INVESTIGATION OF NOVEL SYNTHETIC METHODS
AND THEIR POSSIBLE APPLICATION TO
PROSTAGLANDIN AND PYRETHRIN SYNTHESES

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of the requirements for the degree of

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by

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DECLARATION

The work described in this thesis is my own unless stated otherwise and it has not been submitted in support of an application for another degree. The work was carried out at the Australian National University under the supervision of Professor R.W. Rickards.

Paul Bainton
The highest reward for a man’s toil is not what he gets for it but what he becomes by it.

John Ruskin
ACKNOWLEDGEMENTS

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Publication related to this thesis:

Cyclopentanoids from phenol. Part VII
Abbreviations used in this thesis:

- g.l.c.  
  gas/liquid chromatography

- HMPA  
  hexamethylphosphorus triamide

- \(^1\)H n.m.r.  
  proton nuclear magnetic resonance

- Redal  
  bis(methoxyethoxy)aluminium hydride

- THF  
  tetrahydrofuran

- t.l.c.  
  thin layer chromatography
The work described in this thesis was directed towards the synthesis of two groups of natural products, the prostaglandins and the pyrethrins. Chapter 1 includes a review of selected biological properties and selected syntheses of the prostaglandins via the conjugate addition route and via the Corey lactone. Chapter 1 also includes a review of syntheses of the rethrolones which are constituents of the pyrethrins.

In Chapter 2 a process for converting a 2-cycloalkenone to a 2-alkyl-2-cycloalkenone is explored. The application of such a process to 4-alkoxy-2-cyclopentenones could be useful in the synthesis of 4-alkoxy-2-alkyl-2-cyclopentenones, substrates which have previously been used in prostaglandin syntheses. Attempts were made to C-alkylate enolates derived from the Michael addition of phenylselenide anion to conjugated cycloalkenones. The results presented in this thesis indicate that such a process might not be feasible.

The possible application of the phenol-derived 4-(t-butyldimethylsilyloxy)-3-chloro-2-cyclopentenone (86;X=Cl) to the synthesis of the Corey lactone (26) is explored in Chapters 3 and 4, in two different ways. Firstly in Chapter 3, the normal electrophilic reactivity of compound (86;X=Cl) at C-3 was utilised and replacement of the chloro substitutent with carbanionic reagents was explored. The corresponding cyano-enone (151) was obtained in good yield. Model studies on a similar cyclohexenone substrate established the feasibility of converting a model cyano-enone to a Corey lactone type product, which possessed a γ-lactone ring. Application of this last process to the cyano-enone (151) was investigated.

Secondly in Chapter 4, the normal electrophilic reactivity of compound (86;X=Cl) at C-3 was reversed through chemical transformation in an attempted synthesis of the Corey lactone (26). The preparation of cyclopentenyl carbanionic intermediates was investigated through chloride-lithium exchange on a reduced and suitably protected analogue of compound (86;X=Cl) and by the conversion of compound (86;X=Cl) to stannyl-cyclopentene derivatives and their subsequent transmetallation. A stable cyclopentenyl carbanion was not obtained through chloride-lithium exchange but two stable cyclopentenyl carbanions were obtained through stannyl-lithium exchange. Both carbanionic intermediates appeared to react smoothly with electrophiles, however, application of the most suitable of these intermediates to a synthesis of the Corey lactone (26) was unsuccessful.

In Chapter 5, results from a study into the conversion of a C-3 heterosubstituted cycloalkenone [for example, compound (86;X=Cl)] to a 2,3-dialkyl-2-cycloalkenone are presented. Such a process might have application to the synthesis of the rethrolone portion of the pyrethrin insecticides from precursors such as compound (86;X=Cl). Several C-3 heterosubstituted cycloalkenones were treated with an organocuprate reagent and, where the intermediate enolate was formed, alkylation was attempted. Conditions under which such a process could occur were not established although the results obtained did not rule out such a process.
Finally in Chapter 6, the preparation of a novel organocuprate reagent, \( \text{di(benzyloxymethyl)copper lithium} \), is described. Its reactivity towards unsaturated ketones and esters was determined and its equivalence to an hydroxymethyl carbanion established.
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1.1 GENERAL INTRODUCTION

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   Biological Activity
   Aspects of Prostaglandin Synthesis
   The Conjugate Addition Approach
   The Corey Lactone Approach

1.3 REVIEW OF THE PYRETHRINS
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1.4 PRESENT WORK
1.1 General Introduction

Cyclopentanoids occur widely in nature and play important roles in many metabolic processes. Natural products which contain the cyclopentanoid nucleus include the insecticidal pyrethrins, the physiologically active prostaglandins, the perfume constituent jasmone and the group of antibiotics, of which methylenomycin is a representative. Further examples include the sesquiterpenoid convulsant drug, picrotoxin, and brefeldin A which shows antiviral, antifungal, antimitotic and antitumor activities.

Of specific interest to the present work are prostaglandins which contain the 2,3-dialkylcyclopentanone nucleus and the pyrethrins which contain the 2,3-dialkyl-2-cyclopentenone nucleus.

1.2 Review of the Prostaglandins

Nomenclature

The 2,3-dialkylcyclopentanone nucleus is found in the prostaglandins, a class of naturally occurring C₂₀ fatty acids which has diverse pharmacological properties. Prostaglandin naming is based on prostanoic acid (1), a fully saturated C₂₀ cyclopentanoid fatty acid. The prostaglandins are grouped into several families (A to I) which differ from each other in the type of functionality associated with the cyclopentyl ring. Prostaglandin E₂ (PGE₂) (2) and PGF₂α (3) are examples of prostaglandins which are hydroxylated at C-11 but differ in the oxidation level of the C-9 oxygen substituent. Individual members of each family are distinguished by the number of double bonds in the C-8 and C-12 ring substituents, i.e., the α and ω side-chains, which is denoted by subscripts 1, 2 or 3. A
further subscript, \( \alpha \) or \( \beta \), is included for F-type prostaglandins to identify the orientation of the C-9 hydroxyl group.

\[
\text{(1)}
\]

\[
\text{(2)}
\]

\[
\text{(3)}
\]

**Occurrence**

In 1930, 27 years before the prostaglandins were first isolated by Bergström *et al.*\(^1\), Kurzrok and Lieb\(^2\) reported that human seminal plasma induced contractions of uterine strips. This activity was later to be attributed to the action of specific prostaglandins. Purification and characterisation of the prostaglandins eluded chemists until the late 1950's when PGE\(_1\) and PGF\(_{1\alpha}\) were obtained in crystalline form. By 1962, the structural elucidation of these two prostaglandins and PGF\(_{2\alpha}\) \((3)\) by chemical and spectroscopic means was complete\(^3\) except for their stereochemistry, which was confirmed for PGE\(_1\) by X-ray crystallography in 1966.\(^4\)

Prostaglandins occur widely in the Animal Kingdom.\(^5\) A biosynthetic precursor to the prostaglandins, arachidonic acid is found
both in higher animals and in lower flora and fauna (e.g., protozoa, algae, mosses and ferns). In the lower Animal Kingdom, the marine soft coral *Plexaura homomalla* is a major source of PGA₂ which constitutes 1.5% of its dry weight. Prostaglandins have also been identified in many mammalian organs and tissues including the brain, bronchial muscle, seminal fluid, the stomach, the intestine, the ovaries and other reproductive organs.

**Biological Activity**

The family of prostaglandins shows a diverse range of biological activity and selected aspects of this activity for the important E and F series prostaglandins are summarised here.

Both PGE₂ (2) and PGF₂α (3) have been used clinically to alter the normal course of reproduction and their involvement in associated physiological processes in nature is strongly implied. Experimental observations in rabbits and rats support a physiological role for PGE₂ in ovulation. In one such observation the blockage of ovulation, induced by indomethacin, was overcome by administration of PGE₂. Significant levels of PGE₂ (2) and PGF₂α (3) were measured in both human amniotic fluid and peripheral maternal circulation at full-term spontaneous labour and during spontaneous abortion. Administration of PGE₂ (2) and PGF₂α (3) during second trimester pregnancies was found to be a most effective method for terminating such pregnancies. PGE₂ (2) was also found to be an effective and safe drug for the induction of labour at term.

The regulation of body temperature in animals and humans is important, since minor variations of as little as 2 °C can severely disrupt body functions. Prostaglandins are possible mediators in the
process of fever. Injection of prostaglandins of the E series into the part of the brain which regulates body temperature was found to elevate body temperature. Also consistent with the involvement of prostaglandins in the process of fever is the established fact that antipyretic drugs (e.g., aspirin) inhibit the biosynthesis of prostaglandins.

$PGE_2$ (2) and $PGF_{2\alpha}$ (3) are normally present in the respiratory system and they have mutually antagonistic actions on human bronchial muscle. $PGE_1$ and $PGE_2$ (2) are both effective bronchodilators whilst $PGF_{2\alpha}$ (3) is a potent bronchoconstrictor. The presence of significant levels of prostaglandins in inflamed skin suggests that prostaglandins are also mediators in the process of inflammation. This is supported by the observation that, when applied to human skin, both $PGE_1$ and $PGF_{1\alpha}$ induce both redness and soreness, which are characteristic of inflammation.

In summary, this range of biological activity shown by just a few of the prostaglandins emphasises their diverse actions in many important biological processes.

**Aspects of Prostaglandin Synthesis**

Prostaglandins have an array of functionality as exemplified by $PGE_2$ (2) which contains four chiral centres, a labile $\beta$-ketol function, an allylic hydroxyl function, and three cyclopentyl-ring substituents arranged in the thermodynamically more stable all-trans configuration.

Much work has gone into developing new prostaglandin syntheses and several books have been published which address this subject. The first total synthesis of the two prostaglandins, $PGE_1$
and PGF$_{1a}$, was reported in 1968 by Corey et al. Since then prostaglandins have been synthesised by many different approaches: from acyclic precursors, from bicyclo[2.2.1]heptane and bicyclo[2.2.1]heptene precursors, from functionalised cyclohexane precursors via ring contraction, from a 2-alkyl-1,3,4-cyclopentanetrione and from a 2-alkyl-2-cyclopentenone via conjugate addition reactions, to name a few.

The following discussion focusses on two approaches relevant to the work of this thesis, the Conjugate Addition Approach and the Corey Lactone Approach, both of which provide efficient and stereoselective routes to the prostaglandins.

**The Conjugate Addition Approach**

The Conjugate Addition Approach derives its name from the conjugate addition of organometallic reagents containing the lower ($\omega$)$^+$ prostaglandin side-chain to a cyclopentenone of type (4b). The C-4 oxygen substituent in (4b) controls the stereochemistry of addition of the incoming reagent, containing the $\omega$ side-chain, by directing it away from the $\alpha$ face of the molecule. This affords cyclopentanones of type (5), in which the ring substituents are in the required, thermodynamically more stable all-trans configuration. Two important areas of study are associated with this approach: the synthesis of cyclopentenones of type (4) and the synthesis of organometallic reagents which can be used to transfer the $\omega$ side-chain to such cyclopentenones.

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$^+$ The upper ($\alpha$) and lower ($\omega$) side-chains refer to, in the example of PGE$_2$ (2), the C-8 and C-12 substituents respectively.
Sih et al.\textsuperscript{18(a)} reported that the microorganism Dipodascus uninucleatus effects the reduction of the cyclopentanetrione (6) to the optically pure (4\textit{R})-hydroxycyclopentanedione (7) in 75\% chemical yield. Base-catalysed benzoylation of this diketone then afforded the enol benzoate (8) as the major isomer, with a small amount of the corresponding dibenzoate. Reduction of (8) and subsequent hydrolysis and esterification gave the cyclopentenone (4c). Kurozumi et al.\textsuperscript{19} utilised the inherent reactivity of the cyclopentenone (9) at C-4 towards microbiological oxidation in a synthesis of (4d). Only partial asymmetric induction was achieved, however, even when the most efficient organism for this purpose, Aspergillus niger ATCC 9142, was used.

Chemical resolution was used by Pappo et al.\textsuperscript{20} to obtain (4c) \textit{via} the diastereoisomeric oximes (10), the latent carbonyl function being regenerated with titanium trichloride. A disadvantage of this method is the loss of the enantiomer of (4c).
Gill and Rickards\textsuperscript{21(a),21(b)} reported a synthesis of a cyclopentenone of type (4b) in only eleven high-yielding steps from 2,4,6-trichlorophenol. This readily available and inexpensive starting material was known\textsuperscript{22} to undergo hypochlorite-assisted ring contraction to afford the racemate of acid (11) in which the hydroxyl functions are in the relative \emph{cis} configuration. The acid (11) was resolved \textit{via} its diastereoisomeric brucine salts and the (1\textit{R},4\textit{R})-enantiomer was oxidatively decarboxylated. The geminal chloro-substituents were removed with copper(I) chloride and the hydroxyl function was protected to give the (4\textit{S})-chloro-enone (12). The eventual C-2 (\(\alpha\)) substituent of the cyclopentenone (4b) was incorporated into the chloro-enone (12) by its reaction with Grignard reagent (13) in the presence of copper(I)
The second area of study associated with the Conjugate Addition Approach involves the synthesis of organometallic reagents which are capable of transferring the \( \omega \) side-chain to the cyclopentenone.
Early studies on the application of such reagents were principally confined to organocuprate reagents, renowned for their high regiospecificity and reactivity. In 1972 Sih et al. \(^{18(c)}\) reported a synthesis of PGE\(_1\) by reaction of the chiral (E)-organocuprate (16) with a racemic cyclopentenone of type (4b). This reaction gave, after hydrolysing the protecting groups and ester function, an approximately equal mixture of the desired PGE\(_1\) and the epi-\(\text{-ent}\)-PGE\(_1\) (17). Whilst conjugate addition of the \(\omega\) side-chain proceeded almost exclusively to the less hindered face of the cyclopentenone (4b), the chiral reagent showed little preference for reacting with either the (+) or (-) isomers of (4b). Shortly following this, Fried et al. \(^{24}\) reported a synthesis of 13-(\(Z\))-prostaglandins by reaction of the chiral (\(Z\))-vinylcuprate reagent (18) with a racemic cyclopentenone of type (4b), noting that kinetic resolution was achieved as only the (\(R\))-isomer of (4b) was consumed. In 1972 Fried et al. \(^{25(a)}\) reported kinetic resolution of the racemic (\(Z\))-vinylcuprate reagents.
reagent (18) by a cyclopentenone of type (4b) to furnish only the 15-β-isomer (19). Conversion of the unnatural (13Z)-(15R) configuration of compound (19) to the natural (13E)-(15S) configuration was achieved in 1974 by Stork et al.\textsuperscript{25(b)} via sigmatropic rearrangement of the sulphenate ester of compound (19) and subsequent rearrangement of the sulphoxide intermediate thus obtained. This process has been reviewed by Evans and Andrews.\textsuperscript{26}

The problem of wasting one valuable ligand through using bis-homoorganocuprate reagents\textsuperscript{+} was quickly addressed and mixed organocuprate reagents were developed.\textsuperscript{27} Mixed organocuprate reagents comprise one transferable ligand and one less valuable non-transferable ligand and although their use generally overcame the problem of wastage, they were usually found to be of lower reactivity than bis-homoorganocuprates. Floyd and Weiss\textsuperscript{28} explored the conjugate addition of the alanate (20) to several 2-alkylcyclopentenones, including (4b), and reported that whilst effective in conjugate addition reactions, these reagents were also less reactive than the bis-homoorganocuprate (18). More recently, organozirconium reagents, e.g., (21), have been used in conjugate addition reactions.\textsuperscript{29} Whilst these reagents were of low reactivity by themselves, when mixed with the nickel catalyst, [Ni(acac)\textsubscript{2}·Bu\textsubscript{3}AlH], they afforded the desired

\textsuperscript{+} Organocuprate terminology is briefly discussed in Chapter 6.
conjugate addition products in high yield, including those obtained from protected 4-hydroxy-2-cyclopentenones.

Since the termination of the studies described in this thesis, Noyori et al. have reported a short synthesis of the prostaglandins which is relevant to the present studies on the Conjugate Addition Approach. The key operation of Noyori's strategy is the efficient trapping by aldehydes of a cyclopentenyl enolate, generated by the conjugate addition of an organocuprate reagent to a 4-alkoxy-2-cyclopentenone. Their synthesis of PGE\textsubscript{1}(a) illustrates this three-component-coupling process well. Noyori et al. found that the organocopper reagent (22), containing tributylphosphine as the non-reactive ligand, transferred the eventual \( \omega \) side-chain to the cyclopentenone (23a). The resulting enolate was then cleanly trapped with methyl 7-formylheptanoate to yield the alcohol (24), which was smoothly dehydrated to furnish the enone (25). Conjugate reduction of (25) with

\[
\text{Cu(PBu}_3\text{)}_{2-3} \quad \text{OThp}
\]

(22)

\[
\text{OR}
\]

(23) (a: \( R = \text{Thp} \))

\[
\text{OThp} \quad \text{OThp}
\]

(24)

\[
\text{OThp} \quad \text{OThp}
\]

(25)
zinc in acetic acid-propanol gave the methyl ester of PGE<sub>1</sub> in high overall yield. Noyori et al.\textsuperscript{30(b)} also employed a nitro-olefin to trap the intermediate cyclopentenyl enolate but the yield of this reaction and efficiency of removing the nitro function were considerably lower than for the corresponding steps in the above sequence wherein an aldehyde was employed. Using this three-component-coupling process Noyori et al. prepared most of the natural prostaglandins and some prostaglandin analogues\textsuperscript{30(a)-(f)}, including PGE<sub>1</sub>, PGE<sub>2</sub>, PGF<sub>1a</sub>, PGF<sub>2a</sub>, PGD<sub>1</sub>, PGD<sub>2</sub> and prostacyclin (PGI<sub>2</sub>).

**The Corey Lactone Approach**

The bicyclic Corey lactone (26)\textsuperscript{*} was originally prepared by Corey\textsuperscript{31} and used in a synthesis of PGE<sub>2</sub> (2) and PGF<sub>2a</sub> (3), and it is presently one of the most widely used intermediates in the synthesis of natural prostaglandins and their analogues. For clarity, the convention of numbering the Corey lactone (26) with the eventual prostaglandin numbering has been adopted here in this Chapter. In Chapter 3, more commonly used bicyclic ring numbering has been adopted. Syntheses and applications of the Corey lactone have been reviewed to 1976 by Bindra and Bindra\textsuperscript{14} and by Mitra.\textsuperscript{15}

The Corey lactone (26) was originally prepared from the bicyclo[2.2.1]heptenone (27), accessible from cyclopentadiene in only three steps. Bayer-Villiger oxidation of the ketone function gave a high yield of the bicyclic lactone (28) in which the C-8, C-11, and C-12 positions of the ultimate prostaglandin were functionalised. The C-8 substituent was utilised to introduce the C-9 hydroxyl function: alkaline hydrolysis of the lactone (28) gave the corresponding hydroxy-acid which on iodolactonisation afforded the iodolactone (29).

\textsuperscript{*} The corresponding 11,13-diol, has also been referred to as the Corey lactone. However, for clarity it will be referred to as the Corey lactone-alcohol in this thesis.
The hydroxyl function of (29) was then protected as its p-phenylbenzoyl ester after which deiodination with tributylstannyl hydride followed by hydrogenation to liberate the C-13 hydroxyl group, and subsequent Collins oxidation afforded the Corey lactone (26).

Corey then elaborated the ω side-chain by a Horner-Emmons reaction of the stabilised phosphonate reagent (30) with the lactone (26), protected as its acetate, giving the enone (31;R=Ac). Corey achieved only partial stereoselectivity when the C-15 carbonyl function in (31;R=Ac) was reduced with zinc borohydride. Since then, there have been further studies on the reduction of the C-15 carbonyl function of (31). The highest stereochemical and chemical yield of the (15S)-hydroxylactone (32;R'=Ac,R=H) was obtained by Noyori et al. who used a binaphthol-modified lithium aluminium hydride reagent. In
Corey's synthesis the eventual C-11 hydroxyl function was liberated and the dihydroxylactone (32;R'=R=H) was then protected as its bis-tetrahydropyranyl ether (32;R'=R=Thp). The α side-chain was elaborated by reduction of the lactone (32;R'=R=Thp) with di-α-butylaluminium hydride to give the corresponding lactol and then by reaction of this masked aldehyde function with the phosphorane (33) to give the bis-tetrahydropyranyl ether of PGF$_{2α}$ (3). Other natural prostaglandins synthesised from the Corey lactone include PGE$_2$ (2), PGE$_1$, PGF$_{3α}$ and PGE$_3$. 
Since the major reviews on prostaglandin synthesis were written in 1976/77, several new syntheses of the Corey lactone (26) have been described and a number of novel applications of this important intermediate to prostanoid synthesis have been reported.

Kovacs et al.\textsuperscript{33} reported an efficient partial synthesis of the Corey lactone (26) from the previously prepared chiral lactone (34).

Regio and stereospecific addition of formaldehyde and acetic acid to the double bond, followed by methanolysis, gave the diol (35;R=H). Selective oxidation of the primary alcohol function by the Pfitzner-Moffatt reagent afforded the Corey lactone (26).

Johnson et al.\textsuperscript{34} described a synthesis of PGF\textsubscript{2\alpha} (3) \textit{via} the Corey lactone (26) from the chiral diketone (36) which was obtained from chiral 2-acetoxy succinic anhydride. Base-catalysed cyclisation of the diketone (36) was performed in the presence of a magnesium oxide-
magnesium carbonate buffer which ensured that no racemisation occurred. Hydrogenation of the resultant cyclopentenone (37) over a palladium-barium sulphate catalyst furnished the cyclopentanone (38), in which the C-4, C-5 and C-1 substituents were in a cis-trans relationship. This isomer was obtained after the initially formed cis-cis isomer underwent rapid epimerisation at C-1. The carbonyl function in (38) was reduced by sodium borohydride between pH 5.0 - 5.5 to give the cyclopentanol (39). This triester was hydrolysed with methanolic potassium hydroxide to give the lactone (40) on acidification. Acetylation of the hydroxyl group followed by reduction of the acid function via the acid chloride gave the Corey lactone-alcohol as its acetate (35;R=Ac) which was subsequently converted to PGF$_2\alpha$ (3). Although this synthesis provides access to the Corey lactone in lower
yield and in more steps than the original method, chiral starting material may be used. This obviates the need for chemical resolution which is a wasteful process, especially when incorporated late in the synthesis.

One of the advantages of the Corey lactone lies in its use as an intermediate for the synthesis of prostanoids with modified \( \alpha \) and \( \omega \) side-chains. This versatility is elegantly illustrated by the work of Walker and co-workers\(^{35(a)}\) from ICI who prepared selective and potent gastric antisecretory prostanoids from the Corey lactone (26). Both (15S)-15-methyl-PGE\(_2\) methyl ester (41) and 16,16-dimethyl-PGE\(_2\) (42) were known to be more potent inhibitors of gastric acid secretion than PGE\(_2\) (2) and to markedly enhance the healing of duodenal ulcers. However, undesirable side-effects of diarrhoea, nausea, vomiting and pregnancy
termination were associated with the clinical use of the prostanoids (41) and (42) and this emphasised the need for more selective analogues. In the search for prostanoids with enhanced specificity, Walker and co-workers synthesised twenty-eight prostanoids from the Corey lactone (26), including the PGE$_2$ analogue (43) which combined potent gastric antisecretionary activity and low abortive and diarrhoeic side-effects.

Work from the Schering Laboratories$^{35(b)}$ serves to illustrate another industrial application of the Corey lactone (26) to the synthesis of prostanoids modified at the C-16 position. The ketal-analogue (44) was prepared by reaction of the Corey lactone (26) with the appropriate Wittig reagent, followed by elaboration of the $\alpha$ side-chain using Corey's original methodology. One of the epimers of the ketal-analogue (44) was found to be a potent inducer of luteolysis in pregnant rats (300-500 times the activity of PGF$_{2\alpha}$ (3)). Thus, highly potent chain-modified analogues have been synthesised from the Corey lactone (26) or derivatives thereof. Compounds (45) to (52)$^{36-43}$ are further examples of analogues which were prepared from the lactone (26) in the period 1977 to 1981. These prostanoids illustrate the diverse functionality which can be incorporated into the $\alpha$ and $\omega$ side-chains. In addition to these prostanoid syntheses, thromboxane TXB$_2$ (53) was prepared from the Corey lactone-alcohol (35).$^{44}$
Since 1981 the pharmaceutical industry has further developed Corey's original synthesis of the lactone (26) in two new syntheses. 45
Also, the use of lactone (26) or closely related compounds in the synthesis of PGA₂⁴⁶ and six prostaglandin analogues has been reported in the literature. In these syntheses a noteworthy development was the use by several groups⁴⁷ of more stable analogues of the Corey lactone (26), e.g., compound (54). Presumably replacement of the C-12 aldehyde function in the Corey lactone (26) with a halophenylthioalkyl substituent allows for easier synthetic manipulation of otherwise sensitive intermediates. Among the analogues prepared from the Corey lactone (26) or closely related compounds was the 6a-carba-PI₂ (55)⁴⁸ and the cyclopentano[b]furano-PI₂ (56).⁴⁹

Clearly, the Corey lactone (26) is a valuable and versatile intermediate, which continues to be utilised by the pharmaceutical industry.

1.3 Review of the Pyrethrins

Introduction

The 2,3-dialkyl-2-cyclopentenone nucleus is found in several natural products, including PGB₁ (57), jasmone (58) and the pyrethroid insecticides. The pyrethroid insecticides are a family of six esters
which are present in the flower heads of the plant *Chrysanthemum cinerariae folium*. The alcohol portions of these esters, commonly referred to as rethrolones, are characterised by the 2,3-dialkyl-4-hydroxy-2-cyclopentenone structure. Pyrethrolone (59), cinerolone (60) and jasmololone (61) are the three naturally occurring rethrolones, while allethrolone (62) is an example of a synthetic rethrolone. It is notable that the $S$ configuration at C-4 in the rethrolones is opposite to the $R$ configuration found at C-4 in most natural prostaglandins, a feature which has been used in the synthesis of chiral rethrolones and chiral prostaglandins from the antipodes of a common intermediate.

The rethrolones occur in nature combined with either chrysanthemic acid (63) or pyrethric acid (64) and all six possible esters are found. The two pyrethroids which exhibit highest insecticidal activity are pyrethrin I (65) and pyrethrin II (66). In addition, both esters show low mammalian toxicity and are quickly
biodegraded, properties which make them highly desirable on environmental as well as commercial grounds. Consequently, much effort has been directed towards developing efficient syntheses of both the acid and rethrolone portions of these esters.\textsuperscript{52,53} Synthesis of the rethrolone portion is relevant to work described in Chapter 5 of this thesis.
Selected Rethrolone Syntheses

The structural features which need to be incorporated into any rethrolone synthesis are the cyclopentenone nucleus, the C-2 alkenyl and C-3 methyl substituents, and the C-4 hydroxyl function. Further refinement would be required to generate chiral (4S)-rethrolones. Some key intermediates used in published syntheses are shown in Figure 1. Where the intermediates (68), (69) or (70) were used, the cyclopentenyl nucleus of the rethrolone (67) was formed at a late stage in the synthesis. On the other hand, syntheses which utilised the intermediates (71), (72) or (73) relied upon early formation of the cyclopentenyl ring. The latter two intermediates were used in syntheses of enantiomerically pure rethrolones.

The early rethrolone syntheses were based on the acid or base-catalysed intramolecular cyclisation of appropriately substituted 2,5-dicarbonyl intermediates of type (68). 2,5-Dicarbonyl intermediates have also been implied in the synthesis of rethrolones from furans. Shono et al. 54 reported that dimethoxydihydrofurans of type (74), prepared by anodic methoxylation of the corresponding 2,5-disubstituted furans, underwent sequential acid-catalysed ring-opening and ring-closure to give racemic cinerolone (60) and allethrolone (62). In the synthesis described by Piancatelli et al. 55 Lewis-acid catalysed ring-opening of the compound (75) occurred to give a cationic intermediate which cyclised to the cyclopentenone (76). This compound, when adsorbed onto alumina, underwent facile isomerisation to give racemic allethrolone (62).
A variation of the 2,5-dicarbonyl cyclisation approach was reported by Büchi et al.\textsuperscript{56} 3-Allylacetylacetone was transformed into the sensitive epoxyketone (70;\(R=H\)) by protection of one carbonyl group as its enol methyl ether, reaction of the free carbonyl group with dichloromethyl lithium and subsequent hydrolytic deprotection. When treated with methanolic sodium hydroxide, the epoxyketone (70;\(R=H\)) underwent cyclisation to furnish racemic allethrolone (62).

Disconnection of the C-4/C-5 bond in compound (67) suggests that the keto-aldehyde (69) could be a potential intermediate. Schlessinger et al.\textsuperscript{53} prepared the keto-aldehyde (69;\(R=H\)) by Michael addition of the thermodynamic enolate of methylthioallylacetone (77) to compound (78). After hydrolysis, the resulting aldehyde was cyclised with potassium \(t\)-butoxide to yield racemic allethrolone (62).
A lengthy twelve step synthesis of racemic allethrolone (62) was reported by Fujisawa et al. In a novel approach to vicinal dialkylation, cyclopentadiene was elaborated to give the cyclopentadienylethanol (71). Photooxygenation of the methyl-carbonate ester of this alcohol afforded an endoperoxide which, on reductive cleavage with thiourea and bis-tetrahydropyranylation, gave the cyclopentene (79). The C-2 substituent was then unmasked and elaborated to the propenyl side-chain via the corresponding aldehyde which was treated with methylenetriphenylphosphorane. Reaction of the acid-sensitive cyclopentene (80) with Collins reagent gave the corresponding 2-cyclopentene-1,4-dione. The C-4 carbonyl function was selectively reduced with zinc in acetic acid to give racemic allethrolone (62). This last reaction was also reported by Vandewalle et al.

The next two syntheses to be discussed both used intermediates similar to those previously elaborated to prostaglandins and both syntheses allow the preparation of chiral rethrolones. The first asymmetric synthesis was developed by Kovacs et al. who utilised the intermediate hydroxy-lactone (72), which was prepared from the hydroxy-acid (81), the discarded enantiomer from Corey's early prostaglandin synthesis. Details of the synthesis of the enantiomer of (81) were discussed earlier. Chlorination of the hydroxy-lactone (72)
and reduction with di-\( \alpha \)-butylaluminium hydride gave the lactol (82). Reaction of the lactol function with the appropriate Wittig reagent completed the pentenyl side-chain and also resulted in the concomitant loss of hydrogen chloride to afford the methylenecyclopentanol (83). Treatment with acidified aqueous chromium trioxide then resulted in oxidation of the free hydroxyl function and effected acid-catalysed double bond migration, giving (+)-\( \delta \)-jasmololone (61).

An asymmetric synthesis of (4R)-allethrolone (62) by Yamada et al.\(^6\) utilised the intermediate cyclopentane-1,3,4-trione (73). Asymmetric reduction of (73) with lithium aluminium hydride, partly decomposed with three equivalents of (-)-\( \pi \)-methylephedrine, afforded the (4R)-hydroxycyclopentan-1,3-dione (84). Methylation with diazomethane gave the enol ether (85) as the major isomer. The eventual C-3 methyl substituent was introduced by reaction of compound (85) with methyllithium and subsequent hydrolysis gave the (4R)-epimer of allethrolone (62). Yamada et al.\(^6\) suggest that the optically active reducing complex derived from (+)-\( \pi \)-methylephedrine would give (4S)-allethrolone (62), with the natural rethrolone configuration.
In Section 1.2 of this Chapter the use of 2-alkyl-2-cyclopentenones as synthetic precursors to 2,3-dialkylcyclopentenones of type (5) was discussed with specific reference to the cyclopentenones of type (4b) which are synthetic precursors to the prostaglandins. Hypothetically, the 2-alkyl-2-cyclopentenone intermediates could be synthesised from the unsubstituted cyclopentenones using existing methodology i.e., base-catalysed enolisation followed by alkylation. In practice, however, the conditions used in such reactions are too harsh to be used with sensitive substrates. A potentially mild alternative for the C-2 alkylation of enones using organoselenium chemistry was investigated and the results are discussed in Chapter 2.

The Corey lactone (26), an important intermediate in many prostaglandin syntheses, is widely used by industry for the synthesis of prostaglandin analogues with potent and specific biological activities. Although the Corey lactone (26) had been prepared by several routes, a need still remained for more efficient syntheses of (26) from readily available starting materials and for resolution of intermediates at an early stage in the synthesis. The chloro-enone (86;X=Cl) is available in resolved
form in five high-yielding steps from 2,4,6-trichlorophenol and its conversion to the Corey lactone (26) by two routes was studied. Results from these investigations are discussed in Chapters 3 and 4.

Interest in the synthesis of the 2,3-dialkyl-4-hydroxy-2-cyclopentenone nucleus of the pyrethroid insecticides is demonstrated by the number of syntheses described in this Chapter. One approach to the construction of a 2,3-dialkyl-2-cyclopentenone nucleus not previously reported is to use a C-3 heterosubstituted cyclopentenone of type (86) as an intermediate. Since chiral C-3 heterosubstituted cyclopentenones of type (86) are accessible in only five steps from phenol\textsuperscript{21} such an approach could provide an attractively short route to optically pure rethrolones. The following features would be incorporated: early formation of the cyclopentenyl ring, resolution of an intermediate early in the synthesis and use of the same enantiomer of an intermediate previously converted to most of the prostaglandins. Results from investigations into such an approach are presented in Chapter 5.

Finally, in the course of the synthetic studies described in Chapter 3 a novel functionalised organocuprate reagent, lithium
di(benzyloxymethyl)copper, was developed. The equivalence of this organocuprate reagent to an hydroxymethyl carbanion was demonstrated and the scope of its reactivity was studied. The results from these investigations are discussed in Chapter 6.
INVESTIGATION OF THE C-2 ALKYLATION OF 2-CYCLOALKENONES

2.1 INTRODUCTION AND REVIEW OF PREVIOUS WORK

2.2 SYNTHETIC PLAN

2.3 ENOLATE GENERATION VIA PATH A

2.4 ENOLATE GENERATION VIA PATH B

2.5 ENOLATE GENERATION VIA PATH C

2.6 CONCLUSION
2.1 Introduction and Review of Previous Work

The alkylation of 2-cycloalkenones at C-2 to yield 2-alkyl-2-cycloalkenones of type (87) is a useful synthetic operation. Provided that the conditions used are sufficiently mild, and do not disturb potential chirality at C-4, the application of such an operation to the readily available enone (88) could furnish an important prostaglandin precursor of type (4b). Reaction of this precursor with an appropriately functionalised organocuprate reagent affords, in one high-yielding step, the desirable trans 2,3-dialkylcyclopentanone nucleus (5). A mild C-2 alkylation process in combination with organocuprate methodology could provide a short, two-step synthesis of the prostaglandin nucleus from the enone (88). Such a mild C-2 alkylation process has been investigated and the results are described in this Chapter.

Classically the alkylation of 2-cycloalkenones at C-2 has been effected by deprotonation with a strong base followed by reaction of the thermodynamic dienolate of type (89) thus formed, with a reactive alkyl halide. Two problems are associated with the application of this approach to 4-substituted cyclopentenones of type (88). The reaction can afford substantial amounts of C-2 dialkylated product, and

\[
\text{(87) } n = 0, 1, 2 \ldots 
\]

\[
\text{(88)}
\]
enolisation towards C-4 would preclude the use of this approach for the preparation of the chiral enone (4b).

Stork et al.\textsuperscript{63} reported a procedure for the C-2 alkylation and arylation of 2-cycloalkenones, derivatised as their epoxy-\(N,N\)-dimethylhydrazones. For example, reaction of the isophorone derivative (90) with a primary alkyl or aryl Grignard reagent, followed by hydrolysis of the intermediate 3-hydroxyhydrazone with 3M hydrochloric acid in refluxing ethanol, gave the corresponding 2-alkyl or 2-aryl-2-cyclohexenone of type (91). The hydrolysis conditions required in this reaction could prove too harsh for its application to a synthesis of the chiral enone (4b) because elimination of ROH could occur from C-4/C-5. Fuchs\textsuperscript{64} reported a related C-2 arylation procedure, using the intermediate (92). Treatment of this intermediate with a base afforded the azoene (93) which, as a Michael acceptor, reacted with phenylcopper to give the 2-aryl-(3-hydroxy)tosylhydrazone (94).
Dehydration and hydrolysis of the hydrazone function, catalysed by boron trifluoride etherate, afforded a 2-arylisophorone of type (91). The dehydration and hydrolysis conditions employed in this approach could again prove too harsh for its application to a synthesis of the chiral enone (4b) for the same reason given above.

Fleming and Ager\textsuperscript{65} reported a process which involved the conjugate addition of lithium bis(dimethylphenylsilyl)copper to several 2-cycloalkenones. For the substrate 3-methyl-2-cyclohexenone, the intermediate enolate was alkylated with methyl iodide to yield the compound (95). This intermediate was treated with copper(II) bromide to
give the enone (96). In a similar bromination-debromosilylation reaction, Fleming et al.\textsuperscript{66}, reported that the bromination step was not regioselective, affording the two possible α-bromoketones. For the substrates used by Fleming, this lack of regioselectivity was not a problem because the "wrong" isomer could be equilibrated with hydrobromic acid. However, application of this process to the chiral enone (88) might generate the potentially sensitive ketone (97) which, when subjected to the bromination-debromosilylation reaction, could afford undesired by-products in the debromosilylation step as a result of elimination of ROH from C-4/C-5.

During the course of the present work, Shono et al.\textsuperscript{67} reported that the enolate (98), obtained from phenylthiomagnesium iodide and 2-cyclohexenone, reacted with iso-butyraldehyde to give the aldol (99) in good yield. In principle, the aldol (99) could be transformed into the corresponding 2-cyclohexenone by oxidation and syn-elimination of the resulting sulphoxide substituent.
After completion of the present work, several reports were published which described the hydroxyalkylation or alkoxyalkylation of 2-alkenones. None of the reports describe attempts to simply alkylate the 2-alkenones. Oshima et al.\textsuperscript{68} utilised the methylseleno or phenylthio-dialkylaluminium reagents (100) and (101) in the initial conjugate addition step with 2-cyclohexenone and reported that the corresponding enolates reacted efficiently with aldehydes.

Noyori et al.\textsuperscript{69} developed a one-pot, two-step procedure for the C-2 alkoxyalkylation operation in which 2-cyclohexenone was converted to the silylenol ether (102) by reaction with trimethylsilylphenylselenide and triphenylphosphine. Without isolation, the silylenol ether (102) was reacted with a range of orthoesters and dimethylacetals in the presence of a catalytic quantity of trimethylsilyltrifluoromethanesulphonate. Use of trimethylorthoformate as the electrophile, gave the ketone (103) and oxidation followed by elimination of the selenoxide substituent gave the cyclohexenone (104).

Thus, mild processes for the C-2 hydroxyalkylation and C-2 alkoxyalkylation of 2-cycloalkenones have been reported. However, the C-2 alkylation processes reported are not as mild and it is likely that sensitive substrates would undergo undesired reactions under the conditions employed.

Prior to the publication of the above work from other laboratories on the C-2 hydroxyalkylation and C-2 alkoxyalkylation of 2-alkenones, we investigated a mild method for the C-2 alkylation of 2-alkenones with the objective of functionalising the chiral enone (88). The results from those investigations follow.
2.2 Synthetic Plan

The proposed approach to the C-2 alkylation of 2-cycloalkenones is illustrated in Figure 2. The process requires the formation of the C-3 heterosubstituted enolate (106) by reaction of the precursor cycloalkenone (105) with a nucleophilic heteroatom species. Alkylation of the enolate should then give the substituted cycloalkanone (107) and elimination of the C-3 heterosubstituent should afford the enone of type (87). Where (105) is a 4-hydroxycyclopentenone, a cyclopentenone of type (4b) could be obtained.

Figure 2

The choice of heteroatom was limited to sulphur and selenium, firstly because metallosulphides and metalloselenides undergo conjugate addition to enones and secondly because of the ease with which the resultant organosulphide and organoselenide substituents may be removed by oxidation and syn-elimination. Of these two heteroatoms, selenium was chosen for the present study in preference to sulphur because selenoxides are known to eliminate at considerably lower temperature (ca 40 °C) than their sulphoxide analogues (ca 100 °C). The readily available 2-cyclohexenone was chosen for use in this study as a representative cycloalkenone.

The three methods of generating the enolate (109) explored are illustrated in Figure 3. They are the Michael addition of a metalloselenide to 2-cyclohexenone (Path A), enolisation of
3-phenylselenocyclohexanone (108) (Path B) and cleavage of the silylenol ether (102) (Path C). Both the ketone (108) and the silylenol ether (102) are available from 2-cyclohexenone by known procedures.\textsuperscript{71,72}

As with most synthetic endeavours, there were possible problems and these were recognised at the outset. For example, the Michael addition of the phenylselenide anion to 2-cyclohexenone could be disfavoured and, even if successful, elimination of the heterosubstituent from the enolate (109) could preclude the desired alkylation process. In anticipation of the first of these problems, Paths B and C were explored to ensure the presence of selenium on the cyclohexyl ring from the outset.
2.3 Enolate Generation via Path A

Generation of the enolate (109) was initially explored by the addition of various metalloselenide anions to 2-cyclohexenone (Path A). Sodium arylselenides have been obtained by reductive cleavage of diaryldiselenides with various reagents. Sjoberg and Herdevall\textsuperscript{73} first reported that sodium borohydride effects the cleavage of 2,2'-dinaphthyl diselenide to give the corresponding arylselenide anion in good yield. Grieco and Miyashita\textsuperscript{74} prepared lithium phenylselenide in THF by a similar method. The phenylselenide anion (110) generated in this way is formed with an equal quantity of borane and is reported to undergo Michael addition to conjugated \textit{exo}-methylene lactones. When reacted with 2-cyclohexenone, however, this complex failed to transfer the phenylselenide anion (110) in a conjugate sense. Instead, the reaction afforded reduction products derived from 2-cyclohexenone which were generated by the action of the borane ligand. Liotta \textit{et al.}\textsuperscript{75} prepared uncomplexed sodium phenylselenide by reductive cleavage of diphenyl diselenide with sodium metal. HMPA was required to solubilise the uncomplexed sodium phenylselenide for further use. This method was found to be quite lengthy and unsuitable for small-scale preparations. Dowd and Kennedy\textsuperscript{76} prepared uncomplexed sodium phenylselenide by reaction of diphenyl diselenide with sodium hydride but, as with the previous preparation, it was also found to be unsuitable for small scale preparations.
In principle, the use of trialkylborohydride reagents instead of sodium borohydride should afford phenylselenide anion complexed by the relatively inert trialkylborane ligand. Titration of a yellow solution of diphenyldiselenide in THF with either the readily available lithium or potassium tri-\(\sigma\)-butylborohydride afforded a colourless solution of the corresponding phenylselenide anion, solubilised by the trialkylborane ligand. The complexed lithium phenylselenide generated in this way remained a good nucleophile as confirmed by its reaction with the racemic chloro-enone (86;\(X=\text{Cl}\)). The corresponding phenylseleno-enone (86;\(X=\text{SePh}\)) was obtained in 87% yield (see Chapter 5 for details). The trialkylborane ligand was effectively separated by chromatography on silica gel.

It was desirable to have a means of monitoring the progress of addition of lithium phenylselenide to 2-cyclohexenone, since isolation of the enolate (109) would not be feasible. Attempts were made to monitor the reaction by t.l.c. and ultraviolet spectroscopy but because of the odorous and toxic nature of the substrates, \(^1\)H n.m.r. spectroscopy was not investigated. By t.l.c. 2-cyclohexenone and the ketone (108) could be separated. However, the latter compound can be formed either by protonation of the required enolate (109) or by reaction of 2-cyclohexenone with phenylselenol, which will be present when the reaction mixture is quenched. Hence, t.l.c. is not an appropriate method to monitor the reaction. Ultraviolet spectroscopy could not be employed because absorption maxima associated with lithium phenylselenide occur at 277, 223 and 203 nm and the maximum associated with the enone moiety of 2-cyclohexenone occurs at 230 nm. It is therefore partly obscured by absorption arising from lithium phenylselenide. Also, disappearance of maxima associated with the phenylselenide anion would not necessarily indicate that a Michael
addition to 2-cyclohexenone had occurred, since protonation of the anion would also alter the ultraviolet spectrum. Therefore, because this type of reaction could not be monitored whilst in progress, the following reactions were allowed to proceed for a certain time after which they were quenched and the products then analysed.

Reaction of complexed lithium phenylselenide* with 2-cyclohexenone in THF containing ethanol gave, on buffered work-up, only an 8% yield of the desired ketone (108) together with starting material. When methyl iodide was used as the electrophile, neither the desired 2-methyl-3-phenylselenocyclohexanone nor the ketone (108) were obtained. The electrophile simply reacted with lithium phenylselenide to give a 22% yield of methylphenylselenide and 83% recovered 2-cyclohexenone. Under the aprotic conditions employed in this reaction it seems likely that the balance lies on the left-side of Equation [1].

\[
\text{108} + \text{Li}^+[(\text{PhSe})\text{Bu}_3\text{B}]^- \rightleftharpoons [\text{109}; \text{M} = \text{Li}(\text{Bu}_3\text{B})] \quad [1]
\]

On the other hand, the isolation of methyl phenylselenide indicates that even if the enolate [109; M = Li(B Bu_3)] is present in a significant quantity it reacts more slowly with the electrophile than does complexed lithium phenylselenide. Irrespective of cause, it is apparent that complexed lithium phenylselenide is unsuitable for the present purposes.

* Complexed refers to the associated tri-\(\sigma\)-butylborane.
To increase the reactivity of the phenylselenide anion, the lithium cation was replaced with potassium. This should also have increased the reactivity of the desired enolate (109). Reaction of 2-cyclohexenone with complexed potassium phenylselenide, in the presence of HMPA and ethanol, however, gave only recovered starting material (75%) and none of the ketone (108) was obtained.

It was of interest to determine whether the trialkylborane was interfering with the reaction process. Uncomplexed lithium phenylselenide was prepared by deprotonation of phenylselenol with methyllithium. 2-Cyclohexenone was reacted with this anion in diethyl ether and allyl iodide was subsequently introduced. None of the desired 2-allyl-3-phenylselenocyclohexanone nor any of the ketone (108) were obtained. However, the cyclohexenone dimer (111) was obtained in 37% yield together with some allylphenylselenide and some residual polar material (37% by weight).

There are two possible reaction paths which could explain the formation of (111). Michael addition of lithium phenylselenide to 2-cyclohexenone and reaction of the resulting enolate with a further
molecule of 2-cyclohexenone would afford the enolate (112). Equilibration of (112) to give the isomer (113), followed by elimination of phenylselenide anion would then furnish the dimer (111). The fast elimination of phenylselenide anion from enolates of type (113) is supported by results discussed later in this Chapter. An alternative mechanism to explain the formation of the dimer (111) involves deprotonation of 2-cyclohexenone with lithium phenylselenide, rather than Michael addition, and reaction of the resulting dienolate with a further molecule of 2-cyclohexenone. The reported dimerisation of 2-cyclohexenone by tetraethylammonium cyanide is comparable and lends support to the latter mechanism. Whichever mechanism is operating, the desired product was not obtained.

Whilst this work was in progress, results were published on the reaction of phenylthiomagnesium iodide and iso-butyraldehyde with 2-cyclohexenone in a non-polar solvent to afford the keto-alcohol (99) in 90% yield. When this reaction was attempted, a 50% yield of the keto-alcohol (99) was obtained. An analogous reaction was then applied to the present study, using organoselenium reagents. Thus, phenylselenomagnesium iodide (prepared by reaction of phenylselenol with methylmagnesium iodide) and iso-butyraldehyde with 2-cyclohexenone was investigated. However, even under conditions identical to those described in the literature, a thick gum was obtained which upon trituration with dilute acid and extraction gave, after preparative t.l.c., only 17% of the keto-alcohol (114) as a mixture of diastereoisomers. Treatment of the crude product with hydrogen peroxide, followed by warming to effect selenoxide elimination, failed to simplify this mixture. Thus, using organoselenium reagents the
product yield was considerably lower than that reported using organosulphur reagents. By using formaldehyde as the electrophile instead of iso-butyraldehyde a simpler product mixture containing fewer diastereoisomers should be obtained. This reaction should also give a product with useful C-2 functionality. Contrary to expectations, the reaction gave none of the desired keto-alcohol (115; X=H) but furnished the hydroxymethyl-enone (116) and the ketone (108) in yields of 42% and 36% respectively. The compound (116) showed in its mass spectrum a molecular ion at \( m/z \) 126 and exhibited infrared absorption at 3420 and 1668 cm\(^{-1}\) due to the hydroxyl and carbonyl functions. The \(^1\)H n.m.r. spectrum was consistent with the assigned structure.

There are two possible mechanisms which could explain the formation of these products. Both compounds could be derived from the common desired intermediate (115; X=Mg\(^{+}\)), intermolecular base-assisted elimination of phenylselenol from this intermediate would generate the hydroxymethyl-enone (116) on protonation. (The elimination of phenylselenide anion from enolates such as (109) is shown later to be a
facile process, even at -65 °C). Loss of formaldehyde from the intermediate (115;X=MgI²) through a retro-aldol process could then afford, after protonation of the intermediate enolate, the ketone (108). The ketone (108) could also be formed by reaction of 2-cyclohexenone with phenylselenol which would be present on work-up. It is, however, unlikely that a 42% yield could be obtained via this route since the reaction mixture had been rapidly diluted on work-up. The ketone (108) could, of course, be formed by protonation of any of the enolate (109) which may have been generated in the reaction mixture. Alternatively, the second possible mechanism which could explain the formation of the products obtained involves the deprotonation of 2-cyclohexenone by phenylselenomagnesium iodide to give the thermodynamic dienolate (117) and phenylselenol. Hydroxymethylation of the dienolate (117) at C-2

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\text{(117)}
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followed by conjugation of the double bond could afford the enone (116), while the Michael addition of phenylselenol to 2-cyclohexenone would give the ketone (108).

The complete absence of the expected ketone (115;X=H) together with the fact that 2-cyclohexenone and 5,5-dimethyl-2-cyclohexenone both give their thermodynamic dienolates in the presence of sodium methoxide\textsuperscript{78} and tetraethylammonium cyanide\textsuperscript{77} lend
tentative support to the latter mechanism. Whilst both of these bases are stronger than the phenylselenide reagents used in this study the role of lithium phenylselenide as a base in the formation of the dimer (111) is likely (see earlier in this Chapter).

2.4 **Enolate Generation via Path B**

Generation of the enolate (109) was then explored by enolisation of the phenylseleno-ketone (108) (Path B), prepared by reaction of 2-cyclohexenone with phenylselenol. Posner et al. previously demonstrated that deprotonation of the ketone (118) occurs mainly at C-2, and that regiospecificity is enhanced where the aryl-lithium association is strengthened by increased electron density on the aromatic ring, as in (119) (e.g., X=H<X=Me<X=OMe). By analogy it was anticipated that the phenylseleno substituent in the ketone (108) would also direct enolisation towards the C-2 position. The reaction was performed at -65 °C in accordance with Posner's method, using chlorotrimethylsilane to intercept the intermediate enolate(s). Neither of the silylenol ethers were obtained from this reaction, although it is likely that enolisation occurred towards C-2, as 2-cyclohexenone was obtained in 60% yield with 21% recovered starting material. Elimination of the phenylseleno substituent therefore appears to be a significant
process at -65 °C and even at this temperature it occurs in preference to silylation. At higher temperatures, this elimination would occur more rapidly. The results of this study so far indicate that formation of the enolate (109) (possessing alkali metal countercations) via Path A is an unfavoured process. In addition, alkylation of the enolate is unlikely to be successful, based on the unfruitful attempt to silylate it.

2.5 Enolate Generation via Path C

The silylenol ether (102) is a further possible source of the enolate (109). Unlike Path A, this method of generating (109) should allow the preparation of an enolate in which the phenylseleno substituent is present from the outset, and in contrast to Path B this method ensures regiospecificity. Liotta\(^2\) prepared the silylenol ether (102) in 70% yield by reaction of 2-cyclohexenone with trimethylsilylphenylselenide, in the presence of a catalytic amount of triphenylphosphine. However, using this method, only 20% of the 2-cyclohexenone was converted to the silylenol ether (102). In the absence of solvent, a 55% conversion rate was realised. The reaction was further modified by replacing triphenylphosphine with the more nucleophilic 18-crown-6/potassium cyanide complex and under these conditions the silylenol ether (102) was isolated in 90% yield.

Noyori et al.\(^8\) reported that the trimethylsilylenol ether of cyclohexanone reacted efficiently with benzaldehyde at -78 °C in the presence of 10 mol% of tetrabutylammonium fluoride. Likewise, it may be possible to intercept the enolate (109; M=NBu\(_4\)) with benzaldehyde, provided that elimination of the phenylseleno substituent is sufficiently slow and the aldol reaction is fast enough at -78 °C. This was not found to be the case. Reaction of the silylenol ether (102)
with benzaldehyde in the presence of tetrabutylammonium fluoride gave some unconsumed starting material and 2-cyclohexenone in 55% yield. None of the desired product was detected. This result clearly indicates that elimination of the C-3 heterosubstituent from the enolate (109; M=NBu₄) is more facile than C-2 hydroxybenzylation. It was expected that C-2 alkylation would be less likely at this temperature than C-2 hydroxybenzylation and so enolate alkylation was not attempted.

2.6 Conclusion

In the present work the C-2 alkylation and C-2 hydroxyalkylation of 2-cyclohexenone was investigated using organoselenium reagents. In order to explain why the alkylation reactions in the present work were not successful whereas C-2 hydroxyalkylation and alkoxyalkylation reactions reported in literature were successful, it is necessary to consider the intermediates involved in the different procedures.

Comparing the results of Shono's workІ on the enolate (98) and the results from the present study using enolates of type (109) it is probable that functionalisation of enolates of either type at C-2 will only be successful when intermediates such as (120) are formed, wherein the negative charge of the enolate is localised in a

\[
\begin{align*}
R'X & \quad \text{ionic association} \\
R & \quad \text{extent of charge distribution} \\
M^+ & \quad R' = \text{Me or Ph} \\
X = \text{S or Se}
\end{align*}
\]
metallocycle. When the negative charge is not localised in such a metallocycle, elimination of the C-3 heterosubstituent will be favourable. In the present work where Li\(^+\), K\(^+\) or Bu\(_4\)N\(^+\) were the countercations and either a proton source or an alkylating agent were used as the electrophile, localisation of the negative charge in a metallocycle as described was not possible and elimination of the C-3 heterosubstituent occurred. Reaction of 2-cyclohexenone with phenylselenomagnesium iodide and formaldehyde gave the 2-hydroxyalkylated enone (116). This result might be expected following the above reasoning because the magnesium countercation and formaldehyde provide the necessary components for formation of a metallocycle. However, the formation of (116) via the thermodynamic enolate is the favoured mechanism based on the arguments discussed earlier. It would be worthwhile preparing the magnesium enolate (109;M=MgI) from the silylenol ether (102) and treating it with formaldehyde. A successful reaction would yield a cyclohexanone with useful functionality at C-2 and could confirm the role of magnesium in localising the negative charge in the metallocycle of type (120).

In the related C-2 alkoxyalkylation procedure developed by Noyori et al.\(^69\), the silylenol ether (102) was reacted with either an ortho-ester or an acetal, activated with trimethylsilyltriflate. Although Noyori makes no comment on the possible intermediates involved in this reaction, it seems feasible that the cationic species (121) was a precursor to the product ketone (103). Elimination of phenylselenide anion from this intermediate would, of course, be an unfavoured process.
To conclude then, it has been reported that under certain conditions, C-3 heterosubstituted enolates of type (109) undergo C-2 hydroxyalkylation and silylenol ethers of such enolates undergo C-2 alkoxyalkylation. The present work demonstrates that certain metalloselenides are poor nucleophiles in addition reactions with 2-cyclohexenone. It was also found that elimination of the C-3 phenylseleno substituent from the enolates (109;M=Bu₄N) and (109;M=Li) was rapid at low temperatures. This thwarted attempts to hydroxyalkylate and silylate the respective enolates.
SYNTHETIC STUDIES TOWARDS THE COREY LACTONE VIA A CYCLOPENTENYL CARBOCATION EQUIVALENT

3.1 INTRODUCTION

3.2 SYNTHETIC PLAN BASED ON THE NORMAL REACTIVITY OF THE CHLORO-ENONE (86;X=Cl)

3.3 THE CHLORO-ENONE (86;X=Cl): AN AMBIDENT ELECTROPHILE
Reactivity Towards Charge-Stabilised Carbanionic Nucleophiles
Reactivity Towards Vinylic Cuprate Reagents
Chloride-Cyanide Exchange

3.4 REDUCTION AND LACTONE RING FORMATION - MODEL STUDIES

3.5 APPROACHES TO THE COREY LACTONE

3.6 CONCLUSION
3.1 Introduction

The importance of the Corey lactone (26) as a synthetic intermediate to a wide range of prostanoids continues to provide impetus for new approaches to its synthesis. Stereochemical features of the Corey lactone (26) include the \( cis \)-fused lactone ring and the relative \( cis \) arrangement of the C-6a and C-5 oxygen functions which are \( trans \) to the C-4 aldehyde function. It is important that any effective synthesis of the Corey lactone (26) should incorporate tight stereochemical control in the generation of these asymmetric centres. Furthermore, conditions employed in the synthesis of (26) should be mild enough to preserve the acid and base-sensitive aldol function and the aldehyde function itself.

Two fundamentally different approaches to the Corey lactone (26) are explored in this thesis, one in this Chapter, the other in Chapter 4. The chloro-enone \((86;X=Cl)\), available optically pure in five high-yielding steps from phenol, was the starting material for both approaches. The C-4 oxygen substituent present in this compound \((86;X=Cl)\) should permit the stereospecific introduction of the three additional asymmetric centres in the lactone (26).

The two approaches to the lactone (26) differ fundamentally in the procedures used to functionalise the chloro-enone \((86;X=Cl)\) at C-3. The first approach described in this Chapter utilises the normal
reactivity of compound (86;X=Cl) which may be considered as an operational equivalent to the 5-hydroxy-3-oxo-cyclopentenyl carbocation (122). This type of reactivity has already been exploited by Gill and Rickards\textsuperscript{21(b)} who demonstrated that the epimeric chloro-enone (12) reacts with various carbanions. The second approach to the lactone (26) which is described in Chapter 4 embraces the principle of "reactivity umpolung" via heteroatom exchange. This approach involves the preparation of a cyclopentenyl carbanion of type (123), from the chloro-enone (86;X=Cl) and its subsequent reaction with electrophiles.

3.2 Synthetic Plan Based on the Normal Reactivity of the Chloro-enone (86;X=Cl)

The overall scheme for the synthesis of the Corey lactone (26), utilising the normal reactivity of the chloro-enone (86;X=Cl), is illustrated in Figure 4. The first step requires displacement of the C-3 chloro substituent of (86;X=Cl) with a nucleophile which may be readily converted to an alcohol, aldehyde or acid function. The work of Gill and Rickards\textsuperscript{21(b)} and results from work described in this thesis show that the chloro-enone (86;X=Cl) reacts with various nucleophiles at C-1, C-3 or at both sites.
It was anticipated that the first step in this scheme could be effected by the conjugate addition of a nucleophilic formyl equivalent to the chloro-enone \((86; X = Cl)\) and subsequent elimination of chloride anion to furnish the cyclopentenone \((124)\). This would be followed by stereospecific reduction of the carbonyl function, which has been reported for similar cases.\(^2\) Deprotection of the aldehyde function should then give the cyclopentenecarbaldehyde \((125)\), in which the C-3 and C-5 oxygen functions are in the required \(cis\) configuration.

Esterification of the C-3 hydroxyl function with an acetate equivalent should give the ester \((126)\) which is set up for base-catalysed Michael addition to form the lactone \((127)\). Analysis of

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Resolved intermediates were not used in this work and the stereochemistry depicted in this thesis indicates relative stereochemistry only. The processes are, of course, equally applicable to the readily available resolved chloro-enone \((86; X = Cl)\) if required.
a Drieding stereomodel of (126) suggests that ring closure should proceed in a stereospecific manner to afford a cis-fused lactone. Finally, removal of the activating group (Z) would complete a short, stereospecific synthesis of the Corey lactone (26) from the readily available chloro-enone (86;X=Cl).

At the outset of this study two challenges to the synthetic plan were recognised. Firstly, functionalisation of the chloro-enone (86;X=Cl) at C-3 could be complicated by its ambident C-1/C-3 reactivity towards nucleophiles. Secondly, the sensitive functionality in the Corey lactone (26) requires that the activating group (Z) be carefully selected so that it may be removed under mild conditions.

The results obtained from investigations into this route are presented in three sections. In the first of these sections (3.3) attempts to functionalise the chloro-enone (86;X=Cl) at C-3 with different nucleophiles are described. The Michael addition reaction, used to form the lactone (127), was then explored with the aid of six-membered ring analogues and conditions for the removal of the activating group (Z) were optimised. Results from these studies are presented in the second section (3.4). Application of this methodology to a cyclopentenone of type (124) is then described in the third section (3.5) of this Chapter.

3.3 The Chloro-enone (86;X=Cl): An Ambident Electrophile

Factors which could control the regioselectivity of nucleophilic attack on the ambident electrophile, the chloro-enone (86;X=Cl), include reaction temperature, solvent polarity, steric constraints and the extent of delocalisation of the negative charge on the nucleophile (i.e., softness). The following examples from the literature illustrate the effects that these factors have on regioselectivity.
Shultz et al.\textsuperscript{81} described the reaction of 2-cyclohexenone with methyl 2-lithio-2-phenoxypropionate at -78 °C which afforded the expected C-1 addition product (128) when quenched at -78 °C. On the other hand, when the reaction was quenched after warming to room temperature, the C-3 addition product (129) was obtained. In agreement with other results from similar reactions, C-1 addition products are generally obtained under conditions of kinetic control (i.e., lower temperature) whereas the C-3 addition products are generally obtained under conditions of thermodynamic control (i.e., higher temperature). Also, when the isolated C-1 addition product (128) was treated with lithium diisopropylamide at -78 °C and then subsequently warmed to 25 °C, rearrangement occurred to give the ketone (129).

The influence of dipolar additives on the regiochemical outcome is illustrated by the reaction of 2-lithio-1,3-dithiane with 2-cyclopentenone with and then without HMPA.\textsuperscript{82} When this reaction was performed at -78 °C in the absence of HMPA only the C-1 addition product was obtained. In the presence of between one to two equivalents of HMPA at the same temperature, the C-3 addition product was isolated as the major product with only a trace of the C-1 addition product. The lithium salt of the C-1 addition product did not rearrange in the
presence of HMPA at higher temperature. Similar results were obtained with 2-cyclohexenone.

The effect of steric hindrance at C-3 on the regioselectivity of addition is exemplified by the reaction of 2-cyclohexenone with diphenylsulphonium isopropylide which gave the cyclopropane (130), derived from initial C-3 addition. In contrast, 3-methyl-2-cyclohexenone yielded the unsaturated oxirane (131) as the major product, obtained by C-1 addition. 83

\[
\begin{align*}
(130) & \quad \quad (131) \\
\end{align*}
\]

The effect of the electronic nature of the nucleophile on the regioselectivity of addition is demonstrated by the work of Stork and Maldonado. 84 Reaction of 2-cyclohexenone with the saturated cyanohydrin acetal (132) furnished the C-1 addition product. On the other hand the unsaturated cyanohydrin acetal (133), in which the carbanion is further stabilised through the \( \pi \) system of the adjacent olefin, reacted with 2-cyclohexenone mainly at C-3. In general, as the
charge on the organometallic reagent becomes more delocalised (i.e., as the nucleophile becomes softer) a higher proportion of the C-3 addition product will be obtained. Further examples of nucleophilic addition to conjugated enones are discussed in a review by Krief\(^{85}\) who highlighted the parameters which control the regioselectivity of such additions.

In the present work, the chloro-enone (86;X=Cl) might initially react with a charge-stabilised nucleophile at C-1. However, if this were the case, based on the examples just discussed, it should be possible to functionalise the chloro-enone (86;X=Cl) at C-3, by manipulating the experimental conditions or varying the nucleophile.

**Reactivity of the Chloro-enone (86;X=Cl) Towards Charge-Stabilised Carbanionic Nucleophiles**

Corey and Boger\(^{86}\) reported the use of 2-lithiobenzothiazole as a formyl carbanion equivalent. When the chloro-enone (86;X=Cl) was treated with this reagent at -78 °C in diethyl ether and quenched after 30 min. at that temperature, the alcohol (134) was obtained in 82% yield. Signals in the \(^1\)H n.m.r. spectrum of the alcohol (134)

\[ \text{BT} = 2'-\text{benzothiazoly} \]

suggest that only one diastereoisomer was formed, as only one set of signals was observed for each of the diastereotopic C-5 protons: a doublet of doublets at \(\delta 3.2\) and a doublet of doublets at \(\delta 2.3\). The
absence of other signals in the 63.2 to 2.3 region of the spectrum indicated that only one diastereoisomer was present. Also, based on literature $^1$H n.m.r. data for similar 1,4-cyclopentenediol systems, the large difference in chemical shift between the two sets of signals observed in this region suggested that the isomer obtained was that in which the C-4 and C-1 oxygen functions were cis. This result is expected on steric grounds since the bulky C-4 oxygen substituent in the chloro-enone (86;X=Cl) is likely to direct the reagent to the opposite face of the molecule. In the mass spectrum of the alcohol (134) a base peak was observed at $m/z$ 324 which had a $^{37}$Cl isotope peak at $m/z$ 326 and which corresponded to the fragmentation $\text{M}^+-\text{Bu}^+$. The presence of an alcohol function in (134) was supported by strong infrared absorption at 3315 cm$^{-1}$.

The reaction was repeated in THF in the presence of two equivalents of HMPA and was warmed over 30 min. to 22 °C prior to quenching. The alcohol (134) was again obtained in 82% yield and none of the C-3 addition product was detected. To check whether the initial reaction temperature influenced the regioselectivity of addition, the chloro-enone (86;X=Cl) was treated with 2-lithiobenzothiazole for 30 min. at -20 °C. The reaction was again performed in the presence of two equivalents of HMPA but this time it was quenched at -20 °C. Under these conditions the yield of (134) was only 65% and a 32% yield of (86;X=Cl) was recovered. Thus, raising the initial reaction temperature disfavoured formation of the C-1 addition product to some extent. However, the absence of any C-3 addition product when both starting material and reagent were clearly present in the reaction mixture, confirmed that C-3 addition was completely disfavoured even at this temperature. This could have been caused, in part, by steric hindrance at the C-3 position.
Attention was then turned towards carbanions of dithiane derivatives. 2-Alkyl-2-lithio-1,3-dithianes have been extensively used as acyl carbanion equivalents\(^{87}\) and the anion derived from 1,3-dithiane itself has also been used as a formyl carbanion equivalent.\(^{88}\) When 2-lithio-1,3-dithiane was reacted with the chloro-enone (86;X=Cl) at -78 °C in THF, the alcohol (135) was obtained in 69% yield together with some starting material (16%). The \(^1\)H n.m.r. spectrum of the alcohol (135) included: a singlet at \(\delta 5.91\), the chemical shift of which is characteristic of a non-conjugated olefinic proton in a cyclopentene ring; a doublet of doublets at \(\delta 4.58\), which is similar to the chemical shift of signals due to C-4 protons in analogous cyclopentenol systems\(^{21}\); and a singlet at \(\delta 4.16\) which was assigned to the dithianyl methine proton. Because the signals derived from the C-5 protons were partly obscured by signals from the dithianyl methylene protons it was not possible to accurately measure their chemical shifts or coupling constants both of which would be important criteria for use in determining which diastereoisomer was formed. The sharpness of the downfield signals did, however, suggest that only one isomer was obtained, presumably formed by addition of the nucleophile to the less hindered face of the chloro-enone (86;X=Cl). When the reaction was
repeated in the presence of HMPA at -78 °C, the alcohol (135) and starting material (86;X=Cl) were obtained in yields of 40% and 32%. The desired C-3 addition product (136) was also obtained but only in 8% yield. A comparison of the \(^1\)H n.m.r. spectrum of the enone (136) to that of the alcohol (135) revealed several diagnostic differences. Signals arising from the C-2, C-4 and dithianyl methine protons were all shifted downfield to δ6.28, 5.08 and 4.84 respectively. The mass spectrum of the enone (136) exhibited a molecular ion at \(m/z\) 330 and a base peak at \(m/z\) 273, which was due to \(M^+\)-Bu\(^t\). Infrared absorption at 1722 cm\(^{-1}\) confirmed the presence of a cyclopentenone carbonyl function.

When this reaction was repeated and the temperature allowed to rise to 0 °C before quenching, the alcohol (135), the enone (136) and starting material (86;X=Cl) were obtained in yields of 46%, 9% and 19%. Thus, even under conditions of thermodynamic control the yield of the C-3 addition product remained low. When the reaction was repeated with 2-potassio-l,3-dithiane (i.e., using a "softer" counter-cation) only the alcohol (135) was obtained in 71% yield. The isolated alcohol (135) was also treated with potassium hydride in THF and the reaction mixture was gradually warmed to room temperature. Rearrangement to the C-3 addition product (136) did not occur and the alcohol (135) was recovered in 74% yield.

Clearly, the C-3 and C-4 substituents in the chloro-enone (86;X=Cl) in some way disfavour the reaction of dithiane anions at C-3, since under identical conditions 2-cyclopentenone is reported to react with 2-lithio-l,3-dithiane to furnish the C-3 addition product in high yield. A more charge-delocalised or "softer" formyl carbanion equivalent was sought.

In 1971 Stork et al.\(^{84}\) utilised the carbanion obtained from a cyanohydrin acetal as an acyl carbanion equivalent. The anion
obtained from the formaldehyde-derived cyanohydrin acetal, however, underwent self-condensation and was not synthetically useful. In 1974, Stork et al. developed a viable formyl carbanion equivalent, namely the anion obtained from N,N-diethylaminocyanacetonitrile. This anion underwent rapid polymerisation unless it was generated in the presence of HMPA. Reaction of the chloro-enone (86;X=Cl) with one equivalent of N,N-diethylaminolithioacetonitrile did not proceed to completion, as judged by analytical t.l.c.. By using two equivalents of the reagent, however, all of the chloro-enone (86;X=Cl) was consumed and the alcohol (137;M=X=H) was obtained in 72% yield as a 1:1 mixture of separable diastereoisomers. Infrared absorption in both isomers at 3450 cm⁻¹ indicated the presence of an hydroxyl group, thus confirming that C-1 addition had occurred. Further, signals in the ¹H n.m.r. spectra of the two diastereoisomers indicated that the C-1 and C-4 oxygen substituents in both isomers were both in the cis configuration. Hence, it was tentatively concluded that the epimeric centre at C-1' was the source of diastereoisomerism. This result is consistent with those results obtained from the reactions of (86;X=Cl) with lithiobenzothiazole and with 2-lithio-1,3-dithiane which gave just one diastereoisomer in each case.

Returning to the current reaction where just one equivalent
of $N,N$-diethylaminolithioacetonitrile was employed and incomplete reaction resulted, it is likely that the initially-formed alcoholate ($137; M=H, X=Li$) was sufficiently acidic to be further deprotonated by the $N,N$-diethylaminolithioacetonitrile to give the dianion ($137; M=X=Li$) and protonated reagent. (This dianion would also be present where two equivalents of reagent were used.) Clearly, rearrangement of the dianion ($137; M=X=Li$) to afford the desired C-3 addition product appears extremely unlikely. In an attempt to prepare the monoanion ($137; M=H, X=Li$) and to investigate whether rearrangement of this species is possible, the alcohol ($137; M=X=H$) was isolated and then treated with one equivalent of lithium diisopropylamide at -78 °C. When this reaction mixture was warmed to room temperature, no rearrangement was observed and the alcohol ($137; M=X=H$) was recovered in 85% yield. Thus, even in the case of the monoanion ($137; M=H, X=Li$), rearrangement to the C-3 addition product was disfavoured at room temperature. Reaction of the chloro-enone (86; $X=Cl$) with the potassium derivative of $N,N$-diethylaminopotassioacetonitrile (i.e., with a softer countercation), gave by analytical t.l.c., the same two diastereoisomers of the alcohol ($137; M=X=H$). When this reaction mixture was warmed to room temperature extensive decomposition occurred and neither the C-1 nor C-3 addition products were detected in the product mixture. A more charge-delocalised carbanion equivalent was needed.

In 1979 Wang et al. reported that lithio(phenylthio)-acetonitrile reacted with 2-cyclopentenone at -78 °C, under conditions of kinetic control, to give the C-1 addition product (138). When the initially-obtained alcoholate was warmed to room temperature, they found that rearrangement occurred to furnish the C-3 addition product (139). Of the formyl carbanion equivalents used in this study to this point,
lithio(phenylthio)acetonitrile* has the most extensive charge
delocalisation. This is because the carbanion is flanked by a nitrile
function and a sulphur atom which stabilise the negative charge through
p and d-orbital interactions respectively. The "softness" of this
reagent is emphasised by the experimental observation that HMPA is not
required to facilitate its Michael addition to 2-cyclopentenone.

Reaction of the chloro-enone (86;X=Cl) with one equivalent
of lithio(phenylthio)acetonitrile at -78 ° C, i.e., under kinetic
control, afforded the alcohol (140;M=X=H) in 51% yield as a mixture of
diastereoisomers. Starting material was recovered from this
reaction in 42% yield. From the $^1$H n.m.r. spectrum of (140;M=X=H) it
was evident that two diastereoisomers had been formed. The $^1$H n.m.r.
spectrum showed two singlets at 65.90 and 5.80 which were assigned to

* The equivalence of lithio(phenylthio)acetonitrile to the
hypothetical formyl anion ($\text{CHO}$) still remains to be established
by chemical conversion. However, the unmasking of 2-alkyl-$N$-$N$-
diethylaminoacetonitrile derivatives by hydrolysis provides
a basis for this proposed equivalence through analogy.
the C-2 proton in each diastereoisomer and two singlets at 3.84 and 3.82 which were assigned to the C-1' proton in each diastereoisomer. A broad singlet at 63.05 which disappeared on addition of deuterium oxide was assigned to the exchangeable hydroxyl proton. The two diastereoisomers were inseparable by chromatography, however, integration of the signals at 65.90 and 5.80 indicated that they had been formed in a ratio of 3:2. Analysis of the region of the spectrum revealed that only one diastereoisomer with epimeric centres at C-1 and C-4 had been formed. After comparison of this data to literature 1H n.m.r. data, this compound was tentatively assigned to be the cis-diastereoisomer. The two isomers obtained are therefore likely to be diastereoisomeric at C-1'. The alcohol (140;M=X=H) exhibited infrared absorption at 3430 and 2240 cm⁻¹ (weak) which was indicative of hydroxyl and nitrile functions. The recovery of compound (86;X=Cl) in the present reaction is not unexpected because only one equivalent of the reagent was used and the recovery of starting material may be explained by a similar mechanism to that proposed to explain the formation of the dianion (137;M=X=Li). Deprotonation of the alcoholate
(140; M=H, X=Li) by a second molecule of the reagent would generate the
dianion (140; M=X=Li), protonated reagent and give unconsumed starting
material (86; X=Cl).

Reaction of the chloro-enone (86; X=Cl) with two equivalents
of lithio(phenylthio)acetonitrile and HMPA afforded, on warming from
-78 °C to 0 °C, the desired enone (141) in 65% yield. Neither starting
material nor the alcohol (140; M=X=H) were detected. The \(^1\)H n.m.r.
spectrum of the enone (141) in deuteriochloroform showed a singlet
at δ5.89 which was assigned to the olefinic proton and a singlet
at δ4.74 assigned to the C-1\(^{\prime}\) proton, shifted 0.9 p.p.m. downfield from
the analogous signal in the alcohol (140; M=X=H). Also, a doublet of
doublets was observed at δ5.18 which was due to the C-4 proton, coupled
to the \(\text{cis}\) and \(\text{trans}\) C-5 protons by 6 and 3 Hz respectively. The C-5
proton \(\text{cis}\) to the C-4 proton resonated at δ2.83 as a doublet of
doublets, \(^J_{4,5(\text{cis})}\) 6 Hz, and the other C-5 proton resonated upfield
at δ2.35, also as a doublet of doublets, with coupling constants \(^J_{4,5(\text{trans})}\)
3 Hz and \(^J_{5,5}\) 18 Hz. In the mass spectrum of the enone (141) an
intense signal was observed at \(m/z\) 302 which was assigned to the ion
resulting from the fragmentation \(M^+\text{-But}\). The enone (141) was further
characterised by infrared absorption at 1730 cm\(^{-1}\), arising from the
unsaturated enone function. The ultraviolet spectrum of the enone (141)
showed an absorption maximum at 235 nm in deuteriochloroform and this
was attributed to the cyclopentenone chromophore.\(^{21}\) The reality of this
absorption was established by measuring the wavelength of the maximum at
several concentrations.

The ultraviolet spectra of compound (141) in protic solvents
and diethyl ether provided some unexpected results. In methanol and
ethanol the strong absorption observed at 235 nm in deuteriochloroform
underwent a large red shift to 351 nm which was found to be reversible
when the solvent was replaced with deuteriochloroform. Addition of acetic acid to both alcohol solutions resulted in a small blue shift to 325 nm. The ultraviolet spectrum of compound (141) in diethyl ether exhibited a strong absorption at 312 nm which underwent a red shift to 351 nm when sodium borohydride was added.

A plausible explanation of these results is based on the keto-enol tautomerism illustrated in Equation [2]. In diethyl ether compound (141) may exist in the dienol form which would be deprotonated by sodium borohydride to yield the dienolate (142). The ultraviolet maximum observed for compound (141) in protic solvents corresponded to that observed for the dienolate (142) in diethyl ether mixed with sodium borohydride. It is possible that traces of basic impurities in the methanol deprotonated the enone (141) to give the dienolate (142).

The $^1$H n.m.r. spectrum of compound (141) in tetradeuteriomethanol at 22 °C and -50 °C did not show any signals attributable to either the C-2 proton or the proton adjacent to the nitrile function. This indicated that rapid hydrogen-deuterium exchange occurred in the deuterated solvent even at -50 °C.

Having introduced potentially useful functionality at C-3 of the chloro-enone (86;X=Cl), the next step of the synthetic plan outlined in Figure 4 was examined. This step required stereospecific reduction of
the ketone function in the enone (141). Bis(methoxyethoxy)sodium aluminium hydride (Redal) was the reagent chosen for this reaction because of its reactivity towards carbonyl groups, its lack of reactivity towards nitrile groups and the aprotic nature of the solvent in which it is commonly used, i.e., toluene. This last factor was important because the ultraviolet spectrum of the enone (141) in toluene showed no signals above 300 nm at any sample concentration, suggesting that it exists predominantly in the enone form in this solvent. Sodium borohydride has a similar reactivity profile to Redal but it has to be used in a polar solvent. Such a solvent is unsuitable for the present reaction because the enone (141) would exist predominantly in its enol form and the reducing agent would simply deprotonate it, furnishing the dienolate (142).

Reaction of the enone (141) with Redal in toluene at -20 °C, however, gave only starting material. It is likely that the enone (141) was deprotonated by the Redal, giving the dienolate (142) which would be resistant to reduction. This result further illustrates the lability of the C-1' proton in the enone (141) and supports the spectroscopic assignments just discussed. Clearly, a reducing agent which could be used in an acidic medium was required. The enol form of the enone (141) should then be generated, hopefully together with even a low percentage of the enone (141) itself, through tautomerism. As sodium cyanoborohydride may be used in the presence of acetic acid and is known to reduce ketone functions, it appeared to be a suitable reducing agent for the desired purpose. However, like Redal, this reagent failed to reduce the enone (141), even after 24 hr at room temperature. So, although a C-3 addition product of the type (124) [in the form of the enone (141)] was obtained in good yield, its facile enolisation to the
corresponding enol form prevented its further use in this study. Attention was then directed towards the use of vinyl cuprate reagents.

Reactivity of the Chloro-enone (86;X=Cl) Towards Vinylic Cuprate

Reagents

Vinylic cuprate reagents are possible sources of the required formyl functionality since selective ozonolysis of an acyclic olefin function should allow the masked formyl group to be quickly and simply liberated.

Introduction of the vinyl group into the chloro-enone (86;X=Cl) was first explored by the 'inverse-addition' method. However, reaction of vinylmagnesium bromide (approximately 2 mole equivalents) with compound (86;X=Cl) (1 mole equivalent) in the presence of copper(I) iodide (1 mole equivalent) at -15 °C furnished the cyclopentenone (143) in 42% yield as the only isolable product. The mass spectrum of compound (143) showed a prominent ion at m/z 209, which corresponded to the diagnostic M⁺-But fragmentation. Infrared absorption at 1720 and 1620 cm⁻¹ was indicative of unsaturated carbonyl and olefin functions. The ¹H n.m.r. spectrum of compound (143) included a singlet at δ5.95, characteristic of the olefinic proton at C-2, and further signals
between δ6.0-5.7 and between δ5.14-4.98, which were attributed to the three acyclic olefinic protons. Other signals observed were compatible with the assigned structure. In this reaction, sequential C-3/C-2' conjugate addition occurred, presumably assisted by the reactive nature of the initially-formed intermediate dienone (144;R'=H), in which there is little hindrance to the transfer of a further vinyl group to the C-2' position.

To retard the second step of this double conjugate addition reaction, vinylmagnesium bromide was replaced with propenylmagnesium bromide. It was anticipated that the increased hindrance at C-2' in the desired product (144;R'=Me) would prevent the transfer of a second vinyl group. The propenyl bromide used was a mixture of E and Z isomers.

Reaction of propenylmagnesium bromide with the chloro-enone (86;X=Cl) and copper(I) iodide at -15 °C, in the same proportions used previously, gave recovered starting material, the alcohol (145) and the enone (146) in yields of 10%, 30% and 40%. The 1H n.m.r. spectrum of the alcohol (145) was quite complex in the olefin and ring-methylene regions and for this reason it was not possible to determine if one or two diastereoisomers were formed. From work described elsewhere in this Chapter, however, it is likely that just one diastereoisomer was obtained and that the two ring-oxygen functions in this isomer are cis.
The C-2 proton in the alcohol (145) resonated as a singlet at δ5.95. The infrared spectrum of the alcohol (145) exhibited broad absorption at 3390 cm⁻¹, arising from the hydroxyl group, and absorption at 1625 cm⁻¹ arising from the olefin functions. The mass spectrum of (145) showed an ion at m/z 270 (\(^{37}\text{Cl}\) isotope peak at m/z 272) which corresponded to the fragmentation M⁺-H₂O.

The enone (146) exhibited characteristic infrared absorption at 1718 cm⁻¹ due to the unsaturated carbonyl function, and at 1622 and 1593 cm⁻¹ due to the olefin functions. In the ¹H n.m.r. spectrum of the enone (146), the olefinic ring proton resonated as a singlet at δ5.88 and the C-5 protons, cis and trans to the C-4 proton, resonated as doublets of doublets at δ2.68 and 2.21 respectively, showing the expected coupling constants \(J_{4,5(\text{cis})} = 6\) Hz, \(J_{4,5(\text{trans})} = 3\) Hz and \(J_{5,5} = 18\) Hz. A mixture of Z and E double bond isomers would have been formed since the vinyl halide used to prepare the Grignard reagent was a mixture of Z and E isomers. This factor complicated the ¹H n.m.r. spectra of the alcohol (145) and the enone (146), especially in the olefinic region. The mass spectrum of the enone (146) showed an intense ion at m/z 237, corresponding to the fragmentation, M⁺-Bu⁺.

Two conclusions were drawn from this reaction. First, formation of the organocuprate reagent was not complete and unconsumed Grignard reagent reacted with the chloro-enone (86;X=Cl) at C-1. Second, the increased steric hindrance at C-2' in the intermediate (144;R'=Me), did not prevent the conjugate addition of a second propenyl unit at -15 °C. In an attempt to overcome these problems, preformed lithium di(1-propenyl)copper was used instead of the organomagnesium cuprate reagent and the reaction temperature was lowered. Preparation of the precursor to this organocuprate reagent, i.e., 1-propenyllithium, was first examined using 1-bromopropene. However, when established
procedures were followed, halogen-lithium exchange was found to be very sluggish. The preparation of 1-propenyllithium via transmetallation of 1-propenyltrimethylstannane, previously prepared by Seyferth$^94$, was therefore examined. 1-Propenyltrimethylstannane was treated with butyllithium at -60 °C and subsequently with a solution of copper(I) bromide-dimethylsulphide complex to give a yellow solution. Addition of the chloro-enone (86;X=Cl) to this solution at -60 °C only gave starting material on work-up. As the reaction of butyllithium with the chloro-enone (86;X=Cl) at C-1 did not occur, it was concluded that organocuprate formation was complete. When this reaction was repeated at -40 °C, the enone (147) was obtained in 46% yield together with 45% recovered starting material. Again, the absence of a C-1 addition product, which would be formed by reaction of (86;X=Cl) with any free organolithium reagent, confirmed that the organolithium reagent(s) had been consumed before the substrate was added. The $^1$H n.m.r. spectrum of

The $^1$H n.m.r. spectrum of the enone (147) is shown in Figure 5 and assignment of the signals is based on previously obtained $^1$H n.m.r. data for the methoxy-enone (148) and alcohols of type (149).$^95$ The two signals at $\delta$5.82 and 5.35 were assigned to the two olefinic protons on C-2' and C-2, the C-4' proton resonated at $\delta$4.78 as a doublet of doublets and the methoxyl protons

\[
\begin{align*}
\text{(147)} & \quad \text{(148)} & \quad \text{(149)} \\
\text{R} & = \text{undefined alkyl group}
\end{align*}
\]
Figure 5
resonated as a singlet at δ3.86. The pair of doublets of doublets observed between δ2.38 and 1.64 were assigned to the C-5' protons. The two doublets observed at δ4.67 and 2.78 were assigned to the C-4 and C-5 protons respectively and, as expected, both signals collapsed to singlets when the adjacent proton was irradiated. The relative trans stereochemistry of the C-4 and C-5 protons was confirmed by comparing the observed chemical shifts of the signals and the coupling constant $J_{4,5}$ of 2 Hz with literature data. The mass spectrum of compound (147) showed no molecular ion although fragment ions (with $^{37}$Cl and $^{35}$Cl isotope peaks) were observed at $m/z$ 473, 431 and 413, corresponding to $M^+\text{-Me}$, $M^+\text{-H}_2\text{O}$ and $M^+\text{-Bu}^t$. The loss of water from the molecular ion indicated the presence of an hydroxyl group, which was confirmed by infrared absorption at 3440 cm$^{-1}$. A further fragment ion which indicated the presence of a dimeric-like structure was observed at $m/z$ 242. This signal was assigned to the ionised methoxy-enone (148), which was probably formed by cleavage of the C-5/C-1' bond in (147) through a McLafferty rearrangement to give the corresponding tautomeric enol. The base peak observed at $m/z$ 189 was due to the ion formed by loss of $\text{Bu}^t$ from the ionised chloro-enone (86;X=Cl), also generated in the McLafferty rearrangement.

The dimeric product (147) obtained from this reaction was not expected, although House and Wilkins$^{96(a)}$ reported that organocuprates can enolise carbonyl functions in some instances. The formation of (147) may be explained through enolisation of the chloro-enone (86;X=Cl) by the organocuprate reagent and subsequent reaction with a further molecule of the chloro-enone (86;X=Cl). Displacement of the C-3 chloro substituent with methoxide anion must have occurred when methanol was introduced to quench the reaction.
The contrasting behaviour of the cuprate derived from propenylmagnesium bromide and the cuprate generated in the present reaction requires an explanation. The two cuprate reagents used are certainly different, in that one is a magnesio-cuprate whereas the other is a lithio-cuprate. It seems unlikely, however, that this difference is the cause of the vastly different properties. It is feasible that, in the second reaction, the organolithium reagent used to prepare the organocuprate reagent was not the expected 1-lithiopropene but the organolithium reagent (150), formed by addition of butyllithium to 1-propenyltrimethylstannane. Similar addition reactions of organolithium reagents to vinyl silanes and vinyl germanes have been reported. The organolithium (150) could then have reacted with the copper(I) bromide, generating the corresponding cuprate, which because of its bulk or oxidation potential may have enolised the chloro-enone (86;X=Cl) rather than adding in Michael fashion. Whatever the mechanism, this reaction did not afford the desired product.

To retard the double conjugate addition observed in these vinylic cuprate reactions, in which vinyl and propenyl ligands were employed, the next logical step would be to use a \(\delta\)-butenyl ligand. However, \(\delta\)-butenylbromide was not readily available at the time of the study and therefore the use of a \(\delta\)-butenyllithium-derived cuprate was
not examined. The possibility of exchanging the C-3 chloro-substituent in the chloro-enone (86;X=Cl) with cyanide anion was examined next.

**Chloride-Cyanide Exchange**

The nitrile function is an established equivalent to the formyl group\(^97\), since reduction of a nitrile function with di-\(\sigma\)-butylaluminium hydride followed by hydrolysis of the intermediate imine is known to give the corresponding formyl derivative. Also, the conjugate addition of cyanide anion to enones using diethylaluminium cyanide was reported by Nagata *et al.*\(^98\) In connection with the present work, conjugate addition of cyanide anion to the chloro-enone (86;X=Cl) followed by elimination of the chloride anion would generate the useful nitrile (151). Reduction of the carbonyl and nitrile functions would then, after hydrolysis of the corresponding imine, afford the required cyclopentenecarbaldehyde (125) in only two steps from the chloro-enone (86;X=Cl) (see Figure 4).

Previous studies in these laboratories on heteroatom-cyanide exchange in C-3 heterosubstituted enones similar to (86;X=Cl) had met

\[(151)\]

\[(152)\] R = X = Cl, Z = H
\[(153)\] R = Z = H, X = Cl
\[(154)\] R = Z = H, X = OMe

\[(155)\]
with little success. Hook investigated the reactions of the hydroxytrichloro-enone (152) and its C-4 tetrahydropyranyl derivative with potassium cyanide in a mixture of ethanol and water, under various conditions. Chloride-cyanide exchange did not occur in either case and the hydroxytrichloro-enone (152) was found to be very unstable to base, possibly because of base-catalysed ring-opening. Christie studied the reaction of diethylaluminium cyanide with the hydroxytrichloro-enone (152), the chlorohydroxy-enone (153) and the hydroxymethoxy-enone (154), and obtained the corresponding cyano-enone only from the hydroxymethoxy-enone (154) but only in low yield.

In the present study the chloro-enone (86; X=Cl) was first converted to the methoxy-enone (148), by stirring with a mild base in methanol. The methoxy-enone (148) thus obtained was then treated with diethylaluminium cyanide for 3 hr at room temperature. This reaction furnished the nitrile (151) in 28% yield together with 10% recovered starting material. Spectral data supporting the structure assigned to this product are given later in this Chapter. The substantial decomposition that was observed suggested that either the nitrile (151), the methoxy-enone (148) or both compounds were sensitive to the reagent used. Alternative chloride-cyanide exchange procedures were therefore sought and, in most of the following exploratory reactions, the readily available 3-chloro-2-cyclohexenone was used.

Chloride-cyanide exchange was studied next using potassium cyanide in acetonitrile. 18-Crown-6 was also added to increase the nucleophilicity of the cyanide anion. The increased nucleophilicity, however, was not sufficient as starting material was recovered in 95% yield and only a trace of 3-oxo-1-cyclohexenecarbonitrile was detected. Paquette et al. reported that nitriles could be prepared from vinyl iodides and copper(I) cyanide in HMPA, and House and Fischer reported...
that sodium dicyanocopper in \(N,N\)-dimethylformamide efficiently transformed aryl chlorides to their nitrile derivatives. Reaction of 3-chloro-2-cyclohexenone with either reagent, however, was not successful and starting material was recovered in both cases. Yamamura et al.\(^{103}\) reported the use of tetrakis(triphenylphosphine) palladium(0) to facilitate chloride-cyanide exchange in vinyl halide compounds. Such reactions were reported to proceed via an intermediate palladium-olefin complex. Application of this method to 3-chloro-2-cyclohexenone did furnish some 3-oxo-1-cyclohexenecarbonitrile, although only in 14\% yield and only after refluxing in benzene for 15 hr. Starting material was recovered from this reaction in 64\% yield. The reaction was repeated in the presence of potassium iodide which was added to enhance the reactivity of the vinylogous acid chloride via exchange to its iodide. However, no product was obtained and the recovery of 87\% of the starting material from this reaction suggested that potassium iodide actually retarded chloride-cyanide exchange in this case.

Simchen and Kobler\(^{104}\) reported the application of tetraalkylammonium cyanide reagents to high-yielding syntheses of nitriles from alkyl bromides. The only chlorine-containing substrate used in that study was the reactive chloromethyl methyl ether which afforded just 30\% of the corresponding nitrile. When this procedure was applied to 3-chloro-2-cyclohexenone, extensive decomposition occurred and whilst only 47\% of starting material was recovered, none of the required 3-oxo-1-cyclohexenecarbonitrile was detected. Clearly, either the substrate and/or the product (if formed) were sensitive to the basicity of the tetraethylammonium cyanide. Reaction of the methoxy-enone (148) with tetraethylammonium cyanide also resulted in extensive decomposition and only 61\% starting material was recovered. Reaction of the phenylseleno-enone (155), the preparation of
which is described in Chapter 2, also failed to give the nitrile (151) but in this case starting material was recovered quantitatively.

A novel chloride-cyanide exchange operation was reported by Nesmeyanov and Rubinskaya who treated vinylogous acid chlorides with trimethylamine and then reacted the resulting trimethylammonium salts with aqueous potassium cyanide to give 3-oxo-1-alkenecarbonitriles. Zimmerman and Pasteris prepared 3-oxo-1-cyclopentenecarbonitrile from 3-chloro-2-cyclopentenone in 57% yield using this method. Application of this procedure to the present study was then investigated. Michael addition of trimethylamine to the chloro-enone (86;X=Cl) in diethyl ether proceeded slowly and in lower yield than to 3-chloro-2-cyclopentenone as reported by Zimmerman et al. After a reaction time of 14 days at room temperature, the ammonio-enone (156) was obtained in 43% yield with 53% starting material. A likely cause of the lower reactivity of the chloro-enone (86;X=Cl), compared to 3-chloro-2-cyclopentenone, is the steric hindrance at the C-3 position. In the $^1$H n.m.r. spectrum of the ammonio-enone (156), the presence of a salt was indicated by the signals at 7.22 and 5.75, assigned to the C-2 and C-4 protons. Both signals were shifted approximately 1 p.p.m. downfield from the corresponding signals observed for the chloro-enone (86;X=Cl). A broad singlet
at δ3.89 was assigned to the trimethylammonium protons. In its mass spectrum the ammonio-enone (156) showed ions at m/z 255, 240 and 198 (base peak). These ions were derived from the dimethylamino-enone (157) which was probably formed by thermal N-demethylation of compound (156) on the probe. The latter ions corresponded to m/z 255-Me and m/z 255-But respectively.

It was of interest to determine whether a change in the solvent polarity would increase the yield of the ammonio-enone (156). When the reaction was performed in hexane over 14 days the dimethylamino-enone (157) was obtained in 45% yield with 40% recovered starting material and none of the ammonio-enone (156) was detected. Thus, the reactivity of the chloro-enone (86; X=Cl) towards trimethylamine was still sluggish in a non-polar solvent even though demethylation of the ammonio-enone (156) proceeded efficiently. Sindelar et al. reported that a similar demethylation process occurred when the salt (158) was warmed and suggested that demethylation was caused by the chloride anion. Vinyl chloroformate has also been used for the N-demethylation of tertiary amines. Such reactions presumably proceed via intermediates similar to the salt (158). In the present work, either the chloride anion or trimethylamine may have demethylated the ammonio-enone (156). The structure of the dimethylamino-enone (157) was evident from its spectral properties. The $^1$H n.m.r. spectrum of the dimethylamino-enone (157) exhibited a singlet at δ4.96, due to the C-2 proton, and a doublet of doublets at δ4.94 due to the C-4 proton, which showed coupling to both C-5 protons: $^J_{4,5}(cis)$
6.5 Hz and \( J_{4,5}^{(\text{trans})} 2.5 \text{ Hz} \). The mass spectrum of compound (157) was similar to that of compound (156), as expected.

When the reaction of trimethylamine with the chloro-enone (86;X=Cl) was repeated in acetone, the rates of both the Michael addition and the demethylation reactions increased. After 3.5 hr at room temperature, the dimethylamino-enone (157) was obtained in quantitative yield. If the chloride anion was responsible for demethylation, it could be expected that addition of silver tetrafluoroborate to the reaction should precipitate the chloride anion as silver chloride and furnish the ammonio-enone (156), associated with the non-nucleophilic tetrafluoroborate anion. Whereas addition of silver tetrafluoroborate to the reaction did result in the formation of a precipitate, it did not reduce the extent of demethylation and the dimethylamino-enone (157) was again obtained in high yield. Thus, it is likely that the demethylation of compound (156) was being effected by trimethylamine and not the chloride anion.

When the chloro-enone (86;X=Cl) was originally treated with trimethylamine in diethyl ether at room temperature, salt formation was slow and no demethylation was observed. When this reaction was repeated in diethyl ether at 60 °C and over 24 hr, the dimethylamino-enone (157) was obtained in 94% yield with 6% starting material. Having obtained compound (156) in moderate yield (43%), its conversion to the nitrile was then studied.

A solution of the ammonio-enone (156) in a mixture of aqueous ammonium chloride and benzene was treated with potassium cyanide, under conditions employed by Nesmeyanov \textit{et al.} \cite{105}. The nitrile (151) was obtained in 89% yield after only 15 min. The structure of the nitrile (151) was established using the following spectral data. In its mass spectrum, compound (151) did not exhibit a molecular ion but showed
several fragment ions including those at \( m/z \) 180 (base peak) and 138 due to \( M^+ - \text{Bu}^+ \) and \( M^+ - \text{Bu}^+ - \text{C}_2\text{H}_2\text{O} \). Diagnostic features of the \(^1\text{H} \) n.m.r. spectrum included a doublet at 6.65 due to the C-2 proton coupled by 1 Hz to the C-5 proton and an octuplet at 5.06 which was attributed to the C-5 proton and showed the coupling constants \( J_{5,4}^{\text{cis}} \), \( J_{5,4}^{\text{trans}} \) and \( J_{5,2} \) of 6, 3 and 1 Hz. Infrared absorption at 2230 and 1735 cm\(^{-1} \) confirmed the presence of the nitrile and carbonyl functions respectively. This efficient two-phase reaction demonstrated the importance of removing the base-sensitive nitrile (151) from the basic aqueous phase into the organic phase.

The efficiency of this two-step synthesis of the desired nitrile (151) was only limited by a moderate yield of the ammonio-enone (156). To overcome this problem, the rate of formation of (156) had to be increased whilst its demethylation had to be suppressed. A possible solution could involve treating the chloro-enone (86; \( X = \text{Cl} \)) with trimethylamine and potassium cyanide in a two-phase aqueous-organic system. Thus, as the ammonio-enone (156) is formed, rapid transfer should occur to the aqueous phase where, as just demonstrated, reaction with the potassium cyanide proceeds efficiently. Rapid transfer of compound (156) from the organic phase in this manner should suppress demethylation and subsequent transfer of the nitrile (151) back to the
organic phase should avoid its undue exposure to the basic cyanide reagent. Reaction of the chloro-enone (86;X=Cl) under these conditions indeed overcame the previously experienced problems and the nitrile (151) was obtained directly in 74% yield. This procedure represents an improvement to the original method published by Zimmerman and Pasteris. Thus, with an efficient preparation of the nitrile (151) in hand, the next stages of the synthetic plan illustrated in Figure 4 were explored.

3.4 Reduction and Lactone Ring Formation - Model Studies

Carbonyl reduction and lactone ring formation analogous to that depicted in Figure 4 were initially investigated using a model compound, the nitrile (159), which was prepared by the method of Cronyn and Goodrich. Reaction of the nitrile (159) with two equivalents of an appropriate reducing reagent should allow, in one pot, reduction of the carbonyl function to the corresponding alcohol and reduction of the nitrile function to the corresponding imine.

When compound (159) was treated with two equivalents of lithium tri-µ-butylborohydride, a complex mixture of products was obtained, possibly originating from overreduction of the substrate by
the reducing agent. Reaction of the nitrile (159) with two equivalents of di-iso-butylaluminium hydride, however, furnished the required hydroxy-aldehyde (160) in 96% yield. The mass spectrum of compound (160) exhibited a molecular ion at \( m/z \) 126 and a base peak at \( m/z \) 97, corresponding to \( M^+\)-CHO. The \(^1\)H n.m.r. spectrum showed a singlet at \( \delta \) 9.46 and a multiplet at \( \delta \) 6.67 which were assigned to the unsaturated aldehydic proton and to the olefinic proton. Infrared absorption at 3410 and 1685 cm\(^{-1}\) confirmed the presence of the hydroxyl function and the aliphatic unsaturated aldehyde function. Esterification of the hydroxy-aldehyde (160) was then examined.

Figure 6 illustrates the general reaction scheme, depicting esterification of the hydroxy-aldehyde (160), Michael addition and removal of the activating group (Z), where necessary, to furnish the lactone (161). In addition to the acetate (162;Z=H), the methyl malonate derivative (162;Z=CO\(_2\)Me) and the benzyl malonate derivative (162;Z=CO\(_2\)Bz) were studied.

![Figure 6](image)

The acetoxy-aldehyde (162;Z=H) was prepared in quantitative yield from the hydroxy-aldehyde (160) and acetic anhydride in pyridine. In its mass spectrum, the acetoxy-aldehyde (162;Z=H) exhibited a small molecular ion at \( m/z \) 168. The \(^1\)H n.m.r. spectrum of compound (162;Z=H)
showed a singlet at δ 9.48, due to the aliphatic aldehydic proton, and a multiplet at δ 5.52, due to the C-3 methine proton which was shifted 1 p.p.m. downfield from the corresponding signal in the hydroxy-aldehyde (160). Infrared absorption at 1740 and 1690 cm$^{-1}$ confirmed the presence of the ester and the aldehyde carbonyl groups.

Attempted cyclisation of the acetoxy-aldehyde (162;Z=H) with lithium diisopropylamide in diethyl ether (0.16 M) at -78 °C gave, after quenching with deuterium oxide, 21% recovered starting material and three polar products. Even though the products were separable from the starting material they could not be separated from each other and therefore their characterisation was not possible. However, the infrared spectrum of the product mixture did not exhibit absorption characteristic of a γ-lactone carbonyl function, which suggested that lactonisation had not occurred. Electron impact and chemical ionisation mass spectra of the product mixture were complex but indicated that the desired enolate (164), if formed, may have oligomerised. In principle, it may be possible to avoid this by using higher dilution. Mass spectra of the recovered acetoxy-aldehyde (162;Z=H) showed that deuterium was not present in the molecular ion. This suggested that incomplete ionisation...
had occurred and that some of the lithium diisopropylamide had been consumed by other undesired reactions, to leave at least 21% unenolised starting material. Schlessinger et al.\textsuperscript{110} reported that the conjugate addition of lithium diisopropylamide to ethyl crotonate at -78 °C could be prevented by using a 1:1 complex of the nitrogenous base with HMPA. However, in the present study, treatment of compound (162;Z=H) with this complex at higher dilution (0.036 M) gave a chromatographically similar product mixture to that obtained before, which again showed no infrared absorption characteristic of a γ-lactone function. Attention was therefore directed towards other ester derivatives of the hydroxyaldehyde (160).

The methyl malonate derivative (162;Z=CO$_2$Me) was prepared in 79% yield by reaction of the hydroxy-aldehyde (160) with methyl malonyl chloride and pyridine. The methyl-ester (162;Z=CO$_2$Me) was unstable to chromatography and underwent decomposition when exposed to air for prolonged periods. The $^1$H n.m.r. spectrum of compound (162;Z=CO$_2$Me) showed a singlet at $\delta$9.50 and a multiplet at $\delta$6.64 which were assigned to the aldehydic proton and to the olefinic proton. Further signals assigned to the malonyl methylene protons and the methyl ester protons were observed at $\delta$3.40 and 3.74, and a multiplet at $\delta$5.59 was attributed to the C-3 proton. The mass spectrum of compound (162;Z=CO$_2$Me) showed an unexpected peak at M$^+$$+1$ but no molecular ion. Fragment ions were observed at $m/z$ 197, due to M$^+$$-CHO$, and at $m/z$ 126 which was the base peak and corresponded to the loss of C(O)CH$_2$CO$_2$Me from the protonated molecular ion.

Cyclisation of the methyl-ester (162;Z=CO$_2$Me) was first explored using conditions similar to those described by Barco et al.\textsuperscript{111}, who cyclised the ethyl-ester (165) using potassium ethoxide which was generated from potassium carbonate in ethanol. Treatment of the
methyl-ester (162; Z=CO₂Me) with potassium carbonate in methanol gave the hydroxy-aldehyde (160) in 56% yield which resulted from transesterification of the cyclohexenol ester function. A milder reaction was sought.

Nelson et al. 112 reported an efficient method for effecting the Michael addition of β-dicarbonyl reagents to conjugated unsaturated ketone and ester substrates by refluxing them with the catalyst bis(2,4-pentanedionato)nickel(II), Ni(acac)₂, in chloroform. This mild, non-basic procedure should avoid the transesterification observed in the previous reaction. Treatment of the methyl-ester (162; Z=CO₂Me) with this catalyst, however, furnished only starting material (90%), even after refluxing in chloroform for 60 hr. To explain this lack of reactivity it is necessary to consider the through-space bonding interactions which would be needed for bond formation to occur. Analysis of a Drieding stereomodel of the expected intermediate nickel complex (Figure 7) indicated that, if the complex were planar as reported 113 for other tetracoordinated nickel complexes, overlap between the bond-forming
orbitals (A and B) may have been too small for bond-formation to occur.

An alternative reagent for deprotonating the methyl-ester (162;Z=CO₂Me) was sought which was non-nucleophilic and would afford an intermediate enolate which could undergo the desired Michael addition. Reaction of the methyl-ester (162;Z=CO₂Me) with sodium hydride in THF furnished the lactone-ester (163;Z=CO₂Me) as a diastereoisomeric mixture in quantitative yield. The ⁱH n.m.r. spectrum of this product showed singlets at 69.64 and 9.61 due to the diastereoisomeric aldehydic protons and two signals at 63.82 and 3.79 due to the diastereoisomeric methoxyl groups. Infrared absorption at 1780 and 1735 cm⁻¹ indicated the presence of a lactonic carbonyl function, and saturated aldehydic and ester functions respectively. Without further characterisation of the lactone-ester (163;Z=CO₂Me), attention was turned first towards its demethylation and then towards decarboxylation of the carboxylic acid thus obtained. This type of process has been extensively studied and was recently reviewed.¹¹⁴ The most commonly used reagents for the ester cleavage reaction are alkali metal halides, particularly lithium iodide, in solvents such as pyridine and N,N-dimethylformamide. Corey and
Fuchs employed lithium iodide in pyridine to effect the demethylation/decarboxylation of the ester (166), a precursor to the Corey lactone (26), in 37% yield.

In the present study, reaction of the lactone-ester \((162; Z=CO_2Me)\) with lithium iodide in pyridine gave just 10% of the required lactone (161) as the only isolable product. The mass spectrum of compound (161) exhibited a molecular ion at \(m/z\ 168\). Fragment ions were also observed including those at \(m/z\ 150, 140\) and 139 due to \(M^+-H_2O\), \(M^+-C_2H_4\) (or \(M^+-CO\) and \(M^+-CHO\) respectively. A mechanism for the loss of \(C_2H_4\) from simple lactones has been previously described.\(^{116(a)}\) Further fragment ions were observed at \(m/z\ 126\) and 95 (base peak) which are derived from the fragmentations \(M^+-C_2H_2O\) and \(m/z\ 124\)-CHO. The \(^1H\) n.m.r. spectrum of the lactone (161) showed a singlet at \(\delta 9.66\) due to the aldehydic proton and a multiplet at \(\delta 4.60\) due to the methine proton at C-3a. Infrared absorptions at 1780 and 1720 cm\(^{-1}\) confirmed the presence of the lactone and aldehyde carbonyl functions respectively. Thus, although this reaction furnished the lactone (161), the yield was unworkable. Attempts to demethylate the lactone-ester \((163; Z=CO_2Me)\) using lithium propanethiolate failed, possibly because the acidic malonyl methine...
group was deprotonated thereby deactivating the ester function towards nucleophilic attack or because the aldehyde function was base-sensitive. To eliminate this latter factor the aldehyde group in compound (163; Z=CO₂Me) was reduced prior to attempted demethylation/decarboxylation.

Reaction of the lactone-ester (163; Z=CO₂Me) with an excess of lithium tri-tert-butoxyaluminium hydride in THF furnished the alcohol (167) as a mixture of diastereoisomers. The infrared spectrum of the mixture included absorption at 3 500, 1 775 and 1 740 cm⁻¹, which was assigned to the hydroxyl, lactone and ester functions respectively. Without further purification the alcohol (167) was treated with lithium iodide in pyridine to give the lactone-alcohol (168) in 51% overall yield (not optimised) from the lactone-ester (163; Z=CO₂Me). The mass spectrum of the lactone-alcohol (168) showed a molecular ion at m/z 170 plus fragment ions including those at m/z 152 and 139 derived from the fragmentations M⁺-H₂O and M⁺-CH₂OH. Further fragment ions were observed which were also compatible with the assigned structure. In the ¹H n.m.r. spectrum of the lactone-alcohol (168), the signals observed at δ3.58 and 4.58 were assigned to the hydroxymethyl protons and to the methine proton at C-7a respectively. Infrared absorptions at
$3430$ and $1770 \text{ cm}^{-1}$ confirmed the presence of the hydroxyl and lactone functions.

At this stage with only a moderate-yielding synthesis of the Corey lactone-alcohol analogue (168) and a low-yielding synthesis of the lactone (161), the feasibility of using the benzyl malonyl ester (162; $Z=\text{CO}_2\text{Bz}$) as a precursor to the lactone (161) was examined. Esterification of the hydroxy-aldehyde (160) was initially explored using benzyl malonyl chloride, prepared by treating the corresponding acid with oxalyl chloride. Whilst the benzyl hydrogenmalonate was obtained without difficulty, generation and isolation of the corresponding acid chloride were more difficult. Reaction of benzyl hydrogenmalonate with an excess of distilled oxalyl chloride at room temperature for $3 \text{ hr}$ gave a $4:2:1$ mixture of the required benzyl malonyl chloride, benzyl chloride and malonic acid, as determined by $^1\text{H n.m.r.}$ spectroscopy. Presumably the hydrogen chloride, formed $\text{in situ}$, reacted with the benzyl hydrogenmalonate to yield benzyl chloride and malonic acid. As described in Chapter 6, benzyl chloromethyl ether underwent a similar decomposition at higher temperature. Attempts to disfavour benzyl chloride formation by treating benzyl hydrogenmalonate with one equivalent of oxalyl chloride at $0 \degree C$ for $1.5 \text{ hr}$, resulted in a $33\%$ conversion of starting material to benzyl malonyl chloride. This yield was increased to $80\%$ (judged by $^1\text{H n.m.r.}$) by using benzyl potassium malonate, and benzyl chloride formation was also suppressed. As the sensitivity of benzyl malonyl chloride towards hydrolysis prevented its purification, the crude reaction product was used directly to esterify the hydroxy-aldehyde (160), using pyridine in dichloromethane. The benzyl-ester (162; $Z=\text{CO}_2\text{Bz}$) was obtained in $50\%$ yield but it was difficult to separate from the by-product, benzyl hydrogenmalonate.
This problem was avoided by using the esterification procedure developed by Hassner et al. Thus, reaction of the hydroxy-aldehyde (160) with benzyl hydrogenmalonate in the presence of dicyclohexylcarbodiimide and a catalytic amount of 4-\textit{N},\textit{N}-dimethylaminopyridine, gave the benzyl-ester (162; \( Z = \text{CO}_2\text{Bz} \)) in 90% yield, after chromatography. The mass spectrum of compound (162; \( Z = \text{CO}_2\text{Bz} \)) showed a weak molecular ion at \( m/z \) 302 and a weak protonated molecular ion. Fragment ions observed at \( m/z \) 273 and 195 were derived from the fragmentations \( M^+\text{-CHO} \) and \( M^+\text{-BzO} \) respectively. The base peak observed at \( m/z \) 110 is likely to be derived from the loss of \( \text{O}_2\text{CCH}_2\text{CO}_2\text{Bz} \) by allylic cleavage. The \( ^1\text{H} \) n.m.r. spectrum of the benzyl-ester (162; \( Z = \text{CO}_2\text{Bz} \)) showed diagnostic singlets at \( \delta \) 9.43 and 7.34, assigned to the aldehydic and aromatic protons, and at \( \delta \) 5.18 and 3.45, assigned to the benzylic and malonic methylene protons respectively. Infrared absorption observed at 1745 and 1690 cm\(^{-1}\) confirmed the presence of an ester and an unsaturated aldehyde.

Without characterisation of the intermediates, the benzyl-ester (162; \( Z = \text{CO}_2\text{Bz} \)) was transformed in three steps to the lactone (161). Cyclisation with sodium hydride cleanly afforded the lactone-ester (163; \( Z = \text{CO}_2\text{Bz} \)) using conditions previously established for the methyl-ester (163; \( Z = \text{CO}_2\text{Me} \)). Hydrogenation of the benzyl ester function in the cyclisation product proceeded smoothly over a palladium/charcoal catalyst. An infrared spectrum of the crude product confirmed that overreduction had not occurred since the aldehyde function remained intact. When this crude product was refluxed in ethyl acetate/ethanol, only a small amount of the desired lactone (161) was obtained, as judged by t.l.c. However, when the reaction mixture was refluxed at higher temperature in ethyl acetate/toluene, the lactone (161) was obtained in 60% yield (not optimised).
These model studies demonstrate two important points. Firstly, they show that the aldehyde function of the lactone-ester (163; Z = CO₂Me) is sensitive to lithium iodide in pyridine. Secondly, they show that the Corey lactone analogue (161) and the Corey lactone-alcohol analogue (168) can be synthesised in only five steps from the nitrile (159) in moderately good yields, which are still to be optimised.

3.5 **Approaches to the Corey Lactone (26)**

In Sections 3.3 and 3.4 of this Chapter a direct, high-yielding synthesis of the nitrile (151) from the chloro-enone (86; X = Cl) was described and model studies have established the feasibility of converting the nitrile (159) into the Corey lactone-analogue (161). The work presented now is an account of results obtained from the application of methodology developed in the model studies to the potential Corey lactone precursor, the nitrile (151).

Stereospecific reduction of the nitrile (151) with di-s-butylaluminium hydride was studied first. Reduction proceeded smoothly to give only one product by t.l.c., but attempts to isolate this product by aqueous work-up under acidic, basic or neutral (buffered) conditions invariably gave decomposition products together with the desired cyclopentenecarbaldehyde (125). Since only one component was observed by t.l.c. after the reaction was quenched on silica gel, the total reaction mixture was treated with chromatography-grade silica gel and then diluted with diethyl ether. After 'flash' chromatography of the crude product the cyclopentenecarbaldehyde (125) was obtained in 71% yield. This novel silica gel-assisted work-up not only avoided the aqueous conditions to which compound (125) was extremely unstable, but also facilitated the
concomitant hydrolysis of the imine function and the removal of the aluminium by-products. The infrared spectrum of the cyclopentenecarbaldehyde (125) exhibited absorption at 3 400, 1 695 and 1 625 cm\(^{-1}\) which was attributed to the hydroxyl, aldehyde and olefin functions respectively. Compound (125) did not give a molecular ion in its mass spectrum but diagnostic fragment ions were observed at \(m/z\) 185 and 167, derived from the fragmentations \(M^+ - \text{Bu}^+\) and \(M^+ - \text{Bu}^+ - \text{H}_2\text{O}\). The 100 MHz \(^1\text{H}\) n.m.r. spectrum of compound (125) was incompletely resolved but since two signals were observed in the aldehydic region it was concluded that at least two isomers were present. It was not possible to separate the isomers by chromatography. The 200 MHz \(^1\text{H}\) n.m.r. spectrum of compound (125) in deuteriochloroform confirmed that a major and minor isomer were indeed present. A portion of the spectrum is shown in Figure 8. The two doublets at \(\delta 6.84\) and \(6.81\), in the ratio of approximately 3:1, were assigned to the C-2 protons because of their chemical shifts. The four signals between \(\delta 5.27\) and \(4.72\) were assigned to the C-3 and C-5 protons in the major and minor isomers. The doublet of doublets at \(\delta 4.92\) was assigned to the C-5 proton of the major isomer which was coupled by 7 and 3 Hz to the vicinal C-4 protons and the broad signal at \(\delta 4.72\) was assigned to the C-3 proton in the major isomer. The broadness of this signal was expected because of coupling between the C-3 proton and the vicinal C-4 protons, the C-2 proton and the hydroxyl proton. The remaining signals in this region were not individually assigned because the signals were insufficiently resolved. Indeed it was not possible to establish precisely whether the major product was
the cis or trans diastereoisomer of compound (125), since the upfield geminal C-4 proton signals were also insufficiently resolved.

This configurational problem was solved by derivatisation of compound (125) with acetic anhydride and pyridine to furnish the acetoxy-aldehyde (169) in 51% yield. The acetoxy-aldehyde (169) was selected, because its $^1$H n.m.r. spectrum should be more dispersed than that of the compound (125). It might also be possible to accurately measure the cis/trans ratio by integration of the acetate signals. The 200 MHz $^1$H n.m.r. spectrum of the acetoxy-aldehyde (169) clearly showed first-order coupling (see Figure 9). The multiplets at $\delta$5.56 and 4.96
were assigned to the C-3 and C-5 protons in the major isomer respectively. The following coupling constants were observed: for the C-5 proton $J_{5,4(\text{cis})} 7.5 \text{ Hz}$, $J_{5,4(\text{trans})} 4.7 \text{ Hz}$; and for the C-3 proton $J_{3,4(\text{cis})} 7.5 \text{ Hz}$, $J_{3,4(\text{trans})} 4.7 \text{ Hz}$ and $J_{3,2} 2 \text{ Hz}$. Based on published chemical shift data for C-4 protons in cis-3,5-dihydroxycyclopentenes of type (170), the multiplets at $\delta 2.89$ and $1.80$, due to the geminal C-4 protons in the major isomer, confirmed that isomer to be the required cis isomer of the acetoxy-aldehyde (169). The cis/trans isomer ratio was determined to be 7:3 by integration of the acetate signals. Also, chromatographic separation of the isomeric mixture furnished the cis and trans isomers in yields of 38% and 13%.

- Cyclisation of the acetoxy-aldehyde (169) to the Corey lactone (26) was not attempted because the analogous model studies were unsuccessful. The model studies, however, did show that a benzyl malonyl ester was a suitable derivative for this purpose. The cyclopentene-carbaldehyde (125) was therefore converted to its benzyl malonyl ester derivative by treatment with benzyl hydrogenmalonate, dicyclohexylcarbodiimide and $N,N$-dimethylaminopyridine. The reaction mixture was directly chromatographed since, like the cyclopentene-carbaldehyde (125), the benzyl-ester (126; $Z=\text{CO}_2\text{Bz}$) was also
found to be sensitive to aqueous work-up. Unlike the model reaction, however, which afforded a 90% yield of the analogous benzyl-ester (162;Z=CO₂Bz), the benzyl-ester (126;Z=CO₂Bz) was obtained in only 20% yield contaminated with decomposition products. Attempts to improve this yield by lowering the reaction temperature, reducing the reaction time, or changing the proportions of reagents were unsuccessful. As well as being sensitive towards aqueous work-up, the benzyl-ester (126;Z=CO₂Bz) appeared to decompose on silica gel.

The methyl-ester (126;Z=CO₂Me) proved more accessible and was obtained in 54% yield by reaction of compound (125) with methyl malonyl chloride and pyridine in chilled diethyl ether. Although more stable on silica gel than the benzyl-ester (126;Z=CO₂Bz), the methyl-ester (126;Z=CO₂Me) was still unstable and some decomposition occurred when its purification was attempted on either silica gel or alumina. The methyl-ester (126;Z=CO₂Me) did not show a molecular ion in its mass spectrum but fragment ions were observed at m/z 285, 225, 211 and 185 which were attributed to the fragmentations M⁺-Bu⁺, M⁺-(MeO₂CCH₂CO₂), M⁺-Bu⁺Me₂SiOH and M⁺-Bu⁺-(MeO₂CCH=C=O). The ¹H n.m.r. spectrum of the methyl-ester (126;Z=CO₂Me) showed, as expected, the presence
of two diastereoisomers in the ratio of approximately 7:3, as determined by integration of the C-2 proton signals at δ 6.74 and 6.79. Whereas one signal at δ 9.83 and one at δ 3.75 were observed for the aldehydic and methoxyl protons in the diastereoisomeric mixture, the malonic methylene protons in each isomer resonated separately, at δ 3.41 and 3.39. Infrared absorption at 1755, 1740 and 1695 cm⁻¹ confirmed the presence of two types of ester and an aldehyde.

Cyclisation of the methyl-ester (126; Z=CO₂Me) was then examined, using the conditions established in the model studies. It was anticipated that elimination of the C-5 silyloxy group from the intermediate enolate (171) could occur at the temperature employed in the model reaction, to give the unsaturated aldehyde (172). Therefore the reaction was initially explored at -62 °C using potassium hydride which should be more reactive than sodium hydride at that temperature. The reagent, however, was insoluble at -62 °C and, even after HMPA was added to the mixture, the reagent remained insoluble and no reaction occurred. When this reaction mixture was warmed to 0 °C, vigorous evolution of gas ensued as the potassium hydride was consumed. After 30 min. at 0 °C, analytical t.l.c. showed that all the methyl-ester (126; Z=CO₂Me) had been consumed. Direct preparative t.l.c.
of the reaction mixture furnished several inseparable components in 29% yield. The $^1$H n.m.r. spectrum of the mixture was complicated by the presence of diastereoisomers, although signals arising from aldehydic, Me and Bu protons were observed. No signal observed corresponded to the olefinic proton in the undesired unsaturated aldehyde (172). Infrared absorption at 1780 and 1740 cm$^{-1}$ supported the conclusion that the lactone-ester (127;Z=CO$_2$Me) had been formed.

Because of time constraints, full characterisation of the products from this last reaction was not possible and the remaining steps in Figure 4, leading to the Corey lactone-alcohol (35), were not attempted, i.e., reduction of the aldehyde function and the demethylation/decarboxylation reaction.

3.6 Conclusion

Several important stages in the synthesis of the Corey lactone (26) or the Corey lactone-alcohol (35) from the chloro-enone (86;X=Cl) have been completed in this study. First, the sensitive cyclopentenecarbaldehyde (125) was synthesised in 52% overall yield from the chloro-enone (86;X=Cl) in just two steps. Second, the methyl-ester (126;Z=CO$_2$Me) was synthesised from the cyclopentenecarbaldehyde (125) in
a yield of 54%, which still remains to be optimised. Third, indications have been obtained that cyclisation of the methyl-ester (126;Z=CO$_2$Me) proceeded as required to yield the lactone (127;Z=CO$_2$Me) without loss of the C-4 silyloxy group. Also, model studies provide evidence that reduction of the aldehyde function in the cyclised lactone (127;Z=CO$_2$Me) should proceed in moderate to good yield.

It may also be possible to improve the yield of the sensitive benzyl-ester (126;Z=CO$_2$Bz), which, from the model studies, appears to be the most suitable precursor to the Corey lactone (26) itself.
SYNTHETIC STUDIES TOWARDS THE COREY LACTONE VIA A CYCLOPENTENYL CARBANION EQUIVALENT

4.1 INTRODUCTION

4.2 SYNTHETIC PLAN

4.3 CHLORIDE-LITHIUM EXCHANGE STUDIES ON THE CHLORO-CYCLOPENTENE (174)

4.4 STANNYL-CYCLOPENTENES: PRECURSORS TO LITHIO-CYCLOPENTENES

4.5 CONCLUSION
4.1 Introduction

In Chapter 3 the chloro-enone \(86; X = \text{Cl}\) was employed as an operational equivalent to the 3-oxo-5-hydroxy-1-cyclopentenyl carbocation \(122\) in a synthetic study directed towards the Corey lactone \(26\). In this Chapter the transformation of the chloro-enone \(86; X = \text{Cl}\) and its C-4 tetrahydropyranlyoxy analogue \(173\) into three operational equivalents to the cyclopentenyl carbanion \(123\) is studied. The possible application of one of these equivalents to a synthesis of the Corey lactone is then investigated.

4.2 Synthetic Plan

The first endeavour to prepare an operational equivalent to the cyclopentenyl carbanion \(123\) required direct chlorine-lithium exchange in the chloro-cyclopentene \(174\). The possible application of such an anion to the synthesis of a potential prostanoid intermediate, the cyclopentenecarbaldehyde \(176\), is illustrated in Figure 10. The
starting material chosen for this approach was the chloro-enone (173) which had previously been prepared in these laboratories. \textsuperscript{21}(d) It was expected that stereospecific reduction of the chloro-enone (173) and silylation of the resulting alcohol would yield the chloro-cyclopentene (174). The two protecting groups were chosen after consideration of the results obtained by Gill and Rickards\textsuperscript{119} who found that lithiation of the isomeric chloro-cyclopentene (177) occurred at C-2 and that the tetrahydropyranol-oxygen was necessary for lithiation, stabilising the intermediate organolithium complex (178). On this basis it was anticipated that the potential oxygen-lithium interaction in the organolithium complex (175) might assist in its generation. Protection of the hydroxyl group, formed by reduction of the chloro-enone (173), as its tert-butyldimethylsilyl ether would be essential for its subsequent selective deprotection. Formylation of the organolithium complex (175) and removal of the silyl protecting group should then yield the cyclopentenecarbaldehyde (176).

The second and third approaches to an operational equivalent of the cyclopentenyl carbanion (123) both involve the generation of an organolithium intermediate from an organotin substrate. Organotin
compounds have found considerable application in organic synthesis and usually undergo transmetallation when treated with butyllithium at low temperature. Piers and Morton\textsuperscript{120} reported that 3-tributylstannyl-cyclohexenone can be synthesised from a 3-halocyclohexenone using a stannylcuprate reagent. By analogy, it was expected that reaction of a stannylcuprate reagent with the chloro-enone (86;X=Cl) would generate the stannyl-enone (179), stereospecific reduction of which should then give the stannyl-alcohol (180). This intermediate could then be subjected to the transformations illustrated in Figure 11 to hopefully generate the two alternative operational equivalents to the cyclopentenyl carbanion (123), compounds (181) and (185). Protection of the stannyl-alcohol (180) as its tetrahydropyranyl-ether should give the stannyl-cyclopentene (181). Transmetallation of this compound (181) and reaction of the resulting organolithium intermediate (182) with an electrophile should furnish a substituted cyclopentene of type (183).

The third approach involves protection of the stannyl-alcohol (180) as its acetate and subsequent conversion to the ketene silyl acetal (185). Transmetallation of this compound and formylation of the resulting organolithium intermediate should then furnish the cyclopentenecarbaldehyde (187;E=CHO). Under appropriate conditions, Michael addition of the ketene function to the unsaturated aldehyde might occur to give the Corey lactone (26). The premise for this cyclisation is based on the previously reported\textsuperscript{121} high-yielding Michael addition of ketene silyl acetals to unsaturated carbonyl substrates.
Figure 11

\[ \text{(179)} \]

\[ \text{(180)} \]

\[ \text{(184)} \]

\[ \text{(181)} \equiv \text{(123)} \equiv \text{(185)} \]

\[ \text{(182)} \]

\[ \text{(186)} \]

\[ \text{(183)} \]

\[ \text{(187)} \]
4.3 Chloride-Lithium Exchange Studies on the Chloro-cyclopentene (174)

The chloro-enone (173) was prepared according to the method of Gill and Rickards. Stereospecific reduction of the chloro-enone (173) with lithium tri-α-butylborohydride gave the corresponding alcohol in 83% yield, as a 1:1 mixture of diastereoisomers due to the tetrahydropyranyl group. The mass spectrum of this alcohol did not exhibit a molecular ion, although a fragment ion was observed at m/z 117 which was derived from the fragmentation M⁺-ThpO. Infrared absorption observed at 3410, and 1620 cm⁻¹ was assigned to the hydroxyl and olefin functions. Without further characterisation, this alcohol was treated with chloro-α-butyldimethylsilane and imidazole in N,N-dimethylformamide which gave the chloro-cyclopentene (174) in 73% yield as a 1:1 mixture of diastereoisomers. The mass spectrum of compound (174) did not exhibit a molecular ion although fragment ions were observed including one at m/z 231 which was assigned to the fragmentation, M⁺-ThpO. The ¹H n.m.r. spectrum of the chloro-cyclopentene (174) included two doublets of doublets at δ5.86 and 5.80 (J₃,4 2.5 Hz and J₃,1 1 Hz) which were assigned to the olefinic C-3 proton in each diastereoisomer. Also observed was a singlet at δ0.88, assigned to the Bu⁺ protons. Infrared absorption at 1630 cm⁻¹ confirmed the presence of an olefin function.

Reaction of the chloro-cyclopentene (174) with butyllithium and subsequently quenching the mixture with water afforded an unstable product and none of the desired cyclopentene (188). During the reaction, analytical t.l.c. of the mixture showed that compound (174)
had been consumed and a new compound formed which contained an ultraviolet-absorbing chromophore and which had a larger $R_f$ than compound (174). As the compound thus formed quenched ultraviolet fluorescence at 254 nm, this indicated that the product expected from halogen-lithium exchange, compound (188), had not been formed. The product mixture obtained after quenching with cold water was unstable and could not be purified by chromatography. T.l.c. of the quenched product mixture showed that there was no trace of the compound originally detected in the reaction mixture (first-formed compound) and that another compound had been formed which also contained an ultraviolet-absorbing chromophore but had a smaller $R_f$ value.

Spectral data obtained on the crude product mixture permitted a tentative assignment to be made to the second-formed compound. Ultraviolet and infrared absorption maxima at 231 nm (EtOH) and 1725 cm$^{-1}$ respectively were consistent with a cyclopentenone structure. The $^1$H n.m.r. spectrum of the crude product showed a triplet at δ 7.60 and a multiplet at δ 2.58 which could be assigned to the olefinic C-3 proton and the C-4 and C-5 methylene ring protons in a C-2 substituted cyclopentenone. The mass spectrum of the crude product mixture included a strong ion at $m/z$ 116, with a $^{37}$Cl isotope peak.

\[
\begin{align*}
\text{ThpO}^+ \\
\text{(188)}
\end{align*}
\]
at \( m/z \) 118. High resolution analysis of this ion confirmed its composition to be \( \text{C}_5\text{H}_5\text{Cl}_0 \). All spectral data was consistent with the second-formed compound obtained on work-up being 2-chloro-2-cyclopentenone. A sample of this enone, obtained independently, showed identical spectral properties and t.i.c. behaviour to the second-formed compound generated in the present study.

A plausible mechanism for the formation of 2-chloro-2-cyclopentenone (191) in the present study is shown in Figure 12. Proton abstraction from compound (174) at C-1 by butyllithium could generate the stabilised organolithium complex (189), which on elimination of lithium \( t \)-butyldimethylsilanol would afford the cyclopentadiene (190). The alkoxydiene chromophore of this compound would absorb UV radiation at longer wavelength than non-conjugated cyclopentenes, and would readily hydrolyse on work-up to give compound (191), after double bond migration.

![Figure 12](image)

In an attempt to isolate the first-formed compound generated in this reaction, tentatively assigned to be the
cyclopentadiene (190), the reaction was repeated and the product was directly chromatographed on silica gel without aqueous work-up. Using this procedure, the first-formed ultraviolet-absorbing product was indeed obtained, although only in impure form. Mass spectra of this impure material were complex and uninformative, but infrared absorption at 1625 and 1610 cm\(^{-1}\) was indicative of two types of olefin function and an ultraviolet maximum was observed at 257 nm (EtOH). The nearest analogue to the cyclopentadiene (190), reported in the literature, is 1,2-dimethyl-1,3-cyclopentadiene \(^{123}\) which is reported to exhibit an ultraviolet maximum at 250 nm (MeOH). Although the \(^1\)H n.m.r. spectrum of the present reaction product was complicated by impurities, signals compatible with the cyclopentadiene (190) were observed: two doublets of triplets at 5.26 and 5.42 which could be due to the olefinic C-3 and the C-4 protons; and the multiplet at 2.92 which could be due to the C-5 proton. Signals arising from the tetrahydropyranyl group were also present but they could not be clearly distinguished. No \(^1\)H n.m.r. data was found in the literature for similar compounds, e.g., 1,2-dimethyl-1,3-cyclopentadiene.

The results from these experiments tentatively support the mechanism in Figure 12, leading from the chloro-cyclopentene (174) to 2-chloro-2-cyclopentenone (191), although characterisation of the intermediate (190) and compound (191) is incomplete. It is evident, however, that the expected cyclopentene (188) (see page 109) is totally absent, thereby establishing that the desired halogen-metal exchange did not occur. Accordingly, we then considered generating an operational equivalent of the cyclopentenyl carbanion (123) using organotin methodology.
4.4 Stannyl-cyclopentenes: Precursors to Lithio-cyclopentenes

The use of organostannanes as precursors to organolithium intermediates in the present study via two routes is illustrated in Figure 11. In both routes substitution of the chlorine atom in the chloro-enone (86;X=Cl) with the tributylstannyl group is required. Piers and Morton\textsuperscript{120} obtained high yields of stannyl-cyclohexenones from the corresponding vinylogous acid chlorides. However, similar reaction of the chloro-enone (86;X=Cl) with lithium phenylthio(tributylstannyl)-copper gave only a 26\% yield of the desired stannyl-enone (179) with 62\% recovered starting material. Since bis-homocuprates are reported to be of higher reactivity than heterocuprates, their application to the present reaction was studied. Lithium bis(tributylstannyl)copper was prepared from tributylstannyllithium\textsuperscript{124} and copper(I) bromide-dimethylsulphide complex in dimethylsulphide, and then reacted with the chloro-enone (86;X=Cl) to give the stannyl-enone (179) in 84\% yield. The higher reactivity of bis-homocuprates was evident from this reaction. The mass spectrum of the stannyl-enone (179) exhibited a base peak at \(m/z\) 445, due to the fragmentation, \(M^+\)-Bu. The \(^1\)H n.m.r. spectrum was consistent with the assigned structure and included a doublet at \(\delta 6.30\), due to the C-2 proton coupled by 1 Hz to the C-4 proton, which resonated as a multiplet at \(\delta 4.96\) and was coupled by 1 Hz to the C-2 proton and by 6 and 2.5 Hz to the vicinal \textit{cis} and \textit{trans} C-5 protons. Infrared absorption at 1720 cm\(^{-1}\) was indicative of an unsaturated carbonyl function.

Stereospecific reduction of the carbonyl group in the stannyl-enone (179) with lithium tri-\(\sigma\)-butylborohydride at -78 °C gave the stannyl-alcohol (180) in quantitative yield. The \(^1\)H n.m.r. spectrum of the stannyl-alcohol (180) showed signals at \(\delta 5.99\) and 4.70 which were
assigned to the C-2 and C-4 protons. The pentuplet observed at δ2.70 was assigned to the C-5 proton cis to the C-4 proton and showed the coupling constants $J_{5,4}$ and $J_{5,1}$ of 6.5 Hz each. The signal from the other C-5 proton was obscured by the tributylstannyl resonances. However, from the literature examples it was concluded that reduction exclusively furnished the diastereoisomer in which the two oxygen functions were cis disposed. This result is supported by the work of Gill and Rickards. The presence of an hydroxyl group was indicated by infrared absorption at 3300 cm$^{-1}$. Tetrahydropyranylation of the stannyl-alcohol (180) gave the stannyl-cyclopentene (181) in 95% yield as a 1:1 mixture of diastereoisomers due to the tetrahydropyranyl group.

Tin-lithium exchange between the stannyl-cyclopentene (181) and butyllithium in THF at -78 °C was prohibitively slow as judged by the chromatographic appearance of the destannylated cyclopentene (188). However, with two equivalents of butyllithium at -45 °C, transmetallation was complete after just 45 min., whereupon aqueous quench afforded the cyclopentene (188) in quantitative yield.

The lithio-cyclopentene (182) prepared in this way was chilled to -78 °C and then reacted with ethyl chloroformate to furnish the cyclopentene-ester (183; E=CO$_2$Et) in quantitative yield. The $^1$H n.m.r. spectrum of compound (183; E=CO$_2$Et) was complicated by the presence of two tetrahydropyranyl diastereoisomers. The olefinic proton at C-2 resonated at δ6.71 as a four-line signal, generated by two partly overlapping triplets. The ester methylene protons resonated at δ4.20 and 4.18 as two partly overlapping quartets. When the lithio-cyclopentene (182) was reacted with methyl formate, the unstable aldehyde (183; E=CHO) was obtained in 77% yield. The $^1$H n.m.r. spectrum of this compound was also complicated by the presence of two
diastereoisomers. However, a singlet at $\delta 9.82$ and a multiplet at $\delta 6.85$ were assigned to the aldehyde and C-2 protons. Infrared absorption at 1692 cm$^{-1}$ was indicative of an aldehyde function.

To summarise then, the stannyl-cyclopentene (181) was prepared in three high-yielding steps from the chloro-enone ($86;X=\text{Cl}$) and conditions for the tin-lithium exchange and smooth reaction of the resulting lithio-cyclopentene (182) with two electrophiles were established. Next, attention was turned towards preparing the third possible operational equivalent to the cyclopentenyl carbanion (123), the ketene silyl acetal (185).

The stannyl-alcohol (180) was smoothly acetylated with acetic anhydride in pyridine to give the stannyl-acetate (184). In the mass spectrum of this compound (184) fragment ions were observed at $m/z$ 489 and 429 due to $M^+-\text{Bu}$ and $M^+-\text{Bu-MeCO}_2\text{H}$. The $^1$H n.m.r. spectrum of compound (184) showed the expected signals which included a singlet at $\delta 2.05$, assigned to the acetate protons. Infrared absorption observed at 1740 cm$^{-1}$ was indicative of an ester function. Conversion of the acetate group in compound (184) to a ketene silyl acetal function was then studied.

Ketene silyl acetals have been prepared by several methods, for example, Tamura et al. $^{121}$ obtained the t-butyldimethylsilyloxy-ketene acetal of methyl acetate in 72% yield by low temperature enolisation of this ester and silylation of the resulting enolate in the presence of HMPA. The stannyl-acetate (184) was deprotonated under similar conditions using a slight excess of lithium diisopropylamide at $-78 ^\circ\text{C}$ and the resulting enolate was subsequently treated with HMPA and chloro-t-butyldimethylsilane. Although this furnished a 4:1 ratio of
the ketene silyl acetal (185) and starting material, inconsistent yields of (185) led us to seek a more reliable synthesis.

Reaction of the stannyl-acetate (184) with two equivalents each of lithium diisopropylamide and HMPA reproducibly afforded the ketene silyl acetal (185) in quantitative yield. The mass spectrum of the ketene silyl acetal (185) did not show a molecular ion, but fragment ions were observed at \( m/z \) 369, 291, and 73 (base peak), which were due to \( M^+ - Bu_2 Sn, Bu_2 Sn^+ \) and \( Me_3 Si^+ \). Those ions containing tin exhibited the expected isotope pattern. The ion of mass \( m/z \) 73 is often observed in the mass spectra of compounds which contain the \( t \)-butyldimethylsilyl ether function and Phillipou\(^{126}\) reported that the composition of this ion was \( C_3 H_9 Si \) and that it was formed by migration of a methyl group on to the silicon atom. The \(^1\)H n.m.r. spectrum of the ketene silyl acetal (185) included a triplet at \( \delta 6.18 \) due to the olefinic C-2 proton which showed coupling constants of \( J_{2,1} \) and \( J_{2,4} \) of 1.5 Hz each. This signal was flanked by two small satellite signals which were separated by 32 Hz and resulted from the coupling between the C-2 proton and \(^{119}\)Sn isotope \((I=\frac{1}{2} \text{ and natural abundance }= 7\%)\). Two broad multiplets observed at \( \delta 4.80 \) and 4.65 were assigned to the C-1 and C-4 protons. The signals due to the methylene protons of the ketene acetal occurred at \( \delta 3.56 \) and 3.28 as doublets, coupled to each other by 2.5 Hz. In the infrared spectrum of compound (185), absorption at 1650 cm\(^{-1}\) was attributed to the ketene-olefin function, based on previous literature examples.\(^{121}\)

Tin-lithium exchange between the ketene silyl acetal (185) and butyllithium was investigated next. From the outset it was realised that separation of the destannylated product from the tetrabutyltin by-product would be difficult because of the lability of the ketene silyl acetal function. Therefore, in most of the reactions described in
the remainder of this Chapter the product mixture obtained was comprised of approximately equal proportions of the destannylated product and the relatively inert tetrabutyltin. Since chemical analysis of these products was therefore not feasible, where possible, high resolution mass measurement of prominent ions in the mass spectra of new compounds was performed instead.

The conditions for tin-lithium exchange which had previously been established for the stannyl-cyclopentene (181) were successfully applied to the ketene silyl acetal (185). To preserve the sensitive ketene silyl acetal function on work-up, however, it was necessary to quench the reaction by pouring it into an ice-cold water/pentane mixture. In this way the cyclopentene (187;E=H) was obtained in 90% yield (estimated from the mass recovered and the $^1$H n.m.r. spectrum of the product mixture). In its $^1$H n.m.r. spectrum the cyclopentene (187;E=H) exhibited a multiplet at δ5.80, which was attributed to the two cyclic olefinic protons, and two doublets at δ3.52 and 3.17, due to the ketene olefin protons which were coupled by 2.5 Hz to each other. Signals due to the protons in the two Bu$^t$ groups and those in the tetrabutyltin were observed in the δ1.80-0.80 region. In its mass spectrum the cyclopentene (187;E=H) exhibited a weak molecular ion at $m/z$ 370 and fragment ions at $m/z$ 355, 313, 239 and 197 (base peak) which were due to M$^+$-Me, M$^+$-Bu$^t$, M$^+$-Bu$^t$Me$_2$SiOH and M$^+$-C$_8$H$_{17}$O$_2$Si. High resolution analysis of the fragment ion at $m/z$ 313 (M$^+$-Bu$^t$) confirmed its composition to be $C_{15}H_{30}O_3Si_2$. In the infrared spectrum of compound (187;E=H), absorption was observed at 1650 cm$^{-1}$ which was attributed to the ketene silyl acetal function.

The lithio-cyclopentene (186) was then quenched at -78 °C with ethyl chloroformate. The reaction was kept at this temperature for
30 min. prior to the careful work-up, as used in the previous reaction. The $^1$H n.m.r. spectrum of the product mixture indicated that transmetallation was complete and that the cyclopentene-ester (187; $E=\text{CO}_2\text{Et}$) had been formed in a 4:1 ratio with the cyclopentene (187; $E=\text{H}$). Because of its sensitivity, the cyclopentene-ester (187; $E=\text{CO}_2\text{Et}$) had to be characterized without separation from the cyclopentene (187; $E=\text{H}$) and tetrabutyltin. In the infrared spectrum of the mixture, which consisted mainly of the compound (187; $E=\text{CO}_2\text{Et}$), absorption was observed at 1730 and 1650 cm$^{-1}$ which was indicative of ester-carbonyl and ketene-olefin functions. The mass spectrum of the mixture included fragment ions at $m/z$ 385, 311 and 269 which could be derived from the compound (187; $E=\text{CO}_2\text{Et}$) by the fragmentations $M^+-\text{Bu}^+$, $M^+-\text{Bu}^+\text{Me}_2\text{SiO}$ and $M^+-\text{C}_8\text{H}_{17}\text{OsSi}$. The $^1$H n.m.r. spectrum of the mixture exhibited signals arising from the cyclopentene-ester (187; $E=\text{CO}_2\text{Et}$) and the cyclopentene (187; $E=\text{H}$). A doublet of doublets at 6.71 was assigned to the C-2 proton in compound (187; $E=\text{CO}_2\text{Et}$), which showed coupling constants of $J_{2,3}$ and $J_{2,5}$ of 2 and 1 Hz. The apparent pentuplet (ddd) observed at 2.44, is characteristic of cis 3,5-dihydroxylated cyclopentenes.
and was assigned to the C-4 proton \( \text{cis} \) to the C-5 proton. For this C-4 proton, the following coupling constants were observed: \( J_{4,3}, J_{4,5} \) and \( J_{4,4} \) of 7, 3.5 and 14 Hz. A quartet observed at 3.99 with a coupling constant of 7 Hz was attributed to the methylene protons of the ester function. The remainder of the \( ^1H \) n.m.r. spectrum showed the expected signals for a mixture of the compound (187;\( E=CO_2Et \)) and compound (187;\( E=H \)). Attempts to increase the proportion of the cyclopentene-ester (187;\( E=CO_2Et \)) in the product mixture by changing the reaction parameters of temperature and time were unsuccessful. The presence of the cyclopentene-ester (187;\( E=CO_2Et \)) was confirmed by hydrolysis of the mixture and subsequent isolation and characterisation of the cyclopentene-acetate (243) (see page 117), which was obtained in 35% yield.

Several attempts to react the lithio-cyclopentene (186) with ethyl formate gave widely variable results. However, on one occasion, \( ^1H \) n.m.r. spectral data indicated that the desired cyclopentene-aldehyde (187;\( E=CHO \)) had been formed, possibly in about 50% yield. Since complete characterisation of this product was not possible and because of the inconsistent results, no firm conclusion was drawn from this experiment. Attention was therefore directed towards improving the yield of the cyclopentene-ester (187;\( E=CO_2Et \)) by attempting to decrease the protonation of the lithio-cyclopentene (186) which occurred to some extent when it was treated with ethyl chloroformate. This reagent, of course, had been carefully purified and freed from the possible proton sources of moisture and acid, hence an alternative proton source had to exist.

The use of two equivalents of butyllithium to effect tin-lithium exchange in the stannyl-cyclopentene (185) would afford equimolar proportions of the required lithio-cyclopentene (186) and unconsumed butyllithium. The electrophile could then react with both
carbanions to afford the functionalised cyclopentene \((187; E=\text{CO}_2\text{Et})\) and an equimolar amount of ethyl pentanoate. Should the ethyl pentanoate be generated faster than compound \((187; E=\text{CO}_2\text{Et})\) then it could protonate any unconsumed lithio-cyclopentene \((186)\) with its relatively acidic C-2 protons. If this process was in fact occurring, then the use of \(t\)-butyllithium in the transmetallation reaction might avoid the formation of the cyclopentene \((187; E=\text{H})\), because the ester by-product would, of course, have no acidic (C-2) protons.

Reaction of \(t\)-butyllithium with the ketene silyl acetal \((185)\) in THF at -45 °C immediately gave a dense precipitate which, on addition of ethyl chloroformate, dissolved to give a yellow solution. Work-up of this reaction, however, gave only starting material (87%). The insoluble precipitate may have been the pentavalent tin "ate" complex \((192)\) which, rather than react further to give the lithio-

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Si} & \\
\text{SnBu}_3 & \\
\text{Bu}^+ & \\
\text{Li}^+ \\
\end{align*}
\]

(192)

cyclopentene \((186)\), probably transferred \(t\)-butyllithium to ethyl chloroformate thereby generating ethyl \(t\)-pentanoate and starting material. In any case the cyclopentene-ester \((187; E=\text{CO}_2\text{Et})\) could not be
prepared using t-butyllithium. Also, the undesired proton source remained unidentified. Cyclisation of the cyclopentene-ester (187; E=CO₂Et) [as a 4:1 mixture with the cyclopentene (187; E=H)] to a Corey lactone analogue was then examined.

Tamura et al. reported that ketene silyl acetals underwent efficient Michael addition to unsaturated carbonyl substrates, simply by warming the substrate and the ketene silyl acetal in acetonitrile. When this method was applied to the cyclopentene-ester (187; E=CO₂Et), however, a complex mixture of products was obtained, even after careful work-up. This product mixture did not contain any starting material, as judged from its ¹H n.m.r. spectrum, nor did it contain any product with a γ-lactone function as judged from its infrared spectrum.

The use of a Lewis acid to promote cyclisation was also explored. Reaction of a 4:1 mixture of the cyclopentene-ester (187; E=CO₂Et) and the cyclopentene (187; E=H) with trimethylsilyl trifluoromethanesulphonate gave at least six products as judged by analytical t.l.c.. The ¹H n.m.r. spectrum of the product mixture showed that the starting material had been consumed but an infrared spectrum gave no indication that any of the products contained a γ-lactone function. Because of their instability the products could not be isolated or characterised.

These preliminary studies on the cyclisation of the cyclopentene-ester (187; E=CO₂Et) demonstrate the reactivity of the ketene silyl acetal function, which is probably part of the reason why the desired cyclisation product was not obtained. Since this work was carried out, Yamamoto et al. reported that O-silylated ketene acetals undergo efficient conjugate addition to enones and smoothly react with aldehydes under high pressure and in an inert solvent (CH₂Cl₂). It is
possible that this procedure may effect the cyclisation of the cyclopentene-ester (187; E=CO₂Et). Unfortunately, because of time constraints further study in this area was not possible.

4.5 Conclusion

The synthesis and reactions of three possible operational equivalents, (174), (181), and (185), to the cyclopentenyl carbanion (123) were studied and the possible conversion of compound (185) to a Corey lactone-type product was investigated.

The chloro-cyclopentene (174) was prepared in high yield but when treated with butyllithium the desired lithio-cyclopentene (175) was not obtained. Instead, deprotonation of compound (174) seems to have occurred at C-1 with the resulting carbanion undergoing rearrangement, generating 2-chloro-2-cyclopentenone.

The stannyl-enone (179), a precursor to both the stannyl-cyclopentene (181) and the ketene silyl acetal (185), was prepared in high yield by reaction of the chloro-enone (86; X=Cl) with lithium bis(tributylstannyl)copper. Compound (179) was smoothly converted to the stannyl-cyclopentene (181) and conditions were established for the efficient generation of the lithio-cyclopentene (182) via tin-lithium exchange. The intermediate (182) thus obtained reacted efficiently with various electrophiles, thereby establishing the equivalence of the stannyl-cyclopentene (181) to the cyclopentenyl carbanion (123).

The ketene silyl acetal (185) was obtained in three high-yielding steps from the stannyl-enone (179) and was then converted via efficient tin-lithium exchange to the lithio-cyclopentene (186). Reaction of intermediate (186) with ethyl chloroformate gave the ester
(187;E=CO₂Et) in good yield. However, preliminary studies on the cyclisation of this ester were not successful, and indications were obtained that the intrinsic sensitivity of the ketene silyl acetal function could prevent application of this route to a synthesis of the Corey lactone (26).

To summarise then, the approach to the Corey lactone (26) discussed in Chapter 3, using an operational equivalent to the cyclopentenyl carbocation (122) appears to be a more promising approach than that discussed in this Chapter, using an operational equivalent to the cyclopenteny1 carbanion (123), e.g., the ketene silyl acetal (185). The approach described in Chapter 3 is also more versatile as it provides access to the cyclopentene-carbaldehyde (125) which could also be an attractive intermediate for prostanoid synthesis.
INVESTIGATION OF THE C-2/C-3 VICINAL DIALKYLATION OF C-3 HETEROSUBSTITUTED 2-CYCLOALKENONES

5.1 INTRODUCTION AND SYNTHETIC PLAN

5.2 CONJUGATE ADDITION-ELIMINATION STUDIES:

- 3-Chloro-2-cyclohexenone
- 3-Pyrrolidino-2-cyclohexenone (200a)
- 3-Imidazolyl-2-cyclohexenone (200b)
- 3-Oxo-1-cyclohexenecarbonitrile (159)
- 3-Butylthio-2-cyclohexenone (202)
- Phenylseleno-eneone (193; X=SePh)
- Trimethylstannyl-eneone (193; X=SnMe₃)

5.3 CONCLUSION
5.1 Introduction and Synthetic Plan

Previous syntheses of the 2,3-dialkyl-2-cyclopentenone nucleus, common to the rethrolones (59), (60) and (61), are discussed in Chapter 1. A short and potentially attractive approach to this type of nucleus is investigated in this Chapter. The starting material for this approach is a C-3 heterosubstituted cyclopentenone (193) and steps leading from such a precursor to the 2,3-dialkyl-2-cyclopentenone nucleus are shown in Figure 13. The chloro-enone (12) is an example of such a possible precursor and, as described in Chapter 1, this compound is readily available in only five steps from phenol. Conjugate addition of an organocuprate reagent to (193) is expected to furnish the regiospecific enolate (194) which, on reaction with an alkylating agent, could furnish the ketone of type (195). Elimination of HX from compound (195) would then complete a synthesis of the desired 2,3-dialkyl-2-cyclopentenone nucleus. Such an approach would have wider applications than to rethrolone synthesis alone. The synthesis of PGB₁ (57), jasmone (58) and several other natural products which also contain the 2,3-dialkyl-2-cyclopentenone nucleus may be possible by use of the appropriate organocuprate and alkylating reagents.

Figure 13

![Diagram showing the synthetic plan](image)
Conjugate addition of organocuprate reagents to several C-3 heterosubstituted enones with ensuing elimination of the heterosubstituent has been reported. Substrates used include chloro-enones, iodo-enones and alkylthio-enones. It was recognised at the outset of the present study that elimination of the C-3 heterosubstituent from the intermediate enolate could occur before alkylation, thereby affording a 3-alkyl-2-cyclopentenone. Avoidance of this reaction path would be crucial to the success of the strategy. Results from the first experiments of the study indicated that elimination of the heterosubstituent was indeed a facile process and/or that alkylation of the organocuprate-derived enolates was a slow process, since the C-2 alkylated product was not obtained.

The rate of elimination of the C-3 heterosubstituent is likely to be primarily determined by electronic factors. Electropositive heterosubstituents are expected to be eliminated less readily than electronegative heterosubstituents. To determine which heterosubstituent, if any, was suitable for the present purposes, model studies were carried out on five C-3 heterosubstituted cyclohexenones. These substrates were more accessible than the corresponding cyclopentenones of type although two such cyclopentenones were also prepared and examined. 3-Chloro-2-cyclohexenone was examined first because chlorine is the heterosubstituent which is present in the chloro-enone (12), which is a potential precursor to other C-3 heterosubstituted cyclopentenones of type (193) and to the pyrethrolone nucleus.

Two substrates containing nitrogen directly bonded to the enone were considered, 3-pyrrolidino-2-cyclohexenone and 3-imidazolyl-2-cyclohexenone, the latter bearing a more electropositive heterosubstituent. Two other cyclohexenones were studied, one contained
a cyano substituent and the other an alkylthio substituent. The two
cyclopentenones studied contained selenium and tin-bearing
heterosubstituents, the latter containing the most electropositive of
all the heteroatoms studied. A substrate possessing an oxygen
heterosubstituent was not examined because 3-alkoxy-2-cycloalkenones
generally do not undergo conjugate addition reactions with organocuprate
reagents.\textsuperscript{96(b)} Any products obtained from such reactions are likely to
arise from reaction of the substrate with unreacted organolithium
reagent.

Two types of organocuprate reagent were used in the present
study. Firstly, a magnesio-cuprate which was prepared either by
addition of approximately two equivalents of the Grignard reagent to one
equivalent each of copper(I) iodide and the substrate ('inverse
addition') or simply by addition of approximately two equivalents of a
Grignard reagent to one equivalent of a copper(I) salt, with subsequent
addition of the substrate. Secondly, a lithio-cuprate was used which
was prepared by addition of two equivalents of an organolithium reagent
to one equivalent of copper(I) iodide.

Conjugate addition of an organocuprate reagent, in the
absence of an alkylating agent, to C-3 heterosubstituted cycloalkenones
of the type to be used in this study could afford either or both of the
following products, a 3-alkyl-2-cycloalkenone and a 3,3-dialkyl-
cycloalkanone. A 3-alkyl-2-cycloalkenone will be obtained if the C-3
heterosubstituent is eliminated either during the reaction or on work-up.
If it is eliminated during the reaction, further conjugate addition has
to be disfavoured. A 3,3-dialkylcycloalkanone will be obtained only
when the C-3 heterosubstituent is eliminated during the reaction and
further conjugate addition occurs.
In the present study, conditions were first optimised for the generation of the 3-alkyl-2-cycloalkenone by reaction of the substrate with an organocuprate reagent, without the subsequent addition of an alkylating agent. In cases where this was achieved and in those cases which also appeared favourable, attempts were made to intercept the intermediate enolate by alkylation.

5.2 Conjugate Addition - Elimination Studies

3-Chloro-2-cyclohexenone

The efficient reaction of 3-chloro-2-cyclopentenones with magnesio-cuprate reagents\(^{21}\) prompted the use of this type of reagent for the conjugate addition of an alkyl group to 3-chloro-2-cyclohexenone. This substrate was prepared from oxalyl chloride and 1,3-cyclohexanedione\(^ {130}\) and the organocuprate reagent was prepared from butylmagnesium bromide and copper(I) iodide. Conditions for the formation of the monoaddition product were first optimised using the 'inverse addition' method. Reaction of butylmagnesium bromide (2 equivalents) with 3-chloro-2-cyclohexenone (1 equivalent) and copper(I) iodide (1 equivalent) at 0 °C furnished mainly 3,3-dibutylcyclohexanone.
Therefore, under these reaction conditions elimination of the heterosubstituent from the enolate (198; R=Bu, X=Cl) occurred in situ to give the enone (199) which then underwent further conjugate addition. To retard elimination of the chloro heterosubstituent the reaction temperature was lowered. Since magnesio-cuprate reagents cannot be prepared below -10 °C, the reagent was preformed at this temperature and subsequently chilled to -78 °C. When the previous reaction was repeated at this lower temperature, however, mainly starting material was obtained which suggested that the substrate and reagent were not reactive at -78 °C. To retard the double conjugate addition observed at 0 °C, the quantity of Grignard reagent used was reduced to 1.5 equivalents. Reaction of butylmagnesium bromide with the substrate and copper(I) iodide at -15 °C furnished the desired enone (199) in 82% yield, previously prepared by Conia and Le Cras. In its 1H n.m.r. spectrum the enone (199) showed a singlet at δ5.80, which was attributed to the C-2 olefinic proton.

In attempts to intercept the intermediate enolate (198; R=Bu, X=Cl) in the previous reaction, allyl bromide and formaldehyde were separately employed as electrophiles. Both compounds are highly reactive electrophiles and because formaldehyde is unreactive to organocuprate reagents it may be present in the reaction whilst the enolate is generated. 3-Chloro-2-cyclohexenone was treated first with butylmagnesium bromide according to the method just described and subsequently with allyl bromide. On work-up, however, the enone (199) was obtained in 95% yield as the only product. This result indicates that under the conditions used, elimination of the C-3 heterosubstituent from the enolate (198; R=Bu, X=Cl) occurs in preference to alkylation. Use of monomeric formaldehyde as the electrophile also did not allow
interception of the enolate (198;R=Bu, X=Cl) and the enone (199) was again obtained in high yield.

3-Pyrrolidino-2-cyclohexenone (200a)

3-Pyrrolidino-2-cyclohexenone (200a) should be a more suitable substrate than 3-chloro-2-cyclohexenone because the nitrogen-containing heterosubstituent is more electropositive than chlorine and should therefore be less readily eliminated from the enolate (198;R=Bu, X=pyrrolidino). 3-Pyrrolidino-2-cyclohexenone (200a) was prepared from cyclohexane-1,3-dione and pyrrolidine. Literature examples indicate that conjugate addition of Grignard reagents to acyclic enaminones proceeds in good to high yields (60-90%) in the absence of copper salts, however, it is feasible that the products obtained could be derived by C-1 addition followed by hydrolysis of the alcohol thereby formed. In contrast to these literature precedents, it was found that 3-pyrrolidino-2-cyclohexenone (200a) did not form any addition product with butylmagnesium bromide alone. In this case it is possible that the Grignard reagent deprotonated the substrate at the C-4 position, rendering it unreactive to nucleophilic addition either at C-1 or C-3. Reaction of compound (200a) with butylmagnesium bromide and copper(I) iodide gave only trace amounts of the enone (199) together with just 38% starting material. From this result it appeared that extensive decomposition occurred in the presence of the magnesio-cuprate reagent. Thus the pyrrolidino heterosubstituent was obviously not suited to the present purposes and no attempts were made to intercept the enolate (198;R=Bu, X=pyrrolidino).
3-Imidazolyl-2-cyclohexenone (200b)

The imidazolyl-enone (200b) which contains a more electropositive C-3 heterosubstituent than compound (200a) was studied next. A review of the literature revealed that compound (200b) had not been previously synthesised. As conventional methods of enamine preparation, using cyclohexane-1,3-dione and imidazole were unsuccessful, an alternative approach to the imidazolyl-enone (200b) was sought. This was found in the reaction of 3-chloro-2-cyclohexenone with imidazole and anhydrous potassium carbonate in THF at reflux for 24 hr which furnished the imidazolyl-enone (200b) in quantitative yield. The $^1$H n.m.r. spectrum of compound (200b) exhibited signals expected for an imidazolyl substituent, in the region $\delta$7.96-7.20 and a singlet at $\delta$6.18 corresponding to the C-2 proton. Infrared absorption at 1 670 and 1 630 cm$^{-1}$ was indicative of carbonyl and double bond functions and in the mass spectrum of compound (200b) a molecular ion (base peak) was observed at $m/z$ 162. An intense fragment ion observed at $m/z$ 135 was due to $M^+ - HCN$ and this fragmentation was confirmed by a metastable peak at $m/z$ 112.5.
Reaction of the imidazolyl-enone (200b) with butylmagnesium bromide (1.5 equivalents) and copper(I) iodide at -10 °C afforded the enone (199) and 3,3-dibutylcyclohexanone (197) in yields of 56 and 23%, together with some starting material. Formation of compound (197) indicated that elimination of the imidazolyl anion from the enolate (198;R=Bu, X=imidazolyl) occurred in situ. This elimination must have occurred faster than elimination of chloride anion from the enolate (198;R=Bu, X=Cl), since compound (197) was not obtained under similar conditions from 3-chloro-2-cyclohexenone. This result implies that the enolate (198; R=Bu, X=Cl) has a longer lifetime than the enolate (198; R=Bu, X=imidazolyl) and the lack of any alkylation products in the former case may simply reflect that enolate's lower reactivity. Since the enolate (198;R=Bu, X=Cl) did not react with either allyl bromide or formaldehyde and was apparently more stable than the enolate (198;R=Bu, X=imidazolyl), no attempt was made to alkylate the latter enolate. The nitrile substituent was examined next and lithium dimethylcopper was used instead of the butylmagnesio-cuprate reagent used previously. The different reagent was employed partly to simplify identification of the reaction products.

3-Oxo-1-cyclohexenecarbonitrile (159)

The cyanide group should be less readily eliminated from the enolate (198;R=Me, X=CN) than the heterosubstituents just examined. Indeed, the work of Debal et al.\textsuperscript{137} shows that elimination of the cyanide anion should only occur at room temperature. Debal et al. alkylated several γ-oxo-nitriles at the methine-carbon bearing the nitrile function. Only when the intermediates of the type (198;R=alkyl,
X=CN) obtained were warmed to room temperature did elimination of cyanide anion proceed to give 3-alkyl-2-alkenones.

3-Oxo-1-cyclohexene carbonitrile (159) was prepared according to the method of Cronyn and Goodrich. Reaction of compound (159) initially with lithium dimethylcuprate (0.5 equivalents) at 0 °C and subsequently with allyl bromide and HMPA furnished the saturated nitrile (201) as the major isolable product in 28% yield. Several minor products were formed but they could not be separated and were therefore not characterised. The saturated nitrile (201) was identified by its $^1$H n.m.r. spectrum which included a singlet at $\delta 1.45$, characteristic of a tertiary methyl group, and by its infrared spectrum which exhibited nitrile absorption at 2235 cm$^{-1}$ and saturated carbonyl absorption at 1710 cm$^{-1}$. The mass spectrum of (201) showed an intense molecular ion at $m/z$ 137 and fragment ions at $m/z$ 122 and 109, derived from the fragmentations $M^+-$Me and $M^+-$CO. This result demonstrated that the organocuprate reagent reacted with compound (159) as required at the carbon bearing the nitrile function and that, with respect to elimination, the resulting enolate was relatively stable. However, alkylation of this enolate did not occur and the poor total mass recovery indicated that undesired side-reactions occurred to give polar,
water-soluble by-products. The absence of any alkylation products may be attributed to the low reactivity of the organocuprate-derived enolate, a problem which has been previously discussed.\textsuperscript{138,139}

In an attempt to decrease the side-reactions, the cuprate addition was performed at -20 °C, however, under these conditions conjugate addition was suppressed and 70% of the starting material was recovered. In the light of these results, compound (159) was considered unsuitable for the present aims. It should be noted, however, that interception of the enolate with formaldehyde, although not attempted, could prove fruitful. The use of heterosubstituents containing more electropositive elements, i.e., from the third and fourth rows of the periodic table, was then examined.

3-Butylthio-2-cyclohexenone (202)

Conia\textit{ et al.}\textsuperscript{140} prepared 3-butylthio-2-cyclopentenone from 3-chloro-2-cyclopentenone, butanethiol and sodium hydroxide in 92% yield. By using a slightly modified procedure 3-butylthio-2-cyclohexenone (202) was prepared in 90% yield from 3-chloro-2-cyclohexenone, butanethiol and sodium hydride. Posner and Brunelle\textsuperscript{129} reported that an excess of lithium dimethylcopper reacted with the butylthio-enone (202) to give 3,3-dimethylcyclohexanone in 84% yield. It was expected that by reducing the quantity of organocuprate reagent, the amount of monoalkylated product would be increased.

Reaction of the butylthio-enone (202) with one equivalent of lithium dimethylcopper at 0 °C in the absence of an alkylating agent furnished 61% of the required 3-methyl-2-cyclohexenone, in addition to 14% recovered starting material. 3-Methyl-2-cyclohexenone obtained in
this way was spectrscopically identical to an authentic sample, exhibiting infrared absorption at 1 680 cm\(^{-1}\). Thus, having prevented formation of the dialkylated product, the reaction was repeated and allyl bromide was introduced immediately after the organocuprate reagent. This reaction afforded 3-methyl-2-cyclohexenone in 62% yield and a 17% yield of starting material but none of the desired 2-allylated product was detected. However, two other allylated compounds were obtained: the allyl-enone (203) in 10% yield and the butylthio-enone (204) in 2% yield. These compounds were identified by coupled g.l.c. mass spectrometry.

The structures of these minor products were tentatively assigned on the basis of mass spectral data, being the only spectral data obtained. The mass spectrum of the allyl-enone (203) exhibited a base peak at \(m/z\) 82. It was reported that an ion of this mass was also observed in the mass spectrum of the enone (205).\(^{116(b)}\) The molecular ion of this compound (205) undergoes fragmentation, losing \(\text{C}_5\text{H}_{10}\) via a retro-Diels-Alder reaction, generating the ion \(m/z\) 82 as illustrated in Figure 14. If the allyl-enone (203) also underwent a retro-Diels-Alder fragmentation in the mass spectrometer and if the allyl substituent is
located at C-6 as shown, then an ion of mass $m/z = 82$ should be formed. Such an ion was observed in the mass spectrum of the allyl-enone (203), indicating that the allyl substituent is indeed located at C-6 and not as C-2 as desired. In its mass spectrum, the butylthio-enone (204) exhibited a molecular ion at $m/z = 224$ and fragment ions at $m/z = 168$ and 100. The loss of $C_4H_8$ from the thiobutyl side-chain could explain the formation of the ion at $m/z = 168$. This ion could then undergo further fragmentation via a retro-Diels-Alder reaction to give the ion (206) of mass $m/z = 100$. The allyl-enone (203) and the butylthio-enone (204) could be derived from the kinetic enolates of 3-methyl-2-cyclohexenone and the starting material (202) which could be generated by lithium butanethiolate which itself would be formed as a by-product in the
organocuprate reaction. However, because the butylthio-enone (202) did not react in the desired manner it was considered unsuitable for the present aims.

Two cyclopentenone substrates possessing different C-3 heterosubstituents, phenylseleno and trimethylstannyl, were prepared next and their suitability for the present study was examined.

Phenylseleno-enone (193;X=SePh)

The phenylseleno-enone (193;X=SePh) was synthesised from the chloro-enone (12) in 90% yield by reaction of (12) with lithium phenylselenide, obtained from diphenyldiselenide and lithium tri-o-butylborohydride. The mass spectrum of the phenylseleno-enone (193;X=SePh) showed no molecular ion but diagnostic fragment ions were observed including one at \( m/z \) 311 which could have been derived from the fragmentation \( M^+\text{-But}^+ \). The isotope ratios associated with this fragment ion reflected the presence of one atom of selenium. The \( ^1H \) n.m.r. spectrum of compound (193;X=SePh) showed all the expected signals including a multiplet between \( \delta 7.76-7.36 \) which was attributed to the aromatic protons.

Reaction of methylmagnesium bromide (2 equivalents) with one equivalent each of the phenylseleno-enone (193;X=SePh) and copper(I) iodide at -10 °C in the absence of an alkylating agent furnished the methyl-enone (207) in 26% yield and the cyclopentene-alcohol (208) in 49% yield. The \( ^1H \) n.m.r. spectrum of the methyl-enone (207) exhibited a singlet at \( \delta 5.96 \) due to the C-2 proton, a multiplet at \( \delta 4.76 \) due to the C-4 proton and a singlet at \( \delta 2.13 \) due to the methyl protons. In the infrared spectrum of compound (207), absorption at 1720 cm\(^{-1} \) was
indicative of a conjugated carbonyl function. In its mass spectrum compound (207) showed a weak molecular ion at $m/z$ 226 with fragment ions at $m/z$ 211 and 169 (base peak), due to $M^+\text{-Me}$ and $M^+\text{-Bu}^+$ respectively. For a comparison of infrared and $^1\text{H}$ n.m.r. spectral data of the corresponding C-3 butyl-enone see Gill and Rickards.\(^{21(b)}\)

The cyclopentene-alcohol (208) was obtained as a single diastereoisomer as evidenced from its $^1\text{H}$ n.m.r. spectrum. The two C-5 protons resonated at $\delta 2.36$ (H-5 \text{cis} to H-4) and 1.79 (H-5 \text{trans} to H-4), confirming that addition of the methyl group to C-1 of the methyl-enone (207) occurred at the less hindered face. Other signals observed confirmed the structure of the cyclopentene-alcohol (208), including a slightly broadened singlet at $\delta 1.72$ due to the olefinic methyl group and a sharp singlet at $\delta 1.28$ due to the carbinol methyl group. These spectral data are similar to those obtained by Gill and Rickards\(^{21(b)}\) for an analogous compound. Infrared absorption by compound (208) at 3430 cm\(^{-1}\) indicated the presence of an hydroxyl function which was confirmed by the observation in its mass spectrum of an ion at $m/z$ 224, corresponding to the fragmentation $M^+\text{-H}_2\text{O}$, the molecular ion being observed at $m/z$ 242. It is likely that the
cyclopentene-alcohol (208) was formed by reaction of uncomplexed Grignard reagent with the methyl-enone (207). In an attempt to stop this undesired reaction, lithium dimethylcopper was used and in an effort to retard in situ elimination of the phenylseleno heterosubstituent, a lower reaction temperature was employed.

The phenylseleno-enone (193;X=SePh) was reacted with lithium dimethylcopper at -62 °C, followed by allyl bromide and HMPA. After slowly warming the mixture to room temperature, work-up gave the methyl-enone (207) in 89% yield, but none of the C-2 allylated product was detected. This result showed that elimination of the phenylseleno substituent from the enolate (194;R=Me, X=SePh) was fast at -62 °C relative to alkylation of the organocuprate-derived enolate. In comparison, Posner et al.\textsuperscript{142} reported that an organocuprate-derived cyclopentenyl enolate could be allylated at C-2 at -78 °C, although in that case there was no competition to alkylation from the elimination of a C-3 heterosubstituent.

Attempts to retard elimination by further lowering the reaction temperature to -100 °C simply prevented reaction of the phenylseleno-enone (193;X=SePh) with lithium dimethylcopper, and starting material was recovered in 89% yield. None of the methyl-enone (207) was detected.

To summarise, at higher temperature, elimination of the heterosubstituent occurred exclusively in preference to alkylation of the enolate whereas at low temperature the conjugate addition reaction did not occur. Attention was then directed to the last substrate to be considered in this study.
The final compound examined was a stannyl-enone, containing the most electropositive of all the heteroatoms investigated. The trimethylstannyl-enone (193; X = SnMe₃) had not been previously prepared. Reaction of the chloro-enone (12) with lithium bis(trimethylstannyl) copper at -78 °C and slowly warming to -20 °C gave the desired stannyl-enone (193; X = SnMe₃) in 52% yield together with a 35% yield of compound (209). Raising the initial reaction temperature increased the yield of compound (209) whereas reducing the amount of cuprate reagent used lowered the yield of the stannyl-enone (193; X = SnMe₃), giving more starting material. It is likely that formation of the distannylated product was enhanced by the long C-Sn bond length which could decrease steric hindrance at C-3, although electronic factors could also be contributing to this result. Compound (209) was unstable at room temperature and was therefore only partly characterised by its ¹H n.m.r. and infrared spectra. The ¹H n.m.r. spectrum of (209) exhibited a complex array of signals between δ 2.79 and 2.18, which corresponded to the AB part of an ABX system, attributable to the C-5 protons, and to an A'B' system, attributable to the C-2 protons. Infrared absorption at 1748 cm⁻¹ confirmed the presence of a saturated
cyclopentanyl carbonyl function. The $^1$H n.m.r. spectrum of the stannyl-enone (193;X=SnMe$_3$) exhibited a singlet at δ6.32, a multiplet at δ5.02 and a singlet at δ0.28 due to the C-2, C-4 and trimethylstannyl protons. The mass spectrum of the stannyl-enone (193;X=SnMe$_3$) exhibited a weak molecular ion at $m/z$ 376 and a fragment ion at $m/z$ 319 due to M$^+-$Bu$^+$. Reaction of the stannyl-enone (193;X=SnMe$_3$) with lithium dimethylcupper at -50 °C was surprisingly sluggish, considering the ease of formation of the distannylated compound (209). The reaction was quenched with deuteriomethanol at -50 °C in an attempt to deuterate the enolate (194;R=Me, X=SnMe$_3$). Instead of giving the desired ketone (210), however, this reaction furnished the methyl-enone (207) in 30% yield together with 40% starting material. Thus, the trimethylstannyl heterosubstituent had been eliminated from most of the enolate which had formed during the reaction.

![Structure](210)

5.3 Conclusion

This study demonstrates the difficulty of intercepting the cyclopentenyl and cyclohexenyl-enolates (194) and (198), and did not lead to a synthesis of the desired 2,3-dialkyl-2-cyclopentenyl nucleus.
However, during the study, several compounds not previously described in the literature were prepared. The imidazolyl-enone (200b) was synthesised in high yield from 3-chloro-2-cyclohexenone, and the phenylseleno-enone (193;X=SePh) and stannyl-enone (193;X=SnMe₃) were prepared in good yields from the chloro-enone (12). The procedure employed in the preparation of (193;X=SnMe₃) was also used to prepare the corresponding tributylstannyl-enone (86;X=SnBu₃), which was utilised in the Corey lactone studies described in Chapter 4.

Conjugate addition of organocuprate reagents to the various C-3 heterosubstituted enones proceeded well, with the exception of the pyrrolidino-enone (200a) and the nitrile (159). The pyrrolidino-enone (200a) may simply have been deactivated towards nucleophilic attack, by deprotonation at C-4. The nitrile (159) afforded only a moderate yield of the expected conjugate addition product, perhaps due to the vinyl nitrile moiety undergoing undesired side-reactions.

Protonation of the cyclopentenyl and cyclohexenyl-enolates (194) and (198), derived from the conjugate addition step, succeeded only for the enolate (198;R=Me, X=CN). Clearly this enolate is reasonably stable and further study of this system, e.g., its hydroxyalkylation with a reactive aldehyde such as formaldehyde, may be justified. Attempts to alkylate the cyclopentenyl-enolate (194; R=Me, X=SePh) or other cyclohexenyl-enolates of type (198) at C-2 were unsuccessful. The cause of this lack of desired reactivity could be attributed to the lability of the heterosubstituents in such enolates or to the inherently poor reactivity of organocuprate-derived enolates or, as seems most likely, to both factors. The results of this study do not allow the relative importance of these factors to be assessed.
In support of these findings, Coyle and Taylor et al.\textsuperscript{143} recently described their attempts to alkylate enolates of type (211), prepared by the conjugate addition of organocuprate reagents to dihydrothiin-4-ones, e.g., compound (212). Coyle and Taylor et al. found that the enolate (211) underwent ring-opening at -78 °C in preference to O-silylation or alkylation at C-2. These results confirm that, with the possible exception of the enolate (198;\(R=\text{Me, } X=\text{CN}\)), interception of enolates of type (194) and (198) by alkylation at C-2 is a highly unlikely process.

\[
\begin{align*}
\text{(211)} & \quad \text{(212)} \\
\text{M}^+ &= \text{undefined counter-cation}
\end{align*}
\]
6.1 INTRODUCTION

In Chapter 2 an approach to the Corey lactone (5a) utilizing the chloro-eneone (6a) is described. A crucial step in that approach was the substitution of the C-3 chloro substituent with a nucleophile which could later be transformed into a formal function by reaction of the amine with formaldehyde. This was accomplished with lithium di(benzzyloxy)methylcopper, a α-hydroxyethyl carbamion equivalent. This organocuprate reagent, which has been prepared and utilized for a variety of conjugate additions, conjugate reductions and related transformations, is particularly suitable for the preparation of alkyl and allylic groups to unsaturated carbonyl substrates.164 Organocuprate reagents are generally prepared by addition of either an organolithium or an organocopper reagent to a ketone17 or other an electrophile. Several types of organocuprate reagents have been reported, including lithium-nucleocuprates (711), α-lithio-α-cyclohexenocuprates (712), trans-α-lithio-α-cyclohexenocuprates (716) and α-ethoxy-α-cyclohexenocuprates (718). Both magnesium-exocuprates and lithium-exocuprates (712) are prepared as in the present work and may similarly be prepared according to equations (3) and (4).
6.1 Introduction

In Chapter 3 an approach to the Corey lactone (26) which utilizes the chloro-enone (86;X=Cl) is described. A crucial step in that approach was the substitution of the C-3 chloro substituent with a nucleophile which could later be transformed into a formyl function. Reaction of the chloro-enone (86;X=Cl) with several carbanionic reagents was explored including its attempted reaction with lithium di(benzyloxymethyl)copper, an hydroxymethyl carbanion equivalent. This last reaction was not described in Chapter 3 but the preparation and reaction of lithium di(benzyloxymethyl)copper with the chloro-enone (86;X=Cl) and other substrates are discussed in this Chapter.

Organocuprate reagents have been widely used in organic synthesis, particularly for the conjugate addition of alkyl and alkenyl groups to unsaturated carbonyl substrates. Organocuprate reagents are generally prepared by addition of either an organolithium or an organomagnesium reagent to a copper(I) salt, under an inert atmosphere. Several types of organocuprate reagents have been reported, including lithio-homocuprates (213), mixed lithio-homocuprates (214), lithio-heterocuprates (215) and magnesio-cuprates. Both magnesio-cuprates and lithio-homocuprates (213) are discussed in the present work and may typically be prepared according to Equations [3] and [4].
In recent years functionalised organocuprate reagents have been prepared such as the alkenylcuprate (16) which, as mentioned in Chapter 1, was employed in a prostaglandin synthesis. Other functionalised organocuprate reagents which are synthetically equivalent to oxidised one-, two-, or three-carbon units are listed in Table 1. It can be seen from this table that the majority of work in this area has been directed towards preparing two- and three-carbon synthons and only two reports deal with functionalised one-carbon synthons. Mukaiyama et al. reported that lithium bis[di(phenylthio)methyl]copper (Entry 1, Table 1) undergoes conjugate addition to the sterically unhindered methyl vinyl ketone in 50% yield. However, reaction of the same reagent with more hindered substrates was not described. Mukaiyama et al. also reported that the masked ester reagent, lithium bis[tri(phenylthio)methyl]copper (Entry 2, Table 1) reacted efficiently with a selection of more hindered acyclic C-2 conjugated enones at the C-3 position. In contrast to these results, Groebel and Seebach reported that the organocuprate reagent derived from 2-lithio-1,3-dithiane failed to react with conjugated enones.

Functionalised one-carbon organometallic reagents which are not based on copper have also been developed and these are discussed in Chapter 3. Their Michael addition to C-2 conjugated enones is only successful where the substrate and reagent structure permit and under appropriate reaction conditions. For example, reaction of 2-cyclopentenone with 2-lithio-1,3-dithiane gives the C-3 addition

* The stoichiometry of this type of reagent is unknown.
Table I

<table>
<thead>
<tr>
<th>Entry</th>
<th>Organocuprate Reagent</th>
<th>Equivalent</th>
<th>Reference</th>
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<td>ONE-CARBON UNITS</td>
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<tr>
<td>1</td>
<td>LiCu[CH(SPh)₂]₂</td>
<td>ΩCHO</td>
<td>145, 146</td>
</tr>
<tr>
<td>2</td>
<td>LiCu[C(SPh)₃]₂</td>
<td>ΩCO₂R</td>
<td>145, 146</td>
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<tr>
<td>TWO-CARBON UNITS</td>
<td></td>
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<td></td>
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<tr>
<td>3</td>
<td>LiCu((OEt)₂)</td>
<td>ΩC=O</td>
<td>147, 148</td>
</tr>
<tr>
<td>4</td>
<td>LiCu(SiMe₃)₂</td>
<td>ΩCH₂CHO</td>
<td>147</td>
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<tr>
<td>THREE-CARBON UNITS</td>
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<tr>
<td>5</td>
<td>Li(LigCu(CO₂Me)₂</td>
<td>ΩCO₂Me</td>
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<tr>
<td>6</td>
<td>Li[LigCu(CHOEt)₂]</td>
<td>ΩCHO</td>
<td>150, 151</td>
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<tr>
<td></td>
<td>Lig = 1-hexyne, thiophenoxide and 3,3-dimethyl-1-butyne</td>
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<td>152</td>
</tr>
<tr>
<td>7</td>
<td>LiCu(SiMe₃)₂</td>
<td>ΩRCHCHO</td>
<td>147</td>
</tr>
<tr>
<td>8</td>
<td>LiCu[(CH₂)₃OCH(OEt)Me]₂</td>
<td>ΩCH₂(CH₂)₂OH</td>
<td>153</td>
</tr>
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</table>
product (216) only in the presence of HMPA. However, where the C-3 position in the enone is sterically crowded, conjugate addition of reagents which are equivalent to the formyl carbanion can be disfavoured and C-1 addition predominates.

There are few functionalised organometallic reagents which are equivalent to oxidised one-carbon units that undergo conjugate addition to sterically hindered substrates, and those that do are either masked formyl or ester equivalents. An organocuprate reagent at the hydroxymethyl oxidation level has not been described in the literature and it is possible that such a reagent may be sterically less demanding than the masked formyl or ester reagents based on copper. To explore this, a study of the preparation and reactivity of an organocuprate reagent equivalent to the hydroxymethyl carbanion (\(\text{CH}_2\text{OH}\)) was undertaken. Two possible organocuprate reagents were investigated, the magnesio-cuprate (217) and the lithio-cuprate (218).

![Chemical structures](image)

The benzyl group was selected to protect the hydroxyl function for two reasons. First, organometallic reagents containing the benzyloxymethyl ligand generally have greater thermal stability than reagents containing an alkylloxymethyl ligand. Second, the benzyl group may simply be removed by hydrogenation when deprotection is required. Also, both benzyloxymethylmagnesium chloride and benzyloxymethylolithium, the
respective precursors to the magnesio-cuprate (217) and the lithio-cuprate (218), are reported to be available.

The synthesis of certain geminally heterosubstituted Grignard reagents \(155-157\) is reported to be a difficult operation, mainly because such highly reactive organomagnesium derivatives tend to undergo coupling reactions at approximately the same temperatures to those required for their preparation. This difficulty is clearly evident in the case of methoxymethylmagnesium chloride which has been prepared \(156\) in dimethoxymethane at between \(-5^\circ C\) to \(0^\circ C\) and decomposes above \(10^\circ C\) to give dimethoxyethane. \(155\) However, the potential precursor to the magnesio-cuprate (217), benzyloxymethylmagnesium chloride, was prepared from benzyl chloromethylether in unspecified yield at \(0^\circ C\) using amalgamated magnesium. Whilst still thermally sensitive, this Grignard reagent is reported to be more stable than methoxymethylmagnesium chloride. \(155\)

The potential precursor to the lithio-cuprate (218), benzyloxymethylolithium, was prepared by Still \(158(a)\) in high yield by transmetallation of benzyloxymethyl(tributyl)stannane (219) with butyllithium. The stannane (219) was prepared by the reaction of the sodium salt of benzyl alcohol with tributylstannylmethyl iodide. \(159\)

\[
\text{PhCH}_2\text{OCH}_2\text{SnBu}_3
\]

(219)

6.2 **Synthesis of a Benzyloxymethylcuprate Reagent**

Benzyl chloromethyl ether, which is required for the synthesis of the corresponding Grignard reagent, was obtained as a crude
product in good yield by the method of Connor et al.\textsuperscript{160} Stoichiometric quantities of benzyl alcohol and aqueous formaldehyde solution were saturated with gaseous hydrogen chloride. However, distillation of the crude product from this reaction gave benzyl chloride. This was presumably obtained by the decomposition of benzyl chloromethyl ether which occurred as a result of acid-catalysed attack of chloride anion at the benzylic carbon of benzyl chloromethyl ether. Distilled benzyl chloromethyl ether was eventually obtained by following the procedure of Hill and Keach\textsuperscript{161} wherein a 3:1 ratio of formaldehyde and benzyl alcohol were saturated with hydrogen chloride. The excess formaldehyde may have served to inhibit benzyl chloride formation by functioning as an acid-scavenger.

The synthesis of benzyloxymethylmagnesium chloride was attempted next following the method of Castro\textsuperscript{157} who used benzyl chloromethyl ether and amalgamated magnesium. Cyclohexanone was added to a portion of the reaction mixture obtained in this way to test if the Grignard reagent had been formed. However, none of the expected alcohol (220) was obtained. Hydrolytic work-up of the remainder gave a complex mixture which, by g.l.c. - mass spectrometry, comprised benzyl alcohol as the major product, di(benzyloxy)ethane which was presumably derived by oxidative coupling of the Grignard reagent, and only a trace of benzyl methyl ether which should be formed by protonation of the Grignard reagent. The prospects of generating synthetically useful quantities of benzyloxymethylmagnesium chloride were not good and attention was therefore directed towards preparing the lithio-cuprate (218).
Benzyloxyethyl(tributyl)stannane (219) was prepared as previously reported\textsuperscript{158,159} and transmetallation\textsuperscript{158} with butyllithium at -78 °C in THF afforded benzyloxyethylolithium in quantitative yield, as judged by \textsuperscript{1}H n.m.r. analysis for benzyl methyl ether which was obtained on hydrolytic work-up. Introduction of copper(I) iodide to a colourless solution of benzyloxyethylolithium in THF at -30 °C resulted in the formation of a grey heterogeneous mixture which, on treatment with the chloro-enone (86;X=Cl), afforded the C-1 addition product (221) as a single diastereoisomer in 71\% yield. Since organocuprate reagents do not usually react with unsaturated carbonyl substrates \textit{via} this mode of addition\textsuperscript{*}, it is likely that compound (221) was derived from the lithium reagent and not the corresponding lithio-cuprate reagent. The heterogeneous nature of the reagents may have prevented organocuprate formation and so a soluble copper source was used. Addition of an ethereal solution of copper(I) bromide-dimethyl sulphide to benzyloxyethylolithium in THF at -50 °C afforded a pale-yellow solution. The reagent thus prepared failed to react with the chloro-enone (86;X=Cl) either at C-1 or C-3, which suggested that the benzyloxyethylolithium had been consumed. Also, when the reaction was

\textsuperscript{*} For the only reported exception to this general observation see Entry 5, Table 1. The possibility that the proposed organocuprate reagent had not been formed in that case should not be overlooked.
quenched with D$_2$O, deuterium was not incorporated into the chloro-enone (86;X=Cl) as judged from its mass spectrum. This indicated that enolisation of the substrate had not occurred either. Addition of the less hindered 2-cyclohexenone to a solution of this reagent, however, afforded the benzyloxymethyl-ketone (222) (Table 2, p.153) in 80\% yield, confirming that lithium di(benzyloxymethyl)copper (218) had indeed been formed. The benzyloxymethyl-ketone (222) exhibited a molecular ion at m/z 218 and infrared absorption at 1712 cm$^{-1}$. In its $^1$H n.m.r. spectrum compound (222) exhibited signals at 67.28, 4.49 and 3.42 which were attributed to the phenyl protons, the benzyl methylene protons and the remaining acyclic methylene protons.

The marked difference in reactivity of the lithio-cuprate (218) towards the chloro-enone (86;X=Cl) and 2-cyclohexenone was probably caused by steric and/or electronic differences between the substrates. House$^{96}$ demonstrated that the reactivity of an unsaturated carbonyl substrate towards an organocuprate reagent is linked to its half-wave reduction potential ($E_{\text{red}}$) and that provided the $E_{\text{red}}$ value lies within the range -1.3 to -2.3V, conjugate addition should occur. Also, the half-wave oxidation potential ($E_{\text{ox}}$) of the organocuprate reagent generally needs to be within 0.4V of the $E_{\text{red}}$ value.

An indication of the reactivity of the lithio-cuprate (218) was obtained from its reaction with a selection of unsaturated carbonyl substrates. The $E_{\text{red}}$ values of these substrates were measured to assist with the interpretation of the results obtained.

6.3 Reactivity of Lithium di(benzyloxymethyl)copper (218)

Prior to further discussion on the reactivity of the lithio-cuprate (218) comment needs to be made regarding its thermal
stability. Like other functionalised organocuprate reagents\(^{147}\), lithium di(benzyloxymethyl)copper (218) was found to be thermally sensitive and between \(-15^\circ C\) and \(-10^\circ C\) a pale-yellow solution of (218) rapidly darkened to give a black solution which failed to react with 2-cyclohexenone. Clearly, decomposition of the lithio-cuprate (218) had occurred and this thermal instability will prevent its use at temperatures above \(-15^\circ C\), temperatures which may be required to effect conjugate addition to the less reactive sterically hindered substrates.

The lack of reactivity of the lithio-cuprate (218) towards the chloro-enone (86;\(X=\text{Cl}\)) is quite surprising on electronic grounds because the inductive effect exerted by the C-3 chloro substituent should make electron transfer to (86;\(X=\text{Cl}\)) a more favourable process than in the case of 2-cyclohexenone. Measurement of the reduction potentials of both of these compounds indeed verified that the chloro-enone (86;\(X=\text{Cl}\)) (\(E_{\text{red}} = -1.77V\)) is more easily reduced than 2-cyclohexenone (224) (\(E_{\text{red}} = -1.96V\)). From this it appears that steric rather than electronic factors suppressed the conjugate addition of the lithio-cuprate (218) to the chloro-enone (86;\(X=\text{Cl}\)).

Table 2 shows the effect of substitution at the \(\Delta^{2,3}\)-bond of the substrate on its reactivity towards the lithio-cuprate (218), all reactions except one being carried out under identical conditions (see Table 2, footnote (a)). Unsaturated ketones, monosubstituted and disubstituted at the double bond, e.g., (223), (224), (225) and (227),
### Table 2

**A. Conjugated Olefinic ketones (unhindered)**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$E_{\text{red}}^{(b)}$ measured (Volts)</th>
<th>$E_{\text{red}}^{(c)}$ calculated (Volts)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCH$_2$O</td>
<td>-1.86 (-2.10)</td>
<td></td>
<td>PhCH$_2$O</td>
<td>82</td>
</tr>
<tr>
<td>Me$^-$</td>
<td>-1.96 (-2.10)</td>
<td></td>
<td>Me$^-$</td>
<td>71</td>
</tr>
<tr>
<td>PhCH$_2$OCH$_2$(CH$_2$)$_2$COMe</td>
<td>-1.97 (-2.00)</td>
<td></td>
<td>PhCH$_2$OCH$_2$(CH$_2$)$_2$COMe</td>
<td>51</td>
</tr>
<tr>
<td>Me$^-$</td>
<td>-2.08 (-2.10)</td>
<td></td>
<td>Me$^-$</td>
<td>-</td>
</tr>
<tr>
<td>PhCH$_2$OCH$_2$(Me)CHCH$_2$OMe</td>
<td>-2.08 (-2.10)</td>
<td></td>
<td>PhCH$_2$OCH$_2$(Me)CHCH$_2$OMe</td>
<td>58</td>
</tr>
<tr>
<td>Substrate</td>
<td>$E_{\text{red}}^{(b)}$ measured</td>
<td>$E_{\text{red}}^{(c)}$ calculated</td>
<td>Product</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------------------</td>
<td>---------------------------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image1" alt="Image of substrate" /></td>
<td>-1.77</td>
<td>-2.20</td>
<td><img src="image2" alt="Product image" /></td>
<td>8</td>
</tr>
<tr>
<td>(86; $X = \text{Cl}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image3" alt="Image of substrate" /></td>
<td>-2.02</td>
<td>-2.20</td>
<td><img src="image4" alt="Product image" /></td>
<td></td>
</tr>
<tr>
<td>(228)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image5" alt="Image of substrate" /></td>
<td>-2.12</td>
<td>-2.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(229)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image6" alt="Image of substrate" /></td>
<td>-2.14</td>
<td>-2.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(230)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### C. Conjugated Unsaturated Esters

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$E_{\text{red}}$&lt;sup&gt;(b)&lt;/sup&gt; measured (Volts)</th>
<th>$E_{\text{red}}$&lt;sup&gt;(c)&lt;/sup&gt; calculated</th>
<th>Product</th>
<th>Yield&lt;sup&gt;(a)&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\equiv$-CO$_2$Me</td>
<td>-2.10</td>
<td>-2.10</td>
<td>PhH$_2$CO$_2$Me</td>
<td>82</td>
</tr>
<tr>
<td>(231)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\equiv$-CO$_2$Me</td>
<td>-2.00</td>
<td>-2.20</td>
<td>PhCH$_2$O(CH$_2$)$_3$CO$_2$Me</td>
<td>30</td>
</tr>
<tr>
<td>(232)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>-2.26</td>
<td>-2.30</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(233)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(a) Most of these results were obtained under identical conditions using similar quantities of reagents, the lithio-cuprate (218) and the substrate were reacted at -50 °C for 30 min., warmed to -15 °C and quenched. The only exception was methyl propiolate which was reacted at -40 °C for 30 min. and then quenched.

(b) $E_{\text{red}}$ measurement details are given in the Experimental.

(c) $E_{\text{red}}$ values were calculated using the method of House <i>et al.</i> 96

(d) I am grateful for the sample of pinocarvone supplied by Dr. R. Stephenson, prepared by selenium dioxide-oxidation of pinene. 162

(e) $E_{\text{red}}$ for 3-butenone was measured by House <i>et al.</i> 96
gave moderate to good yields of the desired C-3 addition products. However, 2-cyclopentenone (226) failed to give any of the corresponding C-3 addition product (236), a result which may be partly attributed to the reactive nature of the substrate, which readily undergoes polymerisation. Introduction of a third substituent to the $\Delta^{2,3}$-bond, e.g., (86; $X=Cl$), (228), (229) and (230), severely retarded conjugate addition and, except in the case of carvone (228), no C-3 addition products were obtained. Carvone, which has a 2,2,3-trisubstituted double bond, gave a low yield of the ketone (238), the stereochemistry of which was not determined.

A similar trend was observed for the unsaturated esters (231), (232) and (233). When methyl propiolate (231) was reacted with the lithio-cuprate (218) at -50 °C, the (E)-ester (239) was obtained in 82% yield. The $E$ configuration of the double bond was established from its $^1H$ n.m.r. spectrum wherein a large coupling constant $J_{2,3}$ 16 Hz was observed. The $E$ configuration of the double bond was expected on the basis of work by Corey et al. 163 who had previously described the "cis addition" of organocuprate reagents to alkynyl esters at -78 °C.

A marked decrease in the reactivity of the lithio-cuprate (218) was observed towards methyl acrylate (232), giving only a 30% yield of the C-3 addition product (240). Where the steric hindrance of the olefinic ester is further increased, e.g., as in ethyl crotonate (233), reaction with the lithio-cuprate (218) afforded none of the C-3 addition product. In addition to this trend of decreasing reactivity with increased steric hindrance, a difference between the reactivity of the lithio-cuprate (218) towards unsaturated ketones and unsaturated esters is apparent. For example, 3-pentenone (227), which possesses a disubstituted double bond, reacts with the lithio-cuprate (218) to
furnish the conjugate addition product (237) in 58% yield. In contrast, ethyl crotonate (233), which also possesses a disubstituted double bond, gave no conjugate addition product. Although rather tentative, this result suggests that the lithio-cuprate (218) is more reactive towards unsaturated ketones than towards unsaturated esters.

Thus, having investigated the reactivity of the lithio-cuprate (218) towards unsaturated ketones and esters, liberation of the hydroxyl function by hydrogenolysis of the benzyl group was then investigated.

6.4 Liberation of the Hydroxymethyl Function

Liberation of the masked hydroxymethyl group in the benzyloxymethyl-ketone (222) was first attempted by hydrogenation over a palladium/charcoal catalyst in methanol. In addition to the required debenzylation, however, ketalisation of the carbonyl group also occurred to furnish the dimethyl-ketal (241) in quantitative yield. In its $^1$H n.m.r. spectrum the dimethyl-ketal (241) exhibited two singlets at 3.15 and 3.09 which were attributed to the diastereotopic methoxyl substituents. Assignment of these signals to the axial and equatorial methoxyl groups was not attempted. The infrared spectrum showed broad absorption at 3420 cm$^{-1}$ which confirmed the presence of an hydroxyl group and absorption characteristic of a carbonyl group was not observed. The reason for the facile generation of the ketal is not fully understood, however, the slight acidity of the palladium/charcoal catalyst may have been sufficient to promote ketalisation.
Hydrogenolysis of the benzyl group without concomitant ketalisation was effected in THF to give the hydroxymethyl-ketone (242) in quantitative yield. The infrared spectrum of compound (242) indicated the presence of both hydroxyl and carbonyl functions and the spectral data obtained were in good agreement with those of Matuszak and Dickson who prepared the hydroxymethyl-ketone (242) via a different route.

6.5 Conclusion

In this study, lithium di(benzyloxy)methylcopper (218) was efficiently generated from benzyloxyethyl lithium and copper(I) bromide-dimethyl sulphide. Below -15 °C, the lithio-cuprate (218) underwent conjugate addition to unhindered, unsaturated ketone and ester substrates in moderate to good yields. However, as the steric hindrance of the substrate increased, conjugate addition was found to be severely retarded and this lack of reactivity could not be overcome by using higher temperatures because the lithio-cuprate (218) was unstable above -15 °C. The reactivity of the reagent, lithium di(benzyloxy)methylcopper (218), seems to be controlled more by steric constraints associated with the substrate than by electronic factors, at least within the substrate $E_{\text{red}}$ range of -1.77 to -2.26V.
Since the completion of this study, Lipshutz et al.\textsuperscript{168} has reported that higher-order cuprates of the general formula, $R_2\text{Cu(CN)}\text{Li}_2$, react efficiently and at low temperature with hindered substrates. Moreover, these higher-order cuprates were found to react with $\beta$-substituted conjugated enoates in high yields.\textsuperscript{169} In the light of these results it is feasible that a higher-order benzyloxy methyl-cuprate reagent might react more efficiently with the sterically hindered substrates used in this study.

In principle, all the conjugate addition products can simply be deprotected by catalytic hydrogenation to give the corresponding alcohol. This is exemplified for the benzyloxy-ketone (222) which was smoothly hydrogenated to give the hydroxymethyl-ketone (242). Thus, the lithio-cuprate (218) has been prepared in high yield and its application as a novel and potentially useful source of the hydroxymethyl carbanion has been established.
Notes on Nomenclature

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

   ![1-oxabicyclo[3.4.0]nonane](image)

   1-oxabicyclo[3.4.0]nonane

   ![1-oxabicyclo[3.3.0]octane](image)

   1-oxabicyclo[3.3.0]octane

2. Some compounds in this thesis are depicted as having been resolved. Resolved intermediates were not in fact used and this convention has been adopted to depict relative stereochemistry only.
EXPERIMENTAL

General

Melting points were determined on a Kofler microheating stage and are uncorrected. Elemental analyses were performed by the Microanalytical Unit of the Australian National University. Infrared spectra were obtained on neat samples between sodium chloride plates unless otherwise specified and were recorded on Perkin-Elmer 257 or Perkin-Elmer 683 spectrophotometers, using polystyrene (1602 cm⁻¹) as an external reference.

¹H n.m.r. spectra were obtained on a Jeol Minimar 100 MHz high resolution NMR spectrometer, a Varian HA-100 NMR spectrometer or a JNM-FX 200 Fourier Transform NMR spectrometer. Chemical shifts are given in p.p.m. downfield from tetramethylsilane (internal reference) and multiplicities are abbreviated: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad; and exch. = exchanges with D₂O. ¹H n.m.r. spectra were obtained using deuteriochloroform as solvent unless otherwise specified.

Ultraviolet spectra were recorded on a Pye-Unicam SP 800 spectrophotometer or on a Varian DMS 90 Ultraviolet-Visible spectrophotometer coupled to a Hewlett-Packard 7015B X-Y Recorder. Holmium (360.1 nm) was used as an external reference. Mass spectra were run at 70 eV on either a V.G. Micromass 7070F spectrometer or a GEC-AEI MS-902 spectrometer. Accurate mass measurement was obtained on the AEI MS-902 spectrometer using heptacosa as reference compound. Mass spectral data for ions containing chlorine, selenium or tin are quoted for the most abundant isotopes. In the case of ions containing chlorine, ³⁷Cl and ³⁵Cl peaks are given for the heaviest ions observed. For lighter ions which contain chlorine, only the ³⁵Cl peak is quoted.
and it is denoted with an asterisk. Combined g.l.c. - mass spectral analyses were carried out on a Varian MAT-111 with a 72 x 1/8 in. i.d. glass column containing 2% OV-17 on 80-100 mesh Chromosorb Q.

Routine g.l.c. analyses were carried out on a Varian Aerograph Series 1400 instrument coupled to a Hewlett-Packard 3380A integrator and preparative g.l.c. was carried out on a Varian Aerograph Series 1700 instrument, using glass columns containing 2% OV-17 on 80-100 mesh Chromosorb Q, unless otherwise specified. All g.l.c. analyses assume a unit detector response.

**Polarographic Measurements**

Polarography was performed using a conventional three electrode system with iR drop compensation and a PAR Model 170 analyser. A dropping mercury electrode (d.m.e.), working electrode, platinum coil auxiliary electrode and Ag/AgCl (saturated LiCl) reference electrode (separated from the working compartment via a fine porosity frit), were employed. Solutions were degassed through a standard purge tube, with solvent saturated argon. The solvent employed was freshly distilled, anhydrous N,N-dimethylformamide, containing tetrabutylammonium tetrafluoroborate (10⁻¹ M). Concentrations of the electroactive species were typically 10⁻³ M and studies were performed at ambient temperature (20 ± 2 °C).

Reduction potentials were assigned from direct current polarograms (\(E_0\)) or from the maximum of the low frequency (20 Hz < \(\omega\) < 80 Hz) in-phase alternating current polarogram (\(E_p\)). In all cases the differences between \(E_0\) and \(E_p\) were less than 0.03 V; thus either technique defined the reduction potential (\(E_{red}\)) within experimental error.
**Materials**

Petrol refers to light petroleum of b.p. 40-60 °C. THF and diethyl ether were distilled from sodium benzophenone ketyl immediately prior to use. Dichloromethane used in reactions was distilled from phosphorus pentoxide and stored over activated 4 Å molecular sieves. Reactions were routinely performed under an atmosphere of anhydrous nitrogen using a magnetic stirrer bar, unless otherwise stated.

Merck Kieselgel 60 F<sub>254</sub> was used for t.l.c. and Merck Kieselgel 60 was used for column chromatography, unless otherwise specified. Thin layer chromatograms were developed with either iodine or molybdophosphoric acid (5% in ethanol). Merck Kieselgel 60 (230-400 mesh) was used for 'flash' chromatography.

Copper(I) iodide was continuously extracted with THF in a Soxhlet extractor for 24 hr and dried *in vacuo* at room temperature under a flow of nitrogen and in the dark, prior to use. Copper(I) bromide-dimethyl sulphide complex was obtained using copper(I) bromide, pre-purified by Soxhlet extraction with THF, and dimethyl sulphide which was freshly distilled from calcium hydride. The chloro-enone (86;X=Cl) was obtained by the method of Rickards *et al.* and potassium t-butoxide was purified by sublimation at 190 °C and 0.005 mmHg.

**General Procedures**

*Lithium dimethylcopper*

To a slurry of copper(I) iodide (0.5 mmol) in THF (2 ml) at 0 °C was added methyllithium in diethyl ether. The copper(I) iodide dissolved to give a tan solution of lithium dimethylcopper.
Lithium diisopropylamide

This reagent was prepared by dropwise addition of butyllithium (2 mmol) to a cold (0 °C) solution of diisopropylamine (2 mmol) in THF and subsequently stirring for 30 min.
CHAPTER 2

Reaction of complexed lithium phenylselenide with 2-cyclohexenone and ethanol

To a yellow solution of diphenyldiselenide in THF (1 ml, 0.5M) at 0 °C was added lithium tri-sec-butylborohydride in THF (1 ml, 1M). The resultant colourless solution was warmed to room temperature after which absolute ethanol (0.036 ml, 1 mmol) and 2-cyclohexenone (83 mg, 0.86 mmol) also in THF (2 ml) were added. The reaction was stirred for 4.5 hr whereupon saturated aqueous ammonium chloride (25 ml) was added and the mixture was extracted with diethyl ether (2 x 25 ml). The extracts were dried (MgSO₄) and evaporated to afford, after chromatography on silica gel in methylene dichloride-methanol (100:1 v/v), recovered 2-cyclohexenone (54 mg, 65%) and 3-phenylselenocyclohexanone (108) (18 mg, 8%).

Attempted reaction of complexed lithium phenylselenide with 2-cyclohexenone and methyl iodide

The previous reaction was repeated except that ethanol was replaced with methyl iodide (142 mg, 1 mmol). The reaction was worked-up as previously and chromatography on silica gel in methylene dichloride-methanol (100:1 v/v) afforded recovered 2-cyclohexenone (69 mg, 83%) and methyl phenylselenide (38 mg, 22%).

Reaction of complexed potassium phenylselenide with 2-cyclohexenone and ethanol

To a yellow solution of diphenyldiselenide in THF (0.5 ml, 0.5M) at room temperature was added potassium tri-sec-butylborohydride in THF (0.5 ml, 1M). Ethanol (23 mg, 0.5 mmol) and 2-cyclohexenone (45 mg,
0.47 mmol) also in THF (0.5 ml) containing HMPA (89 mg, 0.5 mmol) were sequentially added. The colourless solution was stirred for 1 hr, diluted with saturated aqueous ammonium chloride (25 ml) and then extracted with diethyl ether (3 x 25 ml). The extracts were washed with brine (2 x 25 ml), dried (MgSO₄) and evaporated to afford, after preparative t.l.c. on silica gel in methylene dichloride, recovered starting material (34 mg, 75%) and none of the ketone (108).

Reaction of uncomplexed lithium phenylselenide with 2-cyclohexenone and allyl iodide

To a solution of phenylselenol (314 mg, 2 mmol) in diethyl ether at 0 °C was added methyllithium in diethyl ether (1.13 ml, 1.77M). The mixture was warmed to room temperature and, after 1.5 hr, 2-cyclohexenone (182 mg, 1.9 mmol) in diethyl ether (0.5 ml) was added. Freshly distilled allyl iodide (0.37 ml, 4 mmol) was introduced after 15 min. and then the mixture was stirred for a further 1 hr before ice-cold water (10 ml) was added. The mixture was extracted with diethyl ether (3 x 25 ml), the extracts were washed with brine (25 ml), dried (MgSO₄) and evaporated to yield a pale-yellow oil (495 mg). Preparative t.l.c. on silica gel in methylene dichloride-methanol (100:1 v/v) gave 2-(3'-oxocyclohexyl)-2-cyclohexenone (111) (67 mg, 37%) as a colourless oil [Kugelrohr, b.p. 65 °C at 0.7 mmHg (lit.170 132-134 °C at 4.0 mmHg)]

(Found: C, 75.03; H, 8.28. C₁₂H₁₆O₂ requires C, 74.95; H, 8.39%), νmax. 1 705 and 1 665 cm⁻¹, δ6.73 (1 H, t, J 6 Hz, 3-H), 3.20-1.50 (15 H, m, remaining H), in agreement with reported values.170 Some allyl phenylselenide was also observed.
**Coupling between 2-cyclohexenone, phenylselenomagnesium iodide and isobutyraldehyde**

To a solution of phenylselenol (314 mg, 2 mmol) in diethyl ether (2 ml) was added methylmagnesium iodide (1.1 ml, 1.79M) and the resulting solution was stirred until the evolution of gas ceased. To this solution of phenylselenomagnesium iodide at 0 °C was added dropwise, a solution of 2-cyclohexenone (192 mg, 2 mmol) and isobutyraldehyde (168 mg, 2 mmol) in diethyl ether (2 ml) over 2 min. The resultant mixture was maintained at room temperature for 3 hr, poured into a large excess of aqueous saturated ammonium chloride and then extracted with diethyl ether (2 x 50 ml). The extracts were dried (MgSO₄) and evaporated to yield a yellow oil (629 mg). Chromatography of this oil on silica gel in methylene dichloride-methanol (100:1 v/v) furnished 2-(1'-hydroxyisobutyl)-3-phenylselenocyclohexanone (114) (111 mg, 17%), m/z (%): 308 (M⁺-H₂O, 38), 151 (M⁺-H₂O-C₆H₅Se, 100), some other unidentified products were also obtained.

**Reaction of 2-cyclohexenone with phenylselenomagnesium iodide and formaldehyde**

To a cold (0 °C) solution of phenylselenol (314 mg, 2 mmol) in diethyl ether (0.64 ml), placed in an efficient hood, was added dropwise a solution of methylmagnesium iodide (1.36 ml, 1.5M) in diethyl ether. After 30 min., 2-cyclohexenone (192 mg, 2 mmol) and formaldehyde in THF (3.3 ml, 1.65M) were added and the mixture was stirred at room temperature for 1.5 hr. The reaction was quenched with saturated aqueous ammonium chloride (5 ml) and extracted with diethyl ether (3 x 25 ml). The extracts were washed with brine (25 ml), dried and evaporated to afford a viscous gum (510 mg). Chromatography on silica gel in methylene dichloride-methanol (50:1 v/v) gave 3-phenylselenocyclohexanone (108) (128 mg, 36%) and 2-hydroxymethyl-
2-cyclohexenone (116) (106 mg, 42%) as a colourless oil which decomposed on distillation (Found: $M^+$, 126.0675. $C_7H_{10}O_2$ requires $M$, 126.0681), $\nu_{\text{max}}$ 3420 and 1668 cm$^{-1}$, m/z (%) 126 ($M^+$, 83), 108 (100), and 98 (49), $\delta$ 6.92 (1 H, $J$ 4 Hz, 3-H), 4.22 (2 H, s, 1'-H), 2.80-1.90 (7 H, t, m, remaining ring-H and OH).

3-Phenylselenocyclohexanone (108)

The ketone (108) was prepared from phenylselenol and 2-cyclohexenone according to the procedure of Pluijm and Wynberg$^{71}$ in 64% yield [b.p. 155 °C at 0.65 mmHg (lit.$^{71}$ 130 °C at 0.1 mmHg)], $\nu_{\text{max}}$ 1710 cm$^{-1}$, 67.65-7.20 (5 H, m, Ph), 3.48 (1 H, m, 3-H), 2.95-1.50 (8 H, m, ring-H).

Enolisation of the ketone (108) and subsequent reaction with chlorotrimethylsilane

A solution of lithium diisopropylamide in THF (1 ml, 0.25 M) containing HMPA (45 mg, 0.25 mmol) was cooled to -65 °C. A solution of the ketone (108) (53 mg, 0.21 mmol) in HMPA (46 mg, 0.25 mmol) was added dropwise and, after 30 min., freshly distilled chlorotrimethylsilane (0.15 ml, 1.6 mmol) was introduced. The reaction was allowed to warm to room temperature, poured into ice-cold water (25 ml) and extracted with diethyl ether (3 x 25 ml). The extracts were dried ($\text{MgSO}_4$) and evaporated to afford a yellow oil (66 mg). Preparative t.l.c. on silica gel in methylene dichloride-methanol (100:1 v/v) gave recovered compound (108) (11 mg, 21%) and 2-cyclohexenone (13 mg, 60%).

Trimethylsilylphenylselenide

Trimethylsilylphenylselenide was prepared by treating diphenyldiselenide with sodium in THF according to the procedure of
Liotta, quenching the resultant sodium phenylselenide with chlorotrimethylsilane. This procedure gave trimethylsilylphenylselenide in 67% yield as a foul-smelling yellow oil (Kugelrohr, b.p. 49 °C at 0.5 mmHg), δ 7.82-7.36 (5 H, m, Ph) and 0.37 (9 H, s, Me₃Si).

3-Phenylseleno-1-trimethylsilyloxy cyclohexene (102)

2-Cyclohexenone (157 mg, 1.6 mmol), trimethylsilylphenylselenide (348 mg, 1.6 mmol) and potassium cyanide/18-crown-6 complex (6 mg) were stirred for 24 hr. The yellow oil was diluted with diethyl ether (50 ml) and rapidly washed with ice-cold aqueous sodium hydrogencarbonate (25 ml). The etheral layer was dried (MgSO₄) and evaporated to yield the silylenol ether (102) (449 mg, 90%) as a pale-yellow oil, δ 7.7-7.2 (5 H, m, Ph), 5.08 (1 H, d, J 4 Hz, 2-H), 4.10 (1 H, m, 3-H), 2.10-1.50 (6 H, m, remaining ring-H), 0.18 (9 H, s, SiMe₂).

Reaction of the silylenol ether (102) with tetrabutylammonium fluoride and benzaldehyde

To a THF solution of tetrabutylammonium fluoride (0.04 ml, 10 mol %) at -78 °C was rapidly added a mixture of the silylenol ether (102) (81 mg, 0.25 mmol) and freshly distilled benzaldehyde (29 mg, 0.27 mmol) in THF (1 ml). The resulting solution was stirred at -78 °C for 3.5 hr, poured into a large amount of hexane (100 ml) and washed with ice-cold water (25 ml). The organic layer was dried (MgSO₄) and evaporated to yield a yellow oil (55 mg). An ¹H n.m.r. spectrum of this oil confirmed, by the olefinic proton signals, the presence of recovered silylenol ether (102) (16%), 2-cyclohexenone (55%) and, by integration of the signal due to the aldehyde proton, benzaldehyde (>90%).
CHAPTER 3

2-Lithiobenzothiazole

Freshly distilled benzothiazole (135 mg, 1 mmol) was added dropwise to a solution of butyllithium in hexane (0.613 ml, 1 mmol) in diethyl ether (3 ml) at -78 °C. A yellow precipitate formed immediately and the reaction was quenched after 30 min., by pouring into deuterium oxide (5 ml). The mixture was extracted with diethyl ether (2 x 25 ml) and the extracts were washed with brine (25 ml), dried (MgSO₄) and evaporated to afford 2-deuteriobenzothiazole (130 mg, 96%). Deuterium incorporation was quantitative as judged by ¹H n.m.r. spectroscopy, no signal was observed at δ9.10 for the C-2 proton.

Reaction of the chloro-enone (86; X=Cl) with 2-lithiobenzothiazole at -78 °C

To a suspension of 2-lithiobenzothiazole in diethyl ether (1 ml, 0.33M) at -78 °C was added a solution of the chloro-enone (86; X=Cl) (62 mg, 0.25 mmol) in diethyl ether (1 ml). The yellow precipitate of the reagent immediately dissolved and, after 30 min., the reaction was quenched with saturated aqueous ammonium chloride (5 ml), further diluted with water (25 ml) and extracted with diethyl ether (2 x 25 ml). The extracts were washed with brine (25 ml), dried (MgSO₄) and evaporated to afford a pale-yellow oil (103 mg). This oil was subjected to preparative t.l.c. on silica gel in methylene dichloride-methanol (50:1 v/v) to give 1-benzothiazol-4-yl-4-(t-butyldimethylsilyloxy)-3-chloro-2-cyclopentenol (134) (78 mg, 82%) as a pale-yellow liquid after distillation (Kugelrohr, b.p. 80 °C at 0.03 mmHg) (Found: C, 56.89; H, 6.12; Cl, 9.12; N, 3.58; S, 8.53. C₁₈H₂₄ClNO₂SSi requires C, 56.60; H, 6.33; Cl, 9.28; N, 3.67; S, 8.39%) (Found: M⁺-Bu⁺, 324.0277.
C_{14}H_{15}ClNO_2Si requires M-Bu^+, 324.0281; \nu_{max} 3315 \text{ cm}^{-1}, m/z (%) 368/366 (M^+-Me, 3), 324[M^+-Bu^+, 100], 288 (M^+-Bu^+-HCl, 34), 214 (85) metastable 256 (324-288), 88.00-7.30 (4 H, m, aromatic-H), 6.01 (1 H, s, 2-H), 4.87 (1 H, dd, J 7 and 4 Hz, 4-H), 4.03 (1 H, br s exch.,OH), 3.20 (1 H, dd, J 15 and 7 Hz, 5-H cis to 4-H), 2.30 (1 H, dd, J 15 and 4 Hz, 5-H trans to 4-H), 0.92 (9 H, s, Bu^+), 0.16 and 0.14 (each 3 H, s, SiMe_2).

Reaction of the chloro-enone (86; \textit{X}=Cl) with 2-lithiobenzothiazole in THF/HMPA:

(a) at 22 °C

To a suspension of 2-lithiobenzothiazole in THF (1 ml, 0.3M) at -78 °C was added the chloro-enone (86; \textit{X}=Cl) (56 mg, 0.23 mmol) in THF (0.5 ml). HMPA (89 mg, 0.5 mmol) was introduced \textit{via} syringe after 10 min. and the green solution was gradually warmed to 22 °C. After 1 hr the solution was poured into saturated aqueous ammonium chloride (5 ml), diluted with water (25 ml) and extracted with diethyl ether (2 x 25 ml). The extracts were washed with brine (25 ml), dried (MgSO_4) and evaporated to yield the \textit{alcohol} (134) (73 mg, 82%).

(b) at -20 °C

To a solution of 2-lithiobenzothiazole in THF (1 ml, 0.3M) at -20 °C was added HMPA (89 mg, 0.5 mmol) and the chloro-enone (86; \textit{X}=Cl) (60 mg, 0.24 mmol) dissolved in THF (5 ml). After 30 min., the solution was poured into saturated aqueous ammonium chloride (5 ml), diluted with water and extracted with diethyl ether (2 x 25 ml). The extracts were washed with brine (25 ml), dried (MgSO_4) and evaporated to afford the \textit{alcohol} (134) (60 mg, 65%) and the \textit{chloro-enone} (86; \textit{X}=Cl) (19 mg, 32%).
2-Lithio-1,3-dithiane

To a stirred solution of 1,3-dithiane (74 mg, 0.61M) in THF (1 ml) at -20 °C was added butyllithium in hexane (0.38 ml, 0.61 mmol) via syringe. After 1 hr an aliquot was removed, added to deuterium oxide (0.5 ml) and the mixture was then extracted with diethyl ether. The extracts were dried (MgSO₄) and the solvent evaporated to give 2-deuterio-1,3-dithiane, containing almost 50% deuterium in the C-2 position (i.e., 1 H exchanged with D almost to the extent of 100%). Deuterium incorporation was 92% as estimated by mass spectrometry of the residue [m/z 121 (M⁺)D/120 (M⁺)H: 92/8, taking into consideration the contribution to the ion at m/z 121 from the undeuterated species].

Reaction of the chloro-enone (86; X=Cl) with 2-lithio-1,3-dithiane in THF

To a stirred solution of 2-lithio-1,3-dithiane in THF (1 ml, 0.6 M) at -78 °C was added dropwise a solution of the chloro-enone (86; X=Cl) (120 mg, 0.49 mmol), in THF (1 ml). The solution immediately became yellow and, after 15 min., the reaction was quenched with aqueous ammonium chloride. The mixture was extracted with diethyl ether (2 x 25 ml) and the extracts were washed with saturated brine (25 ml), dried (MgSO₄) and evaporated to afford a pale-yellow oil. Preparative t.l.c. of this oil on silica gel in methylene dichloride-methanol (50:1 v/v) gave recovered chloro-enone (86; X=Cl) (19 mg, 16%) and 4-(t-butyldimethyldisiloxyl)-3-chloro-1-[2'-(1,3'-dithianyl)]-2-cyclopentenol (135) (113 mg, 69%) as a pale-yellow oil which by ¹H n.m.r. spectroscopy and t.l.c. consisted of one diastereoisomer (Kugelrohr, b.p. 80 °C at 0.05 mmHg) (Found: C, 49.18; H, 7.30; Cl, 9.71; S, 17.69. C₁₅H₂₇D₂Cl₂Si₂ requires C, 49.08; H, 7.41; Cl, 9.66; S, 17.47%) (Found: M⁺, 336.0896.
C_{15}H_{27}O_{2}ClSi requires M, 336.0910, \nu_{\text{max}}. \ 3420 \text{ and } 1 \text{,} 625 \text{ cm}^{-1}, m/z (\%) 368/366 (M^+, <1), 351*(M^+-Me, <1), 348*(M^+-H_2O, 4), 309*(M^+-Bu^+, 19), 291*(M^+-Bu^+-H_2O, 2), 273*(11), 217*(26), 120(C_4H_8S_2, 78), 119 (C_4H_7S_2, 100), 65.91 (1 H, s, 2-H), 4.58 (1 H, dd, J 7 and 5 Hz, 4-H), 4.16 (1 H, s, SCH), 3.00-2.60 (6 H, m, SCH_2CH_2CH_2S, OH and 5-H cis to 4-H), 2.10-1.70 (3 H, m, SCH_2CH_2CH_2S and 5-H trans to 4-H), 0.92 (9 H, s, Bu^+), 0.14 (6 H, s, SiMe_2).

Reaction of the chloro-enone (86;X=Cl) with 2-lithio-1,3-dithiane in THF/HMPA
(a) at -78 °C

The preceding reaction was repeated in the presence of two equivalents of HMPA which was added before the chloro-enone (86;X=Cl). The reaction was quenched as previously to give a yellow oil. Preparative t.l.c. of this oil on silica gel in methylene dichloride-methanol (50:1 v/v) gave the chloro-enone (86;X=Cl) (35 mg, 32%), the alcohol (135) (62 mg, 40%) and 4-(t-butyldimethylsilyloxy)-3-[2'-(1',3'-dithianyl)]-2-cyclopentenone (136) (15 mg, 8%) (Found: M^+, 330.1141. C_{15}H_{26}O_{2}Si requires M, 330.1143), \nu_{\text{max}}. 1 \text{,} 722 \text{ and } 1 \text{,} 620 \text{ cm}^{-1}, m/z (\%) 330 (M^+, <1), 315 (M^+-Me, 2), 273 (M^+-Bu^+, 100), 198 (36), 86.28 (1 H, s, 2-H), 5.08 (1 H, m, 4-H), 4.84 (1 H, s, SCHS), 3.08-2.24 (6 H, m, dithianyl-CH_2, 5-H cis and 5-H trans to 4-H), 0.95 (9 H, s, Bu^+), 0.18 and 0.12 (each 3 H, s, SiMe_2).

(b) initially at -78 °C, then warming to 0 °C

To a stirred solution of 2-lithio-1,3-dithiane in THF (0.5 ml, 1.18M) at -78 °C was added HMPA (0.21 ml, 1.2 mmol) and the chloro-enone (86;X=Cl) (94 mg, 0.38 mmol) in THF (0.5 ml). The reaction temperature was maintained at -78 °C for 25 min. and then raised to 0 °C
over a further 35 min.. The solution was then poured into aqueous ammonium chloride (5 ml) and extracted with diethyl ether (2 x 25 ml). The extract was washed with water (25 ml), dried (MgSO₄) and evaporated to give recovered chlоро-enone (86;X=Cl) (17.5 mg, 19%), the alcohol (135) (65 mg, 46%) and the enone (136) (11 mg, 9%).

Reaction of the chlоро-enone (86;X=Cl) with 2-potassio-1,3-dithiane in THF

Transmetallation of 2-lithio-1,3-dithiane was effected using potassium t-butoxide at -78 °C. Thus, to a stirred solution of 2-lithio-1,3-dithiane in THF (2 ml, 0.25M) were sequentially added potassium t-butoxide (56 mg, 0.5 mmol) in THF (1 ml) and HMPA (0.08 ml). Addition of the chlоро-enone (86;X=Cl) (62 mg, 0.25 mmol) in THF (1 ml) to a solution of the anion at -78 °C over 15 min. produced an orange-coloured mixture. Analytical t.l.c. of a portion of this mixture on silica gel in methylene dichloride-methanol (50:1 v/v) indicated that the alcohol (135) had not rearranged. The reaction mixture was warmed to 0 °C whereupon the solution became dark-green. After 15 min., the reaction was worked-up as previously to exclusively afford the alcohol (135) (63 mg, 71%).

Attempted rearrangement of the potassium alcoholate of the alcohol (135)

Potassium hydride (7 mg, 0.17 mmol) in mineral oil was washed with anhydrous hexane (3 x 1 ml), suspended in anhydrous THF (1 ml) and cooled to 0 °C. Addition of the alcohol (135) (54 mg, 0.15 mmol) to this solution resulted in the rapid evolution of gas. After this had ceased the solution was warmed to room temperature where it was stirred for 2 hr. The reaction was then quenched as previously to afford the alcohol (135) (40 mg, 74%) but none of the rearranged product.
**N,N-Diethylaminoacetonitrile**

*N,N*-Diethylaminoacetonitrile was prepared from diethylamine, sodium cyanide, formaldehyde and sodium hydrogensulphite according to the known procedure and in 60% distilled yield (b.p. 65 °C at 15 mmHg), δ 3.60 (2 H, s, CH₂CN), 2.60 (4 H, q, J 7 Hz, MeCH₂N x 2), 1.10 (6 H, t, J 7 Hz, Me x 2).

**N,N-Diethylaminolithioacetonitrile**

To a solution of lithium diisopropylamide in THF (0.5M) at -78 °C was added HMPA (0.348 ml, 2 mmol). Freshly distilled *N,N*-diethylaminoacetonitrile (224 mg, 2 mmol) was added dropwise to this solution and, after 30 min., the reaction was quenched with deuterium oxide (1 ml) and extracted with diethyl ether (2 x 25 ml). The extracts were dried (MgSO₄) and the solvent evaporated to give deuterio-*N,N*-diethylaminoacetonitrile. Deuterium incorporation was determined to be 87% as estimated by mass spectrometry [m/z 98 (M⁺-Me)/97 (M⁺-Me): 87/13, taking into consideration the contribution from the undeuterated species to the ion at m/z 98].

**NOTE:** Attempts to prepare *N,N*-diethylaminolithioacetonitrile in the absence of HMPA resulted in self-condensation of the reagent.

**Reaction of the chloro-enone (86; X=Cl) with N,N-diethylaminolithioacetonitrile at -78 °C**

A solution of *N,N*-diethylaminolithioacetonitrile in anhydrous THF (2.4 ml, 0.25M) was prepared according to the above procedure. To this solution at -78 °C the chloro-enone (86; X=Cl) (59 mg, 0.23 mmol) in anhydrous THF, was added dropwise. After 90 min., the reaction was quenched with saturated aqueous ammonium chloride (5 ml) and after
diluting with water the mixture was extracted with diethyl ether (2 x 25 ml). The combined extracts were washed with brine (2 x 25 ml), dried (MgSO₄) and evaporated to yield a dark-brown oil (120 mg). Preparative t.l.c. of this oil on silica gel in methylene dichloride-methanol (50:1 v/v) separately afforded two diastereoisomers of 4-(t-butyldimethylsilyloxy)-3-chloro-1-(cyano-N,N-diethylaminomethyl)-2-cyclopentenol (137;M=X=H).

A slower-moving diastereoisomer (31 mg, 36%) (Found M⁺-Me, 343.1608. C₁₆H₂₈C₁N₂O₂Si requires M-Me, 343.1608), νmax. 3 450, 2 230 and 1 630 cm⁻¹, m/z (%) 345/343 (M⁺-Me, <1), 301*(M⁺-Bu⁺,4), 247*(15), 219*(23), 189*(17), 147*(12), 112(25), 109(61), 75(100), 6.578 (1 H, s, 2-H), 4.64 (1 H, m, 4-H), 3.70 (1 H, br s exh., OH), 3.56 (1 H, s, CHCN), 2.90-2.50 (5 H, m, CH₂N x 2 and 5-H cis to 4-H), 1.90 (1 H, dd, J 14 and 4.5 Hz, 5-H trans to 4-H), 1.04 [6 H, t, J 7 Hz, N(CH₂CH₃)₂], 0.92 (9 H, s, Me₂Si). A faster-moving diastereoisomer (31 mg, 36%) (High resolution measurement of M⁺-Me was performed on the mixture.), νmax. 3 450, 2 230 and 1 630 cm⁻¹, m/z 345/343 (M⁺-Me, <1), 329*(6), 314*(6), 301*(M⁺-Bu⁺, 13), 247*(2), 189*(60), 147*(47), 112(100), 109(2), 75(50), 6.57.0 (1 H, s, 2-H), 4.64 (1 H, m, 4-H), 3.70 (1 H, br s, OH), 3.52 (1 H, s, CHCN), 2.80-2.40 (5 H, m, NCH₂Me x 2 and 5-H cis to 4-H), 2.12 (1 H, dd, J 13 and 5 Hz, 5-H trans to 4-H), 1.10 [6 H, t, J 7 Hz, (MeCH₂)₂N], 0.92 (9 H, s, Bu⁺), 0.12 (6 H, s, Me₂Si).

**Attempted rearrangement of the alcoholate (137;M=H, X=Li)**

The alcohol (137;M=X=H) (4.5 mg, 0.012 mmol) was dissolved in anhydrous THF and added dropwise to a solution of lithium diisopropylamide (0.07 ml, 0.17M) in THF, precooled to -78 °C. The reaction mixture was warmed to ambient (31 °C) and then, after 4 hr, quenched with aqueous ammonium chloride. The mixture was extracted with
diethyl ether (2 x 25 ml) and then the extracts were dried (MgSO₄) and evaporated to afford the alcohol (137; M=X=H) (4 mg, 85%).

Reaction of the chloro-enone (86;X=Cl) with N,N-diethylaminopotassio-acetonitrile

N,N-Diethylaminopotassioacetonitrile was prepared by transmetallation of the lithio-derivative with potassium t-butoxide. The chloro-enone (86;X=Cl) (123 mg, 0.5 mmol) in THF (1 ml) was added via syringe to N,N-diethylaminopotassioacetonitrile (1 mmol) in THF at -78 °C and, over 45 min., an orange-coloured solution developed. Analytical t.l.c. of a portion of this mixture on silica gel in methylene dichloride-methanol (50:1 v/v) indicated that it was comprised of two diastereoisomers of the alcohol (137;M=X=H). The mixture was warmed to room temperature whereupon the colour darkened considerably over 1 hr. Work-up as previously described gave a dark-brown oil (160 mg) which, by ¹H n.m.r. and analytical t.l.c., contained many products but neither the alcohol (137;M=X=H) nor the required C-3 addition product were detected.

Phenylthioacetonitrile

Phenylthioacetonitrile was prepared according to the procedure of Wang et al. Thiophenol was treated with equimolar quantities of chloroacetonitrile and triethylamine at room temperature. After 2 hr the mixture was filtered and distillation of the filtrate afforded phenylthioacetonitrile (70%) as a pale-yellow liquid (b.p. 146-147 °C at 14 mmHg).
Reaction of lithio(phenylthio)acetonitrile with the chloro-enone (86;X=Cl):  
(a) at -78 °C

Phenylthioacetonitrile (40 mg, 0.26 mmol) in THF (0.25 ml) was added dropwise to a cold (-78 °C) solution of lithium diisopropylamide in THF (0.25 ml, 1M). After 5 min., the chloro-enone (86;X=Cl) (62 mg, 0.25 mmol) in THF (0.5 ml) was introduced and the solution was stirred for 1 hr. The reaction was quenched with saturated aqueous ammonium chloride (5 ml), diluted with water (25 ml) and extracted with diethyl ether (2 x 25 ml). The extracts were washed with brine (25 ml), dried (MgSO₄) and evaporated to yield a yellow oil (122 mg). Preparative t.l.c. gave recovered chloro-enone (86;X=Cl) (26 mg, 42%) and 4-(t-butyldimethylsiloxyl)-3-chloro-1-[cyano(phenylthio)methyl]-2-cyclopentenol (140;M=X=H) (50 mg, 51%) as a colourless oily mixture of diastereoisomers (Kugelrohr, b.p. 83-85 °C and 105-108 °C at 0.25 mmHg) (Found: C, 57.84; H, 6.40; Cl, 8.72; N, 3.49; S, 8.19. C₁₉H₂₆ClNO₂SSi requires C, 57.62; H, 6.62; Cl, 8.95; N, 3.54; S, 8.10%), ν max. 3430, 2240, 1630 and 1570 cm⁻¹, m/z (%) 379/377 (M⁺-H₂O, <1), 246*(1), 189*[M⁺-Bu⁺, 100], 147*[M⁺-Bu⁺-C₂H₂O, 46], 109 (74), 87.60-7.25 (5 H, m, aromatic-H), 5.90 and 5.80 (0.61 and 0.39 H respectively, s, 2-H), 4.64 (1 H, m, 4-H), 3.84 and 3.82 (1 H, s, CHCN), 3.05 (1 H, br s exch., OH), 2.84 (1 H, dd, J 15 and 7 Hz, 5-H cis to 4-H), 2.04 (1 H, m, 5-H trans to 4-H), 0.92 (9 H, s, Bu⁺), 0.16 and 0.14 (each 3 H, s, Me₂Si). All spectral data were obtained on the mixture of diastereoisomers.
(b) initially at -78 °C, then at 0 °C with HMPA

Lithio(phenylthio)acetonitrile in THF (1.2 ml, 0.42M) was prepared as above and cooled to -78 °C. HMPA (90 mg, 0.5 mmol) and a solution of the chloro-enone (86;X=Cl) (62 mg, 0.25 mmol) in THF (1 ml) were sequentially added to the reaction mixture which was maintained at -78 °C for 1.5 hr and then at 0 °C for 2 hr. The reaction was then quenched with saturated aqueous ammonium chloride (5 ml), diluted with water (25 ml) and extracted with diethyl ether (2 x 25 ml). After washing with brine (25 ml) the extracts were dried (MgSO₄) and evaporated to afford 4-(t-butyldimethylsilyloxy)-3-[cyano(phenylthio)methyl]-2-cyclopentenone (141) (58 mg, 65%) as a white crystalline solid from hexane (m.p. 111-114 °C) (Found: C, 63.16; H, 7.10; N, 3.81; S, 8.49.

C₁₉H₂₅NO₂SSi requires C, 63.47; H, 7.01; N, 3.89; S, 8.92%) (Found: m/z 344 (M⁺-Me) 344.1140 C₁₈H₂₂NO₂SSi requires M-Me, 344.1145), υ_max. (CCl₄) 1 730 and 1 625 cm⁻¹, m/z (%) 344 (M⁺-Me, 4), 302 (M⁺-Bu⁺, 86), 284(3), 302 (M⁺-Bu⁺-C₂H₅O, 3), 227 (14), 194 (100), δ7.60-7.30 (5 H, m, aromatic H), 5.89 (1 H, s, 2-H), 5.18 (1 H, dd, J 6 and 3 Hz, 4-H), 4.74 (1 H, s, CHCN), 2.83 (1 H, dd, J 18 and 6 Hz, 5-H cis to 4-H), 2.36 (1 H, dd, J 18 and 3 Hz, 5-H trans to 4-H), 0.92 (9 H, s, Bu⁺), 0.22 and 0.18 (each 3 H, s, Me₂Si), δ(CD₃OD) 7.24 (5 H, br s, aromatic H), 5.08 (1 H, dd, J 6 and 2 Hz, 4-H), 3.04 (1 H, dd, J 18 and 6 Hz, 5-H cis to 4-H), 2.48 (1 H, dd, J 18 and 2 Hz, 5-H trans to 4-H), 0.94 (9 H, s, Bu⁺), 0.22 and 0.18 (each 3 H, s, Me₂Si) ( NB. the C-2 proton and the CHCN proton were not observed either at 22 °C or at -50 °C in this solvent.), λ_max. (EtOH) 351 and 244 nm, λ_max. (EtOH + acetic acid) 325 and 246 nm, λ_max. (MeOH) 351 and 246 nm, λ_max. (diethyl ether) 312 nm, λ_max. (diethyl ether and sodium borohydride) 351 nm, λ_max. (THF) 320 nm, λ_max. (CDCl₃) 235 nm and λ_max. (CDCl₃ and MeOH) 351 nm.
Attempted reduction of the enone (141):

(a) using bis(methoxyethoxy)sodium aluminium hydride (Redal)

The enone (141) (9 mg, 0.025 mmol) was dissolved in anhydrous toluene (1 ml) and cooled to -78 °C. Redal (0.008 µl, 0.025 mmol) was transferred to this solution via syringe and, after 30 min., analytical t.l.c. of an aliquot of the solution on silica gel in methylene dichloride-methanol (50:1 v/v) indicated that no reduction had occurred. The reaction mixture was warmed to -20 °C and, after 1.5 hr, quenched with methanol (1 ml). The mixture was diluted with water (25 ml) and extracted with diethyl ether (2 x 25 ml). The extracts were dried (MgSO₄) and evaporated to afford, after preparative t.l.c. on silica gel, only recovered enone (141) (7 mg, 78%).

(b) using sodium cyanoborohydride

The enone (141) (1 mg) was dissolved in anhydrous toluene (25 ml) and transferred to ultraviolet-grade quartz cells. No ultraviolet absorption was detected above 270 nm, which is the cut-off point for toluene. On addition of excess sodium cyanoborohydride a strong absorption was observed at 352 nm which then shifted to 325 nm when acetic acid was added. No decrease in the intensity of the absorption at 325 nm was observed over 24 hr.

Vinylmagnesium bromide

A solution of vinylmagnesium bromide in THF was prepared according to the method of Normant. The concentration of this solution was determined to be 1.25M as estimated by quenching an aliquot with excess acid of known molarity and back-titrating with base to measure the amount of acid not consumed by the Grignard reagent.
Copper(I)-mediated addition of vinylmagnesium bromide to the chloro-enone (86;X=Cl)

The chloro-enone (86;X=Cl) (62 mg, 0.25 mmol) in THF (0.5 ml) was added via syringe to a slurry of copper(I) iodide (49 mg, 0.25 mmol) in THF (0.5 ml). The mixture was cooled to -15 °C and vinylmagnesium bromide (0.4 ml, 1.25M) was added dropwise via syringe to produce a dark-green solution over 15 min. After this time the reaction was quenched with saturated aqueous ammonium chloride (5 ml) and following the addition of diethyl ether (25 ml) the mixture was stirred at room temperature for 1 hr, diluted with water (20 ml) and then extracted with diethyl ether (2 x 25 ml). The combined extracts were washed with brine (2 x 25 ml), dried (MgSO₄) and evaporated to yield an oil (50 mg). This oil was subjected to preparative t.l.c. on silica gel in methylene dichloride-methanol (50:1 v/v) which afforded 3-(3'-butenyl)-4-(t-butyldimethylsilyloxy)-2-cyclopentenone (143) (28 mg, 42%) as an oil (Kugelrohr, b.p. 60 °C at 0.2 mmHg) (Found: C, 67.48; H, 9.44. C₁₅H₂₆O₂Si requires C, 67.61; H, 9.84%). $\nu_{\text{max}}$ 1720 and 1620 cm⁻¹, m/z (%) 266 (M⁺, <1), 251 (M⁺-Me, 2), 209 (M⁺-Bu⁺, 66), 191 (8), 181 (7), 167 (M⁺-Bu⁺-C₂H₂O, 11), 135 (22), 107 (38), 75 (100), 55.95 (1 H, s, 2-H), 6.00-5.70 (1 H, m, CH=CH₂), 5.14-4.98 (2 H, m, CH=CH₂), 4.80 (1 H, m, 4-H), 2.70 (1 H, dd, $J$ 16 and 5 Hz, 5-H cis to 4-H), 2.95-2.16 (4 H, m, CH₂CH₂CH₂), 2.26 (1 H, dd, $J$ 16 and 3 Hz, 5-H trans to 4-H), 0.92 (9 H, s, Bu⁺), 0.15 and 0.09 (each 3 H, s, SiMe₂).

1-Propenylmagnesium bromide

A solution of 1-propenylmagnesium bromide in THF was prepared according to the method of Normant. The molarity of the solution was determined to be 0.88M as estimated by quenching an aliquot with excess...
acid of known molarity and back-titrating with base to measure the amount of acid not consumed by the Grignard reagent.

**Copper(I) iodide-mediated reaction of 1-propenylmagnesium bromide with the chloro-enone (86;X=Cl)**

A suspension of copper(I) iodide (48 mg, 0.25 mmol) in THF (2 ml) containing the chloro-enone (86;X=Cl) (62 mg, 0.25 mmol) was stirred vigorously at -15 °C. 1-Propenylmagnesium bromide (0.57 ml, 0.5 mmol) was added dropwise to this mixture and the reaction was maintained between -10 °C and -15 °C for 40 min. The reaction was then quenched with saturated aqueous ammonium chloride (5 ml) and, after addition of diethyl ether (5 ml), the mixture was stirred at room temperature for 1 hr. The mixture was then diluted with water (25 ml), extracted with diethyl ether (2 x 25 ml) and the extracts were washed with saturated brine (25 ml), dried (MgSO₄) and evaporated to give a pale-yellow oil (76 mg). Preparative t.l.c. of this oil allowed separation of the unconsumed chloro-enone (86;X=Cl) (6 mg, 10%) and 4-(t-butyldimethylsilyloxy)-3-(2'-methyl-3'-pentenyl)-2-cyclopentenone (146) (29 mg, 40%) as a colourless oil (Kugelrohr, b.p. 55-57 °C at 0.2 mmHg) (Found: C, 69.57; H, 10.06. C₁₇H₃₀O₂Si requires C, 69.33; H, 10.27%).

ν\text{max.} 1718, 1622 and 1593 cm⁻¹, m/z (%) 294 (M⁺, 2), 279 (M⁺-Me, 4), 237 (M⁺-Bu⁺, 100), 195 (M⁺-Bu⁺-C₂H₂O, 17), δ5.88 (1 H, s, 2-H), 5.60-5.00 (2 H, m, C=CHMe), 4.80 (1 H, m, 4-H), 2.68 (1 H, dd, J 18 and 6 Hz, 5-H \textit{cis} to 4-H), 2.21 (1 H, dd, J 18 and 3 Hz, 5-H \textit{trans} to 4-H), 2.90-0.90 (9 H, m, remaining side-chain protons), 0.92 (9 H, s, Bu⁺), 0.13 and 0.07 (each 3 H, s, Me₂Si). Also obtained was 4-(t-butyldimethylsilyloxy)-3-chloro-1-(1'-propenyl)-2-cyclopentenol (145) (22 mg, 30%) as a colourless unstable oil (Kugelrohr, b.p. 52 °C at 0.4
mmHg) (Found: C, 58.50; H, 8.19. \( \text{C}_{14}\text{H}_{25}\text{ClSiO}_2 \) requires C, 58.21; H, 8.27\%), \( \nu_{\text{max}} \) 3390 and 1625 cm\(^{-1}\), \( m/z \) (\%) 272/270 (\( \text{M}^+\text{-H}_2\text{O}, 6 \)), 237\* (\( \text{M}^+\text{-HCl-Me}, 7 \)), 213\* (\( \text{M}^+\text{-Bu}^t, 10 \)), 195\* (15), 75 (100), 65.95 (1 H, s, 2-H), 5.85 (1 H, d, \( J = 16 \text{ Hz} \), CH=CHMe), 5.70-5.40 (1 H, m, CH=CHMe), 4.50 (1 H, m, 4-H), 2.40-1.90 (6 H, m, 5-H \text{cis} to 4-H, 5-H \text{trans} to 4-H, OH and CHMe), 0.95 (9 H, s, \text{Bu}^t), 0.12 (6 H, s, \text{SiMe}_2).

1-Propenyltrimethyltin

1-Propenyltrimethyltin was prepared according to the known procedure.\(^{94}\) Thus, to 1-propenylmagnesium bromide in THF (50 ml, 0.9M) at room temperature was added dropwise, \( \text{via} \) syringe, a solution of trimethyltin bromide (7.35 g, 0.03 mol) in THF. The reaction mixture temperature rose considerably and a grey precipitate was formed. After 4 hr, the reaction was quenched with saturated aqueous ammonium chloride (100 ml), extracted with diethyl ether (100 ml) and washed with saturated brine (50 ml). The etheral layer was dried (MgSO\(_4\)) and the solvent removed by distillation through a Vigreux column to afford a pale-yellow oil (5.0 g). Further distillation gave, as a mixture of \text{cis} and \text{trans} isomers, pure 1-propenyltrimethyltin (4.2 g, 68\%) as a colourless pungent liquid (b.p. 119-119.5 °C at 760 mmHg) (Found: C, 35.34; H, 7.08; \( \text{C}_6\text{H}_{14}\text{Sn} \) requires C, 35.18; H, 6.89\%), \( \nu_{\text{max}} \) 1605 cm\(^{-1}\), 680-5.60 (2 H, m, \text{cis} and \text{trans} olefinic H), 2.00-1.70 (3 H, m, Me), 0.18 and 0.10 (each 4.5 H, s, \text{SnMe}_3) in agreement with reported values.\(^{94}\)
Preparation of (Z and E) lithium di-(1-propenyl)copper and its reaction with the chloro-enone (86;X=Cl):

(a) at -60 °C

To a solution of 1-propenyltributyltin (103 mg, 0.5 mmol) in anhydrous THF at -60 °C was added butyllithium in hexane (0.31 ml, 0.5 mmol). After 15 min., a solution of copper(I) bromide-dimethylsulphide (51 mg, 0.25 mmol) in dimethylsulphide/THF (0.25 ml each) was added over 30 min., to produce a yellow-coloured solution. A pre-cooled solution of the chloro-enone (86;X=Cl) (62 mg, 0.25 mmol) in THF (1 ml) was rapidly transferred via cannula to the cuprate reagent at -78 °C. After 30 min., the reaction was quenched with methanol. Saturated aqueous ammonium chloride (5 ml) and diethyl ether (5 ml) were added and the mixture was stirred at room temperature for 1 hr. The mixture was then diluted with water (25 ml), extracted with diethyl ether (2 x 25 ml) and the extracts were washed with saturated brine (25 ml), dried (MgSO₄) and evaporated to give a yellow oil (76 mg). This was shown to consist mainly of the chloro-enone (86;X=Cl) by ¹H n.m.r. spectroscopy.

(b) at -40 °C

Lithium di-(1-propenyl)copper (0.25 mmol) was prepared as before and cooled to -78 °C. A pre-cooled solution of the chloro-enone (86;X=Cl) (62 mg, 0.25 mmol) in THF was rapidly transferred via cannula to the cuprate reagent. The dark orange-coloured solution became dark blue when warmed to -40 °C. After 1 hr the reaction was worked-up following the procedure outlined in the previous experiment. The yellow oil (94 mg) thus obtained was subjected to preparative t.l.c. on silica gel in methylene dichloride which afforded the chloro-enone (86;X=Cl) (28 mg, 45%) and 4-(t-butyldimethylsilyloxy)-5-[4'-t-butyldimethylsilyloxy]-3'-chloro-1'-hydroxy-2'-cyclopentenyl]-3-methoxy-2-cyclopentenone (147).
(28 mg, 46%) as colourless needles, recrystallised from pentane, m.p. 110-114 °C and 125-129 °C (Found: $M^+\text{But}^+$, 431.1480. $C_{19}H_{32}ClO_5Si_2$ requires $M^\text{But}^+$, 431.1477), $\nu_{\text{max}}$ (CCl$_4$) 3 440, 1 740, 1 689 and 1 609 cm$^{-1}$, $m/z$ (%) 475/473 ($M^+\text{-Me, <1}$), 431* ($M^+\text{-But}^+$, 5), 413* (2), 299 (4), 242 (2), 231* (2), 227 (1), 189* (100), 185 (35), 147* (75), 143 (55), δ5.82 (1 H, s, 2'-H), 5.35 (1 H, s, 2-H), 5.00 (1 H, s, OH exch. in CD$_3$OD), 4.78 (1 H, dd, J 7 and 2 Hz, 4'-H), 4.67 (1 H, d, J 2 Hz, 4-H), 3.86 (3 H, s, MeO), 2.78 (1 H, d, J 2 Hz, 5-H trans to 4-H), 2.38 (1 H, dd, J 14 and 7 Hz, 5'-H cis to 4'-H), 1.64 (1 H, dd J 14 and 2 Hz, 5'-H trans to 4'-H), 0.88 (18 H, s, Bu$^+$ x 2), 0.12 (12 H, s, Me$_2$Si x 2).

Reaction of the methoxy-enone (148) with diethylaluminium cyanide

The methoxy-enone (148) was prepared according to the previously established method. To a solution of (148) (20 mg, 0.08 mmol) in anhydrous toluene (0.2 ml) was added diethylaluminium cyanide (1 ml, ca. 0.3M) and the resultant mixture was stirred at ambient temperature for 3 hr. The mixture was then diluted with diethyl ether (50 ml), washed with hydrochloric acid (0.5M) (25 ml) and subsequently with water (25 ml). Evaporation of the solvent furnished a yellow oil which, on chromatography on silica gel in petrol-ethyl acetate (1:1 v/v), furnished the nitrile (151) (5.5 mg, 28%) and recovered methoxy-enone (148) (2 mg, 10%). Spectral details for (151) can be found later in this experimental section.
Studies on the chloride/cyanide addition-elimination reaction using 3-chloro-2-cyclohexenone:

(a) employing potassium cyanide and 18-crown-6

To a solution of 3-chloro-2-cyclohexenone (57 mg, 0.44 mmol) and 18-crown-6 (5 mg) in anhydrous acetonitrile (0.5 ml) was added potassium cyanide (29 mg, 0.44 mmol). The mixture was stirred vigorously for 24 hr at ambient temperature, diluted with water (25 ml) and extracted with diethyl ether (2 x 25 ml). The extracts were washed with brine (25 ml), dried (MgSO$_4$) and evaporated to yield an oil (58 mg) which consisted of recovered 3-chloro-2-cyclohexenone (95%) with a little of the required nitrile (15%) (2%) as determined from an $^1$H n.m.r. spectrum of the mixture.

(b) employing copper(I) cyanide and HMPA

A round-bottomed flask, fitted with a reflux condenser was charged with copper(I) cyanide (123 mg, 1.37 mmol), HMPA (6 ml) and 3-chloro-2-cyclohexenone (68 mg, 0.5 mmol). The green mixture was maintained at 100 °C for 24 hr and the progress of the reaction was monitored after 4 and 19 hrs by obtaining $^1$H n.m.r. spectra on aliquots of the mixture. Some decomposition was noted and none of the nitrile (15%) was detected by $^1$H n.m.r. spectroscopy. After 24 hr the mixture was diluted with water (50 ml), extracted with diethyl ether (2 x 50 ml) and the extracts were washed with brine (50 ml). After drying (MgSO$_4$), the extracts were evaporated to afford a yellow oil (75 mg) which by $^1$H n.m.r. spectroscopy was shown to consist of 3-chloro-2-cyclohexenone (65%), together with some undesired and uncharacterised by-products.
(c) employing sodium dicyanocopper

Sodium dicyanocopper (1.26 mmol) was prepared by the method of House and Fischer\textsuperscript{102}, using freshly distilled $N,N$-dimethylformamide. 3-Chloro-2-cyclohexenone (78 mg, 0.6 mmol) in $N,N$-dimethylformamide (2.5 ml) was added \textit{via} syringe to the reagent at 80 °C. The temperature was raised to 95 °C and after 4 hr the reaction mixture was diluted with saturated aqueous ammonium chloride (25 ml) and then stirred with diethyl ether (25 ml) at room temperature for 1 hr. After this time the mixture was diluted with water (25 ml) and extracted with diethyl ether (2 x 25 ml). The extracts were washed with brine (3 x 25 ml), dried (MgSO$_4$) and evaporated to yield a pale-yellow oil (140 mg) which contained none of the nitrile (159) as determined by $^1$H n.m.r. spectroscopy. Preparative t.l.c. on silica gel afforded 3-chloro-2-cyclohexenone (64 mg, 82%).

(d) employing potassium cyanide and tetrakis(triphenylphosphine)palladium(0)

To a solution of 3-chloro-2-cyclohexenone (130 mg, 1 mmol) in anhydrous benzene (2 ml) was added recrystallised tetrakis(triphenylphosphine)palladium(0) (38 mg, 3 mol %), potassium cyanide (75 mg, 1.15 mmol) and 18-crown -6 (28 mg, 7 mol %). The reaction mixture was refluxed under nitrogen for 15 hr and poured into water (25 ml). The mixture was then extracted with diethyl ether (2 x 25 ml) and the extracts were washed with brine (25 ml) and dried (MgSO$_4$). Evaporation afforded a yellow oil (100 mg) which contained recovered 3-chloro-2-cyclohexenone (64%) and the nitrile (159) (14%) as determined by $^1$H n.m.r. spectroscopy and mass recovery.
(e) employing potassium cyanide, tetrakis(triphenylphosphine)palladium(0) and potassium iodide

The previous reaction was repeated in the presence of potassium iodide (98 mg, 1.2 mmol) and after refluxing for 16 hr the reaction mixture was poured into water. The isolation procedure employed previously then afforded a yellow oil (113 mg) which by $^1$H n.m.r. spectroscopy only consisted of 3-chloro-2-cyclohexenone (87%).

(f) employing tetraethylammonium cyanide in acetonitrile

Tetraethylammonium cyanide (89 mg, 0.57 mmol) was dissolved in anhydrous acetonitrile (1 ml). Addition of 3-chloro-2-cyclohexenone (74 mg, 0.57 mmol) in acetonitrile (1 ml) to this colourless solution rapidly afforded a light-brown solution. After 1 hr at room temperature the solution had darkened considerably and it was then poured into water (25 ml); the pH of the water rose to 9.5. The brown-coloured solution was extracted with diethyl ether (2 x 25 ml) and the extracts were washed with brine (25 ml), dried (MgSO$_4$) and evaporated to yield 3-chloro-2-cyclohexenone (35 mg, 47%) as a pale-yellow oil. None of the required nitrile (159) was present, as determined by analysis of an $^1$H n.m.r. spectrum of the product.

Tetrakis(triphenylphosphine)palladium(0)

This complex was prepared from palladium dichloride, triphenylphosphine and hydrazine hydrate according to the known procedure. The complex was isolated as yellow platelets (decomposition point: 115 °C) in 90% yield and stored at 0 °C under dry nitrogen.
Tetraethylammonium cyanide

Tetraethylammonium cyanide was prepared from sodium cyanide (5 g, 0.1 mol) and tetraethylammonium chloride (16 g, 0.1 mol) which were stirred for 1 hr in anhydrous methanol. The reaction mixture was filtered to remove the sodium chloride and the filtrate was evaporated to dryness whilst being protected from moisture. The residue was extracted with anhydrous acetonitrile and the extracts were then evaporated to approximately 25 ml. This liquor was cooled and tetraethylammonium cyanide was then collected on a filter (4.6 g, 29%) as an EXTREMELY HYGROSCOPIC white crystalline solid (Found: C, 68.85; H, 13.14; N, 17.76. C9H20N2 requires C, 69.17; H, 12.90; N, 17.92%).

Reaction of the methoxy-enone (148) with tetraethylammonium cyanide

The methoxy-enone (148) (66 mg, 0.27 mmol) and tetraethylammonium cyanide (53 mg, 0.34 mmol) were dissolved in methylene dichloride (2 ml), maintained at 0 °C for 30 min. and then at room temperature for a further 18 hr. The methylene dichloride was evaporated and the residual gum was triturated with diethyl ether (5 x 5 ml) to give, after evaporation of the solvent, recovered methoxy-enone (148) (41 mg, 61%) as the only diethyl ether-soluble product.

Reaction of the phenylseleno-enone (155) with tetraethylammonium cyanide

The phenylseleno-enone (155) (71 mg, 0.19 mmol) and tetraethylammonium cyanide (77 mg, 0.5 mmol) were dissolved in methylene dichloride (2 ml) and maintained at 0 °C for 30 min.. Analytical t.l.c.
of an aliquot of this solution indicated that compound (155) remained essentially unchanged. The reaction was warmed to room temperature and after 2 hr became black in colour. The solvent was evaporated and the residual black gum was triturated with diethyl ether (5 x 5 ml). Evaporation of the extracts afforded only the phenylseleno-enone (155) (70 mg, 96%).

Reaction of the chloro-enone (86;X=Cl) with trimethylamine:

(a) in diethyl ether at room temperature

A solution of trimethylamine in anhydrous toluene (0.7 ml, 2M) was added to the chloro-enone (86;X=Cl) (166 mg, 0.67 mmol) which was dissolved in anhydrous diethyl ether (2 ml) and the resultant solution was vigorously stirred at room temperature for 14 days. During the course of the reaction an off-white coloured precipitate gradually formed. The mixture was filtered under a stream of dry nitrogen and the off-white coloured solid was washed with anhydrous diethyl ether (3 x 10 ml). After drying under nitrogen 4-(t-butyldimethylsilyloxy)-3-trimethylammonio-2-cyclopentenone chloride (156) (86 mg, 43%) was obtained as a white crystalline solid (Found: M+-MeCl, 255.1657 C_{13}H_{25}NO_{2}Si M-MeCl requires 255.1654), m/z (%): 257/255 (M+-MeCl, 7), 240 (M+-MeCl-Me, 4), 198 (M+-MeCl-Bu^t, 100), 156 (60), 50 (MeCl, 74). δ7.22 (1 H, br s, 2-H), 5.75 (1 H, dd, J 6 and 1 Hz, 4-H), 3.89 (9 H, s, Me_3N^+), 3.15 (1 H, dd, J 18 and 6 Hz, 5-H cis to 4-H), 2.39 (1 H, dd, J 18 and 1 Hz, 5-H trans to 4-H), 0.90 (9 H, s, Bu^t), 0.22 and 0.18 (each 3 H, s, Me_2Si). Evaporation of the filtrate afforded the chloro-enone (86;X=Cl) (86 mg, 53%).
(b) in hexane at room temperature

The chloro-enone (86;X=Cl) (116 mg, 0.47 mmol) was dissolved in anhydrous hexane (2 ml). Trimethylamine in anhydrous toluene (0.47 ml, 2M) was added to the chloro-enone (86;X=Cl) and the solution was stirred vigorously for 14 days at room temperature under an atmosphere of nitrogen. The mixture was filtered and the solid was washed with hexane (25 ml) to yield 4-(t-butyl(dimethyl)silyloxy)-3-N,N-dimethylamino-2-cyclopentenone (157) (54 mg, 45%) as colourless needles, m.p. 119-119.5 °C (Found: C, 61.19; H, 9.63; N, 5.48. \( \text{C}_{13}\text{H}_{25}\text{NOSi} \) requires C, 61.13; H, 9.87; N, 5.48%) (Found: \( M^+ \), 255.1658. \( \text{C}_{13}\text{H}_{25}\text{NOSi} \) requires \( M^+ \), 255.1654), \( \nu_{\text{max.}} \) (CCl\(_4\)) 1 680 and 1 595 cm\(^{-1}\), \( m/z \) 255 (\( M^+ \), 5), 240 (\( M^+ \)-Me, 7), 198 (\( M^+\)-Bu\(^t\), 100), 156 (89), 124 (83), 84.96 (1 H, s, 2-H), 4.94 (1 H, dd, \( J \) 6.5 and 2.5 Hz, 4-H), 3.03 (6 H, br s, \( \text{Me}_2\text{N} \)), 2.73 (1 H, dd, \( J \) 17.5 and 6.5 Hz, 5-H cis to 4-H), 2.32 (1 H, dd, \( J \) 17.5 and 2.5 Hz, 5-H trans to 4-H), 0.90 (9 H, s, Bu\(^t\)), 0.10 and 0.06 (each 3 H, s, \( \text{Me}_2\text{Si} \)). Evaporation of the filtrate afforded the chloro-enone (86;X=Cl) (47 mg, 40%).

(c) in acetone at room temperature

The chloro-enone (86;X=Cl) (123 mg, 0.5 mmol) and trimethylamine in anhydrous acetone (1 ml, 5.8M) were stirred at room temperature for 3.5 hr. A white precipitate which rapidly formed was removed by filtration after 2.5 hr. The solid was dissolved in diethyl ether (50 ml), washed with water (50 ml) and the etheral layer was dried (\( \text{MgSO}_4 \)). Evaporation of the solvent afforded the dimethylamino-enone (157) (131 mg, 100%) as colourless needles.
(d) in acetone at room temperature with silver tetrafluoroborate

The chloro-enone (86;X=Cl) (60 mg, 0.24 mmol) and silver tetrafluoroborate (79 mg, 0.4 mmol) were stirred with trimethylamine in acetone (0.5 ml, 5M) at room temperature. After 15 min., analytical t.l.c. indicated that the chloro-enone (86;X=Cl) had been completely consumed. Work-up as in the previous experiment furnished a diethyl ether-soluble brown solid (60 mg) which, by $^1$H n.m.r. spectroscopy, consisted mainly of the dimethylamino-enone (157) (95%).

(e) in diethyl ether at 60 °C

The chloro-enone (86;X=Cl) (256 mg, 1.04 mmol) and a solution of trimethylamine in diethyl ether (2.5 ml, 2M) were stirred vigorously in a sealed tube for 24 hr at 60 °C. During this time a dense white precipitate formed. After cooling the mixture the precipitate was removed by filtration and was subsequently dissolved in diethyl ether (50 ml) and washed with water (50 ml) so as to remove any tetramethylammonium chloride. The diethyl ether extracts were dried (MgSO$_4$) and evaporated to yield the dimethylamino-enone (157) (250 mg, 94%) as colourless needles. The filtrate was also evaporated to yield the chloro-enone (86;X=Cl) (17 mg, 6%).

5-(t-Butyldimethylsilyloxy)-3-oxo-1-cyclopentene carbonitrile (151) from compound (158)

To a solution of compound (156) (178 mg, 0.58 mmol) in aqueous ammonium chloride (0.5 ml) were sequentially added benzene (2.5 ml) and potassium cyanide (43 mg, 0.67 mmol). The mixture was stirred vigorously for 15 min., after which the benzene layer was decanted from
the mixture. The aqueous layer was extracted with benzene (2 x 5 ml),
the benzene extracts were then combined, washed with brine (10 ml),
dried (Na₂SO₄) and evaporated to afford essentially pure
5-(t-butyldimethylsilyloxy)-3-oxo-1-cyclopentenylcarbonitrile (151)
(123 mg, 89%). This oil was subjected to preparative t.l.c. on silica
gel in methylene dichloride-methanol (50:1 v/v) which gave pure (151)
(115 mg, 83%). Compound (151) crystallised on standing at 0 °C to
afford pale-yellow platelets (Found: M⁺-Bu⁺, 180.0482. C₈H₁₀NO₂Si requires
M-Bu⁺, 180.0481), νmax. 2 230, 1 735 and 1 610 cm⁻¹, m/z (%) 222 (M⁺-Me,
1), 209 (1), 180 (M⁺-Bu⁺, 100), 138 (M⁺-Bu⁺-C₂H₂O, 7), δ6.65 (1 H, d, J 1
Hz, 2-H), 5.06 (1 H, ddd, J 6, 3 and 1 Hz, 5-H), 2.84 (1 H, dd, J 18 and 6
Hz, 4-H cis to 5-H), 2.35 (1 H, dd, J 18 and 3 Hz, 4-H trans to 5-H),
0.93 (9 H, s, Bu⁺), 0.24 and 0.18 (each 3 H, s, Me₂Si).

Preparation of the nitrile (151) directly from the chloro-enone (86; X=Cl)

To a solution of the chloro-enone (86; X=Cl) (251 mg, 1.02 mmol)
in toluene (2 ml) were sequentially added saturated aqueous
trimethylammonium chloride (4 ml), potassium cyanide (195 mg, 3 mmol)
and trimethylamine in toluene (2 ml, 2.5M). The mixture was securely
enclosed in a reaction vessel and efficiently stirred for 22 hr. The
reaction mixture was then poured into hexane (100 ml) which was washed
with water (50 ml) and brine (50 ml). After drying (MgSO₄) the
extracts, the solvent was evaporated to afford a pale-yellow oil (189
mg). 'Flash' chromatography of this oil on Merck Kieselgel 60 (230-400
mesh) grade silica gel in petrol-ethyl acetate (4:1 v/v) afforded the
nitrile (151) (179 mg, 74%).
3-Hydroxy-1-cyclohexene-carbaldehyde (160)

3-Oxo-1-cyclohexene-carbonitrile (159) (1.56 g, 12.9 mmol) was dissolved in anhydrous toluene-hexane (160 ml, 1:1 v/v) and cooled to -78 °C. A solution of di-σ-butylaluminium hydride in hexane (25 ml, 0.93M) was added dropwise to the nitrile (159) over a period of 30 min. Addition of one equivalent of the reducing agent gave a yellow-coloured solution which became colourless on addition of the second equivalent of reagent. After a further 30 min. at -78 °C the reaction mixture was quenched with saturated aqueous ammonium chloride (50 ml), stirred for 30 min. at room temperature and acidified with sufficient 0.5M hydrochloric acid to dissolve the organoaluminium by-products. The solution was extracted with ethyl acetate (4 x 100 ml) and the pH was adjusted to neutral with sodium hydrogen carbonate. The cloudy mixture was saturated with sodium chloride and further extracted with methylene dichloride (2 x 100 ml). The combined organic extracts were dried (MgSO₄) and evaporated to afford 3-hydroxy-1-cyclohexene-carbaldehyde (160) (1.25 g, 96%) as a pale-yellow oil (Kugelrohr, b.p. 45-48 °C at 0.4 mmHg) (Found: C, 66.98; H, 7.96. C₇H₁₀O₂ requires C, 66.65; H, 7.99%)

(Found: M⁺, 126.0683, C₇H₁₀O₂ requires M, 126.0681), νmax. 3 410 and 1 685 cm⁻¹. m/z (%) 126 (M⁺, 60), 97 (M⁺-CHO, 100), δ9.46 (1 H, s, CHO), 6.67 (1 H, m, 2-H), 4.48 (1 H, m, 3-H), 2.30-1.50 (7 H, m, remaining ring-H and OH). (The yield of compound (160) is based on the quantity of reducing agent used.)
3-Acetoxy-1-cyclohexene-carbaldehyde (162; Z=H)

To the alcohol (160) (155 mg, 1.23 mmol) in anhydrous pyridine (0.25 ml) was added distilled acetic anhydride (0.185 ml, 1.84 mmol) and 4-(N,N-dimethylamino)pyridine (7 mg, 5 mol %). The mixture was stirred for 15 hr at room temperature, quenched with ice-cold water (25 ml) and extracted with diethyl ether (2 x 25 ml). The extracts were washed with brine (25 ml), dried (MgSO₄) and evaporated to afford 3-acetoxy-1-cyclohexene-carbaldehyde (162; Z=H) (207 mg, 100%) as a colourless oil (Kugelrohr, b.p. 40-44 °C at 0.2 mmHg) (Found: C, 64.39; H, 7.05. \( \text{C}_9\text{H}_{12}\text{O}_3 \) requires C, 64.27; H, 7.19%), \( \nu_{\text{max}} \) 1740, 1690 and 1650 cm⁻¹, \( m/z \) (%) 168 (\( M^+ \), <1), 139 (\( M^+\)-CHO, 16), 126 (\( M^+\)-\( \text{C}_2\text{H}_2\text{O} \), 100), 97 (47), 69.48 (1 H, s, CHO), 6.63 (1 H, dt, \( J \) 3.5 and 1.5 Hz, 2-H), 5.52 (1 H, m, 3-H), 2.06 (3 H, s, MeCO), 2.34-1.54 (6 H, m, ring-H).

Attempted cyclisation of 3-acetoxy-1-cyclohexene-carbaldehyde (162; Z=H) using lithium diisopropylamide:

(a) at 0.16 M concentration

To a solution of lithium diisopropylamide in diethyl ether (0.6 ml, 0.33M) at -78 °C was rapidly added a solution of compound (162; Z=H) (30 mg, 0.18 mmol) in diethyl ether (0.6 ml). A white solid immediately precipitated from solution and, after 30 min., the reaction was quenched with deuterium oxide (2 ml). The mixture was diluted with water (10 ml) and extracted with diethyl ether (25 ml) and ethyl acetate (25 ml). The combined extracts were dried (MgSO₄) and evaporated to afford a colourless oil (30 mg) which, after preparative t.l.c. on silica gel in methylene dichloride-methanol (50:1 v/v), gave only recovered compound (162; Z=H) (6.5 mg, 21%) and none of the corresponding deuterated species.
[as determined by analysis of its mass spectrum at \( m/z \) 168 \((M+H)/169\) \((M+D)\)]. Three other components with small \( R_f \) values were obtained (15 mg) which were inseparable by chromatography and therefore they were not individually characterised. However, an infrared spectrum of the oily mixture did not indicate the presence of the required lactone moiety.

(b) at 0.036 M concentration

The above reaction was repeated in the presence of HMPA (0.2 mmol) at higher dilution in diethyl ether (5.5 ml) and compound (162;Z=H) was added slowly and dropwise. A similar result to that obtained in the previous experiment was noted and the infrared spectrum of the crude product again did not indicate the presence of the required lactone moiety.

3-(Methoxymalonyloxy)-1-cyclohexenecarbaldehyde (162;Z=CO₂Me)

To the hydroxy-aldehyde (160) (111 mg, 0.88 mmol) in anhydrous methylene dichloride (2 ml) at 0 °C were sequentially added pyridine (0.09 ml, 1.06 mmol) and methoxymalonyl chloride (0.113 ml, 1.06 mmol). After 5 min., a dense pale-yellow precipitate had formed and the reaction was quenched with an ice-water mixture (25 ml). The resultant mixture was extracted with diethyl ether (2 x 50 ml) and the combined extracts were washed with brine (2 x 25 ml), dried (MgSO₄) and evaporated to afford a yellow oil (213 mg). Preparative t.l.c. of this oil on silica gel in methylene dichloride-methanol (50:1 v/v) gave 3-(methoxymalonyloxy)-1-cyclohexenecarbaldehyde (162;Z=CO₂Me) (158 mg, 79%) as a pale-yellow oil (Found: C, 58.57; H, 6.13. \( C_{11}H_{14}O_5 \) requires C, 58.40; H, 6.24%), \( v_{\text{max}} \) 1745 (br) and 1690 \( \text{cm}^{-1} \), \( m/z \) (%)
227 (M^+1, 4), 209 (M^+-17, 1), 197 (M^+-CHO, 3), 126 (100), 101 (33), 97 (47), 89.50 (1 H, s, CHO), 6.64 (1 H, dt, J 3.5 and 2 Hz, 2-H), 5.59 (1 H, m, 3-H), 3.74 (3 H, s, Me), 3.40 (2 H, s, CH2CO2Me), 2.35-1.60 (6 H, m, remaining ring-H).

**Attempted cyclisation of the methyl ester (162;Z=CO2Me):**

(a) using potassium carbonate/methanol

The methyl ester (162;Z=CO2Me) (16 mg, 0.07 mmol) in anhydrous methanol (0.2 ml) was slowly added to a suspension of anhydrous potassium carbonate (15 mg, 0.1 mmol) in methanol (0.45 ml) at room temperature. The reaction was quenched after 30 min. with saturated aqueous ammonium chloride (10 ml) and the mixture thus obtained was extracted with ethyl acetate (3 x 10 ml). The extracts were washed with brine (10 ml), dried (MgSO4) and evaporated to afford a pale-yellow oil (16 mg). Chromatography of this oil on silica gel in methylene dichloride-methanol (50:1 v/v) afforded the alcohol (160) (5 mg, 56%), identified by its ^1H n.m.r. and mass spectra.

(b) using bis(2,4-pentanedionato)nickel(II)

The methyl ester (162;Z=CO2Me) (69 mg, 0.3 mmol) and bis(2,4-pentanedionato)nickel(II), Ni(acac)_2, (5 mg, 1 mol %) were refluxed in distilled chloroform (2 ml) under nitrogen for 60 hr. The mixture was then diluted with diethyl ether (10 ml), filtered through a short column of silica gel and evaporated to afford the methyl ester (162;Z=CO2Me) (62 mg, 90%).
4-Formyl-2-oxo-1-oxabicyclo[3.4.0]nonane (161) from the methyl ester (162; Z=CO₂Me) in two steps

Sodium hydride in mineral oil (12 mg, 50% dispersion, 0.25 mmol) was washed with anhydrous hexane (3 x 1 ml) under nitrogen and suspended in anhydrous THF (1.5 ml). A THF solution of the methyl ester (162; Z=CO₂Me) (1 ml, 0.22M) was added dropwise to the suspension at room temperature. After 2 hr the reaction was quenched with saturated aqueous ammonium chloride (20 ml) and the mixture was extracted with ethyl acetate (3 x 25 ml). The extracts were dried (MgSO₄) and evaporated to yield a colourless oil (49 mg) which comprised a diastereoisomeric mixture of 3-carbomethoxy-4-formyl-2-oxo-1-oxabicyclo[3.4.0]nonane (163; Z=CO₂Me) which was only partially characterised, νmax. 1780 and 1735 cm⁻¹, δ* 9.64 and 9.61 (1 H together, s, CHO), 4.96-4.62 (1 H, m, 1-H), 3.82 and 3.79 (together 3 H, s, MeO), 3.39 (0.9 H, d, J 4 Hz, 3-H), 3.09 (1 H, ddd, J 9, 5 and 4 Hz, tentatively assigned to 3a-H), 2.56-1.20 (approximately 7 H, m, remaining H).

Compound (163; Z=CO₂Me) (60 mg, 0.27 mmol) was dissolved in anhydrous pyridine (0.15 ml). A large excess of anhydrous lithium iodide (178 mg, 1.33 mmol) was added and the resultant solution was refluxed for 2 hr. The reaction was quenched with saturated aqueous ammonium chloride (5 ml) and, after dilution with water (25 ml), extracted with ethyl acetate (3 x 25 ml). The extracts were dried (MgSO₄) and evaporated to yield a yellow oil (20 mg) which, after preparative t.l.c. on silica gel in methylene dichloride-methanol (50:1 v/v), gave 4-formyl-2-oxo-1-oxabicyclo[3.4.0]nonane (161) (5 mg, 10%) as a colourless oil (Kugelrohr, b.p. 69-73 °C at 1.2 mmHg) (Found: C,

* The complications endowed to this ¹H n.m.r. spectrum by the diastereoisomers restricted the analysis to a partial and tentative assignment of signals.
4-Hydroxymethyl-2-oxo-1-oxabicyclo[3.4.0]nonane (168) from compound (163; $Z=\text{CO}_2\text{Me}$)

To the lactone-ester (163; $Z=\text{CO}_2\text{Me}$) (50 mg, 0.22 mmol) in THF (1.5 ml) at -20 °C was added lithium tri-(t-butoxy)aluminium hydride (61 mg, 0.44 mmol) as a suspension (partly solubilised) in THF (2 ml). After 30 min., the reaction was quenched with saturated aqueous ammonium chloride (5 ml) and subsequently stirred at room temperature for 15 min. The mixture was diluted with brine (25 ml) and extracted with ethyl acetate (2 x 25 ml). The extracts were dried (MgSO$_4$) and evaporated to afford 3-carbomethoxy-4-hydroxymethyl-2-oxo-1-oxabicyclo[3.4.0]nonane (167) (45 mg, 90%) as a viscous, colourless oil, $\nu_{\text{max.}}$ 3500, 1775 and 1740 cm$^{-1}$. This oil was used directly in the next step without purification.

To compound (167) (43 mg, 0.19 mmol) in anhydrous pyridine (0.5 ml) was added lithium iodide (134 mg, 1 mmol). The viscous yellow solution was refluxed under nitrogen for 2 hr, quenched with saturated aqueous ammonium chloride (5 ml) and extracted with ethyl acetate (3 x 25 ml). The extracts were dried (MgSO$_4$) and evaporated to afford a pale-yellow oil (24 mg) which was chromatographed on silica gel in methylene dichloride-methanol (50:1 v/v) to yield 4-hydroxymethyl-2-oxo-1-oxabicyclo[3.4.0]nonane (168) (16.5 mg, 51%) as a colourless liquid (Found: C, 63.74; H, 8.00. $C_9H_{14}O_3$ requires C, 63.51; H, 8.29%), $\nu_{\text{max.}}$ 3430 and 1770 cm$^{-1}$, m/z (%) 170 ($M^+$, 7), 169 ($M^+-1$, 3), 152
Benzyl hydrogenmalonate

Benzyl hydrogenmalonate was prepared by the method of Fritsch et al.117 Thus, anhydrous malonic acid (60 g, 0.57 mol) and distilled thionyl chloride (25 ml, 0.34 mol) were protected from atmospheric moisture by a drying tube (CaCl₂) and refluxed for 90 min. Excess thionyl chloride was removed by a water aspirator and the residual solid was dissolved in anhydrous THF (500 ml). Benzyl alcohol (54 g, 0.5 mol) was added dropwise to this solution and then the solvent was immediately evaporated. The mixture was treated with saturated aqueous sodium hydrogen carbonate until the evolution of carbon dioxide ceased. The aqueous layer was extracted with diethyl ether (3 x 200 ml) to remove excess benzyl alcohol, then it was acidified with dilute hydrochloric acid (0.1M) and extracted with diethyl ether (3 x 200 ml). The extracts were dried (MgSO₄) and evaporated to afford a yellow oil (13 g) which partly solidified on cooling to 0 °C. The solid was separated from the oil by pressing the mixture between filter paper. In this way essentially pure benzyl hydrogenmalonate (5.5 g, 5%) was obtained as a pale-yellow solid, m.p. 49-51 °C (lit.,117 49-52 °C).

3-(Benzylloxymalonilloy)-1-cyclohexene-carbaldehyde (162; Z=CO₂Bz)

To the hydroxy-aldehyde (160) (60 mg, 0.48 mmol) in methylene dichloride (2 ml) was added dicyclohexylcarbodiimide (103 mg, 0.5 mmol), 4-(N,N-dimethylamino)pyridine (6 mg, 10 mol %) and benzyl hydrogenmalonate (97 mg, 0.5 mmol) in methylene dichloride (0.5 ml).
Addition of the acid resulted in the immediate precipitation of a white solid. The mixture was stirred at room temperature for 2 hr and then filtered. The mother liquor was dissolved in diethyl ether (50 ml), washed with water (25 ml) and brine (25 ml) and then dried (MgSO₄). Evaporation of the solvent afforded a colourless oil (174 mg) and chromatography of this oil on silica gel in methylene dichloride-methanol (50:1 v/v) yielded 3-(benzyloxym alonyloxy)-1-cyclohexene carbaldehyde (162; Z=CO₂Bz) (130 mg, 90%) as a colourless oil which decomposed on distillation (Found: C, 67.69; H, 6.02. C₁₇H₁₈O₅ requires C, 67.53; H, 6.00%), ᴻ max. 1 745 (br), 1 690 and 1 650 cm⁻¹, m/z (%) 303 (M⁺ + 1, <1), 302 (M⁺, <1), 273 (M⁺-CHO, 1), 211 (<1), 195 (3), 110 (100), 107 (60), 91 (31), 89.43 (1 H, s, CHO), 7.34 (5 H, s, aromatic-H), 6.55 (1 H, dt, J 3.5 and 2 Hz, 2-H), 5.56 (1 H, m, 3-H), 5.18 (2 H, s, PhCH₂O), 3.45 (2 H, s, CH₂CO₂CH₂Ph), 2.32-1.54 (6 H, m, remaining ring-H).

4-Formyl-2-oxo-1-oxabicyclo[3.4.0]nonane (161) from the benzy l ester (162; Z=CO₂Bz) in three steps

Sodium hydride in mineral oil (124 mg, 50% dispersion, 2.58 mmol) was washed with anhydrous hexane (3 x 5 ml) under nitrogen and suspended in anhydrous THF (5 ml). A solution of the benzyl ester (162; Z=CO₂Bz) (650 mg, 2.15 mmol) in THF was added dropwise to the sodium hydride and the resultant mixture was stirred for 3 hr at room temperature. After this time the reaction was quenched with saturated aqueous ammonium chloride (25 ml), diluted with brine (25 ml) and extracted with ethyl acetate (3 x 50 ml). The extracts were dried (MgSO₄) and evaporated to afford 3-carbobenzyl-4-formyl-2-oxo-1-oxabicyclo[3.4.0]nonane (163; Z=CO₂Bz) as a colourless oil (645 mg).
This oil was dissolved in ethyl acetate-ethyl alcohol (10 ml, 1:1 v/v) and hydrogenated over palladium on charcoal (40 mg) until the uptake of hydrogen had ceased. The mixture was filtered through celite and the filtrate evaporated to afford 3-carboxy-4-formyl-2-oxo-1-oxabicyclo[3.4.0]nonane (162; C_{0}H_{2}O_{2} (456 mg, 100%) as a colourless gum. This acid (356 mg, 1.68 mmol) was then dissolved in toluene-ethyl acetate (9 ml, 3:1 v/v) and refluxed under nitrogen for 4.5 hr. Evaporation of the solvent afforded a yellow oil (320 mg) which was subjected to preparative t.l.c. on silica gel to yield 4-formyl-2-oxo-1-oxabicyclo[3.4.0]nonane (161) (168 mg, 60%) as a colourless oil.

5-(t-Butyldimethylsilyloxy)-3-hydroxy-1-cyclopentenecarbaldehyde (125)

To a solution of the nitrile (151) (193 mg, 0.81 mmol) in anhydrous toluene-hexane (6.5 ml, 1:1 v/v) at -78 °C was added dropwise, di-ethylaluminium hydride in hexane (1.83 ml, 0.93 M). The reaction was quenched after 15 min. with silica gel (20 g). After diluting with diethyl ether (20 ml) the mixture was stirred for 10 min. at room temperature. The mixture was then filtered to remove the silica gel and adsorbed aluminium by-products, and the filtrate was evaporated to yield a yellow oil (150 mg). This crude product was subjected to 'flash' chromatography in methylene dichloride-methanol (50:1 v/v). In this way 5-(t-butyldimethylsilyloxy)-3-hydroxy-1-cyclopentenecarbaldehyde (126) (140 mg, 71%) was obtained as an oily mixture of diastereoisomers, inseparable by chromatography (Found: M^{+}-Bu^{t}, 185.0636. C_{8}H_{13}O_{3}Si requires M^{+}-Bu^{t}, 185.0634), \( \nu_{max} \) 3 400, 1 695 and 1 625 cm\(^{-1}\), m/z (%) 227 (M^{+}-Me, <1), 185 (M^{+}-Bu^{t}, 32), 167 (M^{+}-Bu^{t}-H_{2}O, 7), 157 (5), 75 (100),
cis-diastereoisomer δ 9.82 (0.7 H, s, CHO), 6.84 (0.7 H, d, J 2 Hz, 2-H), 4.92 (0.7 H, dd, J 7 and 3 Hz, 5-H), 4.72 (0.7 H, m, 3-H), 2.63 (0.7 H, ddd, J 14, 7 and 7 Hz, 4-H cis to 5-H), 1.76 (0.7 H, ddd, J 14, 3 and 3 Hz, 4-H trans to 5-H), 0.87 (6.3 H, s, Bu$^t$), 0.16 and 0.13 (each 2.1 H, s, Me$_2$Si), trans-diastereoisomer δ 9.80 (0.3 H, s, CHO), 6.81 (0.3 H, d, J 2 Hz, 2-H), 5.27 (0.3 H, m, 3-H), 5.18 (0.3 H, dt, J 6.5 and 1.5 Hz, 5-H), 2.29 (0.3 H, ddd, J 14, 6.5 and 1.5 Hz, 4-H), 2.00 (0.3 H, ddd, J 14, 6 and 5 Hz, 4-H), 0.86 (2.7 H, s, Bu$^t$), 0.14 and 0.10 (each 0.9 H, s, Me$_2$Si). Common to both diastereoisomers: 2.15 (1 H, br s exch., OH).

3-Acetoxy-6-(t-butyldimethylsilyloxy)-1-cyclopentenecarbaldehyde (169)

To the cyclopentenecarbaldehyde (125) (13 mg, 0.05 mmol) in distilled methylene dichloride (0.1 ml) was added anhydrous pyridine (0.01 ml, 0.07 mmol), 4-((N,N-dimethylamino)pyridine (5 mg, 0.04 mmol) and distilled acetic anhydride (0.01 ml, 0.07 mmol). After stirring for 10 min. at room temperature the reaction mixture was diluted with diethyl ether (2 x 0.5 ml) and directly subjected to preparative t.l.c. on silica gel in methylene dichloride. In this way 3-acetoxy-6-(t-butyldimethylsilyloxy)-1-cyclopentenecarbaldehyde (169) was obtained as the cis-diastereoisomer (5.7 mg, 38%) and the trans-diastereoisomer (2 mg, 13%) (Found: M$^+$-Bu$^t$, 227.0745. C$_{10}$H$_{15}$O$_4$Si requires M-Bu$^t$, 227.0739), $\nu_{\text{max}}$ 1745, 1695 and 1630 cm$^{-1}$, m/z (%) 227 (M$^+$-Bu$^t$, 24), 185 (85), 167 (24), 117 (87), 75 (50) and 43 (100), 200 MHz $^1$H n.m.r. cis-diastereoisomer δ 9.84 (1 H, s, CHO), 6.77 (1 H, d, J 2 Hz, 2-H), 5.56 (1 H, ddd, J 7.5, 4.7 and 2 Hz, 3-H), 4.96 (1 H, ddd, J 7.5 and 4.7 Hz, 5-H), 2.89 (1 H, ddd, J 14, 7.5 and 7.5 Hz, 4-H cis to 5-H), 1.80 (1 H, ddd, J 14, 4.7 and 4.7 Hz, 4-H trans to 5-H), 2.09 (3 H, s, MeCO), 0.89 (9 H, s, Bu$^t$), 0.15 and 0.13 (each 3 H, s, Me$_2$Si), the trans-diastereoisomer.
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89.84 (1 H, s, CHO), 6.82 (1 H, d, J 2 Hz, 2-H), 6.00 (1 H, dddd, J 7, 5, 2 and 2 Hz, 3-H), 5.21 (1 H, ddd, J 7, 2 and 2 Hz, 5-H), 2.31 (1 H, ddd, J 14.3, 7 and 2 Hz, 4-H cis to 5-H), 2.14 (1 H, ddd, J 14.3, 7 and 5 Hz, 4-H trans to 5-H)(this signal was partly obscured by the signal at 2.07 p.p.m.), 2.07 (3 H, s, MeCO), 0.87 (9 H, s, Bu\textsuperscript{t}), 0.15 and 0.10 (each 3 H, s, Me\textsubscript{2}Si).

5-(t-Butyldimethylsilyloxy)-3-(methoxymalonyloxy)-1-cyclopentene-carbaldehyde (126; Z=CO\textsubscript{2}Me)

To the cyclopentenecarbaldehyde (125) (53 mg, 0.22 mmol) in anhydrous diethyl ether (1 ml) at -10 °C was added triethylamine (0.04 ml, 0.3 mmol) and methoxymalonyl chloride (0.03 ml, 0.28 mmol). The resultant bright-yellow suspension was stirred at 0 °C for 3 hr after which time the mixture was diluted with diethyl ether (1 ml) and directly subjected to preparative t.l.c. on silica gel in methylene dichloride. In this way 5-(t-butyldimethylsilyloxy)-3-(methoxymalonyloxy)-1-cyclopentene-carbaldehyde (126; Z=CO\textsubscript{2}Me) (39 mg, 54%) was obtained as an inseparable oily mixture of diastereoisomers (Found: M\textsuperscript{+}-Bu\textsuperscript{t}, 285.0795. C\textsubscript{12}H\textsubscript{17}O\textsubscript{6}Si requires M-Bu\textsuperscript{t}, 285.0794), \nu_{\text{max}} \text{ cm}^{-1}, m/z (\%) 285 (M\textsuperscript{+}-Bu\textsuperscript{t}, 22), 225 (25), 211 (10), 185 (89), 168 (14), 167 (29), 101 (100), cis-diastereoisomer 89.83 (0.7 H, s, CHO), 6.74 (0.7 H, d, J 2 Hz, 2-H), 5.64 (0.7 H, m, 3-H), 4.97 (0.7 H, m, 5-H), 3.75 (2.1 H, s, MeO), 3.41 (1.4 H, s, CH\textsubscript{2}CO\textsubscript{2}Me), 2.90 (0.7 H, ddd, J 14, 7 and 7 Hz, 4-H cis to 5-H), 1.84 (0.7 H, ddd, J 14, 5 and 5 Hz, 4-H trans to 5-H), 0.89 (6.3 H, s, Bu\textsuperscript{t}), 0.08 (4.2 H, s, Me\textsubscript{2}Si), trans-diastereoisomer 89.83 (0.3 H, s, CHO), 6.79 (0.3 H, d, J 2 Hz, 2-H), 6.05 (0.3 H, m 3-H), 5.20 (0.3 H, m, 5-H), 3.75 (0.9 H, s, MeO), 3.39 (0.6 H, s, CH\textsubscript{2}CO\textsubscript{2}Me), 2.41-2.10 (0.6 H, m, 4-H cis and trans to 5-H), 0.85 (2.7 H, s, Bu\textsuperscript{t}), 0.08 (1.8 H, s, Me\textsubscript{2}Si).
Attempted cyclisation of the methyl ester (126; Z=CO₂Me)

A 35% suspension of potassium hydride in mineral oil (4.5 mg, 0.11 mmol) was washed with anhydrous hexane (2 x 0.2 ml) and then suspended in THF (0.25 ml) at -62 °C. The methyl ester (126; Z=CO₂Me) (38 mg, 0.11 mmol) in THF (1 ml) was then added to the potassium hydride suspension. After 30 min., the potassium hydride remained unconsumed and analytical t.l.c. of the reaction mixture showed that the starting material was essentially unchanged. HMPA (0.02 ml, 0.11 mmol) was added but had little effect at this temperature. However, on warming the mixture to 0 °C all of the suspended potassium hydride and the methyl ester (126; Z=CO₂Me) were consumed, giving several new components by analytical t.l.c.. After 30 min., the reaction mixture was directly chromatographed on silica gel in ethyl acetate-petrol to furnish a colourless oil (11 mg). The ¹H n.m.r. spectrum of this oil was complicated by the presence of at least two diastereoisomers although signals corresponding to Bu⁺Me₂Si, MeO, and aldehyde protons were observed. Infrared absorption by the same sample at 1780 and 1740 cm⁻¹ indicated the presence of a γ-lactone carbonyl function, and ester and aldehyde carbonyl functions respectively. A mass spectrum of this product was not obtained.
1-(t-Butyldimethylsilyloxy)-3-chloro-4-(tetrahydropyran-2'-yloxy)-2-cyclopentene (174)

3-Chloro-4-(tetrahydropyran-2'-yloxy)-2-cyclopentenone (173) (54 mg, 0.25 mmol), prepared by the method of Gill and Rickards, was dissolved in THF (3 ml) and cooled to -78 °C. Lithium tri-_,butylborohydride in THF (0.27 ml, 1 M) was added slowly to compound (173) and, after 1 hr at this temperature, water (5 ml) was added and the mixture was warmed to room temperature. Further dilution with water (20 ml) and extraction with diethyl ether (2 x 25 ml) gave, after drying (MgSO₄) and evaporation of the extracts, a pale-yellow oil (65 mg). 'Flash' chromatography of this oil in methylene dichloride-methanol (25:1, v/v) afforded 3-chloro-4-(tetrahydropyran-2'-yloxy)-2-cyclopentenol (45 mg, 83%) as a colourless oily mixture of diastereoisomers which was partially characterised, u max. 3 410 and 1 620 cm⁻¹, m/z (%) 119/117 (M⁺-ThpO, 16), 116* (M⁺-ThpOH, 30), 84 (100).

The alcohol (45 mg, 0.21 mmol) thus obtained was dissolved in N,N-dimethylformamide (0.2 ml) and treated firstly with imidazole (36 mg, 0.53 mmol) and then with t-butylchlorodimethylsilane (39 mg, 0.26 mmol). After stirring the solution at room temperature for 1.5 hr it was poured into chilled water (25 ml) and extracted with diethyl ether (2 x 25 ml). The extracts were dried (MgSO₄) and evaporated to afford, after preparative t.l.c. on silica gel in methylene dichloride, 4-(t-butyldimethylsilyloxy)-3-chloro-1-(tetrahydropyran-2'-yloxy)-2-cyclopentene (174) (50 mg, 73%) as a colourless oily mixture of diastereoisomers (Kugelrohr, b.p. 83-85 °C at 0.5 mmHg) (Found: C, 57.51; H, 8.79; Cl, 10.49. C₁₆H₂₉ClO₃Si requires C, 57.72; H, 8.74; Cl,
10.65%, $\nu_{\text{max}}$ 1630 cm$^{-1}$, m/z (%) 233/231 ($M^+ -$Thp0.2), 230* (1), 159 (28), 85 (73), 75 (100), 65.86 and 5.80 (each 0.5 H, dd, $\nu$ 2.5 and 1 Hz, 3-H), 4.96-4.32 (3 H, m, 4-H, 1-H and OCHO), 3.97 and 3.50 (2 H, m, CH$_2$O), 2.82 and 2.75 (each 0.5 H, ddd, $\nu$ 13, 7.5 and 7.5 Hz, 5-H cis to 1-H), 1.95-1.60 (7 H, m, CH$_2$ and 5-H trans to 1-H), 0.88 (9H, s, Bu$^+$), 0.07 (6 H, s, Me$_2$Si).

**Attempted metal-halogen exchange on the chlorocyclopentene (174)**

using butyllithium:

(a) aqueous quench

The chlorocyclopentene (174) (38 mg, 0.11 mmol) was degassed at 0.3 mmHg for 1 hr, dissolved in THF (0.15 ml) and cooled to -45 °C. A solution of butyllithium in hexane (0.34 ml, 1.62 M) was added dropwise and the reaction was efficiently stirred for 2 hr. After this time analytical t.l.c. of an aliquot in methylene dichloride indicated that a new compound had formed which had a larger $R_f$ value than compound (174) and which also quenched the ultraviolet fluorescence. The total reaction mixture was poured into a mixture of ice-cold diethyl ether and water (50 ml, 1:1). The etheral layer was washed with brine (25 ml), dried (MgSO$_4$) and evaporated to afford a pale-yellow oil (47 mg). Analytical t.l.c. of this oil showed that another compound had almost exclusively been formed which possessed a smaller $R_f$ value than the reaction intermediate mentioned above. This product was unstable to chromatographic purification. Spectral data shown below was therefore obtained for the crude reaction mixture, $\nu_{\text{max}}$. 1725 and 1602 cm$^{-1}$, m/z (%) 159 (Bu$^+$Me$_2$Si0Thp$^+$-Bu$^+$, 35) (Found: 159.0841. C$_7$H$_{15}$O$_2$Si requires 159.0842), 132 (12), 118/116 (33) (Found: 116.0024. C$_5$H$_9$Cl0 requires 116.0029), 85 (m/z 159 - Me$_2$Si0), 75 (100),
(b) direct chromatography

The preceding experiment was repeated using the chlorocyclopentene (174) (27 mg, 0.08 mmol), THF (0.05 ml) and butyllithium in hexane (0.34 ml, 1.5 M). The mixture was maintained at -45 °C for 3 hr after which it was diluted with anhydrous diethyl ether (1 ml) and then directly chromatographed on silica gel in methylene dichloride. The faster-moving band was rapidly isolated to yield an extremely unstable pale-yellow oil (8 mg) which was partially characterised, 

\[
\lambda_{\text{max.}} \quad \text{(EtOH)} \quad 231 \text{ nm, } \delta 7.60 (1 \text{ H, t, } J 2 \text{ Hz}), 2.58 (4 \text{ H, m}),
\]

additional signals attributed to Thp and \( t \)-BuMe\(_2\)Si protons were observed in this product mixture.

4-(t-Butyldimethylsilyloxy)-3-(tributylstannyl)-2-cyclopentenone (179)

by the method of Piers and Morton

A solution of tributyltin hydride (294 mg, 1 mmol) in anhydrous THF (0.5 ml) was added dropwise to a solution of diisopropylamide in THF (1 ml, 1 M), precooled to 0 °C. The solution was further cooled to -23 °C and, under a rapid flow of nitrogen, anhydrous phenylthiocopper (170 mg, 1 mmol) was added to afford a deep-red solution. After 15 min., the chloro-enone (86; \( X=\text{Cl} \)) (209 mg, 0.85 mmol) in THF (0.5 ml) was
added dropwise to this solution which was then stirred for a further 30 min. at -23 °C. The reaction was rapidly quenched with saturated aqueous ammonium chloride (25 ml) and, after diluting with diethyl ether (25 ml), the mixture was stirred at room temperature for 1 hr, before it was further diluted with water (25 ml) and extracted with diethyl ether (2 x 25 ml). The extracts were washed with brine (25 ml), dried (MgSO$_4$) and evaporated to afford a brown oil (471 mg). 'Flash' chromatography of this oil on silica gel in petrol-methylene dichloride (3:2 v/v) gave the recovered chloro-enone (86; X=Cl) (130 mg, 62%) and the stannylenone (179) (111 mg, 26%).

4-(t-Butyldimethylsilyloxy)-3-(tributylstannyl)-2-cyclopentenone (179)

A solution of tributyltin hydride (581 mg, 2 mmol) in anhydrous THF (1 ml) was added dropwise to a solution of lithium diisopropylamide in THF (2 ml, 1 M), precooled to 0 °C. After 10 min., the colourless solution was further cooled to -25 °C and a solution of copper(I) bromide-dimethylsulphide (205 mg, 1 mmol) in dimethylsulphide-THF (2 ml, 1:1 v/v) was slowly added. After 30 min., a deep-red solution had developed to which was added the chloro-enone (86; X=Cl) (218 mg, 0.88 mmol) in THF (1 ml). The mixture was stirred at -20 °C for 1 hr and then quenched with saturated aqueous ammonium chloride (25 ml). The mixture was diluted with diethyl ether (25 ml) and stirred at room temperature for 1 hr before it was further diluted with water (25 ml) and extracted with diethyl ether (2 x 25 ml). The extracts were washed with brine (25 ml), dried (MgSO$_4$) and evaporated to yield a pale-yellow oil (800 mg). Preparative t.l.c. on silica gel in methylene dichloride-methanol (50:1 v/v) afforded 4-(t-butyldimethylsilyloxy)-3-(tributylstannyl)-2-cyclopentenone (179) (372 mg, 84%) as a colourless oil (Kugelrohr, b.p. 76-78 °C at 0.04 mmHg) (Found: C, 54.91; H, 8.92.
C_{23}H_{46}O_2SiSn requires C, 55.10; H, 9.24%.
\[ \nu_{max} \] 1720 cm\(^{-1}\), m/z (%): 445 (M\(^+\)-Bu, 100), 389 (15), 86.30 (1 H, d, \(j\) 1 Hz, 2-H), 4.96 (1 H, ddd, \(j\) 6, 2.5 and 1 Hz, 4-H), 2.70 (1 H, ddd, \(j\) 17 and 6 Hz, 5-H cis to 4-H), 2.16 (1 H, ddd, \(j\) 17 and 2.5 Hz, 5-H trans to 4-H), 1.80-0.80 (36 H, m, Bu\(_3\)Sn and Bu\(^t\)), 0.12 and 0.10 (each 3 H, s, Me\(_2\)Si).

4-(t-Butyldimethylsilyloxy)-3-(tributylstannyl)-2-cyclopentenol (180)

Lithium tri-\(\alpha\)-butylborohydride in THF (0.49 ml, 1 M) was added dropwise to a well-stirred solution of the stannyl-enone (179) (240 mg, 0.48 mmol) in THF (7 ml) at -78 °C. After 30 min. at this temperature, water (2 ml) was added and the mixture was warmed to room temperature. Further dilution with water (25 ml) and extraction with diethyl ether (3 x 25 ml) gave, after drying \(\text{MgSO}_4\) and evaporation of the combined extracts, a pale-yellow oil (322 mg). Preparative t.l.c. of this oil on silica gel in methylene dichloride-methanol (50:1 v/v) afforded 4-(t-butyldimethylsilyloxy)-3-(tributylstannyl)-2-cyclopentenol (180) (240 mg, 99%) as a colourless oil (Kugelrohr, b.p. 78-81 °C at 0.04 mmHg) (Found: C, 54.82; H, 9.65. C_{23}H_{46}O_2SiSn requires C, 54.82; H, 9.70%), \[ \nu_{max} \] 3300 cm\(^{-1}\), 59.99 (1 H, d, \(j\) 1.5 and 1.5 Hz, 2-H), 4.70 (1 H, m, 1-H and 4-H), 2.70 (1 H, ddd, \(j\) 13.5, 6.5 and 6.5 Hz, 5-H cis to 4-H), 1.65-0.80 (38 H, Bu, Bu\(^t\), OH and 5-H trans to 4-H), 0.10 (6 H, s, Me\(_2\)Si).

4-(t-Butyldimethylsilyloxy)-1-(tetrahydropyran-2'-yloxy)-3-(tributylstannyl)-2-cyclopentene (181)

Dihydropyran (92 mg, 1.1 mmol) was added dropwise over 30 min. to the stannyl-alcohol (180) (503 mg, 1 mmol) in methylene dichloride (4 ml) containing \(p\)-toluenesulphonic acid (0.01 M). The solution was stirred at room temperature for 16 hr, diluted with diethyl ether (50
ml), washed with aqueous sodium hydrogencarbonate (25 ml) and water (2 x 25 ml) and finally dried (MgSO₄). Evaporation of the solvent furnished 4-(t-butyldimethylsilyloxy)-1-(tetrahydropyran-2'-yloxy)-3-(tributylstannyl)-2-cyclopentene (181) (557 mg, 95%) as a colourless oil (Kugelrohr, b.p. 100 °C at 0.05 mmHg) (Found: C, 57.24; H, 9.63. C₂₈H₅₆O₃SiSn requires C, 57.25; H, 9.60%), δ5.97 (1 H, m, 2-H), 4.82-4.50 (3 H, m, 1-H, 4-H and OCHO), 4.10-3.40 (2 H, m, CH₂O), 2.67 (1 H, ddt, J 12.5, 6.5, 2.5 Hz, 5-H cis to 4-H), 1.90-0.80 (43 H, m, Bu⁺, Bu₂, 3 x CH₂ in tetrahydropyranyl ring and 5-H trans to 4-H), 0.08 (6 H, s, Me₂Si).

Cyclopentene-ester (183;E=CO₂Et)

The stannyl-cyclopentene (181) (30 mg, 0.05 mmol) was degassed at 0.05 mmHg at room temperature for 2 hr and subsequently dissolved in THF (0.3 ml). Butyllithium in hexane (0.033 ml, 3.2 M) was then added dropwise to this solution at -45 °C. After 45 min., transmetallation was complete, as judged by t.l.c., and the reaction mixture was cooled to -78 °C. Freshly distilled ethyl chloroformate (0.021 ml, 0.021 mmol) was added and the resultant solution was maintained at -78 °C for 1 hr before it was quenched with saturated aqueous ammonium chloride (5 ml). The mixture was diluted with diethyl ether (25 ml), washed with brine (25 ml) and water (25 ml). The organic phase was then dried (MgSO₄) and evaporated to furnish a colourless oil (80 mg). Preparative t.l.c. on silica gel in methylene dichloride-methanol (50:1 v/v) furnished the cyclopentene-ester (183;E=CO₂Et) (17.8 mg, 94%) as an oily mixture of diastereoisomers (Kugelrohr, b.p. 81-83 °C at 0.6 mmHg) (Found: C, 61.41; H, 9.22. C₁₉H₃₄O₅Si requires C, 61.58; H, 9.25%), m/z (%) 313 (M⁺-Bu⁺, 1), 271 (M⁺-C₅H₈0-Me, 100), 229 (M⁺-C₅H₈0-Bu⁺, 4), 201 (9),...
δ6.71 (1 H, dt, J 1 and 2 Hz, 2-H), 5.00-4.40 (3 H, m, 1-H, 4-H and OCHO), 4.20 and 4.18 (each 1 H, q, J 7 Hz, CH₂Me), 4.00-3.40 (2 H, m, CH₂O), 2.90-2.50 (1 H, m, 5-H cis to 4-H and 1-H), 1.95-1.45 (7 H, m, 5-H trans to 4-H and CH₂ in tetrahydropyranyl ring), 1.28 (3 H, t, J 7 Hz, MeCH₂), 0.89 (9 H, s, Buᵗ), 0.12 (6 H, s, Me₂Si).

Cyclopentene-aldehyde (183;E=CHO)

A solution of the lithio-cyclopentene (182) was prepared as in the preceding experiment and cooled to -78 °C. To this cold solution was added freshly distilled methyl formate (0.023 ml, 0.28 mmol). After 1 hr most of the lithio-cyclopentene (182) had been consumed, as judged by analytical t.l.c. The reaction was quenched as in the preceding experiment and chromatography of the product mixture on silica gel in methylene dichloride-methanol (50:1 v/v) furnished the cyclopentene-aldehyde (183;E=CHO) (12 mg, 77%) as a colourless oily mixture of diastereoisomers (Kugelrohr, b.p. 95 °C at 0.1 mmHg) (Found: C, 62.40; H, 9.15. C₁₇H₃₀O₄Si requires C, 62.55; H, 9.25%). v max. 1692 cm⁻¹, δ9.82 (1 H, br s, CHO), 6.85 (1 H, m, 2-H), 5.00-4.40 (3 H, m, 1-H, 4-H and CHO), 4.08-3.40 (2 H, m, CH₂O), 3.00-2.66 (1 H, m, 5-H cis to 4-H), 2.00-1.38 (7 H, m, 5-H trans to 4-H and CH₂ in tetrahydropyranyl ring), 0.91 (9 H, s, Buᵗ) [Nb. This ¹H n.m.r. spectrum was obtained on a sample of compound (183;E=CHO) which was contaminated with a small amount of compound (183;E=H)].

1-Acetoxy-4-(t-butyldimethylsilyloxy)-3-(tributylstannyl)-2-cyclopentene (184)

To a solution of the stannyl-alcohol (180) (296 mg, 0.59 mmol) in anhydrous pyridine (0.114 ml) at 0 °C was added distilled acetic anhydride (0.09 ml, 0.88 mmol). The solution was warmed to room
temperature, stirred for 20 hr and quenched with ice-cold, aqueous sodium hydrogen carbonate (25 ml). The resultant mixture was extracted with diethyl ether (3 x 25 ml) and the combined extracts were washed with brine (25 ml), dried (MgSO₄) and evaporated to afford \(1\)-acetoxy-4-(t-butyldimethylsiloxy)-3-(tributylstannyl)-2-cyclopentene (184) (321 mg, quantitative) as a colourless oil (Kugelrohr, b.p. 77-79 °C at 0.6 mmHg) (Found: C, 54.97; H, 9.21. \(\text{C}_{25}\text{H}_{50}\text{O}_{3}\text{SiSn}\) requires C, 55.05; H, 9.24%), \(\nu_{\text{max}}\) 1740 cm\(^{-1}\), \(m/z\) (%) 489 (\(\text{M}^+\)-But, 68), 429 (3), 357 (100), 315 (17), 297 (10), metastable 206.6 (489-357), 85.91 (1 H, dd, \(J\) 1.5 and 1.5 Hz, 2-H), 5.62 (1 H, m, 1-H), 4.73 (1 H, m, 4-H), 2.78 (1 H, ddd \(J\) 12.5, 7 and 7 Hz, 5-H \textit{cis} to 4-H), 2.05 (3 H, s, MeCO), 1.70-0.80 (37 H, m, Bu x 3, \(\text{Bu}^t\) and 5-H \textit{trans} to 4-H), 0.10 (6 H, s, Me₂Si).

\[4-(t\text{-Butyldimethylsiloxy})-1-(1'-(t\text{-butyldimethylsiloxy})\text{ethenyl oxy})-3-(\text{tributylstannyl})-2\text{-cyclopentene (185)}\]

The ketene silyl acetal (185) was prepared from the stanny1-acetate (184) by following a procedure slightly modified from that used by Tamura \textit{et al.}\(^{121}\) Thus, to a THF solution of lithium diisopropylamide (1 ml, 1 M) chilled to -78 °C was added dropwise, a solution of the stanny1-acetate (184) (280 mg, 0.51 mmol) in THF (1 ml). The solution was stirred for 45 min. at this temperature, then HMPA (0.14 ml, 0.8 mmol) was added. After a further 5 min., a solution of \(t\)-butylchlorodimethylsilane (150 mg, 1 mmol) in anhydrous hexane (0.35 ml) was added dropwise. The solution was maintained at -78 °C for 1 hr, warmed to room temperature whereupon it was stirred for a further 1 hr. The reaction mixture was then poured into a mixture of pentane-water (200 ml, 1:1 v/v) at 0 °C, the organic layer was washed with cold brine (50 ml) and quickly dried (MgSO₄). The extracts were evaporated to afford 4-(t-butyldimethylsiloxy)-1-(1'-(t-butyldimethylsiloxy)-...
(t-butyldimethylsilyloxy)ethenyloxyl)-3-(tributylstannyl)-2-cyclopentene (185) (339 mg, quantitative). A sample of compound (185) of the purity required for elemental analysis could not be obtained since decomposition occurred on distillation. Also, because the sample was impure, high resolution mass measurement of the ion \( m/z \) 369 was not performed. \( \nu_{\text{max}} \) 1650 cm\(^{-1}\), \( m/z \) (\%) 369 (\( M^+-\text{Bu}_3\text{Sn}, 11\)), 291 (\( \text{Bu}_3\text{Sn}^+, 58\)), 75 (57) and 73 (100), \( \delta(C_6\text{D}_6) \) 6.18 [1 H, ddd, \( J \) 32 (H-119Sn), 1.5 and 1.5 Hz, 2-H], 4.80 and 4.65 (together 2 H, m, 1-H and 4-H), 3.56 (1 H, d, \( J \) 2.5 Hz, OC=C\( \equiv \)H), 3.28 (1 H, d, \( J \) 2.5 Hz, OC=CH\( ^{119} \)H), 2.63 (1 H, ddd, \( J \) 13, 7 and 7 Hz, 5-H cis to 4-H), 1.90-0.80 (46 H, m, Bu x 3, Bu\(^t\) and 5-H trans to 4-H), 0.23 (6 H, s, Me\(_2\)SiOC=), 0.12 and 0.07 (each 3H, s, Me\(_2\)Si).

Transmetallation of the ketene silyl acetal (185) and subsequent protonation

The ketene silyl acetal (185) (39 mg, 0.06 mmol) was degassed for 1 hr at 0.3 mmHg, dissolved in anhydrous THF (0.2 ml) and cooled to -45 °C. A solution of butyllithium in hexane (0.12 ml, 0.18 mmol) was added dropwise to give a yellow solution which was stirred at -40 °C for 45 min. and was then poured into a mixture of pentane-water (100 ml, 1:1) at 0 °C. The organic layer was washed with chilled brine (50 ml), quickly dried (MgSO\(_4\)) and evaporated to yield a 1:1 mixture of tetrabutyltin and \( 4-(t\text{-butyldimethylsilyloxy})\text{-1-(t\text{-butyldimethylsilyloxy})-ethenyloxyl}-2\text{-cyclopentene} \) (187; \( E=H \)) (38 mg, 90%\(^+\)). The unstable nature of compound (187; \( E=H \)) prevented its separation from Bu\(_4\)Sn by chromatography or distillation and all spectroscopic data were obtained on the mixture (Found: \( M^+-\text{Bu}^t \), 313.1657. \( C_{15\text{H}_{30}\text{O}_3\text{Si}_2} \) requires \( M^+-\text{Bu}^t \), 313.1650), \( \nu_{\text{max}} \) 1650 cm\(^{-1}\), \( m/z \) (\%) 370 (\( M^+ \), 3), 369 (\( M^+-1 \), 27), 355 (\( M^+-\text{Me} \), 4), 313 (\( M^+-\text{Bu}^t \), 12), 239 (5), 197 (100), \( \delta(C_6\text{D}_6) \) 5.80 (2 H, m,\( \text{Me}_2\text{Si} \)).

\(^+\) Estimated from the \( ^1\text{H} \) n.m.r. spectrum and mass recovery.
Transmetallation of the ketene silyl acetal (185) and subsequent reaction with ethyl chloroformate

Transmetallation of the ketene silyl acetal (185) (43 mg, 0.06 mmol) was effected by following the procedure described in the preceding experiment. To a solution of the intermediate lithio-cyclopentene (186) at -78 °C was added dropwise, freshly distilled (acid-free) ethyl chloroformate (28 mg, 0.26 mmol). The reaction was stirred for 30 min. at -78 °C and then poured into a mixture of pentane-water (100 ml, 1:1 v/v) at 0 °C. The organic layer was washed with chilled brine (50 ml), dried (MgSO₄) and evaporated to afford a pale-yellow oil (54 mg) consisting of tetrabutyltin, the cyclopentene (187; E=H) and ethyl 5-(t-butyldimethylsilyloxy)-3-[1′-(t-butyldimethylsilyloxy)ethenyloxy]-1-cyclopentene carboxylate (187; E=CO₂Et). Compounds (187; E=H) and (187; E=CO₂Et) were shown to be present in a ratio of 1:4 by ¹H n.m.r. spectroscopy and, as in the preceding experiment, all spectroscopic data were obtained on a mixture of the products, ν max. 1730 and 1650 cm⁻¹, m/z (%) 385 (M⁺-Bu⁺, 13), 311 (8), 281 (8), 269 (M⁺-C₈H₁₇-O₂Si, 26), 189 (21), 75 (71) and 73 (100), (C₆D₆) (partial spectral details) 6.71 (H++, dd, J 2 and 1 Hz, 2-H), 4.75 (H++, dd, J 7 and 3.5 Hz, 5-H), 4.58 (H++, m, 3-H), 3.99 (H++, q, J 7 Hz, CH₂Me), 3.50

++ This ¹H n.m.r. spectrum was obtained on a mixture and consequently the integration of some signals could not be accurately determined, hence no values are quoted. Also, the C-4 proton trans to the C-5 proton was, as expected, obscured by signals derived from the tetrabutyltin methylene protons.
(H\textsuperscript{+}, d, \textit{J} 2 Hz, OC=CH\textsubscript{2}H), 3.14 (H\textsuperscript{+}, d, \textit{J} 2 Hz, OC=CH\textsubscript{2}H) and 2.44 (H\textsuperscript{+}, m, \textit{J} 14, 7 and 3.5 Hz, 4-H \textit{cis} to 5-H).

**Hydrolysis of the cyclopentene-ester (187;E=CO\textsubscript{2}Et)**

The mixture obtained in the preceding experiment was dissolved in diethyl ether and stirred over wet silica gel for 2 hr under an atmosphere of air. The mixture was diluted with diethyl ether (25 ml), washed with brine (25 ml) and dried (MgSO\textsubscript{4}). Evaporation of the solvent furnished a pale-yellow oil (50 mg) which, after chromatography on silica gel in dichloromethane-methanol (50:1 v/v), gave ethyl 3-acetoxy-5-(t-butyldimethylsilyloxy)-1-cyclopentene-carboxylate (243) as a colourless oil (9 mg, 35%) (Found: M\textsuperscript{+}-Bu\textsuperscript{t}, 271.0997. C\textsubscript{12}H\textsubscript{19}O\textsubscript{5}Si requires M-Bu\textsuperscript{t}, 271.1002), \textdelta 6.19 (1 H, dd, \textit{J} 2 and 1 Hz, 2-H), 5.56 (2 H, m, 3-H and 5-H), 4.19 (2 H, q, \textit{J} 7 Hz, CH\textsubscript{2}Me), 2.92 (1 H, ddd, \textit{J} 14.5, 7.5 and 7.5 Hz, 4-H \textit{cis} to 5-H), 2.02 (3 H, s, MeCO), 1.73 (1 H, ddd, \textit{J} 14.5, 4.5 and 4.5 Hz, 4-H \textit{trans} to 5-H), 1.27 (3 H, t, \textit{J} 7 Hz, MeCH\textsubscript{2}), 0.87 (9 H, s, Bu\textsuperscript{t}).

**Transmetallation of the ketene silyl acetal (185) and subsequent reaction with ethyl formate**

Transmetallation of the ketene silyl acetal (185) (34 mg, 0.05 mmol) was effected by following the procedure described above. To the pale-yellow solution of the lithio-cyclopentene (186) at -78 °C were sequentially added anhydrous HMPA (0.018 ml, 0.11 mmol) and freshly distilled ethyl formate (0.013 ml, 0.161 mmol). The reaction mixture was maintained at -78 °C for 1.25 hr after which it was worked up as in the preceding experiment to furnish a pale-yellow oil (34 mg). Spectral data obtained on this oil showed it to comprise several components. Signals possibly attributable to the cyclopentene-aldehyde (187;E=CHO):
\begin{align*}
\nu_{\text{max.}} & = 1701 \text{ cm}^{-1}, & \delta(C_6D_6) & = 9.44 \text{ (s, CHO)}, 6.26 \text{ (m, 2-H)}, 4.80-3.35 \text{ (m, 1-H and 4-H)}, 3.51 \text{ (d, 2.5 Hz, OC=CH}_2\text{H)}, 3.11 \text{ (d, 2.5 Hz, OC=CH}_2\text{H)}. \\
\text{These signals accounted for approximately 50% of the cyclopentenyl products in the mixture. The reader should note that when this experiment was repeated, widely variable results were obtained.} \\
\text{Attempted transmetallation of the ketene silyl acetal (185) using t-butyllithium} \\
\text{The ketene silyl acetal (185) (39 mg, 0.06 mmol) was degassed for 1 hr at 0.3 mmHg, dissolved in THF and the resultant solution was cooled to -45 °C. When t-butyllithium in hexane (0.11 ml, 0.18 mmol) was added to this solution, a yellow precipitate was immediately formed and the mixture was stirred vigorously for 40 min. before ethyl chloroformate (28 mg, 0.26 mmol) was added. The resultant clear solution was stirred for a further 15 min., quenched with pentane-water (50 ml 1:1 v/v) at 0 °C and the organic layer was washed with chilled brine (25 ml), dried (MgSO}_4\text{) and evaporated to afford the ketene silyl acetal (185) (34 mg, 87%) as a colourless oil. The}^{1}\text{H n.m.r. spectrum of this product indicated that compound (185) was essentially pure.} \\
\text{Attempted cyclisation of the cyclopentene-ester (187;E=CO}_2\text{Et) with trimethylsilyl trifluoromethanesulphonate} \\
\text{The 4:1 mixture of the cyclopentene-ester (187;E=CO}_2\text{Et) and the cyclopentene (187;E=H) obtained previously was dissolved in freshly distilled methylene dichloride (5 ml) and cooled to -62 °C. Trimethylsilyl trifluoromethanesulphonate (0.01 ml, 0.05 mmol) was added dropwise to this solution which was stirred for 80 min. and then quenched with water at 0 °C (10 ml). The product mixture was extracted}
\end{align*}
with diethyl ether (2 x 25 ml) and the extracts were washed with brine (25 ml), dried (MgSO₄) and evaporated to afford a colourless oil (30 mg) which, by analytical t.l.c., was comprised of ten components. Although there were a large number of products, an infrared spectrum of this crude mixture did not indicate that a γ-lactone function was present in any of the products.
3-Chloro-2-cyclohexenone was prepared from cyclohexane-1,3-dione and oxalyl chloride, according to the known procedure\textsuperscript{130} [b.p. 79.5-80.5 °C at 15 mmHg (lit., b.p. 78 °C at 14 mmHg)], 6.16 (1 H, t J 1 Hz, 2-H), 2.68 (2 H, t J 6 Hz, 6-H), 2.40 (2 H, m, 4-H), 2.12 (2 H, m, 5-H).

Conjugate addition-elimination studies on 3-chloro-2-cyclohexenone:
(a) optimum conditions for monoalkylation

A suspension of copper(I) iodide (190 mg, 1 mmol) in THF (7 ml) containing 3-chloro-2-cyclohexenone (130 mg, 1 mmol) was stirred vigorously at -10 °C. Dropwise addition of butylmagnesium bromide in THF (2.8 ml, 0.53 M) produced a green-coloured solution which was quenched with saturated aqueous ammonium chloride (5 ml) after 15 min. The mixture was diluted with diethyl ether (5 ml), stirred at room temperature for 1 hr, further diluted with water (25 ml) and then extracted with diethyl ether (2 x 25 ml). The extracts were washed with brine (25 ml), dried (MgSO\textsubscript{4}) and evaporated to yield a yellow oil (139 mg). Preparative t.l.c. on silica gel in methylene dichloride-methanol (50:1 v/v) afforded 3-butyl-2-cyclohexenone (199) (125 mg, 82%) as a colourless oil [b.p. 57 °C at 0.3 mmHg (lit., 131 119-120 °C at 12 mmHg)], 65.80 (1 H, s, 2-H), 2.40-0.80 (15 H, m, Bu and remaining ring-H).

(b) attempted interception of the intermediate enolate (198; R=Bu, X=Cl) with allyl bromide

The preceding reaction was repeated and allyl bromide (133 mg, 1.1 mmol) was rapidly added subsequent to the butylmagnesium bromide.
After 1 hr the reaction was worked-up as in (a) to afford, after chromatography, the enone (199) (144 mg, 95%).

(a) attempted interception of the intermediate enolate (198; R=Bu, X=Cl) with formaldehyde.

A suspension of copper(I) iodide (190 mg, 1 mmol) in THF (7 ml) containing 3-chloro-2-cyclohexenone (130 mg, 1 mmol) was stirred vigorously at -10 °C. A solution of formaldehyde (monomer)\(^{132}\) in THF (3.2 ml, 1.7 M) was added prior to butylmagnesium bromide in THF (2.8 ml, 0.53 M), which was added dropwise. After 1 hr the reaction was quenched as in (a) to afford, after chromatography, the enone (199) (125 mg, 79%).

3-N-Pyrrolidino-2-cyclohexenone (200a)

Compound (200a) was prepared from cyclohexane-1,3-dione and distilled pyrrolidine in a Dean-Stark apparatus according to the known procedure,\(^{133}\) [m.p. 89.5-91 °C (lit., 84-88 °C)] \(55.00 \ (1 \text{H}, \text{s}, \text{2-H}),\) 3.60-3.00 (4 \text{H}, \text{m}, \text{NCH}_2\text{CH}_2 \times 2), 2.70-1.60 (10 \text{H}, \text{m}, \text{remaining ring-H}, \text{and NCH}_2\text{CH}_2 \times 2).

Conjugate addition-elimination study on 3-pyrrolidino-2-cyclohexenone (200a)

(a) using butylmagnesium bromide

To a solution of compound (200a) (74 mg, 0.45 mmol) in THF (1 ml) cooled to 0 °C was added butylmagnesium bromide in THF (1.6 ml, 0.35 M). A copious white precipitate was observed on addition of the first half of the Grignard reagent which then disappeared on addition of the
remainder of the reagent. The reaction was stirred for 1.5 hr at room temperature whereupon the mixture was poured into ice-cold water and extracted with methylene dichloride (2 x 25 ml) to afford recovered compound (200a) (64 mg, 86%).

(b) using a magnesio-cuprate reagent

A suspension of copper(I) iodide (92 mg, 0.5 mmol) in THF (3 ml) containing compound (200a) (82 mg, 0.5 mmol) was cooled to -10 °C. After addition of butylmagnesium bromide in THF (2.15 ml, 0.35 M), the reaction mixture was stirred for 15 min. before saturated ammonium chloride solution was added. The mixture was diluted with water (25 ml), and extracted with diethyl ether (2 x 25 ml) and methylene dichloride (2 x 25 ml). The extracts were separately evaporated to afford, after drying (MgSO₄), compound (200a) (31 mg, 38%) with a trace of compound (199) (<1%).

3-(N-imidazolyl)-2-cyclohexenone (200b)

To a solution of imidazole (272 mg, 4 mmol) in THF (2.5 ml) was added anhydrous potassium carbonate (552 mg, 4 mmol) and 3-chloro-2-cyclohexenone (260 mg, 2 mmol) in THF (2.5 ml). The mixture was refluxed for 24 hr, cooled, poured into chilled water (20 ml) and extracted with methylene dichloride (3 x 25 ml). The extracts were washed with brine (2 x 25 ml), dried (MgSO₄) and evaporated to afford compound (200b) (324 mg, quantitative) as colourless platelets by sublimation at 100 °C and 0.1 mmHg (m.p. 104-105.5 °C) (Found: C, 66.87; H, 6.04; N, 17.50. C₉H₁₀N₂O requires C, 66.63; H, 6.22; N, 17.28%), \( \nu \) max. (CHCl₃) 1 670 and 1 630 cm⁻¹, m/z (%) 162 (M⁺, 100), 135 (M⁺-27, 47), 134 (M⁺-28, 42), 106 (19), 95 (19), 67 (C₃H₃N₂, 93), metastables 112.5 (M⁺-135), 83.8 (134-106), 67.3 (134-95), 67.96, 7.28
and 7.20 (each 1 H, s, imidazolyl-H), 6.18 (1 H, s, 2-H), 2.87-2.22 (6 H, m, remaining ring-H).

Conjugate addition-elimination study on the imidazolyl-enone (200b)

A suspension of copper(I) iodide (95 mg, 0.5 mmol) in THF (2 ml) containing compound (200b) (81 mg, 0.5 mmol) was stirred vigorously at -10 °C. Butylmagnesium bromide in THF (0.6 ml, 1.3 M) was added dropwise and, after 15 min., saturated aqueous ammonium chloride (5 ml) and diethyl ether (5 ml) were added to the black mixture. This reaction mixture was then stirred for 1 hr at room temperature, diluted with water (25 ml) and extracted with diethyl ether (2 x 25 ml). The extracts were dried (MgSO₄) and evaporated to yield a green oil (90 mg). G.l.c. analysis of the volatiles (85 mg) confirmed the presence of recovered compound (200b) (5%), 3-butyl-2-cyclohexenone (199) (56%) and 3,3-dibutylcyclohexanone (197) (23%)[133]. Compound (197) was subsequently isolated by preparative t.l.c. on silica gel in methylene chloride-methanol (50:1 v/v), v max. 1710 cm⁻¹.

3-Oxo-1-cyclohexene-carbonitrile (159)

The nitrile (159) was prepared by the method of Cronyn and Goodrich[109] [b.p. 80 °C at 0.5 mmHg (lit., 105 °C at 3.8 mmHg)], m/z (%) 121 (M⁺, 38), 93 (100), 66.50 (1 H, t, J 1 Hz, 2-H), 2.80-1.90 (6 H, m, remaining ring-H).

Conjugate addition-elimination studies on the nitrile (159)

A solution of lithium dimethylcopper in THF-diethyl ether (4:1 v/v) (2.5 ml, 1.2 mmol) at 0 °C was added dropwise to a solution of compound (159) (242 mg, 2 mmol) in diethyl ether (2.5 ml) at 0 °C. HMPA (0.36 ml, 2 mmol) and allyl bromide (245 mg, 2 mmol) were then added and
the mixture was stirred for 90 min. The mixture was subsequently quenched with saturated aqueous ammonium chloride (25 ml) and extracted with diethyl ether (3 x 25 ml). The extracts were washed with brine (25 ml), dried (MgSO₄) and evaporated to yield, after preparative t.l.c. on silica gel in methylene dichloride-methanol (50:1 v/v), 1-methyl-3-oxocyclohexanecarbonitrile (201) (76 mg, 28%) as a colourless oil (Found: M⁺, 137.0839. C₈H₁₁NO requires M⁺, 137.0840), v_max. 2235 and 1710 cm⁻¹, m/z (%) 137 (M⁺, 45), 122 (M⁺-Me, 31), 109 (13), 94 (48), 55 (100), 62.70-1.70 (8 H, m, ring-H) and 1.45 (3 H, s, Me).

3-Butylthio-2-cyclohexenone (202)

Compound (202) was prepared by a slightly modified procedure to that reported by Coni et al. Thus, butanethiol (540 mg, 6 mmol) was added dropwise to a suspension of sodium hydride (144 mg, 6 mmol) in THF (10 ml) at 0 °C. After 30 min. when the evolution of hydrogen had ceased, 3-chloro-2-cyclohexenone (520 mg, 4 mmol) in THF (15 ml) was added. The reaction was stirred for 3 hr, poured into ice-cold water and extracted with methylene dichloride (4 x 25 ml). The extracts were dried (MgSO₄) and evaporated in a hood to yield a yellow oil (825 mg) which was chromatographed on silica gel in methylene dichloride-methanol (50:1 v/v) to afford compound (202) (662 mg, 90%) (b.p. 150 °C at 1.5 mmHg), ν_max. 1 660 and 1 575 cm⁻¹, m/z (%) 184 (M⁺, 55), 128 (M⁺-C₄H₈, 37), 127 (M⁺-Bu, 100), 100 (78), 65.84 (1 H, s, 2-H), 2.77 (2 H, t, 7 Hz, SCH₂Pr), 2.50-1.20 (10 H, m, remaining ring-H and SCH₂CH₂CH₂Me), 0.92 (3 H, t, 6 Hz, Me).

Conjugate addition-elimination studies on the butylthio-enone (202):
(a) at 0 °C

A solution of lithium dimethylcopper in THF-diethyl ether (4:1
v/v) (2.5 ml, 0.5 mmol) at 0 °C was rapidly transferred, via cannula, to a solution of compound (202) (183 mg, 1 mmol) in THF (0.6 ml). The colour of the solution rapidly darkened and, after 30 min., the reaction was quenched with ice-cold saturated aqueous ammonium chloride. The mixture was extracted with methylene dichloride (4 x 25 ml) and the extracts were dried (MgSO₄) and then evaporated to afford a pale-yellow oil (134 mg). G.l.c. analysis of the volatiles (120 mg) confirmed the presence of 3-methyl-2-cyclohexenone and recovered 3-butylthio-2-cyclohexenone in yields of 61% and 14% respectively.

(b) attempted interception of the enolate (198; R=Me, X=SBu) with allyl bromide

The preceding reaction was repeated and, after addition of compound (202), the mixture was stirred at 0 °C for 3 min. before allyl bromide (0.17 ml, 2 mmol) was added. This afforded a yellow precipitate. The resulting mixture was stirred for 2 hr at room temperature after which it was quenched with saturated aqueous ammonium chloride and then extracted with methylene dichloride (4 x 25 ml). The extracts were dried (MgSO₄) and evaporated to yield, on distillation, a pale-yellow oil (151 mg), t.l.c. of which indicated it to be mixture of five components. G.l.c. analysis starting at 80 °C and programmed at a 12 °C/min. rise, confirmed the presence of 3-methyl-2-cyclohexenone (62%), \( \nu_{\text{max}} \) 1680 cm⁻¹, recovered compound (202) (17%) and five other components, two of which were tentatively assigned by their g.l.c.-mass spectral data to be 3-methyl-6-(2'-propenyl)-2-cyclohexenone (203) (10%), \( m/z \) (%) 150 (M⁺, 31), 135 (M⁺-Me, 25), 82 (M⁺-C₅H₈, 100), and 3-butylthio-6-(2'-propenyl)-2-cyclohexenone (204) (2%), \( m/z \) (%) 224 (M⁺, 31), 168 (M⁺-C₄H₈, 29), 167 (M⁺-Bu, 58), 135 (22), 100 (100).
4-(t-Butyldimethylsilyloxy)-3-methyl-2-cyclopentenone (207)

To the chloro-enone (12) (246 mg, 1 mmol) and copper(I) iodide in diethyl ether (5 ml) at -10 °C was added methylmagnesium iodide (1.4 ml, 1.16 M) over 30 min. After a further 1 hr, the yellow mixture was quenched with saturated aqueous ammonium chloride (10 ml), diluted with diethyl ether (10 ml) and stirred at room temperature for 1 hr. The mixture was further diluted with water (10 ml) and extracted with diethyl ether (2 x 25 ml). The extracts were washed with brine (25 ml), dried (MgSO₄) and evaporated to give a yellow oil (230 mg). Preparative t.l.c. of this oil on silica gel in methylene dichloride-methanol (25:1 v/v) afforded the recovered chloro-enone (12) (88 mg, 39%) together with the methyl-enone (207) (113 mg, 50%) as colourless platelets, m.p. 29-29.5 °C (Found: C, 63.78; H, 9.62. \( \text{C}_{12}\text{H}_{22}\text{O}_{2}\text{Si} \) requires C, 63.66; H, 9.79%), \( \lambda_{\text{max.}} \) (EtOH) 221.5 nm (ε 16 000), \( \nu_{\text{max.}} \) 1720 and 1630 cm\(^{-1}\), \( m/z \) 226 (M\(^+\), 1), 211 (M\(^+\)-Me, 4), 169 (M\(^+\)-Bu\(^+\), 100), 127 (m/s 169-C₂H₂O, 23), 95 (47), 75 (28), metastable 95.5 (169-127), 65.96 (1 H, s, 2-H), 4.76 (1 H, m, 4-H), 2.75 (1 H, dd, J 18 and 6 Hz, 5-H \text{cis to 4-H}), 2.28 (1 H, dd, J 18 and 3 Hz, 5-H \text{trans to 4-H}), 2.13 (3 H, s, Me), 0.92 (9 H, s, Bu\(^+\)), 0.15 and 0.13 (each 3 H, s, Me₂Si).

4-(t-Butyldimethylsilyloxy)-3-phenylseleno-2-cyclopentenone (193; X=SePh)

To a yellow solution of diphenyldiselenide (156 mg, 0.5 mmol) in THF at 0 °C was added a THF solution of lithium tri-o-butylborohydride (1 ml, 1 M). After 15 min., the chloro-enone (12) (240 mg, 0.97 mmol) also in THF (2 ml) was added dropwise. The reaction was stirred at 0 °C for 45 min. and then poured into cold water (20 ml). The mixture was extracted with diethyl ether (3 x 25 ml) and the extracts were washed with brine (25 ml), dried (MgSO₄) and evaporated to afford the phenylseleno-enone (193; X=SePh) (320 mg, 90%) as colourless platelets from petrol, m.p. 70-71.5 °C (Found: M\(^+\)-Bu\(^+\), 311.0008).
Conjugate addition-elimination studies on the phenylseleno-enone (193;X=SePh):
(a) reaction of the phenylseleno-enone (193;X=SePh) with methylmagnesium bromide and copper(I) iodide at -10 °C

To a suspension of compound (193;X=SePh) (62 mg, 0.16 mmol) and copper(I) iodide (39 mg, 0.2 mmol) in THF (1 ml) at -10 °C was added dropwise methylmagnesium bromide (0.3 ml, 1.15 M). After 1 hr the yellow solution was rapidly poured into saturated aqueous ammonium chloride (25 ml), diluted with diethyl ether (25 ml) and vigorously stirred for a further 1 hr. The mixture was diluted with water (25 ml) and extracted with diethyl ether (3 x 25 ml). The extracts were then washed with brine (25 ml), dried (MgSO₄) and evaporated to yield, after preparative t.l.c. on silica gel in methylene dichloride-methanol (100:1 v/v), the methyl-enone (207) (10 mg, 26%) and 4-(t-butyldimethylsilyloxy)-1,3-dimethyl-2-cyclopentenol (208) (20 mg, 49%) as an unstable colourless oil (Found: M⁺, 242.1699. C₁₃H₂₆O₂Si requires M⁺, 242.1702), ν max. 3430 cm⁻¹, m/z (%) 242 (M⁺, 1), 227 (M⁺-Me, 4), 224 (M⁺-H₂O, 5), 185 (M⁺-Bu⁺, 73), 167 (M⁺-Bu⁺-H₂O, 12), 75 (100), δ5.48 (1 H, s, 2-H), 4.45 (1 H, dd, J 7 and 4 Hz, 4-H), 2.36 (1 H, dd, J 13 and 7 Hz, 5-H cis to 4-H), 1.79 (1 H, dd, J 13 and 4 Hz, 5-H trans to 4-H), 1.72 (4 H, br s, MeC= and OH), 1.28 (3 H, s, MeCOH), 0.89 (9 H, s, Bu⁺), 0.12 (6 H, s, Me₂Si).
(b) reaction of compound (193; X=SePh) with lithium dimethylcopper at -62 °C

To a solution of lithium dimethylcopper in THF-diethyl ether (4:1 v/v) (1 ml, 0.25 mmol) at -62 °C was added compound (193; X=SePh) (46 mg, 0.12 mmol) in THF (0.5 ml). After 30 min., allyl bromide (30 mg, 0.25 mmol) in HMPA (0.045 ml, 0.25 mmol) was added to the mixture, which was then warmed to room temperature and stirred for a further 2 hr. After this time the mixture was quenched with saturated aqueous ammonium chloride (25 ml), diluted with diethyl ether (25 ml) and then stirred for 1 hr at room temperature. The mixture was then extracted with diethyl ether (2 x 25 ml), dried (MgSO₄) and evaporated to afford, after chromatography on silica gel in methylene dichloride-methanol (100:1 v/v), the methyl-enone (207) (25 mg, 89%).

(c) reaction of compound (193; X=SePh) with lithium dimethylcopper at -100 °C

To a solution of lithium dimethylcopper (0.25 mmol) in THF-pentane-diethyl ether (1 ml) (4:4:1 v/v) at -100 °C was slowly added compound (193; X=SePh) (46 mg, 0.12 mmol) in THF-pentane (1 ml) (1:3 v/v). After 1 hr allyl bromide (242 mg, 2 mmol) was added dropwise to the reaction mixture and following a further 1 hr the mixture was poured into saturated aqueous ammonium chloride (25 ml). Product isolation, as in the preceding experiment, afforded only recovered phenylseleno-enone (193; X=SePh) (41 mg, 89%).

4-((t-Butyldimethylsiloxy)-3-(trimethylstannyl)-2-cyclopentenone (193; X=SnMe₃)

To a colourless solution of hexamethyldistannane (330 mg, 1 mmol) in THF (1 ml) at -20 °C was rapidly added methyllithium in diethyl ether (0.72 ml, 1.39 M). The resultant pale-yellow solution was stirred for 20 min. at -20 °C after which a solution of copper(I) bromide-dimethylsulphide complex (102 mg, 0.5 mmol) in diethyl
ether-dimethylsulphide (1 ml, 1:1 v/v) was added dropwise. The light-brown suspension thus obtained was cooled to -78 °C and the chloro-enone (12) (120 mg, 0.49 mmol) in diethyl ether (0.2 ml) was added. After 30 min., the reaction was then warmed to -20 °C over 30 min. and maintained at that temperature for a further 30 min. The black mixture was quenched with saturated aqueous ammonium chloride (5 ml), diluted with diethyl ether (5 ml) and stirred at room temperature for 1 hr. The mixture was diluted with water (25 ml) and extracted with diethyl ether (2 x 25 ml), the extracts were washed with brine (25 ml), dried (MgSO₄) and evaporated to afford a brown oil (236 mg).

Preparative t.l.c. on silica gel in methylene dichloride-methanol (50:1 v/v) gave the trimethylstannyl-enone (193; X=SnMe₃) (96 mg, 52%) as colourless platelets by sublimation at 62 °C and 0.2 mmHg, m.p. 65-66.5 °C (Found: C, 44.99; H, 7.70. C₁₄H₂₈O₂SiSn requires C, 44.82; H, 7.52%). \( \nu_{\text{max}} \) (CHCl₃) 1720 cm⁻¹, m/z (%) 376 (M⁺, <1), 361 (M⁺-Me, 56), 319 (M⁺-Bu⁺ and/or M⁺-Me-C₂H₅O, 25), 305 (8), 281 (Bu⁺Me₂SiOSnMe₂⁺, 37), 239 (Bu⁺Me₂SiOSnMe₃⁺-Bu⁺, 100), 165 (56), metastable 257 (361-305); δ6.32 (1 H, s, 2-H), 5.02 (1 H, m, 4-H), 2.72 (1 H, dd, J 18 and 7 Hz, 5-H cis to 4-H), 2.20 (1 H, dd, J 18 and 4 Hz, 5-H trans to 4-H), 0.90 (9 H, s, Bu⁺), 0.28 (9 H, s, Me₂Sn), 0.13 and 0.11 (each 3 H, s, Me₂Si). Also obtained was 4-(t-butyldimethylsilyloxy)-3,3-bis(trimethylstannyl)cyclopentanone (209) (96 mg, 35%) as an unstable colourless oil which was partially characterised, \( \nu_{\text{max}} \) 1748 cm⁻¹, δ4.81 (1 H, t, J 7 Hz, 4-H), 2.79 (1 H, d, J 18 Hz, 2-H), 2.56 (1 H, dd, J 18 and 7 Hz, 5-H cis to 4-H), 2.46 (1 H, d, J 18 Hz, 2-H), 2.18 (1 H, dd, J 18 and 7 Hz, 5-H trans to 4-H), 0.92 (9 H, s, Bu⁺), 0.2 (9 H, s, Me₃Sn), 0.16 (6 H, s, Me₂Si). The assignments to the complex multiplet between δ2.79 and 2.18 should be taken as tentative only. Because
compound (209) was thermally unstable a satisfactory mass spectrum was not obtained.

Conjugate addition-elimination study on the trimethylstannyl-enone (193;X=SnMe$_3$)

To a solution of lithium dimethylcopper in diethyl ether (0.4 ml) at -78 °C was added compound (193;X=SnMe$_3$) (25 mg, 0.07 mmol) in diethyl ether (0.5 ml). The mixture was maintained at -78 °C for 30 min., and it was then warmed to -50 °C. After a further 30 min., the reaction was quenched with deuteriomethanol (1 ml) and stirred at room temperature for 1 hr with saturated aqueous ammonium chloride (25 ml) and diethyl ether (25 ml). Extraction with further portions of diethyl ether (2 x 25 ml), washing with brine (10 ml), drying (MgSO$_4$) and evaporation afforded a brown oil (20 mg). Preparative t.l.c. on silica gel in methylene dichloride-methanol (50:1 v/v) gave the methyl-enone (207) (4.5 mg, 30%) as the major product together with starting material (193;X=SnMe$_3$) (10 mg, 40%).
Benzy l chloromethyl ether

Benzy l chloromethyl ether was prepared by the method of Hill and Keach and was purified by distillation (b.p. 92-93 °C at 6 mmHg, in agreement with literature data, δ7.24 (5 H, s, Ph), 5.40 (2 H, s, CH₂Ph), 4.64 (2 H, s, OCH₂Cl).

Attempted preparation of benzyloxymethylmagnesium chloride

Amalgamated magnesium was prepared by gently warming magnesium turnings (240 mg, 10 mg-atom) in a solution of mercury(II) chloride (30 mg, 0.1 mmol) in THF (5 ml). The surface of the magnesium darkened considerably and, after 30 min., the mixture was cooled to 0 °C and benzy l chloromethyl ether (1.56 g, 10 mmol) was added over 1 hr.

Cyclohexanone (490 mg, 5 mmol) was added to half of the reaction mixture thus prepared. After 1 hr the reaction was quenched with water (5 ml) and then allowed to warm to room temperature. Dilution with water (25 ml) and extraction with diethyl ether (3 x 25 ml) gave, after drying (MgSO₄) and evaporation of the solvent, a colourless oil (950 mg). Chromatography of this oil on silica gel in methylene dichloride afforded cyclohexanone (470 mg, 95%).

After 3 hr the remaining portion of the reaction mixture was quenched with water (25 ml), extracted with diethyl ether (25 ml) and, after drying (MgSO₄), evaporation of the solvent gave a colourless oil (700 mg). This oil was subjected to g.l.c. - mass spectral analysis, which confirmed the presence of benzy l alcohol (30% of volatiles), 1,2-di(benzyloxy)ethane (10% of volatiles), m/z (%) 212 (M⁺, 30), and benzy l methyl ether (5% of volatiles).
Benzyloxymethyl(tributyl)stannane (219)

Compound (219) was obtained in 38% overall yield following the procedures of Seyferth et al.\textsuperscript{159} and Still.\textsuperscript{158} Compound (219) thus obtained was purified by chromatography on silica gel in pentane-ethyl acetate (10:1 v/v), dried (MgSO\textsubscript{4}) and then stored over molecular sieves (4Å). Prior to its use in the following cuprate reactions, compound (209) was always degassed at 0.5 mmHg and at room temperature. Spectral data on a sample of benzyloxymethyl(tributyl)stannane obtained in this manner were in agreement with literature data.\textsuperscript{158}

Benzyloxymethyllithium

Transmetallation of compound (209) in THF (0.25 M) was effected by treatment with butyllithium for 20 min. at -78 °C. The reaction was quenched with water, extracted with diethyl ether and the extracts were then dried (MgSO\textsubscript{4}). Careful evaporation of the solvent minimised the loss of product and \textsuperscript{1}H n.m.r. analysis of the residue confirmed that, under these conditions, transmetallation proceeded almost quantitatively to give benzylic methyl ether (95%).

Attempted preparation of lithium di(benzyloxymethyl)copper using copper(I) iodide

Copper(I) iodide (48 mg, 0.25 mmol) was added to a solution of benzyloxymethyllithium (0.5 mmol) at -78 °C under a rapid flow of nitrogen. The temperature was allowed to rise to -30 °C but the copper(I) iodide remained unconsumed. After 1 hr the mixture was cooled to -78 °C and the chloro-enone (86; X=Cl) (59 mg, 0.24 mmol) in THF (5 ml) was added dropwise. After a further 15 min., the reaction was quenched with water (5 ml) and extracted with diethyl ether (3 x 20 ml). The extracts were then dried (MgSO\textsubscript{4}) and evaporated under reduced pressure to yield a pale-yellow oil (303 mg). Chromatography on silica gel in methylene dichloride-methanol (50:1 v/v) afforded 1-(benzyloxymethyl)-
4-\((t\text{-}\text{butyl dimethylsilyloxy})\text{-}3\text{-}\text{chloro}-2\text{-}\text{cyclopentenol (221)}\)

(69 mg, 71%) as a single diastereoisomer (Kugelrohr, b.p. 90-94 °C at 0.2 mmHg) (Found: C, 61.94; H, 7.92; Cl, 9.63. \(\text{C}_{19}\text{H}_{29}\text{ClO}_{3}\text{Si}\) requires C, 61.85; H, 7.92; Cl, 9.61%), \(\nu_{\text{max.}}\) 3 400 (br) and 1 628 cm\(^{-1}\), \(m/z\) (%)

\[352/350 \ (M^+\text{-H}_2O, 1), \ 311* \ (M^+\text{-Bu}^t, 1.5), \ 293* \ (M^+\text{-Bu}^t\text{-H}_2O, 12), \ 247^* \ (M^+\text{-PhCH}_2\text{OCH}_2, 100), \ 67.30 \ (5 \text{ H, s, Ph}), \ 5.86 \ (1 \text{ H, s, 2-H}), \ 4.56 \ (2 \text{ H, s, PhCH}_2), \ 4.50 \ (1 \text{ H, m, 4-H}), \ 3.40 \ (2 \text{ H, s, PhCH}_2\text{OCH}_2), \ 2.76 \ (1 \text{ H, br s, OH}), \ 2.58 \ (1 \text{ H, dd, } J 14 \text{ and 8 Hz, 5-H cis to 4-H}), \ 1.86 \ (1 \text{ H, dd, } J 14 \text{ and 4 Hz, 5-H trans to 4-H}), \ 0.90 \ (9 \text{ H, s, Bu}^t), \ 0.12 \text{ and 0.10 (each 3 H, s, SiMe}_2^2).\]

\lithium di(benzyloxymethyl)copper (218)

To a solution of benzyloxymethyl lithium (0.5 mmol) in THF at -50 °C was added dropwise a solution of copper(I) bromide-dimethylsulphide complex (52 mg, 0.5 mmol) dissolved in dimethylsulphide (0.25 ml) and diethyl ether (0.25 ml). The solution became pale-yellow and was maintained at -50 °C for 30 min., before the substrate was added.

\general procedure for the reaction of lithium di(benzyloxymethyl)copper with substrates

The substrate (0.22 mmol) was dissolved in diethyl ether (0.25 ml) and added dropwise to a solution of the lithio-cuprate (218) at -50 °C. After 30 min., the temperature was allowed to rise (over a further 30 min.) to -15 °C, whereupon the reaction was rapidly quenched with saturated ammonium chloride (5 ml). Diethyl ether (10 ml) was added and the mixture was then stirred for 1 hr at room temperature before it was further diluted with water (20 ml) and extracted with diethyl ether (3 x 25 ml). The combined extracts were washed with brine (10 ml), dried (MgSO\(_4\)) and evaporated under reduced pressure to give the
crude product. All products were then purified by preparative t.l.c. on silica gel in methylene dichloride-methanol (50:1 v/v).

**Reaction with 2-cyclohexenone**

2-Cyclohexenone (20 mg, 0.2 mmol) and the lithio-cuprate (218) (0.25 mmol) furnished 3-(benzyloxymethyl)cyclohexanone (222) (35 mg, 80%) (Found: C, 77.17; H, 8.08. C\textsubscript{14}H\textsubscript{18}O\textsubscript{2} requires C, 77.03; H, 8.31%), \(\nu_{\text{max}}\) 1712 cm\(^{-1}\), \(m/z\) (% 218 (M\(^+\), 18), 91 (C\(_7\)H\(_7\)\(^+\), 100), 87.28 (5 H, s, Ph), 4.49 (2 H, s, PhCH\(_2\)), 3.42 (2 H, d, \(J = 5\) Hz, CH\(_2\)OCH\(_2\)Ph), 2.60-1.10 (9 H, m, cyclohexyl ring protons).

**Reaction with pinocarvone (223)**

Pinocarvone (223) (49 mg, 0.33 mmol) and the lithio-cuprate (218) (0.5 mmol) furnished compound (234) (72 mg, 81%) as a colourless oil (Kugelrohr, b.p. 65-67 °C at 0.3 mmHg) (Found: C, 79.22; H, 9.13. C\textsubscript{18}H\textsubscript{24}O\textsubscript{2} requires C, 79.37; H, 9.88%), \(\nu_{\text{max}}\) 1712 cm\(^{-1}\), \(m/z\) (% 272 (M\(^+\), <1), 181 (M\(^+\)-C\(_7\)H\(_7\), 14), 91 (C\(_7\)H\(_7\)\(^+\), 100), 87.29 (5 H, s, Ph), 4.51 (2 H, s, PhCH\(_2\)), 3.59 (2 H, t, \(J = 6\) Hz, OCH\(_2\)CH\(_2\)), 2.80-2.00 and 1.70-1.40 (7 H, two sets of multiplets, ring-H and OCH\(_2\)CH\(_2\)CHCO), 1.23 [3 H, s, Me(b)], 1.18 (1 H, d, \(J = 10\) Hz, 1-H), 0.87 [3 H, s, Me(a)]. The signals at 1.23, 1.18 and 0.87 p.p.m. are tentatively assigned to the protons Me(a), Me(b) and H-1 (see page 234), based on published data and assignments for related bicyclo[3.3.1]heptane structures.\(^{178}\) It was not possible to assign signals within the ranges 83.00-2.80 and 1.70-1.40 to specific protons using the present data.
Reaction with 3-butenone (225)

3-Butenone (225) (23 mg, 0.33 mmol) and the lithio-cuprate (218) (0.5 mmol) afforded 5-benzylxy-2-pentanone (235) (33 mg, 51%) as a colourless oil (Kugelrohr, b.p. 55-57 °C at 0.2 mmHg) (Found: C, 74.71; H, 8.30. C_{12}H_{16}O_2 requires C, 74.79; H, 8.39%), \( \nu_{\text{max}} \) 1715 cm\(^{-1}\), \( m/z \) (% 192 (M\(^+\), <1), 164 (10), 107 (C\(_7\)H\(_7\)O\(^+\), 27), 91 (C\(_7\)H\(_7\)\(^+\), 100), \( \delta \) 7.30 (5 H, s, Ph), 4.48 (2 H, s, PhCH\(_2\)), 3.48 (2 H, t, \( J \) 6 Hz, 5-H), 2.55 (2 H, t, \( J \) 7 Hz, 3-H), 2.12 (3 H, s, Me), 1.89 (2 H, tt, \( J \) 7 and 6 Hz, 4-H).

Reaction with 3-pentenone (227)

3-Pentenone (227) (30 mg, 0.35 mmol) and the lithio-cuprate (218) (0.5 mmol) afforded 4-(benzylxoymethyl)-2-pentanone (237) (43 mg, 58%) as a colourless oil (Kugelrohr, b.p. 58-60 °C at 0.3 mmHg) (Found: C, 75.45; H, 8.48. C\(_{13}H_{18}O_2\) requires C, 75.69; H, 8.79%), \( \nu_{\text{max}} \) 1716 cm\(^{-1}\), \( m/z \) (% 206 (M\(^+\), <1), 164 (13), 148 (7), 115 (M\(^+\)-C\(_7\)H\(_7\), 9), 107 (C\(_7\)H\(_7\)O, 31), 91 (C\(_7\)H\(_7\)^{+}, 100), \( \delta \) 7.29 (5 H, s, Ph), 4.48 (2 H, s, PhCH\(_2\)), 3.31
(2 H, m, PhCH₂OCH₂), 2.70-2.14 (3 H, m, 4-H and 3-H), 2.11 (3 H, s, MeCO), 0.94 (3 H, d, J 6 Hz, MeCH).

Reaction with carvone (228)

Carvone (228) (37 mg, 0.25 mmol) and the lithio-cuprate (218) (0.35 mmol) afforded a mixture of starting material (32 mg, 86%) and the ketone (238) (5 mg, 7%). Yields were determined by g.l.c. analysis of the volatile fraction. Preparative g.l.c. of the mixture permitted the isolation of a sufficient quantity of the ketone for characterisation (Found: M⁺ 272.1768. \( \text{C}_18\text{H}_{24}\text{O}_2 \) requires M, 272.1776), \( \nu_{\text{max}} \) 1712 cm⁻¹, δ7.31 (5 H, s, Ph), 4.90-4.70 (2 H, m, olefinic-CH₂), 4.51 (2 H, s, PhCH₂), 3.45 (2 H, d, J 5 Hz, PhCH₂OCH₂), 2.80-1.90 (7 H, m, ring-H), 1.73 (3 H, m, MeC=CH₂), 1.09 (3 H, d, J 7 Hz, remaining Me).

Reaction with methyl propiolate (231)

Methyl propiolate (231) (38 mg, 0.33 mmol) in diethyl ether (1 ml) was added dropwise to a solution of the lithio-cuprate (218) (0.5 mmol) at -50 °C to give a purple solution. The reaction was stirred at -40 °C for 30 min. and was then worked-up in the usual way to furnish methyl (3E)-4-benzyl oxy-2-butenoate (239) (55 mg, 82%) as a single isomer (Kugelrohr, b.p. 57-60 °C at 0.3 mmHg) (Found: C, 69.90; H, 6.97. \( \text{C}_{12}\text{H}_{14}\text{O}_3 \) requires C, 69.88; H, 6.84%), \( \nu_{\text{max}} \) 1725 and 1665 cm⁻¹, m/z (%) 206 (\( \text{M}^+ \), <1), 175 (\( \text{M}^+-\text{MeO} \), 5), 100 (\( \text{M}^+-\text{C}_7\text{H}_6\text{O} \), 22), 91 (\( \text{C}_7\text{H}_7^+ \), 100), δ7.31 (5 H, s, Ph), 6.99 (1 H, dt, J 16 and 4 Hz, 3-H), 6.12 (1 H, dt, J 16 and 2 Hz, 2-H), 4.56 (2 H, s, PhCH₂), 4.17 (2 H, dd, J 4 and 2 Hz, 4-H), 3.73 (3 H, s, Me).
Reaction with methyl acrylate (232)

Methyl acrylate (13 mg, 0.16 mmol) and the lithio-cuprate (218) (0.25 mmol) afforded methyl 4- (benzyloxy)butanoate (240) (10 mg 30\%)
(Found: $M^+$ 208.109. $C_{12}H_{16}O_3$ requires $M$, 208.290), $\nu_{max}$ 1474 cm$^{-1}$, $m/z$ (%) 208 ($M^+$, <1), 107 ($C_7H_7O^+$, 31), 91 ($C_7H_7^+$, 100), 67.30 (5 H, s, Ph), 4.50 (2 H, s, PhCH$_2$), 3.65 (3 H, s, Me), 3.52 (2 H, t, $J$ 4 Hz, 4-H), 2.44 (2 H, t, $J$ 7.5 Hz, 4-H), 1.96 (2 H, tt, $J$ 7.5 and 6 Hz, 3-H).

Hydrogenation of the benzyloxy methyl-ketone (222) in methanol

Palladium/charcoal catalyst (10 mg) was added to a solution of compound (222) (53 mg, 0.24 mmol) in methanol and the flask was then flushed with hydrogen. The reaction commenced and after 5.8 ml hydrogen (97\% of theory) had been taken up, the catalyst was removed by filtration through celite and the solvent was evaporated under reduced pressure to give 3',3'-dimethoxy cyclohexylmethanol (241) (42 mg) in quantitative yield (Found: $M^+$, 174.1241. $C_9H_{18}O_3$ requires $M$, 174.1255), $\nu_{max}$ 3420 cm$^{-1}$, $m/z$ (%) 174 ($M^+$, 2), 143 ($M^+$-MeO, 100), 125 ($M^+$-MeO-H$_2$O, 27), 111 ($M^+$-MeO-MeOH, 39), 63.43 (2 H, d, $J$ 6 Hz, CH$_2$OH), 3.15 (3 H, s, MeO), 3.09 (3 H, s, MeO), 2.20-0.80 (12 H, m, OH and ring-H).

Hydrogenation of the benzyloxy methyl-ketone (222) in THF

Palladium/charcoal catalyst (10 mg) was added to a solution of compound (222) (35 mg, 0.16 mmol) in THF (2 ml) and the flask was then flushed with hydrogen. After stirring for 2 hr, the mixture had taken up over 4.1 ml of hydrogen (100\% of theory). Filtration through celite and evaporation of the solvent furnished 3-(hydroxymethyl)cyclohexanone (242) (21 mg, 100\%) (Found: $M^+$, 128.0842. $C_7H_{12}O_2$ requires $M$, 128.0837), $\nu_{max}$ 3400 and 1705 cm$^{-1}$, $m/z$ (%) 128 ($M^+$, 14), 110 (21) and 97 ($M^+$-MeO, 100), 63.58 (2 H, d, $J$ 4.5 Hz, CH$_2$OH), 2.50-1.24 (10 H, m, OH and ring-H).
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Errata

p 87  
line 2-up  It is highly unlikely that potassium ethoxide was formed in this reaction and carbonate anion may have effected this cyclisation

p 115  
lines 2-5  The silylating agent was chloro-2-butyldimethylsilane

p 167  
line 14  Compound (114) should be named 2-(1'-hydroxy-2'-methylpropyl)-3-phenylselenocyclohexanone

p 208  
line 5-up  Diisopropylamide should read lithium diisopropylamide