# SYNTHETIC STUDIES DIRECTED TOWARDS THE SESQUITERPENOID GRIMALDONE

by

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A thesis presented in part fulfilment of the
requirements for the Degree of Doctor of Philosophy

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January, 1993



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## DEDICATION

To Mum and Dad

## ACKNOWLEDGEMENTS

I would like to thank my supervisors Dr. E. W. Colvin and Prof. J. D. Connolly for their help and encouragement throughout the course of this PhD.

The help of the technical services namely Dr. D. Rycroft, J. Gall, J. M$^{c}$Iver, T. Ritchie and G. M$^{c}$Culloch and my fellow workers in the Loudon Lab, Henderson Lab and Lab 168, namely Greg, Steph, Davie, Gerry, and John for their friendship over the last three years is much appreciated.

Funding from SERC and extra financial support from Quest International Ltd. , Ashford is gratefully acknowledged.

Finally, I would like to thank my parents for their support throughout the course of this research.

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## SUMMARY

An advanced intermediate in a route to the odoriferous sesquiterpenoid grimaldone has been synthesised using a formal [3+2] cycloaddition reaction as the key step. Subsequent transformation of the intermediate using ring-contraction methodology developed by House failed. Therefore, a new route to grimaldone was devised involving a modified Sharpless oxidative cleavage reaction. Again, an advanced intermediate was attained and model studies on that compound have indicated that a very late-stage precursor to grimaldone can be accessed relatively easily.

# INTRODUCTION

The past 15 years have witnessed an enormous growth in the number and type of reactions which are applicable to the synthesis of five-membered rings. These systems are rapidly emerging as important structural features in a large number of natural products and theoretically interesting molecules. In recent years we have seen a number of $C_5$ annulation procedures, with the majority focussing on multistep sequences based on 1,4-dicarbonyl compounds or their functional equivalents. The reasons for the great activity in this area of chemistry have been described in numerous reviews and will not be discussed here.[1,2]

One particularly attractive and logical approach to a five-membered ring is the [3+2] cycloaddition. This reaction couples a three-carbon $4\pi$ unit directly with a two-carbon $2\pi$ unit, forming two C-C bonds in one operation. The net result is the rapid and efficient construction of complex cyclic structures from simple building blocks. This approach is analogous to the well documented [4+2] cycloaddition-the Diels-Alder reaction. The source of the $C_3$ $4\pi$ fragment is not immediately obvious since it is not a common stable entity. Thus the success of the [3+2] approach depends on the effective synthesis and reactivity of the $C_3$ unit.

The main research effort in the past 15 years has been in the area of transition metal mediated cycloadditions. The organic substrate complexed to the metal generates a reactive intermediate which can function as a three-carbon synthon. In this way, the synthon is stabilised by coordination to the transition metal. By choice of metal and / or ligands attached to the metal, differing degrees of selectivity can be induced.

Transition metal mediated [3+2] cycloaddition reactions can be divided into three main areas. The $C_3$ synthon can be obtained by use

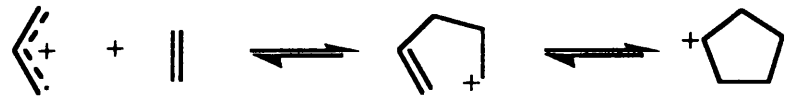
of:

1. 2-Oxyallyl Synthon.
2. Trimethylenemethane Synthon.
3. Dimethylenemethane Synthon.

The following discussion will concentrate on these areas. Emphasis will be placed on the source, reactivity, scope and use of such synthons.

## 1.1 2-Oxyallyl Synthon

The reaction between an allyl cation and an olefin is represented in Scheme 1.

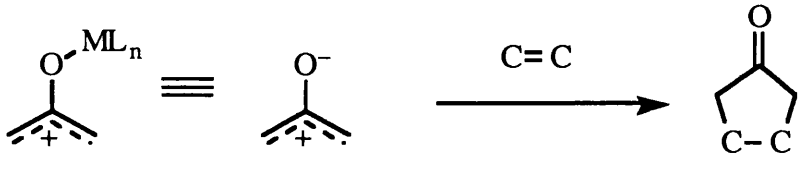


(1) (2)

Scheme 1

This reaction, via a four electron transition state, is thermally forbidden by orbital symmetry rules [3] and is thought to proceed via a step-wise mechanism.[4] Each step in the scheme is reversible and so intermediate (1) must have greater stability than the allyl cation and the cyclopentyl cation (2) must be even more stable than (1) or, if not so, undergo proton elimination or nucleophile capture to give a neutral product which is stable. Thus it is very important to select a $C_3$ synthon which can provide such driving forces.

2-Oxyallyl (3) is a useful $C_3$ synthon in [3+2] cycloadditions because it generates a five-membered ring containing a carbonyl moiety (Scheme 2).



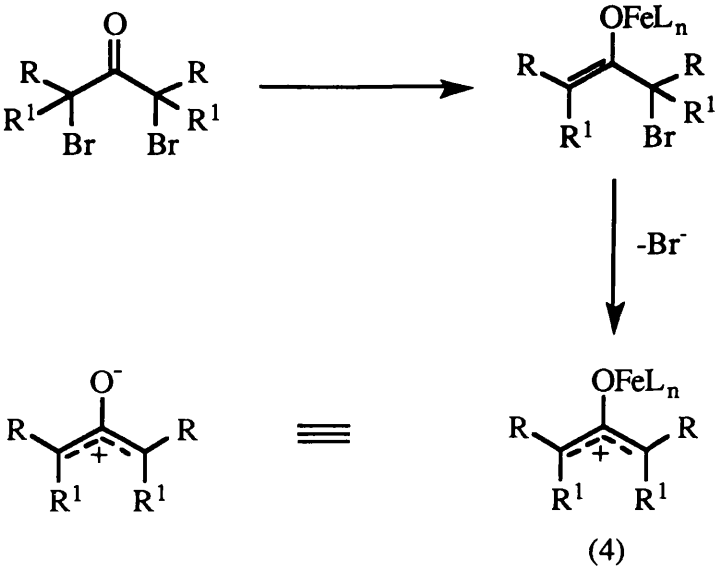

(3)

Scheme 2

### 1.1.1 Oxyallyls from Iron carbonyls and Dibromo Ketones

The transition metal stabilised system (3), which can be generated from easily available starting materials has been used by Noyori.[5]

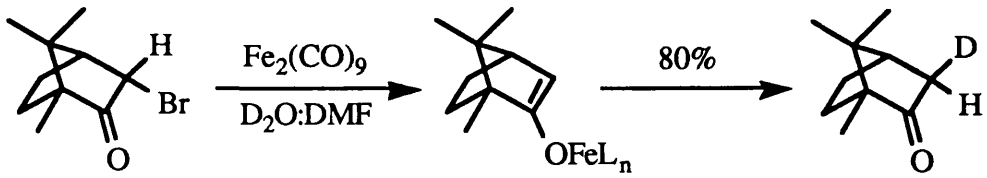
Treatment of an αα'-dibromo ketone with diiron nonacarbonyl resulted in the formation of the reactive oxyallyl species (4) depicted in Scheme 3.




Scheme 3

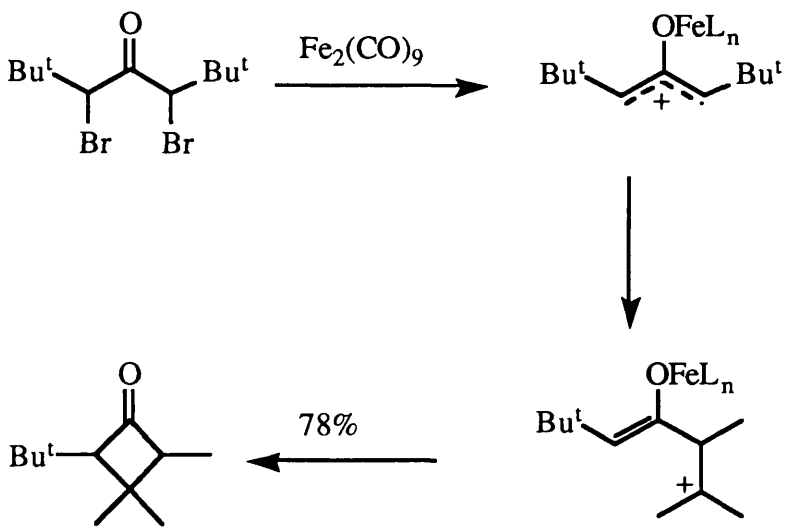
Evidence has shown that the iron enolate is formed by either two-electron reduction of the dibromo ketone or oxidative addition of the dibromo ketone onto zero-valent iron. Finally, an $S_N$-1 type or iron assisted elimination of the allylic bromine atom produces the oxyallyl species.[5]

Noyori and co-workers have shown that the 2-oxyallyl iron species forms in the manner depicted in Scheme 3. They did this in a very elegant manner by a series of detailed experiments. Evidence for formation of the iron enolate species has been shown by reaction of α–bromo ketones and diiron nonacarbonyl in the presence of $D_2O$ (Scheme 4).



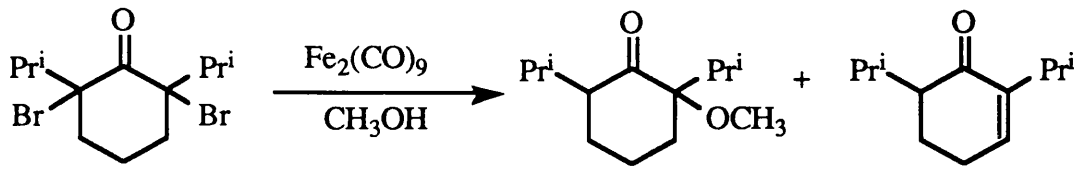

Scheme 4

Enolates of camphor have been shown to protonate from the exo side of the bicyclic system [6,7] and so the product in Scheme 4 indicates the presence of an iron enolate as an intermediate. Reaction of α-bromo ketones with metal ions or metals, such as Cr or Zn, has been shown to produce metal enolates.[8,9] Formation of oxyallyl-iron species has been proved by various starting materials undergoing skeletal rearrangements in the presence of $Fe_2(CO)_9$ (Scheme 5).



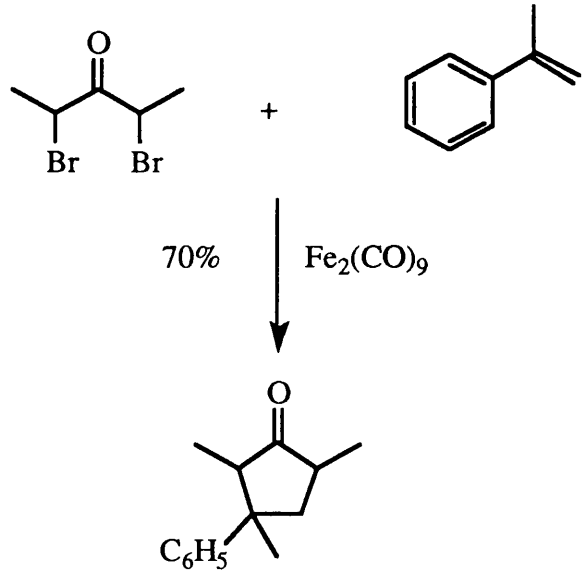

Scheme 5

The di-*tert*-butyl-2-oxyallyl cation did indeed undergo a neopentyl-type rearrangement, already well documented. [10,11] The intermediacy of oxyallyl species was also corroborated by trapping the reactive species with various nucleophiles (Scheme 6).




Scheme 6

These reactive oxyallyl-iron intermediates which are formed from secondary or tertiary α,α'-dibromo ketones and iron carbonyls have been shown to cycloadd across aryl-substituted olefins in a [3+2] to 5 manner, forming 3-aryl-cyclopentanones in good yield.[4] For example, 2,4-dibromo-pentan-3-one reacted with α-methyl styrene in the presence of $Fe_2(CO)_9$ to form a cyclopentanone adduct in good yield as a mixture of *cis* and *trans* diastereoisomers (Scheme 7).

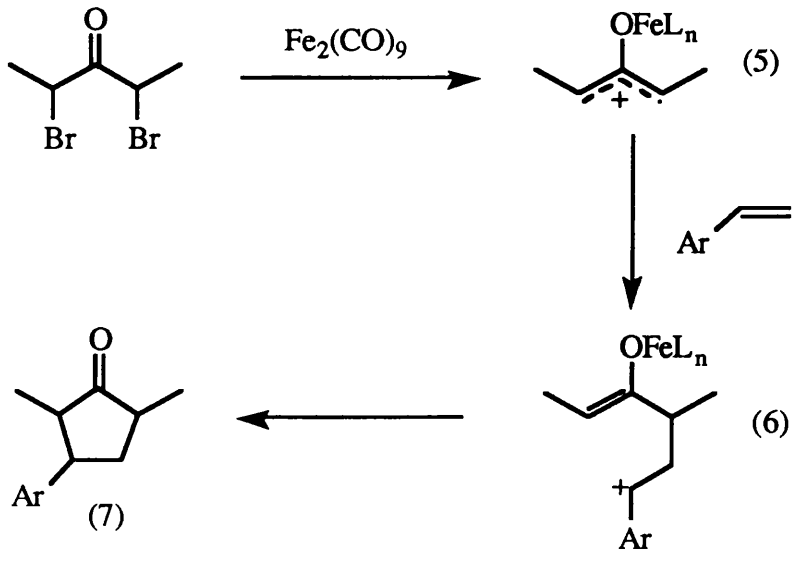



Scheme 7

Other olefins which have been shown to add to α,α'-dibromo ketones include styrene, α-cyclopropyl styrene, 1,1-diphenylethylene and indene.

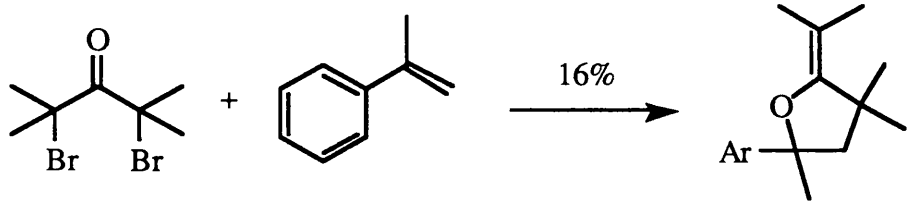
As mentioned previously, the cycloaddition reaction of an allyl cation and olefin belongs to the thermally forbidden [π 2 + π 2] process according to orbital symmetry rules and, in consequence, proceeds via

a stepwise mechanism (Scheme 8).




Scheme 8

The oxygen atom attached to the central $sp^2$-hybridised carbon of (5) decreases the stability of the allylic moiety [12] thus making the first electrophilic addition process easy. (6) is highly stabilised by the aryl substituent and the presence of the oxygen atom again makes the cyclisation step easy since (7) is formed via a stable oxonium ion [13] from which the Lewis acid eliminates giving the neutral cyclopentanone adduct. In certain cases, ring closure has been shown to occur at the O terminus as well as the C terminus [4] (Scheme 9).



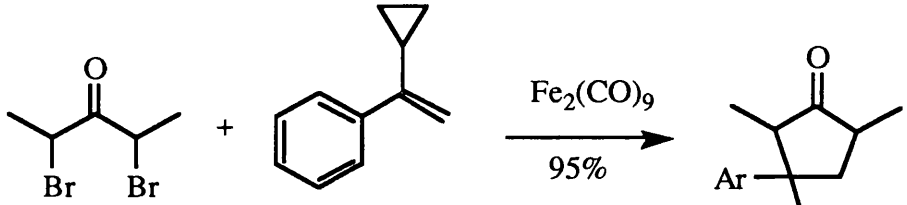

(8)

Scheme 9

Compound (8) was isolated in low yield along with three other products.

In light of the mechanism described previously, it is evident that the reaction is highly chemoselective i.e. only electron rich alkenes participate in the cycloaddition. It should also be noted that the reaction is limited to alkyl substituted oxyallyl systems since both α,α'-dibromoacetone and α,α,α',α'-tetrabromoacetone failed to yield any cycloadduct.

Yields in the cycloaddition reaction are generally good but do depend on the stability of intermediate carbocations and on the steric environment of the olefinic partner. Thus α-cyclopropylstyrene reacted smoothly with dibromide (9) in the presence of $Fe_2(CO)_9$ to give an excellent yield of (10) (Scheme 10).



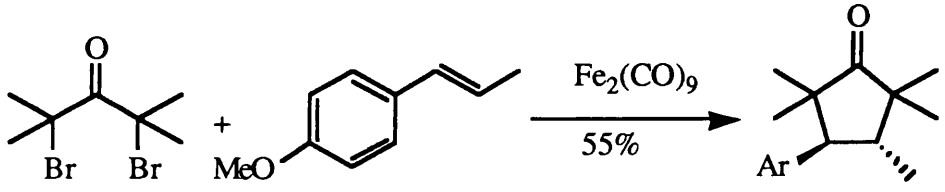

(9) (10)

Scheme 10

The very high yield in this reaction can be attributed to the excellent carbocation-stabilising ability of the phenyl,and cyclopropyl groups.[14]

In the case of the steric environment of the olefin, α-methyl styrene reacts faster than styrene which in turn reacts faster than β-methyl styrene. The increase in rate caused by α-methylation can be attributed to an increase in stability of carbocations such as (6) in Scheme 8 whereas the reduction in rate with a β-methyl substituent is probably due to steric hindrance to electrophilic attack. It is

interesting to note that the order of reactivity described above is similar to that in cationic polymerisation.[15,16] Electron donating substituents on the olefin also increase the rate of reaction e.g. the reaction of *trans*-β-methyl styrene and (11) failed to produce any cyclopentanone adduct yet *trans*-anethole coupled with (11) to give (12) in reasonable yield (Scheme 11).

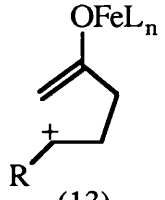



(11) (12)

Scheme 11

This yield can be attributed to the electrodonative property of the methoxyl group.

The [3+2] cycloaddition described has been shown to exhibit excellent regioselectivity. Such regioselectivity is best interpreted in terms of the stability of a zwitterionic intermediate of type (13) (Fig.1).

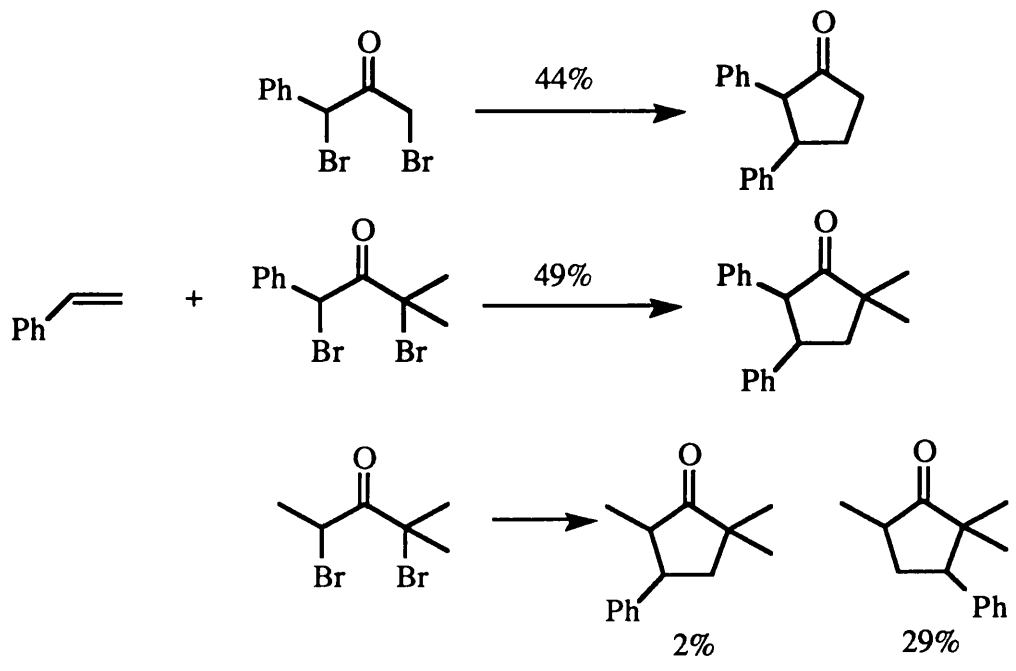



(13)

Fig.1

Since the cationic part of (13) is stabilised by the aromatic group (R=Ph), Noyori [17] has postulated that the factor controlling the regioselectivity in [3+2] cycloaddition reactions is the relative stabilities of enolates. The high regioselectivity is depicted in Scheme

12.




Scheme 12

The stability sequence (Fig.2) agrees with the regioselectivities shown in Scheme 12.

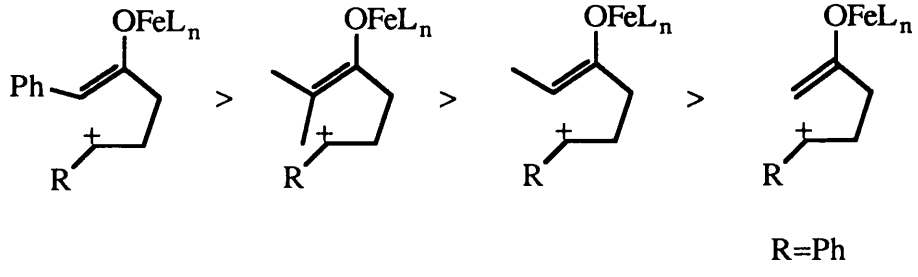



Fig.2

From the LUMO's of the 2-oxyallyls and HOMO of styrene (Fig.3), it can be seen that the directing effect of substituents does not fit with the prediction based on frontier molecular orbital considerations. From these calculations, the dominant interaction between the low-lying LUMO of the oxyallyl and high-lying HOMO of styrene actually produces the zwitterion leading to the regioisomer which was obtained

as a minor component or did not form.

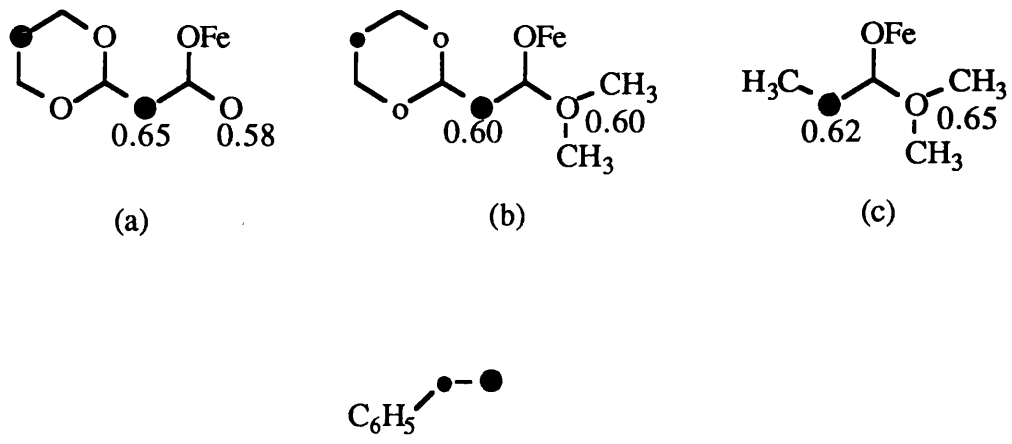
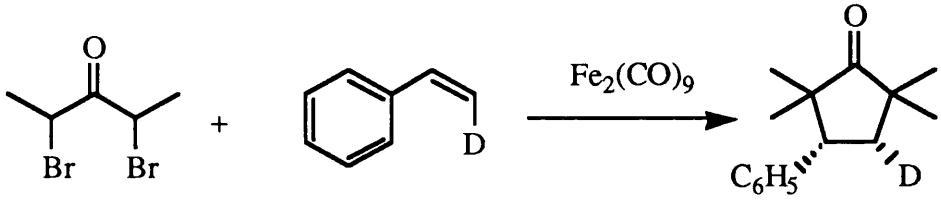



Fig.3

Interestingly, from the MO's of oxyallyl (b) in Fig.3, the reaction was expexted to exhibit poor selectivity, but this was not the case as only one regioisomer was detected (Scheme 12).

As well as being regioselective, the iron carbonyl-mediated [3+2] cycloaddition is stereospecific despite a non-concerted mechanism. The reaction of (9) and *cis*-β-deuteriostyrene gave only the *cis* stereoisomer at low conversion (Scheme 13).




Scheme 13

Although stereospecificity in this cycloaddition may imply a degree of concertedness [18], there are certain stepwise reactions which are known to go with a degree of stereospecificity .[19,20] The stereospecificity of the above cycloaddition is thought to arise from the

formation of a U-shaped intermediate (Fig.4) formed by cisoid approach of the oxyallyl and alkene.

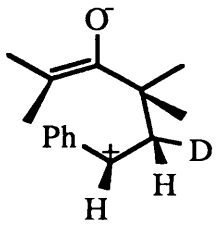
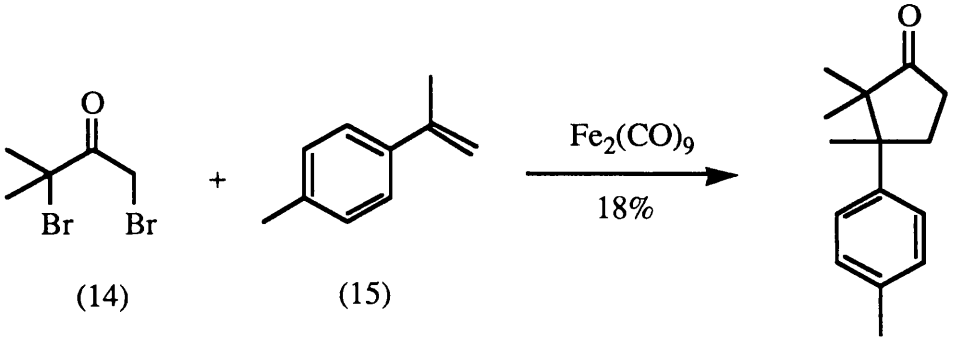



Fig.4

In this species, the structure is fixed rigidly by a charge-transfer interaction between the enolate and cationic centre thus preventing the structure from rotating around the $C_6H_5CH^+$-CD bond. As a result the original stereochemistry is preserved. It should also be noted that *trans*-anethole couples stereospecifically with (11) (Scheme 11).

1.1.2 Oxyallyls in Organic Synthesis

The [3+2] cycloaddition involving an unsymetrically substituted 2-oxyallyl has been used in a one-step synthesis [21,22] of (±)-α-cuparenone from (14) and (15) (Scheme 14).

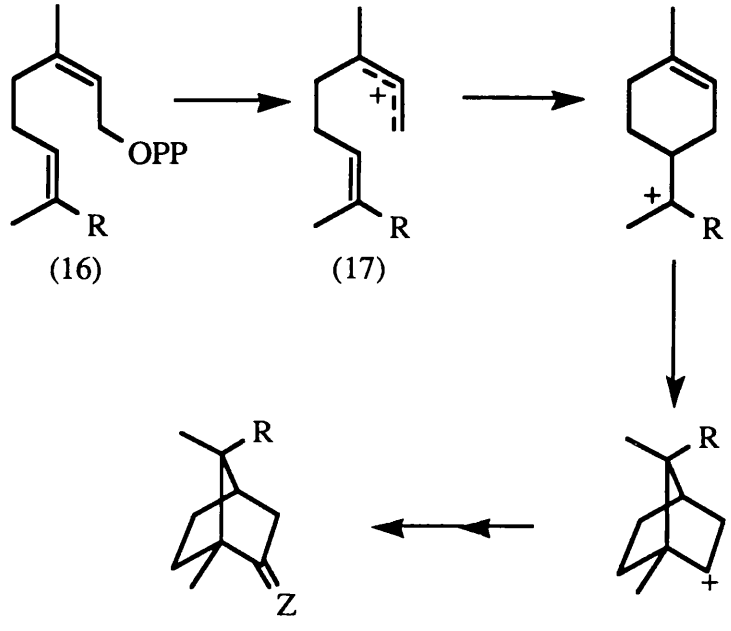



(14) (15)

Scheme 14

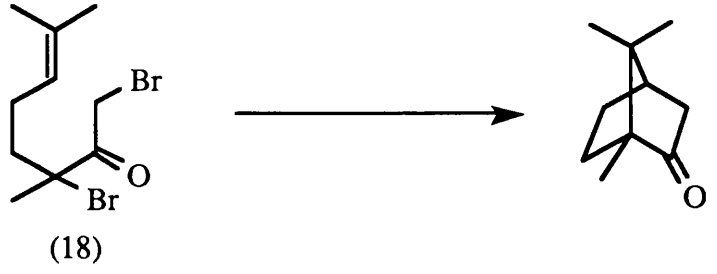
Although the yield is low, it should be compared with other syntheses which have been multi-step and lower yielding. [23]

The intramolecular version of this [3+2] cycloaddition has opened up a route to terpenes with the bicyclo [2.2.1] heptane skeleton. It is thought that terpenes bearing this skeleton are biosynthesised [24] by a double cyclisation of an allylic cation such as (17) generated from (16) (Scheme 15).




Scheme 15

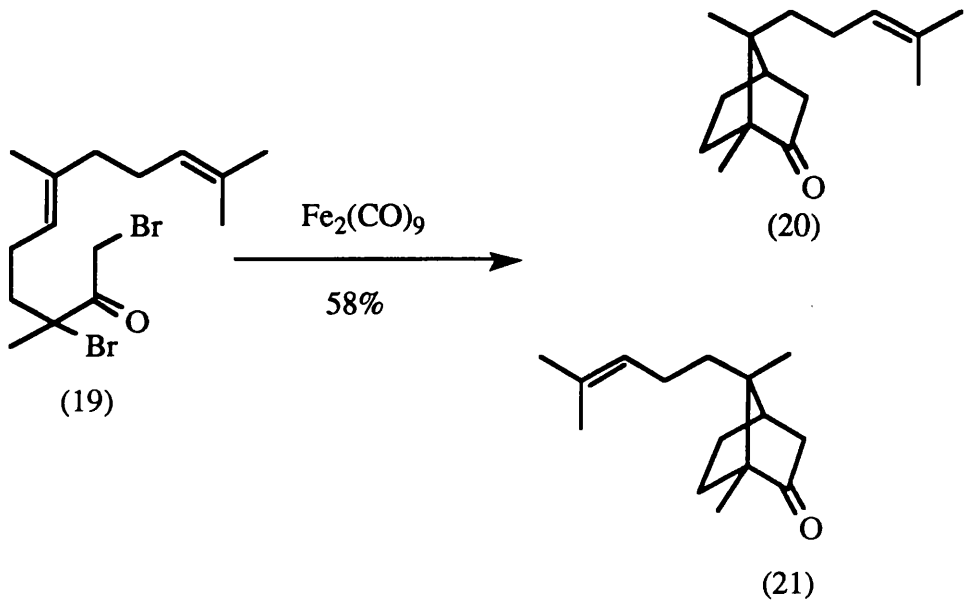
The iron carbonyl-mediated intramolecular [3+2] process has provided an analogue of this bioconversion. Thus, when dibromoketone (18) and $Fe_2(CO)_9$ were reacted in benzene in a pressure bottle at 110 $^oC$ for 1.5 h, (±)-camphor was isolated in 38% yield (Scheme 16).




Scheme 16

Likewise, reaction of dibromoketone (19) and $Fe_2(CO)_9$ under similar conditions, afforded a 2:1 mixture of (±)-campherenone (20) and (±)-

epicampherenone (21) in reasonable yield [25] (Scheme 17).




Scheme 17

When the (Z)-isomer of (19) was used, the product ratios were reversed.

1.1.3 Oxyallyls and Enamines in [3+2] Cycloaddition Reactions

Enamines have been found to be excellent substrates for the [3+2] cycloaddition [26]. Both tertiary and secondary dibromides react with morpholinoenamines in the presence of iron carbonyls to afford the corresponding 3-morpholinocyclopentanones. With enamines, the N lone pair confers stability on the intermediate zwitterion in a similar role to that of the aromatic group in previous examples (Fig.5).

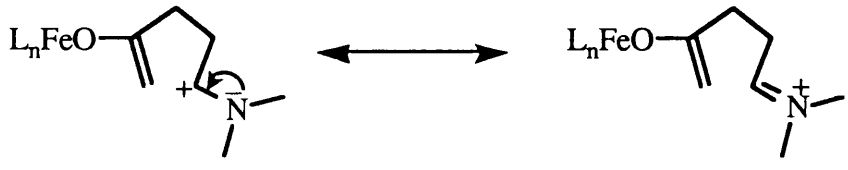
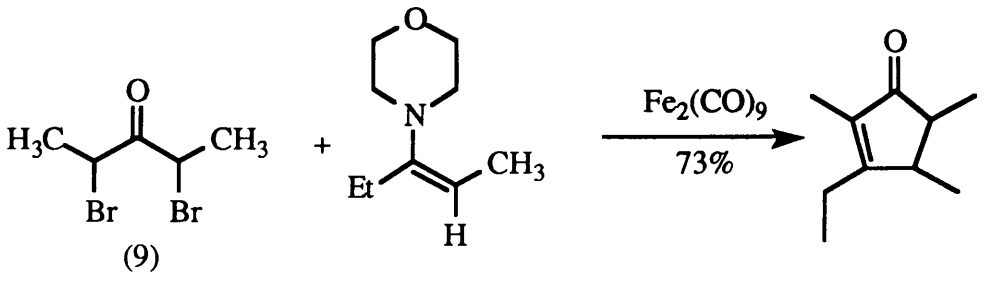


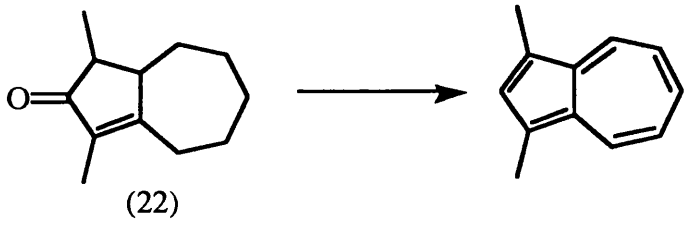

Fig. 5

With secondary dibromides, the initially formed β-morpholinocyclopentanone has an active hydrogen atom α to the carbonyl group and so readily suffers elimination of morpholine to form cyclopentenones (Scheme 18).



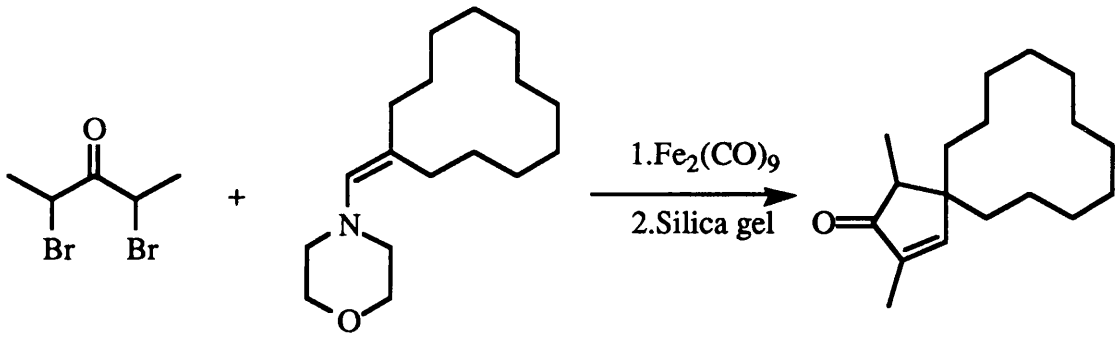

Scheme 18

The [5.3.0] bicyclic enones prepared from dibromo ketones and cycloheptanone enamine are useful intermediates in the synthesis of azulenes. For example, (22) can be converted into 1,3-dimethylazulene by reduction and dehydrogenation (Scheme 19).




Scheme 19

Noyori and co-workers have also shown the enamine cycloaddition to be a versatile tool in the synthesis of spiro [n.4] alkenones [26]. For example, cyclododecane carboxaldehyde reacted with morpholine to form the adduct (23) which then underwent the [3+2] cycloaddition with dibromide (9) to form the fused cyclopentenone in good yield (Scheme 20).



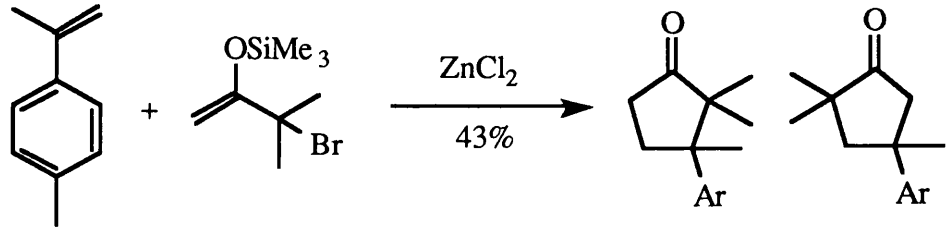

(9) (23)

Scheme 20

In general, the iron carbonyl-promoted cyclisation between secondary dibromo ketones and enamines provides a useful route to α,α'-dialkylcyclopentenones. The only limitation of this methodology is its inability to produce cyclopentenones without α-alkyl groups.

1.1.4 Oxyallyls from Silyl Enol Ethers

Sakurai and co-workers have used the silyl enol ether [27] (24), easily prepared from 3-bromo-3-methyl-butan-2-one to generate an oxyallyl cation in the presence of $ZnCl_2$. With 2-(*p*-methylphenyl) prop-1-ene, the reagent gave a small yield of (±)-α-cuparenone and its regioisomer in a 2:1 ratio (Scheme 21).




(24) 2:1

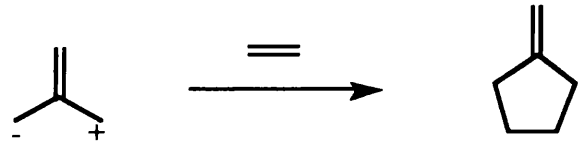
Scheme 21

The mechanism is presumed to be similar to that of the dibromoketone

/ diiron nonacarbonyl system.

## 1.2 Trimethylenemethane Synthon

Trimethylenemethane (TMM) (25) represents a useful synthon leading to cyclopentanoids via a [3+2] cycloaddition with an alkene (Scheme 22).



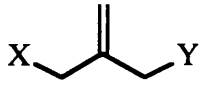
(25)

Scheme 22

The usefulness of such an approach for generating methylene-cyclopentanes depends, however, on finding efficient methods for generating such a synthon. Two major types of precursor have been identified - the bifunctional conjunctive reagents (BCR) and methylenecyclopropanes. [28] Their use in conjunction with transition metal catalysts has opened up a whole new approach to cyclopentanoid synthesis. This chapter will concentrate on methodologies developed in these two closely related areas.

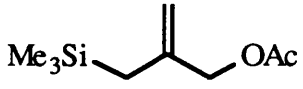
### 1.2.1 Non-substituted Bifunctional Conjunctive Reagents

These can be represented as structure (26) where X is a silyl or stannyl group which serves to generate a carbanion equivalent, and Y is a more reactive leaving group such as methanesulphonate or halide which serves to generate a carbocation equivalent.



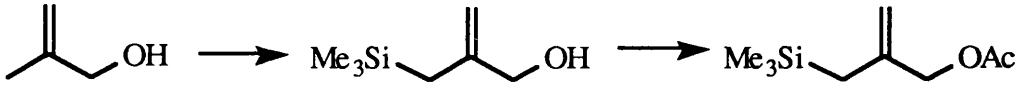

(26)

Trost and co-workers developed (27) as a BCR.




(27)

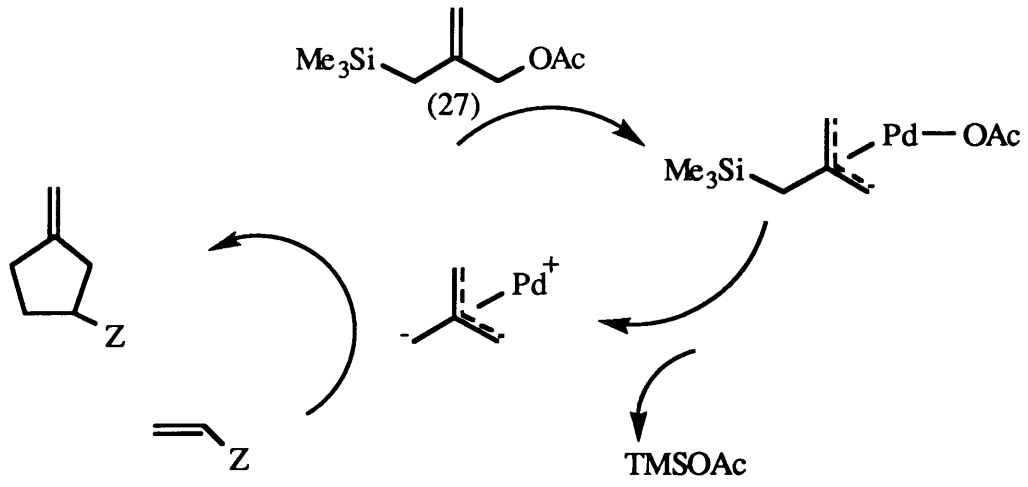
The preparation of this compound from methallyl alcohol is very simple [29,30] (Scheme 23).




(27)

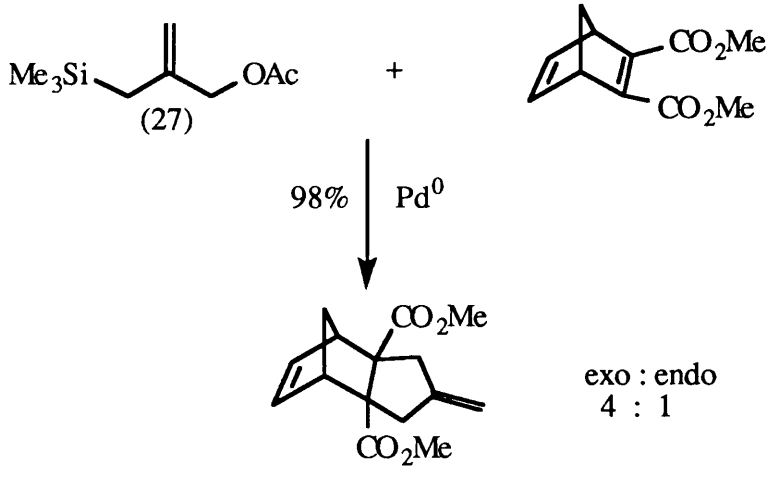
Scheme 23

Compound (27) is a stable entity, and requires activation to serve as a TMM synthon. Palladium (0) complexes serve as such activators as they can readily effect the ionisation of poor leaving groups in allylic positions. [31] In the case of (27), the transition metal promotes the elimination of TMSOAc to form a coordinated trimethylenemethane species which undergoes cyclisation with an electron-deficient alkene to form the methylenecyclopentane adduct and regenerate the catalyst (Scheme 24).




Scheme 24

The nucleophilic nature of the synthon from (27) has been shown by the reaction of (27) and 2,3-dimethoxycarbonylnorbornadiene [32] (Scheme 25).



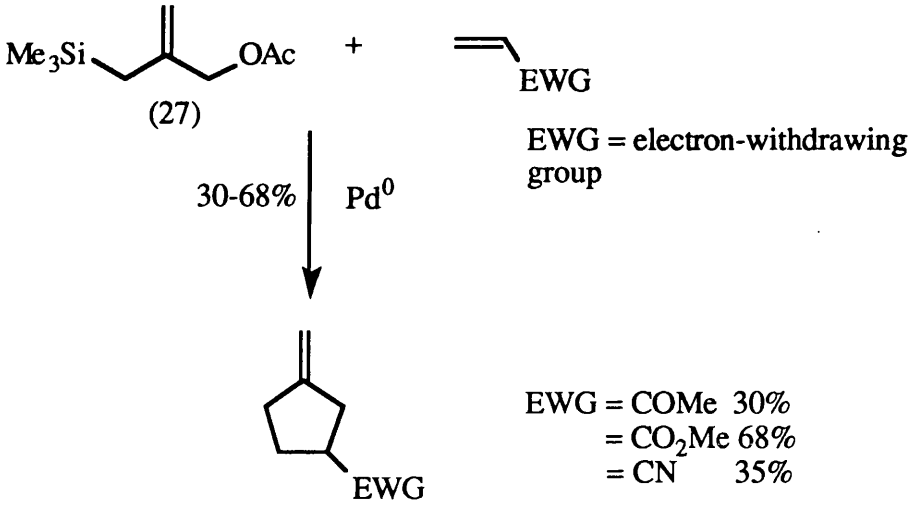

Scheme 25

Electron rich alkenes such as styrene and furan fail to react.

The cycloaddition is normally carried out by heating a solution of the silyl acetate with a suitable alkene in the presence of 5 mol % of catalyst in an aprotic solvent. The catalyst of choice is normally $(PPh_3)_4Pd$ but other catalysts can be generated *in situ* by reaction of

Pd(II) salts such as $Pd(OAc)_2$ with at least two equivalents of triisopropylphosphite. [33]

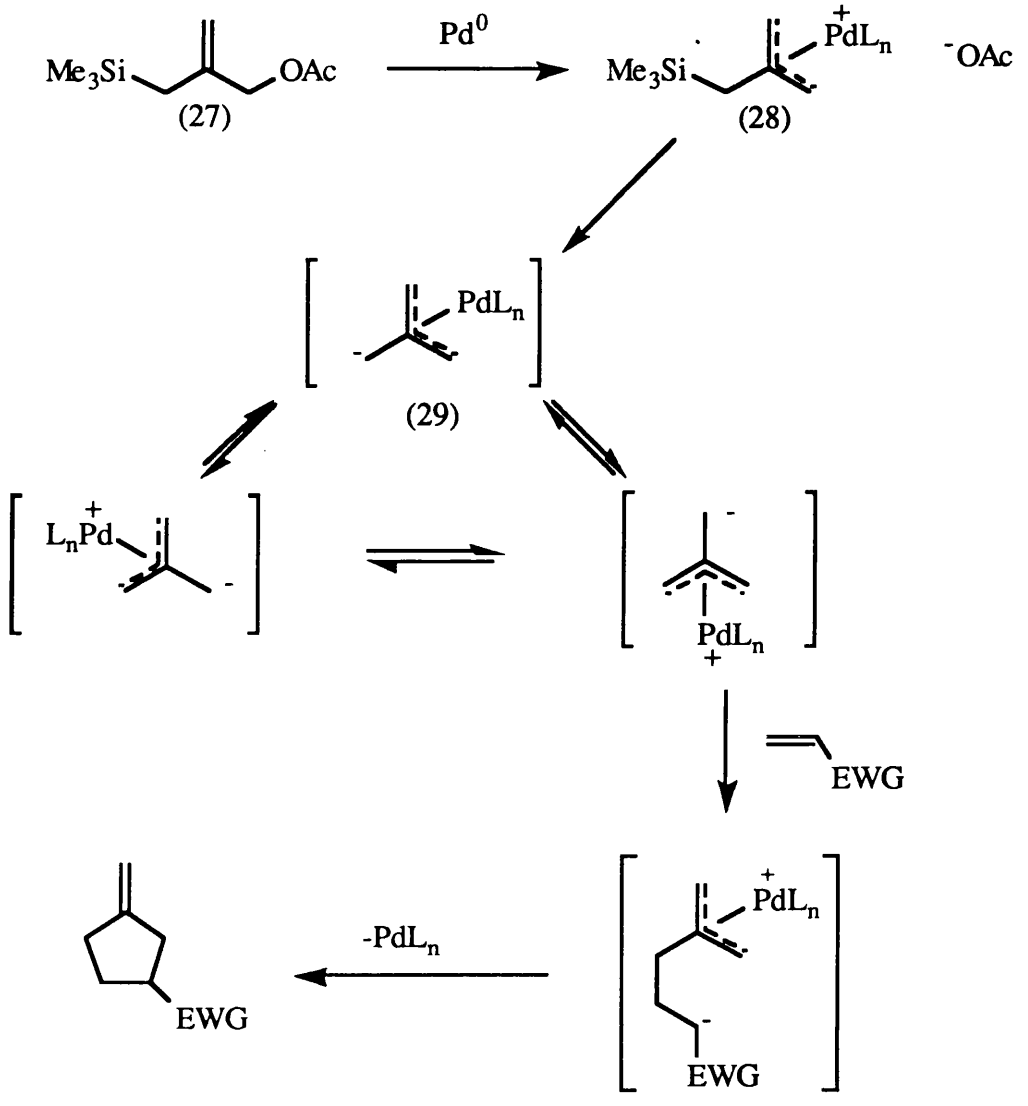
A wide range of alkenes containing ketone, ester and cyano moieties has been shown to react in generally good yield [32] (Scheme 26).




Scheme 26

Extensive mechanistic studies by Trost and co-workers led to the elucidation of the reaction pathway. [34] The details of the experiments will not be discussed but a brief overview of the results will be presented.

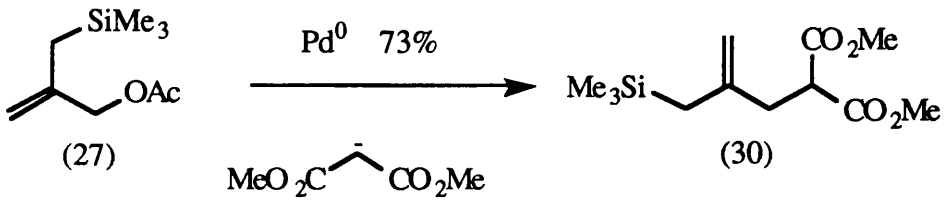
The cycloaddition of (27) has been shown to involve an ($\eta^3$-allyl) Pd complex (28). The initially formed complex is then desilylated to give the unique ($\eta^3$-TMM) Pd complex (29). Both Albright [35] and Trost[36] have shown that this complex is predicted from theoretical considerations. The complex is, as shown, a zwitterion with the organic fragment the anionic portion and the metal and its ligands the cationic portion (Scheme 27).




Scheme 27

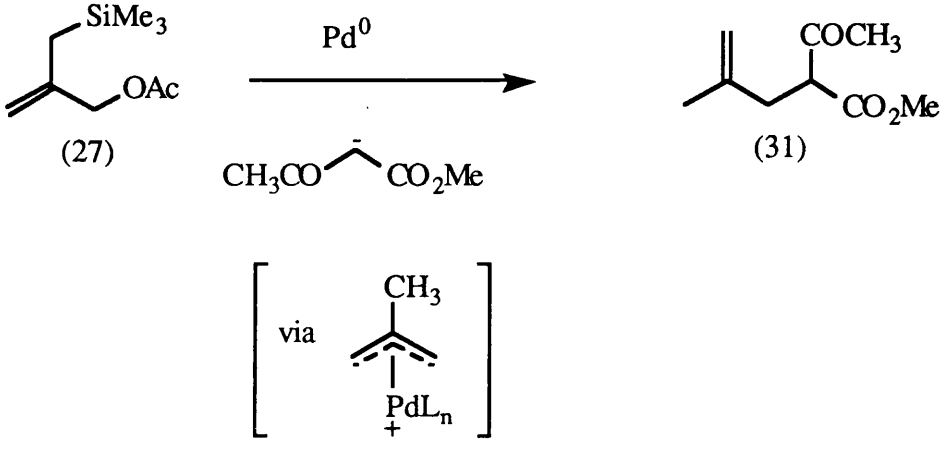
The methylenecyclopentane adduct is presumed to form in a stepwise fashion via Michael addition of the (TMM) Pd intermediate (29) to the alkene, which is then followed by ring closure of the intermediate with concommitant regeneration of the catalyst.

The structure of complex (28) has been proved by trapping with the anion of dimethyl malonate (Scheme 28).




Scheme 28

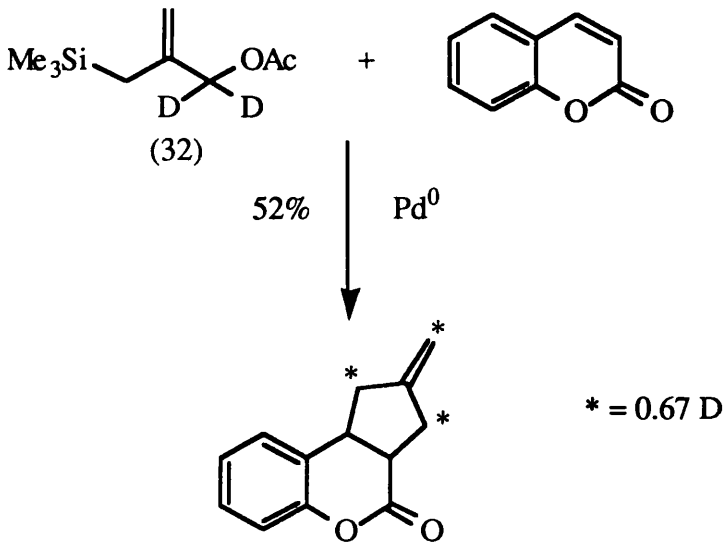
With less reactive nucleophiles (i.e. more stabilised anions) such as methyl acetoacetate, adduct (31) resulted from the reaction of (27) and $Pd^0$. This proves the presence of (29) as an intermediate (Scheme 29).




Scheme 29

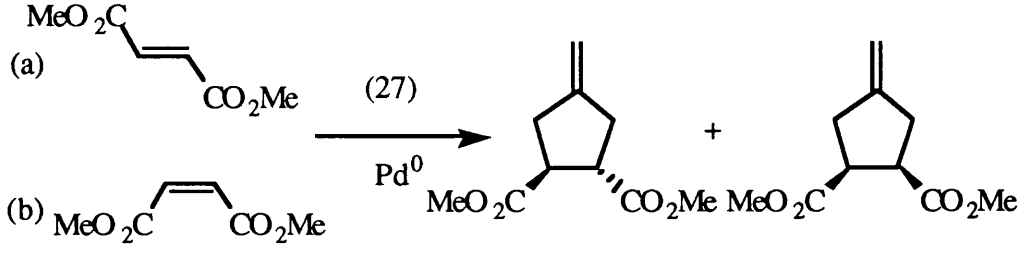
As shown in Scheme 29, adduct (31) is formed via a proton-transfer reaction. Indeed, this step has been proved by reaction of (27) with a deuterated nucleophile.[34]

Although the bonding in (29) indicates a non-equivalence of the carbon terminii on the ligand, there is rapid equilibration among the three $\eta^3$ structures as is shown in Scheme 27. This results in a functionally symmetrical synthon. The interconversion of these structures has been proved by Trost and Chan[34] using a doubly deuterated silyl acetate (32) (Scheme 30).




Scheme 30

The nonconcertedness of the reaction is reflected in the moderate stereoselectivity which the reaction shows.[34,37] Dimethyl fumarate yields essentially all *trans* material in the cycloaddition with (27) while dimethyl maleate yields a mixture of *cis/trans* adducts (Scheme 31).




(a) 99 : 1

(b) 1.3 : 1

Scheme 31

As well as being stereoselective, the reaction has been shown to exhibit excellent diastereoselectivity.[38] To explain the poor reactivity of cyclohexenones in the [3+2] cycloaddition, Trost and co-workers

showed that δ-oxaenones gave enhanced reactivity. This was ascribed to the oxygen atom minimising steric interactions and increasing the electrophilicity of the acceptor via an inductive effect (Fig. 6).

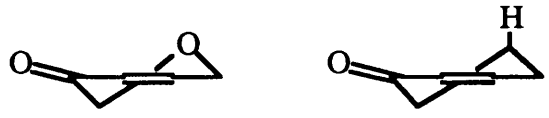
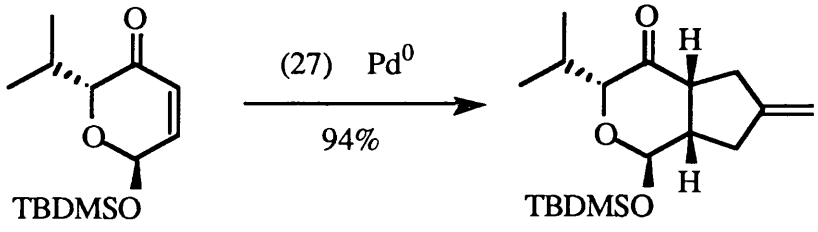


Fig. 6

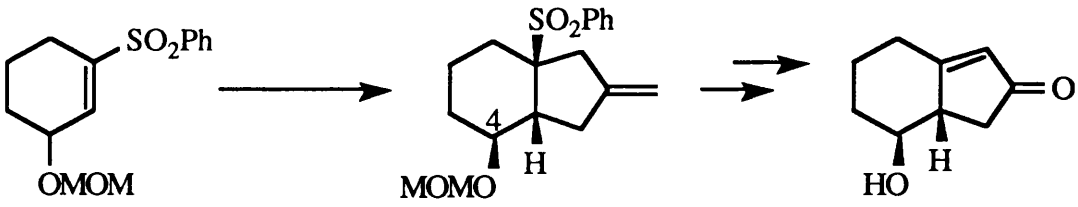
Trost and co-workers also showed that there was excellent diastereoselectivity, e.g., exclusive addition at the less hindered face of (33) was observed in its reaction with (27) (Scheme 32).




(33)

Scheme 32

Diastereoselectivity with sulphone acceptors has particular importance because of the versatility offered by the adducts. The six-membered sulphone (34) gave essentially a single adduct in its reaction with (27) (Scheme 33).[28]




(34) (35) (36)

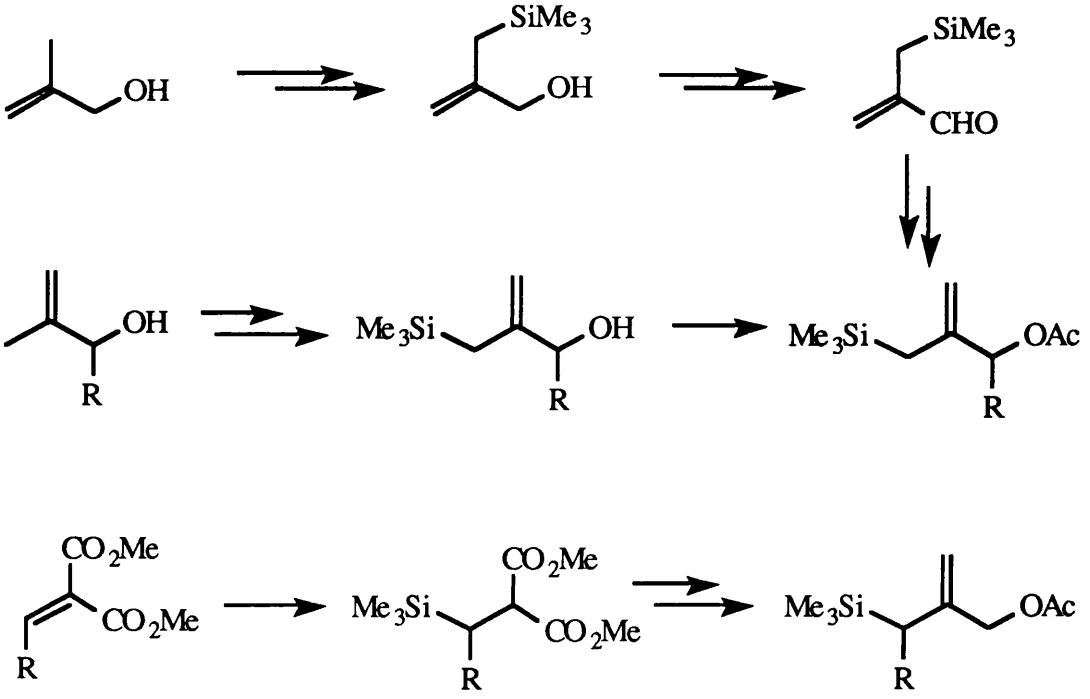
4β : 4α
>9 : 1

Scheme 33

Compound (35) was easily converted by deprotection and ozonolysis to the bicyclic enone (36), an equivalent of a cyclopentenone adduct.

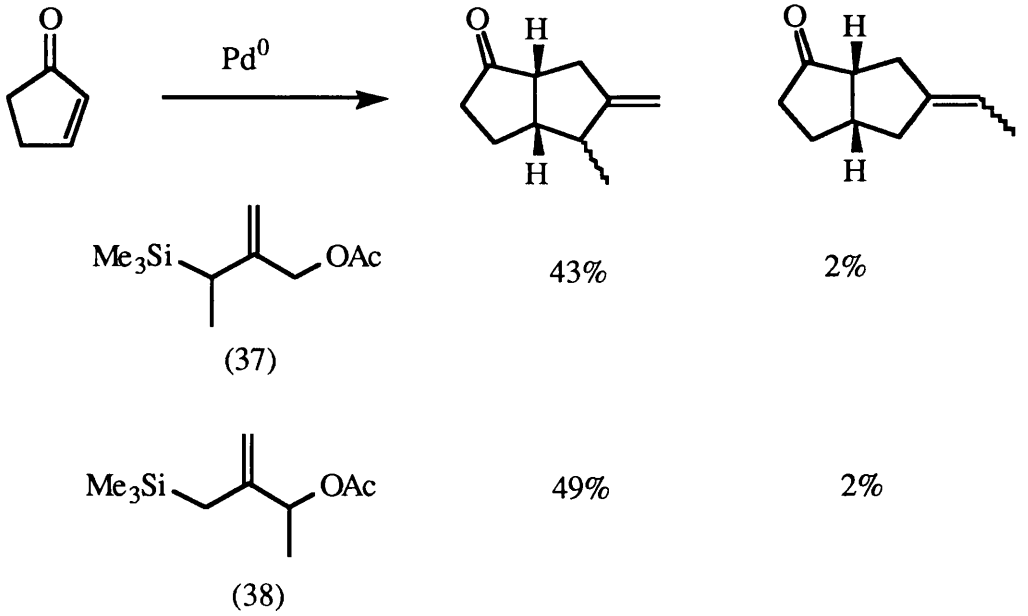
1.2.2. Substituted Bifunctional Conjunctive Reagents

Substituted BCRs represent a further extension of the aforementioned methodology to cyclopentanoid synthesis. Substituted silyl acetate derivatives are easily prepared from readily available starting materials [28] (Scheme 34).



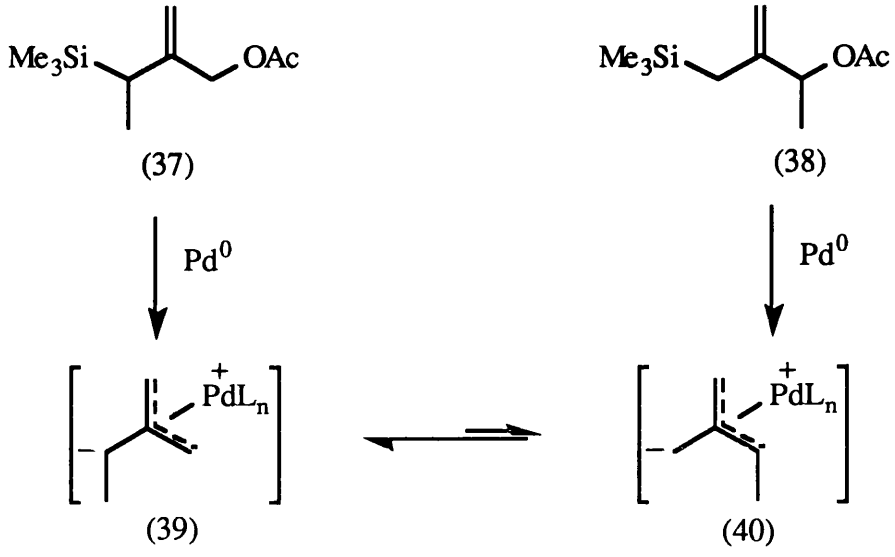
Scheme 34

The reaction of methyl substituted silyl acetates (37) and (38) with cyclopentenone provides a good example of the selectivity shown by substituted silyl acetates in the [3+2] cycloaddition (Scheme 35).



Scheme 35

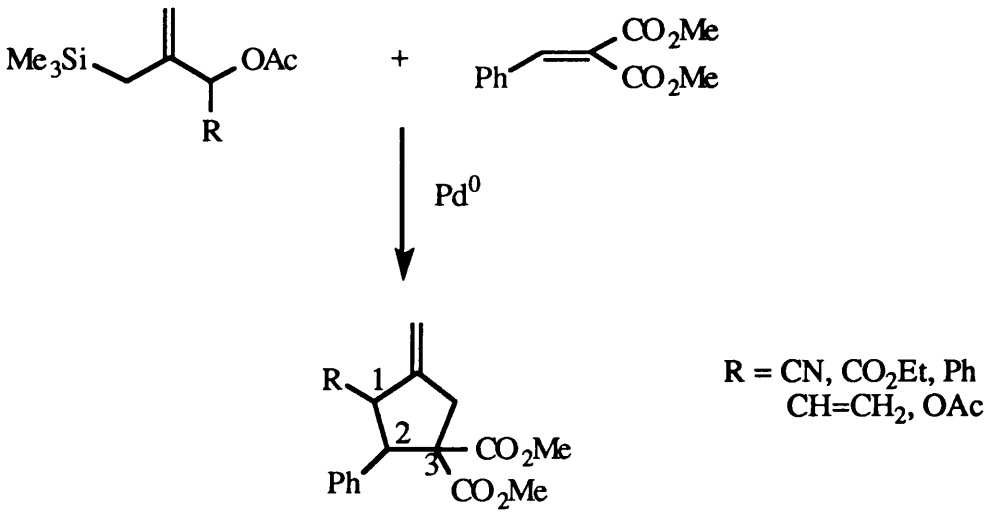
Thus cycloaddition of either (37) or (38) with cyclopentenone produced the same regioisomer with good selectivity ; in either case, the same TMM intermediate (39) undergoes cycloaddition with the enone (Scheme 36).




Scheme 36

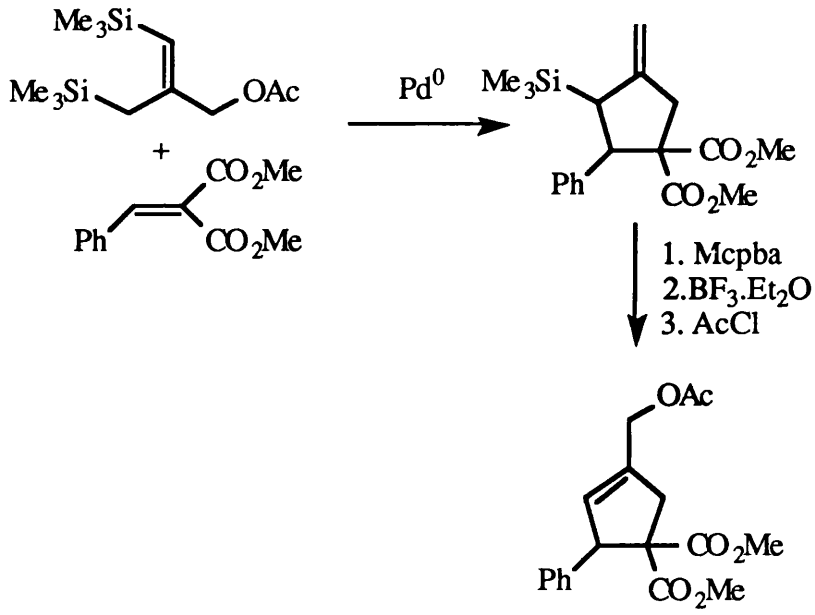
The intermediate (40) from silyl acetate (38) undergoes equilibration to the more reactive isomer (39) faster than it undergoes cycloaddition. This regioselectivity is also predicted from theoretical calculations [36] which indicate that TMM intermediate (39) is the thermodynamically preferred isomer.

In the cycloaddition with substituted silyl acetates, there is a strong preference for formation of the cyclic adduct having a 1,3 relationship between the activating group of the alkene and the substituent on the precursor,[39] as illustrated in Scheme 37.



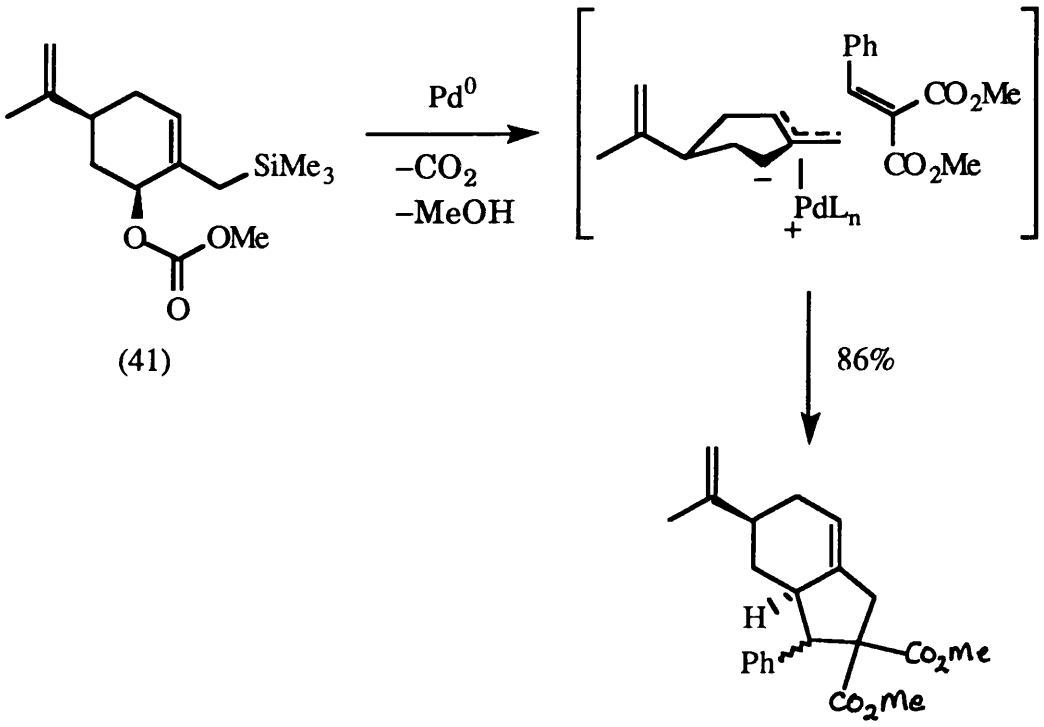

Scheme 37

It can be seen that this TMM synthon can accomodate a number of reactive functional groups without the regioselectivity being affected. The high chemo- and regioselectivity of the substituted TMM precursors combined with their ease of preparation emphasises the utility of such cycloaddition methodology for the synthesis of substituted five-membered rings. In certain cases, the five-membered ring can be further modified. For example, the regiocontrolled formation of allylsilanes in the cycloaddition providing a versatile synthetic intermediate [40,41] (Scheme 38).




Scheme 38

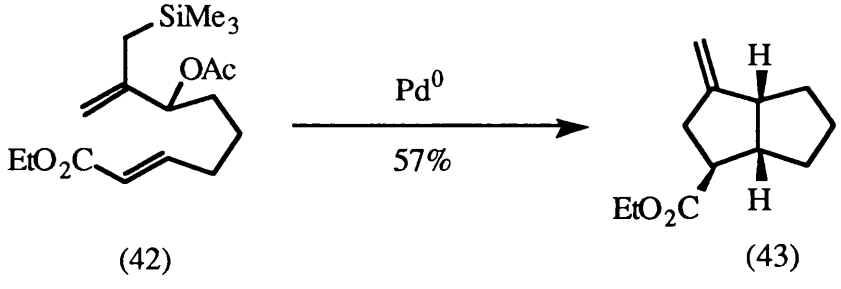
As in the cycloaddition with unsubstituted silyl acetates, the BCR cycloaddition with substituted systems is diastereoselective with respect to the TMM unit.[42] It has been shown that the alkene approaches from the side opposite to the metal centre. This can be seen in the reaction with silyl carbonate (41) with dimethyl benzylidenemalonate (Scheme 39).




Scheme 39

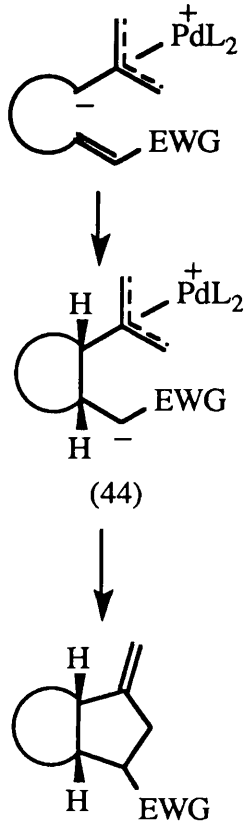
The carbonate leaving group in the initial π-complex formation undergoes decarboxylation to give an alkoxide, which then initiates the desilylation. With the silyl carbonate from *trans*-carveol, the opposite diastereoselectivity is observed.

Intramolecular [3+2] cycloadditions using substituted BCRs are well documented, and provide a unique approach to systems which are not readily accessible by simple means. Silyl acetate (42) cyclised in the presence of $(PPh_3)_4Pd$ and dppe to give a good yield of dicyclopentanoid (43) [43] (Scheme 40).




Scheme 40

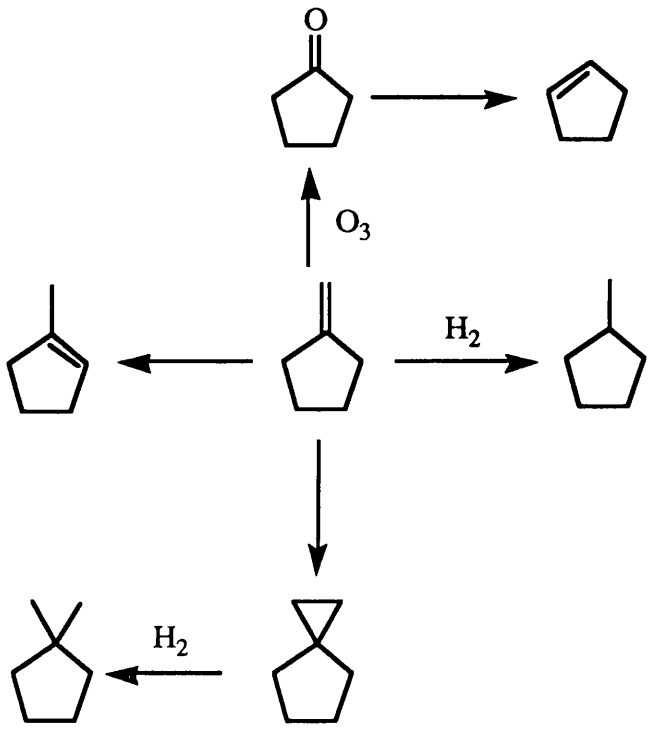
Compound (43) can be further modified by manipulation of either alkene or ester functionalities. Mechanistically, the intramolecular [3+2] cycloaddition has parallels to the methyl substituted series.[36,44] It proceeds in a two-step manner, depicted in Scheme 41.




Scheme 41

The initial addition step which proceeds preferentially to give the *cis* adduct (44) involves conversion of a β-zwitterion like species into one with greater separation of charge. The *cis*-fused adduct minimises this separation more than the *trans*-fused adduct.

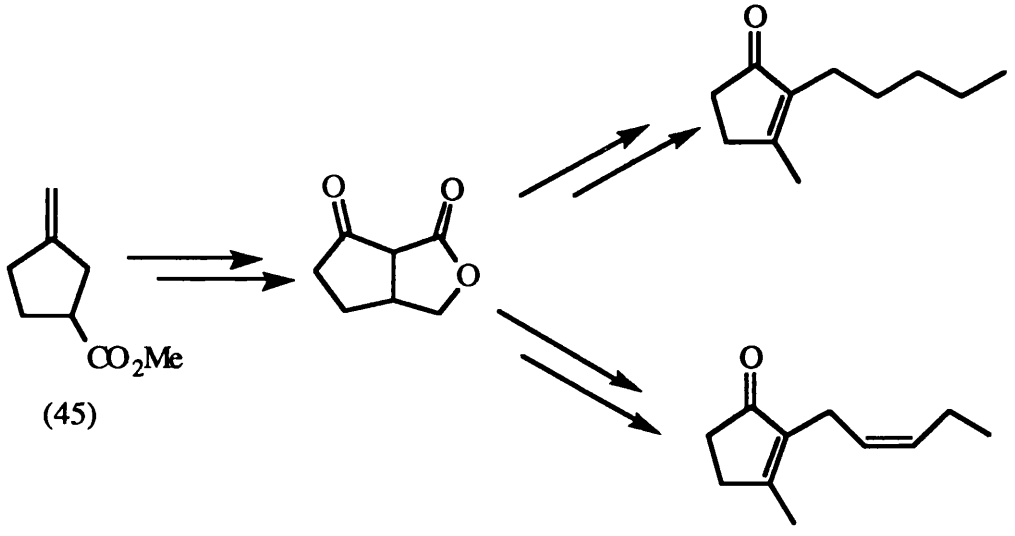
At this point it should be noted that the exocyclic methylene group that arises in syntheses with TMM precursors can serve as a versatile functional group for further elaboration (Scheme 42).




Scheme 42

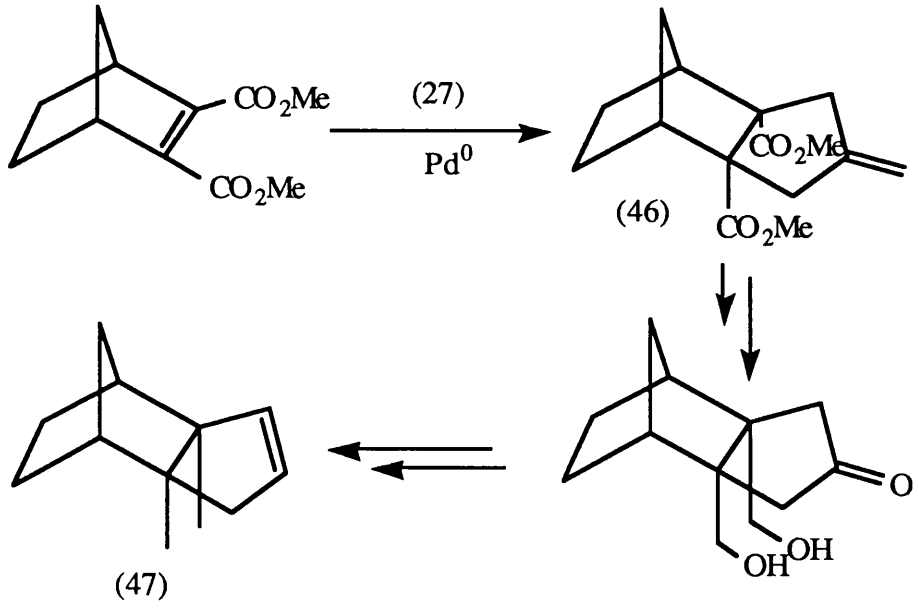
1.2.3 BCR's in Organic Synthesis

As with the 2-oxyallyl synthon, the TMM approach has been applied to a number of total syntheses and synthetic studies of various natural products. [28,45,46] The adduct (45), obtained from methyl acrylate and (27) has been shown to be a valuable starting material in the synthesis of the important perfumery compounds dihydrojasmone and *cis*-jasmone [45] (Scheme 43).




Scheme 43

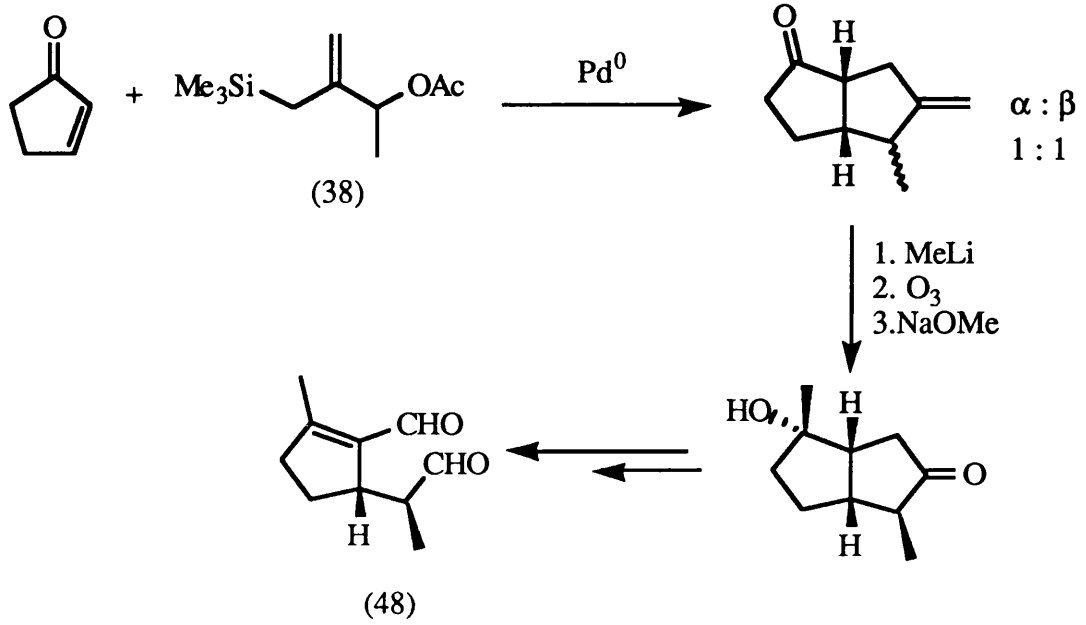
(±)-Albene (47), with a cyclopentene ring fused to a norbornene system, represents a compound which is ideally suited to a TMM mediated synthesis [33] (Scheme 44).




Scheme 44

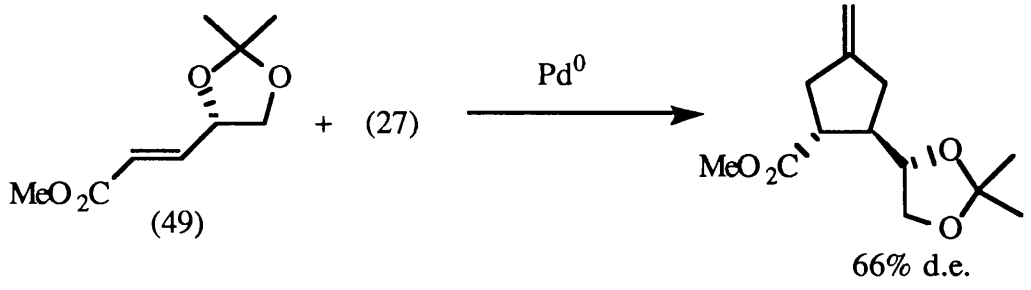
Cycloaddition of (27) occurred only at the *exo* face of 1,2-dimethoxycarbonylnorbornene to produce adduct (46).

Substituted BCRs have also been of use in natural product synthesis. The *seco*-iridoid chrysomelidial (48), a constituent of the larval defence secretion of the chrysomelide beetle, was synthesised using BCR cycloaddition methodology [44] (Scheme 45).




Scheme 45

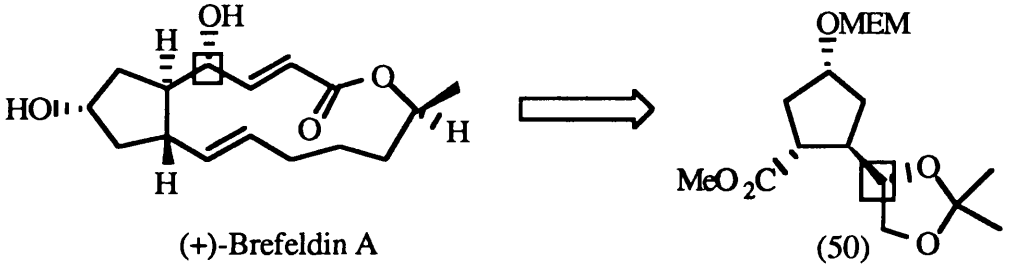
An enantioselective synthesis of (+)-brefeldin A was achieved by Trost and co-workers via diastereoselective annulation of (27) to chiral αβ– unsaturated ester (49) [47] (Scheme 46).




Scheme 46

The adduct was readily elaborated to (50), which possesses all but one

of the chiral centres in (+)-brefeldin A (Scheme 47).




(+)-Brefeldin A (50)

Scheme 47

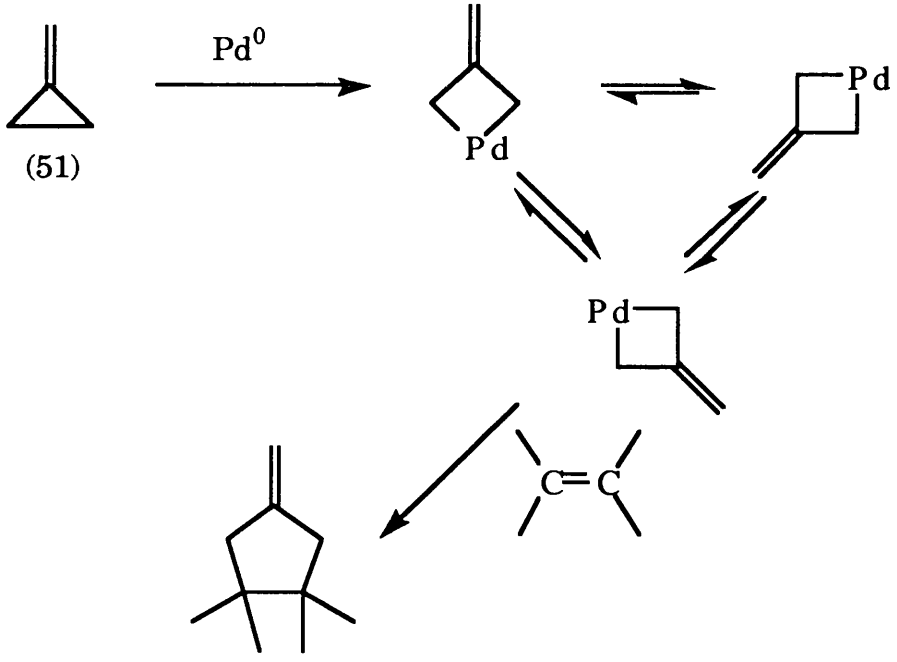
Other examples involving BCRs include ginkgolide A [48], phyllanthocin [49], 2β-hydroxyjatrophone [28,50], and the antileukemic agent (-)-rocaglamide. [51] Thus BCR methodology constitutes a useful approach to many cyclopentanoid natural products in both racemic and chiral form.

## 1.2.4 Methylenecyclopropanes

Methylenecyclopropane (51) and its various derivatives can function as trimethylenemethane synthons in the presence of a transition metal catalyst.[45] Compound (51) can be prepared readily from methallyl chloride on a kilogram scale.[52]

The normal catalysts used are derivatives of Pd and Ni; depending which catalyst is used and whether the cyclopropane is substituted or not, different cycloadducts can result.

With palladium as catalyst and the unsubstituted cyclopropane (51), distal ring-opening cycloaddition occurs with alkenes such as ethene and norbornene (Scheme 48).[53]

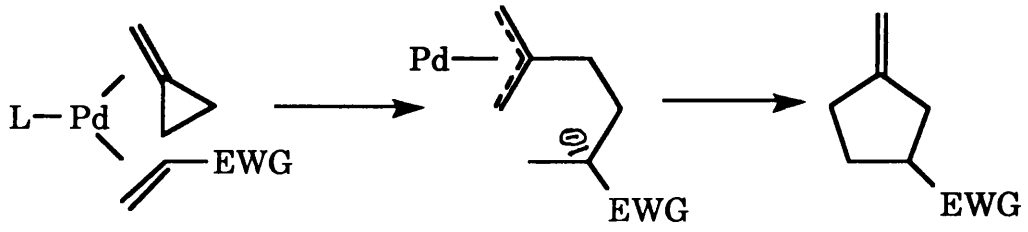



Scheme 48

This is in contrast to Trost's bifunctional conjunctive reagents reacting with only electron deficient alkenes. Electron deficient alkenes do react with methylenecyclopropane e.g. 2,3-dimethoxycarbonylnorbornadiene reacts at both double bonds to an

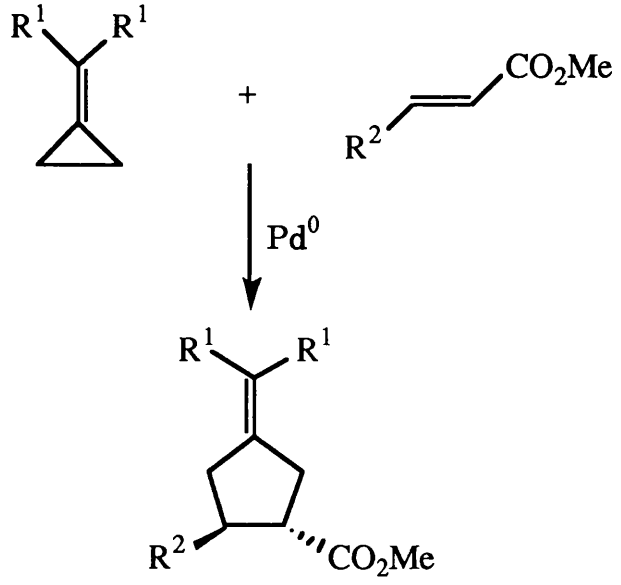
almost equal extent. Similarly, this should be contrasted with the reaction of silyl acetate (27) where only the electron deficient double bond reacts.[32]

Mechanistically, the methylenecyclopropane and the reacting alkene are thought to co-ordinate the metal; subsequent coupling produces the cycloadduct (Scheme 49).[53]




Scheme 49

With substituted methylenecyclopropanes and a Pd catalyst, cycloadducts are formed via distal ring-opening. Disubstituted methylenecyclopropanes have shown excellent ring-opening regioselectivities and yields with a number of alkenes (Scheme 50).[53]



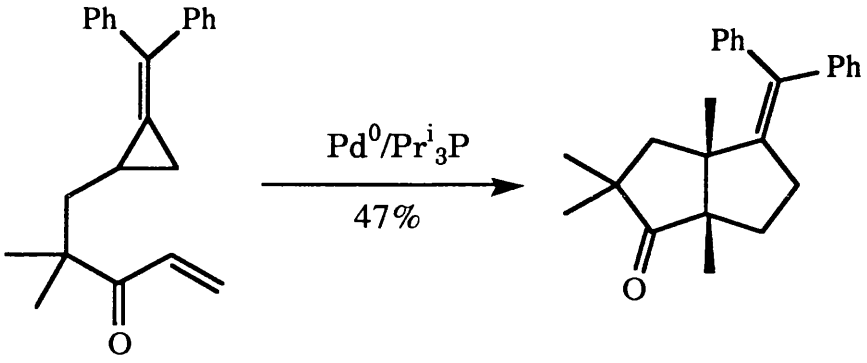

$R^1$=Me $R^2$=Me 71%

$R^1$=Ph $R^2$=H 86%

$R^1$=Ph $R^2$=$CO_2Et$ 100%

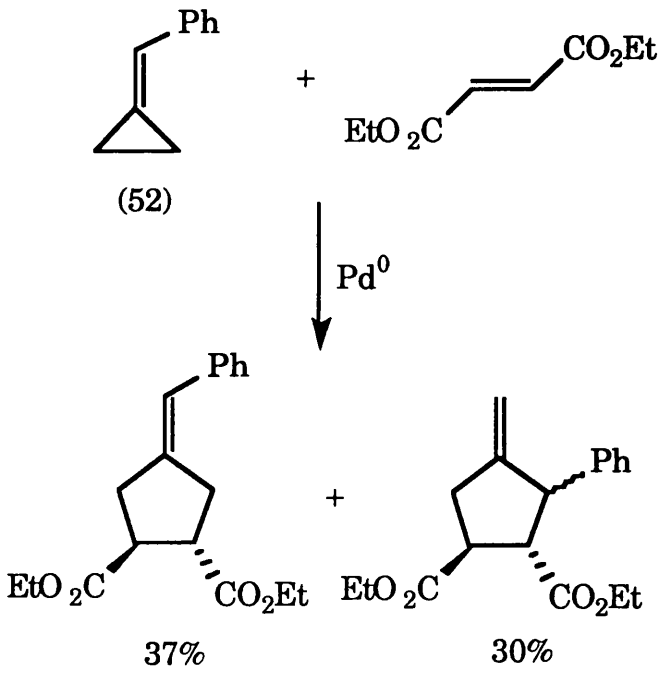
Scheme 50

The reaction of dimethylidenecyclopropane and dimethyl fumarate gives the *trans* adduct only but with dimethyl maleate, a 1:2 *cis*:*trans* mixture results. An elegant synthesis of bicyclo[3.3.0]octanes has been developed by Motherwell and co-workers using a substituted diphenylidenecyclopropane in an intramolecular cycloaddition (Scheme 51).[54]



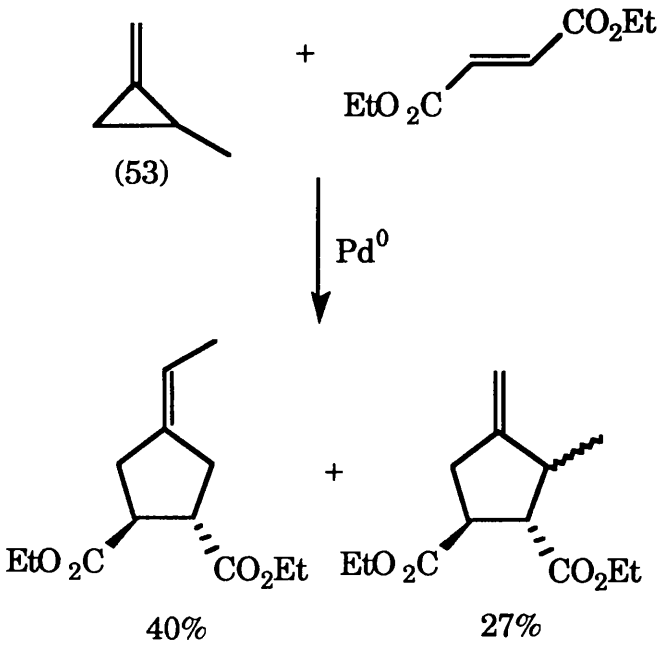

Scheme 51

With only one substituent on the exomethylene terminus, lower regioselectivities have been observed. Diethyl fumarate and (52) gave essentially a 1:1 mixture of adducts (Scheme 52).[45]



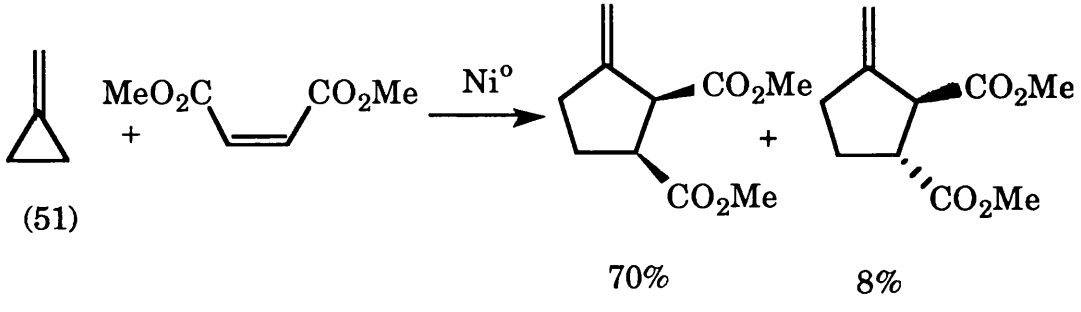

Scheme 52

With substituents on the ring, again regioselectivities are lowered. Compound (53) shows only a low preference for ethylidenecyclopentane formation (Scheme 53).[45]




Scheme 53

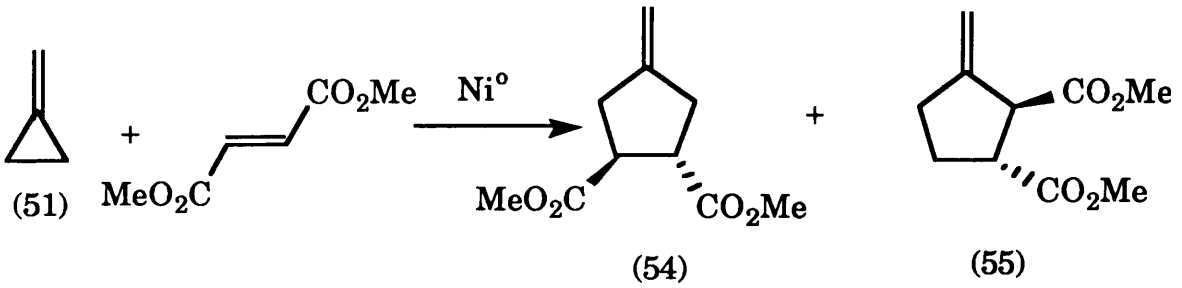
The reactions of (51) with a $Ni^0$ catalyst are dependent on the nature of the ligands attached to the metal and the structure of the reacting alkene.[55,56,57] For example, $Ni(COD)_2$ induces proximal ring-opening of (51) (Scheme 54).




Scheme 54

However, with bis(acrylonitrile)nickel as catalyst, both distal (54) and

proximal (55) ring-opening adducts were observed (Scheme 55).[55]




Scheme 55

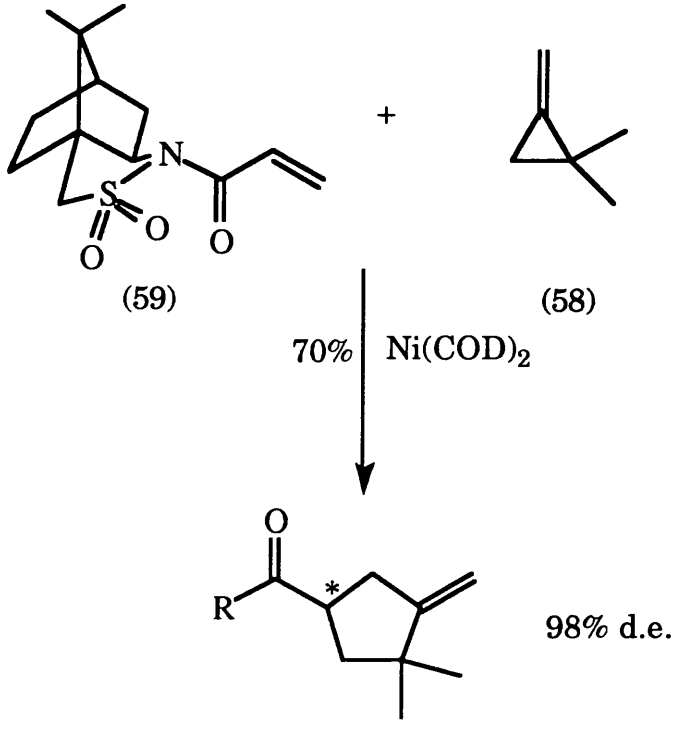
Noyori and co-workers have shown, by deuterium labelling experiments, that the formation of (54) goes via (56) and (55) via (57) (Fig.7).[58]


(56) (57)

Fig.7

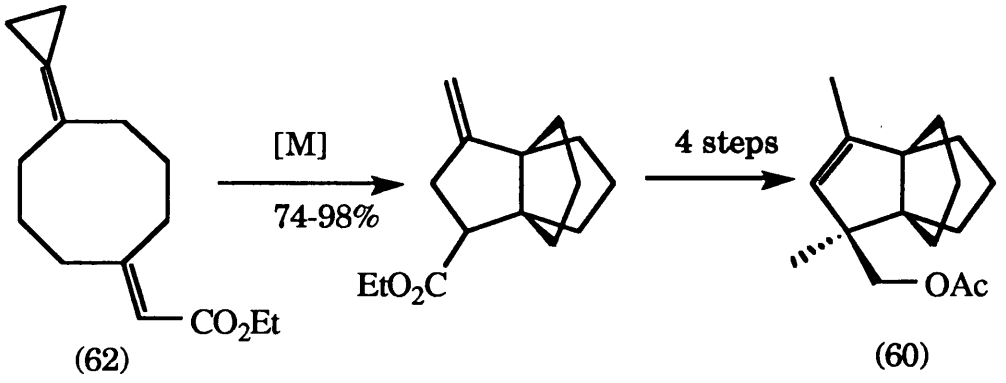
The cycloaddition of substituted methylenecyclopropanes and alkenes using a nickel catalyst is influenced by a number of factors including ligand and alkene structure.[45,49] The many examples of this are well documented and will not be discussed here. One

interesting reaction of a substituted methylenecyclopropane is that of (58) with acrylamide (59). Excellent diastereoselectivity was observed using a nickel catalyst (Scheme 56).[60]

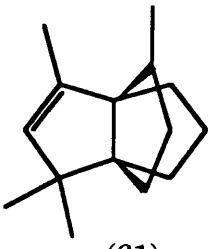



Scheme 56

As with the TMM synthons derived from silyl acetates, methylenecyclopropanes have provided useful entries into many natural products. Silyl acetate (27) and methylenecyclopropane (51) have been used to generate the same cycloadduct in many cases, e.g., in syntheses of (±)-albene, brefeldin-A, and precursors to jasmone and dihydrojasmone. Nakamura and Yamago [61] have prepared the [3.3.3] propellane (60), whose structure is related to the sesquiterpene modhephene (61) [62], from (62) via an intramolecular exocyclic transannular cycloaddition (Scheme 57). Interestingly, both Ni and Pd catalysed the cycloaddition.




(62) (60)

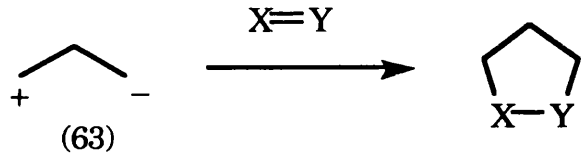


(61)

Scheme 57

## 1.3. Dimethylenemethane Synthon

A dimethylenemethane synthon can be represented as (63) (Scheme 58).



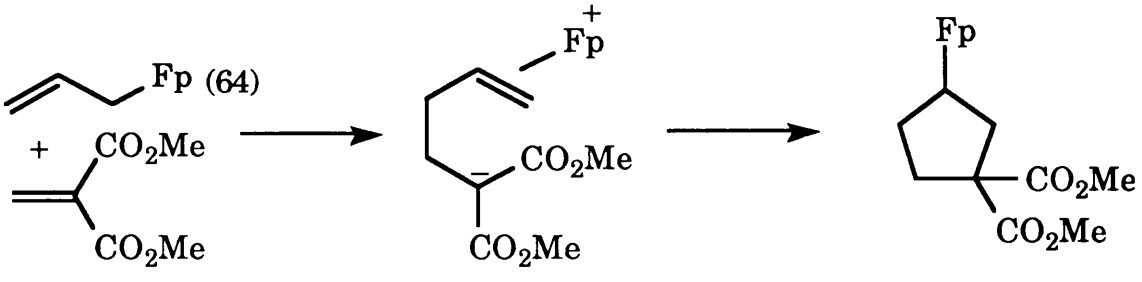

(63)

Scheme 58

A number of these three-carbon synthons has been developed from allylic, alkynyl, allenic and cyclopropyl precursors.

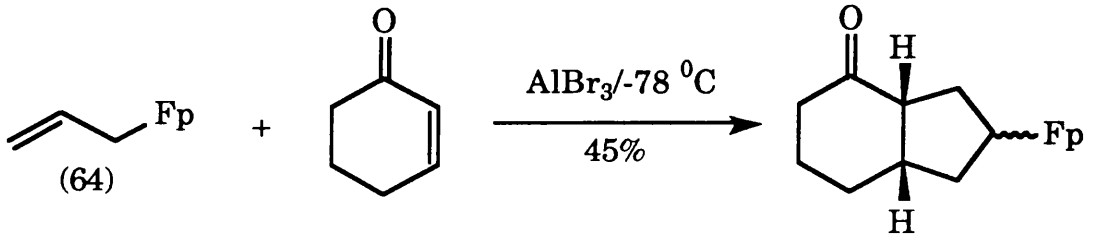
### 1.3.1 Dicarbonyl-$\eta^5$-Cyclopentadienyl Iron Complexes

Work from the laboratories of Rosenblum [63,64] using dicarbonyl-$\eta^5$-cyclopentadienyl iron (Fp) complexes has shown that five-membered rings can be formed by coupling with highly activated, electron-deficient alkenes. For example, complex (64) reacted with dimethyl methylenemalonate to give the Fp-cyclopentane adduct in good yield (Scheme 59).[65]




Scheme 59

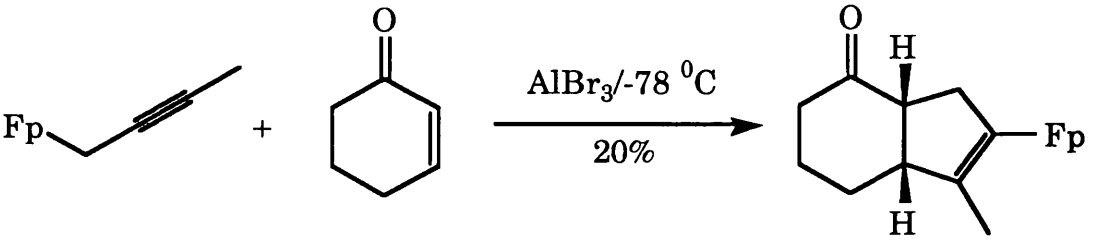
The mechanism is thought to involve Michael addition of the allyl fragment to the alkene. Ring closure is then achieved via attack of the stabilised anion on the activated alkene (Scheme 59). In addition to enones such as cyclohexenone, the reaction requires Lewis acid activation (Scheme 60).[66]




Scheme 60

The Fp fragment may be removed using $Br_2$.[67]

Alkynyl complexes have been used in the [3+2] cycloaddition to give cyclopentene systems (Scheme 61).[66]



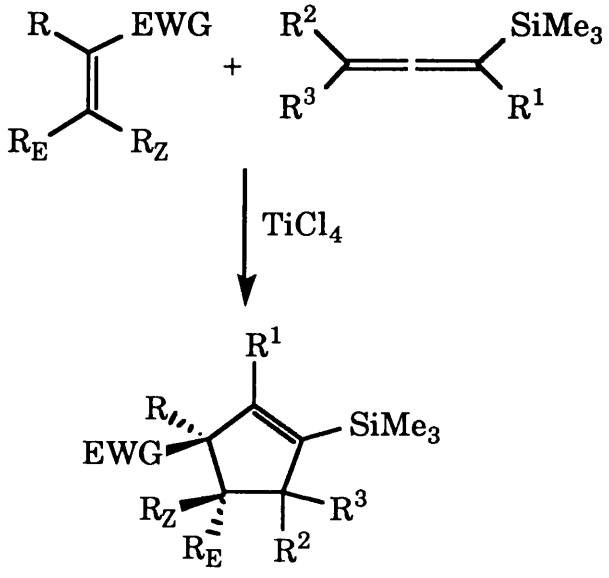

Scheme 61

As can be seen in Scheme 61, yields are lower than the alkenyl series.

1.3.2 (Trimethylsilyl)allenes

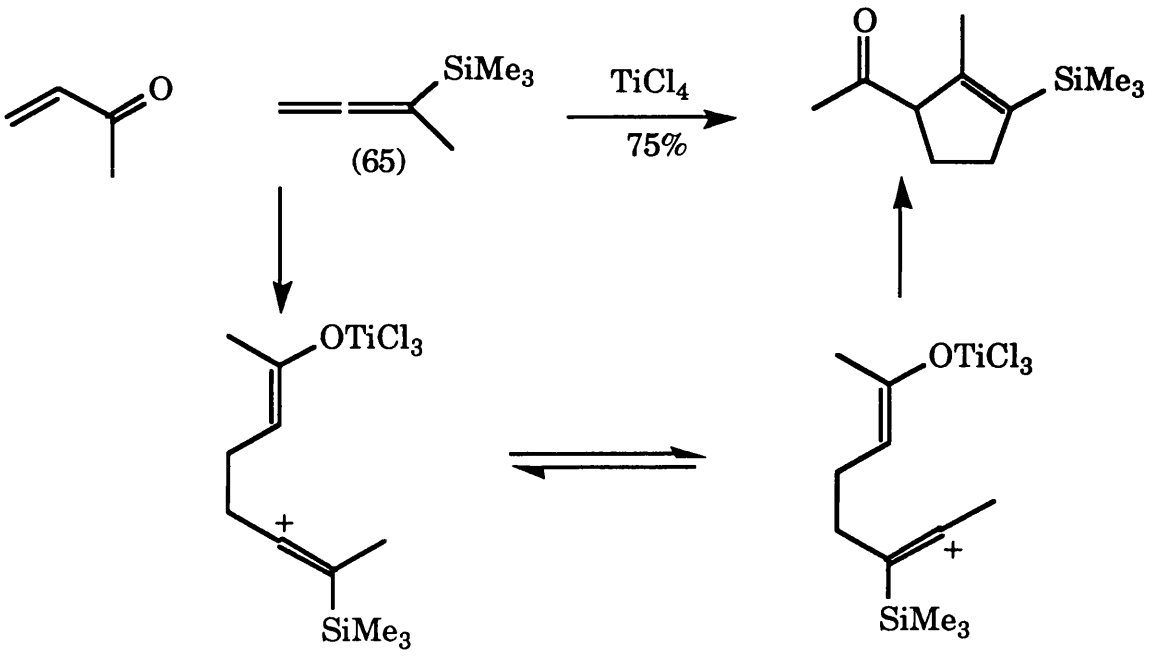
With allenic precursors, Danheiser and co-workers have described a [3+2] annulation approach to five-membered rings [68,69]

which involves the combination of (trimethylsilyl)allenes and electron-deficient alkenes in the presence of $TiCl_4$. The cycloaddition is extremely powerful since it generates five-membered rings regiospecifically. From Scheme 62, it can be seen that the reaction proceeds with high stereoselectivity via the effective suprafacial addition of the three-carbon allene component to the electron-deficient alkene.




Scheme 62

1-Substituted TMS-allenes, readily prepared from propargyl alcohols,[68,69,70] are effective in the [3+2] cycloaddition. 1-Methyl-1-(trimethylsilyl)allene (65) has been shown to cycloadd to methyl vinyl ketone to give a good yield of . . cyclopentene (Scheme 63).[69]

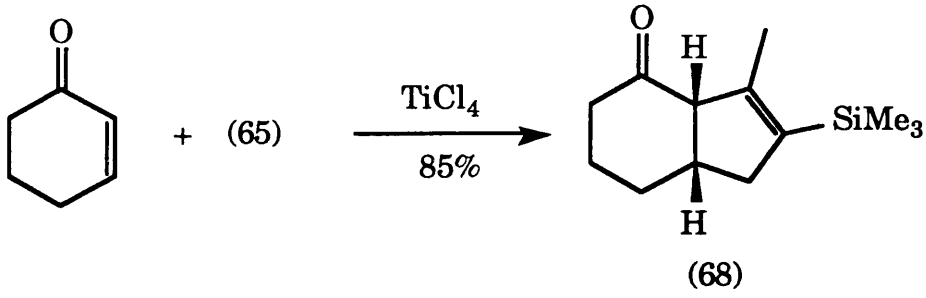



(66) (67)

Scheme 63

The reaction involves complexation of the αβ-unsaturated ketone and $TiCl_4$ to generate an alkoxy allylic carbocation. Regiospecific electrophilic substitution [41] of this cation produces vinyl cation (66) stabilised by interaction with the adjacent carbon-silicon bond. A 1,2 shift of the TMS group then affords the isomeric vinyl cation (67) which is intercepted intramolecularly to yield the cyclic product.

Both cyclic and acyclic enones serve as substrates for the cycloaddition. For example, cyclohexenone and (65) gave the adduct (68) in good yield (Scheme 64).




(68)

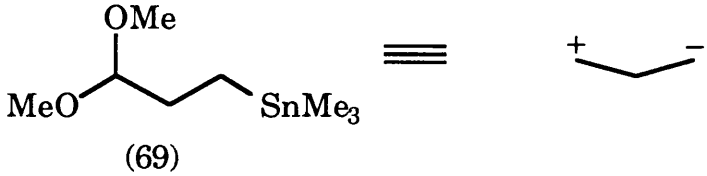
Scheme 64

The vinyl silane moiety can be further transformed via regiospecific electrophilic substitution. [41,69]

1.3.3 Miscellaneous

Other methods of generating dimethylenemethane synthons are known, of which the work of Tsuji [71] and Lee [72,73] are worthy of mention.

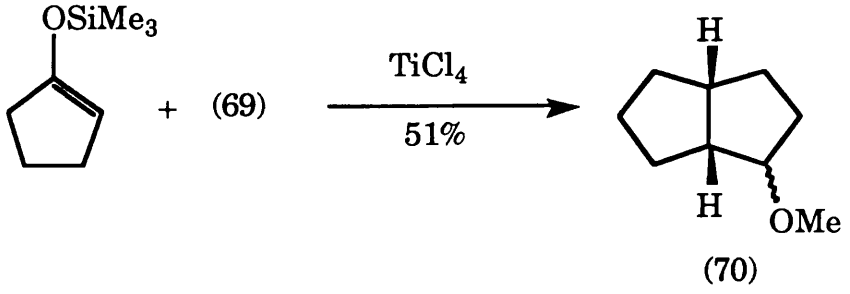
Tsuji has developed a route to cyclopentanes using electron-deficient vinylcyclopropanes and Pd catalysis whilst the late T.V.Lee developed an electrophilic annulation procedure using silyl enol ethers and the acetal stannane (69) (Fig.8).




(69)

Fig.8

For example, the silyl enol ether of cyclopentanone and (69) gave fused adduct (70) in good yield (Scheme 65).




(70)

Scheme 65

Much of the massive research effort into [3+2] cycloadditions has not been discussed here but there are several other areas worthy of mention, such as the 1,3-diyl trapping reactions of Little [74] and 1,3-dipolar synthetic equivalents including the cyclopropenone ketal reactions of Boger [75,76] and the cyclopropylphosphonium salts of Fuchs.[77]

Although the [3+2] cycloaddition strategy is in its infancy compared to its [4+2] counterpart, the research to date has shown it to be a powerful reaction in organic synthesis. Clearly there are many more facets of this reaction to be explored and much more chemistry to be discovered.

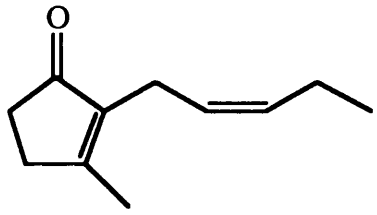
# RESULTS AND DISCUSSION

The perfume industry can be traced back many years and, until the early 1900's was reserved for the wealthiest people in society. Today, fragrances are used not only in *haute couture* perfumes but also in consumer products such as soaps, bleaches, detergents and household cleaners.

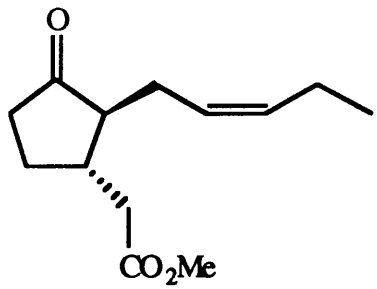
Up until 100 years ago, all perfumes were made of natural materials. Today, the perfumery industry uses synthetic chemicals on the hundreds of thousands of tonnes scale.

The development pattern of synthetic chemicals in the perfume industry closely follows that of the pharmaceutical industry. That is, the perfume material is isolated from a natural source, the major odoriferous components are identified and then synthesised. Analogues of these are normally synthesised and further QSAR (quantitative structure-activity relationship) techniques lead to the synthesis of materials which have improved performance over the natural ones.

One of the most common fragrance materials is jasmine. The extract (ex. *Jasminum grandiflorum*) retails at £ 3000-£ 5000 per kilogram.[78] The major components are jasmone (71) and methyl jasmonate (72).



(71)




(72)

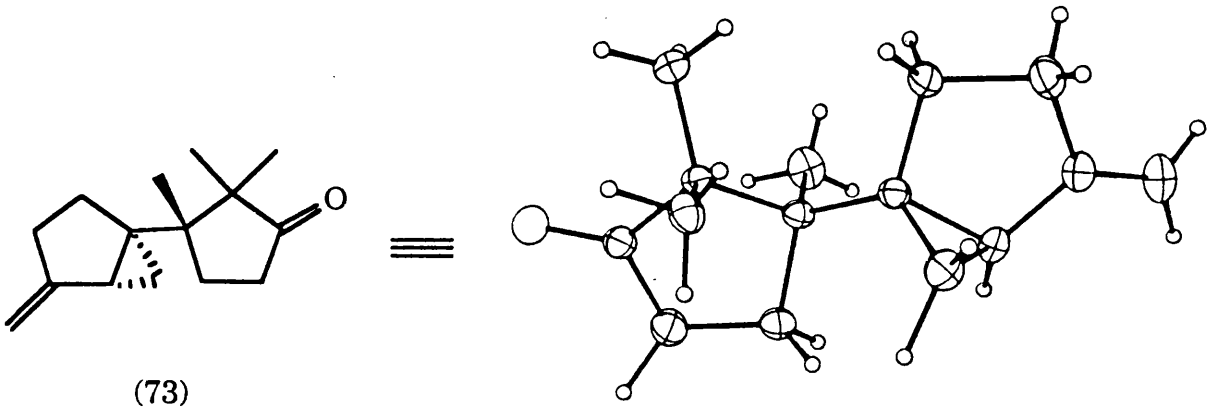
When it is seen that the synthetic versions of these compopunds retail at £ 300-£ 500 per kilogram and simpler analogues at £ 10-£ 50 per kilogram it is not surprising that there has been much synthetic effort directed at these compounds.[79]

Many perfumery compounds now in use have their origins in flowers and plants. In central Europe, the genus *Mannia* compr ises three species namely *Mannia pilosa, Mannia triandra*and the most common, *Mannia fragrans.* This liverwort (primitive plant) occurs in only a few select locations in Germany, Czechoslovakia and Poland but is extremely abundant in Hungary. As the name suggests, *Mannia fragrans* emits a pleasant odour. Indeed, when the thallus is wet, a sensitive nose can detect it at many metres.

## 2.1 Cycloaddition-Ring Contraction Synthetic Approach

In 1975, Huneck and Schreiber[80] isolated an odoriferous ketone from *Mannia fragrans* and named it grimaldone after the old genus name *Grimaldia.* Ten years later, from material collected in

Mongolia, Connolly and co-workers isolated grimaldone (73) and elucidated its structure by NMR and crystal structure analysis [81] (Fig. 9).



(73)

Fig. 9

Indeed, the absolute configuration was established by comparison of its circular dichroism spectrum with that of (+)-S-α-cuparenone (Fig. 10) (see over).

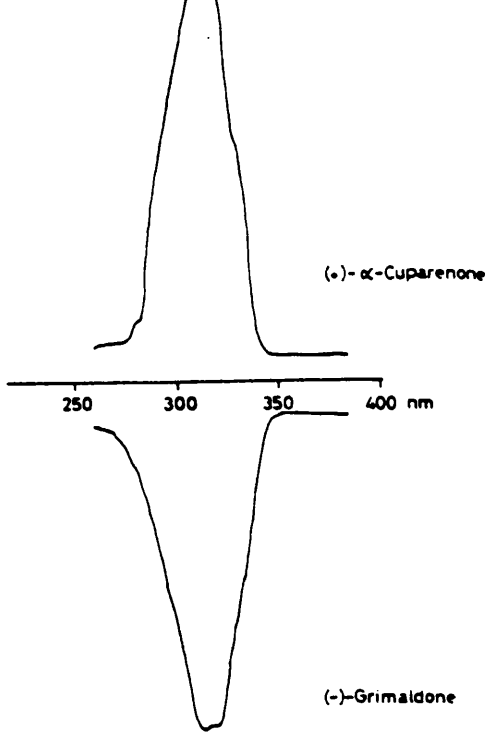
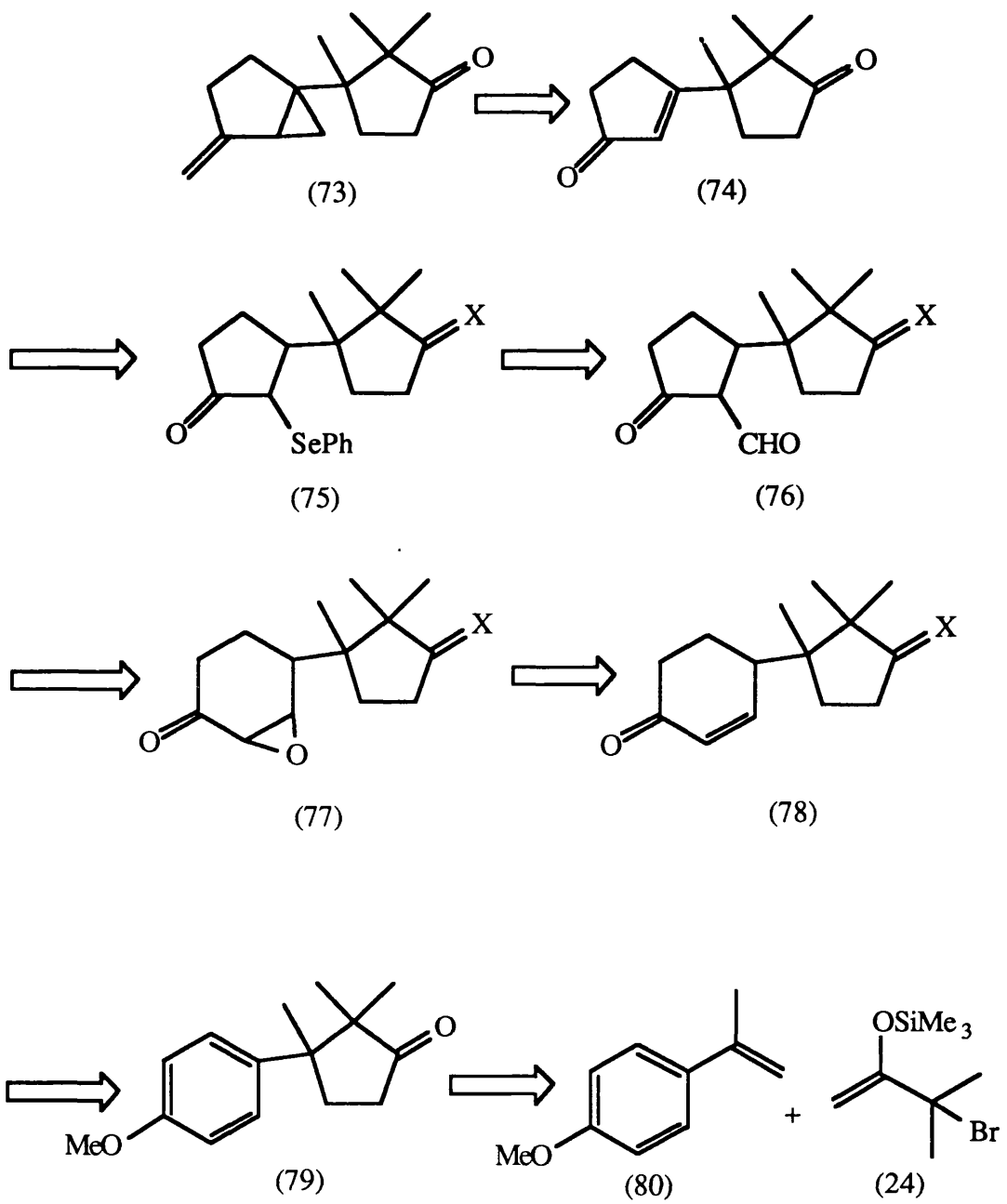



Fig.10

Grimaldone showed a negative Cotton effect and is thus a derivative of *ent*-cuparane. This shows the capacity of liverworts to produce sesquiterpenoids enantiomerically related to those of higher plants. Grimaldone is the first example of a sesquiterpenoid with this tricarbocyclic skeleton. [82] Although it is difficult to obtain this sesquiterpenoid in quantity, the odoriferous properties are sufficiently interesting to justify further investigation of its qualities as a perfumery agent. A possible retrosynthetic route to racemic grimaldone is shown in Scheme 66 (see over).



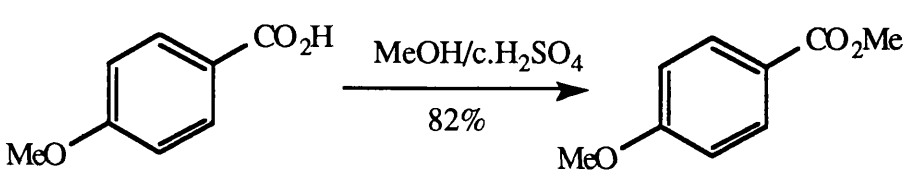

X= carbonyl in protected form

Scheme 66

Retrosynthetic analysis of the bis-cyclopentane system of (73) suggested the enedione (74) as an attractive late-stage intermediate.

Elaboration to the target and its diastereoisomer (not in any way disadvantageous since different diastereoisomers may well show different odoriferous properties) would be achieved *via* Corey-Chaykovsky cyclopropanation[83] using dimethyloxosulphonium methylide followed by Wittig olefination. It was thought that enedione (74) could be achieved from α-formyl-cyclopentanone (76) *via* phenylselenylation[84], deformylation and selenoxide elimination. Compound (76) would arise from αβ enone (78) *via* epoxidation[85] and acid-catalysed 1,2-carbonyl migration.[86,87] The enone (78) could be obtained from the arylcyclopentanone (79) *via* carbonyl protection, Birch reduction[88] and enol ether hydrolysis. It was hoped that key cyclopentanone (79) would come from silyl enol ether (24) and alkene (80) in a formal [3+2] cycloaddition employing the conditions of Sakurai.[27]

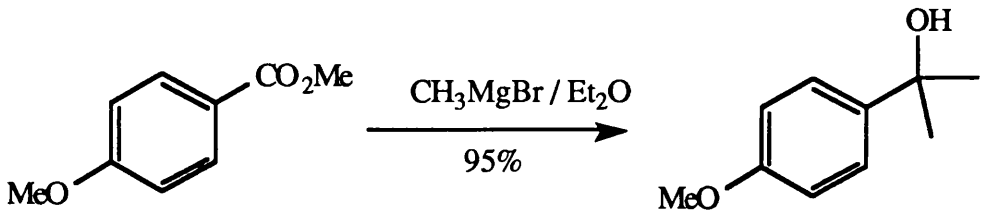
*p*-Isopropenylanisole (80) was synthesised in three easy steps from readily available *p*-anisic acid (81). Treatment of (81) with MeOH and concentrated $H_2SO_4$ according to the method of Radcliffe[89] furnished the methyl ester in good yield (Scheme 67).




(81) (82)

Scheme 67

Grignard reaction of (82) with $CH_3MgBr$ (ex. Aldrich) in $Et_2O$ afforded the tertiary alcohol (83)[90] in excellent yield (Scheme 68).

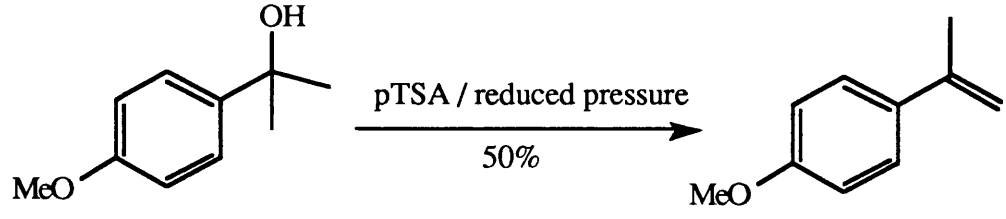



(82) (83)

Scheme 68

The crude alcohol was used in the subsequent step without further purification.

Careful, slow distillation of the tertiary alcohol (83) yielded crystalline alkene (80)[90] in reasonable yield (Scheme 69).

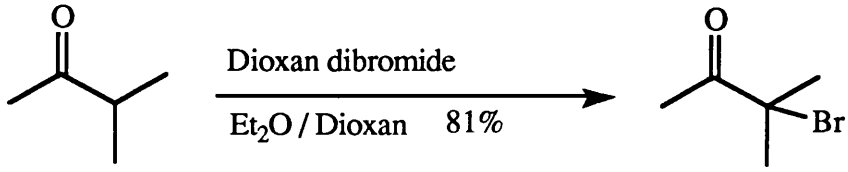



(83) (80)

Scheme 69

It was essential to perform the distillation very slowly as rapid heating resulted in distillation of the alcohol (83). It was also important to use $CH_3MgBr$ as the Grignard reagent and not $CH_3MgI$ as previous workers experienced difficulty[90] in the subsequent dehydration step. The alkene could be stored in the fridge under $N_2$ for a number of months without decomposition.

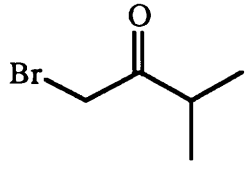
The silyl enol ether (24) was prepared from readily available 3-methylbutan-2-one (84) in two simple steps. Bromination of (84)[91] with dioxan dibromide,[92] a crystalline solid prepared from a 1:1 mixture of dioxan and bromine, proceeded to give the α-bromo ketone (85) in good yield (Scheme 70).




(84) (85)

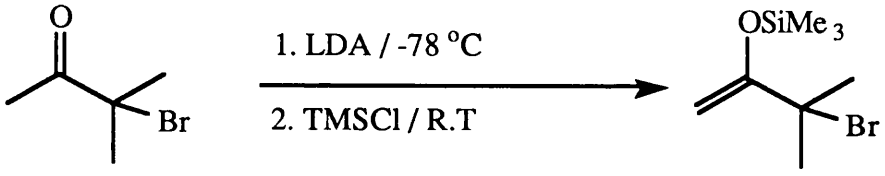
Scheme 70

The isomeric α-bromo ketone (86) was not isolated from the distillation residue.




(86)

Compound (24) was easily obtained by quenching the pre-formed enolate of (85) with trimethylsilyl chloride according to the method of Sakurai [27] (Scheme 71).




(85) (24)

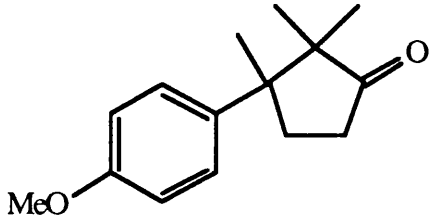
Scheme 71

Compound (24) could be prepared readily on a 20 g scale and was stable in the fridge, under $N_2$, for a number of weeks.

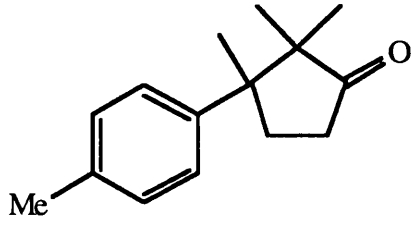
Thus, both (24) and (80) could be obtained in a straight-forward manner from readily available precursors.

With a route to both starting materials in hand, the next step was to couple them in a formal [3+2] cycloaddition employing the conditions reported by Sakurai and co-workers. [27]

At this point, it is worth discussing some of the previous approaches to structures like (79). Most of the research effort [93,94,95] over the last 40 years has been towards α-cuparenone (87) in both chiral and racemic forms.




(79)




(87)

The research effort not only describes the approach to α-cuparenone but also the approaches to synthesising compounds with contiguous quaternary centres.

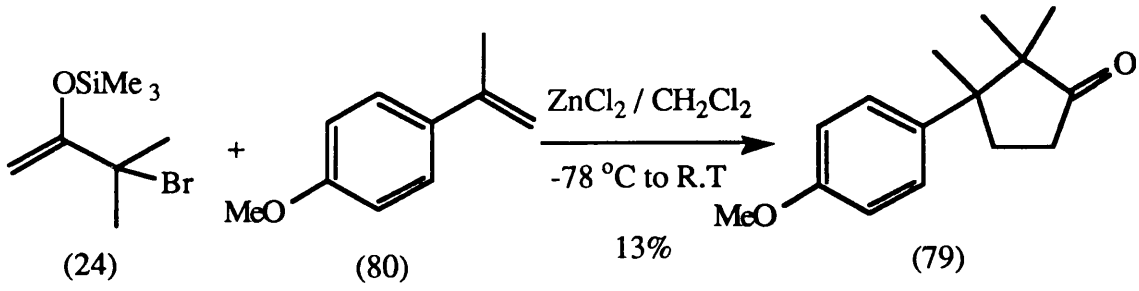
As early as 1962, Raphael [96] and co-workers reported the

synthesis of (±)-α-cuparenone. Since then, many syntheses have been directed towards cuparane type structures in both racemic and chiral forms using different approaches which have included cyclisation,[97,98,99] ring contraction,[100] ring enlargement,[95] cycloaddition, [21,22,27,94] photochemical [101] and enzyme [93] chemistry.

One very attractive approach was that developed by Sakurai and co-workers in the late 70's. [27] As discussed previously (Scheme 21), they used readily available silyl enol ether (24) and 2-(*p*-methylphenyl)prop-1-ene under $ZnCl_2$ catalysis to give a low yield of (±)-α-cuparenone.

Since we required (79), we envisaged that this formal cycloaddition approach would allow us to access (79) relatively quickly. It was hoped that yields in our reaction would be higher than those observed in the synthesis of α-cuparenone, since the *p*-anisyl group should provide greater stabilisation of the carbonium ion intermediate in the two-step formal [3+2] cycloaddition than that provided by the *p*-tolyl group involved earlier.

Under the conditions of Sakurai, (24) and (80) gave a lower yield of (79) than expected (Scheme 72).

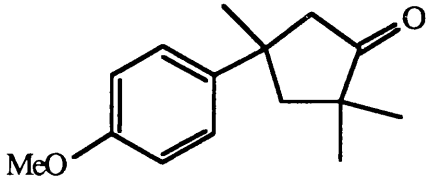



(24) (80) (79)

1 : 2

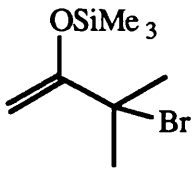
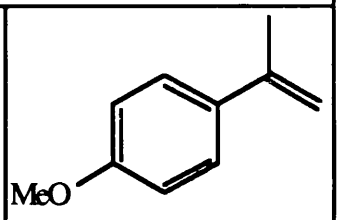
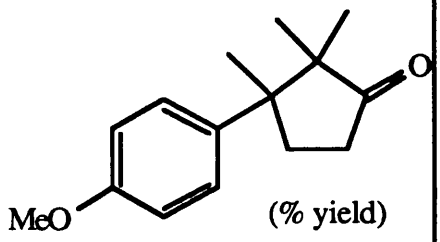
Scheme 72

This result was reproducible over a number of experiments. Ratio of the regioisomeric cyclopentanone (88) (see below) to the desired cyclopentanone (79) varied from 1:6 to 1:3 depending on separation during flash silica gel column chromatography.




(88)

It was thought that the yields may be increased by increasing the amount of silyl enol ether in the mixture since (24) did decompose rapidly compared to (80). Moving to a 1:1 ratio of (24) : (80) gave a modest increase in yield of 3%. However, on moving to a 2:1 ratio of silyl enol ether to alkene (i.e. the reverse of Sakurai's conditions), the yield multiplied virtually 3 fold to 44% ! Again, the results were reproducible and the desired cyclopentanone could be produced in yields varying between 37 and 44%. Scheme 73 tabulates the results of the study on this cycloaddition reaction.

| RATIO | | | |
|---|---|---|---|
|  |  | $ZnCl_2$ (mol %) |  (% yield) |
| 1. 1 | 2 | 100 | 13 # |
| 2. 1 | 1 | 100 | 16 |
| 3. 1 | 1 | 10 | 16 |
| 4. 2 | 1 | 10 | 37 |
| 5. 2 | 1 | 10 | 44 |
| | | | |

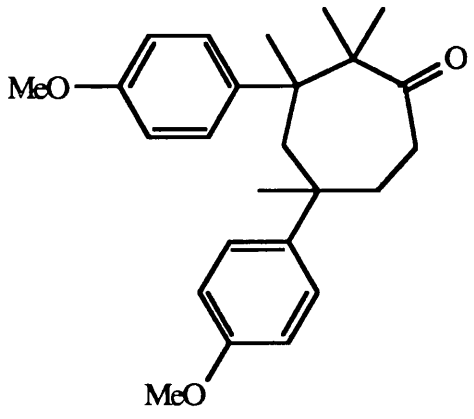
Notes : # Regioisomeric ketone yields vary depending on separation during column chromatography.

Scheme 73

From experiment 3 (Scheme 73), it can be seen that reducing the amount of $ZnCl_2$ had no effect on the yield. The marked change in yield came in experiment 4 when the ratio of silyl enol ether to alkene was increased to 2:1. Experiment 5 was the maximum yield obtained on repeating the experiment a number of times. Reproducible yields, however, were slightly lower.

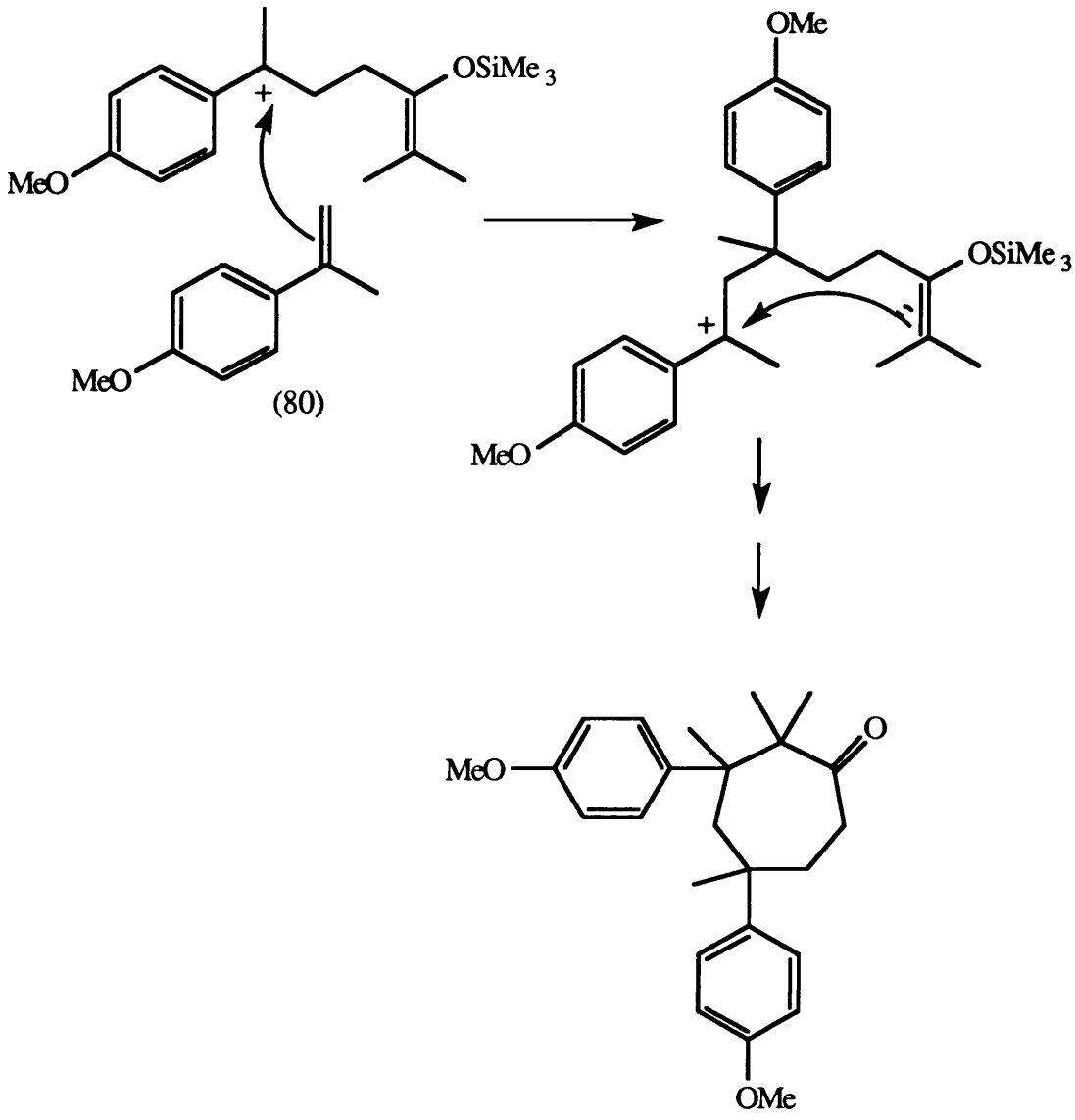
An interesting feature of the cycloaddition was that it had to be done under dilute conditions. On a 17 mmol scale, 320 ml of $CH_2Cl_2$ were required. When the reaction was performed with a x 3 concentration (i.e. 100 ml $CH_2Cl_2$ used), side reactions resulted.

Indeed, (89) was isolated in low yield.




(89)

This compound was believed to form by addition of alkene (80) to an intermediate carbonium ion , followed by ring closure (i.e. double addition of alkene (80)) (Scheme 74).




Scheme 74

It should be noted that the yields of the desired cyclopentanone (79) in the "concentrated" reaction were similar to those in the "dilute" reaction. However, separation of cycloheptanone (89) from (79) was notoriously difficult.

Thus, with a reliable route to (79) in hand, the next step in the synthetic route to grimaldone was protection of the carbonyl moiety [102]

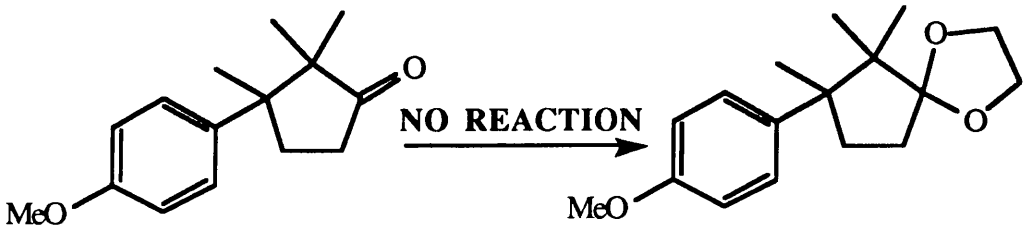
prior to Birch reduction. Attempted ketalisation [103] of (79) using :

(a) ethylene glycol / $BF_3.Et_2O$,

(b) ethylene glycol / pTSA / Dean-Stark conditions ,

(c) bistrimethylsilyl-ethylene glycol / TMSOTf

all failed to furnish the ketal (90) (Scheme 75).



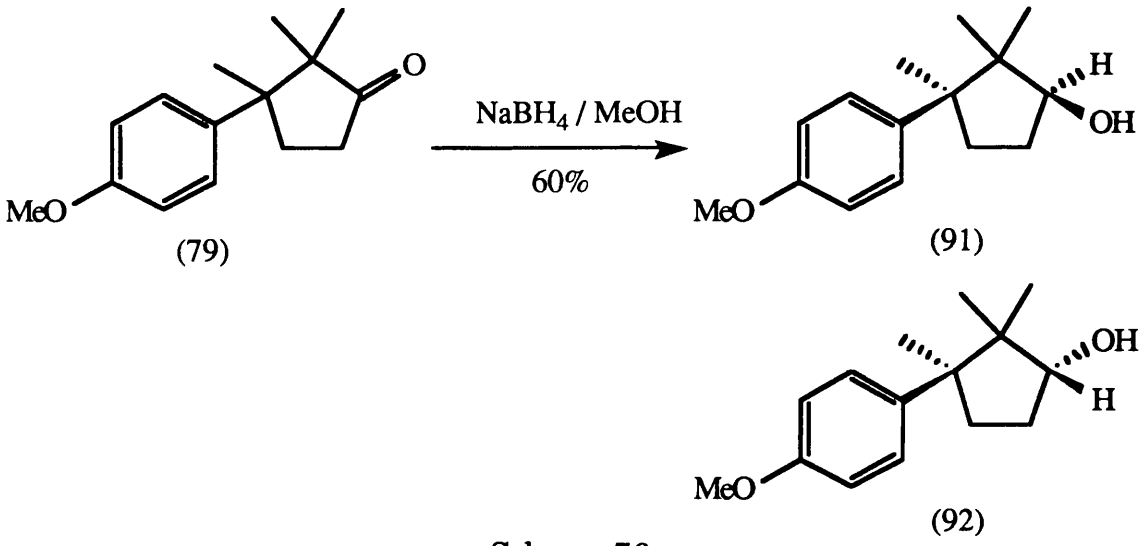

(79) (90)

Scheme 75

In hindsight, a high pressure version of (c) could have been tried. [106]

It was then decided to reduce the ketone (79) to the corresponding alcohol and protect the alcohol prior to Birch reduction.

Compound (79) was reduced in a model experiment with $NaBH_4$ [107] to give a 1:1 mixture of epimeric alcohols, (91) and (92), in good yield (Scheme 76).

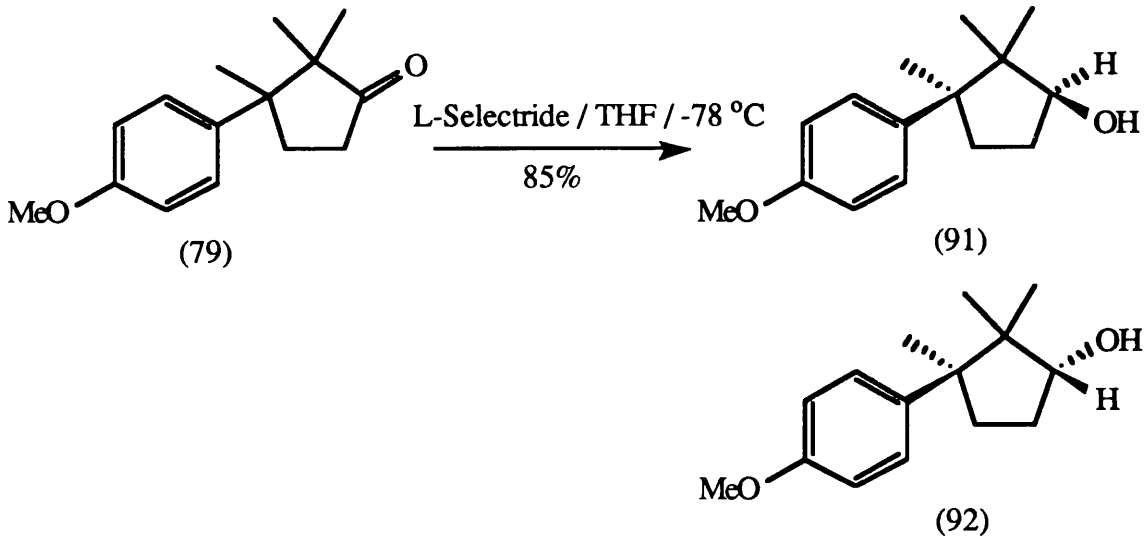



(79) (91) (92)

Scheme 76

For characterisation purposes, it was thought that it would be better to use a reducing agent which would give one alcohol selectively. Lithium -tri-*sec*-butyl borohydride (L-Selectride) has been shown to be a good reagent for the reduction of cyclic and bicyclic ketones with excellent stereoselectivity.[108]

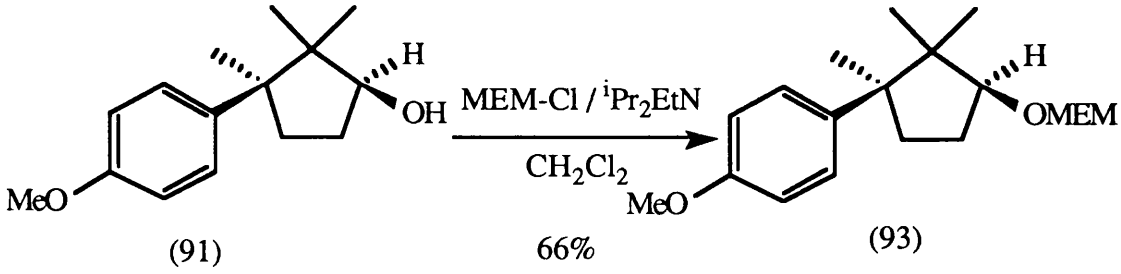
Compound (79) was reduced [109] with L-Selectride (ex. Aldrich) to give alcohols (91) and (92) in a ratio of 7.5 : 1 respectively (Scheme 77).




Scheme 77

Careful flash silica gel column chromatography separated the epimeric alcohols. It was thought that (91) was the major epimer since attack of the bulky reducing agent would be expected to be anti to the aromatic group.

Alcohol (91) was then protected as its MEM ether [110] prior to Birch reduction (Scheme 78).

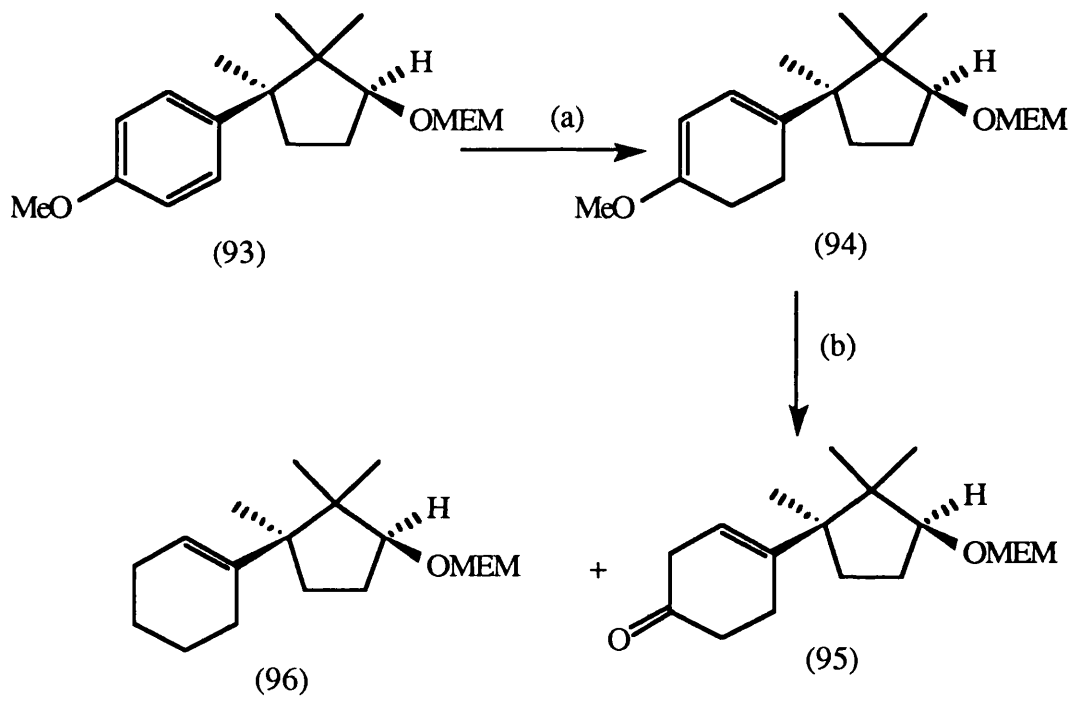



Scheme 78

The MEM protecting group was chosen owing to its stability [102] to a wide variety of conditions including those attending the use of strong

bases, organometallic reagents and mild acids. The actual experimental conditions differed slightly from those in the original report by Corey. The alcohol was stirred with a 3 fold excess of both Hun ig's base and MEM chloride in the presence of molecular sieves for 24 hours. Sometimes, more base and MEM chloride had to be added to ensure the reaction went to completion.

MEM ether (93) was then subjected to Birch reduction [88] conditions using the method of Wilds and Nelson [111] (Scheme 79).



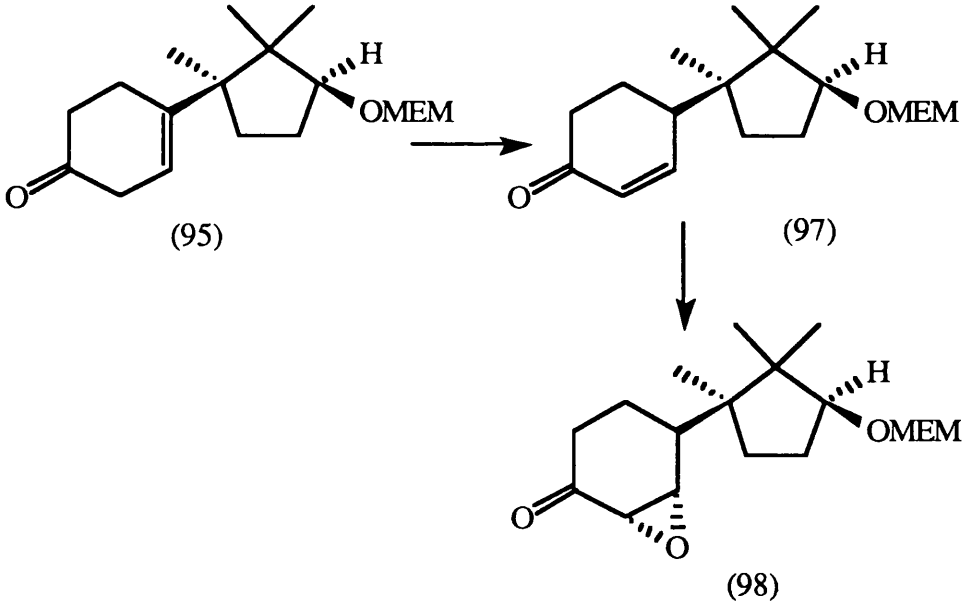

Reagents : (a) 1.Li / liq. $NH_3$ /$Et_2O$ 2. EtOH
(b) 5M HCl (cat.) / $CHCl_3$

Scheme 79

The use of lithium in place of sodium gave a marked improvement in yield in comparison with similar reactions of Birch [112,113] some eight years earlier. It is thought that the higher reduction potential of

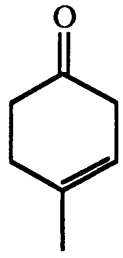
lithium and its solubility in the reaction medium enhances the yield. Compound (94) was never isolated but is likely to have either the indicated 1,3-cyclohexadiene or 1,4-cyclohexadiene structure. Direct hydrolysis resulted in conversion to the desired cyclohexenone (95). The unusual conditions of catalytic 5M HCl in $CHCl_3$ were chosen after observing decomposition of the Birch reduction product in the nmr tube (trace HCl in $CDCl_3$). The yield of (95) was reasonable (67%) based on recovered starting material. Yield of (96) was low (8%) and it is not immediately obvious how it forms.

At this point in the synthesis, with not much of (95) available, it was decided to undertake some model studies. Compound (95) was to be isomerised to (97) and then epoxidised to form αβ-epoxy ketone (98) (Scheme 80).



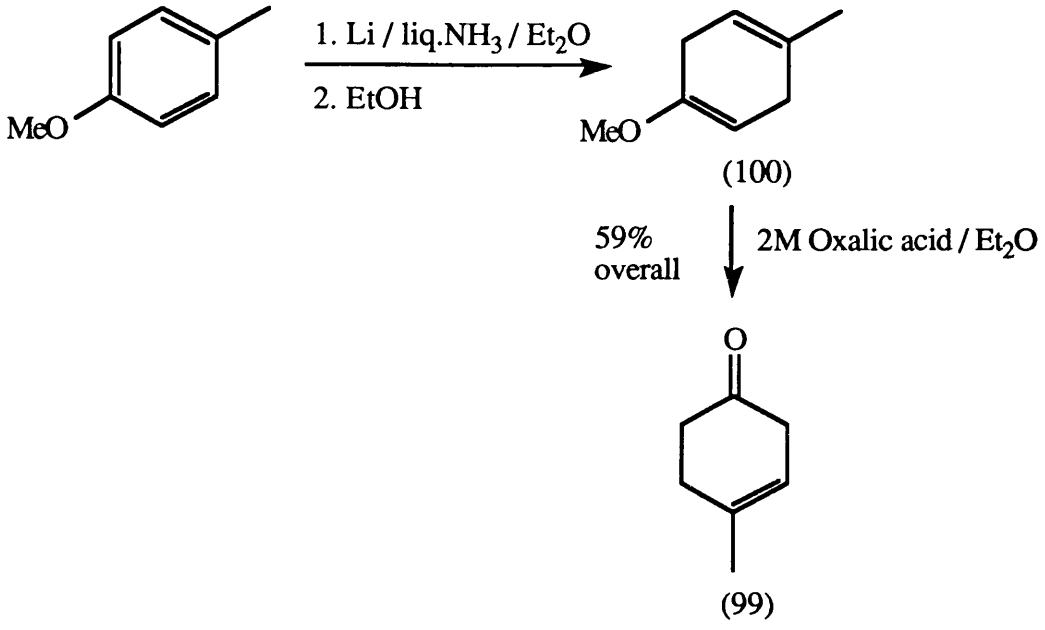

Scheme 80

Enone (99) [113] was chosen as a very simple model for (95).



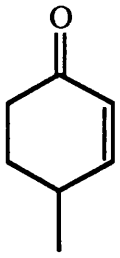
(99)

This was prepared from 4-methylanisole according to the method of Wilds and Nelson [111] (Scheme 81).



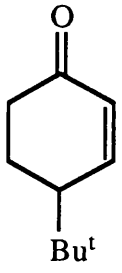

Scheme 81

It was thought that (99) could be equilibrated and epoxidised *in situ* using NaOH / $H_2O_2$. Attempted direct epoxidation of (99) using NaOH and $H_2O_2$ [85], $^tBuOOH$ / triton-B[114] and $^tBuOOH$ / n-BuLi [115] all failed. Thus, isomerisation of (99) to the αβ-enone (101) would have to be done prior to epoxidation.



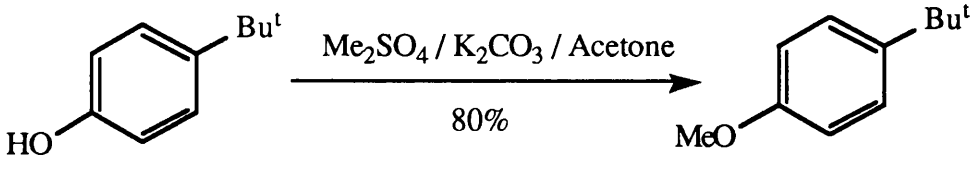
(101)

It was decided to use (102) as a better model for enone (78) (see Scheme 66).



(102)

Compound (102) was synthesised as follows. Methylation[116] of *p-tert*-butylphenol furnished anisole [117] (103) in good yield (Scheme 82).

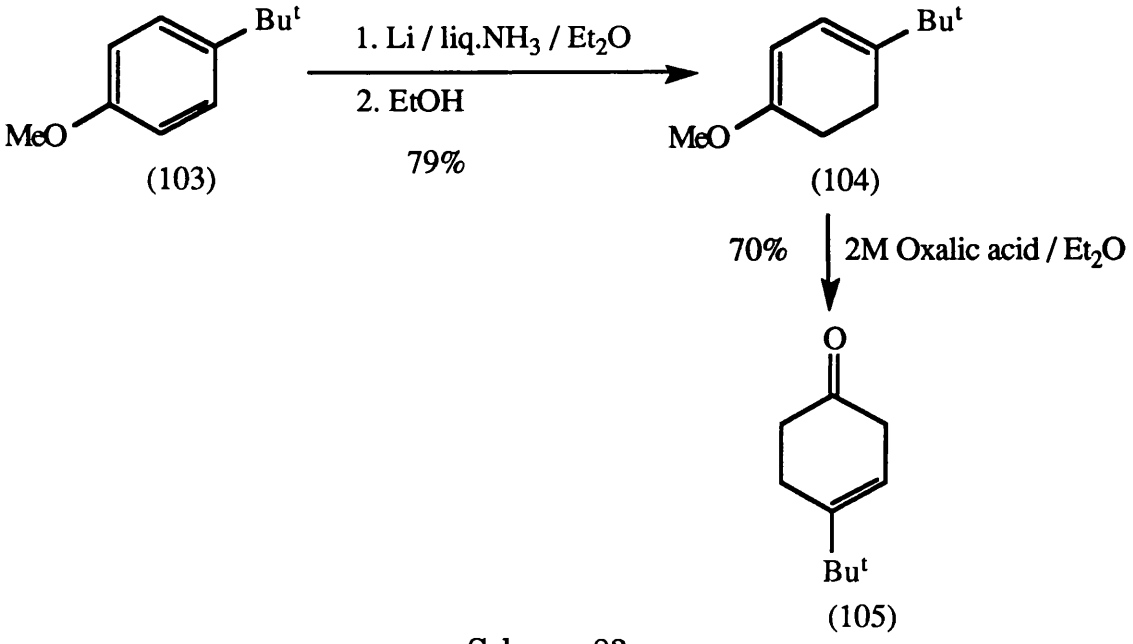



(103)

Scheme 82

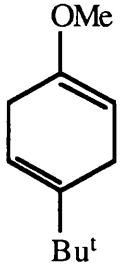
Methyl ether (103) was subjected to Birch reduction conditions according to the method of Masamune and co-workers. [118] The 5,6-

dihydroanisole (104) was hydrolysed to the βγ enone (105) in good yield (Scheme 83).




Scheme 83

It is interesting to note that the Birch reduction product was the 5,6-dihydroanisole and not the expected 3,6-dihydroanisole. Indeed, when cylinder grade liquid $NH_3$ (i.e. not distilled from Na prior to use) was used, compound (106) was formed.

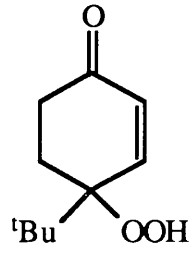



(106)

Compounds (104) and (106) were easily distinguishable using 90 MHz $^1H$ NMR. Using cylinder grade $NH_3$ may have been inconsequential

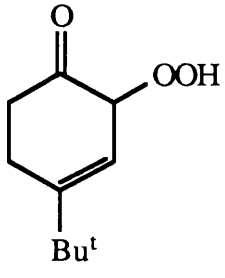
as the reason for production of the non-conjugated diene (106) may have been an insufficient amount of $LiNH_2$ present to allow a catalytic conjugation [119] to occur.

When βγ enone (105) was allowed to stand in the air over a number of weeks, a crystalline substance gradually appeared. This was isolated and analysed for compound (107).



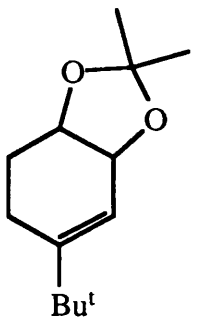

(107)

Masamune and co-workers have reported [118] the formation of (108) from (105) in a similar fashion.



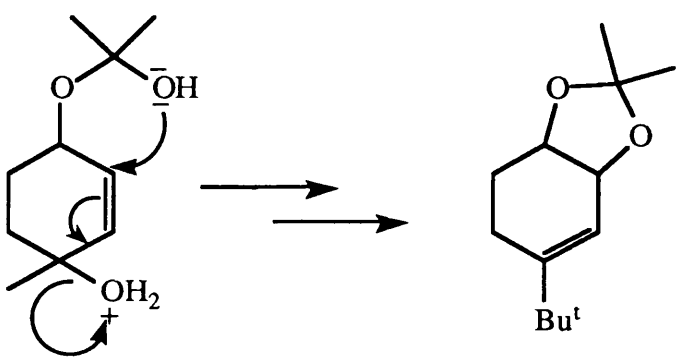

(108)

They based their structure assignment on NMR data and by chemical modification of (108). By reducing (108) with $NaBH_4$, they then formed (109) by reaction with acetone over silica gel.



(109)

However, our proposed structure (107) can also form acetonide (109) *via* intermediate (110) (Scheme 84).



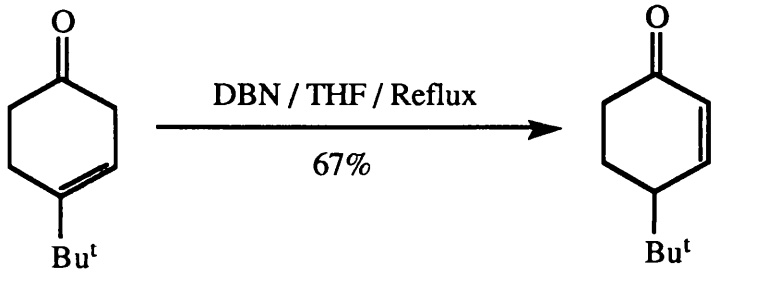
(110) (109)

Scheme 84

Actual preparation of (109) was not required as $^1H$ NMR analysis revealed the α and β protons as a doublet at 6.13 ppm and double doublet at 6.86 ppm respectively. The UV absorption at 216 nm (ε=17 100) was also indicative of αβ unsaturation. It should be noted that (107) exhibits spectral data and m.p. identical to those previously reported.[118]

Acid catalysed equilibration of (105) using HCl afforded a 2:1

mixture of αβ : βγ enones and not the reported [118] 4:1 mixture. DBN (1,5-diazabicyclo[4.3.0]non-5-ene), a well known non-nucleophilic base [120], catalysed the conversion of (105) to (102) in good yield (Scheme 85).

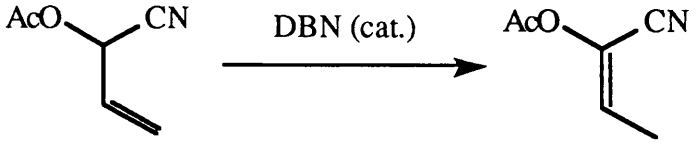



(105) (102)

αβ : βγ = 4 : 1

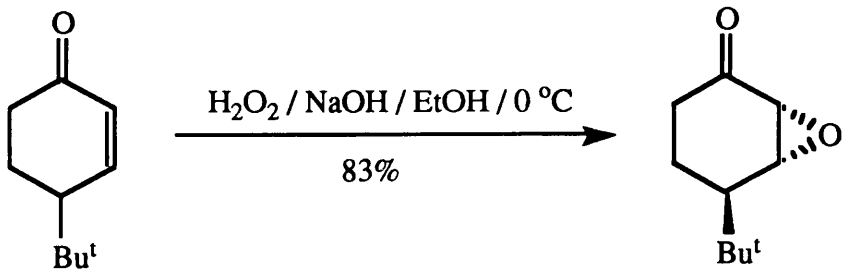
Scheme 85

This was probably not surprising since a group at Bayer [121] had reported the use of DBN in isomerising a βγ unsaturated nitrile to an αβ unsaturated nitrile (Scheme 86).




Scheme 86

Epoxidation of (102) using alkaline hydrogen peroxide [85] proceeded smoothly to give epoxy ketone (111) in excellent yield (Scheme 87).

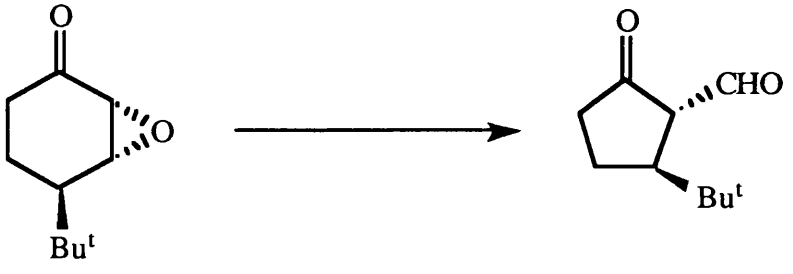



(102) (111)

Scheme 87

Compound (111) is likely to have the structure shown as delivery of "O" should be anti to the bulky *tert*-butyl group.

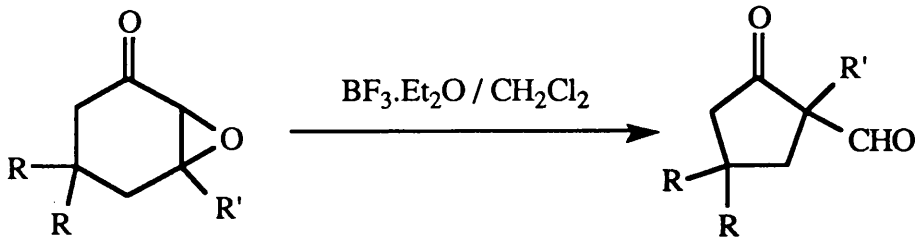
The next step in the synthesis was conversion of (111) to (112) *via* a Lewis acid mediated ring contraction (Scheme 88).




(111) (112)

Scheme 88

This is a model for the actual conversion of (77) to (76) (see Scheme 66). Previous workers [86] in the mid 50's had shown that 2,3-epoxy cyclohexanone derivatives could be isomerised to the corresponding α-formyl cyclopentanones in good yield (Scheme 89).




(a) R = R' = $CH_3$

(b) R = H, R' = $C_6H_5$

(c) R = R' = H

Scheme 89

Reaction of (111) under the conditions of House and Wasson [86] did not furnish the desired cyclopentanone (112). Indeed, subjecting (111) to the following reagents resulted in no reaction or extensive decomposition depending on the reaction time involved:

(a) $BF_3.Et_2O$, $CH_2Cl_2$, 25 °C

(b) $BF_3.Et_2O$, $CH_2Cl_2$, 0 °C

(c) $BF_3.Et_2O$, $C_6H_6$, reflux

(d) TMSOTf, $CH_2Cl_2$, 0 °C

(e) TMSOTf, $^iPr_2EtN$, $CH_2Cl_2$, 0 °C

(f) $TiCl_4$, $CH_2Cl_2$, 0 °C

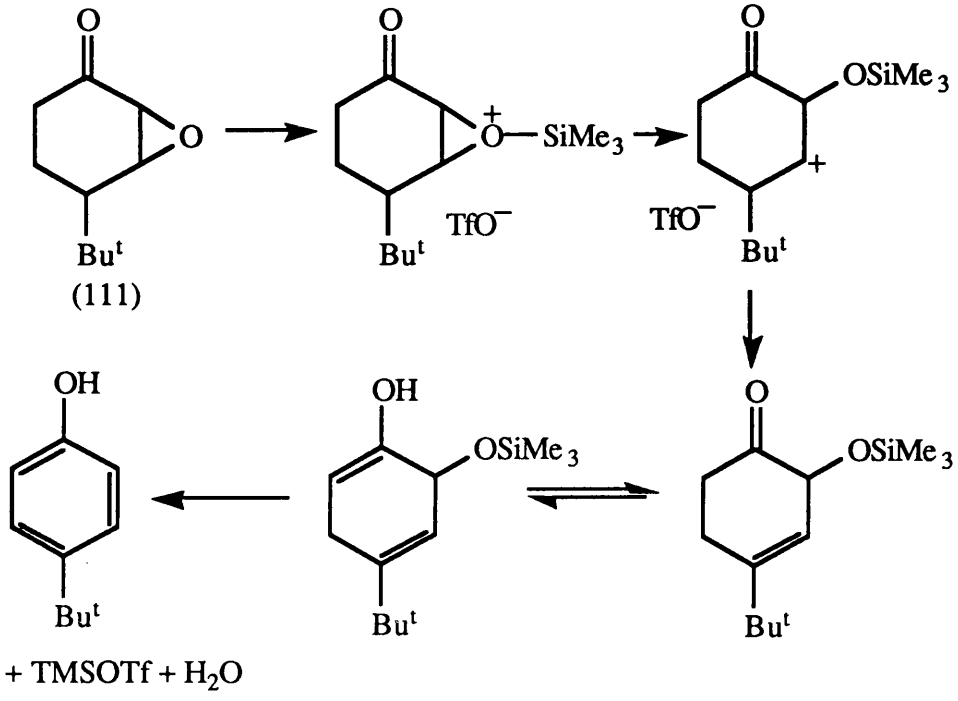
(g) $TiCl_4$, $CH_2Cl_2$, -78 °C

(h) $ZnCl_2$, $C_6H_6$, reflux

(i) $Ti(O^iPr)_4$, $CH_2Cl_2$, 0 °C

Only conditions in (e) gave any product. 4-*tert*-butylphenol was isolated in 17% yield along with 34% recovered starting material. It is

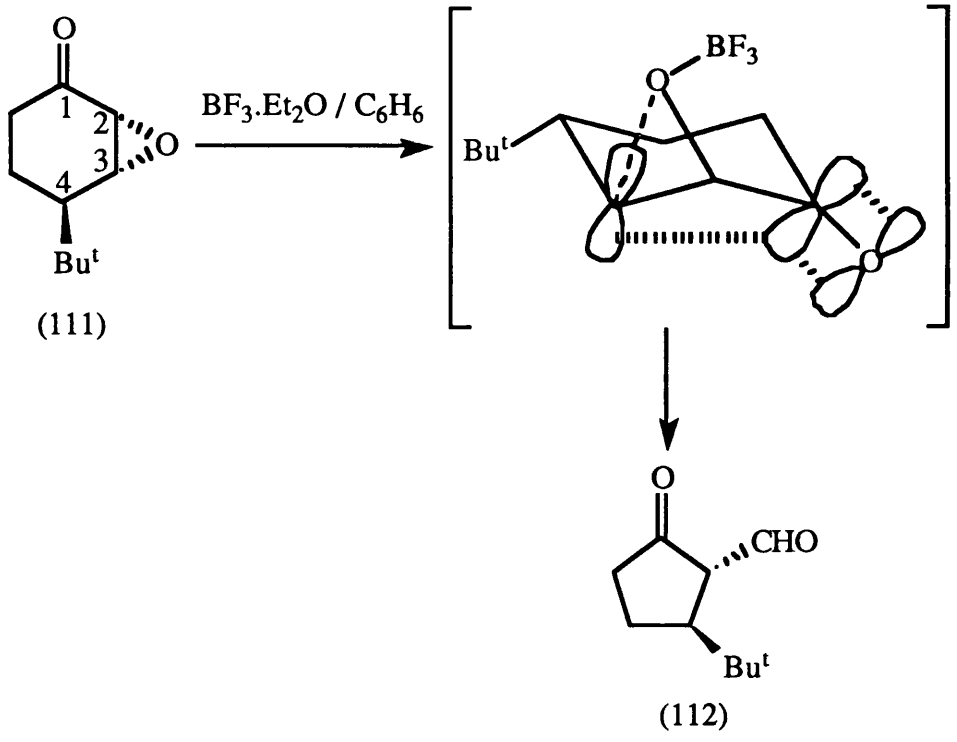
thought that the phenol could form by the postulated mechanism outlined in Scheme 90.




Scheme 90

Considering the phenol was a starting material for a five-step synthesis of (111), it is debatable whether it should be described a result or not!

Bach and Klix [87] have suggested that there has to be certain geometric requirements for a concerted 1,2-carbonyl migration to occur in αβ-epoxy ketones (Scheme 91).

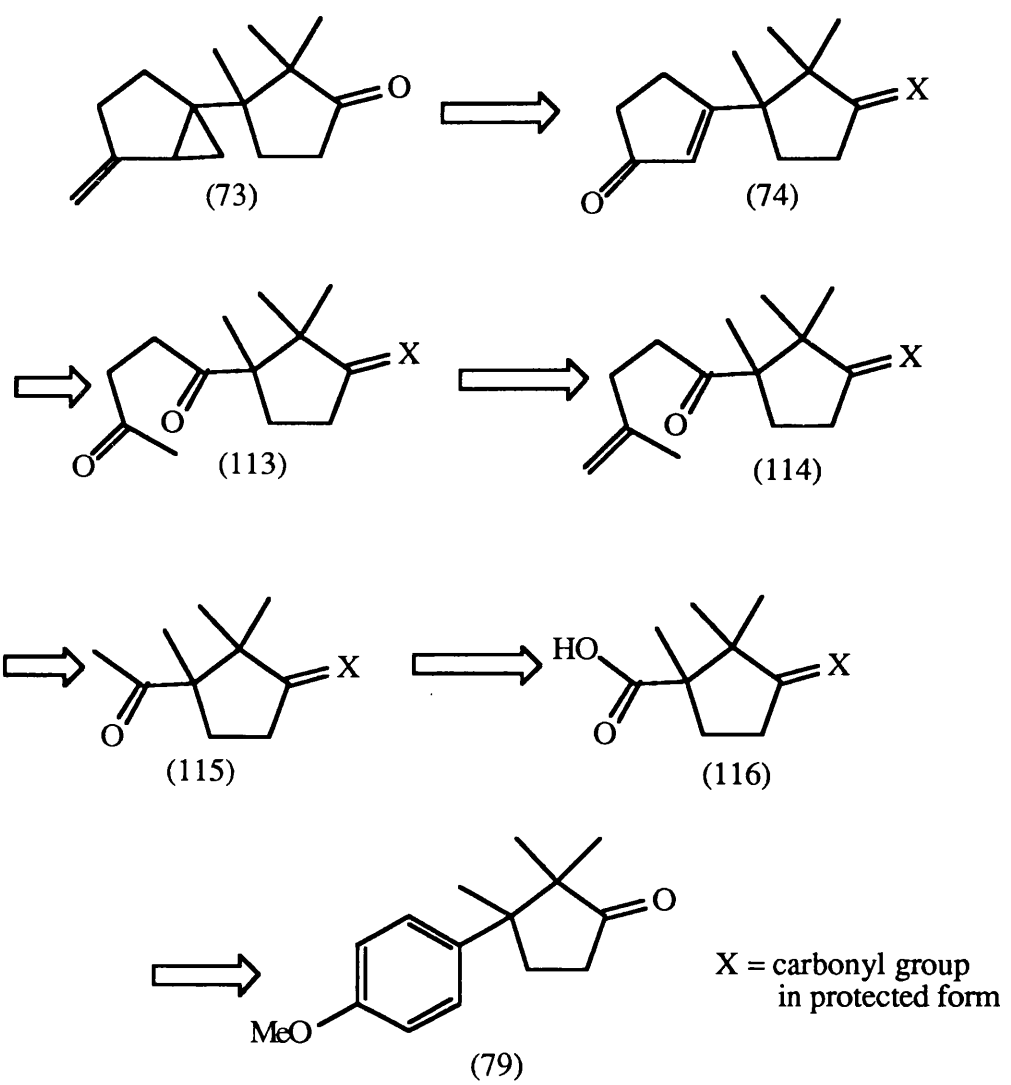



Scheme 91

They have suggested that the C-C σ bond at the migration origin must be parallel, or nearly so, to the developing vacant p orbital at C-3. The atomic p orbital should also be able to achieve coplanarity with the C-2-C-3 bond axis in order for developing Walsh orbitals to disperse the positive charge in the transition state. By examining Dreiding models, (111) can achieve these criteria, yet no migration occurs. The lack of migration may be ascribed to the stability of the developing carbonium ion at C-3 i.e. secondary as opposed to a more stable tertiary carbonium ion. Indeed, virtually all reported ring contractions in epoxy ketones involve migration to a tertiary centre, although House [86] has reported 2,3-epoxy cyclohexanone undergoing a ring contraction, albeit in low yield.

## 2.2 Cycloaddition-Ring Cleavage Synthetic Approach

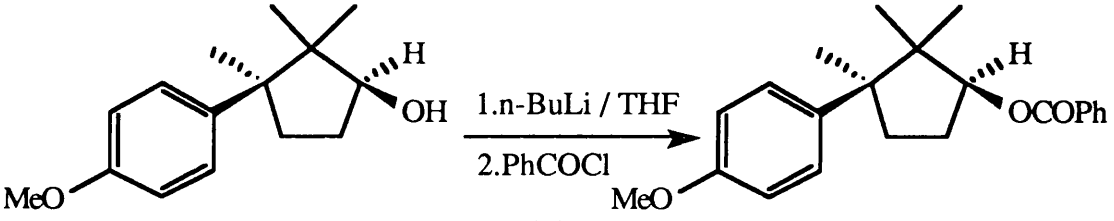
Thus, with the supposedly facile ring contraction failing, a new route to grimaldone was devised. This was based on a report by Spanish workers [122] that a phenyl group could act as a masked carboxylic acid. A new retrosynthetic route to grimaldone is shown in Scheme 92.




Scheme 92

It was envisaged that cyclopentanone (79), a key intermediate in the previous synthetic approach (Section 2.1), could be protected, cleaved to acid (116) *via* a modified [122] $RuO_4$ oxidation and then elaborated to (74) *via* methylation, methallylation, ozonolysis and aldol closure. Access to grimaldone (73) would be as before.

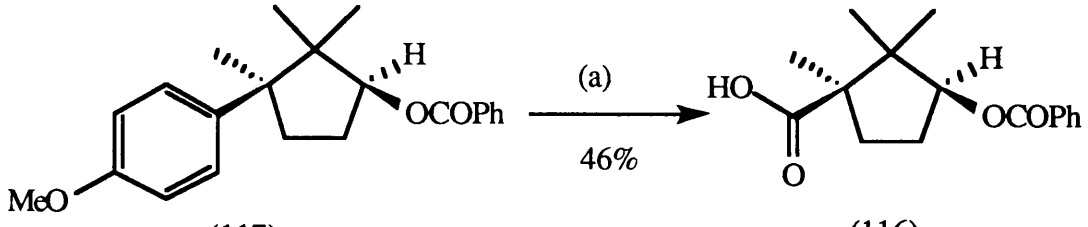
Ketone (79) was reduced with L-Selectride as before. Protection of the alcohol moiety as its benzoate ester [123] , a group compatible with $RuO_4$ oxidation, furnished benzoate ester (117) in good yield (Scheme 93).




(91) (117)

Scheme 93

Subjecting (117) to Martin's [122] modified Sharpless oxidation [124] cleaved the aromatic group to the acid (116) in reasonable yield (Scheme 94).



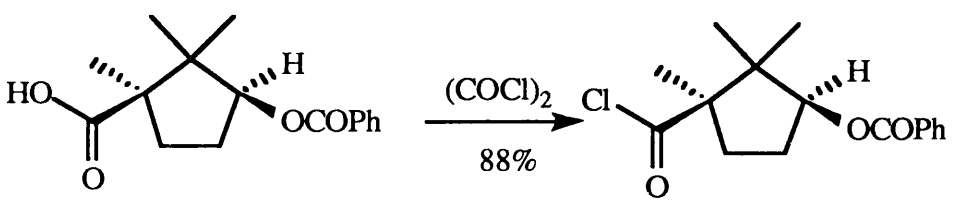

(117) (116)

Reagents; (a) $RuCl_3.xH_2O$ / $H_5IO_6$ / $CH_3CN$ / $CCl_4$ / $H_2O$

Scheme 94

It was essential to perform the reaction in an open necked flask to avoid pressurisation by the $CO_2$ generated. $RuCl_3.xH_2O$ also gave higher yields than $RuO_2$. The moderate yield of 46% could probably have been increased by alkaline extraction on work-up instead of flash silica gel column chromatography.

Treatment of acid (116) with an excess of neat $(COCl)_2$ according to the method of Adams and Ulich [125] furnished the crude acid chloride (118) in good yield (Scheme 95).

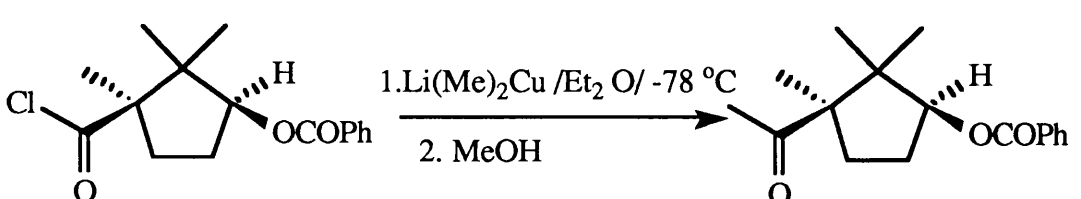



(116) (118)

Scheme 95

The crude acid chloride was used in the next step without further purification or analysis.

Methylation of (118) using organocopper chemistry [126,127] gave the methyl ketone (115) in good yield (Scheme 96).

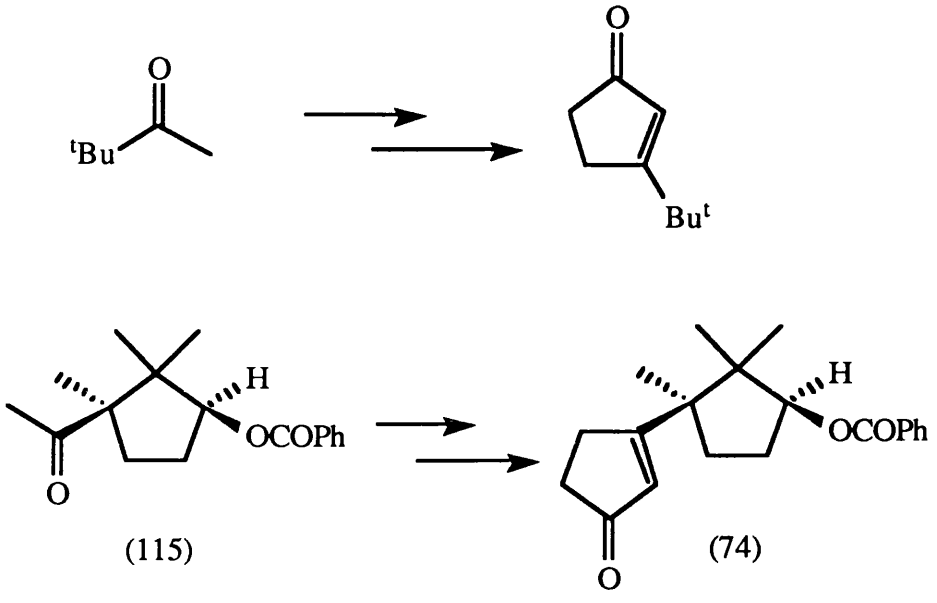



(118) (115)

Scheme 96

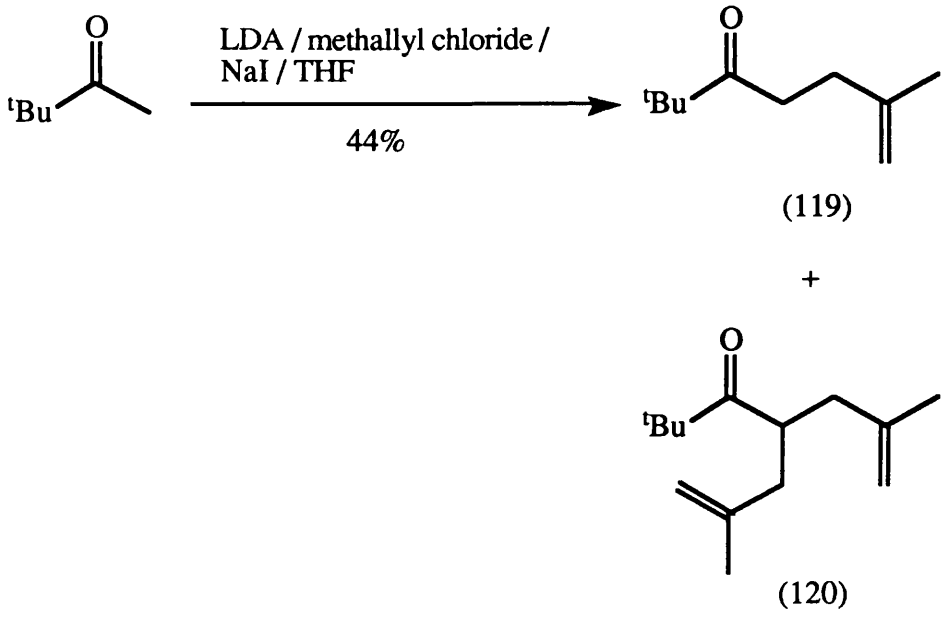
$CH_3Li$ was not used owing to its reactivity towards ester functionality.

Attempted methallylation of (115) with LDA / methallyl chloride / NaI failed. Since stocks of (115) were low, a model study was undertaken using pinacolone as a simple model for testing the possible elaboration of (115) to (74) (Scheme 97).




Scheme 97

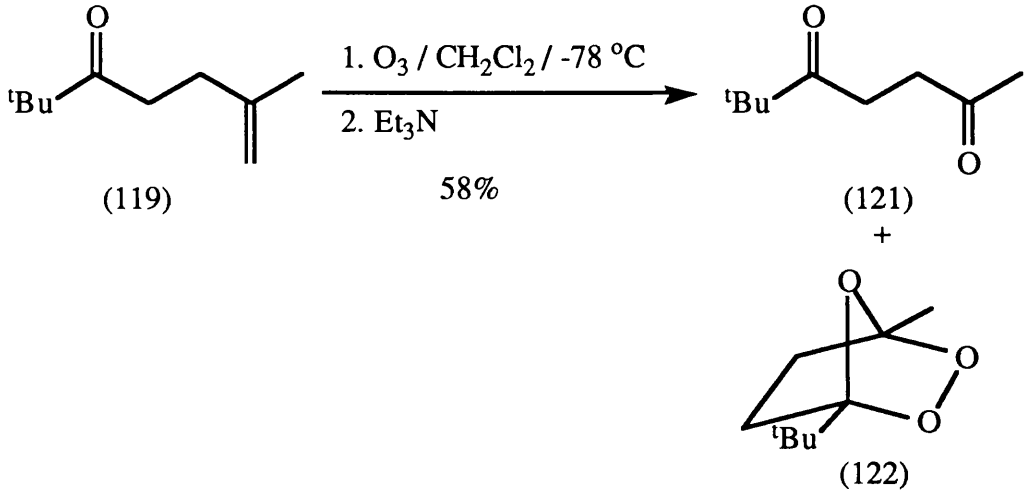
Methallylation [128] of pinacolone using LDA[129] / methallyl chloride / NaI proceeded to give a low yield of (119) and diallylated ketone (120) in a 2.4 : 1 ratio (Scheme 98).




Scheme 98

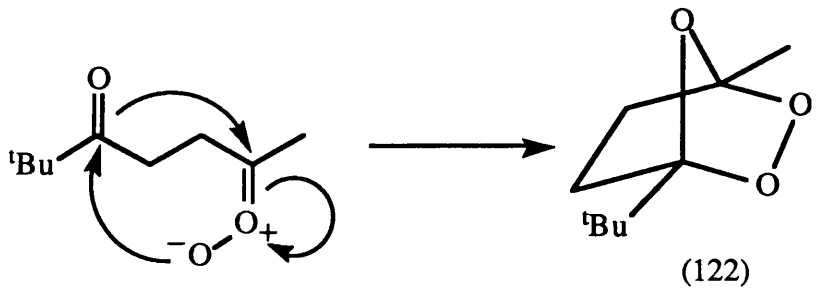
Careful flash silica gel column chromatography separated (119) from (120).

Ozonolysis [130] of (119) gave an unexpected 1:1 mixture of (121) and (122) in good yield (Scheme 99).




Scheme 99

Compound (121) arises *via* the expected ozonolysis pathway [131] whilst cyclobutene ozonide (122) forms *via* an intramolecular competing reaction (Scheme 100).

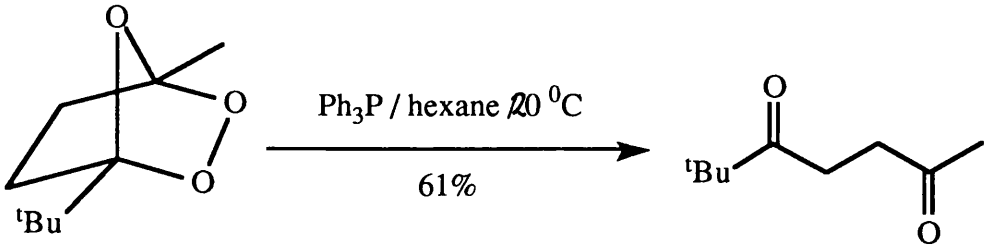



(122)

Scheme 100

Criegee and co-workers have observed similar competing pathways during ozonolyses of various substituted cyclopentenes.[132] In a separate study, Adam and co-workers [133] showed that bicycloozonides like (122) could be formed *via* addition of singlet-oxygen to furans followed by reductive trapping with diazene.

The structure of (122) was elucidated by reductive cleavage [133] to the diketone (121) using $Ph_3P$ (Scheme 101).

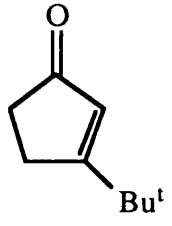



(122) (121)

Scheme 101

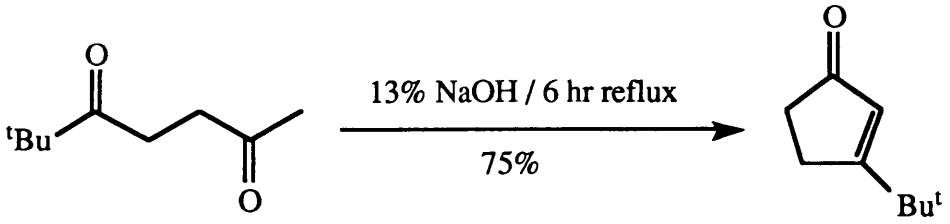
In addition, the two acetal carbons of (122) were very distinct at 110.7 and 117.1 ppm. Compound (121) was identical in all respects to that obtained from the ozonolysis reaction. In hindsight, had $Ph_3P$ been used as reductant instead of $Et_3N$, it is unlikely that (122) would have formed at all.

With diketone (121) in hand, it was envisaged that cyclisation techniques well displayed in jasminoid synthesis [79] would allow us to access cyclopentenone (123).




(123)

Repeated attempts to cyclise (121) with NaOH [134] all failed. It was found that cyclisation could be effected using an oxygen free solution of NaOH as base. Thus, the NaOH solution was thoroughly degassed and then purged with $N_2$ before addition of (121). With this method, yields of cyclopentenone (123) were excellent (Scheme 102).

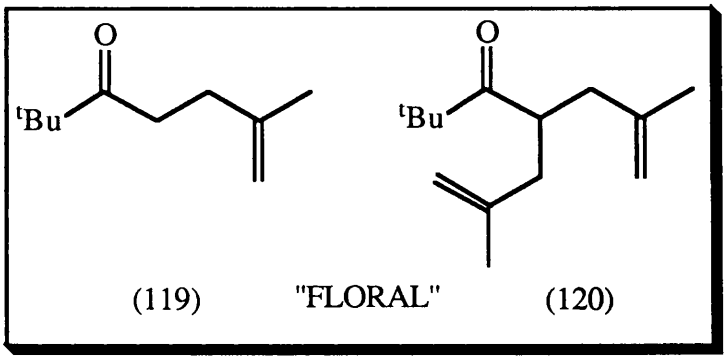



(121) (123)

Scheme 102

## 2.3 Odoriferous Compounds

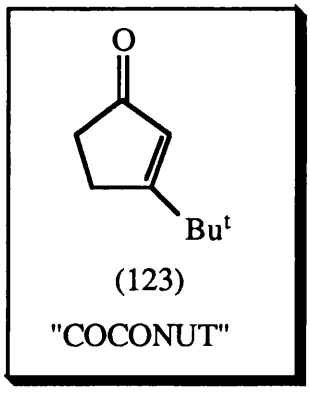
With additional funding from Quest International Ltd., a major flavour and fragrance manufacturer, it was hoped that some of the synthetic intermediates en route to grimaldone would have odoriferous properties. Unfortunately, very few compounds had any odoriferous properties worthy of mention. The anisole based compounds, (102) to (106) and (111) all have the characteristic smell of aniseed. Methallyl ketones (119) and (120) have a much more interesting "floral" note.




(119) "FLORAL" (120)

Probably the most interesting compound appears to be the

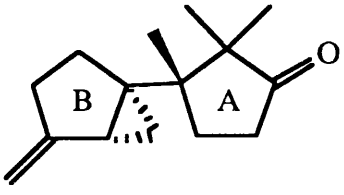
cyclopentenone (123) which has a very pleasant smell of coconut.




(123)

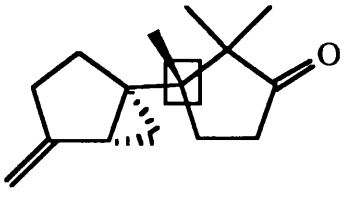
"COCONUT"

It is interesting to note that the compounds possessing ring A structural features of grimaldone have no odoriferous properties at all.




(73)

Perhaps the odoriferous properties arise from a special structural feature in ring B. Since all the compounds synthesised during this research having a *tert*-butyl group are odoriferous, then the tertiary centre marked below may have particular importance.

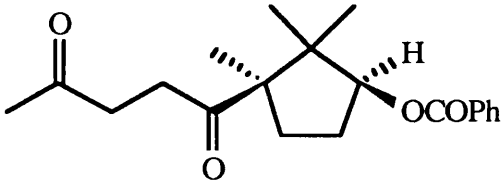



(73)

However, all this is pure speculation and QSAR studies would have to be undertaken to gain any further insight into the structural features required for exhibiting odoriferous properties.

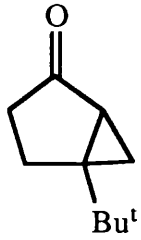
## 2.4 Future Work

Had more time been available, (115) would have been elaborated as far as possible. Although preliminary methallylation studies failed, model studies indicated that methallylation of (115) should take place. Ozonolysis should go without incident if $Ph_3P$ is used as reductant. Choice of protecting group in (113) may have to be considered prior to cyclisation.

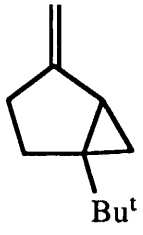



(113)

As an aside it would have been interesting to synthesise compounds (124) and (125).




(124)

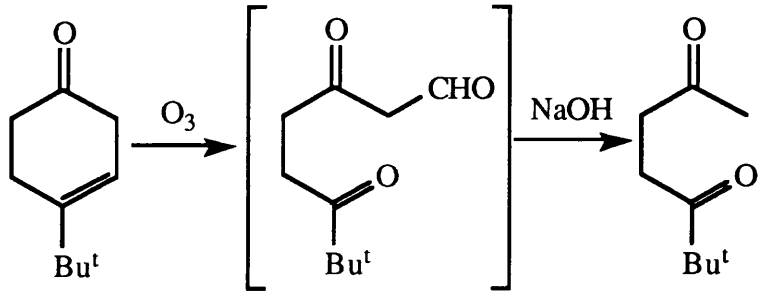



(125)

Hindered enone may not be susceptible to Corey-Chaykovsky

cyclopropanation. The cyclopropanation step will no doubt require some experimentation. Synthesis of (124) and (125) will also provide two ring B analogues of grimaldone for testing.

Finally, a synthetic approach to diketone (113) may be considered using enone (105) as a model (Scheme 103).




(105) (126) (121)

20% overall

Preliminary investigations have indicated formation of diketoaldehyde (126) along with other compounds. Base treatment resulted in a 20% overall isolable yield of (121).

# EXPERIMENTAL

General:

Melting points were determined on a Kofler hot stage melting point apparatus and are uncorrected. Bulb to bulb distillations were carried out on a Büchi GKR-50 Kugelrohr. $^{1}H$ NMR Spectra were recorded either on a Perkin Elmer R32 spectrometer operating at 90 MHz or a Bruker WP 200 SY spectrometer operating at 200 MHz or a Bruker AM 200 spectrometer operating at 200 MHz. $^{13}C$ NMR Spectra were recorded on the aforementioned Bruker instruments operating at 50 MHz. All spectra were recorded using deuteriochloroform as solvent. Chemical shifts ($\delta$) are in ppm with reference to $C\underline{H}Cl_3$ at 7.25 ppm and $\underline{C}DCl_3$ at 77.0 ppm.The following abbreviations are used: s- singlet, d- doublet, t- triplet, q- quartet, m- multiplet, dd- double-doublet. Infra red spectra were determined with either a Perkin Elmer 580 or 953 spectrometer. Low resolution mass spectra were determined using a VG updated MS 12 spectrometer while high resolution mass spectra were determined using a VG updated MS 902 spectrometer.

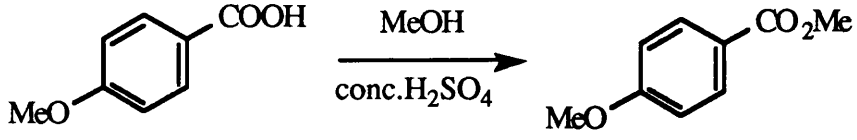
Flash column chromatography employed Sorbsil silica gel C 60-M. Preparative TLC was carried out on Merck silica gel $GF_{254}$ plates. Analytical TLC was carried out using Merck Kieselgel 60 $F_{254}$ glass backed plates. Plates were visualised by use of UV lamp or by spraying with ceric sulphate, followed by heating.

Unless otherwise stated, $NH_3$ was distilled from Na prior to use. The concentration of butyl lithium was determined by titration against diphenylacetic acid.

Solvents were distilled before use: $Et_2O$ and THF from sodium

benzophenone ketyl, $CH_2Cl_2$ from $P_2O_5$, acetone from anhydrous $K_2CO_3$ and MeOH from $Mg/I_2$. Pentane was dried and stored over Na wire. All organic solutions were dried over $MgSO_4$ and evaporated on a Büchi rotary evaporator under reduced pressure unless otherwise stated.

## Methyl 4-methoxybenzoate




(81) (82)

Procedure: [89]

To a 250 ml round bottomed flask equipped with reflux condenser and $CaCl_2$ guard tube were added *p*-anisic acid (22.8 g, 0.15 mol), absolute methanol (40.0 g, 50.6 ml, 1.25 mol) and conc. $H_2SO_4$ (1 ml, 0.02 mol). The mixture was refluxed for 5 h and then cooled to room temperature. The resulting solution was then added to ice-water/ether (250 ml, 1:1). The organic layer was separated and the aqueous layer extracted with ether (3 x 75 ml). The combined organic layers were washed with 10% aqueous $NaHCO_3$ solution (1 x 100 ml) and water (1 x 100 ml). After drying, the organic layer was concentrated in vacuo. Recrystallisation from petroleum ether (40-60 $^oC$) yielded the title compound (20.5 g, 82%) as white needles, m.p. 48-49 $^oC$ (lit.[89], 48 $^oC$).

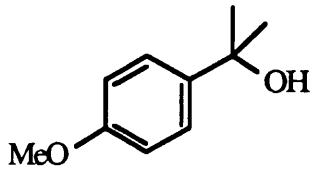
$\upsilon_{max}$ (KBr disc): 1720 and 850 $cm.^{-1}$

$\delta_H$ (200 MHz): 7.89 (2H, d, *J* 9, Ar H), 6.79 (2H, d, *J* 9, Ar H), 3.77 (3H, s, $ArOCH_3$), 3.71 (3H, s, $CO_2CH_3$)

$\delta_C$ (50 MHz): 166.4 (s, Ar CO), 163.0 (s, Ar<u>C</u>$OCH_3$), 131.2 (d, Ar CH), 122.2 (s, Ar<u>C</u>CO), 113.2 (d, Ar CH), 54.9 (q, $OCH_3$), 51.4 (q, $CO_2$<u>C</u>$H_3$).

Found: $M^+$, 166.0616, $C_9H_{10}O_3$ requires $M$, 166.0630.

2-(4'-Methoxyphenyl)-propan-2-ol




(83)

Procedure:[90]

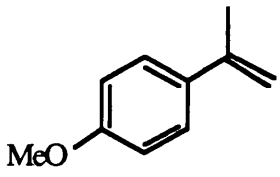
To a 500 ml 3-necked round bottomed flask equipped with reflux condenser and $N_2$ balloon were added ester (82) (16.0 g, 0.095 mol) and anhydrous ether (250 ml). Methylmagnesium bromide (72.0 ml of a 3.0 M solution in $Et_2O$, 0.216 mol) was added dropwise via syringe. The mixture was transferred to a pre-equilibrated oil bath at 60 $^oC$ and refluxed gently for 2 h. The reaction mixture was then cooled to room temperature and treated with ice-cold, saturated aqueous $NH_4Cl$ solution (200 ml) to dissolve the precipitate. The ether layer was separated and the aqueous layer extracted with ether (3 x 75 ml). The combined organic layers were washed with aqueous sodium thiosulphate solution (1 x 150 ml) and water (1 x 150 ml). The organic solution was dried,filtered and concentrated in vacuo to yield the title compound (15.0 g, 95%) as a pale yellow oil.

$\upsilon_{max}$ (thin film): 3420 $cm.^{-1}$

$\delta_H$ (200 MHz): 7.42 (2H, d, *J* 9,Ar H), 6.87 (2H, d, *J* 9,Ar H), 3.81(3H, s, $ArOCH_3$), 1.89 (1H, s, OH), 1.57 (6H, s, $2xCH_3$)

Found:$M^+$, 166.1012; $C_{10}H_{14}O_2$ requires *M*, 166.0994.

2-(4'-Methoxyphenyl)-prop-1-ene




(80)

Procedure: [90]

Slow distillation of the tertiary alcohol (83) (8.0 g, 0.048 mol) with pTSA (5 mg, 0.026 mmol) using the Kugelrohr apparatus afforded the title compound (3.6 g, 50%) as a white solid, m.p. 34-35 °C (lit.[90], 34 °C); b.p. 61-63 °C/0.4 mm Hg (lit.[90], 63-65 °C/0.5 mm Hg).

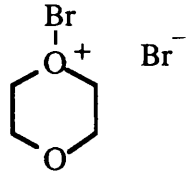
$\upsilon_{max}$ (KBr disc): 1610 and 885 $cm.^{-1}$

$\delta_H$ (200 MHz): 7.43 (2H, d, *J* 9, Ar H), 6.88 (2H, d, *J* 9, Ar H), 5.3 (1H, m, C=C<u>H</u>H), 5.01 (1H, m, C=H<u>H</u>), 3.81 (3H, s, $ArOCH_3$), 2.15 (3H, m, $CH_3$).

$\delta_C$ (50 MHz): 160.0 (s, Ar<u>C</u>$OCH_3$), 142.5 (s, Ar<u>C</u>=C), 133.7 (s, Ar<u>C</u>$C(CH_3)=CH_2$), 128.5 (d, ArCH), 113.5 (d, ArCH), 110.6 (t, ArC=<u>C</u>$H_2$), 55.2 (q, $ArOCH_3$), 21.9 (q, $CH_3$).

Found: $M^+$, 148.0887; $C_{10}H_{12}O$ requires *M*, 148.0888.

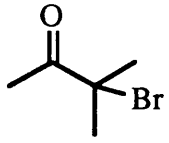
Dioxan dibromide



Procedure: [92]

To a 250 ml round bottomed flask was added dioxan (21.2 g, 0.24 mol). Bromine (40.0 g, 12.9 ml, 0.25 mol) was added with vigorous stirring and the warm solution poured into light petroleum (100 ml, b.p. 40-60 $^{o}$C), precooled to -20 $^{o}$C. The orange precipitate was filtered and well dried under vacuum. The product (42.0 g, 62%), m.p. 60-62 $^{o}$C (lit.[92], 60-61 $^{o}$C) was used without further purification.

3-Bromo-3-methylbutan-2-one




(85)

Procedure:[91]

To a 250 ml conical flask were added methyl isopropyl ketone (84) (16.9 g, 0.196 mol), dioxan (8 ml) and absolute ether (80 ml). Dioxan dibromide (48.7 g, 0.196 mol) was added portionwise over 3 h and the reaction mixture stirred at room temperature for a further 16 h. The ether/ketone layer was washed well with water (4 x 75 ml). After drying, the organic layer was concentrated in vacuo to leave a red oil which was purified by distillation to yield the title compound (26.5 g, 81%) as a colourless oil, b.p. 49-50 $^{o}$C/20mm Hg (lit.[91], 54-55 $^{o}$C/50mm Hg).

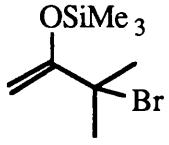
$\upsilon_{max}$ (thin film): 1720 cm.$^{-1}$

$\delta_H$ (200 MHz): 2.39 (3H, s, -COCH$_3$ ), 1.61 (6H, s, CBr(CH$_3$)$_2$).

$\delta_C$ (50 MHz): 203.3 (s, -CO), 63.6 (s, -CBr(CH$_3$)$_2$), 29.4 (q, CBr(CH$_3$)$_2$), 24.0 (q, -COCH$_3$).

Found: $M^+$, 165.9811 ($^{81}$Br); $C_5H_9BrO$ requires $M$ 165.9817.

3-Bromo-3-methyl-2-trimethylsilyloxybut-1-ene




(24)

Procedure:[27]

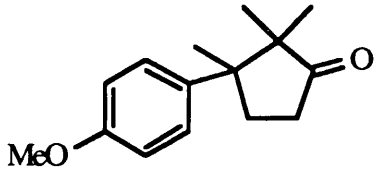
To a 500 ml 3-necked round bottomed flask under $N_2$ were added diisopropylamine (10.15 g, 14.06 ml, 0.10 mol) and THF (100 ml). Butyllithium (34.84 ml of a 2.87 M solution in hexane, 0.10 mol) was added dropwise at 0 °C. The solution was cooled to -78 °C and α–bromoketone(85) (15.0 g, 0.091 mol) in THF (20 ml) was added dropwise. The solution was stirred for a further 30 min at -78 °C and then chlorotrimethylsilane (13.3 ml, 0.101 mol) in THF (20 ml) was added to the mixture. The cooling bath was removed and the mixture stirred at room temperature overnight. The mixture was filtered through a medium length column of oven-dried Celite and the solvent evaporated. Pentane (100 ml) was added and the solution filtered through Celite again. The organic solution was concentrated in vacuo to leave a red oil, which was purified by vacuum distillation to yield the title compound (17.0 g, 79%) as a colourless oil, b.p. 63-64 °C/10mm Hg (lit.[27], 63 °C/10mm Hg).

$\upsilon_{max}$ (thin film): 1620 and 925cm$^{-1}$.

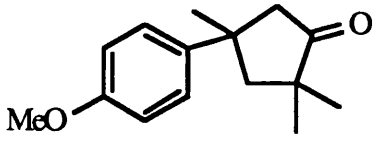
$\delta_H$ (90 MHz): 4.6 (1H,d,*J* 2, RR'C=HH), 4.1 (1H, d, *J* 2, RR'C=CHH), 1.95 (6H, s, -CBr($CH_3$)$_2$), 0.4 (9H, s, -$SiMe_3$).

Found: *M*+ 238.0210 ($^{81}$Br); $C_8H_{17}BrOSi$ requires *M* 238.0194.

3-(4'-Methoxyphenyl)-2,2,3-trimethylcyclopentanone (79)




(79)




(88)

Procedure:[27]

In a 500 ml 3-necked round bottomed flask was placed $ZnCl_2$ (0.459 g, 3.36 mmol). The flask was gently flame-dried under high vacuum and the vacuum then released with $N_2$. Dry $CH_2Cl_2$ (300 ml) was then added followed by alkene (80) (2.5 g, 16.8 mmol) in $CH_2Cl_2$ (10 ml). The mixture was cooled to -78 $^oC$ and silyl enol ether (24) (8.0 g, 33.7 mmol) in $CH_2Cl_2$ (10 ml) added dropwise over 10 min. The mixture was warmed to room temperature over 1 h and stirred at room temperature for a further 2.5 h. Saturated aqueous $NH_4Cl$ solution (150 ml) was added to the mixture followed by $Et_2O$ (300 ml). The organic layer was separated and washed with brine (200 ml) and $H_2O$ (100 ml). After drying, the organic layer was concentrated in vacuo to give a red oil which was purified by flash silica gel column chromatography using 7.5% EtOAc in hexane as eluent to yield the regio-isomeric cyclopentanone (88) (0.30 g, 8%) as a pale yellow oil.

$\upsilon_{max}$ ($CHCl_3$): 1740cm.$^{-1}$

$\delta_H$ (200 MHz): 7.21 (2H, d, *J* 8.9, Ar-H), 6.84 (2H, d, *J* 8.9, Ar-H), 3.79 (3H, s, $-OCH_3$), 2.91 (1H, d, *J*

16.9, -C$\underline{H}_2$CO), 2.50 (1H, d,*J* 16.9, -C$\underline{H}_2$CO), 2.29 (1H, d, *J* 13.3, -C$\underline{H}_2$C(CH$_3$)$_2$), 2.14 (1H, d, *J* 13.3, -C$\underline{H}_2$C(CH$_3$)$_2$). 1.36 (3H, s, -CH$_3$), 1.18 (3H, s, -CH$_3$), 0.92 (3H, s, -CH$_3$).

$\delta_C$ (50 MHz): 222.8 (s,-CO), 158.0 (s,Ar$\underline{C}$-OCH$_3$), 141.4 (s, Ar$\underline{C}$-C(CH$_3$)CH$_2$-), 126.4 (d,ArC-H), 113.5 (d, ArC-H), 55.2 (q, Ar-OCH$_3$), 52.3 (t,-C$\underline{H}_2$-), 51.0 (t,-C$\underline{H}_2$-), 44.9 (s, -$\underline{C}$(CH$_3$)$_2$CO), 40.3 (s, -$\underline{C}$(CH$_3$)Ar), 31.8 (q,-CH$_3$), 27.7 (q, -CH$_3$), 26.9 (q,-CH$_3$).

Found:$M^+$ ,232.1460; $C_{15}H_{20}O_2$ requires *M* 232.1463.

Further elution gave the <u>title compound</u> (1.50g, 38%) which was recrystallised from methanol as white needles, m.p. 47-48 °C.

$\upsilon_{max}$ ($CCl_4$): 1740cm.$^{-1}$

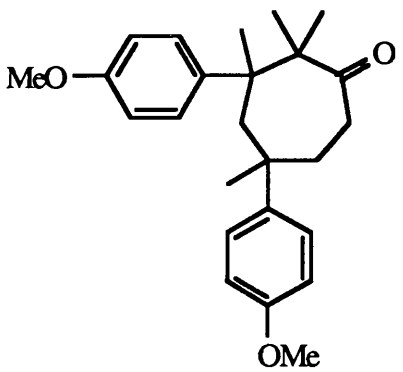
$\delta_H$ (200 MHz): 7.28 (2H, d, *J* 9, Ar-H), 6.89 (2H, d, *J* 9, Ar-H), 3.80 (3H, s, -OCH$_3$), 1.80-2.95 (4H, m, -CH$_2$CH$_2$-), 1.23 (3H, s, -CH$_3$),1.14 (3H, s, -CH$_3$), 0.60 (3H, s, -CH$_3$).

$\delta_C$ (50 MHz): 222.6 (s,-CO), 157.8 (s,Ar$\underline{C}$-OCH$_3$),

136.9 (s,Ar<u>C</u>-C($CH_3$)$_2$$CH_2$-), 127.5 (d,ArC-H), 113.4 (d, ArC-H), 55.1 (q,Ar-O$CH_3$), 53.2(s, -<u>C</u>($CH_3$)$_2$), 47.9 (s, -<u>C</u>($CH_3$)Ar), 33.5 (t, -<u>C</u>$H_2$-), 29.7 (t, -<u>C</u>$H_2$-), 25.3 (q, -$CH_3$), 22.1 (q, -$CH_3$), 18.3 (q,-$CH_3$).

Found: $M^+$, 232.1460; $C_{15}H_{20}O_2$ requires $M$, 232.1463.

3,5-(4'-Methoxyphenyl)-2,2,3,5-tetramethylcycloheptanone




(89)

Procedure: [27]

In a 100 ml 3-necked round bottomed flask was placed $ZnCl_2$ (0.194 g, 1.4 mmol). The flask was gently flame-dried under high vacuum and the vacuum then released with $N_2$. Dry $CH_2Cl_2$ (40 ml) was then added followed by the alkene (80) (1.06 g, 7.16 mmol) in $CH_2Cl_2$ (5 ml). The mixture was cooled to -78 $^oC$ and the silyl enol ether (24) (3.40 g, 14.2 mmol) in $CH_2Cl_2$ (5 ml) added dropwise over 10 min. The mixture was warmed to room temperature over 1 h and stirred at room temperature for a further 3 h. Saturated aqueous $NH_4Cl$ solution (50 ml) was added to the mixture followed by $Et_2O$ (100 ml). The organic layer was separated, washed with brine (50 ml) and then $H_2O$ (50 ml). After drying, the organic layer was concentrated in vacuo to yield a red oil, which was purified by flash silica gel column chromatography using 7.5% EtOAc in hexane as eluent to give cyclopentanone (88) (0.10 g, 6%) as a pale yellow oil. Further elution furnished a mixture of cyclopentanone (79) and cycloheptanone (89) (0.70 g,42% combined yield) as a colourless oil. Trituration with light petrol induced slow crystallisation of the title compound (0.12 g,4.5%) as fine white needles, m.p.72-73$^oC$.

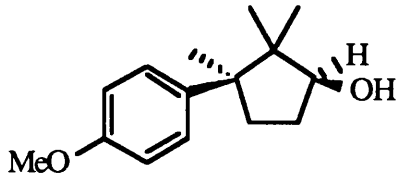
$\upsilon_{max}$ ($CHCl_3$): 1730 $cm.^{-1}$

$\delta_H$ (200 MHz): 7.22 (2H, d, *J* 8.5, Ar-H), 7.16 (2H, d, *J* 8.9, Ar-H), 6.85 (2H, d, *J* 9.0, Ar-H), 6.78 (2H, d, *J* 8.9, Ar-H), 3.81 (3H, s, $-OCH_3$), 3.78 (3H, s, $-OCH_3$), 1.60-2.27 (6H, m, $-CH_2-$), 1.17 (3H, s, $-CH_3$), 1.13 (3H, s, $-CH_3$), 0.75 (3H, s, $-CH_3$), 0.39 (3H, s, $-CH_3$).

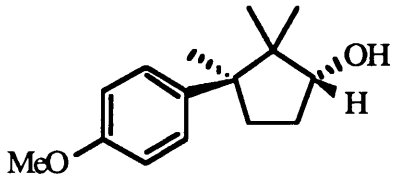
$\delta_C$ (50 MHz): 222.9 (s, -CO), 157.7 (s, Ar<u>C</u>$-OCH_3$), 157.3 (s, Ar<u>C</u>$-OCH_3$), 141.4 (s, Ar<u>C</u>$-C(CH_3)$), 136.3 (s, Ar<u>C</u>$-C(CH_3)$), 128.0 (d, ArC-H), 126.7 (d,ArC-H), 113.2 (2xd, 2x ArC-H), 56.1 (s, $-\underline{C}(CH_3)_2$), 55.1 (2xq, 2x$-OCH_3$), 51.1 (s, Ar-<u>C</u>$(CH_3)$), 47.8 (t, $-CH_2-$), 37.5 (s, Ar-<u>C</u>$(CH_3)$), 36.1 (q,$-CH_3$), 33.5 (t, $CH_2-$), 26.6 (q,$-CH_3$), 23.2 (t,$-CH_2-$), 21.5 (q,$-CH_3$), 17.5 (q,$-CH_3$).

Found: $M^+$, 380.2345; $C_{25}H_{32}O_3$ requires *M* 380.2351.

(±)-*syn*-3-(4'-Methoxyphenyl)-2,2,3-trimethylcyclopentanol (91)




(91)




(92)

Procedure:[107]

To a 10 ml round bottomed flask at 0 °C was added cyclopentanone (79) (0.13 g, 0.56 mmol) in 80% aqueous MeOH (5 ml). The solution was stirred for 10 min and $NaBH_4$ (0.10 g, 2.64 mmol) added portionwise over 5 min. After stirring for 2.5 h at 0 °C, the reaction mixture was decomposed by the addition of NaOH solution (10% w/v, 5 ml). The mixture was diluted with brine (10 ml) and extracted with $Et_2O$ (3 x 20 ml). The combined organic layers were washed with brine (1 x 20 ml) and $H_2O$ (1 x 20 ml). After drying, the organic layer was concentrated *in vacuo* to give a colourless oil which was purified by preparative TLC using 10% EtOAc in hexane as eluent (3 runs) to give the title compound (40 mg, 40%) as a colourless oil.

$\upsilon_{max}$ ($CCl_4$): 3630cm.$^{-1}$

$\delta_H$ (200 MHz): 7.18 (2H, d, *J* 9,Ar-H), 6.83 (2H, d, *J* 9, Ar-H), 3.81 (1H, m, -C(H)OH), 3.78 (3H, s, -$OCH_3$), 1.65-2.40 (4H, m, -$CH_2CH_2$-), 1.34 (3H, d, *J* 1,-$CH_3$), 0.99 (3H, s, -$CH_3$), 0.53 (3H, s, -$CH_3$).

$\delta_C$ (50 MHz): 157.3 (s, ArC-$OCH_3$), 139.7 (s, ArC-

$C(CH_3)$), 128.1 (d, ArC-H), 112.7 (d, ArC-H), 80.5 (d, -C(H)OH), 55.1 (q, $-OCH_3$), 49.2 (s, $-\underline{C}(CH_3)_2$), 46.9 (s, Ar-$\underline{C}(CH_3)$), 34.9 (t, $-CH_2-$), 31.0 (t,$-CH_2-$), 24.7 (q, $-CH_3$), 23.9 (q, $-CH_3$), 17.8 (q, $-CH_3$).

Found $M^+$ , 234.1624; $C_{15}H_{22}O_2$ requires $M$ 234.1620.

Lower band from the prep. TLC plate gave cyclopentanol (92) (36 mg, 36%) as a colourless oil.

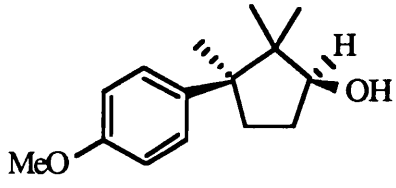
$\upsilon_{max}$ ($CCl_4$): 3630cm.$^{-1}$

$\delta_H$ (200 MHz): 7.28 (2H, d, $J$ 9, Ar-H), 6.84 (2H, d, $J$ 9, Ar-H), 4.15 (1H, m, -C($\underline{H}$)OH), 3.79 (3H, s, $-OCH_3$), 1.40-2.40 (4H, m, $-CH_2CH_2-$), 1.24 (3H, s, $-CH_3$), 1.06 (3H, s, $-CH_3$), 0.52 (3H, s, $-CH_3$).

$\delta_C$ (50 MHz): 157.5 (s, ArC-$OCH_3$), 139.0 (s, Ar$\underline{C}$-$C(CH_3)$), 127.7 (d, ArC-H), 113.0 (d, ArC-H), 80.8 (d, -CH(OH)), 55.2 (q, $-OCH_3$), 49.3 (s, $-\underline{C}(CH_3)_2$), 47.0 (s, Ar-$\underline{C}(CH_3)$), 32.9 (t, $-CH_2-$), 29.7 (t, $-CH_2-$), 25.4 (q, $-CH_3$), 21.4 (q, $-CH_3$), 18.3 (q, $-CH_3$).

Found: $M^+$, 234.1623; $C_{15}H_{22}O_2$ requires $M$, 234.1620.

(±)-*syn*-3-(4'-Methoxyphenyl)-2,2,3-trimethylcyclopentanol

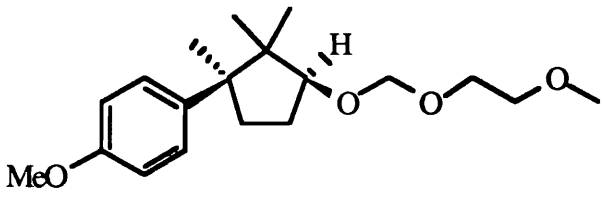



(91)

Procedure: [109]

To a 250 ml round bottomed flask with side-arm under $N_2$ were added cyclopentanone (79) (1.45 g, 6.25 mmol) and dry THF (50 ml). The solution was cooled to -78 $^oC$ and L-Selectride (12.5 ml of a 1.0 M solution in THF, 12.5 mmol) was added dropwise. After warming to rooom temperature over 1 h and stirring for a further 1 h, 1M NaOH solution (12.5 ml, 12.5 mmol), 30% $H_2O_2$ solution (3.75 ml, 37.5 mmol) and EtOH (20 ml) were added. The mixture was refluxed for 2 h and then cooled to room temperature. The resulting solution was diluted with EtOAc (150 ml) and washed with $Na_2SO_3$ solution (1 x 50 ml) and brine (1 x 50 ml). The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 50 ml). The combined organic layers were washed with $H_2O$ (1 x 100 ml) and after drying, concentrated in vacuo to leave a pale brown oil which was purified by flash silica gel column chromatography using 15% EtOAc in hexane as eluent to give the title compound (1.10 g, 75%) as a colourless oil. Further elution gave the epimeric alcohol (92) (0.14 g, 10%) as a colourless oil. (Both compounds identical in all respects to those obtained from the previous experiment.)

(±)-*syn*-3-(4'-Methoxyphenyl)-2,2,3-trimethylcyclopentyl 2-methoxy ethoxy methyl Ether




(93)

Procedure:[110]

To a 100 ml round bottomed flask with side arm under $N_2$ were added activated 4A molecular sieves (5 g), $CH_2Cl_2$ (30 ml), alcohol (91) (0.53 g, 2.14 mmol) and diisopropylethylamine (0.87 g, 1.18 ml, 6.8 mmol). MEM chloride (0.84 g, 771 µl, 6.8 mmol) was added dropwise at 0 $^oC$, the cooling bath removed and the reaction mixture stirred at room temperature for 24 h. The solution was diluted with $Et_2O$ (150 ml) and washed sequentially with 1N HCl (1 x 50 ml), $H_2O$ (1 x 50 ml), saturated aqueous $NaHCO_3$ solution (1 x 50 ml) and $H_2O$ (1 x 50 ml). After drying, the organic layer was concentrated in vacuo to leave a yellow oil which was purified by flash silica gel column chromatography using 20% EtOAc in hexane as eluent to give the title compound (0.48 g, 66%) as a colourless oil.

$\upsilon_{max}$ ($CHCl_3$): 1050 and 830 $cm.^{-1}$

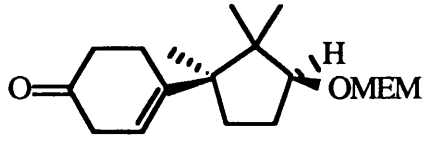
$\delta_H$ (200 MHz): 7.20 (2H, d, *J* 8.8, Ar-H), 6.80 (2H, d, *J* 8.8, Ar-H), 4.71 (1H, d, *J* 6.8, -$OCH_2O$-),.4.64 (1H, d, *J*

6.8, -$OCH_2O$-),.3.78 (3H, s, Ar-$OCH_3$), 3.48-3.73 (5H, m, -$OCH_2CH_2O$- and -C(H)OMEM), 3.36 (3H, s, -$OCH_3$), 1.65-2.35 (4H, m, -$CH_2CH_2$-), 1.31 (3H, s, -$CH_3$), 0.98 (3H, s, -$CH_3$), 0.54 (3H, s, -$CH_3$).

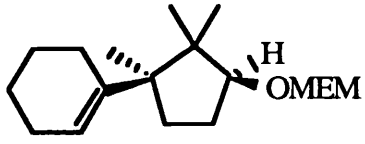
$\delta_C$ (50 MHz): 157.3 (s, Ar<u>C</u>-$OCH_3$), 139.7 (s, Ar<u>C</u>-$C(CH_3)$), 128.2 (d, ArC-H), 112.7 (d, ArC-H), 95.2 (t,-$OCH_2O$-), 85.5 (d, -CH(OMEM)), 71.7 (t, -O<u>C</u>$H_2CH_2O$-), 66.5 (t, -$OCH_2$<u>C</u>$H_2O$-), 58.9 (q, -$OCH_3$), 55.1 (q, Ar-$OCH_3$), 48.9 (s, -<u>C</u>$(CH_3)_2$), 46.9 (s, ArC-<u>C</u>$(CH_3)$), 35.1 (t, -$CH_2$-), 29.0 (t, -$CH_2$-), 24.5 (q, -$CH_3$), 24.1(q, -$CH_3$), 18.5 (q, -$CH_3$).

Found: $M^+$, 322.2142; $C_{19}H_{30}O_4$ requires $M$ 322.2144.

(±)-*syn*-4-[3-(2-methoxyethoxymethoxy)-1,2,2-trimethylcyclopentyl] cyclohex-3-en-1-one (95)




(95)




(96)

Procedure:[111]

To a 50 ml 3-necked conical flask equipped with dry-ice/acetone condenser were added liquid $NH_3$ (14 ml) and dry $Et_2O$ (4 ml). MEM ether (93) (0.272 g, 0.84 mmol) in dry $Et_2O$ (1 ml) was added and the reaction mixture stirred for 15 min. Lithium (58 mg, 8.4 mmol) was added and a deep blue colour appeared. The solution was stirred for a further 30 min and then EtOH (0.387 g, 0.494 ml, 8.3 mmol) was added dropwise (CAUTION!). $NH_3$ was allowed to evaporate overnight and the reaction slurry then quenched with 1N HCl (10 ml) and extracted with EtOAc (3 x 30 ml). The combined organic layers were washed with $H_2O$ (1 x 20 ml) and, after drying, concentrated in vacuo to leave a yellow oil which was dissolved in $CHCl_3$ (10 ml). 5M HCl (1 drop) was added and the solution stirred for 24 h. The reaction mixture was diluted with $CHCl_3$ (30 ml) and washed with saturated aqueous $NaHCO_3$ solution (10 ml) and $H_2O$ (10 ml). After drying, the organic layer was concentrated in vacuo to leave a yellow oil which was purified by flash silica gel column chromatography using 0-100% EtOAc in hexane as eluent to give the cyclohexene (96) (20 mg, 8%) as a colourless oil.

$\upsilon_{max}$ ($CCl_4$): 1050 $cm.^{-1}$

$\delta_H$ (200 MHz): 5.40 (1H, t, *J* 3.7, C=CH), 4.73 (1H, d, *J* 6.8, -$OCH_2O$-), 4.64 (1H, d, *J* 6.8, -$OCH_2O$), 3.49-3.76 (5H, m, -$OCH_2CH_2O$- and -CH(OR)), 3.37 (3H, s, -$OCH_3$), 1.4-2.1 (12H, m, ring -$CH_2$s), 1.01 (3H, s, -$CH_3$), 0.89 (3H, s, -$CH_3$), 0.76 (3H, s, -$CH_3$)

$\delta_C$ (50 MHz): 143.5 (s, C=CH), 121.0 (d, C=CH), 95.2 (t, -$OCH_2O$-), 86.4 (d,-CH(OR)), 71.8 and 66.6 (both t, -$OCH_2CH_2O$-), 59.0 (q, -$OCH_3$), 50.4 (s, -$C(CH_3)_2$), 46.7 (s, C=C-$C(CH_3)$), 34.9 (t, -$CH_2$-), 27.5 (t, -$CH_2$-), 25.7 (t, -$CH_2$-), 24.5 (q, -$CH_3$), 23.4 (t, -$CH_2$-), 22.4 (t, -$CH_2$-), 22.3 (q,-$CH_3$), 19.2 (q, -$CH_3$).

Found: $M^+$, 296.2347; $C_{18}H_{32}O_3$ requires $M$, 296.2351.

Further elution gave MEM ether (93) (0.124 g, 46%) as a colourless oil. Further elution gave the cyclohex-3-enone (95) (95 mg, 37%) as a colourless oil. (67% based on recovered starting material).

$\upsilon_{max}$ ($CCl_4$): 1725 and 1050 $cm.^{-1}$

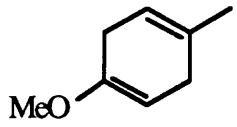
$\delta_H$ (200 MHz): 5.45 (1H, t, *J* 3.9, C=CH), 4.66 (1H, d, *J*

6.9, -$OCH_2O$-), 4.61 (1H, d, *J* 6.9, -$OCH_2O$-), 3.46-3.71 (5H, m, -$OCH_2CH_2O$- and -CH(OR)), 3.32 (3H, s, -$OCH_3$), 2.83 (2H, m, -$C\underline{H}_2CH$=C), 2.35 (4H, m, -$CH_2CH_2CO$), 1.4-2.2 (4H, m, -$CH_2CH_2$-), 1.04 (3H, s, -$CH_3$), 0.89 (3H, s, -$CH_3$), 0.75 (3H, s, -$CH_3$).

$\delta_C$ (50 MHz): 211.6 (s, -CO), 145.4 (s, $\underline{C}$=CH), 117.8, (d, C=$\underline{C}$H), 94.9 (t, -$OCH_2O$-), 86.0 (d, -$\underline{C}$H(OR)), 71.6 and 66.5 (both t, -$OCH_2CH_2O$-), 58.8 (q, $OCH_3$), 50.5 (s, -$\underline{C}(CH_3)_2$), 46.6 (s, -C=C-$\underline{C}(CH_3)$, 39.9 (t, -$CH_2$-), 38.6 (t, -$CH_2$-), 34.6 (t, -$CH_2$-), 28.6 (t, -$CH_2$-), 26.6 (t, -$CH_2$-), 24.5 (q, -$CH_3$), 21.9 (q, -$CH_3$), 19.1 (q,-$CH_3$).

Found: $M^+$, 310.2133; $C_{18}H_{27}O_4$ requires $M$, 310.2144.

1-Methoxy-4-methyl-1,4-cyclohexadiene



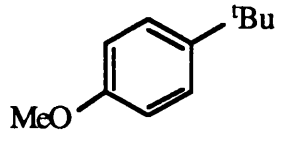

(100)

Procedure: [111]

To a 100 ml 3-necked round bottomed flask equipped with dry-ice/acetone condenser were added liquid $NH_3$ (32 ml) and dry $Et_2O$ (10 ml). 4-Methylanisole (2.38 g, 19.5 mol) in dry $Et_2O$ (2 ml) was added and the reaction mixture stirred for 15 min. Lithium (0.79 g, 114 mmol) was added and a deep blue colour appeared. The solution was stirred for a further 40 min and then EtOH (5.58 g, 7.1 ml, 119 mmol) was added dropwise. Stirring was continued until the blue colour had disappeared and $NH_3$ was then allowed to evaporate overnight. Ice/water (20 ml) was added to the slurry which was extracted with $Et_2O$ (3 x 50 ml). The combined organic layers were washed with $H_2O$ (1 x 50 ml). After drying, the organic solution was concentrated in vacuo to leave a pale yellow oil which was purified by vacuum distillation to yield the title compound (1.8 g, 74%) as a colourless oil, b.p. 78-80 $^oC$/20 mm Hg (lit.[113], 167-170 $^oC$/760 mm Hg).

$\delta_H$ (90 MHz): 5.37 (1H, m, MeC=C<u>H</u>), 4.62 (1H, m, MeOC=C<u>H</u>), 3.55 (3H, s, -$OCH_3$), 2.72 (4H, m, -$CH_2$-), 1.71 (3H, m, -$CH_3$).

## 4-*tert*-Butylanisole




(103)

Procedure: 116, 117

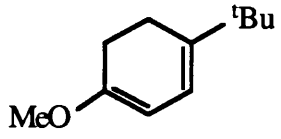
To a 500 ml 3-necked round bottomed flask equipped with mechanical stirrer were added 4-*tert*-butylphenol (20.0 g, 0.133 mol), $Me_2SO_4$ (18.45 g, 13.83 ml, 0.145 mol), anhydrous $K_2CO_3$ (47.25 g, 0.33 mol) and dry acetone (250 ml). The mixture was refluxed for 8 h and, after cooling, the solution was filtered and the residue washed with acetone (150 ml). The filtrate was evaporated to leave an oil which was dissolved in $Et_2O$ (100 ml). This was washed with $NH_3$ solution (10%, 4 x 50 ml), NaOH solution (10%, 4 x 50 ml) and $H_2O$ (3 x 50 ml). The organic solution was dried and concentrated in vacuo to leave a yellow oil which was purified by vacuum distillation to yield the title compound (19.0 g, 80%) as a colourless oil , b.p. 105 $^oC$/20 mm Hg (lit.[117], 223.2 $^oC$/760 mm Hg).

$\upsilon_{max}$ ($CCl_4$): 1040 and 825 $cm.^{-1}$

$\delta_H$ (90 MHz): 7.30 (2H, d, *J* 9, Ar-H), 6.85 (2H, d, *J* 9, Ar-H), 3.80 (3H, s, $-OCH_3$), 1.35 (9H, s, $-C(CH_3)_3$).

Found: $M^+$, 164.1194; $C_{11}H_{16}O$ requires *M*, 164.1201.

1-Methoxy-4-*tert*-butyl-1,3-cyclohexadiene.



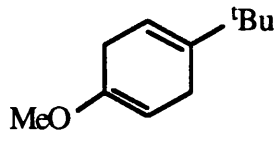

(104)

Procedure: [118]

To a 1 l 3-necked round bottomed flask equipped with dry-ice/acetone condenser were added liquid $NH_3$ (300 ml) and dry $Et_2O$ (120 ml). Methyl ether (103) (10.0 g, 0.06 mol) in $Et_2O$ (10 ml) was added and the reaction mixture stirred for 15 min. Small pieces of lithium (3.37 g, 0.48 mol) were added. The solution was stirred for a further 40 min and then EtOH (22.1 g, 28.8 ml, 0.48 mol) was added dropwise. Stirring was continued until the blue colour had disappeared and $NH_3$ was then allowed to evaporate overnight. $H_2O$ (150 ml) was added to the slurry which was extracted with $Et_2O$ (2 x 200 ml). The combined organic solutions were washed with $H_2O$ (1 x 100 ml) and, after drying, concentrated in vacuo to leave a yellow oil which was purified by vacuum distillation to yield the title compound (8.0 g, 79%) as a colourless oil, b.p. 99-100 $^oC$/20 mm Hg (lit.[118], 86-87 $^oC$/8 mm Hg).

$\delta_H$ (90 MHz): 5.65 (1H, d, *J* 6.5, $^tBuC=CH$), 4.90 (1H, d, *J* 6.5, MeOC=CH), 3.55 (3H, s, $-OCH_3$), 2.25 (4H, s, $-CH_2CH_2-$), 1.05 (9H, s, $-C(CH_3)_3$).

1-Methoxy-4-*tert*-butyl-1,4-cyclohexadiene




(106)

Procedure:[118]

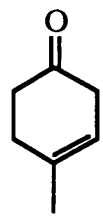
To a 1 l 3-necked round bottomed flask equipped with dry-ice/acetone condenser were added cylinder grade liquid $NH_3$ (300 ml) and dry $Et_2O$ (120 ml). Methyl ether (103) (10.0 g, 0.06 mol) in $Et_2O$ (10 ml) was added and the reaction mixture stirred for 15 min. Lithium (3.37 g, 0.48 mol) was then added. The solution was stirred for a further 40 min and EtOH (22.1 g, 28.8 ml, 0.48 mol) was added dropwise. Stirring was continued until the blue colour had disappeared and $NH_3$ was then allowed to evaporate overnight. $H_2O$ (150 ml) was added to the resulting slurry which was extracted with $Et_2O$ (2 x 200 ml). The organic solution was washed with $H_2O$ (1 x 100 ml) and, after drying, concentrated in vacuo to leave a yellow oil which was purified by vacuum distillation to yield the title compound (7.9 g,78%) as a colourless oil b.p. 99-100 $^oC$/20 mm Hg.

$\upsilon_{max}$ ($CCl_4$): 1695 and 1655 $cm.^{-1}$

$\delta_H$ (90 MHz): 5.40 (1H, m, $^tBuC=CH$), 4.60 (1H, m, MeOC=CH), 3.50 (3H, s, $-OCH_3$), 2.75 (4H, m, $-CH_2$s), 1.00 (9H, s, $-C(CH_3)_3$).

Found: $M^+$, 166.1354; $C_{10}H_{18}O$ requires $M$, 166.1357.

4-Methylcyclohex-3-enone.



(99)

Procedure: [111]

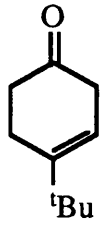
To a 50 ml round bottomed flask were added diene (100) (1.8 g, 14.5 mmol), oxalic acid (10 ml of a 2 M solution, 20 mmol) and $Et_2O$ (10 ml). The reaction mixture was stirred for 18 h at room temperature and then diluted with $Et_2O$ (50 ml). The ether layer was separated and the aqueous layer extracted with $Et_2O$ (2 x 25 ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (1 x 25 ml) and $H_2O$ (1 x 25 ml). After drying, the organic layer was concentrated *in vacuo* to leave a pale yellow oil which was purified by vacuum distillation to yield the title compound (1.25 g, 79%) as a colourless oil b.p. 76-77 $^oC$/20 mm Hg (lit.[113], 74 $^oC$/17 mm Hg).

$\upsilon_{max}$ ($CCl_4$): 3200, 1760, 1730 $cm^{-1}$.

$\delta_H$ (90 MHz): 5.50 (1H, m, $CH_3C{=}C\underline{H}$), 2.90 (2H, m, $COC\underline{H}_2C{=}C$), 2.50 (4H, m, $-CH_2CH_2-$), 1.85 (3H, s, $-CH_3$).

Found: $M^+$, 110 (41%); $C_7H_{10}O$ requires $M$, 110.

4-*tert*-Butylcyclohex-3-en-1-one




(105)

Procedure:[111]

To a 100 ml round bottomed flask were added diene (104) (8.64 g, 0.052 mol), oxalic acid (30.9 ml of a 2 M solution, 0.062 mol) and $Et_2O$ (60 ml). The reaction mixture was stirred for 18 h at room temperature and then diluted with $Et_2O$ (50 ml). The ether layer was separated and the aqueous layer extracted with $Et_2O$ (2 x 50 ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (1 x 50 ml) and $H_2O$ (1 x 50 ml). After drying, the organic layer was concentrated in vacuo to leave a yellow oil which was purified by vacuum distillation to yield the title compound (6.04 g, 76%) as a colourless oil b.p. 37-39 °C/0.7 mm Hg. (lit.[118], 95-97 °C/9 mm Hg).

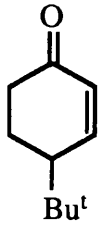
$\upsilon_{max}$ ($CCl_4$): 1725 and 810 $cm.^{-1}$

$\delta_H$ (200 MHz): 5.50 (1H, t, *J* 3.5, C=CH), 2.80 (2H, d, *J* 3.5, -C$\underline{H}_2$CH=C), 2.42 (4H, m, -$CH_2CH_2$-), 1.05 (9H, s, -$C(CH_3)_3$).

$\delta_C$ (50 MHz): 212.0 (s, -CO), 147.3 (s, $^tBu\underline{C}$=CH), 126.1 (d, C=$\underline{C}$H), 39.8 (t, -$CH_2$-), 39.0 (t, -$CH_2$-), 35.5 (s, -$\underline{C}(CH_3)_3$), 28.5 (q, -C($\underline{C}H_3)_3$), 24.7 (t, -$CH_2$).

Found $M^+$, 152.1200; $C_{10}H_{16}O$ requires $M$, 152.1201.

4-*tert*-Butylcyclohex-2-en-1-one

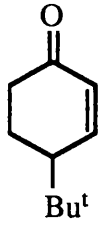



(102)

Procedure:

To a 100 ml round bottomed flask with side-arm equipped with reflux condenser and $N_2$ balloon were added enone (105) (7.8 g, 0.051 mol), DBN (0.93 g, 0,93 ml, 0.0075 mol) and dry THF (80 ml). The solution was refluxed for 48 h and then diluted with EtOAc (100 ml) and washed sequentially with HCl (5%, 1 x 50 ml), saturated aqueous $NaHCO_3$ (1 x 50 ml) and $H_2O$ (1 x 50 ml). The combined aqueous layers were then extracted with EtOAc (2 x 50 ml). The combined organic layers were finally washed with $H_2O$ (1 x 50 ml). After drying, the organic layer was concentrated in vacuo to leave a black oil which was purified by vacuum distillation to yield a mixture of title compound and starting material (5.2 g, 67%) as a colourless oil, b.p. 37-41 $^oC$/0.7 mm Hg. This was shown to be a 4:1 mixture of αβ:βγ enones by 200 MHz n.m.r. This was used in the epoxidation reaction without further purification or analysis.

4-*tert*-Butylcyclohex-2-en-1-one

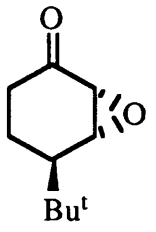



(102)

Procedure:[118]

To a 25 ml round bottomed flask equipped with reflux condenser were added βγ enone (105) (0.50 g, 3.28 mmol) and HCl (10 ml of a 2 M solution, 20 mmol). The solution was refluxed for 3 h (bath temperature 145 °C). After cooling to room temperature, the solution was diluted with $Et_2O$ (25 ml) and washed sequentially with saturated aqueous $NaHCO_3$ solution (1 x 15 ml) and $H_2O$ (1 x 15 ml). After drying, the organic layer was concentrated *in vacuo* to leave a red oil (0.35 g, 70%) which was shown to be a 2:1 mixture of αβ:βγ enones by 200 MHz n.m.r.

5-*tert*-Butyl-7-oxabicyclo[4.1.0]heptan-2-one




(111)

Procedure:[85]

To a 50 ml round bottomed flask at 0 $^oC$ were added enone (102) (2.3 g in 2.8 g of a 4:1 αβ:βγ mixture, 15.1 mmol) and EtOH (20 ml). $H_2O_2$ (5.1 ml of a 30% w/v solution, 45.3 mmol) was then added followed by dropwise addition of NaOH (1.5 ml of a 5 M solution, 7.5 mmol). The cooling bath was removed and the mixture stirred at room temperature for 8 h. The solution was then flooded with $H_2O$ (30 ml) and extracted with $Et_2O$ (3 x 50 ml). After drying, the organic layer was concentrated in vacuo to leave a yellow oil which was purified by vacuum distillation to yield the title compound (2.1 g, 83%) as a colourless oil, b.p. 99-100 $^oC$/0.9 mm Hg.

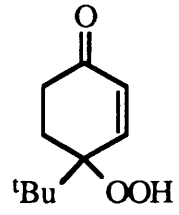
$\upsilon_{max}$ ($CHCl_3$): 1715 $cm.^{-1}$

$\delta_H$ (200 MHz): 3.45 (1H, m, H-6), 3.12 (1H, d, *J* 3.9, H-1), 1.96 (4H, m, $-CH_2CH_2-$), 1.65 (1H, m, $^tBuC-H$), 0.97 (9H, s, $-C(CH_3)_3$).

$\delta_C$ (50 MHz): 208.3 (s, CO), 61.4 (d, C-6), 55.1 (d, C-1), 43.4 (d, $^tBuC$-H), 41.2 (t, -$CH_2$-), 34.6 (t, -$CH_2$-), 32.5 (s, -$\underline{C}(CH_3)_3$), 27.5 (q, -$C(\underline{C}H_3)_3$).

Found : $M^+$ 169 (0.6%); $C_{10}H_{16}O_2$ requires $M$, 169.

4-*tert*-Butyl-4-hydroperoxycyclohex-2-en-1-one




(107)

Procedure:

When compound (105) was allowed to stand in the air at room temperature, a crystalline substance gradually separated out. Recrystallisation from $CCl_4$ afforded the title compound as cubes, m.p. 105.5-106.5 °C. (Lit.[118], 106-107 °C).

$\lambda_{max}$(EtOH): 216 nm.

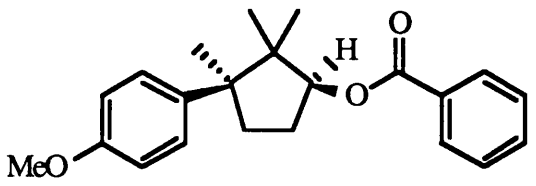
$\upsilon_{max}$ (nujol mull): 3220 and 1660 $cm.^{-1}$

$\delta_H$ (200 MHz): 8.90 (1H, bs, -OOH), 6.86 (1H, dd, *J* 10.5, 1, H-3), 6.13 (1H, d, *J* 10.5, H-2), 2.08-2.87 (4H, m, $-CH_2CH_2-$), 0.96 (9H, s, $-C(CH_3)_3$).

$\delta_C$ (50 MHz): 200.9 (s, -CO), 148.6 (d, C-3), 132.3 (d, C-2), 83.6 (s, C-4), 38.2 (s, $-\underline{C}(CH_3)_3$), 35.1 (t, C-6), 25.8 (t, C-5), 25.4 (s, $-C(\underline{C}H_3)_3$).

Found: $M^+$, 166.0997, ($M-H_2O$); $C_{10}H_{16}O_3$ requires *M*, 184.1099 (166.0994, $M-H_2O$).

(±)-*syn*-3-(4'-Methoxyphenyl)-2,2,3-trimethylcyclopentyl benzoate




(117)

Procedure:[123]

To a 50 ml round bottomed flask with side-arm, equipped with reflux condenser and $N_2$ balloon was added alcohol (91) (1.00 g, 4.27 mmol). Butyl lithium (1.64 ml of a 2.87 M solution in hexane, 4.7 mmol) was then added. After 30 min, the resulting solution was treated during 5 min by the dropwise addition of benzoyl chloride (0.66 g, 4.7 mmol) in THF (10 ml). The mixture was refluxed for 1 h and, after cooling to 0 °C, quenched by careful addition of $H_2O$ (10 ml). After extraction with $Et_2O$ (3 x 50 ml), the organic solution was concentrated in vacuo to leave a yellow oil which was purified by flash silica gel column chromatography using 25% EtOAc in hexane as eluent to yield the title compound (1.07 g, 74%) as off-white plates, m.p. 92-93 °C.

$\upsilon_{max}$ ($CHCl_3$): 1710 $cm.^{-1}$

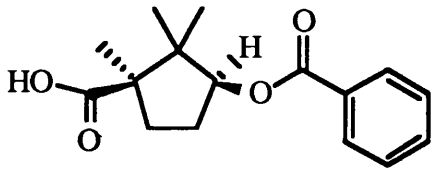
$\delta_H$ (200 MHz):8.06 (2H, d, *J* 9, Ar-H), 6.85 (2H, d, *J* 9, Ar-H), 7.25-7.61 (5H, m, Ar-H), 5.11 (1H, m, -C(H)OCO), 3.80 (3H, s, Ar-$OCH_3$), 2.41-2.65 (2H, m, -$CH_2$-), 1.79-1.99 (2H, m, -$CH_2$-), 1.47 (3H, s, -$CH_3$), 1.15

(3H, s, -$CH_3$), 0.65 (3H, s, -$CH_3$).

$\delta_C$ (50 MHz): 166.2 (s, -OCOAr), 157.6 (s, C-4'), 138.7 (s, C-1'), 132.8 (d, C-4''), 130.8 (s, C-1''), 129.5 (d, C-2'', 6''), 128.4 (d, C-3'', 5''), 127.9 (d, C-3', 5'), 113.0 (d, C-2', 6'), 83.3 (d, C(H)OCO), 55.2 (q, Ar-$OCH_3$), 49.5 (s, -$C(CH_3)_2$), 47.5 (s, -$C(CH_3)$Ar), 34.9 (t, -$CH_2$-), 29.0 (t, -$CH_2$-), 24.7 (q, -2 x $CH_3$), 18.8 (q, -$CH_3$).

Found: $M^+$, 338.1866; $C_{22}H_{26}O_3$ requires $M$, 338.1882.

(±)-*syn*-4-Benzoyloxy-2,3,3-trimethylcyclopentanecarboxylic acid




(116)

Procedure:[122]

A 50 ml round bottomed flask with stirring bar was charged with ester (117) (1.07 g, 3.17 mmol), periodic acid (10.26 g, 45 mmol), $CH_3CN$ (6 ml), $CCl_4$ (6 ml) and $H_2O$ (9 ml). The mixture was stirred vigorously until both phases became clear. $RuCl_3.xH_2O$ (0.04 g, 5 mol%) was added and the reaction mixture stirred for 4 h. The reaction mixture was cooled to 0 °C and ether (20 ml) added. The ether layer was separated and the aqueous layer extracted with EtOAc (5 x 40 ml). The combined organic solutions were washed with brine (2 x 50 ml). After filtering through a pad of celite and drying, the organic layer was concentrated in vacuo to give a brown oil which was purified by flash silica gel column chromatography using 0-100% EtOAc in hexane as eluent (10% increments) to yield the title compound (0.40 g, 46%) as a yellow solid, m.p. 125-127 °C.

$\upsilon_{max}$ ($CHCl_3$): 2990, 1720, 715 $cm.^{-1}$

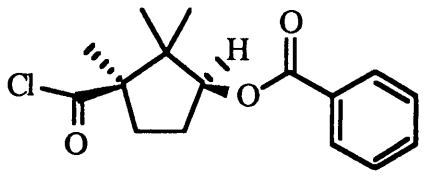
$\delta_H$ (200 MHz): 9.01 (1H, bs, $-CO_2H$), 8.03 (2H, m, Ar-H), 7.48 (3H, m, Ar-H), 5.25 (1H, m, -CH(OCOAr)), 2.46

(2H, m, -$CH_2$-), 1.74 (2H, m, -$CH_2$-), 1.41 (3H, s, -$CH_3$), 1.16 (3H, s, -$CH_3$), 1.06 (3H, s, -$CH_3$).

$\delta_C$ (50 MHz): 182.9 (s, -$CO_2H$), 166.0 (s, -OCOAr), 133.0 (d, ArC-H), 130.5 (s, Ar<u>C</u>-CO), 129.5 (d, ArC-H), 128.4 (d, ArC-H), 83.6 (d, -<u>C</u>H(OCOAr)), 54.3 (s, -<u>C</u>$(CH_3)_3$), 47.3 (s, -<u>C</u>$(CH_3)CO_2H$), 32.5 (t, -$CH_2$-), 28.5 (t, -$CH_2$-), 24.3 (q, -$CH_3$), 21.1 (q, -$CH_3$), 18.3 (q, -$CH_3$).

Found: $M^+$, 276.1360; $C_{16}H_{20}O_4$ requires $M$, 276.1361.

(±)-*syn*-4-Benzoyloxy-2,3,3-trimethylcyclopentanecarboxylic acid chloride

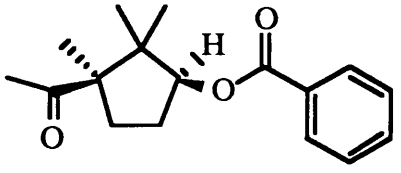



(118)

Procedure:[125]

To a 5 ml round bottomed flask equipped with reflux condenser and $CaCl_2$ guard tube were added the acid (116) (0.16 g, 0.58 mmol) and oxalyl chloride (0.34 g, 0.24 ml, 2.7 mmol). Gas evolution started almost immediately, continued for 20 min, and then ceased. The mixture was refluxed for 2 h and concentrated *in vacuo* to yield the title compound (0.15 g, 88%) as a brown oil. This was used in the next step without further purification or analysis.

(±)-*syn*-(3-Benzoyloxy-1,2,2-trimethylcyclopentyl) methyl ketone



(115)

Procedure:[127]

To a 25 ml round bottomed flask under $N_2$ was added CuI (0.354 g, 1.86 mmol). The flask was gently flame-dried under vacuum and the vacuum then released with $N_2$. Dry $Et_2O$ (6 ml) was added and the solution cooled to 0 °C. MeLi (2.48 ml of a 1.5 M solution in $Et_2O$, 3.72 mmol) was added and, after 5 min at 0 °C, the solution was cooled to -78 °C. A pre-cooled solution of acid chloride (118) (0.182 g, 0.62 mmol) in $Et_2O$ (1 ml) was added dropwise. After 15 min, absolute MeOH (0.218 g, 0.172 ml, 6.81 mmol) was added and the reaction mixture allowed to warm to room temperature over 1.5 h. The resulting mixture was added with stirring to saturated aqueous $NH_4Cl$ solution (12 ml) and extracted with EtOAc (3 x 50 ml). After drying, the organic layer was concentrated in vacuo to leave a brown oil which was purified by flash silica gel column chromatography using 20% EtOAc in hexane as eluent to yield the title compound (0.118 g, 70%) as a colourless oil.

$\upsilon_{max}$ ($CHCl_3$): 1710 and 715 $cm.^{-1}$

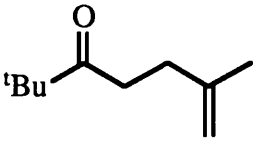
$\delta_H$ (200 MHz): 8.03 (2H, m, Ar-H), 7.47 (3H, m, Ar-H),

5.12 (1H, m, -CH(OCOAr), 2.30-2.55 (2H, m, $-CH_2-$), 2.18 (3H, s, $-COCH_3$), 1.50-1.85 (2H, m, $-CH_2-$), 1.38 (3H, s, $-CH_3$), 1.19 (3H, s, $-CH_3$), 0.96 (3H, s, $-CH_3$).

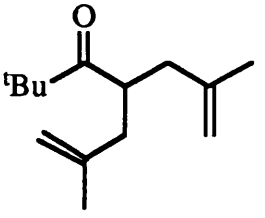
$\delta_C$ (50 MHz): 212.6 (s, $-\underline{C}OCH_3$), 165.9 (s, -OCOAr), 132.9 (d, ArC-H), 130.5 (s, Ar$\underline{C}$-CO), 129.5 (d, ArC-H), 128.4 (d, ArC-H), 84.3 (d, -$\underline{C}$H(OCOAr), 59.4 (s, -$\underline{C}(CH_3)_2$), 47.1 (s, $-\underline{C}(CH_3)COCH_3$), 32.6 (t, $-CH_2-$), 28.5 (t, $-CH_2-$), 28.4 (q, $-CH_3$), 24.3 (q, $-CH_3$), 21.3 (q, $-CH_3$), 18.9 (q, $CH_3$).

Found: $M^+$ 274.1567; $C_{17}H_{22}O_3$ requires $M$, 274.1569.

2,2,6-Trimethylhept-6-en-3-one.(119)




(119)




(120)

Procedure:

To a 250 ml 3-necked round bottomed flask under $N_2$ was added NaI (5.63 g, 0.0375 mol). Diisopropylamine (8.34 g, 11.55 ml, 0.082 mol) and THF (100 ml) were then added. Butyl lithium (37 ml of a 2.21 M solution in hexane, 0.082 mol) was then added at 0 °C. The solution was cooled to -78 °C and pinacolone (7.5 g, 9.4 ml, 0.075 mol) in THF (20 ml) was added dropwise. After stirring for 30 min at -78 °C, methallyl chloride (6.9 g, 7.5 ml, 0.075 mol) in THF (20 ml) was added dropwise. The solution was warmed to room temperature and stirred at room temperature for 72 h. The mixture was added to saturated aqueous $NH_4Cl$ solution (200 ml) and extracted with $Et_2O$ (3 x 75 ml). The organic layer was washed with HCl solution (5%, 1 x 50 ml), $NaHCO_3$ solution (10%, 1 x 50 ml) and brine (1 x 50 ml). After drying, the organic layer was concentrated *in vacuo* to leave a red oil which was purified by positive pressure column chromatography using 5% $Et_2O$ in hexane as eluent to yield compound (120) (2.00 g, 13%) as a colourless oil.

$\upsilon_{max}$ ($CHCl_3$): 2970, 1700, 895 $cm.^{-1}$

$\delta_H$ (200 MHz): 4.72 (2H, m, -C=CH<u>H</u>), 4.67 (2H, m, -C=C<u>H</u>H), 3.32 (1H, quintet, *J* 6.9, -CHCO), 2.27 (2H, dd, *J* 13.8, 7.2, -$CH_2$-), 1.96 (2H, dd, *J* 13.8, 6.7, -$CH_2$-), 1.70 (6H, m, 2 x -$CH_3$), 1.10 (9H, s, -$C(CH_3)_3$).

$\delta_C$ (50 MHz): 217.8 (s, -CO), 142.9 (s, -<u>C</u>=$CH_2$), 113.1 (t, -C=<u>C</u>$H_2$), 44.3 (d, -<u>C</u>HCO), 42.1 (t, -$CH_2$-), 40.3 (s, -<u>C</u>$(CH_3)_3$), 27.4 (q, -C(<u>C</u>$H_3)_3$), 22.3 (q, -$CH_3$).

Found: *M*+, 208.1821; $C_{14}H_{24}O$ requires *M*, 208.1827.

Further elution furnished the <u>title compound</u> (3.5g, 31%) as a colourless oil.

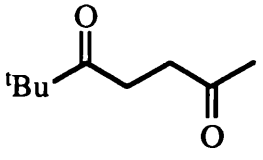
$\upsilon_{max}$ ($CCl_4$): 2970, 1710, 895 $cm.^{-1}$

$\delta_H$ (200MHz): 4.68 (2H, m, -C=$CH_2$), 2.63 (2H, m, -$COCH_2$-), 2.25 (2H, m, -C<u>H</u>$_2$C=$CH_2$), 1.17 (3H, m, -$CH_3$), 1.15 (9H, s, -$C(CH_3)_3$).

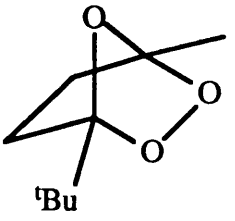
$\delta_C$ (50 MHz): 215.2 (s,-CO), 145.0 (s, -<u>C</u>$(CH_3)$=$CH_2$), 109.8 (t, -C=<u>C</u>$H_2$), 44.1 (s, -<u>C</u>$(CH_3)_3$), 34.7 (t, -$CH_2$-), 31.5 (t, -$CH_2$-), 27.3 (q, -C(<u>C</u>$H_3)_3$), 22.7 (q, -$CH_3$).

Found: *M*+, 154.1363; $C_{10}H_{18}O$ requires *M*, 154.1358.

2, 2-Dimethylheptan-3, 6-dione (121)



(121)



(122)

Procedure:

To an ozonolysis flask at -78 °C was added ketone (119) (1.40 g, 9.1 mmol) and $CH_2Cl_2$ (45 ml). $O_3$ was bubbled through the solution until it remained blue in colour. $Et_3N$ (1.82 g, 2.50 ml, 18 mmol) was added dropwise and the solution warmed to room temperature and then stirred for a further 4 h. The resulting mixture was concentrated *in vacuo* and $Et_2O$ (5 ml) was added. The precipitated triethylamine-N-oxide was removed by filtration through a short pad of silica. Concentration of the organic solution *in vacuo* afforded a yellow oil which was purified by flash silica gel column chromatography using 10% EtOAc in hexane as eluent to yield endoperoxide (122) (0.40 g, 26%) as a colourless oil.

$\upsilon_{max}$ ($CHCl_3$): 2980, 1390, 1170 $cm.^{-1}$

$\delta_H$ (200MHz): 1.80-2.25 (4H, m, $-CH_2CH_2-$), 1.63 (3H, s, $-CH_3$), 1.09 (9H, s, $-C(CH_3)_3$).

$\delta_C$ (50 MHz): 117.1 (s, -<u>C</u>-C$(CH_3)_3$), 110.7 (s, -<u>C</u>$CH_3$), 35.1 (t, -$CH_2$-), 32.9 (s, -<u>C</u>$(CH_3)_3$), 30.0 (t, -$CH_2$0-), 25.7 (q, -C(<u>C</u>$H_3)_3$), 15.0 (q, -$CH_3$).

Further elution gave the <u>title compound</u> (0.45 g, 32%) as a pale yellow oil. Vacuum distillation gave pure diketone (121) (0.42 g, 30%) as a colourless oil, b.p. 95 $^oC$/25 mm Hg.

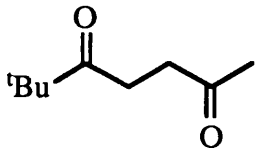
$\upsilon_{max}$ ($CHCl_3$): 1710 and 1700 $cm.^{-1}$

$\delta_H$ (200 MHz): 2.61-2.79 (4H, m, -$CH_2CH_2$-), 2.16 (3H, s, -$CH_3$), 1.13 (9H, s, -C$(CH_3)_3$).

$\delta_C$ (50 MHz): 214.6 (s, -CO$^t$Bu), 207.5 (s, -<u>C</u>O$CH_3$), 43.8 (s, -<u>C</u>$(CH_3)_3$), 36.9 (t, -$CH_2$-), 30.5 (t, -$CH_2$-), 30.0 (q, -$CH_3$), 26.5 (q, -C(<u>C</u>$H_3)_3$).

Found: $M^+$, 156.1163; $C_9H_{16}O_2$ requires $M$, 156.1151.

2, 2-Dimethylheptan-3, 6-dione

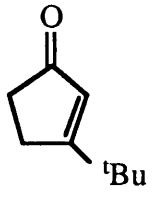



(121)

Procedure:[133]

To a 50 ml round bottomed flask at 0 °C were added endoperoxide (122) (0.40 g, 2.3 mmol) and hexane (10 ml). $Ph_3P$ (1.32 g, 5.06 mmol) in hexane (10 ml) was added dropwise, the cooling bath removed and the reaction mixture stirrred at room temperature overnight. The precipitated $Ph_3PO$ was removed by filtration through a short pad of silica. The filtrate was concentrated in vacuo to leave a yellow oil which was purified by vacuum distillation to yield the title compound (0.22 g, 61%) as a colourless oil, identical in all respects to that obtained from the ozonolysis reaction.

3-*tert*-Butylcyclopent-2-en-1-one




(123)

Procedure:[134]

To a 50 ml round bottomed flask with side-arm equipped with reflux condenser and $N_2$ balloon were added diketone (121) (0.20 g, 1.28 mmol) and NaOH solution (13% w/v, 23.3 ml). The solution was purged with $N_2$ for 5 min and then refluxed for 6 h. After cooling to room temperature, the mixture was extracted with $Et_2O$ (3 x 50 ml). The organic solution was washed with $H_2O$ (2 x 50 ml) and brine (1 x 50 ml). After drying, the organic layer was concentrated in vacuo to yield the title compound (0.15 g, 85%) as a yellow oil. Distillation afforded the title compound (0.13 g,74%) as a colourless oil, b.p. 95 °C / 25 mm Hg.

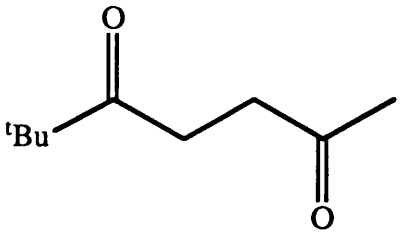
$\upsilon_{max}$ ($CHCl_3$): 2980, 1700 and 1675 $cm.^{-1}$

$\delta_H$ (200 MHz): 5.95 (1H, m, -C=CH), 2.39-2.70 (4H, m, -$CH_2$s), 1.20 (9H, s, -$C(CH_3)_3$).

$\delta_C$ (50 MHz): 210.6 (s, -CO), 191.2 (s, -<u>C</u>=CH), 127.2 (d, -C=<u>C</u>H), 35.4 (t, -<u>C</u>$H_2$CO), 28.7 (q, -C(<u>C</u>$H_3)_3$), 27.6 (t, -<u>C</u>$H_2$C=C), 26.5 (s, -<u>C</u>$(CH_3)_3$).

Found : $M^+$, 138.1034; $C_9H_{14}O$ requires $M$, 138.1045.

2,2-Dimethylheptan-3,6-dione




(121)

Procedure:

To an ozonolysis flask at -78 °C was added ketone (105) (1.00 g, 6.6 mmol) and $CH_2Cl_2$ (15 ml). $O_3$ was bubbled through the solution until it remained blue in colour. $Me_2S$ (1.00 ml, 13.6mmol) was added dropwise and the solution warmed to room temperature and stirred for a further 4 hours. The resulting mixture was concentrated in vacuo and $Et_2O$ (20 ml) added. NaOH solution (5 M, 10 ml, 50 mmol) was added and the resulting orange solution shaken in a separating funnel for 5 minutes. The resulting solution was acidified with HCl (2 M, 30 ml, 60 mmol) and extracted with $Et_2O$ (3 x 50 ml). The organic solution was washed with $H_2O$ (1 x 50 ml). After drying, the organic solution was purified by flash silica gel column chromatography using 0-100% EtOAc in hexane as eluent to yield the title compound (0.20g, 20%) as a colourless oil, identical in all respects to that obtained previously.

# Appendix

## Trimethylsilyl trifluoromethanesulphonate

Procedure:[135]

To a 25 ml round bottomed flask with side-arm under argon at 0 °C was added trifluoromethanesulphonic acid (1.51 g, 0.89 ml, 10 mmol). Tetramethylsilane (1.10 g, 1.70 ml, 12.5 mmol) was added and the mixture stirred for 15 min. A further portion of tetramethylsilane (0.22 g, 0.34 ml, 2.5 mmol) was added and the mixture allowed to warm to room temperature. The mixture was stirred for a further 15 min and then transferred directly to a Kugelrohr bulb under a stream of argon. Distillation afforded TMS-triflate (2.1 g, 94%) as a colourless oil; b.p. 70 °C/35 mm Hg (lit.[135], 40 °C/11 mm Hg). The reagent was stored as a 0.95M solution by addition of 10 ml $CH_2Cl_2$.

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