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.

James M. Hook
ACKNOWLEDGEMENTS

I would like to thank Dr. L.N. Mander for his advice and encouragement during his supervision of this research.

I am also grateful to Professor R.W. Rickards for helpful discussions, to Val Richardson for valuable technical assistance, and to Dr. Mike Woolias and Rudolph Urech for their assistance in proof-reading the manuscript.

Grateful acknowledgement is made of the support provided by the A.N.U. Ph.D. Scholarship.

Special thanks are due to Vicki for her help in compiling this work, and to my parents, for their long-standing support and interest.
SUMMARY

This thesis describes the reductive alkylation of 2,5-dimethoxybenzoic acid 24, and the application of this reaction to an ABC+D approach to gibberellin synthesis. The results are presented in six chapters.

In Chapter 1, the reductive methylation of the benzoic acid 24 is described. The outcome of this reaction demonstrates that the lithium-ammonia reduction of the benzoic acid 24 proceeds via the dianion 29, with no loss of the 2-methoxy group. The significance of this is discussed in relation to the behaviour of other methoxybenzoic acids under similar conditions.

Chapter 2 describes a short and efficient synthesis of hydrofluorene derivatives, based on the alkylation of the dianion 29 with benzyl bromides. Cyclisation of the alkylated acids 36 and 46 with 85% sulphuric acid leads to the hydrofluorenones 42 and 44 respectively, whereas cyclisation of these acids with boron trifluoride etherate leads to the angularly substituted hydrofluorenes 43 and 50 respectively. The possible pathways of these cyclisations are considered. Attempts to prepare the unsubstituted hydrofluorenone 58 define a limitation to this approach.
In Chapter 3, an equally efficient synthesis of hydrophenanthrene derivatives, based on the alkylation of the dianion 29 with 2-arylethyl iodides, is presented.

Chapter 4 deals with the elaboration of the hydro­fluorenone 44 to the gibbane derivative 15. Studies of the B,C-ring fusion in this compound 15, suggest that the trans configuration is more accessible than the desired cis configuration. This particular route, therefore, appeared to be unsatisfactory for gibberellin synthesis.

Chapter 5 describes the adaption of the strategy developed in Chapter 2, to the synthesis of 8-methoxy­carbonyl-hydrofluorenone. Although the cyclisations of the alkylated acids 106 and 114 were unsuccessful, the cyclisation of the alkylated acid 126 gave the hydro­fluorenone 127, and its olefinic isomer 128, in good yield.

Finally, in Chapter 6, the elaboration of the hydro­fluorenone 127 and 128 to the gibbane derivative 136 is described, together with some preliminary investigations directed towards the introduction of the B-ring carboxyl group into the derivatives 137 and 138.
## CONTENTS

**INTRODUCTION**

**RESULTS AND DISCUSSION**

<table>
<thead>
<tr>
<th>CHAPTER 1</th>
<th>The reductive methylation of 2,5-dimethoxybenzoic acid 24.</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAPTER 2</td>
<td>2.1 Preparation of the hydrofluorenone 42 and the angularly substituted derivative 43.</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>2.2 Preparation of the hydrofluorenone 44 and 49 and 50.</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>2.3 A limitation to this approach.</td>
<td>50</td>
</tr>
<tr>
<td>CHAPTER 3</td>
<td>3.1 Preparation of the hydrophenanthrenones 60 and 64, and the angularly substituted derivative 65.</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>3.2 Preparation of the hydrophenanthrene 68.</td>
<td>61</td>
</tr>
<tr>
<td>CHAPTER 4</td>
<td>4.1 Preparation of the tetracyclic ketone 15.</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>4.2 Studies of the B,C-ring fusion in the ketone 15.</td>
<td>72</td>
</tr>
<tr>
<td>CHAPTER 5</td>
<td>5.1 Alkylation of the dianion 29 with methyl 2-bromomethylbenzoate 95.</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>5.2 Attempts to prepare the hydrofluorenone 108.</td>
<td>96</td>
</tr>
</tbody>
</table>
5.3 Attempts to prepare the hydrofluorenone 116.

5.4 Preparation of the hydrofluorenones 127 and 128.

CHAPTER 6 Preparation of the tetracyclic compound 136 and some experiments directed towards the introduction of the B-ring carboxyl group.

EXPERIMENTAL

General Topics 119
General Procedures 122
Notes on Nomenclature 123
CHAPTER 1 124
CHAPTER 2 126
CHAPTER 3 142
CHAPTER 4 147
CHAPTER 5 162
CHAPTER 6 183
REFERENCES 194
INTRODUCTION

It is quite remarkable that the observation of some "falsely growing rice seedlings" in a Japanese paddy field over eighty years ago could have led to the discovery of compounds of central importance in the plant kingdom. These compounds, the gibberellins, were first isolated in the late 1950s from the fungus, Gibberella fujikuroi, which infected the rice, and were shown to be responsible for the anomalous growth. Extensive investigations have since revealed that the gibberellins play a fundamental role in regulating plant growth, and when applied exogenously, induce dramatic changes in plant physiology. As a consequence, several of the more active gibberellins are produced commercially by fermentation of G. fujikuroi, and are widely used in agriculture and horticulture for controlling the life cycles of economic crops.

More than fifty gibberellins have so far been isolated from various plant and fungal sources. They are classified as diterpenoids and are structurally based on the octa-gibberellane carbocyclic skeleton.

1. This is a translation of the name "hakka-nai" given to the disease which infected the rice.
It is quite remarkable that the observation of some "foolishly growing rice seedlings"* in a Japanese paddy field over eighty years ago could have led to the discovery of compounds of central importance in the plant kingdom. These compounds, the gibberellins, were first isolated in the late 1930's from the fungus, *Gibberella fujikuroi*, which infected the rice, and were shown to be responsible for the anomalous growth. Extensive investigations have since revealed that the gibberellins play a fundamental role in regulating plant growth, and when applied exogenously, induce dramatic changes in plant physiology. As a consequence, several of the more active gibberellins are produced commercially by fermentation of *G. fujikuroi*, and are used widely in agriculture and horticulture for controlling the life cycles of economic crops.

More than fifty gibberellins have so far been isolated from various plant and fungal sources. They are classified as diterpenes and are structurally based on the ent-gibberellane carbocyclic skeleton.

---

* This is a translation of the name "baka-nae" given to the disease which infected the rice.
The biosynthesis of the gibberellins is known in considerable detail.\(^8\) Oxidative modification of \textit{ent}-kaurene \(2\), and contraction of the B-ring affords \(C_{20}\) gibberellins, from which \(C_{19}\) gibberellins are derived by loss of the C-20 carbon atom\(^8\) (Scheme 1).

The total synthesis of these complex natural products, of which gibberellic acid (GA\(_3\)), \(3\),\(^9\) is the ultimate target, is a task both challenging and formidable. The difficulties arise from the dense array of highly labile functional groups, together with at least seven asymmetric centres embedded in the interesting tetracyclic framework of, for example, \(3\).

\[
\begin{align*}
&\text{O} \\
&\text{CO} \\
&\text{HO} \\
&\text{CO}_2\text{H}
\end{align*}
\]

Efforts directed towards the total synthesis of gibberellic acid \(3\),\(^{10}\) as with work on other biologically active molecules such as the steroids,\(^{11}\) prostaglandins\(^{12}\) and most recently the anthracyclines,\(^{13}\) have made an enormous
In principle, the total synthesis of C₁₉ gibberellins could be achieved via a C₂₀ gibberellin intermediate along biomimetic lines, though by selective elision of the C₂₀ carbon atom 14, 15 to form the C₁₉ compound. Scheme I illustrates a typical intermediate in these studies: hydrophenanthrene nucleus, which has been used to reduce the number of stereochemical problems prior to formation of the gibberellin structure. The synthesis has now been completed with the use of novel compounds 16, 17, or in a formal sense, it has been improved.

Several conceptually more direct approaches for

Scheme I
contribution to the reservoir of synthetic method and design. In this present work, attention has been primarily focussed on an efficient synthesis of tetracyclic intermediates suitable for elaboration to 13-hydroxy C\textsubscript{19} gibberellins such as GA\textsubscript{3},\textsuperscript{3}. In addition, it is expected that the strategies developed in this work will also find application to the synthesis of other carbocyclic compounds.

In principle, the total synthesis of C\textsubscript{19} gibberellins could be achieved via a C\textsubscript{20} gibberellin intermediate along biomimetic lines, that is, by selective elimination of the C-20 carbon atom.\textsuperscript{14,15} As an illustration, the conversion of GA\textsubscript{13} to GA\textsubscript{4} is shown in Scheme 2. Several C\textsubscript{20} gibberellins have been prepared,\textsuperscript{10} for example, GA\textsubscript{12}, GA\textsubscript{15}, GA\textsubscript{17},\textsuperscript{18} GA\textsubscript{37}.\textsuperscript{18} A typical intermediate in these studies is the hydrophenanthrene nucleus, which has been used to reduce the number of stereochemical problems, prior to formation of the gibberellin skeleton.\textsuperscript{17} However, these syntheses have only been completed with the use of relay compounds,\textsuperscript{16,18} or in a formal sense, with the exception of the synthesis of GA\textsubscript{15} by Nagata and co-workers,\textsuperscript{17} which required nearly forty steps. Moreover, the strategies employed do not appear to be sufficiently flexible to allow incorporation of the 13-hydroxyl group. Thus, it would seem that the synthesis of C\textsubscript{20} gibberellins is in itself, a monumental task and unsuitable for the present purpose.

Several conceptually more direct approaches for

\textsuperscript{16,18} At no stage in these sequences was a resolution of totally synthetic material undertaken.
Assembling C₁₀ gibberellins have been devised. In the first of these, rapid entry to the hydroxyflavone nucleus bearing an aromatic C-ring is gained by a cycloaddition reaction (forming the A-ring) followed by intramolecular acylation of the subsequently derived anhydride (Scheme 3). The central carbonyl function is then formed by homologation of the C-6* ketone (Scheme 3). Addition of the Boring ac shown on the model substrate has also been reported (Scheme 4). But the product clearly requires further manipulation to arrive at the desired array of GA₄, 2. The substitution at C-3 is also lacking.

In an effort to synthesize GA₄, 2, it was decided to consider a synthesis via a keto acid in this paper. It has been shown that it undergoes aromatisation or rearrangement has long been known. In contrast, the C₆ portion of the molecule rearranges only under more forcing conditions. Hence, it would seem prudent to delay assembly of the A-ring until late in the synthetic sequence. This consideration may be dealt with either by adding the A-ring elements to a preformed B,C,D-unit or by constructing the gibberellin skeleton from a hydroxyflavone nucleus bearing an aromatic A-ring.

The numbering system of 1 will be used where indicated to assist correlation of synthetic structures with those of the gibberellins.
assembling \( \text{C}_{19} \) gibberellins have been devised. In the first of these, rapid entry to the hydrofluorene nucleus bearing an aromatic C-ring \( \text{4}_{19} \) is gained by a cycloaddition reaction (forming the A-ring) followed by intramolecular acylation of the subsequently derived anhydride \( \text{19} \) (Scheme 3). The central carboxyl function is then formed by homologation of the C-\( 6^* \) ketone \( \text{20} \) (Scheme 3). Addition of the D-ring as shown on the model substrate \( \text{5} \) has also been reported \( \text{21} \) (Scheme 4), but the product clearly requires further manipulation to arrive at the desired array of GA\(_3\), \( \text{3} \). Substitution at C-3 is also lacking.

An important consideration in a synthesis of GA\(_3\), \( \text{3} \), neglected in the previous example, is the chemical sensitivity of the A-ring of GA\(_3\), \( \text{3} \). The ease with which it undergoes aromatisation or rearrangement has long been known \( \text{22} \). In contrast, the C,D-portion of the molecule rearranges only under more forcing conditions \( \text{22} \). Hence, it would seem prudent to delay assembly of the A-ring until late in the synthetic sequence. This consideration may be dealt with either by adding the A-ring elements to a preformed B,C,D-unit \( \text{23} \) or by constructing the gibberellin skeleton from a hydrofluorene nucleus bearing an aromatic A-ring \( \text{24} \).

\* The numbering system of \( \text{1}^7 \) will be used where indicated, to assist correlation of synthetic structures with those of the gibberellins.
The recent report of the first total synthesis of \( \text{DA}_3 \) by Corey et al. serves as an outstanding example of the former approach. The key intermediate \( \text{CN} \) prepared by the distinct route was used to construct the 3,5-cyclization. The intramolecular cyclization of the diene 3 was not performed by the cyclization of the diene 5.

The synthesis of the pivotal intermediate \( \text{CN} \) required twenty-four steps (route a) and twenty-nine steps (route b) respectively.

The second approach, that of introducing an aromatic ring into the core molecule, is illustrated by the synthesis of the tolyl A-ring of \( \text{DA}_4 \) and the steroidal sesterpenes via spirocyclic lactones and amides.

The synthesis of these alkaloids was achieved through a lengthy and classical elaboration of the tolyl A-ring of \( \text{DA}_5 \) and was completed in a formal sense. Once again, the success of this approach in the total synthesis of \( \text{DA}_5 \) also points to the potential of the concept of an aromatic ring in the design of the synthetic approach.
The recent report* of the first total synthesis of GA₃, 3 by Corey * et al. ** serves as an outstanding example of the former approach. The key intermediate, 6 (R=H), prepared by two distinct routes, was used to construct the A-ring by an intramolecular cycloaddition reaction 6 (R=-COCH=CHCl) (Scheme 5). Subsequent manipulation of the diene 7, along previously disclosed lines, gave GA₃, 3. 25 The synthesis of the pivotal intermediate 6, however, required twenty-five (route a) and twenty-nine steps (route b), respectively.

The second approach, that of using an aromatic ring as an A-ring precursor in a hydrofluorene skeleton is illustrated by the synthesis† of GA₂, A₄, A₉ and A₁₀. 28 Proceeding via epigibberic acid 8, the synthesis of these gibberellins was achieved through a lengthy and classical elaboration of the tolyl A-ring of 8, and was completed in a formal sense. 28 Once again, its success

---

* This report appeared near the completion of the work in this thesis.
† At no stage does a resolution of totally synthetic material appear to have been performed. 28
The transformation of compound 7, as shown in Scheme 5, would be expected to give the natural stereochemistry at C-3 and C-9 when applied to the intermediate 10.
depended on the use of relay compounds, and is notable more for persistence and fortitude, than ingenuity. 28

A more elegant modification of this second approach demonstrates that the 2-methoxybenzoic acid moiety is a particularly attractive A-ring precursor30,31 (Scheme 6). In addition, the stereochemical outcome of such a transformation is controlled by the presence of a substituent at C-632 (Scheme 7).

Of central importance to this approach is the source of the C-6 carboxyl group. It may be derived from a C-6 ketone20 as previously mentioned, (Scheme 3) or, alternatively, by carboxylation of the benzylic anion 9, the generation of which, is assisted by the C-4 carbonyl function (Scheme 8; R=NHCH3,32 NHC2H5,33 OH,32 OCH3,34).

Although the tetracyclic intermediates 1033 and 1134 have been prepared, it would seem that only from 11 could the stereochemistry of the natural gibberellin 3 be secured.*

* The transformation shown in Scheme 7, would be expected32 to give the incorrect relative stereochemistry at C-4 and C-9 when applied to the intermediate 10.
It is worth noting here that, whilst the intermediate 11 could conceivably be transformed into a natural gibberellin (e.g. GA<sub>3</sub>), the overall strategy used does not appear to be compatible with incorporation of the 13-hydroxyl group.

Of the numerous methods available for construction of the C9-portion of GA<sub>3</sub>, acid-catalyzed cyclization of urethane dimers which in turn was provided by the diol 12 (Scheme 10).

The intermediate 9 provides a useful framework, the aromatic A-ring, and the cyclo[3.2.1]octane moiety together with the tertiary hydroxylated hydroxyl group, from which 13-hydroxylated gibberellins may be synthesized. In this way, the intermediate 9 can be converted into the skeleton of the tricyclic gibberellin 12. While 6 is readily available from the unsubstituted clavulane 10, the compound 12 is prepared in low yield and separated itself by a lengthy sequence of reactions.
It is worth noting here that, whilst the intermediate 11 could conceivably be transformed into a natural gibberellin (e.g. GA₄), the overall strategy used doesn't appear to be compatible with incorporation of the 13-hydroxyl group.

Of the numerous methods available for construction of the C,D-portion of GA₅, acid-catalysed cyclisation of unsaturated diazoketones, has particular merit: it leads directly to the bicyclo[3.2.1]octane system, provides a pro-C-16-keto function which may be readily homologated (e.g. a Wittig reaction) and is sufficiently flexible to incorporate the pro-C-13-hydroxyl group (Scheme 9). This strategy has been used for the preparation of a tetracyclic intermediate, from the diazoketone 14, which in turn was prepared from the β,γ-unsaturated ketone (Scheme 10).

The intermediate, provides the basic framework - the aromatic A-ring, and the bicyclo[3.2.1]octane moiety together with the tertiary bridgehead hydroxyl group - from which 13-hydroxy C₁₉ gibberellins such as may, in principle, be derived.

Problematical to this approach (Scheme 10) however, is the source of the tricyclic ketone 13. While it is readily available from the disubstituted fluorene 16, this compound is prepared in low yield from fluorene itself by a lengthy sequence of reactions.*

* This is still the case in spite of a recent modification.
Other potential routes to tricyclic ketones such as 15 would be either inefficient due to multi-step procedures involved or simply inflexible. The proposal aimed at overcoming these limitations is outlined in Scheme 11.

Scheme 9

12 \[ R = H, \text{CH}_3, \text{OR}' \]

Scheme 10

As the cycloaddition of 2-benzylcyclohexanesene, similar to 16 has been reported, the current problem remains to find a suitable operational equivalent to the 1,4-cyclohexadiene union 17.
Other potential routes to tricyclic ketones such as 14 would be either inefficient due to multi-step procedures involved, or simply inflexible. The proposal aimed at overcoming these limitations is outlined in Scheme 11.

As the cyclodehydration of 2-benzylcyclohexanones similar to 18 has been reported, the task that remains is to find a suitable operational equivalent to the 1,4-cyclohexadione anion 17.
It will be demonstrated in Chapter 1 that the lithium-ammonia reduction of 2,5-dimethoxybenzoic acid readily provides such an equivalent. The use of this reduction in realising the proposal outlined in Scheme 12, together with the synthesis of some angularly substituted hydrofluorene derivatives is presented in Chapter 2. In Chapter 3, this strategy is extended to a very short synthesis of hydrophenanthrenones:

The tetracyclic ketone, 15, seems well suited to the primary aim of this thesis for reasons already mentioned. Its successful elaboration hinges on producing the desired cis B,C-ring fusion, which could be achieved by a stereospecific reduction of the 9,11-double bond (see 15). Alternatively, the stereochemistry of this ring fusion could
conceivably be controlled by a base-catalysed process involving the tertiary hydroxyl group (Scheme 12).

![Scheme 12](image)

The feasibility of these suggestions using the ketone 15 is examined in Chapter 4. A more reliable sequence of reactions leading to the tetracyclic compound 15 is also presented.

The usefulness of the benzoic acid moiety as an A-ring precursor has been emphasised in the preceding discussion. The incorporation of a carboxyl group at pro-C-4 in the precursor 19, may in fact, lead to a more convergent synthesis of the target molecule, 3. In Chapter 5, it will be shown that the strategy outlined in Scheme 11 can be readily adapted to the synthesis of a pro-C-4 carbomethoxy derivative of the tricyclic ketone 19.

Finally, in Chapter 6, the preparation of a tetracyclic intermediate possessing all the necessary functionality for a stereospecific synthesis of 13-hydroxy C19 gibberellins such as GA3, 3, is described.
CHAPTER 1

The reductive methylation

of 2,5-dimethoxybenzoic acid 24.
In order to overcome the problems associated with the preparation of tricyclic ketones such as 19, an operational equivalent to the cyclohexa-1,4-dione anion 17 was required. Cyclohexa-1,4-dione 20 is obviously inappropriate for this purpose, since selectivity of anion formation could hardly be expected on such a substrate. The ketal ketone 21 (or the corresponding enamine 22) would ensure such selectivity, but the preparation of this compound 21 may in turn be complicated by the need to achieve selective ketalisation of cyclohexa-1,4-dione, 20.
The β-ketoester 23 circumvents the difficulties of using 20 or 21, and has been employed as an operational equivalent to 17. The preparation of 23 requires, however, four steps from furfural, and before this was undertaken a more direct approach based on the lithium-ammonia reduction of the commercially available 2,5-dimethoxybenzoic acid 24 was examined.

\[
\begin{align*}
23 & \quad 24 \\
R &= \text{CH}_3, \text{C}_2\text{H}_5
\end{align*}
\]

Scheme 13

The ionic transformation is referred to as reductive alkylation and was applied to 2- and 3-methoxybenzoic.
The metal-ammonia reduction of benzoic acid is known to proceed \textit{via} the dianion \(25\), which arises from the addition of two electrons and one proton to the ionised acid.\(^{48}\) If the reduction is conducted in the presence of a hydroxylic proton donor, for example ethanol, the dianion \(25\) simply protonates at C-1 affording the dihydro acid \(26\) (R=H).\(^{48}\) If, on the other hand, the reduction is carried out in the absence of a proton donor,\(^*\) then the dianion \(25\) may be alkylated \textit{in situ}, with for example, methyl iodide, to give the acid \(26\) (R=CH\(_3\)) (Scheme 13).\(^{48}\)

\begin{equation*}
\begin{array}{c}
\text{CO}_2\text{H} \quad \text{2M, H}^+ \quad \text{CO}_2^- \quad \text{R} \quad \text{CO}_2\text{H} \\
\text{25} \quad \text{26}
\end{array}
\end{equation*}

\textbf{Scheme 13}

The latter transformation is referred to as reductive alkylation,\(^{30,49}\) and when applied to 2- and 3-methoxybenzoic

\(^*\) Excluding the ammonia and the ammonium ions generated by the ionisation of the acid.
acids, it provides a particularly straightforward route to 2- and 3-alkylcyclohexenone derivatives, respectively. As an example, the reductive alkylation of the acid 27, followed by suitable processing of the alkylated intermediate, affords the 2-alkylcyclohexenones 28.

This example also serves to highlight a problem frequently encountered with the reductive alkylation of 2-methoxybenzoic acid and its derivatives: that is, partial or complete loss of the 2-methoxy group during the reduction step. In the case cited above, the low overall yields (27 → 28, c.30%) can be readily ascribed to this phenomenon, which will be discussed presently.

Chapman and Fitton have reported the reduction of 2,5-dimethoxybenzoic acid 24 in the presence of methanol.

* 4-methoxybenzoic acid loses its methoxy group completely, when reduced with metal-ammonia solutions.
Scheme 14
(Scheme 14; path $a$), and although they used the dihydrobenzoic acid, 30, for a different purpose, the hydrolysis and decarboxylation of this compound would be expected to give cyclohexa-1,4-dione 20 (Scheme 14). If the reduction of the benzoic acid 24 proceeds via the dianion 29 by analogy with the reduction of benzoic acid, then alkylation in situ (Scheme 14; path $b$), and suitable processing of the product 31 would lead to a very convenient preparation of 2-alkyl-cyclohexa-1,4-diones, 18 (cf. Scheme 11). Therefore, providing there was no loss of the 2-methoxy group during the reduction step, the dianion 29 would be a most suitable operational equivalent to the cyclohexa-1,4-dione anion 17.

The reductive alkylation was first attempted using methyl iodide as an alkylating agent, so as to simplify product analysis. In the event, the acid 24 consumed c. 2.5 equivalents of lithium before a deep blue colour* was obtained. Quenching with methyl iodide, followed by careful acidic work-up ($0^\circ$) afforded a single product in 77% yield.

Two features were immediately evident on examination of the $^1$H nuclear magnetic resonance (n.m.r.) spectrum of this product. Absorptions due to two vinyl protons ($\delta=4.68, t, J=4\text{Hz}; \delta=4.45, s$), and six methoxy protons ($\delta=3.54, s$), indicated beyond doubt that there was no loss of the 2-methoxy substituent. Signals associated with the product 32 expected from loss of the 2-methoxy group, ($\delta=5.7, s, 2H$)56

* Indicative of an excess of metal in the ammonia solution.55
were notably absent. Secondly, a singlet at higher field 
(δ=1.42,3H), indicated complete methylation at C-1. On the 
basis of this, and other evidence obtained from the Infra-red 
(I.r.) spectrum, the mass spectrum (m.s.) and analysis, the 
product is formulated as the alkylated acid 33.

In the course of this study of the reductive methylation 
of the acid 24, a reaction was discovered which opens up the 
possibility of distinguishing the two potential ketone 
functions (cf. the β-ketoester 23). Thus, when the reductive 
methylation was performed as described, and acidic work-up 
conducted without cooling, lactonisation onto C-5 occurred, 
affording the lactone 34 as the sole product (I.r.:1770cm⁻¹; 
¹H n.m.r.:δ=4.55,t,1H,δ=3.50,s,3H,δ=3.48,s,3H).

\[ \text{CH}_3\text{O} \quad \text{CH}_3 \]
\[ \text{CO}_2\text{H} \quad \text{CO}_2\text{H} \]
\[ \text{OCH}_3 \quad \text{OCH}_3 \]

32 33

\[ \text{CH}_3\text{O} \quad \text{CH}_3 \]
\[ \text{CO} \quad \text{O} \]
\[ \text{OCH}_3 \]

34
Although further reactions with the lactone 34 were not explored, it seems highly likely that operations at C-2 could be performed selectively (e.g. hydrogenation or hydrolysis) without disturbing the functionality at C-5.

Since the complete retention of the 2-methoxy group during the reductive alkylation of 2,5-dimethoxybenzoic acid is in marked contrast with the behaviour of other 2-methoxybenzoic acid derivatives under similar conditions, it may be worthwhile considering some aspects of this behaviour a little more closely.

The outcome of the reduction of methoxybenzoic acids might at first sight be expected to be determined by the independent directing effects\(^{57}\) of the carboxyl group (1,4-reduction) and the methoxy group (2,5-reduction). In 4-methoxybenzoic acid, for example, the directing effects of these two substituents are diametrically opposed and the reduction of this nucleus may therefore give rise to products resulting from 1,4- and 2,5-reduction. Experimentally the course of this reduction is dominated solely by the carboxyl group, (1,4-reduction) with complete loss of the methoxy group.* This loss may be formulated as an elimination of the methoxide ion from one of the anionic intermediates, in

* Complete loss of the methoxy substituent during the reductive alkylation of 4-methoxyacetophenone has also been observed.\(^{58}\)
which the negative charge is favourably localised over C-1 and C-4 (# = one electron, two electrons or a proton).

With 2-methoxybenzoic acid, the independent directing effects of the two substituents do not appear to be in conflict as in the previous case, and localisation of the negative charge over C-1 and C-4 seems quite compatible with both groups. On this basis, the reductive alkylation of might be expected to proceed without any complications. The observation of 70% cleavage of the methoxy group therefore, appears to be quite incongruous.

In an effort to account for this incongruity, Birch and Slobbe have suggested that the radical dianion formed by the addition of one electron to the aromatic ring is too unstable, and without rapid protonation by a
hydroxylic proton source, it loses the methoxide ion either by path b or path c* (Scheme 15).

House et al.\textsuperscript{32} have suggested more specifically, that the radical dianion X (G=H), protonates preferentially at C-2 (path b),\textsuperscript{†} and, after further reduction of the resultant anion Z (G=H), the methoxide ion is eliminated with concomitant re-aromatisation.

Both of these suggestions imply therefore, that the loss of the methoxy group is due to localisation of the negative charge at C-2 and C-5, apparently quite at variance with the independent directing effects of the two substituents.

When this rather rudimentary method of analysis is applied to 2,5-dimethoxybenzoic acid 24, the independent directing effects of the three substituents again appear to be quite compatible with 1,4-reduction, as indeed was found to be the case (\textit{vide supra}). The marked contrast of these results may be due to the effect of the C-5 methoxy group on the charge distribution of the radical dianion X (G=OCH\textsubscript{3}). Since a methoxy substituent tends to destabilize carbanion formation on the carbon to which it is attached,\textsuperscript{‡+59} the effect of the C-5 methoxy group may be to favour the contribution from the resonance structure X\textsubscript{1} more than from

\* In Scheme 15, path c seems unlikely since the \(\pi\)-orbitals and the carbon-oxygen bond would be expected to be orthogonal, and therefore provide no overlap for bond fission.

\textsuperscript{†} Protonation at C-4 (Scheme 15, path a) would inevitably lead to retention of the methoxy group, on the assumption that protonation at this position is irreversible.\textsuperscript{48}

\textsuperscript{‡+} Hine \textit{et al.} have suggested that this is due to unfavourable interactions between the unshared electron pairs on the oxygen atom, and that of the developing carbanion.\textsuperscript{59}
Scheme 15

At and X3 (O-CH3), thereby leading to a 3-reduction by path e and no loss of the 3-etheroxy group (see Scheme 15). Thus, it would appear that some support for the suggestions of Bines, and Birch and Gloebe provided by exchanging O-H for O-CH3.

Interestingly, the reductive alkylation of 3-anhydro-2-methoxybenzoic acid results in less than 40% loss of the 2-methoxy group. An alkyl group also leads to the formation of carbon dioxide, the effect of an alkyl group at C-2.

In most of the examples cited above, the addition of potassium for the reduction of the aromatics results in a significantly smaller percentage of the methoxy group. Thus, reductive alkylation of 3-anhydro-2-methoxybenzoic acid leads to a loss of the 40% of the methoxy group, but there is no loss at all.

Another important factor connected with the reductive alkylation of the 3-methoxy group is the effect of the potassium source available during the reduction step. In all of the examples cited above, the only potassium source available was the ammonium ions generated by isopinocamphor or potassium tert-butoxide. The reaction of the anhydride with potassium tert-butoxide or sodium prior to reductive alkylation leads to complete.
X_2 and X_3 (G=OCH_3), thereby leading to 1,4-reduction by path a and no loss of the 2-methoxy group (see Scheme 15). Thus, it would appear that some support for the suggestions of House, and Birch and Slobbe, is provided by exchanging G=H for G=OCH_3.

Interestingly, the reductive alkylation of 5-alkyl-2-methoxybenzoic acids results in less than 40% loss of the 2-methoxy group. As alkyl groups also tend to destabilize carbanions, the effect of an alkyl group at C-5 may be similar to the effect described for a methoxy group at C-5.

In most of the examples cited above, lithium was used for the reduction of the aromatic ring. The use of sodium or potassium for the reduction step also results in the cleavage of a significantly smaller percentage of the 2-methoxy group. Thus, reductive alkylation of 27 using sodium leads to the loss of 40% of the methoxy group, while the use of potassium results in no loss at all.

Another important factor connected with the variable loss of the 2-methoxy group is the effect of the proton source available during the reduction step. In all of the examples cited above, the only proton source available was the ammonium ions generated by ionisation of the acid, and the ammonia itself. Mander and Woolias have shown that reaction of the acid 27 with potassium t-butoxide or sodium amide prior to reductive alkylation leads to complete

* Loewenthal et al. used sodium.
† These reactions effectively convert the ammonium ions that would be generated by the ionisation of the acid in ammonia, to the weaker proton donors, t-butanol and ammonia, respectively.
retention of the methoxy group, irrespective of the metal used (lithium, sodium or potassium). This result strongly implicates the ammonium ions as being intimately involved with the cleavage of the methoxy group.

In the absence of additional data, it is difficult to arrive at a definite conclusion as to the actual process(es) involved in the variable loss of the 2-methoxy group. Hopefully, the factors highlighted in the foregoing discussion - the effects of a substituent para to the methoxy group, the metal used for the reduction, and the proton source available - will provide a foundation on which a systematic study of this phenomenon could be based.
CHAPTER 2

2.1 Preparation of the hydrofluorenone 42 and the angularly substituted derivative 43.

2.2 Preparation of the hydrofluorenone 44 and the angularly substituted derivatives 49 and 50.

2.3 A limitation to this approach.
In the preceding chapter it was established that the lithium-ammonia reduction of 2,5-dimethoxybenzoic acid 24, provides a readily accessible operational equivalent to the cyclohexa-1,4-dione anion 17, that is, the dianion 29.

The next task was the exploitation of this reduction for the synthesis of hydrofluorenones as exemplified by 19. At its very base, the proposal outlined in Scheme 11, has the potential for overcoming the limitations inherent in other possible routes to these compounds.
The methyl vinyl ketone annulation of $\beta$-indanones, for example, may be complicated by isomeric mixtures resulting from reaction at the two equivalent sites $\alpha$ to the carbonyl group. The more recently reported annulation of cycloalkanones, may be applicable to $\alpha$-indanones, but involves a six-step sequence. Similarly, the classical route from fluorene, requires a multi-step sequence, the scope of which could be broadened only at the expense of efficiency. A further limitation to a possible route using the $\beta$-ketoester is that the C-2 anion of 23 is less reactive than the dianion 29.

\[
\begin{align*}
\text{R} & = \text{CH}_3, \text{C}_2\text{H}_5 \\
\end{align*}
\]

* This annulation sequence has been successfully applied to $\alpha$-tetralones.
2.1 As Scheme 11 suggests, the synthesis of the hydrofluorenone 19 entails alkylation of the dianion 29 with a benzyl halide, followed by acid-promoted cyclodehydration of the subsequently derived 2-benzylcyclohexa-1,4-dione 18. To this end, alkylation with 3,5-dimethoxybenzyl bromide 35, was chosen initially for a number of reasons. The methoxy groups are located so as to provide maximum activation for the cyclodehydration, and to eliminate any possibility of isomeric mixtures that might result from this step.\textsuperscript{38,43b,63} Also, this particular aromatic nucleus could allow, at some later stage in a projected synthesis of the gibberellins, selective functionalisation at the C-4* position.\textsuperscript{†}

\* Gibberellin numbering.
\† The orcinol derivative, A, formylates exclusively at C-2,\textsuperscript{64} with the Vilsmeier reagent.

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{CH}_3\text{O} \\
4 & \quad 2 \quad R \\
\text{CH}_3\text{O} & \quad \text{CH}_3\text{O} \\
2 & \quad \text{CHO} \quad R \\
\end{align*}
\]

A

\[
R = \text{CH}_2\text{OAc} = (\text{CH}_2)_3\text{CO}_2\text{CH}_3
\]
Alkylation of the dianion 29, in an ammonia-tetrahydrofuran solution with the bromide 35, furnished, on acidic work-up, the acid 36 in 68% yield. In accordance with the synthetic plan, efforts were first directed at transforming the acid 36 into the corresponding diketone. This apparently straightforward step proved to be unexpectedly troublesome, and as will be shown, was unnecessary for the task at hand. It does however, provide some insight into the cyclodehydration step.

The acid 36 was exposed to mildly acidic conditions (1NHCl, acetone, 25°) in order to hydrolyse the enol ether functions and remove the carboxyl group (β-ketoacid). The sole product isolated in 90% yield was not the expected diketone but a compound with the properties of a carboxylic acid (soluble in aq. NaHCO₃; I.r.: 2600, 1720 cm⁻¹). The ¹H n.m.r. and I.r. data suggested that cyclisation had
already occurred without dehydration (δ=6.34,1H and δ=6.20, 1H; 3520 cm⁻¹). The mass spectrum, curiously enough, showed no molecular ion corresponding to the formula, C₁₆H₁₈O₆, obtained by analysis, and, in addition, the product rapidly evolved a gas at its melting point (c. 170°C). Both these observations strongly suggested the loss of carbon dioxide.

In itself, this evidence does not readily distinguish the two isomeric acids 37 (R=CO₂H) and 38 which could result from cyclisation of the intermediate diketo-acid (Scheme 16).
This issue was clarified by attempting to dehydrate the cyclisation product (p-toluenesulphonic acid, benzene, reflux). The acid 38 would be expected to dehydrate very readily, whereas its isomer 37, with the hydroxyl group situated at the bridgehead of a bicyclo[3.3.1]nonane skeleton, would not be expected to undergo dehydration.* The product obtained from this reaction had clearly retained the hydroxyl group (I.r.: 3500 cm⁻¹), and instead had decarboxylated, † as was evident from the mass spectrum (M⁺: 262) and analysis (C₁₅H₁₈O₄). This evidence is consistent

* The flagrant violators of Bredt's rule, bicyclo[3.3.1]non-1-enes, have been prepared, albeit under drastic conditions, and not as yet, from such alcohols.  
† This reaction would appear to require the formation of a bridgehead enol, and therefore constitutes a violation of Bredt's rule. However, Ferris and Miller have suggested that the decarboxylation of such bridged bicyclic S-ketoacids, depends not so much on the strain involved in an enolic transition state, but more on the attainment of a conformation in which the dihedral angle, θ, between the carboxyl and carbonyl groups, approaches 90° (see Fig. 1). When this is not possible, no loss of carbon dioxide is observed. Examination of a Dreiding model reveals that the acid 37 (R=CO₂H) can adopt a conformation in which θ~70°, thus fulfilling the aforementioned requirements.

Fig. 1
only with the cyclisation product being the acid 37 (R=CO$_2$H) and hence the decarboxylated product is formulated as the derivative 37 (R=H).

As shown in Scheme 16, there are two modes of cyclisation which, a priori, are possible: attack by the aromatic nucleus at the C-5 ketone forming a six-membered ring, that is, the bicyclo[3.3.1]nonane 37 (R=CO$_2$H), and attack at the C-2 ketone forming a five-membered ring, that is, the hydrofluorene 38. Examination of a Dreiding model of the postulated intermediate diketoacid (Scheme 16) reveals however, that there is a distinct preference for cyclisation leading to a six-membered ring. The conformation providing adequate overlap of the aromatic $\pi$-system with the C-5 ketone can be constructed without exerting any strain on the system (Fig. 2). In contrast, the same degree of overlap of the aromatic $\pi$-system and the C-2 ketone is difficult to achieve without exerting strain on the system (Fig. 3).
The formation of a six-membered ring in preference to a five-membered ring in similarly constrained systems* has been reported previously. To illustrate, cyclisation of 1-benzylcyclohexan-1-ols \( \text{39} \) (\( R=\text{H}, \text{OCH}_3 \)) affords the strain-free bicyclo[3.3.1]nonanes \( \text{40} \), and not the relatively strained hexahydrofluorenes, \( \text{41} \).

While these findings did not augur well for the preparation of the hydrofluorenones, there were examples in the literature\(^{41a,70} \) which suggested the desired transformation could be induced with polyphosphoric acid (PPA). The hydrolysis step was therefore pursued no

---

* Even without this constraint, cyclisation leading to a six-membered ring is preferred.\(^{71} \)
further, and instead, the acid 36, was treated directly with PPA (70 min., 25°). This effected the combined processes of hydrolysis, decarboxylation, and cyclodehydration to afford the crystalline ketone 42 in 85% yield.

Since the virtual immobility of PPA at room temperature made the handling of it difficult, the transformation was also attempted with 85% sulphuric acid* (70 min., 25°), and again resulted in a high yield of the ketone 42 (63% overall from the acid 24).

The formation of the hydrofluorenone 42, to the apparent exclusion of the bicyclo[3.3.1]nonane 37 (R=CO₂H or H), may be accounted for by consideration of the probable pathways leading to these two products. Cyclisation to give the bicyclo[3.3.1]nonane 37 in the strongly acidic medium, could conceivably be a reversible process, simply by reprotonation of the aromatic nucleus† and subsequent

* This reagent is the medium of choice.
† The reprotonation would most certainly be facilitated by the highly reactive aromatic ring.
The reaction may therefore initially proceed by the more sterically favourable path \( a \), and, given sufficient time would eventually continue irreversibly by path \( b \)\(^*\) (Scheme 17).

Although no attempt was made to quench the reaction of the acid \( 36 \) in 85\% sulphuric acid, and analyse the product distribution, a further reaction of the bicyclo[3.3.1]nonane \( 37 \) (\( R=CO_2H \)) merits attention. Addition of this compound \( 37 \) (\( R=CO_2H \)) to 85\% sulphuric acid (70 min., \( 25^\circ \)), yielded on work-up, the hydrofluorenone \( 42 \) as the sole product. This result gives much credence to the considerations outlined above, and suggests that the bicyclo[3.3.1]nonane \( 37 \) (\( R=CO_2H \)) well be a reaction intermediate in this cyclisation.

In contrast to the reactions of the acid \( 36 \) with PPA and 85\% sulphuric acid, cyclisation to the hydrofluorenone skeleton with retention of the tertiary carboxyl group could be effected with a Lewis acid in a non-polar solvent. Thus, treatment of the acid \( 36 \) with boron trifluoride etherate (1.1 equivalents, 60 min., \( 25^\circ \)) in dichloromethane afforded,

\(^*\) Since any of the intermediates suggested in Scheme 17 would be easily prone to decarboxylation in the strongly acidic medium, the exact nature of the \( R \) group seems immaterial.
after chromatography on silica gel, the unsaturated lactone 43 in 65% yield.

This structure follows unambiguously from spectroscopic and analytical data (I.r.:1765 cm$^{-1}$; $^1$H n.m.r.: $\delta$=6.16, t, 1H and $\delta$=3.56, s, 3H). Presumably, the sequence of events in the formation of the tricyclic compound 43 is first lactonisation, rendering the C-5 ketone unreactive towards further nucleophilic attack, and then cyclisation and loss of methanol (Scheme 18).

Also worth noting, is the potential that compounds such as 43 may have as intermediates in gibberellin synthesis, whereby construction of the D-ring is initiated from the angular group at C-8. * This approach has received considerable attention from several groups, and to illustrate, the

* Gibberellin numbering.
2.2 With the initial investigations of this new approach successfully completed, attention was directed towards the preparation of the hydrofluorenone 44, which was required for further study (see Chapter 4).

\[
\text{44}
\]

Alkylation of the dianion 29 with the bromide 45 in an ammonia-tetrahydrofuran solution proceeded without incident to afford the suitably substituted acid 46 in 75% yield.

\[
\text{45} \quad \text{29} \quad \text{46}
\]

Cyclisation of the acid 46, following the previous example, was attempted directly with PPA (2hr, 25°) but gave...
a complex mixture as determined by thin layer chromatography (t.l.c.), from which the desired hydrofluorenone 44 could be separated only in 30% yield by chromatography. With 85% sulphuric acid (70 min., 25°), however, this compound was obtained as the sole product (t.l.c.; \(^1\)H n.m.r.) in 89% yield. This efficient two-step procedure, is therefore, a significant improvement upon the literature methods for the preparation of this compound. 38, 39, 40 Interestingly, the isomer 47, which might be expected as a product in this cyclisation, 38, 43b, 63 could not be detected in any appreciable amount.

![Chemical Structure](image)

In view of the interest in angularly substituted hydrofluorenone derivatives, 10, 41a, 73, 74 further transformations of the acid 46 were explored with the aim of preserving the tertiary carboxyl group. This could be achieved by esterification prior to acid-induced cyclisation. Thus, the
acid 46 was treated with diazomethane, and furnished the crystalline ester 48 in virtually quantitative yield.

Cyclisation with 85% sulphuric acid* (30 min., 25°) and ketalisation of the crude product under the usual conditions, afforded after chromatography on silica gel, the unsaturated ketal ester 49 in 50% overall yield based on 2,5-dimethoxybenzoic acid 24 (4 steps).†

Alternatively, cyclisation of the acid 46 could be induced directly with boron trifluoride etherate, as was

* PPA gave inferior results (cf. ref. 41a).
† The ethyl ester of 49 has been prepared from the β-ketoester 23 in 30% overall yield (3 steps). 41a
demonstrated in the previous section (2.1), and provided the unsaturated lactone 50, in 92% yield, after optimization of the reaction conditions.

Catalytic reduction of the unsaturated compound 49 is known to give largely the trans isomer, resulting from addition of hydrogen to the less hindered face of the molecule. The unsaturated lactone 50 was subjected to similar conditions in order to determine what effect the lactone might have in directing such a reduction. It was thought that if the cis B,C-ring junction could be introduced by this means, the unsaturated lactone 50 might also be useful as an intermediate for gibberellin synthesis.

Indeed, catalytic hydrogenation of the unsaturated lactone 50 gave a single stereoisomer 51, as determined by spectroscopic and physical methods. In order to assign the stereochemistry, attempts were made to convert the saturated lactone 50 to ketone 44 by treatment with 85% sulphuric acid (15 min., 25°), which rapidly effected hydrolysis and decarboxylation (β,γ-unsaturated acid).

* This compound could also be converted to the ketone 44 by treatment with 85% sulphuric acid (15 min., 25°), which rapidly effected hydrolysis and decarboxylation (β,γ-unsaturated acid).

† That is, 9α hydrogen (gibberellin numbering).
lactone 51 to the ketal acid 52, * the two isomers of which have been fully characterised. 41a, 73

Hydrolysis of the acetal function (aq. HClO₄, tetrahydrofuran, 18hr, 25°C) gave the ketoacid 53, which was subjected to the usual ketalising conditions, and gave a crystalline product, apparently the cis isomer of the ketal acid 52, that is, 9β hydrogen (m.p., ¹H n.m.r., m.s.). The I.r. spectrum however, exhibited

* The acetal function of the saturated lactone 51 was stable to the usual ketalising conditions, and rendered direct ketalisation useless.
features more readily accomodated by the lactone 54 (3400, 1760 cm\(^{-1}\)), isomeric with the ketal acid 52.

![Chemical structures](image)

This result actually suggested that the \textit{trans} isomer (i.e. \(9\alpha\) hydrogen) had been formed in the catalytic hydrogenation of the unsaturated lactone 50. The carboxyl group in this isomer of the ketoacid 53 is fixed rigidly in the axial position and would be favourably located for relactonisation to occur \(^*\) 41a (Fig.4).

![Chemical structure](image)

\* In contrast, the carboxyl group in the \textit{cis} isomer of the ketoacid 53 would be expected to be largely equatorial.41a
Confirmation of this assignment was obtained when the lactone 51 was converted to the ketal ester 55 by esterification (methanol, sulphuric acid, reflux, 40hr) and ketalisation, and was identical (m.p., m.m.p., I.r., $^1$H n.m.r.) with the product obtained by catalytic hydrogenation of the unsaturated ketal ester 49.\textsuperscript{41a}

Thus it appears that the lactone bridge of the tricyclic compound 50 directs the addition of hydrogen to the 9,11-double bond from the less hindered $\alpha$ face, as is the case with the ketal ester 49.\textsuperscript{41a} Clearly, other strategies\textsuperscript{41a} would have to be used if the unsaturated lactone 50 is to be employed as an intermediate for gibberellin synthesis.
2.3 The scope of this two-step sequence was briefly examined using the unsubstituted aromatic ring, which is clearly less reactive than the aromatic rings in the previous examples. Nevertheless, there are cases in the literature which suggest that the unsubstituted ring may be sufficiently active for the cyclisation to occur.\textsuperscript{43c,75}

The required acid \textbf{56} was prepared in 74\% yield, by alkylation of the dianion \textbf{29} with benzyl bromide.

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{OCH}_3 \\
\text{Br} & \quad \text{CO}_2\text{H} \\
\text{CH}_3\text{O} & \\
\text{Br} & \quad \text{CO}_2\text{H} \\
\text{OCH}_3 & \\
\text{CO}_2\text{H} & \quad \text{OCH}_3
\end{align*}
\]

Addition of the acid \textbf{56} to 85\% sulphuric acid produced a vigorous reaction with gas evolution. Assay of the reaction mixture after 2 hrs (t.l.c.) indicated a mixture of three products, from which the major component could be separated by chromatography in 72\% yield. This major product was readily
identified as the bicyclo[3.3.1]nonane 57, on the basis of the spectroscopic data obtained (\(^1\)H n.m.r.: \(\delta = 7.70, 1\)H, \(\delta = 7.2, 3\)H, \(\delta = 4.0, 1\)H, exchanged with D₂O; I.r.: 3400, 1715 cm\(^{-1}\); m.s.: M⁺ 202).

![Structure of 57]

When the cyclisation was conducted at a higher temperature (50°), the bicyclo[3.3.1]nonane 57 was also the major product obtained.

The outcome of the cyclisations of the acid 56, may be understood in the light of the results obtained for the acid 36 (see 2.1). It was suggested that the formation of the bicyclo[3.3.1]nonane 37, is initially favoured for steric reasons but is also reversible, due to presence of the methoxy groups which assist reprotonation of the aromatic nucleus (and hence retro-cyclisation) (cf. Scheme 17).*

It would appear that the cyclisation of the acid 56 is following a similar course, but, in this case, the aromatic

* Although no evidence was sought, it is assumed that this rationalisation also applies to the cyclisation of the acid 46 (section 2.2).
nucleus of the initial product 57 is insufficiently active to undergo the reprotonation step. As a result, the equilibrium would be maintained largely in favour of the bicyclo[3.3.1]nonane.

Since no attempts were made to isolate any of the minor products from the cyclisation, or to prolong the reaction time, it is difficult to determine whether any

* The ease with which the hydrofluorenones 42 and 44 undergo decomposition when exposed to air or strongly acidic conditions for prolonged periods would seem to preclude this option.
of the desired compound 58* had formed. Inspection of the
\(^1\text{H} \text{n.m.r.}\) of the crude mixture however, gave little
indication of the hydrofluorenone 58 being present.

![Chemical Structure](image)

This example therefore serves to illustrate a limitation
to this approach that is, with a relatively unreactive
aromatic nucleus, the bicyclo[3.3.1]nonane is likely to be
the major product isolated, rather than the hydrofluorenone.
Although this limitation could conceivably be overcome with
the use of a stronger acid, for example, the "super acid"
HF-SbF\(_5\),\(^76\) this option was not examined.

* This compound has been prepared by another route.\(^42\)
In the previous chapter, a particularly short and efficient preparation of hydrofluorenone 42 and 44, based on the reductive alkylation of 3,6-dimethoxybenzoate 43, was described.

3.1 Preparation of the hydrophenanthrenones 60 and 64, and the angularly substituted derivative 65.

3.2 Preparation of the hydrophenanthrenone 68.
In the previous chapter, a particularly short and efficient preparation of hydrofluorenones 42 and 44, based on the reductive alkylation of 2,5-dimethoxybenzoic acid 24, was described.

\[
\begin{align*}
R & = \text{OCH}_3 \\
R & = \text{H}
\end{align*}
\]

With a view to extending the strategy involved, the synthesis of the closely related hydrophenanthrenones such as 59 was initiated.
Additional stimulus was provided by the observation that these types of compounds, that is 59, may also be valuable intermediates for the synthesis of 13-hydroxy C19 gibberellins, as well as other biologically active substances such as 19-norsteroids, and phenanthrenoid phytoalexins.

The existing routes to these compounds 59, are very similar to those that could be used for the preparation of the lower homologues, the hydrofluorenones. The limitations of the methods based on the alkylation of the β-ketoester 23, and the annulation of α-tetralones, have already been enumerated. The annulation of β-tetralones also does not appear to be very efficient.

The basic plan involved two steps: alkylation of the dianion 29, with a suitably substituted 2-arylethyl moiety, followed by acid-promoted cyclisation.
3.1 Since the hydrophenanthrenone 60 is a known compound that has been prepared by other routes,* it was chosen as the initial target in this study.

The alkylation of the dianion 29, derived as usual from the lithium-ammonia reduction of 2,5-dimethoxybenzoic acid 24, was first attempted with the tosylate 61 (R=OTs).†,83

The alkylated of the dianion 29, derived as usual from the lithium-ammonia reduction of 2,5-dimethoxybenzoic acid 24, was first attempted with the tosylate 61 (R=OTs).†,83

---

* This compound has been prepared in four steps from 6-methoxy-1-tetralone in 25% overall yield,78 and in two steps from the β-ketoester 23 in 29% overall yield.80

† A recent report suggested that the tosylate 61 (R=OTs), was less prone to elimination reactions when used as an alkylating agent than the corresponding bromide 61 (R=Br).84
This failed to produce any of the desired product 62, and, furthermore the alkylating agent 61 (R=OTs) was recovered unchanged. It would seem that under the conditions of this alkylation (liquid NH$_3$, -33°), the tosylate is insufficiently reactive to undergo either alkylation or elimination.

The next logical choice appeared to be the use of either the bromide 61 (R=Br) or the iodide 61 (R=I), which it was thought, might be more reactive under these conditions.* There are a number of convenient methods for converting alcohols directly into bromides and iodides apart from the more traditional procedures. One of these, involving the reaction of an alcohol with triphenyl phosphite-methyl iodide to give the corresponding iodide, appeared to be particularly suitable for the task at hand. Using this method, the alcohol 61 (R=OH) was converted to the required iodide 61 (R=I) in 58% yield after chromatography on florisil.†

Alkylation of the dianion 29 with this alkylating agent 61 (R=I), (1.3 equivalents) was successful and afforded the acid 62 in 63% yield. A cursory examination ($^1$H n.m.r.) of

* Both alkyl bromides and iodides have been used in the reductive alkylation of benzoic acids, to give the alkylated products in >90% yields.† Separation of the iodide 61 (R=I) from the diphenyl methylphosphonate proved to be somewhat tedious.
the neutral by-products suggested that the iodide 61 \((R=I)\) may well have undergone some elimination to give the styrene 63 \(^1H\ n.m.r.:\delta=5.61,d,1H,J=18Hz;\delta=5.10,d,1H,J=11Hz)\).*

![Reaction diagram]

By analogy with the studies in Chapter 2, the cyclisation of the acid 62 was attempted directly. It was expected that the desired hydrophenanthrenone 60, could be obtained without the competing formation of a seven-membered ring\(^*\) (cf. Chapter 2).

---

* Stothers et al.\(^{88}\) have reported the following values for some similar compounds: for \(R=H, 4-OCH_3, 4-CH_3, 3-CH_3\): \(\delta_a\approx5.7, J_{ac}\approx18Hz\) and \(\delta_b\approx5.2, J_{bc}\approx11Hz\).

\(\uparrow\) The formation of a six-membered ring is preferred.\(^{71}\)
Cyclisation of the acid 62 (85% H₂SO₄, 10 min., 25°C) afforded a mixture of two compounds, readily separable by chromatography. The less polar compound obtained in 35% yield, was identified as the hydrophenanthrenone 60 on the basis of spectroscopic data, which were in good agreement with the reported values⁷⁸ (Ultra-violet (u.v.): λmax 274 nm (ε16,200); I.r.: 1720 cm⁻¹; m.s.: M⁺228).

The more polar product from the cyclisation, obtained in 56% yield, appeared to be isomeric with the hydrophenanthrenone 60, since the mass spectrum of this more polar compound also showed a strong molecular ion (M⁺228), consistent with the formula C₁₅H₁₆O₂. The ¹H n.m.r. spectrum indicated quite clearly that it was a cyclised product (δ=7.14, 1H, δ=6.74, 1H, δ=6.60, 1H), and a signal in the olefinic region suggested that the double bond was in a trisubstituted position (δ=5.96, 1H). This evidence alone, points to the isomeric hydrophenanthrenone 64.⁸⁹

* As this more polar product could not be crystallised, the accurate mass was measured.
Additional support for this structure was obtained from the I.r. and u.v. spectra (1660 cm$^{-1}$; 223 nm) which together with the $^1$H n.m.r. data, leave no doubt as to the location of the double bond. Thus, the overall yield for this two-step procedure based on the 2,5-dimethoxybenzoic acid 24, is 57%. Although a mixture of isomers was the expected outcome of this cyclisation, it is curious that the other reports detailing the preparation of the hydrophenanthrene 60, do not mention isolation of the isomeric compound 64.

Cyclisation of the acid 62 with boron trifluoride etherate in dichloromethane was also investigated, and as with the hydrofluorenone examples (Chapter 2), the reaction proceeded with retention of the tertiary carboxyl group, to afford the unsaturated lactone 65 in 63% yield after chromatography (I.r.: 1755 cm$^{-1}$; $^1$H n.m.r.: $\delta$ = 6.16, t, 1H and $\delta$ = 3.52, s, 3H).
3.2 As a further example, the acid 67, bearing the unsubstituted aromatic ring was briefly examined.

The preparation of the required alkylating agent 66 (R=I), was readily achieved by reaction of the alcohol 66 (R=OH), with triphenyl phosphite-methyl iodide (69% yield).

Alkylation of the dianion 29 with the iodide 66 (R=I) proceeded without incident, to furnish the acid 67 in 70% yield.

Since the aromatic nucleus in the acid 67 is relatively unreactive, (cf. section 2.3), some difficulty in the cyclisation was expected. Indeed, the use of the same conditions as described for the acid 62, gave unsatisfactory results. However, when the cyclisation of the acid 67 was conducted in warm 85% sulphuric acid (1hr, 45°), a single crystalline product was obtained in 87% yield. From analysis
of the $^1$H n.m.r. spectrum, it was evident that the product was the hydrophenanthrenone 68 ($\delta=5.96, 1H$). This was confirmed by other data (I.r.: 1680 cm$^{-1}$; u.v.: 236 nm).

None of the isomer 69 could be detected in the crude product by the usual analytical means (t.l.c. and $^1$H n.m.r.). This result is apparently in contrast with the cyclisation of the acid 62, in which both the $\beta,\gamma$- and $\alpha,\beta$-unsaturated ketones 60 and 64 respectively, were produced. In the case of the ketones 60 and 64, the equilibrium may be affected by the p-methoxy group. However, the cyclisation parameters (time and temperature) are sufficiently different to make direct comparisons of the results obtained for the acids 62 and 67 difficult, without conducting further experiments.
Although only two examples were studied, the results indicate that this particular approach to the synthesis of hydrophenanthrenones such as 59, has distinct advantages over previously reported methods\textsuperscript{78b,80,81,82} in that it is shorter and more efficient. It has already been successfully applied to the preparation of the hydrophenanthrene 70 and its olefinic isomer,\textsuperscript{91} which would be difficult to prepare by the other routes.\textsuperscript{78,80}

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

\textbf{70}

Also, it is anticipated that this approach will be generally applicable to the synthesis of 9,10-dihydrophenanthrene\textsuperscript{92,93,94} and fully aromatic phenanthrene derivatives.\textsuperscript{94} The latter may be derived from the former by dehydrogenation with, for example, dichlorodicyanoquinone (DDQ),\textsuperscript{95} while the former may be obtained by the reaction of the hydrophenanthrenones such as 59 with cupric bromide-methanol.\textsuperscript{96}
CHAPTER 4

4.1 Preparation of the tetracyclic ketone 15.

4.2 Studies of the B,C-ring fusion in the ketone 15.
The tetracyclic ketone 15 displays both the structural features and functionality which make it a ready choice for a projected synthesis of 13-hydroxy C_{19} gibberellins.

It has the hydrofluorene skeleton forming the A,B,C-ring system, and the two-carbon bridge which constitutes the D-ring. Also, it possesses functional groups from which the desired functional array of gibberellic acid 3, in principle, may be derived: the anisole nucleus may be viewed as a precursor for the oxygenated A-ring, and the α-hydroxy ketone as a precursor for the allylic tertiary hydroxyl moiety of the C- and D-rings.

The successful elaboration of this intermediate to a gibberellin hinges first and foremost on procuring the cis B,C-ring fusion that is found in the natural product.

* Gibberellin numbering will be used throughout this chapter.
Effectively, this amounts to the introduction of a β hydrogen at C-9 in the ketone 15. The study of this transformation required a ready supply of the ketone 15, the preparation of which would also serve as a model for the elaboration of more complex tetracyclic ketones.
4.1 Although the ketone 15 had been prepared previously,\textsuperscript{38} certain features of the approach demanded revision to ensure the supply of this substrate in synthetically useful amounts (\textit{vide infra}). With the initial problems in availability of the starting material 44 overcome (see Chapter 2), attention was focussed on the addition of the two-carbon bridge to this compound, using the route outlined in Scheme 19.\textsuperscript{38}

\begin{center}
\includegraphics[width=\textwidth]{scheme19.png}
\end{center}

**Scheme 19**
The first stage of this sequence required conversion of the ketone 44 to the hydroxy acid 74. A number of reagents could be considered for use in this regard: for example, dichloromethyl-lithium or bis(methylthio)methyl-lithium may be viewed as latent carboxylate anion equivalents. However, the carbonyl function of this substrate would be expected to undergo enolisation rather than nucleophilic attack with such strongly basic nucleophiles, because of the relatively acidic nature of the adjacent methylenes. \(^*\) In contrast, the cyanide ion, which combines the properties of a weak base and an effective nucleophile, seemed well suited to this purpose, for unlike the other reagents, it may be added to ketones under conditions of equilibrium. Also, the ease of direct conversion to the carboxyl group by acidic hydrolysis appeared to be another point favouring its use.

The ketone 44 was therefore treated with sodium cyanide and hydrochloric acid in a two-phase system, to give the crystalline cyanohydrin 71 in 80% yield (I.r: 3400, 2200 cm\(^{-1}\)).

\[ \text{CH}_3\text{O} \quad \text{OH} \quad \text{CN} \]

* The ketone 44 may be viewed as a vinylogous \(\beta\)-tetralone.
Direct hydrolysis of the nitrile to the carboxyl group following reported procedures,37,38,100 was however completely unsuccessful. Heating the cyanohydrin 71 in concentrated hydrochloric acid37,38,100 resulted in a low return of poor quality material, and the use of glacial acetic acid as a co-solvent showed little improvement.

Eventually, this difficulty was overcome by converting the cyanohydrin 71 to the hydroxy acid 74 via the hydroxy methyl ester 73. Following a method reported by Birch et al.,101 a suspension of the cyanohydrin 71 in absolute methanol, was treated with hydrogen chloride gas, and the resultant imidate 72 hydrolysed by the addition of water. The methyl ester 73 so obtained was then hydrolysed further under alkaline conditions (aq. KOH, methanol-tetrahydrofuran, 1hr, 25°),* to afford the required acid 74 in 80% overall yield.

\[
71 \rightarrow \begin{array}{c}
\text{OH} \\
\text{R} \\
\text{CH}_3\text{O} \\
\end{array} \rightarrow 74
\]

\[
72 \quad R = \text{C}=\text{NH}_2\text{Cl}^+ \\
73 \quad R = \text{CO}_2\text{CH}_3
\]

* The more forcing conditions used for the hydrolysis of similar α-hydroxy esters (several hours, reflux),38,102 were found to be unnecessary. Presumably, the α-hydroxyl group is providing assistance for this conversion.103
The next stage of the sequence outlined in Scheme 19, required the conversion of the hydroxy acid 74 to the diazoketone 76, in which the hydroxyl group was suitably masked. Previous studies\textsuperscript{37,99} have shown that this masking step is necessary in order to prevent the tertiary hydroxyl group from intercepting the protonated diazoketone during the cyclisation to form the D-ring (see Scheme 19). The trifluoroacetyl (TFA) residue was originally chosen as the masking group,\textsuperscript{37,38} but owing to its lability, the use of other electron-deficient esters such as dichloroacetate (DCA) and trichloroacetate (TCA), was considered. Although the use of the latter has led to marginally better yields of cyclised products,\textsuperscript{104} it was thought that for the present work the use of the former would be satisfactory.\textsuperscript{*} In addition, the dichloroacetoxy group may be observed by \textsuperscript{1}H n.m.r. spectroscopy,\textsuperscript{†} and has been shown to be less labile than the trichloroacetoxy group.\textsuperscript{104}

Reaction of the hydroxy acid 74 with dichloroacetyl chloride in refluxing 1,2-dichloroethane, gave after work-up with aqueous acetone,\textsuperscript{‡‡} the dichloroacetoxy acid 75 (R=OH) in 93% yield (\textsuperscript{1}H n.m.r.: $\delta=5.84$, s; I.r.: 1760, 1710 cm$^{-1}$).

\* The styrene bond is thought to be more nucleophilic than the anisole moiety towards the protonated diazoketone.\textsuperscript{104}  
\† The dichloroacetate group exhibits a sharp singlet at about 5.9 ppm.\textsuperscript{104}  
\‡‡ This procedure destroys acid anhydride formed during the dichloroacetylation.
The acid chloride 75 (R=Cl) prepared by reaction of the acid 75 (R=OH) with oxalyl chloride-pyridine in dichloromethane, was added to an excess of ethereal diazomethane, and afforded the diazoketone 76 (I.r.: 2080 cm\(^{-1}\)).

\[ \text{R} = \text{OH} \quad \text{R} = \text{Cl} \]

Acid-catalysed cyclisation\(^{104}\) of the crude diazoketone 76 (trifluoroacetic acid-dichloromethane, \(-20^\circ\)), and chromatography of the product on silica gel, furnished the crystalline tetracyclic compound 77 in 41% overall yield from the hydroxy acid 74.
The overall yield was lower than expected, and with the aim of improving these last steps in the sequence, some explanation was sought. With purified diazoketone 76, cyclisation to the tetracyclic compound 77 was found to be high-yielding (>90%) and immediately discounted this step as the source of the problem. Closer scrutiny of the $^1$H n.m.r. spectrum of the crude diazoketone 76, revealed however, that the yield of this compound was only c. 60%. As the diazoketone preparation depended in turn on the acid chloride formation, improvement of this latter step by varying the reaction conditions was attempted but showed little promise.

To complete the final stage of the sequence, the dichloroacetate group of the tetracyclic compound 77 was removed by brief exposure to base (K$_2$CO$_3$, water-methanol-tetrahydrofuran, 10 min., 25°) to give the crystalline ketone 15 in 90% yield.

* This was determined by comparing the integrals of the resonances due to the dichloroacetate hydrogen and the diazoketone hydrogen.
4.2.1. Several methods were examined as possible means for obtaining the cis B,C-ring-fused compound 78 from the unsaturated ketone 15. The most direct approach appeared to be reduction of the styrenoid bond, either by catalytic hydrogenation or by lithium in ammonia. As the former method could be applied to the unsaturated compound 15 under conditions which would not require protection of the C-16 ketone, this approach was chosen initially for study.

Catalytic hydrogenation of the olefin 15 (10% palladium-on-carbon, ethyl acetate) gave a crystalline solid m.p. 90-140°, which was found to be a mixture of epimers at C-9 in the ratio c. 65:35, as determined by $^1$H n.m.r. spectroscopy. Although a mixture was expected, it was thought that the two isomers might be separable. Unfortunately, all attempts to resolve this mixture by

* The chemical shifts of H-1 (d,J=8Hz) and the methoxy group were sufficiently different to assess this ratio.
chromatography using a variety of eluants were uniformly unsuccessful. Only the major isomer m.p. 160-163°, could be separated cleanly by fractional crystallisation.

The problem of assigning the respective structures to the two isomers could not be readily solved by observing H-9 in the 1H n.m.r. spectrum, as the signals due to this proton were obscured by other resonances. However, it has been suggested that the configuration at C-9 in compounds of this type may be deduced from the chemical shifts of the C-6 benzylic protons, which give rise to an AB quartet with a coupling constant $J_{AB} \approx 16$ Hz. In the compounds with 9α hydrogen, the respective signals of the AB quartet occur consistently at higher field than those with a 9β hydrogen. 24c, 106, 107

Inspection of the 1H n.m.r. spectrum of the major isomer revealed an AB quartet clearly visible at $\delta_A = 2.98$, $\delta_B = 2.61$ ppm ($J_{AB} = 15$ Hz). The location of the AB quartet of the minor isomer at $\delta_A = 3.10$ and $\delta_B = 2.76$ ppm ($J_{AB} = 15$ Hz), could then be inferred from the signals at 3.19, 3.04 and 2.82 ppm, which were present in the 1H n.m.r. spectrum of the mixture, but were absent (3.19 and 2.82 ppm) or greatly diminished (3.04 ppm) in that of the major isomer. On this
basis, the minor isomer was tentatively assigned the *cis* stereochemistry, that is, 78, and the major isomer, the *trans* stereochemistry, that is, 79.

With the hope of finding an additional means of distinguishing the isomers 78 and 79, the mass spectra of the mixture and the pure isomer were examined, but they proved to be of little assistance because the fragmentation patterns of both compounds were virtually identical.

$^{13}$C n.m.r. spectroscopy was also considered as this type of analysis has proved useful for distinguishing *cis* and *trans* isomers at the B,C-ring junction in other gibberellin analogues. These studies have shown that a slight upfield shift (1-4 ppm) is observed for C-ring carbons of the *cis* isomers, which has been attributed to the steric effects arising from the C-ring adopting a boat-like conformation.

The $^{13}$C n.m.r. spectrum of the major (*trans*) isomer 79 exhibited signals at 36.5 (triplet) and 81.3 (singlet), which
were assigned to C-12 and C-13 respectively. The signals of the corresponding carbons in the minor (cis) isomer 78 were located slightly upfield at 35.1 (triplet) and 79.5 (singlet), which is apparently consistent with these previous studies. Surprisingly, the chemical shift of the signal assigned to C-11 was identical in both the isomers 78 and 79 (22.0, t), which may raise the question as to the actual conformation of the C-ring in the cis compound 78.† One explanation may be deduced from the examination of a Dreiding model of the cis isomer 78. This reveals that the C-ring is flexible enough to adopt a chair-like conformation (Fig. 5), which relieves the prow interaction between

* This inference is made with caution as the substrates mentioned in these reports contain an ester group at C-6.
† The boat-like conformation would be expected (see Fig. 6).109,110
C-11 and C-14* (Fig. 6). However, the chair-like conformation appears to be energetically less favourable, as it introduces bond angle strain, causing the C-ring to readily revert to the boat-like conformation shown in Figure 5.

The similarities in chemical shift of the remainder of the saturated carbons made it difficult to obtain additional stereochemical information from the $^{13}\text{C}$ n.m.r. spectra.

By analogy with other reports it might be expected that hydrogenation of the unsaturated ketone 15 would

* This interaction is thought to be responsible for the upfield shift of C-11 in the $^{13}\text{C}$ n.m.r. spectra of the cis B,C-ring-fused compounds. It does not arise in the trans compounds because the C-ring adopts a chair conformation (Fig. 7).

![Fig. 7](image-url)
produce the trans isomer 79 as the major product. For example, it has been shown that hydrogenation of gibberone 80 using the same catalyst (palladium-on-carbon) produces a mixture from which the trans isomer is isolated as the major product. Comparable results have been obtained with the 13-deoxy derivative of the hydroxy ketone 15, that is, the tetracyclic ketone 81.36

A more rigorous proof of the stereochemical assignments of the products obtained from the hydrogenation of the olefin 15, by degradation to known hexahydrofluorene derivatives, was considered but not undertaken. Nevertheless, the assignments appear to be consistent with results obtained from the reduction of similar systems.24c,36,105,106 Other methods utilising a C-16 endo alcohol which may direct hydrogenation from the more hindered β face were not explored.

* Compare also with the hydrogenation of the unsaturated lactone 50 (section 2.2) which gave the trans isomer exclusively.
4.2.2. From the preceding study, it would appear that the formation of the \textit{trans} isomer 79 is favoured for steric reasons. However, heterogeneous catalytic hydrogenation gives little or no indication as to the relative thermodynamic stabilities of the products formed. A reaction which might provide information in this regard, and possibly even access to the \textit{cis} isomer 78 was seen to be isomerisation of the \(\alpha\)-ketols 78 and 79 as shown:

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{\(\rightarrow\)} \quad \text{OH} \quad \text{\(\leftarrow\)} \quad \text{CH}_3\text{O} \\
\text{79} & \quad \text{78}
\end{align*}
\]

The ability of tertiary \(\alpha\)-hydroxy ketones to undergo isomerisation in the presence of acid or base is a well-documented process. 112-114

* A recent report\textsuperscript{74} dealing with the hydrogenation of a system very similar to the olefin 15, appears to exclude the possibility of isomerisation. 115
Although reference to it has been made in the study of compounds related to the gibberellins, there appears to be only one report in which it has been used intentionally. This type of rearrangement is similar to the acid-promoted conversion of allogibberic acid to gibberic acid in that it also involves a shift of the C-12, C-13 bond to C-16, resulting in inversion of the D-ring.

With the isomerisation of the α-ketols and , the outcome would be expected to be determined by the relative thermodynamic stabilities of these two isomers, whereas the conversion of the acid to the acid appears to be irreversible.

Studies of this so-called acyloin (α-hydroxy ketone) rearrangement in other fields, suggested that the conversion could be effected specifically with a Lewis acid, as well as with a base such as sodium hydroxide or butyl lithium. Several reagents were therefore examined and the outcomes assessed using n.m.r. and
13C n.m.r. spectroscopy.

The reaction was first attempted by treating a mixture of the α-ketols 78 and 79 with sodium hydride in tetrahydrofuran.* The resultant precipitate, presumably the sodium salts of 78 and 79, was then dissolved by the addition of hexamethylphosphoramide (HMPA), and warming to 60°. After 16 hours at 25°, the reaction was worked up and the crude product purified by chromatography on silica gel to give a crystalline solid in 50% yield.

Analysis of the 1H and 13C n.m.r. spectra, revealed that this product consisted mainly of the isomer which had previously been assigned the trans stereochemistry, that is, the ketol 79 (1H n.m.r.: δ=6.96, d, J=5 Hz; δA=2.98, δB=2.61, JAB=15 Hz; 13C n.m.r. δ=36.5). Although the cis isomer 78 could not be detected in the 1H n.m.r. spectrum, there was a signal of very low intensity at 35.2 ppm in the 13C n.m.r. spectrum that could be attributed to this compound.

As the return of material using sodium hydride to induce the isomerisation was only moderate, milder conditions were sought. Exposure of the α-ketols 78 and 79 to potassium carbonate in methanol (16 hr, 25°) gave a cleaner product in 90% yield, which, by the same techniques of analysis (1H and 13C n.m.r.) was also found to be predominantly the

* Exclusion of oxygen is of vital importance as the α-hydroxy ketone readily oxidises, breaking the C-13, C-16 bond.
trans isomer 79. Similarly, treatment of the α-ketols 78 and 79 with boron trifluoride etherate in dichloromethane (16 hr, 25°), gave mainly the trans isomer 79 with 90% return of material. In contrast, diazabicyclononene (DBN) in deuterochloroform did not affect the isomer distribution even after 48 hours, and the mixture was returned apparently unchanged (1H n.m.r. analysis).

These results indicate that the isomer with the trans B,C-ring junction 79 is thermodynamically more stable.∗ An explanation for this may be found by examining Dreiding models of the isomers 78 and 79. As mentioned previously (section 4.2.1) the C-ring of the cis isomer 78 may adopt the boat-like conformation which involves non-bonded interactions (see Fig. 5) or the chair-like conformation which involves bond angle strain (see Fig. 6). On the other hand, the C-ring of the trans compound 79 is locked in a chair conformation (see Fig. 7) which does not appear to involve such severe strain and non-bonded interactions.†

The driving force of the isomerisation (78→79) may therefore

∗ This is in marked contrast with angularly substituted hexahydrofluorene derivatives, in which the cis configuration at the B,C-ring junction is known to be more stable.120
† There may be non-bonded interactions between the hydrogen on C-15 and the axial hydrogen on C-11 (see Fig. 8).
arise from relief of these unfavourable interactions in going from the cis isomer 78 to the trans isomer 79 (Fig. 8).

![Fig. 8](image)

A similar view has recently been advanced by Corey, Danheiser and co-workers, who have noted the ready isomerisation of the tricyclic cis compound 84 to the trans isomer.

![84](image)

It is worth mentioning that the compound 84 could be treated with a hindered amine base (diisopropylethylamine) apparently without inducing isomerisation. This is in accord with the result obtained by exposure of the α-ketols 78 and 79 to DBN mentioned earlier.
The relative instability of the cis B,C-ring fusion may be inferred from the work of Mori.\textsuperscript{116} While attempting to convert the α-ketol 85 (R=H) to (−)-epiallogibberic acid by aqueous base hydrolysis of the ester group and Wittig methylenation of the C-16 ketone, he obtained the compound 86 as the major product, in which the D-ring is inverted.

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {85};
  \node at (2,0) {86};
\end{tikzpicture}
\end{center}

This result noted by Mori\textsuperscript{116} has been confirmed by work in these laboratories. The acetate 85 (R=Ac) was exposed to mildly basic conditions, and resulted in removal of the acetate group, complete inversion of the D-ring and epimerisation of the C-6 ester function, to give the isomeric α-ketol.\textsuperscript{122}
4.2.3. Although the lithium-ammonia reduction of styrenoid bonds has been the subject of extensive investigations, the application of this reaction to tetracyclic compounds such as 15, appears to have received little attention. It was therefore of interest to investigate the reduction of this compound 15 under these conditions and determine whether stereo-chemical control of the B,C-ring fusion could be achieved in this manner. To ensure the survival of the C-16 ketone it was decided to protect this functional group as the ethylene ketal prior to the reduction step.

The unsaturated ketone 15 appeared to be inert to several methods of ketalisation, and starting material was returned unchanged. However, it was found that the reaction proceeded quite smoothly when an excess of ethylene glycol (10-20 equivalents) in boiling 1,2-dichloroethane (20hr) was used. In this way the crystalline ketal 87 was obtained in 70% yield (\textsuperscript{1}H n.m.r. : \(\delta=3.96,4H\)).

\begin{center}
\includegraphics[width=\textwidth]{87}
\end{center}

* For example: (i) ethylene glycol (2 equivalents), p-toluenesulphonic acid, benzene, reflux (ii)2-ethyl-2-methyl -1,3-dioxalane, boron trifluoride etherate, benzene,250,24c
Reduction of the 9,11-double bond of this substrate 87, with lithium in ammonia gave what appeared to be a single isomer. $^1$H n.m.r. analysis of the crude product indicated a well resolved AB quartet $\delta_a 2.87, \delta_B 2.43 (J_{AB} = 16\text{Hz})$, and a sharp singlet for the methoxy group. Only the signal due to H-1 ($\delta = 6.96, d, J = 8\text{Hz}$) which was broadened at the base of the peaks, suggested the presence of another isomer. The wide melting range (125-135°) was in agreement with this, but one recrystallisation gave a product with m.p. 137-140°, the $^1$H n.m.r. spectrum of which was not significantly different from the crude product. It was therefore assumed that the lithium-ammonia reduction of the compound 87 gave predominantly one isomer, which was either the cis B,C-ring-fused compound 88 or the trans compound 89.

The stereochemistry at C-9 of the major isomer could not be readily defined by spectroscopic methods as it was for the corresponding ketones 78 and 79, since the minor isomer was not produced in sufficient amounts. Some other reactions were therefore examined which were expected to
provide samples of the \textit{trans} isomer 89. Hydrogenation* of the unsaturated ketal 87 (10\% palladium-on-carbon, ethyl acetate) gave a product, the $^1$H n.m.r. of which was very similar to the major product from the lithium-ammonia reduction of the same compound 87 ($^1$H n.m.r. analysis), and when recrystallised had a melting point 139-141\°. Admixture of the two samples derived by these different means showed no depression of the melting point. Similarly, ketalisation of the \textit{trans} ketone 79 (section 4.2.1) gave a single compound†, identical with the purified product from the lithium-ammonia reduction of the unsaturated ketal 87. This leads to the conclusion that the major product from the reduction of the olefin 87 is the \textit{trans} compound 89.

Presumably the lithium-ammonia reduction proceeds via the benzylic carbanion 90 which arises from the addition of 2 electrons and one proton, to the olefin 87.\textsuperscript{41a,123}

$^*$ Cf. section 4.2.1.
† This was evident from 13C n.m.r. analysis of the crude product. As complete inversion of the D-ring would not be expected under these conditions which clearly involve an equilibrium (see section 4.2.2.), it follows that this product is the \textit{trans} ketal 89.
The addition of the second proton then appears to be determined by several factors: the relative stabilities of the two conformers 90a and 90b, the degree of overlap that the sp\(^3\) carbanion can achieve with the aromatic nucleus, and the relative degree of steric hindrance the proton source encounters on approaching the carbanion.\(^{41a,123,124}\) Examination of Dreiding models reveals that both conformers 90a and 90b provide equally good overlap with the π-system of the aromatic nucleus. Also, there appears to be only a marginal difference between the two conformers in terms of steric hindrance to the approaching proton donor. Thus, assuming that the transition state resembles the conformation which minimises non-bonded interactions, and is therefore of lowest energy,\(^{123,124}\) the trans form 90b would be expected to serve as the precursor for the observed product 89.*

\[\text{CH}_3\text{O}-\]
\[\text{O(H)}\]

90a

\[\text{CH}_3\text{O}-\]
\[\text{O(H)}\]

90b

* Cf. section 4.2.2.
While the outcome of the studies of the B,C-ring fusion in the tetracyclic ketone 15 detracts from its use as an intermediate for gibberellin synthesis, the results are seen to be valuable for designing approaches to more complex substrates. For example, it has been shown that inversion of the D-ring can be readily achieved in high yield under mild conditions. Certainly, further study of this process with a view to obtaining kinetic control may be worthwhile. Also, it has been demonstrated that the sensitive α-hydroxy ketone moiety can be protected with a group which would be stable to a variety of reagents.

The difficulties with introducing the desired cis B,C-ring fusion into the tetracyclic ketone 15 prompted the investigation of an alternate approach which is presented in the following chapters.
CHAPTER 5

5.1 Alkylation of the dianion 29 with methyl 2-bromomethylbenzoate 95.

5.2 Attempts to prepare the hydrofluorenone 108.

5.3 Attempts to prepare the hydrofluorenone 116.

5.4 Preparation of the hydrofluorenones 127 and 128.
The utility of the benzoic acid moiety for assembling the gross structures of the A- and B-rings of the C₁₉ gibberellins has been ably demonstrated by the studies of Loewenthal, House and Baker. The incorporation of this aromatic nucleus into hydrofluorene derivatives allows for the ready introduction of the C-6 carboxyl function and the C-4 methyl group. It also provides an unsaturated acid suitably disposed for the formation of the A-ring γ-lactone (Scheme 20).

Scheme 20
An additional feature of the approach outlined in Scheme 20, is that the stereochemistry of the asymmetric centres, particularly at the B,C-ring junction, may be controlled to give the configuration of the natural gibberellins. The tetracyclic compound 91 was therefore seen as an attractive intermediate, which could lead, in principle, to a very efficient synthesis of 13-hydroxy C₁₉ gibberellins.

As the introduction of the carboxyl group or its equivalent (for example, bromine) into the tetracyclic compound 15 did not seem practicable, a route to the hydrofluorenone 93, based on the reductive alkylation of 2,5-dimethoxybenzoic acid, was explored (Scheme 21).

* The presence of the 9,11-double bond would appear to preclude the use of electrophilic reagents. Even in the absence of this functionality, electrophiles (e.g. Br⁺, CH₃CO⁺) would be expected to react preferentially at C-2.
In order to establish the feasibility of the approach outlined in Scheme 21, it seemed necessary to determine first whether the bulk of the ensuing alkylating agent 92 would hinder the reaction with the diations 29. The bromo ether 92 was chosen initially as its preparation and use as an alkylating agent could serve as a model for relatively less accessible derivatives 29.

Two methods were suitable for the preparation of the bromo esters. Either bromination of the benzylic alcohol 94 (R=OH) with phosphorus tribromide, or photobromination of the toluic ether 94 (R=H). Although the results obtained with both methods were satisfactory.

Scheme 21

91

92

94

95

93

92

94

95

4.1 This compound could be prepared by hydrolysis of phthalide, and esterification of the resultant 3-hydroxyethylbenzoic acid 199.

3. The bromo ether 92 could be prepared in the presence of pyridine (3.5 equivalents) in the absence of this base, the major product obtained was phthalide (see Experimental).
5.1 In order to establish the feasibility of the approach outlined in Scheme 21, it seemed necessary to determine first whether the bulk of the ester in the alkylating agent 92 would hinder the reaction with the dianion 29. The bromo ester 95 was chosen initially, as its preparation and use as an alkylating agent could serve as a model for relatively less accessible derivatives 92.

Two methods appeared to be suitable for the preparation of the bromo ester 95: either bromination of the benzyl alcohol 94 (R=OH)* with phosphorus tribromide, or photobromination* of the toluic ester 94 (R=H). Although the results obtained using the former method were satisfactory,†

* This compound could be prepared by hydrolysis of phthalide, and esterification of the resultant 2-hydroxymethylbenzoic acid. 126
† The bromo ester 95 could be prepared in the presence of pyridine (3.5 equivalents); in the absence of this base, the major product obtained was phthalide (see Experimental).
more attention was directed towards the latter, as it was thought that the toluic esters would, in general, be more readily available than the 2-hydroxymethylbenzoates.

Following the procedure reported by Eliel *et al.*, the toluic ester 94 (R=H) was photobrominated using bromine (1 equivalent) and a light source. The crude product obtained in this way, appeared to be contaminated with a significant amount of the dibrominated product 96 (\(^1\)H n.m.r. analysis) which was difficult to separate from the desired compound 95.

However, when the reaction was terminated after about 70% of the starting ester 94 (R=H) had been consumed (\(^1\)H n.m.r. analysis), the bromo ester 95 could be readily isolated in 61% yield by crystallisation.

Alkylation of the dianion 29 in ammonia-tetrahydrofuran was then attempted using a two-fold excess of the bromo ester 95 and, after acidic work-up, a mixture of two compounds
was obtained. The major product, surprisingly enough, was not an acid, but was identified as phthalimidine \(97\) (m.p.: \(150-152 ^\circ C\); * I.r.: \(3200,1690 \text{ cm}^{-1}\); m.s.: \(M^+ 133\)).

\[
\begin{align*}
\text{97} & \quad \text{98}
\end{align*}
\]

The minor product was then isolated using extraction techniques, and identified as the desired acid \(98\) from its spectroscopic data. Presumably the lactam \(97\) arises from ring closure of the amino ester \(94\) (\(R=NH_2\)), † formed by the reaction of the excess of alkylating agent \(95\) with ammonia. By using less of the bromo ester \(95\) (1.3 equivalents) for the alkylation of the dianion \(29\), and modifying the work-up procedure, ‡‡ the acid \(98\) was obtained free of the by-product \(97\) in 60% yield (not optimized). This result clearly demonstrated that the alkylation of the dianion \(29\) proceeded without difficulty. As it seemed unlikely that the acid \(98\)

* Lit. \(150^\circ C\) 128
† This compound readily forms phthalimidine \(97\) under basic conditions. 129
‡‡ See Experimental section.
with such a deactivated aromatic nucleus would cyclise to a hydrofluorenone, this reaction was not attempted.

Also, this aromatic nucleus as the acid, would be expected to lose the methoxy group completely when subjected to reductive methylation (see Chapter 1), and thereby provide an A-ring precursor for several of the natural C_{10} gibberellins.
5.2 The bromo ester 105 was selected next for study, to determine if one methoxy ortho to the position of cyclisation would activate the aromatic ring sufficiently for electrophilic attack.

\[ R = \text{H} \quad \text{104} \\
R = \text{Br} \quad \text{105} \]

Also, this aromatic nucleus as the acid, would be expected to lose the methoxy group completely when subjected to reductive methylation (see Chapter 1), and thereby provide an A-ring precursor for several of the natural C\textsubscript{19} gibberellins.

\[ \text{CH}_3\text{O} \quad \text{CO}_2\text{CH}_3 \]

\[ \text{CH}_3\text{O} \quad \text{CO}_2\text{H} \quad \text{CO}_2\text{H} \]

The toluic ester 104 appeared to be a suitable precursor for the required alkylating agent 105 by using the photobromination procedure described in the previous section (5.1).
The preparation of the toluic ester 104 was accomplished using standard literature procedures based on \textit{m}-methoxytoluene 99 (Scheme 22). Acylation\textsuperscript{130} of this toluene 99 gave a 4:1 mixture of the acetophenones 100 and 101 (\textit{\textsuperscript{1}H n.m.r. analysis) which was oxidised directly to the toluic acids 102 and 103 with hypochlorite.\textsuperscript{131,132} The desired acid 102 could be readily separated from the regioisomer 103 by fractional crystallisation (60\% overall yield).

\begin{center}
\begin{tikzpicture}
\node (a) {99};
\node (b) [right=of a] {100};
\node (c) [right=of b] {101};
\node (d) [below=of a] {102};
\node (e) [right=of d] {103};
\end{tikzpicture}
\end{center}

Esterification gave the toluic ester 104, which was photo-
brominated (Br\textsubscript{2}, 500W lamp) to provide the bromo ester 105\textsuperscript{133} in 50\% yield after crystallisation. Alkylation of the dianion 29 in ammonia-tetrahydrofuran with the bromo ester 105
afforded the acid 106 in 75% yield.*

Cyclisation of this acid 106 directly to the hydrofluorenone 108 however, met with little success. Most attempts† resulted in only hydrolysis of the enol ethers and decarboxylation to give the diketone 107 (¹H n.m.r. analysis).

* Alkylation of the dianion 29 after removal of the ammonia gave the acid 106 in 84% yield.
† For example: hydrochloric acid, methanol, reflux;¹³⁴ phosphorus pentoxide-methanesulphonic acid, 500;¹³⁵ p-toluenesulphonic acid, benzene, reflux;¹³⁶ trifluoroacetic acid, 500. Cyclisation with 85% H₂SO₄ was not attempted, as this medium would also hydrolyse the aromatic ester (see section 5.3)
Only the use of PPA (1 hr, 60°) gave any encouragement: a product was isolated from this reaction in about 30% yield, the spectroscopic data of which were consistent with the hydrofluorenone 109 \(^{11}\)H n.m.r.: \(\delta=6.00, 1H\); m.s.: \(M^+ 272\)), but its lability hampered more rigorous characterisation.

![Chemical structure of 109](image)

An alternative approach to the hydrofluorenones 108 and 109* via the unsaturated lactone 110 was also considered.

![Chemical structure of 110](image)

* A mixture would be expected (see section 5.4).
By analogy with an example described previously (see section 2.2), it was thought that this compound 110 could be converted directly to the tricyclic ketones 108 and 109. However, reaction of the acid 106 with boron trifluoride etherate (1.1 equivalents, dichloromethane, 1 hr, 25°) produced a complex mixture (1H n.m.r. and t.l.c. analysis), which did not appear to contain any of the desired lactone 110.

![Chemical structure](image)

The chloroester 112 second readily added to the synthesized objective outlined in Scheme 21 for two reasons. The presence of the two methoxy groups suggested that this molecule would be sufficiently active for the projected cyclization. Also, the reductive methylation of the corresponding benzoic acid moiety, could provide a very useful 4-ring precursor for gibberellin synthesis.

*Complete loss of the 3-methoxy group would be expected under these conditions.*
5.3 During the course of this study, Dean and Rapoport reported a very elegant preparation of the chloro ester 112 \((R=C_2H_5)\) from the tertiary amine 111.

The chloro ester 112 seemed ideally suited to the synthetic objective outlined in Scheme 21 for two reasons. The presence of the two methoxy groups suggested that this nucleus would be sufficiently active for the projected cyclisation. Also, the reductive methylation of the corresponding benzoic acid moiety, \(^*\) could provide a very useful A-ring precursor for gibberellin synthesis.

\(^*\) Complete loss of the \(\omega\)-methoxy group would be expected under these conditions.\(^{52}\)
Accordingly, the tertiary amine 111 was converted to the chloro ester 112 (R=CH₃) in 91% yield. However, alkylation of the dianion 29 in ammonia-tetrahydrofuran with this compound 112 was unsuccessful and the chloro ester 112 was returned unchanged. The use of the corresponding iodide 113† under the same conditions showed more promise, but the desired acid 114 could only be isolated in 25% yield. It seemed likely that the ammonia was competing for the reactive alkylating agent 113, so this solvent was removed after generation of the dianion 29, and the alkylation performed in tetrahydrofuran. In this way, the acid 114 was obtained in

* Presumably the chloro ester 112 arises from the displacement of the quaternised nitrogen by chloride ion.

† Displacement of the chloride by bromide (LiBr, dimethylformamide (DMF); NaBr, acetone) was unsuccessful.
Unfortunately, cyclisation of the acid 114 with 85% sulphuric acid (2 hr, 25°)* afforded the bicyclo[3.3.1]nonane 115 as the major product (52% yield), which was obtained by esterification of the crude product (diazomethane) and chromatography.

The use of PPA (80 min., 50°) gave a complex mixture (t.l.c.), which contained little, if any, of the desired hydrofluorenone.

* These conditions also hydrolysed the aromatic ester.
The alternative approach via the unsaturated lactone 117 was also unsuccessful, as the reaction of the acid 114 with boron trifluoride etherate (3 equivalents) in dichloromethane gave no useful results.
5.4 As a possible precursor to a hydrofluorenone bearing an ester in the aromatic A-ring, the acid 126 was also examined.

![Chemical structures](image)

The first approach to the required alkylating agent 121 was via the toluic ester 120 which has been prepared previously by the route outlined in Scheme 23.
Base-catalysed Michael addition of ethyl acetoacetate to crotonaldehyde and acid-catalysed condensation of the resultant adduct\textsuperscript{138} afforded the cyclohexenone \textsuperscript{118}, which was aromatised\textsuperscript{139,140} to give the phenolic ester \textsuperscript{119,140,141}. Hydrolysis with aqueous base and permethylation then provided the toluic ester \textsuperscript{120} in 20\% overall yield from crotonaldehyde. The photobromination\textsuperscript{141} of this compound \textsuperscript{120}, using the method described in section 5.1, did produce the required bromo ester \textsuperscript{121}(\textsuperscript{1}H n.m.r. analysis), but in contrast with the previous examples (the bromo esters \textsuperscript{95} and \textsuperscript{105}), it could not be induced to crystallise. Moreover, attempts to alkylate the dianion \textsuperscript{29} with the crude reaction product gave unsatisfactory results, and so another route to the alkylating agent was explored.

In the preceding section, the directed metalation of an aromatic ring was used to obtain a 1,2,3,4-tetra-substituted benzene. It was thought this procedure could be exploited for the preparation of the required alkylating agent using the tertiary amine \textsuperscript{122}. However, metalation of this substrate \textsuperscript{122} in tetrahydrofuran (\textit{n}-BuLi, 3 hr, 0\textdegree) did not appear to be as regiospecific, since the desired product \textsuperscript{124}, obtained after acylation with methyl chloroformate, was found to be contaminated with a small amount (c. 10\%) of a regioisomer (\textsuperscript{1}H n.m.r.: \textit{\delta}=7.88, d, 1H, J=8Hz).

![Diagram](image-url)
The difficulty in obtaining regioselective metalation of the amine 122 was overcome by using diethyl ether instead of tetrahydrofuran as a solvent. Although the acylation with methyl chloroformate went quite smoothly, the displacement of the nitrogen function was impeded by the insolubility of the quaternised nitrogen salt in this less polar solvent. It was decided therefore, to effect the transformation of the tertiary amine 122 to the chloro ester 124 in two steps. Thus, metalation of the amine 122 (n-BuLi, diethyl ether, 20 hr, 25°) and acylation of the lithium derivative with dimethyl carbonate afforded, after chromatography on silica gel, the amino ester 123 in 90% yield.

Displacement of the nitrogen function of this compound 123 was then readily accomplished using methyl chloroformate in tetrahydrofuran (16 hr, 25°) to provide the chloro ester 124 in 95% yield.

* This was necessary in order to separate the product 123 from some unreacted starting material 122.
On the basis of the results in the previous section, it was assumed that the chloro ester 124 would not react with the dianion 29. Thus, the chloro ester 124 was converted to the iodo ester 125 (NaI, acetone, 90 min., 25°) and this reagent was used for the alkylation of the dianion 29. This reaction proceeded without incident to furnish the required acid 126 in 84% overall yield from the chloro ester 124.

\[
\text{CH}_3\text{O} \quad \text{I} \quad \text{CO}_2\text{CH}_3
\]

\[
\text{CH}_3\text{O} \quad \text{CO}_2\text{CH}_3 \quad \text{CO}_2\text{H} \quad \text{OCH}_3
\]

Cyclisation of the acid 126 with PPA (5 hr, 25°), gave a mixture which appeared to contain the hydrofluorenone 127 and the more polar isomer 128 (\textsuperscript{1}H n.m.r., m.s., and t.l.c. analysis). Indeed, the compound 127 could be isolated in 36% yield by chromatography on silica gel, and exhibited spectroscopic properties in full agreement with this structure. Unfortunately, the more polar isomer 128 appeared to be too labile to allow a clean separation. Its existence was inferred from the spectra of the mixture (\textsuperscript{1}H n.m.r.):
\[ \delta = 6.00, 1H; \text{i.r.: } 1660 \text{ cm}^{-1} \] and subsequent conversions described in the following chapter.

By modifying the reaction conditions (PPA, 1 hr, 60°), and the work-up procedure, the hydrofluorenones 127 and 128 could be obtained in 70-80\% combined yield in the ratio 4:1 (\(^1\)H n.m.r. analysis).

It is worth mentioning that the alternative approach via the unsaturated lactone 129 also met with success. Thus, cyclisation of the acid 126 with boron trifluoride etherate in dichloromethane (1 hr, 25°) afforded the unsaturated lactone 129 in 70\% yield. Conversion to the hydrofluorenones 127 and 128 (2:1 ratio) was then accomplished in 90\% yield.
by hydrolysis and decarboxylation with 85% $\text{H}_2\text{SO}_4$ (15 min., $25^\circ$).

In view of the success of the cyclisations of the acid 126, it is puzzling that the cyclisations of the other acids 106 and 114, also bearing the methoxycarbonyl substituent in the aromatic ring, apparently failed to produce hydrofluorenones. It would appear that in the case of the acid 106, some hydrofluorenone was formed but was too unstable to be fully characterised. Similarly, the results from the cyclisation of the acid 24 suggest that the aromatic nucleus is sufficiently reactive to produce the hydrofluorenone. As the successful cyclisation of these compounds would also provide intermediates for gibberellin synthesis, a more exhaustive study of the acids 106 and 114 could prove useful.
In the preceding chapter, an efficient preparation of the hydrofluorones 127 and 128 was described. The next task was the addition of the two-carbon bridge to give the tetracyclic ketone 136, using the procedures developed in section 4.1 (cf. Scheme 19).

CHAPTER 6

Preparation of the tetracyclic compound 136

and some experiments directed towards the introduction of the B-ring carboxyl group.

*In spite of the precautions taken to exclude oxygen during this reaction, some decomposition of this compound was also evident. As a result, the yield of the cyanohydrin 129 was lower than expected (85-70%).*
In the preceding chapter an efficient preparation of the hydorfluorenones 127 and 128 was described. The next task was the addition of the two-carbon bridge to give the tetracyclic ketone 136, using the procedures developed in section 4.1 (cf. Scheme 19).

The first stage of the sequence required the conversion of the ketones 127 and 128 to the hydroxy acid 132. Although the \( \alpha, \beta \)-unsaturated ketone 128 was found to be less reactive towards hydrogen cyanide than 127, a modification of the procedure ensured its complete conversion to the cyanohydrin 130 (I.r.: 3500, 2240 cm\(^{-1}\)).

In spite of the precautions taken to exclude oxygen during this reaction, some decomposition of this compound was also evident. As a result, the yield of the cyanohydrin 130 was lower than expected (65-70%).
Methanolysis\textsuperscript{101} of the cyanohydrin 130 then gave the diester 131. Selective hydrolysis of the saturated ester group could be readily effected (KOH, water-methanol-tetrahydrofuran, 2 hr, 25°), to provide the hydroxy acid 132 in 52% overall yield from the ketones 127 and 128.

\[
\begin{align*}
131 & \quad R = \text{OCH}_3 \\
132 & \quad R = \text{OH}
\end{align*}
\]

The next stage of the sequence required the transformation of the hydroxy acid 132 to the diazoketone 134 with the tertiary hydroxyl group protected as a dichloroacetate. The hydroxy acid 132 was therefore treated with dichloroacetyl chloride in refluxing 1,2-dichloroethane to provide the protected acid 133 (R=OH). In view of the difficulties encountered previously with the acid chloride formation using pyridine as a catalyst (see section 4.1), DMF\textsuperscript{143} was employed in this capacity to prepare the acid chloride 133 (R=Cl)(I.r.:1790,1760, 1740 cm\textsuperscript{-1}). Addition of this compound

* Some of the hydroxy acid 132 was also produced during the work-up of this reaction (see Experimental).
to an excess of ethereal diazomethane gave the diazoketone 134, again in about 60% yield (\(^1\)H n.m.r. analysis).

\[
\begin{align*}
\text{R} &= \text{OH} \\
\text{R} &= \text{Cl}
\end{align*}
\]

Cyclisation of the crude diazoketone 134 in trifluoroacetic acid-dichloromethane (-20°), and chromatography of the product on silica gel, gave the crystalline tetracyclic compound 135 in 33% overall yield from the hydroxy acid 132. Removal of the protecting group in the presence of mild aqueous base (NaHCO\(_3\), water-methanol-tetrahydrofuran, 3 hr, 25°),* provided the \(\alpha\)-hydroxy ketone 136 in 75% yield.

\[
\begin{align*}
\text{135} &\quad \text{R} = \text{CCHCl}_2 (\text{DCA}) \\
\text{136} &\quad \text{R} = \text{H}
\end{align*}
\]

* This procedure\(^{144}\) gave a cleaner product (cf. section 4.1).
With the synthesis of the tetracyclic ketone 136 completed, the introduction of the B-ring carboxyl group was then briefly examined. It has been shown that in similar substrates with a secondary amide at C-4, * the benzylic (C-6) carbanion may be generated using a strong base such as n-butyl-lithium. After carboxylation of this carbanion, the C-4 amide is then converted to the acid by nitrosation and hydrolysis. While this approach appeared to be suitable, a more direct route developed by Loewenthal and Schatzmiller was considered. These workers have demonstrated that carboxylation at the benzylic position can be readily accomplished with an ester group at C-4, provided that the highly hindered base, lithium N-cyclohexyl-N-t-butyramide is used to generate the carbanion. Initially, it was thought that this carboxylation procedure could be applied to the tetracyclic ketal ester 137 in which the tertiary hydroxyl group remained unprotected.

* Gibberellin numbering.
† With other lithium bases such as those derived from N-cyclohexyl-N-isopropylamine and 2,2,6,6-tetramethyl-piperidine, attack at the C-4 ester function to give the respective tertiary amides, was observed.
The ketal ester 137 was therefore prepared and subjected to the carboxylation procedure mentioned above. Although an excess of the lithium dialkylamide was used (2.8 equivalents), and a deep purple colour obtained, * reaction with carbon dioxide produced very little acidic material (<10%). Attempts to react the presumed carbanion with dimethyl carbonate or deuterium oxide were also unsuccessful, and the starting ketal ester was returned unchanged. From these results it was inferred that the original assumption was erroneous and that protection of the free tertiary hydroxyl would be necessary. The methoxymethyl ether 145 appeared to be suitable for this purpose because of the ease with which it may be introduced, its stability under strongly basic conditions, and the ease with which it may be removed. † Thus, the hydroxy ketal ester 137 was treated with methoxymethyl chloride in the presence of diisopropylethylamine to afford the crystalline ether 138 in 98% yield. This compound could be successfully deuterated by first generating the benzylic carbanion with lithium cyclohexyl-t-butylamide (5 equivalents) and then quenching the resultant deep purple solution with deuterium oxide (m.s. analysis). Analysis of the $^1$H n.m.r. 

* Presumably, this colour is due to the benzylic carbanion. 34  
† This group is readily cleaved under ketalising conditions. 146
spectrum left no doubt as to the position of deuterium incorporation, as the signals due to the C-6 benzylic protons were greatly diminished while the signals of the protons at the other possible site of metalation (C-12) remained intact. Hence, the product is formulated as the deuterated compound 139. On this basis, it would appear that the introduction of the carboxyl group would be a straightforward task.

By analogy with Loewenthal's work on the 13-deoxy analogue it has been assumed that the carboxylation at C-6 would produce the 6α acid from which the desired cis B,C-
ring-fused compound 141 could be obtained by hydrogenation (cf. 140 → 142).$

\[
\begin{align*}
\text{CH}_3O & \quad \text{CH}_3O \\
\text{H}_3\text{CO}_2\text{C} & \quad \text{H}_3\text{CO}_2\text{C} \\
\text{6} & \quad \text{CO}_2\text{H} \\
\end{align*}
\]

However, a recent communication from Professor Loewenthal$^{147}$ suggests that the introduction of the C-4 methyl group into derivatives of the acid 142 gives the incorrect stereochemistry at this position, in spite of the promising results obtained by House and co-workers on a model system$^{32}$ (see Introduction, Scheme 7). A re-evaluation of the synthetic strategy would appear to be necessary before further work in this area is considered. One possible solution to this problem may be the use of the lactone 143 to control the stereochemistry at C-4.$^*$

\[
\begin{align*}
138 & \quad R = \text{OCH}_2\text{OCH}_3 \\
140 & \quad R = \text{H} \\
141 & \quad R = \text{OCH}_2\text{OCH}_3 \\
142 & \quad R = \text{H} \\
\end{align*}
\]

$^{*}$ Cf. ref. 23a and ref. 25.
While it remains to be shown that the aromatic ring would reduce preferentially, Professor Loewenthal has indicated that reductive methylation may be successfully applied to aromatic esters such as those derived from the acid 142.147
General Topics

(i) Melting points were determined on a Kofler hot-stage apparatus. Melting points and boiling points (b.p.) are uncorrected.

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

(iii) Infrared spectra were recorded on a Jarrell-Ash 1100 spectrophotometer. Molar mulls were used unless otherwise indicated.

(iv) 1H n.m.r. spectra were recorded on a Jeol JNM-GX400 400 MHz spectrometer. Data are given in the following order: chemical shift relative to TMS, multiplicity, intensity as number of protons, coupling constant (Hz), assignment. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; exch., signal disappears on addition of D2O; e, envelope.

The mass spectra were recorded on an AEI MS2002 double-focusing mass spectrometer. High resolution mass spectra were determined using heptacosanone as the reference. The data are presented in the following order: m/z value, relative intensity.
General Topics

(i) Melting points were determined on a Reichert hot-stage apparatus. Melting points and boiling points (b.p.) are uncorrected.

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

(iii) Infra-red spectra were recorded on a Jasco IRA-1 spectrophotometer. Nujol mulls were used unless otherwise indicated.

(iv) $^1$H n.m.r. spectra were recorded on a Jeol Minimar 100 spectrometer operating at 100 MHz. The spectra were measured in deuterochloroform, unless otherwise stated, using tetramethylsilane (TMS) as an internal standard ($\delta$ 0.00 ppm). Data are given in the following order: chemical shift relative to TMS; multiplicity; intensity as number of protons; coupling constant (Hz); assignment. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; exch., signal disappears on addition of D$_2$O; e, envelope.

(v) The mass spectra were recorded on an AEI MS902 double-focussing mass spectrometer. High resolution mass data were determined using heptacosfluorotributylamine as the reference. The data are presented in the following order: m/z value; relative intensity.
as a percentage of the base peak.

(vi) $^{13}$C n.m.r. spectra were recorded on a Jeol FX60 spectrometer operating at 15.04 MHz. The spectra were measured using deuterochloroform as a solvent. The data are given in the following order: chemical shifts ($\delta$) relative to TMS; multiplicity; coupling constant (Hz); assignment. Both proton coupled and proton decoupled spectra were usually recorded.

(vii) Ultra-violet spectra were recorded on a Unicam S.P. 800 Ultra-violet Spectrophotometer, using ethanol as a solvent.

(viii) Column chromatography was carried out using Merck Kieselgel H as the absorbent. Preparative thick layer chromatography (p.l.c.) was carried out on plates (20x20 cm; 1 mm thick) coated with Merck Kieselgel KGF$_{254}$. Analytical t.l.c. was performed on micro-slides coated with a layer of Merck Kieselgel KGF$_{254}$. The micro-slides were visualised using first an ultra-violet light and then by spraying with a solution of 5% (w/v) vanillin in concentrated sulphuric acid and heating at 180°. The eluant used for all of these operations is denoted in brackets. Solvent mixtures are expressed as v/v percentages. Light petroleum refers to the fraction which boils between 60° and 80°.

(ix) Anhydrous solvents were prepared using standard procedures. In particular, tetrahydrofuran (THF)
and diethyl ether (ether) were distilled from the ketyl formed by the reaction of sodium with benzophenone. Hexamethylphosphoric triamide (HMPA) was distilled from sodium, and stored over 4Å sieves. DMF was dried over 3Å sieves. All these operations were carried out under an atmosphere of dry nitrogen.

Organic extracts were dried over anhydrous sodium sulphate unless otherwise indicated. The bulk of the solvent was then evaporated on a Büchi rotary evaporator (water aspirator pressure), and the last traces of solvent removed under high vacuum (c. 0.1 mm).

85% sulphuric acid (w/w) was prepared by adding concentrated sulphuric acid (3 volumes) to water (1 volume). PPA was prepared by adding phosphorus pentoxide (500g) to 85% orthophosphoric acid (375g) at such a rate to maintain the internal temperature at 90° (about 40 min.). After heating at 120° for an additional 3 hr, the resultant colourless syrup was stored in a dessicator.

Ethereal diazomethane was prepared from N-nitroso N-methylurea. For the preparation of methyl esters it was used directly, and for the preparation of diazoketones it was dried over potassium hydroxide pellets (3 hr) before use.
General Procedures

Reductive Alkylation of 2,5-dimethoxybenzoic acid 24

Lithium metal (c. 12.5 mg-atom) was added piecewise to a stirred suspension of the acid 24 (5 mmol) in liquid ammonia (100 ml) and dry THF (10 ml) at -33° under nitrogen, until a deep blue colour persisted. After 20 min. the dianion 29 generated in this manner was then alkylated using one of the following methods, unless otherwise indicated:

Method A: a solution of the alkylating agent (7.5 mmol) in dry THF (5 ml) was added dropwise over 5 min., stirring continued for an additional 60 min., and then the ammonia allowed to evaporate. The residue obtained was dissolved in water (c. 50 ml) and extracted with ethyl acetate (2x50 ml) to remove unwanted neutral by-products. The basic aqueous phase was then cooled to 0°, saturated with sodium chloride, layered with fresh ethyl acetate (100 ml), and acidified to pH 5.5 with 5N hydrochloric acid. The layers were separated, and the aqueous phase extracted further with ethyl acetate (2x50 ml). The extracts were washed with water (50 ml), brine (50 ml) and dried. Removal of the solvent gave the (usually) crystalline alkylated acid in a high state of purity.

Method B: As for Method A, except that after addition of the alkylating agent, the reaction mixture was stirred for an additional 2 hr at -33°.

Method C: The ammonia was removed under a stream of nitrogen, ensuring that the internal temperature did not rise above 0°. To the resultant yellow suspension was added the alkylating
agent (6 mmol) in dry THF (15 ml) at 0°C. After removing the ice-bath, the reaction was stirred for an additional 16 hr, then concentrated in vacuo to give a residue which was dissolved in water (50 ml), the solution made basic (pH 10) with concentrated ammonium hydroxide and then worked up as for Method A.

Notes on Nomenclature

Compounds described in the Experimental have been named, where appropriate, as derivatives of the following:

5,9-Methanobenzocyclooctene (Ref. 153).

3H-3,10a-Methano-1H-indeno[2,1-c]oxepin (Ref. 154).

Gibba-1,3,4a(10a),4b-tetraene (Ref. 155).
CHAPTER 1

2,5-Dimethoxy-1-methyl-2,5-cyclohexadiene-1-carboxylic acid 33

Methyl iodide (25g, 176 mmol) was added dropwise to stirred suspension of the dianion 29 (from the acid 24; 7.28g, 40 mmol) in liquid ammonia (500 ml) and dry THF (80 ml) at -33° under nitrogen. After the addition was complete, the colourless solution was stirred for 20 min. and then the ammonia evaporated. The residue obtained was dissolved in water (200 ml), the solution layered with dichloromethane (200 ml), cooled to 0°, and with vigorous stirring, acidified to pH 5 with 5N hydrochloric acid. The layers were separated and the aqueous phase extracted with fresh dichloromethane (2x100 ml). The extracts were washed with water (1x100 ml), brine (1x100 ml) and dried. Removal of the solvent gave the acid 33 (6.1g, 77%), as a pale orange semi-crystalline solid, homogeneous by t.l.c. (Rf≈0.5; 7% methanol-dichloromethane). Repeated recrystallisation from light petroleum gave white crystals, m.p. 88-90° (Found: C, 60.83; H, 7.12. C<sub>10</sub>H<sub>14</sub>O<sub>4</sub> requires C, 60.59; H, 7.12).

ν<sub>max</sub> 2630, 2520, 1695 (acid), 1660 (C=C-OCH<sub>3</sub>) cm<sup>-1</sup>.  δ 4.68 (t, 1H, J=4Hz, H-3), 4.45 (s, 1H, H-6), 3.54 (s, 6H, 2xC=C-OCH<sub>3</sub>), 2.84 (d, 2H, J=4Hz, C-4 allylic protons), 1.42 (s, 3H, -CH<sub>3</sub>).

m/z 198 (20%, M<sup>+</sup>), 154 (78), 153 (100), 139 (75), 123 (83), 111 (46).
2,5-Dimethoxy-1-methyl-6-oxabicyclo[3.2.1]oct-2-en-7-one 34

Methyl iodide (18.2g, 128 mmol) was added dropwise to a solution of the dianion 29 (from the acid 24; 5.5g, 30 mmol) in liquid ammonia (400 ml) and dry THF (60 ml) at -33° under nitrogen. The residue, obtained after evaporation of the ammonia, was dissolved in water (100 ml) and layered with dichloromethane (100 ml). The two-phase system was then stirred vigorously and acidified rapidly with 5N HCl to pH 5 (sl. exothermic). The layers were separated, the aqueous phase extracted with a fresh portion of dichloromethane (1x100 ml), the extracts washed with water (1x100 ml), brine (1x100 ml) and dried. Evaporation of the solvent left a dark red oil (4.6g), which was homogeneous by t.l.c. (Rf=0.3 dichloromethane). The oil was extracted with hot light petroleum, (3x50 ml) and then the solvent evaporated from the extracts to leave the pure lactone 34 (3.6g, 60%) as a yellow oil which slowly crystallised. Recrystallisation from light petroleum gave large colourless crystals, m.p. 73-74° (Found: C, 60.86; H, 7.21. C_{10}H_{14}O_{4} requires C, 60.59; H, 7.12).

ν_{max} 1770 (C=O), 1650 (C=C-CH_{3}) cm^{-1}.

δ 4.55 (t, 1H, J=4Hz, H-3), 3.50 (s, 3H), 3.48 (s, 3H), 2.60 (m, 2H, C=CH-CH_{2}-), 2.09 and 2.19 (ABq, J_{AB}=12Hz, C-8 protons).

m/z 198 (5%, M^{+}), 170 (12), 154 (81), 139 (76), 123(100), 111(55).
CHAPTER 2

3,5-Dimethoxybenzyl bromide 35

(i) Methyl 3,5-dimethoxybenzoate (39.6g; 0.2 mol) was reduced with lithium aluminium hydride (7g; 0.18 mol) in dry THF (250 ml) to give, after work-up with sat. sodium sulphate solution, 3,5-dimethoxybenzyl alcohol (33g, 98%), m.p. 45-48° (lit. 156 45-47°).

(ii) The method of bromination is essentially that of Gall and Shulgin. Thus, freshly distilled phosphorus tribromide (4 ml, 0.042 mol) was added dropwise to a stirred solution of 3,5-dimethoxybenzyl alcohol (16.8g, 0.1 mol) in dry carbon tetrachloride (200 ml) and dry dichloromethane (100 ml) at 0° (drying tube). After 2 hr, water (400 ml) was added and the layers separated. The organic layer was washed successively with water (200 ml), aqueous 10% sodium bicarbonate solution (100 ml), brine (100 ml) and then dried. Evaporation of the solvent afforded the crystalline bromide 35 (21g, 91%), m.p. 66-68° (lit. 156 70°). (Caution! This compound is a powerful lachrymator and vesicant. It rapidly discolours on exposure to light).

2,5-Dimethoxy-1-(3',5'-dimethoxyphenyl)methyl-2,5-cyclohexadiene-1-carboxylic acid 36

The dianion 29 (from the acid 24; 4.2g, 23 mmol) was alkylated with the bromide 35 (Method A) to give the acid 36 (5.5g, 68%) as a white crystalline solid, m.p. 144-148°. Recrystallisation from ethyl acetate-ether provided an
analytical sample, m.p. 146-148° (Found: C, 64.95; H, 6.83. C_{18}H_{22}O_{6} requires C, 64.66; H, 6.63%).

\( \nu_{\text{max}} \) 2600 (acid), 1700 (C=O), 1660 (C=C, enol ether), 1590 cm\(^{-1}\).

\( \delta \) (CDCl\(_3\)/CD\(_3\)\(_2\)SO) 6.14 (s, 3H, 3xArH), 4.48 (t, 1H, J=4Hz, H-3), 4.41 (s, 1H, H-6), 3.62 (s, 6H, 2xArOCH\(_3\)), 3.48 (s, 3H, C=COCH\(_3\)), 3.44 (s, 3H, C=COCH\(_3\)), 3.18 and 2.82 (ABq, \( J_{AB}=14Hz, \text{ArCH}_2 \)) 2.58* (dd, 1H, \( J_1=20Hz, J_2=4Hz \)), 2.24* (dd, 1H, \( J_1=20Hz, J_2=4Hz \)).

m/z 334 (8%, \( M^+ \)), 290 (97), 288 (74), 275 (23), 152 (77), 151 (100), 139 (74).

2,4-Dimethoxy-5,6,7,8,9,10-hexahydro-5-hydroxy-8-oxo-5,9-methanobenzocyclooctene-9-carboxylic acid 37 (R=CO\(_2\)H)

A solution of the acid 36 (167 mg, 0.5 mmol) in acetone (5 ml) was treated with 1N hydrochloric acid (3 ml) at 25°. After 18 hr, water was added, and the solution extracted with ethyl acetate (3x10 ml), the extracts washed with brine (2x10 ml) and dried. Evaporation of the solvent gave the acid 37 (R=CO\(_2\)H) (150 mg, 90%), m.p. 167-169° (decarboxylates). An analytical sample was obtained by recrystallisation from ethyl acetate-light petroleum (Found: C, 62.57; H, 5.99. C_{16}H_{18}O_{6} requires C, 62.74; H, 5.92%).

\( \nu_{\text{max}} \) 3520 (hydroxyl), 3460, 2600 (acid), 1720 (acid),

* A rigorous examination of the spin-system due to H-3 and C-4 methylene protons, which presumably constitutes an ABX system, was not performed. The values given are those obtained directly from the spectrum. AB quartets have been analysed using the formula described by Jackman and Sternelli[58b]
1700 (ketone), 1605, 1595 (aromatic) cm\(^{-1}\).
\[ \delta (\text{CDCl}_3/(\text{CD}_3)\text{SO}) \]
6.34 (d, 1H, J=2Hz, ArH), 6.20 (d, 1H, J=2Hz, ArH), 4.90 (broad, 1H, exch.), 3.82 (s, 3H, ArOCH\(_3\)), 3.68 (s, 3H, ArOCH\(_3\)), 3.27 and 2.91 (ABq, 2H, J\(_{AB}\)=18Hz, ArCH\(_2\)), 2.8-1.8 (m, 6H).

m/z (no M\(^+\)), 249 (31), 205 (100).

The methyl ester 37 (R=CO\(_2\)CH\(_3\)) was prepared by treating a solution of the acid 37 (R=CO\(_2\)H) in THF (10 ml) with an excess of ethereal diazomethane (quantitative). Recrystallisation from ether-light petroleum gave colourless crystals, m.p. 163-167\(^\circ\) (Found: C, 63.93; H, 6.32. C\(_{17}\)H\(_{20}\)O\(_6\) requires C, 63.74; H, 6.29%).

\[ \nu_{\text{max}} \]
3520 (OH), 1740 (ester), 1710 (ketone), 1605, 1595 (C=C).

6.40 (d, 1H, J=2Hz, ArH), 6.32 (d, 1H, J=2Hz, ArH), 5.00 (s, 1H, exch.), 3.86 (s, 3H, ArOCH\(_3\)), 3.74(s, 6H, ArOCH\(_3\), CO\(_2\)CH\(_3\)), 3.37 and 3.03 (ABq, 2H, J\(_{AB}\)=18Hz, ArCH\(_2\)) 2.80-2.10 (m, 6H).

m/z 320 (4%, M\(^+\)), 263 (100), 205 (22).

2,4-Dimethoxy-5-hydroxy-6,7,9,10-tetrahydro-5,9-methano-benzocyclo"octen-8(5\(\#\))-one 37 (R=H)

A solution of the acid 37 (R=CO\(_2\)H) (120 mg; 0.4 mmol) and p-toluenesulphonic acid (5 mg) in benzene (20 ml) was heated under reflux for 2 hr. Analysis by t.l.c. (7% methanol-dichloromethane) showed the starting material (Rf\(~0.3\)), and product (Rf\(~0.7\)). The cooled solution was
washed with 10% sodium bicarbonate solution (10 ml), brine (10 ml) and dried. Evaporation of the solvent and crystallisation of the residue from ether-light petroleum afforded the ketone 37 (R=H), m.p. 122-124° (50 mg, 48%) (Found: C, 68.53; H, 6.76. \(C_{15}H_{18}O_4\) requires C, 68.69; H, 6.92%).

\(v_{\text{max}}\) 3500 (OH), 1700 (C=O), 1610, 1590 (C=C).

\(\delta\) 6.28 (d, 1H, J=2Hz, ArH), 6.18 (d, 1H, J=2Hz, ArH), 5.00 (s, 1H, exch.), 3.80 (s, 3H, ArOCH\(_3\)), 3.68 (s, 3H, ArOCH\(_3\)), 3.18 (dd, 1H, J\(_1\)=16Hz, J\(_2\)=3Hz, H-10), 2.84 (m, 1H), 2.63 (d, 1H, J=16Hz, H-10), 2.40-1.90 (m, 6H).

m/z 262 (3%, \(M^+\)), 205 (100).

3,4-Dihydro-5,7-dimethoxyfluoren-2(1H)-one 42

(i) The acid 36 (334 mg, 1 mmol) was added to vigorously stirred 85% H\(_2\)SO\(_4\) (4 ml) at 25° under nitrogen. After the evolution of gas subsided (c. 10 min.), the bright yellow reaction mixture was stirred for an additional 60 min. The product was then isolated by pouring onto cracked ice (30g), and extracting with dichloromethane (2x20 ml). The extracts were washed with water (2x20 ml), brine (1x20 ml) and dried. Evaporation of the solvent gave the ketone 42, a colourless crystalline solid (225 mg, 92%), which oxidised rapidly on exposure to heat or air and which was homogeneous by t.l.c. (Rf=0.5, dichloromethane). Recrystallisation from acetone-light petroleum gave pale green needles, m.p. 148-150° (Found: C, 73.45; H, 6.62. \(C_{15}H_{16}O_3\) requires C, 73.75;
H, 6.60%).

\[ \nu_{\text{max}} (\text{CHCl}_3) 1710 (\text{C}=\text{O}) 1600, 1580 (\text{C}≡\text{C}) \text{ cm}^{-1} \]

\[ \delta 6.50 (d, 1\text{H}, J=2\text{Hz}, \text{ArH}), 6.38 (d, 1\text{H}, J=2\text{Hz}, \text{ArH}), 3.72 (s, 6\text{H}, 2\times\text{ArOCH}_3), 3.12 (s, 4\text{H}, \text{C}-1 \text{ and } \text{C}-9 \text{ methylene protons}), 3.08 (2\text{H}, m, \text{C}-4 \text{ methylene protons}), 2.56 (t, 2\text{H}, J=8\text{Hz}, \text{C}-3 \text{ methylene protons}). \]

m/z 244 (100%, M⁺), 216 (51), 215 (18), 202 (28), 201 (23), 188 (31), 173 (18).

(ii) The acid 37 (R=\text{CO}_2\text{H}) (102 mg, 0.33 mmol) was added to vigorously stirred 85% sulphuric acid (1.5 ml) at 25° under nitrogen. After the evolution of gas subsided (c. 5 min.), the bright yellow solution was stirred for an additional 65 min. then worked up as described in (i). The product was identical to the ketone 42 (t.l.c., I.r., \(^1\)H n.m.r.) obtained by the previous procedure.

4,10-Dihydro-3,6,8-trimethoxy-3\#-3,10a-methano-1\#-indenol[e]2,1-c]oxepin-1-one 43

Boron trifluoride etherate (0.047 ml) was added to a stirred suspension of the acid 36 (111 mg, 0.33 mmol) in dry dichloromethane (3 ml) at 25° under nitrogen. The solid immediately dissolved and the solution became very dark in colour. After stirring for 60 min., the solution was diluted with brine (20 ml) and dichloromethane (20 ml), and the layers separated. The organic phase was washed with water (1x20 ml), aqueous 10% sodium bicarbonate solution (1x20 ml),
brine (1x20 ml) and dried. Removal of the solvent gave a colourless oil (99 mg) which was purified by p.l.c. (Rf~0.3, dichloromethane), to give the product 43, as a white crystalline solid (65 mg, 65%). A sample recrystallised from ether as small white needles, m.p. 138-140° (Found: C, 67.54; H, 6.03. \( \text{C}_{17}\text{H}_{18}\text{O}_5 \) requires C, 67.54; H, 6.00%). 

\[ \nu_{\text{max}} \text{1765 (C=O), 1605, 1585 (C=C) cm}^{-1}. \]  

\[ \delta 6.48 (\text{d, 1H, J}=2\text{Hz, ArH}), 6.34 (\text{d, 1H, J}=2\text{Hz, ArH}), 6.26 (\text{t, 1H, J}=4\text{Hz, C-5 proton}), 3.86 (\text{s, 3H, ArOCH}_3), 3.84 (\text{s, 3H, ArOCH}_3), 3.58 (\text{s, 3H, C-3 methoxy protons}), 3.57 \text{ and } 3.03 (\text{ABq, J}_{AB}=16\text{Hz, C-10 protons}), 2.80 (\text{m, 2H, C-4 protons}), 2.59 \text{ and } 2.19 (\text{ABq, J}_{AB}=11\text{Hz, C-11 protons}). \] 

\[ \text{m/z} 302 (40\%, \text{M}^+), 274 (12), 258 (100), 256 (62), 243 (67), 241 (61), 227 (60), 226 (84), 215 (51). \]  

u.v. \( \lambda_{\text{max}} \text{224 (}\varepsilon \text{25,700), 273 (}\varepsilon \text{23,300) nm.} \]

\( m \)-Methoxybenzyl bromide 45

Freshly distilled phosphorus tribromide (40 ml; 0.42 mol) was added dropwise over 25 min. to a stirred solution of \( m \)-methoxybenzyl alcohol (138g, 1 mol) in dry dichloromethane (400 ml) at 0° (drying tube). After 2 hr, water (400 ml) was added and the layers separated. The organic phase was washed with water (1x400 ml), brine (1x400 ml) and dried over anhydrous sodium carbonate. Removal of the solvent gave the oily bromide (188g, 94%) (\textit{Caution! This compound is a potent lachrymator}). The I.r. showed no hydroxyl absorption, and t.l.c. showed one spot Rf~0.8 (dichloromethane).
2,5-Dimethoxy-1-(3'-methoxyphenyl)methyl-2,5-cyclohexadiene-1-carboxylic acid 46

(i) The dianion 29 (from the acid 24; 20g, 0.11 mol) was alkylated with the bromide 45 (29g, 0.144 mol) using Method A, to give the acid 46. Crystallisation from ether-light petroleum gave cream-coloured crystals (25g, 75%), m. p. 134-136° (Found: C, 66.98; H, 6.77. C₁₇H₂₀O₅ requires C, 67.09; H, 6.62%).

νₘₐₓ 2600, 1690 (acid), 1660 (C=C, enol ether), 1610, 1590 (C=C) cm⁻¹.
δ 9.7 (broad, 1H, exch., COOH), 7.00 (t, 1H, J=8Hz, ArH, H-5'), 6.60 (m, 3H, 3xArH), 4.52 (t, 1H, J=4Hz, H-3), 4.44 (s, 1H, H-6), 3.71 (s, 3H, ArOCH₃), 3.54 (s, 6H, 2xC=C-OCH₃), 3.20 and 2.92 (ABq, Jₐₗₚ=12Hz, ArCH₂), 2.62* (dd, 1H, J₁=20Hz, J₂=4Hz, H-4), 2.24 (dd, 1H, J₁=20Hz, J₂=4Hz, H-4).

(ii) The dianion 29 (from the acid 24; 1.82g, 10 mmol) was alkylated with the bromide (2.4g, 12 mmol) using Method C, to give the acid 46 (2.7g, 88%), m. p. 134-136°.

3,4-Dihydro-7-methoxyfluoren-2(1H)-one 44

(i) The acid 46 (152 mg, 0.5 mmol) was mixed intimately with PPA (2g) at 25°, and stirred occasionally with a glass rod during 2 hr. The dark orange reaction mixture was then decomposed with ice (20g), and extracted with dichloromethane (2x20 ml). Analysis by t.l.c. (dichloromethane) showed six compounds. The extracts were washed with water (1x20 ml),

* See footnote p. 127.
brine (1x20 ml) and dried. Removal of the solvent and chromatography of the residue (p.l.c.; dichloromethane) gave the ketone 44 (40 mg), m.p. 82-89°. Recrystallisation from acetone-light petroleum gave pale green crystals, m.p. 86-89° (lit. 39 89-91°). This compound was identical (t.l.c., I.r., 1H n.m.r.) with the product derived from 7-methoxyfluoren-2-ol. 39

(ii) The acid 46 (304 mg, 1 mmol) was added to vigorously stirred 85% H₂SO₄ (4 ml) at 25° under nitrogen. After the evolution of gas subsided (c. 10 min.), the dark orange reaction mixture was stirred for an additional 60 min., then poured onto cracked ice (20g). Extraction with dichloromethane gave the ketone 42 as the sole product (Rf~0.4, dichloromethane), in the form of a pale green semi-crystalline solid (190 mg, 89%). This compound also tended to oxidise on exposure to air. Cyclisation of the acid 46 on a larger scale (12g) gave other unidentified compounds, presumably due to the decomposition of the product 44. However, the ketone 44 could be obtained in a high state of purity (70-75% yield) using ether instead of dichloromethane for the isolation.

**Methyl 2,5-Dimethoxy-1-(3'-methoxyphenyl)methyl-2,5-cyclohexadiene-1-carboxylate 48**

A solution of the acid 46 (2.4g, 7.9 mmol) in THF (100 ml) was treated with an excess of ethereal diazomethane. Removal of the solvent revealed the methyl ester 48 as a colourless viscous oil which crystallised, m.p. 61-65°.
Purification was found to be unnecessary (Found: C, 67.95; H, 6.90. \( \text{C}_{18}\text{H}_{22}\text{O}_{5} \) requires C, 67.91; H, 6.97%).

\( \nu_{\text{max}} \) 1730 (C=O), 1660 (C=C, enol ether), 1600, 1590 (C=C) cm\(^{-1}\).

\( \delta \) 7.00 (t, 1H, ArH, H-5'), 6.60 (m, 3H, 3xArH), 4.48 (t, 1H, J=4Hz, H-3), 3.64 (s, 6H, ArOCH\(_3\) and CO\(_2\)CH\(_3\)), 3.54 (s, 6H, 2xC=COCH\(_3\)), 3.27 and 2.95 (ABq, J\(_{AB}\)=12Hz, ArCH\(_2\)), 2.54* (dd, 1H, J\(_1\)=20Hz, J\(_2\)=4Hz, H-4), 2.18* (dd, 1H, J\(_1\)=20Hz, J\(_2\)=4Hz).

m/z 318 (6%, M\(^+\)), 286 (1), 259 (3), 196 (40), 165 (100), 118 (33), 101 (44).

Methyl 3',9'-Dihydro-7'-methoxyspiro[1,3-dioxalane-2,2'-
[2\(^{2H}\)]fluorene]-9'(1'H)-carboxylate

The methyl ester 48 (500 mg, 1.6 mmol) was added to 85% \( \text{H}_2\text{SO}_4 \) (6 ml), and the resultant orange solution stirred for 30 min. at 25\(^\circ\) under nitrogen. The reaction mixture was then poured onto cracked ice (40g), extracted with dichloromethane (2x50 ml), the extracts washed with water (1x50 ml), brine (1x50 ml), and dried. Removal of the solvent gave a semi-crystalline solid (Rf\(\sim\)0.2, dichloromethane) which coloured rapidly. The crude product was dissolved in 1,2-dichloroethane (100 ml), p-toluenesulphonic acid (5 mg) and ethylene glycol (1 ml) added, and the solution heated under reflux for 48 hr with azeotropically removing of water (reverse Dean and Stark apparatus). The cooled solution was washed with water (1x100 ml), aqueous 10% sodium bicarbonate solution (1x50 ml), brine (1x100 ml) and dried. Removal of

* See footnote p. 127.
the solvent gave a dark orange residue which was purified by column chromatography on silica gel (10g, chloroform), and then crystallisation to give the ketal ester 49 (290 mg, 57%), m.p. 133-135°C (lit. 41a 134-135°C).

4,10-Dihydro-3,8-dimethoxy-3H-3,10a-methano-1H-indeno[2,1-c]oxepin-1-one 43

Boron trifluoride etherate (0.14 ml) was added to a stirred solution of the acid 46 (304 mg, 1 mmol) in dry dichloromethane (5 ml) at 25°C under nitrogen. After stirring for 70 min., the dark green solution was diluted with brine (20 ml) and dichloromethane (20 ml), and the layers separated. The organic phase was washed with water (1x20 ml), aqueous 10% sodium bicarbonate solution (1x10 ml), brine (1x10 ml), and dried. Evaporation of the solvent revealed the unsaturated lactone 50, (251 mg, 92%) as an off-white solid, m.p. 141-145°C. Recrystallisation of a sample from ether gave shiny white crystals, m.p. 144-145°C for analysis (Found: C, 70.53; H, 5.84. C_{16}H_{16}O_4 requires C, 70.58; H, 5.92%).

$\nu_{\text{max}}$ 1755 (C=O), 1605, 1590 (C=C) cm$^{-1}$.

$\delta$ 7.28 (d, 1H, J=9Hz, H-6), 6.76 (m, 2H, H-7 and H-9), 5.86 (t, 1H, J=4Hz, H-5), 3.78 (s, 3H, ArOCH$_3$), 3.52 (s, 3H, C-3 methoxy protons), 3.51 and 2.97 (ABq, $J_{AB}$=16Hz, C-10 protons), 2.76 (m, 2H, C-4 protons), 2.56 and 2.08 (ABq, $J_{AB}$=11Hz, C-11 protons).

m/z 272 (35% M$^+$), 244 (15), 228 (100), 226 (80), 213 (55), 211 (86), 197 (77), 196 (88).
δ 175.1 (s, C-1), 160.8 (s, C-8), 145.7 (s), 144.3 (s), 129.1 (s), 121.6 (d, J=160Hz, C-6), 114.1 (d, J=162Hz, C-9), 110.8 (d, J=165Hz, C-5), 109.7 (d, J=152Hz, C-7), 108.2 (s, C-3), 55.3 (q, J=142Hz, ArOCH₃), 54.8 (s, C-10a), 50.9 (q, J=145Hz, COCH₃), 40.5 (t, J=131Hz, C-10), 34.9 (t, J=131Hz, C-11*), 33.9 (t, J=133Hz, C-4*).

λ<sub>max</sub> 212 (ε 19,700), 220 (21,700), 264 (26,000), 270 (24,200), 302 (9,200), 313 (8,300).

**Conversion of the unsaturated lactone 50 to the tricyclic ketone 44**

The unsaturated lactone 50 (55 mg, 0.2 mmol) was added to 85% sulphuric acid (2 ml) at 25° under nitrogen. There was an immediate evolution of gas, which subsided after 10 min. After 15 min. the dark orange reaction mixture was poured onto ice (20 g) and then extracted with dichloromethane (1×20 ml). The extract was washed with water (1×20 ml), brine (1×20 ml) and dried. Removal of the solvent gave a pale green crystalline solid (31 mg, 72%), identical with the ketone 44 (t.l.c., H<sub>1</sub>n.m.r., I.r.).

(±)(3α,5αα,10αβ)-3,8-Dimethoxy-4,5,5α,10-tetrahydro-3H-3,10α-methano-1H-indeno[2,1-c]oxepin-1-one 51

The unsaturated lactone 50 (200 mg, 0.74 mmol) and 10% palladium-on-carbon (30 mg) in ethyl acetate (30 ml), were stirred under hydrogen at atmospheric pressure for 2 hr.

* These assignments may be interchanged.
The filtered solution (celite) was concentrated in vacuo, to give a colourless crystalline solid (198 mg, 98%), m.p. 161-164°. Recrystallisation from acetone-hexane gave the trans lactone 51 (160 mg, 80%) as shiny colourless plates, m.p. 162-163°. (Found: C, 69.82; H, 6.54. \( \text{C}_{16}\text{H}_{18}\text{O}_{4} \) requires C, 70.06; H, 6.61%).

\( \nu_{\text{max}} \) 1760 (C=O), 1610, 1580 (C=C) cm\(^{-1}\).

\( \delta \) 6.94 (d, 1H, J=8Hz, H-6), 6.82 (d, 1H, J=2Hz, H-9), 6.66 (dd, 1H, \( J_1 =8\text{Hz}, J_2 =2\text{Hz}, H-7 \)), 3.72 (s, 3H, ArOCH\(_3\)), 3.43 (s, 3H, C-3 methoxy group), 3.11 and 2.83 (ABq, \( J_{AB} =16\text{Hz}, C-10 \text{ protons} \)), 3.10 (m, 1H, H-5a), 2.74-1.24 (complex, 6H).

m/z 274 (100%, M\(^+\)), 246 (40), 230 (30), 229 (20), 215 (15), 202 (25), 172 (57), 159 (65), 158 (82).

\( \delta \) 175.7 (m, C-1), 159.2 (s, C-8), 143.9 (m), 133.2 (s), 122.6 (d, J=158Hz, C-6), 112.2 (d, J=158Hz), 110.3 (d, J=158Hz), 108.6 (s, C-3), 59.0 (s, Cl0a), 55.2 (q, J=142Hz, ArOCH\(_3\)), 50.9 (q, J=143Hz, OCOCH\(_3\)), 50.4 (d, J=127Hz, C-5a), 42.9 (t, J=133Hz), 35.3 (t, J=133Hz), 31.6 (t, J=129Hz, C-4), 23.4 (t, J=129Hz, C-5).

\( (\pm)(4\alpha\alpha,9\alpha\beta)-7\text{-Methoxy-2-oxo-3,4,4a,9a-tetrahydrofluorene-9a(1H)}\text{-carboxylic acid} 53 \)

A solution of the saturated lactone 51 (198 mg, 0.72 mmol) in THF (10 ml) was treated with aqueous 3% perchloric acid (3 ml), at 25° under nitrogen. After stirring for 16 hr, the solution was concentrated in vacuo, and the residue partitioned between dichloromethane (30 ml) and water (30 ml).
The layers were separated and the organic phase washed with water (2x30 ml), brine (1x30 ml), and dried. Removal of the solvent revealed the ketoacid 53 (180 mg; 96%). A sample for analysis recrystallised from acetone-light petroleum as shiny needle clusters, m.p. 171-173\(^\circ\) (Found: C, 69.11; H, 6.18. \(\text{C}_{15}\text{H}_{16}\text{O}_{4}\) requires C, 69.22; H, 6.20%).

\[\nu_{\text{max}} 3400, 2700 (\text{acid}), 1740 (\text{acid and ketone}), 1620, 1580 (\text{C} = \text{C}) \text{ cm}^{-1}.\]

\[\delta 6.94 (\text{d}, 1\text{H}, J = 8\text{Hz}, \text{H}-5), 6.82 (\text{d}, 1\text{H}, J = 2\text{Hz}, \text{H}-6), 6.66 (\text{dd}, 1\text{H}, J_1 = 8\text{Hz}, J_2 = 2\text{Hz}), 3.72 (\text{s}, 3\text{H}, \text{ArOCH}_3), 3.12\] and 2.82 (ABq, J\(_{AB}\) = 16Hz, C-9 protons), 3.10 (m, 1H, H-4a), 2.60-1.40 (complex, 6H).

m/z 260 (100%, M\(^+\)), 242 (5), 232 (31), 215 (24), 202 (16), 200 (15), 172 (20), 159 (42), 158 (28).

\((\pm)(3\alpha, 5\alpha, 10\alpha)-3(2-\text{Hydroxyethoxy})-7-\text{methoxy}-4,5,5a,10-\text{tetrahydro}-3\text{H}-3,10\alpha-\text{methano}-1\text{H}-\text{indeno}[2,1-\text{c}]\text{oxepin-1-one} 54\)

A mixture of the ketoacid 53 (100 mg; 0.38 mmol) \(p\)-toluenesulphonic acid (5 mg), ethylene glycol (1 ml) and benzene (100 ml), was heated at reflux under nitrogen, with azeotropie removal of water (Dean and Stark apparatus). After 36 hr, t.l.c. analysis (5% methanol-dichloromethane) showed the product Rf~0.37 and starting material Rf~0.33. The cooled solution was washed with water (2x100 ml), brine (1x100 ml) and dried. Removal of the solvent gave a brown residue, which crystallised from acetone-light petroleum as shiny brown laths (90 mg; 78%), m.p. 163-167\(^\circ\).
\( \nu_{\text{max}} \) 3400 (OH), 1760 (C=O), 1610, 1580 (C=C) cm\(^{-1}\).

\( \delta \) 6.94 (d, 1H, J=8Hz, H-6), 6.82 (d, 1H, J=2Hz, H-9), 6.66 (dd, 1H, \( J_1 =8\)Hz, \( J_2 =2\)Hz, H-7), 3.95 (m, 4H, OCH\(_2\)CH\(_2\)OH), 3.76 (s, 3H, ArOCH\(_3\)), 3.12 and 2.83 (ABq, \( J_{AB} =16\)Hz, C-10 protons), 3.05 (m, 1H, H-5a), 2.70-1.40 (complex, 6H).

m/z 304 (100%, M\(^+\)), 276 (64), 260 (15), 215 (51), 200 (62), 198 (59), 172 (89), 159 (88), 158 (99).

(\( \pm \))(4'\alpha,9'\alpha\beta)-7'-Methoxy-3',4',4'a,9'-tetrahydro-spiro[1,3-dioxalane-2,2'-[2\( \beta\)]-fluorene]-9'a(1'\H)-carboxylic acid methyl ester 55

(i) A solution of the saturated lactone 51 (180 mg, 0.66 mmol) and 36N sulphuric acid (5 drops) was boiled for 40 hr under nitrogen. The solution was concentrated in vacuo, and the residue partitioned between dichloromethane (40 ml) and water (40 ml). The organic layer was separated, and washed with water (1x40 ml), aqueous 10% sodium bicarbonate solution (1x20 ml), brine (1x40 ml), and dried. Removal of the solvent gave a residue, which was crystallised from ether to furnish (\( \pm \))(4\alpha\alpha,9\alpha\beta)-7-Methoxy-2-oxo-3,4,4a,9a-tetrahydrofluorene-9a(1\H)-carboxylic acid methyl ester, as shiny needles (130 mg, 72%), m.p. 117-119\(^0\) (Found: C, 69.75; H, 6.54. \( \text{C}_{16}\text{H}_{18}\text{O}_4 \) requires C, 70.06; H, 6.61%).

\( \nu_{\text{max}} \) 1740, 1700 cm\(^{-1}\).

\( \delta \) 7.00 (d, 1H, J=8Hz, C-5), 6.88 (d, 1H, J=2Hz, C-8), 6.72 (dd, 1H, \( J_1 =8\)Hz, \( J_2 =2\)Hz), 3.80 (s, 3H, ArOCH\(_3\)), 3.56 (s, 3H, CO\(_2\)CH\(_3\)), 3.40-1.80 (complex, 9H).
m/z 274 (100%, \( \text{M}^+ \)), 246 (27), 215 (44), 204 (10), 172 (28), 159 (34).

(ii) The ketoester from (i) (100 mg, 0.36 mmol), was dissolved in 1,2-dichloroethane (100 ml), \( p \)-toluenesulphonic acid (2 mg) and ethylene glycol (0.5 ml) added, and the solution heated at reflux under nitrogen with azeotropic removal of water. After 20 hr, the cooled solution was washed with aqueous 10% sodium carbonate solution (1x20 ml), water (1x100 ml), brine (1x100 ml), and dried. Evaporation of the solvent, and crystallisation of the residue from ether-light petroleum gave small plates (80 mg, 70%), m.p. 144-147° (lit. 41a 143-145°). This product was identical (m.p., m.m.p., I.r.) with the compound obtained by hydrogenating the unsaturated ketal ester 49. 41a

2,5-Dimethoxy-1-phenylmethyl-2,5-cyclohexadiene-1-carboxylic acid 56

The dianion 29 (from the acid 24; 1.82g, 10 mmol) was alkylated with benzyl bromide (1.5 ml) using Method A. The acid 56 was obtained as cream-coloured crystals from ether-light petroleum (2.07g, 74%), m.p. 123-125° (Found: 70.06; H, 6.59. \( \text{C}_{16}\text{H}_{18}\text{O}_4 \) requires C, 70.06; H, 6.61%).

\( \nu_{\text{max}} \) 2600, 1700 (acid), 1660 (C=C, enol ether), cm\(^{-1}\).

\( \delta \) 7.10 (m, 5H, 5xArH), 4.56 (t, 1H, \( J=4 \text{Hz} \), H-3), 4.50 (s, 1H, H-6), 3.50 (s, 6H, 2xC=COCH\(_3\)), 3.34 and 2.96 (ABq, \( J_{\text{AB}}=14 \text{Hz}, \text{ArCH}_2\), 2.62* (dd, 1H, \( J_1=21 \text{Hz} \), \( J_2=4 \text{Hz} \)), 2.16* (dd, 1H, \( J_1=21 \text{Hz} \), \( J_2=4 \text{Hz} \)).

* See footnote p. 127.
m/z 274 (4%, $\text{M}^+$), 230 (38), 228 (13), 215 (16), 182 (29), 165 (42), 139 (83), 124 (34), 91 (100).

5-Hydroxy-6,7,9,10-tetrahydro-5,9-methanobenzocycloocten-8(5H)-one 57

The acid 56 (100 mg, 0.36 mmol) was added to vigorously stirred 85% sulphuric acid (2 ml), at 25° under nitrogen. After the evolution of gas subsided (c. 5 min.), the orange reaction mixture was stirred for an additional 2 hr at 25°, then poured onto ice (20g). The mixture was extracted with dichloromethane (2x20 ml), the extracts washed with water (1x20 ml), brine (1x20 ml) and dried. Analysis by t.l.c. revealed a mixture of three components. The major product isolated by p.l.c. ($\text{Rf}$=0.3, 4% methanol-dichloromethane) was obtained as a colourless gum (52 mg, 72%), and identified on the basis of its spectroscopic features, as the ketone 57. (Accurate mass, Found: 202.0095. $\text{C}_{13}\text{H}_{14}\text{O}_2$ requires 202.0994).

$\nu_{\max}$ (film) 3400 (OH), 1710 (C=O) cm$^{-1}$.

$\delta$ 7.70 (m, 1H, ArH), 7.20 (m, 3H, 3xArH), 4.0 (broad, 1H, exch., OH), 3.20 (dd, 1H, $J_1=14$Hz, $J_2=6$Hz, ArCH), 2.94 (m, 1H), 2.74 (d, 1H, $J=14$Hz), 2.40-1.80 (complex, 6H).

m/z 202 (6%, $\text{M}^+$), 184 (<1%), 145 (100).
CHAPTER 3

2-(3-Methoxyphenyl)ethyl iodide 61 (R=I)

The procedure followed was that of Landauer and Rydon. Thus, a mixture of 2-(3-methoxyphenyl)ethyl alcohol 84 61 (R=OH) (5.1g, 33 mmol), triphenyl phosphite (11.21g 36 mmol), and methyl iodide (7.5g, 53 mmol), was heated under gentle reflux for 30 hr (drying tube). The resultant straw-coloured liquid was diluted with ether (200 ml), and extracted with 0.1N sodium hydroxide solution (3x200 ml), brine (1x200 ml), and dried. Removal of the solvent gave an oil, which was found to be a mixture of the iodide 61 (R=I) and diphenyl methylphosphonate (1H n.m.r. analysis). The oil was dissolved in a minimum amount of benzene, and the solution applied to a column of florisil. Elution with light petroleum gave the iodide 61 (R=I) (5g, 58%), b.p. 59-65°C/0.09 mm (lit. 84 85-90/0.01).

\( \nu_{\text{max}} \) (no OH), 1600 cm\(^{-1}\).

\( \delta \) 7.08 (t, 1H, J=8Hz, ArH), 6.70 (m, 3H, 3xArH), 3.70 (s, 3H, ArOCH\(_3\)), 3.16 (m, 4H, ArCH\(_2\)CH\(_2\)I).

m/z 262 (31), 135 (100).

2,5-Dimethoxy-1-(3-methoxyphenyl)ethyl-2,5-cyclohexadiene-1-carboxylic acid 62

The dianion 29 (from the acid 24; 0.91g, 5mmol) was alkylated with the iodide 61 (R=I) (1.7g, 6.5 mmol) using Method B, to provide the acid 62 (1g, 63%), m.p. 121-125°C, as a cream-coloured crystalline solid (Found: C, 68.00; H,
7.01. \( \text{C}_{18} \text{H}_{22} \text{O}_{5} \) requires C, 67.91; H, 6.97%.

\( \nu_{\text{max}} \) 2600, 1705 (acid), 1660 (C=O, enol ether), 1610, 1580 (C=C) cm\(^{-1}\).

\( \delta \) 7.13 (t, 1H, \( J=8\text{Hz} \), H-5', Ar\( \text{H} \)), 6.70 (m, 3H, 3xAr\( \text{H} \)), 4.80 (t, 1H, \( J=4\text{Hz} \), H-3), 4.40 (s, 1H, H-6), 3.74 (s, 3H, ArOCH\(_3\)), 3.52 (s, 6H, 2xC=COCH\(_3\)), 2.86 (d, 2H, \( J=4\text{Hz} \), C-4 protons), 2.60-1.80 (m, 4H, ArCH\(_2\)CH\(_2\)).

m/z 318 (36%, M\(^+\)), 274 (69), 273 (24), 272 (22), 153 (100), 151 (41), 139 (40), 137 (46), 121 (78).

---

7-Methoxy-3,4,9,10-tetrahydrophenanthren-2(1H)-one 60 and
7-Methoxy-4,4a,9,10-tetrahydrophenanthren-2(3H)-one 64

The acid 62 (100 mg, 0.31 mmol) was added to vigorously
stirred 85% sulphuric acid (3 ml) at 23° under nitrogen.
After the vigorous evolution of gas subsided (c. 10 min.),
the orange-coloured reaction mixture was poured onto cracked
ice (20g). The products were extracted with dichloromethane
(2x20 ml), the extracts washed with water (2x20 ml), brine
(1x20 ml) and dried. Analysis by t.l.c. (dichloromethane)
showed two compounds, Rf\( \sim 0.6 \) and Rf\( \sim 0.4 \). The solvent was
evaporated, and the air-sensitive residue subjected to p.l.c.
(dichloromethane). The less polar compound was identified
as the hydrophenanthrenone 60 (25 mg, 35%). It could not be
obtained in crystalline form.

\( \nu_{\text{max}} \) (CHCl\(_3\)), 1720 (C=O), 1610, 1585 cm\(^{-1}\) (lit. 78 1718 cm\(^{-1}\)).

\( \delta \) 7.10 (d, 1H, \( J=9\text{Hz} \), H-5), 6.70 (2H, m, H-6, H-8), 3.76
(s, 3H, ArOCH\(_3\)), 3.00 (broad, 2H, C-1 protons),
2.88-2.52 (m, 6H), 2.18 (t, 2H, \( J=8\text{Hz} \)).
m/z 228 (100%, M⁺), 226 (10), 199 (20), 186 (72), 171 (23).

λ_max 215 (ε 19,700), 274 (16,200) nm (lit. 78 273 (16,100)).

The more polar isomer was identified as the hydro-
phenanthrenone 64 (40 mg, 56%), which could not be obtained
in crystalline form (Accurate mass, Found: 228.1151.

C₁₅H₁₆O₂ requires 228.1150).

v_max (CHCl₃) 1660 (α,β-unsat. ketone), 1625, 1610, 1590 cm⁻¹.

δ 7.14 (d, 1H, J=9Hz, H-5), 6.74 (dd, 1H, J₁=9Hz, J₂=3Hz,
H-6), 6.60 (d, 1H, J=3Hz, H-8), 5.96 (m, 1H, H-1), 3.72
(s, 3H, ArOCH₃), 3.66 (m, 1H, H-49), 2.82 (m, 2H), 2.70-1.60
(m, 6H).

m/z 228 (100%, M⁺), 200 (35), 199 (16), 186 (64), 171 (27).

λ_max 232 (ε 19,000) nm.

3,9-Dimethoxy-2,3,6,7-tetrahydro-5H-3,5a-methanonaphth
[2,1-c]oxepin-1-one* 65

A solution of the acid 62 (100 mg, 0.31 mmol) in dry
dichloromethane (2 ml) was treated with boron trifluoride
etherate (0.04 ml, 0.31 mmol), at 23° under nitrogen. After
stirring for 60 min., brine was added and the layers
separated. The organic phase was washed with water (1x2 ml),
brine (1x2 ml), and dried. The solvent was removed, and the
residue chromatographed (p.l.c., 3% methanol-dichloromethane)
to provide the crystalline unsaturated lactone 65 (56 mg,
65%). A sample for analysis recrystallised from ether as
pale green needles, m.p. 142-144° (Found: C, 71.22; H, 6.26.

* cf. ref. 161.
$C_{17}H_{18}O_4$ requires C, 71.31%; H, 6.34%.

$\nu_{\text{max}}$ 1755 (C=O), 1600 cm$^{-1}$.

$\delta$ 7.44 (d, 1H, J=9Hz, H-11), 6.70 (m, 2H, H-8 and H-10),
6.16 (t, 1H, J=4Hz, H-1), 3.80 (s, 3H, ArOCH$_3$), 3.52 (s,
3H, OCOCH$_3$), 3.00-1.80 (m, 8H).

m/z 286 (55%, $M^+$), 258 (100), 24 (30), 227 (30), 225 (15),
211 (75), 210 (50), 200 (32).

2-Phenylethyl iodide 66 (R=I)

This compound was prepared according to the procedure of Landauer and Rydon, $^{87a}$ in 69% yield, b.p. 59-62°/0.25 mm (lit. $^{87a}$ 94-95°/1.5).

2,5-Dimethoxy-1-phenylethyl-2,5-cyclohexadiene-1-carboxylic acid 67

The dianion 29 (from the acid 24; 0.91g, 5 mmol) was alkylated with the iodide 66 (R=I) (1.5g, 6.5 mmol) using Method B, to provide the acid 67 (1g, 70%). A sample was recrystallised from acetone-hexane for analysis, m.p. 144-
147° (Found: C, 70.50; H, 6.97. $C_{17}H_{17}O_4$ requires C, 70.81;
H, 6.99).

$\nu_{\text{max}}$ 2600, 1705 (acid), 1665 (C=C, enol ether), 1600 cm$^{-1}$.

$\delta$ 8.80 (broad, 1H, exch., CO$_2$H), 7.20 (m, 5H, 5xArH), 4.84
(t, 1H, J=4Hz, H-3), 4.44 (s, 1H, H-6), 3.52 (s, 6H,
C=COCH$_3$), 2.90 (d, 2H, J=4Hz), 2.60-1.80 (m, 4H, ArCH$_2$CH$_2$).
m/z 288 (20%, $M^+$), 244 (60), 242 (40), 91 (100).
4,4a,9,10-Tetrahydrophenanthren-2(3\textnu)-one 68

The acid 67 (100 mg, 0.34 mmol) was added to vigorously stirred 85% sulphuric acid (2 ml) at 45° (internal temperature), under nitrogen. After the evolution of gas subsided (c. 10 min.), the dark red solution was stirred for an additional 50 min., then poured onto ice (10 g). The reaction mixture was extracted with dichloromethane (2 x 10 ml), the extracts washed with water (1 x 10 ml), aqueous 10% sodium bicarbonate (1 x 5 ml), brine (1 x 10 ml) and dried. Removal of the solvent gave the hydrophenanthrenone 68 as a colourless crystalline solid (60 mg, 87%), which was homogeneous by t.l.c. (Rf ~ 0.15, dichloromethane), (colours rapidly in air). A sample crystallised from ether for analysis had m.p. 94-95° (long needles) (Found: C, 84.72; H, 6.95. C\textsubscript{14}H\textsubscript{14}O requires C, 84.81; H, 7.12%).

ν\textsubscript{max} 1680 (C=O) cm\textsuperscript{-1}.

δ 7.20 (m, 4H, 4×ArH), 5.96 (m, 1H, H-1), 3.70 (m, 1H, H-4a), 3.00-1.60 (m, 8H).

m/z 198 (92%, M\textsuperscript{+}), 170 (17), 156 (100), 155 (21), 141 (57), 128 (22), 115 (22).

λ\textsubscript{max} 236 (ε 17,500) nm.
CHAPTER 4

3,4-Dihydro-2-hydroxy-7-methoxyfluorene-2(1H)-carbonitrile 71

The method used is essentially that of Mander et al. 38

The ketone 44 (2.14g, 10 mmol) was dissolved in THF (50 ml), then ether (50 ml) and water (50 ml) were added and the two-phase system purged of oxygen with a stream of nitrogen for 1 hr. Sodium cyanide (1.96g, 40 mmol) was added all at once, followed by the dropwise addition of hydrochloric acid (4 ml, 10M) over 1 hr, with vigorous stirring. After the addition was completed, t.l.c. analysis showed a single spot Rf^0.2 (dichloromethane). Ethyl acetate (100 ml) was added and the layers separated. The organic phase was washed with water (5x100 ml), brine (1x100 ml) and dried. Evaporation of the solvent, and trituration of the residue with ether, gave the cyanohydrin 71 (1.93g, 80%). A sample recrystallised from ether as pale green needles, m.p. 143-147º (Found: C, 74.84; H, 6.45; N, 5.52. C_{15}H_{15}NO_2 requires C, 74.67; H, 6.27; N, 5.80%).

ν\text{max} 3400 (OH), 2200 (CN) cm^{-1}.

δ 6.86 (d, 1H, J=8Hz, H-5), 6.84 (d, 1H, J=2Hz, H-8), 6.66 (dd, 1H, J_1=8Hz, J_2=2Hz, H-6), 3.70 (s, 3H, ArOCH_3), 3.12 (broad s, 2H, C-9 protons), 2.80 (e, 2H, C-1 protons), 2.54 (broad e, 2H, C-4 protons), 2.10 (m, 2H, C-3 protons).

Methyl 3,4-Dihydro-2-hydroxy-7-methoxyfluorene-2(1H)-carboxylate 73

The method used is essentially that of Birch et al. 101
Thus, a suspension of the cyanohydrin 71 (2.8g, 11.6 mmol) in absolute methanol (159 ml) was cooled to 0°C, and then treated with hydrogen chloride gas until the reaction mixture was saturated (c. 20-30 min.). The flask was then stoppered securely and allowed to warm to room temperature, overnight. Ice (c. 150g) was added, the reaction mixture stirred vigorously for an additional 60 min., and then extracted with dichloromethane (3×100 ml). The extracts were washed with water (2×100 ml), aqueous 10% sodium bicarbonate solution (1×50 ml), brine (1×100 ml) and then dried. Removal of the solvent gave the crude hydroxy methyl ester 73 (2.84g) as a tan solid, m.p. 110-115°C, which was used directly in the next experiment. The pure methyl ester 73 was obtained by filtering a sample through silica gel (10g; chloroform); recrystallisation from ether then gave colourless needles, m.p. 125-128°C (Found: C, 69.98; H, 6.41. C_{16}H_{18}O_{4} requires C, 70.06; H, 6.61%).

ν_{max} 3400 (OH), 1720 (C=O).

δ 7.00 (d, 1H, J=8Hz, H-5), 6.88 (d, 1H, J=2Hz, H-8), 6.70 (dd, 1H, J_1=8Hz, J_2=2Hz, H-6), 3.72 (s, 6H, ArOCH_3 and CO_2CH_3), 3.18 (broad s, 2H, C-9 protons), 3.00 (s, 1H, exch., OH), 2.96 (m, 1H), 2.54 (m, 3H), 2.00 (m, 2H, C-3 protons).

m/z 274 (31%, M^+), 256 (33), 172 (100).
3,4-Dihydro-2-hydroxy-7-methoxyfluorene-2(1H)-carboxylic acid 74

The crude methyl ester 73 (2.84 g, 10.4 mmol) was dissolved in THF (20 ml) and the solution diluted with methanol (20 ml) and water (5 ml), and purged of oxygen with a stream of nitrogen for 1 hr. Potassium hydroxide pellets (1.2 g, 21 mmol) were added and the reaction stirred at 25°C for 1 hr, after which time t.l.c. analysis showed that the starting material (Rf~0.5, 2% methanol-dichloromethane) had been consumed. The solution was concentrated in vacuo, diluted with water (50 ml) and extracted with ethyl acetate (2×50 ml). The basic aqueous phase was then acidified to pH 1 with 10N hydrochloric acid and the precipitate collected by filtration and dried (2.4 g, 90%), m.p. 211-215°C (lit. 38 215-218°C). This product was identical to an authentic sample of the hydroxy acid 74 prepared previously162 (t.l.c., I.r.).

2-Dichloroacetoxy-3,4-dihydro-7-methoxyfluorene-2(1H)-carboxylic acid 75 (R=OH)

This method is a slight modification of the one described by Mander et al..104 Dichloroacetyl chloride (4.2 ml) was added to a suspension of the hydroxy acid 74 (3.6 g, 13.8 mmol) in 1,2-dichloroethane (60 ml) and the mixture heated under reflux for 3 hr (drying tube). The solution was concentrated in vacuo, the oily residue dissolved in acetone (60 ml) and then treated with water (30 ml). After stirring for 16 hr at 25°C, the solution was
concentrated in vacuo, and the dark green precipitate collected, washed with cold water (3x50 ml), and dried at 80° for 48 hr. The dichloroacetoxy acid 75 (R=OH) (4.77g, 93%) obtained in this way, was homogeneous by t.l.c. (Rf~0.4, 10% methanol-dichloromethane), and had m.p. 188-192°. Recrystallisation (twice) from acetone light-petroleum gave shiny pale green crystals, m.p. 191-195°. Satisfactory analysis could not be obtained. (Found: C, 55.25; H, 4.51; Cl, 18.72. C_{17}H_{16}Cl_{2}O_{5} requires C, 55.00; H, 4.34; Cl, 19.10%)

ν_{max} 1760 (dichloroacetate), 2600, 1710 (acid), 1610, 1580 (C=O) cm^{-1}.

δ (CDCl_{3}/(CD_{3})_{2}SO) 7.00 (d, 1H, J=8Hz, H-5), 6.90 (d, 1H, J=2Hz, H-8), 6.70 (dd, 1H, J_{1}=8Hz, J_{2}=2Hz, H-6), 5.84 (s, 1H, COCHCl_{2}), 3.70 (s, 3H, ArOCH_{3}), 3.20 (broad s, 2H), 3.00 (m, 2H), 2.60-2.1 (m, 4H).

(\pm)(7a,9a\beta)-7-Dichloroacetoxy-2-methoxy-gibba-1,3,4a(10a),4b-tetraen-8-one 77

A suspension of the dichloroacetoxy acid 75 (R=OH) (2g, 5.4 mmol) and dry pyridine (0.216g, 2.7 mmol) in dry dichloromethane (15 ml), was added to a stirred solution of oxalyl chloride (1.7 ml) in dry dichloromethane (3 ml) at 0° (drying tube). After stirring for 48 hr at 25°, the volatiles were removed in vacuo, the residue treated with cold dry benzene (20 ml), filtered, and the precipitate washed with fresh dry benzene (2x20 ml). The benzene was evaporated, and the last traces of hydrogen chloride removed.
under high vacuum, to give the acid chloride 75 (R=Cl) as a
dark green gum (2.1g).

$\nu_{\text{max}}$ (film) 1790-1760 (-COCl and -COCHCl$_2$) cm$^{-1}$.

A solution of the acid chloride 75 (R=Cl) (2.1g) in
dry dichloromethane (10 ml) was added to diazomethane (from
5.5g of $N$-nitroso-$N$-methylurea) in ether (100 ml) at $-20^\circ$
(CC$_4$-CO$_2$ bath), under nitrogen. The solution was allowed to
warm to room temperature overnight, and then concentrated
in vacuo to leave the crude diazoketone 76 (2.1g) as an
orange gum, which was cyclised immediately.

$\nu_{\text{max}}$ (CHCl$_3$), 2080 (HCN$_2$), 1760 (COCHCl$_2$), 1640-1610 (COCHN$_2$),
1580 (C=C) cm$^{-1}$.

A solution of the crude diazoketone 76 (2.1g) in dry
dichloromethane (15 ml) was added dropwise to a vigorously
stirred slurry of trifluoroacetic acid (35 ml) and dry
dichloromethane (20 ml) at $-20^\circ$ (CC$_4$-CO$_2$ bath) under
nitrogen. After 10 min. the dark red solution was diluted
with dichloromethane (50 ml) and water (100 ml), and the
layers separated. The organic phase was washed with water
(2x100 ml), aqueous 10% sodium bicarbonate solution (1x50 ml),
brine (1x100 ml) and dried. Removal of the solvent, gave a
dark red residue which was chromatographed on a column of
silica gel (40g, chloroform), to provide the dichloroacetoxy
ketone 77 (810 mg, 41%) as a pale yellow crystalline solid.
Recrystallisation from acetone-light petroleum gave
colourless leaflets for analysis, m.p. 160-162$^\circ$. (Found: C, 58.79; H, 4.44; Cl, 19.41. $C_{18}H_{16}Cl_2O_4$ requires C, 58.87;
H, 4.39; Cl, 19.31).

$\nu_{\text{max}}$ 1765 (COCHCl$_2$), 1750 (ketone), 1600, 1580 (C=C) cm$^{-1}$.

$\delta$ 7.23 (d, 1H, J=8Hz, H-4), 6.90 (m, 2H, H-1 and H-3), 5.90 (s, 1H, COCHCl$_2$), 5.65 (t, 1H, J=4Hz, H-5), 3.70 (s, 3H, ArOCH$_3$), 3.2-2.2 (complex m, 8H).

m/z 368 (21), 366 (32%, M$^+$), 238 (100), 213 (16), 210 (42), 195 (41), 185 (42).

$\delta$ 210.3 (s, C-8), 163.1 (s, COCHCl$_2$), 160.9 (s, C-2), 150.2 (s), 145.3 (s), 129.8 (s), 122.2 (d, J=161Hz, C-4), 114.1 (d, J=160Hz), 110.1 (d, J=158Hz), 108.0 (dt, $J_1=163$Hz, $J_2=8$Hz, C-5), 87.7 (s, C-7), 64.1 (d, J=179Hz, COCHCl$_2$), 55.5 (q, J=145Hz, ArOCH$_3$), 51.5 (t, J=129Hz, C-9), 45.9 (s, C-9a), 40.2 (t, J=133Hz, C-10 or C-11), 39.6 (t, J=132Hz, C-11 or C-10), 36.1 (t, J=132Hz, C-6).

A sample of the diazoketone 76 was purified by p.l.c. (Rf=0.7, dichloromethane), to give a pale yellow gum.

$\delta$ 7.00 (d, 1H, J=8Hz, H-5), 6.90 (d, 1H, J=2Hz, H-8), 6.70 (dd, 1H, $J_1=8$Hz, $J_2=2$Hz, H-6), 5.90 (s, 1H, COCHCl$_2$), 5.40 (s, 1H, N$_2$CHCO), 3.75 (s, 3H, ArOCH$_3$), 3.20 (broad s, 2H), 3.0-2.0 (m, 6H).

A solution of the pure diazoketone 76 (60 mg, 0.15 mmol) was cyclised as described above, to give the dichloroacetoxy ketone (50 mg, 90%), m.p. 158-162$^\circ$. 
(±)(7a,9aβ)-7-Hydroxy-2-methoxy-gibba-1,3,4a(10a),4b-tetraen-8-one 15

A solution of the dichloroacetoxy ketone 77 (732 mg, 2 mmol) in methanol (10 ml), THF (20 ml) and water (5 drops) was purged of oxygen with a stream of nitrogen for 1 hr. Anhydrous potassium carbonate (552 mg, 4 mmol) was added and the two-phase system stirred for 10 min. The volatiles were removed \textit{in vacuo} and the residue partitioned between dichloromethane (50 ml) and water (50 ml). The layers were separated, and the organic phase washed with brine (1x50 ml) and dried. Removal of the solvent gave a red solid, homogeneous by t.l.c. (Rf~0.2, 2% methanol-dichloromethane). Recrystallisation from acetone-hexane gave pale pink crystals in two crops (457 mg, 90%), m.p. 178-182° (lit. 179-181°). All other spectroscopic data have been recorded except for the $^{13}$C n.m.r. spectra.

$\delta$ 219.1 (s, C-8), 160.4 (s, C-2), 149.6 (s), 145.1 (s), 130.1 (s), 121.8 (d, J=161Hz, C-4), 113.8 (d, J=161Hz), 109.9 (d, J=160Hz), 109.6 (d, J=160Hz), 80.8 (s, C-7), 55.3 (q, J=144Hz, ArOCH$_3$), 51.3 (t, J=132Hz, C-9), 45.3 (s, C-9a), 44.3 (t, J=133Hz, C-11), 40.1 (t, J=132Hz, C-10), 38.8 (t, J=133Hz, C-6).

Hydrogenation of the unsaturated ketone 15

A solution of the unsaturated ketone 15 (210 mg, 0.82 mmol) in ethyl acetate (35 ml), containing 10% palladium-on-carbon (30 mg), was hydrogenated while stirring at room temperature and atmospheric pressure. The filtered (celite)
solution was concentrated to give a colourless crystalline solid (210 mg), m.p. 90-140°. The two components ran as one spot in several solvent systems (Rf~0.1, 30% dichloromethane-benzene; Rf~0.35, 2% methanol-dichloromethane; Rf~0.4, 25% ethyl acetate-benzene; Rf~0.7, 20% light petroleum-ethyl acetate). The ratio of the two components was deduced from the $^1$H n.m.r. spectrum. The minor isomer exhibited signals at 7.00 ppm (d, J=8Hz, H-4) and 3.76 ppm (s, ArOCH$_3$), while for the major isomer these signals occurred at 6.96 ppm (d, J=8Hz, H-4) and 3.74 ppm (s, ArOCH$_3$). The m.s. of the mixture was identical to the m.s. of the major isomer (vide infra). The $^{13}$C n.m.r. data for the mixture is as follows: \[ \delta 219.9 \text{ (s)}, 218.2 \text{ (s)}, 158.7 \text{ (s)}, 143.9 \text{ (s)}, 143.0 \text{ (s)}, 137.4 \text{ (s)}, 136.0 \text{ (s)}, 123.0 \text{ (d, J=158Hz)}, 112.1, 111.4, 111.0, 81.4 \text{ (s)}, 79.5 \text{ (s)}, 55.3 \text{ (q, J=145Hz)}, 50.5, 49.6, 48.3, 47.0, 45.5, 44.1, 42.1, 36.5 \text{ (t, J=130Hz)}, 35.1 \text{ (t, J=130Hz)}, 22.0 \text{ (t, J=132Hz)}. \]

Fractional crystallisation from methanol (twice) gave the major isomer (35 mg), (+) (4βα,7α,9αβ)-7-Hydroxy-2-methoxy-gibba-1,3,4α(10α)-trien-8-one 79, as small rectangular prisms, m.p. 160-163° (Found: C, 74.53; H, 7.00. \[ \text{C}_{16}\text{H}_{18}\text{O}_3 \text{ requires C, 74.40; H, 7.02%}. \]

\[ \nu_{\text{max}} 3400 \text{ (OH)}, 1740 \text{ (C=O)} \text{ cm}^{-1}. \]
\[ \delta 6.96 \text{ (d, 1H, J=8Hz, H-4)}, 6.80 \text{ (d, 1H, J=2Hz, H-1)}, 6.69 \text{ (dd, 1H, J$_1$=8Hz, J$_2$=2Hz, H-3)}, 3.74 \text{ (s, 3H, ArOCH$_3$)}, 3.00 \text{ (m, 1H, H-4b)}, 2.98 \text{ and 2.61 (ABq, J$_{AB}$=15Hz, C-10 protons)}, 2.92 \text{ (s, 1H, exch., OH)}, 2.42-1.20 \text{ (complex, 8H)}. \]
m/z 258 (72%, M⁺), 230 (6), 215 (20), 214 (21), 172 (100), 159 (63).

δ 217.9 (s, C-8), 158.8 (s, C-2), 143.9 (s), 135.8 (s), 123.0 (d, J=158Hz, C-4), 111.4 (d, J=160Hz), 111.0 (d, J=160Hz), 81.3 (s, C-7), 55.3 (q, J=145Hz, ArOCH₃), 50.5 (d), 48.4 (s, C-9a), 45.5 (t, J=130Hz), 44.0 (t, J=130Hz), 42.1 (t, J=130Hz), 36.5 (t, J=132Hz, C-6), 22.0 (t, J=127Hz, C-5).

Isomerisation reactions of the α-ketols 78 and 79

The mixture of α-ketols 78 and 79 used in the following experiments was that obtained by hydrogenation of the unsaturated ketone 15 (vide supra).

(i) A stirred solution of the α-ketols 78 and 79 (77 mg; 0.30 mmol) in dry THF (10 ml), was treated with granular sodium hydride (15 mg; 0.63 mmol) at 25° under nitrogen. The evolution of gas was accompanied by the formation of a precipitate, which was dissolved by the addition of dry HMPA (0.06 ml) and warming to 60° for 20 min. The dark solution was then allowed to cool, and stirring continued overnight. The solution was then acidified to pH 6.5 with 1N hydrochloric acid, diluted with water (20 ml) and extracted with dichloromethane (2x20 ml). The extracts were washed with water (1x20 ml), brine (1x20 ml) and dried. Removal of the solvent gave a gum which was purified by p.l.c. (4% methanol-dichloromethane). The colourless crystalline solid obtained (38 mg, 50%) was identical
(1H n.m.r. and 13C n.m.r.) with the major isomer 79. Only a trace of the minor isomer 78 could be detected (13C n.m.r. spectra).

(ii) The mixture of α-ketols 78 and 79 (60 mg, 0.23 mmol) was dissolved in absolute methanol (10 ml) and the solution purged of oxygen with a stream of nitrogen for 2 hr. Anhydrous potassium carbonate (63 mg, 0.43 mmol) was added, and the two-phase system stirred for 16 hr at 25°. The reaction mixture was then diluted with dichloromethane (20 ml) and water (10 ml), and the layers separated. The organic phase was washed with water (2x20 ml), brine (1x20 ml) and dried. Removal of the solvent gave a pale yellow crystalline solid (54 mg; 90%), which was found to consist mainly of the major isomer 79 (1H n.m.r. and 13C n.m.r.). The minor isomer 78 could not be detected by 1H n.m.r. spectroscopy.

(iii) A stirred solution of the mixture of α-ketols 78 and 79 (65 mg; 0.25 mmol) in dry dichloromethane (1 ml) was treated with freshly distilled boron trifluoride etherate (0.03 ml) at 25° under nitrogen. After stirring for 16 hr, dichloromethane (20 ml) and brine (10 ml) were added to the dark solution and the layers separated. The organic phase was washed with water (1x10 ml), brine (1x10 ml) and dried. The solvent was evaporated to leave a semi-crystalline residue (58 mg, 90%), which was found to consist mainly of the major isomer 79 (1H n.m.r. and 13C n.m.r.).

(iv) A solution of the α-ketols 78 and 79 (33 mg, 0.13 mmol) in deuterochloroform (1.5 ml), was treated with 1,5-
diazabicyclo[4.3.0]non-5-ene (0.03 ml), and the reaction monitored by $^1$H n.m.r. spectroscopy. After 48 hr at 25°C, there appeared to be little change. The solution was diluted with dichloromethane (10 ml) and washed with 0.1N hydrochloric acid (1x5 ml), water (1x10 ml), brine and dried. Removal of the solvent returned the mixture of α-ketols 78 and 79 (25 mg).

$(\pm)(7a,9a\delta)$-8,8-[1,2-Ethanediylbis(oxy)]-2-methoxy-gibba-1,3,4a(10a),4b-tetraen-7-ol 87

A solution of the unsaturated ketone 15 (330 mg, 1.3 mmol), p-toluenesulphonic acid (5 mg) and ethylene glycol (1 ml) in 1,2-dichloroethane (100 ml) was heated at reflux* for 24 hr with azeotropic removal of water (reverse Dean and Stark apparatus). The cooled solution was washed with water (1x100 ml), aqueous 10% sodium bicarbonate solution (1x50 ml), brine (1x100 ml) and dried. Removal of the solvent gave a crystalline solid (400 mg), homogeneous by t.l.c. (Rf~0.37, 2% methanol-dichloromethane). Recrystallisation from acetone-light petroleum gave two crops of the ketal 87 (280 mg, 70%) as small shiny cubes, m.p. 163-165°C (Found: C, 71.68; H, 6.47. C$_{18}$H$_{20}$O$_4$ requires C, 71.98; H, 6.71%).

$\nu_{max}$ 3500 (OH), 1600, 1590 (C-C) cm$^{-1}$.

$\delta$ 7.26 (d, 1H, J=8Hz, H-4), 6.70 (m, 2H, H-1 and H-3), 5.86 (t, 1H, J=4Hz, H-5), 3.92 (m, 4H, OCH$_2$CH$_2$O), 3.72 (s, 3H, ArOCH$_3$), 3.52 (s, 1H, exch., OH), 3.02 and 2.68 (ABq, $J_{AB}$=16Hz, C-10 protons), 2.60 (m, 2H, C-6 protons), 2.40-1.80 (complex,

* This reaction was conducted under nitrogen.
4H, C-9 and C-11 protons).

m/z 300 (70%, M⁺), 282 (10), 255 (10), 243 (11), 238 (100), 214 (38), 213 (57), 210 (38), 185 (40).

δ 160.1 (s, C-2), 149.3 (s), 145.4 (s), 131.0 (s), 121.9 (d, J=159Hz, C-4), 114.9 (s, C-8), 113.4 (d, J=162Hz), 110.6 (d, J=160Hz), 109.9 (d, J=160Hz), 80.0 (s, C-7), 66.0 (t, J=150Hz, OCH₂CH₂O), 65.0 (t, J=150Hz, OCH₂CH₂O), 55.4 (q, J=142Hz, ArOCH₃), 51.8 (t, J=130Hz, C-9), 46.5 (t, J=130Hz, C-11), 45.7 (s, C-9a), 40.7 (t, J=131Hz, C-10), 35.0 (t, J=127Hz, C-6).

Lithium-ammonia reduction of the unsaturated ketal 87

A solution of the unsaturated ketal 87 (57 mg, 0.19 mmol) in dry THF (1 ml), was added dropwise to a deep blue solution of lithium metal (3.8 mg, 0.54 mg atom) in anhydrous, refluxing, liquid ammonia (distilled from sodium, 15 ml). After 35 min., ammonium chloride (0.5g) was added and the ammonia allowed to evaporate. The residue was partitioned between ether (20 ml) and water (10 ml), and the layers were separated. The organic phase was washed with brine (1x20 ml) and dried. Removal of the solvent gave a crystalline solid (50 mg), m.p. 125-135°. Analysis by t.l.c. (2% methanol-dichloromethane) showed two, closely running spots (Rf~0.4), which could not be resolved completely. An attempt to separate the major component by p.l.c. (4% methanol-dichloromethane) was unsuccessful. The spectroscopic data of the crude product are essentially the same as those
given below. The crude product was recrystallised from ether-light petroleum to give the major isomer, (±) (4β, 7α, 9αβ)-8, 8-[1, 2-Ethandiylbis(oxy)]-2-methoxy-gibba-1, 3, 4a (10a)-trien-7-ol 89, as small colourless plates (37 mg, 65%), m.p. 137-140° (Found: C, 71.73; H, 7.38. \( \text{C}_{18}\text{H}_{22}\text{O}_4 \) requires C, 71.50; H, 7.33%).

\( \nu_{\text{max}} \) 3500 (OH) cm\(^{-1}\).

\( \delta \) 6.96 (d, 1H, \( J=8\text{Hz} \), C-4), 6.68 (m, 2H, C-1 and C-3), 3.90 (m, 4H, O\( \text{CH}_2\text{CH}_2\text{O} \)), 3.68 (s, 3H, ArO\( \text{CH}_3 \)), 2.87 and 2.43 (ABq, \( J_{AB}=16\text{Hz} \), C-10 protons), 2.70 (m, 1H, H-46), 2.40 (s, 1H, exch., OH), 2.30-1.40 (complex, 8H).

m/z 302 (100%, M\(^+\)), 284 (5), 274 (4), 243 (13), 232 (39), 216 (49), 214 (84), 198 (47), 172 (49), 159 (66).

Hydrogenation of the unsaturated ketal 87

The unsaturated ketal 87 (100 mg, 0.33 mmol) in ethyl acetate (20 ml), was hydrogenated at atmospheric pressure using 10% palladium-on-carbon as a catalyst (10 mg). The filtered solution (celite) was concentrated in vacuo, to give a white crystalline solid (98 mg), which was homogeneous by t.l.c. (Rf=0.4, 4% methanol-dichloromethane). Although the \( ^1\text{H} \) n.m.r. spectrum suggested that a single isomer was produced, the \( ^13\text{C} \) n.m.r. spectrum indicated that a small amount of the isomer 88 had been produced (see below for the \( ^13\text{C} \) n.m.r. data of the major isomer).

\( \delta \) 158.7 (s), 144.6 (s), 143.7 (s), 138.7 (s), 137.0 (s), 123.2 (d, \( J=160\text{Hz} \)), 115.0, 113.7 (s), 111.8, 111.2, 110.8,
80.2 (s), 79.3, 65.6 (t), 64.6 (t), 55.4 (q), 51.3 (d), 50.5, 49.1, 47.4 (t), 44.8 (t), 43.9, 42.6 (t), 32.5 (t), 30.3, 22.1 (t).

Recrystallisation of the crude product from ether gave the major isomer as diamond-shaped plates (57 mg), m.p. 139-141°. This compound was identical to the major product from the previous experiment (m.m.p., $^1$H n.m.r.). The $^{13}$C n.m.r. spectrum of the pure trans compound 89 was recorded:

$\delta$ 158.7 (s, C-2), 144.6 (s), 137.0 (s), 123.2 (d, $J\sim$160Hz, C-4), 113.7 (s, C-8), 111.1 (d, $J\sim$160Hz), 110.8 (d, $J\sim$160Hz), 80.2 (s, C-7), 65.6 (t, $J=149$Hz, $\text{OCH}_2\text{CH}_2\text{O}$), 64.6 (t, $J=151$Hz, $\text{OCH}_2\text{CH}_2\text{O}$), 55.4 (q, $J=142$Hz, Ar$\text{OCH}_3$), 51.3 (d), 49.1 (s), 47.7 (t, $J=128$Hz), 44.8 (t, $J=129$Hz), 42.6 (t, $J=130$Hz), 32.5 (t, $J=127$Hz, C-6), 22.1 (t, $J=126$Hz, C-5).

Ketalisation of the trans ketone 79

A mixture of the pure ketone 79 (35 mg, 0.14 mmol), p-toluenesulphonic acid (2 mg), and ethylene glycol (1 ml) in 1,2-dichloroethane (100 ml) was heated at reflux under nitrogen, with azeotropie removal of water (reverse Dean and Stark apparatus). After 24 hr, the cooled solution was washed with water (1x100 ml), aqueous 10% sodium bicarbonate (1x20 ml), brine (1x100 ml) and dried. Removal of the solvent gave a colourless crystalline solid (36 mg), which was identical ($^1$H n.m.r., $^{13}$C n.m.r.) to the major isomer obtained in the previous experiment. Recrystallisation of the crude product from ether-light petroleum gave
colourless crystals, m.p. 139-141°, which was not depressed when admixed with the major product 89 from the two previous experiments.

A stirred solution of methyl N-hydroxymethylbenzoate 84 (3008) (165 mg, 3 mmol) and dry pyridine (0.28 ml) in dry ether (1 ml) at 0° under nitrogen, was treated dropwise with freshly distilled phosphorus tribromide (0.94 ml) in dry ether (2 ml). After stirring at room temperature overnight, the reaction mixture was poured into aqueous 10% sodium bicarbonate solution (20 ml) and the layers separated. The organic phase was washed with brine (1x5 ml) and dried. Removal of the solvent gave a colourless oil which by i.r. analysis (dichloromethane) was found to be a mixture of the bromo ester 85, R=0.8 and pyridine bromide. In the absence of pyridine, a mixture of pthalide (68%, R=0.8, Rf=5.3, v, 

\[\text{ArCH}_2\text{CH}_2\text{Ar}\] and the bromo ester 85 (40%, Rf0.3, Rf=4.8, v, ArCH_2) was obtained.

(1) This method is a slight modification of the procedure described by E. Del and Rivard. A solution of the toluene ester 64 (308) (16.6 g, 47.1 mmol) in dry carbon tetrachloride (100 ml) was brought to reflux by irradiating with a 500W tungsten lamp. A solution of bromine in dry carbon tetrachloride was added dropwise, and the reaction monitored by H_nmr spectroscopy. After about 70% of the starting ester had been consumed, the solution was dried over anhydrous sodium bicarbonate, and then the solution remixed. The oily residue obtained was dissolved in light petroleum and cooled to -78° (dry ice-acetone bath).
Methyl 2-Bromomethylbenzoate 95

(i) A stirred solution of methyl 2-hydroxymethylbenzoate 94 (R=OH) (166 mg, 1 mmol) and dry pyridine (0.28 ml) in dry ether (1 ml) at 0° under nitrogen, was treated dropwise with freshly distilled phosphorus tribromide (0.04 ml) in dry ether (2 ml). After stirring at room temperature overnight, the reaction mixture was poured into aqueous 10% sodium bicarbonate solution (10 ml) and the layers separated. The organic phase was washed with brine (1x5 ml) and dried. Removal of the solvent gave a colourless oil which by t.l.c. analysis (dichloromethane) was found to be a mixture of the bromo ester 95, Rf~0.8 and pyridine Rf~0.1. In the absence of pyridine, a mixture of phthalide (60%; Rf~0.5; δ=5.1, s, ArCH₂) and the bromo ester 95 (40%; Rf~0.8; δ=4.84, s, ArCH₂) was obtained.

(ii) This method is a slight modification of the procedure described by Eliel and Rivard. Thus, a solution of the toluic ester 94 (R=H) (16.6g, 111 mmol) in dry carbon tetrachloride (100 ml) was brought to reflux by irradiating with a 500W tungsten lamp. A solution of bromine in dry carbon tetrachloride was added dropwise, and the reaction monitored by ¹H n.m.r. spectroscopy. After about 70% of the starting ester had been consumed, the solution was dried over anhydrous sodium bicarbonate, and then the volatiles removed. The oily residue obtained was dissolved in light petroleum and cooled to -78° (dry ice-acetone bath). The
solid obtained was then recrystallised from light petroleum (0°) to give the bromo ester 95 (9.5g) as white needles, m.p. 30-32° (lit.127 32-32.5°). A further crop (4.5g), m.p. 29-32°, was obtained from the mother liquors. This crop was pure by t.l.c. and 1H n.m.r. analysis (total yield: 61%).

δ (CCl4), 7.88 (d, 1H, J=8Hz, ArH), 7.30 (m, 3H, 3xArH), 4.84 (s, 2H, ArCH2), 3.80 (s, 3H, CO2CH3).

2,5-Dimethoxy-1-(2-methoxycarbonylphenyl)methyl-2,5-cyclohexadiene-1-carboxylic acid 98

(i) A solution of the bromo ester 95 (2.3g, 10 mmol) in dry THF (5 ml) was added dropwise to a stirred suspension of the dianion 29 (from the acid 24; 0.91g, 5 mmol) in liquid ammonia (50 ml) and dry THF (5 ml) at -33° under nitrogen. After the addition was complete, the resultant clear orange solution was stirred for an additional 2 hr at -33°, and then the ammonia was allowed to evaporate. The yellow residue obtained was dissolved in water (70 ml) and extracted with 50% light petroleum-ether (2x100 ml), and the extracts discarded. The basic aqueous phase was cooled to 0°, saturated with sodium chloride, layered with ethyl acetate (100 ml), and acidified to pH 5 with 5N hydrochloric acid. The layers were separated and the aqueous phase extracted further with ethyl acetate (2x50 ml). The extracts were washed with water (2x50 ml), brine (1x100 ml) and dried. Removal of the solvent gave a cream-coloured solid (1.2g). Fractional crystallisation from ether gave
phthalimidine 97 (300 mg), m.p. 150-152° (lit. 128 150°).

$\nu_{\text{max}}$ 3200 (NH), 1690 (C=O) cm$^{-1}$.

$\delta$ 8.30 (broad, 1H, NH), 7.80 (m, 1H, ArH), 7.50 (m, 3H, 3xArH), 4.40 (s, 2H, ArCH$_2$).

m/z 133 (100%, M$^+$), 132 (44), 105 (47), 104 (52).

The acid 98 was then isolated from the mother liquors by extraction techniques (see below for data).

(ii) The dianion 29 (from the acid 24; 440 mg, 2.4 mmol) was alkylated with the bromo ester 95 (0.73g; 3.1 mmol) using Method A. The acid 98 was obtained as a cream-coloured crystalline solid (480 mg, 60%), m.p. 142-143° (Found: C, 64.93; H, 6.13. C$_{18}$H$_{20}$O$_6$ requires C, 65.05; H, 6.07).

$\nu_{\text{max}}$ 2600 (acid), 1720 (ester), 1700 (acid), 1660 (C=C, enol ether), 1600, 1590 cm$^{-1}$.

$\delta$ 11.32 (broad, 1H, exch., CO$_2$H), 7.64 (1H, dd, $J_1$=8Hz, $J_2$=2Hz, ArH), 7.1 (m, 3H, 3xArH), 4.50 (t, 1H, $J$=4Hz, H-3), 4.40 (s, 1H, H-6), 3.80 (s, 3H, CO$_2$CH$_3$), 3.75 and 3.50 (2H, ArCH$_2$), 3.48 (s, 3H, C=COCH$_3$), 3.40 (s, 3H, C=COCH$_3$), 2.54* (dd, $J_1$=20Hz, $J_2$=4Hz, H-4), 2.08* (dd, $J_1$=20Hz, $J_2$=4Hz, H-4).

m/z 332 (5%, M$^+$), 301 (5), 288 (7), 286 (6), 255 (24), 183 (73), 182 (55), 165 (100), 139 (60), 124 (42).

Methyl 2-Bromomethyl-4-methoxybenzoate 105

This compound was prepared in 4 steps from m-methoxytoluene 99, and is similar to the route used by

* See footnote p. 127.
Brossi et al.\textsuperscript{133}

(i) The procedure for the acylation is a slight modification of the method reported by Adams and Noiler.\textsuperscript{130} Thus, acetic anhydride (15.5g, 0.152 mol) was added drop-wise over 20 min. to a stirred solution of the ether 99 (18.3g, 0.15 mol) and aluminium trichloride (40g, 0.3 mol) in dry dichloromethane (40 ml) at 0\textdegree (drying tube). The ice-bath was then removed and the red solution stirred for an additional 20 min. Analysis by t.l.c. (60% ether-light petroleum) after this period, indicated that the starting material (Rf~0.8) had been consumed. The solution was poured onto ice (100g), and extracted with dichloromethane (3x100 ml), the extracts were washed with 1N sodium hydroxide solution (1x50 ml), brine (1x100 ml) and dried. Removal of the solvent gave a colourless oil (25g), which was used in the next step without purification. The major product 100 (c. 80\%) exhibited the following signals in the $^1$H n.m.r. spectrum:

\begin{align*}
\delta & 7.78 (d, 1H, J=8Hz, ArH), 3.74 (s, 3H, ArOCH$_3$), 2.40 (s, 3H). The respective signals for the minor product 101 (c. 20\%) occurred at 7.52, 3.82 and 2.32. 
\end{align*}

(ii) The crude mixture of acetophenones 100 and 101 (25g) was oxidised with sodium hypochlorite, according to the method described by Holmes and Newman.\textsuperscript{132} The crude solid (20g) obtained, was recrystallised from 95\% ethanol to give 4-methoxy-2-methylbenzoic acid 102 as colourless needles (15g, 60\%) in two crops, m.p. 177-179\degree (lit.\textsuperscript{131} 175\degree).
2-methoxy-4-methyl benzoic acid 103, obtained from the mother liquors was identical with an authentic sample, m.p., m.m.p. 102-105°.

(iii) The acid 102 (10g; 66 mmol) was esterified with methanol-sulphuric acid, to give methyl 4-methoxy-2-methylbenzoate 104 (10.6g; 90%), after chromatography on silica gel (200g, benzene).

\[ \delta (\text{CCl}_4) \]: 7.84 (d, 1H, J=9Hz, H-6), 6.62 (m, 2H, H-3 and H-5), 3.78 (s, 6H, \text{CO}_2\text{CH}_3 \text{ and } \text{ArOCH}_3), 2.56 (s, 3H, \text{ArCH}_3).

(iv) The toluic ester 104 (9g, 50 mmol) was brominated using the method described previously for o-toluic acid methyl ester. The crude oily product obtained, was dissolved in boiling light petroleum, and gave, on cooling, the bromo ester 105 (6.5g, 50%) as white needles, m.p. 63-67° (lit. 66-67°).

\[ \delta (\text{CCl}_4) \]: 7.92 (d, 1H, J=9Hz, C-6), 6.94 (d, 1H, J=2Hz, H-3), 6.76 (dd, 1H, \text{J}_1=9Hz, \text{J}_2=2Hz, H-5), 4.94 (s, 2H, \text{ArCH}_2), 3.84 (s, 6H, \text{CO}_2\text{CH}_3 \text{ and } \text{ArOCH}_3).

2,5-Dimethoxy-1-(5'-methoxy-2'-methoxycarbonylphenyl)methyl-2,5-cyclohexadiene-1-carboxylic acid 106

(i) The dianion 29 (from the acid 24; 1.37g, 7.5 mmol) was alkylated with the bromo ester 105 (2.58g, 10 mmol) using Method A, to give the acid 106 (2g, 74%). A sample was recrystallised from ethyl acetate for analysis, m.p. 159-162° (Found: C, 62.79; H, 6.15. \text{C}_{19}\text{H}_{22}\text{O}_7 \text{ requires C, 62.98; H, 6.12%}).
\( \nu_{\text{max}} \) 2600, 1710, 1695, 1660 (C=C, enol ether), 1600, 1580

\( \delta \) (CDCl\(_3\)/(CD\(_3\))\(_2\)SO), 7.70 (d, 1H, J=8Hz, ArH, H-3), 6.66 (m, 2H, 2xArH, H-4' and H-6'), 4.50 (t, 1H, J=4Hz, H-3), 4.40 (s, 1H, H-6), 3.72 (s, 3H), 3.70 (s, 3H), 3.80 and 3.50 (2H, ArCH\(_2\)), 2.50* (dd, 1H, \( J_1=20\)Hz, \( J_2=4\)Hz, H-4), 2.08* (dd, 1H, \( J_1=20\)Hz, \( J_2=4\)Hz).

m/z 362 (1%, M\(^+\)), 331 (3), 318 (30), 271 (17), 180 (65), 139 (100).

(ii) The dianion 29 (from the acid 24; 1.76g, 9.7 mmol) was alkylated with the bromo ester (3g, 11.6 mmol) using Method C, to give the acid 106 (2.95g, 84%), m.p. 158-162\(^\circ\).

Attempts to prepare Methyl 5-Methoxy-2-oxo-1,2,3,4-tetrahydrofluorene-8-carboxylate 108

(i) A solution of the acid 106 (100 mg, 0.27 mmol) and p-toluenesulphonic acid (10 mg), in benzene (20 ml), was heated under reflux for 16 hr. The cooled solution was washed with aqueous 10% sodium bicarbonate solution (1x10 ml), brine (1x20 ml) and dried. Removal of the solvent gave a residue, which appeared to be the diketone 107.

\( \delta \) 7.90 (d, 1H, J=9Hz, ArH), 6.70 (m, 2H, 2xArH), 3.80 (s, 6H, CO\(_2\)CH\(_3\) and ArOCH\(_3\)), 3.00-2.20 (m, 9H).

(ii) The acid 106 (100 mg, 0.27 mmol) was added to trifluoroacetic acid (2 ml), at 25\(^\circ\) under nitrogen. After 30 min., the reaction mixture was poured onto ice (20g) and

* See footnote p. 127.
extracted with dichloromethane (2x20 ml). The extracts were washed with water (1x20 ml), brine (1x20 ml) and dried. Removal of the solvent gave a crude product, which was identical to the one described above (\(^1\)H n.m.r. analysis).

(iii) The acid 106 (100 mg, 0.27 mmol) was added to 10% phosphorus pentoxide-methanesulphonic acid,\(^\text{135}\) (5g), stirring at 50\(^\circ\) under nitrogen. After 1 hr, the product was isolated as described for (ii), and was found to be the diketone 107 (\(^1\)H n.m.r. analysis).

(iv) A suspension of the acid 106 (100 mg, 0.27 mmol) in methanol (5 ml) was treated with 10N hydrochloric acid (1 ml). The resultant solution was stirred at 25\(^\circ\) for 18 hr, then heated under reflux for 2 hr. Work-up gave a single product, identical with the diketone 107 (t.l.c. and \(^1\)H n.m.r. analysis).

(v) The acid 106 (362 mg; 1 mmol) was mixed intimately with PPA (6g), which was preheated to 60\(^\circ\). A vigorous evolution of gas ensued, which subsided after 10 min. The dark red mixture was kept at this temperature for an additional 50 min., with occasional stirring, then decomposed with ice (30g), and extracted with ethyl acetate (2x20 ml). The extracts were washed with water (2x20 ml), aqueous 10% sodium bicarbonate solution (1x20 ml), brine (1x20 ml) and dried. Removal of the solvent gave a bright yellow semi-crystalline residue. Trituration with THF gave a bright yellow solid (82 mg, 30%). The following spectroscopic data obtained with this sample, appear to be consistent
the hydrofluorenone 109:
δ 7.90 (d), 6.80 (d), 6.00 (m), 3.80 (s).
m/z 272 (100%, M+), 244 (16), 241 (19), 230 (69).
An attempt to purify this product by p.l.c. (2% methanol-
dichloromethane) led to extensive decomposition. No further
investigations were carried out.

Methyl 6-Chloromethyl-2,3-dimethoxybenzoate 112 (R=CH₃)

The chloro ester 112 (R=CH₃) was prepared according to
the procedure of Dean and Rapoport, 137 except that methyl
chloroformate was used in place of ethyl chloroformate. The
chloro ester 112 (R=CH₃) was obtained as a colourless liquid
(91%) after distillation, b.p. 130-150°/0.05 mm (Kugelrhon).
ν_max (film) 1730 (C=O) cm⁻¹.
δ 7.10 (d, 1H, J=8Hz), 6.86 (d, 1H, J=8Hz), 4.54 (s, 2H,
ArCH₂), 3.90 (s, 3H), 3.82 (s, 6H).
m/z 246 (19), 244 (55%, M+), 215 (14), 214 (37), 213 (44),
212 (100), 209 (80).

Methyl 6-Iodomethyl-2,3-dimethoxybenzoate 113

A solution of the chloro ester 112 (1.4g, 5.4 mmol) in
acetone (70 ml) was added dropwise to a stirred solution of
sodium iodide (4g, 27 mmol) in acetone (70 ml). After 2 hr,
the filtered solution was concentrated in vacuo, and the
residue partitioned between ether (100 ml) and water (100 ml).
The layers were separated and the organic phase washed with
aqueous 5% sodium thiosulphate solution (1x50 ml), brine
(1x100 ml), and dried. Removal of the solvent gave the oily iodo ester 113 (1.7g, 94%), which was used without purification. (Caution! This compound is a potent lachrymator). \( \nu_{\text{max}} \) (film) 1730 (C=O) cm\(^{-1}\).
\[ \delta \] 7.04 (d, 1H, J=8Hz, ArH), 6.80 (d, 1H, J=8Hz, ArH), 4.40 (s, 2H, ArCH\(_2\)), 3.92 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H).
m/z 336 (1), 305 (4), 210 (18), 209 (100).

2,5-Dimethoxy-1-(3',4'-dimethoxy-2'-methoxycarbonylphenyl)-methyl-2,5-cyclohexadiene-1-carboxylic acid 114

The dianion 29 (from the acid 24; 1.82g, 10 mmol) was alkylated with the iodo ester 113 (4g, 12 mmol) using Method C to give the acid 114 (3g, 75%), m.p. 130-133\( ^\circ \) (Found: C, 61.46; H, 6.39. \( C_{20}H_{24}O_8 \) requires C, 61.22; H, 6.16%).
\( \nu_{\text{max}} \) 2600 (broad), 1740 (ester), 1705 (acid), 1660 (C=, enol ether) cm\(^{-1}\).
\[ \delta \] 6.76 (s, 2H, 2xArH), 4.72 (t, 1H, J=4Hz, H-3), 4.25 (s, 1H, H-6), 3.90 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.59 (s, 3H, C=COCH\(_3\)), 3.51 (s, 3H, C=COCH\(_3\)), 3.28 and 3.04 (ABq, J\(_{AB}\)=14Hz, ArCH\(_2\)), 2.68* (dd, 1H, J\(_1\)=20Hz, J\(_2\)=4Hz, H-4), 2.32 (dd, 1H, J\(_1\)=20Hz, J\(_2\)=4Hz, H-4).
m/z 392 (<1%, M\(^+\)), 348 (9), 346 (36), 283 (27), 193 (100), 192 (36), 178 (68), 164 (82), 162 (39).

* See footnote p. 127.
Dimethyl 2,3-Dimethoxy-5,6,7,8,9,10-hexahydro-5-hydroxy-8-oxo-5,9-methanobenzocyclooctene-1,9-dicarboxylate 115

The acid 114 (110 mg; 0.28 mmol) was added to vigorously stirred 85% sulphuric acid (2 ml) at 25° under nitrogen. After 2 hr, the dark orange reaction mixture was poured onto ice (10 g), and extracted with dichloromethane (2 x 10 ml). The extracts were washed with water (1 x 10 ml), brine (1 x 10 ml) and dried. Evaporation of the solvent gave a crystalline solid, which was dissolved in THF (10 ml) and treated with an excess of ethereal diazomethane. The volatiles were removed and the residue purified by p.l.c. (5% methanol-dichloromethane). The major product (Rf ~ 0.3), crystallised from ether as shiny prisms (55 mg, 52%), m.p. 185-187° (Found: C, 60.24; H, 5.61. C_{19}H_{22}O_{8} requires C, 60.31; H, 5.86).

\( \nu_{\text{max}} \) 3500 (OH), 1740 (ester), 1710 (ketone) cm\(^{-1}\).
\( \delta \) 7.23 (s, 1H, H-4), 3.86 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 3.14 and 2.82 (ABq, \( J_{\text{AB}} = 14 \text{Hz}, \text{ArCH}_2 \)), 3.02 (m, 1H), 2.60-1.90 (m, 6H).

m/z 378 (45\%, M\(^+\)), 347 (25), 346 (23), 320 (9), 318 (15), 288 (100), 231 (25).

Methyl 6-Bromomethyl-2-methoxybenzoate 121

The bromo ester 121 was prepared in 6 steps from crotonaldehyde. 138, 140

(i) Ethyl 6-methylcyclohex-3-en-2-one-1-carboxylate 118, was prepared from crotonaldehyde and ethyl acetoacetate.
according to the method of Piskov\textsuperscript{138} in 50\% yield, b.p. 90-102°C/0.5 mm (lit.\textsuperscript{138} 93-95°C/0.8).

(ii) The crude ester \textsuperscript{118} (36g, 0.198 mol) was brominated\textsuperscript{138} using \(N\)-bromosuccinimide (42g, 0.236 mol), dibenzoyl peroxide (0.5g), in refluxing carbon tetrachloride (500 ml). After 2 hr, the succinimide was removed by filtration and the filtrate concentrated \textit{in vacuo}. The oily residue was dissolved in DMF (100 ml) and then treated with lithium carbonate (40g), followed by lithium bromide\textsuperscript{139} (34g). There was a vigorous exothermic reaction, which subsided after 30 min.. The cooled reaction mixture was poured onto ice (300g) and the resultant mixture acidified to pH 1 cautiously, with 10N hydrochloric acid. The dark solution was then extracted with ether (3x200 ml), the extracts were washed with brine (1x200 ml) and dried. Evaporation of the solvent left a dark red oil (36g), which was chromatographed on a column of silica gel (500g, 20\% dichloromethane-light petroleum), to give ethyl 2-hydroxy-6-methylbenzoate \textsuperscript{119} (13g), m.p. 40-42°C (lit.\textsuperscript{141} 42.5°C).

\(\delta\) (\(\text{CCl}_4\)), 11.3 (s, 1H, ArOH), 7.10 (t, 1H, J=8Hz, H-3), 6.64 (d, 1H, J=8Hz, Ar\textsubscript{H}), 6.54 (d, 1H, J=8Hz, Ar\textsubscript{H}), 4.28 (q, 2H, J=7Hz, \(\text{CO}_2\text{CH}_2\text{CH}_3\)), 2.42 (s, 3H, Ar\textsubscript{CH}_3), 1,34 (t, 3H, J=7Hz, \(\text{CO}_2\text{CH}_2\text{CH}_3\)).

(iii) A solution of the phenolic ester (12g, 67 mmol) and potassium hydroxide (14g) in methanol (50 ml) and water (5 ml) was boiled for 18 hr. The cooled solution was diluted with water (100 ml) and extracted with ether (2x100 ml). The
The basic aqueous phase was then acidified to pH 1 with 10N hydrochloric acid, and extracted with ethyl acetate (2x100 ml). The extracts were washed with brine (1x100 ml), dried and the solvent evaporated to give a cream-coloured solid. Recrystallisation from chloroform gave 2-hydroxy-6-methylbenzoic acid, as long white needles in 3 crops (9.5g, 95%), m.p. 171-172° (lit. 164-173°). The phenolic acid (2g, 13 mmol) was permethylated using dimethylsulphate (4.2g, 33 mmol) and anhydrous potassium carbonate (5g, 36 mmol) in refluxing acetone (100 ml). Methyl 2-methoxy-6-methylbenzoate 120 (2.3g; 98%) was obtained as an oil (t.l.c.: Rf 0.7 dichloromethane).

δ (CCl₄) 7.10 (t, 1H, J=8Hz, H-4), 6.70 (m, 2H), 3.80 (s, 3H), 3.68 (s, 3H), 1.20 (s, 3H, ArCH₃).

(iv) The toluic ester 120 (3.1g; 17 mmol) was photo-brominated using the method described for the bromination of o-toluic methyl ester 94. Attempts to purify the bromo ester 121 obtained in this way, by crystallisation or chromatography were unsuccessful. That bromination had occurred exclusively on the methyl group was established by converting the crude bromo ester 121 to the amino ester 123. Thus, a solution of the crude product from the bromination in dry DMF (5 ml) was added to a stirred solution of anhydrous dimethylamine (10 ml) in dry DMF (10 ml) at -20° under nitrogen. After stirring overnight, the clear solution was diluted with water (50 ml) and then extracted with ether (2x50 ml). The organic extracts were washed with brine (1x50 ml) and dried. Removal of the
solvent gave an oily residue which consisted of two compounds (t.l.c.: Rf~0.8 and Rf~0.1, dichloromethane). The less polar product (Rf~0.8), obtained in 50% yield, was identified as the toluic ester 120 (t.l.c. and $^1$H n.m.r. analysis). The more polar product (Rf~0.1), obtained in 34% yield, was identical with the amino ester 123 (t.l.c., $^1$H n.m.r., m.s.) (vide infra).

$N$-[(3-Methoxyphenyl)methyl]-$N,N$-dimethylamine 122

The tertiary amine 122 could be prepared from $m$-methoxybenzaldehyde in 30% yield by reaction with 90% formic acid and DMF. A less tedious method involved a modification of the procedure described by Eliel. Thus, $m$-methoxybenzyl bromide (201g, 1 mol) was added dropwise over 40 min. to a stirred and cooled (-20°) solution of anhydrous dimethylamine (500 ml) and dry DMF (500 ml). After stirring for 16 hr at 25°, the solution was concentrated in vacuo, and the residue acidified with 5N hydrochloric acid to pH 4. The acidic solution was extracted with ether (2x200 ml), and then made alkaline (pH 13) by cautiously adding potassium hydroxide pellets. The basic aqueous phase was extracted with ether (3x200 ml), the ether extracts were washed with water (1x200 ml), brine (1x200 ml) and dried over potassium hydroxide pellets. Removal of the solvent, and distillation of the residue gave the tertiary amine 122 (154g, 91%), b.p. 84-85°/2.7 mm (lit. 99-101°/8.8).
Methyl 6-\((N,N\text{-Dimethylamino})\text{methyl-2-methoxybenzoate}\) 123

A solution of the tertiary amine 122 (9.15g, 55 mol) in dry ether (100 ml) under argon was treated with \(n\)-butyllithium (53 ml, 1.6M in hexane) at room temperature. After 20 hr, dry dimethyl carbonate (12 ml, 0.142 mol) was added to the deep orange solution at such a rate to maintain a gentle reflux. When the addition was complete, the reaction mixture was stirred for an additional 4 hr, before water (200 ml) was added. The layers were separated, and the organic layer was extracted with 5N hydrochloric acid (2x50 ml). The acidic extracts were combined, and made alkaline (pH 13) by cautiously adding potassium hydroxide pellets. The alkaline solution was then extracted with ether (3x100 ml), the extracts were washed with brine (1x100 ml), and dried. Removal of the solvent gave a pale yellow oil, consisting of the amino ester 123 (Rf=0.4) and the starting material 122 (Rf=0.3, 7% methanol-dichloromethane). After chromatography of the crude product on silica gel (120g, chloroform), the amino ester 123 could be obtained in 90% yield (11.0g).* Distillation of a sample gave a colourless liquid, b.p. 100-104°/0.3 mm, which crystallised, m.p.~30°. Satisfactory analytical data could not be obtained (Accurate mass; Found 223.1205. \(C_{12}H_{17}NO_3\) requires 223.1208).

\(\nu_{\text{max}}\) (film) 1740 (C=O), 1585 cm\(^{-1}\).
\(\delta\) 7.20 (t, 1H, \(J=8\text{Hz}, \text{H-4}\)), 6.84 (d, 1H, \(H=8\text{Hz}, \text{ArH}\)), 6.78

* On a larger scale (0.7 mol) the amino ester 123 was purified by distillation (~80% yield),168
Methyl 6-Chloromethyl-2-methoxybenzoate 124

A solution of the amino ester 123 (30g; 0.135 mol) in dry THF (150 ml) was added dropwise over 45 min., to a stirred solution of freshly distilled methyl chloroformate (32 ml, 0.415 mol) in dry THF (150 ml) at 25°C under nitrogen. After stirring for 18 hr, the volatiles were removed and the residue partitioned between ether (22 ml) and water (pH 5, 100 ml). The layers were separated, and the organic phase washed with water (2x100 ml), brine (1x100 ml) and dried. Removal of the solvent, gave the chloro ester 124 (27g, 95%). A sample (c. 1g) was distilled to give a colourless liquid, b.p. 80-85°C/0.05 mm (Kugelrhôr), but satisfactory analytical data could not be obtained. However, it was sufficiently pure to use in the next step (t.l.c.: one spot, Rf=0.7, dichloromethane) (Accurate mass; Found: 214.0397. \( \text{C}_{10}\text{H}_{11}\text{ClO}_3 \) requires 214.0399). 

\( \nu_{\text{max}} \) (film) 1740 (C=O) cm\(^{-1}\).

\( \delta \) 7.32 (t, 1H, J=8Hz, H-4), 6.98 (d, 1H, J=8Hz, ArH), 6.88 (d, 1H, J=8Hz, ArH), 4.56 (s, 2H, ArCH\(_2\)), 3.86 (s, 3H), 3.73 (s, 3H).

m/z 216 (10), 214 (32%, M\(^+\)), 185 (17), 184 (37), 183 (50), 182 (100). On a similar run (0.15 mol scale), an attempt was made to purify the product by distillation and gave
7-methoxyphthalide in virtually quantitative yield, * m.p. 107-109 (lit. \(^{169} 107-109^\circ\)).

\( \nu_{\text{max}} \) 1750 (C=O) cm\(^{-1}\).

\( \delta \) 7.64 (t, 1H, J=9Hz), 7.04 (d, 1H, J=8Hz), 6.94 (d, 1H, J=8Hz), 5.24 (s, 2H, ArCH\(_2\)), 4.00 (s, 3H, ArOCH\(_3\)).

m/z 164 (70%, M\(^+\)), 163 (28), 146 (50), 135 (91), 134 (23), 118 (100).

**Methyl 6-Iodomethyl-2-methoxybenzoate 125**

A solution of the chloro ester 124 (18.5g, 86 mmol) in acetone (100 ml), was added dropwise over 20 min. to a stirred solution of sodium iodide (32g; 213 mmol) in acetone (140 ml) (drying tube). After 1.5 hr, the filtered solution was concentrated *in vacuo*, and the dark orange residue (Caution! potent lachrymator), partitioned between ether (200 ml) and water (100 ml). The layers were separated and the organic phase was washed with water (1x100 ml), aqueous 5% sodium thiosulphate solution (1x100 ml), brine (1x200 ml) and dried. Evaporation of the solvent gave the iodo ester 125 (25.5g, 96%) as a pale yellow oil, homogeneous by t.l.c. (Rf\(^{\sim}0.8\), dichloromethane). This alkylating agent was used without purification.

\( \nu_{\text{max}} \) (film) 1720-1740 (C=O) cm\(^{-1}\).

\( \delta \) 7.26 (t, 1H, J=8Hz, H-4), 6.94 (d, 1H, J=8Hz, ArH), 6.80 (d, 1H, J=8Hz, ArH), 4.40 (s, 2H, ArCH\(_2\)), 3.86 (s, 3H), 3.72 (s, 3H).

* Cf. ref. 170.
m/z 306 (5), 275 (6), 179 (100), 149 (24), 148 (29), 105 (23).

2,5-Dimethoxy-1-(3'-methoxy-2'-methoxycarbonylphenyl)methyl-2,5-cyclohexadiene-1-carboxylic acid 126

The dianion 29 (from the acid 24; 12g, 66 mmol) was alkylation with the iodo ester 125 (25g, 81 mmol) using Method C. The acid 126 (21g, 88%) was obtained as a cream-coloured crystalline solid. An analytical sample was obtained by recrystallisation from acetone-hexane (shiny colourless crystals), m.p. 138-140° (Found: C, 63.16; H, 6.03. C₁₉H₂₂O₇ requires C, 62.98; H, 6.12%).

ν max 2600 (acid), 1740 (ester), 1705 (acid), 1660 (C=C, enol ether) cm⁻¹.

δ 11.40 (broad, 1H, CO₂H), 7.28 (t, 1H, J=8Hz, H-4), 6.70 (m, 2H, H-3 and H-5), 4.72 (t, 1H, J=4Hz, H-3), 4.48 (s, 1H, H-6), 3.88 (s, 3H), 3.76 (s, 3H), 3.58 (s, 3H, C=COCH₃), 3.52 (s, 3H, C=COCH₃), 3.37 and 3.12 (ABq, JAB=14Hz, ArCH₂), 2.70* (dd, 1H, J₁=21Hz, J₂=4Hz, H-4), 2.34* (dd, 1H, J₁=21Hz, J₂=4Hz, H-4).

m/z 362 (2%, M⁺), 331 (16), 318 (69), 285 (18), 271 (28), 255 (23), 180 (100), 165 (34), 148 (90), 139 (77).

Methyl 7-Methoxy-2-oxo-1,2,3,4-tetrahydrofluorene-8-carboxylate 127 and Methyl 7-Methoxy-2-oxo-2,3,4,4a-tetrahydrofluorene-8-carboxylate 128

(i) The acid 126 (362 mg, 1 mmol) was mixed intimately

* See footnote p. 127.
with PPA (6g) at 25° (gas evolution), and kept at this temperature with occasional stirring, for 5 hr. The dark red reaction mixture was decomposed with ice (30g), and then extracted with ethyl acetate (2x30 ml). The extracts were washed with water (1x30 ml), brine (1x30 ml) and dried. Removal of the solvent, gave a bright yellow, semi-crystalline residue, which was a mixture, consisting of one major component (Rf~0.4) and four minor components (Rf~0.3, 0.2, 0.1, 0.05; 2% methanol-dichloromethane). The major component isolated by p.l.c. (5% methanol-dichloromethane), was obtained as a colourless crystalline solid (98 mg, 36%), which oxidised rapidly in air. Recrystallisation from benzene gave pale yellow crystals m.p. 162-165°. Attempts to prepare an analytical sample were unsuccessful (Accurate mass; Found: 272.1048 C_{16}H_{16}O_{4} requires 272.1049).

ν_{max} 1715 (C=O), 1580 (C=C) cm^{-1}.
δ 7.30 (d, 1H, J=8Hz, H-5), 6.94 (d, 1H, J=8Hz, H-6), 3.94 (s, 3H), 3.90 (s, 3H), 3.45 (broad s, 2H, C-9 protons), 3.26 (broad s, 2H, C-1 protons), 2.72 (m, 4H, C-3 and C-4 protons).

m/z 272 (100%, M^{+}), 244 (7), 241 (24), 240 (22), 230 (16), 212 (41), 198 (44).

λ_{max} 208 (ε 16,800), 268 (14,400), 277 (sh)(11,000) nm.

(ii) The acid 126 (10.86g, 30 mmol) was added to mechanically stirred PPA (300g) at 60° (foams). After the evolution of gas subsided (c. 15 min.), the orange reaction
mixture was stirred rapidly at this temperature for an additional 45 min., then cooled to about 35°C and poured onto ice (total, c. 1000g) in five portions, with vigorous stirring. The bright yellow solid obtained was then extracted into ethyl acetate (3x500 ml), the extracts were washed with water (1x500 ml), aqueous 5% sodium bicarbonate (1x500 ml), brine (1x500 ml) and dried. Removal of the solvent gave a yellow crystalline solid (6.2g, 75%), which was a 4:1 mixture (1H n.m.r. analysis) of the ketones 127 and 128 (t.l.c. 5% methanol-dichloromethane, Rf~0.7 and Rf~0.6 respectively).

The following data of the mixture were obtained:

\[ \nu_{\text{max}} (\text{CHCl}_3) \ 1720-1710, \ 1660, \ 1585 \ \text{cm}^{-1}. \]
\[ \delta (\text{In addition to the signals of the ketone 127}) \ 7.32 (d, J=8Hz), \ 6.92 (d, J=8Hz), \ 6.00 (m), \ 2.60 (m). \]

m/z 272 (100), 244 (9), 241 (31), 240 (34), 230 (20), 212 (62), 198 (70).

Acidification of the bicarbonate wash from this experiment (5N HCl) and extraction (ethyl acetate), gave a dark red solid (c. 1.2g) which appeared to be a mixture of the C-8 carboxylic acid derivatives of 127 and 128 (1H n.m.r. and m.s. analysis). However, this material was not investigated any further.

(iii) The unsaturated lactone 129 (90 mg, 0.27 mmol) was added to 85% sulphuric acid (2 ml), stirring at 25°C under nitrogen. After the evolution of gas subsided (c. 10 min.), the dark red solution was stirred for an additional 5 min., and then poured onto ice (10g). The resultant
mixture was extracted with dichloromethane (2x10 ml), the extracts were washed with water (1x10 ml), brine (1x10 ml) and dried. Removal of the solvent and trituration of the residue with ether, gave a tan-coloured solid (67 mg, 90%), the two components of which, were identical (t.l.c., $^1$Hn.m.r.) with the ketones 127 and 128.

Methyl 4,10-Dihydro-3,8-dimethoxy-1-oxo-3$H$-3,10a-methano-1$H$-indeno[2,1-c]oxepin-9-carboxylate 129

A stirred solution of the acid 126 (362 mg; 1 mmol) in dry dichloromethane (3 ml) at 25° under nitrogen, was treated with boron trifluoride etherate (0.14 ml, 1 mmol). After 80 min., brine (10 ml) and dichloromethane (20 ml) were added to the dark solution and the layers separated. The organic phase was washed with water (1x20 ml), aqueous 10% sodium bicarbonate solution (1x10 ml), brine (1x20 ml) and dried. Removal of the solvent gave a residue, which crystallised on trituration with ether, to provide the unsaturated lactone 129 (230 mg, 70%) as a white solid (one spot $R_f$=0.5, 2% methanol-dichloromethane). A sample for analysis crystallised from ether-dichloromethane, m.p. 143-145° (Found: C, 65.24; H, 5.47. C$_{18}$H$_{18}$O$_6$ requires C, 65.45; H, 5.49%).

$\nu_{\text{max}}$ 1760 (lactone), 1740 (ester), 1600 (C=O) cm$^{-1}$.

$\delta$ 7.42 (d, 1H, $J$=8Hz, H-6), 6.82 (d, 1H, $J$=8Hz, H-7), 5.94 (t, 1H, $J$=4Hz, H-5), 3.86 (s, 3H), 3.82 (s, 3H), 3.51 (s, 3H, C-3 methoxyl protons), 3.65 and 3.17 (ABq, $J_{AB}$=16Hz, C-10.
protons), 2.76 (m, 2H, C-4 protons), 2.57 and 2.09 (ABq, 
\(J_{AB}=11\text{Hz}\), C-11 protons).
m/z 330 (38%, \(M^+\)), 302 (18), 299 (28), 286 (100), 284 (83).

The mixture of anions 177 and 128 (15g, 55 mmol) was
saturated in THF (600 ml), then ether (300 ml) and water
(300 ml) were added, and the two-phase system purged of
oxygen with a stream of nitrogen for 3 hrs. Sodium cyanide
(16.2g, 300 mmol) was added (the organic phase turned dark
red), followed by the dropwise addition of hydrochloric acid
(300 ml, 3 N) over 70 min. (cautiously from below). After
the addition was completed, t.l.c. analysis showed a single
spot Rf=0.1 (25% methanol-dichloromethane). The excess
hydrogen cyanide was then removed by bubbling nitrogen
through the system for several hours (anhydrous permanganate
trap). Ethyl acetate (300 ml) was added and the layers
separated. The organic phase was washed with water (3x300 ml)
and brine (1x300 ml) and dried. Removal of the solvent gave a
residue, which crystallized on trituration with ether, to
provide the cyanohydrin 130 as a pink solid (10.4g, 64%). A
sample crystallized from ethyl acetate-light petrol ether as
pale pink crystals, d.p. 185-189°C (Found: C, 68.00; H, 5.34;
N, 4.40. C_{17}H_{17}NO requires C, 68.22; H, 5.72; N, 4.68%).

IR (KBr): 3500 (OH), 2280 (CN), 1715 (C=O), 1340 (C-NC) cm^{-1}.

\( \delta \) (4, 1H, J=7.5 Hz, 8-5), 4.02 (s, 2H, J=6 Hz, 4-6), 2.94
(s, 3H), 2.90 (s, 2H), 2.50 (s, 1H, 4-9), 2.4 (broad
s, 2H, C-9 protons); 2.90 (m, 2H, C-12 protons),
2.69 (s, 2H, C-9 protons), 2.25 (s, 2H, C-9 protons).
CHAPTER 6

Methyl 2-Cyano-3,4-dihydro-2-hydroxy-7-methoxyfluorene-8(1H)-carboxylate 130

The mixture of ketones 127 and 128 (15g, 55 mmol) was dissolved in THF (500 ml), then ether (200 ml) and water (300 ml) were added, and the two-phase system purged of oxygen with a stream of nitrogen for 3 hr. Sodium cyanide (16.2g, 330 mmol) was added (the organic phase turned dark red), followed by the dropwise addition of hydrochloric acid (200 ml, c. 1.7N) over 70 min. (Caution! fume-hood). After the addition was completed, t.l.c. analysis showed a single spot Rf≈0.1 (2% methanol-dichloromethane). The excess hydrogen cyanide was then removed by bubbling nitrogen through the system for several hours (aqueous permanganate trap). Ethyl acetate (200 ml) was added and the layers separated. The organic phase was washed with water (6x300 ml), brine (1x300 ml) and dried. Removal of the solvent gave a residue, which crystallised on trituration with ether, to provide the cyanohydrin 130 as a pink solid (10.5g, 64%). A sample crystallised from ethyl acetate-light petroleum as pale pink crystals, m.p. 165-169° (Found: C, 68.00; H, 5.92; N, 4.40. C_{17}H_{17}NO_{4} requires C, 68.22; H, 5.72; N, 4.68%).

$v_{\text{max}}$ 3500 (OH), 2240 (CN), 1715 (C=O), 1585 (C=C) cm$^{-1}$.

$\delta$ 7.26 (d, 1H, J=8Hz, H-5), 6.92 (d, 1H, J=8Hz, H-6), 3.94 (s, 3H), 3.90 (s, 3H), 3.50 (s, 1H, OH), 3.42 (broad s, 2H, C-9 protons), 2.90 (m, 2H, C-1 protons), 2.66 (e, 2H, C-4 protons), 2.22 (e, 2H, C-3 protons).
m/z 299 (<1%, M⁺), 272 (100), 241 (25), 240 (20), 230 (15), 212 (42), 198 (45).

Dimethyl 3,4-Dihydro-2-hydroxy-7-methoxyfluorene-2,8(1H)-carboxylate 131

A stirred suspension of the cyanohydrin 130 (10.5g, 35 mmol), in absolute methanol (300 ml) was cooled to 0°C and then treated with hydrogen chloride gas until the methanol was saturated. The flask was then stoppered securely and the reaction allowed to warm to room temperature overnight. The resultant dark solution was concentrated to about half the volume, and then poured onto ice (300g), with vigorous stirring. After 2 hr, the precipitate that had formed was extracted into ethyl acetate (3x200 ml). Analysis by t.l.c. (5% methanol-dichloromethane) showed 2 spots, Rf~0.5 (ester) and Rf~0.0 (acid). The ethyl acetate extracts were washed with water (1x100 ml), aqueous 10% sodium bicarbonate solution (2x50 ml), brine (1x200 ml) and dried. Removal of the solvent revealed the hydroxy ester 131 as a tan-coloured solid (7.7g, 66%). An analytical sample was obtained by filtering a solution of the crude hydroxy ester 131 through silica gel (chloroform), and then crystallisation from ether, m.p. 118-120°C (diamond-shaped plates). (Found: C, 64.83; H, 6.39. C₁₈H₂₀O₆ requires C, 65.05; H, 6.07%).

νmax 3450 (OH), 1740, 1720 (esters), 1590 (C=C) cm⁻¹.

δ 7.22 (d, 1H, J=8Hz, H-5), 6.86 (d, 1H, J=8Hz, H-6), 3.92 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.39 (broad s, 2H,
C-10 protons), 3.26 (s, 1H, OH), 2.90 (e, 1H), 2.62 (e, 3H), 2.00 (e, 2H).

m/z 332 (56%, M⁺), 314 (52), 301 (17), 282 (6), 273 (12), 272 (9), 230 (27), 198 (100).

The bicarbonate wash from this experiment was acidified to pH 1 with 10N hydrochloric acid, and the resultant precipitate extracted into 20% THF-ethyl acetate (3x50 ml). The extracts were washed with brine (1x50 ml) and dried. Removal of the solvent gave a white solid (2.3g), m.p. 226-230°, which was identified as the hydroxy acid 132 (see below).

3,4-Dihydro-2-hydroxy-7-methoxy-8-methoxycarbonylfluorene-2(1H)-carboxylic acid 132

The hydroxy ester 131 (7.5g, 22.6 mmol) was dissolved in THF (100 ml), methanol (100 ml) and water (10 ml) and the solution purged of oxygen with a stream of nitrogen for 1 hr. Potassium hydroxide pellets (2.53g, 45 mmol) were added and the reaction was stirred at 25° for 2 hr. The solution was concentrated in vacuo at 20°, the residue dissolved in water (60 ml) and extracted with ethyl acetate (3x50 ml). The basic aqueous phase was then cooled to 0°, acidified to pH 1 with 10N hydrochloric acid, the precipitate collected by filtration and dried to give the hydroxy acid 132 (6.7g, 93%) as a white solid, m.p. 225-230°, homogeneous by t.l.c. (Rf~0.4, 10% methanol-dichloromethane). A sample crystallised from THF-light petroleum as small white needles, m.p. 230-232° (Found: C, 64.38; H, 5.74. C₁₇H₁₈O₆ requires C, 64.14; H,
5.70%).

$\nu_{\text{max}}$ 3440 (OH), 1739-1710 (C=O), 1590 (C=C) cm$^{-1}$.

$\delta$ (CDCl$_3$/(CD$_3$)$_2$SO), 7.26 (d, 1H, J=8Hz, H-5), 6.94 (d, 1H, J=8Hz, H-6), 3.86 (s, 3H), 3.82 (s, 3H), 3.30 (e, 2H, C-9 protons), 2.90 (m, 1H), 2.50 (e, 3H), 2.00 (e, 2H).

m/z 318 (51%, M$^+$), 300 (21), 287 (15), 230 (37), 198 (100).

2-Dichloroacetoxy-3,4-dihydro-7-methoxy-8-methoxycarbonylfluorene-2(1H)-carboxylic acid 133 (R=OH)

This compound 133 (R=OH) was prepared from the hydroxy acid 132 (5g, 15.7 mmol), using the procedure described previously (see the preparation of 75 (R=OH)). It was obtained as a colourless solid (6.23g, 93%), m.p. 182-186$^\circ$.

The analytical sample, obtained after crystallisation from acetone-light petroleum, had m.p. 185-188$^\circ$ (Found: C, 53.13; H, 4.39; Cl, 16.23. $C_{19}H_{18}Cl_2O_7$ requires C, 53.16; H, 4.23; Cl, 16.52%).

$\nu_{\text{max}}$ 1760 (COCHCl$_2$), 1730-1710, 1585 (C=C) cm$^{-1}$.

$\delta$ (CDCl$_3$/(CD$_3$)$_2$SO), 7.25 (d, 1H, J=8Hz, H-5), 6.93 (d, 1H, J=8Hz, H-6), 5.96 (s, 1H, COCHCl$_2$), 3.85 (s, 3H), 3.82 (s, 3H), 3.30 (broad s, 2H, C-9 protons), 2.90 (m,1H), 2.50 (e, 2H).

m/z 393/392 (1%, M$^+$-HCl), 358 (5), 300 (100), 298 (15), 269 (18), 268 (30), 267 (24), 266 (26).
(±)(7α,9αβ) Methyl 7-Dichloroacetoxy-2-methoxy-8-oxo-gibba-1,3,4a(10α),4b-tetraene-1-carboxylate 135

Dry DMF (0.1 ml) was added to a stirred suspension of the dichloroacetoxy acid 133 (R=OH) (6g, 14 mmol), in oxalyl chloride (4 ml) and dry dichloromethane (50 ml) at 0° (drying tube). There was a vigorous evolution of gas, and after 45 min., the suspension had dissolved. After 16 hr at 25°, the volatiles were removed in vacuo, and the residue treated with cold dry benzene (20 ml), filtered, and the precipitate washed with fresh portions of dry benzene (3x20 ml). The filtrate was concentrated, and treatment of the residue with dry benzene repeated. The benzene was then evaporated, and the last traces of hydrogen chloride removed under high vacuum (20 hr) to give the acid chloride 133 (R=Cl) as a pale orange-coloured glass (6.2g).

\[ \nu_{\text{max}} (\text{CH}_2\text{Cl}_2) \ 1790 (\text{COCl}), \ 1760 (\text{COCHCl}_2), \ 1740 (\text{CO}_2\text{CH}_3) \ \text{cm}^{-1}. \]

A solution of the acid chloride 133 (R=Cl) (6.2g) in dry dichloromethane (60 ml) was added to diazomethane (from 20g of \(N\)-nitroso-\(N\)-methylurea) in ether (250 ml) at -20° under nitrogen. The yellow solution was allowed to warm to room temperature overnight, and then concentrated in vacuo to give the crude diazoketone 134 as an orange gum (6g) which was cyclised without purification.

\[ \nu_{\text{max}} (\text{CHCl}_3), \ 2120 (\text{CHN}_2), \ 1765 (\text{COCHCl}_2), \ 1720 (\text{CO}_2\text{CH}_3), \ 1645 (\text{COCHN}_2), \ 1590 \ \text{cm}^{-1}. \]

Analysis of the \(^1\text{H}\) n.m.r. spectrum (CDCl\(_3\)) indicated that this preparation had proceeded in c. 60% yield:
A solution of the crude diazoketone 134 (6g) in dry dichloromethane (60 ml) was added dropwise over 10 min., to a slurry of trifluoroacetic acid (120 ml) and dry dichloromethane (60 ml) stirred vigorously at -20° under nitrogen. After 10 min., ice (100g) was added, and the layers separated. The organic phase was washed with water (2x100 ml), brine (1x100 ml) and dried. Evaporation of the solvent left a dark red gum which was chromatographed on silica gel (100g, 10% benzene-chloroform), to give, in the fractions collected first, the dichloroacetoxy ketone 135 (2.1g, 35%) as a pale yellow crystalline solid. A sample for analysis crystallised as colourless cubes from acetone-light petroleum, m.p. 162-165° (Found: C, 56.44; H, 4.29; Cl, 16.60. C₂₀H₁₈Cl₂O₆ requires C, 56.49; H, 4.27; Cl, 16.67%).

νₘₐₓ 1765 (COCHCl₂), 1750 (ketone), 1720 (CO₂CH₃), 1600, 1590 (C=C) cm⁻¹.

δ 7.30 (d, 1H, J=8Hz, H-4), 6.72 (d, 1H, J=8Hz, H-3), 5.88 (s, 1H, COCHCl₂), 5.60 (t, 1H, J=4Hz, H-5), 3.82 (s, 3H), 3.78 (s, 3H), 3.10-2.10 (complex m, 8H).

m/z 426 (34%, M⁺+2), 424 (51, M⁺), 395 (13), 393 (17), 314 (70), 296 (65), 264 (100), 211 (73).

δ 210.1 (s, C-8), 166.9 (s, CO₂CH₃), 163.1 (s, COCHCl₂), 149.4 (s), 144.8 (m), 130.3 (s), 124.4 (d, J=162Hz, C-4), 119.3 (s, C-1), 111.4 (d, J=162Hz, C-3), 109.3 (d of t, J₁=162Hz, J₂=8Hz, C-5), 87.6 (s, C-7), 63.9 (d, J=181Hz, COCHCl₂), 56.4 (q, J=145Hz, ArOCH₃), 52.1 (q, J=146Hz,
CO₂CH₃), 51.1 (t, J=130Hz, C-9), 45.6 (s, C-9a), 40.0 (t, J=130Hz, C-10 or C-11), 39.4 (t, J=130Hz, C-11 or C-10), 36.1 (t, J=134Hz, C-6).

(±)(7α,9αS) Methyl 7-Hydroxy-2-methoxy-8-oxo-gibba-1,3,4a(10a), 4b-tetraene-1-carboxylate 136

The dichloroacetoxy ketone 135 (1.82g, 4.29 mmol) was dissolved in THF (30 ml), methanol (20 ml), and water (5 drops), and the solution purged of oxygen with a stream of nitrogen, for 30 min. Sodium bicarbonate (0.72g, 8.6 mmol) was added and the two-phase system stirred at 25° for 3 hr. Dichloromethane (100 ml) and water (50 ml) were added and the layers separated. The organic phase was washed with water (1x100 ml), brine (1x100 ml) and dried. Removal of the solvent gave a pale pink solid (1.3g) which was recrystallised from acetone-hexane to give the α-hydroxy ketone 136 (1g, 75%) as colourless crystals, m.p. 150-152° (Found: C, 68.72; H, 5.64. C₁₈H₁₈O₅ requires C, 68.78; H, 5.77).

νₘₐₓ 3420 (OH), 1740-1715 (ester and ketone), 1600, 1585 (C=C) cm⁻¹.

δ 7.38 (d, 1H, J=8Hz, H-4), 6.78 (d, 1H, J=8Hz, H-3), 5.72 (t, 1H, J=4Hz, H-5), 3.88 (s, 3H), 3.84 (s, 3H), 3.25 and 3.05 (ABq, J_AB=16Hz, C-10 protons), 2.78-2.14 (complex, 6H).

m/z 314 (100%, M⁺), 286 (4), 283 (20), 282 (18), 243 (16), 211 (70).

δ 218.6 (s, C-8), 167.0 (s, CO₂CH₃), 158.4 (s, C-2), 149 (s), 1448 (m), 130.8 (s), 124.1 (d, J=160Hz, C-4), 110.9 (d of t,
J₁=162Hz, J₂=7Hz), 80.8 (s, C-7), 56.5 (q, J=145Hz, ArOCH₃),
51.9 (q, J=147Hz, CO₂CH₃), 51.4 (t, J=129Hz, C-9), 45.1 (s,
C-9a), 44.3 (t, J=130Hz, C-11), 39.9 (t, J=131Hz, C-10), 38.8
(t, J=130Hz, C-6).

(±)(7α,9αβ) Methyl 8,8-[1,2-Ethanediylbis(oxy)]-7-hydroxy-
2-methoxy-gibba-1,3,4a(10a),4b-tetraene-1-carboxylate 137

The α-hydroxy ketone 136 (650 mg, 2.07 mmol), ethylene
glycol (1 ml), p-toluenesulphonic acid (.5 mg) and 1,2
dichloroethane (100 ml) were combined and heated at reflux
under nitrogen, with azeotropic removal of water (reverse
Dean and Stark apparatus). After 20 hr, t.l.c. analysis (2%
methanol-dichloromethane) showed the starting ketone (Rf<0.3)
and the product (Rf<0.4). After 40 hr, the cooled solution
was washed with water (1x100 ml), aqueous 10% sodium
bicarbonate solution (1x50 ml), brine (1x100 ml) and dried.
Removal of the solvent gave a solid which was chromatographed
on a column of silica gel (12g, chloroform). The hydroxy
ketal 137 eluted first and was obtained as a white crystalline
solid (553 mg, 75%). Recrystallisation of a sample from
acetone-light petroleum gave white crystals, m.p. 162-165°
(Found: C, 67.23; H, 6.09. C₂₀H₂₂O₆ requires C, 67.03; H,
6.19%).

νmax 3500 (OH), 1730 (ester), 1600, 1595 (C=C) cm⁻¹.
δ 7.34 (d, 1H, J=8Hz, H-4), 6.74 (d, 1H, J=8Hz), 5.78 (t, 1H,
J=4Hz, H-5), 3.92 (s, 4H, OCH₂CH₂O), 3.84 (s, 3H), 3.80 (s,
3H), 3.10 and 2.80 (ABq, J_AB=18Hz, C-10 protons), 2.84 (s,
1H, exch., OH), 2.60 (m, 2H, C-6 protons), 2.00 (m, 4H, C-9 and C-11 protons).
m/z 358 (100%, M⁺), 340 (7), 327 (23), 301 (7), 296 (42),
272 (30), 264 (37).
δ 167.4 (s, CO₂CH₃), 157.9 (s, C-2), 148.7 (s), 145.0 (m),
131.5 (s), 124.1 (d, J=160Hz, C-4), 119.2 (s, C-1), 114.9
(s, C-8), 111.9 (d of t, J₁=160Hz, J₂=8Hz, C-5), 110.8 (d,
J=161Hz, C-3), 79.9 (s, C-7), 66.0 (t, J=149Hz, OCH₂CH₂O),
65.0 (t, J=150Hz, OCH₂CH₂O), 56.4 (q, J=144Hz, ArOCH₃),
52.0 (q, J=147Hz, CO₂CH₃), 52.0 (t, J=129Hz, C-9), 46.4 (t,
J=130Hz, C-11), 45.6 (s, C-9a), 40.3 (t, J=130Hz, C-10),
35.1 (t, J=129Hz, C-6).
Later fractions from the column gave the α-hydroxy ketone
136 (60 mg, 0.2 mmol), m.p. 150-152°.

(±)(7a, 9αβ) Methyl 8, 8-[1,2-Ethanediylbis(oxy)]-2-methoxy-
7-methoxymethyloxy-gibba-1,3,4a(10a),4b-tetraene-
1-carboxylate 138

A stirred solution of the hydroxy ketal ester 137
(72 mg, 0.2 mmol) in dry dichloromethane (0.5 ml) and N-
disopropyl-N-ethylamine (1.4 ml) under nitrogen, was cooled
to 0°, and treated dropwise with methoxymethyl chloride
(0.3 ml, 4 mmol). After stirring for 16 hr at 25°, ice (5g)
and methylene chloride (10 ml) were added and the layers
separated. The organic phase was washed with water (1x10 ml),
aqueous 50% acetic acid (1x5 ml), aqueous 2% ammonium
hydroxide (1x5 ml), brine (1x10 ml) and dried. Removal of the
solvent and trituration of the residue with 50% ether-light petroleum gave the methoxymethyl ether 138, as a pale yellow crystalline solid (78 mg, 98%), m.p. 122-125° (Found: C, 65.82; H, 6.41. C_{22}H_{26}O_{7} requires C, 65.66; H, 6.51%).

ν_{max} (no OH), 1730 (ester), 1590 (C=C) cm^{-1}.

δ 7.34 (d, 1H, J=8Hz, H-4), 6.74 (d, 1H, J=8Hz, H-3), 5.74 (t, 1H, J=4Hz, H-5), 4.97 and 4.67 (ABq, J_{AB}=7Hz, OCH_{2}OCH_{3}), 3.90 (m, 4H, OCH_{2}CH_{2}O), 3.84 (s, 3H), 3.80 (s, 3H), 3.56 (s, 3H, OCH_{2}OCH_{3}), 3.12 and 2.84 (ABq, J_{AB}=16Hz, C-10 protons), 2.64 (m, 2H, C-6 protons), 2.41 and 1.95 (ABq, J_{AB} 11Hz, C-11 protons), 2.04 (s, 2H, C-9 protons).

m/z 402 (31%, M^+), 371 (44), 370 (55), 358 (8), 357 (34), 341 (13), 340 (12), 316 (12), 315 (52), 296 (21), 284 (18), 271 (24), 270 (28), 254 (28), 239 (100), 211 (99).

δ 167.1 (s, CO_{2}CH_{3}), 157.8 (s, C-2), 148.4 (s), 144.9 (s), 131.2 (s), 124.0 (d, J=160Hz, C-4), 119.0 (s, C-1), 115.6 (s, C-8), 111.3 (d of t, J_1=158Hz, J_2=8Hz, C-5), 110.6 (d, J=161Hz, C-3), 92.3 (t, J=167Hz, OCH_{2}OCH_{3}), 85.4 (s, C-7), 65.6 (t, J=149Hz, OCH_{2}CH_{2}O), 64.8 (t, J=151Hz, OCH_{2}CH_{2}O), 56.4 (q, J=144Hz, ArOCH_{3}), 55.2 (q, J=142Hz, OCH_{2}OCH_{3}), 51.8 (q, J=147Hz, CO_{2}CH_{3}), 51.8 (t, J=130Hz, C-9), 45.6 (s, C-9a), 41.7 (t, J=130Hz), 40.4 (t, J=131Hz), 35.5 (t, J=129Hz, C-6).

Deuteration of the ether ketal ester 138

A stirred solution of the ether ketal ester 138 (30 mg, 0.07 mmol) in dry THF (2 ml) and HMPA (0.05 ml) under nitrogen, was cooled to -20° (CCl_{4}-CO_{2} bath) and treated
dropwise with lithium $N$-cyclohexyl-$t$-butylamide$^{34}$ (1 ml, 0.5M in hexane/benzene). The resultant deep purple solution was stirred for 30 min. at $-20^\circ$, then transferred under a positive pressure of nitrogen into THF (1 ml) and deuterium oxide (0.5 ml) at $0^\circ$. The deep purple colour discharged immediately to give a clear solution. Evaporation of the solvent gave a residue which was dissolved in ether (10 ml) and then washed with water (4x10 ml), brine (1x10 ml) and dried. Removal of the solvent gave a gum (26 mg), which by m.s. and $^1$H n.m.r analysis, consisted mainly of the deuterated compound 139.

m/z 403 (55%), 402 (18), 372 (55), 371 (100), 370 (30), 359 (33), 358 (12), 342 (15), 341 (18), 340 (6), 316 (48), 315 (18), 272 (24), 271 (36), 270 (4), 255 (58), 254 (21), 240 (61), 239 (63).

Analysis of the $^1$H n.m.r. spectrum revealed a singlet at 2.70 ppm, and weak signals at 3.06 and 2.90, due to the benzylic protons of the ether ketal ester 138. All other signals were identical to those in the $^1$H n.m.r. spectrum of the ether ketal ester 138.

$N$-Cyclohexyl-$t$-butylamine

This compound was prepared from cyclohexanone and $t$-butylamine using the method reported by Stowell and Padegimas, 171 except that the hydrogenation was conducted at atmospheric pressure (c. 20 hr). The amine was obtained as a colourless liquid, b.p. 80/25 mm in 77% yield. The alternative procedure, 34,172 using cyclohexanone and $t$-butylformamide gave this amine in 15% yield.
1. J. Hori, "Soft abietane esters," (Nippon Gakko, 13, 110 (1968); see ref. 8a.
1. S. Hori, *Noji Shikenjo Seiseki*, (Reports from Exptl. Agric. Station), 12, 110 (1898); see ref. 8a.


24. For example see: a) G. Hoornaert, G. Jammaer and H. Martens, *Tetrahedron*, 31, 2293 (1975);


27. T.M. Brennan, R.L. Carney and E.J. Corey, *ibid.*, 93, 7316 (1971); see also ref. 23a.


41. For example: a) H.W. Thompson, *J. Org. Chem.*, 36, 2577 (1971);
51. The reductive alkylation of 2-methoxy-6-methylbenzoic acid using lithium as the metal results in >90% loss of the methoxy group. J. Slobbe, unpublished results.
52. The reductive alkylation of 2,3-dimethoxybenzoic acid using lithium as a metal, results in complete loss of the 2-methoxy group. L.N. Mander, unpublished results.
2-alkylcyclohex-2-enone derived from 5-isopropyl-2-methoxybenzoic acid by reductive alkylation using lithium as the metal, is due to at least 30% cleavage of the 2-methoxy substituent.


56. The $^1$H-n.m.r. spectrum of this compound, 32, was kindly provided by J. Slobbe.


60. The reductive alkylation of 2-methoxy-5-methylbenzoic acid using lithium as a metal results in 25% loss of the 2-methoxy group. J. Slobbe, unpublished results.


64. M. Kenny, L.N. Mander and R. Urech, unpublished results.

b) J.R. Wiseman, *ibid.*, 89, 5966 (1967);

67. a) J.P. Ferris and N.C. Miller, *J. Amer. Chem. Soc.*, 85, 1352 (1963);


78. a) W. Nagata and T. Terasawa, *Chem. Pharm. Bull.*, 9, 267 (1961);


83. 2-(m-methoxyphenyl)ethyl toluene-p-sulphonate was generously provided by P.H.C. Mundill (see ref. 84).


87. a) S.R. Landauer and H.N. Rydon, *J. Chem. Soc.*, 2224 (1953);


91. R. Urech, personal communication. These efforts have been combined and accepted for publication: J.M. Hook, L.N. Mander and R. Urech, *Synthesis*, in press.


96. a) A.W. Fort, *J. Org. Chem.*, 26, 765 (1961);


123. Ref. 55, pp. 226-231.
124. Cf. a) Ref. 115, pp. 176-181;
126. A sample of this compound was kindly provided by L.N. Mander.


144. R. Urech, personal communication.


146. L. Lombardo, personal communication.


153. Chemical Abstracts, 9th Collective Index, Chemical Substance Index, 76-85, 23104CS (1972-76).

154. Chemical Abstracts, 9th Collective Index, Chemical Substance Index, 76-85, 23180CS (1972-76).

155. Chemical Abstracts, 9th Collective Index, Chemical Substance Index, 76-85 17235CS (1972-76). (See also 17240CS (1972-76)).


158. a) L.M. Jackman and S. Sternhell, "Applications of
b) *ibid.*, pp. 129-30.


161. Chemical Abstracts, 9th Collective Index, Chemical Substance Index, 76-85, 23271CS (1972-76).

162. An authentic sample of this compound was kindly provided by L.N. Mander (see ref. 38).


165. Ref. 139, p. 295.


168. The large-scale preparation of this compound was performed by V. Richardson.
