, 25 % ethyl acetate in pentane), which was used directly without further purification.

¹H NMR (CDCl₃, 300 MHz), δ 6.64, 6.62, 6.58 (3 x s(br), 3 x 1H, ArH), 4.39 (t, 2H, ³J₈,7 = 6.4 Hz, H₈), 3.77 (s, 3H, 3-OMe), 2.98 (t(br), 2H, ³J₇,8 = 6.4 Hz, H₇), 2.86 (s, 3H, -OSO₂Me), 2.31 (s(br), 3H, 5-Me).

¹³C NMR (CDCl₃, 300 MHz), δ 159.8 (C₃), 139.9, 137.5 (C₁, C₅), 122.1 (C₆), 113.1 (C₄), 111.6 (C₂), 55.0 (3-OMe), 70.3 (C₈), 37.0 (8-OSO₂Me), 35.4 (C₇), 21.4 (5-Me).
IR (CHCl₃, cm⁻¹) 2960 (C-H str), 2840 (C-H str), 1600(s) (Ar C=C str), 1460(s) (Ar C=C str), 1360(s,br) (S=O asym str), 1295 (C-O str), 1170(s) (S=O sym str), 1075 (C-O str), 955 (S-O str), 840(s) (C-H oop bend).

MS, m/z (relative intensity, %) 244 (M⁺, 14.5), 149 (20), 148 (100), 136 (5), 135 (35), 119 (5), 117 (7), 105 (10), 91 (17), 77 (10).

ANALYSIS: Calcd for C₁₁H₁₆O₄S: C, 54.08; H, 6.60; S, 13.12.

Found: C, 53.98; H, 6.53; S, 13.29.

1-(2-Iodoethyl)-3-methoxy-5-methylbenzene 58.

NaI (5.0 eq, 100 g, 670 mmol) was added to a stirred solution of the mesylate 80 (32.0 g, 131 mmol) in acetone (280 mL) at room temperature over ca. 5 min, and the solution was maintained at reflux temperature under nitrogen for 2 h.

Ether was added to the cooled reaction mixture, and the resulting slurry was washed sequentially with water, 1M NaHSO₃, water and brine and dried over MgSO₄. Evaporation of the solvent gave pure iodide 58 (Rf = 0.9, 25% ethyl acetate in pentane) as a pale yellow oil (33.3 g, 92%), which was used directly without further purification.

¹H NMR (CDCl₃, 300 MHz), δ 6.66, 6.64, 6.58 (3 x s(br), 3 x 1H, ArH), 3.81 (s, 3H, 3-OMe), 3.36 (m, 2H, H7), 3.14 (m, 2H, H8), 2.36 (s(br), 3H, 5-Me).
\(^{13}\)C NMR (CDCl\(_3\), 300 MHz), \(\delta\): 159.7 (C3), 141.8 (C1), 139.6 (C5), 121.4 (C6), 112.9 (C4), 110.9 (C2), 55.0 (3-OMe), 40.3 (C7), 21.4 (5-Me), 5.3 (C8).

IR (CHCl\(_3\), cm\(^{-1}\)) 2960 (C-H str), 2840 (C-H str), 1595 (s) (Ar C=C str), 1460 (s) (Ar C=C str), 1290 (s) (C-O str), 1260 (s), 1170 (s), 1150 (s), 1065 (s) (C-O str), 840 (C-H oop bend).

MS, m/z (relative intensity, %): 277 (M\(^{+}\) + 1, 2.8), 276 (M\(^{+}\), 26.5), 150 (11), 149 (100), 134 (16), 119 (28), 117 (17), 115 (10), 91 (48), 77 (23).

ANALYSIS: Calcd for C\(_{10}\)H\(_{13}\)I: C, 43.50; H, 4.75; I, 45.96.

Found: C, 43.44; H, 4.74; I, 46.03.

1,4-Dihydro-1-[2-(3-methoxy-5-methylphenyl)ethyl]benzoic Acid 76.

Benzoic acid (10.9 g, 89.5 mmol) was added to a solution of freshly distilled, dry NH\(_3\) (400 mL) and dry THF (100 mL) in a 3-necked flask fitted with a dry-ice condenser and a nitrogen inlet, at -78\(^\circ\)C. Lithium metal (1.31 g, 2.1 eq) was added in small aliquots until the reaction mixture sustained a persistent blue colour. The solution was maintained at reflux temperature (-30\(^\circ\)C) for 20 min and then cooled to -78\(^\circ\)C while a solution of the iodide 58 (26.0 g, 94.2 mmol) in dry THF (50 mL) was added dropwise, via a syringe, over ca. 10 min. The reaction mixture was refluxed at -30\(^\circ\)C for 0.5 h and the NH\(_3\) was allowed to boil off over 3 h.

The volatile components were removed in vacuo and the residue partitioned between water and pentane. The layers were separated and the aqueous phase, after acidification to pH 2
with 2M HCl, was extracted with ether. The combined ether phases were washed with water and brine and dried over MgSO4. Removal of solvent in vacuo gave the acid 76 as a white solid (28.9 g, 98% based on the amount of benzoic acid used).

1H NMR (CDCl3, 300 MHz), δ 6.61, 6.57, 6.54 (3 x s(br), 3 x 1H, ArH), 6.00 (m, 2H, H3, H5), 5.85 (m, 2H, H2, H6), 3.79 (s, 3H, 5'-OMe), 2.75-2.68 (m, W1/2 = 8.5 Hz, 2H, H4), 2.54-2.48 (m(br), 2H, H1')*, 2.31 (s(br), 3H, 7'-Me), 2.08-2.00 (m, 2H, H2')*

13C NMR (CDCl3, 300 MHz), δ 181.3 (-CO2H), 159.6 (C5'), 143.2 (C7')*, 139.0 (C3')*, 126.6 (C2, C6), 126.3 (C3, C5), 121.6 (C8'), 112.1 (C4')†, 110.9 (C6')†, 55.0 (5'-OMe), 47.7 (Cl), 41.0 (C4), 30.6 (C1')‡, 26.1 (C2')‡, 21.4 (7'-Me).

IR (CHCl3, cm⁻¹) 3500-2420(br) (O-H str), 2950 (C-H str), 1700(s) (C=O str), 1595(s) (Ar C=C str), 1460 (Ar C=C str), 1295 (C-O str), 1150(s) (C-O str), 1065 (C-O str), 840 (C-H oop bend).

MS, m/z (relative intensity, %) 272 (M+, 4.0), 227 (11), 150 (100), 149 (57), 135 (40), 119 (13), 105 (87), 91 (50), 79 (28), 77 (30).

ANALYSIS: Calcd for C17H20O3: C, 74.97; H, 7.40.
Found: C, 74.96; H, 7.19.

1Assignments followed by the same superscript symbol (i.e., *, †, ‡, or ¥) may be interchanged.
Methyl 1,4-Dihydro-1-[2-(3-methoxy-5-methylphenyl)ethyl]benzoate 81.

![Chemical structure](image)

An ethereal solution of the acid 76 (23.7 g, 87.1 mmol), in an unscratched Erlenmeyer flask, was cooled to 0°C and a freshly prepared solution of diazomethane in ether was added dropwise until the solution maintained a constant yellow colour. Excess diazomethane was back-titrated with glacial acetic acid, and the solvents removed in vacuo to afford the pure ester 81 (R_f = 0.63, 25% ethyl acetate in pentane), as a pale yellow oil (24.9 g, 100%).

**1H NMR (CDCl₃, 300 MHz), δ 6.60, 6.56, 6.54 (3 x s(br), 3 x 1H, ArH), 5.97 (m, 2H, H3, H5), 5.85 (m, 2H, H2, H6), 3.78 (s, 3H, 5'-OMe), 3.71 (s, 3H, -CO₂Me), 3.71 (s, 3H, -CO₂Me), 2.73-2.68 (m(br), W_1/2 = 6.5 Hz, 2H, H4), 2.51-2.44 (m, 2H, H1'), 2.31 (s(br), 3H, 7'-Me), 2.03-1.96 (m, 2H, H2').

**13C NMR (CDCl₃, 300 MHz), δ 175.0 (-CO₂Me), 159.6 (C5'), 143.3, 139.2 (C3', C7'), 126.8 (C2, C6), 126.0 (C3, C5), 121.5 (C8'), 111.9, 110.9 (C4', C6'), 54.9 (5'-OMe), 52.0 (-CO₂Me), 47.7 (C1), 41.1 (C4), 30.6, 26.0 (C1', C2'), 21.3 (7'-Me).

**IR (CHCl₃, cm⁻¹) 2950(s) (C-H str), 1730(s) (C=O str), 1598(s) (Ar C=C str), 1460(s) (Ar C=C str), 1230(s) (C-O str), 1070(s) (C-O str), 840 (C-H oop bend), 695 (C-H oop bend).

**MS, m/z (relative intensity, %) 286 (M⁺, 23.8), 227 (40), 150 (100), 105 (79), 137 (11), 135 (39), 91 (30).

**ANALYSIS:** Caclcd for C₁₈H₂₂O₃: C, 75.50; H, 7.74.

Found: C, 75.64; H, 7.78.
Methyl 1,4-Dihydro-1-[2-(3-methoxy-5-methylphenyl)ethyl]-4-oxobenzoate 59.

\[
\begin{align*}
\text{MeO} & \quad \text{CO}_2\text{Me} \\
\text{81} & \quad \text{CrO}_3 / \text{DMP} \\
\text{MeO} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

Dry \text{CrO}_3 (19.5 g, 195 mmol) was added to a 2-necked flask, fitted with a nitrogen inlet and charged with \text{CH}_2\text{Cl}_2 (150 mL), and this suspension was cooled to -20°C. \text{3,5-Dimethylpyrazole} (19.6 g, 200 mmol) was added in one portion and the resulting dark brown solution was stirred for a further 20 min at -10°C. A solution of the diene \text{81} (7.00 g, 24.5 mmol) in \text{CH}_2\text{Cl}_2 (10 mL) was added dropwise over \text{ca.} 2 \text{ min, and the temperature was allowed to rise to } -5°C \text{ over } 3 \text{ h.}

A solution of 5\text{M NaOH} (100 mL, 500 mmol) was slowly added and the temperature was allowed to rise to 0°C over 30 min. Florisil (~30 g) was added and the resulting green slurry was stirred at 0°C for 15 min, then filtered through a plug of silica gel. The filtrate was concentrated, diluted with ether and washed sequentially with 2\text{M HCl, 2M NaHSO}_3, water, saturated NaHCO₃ and brine. The solution was dried (MgSO₄), concentrated and chromatographed (25% ethyl acetate in pentane) to give the dienone 59 (Rₙ = 0.21), as a pale yellow oil (4.8 g, 65%).

\(^1\text{H NMR (CDCl}_3, 300 \text{ MHz}, \delta 7.09 (d, 2\text{H}, J_{2,3} = J_{6,5} = 9.8 \text{ Hz, H2, H6}, 6.56, 6.53, 6.46 (3 \times \text{s(br), 3} \times 1\text{H, ArH}, 6.40 (d, 2\text{H}, J_{3,2} = J_{5,6} = 9.8 \text{ Hz, H3, H5}, 3.76, 3.75 (2 \times \text{s, 2} \times 3\text{H, 5'-OMe, -CO}_2\text{Me}, 2.48-2.43 (m, 2\text{H, H2}')*, 2.30-2.20 (m, 2\text{H, H1}')*, 2.20 (s, 3\text{H, 7'-Me}).
Methyl (4βα, 8αα)-4b,5,9,10-Tetrahydro-2-methoxy-4-methyl-6-oxophenanthrene-8α(6H)-carboxylate 48.

Neat dienone 59 (3.50 g, 11.7 mmol) was added to a dry, 2-necked flask fitted with a mechanical stirrer and a nitrogen inlet. Warm PPA (100 mL) was added and the mixture was stirred at 35°C for 2 h.

The resulting viscous, dark brown mixture was poured over ice-chips (250 g) and the rate of hydrolysis was increased by rigorous agitation with a stirring rod. The resulting mixture was extracted once with ether and twice with ethyl acetate and the combined organic phases were washed with saturated bicarbonate solution and brine, then dried over MgSO4. Evaporation of solvent and repeated chromatography (25% ethyl acetate in pentane) afforded an 8:1 mixture of regioisomers 48 (2.8 g, 80%) and 82 (350 mg, 10%). The desired
isomer 48 ($R_f = 0.19$) was recrystallised from ethyl acetate/pentane to give colourless cubes, mp 133-134°C.

$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$ 6.97 (d, 1H, $^3J_{8,7} = 10.3$ Hz, H8), 6.50, 6.46 (2 x dd(br), 2 x 1H, $^4J_{1,3} = 4J_{3,1} = 2.0$ Hz, H1, H3), 6.07 (dd, 1H, $^3J_{7,8} = 10.3$ Hz, $^4J_{7,5a} = 0.9$ Hz, H7), 3.96 (dd(br), 1H, $^3J_{4b,5b} = 14.1$ Hz, $^3J_{4b,5a} = 4.4$ Hz, H4b), 3.73 (s, 3H, 2-OMe), 3.65 (s, 3H, -CO$_2$Me), 2.98-2.78 (m, 2H, H10), 2.67 (ddd, 1H, $^2J_{5a,5b} = 17.1$ Hz, $^3J_{5a,4b} = 4.4$ Hz, $^4J_{5a,7} = 0.9$ Hz, H5α), 2.41 (m, 1H, H9α), 2.33 (s(br), 3H, 4-Me), 2.32 (dd, 1H, $^2J_{5b,5a} = 17.1$ Hz, $^3J_{5b,4b} = 14.1$ Hz, H5β), 2.02 (m, 1H, H9β).

$^{13}$C NMR (CDCl$_3$, 300 MHz), δ 198.1 (C6), 173.5 (-CO$_2$Me), 157.7 (C2), 152.0 (C8), 137.1 (C10α), 134.7 (C4), 128.8 (C7), 128.2 (C4a), 115.0 (C3)*, 111.4 (C1)*, 55.0 (2-OMe), 52.7 (-CO$_2$Me), 49.2 (C8α), 41.7 (C5), 35.7 (C4b), 27.4 (C10†), 26.1 (C9†), 18.9 (4-Me).

IR (CHCl$_3$, cm$^{-1}$) 2950 (C-H str), 2840 (C-H str), 1735 (C=O str, ester), 1685 (C=O str, enone), 1605 (Ar C=C str), 1485 (Ar C=C str), 1255 (C-O str), 1145 (C-O str), 1060 (C-O str), 855 (C-H oop bend), 805 (C-H oop bend), 780 (C-H oop bend), 755 (C-H oop bend).

MS, $m/z$ (relative intensity, %) 301 (M$^+$+1, 19.7), 300 (M$^+$, 97.9), 242 (12), 241 (64), 240 (25), 148 (100), 212 (11), 149 (15), 135 (13).

ANALYSIS: Calcd for C$_{18}$H$_{20}$O$_4$: C, 71.98; H, 6.71.

Found: C, 72.12; H, 7.03.
Methyl (4bα, 8aα)-4b,5,9,10-Tetrahydro-4-methoxy-2-methyl-6-oxophenanthrene-8a(6H)-carboxylate 82.

The minor isomer 82 (R_f = 0.26) was recrystallised from ethyl acetate/pentane to give colourless plates, mp 121-123°C.

1H NMR (CDCl₃, 300 MHz), δ 6.95 (d, 1H, 3J₈,₇ = 10.1 Hz, H₈), 6.52 (s(br), 2H, H₁, H₃), 6.08 (d(br), 1H, 3J₇,₈ = 10.1 Hz, H₇), 4.14 (dd(br), 1H, 3J₄b,₅β = 13.8 Hz, 3J₄b,₅α = 4.6 Hz, H₄b), 3.81 (s, 3H, 4-OMe), 3.67 (s, 3H, -CO₂Me), 2.95 (dd(br), 1H, 2J₅α,₅β = 17.0 Hz, 3J₅α,₄b = 4.6 Hz, H₅α), 2.92-2.74 (m, 2H, H₁₀), 2.35 (m, 1H, H₉α) 2.28 (s, 3H, 2-Me), 2.24 (dd, 1H, 2J₅β,₅α = 17.0 Hz, 3J₅β,₄b = 13.8 Hz, H₅β), 1.97 (m, 1H, H₉β).

13C NMR (CDCl₃, 300 MHz), δ 198.2 (C₆), 173.1 (-CO₂Me), 156.4 (C₄), 151.2 (C₈), 136.4 (C₁₀α), 134.2 (C₂), 128.4 (C₇), 123.2 (C₄α), 121.3 (C₃)*, 108.7 (C₁)*, 54.9 (4-OMe), 52.3 (-CO₂Me), 49.2 (C₈α), 40.4 (C₅), 32.8 (C₄b), 26.6 (C₁₀)†, 26.1 (C₉)†, 21.1 (2-Me).

IR (CHCl₃, cm⁻¹) 2960 (C-H str), 1735(s) (C=O str, ester), 1680(s) (C=O str, enone), 1615 (C=C str), 1585 (Ar C=C str), 1460 (Ar C=C str), 1245 (C-O str), 1180 (C-O str), 1060 (C-O str), 830 (C-H oop bend).

MS, m/z (relative intensity, %) 301 (M⁺+1, 19.1), 300 (M⁺, 100), 242 (12), 241 (67), 240 (21), 212 (9), 148 (25).

ANALYSIS: Calcd for C₁₈H₂₀O₄: C, 71.98; H, 6.71.
Found: C, 72.33; H, 7.01.
Cyclisation Using Titanium Tetrachloride.

To a solution of the dienone 59 (100 mg, 0.33 mmol) in dry CH₂Cl₂ (3 mL) under nitrogen, was added TiCl₄ (50 µl) dropwise at -20°C. The resulting dark red solution was allowed to warm to room temperature over 20 min and was then quenched by the dropwise addition of water (1 mL). The mixture was extracted with ether and the combined organic phases washed sequentially with water and brine, and dried over MgSO₄. Removal of solvent in vacuo afforded a pale yellow oil (92 mg), which was determined by the ¹H nmr spectrum to contain ca. 4:1 mixture in favour of the undesired regioisomer 82.

**Methyl (4bα,8α,8aα)-4b,5,9,10-Tetrahydro-2-methoxy-4,8-dimethyl-6-[dimethyl-(1,1-dimethylethyl)silyl]oxyphenanthrene-8a(8H)-carboxylate 89.**

Methyl lithium (1.60M, 100 mL, 160 mmol) was added dropwise to a stirred suspension of dry CuI (15.3 g, 80.3 mmol) in dry THF (100 mL) at -20°C under a nitrogen atmosphere. The resulting pale yellow solution of Me₂CuLi was allowed to warm to -10°C over 15 min. The reaction mixture was again cooled to -20°C, a mixture of the ketone 48 (8.00 g, 24.0 mmol), t-butyldimethylsilyl chloride (4 eq, 14.5 g, 96.3 mmol) and HMPA (8.4 mL) in THF (30 mL) was added dropwise over ca. 5 min, and the solution was allowed to warm to 0°C over 2 h.

The reaction mixture was poured into ice-cold 2M NH₃ and the resulting blue mixture extracted with ether. The extracts were washed with sufficient 2M NH₃ to remove all remaining traces of copper, then with water and finally with brine. The ether phase was dried over MgSO₄ and concentrated in vacuo, and residual silicon containing impurities were
removed under high vacuum at 70°C to give a clear oil which solidified on standing. The
pure enol ether 89 (Rf = 0.85, 17% ethyl acetate in pentane) was filtered, washed with
pentane and crystallised further from ethyl acetate/pentane to give colourless cubes, mp 102-
104°C. Flash chromatography of the concentrated mother liquor gave an overall yield of
10.4 g (91%).

$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$ 6.24, 6.10 (2 x d(br), 2 x 1H, $^4$J$_{1,3} = ^4$J$_{3,1} = 2.2$ Hz, H1, H3), 4.57 (dd, 1H, $^3$J$_{7,8} = 5.3$ Hz, $^4$J$_{7,5\beta} = 1.5$ Hz, H7), 3.41 (s, 3H, 2-OMe), 3.22 (s, 3H, -CO$_2$Me), 3.18 (dd(br, partially obscured), 1H, $^3$J$_{4b,5\beta} = 11.2$ Hz, $^3$J$_{4b,5\alpha} = 6.8$ Hz, H4b), 2.62-2.41 (m, 2H, H10), 2.05 (s(br), 3H, 4-Me), 2.02 (dd, 1H, $^2$J$_{5\alpha,5\beta} = 18.0$ Hz, $^3$J$_{5\alpha,4b} = 6.8$ Hz, H5$\alpha$), 2.01 (m, 1H, H8), 1.83-1.67 (m, 2H, H9), 1.44 (dddd, 1H, $^2$J$_{5\beta,5\alpha} = 18.0$ Hz, $^3$J$_{5\beta,4b} = 11.2$ Hz, $^4$J$_{5\beta,7} = 1.5$ Hz, $^5$J$_{5\beta,8} = 1.5$ Hz, H5$\beta$), 0.63 (d, 3H, $^3$J$_{Me,8} = 6.8$ Hz, 8-Me), 0.59 (s, 9H, -SiC(Me)$_3$), -0.16, -0.20 (2 x s, 2 x 3H, -Si(Me)$_2$).

$^{13}$C NMR (CDCl$_3$, 300 MHz), $\delta$ 176.0 (-CO$_2$Me), 157.0 (C2), 147.0 (C6), 136.2, 134.6 (C10a, C4), 132.5 (C4a), 113.9 (C3)*, 111.4 (C1)*, 107.9 (C7), 54.8 (2-OMe), 51.2 (-CO$_2$Me), 48.6 (C8a), 38.0 (C4b), 34.8 (C5), 30.7 (C8), 27.0 (C10)$^\dagger$, 26.0 (C9)$^\dagger$, 25.5 (-SiC(Me)$_3$), 19.6 (4-Me), 18.8 (8-Me), 17.9 (-SiC(Me)$_3$), -4.4, -4.7 (-Si(Me)$_2$).

IR (CHCl$_3$, cm$^{-1}$) 2950(s) (C-H str), 2860(s) (C-H str), 1725(s) (C=O str), 1680 (C=C str), 1610(s) (Ar C=C str), 1460(s) (Ar C=C str), 1260(s,br) (C-O str, Si-Me sym bend), 1170(s) (C-O str), 1050(s) (Si-O str, C-O str), 840(s,br) (Si-O str, Si-C str, C-H oop bend)).

MS, m/z (relative intensity, %) 430 (M$^+$, 4.1), 373 (7), 233 (15), 232 (100), 201 (6), 173 (13), 141 (9), 75 (59).

HRMS: Calcd for C$_{25}$H$_{38}$O$_4$Si: 430.2539. Found: 430.2539.
ANALYSIS: Calcd for C$_25$H$_{39}$O$_4$Si: C, 69.72; H, 8.89.
                      Found: C, 70.02; H, 9.02.

Methyl (4$\alpha$,7$\beta$,8$\alpha$,8$\alpha$$\alpha$)-4$\beta$,5,7,8,9,10-Hexahydro-7-hydroxy-2-methoxy-4,8-dimethyl-6-oxophenanthrene-8$\alpha$(6$H$)-carboxylate 90.

The enol ether 89 (3.56 g, 8.28 mmol) was added to a stirred solution of NMMO (1.6 eq, 1.55 g, 13.2 mmol) in a 30:20:1 mixture of acetone, water and t-butanol (150 mL) at room temperature under nitrogen. The solution was cooled to -5°C and a catalytic amount of OsO$_4$ (3 large crystals) in t-butanol (2 mL), was added dropwise. The cooling bath was removed and the solution was stirred at ambient temperature for 24 h.

The reaction mixture was diluted with ether and washed sequentially with 2M HCl, water, saturated bicarbonate and brine and dried over MgSO$_4$. The volatile components were removed in vacuo and the resulting black oil chromatographed to give the $\alpha$-hydroxyketones (2.17 g, 79%) as a 4:3 mixture of $\beta$- and $\alpha$-epimers. The $\beta$-epimer 90 ($R_f = 0.31$, 33% ethyl acetate in pentane) recrystallised from ethyl acetate/pentane as white needles.

$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$ 6.57, 6.44 (2 $\times$ d(br), 2 $\times$ 1H, $^4$J$_{1,3} = 4$J$_{3,1} = 2.6$ Hz, H1, H3), 4.46 (d(br), 1H, $^3$J$_{7,8} = 12.3$ Hz, H7), 4.12 (ddd, 1H, $^3$J$_{4b,5\beta} = 13.6$ Hz, $^3$J$_{4b,5\alpha} = 4.2$ Hz, $^4$J$_{4b,9\alpha} = 0.9$ Hz, H4b), 3.74 (s, 3H, 2-OMe), 3.63 (s, 3H, -CO$_2$Me), 3.41-3.48 (s(br), 1H, 7-OH), 3.00 (ddd(br), 1H, $^2$J$_{10,10'} = 17.9$ Hz, $^3$J$_{10,9\beta} = 12.1$ Hz, $^3$J$_{10,9\alpha} = 6.6$ Hz, H10), 2.79 (dd(br), 1H, $^2$J$_{10',10} = 17.9$ Hz, $^3$J$_{10',9\beta} = 6.8$ Hz, H10'), 2.75 (dd, 1H, $^2$J$_{5\alpha,5\beta} = 19.6$ Hz, $^3$J$_{5\alpha,4b} = 4.2$ Hz, H5$\alpha$), 2.44 (dd, 1H, $^2$J$_{5\beta,5\alpha} = 19.6$ Hz, $^3$J$_{5\beta,4b} = 13.6$ Hz, H5$\beta$), 2.38 (ddd, 1H, $^2$J$_{9\alpha,9\beta} = 13.8$ Hz, $^3$J$_{9\alpha,10} = 6.6$ Hz, $^3$J$_{9\alpha,10'} = 1$ Hz,
$^{4}J_{9\alpha,4b} = 0.9$ Hz, $H_{9\alpha}$), 2.28 (s(br), 3H, 4-Me), 1.72 (ddd, 1H, $^{2}J_{9\beta,9\alpha} = 13.8$ Hz,
$^{3}J_{9\beta,10} = 12.1$ Hz, $^{3}J_{9\beta,10'} = 6.8$ Hz, $H_{9\beta}$), 1.59 (dq, $^{3}J_{8,7} = 12.3$ Hz, $^{3}J_{8,Me} = 7.0$ Hz,
H8), 1.14 (d, 3H, $^{3}J_{Me,8} = 7.0$ Hz, 8-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz), δ 211.4 (C6), 173.9 (-CO$_2$Me), 157.7 (C2), 137.2, 136.2
(C10a, C4), 126.7 (C4a), 114.9 (C3)*, 111.2 (C1)*, 74.8 (C7), 54.9 (2-OMe), 51.6
(-CO$_2$Me), 49.4 (C8a), 44.1 (C8), 40.5 (C5), 32.3 (C4b), 27.8 (C10)↑, 26.8 (C9)↑, 19.1
(4-Me), 13.1 (8-Me).

IR (CHCl$_3$, cm$^{-1}$) 3470(br,s) (O-H str), 2950 (C-H str), 2840 (C-H str), 1725(s) (C=O
str), 1605(s) (C=C str), 1160 (C-O str).

MS, $m/z$ (relative intensity, %) 332 (M+, 100), 314 (9), 273 (22), 255 (30), 246 (50), 232
(50), 201 (45), 173 (31).

ANALYSIS: Calcd for C$_{19}$H$_{24}$O$_{5}$: C, 68.66; H, 7.28.
Found: C, 68.65; H, 7.57.

Methyl (4ba,7a,8a,8aa)-4b,5,7,8,9,10-Hexahydro-7-hydroxy-2-methoxy-
4,8-dimethyl-6-oxopentahydro-8α(6H)-carboxylate 91.

The α-epimer 91 (R$_f$ = 0.22) recrystallised from ethyl acetate/pentane as white needles, mp
161-166°C (dec.).

$^{1}$H NMR (CDCl$_3$, 300 MHz), δ 6.58 , 6.44 (2 x d(br), 2 x 1H, $^{4}J_{1,3} = 4^{3}J_{3,1} = 2.6$ Hz, H1,
H3), 4.65 (d(br), 1H, $^{3}J_{7,8} = 6.2$ Hz, H7), 3.80 (ddd, 1H, $^{3}J_{4b,5\beta} = 13.2$ Hz, $^{3}J_{4b,5\alpha} =$
5.3 Hz, $^{4}J_{4b,9\alpha} = 0.9$ Hz, H4b), 3.73 (s, 3H, 2-OMe), 3.62 (s, 3H, -CO$_2$Me), 3.42-3.52
(s(br), 1H, 7-OH), 2.95 (m, 1H, H10), 2.78 (m, 1H, H10'), 2.75 (dq, 1H, $^{3}J_{8,Me} = 7.3$
Hz, $^{3}J_{8,7} = 6.2$ Hz, H8), 2.73 (dd, 1H, $^{2}J_{5\alpha,5\beta} = 14.9$ Hz, $^{3}J_{5\alpha,4b} = 5.3$ Hz, H5α), 2.56
(m, 1H, H9β), 2.33 (dd, 1H, \(^2J_{5β,5α} = 14.9\) Hz, \(^3J_{5β,4b} = 13.2\) Hz (partially obscured), H5β), 2.33 (s(br), 3H, 4-Me), 2.32 (m, 1H, H9α), 0.82 (d, 3H, \(^3J_{Me,8} = 7.3\) Hz, 8-Me).

\(^{13}\)C NMR (CDCl₃, 300 MHz), \(\delta\) 209.3 (C6), 174.0 (-CO₂Me), 157.5 (C2), 136.7, 134.4 (C10a, C4), 129.1 (C4a), 114.8 (C3)*, 111.6 (C1)*, 73.9 (C7), 54.9 (2-OMe), 52.0 (-CO₂Me), 51.1 (C8a), 45.5 (C8), 42.5 (C5), 35.5 (C4b), 27.9 (C10)*, 25.9 (C9)*, 18.8 (4-Me), 9.8 (8-Me).

IR (CHCl₃, cm⁻¹) 3470(br,s) (O-H str), 2950 (C-H str), 2840 (C-H str), 1720(s) (C=O str), 1605(s) (C=C str), 1145 (C-O str).

MS, m/e (relative intensity, %) 332 (M⁺, 19.6), 314 (10), 255 (33), 246 (20), 232 (26), 201 (27), 187 (20), 173 (23), 148 (17), 128 (18).

ANALYSIS: Calcd for C₁₉H₂₄O₅: C, 68.66; H, 7.28. Found: C, 68.64; H, 7.25.

**Methyl \([10R-(1α,2β)]-1,2,3,4-Tetrahydro-6-methoxy-2-(methoxycarbonyl)-8-methyl-2-(1-oxoprop-2-yl)naphthalene-1-acetate 71.**

LTA (3.21 g, 7.22 mmol) was added in one portion to a solution of the \(α\)-hydroxketones 90 and 91 (2.00 g, 6.02 mmol) in a mixture of 35% methanol in CH₂Cl₂ (60 mL) at room temperature under nitrogen. After 5 min, the reaction mixture was quenched with cold saturated NaHCO₃ solution and the resulting brown slurry extracted with ether. The combined ether phases were then washed with water and brine, and dried over MgSO₄.
Removal of solvent *in vacuo* followed by flash chromatography (25% ethyl acetate in pentane) of the residue afforded the pure aldehyde 71 (R_f = 0.39) as a colourless oil (1.96 g, 90%).

**1H NMR (CDCl₃, 300 MHz), δ 10.02 (d, 1H, _J_{11,10} = 2.2 Hz, H11), 6.49, 6.43 (2 x s(br), 2 x 1H, H5, H7), 4.20 (dd(br), 1H, _J_{1,9'} = 7.6 Hz, _J_{1,9} = 5.4 Hz, H1), 3.71 (s, 3H, 6-OMe), 3.60 (s, 3H, 9-C{H}Me), 3.37 (s, 3H, 2-CO₂Me), 3.02-2.84 (m, 2H, H4), 2.85 (dd, 1H, _J_{9,9'} = 14.7 Hz, _J_{9,1} = 5.4 Hz, H9), 2.60 (m, 1H, H3α), 2.48 (dq, 1H, _J_{10,Me} = 6.8 Hz, _J_{10,11} = 2.2 Hz, H10), 2.36 (dd, 1H, _J_{9',9} = 14.7 Hz, _J_{9',1} = 7.6 Hz, H9'), 2.25 (s(br), 3H, 8-Me), 1.68 (m, 1H, H3β), 1.06 (d, 1H, _J_{Me,10} = 6.8 Hz, 10-Me).**

**13C NMR (CDCl₃, 300 MHz), δ 202.7 (C1), 173.1, 172.3 (2 x -CO₂Me), 157.9 (C6), 136.7, 136.6 (C4α, C8), 128.9 (C8α), 113.8 (C7), 110.9 (C5), 54.7 (6-OMe), 53.4 (C2), 51.5, 51.4 (2 x -CO₂Me), 49.8 (C10), 35.9 (C1), 35.6 (C9), 25.4 (C4), 24.4 (C3), 18.9 (8-Me), 9.8 (10-Me).**

**IR (CHCl₃, cm⁻¹) 2945 (C-H str), 2840 (C-H str), 1725(s) (C=O str, ester & aldehyde), 1605(s) (Ar C=C str), 1480(s) (Ar C=C str), 1300 (C-O str), 1260 (C-O str), 1150(s) (C-O str), 860 (C-H oop bend).**

**MS, m/z (relative intensity, %) 362 (M⁺, 18.9), 233 (48), 201 (100), 199 (35), 189 (33), 173 (70), 128 (28), 115 (30), 83 (48), 59 (39).**

**HRMS: Calcd for C₂₀H₂₆O₆: 362.1729. Found: 362.1726.**
Methyl (1′a,2′b,4a)-3′,4,4′,5-Tetrahydro-5′,6′-dimethoxy-4,8′-dimethyl-2-
oxospiro[furan-3(2H),2′(1′H)-naphthalene]-1′-acetate 92.

Depending on the purity of the LTA used in the experiment, another product 92 (Rf = 0.34), whose yield ranged from 0 to ~15% of the isolated materials could be detected.

\[ \text{1H NMR (CDCl}_3, 300 MHz), \delta 6.59, 6.45 (2 x d(br), 2 x 1H, \text{J}_{5′,7′} = \text{J}_{7′,5′} = 2.6 \text{ Hz,} \]
\[ \text{H5′, H7′}), 4.93 (d, 1H, \text{J}_{5′,4′} = 5.7 \text{ Hz,} \text{H5}), 3.84 (\text{ddd, 1H, J}_{1′,3′,6′} = 8.6 \text{ Hz,} \text{J}_{1′,9′} = 2.6 \text{ Hz,}} \]
\[ \text{J}_{1′,3′} = 1.3 \text{ Hz, H1′), 3.74 (s, 3H, 6'O-Me), 3.68 (s, 3H, -CO}_2\text{Me), 3.55 (s, 3H,}} \]
\[ \text{5′OMe), 2.98-2.81 (m, 2H, H4′), 2.67 (\text{ddd, 1H, J}_{9′,9′} = 17.4 \text{ Hz, J}_{9′,1′} = 8.6 \text{ Hz,} \text{H9′),}} \]
\[ \text{J}_{9′,3′} = 2.6 \text{ Hz, H9′), 2.50 (dq, 1H, J}_{4,M_e} = 7.0 \text{ Hz, J}_{4,5} = 5.7 \text{ Hz, H4), 2.28 (dd, 1H, J}_{9′,9′} = 17.4 \text{ Hz,}} \]
\[ \text{J}_{9′,1′} = 2.6 \text{ Hz, H9′), 2.24 (s(br), 3H, 8′-Me), 1.99 (m, 1H, H3′β), 1.77 (m, 1H,}} \]
\[ \text{H3′α), 1.12 (d, 3H, J}_{3,M_e,4} = 7.0 \text{ Hz, 4-Me).} \]

\[ \text{13C NMR (CDCl}_3, 300 MHz), \delta 176.6 (C2), 172.7 (-CO}_2\text{Me), 157.4 (C6′), 136.6, 135.9} \]
\[ \text{(C4′a, C8′), 129.7 (C8′a), 115.0 (C7′)\text{, 110.4 (C5′), 108.2 (C5), 57.8 (5-O-Me), 54.9} \]
\[ \text{(6′-OMe), 51.9 (-CO}_2\text{Me), 48.6 (C3), 43.7 (C9′), 38.5 (C1′), 37.1 (C4), 26.2 (C4′)\text{,}} \]
\[ \text{21.1 (C3′)\text{, 19.2 (8′-Me), 11.6 (4-Me).} \]

IR (CHCl$_3$, cm$^{-1}$) 2950 (C-H str), 1775(s) (C=O str, lactone), 1730(s) (C=O str, ester), 1610 (Ar C=C str), 1465 (Ar C=C str), 1250 (C-O str), 1210 (C-O str), 1155(s) (C-O str), 970 (C-H oop bend), 885 (C-H oop bend).

MS, m/z (relative intensity, %) 362 (M$^+$, 2.5), 290 (5), 279 (4), 245 (7), 213 (4), 150 (6), 149 (51), 115 (7), 113 (20), 97 (6).

HRMS: Calcd for C$_{20}$H$_{26}$O$_6$: 362.1729. Found: 362.1726.
2.2 **Des-Methyl Series**

3-Methoxybenzeneethanol 94.

\[
\text{MeO} - \text{CO}_2\text{H} \xrightarrow{\text{LiAlH}_4 \text{Et}_2\text{O}} \xrightarrow{\uparrow} \text{MeO} - \text{OH}
\]

The acid 93 (71.1 g, 428 mmol) was reduced to the carbinol 94 using LiAlH₄ (16.0 g, 400 mmol) in diethyl ether (400 mL), in a manner similar to that used for the conversion of 57 to 79. Work up afforded the carbinol 94 as a colourless oil (63.1 g, 97%).

\[ \text{H NMR (CDCl}_3, 200 MHz), \delta 7.22 (dd, 1H, } ^3J_{5,4} = 8.5 \text{ Hz, } ^3J_{5,6} = 7.5 \text{ Hz, H5) 6.70-6.86 (m, 3H, H2, H4, H6), 3.83 (m, 2H, H8), 3.78 (s, 3H, 3-OMe), 2.81 (t, 2H, } ^3J_{7,8} = 6.7 \text{ Hz, H7), 1.89 (s, 1H, 8-OH).} \]

\[ \text{C NMR (CDCl}_3, 200 MHz), \delta 159.3 (C3), 140.0 (C1), 129.0 (C2), 121.0 (C5), 114.4 (C6), 111.3 (C4), 63.0 (C8), 54.7 (3-OMe), 38.9 (C7). \]

\[ \text{IR (film, cm}^{-1}) 3400(s,br) (O-H str), 2940(s) (C-H str), 1600(s) (Ar C=C str), 1580(s), 1490(s) (Ar C=C str), 1255(s,br) (C-O str), 1165(s) (C-O str), 1150(s) (C-O str). \]

3-Methoxybenzeneethanol Methanesulphonate 95.

\[
\text{MeO} - \text{OH} \xrightarrow{\text{MeOSOCl \text{Pyridine, -5°C}}} \xrightarrow{\uparrow} \text{MeO} - \text{OSO}_2\text{Me}
\]

The carbinol 94 (63.0 g, 414 mmol) was converted to the methanesulphonate 95 with methanesulphonyl chloride (41.5 mL, 538 mmol) in pyridine (400 mL), in a manner similar
to that for the conversion of 79 to 80. Work up gave the mesylate as a pale yellow oil (86.0 g, 91%).

1-(2-Iodoethyl)-3-methoxybenzene 96.

The methanesulphonate 95 (86.0 g, 374 mmol) was converted to the iodide 96 using sodium iodide (450 g, 3.00 mol) in boiling acetone (2.0 L), in a manner similar to that for the conversion of 80 to 58. Work up gave the iodide as a pale yellow oil (88.2 g, 90%).

$^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 3.00-3.17 (m, 2H, H7), 3.25-3.80 (m, 2H, H8), 3.79 (s, 3H, 3-OMe), 6.70-6.81 (m, 3H, H2, H4, H6), 7.20 (dd, 1H, $^3J_{5,4} = 8.2$ Hz, $^3J_{5,6} = 7.6$ Hz, H5).

$^{13}$C NMR (CDCl$_3$, 200 MHz) $\delta$ 159.5 (C3), 141.9 (C1), 129.4 (C2), 120.4 (C5), 113.9 (C6), 111.9 (C4), 55.0 (3-OMe), 40.2 (C7), 5.3 (C8).

IR (film, cm$^{-1}$) 3000 (C-H str), 2960 (C-H str), 2830 (C-H str), 1600(s) (Ar C=C str), 1585(s), 1490(s) (Ar C=C str), 1265 (C-O str), 1165, 1150, 1050 (C-O str).
1,4-Dihydro-1-[2-(3-methoxyphenyl)ethyl]benzoic Acid 97.

The dianion derived from the reaction of benzoic acid (19.6 g, 161 mmol) and lithium (2.23 g, 320 mmol), was alkylated with the iodide 96 (43.9 g, 168 mmol) in a manner similar to that for the conversion of 58 to 76. Work up gave the acid 97, which was recrystallised from pentane/ethyl acetate to give colourless plates (40.2 g, 97% based on the amount of benzoic acid used), mp 121-123°C.

$^1$H NMR (CDCl$_3$, 300 MHz), δ 7.19 (ddd, 1H, H7'), 6.79-6.70 (m, 2H, H6', H8'), 6.72 (s(br), 1H, H4'), 5.98 (m, 2H, H3, H5), 5.83 (m, 2H, H2, H6), 3.78 (s, 3H, 5'-OMe), 2.71 (m, 2H, H4), 2.57-2.50 (m, 2H, H2'), 2.06-1.98 (m, 2H, H1')

$^{13}$C NMR (CDCl$_3$, 300 MHz) δ 181.1 (-CO$_2$H), 159.6 (C5'), 143.5 (C3'), 129.3 (C7'), 126.7 (C3, C5)*, 126.3 (C2, C6)*, 120.8 (C8'), 114.0 (C4')†, 111.2 (C6')†, 55.1 (5'-OMe), 47.7 (C1), 40.9 (C4), 30.7 (C2')‡, 26.1 (C1')‡.

IR (CHCl$_3$, cm$^{-1}$) 3400-2500(br) (O-H str), 2950(s) (C-H str), 1700(br,s) (C=O str), 1600(s) (Ar C=C str), 1585(s) (C=C str), 1490(s) (Ar C=C str) 1260 (C-O str), 1150(s) (C-O str), 855 (C-H oop bend).

MS, m/z (relative intensity, %) 258 (M*, 6.3), 213 (7), 212 (7), 136 (56), 135 (68), 122 (12), 121 (61), 105 (100), 91 (52).

ANALYSIS: Calcd for C$_{16}$H$_{18}$O$_3$: C, 74.40; H, 7.02.

Found: C, 74.29; H, 6.94.
Methyl 1,4-Dihydro-1-[2-(3-methoxyphenyl)ethyl]benzoate 98.

The acid (40.2 g, 156 mmol) was treated with an ethereal solution of diazomethane in a manner similar to that for the conversion of 1 to 2. Work up afforded pure ester (42.9 g, 100%), as a pale yellow oil.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.18 (ddd, 1H, H7'), 6.79-6.70 (m, 2H, H6', H8'), 6.71 (s(br), 1H, H4'), 5.95 (m, 2H, H3, H5), 5.83 (m, 2H, H2, H6), 3.79 (s, 3H, 5'-OMe), 3.70 (s, 3H, -CO$_2$Me), 2.70 (m, 2H, H4), 2.54-2.46 (m, 2H, H2'), 2.02-1.95 (m, 2H, H1').

$^{13}$C NMR (CDCl$_3$, 300 MHz) $\delta$ 175.1 (-CO$_2$Me), 159.5 (C5'), 143.6 (C3'), 129.2 (C7'), 126.8 (C3, C5)*, 126.1 (C2, C6)*, 120.7 (C8'), 113.9 (C4')$, 111.0 (C6)$, 55.0 (5'-OMe), 52.1 (-CO$_2$Me), 47.8 (Cl), 41.0 (C4), 30.7 (C2')$, 26.0 (C1')$.

IR (CHCl$_3$, cm$^{-1}$) 2950(s) (C-H str), 1725(s) (C=O str), 1600(s) (Ar C=C str), 1585(s) (C=C str), 1490 (Ar C=C str), 1245(s) (C-O str), 1040(s) (C-O str), 875 (C-H oop bend).

MS, m/z (relative intensity, %) 272 (M$, 1.5), 218 (4), 213 (8), 138 (9), 137 (13), 136 (23), 135 (45), 121 (21), 105 (100).

HRMS: Calcd for C$_{17}$H$_{20}$O$_3$: 272.1412. Found: 272.1412.

ANALYSIS: Calcd for C$_{17}$H$_{20}$O$_3$: C, 74.97; H, 7.40.

Found: C, 75.25; H, 7.53.
Methyl 1,4-Dihydro-1-[2-(3-methoxyphenyl)ethyl]-4-oxobenzoate 99.

The diene 98 (10.0 g, 35.0 mmol), was reacted with chromium trioxide-dimethylpyrazole complex (18.38 g, 183.8 mmol CrO$_3$; 18.10 g, 184.7 mmol, DMP), for 5 h at -10°C, in a manner similar to that for the conversion of 81 to 59. Work up afforded the dienone 99 (R$_f$ = 0.43, 25% ethyl acetate in pentane), as a pale yellow oil (9.25 g, 88%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.16 (m, 1H, H7'), 7.07 (d, 2H, $^3$J$_{2,3}$ = $^3$J$_{6,5}$ = 10.3 Hz, H2, H6), 6.72 (m, 1H, H6'), 6.69 (m, 1H, H8'), 6.64 (m, 1H, H4'), 6.38 (d, 2H, $^3$J$_{3,2}$ = $^3$J$_{5,6}$ = 10.3 Hz, H3, H5), 3.75 (s, 3H, 5'-OMe), 3.72 (s, 3H, -CO$_2$Me), 2.50-2.44 (m, 2H, H1'), 2.28-2.22 (m, 2H, H2').

$^{13}$C NMR (CDCl$_3$, 300 MHz) $\delta$ 184.9 (C4), 170.4 (-CO$_2$Me), 159.6 (C5'), 147.5 (C2, C6), 141.7 (C3'), 129.4 (C7'), 130.3 (C3, C5), 120.4 (C8'), 113.9 (C4')$, \dagger$, 111.5 (C6')$, \dagger$, 54.9 (5'-OMe), 53.0 (-CO$_2$Me), 51.1 (C1), 39.5 (C2')$, \ddagger$, 36.4 (C1')$. 

MS, m/z (relative intensity, %) 286 (M$^+$, 8.4), 227 (9), 226 (4), 165(5), 152 (28), 136 (11), 135 (100), 134 (35), 121 (87), 105 (31).

HRMS: Calcd for C$_{17}$H$_{18}$O$_4$: 286.1205. Found: 286.1231.
Methyl (4bα,8aα)-4b,5,9,10-Tetrahydro-2-methoxy-6-oxophenanthen-8a(6H)-carboxylate 100.

TiCl₄ (5.32 mL, 48.5 mmol), was added dropwise to a stirred solution of the dienone 99 (9.25 g, 32.3 mmol) in dry CH₂Cl₂ (150 mL), at -10°C under nitrogen. The resulting dark red solution was allowed to warm to 0°C over 20 min. Water (5 mL) was then added dropwise until the reaction mixture had gone clear. More water was added and the organic phase was washed sequentially with saturated NaHCO₃ solution, water and brine, then dried over MgSO₄. Removal of solvent in vacuo followed by flash chromatography (33% ethyl acetate in pentane) afforded the α,β-unsaturated ketone 100 (Rf = 0.35), as a colourless oil (8.35 g, 90%).

1H NMR (CDCl₃, 300 MHz) δ 7.10 (d(br), 1H, 3J₄,₃ = 8.4 Hz, H₄), 6.98 (d, 1H, 3J₈,₇ = 10.3 Hz, H₈), (dd, 1H, 3J₃,₄ = 8.4 Hz, 4J₃,₁ = 2.9 Hz, H₃), 6.53 (d, 1H, 3J₇,₈ = 10.3 Hz, H₇), 6.03 (d(br), 1H 4J₁,₃ = 2.9 Hz, H₁), 3.88 (dd(br), 3J₄b,₅a = 4.8 Hz, 3J₄b,₅b = 10.4 Hz, H₄b), 3.75 (s, 3H, 2-OMe), 3.72 (s, 3H, -CO₂Me), 2.90-2.75 (m, 2H, H₁₀), 2.80-2.58 (dd, 1H, 2J₅α,₅β = 16.9 Hz, 3J₅α,₄b = 4.8 Hz, H₅α; dd, 1H, 2J₅β,₅α = 16.9 Hz, 3J₅β,₄b = 10.3 Hz, H₅β), 2.30 (m, 1H, H₉α), 2.06 (m, 1H, H₉β).

13C NMR (CDCl₃, 300 MHz) δ 197.6 (C₆), 173.4 (-CO₂Me), 157.8 (C₂), 149.9 (C₈), 134.9 (C₁₀α), 129.3 (C₇), 129.0 (C₄), 128.8 (C₄α), 113.2 (C₃)*, 112.8 (C₁)*, 54.9 (ArOMe), 52.5 (-CO₂Me), 48.3 (C₈α), 43.1 (C₅), 37.9 (C₄b), 28.1 (C₁₀)†, 26.6 (C₉)†.
IR (CHCl3, cm⁻¹) 2950(s) (C-H str), 2840 (C-H str), 1730(s) (C=O str, ester), 1685(s) (C=O str, enone), 1610 (Ar C=C str), 1505(s) (Ar C=C str), 1260(s) (C-O str), 1045(s) (C-O str), 810 (C-H oop bend).

MS, m/z (relative intensity, %) 287 (M⁺+1, 6.6), 286 (M⁺, 38.8), 228 (17), 227 (100), 226 (61), 199 (13), 198 (28), 197 (9), 134 (11), 115 (7).


ANALYSIS: Calcd for C₁₇H₂₀O₃: C, 71.31; H, 6.34.

Found: C, 71.64; H, 6.59.

**Methyl (4bα,8α,8αα)-4b,5,9,10-Tetrahydro-2-methoxy-8-methyl-6-[dimethyl-(1,1-dimethylethyl)silyl]oxyphenanthrene-8a(8H)-carboxylate 101.**

The α,β-unsaturated ketone 100 (5.60 g, 19.6 mmol) was converted to the silyl enol ether 101 with Me₂CuLi (11.4 g, 59.8 mmol CuI; 74.4 mL, 1.6M, 119 mmol MeLi) and TBDMSCl (12.0 g, 79.6 mmol) in the presence of HMPA (7 mL) in a manner similar to that for the conversion of 48 to 89. Work up and flash chromatography gave the enol ether 101 (Rf = 0.85), as a clear oil (7.54 g, 93%).

₁H NMR (CDCl₃, 300 MHz) δ 7.03 (d(br), 1H, 3J₄,3 = 8.4 Hz, H₄), 6.68 (dd, 1H, 3J₃,4 = 8.4 Hz, 4J₃,1 = 2.6 Hz, H₃), 6.57 (d(br), 1H 4J₁,3 = 2.6 Hz, H₁), 4.88 (dd, 1H, 3J₇,8 = 5.5 Hz, 4J₇,5₈ = 1.5 Hz, H₇), 3.75 (s, 3H, 2-OMe), 3.56 (s, 3H, -CO₂Me), 3.38 (dd(br),
$^{1}H$, $^{3}J_{4b,5\beta} = 10.8$ Hz, $^{3}J_{4b,5\alpha} = 7.0$ Hz, $H_{4b}$), 2.90-2.70 (m, 2H, H10), 2.37 (ddq, 1H, $^{5}J_{8,5\beta} = 1.5$ Hz, $^{3}J_{8,7} = 5.5$ Hz, $^{3}J_{8,Me} = 6.8$ Hz, H8), 2.29 (dd, 1H, $^{2}J_{5\alpha,5\beta} = 18.0$ Hz, $^{3}J_{5\alpha,4b} = 7.0$ Hz, H5a), 2.13-1.96 (m, 2H, H9), 1.84 (dddd, 1H, $^{2}J_{5\beta,5\alpha} = 18.0$ Hz, $^{3}J_{5\beta,4b} = 10.8$ Hz, $^{4}J_{5\beta,7} = 1.5$ Hz, $^{5}J_{5\beta,8} = 1.5$ Hz, H5\beta), 0.95 (d, 3H, $^{3}J_{Me,8} = 6.8$ Hz, 8-Me), 0.90 (s, 9H, -Si(CMe)$_3$), 0.15, 0.11 (s, 6H, -Si(Me)$_2$).

$^{13}C$ NMR (CDCl$_3$, 300 MHz) δ 176.0 (-CO$_2$Me), 157.6 (C2), 147.0 (C6), 134.4 (C10\alpha)*, 134.1 (C4\alpha)*, 128.9 (C4), 113.8 (C3)†, 112.0 (C1)†, 107.7 (C7), 55.0 (2-OMe), 51.2 (-CO$_2$Me), 48.4 (C8\alpha), 38.2 (C4b), 38.1 (C5), 34.5 (C8), 26.8 (C10)‡, 26.4 (C9)‡, 26.5 (-Si(CMe)$_3$), 19.8 (8-Me), 17.9 (-Si(CMe)$_3$), -4.0, -4.4 (-Si(Me)$_2$).

IR (CHCl$_3$, cm$^{-1}$) 2970 (s) (C-H str), 2850 (C-H str), 1735 (s) (C=O str), 1680 (C=C str), 1610 (Ar C=C str), 1500 (s) (Ar C=C str), 1260 (C-O str), 1040 (C-O str), 840 (C-H oop bend).

MS, m/z (relative intensity, %) 416 (M$^+$, 0.6), 401 (0.3), 359 (1), 357 (1), 356 (1), 341 (1), 285 (1), 225 (2), 219 (4), 218 (29), 159 (5).

HRMS: Calcd for C$_{24}$H$_{36}$O$_4$Si: 416.2383. Found: 416.2381.

Methyl (4b\alpha,7\beta,8\alpha,8a\alpha)-4b,5,7,8,9,10-Hexahydro-7-hydroxy-2-methoxy-8-methyl-6-oxophenanthrene-8a(6H)-carboxylate 102.

The silyl enol ether 101 (7.50 g, 18.0 mmol), was converted to a mixture of $\alpha$-hydroxyketones with a catalytic amount of OsO$_4$ (2 crystals), and NMMO (2.8 g, 24
mmol), in a manner similar to that for the conversion of 89 to 90 and 91. Work up and chromatography afforded the α-ketols as a white solid (4.74 g, 83 %), together with a small amount of starting material (0.5 g, 7%). The least polar compound (Rf = 0.25) was the C(7β)-OH epimer 102, which was crystallised from ethyl acetate/pentane as white needles, mp 132-133°C

\(^1\)H NMR (CDCl\(_3\), 300 MHz) δ 7.16 (d, 1H, \(^3\)J\(_{4,3}\) = 8.6 Hz, H4), 6.73 (dd, 1H, \(^3\)J\(_{3,4}\) = 8.6 Hz, \(^4\)J\(_{3,1}\) = 2.8 Hz, H3), 6.61 (d(br), 1H \(^4\)J\(_{1,3}\) = 2.8 Hz, H1), 4.51 (ddd, 1H, \(^3\)J\(_{7,8}\) = 13.6 Hz, \(^4\)J\(_{7,5α}\) = 0.9 Hz, H7), 3.78 (s, 3H, 2-OMe), 3.77 (m, partially obscured, 1H, H4b), 3.75 (s, 3H, -CO\(_2\)Me), 3.38 (d, 1H, \(^3\)J\(_{OH,7}\) = 3.5 Hz, 7-OH), 3.04 (dd, 1H, \(^2\)J\(_{5α,5β}\) = 15.8 Hz, \(^3\)J\(_{5α,4b}\) = 5.6 Hz, H5α), 2.95 (dddd, 1H, \(^2\)J\(_{5β,5α}\) = 15.8 Hz, \(^3\)J\(_{5β,4b}\) = 5.6 Hz, H5β), 2.90-2.67 (m, 2H, H10), 2.31 (m, 1H, H9α), 1.97 (m, 1H, H9β), 1.74 (dq, 1H, \(^3\)J\(_{8,7}\) = 11.6 Hz, \(^3\)J\(_{8,Me}\) = 6.7 Hz, H8), 1.24 (d, 3H, \(^3\)J\(_{Me,8}\) = 6.7 Hz, 8-Me).

\(^{13}\)C NMR (CDCl\(_3\), 300 MHz) δ 209.9 (C6), 175.0 (-CO\(_2\)Me), 157.9 (C2), 136.7 (C10α), 128.3 (C4), 126.7 (C4α), 113.6 (C3)*, 112.3 (C1)*, 75.7 (C7), 55.0 (2-OMe), 51.8 (-CO\(_2\)Me), 49.5 (C8α), 41.4 (C8), 40.9 (C4b), 40.1 (C5), 28.5 (C10)†, 25.8 (C9)†, 11.4 (8-Me).

IR (CHCl\(_3\), cm\(^{-1}\)) 3560-3380(br) (O-H str), 2950(s) (O-H str), 1720(s) (C=O str), 1610 (Ar C=C str), 1505(s) (Ar C=C str), 1235(s) (C-O str), 1040(s) (C-O str), 810 (C-H oop bend).

MS, m/z (relative intensity, %) 318 (M\(^+\), 14.4), 300 (13), 286 (19), 241 (40), 232 (94), 218 (46), 187 (58), 173 (72), 159 (46), 115 (57), 84 (100).

ANALYSIS: Caled for C\(_{18}\)H\(_{22}\)O\(_5\): C, 67.91; H, 6.96.
Found: C, 68.08; H, 7.14.
Methyl (4bα,7α,8α,8aα)-4b,5,7,8,9,10-Hexahydro-7-hydroxy-2-methoxy-8-methyl-6-oxophenanthrene-8a(6H)-carboxylate 103.

The most polar compound (Rf = 0.32) was the C(7α)-OH epimer 103, which recrystallised from ethyl acetate/pentane as colourless needles.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 6.98 (d, 1H, $^3$J$_{4,3}$ = 8.6 Hz, H4), 6.72 (dd, 1H, $^3$J$_{3,4}$ = 8.6 Hz, 4$^4$J$_{3,1}$ = 2.8 Hz, H3), 6.58 (d(br), 1H $^4$J$_{1,3}$ = 2.8 Hz, H1), 4.62 (ddd, 1H, $^3$J$_{7,8}$ = 4.4 Hz, $^4$J$_{7,5β}$ = 1.4 Hz, H7), 3.75 (s, 3H, 2-OMe), 3.71 (ddd, 1H, $^3$J$_{14b,5α}$ = 13.0 Hz, $^4$J$_{14b,9α}$ = 5.8 Hz, $^4$J$_{14b,9α}$ = 1.4 Hz, H4b), 3.64 (s, 3H, -CO$_2$Me), 3.46 (d, 1H, $^3$J$_{OH,7}$ = 4.2 Hz, 7-OH), 2.91-2.71 (m, 2H, H10), 2.74 (dq, 1H, $^3$J$_{8,7}$ = 4.4 Hz, $^3$J$_{8,Me}$ = 7.2 Hz, H8), 2.71 (dd, 1H, $^2$J$_{5α,5β}$ = 14.8 Hz, $^3$J$_{5α,4b}$ = 5.8 Hz, H5α), 2.50 (m, 1H, H9β), 2.45 (ddd, 1H, $^2$J$_{5β,5α}$ = 14.8 Hz, $^3$J$_{5β,4b}$ = 13.0 Hz, $^4$J$_{5β,7}$ = 1.4 Hz, H5β), 2.32 (m, 1H, H9α), 0.79 (d, 3H, $^3$J$_{Me,8}$ = 7.2 Hz, 8-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) δ 209.1 (C6), 173.9 (-CO$_2$Me), 157.8 (C2), 134.1 (C10α), 130.6 (C4α), 129.3 (C4), 113.5 (C3)*, 112.6 (C1)*, 73.6 (C7), 54.9 (2-OMe), 51.9 (-CO$_2$Me), 50.6 (C8α), 45.3 (C5), 45.2 (C8), 38.2 (C4b), 27.4 (C10)*, 26.0 (C9)*, 9.0 (8-Me).

MS, m/z (relative intensity, %) 318 (M+, 1.6), 301 (7), 300 (32), 286 (4), 272 (6), 242 (18), 241 (100), 240 (16), 232 (17), 213 (19), 212 (11), 187 (20), 173 (27), 159 (21), 115 (27).

ANALYSIS: Calcd for C$_{18}$H$_{22}$O$_5$: C, 67.91; H, 6.96.

Found: C, 67.64; H, 7.34.
Methyl \([10R-\text{l1,2-})-1,2,3,4\text{-Tetrahydro-6-methoxy-2-}(-\text{methoxycarbonyl)-2-}(-\text{oxoprop-2-y}l)naphthalene-1\text{-acetate 104.}\]

The mixture of \(\alpha\)-ketols 102 and 103 (1.50 g, 4.72 mmol) was converted to the aldehyde 104, with LTA (2.51 g, 5.66 mmol) in a manner similar to that for the conversion of 90 and 91 to 71. Work up followed by flash chromatography gave the aldehyde \((R_f = 0.36)\) as a colourless oil (1.60 g, 95%).

\(^1\)H NMR (CDCl₃, 300 MHz) \(\delta\) 9.85 (d, 1H, \(3J_{11,10} = 3.0\) Hz, H11), 6.93 (m, 1H, H8), 6.56 (m, 2H, H5, H7), 3.80 (ddd, 1H, \(3J_{1,9} = 10.9\) Hz, \(3J_{1,9'} = 3.2\) Hz, \(4J_{1,3\alpha} = 1.3\) Hz, H1), 3.72 (s, 3H, 6-OMe), 3.60, 3.46 (2 x s, 2 x 3H, 2 x -CO₂Me), 3.11-2.82 (m, 2H, H4), 2.87 (dd, 1H, \(2J_{9,9'} = 14.6\) Hz, \(3J_{9,9'} = 3.2\) Hz, H9'), 2.52 (m, 1H, H3\(\alpha\)) 2.47 (dq, 1H, \(3J_{10,Me} = 7.2\) Hz, \(3J_{10,11} = 3.0\) Hz, H10), 2.31 (dd, 1H, \(2J_{9,9'} = 14.6\) Hz, \(3J_{9,1} = 10.9\) Hz, H9), 1.58 (m, 1H, H3\(\beta\)), 1.05 (d, 3H, \(3J_{Me,10} = 7.2\) Hz, 10-Me).

\(^{13}\)C NMR (CDCl₃, 300 MHz) \(\delta\) 202.6 (C11), 173.5, 171.9 (2 x -CO₂Me), 158.6 (C6), 136.4 (C4\(\alpha\)), 129.7 (C8\(\alpha\)), 129.5 (C8), 113.4 (C7)*, 111.7 (C5)*, 54.9 (6-OMe), 52.0 (C2), 51.6, 51.5 (2 x -CO₂Me), 50.1 (C10), 39.1 (C1), 36.6 (C9), 25.4 (C4)*, 24.8 (C3)*, 9.9 (10-Me).

IR (CHCl₃, cm\(^{-1}\)) 2950 (C-H str), 1730(s) (C=O str), 1610 (Ar C=C str), 1505(s) (Ar C=C str), 1260 (C-O str), 1120 (C-O str), 850 (C-H oop bend).

MS, \(m/z\) (relative intensity, %) 348 (M\(^{+}\), 8.2), 330 (4), 316 (13), 300 (6), 290 (43), 259 (14), 230 (21), 187 (18), 115 (13).
An excess of Zn(OMe)$_2$ (as an ethereal solution) was added dropwise to a stirred solution of the aldehyde 71 (880 mg, 2.65 mmol) in ether/DMP (1:1, 20 mL) at room temperature under nitrogen. After 30 min, the cooled reaction mixture was diluted with ether and carefully quenched with sufficient dilute HCl to dissolve the resulting precipitate. The organic phase was washed sequentially with water and brine, then dried over MgSO$_4$. Removal of solvent in vacuo afforded a ca. 2:2 mixture of the desired 3-membered lactone 110 (δ$_y$ = 0.30) in conjunction with a 7-membered lactone by-product 111 (δ$_y$ = 0.25). The mixture could be flash chromatographed to give 110 (580 mg, 72%) as a colourless oil, followed by 111 (161 mg, 20%).

H NMR (CDCl$_3$, 300 MHz) δ 6.38, 6.26 (2 x d, J = 4.6 Hz), 2 x H, 4.22 (s, 3H, 3$_y$, 3$_z$, 3.77 (s, 3H, 4$_y$, 4$_z$, 8.0 Hz, 2.71 (s, 3H, 6$_D$m), 3.77 (s, 3H, -CO$_2$Me), 3.79 (s, 3H, 11H, 3.25-3.60 (m, 2H, 8$_D$m), 2.73 (t, 3H, 2$\times$Me), 2.54 (s, 3H, 8$_D$m), 2.44 (s, 3H, 8$_D$m), 1.82 (s, 3H, 11H, 3.25-3.60 (m, 2H, 8$_D$m), 2.73 (t, 3H, 2$\times$Me), 2.54 (s, 3H, 8$_D$m), 2.44 (s, 3H, 8$_D$m), 1.82 (s, 3H, 11H, 3.25-3.60 (m, 2H, 8$_D$m), 2.73 (t, 3H, 2$\times$Me), 2.54 (s, 3H, 8$_D$m), 2.44 (s, 3H, 8$_D$m), 1.82 (s, 3H, 11H).
CHAPTER 3
EXPERIMENTAL

4.1 Aromatic Methyl Spirolactone Series

Methyl (1'α,2'β,4α)-3',4,4',5-Tetrahydro-6'-methoxy-4,8'-dimethyl-2-oxospiro[furan-3(2H),2'(1'H)-naphthalene]-1'-acetate 110.

An excess of Zn(BH₄)₂₈₉ (as an ethereal solution) was added dropwise to a stirred solution of the aldehyde 71 (880 mg, 2.65 mmol), in ether/DMF (3:1, 20 mL) at room temperature under nitrogen. After 30 min, the cooled reaction mixture was diluted with ether and carefully quenched with sufficient dilute HCl to dissolve the resulting precipitate. The organic phase was washed sequentially with water and brine, then dried over MgSO₄. Removal of solvent in vacuo afforded a ca. 3:2 mixture of the desired 5-membered lactone 110 (Rₓ = 0.30) in conjunction with a 7-membered lactone by-product 111 (Rₓ = 0.25). The mixture could be flash chromatographed to give 110 (580 mg, 72%) as a colourless oil, followed by 111 (161 mg, 20%).

1H NMR (CDCl₃, 300 MHz) δ 6.58 , 6.46 (2 x d(br), 2 x 1H, 4J₅',₇' = 4J₇',₅' = 2.6 Hz, H5', H7'), 4.42 (dd, 1H, 2J₅₅' = 9.0 Hz, 3J₅₄ = 7.3 Hz, H5), 3.77 (dd, 1H, 2J₅₄ = 9.0 Hz, 3J₅₄ = 7.7 Hz, H5'), 3.73 (s, 3H, 6'-OMe), 3.71 (s, 3H, 6'-Me), 3.70 (m, 1H, H1'), 2.64 (ddq, 1H, 3J₄₅ = 7.7 Hz, 3J₄₅ = 7.3 Hz, 3J₄,Me = 6.6 Hz, H4), 2.28 (dd, 1H, 2J₉₉' = 18.3 Hz, 3J₉₉' = 8.8 Hz, H9'), 2.23 (s(br), 3H, 8'-Me), 1.97-1.80 (m, 2H, H3'), 1.05 (d, 3H, 3J₃,Me,₄ = 6.6 Hz, 4-Me).
$^{13}$C NMR (CDCl$_3$, 300 MHz) $\delta$ 178.4 (C2), 172.9 (-CO$_2$Me), 157.4 (C6'), 136.3 (C8')*, 136.0 (C4'a)*, 129.6 (C8'a), 114.9 (C7')†, 110.5 (C5')†, 70.7 (C5), 54.8 (6'-OMe), 51.7 (-CO$_2$Me), 47.0 (C3/C2'), 38.6 (C9'), 37.5 (Cl')‡, 36.3 (C4)‡, 26.1 (C4)#, 19.5 (C3)#, 19.1 (8'-Me), 12.8 (4-Me).

IR (CHCl$_3$, cm$^{-1}$) 2950 (C-H str), 2840 (C-H str), 1765(s) (C=O str, lactone), 1730(s) (C=O str, ester), 1610(s) (Ar C=C str), 1480(s) (Ar C=C str), 1260 (C-O str), 1165(s) (C-O str), 1145(s) (C-O str), 1050 (C-O str), 1030 (C-O str), 980, 930, 860 (C-H oop bend).

MS, m/z (relative intensity, %) 332 (M+, 42.2), 272 (11), 259 (89), 215 (100), 188 (25), 160 (28), 128 (17), 115 (19).

HRMS: Calcd for C$_{19}$H$_{24}$O$_5$: 332.1624. Found: 332.1622.

**Methyl (5α,5αα,11βα)-1,4,5,6,7,11b-Hexahydro-9-methoxy-5,11-dimethyl-2-oxonaphth[1,2-d]oxepin-5a(2H)-carboxylate** 111.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 6.62, 6.37 (2 x d, 2 x 1H, $^4$J$_{8,10}$ = $^4$J$_{10,8}$ = 2.6 Hz, H8, H10), 4.60 (d, 1H, $^2$J$_{4,4'}$ = 13.4 Hz, H4), 4.11 (dd, 1H, $^2$J$_{4',4}$ = 13.4 Hz, $^3$J$_{4',5}$ = 5.1 Hz, H4'), 3.72 (s, 3H, 9-OMe), 3.67 (d(br), 1H, $^3$J$_{11b,1β}$ = 12.4 Hz, H11b), 3.57 (s, 3H, -CO$_2$Me), 2.92-2.64 (m, 2H, H7), 2.75 (dd, 1H, $^2$J$_{1β,1α}$ = 14.5 Hz, $^3$J$_{1β,11b}$ = 12.4 Hz, H1β), 2.40 (s, 3H, 11-Me), 2.38 (dd, 1H, $^2$J$_{1α,1β}$ = 14.5 Hz, $^3$J$_{1α,11b}$ = 1.4 Hz, 1α), 2.32 (m, 1H, H6β), 2.18 (dq, 1H, $^3$J$_{5,Me}$ = 7.2 Hz, $^3$J$_{5,4'}$ = 5.1 Hz, H5), 2.05 (m, 1H, H6α), 1.02 (d, 3H, $^3$J$_{Me}$, s = 7.2 Hz, 5-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) $\delta$ 174.9 (C2), 174.0 (-CO$_2$Me), 157.8 (C9), 137.5 (C11)*, 134.4 (C7a)*, 130.1 (C11a), 157.3 (C10)†, 110.9 (C8)†, 67.0 (C4), 54.8 (9-OMe), 51.9
(-CO₂Me), 51.1 (C5α), 40.7 (C11β), 37.9 (C1), 31.4 (C5), 26.6 (C7), 25.6 (C6), 18.9 (11-Me), 12.9 (5-Me).

IR (CHCl₃, cm⁻¹) 2950 (C-H str), 2840 (C-H str), 1730 (s, br) (C=O str, lactone & ester), 1610 (Ar C=C str), 1480 (Ar C=C str), 1275 (C-O str), 1250 (C-O str), 1145 (s) (C-O str), 1115 (C-O str), 1060 (C-O str), 910, 860 (C-H oop bend).

MS, m/z (relative intensity, %) 333 (M⁺+1, 17.5), 332 (M⁺, 85.0), 275 (11), 273 (16), 272 (19), 259 (78), 246 (41), 231 (37), 215 (100), 201 (28), 188 (33), 173 (46), 115 (38).


Reduction of the Aldehyde With Sodium Borohydride.

To a solution of the aldehyde 71 (100 mg, 0.276 mmol) in MeOH (10 mL) at 0°C, was added NaBH₄ (20 mg). After 10 min, the reaction mixture was quenched with 1M HCl and extracted with ether. The ether extracts were washed with water and brine, and dried over MgSO₄. Evaporation of solvent afforded a ca. 1:1 mixture of the 5- and 7-membered lactones 110 and 111 (90 mg, 98% recovery).

Reduction of the Aldehyde With Sodium Cyanoborohydride and Subsequent Lactonisation 109.

A solution of the aldehyde 71 (100 mg, 0.277 mmol) and a trace of bromocresol green (ca. 1 mg) in dry MeOH (10 mL) was cooled to 0°C. Na(CN)BH₃ (50 mg, 0.81 mmol) was
added in one portion and the acidity was maintained around pH 4 by the periodic dropwise addition of 2M HCl in MeOH.

After the reaction was complete (ca. 0.5 h), water was added and the reaction mixture extracted with ether. The ether phases were then washed with water and brine, and dried over MgSO4. Removal of solvent *in vacuo* followed by flash chromatography afforded the alcohol 109 (Rf = 0.2; 25% ethyl acetate in pentane) as an amorphous white solid (72 mg, 71%). The lactol 92 (12 mg, 12%) was also isolated.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 6.48, 6.39 (2 x d(br), 2 x 1H, $^4$J$_{5,7}$ = $^4$J$_{7,5}$ = 2.6 Hz, H5, H7), 4.11 (ddd, 1H, $^3$J$_{1,9}$ = 7.0 Hz, $^3$J$_{1,9'}$ = 6.3 Hz, $^4$J$_{1,3\alpha}$ = 1.8 Hz, H1), 4.04 (dd(br), 1H, $^2$J$_{11,11'}$ = 11.3 Hz, $^3$J$_{11,10}$ = 3.6 Hz, H11), 3.70 (s, 3H, 6-OMe), 3.62 (s, 3H, 9-CO$_2$Me), 3.51 (dd, 1H, $^2$J$_{11',11}$ = 11.3 Hz, $^3$J$_{11',10}$ = 6.9 Hz, H11'), 3.35 (s, 3H, 2-CO$_2$Me), 2.95-2.78 (m, 2H, H4), 2.64 (dd, 1H, $^2$J$_{9',9}$ = 15.0 Hz, $^3$J$_{9',1}$ = 6.3 Hz, H9'), 2.57 (m, 1H, H3\alpha), 2.26 (s(br), 3H, 8-Me), 2.21 (dd, 1H, $^2$J$_{9,9'}$ = 15.0 Hz, $^3$J$_{9,1}$ = 7.0 Hz, H9), 1.74 (ddq, 1H, $^3$J$_{10,11'}$ = 6.9 Hz, $^3$J$_{10,Me}$ = 6.9 Hz, $^3$J$_{10,11}$ = 3.6 Hz, H10), 1.59 (m, 1H, H3\beta), 1.02 (d, 3H, $^3$J$_{Me,10}$ = 6.9 Hz, 10-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) δ 175.1, 173.9 (2 x -CO$_2$Me), 157.9 (C6), 137.1 (C8)*, 136.7 (C4a)*, 130.6 (C8a), 114.1 (C7), 110.9 (C5), 64.1 (C11), 54.8 (6-OMe), 52.6 (C2), 51.8, 51.3 (2 x -CO$_2$Me), 41.2 (C10), 36.3 (C9), 35.3 (C1), 25.6 (C4), 24.5 (C3), 19.0 (8-Me), 12.9 (10-Me).

A solution of the alcohol 109 (50 mg, 0.14 mmol) in acetone (5 mL), was heated to reflux in the presence of a catalytic amount of PTSA (ca. 10 mg) for 12 h. Dilute NaHCO$_3$ was added and the solution extracted with ether. The combined ether extracts were then washed with brine, dried over MgSO$_4$, and concentrated *in vacuo* to give the clean lactone 110 (46.2 mg, 100%).
(1'α,2'β,4α)-3',4,4',5-Tetrahydro-6'-methoxy-4,8'-dimethyl-2-oxospiro[furan-3(2H),2'(1'H)-naphthalene]-1'-acetic Acid 112.

Aqueous 3M NaOH (2 mL) was added slowly to an ethanolic solution of the ester 110 (580 mg, 1.82 mmol) at room temperature, and the resulting homogenous mixture was stirred for a further 3 h. The volatile components were then removed under vacuum and the residue diluted with water and washed with ether. The aqueous phase was collected, acidified to pH 2 with dilute HCl, stirred at room temperature for a further 15 min, and then thoroughly extracted with ether. The combined ether phases were washed successively with water and brine, and dried over MgSO4. Removal of solvent \textit{in vacuo} gave a ca. 4:1 mixture of the 5-membered lactone acid 112 and what appeared to be the 7-membered lactone acid 113 as a white solid (510 mg, 92%). 113 was removed by washing the mixture twice with ice cold ether to give clean acid 112 as a white amorphous solid (430 mg, 77%). The remaining mixture, which contained the acid 113 (83.3 mg, 15%) could then be recycled (113 was not characterised).

$^1$H NMR (CDCl$_3$, 300 MHz) δ 6.59, 6.46 (2 x d(br), 2 x 1H, $^4J_{5',7'}=^4J_{7',5'}=2.6$ Hz, H5', H7'), 4.45 (dd, 1H, $^2J_{5',5'}=9.0$ Hz, $^3J_{5,4}=7.3$ Hz, H5), 3.78 (dd, 1H, $^2J_{5',5'}=9.0$ Hz, $^3J_{5',4}=7.5$ Hz, H5'), 3.74 (s, 3H, 6'-OMe), 3.70 (m, 1H, H1'), 3.09-2.81 (m, 2H, H4'), 2.76 (dd, 1H, $^2J_{9',9''}=18.6$ Hz, $^3J_{9',1'}=8.7$ Hz, H9'), 2.71 (ddq, 1H, $^3J_{4,5'}=7.5$ Hz, $^3J_{4,5}=7.3$ Hz, $^3J_{4,Me}=6.8$ Hz, H4), 2.34 (dd, 1H, $^2J_{9',9''}=18.6$ Hz, $^3J_{9',1'}=1.9$ Hz, H9''), 2.25 (s(br), 3H, 8'-Me), 1.96-1.84 (m, 2H, H3'), 0.92 (d, 3H, $^3J_{Me,4}=6.8$ Hz, 4-Me).
$^{13}$C NMR (CDCl$_3$, 300 MHz) δ 178.5 (C2), 175.9 (-CO$_2$H), 157.5 (C6'), 136.6 (C4'a)*, 136.1 (C8')*, 129.4 (C8'a), 115.2 (C7')†, 110.4 (C5')†, 70.7 (C5), 55.0 (6'-OMe), 46.9 (C3/C2'), 38.2 (C9'), 37.6 (C1')‡, 36.1 (C4')‡, 26.1 (C4')#, 19.5 (C3')#, 19.4 (8'-Me), 12.4 (4-Me).

IR (CHCl$_3$, cm$^{-1}$) 2950 (s) (C-H str), 2840 (C-H str), 1765 (s) (C=O str, lactone), 1730 (s) (C=O str, acid), 1610 (s) (Ar C=C str), 1480 (Ar C=C str), 1050 (s) (C-O str).

MS, m/z (relative intensity, %) 318 (M+, 36), 272 (10), 260 (12), 259 (68), 216 (21), 215 (100), 206 (11), 173 (16), 161 (20), 160 (25), 128 (19), 115 (22).

$^{1'}\alpha,2'^\beta,4\alpha$-3',4,4',5-Tetrahydro-6'-methoxy-4,8'-dimethyl-2-oxospiro-[furan-3(2H),2'(1'H)-naphthalene]-1'-acetic Acid, Anhydride with Methyl Hydrogen Carbonate 118.

![Chemical Structure](Image)

Dry triethylamine (0.16 mL, 1.13 mmol) was added to a stirred solution of the acid 112 (300 mg, 0.943 mmol) in dry CH$_2$Cl$_2$ (15 mL) under nitrogen. The solution was cooled to 0°C (ice bath) and methyl chloroformate (81 µL, 1.0 mmol) was added dropwise. After 15 min, the reaction mixture was diluted with CH$_2$Cl$_2$, washed sequentially with 0.2M HCl, water and brine, and dried over MgSO$_4$. Evaporation of solvent gave essentially pure anhydride 118 as a pale yellow oil (355 mg), which was used directly without further purification.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 6.61, 6.47 (2 x d, 2 x 1H, $^4$J$_5',7$ = $^2$J$_7',5'$ = 2.7 Hz, H5', H7'), 4.44 (dd, 1H, $^2$J$_5,5'$ = 9.0 Hz, $^3$J$_5,4 = 6.3$ Hz, H5), 3.92 (s, 3H, 6'-OMe), 3.80 (dd,
1H, $^{2}J_{5',5} = 9.0$ Hz, $^{3}J_{5',4} = 6.0$ Hz, H5’), 3.75 (s, 3H, 11'-OMe), 3.71 (d(br), 1H, $^{3}J_{1',9'} = 7.8$ Hz, H1’), 3.08-2.81 (m, 2H, H4’), 2.86 (dd, 1H, $^{2}J_{9',9'} = 19.2$ Hz, $^{3}J_{9',1'} = 7.8$ Hz, H9’), 2.69 (ddq, 1H, $^{3}J_{4,Me} = 6.9$ Hz, $^{3}J_{4,5} = 6.3$ Hz, $^{3}J_{4,5'} = 6.0$ Hz, H4), 2.48 (dd, 1H, $^{2}J_{9',9'} = 19.2$ Hz, $^{3}J_{9',1'} = 1.9$ Hz, H9”), 2.24 (s, 3H, 8'-Me), 1.93-1.87 (m, 2H, H3’), 1.01 (d, 3H, $^{3}J_{Me,4} = 6.9$ Hz, 4-Me).

$^{13}C$ NMR (CDCl3, 300 MHz) δ 178.6 (C2), 167.6 (Cl0’), 157.9 (C6’), 149.6 (C11’), 136.7 (C4’a)*, 136.2 (C8’)*, 129.0 (C8’a), 115.4 (C7’)*, 110.7 (C5’)*, 70.6 (C5), 56.1 (11'-OMe), 54.9 (6'-OMe), 46.7 (C3/C2’), 38.7 (C9’), 37.5 (C1’), 35.8 (C4), 25.9 (C4’)*, 19.2 (C3’)*, 19.1 (8’-Me), 12.5 (4-Me).

MS, m/z (relative intensity, %) 376 (M+, 0.6), 332 (2), 272 (1), 259 (6), 215 (7), 188 (2), 160 (3), 44 (100).


(1'α,2'β,4α)-1’-[(1-Diazo-2-oxoprop-3-yl)-3’,4’,5-tetrahydro-6’-methoxy-4,8’-dimethylspiro[furan-3(2H),2'(1'H)-naphthalene]-2-one 119.

An unscratched, 1-necked flask, charged with a freshly prepared, ethanol-free solution of CH2N2 in ether (ca. 10-fold excess) was cooled to 0°C under nitrogen. A solution of the crude anhydride 118 (355 mg) in CH2Cl2 (5 mL) was added dropwise and the reaction mixture was stirred at 5°C for 24 h.
Excess solvent and CH₂N₂ were removed on a rotary evaporator in a well ventilated fumehood. Flash chromatography (33% ethyl acetate in pentane) of the resulting yellow oil gave pure diazoketone 119 (R₉ = 0.3) as clear, pale yellow needles (323 mg, 72% overall yield for 2 steps).

**¹H NMR (CDCl₃, 300 MHz)** δ 6.55, 6.45 (2 x d, 2 x 1H, ⁴J₅,₇' = ⁴J₇',₅' = 2.5 Hz, H₅', H₇'), 5.14 (s(br), 1H, H₁¹'), 4.48 (dd, 1H, ²J₅,₅' = 9.0 Hz, ³J₅,₄ = 7.0 Hz, H₅), 3.87 (dd(br), 1H, ³J₁',₉' = 7.7 Hz, ³J₁',₉'' = 2.0 Hz, H₁¹'), 3.75 (dd, 1H, ²J₅,₅ = 9.0 Hz, ³J₅',₄ = 6.6 Hz, H₅'), 3.71 (s, 3H, ₆'-OMe), 3.11-2.77 (m, 2H, H₄'), 2.75 (m(br), 1H, H₉'), 2.61 (ddq, 1H, ³J₄,Me = 7.0 Hz, ³J₄,₅ = 7.0 Hz, ³J₄,₅' = 6.6 Hz, H₄), 2.26 (d(br), 1H, ²J₉'',₉' = 19.4 Hz, H₉''), 2.15 (s, 3H, ₈'-Me), 1.84-1.81 (m, 2H, H₃'), 1.03 (d, ³J₉,₄ = 7.0 Hz, 4-Me).

**¹³C NMR (CDCl₃, 300 MHz)** δ 192.8 (C₁₀'), 179.1 (C₂), 157.5 (C₆'), 136.7 (C₄'a), 136.3 (C₈'), 129.9 (C₈'a), 114.9 (C₇'), 110.4 (C₅'), 70.9 (C₅), 54.7 (₆'-OMe), 54.1 (C₁¹'), 46.9 (C₃/₂'), 45.1 (C₉'), 37.3 (C₁'), 34.1 (C₄), 25.8 (C₄'), 19.4 (C₃'), 19.0 (₈'-Me), 13.1 (4-Me).

IR (CHCl₃, cm⁻¹) 2900-3000(s,br) (C-H str), 2840 (C-H str), 2100(s) (C=N=N asym str), 1760(s,br) (C=O str, ester & lactone), 1640(s) (C=O str, ketone), 1610 (Ar C=C str), 1480 (Ar C=O str), 1365(s,br) (C=N=N sym str), 1320(s) (C-O str), 1140(s) (C-O str), 1050(s) (C-O str), 980, 940, 860 (C-H oop bend).

**MS, m/z (relative intensity, %)** 314 (M⁺-N₂, 8.6), 286 (14), 260 (20), 259 (100), 216 (19), 215 (99), 201 (14), 200 (15), 185 (11), 173 (32), 159 (23), 141 (20), 128 (27), 115 (32), 86 (40), 84 (60).

A solution of the diazoketone 119 (40 mg, 0.12 mmol) in CH₂Cl₂ (1 mL) was added dropwise to a gently boiling suspension of rhodium mandelate (ca. 2 mol %) in CH₂Cl₂ (2 mL) under argon. After 5 min, an aliquot from the reaction mixture was filtered through a plug of cotton wool, and the filtrate concentrated *in vacuo* to afford essentially clean 130 (>90%) as a pale green oil (R<sub>f</sub> = 0.45; 25% ethyl acetate in pentane). The unstable cycloheptatriene was used directly for analysis without further purification.

**<sup>1</sup>H NMR** (CDCl₃, 300 MHz) δ 5.79 (s(br), 1H, H₈), 5.54 (s(br), 1H, H₆), 4.33 (dd, 1H, <sup>2</sup>J<sub>5',5"</sub> = 9.3 Hz, <sup>3</sup>J<sub>5',4</sub> = 7.3 Hz, H₅'), 3.87 (dd, 1H, <sup>2</sup>J<sub>5",5</sub> = 9.3 Hz, <sup>3</sup>J<sub>5",4'</sub> = 6.3 Hz, H₅"), 3.61 (s, 3H, 7-OMe), 3.32 (m, 1H, H₂a), 2.82 (m(vbr), 1H, H₉a), 2.57 (ddq, 1H, <sup>3</sup>J<sub>4',5</sub> = 7.3 Hz, <sup>3</sup>J<sub>4',Me</sub> = 7.1 Hz, <sup>3</sup>J<sub>4",5"</sub> = 6.3 Hz, H₄’), 2.52 (ddd, 1H, <sup>2</sup>J<sub>12,2'</sub> = 17.9 Hz, <sup>3</sup>J<sub>12,2a</sub> = 17.9 Hz, <sup>3</sup>J<sub>12,9a</sub> = 1.0 Hz, H₂'), 2.44-2.38 (m, 2H, H₅), 2.40 (ddd, 1H, <sup>2</sup>J<sub>2,2'</sub> = 17.9 Hz, <sup>3</sup>J<sub>2,2a</sub> = 8.7 Hz, <sup>4</sup>J<sub>2,9a</sub> = 1.0 Hz, H₂), 2.15-1.90 (m, 2H, H₄), 1.85 (s(br), 3H, 9-Me), 1.18 (d, 3H, <sup>3</sup>J<sub>Me,4'</sub> = 7.1 Hz, 4'-Me).

**<sup>13</sup>C NMR** (CDCl₃, 300 MHz) δ 215.1 (Cl), 181.6 (C₂'), 159.2 (C7), 133.0, 126.6, 125.2 (C₅a, C₉, C₉b), 121.1 (C₈), 104.3 (C₆), 72.4 (C₅'), 54.6 (7-OMe), 53.0 (C₉a), 45.5 (C₃/C₃'), 41.8 (C₂a), 40.8 (C2), 33.4 (C₄'), 25.9 (C₅)*, 25.8 (C₄)*, 20.2 (9-Me), 14.3 (4'-Me).

IR (CHCl₃, cm⁻¹) 3000 (C-H str), 2940 (C-H str), 2840 (C-H str), 1760(s) (C=O str, lactone), 1745(s) (C=O str, ketone), 1160 (C-O str), 910 (C-H oop bend).
MS, \textit{m/z} (relative intensity, \%) 315 (M$^+$+1, 20.1), 314 (M$^+$, 100), 300 (10), 299 (25), 287 (12), 286 (64), 272 (22), 271 (25), 257 (17), 227 (21), 202 (38), 199 (22), 174 (87), 173 (62), 128 (37), 115 (49), 91 (38).

HRMS: Calcd for C$_{19}$H$_{22}$O$_4$: 314.1518. Found: 314.1518.

(2\textit{a}α,3\textit{a},4'β)-2,2\textit{a},4,4',5,5'-Decahydro-7-methoxy-4',9-dimethylspiro-
[[1\textit{H}]benz[cd]azulene-3(8\textit{H}),3'(2'\textit{H})-furan]-1,2'dione 157.

To the reaction mixture of 130 in CH$_2$Cl$_2$ was added DBU (1-2 drops). After stirring for a further 5 min, the golden-coloured solution was washed sequentially with 0.5M HCl, water and brine, and dried over MgSO$_4$. The organic phase was concentrated \textit{in vacuo} and the resulting oil chromatographed (25% ethyl acetate in pentane) to give the ketone 157 (R$_f$ = 0.4) as a pale yellow solid (31 mg, 85% overall yield for two steps).

$^1$H NMR (CDCl$_3$, 300 MHz) δ 5.17 (s(br), 1H, H6), 4.34 (dd, 1H, $^2$J$_{5',5''}$ = 9.3 Hz, $^3$J$_{5',4'}$ = 7.6 Hz, H5'), 3.82 (dd, 1H, $^2$J$_{5',5''}$ = 9.3 Hz, $^3$J$_{5'',4'}$ = 6.6 Hz, H5''), 3.56 (s, 3H, 7-OMe), 3.31 (m, 1H, H2a), 2.97 (dd, 1H, $^2$J$_{8,8'}$ = 12.4 Hz, $^4$J$_{8,6}$ = 2.1 Hz, H8), 2.68-2.44 (m, 2H, H5), 2.58 (dd, 1H, $^2$J$_{2,2'}$ = 18.0 Hz, $^3$J$_{2,2a}$ = 8.8 Hz, H2), 2.57 (ddq, 1H, $^3$J$_{4',5'}$ = 7.6 Hz, $^3$J$_{4',Me}$ = 7.0 Hz, $^3$J$_{4',5''}$ = 6.6 Hz, H4'), 2.38 (s(br), 3H, 9-Me), 2.40 (dd, 1H, $^2$J$_{2',2}$ = 18.0 Hz, $^3$J$_{2',2a}$ = 8.2 Hz, H2'), 2.09 (d(br), 1H, $^2$J$_{8',8}$ = 12.4 Hz, H8'), 2.07-1.91 (m, 2H, H4), 1.09 (d, 3H, $^3$J$_{Me,4'}$ = 7.0 Hz, 4'-Me).
$^{13}$C NMR (CDCl$_3$, 300 MHz) δ 205.1 (C1), 182.0 (C2'), 146.7 (C7), 136.0 (C9), 134.1, 131.7, 131.5 (C5a, C9a, C9b), 99.5 (C6), 72.4 (C5'), 56.1 (7-OMe), 45.8 (C3/C3'), 41.8 (C2a), 40.6 (C2), 40.2 (C8), 33.5 (C4'), 27.9 (C5'), 25.2 (C4'), 20.4 (9-Me), 14.4 (4'-Me).

MS, m/z (relative intensity, %) 315 (M$^+$+1, 20.3), 314 (M$^+$, 100), 299 (29), 272 (35), 271 (12), 257 (26), 227 (17), 202 (80), 187 (24), 174 (43), 173 (21), 159 (44), 141 (37), 128 (46), 115 (63), 91 (53).

HRMS: Calcd for C$_{19}$H$_{22}$O$_4$: 314.1518. Found: 314.1518.

3.2 Des-Methyl Spirolactone Series

Methyl (1'$\alpha$,2'$\beta$,4$\alpha$)-3',4,4',5-Tetrahydro-6'-methoxy-4-methyl-2-oxospiro-[furan-3(2H),2'(1'H)-naphthalene]-1'-acetate 122.

A solution of the aldehyde 121 (920 mg, 2.64 mmol) in ether/DMF (3:1, 30 mL) was converted to the spirolactone 122 with Zn(BH$_4$)$_2$ in a manner similar to that for the conversion of 71 to 110. Work up gave the desired lactone as the major component. Flash chromatography gave the desired lactone (R$_f$ = 0.3; 25% ethyl acetate in pentane) as a colourless oil (725 mg, 86%).

$^1$H NMR (CDCl$_3$, 300 MHz) δ 6.96 (d, 1H, $^3$J$_8,7'$ = 8.5 Hz, H$8'$), 6.69 (dd, 1H, $^3$J$_7,8'$ = 8.5 Hz, $^4$J$_7,5'$ = 2.7 Hz, H$7'$), 6.65 (d, 1H, $^4$J$_5,7'$ = 2.7 Hz, H$5'$), 4.31 (dd, 1H, $^2$J$_5,5'$ =
9.2 Hz, $^3J_{5',4} = 7.7$ Hz, H5), 3.75 (s, 3H, 6'-OMe), 3.71 (t, 1H, $^3J_{5',4} = 9.2$ Hz, H5'), 3.67 (s, 3H, -CO2Me), 3.56 (m, 1H, H1'), 3.03-2.90 (m, 2H, H4'), 2.69-2.55 (m, 2H, H9'), 2.50 (dd, 1H, $^3J_{4,5} = 7.7$ Hz, $^3J_{4,5'} = 9.2$ Hz, $^3J_{4,Me} = 6.8$ Hz, H4), 2.03-1.86 (m, 2H, H3'), 0.78 (d, 3H, $^3J_{Me,4} = 6.8$ Hz, 4-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) $\delta$ 180.3 (C2), 172.8 (-CO2Me), 158.3 (C6'), 137.7 (C4'a), 129.8 (C8'a), 127.6 (C8'), 113.1 (C7')*, 112.0 (C5')*, 70.7 (C5), 55.0 (6'-OMe), 51.8 (-CO2Me), 47.5 (C3/C2'), 39.2 (C1'), 37.1 (C9'), 36.5 (C4), 25.8 (C4')†, 22.1 (C3')†, 12.3 (4-Me).

IR (CHCl$_3$, cm$^{-1}$) 2950 (C-H str), 2840 (C-H str), 1765(s) (C=O str, lactone), 1730(s) (C=O str, ester), 1610 (Ar C=C str), 1500(s) (Ar C=C str), 1255 (C-O str), 1165(s) (C-O str), 1030(s) (C-O str).

MS, m/z (relative intensity, %) 319 (M$^+$+1, 7.2), 318 (M$^+$, 36.4), 290 (15), 176 (12), 258 (62), 245 (36), 216 (42), 201 (100), 175 (47), 146 (43), 115 (70).

HRMS: Calcd for C$_{18}$H$_{22}$O$_5$: 318.1467. Found: 318.1470.

(1'α,2'β,4α)-3',4,4',5-Tetrahydro-6'-methoxy-4-methyl-2-oxospiro[furan-3(2H),2'(1'H)-naphthalene]-1'-acetic Acid 124.

The ester 122 (650 mg, 2.04 mmol) was converted to the acid with NaOH in aqueous ethanol, in a manner similar to that for the conversion of 110 to 112. Work up gave the
acid 124 as an amorphous white solid (560 mg, 90% recovery). There was little evidence for the presence of the corresponding 7-membered lactone acid.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.01 (d, 1H, $^3$J$_{8',7'}$ = 8.5 Hz, H$^{8'}$), 6.72 (dd, 1H, $^3$J$_{7',8'}$ = 8.5 Hz, $^4$J$_{7',5'}$ = 2.7 Hz, H$^{7'}$), 6.66 (d, 1H, $^4$J$_{5',7'}$ = 2.7 Hz, H$^{5'}$), 4.28 (dd, 1H, $^2$J$_{5,5'}$ = 9.0 Hz, $^3$J$_{5,4}$ = 7.7 Hz, H$^5$), 3.76 (s, 3H, 6'-OMe), 3.70 (t, 1H, $^2$J$_{5,5'}$ = 9.0 Hz, $^3$J$_{5,4}$ = 7.7 Hz, H$^{5'}$), 3.56 (m, 1H, H$^{1'}$), 3.03-2.90 (m, 2H, H$^{4'}$), 2.76-2.56 (m, 2H, H$^{9'}$), 2.46 (ddq, 1H, $^3$J$_{4,5'}$ = 9.0 Hz, $^3$J$_{4,5}$ = 7.7 Hz, $^3$J$_{4,Me}$ = 6.6 Hz, H$^4$), 2.06-1.87 (m, 2H, H$^{3'}$), 0.73 (d, 3H, $^3$J$_{Me,4}$ = 6.6 Hz, 4-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) $\delta$ 180.6 (C2), 178.3 (-CO$_2$H), 158.4 (C6'), 137.8 (C4'a), 129.5 (C8'a), 127.3 (C8'), 113.2 (C7')*, 112.0 (C5')*, 70.8 (C5), 55.0 (6'-OMe), 47.8 (C3/C32'), 38.7 (C1'), 36.6 (C9'), 36.3 (C4), 25.8 (C4')$, 22.3 (C3')$, 12.2 (4-Me).

IR (CHCl$_3$, cm$^{-1}$) 3500-2430(br) (O-H str), 2940 (C-H str), 1765(s) (C=O str, lactone), 1710(s) (C=O str, acid), 1610(s) (Ar C=C str), 1500(s) (Ar C=C str), 1260 (C-O str), 1160(s) (C-O str), 1040(s) (C-O str), 870 (C-H oop bend).

MS, $m/z$ (relative intensity, %) 305 (M$^{++}$+1, 4.5), 304 (M$, 24.7$), 276 (8), 262 (7), 259 (10), 258 (56), 246 (11), 245 (26), 243 (13), 216 (45), 202 (25), 201 (100), 199 (12), 192 (30), 187 (20), 175 (22), 174 (27), 173 (21), 172 (17), 171 (28), 159 (32), 147 (35), 146 (40), 128 (39), 115 (60).
(1'α,2'β,4α)-1'-(1-Diazo-2-oxoprop-3-yl)-3',4',4',5-tetrahydro-6'-methoxy-4-methylspiro[furan-3(2H),2'(1'H)-naphthalene]-2-one 126.

A solution of the acid 124 (500 mg, 1.64 mmol) in dry CH₂Cl₂ (2 mL) under a nitrogen atmosphere was cooled to 0°C (ice bath) and oxalyl chloride (1.44 mL, 16.4 mmol) was added dropwise. DMF (ca. 5 drops) was then added dropwise and the resulting yellow solution stirred at 0°C for a further 30 min.

The volatile components were removed in vacuo and dry benzene added. The benzene was then removed in vacuo and the procedure repeated twice more. Finally the residue was taken up into dry ether and filtered through a plug of cotton wool into fresh ethereal diazomethane (ca. 10-fold excess) at -20°C (dry-ice/acetone) under nitrogen. After 30 min, the cooling bath was removed and the volatile components removed in vacuo to afford a yellow oil. Flash chromatography (33% ethyl acetate in pentane) gave the pure diazoketone 126 (R_f = 0.25) as pale yellow oil (385 mg, 83%).

^1H NMR (CDCl₃, 300 MHz) δ 7.08 (d(br), 1H, 3J₈',₇' = 8.5 Hz, H₈'), 6.72 (dd, 1H, 3J₇',₈' = 8.5 Hz, 4J₇',₅' = 2.6 Hz, H₇'), 6.65 (d, 1H, 4J₅',₇' = 2.6 Hz, H₅'), 5.28 (s(br), 1H, H₁'), 4.34 (dd, 1H, 2J₅',₄' = 9.0 Hz, 3J₅',₄ = 7.7 Hz, H₅'), 3.77 (s, 3H, 6'-O-Me), 3.73 (t, 1H, 2J₅',₅ = 9.0 Hz, 3J₅',₄ = 9.0 Hz, H₅'), 3.56 (m, 1H, H₁'), 3.07-2.80 (m, 2H, H₄'), 2.69-2.54 (m, 2H, H₉'), 2.50 (ddq, 1H, 3J₄',₅' = 9.0 Hz, 3J₄',₅ = 7.7 Hz, 3J₄',₄Me = 6.6 Hz, H₄), 2.06-1.87 (m, 2H, H₃'), 0.78 (d, 3H, 3J_Me₄ = 6.6 Hz, 4-Me).
$^{13}$C NMR (CDCl$_3$, 300 MHz) δ 193.0 (C10'), 180.2 (C2), 158.0 (C6'), 137.3 (C4'a), 129.4 (C8'a), 128.0 (C8'), 112.8 (C7'), 111.7 (C5'), 111.7 (C5'a), 108.0 (C5), 54.9 (C11', 6'-OMe), 47.9 (C3/C2'), 43.6 (C9'), 38.9 (C1'), 36.5 (C4), 25.8 (C4'), 22.2 (C3')$^\dagger$, 12.6 (4-Me).

IR (CHCl$_3$, cm$^{-1}$) 2940 (C-H str), 2105 (s) (C=N=N asym str), 1765 (s) (C=O str, lactone), 1640 (s, br) (C=O str, ketone), 1610 (Ar C=C str), 1500 (s) (Ar C=C str), 1370 (s, br) (C=N=N sym str), 1050 (C-O str).

MS, m/z (relative intensity, %) 328 (M$^+$, 8), 300 (14), 258 (15), 245 (55), 214 (10), 113 (20), 202 (20), 201 (94), 189 (10), 188 (69), 187 (19), 186 (16), 185 (13), 173 (18), 172 (14), 171 (18), 159 (44), 145 (30), 128 (33), 115 (52).

(2α,3α,4β,9αβ)-2,2α,4,4',5,5'-Decahydro-7-methoxy-4'-methylspiro-
[[1H]benz[cd]azulene-3(9aH),3'(2'H)-furan]-1,2'-dione 135.

The diazoketone 126 (200 mg, 0.610) in CH$_2$Cl$_2$ (1.5 mL), was treated with a catalytic amount of rhodium mandelate in boiling CH$_2$Cl$_2$ (2 mL) under nitrogen, in a manner similar to that for the conversion of 119 to 130. An aliquot was removed from the reaction mixture and the $^1$H nmr spectrum indicated a ca. 6:3:2 mixture of the expected cycloheptatriene 135, the H(9αα)-epimer 136, and the phenalene 137. No attempt was
made to isolate the two cycloheptatrienes by chromatography, but useful $^1$H nmr data were gleaned from the spectrum.

$^1$H NMR (CDCl$_3$, 300 MHz) 6.00 (dt, 1H, $^3$J$_{8,9}$ = 9.9 Hz, $^4$J$_{8,6}$ = 2.0 Hz, $^4$J$_{8,9a}$ = 2.0 Hz, H8), 5.50 (s(br), 1H, H6), 5.49 (dd, 1H, $^3$J$_{9,8}$ = 9.9 Hz, $^3$J$_{9,9a}$ = 4.4 Hz, H9), 4.35 (dd, 1H, $^2$J$_{5',5''} = 9.2$ Hz, $^3$J$_{5',4'} = 7.5$ Hz, H5''), 3.88 (dd, 1H, $^2$J$_{5',5''} = 9.2$ Hz, $^3$J$_{5',4'} = 5.9$ Hz, H5''), 3.62 (s, 3H, 7-OMe), 3.32 (m, 1H, H2a), 3.05 (s(br), 1H, H9a), 2.55-2.36 (m, 4H, H2, H4', H5a, H5p), 2.22-1.96 (m, 3H, H2', H4a, H4p), 1.20 (d, 2H, $^3$J$_{Me,4'}$ = 7.0 Hz, 4'-Me).

(2$\alpha$,3$\alpha$,4'$\beta$,9$\alpha$)-2,2a,4,4',5,5'-Hexahydro-7-methoxy-4'-methylspiro-
[[1$H$benz[cd]azulene-3(9$\alpha$H),3'(2'H)-furan]-1,2'-dione 136.

$^1$H NMR (CDCl$_3$, 300 MHz) 6.96 (dt, 1H, $^2$J$_{8,9}$ = 10.5 Hz, $^4$J$_{8,6}$ = 2.4 Hz, $^4$J$_{8,9a}$ = 2.4 Hz, H8), 5.40 (s(br), 1H, H6), 5.28 (dd, 1H, $^3$J$_{9,8}$ = 10.5 Hz, $^3$J$_{9,9a}$ = 3.5 Hz, H9), 4.30 (dd, 1H, $^2$J$_{5',5''} = 9.2$ Hz, $^3$J$_{5',4'} = 7.5$ Hz, H5''), 3.83 (dd, 1H, $^2$J$_{5',5''} = 9.2$ Hz, $^3$J$_{5',4'} = 6.6$ Hz, H5''), 3.60 (s, 3H, 7-OMe), 3.32 (m, 1H, H2a), 3.34 (s(br), 1H, H9a), 2.55-2.36 (m, 4H, H2, H4', H5a, H5p), 2.17-1.96 (m, 3H, H2', H4a, H4p), 1.04 (d, 2H, $^3$J$_{Me,4'}$ = 7.0 Hz, 4'-Me).

(2$\alpha$,3$\alpha$,4'$\beta$)-2,2a,4,4',5,5'-Hexahydro-7-methoxy-4'$\beta$-methylspiro-
[[1$H$benz[cd]azulene-3(8$\alpha$H),3'(2'H)-furan]-1,2'-dione 156.
Addition of DBU to the reaction mixture followed by work up and chromatography gave the α,β-unsaturated ketone 156 (Rf = 0.24; 25% ethyl acetate in pentane) as a yellow oil (105 mg, 57%).

\[1H \text{ NMR (CDCl}_3, 300 \text{ MHz)} \delta 6.07 (dd(br), 1H, J_{9,8} = 8.6 \text{ Hz}, J_{9,8'} = 5.6 \text{ Hz}, H9), 5.25 (s(br), 1H, H6), 4.37 (dd, 1H, J_{5',5''} = 9.2 \text{ Hz}, J_{5',4'} = J_{9',5''} = 7.5 \text{ Hz}, H5'), 3.87 (dd, 1H, J_{5',5''} = 9.2 \text{ Hz}, J_{5',4'} = 6.4 \text{ Hz}, H5''), 3.60 (s, 3H, 7-OMe), 3.42 (m, 1H, H2a), 3.23 (ddd, 1H, J_{18,9} = 13.8 \text{ Hz}, J_{8,9} = 8.6 \text{ Hz}, J_{8,6} = 2.2 \text{ Hz}, H8), 2.74-2.50 (m, 2H, H5), 2.64 (dd, 1H, J_{2,2'} = 18.2 \text{ Hz}, J_{2,2a} = 8.6 \text{ Hz}, H2), 2.50 (ddq, 1H, J_{4',5'} = 7.5 \text{ Hz}, J_{4',Me} = 7.0 \text{ Hz}, J_{4',5''} = 6.4 \text{ Hz}, H4'), 2.29 (dd, 1H, J_{2,2'} = 18.2 \text{ Hz}, J_{2,2a} = 8.1 \text{ Hz}, H2'), 2.28 (dd(br), 1H, J_{8,8'} = 13.8 \text{ Hz}, J_{8,9} = 5.6 \text{ Hz}, H8'), 2.15-1.99 (m, 2H, H4), 1.13 (d, 2H, J_{Me,4'} = 7.0 \text{ Hz}, 4'-Me).

\[13C \text{ NMR (CDCl}_3, 300 \text{ MHz)} \delta 203.8 (C1), 181.5 (C2'), 147.1 (C7), 138.1, 113.9, 132.1 (C5a, C9b, C9a), 117.3 (C9), 100.5 (C6), 72.5 (C5'), 56.2 (7-OMe), 45.6 (C3/C3'), 40.9 (C2a), 39.1 (C2), 33.3 (C4'), 32.4 (C8), 28.4 (C5), 25.5 (C4), 14.6 (4'-Me).

IR (CHCl3, cm⁻¹) 2985 (C-H str), 1765(s) (C=O str, lactone), 1715(s,br) (C=O str, enone), 1625(br) (C=C str), 1260(s) (C-O str), 1170(s) (C-O str), 1040(s) (C-O str), 875 (C-H oop bend).

MS, m/z (relative intensity, %) 300 (M⁺, 5.9), 258 (8), 188 (9), 185 (4), 160 (8), 115 (6), 86 (60), 84 (100).


2',3',4,5,9',9'a-Hexahydro-8'-methoxy-4-methylspir[furan-3(2H),1'-[1H]phenalene]-2,8'(7'H)-dione 137.

The phenalene 137, which was the second eluting component, was also characterised.
$^1$H NMR (CDCl$_3$, 300 MHz) δ 6.59, 6.56 (2 x s(br), 2 x 1H, H4', H6'), 4.37 (dd, 1H, 2$^{J}_{5,5'}$ = 9.0 Hz, 3$^{J}_{5,4}$ = 7.5 Hz, H5), 3.88 (dd, 1H, 2$^{J}_{5',5}$ = 9.0 Hz, 3$^{J}_{5',4}$ = 9.0 Hz, H5'), 3.77 (s, 3H, 5'-OMe), 3.65 (d(br), 1H, 2$^{J}_{7',7}$ = 19.1 Hz, H7'), 3.54 (d, 1H, 2$^{J}_{7',7}$ = 19.1 Hz, H7''), 3.02-2.83 (m, 2H, H3'), 2.60 (dd, 1H, 2$^{J}_{9',9}$ = 15.8 Hz, 3$^{J}_{9',9}$ = 13.2 Hz, 3$^{J}_{9',9}$ = 19.1 Hz, H9'), 3.42 (dd(br), 1H, 3$^{J}_{9,a,9}$ = 13.2 Hz, 3$^{J}_{9,a,9}$ = 4.2 Hz, H9a), 2.04-1.75 (m, 2H, H2'), 1.09 (d, 3H, 3$^{J}_{Me,4}$ = 6.8 Hz, 4-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) δ 208.6 (C8'), 180.6 (C2), 158.4 (C5'), 136.5 (C3'a)*, 134.4 (C6'a)*, 125.7 (C9'b), 112.2 (C4')†, 111.9 (C6')†, 71.6 (C5), 55.2 (5'-OMe), 45.4 (C7'), 41.1 (C9'), 38.4 (C9'a), 35.7 (C3/C1'), 26.0 (C3')‡, 23.2 (C2')‡, 13.2 (4-Me).

IR (CHCl$_3$, cm$^{-1}$) 2940 (C-H str), 1765(s) (C=O str, lactone), 1720(s) (C=O str, ketone), 1610 (Ar C=C str), 1480 (Ar C=C str), 1270 (C-O str), 1145(s) (C-O str), 1025 (C-O str), 910 (C-H oop bend).

MS, m/z (relative intensity, %) 300 (M$^+$, 2.6), 258 (4), 213 (2), 188 (11), 160 (3), 149 (12), 105 (9), 84 (100).

HRMS: Calcd for C$_{18}$H$_{20}$O$_4$: 300.1362. Found: 300.1360.
4.1 Aromatic Methyl Olefin Series

Methyl [10R-(1α,2β)]-2-(But-1-en-3-yl)-1,2,3,4-tetrahydro-6-methoxy-2-(methoxycarbonyl)-8-methylnaphthalene-1-acetate 163.

Excess Lombardo's reagent,59 as a suspension in THF, was added at a moderate rate to a well stirred solution of the aldehyde 71 (395 mg, 1.09 mmol) in dry THF (10 mL), at room temperature under nitrogen. After 5 min, the reaction mixture was quenched with saturated NaHCO₃ and extracted with ethyl acetate. The combined organic phases were then washed with water and brine, and dried over MgSO₄. Concentration of solvent in vacuo followed by flash chromatography afforded the olefin 163 (Rᵣ = 0.52; 20% ethyl acetate in pentane) as a colourless, somewhat mobile oil (242 mg, 62%).

1H NMR (CDCl₃, 300 MHz) δ 6.45, 6.41 (2 x d, 2 x 1H, 4J₅,₇ = 4J₇,₅ = 2.5 Hz, H₅, H₇), 6.07 (ddd, 1H, 2J₁₂cis,₁₂trans = 1.4 Hz, 3J₁₂cis,₁₁ = 10.3 Hz, H₁₂cis), 5.09 (dd, 1H, 2J₁₂trans,₁₂cis = 1.4 Hz, 3J₁₂trans,₁₁ = 17.1 Hz, H₁₂trans), 3.93 (ddd, 1H, 2J₁₉,₁₀ = 13.8 Hz, 4J₁₉,₁ = 4.3 Hz, H₁₉), 2.62 (m, 1H, H₃α), 2.24 (dq, 1H, 3J₁₀,₁₁ = 8.9 Hz, 4J₁₀,Me = 7.0 Hz, H₁₀), 2.25 (s(br), 3H, 8-Me), 2.22 (dd, 1H, 2J₉,₉' = 13.8 Hz, 3J₉,₁ = 9.5 Hz, H₉), 1.58 (m, 3H, 3J₃,₃α = 1.5 Hz, H₃), 1.00 (d, 3H, 3J₉,₁₀ = 7.0 Hz, 10-Me).
\[13C \text{ NMR (CDCl}_3, 300 MHz) \delta 173.7, 172.5 \text{(2 x -CO}_2\text{Me}), 157.9 \text{(C6), 139.9 (C11),}

137.3 \text{(C4a)*, 137.4 (C8)*, 130.3 (C8a), 115.7 (C12), 113.8 (C7), 111.0 (C5), 54.8}

(6-OMe), 53.7 (C2), 51.4, 51.0 \text{(2 x -CO}_2\text{Me), 44.5 (C10), 35.9 (C1), 34.9 (C9), 25.8}

(C4), 24.9 (C3), 18.9 (8-Me), 16.6 (10-Me).}

IR (CHCl\textsubscript{3}, cm\textsuperscript{-1}) 2950(s) (C-H str), 2840 (C-H str), 1725(br,s) (C=O str), 1605(s) (Ar C=C str), 1480 (Ar C=C str), 1300 (C-O str), 1145(s) (C-O str), 1060 (C-O str), 920 (C-H

oop bend), 860 (C-H oop bend).

MS, m/z (relative intensity, %) 361 (M\textsuperscript{+}+1, 6.3), 360 (M\textsuperscript{+}, 26), 319 (4), 300 (4), 287 (11),

274 (5), 273 (26), 245 (10), 233 (60), 232 (16), 231 (40), 227 (18), 201 (12), 199 (21),

189 (18), 185 (31), 173 (27), 172 (23), 160 (12), 129 (16), 115 (16).

HRMS: Calcd for C\textsubscript{20}H\textsubscript{26}O\textsubscript{5}: 360.1937. Found: 360.1936.

\[10R-(1\alpha,2\beta)]-2-(\text{But-1-en-3-yl})-1,2,3,4-tetrahydro-6-methoxy-2-

(methoxycarbonyl)-8-methylnaphthalene-1-acetic Acid 171.

Aqueous NaOH (3M, 5 mL) was added slowly to a stirred solution of the ester 163 (302 mg, 0.84 mmol) in ethanol (20 mL). After stirring for 2 h at room temperature, the volatile components were removed in vacuo, and the aqueous residue partitioned between water and ether. The aqueous phase was collected and washed with ether, acidified to pH 2 with 2M HCl, then extracted thoroughly with ether. The combined ether phases were washed with
water and brine, and dried over MgSO₄. Removal of solvent in vacuo gave the clean acid 171 as a white solid (290 mg, 100% recovery).

¹H NMR (CDCl₃, 300 MHz) δ 6.46, 6.41 (2 x d, 2 x 1H, 4J₅,₇ = 4J₇,₅ = 2.5 Hz, H₅, H₇), 6.06 (ddd, 1H, 3J₁₁,₁₂trans = 17.0 Hz, 3J₁₁,₁₂cis = 10.4 Hz, 3J₁₁,₁₀ = 9.0 Hz, H₁₁), 5.12 (dd, 1H, 2J₁₂cis,₁₂trans = 1.5 Hz, 3J₁₂cis,₁₁ = 10.4 Hz, H₁₂cis), 5.10 (dd, 1H, 2J₁₂trans,₁₂cis = 1.5 Hz, 3J₁₂trans,₁₁ = 17.0 Hz, H₁₂trans), 3.94 (ddd, 1H, 3J₁,₉ = 9.5 Hz, 3J₁,₉' = 4.0 Hz, 4J₁,₃α = 1.5 Hz, H₁), 3.72 (s, 3H, 6-OMe), 3.36 (s, 3H, -CO₂Me), 2.90 (m, 2H, H₄), 2.72 (dd, 1H, 2J₉,₉' = 14.1 Hz, 3J₉,₁ = 4.0 Hz, H₉'), 2.64 (m, 1H, H₃α), 2.34 (dq, 1H, 3J₁₀,₁₁ = 9.0 Hz, 3J₁₀,Me = 7.0 Hz, H₁₀), 2.25 (s(br), 3H, 8-Me), 2.22 (dd, 1H, 2J₉,₉' = 14.1 Hz, 3J₉,₁ = 9.5 Hz, H₉), 1.57 (m, 1H, H₃β), 0.99 (d, 3H, 3J₉,₁₀ = 7.0 Hz, 10-Me).

¹³C NMR (CDCl₃, 300 MHz) δ 179.3 (-CO₂H), 174.3 (-CO₂Me), 157.8 (C₆), 139.7 (C₁₁), 137.3 (C₄α), 137.3 (C₈), 130.1 (C₈α), 115.7 (C₁₂), 113.8 (C₇)*, 111.0 (C₅)*, 54.7 (6-OMe), 53.7 (C₂), 51.0 (-CO₂Me), 44.6 (C₁₀), 35.7 (C₁), 34.9 (C₉), 25.7 (C₄)†, 24.9 (C₃)†, 19.0 (8-Me), 16.6 (10-Me).

IR (CHCl₃, cm⁻¹) 3450-2500(br) (O-H str), 2950 (C-H str), 2840 (C-H str), 1720(s, br) (C=O str, ester & acid), 1605(s) (Ar C=C str), 1480 (Ar C=C str), 1300 (C-O str), 1145(s) (C-O str), 1055 (C-O str), 920 (C-H oop bend), 850(br) (C-H oop bend).

MS, m/z (relative intensity, %) 347 (M⁺+1, 3), 346 (M⁺, 14), 319 (14), 233 (33), 232 (12), 231 (26), 201 (13), 199 (50), 185 (15), 173 (21), 172 (17), 129 (14), 128 (13), 115 (17), 105 (21).
Methyl \([10R-(1\alpha,2\beta)]-2-(\text{But}-1-en-3-yl)-1-(1\text-diazo-2-\text{oxoprop-3-yl})-1,2,3,4-\text{tetrahydro}-6\text{-methoxy}-8\text{-methylnaphthalene}-2\text{-carboxylate} 164.

\[
\begin{array}{c}
\text{MeO} \\
\text{HO}_2\text{C}
\end{array}
\xrightarrow{1. \text{(COCl)}_2} \\
\text{CH}_2\text{Cl}_2, 0^\circ\text{C}
\begin{array}{c}
\text{MeO} \\
\text{CO}_2\text{Me}
\end{array}
\xrightarrow{2. \text{CH}_2\text{N}_2}
\begin{array}{c}
\text{MeO} \\
\text{HO}_2\text{C}
\end{array}
\xrightarrow{2. \text{CH}_2\text{N}_2}
\begin{array}{c}
\text{MeO} \\
\text{CO}_2\text{Me}
\end{array}
\]

To a solution of the acid 171 (138 mg, 0.400 mmol) in dry CH\(_2\)Cl\(_2\) (5 mL) at 0°C under nitrogen, was added excess (COCl\(_2\)) (348 µL, 4.00 mmol) dropwise over 2 min. The reaction rate was increased upon addition of a catalytic amount (ca. 5 drops) of DMF and, after stirring for 30 min, the volatile components were removed under vacuum to give an oily residue. Any remaining oxalyl chloride was removed by successive addition/evaporation of dry benzene (3 x 2 mL), dissolved in ether (5 mL), and added dropwise to a stirred ethereal solution of excess diazomethane at -20°C under nitrogen.

After 2 h, the volatile components (including the remaining diazomethane) were removed on a rotary evaporator in a well ventilated fumehood. The residue was purified by flash chromatography (25% ethyl acetate in pentane) to afford the diazoketone 164 \((R_f = 0.24)\) as a pale yellow solid (134 mg, 91%).

\(^1\text{H NMR (CDCl}_3, 300 \text{ MHz)} \delta 6.46, 6.41 (2 \times \text{s (br)}, 2 \times 1\text{H, H5, H7}), 6.10 \text{ (ddd, 1H, H9'), 5.70 (s, 1H, H9)\)}, 5.18 (m, 1H, H14\text{cis}), 5.14 (m, 1H, H14\text{trans}), 4.87 (s(br), 1H, H11), 3.87 (d(br), 1H, 3J\text{13,12} = 9.6 \text{ Hz, H13}), 3.70 (s, 3H, \text{-CO}_2\text{Me}), 2.81-3.00 (m, 2H, H4), 2.63 (dd, 1H, 2J\text{9',9} = 12.6 \text{ Hz, 3J\text{9',1} = 3.2 Hz, H9'}), 2.60 (m, 1H, H3\alpha), 2.35 (dq, 1H, 3J\text{12,13} = 9.1 Hz, 3J\text{12,Me} = 6.9 Hz, H12), 2.18 (s(br), 3H, H8-Me), 2.14 (dd, 1H, 2J\text{9,9'} = 12.6 Hz, 3J\text{9,1} = 9.6 Hz, H9), 1.54 (m, 1H, H3\beta), 0.97 (d, 3H, 3J\text{Me,12} = 6.9 Hz, 12-Me).
$^{13}$C NMR (CDCl$_3$, 300 MHz) $\delta$ 193.4 (C11), 174.2 (-CO$_2$Me), 157.8 (C6), 140.0 (C13), 137.4 (C4a)*, 137.1 (C8)*, 130.0 (C8a), 115.7 (C14), 113.5 (C7)$^\dagger$, 111.2 (C5)$^\ddagger$, 54.7 (6-OMe), 53.4 (C2), 51.0 (-CO$_2$Me), 44.5 (C12), 41.5 (C9), 36.6 (C1), 25.6 (C4)$^+$, 24.9 (C3)$^\ddagger$, 19.0 (8-Me), 16.6 (12-Me).

IR (CHCl$_3$, cm$^{-1}$) 2950 (C-H str), 2840 (C-H str), 2100(s) (C=N=N asym str), 1720(s) (C=O str, ester), 1635 (C=O str, ketone), 1610(s) (Ar C=C str), 1480 (Ar C=C str), 1360(s,br) (C=N=N sym str), 1145(s) (C-O str), 1055 (C-O str), 920 (C-H oop bend), 850(br) (C-H oop bend).

MS, m/z (relative intensity, %) 370 (M+,<1), 342 (3), 287 (7), 286 (4), 285 (17), 255 (18), 233 (20), 201 (10), 174 (10), 173 (23), 172 (12), 115 (11).

HRMS: Calcd for C$_{21}$H$_{26}$O$_4$N$_2$: 370.1893. Found: 370.1889.

**Methyl [(10R-(2α,3α,9α)-3-(But-1-en-3-yl)-2,2a,3,4,5,9a-hexahydro-7-methoxy-9-methyl-1-oxo-1H-benz[cd]azulene-3-carboxylate 165.**

A solution of the diazoketone 164 (130 mg, 0.35 mmol), in CH$_2$Cl$_2$ (1 mL) was added slowly to a suspension of rhodium mandelate (ca. 2 mol %) in boiling CH$_2$Cl$_2$ (2 mL) under argon, over 5 min. An aliquot was removed, filtered through a plug of cotton wool and solvent removed in vacuo to afford a ca. 8:1 mixture (by inspection of the $^1$H nmr) of the cycloheptatriene ($R_f = 0.43$, 20% ethyl acetate in pentane) and the cyclopropane ($R_f = 0.26$) as a light green oil. The cycloheptatriene 165 was analysed without further purification.
$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 5.82 (ddd, 1H, $^3J_{11,12}^{trans} = 16.7$ Hz, $^3J_{11,12}^{cis} = 10.8$ Hz, $^3J_{11,10} = 8.7$ Hz, H11), 5.79 (s(br), 1H, H8), 5.60 (s(br), 1H, H6), 4.98 (dd, 1H, $^2J_{12}^{cis,12} = 1.6$ Hz, $^3J_{12}^{cis,11} = 10.8$ Hz, H12$_{cis}$), 4.94 (dd, 1H, $^2J_{12}^{trans,12} = 1.6$ Hz, $^3J_{12}^{trans,11} = 16.7$ Hz, H12$_{trans}$), 3.71 (s, 3H, 7-OMe), 3.62 (s, 3H, -CO$_2$Me), 3.38-3.26 (m, 1H, H2a), 3.09 (ddd, 1H, $^2J_{2\beta,2\alpha} = 18.9$ Hz, $^3J_{2\beta,2\alpha} = 11.4$ Hz, $^4J_{2\beta,9a} = 1.8$ Hz, H2$\beta$), 2.76 (m, 1H, H9$\alpha$), 2.77 (dq, 1H, $^3J_{10,Me} = 7.0$ Hz, $^3J_{10,11} = 8.7$ Hz, H10), 2.65 (dd(br), 1H, $^2J_{2\alpha,2\beta} = 18.9$ Hz, $^3J_{2\alpha,2\alpha} = 7.3$ Hz, H2$\alpha$), 2.50-2.33 (m, 2H, H5), 2.24-2.33 (m, 1H, H4$\alpha$), 1.85 (m, 1H, H4$\beta$), 1.86 (s(br), 3H, 9-Me), 1.16 (d, 3H, $^3J_{Me,10} = 7.0$ Hz, 10-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) $\delta$ 217.2 (Cl), 176.5 (-CO$_2$Me), 158.8 (C7), 142.3 (C11), 133.2 (C9), 126.7 (C5$\alpha$)*, 126.1 (C9$\beta$)*, 120.8 (C8), 115.5 (C12), 104.9 (C6), 54.6 (7-OMe), 53.5 (C9$\alpha$), 51.5 (-CO$_2$Me), 48.5 (C3), 43.2 (C10), 43.1 (C2), 38.6 (C2$\alpha$), 29.2 (C5)*, 26.0 (C4)*, 20.2 (9-Me), 18.1 (10-Me).

IR (CHCl$_3$, cm$^{-1}$) 2950 (C-H str), 1725(s) (C=O str, ester & ketone), 1635 (C=C str), 1605 (C=C str), 1230 (C-O str), 1165(s) (C-O str), 920 (C-H oop bend).

MS, m/z (relative intensity, %) 343 (M$^+$+1, 2.1), 342 (M$^+$, 9.1), 314 (3), 286 (6), 285 (27), 259 (13), 255 (34), 185 (12), 174 (19), 173 (73), 141 (12), 128 (13), 115 (17).

HRMS: Calcd for C$_{21}$H$_{26}$O$_4$: 342.1831. Found: 342.1834.
Methyl [10R-(2α,3α)]-3-(But-1-en-3-yl)-2,2a,3,4,5,8-hexahydro-7-methoxy-9-methyl-1-oxo-1H-benz[cd]azulene-3-carboxylate 183.

To the remaining solution was added DBU (1-2 drops) at room temperature. After 5 min, the reaction mixture was quenched with 0.2M HCl, washed with water and brine, and dried over MgSO₄. Removal of solvent in vacuo followed by flash chromatography afforded the clean enone 183 (Rf = 0.39) as a pale yellow oil (93 mg, 77%).

1H NMR (CDCl₃, 300 MHz) δ 5.80 (ddd, 1H, 3J₁1,10 = 8.3 Hz, 3J₁1,12cis = 10.4 Hz, 3J₁1,12trans = 16.9 Hz, H11), 5.17 (s(br), 1H, H6), 4.98 (dd, 1H, 2J₁2cis,12trans = 1.2 Hz, 3J₁2cis,11 = 10.4 Hz, H12cis), 4.96 (dd, 1H, 2J₁2trans,12cis = 1.2 Hz, 3J₁2trans,11 = 16.9 Hz, H12trans), 3.70 (s, 3H, 7-OMe), 3.59 (s, 3H, -CO₂Me), 3.44 (m, 1H, H2a), 2.93 (dd, 1H, 2J₈,₈' = 12.0 Hz, 4J₈,₆ = 1.9Hz, H8), 2.78 (dd, 2J₂,₂' = 18.1 Hz, 3J₂,₂a = 9.2 Hz, H2), 2.67 (dd, 1H, 2J₂,₂a = 18.1 Hz, 3J₂,₂a = 8.5 Hz, H2'), 2.66 (dq, 1H, 3J₁₀,Me = 7.0 Hz, 3J₁₀,11 = 8.3 Hz, H10), 2.52-2.41 (m, 2H, H5), 2.39 (s(br), 3H, 9-Me), 2.11 (d, 2J₈,₈' = 12.4 Hz, H8'), 2.07-1.92 (m, 2H, H4), 1.10 (d, 3H, 3J₈,₈ = 7.0 Hz, 10-Me).

13C NMR (CDCl₃, 300 MHz) δ 206.3 (C1), 176.7 (-CO₂Me), 146.9 (C7), 141.4 (C11), 136.0 (C9)*, 134.6 (C5a)*, 132.3 (C9b)*, 131.2 (C9a)*, 115.6 (C12), 99.7 (C6), 56.0 (7-OMe), 51.5 (-CO₂Me), 49.0 (C3), 42.8 (C10)†, 41.8 (C2)†, 39.8 (C2a), 28.7 (C5)‡, 28.0 (C4)‡, 20.2 (9-Me), 16.9 (10-Me).

IR (CHCl₃, cm⁻¹) 2950 (C-H str), 1720(s) (C=O str, ester), 1700(s) (C=O str, enone), 1630(br) (C=C str), 1260 (C-O str), 1115 (C-O str), 1040 (C-O str), 910(s) (C-H oop bend).
Methyl (1α,2α,2α,8bα,10αα)-1,1α,2,3,4,8b,9,10α-Octahydro-6-methoxy-2,8-dimethyl-10-oxocyclopropa[4,5]cyclohepta[1,2-a]naphthalene-2α(10H)-carboxylate 179.

The cyclopropane 179 eluted as the second component (9 mg, 8%), and was also characterised at this stage.

1H NMR (CDCl₃, 300 MHz) δ 6.58, 6.44 (2 x d(br), 2 x 1H, H5, H7), 4.56 (ddd, 1H, 3J8b,9β = 12.4 Hz, 3J8b,9α = 3.1 Hz, 4J8b,3α = 1.7 Hz, H8b), 3.74 (s, 3H, 6-OMe), 3.04 (dd(br), 1H, 2J4α,4β = 18.1 Hz, 3J4α,3β = 10.1 Hz, 3J4α,3α = 7.9 Hz, H4α), 2.82 (dd, 1H, 2J4β,4α = 18.1 Hz, 3J4β,3β = 8.1 Hz, 3J4β,3α = 1.0 Hz, H4β), 2.57 (ddd, 1H, 2J9α,9β = 18.4 Hz, 3J9α,8b = 3.1 Hz, H9α), 2.49 (dd, 1H, 2J9β,9α = 18.4 Hz, 3J9β,8b = 12.4 Hz, H9β), 2.37 (ddddd, 1H, 2J3α,3β = 14.0 Hz, 3J3α,4α = 7.9 Hz, 3J3α,4β = 1.0 Hz, 4J3α,8b = 1.7 Hz, H3α), 2.37 (s(br), 3H, 8-Me), 2.09 (dd, 1H, 3J10α,1a = 9.0 Hz, 3J10α,1 = 8.4 Hz, 3J10a,1' = 5.3 Hz, H10α), 1.48 (ddd, 1H, 2J3β,3α = 14.0 Hz, 3J3β,4α = 10.1 Hz, 3J3β,4β = 8.1 Hz, H3β), 1.38 (ddddd, 1H, 3J1a,2 = 11.3 Hz, 3J1a,10a = 9.0 Hz, 3J1a,1 = 7.8 Hz, 3J1a,1' = 5.3 Hz, H1a), 1.04 (d, 3H, 3JMe,2 = 6.8 Hz, H1'), 0.97 (dd, 1H, 2J1,1' = 5.3 Hz, 3J1,10a = 8.4 Hz, 3J1,1a = 7.8 Hz, H1), 0.72 (dq, 1H, 3J2,1a = 11.3 Hz, 3J2,Me = 6.8 Hz, H2), 0.51 (q, 1H, 2J1',1 = 5.3 Hz, 3J1',1a = 5.3 Hz, 3J1',10a = 5.3 Hz, H1').

13C NMR (CDCl₃, 300 MHz) δ 206.6 (C10), 174.5 (-CO₂Me), 157.9 (C6), 136.8 (C4a)*, 136.6 (C8)*, 128.9 (C8a), 114.9 (C5)†, 110.9 (C7)†, 54.9 (6-OMe), 52.1 (C2a), 51.3 (-CO₂Me), 46.6 (C9), 43.7 (C8b), 36.5 (2), 26.4 (C4)‡, 25.2 (C10a), 24.8 (C3)‡, 18.9 (8-Me), 16.1 (C1α), 15.8 (2-Me), 8.8 (C1).

IR (CHCl₃, cm⁻¹) 2950 (C-H str), 1720(s) (C=O str, ester), 1700(s) (C=O str, ketone), 1605(s) (Ar C=C str), 1480 (Ar C=C str), 1300 (C-O str), 1150(s) (C-O str), 1055 (C-O str), 925 (C-H oop bend), 860 (C-H oop bend).
MS, m/z (relative intensity, %) 343 (M+1, 3.6), 342 (M+, 15.3), 327 (3), 246 (5), 232 (20), 187 (10), 173 (14), 111 (19), 105 (21), 83 (100).

HRMS: Calcd for C_{21}H_{26}O_4: 342.1831. Found: 342.1829.

4.2 Des-Methyl Olefin Series

Methyl [10R-(1\alpha,2\beta)]-2-(But-1-en-3-yl)-1,2,3,4-tetrahydro-6-methoxy-2-(methoxycarbonyl)naphthalene-1-acetate 172.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO}_2C & \quad \text{MeO}_2C \\
\text{O} & \quad \text{O} \\
\text{71} & \quad \text{172}
\end{align*}
\]

The aldehyde 71 (500 mg, 1.38 mmol), as a solution in THF (20 mL), was alkylated using an excess of Lombardo's reagent at room temperature, in a manner similar to that for the conversion of 71 to 163. Work up and chromatography (25% ethyl acetate in pentane) afforded the olefin 172 (R_f = 0.65) as a colourless, mobile oil (302 mg, 61%).

\[\text{1H NMR (CDCl}_3, 300 MHz) \delta 6.69 (m, 1H, H8), 6.57 (m, 1H, H7), 6.56 (s(br), 1H, H5), 6.07 (ddd, 3J_{11,12trans} = 17.3 Hz, 3J_{11,12cis} = 10.8 Hz, 1H, 3J_{11,10} = 9.3 Hz, H11), 5.14 (dd, 1H, 2J_{12cis,12trans} = 1.4 Hz, 3J_{12cis,11} = 10.8 Hz, H12cis), 5.07 (dd, 1H, 2J_{12trans,12cis} = 1.4 Hz, 3J_{12trans,11} = 17.3 Hz, H12trans), 3.73 (s, 3H, 6-OMe), 3.70 (ddd, 1H, 3J_{1,9} = 11.0 Hz, 3J_{1,9'} = 2.8 Hz, 4J_{1,3a} = 2.1 Hz, H1), 3.58 (s, 3H, 9-CO_2Me), 3.44 (s, 3H, 2-CO_2Me), 3.04-2.80 (m, 2H, H4), 2.77 (dd, 1H, 2J_{9',9} = 14.4 Hz, 3J_{9',1} = 2.8 Hz, H9'), 2.52 (m, 1H, H3a), 2.30 (dq, 1H, 3J_{10,11} = 9.3 Hz, 3J_{10,Me} = 7.0 Hz, H10),\]
2.17 (dd, 1H, $2J_{9,9'} = 14.4$ Hz, $3J_{9,1} = 11.0$ Hz, H9), 1.55 (m, 1H, H3β), 1.00 (d, 3H, $3J_{\text{Me,10}} = 7.0$ Hz, 10-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) δ 173.7, 172.5 (2 x -CO$_2$Me), 158.2 (C6), 139.5 (C11), 136.1 (C4a), 131.0 (C8a), 129.8 (C8), 115.4 (C12), 113.2 (C5)*, 111.4 (C7)*, 54.8 (6-OMe), 52.0 (C2), 51.3, 51.1 (2 x -CO$_2$Me), 44.2 (C10), 39.4 (C1), 36.4 (C9), 25.6 (C4)†, 24.7 (C3)†, 16.8 (10-Me).

IR (CHCl$_3$, cm$^{-1}$) 2950(s) (C-H str), 2840 (C-H str), 1725(s) (C=O str), 1610(s) (Ar C=C str), 1500(s) (Ar C=C str), 1270(br,s) (C=O str), 1160 (C-O str), 1040 (C-O str), 920 (C-H oop bend), 845 (C-H oop bend).

MS, m/z (relative intensity, %) 367 (M$^+$+1, 1.3), 346 (M$^+$, 5.9), 291 (7), 287 (8), 286 (21), 260 (17), 259 (100), 231 (17), 219 (17), 213 (24), 175 (22), 171 (27), 159 (21), 158 (17), 115 (26).

HRMS: Calcd for C$_{20}$H$_{26}$O$_5$: 346.1780. Found: 346.1779.

**Formation of 172 Using a Methylene Wittig Reagent.**

To a suspension of [Ph$_3$P+CH$_2$] I $^-$ (116.2 mg, 0.368 mmol) in dry THF (10 mL) under nitrogen was added NaN(TMS)$_2$ (0.34 mL, 0.34 mmol) as a 1.0M solution in THF, and the resulting bright yellow solution was stirred at room temperature for a further 15 min. The reaction mixture was cooled to -78°C and a solution of the aldehyde 71 (100 mg, 0.287 mmol) in dry THF (5 mL) was added dropwise and the cooling bath was removed. After further 30 min, the solution was quenched with water and extracted ether, washed with water and brine and dried over MgSO$_4$. Removal of the solvent in vacuo afforded a 2:1 mixture of the olefin 172 and the cyclopentanone 173 (vide infra) which was chromatographed to give the pure olefin (38 mg, 40%).
The ester 172 (300 mg, 0.87 mmol) in EtOH (10 mL) was hydrolysed using aqueous NaOH (5M, 3 mL) at room temperature, in a manner similar to that for the conversion of 163 to 171. Work up afforded the acid 177 (290 mg, 100% recovery), which crystallised from ethyl acetate as colourless prisms, mp 159°C.

\[
\begin{align*}
& {^1}H\text{ NMR (CDCl}_3, 300 MHz) \delta 7.05 (m, 1H, H8), 6.59 (m, 1H, H7), 6.57 (s(br), 1H, H5), 6.07 (ddd, 1H, 3J_{11,12}^{\text{trans}} = 17.2 Hz, 3J_{11,12}^{\text{cis}} = 10.8 Hz, 3J_{11,10} = 9.3 Hz, H11), 5.12 (m, 1H, H12^{\text{trans}}), 5.10 (m, 1H, H12^{\text{cis}}), 3.74 (s, 3H, 6-OMe), 3.70 (ddd, 1H, 4J_{1,9} = 11.2 Hz, 4J_{1,3\alpha} = 1.5 Hz, H1), 3.45 (s, 3H, -CO_2Me), 3.05-2.80 (m, 2H, H4), 2.84 (dd, 1H, 2J_{9',9} = 15.2 Hz, 3J_{9',1} = 2.2 Hz, H9'), 2.54 (m, 1H, H3\alpha), 2.32 (dq, 1H, 3J_{10,11} = 9.3 Hz, 3J_{10,Me} = 7.0 Hz, H10), 2.21 (dd, 1H, 2J_{9,9'} = 15.2 Hz, 3J_{9,1} = 11.2 Hz, H9), 1.55 (m, 1H, H3\beta), 1.01 (d, 3H, 3J_{Me,10} = 7.0 Hz, 10-Me).
\end{align*}
\]

\[
\begin{align*}
& {^{13}}C\text{ NMR (CDCl}_3, 300 MHz) \delta 178.6 (-CO_2H), 173.9 (-CO_2Me), 158.3 (C6), 139.5 (C11), 136.2 (C4a), 131.1 (C8a), 130.0 (C8), 115.6 (C12), 113.4 (C5)*, 111.7 (C7)*, 55.0 (6-OMe), 52.1 (C2), 51.3 (-CO_2Me), 44.5 (C10), 39.1 (C1), 36.5 (C9), 25.7 (C4)†, 24.9 (C3)†, 16.9 (10-Me).
\end{align*}
\]

IR (CHCl_3, cm\(^{-1}\)) 3400-2500(br) (O-H str), 2950(s) (C-H str), 2840 (C-H str), 1740(s) (C=O str, ester & acid), 1610(s) (Ar C=C str), 1500(s) (Ar C=C str), 1270 (C-O str), 1040(s) (C-O str), 920(s) (C-H oop bend), 845 (C-H oop bend).
MS, \( m/z \) (relative intensity, \%) 332 (M\(^+\), 10), 286 (5), 277 (5), 273 (10), 272 (22), 259 (22), 246 (10), 245 (60), 231 (13), 219 (17), 217 (20), 213 (17), 192 (32), 171 (22), 159 (22), 158 (18), 115 (26).

**Methyl \([12R-(\alpha,\beta)]\)-2-(But-1-en-3-yl)-1-(1-diazo-2-oxoprop-3-yl)-1,2,3,4-tetrahydro-6-methoxynaphthalene-2-carboxylate 178.**

The acid 177 (240 mg, 0.722 mmol) was converted to the diazoketone 178 upon treatment with (COCl)\(_2\) (630 \( \mu \)L, 7.22 mmol) and a catalytic amount (3-4 drops) of DMF in CH\(_2\)Cl\(_2\) (6 mL) at 0\( ^\circ \)C, followed by ethereal diazomethane at -20\( ^\circ \)C, in a manner similar to that for the conversion of 171 to 164. Work up and chromatography (25% ethyl acetate in pentane) afforded 178 (R\(_f\) = 0.45) as a pale yellow oil (245 mg, 95%).

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \( \delta \) 6.88 (m, 1H, H8), 6.53 (m, 1H, H7), 6.51 (s(br), 1H, H5), 6.06 (ddd, 1H, \( J_{13,14}^{trans} = 17.1 \text{ Hz}, J_{13,14}^{cis} = 10.3 \text{ Hz}, J_{13,12} = 9.1 \text{ Hz}, H13), 5.12 (dd, 1H, \( J_{14}^{cis} = 1.4 \text{ Hz}, J_{14}^{cis} = 1.4 \text{ Hz}, J_{11} = 13.6 \text{ Hz}, H14^{cis}), 5.04 (dd, 1H, \( J_{14}^{trans} = 1.4 \text{ Hz}, J_{14}^{trans} = 17.1 \text{ Hz}, H14^{trans}), 5.02 (s(br), 1H, H11), 3.68 (s, 3H, 6-OMe), 3.66 (ddd, 1H, \( J_{1,9} = 9.0 \text{ Hz}, J_{1,9} = 2.4 \text{ Hz}, J_{1,3} = 1.5 \text{ Hz}, H1), 3.39 (s, 3H, -CO\(_2\)Me), 3.05-2.75 (m, 2H, H4), 2.70 (dd, 1H, \( J_{9,9} = 13.6 \text{ Hz}, J_{9,1} = 2.4 \text{ Hz}, H9)), 2.54 (m, 1H, H3\( \alpha \)), 2.32 (dq, 1H, \( J_{12,13} = 9.1 \text{ Hz}, J_{12,Me} = 6.8 \text{ Hz}, H12), 2.10 (dd(br), 1H, \( J_{9,9} = 13.6 \text{ Hz}, J_{9,1} = 9.0 \text{ Hz}, H9), 1.51 (m, 1H, H3\( \beta \)), 0.96 (d, 3H, \( J_{Me,12} = 6.8 \text{ Hz}, 12-Me)).

\(^{13}\)C NMR (CDCl\(_3\), 300 MHz) \( \delta \) 194.3 (C10), 173.8 (-CO\(_2\)Me), 158.0 (C6), 139.6 (C13), 135.9 (C4\( \alpha \)), 130.7 (C8\( \alpha \)), 130.1 (C8), 115.5 (C14), 113.3 (C5\( *)\), 111.2 (C7\( *)\), 54.8
(6-OMe), 52.9 (C2), 51.1 (-CO2Me), 44.2 (C12), 42.8 (C1), 39.6 (C9), 25.5 (C4)\textsuperscript{t}, 24.6 (C3)\textsuperscript{t}, 16.7 (12-Me).

IR (CHCl₃, cm\textsuperscript{-1}) 2950(s) (C-H str), 2100(s) (C=N=N asym str), 1720(s) (C=O str, ester), 1635(s) (C=O str, ketone), 1610(s) (Ar C=C str), 1500(s) (Ar C=C str), 1365(s) (C=N=N sym str), 1270 (C-O str), 1040 (C-O str), 920 (C-H oop bend), 845 (C-H oop bend).

MS, m/z (relative intensity, %) 356 (M\textsuperscript{+}, <1), 328 (1), 273 (12), 271 (5), 241 (8), 219 (20), 213 (14), 188 (42), 159 (17), 115 (13).

Methyl [10R-(2α,3α,9α)]-2-(But-1-en-3-yl)-2,2a,3,4,5,9a-hexahydro-7-methoxy-1-oxo-1H-benz[cd]azulene-3-carboxylate 180.

The diazoketone 178 (50 mg, 0.140mmol) in CH₂Cl₂ (1 mL) was added to rhodium mandelate (ca. 2 mol %) in boiling CH₂Cl₂ (1 mL) under nitrogen, in a manner similar to that for the conversion of 164 to 165. After 10 min, an aliquot was removed, filtered through a plug of cotton wool and concentrated in vacuo to afford a ca. 7:1 mixture of the cycloheptatriene (R\textsubscript{f} = 0.45; 20% ethyl acetate in pentane) and the cyclopropane (R\textsubscript{f} = 0.3) as a pale green oil. The cycloheptatriene 180 was analysed without further purification.

\textsuperscript{1}H NMR (CDCl₃, 300 MHz) \textit{δ} 5.99 (ddd, 1H, 3\textit{J}_{8,9} = 10.1 Hz, 4\textit{J}_{8,6} = 2.0 Hz, 4\textit{J}_{8,9a} = 1.8 Hz, H8), 5.82 (m, 1H, H11), 5.54 (s(br), 1H, H6), 5.49 (dd, 1H, 3\textit{J}_{9,8} = 10.1 Hz, 3\textit{J}_{9,9a} = 4.4 Hz, H9), 4.95-5.02 (m, 2H, H12), 3.70 (s, 3H, 7-OMe), 3.63 (s, 3H, -CO₂Me), 3.36-3.27 (m, 1H, H2a), 3.26-3.14 (ddd, 2\textit{J}_{2β,2α} = 16.9 Hz, 3\textit{J}_{2β,2α} = 12.4 Hz, 4\textit{J}_{2β,9a} = 1.8 Hz, H2β), 3.02-2.97 (m, 1H, H9a), 2.77 (dq, 1H, 3\textit{J}_{10,11} = 8.6 Hz, 3\textit{J}_{10,Me
-165-

= 7.0 Hz, H10), 2.60 (dd(br), 1H, 2J_{2\alpha,2\beta} = 16.9 Hz, 3J_{2\alpha,2a} = 7.3 Hz, H2\alpha), 2.43-2.27 (m, 3H, H4, H5), 1.85 (m, 1H, H4'), 1.18 (d, 3H, 3J_{Me,10} = 7.0 Hz, 10-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) δ 215.9 (Cl), 176.1 (-CO$_2$Me), 158.8 (C7), 142.3 (C11), 126.4 (C5a)*, 125.9 (C9b)*, 125.1 (C9)†, 123.8 (C8)†, 115.5 (C12), 105.7 (C6), 54.6 (7-OMe), 51.6 (-CO$_2$Me), 50.1 (C9a), 48.2 (C3), 43.2 (C10), 42.5 (C2), 38.4 (C2a), 29.5 (C5)‡, 26.8 (C4)‡, 18.1 (10-Me).

IR (CHCl$_3$, cm$^{-1}$) 2950 (C-H str), 2840 (C-H str), 1740 (s) (C=O str, ester), 1720 (s) (C=O str, ketone), 1620 (s) (C=C str), 1550 (C=C str), 1170 (s) (C-O str), 920 (C-H oop bend), 910 (C-H oop bend), 830 (C-H oop bend).

MS, m/z (relative intensity, %) 328 (M+, 8.4), 287 (16), 273 (9), 272 (10), 271 (44), 241 (25), 213 (16), 188 (18), 185 (11), 173 (13), 160 (19), 159 (23), 141 (15), 128 (16), 115 (25), 85 (63), 83 (100).

HRMS: Calcd for C$_{20}$H$_{24}$O$_4$: 328.1675. Found: 328.1672.

Methyl [10R-(2\alpha,3\alpha)-2-(But-1-en-3-yl)-2,2a,3,4,5,8-hexahydro-7-methoxy-1-oxo-1H-benz[cd]azulene-3-carboxylate 182.

The remaining reaction mixture was treated with DBU (1-2 drops) in a manner similar to that for the conversion of 165 to 183. Work up and chromatography gave the enone 182 (R$_f$ = 0.40) as a pale yellow oil (34 mg, 73%).
1H NMR (CDCl₃, 300 MHz) δ 6.02 (dd(br), 1H, 3J₉,₈ = 8.6 Hz, 4J₉,₈’ = 5.7 Hz, H9), 5.79 (ddd, 1H, 3J₁₁,₁₂trans = 17.1 Hz, 3J₁₁,₁₂cis = 10.3 Hz, 3J₁₁,₁₀ = 8.6 Hz, H11), 5.25 (s(br), 1H, H6), 4.99-4.89 (m, 2H, H12), 3.72 (s, 3H, 7-OMe), 3.60 (s, 3H, -CO₂Me), 3.45 (m, 1H, H2a), 3.18 (ddd, 1H, 3J₁₈,₁₂ = 13.6 Hz, 3J₈,₉ = 8.6 Hz, 4J₈,₆ = 2.2 Hz, H8), 2.90 (dd, 1H, 2J₂,₂’ = 18.9 Hz, 3J₂,₂a = 9.0 Hz, H2), 2.70 (dd(br), 1H, 2J₂,₂’ = 18.9 Hz, 3J₂,₂a = 8.6 Hz, H2’), 2.66 (dq, 1H, 3J₁₀,₁₁ = 8.6 Hz, 3J₁₀,Me = 7.0 Hz, H10), 2.57-2.49 (m, 2H, H5), 2.24 (dd(br), 2J₈,’₉ = 13.6 Hz, 3J₈,’₉ = 5.7 Hz, H8’), 2.19 (m, 1H, H4), 1.97 (m, 1H, H4’), 1.11 (d, 3H, 3JMe,₁₀ = 7.0 Hz, 10-Me).

IR (CHCl₃, cm⁻¹) 2950 (C-H str), 2840 (C-H str), 1720(s) (C=O str, ester), 1630 (C=O str, enone), 1550 (C=C str), 1260 (C-O str), 1170(s) (C-O str), 1010 (C-O str), 920 (C-H oop bend), 840 (C-H oop bend).

MS, m/z (relative intensity, %) 329 (M⁺+1, 9.2), 328 (M⁺, 40.5), 287 (11), 274 (16), 273 (88), 272 (16), 271 (18), 259 (20), 241 (24), 213 (24), 213 (24), 188 (68), 160 (55), 159 (22), 128 (28), 115 (38).


Methyl (1α₂,2α₂,2α₂,8bα,10αα)-1,1α₂,2,3,4,8b,9,10α-Octahydro-6-methoxy-2-methyl-10-oxocyclopropa[4,5]cyclohepta[1,2-a]naphthalene-2α-carboxylate 181.

The cyclopropane 181 eluted as the second component (6 mg, 13%), and was characterised by nmr.

1H NMR (CDCl₃, 300 MHz) δ 7.06 (d, 1H, 3J₈,₇ = 8.5 Hz, H8), 6.70 (dd, 1H, 3J₇,₈ = 8.5 Hz, 4J₇,₅ = 1.7 Hz, H7), 6.56 (dd(br), 4J₅,₇ = 1.7 Hz, H5), 4.40 (ddd, 1H, 3J₈b,₉b = 13.0 Hz, 3J₈b,₉α = 3.9 Hz, 4J₈b,₃α = 1.5 Hz, H8b), 3.75 (s, 3H, 6-OMe), 3.58 (s, 3H, -CO₂Me), 3.04 (ddd, 1H, 2J₄α,₄β = 18.2 Hz, 3J₄α,₃β = 11.5 Hz, 3J₄α,₃α = 7.5 Hz, H₄α),
2.78 (ddd, 1H, $2J_{4\beta,4\alpha} = 18.2$ Hz, $3J_{4\beta,3\beta} = 7.4$ Hz, $3J_{4\beta,3\alpha} = 2.0$ Hz, H4$\beta$), 2.68 (dd, 1H, $2J_{9\alpha,9\beta} = 18.9$ Hz, $3J_{9\alpha,8b} = 3.9$ Hz, H9$\alpha$), 2.49 (ddd, 1H, $2J_{9\beta,9\alpha} = 18.9$ Hz, $3J_{9\beta,8b} = 13.0$ Hz, H9$\beta$), 2.34 (ddd, 1H, $2J_{3\alpha,3\beta} = 14.0$ Hz, $3J_{3\alpha,4\alpha} = 7.5$ Hz, $3J_{3\alpha,4\beta} = 2.0$ Hz, $4J_{3\alpha,8b} = 1.5$ Hz, H3$\alpha$), 2.12 (ddd, 1H, $2J_{10a,1a} = 8.6$ Hz, $3J_{10a,1} = 8.2$ Hz, $3J_{10a,1'} = 5.3$ Hz, H10a), 1.45 (ddd, 1H, $2J_{3\beta,3\alpha} = 14.0$ Hz, $3J_{3\beta,4\alpha} = 11.5$ Hz, $3J_{3\beta,4\beta} = 7.4$ Hz, H3$\beta$), 1.34 (ddd, 1H, $2J_{1\alpha,2} = 11.4$ Hz, $3J_{1\alpha,10a} = 8.6$ Hz, $3J_{1\alpha,1} = 8.0$ Hz, $3J_{1\alpha,1'} = 5.3$ Hz, H1a), 1.04 (d, 3H, $3J_{Me,2} = 6.8$ Hz, 2-Me), 0.95 (ddd, 1H, $2J_{1,1'} = 5.3$ Hz, $3J_{1,10a} = 8.2$ Hz, $3J_{1,1a} = 8.0$ Hz, H1), 0.67 (dq, 1H, $3J_{2,Me} = 6.8$ Hz, $3J_{2,1a} = 11.4$ Hz, H2), 0.49 (q, 1H, $2J_{1,1'} = 5.3$ Hz, $3J_{1,1a} = 5.3$ Hz, $3J_{1,10a} = 5.3$ Hz, H1').

$^{13}$C NMR (CDCl$_3$, 300 MHz) $\delta$ 209.6 (C10), 174.2 (-CO$_2$Me), 158.1 (C6), 136.3 (C4a), 130.4 (C8a), 130.2 (C8), 113.0 (C7)*, 112.9 (C5)*, 55.1 (6-OMe), 52.0 (C2a), 51.4 (-CO$_2$Me), 49.9 (C9), 43.5 (C2), 40.3 (C8b), 29.7 (C4)$^\dagger$, 25.6 (C10a), 24.9 (C3)$^\dagger$, 16.1 (C1a), 16.0 (2-Me), 8.9 (C1).

4.3 Aromatic Methyl Series - Aldehyde Homologation and Rhodium Cyclisation

Methyl [10R-(1α,2α)]-1,2,3,4-Tetrahydro-6-methoxy-2-(1-methoxybut-1-en-3-yl)-2-(methoxycarbonyl)-8-methylnaphthalene-1-acetate 158/159.

NaN(TMS)$_2$ (1.0$M$ in hexanes, 15.5 mL, 15.5 mmol) was added dropwise to a stirred suspension of exhaustively dried [Ph$_3$PCH$_2$OCH$_3$]+Cl$^-$ (5.79 g, 16.9 mmol) in dry THF (80 mL) at room temperature under nitrogen. After 15 min, the deep red solution was
cooled to -78°C and a solution of the aldehyde 71 (5.10 g, 14.1 mmol) in dry THF (15 mL) was added dropwise over ca. 5 min. The cooling bath was removed and the solution left to stir for a further 2.5 h.

The reaction mixture was quenched with water and extracted with ether. The ether phases were washed sequentially with water and brine, dried over MgSO₄ and concentrated in vacuo to afford a pale yellow oil. Flash chromatography gave ca. 6:3:1 mixture of the (E)-methyl enol ether 158, the (Z)-isomer 159 and the cyclopentanone 184 as a colourless oil, which was used directly without further purification. The (E,Z)-isomers from a portion of the mixture were separated by repeated flash chromatography (20% ethyl acetate in pentane) to provide sufficient material for analysis. The (Z)-isomer (Rf = 0.58) was the first eluting component and was crystallised from ethyl acetate/pentane to give colourless prisms, mp 87-89°C.

$^1$H NMR (CDCl₃, 300 MHz), δ 6.44, 6.42 (2 x s(br), 2 x 1H, H5, H7), 6.01 (d, 1H, $^3$J₁₂,₁₁ = 6.4 Hz, H12), 4.63 (dd, 1H, $^3$J₁₁,₁₀ = 10.6 Hz, $^3$J₁₁,₁₂ = 6.4 Hz, H11), 3.93 (ddd, 1H, $^3$J₁₁, = 10.7 Hz, $^3$J₁,₁₂ = 3.3 Hz, $^4$J₁,₁₃ₐ = 1.5 Hz, H1), 3.71 (s, 3H, 6-OMe), 3.60 (s, 3H, 9-CO₂Me), 3.50 (s, 3H, 2-CO₂Me), 3.35 (s, 3H, 12-OMe), 2.94-2.87 (m, 2H, H4), -2.86 (m (partially obscured), 1H, H10), 2.80 (dd, 1H, $^2$J₉,₉ = 13.5 Hz, $^3$J₉,₁ = 3.3 Hz, H9'), 2.64 (m, 1H, H3α), 2.24 (s(br), 3H, 8-Me), 2.17 (dd, 1H, $^2$J₉,₉ = 13.5 Hz, $^3$J₉,₁ = 10.7 Hz, H9), 1.58 (m, 1H, H3β), 0.91 (d, 3H, $^3$J₉ₐ,₁₀ = 7.0 Hz, 10-Me).

$^{13}$C NMR (CDCl₃, 300 MHz), δ 174.7, 173.8 (2 x -CO₂Me), 157.7 (C6), 146.3 (C12), 137.6 (C₄α)†, 137.2 (C8)†, 130.3 (C₈α), 113.5 (C₅)†, 111.0 (C7)†, 108.0 (C11), 59.4 (12-OMe), 54.7 (6-OMe), 53.9 (C2), 51.2, 50.9 (2 x -CO₂Me), 36.6 (C₁₀), 35.0 (C1), 34.9 (C9), 25.8 (C₄)‡, 25.0 (C3)‡, 18.8 (8-Me), 17.0 (10-Me).

MS, m/z (relative intensity, %) 390 (M⁺, 0.4), 245 (0.3), 231 (0.7), 199 (0.3), 185 (0.8), 171 (0.4), 169 (0.4), 158 (0.4), 149 (0.4), 129 (0.6), 115 (0.7), 86 (5), 85 (100).
HRMS: Calcd for C_{22}H_{30}O_{6}: 390.2042. Found: 390.2041.

ANALYSIS: Calcd for C_{22}H_{30}O_{6}: C, 67.68; H, 7.74.
Found: C, 67.48; H, 7.98.

The second eluting component was the (E)-isomer (R_f = 0.57), which was obtained as a colourless oil:

{H NMR (CDCl_3, 300 MHz), δ 6.46, 6.41 (2 x dd, 2 x 1H, 4J = 2.7 Hz, H5, H7), 6.35 (d, 1H, 3J_{12,11} = 12.8 Hz, H12), 4.99 (dd, 1H, 3J_{11,12} = 12.8 Hz, 3J_{11,10} = 9.9 Hz, H11), 3.96 (ddd, 1H, 3J_{1,9} = 9.3 Hz, 3J_{1,9'} = 4.0 Hz, 4J_{1,3α} = 1.6 Hz, H1), 3.71 (s, 3H, 6-OMe), 3.60 (s, 3H, 9-CO2Me), 3.54 (s, 3H, 2-CO2Me), 3.36 (s, 3H, 12-OMe), 2.94-2.86 (m, 2H, H4), 2.63 (dd, 1H, 2J_{9',9} = 13.9 Hz, 3J_{9',1} = 4.0 Hz, H9'), 2.62 (m, 1H, H3α), 2.25 (dq, 1H, 3J_{10,11} = 9.9 Hz, 3J_{10,Me} = 6.9 Hz, H10), 2.24 (s(br), 3H, 8-Me), 2.16 (dd, 1H, 2J_{9,9'} = 13.9 Hz, 3J_{9,1} = 9.3 Hz, H9), 1.58 (m, 1H, H3β), 0.98 (d, 3H, 3J_{Me,10} = 6.9 Hz, 10-Me).

{C NMR (CDCl_3, 300 MHz), δ 174.6, 173.4 (2 x -CO2Me), 157.9 (C6), 147.9 (C12), 137.4 (C4α)*, 137.2 (C8)*, 130.7 (C8α), 113.7 (C5)†, 111.1 (C7)†, 104.6 (C11), 56.0 (12-OMe), 54.8 (6-OMe), 54.0 (C2), 51.5, 51.0 (2 x -CO2Me), 39.4 (C10), 35.9 (C1), 34.9 (C9), 25.9 (C4)†, 25.0 (C3)‡, 18.9 (8-Me), 18.4 (10-Me).

MS, m/z (relative intensity, %) 390 (M+, 0.2), 231 (0.4), 185 (1), 173 (1), 149 (1), 141 (1), 129 (1), 115 (1), 86 (5), 85 (100).

HRMS: Calcd for C_{22}H_{30}O_{6}: 390.2042. Found: 390.2041.
Methyl [10R-(1α,2α)]-1,2,3,4-Tetrahydro-6-methoxy-2-(1,1-dimethoxybut-3-yl)-2-(methoxycarbonyl)-8-methylnaphthalene-1-acetate 160.

A catalytic amount of PTSA (150 mg) was added to a solution of the mixture of methyl enol ethers and the cyclopentanone (ca. 4.8 g) in methanol (70 mL). (MeO)3CH (1 mL) was added and the resulting solution stirred at reflux for 2 h. The reaction mixture was then diluted with ether, washed with dilute NaHCO₃ solution, water and brine, and dried over MgSO₄. Removal of solvent in vacuo and flash chromatography (20% ethyl acetate in pentane) afforded the acetal 160 (Rᵣ = 0.35) as the second eluting component, which crystallised from pentane/ethyl acetate to give a white semicrystalline oil (4.50 g, 76% overall yield for two steps).

1H NMR (CDCl₃, 300 MHz), δ 6.45, 6.41 (2 x d, 2 x 1H, 4J₅,₇ = 4J₇,₅ = 2.2 Hz, H₅, H₇), 4.46 (dd, 1H, 3J₁₂,₁₁ = 8.1 Hz, 3J₁₂,₁₁’ = 3.3 Hz, H₁₂), 4.06 (ddd, 1H, 3J₁,₁₉ = 9.7 Hz, 3J₁,₉’ = 4.0 Hz, 4J₁,₉ = 11.1 Hz, H₁), 3.71 (s, 3H, 6-OMe), 3.56 (s, 3H, 9-C₆HMe), 3.37, 3.36 (2 x s, 6H, 12-OMe), 3.33 (s, 3H, 2-C₆HMe), 2.84 (m, 2H, H₄), 2.66 (dd, 1H, 2J₉,₉’ = 14.1 Hz, 3J₉,₁ = 4.0 Hz, H₉’), 2.68-2.59 (m, 1H, H₃a), 2.35 (dd(br), 1H, 2J₁₁,₁₁ = 14.0 Hz, 3J₁₁,₁₂ = 8.1 Hz, 3J₁₁,₁₁ = 2.3 Hz, H₁₁), 2.24 (s(br), 3H, 8-Me), 2.20 (dd, 1H, 2J₉,₉’ = 14.1 Hz, 3J₉,₁ = 9.7 Hz, H₉), 1.77 (ddq, 1H, 3J₁₀,₁₁’ = 11.4 Hz, 3J₁₀,Me = 6.8 Hz, 3J₁₀,₁₁ = 2.3 Hz, H₁₀), 1.54 (m, 1H, H₃β), 1.39 (ddd, 1H, 2J₁₁’,₁₁ = 14.0 Hz, 3J₁₁’,₁₀ = 11.4 Hz, 3J₁₁’,₁₂ = 3.3 Hz, H₁₁’), 0.93 (d(br), 3H, 3J₆₆,₁₀ = 6.8 Hz, 10-Me).

13C NMR (CDCl₃, 300 MHz), δ 174.2, 173.1 (2 x -CO₂Me), 157.7 (C₆), 137.2, 137.1 (C₄α, C₈), 130.0 (C₈α), 113.7, 110.9 (C₇, C₅), 103.7 (C₁₂), 54.8 (6-OMe), 53.9 (C₂),
53.3, 52.8 (12-(OMe)₂), 51.6, 51.1 (2 x -CO₂Me), 35.3 (C9), 35.1, 35.0 (C10, C1), 33.7 (C11), 26.0, 25.4 (C4, C3), 19.1 (8-Me), 15.2 (10-Me).

IR (CHCl₃, cm⁻¹) 2950 (C-H str), 2840 (C-H str), 1725(s) (C=O str, esters), 1605(s) (Ar C=C str), 1480 (Ar C=C str), 1300 (C-O str), 1260 (C-O str), 1150 (C-O str), 1120 (C-O str), 1050 (C-O str), 860 (C-H oop bend).

MS, m/z (relative intensity, %) 422 (M⁺, 0.6), 273 (0.6), 257 (0.8), 233 (0.9), 232 (0.8), 231 (1), 225 (0.9), 201 (2), 199 (2), 115 (5), 85 (100).

Methyl (3α,9βα)-1,4,5,9b-Tetrahydro-7-methoxy-3,9-dimethyl-2-oxo-2H-benz[e]indene-3a(3H)-carboxylate 184.

The cyclopentanone 184 (Rf = 0.48; 20% ethyl acetate in pentane), formed in the previous experiment, was the first eluting component and was characterised at this stage.

¹H NMR (CDCl₃, 300 MHz), δ 6.60, 6.47 (2 x d(br), 2 x 1H, ⁴J₆,₈ = ⁴J₈,₆ = 2.6 Hz, H6, H8), 3.94 (dd(br), 1H, ³J₉b,₁' = 11.0 Hz, ³J₉b,₁ = 9.7 Hz, H9b), 3.75 (s, 3H, 7-OMe), 3.69 (s, 3H, -CO₂Me), 3.00 (ddd, 1H, ¹J₁,₁' = 19.4 Hz, ³J₁,₉b = 9.7 Hz, ⁴J₁,₃ = 1.2 Hz, H1'), 2.96-2.76 (m, 2H, H5), 2.71 (dq, 1H, ³J₃,Me = 7.1 Hz, ⁴J₃,₁ = 1.2 Hz, H3), 2.30 (s(br), 3H, 9-Me), 2.27 (m, 1H, H4α), 1.97 (dd, 1H, ²J₁',₁ = 19.4 Hz, ³J₁',₉b = 11.0 Hz, H1'), 1.30 (m, 1H, H4β), 1.13 (d, 3H, ³J₃Me,₃ = 7.1 Hz, 3-Me).

¹³C NMR (CDCl₃, 300 MHz), δ 215.8 (C2), 174.9 (-CO₂Me), 157.7 (C7), 137.9 (C5a)*, 135.6 (C9)*, 127.7 (C9a), 114.6 (C6), 110.9 (C8), 55.0 (7-OMe), 54.7 (C3), 52.3 (-CO₂Me), 52.1 (C3a), 42.6 (C1), 36.8 (C9b), 26.8 (C5), 21.2 (C4), 19.5 (9-Me), 7.6 (3-Me).
IR (CHCl₃, cm⁻¹) 2950 (C-H str), 2840 (C-H str), 1735(s,br) (C=O str, ester & ketone), 1610 (Ar C=C str), 1485 (Ar C=C str), 1260 (C-O str), 1150 (C-O str), 1045 (C-O str), 855 (C-H oop bend).

MS, m/z (relative intensity, %) 362 (M⁺, 2.5), 290 (5), 279 (4), 145 (7), 201 (5), 167 (8), 149 (51), 113 (20).


[10R-(1α,2α)]-1,2,3,4-Tetrahydro-6-methoxy-2-(1,1-dimethoxybut-3-yl)-2-(methoxycarbonyl)-8-methylnaphthalene-1-acetic Acid 185.

Aqueous 2M NaOH (30 mL) was added dropwise to a stirred solution of the ester 160 (4.5 g, 10.7 mmol) in ethanol (100 mL) at room temperature. After 3 h, the reaction mixture was concentrated in vacuo and the residue diluted with ether, cooled to 5°C (ice bath), and carefully acidified to pH 2 with 1M HCl. The phases were separated and the aqueous phase was thoroughly extracted twice more with ether, which was then washed with water and brine, and dried over MgSO₄. Evaporation of the solvent gave the clean acid 185 (4.25 g, 98% recovery) as a white solid, which was used without further purification.

¹H NMR (CDCl₃, 300 MHz), δ 6.47, 6.41 (2 x d, 2 x 1H, ⁴J₅,₇ = ⁴J₇,₅ = 2.7 Hz, H₅, H₇), 4.45 (dd, 1H, ³J₁₂,₁₁ = 8.3 Hz, ³J₁₂,₁₁' = 3.1 Hz, H₁₂), 4.08 (ddd, 1H, ³J₁,₉ = 9.3 Hz, ³J₁,₉' = 3.8 Hz, ⁴J₁,₃α = 1.4 Hz, H₁), 3.72 (s, 3H, 6-OMe), 3.36 (s, 3H, 12-OMe)*, 3.34 (s, 3H, 12-OMe)*, 3.33 (s, 3H, -CO₂Me)*, 3.33 (s, 3H, -CO₂Me)*, 2.92-2.84 (m, 2H, H₄), 2.70-2.59 (m, 1H, H₃α), 2.68 (dd, 1H, ²J₉,₉' = 14.4 Hz, ³J₉,₁ = 3.8 Hz, H₉), 2.34 (ddd, 1H, ²J₁₁,₁₁' =
11.5 Hz, $^3J_{11,12} = 8.3$ Hz, $^3J_{11,10} = 1.9$ Hz, H11), 2.26 (s(br), 3H, 8-Me), 2.20 (dd, 1H, $^2J_{9',9} = 14.4$ Hz, $^3J_{9',9} = 9.3$ Hz, H9'), 1.77 (ddq, 1H, $^3J_{10,11'} = 11.5$ Hz, $^3J_{10,Me} = 6.7$ Hz, $^3J_{10,11} = 1.9$ Hz, H10), 1.53 (m, 1H, H3β), 1.37 (ddd, 1H, $^2J_{11',11} = 11.5$ Hz, $^3J_{11',10} = 11.5$ Hz, $^3J_{11',12} = 3.8$ Hz, H11'), 0.94 (d(br), 3H, $^3J_{Me,10} = 6.7$ Hz, 10-Me).

$^1$C NMR (CDCl$_3$, 300 MHz), δ 177.9 (-CO$_2$H), 174.0 (-CO$_2$Me), 157.6 (C6), 137.1 (C4a, C8), 130.0 (C8a), 113.8, 110.9 (C7, C5), 103.7 (C12), 54.8 (6-OMe), 53.9 (C2), 53.3, 52.6 (12-(OMe)$_2$), 51.0 (-CO$_2$Me), 35.3 (C9), 35.1, 34.9 (C10, C1), 34.0 (C11), 26.0, 25.4 (C4, C3), 19.2 (8-Me), 15.3 (10-Me).

IR (CHCl$_3$, cm$^{-1}$) 2940 (C-H str), 2840 (C-H str), 1720 (s) (C=O str, acid & ester), 1605 (Ar C=C str), 1480 (Ar C=C str), 1300 (C-0 str), 1150 (s) (C-O str), 1125 (C-O str), 1055 (C=O str), 860 (C-H oop bend).

MS, m/z (relative intensity, %) 408 (M$^+$, 0.7), 344 (1), 257 (0.8), 233 (2), 232 (7), 231 (2), 199 (2), 173 (4), 115 (4), 85 (100).

[10R-(1α,2α)]-1,2,3,4-Tetrahydro-6-methoxy-2-(1,1-dimethoxybut-3-yl)-2-(methoxycarbonyl)-8-methylnaphthalene-1-acetic Acid, Anhydride with Methyl Hydrogen Carbonate 186.

Dry triethylamine (1.71 mL, 12.3 mmol) was added to a stirred solution of the acid 185 (4.10 g, 10.0 mmol) in dry CH$_2$Cl$_2$ under N$_2$. The solution was cooled to 0°C (ice bath) and methyl chloroformate (0.88 mL, 11.3 mmol) was added dropwise. After 15 min, the reaction mixture was diluted with CH$_2$Cl$_2$, washed sequentially with 0.2M HCl, water and...
brine, and dried over MgSO₄. Evaporation of the solvent gave essentially pure anhydride 186 (R_f = 0.41; 25% ethyl acetate in pentane) as a pale yellow oil (4.7 g, 100% recovery), which was used directly without further purification.

1H NMR (CDCl₃, 300 MHz), δ 6.47, 6.41 (2 x d, 2 x 1H, ^4J_5,7 = ^4J_7,5 = 2.7 Hz, H5, H7), 4.43 (dd, 1H, ^3J_{14,13} = 8.1 Hz, ^3J_{14,13'} = 3.1 Hz, H14), 4.11 (ddd, 1H, ^3J_{1,9} = 9.5 Hz, ^3J_{1,9'} = 3.7 Hz, H1, H1), 3.82 (s, 3H, 6-OMe), 3.70 (s, 3H, 11-OMe), 3.36 (s, 3H, 2-CO₂Me)*, 3.35 (s, 3H, 14-OMe)*, 3.34 (s, 3H, 14-OMe)*, 2.92-2.83 (m, 2H, H4), 2.84 (dd, 1H, ^2J_{9,9} = 15.3 Hz, ^3J_{9,1} = 3.7 Hz, H9'), 2.67 (m, 1H, H3α), 2.34 (dd, 1H, ^2J_{9,9'} = 15.3 Hz, ^3J_{9,1} = 9.5 Hz, H9), 2.30 (s, 3H, 8-Me), 2.26 (ddd, 1H, ^2J_{13,13'} = 11.2 Hz, ^3J_{13,14} = 8.1 Hz, ^3J_{13,12} = 2.2 Hz, H13), 1.75 (ddq, 1H, ^3J_{12,13'} = 11.0 Hz, ^3J_{12,Me} = 6.8 Hz, ^3J_{12,13} = 2.2 Hz, H12), 1.51 (m, 1H, H3β), 1.36 (ddd, 1H, ^2J_{13',13} = 11.2 Hz, ^3J_{13',12} = 11.0 Hz, ^3J_{13',14} = 3.1 Hz, H13'), 0.94 (d(br), 3H, ^3J_{Me,12} = 6.8 Hz, 12-Me).

^13C NMR (CDCl₃, 300 MHz), δ 173.8 (2-CO₂Me), 166.8 (C10), 157.8 (C6), 149.4 (C11) 137.3, 137.2, (C4a, C8), 129.1 (C8α), 114.0, 111.0 (C7, C5), 103.5 (C14), 55.7 (6-OMe), 54.8 (11-OMe), 53.9 (C2), 53.7, 52.6 (14-(OMe)₂), 51.1 (2-CO₂Me), 35.2 (C9), 35.1, 34.5 (C12, C1), 34.0 (C13), 25.9, 25.4 (C4, C3), 19.2 (8-Me), 15.4 (12-Me).

IR (CHCl₃, cm⁻¹) 2950 (C-H str), 2840 (C-H str), 1825(s) (C=O str, anhydride), 1765 (C=O str, anhydride), 1725(s) (C=O str, ester), 1605(s) (Ar C=C str), 1480(s) (Ar C=C str), 1300 (C-O str), 1150(s) (C-O str), 1090(s,br) (C-O str), 855 (C-H oop bend).

MS, m/z (relative intensity, %) 466 (M⁺, 0.4), 359 (0.5), 349 (0.6), 299 (0.6), 271 (0.6), 257 (1), 188 (4), 160 (3), 127 (3), 115 (8), 85 (100), 75 (51).

HRMS: Calcd for C₂₄H₃₄O₉: 466.2203. Found: 466.2198.
[12R-(1α,2α)]-Methyl 1-(1-Diazo-2-oxoprop-3-yl)-1,2,3,4-tetrahydro-6-methoxy-2-(1,1-dimethoxybut-3-yl)-8-methylnaphthalene-2-carboxylate 161.

An unscratched, 1-necked flask, charged with a freshly prepared, ethanol-free solution of CH₂N₂ in ether (ca. 10-fold excess) was cooled to 0°C under nitrogen. A solution of the crude anhydride 186 (4.7 g) in ether (15 mL) was added dropwise and the reaction mixture was stirred at 5°C for 24 h.

Excess solvent and CH₂N₂ were removed on a rotary evaporator in a well ventilated fumehood. Flash chromatography (25% ethyl acetate in pentane) of the resulting yellow oil gave pure diazoketone 161 (Rf = 0.20) as clear, pale yellow needles (3.3 g, 75% overall yield for 2 steps), mp 80°C

¹H NMR (CDCl₃, 300 MHz), δ 6.44, 6.41 (2 x d(br), 2 x 1H, 4J₅,7 = 4J₇,5 = 2.4 Hz, H₅, H₇), 4.99 (s(br), 1H, H₁₁), 4.46 (dd, 1H, 3J₁₄,₁₃ = 8.1 Hz, 3J₁₄,₁₃' = 3.0 Hz, H₁₄), 4.03 (d(br), 1H, 3J₁₉,₁ = 9.9 Hz, H₁), 3.71 (s, 3H, 6-OMe), 3.39 (s, 3H, -CO₂Me)*, 3.37 (s, 3H, 14-OMe)*, 3.32 (s, 3H, 14-OMe)*, 2.99-2.78 (m, 2H, H₄), 2.69-2.58 (m, 1H, H₃α), 2.59 (dd, 1H, 2J₉,₉' = 13.0 Hz, 3J₉,₁ = 3.1 Hz, H₉), 2.41 (dd(br), 1H, 2J₁₃,₁₃' = 13.8 Hz, 3J₁₃,₁₄ = 8.1 Hz, H₁₃), 2.20 (s, 3H, 8-Me), 2.12 (dd(vbr), 1H, 2J₉,₉' = 13.0 Hz, 3J₉,₁ = 9.9 Hz, H₉'), 1.77 (ddq, 1H, 3J₁₂,₁₃ = 11.4 Hz, 3J₁₂,Me = 6.8 Hz, 3J₁₂,₁₃ = 2.2 Hz, H₁₂), 1.50 (m, 1H, H₃β), 1.36 (ddd, 1H, 2J₁₃',₁₃ = 13.8 Hz, 3J₁₃',₁₂ = 11.4 Hz, 3J₁₃',₁₄ = 3.0 Hz, H₁₃'), 0.92 (d(br), 3H, 3J₉,₁₂ = 6.8 Hz, 12-Me).

¹³C NMR (CDCl₃, 300 MHz), δ 194.1 (C₁₀), 174.1 (-CO₂Me), 157.6 (C₆), 137.3, 137.0, (C₄α, C₈), 130.0 (C₈α), 113.6, 111.0 (C₇, C₅), 103.8 (C₁₄), 55.0 (C₁₁), 54.8
(6-OMe), 53.9 (14-OMe), 53.6 (C2), 52.8 (14-OMe), 51.1 (-CO₂Me), 41.8 (C9), 35.7 (C1), 34.9 (C12), 34.0 (C13), 25.9 (C4), 25.4 (C3), 19.3 (8-Me), 15.4 (12-Me).

IR (CHCl₃, cm⁻¹) 2950 (C-H str), 2840 (C-H str), 2100 (s) (C=N=N asym str), 1720 (s) (C=O str, ester), 1630 (s) (C=O str, ketone), 1605 (s) (Ar C=C str), 1480 (Ar C=C str), 1360 (s) (C=N=N sym str), 1300 (C-O str), 1160 (s,br) (C-O str), 1150 (s) (C-O str), 1050 (s) (C-O str), 905 (C-H oop bend), 855 (w,br) (C-H oop bend).

MS, m/z (relative intensity, %) 372 (2), 349 (8), 285 (11), 115 (16), 85 (78), 75 (100).

ANALYSIS: Calcd for C₂₃H₃₂O₆N₂: C, 63.87; H, 7.46; N, 6.48.
Found: C, 63.02; H, 7.84; N, 5.95.

Methyl [10R-(2α,3α,9α)]-2,2a,3,4,5,9a-Hexahydro-7-methoxy-3-(1,1-dimethoxy-but-3-yl)-9-methyl-1-oxo-1H-benz[c,d]azulene-3-carboxylate 162.

A solution of the diazoketone 161 (2.25 g, 5.23 mmol) in CH₂Cl₂ (15 mL) was added dropwise to a gently boiling suspension of rhodium mandelate (ca. 2 mol %) in CH₂Cl₂ (5 mL) under argon. After 5 min, an aliquot from the reaction mixture was filtered through a plug of cotton wool (to remove undissolved catalyst), and the filtrate concentrated in vacuo to afford an 8:1 mixture of the unstable cycloheptatriene 162 (Rf = 0.4; 20% ethyl acetate in pentane) and the by-product 196 (Rf = 0.3) as a green oil. This mixture was used directly for analysis without further purification.
1H NMR (CDCl₃, 300 MHz), δ 5.77 (s(br), 1H, H8), 5.56 (s(br), 1H, H6), 4.39 (dd, 1H, 3J₁₂,₁₁ = 7.9 Hz, 3J₁₂,₁₁' = 3.1 Hz, H12), 3.66 (s, 3H, 7-OMe), 3.60 (s, 3H, -CO₂Me), 3.27 (s, 3H, 12-OMe), 3.26 (m(obscured), 1H, H2a), 3.26 (s, 3H, 12-OMe), 2.82 (ddd, 1H, 2J₂β₂a = 17.8 Hz, 3J₂β₂a = 12.5 Hz, 4J₂β₉a = 1.8 Hz, H2β), 2.77 (s(br), 1H, H9a), 2.69 (ddd, 1H, 2J₂α₂β = 17.8 Hz, 3J₂α₂a = 8.4 Hz, 4J₂α₉a = 0.9 Hz, H2α), 2.20-2.14 (m, 3H, H5α, H5β, H4), 2.06 (ddq, 1H, 3J₁₀,₁₁' = 10.5 Hz, 3J₁₀,Me = 6.8 Hz, 3J₁₀,₁₁ = 1.3 Hz, H10), 1.88 (m, 1H, H₄'), 1.87 (s, 3H, 9-Me), 1.69 (dddd, 1H, 2J₁₁,₁₁' = 13.4 Hz, 3J₁₁,₁₂ = 7.9 Hz, 3J₁₁,₁₀ = 1.3 Hz, 4J₁₁,Me ~ 1.0 Hz, H11), 1.26 (ddd, 1H, 2J₁₁',₁₁ = 13.4 Hz, 3J₁₁',₁₀ = 10.5 Hz, 3J₁₁',₁₂ = 3.1 Hz, H11'), 1.11 (d(br), 3H, 3J₉,M,₁₀ = 6.8 Hz, 10-Me).

13C NMR (CDCl₃, 300 MHz), δ 216.0 (C1), 176.7 (-CO₂Me), 158.4 (C7), 133.1, 126.7, 126.1 (C9, C9b, C5a), 120.6 (C8), 104.8 (C6) 103.6 (C12), 54.6 (7-OMe), 53.6 (C9a), 53.0, 52.5 (12-(OMe)₂), 51.6 (-CO₂Me), 48.8 (C3), 42.8, 42.6 (C2a, C2), 37.0 (C11), 30.1 (C10), 28.5 (C5), 26.5 (C4), 20.4 (9-Me), 15.8 (10-Me).

IR (CHCl₃, cm⁻¹) 2950 (C-H str), 2840 (C-H str), 1740(s) (C=O str, ketone), 1720(s) (C=O str, ester), 1160 (C-O str), 1050(s) (C-O str), 930 (C-H oop bend).

MS, m/z (relative intensity, %) 404 (M⁺, <1), 372 (11), 286 (10), 285 (53), 174 (13), 173 (14), 85 (100), 75 (65).

Methyl [10R-(2α,3α)]-2,2a,3,4,5,8-Hexahydro-7-methoxy-3-(1,1-dimethoxybut-3-yl)-9-methyl-1-oxo-1H-benz[cd]azulene-3-carboxylate 201.

To the crude reaction mixture in CH₂Cl₂, at room temperature, was added DBU (3-4 drops). After 10 min, resulting pale brown solution was washed with 0.1M HCl, water and brine, and dried over MgSO₄. Removal of solvent in vacuo afforded a pale green oil which was flash chromatographed to give the acetal 201 (Rf = 0.36) as a yellow oil (1.71 g, 81% overall yield for two steps).

1H NMR (CDCl₃, 300 MHz), δ 5.13 (s(br), 1H, H₆), 4.41 (dd, 1H, 3J₁₂,₁₁ = 7.7 Hz, 3J₁₂,₁₁’ = 3.3 Hz, H₁₂), 3.68 (s, 3H, 7-OMe), 3.58 (s, 3H, -CO₂Me), 3.50 (dd(br), 1H, 3J₁₂a,₂ = 10.5 Hz, 3J₂a,₂ = 7.7 Hz, H₂a), 3.28 (s, 6H, 12-(OMe)₂), 2.90 (dd, 1H, 2J₈,₈’ = 12.5 Hz, 4J₈,₆ = 2.0 Hz, H₈), 2.70 (dd, 1H, 2J₂,₂’ = 17.4 Hz, 3J₂,₂a = 7.7 Hz, H₂’), 2.36-2.43 (m, 2H, H₅), 2.38 (s, 3H, 9-Me), 2.13 (d(br), 1H, 2J₈,₈’ = 12.5 Hz, H₈’), 2.14-2.05 (m, 1H, H₄a), 2.03 (ddq, 1H, 3J₁₀,₁₀ = 11.2 Hz, 3J₁₀,₁₀ = 11.2 Hz, H₁₀), 1.81 (m, 1H, H₄β), 1.77 (m, 1H, ₂J₁₁,₁₁’ = 14.1 Hz, 3J₁₁,₁₂ = 7.7 Hz, 3J₁₁,₁₀ = 2.0 Hz, H₁₁), 1.24 (dd, 1H, ₂J₁₁,₁₁’ = 14.1 Hz, 3J₁₁,₁₂ = 7.7 Hz, 3J₁₁,₁₀ = 2.0 Hz, H₁₁’), 1.02 (d(br), 3H, 3J₉,₁₀ = 6.8 Hz, 10-Me).

13C NMR (CDCl₃, 300 MHz), δ 205.0 (C₁), 176.2 (-CO₂Me), 146.7 (C₇), 136.3 (C₉), 133.7, 131.8, 131.0 (C₉a, C₉b, C₅a), 103.2 (C₁₂), 99.6 (C₆), 55.7 (7-OMe), 53.0, 52.6 (12-(OMe)₂), 51.5 (-CO₂Me), 49.3 (C₃), 42.8 (C₂), 41.7 (C₈), 40.8 (C₂a), 35.8 (C₁₁), 32.3 (C₁₀), 29.0 (C₅), 26.8 (C₄), 19.9 (9-Me), 15.1 (10-Me).
IR (CHCl₃, cm⁻¹) 2950 (C-H str), 2840 (C-H str), 1705(s) C=O str, ester & enone), 1620(s) (C=C str), 1560 (C=C str), 1120 (C-O str), 1045(s) (C-O str), 905 (C-H oop bend).

MS, m/z (relative intensity, %) 404 (M⁺, 0.3), 402 (0.3), 387 (0.3), 373 (2), 372 (4), 341 (2), 340 (1), 313 (2.5), 311 (1), 286 (5.6), 285 (25), 281 (3), 255 (6.6), 249 (4), 227 (3), 201 (3), 174 (7), 173 (7), 115 (8), 85 (100).


[12R-(5αα,11ββ)]-5α,6,7,11b-Tetrahydro-2,9-dimethoxy-5a-(1,1-dimethoxy-but-3-yl)-11-methylnaphth[2,1-c]oxepin-5(1H)-one 196.

The second eluting component, by-product 196 was also purified and characterised at this stage (210 mg, 10%).

¹H NMR (CDCl₃, 300 MHz), δ 6.42, 6.40 (2 x d, 2 x 1H, 4J₈,₁₀ = 4J₁₀,₈ = 2.2 Hz, H₈, H₁₀), 5.97 (s, 1H, H₃), 4.51 (dd, 1H, ³J₁₄,₁₃ = 10.3 Hz, ³J₁₄,₁₃' = 2.6 Hz, H₁₄), 3.88 (ddd, 1H, ³J₁₀b₁α = 9.0 Hz, ³J₁₀b₁β = 3.5 Hz, ⁴J₁₀b₆α = 1.5 Hz, H₁₀b), 3.72 (s, 3H, 9-OMe), 3.55, 3.52 (2 x s, 2 x 3H, 14-(OMe)₂), 3.41 (s, 3H, 2-OMe), 3.05-2.78 (m, 2H, H₇), 2.61 (ddd, ²J₁₃,₁₃' = 15.1 Hz, ³J₁₃,₁₄ = 10.3 Hz, ³J₁₃,₁₂ = 4.4 Hz, H₁₃), 2.46 (m, 1H, H₆α), 2.35 (s, 3H, 11-Me), 2.35-2.20 (m, 2H, H₁), 1.93 (ddq, ³J₁₂,Me = 7.2 Hz, ³J₁₂,₁₃ = 4.4 Hz, ³J₁₂,₁₃' = 3.4 Hz, H₁₂), 1.70 (m, 1H, H₆β), 1.26 (ddd, 1H, ²J₁₃',₁₃ = 15.1 Hz, ³J₁₃',₁₂ = 3.4 Hz, ³J₁₃',₁₄ = 2.6 Hz, H₁₃'), 0.95 (d, 3H, ³JMe,₁₂ = 7.2 Hz, 12-Me).

¹³C NMR (CDCl₃, 300 MHz), δ 175.0 (C₅), 157.6 (C₉), 140.9 (C₃), 131.6 (C₁₁α), 137.6, 137.2 (C₁₁,C₇α)*, 136.8 (C₂)*, 114.4, 110.3 (C₈, C₁₀), 108.1 (C₁₄), 59.6,
(2-OMe), 55.9 (9-OMe), 54.8 (14-OMe), 52.0 (C5a), 51.1 (14-OMe), 37.8 (C11b)\textsuperscript{1}, 36.7 (C1), 35.6 (C12)\textsuperscript{1}, 31.2 (C13), 26.3 (C7), 25.2 (C6), 19.2 (11-Me), 18.9 (12-Me).

IR (CHCl\textsubscript{3}, cm\textsuperscript{-1}) 2950 (C-H str), 2940 (C-H str), 2840 (C-H str), 1720 (s) (C=O str), 1605 (s) (Ar C=C str), 1480 (Ar C=C str), 1300 (C-O str), 1150 (s) (C-O str), 1135 (s) (C-O str), 1055 (C-O str), 860 (w,br) (C-H oop bend).

MS, m/z (relative intensity, %) 404 (M\textsuperscript{+}, 2.1), 232 (0.3), 201 (0.5), 199 (0.4), 173 (0.6), 158 (0.3), 141 (0.5), 129 (0.6), 128 (0.6), 115 (0.8), 86 (5), 85 (100).

4.4 Des-Methyl Series - Aldehyde homologation and Rhodium Cyclisation

Methyl [10R-(1α,2α)]-1,2,3,4-Tetrahydro-6-methoxy-2-(1-methoxybut-1-en-3-yl)-2-(methoxycarbonyl)naphthalene-1-acetate 187/188.

\begin{equation}
\text{MeO} \quad \text{MeO} \quad \text{CO}_2\text{Me} \\
\text{MeO}_2\text{C} \quad \text{Ph}_3\text{P} = \text{CH}_2\text{OMe} \quad \text{THF, -78°C to r.t} \quad \text{MeO} \quad \text{MeO}_2\text{C} \\
\text{104} \quad \text{Ph}_3\text{P} = \text{CH}_2\text{OMe} \quad \text{THF, -78°C to r.t} \quad \text{187 11-Z} \quad \text{188 11-E} \\
\end{equation}

The aldehyde 104 (400 mg, 1.15 mmol) was converted to an (E,Z)-mixture of methyl enol ethers with the ylide Ph\textsubscript{3}P=CHOMe, preformed from [Ph\textsubscript{3}PCH\textsubscript{2}OMe]\textsuperscript{+Cl}\textsuperscript{-} (543 mg, 1.50 mmol) and NaN(TMS)\textsubscript{2} (1.38 mL), in a manner similar to that for the conversion of 71 to 158 and 159. Work up and flash chromatography afforded a ca. 2:1: mixture of the (E)- and (Z)-enol ethers (290 mg, 67%). The purest fractions, containing only the enol ethers (R\textsubscript{f} = 0.68; 25% ethyl acetate in pentane), were chromatographed further to give the (Z)-isomer 187:
\[ ^1H \text{ NMR (CDCl}_3, 300 \text{ MHz)} \delta 6.77 (m, 1H, H8), 6.60 (m, 2H, H5, H7), 6.98 (d, 1H, 3J_{12,11} = 6.4 \text{ Hz, H12}), 4.62 (dd, 1H, 3J_{11,10} = 10.7 \text{ Hz, } 3J_{11,12} = 6.4 \text{ Hz, H11}), 3.73 (s, 3H, 6-OMe), 3.72 (d(br), 1H, 3J_{1,2'} = 11.6 \text{ Hz, H1}), 3.57, 3.58, 3.44 (3 \times s, 3 \times 3H, 12-OMe, 9-CO_2Me, 2-CO_2Me), 3.09-2.74 (m, 2H, H4), 2.85 (m, 1H, H2), 2.79 (m, 1H, H10), 2.51 (m, 1H, H3\alpha), 2.12 (dd, 1H, 2J_{2',2} = 14.5 \text{ Hz, } 3J_{2',1} = 11.6 \text{ Hz, H2'}), 1.55 (m, 1H, H3\beta), 0.95 (d, 3H, 3fMe, 10-Me). \]

\[ ^13C \text{ NMR (CDCl}_3, 300 \text{ MHz)} \delta 174.2, 173.4 (2 \times -CO_2Me), 158.1 (C6), 145.8 (C12), 136.2 (C4a), 131.4 (C8a), 129.9 (C8), 113.3, 111.5 (C5, C7), 107.9 (C11), 59.5 (12-OMe), 55.0 (6-OMe), 52.4 (C2), 51.3, 51.2 (2 \times -CO_2Me), 40.1 (C10), 37.0 (C9), 34.7 (C1), 26.0 (C4)*, 24.7 (C3)*, 17.1 (10-Me). \]

and the (E)-isomer 188:

\[ ^13C \text{ NMR (CDCl}_3, 300 \text{ MHz)} \delta 174.2, 173.5 (2 \times -CO_2Me), 158.3 (C6), 147.7 (C12), 136.3 (C4a), 131.4 (C8a), 129.9 (C8), 113.4, 111.6 (C5, C7), 104.1 (C11), 56.0 (12-OMe), 55.0 (6-OMe), 52.4 (C2), 51.5, 51.1 (2 \times -CO_2Me), 39.4, 39.2, 34.7 (C1, C9, C10), 25.8 (C4)*, 24.9 (C3)*, 18.6 (10-Me). \]

Methyl [10R-(1\alpha,2\alpha)]-1,2,3,4-Tetrahydro-6-methoxy-2-(1,1-dimethoxybut-3-yl)-2-(methoxycarbonyl)naphthalene-1-acetate 189.

\[
\text{MeO} \quad \text{CO}_2\text{Me} \\
\begin{array}{c}
\text{MeO}_2\text{C} \\
\text{MeO} \\
\text{MeO}_2\text{C}
\end{array}
\]

187, 188

\[
\text{MeO} \quad \text{CO}_2\text{Me} \\
\begin{array}{c}
\text{MeO}_2\text{C} \\
\text{OMe}
\end{array}
\]

189

The enol ethers (290 mg, 0.94 mmol) were converted to the dimethyl acetal 189 with a catalytic amount of PTSA (50 mg) in refluxing methanol (20 mL), in a manner similar to that for the conversion of 158 and 159 to 160. Work up and flash chromatography afforded
two compounds. The most polar component was 189 ($R_f = 0.4$; 25% ethyl acetate in pentane), which crystallised from ethyl acetate to give the acetal as colourless prisms (302 mg, 95%), mp 118°C.

$^{1}$H NMR (CDCl$_3$, 300 MHz) $\delta$ 6.94 (m, 1H, H8), 6.57 (m, 1H, H7), 6.55 (s(br), 1H, H5), 4.44 (dd, 1H, $^{3}J_{12,11}$ = 8.6 Hz, $^{3}J_{12,11}$ = 2.9 Hz, H12), 3.82 (d(br), 1H, $^{3}J_{1,9}$ = 11.6 Hz, H1), 3.73 (s, 3H, 6-OMe), 3.60 (s, 3H, 9-CO$_2$Me), 3.42 (s, 1H, 2-CO$_2$Me), 3.35 (s, 6H, 12-(OMe)$_2$), 3.07-2.78 (m, 2H, H4), 2.76 (dd, 1H, $^{2}J_{9',9}$ = 14.7 Hz, $^{3}J_{9',1}$ = 2.9 Hz, H9'), 2.52 (m, 1H, H3α), 2.24, (ddd, 1H, $^{2}J_{11',11}$ = 11.2 Hz, $^{3}J_{11',12}$ = 8.6 Hz, $^{3}J_{11',10}$ = 1.8 Hz, H11'), 2.16 (dd, 1H, $^{2}J_{9,9'}$ = 14.7 Hz, $^{3}J_{9,1}$ = 11.6 Hz, H9), 1.75 (ddq, 1H, $^{3}J_{10,Me}$ = 6.8 Hz, $^{3}J_{10,11}$ = 11.0 Hz, $^{3}J_{10,11'}$ = 1.8 Hz, H10), 1.49 (m, 1H, H3β), 1.36 (ddd, 1H, $^{2}J_{11,11'}$ = 11.2 Hz, $^{3}J_{11,10}$ = 11.0 Hz, $^{3}J_{11,12}$ = 2.9 Hz, H11), 0.94 (d, 3H, $^{3}J_{Me,10}$ = 6.8 Hz, 10-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) $\delta$ 174.1, 173.0 (2 x -CO$_2$Me), 158.3 (C6), 136.3 (C4α), 130.8 (C8α), 129.9 (C8), 113.3 (C7)*, 111.6 (C5)*, 103.6 (C12), 54.9 (6-OMe), 53.8 (C2), 52.3 (12-(OMe)$_2$), 51.5, 51.2 (2 x -CO$_2$Me), 38.8 (C1), 36.8 (C9), 34.5 (C10), 33.7 (C11), 25.8 (C4)†, 24.9 (C3)†, 15.2 (10-Me).

IR (CHCl$_3$, cm$^{-1}$) 2950(s) (C-H str), 2840 (C-H str), 1725(s) (C=O str), 1610 (Ar C=C str), 1500(s) (Ar C=C str), 1250 (C-O str), 1125 (C-O str), 1050 (C-O str).

MS, $m/z$ (relative intensity, %) 408 (M+, <0.1), 376 (1), 345 (1), 344 (1), 316 (2), 302 (2), 271 (1), 259 (10), 85 (100)

ANALYSIS: Calcd for C$_{22}$H$_{32}$O$_{7}$: C, 64.69; H, 7.90.

Found: C, 64.76; H, 7.78.
Methyl (3α,9bα)-1,4,5,9b-Tetrahydro-7-methoxy-3-methyl-2-oxo-2H-benz[e]indene-3a(3H)-carboxylate 173.

The least polar compound (Rf = 0.65), which was sometimes formed in the Wittig reaction (up to 20%), was the cyclopentanone 173.

$^{1}$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.04 (d, 1H, $^3$J$_{9,8}$ = 8.6 Hz, H9), 6.72 (dd, 1H, $^3$J$_{8,9}$ = 8.6 Hz, $^4$J$_{8,6}$ = 2.6 Hz, H8), 6.58 (d(br), 1H, $^4$J$_{6,8}$ = 2.6 Hz, H6), 3.94 (dd(br), 1H, $^3$J$_{9b,1}'$ = 11.0 Hz, $^4$J$_{9b,4a}$ = 1.3 Hz, H9b), 3.76 (s, 3H, 7-OMe), 3.70 (s, 3H, $-CO_2$Me), 2.90 (ddd, 1H, $^2$J$_{1,1'}$ = 19.3 Hz, $^3$J$_{1,9b}$ = 9.7 Hz, $^4$J$_{1,3}$ = 1.3 Hz, H1), 2.90-2.72 (m, 2H, H5), 2.70 (dq, 1H, $^3$J$_{3,Me}$ = 7.4 Hz, $^4$J$_{3,1}$ = 1.3 Hz, H3), 2.29 (m, 1H, H4α), 2.10 (dd, 1H, $^2$J$_{1,1'}$ = 19.3 Hz, $^3$J$_{1',9b}$ = 11.0 Hz, H1'), 1.32 (m, 1H, H4β), 1.12 (d, 3H, $^3$J$_{Me,3}$ = 7.4 Hz, 3-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) $\delta$ 215.4 (C2), 174.9 ($-CO_2$Me), 158.1 (C7), 135.4 (C5α), 130.2 (C9), 129.0 (C9α), 113.5 (C6), 112.(C8), 55.2 (7-OMe), 55.0 (C3), 52.3 ($-CO_2$Me), 51.3 (C3a), 44.9 (C1), 38.8 (C9b), 26.5 (C5), 21.6 (C4), 7.8 (3-Me).

IR (CHCl$_3$, cm$^{-1}$) 2960 (C-H str), 1735(s) (C=O str), 1610 (Ar C=C str), 1500(s) (Ar C=C str), 1270 (C-O str), 1160(s) (C-O str), 1070 (C-O str), 1040 (C-O str), 850 (C-H oop bend).

MS, m/z (relative intensity, %) 289 (M$^+1$, 7.2), 288 (M$^+$, 42.1), 273 (2), 260 (31), 230 (13), 229 (82), 228 (51), 213 (20), 201 (21), 200 (100), 187 (65), 186 (16), 185 (23), 173 (18), 172 (21), 171 (18), 159 (159), 158 (20), 141 (19), 129 (25), 128 (37), 115 (60), 91 (36).

HRMS: Calcd for C$_{17}$H$_{20}$O$_4$: 288.1360. Found: 288.1362.
[10R-(1α,2α)]-1,2,3,4-Tetrahydro-6-methoxy-2-(1,1-dimethoxybut-3-yl)-2-(methoxycarbonyl)naphthalene-1-acetic Acid 190.

The ester 189 (325 mg, 0.800 mmol) was converted to the acid 190 with 3M NaOH in aqueous ethanol, in a manner similar to that for the conversion of 160 to 185. Work up afforded the acid as a white solid (309 mg, 98% recovery). Recrystallisation from ethyl acetate/pentane gave colourless prisms, mp 136°C.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 7.03 (m, 1H, H8), 6.58 (m, 1H, H7), 6.57 (s(br), 1H, H5), 4.46 (dd, 1H, $^3$J$_{12,11}$= 8.6 Hz, $^3$J$_{12,11}$ = 2.9 Hz, H12), 3.83 (d(br), 1H, $^3$J$_{1,9}$ = 11.2 Hz, H1), 3.73 (s, 3H, 6-OMe), 3.42 (s, 1H, -CO$_2$Me), 3.36, 3.34 (2 x s, 2 x 3H, 12-(OMe)$_2$), 3.07-2.78 (m, 2H, H4), 2.83 (dd, 1H, $^2$J$_{9',9}$ = 15.4 Hz, $^3$J$_{9',1}$ = 2.0 Hz, H9$'$), 2.52 (m, 1H, H3$\alpha$), 2.23 (ddd, 1H, $^2$J$_{11',11}$ = 11.2 Hz, $^3$J$_{11',12}$ = 8.6 Hz, $^3$J$_{11',10}$ = 1.8 Hz, H11$'$), 2.17 (dd, 1H, $^2$J$_{9,9'}$ = 15.4 Hz, $^3$J$_{9,1}$ = 11.2 Hz, H9), 1.75 (ddq, 1H, $^3$J$_{10,11}$ = 11.0 Hz, $^3$J$_{10,Me}$ = 6.6 Hz, $^3$J$_{10,11'}$ = 1.8 Hz, H10), 1.47 (m, 1H, H3$\beta$), 1.36 (ddd, 1H, $^2$J$_{11,11'}$ = 11.2 Hz, $^3$J$_{11,10}$ = 11.0 Hz, $^3$J$_{11,12}$ = 2.9 Hz, H11), 0.94 (d, 3H, $^3$J$_{Me,10}$ = 6.6 Hz, 10-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) δ 178.2 (-CO$_2$H), 173.0 (-CO$_2$Me), 158.4 (C6), 136.3 (C4a), 130.7 (C8a), 129.9 (C8), 113.3 (C7)*, 111.8 (C5)*, 103.6 (C12), 55.0 (6-OMe), 54.0 (C2), 52.2 (12-(OMe)$_2$), 51.3 (-CO$_2$Me), 38.5 (C1), 36.6 (C9), 34.6 (C10), 33.8 (C11), 25.8 (C4)$^\dagger$, 24.9 (C3)$^\dagger$, 15.3 (10-Me).
IR (CHCl₃, cm⁻¹) 3300-2800(br) (O-H str), 2950(s) (C-H str), 2840 (C-H str), 1720(s) (C=O str), 1610 (Ar C=C str), 1500(s) (Ar C=C str), 1270 (C-O str), 1120 (C-O str), 1040 (C-O str).

MS, m/z (relative intensity, %) 394 (M⁺, <1), 362 (1), 330 (1), 302 (2), 271 (1), 245 (3), 218 (2), 159 (2), 85 (100).

ANALYSIS: Calcd for C₂₁H₃₀O₇: C, 64.69; H, 7.90.

Found: C, 64.76; H, 7.78.

\[ 12R-(\alpha, 2\alpha)]-1,2,3,4-Tetrahydro-6-methoxy-2-(1,1-dimethoxybut-3-yl)-2-(methoxycarbonyl)naphthalene-1-acetic Acid, Anhydride with Methyl Hydrogen Carbonate 191.

The acid 190 (309 mg, 0.784 mmol) was converted to the mixed anhydride 191 with CICO₂Me (91 µL) and triethylamine (169 µL), in a manner similar to that for the conversion of 185 to 186. Work up provided the title compound as a pale yellow oil (337 mg, 95% recovery) which solidified on standing. Recrystallisation from ethyl acetate/pentane gave pure anhydride as white needles, mp 84°C.

\(^1\)H NMR (CDCl₃, 300 MHz) δ 7.07 (d, 1H, J₈,₇ = 8.4 Hz, H₈), 6.60 (dd, 1H, J₇,₈ = 8.4 Hz, 4J₇,₅ = 2.2 Hz, H₇), 6.57 (d, 1H, 4J₅,₇ = 2.2 Hz, H₅), 4.44 (dd, 1H, 3J₄₁₃ = 8.6 Hz, 3J₁₄,₁₃ = 2.4 Hz, H₁₄), 3.87 (s, 3H, 6-OMe), 3.86 (m, 1H, H₁), 3.73 (s, 3H, 11-OMe), 3.42 (s, 1H, 2-CO₂Me), 3.35 (s, 3H, 14-OMe), 3.33 (s, 3H, 14-OMe), 3.08-2.78 (m, 2H, H₄), 2.98 (dd, 1H, 2J₉',₉ = 15.5 Hz, 3J₉',₁ = 2.2 Hz, H₉'), 2.53 (m, 1H,
H3α), 2.26 (dd, 1H, 2J9,9′ = 15.5 Hz, 3J9,1 = 11.2 Hz, H9), 2.20 (ddd, 1H, 2J13′,13 = 11.3 Hz, 3J13′,14 = 8.6 Hz, 3J13′,12 ~ 1.0 Hz, H13′), 1.73 (ddq, 1H, 3J12,13 = 11.0 Hz, 3J12,Me = 6.8 Hz, 3J12,13′ ~ 1.0 Hz, H12), 1.44 (m, 1H, H3β), 1.33 (ddd, 1H, 2J13,13′ = 11.3 Hz, 3J13,12 = 11.0 Hz, 3J13,14 = 2.4 Hz, H13), 0.94 (d, 3H, 3JMe,12 = 6.8 Hz, 12-Me).

13C NMR (CDCl3, 300 MHz) δ 173.4 (2-CO2Me), 166.9 (C10), 158.5 (C6), 145.1 (C11), 136.2 (C4a), 130.2 (C8), 130.0 (C8a), 113.5 (C7)*, 111.8 (C5)*, 103.4 (C14), 55.8 (11-OMe), 55.0 (6-OMe), 54.2 (C2), 52.8, 51.9 (14-(OMe)2), 51.3 (2-CO2Me), 38.3 (C1), 37.0 (C9), 34.6 (C12), 33.8 (C13), 25.7 (C4)†, 24.8 (C3)†, 15.4 (12-Me).

IR (CHCl3, cm−1) 2950(s) (C-H str), 2840 (C-H str), 1825(s) (C=O str, anhydride), 1760(s,br) (C=O str, anhydride), 1720(s) (C=O str, ester), 1610(s) (Ar C=C str), 1500(s) (Ar C=C str), 1270(s) (C-O str), 1240(s) (C-O str), 1120(s) (C-O str), 1090(s) (C-O str).

MS, m/z (relative intensity, %) 452 (M+, 3), 377 (1), 345 (3), 344 (2), 316 (3), 259 (9), 146 (5), 115 (19), 85 (100).

Methyl [12R-(1α,2α)]-1-(1-Diazo-2-oxoprop-3-yl)-1,2,3,4-tetrahydro-6-methoxy-2-(1,1-dimethoxybut-3-yl)naphthalene-2-carboxylate 192.

The anhydride 191 (325 mg) was converted to the diazoketone, with freshly prepared ethereal diazomethane, in a manner similar to that for the conversion of 186 to 161. Evaporation of the volatile components followed by flash chromatography gave the diazoketone as a pale yellow solid (230 mg, 70% overall yield for 2 steps). Further
recrystallisation from ethyl acetate/pentane gave the pure diazoketone as pale yellow needles, mp 61-62°C

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 6.93 (d(br), 1H, $^3J_{8,7} = 8.6$ Hz, H8), 6.57 (dd, 1H, $^3J_{7,8} = 8.6$ Hz, $^4J_{7,5} = 2.7$ Hz, H7), 6.55 (s(br), 1H, H5), 5.03 (s(br), 1H, H11), 4.44 (dd, 1H, $^3J_{14,13} = 8.3$ Hz, $^3J_{14,13} = 2.6$ Hz, H14), 3.87 (d(br), 1H, $^3J_{1,9} = 11.0$ Hz, H1), 3.72 (s, 3H, 6-OMe), 3.41 (s, 1H, -CO$_2$Me), 3.35 (s, 3H, 14-OMe), 3.34 (s, 3H, 14-OMe), 3.08-2.76 (m, 2H, H4), 2.69 (dd, 1H, $^2J_{9',9} = 14.1$ Hz, $^3J_{9',1} = 2.4$ Hz, H9'), 2.51 (m, 1H, H3α), 2.28 (ddd, 1H, $^2J_{13',13} = 11.4$ Hz, $^3J_{13',14} = 8.3$ Hz, $^3J_{13',12} = 1.8$ Hz, H13'), 2.12 (dd(br), 1H, $^2J_{9,9'} = 14.1$ Hz, $^3J_{9,1} = 11.0$ Hz, H9), 1.74 (ddq, 1H, $^3J_{12,13} = 11.2$ Hz, $^3J_{12,Me} = 6.8$ Hz, $^3J_{12,13'} = 1.8$ Hz, H12), 1.46 (m, 1H, H3β), 1.33 (dd, 1H, $^2J_{13,13'} = 11.4$ Hz, $^3J_{13,12} = 11.2$ Hz, $^3J_{13,14} = 2.6$ Hz, H13), 0.94 (d, 3H, $^3J_{Me,12} = 6.8$ Hz, 12-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) $\delta$ 193.8 (C10), 174.1 (-CO$_2$Me), 158.2 (C6), 136.1 (C4a), 130.9 (C8a), 130.4 (C8), 113.3 (C7)*, 111.5 (C5)*, 103.6 (C14), 55.4 (C11), 55.0 (6-OMe), 54.0 (C2), 52.4, 52.2 (14-(OMe)$_2$), 51.2 (-CO$_2$Me), 42.9 (C9), 38.9 (C1), 34.5 (C12), 33.8 (C13), 25.8 (C4)†, 25.0 (C3)†, 15.3 (12-Me).

IR (CHCl$_3$, cm$^{-1}$) 2950(s) (C-H str), 2835 (C-H str), 2100(s) (C=N=N asym str), 1720(s) (C=O str, ester), 1635 (C=O str, ketone), 1610 (Ar C=C str), 1500 (Ar C=C str), 1365 (C=N=N sym str), 1125(s) (C-O str), 1040 (C-O str).

MS, m/z (relative intensity, %) 358 (1), 335 (13), 149 (10), 115 (23), 89 (15), 85 (67), 75 (100), 59 (39), 55 (20).
Methyl [10R-(2α,3α,9αβ)]-2,2a,3,4,5,9a-Hexahydro-7-methoxy-3-(1,1-dimethoxy-but-3-yl)-1-oxo-1H-benz[cd]azulene-3-carboxylate 199.

The diazoketone 192 (40 mg, 96 µmol) was converted to the intermediate cycloheptatriene 199 with a catalytic amount of rhodium mandelate in boiling CH₂CL₂, under nitrogen. An aliquot was removed from the reaction mixture and analysed.

$^1$H NMR (CDCl₃, 300 MHz) δ 5.96 (dt, 1H, $^3$J₈,₉ = 10.0 Hz, $^4$J₈,₉α = 1.8 Hz, $^4$J₈,₆ = 1.8 Hz, H₈), 5.52 (s(br), 1H, H₆), 5.51 (dd, 1H, $^3$J₉,₈ = 10.0 Hz, $^3$J₉,₉α = 4.3 Hz, H₉), 4.38 (dd, 1H, $^3$J₁₂,₁₁ = 8.1 Hz, $^3$J₁₂,₁₁' = 3.1 Hz, H₁₂), 3.65 (s, 3H, 7-OMe), 3.61 (s, 3H, -CO₂Me), 3.26 (s, 6H, 12-(OMe)₂), 3.26 (m, 1H, H₂a), 3.00 (m, 1H, H₉α), 2.97 (ddd, 1H, $^3$J₂₂,₂α = 16.7 Hz, $^3$J₂₂,₂α = 13.1 Hz, $^4$J₂₂,₉α = 1.9 Hz, H₂β), 2.65 (dd, 1H, $^2$J₂α,₂β = 16.7 Hz, $^3$J₂α,₂α = 7.4 Hz, $^4$J₂α,₉α = 0.9 Hz, H₂α), 2.47-2.24 (m, 2H, H₅), 2.25 (ddd, 1H, $^2$J₄α,₄β = 14.2 Hz, $^3$J₄α,₅ = 5.7 Hz, $^3$J₄α,₅' = 2.5 Hz, H₄α), 2.08 (ddq, 1H, $^3$J₁₀,₁₁' = 10.6 Hz, $^3$J₁₀,Me = 6.9 Hz, $^3$J₁₀,₁₁ = 1.6 Hz, H₁₀), 1.85 (ddd, 1H, $^2$J₄β,₄α = 14.2 Hz, $^3$J₄β,₅ = 11.2 Hz, $^3$J₄β,₅' = 4.7 Hz, H₄β), 1.68 (ddddd, 1H, $^2$J₁₁,₁₁' = 13.9 Hz, $^3$J₁₁,₁₂ = 8.1 Hz, $^3$J₁₁,₁₀ = 1.6 Hz, $^4$J₁₁,Me = 1.0 Hz, H₁₁'), 1.27 (ddd, 1H, $^2$J₁₁',₁₁ = 13.9, $^3$J₁₁',₁₀ = 10.6 Hz, $^3$J₁₁',₁₂ = 3.1 Hz, H₁₁'), 1.14 (d(br), 3H, $^3$J₃Me,₁₀ = 6.9 Hz, 10-Me).

$^{13}$C NMR (CDCl₃, 300 MHz) δ 215.8 (C1), 176.9 (-CO₂Me), 158.9 (C7), 126.6, 126.2 (C₅α, C₉b), 125.2 (C₈), 123.9 (C₉), 105.8 (C₆), 103.8 (C₁₂), 54.5 (7-OMe), 53.7, 52.3, (12-(OMe)₂), 51.5 (-CO₂Me), 49.6 (C₉α), 48.5 (C₃), 42.4 (C₂α), 41.8 (C₂), 37.2 (C₁₁), 29.3 (C₁₀), 28.7 (C₅), 27.0 (C₄), 15.8 (10-Me).
IR (CHCl₃, cm⁻¹) 2950 (s) (C-H str), 2835 (C-H str), 1745 (s) (C=O str, ester), 1720 (s) (C=O str, ketone), 1635 (C=C str), 1610 (C=C str), 1260 (C-O str), 1165 (C-O str), 1120 (C-O str), 1050 (br) (C-O str), 960 (C-H oop bend), 820 (C-H oop bend).

MS, m/z (relative intensity, %) 390 (M⁺, <1), 388 (<1), 358 (4), 272 (4), 271 (13), 265 (3), 115 (5), 85 (100).


Methyl [10R-(2α,3α)]-2,2a,3,4,5,8-Hexahydro-7-methoxy-3-(1,1-dimethoxybut-3-yl)-1-oxo-1H-benz[cd]azulene-3-carboxylate 200.

Addition of DBU to the reaction mixture followed by work up and chromatography gave the α,β-unsaturated ketone 200 as a yellow oil (27 mg, 72% overall yield for 2 steps).

¹H NMR (CDCl₃, 300 MHz) δ 6.01 (dd(br), 1H, 3J₉,₈ = 8.6 Hz, 3J₁₀,₂₀ = 5.9 Hz, H9), 5.21 (s(br), 1H, H6), 4.41 (dd, 1H, 3J₁₂,₁₁ = 7.9 Hz, 3J₁₂,₁₁' = 3.4 Hz, H12), 3.69 (s, 3H, 7-OMe), 3.59 (s, 3H, -CO₂Me), 3.49 (ddddd, 1H, 3J₂a,₂' = 10.1 Hz, 3J₂a,₂ = 7.9 Hz, 4J₂a,₅ = 1.5 Hz, 4J₂a,₅ = 0.5 Hz, H2a), 3.28 (s, 3H, 12-OMe), 3.27 (s, 3H, 12-OMe), 3.18 (dddd, 1H, 2J₈,₈' = 13.6 Hz, 3J₈,₉ = 8.6 Hz, 4J₈,₆ = 2.2 Hz, H8), 2.74 (dd, 1H, 2J₂,₂' = 18.0 Hz, 3J₂,₂a = 7.9 Hz, H2), 2.58 (dd, 1H, 2J₂',₂ = 18.0 Hz, 3J₂',₂a = 10.1 Hz, H2'), 2.50-2.42 (m, 2H, H5), 2.23 (dddd, 1H, 2J₈,₈ = 13.6 Hz, 3J₈,₉ = 5.9 Hz, 4J₈,₆ = 0.4 Hz, H8'), 2.07 (ddq (partially obscured), 1H, 3J₁₀,₁₁ = 11.0 Hz, 3J₁₀,₁ = 7.0 Hz, 3J₁₀,₁₁ = 0.9 Hz, H10), 2.14-1.95 (m, 2H, H4), 1.75 (ddddd, 1H, 2J₁₁,₁₁ = 14.1 Hz, 3J₁₁,₁₂ = 7.9
Hz, $^3J_{11,10} = 0.9$ Hz, $^4J_{11,\text{Me}} \sim 0.5$ Hz, H11), 1.28 (ddd, 1H, $^2J_{11',11} = 14.1$ Hz, $^3J_{11',10} = 11.0$ Hz, $^3J_{11',12} = 3.4$ Hz, H11'), 1.02 (d(br), 3H, $^3J_{\text{Me,10}} = 7.0$ Hz, 10-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz) δ 205.2 (C1), 176.9 (-CO$_2$Me), 147.5 (C7), 138.9, 134.6, 133.8 (C9a, C5a, C9b), 115.9 (C9), 103.8 (C12), 100.8 (C6), 56.0 (7-OMe), 53.0, 52.5, (12-(OMe)$_2$), 51.6 (-CO$_2$Me), 48.8 (C3), 41.4 (C2a), 41.1 (C2), 36.2 (C8), 32.3 (C11), 31.4 (C10), 29.3 (C5), 27.1 (C4), 15.3 (10-Me).

IR (CHCl$_3$, cm$^{-1}$) 3000 (C-H str), 2950 (C-H str), 2835 (C-H str), 1715(br) (C=O str, ester), 1625 (C=O str, enone, C=C str), 1260(s) (C-O str), 1170(s) (C-O str), 1125 (C-O str), 1050(br) (C-O str), 910 (C-H oop bend), 820 (C-H oop bend).

MS, m/z (relative intensity, %) 390 (M$^+$, 0.7), 360 (1), 358 (9), 271 (25), 241 (9), 188 (9), 160 (12), 115 (10), 85 (100).

HRMS: Calcd for C$_{22}$H$_{30}$O$_6$: 390.2042. Found: 390.2041.
CHAPTER 5
EXPERIMENTAL

Methyl [10R-(2α,3α)]-2,2a,3,4,5,8-Hexahydro-7-methoxy-9-methyl-1-oxo-3-(1-oxobut-3-yl)-1H-benz[cd]azulene-3-carboxylate 70.

To a solution of the acetal 201 (500 mg, 1.24 mmol) in dry acetone (20 mL) under nitrogen was quickly added a catalytic amount (20 mg) of 215 (the preparation of 215 is detailed in ref. 135). The resulting homogeneous mixture was stirred at ambient temperature for 30 min. The progress of the reaction was monitored by tlc and if starting material remained after this time, another aliquot of catalyst was added. The solution was diluted with ether, washed with water and brine, and dried over MgSO₄. Removal of solvent in vacuo afforded a pale yellow oil which was chromatographed (20% ethyl acetate in pentane) to give the aldehyde 70 (Rf = 0.30; 332 mg, 75%) as very pale yellow needles, mp 147°C.

¹H NMR (CDCl₃, 300 MHz), δ 9.72 (d, 1H, ³J₁₂,₁₁ = 2.0 Hz, H12), 5.15 (s(br), 1H, H6), 3.72 (s, 3H, 7-OMe), 3.59 (s, 3H -CO₂Me), ~3.56 (m, 1H, H2a), 2.93 (dd, 1H, ²J₈,₈ = 12.3 Hz, ⁴J₈,₆ = 2.0 Hz, H8), 2.60 (dd, 1H, ²J₂,₄ = 16.9 Hz, ³J₂,₂a = 7.7 Hz, H2), 2.56 (m, 1H, H10), 2.48-2.39 (m, 2H, H5), 2.39 (s(br), 3H, 9-Me), 2.39 (dd, 1H, ²J₂,₂ = 16.9 Hz, ³J₂,₂a = 10.5 Hz, H2'), 2.22 (ddd, 1H, ²J₁₁,₁₁' = 17.6 Hz, ³J₁₁,₁₀ = 10.8, ³J₁₁,₁₂ = 2.0 Hz, H11), 2.18-2.08 (m, 1H, H4α), 2.13 (d(br), 1H, ²J₈,₈ = 12.3 Hz, H8'), 1.86 (ddd, 1H, ²J₄β,₄α = 13.6 Hz, ³J₄β,₅ = 6.0 Hz, ³J₄β,₅' = 5.8 Hz, H4β), 1.35-1.20 (m, 1H, H11'), 1.02 (d(br), 3H, ³J₆,₁₀ = 6.6 Hz, 10-Me).
\(^{13}\)C NMR (CDCl\(_3\), 300 MHz), 8 204.9 (C1), 201.2 (C12), 176.4 (-CO\(_2\)Me), 147.1 (C7), 135.8, 134.8, 131.8, 131.4 (C5a, C9, C9a, C9b), 99.8 (C6), 55.9 (7-OMe), 51.8 (-CO\(_2\)Me), 48.7 (C3), 48.1 (C11), 42.9 (C8), 41.8 (C2), 40.9 (C2a), 29.9, 29.0 (C4, C5), 26.8 (C10), 20.0 (9-Me), 16.1 (10-Me).

IR (CHCl\(_3\), cm\(^{-1}\)) 2950 (C-H str), 2840 (C-H str), 1720 (s) (C=O str), 1705 (s) (C=O str), 1620 (br) (C=C str), 1560 (C=C str), 1260 (C-O str), 1115 (C-O str), 1045 (C-O str), 845 (C-H oop bend).

MS, m/z (relative intensity, %) 358 (M\(^+\), 61), 285 (36), 255 (27), 202 (93), 174 (36), 159 (32), 115 (35), 85 (35), 43 (100).

ANALYSIS: Calcd for C\(_{21}\)H\(_{26}\)O\(_5\): C, 70.37; H, 7.31.

Found: C, 70.40; H, 7.55.

**Cleavage of the Acetal Group Using the Catalyst Lutidinium Tosylate.**

A catalytic amount of lutidinium tosylate (70 mg) was added to a solution of the acetal 201 (580 mg, 1.43 mmol) in acetone (20 mL) under a nitrogen atmosphere. Water (3 drops) was added and the reaction mixture was maintained at reflux for 7 h.

The resulting yellow solution was cooled to room temperature, diluted with ether, washed successively with water and brine, and dried over MgSO\(_4\). Separation of the products by repeated flash chromatography (20% ethyl acetate in pentane) provided four compounds: i)
recovered starting material 201 (110 mg, 19%), ii) the desired aldehyde 70 (257 mg, 50%), iii) the tautomeric acetal 204 (18 mg, 3%), and iv) the tautomeric aldehyde 203 (37 mg, 7%).

**Methyl [10R-(2α,3α)]-2,2a,3,4,5,6-Hexahydro-7-methoxy-9-methyl-1-oxo-3-(1-oxobut-3-yl)-1H-benz[cd]azulene-3-carboxylate 203.**

\[ \mathrm{H} \text{NMR (CDCl}_3, 300 \text{ MHz), } \delta 9.70 (d, 1H, J_{12,11} = 2.1 \text{ Hz, H12}), 5.37 (s(br), 1H, H8), 3.70 (s, 3H, 7-OMe), 3.68 (s, 3H, 3-C\text{Me}), 3.14 (m, 1H, H2a), 2.73 (dd, 1H, J_6,6' = 13.3 \text{ Hz, } J_{6,8} = 2.3 \text{ Hz, H6}), 2.68 (dd, 1H, J_{2,2'} = 17.0 \text{ Hz, } J_{2,2a} = 7.8 \text{ Hz, H2}), 2.62 (m, 1H, H10), 2.69-2.20 (m, 6H, H2', H3, H4, H6', H11'), 1.82 (m, 1H, H4), 1.06 (d, 3H, J_{10-Me} = 7.0 \text{ Hz, 10-Me}). \]

\[ \mathrm{C} \text{NMR (CDCl}_3, 300 \text{ MHz), } \delta 206.3 (C1), 201.2 (C12), 177.0 (-CO}_2\text{Me}), 156.3 (C7), 146.1 (C9), 137.5, 128.4, 120.8 (C5a, C9a, C9b), 103.5 (C8), 56.4 (7-OMe), 51.7 (-CO}_2\text{Me}), 49.3 (C3), 47.8 (C11), 41.5 (C2), 41.2 (C2a), 37.1 (C6), 29.2, 28.5 (C5, C4), 26.9 (C10), 21.3 (9-Me), 16.8 (10-Me). \]

\[ \text{IR (CHCl}_3, \text{cm}^{-1}) 2950 (\text{C-H str}), 2840 (\text{C-H str}), 1720(s) (\text{C=O str}), 1690(s) (\text{C=O str}), 1655(s) (\text{C=C str}), 1605 (\text{C=C str}), 1510(s,br), 1115(s) (\text{C-O str}), 855 (\text{C-H oop bend}), 810 (\text{C-H oop bend}). \]

\[ \text{MS, } m/z (\text{relative intensity, } \%) 359 (M^++1, 19.6), 358 (M^+, 90), 299 (16), 288 (12), 287 (64), 286 (10), 285 (48), 281 (25), 255 (18), 227 (23), 203 (11), 202 (43), 190 (20), 189 (16), 159 (15), 141 (18), 129 (17), 128 (27), 115 (29). \]

HRMS: Calcd for C\text{21}H\text{26}O\text{5}: 358.1780. Found: 358.1780.
Methyl [10R-(2α,3α)·-2,2a,3,4,5,6-Hexahydro-7-methoxy-3-(1,1-dimethoxybut-3-yl)-9-methyl-1-oxo-1H-benz[cd]azulene-3-carboxylate 204.

1H NMR (CDCl3, 300 MHz), δ 5.36 (s(br), 1H, H8), 4.40 (dd, 1H, 3J12,11 = 7.8 Hz, 3J12,11' = 2.7 Hz, H12), 3.67 (s, 3H, 7-OMe), 3.66 (s, 3H, -CO2Me), 3.28, 3.24 (2 x s, 2 x 3H, 12-(OMe)2), 3.05 (m, 1H, H2a), 2.90 (dd, 1H, 2J6,6' = 13.3 Hz, 4J6,8 = 2.4 Hz, H6), 2.70 (d, 2H, 3J2,2a = 9.2 Hz, H2), 2.60-2.17 (m, 3H, H5, H4a), 2.48 (s, 3H, 9-Me), 2.26 (d(br), 1H, 2J6',6 = 13.3 Hz, H6'), 2.12 (dddq, 1H, 3J10,11' = 10.8 Hz, 3J10,Me = 7.0 Hz, 7J10,11 = 1.4 Hz, H10), 1.82 (m, 1H, H4β), 1.69 (ddd, 1H, 2J11,11' = 14.2 Hz, 3J11,12 = 7.8 Hz, 3J11,10 = 1.4 Hz, H11), 1.32 (ddd, 1H, 2J11',11 = 14.2 Hz, 3J11',10 = 10.8 Hz, 3J11',12 = 2.7 Hz, H11'), 1.05 (d(br), 3H, 3JMe,10 = 7.0 Hz, 10-Me).

13C NMR (CDCl3, 300 MHz), δ 206.8 (C1), 177.1 (-CO2Me), 155.9 (C7), 145.3 (C9), 137.9, 128.8, 120.9 (C5a, C9a, C9b), 103.5 (C12), 103.3 (C8), 56.5 (7-OMe), 52.9, 52.7 (12-(OMe)2), 51.6 (-CO2Me), 48.5 (C3), 41.4 (C2), 41.4 (C6), 37.2 (C2a), 36.8 (C11), 29.9 (C10), 29.6 (C5), 28.3 (C4), 21.4 (9-Me), 16.0 (10-Me).

MS, m/z (relative intensity, %) 404 (M+, ~4), 373 (7), 372 (13), 340 (5), 313 (5), 287 (8), 286 (10), 285 (49), 281 (9), 255 (5), 253 (5), 227 (8), 128 (9), 115 (13), 85 (100), 75 (100).


Cleavage of the Acetal Using Bromodimethylborane.

To a solution of the trienone 201 (20 mg, 50 µmol) in dry CH2Cl2 (0.5 mL) under nitrogen was added 2 drops of Me2BBr from a 50 µL syringe, at -78°C. The resulting pink solution was immediately quenched with a solution of NaHCO3 and the phases separated. The aqueous fraction was extracted further with CH2Cl2 and the combined organic phases washed with water and brine, and dried over MgSO4. Removal of solvent in vacuo afforded
a yellow oil (15 mg). $^1$H nmr analysis indicated that the crude mixture contained the tautomeric aldehyde 203 (40%), the desired aldehyde 70 (25%), the tautomeric acetal 204 (20%) and recovered starting material (15%).

Methyl (3α,5α,5α,7aβ)-1,2,4,5,6,7,7a,a,8,9-Octahydro-3-hydroxy-5,11-dimethyl-1,9-dioxo-3H-indeno[4,5-cd]azulene-5a(9H)-carboxylate 207.

A solution of the enone 201 (70 mg, 0.17 mmol) in dry CH$_2$Cl$_2$ (2 mL) was treated at -78°C with a 3-fold excess (17 µL) of Me$_2$BBr. The reaction mixture was quenched after ca. 15 seconds and work up as previously described afforded a dark yellow oil. Flash chromatography gave 207 as the major product (28 mg, 47%) as an amorphous white solid.

$^1$H NMR (CDCl$_3$, 300 MHz), δ 5.94 (d, 1H, $^4$J$_{10,8a}$ = 0.9 Hz, H10), 4.26 (d(br), 1H, $^3$J$_{OHH,3}$ = 4.2 Hz, 3-OH), 3.72 (m, 1H, H3), 3.69 (s, 3H, -CO$_2$Me), 3.04 (dddd, 1H, $^3$J$_{11a,7a}$ = 12.5 Hz, $^3$J$_{11a,8a}$ = 12.1 Hz, $^3$J$_{11a,8a}$ = 12.1 Hz, $^3$J$_{11a,7a}$ = 7.5 Hz, $^3$J$_{7a,8a}$ = 6.6 Hz, H7a), 2.82 (d, 1H, $^2$J$_{2,2'}$ = 16.3 Hz, H2), 2.55 (dd, 1H, $^3$J$_{8a,7a}$ = 6.6 Hz, $^4$J$_{8a,10}$ = 0.9 Hz, H8a), 2.54 (d, 1H, $^3$J$_{8b,7c}$ = 12.1 Hz, H8β), 2.19 (s, 3H, 11-Me), 2.20-1.83 (m, 5H, H4a, H4β, H5, H6a, H7α), 1.85 (d, 1H, $^2$J$_{2',2'}$ = 16.3 Hz, H2'), 1.67 (m, 1H, H6β), 1.54 (ddd(br), $^2$J$_{11a,7a}$ = 12-14 Hz, $^3$J$_{11a,7a}$ = 12.5 Hz, $^3$J$_{11a,6a}$ = 10-12 Hz, H7β), 1.02 (d, 3H, $^3$J$_{Me,5}$ = 6.6 Hz, 5-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz), δ 204.2 (C1), 201.2 (C9), 180.5 (C11), 174.2 (-CO$_2$Me), 146.1 (C11b), 136.3 (C7a), 130.7 (C10), 78.4 (C3), 58.2, 56.9 (C5a, C11a), 51.2
(-CO₂Me), 49.1 (C8), 48.0 (C2), 40.8 (C4), 36.1 (C2a), 33.0 (C5), 28.9 (C7), 23.2 (11-Me), 22.9 (C6), 14.0 (5-Me).

MS, m/z (relative intensity, %) 344 (M⁺, 27), 273 (100), 225 (29), 213 (48), 185 (24), 141 (25), 128 (28), 115 (29), 91 (31), 77 (32).

The enone 201 (20 mg, 50 µmol) in dry CH₂Cl₂ (0.5 mL) at -78°C under nitrogen, was treated with a slight excess of Me₂BBr (ca. 10 µL). Usual work up afforded a mixture of the tautomeric aldehyde 203 (45%), the aldol product 207 (40%), and the desired aldehyde 70 (~5%), as an intense yellow oil.

Methyl (1α,3α,3aα,10αα,10βα)-1,2,3,3a,6,9,10,10βα-Octahydro-3-hydroxy-7-methoxy-1,5-dimethyl-4-oxocyclohept[b]acenaphthylene-10α(4H)-carboxylate 69.

![Chemical structure of 69]

Catalytic amounts of K₂CO₃ (15 mg) and NaHCO₃ (15 mg) were added to a solution of the aldehyde 70 (220 mg, 0.614 mmol) in methanol (5 mL). After the resulting suspension was stirred at r.t. for 4 h, volatile components were removed in vacuo. The residue was diluted with ether, washed with water and brine, and dried over MgSO₄. Concentration in vacuo gave a pale yellow solid which was purified by flash chromatography (33% pentane in diethyl ether) to afford a 6:1 mixture of the α-carbinol 69 (161 mg, 73%, Rf = 0.42) and its β-epimer 218 (22 mg, 10%, Rf = 0.52).
C(3α)-OH epimer 69:

$^1$H NMR (CDCl$_3$, 500 MHz), $\delta$ 5.14 (s(br), 1H, H8), 3.71 (s, 3H, 7-OMe), 3.68 (s, 3H, -CO$_2$Me), 3.34 (ddd, 1H, $^3$J$_{3,2\alpha}$ = 10.5 Hz, $^3$J$_{3,3\alpha}$ = 9.9 Hz, $^3$J$_{3,2\beta}$ = 4.8 Hz, H3), 3.30 (d(br), 1H, $^3$J$_{10b,3\alpha}$ = 7.3 Hz, H10b), 2.93 (dd, 1H, $^2$J$_{6,6'}$ = 12.5 Hz, $^4$J$_{6,8}$ = 2.0 Hz, H6), 2.82 (dd, 1H, $^3$J$_{3a,3}$ = 9.9 Hz, $^3$J$_{3a,10b}$ = 7.3 Hz, H3a), 2.77 (s(br), 1H, 3-OH), 2.52-2.33 (m, 3H, H9a, H9b, H10a), 2.43 (s(br), 3H, 5-Me), 2.20 (d(br), 1H, $^2$J$_{6',6}$ = 12.5 Hz, H6'), 1.87 (ddq, 1H, $^3$J$_{1,2\alpha}$ = 12.3 Hz, $^3$J$_{1,Me}$ = 7.0 Hz, $^3$J$_{1,2\beta}$ = 3.1 Hz, H1), 1.78-1.67 (m, 2H, H2β, H10β), 1.64 (ddd, 1H, $^2$J$_{2,2\alpha,2\beta}$ = 12.2 Hz, $^3$J$_{2,1\alpha}$ = 12.3 Hz, $^3$J$_{2,3,2\alpha}$ = 10.5 Hz, H2α), 0.98 (d, 3H, $^3$J$_{Me,1}$ = 7.0 Hz, 1-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz), $\delta$ 208.8 (C4), 176.0 (-CO$_2$Me), 147.0 (C7), 139.2 (C5), 133.4, 130.5, 130.3 (C4a, C8a, C10c), 99.1 (C8), 69.2 (C3), 57.8 (C3a), 56.0 (7-OMe), 51.4 (-CO$_2$Me), 45.7 (C10a), 42.5 (C10b), 42.0 (C6), 35.9 (C2), 28.8 (C1), 26.4 (C9, C10), 20.6 (5-Me), 16.4 (1-Me).

IR (CHCl$_3$, cm$^{-1}$) 3600-3300(br) (O-H str), 2965 (C-H str), 1720(s) (C=O str, ester), 1695(s) (C=O str, enone), 1635 (C=C str), 1610 (C=C str), 1570 (C=C str), 1260 (C-O str), 1075(s) (C-O str).

MS, m/z (relative intensity, %) 359 (M$^+$+1, 19.6), 358 (M$^+$, 92.4), 340 (52), 326 (21), 325 (17), 285 (22), 281 (100), 280 (48), 265 (27), 253 (20), 227 (19), 165 (17), 141 (22), 128 (26), 115 (34).

HRMS: Calcd for C$_{21}$H$_{26}$O$_5$: 358.1780. Found: 358.1780.

C(3β)-OH epimer 218:

$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$ 5.16 (s(br), 1H, H8), 4.36 (dddd, 1H, $^3$J$_{3,OH}$ = 6.5 Hz, $^3$J$_{3,3\alpha}$ = 5.3 Hz, $^3$J$_{3,2\beta}$ = 3.5 Hz, $^3$J$_{3,2\alpha}$ = 2.6 Hz, H3), 3.70 (s, 3H, 7-OMe), 3.57 (s, 3H,
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-\textit{CO}_2\textit{Me}), 3.19 \text{ (m, 1H, H10b)}, 3.07 \text{ (dd, 1H, } 3J_{3\alpha,10b} = 7.9 \text{ Hz, } 3J_{3\alpha,3} = 5.3 \text{ Hz, H3a)}, \\
2.92 \text{ (dd, 1H, } 2J_{6,6'} = 12.6 \text{ Hz, } 4J_{6,8} = 2.1 \text{ Hz, H6)}, 2.68-2.33 \text{ (m, 3H, H9, H9', H10)}, \\
2.46 \text{ (s(br), 3H, 5-Me)}, 2.32 \text{ (ddq, 1H, } 3J_{1,2\alpha} = 11.4 \text{ Hz, } 3J_{1,\text{Me}} = 7.0 \text{ Hz, } 3J_{1,2\beta} = 3.8 \\
\text{Hz, H1)}, 2.24 \text{ (d(br), 1H, } 2J_{6',6} = 12.6 \text{ Hz, H6'}), 1.76 \text{ (m, 1H, H10')}, 1.76 \text{ (m, 1H, H2a), 1.67} \\
\text{ (ddd, 1H, } 2J_{2\beta,2\alpha} = 13.9 \text{ Hz, } 3J_{2\beta,1} = 3.8 \text{ Hz, } 3J_{2\beta,3} = 3.5 \text{ Hz, H2b)}, 1.36 \text{ (d,} \\
1\text{H, } 3J_{\text{OH},3} = 6.5 \text{ Hz, 3-OH)}, 0.98 \text{ (d, 3H, } 3J_{\text{Me},1} = 7.0 \text{ Hz, 1-Me}).

^{13}\text{C NMR (CDCl}_3, 300 \text{ MHz)}, \delta 208.3 \text{ (C4), 176.1} \text{ (-CO}_2\text{Me), 147.1} \text{ (C7), 137.5} \text{ (C5),} \\
135.0, 132.6, 129.4 \text{ (C4a, C8a, C10c), 99.0} \text{ (C8), 67.9} \text{ (C3), 56.0} \text{ (7-OMe), 54.2} \text{ (C3a),} \\
51.4 \text{ (-CO}_2\text{Me), 45.8} \text{ (C10a), 42.0} \text{ (C6), 40.4} \text{ (C10b), 36.6} \text{ (C2), 27.3,} \text{ 26.6} \text{ (C9, C10),} \\
22.3 \text{ (C1), 20.8} \text{ (5-Me), 16.4} \text{ (1-Me).}

\textit{Methyl (1a,3a,3\alpha\alpha,4\beta,10\alpha\alpha)-2,3,3a,4,6,9,10,10b-Octahydro-3,4-
\textit{dihydroxy-7-methoxy-1,5-dimethylcyclohept[bc]acenaphthylene-10\alpha(1H)-}
carboxylate 202.}

\begin{align*}
\text{MeO} & \quad \text{CO}_2\text{Me} \\
\text{MeO} & \quad \text{NaBH}_4 \\
\text{EtOH, r.t.} & \quad \text{EtOH, r.t.}
\end{align*}

A solution of the hydroxyketone 69 (126 mg, 0.352 mmol) and a catalytic amount (ca. 5 mg) of CeCl\textsubscript{3}.H\textsubscript{2}O in MeOH (5 mL) were cooled to 0°C and NaBH\textsubscript{4} (20 mg) was added. After 10 minutes, the solution was diluted with 0.1\textit{M} HCl and extracted with ether. The combined ether extracts were washed with water and brine, and dried over MgSO\textsubscript{4}. Evaporation of solvent afforded the diol 202 as a colourless foam (127 mg, 100%), which was used without further purification.
$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$ 5.03 (dd(br), 1H, $^3J_{4,3a} = 6.8$ Hz, $^3J_{4,OH} = 5.3$ Hz, H4), 4.93 (s(br), 1H, H8), 3.71 (s, 3H, 7-OMe), 3.61 (m, 1H, H3), 3.55 (s, 3H, -CO$_2$Me), 3.20 (d(br), 1H, $^3J_{OH,3} = 2.6$ Hz, 3-OH), $^2$H, 1H, $^3J_{10b,3a} = 7$Hz, H10b), $^2$H, 1H, $^3J_{3a,3} = 9.8$ Hz, $^3J_{3a,10b} = 7$ Hz, $^3J_{3a,4} = 6.8$ Hz, H3a), 2.68 (d(br), 1H, $^3J_{OH,4} = 5.3$ Hz, H3a), 2.63 (dd, 1H, $^2J_{6,6'} = 13.6$ Hz, $^2J_{6,8} = 2.2$ Hz, H6), 2.50 (d(br), 1H, $^2J_{6,6'} = 13.6$ Hz, H6'), 2.44-2.12 (m, 3H, H9a, H9b, H10a), 2.09 (s(br), 3H, 5-Me), 1.86 (ddq, 1H, $^3J_{1,2'} = 8.1$ Hz, $^3J_{1,Me} = 6.9$ Hz, $^3J_{1,2} = 5.6$ Hz, H1), 1.76-1.52 (m, 3H, H2, H10$\beta$), 0.94 (d, 3H, $^3J_{Me,1} = 6.9$ Hz, 1-Me).

$^{13}$C NMR (CDCl$_3$, 300 MHz), $\delta$ 176.4 (-CO$_2$Me), 149.6 (C7), 136.0, 132.2, 129.6, 128.1 (C4a, C5, C8a, C10c), 97.7 (C8), 75.0 (C4), 68.9 (C3), 55.5 (7-OMe), 51.3 (-CO$_2$Me), 50.0 (C3a), 46.2 (C10a), 44.6 (C10b), 40.0 (C6), 37.1 (C2), 28.5 (C1), 26.9 (C9$^*$), 26.6 (C10$^*$), 21.2 (5-Me), 16.4 (1-Me).

IR (CHCl$_3$, cm$^{-1}$) 3660-3200(br) (O-H str), 2960 (C-H str), 1720(s) (C=O str), 1640 (C=C str), 1585 (C=C str), 1080 (C-O str), 910 (C-H oop bend).

MS, m/z (relative intensity, %) 361 (M$^+$+1, 7.2), 360 (M$^+$, 29.6), 342 (37), 283 (18), 282 (10), 281 (11), 269 (13), 267 (19), 265 (12), 239 (12), 165 (11), 148 (22), 141 (15), 128 (15), 115 (17), 91 (24).

HRMS: Calcd for C$_{21}$H$_{28}$O$_5$: 360.1937. Found: 360.1936.
(1α,3αα,10α,10αβ,10ββ)-3α,5,8,10,10α,10β-Hexahydro-10-hydroxy-7-methoxy-9,11-dimethyl-1,3α-ethano-1H-cyclohept[3,4]indeno[1,7-cd]pyran-3(4H)-one 43.

A solution of the diol 202 (20 mg, 55 µmol) and anhydrous K₂CO₃ (5 mg) in dry MeOH (3 mL) was heated at reflux for 4 h. The cooled reaction mixture was diluted with water, then extracted with ether, washed with water and brine, and dried over MgSO₄. Removal of solvent in vacuo afforded a 1:3 mixture of the desired lactone 43 and unreacted starting material as a yellow oil. Flash chromatography (25% ethyl acetate in pentane) gave clean lactone as a pale yellow oil (4 mg, 22%).

¹H NMR (CDCl₃, 500 MHz), δ 5.30 (s(br), 1H, H₆), 5.10 (dd, 1H, ³J₁₀,₁₀α = 6.2 Hz, ³J₁₀,OH = 4.6 Hz,H₁₀), 4.84 (m, 1H, H₁), 3.60 (s, 3H, 7-OMe), 2.98 (dddd, 1H, ³J₁₀α,₁₀β = 11.9 Hz, ³J₁₀α,₁₀ = 6.2 Hz, ³J₁₀α,₁ = 4.6 Hz, ⁴J₁₀α,₁₂(pro-S) = 1.5 Hz, H₁₀α), 2.93 (d(br), 1H, ³J₁₀β,₁₀α = 11.9 Hz, H₁₀β), 2.79 (dd, 1H, ³J₈,₈ = 13.1 Hz, ³J₈,₆ = 2.1 Hz, H₈), 2.78 (ddd, 1H, ³J₁₂,₁₂ = 14.2 Hz, ³J₁₂,₁₁ = 10.1 Hz, ³J₁₂,₁ = 2.1 Hz, pro-R H₁₂), 2.60 (dd(br), 1H, ³J₅,₅ = 18.1 Hz, ³J₅,₄β = 7.7 Hz, H₅), 2.38 (ddd(br) ³J₅',₅ = 18.1 Hz, ³J₅',₄β = 12.6 Hz, ³J₅',₄α = 7.3 Hz, H₅'), 2.25 (d(br), ³J₈,₈ = 13.1 Hz, H₈'), 2.22 (m, 1H, H₁₁), 2.19 (dd(br), 1H, ³J₄α,₄β = 14.2 Hz, ³J₄α,₅ = 7.3 Hz, H₄α), 2.02 (s, 3H, 9-Me), 1.82 (ddd, 1H, ³J₄β,₄α = 14.2 Hz, ³J₄β,₅ = 12.6 Hz, ³J₄β,₅ = 7.7 Hz, H₄β), 1.37 (ddd, ³J₌₂',₁₂ = 14.2 Hz, ³J₁₂',₁₁ = 7.9 Hz, ³J₁₂',₁ = 3.3 Hz, ³J₁₂',₁₀α = 1.5 Hz, pro-S H₁₂), 1.19 (d, 1H, ³J₈H₁₀ = 4.6 Hz, 10-OH), 0.96 (d, 3H, ³J₉Me₁₁ = 7.0 Hz, 11-Me).
\(^{13}\)C NMR (CDCl\(_3\), 300 MHz), \(\delta\) 178.3 (C3), 149.3 (C7), 140.6, 131.5, 129.0, 123.7 (C5a, C9, C9a, C10c), 98.8 (C6), 78.1 (C1), 72.2 (C10), 55.6 (7-OMe), 46.2 (C10a), 43.7 (C3a), 42.2 (C10b), 39.5 (C8), 29.5 (C11), 28.0 (C5), 24.1 (C12), 23.4 (C4), 20.4 (9-Me), 18.7 (12-Me).

MS, \(m/z\) (relative intensity, %) 329 (M\(^+\)+1, 8.1), 328 (M\(^+\), 39.6), 327 (17), 314 (3), 313 (15), 297 (2), 269 (3), 209 (8), 149 (29), 133 (10), 119 (20), 118 (12), 105 (47), 91 (100).

HRMS: Calcd for C\(_{20}\)H\(_{24}\)O\(_4\): 328.1672. Found: 328.1675.
CHAPTER 6
EXPERIMENTAL

Methyl (1'α,4β,5β)-3',4',4',5-Tetrahydro-5-(hydroxymethyl)-6'-methoxy-4-methyl-2-oxospiro[furan-3(2H),2'(1'H)-naphthalene]-1'-acetate 235.

A solution of the olefin 172 (270 mg, 0.78 mmol) and NMMO (100 mg) in acetone/t-butanol (10:1, 20 mL) was cooled to -10°C and OsO₄ (1 large crystal) was added. The reaction mixture was allowed to warm to room temperature over 12 h and was then diluted with ether, washed with water and brine, and dried over MgSO₄. Concentration in vacuo followed by flash chromatography afforded pure lactone 235 (230 mg, 85%) as a white crystalline solid.

1H NMR (CDCl₃, 300 MHz) δ 6.96 (d, 1H, 3J₈',₇' = 8.6 Hz, H₈'), 6.69 (dd, 1H, 3J₁₁',₅' = 8.6 Hz, H₇'), 3.76 (s, 3H, 6'-OMe), 3.67 (s, 3H, 9'-C(hMe), 3.61 (m, 1H, H₁'), 3.61 - 3.54 (m, 2H, H₁', H₆), 2.97 - 2.78 (m, 2H, H₄'), 2.74-2.58 (m, 2H, H₉', H₉''), 2.46 (dq, 1H, 3J₄,₅ = 10 Hz, 3J₄,₆Me = 6.8 Hz, H₄), 2.01 - 1.96 (m, 2H, H₃'), 0.70 (d, 3H, 3fMe, 4-Me).

13C NMR (CDCl₃, 300 MHz) δ 179.6 (C2), 172.6 (-CO₂Me), 158.0 (C₆'), 129.5 (C₄'α), 127.4 (C₈'), 127.3 (C₈'a), 112.9 (C₅')*, 111.8 (C₇')*, 83.1 (C₅), 61.1 (C₆), 55.0 (6'-OMe), 51.9 (-CO₂Me), 48.9 (C₂'), 39.3 (C₁'), 36.6 (C₉'), 36.5 (C₄), 26.2 (C₄')†, 23.3 (C₃')†, 11.7 (4-Me).
IR (CHCl₃, cm⁻¹) 3580-3300 (s, br) (O-H str), 2950 (s) (C-H str), 1765 (s) (C=O str, lactone), 1730 (s) (C=O str, ester), 1610 (Ar C=C str), 1505, 1170 (s) (C-O str), 1040 (s) (C-O str).

MS, m/e (relative intensity, %) 348 (M+, 46), 288 (100), 276 (52), 260 (56), 216 (59), 201 (47), 187 (76), 175 (52), 174 (58), 173 (66), 171 (55), 115 (55).

ANALYSIS: Calcd for C₁₇H₂₀O₃: C, 65.50; H, 6.94.
Found: C, 65.60; H, 7.21.
REFERENCES


7. M. G. Banwell, private communication.


26. A relevant example concerns the isolation of taxol and the consequent affect on the environment: "The most recent harvest, which requires sacrifice of ca. 12 000 trees to obtain ca. 60 000 pounds of bark and 2.5 Kg of taxol, threatens the survival of the pacific yew and its habitat, the virgin rainforest, and is a subject of considerable enviromental concern." (ref. 5).

27. CRC Handbook of Terpenoids, CRC Press, Vol IV.


58. F. W. Russkamp, unpublished results.
80. A. C. Willis, L. N. Mander and D. H. Rogers, unpublished results.
101. V. Choi, 1985, unpublished results.


113. L. N. Mander, unpublished results.


135. The dppePt(OTf)$_2$ complex was kindly provided by Dr Hans Militzer. A recipe is provide below.

   **DppePtMe$_2$:** dppe (1.79 g, 4.5 mmol) was added to a solution of CODPtMe$_2$\textsuperscript{136} (1.5 g, 4.5 mmol) in dry CH$_2$Cl$_2$ (30 mL) and was stirred at room temperature for 30 min, and then at reflux for 1 h. Hexane was added and the resulting precipitate filtered and dried *in vacuo* (>95% yield).

   **DppePt(OTf)$_2$:** triflic acid (543 mL, 6.14 mmol) was added dropwise to a solution of the dppePtMe$_2$ (1.915 g, 3.07 mmol) in CH$_2$Cl$_2$ at -78°C under Ar. The solution was allowed to heat to room temperature over 2 h. Ether was then added and the product was isolated by removing the solvents by decantation and drying under high vacuum (*ca.* 100%).