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SYNTHESIS AND PHOTODEGRADATION STUDIES OF ANALOGUES OF THE HOP-DERIVED ISO-α-ACIDS

A Thesis Presented by

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Declaration

I, Alex Nigel Cayley, confirm that the work presented in this thesis is my own. Where work has been derived from other sources, I confirm that this has been indicated in the thesis.

Alex Nigel Cayley
December 2006

Abstract

This thesis describes the synthesis and photodegradation studies of some analogues of the isohumulones, a class of polycarbonyl organic compounds present in beer. Studies have been initiated in an attempt to elucidate the mechanism of the so called "sunstruck effect", a photodegradation reaction of the isohumulones which occurs in beer when it is left in sunlight.

The first chapter of the thesis is concerned, primarily, with the biosynthesis and reactivity of the isohumulones and contains a brief review of literature methods for the synthesis of these compounds and their analogues, including descriptions of synthetic methods for the formation of the key functional groups present in these types of structures.

The second chapter presents the results and gives a discussion of the research carried out. The production of some simple isohumulone analogues by the use of thioacetal anion chemistry is described, along with the results of investigations into the synthesis of isohumulone analogues via the ring contraction reaction of analogues of the natural product, humulone. Results of studies into the direct formation of polycarbonyl cyclopentanoids are also reported. This is followed by the results of preliminary photolysis studies carried out on the compounds synthesised.

Chapter three of the thesis presents the conclusions which have been drawn from the work presented in chapter two and provides suggestions for possible directions of this research in the future.

The final chapter provides a formal account of the experimental procedures developed during the work described in this thesis.

Contents

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This work would not have been possible without the dedicated technical staff of the UCL chemistry department. I would particularly like to thank Dave Butler and Dr Abil Aliev for all their help with all aspects of NMR spectroscopy.

Outside of the chemistry department I would like to thank my friends who always provide welcome relief during my time away from the lab. Special thanks to Gavin Hamilton, more for his help in consuming beer than studying it.

I am, of course, indebted to my family for their unwavering support and encouragement throughout my entire life, whatever I choose to do. Thank you Mum and Dad for always providing a place for me to escape to and the constant repairs to my motorbike, and to the rest of my family for the jokes and laughter to help me forget my worries.

Finally, and most importantly, I would like to thank my fiancée Rachael for her constant friendship and companionship. She celebrated with me during the highs, lifted my spirits during the lows and managed to keep me sane through the whole thing.

For Rachael, With All My Love.

In "light" of her putting up with my "slow degradation" during the writing of this thesis.

Abbreviations

Ac	Acetyl
acac	Acetylacetonate
AIBN	α, α'-Azobisisobutyronitrile
aq.	Aqueous
Ar	Aromatic
bp	Boiling point
br	Broad
cat.	Catalytic (amount)
CI	Chemical ionisation
CSA	(±)-Camphor-10-sulfonic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
EI	Electron impact
eq.	Equivalent
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
FAB	Fast atom bombardment
g	Gram(s)
GC	Gas chromatography
h	Hour(s)
HMPA	Hexamethylphosphoramide
HOMO	Highest occupied molecular orbital
Hz	Hertz
hv	Light
^{i}Pr	*iso*-Propyl
IR	Infrared
J	Coupling constant
L	Unspecified ligand
LA	Lewis acid
LC	Liquid chromatography
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
LUMO	Lowest unoccupied molecular orbital
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minute(s)
ml	Millilitres
mmol	Millimole(s)

mol	Mole(s)
MoOPh	Oxidodiperoxymolybdenum(pyridine) (hexamethylphosphoric triamide)
mp	Melting point
MS	Mass spectrum
NBS	N-Bromosuccinimide
^{n}Bu	*n*-Butyl
NCS	N-Chlorosuccinimide
NMR	Nuclear magnetic resonance
o/n	Overnight
P	Unspecified protecting group
Ph	Phenyl
Pr	Propyl
R	Unspecified carbon substituent
r.t.	Room temperature
RF	Riboflavin
SOMO	Singly occupied molecular orbital
TBAT	Tetrabutylammonium triphenyldifluorosilicate
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
^{t}Bu	*tert*-Butyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
tlc	Thin layer chromatograph
TMEDA	N,N,N',N' -Tetramethylethylene diamine
TMOF	Trimethyl orthoformate
TMS	Trimethylsilyl
Ts	*para*-Toluenesulfonyl
X	Halogen
Δ	Heat
δ	Chemical shift

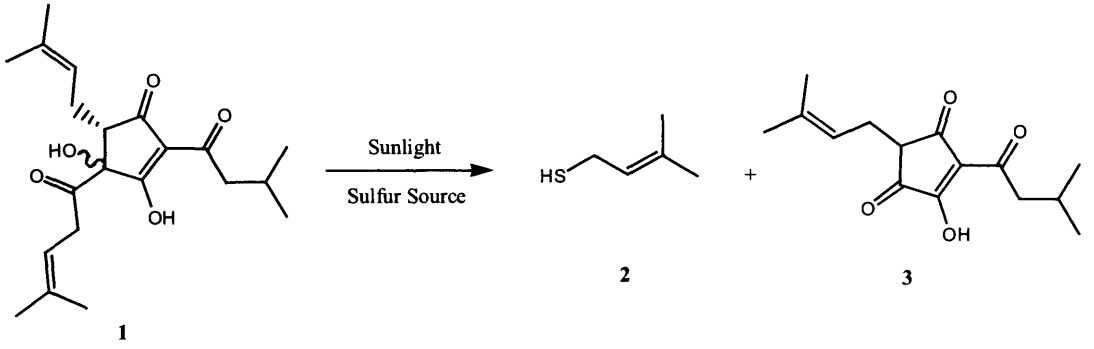
CHAPTER 1

Introduction

1.1 Objectives.

The present thesis is concerned with the photodegradation reaction of the hop-derived compounds, the isohumulones (**1**). These molecules (**1**) are present in significant quantities in beer and, upon irradiation of the drink with sunlight, undergo a photoinduced reaction, combining with a sulfur source in the beverage to produce the thiol, 3-methyl-2-butenethiol (3-MBT) (**2**) and dehydrohumulinic acid (**3**) (Scheme 1). The presence of the 3-MBT (**2**) in beer causes an offending odour and taste known as the "sunstruck flavour", a characteristic which is extremely detrimental to beer quality.

Although this reaction is tremendously important to the brewing industry the mechanism of the "sunstruck reaction" is currently not very well understood. It is generally agreed that improved mechanistic insight into the transformation would inevitably lead to a means of completely preventing the formation of the problematic 3-MBT (**2**) in beer.



1 2 3

Scheme 1

In this study, we elected to adopt a novel approach to this problem by attempting to further elucidate the mechanism of this photodegradation reaction through the synthesis and photolysis of simpler analogues of the isohumulones (**1**).

It is, therefore, appropriate in the present introduction to this thesis to provide a series of brief overviews on areas of chemistry of relevance in our studies. A description of the origins of the isohumulones (**1**), their reactions and the problems associated with these compounds will be given along with a brief review of some of the current methods for assembly of highly functionalised cyclopentane derivatives.

1.2 The Iso-α-acids: Structure And Function.

The isohumulones (**1**) are, in fact, examples of a wider class of organic molecule present in beer known as the iso-α-acids (**1**, **4**, **5**). These compounds are typically detected in beer in concentrations varying between 15 and 100 ppm and play a number of fundamental roles in the drink.[1-6]

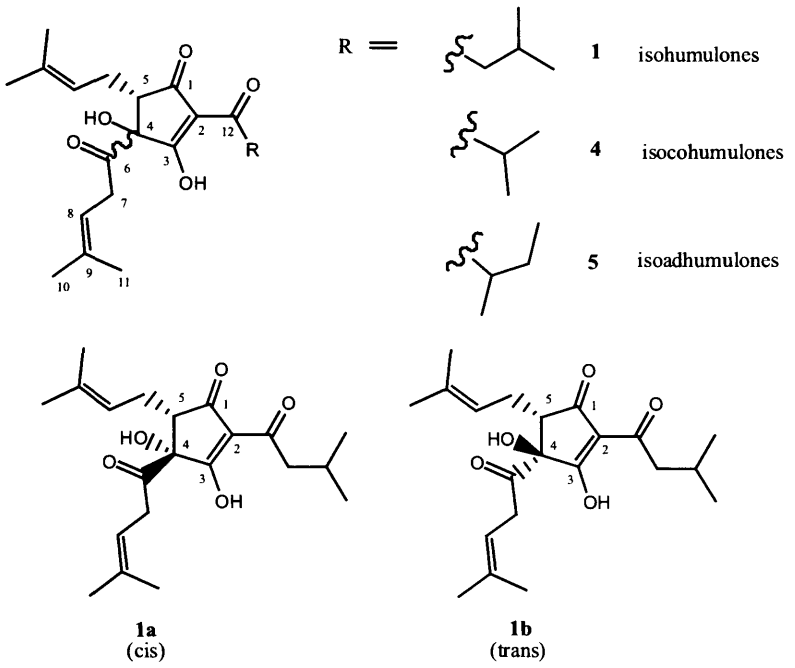


Fig. 1

The molecules all contain a 2-acylcyclopentane-1,3-dione ring system and an adjacent quaternary centre comprising an α-hydroxyketone moiety (C4-C6) and differ in the acyl side chain attached to this core unit (C2) (Fig. 1). The isohumulones (**1**), isocohumulones (**4**) and isoadhumulones (**5**) are the most abundant of the iso-α-acids and are present in beer as mixtures of diastereoisomers in a ratio of 5: 3.7: 1.3.[7]

It has been determined by chemical modification[8] and circular dichromism spectral studies[9] that the chiral centre at C5 of the iso-α-acids has the (*S*) - absolute configuration and that this chirality is fixed in each of the two diastereoisomers of compounds (**1**), (**4**) and (**5**). The diastereomers of Isohumulone (**1**) have been assigned as *cis*-isohumulone, when the alkyl (C5) and acyl (C4) functionality are on opposite

faces (4*R*, 5*S*) of the cyclopentane ring (**1a**) and *trans*-isohumulone, when the alkyl (C5) and acyl functionality (C4) are on the same face (4*S*, 5*S*) (**1b**) (Fig. 1).

Whilst the structure of these polycarbonyl cyclopentanoids (**1**, **4**, **5**) appears deceptively simple at first sight a closer analysis reveals many beautiful and interesting structural features in the iso-α-acids (**1**, **4**, **5**), which combine to give rise to their unique chemical reactivity.

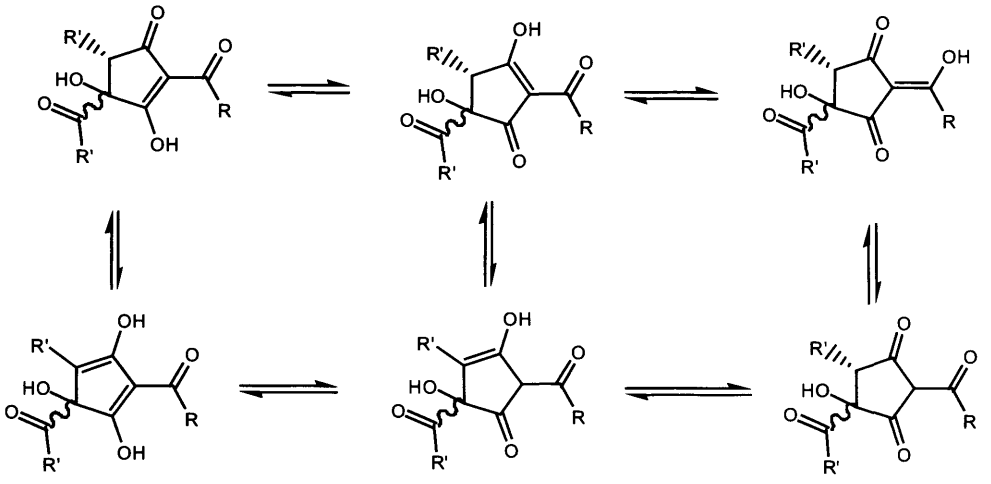


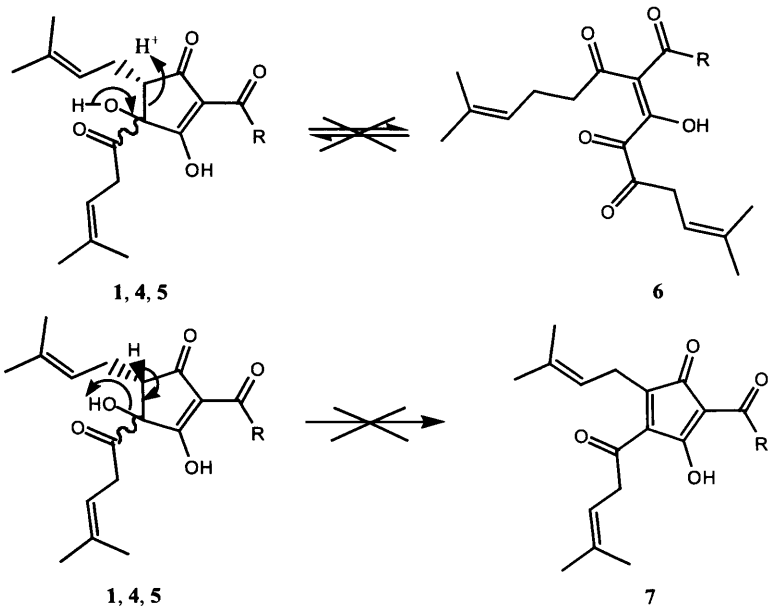
Fig. 2

One such interesting moiety is the conjugated "2-acylcyclopentane-1,3-dione" tricarbonyl unit (C1, C3, C12) present in the iso-α-acids. This can exist in numerous tautomeric forms and Fig. 2 shows the types of keto-enol interconversion which can be imagined in this system. Obviously some of the tautomers depicted will be more prevalent than others due to their stability but this tautomerisation highlights a dynamic in the molecules which makes the chemistry of the iso-α-acids extremely interesting.

As a further example of this dynamic nature it would be easy to envisage the iso-α-acids (**1**, **4**, **5**) undergoing a retro-aldol reaction at their C4-C5 bond and the molecules existing in equilibrium with an open chain polycarbonyl compound (**6**) (Scheme 2). It seems unlikely, however, that this process actually occurs in beer since no racemisation of the chiral centre at C5 of the iso-α-acids (**1**, **4**, **5**) has been observed in the drink. It should be noted, at this point, that a retro-aldol reaction of this type cannot be completely ruled out since, in such a complex medium, it may be that enantiospecific

ring closure of the polycarbonyl compound (**6**) can be achieved to reform the iso-α-acids.

The fact that the chiral centre at C5 of the iso-α-acids is not epimerised in beer also indicates that these compounds do not undergo an acid catalysed reversible dehydration-hydration reaction at the C4-C5 bond. This is presumably due to the fact that this process would result in the production of molecules with tautomeric forms possessing antiaromatic character (**7**) (Scheme 2).



Scheme 2

The iso-α-acids also contain a key α-hydroxyketone unit (C4-C6) attached to the cyclopentane ring to form a tertiary alcohol centre (C4). From a synthetic standpoint, this is a system which would be difficult to form in a selective fashion due to the numerous other functional groups present in the molecules (**1**, **4**, **5**). This moiety is, of course, of intrinsic interest in our studies (C4-C6), since it is the bond between the alcohol (C4) and the pendant unsaturated carbonyl chain (C6) which breaks during the photodegradation of the isohumulones (**1**).

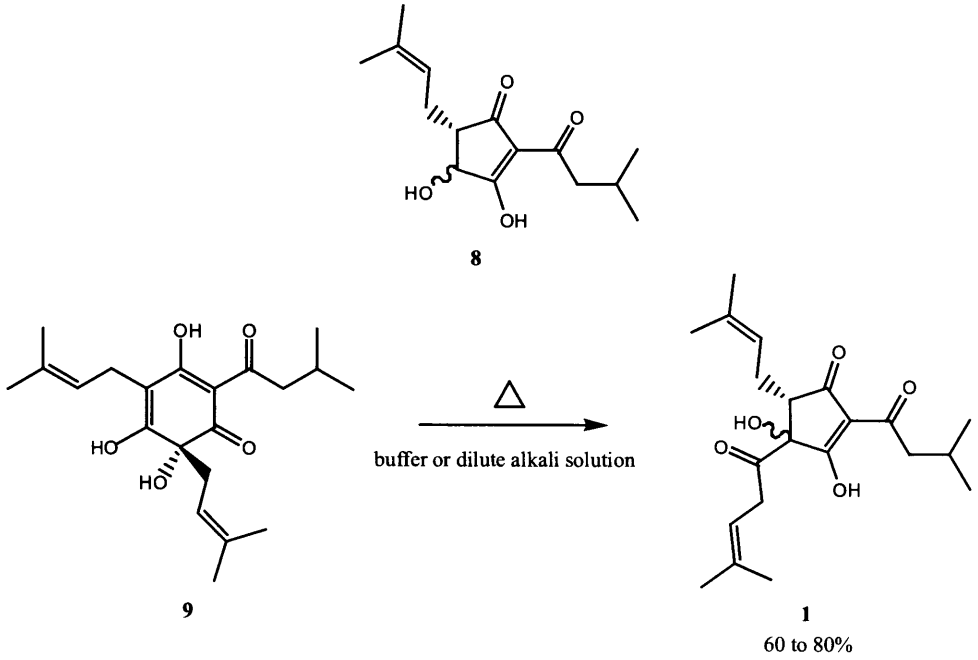
As well as displaying these many interesting structural characteristics and being fascinating molecules in their own right these small polycarbonyl compounds (**1**, **4**, **5**) also perform a number of fundamental roles in beer. Arguably the most important of

these are played by the most abundant iso-α-acids, the isohumulones (**1**). These iso-α-acids (**1**) are the major cause of the typical bitter taste of beer[1, 2] and also play a part in foam stabilisation[3, 4] as well as possessing antibacterial properties.[5, 6] The antibacterial nature of the isohumulones (**1**) is a characteristic not as important to the modern brewing industry due to aseptic packaging and storage techniques but in the past this property gave beer a major advantage over other beverages. Even when bearing this in mind these various qualities still make the isohumulones (**1**) an integral component of beer today and their presence in the finished product crucial. It is due to the abundance and importance of the isohumulones (**1**) that this research is primarily concerned with these iso-α-acids.

1.3 Origins Of The Isohumulones (1).

The structure of isohumulone (**1**) was first proposed by H. Weiland[10] over fifty years ago as an intermediate in the production of the humulinic acids (**8**). Isolation of a mixture of the iso-α -acids (**1**, **4**, **5**) was achieved shortly after this by W. Windisch *et al.*[11] and the data they obtained was in agreement with this proposed structure. This research showed that the isohumulones (**1**) could be formed by boiling the hop derived natural product, (-) humulone (**9**), in a dilute alkaline or buffer solution (Scheme 3).

It is thought that the isohumulones (**1**) are generated in the same way during the fermentation of beer, at a stage of brewing known as wort boiling. During this process the raw ingredients are heated and the (-) humulone (**9**) present in the hops undergoes a thermally induced ring contraction reaction to form the isohumulones (**1**) as a mixture of diastereoisomers.



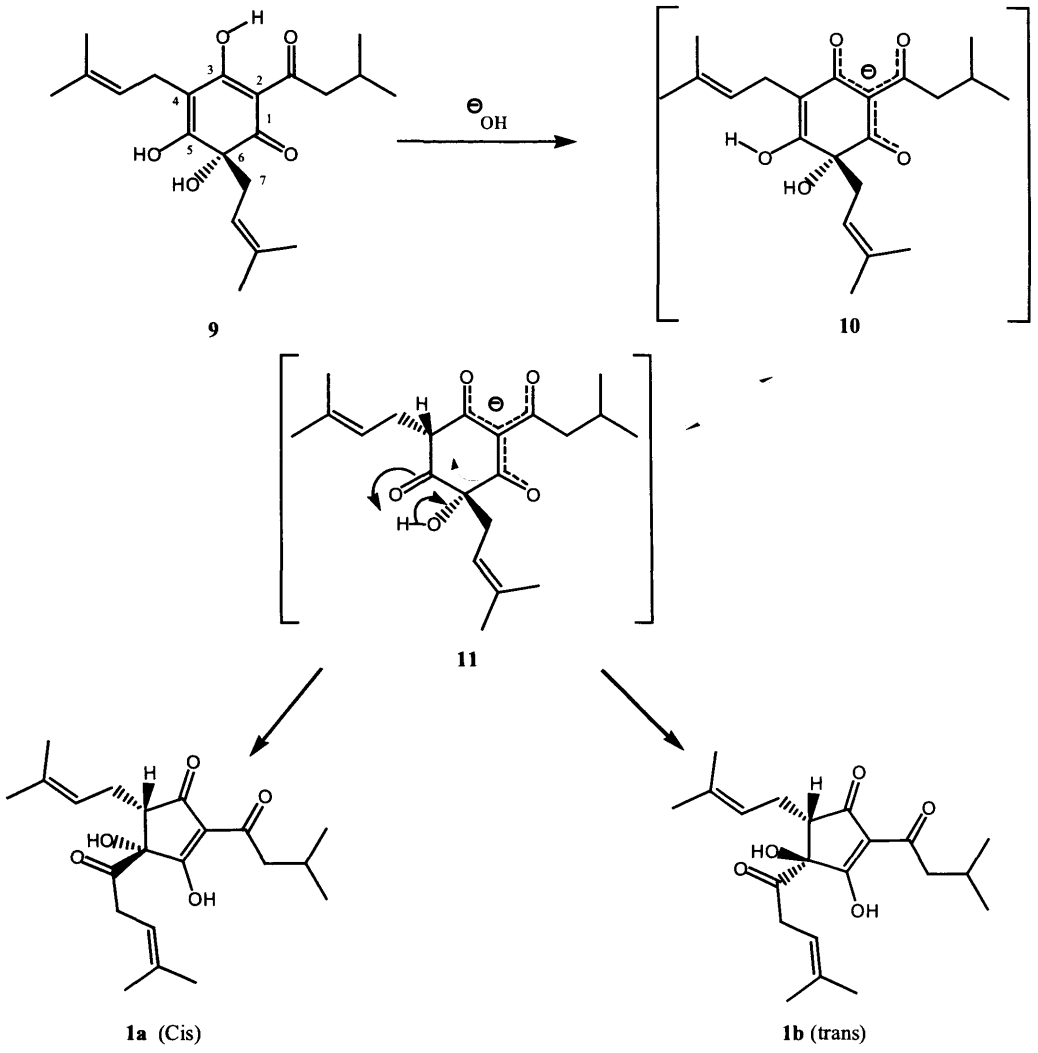
Scheme 3

Along with this initial research into the transformation there has been a great deal of subsequent investigation into its mechanism and means of facilitation.[11-15] The reaction has been carried out in the laboratory under a number of different thermal conditions[1, 12, 14] and, interestingly, research has also shown that isolated samples of (-) humulone (**9**) perform the ring contraction reaction upon irradiation with light and in this case only *trans*-isohumulone is formed.[15]

1.31 Mechanisms Of The Ring Contraction of (-) Humulone (9)

The numerous studies of the reaction have provided a well established mechanism[8, 16, 17] for the alkali induced thermal isomerisation of (-) humulone (**9**) to the isohumulones (**1**). This mechanism is shown in Scheme 4 and involves initial deprotonation of (-) humulone (**9**) under the basic conditions to form a tricarbonyl stabilised anion (**10**). Tautomerisation of the remaining enol function in the ring (C5) leads to the α-hydroxyketone compound (**11**) which can then undergo an acyloin rearrangement (C1-C5), producing the isohumulones (**1**). The bond migration is regioselective and the alternative rearrangement of intermediate (**11**) (C7-C5) to yield a six membered ring regioisomer of (-) humulone (**9**) is not seen, presumably due to the lower migratory aptitude of the alkenyl side chain.

A similar product arising from an acyloin rearrangement with bond migration to the carbonyl at C1 of the compound, is, of course, not observed due to the fact that this centre is protected as an extensively delocalised anion during the isomerisation process.

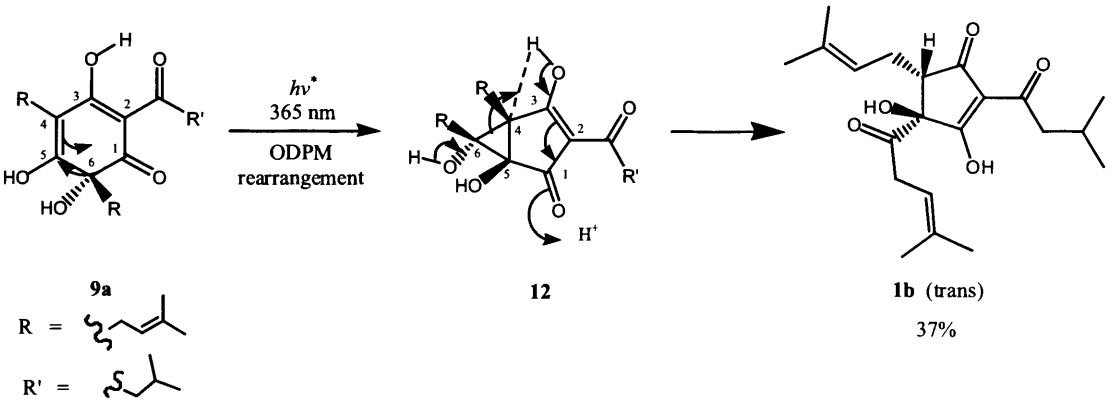


Scheme 4

Contrastingly, the mechanism for the photoinduced ring contraction of (-) humulone (**9**) to *trans*-isohumulone (**1**)[15] follows a different pathway to that of the thermal isomerisation and is shown in Scheme 5.

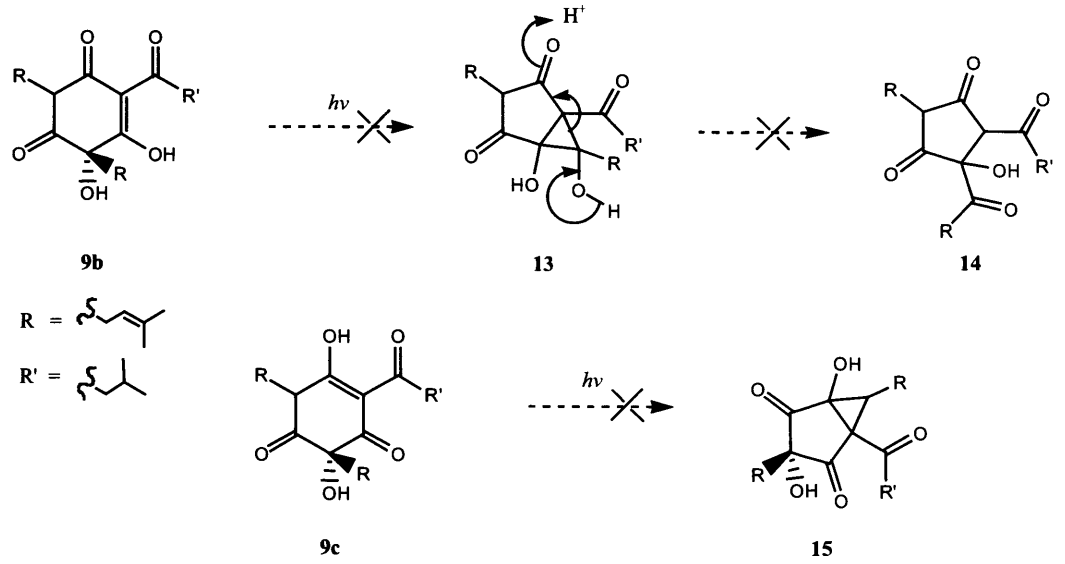
The reaction is thought[1] to proceed via an oxa-di-π-methane rearrangement (ODPM)[18] upon excitation of the molecule by light. This photoinduced rearrangement is known to occur in molecules containing a β,γ unsaturated carbonyl moiety and can formally be viewed as a 1, 2-acyl shift from C6 to C5 of the compound (**9**) with concomitant three

membered ring formation between C4 and C6, creating the cyclopropanol containing intermediate (**12**). This fused bicyclic compound (**12**), however, has not been isolated due to the rapid hydroxyl group assisted cyclopropane ring opening to the final *trans*-isohumulone (**1b**) product.



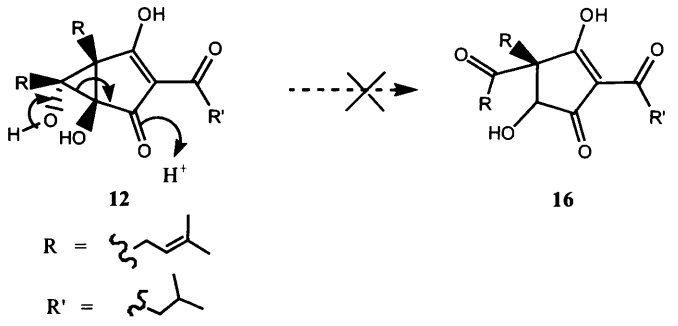
Scheme 5

A facet of this process, which is extremely interesting, is the regioselectivity observed in the formation of the cyclopropane containing intermediate (**12**). There are, of course, a number of different tautomeric forms of humulone (**9**) which can be invoked, each of which could undergo a similar rearrangement to form a different cyclopropane containing intermediate, as shown in Scheme 6. While it may be true that forming an unstable fused ring system such as (**15**) may not be energetically favourable, there is no reason why the fused bicyclic cyclopropane intermediate (**13**), formed from tautomer (**9b**), could not be opened, producing a structural isomer of the isohumulones (**14**). The regioselectivity observed is, presumably, a consequence of the way in which the humulone (**9**) chromophore interacts with light, with the lowest electronically excited state arising from the tautomer, (**9a**). Indeed, the conjugated dienone present in this tautomer (**9a**) is one of the most extended chromophores that can be formed in this system.



Scheme 6

Furthermore, in the opening of intermediate (**12**) it is easy to imagine an alternative cleavage of the cyclopropane ring to form compound (**16**) (Scheme 7). However, this ring opening is regioselective and only the *trans*-isohumulone product (**1b**) is obtained (Fig. 7). This selectivity is, again, difficult to account for.



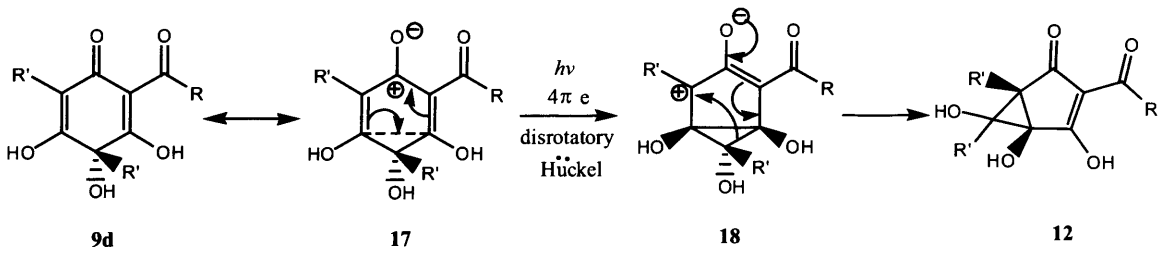
Scheme 7

The diastereoselectivity of the reaction has been rationalised[1] by the fact that the opening of the fused bicyclic intermediate (**12**) is essentially an internal electrophilic substitution reaction. Therefore, the ideal reaction geometry is such that the proton of the enol at C3 is attacking the antibonding orbital of the σ bond being broken (C4-C6) (Scheme 5). This approach leads to an inversion of configuration at the reaction centre (C4) and a *trans* relationship between the alkenyl chain at this carbon (C4) and the hydroxyl group of the adjacent carbon centre (C5). This explanation, however, is made

a little improbable by the fact that the conformation of this system means that the enolic hydrogen at C3 is held at a long distance from the reaction centre at C4.

Finally, the stereoselectivity of the ring contraction has been ascribed to the pericyclic character of this ODPM rearrangement, the mechanism invoked[1] to explain the production of *trans*-isohumulone being a concerted $_{\sigma}2_a + _{\pi}2_a$ cycloaddition between the double bond at C4-C5 and the sigma bond at C1-C6, within a Hückel-system. This explanation, however, seems unlikely due to the orbital overlap required for such a process to occur. Doubly antarifacial cycloadditions are rare due to this bad overlap and, in this case, the interacting orbitals are held at a distance from one another making this simultaneous bond formation even more unfavourable. Indeed, it may be that this ODPM rearrangement occurs as a stepwise process and that it is geometrical restrictions which lead to the stereoselectivity observed.

It is our belief that the formation of the fused ring system (**12**), may also be rationalised by the stepwise mechanism depicted in Scheme 8. This type of rearrangement is known to occur in 2,5-cyclohexadienone systems and was first rationalised by Zimmerman and Schuster.[19] The transformation can be considered as a photoinduced Nazarov cyclisation, which is then followed by a [1,4]-sigmatropic shift to form intermediate (**12**). The stereoselectivity observed in the process can be attributed to the concerted nature of the initial cyclisation reaction.[20]



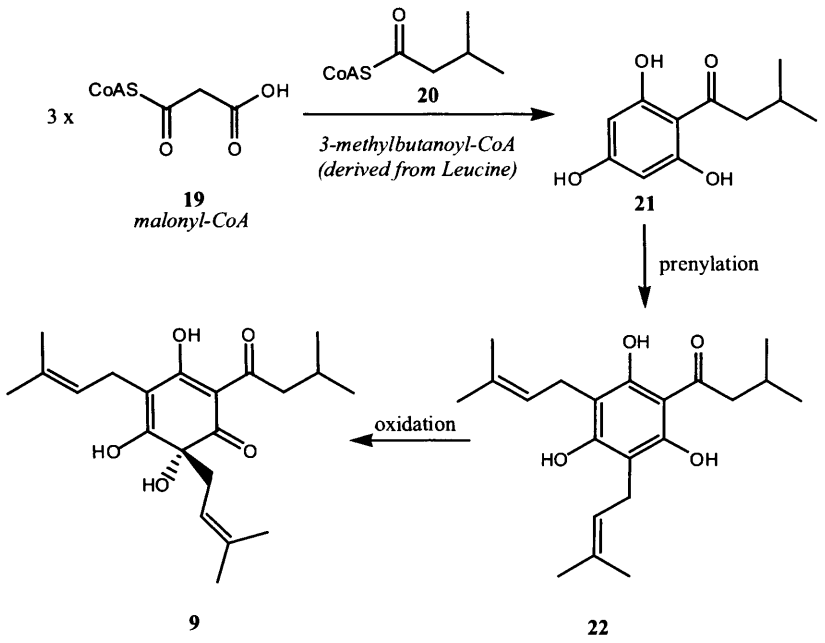
9d **17** **18** **12**

Scheme 8

1.32 Biosynthesis Of (-) Humulone (9).

Since it has been established that the isohumulones (**1**) present in beer originate from the natural product (-) humulone (**9**) the biosynthesis of this compound is also worthy of some discussion in this introduction.

The evolution of (-) humulone (**9**) during the ripening of hops has been studied in some detail[21] and the compound is thought to originate from sequential prenylation and oxidation of phloroisovalerophenone (**21**) (Scheme 9) which is, in turn, formed by the cyclisation of the open chain polyketide derived from the head to tail connection of three units of acetyl-CoA (**19**) and one of 3-methylbutanoyl-CoA (**20**).[22] The prenyl residues incorporated during the synthesis are produced from acetic acid along a pathway involving acetylcoenzyme A and mevalonic acid. It appears that the regiospecific hydroxylation of the intermediate deoxyhumulone (**22**) in the final step of the sequence also occurs in an enantiospecific manner in as much as only (*R*)-(-)-humulone (**9**) is produced in hops.[1]



Scheme 9

1.4 Reactivity Of The Isohumulones (1).

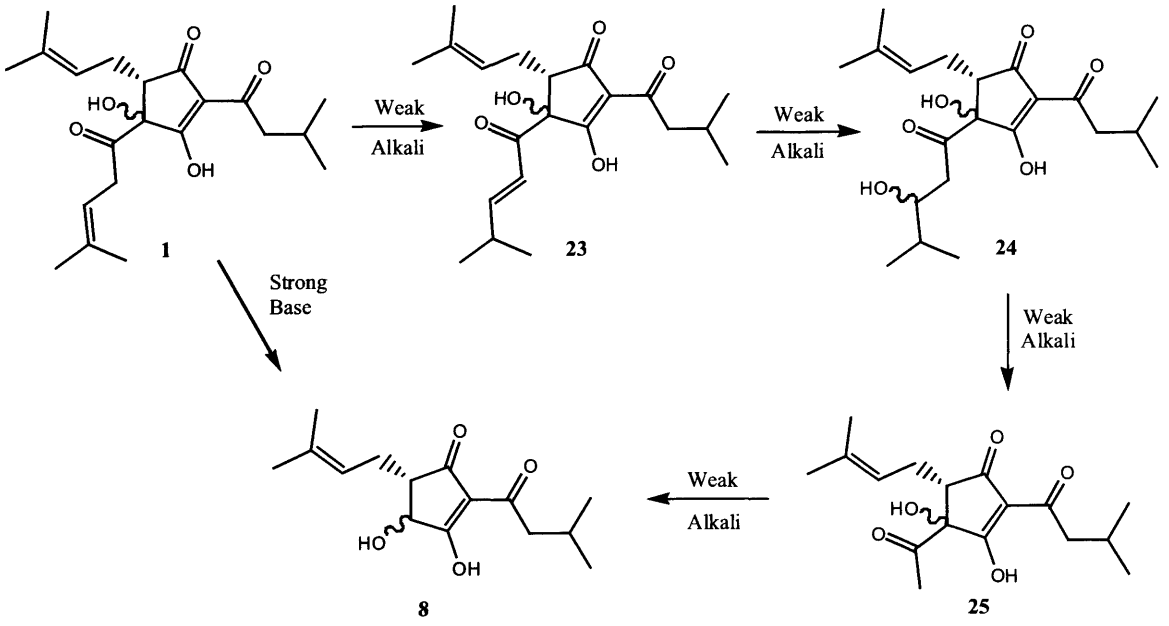
As a consequence of extensive research the synthesis of the isohumulones (**1**) from humulone (**9**) can now be considered as a well developed and simple process, however, the storage of the compounds (**1**) once they have been produced is not so trivial. The isohumulones (**1**) are relatively unstable and undergo decomposition readily.

A study of this problem carried out by H.A. Thorton *et al.*[23] determined that an effective means of storing the isohumulones (**1**) is as their dicyclohexylamine salts which are crystalline and can be kept without decomposition. Another benefit of utilising these salts was discovered when it was shown that the *trans*-isohumulone dicyclohexylamine salt could be selectively precipitated from a mixed solution of the two diastereomers. This procedure can, therefore, be employed as a simple method of isolating both pure *cis* and *trans*-isohumulone (**1a, 1b**).

1.41 Reactions Of The Isohumulones (1) Under Basic Conditions.

It has been established that, even in the formation of the isohumulones (**1**) from humulone (**9**), the compounds (**1**) are prone to degradation. The isohumulones (**1**) are particularly unstable under strongly basic conditions and can be converted directly to the humulinic acids (**8**) (Scheme 10).[24]

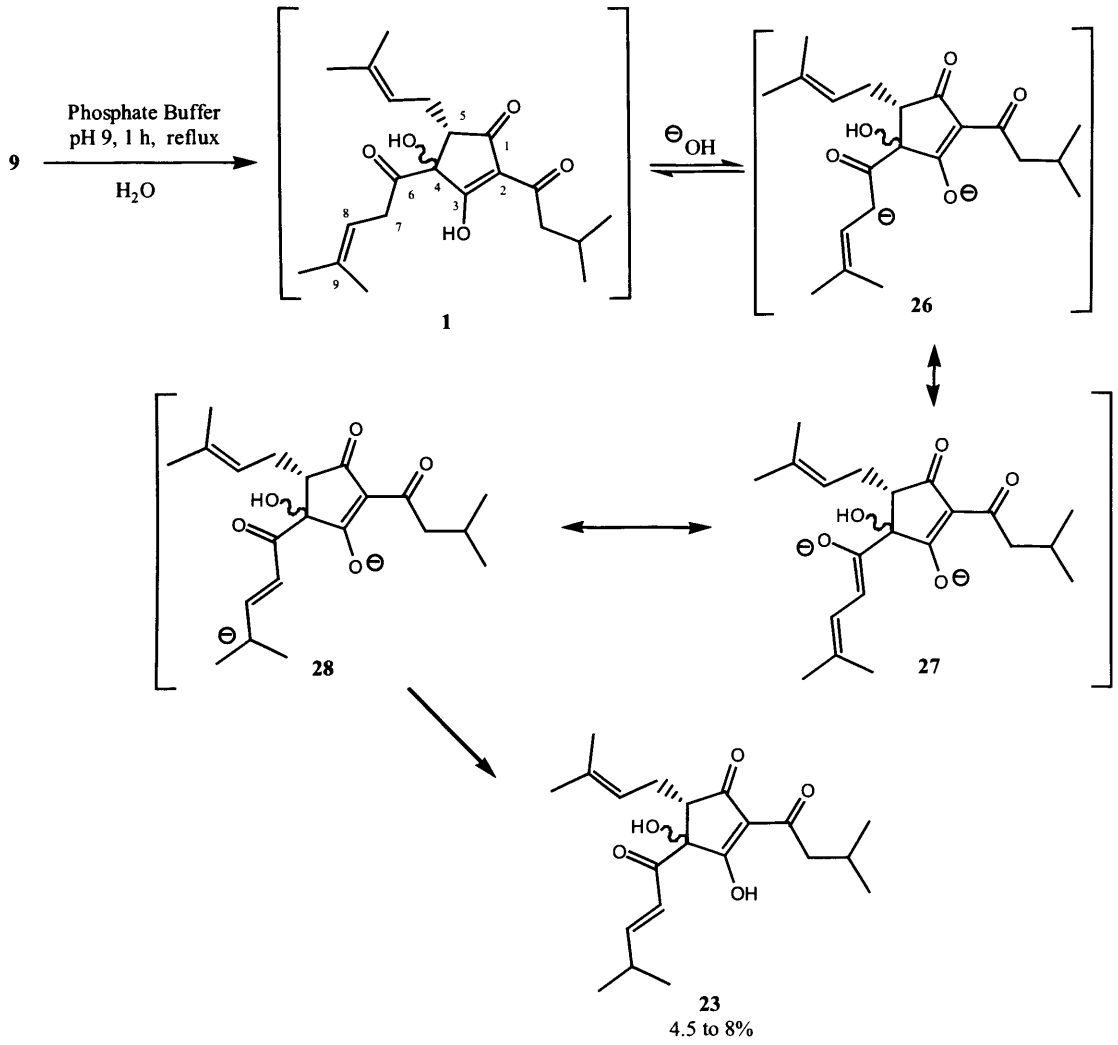
Under weakly basic conditions the isohumulones (**1**) carry out this transformation in a stepwise fashion and all of the intermediates (**23**, **24**, **25**) leading to the production of the humulinic acids have been isolated and characterised (Scheme 10).[1, 14, 25]



Scheme 10

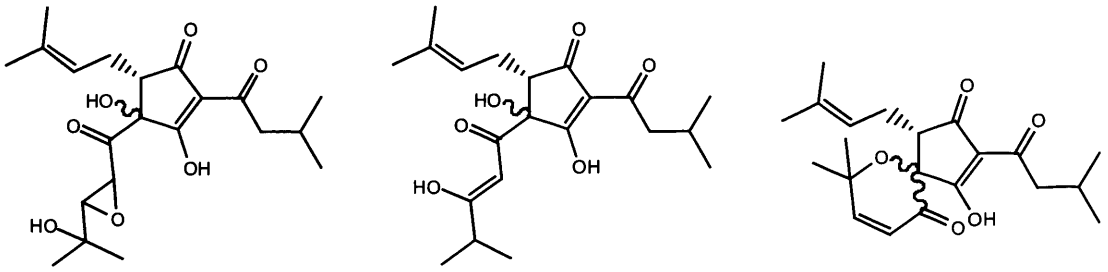
This reaction cascade commences with the base induced isomerisation of the double bond at C8-C9 of the isohumulones (**1**) to form the allo-isohumulones (**23**). The isohumulones (**1**), generated *in situ* by boiling humulone (**9**) in an alkali buffer solution, are doubly deprotonated (**26**) under these conditions and undergo rearrangement, forming the conjugated dianion species (**27** ↔ **28**). Quenching of this dianion produces some allo-isohumulones (**23**) as the thermodynamic product of the reaction (Scheme 11).[1, 14]

It must be noted that, in the production of isohumulone (**1**) from humulone (**9**), impurities arising from this double bond isomerisation process can be minimised by careful monitoring of reaction time and temperature.



Scheme 11

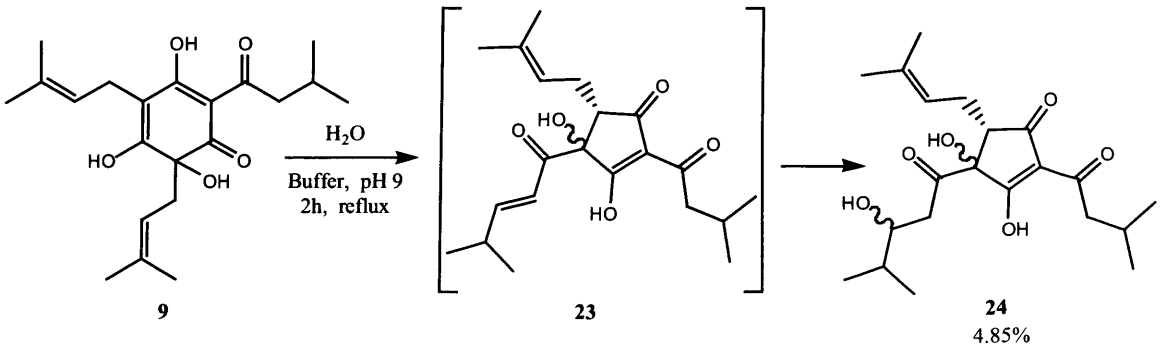
The low yield of the allo-isohumulones (**23**) which can be obtained[14] (Scheme 11), is not only due to the further reaction of these compounds (**23**) *en route* to the formation of the humulinic acids (**8**) (Scheme 10) but can also be attributed to the susceptibility of the α-hydroxy carbonyl side chain to numerous oxidative side reactions. Thus, the epoxides (**29**)[26] along with the 1, 3-acyclic dicarbonyl compounds (**30**)[1] and the spiro compounds (**31**)[1] have all been detected in the reaction mixture (Fig. 3).



29 **30** **31**

Fig. 3

Extending the reaction times under these conditions facilitates the production of the hydrated allo-isohumulones (**24**). These compounds, which originate from the 1,4 addition of water to the α,β-unsaturated carbonyl unit present in the allo-isohumulones (**23**), have been isolated but are not very well characterised since they are also unstable (Scheme 12).[1, 25]

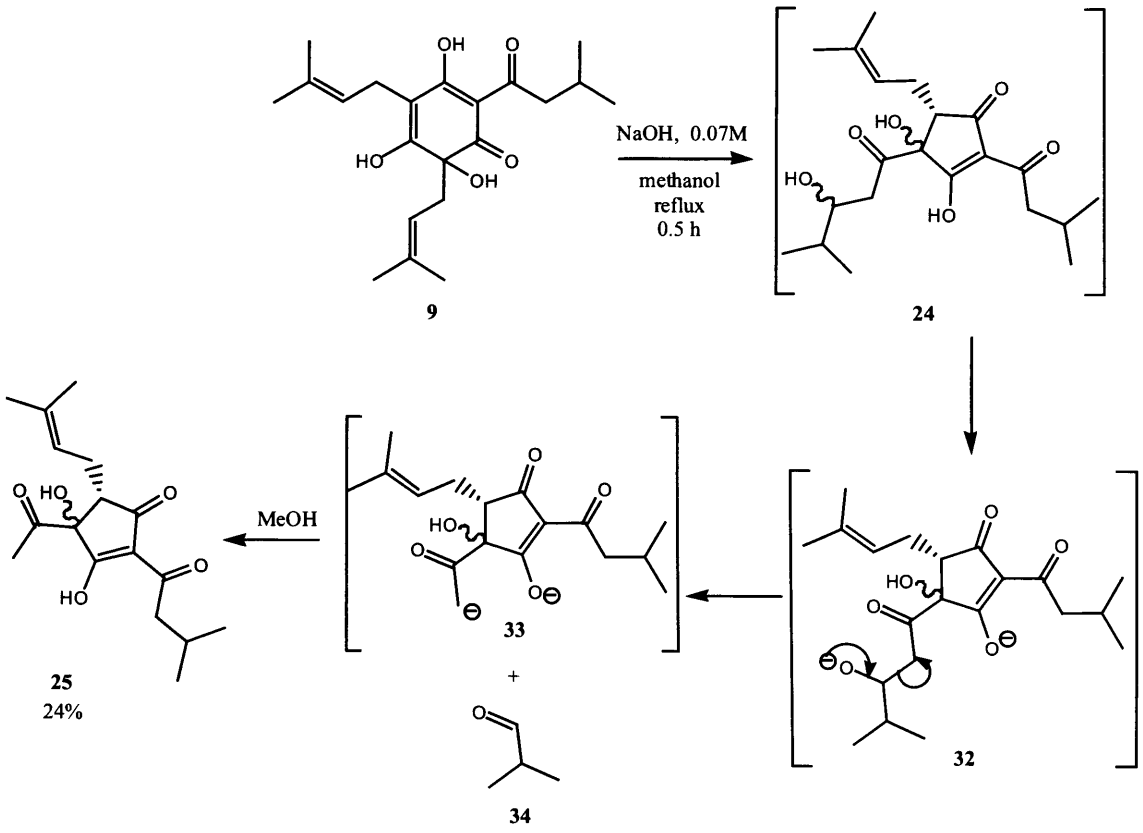


9 **23** **24**
4.85%

Scheme 12

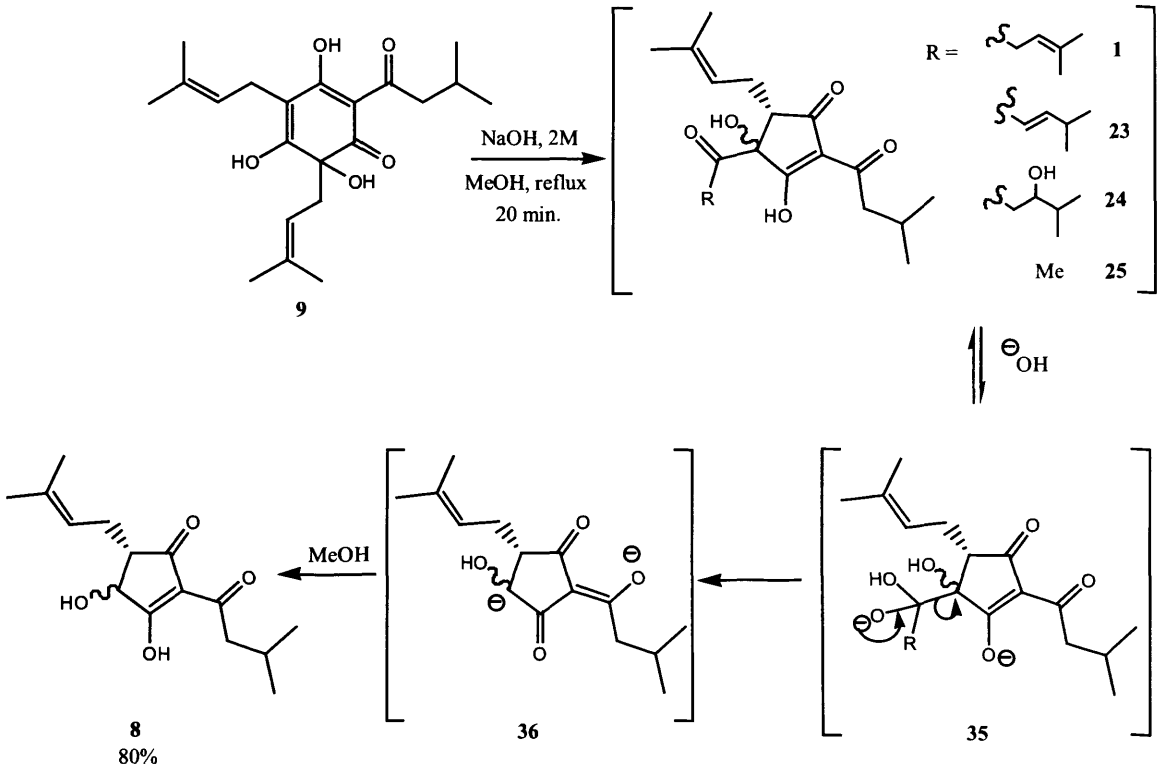
By heating humulone (**9**) under more basic conditions it is possible to isolate yet another degradation product from the reaction, the acetylhumulinic acids (**25**). It has been proposed that these compounds (**25**) are derived from the hydrated allo-

isohumulones (**24**) which perform a retro-aldol reaction (**32**) to produce the acetylhumulinic acids (**25**) in a yield of 24% (Scheme 13).[1]



Scheme 13

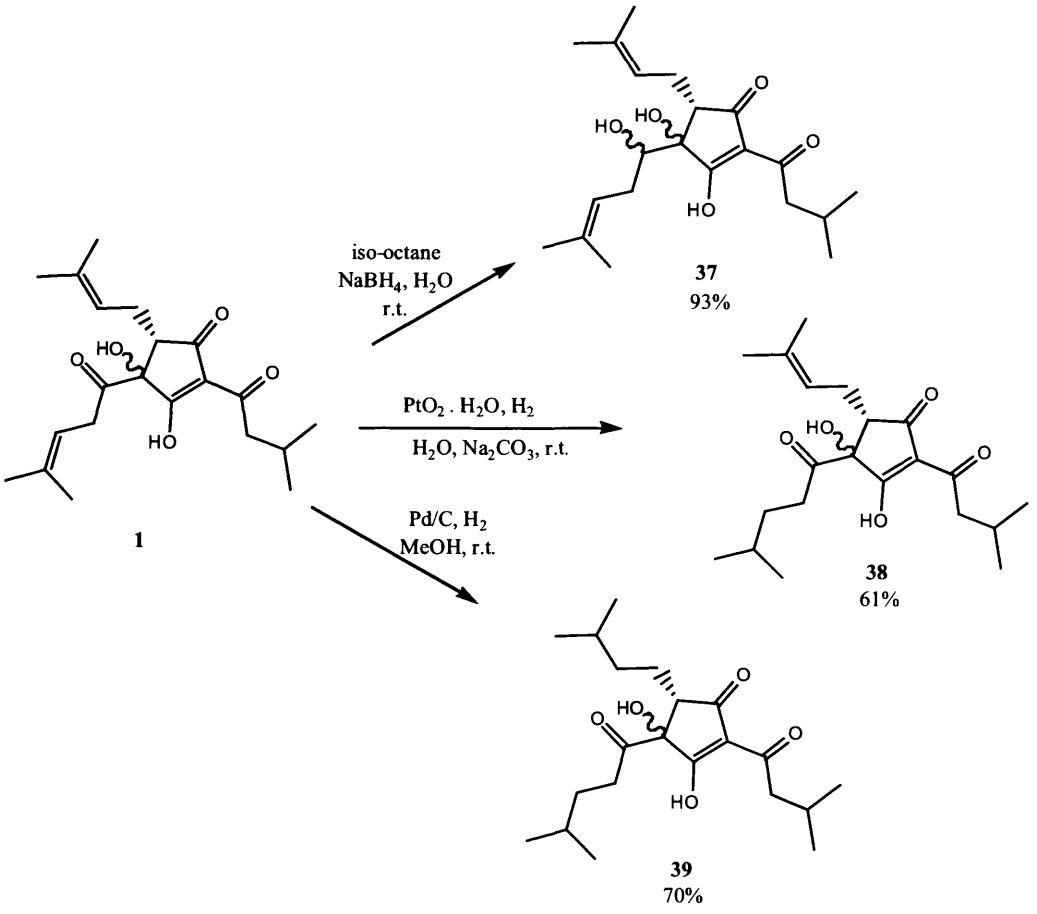
Indeed, direct conversion of the isohumulones (**1**) to the humulinic acids (**8**) can also be achieved under these strongly basic conditions.[24] The mechanism proposed for this reaction commences with the nucleophilic attack of a hydroxide anion on the carbonyl at C6 of either the isohumulones (**1**) or another intermediate generated in the reaction solution (**23-25**). Elimination of a carboxylic acid fragment from the tetrahedral intermediate (**35**) produces the dianion (**36**), which leads to a mixture of the *cis* and *trans* humulinic acid (**8**) (Scheme 14).[1]



Scheme 14

1.42 Reduction Of The Isohumulones (1).

Along with the selection of different compounds (**8, 23-25**) that can be generated from the isohumulones (**1**) under alkaline conditions a number of synthetic derivatives have also been formed by the reduction of these iso-α-acids (**1**). Hydrogenation of the isohumulones (**1**) can yield either the dihydro-isohumulones (**38**) or the tetrahydro-isohumulones (**39**),[27] whilst treatment of the compounds (**1**) with sodium borohydride leads to selective reduction of the carbonyl group at C6, producing the rho-isohumulones (**37**)[28, 29] (Scheme 15). The latter reaction presumably occurs in a chemoselective fashion as a consequence of protection of the 2-acyl-cyclopentane-1,3-dione unit as an anion under the basic borohydride conditions.



Scheme 15

1.5 Photodegradation Of The Isohumulones (1).

Thus far in this introduction the many and varied functions that the isohumulones (**1**) perform in beer have been discussed (Section 1.2), along with the inherent chemical reactivity of these compounds (**1**) (Section 1.4). It is, in fact, both these aspects that make the isohumulones (**1**) so problematic to the brewing industry. Their chemical lability means that they undergo a photodegradation reaction upon irradiation with light in the presence of a sulfur source to form the unpleasant 3-MBT (**2**) (Section 1.1), whilst the many beneficial roles that the isohumulones (**1**) play in beer mean that this problem cannot be solved by simple removal of the compounds (**1**) from the product.

In the present work we hoped that a solution to this conundrum lay in a better understanding of the chemical and photochemical mechanisms involved in the reaction itself.

Detailed examination of the literature revealed that the offending odour and taste that beer develops when exposed to sunlight was first attributed to the photolysis of the iso-α-acids (**1**, **4**, **5**) and the production of the thiol, 3-MBT (**2**), in the seminal work of Kuroiwa.[30, 31] Subsequent synthesis of the thiol (**2**) and comparisons with beer samples[2] along with gas chromatography studies of irradiated beer[32] have proven unequivocally that this mercaptan (**2**) is the cause of the "sunstruck flavour" in the drink. The presence of 3-MBT (**2**) in the beer is appreciable in quantities as small as a few parts per trillion (with maximum concentrations of 10^{-3} ppm)[1, 7] and its production can be attributed to the degradation of only a very small percentage of the isohumulones (**1**) present in the beverage. The reaction can occur on storage of the product in glass bottles under bright light and the effect can be detected after standing a glass of beer in direct sunlight for 0.5 hours. The degradation process does not occur considerably, however, when the beverage is stored in brown bottles due to the filtering of the light through the glass.

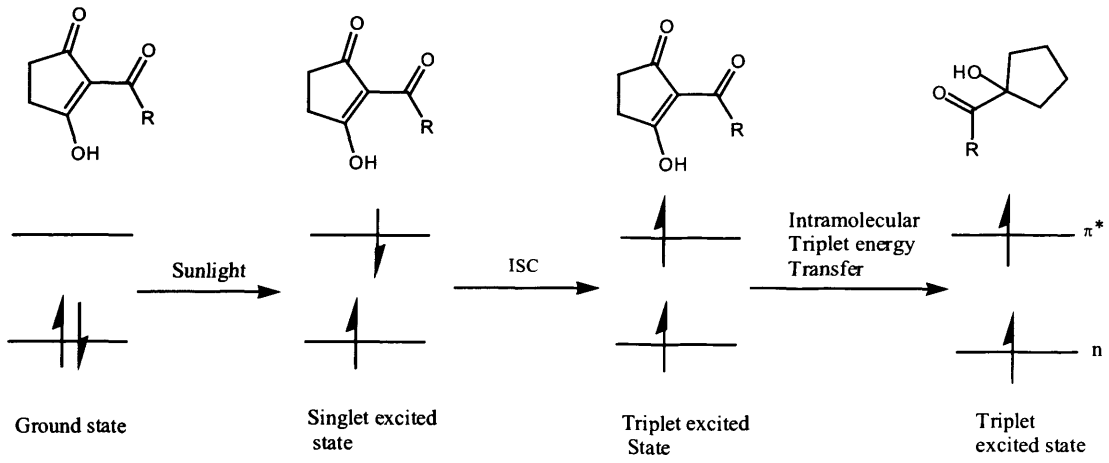
1.51 Current Postulated Mechanism.

The mechanism leading to the production of 3-MBT (**2**) and methods to suppress its formation have not been well researched in the past[2, 33-37] and there has been little progress towards finding a solution to this problem which is both effective and natural, the ideal for beer manufacturers.

Nevertheless, the fact that irradiation of an isolated sample of the isohumulones (**1**) in the presence of a sulfur source is, in itself, enough to facilitate the production of 3-MBT suggests that the reaction follows a radical mechanism, perhaps involving the homolytic cleavage of the C4-C6 bond of the α-hydroxyketone moiety present in the compounds (**1**). It is thought unlikely that the carbonyl group of the α-hydroxyketone unit could absorb energy directly from sunlight to undergo this fission, since previous research[38, 39] has shown that such chromophores require short wavelengths of light (340 nm and below) to be cleaved photochemically.

A more plausible mechanistic proposition has been put forward by C. S. Burns *et al.*[34] as a result of time-resolved electron paramagnetic resonance studies and computer modelling of the reaction. The photodegradation process is thought to begin with

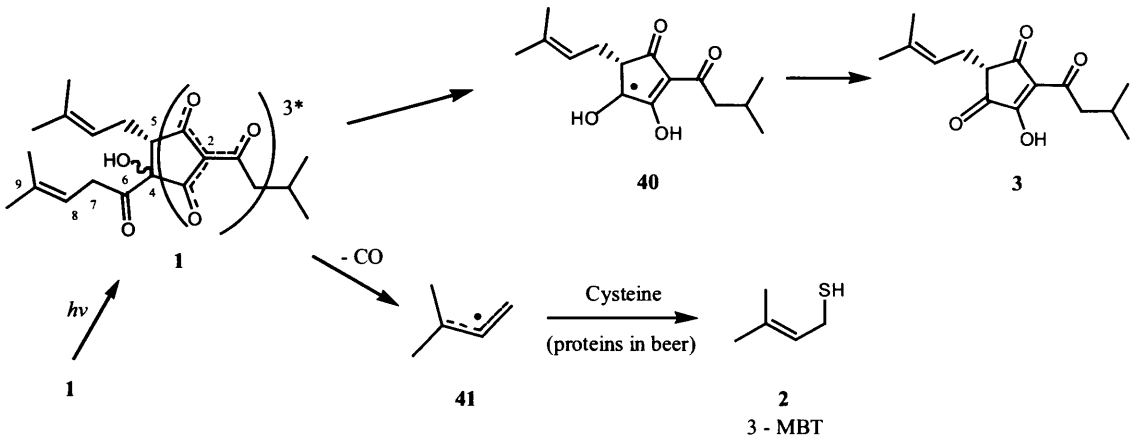
excitation of an electron in the 2-acylcyclopentan-1,3-dione system of the isohumulones (**1**). This initial singlet excited state, with the electrons spin paired in their orbitals, then undergoes intersystem crossing, producing a spin parallel triplet excited state (Scheme 16).



Scheme 16

At this point, transfer of energy is thought to occur intramolecularly from the triplet excited state of the tricarbonyl unit present in molecule (**1**) to the α-hydroxyketone functionality (C4-C6), leading to the promotion of an electron from an n to a π^* orbital in the ketone of this moiety (Scheme 16).

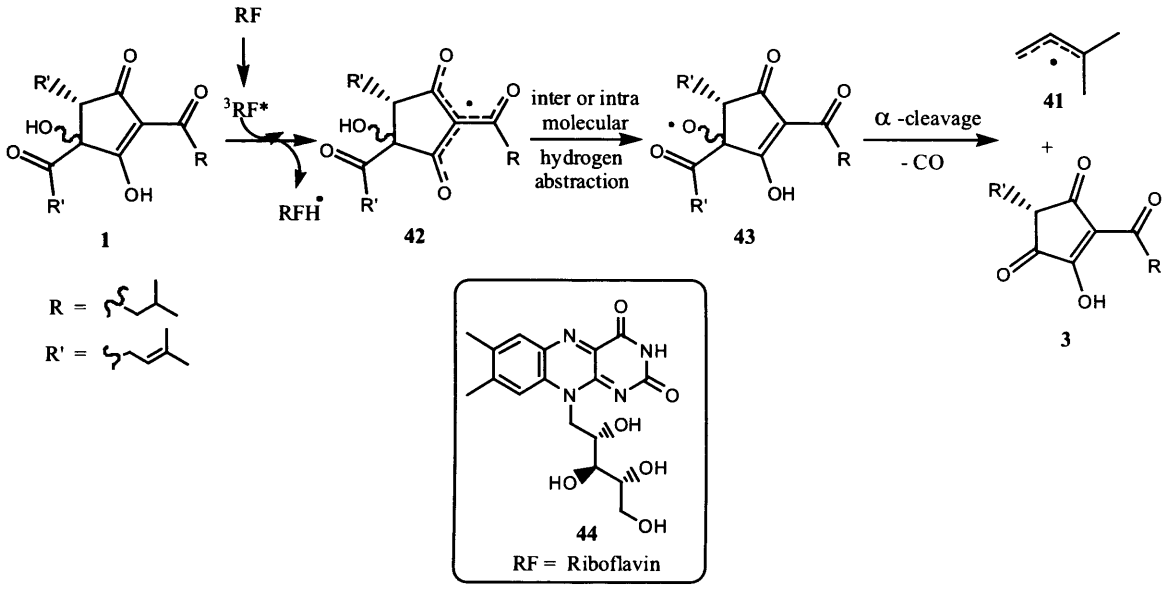
Excitation of this carbonyl group then induces a Norrish type I[40] homolytic cleavage of the C4-C6 bond to give two radical species (**40**, **41**) with concomitant loss of carbon monoxide (Scheme 17). The first radical species (**40**) produced during this process undergoes a further oxidative step forming dehydrohumulinic acid (**3**), which causes no further problems in the beer since it is a compound already present in the drink. The allylic radical (**41**) which is also generated, however, then goes on to combine with a sulfur source, to produce the 3-MBT (**2**) (Scheme 17). It is generally agreed that in beer the sulfur incorporated into the product (**2**) originates from protein residues found in the drink and in the model studies this role was fulfilled by cysteine.[34, 35]



Scheme 17

In fact, it has been suggested that in beer a photosensitiser also plays some role in this photodegradation process. To investigate this hypothesis K. Huvaere *et al.*[37] have recently carried out time-resolved electron paramagnetic resonance studies, using riboflavin as a photosensitiser in model reactions. Results of the preliminary investigations in this area have led to the suggestion that the triplet excited photosensitiser may facilitate the production of the alkoxyl radical (**43**) and that it is subsequent cleavage of this species which produces the allylic radical (**41**), as shown in Scheme 18. This theory, however, is still very much in its infancy and, in our view, seems questionable. If a stable tricarbonyl based radical such as (**42**) were formed in the reaction it seems highly unlikely that this species would then abstract a hydrogen atom to form an unstable alkoxyl radical (**43**), in a process which would be extremely energetically unfavourable.

Within the brewing industry, it is the mechanism shown in Scheme 17 which is generally invoked to account for the production of 3-MBT (**2**) in beer.



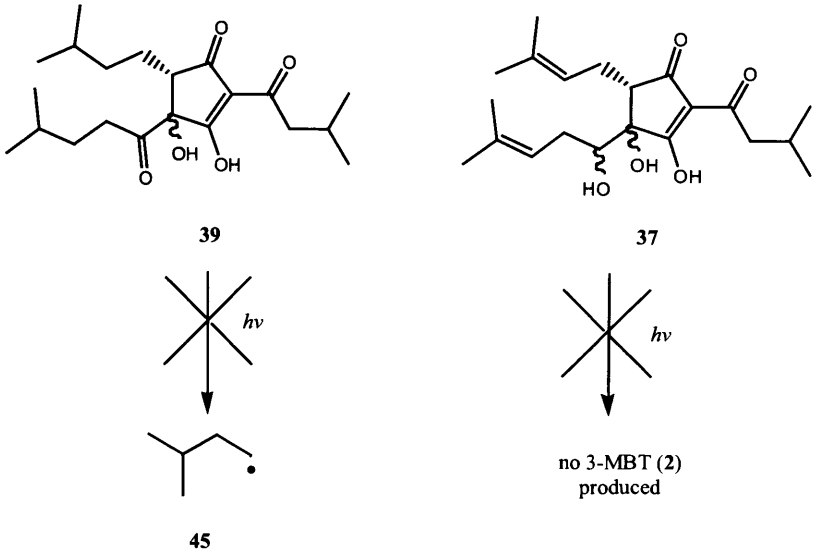
Scheme 18

The "mechanisms" postulated in Scheme 17 and Scheme 18 have not generally been well researched. Apart from the results obtained from these time-resolved electron paramagnetic resonance studies all that is known definitively is that the isohumulones (**1**) in beer decompose upon irradiation with light to produce the two compounds, 3-MBT (**2**) and dehydrohumulinic acid (**3**), accompanied by the evolution of carbon monoxide.[35]

1.52 Evidence To Support The Postulated Mechanism.

Other experiments carried out relating to the "sunstruck flavour"[41, 42] have uncovered some interesting results which support, at least to a certain degree, the "mechanisms" currently postulated for the reaction (Scheme 17, Scheme 18).[34, 37] Thus, It has been established that removal of the β,γ-unsaturated double bond (C8-9) in the isohumulones (**1**), producing the tetrahydro-isohumulones (**39**), stops the degradation reaction completely (Scheme 19).[41] Presumably, the alkyl radical (**45**) which would be produced by homolytic cleavage of the C5-C6 bond in this compound (**39**) is much less stable than the allylic radical usually formed (**41**), thus making the reaction pathway less energetically favourable. Likewise, reduction of the carbonyl group (C6) of the α-hydroxyketone unit of the isohumulones to an alcohol, producing the rho-isohumulones (**37**), also has the effect of stopping the photodegradation reaction completely (Scheme

19).[42] Again this observation lends support to the postulated mechanism since carbonyl group photochemistry with loss of carbon monoxide and formation of a stabilised allylic radical (**41**) cannot occur.



Scheme 19

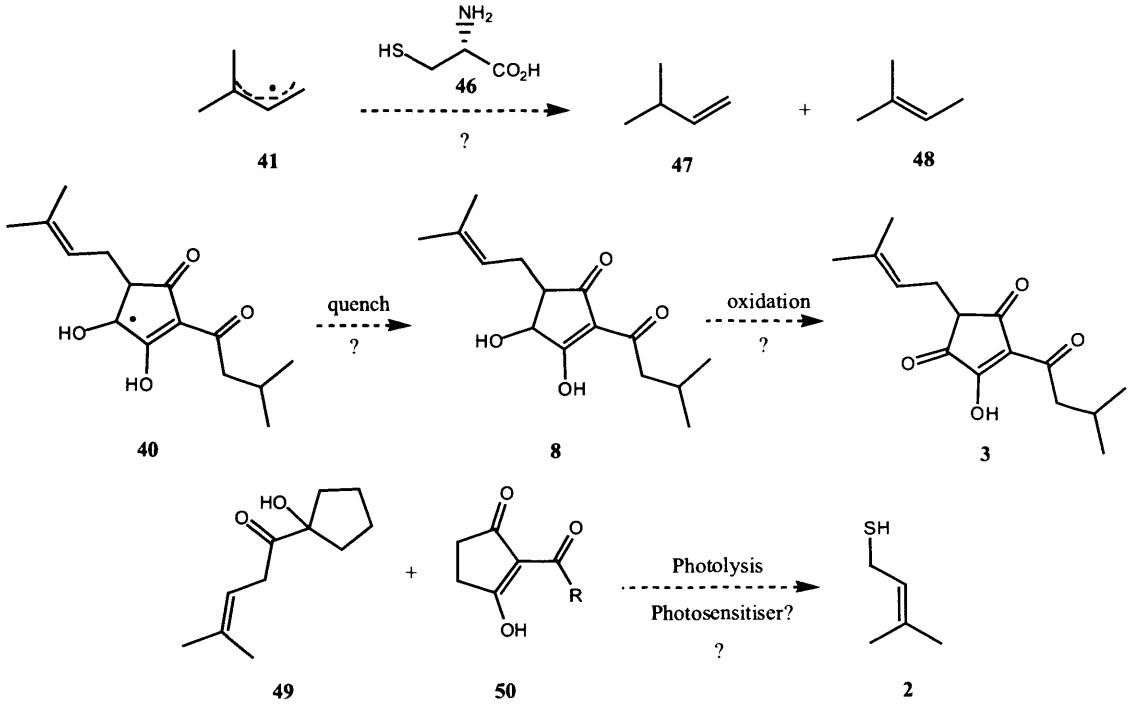
Although alteration of the isohumulone molecule in both of the aforementioned ways prevents the problematic photodegradation reaction from occurring, neither of these transformations are viable methods for the eradication of the "sunstruck flavour" from beer since slight changes in the isohumulone structure have a large effect on the intrinsic characteristics of the molecules produced (**37**, **39**). For example, the tetrahydro-isohumulones (**39**) are less bitter than the isohumulones (**1**) and this has a significant effect on the taste of the beer if they are substituted for the isohumulones (**1**) during the brewing process.

The brewing industry also shun such modified compounds (**37**, **39**) because they are not "natural" and so would either have to be produced, in some manner, from the isohumulones (**1**) present in beer, or put into the drink as synthetic additives. Although some beers are currently brewed with a pre-isomerised hop extract that has been reduced with sodium borohydride to form the rho-isohumulones (**37**),[43] this approach is not appealing to most beer manufacturers in a market where a "natural" product is extremely important.

1.53 Questions Remaining About Current Postulated Mechanism.

Even when the evidence in support of the proposed "mechanisms" for the photodegradation reaction of the isohumulones (**1**) (Scheme 19) is taken into account there are still a number of fundamental questions which remain unanswered.

For example, the fact that 3-MBT (**2**) can be produced by irradiation of an isolated sample of the isohumulones (**1**) in the presence of cysteine has already been discussed. Even from the most simplistic mechanistic standpoint, it is apparent that a thiol such as cysteine *per se* is not acting as a trap for the allylic radical (**41**), since hydrogen atom capture from a mercaptan by a carbon centred radical is one of the most efficient radical reactions known.[44, 45] In the present instance such a reaction would lead to the formation of the alkenes (**47**) and (**48**) (Scheme 20). Clearly the chemistry involved in this reaction is much more complex.



Scheme 20

There are also questions to be raised over the role that a photosensitiser plays in this reaction. Little research[36, 37] has been carried out into the effects of different photosensitisers on the photodegradation reaction of the isohumulones (**1**) in the presence of a sulfur source and the recent research in this area carried out by K.

Huvaere *et al.*[37] has already challenged the perceived "mechanism" of the reaction (Scheme 18).

Furthermore, a problem presents itself in terms of evolution of dehydrohumulinic acid (**3**) from the radical intermediate (**40**). Although it has little effect on beer quality, this transformation requires some explanation since production of dehydrohumulinic acid (**3**) from the α-hydroxy radical (**40**) would require some kind of oxidative process. One plausible explanation is that the humulinic acids (**8**) are formed initially from radical (**40**) by hydrogen atom capture and these compounds are then oxidised in the reaction medium to dehydrohumulinic acid (**3**) (Scheme 20). Obviously, the recently proposed alkoxyl radical based "mechanism",[37] shown in Scheme 18, could also explain the oxidation which is observed at this centre, but only when the reaction occurs upon interaction with a photosensitiser.

Finally, the transfer of energy from the 2-acylcyclopentane-1,3-dione moiety of the isohumulones (**1**) to the carbonyl group of the α-hydroxyketone unit (C4-C6) during the photodegradation reaction poses a number of questions. In the absence of a photosensitiser it is thought that the triplet energy transfer occurs in an intramolecular process. However, the only reasoning for this is based on the proposition that triplet state energy transfer is slow between two different molecules in solution.[34] Investigations into the photolysis of simple α-hydroxyketones such as (**49**) in the presence of molecules containing a similar tricarbonyl chromophore to that found in the isohumulones (**50**) may, therefore, provide more definitive answers about this transfer of energy (Scheme 20).

1.6 Previous Synthetic Approaches To The Isohumulones (1) And Their Analogues.

As explained previously (Section 1.1), during this research we aim to answer some of the many questions surrounding the mechanism of the photodegradation reaction of the isohumulones (**1**) by carrying out investigations into the effect of irradiating synthetic analogues of the molecules (**1**) with natural light. A necessary prerequisite for this study

is, of course, that viable synthetic routes to the model compounds required will first have to be developed.

There has been little research into the direct synthesis of the isohumulones (**1**) due to the reactive nature of the compounds (Section 1.4) and in the fifty years since they were first isolated only one remarkable but low yielding total synthesis of the molecules (**1**) has been reported in a paper published by P. R. Ashurst and D. R. J. Laws in 1966.[46]

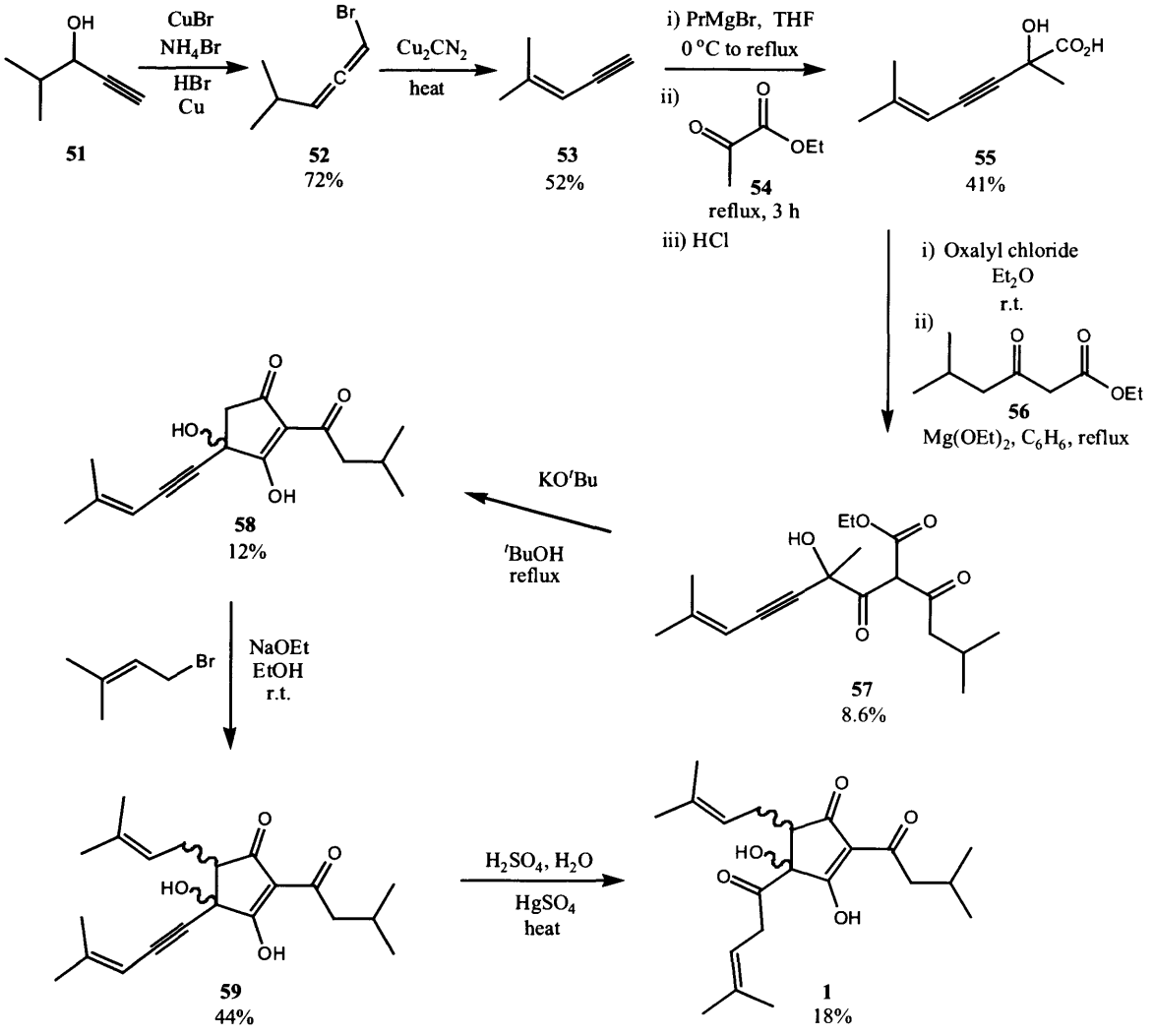
This wonderfully unusual synthesis begins with the preparation of the reactive allene, 1-bromo-4-methylpenta-1, 2-diene (**52**) from 4-methylpent-1-yn-3-ol (**51**). A 1,4-elimination reaction of this allene (**52**) in the presence of copper (I) cyanide then produces 2-methyl-2-penten-4-yne (**53**) and addition of the acetylide anion of this conjugated enyne (**53**) to ethyl pyruvate (**54**), followed by hydrolysis affords the carboxylic acid (**55**) in moderate yield (Scheme 21).

With this functionalised alkyne (**55**) in hand the authors must have found it incredibly disheartening, at such an advanced stage in the route, to discover an extremely inefficient conversion in the next step of the sequence. Thus, formation of an acid chloride from the carboxylic acid (**55**) followed by addition of ethyl-5-methyl-2-oxohexanoate (**56**) to this intermediate in the presence of magnesium ethoxide produced the polyoxygenated alkyl chain (**57**) in a yield of only 8.6%.

Amazingly, heating (**57**) under basic conditions induced a remarkable intramolecular cyclisation, producing the functionalised cyclopentane (**58**), again, in a disappointingly low yield. This peculiar transformation is extremely hard to rationalise, since it has no direct literature precedent and, we feel, no apparent logical mechanism. The authors do not suggest a reasonable explanation of this key reaction and merely comment that the cyclisation is achieved, albeit in low yield.

After such a strange reaction, production of the racemic isohumulones (**1**) was finally accomplished by prenylation of the oxygenated cyclopentane (**58**) with 1-bromo-3-methyl-2-butene in the presence of sodium ethoxide, followed by mercury (II) catalysed hydration of (**59**), giving a mixture of products from which the iso-α-acid (**1**) was

isolated by thin-layer chromatography (Scheme 21). The overall yield of the total synthesis, starting from 2-methyl-2-penten-4-yne (**53**), amounts to only 0.03%.



Scheme 21

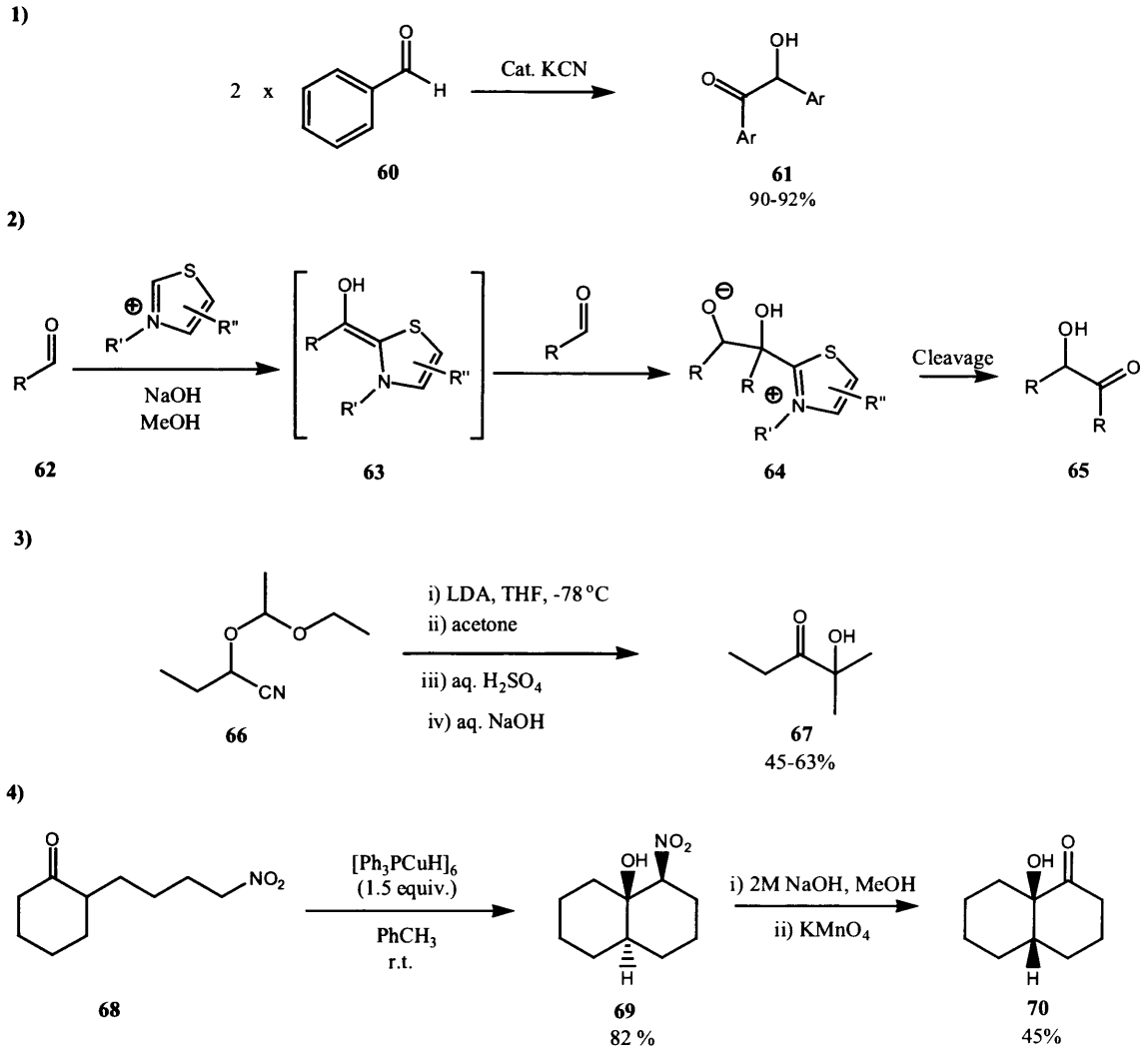
Although there has been little research into the synthesis of the isohumulones (**1**) themselves there is a considerable body of work on the synthesis of highly functionalised and oxygenated cyclopentanoids. Since the formation of some of these characteristic structural features will be necessary for the production of the isohumulone analogues required in our studies, a brief literature review of some relevant methodology is, therefore, appropriate.

1.61 Formation Of The α-Hydroxyketone Moiety.

It could be argued that, from our perspective, the most important functional group present in the isohumulones (**1**) is the α-hydroxyketone unit since it is, of course, the C-C bond of this moiety which breaks during the photodegradation reaction of the compounds (**1**).

In fact, a number of synthetic methods have been devised to form the carbon-carbon bond of such systems. Perhaps the oldest and best known of these reactions is the classical benzoin condensation which employs catalytic cyanide ions to couple two aromatic aldehydes (**60**) (Reaction 1, Scheme 22).[47, 48] Indeed, this work has subsequently led to the development of protocols using catalytic thiazolium salts in place of cyanide anion, in a process generally known as the Stetter reaction (Reaction 2, Scheme 22).[49, 50] Unfortunately, both these acyloin forming methods are limited by the fact that attempts to carry out cross coupling reactions can lead to product mixtures.

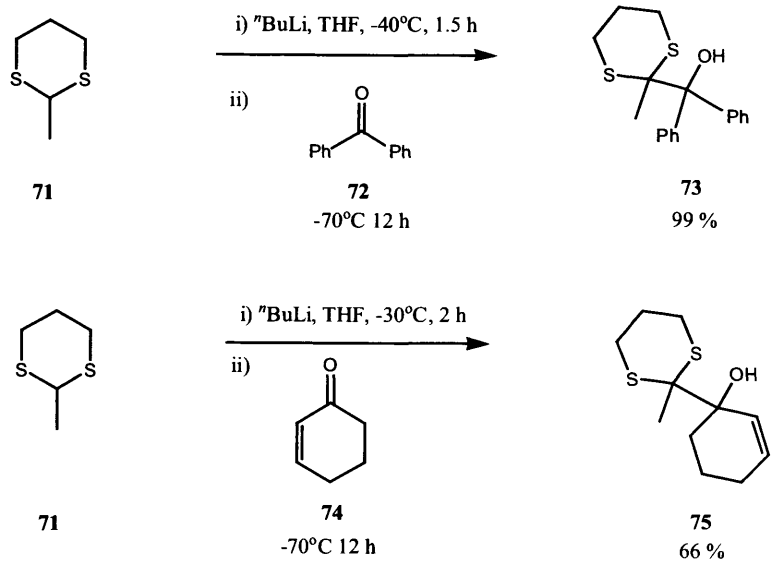
Chemistry developed by Stork,[51] also inspired by the benzoin condensation, alleviates this problem by employing preformed lithium derivatives of protected cyanohydrins (**66**) and has been used to produce the α-hydroxyketone moiety (**67**) (Reaction 3, Scheme 22).[52] Formation of the masked carbonyl substrates (**66**) employed in these reactions usually requires the use of stoichiometric quantities of toxic cyanide salts, and so this approach has its own disadvantages.



Scheme 22

Formation of an α-hydroxyketone unit in this way can also be carried out in two discrete steps and an unusual example of such a process is shown in Scheme 22 (Reaction 4). An intramolecular Henry reaction produces a vicinal nitro alcohol (**69**) and a subsequent Nef reaction then unmasks the acyloin moiety (**70**).[53]

Thioacetals have been widely used in organic synthesis as umpolung reagents due to their ability to function as acyl anion equivalents when treated with a strong base such as butyllithium.[54] 2-Lithio-1,3-dithiane derivatives have been the most broadly applied reagents in this area following the seminal work of Corey and Seebach.[55] This class of compound has been reacted with scores of electrophiles including alkyl halides,[55-59] epoxides,[59-62] electron poor olefins[59, 63, 64] in C-C bond forming reactions and, most importantly in the present context, with carbonyl compounds to create a protected α-hydroxycarbonyl moiety (**73**, **75**)[55, 59, 65, 66] (Scheme 23).

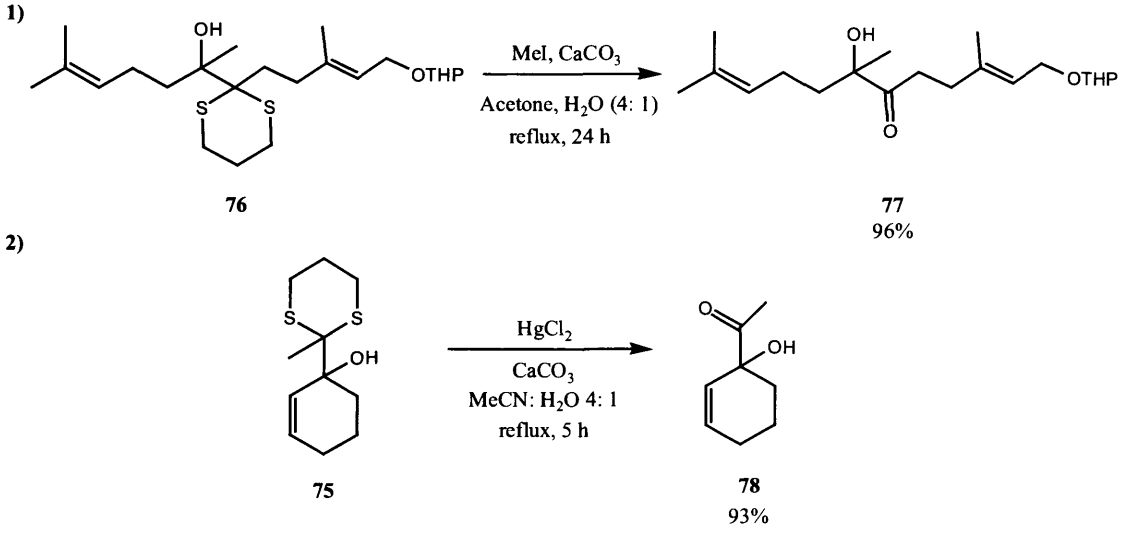


71 — 72 (-70°C 12 h) — 73 (99 %)

71 — 74 (-70°C 12 h) — 75 (66 %)

Scheme 23

Following this addition reaction many methods have been developed to hydrolyse this dithiane protecting group to unmask the required α-hydroxycarbonyl unit.[67-69] The reactions shown in Scheme 24 are illustrative of such protocols.



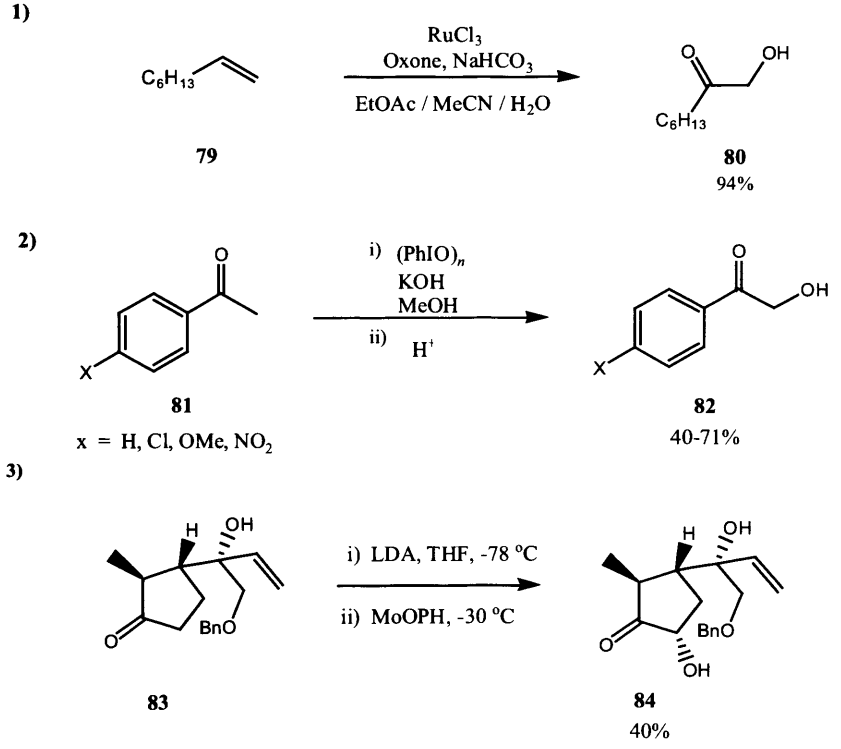
76 — 77 (96%)

75 — 78 (93%)

Scheme 24

Since the 1, 3-dithiane protecting group is stable to both acidic and basic conditions, numerous transformations can be carried out on protected intermediates before unveiling the α-hydroxyketone functionality in the final stages of a synthetic route. For all of the above reasons, the use of dithiane chemistry was considered to be particularly advantageous in our own studies.

Although, it is true that, in a lot of cases, the α-hydroxyketone unit is generated using C-C bond forming reactions it can also be constructed by employing oxidation protocols. Recently B. Plietker[70, 71] has utilised a ruthenium tetroxide catalyst in the oxidation of alkenes (**79**), a reaction which shows a high regioselectivity, which, unfortunately, is not currently easy to predict (Reaction 1, Scheme 25). Moriarty and co-workers[72, 73] have applied the oxidising capabilities of hypervalent iodine in the α-hydroxylation of carbonyl compounds (**81**) (Reaction 2, Scheme 25) and the molybdenum complex, oxidodiperoxymolybdenum (pyridine) (hexamethylphosphoric triamide) (MoOPH), has also been widely used in the formation of α-hydroxyketone containing compounds (**84**) from ketones (**83**) (Reaction 3, Scheme 25).[74-76] Regrettably, such methods of producing the acyloin moiety may present problems if applied to our chemistry. The regioselectivity of the ruthenium tetroxide reaction is not well understood and the ketone α-hydroxylation protocols rely on selective enolate anion formation to control the regiochemical outcome of the reactions.

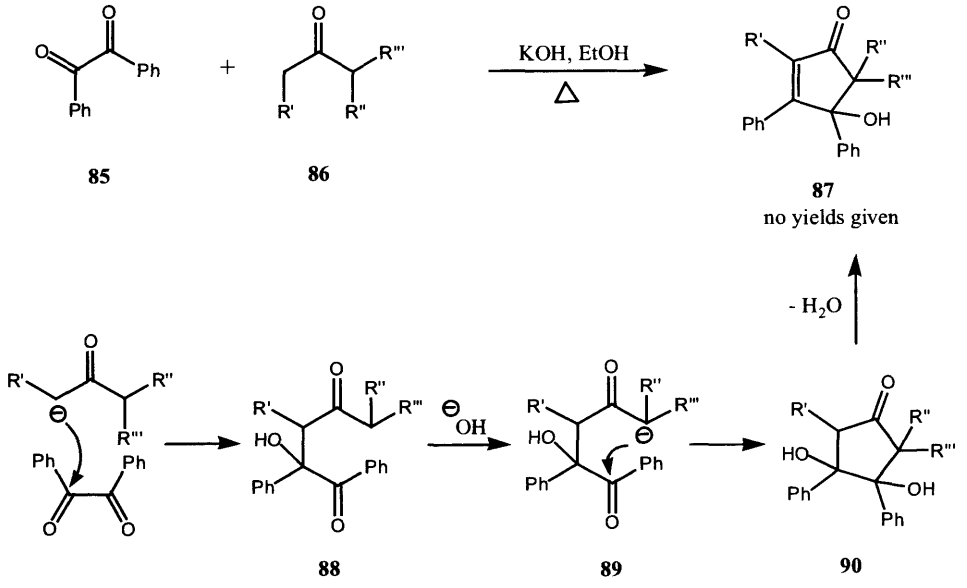


Scheme 25

1.62 Synthesis Of Cyclopentanoids.

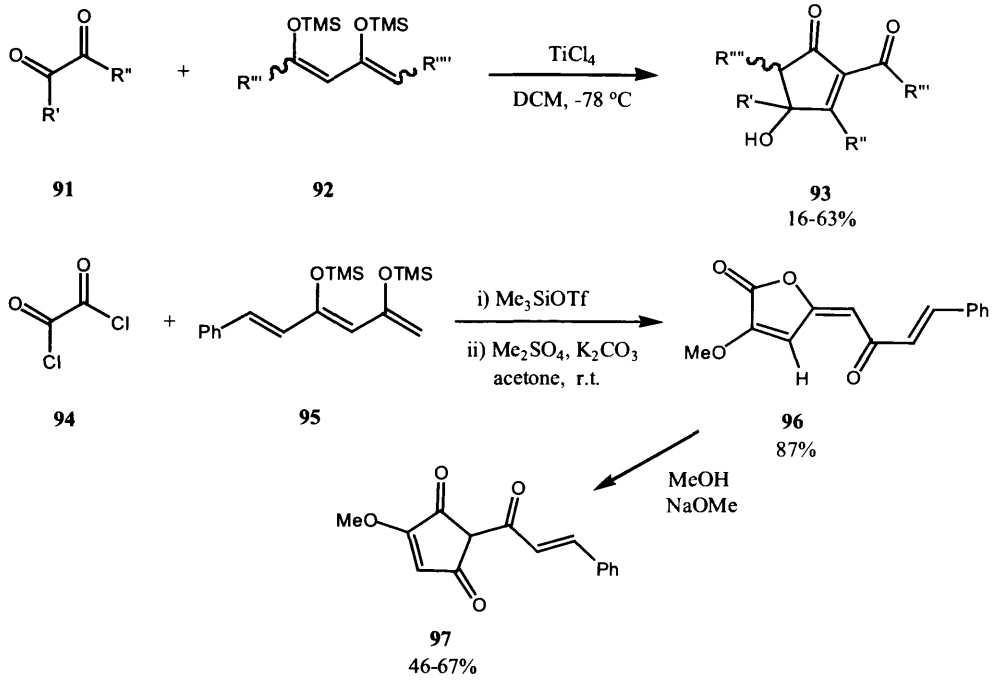
Although the α-hydroxyketone moiety is a crucial feature of the isohumulones (**1**), the chromophoric core of the structure (**1**) lies in the polycarbonyl cyclopentanoid unit around which the molecules (**1**) are based. The vast majority of approaches for the synthesis of such systems focus on the formation of an open chain polycarbonyl precursor followed by a final cyclisation. This process has been carried out in a stepwise fashion, as in the case of the total synthesis of the isohumulones (**1**) described previously (Scheme 21), or, more successfully, in a single pot by utilising dianion chemistry.[77-79]

Enolate anion mediated ring formation of this type was initially explored by Japp and co-workers, who investigated the reaction of the symmetric α-diketone, benzil (**85**), with various ketones (**86**) under strongly basic conditions, to produce 4-hydroxy-substituted cyclopentenones (**87**) (Scheme 26).[80-83] In most cases, ring formation is thought to proceed by two consecutive addition reactions, as illustrated in Scheme 26. However, in cases where the substrate ketone (**86**) possesses additional electron withdrawing substituents, the generation and reaction of a dianion in the transformation cannot be ruled out.



Scheme 26

This original work has been adapted and modernised in recent times, employing more selective bases and using masked dianion equivalents (**92**, **95**).[77-79] This chemistry has been used to produce 4-hydroxycyclopent-2-enones (**93**) (Scheme 27), which share many structural features with the polycarbonyl system of the isohumulones (**1**).[84] In conceptually similar fashion, the enol lactone (**96**) has also been formed and then rearranged to give lucidone (**97**) (Scheme 27).[85]



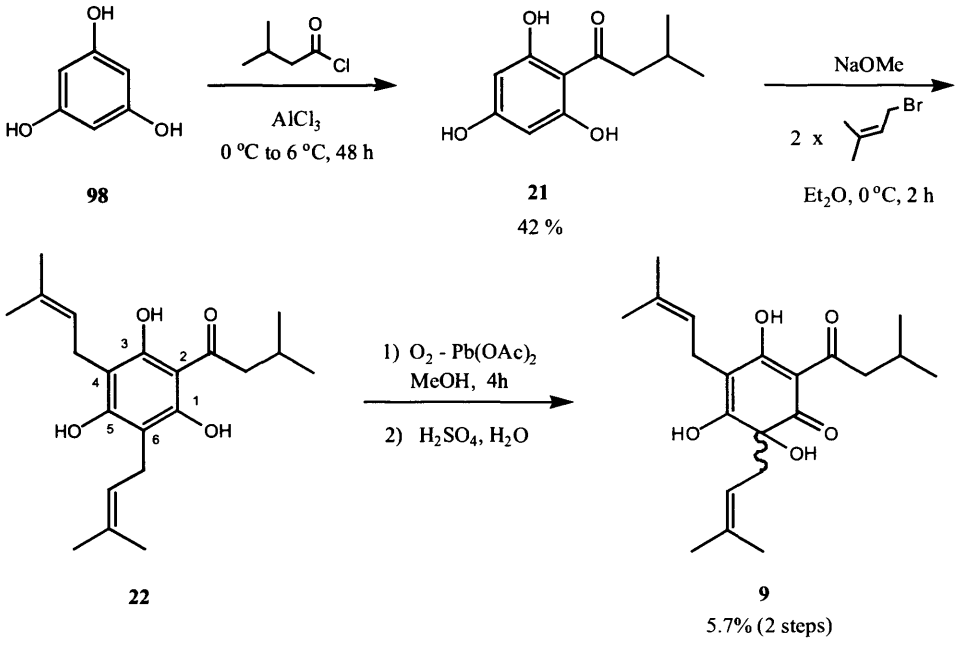
Scheme 27

1.63 Formation And Ring Contraction Of Humulone (9) And Its Analogues.

One very attractive method of producing all of the important functional groups present in the isohumulones (**1**) in a single step can be found in the ring contraction chemistry of humulone type systems. This biomimetic approach has often been used for the synthesis of both the isohumulones (**1**) [11-15] and their analogues.[86-89]

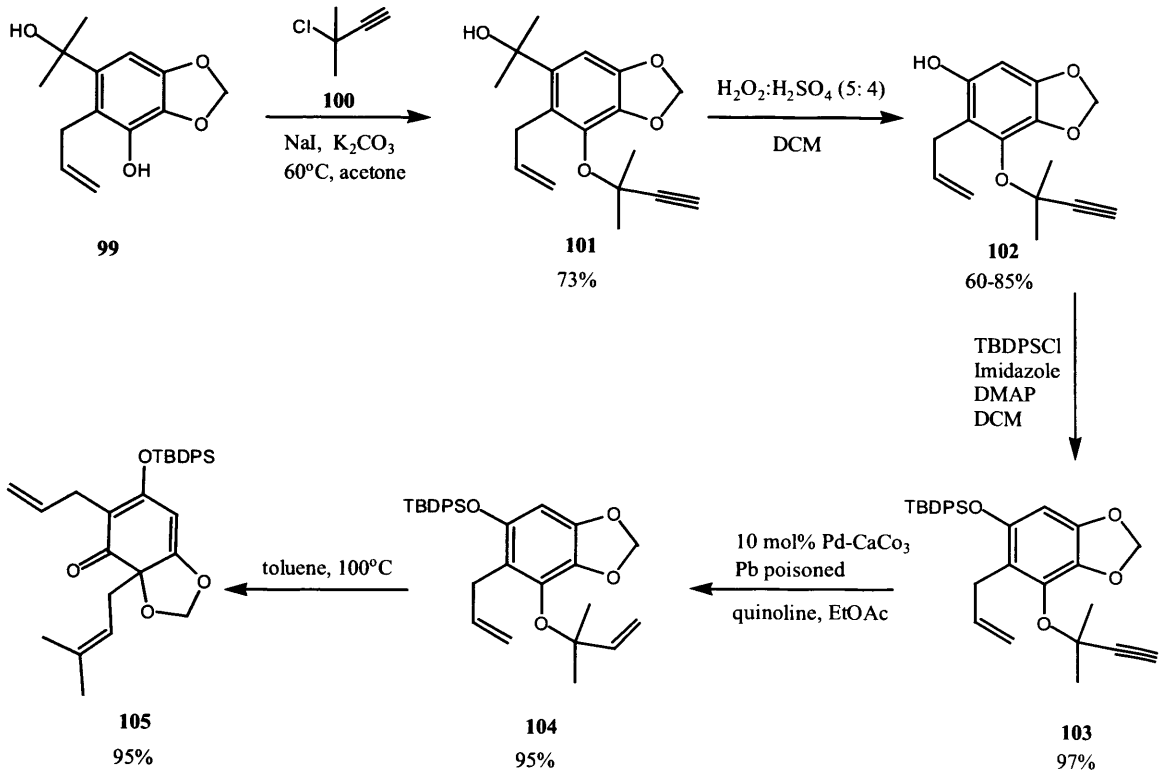
The most effective total synthesis of humulone (**9**) developed to date[1, 90, 91] starts with a Friedel-Crafts acylation of commercially available, phloroglucinol (**98**), producing phloroisovalerophenone (**21**). The acylated derivative (**21**) can also behave as a polycarbonyl system and, when deprotonated with sodium methoxide, undergoes a double addition reaction with 1-bromo-3-methyl-2-butene to give deoxyhumulone (**22**).

At this point, the synthesis runs into difficulties since a method for selective oxidation at the C4/C6 position of the aromatic compound (**22**) is required to produce humulone (**9**). Although a very curious method for this oxidation has been developed using lead (II) acetate and oxygen the final racemic humulone product is only formed in a very low yield of 5.7% (Scheme 28).



Scheme 28

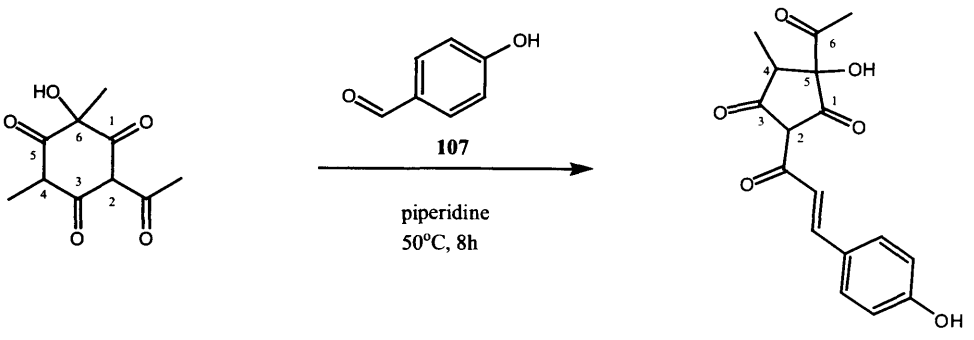
Another, more elegant, route towards polycarbonyl systems of the humulone type has recently been described by T. R. R. Pettus *et al.*,[92] and an example of this chemistry is shown in Scheme 29. Formation of the key enol ether (**104**) from the protected polyoxygenated aromatic compound (**99**) was followed by a Claisen rearrangement, to produce the protected humulone analogue (**105**) (Scheme 29). In their work, T. R. R. Pettus *et al.* discuss the possibility for the application of this chemistry to the production of humulone (**9**) and acknowledge the difficulties associated with the synthesis of this natural product in the past.[93] This route could, with small adaptations, present an effective means of producing humulone (**9**).



Scheme 29

Along with humulone (**9**) itself, a number of analogues of the natural product have also been prepared by application of some of the chemistry shown in Scheme 28.[86-89] Several of these model compounds have then subsequently been subjected to conditions which induce a contraction of the cyclohexane ring, producing isohumulone analogues.

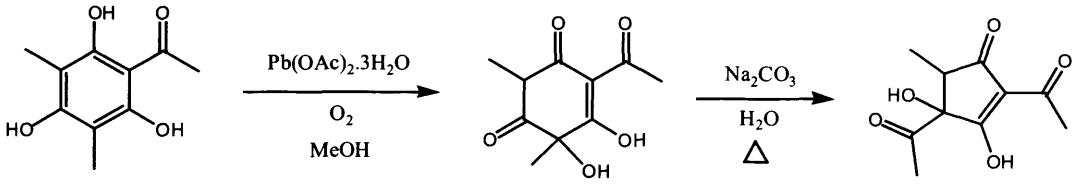
Thus, in work by H. Obara *et al.*[89] attempts were being made to carry out a simple aldol condensation between (**106**) and *p*-hydroxybenzaldehyde (**107**). The basic conditions employed in this reaction led, not only to an aldol condensation but also to ring contraction, producing the polycarbonyl cyclopentanoid (**108**). Indeed, the authors suggested a mechanism similar to that of the ring contraction isomerisation of humulone (**9**) to explain this result (Scheme 30).



106 **108** 22%

Scheme 30

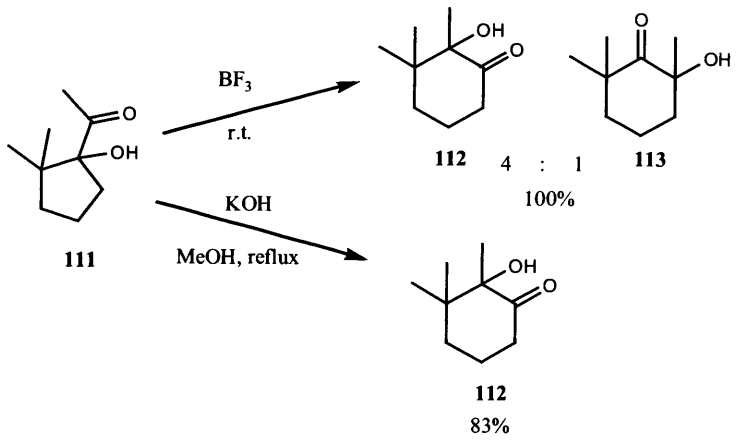
P. M. Brown and G. A. Howard[86] have also carried out a ring contraction of the same humulone analogue (**106**), which underwent isomerisation when boiled in a sodium carbonate solution to produce the isohumulone analogue (**110**) (Scheme 31). Unfortunately analogues such as (**110**), *per se*, are of little value for our own studies since their photodegradation could only lead to generation of a high energy methyl radical.



109 **106** 57% **110** no yield given

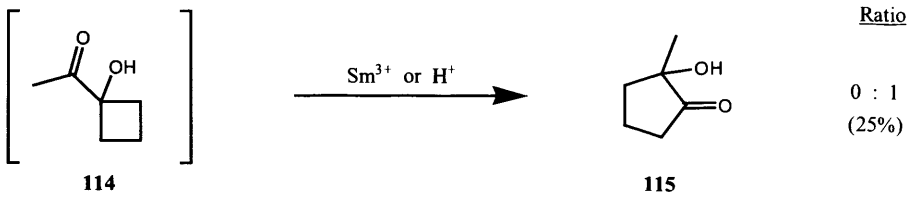
Scheme 31

In the wider context, these reactions can be viewed as examples of the acyloin rearrangement. This type of isomerisation can be induced by a base or a Lewis acid but, unfortunately, has found limited application in the area of organic synthesis. The majority of the examples to be found in the literature involve the ring expansion of α-hydroxyketones (**111**), with product distributions being dependant on the conditions employed, as illustrated in Scheme 32.[94, 95] It is extremely interesting to note that the transformation of humulone (**9**) to isohumulone (**1**) is one of a few notable reactions[96] where ring contraction from a six to a five membered ring is achieved using these rearrangement conditions, rather than the converse.



Scheme 32

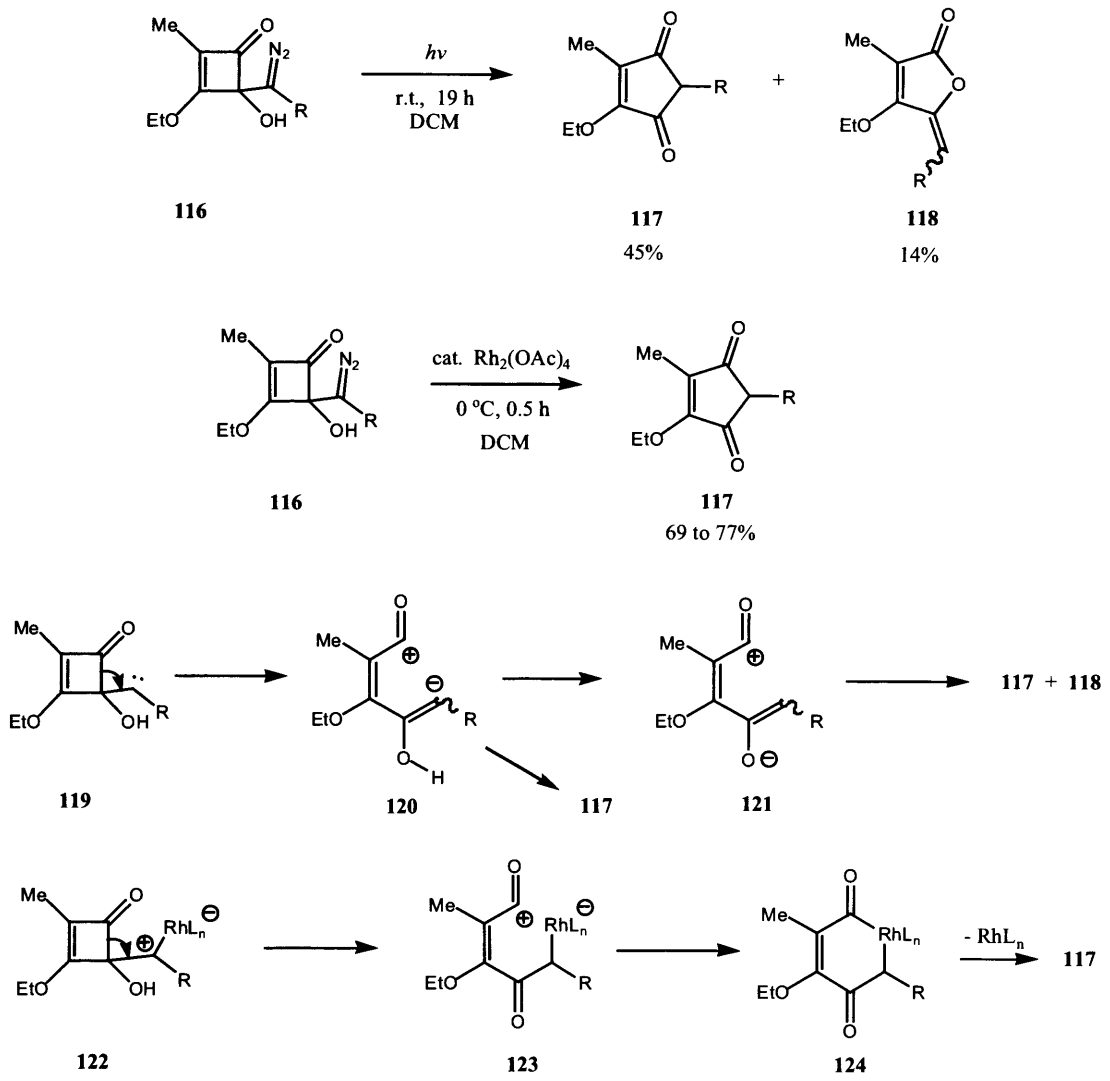
Product mixtures can be obtained as a result of the equilibrium positions of these acyloin rearrangments. H. Brunner and coworkers[97] have cleverly avoided this problem by carrying out the isomerisation of strained ring systems. Thus, isomerisation of cyclobutane (**114**), produces solely the ring expanded isomer (**115**) (Scheme 33).



Scheme 33

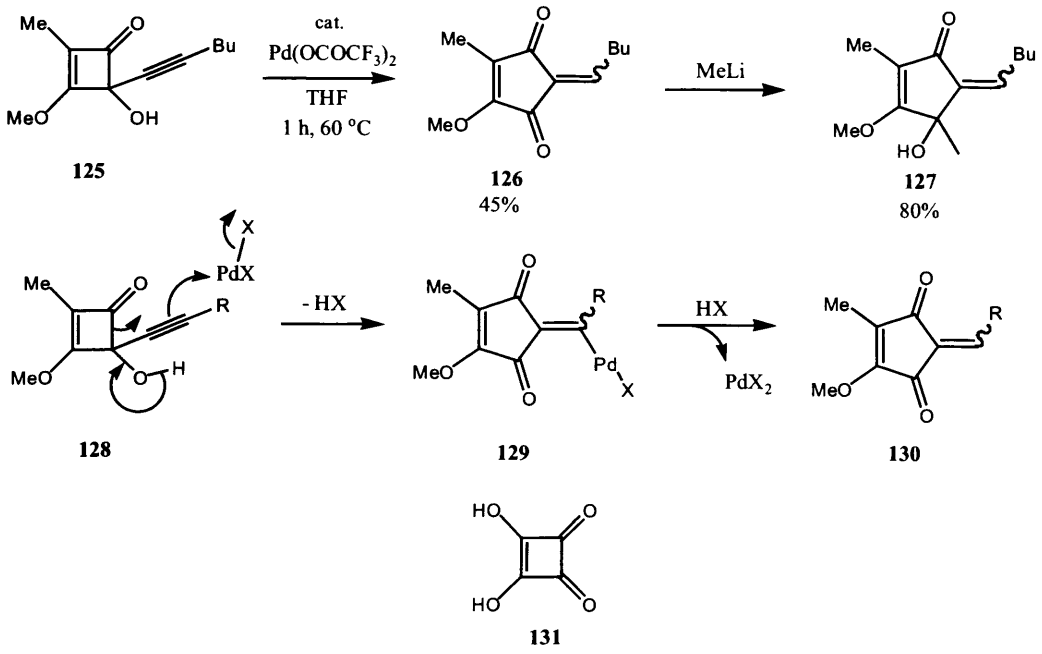
1.64 Alternative Ring Expansion Protocols.

Another, less well researched but expedient route to polycarbonyl cyclopentanoid structures can be found in the work of M.Ohno *et al.*.[98] This research describes the ring expansion of diazo-functionalised 4-hydroxycyclobutenones (**116**) to protected cyclopentatriones (**117**) and substituted furanones (**118**), with the key expansion reaction being achieved either by the use of a rhodium catalyst or by photolysis of the starting material (Scheme 34). The mechanisms invoked by the authors[98] to rationalize these elegant ring expansion reactions are depicted in Scheme 34 and involve the generation and subsequent rearrangement of a carbene (**119**) or carbenoid (**122**) species (Scheme 34).



Scheme 34

Related studies carried out by L. S. Liebeskind *et al.*[99] have shown that heating an alkynyl substituted cyclobutenone ring, such as (**125**), in the presence of catalytic amounts of a palladium II salt also induces a ring expansion (Scheme 35). The substituted cyclopenta-1,3-dione derivative (**126**) produced from one such reaction was then treated with methyllithium to generate the 4-hydroxycyclopent-2-enone (**127**) (Scheme 35). The mechanism of the key ring expansion reaction in this sequence is thought to proceed via electrophilic attack of the palladium (II) species on the alkyne of the starting material, effecting a ring expansion (**128**). The vinylpalladium complex formed (**129**) from this process then undergoes protonation to give the final product (**130**) (Scheme 35).



Scheme 35

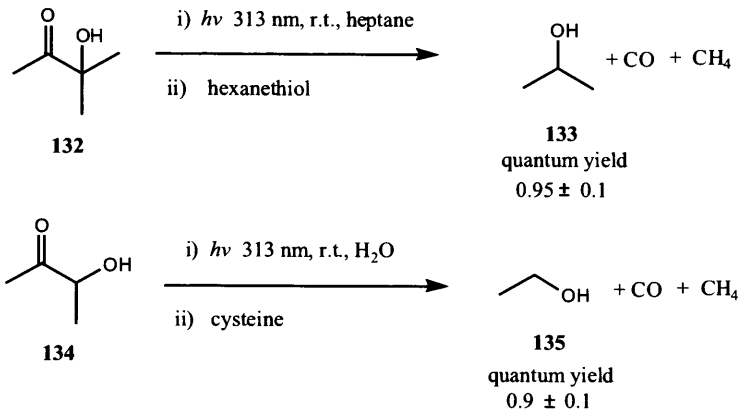
This approach to the production of polycarbonyl cyclopentane structures has the potential to be of considerable use in the synthesis of isohumulone analogues, since it facilitates the formation of highly substituted cyclopentane systems in just a few synthetic steps from commercially available squaric acid (**131**).

1.7 Photochemical Behaviour Of The α-Hydroxyketone Unit.

In anticipation of our intended application of the isohumulone analogues to be prepared in this study, some discussion of the basic photochemical behaviour of the α-hydroxyketone moiety is appropriate. It has already been established (Section 1.5) that there is limited research into the photochemistry of the isohumulones (**1**) themselves. There has, however, been more research into the photo-cleavage of the α-hydroxyketone C-C bond in other systems.

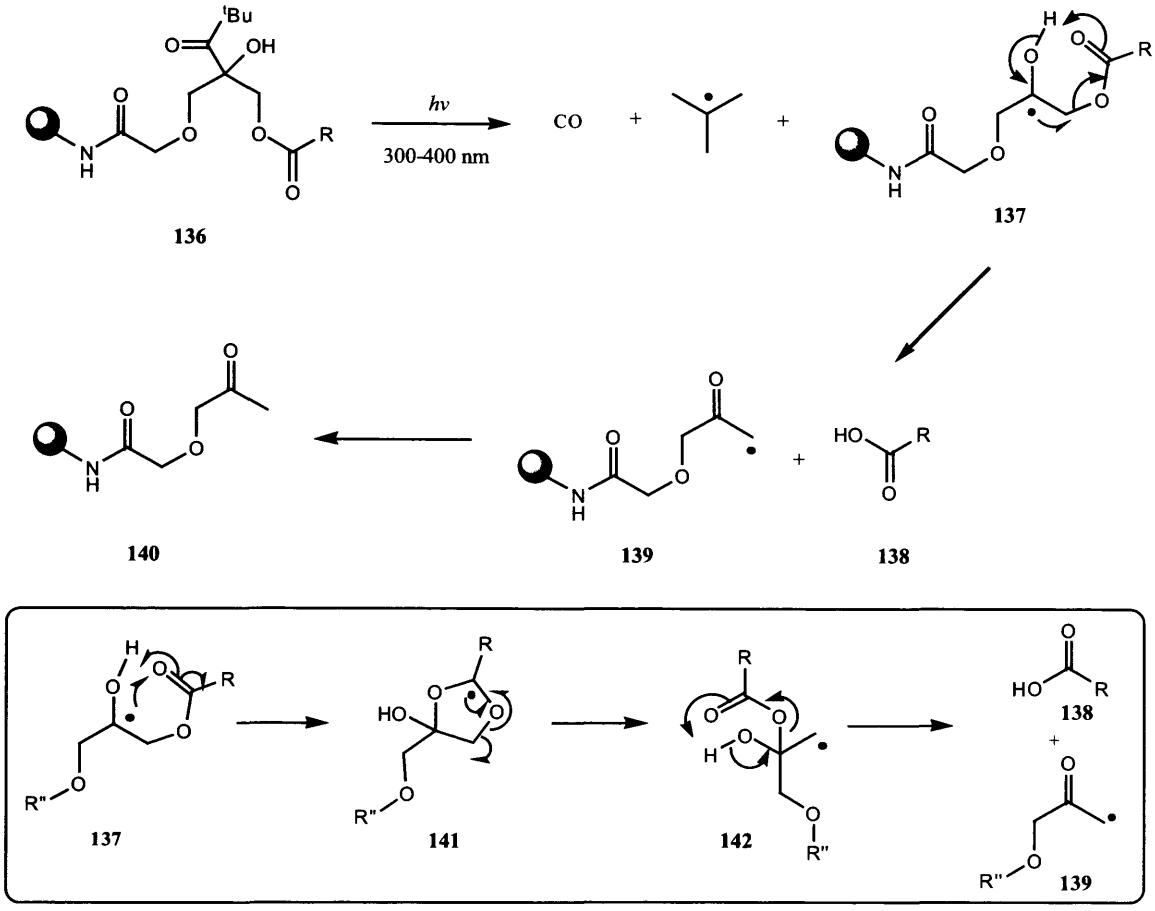
By way of illustration, research carried out by M.V.Encinas, A.M.Rufs and E.A.Lissi[39] determined that Norrish type I cleavage of the moiety can occur in the absence of any other functionality or sensitisers upon irradiation of this chromophore with light at a wavelength of 313 nm. Hexanethiol and cysteine were used in their expected roles as hydrogen atom capture reagents to quench the alkoxyl and hydroxyalkyl radicals

generated during these reactions and the products (**133**, **135**) were detected using gas chromatography, as illustrated in Scheme 36.



Scheme 36

S. Peukert and B. Giese[100] have also taken advantage of the photodegradation of α-hydroxyketones by incorporating such a step in the development of a photolabile linker for use in solid phase synthesis. The linkers developed (**136**) have been irradiated with light at wavelengths between 300 – 400 nm which induces homolytic cleavage of the carbon-carbon bond of the α-hydroxyketone unit present in the tether. Carbon monoxide is evolved and a stabilised *t*-butyl radical formed, in a similar fashion to the process seen in the "sunstruck" reaction. The other radical generated (**137**) undergoes further rearrangement resulting in the cleavage of the linker substrate bond, producing the carboxylic acid (**138**) and the polymer fragment (**140**) (Scheme 37). It was suggested by S. Peukert and B. Giese[100] that the degradation of radical (**137**) occurs through a seven-membered hydrogen-bridged transition state to form the radical (**139**). This concerted elimination mechanism, however, appears to have no precedent and a stepwise mechanism such as that shown in Scheme 37 seems more probable. These photolabile linkers were, in fact, inspired by previous investigations carried out by this group into the mechanism of the radical cleavage of lipids and DNA in biological systems.[101-103]



Scheme 37

The research into the degradation of α-hydroxyketone systems under UV light highlighted in this section has shown that a wavelength of 300nm or less is required for homolytic cleavage of the carbon-carbon bond of this moiety in most cases. The fact that the isohumulones (**1**) perform this type of bond fission in natural light suggests either, that this bond is somehow activated in these compounds (**1**) relative to simpler α-hydroxyketone units, or that energy transfer occurs from another chromophore present in beer, as postulated in Section 1.51.

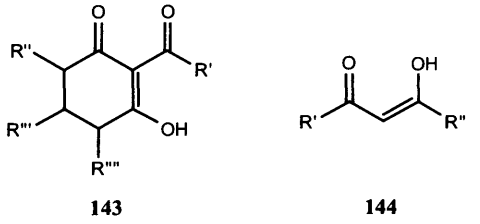


Fig. 4

Studies of the ultraviolet spectra of 2-acylcyclohexane-1, 3-diones (**143**)[104] as well as simpler acyclic 1, 3-dicarbonyl compounds (**144**) (Fig. 4) and their metal chelate complexes[105] have revealed that the absorption spectra of these chromophores change drastically with pH and metal ion complexation. Beer contains many different metal ions and these results suggest that an interaction in the solution may affect the way in which the isohumulones (**1**) absorb light in this medium. It is also possible that these interactions in the drink influence the wavelength at which the α-hydroxyketone bond of the isohumulones (**1**) is cleaved.

1.8 Conclusions And Objectives Of The Present Study.

The foregoing introduction has, hopefully, given a broad overview of the fascinating and complex chemistry associated with both humulone (**9**) and the isohumulones (**1**) and also indicated that, in spite of the lack of stereochemical complexity, the synthesis of highly oxygenated cyclopentanoids can present formidable challenges.

In terms of understanding the sunstruck reaction, the approach taken in the present study was to prepare a series of isohumulone analogues (**49**,**145-149**) of increasing complexity by growing the chromophore around the cyclopentane nucleus, as illustrated in Fig. 5.

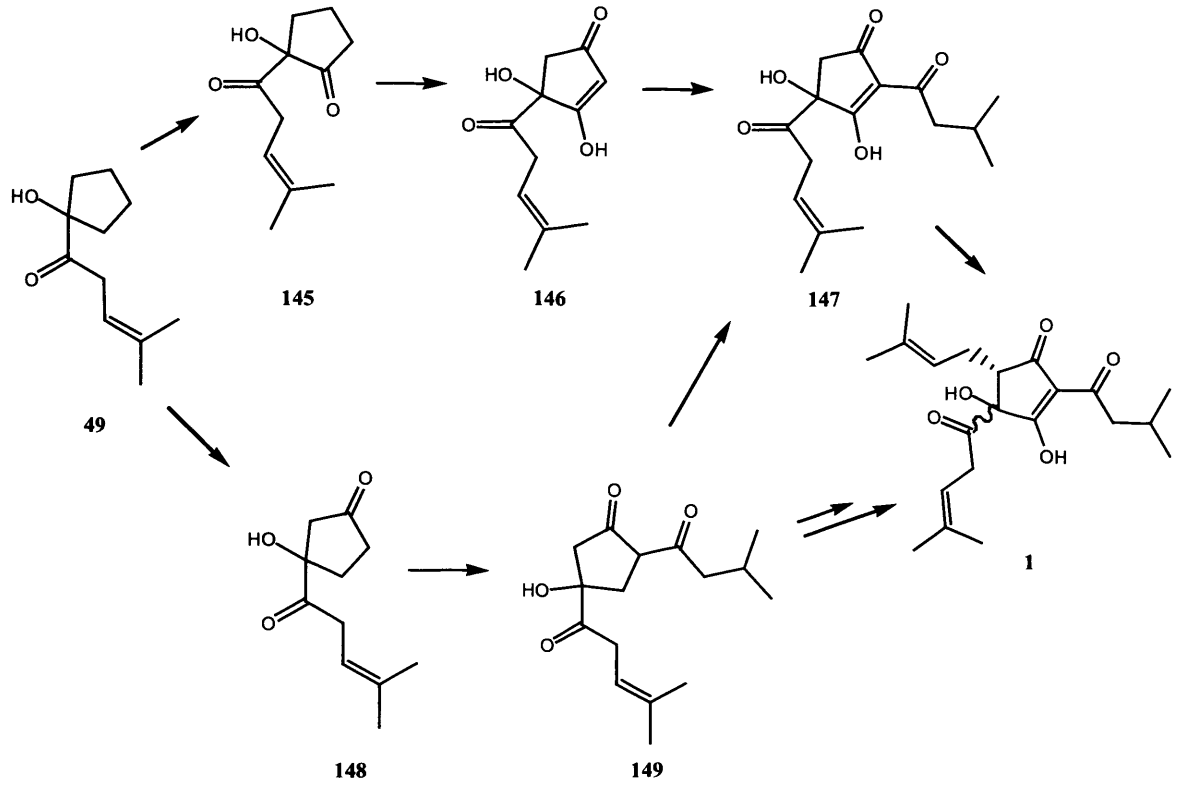


Fig. 5

Since it is the C4-C6 carbon-carbon bond of the α-hydroxyketone moiety of the isohumulones (**1**) which breaks on photolysis, this unit was incorporated into all of the model compounds produced. Thus, the simplest analogue will contain only this functionality (**49**), with the most complex being the isohumulones (**1**) themselves.

With such a set of analogues in hand, our objective was then to examine their photochemical behaviour in the presence of a sulfur source such as cysteine, and through product isolation and detection of 3-MBT (**2**), to gain an insight into possible mechanisms involved.

By taking such an approach, we considered that the essential functional groups involved in the photodegradation of the isohumulones (**1**) would be revealed and that the results could give rise to a better model for the mechanism of the "sunstruck reaction".

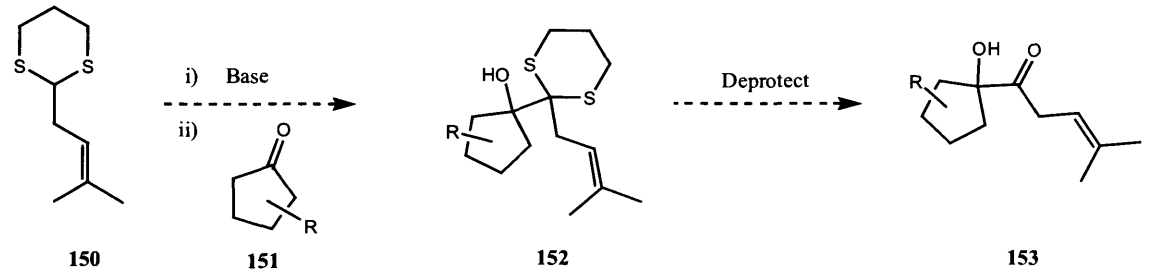
CHAPTER 2

Results And Discussion

2.1 Synthesis Of Isohumulone Analogues Using Dithiane Chemistry.

As an initial approach to the production of some simple isohumulone analogues attention was directed towards the key α-hydroxyketone unit present in the isohumulones (**1**) (C6-C7). It was deemed essential in this research to be able to synthesise compounds in which a tertiary alcohol is attached to an exocyclic ketone possessing a β-γ unsaturated alkenyl side chain.

The versatility of dithiane anion chemistry as a means of producing the α-hydroxyketone moiety (Introduction 1.61) made this approach an extremely attractive starting point for any investigations in this area. Indeed, this type of bond formation has precedent in the work carried out by its pioneers D. Seebach and E. J. Corey.[55, 66] We envisioned that addition of the anion of the prenylated dithiane (**150**) to substituted cyclopentanones (**151**) should facilitate the production of masked derivatives (**152**), which, after deprotection, would furnish model isohumulone analogues (**153**) for use in photolysis studies (Scheme 38).



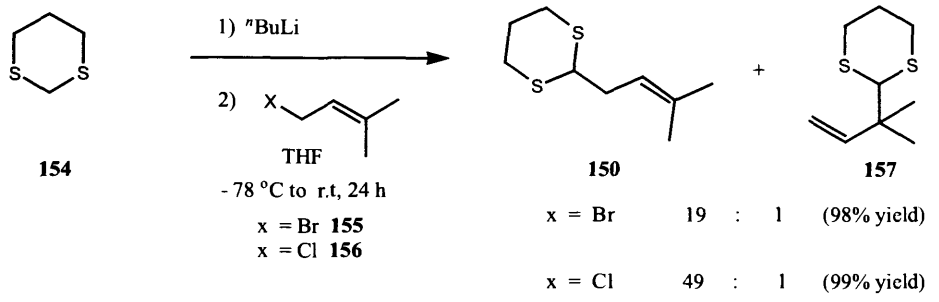
150 **151** **152** **153**

Scheme 38

2.11 Addition Of Thioacetal Anions To Carbonyl Compounds.

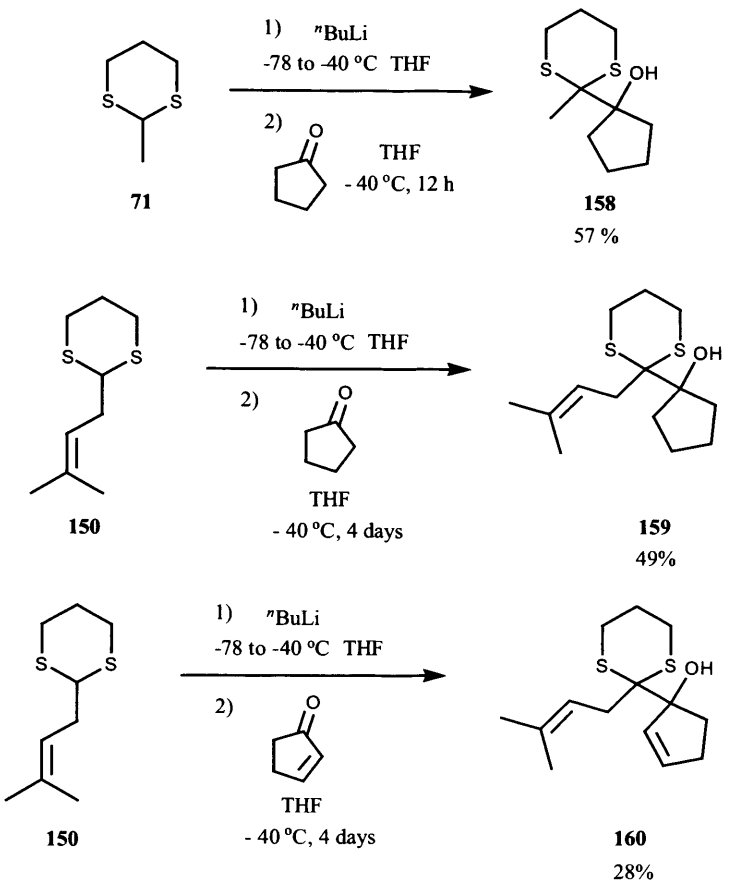
Accordingly, our studies commenced with the production of the thioacetal (**150**), required in all subsequent reactions in this strategy. To our surprise, the synthesis of this particular dithiane (**150**) had not been reported in the literature but it was felt that this compound (**150**) could be obtained by the application of some simple dithiane chemistry. 1, 3 Dithiane (**154**) was deprotonated with ^{n}BuLi at low temperature and the resultant anion quenched by the addition of 1-bromo-3-methyl-2-butene (**155**), to

produce the alkenyl dithiane (**150**) in 98% yield (Scheme 39). Although, on first impression, the high yield of this reaction was gratifying, careful analysis of the NMR spectral data of the product (**150**) revealed the presence of a trace impurity which could not be eradicated. Investigation revealed that this contaminant appeared to be the thioacetal regioisomer (**157**), perhaps arising from the S_N2' reaction of the allylic bromide (**155**) with the 1,3-dithiane anion. Interestingly, we discovered that the purity of the desired product (**150**) could be increased by utilising 1-chloro-3-methyl-2-butene (**156**) as the electrophile in the transformation (Scheme 39).



Scheme 39

With the required alkenyl thioacetal (**150**) in hand, albeit slightly impure, investigations were begun into the reaction of this compound with a variety of cyclic ketones. Initial reaction condition optimisation studies were performed using commercially available 2-methyl-1,3-dithiane (**71**) and cyclopentanone (Scheme 40). Following these test reactions we were extremely pleased to observe that application of the protocol developed to the reaction of thioacetal (**150**) with both cyclopentanone and its α, β unsaturated congener, produced the expected unsaturated α-hydroxythioketals (**159**) and (**160**) in moderate yields (Scheme 40). The products (**159**) and (**160**) showed no impurities arising from reaction of the thioacetal by-product (**157**). Presumably, such contaminants were either not formed as a consequence of increased steric bulk around the dithiane anion or were successfully removed during purification.

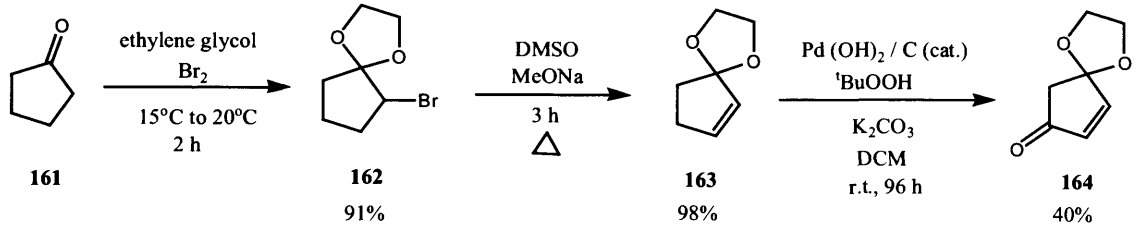


Scheme 40

It should be noted that these reactions required long periods at low temperatures due to the acidic nature of the cyclopentyl protons adjacent to the carbonyl group in the electrophiles employed. If such addition reactions are attempted at more elevated temperatures the lithiodithiane intermediate functions as a base rather than a nucleophile, resulting only in the recovery of starting materials. The conditions selected suppress this process to a large degree, although, invariably some starting dithiane (**150**) was separated from the reaction mixtures along with the required products (**159**) and (**160**).

The dithiane chemistry developed thus far had been both simple and consistently successful, but had reached its limits in terms of commercially available substrates. Consequently, attention was directed to the production of more highly functionalised cyclopentanone derivatives.

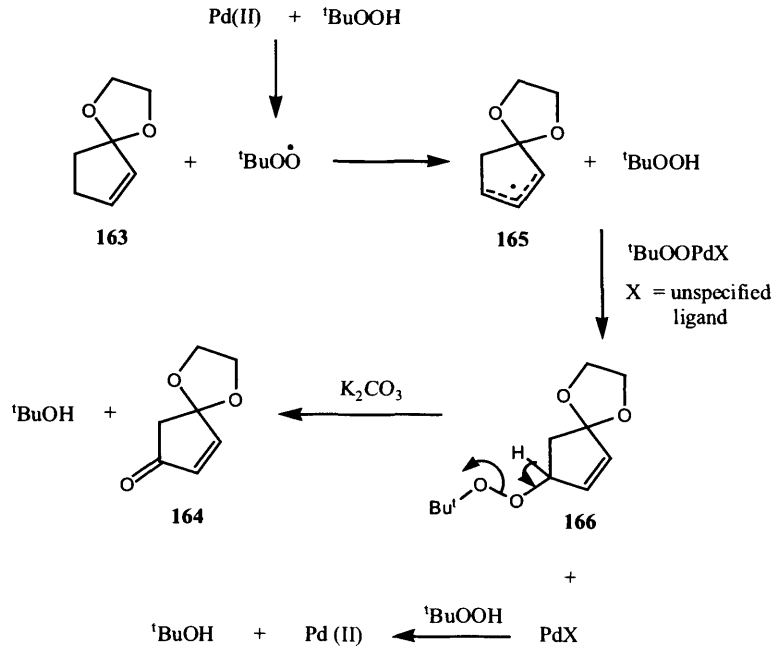
In terms of growing the chromophore, the monoprotected cyclopentene-1,3-dione (**164**) was an ideal candidate and its synthesis had recently been reported[106] via allylic oxidation of 2-cyclopenten-1-one ethylene ketal (**163**). Recourse to the literature revealed that the ethylene ketal (**163**) was, in turn, easily accessible on a large scale and in high yield according to an elegant procedure developed by E.W.Garbisch Jr..[107] Following this method, simultaneous acetal protection and alpha bromination of cyclopentanone (**161**) and subsequent dehydrobromination produced the protected cyclopentenone (**163**) (Scheme 41). This was then oxidised according to the conditions developed by J.Q.Yu and E.J.Corey,[106] employing palladium hydroxide on carbon as a catalyst in the presence of *tert*-butylhydroperoxide as a stoichiometric oxidant, to furnish the desired α, β unsaturated ketone (**164**) (Scheme 41).



Scheme 41

We were disappointed to find that, in our hands, this final allylic oxidation proceeded in a maximum yield of 40%, this being considerably lower than the 80% quoted in the literature.[106] All attempts to increase the yield of this reaction by altering conditions proved futile. Modifications such as increasing reaction times or employing anhydrous *tert*-butylhydroperoxide had no appreciable effect on the transformation.

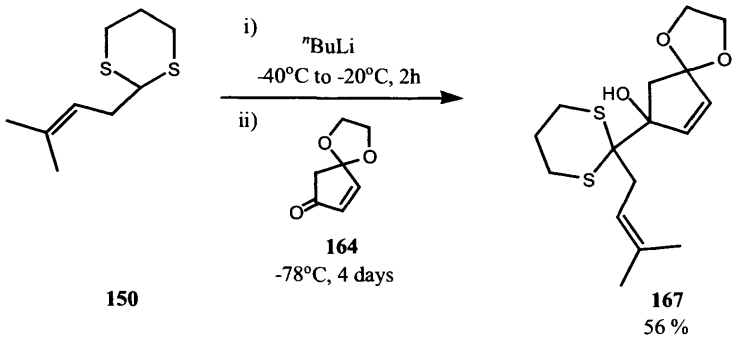
According to J.Q.Yu and E.J.Corey,[106] the mechanism of this problematic oxidation begins with the generation of a *tert*-butylperoxy radical from the interaction of *tert*-butylhydroperoxide with the palladium (II) salt. This reactive species then abstracts a hydrogen atom from the protected enone (**163**) to produce an allylic radical (**165**). Combination of this stabilised radical (**165**) with a *tert*-butylhydroperoxide palladium complex forms the peroxide (**166**), which subsequently undergoes elimination *in situ* to form the α, β-unsaturated ketone (**164**) (Scheme 42).



Scheme 42

Although the lower yield observed in the final transformation of this sequence was frustrating, the product had nevertheless been isolated in sufficient quantities and so investigations were initiated into the reactivity of this unsaturated monoprotected 1, 3-dicarbonyl (**164**).

Coupling of enone (**164**) with thioacetal (**150**) was carried out under similar conditions to those employed previously (Scheme 40) and, to our delight, produced the new protected isohumulone analogue (**167**) as a white crystalline solid in a good yield (Scheme 43). Once again, extended reaction times and low temperatures were necessary to prevent the competative quenching reaction of the anion of (**150**) by the relatively acidic protons of the cyclopentenone (**164**).

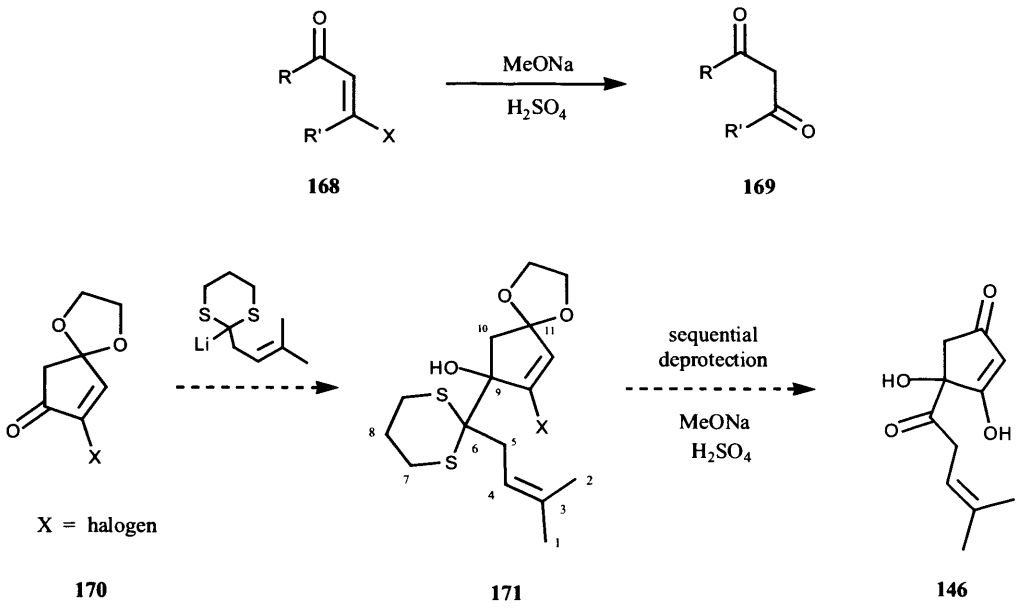


Scheme 43

Following on from this very encouraging result attempts were then made to use an even more highly functionalised ketone in this dithiane addition reaction.

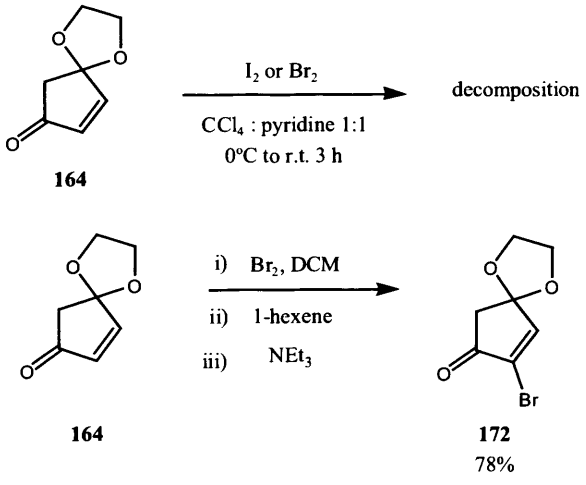
In particular we were interested in adding an additional latent carbonyl group to the cyclopentanoid structure to form an analogue containing a 1, 3-dicarbonyl moiety on the cyclopentane ring.

Research in this area has shown that such 1,3-dicarbonyl units (**169**) can be generated from vinylgous acid chlorides such as (**168**) upon treatment with sodium methoxide and then sulfuric acid (Scheme 44).[108] We therefore envisaged that an α halo enone such as (**170**) would be required for coupling with the dithiane (**150**). Subsequent deprotection of the intermediate (**171**) formed and application of the conditions developed by G. G. Melikyan *et al.*[108] should then facilitate the production of a further isohumulone analogue (**146**), as shown in Scheme 44.



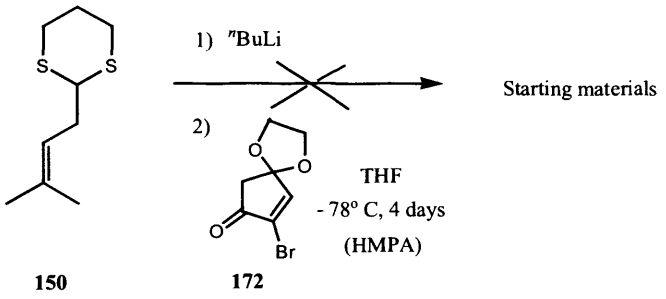
Scheme 44

It was initially anticipated that ketone (**170**) might be produced by halogenation of the protected enone (**164**), following a literature precedent.[109] However, preliminary experiments were disappointing and treatment of the α, β – unsaturated enone system of (**164**) with a halogen in the presence of pyridine gave a complex mixture of inseparable products (Scheme 45). However, to our relief, a slightly different procedure,[110] involving the sequential addition of halogen and then base, gave much better results in this addition-elimination reaction. The vinyl bromide (**172**) was isolated from this process as a crystalline solid in a yield of 78% (Scheme 45).



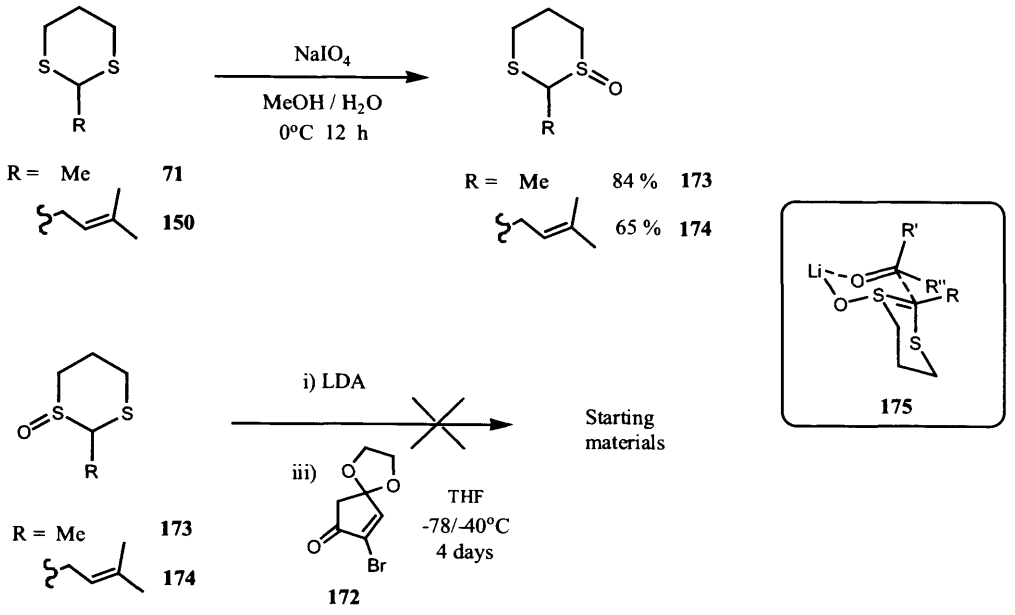
Scheme 45

Unfortunately, subsequent utilisation of the halogenated carbonyl substrate (**172**) in an addition reaction with the lithioanion of dithiane (**150**), highlighted, for the first time, a limitation in this acyl anion chemistry. The experiments were completely unsuccessful and resulted only in the recovery of starting materials (Scheme 46). The reason for the failure of these reactions was unclear, however, it was postulated that the steric bulk of the bromine atom alpha to the carbonyl group in compound (**172**) could hinder the approach of the dithiane anion. The necessity of carrying out these reactions at such low temperatures, as explained previously, only serves to further slow any reaction between the two reactants and so a method of increasing the reactivity of this system was sought.



Scheme 46

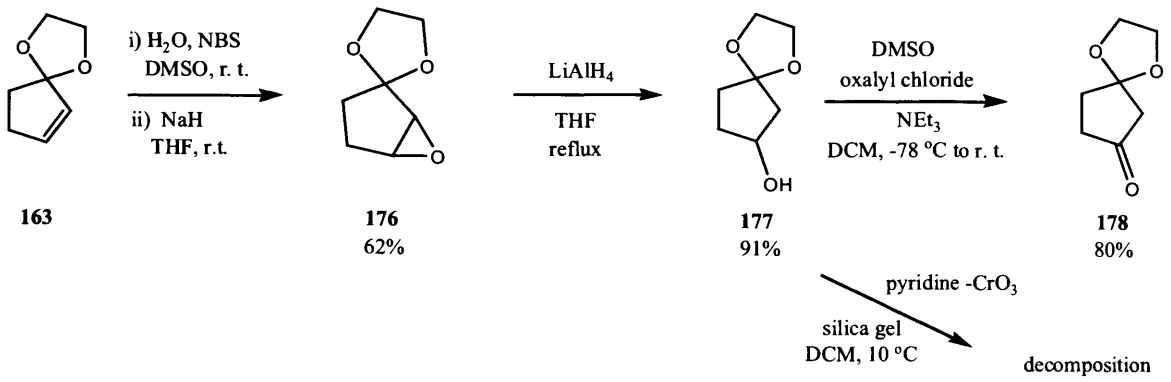
In the first instance the renowned additive, HMPA, known to activate lithio anions,[111] was employed, but to no effect. As a clever alternative method of increasing the reactivity of the unsaturated dithiane (**150**), its derived thioacetal sulfoxide (**174**) was prepared by monooxidation of (**150**) with sodium periodate (Scheme 47).[112] Anions of such sulfoxides (**173**, **174**) have been reported to be more reactive in nucleophilic addition reactions, possibly as a consequence of the formation of a cyclic six membered metal chelate ring system (**175**) during the addition (Scheme 47).[113] Unfortunately, in this case, the use of thioacetal sulfoxide (**174**) had no effect on the outcome of the reaction and once again only starting materials were recovered (Scheme 47). A control experiment employing the less bulky methyl substituted sulfoxide (**173**) was, likewise, unsuccessful (Scheme 47).



Scheme 47

At this point the foregoing problematic reaction was abandoned and attention turned to the construction of the slightly simpler cyclopentan-1,3-dione monoethylene ketal (**178**). We felt that reaction of this ketone (**178**) with a thioacetal anion would be more straightforward and had the potential to produce a compound as yet unsynthesised in the protected isohumulone series.

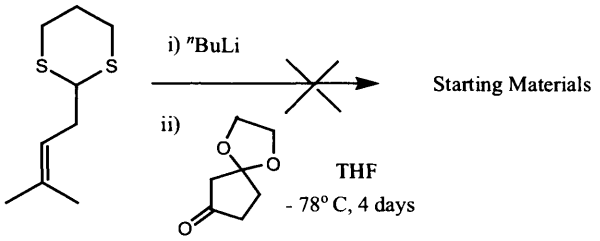
This monoprotected 1,3-dicarbonyl compound (**178**) was easily accessible by minor adaptation of the synthesis reported by Y. D. Vankar *et al.*[114] Formation of epoxide (**176**) from 2-cyclopenten-1-one ethylene ketal (**163**) via the bromohydrin[115] and then regioselective ring opening of this epoxide[114] (**176**) proceeded smoothly, according to this literature precedent. However, problems were encountered upon attempting oxidation of alcohol (**177**) with chromium trioxide, following this work.[114] This difficulty was circumvented by the selection of Swern oxidation conditions, which furnished the required ketone (**178**) in a good yield (Scheme 48). The observed regioselectivity in the opening of epoxide (**176**) in this sequence is extremely interesting and it is plausible that this arises as a result of the oxygen atoms of the ketal moiety of the compound (**176**) chelating the metal hydride species, directing regioselective attack of the epoxide.



163 **176** 62% **177** 91% **178** 80%

Scheme 48

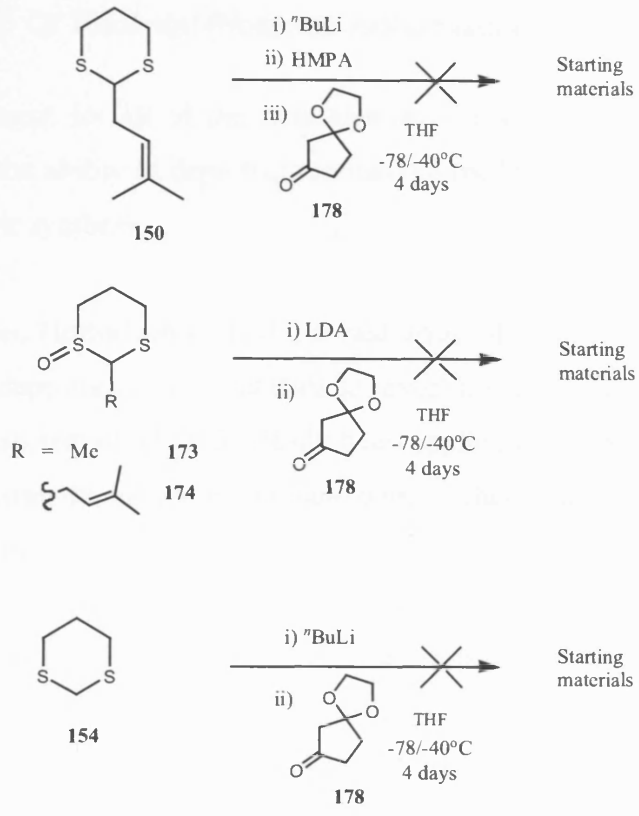
Regrettably, and in contrast to the behaviour of the unsaturated congener (**164**), reaction of this monoprotected cyclopentane-1,3-dione (**178**) with the anion of the thioacetal (**150**) only resulted in the recovery of starting materials (Scheme 49).



150 **178**

Scheme 49

Again, nucleophile activation techniques were employed in an effort to increase the reactivity of the thioacetal anion in this reaction, but to no avail (Scheme 50). Finally, a model reaction was carried out and attempts were made to react compound (**178**) with the anion of the less hindered commercially available 1, 3-dithiane (**154**). Astonishingly, this experiment also led only to the recovery of starting materials (Scheme 50).



Scheme 50

One conceivable explanation for the failure to achieve dithiane addition at the carbonyl centre of the saturated compound (**178**) may reside in the conformation of the spirocyclic ring of ketone (**178**) relative to its more planar "flattened" unsaturated congener (**164**). The additional sp^3 centres in (**164**) lead to a more puckered conformation which in turn could result in attack of the approaching nucleophile from the required Bürgi-Dunitz angle of around 107° [116] being blocked by the ethylene ketal group of the molecule, as shown in Fig. 6.

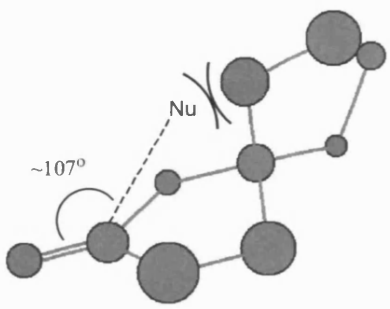


Fig. 6

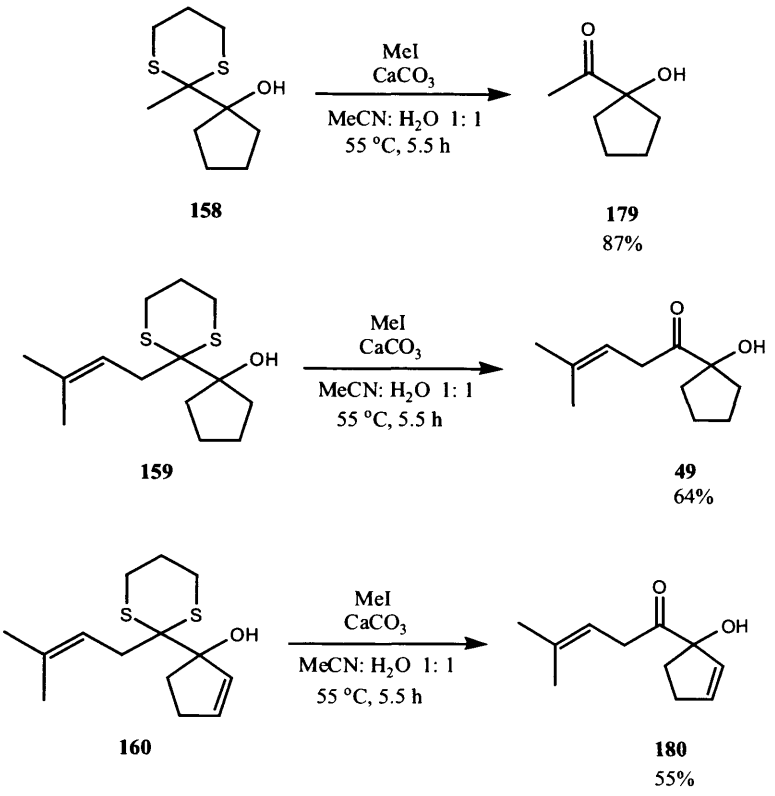
MM2 energy minimised conformation of cyclopentan-1,3-dione monoethylene ketal (178)

2.12 Deprotection Of Thioketal Protected Isohumulone Analogues.

A critical requirement for all of the strategies involving 1,3-dithiane anion chemisty lies, of course, in the ability to deprotect the masked model compounds (**158**, **159**, **160**, **167**) following their synthesis.

As previously noted (Introduction 1.61), a vast array of different methods have been developed for the deprotection of thioketals to reveal a ketone.[68] From this large choice conditions were selected which had already been applied to the deprotection of similar compounds possessing the α-hydroxydithiane unit.[117] This method required treatment of the thioketal with N-chlorosuccinimide in a biphasic solvent system of dichloromethane: water, and, when applied to dithiane (**158**), produced a yellow oil. Unfortunately, it was not possible to characterise this product before it decomposed to a black tar. We proposed that this degradation was caused by acidic residues present in the crude product, since the α – hydroxyketone moiety may undergo rearrangement reactions under these conditions.

This assertion was vindicated when a neutral deprotection method proved effective for the masked isohumulone analogues (**158**, **159**, **160**). Heating the protected compounds (**158**, **159**, **160**) with methyl iodide in a solvent system of acetonitrile: water (1: 1), in the presence of calcium carbonate, furnished the required α – hydroxyketones (**49**), (**179**) and (**180**) in good yields (Scheme 51).[118]



Scheme 51

At this point, we were extremely surprised to discover that even the simple isohumulone analogues (**49**) and (**180**) displayed some of the same physical characteristics as the isohumulones themselves (**1**), namely they were chemically unstable and slowly degraded upon storage. Compounds (**49**) and (**180**) underwent reaction at their prenyl side chains (C1 to C5), combining with the oxygen present in air to produce hydroperoxides (**181**, **182**) (Fig. 7).

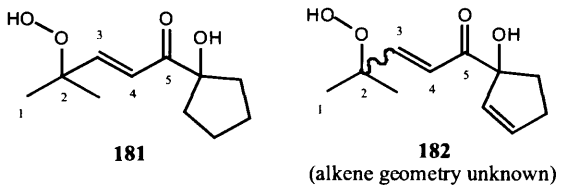
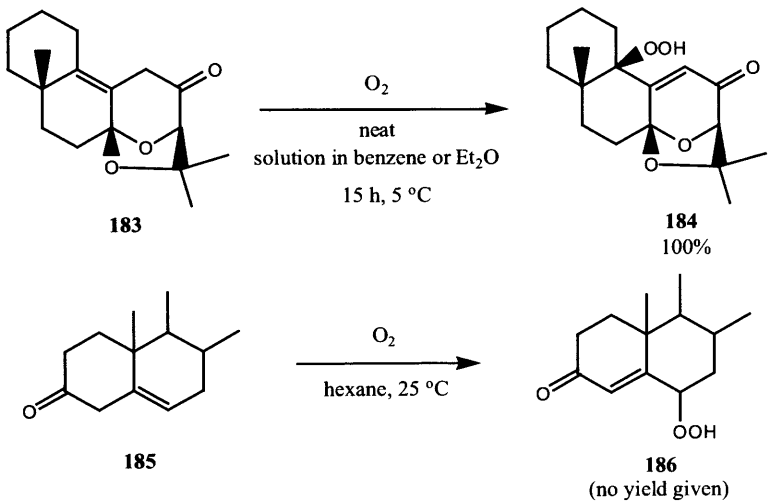


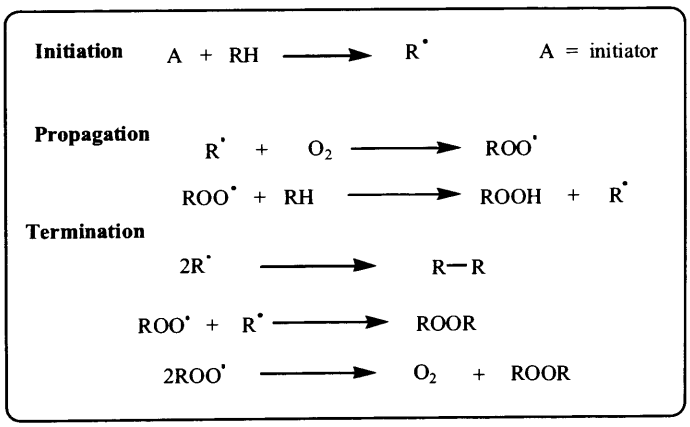
Fig. 7

The autooxidation of organic molecules by air has been well documented[119, 120] and has been found to occur in solutions of compounds containing similar β,γ-unsaturated carbonyl moieties (**183**, **185**) (Scheme 52).[121-123] However, to the best of our

knowledge, this is the first instance that such an autooxidation to form allyic hydroperoxides (**181**, **182**) has been observed in hop acid analogues. Such transformations are thought to occur via a radical chain reaction,[119] as shown in Scheme 52.

Triplet ground state oxygen itself is too unreactive to abstract a hydrogen atom directly to begin the reaction and so it is generally assumed that a trace of the alkyl free radical is produced by some initiating process and then combines with triplet oxygen to produce an alkyl peroxy radical. This species is then capable of abstracting a hydrogen atom from another substrate molecule, in a slow rate determining step, to propagate the radical chain and produce the hydroperoxide. Termination occurs upon combination of two of the free radical species.

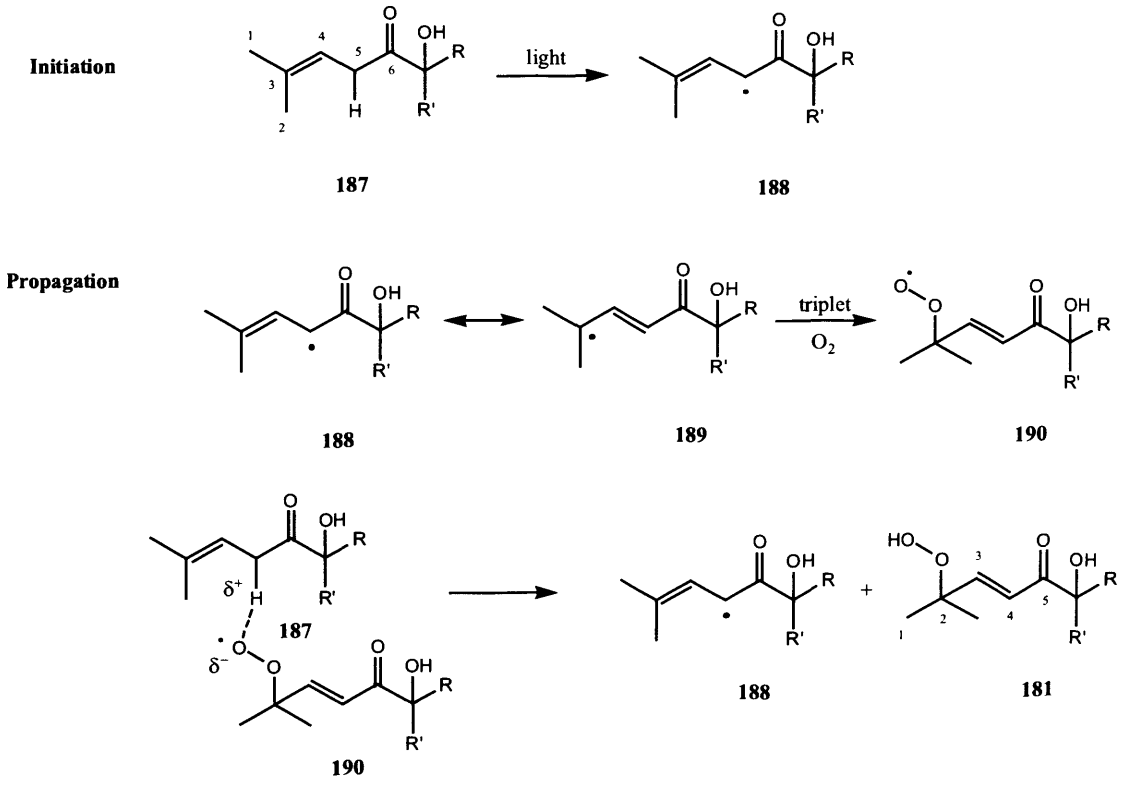




Scheme 52

Very curiously only traces of such an oxidised product (**182**) were observed in the NMR spectrum of analogue (**180**), whereas the saturated cyclopentanoid congener (**49**) underwent complete conversion, cleanly, to the hydroperoxide (**181**) (Fig. 7) upon storage at –20°C in air for a few months. This hydroperoxide (**181**) was a crystalline solid which could be fully characterised and produced a single geometric isomer with the *trans* configuration at the newly formed double bond between C3 and C4 (Fig. 7).

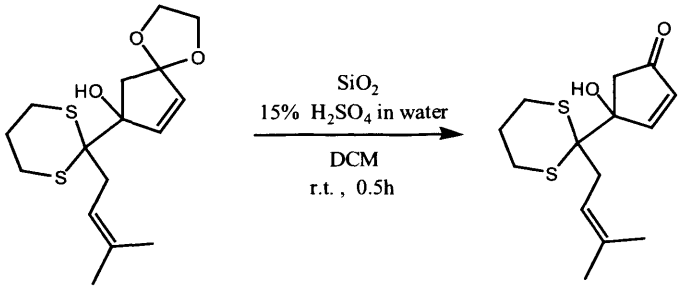
The model compounds produced during these studies are particularly prone to this autooxidation due to the relative stability of the allylic radical (**188**) formed upon initiation of the free radical chain process, not to mention the thermodynamic stability gained by moving a double bond into conjugation with a carbonyl group in the product of the reaction (**181**) (Scheme 53). Moreover, in spite of the fact that an alkylperoxy radical is a relatively poor hydrogen atom abstractor relative to an alkoxyl radical, this propagation step is certainly favoured by the polar characteristics of the β,γ-unsaturated carbonyl substrate in the present instance, as outlined in Scheme 53. It is unclear what initiates the radical cascade in this case, but it is known that such autooxidations can be catalysed by light.[119, 120] Compound (**181**) is clearly formed as the thermodynamic product of such a chain reaction.



Scheme 53

We soon established that this problem could be alleviated by storing the model compounds (**49**, **180**) under nitrogen at –20 °C and frozen in benzene. At present however, we have no explanation for the enormous difference in reactivity as a function of substrate structure, given that the only difference is the presence or absence of a remote double bond.

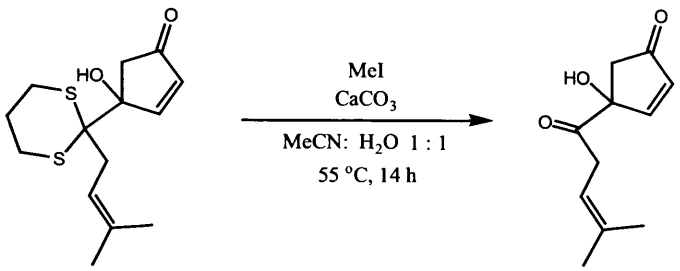
Our attention then returned to the necessary deprotection sequences. Analogue (**167**) required the removal of both the thioketal and also the hydrolysis of the ketal protecting group. Treatment of compound (**167**) with a strong acid in a solvent of either water or acetone in an effort to carry out this hydrolysis resulted, disappointingly, in the recovery of a complex mixture of products. Milder deprotection conditions were, therefore, sought and discovered in chemistry developed by F.Huet *et al.*.[124] Thus, stirring (**167**) with acidified silica in dichloromethane produced the partially deprotected compound (**191**) in a yield of 58% (Scheme 54).



167 **191** 58%

Scheme 54

Intermediate (**191**) was then further deprotected using the previously successful conditions,[118] to unmask the second carbonyl group of the molecule. In this case it was established that longer reaction times were necessary for the reaction to go to completion, producing the isohumulone analogue (**192**) in a yield of 40% (Scheme 55).



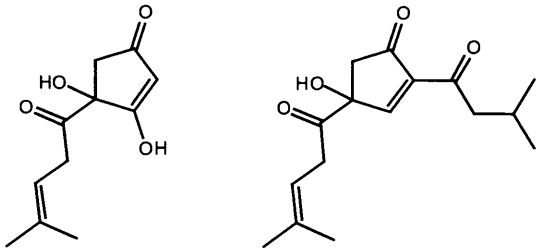
191 **192** 40%

Scheme 55

2.13 Manipulation Of Intermediates To Form New Isohumulone Analogues.

Thus far, the utilisation of thioacetal anion chemistry in our research had yielded a number of isohumulone analogues at varying levels of unsaturation and oxidation. Attempts were then made to exploit these molecules in the creation of further model compounds, incorporating additional chromophoric units.

An ideal candidate for further variation via its protected derivatives (**167**) and (**191**) was the most functionalised analogue (**192**). It was envisaged that further functionalisation of the cyclopentenone moiety of (**192**) could lead to the introduction of the highly desirable "1, 3-dicarbonyl" motifs present in (**146**) and (**193**) (Fig. 8).

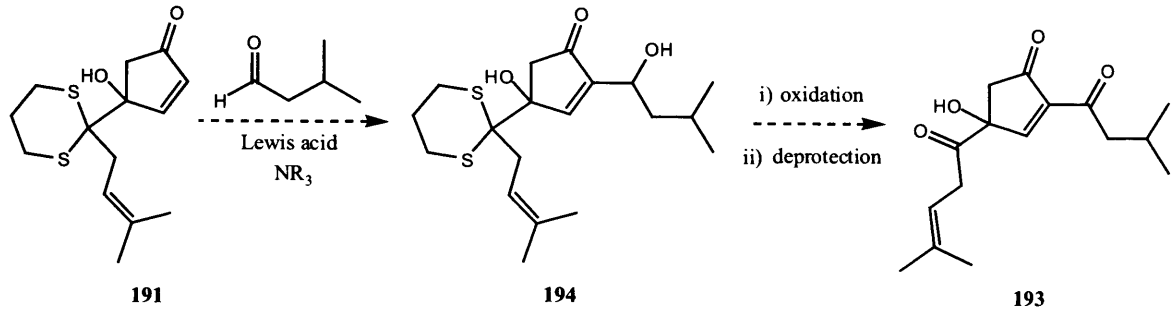


146 **193**

Fig. 8

Analysis of the pattern of functionality present in compound (**193**) inspired an attractive approach to this molecule which centred around the application of Baylis-Hillman chemistry on the partially protected intermediate (**191**). We envisioned that treatment of the enone unit of (**191**) with isovaleryl aldehyde in the presence of a tertiary amine

and/or Lewis acid would result in the formation of the addition product (**194**). The resultant alcohol (**194**) could then be oxidised and subsequent deprotection would then afford the isohumulone analogue (**193**) (Scheme 56).

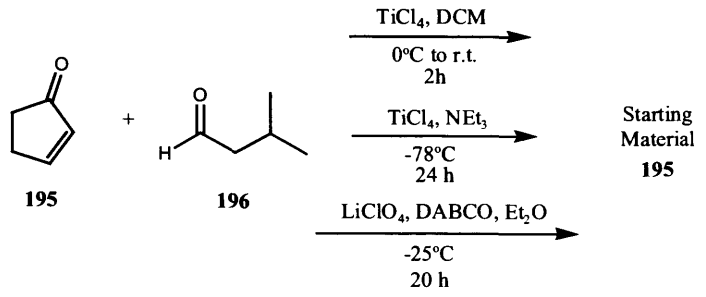


191 **194** **193**

Scheme 56

In the first instance, it seemed wise to test the validity of this strategy (Scheme 56) on an appropriate model α, β – unsaturated ketone, prior to commitment of our valuable enone (**191**). Cyclopent-2-enone (**195**) was, therefore, selected for reaction with isovaleryl aldehyde (**196**) under Baylis-Hillman conditions.

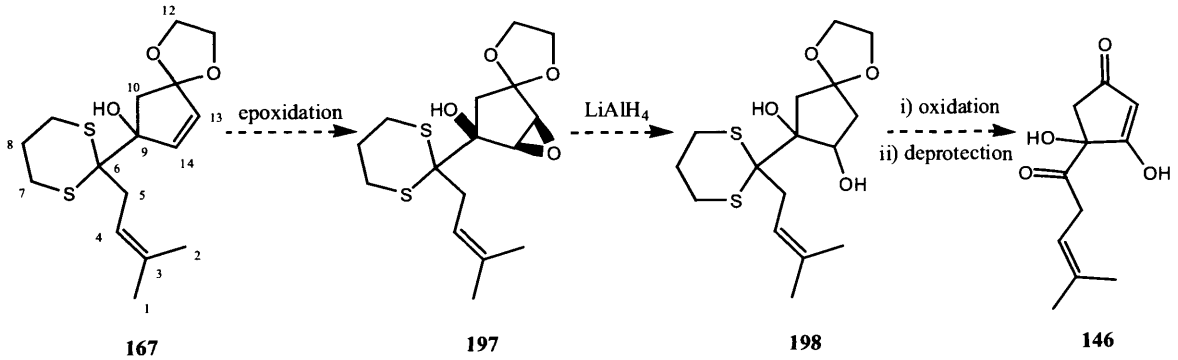
Careful examination of the literature revealed that the major drawbacks of the Baylis-Hillman protocol are its slow reaction rates and limited substrate scope.[125-127] G. Li *et al.*[126] claimed to extend the scope of this reaction by carrying out the coupling of aliphatic and aromatic aldehydes with cyclic α,β-unsaturated ketones, including cyclopent-2-enone (**195**), employing only the Lewis acid, $TiCl_4$. No tertiary amine or phosphine was required under these modified conditions, an observation rationalised by the suggestion that a small amount of chloride anion generated *in situ* fulfils the function of the nucleophile in the reaction mechanism. Regrettably, application of these conditions in our studies proved completely ineffective (Scheme 57). Employing more traditional protocols in the transformation, such as titanium tetrachloride and triethylamine[127] or lithium perchlorate and 1, 4-diazabicyclo[2, 2, 2]octane (DABCO),[128] also, unfortunately, failed to induce any reaction (Scheme 57).



Scheme 57

Since this chemistry was proving ineffective in the "straightforward" coupling of 2-cycopenten-1-one (**195**) with isovalerylaldehyde (**196**) we were of the opinion that any reaction between the more complex isohumulone analogue (**191**) and isovalerylaldehyde (**196**) would also be unproductive and, as a consequence, this approach to isohumulone analogue (**193**) was not explored any further.

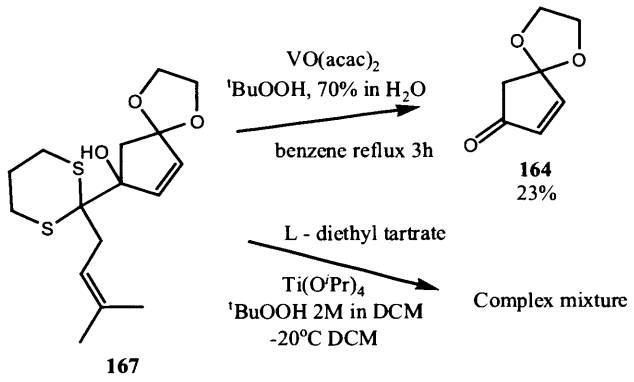
Accordingly, the focus of our attention turned to the production of the substituted cyclopentane-1,3-dione (**146**). An interesting and potentially useful transformation had already been noted in the production of cyclopentan-1,3-dione monoethylene ketal (**178**), whereby regioselective ring opening of the epoxide (**176**) had been directed by coordination to the ketal group and subsequent oxidation had led to the monoprotected 1, 3-dicarbonyl unit (Section 2.11 Scheme 48). The synthetic route outlined in Scheme 58 was consequently planned for production of analogue (**146**).



Scheme 58

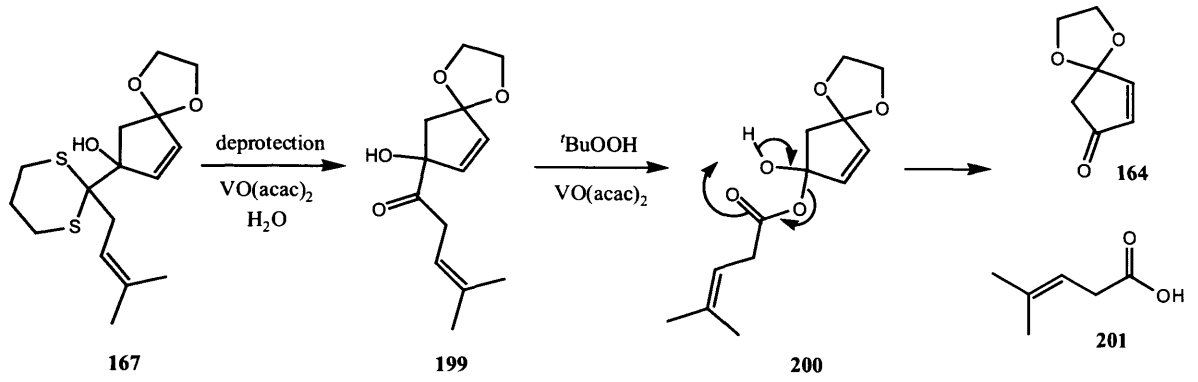
Central to the viability of this synthetic route was the ability to take advantage of the hydroxyl group at C9 of (**167**) to direct allylic epoxidation to the C13-C14 double bond

of this system, as opposed to the isolated C3-C4 double bond of the prenyl unit. Moreover, since only the "*cis*" epoxy alcohol (**197**) should be formed, we then reasoned that the necessary *trans* delivery of hydride for epoxide ring opening would involve the aforementioned coordination to the ketal and ensure regioselectivity. In the event, selective epoxidation of this allylic alcohol unit was attempted both by employing a vanadium catalyst in the presence of *tert*-butylhydroperoxide,[129] as well as subjecting the compound to classic Sharpless asymmetric epoxidation conditions (Scheme 59).[130] In the latter case, we imagined a best case scenario in which the reaction conditions would also effect a kinetic resolution of the starting material (**167**), leading to enantiomeric enrichment in the final product (**197**). In reality, the Sharpless epoxidation conditions resulted in a complex mixture of products, which could not be separated. On the other hand, the vanadium catalysed reaction led, intriguingly, to the isolation of the carbonyl compound (**164**), in 23% yield (Scheme 59).



Scheme 59

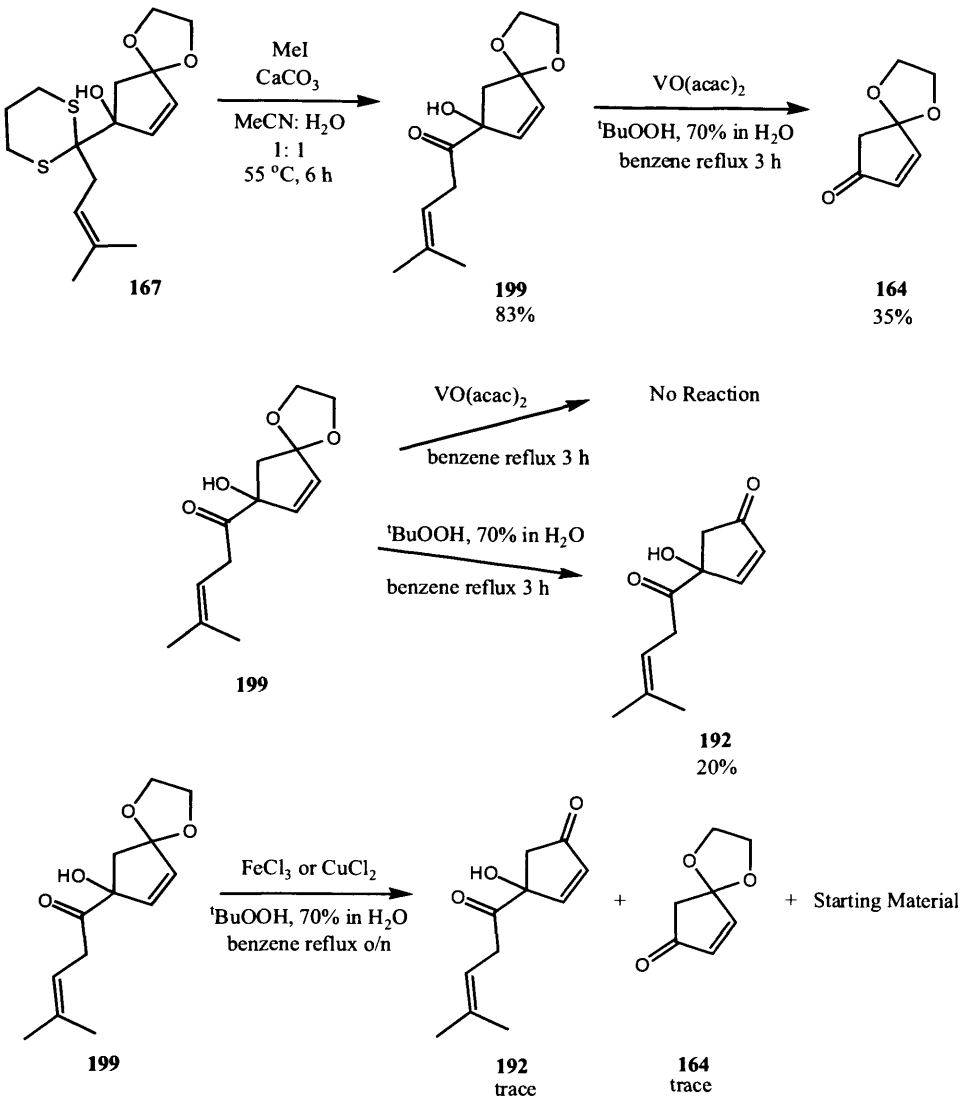
An initial theory put forward to explain this strange result was that this product (**164**) was arising via a retro-dithiane addition of the starting material (**167**), but this proposition was deemed improbable, especially since none of the relevant dithiane was recovered from the reaction.



Scheme 60

Another, more likely, hypothesis is that the isohumulone analogue (**167**) undergoes initial deprotection of the thioketal, mediated by vanadium, to give ketone (**199**), before participating in a typical Baeyer-Villiger oxidation to form the acylated hemiketal (**200**). Intermediate (**200**) can then cleave to form the ketone (**164**) and the carboxylic acid (**201**), with the latter being lost during the aqueous work up of the reaction (Scheme 60). Unfortunately, we could not find any examples in the literature of acyloin systems undergoing a similar Baeyer-Villiger reaction to support this proposition.

In order to test this theory, the partially deprotected analogue (**199**) was produced and subjected to the same conditions. In this case, once again compound (**164**) was isolated (Scheme 61), a result in support of the Baeyer-Villiger oxidation hypothesis. Reaction in the absence of the metal catalyst led only to deprotection of the ketal group to give (**192**) (Scheme 61). This observation proves that the vanadium complex also plays some role in this oxidation, perhaps through activation of the reacting carbonyl centre by chelation, in an analogous fashion to the Lewis acids in Baeyer-Villiger type oxidations which employ hydrogen peroxide.[131]



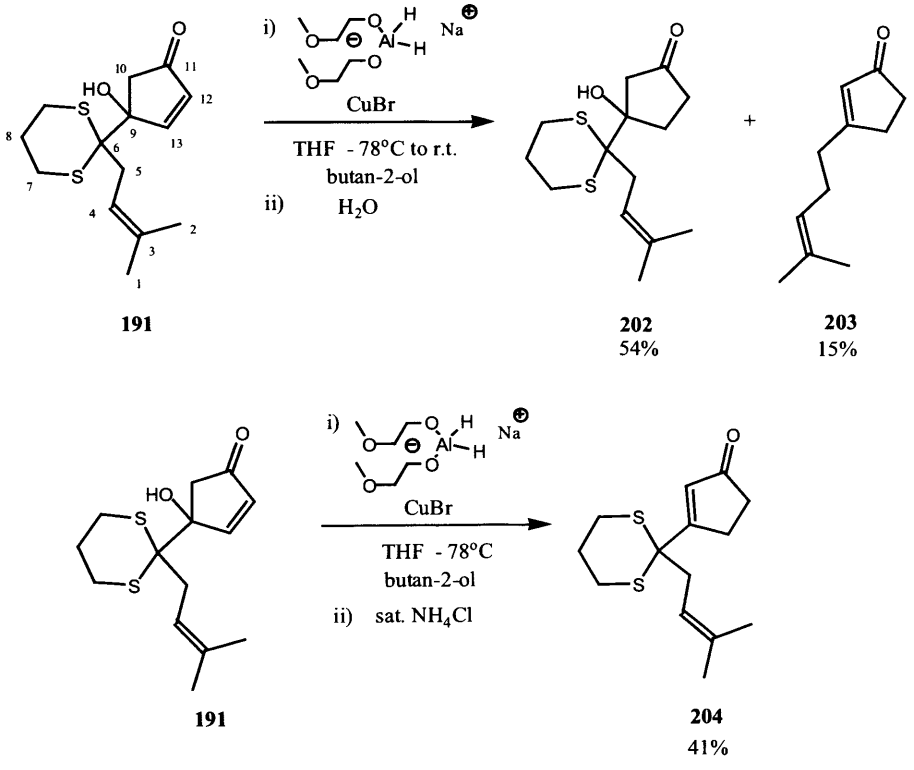
Scheme 61

Further investigation of the process revealed that enone (**164**) could also be detected, albeit only in trace quantities by NMR analysis, by employing either iron (III) chloride or copper (II) chloride as the metal catalyst in the reaction (Scheme 61).

Whilst the chemistry involving attempted epoxidation of protected isohumulone analogues (**167**) and (**191**) had produced some interesting results it did not, in fact, further our search for new model compounds.

A more straightforward reaction involved the selective reduction of the enone double bond (C12-C13) of compound (**191**). It was hoped that reduction followed by deprotection of this cyclopentenone (**191**) would facilitate the production of an isohumulone analogue which had, as yet, not been synthesised, due to shortcomings in

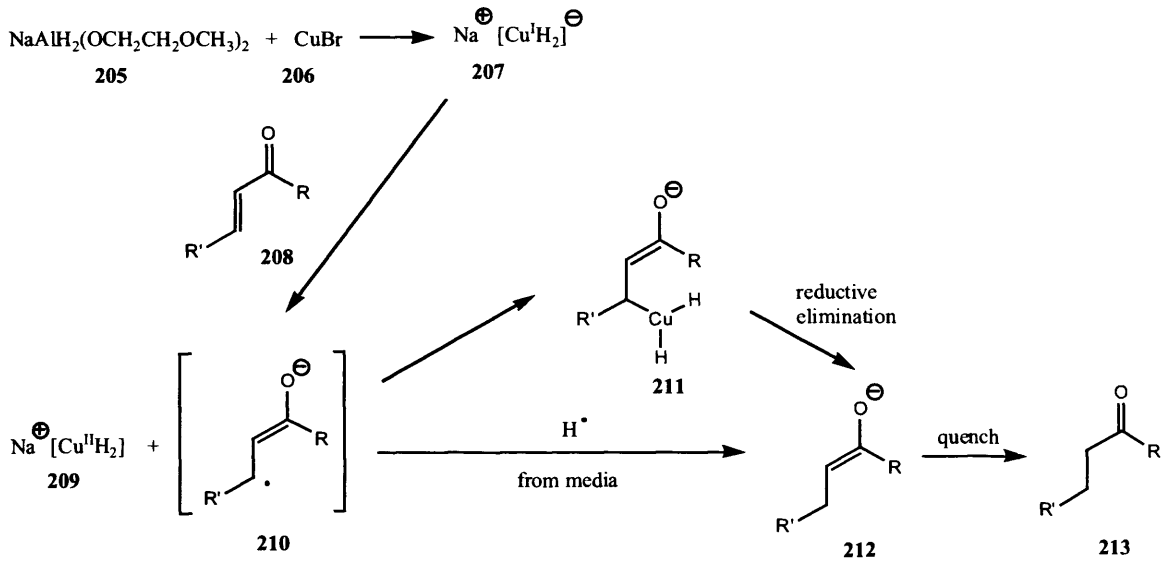
the dithiane addition chemistry (Section 2.11, Scheme 49). We were pleased to discover that a known reducing system,[132] combining sodium bis(2-methoxyethoxy)aluminium hydride (RED-Al) and cuprous bromide, proved both successful and selective in this reduction, giving the substituted 3-hydroxycyclopentanone (**202**) in a yield of 54% (Scheme 62). As anticipated great care had to be exercised with this protocol, since the β-hydroxycarbonyl moiety in the cyclopentane ring of (**202**) is extremely prone to the elimination of water and a slightly acidic work up procedure led solely to the isolation of the enone (**204**) from the reaction (Scheme 62). These observations reinforce the idea that the presence of an additional carbon-carbon double bond in the cyclopentanoid unit of the iso-α-acids (**1**, **4**, **5**) prevents dehydration since an antiaromatic system would be formed (Introduction, Section 1.2).



Scheme 62

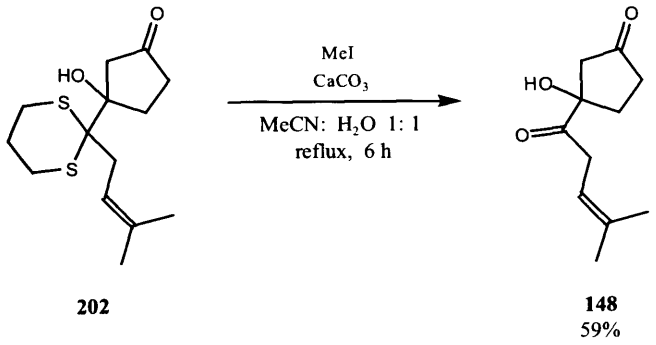
Further evidence for the temperamental nature of this transformation was provided when, on one occasion, along with the desired dithiane (**202**) an intriguing by-product was recovered from the reaction. After a lot of deliberation the structure of this mystery impurity was assigned as the enone (**203**). It appears that these conditions can not only lead to the dehydration of compound (**202**) but can also facilitate the reductive elimination of the dithiane present in the molecule (**202**). In retrospect this result is not without precedent since exposing a thioketal to copper ions in the presence of a hydride source is a technique which has been previously employed for reductive removal of thioketals.[133]

M. F. Semmelhack *et al.*[132] have suggested that this conjugate reduction of enones is performed by a copper hydride species (**207**), generated from RED-Al (**205**) and cuprous bromide (**206**) (Scheme 63). This complex (**207**) acts as an electron source, forming the radical anion (**210**) of the enone (**208**). Conversion of this reactive intermediate (**210**) to the final product is then effected, either by direct hydrogen atom abstraction from the reaction media or by coupling with the copper hydride species (**209**), followed by reductive elimination (Scheme 63). It is thought that the 2-butanol present in the reaction acts as a proton donor and speeds formation of the key copper complex (**211**), minimising side products arising from the dimerisation of the radical anion (**210**). However, the precise function of the alcohol is unclear.



Scheme 63

Deprotection of the reduced derivative (**202**) obtained from this procedure was successfully achieved using the method employed previously, yielding the new isohumulone analogue (**148**) in a yield of 59% (Scheme 64).

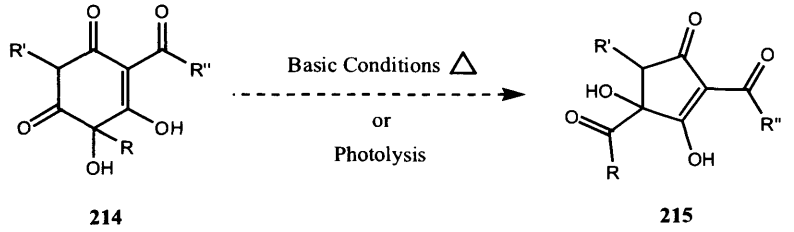


Scheme 64

Thus, the production of the labile α-hydroxyketone (**148**) had proven to be our only success in attempts to achieve further variation of the advanced chromophoric analogue (**192**). Moreover, since the dithiane anion chemistry had failed when the cyclopentyl systems had become too complex (Section 2.11), it seemed that this approach was limiting. We therefore concluded that further strategies were now required in order to form additional model compounds.

2.2 Attempted Synthesis And Isomerisation Of Humulone (9) And Its Analogues.

As we have seen in the introductory overview (Section 1.63) the synthesis[1, 12, 14, 90, 91] and ring contracting isomerisation of the natural product, humulone (**9**), to form the isohumulones has been very well documented.[11-13, 15, 34] Indeed, this type of transformation has already found application in the production of polycarbonyl cyclopentanoids in the work of P. M. Brown and G. A. Howard[86] and H. Obara *et al.*[89] (Introduction, Section 1.63). Encouraged by this literature precedent we therefore intended to prepare humulone analogues such as (**214**) and subject these compounds (**214**) to the ring contraction conditions used in the isomerisation of humulone (**9**), thus constructing even more highly functionalised isohumulone analogues (**215**) (Scheme 65).



214 **215**

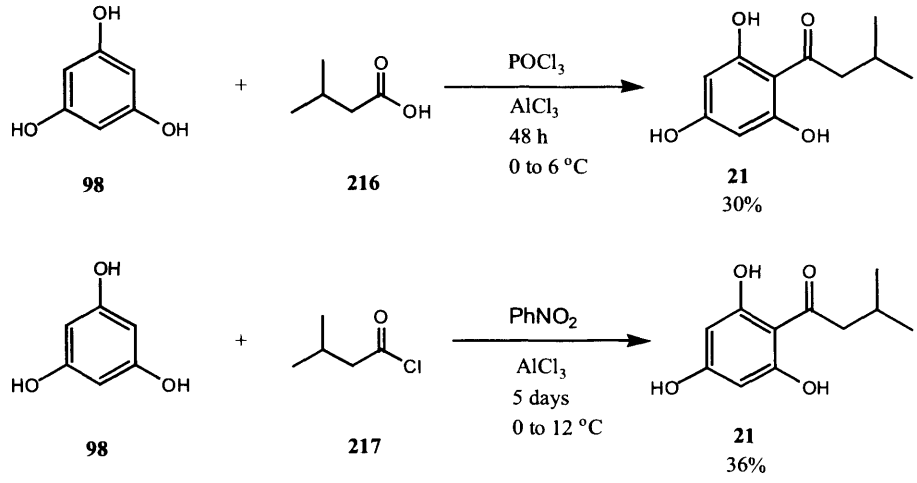
Scheme 65

2.21 Attempted Synthesis Of Humulone (9).

Our preliminary studies centred on the production of humulone (**9**) itself, following the well established route which involves initial functionalisation of the commercially available compound, phloroglucinol (**98**), followed by oxidation of the resultant polysubstituted aromatic (**22**) to produce humulone (**9**) (Introduction, Section 1.63, Scheme 28). It is the final oxidation step of this sequence which is currently very low yielding and it was felt that increasing the efficiency and selectivity of this reaction would be the key to making this synthetic route viable.

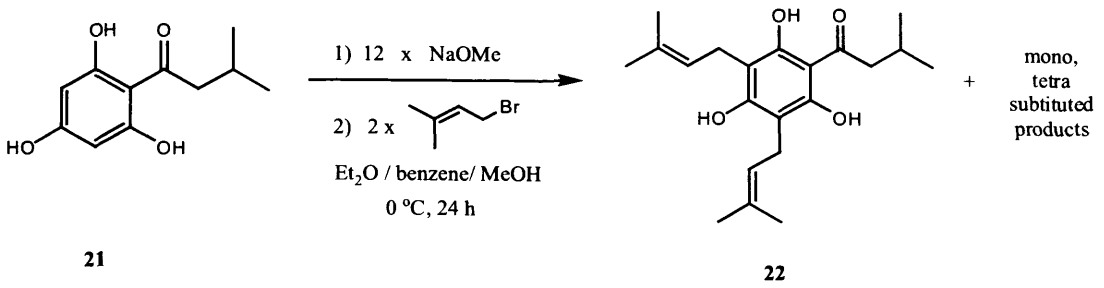
Work commenced with the acylation of phloroglucinol (**98**). Phloroisovalerophenone (**21**) was prepared via a classical Friedel-Crafts reaction of the aromatic compound (**98**) with an acid chloride (**216**), in the presence of aluminium trichloride (Scheme 66). Two

methods were examined and similar results were obtained either when isovaleryl chloride (**217**) was generated *in situ*, according to a procedure by van Klink *et al.*,[91] or when it was added directly to the reaction using a procedure described by T. Nomura *et al.*.[134] The protocol of generating the acid chloride *in situ*, however, held the advantage of a much simpler work up procedure, circumventing problems associated with the removal of nitrobenzene from the crude product (Scheme 66).



Scheme 66

Initial attempts to prenylate this acylated phloroglucinol (**21**) followed a well established procedure.[1] In this approach the cyclohexyl ring of phloroisovalerophenone (**21**) is considered as a polycarbonyl unit and treatment of this molecule with sodium methoxide is purported to form the di-sodium salt of phloroisovalerophenone (**21**). Sequential quenching of such an intermediate with 1-bromo-3-methyl-2-butene is then claimed to yield deoxyhumulone (**22**).[1] In our hands this protocol produced a mixture of substituted cyclic compounds, with NMR analysis suggesting the presence of some of the required deoxyhumulone (**22**), along with what appeared to be the mono and tetrasubstituted derivatives (Scheme 67). This complex mixture could not be separated effectively or characterised.

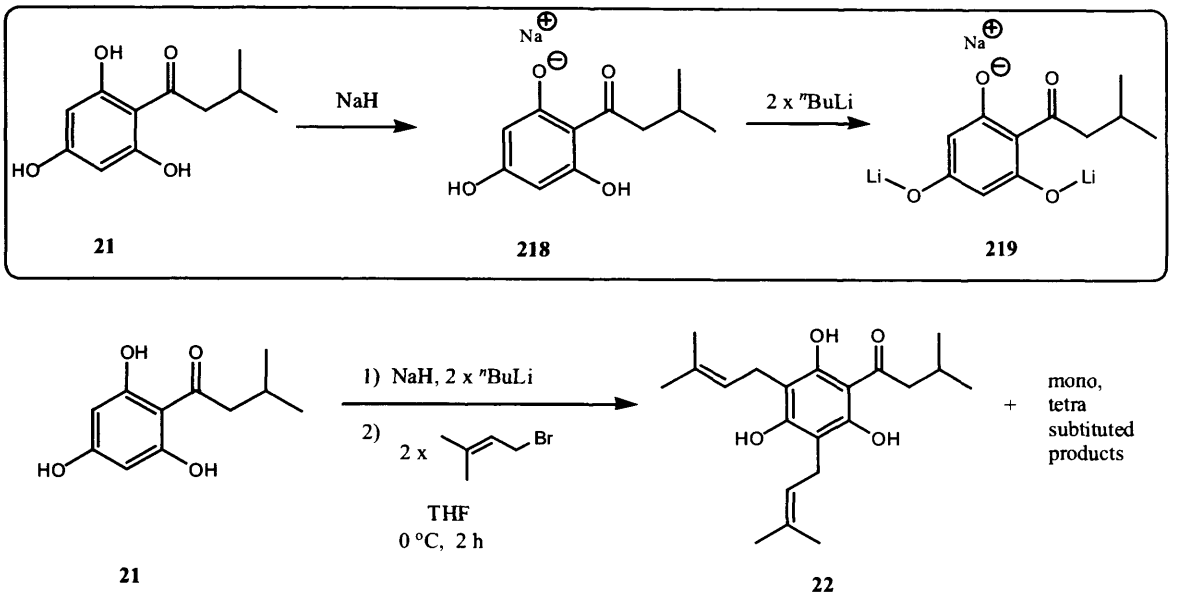


21 22

Scheme 67

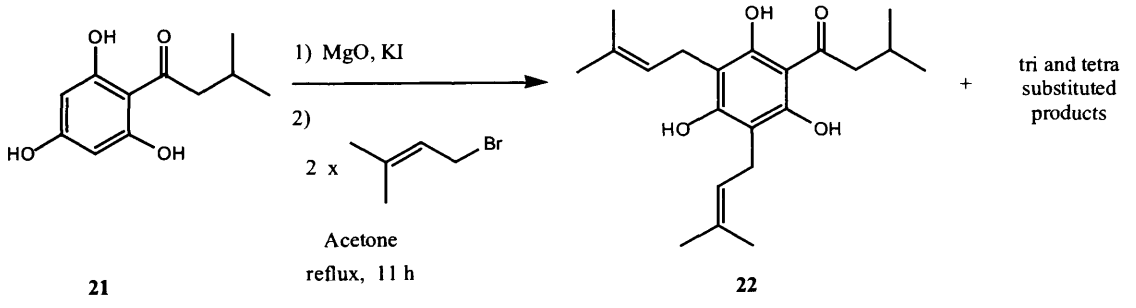
We reasoned, at this point, that the failure of this synthesis was largely due to the excess of unselective base which was employed in the transformation. Even if the mechanism does indeed proceed via the alkenylation of a disodium salt of isovalerophenone (**20**), as reported,[1] with such a large amount of sodium methoxide in the reaction there is nothing to prevent further substitution of the product from occurring.

In order to combat this problem we elected to devise a more selective method of forming deoxyhumulone (**22**) involving generation of a potentially more covalent di-lithio intermediate. Firstly, removal of the most acidic proton in the "centre" of the tricarbonyl unit of phloroisovalerophenone (**21**) would be achieved using one equivalent of sodium hydride, thus forming a mono-anion (**218**). Two equivalents of ^{n}BuLi would then be added to remove two further acidic protons and form the di-lithio species (**219**) (Scheme 68). Finally, addition of 1-bromo-3-methyl-2-butene to this intermediate would, in theory, yield the required product (**22**). Unfortunately, in the event, application of this strategy also only led to a complex mixture of products (Scheme 68).



Scheme 68

Hope was revived when recourse to the literature revealed yet another procedure for the production of deoxyhumulone (**22**), developed by L. Givaudan[135] and utilising magnesium oxide and potassium iodide in acetone as solvent. Frustratingly, this reaction turned out to be unreliable, giving a mixture of products, which were again tentatively assigned by NMR analysis as molecules arising as a result of varying degrees of substitution on the six membered ring (Scheme 69). These compounds could not be separated and at this stage this approach to forming deoxyhumulone (**22**) was not pursued further.



Scheme 69

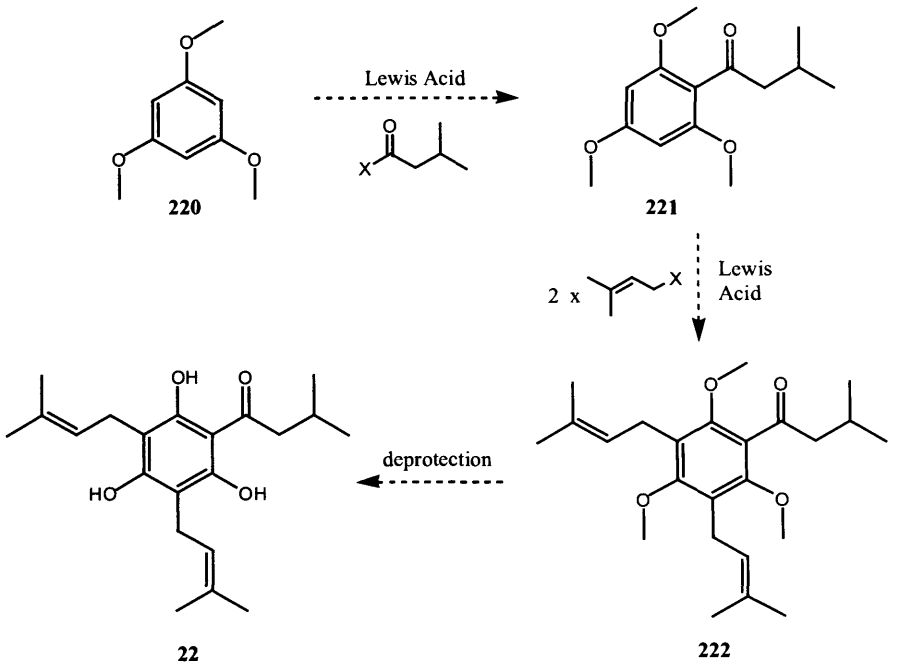
Many of the problems encountered thus far regarding the attempted production of deoxyhumulone (**22**) could be attributed to the inherent tautomerisation characteristics of the phloroglucinol ring. The aromatic configuration of phloroisovalerophenone (**21**)

exists in equilibrium with polycarbonyl tautomers and so over substitution of the ring is a facile process, leading to a product mixture of similar compounds which are hard to separate, as highlighted in Scheme 67-69.

2.22 Attempted Synthesis Of Protected Humulone (9) Compounds.

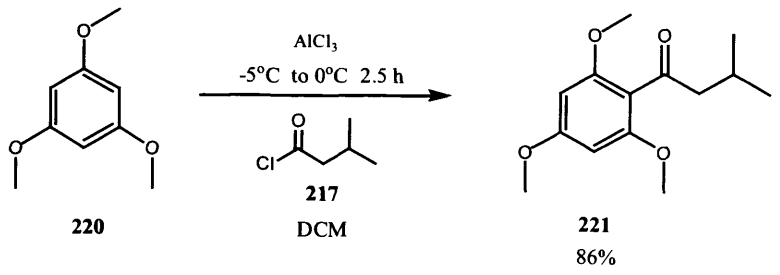
We reasoned that the problems associated with preparation of deoxyhumulone (**21**) would be alleviated if this ring system could be locked into the aromatic configuration, thus preventing over substitution.

A simple method of achieving this involved exploitation of commercially available phloroglucinol trimethyl ether (**220**). Functionalisation of this compound using classical Friedel-Crafts chemistry followed by deprotection was considered an ideal method for the clean production of deoxyhumulone (**22**) (Scheme 70).



Scheme 70

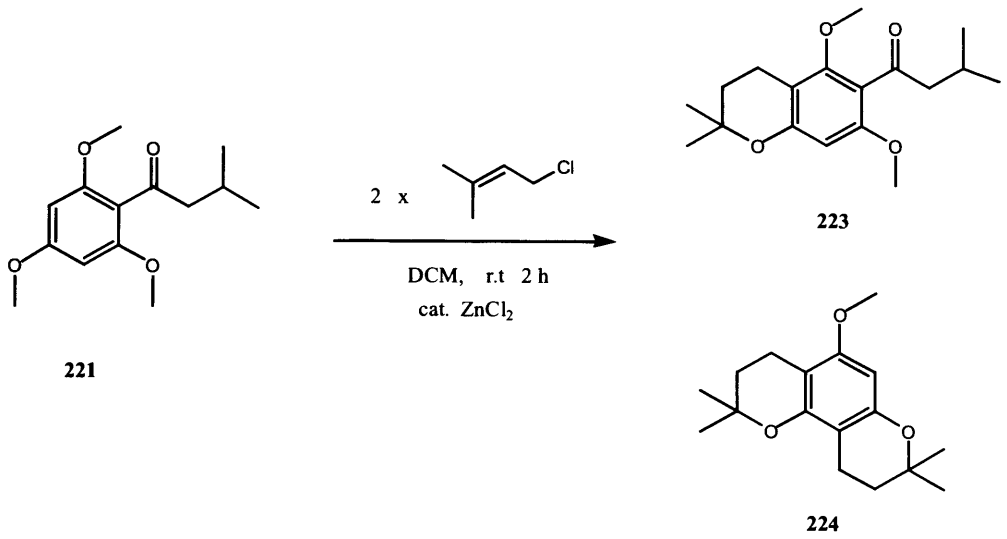
Pleasingly, we discovered that the acylated protected phloroglucinol derivative (**221**) could be synthesised according to a literature procedure,[136] in a yield of 86% (Scheme 71).



Scheme 71

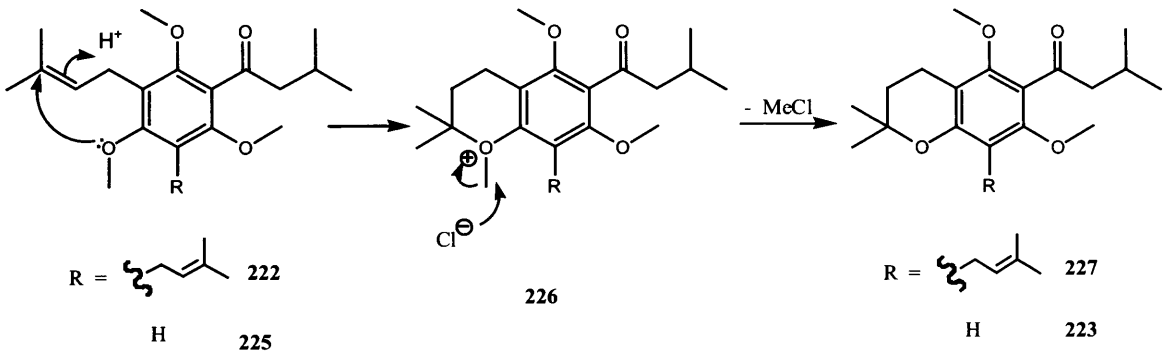
With Compound (**221**) in hand, investigations then commenced into the formation of deoxyhumulone trimethyl ether (**222**). Phloroisovalerophenone trimethyl ether (**221**) was stirred with two equivalents of 1-bromo-3-methyl-2-butene in the presence of aluminium trichloride, in an attempt to induce a Friedel-Crafts alkylation reaction. Somewhat surprisingly, only the starting aromatic compound (**221**) and what appeared to be a polymerised alkyl chain were recovered from this experiment. Investigations into the origins of this polymerised product revealed that stirring the allylic bromide in the presence of aluminium trichloride was enough to facilitate this decomposition. The reactive allylic bromide and strong Lewis acid employed in this procedure is obviously a combination which results in complete consumption of this substrate before any aromatic substitution can occur.

After a small amount of experimentation, we established that by using prenyl chloride in this reaction in place of the bromide and employing the milder Lewis acid, zinc chloride, this decomposition could be completely avoided. While this protocol appeared promising, a careful NMR study of the crude product revealed that the desired prenylated aromatic (**222**) had not been formed under these conditions. The crude oil appeared to consist of a mixture of two aromatic ethers which were tentatively assigned as (**223**) and (**224**) (Scheme 72). All attempts to separate and purify these compounds failed. These types of ethers have been observed in beer and are known to originate from derivatives of humulone (**9**),[1, 33] and have also been produced during the alkenylation of phloroglucinol derivatives.[90, 137-139]



Scheme 72

In this case, we believe that these fused polycyclic systems (**223**, **224**) originate from further reaction of the alkenyl side chains of the prenylated products (**222**, **225**) with the methoxy groups of the aromatic ring under the acidic conditions generated during the initial prenylation reaction, as shown in Scheme 73. In product (**224**) cyclic ether formation occurred twice and was also accompanied by loss of the acyl side chain from the aromatic ring, a process which is also facilitated by the acidic conditions.

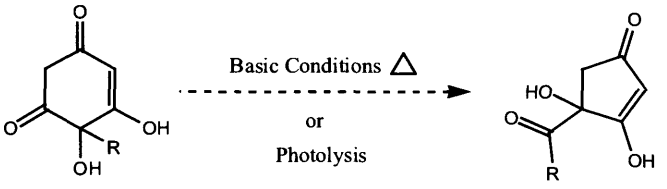


Scheme 73

At this point alternative methods for the synthesis and ring contraction of humulone analogues were of obvious interest.

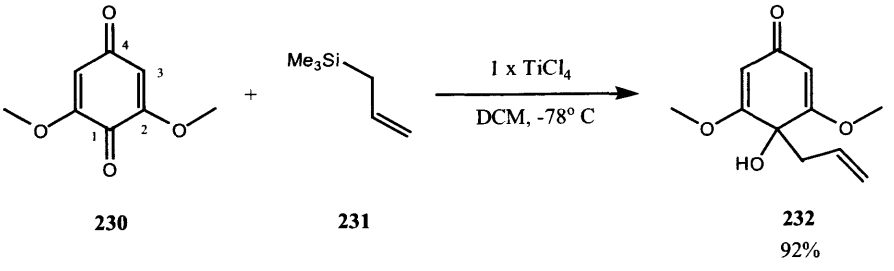
2.23 Attempted Isomerisation Of Humulone Analogues.

For this approach we elected, in the first instance, to prepare simple humulone analogues with the core structure (**228**). We considered that such compounds would be simpler to synthesise than the natural product (**9**) itself. Moreover, if a ring contraction reaction could be induced isohumulone analogues with structure (**229**) would be produced, and these would be extremely useful in photodegradation studies (Scheme 74).



Scheme 74

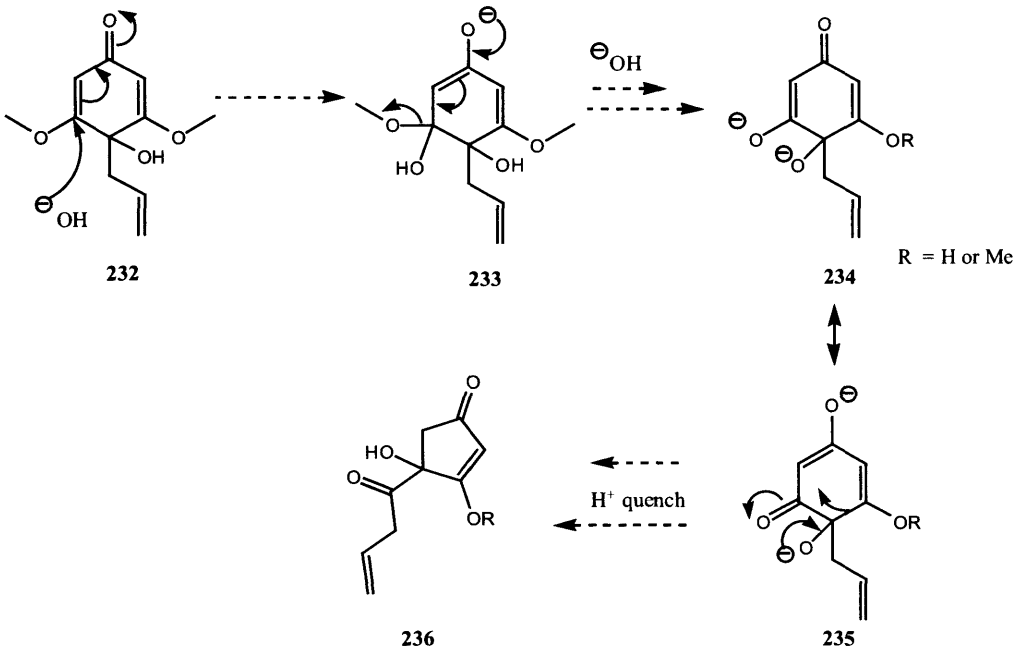
Fortunately, A. Hosomi and H. Sakurai have described the preparation of a protected derivative of just such a polyoxygenated cyclohexane, where R is an allyl group (**228**).[140] Their procedure was simple to follow, and addition of allyltrimethyl silane (**231**) to commercially available 2,6-dimethoxy-*p*-benzoquinone (**230**) in the presence of titanium tetrachloride, furnished the required substituted quinone (**232**) in an excellent yield (Scheme 75). Deactivation of the carbonyl at C4 of the starting material (**230**) by conjugation with the methyl enol ethers explains the regiospecific nature of this addition.



Scheme 75

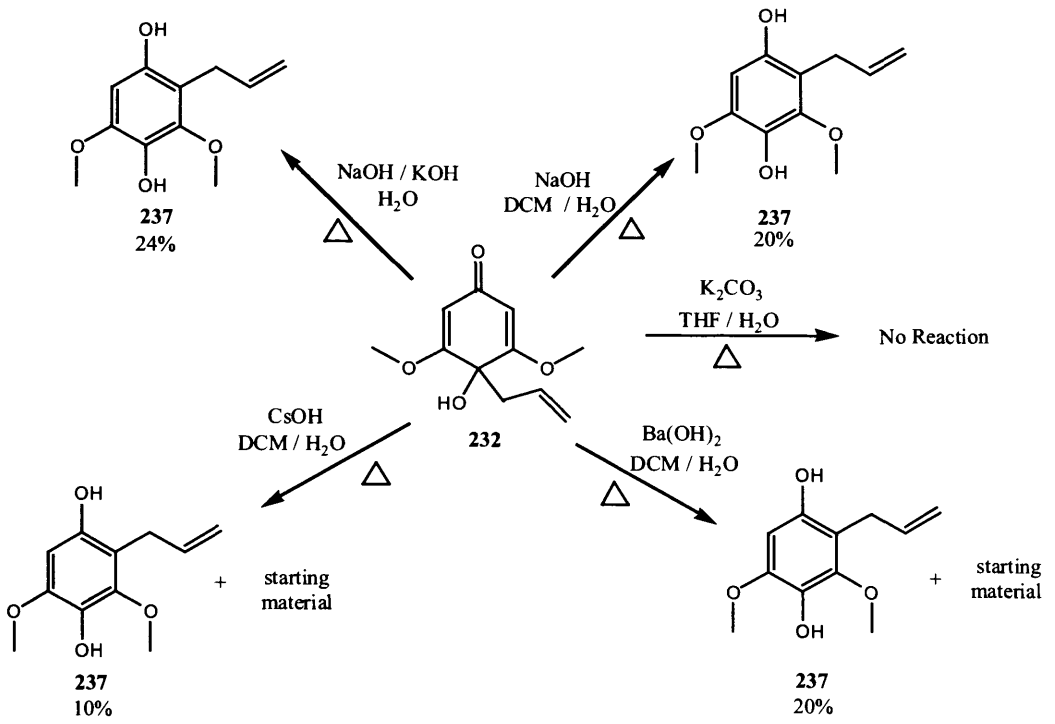
The resultant methyl enol ether (**232**) obtained from this process required only deprotection before a ring contraction reaction could be attempted. We initially

conceived a method whereby both transformations might be carried out in a single vessel using hydroxide anion both as a nucleophile and as a base. Thus, given the symmetry of the quinone (**230**), hydroxide anion should first act as a means of deprotecting either one or both of the methyl enol ethers of (**232**) to produce intermediate (**234**). This deprotection method has some literature precedent[141-143] and occurs via a conjugate addition-elimination reaction, as shown in Scheme 76. It was hoped that the basic conditions of the reaction would then facilitate ring contraction of (**235**) (Scheme 76), in an analogous fashion to the base induced isomerisation of humulone (**9**) to isohumulone (**1**) (Introduction, Section 1.31, Scheme 4).



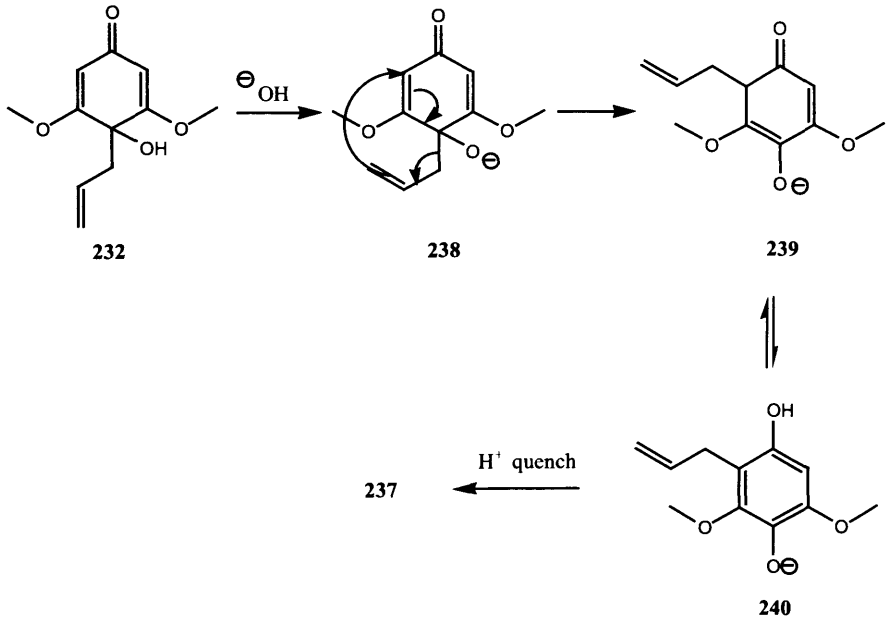
Scheme 76

To this end, a selection of different hydroxide bases were employed under various different reaction conditions. Unfortunately the only product isolated from all these experiments along with starting material was the allyl substituted aromatic compound (**237**) (Scheme 77).



Scheme 77

Formation of hydroquinone (**237**) can be explained if initial deprotonation of (**232**) to form alkoxide anion (**238**) is followed by an anion assisted oxy-Cope rearrangement, as shown in Scheme 78.



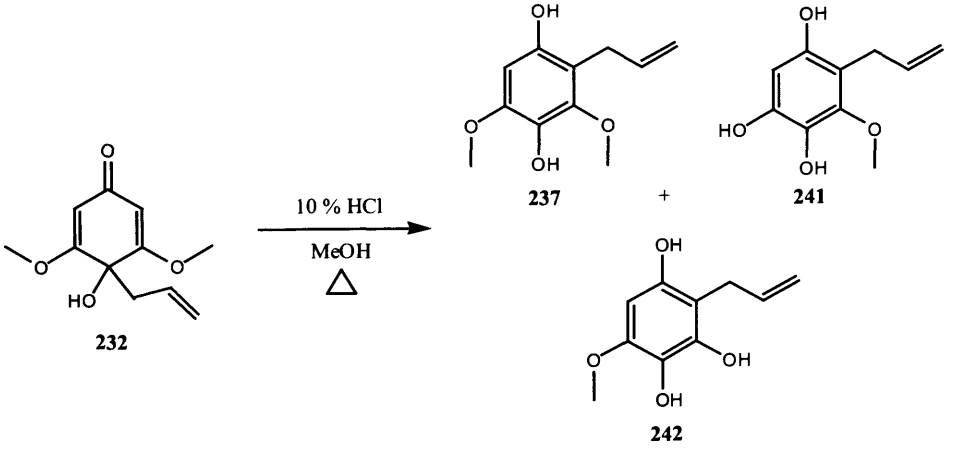
Scheme 78

This type of rearrangement is favoured both by the formation of the anion on oxygen, a kinetic effect first noted by D. A. Evans,[144] and furthermore in the present instance, by the fact that a thermodynamically stable aromatic system is formed in the process. Clearly, with hindsight, this reaction will be faster than the deprotection or ring contraction reaction we had envisioned. Indeed, such isomerisations have been observed in very similar compounds, albeit under Lewis acidic conditions.[140, 145]

Since the foregoing experiments had exposed a fundamental problem with our one-pot deprotection-ring contraction strategy, attempts were now made to carry out these two steps in a sequential fashion.

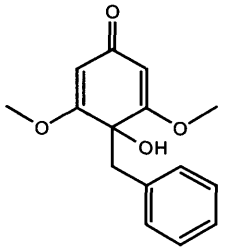
Thus, compound (**232**) was treated with a 10% aqueous HCl solution in methanol with a view to unmasking the two methyl enol ether groups (Scheme 79). NMR analysis of the crude product revealed a complex mixture which appeared, once again, to originate from the [3,3] sigmatropic rearrangement of the alcohol (**232**) at various stages of deprotection. These aromatic compounds were cautiously assigned as (**237**), (**241**) and (**242**) but could not be separated effectively or fully characterised (Scheme 79). This finding only served to reinforce the facile nature of this particular rearrangement, since such oxy-Cope reactions are known to be a lot slower when not anion assisted.[144]

In a final effort to effect this deprotection reaction, avoiding the rearrangement, a solution of compound (**232**) was treated with BBr_3. Frustratingly, these milder conditions led only to the recovery of starting material.



Scheme 79

It was felt that a simple solution to the considerable problem being posed by this oxy-Cope reaction lay in synthesising a humulone derivative where the pendant functionality does not contain an allylic double bond, and cannot therefore, undergo this rearrangement. The benzyl group seemed an ideal candidate to fulfil this role, due to its radical stabilising capabilities. Thus, if a ring contraction could be effected on such a compound (**243**) (Fig. 9), the resulting isohumulone analogue, could, potentially, produce a stabilised benzylic radical during photolysis studies.



243

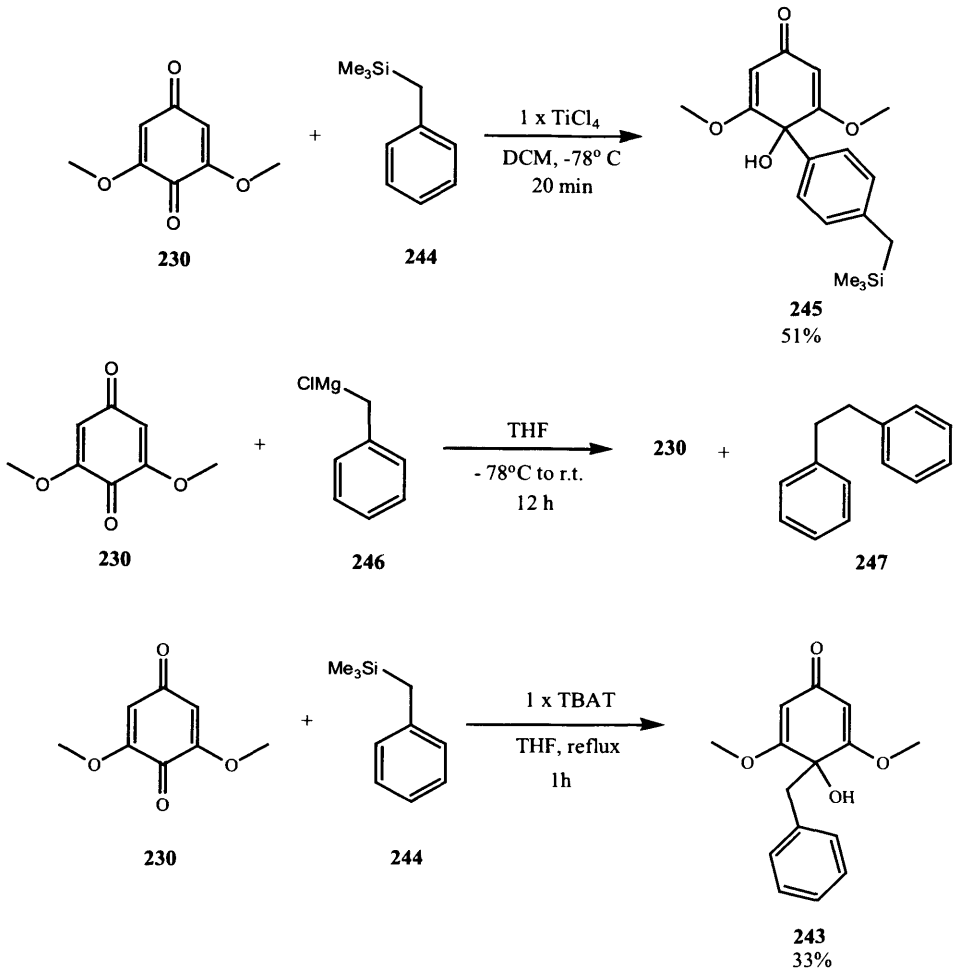
Fig. 9

Preliminary investigations into the formation of the benzyl analogue (**243**) followed the chemistry employed in the preparation of the allylic derivative (**232**), reacting 2,6-dimethoxy-*p*-benzoquinone (**230**) with trimethylbenzyl silane (**244**) in the presence of titanium tetrachloride. Unexpectedly, in this case these conditions led to the isolation of the cross conjugated hydroxydienone (**245**) in 51% yield, which appeared to originate from a Friedel-Crafts reaction between the quinone (**230**) and the aromatic ring of the benzyl silane (**244**) (Scheme 80).

In an alternative approach, treatment of 2,6-dimethoxy-*p*-benzoquinone (**230**) with benzyl magnesium bromide (**246**) as the nucleophile resulted in the recovery of starting material (**230**) contaminated by a homo coupling product (**247**) derived from the benzyl Grignard (**246**) (Scheme 80).

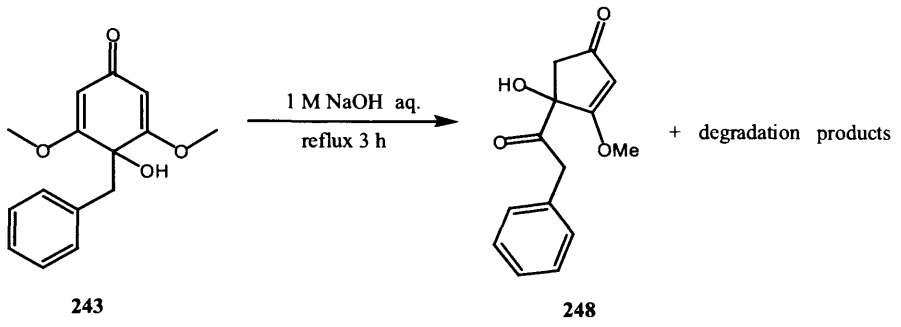
Addition of the silane (**244**) to the quinone (**230**) was eventually achieved by selection of the reaction conditions developed by DeShong *et al.*,[146, 147] which have been employed previously to promote nucleophilic attack of silanes on numerous different electrophiles.[147] Thus, the anhydrous fluoride source, tetrabutylammonium triphenyldifluorosilicate (TBAT), was used as a means of activating trimethylbenzyl

silane (**244**) and, to our delight, this furnished the required product (**243**) in 33% yield (Scheme 80).



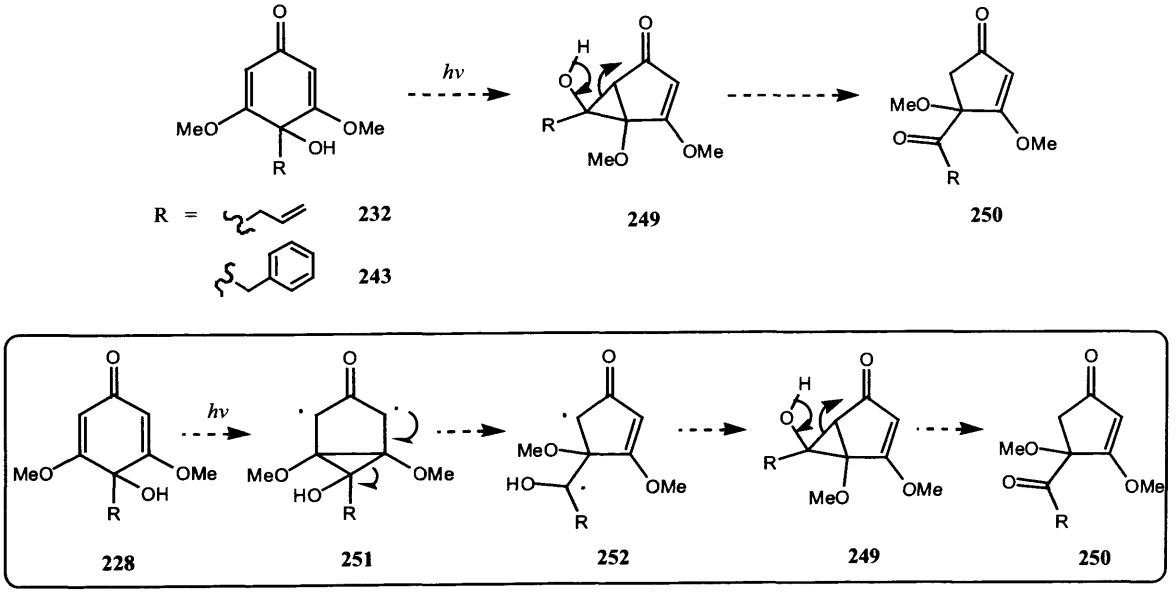
Scheme 80

Sadly, investigations into the ring contraction of this benzyl congener (**243**) under basic conditions were uniformly unsuccessful. Heating the compound (**243**) in an aqueous solution of sodium hydroxide produced a black oil, which appeared,by NMR analysis to contain a small amount of the required ring contracted compound (**248**) together with a complex mixture of degradation products (Scheme 81). Attempted optimisation studies only went to prove that the high temperature and excess of strong base necessary to facilitate the transformation also led to further unwanted reactions. All efforts to isolate the small quantities of the desired product (**248**) from these mixtures were unsuccessful.



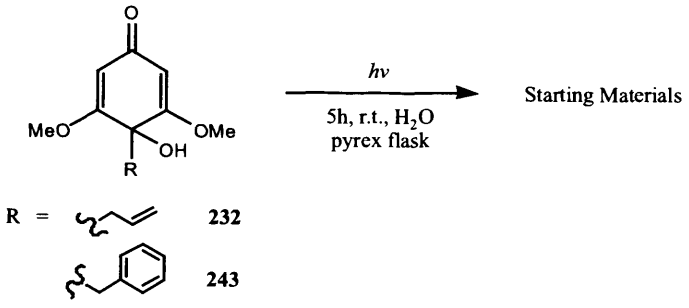
Scheme 81

In order to avoid the use of these problematic alkaline conditions we attempted the photochemical ring contraction of protected humulone analogues (**232**) and (**243**) in an analogous fashion to the protocol developed by F. R. Sharpe and I. H. L. Ormrod for the isomerisation of humulone (**9**) (Introduction, Section 1.31).[15] Thus, it was envisaged that the cross conjugated dienones (**232** or **243**) would undergo a photoinduced rearrangement to form an intermediate cyclopropane (**249**) which could then open to yield the protected isohumulone analogue (**250**). It is unclear whether such a transformation would be the result of a di-π-methane (DPM) rearrangement,[18] as depicted in Scheme 82, or the Zimmerman-Schuster reaction,[19, 20] described in the introduction to this thesis (Section 1.31, Scheme 8), but since both mechanisms would lead to the same intermediate (**249**), this aspect was of little consequence.



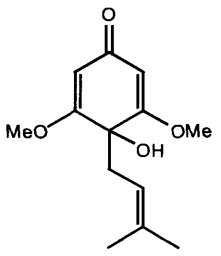
Scheme 82

A brief study of this approach was disappointing and only starting materials were recovered from the experiments attempted (Scheme 83).



Scheme 83

Since the addition of nucleophiles to 2,6-dimethoxy-*p*-benzoquinone (**230**) had been successful but subsequent ring contraction of the products (**232**, **243**) was proving problematic, a route towards the humulone analogue (**253**) (Fig. 10) was then considered, in the hope that the extra methyl groups present on the pendant prenyl chain would cause sufficient steric hindrance to subdue the facile oxy-Cope rearrangement observed in some of the previous reactions (Scheme 77).

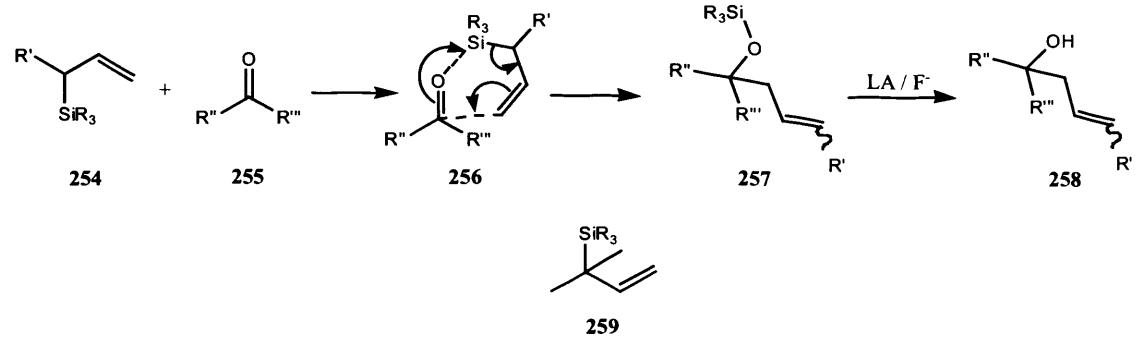


253

Fig. 10

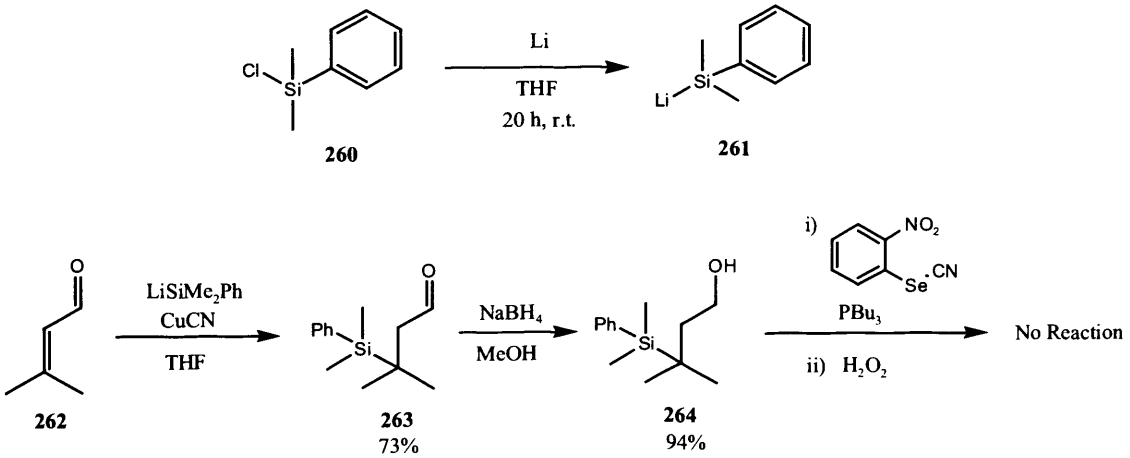
We soon realised that preparation of the allyl silane required for construction of such a derivative (**253**), would not be as trivial as it initially appeared. The reaction of allyl silanes with ketones is known to occur through a six membered transitions state (**256**), with transposition of the double bond during the process, as shown in Scheme 84.[148] Hence, the allyl silane required for our studies, (**259**) (Scheme 84), carries the silicon substituent bonded to the most substituted carbon atom of the allylic system. Unfortunately, the vast majority of reactions developed to synthesise this class of

molecule lead to the silicon atom being attached to the least hindered carbon atom of the allyl moiety.[148-151]



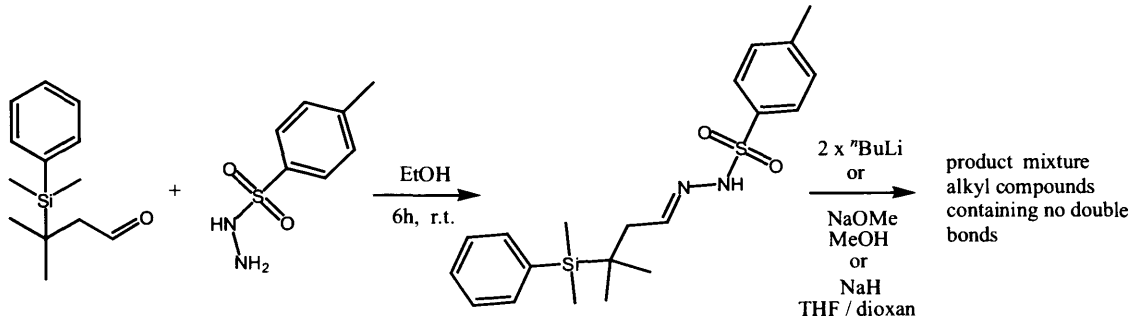
Scheme 84

One of the few regioselective methods of constructing allylic silanes can be found in the elegant work of Fleming and Waterson,[152] based on the conjugate addition of a silyl lithium reagent (**261**) to an enone. Accordingly, dimethyl(phenyl)silyllithium (**261**) was prepared by stirring lithium shot with the relevant silyl chloride (**260**) (Scheme 85) and then utilised in the reaction sequence shown in Scheme 85, to produce the alcohol (**264**). In the work of Fleming and Waterson[152] this primary alcohol (**264**) was then transformed into the terminal alkene (**259**) via formation and subsequent elimination of a selenoxide. However, in our hands this final step proved difficult and, moreover, required the use of stoichiometric quantities of toxic selenium compounds.



Scheme 85

An alternative elimination was therefore required, and to this end, the tosyl hydrazone (**266**) of aldehyde (**263**) was formed by modification of a known literature procedure (Scheme 86).[153] It was thought that this tosyl hydrazone (**266**) could undergo either the reaction developed by Bamford and Stevens,[154, 155] or the variation of this transformation discovered by Shapiro.[156] Both of these protocols can be used to produce alkenes by treatment of tosyl hydrazones with a base. The first employs bases such as NaOMe and metal hydrides, whereas, the second employs alkyl lithiums such as ^{n}BuLi.

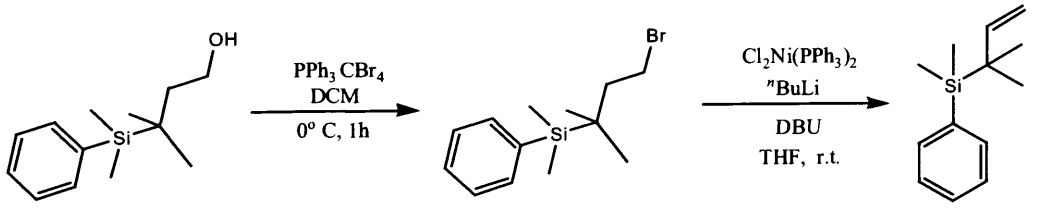


263 **265** **266** 93%

Scheme 86

Unfortunately, the strongly basic conditions required to carry out either a Shapiro or Bamford-Stevens reaction led to extensive decomposition of the starting tosyl hydrazone (**266**) and NMR analysis revealed a mixture of products which did not contain double bonds (Scheme 86).

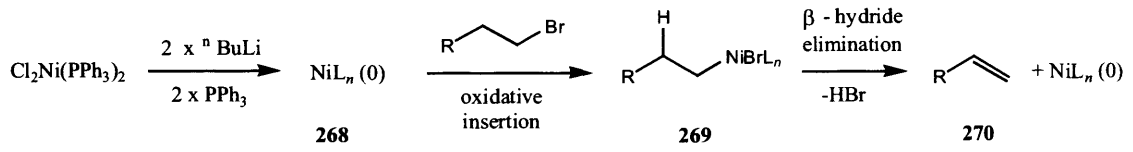
E. Smith *et al.*[157, 158] have described the elimination of terminal bromides by the use of nickel (0) complexes and application of this method gave better results. The bromide (**267**) was formed and then treated with a Nickel (0) species, generated *in situ*, to produce the desired tertiary allylic silane in a yield of 60% (Scheme 87).



264 **267** 98% **259** 60%

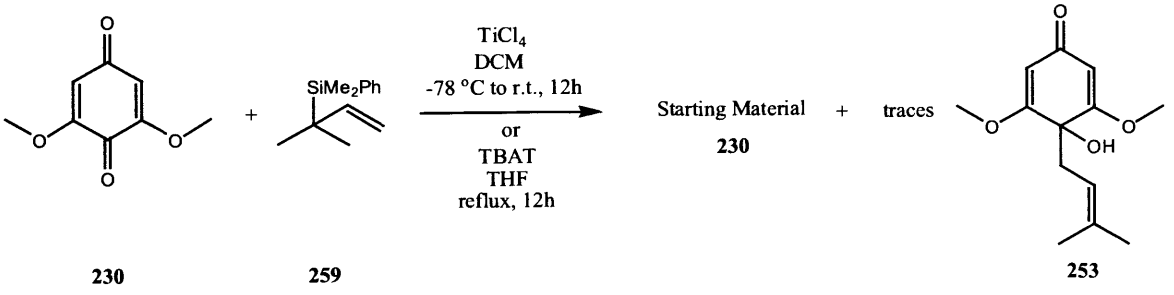
Scheme 87

From a mechanistic standpoint, the key step in this sequence is thought[158] to involve nickel (0) mediated oxidative addition to the alkyl bromide and then β-hydride elimination of the nickel (II) complex formed (**269**), as shown in Scheme 88. The progression depicted terminates with the regeneration of a nickel (0) complex, implying that the reaction could be made catalytic. Regrettably, all investigations in this area made by E. Smith *et al.*[158] proved unsuccessful. However, this was a minor inconvenience when bearing in mind the cheapness of the nickel reagent employed in the transformation.



Scheme 88

With the required allyl silane (**259**) in hand, attempts were made to carry out the addition of this compound to the quinone (**230**) in an analogous fashion to the successful additions of both allyl silane (**231**) and benzyl silane (**244**) (Scheme 75, Scheme 80). Disappointingly, both Lewis acid and fluoride ion activation resulted mainly in the recovery of starting material (**230**) and only traces of the desired product (**253**) could be tentatively assigned by NMR analysis (Scheme 89). Attempts to drive the reaction by heating were also unsuccessful.

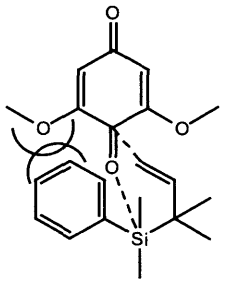


Scheme 89

The failure of this nucleophilic addition reaction can no doubt be attributed to the unfavourable steric interactions between the large dimethylphenyl silyl group present in

the allyl silane (**259**) and the methoxy groups of the quinone structure (**230**), in the cyclic six membered transition state invoked, as shown in Fig. 11.

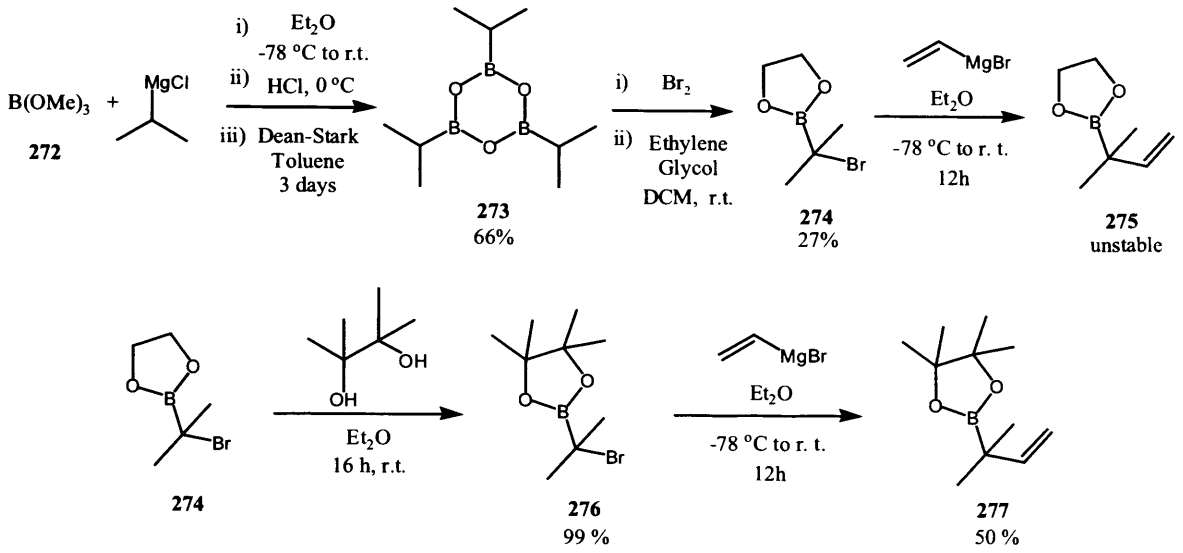
This is a problem which is not easily rectified since the production of the less bulky trimethylsilyl analogue of the allylsilane (**259**) by the route developed requires the production of trimethylsilyllithium, a reagent which is known to cause difficulties in these reactions and which cannot be prepared in the same manner as other silyl lithium reagents.[159, 160]



271

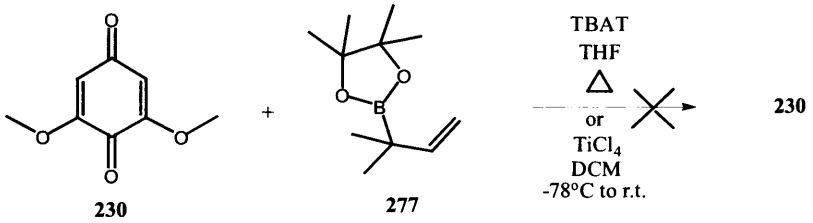
Fig. 11

As an alternative to an allyl silane reagent the analogous boronic ester was prepared according to a method developed by D. S. Matteson and D. Fernando.[161] The synthesis started with the addition of one equivalent of an isopropyl Grignard reagent to trimethyl borate (**272**) to form a boronic ester, which was subsequently hydrolysed and dehydrated to produce the cyclic boronic anhydride (**273**) (Scheme 90). Light induced radical bromination of boroxine (**273**) with bromine afforded a halogenated boroxine intermediate, which was immediately reacted with ethylene glycol to form the brominated boronic ester (**274**). Treatment of (**274**) with the vinyl Grignard reagent then furnished the required allylic boronic ester (**275**) directly but this compound (**275**) proved to be unstable. We were pleased to discover that this problem could be avoided by the formation of the pinacol ester (**277**), as shown in Scheme 90.



Scheme 90

Sadly, however, reaction of this allylborane (**277**) with the quinone (**230**) proved unsuccessful under a variety of conditions (Scheme 91).[162-165] It is extremely probable that the problems encountered with this addition can also be attributed to the same factors preventing the success of the reaction utilising allylsilane (**259**), namely steric hindrance.



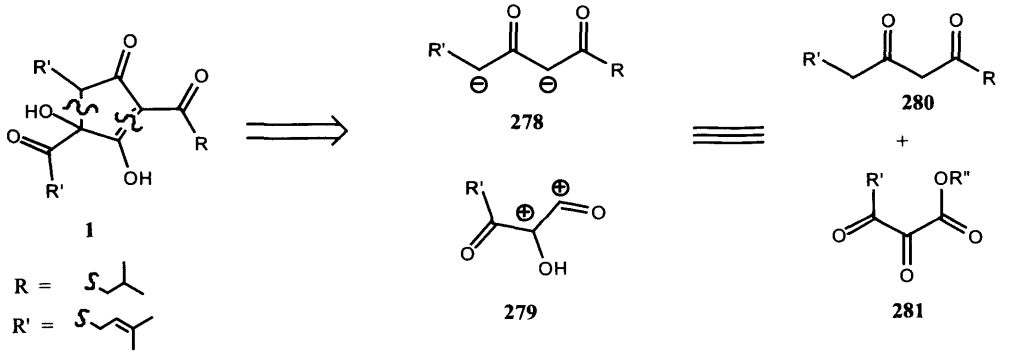
Scheme 91

2.3 Attempted Production Of Isohumulone Analogues By Direct Formation Of A Cyclopentane Ring.

With the aforementioned ring contraction studies presenting a plethora of difficulties, the focus of our research then turned to more direct methods for construction of cyclopentanoid ring structures. Thus far in our work, no attempt had been made to directly synthesise the cyclic core of the isohumulones (**1**) via the closure of an open chain fragment. Consequently, investigations in this area were commenced.

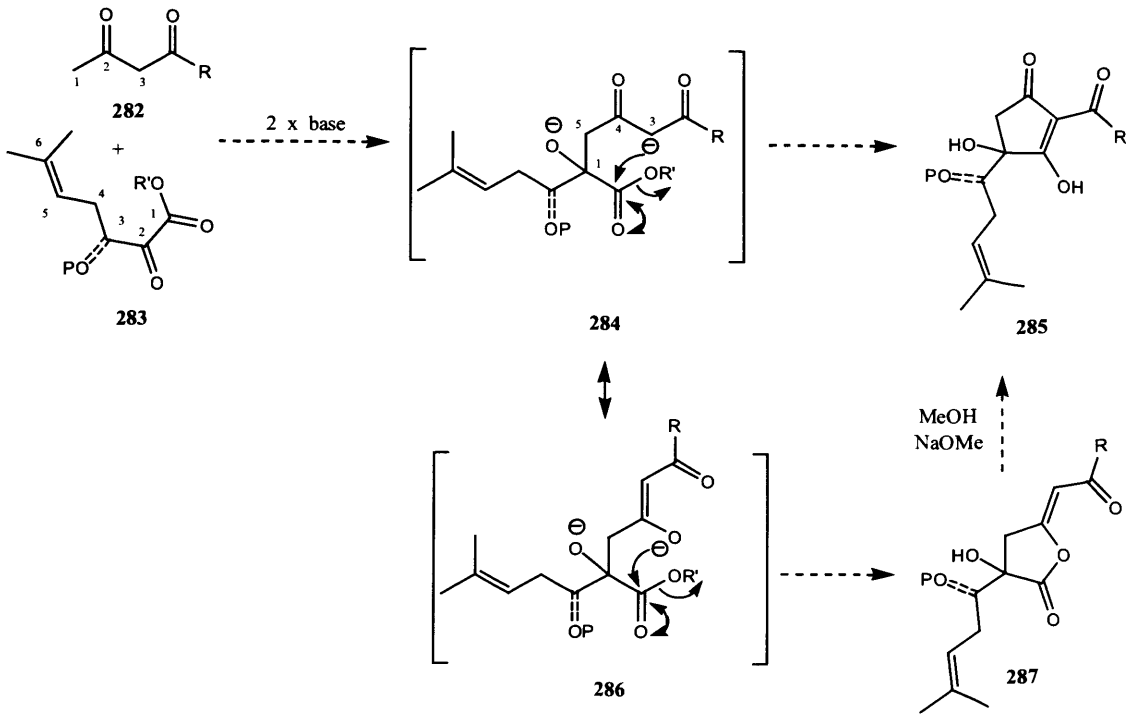
2.31 Attempted Synthesis Of Cyclopentanoids Using Dianion Chemistry.

An extremely expedient and elegant approach for the assembly of this type of functionalised cyclopentanoid involves the use of dianion chemistry, as reviewed in the introduction to this thesis (Section 1.62). Inspiration was taken from this work and a retrosynthetic analysis of isohumulone (**1**) was carried out to form the two synthons, (**278**) and (**279**) which could be represented by the compounds (**280**) and (**281**) (Scheme 92), bearing a close resemblance to the reagents used in the dianion chemistry of Langer *et al.*[77, 78] (Introduction, Section 1.62, Scheme 26).



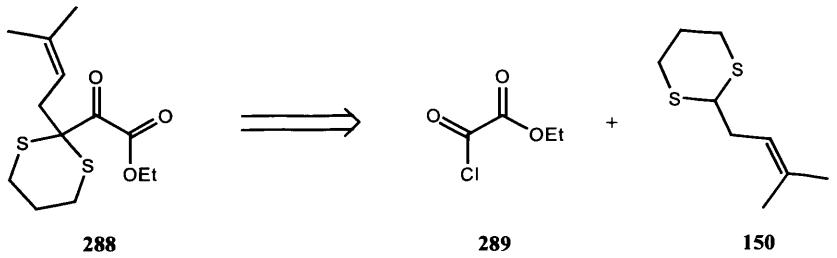
Scheme 92

From a synthetic standpoint, we imagined that addition of a 1, 3-dicarbonyl dianion (**282**) to a suitably protected polycarbonyl fragment such as (**283**), should produce the intermediate (**284**) (Scheme 93), originating from reaction of the more reactive anion with the unprotected ketone (C2) of the "tricarbonyl" unit in (**283**). Subsequent ring closure of (**284**) would then produce a cyclopentane ring (**285**) (Scheme 93). It is, of course, also possible to imagine ring closure of intermediate (**284**) occurring through the oxygen atom of the enolate anion, forming the enol lactone (**287**). However, if this were the case, we felt that it would be possible to effect subsequent rearrangement of this compound (**287**) to the desired product using sodium methoxide (Introduction, Section 1.62, Scheme 27).[85, 166]



Scheme 93

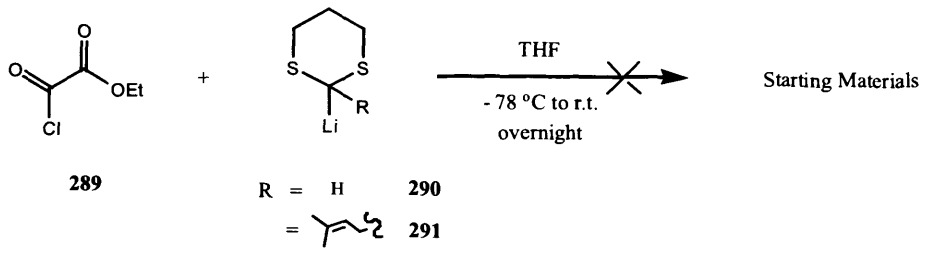
Ensuing studies centred on the production of the masked tricarbonyl unit (**283**), since model 1,3-dicarbonyl compounds (**282**) are readily available. Our experience with thioacetals (Section 2.1) made this moiety an ideal candidate for the protection of the carbonyl at C3 of (**283**). Selection of this group also ensured that a simple disconnection of (**288**) could be made, with formation being achieved by the addition of the dithiane anion of thioacetal (**150**) to ethyl oxalyl chloride (**289**) (Scheme 94).



Scheme 94

Regrettably, initial attempts to carry out this dithiane addition reaction proved unsuccessful, affording only the starting thioacetal (**150**) (Scheme 95). We envisaged that this lack of reactivity could be due to the steric bulk of the dithiane anion being generated and so to combat this problem the unhindered 1,3-dithiane anion (**290**) was

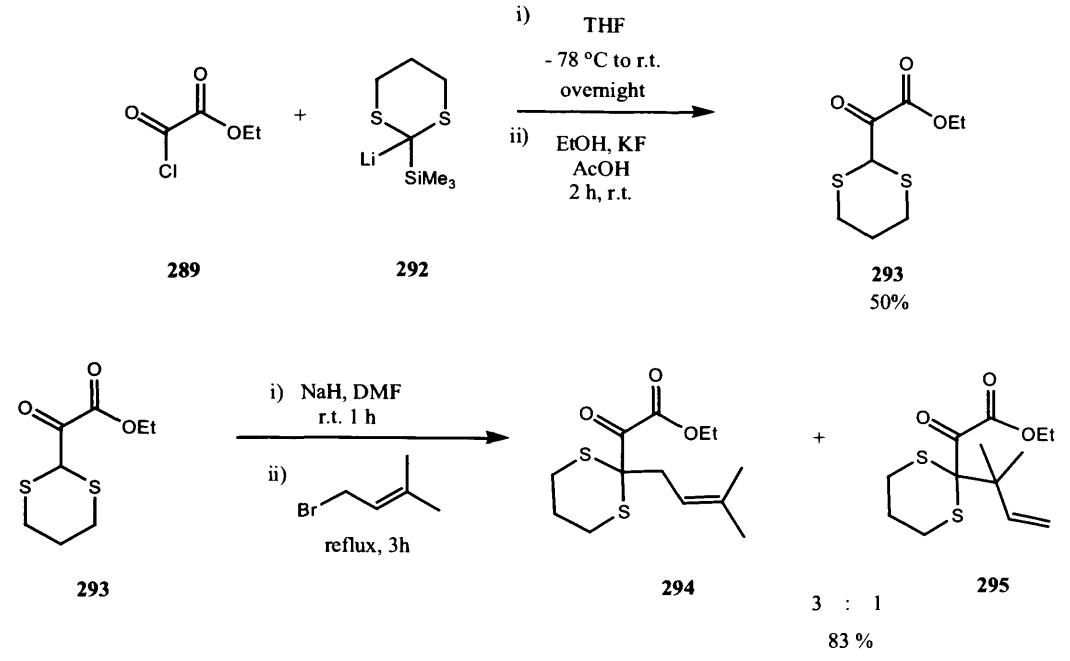
utilised in the reaction, in the hope that the prenyl unit could be introduced at a later stage in the synthesis. Again, these experiments resulted in the recovery of starting materials and it became clear that steric bulk was not the only factor suppressing this transformation (Scheme 95).



Scheme 95

Work carried out by D. Seebach and E.J.Corey[55] into the addition of dithiane anions to acid chlorides has shown that these reactions are not trivial. The procedures normally require a large excess of acid chloride and difficulties can be encountered due to the acidic nature of the α-ketothioacetal protons present in the products.

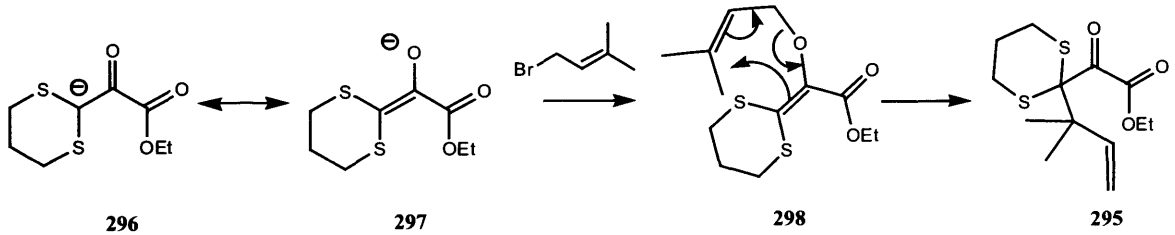
After a little investigation it was established that these problems could be alleviated by utilisation of the protected thioacetal, trimethylsilyl 1,3-dithiane. Treatment of ethyl oxalyl chloride (**289**) with the lithio anion of compound (**292**) provided a product mixture containing both silyl protected and deprotected products. It was determined through optimisation studies that partial deprotection could not be avoided during the reaction and so conditions were employed whereby the crude mixture was fully desilylated during the work up procedure, to form the masked tricarbonyl fragment (**293**) in a yield of 50% (Scheme 96). Prenylation of this α-ketothioacetal (**293**) was then achieved by the application a protocol developed by L. Colombo *et al.*.[69] Deprotonation of the molecule (**293**) with sodium hydride and then quenching of the resultant anion with 1-bromo-3-methyl-2-butene, yielded the desired acyclic α-keto ester (**294**) together with its regioisomer (**295**) as an inseparable mixture in a ratio of 3: 1 (by NMR spectroscopy) (Scheme 96).



Scheme 96

Due to our previous experience of reacting prenyl halides with dithiane anions (Section 2.11, Scheme 39) the formation of the rearranged isomer (**295**) in this reaction was not unexpected. However, the significantly higher percentage of this regioisomer (**295**) formed in this experiment did require some explanation.

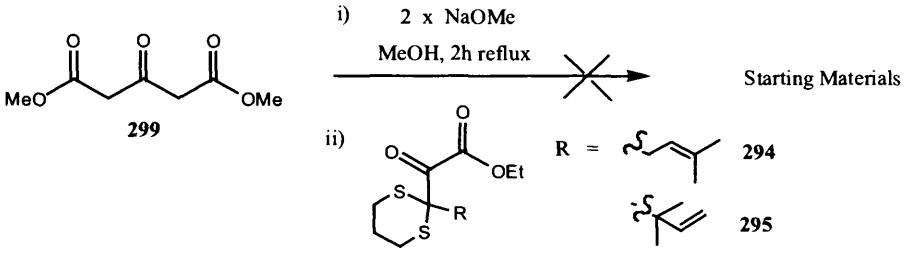
It is, in fact, plausible that (**295**) is formed as a result of 1-bromo-3-methyl-2-butene reacting with the conjugated α-ketodithiane anion (**297**) through the oxygen atom of this system, with the resultant enol ether then undergoing a Claisen rearrangement, as shown in Scheme 97.



Scheme 97

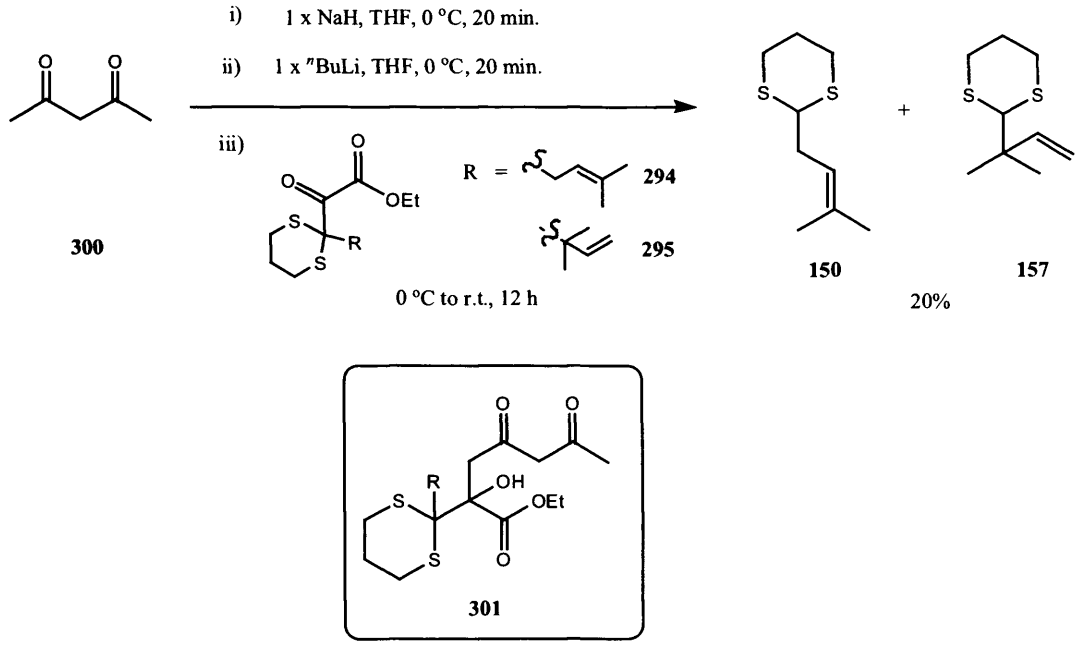
This mixture of regioisomers (**294**, **295**) was deemed acceptable for use in subsequent reactions since experience had taught us that the products might be separated more easily at a later stage in the synthesis (Section 2.11 Scheme 40, 43). Thus, studies into

the reactivity of these α-ketoesters (**294**, **295**) with dianions were initiated. In an adaptation of a protocol developed by J. H. Boothe *et al.*,[167] the protected carbonyl compounds (**294**, **295**) were added to a solution of the dianion of dimethylacetonedicarboxylate (**299**), generated by the treatment of the 1, 3, 5-tricarbonyl compound (**299**) with sodium methoxide and the solution heated to reflux. Regrettably, this experiment proved to be unfruitful and only led to the recovery of starting materials (Scheme 98).



Scheme 98

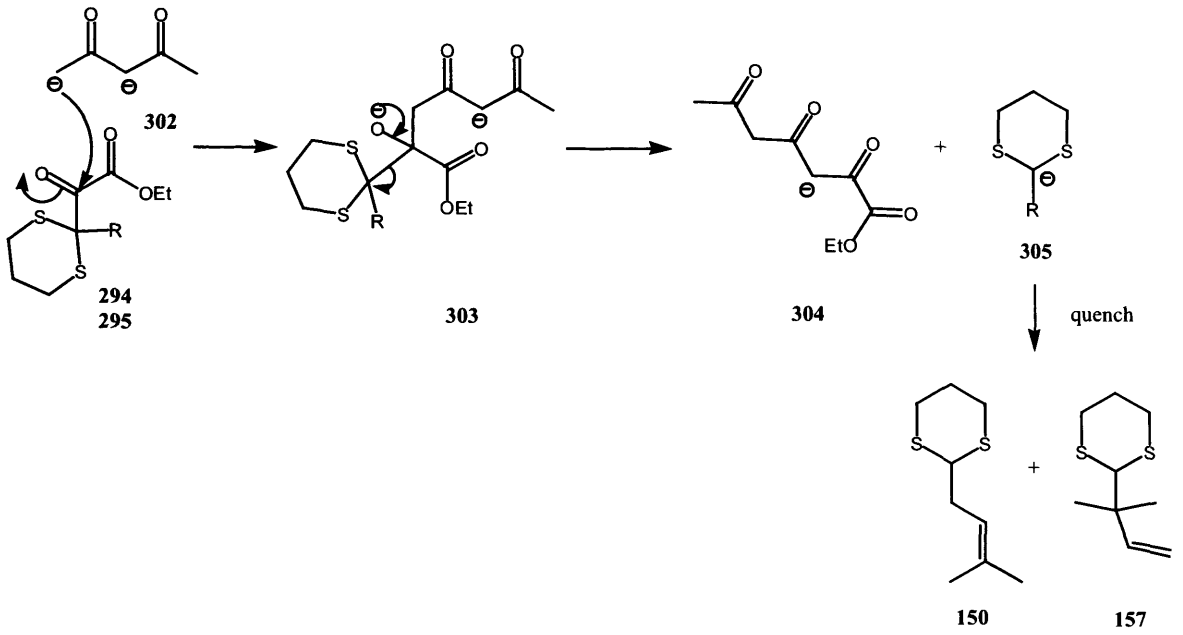
The failure of this reaction was, in all probability, due to the relatively unreactive nature of the dianion formed from dimethylacetonedicarboxylate (**299**) and the strong and unselective base with which it was generated. In an attempt to address both of these problems the more recent work of Langer *et al.*[78] was taken as an example and pentane-2,4,-dione (**300**) employed in the strategy. The dianion of this compound (**300**) was formed by the sequential addition of sodium hydride and then ^{n}BuLi to acetylacetone (**300**) in tetrahydrofuran. Treatment of the dianion generated with the mixture of masked tricarbonyl compounds (**294**, **295**) resulted, surprisingly, in the recovery of a mixture of the two thioacetals (**150**) and (**157**) (Scheme 99). Monitoring of the process by NMR spectroscopy revealed that the open chain polycarbonyl (**301**) appeared to be forming during the transformation, but then reacting further to produce the two thioacetal compounds (**150**, **157**).



Scheme 99

To our disappointment, attempts to isolate and purify the intermediate (**301**) were futile and, although the structure (**301**) could be tentatively assigned by NMR spectroscopy, it was always obtained together with a considerable number of other impurities and underwent degradation during any manipulation.

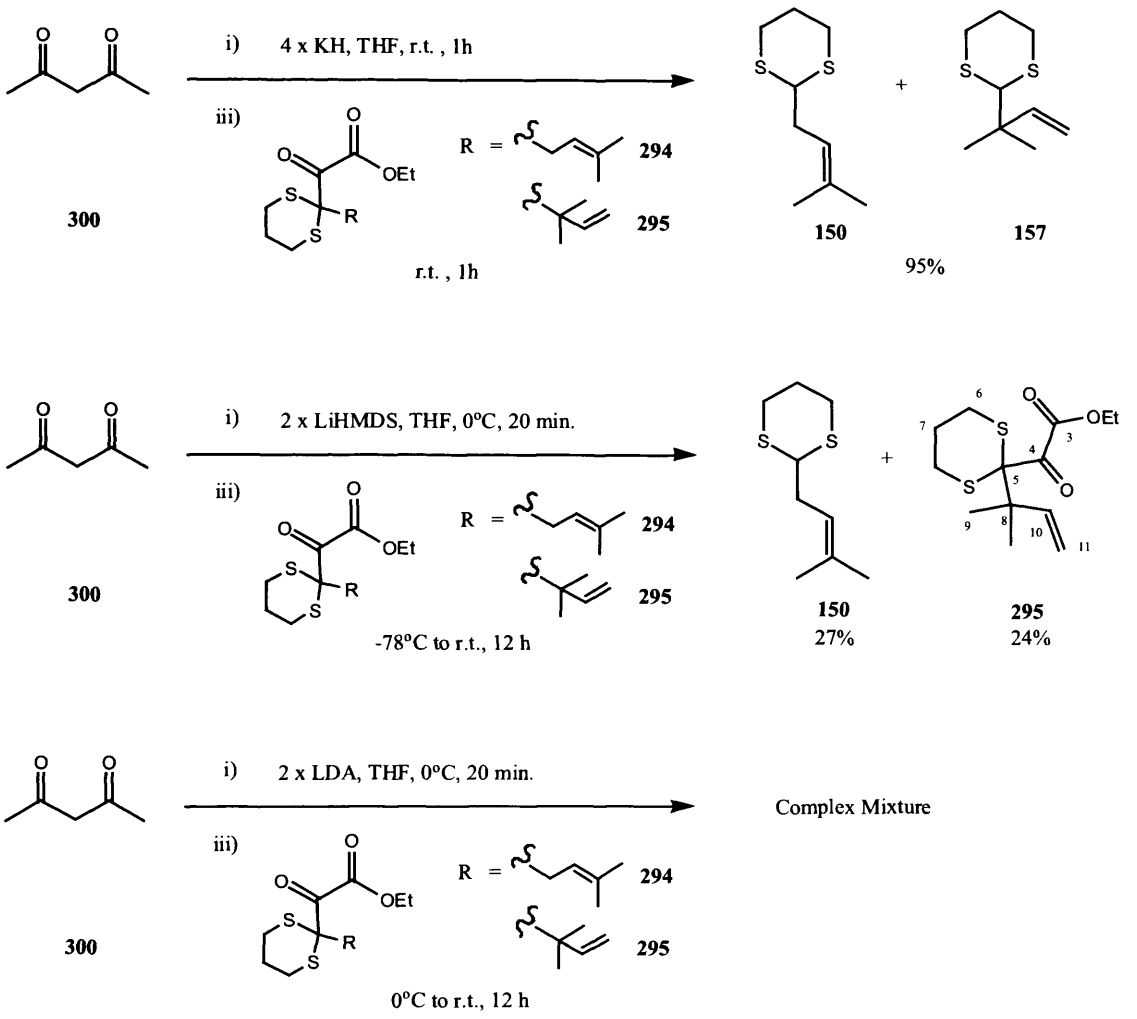
With regard to the mechanism of the transformation, the detection of the adduct (**301**) implies that initial attack of the acetyl acetone dianion (**302**) on the α-ketoesters (**294**, **295**) proceeds as expected. However, instead of the second anion effecting ring closure to form a cyclopentane this intermediate (**303**) then undergoes a retro-dithiane addition with elimination of a stable thioacetal anion (**305**) and concomitant production of a polyketide like fragment (**304**), as shown in Scheme 100. Upon work up of the reaction the two dithianes (**150**, **157**) are isolated whilst the polycarbonyl compound is lost.



Scheme 100

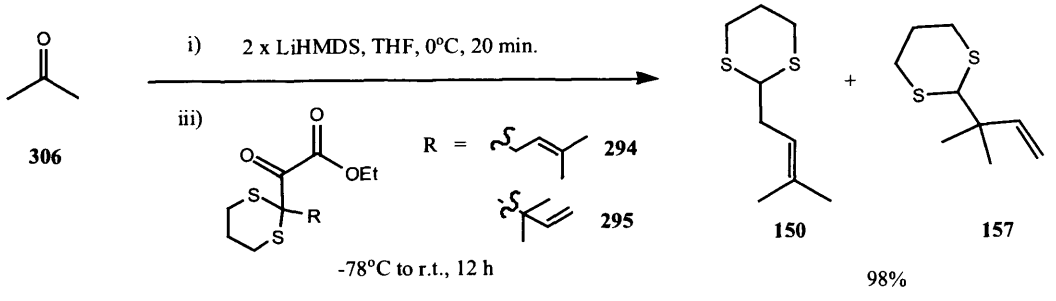
Comfort was taken from the fact that the intermediate (**301**) had been identified during this reaction and so further investigations were made into the use of various different conditions and bases in an attempt to effect ring closure of dianion (**303**) to form the required cyclopentanoid (**285**) (Scheme 101). Unfortunately, none of these modifications produced the desired result, with most reactions yielding only the same two thioacetals (**150**, **157**).

An interesting outcome was, however, observed when lithium hexamethyldisilazide (LiHMDS) was employed as a base in this experiment, with one of the two dithiane starting materials (**295**) being recovered along with the thioacetal (**150**) (Scheme 101). This selective reactivity is presumably due to steric factors surrounding the reacting carbonyl centres of the α-ketoesters (**294**) and (**295**). The two methyl groups in the masked tricarbonyl unit (**295**) (C9) are close to the carbonyl group (C4) and so will significantly slow any attack of a nucleophile at this position, a factor which, in this case, results in the recovery of this substrate (**295**) from the product mixture.



Scheme 101

With a view to forming a less stable, more reactive, second anion to perform ring closure more rapidly, acetone (**306**) was deprotonated and used as the nucleophile in the reaction. Disappointingly, yet somewhat predictably, these conditions again produced the thioacetals (**150**) and (**157**) (Scheme 102).

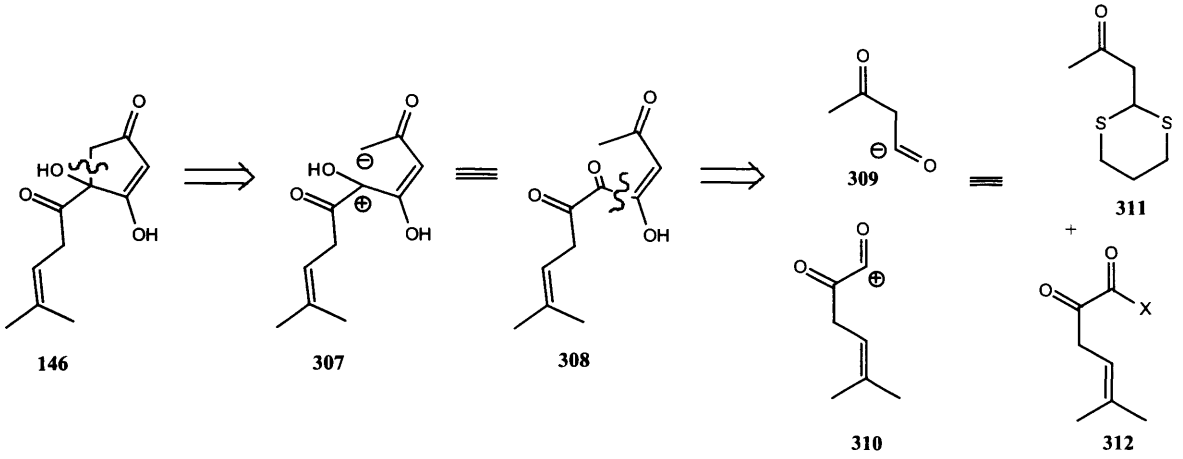


Scheme 102

It appears that the elimination of the thioacetal anion (**305**) from intermediate (**303**) is therefore an extremely facile process and occurs in preference to any alternative reaction pathway under any of the conditions employed during this study.

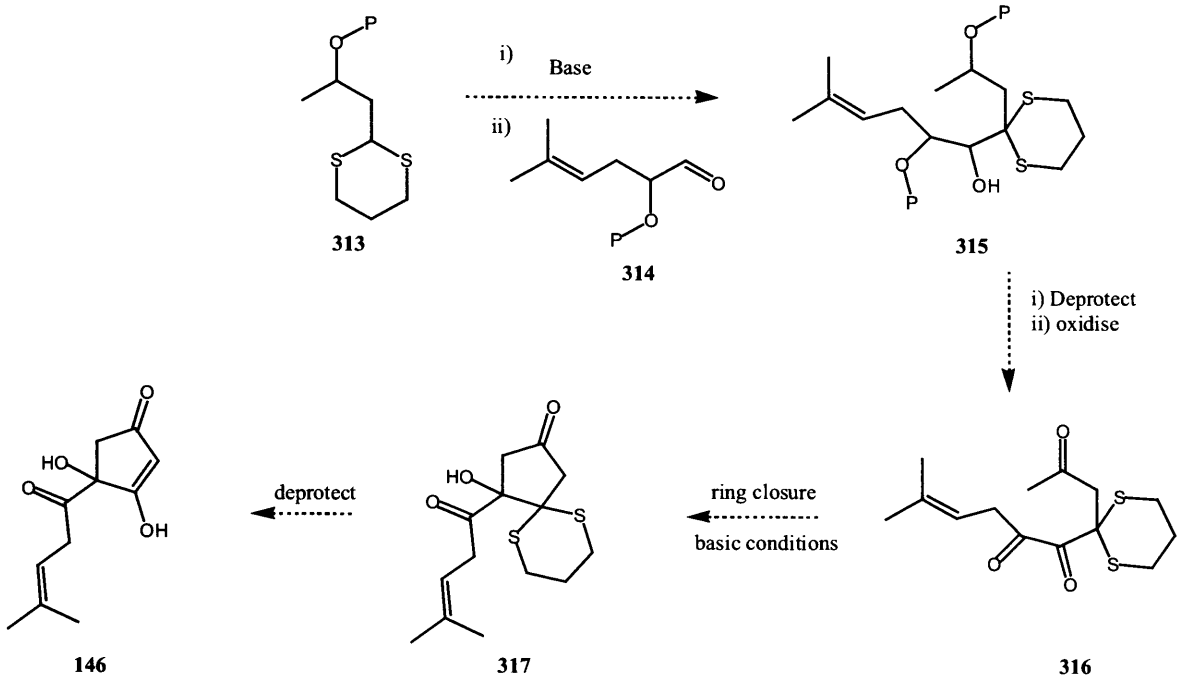
2.32 Attempted Stepwise Synthesis Of Cyclopentanoids.

In parallel to the work carried out utilising dianion chemistry, investigations were also made into the synthesis of cyclopentanoid structures using a slightly different retrosynthetic analysis. This disconnection of the five membered ring (**146**) (Scheme 103) led to the proposal of the two synthons (**309**) and (**310**). It was thought that an equivalent reagent to the synthon (**309**) might again exploit thioacetal umpolung chemistry using a dithiane such as (**311**), while the other species (**310**) could be represented by an α-keto acid derivative (**312**).



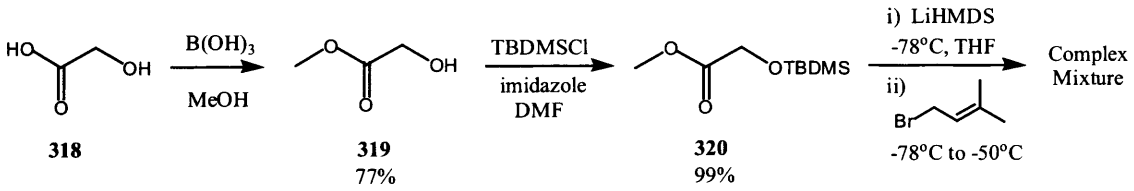
Scheme 103

A closer analysis of this strategy instigated the development of the reaction sequence shown in Scheme 104. This route involves initial formation of a protected linear precursor (**315**), by addition of the anion of thioacetal (**313**) to the protected α-hydroxy aldehyde (**314**). Deprotection of the hydroxyl groups followed by global oxidation of this compound (**315**) would then generate tricarbonyl intermediate (**316**), which, we postulated, would perform a base induced aldol reaction, cyclising to form the kinetically more favourable five membered ring. Finally, deprotection of the spirocyclic dithiane produced (**317**) should give the desired isohumulone analogue (**146**) (Scheme 104).



Scheme 104

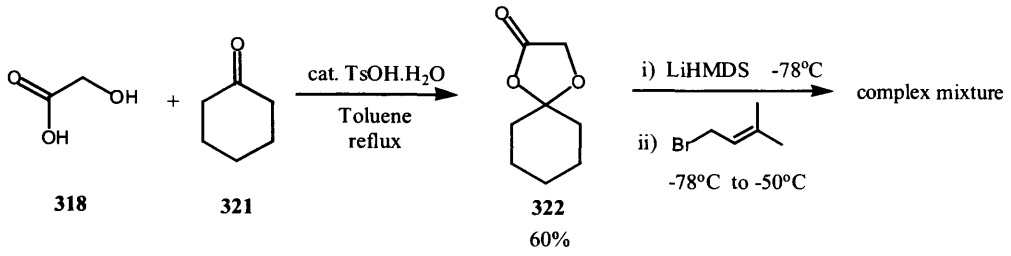
Early studies into the synthesis of the aldehyde (**314**) centred on the protection of glycolic acid (**318**) as its methyl ester (**319**) and then silylation of the alcohol with *tert*-butyldimethylchlorosilane according to literature procedures[168, 169] to give the derivative (**320**) in a good yield. However, all attempts to deprotonate this compound and quench the resultant enolate anion with 1-bromo-3-methylbut-2-ene furnished a complex mixture of products (Scheme 105). Rather belated recourse to the literature revealed that the difficulties associated with the alkylation of protected α-hydroxy acids (**320**) with aliphatic chains have already been documented[170] and so, at this point, the approach was abandoned.



Scheme 105

In related work in this area[171-175] protection of both the acid and alcohol groups of glycolic acid (**318**) has been achieved by reaction with cyclohexanone (**321**) (Scheme 106). Once again however, preparation and attempted alkylation of this "ketal" (**322**) with 1-bromo-3-methylbut-2-ene led to a complex mixture of products. This result

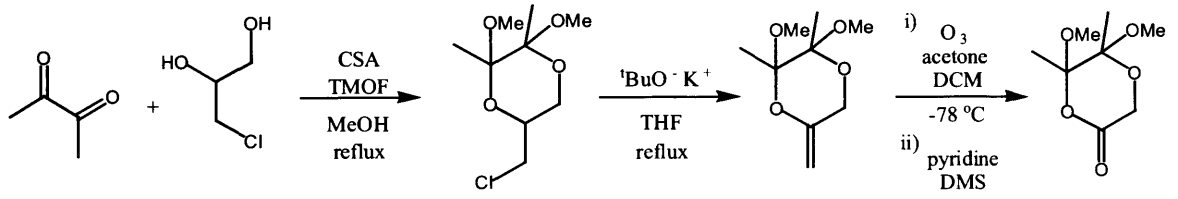
could be explained by the inherent instability of these derivatives, since the corresponding acetone congener was readily hydrolysed in air. It is also plausible that the ester enolate anion formed on deprotonation of (**322**) may undergo elimination with loss of cyclohexanone, before it has a chance to react with the alkenyl bromide.



318 **321** **322** 60%

Scheme 106

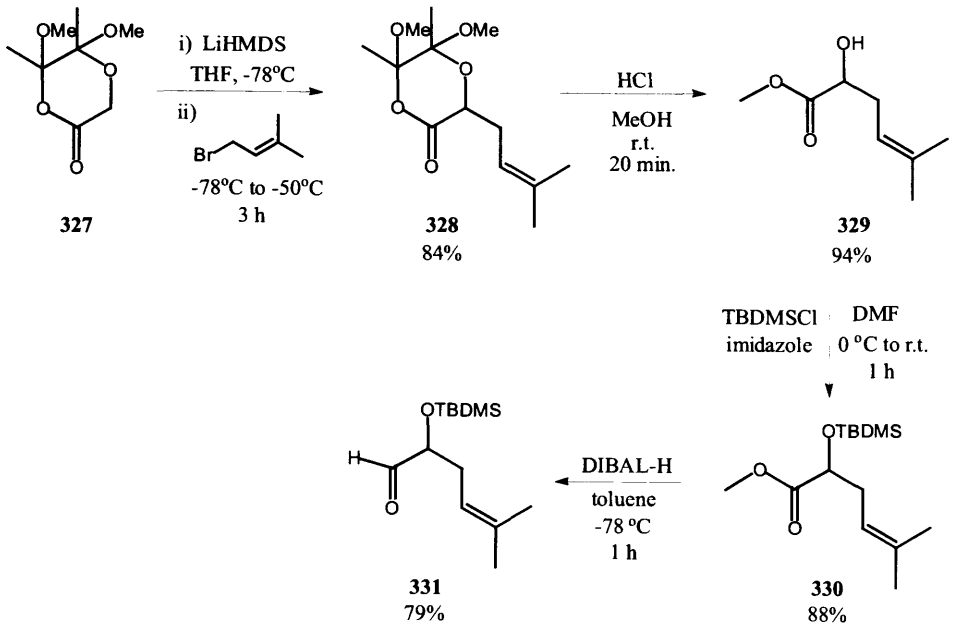
In order to alleviate this problem, a more stable protecting group was employed following work by the group of S. V. Ley in the area of protected α-hydroxy acids.[176] The protected glycolic acid derivative (**327**) was, therefore, produced according to Scheme 107.



323 **324** **325** **326** **327** 50% (over 3 steps)

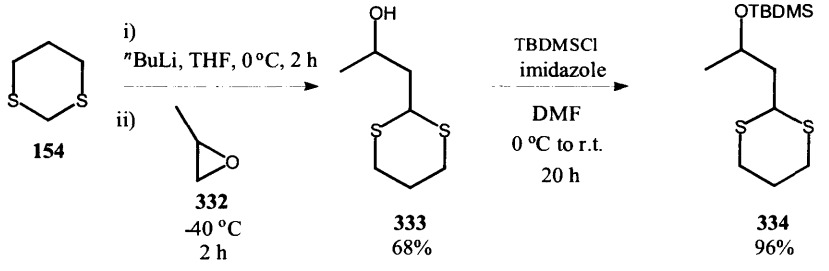
Scheme 107

To our delight, we discovered that deprotonation of (**327**) followed by treatment with 1-bromo-3-methylbut-2-ene, furnished the prenylated lactone (**328**) in a yield of 84% (Scheme 108) and a subsequent reaction with acidic methanol afforded the α-hydroxyester (**329**) in a good yield. The hydroxyl group of this molecule was then masked with a silyl protecting group (**330**) (Scheme 108) and further reduction with diisobutylaluminium hydride (DIBAL-H) furnished the desired aldehyde (**331**) in a lengthy but efficient process (Scheme 108).



Scheme 108

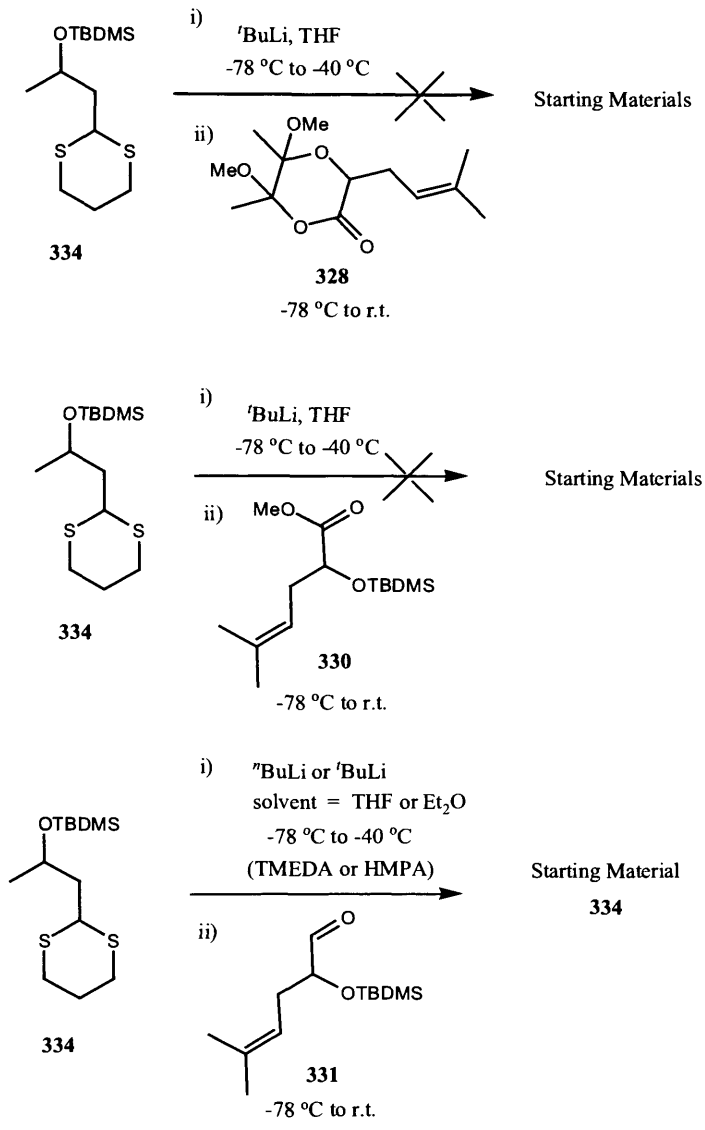
With these various protected α-hydroxycarbonyl compounds (**328**, **330**, **331**) in hand, attention turned to the preparation of the dithiane required for the next stage of the synthetic strategy. The preparation of (**334**) was relatively simple and followed literature precedent.[177, 178] Thus, ring opening of propylene oxide (**332**) with the anion of 1,3-dithiane (**154**), followed by silyl protection of the alcohol formed (**333**), gave the dithiane (**334**) in a good yield (Scheme 109).



Scheme 109

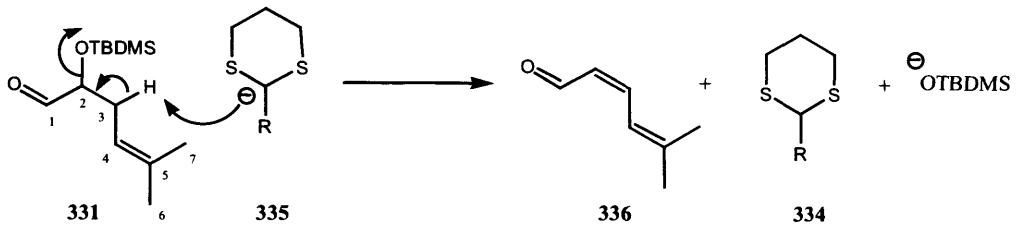
The coupling of this dithiane (**334**) with the masked α-hydroxycarbonyl compounds (**328**, **330**, **331**) did not, unfortunately, prove so straightforward. Reactions carried out employing either the lactone (**328**) or the ester (**330**) led to the recovery of starting materials, a result not entirely unexpected due to the lesser reactivity of such carbonyl centres (Scheme 110). In the case of the aldehyde (**331**) we were more hopeful, but, of

the numerous different conditions employed all resulted in the retrieval of only starting thioacetal (**334**) (Scheme 110).



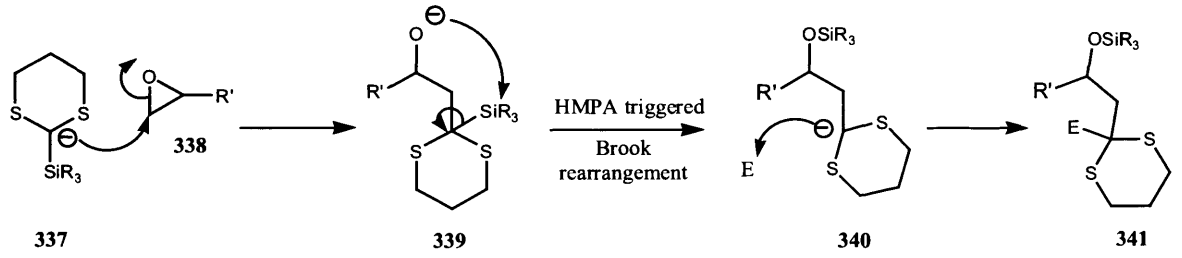
Scheme 110

This last finding suggested that the aldehyde (**331**) was being consumed, in some manner, during the course of the reaction, without the expected addition of the dithiane anion. One theory put forward to explain this was that the anion of (**334**) was acting as a base. Deprotonation of compound (**331**) at C3 could effect the elimination of a siloxy anion from the molecule to give the conjugated aldehyde (**336**) which may then have undergone further degradation or been lost during the work up procedure (Scheme 111). Another, simpler explanation, was that the thioacetal anion was not forming at all during the reaction and the reagents, such as the strong base, led to the decomposition of the aldehyde (**331**).



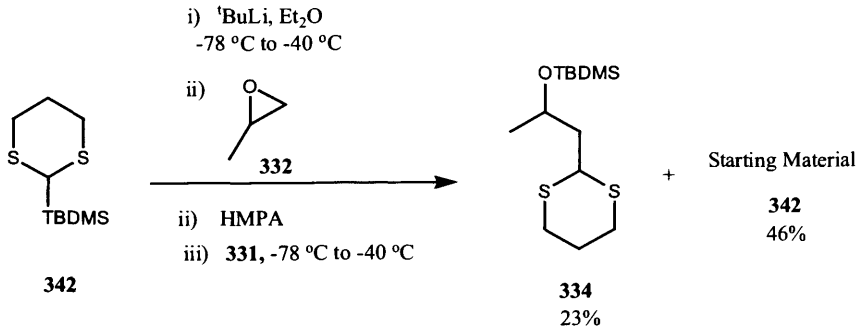
Scheme 111

Difficulties associated with the formation of anions from oxygenated thioacetals such as (**334**) have been documented in the literature[179-181] and a solution to this problem has been developed by Amos B. Smith III *et al.*.[182, 183] This elegant chemistry involves the initial generation of a 2-trialkylsilyl-1,3-dithiane anion (**337**), which is reacted with an epoxide (**338**) to give the alkoxide (**339**). This anion (**339**) then undergoes a solvent triggered Brook rearrangement to reform a dithiane anion which can be quenched by the addition of a second electrophile to form structures such as (**341**) (Scheme 112).



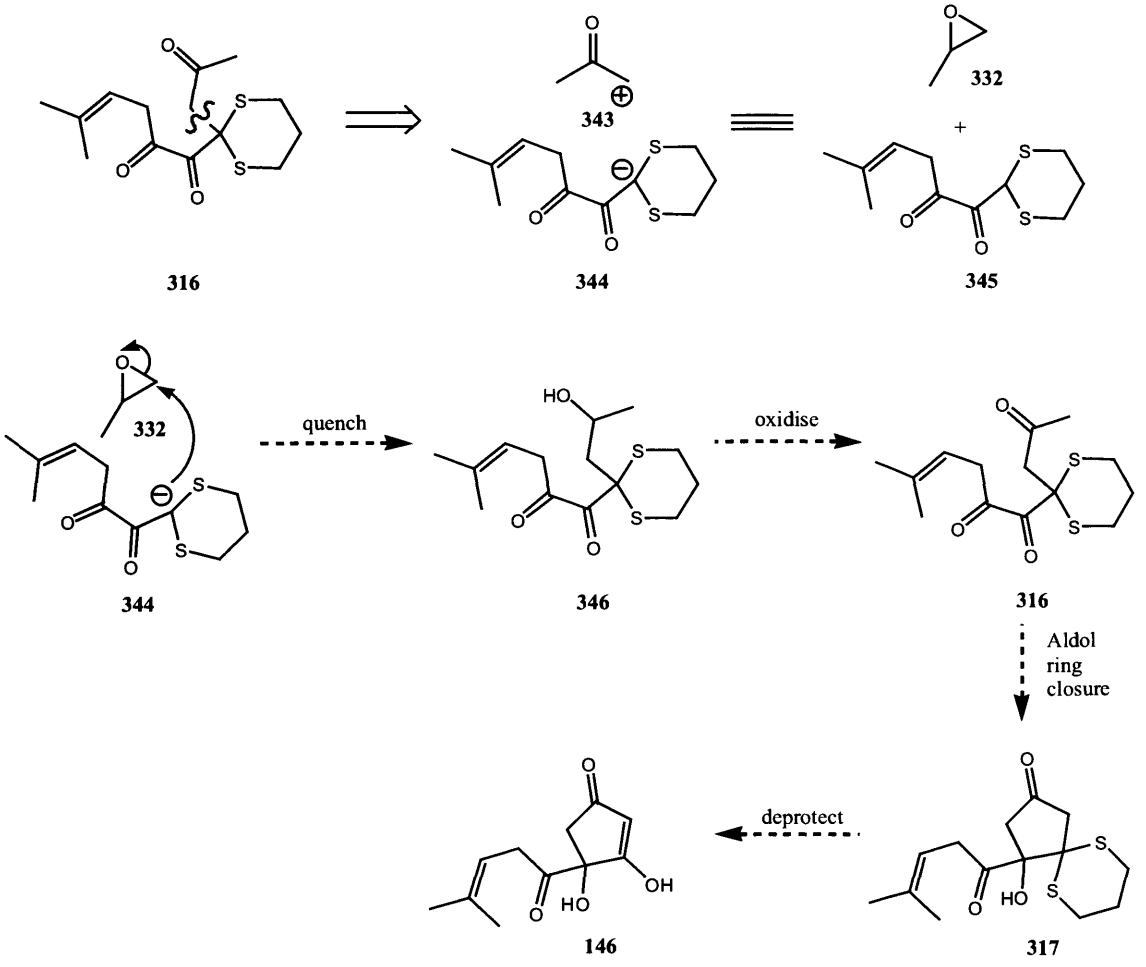
Scheme 112

Applying this strategy to our research, regrettably, only yielded the intermediate compound (**334**) and the starting dithiane (**342**) (Scheme 113). Once again, the starting aldehyde was not recovered from this reaction, an indication that the thioacetal anion formed from the dithiane (**334**) does indeed facilitate the degradation of aldehyde (**331**).



Scheme 113

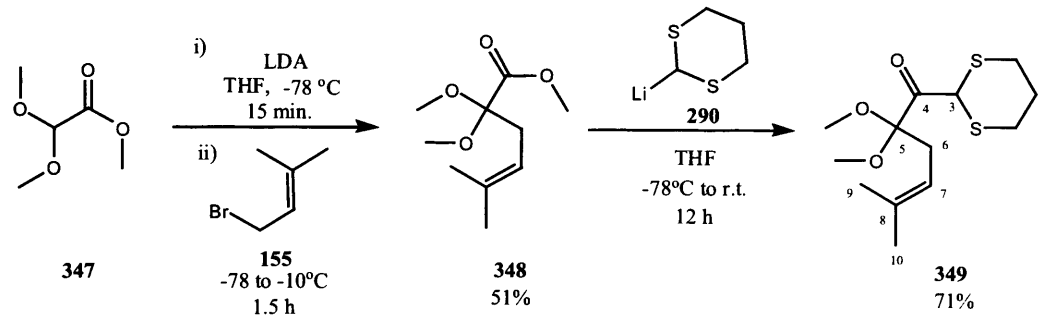
It was clear, at this point, that the thioacetal addition reaction would prove a major obstacle in this synthetic route. In an attempt to circumvent this problem a slightly different retrosynthetic disconnection of the acyclic dithiane protected aldol precursor (**316**) was made. This cleavage led back to two molecules, a masked tricarbonyl unit (**345**) and propylene oxide (**332**) (Scheme 114). We reasoned that a reaction sequence similar to that depicted in Scheme 114, involving the opening of propylene oxide (**332**) with the dithiane anion (**344**), oxidation (**316**), ring closure (**317**) and then deprotection, would yield the isohumulone analogue (**146**). Even more confidence was inspired when we discovered that this sort of chemistry has precedent in work carried out by P. C. Bullman Page *et al.*[184] which describes the synthesis of cyclohexane rings by an aldol reaction after an inital 1,4-addition of an α-ketothioacetal anion to an enone.



Scheme 114

A route to compound (**345**) was developed by adaptation of known literature procedures.[185, 186] Thus, deprotonation of the dimethyl acetal of methyl glyoxylate (**347**) and alkenylation with 1-bromo-3-methyl-2-butene (**155**) produced functionalised

ester (**348**)[185] which was then reacted with the lithioanion of 1,3-dithiane (**290**) to give the acyl dithiane (**349**) in good yield (Scheme 115).[186]

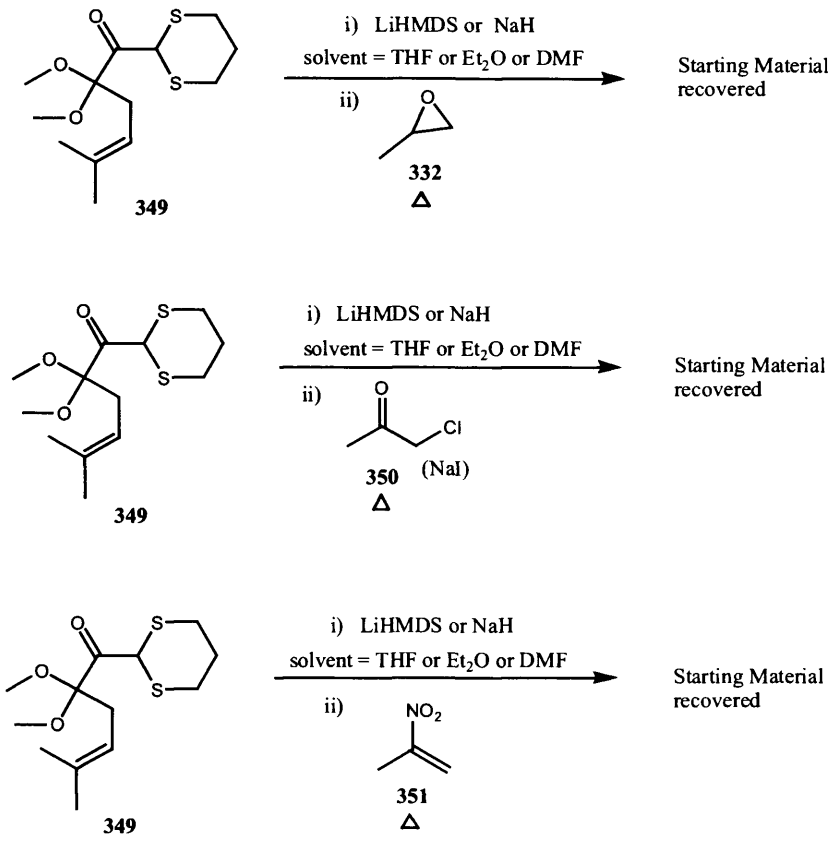


Scheme 115

The doubly protected tricarbonyl fragment (**349**) produced from this short sequence seemed an ideal candidate for reaction with propylene oxide (**332**). It held an advantage over a monoprotected compound such as (**345**) (Scheme 114) in that any aldol ring closure of a polycarbonyl generated from this structure (**349**) would, inevitably, lead to the formation of the five membered ring desired (Scheme 114 step **316** to **317**).

Following this reasoning, studies were then commenced into reaction of the anion of (**349**) with propylene oxide (**332**). Unfortunately, conditions could not be established that resulted in anything other than the recovery of starting material (Scheme 116). The problems encountered appeared to be associated with the lack of reactivity of both the epoxide (**332**) and the relatively stable anion being generated. In some cases[69, 187] α-ketothioacetal anions require heating before they will react with an electrophile. In this case these conditions were not effective and only led to the slow loss of the volatile propylene oxide (**332**) from the reaction vessel. Even when a vast excess of the propylene oxide reagent (**332**) was used no reaction was observed.

In an attempt to alleviate at least some of the problems associated with this reaction α-chloroacetone (**350**) and the soft Michael acceptor 2-nitropropene (**351**) were employed as alternative reagents to the epoxide (**332**). Regrettably, both of these electrophiles (**350, 351**) did not react with the α-ketothioacetal anion even at elevated temperatures, with the 2-nitropropene (**351**) undergoing significant degradation with these conditions (Scheme 116). As yet, a method for successful introduction of this acetyl group into the α-ketothioacetal (**349**) has not been discovered.



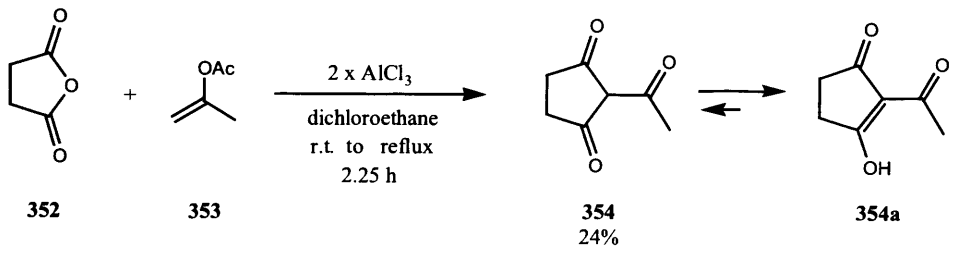
Scheme 116

2.4 Synthesis Of A Tricarbonyl Chromophore And Its Interaction With Cysteine.

Although the majority of the results and discussion section of the present thesis focuses on synthetic studies towards the production of chromophoric analogues of the isohumulones (**1**) of increasing complexity, the chemical behaviour and photochemical reactions of these compounds were also of great interest.

It has already been noted that the 2-acylcyclopentane-1,3-dione unit of the isohumulones (**1**) is thought to play a pivotal role in the absorption of light by these systems[34, 37] (Introduction, Section 1.51) and it was therefore of relevance to explore the reactivity of such systems in isolation.

Accordingly, the parent compound 2-acetyl-1,3-cyclopentanedione (**354**) was readily prepared in a single step from succinic anhydride (**352**), according to a method published by F. Merényi and M. Nilsson (Scheme 117).[188]



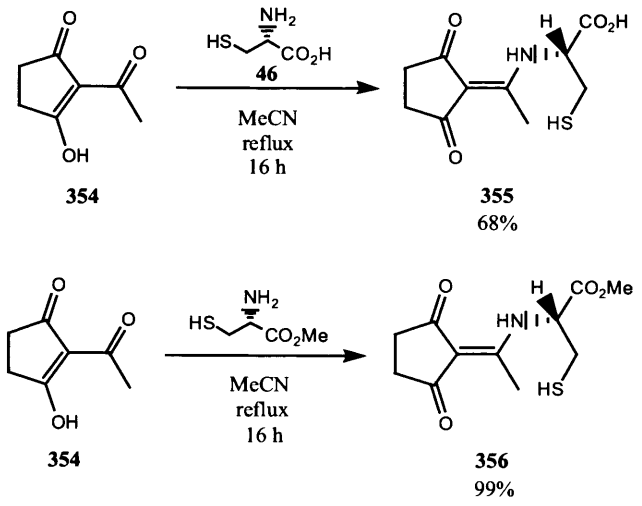
352 353 354 354a
24%

Scheme 117

As explained in the introduction, the mechanism by which the isohumulones (**1**) combine with cysteine to produce 3-MBT (**2**) during photodegradation is currently unclear (Introduction, Section 1.53). Albeit that this conjugated tricarbonyl unit is less reactive than the isolated carbonyl group at C6 of the isohumulones (**1**) a simple model study was made into the reactivity of (**354**) with this amino acid.

Thus, heating this molecule (**354**) with L-cysteine (**46**) in acetonitrile furnished a single new compound (Scheme 118). Analysis of the spectral data of this product indicated the formation of a vinylgous amide between L-cysteine (**46**) and one of the carbonyl groups of (**354**). Difficulties were encountered when assigning the regiochemistry of the reaction but, results obtained by G. Uray *et al.*[189] when condensing similar tricarbonyl units with amines, suggested that the amine would react selectively with the exocyclic carbonyl group of this system. HMBC (heteronuclear multiple quantum coherence) NMR analysis confirmed this prediction, revealing that compound (**355**) was formed as the sole product of the reaction. Presumably, this regioselectivity is observed as a result of the amine attacking the most reactive carbonyl group of the tricarbonyl unit, since the other two endocyclic ketones are known to exist preferentially as enols in the major tautomer of the starting material (**354a**).

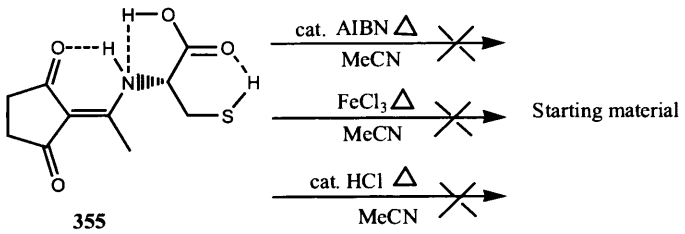
The reaction was also carried out with methyl ester of L-cysteine in order to produce a more soluble product. This variation of the procedure gave similar results, producing the congener (**356**) in very good yield (Scheme 118).



Scheme 118

We were extremely surprised to note that the thiol groups present in (**355**) and (**356**) did not attack the enedione moiety to form a cyclic thiazolidine system as might be expected. This result was hard to rationalise and, in an attempt to study the further reactivity of (**355**), a variety of conditions were employed to encourage further addition of the thiol either to the double bond or to a carbonyl group. Astonishingly, all of the reactions shown in Scheme 119 resulted in the recovery of the starting material (**355**).

One theory proposed to account for these finding was that compound (**355**) was in fact the corresponding disulfide. This explanation, however, was rejected when LC-MS analysis revealed the presence of only traces of this oxidised product. The only other justification hesitantly suggested was that hydrogen bonding holds the compound in a rigid conformation in which the thiol is positioned such that it cannot attack the double bond of the enone moiety. It is plausible that a cyclic hydrogen bonded system may be formed involving the amino and/or thiol groups, as shown in Scheme 119.



Scheme 119

2.5 Photodegradation Studies Of The Isohumulone Analogues.

With a number of model compounds in hand we were extremely keen to establish how these molecules would behave upon irradiation with sunlight in the presence of cysteine. Thus, the chromophores of significance depicted in Fig. 12 were submitted for such analysis, which was kindly perfomed by an industrial colleague.

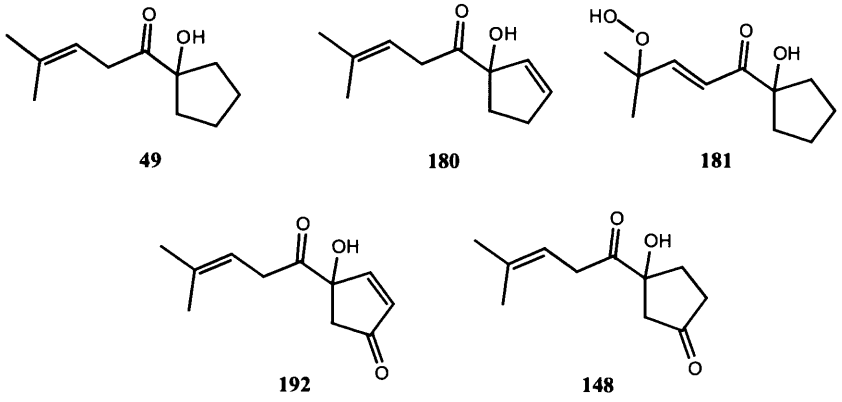


Fig. 12

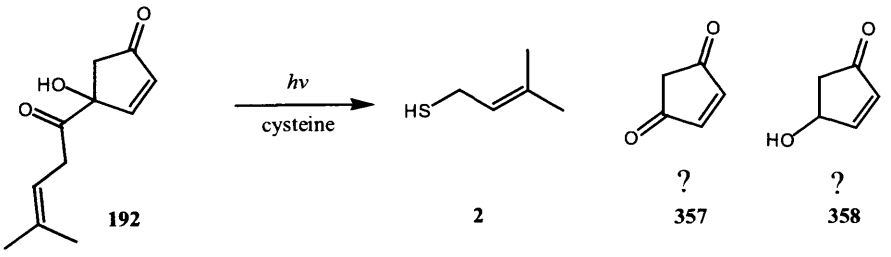
All photolysis experiments carried out were to be monitored using LC-MS or GC-MS and so our first priority was to establish the correct protocol in order to analyse the products of any reactions. Therefore, initial optimisation procedures involving LC or GC MS analysis of the model compounds (**49**), (**148**), (**180**), (**181**) and (**192**) were carried out and showed that all of the compounds were pure and that the MS data obtained was in agreement with our structural assignments.

With this necessary calibration complete, preliminary irradiation studies were begun involving simple irradiation of those molecules (**49**, **148**, **180**, **181**, **192**) containing the key α-hydroxyketone unit and prenyl side chain, in the presence of a sulfur source. As a method of mimicking the medium of beer, these model compounds were dissolved in a solvent system of water: ethanol 95: 5 buffered to pH 4.2 in a clear glass vial and L-cysteine was added to this solution. This was followed directly by irradiation in an atlas suntest sunbox for 30 minutes before the mixture was analysed by either LC or GC MS. A control experiment was also performed by repeating this procedure without exposure of the reaction mixture to sunlight. The results of these investigations are summarised in Table 1.

Compound	3-MBT Detected Before Irradiation	3-MBT Detected After Irradiation	Other Products Detected In Reaction Mixture After Irradiation
49	No	No	Various unknowns
180	No	No	None
148	No	No	None
181	No	No	One unknown
192	No	Yes	Two unknowns

Table 1

To our delight, even these very simple initial investigations have produced a number of interesting results. Indeed, our most functionalised isohumulone analogue (**192**) produced some 3-MBT (**2**), along with two unknown compounds upon irradiation under the above conditions. Although, at this point, we do not have any evidence it is plausible that these mystery products could be cyclopent-4-ene-1,3-dione (**357**) and/or 4-hydroxy-cyclopent-2-enone (**358**), formed as a result of the quenching of the other radical produced during the predicted photolysis process (Scheme 120).



Scheme 120

The analogues (**49**) and (**181**) also underwent reaction during these studies without producing 3-MBT (**2**). The instability of (**49**) has already been noted (Section 2.12) and it is likely that irradiation of this compound (**49**) would inevitably induce some autooxidation to produce hydroperoxide (**181**). This reactive compound (**181**) may, in turn, undergo subsequent transformations, explaining the presently unknown products observed in both reactions.

Unfortunately, because of time constraints, only a limited amount of results have been collected thus far and further product isolation and photolyses studies are necessary before a full mechanistic picture can be constructed.

CHAPTER 3

Conclusions And Perspectives

3.1 Synthesis Of Isohumulone Analogues.

In terms of preparing model isohumulone substrates to study the "sunstruck reaction" our objective was to grow the chromophore through the series of compounds depicted in Fig. 13.

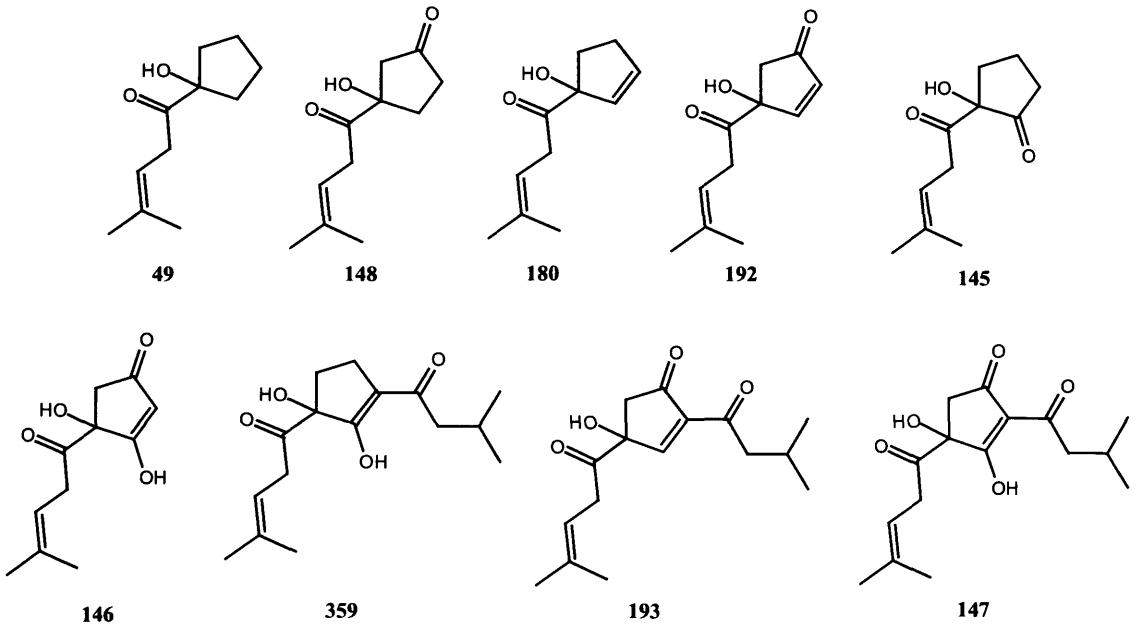


Fig. 13

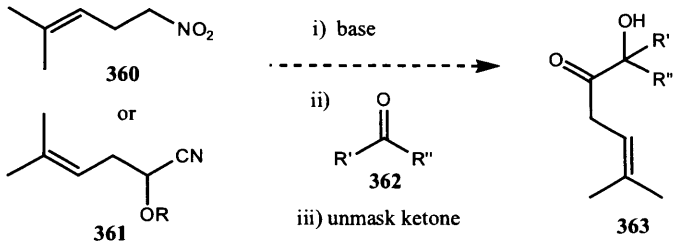
Thanks, in large measure, to the efficiency of dithiane anion chemistry, compounds (**49**), (**148**), (**180**) and (**192**) were successfully synthesised.

With the wisdom of hindsight however, it is clear that the assembly of more highly oxygenated and unsaturated cyclopentanoids such as (**146**), (**147**), (**193**) and (**359**) is not a trivial task, and with these thoughts in mind, the following suggestions based on our own experiences may prove useful for future work in the area.

3.11 Alternative Umpolung Reagents To Dithianes.

Difficulties were encountered when attempts were made to utilise thioacetal anion chemistry in the production of relatively highly substituted model compounds (Section 2.1).

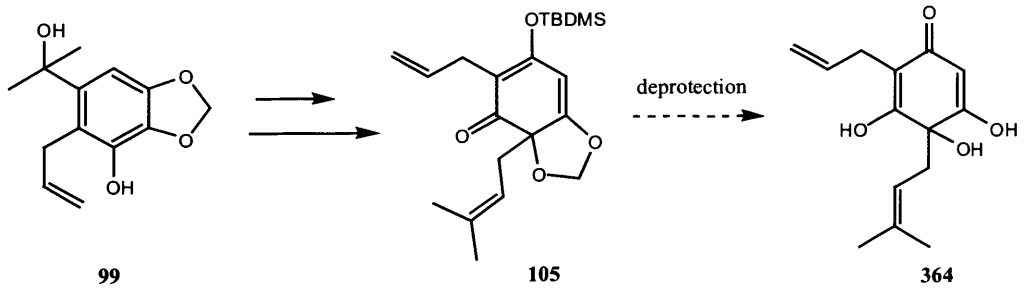
It may, therefore, prove more fruitful for future studies in this area to employ alternative masked reagents such as the nitro compound (**360**) or cyanohydrin ethers (**361**) in analogous nucleophilic addition reactions, as shown in Scheme 121.



Scheme 121

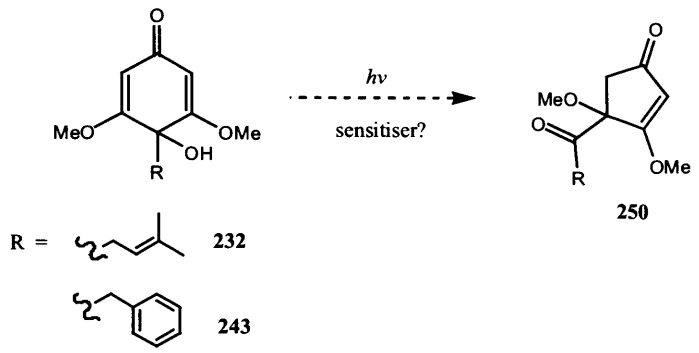
3.12 Production And Ring Contraction Of Humulone Analogues.

The chemistry developed by T. R. R Pettus *et al.*[92] and described in the introduction to this thesis (Section 1.63, Scheme 29) may present an attractive approach to humulone analogues for use in subsequent isomerisation reactions. Indeed, direct application of this work followed by deprotection would be a simple method of producing humulone analogue (**364**) (Scheme 122).



Scheme 122

Unfortunately, time constraints limited us to only the most rudimentary of studies into the photoinduced isomerisation of the protected humulone analogues (**232**) and (**243**) (Section 2.23, Scheme 83), and it may yet be possible to carry out such a rearrangement by exploring the effects of a more powerful light source, varying solvent, or perhaps by employing a sensitiser in the reaction (Scheme 123).

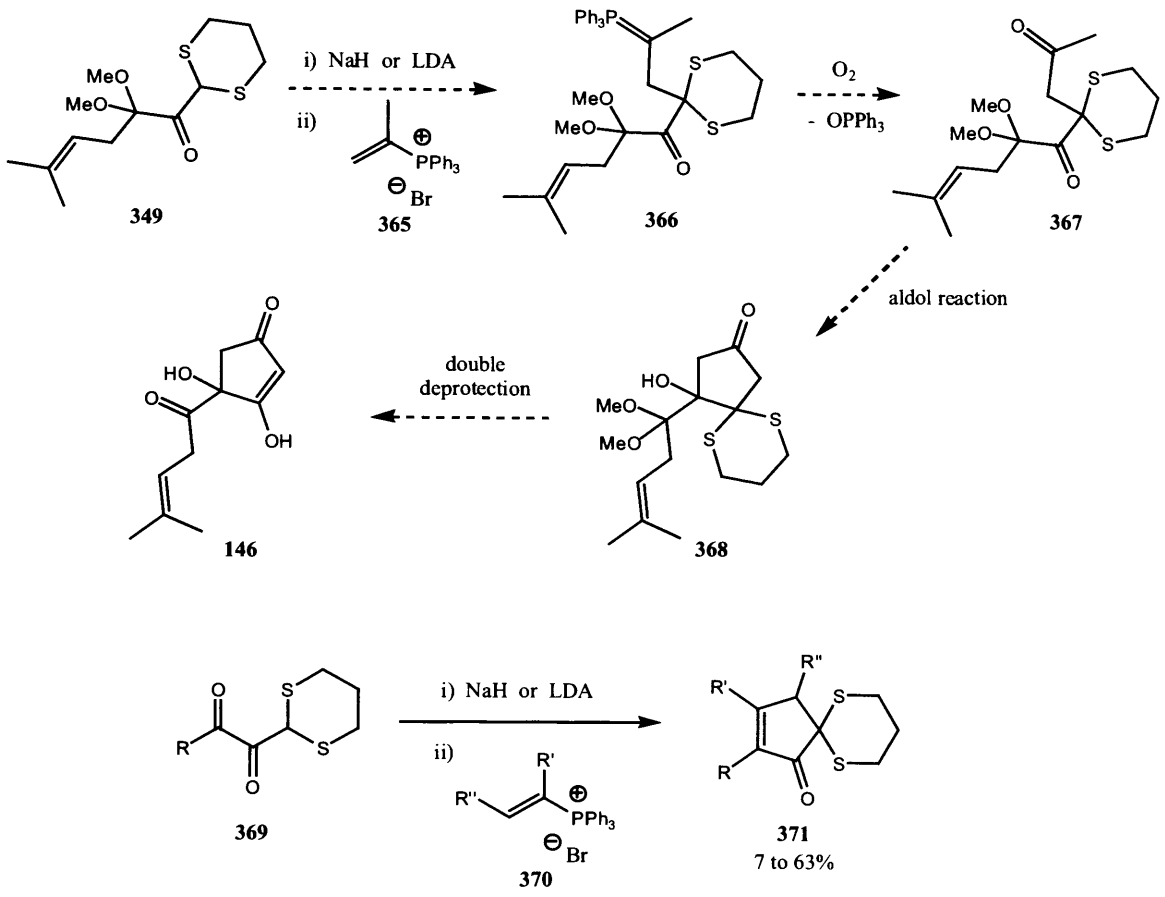


Scheme 123

3.13 Direct Formation Of A Cyclopentane Ring.

Our investigations into the construction of model isohumulone compounds via the formation and cyclisation of polyoxygenated alkyl chains, regrettably, ran into many difficulties (Section 2.3).

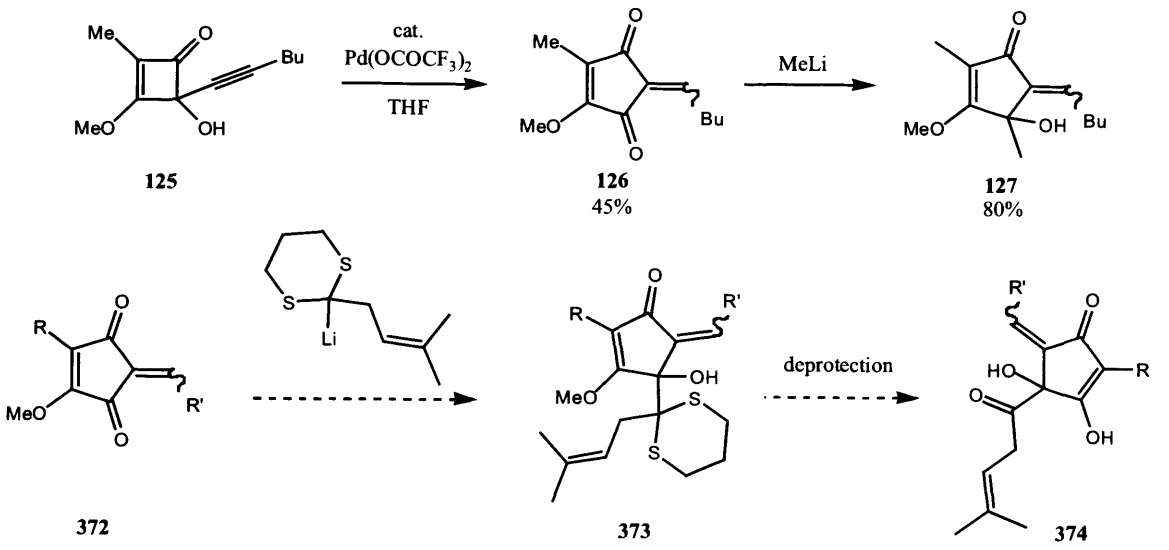
For example, attempts to react thioacetal (**349**) with various electrophiles all failed (Section 2.32, Scheme 116). It is possible, however, that better results might be obtained by coupling the α-ketodithiane (**349**) with a vinyl triphenylphosphonium salt such as (**365**) (Scheme 124). Our confidence in this reaction is based on literature precedent. Thus, I. Kawamoto *et al.*[190] have produced spiro dithianes (**371**) by reacting anions of α-ketothioacetals (**369**) with phosphonium salts (**370**) (Scheme 124). In the proposed reaction the subsequent intramolecular Wittig reaction is highly improbable since a cyclobutene would be formed, and we feel that the unstable phosphorous ylide produced (**366**) would, upon exposure to oxygen, afford intermediate (**367**). Cyclisation followed by deprotection of this compound (**367**) would then yield isohumulone analogue (**146**) (Scheme 124).



Scheme 124

3.14 Ring Expansion Chemistry.

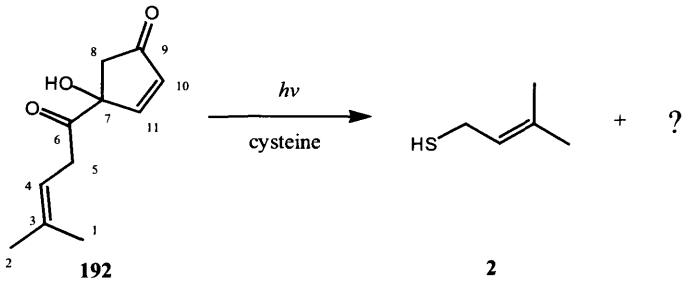
Chemistry described in the introduction to this thesis, which we were disappointed not to have time to explore, involves the ring expansion of squaric acid derived compounds (Section 1.64). Research in this field which seems particularly relevant to our studies has been described by L. S. Liebeskind *et al.*[99] and applied to the production of (**127**) (Scheme 125). We envisage that a slight adaptation of this chemistry, employing a dithiane anion in place of methyllithium in the sequence, may lead to the production of new and interesting isohumulone analogues such as (**374**), as depicted in Scheme 125.



Scheme 125

3.2 Photolysis Studies.

Unfortunately, because of time limitations, only the most preliminary photochemical studies were performed on the isohumulone analogues (**49**) (**148**) (**180**), (**181**) and (**192**) in the presence of a sulfur source (Section 2.5). Nevertheless, the detection of 3-MBT (**2**) from (**192**) (Scheme 126) was a significant result. However, isolation of intermediates and cyclopentanoid compounds produced during this process would be essential prior to any mechanistic speculation.



Scheme 126

Interestingly, the limited results we obtained could be viewed as being inconsistent with the newly published proposal of K. Huvaere *et al.*.[198] In their work electron paramagnetic resonance spectroscopy was used to show that a sulfhydryl radical can be generated from cysteine upon irradiation of the amino acid with visible light in the presence of a photosensitiser. The authors suggest that it is this sulfur centred radical

which recombines with a 3-methyl-but-2-enyl radical in beer, to produce 3-MBT (**2**). Since we did not employ a photosensitiser in our studies and 3-MBT (**2**) was still produced it seems unlikely, in this case, that such a mechanism is in operation.

3.3 Reaction Of The 2-Acylcyclopentane-1,3-dione Unit With Cysteine.

The reaction of 2-acylcyclopentane-1,3-dione (**354**) with cysteine was interesting inasmuch as the thiol group remains intact in the product (**355**) (Fig. 14) (Section 2.4, Scheme 118). If cysteine reacted in the same way with the tricarbonyl unit present in the isohumulones to form structure (**375**) (Fig. 14) the thiol group would, presumably, act as a hydrogen atom trap for radicals formed during the photodegradation reaction of such a compound (**375**), rather than as a sulfur source. It is more probable, however, that the amino acid would attack the most reactive carbonyl of the isohumulone system, that is to say the pendant carbonyl group of the α-hydroxyketone unit, perhaps forming compound (**376**) in the first instance (Fig. 14). Future studies should, therefore, concentrate on reactions of cysteine with an acyloin unit in model compounds of increasing chromophoric complexity and chemical reactivity.

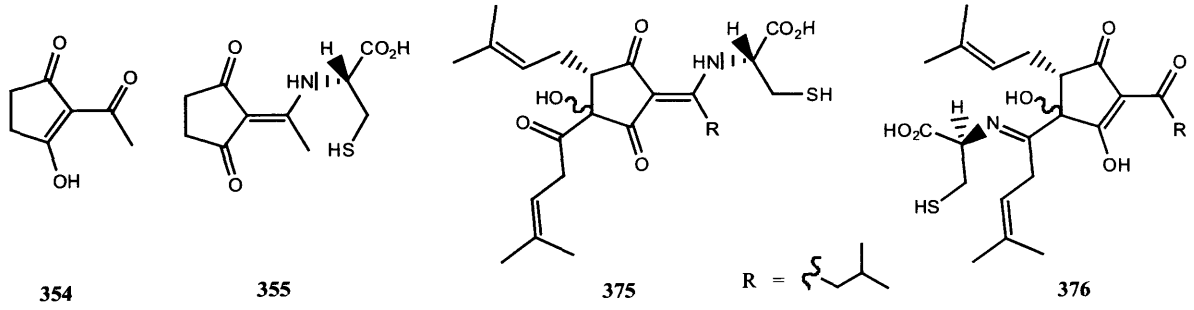


Fig. 14

CHAPTER 4

Experimental

4.1 General Experimental Procedures.

4.11 Solvents and Reagents.

Unless otherwise stated, all reactions were performed under an atmosphere of nitrogen using oven dried glassware, which was cooled under a flow of nitrogen prior to use. Anhydrous benzene and DMSO were prepared by distillation of the solvent from calcium hydride; THF, CH_2Cl_2, Et_2O, MeCN, toluene and *n*-hexane, were prepared as anhydrous, degassed solvents from anhydrous engineering® zeolite drying apparatus. Anhydrous methanol was prepared by distillation from magnesium methoxide. Petrol refers to light petroleum ether bp 40-60°C. All compounds were used as supplied by the manufacturers, unless otherwise stated.

Flash column chromatography was performed using BDH silica gel (40-60 μm) at a low positive pressure, unless otherwise stated. Analytical thin layer chromatography was performed on aluminium sheets pre-coated with Merck silica gel 60 F_{254}, and visualised with ultraviolet light (254 nm), iodine, potassium permanganate and aqueous ammonium (IV) molybdate solutions, as appropriate.

4.12 Data Collection.

Melting points were performed on a Reichert hot-stage apparatus and are uncorrected. Boiling points were measured during distillation.

Proton magnetic resonance (^{1}H NMR) spectra were recorded at 300 MHz on a Bruker AMX300 spectrometer or at 400 MHz on a Bruker Advance 400 spectrometer, unless otherwise stated, and are reported as follows: chemical shift δ (ppm) (number of protons, multiplicity, coupling constant J (Hz), assignment). The coupling constants are quoted to the nearest 0.1 Hz (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, sept.= septet, m=multiplet, br=broad) and are reported as measured splittings on each individual resonance. The residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm, s), DMSO (δ_H = 2.50 ppm, qn), C_6H_6 (δ_H = 7.16 ppm, s) or MeOH (δ_H = 3.30 ppm, q) was used as an internal reference. ^{13}C spectra were recorded at 75 MHz on a Bruker AMX300

spectrometer (^{13}C NMR). The central reference of $CDCl_3$ (δ_C = 77.0 ppm, t), DMSO (δ_C = 39.4 ppm, septuplet) or MeOH (δ_C = 49.0 ppm, septuplet) was used as an internal reference. Chemical shifts are reported in parts per million (ppm) to the nearest 0.01 ppm.

Infrared spectra were carried out on a Perkin-Elmer 1600 fourier transform spectrometer and are recorded as a neat oil or a nujol® mull in between KBr disks. Absorption maxima are reported in wavenumbers (cm^{-1}) and only selected absorbencies are reported.

Mass spectra and accurate mass measurements were recorded using VG ZAB 2SE, VG-7070 and VG70-SE spectrometers in the University College London Chemistry Department mass spectroscopy laboratory.

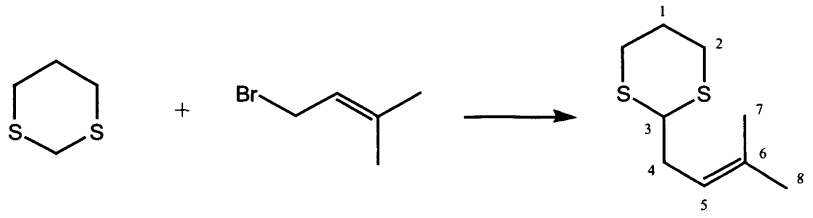
Microanalyses were performed in the University College London Chemistry Department microanalytical laboratory.

Liquid chromatography was carried out using a Waters (Milford, MA, USA) 2690 system for injecting the sample (10µl) and delivering the mobile phase. The analytical column was a 250 mm x 4.6 mm I.D. stainless-steel column containing 5 µm Inertsil ODS–2 particles (Supelco, Bellefonte, PA, USA). HPLC-grade water was prepared by purifying demineralised water in a Milli-Q (Millipore, Bedford, MD, USA) filtration system. HPLC gradient grade acetonitrile and methanol were obtained from Fluka. (Buchs, Switzerland). Formic acid (98-100%) was purchased from Riedel-de Haën (Seelze, Germany). Elution was carried out using a water: formic acid: acetonitrile solvent system gradient. The LC outlet was connected via a micro splitter (Upchurch Scientific Inc. (Oak Harbor, WA, USA) to a Micromass (Manchester, UK) QTOFII-MS via an electrospray (ESI) interface. The final flow entering the mass spectrometer was set at 250 µl/min. All data were acquired on a Compaq data system using Masslynx (Micromass) software. A solution of poly-DL-alanine in methanol was used to calibrate the mass spectrometer both in positive and negative mode for some 15 masses over the range of 50-800 amu. The mass spectrometer was tuned both in ESI^+ and ESI^- for mass resolution and sensitivity.

Gas chromatography was carried out using a 1 µl split 60:1, at 260°C, to inject the sample. The analytical column was a Varian CP-wax 52CB 30m x 0.25mm x 0.25µm column. Helium, 1 ml/min, was used as an elution gas and a constant flow oven program 50°C (2 min), 10°C/min rise to 260°C (hold 2 min) was employed. All data was obtained using a Micromass GCT high resolution Time-of-Flight mass spectrometer, analysing over the mass range m/z 33 to 500. The ionisation modes EI+ and CI+ (methane) were used.

4.2 Experimental For Chapter 2.

2-(3-Methylbut-2-enyl)-[1,3]dithiane (150).

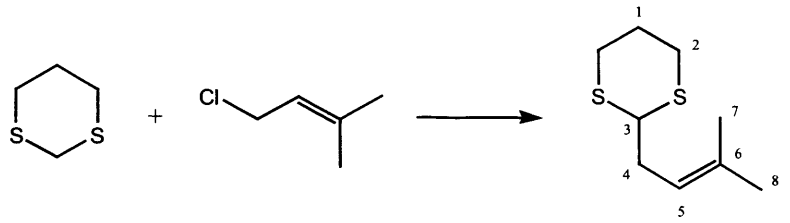


154 **155** **150**

$C_9H_{16}S_2$
Mol. Wt.: 188.35

A solution of ^{n}BuLi in hexanes (2.22M, 7.85 ml, 17.4 mmol) was added dropwise to a vigorously stirring solution of 1,3-dithiane (**154**) (2.00 g, 16.6 mmol) in anhydrous tetrahydrofuran (20 ml) at -40 °C. The solution was then allowed to warm to –20 °C and left at this temperature for 1.5 h before being cooled to –78 °C and 1-bromo-3-methyl-2-butene (**155**) (2.48 g, 1.92 ml, 16.6 mmol) was added dropwise. The solution was warmed to –20 °C and left at this temperature for 2 h before being allowed to warm to room temperature overnight. The reaction was quenched with water (20 ml), and the aqueous layer extracted with diethyl ether (3 x 20 ml). The organic layers were combined, washed with water (20 ml) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give the crude product which was purified by flash column chromatography (9: 1, petrol: ethyl acetate) yielding the *dithiane* (**150**) as a non-viscous colourless liquid (3.05 g, 16.2 mmol, 98%). υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 2897.8 (s, C-H), 2856.4 (s), 1768.6 (w), 1674.1 (w, C=C), 1422.4 (s), 1375.2 (m), 1275.8 (s), 1243.0 (m), 1177.5 (m), 1104.2 (m), 1039.6 (m), 907.4 (m), 842.8 (w) and 786.9 (m); δ_H (300 MHz; $CDCl_3$), 1.60 (3H, s, H7/8), 1.69 (3H, s, H7/8), 1.77-1.88 (1H, m, H1), 2.02-2.12 (1H, m, H1), 2.40 (2H, t *J* 7.0 Hz, H4), 2.73-2.89 (4H, m, H2), 4.02 (1H, t *J* 7.0 Hz, H3) and 5.18 (1H, m, H5); δ_C (75 MHz; $CDCl_3$) 18.05, 25.72, 25.87, 30.53, 34.15, 48.14, 119.66 and 134.80; *m/z* (CI + methane), 189 (MH^+, 100%), 175 (60), 119 (M – C_5H_9, 83) and 107 (75). Found (CI + methane): [MH^+] 189.07648, $C_9H_{17}S_2$ requires 189.07716. The NMR spectral data showed the presence of a trace impurity (**157**) in the product arising from allylation at the tertiary allylic site (product 95% pure by NMR spectroscopy).

Improved preparation of 2-(3-Methylbut-2-enyl)-[1,3]dithiane (150).

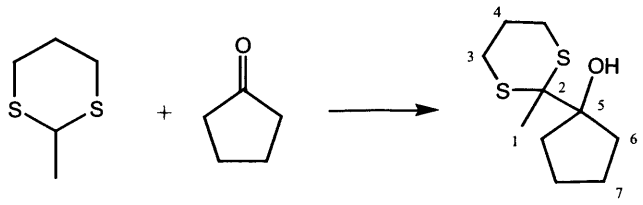


154 **156** **150**

$C_9H_{16}S_2$
Mol. Wt.: 188.35

A solution of ^{n}BuLi in hexanes (2.32M, 21.6 ml, 50.2 mmol) was added dropwise to a vigorously stirring solution of 1,3-dithiane (**154**) (5.75 g, 47.8 mmol) in anhydrous tetrahydrofuran (100 ml) at –40 °C. The reaction was then allowed to warm to –20 °C and left at this temperature for 1.5 h before being cooled to –78 °C and 1-chloro-3-methyl-2-butene (**156**) (5.00 g, 5.39 ml, 47.8 mmol) was added dropwise. The solution was warmed to –20 °C and left at this temperature for 2 h before being slowly warmed to room temperature and stirred overnight. The reaction was quenched with water (100 ml) and the aqueous layer extracted layer with diethyl ether (3 x 100 ml). The organic layers were combined, washed with water (100 ml) and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give the crude product which was purified by flash column chromatography (9:1, petrol: ethyl acetate) yielding the *dithiane* (**150**) as a non-viscous colourless liquid (8.89 g, 47.3 mmol, 99%). The spectral data obtained was identical to that previously described except that NMR data showed fewer impurities caused by allylation at the tertiary allylic site (product 98% pure by NMR spectroscopy).

1-(2-Methyl-[1,3]dithian-2-yl)-cyclopentanol (158).

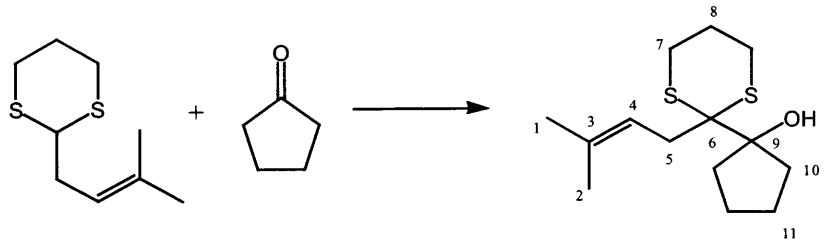


71 **158**

$C_{10}H_{18}OS_2$
Mol. Wt.: 218.38

A solution of ^{n}BuLi in hexanes (2.16M, 5.35 ml, 11.6 mmol) was added dropwise to a solution of 2-methyl-1,3-dithiane (**71**) (1.50 g, 1.34 ml, 11.2 mmol) in anhydrous tetrahydrofuran (20ml) at –40 °C. The reaction was then allowed to warm to –20 °C and kept at this temperature for a further 1.5 h before being cooled back down to –78 °C. Cyclopentanone (0.93 g, 0.97 ml, 11.1 mmol) was added dropwise to the solution and the reaction left at this temperature for 1 h before being warmed to –20 °C and stirred at this temperature for a further 12 h. The reaction was then allowed to warm to room temperature and quenched with a saturated NH_4Cl solution (20 ml). Dichloromethane (20 ml) was added and the two layers that had formed separated, the aqueous layer being further extracted with dichloromethane (2 x 20 ml). The organic extracts were combined, washed with water (2 x 20 ml), dried over $MgSO_4$ and the volatiles evaporated *in vacuo*. The crude product was purified by flash column chromatography (9: 1, petrol: ethyl acetate) producing the *title compound* (**158**) as a viscous colourless oil (1.36 g, 6.24 mmol, 57%). υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 3474.5 (s, O-H), 2953.8 (s, C-H), 2868.9 (s), 1727.1 (w), 1450.4 (m), 1419.5 (m), 1346.2 (m), 1274.9 (m), 1200.6 (m), 1111.9 (m), 1002.0 (s) and 910.3 (m); δ_H (300 MHz; $CDCl_3$), 1.53-1.68 (4H, m, H7), 1.73-1.91 (3H, m, H4,6), 1.78 (3H, s, H1), 1.97-2.14 (3H, m, H4,6) 2.23 (1H, br s, OH), 2.72-2.80 (2H, m, H3 eq.) and 2.94 (2H, td *J* 10.5, 3.5 Hz, H3 ax.); δ_C (75 MHz; $CDCl_3$) 23.44, 24.91, 25.06, 26.65, 35.84, 58.89 and 88.24; *m/z* (CI + methane), 217 (25%), 215 (25), 201 (60), 165 (25), 113 (70), 111(60), 107 (100) and 95 (70). Found (CI + methane): $[MH^+]$ 219.08645, $C_{10}H_{19}OS_2$ requires 219.08773.

1-[2-(3-Methylbut-2-enyl)-[1,3]dithian-2-yl]-cyclopentanol (159).



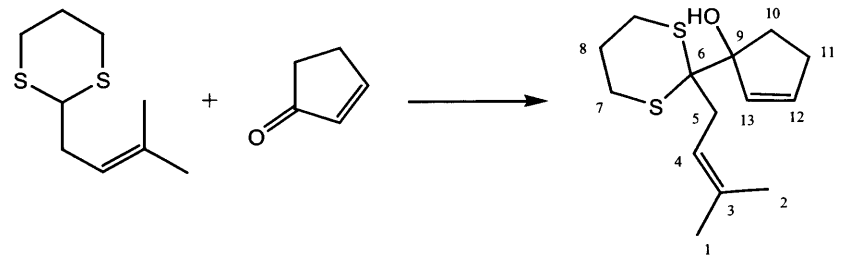
150 **159**

$C_{14}H_{24}OS_2$
Mol. Wt.: 272.47

A solution of ^{n}BuLi in hexanes (2.22M, 2.5 ml, 5.58 mmol) was added dropwise to a solution of 2-(3-Methyl-but-2-enyl)-[1,3]dithiane (**150**) (1.00 g, 5.31 mmol) in anhydrous tetrahydrofuran (15 ml) at –40 °C. The reaction solution was then allowed to

warm to –20 °C and kept at this temperature for a further 1.5 h before being cooled back down to –78 °C. Cyclopentanone (0.44 g, 0.46 ml, 5.24 mmol) was added dropwise to the vigorously stirring mixture and the reaction kept at this temperature for 1 h before being allowed to warm to –40 °C and stirred at this temperature for 4 days in a cold bath. The reaction was quenched with a saturated NH_4Cl solution (20 ml), dichloromethane (20 ml) was added and the two phases that formed separated. The aqueous layer was further extracted with dichloromethane (2 x 20 ml). The organic extracts were combined, washed with water (2 x 20 ml), dried over $MgSO_4$ and the volatiles evaporated *in vacuo* giving the crude product which was purified by flash column chromatography (9: 1, petrol: ethyl acetate) to give the *title compound* (**159**) as a viscous colourless oil (0.70 g, 2.57 mmol, 49%). υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 3503.5 (s, O-H), 2930.6 (s, C-H), 2868.9 (s), 1711.1 (w), 1635.5 (w), 1435.9 (m), 1423.4 (m), 1375.2 (m), 1349.1 (m), 1274.9 (m), 1197.7 (m), 1111.9 (w), 997.1 (m) and 909.4 (w); δ_H (300 MHz; $CDCl_3$), 1.50-2.44 (10H, m, H8,10,11), 1.66 (3H, s, H1/2), 1.71 (3H, s, H1/2), 2.70-2.90 (7H, m, H5,7,OH) and 5.49-5.57 (1H, m, H4); δ_C (75 MHz; $CDCl_3$) 18.45, 24.31, 24.55, 26.07, 26.96, 35.48, 36.65, 61.92, 89.40, 121.72 and 133.75; *m/z* (FAB +), 295 (M + Na, 25%), 199 (30) and 176 (100). Found (FAB +): [M + Na] 295.11688, $C_{14}H_{24}S_2ONa$ requires 295.11662.

1-[2-(3-Methylbut-2-enyl)-[1,3]dithian-2-yl]-cyclopent-2-enol (160).



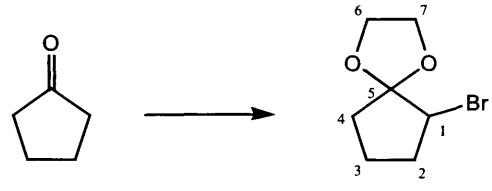
150 **160**

$C_{14}H_{22}OS_2$
Mol. Wt.: 270.45

A solution of ^{n}BuLi in hexanes (2.17M, 0.26 ml, 0.56 mmol) was added dropwise to a solution of 2-(3-Methyl-but-2-enyl)-[1,3]dithiane (**150**) (0.10 g, 0.53 mmol) in anhydrous tetrahydrofuran (5 ml) at –40 °C. The solution was allowed to warm to –20 °C and kept at this temperature for a further 1.5 h before being recooled to –78 °C. Cyclopent-2-enone (0.043 g, 0.044 ml, 0.53 mmol) was added dropwise to the

vigorously stirring reaction mixture and the reaction stirred at this temperature for 1 h before being warmed to –40 °C and stirring continued at this temperature for 4 days in a cold bath. The reaction was quenched with a saturated NH_4Cl solution (10 ml), the aqueous layer was extracted with dichloromethane (3 x 10 ml), the organic extracts combined, washed with water (2 x 10 ml), dried over $MgSO_4$ and the volatiles evaporated under reduced pressure. The crude product was purified by flash column chromatography (1: 1, petrol: diethyl ether) to give the *title compound* (**160**) as a viscous colourless oil (0.04 g, 0.15 mmol, 28%). υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 3481.3 (m, O-H), 3047.3 (w), 2916.2 (s, C-H), 2850.6 (m, C-H), 1664.4 (w, C=C), 1622.0 (w, C=C), 1442.7 (m), 1423.4 (m), 1375.2 (m), 1355.9 (m), 1325.0 (w), 1274.9 (m), 1110.9 (w), 1058.8 (s), 962.4 (w), 910.3 (w) and 785.0 (w); δ_H (300 MHz; $CDCl_3$), 1.66 (3H, s, H1/2), 1.72 (3H, s, H1/2); 1.80-1.90 (2H, m, H10), 1.91-2.04 (1H, m, H8), 2.25-2.39 (1H, m, H8), 2.49-2.60 (2H, m, H11), 2.62 (1H, s, OH), 2.77 (2H, d *J* 7.2 Hz, H5), 2.82-2.87 (4H, m, H7), 5.50-5.54 (1H, m, H4), 5.93 (1H, dt *J* 5.7, 1.9 Hz, H13) and 5.98 (1H, dt *J* 5.7, 2.2 Hz, H12) δ_C (75 MHz; $CDCl_3$) 18.42, 24.53, 26.07, 26.68, 26.74, 31.49, 34.59, 35.40, 61.70, 93.35, 121.21, 133.27, 133.98 and 135.57; *m/z* (CI + methane) 271 (M^{+}+ H, 76%), 253 (M^{+}- OH, 100), 201 (M^{+}- C_5H_9, 80), 187 (97), 185 (86) and 183 (85); Found (CI + methane) [M^{+} + H] 271.11821, $C_{14}H_{23}S_2O$ requires 271.11902.

2-bromocyclopentan-1-one ethylene ketal (162).[107]



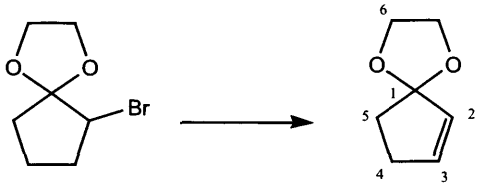
161 **162**

$C_7H_{11}BrO_2$
Mol. Wt.: 207.07

To a stirred solution of cyclopentanone (**161**) (10.0 g, 10.5 ml, 118 mmol) in ethylene glycol (147.5 ml) was added a small portion of bromine (0.60 ml, 1.87 g, 11.7 mmol) at room temperature. The solution was warmed with a heat gun with stirring until the reaction was initiated and the colour of the bromine disappeared. The reaction was then cooled to approximately 15 °C and the remainder of the bromine added (5.45 ml, 17.0 g, 107 mmol) at such a rate that a faint colouration of the bromine remained at all times in

the reaction mixture and the temperature of the reaction remained between 15-20 °C. The solution was then poured onto a stirred suspension of Na_2CO_3 (29.5 g) and petrol (100 ml). Water (150 ml) was added to this mixture, and the aqueous layer extracted with petrol (2 x 100 ml). The organic layers were combined, dried over $MgSO_4$ and the volatiles evaporated to give the crude product (**162**) which required no further purification (22.3 g, 108 mmol, 91%). ν_{max}/cm^{-1} (KBr plates / cm^{-1}) 2958.6 (s, C-H), 2887.2 (s), 1471.6 (w), 1434.9 (w), 1334.6 (m), 1317.3 (m), 1205.4 (m), 1159.1 (m), 1109.0 (s), 1062.7 (s), 1035.7 (s), 1008.7 (s), 966.3 (m), 948.9 (m) and 833.2 (w); δ_H (300 MHz; $CDCl_3$), 1.61-2.42 (6H, m, H2-4) and 3.88 - 4.18 (5H, m, H1,6,7); δ_C (75 MHz; $CDCl_3$) 19.69, 32.19, 33.88, 54.96, 65.13, 65.48, and 116.27; *m/z* (EI) 206 (M^{+}, 15%), 177 (30) and 99 (90).

2-Cyclopenten-1-one ethylene ketal (163).[107]



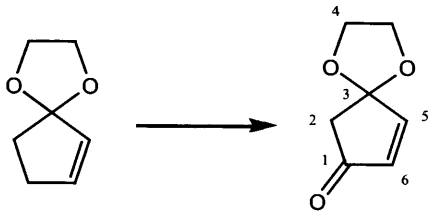
162 **163**

$C_7H_{10}O_2$
Mol. Wt.: 126.15

Sodium methoxide (2.56 g, 47.2 mmol) (freshly prepared by dissolving sodium in methanol) was added to a solution of the ketal (**162**) (3.50 g, 16.9 mmol) in DMSO (8 ml) and the reaction mixture was heated to reflux for 3 h. After this time the reaction was allowed to cool, poured into a saturated NaCl solution (30 ml) and the aqueous solution extracted with petrol (3 x 30 ml). The organic layers were then combined, dried over $MgSO_4$ and the volatiles evaporated under reduced pressure at room temperature. This gave the crude product which was purified by distillation under reduced pressure (b.p. 38 °C at 0.75 mmHg) (lit.[107] b.p. 64-65.5 °C at 22 mmHg) to give the title compound (**163**) as a clear colourless oil (2.08 g, 16.5 mmol, 98%). ν_{max}/cm^{-1} (KBr plates / cm^{-1}) 3057.0 (w), 2947.0 (s, C-H), 2881.5 (s), 1618.2 (m, C=C), 1475.4 (w), 1452.3 (m), 1429.2 (w), 1363.6 (s), 1265.2 (m), 1155.3 (s), 1080.1 (s), 1028.0 (s), 979.8 (w), 947.0 (s), 910.3 (s) and 786.9 (m); δ_H (300 MHz; $CDCl_3$), 2.03-2.07 (2H, m, H5), 2.37-2.42 (2H, m, H4), 3.94 (4H, s, H6), 5.68-5.71 (1H, m, H2/3) and 6.06-6.09 (1H, m,

H2/3); δ_C (75 MHz; $CDCl_3$) 29.59, 34.27, 65.13, 120.39, 130.33 and 137.21; *m/z* (EI) 126 (M^{+}, 35%), 99 (30), 86 (45), 82 (30), 55 (20) and 39 (30).

2-Cyclopenten-1,4-dione monoethylene ketal (164).[106]

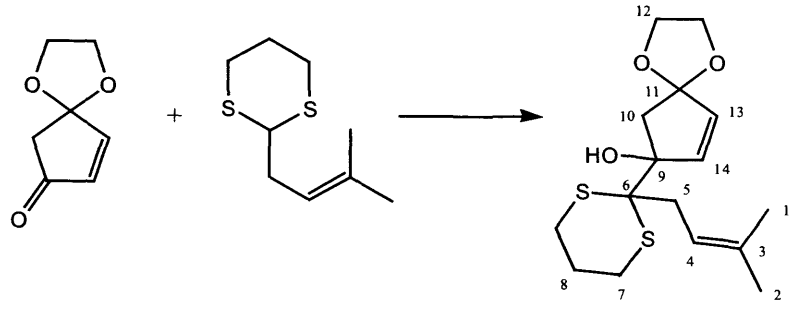


163 **164**

$C_7H_8O_3$
Mol. Wt.: 140.14

A slurry of 2-cyclopenten-1-one ethylene ketal (**163**) (1.00 g, 7.94 mmol), 20mol% palladium hydroxide on carbon (containing 50% water by mass) (0.40 g, 0.40 mmol), potassium carbonate (0.14 g, 1.01 mmol) and dichloromethane (12 ml) was formed in air. The reaction mixture was cooled with stirring to 4 °C before ^{t}BuOOH in water (70 wt.%, 2.72 ml, 19.8 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and left stirring for 24 h at this temperature before second portions of palladium hydroxide on carbon (0.20 g, 0.20 mmol), potassium carbonate (0.07 g, 0.51 mmol) and ^{t}BuOOH in water (70 wt.%, 1.36 ml, 9.92 mmol) were added. After an additional 24 h stirring at room temperature third batches of palladium hydroxide on carbon (0.20 g, 0.20 mmol), potassium carbonate (0.07 g, 0.51 mmol) and ^{t}BuOOH in water (70 wt.%, 1.36 ml, 9.92 mmol) were added and the mixture stirred for another 24 h, (leaving the reaction for a longer period does not lead to any increase in yield). Filtration of the reaction mixture, removal of the volatiles from the filtrate and flash column chromatography of the crude residue (1: 1, petrol: diethyl ether) produced the enone (**164**) as a clear colourless oil (0.44 g, 3.15 mmol, 40%). δ_H (300 MHz; $CDCl_3$), 2.69 (2H, s, H2), 4.04 (4H, s, H4), 6.20 (1H, d *J* 5.8 Hz, H6) and 7.22 (1H, d *J* 5.8 Hz, H5); δ_C (75 MHz; $CDCl_3$) 45.52, 65.46, 111.95, 135.65, 156.65 and 204.35; *m/z* (CI + methane), 157 (M + CH_4, 15 %), 149 (72), 141 (MH^{+}, 60) and 113 (35).

4-Hydroxy-4-[2-(3-Methylbut-2-enyl)-[1,3]dithian-2-yl]-2-cyclopenten-1-one ethylene ketal (167).



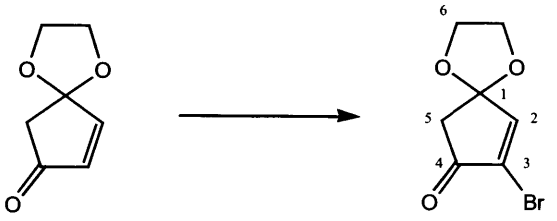
164 **150** **167**

$C_{16}H_{24}O_3S_2$
Mol. Wt.: 328.49

A solution of ^{n}BuLi in hexanes (1.8M, 0.50 ml, 0.90 mmol) was added dropwise to a solution of 2-(3-Methyl-but-2-enyl)-[1,3]dithiane (**150**) (0.16 g, 0.86 mmol) in anhydrous tetrahydrofuran (10 ml) at –40 °C with stirring. The reaction solution was warmed to -20 °C and kept at this temperature for a 1.5 h before cooling back down to –78 °C. 2-Cyclopenten-1,4-dione monoethylene ketal (**164**) (0.44 g, 0.46 ml, 5.32 mmol) was added dropwise to the vigorously stirring reaction mixture and stirring continued at –78 °C for 4 days. The reaction was then quenched with a saturated NH_4Cl solution (10 ml) at –78 °C, the organic layer separated from the biphasic mixture and the aqueous layer further extracted with dichloromethane (3 x 15 ml). The organic extracts were combined, dried over $MgSO_4$, the volatiles evaporated under reduced pressure and the crude product purified by flash column chromatography (1: 1, petrol: diethyl ether) and then recrystallisation from diethyl ether, producing the *title compound* (**167**) as a white solid (0.16 g, 0.49 mmol, 56%). mp 87-90 °C (petrol / diethyl ether); (Anal calcd. for $C_{16}H_{24}O_3S_2$ C, 58.50; H, 7.36; S, 19.52% Found C, 58.40; H, 7.43; S, 19.56%); υ_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 3404.1 (m, O-H), 2923.9 (s, C-H), 2852.5 (s), 1461.9 (m), 1377.1 (m), 1353.9 (w), 1269.1 (w), 1159.1 (w), 1083.9 (m), 1066.6 (m) and 825.5 (w); δ_H (300 MHz; C_6D_6), 1.71 (3H, s, H1/2), 1.76 (3H, s, H1/2), 2.41-2.58 (4H, m, H7,8), 2.49 (1H, d *J* 14.7 Hz, H10), 2.75 (1H, dd *J* 15.7, 6.7 Hz, H5), 2.89-2.98 (3H, m, H5,7), 3.20 (1H, d *J* 14.7 Hz, H10), 3.53 (4H, s, H12), 5.82 (1H, d *J* 5.8 Hz, H13), 5.87-5.94 (1H, m, H4) and 6.47 (1H, d *J* 5.8 Hz, H14); δ_C (75 MHz; $CDCl_3$) 18.41, 24.23, 26.01, 26.89, 27.01, 35.76, 46.93, 60.21, 64.87, 65.03, 90.31, 117.43, 120.63, 133.23, 134.19 and 139.01; *m/z* (CI + methane), 329 (MH^+, 12%), 311 (75), 259 (40), 243 (45),

187 (100) and 135 (25). Found (CI + methane): [MH^+] 329.12407, $C_{16}H_{25}O_3S_2$ requires 329.1245.

3-Bromocyclopent-2-en-1,4-dione monoethylene ketal (172).



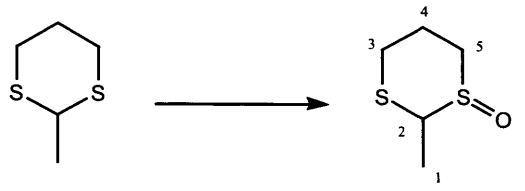
164 **172**

$C_7H_7BrO_3$
Mol. Wt.: 219.03

Bromine (0.20 g, 0.06 ml, 1.25 mmol) was added dropwise to a stirred solution of enone (**164**) (0.10 g, 0.71 mmol) in dichloromethane (2 ml) at –78 °C. The reaction was allowed to warm to 0 °C and left stirring at this temperature for 30 minutes before cyclohexene (0.07 g, 0.085 ml, 0.84 mmol) was added dropwise. The solution was then warmed to room temperature and stirred for 30 minutes before being cooled back down to 0 °C followed by the dropwise addition of triethylamine (0.26 g, 0.36 ml, 2.59 mmol) in dichloromethane (1 ml). Stirring was continued at this temperature for 1.5 h and then the reaction was quenched with a saturated NH_4Cl solution (4 ml). The mixture was diluted with diethyl ether (5 ml), the organic and the aqueous layer separated and the aqueous phase further extracted with diethyl ether (2 x 10 ml). The organic extracts were combined and washed with saturated $Na_2S_2O_3$ solution (20 ml), saturated NH_4Cl solution (20 ml) and a saturated NaCl solution (20ml) and then dried over $MgSO_4$. Evaporation of the volatiles under reduced pressure yielded the *title compound* (**172**) as colourless needles which required no further purification (0.12 g, 0.55 mmol, 78%). Mp 88-90 °C (diethyl ether); (Anal calcd. for $C_7H_7O_3Br$ C, 38.38; H, 3.22; Br, 36.48% Found C, 38.24; H, 3.24; Br, 36.15%); υ_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 3053.1 (m), 2910.4 (s, C-H), 2854.5 (m), 1732.0 (s, C=O), 1697.2 (m, C=C), 1681.8 (w), 1589.2 (m), 1460.0 (m), 1402.2 (m), 1311.5 (m), 1261.4 (w), 1215.1 (m), 1180.4 (m), 1068.5 (s), 1006.8 (s), 948.9 (m), 921.9 (m), 850.5 (w) and 705.9 (w); δ_H (300 MHz; $CDCl_3$), 2.73 (2H, s, H5), 4.02 (4H, s, H6) and 7.35 (1H, s, H2); δ_C (75 MHz; $CDCl_3$) 44.93, 65.50, 110.24, 128.90, 154.69 and 196.33. *m/z* (FAB +), 219 (MH^+, 100%), 203

(M – O, 25), 191 (M – C_2H_4, 12), 178(14), 163 (25), 161 (45) and 159 (40). Found (FAB +): [MH^+] 218.96535, $C_7H_8O_3Br$ requires 218.96568.

2-Methyl-[1,3]-dithiane-1-oxide (173).[112]

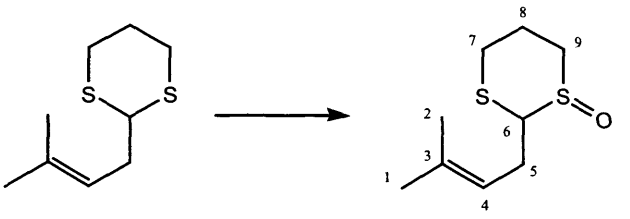


71 **173**

$C_5H_{10}OS_2$
Mol. Wt.: 150.26

A solution of sodium metaperiodate (1.67 g, 7.82 mmol) in water (16 ml) was added dropwise to a solution of 2-methyl-1,3-dithiane (**71**) (1.00 g, 7.45 mmol) in methanol (60 ml) at –10 °C. The resulting slurry was stirred at –10 °C for a further 1 h and then refrigerated at 5 °C for 16 h. The reaction mixture was filtered and the precipitate washed with chloroform (2 x 30 ml). The volatiles were removed from the combined filtrate and washings under reduced pressure, water (20 ml) and chloroform (20 ml) added to the residue and the two layers separated. The aqueous layer was further extracted with chloroform (2 x 20 ml), the organic layers combined, washed with a saturated NaCl solution (2 x 20 ml) and dried over Na_2SO_4. The crude mixture of *cis* and *trans* dithiane oxide (**173**) was purified by recrystallisation from dichloromethane: diethyl ether. This produced the *trans*-2-Methyl-[1,3]dithiane 1-oxide (**173**) as small colourless needles (0.51 g, 3.35 mmol, 46%); mp 94-96 °C (dichloromethane / diethyl ether) (lit.[112] m.p. 92-94 °C (dichloromethane / diethyl ether)); δ_H (300 MHz; $CDCl_3$), 1.63 (3H, d *J* 7.0 Hz, H1), 2.20-2.73 (5H, m, H3-5), 3.38-3.48 (1H, m, H5) and 3.60 (1H, q *J* 7.0 Hz, H2); δ_C (75 MHz; $CDCl_3$) 15.27, 29.66, 30.20, 53.66 and 60.31; *m/z* (EI), 150 ($M^{\cdot+}$, 100%), 133 (20), 106 (10), 90 (98) and 87 (40) .

2-(3-Methylbut-2-enyl)-[1,3]dithiane-1-oxide (174).

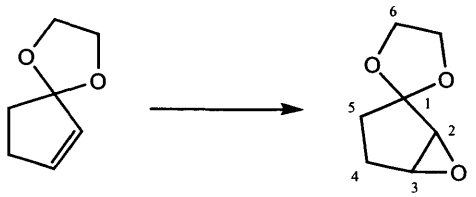


150 **174**

$C_9H_{16}OS_2$
Mol. Wt.: 204.35

A solution of sodium metaperiodate (0.36 g, 1.68 mmol) in water (4 ml) was added dropwise to a solution of 2-(3-Methyl-but-2-enyl)-[1,3]dithiane (**150**) (0.30 g, 1.59 mmol) in methanol (15 ml) at –10 °C. The resulting slurry was stirred at –10 °C for a further 1 h and then refrigerated at 5 °C for 16 h. The reaction mixture was filtered and the precipitate washed with chloroform (2 x 10 ml). The volatiles were removed from the combined filtrate and washings under reduced pressure, water (10 ml) and chloroform (10 ml) added to the residue and the two layers separated. The aqueous layer was further extracted with chloroform (2 x 10 ml), the organic layers combined, washed with a saturated NaCl solution (2 x 10 ml) and dried over Na_2SO_4. The crude dithiane oxide (**174**) was purified by trituration with petrol. This produced a mixture of *cis* and *trans-2-(3-Methyl-but-2-enyl)-[1,3]dithiane 1-oxide* (**174**) as clear colourless prisms (0.21 g, 1.03 mmol, 64%); mp 68-70 °C (petrol / diethyl ether); Anal calcd. for $C_9H_{16}OS_2$ C, 52.90; H, 7.89% Found C, 50.68; H, 7.84%; υ_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 2912.3 (s, C-H), 2852.5 (s, C-H), 1672.2 (w, C=C), 1448.4 (m), 1429.2 (m), 1377.1 (m), 1311.5 (w), 1271.0 (w), 1014.5 (s), 941.2 (w), 914.2 (w), 875.6 (w), 833.2 (w), 783.0 (w), 700.1 (w) and 667.3 (w); δ_H (300 MHz; $CDCl_3$), 1.62 (3H, s, H1/2), 1.70 (3H, s, H1/2), 2.36 – 2.72 (6H, m, H7-9), 2.87 – 2.99 (1H, m, H5), 3.35 – 3.44 (1H, m, H5), 3.58 (1H, dd *J* 9.0, 3.5 Hz, H6) and 5.16 (1H, br t *J* 7.2 Hz, H4); δ_C (75 MHz; $CDCl_3$) 18.12, 25.83, 27.28, 29.57, 30.01, 53.82, 66.65, 117.43 and 136.53; *m/z* (EI), 221 (22%), 205 (M^{+} + H, 54), 135 (M^{+} - C_5H_9, 27), 123 (100) and 113 (22). Found (EI): [M^{+}] 204.06362, $C_9H_{16}S_2O$ requires 204.06425.

2,3-epoxycyclopentan-1-one ethylene ketal (176).[115]

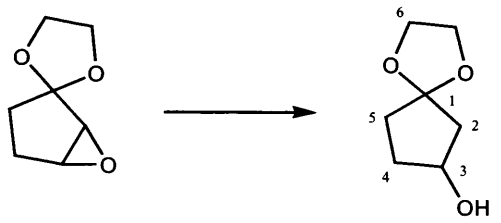


163 **176**

$C_7H_{10}O_3$
Mol. Wt.: 142.15

2-Cyclopenten-1-one ethylene ketal (**176**) (0.20 g, 1.59 mmol) was dissolved in dimethylsulfoxide (5 ml) and water (0.06 g, 0.06 ml, 3.18 mmol) was added to this solution. The reaction was cooled to 10 °C and *N*-bromosuccinimide (0.57 g, 3.18 mmol) added in one portion (the solution became warm developing a yellow colour). The reaction was allowed to warm to room temperature and stirred at this temperature for 0.5 h. After this time water (15 ml) and diethyl ether (15 ml) were added and the organic phase separated from the aqueous. The aqueous phase was further extracted with diethyl ether (3 x 15 ml) and the organic phases were combined and washed with a saturated NaCl solution (2 x 15 ml). The ethereal solution was dried over $MgSO_4$ and the volatiles removed under reduced pressure to give the crude bromohydrin. This crude intermediate was dissolved in anhydrous tetrahydrofuran (5 ml) and treated with sodium hydride (60% dispersion in mineral oil, 0.14 g, 2.02 mmol) at room temperature. After 0.5 h at room temperature water (10 ml) and diethyl ether (10 ml) were added to the mixture, the aqueous phase was separated from the organic and further extracted with diethyl ether (3 x 10ml). The organic phases were combined washed with a saturated NaCl solution (2 x 10 ml) and dried over $MgSO_4$. Removal of the volatiles under reduced pressure gave the crude epoxide (**176**) which was purified by flash column chromatography (1: 1, petrol: diethyl ether) producing epoxide (**176**) as a clear colourless oil (0.14 g, 0.99 mmol, 62%); υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 2956.7 (m, C-H), 2889.2 (m, C-H), 1479.3 (w), 1446.5 (w), 1398.3 (m), 1348.1 (s), 1238.2 (m), 1178.4 (m), 1132.1 (s), 1097.4 (m), 1066.6 (w), 1014.5 (s), 975.9 (m), 939.3 (s), 912.3 (m), 852.5 (s) and 812.0 (m); δ_H (300 MHz; $CDCl_3$), 1.58-1.69 (1H, m, H4), 1.71-1.88 (2H, m, H4,5), 2.02-2.15 (1H, m, H5), 3.22 (1H, d *J* 2.7 Hz, H2), 3.48 (1H, m, H3) and 3.88-4.10 (4H, m, H6); δ_C (75 MHz; $CDCl_3$) 25.05, 29.33, 55.52, 55.69, 64.86, 65.23 and 114.65; *m/z* (CI - methane), 207 (48%), 205 (50), 143 (M^{+}+ H, 55), 125 (10) and 99 (100).

3-hydroxycyclopentan-1-one ethylene ketal (177).[114]

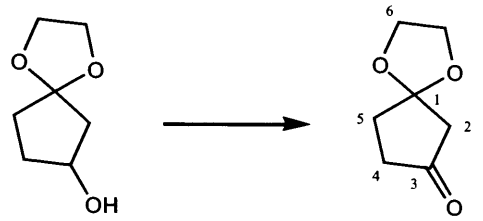


176 **177**

$C_7H_{12}O_3$
Mol. Wt.: 144.17

Lithium aluminium hydride (0.18 g, 4.82 mmol) was slurried in anhydrous tetrahydrofuran (5 ml) and a solution of the epoxy ketal (**176**) (0.13 g, 0.92 mmol) in tetrahydrofuran (1 ml) was added dropwise. The mixture was heated to reflux for 24 h then cooled and poured onto a saturated solution of Rochelle's salt (potassium sodium tartrate) (20 ml). This slurry was extracted with diethyl ether (3 x 10 ml), the organic layers combined, washed with a saturated NaCl solution (2 x 10 ml) and dried over $MgSO_4$. The volatiles were removed under reduced pressure to give the crude alcohol (**177**) which was purified by flash column chromatography (1: 2, petrol: diethyl ether). This gave the title compound (**177**) as a clear colourless oil (0.12 g, 0.83 mmol, 91%); υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 3462.0 (br, O-H), 2964.4 (s, C-H), 2891.1 (s, C-H), 1469.7 (m), 1434.9 (m), 1350.1 (m), 1209.3 (s), 1093.6 (s), 1047.3 (s), 1024.1 (s), 948.9 (s), 921.9 (m) and 839.0 (w); δ_H (300 MHz; $CDCl_3$), 1.56-1.67 (2H, m, H4), 1.70-1.82 (2H, m, H5), 1.87-1.99 (2H, m, H2), 2.30 (1H, br s, OH), 3.72-3.77 (1H, m, H3) and 3.93 (4H, s, H6); δ_C (75 MHz; $CDCl_3$) 18.85, 31.48, 32.66, 64.98, 65.13, 74.84 and 116.48; *m/z* (EI), 144 (M^{+}, 7%), 99 (100) and 88(14). Found (EI): [M^{+}] 144.07850, $C_7H_{12}O_3$ requires 144.07864.

Cyclopentan-1,3-dione monoethylene ketal (178).[114]

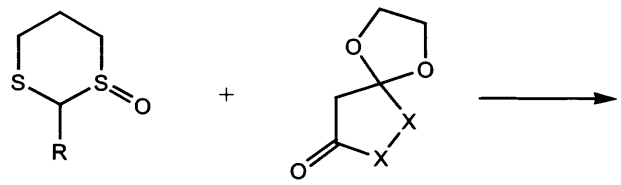


177 **178**

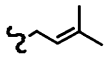
$C_7H_{10}O_3$
Mol. Wt.: 142.15

Dimethylsulfoxide (1.15 g, 1.04 ml, 14.7 mmol) in anhydrous dichloromethane (3 ml) was added dropwise to a solution of oxalyl chloride (0.83 g, 0.56 ml, 6.53 mmol) in anhydrous dichloromethane (20 ml) at –78 °C. After stirring for 15 minutes at this temperature a solution of the alcohol (**177**) (0.47 g, 3.26 mmol) in anhydrous dichloromethane (20 ml) was added dropwise and stirring continued for a further 20 minutes. Triethylamine (2.97 g, 4.07 ml, 29.4 mmol) was then added, the solution stirred for 10 minutes and then allowed to warm to room temperature over 2 h. Water (20 ml) was added to the reaction solution and the two layers separated. The aqueous layer was further extracted with dichloromethane (3 x 20 ml), the organic layers combined, washed with a saturated NaCl solution (2 x 20 ml) and dried over $MgSO_4$. Removal of the volatiles under reduced pressure gave the crude ketone (**178**) which was purified by flash column chromatography (1: 1, petrol: diethyl ether) giving the ketone (**178**) as a clear colourless oil (0.37 g, 2.16 mmol, 80%); υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 2975.0 (m, C-H), 2901.7 (m, C-H), 1753.2 (s, C=O), 1467.7 (w), 1436.9 (w), 1403.1 (w), 1353.0 (w), 1335.6 (w), 1302.8 (w), 1216.0 (m), 1191.0 (m), 1171.7 (m), 1156.2 (m), 1039.6 (s), 1002.0 (m), 987.5 (m), 945.1 (m), 828.4 (m) and 810.0 (w); δ_H (300 MHz; $CDCl_3$), 1.87 – 1.99 (2H, m, H5), 2.02 – 2.07 (2H, m, H4), 2.25 (1H, d *J* 7.3 Hz, H2), 2.27 (1H, d *J* 7.3 Hz, H2), 4.00–4.04 (2H, m, H6) and 4.14-4.19 (2H, m, H6); δ_C (75 MHz; $CDCl_3$) 17.14, 32.60, 34.65, 65.26, 106.69 and 214.37; *m/z* (EI), 143 (M^{+}+ H, 12%), 127 (90), 86 (100), 61 (50), 55 (75) and 41 (50).

Attempted addition of substituted-[1,3]-dithiane-1-oxides (173, 174) to carbonyl compounds (172, 178).

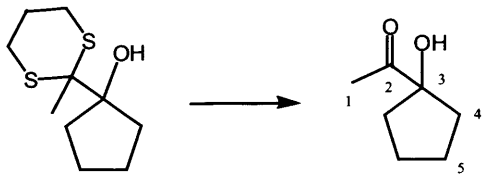


R = Me **173** X—X = $H_2C—CH_2$ **178**

 **174** BrC=CH **172**

A solution of ^{n}BuLi in hexanes (2.17M, 0.24 ml, 0.51 mmol) was added dropwise to a solution of diisopropyl amine (0.056 g, 0.077 ml, 0.55 mmol) in anhydrous tetrahydrofuran (10 ml) at –5 °C and the reaction stirred at this temperature for 25 minutes. The reaction was then cooled to –78 °C and a solution of 2-methyl-[1,3]-dithiane-1-oxide (**173**) (0.07 g, 0.46 mmol) or 2-(3-Methylbut-2-enyl)-[1,3]dithiane-1-oxide (**174**) (0.094 g, 0.46 mmol) in tetrahydrofuran (2 ml) was added dropwise. After 30 minutes either cyclopentan-1,3-dione monoethylene ketal (**178**) or 3-Bromocyclopent-2-en-1,4-dione monoethylene ketal (**172**) (0.46 mmol) was added dropwise to the reaction solution and stirring continued at –78 °C for 30 minutes. The reaction was then either quenched at this temperature by the addition of acetic acid (0.14 g, 0.14 ml, 2.3 mmol), or allowed to slowly warm to room temperature before being quenched with water (10 ml). Ethyl acetate (10 ml) was added to the reaction, the two phases that formed separated and the aqueous phase further extracted with ethyl acetate (3 x 10 ml). The organic phases were combined, washed with water (2 x 10 ml) and dried over $MgSO_4$ to give the crude product mixture. In all cases only starting materials were recovered from the reaction.

1-(1-Hydroxycyclopentyl)-ethanone (179).



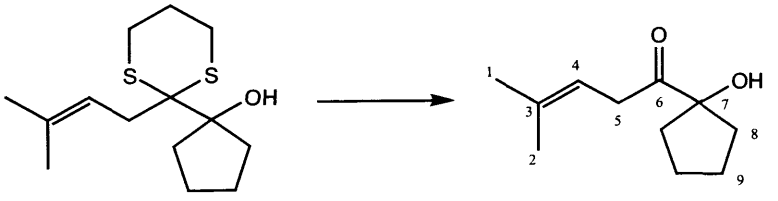
158 **179**

$C_7H_{12}O_2$

Mol. Wt.: 128.17

Methyl iodide (3.88 g, 1.70 ml, 27.3 mmol) was added to a stirred suspension of the dithiane (**158**) (0.5 g, 2.30 mmol) and calcium carbonate (2.53 g, 25.3 mmol) in a solvent system of acetonitrile: water 1: 1 (20 ml). This solution was heated for 1 h (oil bath temperature 55 °C) before a second portion of methyl iodide (0.96 g, 0.42 ml, 6.77 mmol) was added and heating continued for a further 2 h. A third portion of methyl iodide (2.28 g, 1.00 ml, 16.1 mmol) was added and heating continued for a further 3 h before the mixture was allowed to cool. The solids were filtered off by suction filtration, washed with water (20 ml) and then diethyl ether (20 ml). The organic layer was separated from the filtrate and the aqueous layer further extracted with diethyl ether (2 x 20 ml). The organic extracts were combined, dried over $MgSO_4$ and the volatiles evaporated *in vacuo*. The crude product was purified by flash column chromatography (2: 1, petrol: diethyl ether) to give the α-hydroxyketone (**179**) as a clear nonviscous oil with a yellow tint (0.25 g, 1.95 mmol, 85%).[191] υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 3448.5 (s, O-H), 2963.4 (s, C-H), 2872.8 (s), 1700.1 (m, C=O), 1631.7 (w), 1419.5 (m), 1355.9 (m), 1170.7 (m), 1104.2 (w), 1055.0 (m), 1023.2 (m) and 926.7 (m); δ_H (300 MHz; $CDCl_3$), 1.61-1.85 (4H, m, H5), 1.85-2.07 (4H, m, H4), 2.20 (3H, s, H1) and 3.55-3.82 (1H, br s, OH); δ_C (75 MHz; $CDCl_3$) 23.61, 25.50, 38.95, 87.00 and 212.03; *m/z* (CI-methane), 148 (85%), 126 (M - 2H, 56), 110 (30) and 81 (100). Found (CI - methane): [M - H] 127.07547, $C_7H_{11}O_2$ requires 127.07590.

1-(1-Hydroxycyclopentyl)-4-methylpent-3-en-1-one (49).



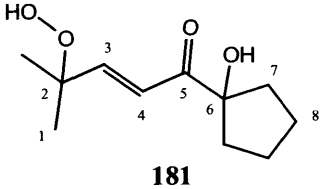
159 **49**

$C_{11}H_{18}O_2$
Mol. Wt.: 182.26

Methyl iodide (4.56 g, 2.00 ml, 32.1 mmol) was added to a stirred suspension of the dithiane (**159**) (0.64 g, 2.35 mmol) and calcium carbonate (2.59 g, 25.9 mmol) in a solvent system of acetonitrile: water 1: 1 (20 ml). The solution was heated for 1 h (oil bath temperature 55 °C) before a second portion of methyl iodide (1.14 g, 0.50 ml, 8.0 mmol) was added and heating continued for a further 2 h. After this time a third portion

of methyl iodide (1.71 g, 0.75 ml, 11.4 mmol) was added and heating continued for 3 h. The reaction mixture was cooled, the solids removed by suction filtration, washed with water (20 ml) and then diethyl ether (20 ml). The organic layer was separated from the filtrate and the aqueous layer further extracted with diethyl ether (2 x 20 ml). The organic extracts were combined, washed with water (2 x 20 ml) and dried over $MgSO_4$. The volatiles were removed under reduced pressure and the crude product purified by flash column chromatography (2: 1, petrol: diethyl ether) producing the *α-hydroxyketone* (**49**) as a clear colourless nonviscous oil (0.27 g, 1.48 mmol, 64%). υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 3447.5 (s, O-H), 2936.4 (s, C-H), 2872.8 (s), 1700.1 (s, C=O), 1631.7 (w), 1436.9 (m), 1376.1 (m), 1306.1 (w), 1182.3 (w), 1112.9 (w), 1052.2 (w), 1016.4 (w), 911.3 (m) and 733.9 (s); δ_H (300 MHz; C_6D_6), 1.50-1.63 (4H, m, H9), 1.53 (3H, s, H1/2), 1.69 (3H, s, H1/2), 1.82-1.93 (4H, m, H8), 3.15 (2H, d *J* 6.8 Hz, H5), 3.67 (1H, br s, OH) and 5.52 (1H, m, H4); δ_C (75 MHz; C_6D_6) 17.92, 25.46, 25.54, 35.97, 39.58, 87.13, 117.10, 134.64 and 211.60; *m/z* (CI- methane), 198 (M + CH_4, 55%), 181 (M - H, 100) and 129 (15). Found (CI - methane): [M - H] 181.12242, $C_{11}H_{17}O_2$ requires 181.12285. On storage, this compound undergoes slow oxidation to the hydroperoxide (**181**).

***trans* - 4-Hydroperoxy-1-(1-hydroxycyclopentyl)-4-methylpent-2-en-1-one (181).**



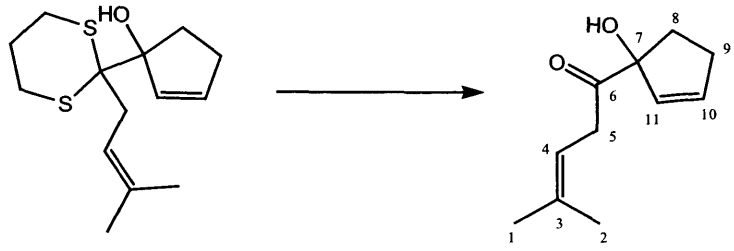
181

$C_{11}H_{18}O_4$
Mol. Wt.: 214.26

Storage of the α-hydroxyketone (**49**) at –18°C for two months led to complete conversion to the peroxide *trans-4-hydroperoxy-1-(1-hydroxycyclopentyl)-4-methylpent-2-en-1-one* (**181**) which required no subsequent purification. mp 79-81 °C (petrol / diethyl ether); (Anal calcd. for $C_{11}H_{18}O_4$ C, 61.66; H, 8.47% Found C, 61.34; H, 8.45%); υ_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 3394.5 (br, O-H), 2974.0 (s, C-H), 2873.7 (m), 1687.6 (s, C=O), 1625.9 (s, C=C), 1361.7 (m), 1284.5 (s), 1145.6 (m), 1114.8 (m), 1053.1 (m), 1014.5 (m), 979.8 (m) and 850.5 (w); δ_H (300 MHz; $CDCl_3$), 1.40 (6H, s, H1), 1.60-1.89 (4H, m, H8), 1.90-2.10 (4H, m, H7), 3.85 (1H, br s, OH), 6.52 (1H, d *J* 15.8 Hz, H4), 7.12 (1H, d *J* 15.8 Hz, H3) and 8.20 (1H, br s, OOH); δ_C

(75 MHz; $CDCl_3$) 24.16, 25.68, 39.07, 82.10, 86.44, 121.08, 151.21 and 202.48; *m/z* (CI + methane), 215 (MH^+, 62%), 197 (M – OH, 42), 181 (M – OOH, 100) and 165 (37). Found (CI + methane): [MH^+] 215.12783, $C_{11}H_{19}O_4$ requires 215.12833. (positive starch iodide paper test).

1-(1-Hydroxycyclopent-2-enyl)-4-methylpent-3-en-1-one (180).



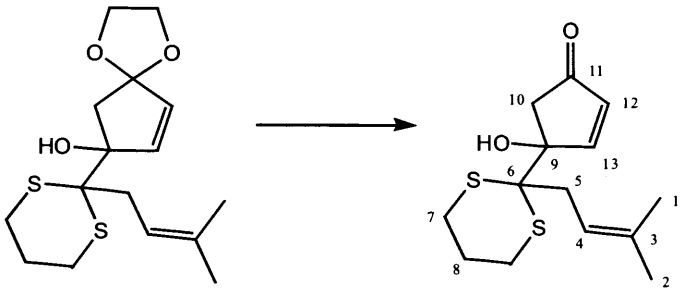
160 **180**

$C_{11}H_{16}O_2$
Mol. Wt.: 180.24

Methyl iodide (4.73 g, 2.15 ml, 33.3 mmol) was added to a stirred suspension of the dithiane (**160**) (0.76 g, 2.81 mmol) and calcium carbonate (3.10 g, 31.0 mmol) in a solvent system of acetonitrile: water 1: 1 (40 ml). The solution was then heated for 1 h (oil bath temperature 55°C) before a second portion of methyl iodide (1.14 g, 0.52 ml, 8.03 mmol) was added and heating continued for a further 2 h. A third portion of methyl iodide (2.79 g, 1.27 ml, 19.6 mmol) was then added and heating continued for a further 3 h before the mixture was allowed to cool. The solids were removed by suction filtration, washed with water (30 ml) and then ether (30 ml). The organic layer was separated from the filtrate and the aqueous layer further extracted with diethyl ether (2 x 30 ml). The organic extracts were combined, washed with water (2 x 30 ml), dried over $MgSO_4$ and the volatiles evaporated *in vacuo*. The crude product was purified by flash column chromatography (2: 1, petrol: diethyl ether) to give the *title compound* (**180**) as a clear nonviscous oil (0.28 g, 1.56 mmol, 55%). υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 3397.4 (br, O-H), 2976.9 (s, C-H), 2934.5 (m, C-H), 1701.1 (s, C=O), 1652.9 (m, C=C), 1631.7 (m), 1363.6 (m), 1351.0 (m), 1285.5 (m), 1192.9 (m), 1158.2 (m), 1063.7 (w), 982.7 (m), 916.1 (w) and 756.0 (w); δ_H (300 MHz; $CDCl_3$), 1.56 (3H, s, H1,2), 1.71 (3H, s, H1,2), 1.92 (1H, ddd *J* 14.3, 9.2, 5.3 Hz, H8), 2.29 (1H, ddd *J* 14.3, 8.9, 3.9 Hz, H8), 2.45-2.60 (1H, m, H9), 2.68-2.80 (1H, m, H9), 3.09 (1H, dd *J* 17.5, 6.9 Hz, H5), 3.17 (1H, dd *J* 17.5, 6.8 Hz, H5), 4.23 (1H, s, OH), 5.21-5.25 (1H, m, H4), 5.53 (1H, dt *J* 5.6, 2.3 Hz, H11) and 6.19 (1H, dt *J* 5.6, 2.4 Hz, H10); δ_C (75 MHz; $CDCl_3$) 18.03,

25.65, 32.18, 35.40, 35.73, 90.61, 115.44, 132.37, 135.79, 138.14 and 210.90; *m/z* (CI+ methane), 179 (M^{+}-H, 80%), 163 (28), 161 (40), 137 (30), 121 (47) and 113 (100); Found (CI+ methane) [M^{+} + H] 181.12291, $C_{11}H_{17}O_2$ requires 181.12285.

4-Hydroxy-4-[2-(3-Methylbut-2-enyl)-[1,3]dithian-2-yl]-2-cyclopenten-1-one (191).

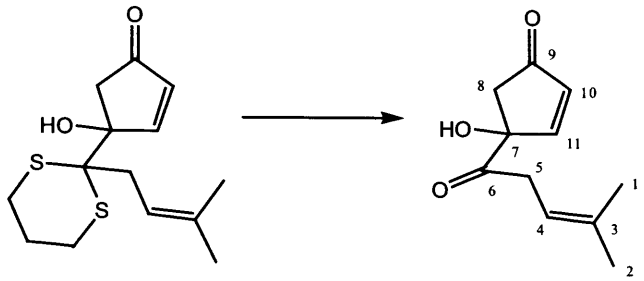


167 **191**

$C_{14}H_{20}O_2S_2$
Mol. Wt.: 284.44

A 15% sulfuric acid solution in water (0.3 g, 10-11 drops) was added dropwise to a vigorously stirring suspension of silica gel (3.00 g) in dichloromethane (15 ml). After a few minutes the water phase disappeared as it was absorbed onto the silica gel surface and then the acetal compound (0.50 g, 1.52 mmol) (**167**) was added to the reaction mixture. The stirring was continued at room temperature for 0.5 h before the solid phase was separated from the reaction by suction filtration, washing the solid several times with dichloromethane (2 x 15 ml). Evaporation of the volatiles from the filtrate under reduced pressure gave the crude product which was purified by flash column chromatography (1: 1, petrol: diethyl ether) producing the *enone* (**191**) as a viscous colourless oil (0.27 g, 0.97 mmol, 62%). υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 3444.6 (br, O-H), 2918.1 (s, C-H), 2829.4 (w), 1737.7 (s, C=O), 1732.0 (s), 1716.5 (s), 1423.4 (m), 1373.2 (m), 1278.7 (m), 1245.9 (m), 1170.7 (m), 1047.3 (m), 908.4 (w) and 806.2 (w); δ_H (300 MHz; CD_3CN), 1.60 (3H, s, H1/2), 1.69 (3H, s, H1/2), 1.76-1.97 (2H, m, H8), 2.25 (1H, d *J* 18.5 Hz, H10), 2.66-2.90 (6H, m, H5,7), 3.05 (1H, d *J* 18.5 Hz, H10), 5.41 (1H, m, H4), 6.11 (1H, d *J* 5.8 Hz, H12) and 7.71 (1H, d *J* 5.8 Hz, H13); δ_C (75 MHz; CD_3CN) 18.61, 25.16, 26.25, 27.58, 27.85, 36.62, 47.88, 60.65, 87.85, 121.82, 134.59, 134.73, 164.65 and 207.06; *m/z* (CI + methane), 285 (MH^{+}, 32%), 268 (43), 267 (M – OH, 70), 215 (M - C_5H_9, 50), 199 (55) and 187 (62). Found (CI + methane): [MH^{+}] 285.09769, $C_{14}H_{21}O_2S_2$ requires 285.09829.

4-Hydroxy-4-(4-methylpent-3-enoyl)-cyclopent-2-enone (192).

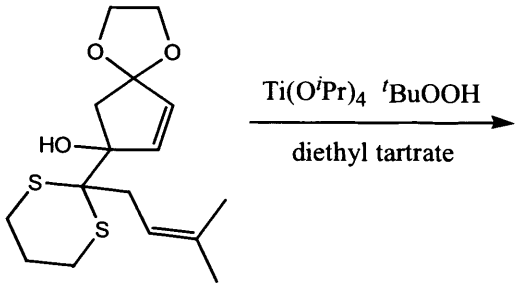


191 **192**

$C_{11}H_{14}O_3$
Mol. Wt.: 194.23

Methyl iodide (2.80 g, 1.23 ml, 19.7 mmol) was added to a stirred suspension of dithiane (**191**) (0.44 g, 1.58 mmol) and calcium carbonate (1.83 g, 18.3 mmol) in a solvent system of acetonitrile: water 1: 1 (20 ml). The solution was heated for 1 h (oil bath temperature 55 °C) before a second portion of methyl iodide (0.68 g, 0.30 ml, 4.79 mmol) was added and heating continued for a further 2 h. A third portion of methyl iodide (1.66 g, 0.73 ml, 11.7 mmol) was then added to the reaction mixture and heating continued for a further 11 h before the mixture was allowed to cool, the solids removed by suction filtration and washed with water (20 ml) and diethyl ether (20 ml). The organic layer was separated from the filtrate and the aqueous further extracted with diethyl ether (2 x 20 ml). The organic extracts were then combined, dried over $MgSO_4$, volatiles evaporated and the crude product purified by flash column chromatography (1: 1, petrol: diethyl ether). This produced the *α-hydroxyketone* (**192**) as a clear colourless viscous oil (0.14 g, 0.74 mmol, 40%). υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 3431.1 (s, O-H), 2972.1 (w, C-H), 2927.7 (w), 1710.7 (s, C=O), 1631.7 (m), 1589.2 (m), 1332.7 (m), 1257.5 (m), 1053.1 (m), 808.1 (m) and 786.9 (m); δ_H (300 MHz; C_6D_6), 1.31 (3H, s, H1/2), 1.54 (3H, s, H1/2), 2.32 (1H, d *J* 18.5 Hz, H8), 2.51 (1H, d *J* 18.5 Hz, H8), 2.79 (1H, dd *J* 17.3, 7.0 Hz, H5), 2.90 (1H, dd *J* 17.3, 7.0 Hz, H5), 5.13-5.22 (1H, m, H4), 5.93 (1H, d *J* 5.6 Hz, H10) and 6.67 (1H, d *J* 5.6 Hz, H11); δ_C (75 MHz; C_6D_6) 17.87, 25.53, 35.66, 46.56, 84.52, 115.50, 136.17, 136.21, 161.13, 204.75 and 206.91. *m/z* (CI - methane), 245 (100%), 210 (M+ CH_4, 100), 192 (M, 100), 176 (45) and 125 (100). Found (CI - methane): [M - H] 193.08740, $C_{11}H_{13}O_3$ requires 193.08646.

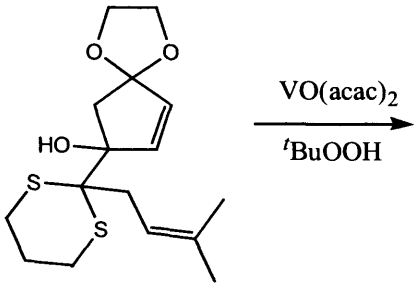
Attempted epoxidation of 4-hydroxy-4-[2-(3-Methylbut-2-enyl)-[1,3]dithian-2-yl]-2-cyclopenten-1-one ethylene ketal (167).



167

A one necked round bottomed flask was charged with 4Å powdered molecular sieves (0.1 g), anhydrous dichloromethane (5 ml) and L-(+)-diethyl tartrate (0.076 g, 0.06 ml, 0.37 mmol) and cooled to –20 °C. Titanium (IV) isopropoxide (0.085g, 0.09 ml, 0.30 mmol) was added to the reaction mixture followed by an anhydrous solution of ^{t}BuOOH in dichloromethane (3M, 0.20 ml, 0.60 mmol) and the suspension stirred –20 °C for a further 30 minutes. A solution of the protected isohumulone analogue (**167**) (0.10g, 0.30 mmol) in the minimum amount of anhydrous dichloromethane was added dropwise to the mixture whilst maintaining the temperature at –20 °C. The reaction was stirred at –10 °C for 5 h and then water (5 ml) added and the mixture allowed to slowly warm to room temperature. A 30% aqueous NaOH solution (2 ml) was then added and stirring continued for a further 1 h. The two phases of the reaction were separated, the aqueous phase further extracted with dichloromethane (3 x 5 ml), the organic extracts combined and dried over $MgSO_4$. Evaporation of the volatiles under reduced pressure gave the crude product as a yellow oil (0.05 g). The NMR spectra of this crude oil showed a complex mixture of degradation products. Attempts to purify and separate the mixture by flash column chromatography proved unsuccessful.

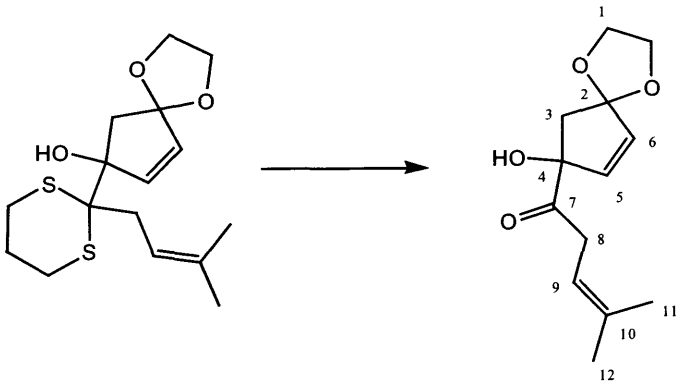
Attempted epoxidation of 4-hydroxy-4-[2-(3-Methylbut-2-enyl)-[1,3]dithian-2-yl]-2-cyclopenten-1-one ethylene ketal (167).



167

^{t}BuOOH in water (70 wt.%, 0.091 ml, 0.67 mmol) was added dropwise to a solution of the protected isohumulone analogue (**167**) (0.2 g, 0.61 mmol) and vanadyl acetylacetonate (0.005 g, 0.018 mmol) in benzene (5 ml) at reflux. Heating to reflux was continued for 4 h before the reaction mixture was cooled to room temperature, water (10 ml) was added and the two layers that formed separated. The aqueous phase was further extracted with diethyl ether (3 x 10 ml), the organic phases combined, washed with water (2 x 10 ml) and dried over $MgSO_4$. Evaporation of the volatiles under reduced pressure gave a crude product which was purified by flash column chromatography (1: 1, petrol: diethyl ether) yielding 2-cyclopenten-1,4-dione monoethylene ketal (**164**) (0.02 g, 0.14 mmol, 24%) as the only isolatable product of the reaction. The spectral data obtained of the product were identical to that described previously.

1-(7-Hydroxy-1,4-dioxaspiro[4.4]non-8-en-7-yl)-4-methylpent-3-en-1-one (199).

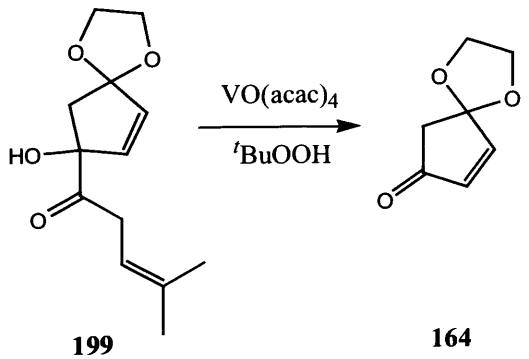


167 **199**

$C_{13}H_{18}O_4$
Mol. Wt.: 238.28

Methyl iodide (1.03 g, 0.45 ml, 7.26 mmol) was added to a stirred suspension of the dithiane (**167**) (0.20 g, 0.61 mmol) and calcium carbonate (0.67 g, 6.71 mmol) in a solvent system of acetonitrile: water 1: 1 (20 ml). The solution was heated for 1 h (oil bath temperature 55 °C) before a second portion of methyl iodide (0.23 g, 0.10 ml, 1.60 mmol) was added and heating continued for a further 2 h. A third portion of methyl iodide (0.62 g, 0.27 ml, 4.33 mmol) was then added and heating continued for a further 3 h before the mixture was allowed to cool. The solids were removed by suction filtration, washed with water (20 ml) and then diethyl ether (20 ml). The organic layer was separated from the filtrate and the aqueous layer further extracted with diethyl ether (2 x 20 ml). The organic extracts were combined, dried over $MgSO_4$ and the volatiles evaporated *in vacuo*. The crude product was purified by flash column chromatography (3: 1, petrol: diethyl ether) to give the *α-hydroxyketone* (**199**) as a clear nonviscous oil with a yellow tint (0.12 g, 0.50 mmol, 83%). υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 3448.5 (s, O-H), 2979.8 (s, C-H), 2889.2 (s), 1712.7 (s, C=O), 1625.9 (w, C=C), 1348.1 (m), 1267.1 (m), 1166.9 (m), 1124.4 (m), 1066.6 (s), 1008.7 (s), 948.9 (m), 850.6 (m) and 798.5 (w); δ_H (300 MHz; C_6D_6), 1.50 (3H, s, H11/12), 2.35 (1H, d *J* 15.0 Hz, H3), 2.41 (1H, d *J* 15.0 Hz, H3), 3.14 (1H, dd *J* 17.8, 6.8 Hz, H8), 3.27-3.51 (5H, m, H1,8), 4.60 (1H, s, OH), 5.46 (1H, tsept. *J* 6.8, 1.4 Hz, H9), 5.52 (1H, d *J* 5.6 Hz, H5/6) and 5.78 (1H, d *J* 5.6 Hz, H5/6); δ_C (75 MHz; C_6D_6) 17.99, 25.63, 35.42, 47.80, 64.74, 65.01, 87.33, 116.62, 118.35, 135.15, 135.94, 137.94 and 209.28; *m/z* (CI + methane), 239 (MH^+, 85%), 237 (M – H, 90), 221 (M – OH, 60), 187 (60) and 141 (M – C_6H_9O, 100). Found (CI + methane): [M + H] 239.12857, $C_{13}H_{19}O_4$ requires 239.12833.

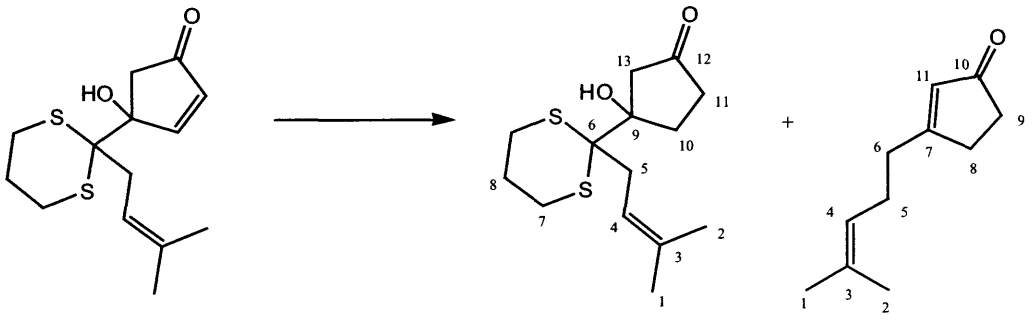
Elimination reaction of 1-(7-Hydroxy-1,4-dioxaspiro[4.4]non-8-en-7-yl)-4-methylpent-3-en-1-one (199).



199 **164**

^{t}BuOOH in water (70 wt.%, 0.028 ml, 0.21 mmol) was added dropwise to a solution of the partially protected isohumulone analogue (**199**) (0.05 g, 0.21 mmol) and vanadyl acetylacetonate (0.002 g, 0.0006 mmol) in benzene (5 ml) at reflux. Heating to reflux was continued for 4 h before the reaction mixture was cooled to room temperature, water (5 ml) was added and the two layers that formed separated. The aqueous phase was further extracted with diethyl ether (3 x 10 ml), the organic phases combined, washed with water (2 x 10 ml) and dried over $MgSO_4$. Evaporation of the volatiles under reduced pressure gave a crude product which was purified by flash column chromatography (1: 1, petrol: diethyl ether) yielding 2-Cyclopenten-1,4-dione monoethylene ketal (**164**) as a clear colourless oil (0.01 g, 0.07 mmol, 35%). The spectral data obtained of the product was identical to that described previously.

3-Hydroxy-3-[2-(3-methylbut-2-enyl)-[1,3]dithian-2-yl]-cyclopentanone (202) and 3-(4-methylpent-3-enyl)-cyclopent-2-enone (203).



191

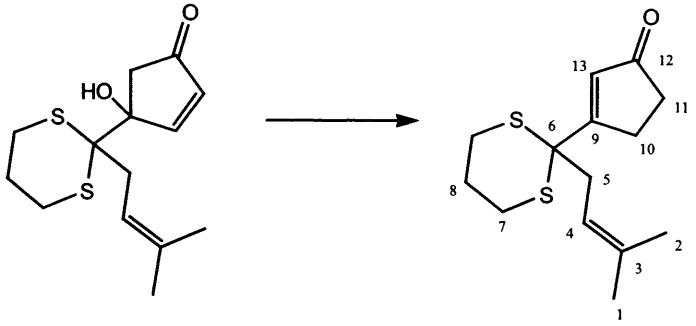
202
$C_{14}H_{22}O_2S_2$
Mol. Wt.: 286.45

203
$C_{11}H_{16}O$
Mol. Wt.: 164.24

A solution of sodium bis(2-methoxyethoxy)aluminium hydride (REDAl) in benzene (70 wt%, 2.03 g, 1.96 ml, 7.04 mmol) was added dropwise to a suspension of Cuprous bromide (1.01 g, 7.04 mmol) in anhydrous tetrahydrofuran (25 ml) at 0 °C. The resulting brown/black solution was stirred at 0 °C for a further 0.5 h and then cooled to –78 °C. Freshly distilled 2-butanol (1.96 g, 2.45 ml, 26.4 mmol) was added rapidly to the reaction mixture followed within 5 minutes by the dropwise addition of a solution of the enone (**191**) (0.50 g, 1.76 mmol) in anhydrous tetrahydrofuran (5 ml). Stirring was continued at –78°C for 10 minutes and then at –20 °C for 1 h and the reaction was allowed to warm to room temperature. The reaction was quenched by the addition of water (5 ml), poured into a saturated solution of Rochelle's salt (potassium sodium

tartrate) (25 ml) and diethyl ether added (25 ml). The organic layer was separated and the aqueous layer further extracted with diethyl ether (3 x 25 ml). The combined organic extracts were washed with water (2 x 25 ml), dried over $MgSO_4$ and the volatiles removed under reduced pressure to give the crude product. The mixture of products (**202**) and (**203**) were separated and purified by flash column chromatography (1: 1, petrol: diethyl ether) yielding the *dithiane* (**202**) as a clear colourless oil (0.27 g, 0.94 mmol, 54%) and varying amounts of the by-product *enone* (**203**) (maximum yield 0.043 g, 0.26 mmol, 15%). *3-Hydroxy-3-[2-(3-methylbut-2-enyl)-[1,3]dithian-2-yl]-cyclopentanone* (**202**); υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 3471.6 (br, O-H), 2916.2 (s, C-H), 1735.8 (s, C=O), 1442.7 (m), 1380.9 (m), 1350.1 (m), 1272.9 (m), 1164.9 (m), 1110.9 (w), 1072.3 (w), 995.2 (m), 941.2 (w), 910.3 (w), 871.8 (w) and 810.0 (w); δ_H (300 MHz; $CDCl_3$), 1.65 (3H, s, H1/2), 1.71 (3H, s, H1/2), 1.82-2.92 (15H, m, H5,7,8,10,11,13 and OH) and 5.50 (1H, br t, *J* 6.9 Hz, H4); δ_C (75 MHz; $CDCl_3$) 18.51, 24.07, 26.07, 26.62, 26.72, 32.25, 35.29, 36.29, 49.02, 60.82, 85.88, 120.80, 134.60 and 216.50; *m/z* (EI) 217 (M^+- C_5H_9, 60%), 205 (40), 187 (40), 96 (35), 89 (90) and 88 (100); Found (EI) [M^+] 286.10552, $C_{14}H_{22}S_2O_2$ requires 286.10612. *3-(4-Methylpent-3-enyl)-cyclopent-2-enone* (**203**); υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 2964.4 (m, C-H), 2923.9 (m), 2858.3 (m), 1701.1 (s, C=O), 1664.4 (s, C=O), 1618.2 (s, C=C), 1438.8 (w), 1263.3 (m), 1184.2 (m), 1018.3 (m) and 794.6 (m); δ_H (300 MHz; $CDCl_3$), 1.61 (3H, s, H1/2), 1.68 (3H, s, H1/2), 2.22 – 2.33 (2H, m, H5/H6/H8/H9), 2.37 – 2.48 (4H, m, H5/H6/H8/H9), 2.55 – 2.61 (2H, m, H5/H6/H8/H9), 5.04 – 5.13 (1H, m, H4) and 5.95 (1H, t *J* 1.5 Hz, H11); δ_C (75 MHz; $CDCl_3$) 17.70, 25.53, 25.57, 31.56, 33.55, 35.25, 122.62, 129.55, 132.97, 182.67 and 210.14; *m/z* (CI + methane) 165 (MH^+, 100%), 147 (18), 119 (6), 109 (M – C_4H_7, 10) and 97 (32); Found (CI + methane) [MH^+] 165.1279, $C_{11}H_{17}O$ requires 165.1279.

3-[2-(3-Methylbut-2-enyl)-[1,3]dithian-2-yl]-cyclopent-2-enone (204).



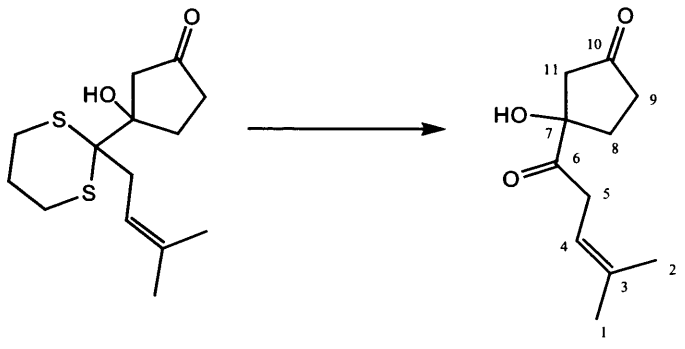
191 **204**

$C_{14}H_{20}OS_2$
Mol. Wt.: 268.44

A solution of sodium bis(2-methoxyethoxy)aluminium hydride (REDAl) in benzene (70wt%, 0.58 g, 0.56 ml, 2.88 mmol) was added dropwise to a suspension of Cuprous bromide (0.21 g, 1.46 mmol) in anhydrous tetrahydrofuran (10 ml) at 0 °C. The resulting brown/black solution was stirred at 0 °C for a further 0.5 h and then cooled to –78 °C. Freshly distilled 2-butanol (0.40 g, 0.50 ml, 5.40 mmol) was added rapidly to the reaction mixture followed within 5 minutes by the dropwise addition of a solution of the enone (**191**) (0.10 g, 0.35 mmol) in anhydrous tetrahydrofuran (2 ml). Stirring was continued at –78 °C for 10 minutes and then at –20 °C for 1 h. The reaction was quenched by the addition of water (5 ml), poured into a saturated solution of aqueous NH_4Cl (15 ml), stirred for 10 minutes and then diethyl ether added (20 ml). The organic layer was separated and the aqueous layer extracted with diethyl ether (3 x 20 ml). The combined organic extracts were washed with a saturated solution of NH_4Cl (2 x 20 ml), dried over $MgSO_4$ and the volatiles removed under reduced pressure to give the crude product which was purified by flash column chromatography (1: 1, petrol: diethyl ether) yielding the *title compound* (**204**) as a clear colourless oil (0.04 g, 0.15 mmol, 41%). υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 2916.2 (s, C-H), 2854.5 (w), 1712.7 (s, C=O), 1627.8 (w), 1596.9 (w), 1434.9 (w), 1380.9 (w), 1257.5 (m), 1172.6 (w), 1103.2 (m), 1018.3 (m), 871.8 (w) and 794.6 (m); δ_H (300 MHz; $CDCl_3$), 1.61 (3H, s, H1/2), 1.68 (3H, s, H1/2) 1.78-1.98 (1H, m, H8), 2.02-2.14 (1H, m, H8), 2.51-2.55 (2H, m, H10/11), 2.64 (2H, d *J* 6.1 Hz, H5), 2.68-2.78 (6H, m, H7,10/11), 4.97-5.07 (1H, m, H4) and 6.43 (1H, t *J* 1.7 Hz, H13); δ_C (75.4 MHz; $CDCl_3$) 18.26, 24.77, 25.88, 27.55, 28.63, 36.61, 39.27, 55.55, 116.34, 135.02, 136.54, 181.26 and 209.44; *m/z* (FAB+) 291 (M + Na, 20%), 242 (10),

199 (M – C_5H_9, 30) and 173 (100); Found (FAB+) [M + Na] 291.08486, $C_{14}H_{20}S_2ONa$ requires 291.08532.

3-Hydroxy-3-(4-methylpent-3-enoyl)-cyclopentanone (148).



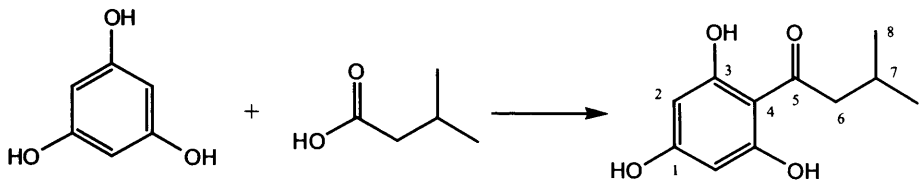
202 **148**

$C_{11}H_{16}O_3$
Mol. Wt.: 196.24

Methyl iodide (0.91 g, 0.40 ml, 6.43 mmol) was added to a stirred suspension of the dithiane (**202**) (0.16 g, 0.55 mmol) and calcium carbonate (0.65 g, 6.49 mmol) in a solvent system of acetonitrile: water 1: 1 (10 ml). The solution was heated for 1 h (oil bath temperature 55 °C) before a second portion of methyl iodide (0.23 g, 0.10 ml, 1.61 mmol) was added and heating continued for a further 2 h. A third portion of methyl iodide (0.68 g, 0.30 ml, 4.82 mmol) was then added and heating continued for 3 h before the mixture was allowed to cool. The solids were removed from the reaction by suction filtration, washed with water (20 ml) and then diethyl ether (20 ml). The layers of the filtrate were separated and the aqueous layer further extracted with diethyl ether (2 x 20ml). The organic extracts were combined, dried over $MgSO_4$ and volatiles evaporated *in vacuo*. The crude product was purified by flash column chromatography (2: 1, petrol: diethyl ether) to give the *α-hydroxyketone* (**148**) as a clear colourless nonviscous oil (0.064 g, 0.33 mmol, 59%). υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 3423.4 (br, O-H), 2972.1 (m, C-H), 2918.1 (m), 2860.2 (m), 1743.5 (s, C=O), 1712.7 (s, C=O), 1625.9 (m, C=C), 1448.4 (m), 1377.1 (m), 1359.7 (m), 1278.7 (m), 1232.4 (m), 1164.9 (m), 1128.3 (m), 1072.3 (m), 1012.6 (m), 985.6 (w), 933.5 (w), 848.6 (w) and 785.0 (w); δ_H (300 MHz; $CDCl_3$), 1.61 (3H, s, H1/2), 1.73 (3H, s, H1/2), 2.03-2.15 (1H, m, H8), 2.25-2.64 (4H, m, H8,9,11), 2.69 (1H, d *J* 17.9, H11), 3.37 (2H, d *J* 7.0 Hz, H5), 3.81 (1H, s, OH) and 5.27 (1H, m, H4); δ_C (75 MHz; $CDCl_3$) 18.19, 25.70, 34.39, 36.06, 36.26, 49.54, 83.59, 114.88, 136.63 210.48 and 215.25; *m/z* (EI) 197 (M^{+}+ H, 85%), 195 (M^{+}-

H, 100), 179 (M^+- OH, 98), 177 (90), 169 (85) and 151 (85); Found (EI) [M^+] 196.10934, $C_{11}H_{16}O_3$ requires 196.10994.

Phloroisovalerophenone (21). [91]

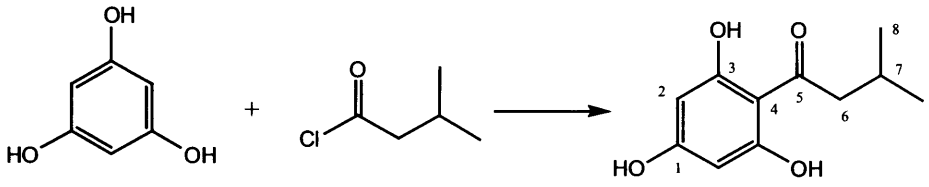


98 **216** **21**

$C_{11}H_{14}O_4$
Mol. Wt.: 210.23

Anhydrous phloroglucinol (**98**) (3.00 g, 23.8 mmols) (prepared by heating hydrated phloroglucinol in an oven at 120°C overnight) was added to a stirred solution of phosphorous oxychloride (36 ml) and aluminium chloride (9.52 g, 71.4 mmol). The reaction mixture was cooled to 0 °C and the isovaleric acid (**216**) (2.43 g, 2.6 ml, 23.8 mmol) added dropwise and stirring continued at 0 °C for a further 8 h and then at 6 °C for 48 h. The reaction mixture was then quenched by pouring onto crushed ice (*c.a.* 100 g) and extracted with diethyl ether (2 x 200 ml). The combined ethereal extracts were washed with saturated $NaHCO_3$ (500ml) and dried over $MgSO_4$. The diethyl ether was removed under reduced pressure to produce an oily residue. The crude product was purified by flash column chromatography (5: 1, petrol: ethyl acetate) producing phloroisovalerophenone (**21**) as a pale yellow solid (2.06 g, 9.80 mmol, 41%); mp 145-147 °C (petrol / ethyl acetate) (lit.[134] mp 146 °C (water)); υ_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 3329.0 (br, O-H), 3271.0 (m), 2924.8 (s, C-H), 2853.5 (s), 1634.6 (m, C=O), 1604.7 (m, C=C), 1519.8 (w), 1465.8 (m), 1377.1 (w), 1287.4 (w), 1204.5 (w), 1161.1 (w), 1079.1 (w) and 819.7 (w); δ_H (300 MHz; D_6-DMSO), 0.90 (6H, d *J* 6.7 Hz, H8), 2.05-2.19 (1H, m, H7), 2.85 (2H, d *J* 6.7 Hz, H6), 5.79 (2H, s, H2), 10.33 (1H, s, OH) and 12.25 (2H, s, OH); δ_C (75 MHz; D_6-DMSO) 22.55, 24.73, 51.85, 94.57, 103.88, 164.14, 164.43 and 204.69; *m/z* (CI + methane) 239 (45%), 211 (MH^+, 100), 195 (35), 153 (M - C_4H_9, 50), 103 (35) and 85 (30).

Phloroisovalerophenone (21). [134]

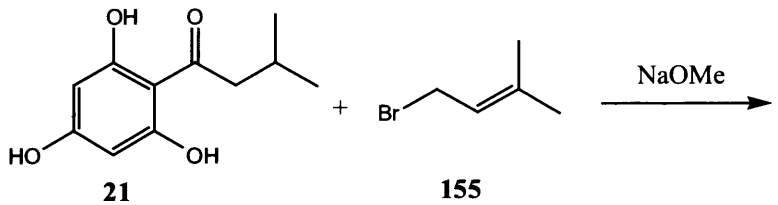


98 **217** **21**

$C_{11}H_{14}O_4$
Mol. Wt.: 210.23

Anhydrous phloroglucinol (**98**) (1.26 g, 10.0 mmols) (prepared by heating hydrated phloroglucinol in an oven at 120°C overnight) and aluminium chloride (4.00 g, 30.0 mmol) were dissolved in nitrobenzene (15 ml) and the reaction mixture cooled to 0 °C. Isovaleryl chloride (**217**) (1.21 g, 1.23 ml, 10.0 mmol) was added dropwise to this solution and stirring continued at 0 °C for a further 8 h and then at 12 °C for 5 days. The reaction was then quenched by pouring onto crushed ice (*c.a.* 50 g) and extracted with diethyl ether (2 x 100 ml). The combined ethereal extracts were washed with saturated $NaHCO_3$ (200 ml) and dried over $MgSO_4$. The volatiles were removed under reduced pressure to produce an oily slurry. This nitrobenzene containing slurry was purified by flash column chromatography (5: 1, petrol: ethyl acetate) producing phloroisovalerophenone (**21**) as a pale yellow solid (0.76 g, 3.62 mmol, 36%) with spectral data identical to that previously described.

Attempted diprenylation of phloroisovalerophenone (21). [1]

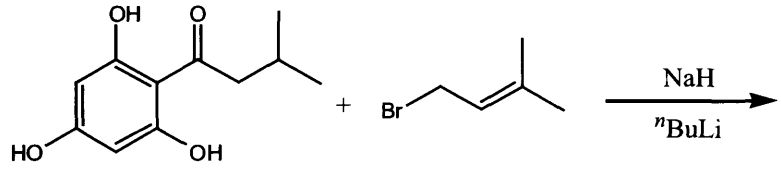


21 **155**

Phloroisovalerophenone (**21**) (0.085 g, 0.41 mmol) was dissolved in a mixture of diethyl ether (8 ml) and benzene (4 ml) under an atmosphere of nitrogen. A solution of freshly prepared sodium methoxide (0.113 g of sodium in 3 ml of methanol, 4.91 mmol) was added dropwise to the reaction mixture at 0 °C with stirring and the solution left stirring at this temperature for 15 minutes. The solvents were then evaporated under reduced pressure and benzene added to the crude reaction mixture (10 ml). The volume of the

benzene solution was reduced to *c.a.* 4 ml by rotary evaporation before the reaction was cooled to 0 °C and 1-bromo-3-methyl-2-butene (0.227 g, 0.18 ml, 1.52 mmol) added dropwise. The mixture was then cooled in the refrigerator overnight. Water was added to the reaction and the aqueous layer extracted with diethyl ether (3 x 10 ml). The organic extracts were combined, dried over $MgSO_4$ and the solvents evaporated under reduced pressure to give the crude product as a yellow oil (0.12 g) which appeared, by NMR spectrscopy, to be a mixture of mono, di, and tetra prenylated phloroisovalerylphenone compounds. All attempts to purify this crude product mixture by flash column chromatography proved unsuccessful.

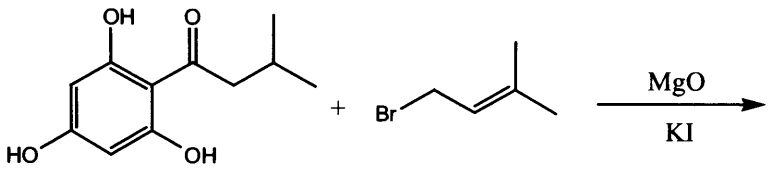
Attempted diprenylation of phloroisovalerophenone (21).



21 **155**

A solution of phloroisovalerophenone (**21**) (0.2 g, 0.95 mmol) in anhydrous tetrahydrofuran (5 ml) was added dropwise to a slurry of sodium hydride (60% in mineral oil, 0.038 g, 0.95 mmol) in anhydrous tetrahydrofuran (5 ml) at 0 °C. The reaction mixture was stirred at this temperature for 30 minutes before a solution of ^{n}BuLi in hexanes (2.16M, 0.88 ml, 1.90 mmol) was added dropwise and stirring continued at 0 °C for another 30 minutes. 1-Bromo-3-methyl-2-butene (**155**) (0.28 g, 0.22 ml, 1.90 mmol) was then slowly added and the reaction left at 0 °C for 2 h before being allowed to warm to room temperature and quenched by the addition of water (5 ml). Diethyl ether (10 ml) was added to the reaction solution the aqueous phase acidified with a 2M HCl solution (5 ml) and the organic and aqueous phases separated. The aqueous phase was further extracted with diethyl ether (3 x 10 ml), the organic phases combined, washed with water (2 x 10 ml) and dried over $MgSO_4$. Evaporation of the volatiles under reduced pressure gave the crude product as a yellow oil (0.22 g) which appeared, by NMR spectroscopy, to consist of a mixture of mono, di, and tetra prenylated phloroisovalerylphenone compounds. All attempts to purify this crude product mixture by flash column chromatography proved unsuccessful.

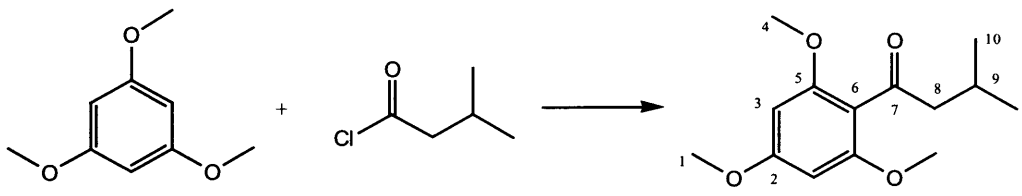
Attempted diprenylation of phloroisovalerophenone (21). [135]



21 **155**

Magnesium oxide (0.29 g, 7.14 mmol), potassium iodide (0.12 g, 0.71 mmol) and 1-bromo-3-methyl-2-butene (**155**) (0.43 g, 0.33 ml, 2.86 mmol) were added consecutively to a solution of phloroisovalerophenone (**21**) (0.3 g, 1.43 mmol) in acetone (5 ml) at room temperature under an atmosphere of nitrogen. The reaction was heated to reflux for 11 h before being cooled to room temperature water (10 ml) and diethyl ether (10 ml) added and the two phases were separated. The aqueous phase was further extracted with diethyl ether (3 x 10 ml) and the combined organic phases washed with a 2M HCl solution (2 x 10 ml). After drying the organic phase over $MgSO_4$ the volatiles were removed *in vacuo* to give the crude product as a yellow oil (0.1 g) which appeared, by NMR spectroscopy, to consist of a complex mixture of substituted phloroisovalerylphenone compounds. All attempts to purify this crude product mixture by flash column chromatography proved unsuccessful.

2-Isovaleryl-1, 3, 5-trimethoxybenzene (221). [136]



220 **217** **221**

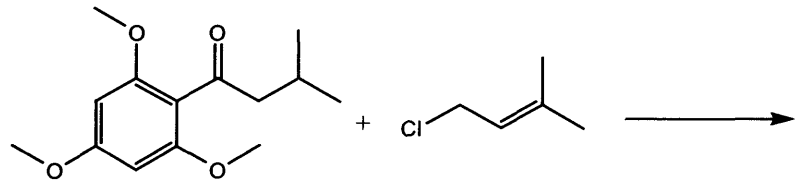
$C_{14}H_{20}O_4$

Mol. Wt.: 252.31

Aluminium trichloride (2.02 g, 15.1 mmol) was added in small portions with stirring to a solution of 1, 3, 5-trimethoxybenzene (**220**) (3.00 g, 17.8 mmol) and isovaleryl chloride (**217**) (2.25 g, 2.30 ml, 18.7 mmol) in anhydrous dichloromethane (36 ml) at –5 to –10 °C over 2 h. The resulting yellow solution was stirred at 0 °C for a further 30 minutes and then treated carefully with water (4 ml). The reaction was then diluted with

diethyl ether (40 ml) and the organic extract washed with a saturated aqueous $NaHCO_3$ solution (4 x 10 ml) and then with water (3 x 10 ml). The organic layer was dried over $MgSO_4$, the volatiles removed under reduced pressure and the crude product purified by flash column chromatography (1: 1, petrol: diethyl ether). This gave the title compound (**221**) as a clear colourless oil (3.86 g, 15.3 mmol, 86%). υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 2956.7 (s, C-H), 2869.9 (s), 2841.0 (s), 1701.1 (s, C=O), 1589.2 (s, C=C), 1456.2 (s), 1415.7 (s), 1365.5 (m), 1338.5 (m), 1290.3 (m), 1207.4 (s), 1006.8 (m), 950.8 (m) and 813.9 (m); δ_H (300 MHz; $CDCl_3$), 0.91 (6H, d *J* 6.7, H10), 2.06-2.25 (1H, m, H9), 2.58 (2H, d *J* 6.8 Hz, H8), 3.73 (6H, s, H4), 3.77 (3H, s, H1) and 6.07 (2H, s, H3); δ_C (75 MHz; $CDCl_3$) 22.64, 24.73, 53.41, 55.36, 55.73, 90.73, 114.08, 158.13, 162.13 and 204.31; *m/z* (CI + methane) 253 (MH^+, 60%), 195 (45), 169 (40), 155 (30) and 58 (100).

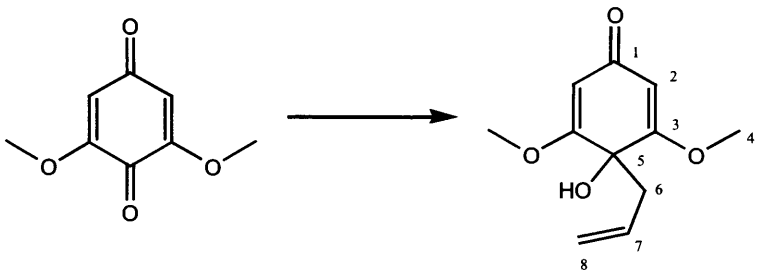
Attempted diprenylation of 2-Isovaleryl-1, 3, 5-trimethoxybenzene (221).



221 **156**

A solution of zinc chloride in dichloromethane (1M, 0.04 ml, 0.04 mmol) was added to a solution of 2-isovaleryl-1, 3, 5-trimethoxybenzene (**221**) (0.2 g, 0.79 mmol) and 1-chloro-3-methyl-2-butene (**156**) (0.17 g, 0.18 ml, 1.6 mmol) in anhydrous dichloromethane (5 ml) at room temperature. The reaction was stirred at this temperature for 12 h before water (10 ml) was added and the two phases that formed separated. The aqueous phase was further extracted with dichloromethane (3 x 10 ml), the organic phases combined, washed with water and dried over $MgSO_4$. This gave the crude product as an oil which, by NMR spectroscopy, contained a number of different ether containing compounds. All attempts to purify and separate these compounds proved unsuccessful.

4-Allyl-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (232).[140]

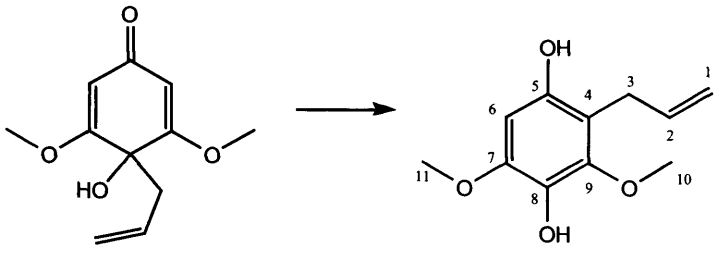


230 **232**

$C_{11}H_{14}O_4$
Mol. Wt.: 210.23

A solution of titanium tetrachloride in dichloromethane (1M, 13.0 ml, 13.0 mmol) was added dropwise to a solution of 2,6-dimethoxy-[1,4]benzoquinone (**230**) (2.00 g, 11.9 mmol) in anhydrous dichloromethane (40 ml) at –78 °C (a red solution formed). This was followed directly by the dropwise addition of allyltrimethylsilane (1.36 g, 1.90 ml, 11.9 mmol) and the reaction was left stirring at –78 °C for a further 20 minutes before being allowed to warm to –20°C and being quenched by the addition of water (40 ml). The aqueous phase was separated from the organic and extracted with dichloromethane (3 x 30 ml). The organic extracts were then combined, washed with water (2 x 40 ml) and dried over $MgSO_4$. After removal of the volatiles under reduced pressure the crude product appeared as a pale yellow solid which could be purified by washing with petrol (3 x 30 ml) or recrystallisation from diethyl ether. Both purification procedures gave the title compound (**232**) as a colourless crystalline solid (2.30 g, 10.9 mmol, 92%). mp 106-107 °C (diethyl ether) (lit.[192] m.p. 107-108 °C (petrol / diethyl ether)); υ_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 3257 (br, O-H), 2925.8 (s, C-H), 2852.5 (s), 1654.8 (s, C=O), 1610.5 (m, C=C), 1587.3 (m), 1460.0 (m), 1375.2 (m), 1348.1 (w), 1244.0 (m), 1211.2 (s), 1172.6 (w), 1147.6 (m), 1047.3 (m), 999.1 (w), 929.6 (w) and 848.6 (m); δ_H (300 MHz; $CDCl_3$), 2.72 (2H, d *J* 7.2 Hz, H6), 3.72 (6H, s, H4), 4.50 (1H, br s, OH), 4.95 (1H, d *J* 9.9 Hz, H8), 4.97 (1H, d *J* 17.1 Hz, H8), 5.27-5.43 (1H, m, H7) and 5.48 (2H, s, H2); δ_C (75 MHz; $CDCl_3$) 42.80, 56.40, 72.84, 100.69, 119.48, 130.38, 171.57 and 187.73; *m/z* (EI), 212 ($M^{\cdot+}$+ 2H, 25%), 211 ($M^{\cdot+}$+ H, 70), 210 ($M^{\cdot+}$, 55), 170 (35), 169 ($M^{\cdot+}$- C_3H_5, 100) and 154 (35); Found (EI): [$M^{\cdot+}$] 210.08983, $C_{11}H_{14}O_4$ requires 210.08920.

Attempted ring contraction of 4-Allyl-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (232).



232 **237**

$C_{11}H_{14}O_4$
Mol. Wt.: 210.23

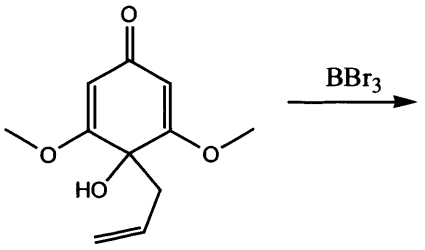
Base	Solvent System	Yield Of Compound **237**
NaOH	H_2O	24%
KOH	DCM: H_2O (1: 1)	24%
NaOH	DCM: H_2O (1: 1)	20%
K_2CO_3	THF: H_2O (1: 1)	no reaction
CsOH	DCM: H_2O (1: 1)	10%
$Ba(OH)_2$	DCM: H_2O (1: 1)	20%

Table 2

4-Allyl-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (**232**) (0.10 g, 0.48 mmol) was added to a solution of one of the bases listed in Table 2 (1.92 mmol) in the solvent system shown in the table (10 ml) at room temperature. Stirring was continued at this temperature for 24 h and in some cases the reaction solution developed a dark brown colouration. The reaction was then acidified with a 2M hydrochloric acid solution (5 ml) and dichloromethane added (10 ml). The two phases were separated and the aqueous phase further extracted with dichloromethane (3 x 10 ml). The organic phases were combined, washed with a saturated NaCl solution (2 x 10 ml) and dried over $MgSO_4$. The volatiles were removed under reduced pressure to give a mixture of starting material (**232**) and the aromatic compound (**237**). This mixture was separated and purified by flash column chromatography (diethyl ether), leading to the isolation of the aromatic compound (**237**) as a clear colourless oil in the yields given in Table 2; υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 3419.6 (br, O-H), 3078.2 (m), 2939.3 (m, C-H), 2844.8 (m,

C-H), 1683.7 (m), 1600.8 (s, C=C), 1506.3 (s), 1446.5 (s), 1492.2 (s), 1298.0 (m), 1244.0 (s), 1193.9 (m), 1122.5 (s), 1064.6 (s), 912.3 (m), 866.0 (m), 813.9 (w) and 736.8 (w); δ_H (300 MHz; $CDCl_3$), 3.42 (2H, dt *J* 5.8, 1.7 Hz, H3), 3.82 (6H, s, H10,11), 4.88 (1H, br s, OH), 5.13 (1H, dq *J* 16.3, 1.7 Hz, H1), 5.13 (1H, dq *J* 11.0, 1.7 Hz, H1), 5.17 (1H, br s, OH), 5.93-6.06 (1H, m, H2) and 6.29 (1H, s, H6); δ_C (75 MHz; $CDCl_3$) 27.96, 56.14, 61.17, 96.33, 110.86, 115.85, 132.77, 136.62, 145.39, 146.41 and 147.48; *m/z* (CI + methane), 211 (MH^+, 100%), 210 (M, 49), 195 (5), 183 (20), 179 (10) and 170 (7); Found (CI + methane): [MH^+] 211.09739, $C_{11}H_{15}O_4$ requires 211.09703.

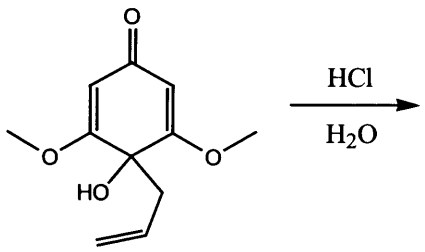
Attempted deprotection of 4-Allyl-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (232).



232

Boron tribromide (0.12 g, 0.045 ml, 0.48 mmol) was added to a solution of 4-Allyl-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (**232**) (0.1 g, 0.48 mmol) in anhydrous dichloromethane (7 ml) at –78 °C. This solution was then slowly allowed to warm to room temperature and stirred at this temperature for 12 h. The reaction was quenched by the addition of water (10 ml) and the aqueous and organic layers separated. The aqueous layer was further extracted with dichloromethane (3 x 10 ml), the organic extracts combined, washed with water (2 x 10 ml) and then dried over $MgSO_4$. Evaporation of the volatiles under reduced pressure led to a quantitative recovery of the starting material (**232**) from the reaction.

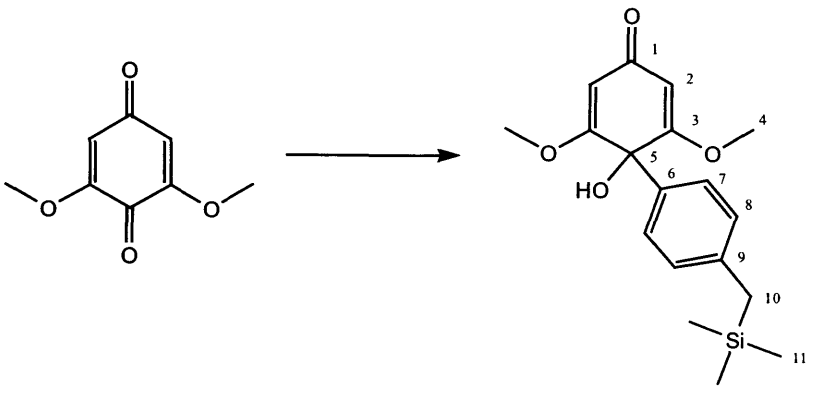
Attempted deprotection of 4-Allyl-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (232).



232

An aqueous solution of HCl (12M, 0.7 ml, 8.4 mmol) was added dropwise to a solution of 4-Allyl-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (**232**) (0.1 g, 0.48 mmol) in methanol (7 ml) at room temperature. The reaction was heated to reflux for 1 h before being cooled to room temperature and stirred at this temperature for 48 h. The solution was then diluted with diethyl ether (10 ml) and water added (10 ml). The two phases that formed were separated and the aqueous phase further extracted with ethyl acetate (3 x 10 ml). The organic phases were combined, washed with water (2 x 10 ml) and dried over $MgSO_4$. Removal of the volatiles *in vacuo* gave the crude product which, by NMR spectral analysis, was a complex mixture of numerous products and starting material. Attempts to separate and purify this mixture by flash column chromatography (1: 1, diethyl ether: ethyl acetate) led to the isolation of a mixture of partially protected aromatic compounds (0.06 g) which could not be separated further.

4-Hydroxy-3,5-dimethoxy-4-(4-trimethylsilanylmethylphenyl)-cyclohexa-2,5-dienone (245).



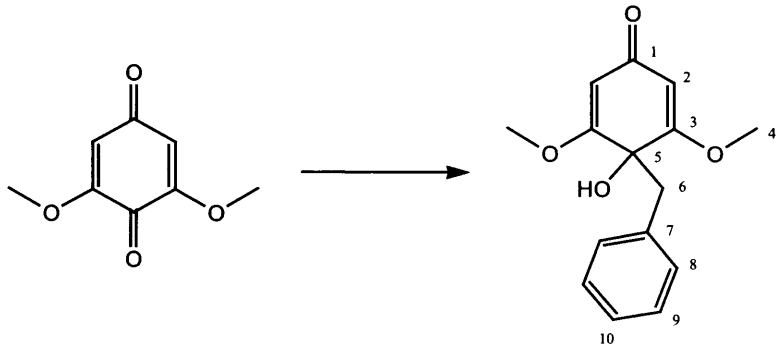
230 **245**

$C_{18}H_{24}O_4Si$
Mol. Wt.: 332.47

A solution of titanium tetrachloride in dichloromethane (1M, 1.90 ml, 1.19 mmol) was added dropwise to a solution of 2,6-dimethoxy-[1,4]benzoquinone (**230**) (0.20 g, 1.19 mmol) in anhydrous dichloromethane (7 ml) at –78 °C (a red solution formed). This was followed directly by the dropwise addition of the benzyl trimethylsilane (0.29 g, 0.34 ml, 1.79mmol) and the reaction was left stirring at –78 °C for a further 20 minutes before being allowed to slowly warm to room temperature and then quenched by the addition of water (10 ml). The aqueous phase was separated from the organic and extracted with dichloromethane (3 x 10 ml). The organic extracts were combined, washed with water (2 x 10 ml) and dried over $MgSO_4$. After removal of the volatiles under reduced pressure the crude product appeared as a pale yellow solid which was purified by recrystallisation from diethyl ether (hot filtering), yielding the *title compound* (**245**) as fluffy colourless needles (0.20 g, 0.60 mmol, 51%). mp 189 – 191 °C (diethyl ether); Anal calcd. for $C_{18}H_{24}O_4Si$ C, 65.03; H, 7.28% Found C, 64.96; H, 7.36%; υ_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 3186.2 (br, O-H), 2922.0 (s, C-H), 2852.5 (s), 1651.0 (m, C=O), 1614.3 (m, C=C), 1596.9 (m), 1456.2 (m), 1411.8 (w), 1375.2 (m), 1359.7 (m), 1334.6 (w), 1242.1 (m), 1215.1 (s), 1174.6 (w), 1107.1 (w), 1083.9 (m), 1008.7 (w), 854.4 (m) and 694.3 (w); δ_H (300 MHz; $CDCl_3$), -0.03 (9H, s, H11), 2.06 (2H, s, H10), 3.32 (1H, s, OH), 3.67 (6H, s, H4), 5.49 (2H, s, H2), 6.96 (2H, d *J* 8.2 Hz, H8) and 7.28 (2H, d *J* 8.2 Hz, H7); δ_C (75 MHz; $CDCl_3$) –1.88, 26.83, 56.43, 74.07, 100.16, 124.85, 128.10, 134.73, 140.95, 171.58 and 187.61; *m/z* (EI), 332

(M^{+}, 13%), 315 (M^{+}- OH, 30), 301 (M^{+}- OMe, 40), 285 (25), 242 (100) and 199 (35); Found (EI): [M^{+}] 332.14487, $C_{18}H_{24}O_4Si$ requires 332.14438.

4-Benzyl-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (243).



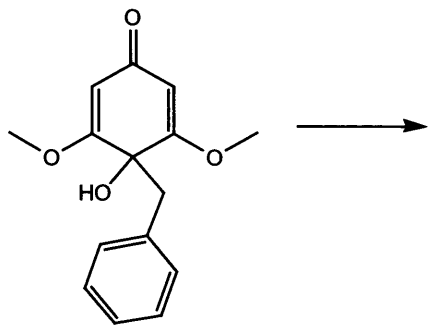
230 **243**

$C_{15}H_{16}O_4$
Mol. Wt.: 260.29

Dry tetrabutylammonium triphenyldifluorosilicate (TBAT) (0.64 g, 1.19 mmol, dried by azeotropic removal of water by 3 x rotary evaporation of a toluene solution) was added to a stirred solution of 2,6-dimethoxy-[1,4]benzoquinone (**230**) (0.20 g, 1.19 mmol) and benzyl trimethyl silane (0.29 g, 0.34 ml, 1.79 mmol) in anhydrous tetrahydrofuran (7 ml). The reaction mixture was heated to reflux for 1 h and developed a very dark colouration. The solution was cooled and quenched with water (10ml), dichloromethane (10 ml) was added and the two phases separated. The aqueous phase was further extracted with dichloromethane (3 x 10 ml), the organic phases combined, washed with water (2 x 10 ml) and dried over $MgSO_4$. The volatiles were removed under reduced pressure to give the crude product which was purified by flash column chromatography (diethyl ether), producing the *title compound* (**243**) as small beige platelets (0.10 g, 0.38 mmol, 33%); mp 209 – 211 °C (diethyl ether); ν_{max}/cm^{-1} (KBr plates nujol mull/ cm^{-1}) 3253.7 (br, O-H), 2923.9 (s, C-H), 2852.5 (s, C-H), 1654.8 (m, C=O), 1610.5 (w), 1587.3 (m), 1456.2 (m), 1377.1 (m), 1244.0 (m), 1201.6 (m), 1166.9 (m), 1089.7 (m), 1055.0 (w), 1035.7 (w), 869.8 (w) and 725.2 (w); δ_H (300 MHz; $CDCl_3$), 2.95 (1H, br s, OH), 3.32 (2H, s, H6), 3.80 (6H, s, H4), 5.28 (2H, s, H2), 6.89-6.95 (2H, m, H8-10) and 7.15-7.21 (3H, m, H8-10); δ_C (75 MHz; $CDCl_3$), 44.98, 56.08, 74.05, 101.74, 127.29, 128.20, 129.32, 134.10, 169.43 and 186.71; *m/z* (EI), 260 (M^{+}, 30%), 169 (M^{+} - C_7H_7,

30), 154 (10), 92 (11) and 91 (C_7H_7, 100). Found (EI): [M^+] 260.10433, $C_{15}H_{16}O_4$ requires 260.10485.

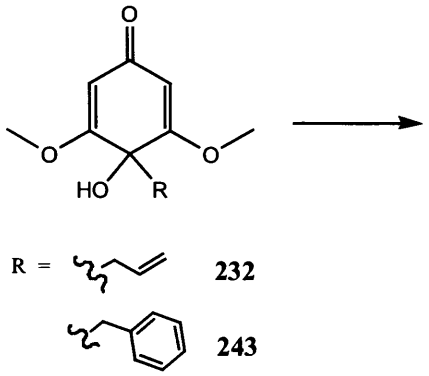
Attempted ring contraction of 4-benzyl-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (243).



243

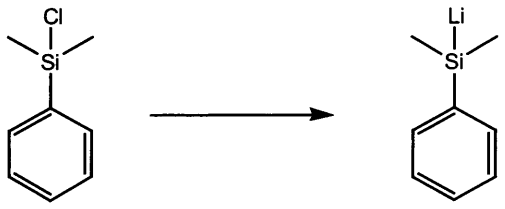
4-benzyl-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (**243**) (0.05 g, 0.19 mmol) was added to a solution of sodium hydroxide (0.023 g, 0.58 mmol) in water (5 ml) at room temperature. The reaction was heated to reflux for 3 h after which time the solution had developed a dark brown colouration. Acidification was then carried out with a 2M hydrochloric acid solution (5 ml) and dichloromethane added (10 ml). The two phases that formed were separated and the aqueous phase further extracted with dichloromethane (3 x 10 ml). The organic phases were then combined, washed with a saturated NaCl solution (2 x 10 ml) and dried over $MgSO_4$. The volatiles were removed under reduced pressure to give a crude product which appeared, by NMR spectroscopy, to contain some of the desired ring contracted compound (**248**) along with a lot of degradation products. All attempts to purify this product mixture proved unsuccessful.

Attempted photoinduced ring contraction of 4-allyl-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (232) and 4-benzyl-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (243).



Compound (**232**) or (**243**) (0.1 g) was dissolved in water (10 ml) in a pyrex round bottomed flask. This stirring solution was then irradiated with a Phillips HPK 125W mercury lamp for 5 h, whilst the lamp and the reaction vessel were cooled with a fan. After this time irradiation was stopped and dichloromethane (10 ml) added to the reaction. The two phases that formed were then separated and the aqueous phase further extracted with dichloromethane (2 x 10 ml). These organic extracts were combined, washed with water (10 ml), dried over $MgSO_4$ and the volatiles removed under reduced pressure. This process led to the quantitative recovery of starting material from both reactions (**232** and **243**).

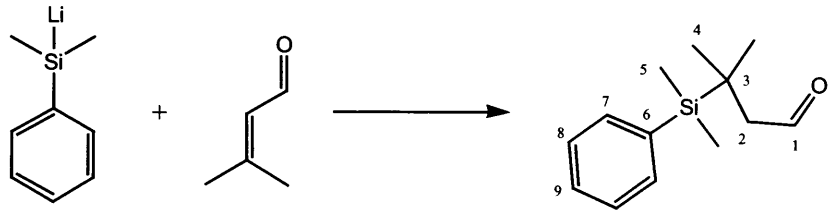
Dimethyl(phenyl)silyllithium (261).[159]



260 **261**

Chlorodimethylphenylsilane (**260**) (3.40 g, 2.27 ml, 20.0 mmol) and lithium shot (1.00 g, 140 mmol) were stirred in anhydrous tetrahydrofuran (35 ml) for 18 h. The resulting red solution was titrated according to the method of Whitesides *et al.*[193] and used without further purification. The reagent could be stored for several weeks at –20 °C without appreciable decomposition.

3-(Dimethylphenylsilanyl)-3-methylbutyraldehyde (263).

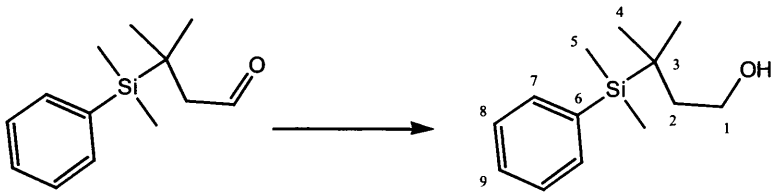


261 **262** **263**

$C_{13}H_{20}OSi$
Mol. Wt.: 220.38

Dimethyl(phenyl)silyllithium (**261**) in tetrahydrofuran (0.22M, 9.00 ml, 2.00 mmol) was added dropwise to copper cyanide (0.090 g, 1.01 mmol) at 0 °C under an atmosphere of nitrogen. The reaction mixture was stirred for a further 20 minutes at this temperature and then cooled to –20 °C. 3-Methylbut-2-enal (**262**) (0.084 g, 0.10 ml, 1.00 mmol) was added dropwise and stirring continued at –20 °C for 1 h before the reaction was allowed to slowly warm to room temperature over 1.5 h and quenched with a saturated NH_4Cl solution (5 ml). Petrol (10 ml) was added and the two phases separated. The aqueous phase was further extracted with petrol (3 x 5 ml), the organic extracts combined and washed with a saturated NH_4Cl solution (2 x 10 ml). This gave the crude silyl aldehyde (**263**) which was used without any further purification. Purification of the crude product could be achieved by flash column chromatography (4: 1, petrol: diethyl ether). This produced the *aldehyde* (**263**) as a clear colourless oil (0.16 g, 0.73 mmol, 73%); ν_{max}/cm^{-1} (KBr plates / cm^{-1}) 3068.5 (m, C-H), 3047.3 (m), 2956.7 (s, C-H), 2864.1 (m, C-H), 1718.5 (s, C=O), 1676.0 (m), 1637.7 (w), 1569.9 (m), 1460.0 (m), 1427.2 (m), 1407.9 (m), 1384.8 (m), 1365.5 (m), 1251.7 (s), 1178.4 (m), 1112.9 (s), 981.7 (m), 945.1 (m), 815.8 (s), 773.4 (m), 736.8 (m) and 702.0 (s); δ_H (300 MHz; $CDCl_3$), 0.35 (6H, s, H5), 1.13 (6H, s, H4), 2.25 (2H, d *J* 3.2 Hz, H2), 7.35-7.41 (3H, m, H7-9), 7.53 (2H, m, H7-9) and 9.80 (1H, t *J* 3.2 Hz, H1); δ_C (100 MHz; $CDCl_3$), -6.17, 20.33, 23.42, 51.76, 127.68, 129.23, 134.47, 136.04 and 204.34; *m/z* (FAB +) 281 (90%), 221 (MH^+, 30), 209 (25), 207 (32), 193 (20) and 191 (15). Found (FAB +): [MH^+] 221.13532, $C_{13}H_{21}OSi$ requires 221.13616.

3-(Dimethylphenylsilanyl)-3-methylbutan-1-ol (264).

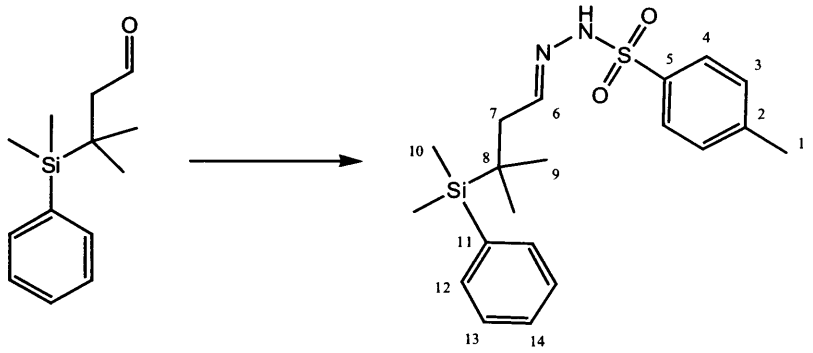


263 **264**

$C_{13}H_{22}OSi$
Mol. Wt.: 222.40

Sodium borohydride (0.75 g, 19.8 mmol) was added dropwise to a solution of the freshly prepared crude aldehyde (**263**) (15.0 mmol based on starting material) in methanol (30 ml) at room temperature. The reaction was stirred at this temperature for 1 h and then quenched by the dropwise addition of water (20 ml). Diethyl ether was added (20 ml) and the two phases separated, the aqueous phase was further extracted with diethyl ether (3 x 20 ml), the organic layers combined, washed with water (2 x 20 ml) and dried over $MgSO_4$. This gave the crude alcohol (**264**) which was purified by flash column chromatography (1: 1, petrol: diethyl ether) producing the alcohol (**264**) as a clear colourless oil (3.13 g, 14.1 mmol, 94% over two steps); ν_{max}/cm^{-1} (KBr plates / cm^{-1}) 3355.9 (br, O-H), 2954.7 (s, C-H), 2860.2 (m, C-H), 1465.8 (w), 1427.2 (m), 1249.8 (s), 1112.9 (s), 1039.6 (m), 1012.6 (m), 825.5 (s), 817.8 (s), 769.5 (s), 736.8 (s) and 702.0 (s); δ_H (300 MHz; $CDCl_3$), 0.30 (6H, s, H5), 0.96 (6H, s, H4), 1.44 (1H, br s, OH), 1.57 (2H, t *J* 7.9 Hz, H2), 3.65 (2H, t *J* 7.9 Hz, H1), 7.26-7.40 (3H, m, H7-9) and 7.53 (2H, m, H7-9); δ_C (75 MHz; $CDCl_3$), 0.06, 19.05, 23.35, 41.33, 59.40, 127.58, 128.93, 134.58 and 137.43; *m/z* (FAB +) 245 (M + Na, 16%), 209 (18), 199 (25) and 176 (100). Found (FAB +): [M + Na] 245.13455, $C_{13}H_{22}OSiNa$ requires 245.13375.

3-(Dimethylphenylsilanyl)-3-methylbutyraldehyde tosylhydrazone (266).

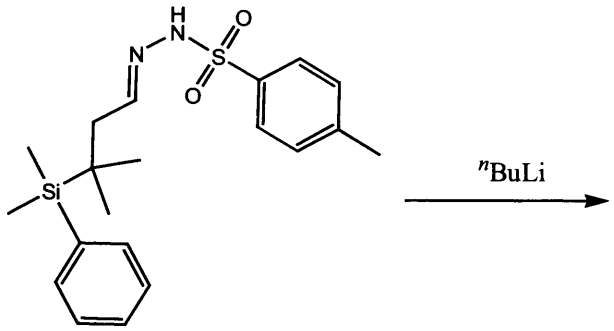


263 **266**

$C_{20}H_{28}N_2O_2SSi$
Mol. Wt.: 388.60

The aldehyde (**263**) (0.050 g, 0.23 mmol) and *p*-toluenesulfonyl hydrazine (0.047 g, 0.25 mmol) were put in absolute ethanol (2 ml) and the reaction mixture was heated to 40 °C until all solids had dissolved. The solution was stirred for 6 h at room temperature before the solvent was removed under reduced pressure and the residue purified by trituration with a cold methanol/water (80: 20) mixture (2 ml). The precipitate was filtered, washed with the cold methanol/water (80: 20) mixture (2 ml) and dried under reduced pressure to give the *hydrazone* (**266**) as a white powdery solid (0.083 g, 0.21 mmol, 93%); mp 111-112 °C (water / methanol); Anal calcd. for $C_{20}H_{28}N_2O_2SSi$ C, 61.82; H, 7.26; N, 7.21; S 8.25% Found C, 61.70; H, 7.35; N, 7.18; S, 8.30%; υ_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 3190.0 (br, N-H), 2902.0 (s, C-H), 2852.5 (s), 1596.9 (m), 1456.2 (s), 1377.1 (s), 1317.3 (m), 1292.2 (m), 1245.9 (w), 1190.0 (w), 1155.3 (m), 1093.6 (w), 1064.6 (w), 1028.0 (w), 972.1 (w), 912.3 (w), 835.1 (w), 815.8 (m), 736.8 (m) and 634.5 (w); δ_H (300 MHz; $CDCl_3$), 0.19 (6H, s, H10), 0.82 (6H, s, H9), 2.11 (2H, d *J* 6.2 Hz, H7), 2.41 (3H, s, H1), 6.92 (1H, t *J* 6.2 Hz, H6), 7.26-7.42 (8H, m, H3/4/12-14 including NH) and 7.82 (2H, d *J* 8.3 Hz, H3/4/12-14); δ_C (100 MHz; $CDCl_3$) –6.17, 20.73, 21.49, 23.44, 41.42, 127.52, 127.94, 129.04, 129.50, 134.48, 135.24, 136.64, 144.01 and 151.62; *m/z* (CI + methane), 389 (MH^+, 80%), 373 (M - CH_3, 37), 338 (33), 311 (M - C_6H_5, 100), 253 (48) and 233 (58); Found (CI + methane): [MH^+] 389.17242, $C_{20}H_{29}N_2O_2SSi$ requires 389.17189.

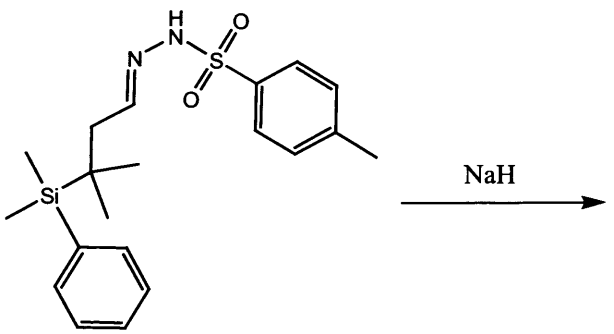
Attempted Elimination reaction of 3-(Dimethylphenylsilanyl)-3-methylbutyraldehyde tosylhydrazone (266).



266

A solution of ^{n}BuLi in hexanes (2.48M, 0.22 ml, 0.54 mmol) was added dropwise to a solution of the tosylhydrazone (**266**) (0.1 g, 0.27 mmol) in anhydrous tetrahydrofuran (7 ml) at –78°C. The reaction solution was stirred at this temperature for 0.5 h before being slowly allowed to warm to room temperature over a period of 2 h. Stirring was continued at room temperature for 1 h and then the reaction was quenched by the addition of water (5 ml). Diethyl ether (5 ml) was added to the vessel, the two phases separated and the aqueous phase further extracted with diethyl ether (3 x 5 ml). The organic phases were combined, washed with water (2 x 5 ml) and dried over $MgSO_4$. Removal of the volatiles *in vacuo* gave a crude product as a dark coloured oil which appeared, by NMR spectral analysis, to be a complex mixture of degradation products. All attempts to separate and purify this mixture were unsuccessful.

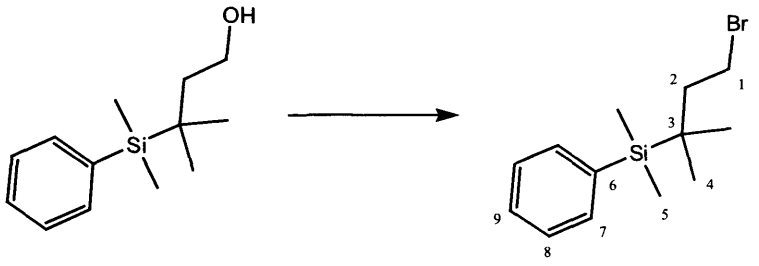
Attempted Elimination reaction of 3-(Dimethylphenylsilanyl)-3-methylbutyraldehyde tosylhydrazone (266).



266

A solution of the tosylhydrazone (**266**) (0.10 g, 0.26 mmol) in anhydrous 1, 4-dioxane (2 ml) was added dropwise to a slurry of sodium hydride (60% in mineral oil, 0.10 g, 2.6 mmol) in anhydrous 1, 4-dioxane (5 ml) at reflux. The suspension was stirred and heated to reflux for 4 h before being allowed to cool to room temperature and filtered (CAUTION solids contain excess sodium hydride). Diethyl ether (10 ml) and Water (10 ml) were added to the filtrate, the two layers were separated and the aqueous layer further extracted with diethyl ether (3 x 5 ml). The organic layers were combined, washed with water (2 x 5 ml) and dried over $MgSO_4$. The volatiles were removed *in vacuo* giving the crude product as a dark coloured oil which appeared, by NMR spectral analysis, to be a complex mixture of degradation products. All attempts to separate and purify this mixture were unsuccessful.

(3-Bromo-1,1-dimethylpropyl)-dimethylphenylsilane (267).



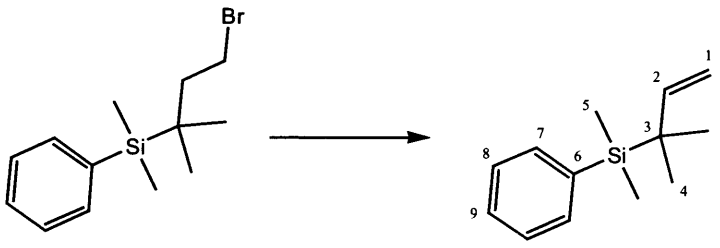
264 **267**

$C_{13}H_{21}BrSi$
Mol. Wt.: 285.30

A solution of the alcohol (**264**) (0.20 g, 0.90 mmol) and carbon tetrabromide (0.36 g, 1.08 mmol) was formed in anhydrous dichloromethane (10 ml) and the reaction mixture was cooled to 0 °C. Triphenyl phosphine (0.33 g, 1.26 mmol) dissolved in anhydrous dichloromethane (5 ml) was added dropwise to the reaction solution over 10 minutes and stirring continued for 1 h at 0 °C. The reaction was then allowed to warm to room temperature, the volatiles evaporated under reduced pressure and the crude residue flushed through a plug of silica gel with diethyl ether. The volatiles were removed under reduced pressure and the crude product purified by flash column chromatography (4: 1, petrol: diethyl ether), giving the *bromide* (**267**) as a clear colourless oil (0.25 g, 0.88 mmol, 98%). Anal calcd. for $C_{13}H_{21}BrSi$ C, 54.73; H, 7.42; Br, 28.01% Found C, 54.92; H, 7.67; Br, 27.93%; ν_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 3068.5 (m, C-H), 3020.3 (m, C-H), 2956.7 (s, C-H), 2860.2 (m), 1467.7 (m), 1427.2 (s), 1384.8 (w), 1363.6 (w),

1325.0 (w), 1249.8 (s), 1222.8 (m), 1110.9 (s), 831.3 (s), 815.8 (s), 771.5 (s), 736.8 (s) and 655.8 (s); δ_H (300 MHz; $CDCl_3$), 0.31 (6H, s, H5), 0.94 (6H, s, H4), 1.89 (2H, m, H2), 3.35 (2H, m, H1), 7.26-7.41 (3H, m, H7-9) and 7.51-7.56 (2H, m, H7-9); δ_C (75 MHz; $CDCl_3$), –5.93, 21.85, 22.45, 29.83, 42.36, 127.70, 129.13, 134.52 and 136.80.

(1,1-Dimethylallyl)-dimethylphenylsilane (259).



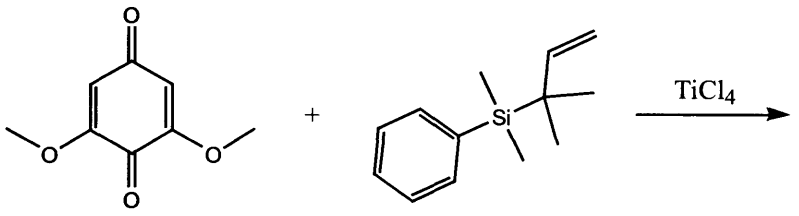
267 **259**

$C_{13}H_{20}Si$
Mol. Wt.: 204.38

Dichlorobis(triphenylphosphine)nickel(II), (prepared according to the method described by M.C.Henningsen *et al.*[157]), (1.60 g, 2.45 mmol) was slurried in anhydrous tetrahydrofuran (60 ml) containing triphenylphosphine (1.29 g, 4.90 mmol). This slurry was subjected to four cycles of evacuation followed by nitrogen ingress to ensure removal of dissolved oxygen from the solvent. A solution of ^{n}BuLi in hexanes (2.5M, 1.96 ml, 4.90 mmol) was then added dropwise to the reaction mixture and after this addition the mixture was rich brick red in colour. If this colour does not develop the reaction should be abandoned. A solution of the alkyl halide (**267**) (0.70 g, 2.45 mmol) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.75 g, 0.75 ml, 4.90 mmol) in anhydrous tetrahydrofuran (20 ml) was degassed as described above and then added dropwise to the reaction solution. The mixture was stirred overnight at room temperature and then stirred in the air for 5 minutes before removing the volatiles from the reaction under reduced pressure. The residue was triturated with petrol (20 ml) to remove the majority of triphenylphosphine and the triturate filtered through a pad of silica gel. The crude silyl alkene (**259**) was purified by flash column chromatography (4: 1, petrol: diethyl ether) producing the title compound (**259**) as a clear colourless oil (0.30 g, 1.47 mmol, 60%). ν_{max}/cm^{-1} (KBr plates/ cm^{-1}) 3068.5 (m, C-H), 2958.6 (s, C-H), 2860.2 (m, C-H), 1625.9 (m, C=C), 1465.8 (m), 1427.2 (s), 1247.9 (s), 1114.8 (s), 1028.0 (m), 1006.8 (m), 894.9 (s), 819.7 (s), 773.4 (s), 734.8 (s), 700.1 (s) and 655.8 (m); δ_H (400 MHz; $CDCl_3$), 0.27 (6H, s, H5), 0.98 (6H, s, H4), 4.71 (1H, dd *J* 17.3, 1.5

Hz, H1), 4.89 (1H, dd *J* 10.7, 1.5 Hz, H1), 5.82 (1H, dd *J* 17.3, 10.7 Hz, H2), 7.24-7.36 (3H, m, H7-9) and 7.48-7.51 (2H, m, H7-9); δ_C (75 MHz; $CDCl_3$), -5.92, 21.85, 22.47, 29.82, 42.38, 113.53, 127.71, 129.14 and 134.52; *m/z* (FAB +) 201 (70%), 185 (65) and 135 (65).

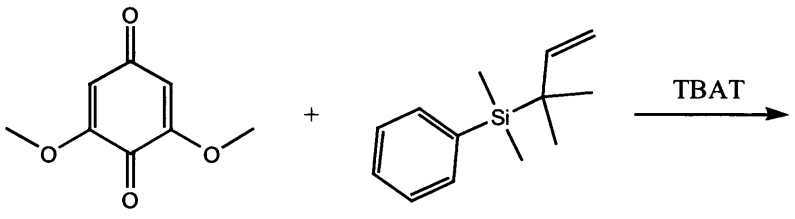
Attempted reaction of (1,1-dimethylallyl)-dimethylphenylsilane (259) with 2,6-dimethoxy-[1,4]benzoquinone (230).



230 **259**

A solution of titanium tetrachloride in dichloromethane (1M, 0.26 ml, 0.26 mmol) was added dropwise to a solution of 2,6-dimethoxy-[1,4]benzoquinone (**230**) (0.04 g, 0.22 mmol) in anhydrous dichloromethane (5 ml) at –78 °C (a red solution formed). This was followed directly by the dropwise addition of the allylic trialkylsilane (**259**) (0.05 g, 0.25 mmol) and the reaction was left stirring at –78 °C for a further 1 h before being allowed to warm to –20°C and being quenched by the addition of water (5 ml). The aqueous phase was separated from the organic and extracted with dichloromethane (3 x 5 ml). The organic extracts were then combined, washed with water (2 x 5 ml) and dried over $MgSO_4$. After removal of the volatiles under reduced pressure the crude product appeared as a pale yellow oily solid which, by NMR spectral analysis, consisted mainly of the starting materials (**230**) and (**259**). Traces of what appeared to be the desired addition product (**253**) were observed in the crude NMR spectra but all attempts to isolate the compound by flash column chromatography were unsuccessful.

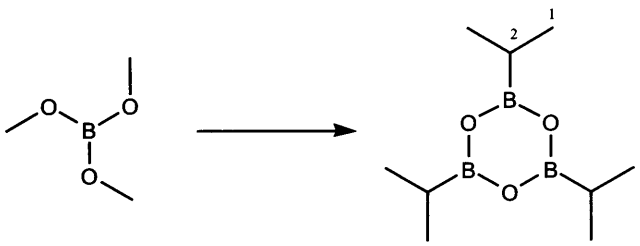
Attempted reaction of (1,1-dimethylallyl)-dimethylphenylsilane (259) with 2,6-dimethoxy-[1,4]benzoquinone (230).



230 **259**

Dry tetrabutylammonium triphenyldifluorosilicate (TBAT) (0.12 g, 0.22 mmol, dried by azeotropic removal of water by 3 x rotary evaporation of a toluene solution) was added to a stirred solution of 2,6-dimethoxy-[1,4]benzoquinone (**230**) (0.04 g, 0.22 mmol) and the allylic trialkylsilane (**259**) (0.05 g, 0.25 mmol) in anhydrous tetrahydrofuran (5 ml). The reaction mixture was heated to reflux for 12h and developed a very dark colouration. The solution was cooled and quenched with water (5 ml), dichloromethane (5 ml) was added and the two phases separated. The aqueous phase was further extracted with dichloromethane (3 x 5 ml), the organic phases combined, washed with water (2 x 5 ml) and dried over $MgSO_4$. The volatiles were removed under reduced pressure to give the crude product which, by NMR spectral analysis, consisted mainly of the starting materials (**230**) and (**259**) along with numerous degradation products. Traces of what appeared to be the desired addition product (**253**) were observed in the crude NMR spectra but all attempts to isolate this or any other product from the reaction by flash column chromatography were unsuccessful.

2,4,6-Triisopropyl cyclotriboroxane (273).[161]

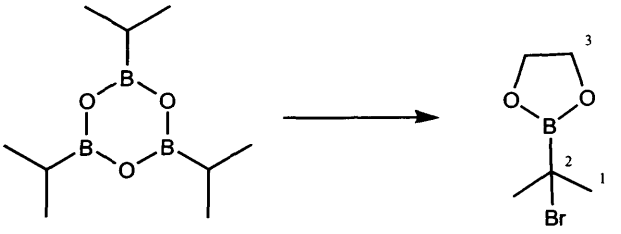


272 **273**

$C_9H_{21}B_3O_3$
Mol. Wt.: 209.69

Isopropyl magnesium chloride in anhydrous diethyl ether (2.0M, 21.1 ml, 42.2 mmol) and trimethyl borate (**272**) (4.60 g, 5.00 ml, 44.3 mmol) were added dropwise simultaneously over a period of 20 minutes to vigorously stirred anhydrous diethyl ether (40 ml) at –78 °C. The reaction solution was allowed to warm to room temperature over a period of 3 h and stirred at this temperature overnight. The reaction was then cooled to 0 °C and a HCl solution in water (2.0M, 21.1 ml, 42.2 mmol) added dropwise until the white precipitate that had formed dissolved. The organic layer was separated from the biphasic mixture and the aqueous layer extracted with diethyl ether (3 x 30 ml). The combined organic extract was washed with water (2 x 40 ml), dried over $MgSO_4$ and the volatiles removed by distillation at atmospheric pressure. Cyclohexane (25 ml) was added to the reaction and the solution heated to reflux under a Dean-Stark trap for 3 days. The cyclohexane was distilled from the reaction solution followed by the product (**273**) (60 °C, 5 torr) (lit.[161] 70 °C, 10 torr), distilling as a clear colourless oil (1.94 g, 9.26 mmol, 66%). (Analysis showed trace impurities caused by autooxidation of compound (**273**) in the air). ν_{max}/cm^{-1} (KBr plates/ cm^{-1}) 2974.0 (s, C-H), 2929.7 (m, C-H), 2875.7 (w), 1469.7 (s), 1379.0 (s), 1326.9 (s), 1261.4 (w), 1174.6 (m), 1122.5 (s), 952.8 (m), 837.0 (w), 727.1 (w) and 665.4 (m); δ_H (300 MHz; $CDCl_3$), 1.02 (18H, d *J* 6.7 Hz, H1) and 1.12-1.26 (3H, m, H2); δ_C (75 MHz; $CDCl_3$), 14.61 br and 17.54; *m/z* (FAB +) 199 (20%), 168 (40) and 153 (100).

2-(1-Bromo-1-methylethyl)-[1,3,2]dioxaborolane (274).[161]



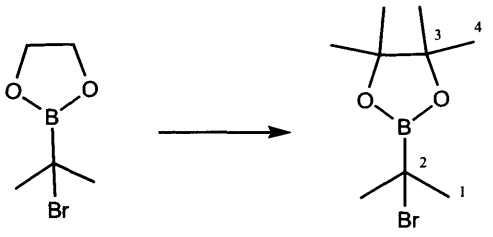
273 **274**

$C_5H_{10}BBrO_2$
Mol. Wt.: 192.85

The freshly prepared boroxine (**273**) (1.88 g, 8.97 mmol), which undergoes oxidation by air upon storage, was stirred rapidly under fluorescent lighting and an atmosphere of nitrogen. Bromine (3.93 g, 1.26 ml, 24.6 mmol) was added dropwise to the boroxine (**273**) until the colour of the bromine persisted in the reaction. The brominated boroxine began to crystallise from the reaction and this crude intermediate was dissolved in

dichloromethane (10 ml). Ethylene glycol (1.82 g, 1.64 ml, 29.4 mmol) was added to this solution and an aqueous layer formed. The aqueous layer was separated from the organic and further extracted with dichloromethane (3 x 20 ml). The organic extracts were combined, washed with water (2 x 20 ml) and dried over $MgSO_4$. Distillation under reduced pressure (55 °C, 2 torr) (lit.[161] 42 °C 1 torr) gave the title compound (**274**) as a clear colourless oil (1.40 g, 7.29 mmol, 27%). δ_H (300 MHz; $CDCl_3$), 1.76 (6H, s, H1) and 4.27 (4H, s, H3); δ_C (75 MHz; $CDCl_3$), 30.42 and 66.31; *m/z* (CI + isobutane) 155 (52%), 115 (20), 114 (35), 113 (100), 112 (M – Br, 85) and 105 (97).

2-(1-Bromo-1-methylethyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (276).[161]

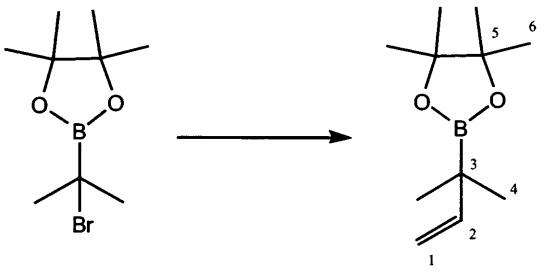


274 **276**

$C_9H_{18}BBrO_2$
Mol. Wt.: 248.95

A solution of the boronic ester (**274**) (0.40 g, 2.08 mmol) and pinacol (0.25 g, 2.08 mmol) in anhydrous diethyl ether (10 ml) was stirred for 16 h. The two phases that formed were separated and the ethereal phase washed with a saturated NH_4Cl solution (20 ml). The aqueous phases were combined and further extracted with diethyl ether (3 x 20 ml). The ethereal phases were then combined, washed with water (2 x 20 ml) and dried over $MgSO_4$. Removal of the volatiles under reduced pressure gave the title compound (**276**) as a clear colourless viscous oil (0.50 g, 2.04 mmol, 98%). ν_{max}/cm^{-1} (KBr plates/ cm^{-1}) 2983.7 (m, C-H), 2958.6 (m, C-H), 2912.3 (m, C-H), 2866.0 (w), 1481.2 (m), 1461.9 (s), 1404.1 (s), 1386.7 (s), 1375.2 (s), 1344.3 (m), 1253.6 (w), 1234.4 (s), 1163.0 (s), 1089.7 (s), 1010.6 (s), 947.0 (m), 902.6 (m), 804.3 (w) and 661.5 (w); δ_H (300 MHz; $CDCl_3$), 1.27 (12H, s, H4) and 1.76 (6H, s, H1); δ_C (75 MHz; $CDCl_3$), 24.39, 30.26 and 84.22.

2-(1,1-Dimethylallyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (277).[194]

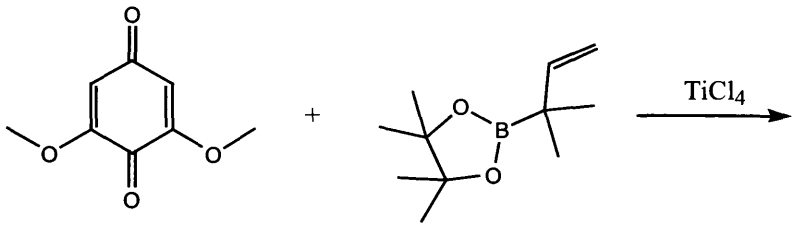


276 **277**

$C_{11}H_{21}BO_2$
Mol. Wt.: 196.09

A solution of vinyl magnesium bromide in tetrahydrofuran (1M, 2.05 ml, 2.05 mmol) was added dropwise to a solution of the bromide (**276**) (0.50 g, 2.01 mmol) in anhydrous diethyl ether (10 ml) at –78 °C. The reaction was left at this temperature for 0.5 h before being allowed to slowly warm to room temperature overnight. The volatiles were removed *in vacuo*, the residue redissolved in petrol (10 ml) and water added (10 ml). The two phases were separated and the aqueous phase further extracted with petrol (2 x 10 ml). The organic phases were combined, washed with a saturated NaCl solution (2 x 10 ml) and dried over $MgSO_4$. Removal of the volatiles under reduced pressure gave the crude product which was purified by flash column chromatography (95: 5, petrol: ethyl acetate). This produced the boronic ester (**277**) as a clear colourless oil (0.20 g, 1.02 mmol, 50%); ν_{max}/cm^{-1} (KBr plates/ cm^{-1}) 2977.9 (s, C-H), 2958.6 (s, C-H), 2869.9 (m, C-H), 1633.5 (w, C=C), 1471.6 (s), 1388.7 (s), 1371.3 (s), 1315.4 (s), 1274.9 (m), 1217.0 (m), 1145.6 (s), 1091.6 (w), 1024.1 (w), 968.2 (m), 900.7 (w), 858.3 (m), 686.6 (m) and 671.2 (m); δ_H (300 MHz; $CDCl_3$), 1.05 (6H, s, H4), 1.21 (12H, s, H6), 4.90 (1H, dd *J* 17.9, 1.6 Hz, H1), 4.90 (1H, dd *J* 10.2, 1.6 Hz, H1) and 5.94 (1H, dd *J* 17.9, 10.2 Hz, H2); δ_C (75 MHz; $CDCl_3$), 23.45, 24.54, 83.15, 109.97 and 146.59.

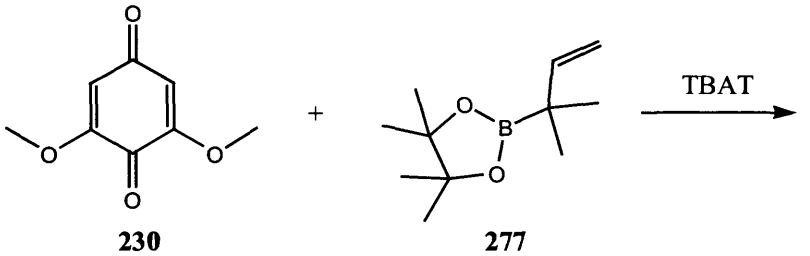
Attempted reaction of 2-(1,1-dimethylallyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (277) with 2,6-dimethoxy-[1,4]benzoquinone (230).



230 **277**

A solution of titanium tetrachloride in dichloromethane (1M, 0.25 ml, 0.25 mmol) was added dropwise to a solution of 2,6-dimethoxy-[1,4]benzoquinone (**230**) (0.049 g, 0.29 mmol) in anhydrous dichloromethane (5 ml) at –78 °C (a red solution formed). This was followed directly by the dropwise addition of the allylic boronic ester (**277**) (0.05 g, 0.25 mmol) and the reaction was left stirring at –78 °C for a further 1 h before being allowed to warm to –20°C and being quenched by the addition of water (5 ml). The aqueous phase was separated from the organic and extracted with dichloromethane (3 x 5 ml). The organic extracts were then combined, washed with water (2 x 5 ml) and dried over $MgSO_4$. Removal of the volatiles under reduced pressure led only to the recovery of starting material (**230**) from the reaction.

Attempted reaction of 2-(1,1-dimethylallyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (277) with 2,6-dimethoxy-[1,4]benzoquinone (230).

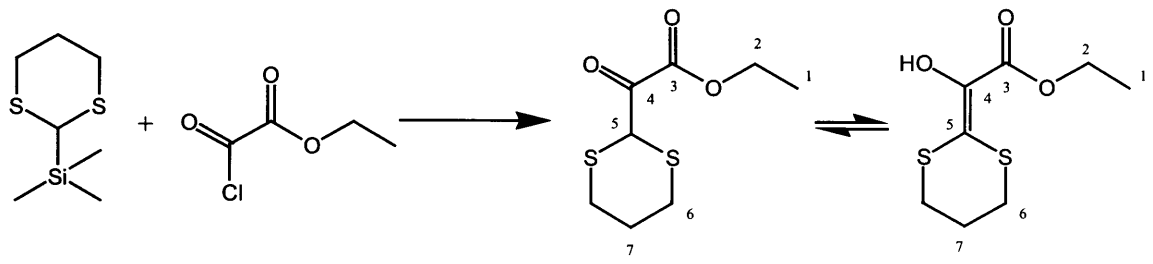


230 **277**

Dry tetrabutylammonium triphenyldifluorosilicate (TBAT) (0.05 g, 0.10 mmol, dried by azeotropic removal of water by 3 x rotary evaporation of a toluene solution) was added to a stirred solution of 2,6-dimethoxy-[1,4]benzoquinone (**230**) (0.017 g, 0.10 mmol) and the allylic boronic ester (**277**) (0.020 g, 0.10 mmol) in anhydrous tetrahydrofuran (2 ml). The reaction mixture was heated to reflux for 12 h and developed a very dark colouration. The solution was cooled and quenched with water (5 ml), dichloromethane

(5 ml) was added and the two phases separated. The aqueous phase was further extracted with dichloromethane (3 x 5 ml), the organic phases combined, washed with water (2 x 5 ml) and dried over $MgSO_4$. Removal of the volatiles under reduced pressure led only to the recovery of starting material (**230**) from the reaction.

[1,3]Dithian-2-yloxoacetic acid ethyl ester (293).



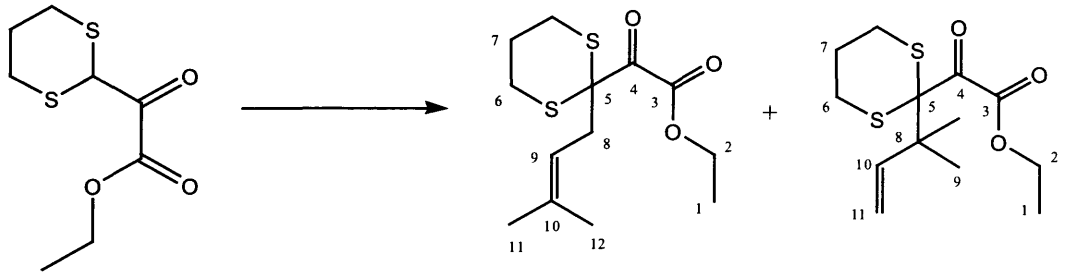
289 **293** **293a**

$C_8H_{12}O_3S_2$
Mol. Wt.: 220.31

Trimethylsilyl [1,3]-dithiane (6.00 g, 6.00 ml, 31.2 mmol) was dissolved in anhydrous tetrahydrofuran (70 ml) and the solution cooled to –40 °C before a solution of ^{n}BuLi in hexanes (1.36M, 24 ml, 32.7 mmol) was added dropwise to the reaction. The solution was slowly allowed to warm to –20 °C and kept at this temperature for a further 1.5 h. The reaction was then recooled to –78 °C and transferred by cannular dropwise into a solution of ethyl oxalyl chloride (**289**) (6.81 g, 5.59 ml, 49.9 mmol) (distilled immediately prior to use) in anhydrous tetrahydrofuran (5 ml) also at –78 °C. The reaction was kept at –78 °C for a further 1 h before being allowed to warm to room temperature overnight. The reaction was quenched by the addition of water (50 ml) and the organic layer diluted with diethyl ether (50 ml). The aqueous phase was separated from the organic and further extracted with diethyl ether (3 x 50 ml). The organic phases were combined, washed with a saturated NaCl solution (2 x 50 ml) and dried over $MgSO_4$. Removal of the volatiles under reduced pressure gave the crude silyl protected product which was redissolved in ethanol (40 ml). Potassium fluoride (1.93 g, 33.3 mmol) was added to this solution followed by dropwise addition of acetic acid (2.00 g, 2.10 ml, 33.3 mmol) and the solution stirred for 2 h at room temperature. The solution was diluted with water (50 ml) and this aqueous solution extracted with diethyl ether (3 x 40 ml). The ethereal phases were combined, washed with a saturated NaCl solution (2 x 50 ml) and dried over $MgSO_4$. This gave the crude product which was purified by flash column chromatography (1: 1, petrol: diethyl ether). The α-

ketodithiane (**293**) was produced as a clear colourless oil (3.40 g, 15.5 mmol, 50%). υ_{max}/cm^{-1} (KBr plates / cm^{-1}) 2960.5 (m, C-H), 2935.5 (m, C-H), 2906.5 (m), 2871.8 (w), 1724.2 (s, EtOC=O), 1691.5 (m, C=O), 1527.5 (w), 1465.8 (w), 1425.3 (w), 1388.7 (w), 1367.4 (w), 1282.6 (s), 1224.7 (s), 1186.1 (s), 1155.3 (m), 1055.0 (s), 1008.7 (m), 914.2 (w), 856.3 (w), 817.8 (w) and 717.5 (w); δ_H (300 MHz; $CDCl_3$), 1.35 (3.83H, t *J* 7.2 Hz, H1 **293** + **293a**), 1.90-193 (0.28H, m, H7 **293a**), 1.94-2.02 (1H, m, H7 **293**), 2.06-2.16 (1.56H, m, H7 293 and **293a** including OH of **293a**), 2.51 (2H, dddd *J* 14.5, 4.5, 3.1, 0.7 Hz, H6 eq. **293**), 2.85 – 3.03 (1.11H, m, H6 **293a**), 3.11 (2H, ddd *J* 14.5, 12.5, 2.2 Hz, H6 ax. **293**), 4.33 (2.56H, q *J* 7.2 Hz, H2 **293** and **293a**) and 4.94 (1H, s, H5 **293**); δ_C (75 MHz; $CDCl_3$) 13.96, 24.54, 24.77, 40.84, 63.03, 161.10 and 180.97; *m/z* (EI) 221 ($M^{\cdot+}$+ H, 20%), 220 ($M^{\cdot+}$, 10), 219 ($M^{\cdot+}$- H, 12), 203 (18), 191 ($M^{\cdot+}$- C_2H_5, 18) and 119 ($M^{\cdot+}$- $C_4H_5O_3$, 90); Found (EI) [$M^{\cdot+}$] 220.02185, $C_8H_{12}O_3S_2$ requires 220.02278.

[2-(3-Methylbut-2-enyl)-[1,3]dithian-2-yl]-oxoacetic acid ethyl ester (294) and [2-(1,1-Dimethylallyl)-[1,3]dithian-2-yl]-oxoacetic acid ethyl ester (295).



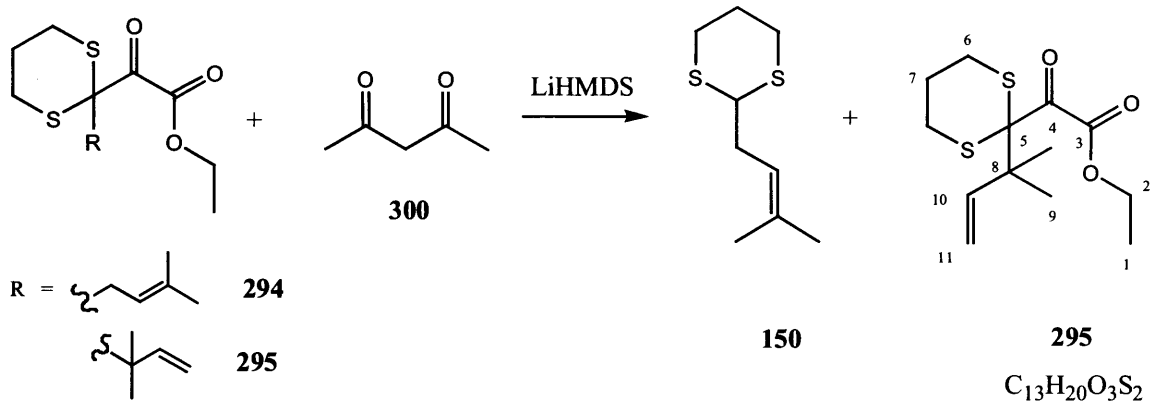
293 **294** **295**

$C_{13}H_{20}O_3S_2$
Mol. Wt.: 288.43

Sodium hydride, 60% in mineral oil (0.42 g, 10.4 mmol) was washed with anhydrous diethyl ether (2 x 20 ml) to remove the mineral oil and then dissolved in anhydrous DMF (25 ml). The α - ketodithiane (**293**) (1.91 g, 8.66 mmol) was added dropwise to this solution and stirring continued at room temperature for 1 h before the solution was cooled to 0 °C. The 1-bromo-3-methyl-2-butene (1.29 g, 1.00 ml, 8.66 mmol) was added dropwise at this temperature, the reaction was allowed to warm to room temperature, heated to reflux for 3 h and then cooled and stirred at room temperature for 12 h. The reaction was quenched by the addition of a saturated NaCl solution (20 ml), diethyl ether added (20 ml) and the organic layer separated from the aqueous. The

aqueous layer was further extracted with diethyl ether (3 x 30 ml), washing the combined organic extracts with water (2 x 20 ml) and drying over $MgSO_4$. The volatiles were then removed under reduced pressure to give the crude product which was purified by flash column chromatography (1: 1, petrol: diethyl ether). This gave a mixture of two structural isomers [*2-(3-Methylbut-2-enyl)-[1,3]dithian-2-yl]-oxoacetic acid ethyl ester* (**294**) and *[2-(1,1-Dimethylallyl)-[1,3]dithian-2-yl]-oxoacetic acid ethyl ester* (**295**) in a ratio of 3:1 (by NMR spectroscopy) as a clear colourless oil (1.2 g, 4.17 mmol, 48%). The two compounds (**294**, **295**) could not be separated by flash column chromatography. ν_{max}/cm^{-1} (KBr plates / cm^{-1}) 2979.8 (m, C-H), 2912.3 (m, C-H), 1735.8 (s, C=O), 1716.5 (s, C=O), 1425.3 (m), 1384.8 (w), 1367.4 (w), 1269.1 (s), 1197.7 (w), 1076.2 (s), 1026.1 (m), 950.8 (w), 908.4 (w), 813.9 (w) and 659.6 (w); δ_H (300 MHz; $CDCl_3$), 1.26 (2H, s, H9 **295**), 1.29 (4H, t *J* 7.0 Hz, H1 **294** and **295**), 1.58 (3H, s, H11/12 **294**), 1.63 (3H, s, H11/12 **294**), 1.63 – 1.74 (1.33H, m, H7 **294** and **295**), 1.90-2.05 (1.33H, m, H7 **294** and **295**), 2.60 (2.66H, m, H6 **294** and **295**), 2.77-2.87 (4.66H, m, H6,8 **294** and H6 **295**), 4.26 (2.66H, q *J* 7.0 Hz, H2 **294** and **295**), 4.98-5.05 (1.66H, m, H9 **294** and H11 **295**) and 6.12 (0.33H, dd *J* 17.3, 10.9 Hz, H10 **295**); δ_C (75 MHz; $CDCl_3$) (both structural isomers), 13.83, 13.94, 18.29, 23.58, 23.66, 23.92, 25.88, 27.54, 27.86, 36.98, 45.50, 60.53, 62.12, 68.98, 113.92, 115.78, 137.27, 142.21, 163.96, 165.81, 188.98 and 195.86; *m/z* (EI) 291 (47%), 290 (65), 289 ($M^{\cdot+}$+H, 87), 288 ($M^{\cdot+}$, 20), 287 (30), 277 (70), 276 (63), 221 (45), 220 (60), 219 ($M^{\cdot+}$-C_5H_9, 68), 189 (76), 188 (89), 187 ($M^{\cdot+}$- $C_4H_5O_3$, 100), 186 (75) and 119 (70). Found (EI): [$M^{\cdot+}$] 288.08542, $C_{13}H_{20}O_3S_2$ requires 288.08538.

Attempted reactions of [2-(3-Methylbut-2-enyl)-[1,3]dithian-2-yl]-oxoacetic acid ethyl ester (294) and [2-(1,1-Dimethylallyl)-[1,3]dithian-2-yl]-oxoacetic acid ethyl ester (295) with 2,4-pentanedione (300).

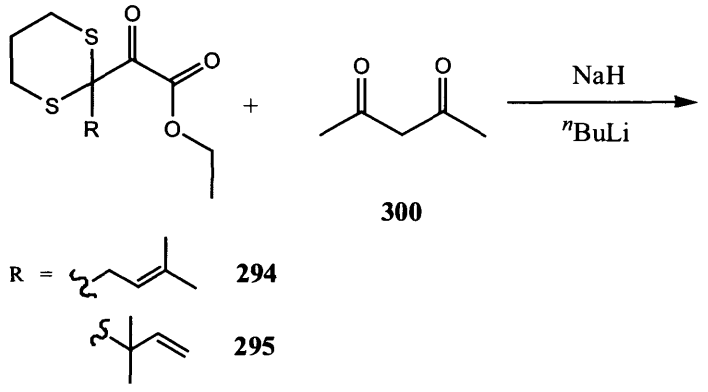


$C_{13}H_{20}O_3S_2$
Mol. Wt.: 288.43

A solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (0.75M, 0.79 ml, 0.59 mmol) was diluted further with anhydrous tetrahydrofuran (7 ml) and then cooled to 0 °C. Freshly distilled 2,4-pentanedione (**300**) (0.030 g, 0.031 ml, 0.30 mmol) was added dropwise to this solution and the reaction left stirring for 20 minutes at this temperature. The reaction was then cooled to –78 °C and a solution of the mixture of masked tricarbonyl compounds (**294**) and (**295**) (0.085 g, 0.30 mmol) in anhydrous tetrahydrofuran (2 ml) added dropwise. Stirring was continued at –78 °C for 1 h before the reaction was allowed to warm to room temperature over 1.5 h and then stirred at this temperature overnight. Water (10 ml) and diethyl ether (10 ml) were added to the reaction vessel, the two phases separated and the aqueous phase further extracted with diethyl ether (2 x 10 ml). The organic extracts were combined, washed with a saturated NaCl solution (2 x 10 ml) and dried over $MgSO_4$. The crude product mixture was separated and purified by flash column chromatography (1: 1, petrol: diethyl ether). This produced the *dithiane* (**150**) (0.015 g, 0.08 mmol, 27%) and the unreacted *masked tricarbonyl* (**295**) (0.021 g, 0.07 mmol, 24%) both as clear colourless oils. *2-(3-Methylbut-2-enyl)-[1,3]dithiane* (**150**) gave identical spectral data to that reported previously. *[2-(1,1-Dimethylallyl)-[1,3]dithian-2-yl]-oxoacetic acid ethyl ester* (**295**); ν_{max}/cm^{-1} (KBr plates / cm^{-1}) 2979.8 (m, C-H), 2931.6 (m, C-H), 1732.0 (s, C=O), 1705.0 (m, C=O), 1461.9 (w), 1384.8 (w), 1367.4 (w), 1263.3 (m), 1151.4 (m), 1066.6 (s), 1043.4 (m), 1010.6 (w) and 920.0 (w); δ_H (300 MHz; $CDCl_3$), 1.32-1.36 (9H, m, H1,9), 1.71-187 (1H, m, H7), 1.95-2.06 (1H, m, H7), 2.69 (2H, dt *J* 14.6, 4.0 Hz, H6

eq.), 2.93 (2H, td *J* 14.6, 2.9 Hz, H6 ax.), 4.33 (2H, q *J* 7.2 Hz, H2), 5.09 (1H, d *J* 17.3 Hz, H11), 5.12 (1H, d *J* 11.0 Hz, H11) and 6.21 (1H, dd *J* 17.3, 11.0 Hz, H10); δ_C (75 MHz; $CDCl_3$), 13.87, 23.63, 23.73, 27.94, 45.59, 62.19, 69.07, 114.01, 142.29, 165.89 and 195.96; *m/z* (CI + methane) 289 (M + H, 20%), 221 (55), 187 (67), 183 (47) and 111 (100). Found (CI + methane): [M^+] 289.09385, $C_{13}H_{21}O_3S_2$ requires 289.09321.

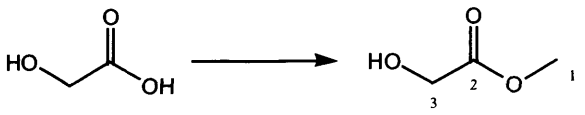
Attempted reaction of [2-(3-Methylbut-2-enyl)-[1,3]dithian-2-yl]-oxoacetic acid ethyl ester (294) and [2-(1,1-Dimethylallyl)-[1,3]dithian-2-yl]-oxoacetic acid ethyl ester (295) with 2,4-pentanedione (300).



Freshly distilled 2,4-pentanedione (**300**) (0.017 g, 0.018 ml, 0.17 mmol) was added dropwise to a slurry of sodium hydride (60% in mineral oil, 0.007 g, 0.17 mmol) in anhydrous tetrahydrofuran (5 ml) at 0 °C and the reaction was stirred at this temperature for 0.5 h. A solution of ^{n}BuLi in hexanes (1.8M, 0.11 ml, 0.19 mmol) was then added dropwise and stirring continued at 0 °C for a further 0.5 h. A mixture of α-ketodithiane compounds (**294**) and (**295**) (0.05 g, 0.17 mmol) was added dropwise and the reaction slowly allowed to warm to room temperature and stirred at this temperature for 12 h. Water (5 ml) was added to quench the reaction and then ethyl acetate (5 ml) and the two phases that formed were separated. The aqueous phase was further extracted with ethyl acetate (3 x 5 ml), the organic phases combined, washed with water (2 x 5 ml) and dried over $MgSO_4$. The solvents were removed *in vacuo* to give the crude product as a pale yellow oil. Attempts to purify this crude product by flash chromatography led to the isolation of a mixture of the inseparable unsaturated dithianes (**150**) and (**157**) (0.006 g, 0.034 mmol, 20%) in a ratio of 3: 1 (by NMR spectroscopy) as the only identifiable products of the reaction. Quenching this reaction with water (5 ml) after only 1 h at room temperature produced a crude product which appeared, by NMR spectroscopy, to

contain some of the coupled product (**301**) but all attempts to isolate this compound failed and led only to degradation of this product (**301**).

Hydroxy-acetic acid methyl ester (319).[168]

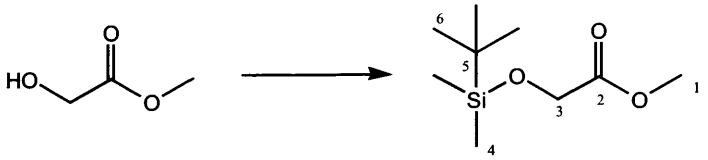


318 **319**

$C_3H_6O_3$
Mol. Wt.: 90.08

Boric acid (0.81 g, 13.2 mmol) was added to a solution of glycolic acid (**318**) (10.0 g, 132 mmol) in methanol (150 ml) and the reaction stirred for 18 h at room temperature. The reaction mixture was concentrated *in vacuo* with mild heating (40-60 °C) (the catalyst was removed as trimethyl borate). The methyl ester (**319**) was obtained from this process as a clear colourless oil (9.11 g, 101 mmol, 77%) and was of sufficient purity for further synthetic manipulation; ν_{max}/cm^{-1} (KBr plates/ cm^{-1}) 3445.0 (br, O-H), 2935.5 (s, C-H), 2581.5 (m), 1748.0 (m, C=O), 1652.9 (m), 1614.3 (m), 1201.6 (s), 1090.7 (s), 990.4 (m) and 883.3 (m); δ_H (300 MHz; $CDCl_3$), 3.75 (3H, s, H1) and 4.16 (2H, s, H3); δ_C (75 MHz; $CDCl_3$), 52.32, 60.44 and 173.88; *m/z* (EI) 132 (25%), 117 (50), 100 (19), 74 (100) and 73 (M^+- OH, 40).

(tert-Butyldimethylsilanyloxy)-acetic acid methyl ester (320).[195, 196]



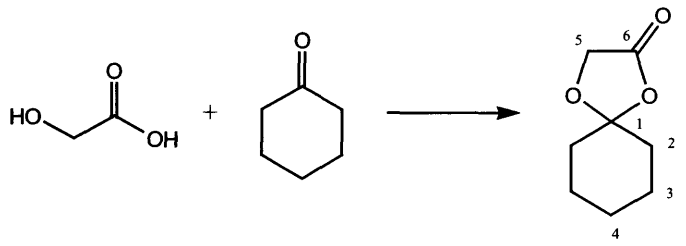
319 **320**

$C_9H_{20}O_3Si$
Mol. Wt.: 204.34

Imidazole (2.73 g, 40.0 mmol) was added to a solution of the alcohol (**319**) (3.00 g, 33.3 mmol) in anhydrous DMF (20 ml) at 0 °C and then *tert*-butyldimethylsilyl chloride (6.03 g, 40.0 mmol) added immediately afterwards. The reaction was allowed to warm to room temperature and then stirred at this temperature for a further 1 h. The reaction was quenched with water (30 ml), extracted with diethyl ether (3 x 40ml) and the

combined organic extracts washed with a saturated NaCl solution (2 x 40 ml). The organic phase was dried over $MgSO_4$ and the volatiles removed under reduced pressure to give crude product which was purified by flash column chromatography (4: 1, petrol: diethyl ether). This gave compound (**320**) as a clear colourless oil (6.71 g, 32.9 mmol, 99%); ν_{max}/cm^{-1} (KBr plates/ cm^{-1}) 2952.8 (s, C-H), 2858.3 (s, C-H), 1766.7 (s, C=O), 1741.6 (s), 1473.5 (s), 1463.9 (m), 1434.9 (m), 1361.7 (m), 1255.6 (s), 1213.1 (m), 1188.1 (m), 1147.6 (s), 1006.8 (w), 991.3 (w), 839.0 (s), 781.1 (s), 696.3 (w) and 663.5 (w); δ_H (300 MHz; $CDCl_3$), 0.07 (6H, s, H4), 0.90 (9H, s, H6), 3.72 (3H, s, H1) and 4.23 (2H, s, H3); δ_C (75 MHz; $CDCl_3$), -5.56, 18.32, 25.66, 51.58, 61.58 and 172.02; *m/z* (FAB +) 247 (53%), 191 (35), 189 (M- CH_3, 50), 175 (55), 133 (84) and 89 (100).

1,4-Dioxa-spiro[4.5]decan-2-one (322).[171]



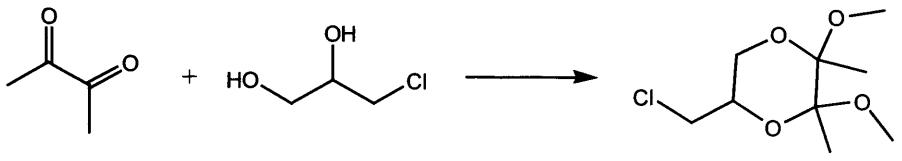
318 **321** **322**

$C_8H_{12}O_3$
Mol. Wt.: 156.18

A solution of cyclohexanone (**321**) (8.05 g, 8.50 ml, 82.1 mmol) and toluene-*p*-sulfonic acid hydrate (0.02 g, 0.105 mmol) in toluene (40 ml) was heated to reflux under a Dean-Stark trap. A solution of glycolic acid (**318**) (5.00 g, 65.7 mmol) in water (3 ml) was added dropwise to the reaction vessel over a period of 30 minutes. The mixture was kept at reflux for a further 5 h and water removed periodically from the Dean and Stark apparatus. The reaction was then cooled, treated with anhydrous sodium acetate (0.05 g, 0.646 mmol) and stirred for 1 h. Filtration and evaporation of the volatiles from the filtrate under reduced pressure gave the crude product which was purified by distillation (b.p. 70 °C 2 mmHg) (lit.[171] b.p. 70 °C 0.5 mmHg) to give compound (**322**) as a clear colourless liquid which solidified upon storage to colourless needles (6.14 g, 39.4 mmol, 60%); mp 30-31 °C (petrol) (lit.[171] mp 30-31 °C (toluene)); ν_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 2939.3 (s, C-H), 2864.1 (s, C-H), 1799.5 (s, C=O), 1709.8 (m), 1674.1 (w), 1450.4 (s), 1371.3 (s), 1338.5 (m), 1268.1 (s), 1221.8 (s), 1159.1 (s), 1104.2

(s), 1079.1 (m), 1046.3 (m), 1032.8 (m), 965.3 (m), 928.7 (s), 902.6 (m), 846.7 (m), 831.3 (m), 683.7 (w) and 500.5 (w); δ_H (300 MHz; $CDCl_3$), 1.38 – 2.07 (10H, m, H2-4) and 4.30 (2H, s, H5); δ_C (75 MHz; $CDCl_3$) 22.94, 24.36, 35.27, 63.20, 113.39 and 171.44; *m/z* (EI) 156 (M^{+}, 29%), 113 (69), 112 (10), 98 (100), 85 (13) and 80 (17).

5-Chloromethyl-2,3-dimethoxy-2,3-dimethyl-[1,4]dioxane (325).[176]

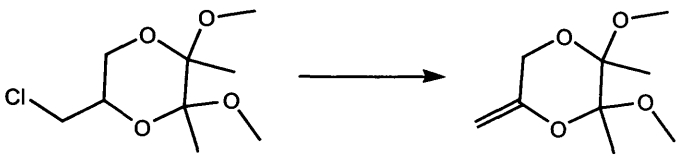


323 **324** **325**

$C_9H_{17}ClO_4$
Mol. Wt.: 224.68

2, 3-Butanedione (**323**) (13.7 ml, 13.4 g, 156 mmol), trimethylorthoformate (31.4 g, 32.5 ml, 296 mmol) and (±)-camphor sulfonic acid (3.25 g, 14.0 mmol) were added sequentially to a solution of (±)-3-chloro-1,2-propanediol (**324**) (15.6 g, 11.8 ml, 141 mmol) in anhydrous methanol (80 ml) and the mixture heated to reflux for 90 minutes. The reaction was cooled to room temperature, quenched with triethylamine (1.56 g, 2.15 ml, 15.4 mmol) and poured onto a saturated solution of $NaHCO_3$ (150 ml). Diethyl ether (150 ml) was added and the two phases separated. The aqueous phase was further extracted with diethyl ether (2 x 150 ml), the combined organic extracts washed with a saturated NaCl solution (2 x 150 ml) and dried over $MgSO_4$. The volatiles were removed under reduced pressure to give crude (**325**) as pale yellow oil. The NMR data of this crude product (**325**) was in accord with that obtained by S.V. Ley *et al.*[176] and it was used in subsequent reactions without any further purification. (Full characterisation given by S.V. Ley *et al.*[176]).

2,3-Dimethoxy-2,3-dimethyl-5-methylene-[1,4]dioxane (326).[176]

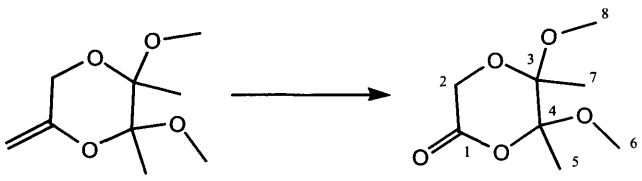


325

326
$C_9H_{16}O_4$
Mol. Wt.: 188.22

Fresh potassium *tert*-butoxide (31.6 g, 282 mmol) was added to a solution of the crude chloride (**325**) (assume 141 mmol) in anhydrous tetrahydrofuran (280 ml) and the reaction mixture heated to reflux for 80 minutes. The reaction was cooled, poured onto water (200 ml) and diethyl ether added (200 ml). The two phases were separated and the aqueous phase further extracted with diethyl ether (2 x 200 ml). The organic extracts were combined, washed with a saturated NaCl solution (2 x 200 ml) and dried over $MgSO_4$. This gave the crude alkene (**326**) as a pale yellow oil. The NMR data of this crude product was in accord with that obtained by S.V. Ley *et al.*[176] and it was used in subsequent reactions without any further purification. (Full characterisation given by S.V. Ley *et al.*[176]).

5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (327).[176]



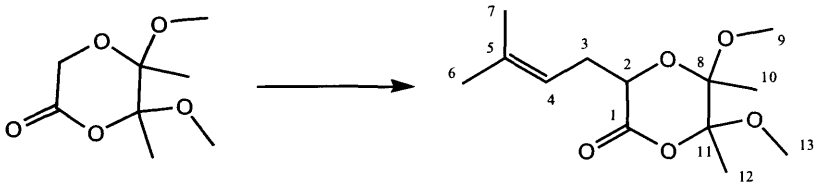
326

327
$C_8H_{14}O_5$
Mol. Wt.: 190.19

A solution of the crude enol ether (**326**) (assumed to be 141 mmol) in acetone (30 ml) and dichloromethane (120 ml) was formed in a two necked flask fitted with a bubbler submerged under the surface of the solution. The solution was degassed by passing a stream of oxygen through it for 5 minutes at –78 °C. Ozone was then passed through the solution at –78 °C until the solution was saturated with ozone, (4h, permanent blue colour). Oxygen was passed through the solution until the blue colour disappeared and the reaction solution was treated with dimethylsulfide (10.5 g, 12.4 ml, 168.2 mmol) and pyridine (5.00 g, 5.10 ml, 63.2 mmol). The reaction was allowed to warm to room

temperature over 3 h and then concentrated under reduced pressure to give the crude lactone (**327**) as a yellow oil. The crude product was purified by flash column chromatography (80: 20: 1, petrol: diethyl ether: triethylamine) to give compound (**327**) as a white crystalline solid (13.2 g, 69.5 mmol, 50% over three steps); mp 64-65 °C (diethyl ether / petrol) (lit.[176] mp 64-65 °C (diethyl ether)); ν_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 2922.0 (s, C-H), 2852.5 (s, C-H), 1737.7 (m, C=O), 1463.9 (m), 1377.1 (m), 1321.1 (w), 1274.9 (m), 1120.6 (m), 1072.3 (m), 1028.0 (m), 964.3 (m), 904.6 (w), 889.1 (w) and 858.3 (w); δ_H (300 MHz; $CDCl_3$), 1.38 (3H, s, H5/7), 1.49 (3H, s, H5/7), 3.30 (3H, s, H6/8), 3.43 (3H, s, H6/8), 4.13 (1H, d *J* 17.7 Hz, H2) and 4.29 (1H, d *J* 17.7 Hz, H2); δ_C (75 MHz; $CDCl_3$) 16.95, 17.83, 49.11, 50.35, 60.36, 97.78, 105.06 and 167.55; *m/z* (CI + methane) 159 (M – OMe, 58%), 116 (13), 115 (100), 101 (34), 97 (11) and 85 (10).

5,6-Dimethoxy-5,6-dimethyl-3-(3-methylbut-2-enyl)-[1,4]dioxan-2-one (328).



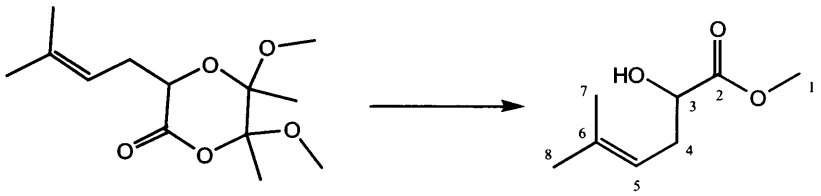
327 **328**

$C_{13}H_{22}O_5$
Mol. Wt.: 258.31

A solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (0.75M, 33.3 ml, 25.0 mmol) was added dropwise to a solution of the lactone (**327**) (5.00 g, 26.3 mmol) in tetrahydrofuran (50 ml) at –78 °C and the reaction was stirred at this temperature for 15 minutes. 1-Bromo-3-methyl-but-2-ene (3.00 g, 3.35 ml, 29 mmol) was then added dropwise to the reaction and the solution stirred at –78 °C for 1 h before being warmed to –50 °C (in a MeCN dry ice bath) and then slowly warmed to room temperature over 2 h. The reaction was quenched by the addition of acetic acid (1.90 g, 1.80 ml, 31.56 mmol) and diluted with diethyl ether (50 ml). The precipitated salts were filtered off through a plug of silica, volatiles evaporated under reduced pressure and the crude product purified by flash column chromatography (2: 1, petrol: diethyl ether) yielding the *substituted lactone* (**328**) as a clear colourless oil which solidifies to a white powder

upon storage in a fridge (5.4 g, 21.0 mmol, 84%). mp 48-49 °C (diethyl ether / petrol); Anal calcd. for $C_{13}H_{22}O_5$ C, 60.45; H, 8.58% Found C, 60.05; H, 8.69%; ν_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 2922.9 (s, C-H), 2853.5 (s, C-H), 1737.7 (s, C=O), 1461.9 (s, C-H), 1379.0 (m), 1148.5 (m), 1131.2 (m), 1108.0 (m), 1037.6 (s), 969.2 (w), 947.9 (w), 886.2 (w), 861.2 (w), 782.1 (w) and 713.6 (w); δ_H (300 MHz; $CDCl_3$), 1.35 (3H, s, H6/7/10/12), 1.43 (3H, s, H6/7/10/12), 1.58 (3H, s, H6/7/10/12), 1.67 (3H, s, H6/7/10/12), 2.45 (1H, dt *J* 14.8 , 4.4 Hz, H3), 2.57 (1H, dt *J* 14.8, 6.7 Hz, H3), 3.26 (3H, s, H9/13), 3.36 (3H, s, H9/13), 4.13 (1H, dd *J* 6.7, 4.4 Hz, H2) and 5.25 (1H, m, H4); δ_C (75 MHz; $CDCl_3$) 16.97, 17.89, 25.84, 31.30, 48.99, 49.82, 70.90, 98.11, 104.86, 118.58, 134.61 and 169.91; *m/z* (FAB +) 259 (MH^+, 48%), 227 (49) and 154 (100). Found (FAB +): [MH^+] 259.15479, $C_{13}H_{23}O_5$ requires 259.15454.

2-Hydroxy-5-methylhex-4-enoic acid methyl ester (329).



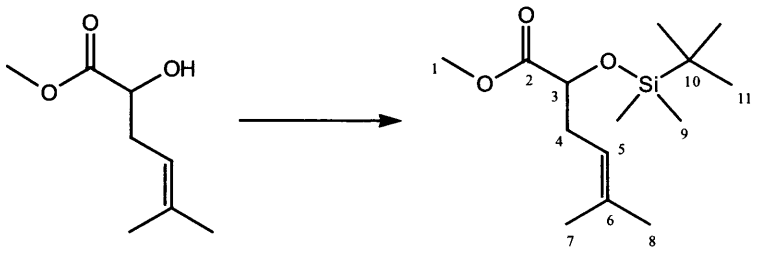
328 **329**

$C_8H_{14}O_3$
Mol. Wt.: 158.19

A methanolic HCl solution was formed by the addition of acetyl chloride (4.08 g, 3.71 ml, 52.0 mmol) to methanol (100 ml) and to this solution was added the lactone (**328**) (5.30 g, 20.5 mmol) and the reaction stirred at room temperature for 20 minutes. The volatiles were removed from the reaction under reduced pressure to give the crude *α-hydroxyester* (**329**) as a pale yellow oil which could be used directly for the subsequent silyl protection reaction. The crude product (**329**) could be purified by flash column chromatography (2: 1, petrol: diethyl ether) yielding the *title compound* (**329**) as a clear colourless oil (3.04 g, 19.2 mmol, 94%); ν_{max}/cm^{-1} (KBr plates / cm^{-1}) 3394.5 (br, O-H), 2970.2 (s, C-H), 2638.4 (w), 1735.8 (s, C=O), 1458.1 (m), 1373.2 (m), 1211.2 (s), 1141.8 (m), 1087.8 (m), 948.9 (w), 840.9 (w) and 748.3 (w); δ_H (300 MHz; $CDCl_3$), 1.61 (3H, s, H7/8), 1.70 (3H, s, H7/8), 2.36-2.58 (2H, m, H4), 2.70 (1H, br s, OH), 3.75 (3H, s, H1), 4.22 (1H, dd *J* 6.2, 4.8 Hz, H3) and 5.09-5.16 (1H, m, H5); δ_C (75 MHz; $CDCl_3$) 17.88, 25.86, 33.07, 52.37, 70.50, 117.72, 135.91 and 175.14; *m/z* (CI +

methane) 159 (MH^+, 20%), 141 (M – OH, 23) and 99 (100). Found (FAB +): [$M^{\cdot+}$ + H] 159.10158, $C_8H_{15}O_3$ requires 159.10211.

2-(*tert*-Butyldimethylsilanyloxy)-5-methylhex-4-enoic acid methyl ester (330).

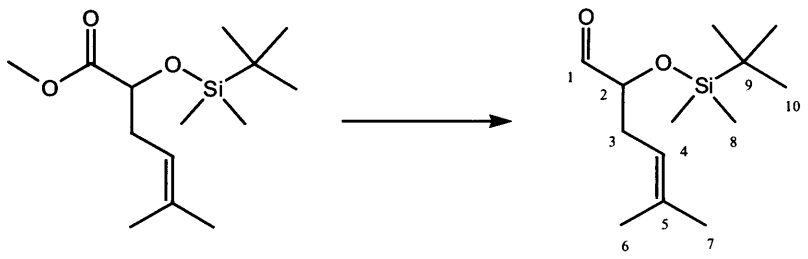


329 **330**

$C_{14}H_{28}O_3Si$
Mol. Wt.: 272.46

Imidazole (2.00 g, 30.8 mmol) and *tert*-butyldimethylsilyl chloride (4.63 g, 30.8 mmol) were added sequentially to a solution of the crude alcohol (**329**) (assume 20.5 mmol) in anhydrous DMF (15 ml) at 0 °C. The reaction was allowed to warm to room temperature and then stirred at this temperature for 1 h. The reaction was then quenched with water (30 ml), extracted with diethyl ether (3 x 40 ml) and the combined organic extracts washed with a saturated NaCl solution (2 x 40 ml). The organic phase was dried over $MgSO_4$ and the volatiles removed under reduced pressure to give crude compound (**330**) which was purified by flash column chromatography (3: 1, petrol: diethyl ether). This gave the *ester* (**330**) as a clear colourless oil (4.90 g, 18.1 mmol, 88% over two steps); ν_{max}/cm^{-1} (KBr plates/ cm^{-1}) 2929.7 (s, C-H), 2887.2 (s, C-H), 2857.3 (s, C-H), 1759.0 (s, C=O), 1737.7 (s), 1473.5 (m), 1462.9 (m), 1436.9 (m), 1361.7 (w), 1256.5 (m), 1133.1 (m), 941.2 (m), 838.0 (s) and 778.2 (s); δ_H (300 MHz; $CDCl_3$), 0.03 (3H, s, H9), 0.06 (3H, s, H9), 0.88 (9H, s, H11), 1.60 (3H, s, H7/8), 1.68 (3H, s, H7/8), 2.39 (2H, br t *J* 6.7 Hz, H4), 3.71 (3H, s, H1), 4.16 (1H, t *J* 6.7 Hz, H3) and 5.10-5.16 (1H, m, H5); δ_C (75 MHz; $CDCl_3$), -5.33, -5.07, 17.86, 18.31, 25.66, 25.79, 34.09, 51.68, 72.53, 119.21, 134.56 and 173.88; *m/z* (FAB +) 273 (MH^+, 65%), 215 (M - C_4H_9, 100) and 213 (30). Found (FAB +): [MH^+] 273.18927, $C_{14}H_{28}O_3Si$ requires 273.18859.

2-(*tert*-Butyldimethylsilanyloxy)-5-methylhex-4-enal (331).

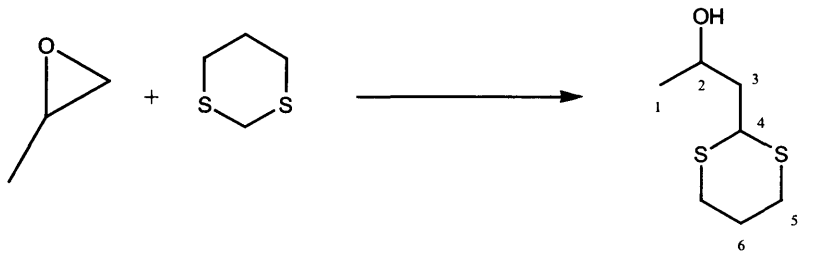


330 **331**

$C_{13}H_{26}O_2Si$
Mol. Wt.: 242.43

A solution of DIBAL-H in hexanes (1M, 0.53 ml, 0.53 mmol) was added dropwise to a solution of the ester (**330**) (0.14 g, 0.52 mmol) in toluene (10 ml) at –78 °C and the reaction stirred at this temperature for 2 h. Another 0.5 equivalents of DIBAL-H in hexanes (1M, 0.26 ml, 0.26 mmol) was then added dropwise to the reaction solution and stirring continued for a further 1 h at –78 °C. The reaction was quenched at this temperature by the addition of a saturated solution of Rochelle's salt (potassium sodium tartrate) (10 ml) and the mixture stirred for 1 h before extracting with diethyl ether (3 x 10 ml), washing the combined organic extracts with water (2 x 10 ml), drying over $MgSO_4$ and evaporating the volatiles under reduced pressure to give the crude aldehyde (**331**). The crude product was purified by flash column chromatography (4: 1, petrol: diethyl ether) to give *2-(tert-Butyl-dimethyl-silanyloxy)-5-methyl-hex-4-enal* (**331**) as a clear colourless oil (0.1 g, 0.41 mmol, 79%); ν_{max}/cm^{-1} (KBr plates / cm^{-1}) 2942.0 (s, C-H), 2857.3 (s, C-H), 1731.0 (s, C=O), 1462.9 (s), 1384.0 (m), 1361.7 (m), 1254.6 (s), 1105.1 (s), 1005.8 (m), 939.3 (m), 838.0 (s), 778.2 (s) and 668.3 (w); δ_H (300 MHz; $CDCl_3$), 0.04 (3H, s, H8), 0.08 (3H, s, H8), 0.89 (9H, s, H10), 1.60 (3H, s, H6/7), 1.69 (3H, s, H6/7), 2.33 (2H, br t *J* 6.4 Hz, H3), 3.96 (1H, td *J* 6.4, 1.6 Hz, H2), 5.10-5.16 (1H, m, H4) and 9.61 (1H, d *J* 1.6 Hz, H1); δ_C (75 MHz; $CDCl_3$) –4.93, -4.76, 17.93, 18.22, 25.71, 25.80, 31.76, 77.83, 118.37, 134.93 and 203.93 ; *m/z* (FAB +) 244 (17%), 243 (MH^+, 100), 227 (56), 225 (79), 213 (47), 185 (92). Found (FAB +): [MH^+] 243.17769, $C_{13}H_{27}O_2Si$ requires 243.17802.

1-[1,3]Dithian-2-ylpropan-2-ol (333).[177]

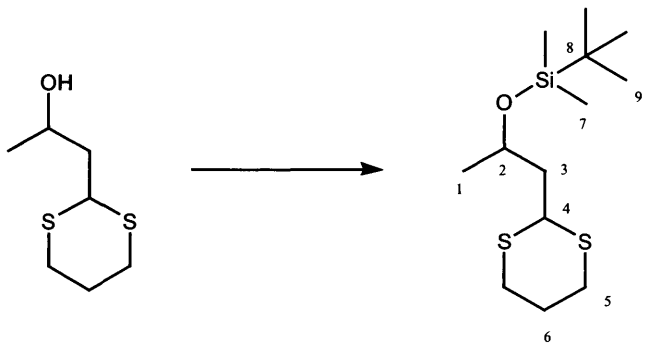


332 **154** **333**

$C_7H_{14}OS_2$
Mol. Wt.: 178.32

A solution of ^{n}BuLi in hexanes (2.5 M, 9.96 ml, 24.9 mmol) was added dropwise to a solution of 1,3-dithiane (**154**) (2.00 g, 16.6 mmol) in anhydrous tetrahydrofuran (40 ml) at –40 °C. The reaction was stirred at this temperature for 2 h and then for a further 2 h at 0 °C. The solution was then recooled to –40 °C and propylene oxide (**332**) (0.82 g, 0.99 ml, 14.1 mmol) added dropwise and stirring continued at –40 °C for 2 h. The reaction mixture was quenched by the addition of saturated solution of NH_4Cl (40 ml) and extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were washed with water (2 x 30 ml) and then dried over $MgSO_4$. Evaporation of the volatiles from the filtrate gave the crude product which was purified by flash column chromatography (2: 1, petrol: diethyl ether), producing 1-[1,3]Dithian-2-yl-propan-2-ol (**333**) as a clear colourless oil (1.72 g, 9.55 mmol, 68%). ν_{max}/cm^{-1} (KBr plates / cm^{-1}) 3409.9 (br, O-H), 2962.5 (s, C-H), 1419.5 (s), 1373.2 (s), 1272.9 (s), 1242.1 (s), 1180.4 (m), 1072.3 (m), 1033.8 (s), 941.2 (m), 910.3 (m), 871.8 (m) and 763.8 (m); δ_H (300 MHz; $CDCl_3$), 1.18 (3H, d *J* 6.2 Hz, H1), 1.79–1.91 (3H, m, H3,6), 2.05-2.15 (1H, m, H6), 2.15 (1H, br s, OH), 2.77-2.88 (4H, m, H5), 4.06-4.09 (1H, m, H2) and 4.20 (1H, dd *J* 8.4, 6.0 Hz, H4); δ_C (75 MHz; $CDCl_3$) 23.58, 25.90, 30.09, 30.30, 44.31 and 64.92; *m/z* (EI) 178 (M^{+}, 100%), 160 (M^{+} - H_2O, 23), 145 (67), 133 (28), 119 (90) and 74 (33); Found (EI): [M^{+}] 178.04879, $C_7H_{14}S_2O$ requires 178.04860.

***tert*-Butyl-(2-[1,3]dithian-2-yl-1-methylethoxy)-dimethylsilane (334).**[178]

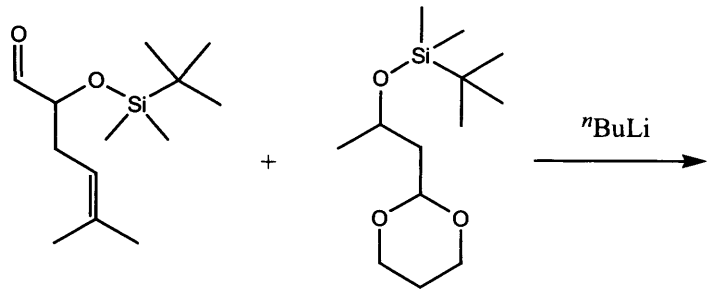


333 **334**

$C_{13}H_{28}OS_2Si$
Mol. Wt.: 292.58

Imidazole (0.46 g, 6.75 mmol) was added to a solution of the alcohol (**333**) (1.00 g, 5.62 mmol) in anhydrous DMF (10 ml) at 0°C followed directly by the addition of *tert*-butyldimethylsilyl chloride (1.02 g, 6.74 mmol). The reaction was allowed to warm to room temperature and then stirred at this temperature for a further 20 h. The reaction was then quenched with water (20 ml), extracted with diethyl ether (3 x 30 ml) and the combined organic extracts washed with a saturated NaCl solution (2 x 30 ml). The organic phase was dried over $MgSO_4$ and the volatiles removed under reduced pressure to give crude compound (**334**) which was purified by flash column chromatography (4: 1, petrol: diethyl ether). This gave the title compound (**334**) as a clear colourless oil (1.57 g, 5.39 mmol, 96%). ν_{max}/cm^{-1} (KBr plates/ cm^{-1}) 2928.7 (s, C-H), 2896.9 (s, C-H), 2855.4 (s, C-H), 1471.6 (m), 1461.9 (m), 1423.4 (m), 1414.7 (m), 1360.7 (m), 1256.5 (s), 1188.1 (w), 1138.9 (s), 1087.8 (m), 1052.1 (s), 973.0 (m), 914.2 (w), 899.7 (w), 836.1 (s), 808.1 (m), 775.3 (s), 725.2 (w), 667.3 (w), 659.6 (w) and 474.5 (w); δ_H (300 MHz; $CDCl_3$), 0.06 (3H, s, H7), 0.07 (3H, s, H7), 0.87 (9H, s, H9), 1.12 (3H, d *J* 5.9 Hz, H1), 1.65-1.92 (3H, m, H3,6), 2.02-2.15 (1H, m, H6), 2.76-2.87 (4H, m, H5), 4.01-4.11 (1H, m, H2) and 4.09 (1H, dd *J* 9.6, 5.1 Hz, H4); δ_C (75 MHz; $CDCl_3$), -4.78, -4.36, 18.05, 24.00, 25.88, 26.10, 30.03, 30.59, 44.22, 45.10 and 64.83; *m/z* (FAB +) 293 (MH^+, 41%), 291 (25), 235 (M - C_4H_9, 100), 191 (66), 160 (42) and 159 (100). Found (FAB +): [MH^+] 293.14223, $C_{13}H_{29}S_2OSi$ requires 293.14290.

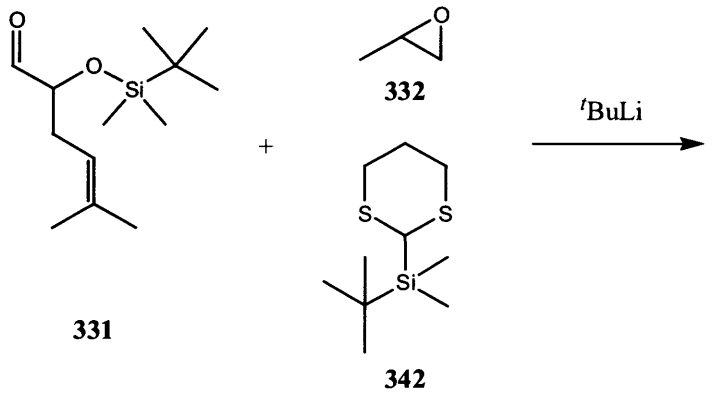
Attempted reaction of 2-(*tert*-butyldimethylsilanyloxy)-5-methylhex-4-enal (331) with *tert*-butyl-(2-[1,3]dithian-2-yl-1-methylethoxy)-dimethylsilane (334).



331 **334**

A solution of ^{n}BuLi in hexanes (2.5M, 0.16 ml, 0.39 mmol) was added dropwise to a solution of the dithiane (**334**) (0.1 g, 0.37 mmol) in anhydrous tetrahydrofuran (5 ml) at –40 °C. The reaction was stirred at this temperature for 0.5 h and then allowed to warm to –20 °C and stirred at this temperature for a further 1.5 h. After recooling to –78 °C, the aldehyde (**331**) (0.09 g, 0.37 mmol) was added dropwise to the solution and stirring continued for 0.5 h before the reaction was allowed to slowly warm to room temperature over 2 h. Water (5 ml) was then added and the two phases that formed separated, the aqueous phase being further extracted with diethyl ether (3 x 5 ml). The organic extracts were combined, washed with water (2 x 5 ml) and dried over $MgSO_4$. Removal of the solvents under reduced pressure led to the quantitative recovery of the starting dithiane (**334**) from this reaction.

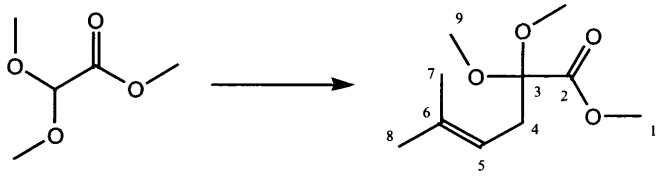
Reaction of 2-(*tert*-butyldimethylsilanyloxy)-5-methylhex-4-enal (331) with *tert*-butyl-[1,3]dithian-2-yl-dimethyl-silane (342) and propylene oxide (332).



331 **332** **342**

A solution of ^{t}BuLi in hexanes (2.5M, 0.17 ml, 0.43 mmol) was added dropwise to a solution of tert-Butyl-[1,3]dithian-2-yl-dimethyl-silane (**342**) (prepared according to the procedure of A. B. Smith III and A. M. Boldi)[183] (0.096 g, 0.41 mmol) in diethyl ether (7 ml) at –78 °C. The reaction was warmed to –25 °C and stirred at this temperature 2 h before being cooled back down to –78 °C and propylene oxide (**332**) (0.024 g, 0.029 ml, 0.41 mmol) added dropwise. The solution was again allowed to warm to warm to –25 °C over 2 h and then recooled to –78 °C. Distilled hexmethylphosphoramide (HMPA) (0.026 g, 0.029 ml, 0.16 mmol) was added to the reaction followed by the dropwise addition of the aldehyde (**331**) (0.10 g, 0.41 mmol). The reaction was slowly allowed to warm to room temperature and left stirring for 12 h. Water (5 ml) was added and the two phases that formed separated. The aqueous phase was further extracted with diethyl ether (3 x 5 ml), the organic extracts combined, washed with water (2 x 5 ml) and dried over $MgSO_4$. Evaporation of the volatiles under reduced pressure produced the crude product which was purified by flash column chromatography (1: 1 petrol: diethyl ether) and led to the isolation of the starting dithiane (**342**) (0.044 g, 0.19 mmol, 46%) and *tert*-Butyl-(2-[1,3]dithian-2-yl-1-methylethoxy)-dimethylsilane (**334**) (0.028 g, 0.09 mmol, 23%).

2,2-Dimethoxy-5-methylhex-4-enoic acid methyl ester (348).



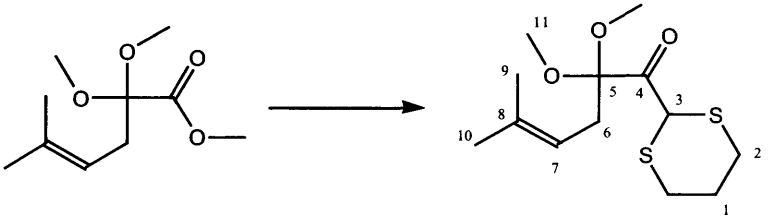
347 **348**

$C_{10}H_{18}O_4$
Mol. Wt.: 202.25

A solution of ^{n}BuLi in hexanes (2.5M, 4.48 ml, 11.2 mmol) was added dropwise to a solution of diisopropyl amine (1.13 g, 1.57 ml, 11.2 mmol) in anhydrous tetrahydrofuran (20 ml) at –5 °C and the reaction stirred at this temperature for 25 minutes. The reaction was then cooled to –78 °C and a solution of dimethoxyacetic acid methyl ester (**347**) (1.50 g, 1.50 ml, 11.2 mmol) in tetrahydrofuran (5 ml) added dropwise over 15 minutes. Stirring was continued for 15 minutes and then a solution of 4-bromo-2-methyl-2-butene (1.67 g, 1.30 ml, 11.2 mmol) added dropwise over 15 minutes. The reaction was stirred at –78 °C for 20 minutes before being allowed to

slowly warm to –10 °C over 1.5 h and then quenched at this temperature by the addition of water (20 ml). Diethyl ether (20 ml) was added to the reaction vessel and the aqueous and organic layers separated. The aqueous phase was further extracted with diethyl ether (2 x 20 ml), the organic layers combined, washed with a saturated NaCl solution (2 x 20 ml) and dried over $MgSO_4$. Removal of the volatiles under reduced pressure gave the crude product which was purified by flash column chromatography (1: 1, petrol: diethyl ether) producing the *title compound* (**348**) as a clear colourless oil (1.21 g, 5.94 mmol, 53%). ν_{max}/cm^{-1} (KBr plates / cm^{-1}) 2949.0 (s, C-H), 2835.2 (s, C-H), 1747.4 (s, C=O), 1446.5 (s), 1379.0 (m), 1321.1 (m), 1193.9 (s), 1143.7 (s), 1089.7 (s), 1062.7 (s), 954.7 (m), 873.7 (m), 844.8 (w), 806.2 (m), 779.2 (w) and 763.8 (w); δ_H (300 MHz; $CDCl_3$) 1.54 (3H, s, H7/8), 1.63 (3H, s, H7/8), 2.55 (2H, d *J* 7.2 Hz, H4), 3.22 (6H, s, H9), 3.71 (3H, s, H1) and 4.94 (1H, tsept. *J* 7.2, 1.5 Hz, H5); (75 MHz; $CDCl_3$) 17.78, 25.79, 32.87, 49.84, 52.32, 102.43, 115.79, 135.57 and 169.40; *m/z* (FAB +) 225 (M + Na, 100%). Found (FAB +): [M + Na] 225.10985, $C_{10}H_{18}O_4Na$ requires 225.11027.

1-[1,3]Dithian-2-yl-2,2-dimethoxy-5-methylhex-4-en-1-one (349).



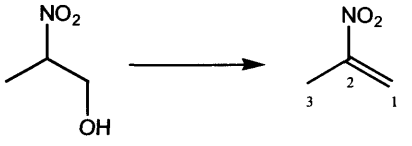
348 **349**

$C_{13}H_{22}O_3S_2$
Mol. Wt.: 290.44

A solution of 1,3-dithiane (1.80 g, 14.9 mmol) in tetrahydrofuran (60 ml) was cooled to –78 °C and a solution of ^{n}BuLi in hexanes (2.5M, 5.96 ml, 14.9 mmol) added dropwise. The reaction was allowed to warm to –10 °C and stirred at this temperature for 1.5 h. The reaction solution was then recooled to –78 °C before being transferred by cannular dropwise into a solution of the ester (**348**) (3.00 g, 14.9 mmol) in tetrahydrofuran (10 ml) also at –78 °C. The solution was left stirring at this temperature for 1 h and then allowed to warm to room temperature overnight and quenched by the addition of water (50 ml). The organic layer was diluted with diethyl ether (50 ml) and the two layers separated. The aqueous layer was further extracted with diethyl ether (2 x 50 ml), the

organic layers combined and washed with a saturated NaCl solution (2 x 50 ml). The organic phase was dried over $MgSO_4$ and the volatiles removed under reduced pressure to give the crude product. Purification was achieved by flash column chromatography (4: 1, petrol: diethyl ether). This produced the *α-ketodithiane* (**349**) as small colourless plates (3.22 g, 11.1 mmol, 75%); mp 81-83 °C (diethyl ether); Anal calcd. for $C_{20}H_{28}N_2O_2SSi$ C, 53.76; H, 7.63; S 22.08% Found C, 53.70; H, 7.64; S, 22.19%; ν_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 2925.8 (s, C-H), 2854.5 (s, C-H), 1716.5 (s, C=O), 1456.2 (m), 1421.4 (m), 1375.2 (m), 1236.3 (w), 1190.0 (w), 1136.0 (m), 1068.5 (m), 1029.9 (m), 968.2 (w), 846.7 (w), 732.9 (w), 655.8 (w) and 582.5 (w); δ_H (300 MHz; $CDCl_3$), 1.57 (3H, s, H9/10), 1.67 (3H, s, H9/10), 1.88 – 2.05 (1H, m, H1), 2.09 - 2.20 (1H, m, H1), 2.44 (2H, dt *J* 13.7, 4.0 Hz, H2 eq.), 2.55 (2H, d *J* 7.5 Hz, H6), 3.21 – 3.39 (2H, m, H2 ax.), 3.25 (6H, s, H11), 4.59 (1H, s, H3) and 4.98 (1H, tsept. *J* 7.5, 1.3 Hz, H7); δ_C (75 MHz; $CDCl_3$) 17.98, 24.64, 25.18, 25.98, 33.09, 38.16, 49.89, 105.15, 115.71, 136.34 and 200.59; *m/z* (FAB +) 313 (M + Na, 35%), 199 (15) and 176 (100). Found (FAB +): [M + Na] 313.09108, $C_{13}H_{22}O_3S_2Na$ requires 313.09080.

2-Nitropropene (351).[197]



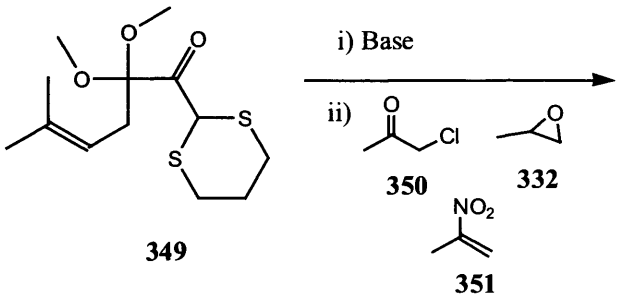
351

$C_3H_5NO_2$
Mol. Wt.: 87.08

Methanesulfonyl chloride (2.72 g, 1.85 ml, 23.8 mmol) was added dropwise to a solution of 2-nitropropan-1-ol (2.5 g, 23.8 mmol) in diethyl ether (20 ml) at 0 °C. This was followed immediately by the dropwise addition of triethylamine (4.80g, 6.60 ml, 47.6 mmol) to the reaction vessel and the reaction was stirred at 0°C for 1 h before being allowed to slowly warm to room temperature. The solution and precipitate was filtered through a plug of silica, washing through with diethyl ether (3 x 20 ml). The volatiles were removed from the filtrate under reduced pressure to produce 2-nitropropene (**351**) as a pale yellow oil (0.9 g, 10.3 mmol, 43%) which froze upon storage at –10 °C and required no further purification; δ_H (300 MHz; $CDCl_3$), 2.23 (3H, s, H3), 5.58 (1H, s, H1) and 6.38 (1H, s, H1); δ_C (75 MHz; $CDCl_3$) 16.77, 117.89 and

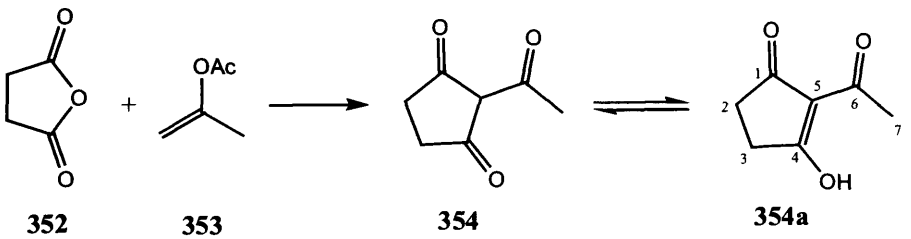
154.02; *m/z* (CI + methane), 91 (100%), 88 (MH^+, 40) and 79 (10). Found (CI + methane): [M + H] 88.04009, $C_3H_6O_2N$ requires 88.03985.

Attempted reaction of 1-[1,3]dithian-2-yl-2,2-dimethoxy-5-methylhex-4-en-1-one (349) with electrophiles.



Either sodium hydride (60% in mineral oil, 0.008 g, 0.19 mmol) or a solution of lithium hexamethyldisilazide (LiHMDS) (0.75M, 0.23 ml, 0.17 mmol) was added to a solution the α-ketodithiane compound (**349**) (0.05 g, 0.17 mmol) in a solvent of either, anhydrous tetrahydrofuran, anhydrous diethyl ether or anhydrous dimethylformamide (5 ml) at –10 °C. The reaction was stirred at this temperature for 0.5 h and then one of the electrophiles (**332**), (**350**) or (**351**) (0.17 mmol) was added dropwise. The mixture was left at this temperature for 1 h and then allowed to warm to room temperature, stirred for 3 h and then heated to reflux for 3 h. After being allowed to cool the reaction was quenched by the addition of water (5 ml) and then diethyl ether (5 ml) added. The two layers that formed were separated and the aqueous phase further extracted with diethyl ether (3 x 5 ml). The organic layers were combined, washed with water (2 x 5 ml) and dried over $MgSO_4$. Evaporation of the volatiles under reduced pressure led to the recovery of the starting α-ketodithiane compound (**349**) in all cases.

2-Acetyl-3-hydroxy-2-cyclopenten-1-one (354).[188]

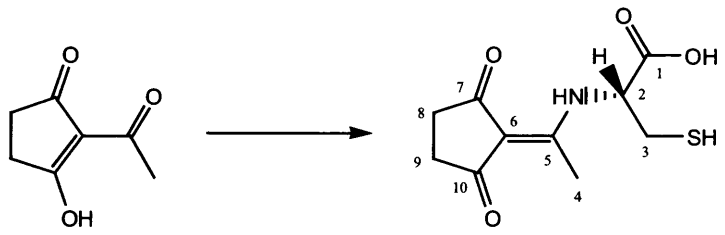


352 **353** **354** **354a**

$C_7H_8O_3$
Mol. Wt.: 140.13

A three neck flask fitted with a reflux condenser a calcium chloride drying tube and dropping funnel was charged with finely powdered succinic anhydride (**352**) (2.38 g, 23.8 mmol), freshly crushed aluminium chloride (6.35 g, 47.6 mmol) and anhydrous 1, 2-dichloroethane (24 ml). The mixture was stirred vigorously at room temperature for 2 h to dissolve as much of the reagents as possible. Isopropenyl acetate (**353**) (2.38 g, 2.67 ml, 23.8 mmols) was added through the dropping funnel and the reaction started immediately (indicated by a temperature rise to 60 °C to 70 °C). The reaction mixture was heated to reflux for 15 minutes and then the hot mixture (containing a sticky oil) was quenched by pouring onto a stirred solution of concentrated hydrochloric acid (9.5 ml) in ice (48 g). When the dark mass had dissolved, concentrated hydrochloric acid (9.5 ml) was added and the biphasic mixture stirred for 3 h. The 1, 2-dichloroethane phase was then separated from the aqueous and the aqueous phase further extracted with dichloromethane (8 x 30 ml). The organic extracts were combined and extracted with saturated $NaHCO_3$ solution (1 x 30 ml, 2 x 10 ml). The combined $NaHCO_3$ extracts were washed with dichloromethane (10 ml) and then acidified with concentrated hydrochloric acid (8 ml) with vigorous stirring. The acidic solution was extracted with dichloromethane (1 x 30 ml, 4 x 20 ml). The dichloromethane was removed under reduced pressure (taking care when only a small amount of solvent is left to remove it below room temperature at reduced pressure so as not to lose product). The crude product was then purified by recrystallisation from diisopropyl ether to give 2-Acetyl-3-hydroxy-2-cyclopenten-1-one (**354**) as colourless prisms (0.78 g, 5.57 mmol, 24%); mp 74 °C (diisopropyl ether) (lit.[188] mp 73-74 °C (diisopropyl ether)); ν_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 2922.9 (s, C-H), 2853.5 (s), 1700.1 (m, C=O), 1643.2 (m, C=C), 1585.4 (m), 1436 (m), 1365 (w), 1314.4 (w), 1276.8 (w) and 1163.0 (w); δ_H (300 MHz; $CDCl_3$), 2.47-2.52 (2H, m, H2/3), 2.49 (3H, s, H7), 2.70-2.75 (2H, m, H2/3) and 13.61 (1H, br s, OH); δ_C (75 MHz; $CDCl_3$) 25.75, 28.50, 33.70, 114.54, 198.64, 199.90 and 204.12; *m/z* (CI + methane) 141 (MH^+, 100%). Found (CI + methane): [MH^+] 141.05481, $C_7H_9O_3$ requires 141.05517.

2-[1-(2,5-Dioxocyclopentylidene)-ethylamino]-3-mercaptopropionic acid (355).

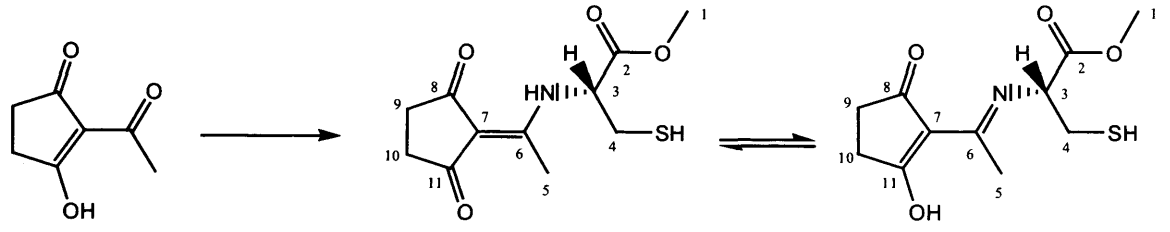


354 **355**

$C_{10}H_{13}NO_4S$
Mol. Wt.: 243.28

2-Acetylcyclopentane-1,3-dione (**354**) (0.05 g, 0.36 mmol) and L-cysteine (**46**) (0.04 g, 0.36 mmol) were slurried in acetonitrile (5 ml) and this mixture heated to reflux for 16 h. The reaction mixture was then cooled, filtered and the small amount of solid washed with methanol (2 x 5 ml). The solvents were evaporated from the filtrate under reduced pressure to give the crude product which was purified by triturating with chloroform (2 x 5 ml), to produce the *title compound* (**355**) as small colourless needles (0.06 g, 0.25 mmol, 69%); mp 188-190 °C (chloroform); (Anal calcd. for $C_{10}H_{13}O_4NS$ C, 49.37; H, 5.39% Found C, 49.01; H, 5.65%); ν_{max}/cm^{-1} (KBr plates nujol mull / cm^{-1}) 2922.9 (s, C-H), 2853.5 (s), 2516.0 (br, S-H), 1729.1 (m, C=O), 1674.1 (m), 1573.8 (m), 1494.7 (m), 1461.9 (s), 1377.1 (m), 1297.0 (m), 1240.1 (m), 1226.6 (m), 1195.8 (m), 1112.9 (w), 864.1 (w) and 722.3 (w); δ_H (300 MHz; D_6 - DMSO), 2.29-2.38 (4H, m, H8,9), 2.53 (3H, s, H4), 3.02-3.04 (2H, m, H3), 4.91 (1H, dt *J* 8.8, 4.5 Hz, H2) and 12.05 (1H, d *J* 8.8 Hz, NH); δ_C (75 MHz; D_6 - DMSO) 13.82, 26.43, 32.13, 33.77, 56.27, 106.05, 169.77, 169.84, 201.23 and 204.96; *m/z* (FAB +) 266 (18%), 244 (MH^+, 100), 198 (M - CO_2H, 10), 166 (28) and 154 (18). Found (FAB +): [MH^+] 244.06469, $C_{10}H_{14}O_4NS$ requires 244.06435.

2-[1-(2,5-Dioxocyclopentylidene)-ethylamino]-3-mercaptopropionic acid methyl ester (356).

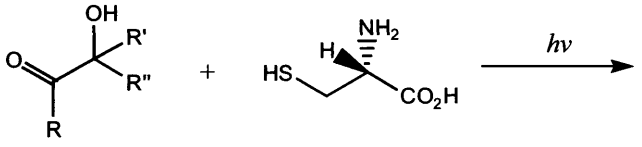


354 **356** **356a**

$C_{11}H_{15}NO_4S$
Mol. Wt.: 257.31

2-Acetylcyclopentane-1,3-dione (**354**) (0.05 g, 0.36 mmol) and L-cysteine methyl ester (0.05 g, 0.36 mmol) were slurried in acetonitrile (5 ml) and this mixture heated to reflux for 16 h. The reaction mixture was cooled, the solvents evaporated from the filtrate under reduced pressure to give the *title compound* (**356**) as a colourless oil which required no further purification (0.09 g, 0.35 mmol, 97%); ν_{max}/cm^{-1} (KBr plates / cm^{-1}) 3418.6 (br, N-H), 2926.8 (m, C-H), 2543.0 (w, S-H), 1741.6 (s, C=O), 1672.2 (m, C=C), 1593.1 (s), 1493.8 (m), 1392.5 (m), 1297.0 (m), 1230.5 (m), 1181.3 (m), 1116.7 (m), 853.4 (w) and 653.8 (w); δ_H (300 MHz; $CDCl_3$) 1.66 (1.6H, t *J* 9.1 Hz, SH **356** and **356a**), 2.37-2.72 (11.2H, m, H5,9,10 **356** and **356a**), 2.92 – 3.18 (2.6H, m, H4 **356** and **356a**), 3.29 (0.6H, dd *J* 14.4, 4.7 Hz, H4 **356a**), 3.80 (4.8H, s, H1 **356** and **356a**), 4.56-4.66 (1H, m, H3 **356**), 4.68-4.80 (0.6H, m, H3 **356a**), 12.25 (1H, d *J* 9.1 Hz, NH **356**) and 12.32 (0.6H, br s, OH **356a**); δ_C (75 MHz; $CDCl_3$) 14.25, 14.39, 27.08, 32.64, 34.22, 40.18, 53.36, 53.48, 54.38, 57.27, 107.33, 168.37, 168.62, 170.29, 170.48, 202.68 and 206.51; *m/z* (EI) 258 (M^{+} + H, 100%), 257 (M^{+}, 70), 224 (50), 210 (65), 171 (50) and 123 (55). Found (EI): [M^{+}] 257.07159, $C_{11}H_{15}O_4NS$ requires 257.07218.

Photolysis studies of Isohumulone analogues.



49, 148, 180, 181, 192 **46**

L-Cysteine (**46**) (15 mg / L) was added to a solution of the isohumulone analogue (**49**, **148**, **180**, **181** or **192**) (15 mg / L) in a solvent system of water: ethanol (19: 1) buffered to pH 4.2 with a phosphate buffer, at room temperature in a clear glass vial. LCMS or GCMS analysis was performed on this solution. The reaction solution was then irradiated with natural light in an Atlas suntest box for 0.5 h before being resubmitted for LCMS or GCMS analysis. The results of these studies are given in the results and discussion section of this thesis (Section 2.6, Table 1).

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