SYNTHETIC STUDIES DIRECTED TOWARDS THE ODORIFEROUS SESQUITERPENOID GRIMALDONE

by

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SUMMARY

Progress has been made towards the synthesis of the odoriferous tricyclic sesquiterpenoid grimaldone. A bicyclic intermediate with the necessary functionality to allow construction of the final ring has been synthesised. Unfortunately, attempts to alkylate this intermediate, to set up the necessary carbon skeleton for the construction of the final ring, met with failure. Although alternative methodology could have been used to construct the final ring, the 11 step synthetic route towards this advanced intermediate contained a few inconsistent steps so attention was turned towards devising a shorter route.

A tandem reaction of an α-epoxy mesylate to form the required bicyclic ring and a new epoxide looked an interesting option. Unfortunately the requisite α-epoxy mesylate could not be synthesised.

A new route to a bicyclic intermediate was devised. Unfortunately extra steps had to be incorporated to deal with the unforeseen etherification problems encountered during ketone protection. However, a robust route to a bicyclic methyl ketone was now available. This intermediate methyl ketone was converted to a 1,4-dione by a copper chloride mediated coupling of enolates. Unfortunately attempts to form the final cyclopentyl ring *via* aldol condensation of the 1,4-dione were unsuccessful.

No further progress was made towards the synthesis of grimaldone but an advanced intermediate was attained which should allow grimaldone to be accessed relatively easily.

DEDICATION

To Mum and Dad

ACKNOWLEDGEMENTS

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CONTENTS

Abbreviations

Ether	diethyl ether
DCM	dichloromethane
DMAP	dimethylaminopyridine
DMF	dimethylformamide
LDA	lithium di-*iso*-propyl amide
Light petroleum	petroleum ether 40-60 °C (unless otherwise stated)
MVK	methyl vinyl ketone
MCPBA	*meta*-chloro *per*-benzoic acid
PyTsOH	Pyridinium tosylate
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDMSCl	*tert*-butyldimethylsilyl chloride
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethane sulphonate

Foreword

Grimaldone is a sesquiterpenoid isolated from the liverwort *Mannia fragrans*. The odoriferous properties of grimaldone suggest that it may be useful as a perfumery product. Since it is difficult to obtain a sufficient quantity of material from the plant for evaluation, studies were undertaken in order to devise a synthetic route to grimaldone. The chirality of grimaldone has been established and only one stereoisomer (of a possible four) has been isolated to date. Since the other stereoisomers might have interesting olfactory properties, the synthetic route was aimed towards racemic grimaldone. Additionally this would make the proposed synthesis easier and would fulfil some of the major criteria for a synthetically useful perfume, low cost and ease of synthesis.

1. THE PERFUME INDUSTRY

1.1. The history of perfume use

The use of perfumes and cosmetics dates back to before civilisation. The use of paints has been revealed in thin layers of red ochre spread over the body in prehistoric graves.[1] However very few traces of perfumes have been reported. The Egyptians certainly made extensive use of perfumes. Archaeological excavations have uncovered remains of vessels and equipment that may have been used for the manufacture and storage of perfumes and ointments. However, with residues of these complex mixtures having suffered the ravages of time, even with modern analytical equipment, it is difficult to provide conclusive evidence for perfume use in this era.

However, the Egyptians were adept at keeping records and there have been bodies of ancient text uncovered documenting the thorough cleansing rituals in which the Egyptians indulged. They bathed frequently and applied oils and creams to protect their skin from the sun. These skin ointments were perfumed and were used equally by all strata of Egyptian society.

Perfumes also had a large religious significance. The ritual application of emollient to the statues of the gods, the worshippers and the dead is a frequent theme in ancient Egyptian literature. The manufacture of these 'holy oils' was an intricate mixture of techniques and ritual. The ancient Egyptian "unguent of the gods took 93 days to prepare, the heken oil 365 days" before it was suitable for the service of the gods.[1]

The Egyptians had three main methods for obtaining perfumes[a] from flowers, fruits or seeds- enfleurage, maceration and pressing.

Enfleurage – the saturation of layers of fat with perfumes by steeping flowers into the fat and replacing them as soon as their perfumes had penetrated the fat.

Maceration – dipping flowers, seeds e.t.c. into hot fat/oil at about 65 °C. This is the most popular method in early recipes.

Pressing – squeezing essential oils from their seeds and flowers. Presses were made

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[a] All Egyptian perfumes were of plant origin. The extensive extraction technology for procuring perfumes from animals was not available to the ancient civilisations.

from linen cloth and were folded around two sticks in such a way that when the sticks were twisted in opposite directions pressure was applied to the contents of the linen bag. Of course, the earliest form of press was simply treading a base material in a tub or a basin.

The perfume then took many forms in contrast to our modern perfumes today, which inevitably are in the form of bottles of liquid. An inhabitant of the ancient world would be just as likely to enjoy perfume in the form of a thick ointment to be smeared liberally over the body, or a fragrant smoke, infusing the air with its odour. Indeed our own word 'perfume' literally means 'to smoke through', indicating the importance this method of imparting fragrance had for our ancestors.[2]

Incense was in common usage in Egyptian times, especially surrounding the deceased. It was thought to provide the deceased with a scent similar to that of the gods, who were, in fact, believed to sweat incense. Thus sweetened, the deceased could enter into olfactory dialogue with the gods and request entry into their company. The incense smoke was also thought of as a means for the deceased to climb up to the gods. Incense therefore both made the deceased acceptable to the gods and provided a means of reaching their domain.

The Greeks were aware of the extensive use of perfumes by the Egyptians and also made substantial contributions to perfume. The incredible beauty of 'Helen of Troy', whose abduction brought about the Trojan War, was supposed to be due to her cosmetic secrets. She was known to share these secrets with her admirers and showed them recipes of the cosmetic products she used. This is postulated as being the beginning of the sophisticated Greek use of perfume. The Greeks were very adept at extracting the odorous principles from plants and resins using olive oil. While the Greeks used perfumes liberally, the Romans used them sparingly. In fact they scoffed at the enthusiastic consumption of odorants by their Greek and Egyptian ancestors.

The industrial development of steam distillation and the procedure for making high-grade alcohol were huge stepping stones to the modern production of perfumes. In the 10th century, the Arabs introduced Rose oil and Rose water with such techniques. Soon these extracts were produced on a large scale and were exported worldwide. Using this technology, other extracts and essential oils soon became available. This technology provided perfumes that were in use right up to the end of the last century.

Only the rapid development of organic chemistry has enabled the industry to move on. These advances now allowed the analysis and synthesis of some natural products. Improvements in crystallisation and vacuum distillation techniques allowed the isolation of natural products. However, the development of the modern perfume industry began only with the discovery of synthetic techniques that allowed odorants to be produced on a large scale. Some of the most important synthetic discoveries are shown in Table 1.1. below.[3]

Table 1.1. Industrial syntheses of natural odorants in the 19th century.

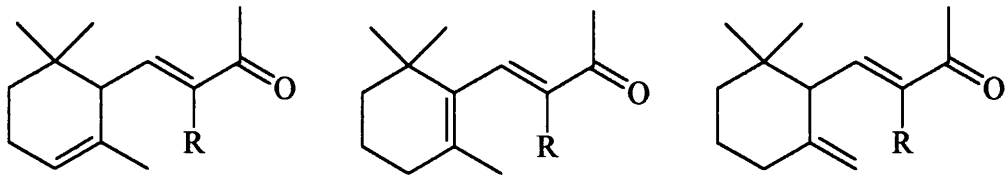
Year	Substance	Discoverer
1855	Benzyl alcohol	S. Cannizzaro
1855	Phenyl acetic acid	S. Cannizzaro
1866	Coumarin	W. H. Perkin
1870	Benzaldehyde	F. W. Wilhemi
1876	Salicylaldehyde	K. Reimer
1876	Vanillin	K. Reimer, F. Tiemann
1878	Cinnamic acid	W. H. Perkin
1883	Phenylacetaldehyde	E. Erlenmeyer, A. Lipp
1884	Cinnamaldehyde	G. Peine
1885	α-Terpineol	O. Wallach
1886	Methyl salicylate	Schimmel & Co.
1890	Piperonal	G. Ciamician, P. Silber
1891	Nitromusk	A. Baur
1893	Ionone	F. Tiemann, P. Krueger

1.2. The modern perfume industry

Until the middle of the 19th century, perfumes were reserved for the wealthiest strata of society. This is in stark contrast to the picture we see today. We have come to accept that perfumes are used not only in cosmetics, but also in a wide range of consumer products such as soaps, detergents and household cleaners. This change has come about as a consequence of advances in synthetic chemistry, which has reduced the cost of perfumes dramaticallly. Up until 100 years ago all perfumes were

made entirely of natural materials. One of the major turning points was in 1921 when the famous perfume Chanel No.5 was launched.[4] This was the first perfume to use synthetic odorants to create a new fragrance. This perfume relies heavily on the methylionones (**4**, **5** and **6**), in particular α-isomethylionone (**4**), which are synthetic analogues of the naturally occurring ionones (**1**, **2** and **3**). The immediate success of Chanel No. 5 led to a burgeoning interest in synthetic odorants.

Figure 1.1. Synthetic (R=Me) and natural (R=H) ionones.



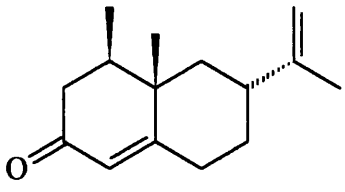
R=H (**1**) R=H (**2**) R=H (**3**)

R=Me, α-Isomethylionone (**4**) R=Me (**5**) R=Me (**6**)

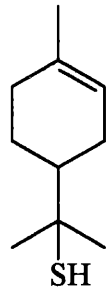
The development of new perfumes follows a similar path to the pharmaceutical industry. The starting point is the isolation and identification of the active component present in the plant extract. The organic chemist can then devise a synthetic route to the natural product. Simpler analogues can then be synthesised, and with the help of QSAR (Quantitative Structure-Activity Relationships) techniques, synthetic products can be chosen which have improved performance over the natural product.

With increasingly sophisticated analytical machines becoming available, more of nature's secrets can be unlocked. In particular greater sensitivity has allowed identification of components present at lower and lower concentrations. For example, for years it was believed that nootkatone (**7**) was the most important flavour/odour component of grapefruit (Figure 1.2.). However the thioterpineol (**8**) has been shown[5] to be a more important component and is present at very low levels in grapefruit. It is detectable at concentrations as low as 1 part in 10^{14}.

Figure 1.2. Important odorants in grapefruit.



(7) Nootkatone



(8) Grapefruit thioterpineol

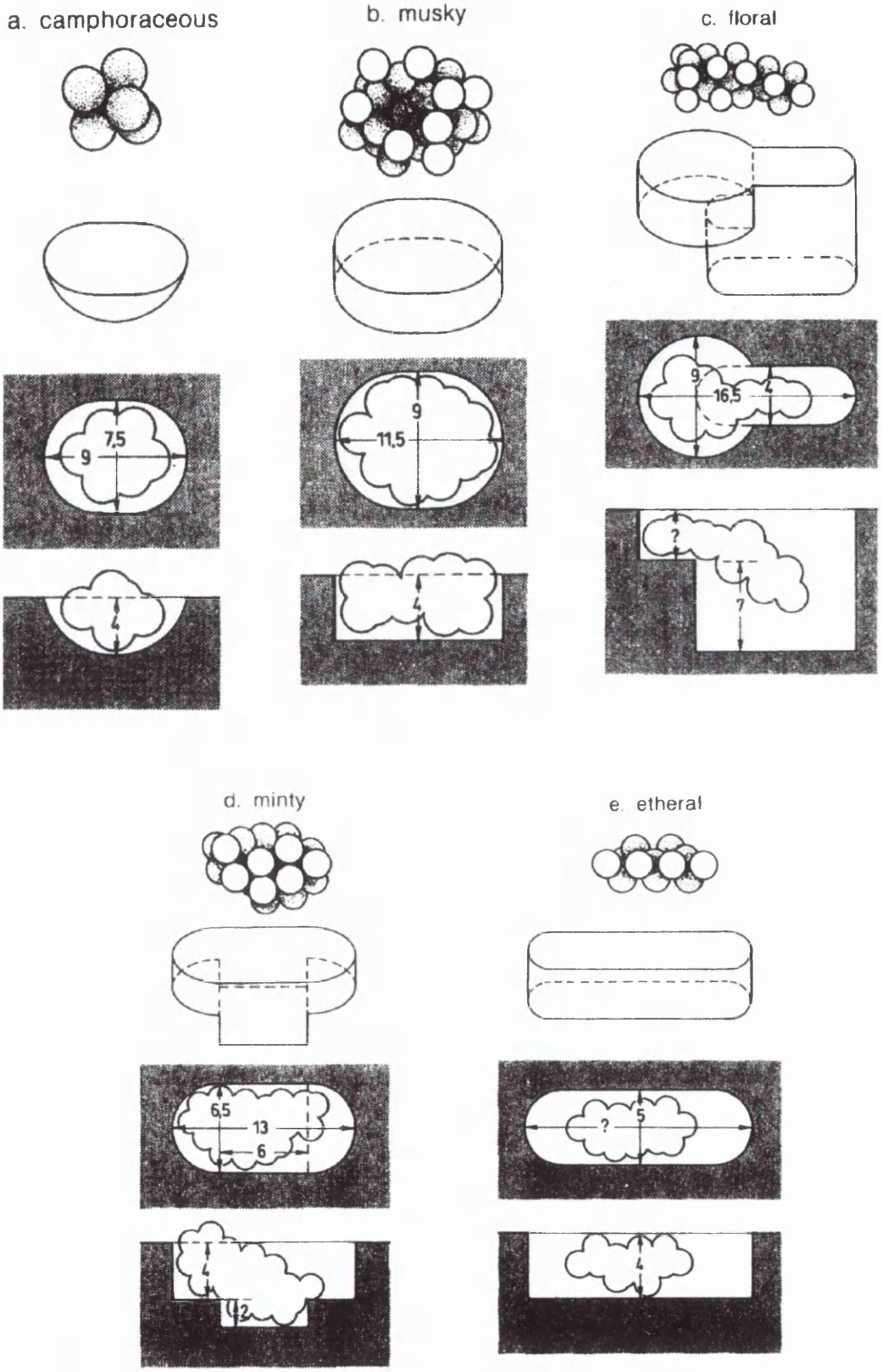
The range of applications for odoriferous compounds is growing, so there is ever increasing demand for novel perfumes. With QSAR techniques, it is easy to select odorants that will perform well in products. It is more difficult to try to design new perfumes. Odour is a subjective phenomenon and there is no real understanding of the mechanisms of smell. However, there have been empirical rules developed, which can give useful guidance in designing new perfumes.

2. PERFUME STRUCTURE

2.1. Introduction

Understanding how perfumes work would help a great deal in designing new fragrances. Many theories have attempted to explain how we perceive odours. Among the more bizarre of these is the radiation theory, first postulated by Aristotle in the fourth century BC, which proposes that odorous substances emit radiation that is detected by the olfactory receptor. Other outdated theories include M. M. Mozell's chromatography theory (1970); the thermodynamic activity theory, first put forward by P. Givaudan (1948) and the membrane penetrating theory of J. T. Davies (1971).
All these theories do, however, relate to the solubility and/or volatility of the odorant molecule, which are important properties in determining the effective transport of the molecule from source to receptor, but do not necessarily give any indication of how these molecules interact with the receptor.[6] One of the best known theories is that of Amoore.[7]
Amoore postulates that there is a limited number of receptor types located in the nose, each of which recognises a particular shape of molecule, and when triggered generates a signal corresponding to a primary odour. These primary odours work for smell in much the same way as the primary colours work for sight. Therefore, the enormous variety of smells we can experience is due to only a handful of primary receptors.
He proposed shaped receptors for 5 primary odours – ethereal, camphoraceous, musky, floral and minty (Figure 2.1). He also proposed a further two primary odours – pungent and putrid – that were caused by positively and negatively charged species respectively. Later, he postulated that, if these primary odours existed, then they should correspond to specific anosmias – the inability of certain groups of people to detect particular odours. By examining the reactions of a large number of people Amoore attempted to identify anosmias and hence primary odours. The results he obtained were not in line with his initial list of primary odours – of the four most common anosmias (musk, sandalwood, ambergris and urine) only one (musk) corresponded to his original postulation.

Figure 2.1. Amoore's proposed odour receptors.



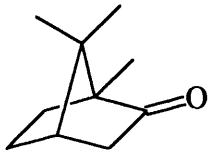
Representative molecules: **a** hexachloroethane, **b** musk xylol, **c** α-amylpyridine, **d** menthol, **e** diethyl ether.

The size of a molecule is undoubtedly important in determining the nature of the odorant but it does not tell the whole story. Many other features are necessary, such as the steric environment, relationship of functional groups to one another and molecular conformation. Rules have been ascertained for various classes of odours regarding their structures. These allow the synthesis of odorants with specific smells. However these rules always have exceptions and should be treated only as good guidelines.

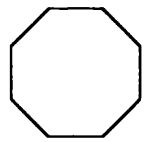
2.2. Camphoraceous

The camphoraceous odour is fairly common in everyday life and can be found in products such as vapour rub and older versions of moth repellent. The ingredient responsible for the characteristic odour is bicyclic ketone, camphor (**9**) which is obtained naturally from camphor oil or synthetically from pinene.[9] However, many compounds share this characteristic odour (Figure 2.2.) from a hydrocarbon (**10**) with no functionality through to a compound (**12**) containing functionality which is usually associated with unpleasant odours (nitrogen, phosphorus, sulphur and chlorine).

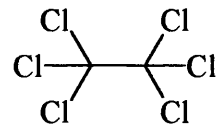
Figure 2.2. Compounds with a camphoraceous odour.



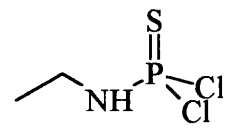
camphor
(**9**)



cyclo-octane
(**10**)



hexachloroethane
(**11**)



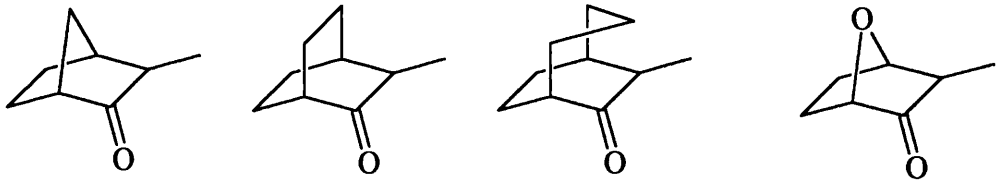
thiophosphoric acid dichloride ethyl amide
(**12**)

This class of odorants is unique. It is the only odour area where there appears to be no need for specific chemical functionality. The only common features are shape and size which fit quite well with Ammore's[7] postulate mentioned previously. One explanation for the observation that both non-polar and polar molecules can possesss strong camphoraceous odours was proposed by Beets[8]. He considered that the interaction of an odoriferous molecule with the receptor system was characterised by

both the affinity of the molecule to the receptor surface and its efficacy, that is the ability of the molecule, when absorbed, to trigger a stimulus. Beets believed that the affinity was mainly determined by the functional group(s) present and the efficacy by the profile and orientation of the molecule. A high affinity and well-defined odour would be due to compounds with one easily accessible functional group, the reason being that, in such cases, practically all the molecules would be found in one strong orientation at the receptor surface. For molecules with more than one functional group the randomness of orientation increases and a more complex odour is perceived due to the unselective interaction at the receptor surface. For spherical compounds such as the camphoraceous odours, the profile of the molecule would be similar in any orientation. Therefore, there is little difference between the statistical profile of a population of spherical hydrocarbons in a random orientation and that of a population of spherical, rigid polar molecules in a highly specific orientation.

However there does appear to be at least one exception to the concept of shape/size as the only determining factor in molecules with camphor-like odours. The replacement of the methylene bridge of homocamphenilone (**13**) by an oxygen atom as in **16** completely destroys the camphoraceous odour, whereas replacement of the methylene group with an ethylene as in **14** or propylene as in **15** has no dramatic effect on the odour (Figure 2.3.). This is probably related to the volatility with the ether (**16**) obviously being more polar than the hydrocarbon analogues and hence less volatile.

Figure 2.3. Compounds with a camphoraceous odour.



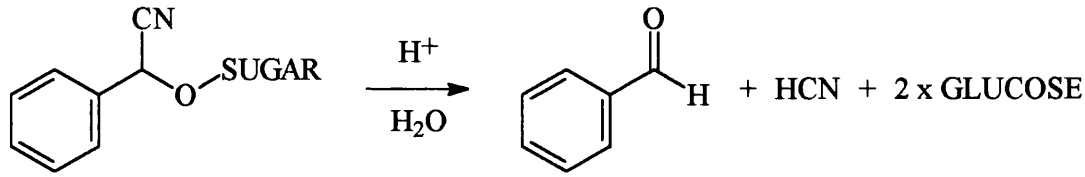
(**13**) (**14**) (**15**) (**16**) odourless

2.3. Bitter Almond

The classical molecules having this smell are hydrogen cyanide (**19**) and benzaldehyde (**18**). Both of these materials are produced by the hydrolysis of

amygdaline (**17**) (Scheme 2.1.), one of the constituents of bitter almonds.[9]

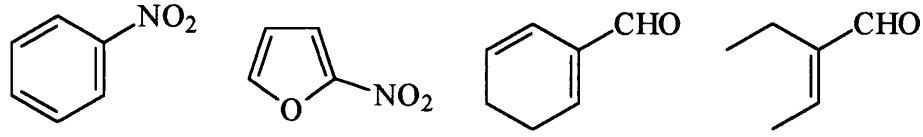
Scheme 2.1. Hydrolysis of amygdaline.



(**17**) (**18**) (**19**)

The aldehyde group of benzaldehyde (**18**) can be replaced by other electron withdrawing groups of similar size such as nitrobenzene (**20**) with little variation in odour (Figure 2.4.). The benzene ring is not a specific requirement as is demonstrated by the heteroaromatic (**21**) and aliphatic (**22** and **23**) bitter almond odorants.

Figure 2.4. Bitter almond odorants.

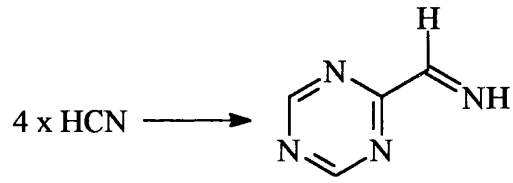


(**20**) (**21**) (**22**) (**23**)

It seems that the conjugation of the functional group is the determining factor. The notable exception to this rule is of course hydrogen cyanide as it does not have any conjugation of the nitrile moiety. Klouwen[10], suggested that if hydrogen cyanide tetramized to form the triazine (**24**) this would fit with the model (Figure 2.5.). Unfortunately, no experimental evidence is available to back up this theory.

Other workers believe that anosmia for hydrogen cyanide could suggest that there are receptor sites corresponding to the smell of bitter almonds, one of the hydrogen cyanide type and one of the benzaldehyde type. Since hydrogen cyanide and benzaldehyde occur together in nature, Sell[10] argues that the correlation in odour between these two compounds could be as a result of learning at higher levels in the brain/neurone system rather than events at receptor level.

Figure 2.5. Proposed hydrogen cyanide tetramer.



(19) **(24)**

2.4. Floral

Considering the vast variety of floral odours it is difficult to believe that there exists a relationship between the chemical structure of floral odours in general. However, Boelens[10] suggested that the structural features for a floral odour are: -

(1) The presence of a substituted medium sized ring or isosteric structure and

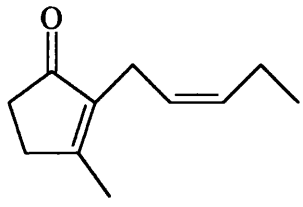
(2) A carbon chain (C2 to C8) possessing an alcohol, carbonyl, ester or ether functional group.

These rather broad specifications can be pruned for individual floral types.

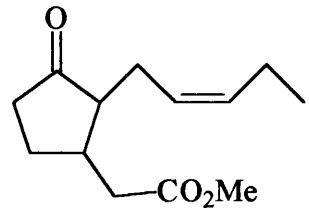
2.4.1. Jasmine

Jasmine absolute contains many components (>200) of which only two, jasmone (**25**) and methyl jasmonate (**26**), have the characteristic odour of jasmine (Figure 2.6.).

Figure 2.6. Essential odoriferous compounds of Jasmine extract.



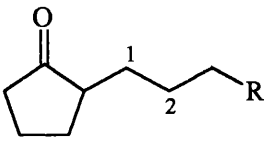
(25) jasmone



(26) methyl jasmonate.

Since compounds with jasmine odours are usually expensive, Sell and Dorman[10] synthesised a range of cyclopentanones containing branched and cyclic side chains to explore the effect they had on the jasmine odour. Their findings are summarised over the page (Figure 2.7.).

Figure 2.7. The effect of modifications to the side-chain on jasmine odour.



(27)

(1) 2-*n*-Alkylcyclopentanones exhibit predominantly jasmine odours if the chain contains 5, 6 or 7 carbon atoms.

(2) A substituent on the first carbon of the side chain virtually destroys the jasmine odour.

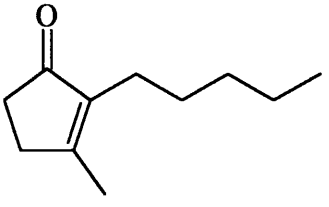
(3) A substituent on the second carbon of the side chain has the effect of replacing the jasmine character by rose.

(4) Substituents further down the chain have relatively little effect on the odour.

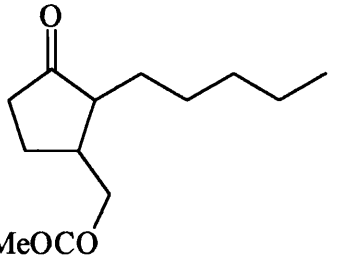
(5) 2-Alkylcyclopentanones with short, highly substituted side chains tend to be camphoraceous as they fulfil the size/shape requirements postulated by Amoore[7] for this odour (Figure 2.1.).

The hydrogenated versions of jasmone (**25**) and methyl jasmonate (**26**), dihydrojasmone (**28**) and methyl dihydrojasmonate (**29**) respectively, obviously conform to the above rules and consequently share the jasmine odour (Figure 2.8).

Figure 2.8. Cyclopentanone derivatives with jasmine odour.



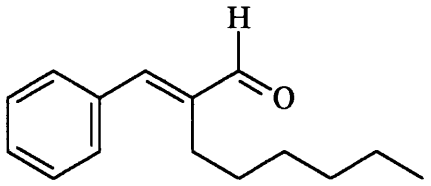
(28) dihydrojasmone



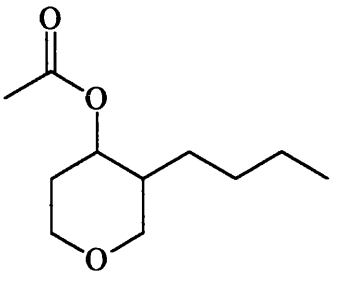
(29) methyl dihydrojasmonate

There are however exceptions to the above rules (Figure 2.9.) as demonstrated by α-hexylcinnamic aldehyde (**30**) and the pyran (**31**) which both have jasmine odours.

Figure 2.9. Unrelated structures with jasmine odour.



(30)



(31)

Thus, the jasmine odour can be represented by four groups of chemicals, with approximately a 10-fold price difference between the groups.[4]

(1) Jasmine absolute will cost £3000-5000 / kg.

(2) The synthetic nature-identical compounds 25 and 26 will cost £300-500 / kg.

(3) Simpler cyclopentanone analogues such as 28 and 29 will cost £10-50 / kg.

(4) Unrelated structure types such as 30 and 31 will cost £2-5 / kg.

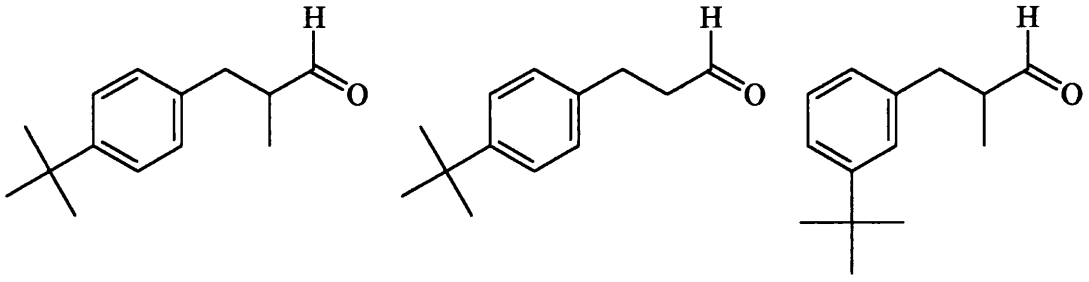
2.4.2. Lily of the Valley (Muguet)

Another important floral scent is that of the flowers of the lily of the valley (muguet). This odour is peculiar in that no component of the characteristic muguet odour has yet been identified. However, there are synthetic compounds that have similar characteristic odours such as Lilial (**32**), Bourgeonal (**33**) and Lilestralis 33 (**34**) (Figure 2.10.). These synthetic perfumes have odours that are heavier than that of the living flower, which is soft and quite roselike. Therefore, the term 'Lily of the Valley' is used to describe compounds that have odours similar to these synthetic versions and not odours similar to that of the actual flower. This is due to the fact that the flowers of the lily of the valley plant are so small that it is extremely difficult to extract and hence impossible to obtain a blossom oil.

The examples given in Figure 2.10. and the earliest muguet odorants, which were all aldehydes, indicates that this functionality is very important to this class of odorants. A large proportion of these odorants also has a benzene nucleus on the β position. Berends and van der Linde[10] evaluated the floral character of 25 similar phenylpropanals. They concluded that *iso*-propyl, *tert*-butyl or *tert*-amyl groups in the *para* or *meta* positions had odours reminiscent of cyclamen flowers. The odour becomes more muguet if the branching is further removed from the aromatic nucleus,

such as the *neo*-pentyl or *iso*-pentyl cases. The introduction of an alkyl substituent at the α or β position of the aldehyde chain reduces the odour intensity. Hence, Lilial (**32**) is 2-4 times less intense than Bourgeonal (**33**) at the same concentration. In the case of Lilestralis/Lilial, the *meta* isomer Lilestralis 33 (**34**) is more intense than the *para* isomer Lilial (**32**) although this is not always the case. However, *ortho* isomers always tend to be much weaker than their *meta/para* analogues.

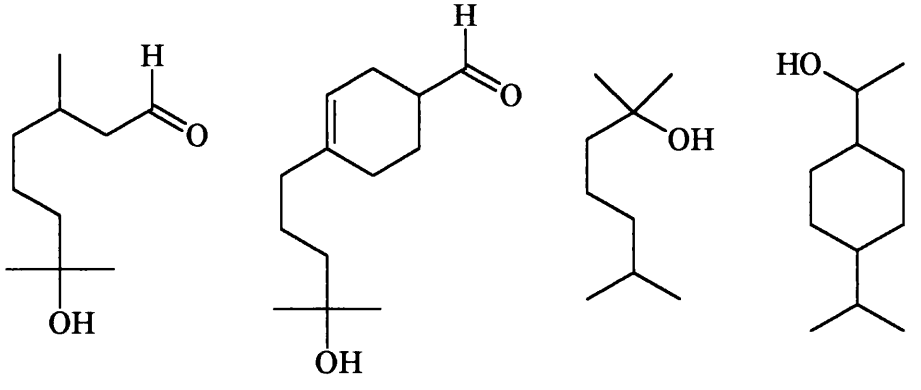
Figure 2.10. Synthetic muguet odorants.



(**32**) Lilial (**33**) Bourgeonal (**34**) Lilestralis 33

Aldehydes are not the only functionality present in muguet odours. Alcohols account for a substantial number of these odorants (Figure 2.11.). However, as can be seen from these examples, in particular **35** and **36**, both functional groups are sometimes present and it is unclear whether the odour requires an alcohol or aldehyde or indeed both.[11]

Figure 2.11. 'Lily of the valley' alcohols.

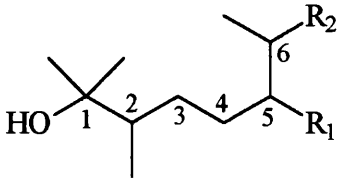


(**35**) hydroxycitronellal (**36**) Lyral (**37**) Freesiol (**38**) Mugetanol

It is likely that the muguet odorant requires only one functional group. Pelzer[10] states that the two different functional groups, alcohol (**39**) and carbonyl (**40**), exhibit

different alkyl substitution patterns around the key functional group (Figure 2.12.). He studied a large number of muguet odorants and constructed a set of rules from the observation of these substitution patterns. The use of these rules led to the synthesis of a series of new fragrances, the most notable of which was Mugetanol (**38**).

Figure 2.12. Pelzer's muguet odorants

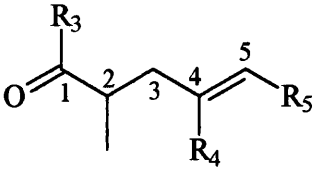


(**39**) Alcohol

(1) C1 is substituted by 1-3 alkyl groups, ideally 3, provided that the hydroxyl is not too sterically crowded.

(2) C2, C5 and to a lesser extent C6 and C7 are substituted by a single alkyl group (ideally methyl).

(3) Where a double bond is present, it should preferably be at C4 or C6.



(**40**) Carbonyl

(1) An aldehyde is always better than a ketone function,

(2) C2 should be substituted by one or two methyl groups, preferably one, and

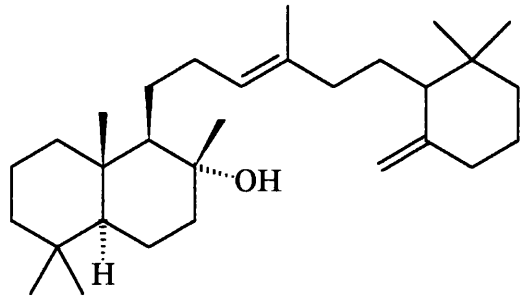
(3) C4 should be alkyl substituted. A double bond at C4 is particularly advantageous and may be part of an aromatic system.

2.5. Ambergris

Ambergris has been one of the most sought after perfumes since ancient times. The name is derived from the French, *ambre gris* - grey amber. It is secreted from the stomach or intestinal tract of the sperm whale into the sea in the form of dark lumps.[12] These lumps are rarely more than 20 cm in diameter but a piece weighing approximately 400 kg was removed from the intestine of a whale which had been killed.[13] Ambergris is made up of 46 % cholestanol type steroids and 25-45 % of a triterpene, ambrein (**41**). When first formed Ambergris is dark brown to black in colour but on exposure to sunlight, air and seawater it gradually loses colour to become light grey or creamy in colour. This decomposition gives rise to a number of products which

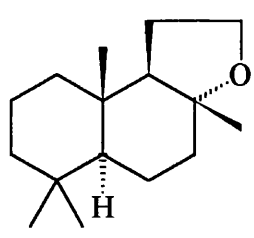
give ambergris its characteristic smell. The most important of these is shown below in Figure 2.14..

Figure 2.13. Ambrein – One of the major components of Ambergris

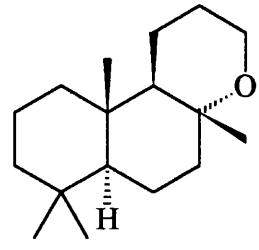


(**41**) Ambrein

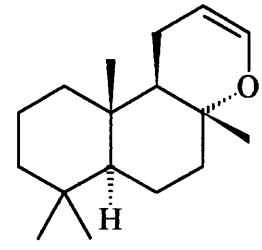
Figure 2.14. Oxidative degradation products of ambrein (41).



(**42**) Ambrox



(**43**)

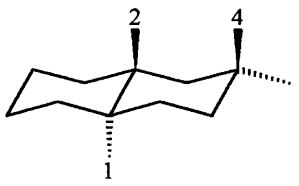


(**44**)

Ambrox (**42**) is a key ambergris ingredient and is known by various trade names, Ambrox (Firmenich), Ambroxan (Henkel) and Amberlyn (Quest). Ambrox (**42**) along with its less potent diastereomer isoambrox is used in amounts of up to 0.02 % in approx. 40 % of all perfumes created from 1980-1990.[3] The high demand for these odorants has led to a lot of research in the area to try to identify more accessible and cheaper substitutes.

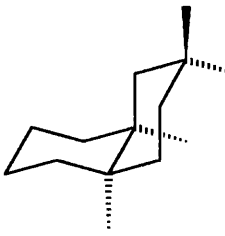
The preparation of a large number of tricyclic 5 and 6 membered ring ethers led to Ohloff's well known structure-activity relationship, the "Triaxial rule".[3] This requires that for a compound to possess an ambergris-like odour it must possess a decalin system with three axial groups. These groups should be located 1, 2 and 4 relative to each other. The substituents in the 1 and 2 position may be hydrogen since their only purpose is to ensure a *trans* configuration of the rings (**45**) as *cis*-decalins (**46**) tend to be inactive (Figure 2.15.).

Figure 2.15. Triaxial rule of ambergris odours.



Trans decalins with1,2,4 axial relationship tend to be active.

(45)

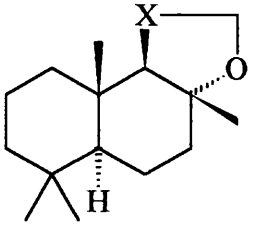


Cis decalins tend to be inactive

(46)

The ethereal ring in compounds such as ambrox (**42**) has been investigated by Cambie and Palmer.[14] The acetal derivatives (**49** - **52**) have weaker smells than their ethereal counterparts (**42**,**43**,**47** and **48**) (Figure 2.16.). The strength of the odour weakens as the ring size increases. This effect is more marked in the acetal case with the 8-membered ring (**52**) having a dull waxy smell.

Figure 2.16. Effect of ring size on ambergris odour.



(**42**) X = $-CH_2-$ Very strong Ambergris

(**43**) X = $-(CH_2)_2-$

(**47**) X = $-(CH_2)_3-$

(**48**) X = $-(CH_2)_4-$ Weak Ambergris

(**49**) X = -O- Strong Ambergris

(**50**) X = $-CH_2O-$

(**51**) X = $-(CH_2)_2O-$

(**52**) X = $-(CH_2)_3O-$ Dull waxy

2.6. Musky

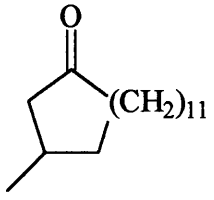
Musk odorants probably have more widespread use than ambergris odorants and like ambergris, musk fragrances originated from animal sources.

2.6.1. Macrocyclic and steroid based musks.

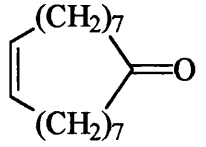
From the animal kingdom we obtain a number of macrocyclic ketones, such as muscone (**53**) from the musk deer, civetone (**54**) from the civet cat and

cyclopentadecanone (**55**) from the musk rat (Figure 2.17.). The plant kingdom also has furnished us with a limited supply of musks, macrocyclic lactones such as ambrettolide (**56**) from ambrette seed oil and exaltolide (**57**) from Angelica root (Figure 2.18.)

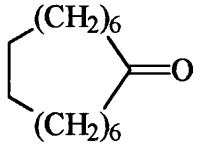
Figure 2.17. Musks from the animal kingdom.



(**53**) muscone
(musk deer)

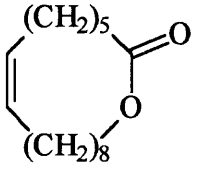


(**54**) civetone
(civet cat)

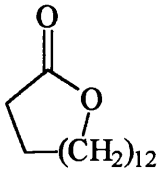


(**55**) cyclopentadecanone
(Louisana musk rat)

Figure 2.18. Musks from the plant kingdom



(**56**) Ambrolette
(Ambrette seed oil)



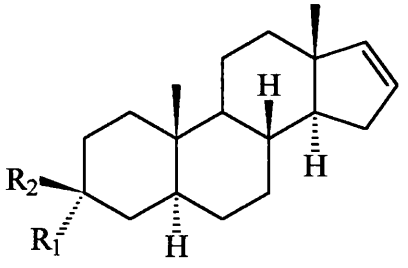
(**57**) Exaltolide
(Angelica root)

The most important aspect of macrocyclic musks appears to be ring size. According to Carothers[15,16] an aliphatic ring of 14 or 15 atoms with a carbonyl functionality (ketone, lactone, carbonate, oxalate or anhydride) will almost certainly have a musk-like odour. Larger ring sizes (17 and 18) will give a more civetone musk for ketones and lactones. As the ring size of macrocyclic ketones decreases the odour becomes more camphoraceous then changes to the characteristic bitter almond/menthol cyclohexanone odour at rings below 8 in size. Varying the carbon backbone of the macrocycle by incorporating ether linkages or a second lactone functionality does not seem to affect the quality of the odour. Although the intensity of the odour does tend to be less than for the aliphatic analogues, which is probably due to the decrease in volatility.

The musky odour of these flexible macrocycles does raise the question of – "which conformation(s) is/are responsible for the perceived odour?" Comparisons have been drawn with the more rigid steroid-based musks[17] (Figure 2.19.). The two isomeric

alcohols, (**58**) and (**59**), were first isolated from hog testicles.[18,19] The β isomer (**59**) is found to be odourless. The corresponding ketone (**60**) has been found in the sweat and urine of human males and has a stronger and more urinous odour[20] than the alcohol (**58**).

Figure 2.19. Steroid based musks.



(**58**) R_1 = OH, R_2 = H, 5α-androst-16-en-3α-ol, Animalic-Musky odour.

(**59**) R_1 = H, R_2 = OH, 5α-androst-16-en-3β-ol, Odourless.

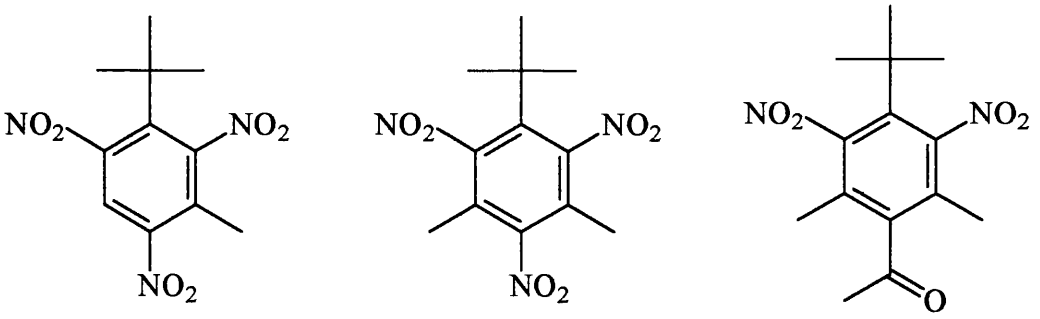
(**60**) R_1,R_2 = O, 5α-androst-16-en-3-one, Strong Urinous-Musky odour

Comparison of the steroid based musks with the macrocyclic musks suggest that the macrocycles adopt a stretched conformation with two long parallel hydrocarbon chains rather than a more circular one. Crystal structure analysis of these compounds is quite difficult due to the high degree of disorder that they exhibit, although, Bernardinelli[21] has obtained crystal structures of DNP derivatives of a number of macrocyclic ketones. Of course, the crystal structure of a solid derivative does not necessarily give any information relating to the conformation of the odorant at the receptor.

2.6.2. Nitro musks

A certain degree of serendipity was involved in the opening up of this area of new musks. In 1888 Bauer[10] was synthesising explosive compounds and discovered that 2-*tert*-butyl-4-methyl-1,3,5-trinitrobenzene (**61**) had a musky odour. This led to the discovery of a number of further nitromusks such as musk xylene (**62**) and musk ketone (**63**) (Figure 2.20.)

Figure 2.20. Aromatic nitro musks.

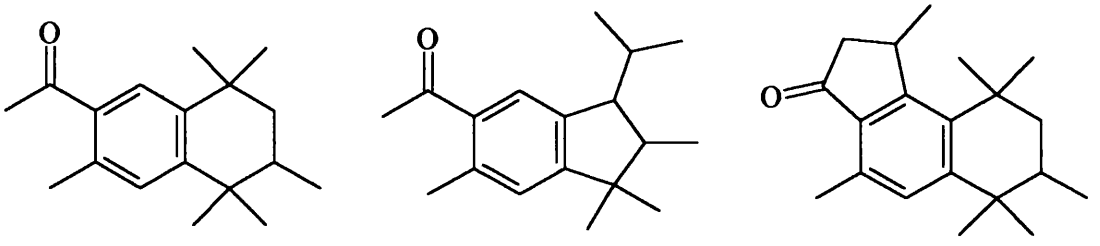


(61) Musk toluene **(62)** Musk xylene **(63)** Musk ketone

2.6.3. Non-nitro aromatic musks

There is also a large number of non-nitro aromatic musks. These tend to consist of aromatic rings fused to a cyclohexyl ring as in Tonalid **(64)** or to a cyclopentyl ring as in Traseolide **(65)**. Both of these are commercial musks, but there exists a variety of analogues with varying potencies. (Figure 2.21.)

Figure 2.21. Non-nitro aromatic musks



(64) Tonalide **(65)** Traseolide **(66)**

These 3 compounds have a lot of similarities and along with other non-nitro aromatic musks generally require the following structural features :-

(1) 14-20 Carbon atoms (optimum 16-18).

(2) An aromatic ring substituted with a functional group (this is usually an aldehyde or ketone, but in certain cases can be an ether or nitrile).

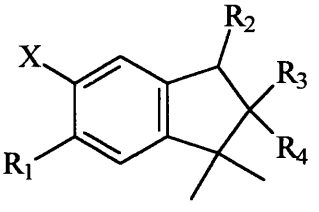
(3) Two quaternary carbon atoms positioned ortho or meta to each other (in the ortho position they are both part of a fused 5 or 6 membered ring). Para isomers tend to be odourless.

(4) The functional group must be unhindered.

(5) The odorant should have a close packed structure.

Traseolide (**65**) appears to flaunt rule 3, but it was prepared when Boelens[10] was investigating the boundaries of this same rule. He reasoned that it might be possible to replace one of the quaternary centres, with a tertiary carbon with a bulky substituent. He found that this was the case and prepared a variety of analogues (**67**) (Figure 2.22.) based on musk phantolid (**69**), of which traseolide (**65**) was the most potent. Spoelstra and co-workers[22] investigated the effect of changing the methyl ketone (**69**) to an aldehyde (**68**). He found that the aldehyde was a more potent odorant and the corresponding ethyl ketone (**70**) less potent. This is probably a consequence of the functionality being less hindered as described by rule 4.

Figure 2.22. Analogues of Musk Phantolid.



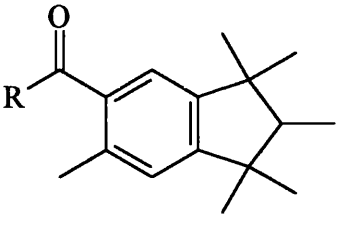
(67)

X = Aldehyde, acyl, nitro or nitrile.

R_1 = H, Me or Et.

R_2 = i-Pr or t-Bu.

R_3, R_4 = H or Me.



(68) R = H

(69) R = Me, Musk Phantolid

(70) R = Et

2.6.4. General musks

Although the three main types (macrocyclic, nitro aromatic and non-nitro aromatic) of musk odorants appear to be quite different structurally there have been attempts to devise a general set of rules. Theimer and Davies[23] studied more than 50 musk odorants and devised the following physical limits.

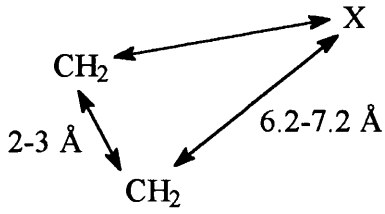
(1) A desorption rate from a water surface into air of 0.4-1.7.

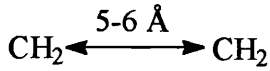
(2) A molecular cross section of 40-57 $Å^2$.

(3) A length to breadth ratio of 2.8-3.3.

Bersuker[10] and co-workers established the following set of rules for the structure of musk odorants (Figure 2.23.).

Figure 2.23. Bersuker's musk activity fragments.





Fragment 1 (X = CO, NO_2 or CN) Fragment 2

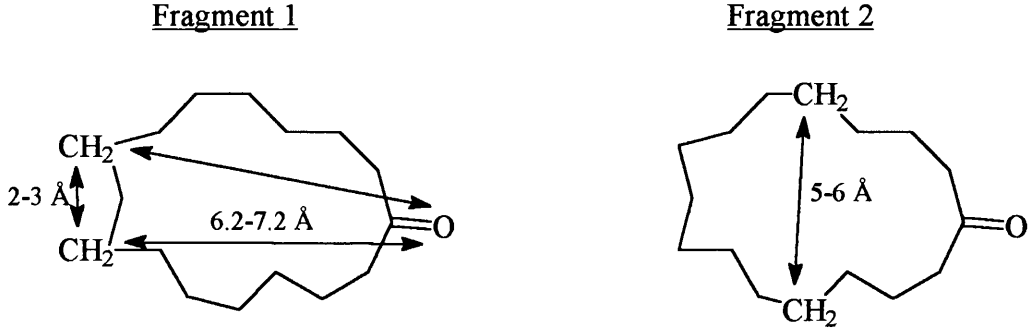
(1) Fragment 1 : a functional group (CO, NO_2, CN) whose electronegative atom is situated symmetrically with respect to two methyl (or methylene) groups and at a distance of 6.2-7.2 Å. The distance of the two methyl / methylene groups is 2.0-3.0 Å

(2) Fragment 2 : two methyl (or methylene) groups separated by a distance of 5.0-6.0 Å.

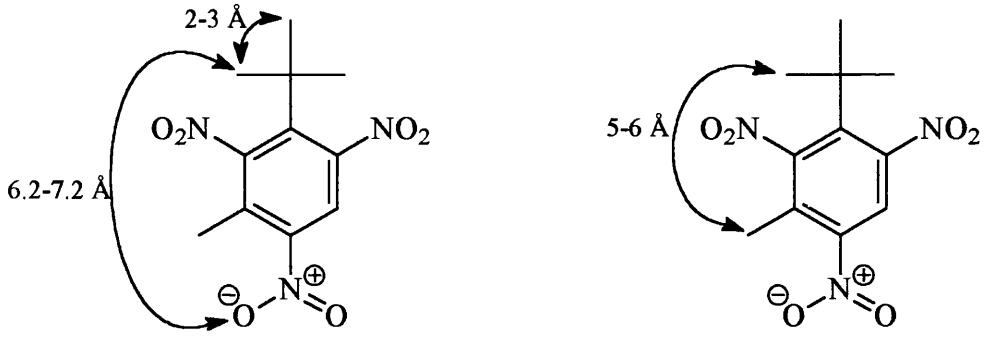
(3) Steric accessibility to the two fragments.

These rules work very well for a number of musks as can be seen from (Figure 2.24.). The conditions are satisfied if it is assumed that the macrocyclic musks occupy an ellipsoidal orientation. The conditions can only be met with macrocycles containing 13-17 members. The rules work equally well for the non-nitro and nitro, aromatic musks. Some nitro-aromatic musks appear to be exceptions to the rules. It has been suggested the corresponding dimeric form actually conforms.

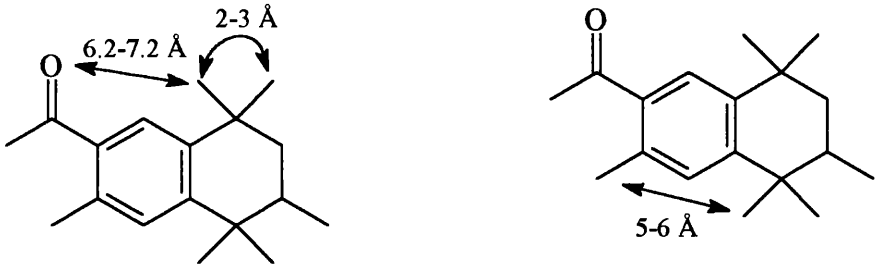
Figure 2.24. Compounds obeying Bersuker's rules for musk odorants.



(71) cyclohexadecanone



(61) musk toluene



(64) Tonalide

3. Grimaldone

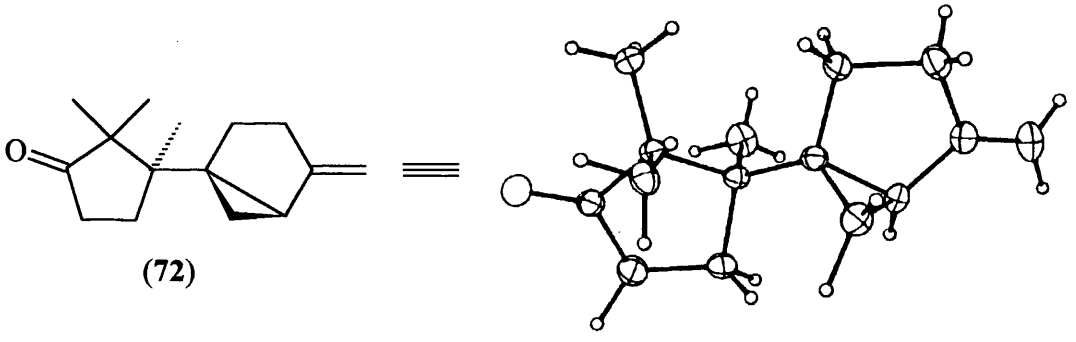
3.1. Structure and origin

In central Europe, the liverworts of genus *Mannia* comprise three species, *M. pilosa*, *M. triandra* and the most common *M. fragrans*. As its name suggests *Mannia fragrans* is an odoriferous plant. It emits an intense odour when the thallus is wet which can be detected at many metres by a sensitive nose. It occurs in a few locations in Germany, Czechoslovakia and Poland but is extremely abundant in Hungary.

3.1.1. Isolation.

In 1975, Huneck and Schreiber[24] isolated an odoriferous ketone from *M. fragrans*, collected in Hungary, and named it grimaldone after the old genus name *Grimaldia*. Ten years later, from material collected in Mongolia, Connolly and co-workers[25] isolated grimaldone (**72**) and elucidated its structure by NMR and crystal structure analysis (Figure 3.1.).

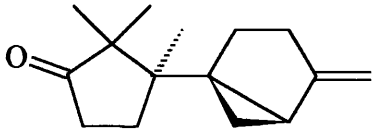
Figure 3.1. Crystal Structure of Grimaldone (72).



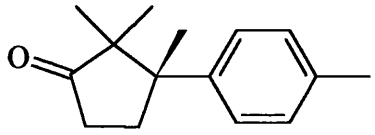
(**72**)

The absolute configuration (Figure 3.2.) was established by comparison of its circular dichroism spectrum with that of (+)-S-α-cuparenone (**73**). (+)-S-α-cuparenone (**73**) gives rise to a positive CD. Similiarly grimaldone (**72**) gives a negative CD and hence must be a derivative of *ent*-cuparene (**74**). This is an example of the capacity of liverworts to produce sesquiterpenoids enantiomerically related to those of higher plants. Indeed (-)-R-α-cuparenone has been isolated from *M. fragrans*.[26]

Figure 3.2. Absolute configuration of grimaldone (72).



(**72**) grimaldone

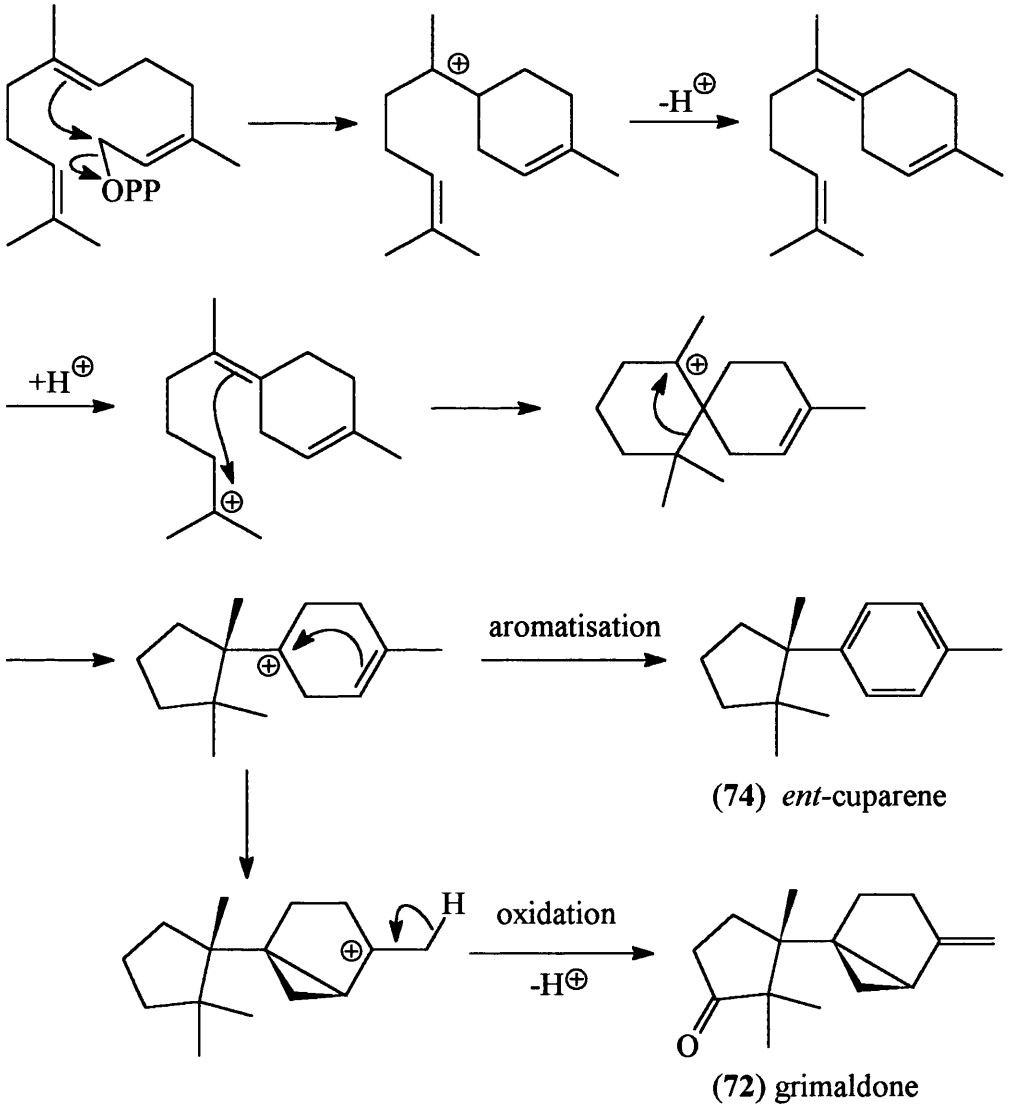


(**73**) (+)-S-α-cuparenone.

3.1.2. Possible Biosynthesis

Grimaldone is of course a sesquiterpene and hence the biosynthesis is based on the mevalonate unit. The route probably follows the biosynthesis[27] of *ent*-cuparene (**74**) quite closely (Scheme 3.1.).

Scheme 3.1. Proposed biosynthesis of grimaldone.



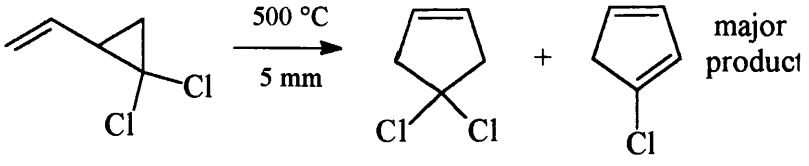
3.2. Synthesis

In the synthesis of cyclopropane-containing compounds the construction of the cyclopropane ring is often left to the later stages. This notion is based on the greater reactivity of the cyclopropyl ring compared with other rings due to the high degree of ring strain. It is well known that cyclopropyl rings can undergo a variety of rearrangements,[28] and are reactive intermediates in a number of synthetic transformations such as the Favorskii rearrangement.[29] Cyclopropyl rings can be opened by a wide range of reagents, including electrophiles,[30] nucleophiles[31] and reductants.[32] In some ways cyclopropyl rings should be treated as a functional group. However, as a functional group they are not very reactive, generally requiring high temperatures and/or the presence of an activating group to induce reactivity. Nevertheless, under the correct circumstances they can be quite useful as synthetic intermediates.

3.2.1. Vinylcyclopropanes

For synthetic purposes, activated cyclopropanes are most useful and in particular the rearrangement of vinylcyclopropanes has been well documented.[33] Since grimaldone (**72**) is a vinyl cyclopropane it is worth discussing the possible rearrangements of this fragment. The first reported rearrangement was by Neureiter[34] in 1959 (although there were undoubtedly many unreported rearrangements prior to this). A vinyl cyclopropane (**75**) derived from butadiene was heated under vacuum to give 2,2-dichlorocyclopentene (**76**) as one of the minor products (Scheme 3.2.). The major product, monochlorocyclopentadiene (**77**) was almost certainly produced by loss of hydrogen chloride from this dichloroalkene (**76**).

Scheme 3.2. First reported vinylcyclopropane rearrangement.



(**75**) (**76**) (**77**)

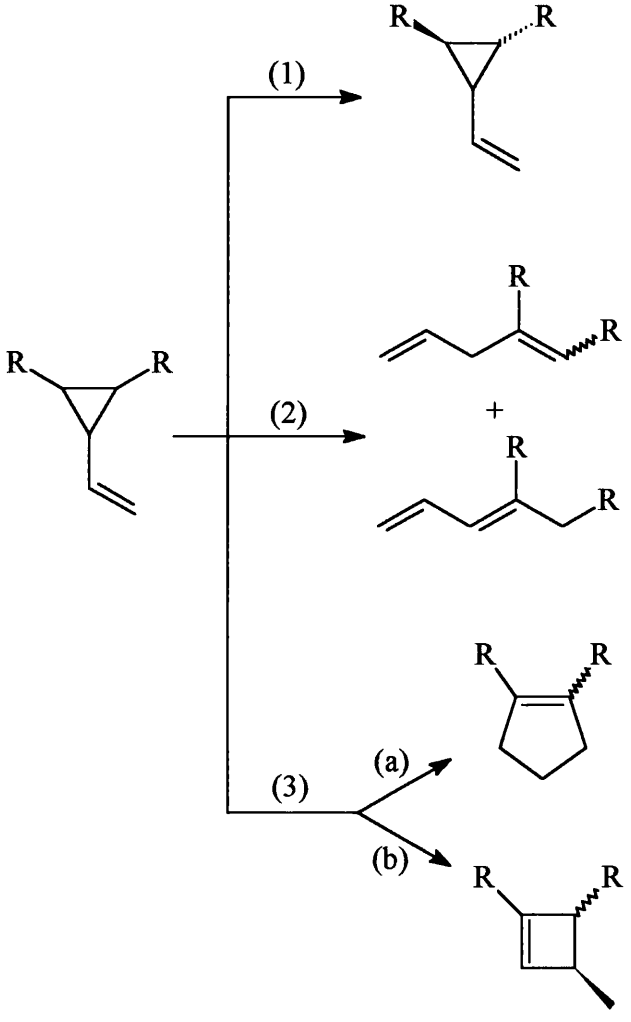
In general, vinylcyclopropanes undergo three fundamental types of bond reorganisation processes (Scheme 3.3.) : -

(1) *Cis-trans* isomerisation.

(2) Ring opening to pentadienes.

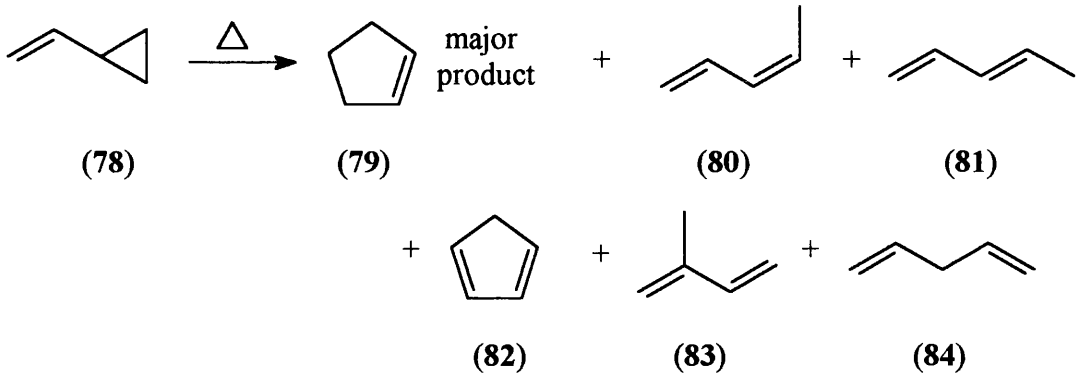
(3) Ring enlargement to (a) cyclopentenes[35] and (b) methylcyclobutenes.

Scheme 3.3. Rearrangements of vinylcyclopropanes.



The rearrangement pathway is dependent on the conditions used and the substituents present on the vinylcyclopropane. The parent vinylcyclopropane will undergo a thermal reaction to give cyclopentene (**79**) as the major product (Scheme 3.4.). A number of minor products have also been identified in the reaction mixture such as *cis*-1,3-pentadiene (**80**), *trans*-1,3-pentadiene (**81**), cyclopentadiene (**82**), isoprene (**83**) and 1,4-pentadiene (**84**).

Scheme 3.4. Thermal rearrangement of vinylcyclopropane (78).

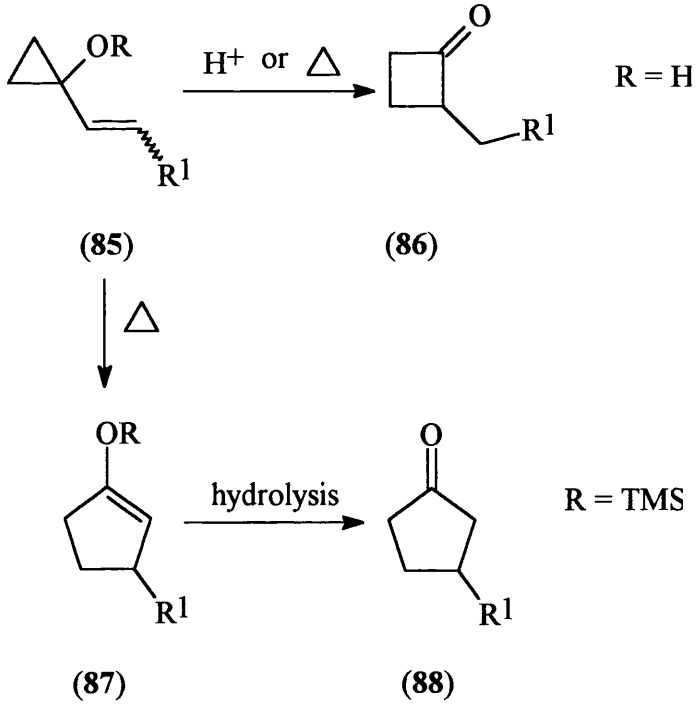


(78) (79) (80) (81)

(82) (83) (84)

The expansion of vinylcyclopropanes to cyclobutanes is facilitated by the presence of an oxygen bonded to the cyclopropyl at the allylic position. Treating vinylcyclopropanols (**85**) with a suitable electrophile or heating will furnish the corresponding cyclobutanone[36] (**86**) (Scheme 3.5.). However, with a slight modification, the reaction can be pushed towards cyclopentene type products. Hence, heating the TMS ether will give the intermediate TMS enol ether (**87**) which can be hydrolysed to the corresponding cyclopentanone[36b] (**88**).

Scheme 3.5. Rearrangements of vinylcyclopropanols (85).



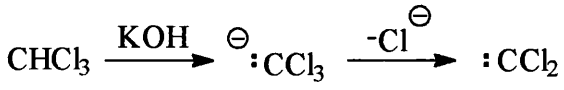
Isomerisations of vinylcyclopropanes do not necessarily require high temperature. One-electron oxidants such as $(p\text{-}BrC_6H_4)_3N^{\bullet+}SbF_6^-$ have been used to carry out *cis-trans* isomerisations[37] and the vinylcyclopropane-cyclopentene rearrangement at low temperatures.[38] Vinylcyclopropanes can also rearrange photochemically[39] as well as under thermal or chemical conditions.

It is clear that cyclopropanes, and in particular vinylcyclopropanes, are extremely useful and versatile synthetic intermediates but they are stable and appear in a number of natural products, including, of course, grimaldone (**72**).

3.2.2. Cyclopropyl/bicyclohexyl rings

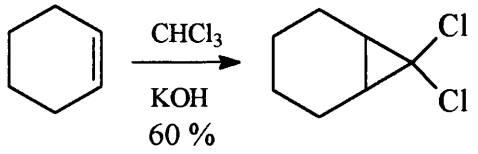
The [3.1.0]bicyclohexanone ring of grimaldone (**72**) will require construction of a cyclopropyl ring. The formation of cyclopropyl compounds is generally carried out using addition of a carbene or carbenoid to an alkene. One of the simplest methods of generating a carbene is to treat chloroform with a strong base such as potassium hydroxide. Chloroform (**89**) loses a proton under these conditions to give the trichloromethanide anion (**90**) which loses a chloride ion to generate dichlorocarbene (**91**) (Scheme 3.6.). If dichlorocarbene (**91**) is generated in the presence of an alkene then a cyclopropane ring is formed. Hence, cyclohexene (**92**) gives the bicyloheptane (**93**) in moderate yield (Scheme 3.7.). A phase transfer catalyst and a biphasic reaction medium are sometimes used but the yields are generally less than 70 % and the products from this type of reaction give di-halogenated cyclopropanes. Attempts to carry out the reaction with less halogenated starting materials such as dichloromethane results in no reaction or very low yields.

Scheme 3.6. Generation of dichlorocarbene.



(89) **(90)** **(91)**

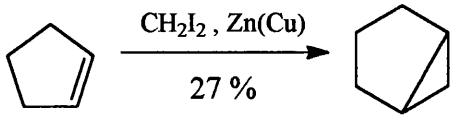
Scheme 3.7. Reaction of dichlorocarbene.



(92) **(93)**

The best method for generating non-halogenated cyclopropanes from alkenes is the Simmons-Smith reaction, first reported in 1958 by the DuPont workers whose names it now bears.[40] For instance, cyclopentene (**79**), methylene iodide and a zinc-copper couple are stirred at reflux in anhydrous ether for 48 hours to generate bicyclo[3.1.0]hexane (**94**) in low yield (Scheme 3.8.). The yields of the initial reactions were variable and usually not very high (typically less than 50 %) and the reaction times were usually quite long (15-70 hours).

Scheme 3.8. Simmons-Smith cyclopropanation of cyclopentene (79).



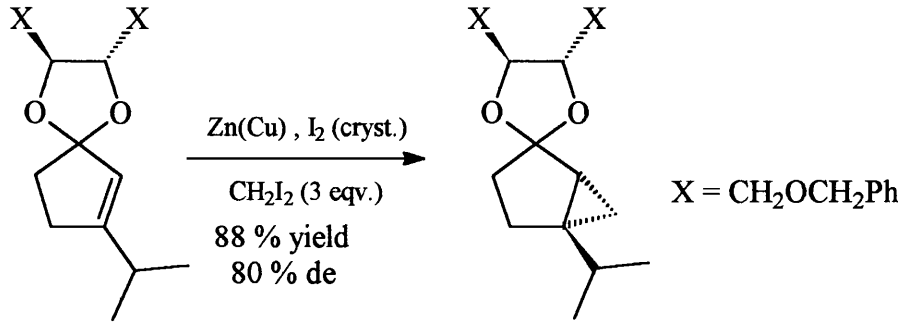
(79) **(94)**

However, great steps have been made in this type of chemistry since the early efforts. One of the earliest improvements was by Furukawa and co-workers[41] in 1966 where the insoluble zinc-copper couple was replaced by diethyl zinc, dramatically reducing reaction times. But, perhaps the most significant observation was the strong directing effect of allylic alcohols reported first in 1959 by Winstein and co-workers.[42] Since then a number of chiral auxiliaries have utilised the alcohol functionality to impart selectivity to the cyclopropanation.[43]

As well as allylic alcohols, α,β-unsaturated ketones have been used in the control of selectivity in Simmons-Smith cyclopropanations.[44,45] Selectivity is attained through protection of the ketone with a ketal possesssing the appropriate chirality.

Mash and Nelson[44] used 1,4-di-*O*-benzyl-L-threitol as the diol to make the ketals of α,β-unsaturated ketones. For example, 3-isopropyl-cyclopentenone was converted to its ketal (**95**) then cyclopropanated in high yield with reasonable selectivity (Scheme 3.9.). The ketal is easily installed and removed by the usual methods in high yield.

Scheme 3.9. Homochiral ketals in diastereoselective cyclopropanations.

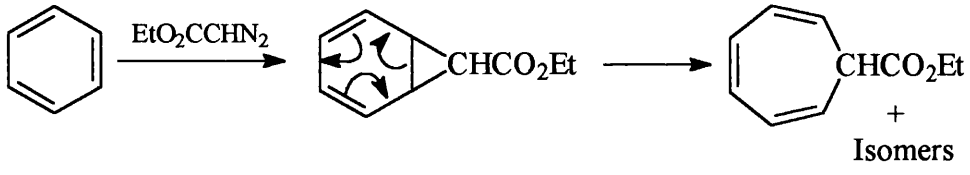


(95) **(96)**

The Simmons-Smith reaction has developed into a very powerful tool for the organic chemist with high yields and high selectivities. However, there are alternative carbeoid based-cyclopropanation reactions, which give higher selectivities.

Diazo compounds have been around for over a century and are probably the most widely used carbene precursors. The addition of ethoxycarbonylcarbene, generated by thermolysis of ethyl diazoacetate, to benzene is one of the oldest carbene reactions known (Scheme 3.10.). It was investigated by Curtius and Buchner[46] in 1885, and in 1896, the initial product was correctly assigned as the norcaradiene (**98**), although this readily rearranges to a mixture of cycloheptatrienyl esters (**99**).

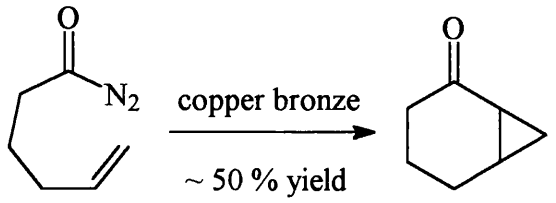
Scheme 3.10. Early carbene reactions.



(97) **(98)** **(99)**

Diazoketones have been used for considerable time for generating carbenes in order to carry out cyclopropanations. The first example of the use of a tethered diazoketone to perform an intramolecular cyclopropanation was in 1961.[47] The diazo ketone (**100**) was refluxed in cyclohexane in the presence of copper bronze to give bicyclo[4.1.0]heptan-2-one (**101**) in moderate yield (Scheme 3.11.).

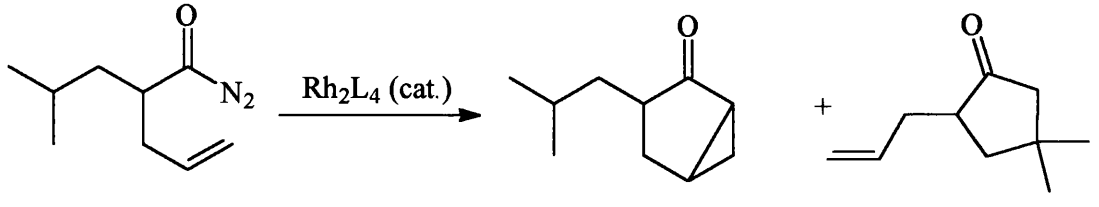
Scheme 3.11. First intramolecular cyclization of unsaturated diazoketone.



(100) **(101)**

Carbenes are also known to insert into C-H bonds, in particular tertiary C-H bonds. Therefore, if there is also a suitably placed C-H bond in the unsaturated diazoketone there exists the possible competition between C-H insertion and cyclopropanation. Padwa and co-workers[48] investigated this possibility (Scheme 3.12.) and obtained some remarkable results (Table 3.1.). They used a rhodium catalyst to catalyse the decomposition of the diazoketone and could switch totally between C-H insertion and cyclopropanation, by simply varying the ligand on the rhodium. The reason for this selectivity is not totally clear but is partially explained by the fact that the most electrophilic ligand (*per*fluorobutyrate) caused C-H insertion to be favoured over cyclopropanation.

Scheme 3.12. Rhodium catalysed unsaturated diazoketone cyclisations.



(102) **(103)** **(104)**

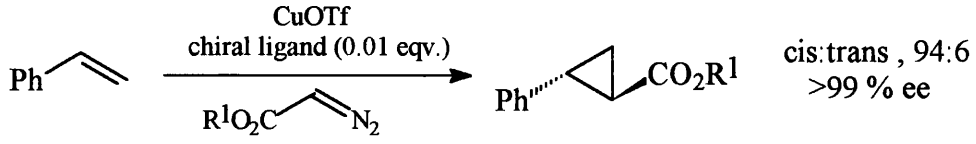
Table 3.1. Effects of ligands on reaction selectivity.

Ligand (L)	yield %	103	104
perfluorobutyrate	56	0	100
acetate	97	44	56
caprolactamate	76	100	0

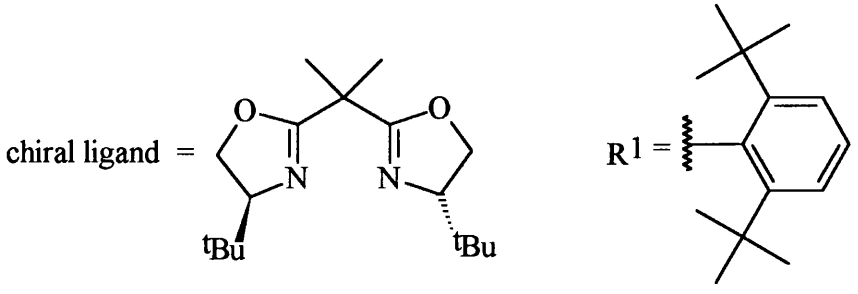
Stereoselectivity has been achieved in these rhodium-assisted cyclopropanations with

the use of various chiral auxiliaries.[49] However, the best selectivities have been obtained with copper-heterocyclic complexes.[50] Evans and co-workers used a bisoxazoline ligand (**107**) and a bulky group on the diazoester to effect excellent selectivity on the cyclopropanation of styrene (**105**) (Scheme 3.13.).[51]

Scheme 3.13. Bisoxazoline-copper catalysed stereoselective cyclopropanation.



(105) **(106)**

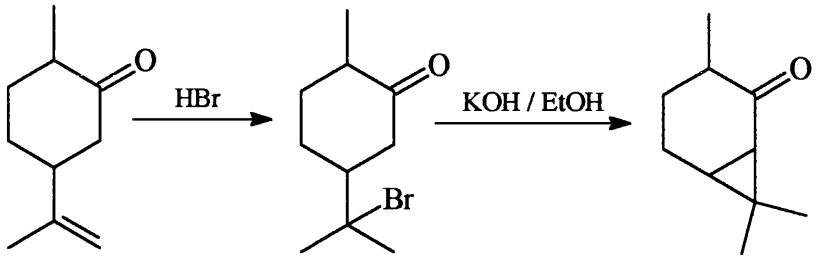


(107)

However, there are alternatives to the carbenoid based cyclopropanation chemistry. Simply generating a nucleophilic centre in the presence of a suitably placed electrophilic centre can generate a cyclopropyl ring.

Ketones with a leaving group in the γ position can form cyclopropanes under basic conditions.[52] The most common leaving groups used include bromides, chlorides and tosylates. This type of rearrangement is well known in natural product chemistry and has been around since the end of the 19th century. For example in 1894, Baeyer[9] synthesised carone (**110**) from dihydrocarvone (**108**) *via* an intermediate γ-bromo ketone (**109**) (Scheme 3.14.).

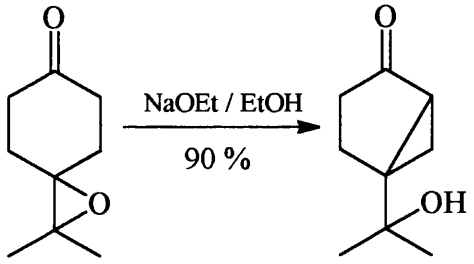
Scheme 3.14. Synthesis of a cyclopropane (110) from a γ-bromo ketone (109).



(108) **(109)** **(110)**

γ,δ-Epoxy ketones have also been used to good effect to form cyclopropyl compounds (Scheme 3.15.).[53] The advantage of this approach is the ready availability of the epoxide from the corresponding alkene and the formation of a new functional group.

Scheme 3.15. Synthesis of a cyclopropane (112) from a γ,δ-epoxy ketone (111).



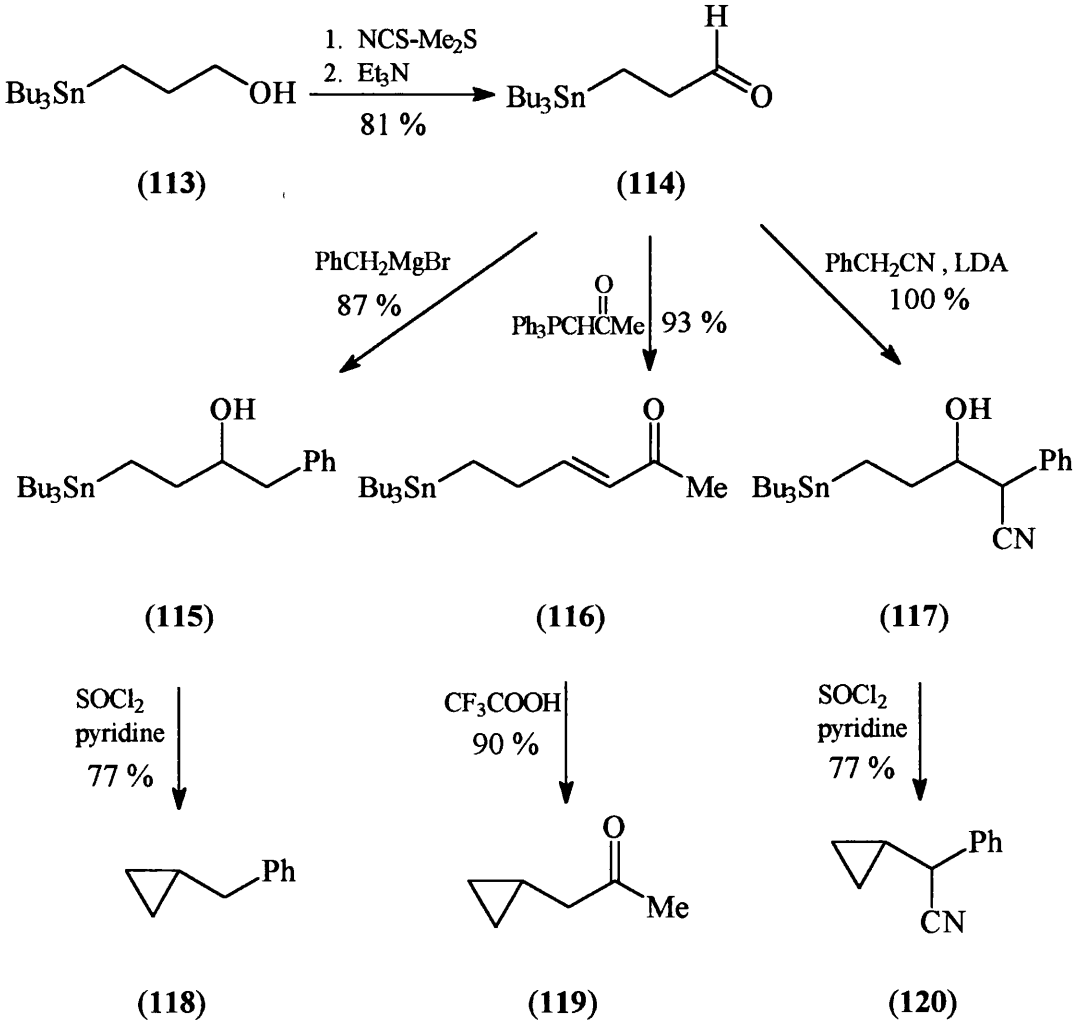
(111) **(112)**

However, there exists the possibility of the reverse of this protocol. Instead of generating a nucleophile (enolate) in the presence of an electrophile (tosylate, halide, epoxide), it should be possible to generate an electrophile (cation) in the presence of a nucleophile (organometallic) to obtain similar results.

β-Stannyl propionaldehyde (**114**) was developed as useful precursor for cyclopropanes.[54] Oxidation of the easily accessible[55] 3-tributylstannyl propanol (**113**) provides β-stannyl propionaldehyde (**114**) which can be converted to a number of useful cyclopropyl precursors (Scheme 3.16.). The aldehyde (**114**) can be converted to alkenes (**116**) *via* Wittig methodology or attacked with nucleophiles, such as Grignards to form the alcohol (**115**). Simply treating the homoallylstannane (**116**) with trifluoroacetic acid overnight gives the cyclopropane (**119**) in high yield.

Similarly, stirring the alcohols (**115** and **117**) with thionyl chloride/pyridine overnight yielded the corresponding cyclopropanes (**118** and **120**, respectively) in good yield. The most likely mode of action is formation of a carbocation at the γ position followed by destannylation. Fleming and Urch[56] showed that the reaction for the stannyl alcohols proceeds with inversion of configuration at the alcohol and stannyl centres.

Scheme 3.16. The use of stannyl compounds for the synthesis of cyclopropanes.



3.2.3. Cyclopentyl rings.

The synthesis of grimaldone (**72**) requires the construction of a cyclopentyl ring. One of the most common and oldest strategies for generating cyclopentyl rings is the intramolecular condensation of a 1,4 diketone to give the corresponding

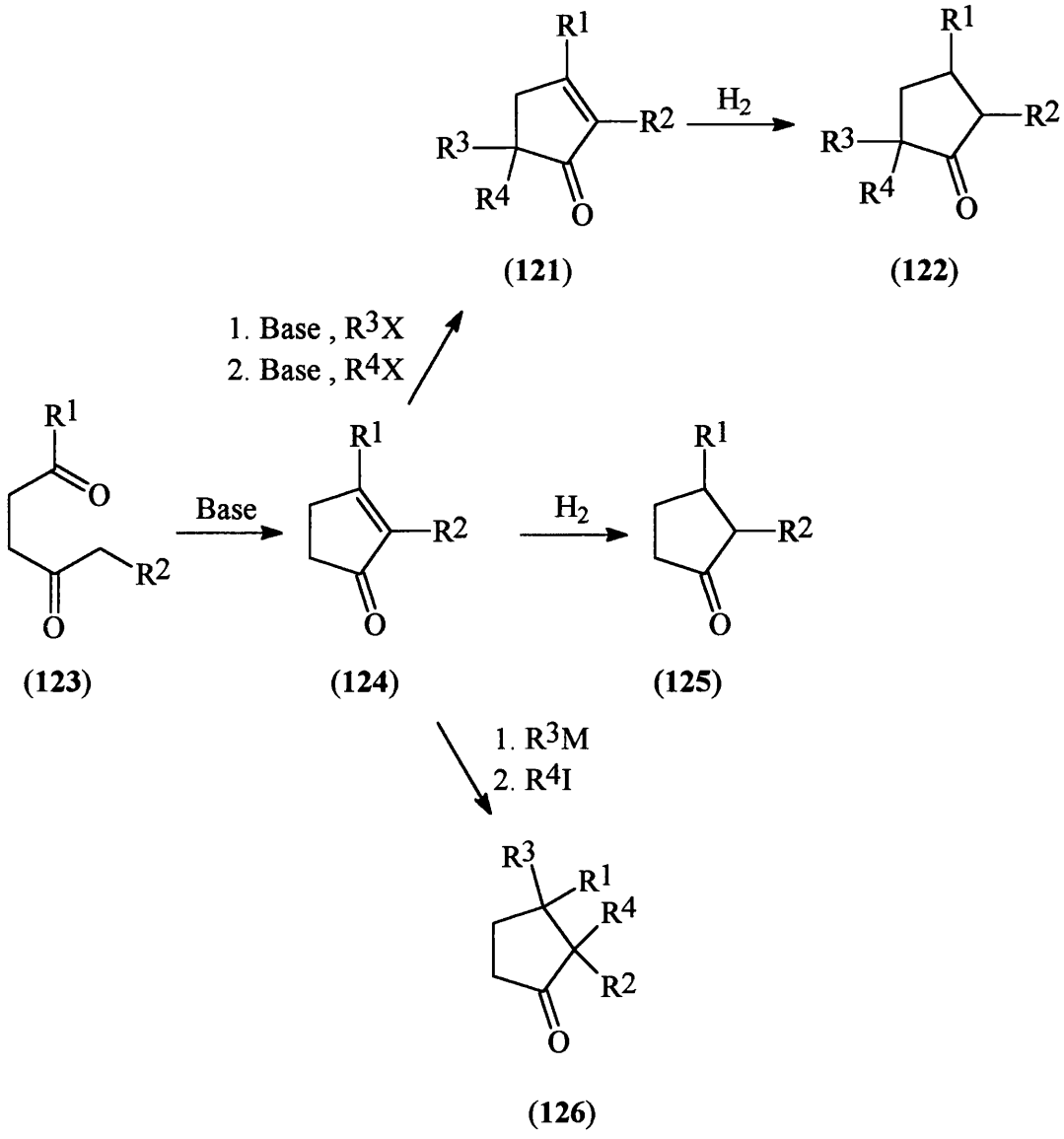
cyclopentenone. If one side of the diketone (**123**) has a group containing no enolisable protons then a single product (**124**) can be obtained. This type of cyclisation has been well documented in jasmonoid syntheses.[57]

The resulting cyclopentenone (**124**) can form the basis of a number of cyclopentanones with different alkyl substitution patterns. A few simple strategies are shown in Scheme 3.17. The cyclopentanone (**125**) can then be generated by hydrogenation. The double bond can be used to advantage by allowing alkylation of one side of the ketone before reducing back to the cyclopentanone (**122**). Addition of organometallic reagents such as cuprates to the enone system is also possible. Quenching the intermediate enolate with electrophiles such as alkyl iodides can introduce further substituents to the cyclopentanone (**126**).

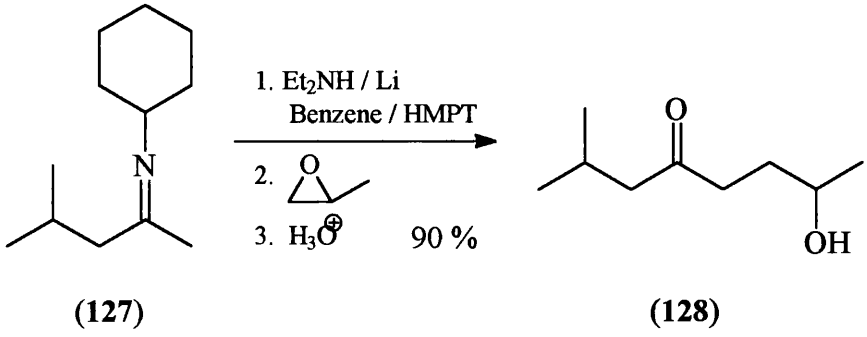
It is clear that the intramolecular cyclisation of diketones can open a wealth of synthetic possibilities. However, this does rely on a successful synthetic route to the corresponding diketones being available.

A fairly direct route to 1,4 diketones would be the opening of an epoxide with an enolate, followed by oxidation of the alcohol. Unfortunately, enolates themselves are not nucleophilic enough, but the anion of the corresponding imine is. Hence the lithiated anion of the imine (**127**) derived from *sec*-butylmethyl ketone was utilised to open propylene oxide specifically at the least hindered site to give the γ-hydroxy ketone (**128**) in high yield (Scheme 3.18.).[58] The diketone can then be generated by any number of oxidative methods.

Scheme 3.17 Generation of different cyclopentanone alkyl substitution patterns.



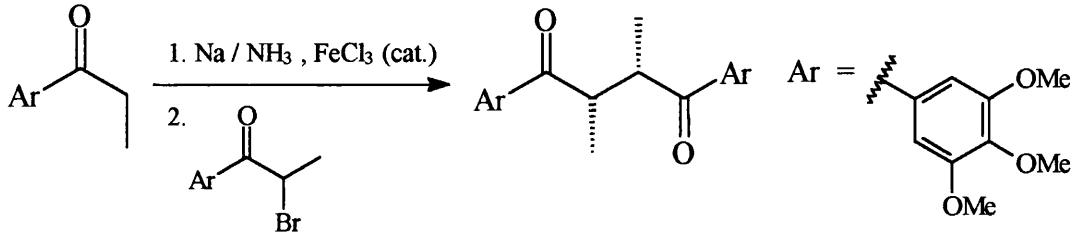
Scheme 3.18. Epoxide opening with α-lithiated imine anions.



The drawback of this approach and others which rely on increasing the nucleophilicity of the enolate, for example by converting the ketone to the oxime[59] or

hydrazone,[60] is that they incur extra (albeit high yielding) steps in the synthetic route. A more direct approach is to use the enolate to attack an α-bromoketone.[61] 3,4,5-Trimethoxypropiophenone (**129**) was thus alkylated with the α-bromoketone (**130**) to yield the racemic 1,4 diketone (**131**) in high yield (Scheme 3.19.).

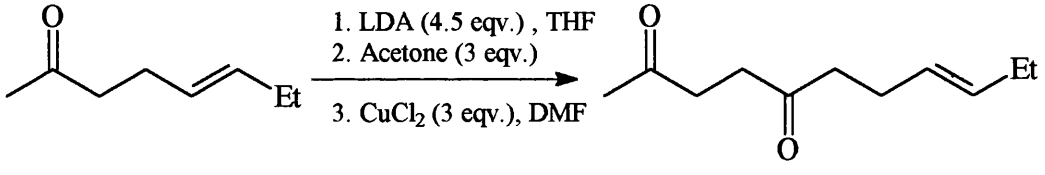
Scheme 3.19. Alkylation of enolates with α-bromoketones.



(**129**) (**130**) (**131**)

Enolates themselves can be oxidatively coupled with copper chloride.[62] The coupling tends to be fairly specific to the least hindered enolates, hence methyl enolates will couple preferentially. Obviously, this works best with one ketone to produce symmetrical diketones. Using two different ketones will inevitably produce a complex mixture of diketones. However using one ketone in excess can drive the reaction to form a specific unsymmetrical ketone. Using three equivalents of acetone to one oct-5-en-2-one (**132**) resulted in formation of undecan-2,5-dione (**133**) in moderate yield (Scheme 3.20.).

Scheme 3.20. Oxidative cross-coupling of enolates with copper chloride.

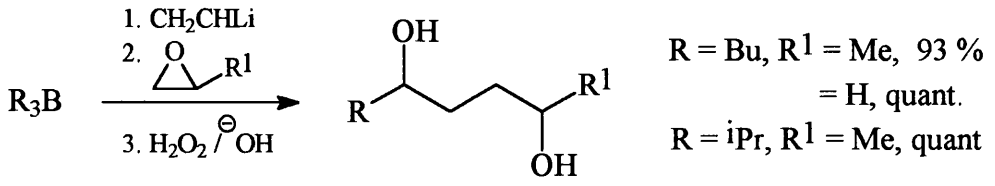


(**132**) (**133**) 68 %

Although the synthesis of 1,4-diols might seem to be a step back, they can be produced relatively easily *via* lithium trialkylvinylborates (Scheme 3.21.).[63] Trialkyl boranes (**134**) can react with vinyllithium to give the trialkylvinylboranate (**136**) which can attack an epoxide to form an oxaborinane (**137**) (Scheme 3.22.). Oxidative

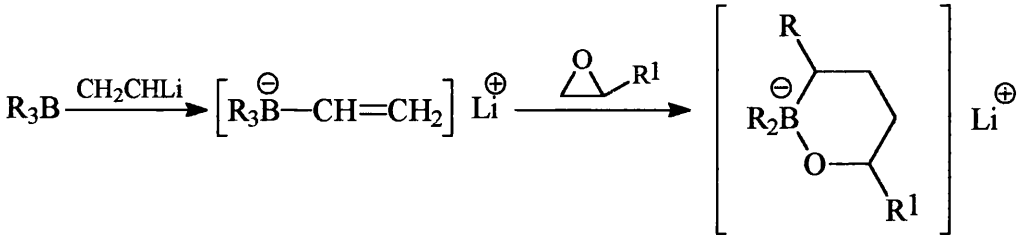
work-up furnishes the diol (**135**) in excellent yields. The diol can then be converted to the required diketone by a number of oxidative methods.

Scheme 3.21. Preparation of 1,4-diols using boranes.



(134) **(135)**

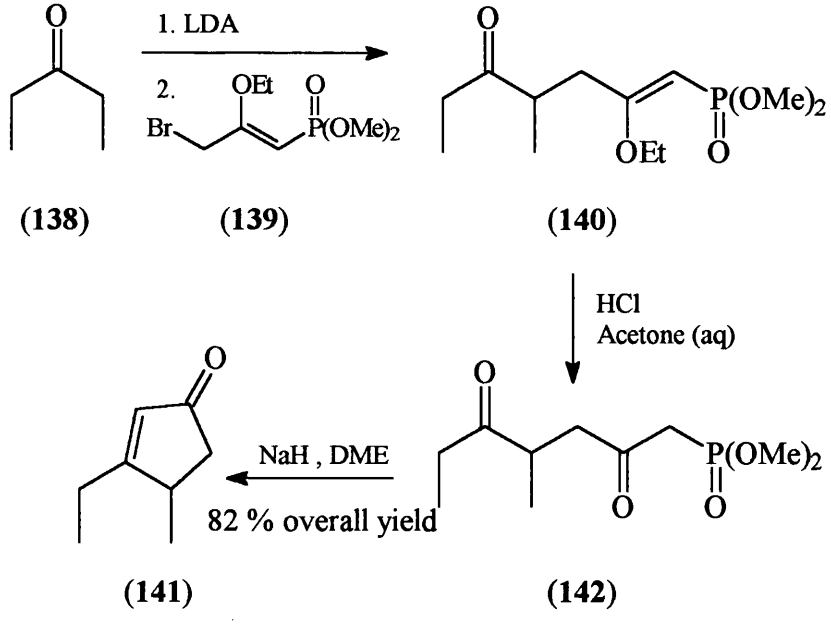
Scheme 3.22. Intermediate species in the preparation of 1,4-diols using boranes.



(134) **(136)** **(137)**

There are alternatives to the 1,4-diketone approach to cyclopentenone synthesis. The use of intramolecular Wittig reactions can provide a direct route to cyclopentenones.[64] The Wittig reagent is appended to the ketone *via* attack of the enolate on dimethyl 3-bromo-2-ethoxypropenylphosphonate (**139**) in quantitative yield (Scheme 3.23.). Hydrolysis of the enol ether (**140**) proceeds in quantitative yield to give the diketophosphonate (**142**). Treatment of the diketophosphonate (**142**) with sodium hydride induces the intramolecular Wittig to give the cyclopentenone (**141**) in very good overall yield.

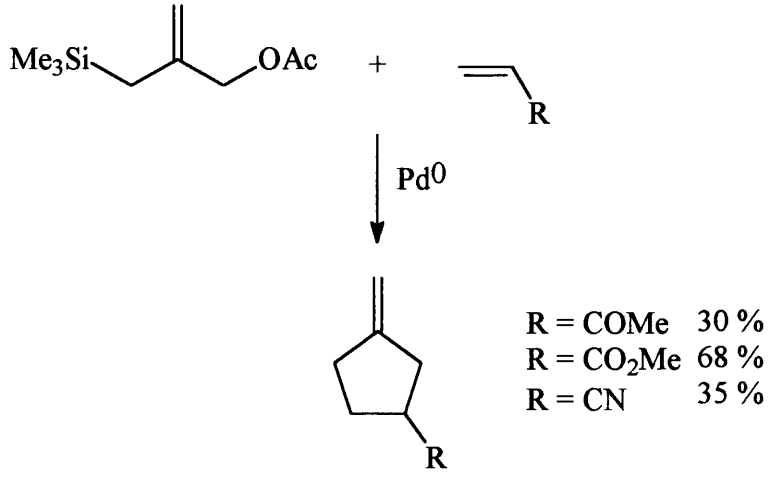
Scheme 3.23. Cyclopentenone synthesis *via* an intramolecular Wittig reaction.



(138) **(139)** **(140)** **(141)** **(142)**

Cyclopentyl systems can also be synthesised by [3+2] cycloadditon. This reaction couples a three-carbon 4π unit directly with a two-carbon 2π unit, forming two C-C bonds in one operation, analagous to the [4+2] Diels-Alder reaction. Trost and co-workers have developed a suitable precursor to a three-carbon 4π unit.[65] A wide range of alkenes has shown to react in generally good yield[66] (Scheme 3.24.).

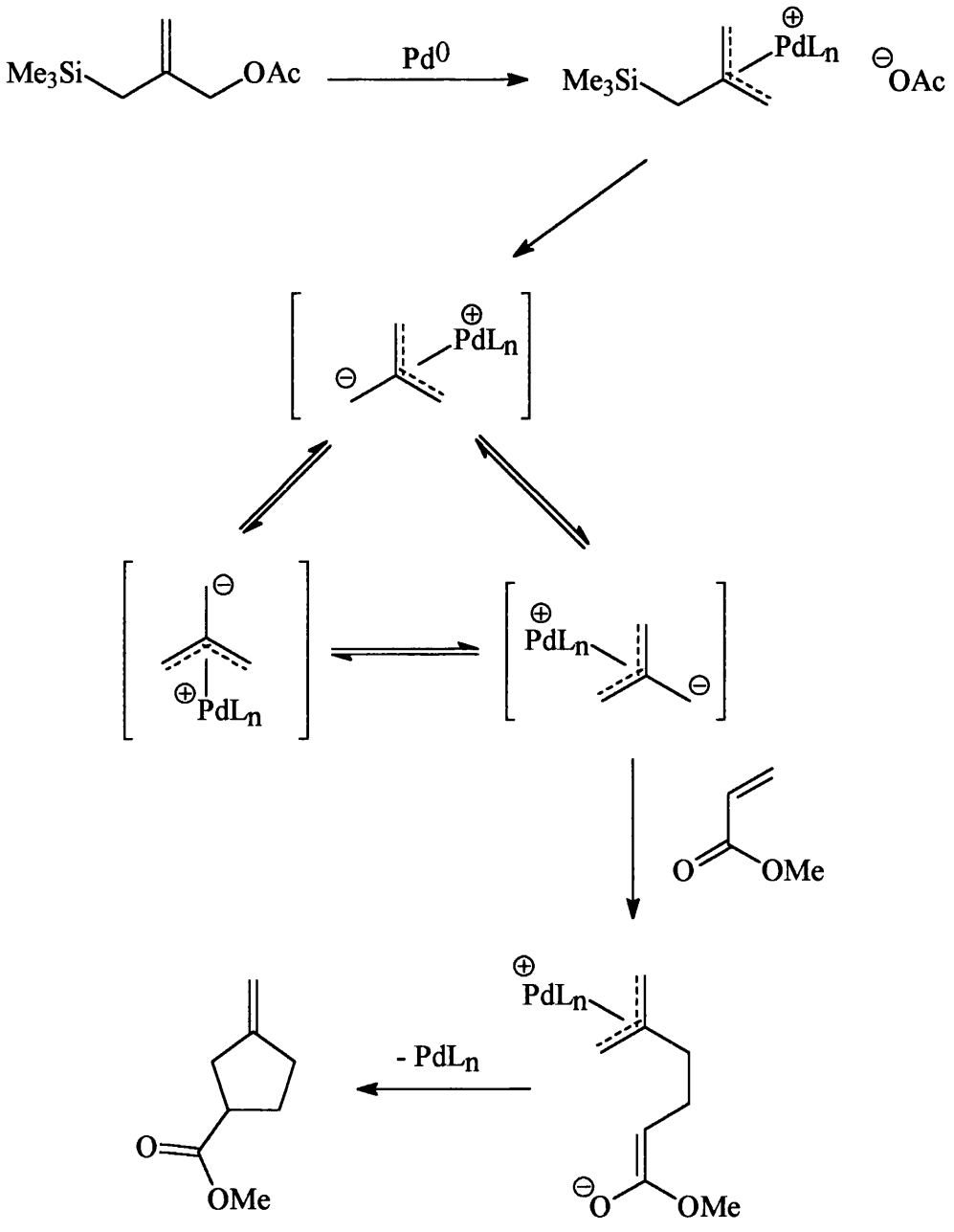
Scheme 3.24



It is noteworthy that the examples given all have electron withdrawing groups on the alkene. As can be seen with the mechanism[67] (Scheme 3.25.) it is vital for the alkene

to have such a group so that the trimethylenemethane-Pd intermediate can attack the alkene Michael style, to give the stabilised anion which then undergoes ring closure to form the product and regenerate the palladium species.

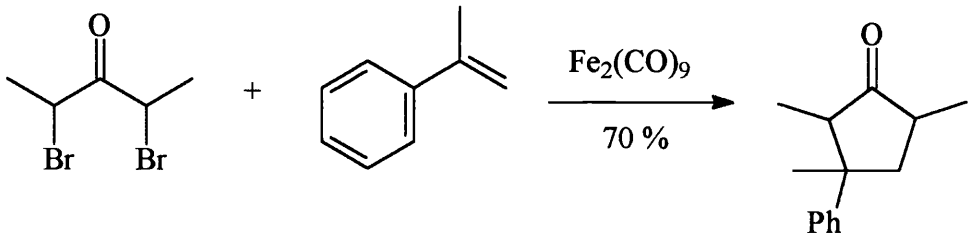
Scheme 3.25. Proposed mechanism.



Cyclopentyls can also be formed by coupling a 3-carbon 2π unit with a 2-carbon 2π forming two new bonds. Oxyallyls generated from complexation of dibromoketones with iron carbonyls can provide a very good source of the 3 carbon 2π unit.[68]

For example 2,4-dibromo-pentan-3-one (**143**) reacted with α-methyl styrene (**144**) in the presence of $Fe_2(CO)_9$ to form a cyclopentanone (**145**) adduct in good yield as a mixture of *cis* and *trans* diastereomers (Scheme 3.26.).[69]

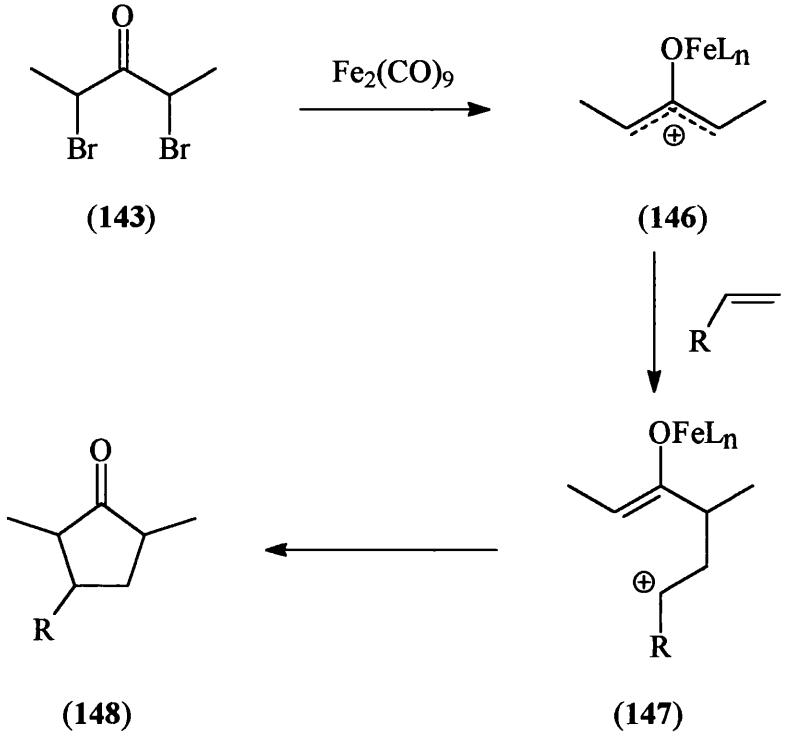
Scheme 3.26.



(143 **(144)** **(145)**

The reaction proceeds via the oxyallyl species (**146**) formed from the treatment of the dibromo (**143**) compound with diiron nonacarbonyl as depicted in Scheme 3.27.[70] The reaction proceeds in a stepwise manner with the formation of the cationic intermediate (**147**), then collapse of the iron enolate to give the product (**148**).

Scheme 3.27. Proposed mechanism.

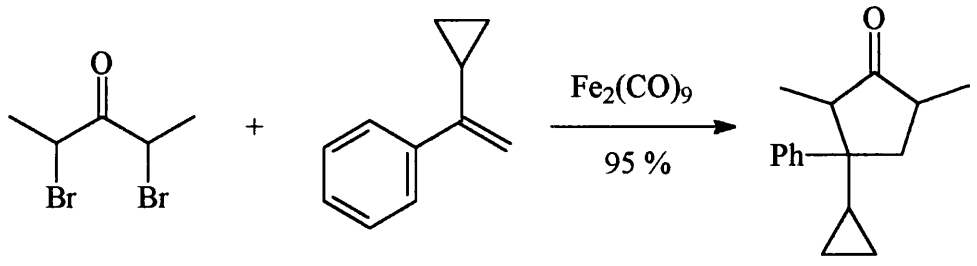


(143) **(146)** **(147)** **(148)**

This reaction proceeds only with electron rich alkenes, presumably because of the

requirement for stabilisation of the intermediate cation (**147**). Indeed the reaction proceeds in excellent yield with α-cyclopropylstyrene (**149**) to form the cyclopentanone (**150**) (Scheme 3.28.). Cyclopropyl compounds are well known for their ability to stabilise electron-deficient centres[28] as are phenyl groups.

Scheme 3.28.



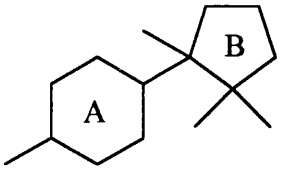
(143) **(149)** **(150)**

3.2.4. Similar molecules.

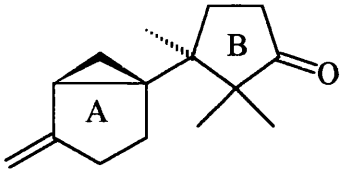
Most natural sesquiterpenoids with the cuparane skeleton[71] (**151**) have two rings (a cyclopentyl ring joined to a cyclohexyl or toluene residue) such as cuparene (**153**), α-cuparenone (**73**) and cuprenenol (**154**) (Scheme 3.29.). Two exceptions are grimaldone[25] (**72**) and microbiotol[72] (**152**) which share the same tricylic skeleton[a] (Scheme 3.29.). A.V. Tkachev and co-workers[72] claimed that the structure of microbiotol (**152**) represented a new type of carbon skeleton. However, the isolation of the enantiomer of microbiotol had been reported by Asakawa and co-workers[73] seven years previously.

[a] As discussed previously the absolute stereochemistry of a liverwort natural product (e.g. grimaldone (**72**) from *Mannia fragrans*) is often opposite to that of a similar natural product isolated from a higher plant (e.g. microbiotol (**152**) from the evergreen bush *Microbiota decussata*).

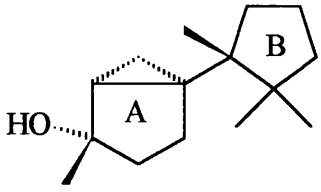
Scheme 3.29. Sesquiterpenoids with cuparane skeleton (151).



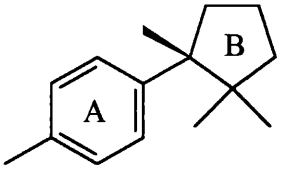
cuparane skeleton (**151**)



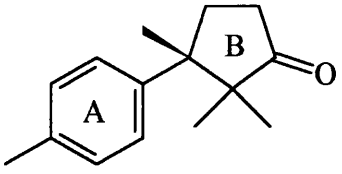
grimaldone (**72**)



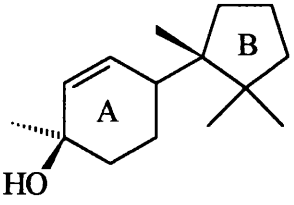
microbiotol (**152**)



cuparene (**153**)



α-cuparenone (**73**)

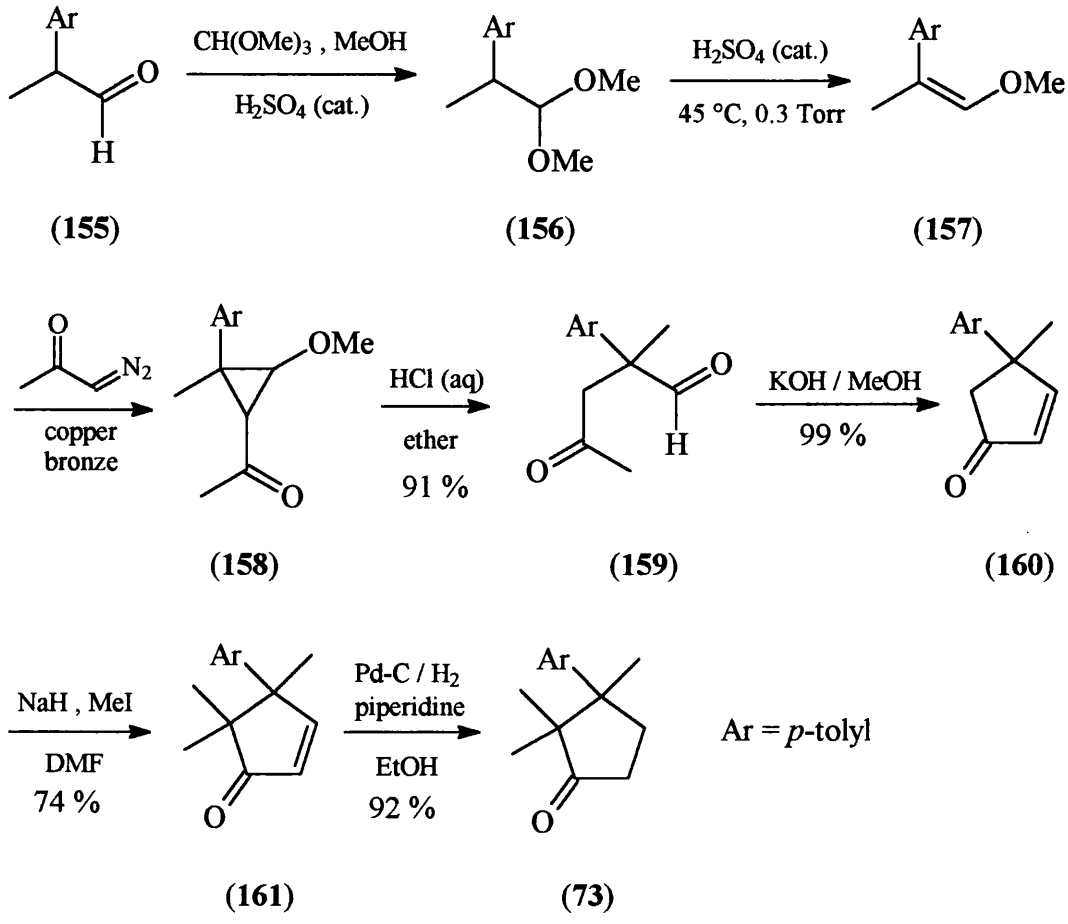


cuprenenol (**154**)

Hence, the majority of cuparane type syntheses have been of the bicyclic type, particularly directed towards α-cuparenone (**73**).

An interesting synthesis of α-cuparenone (**73**) is from the acid catalysed rearrangement of an oxycyclopropane (**158**) (Scheme 3.30.).[74] The starting material (**155**) for the synthetic route is obtained from the chromyl chloride oxidation of *p*-cymene in low yield. The rearrangement of the oxycyclopropane (**158**) proceeds *via* initial protonation of the carbonyl which pulls the electrons from the ether through the cyclopropane carbon network to break the ring. Hydrolysis then gives the keto/aldehyde (**159**). The remainder of the synthesis is fairly routine with the alkene moiety being retained until the final step to allow dimethylation of the cyclopentyl ring at the appropriate position.

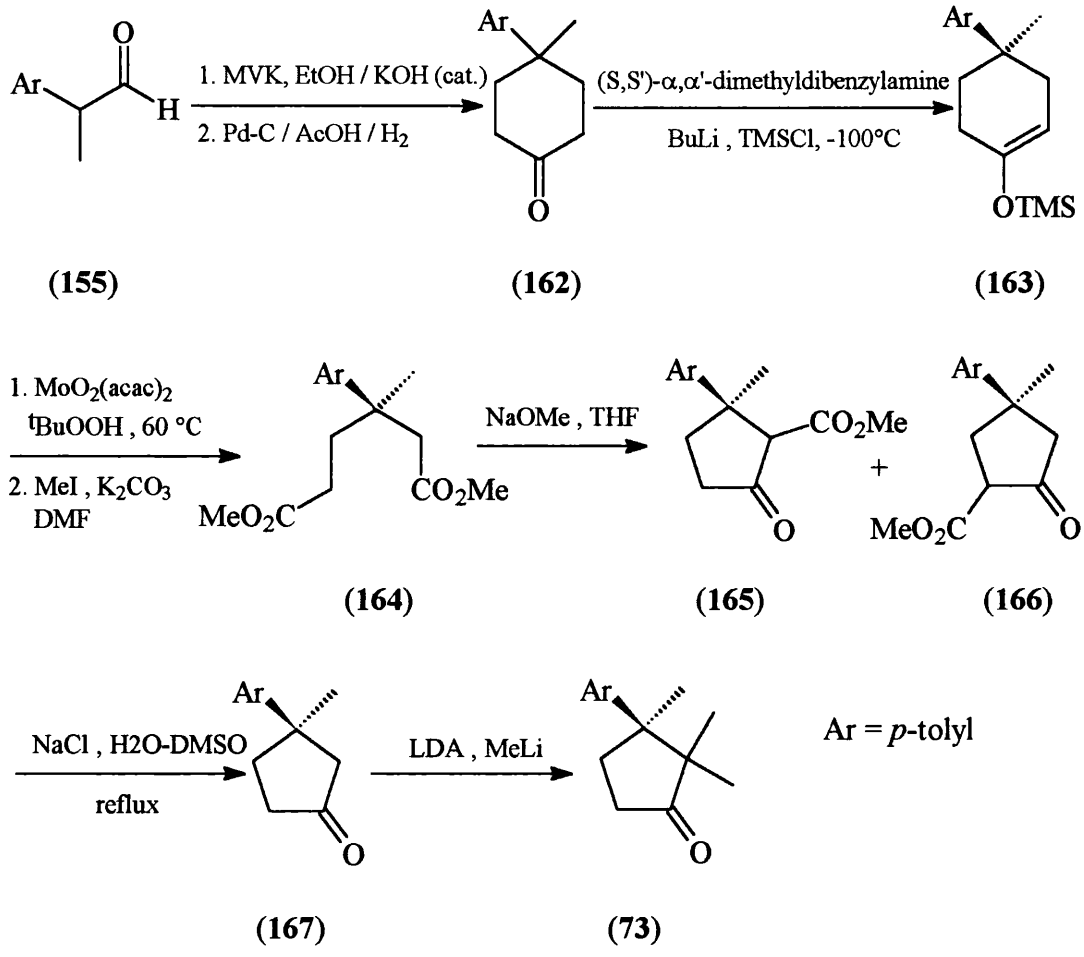
Scheme 3.30. α-Cuparenone (73) *via* acid-catalysed rearrangement of an oxycyclopropane (158).



Utilising the same aldehyde (**155**) Honda and co-workers[75] synthesised α-cuparenone (**73**) enantioselectively (Scheme 3.31.). The key step was the enantioselective deprotonation of the intermediate cyclohexanone (**162**) with a chiral base. This allowed formation of the silyl enol ether (**163**) as a single enantiomer. Oxidative cleavage of the silyl enol ether followed by esterification yielded the dimethyl diester (**164**). Condensation of the diester gave a mixture of two regioisomeric β-keto esters (**165**) and (**166**). Removal of the ester group gave the cyclopentanone (**167**) which was dimethylated to give the product (**73**).

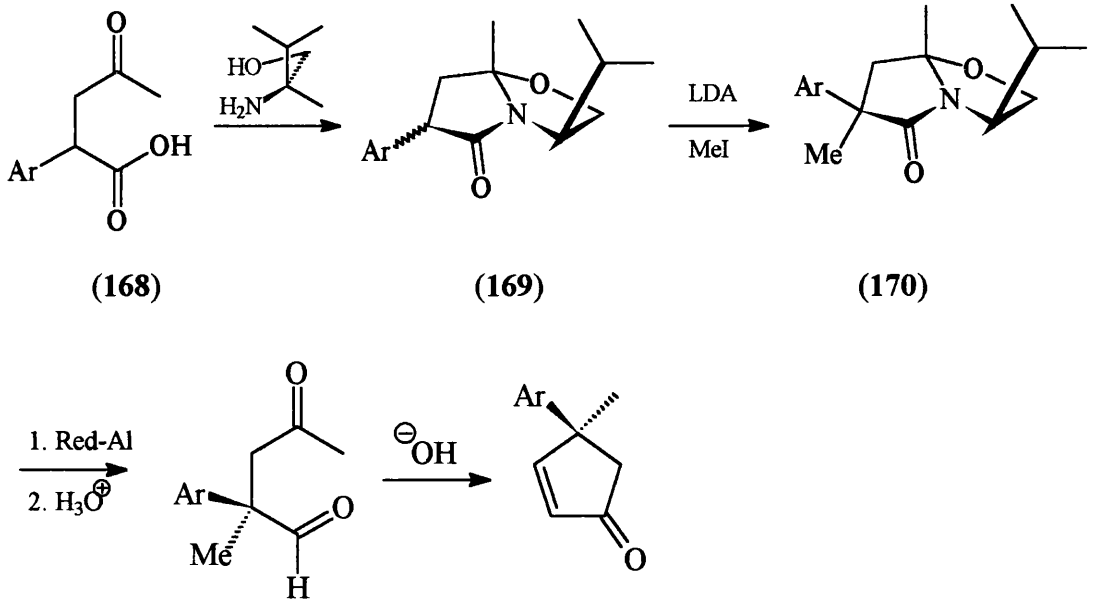
This final step appears to alkylate in the most sterically demanding position. However, the lithium enolate preferentially forms at the side nearest the aryl ring. It has been postulated that the π electrons of the aryl group coordinate to the lithium thereby directing enolate formation.[76]

Scheme 3.31. Stereoselective synthesis of α-cuparenone (73) *via* enantioselective deprotonation.



Schwarz and Meyers[77] achieved diastereoselective deprotonation of a bicyclic lactam (**169**) to allow the methylation necessary to set up the chirality in α-cuparenone (Scheme 3.32.). The bicyclic methylated bicyclic lactam (**170**) was partially reduced then hydrolysed to give the keto-aldehyde (**159a**) as a single enantiomer. This was cyclised to give the enone (**160a**) which was dimethylated as described previously (Scheme 3.30.) to give α-cuparenone as a single enantiomer.

Scheme 3.32. Enantioselective deprotonation using a chiral bicyclic lactam.



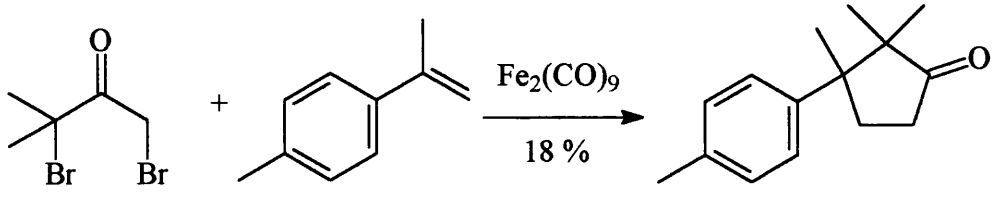
(168) **(169)** **(170)**

(159a) **(160a)**

51 % yield from **168**

However, racemic α-cuparenone (**73**) can be synthesised in fewer steps although in low yield. Noyori and Hayakawa[78] used an iron carbonyl oxyallyl approach to generate α-cuparenone (**73**) in 18 % yield from the dimethylstyrene (**172**) (Scheme 3.33.).

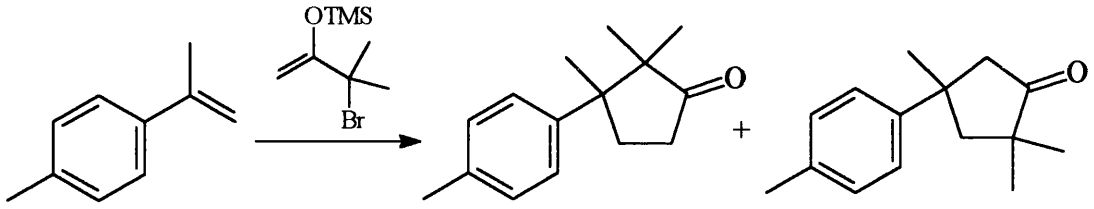
Scheme 3.33. α-Cuparenone (73) *via* an iron oxyallyl cation.



(171) **(172)** **(73)**

Sakurai[79] and co-workers used a silyl enol ether as the basis for an oxyallyl cation to synthesis a mixture of α-cuparenone (**73**) and β-cuparenone (**173**) (Scheme 3.34.).

Scheme 3.34. α-Cuparenone (73) *via* a silyl oxyallyl cation.



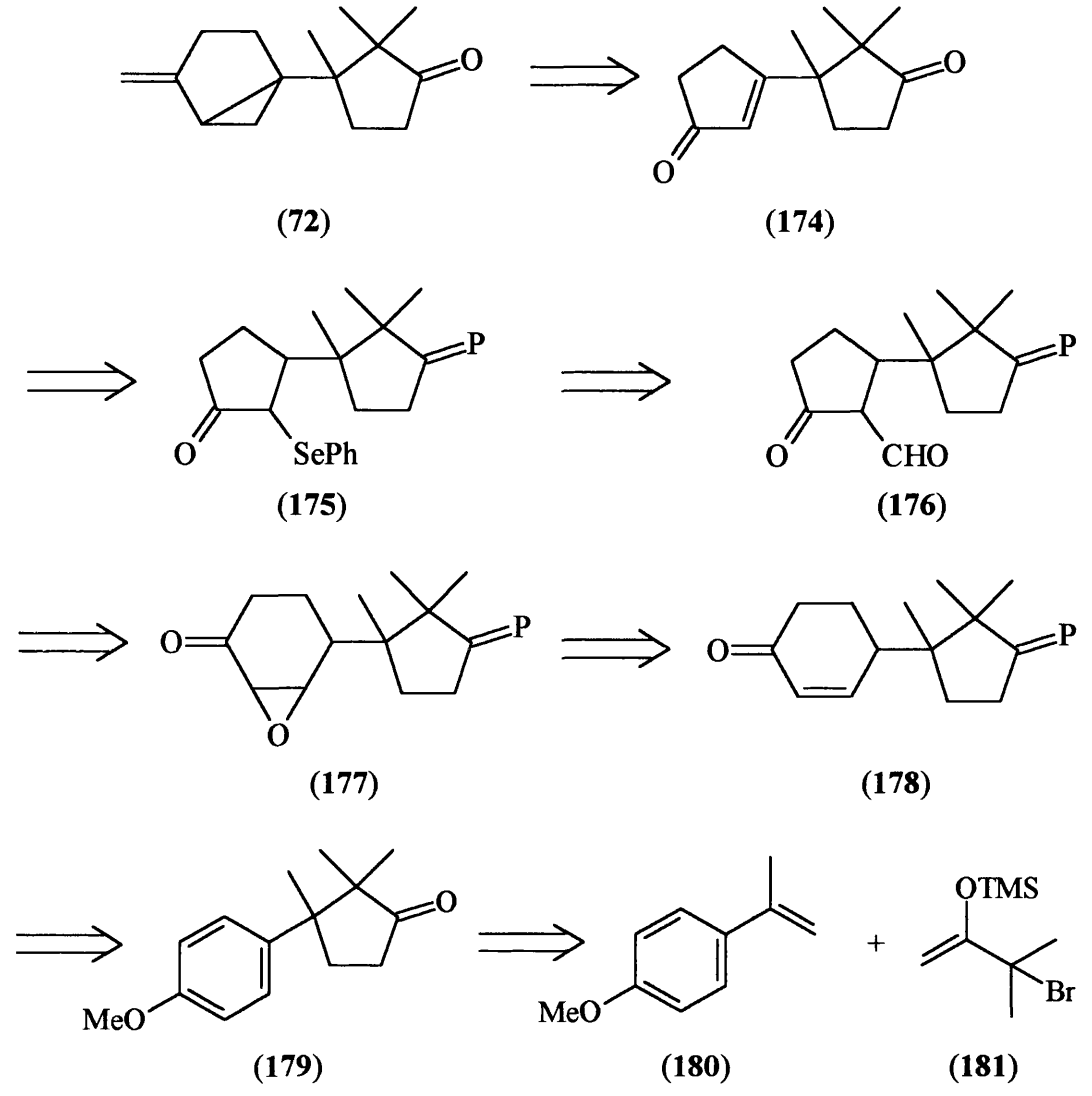
(172) (73) 27 % (173) 16 %

3.3. Previous attempts.

A synthesis of racemic grimaldone has been attempted previously by Calderwood.[70] His initial retrosynthetic analysis is shown in Scheme 3.35.. He envisaged endione (**174**) as a late intermediate. Elaboration of the enedione (**174**) by any of the previously discussed 'carbene-based' cyclopropanation procedures, followed by Wittig olefination could provide the target molecule (**72**). The enedione (**174**) could be achieved from α-formyl-cyclopentanone (**176**) *via* phenylselenylation,[80] deformylation and selenoxide elimination. The cyclopentanone (**176**) could be obtained from α,β enone (**178**) *via* epoxidation,[81] and acid catalysed 1,2-carbonyl migration.[82,83] Enone (**178**) could arise from the arylcyclopentanone (**179**) *via* carbonyl protection, Birch reduction and enol ether hydrolysis. The arylcyclopentanone (**179**) would be obtained from alkene (**180**) and silyl enol ether (**181**) in a cycloaddition employing the conditions of Sakurai.[79]

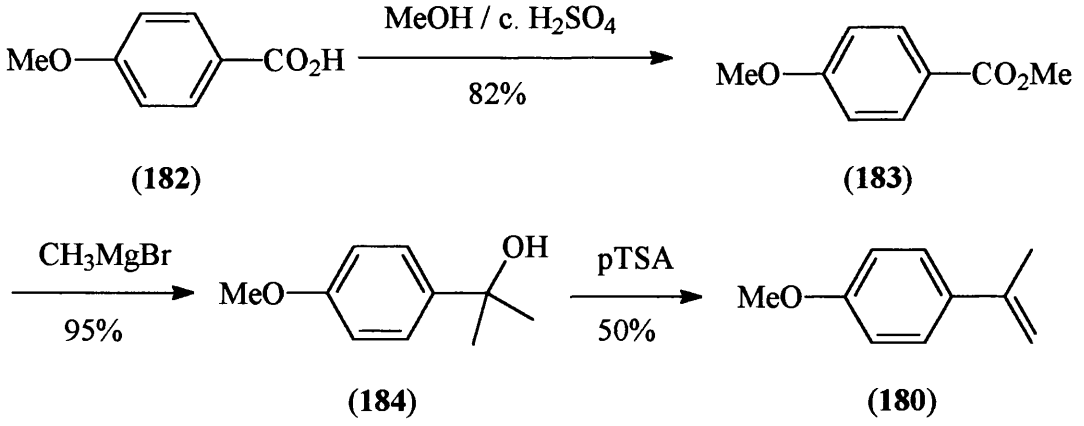
The required alkene (**180**) was prepared from *p*-anisic acid (**182**) (Scheme 3.36.). The acid (**182**) was initially transformed into the methyl ester (**183**), then to the tertiary alcohol (**184**) *via* Grignard addition. Slow distillation from *p*-toluene sulphonic acid yielded the desired starting material (**180**).

Scheme 3.35. Calderwood's initial retrosynthetic analysis.



(72) (174) (175) (176) (177) (178) (179) (180) (181)

Scheme 3.36. Synthesis of *p*-isopropenylanisole (180).

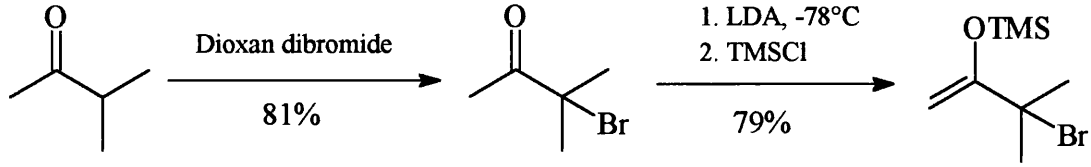


(182) (183) (184) (180)

The silyl enol ether (**181**) was prepared from 3-methylbutan-2-one (**185**) in two

simple steps (Scheme 3.37.). Bromination of 3-methylbutan-2-one (**185**) with dioxan dibromide gave α-bromo ketone (**186**) in good yield. The silyl enol ether (**181**) was then simply formed *via* trimethylsilyl chloride quenching of the pre-formed enolate of **186**.

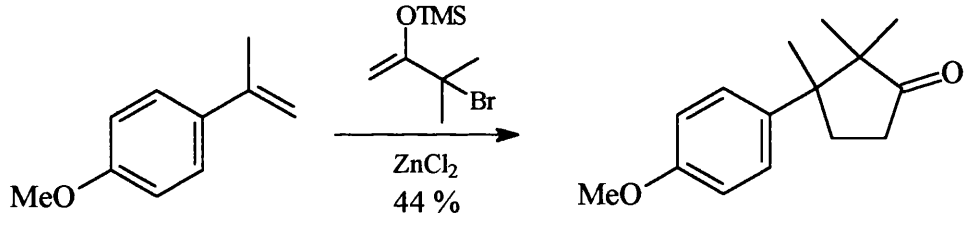
Scheme 3.37. Synthesis of silyl enol ether (181).



(185) **(186)** **(181)**

Using the conditions of Sakurai[79] the silyl enol ether (**181**) and alkene (**180**) were coupled together to give cyclopentanone (**179**) (Scheme 3.38).

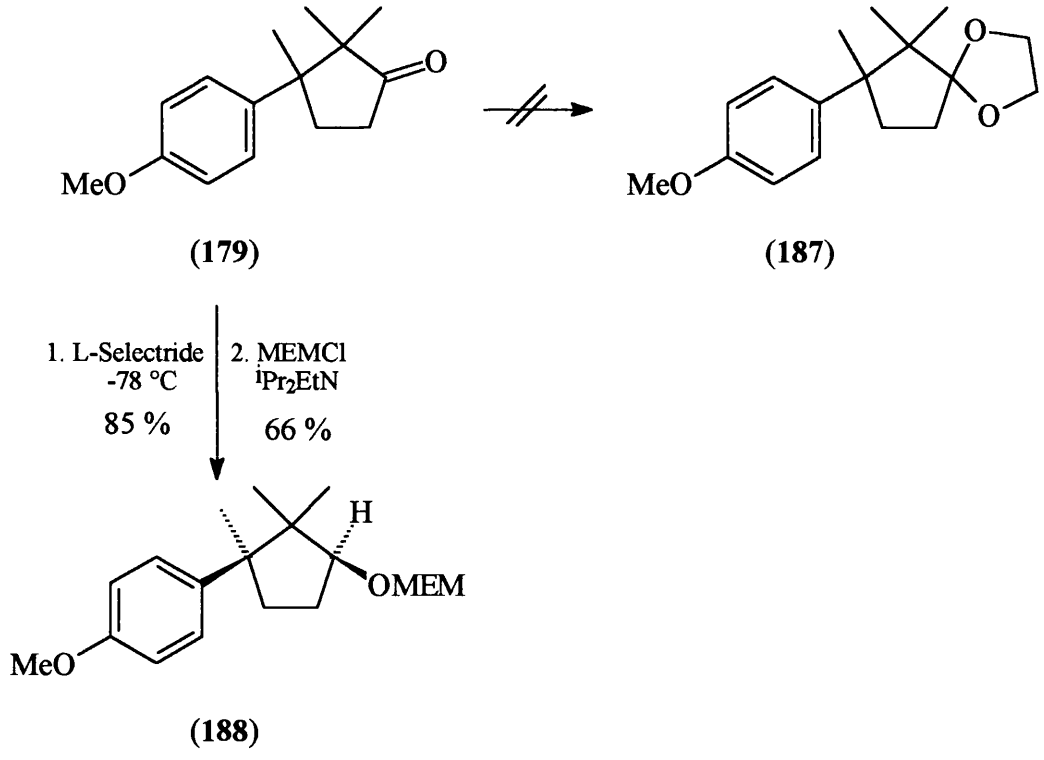
Scheme 3.38. Sakurai coupling.



(180) **(179)**

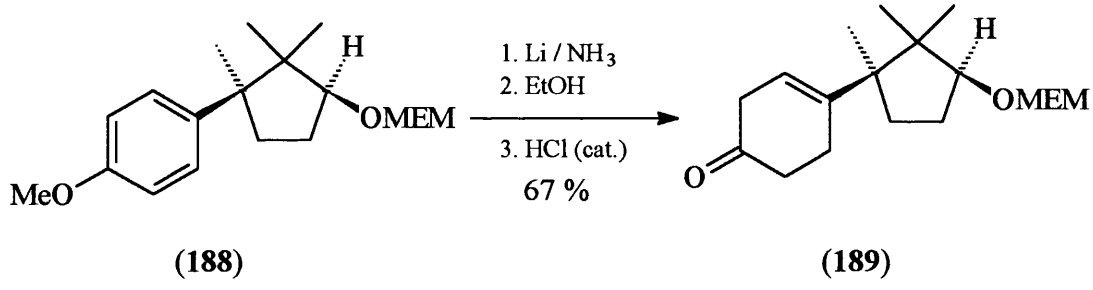
Attempts to protect the ketone (**179**) as its ketal (**187**) failed under a number of conditions. Calderwood decide to reduce the ketone (**179**) and protect as the alcohol (Scheme 3.39.). For characterisation purposes lithium-tri-*sec*-butyl borohydride (L-Selectride) was used to give one alcohol diastereoselectively (15:2). The alcohol was protected as its MEM ether (**188**).

Scheme 3.39. Protection of cyclopentanone (179).



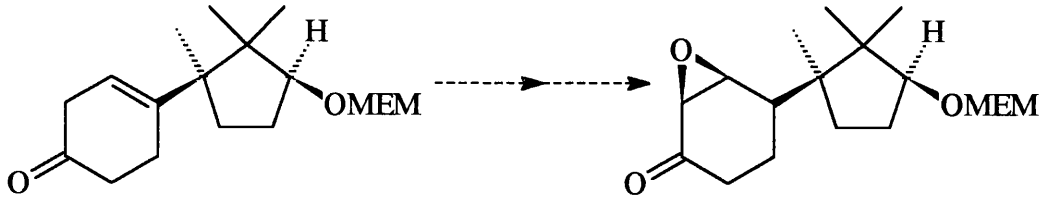
MEM ether (**188**) was then subjected to Birch reduction using the method of Wilds and Nelson,[84] followed by hydrolysis of the enol ether to give β,γ-unsaturated ketone (**189**) (Scheme 3.40.)

Scheme 3.40. Synthesis of cyclohexenone (189).



β,γ-unsaturated ketone (**189**) was to be isomerised to the α,β-unsaturated ketone and epoxidised to give the αβ-epoxy ketone (**190**) (Scheme 3.41.). At this stage, however, with a limited supply of (**189**) available Calderwood decided to undertake some model studies.

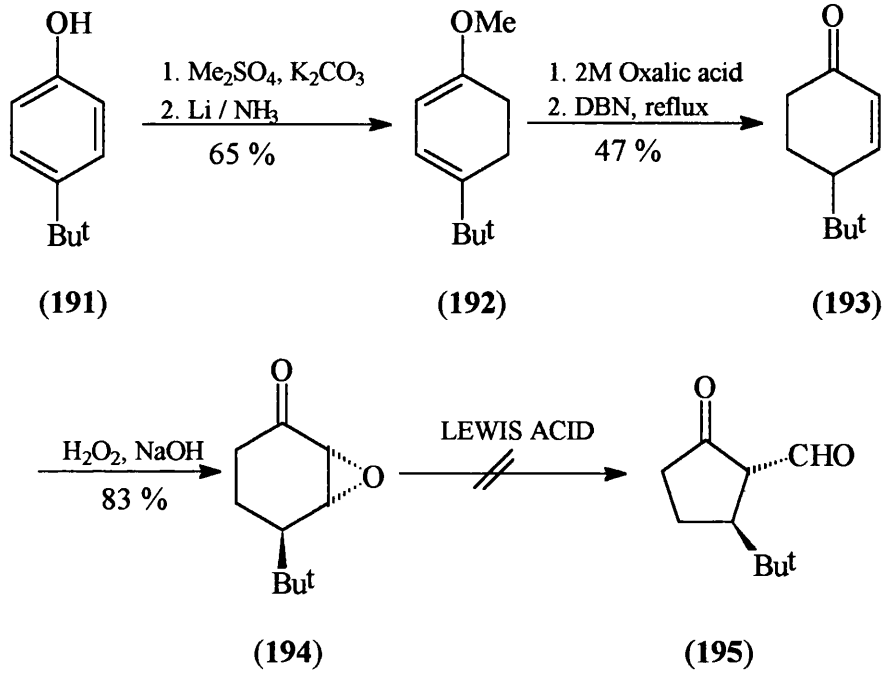
Scheme 3.41.



(189) **(190)**

α,β-Epoxy ketone (**194**) was chosen as a suitable model for compound **190** and was prepared easily from *p-tert*-butylphenol (**191**) (Scheme 3.42.). Unfortunately the subsequent Lewis acid mediated ring contraction to produce α-formyl pentanone (**195**) failed under a number of conditions.

Scheme 3.42. Ring contraction model study.

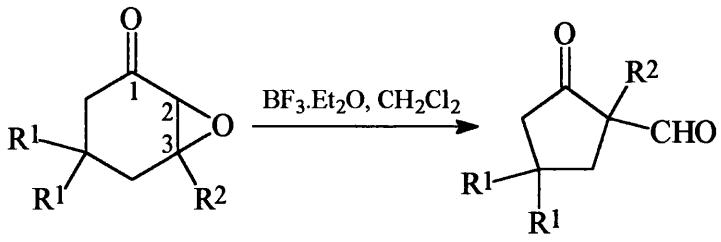


(191) **(192)** **(193)**

(194) **(195)**

House and Wasson[82] have described a number of these Lewis acid mediated contractions (Scheme 3.43.). Most of these reactions have a tertiary centre at C-3, with the exception of example (c) which gave a low yield. Hence, the lack of reactivity in the previous case (Scheme 3.42.) is attributed to the lack of stabilisation of the developing carbonium centre at C-3 i.e. secondary as opposed to the more stable tertiary carbonium.

Scheme 3.43. Examples of Lewis acid mediated ring contractions.



(196) **(197)**

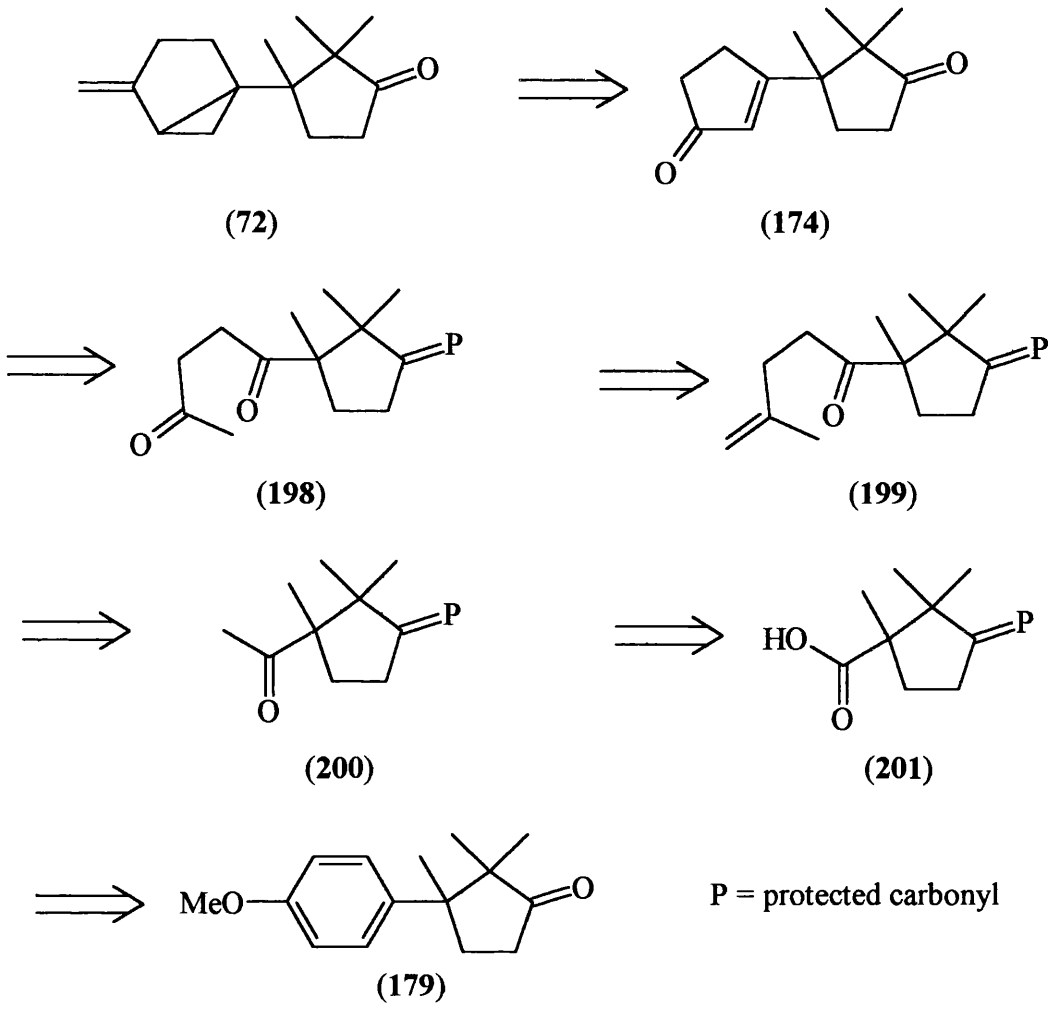
(a) $R^1 = R^2 = Me$, yield = 70 %.

(b) $R^1 = H$, $R^2 = Ph$, 60 %.

(c) $R^1 = R^2 = H$, 30 %.

Therefore, with the ring contraction step failing a new route to grimaldone was proposed. This method was based on work done by Dunez and Martin[85] where they used a phenyl group as a masked carboxylic acid. A second retrosynthetic analysis is shown below (Scheme 3.44.).

Scheme 3.44. Calderwood's second retrosynthetic analysis.

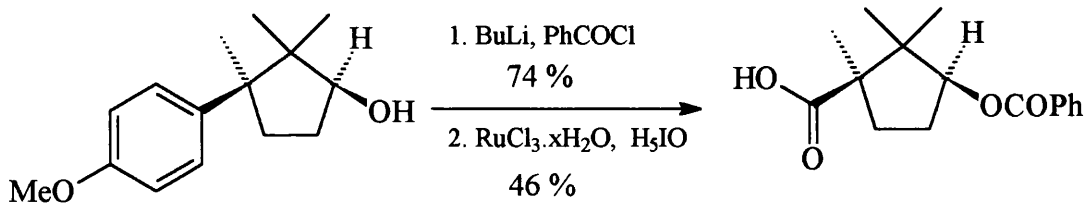


(72) (174) (198) (199) (200) (201) (179)

It was envisaged that cyclopentenone (**174**) would arise *via* aldol condensation of diketone (**198**), followed by deprotection. The diketone (**198**) could be obtained from the methyl ketone (**200**) *via* methylallylation and ozonolysis. Methylation of the corresponding acid chloride of **201** would provide methyl ketone (**200**). The carboxylic acid (**201**) would be obtained on oxidative cleavage of the phenyl ring of compound **179**, a key intermediate in the previous retrosynthetic approach.

Ketone (**179**) was reduced as before with L-Selectride. The alcohol (**202**) was protected as its benzoate ester (a group compatible with RuO_4 oxidation) and the *p*-anisole moiety cleaved to furnish acid (**203**) utilising Martin's[85] modified Sharpless oxidation (Scheme 3.45.).

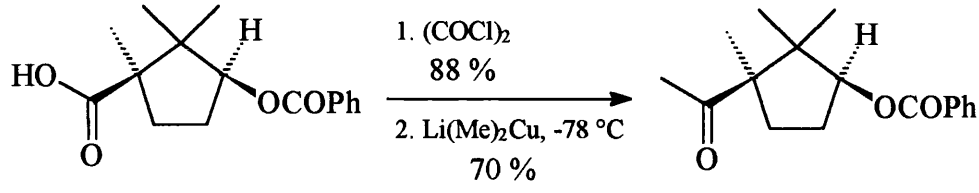
Scheme 3.45. Oxidative cleavage of anisole (202).



(202) **(203)**

The acid (**203**) was converted to the corresponding acid chloride and methylated using an organo-cuprate to give methyl ketone (**204**) in good yield (Scheme 3.46.).

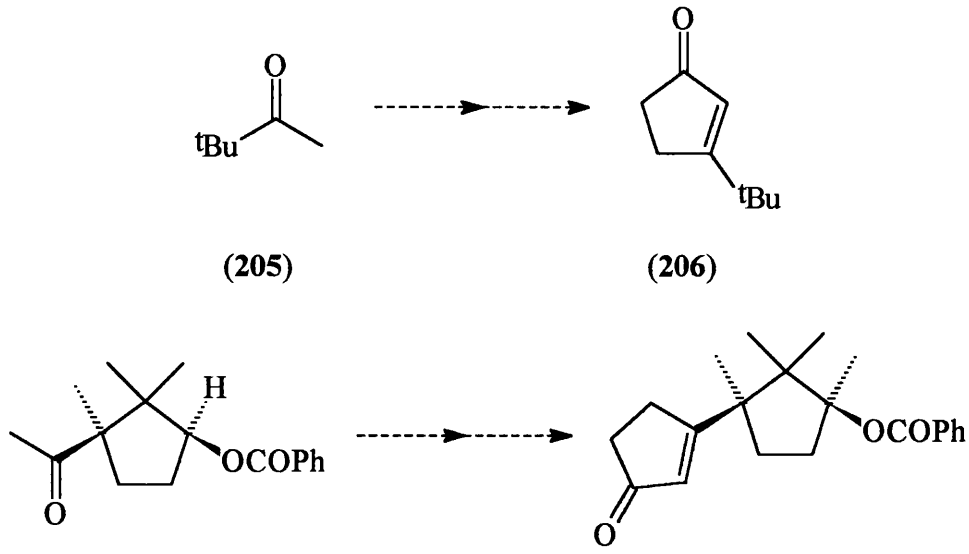
Scheme 3.46. Methylation of Acid (203).



(203) **(204)**

Attempted methallylation of the methyl ketone (**204**) with LDA / methallylchloride / NaI failed. With stocks of the methyl ketone (**204**) low, Calderwood embarked on further model studies, using pinacolone as a model for testing the conversion of **204** to **207** (Scheme 3.47.).

Scheme 3.47. Model Studies.

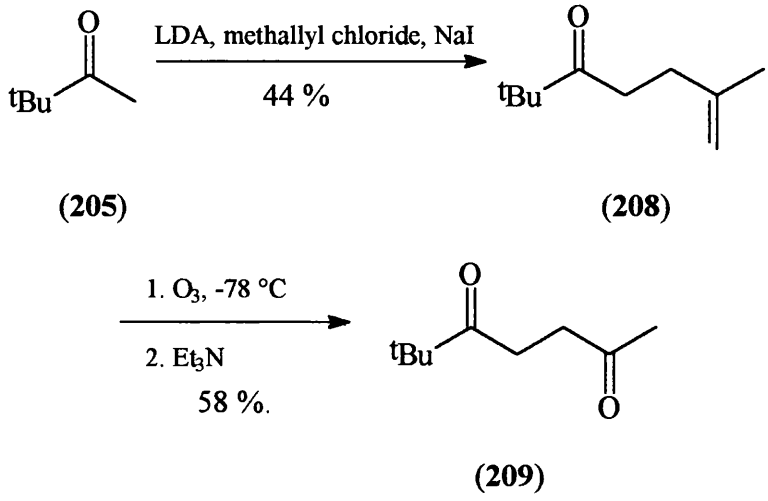


(205) (206)

(204) (207)

Methylallylation[86,87] of pinacolone (**205**) proceeded in low yield to give the γ,δ unsaturated ketone (**208**) Scheme 3.48.). Ozonolysis yielded diketone (**209**) in moderate yield.

Scheme 3.48. Synthesis of diketone (209).

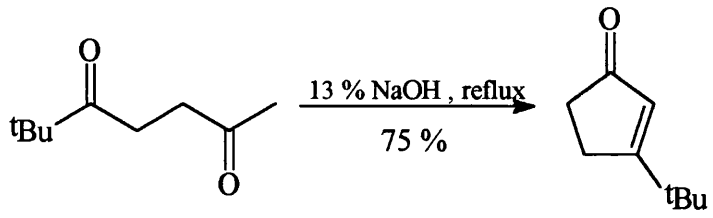


(205) (208)

(209)

Initial attempts to cyclise diketone (**209**) with NaOH met with failure. Finally Calderwood succeeded using an oxygen free NaOH solution (Scheme 3.49.).

Scheme 3.49. Cyclisation of diketone (209).



(209) **(206)**

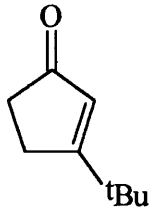
Unfortunately due to time constraints this line of research could not be brought to a satisfactory conclusion. He had shown through model studies that cyclopentenone (**207**) could be prepared. However initial experiments had indicated that methallylation of methyl ketone (**199**) was not trivial. Protection for the alcohol might have to be reconsidered, as the benzoate ester[88] would probably not be compatible with refluxing sodium hydroxide solution in the cyclisation step. The cyclopropanation could be difficult due to steric hindrance at the β-position although steric hindrance is usually more of a problem at the α-position.

4. RESULTS and DISCUSSION

4.1. Basic Strategy

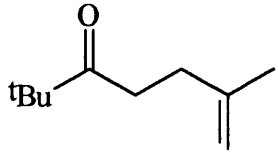
It was hoped that during the synthetic pathway some of the intermediates might have some odoriferous properties that were different from, or related to, those of the target molecule. The only odoriferous compounds which Calderwood[70] encountered during his synthetic studies were the anisole-based compounds (which unsurprisingly had the characteristic aniseed aroma), and three unsaturated ketones; **206**, **208** and **210** (Figure 4.1.). The sweet smell of the cyclopentenone (**206**) is characteristic of small ring ketones and is also similar to the bitter almond odorants (Figure 2.4.) The floral nature of the ketones **208** and **210** is expected if we invoke the rules for 'Lily of the valley odorants' determined by Pelzer[10] (Figure 2.12., page 15). Since Calderwood noted that none of the compounds which he made with the structural features of ring A of grimaldone (**72**) (Figure 4.2.) had odoriferous properties it was felt that ring B might hold the key to the odoriferous nature of the molecule.

Figure 4.1. Calderwood's odoriferous intermediates.



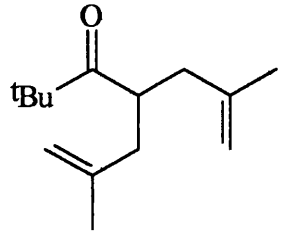
(206)

"Coconut"



(208)

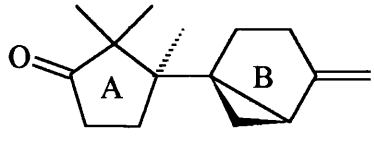
"Floral"



(210)

"Floral"

Figure 4.2. Grimaldone.



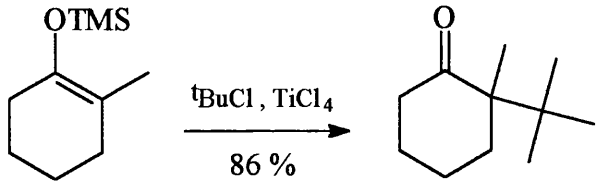
(72)

Our synthetic strategy, therefore, involved the synthesis of an intermediate molecule which had the structural features associated with ring B but with sufficient functionality to generate ring A.

4.2. Approach 1 – Lewis Acid induced α-alkylation of a silyl enol ether to form contiguous tertiary centres.

The α-alkylation of carbonyl compounds is one of the most important C-C forming reactions used by synthetic chemists. The carbonyl compound can be treated with base to generate the enolate which can be used to attack alkyl groups bearing a leaving group in a S_N2 process. The basicity of the enolate can cause problems in these reactions. Usually only active halides can be used such as allyl, benzyl and a limited number of primary halides. Secondary halides suffer from the problem of competing H-X elimination. Tertiary halides are totally useless as H-X elimination is usually very rapid. However, tertiary halides can be utilised if the silyl enol ether is formed from the carbonyl compound.[89] A Lewis acid can then be used to generate a cationic species from the halide. The non-basic silyl enol ether will then trap the cation. Thus, Reetz and Maier[90] produced 2-*tert*-butyl-2-methyl-cyclohexanone (**212**) in excellent yield from the silyl enol ether (**211**) of 2-methylcyclohexanone (Scheme 4.1.).

Scheme 4.1. α-*tert*-Alkylation of 2-methylcyclohexanone.

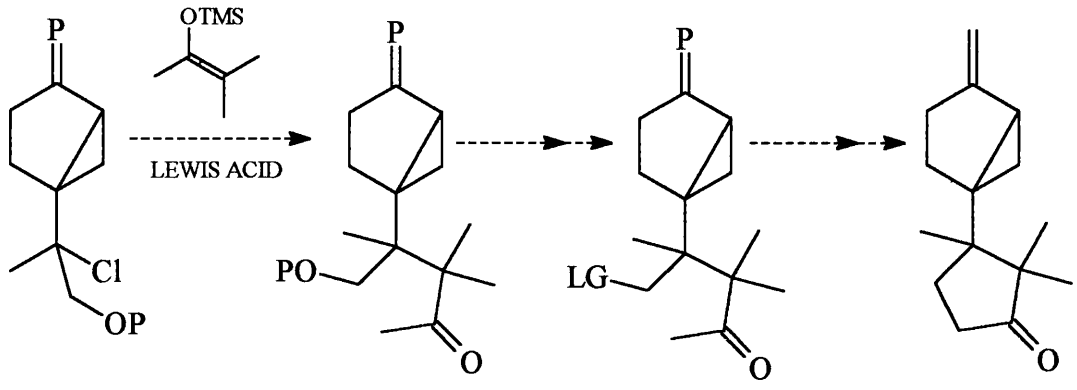


(**211**) (**212**)

This reaction has produced two contiguous tertiary centres. This strategy would appear to lend itself to the synthesis of grimaldone (**72**) since the cyclopentyl ring also has two contiguous tertiary centres. Hence, if the tertiary chloride (**213**) could be

prepared then it could be used to alkylate the silyl enol ether formed from the thermodynamic enolate of 3-methylbutan-2-one (Scheme 4.2.). The protected alcohol (**214**) could then be converted to a suitable leaving group (**215**) which would allow the cyclopentyl ring to be closed.

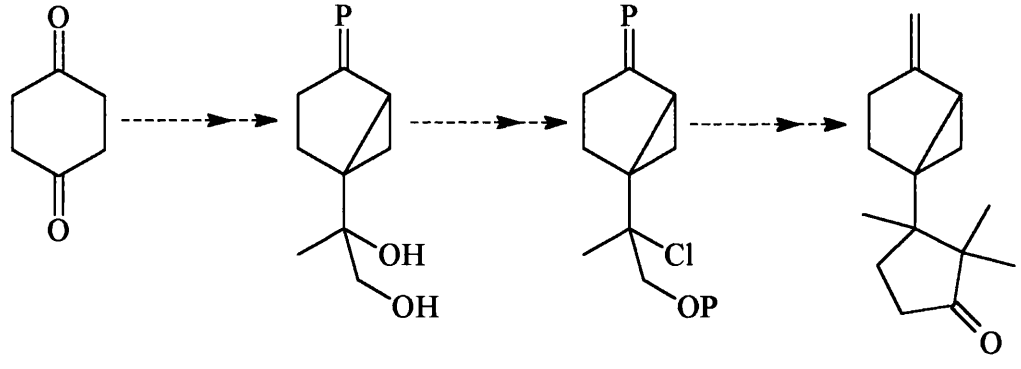
Scheme 4.2. Proposed route to cyclopentyl ring structure.



(213) **(214)** **(215)** **(72)**

The first synthetic target was diol **217** (Scheme 4.3.). This could be converted to the tertiary chloride (**213**) with suitable protection for the primary alcohol.

Scheme 4.3. Initial synthetic strategy.



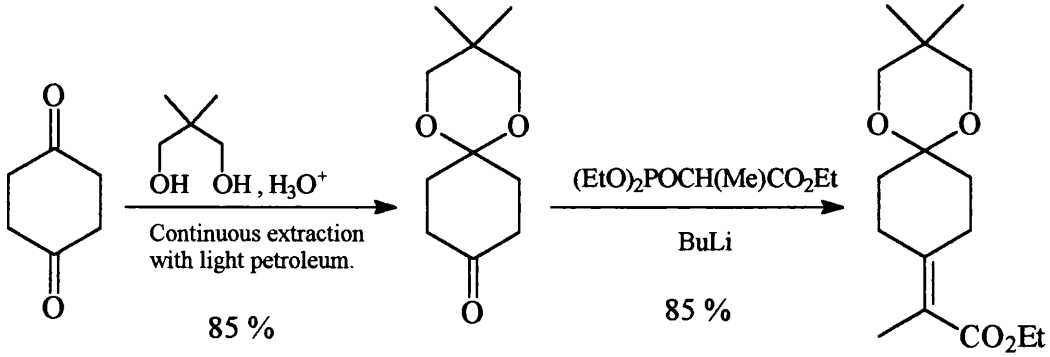
(216) **(217)** **(213)** **(72)**

The starting material for this route was cyclohexane-1,4-dione (**216**) which was converted to the monoprotected ketal (**218**) in good yield. Continuous extraction[91] of the aqueous reaction mixture with light petroleum selectively removed the monoketal (**216**) (Scheme 4.4.). Some bisketal was present in the worked-up reaction product

(<2%) but as this was unreactive in the next reaction and easily removed the product could be used in the next stage without further purification. The monoketal was purified further for analytical purposes by recrystallisation. Initially ethylene glycol was used as the ketal but this gave higher levels of bisketal which were more difficult to remove.

The monoketal was converted to the α,β-unsaturated ester (**219**) *via* a Wittig-Horner reaction.[92] Initial attempts at this transformation with sodium hydride in diglyme proved fruitless. This was thought to be due to poor quality sodium hydride. However changing to BuLi in THF produced a good yield of product after distillation (Scheme 4.4.).

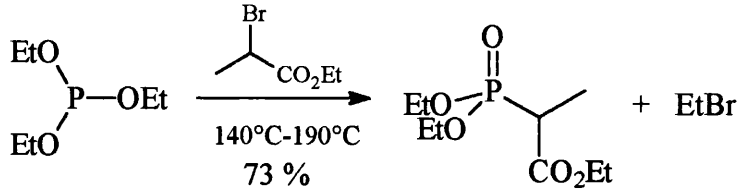
Scheme 4.4.



(**216**) (**218**) (**219**)

The phosphonate ester (**221**) required for the Wittig reaction was constructed from an Arbuzov[93] reaction between triethylphosphite (**220**) and ethyl 2-bromopropionate (**226**) (Scheme 4.5.). The reaction proceeded in good yield unlike earlier attempts using trimethylphosphite (Scheme 4.6.). The major products of the reaction with trimethylphosphite (**223**) were methyl dimethylphosphonate (**224**) and the unreacted ethyl 2-bromopropionate (**226**).

Scheme 4.5. Arbuzov reaction using triethylphosphite.

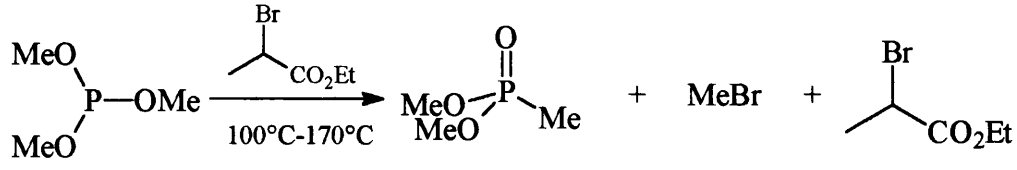


(220) **(221)** **(222)**

The reaction conditions were the same in each case except for the temperature range which was dictated by the relative boiling points of the phosphites (triethylphosphite; b.p. 156 °C[94], trimethylphosphite; 111-112 °C[94]). The bromide is dripped into the phospite at the lower temperature. The temperature is then raised to drive off the alkyl bromide.

In the reaction with trimethylphosphite (**223**), the required product must have formed initially (in low yield), liberating methyl bromide (**225**). Methyl bromide (**225**) can then react with trimethylphosphite (**223**) converting it to the phosphonate (**224**) producing more methyl bromide (**225**). Methyl bromide (**225**) is effectively catalysing the isomerisation from phosphite (**223**) to phosphonate (**224**). Even at the reaction temperature (>100 °C), methyl bromide (**225**) (b.p. 4 °C[94]) is a sufficiently strong alkylating reagent that it reacts with the phosphite (**223**) before it can boil off. Ethyl bromide (**222**) (b.p. 37-40 °C[94]), although a reasonable alkylating agent, is significantly less potent than methyl bromide and hence volatilises before it reacts.

Scheme 4.6. Arbuzov reaction using trimethylphosphite.

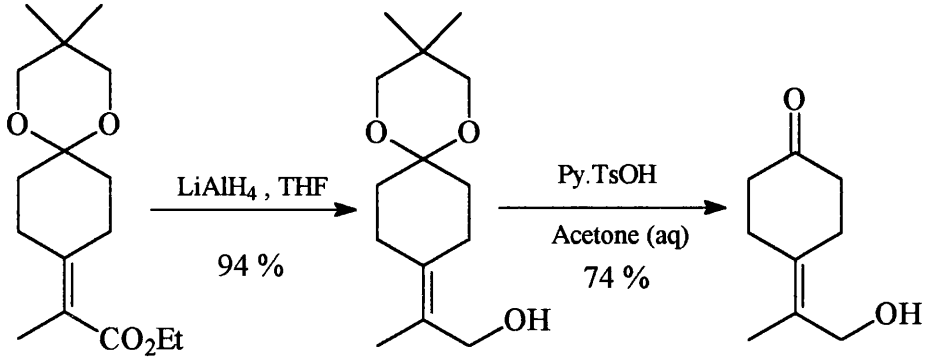


(223) **(224)** **(225)** **(226)**

The α,β unsaturated ester (**219**) was reduced to the corresponding allylic alcohol (**227**) with $LiAlH_4$ in THF, then deprotected to the cyclohexanone (**228**) (Scheme 4.7.).[92] The deprotection of the ketal (**227**) proved troublesome. Initial attempts using stronger acids (e.g. HCl in aqueous acetone or THF, and aqueous acetic acid)

gave more complex mixtures, which were more difficult to purify, and also gave lower yields. Unfortunately pyridinium tosylate[95] did not push the reaction to completion, and there was always unreacted starting material at the end of reaction. However, there were no other products and the desired cyclohexanone (**228**) was easier to purify by flash chromatography.

Scheme 4.7. Reduction of ester and deprotection of ketal.

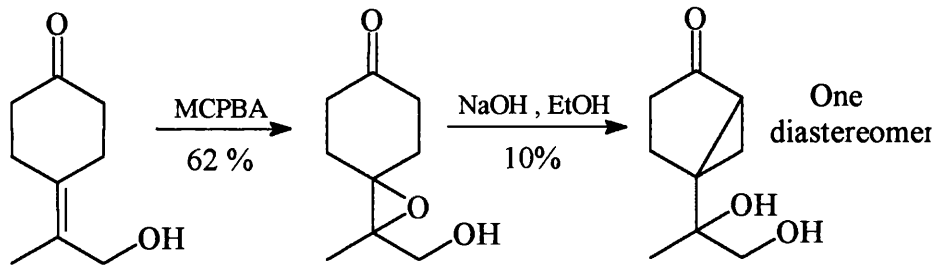


(**219**) (**227**) (**228**)

The allylic alcohol (**228**) was epoxidised using MCPBA.[96] This reaction was temperamental with the product sometimes undergoing further oxidation (Baeyer-Villiger). There was never any evidence of Baeyer-Villiger oxidation on its own. These problems were probably due to reaction times that were too long although sometimes the oxidative transformations seemed to be in excess of the corresponding equivalents of MCPBA (MCPBA was reacted with excess iodide and back titrated with sodium thiosulphate to confirm the strength).

The epoxide (**229**) was then isomerised in base to the bicyclohexanone (**230**) in poor yield (Scheme 4.8).[53] This may have been due to the difficulty associated with isolating such a polar molecule from an aqueous reaction mixture. The reaction however gave only one major diastereomer (The degree of diastereoselectivity was not determined).

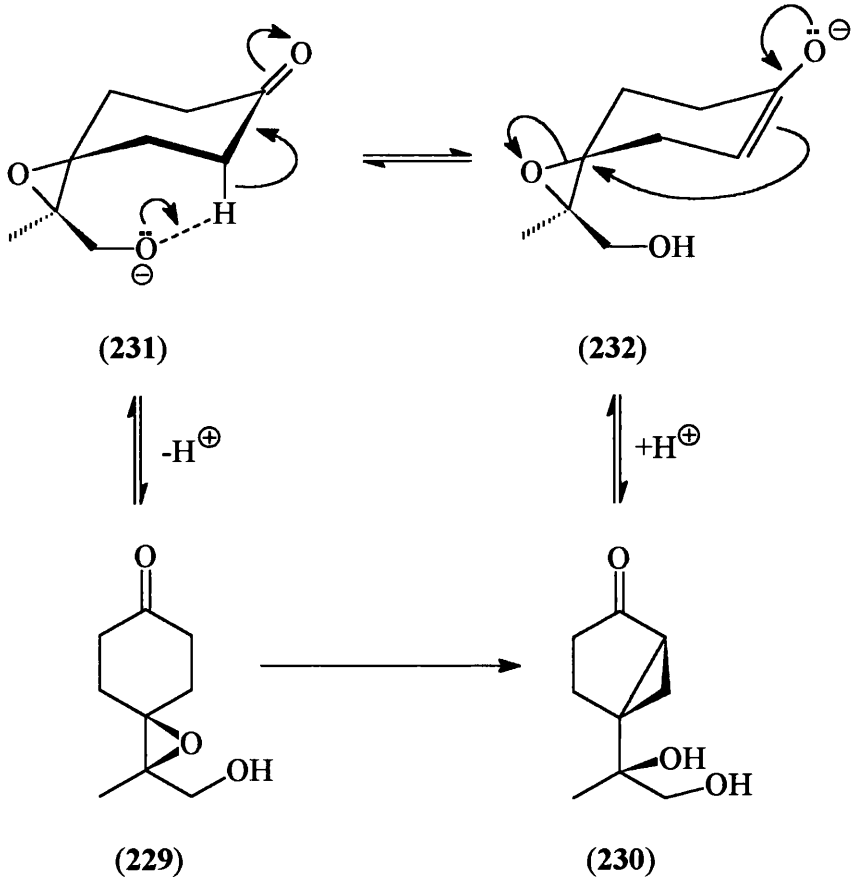
Scheme 4.8. Epoxidation and ring closure.



(228) (229) (230)

The diastereoselectivity of the reaction was attributed to the effect of the primary alcohol. This was thought to act as an intramolecular base (when deprotonated), via the seven membered transition state (**231**) (Scheme 4.9.).

Scheme 4.9. Diastereoselectivity in cyclopropyl formation.[a]



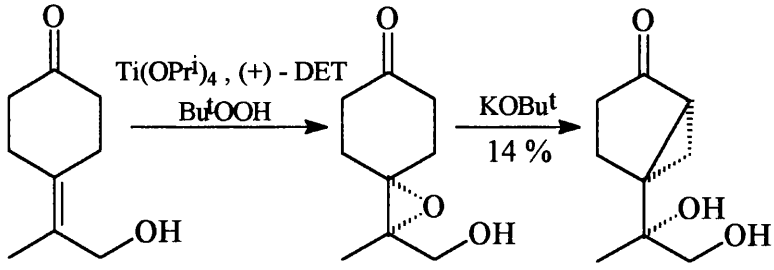
(231) (232)

(229) (230)

[a] The stereochemistry was not confirmed spectroscopically and so the deprotonation may have occurred on the opposite side of the ketone.

Subsequently a literature report was found where Hamon and Shirley[97] had previously achieved this identical transformation. They used potassium *tert*-butoxide as their base in DME, but still obtained a poor yield. Additionally, they utilised Sharpless[98] methodology on the previous epoxidation to achieve only one enantiomer **(233)** (Scheme 4.10.).

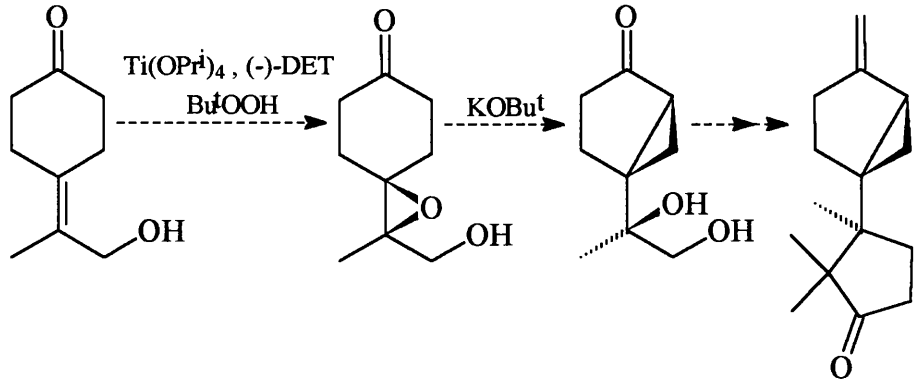
Scheme 4.10. Chiral control in cyclopropyl formation.



(228) e.e 90 % **(233)** d.e. 84 % **(234)**

These two sets of reactions therefore control the three chiral centres in grimaldone **(72)**. It is easy to see how you could select the appropriate chirality for the cyclopropyl ring but to transform the diol **(236)** into the cyclopentyl ring (retaining chirality at the tertiary centre) would prove a little more demanding (Scheme 4.11.).

Scheme 4.11. Control of chirality in grimaldone (72) synthesis.



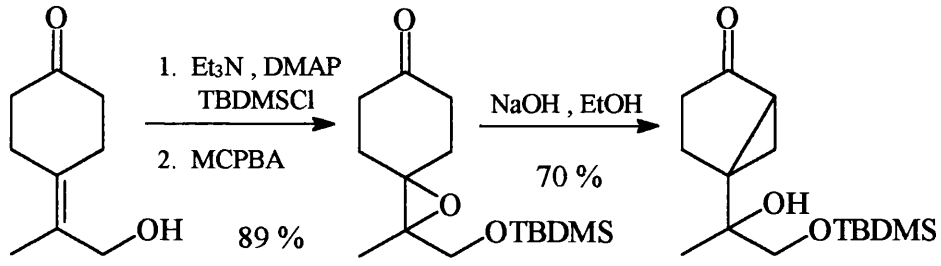
(228) **(235)** **(236)** **(72)**

Although the stereospecificity of these reactions was interesting, it was more important to concentrate on yields. With this in mind the allylic alcohol **(228)** was

converted to the TBDMS ether[99] in quantitative yield then epoxidised (Scheme 4.12).[96] The epoxidation reaction initially caused the problems of over-oxidation described previously. These were alleviated by cutting down the reaction times to 10 minutes and working-up the reaction mixture with aqueous sodium bisulphite.

The epoxide (**237**) was then converted to the bicyclohexanone (**238**), as an equimolar mixture of diastereomers, in improved yield (Scheme 4.12).[53] The loss of diastereoselectivity in the cyclopropyl formation lends weight to the proposed mechanism (Scheme 4.9.). Hamon and Shirley also noticed loss of diastereoselectivity when they protected the primary alcohol as a MOM ether.

Scheme 4.12.

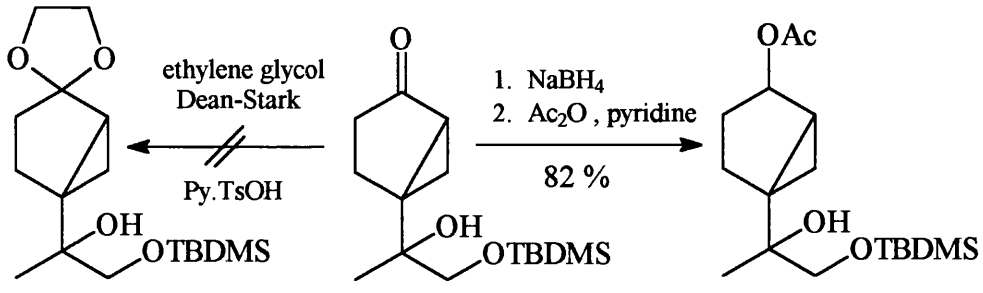


(**228**) (**237**) (**238**)

Attempts to protect the bicyclohexanone (**238**), as the ethylene ketal (**239**) proved unsuccessful (Scheme 4.13.), giving a complex mixture by TLC. The primary silyl ether may have been cleaved under the reaction conditions but it is not clear what further transformations had taken place.

It was decided to protect the ketone (**238**) as the acetate (**240**), hence the alcohol was prepared by reduction with sodium borohydride[100] and then acylated[101] with acetic anhydride in pyridine (Scheme 4.13.). The acetate was isolated as a set of two diastereomers. Clearly, there are a possible four diastereomers and hence the reduction appears to have been diastereoselective (the level and direction of diastereoselectivity was not determined).

Scheme 4.13. Protection of bicyclohexanone (238).

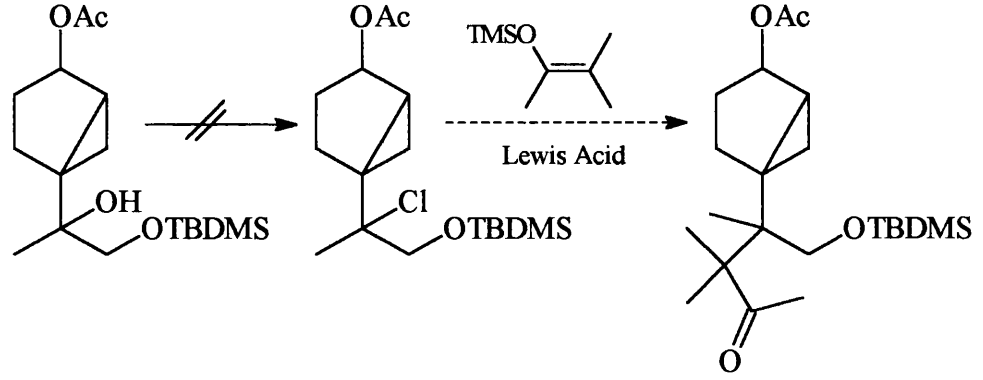


(239) (238) (240)

Attempts to chlorinate the tertiary alcohol (**240**) proved fruitless (Scheme 4.14.), either with $POCl_3$ or $POCl_3$/tetramethylurea.[102] $POCl_3$ reacts with tetramethylurea to give the chlorinating agent, presumably shown as overleaf (**243**) (Scheme 4.15.). This reagent was used immediately without purification.[a]

The worked-up reaction mixture was a thick brown oil that rapidly (within minutes) changed to a black liquid on exposure to air. All attempts to characterise any of the components of the mixture were unsuccessful.

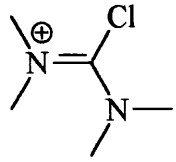
Scheme 4.14. Attempted chlorination and alkylation.



(240) (241) (242)

[a] Analysis of the crude reagent revealed that it was >95 % pure by measurement of ^1H NMR integral. δ_H 2.8 for tetramethyl urea, δ_H 3.28 for chlorinating agent.

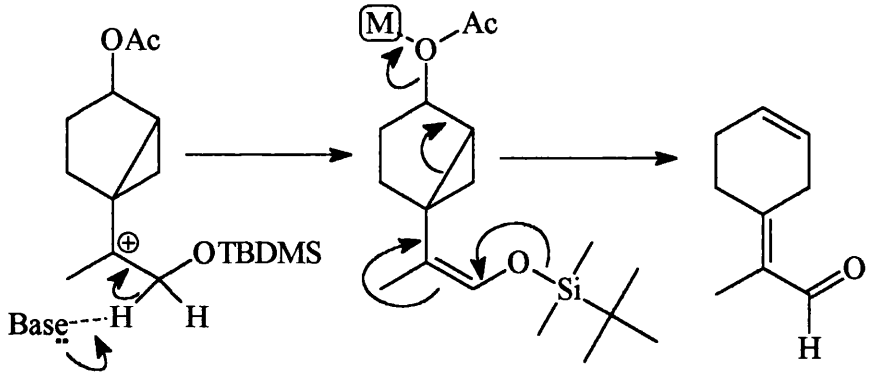
Scheme 4.15. Chlorinating agents used for attempted chlorination.

1. $POCl_3$
2. $POCl_3$ / tetramethylurea ≡  PO_2Cl_2

(243)

Attempts to carry the crude mixture (from the chlorination) through to the next stage using either $TiCl_4$, $ZnCl_2$ or $BF_3.Et_2O$ as the Lewis acid also resulted in failure. The NMR spectra of the resulting complex mixtures showed the presence of double bonds and aldehydes. One route to these compounds is outlined below (Scheme 4.16.). The cation (**244**) generated from the alcohol (**240**) could lose a proton to give the silyl enol ether (**245**). The presence of a Lewis acid would facilitate the leaving of the acetate and the collapse of the bicyclic ring structure to give the aldehyde (**246**) as shown. Whatever the source of the problem the choice of protecting groups was poor considering that the reaction required a strong Lewis acid ($TiCl_4$ or $ZnCl_2$).

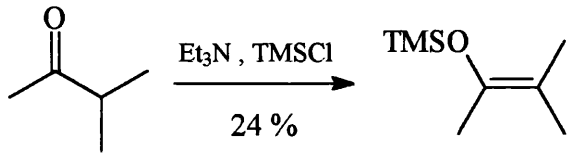
Scheme 4.16. Possible route to aldehydes and alkenes.



(244) **(245)** **(246)**

The silyl enol ether (**248**) required for the alkylation was very straightforward to make (Scheme 4.17.).[103] The low yield was probably due to product lost during Kugelrohr distillation. The distillation was carried out under vacuum, lowering the boiling point to 40 °C.

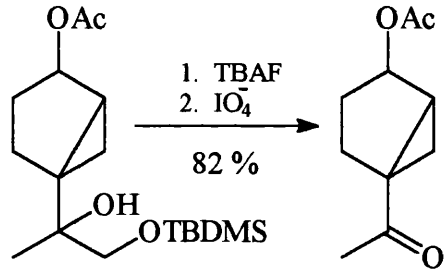
Scheme 4.17. Synthesis of the silyl enol ether (248).



(247) (248)

It was decided that the tertiary alcohol, alpha to the cyclopropyl ring posed too many problems, and so it was converted to the methyl ketone (**249**) by removal of the silyl protection with TBAF,[104] followed by periodate cleavage[105] of the resulting diol (Scheme 4.18).

Scheme 4.18. Formation of the methyl ketone (249).



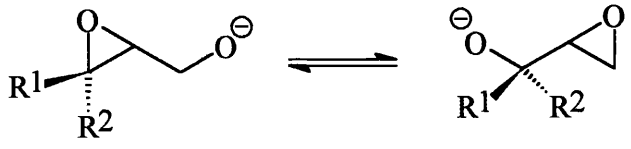
(240) (249)

The methyl ketone (**249**) would provide an ideal basis to build the final cyclopentyl ring, with possible reconsideration of the choice of protecting group depending on the proposed synthetic route. Although the overall yield from cyclohexanedione (**216**) to the methyl ketone (**249**) was around 21 % which is reasonable for an 11 step process, there were a few steps for which the yields were not consistent (in particular, the deprotection of ketal **227** and the epoxidation of alkene **228**). The presence of the primary alcohol throughout the synthesis was not required and only added extra steps. It was decided that a new route should be found which was shorter but utilised similar chemistry.

4.3. Approach 2 - Cascade reactions of epoxides.

In the Payne[106] rearrangement, an α-epoxy-alcohol (**250**) in basic solution can rearrange to form a new epoxide (**251**) (Scheme 4.19.). The major product (**250**) is usually the one with the more acidic alcohol (generally less substituted) or the more highly substituted epoxide. However steric effects play a major role and the position of the equilibrium is difficult to predict (let alone control) with any degree of accuracy.

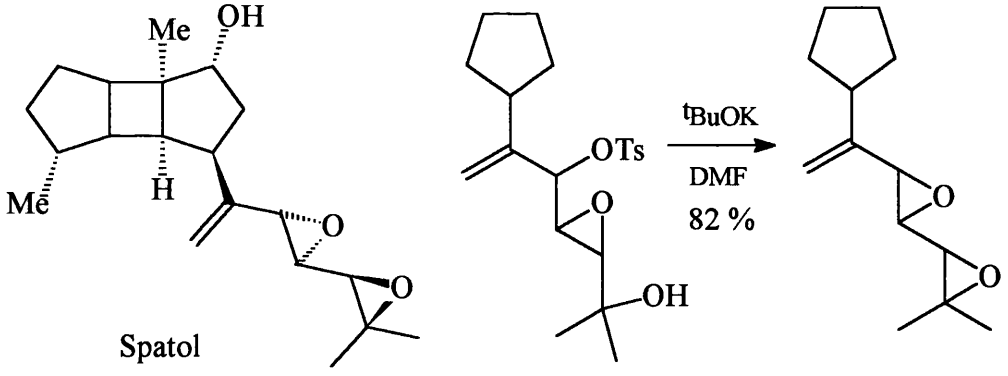
Scheme 4.19. Payne Rearrangement.



(250) **(251)**

However, if a suitable leaving group is placed next to the new alkoxide then this can be used to trap the alkoxide, forming a second epoxide. This idea was used in a synthesis of the diepoxide, Spatol[107] (**252**) (Scheme 4.20.).

Scheme 4.20.

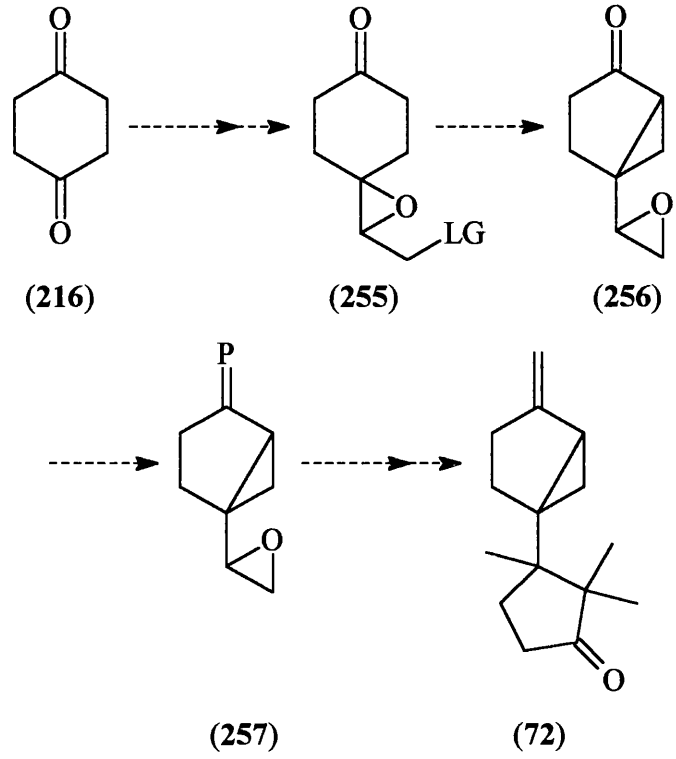


(252) **(253)** **(254)**

Our second synthetic route was based on this idea (Scheme 4.21.). If epoxide **255** could be synthesised then, upon treatment with base, the cyclopropyl ring would form as before and the resulting alkoxide could displace the leaving group forming a new epoxide (**256**). Epoxides are extremely versatile functional groups and can undergo a

number of synthetically useful rearrangements and functional group transformations.[108] Therefore, this epoxide (**256**) (with suitable protection for ketone) could be transformed to form the second cyclopentyl ring. This would represent a significant improvement in the number of steps over the previous route.

Scheme 4.21. Second synthetic route.

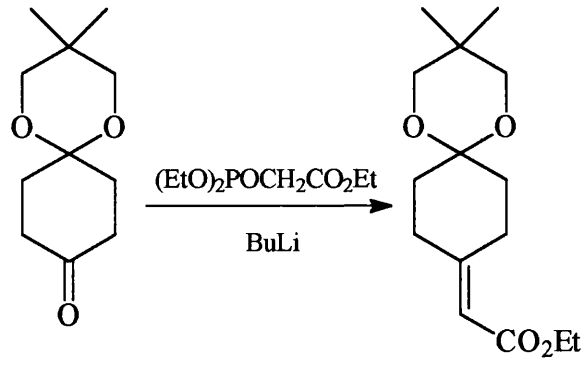


(**216**) (**255**) (**256**)

(**257**) (**72**)

The starting material was the monoketal (**218**) used in the previous route, which was converted to the unsaturated ester (**258**) using a Wittig Horner[92,93] transformation in high yield (Scheme 4.22.).

Scheme 4.22. Wittig Horner.

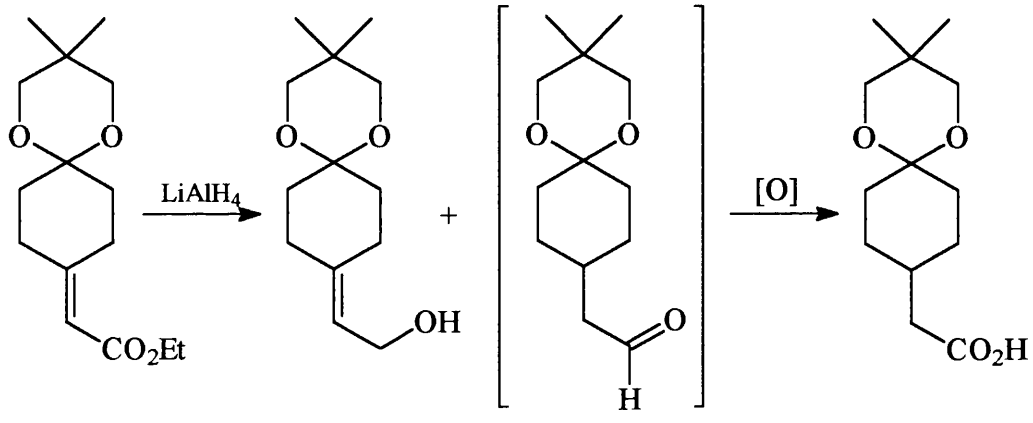


(**218**) (**258**)

Initial attempts to reduce the α,β-unsaturated ester (**258**) to the allylic alcohol (**259**) using the same conditions[92] as before (Scheme 4.7., $LiAlH_4$ in THF) gave almost a 1:1 mixture of the desired alcohol (**259**, 41%) and an aldehyde (**260**, 36%) (Scheme 4.23.). The aldehyde (**260**) was unstable and readily oxidised in air within a few days to the corresponding acid (**261**).

Changing the solvent from THF to ether dramatically improved the selectivity of the reduction from ~1:1 to ~12:1, giving an 89 % yield of product. Polar solvents are more likely to encourage 1,4 addition over 1,2 addition. Therefore, THF would facilitate the initial 1,4 hydride transfer required to form the aldehyde (**260**) better than diethyl ether.

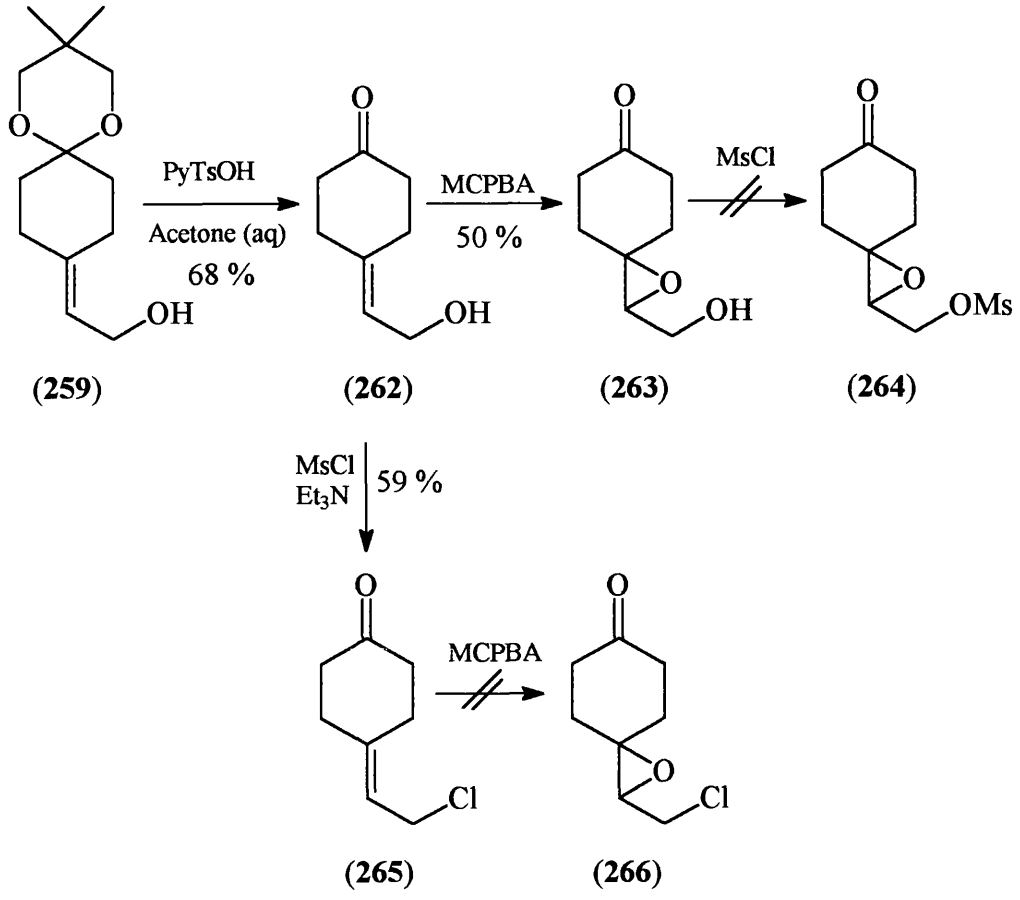
Scheme 4.23. Hydride reduction of α,β-unsaturated ester (258).



(**258**) (**259**) (**260**) (**261**)

The deprotection[95] of the ketal again proved troublesome but the cyclohexanone (**262**) could be produced in moderate yield (Scheme 4.24.). Starting material was also recovered (14 %). Unfortunately, epoxidation of the allylic alcohol (**262**) was not trivial. The resulting worked-up reaction mixture could not be purified sufficiently to isolate the epoxide. Similarly, attempts to make the allylic mesylate or tosylate met with failure. Eventually the allylic chloride (**265**) was isolated during attempted mesylation.[109] This is not that surprising considering the allylic nature of the substrate. The yield could have probably been increased if an additional chloride source had been present in the reaction mixture. However attempts to make the epoxy chloride (**266**) also proved to be unsuccessful, yielding a complex mixture from which no products could be isolated.

Scheme 4.24.

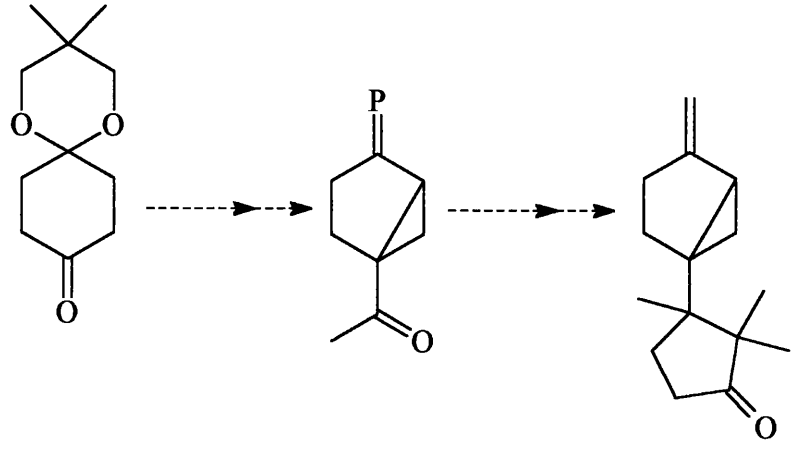


With progress along this route grinding to a rapid halt, work started on an alternative strategy.

4.4. Approach 3 – α-alkylation of a methyl ketone.

The methyl ketone (**249**) produced in the first approach was a good target to aim for if the protecting group was changed and it could be produced in fewer steps (Scheme 4.25.).

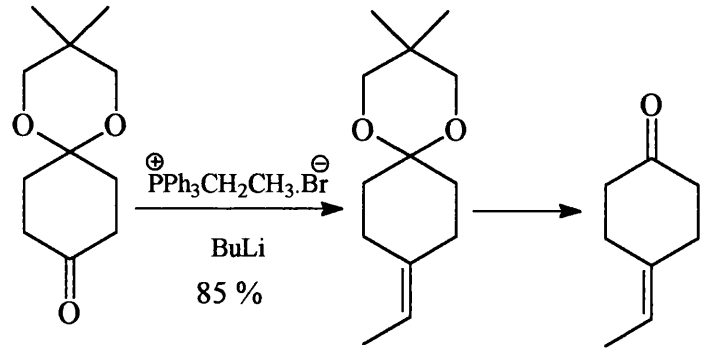
Scheme 4.25. Proposed third route to grimaldone (72).



(218) **(267)** **(72)**

The monoketal (**218**) was again used as the starting material for the third route. This was converted to the alkene (**268**) *via* Wittig[110] olefination in good yield Scheme 4.26.). The deprotection step again caused problems. Quite often during distillation the ketal would reform as the diol was often not fully washed out during work-up. Chromatography proved to be unsuccessful at completely removing all traces of diol and similar reketalisation problems were encountered. Pushing the reaction to completion proved extremely difficult under a variety of conditions (Table 4.1.). The use of sulphuric acid or hydrochloric acid in aqueous acetone, THF or MeOH gave inconsistent results. Pyridinium tosylate in acetone gave incomplete hydrolysis. The use of wet silica[111] in DCM also gave equally incomplete hydrolysis.

Scheme 4.26. Wittig and Ketal Deprotection.



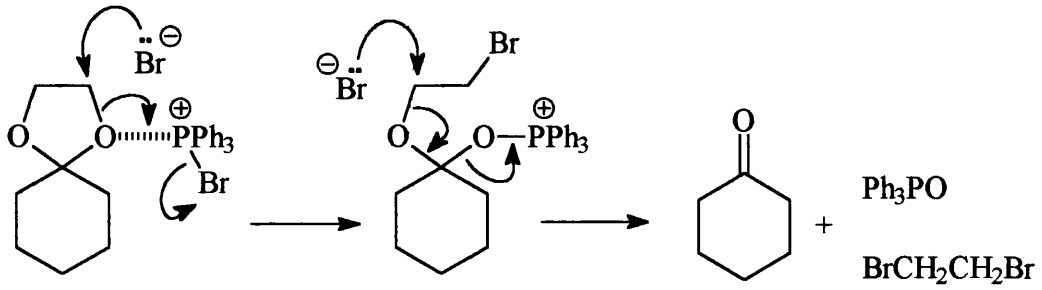
(218) (268) (269)

Table 4.1. Deprotection methods.

Acid	Solvent / Media	Results / Comments
H_2SO_4 or HCl	Acetone (aq) or MeOH (aq) or THF (aq)	Poor yields, incomplete hydrolysis – very inconsistent
Py.TsOH	Acetone (aq)	Incomplete hydrolysis
H_2SO_4	CH_2Cl_2 / Wet silica	Incomplete hydrolysis
PPh_3 / CBr_4	Acetone	Complex mixture
AcOH	50 % AcOH	90 % yield, reproducible results

A method of ketal deprotection using triphenyl phosphine and carbon tetrabromide was recently reported in the literature.[112] This involves adding 2 equivalents of triphenyl phosphine to a solution of 2 equivalents of carbon tetrabromide and the ketal. The proposed mechanism (Scheme 4.27.) involves coordination (**270**) of one of the ketal oxygens to the electrophilic phosphonium species generated from triphenyl phosphine and carbon tetrabromide. Subsequent attack of this species by two bromide anions will regenerate the ketone (**272**) along with triphenylphosphineoxide and 1,2-dibromoethane.

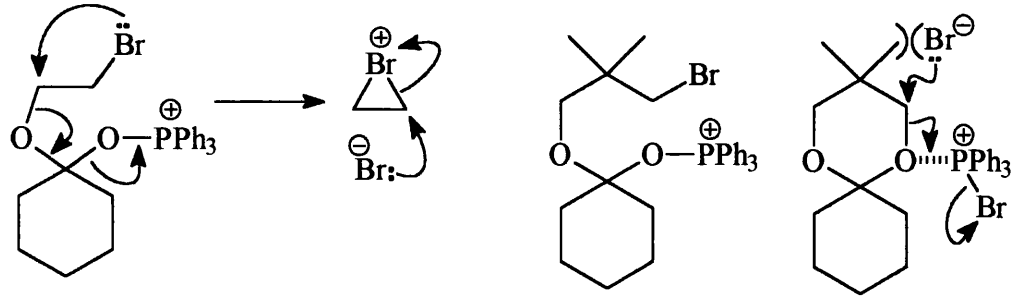
Scheme 4.27. Proposed deketalization mechanism.



(270) (271) (272)

Unfortunately attempts to apply this methodology to ketal **268** gave only a complex mixture from which no identifiable products were isolated. If the mechanism outlined in Scheme 4.27. is correct then an intermediate like **271** will almost certainly fragment initially intramolecularly *via* the three-membered bromonium species (**273**) shown in Scheme 4.28. With an extra carbon atom in the ketal ring the intermediate (**274**) could not form a three-membered bromonium ion. This might explain why the reaction did not work. Alternatively, the presence of the dimethyl group on the ketal ring could have caused sufficient steric hinderance to block the initial attack of the bromine ion on the phosphonium-coordinated ketal (**275**).

Scheme 4.28.



(271) (273) (274) (275)

Finally a solution of 50 % acetic acid[113] was tried and furnished the ketone (**269**) in high yield, but more importantly with good reproducibility.

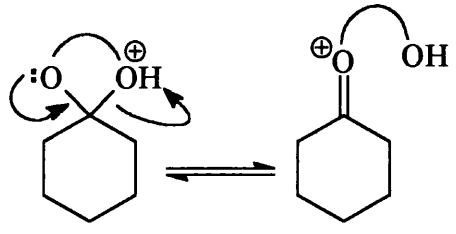
At this point, it is worth discussing the stability of ketals formed from different types of ketones and diols.

(a) **Ketones.**

(i) Saturated/unsaturated – ketones which have α,β unsaturation form less stable ketals due to the extra stabilisation obtained from conjugation.

(ii) Ring size – cyclohexyl rings form more stable ketals than cyclopentyl rings. This is due to the fact that an exocyclic double bond is preferred on a cyclopentyl over a cyclohexyl ring, and the rate determining step in ketal hydrolysis is known to involve the cleavage of one of the ketal oxygens with formation of an intermediate oxonium species (**277**) (Scheme 4.29.). For ketals from ethylene glycols, cyclopentanone ketals are hydrolysed approximately 13 times faster than cyclohexanone ketals.[114]

Scheme 4.29. Rate determining step in ketal hydrolysis.



(276) (277)

(b) **Diols.**

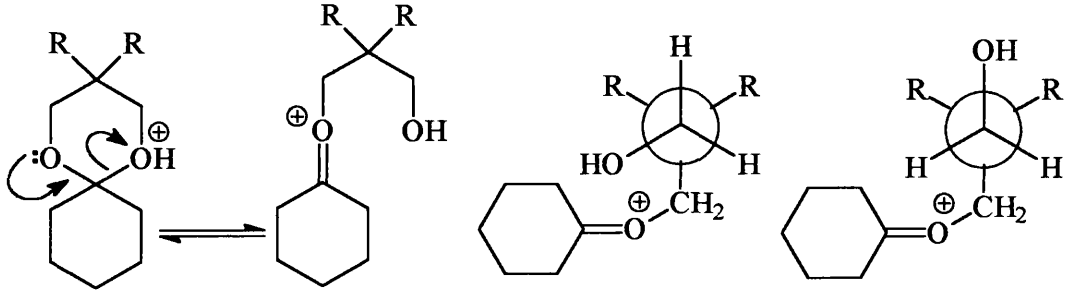
(i) Chain size :- The longer the chain the more easy is the cleavage of the ketal. Essentially, shorter chains will reform the ketal (**276**) more easily from the oxonium species (**277**) than longer chains, due to the proximity of the available nucleophile. For ketals of cyclohexanone, the 1,3-propanediol ketal is hydrolysed approximately 30 times faster than the ethylene glycol ketal.[114]

(ii) *Gem*-dialkyl effect. The presence of a *gem*-dialkyl group on the 2 position of the 1,3-propanediol will aid cyclisation and consequently hinder the hydrolysis of the corresponding ketal. The reason for this can best be explained by steric arguments. The Newman projection of the oxonium species (**279**) formed in the rate determining step of ketal hydrolysis (Figure 4.3.) shows that for the parent 1,3-propanediol (with R=H) the preferred conformation (**279b**) will be with the oxygen atoms in an *anti* configuration. As the size of the *gem*-dialkyl group on the 2-position is increased the preferred orientation (**279a**) will be with the oxygen atoms closer together.

Therefore, with a *gem*-dialkyl group present on the 2 position of the 1,3-propanediol, the oxonium anion (**279**) formed in the rate-determining step of the ketal hydrolysis will be statistically more likely to occupy an orientation (**279a**) which is conducive to reforming the ketal (**278**). With no *gem*-dialkyl group present then the oxonium anion (**279**) would be more likely to occupy an orientation (**279b**) which would reduce the rate of ketal (**278**) reformation.

For ketals of cyclohexanone, the presence of a *gem*-dimethyl group on the 1,3-propanediol at the 2 position reduces the hydrolysis rate of the corresponding ketal from 30 times down to only 2 times that of the ethylene glycol ketal. Adding bulkier alkyl groups slows the relative rate even further – down to 0.9 and 0.3 times respectively for diethyl and diisopropyl.[114,115]

Figure 4.3. *Gem*-dialkyl effect on preferred orientation.



(278) **(279)** **(279a)** **(279b)**

R = H, orientation 'b' is most favourable.

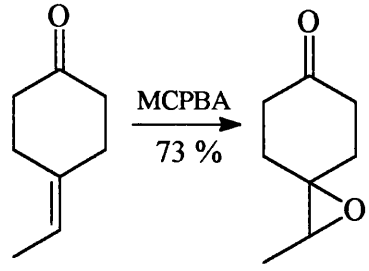
R = large alkyl, orientation 'a' is most favourable.

Hence, the hydrolysis of the ketal (**268**) should have proved no more difficult than the hydrolysis of the ethylene glycol ketal of cyclohexanone, although the olefinic moiety will exert some influence.

With the γ,δ unsaturated ketone (**269**) in hand the epoxide (**280**) could be made (Scheme 4.30.). As with previous epoxidations of γ,δ unsaturated ketones Baeyer Villiger oxidation of the product was sometimes a problem especially on larger scale reactions. This was thought to be due to the reaction overheating due to the poorer cooling on the bigger scale (smaller surface to volume ratio). So over-oxidation was avoided by adding a solution of MCPBA to the alkene,[116] working up after 10

minutes with bisulphite and not working on too large a scale (although up to 2.5 g of alkene was used without problem, which was sufficient for the purposes of this work).

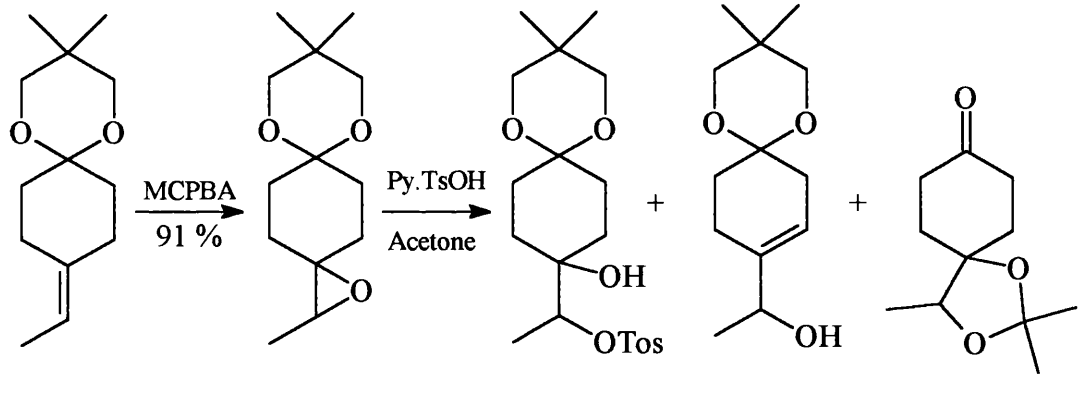
Scheme 4.30. Epoxidation.



(269) **(280)**

With the initial problems caused by the epoxidation and deketalisation reactions, alternative strategies were attempted. Changing the order of reactions was considered, i.e. the epoxidation then the deprotection. The epoxidation[116] worked extremely well and gave the required epoxide (**281**) in high yield. The deprotection at first glance gave a strange mixture (Scheme 4.31. and Table 4.2.).

Scheme 4.31. Epoxidation and attempted deketalisation.



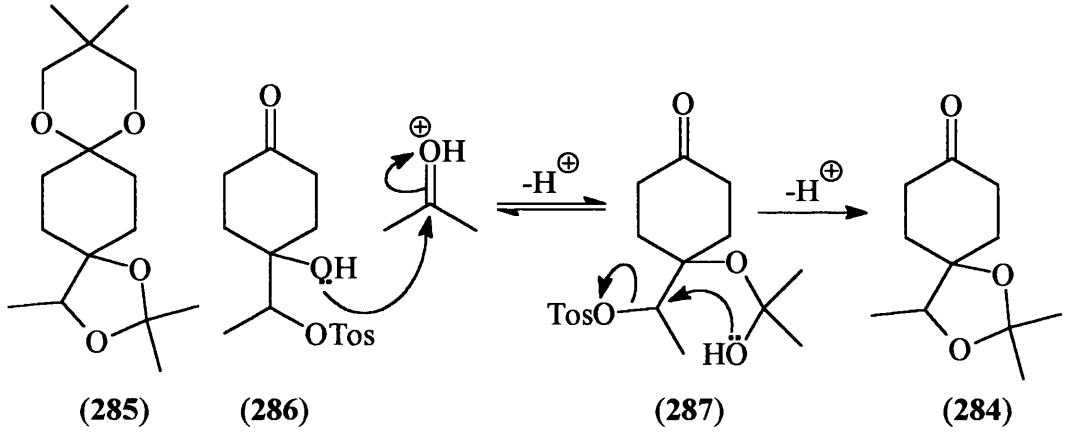
(268) **(281)** **(282)** **(283)** **(284)**

Table 4.2.

Reaction Conditions	Compound			
	281	**282**	**283**	**284**
1 hr reflux	21%	34 %	26 %	-
2 hr reflux, 12 hr stir	-	trace	24 %	26 %

The 1,2-hydroxy-tosylate (**282**) must have formed from the attack of the tosylate on the less hindered side of the epoxide (**281**). The allylic alcohol (**283**) is formed from an acid catalysed isomerisation of the epoxide (**281**). The formation of the acetonide (**284**) is more difficult to envisage but Table 4.2. indicates that as the reaction progresses the amount of 1,2-hydroxy-tosylate (**282**) decreases and the amount of acetonide (**284**) increases. If it is assumed that the 1,2-hydroxy-tosylate is being converted to the acetonide then Scheme 4.32. shows how this might happen. The only puzzle remaining is - What happened to the ketal protecting group? It must have been cleaved at some stage but since no intermediate such as **285** or **286** was isolated it is unclear which step happened first. As can be seen from the table, only half of the organic material was isolated and identified in the second run. The unidentified remainder could have concealed one of these intermediates.

Scheme 4.32. Formation of acetonide (284).



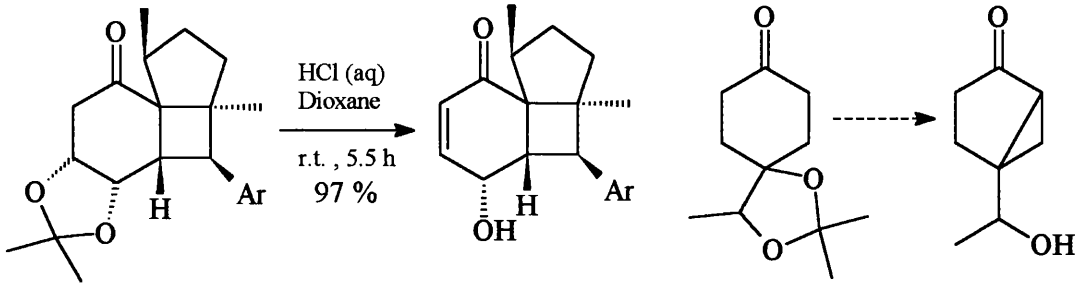
(**285**) (**286**) (**287**) (**284**)

β,γ-acetonido-ketones can be converted to the corresponding α,β-unsaturated ketones in high yield under basic[117] and acidic[118] conditions. For example, the acetonide (**288**) was converted to the α,β-unsaturated ketone (**289**) yield in almost quantitative yield with hydrochloric acid in dioxane (Scheme 4.33.).[118a]

It might have been interesting to see if the γ,δ-acetonide (**284**) could be converted to the α,β-cyclopropyl ketone (**290**.). For this procedure a strategy which might be considered is outlined in Scheme 4.34. The ketone (**284**) would be converted to the silyl enol ether (**291**). A Lewis acid would then be used to cleave the acetonide with the silyl enol ether collapsing to quench the resultant cationic centre yielding the

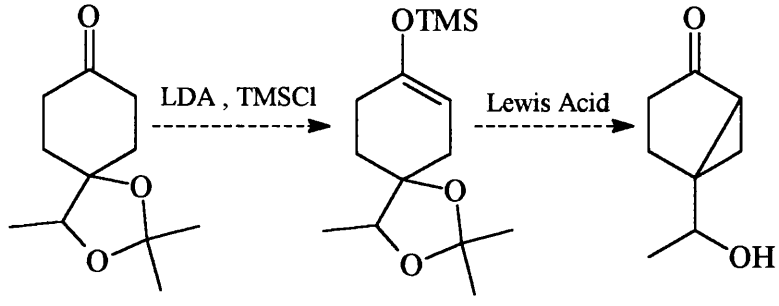
bicyclohexanone (**290**). Unfortunately, the yield of acetonide (**284**) from the deprotection reaction did not justify pursuing this route any further.

Scheme 4.33. Rearrangement of ketonic-acetonides.



(**288**) (**289**) (**284**) (**290**)

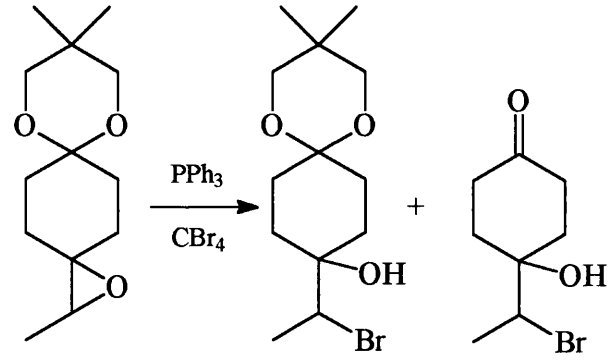
Scheme 4.34. Proposed conversion of acetonide to bicyclohexanone.



(**284**) (**291**) (**290**)

Deprotection[112] of the ketal (**281**) with triphenyl phosphine and carbontetrabromide was also attempted (Scheme 4.35.). Considering the complex mixture that was obtained when this methodology was applied to alkene **268**, it may have seemed highly optimistic to expect to obtain better results from the epoxide (**281**). In the event the epoxide was not tolerant to the reaction conditions and gave mainly the bromohydrin although partial deprotection did take place (Scheme 4.35.). If the reaction could have been forced to give the ketone (**293**) in high yield then it may have been useful, as the epoxide (**280**) could have been formed from it. However attempts to push the reaction to the fully deprotected bromohydrin (**293**) with more equivalents of triphenylphosphine and carbon tetrabromide, resulted in lower yields and more complex mixtures.

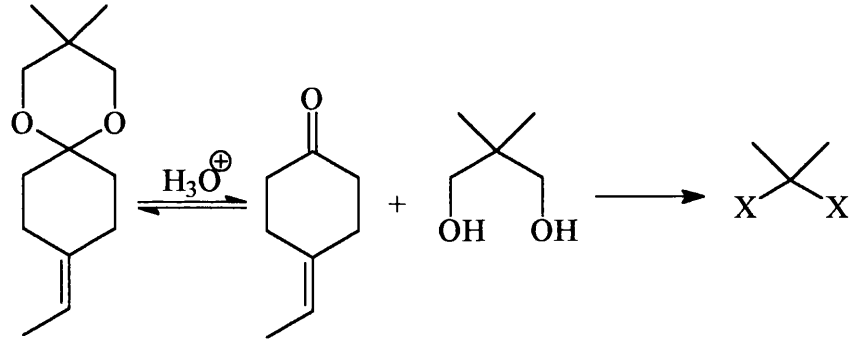
Scheme 4.35. Attempted deprotection with Ph_3P and CBr_4.



(281) **(292)**, 41 % **(293)**, 27 %

An alternative strategy for the deprotection was to convert the diol (**294**) to another functional group so that reketalisation could not occur. This is essentially the reason why aqueous acetic acid (Table 4.1.) worked for the deprotection of the ketal (**268**) (Scheme 4.26.), by converting the free diol (**294**) to the acetate (**295a**) (Scheme 4.36.).

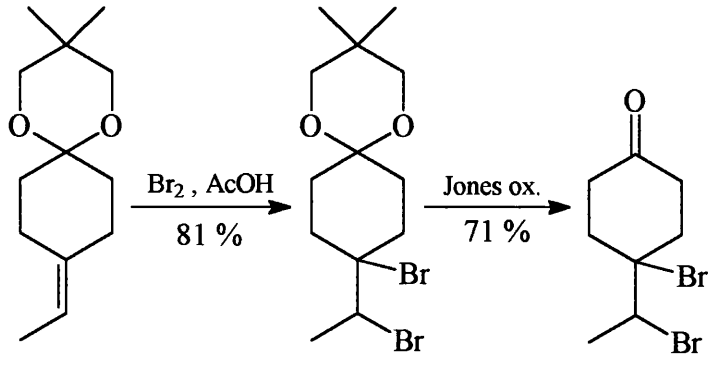
Scheme 4.36. Deprotection strategy.



(268) **(269)** **(294)** **(295a)** X = CH_2OAc.
(295b) X = CO_2H

Converting the diol (**294**) to the corresponding diacid (**295b**) would also be a viable strategy for the deprotection. However, the presence of the olefinic function would rule out strong oxidisers. Hence, the alkene (**268**) was converted[119] to the dibromide (**296**) in reasonable yield. The dibromo-ketal (**296**) was then easily deprotected[120] in good yield to give the dibromo-ketone (**297**). The advantage of this method was that there was a leaving group already in place for the base induced ring closure.

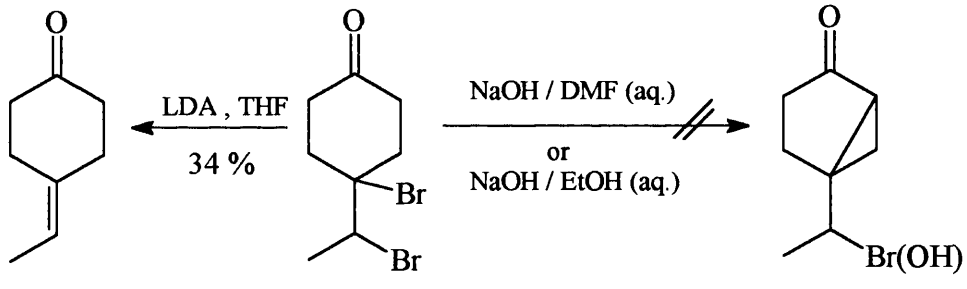
Scheme 4.37.



(268) **(296)** **(297)**

However, attempts to form the bicyclic compound, either as the alcohol (**290**) or bromide (**298**) (it was thought that the secondary bromide would be easily converted to the alcohol under the reaction conditions) were fruitless (Scheme 4.38.). The reaction gave a complex mixture which showed a number of olefinic residues by NMR. As well as NaOH in DMF, KOH (or NaOH) in EtOH, and LDA in THF were also tried with similar results. However, the LDA in THF experiment yielded some of the previously prepared alkene (**269**) in 34 % yield.

Scheme 4.38. Attempted cyclopropyl formation



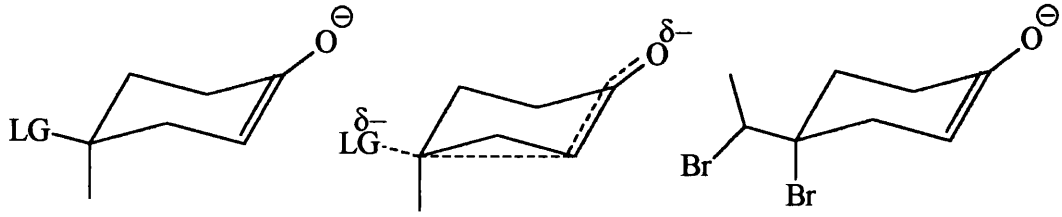
(269) **(297)** **(298)**

The most probable explanation for the failure of this transformation involves steric effects. For transformations of this type the leaving group needs to occupy an equatorial position[52d] (**299**) to allow initial interaction of the enolate with the leaving group to form transition states like **300** (Figure 4.4.). The ethyl bromide moiety, being more bulky than the bromine, will prefer to occupy the equatorial position. With the bromine occupying an axial position then *trans*-diaxial elimination of

hydrogen bromide will predominate, hence the prevalence of olefinic residues in the reaction mixture.

Of course, the conversion of the dibromide (**297**) back to the alkene (**269**) could have been improved. However, this would mean a three step sequence (di-bromination, deketalisation and debromination) for the deprotection of the ketal (**268**) which is clearly very inefficient.

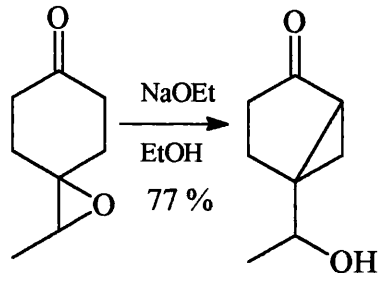
Figure 4.4. Desired orientation of leaving group for attack of enolate.



(**299**) (**300**) (**301**)

Although these routes did not provide a workable alternative, the original deprotection/epoxidation route had been developed so that the epoxide (**280**) could be produced consistently in good yield. With the epoxide in hand it was easy to obtain the required bicyclic compound (**290**) in good yield (Scheme 4.39.).[53]

Scheme 4.39. Cyclopropyl formation.

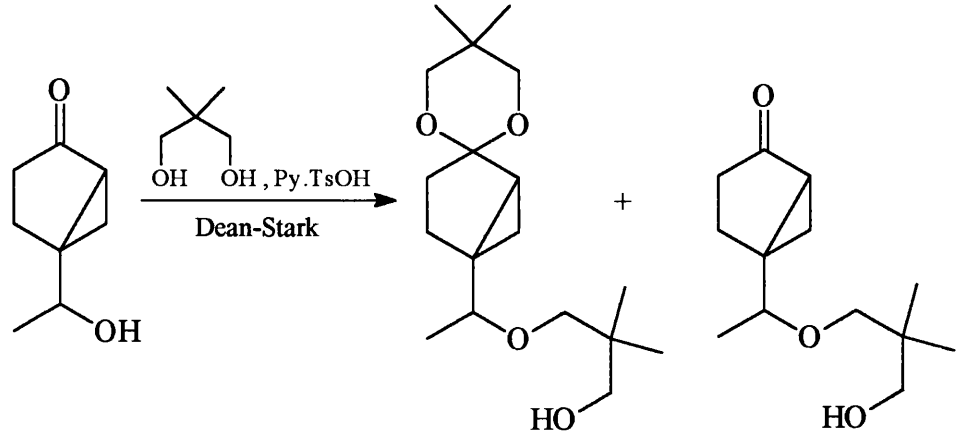


(**280**) (**290**)

The protection[121] of the ketone as its ketal provided a major headache. The isolated major product (as a mixture of diastereomers) proved difficult to assign at first. Initially it was assumed that the desired ketal had formed, but was impure with a number of extra quaternary, methylene and methyl peaks in the ^{13}C NMR. Attempts to purify the product resulted in partial separation of the diastereomers, which showed

that the 'extra' peaks were part of the product. Hence, the major product was assigned structure (**302**). The mass spectrum also confirmed a molecular ion consistent with the assigned structure. Similarly, the minor product was also shown to be an ether (**303**).

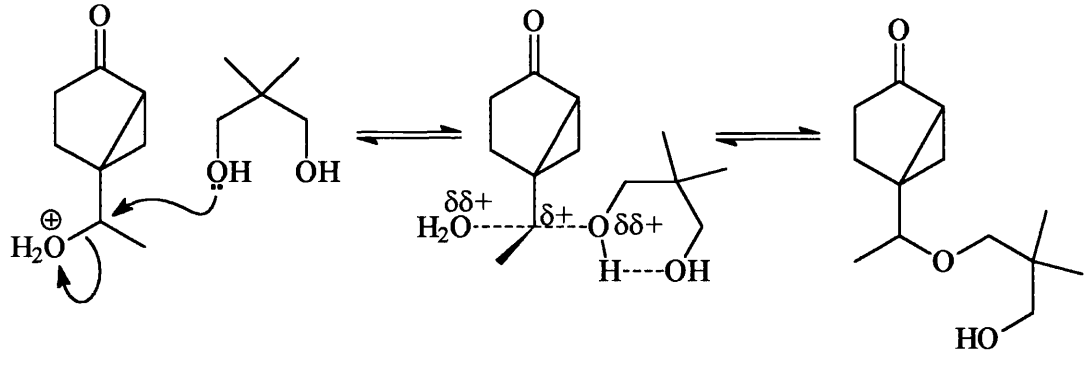
Scheme 4.40 Attempted ketalisation of ketone (290).



(**290**) (**302**), 52 % (**303**), 20 %

Obviously, ether formation does not normally occur under such mild conditions and it is assumed that the cyclopropyl group is stabilising the positive charge which develops on the adjacent carbon atom in the proposed transition state (**305**) (Scheme 4.41.).

Scheme 4.41. Proposed mechanism of ether formation.

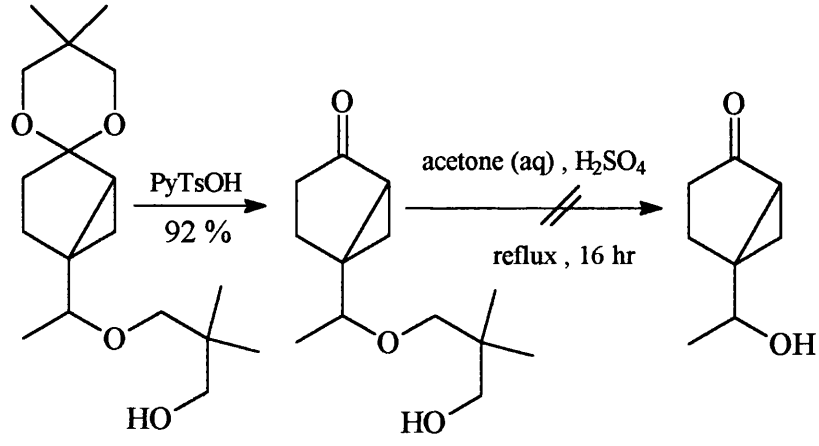


(**304**) (**305**) (**303**)

With the proposed mechanism, the equilibrium should be shifted back towards the alcohol (**290**) with water. However attempts to hydrolyse the ether met with failure

(Scheme 4.42.). The ether proved to be stable to quite strong conditions (16 hours at reflux in aqueous sulphuric acid/acetone). Using harsher conditions resulted in the formation of a number of unidentified products. The protonated ether (**305**), of course, can gain extra stabilisation from hydrogen bonding to the other hydroxyl as indicated previously, which may result in a poorer leaving group.

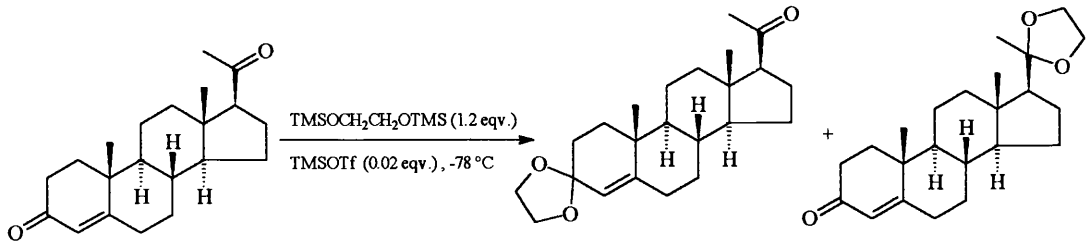
Scheme 4.42. Attempted ether cleavage.



(302) **(303)** **(290)**

Ketalisation can also be carried out *via* a Lewis acid/silyl ether route.[122] This method essentially uses the TMS as a bulky proton and proceeds with a similar mechanism to the standard acid catalysed ketalisation. However, it is a more selective ketalisation method. For compounds with more than one ketone, the less sterically hindered ketone is ketalised preferentially. For example the ketalisation of progesterone (**306**) proceeded with almost 3:1 selectivity for the less sterically hindered ketone (Scheme 4.43.). Under standard Dean-Stark ketalisation conditions the acetyl ketone would have been ketalised preferentially.

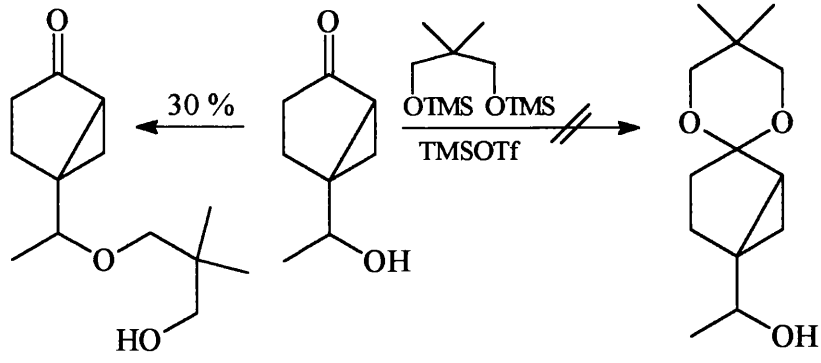
Scheme 4.43. Selective ketalisation of progesterone (306).



(306) **(307)** **(308)**

It was hoped that this methodology might improve the selectivity between ketalisation and ether formation with the ketone (**290**). Unfortunately, attempts to apply this methodology to the ketalisation of the ketone (**290**) proved unsuccessful (Scheme 4.44.). Using 1.2 equivalents of the bis-TMS ether resulted in a complex mixture from which no material could be isolated or characterised. Using more equivalents of the bis-TMS ether (3.0 eqv.) also gave a complex mixture from which only the previously prepared ether (**303**) was isolated. Both the bis-TMS ether of ethylene glycol (ex. Aldrich) and the bis-TMS ether of 2,2-dimethy-1,3-propanediol (which was synthesised from the diol (**294**), TMSCl and Et_3N in THF[123]) were used in this reaction.

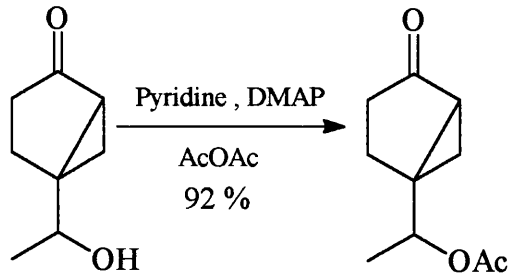
Scheme 4.44. Attempted Lewis acid induced ketalisation.



(303) **(290)** **(309)**

It was decided to protect the alcohol and attempt the ketalisation again. The alcohol (**290**) was therefore protected[101] as the acetate (**310**) which proceeded without incident (Scheme 4.45.).

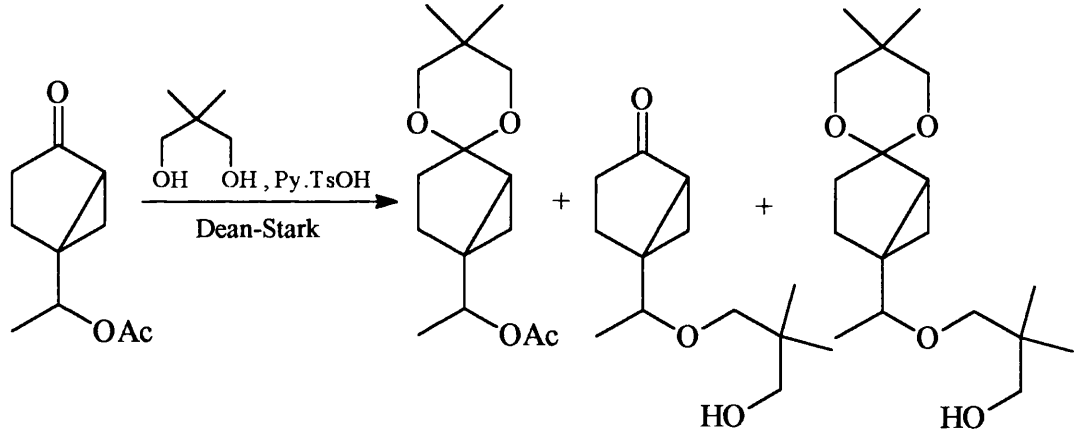
Scheme 4.45. Acylation of alcohol (290).



(290) **(310)**

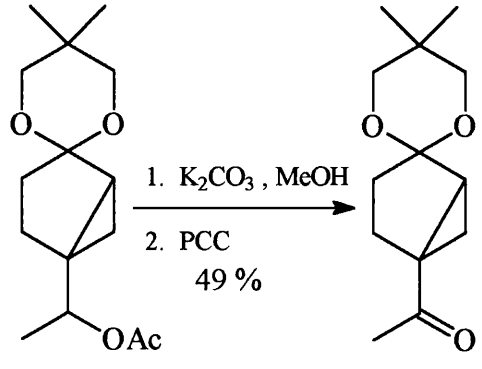
Attempted ketalisation[121] of the acetate (**310**) gave disappointing results (Scheme 4.46.). Some of the desired product was obtained (**311**), and the acetate could be cleaved[88] and the resultant alcohol oxidised[124] to the methyl ketone (**312**) (Scheme 4.47).

Scheme 4.46. Ketalisation of ketone (310).



(310) **(311)** 39 % **(303)** 3 % **(302)** 32 %

Scheme 4.47. Acetate cleavage and oxidation to the methyl ketone (312).

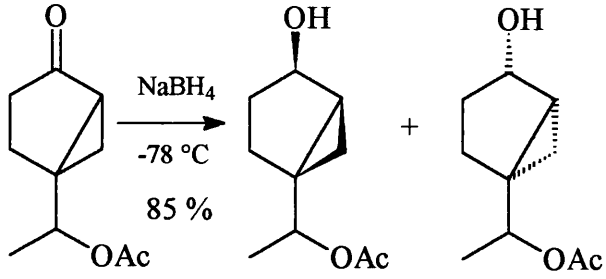


(311) **(312)**

Since the combined yield for these last three steps (ketalisation (Scheme 4.46.), acetate deprotection and alcohol oxidation (Scheme 4.47.)) was less than 20 % an alternative route was sought. It was decided that the ketone should be protected as its corresponding alcohol. However, since there were already two pairs of diastereomers a stereoselective reduction would be desired.

Initially K-Selectride[125] in THF at –78 °C was used but the selectivity[a] was only 6:1 for the α-isomers. $NaBH_4$ had previously been demonstrated to reduce[100] a similar ketone (**238**) diastereoselectively (Scheme 4.13.). Using $NaBH_4$ in EtOH at –10 °C resulted in similar selectivity to the K-Selectride. However, lowering the temperature to –78 °C with $NaBH_4$ gave high selectivity for the α-isomers (>20:1) (Scheme 4.48.)

Scheme 4.48. Diastereoselective reduction of ketone (310).



(310) **(313a)** **(313b)**

The relative stereochemistry was shown by NOE difference experiments (Scheme 4.49.). The diastereoselectivity is most probably due to the cyclopropyl ring blocking one side of the ring from attack of hydride. The cyclopropyl group in bicyclohexanone rings lies almost perpendicular to the cyclopentyl ring with one of the cyclopropyl hydrogens pointing towards the centre of the ring, blocking one face from hydride attack. However, this does not explain why the more bulky reagent was less selective. There is the remote possibility of incorporating the acetate as a delivery arm for the borohydride but this would require the formation of a strained 9-membered ring transition state. Also the diastereoselectivity of hydride delivery by K-Selectride can often be attributed to the nature of the reaction solvent.

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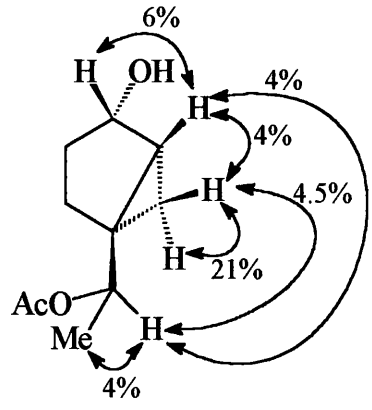
[a] Determined by ^1H NMR integral measurement.

Scheme 4.49. NOE for the diastereoselectively reduced alcohol (313).

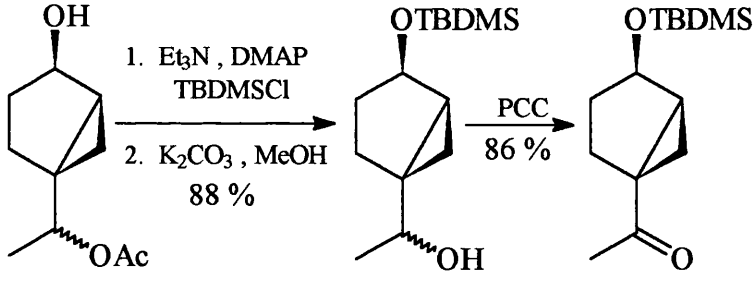


(313)

The free alcohol (**313**) (as a mixture of diastereomers) was then protected[99] as its TBDMS ether and the acetate cleaved.[88] The resulting alcohol (**314**) was oxidised[124] to the methyl ketone (**315**) in good overall yield (Scheme 4.50.).

The overall yield of methyl ketone (**315**) from cyclohexan-1,4-dione is 22 % for a 10 step route. Although this is only a slight improvement over the 11 step route (in the initial strategy) to yield methyl ketone (**249**) in 21 % yield, the big improvement is that the reaction yields to produce the methyl ketone (**315**) are reproducible.

Scheme 4.50. Preparation of methyl ketone (315).

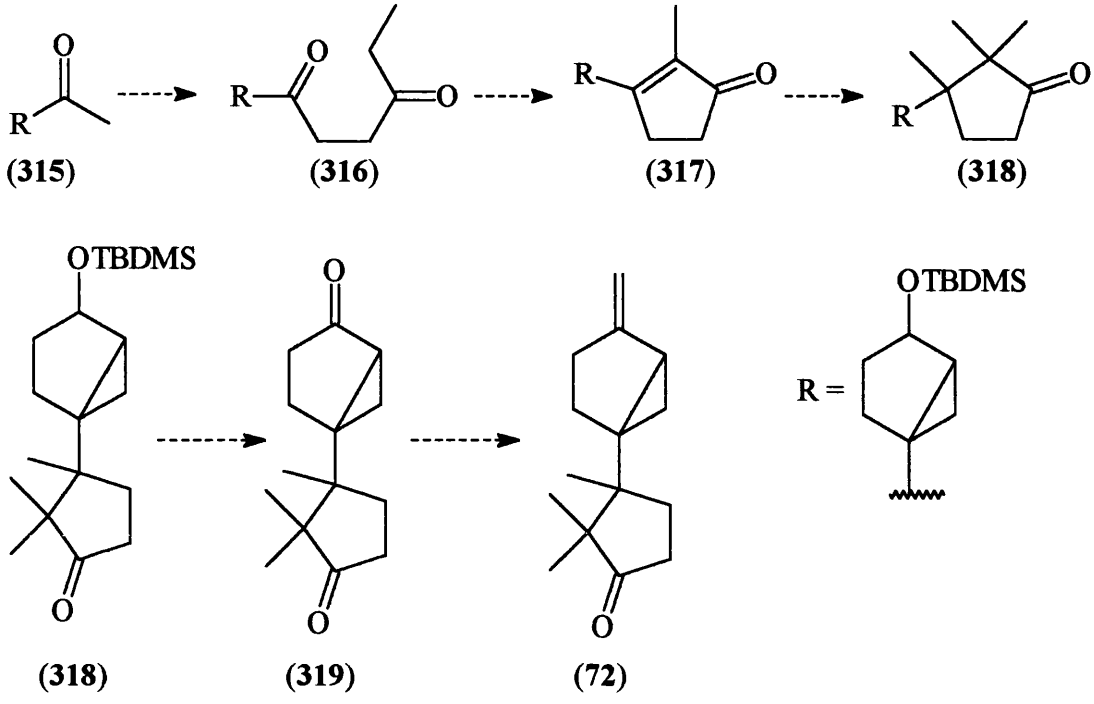


(313) **(314)** **(315)**

With a suitable route to methyl ketone (**315**) in hand, work began on the construction of the final ring. It was decided to construct the cyclopentyl ring from a 1,4 dione (**316**). The methyl groups could be inserted by a methylcuprate addition followed by methyl iodide quench. With the cyclopentane ring (**318**) complete all that would remain is removal of the TBDMS group and oxidation of the resulting alcohol to the ketone (**319**). Olefination by Wittig or similar methodology would proceed,

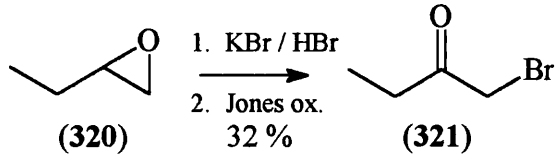
hopefully, selectively at the less hindered ketone to furnish grimaldone (**72**).

Scheme 4.51. Final proposed reaction route.



The 1,4-dione (**316**) was to be constructed by alkylation with 1-bromo-2-butanone (**321**). This was manufactured by first forming the bromohydrin from epoxy-butane (**320**) (Scheme 4.52).[126] The crude mixture of bromohydrins (~3:1 selective for the desired regioisomer) was used without separation. Oxidation[120] using Jones' reagent furnished the bromomethyl ketone (**321**). The undesired regioisomer would have been converted to 2-bromo-butanoic acid and washed out during basic work-up. Although the yield was low, it worked out a lot cheaper than buying 1-bromo-butanone[94] (1-bromo-butan-2-one; 1g - £28.80. 1,2-epoxybutane; 250 ml - £5.70).

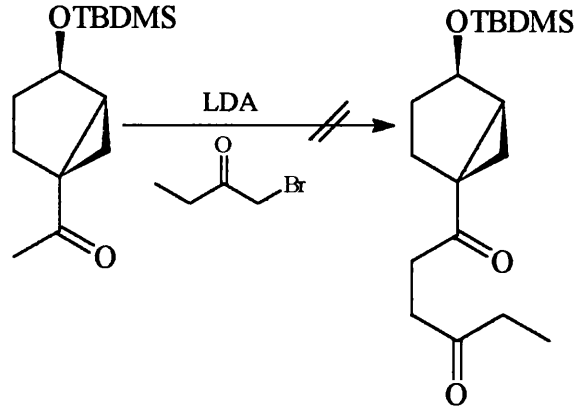
Scheme 4.52. Bromomethyl ketone (321) from 1,2-epoxy butane (320).



Initially, alkylation was attempted using the enolate generated from the methyl ketone (**315**) (Scheme 4.53.). The NMR of the crude reaction mixture showed no trace of

the bromomethyl ketone (**321**). Chromatography showed no trace of the required dione (**316**) and the methyl ketone (**315**) was recovered (82 %). The acidity of the hydrogens on the bromine carbon of 1-bromo-butan-2-one (**321**) will be greater than that of the hydrogens on the methyl ketone (**315**). Hence, the enolate of the methyl ketone (**315**) most probably abstracted a proton from the bromomethyl ketone (**321**), rather than displace the bromide nucleophilically. The bromobutanone enolate must have then reacted with other α-bromoketones to produce a variety of products.

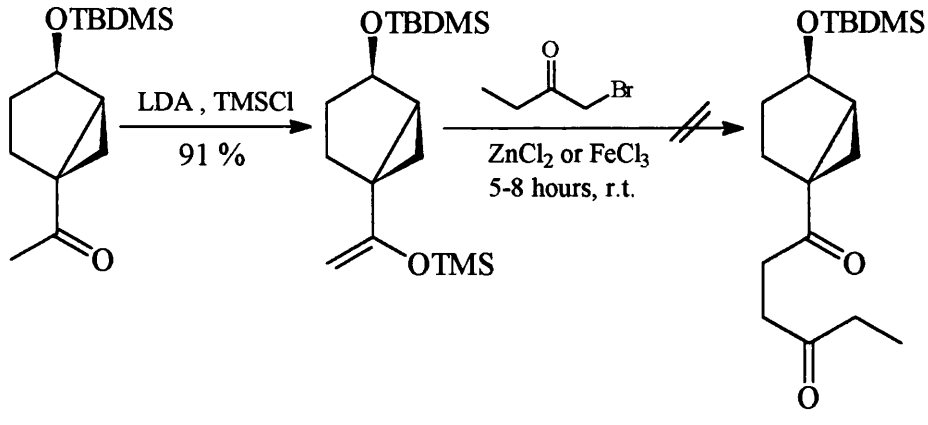
Scheme 4.53. Attempted alkylation of methyl ketone (315) with 1-bromo-butan-2-one.



(315) **(316)**

Since it was thought that the basicity of the enolate was causing problems the silyl enol ether (**322**) was prepared[127] in high yield (Scheme 4.54.). However, reaction[90] of the silyl enol ether (**322**) with the bromomethyl ketone (**321**) in the presence of a Lewis acid proved disappointing. The silyl enol ether (**322**) was still present in the worked-up reaction mixture along with the methyl ketone (**315**) and the bromomethyl ketone (**321**), with no sign of product. The reaction may have needed a stronger Lewis acid or higher reaction temperatures. A problem may have been that the silyl enol ether (**322**) did not appear to be particularly reactive, probably due to stabilising conjugation with the cyclopropyl group.

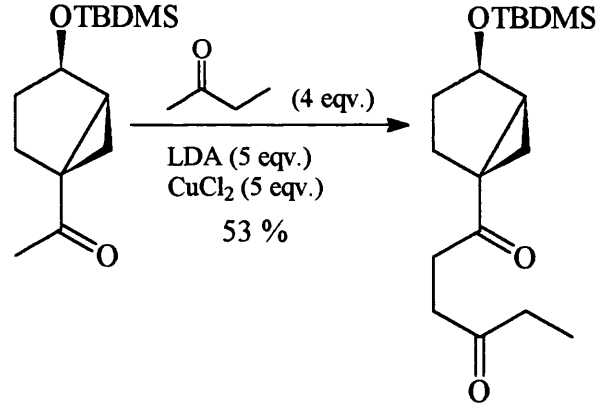
Scheme 4.54. Attempted Lewis acid induced coupling of silyl enol ether (322) with 1-bromo butan-2-one.



(315) **(322)** **(316)**

With alkylation using 1-bromobutan-2-one failing, it was decided to attempt an oxidative copper chloride catalysed coupling of enolates.[62] In this way the desired diketone (**316**) was produced in moderate yield (Scheme 4.55.). The reaction mixture, as expected, was quite messy and extensive chromatography was required to obtain the dione (**316**) relatively purely.

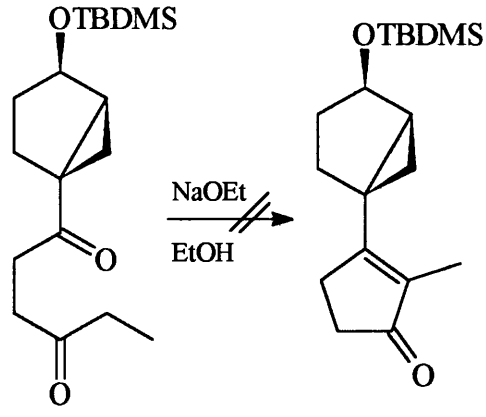
Scheme 4.55. Copper chloride catalysed coupling of enolates.



(315) **(316)**

The aldol condensation[128] of the dione (**316**) to give the cyclopentenone (**317**) was unsuccessful (Scheme 4.56.). A complex mixture resulted from which no products were identified.

Scheme 4.56. Attempted aldol condensation of 1,4-diketone (316).

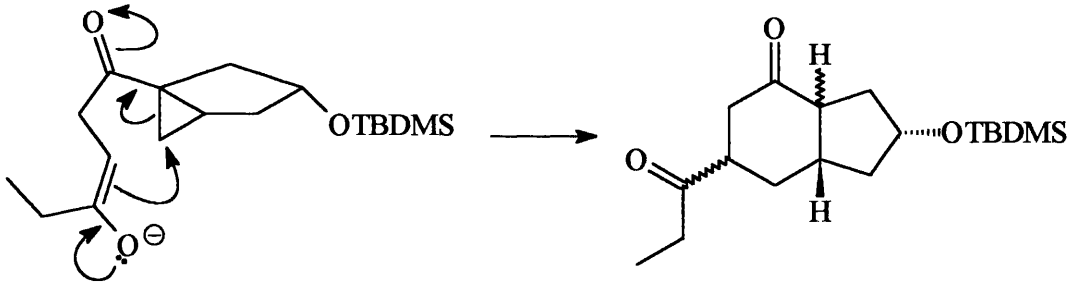


(316) **(317)**

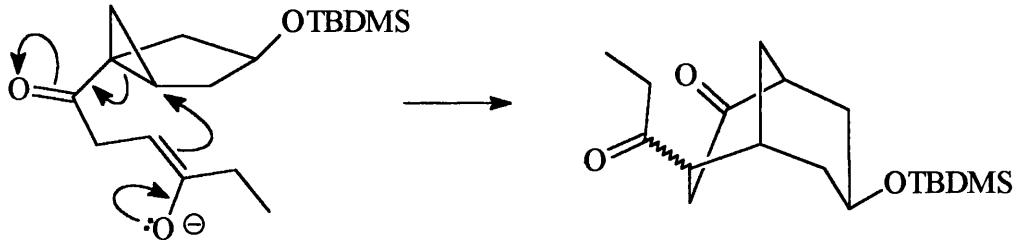
A possible explanation for the complex mixture of products may be attack of an enolate on the cyclopropane to give products of the type shown in Scheme 4.57.. There were however olefinic residues in the product mixture indicating the remote possiblity of product formation, although the two diketones (**323** and **325**) could also undergo aldol condensation.

Unfortunately lack of time did not allow any further progress to be made.

Scheme 4.57. Possible routes to multiple products.



(323) **(324)**



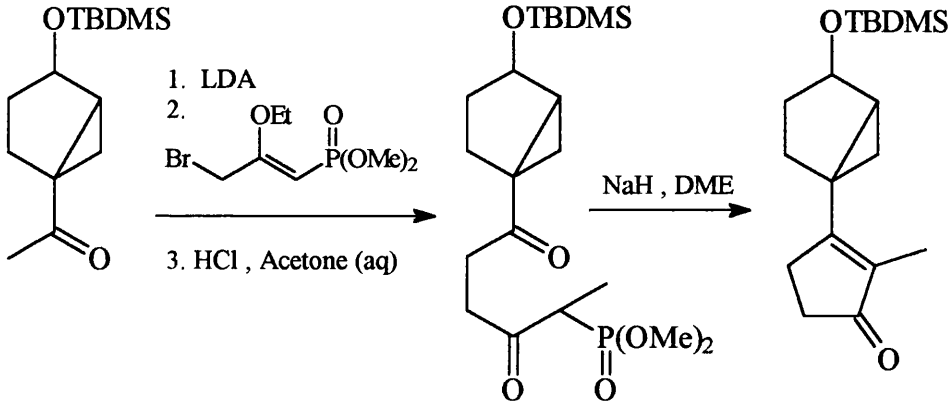
(323) **(325)**

4.5. Future Work.

4.5.1. Completion of synthesis.

With the aldol condensation failing and the synthesis of the diketone (**316**) not very efficient, an alternative route would probably have to be devised to manufacture the cyclopentyl ring. A promising route could be *via* the intramolecular Wittig approach discussed previously (Scheme 3.23.). If the methyl ketone (**315**) could be converted to the phosphonate (**326**) then the intramolecular Wittig would furnish the required cyclopentenone (**317**) (Scheme 4.58.)

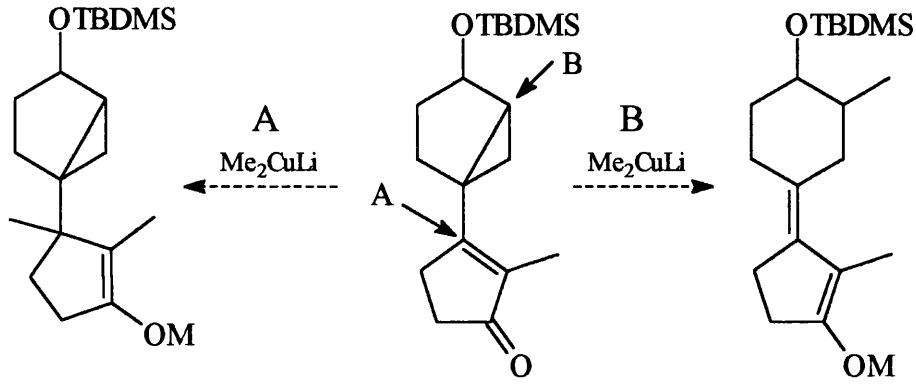
Scheme 4.58. Proposed synthesis of cyclopentenone (317).



(**315**) (**326**) (**317**)

With the cyclopentenanone (**317**) available, the remaining difficulty in the synthesis would be the addition of a methyl cuprate species to the enone system to give the required tertiary methyl. However, the addition of a methyl at the required position (A) might be quite challenging because of the steric environment (Scheme 4.59.). There is always the possibility that the methyl could attack the cyclopropane ring (position B) to generate the dienolate (**328**).

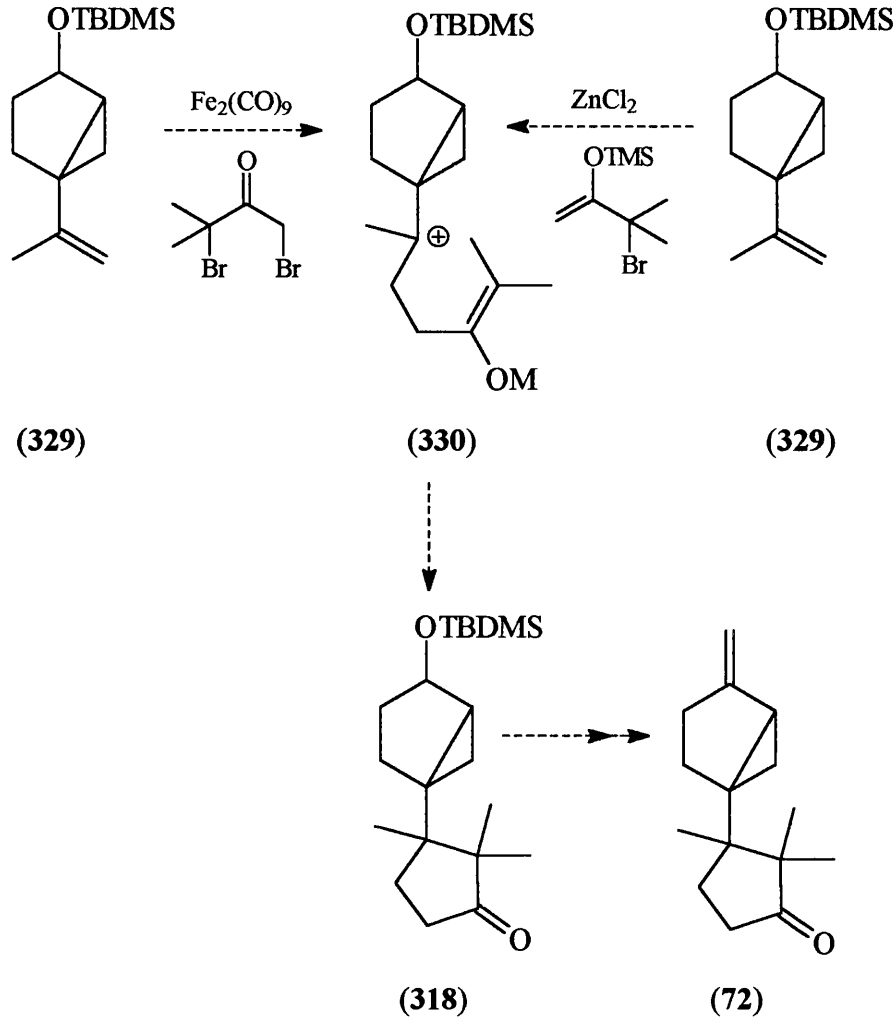
Scheme 4.59. Methyl cuprate addition to bicyclohexane-pentenone (317).



(327) **(317)** **(328)**

It might be worth considering some of the more direct (albeit low yielding) approaches to generating the cyclopentyl skeleton. In particular the oxyallyl methods of Noyori[78] and Sakurai[79] used in the synthesis of α-cuparenone (**73**) which were discussed previously (Scheme 3.33. and Scheme 3.34.). As can be seen from the proposed reaction scheme (Scheme 4.60.) both methods would go through a similar intermediate, the α-cyclopropyl cation (**330**), which is quenched internally by the enol ether to give the cyclopentane (**318**). Stabilisation of the intermediate cation (**330**) would be provided by conjugation with the cyclopropyl group. The required starting material (**329**) for this reaction sequence would be easily prepared by Wittig methylenation of the methyl ketone (**315**).

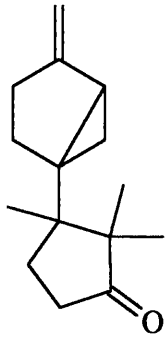
Scheme 4.60. Proposed route to direct cyclopentyl synthesis.



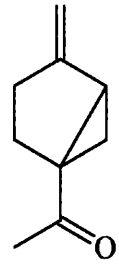
4.5.2. Odoriferous compounds.

Unfortunately, none of the intermediates produced in any of the synthetic routes had any odoriferous properties of note. The most fragrant compound without doubt was 4-ethylidene-cyclohexanone (**269**) which had a very sweet bitter-almond smell which, of course, is very characteristic of cyclohexanones. It is no coincidence that the most odoriferous compound produced, was the only one containing one heteroatom. Therefore, the main reason for the lack of odoriferous compounds produced during any of the synthetic routes is probably because most compounds were reasonably polar and hence not volatile enough. If time had allowed it would have been interesting to produce some vinyl cyclopropanes from some of the intermediates which may be potential grimaldone analogues (Scheme 4.61.).

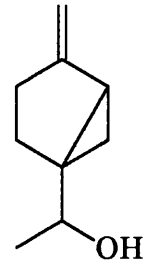
Scheme 4.61. Proposed olfactory vinylcyclopropane grimaldone analogues.



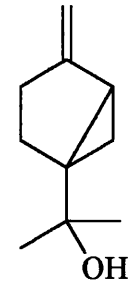
(72)



(331)



(332)



(333)

4.6. Summary.

The first strategy employed in the synthesis of grimaldone (**72**), which proposed to use a Lewis acid to aid the alkylation of a silyl enol ether (**248**) with a tertiary chloride (**241**) (Scheme 4.2.), was unsuccesful. The required chloride (**241**) could not be prepared from the alcohol (**240**) (Scheme 4.14.). However, the alcohol (**240**) was converted to the methyl ketone (**249**) (Scheme 4.18.) which could allow further progress to be made. Unfortunately, the synthesis of the methyl ketone (**249**) required an 11 step synthesis which did not give consistent yields. The decision was taken to abandon this pathway in search of a shorter, more robust route.

The second strategy was based around a proposed cascade reaction of a γ,δ-epoxy-ketone (**255**) to form an α,β-cyclopropyl-ketone (**256**) (Scheme 4.21.). The required γ,δ-epoxy-ketone (**255**) could not be synthesised (Scheme 4.24.) and hence the cascade reaction could not be attempted.

The third strategy involved the initial synthesis of a methyl ketone (**267**) (Scheme 4.25.). This target was similar to the methyl ketone (**249**) (Scheme 4.18.) produced in the first strategy. However, it was hoped that the methyl ketone (**267**) could be produced in fewer steps, with greater consistency. Unfortunately, unforeseen problems with the ketalisation (Scheme 4.40.) of the bicyclohexanone (**290**) forced extra steps to be incorporated into the synthetic sequence. Hence, the methyl ketone (**315**) was produced in a 10 step synthesis but with reproducible reaction yields. The

methyl ketone (**315**) was converted to the dione (**316**) (Scheme 4.55.) in moderate yield. Unfortunately the subsequent aldol condensation (Scheme 4.56.) to convert the dione (**316**) to the cyclopentenone (**317**) failed. No further progress was made towards the synthesis of grimaldone (**72**). However, the methyl ketone (**315**) does provide an ideal basis on which to build the final cyclopentyl ring and complete the synthesis.

5. EXPERIMENTAL

General

Melting points were determined on a Kofler hot stage melting point apparatus and are uncorrected. Bulb to bulb distillations were carried out on a Büchi GKR-50 Kugelrohr.

^{1}H NMR spectra were recorded on a Bruker AM360SY spectrometer operating at 360 MHz or, either a Bruker AM200SY spectrometer or Bruker WP200SY spectrometer operating at 200 MHz. ^{13}C NMR were recorded on the aforementioned machines operating at 90, 50 and 50 MHz respectively. All spectra were recorded using $CDCl_3$ as solvent unless otherwise stated. Chemical shifts (δ) are in ppm with reference to $C\underline{H}Cl_3$ at 7.25 ppm and $\underline{C}DCl_3$ at 77.0 ppm. Coupling constants are recorded in Hertz and are ^{1}H-^{1}H unless otherwise stated. The following abbreviations are used s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet, br - broad, ABq - AB quartet. The multiplicities of the carbon atoms (i.e. C, CH, CH_2 or CH_3) were determined from the corresponding DEPT spectra.

Infrared spectra were determined with either a Perkin Elmer FT-IR spectrometer or a Paragon 1000 spectrometer. All spectra were recorded as a thin film unless otherwise stated..

Low resolution mass spectra were determined using a Kratos MS12 spectrometer while high resolution mass spectra were determined using a Kratos MS902S spectrometer.

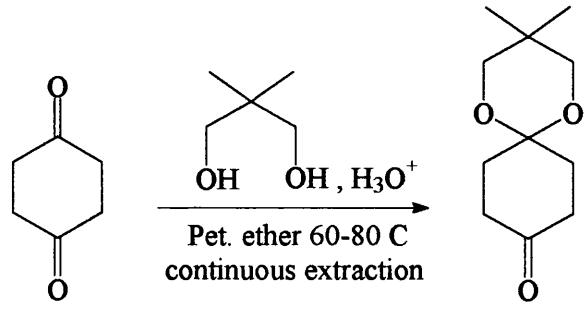
Column chromatography employed silica gel 60 for positive pressure chromatography or silica gel GF_{254} for dry flash chromatography. Preparative TLC was carried out on plates coated with 0.75mm silica gel GF_{254}. Analytical TLC was carried out using Merck Kieselgel 60 F_{254} foil backed plates.

The concentration of butyl lithium in hexanes was determined by titration against diphenylacetic acid. TBAF was used as a standard solution in THF. Titanium tetrachloride was diluted prior to use with dry DCM.

Solvents were distilled before use: Et_2O and THF from sodium/benzophenone, CH_2Cl_2 and $CHCl_3$ from P_2O_5, acetone from anhydrous K_2CO_3, MeOH from Mg/I_2, pentane and toluene from sodium, Et_3N and pyridine from KOH, and DMF from BaO. All organic solutions were dried with $MgSO_4$ and evaporated on a Büchi rotary evaporator under reduced pressure unless otherwise stated.

Where reactions have required a nitrogen atmosphere, all reagents were transferred using an oven dried syringe (cooled in a desiccator) under a nitrogen atmosphere unless otherwise stated.

3,3-Dimethyl-1,5-dioxa-spiro{5.5}undecan-9-one (218)



(216) **(218)**

Procedure: [91]

An acidic solution (500 ml, 0.2M H_2SO_4) of 1,4-cyclohexanedione (**216**) (16 g, 14.3 mmols) and 2,2-dimethyl-1,3-propanediol (18.5 g, 17.8 mmols) was continuously extracted with light petroleum (60-80 °C) for 10 days. Solid $NaHCO_3$ (1 g) was added to the extraction flask to prevent any hydrolysis of the extracted products. To the cooled light petroleum solution was added ether (100 ml), the solution filtered and solvent removed *in vacuo*. The crude product (25 g) was dissolved in light petroleum-ether (150 ml, 1:1) and washed with water (100 ml), followed by saturated aqueous NaCl (3 x 100 ml). The organic solution was dried and concentrated *in vacuo* to leave the title compound (**218**) (23.5 g, 85%) as a white solid shown to be >98% pure[a] (R_f 0.34, light petroleum-EtOAc (4:1)). An analytical sample was prepared by recrystallisation, m.p. 51-52 °C (from light petroleum)(lit.[91] 44-46 °C).

(Found : C, 66.7; H, 9.1. $C_{11}H_{18}O_3$ requires C, 66.7; H, 9.1%)

ν_{max}/cm^{-1}($CHCl_3$) 1715 (C=O), 1396,1365 (CMe_2), 1123 (C-O-R).

δ_H 3.51 (4H, s, $C\underline{H_2}$-OR), 2.37 (4H, t, J 6.8, $C\underline{H_2}$-C=O), 2.10 (4H, t, J 6.8, $C\underline{H_2}$-$C(OR)_2$), 0.96 (6H, s, Me).

δ_C 209.9 (C=O), 95.7 ($C(OR)_2$), 70.0 (CH_2-OR), 36.5 (CH_2-C=O), 30.7 (CH_2-$C(OR)_2$), 29.8 ($C(Me)_2$), 22.2 (Me).

[Found : M^+ 198.1264, $C_{11}H_{18}O_3$ requires 198.1256] ; m/z 198 (2%, M^+), 141 (100, $C_8H_{13}O_2$), 113 (12, $C_6H_9O_2$).

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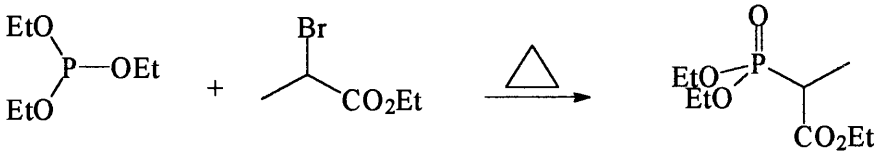
[a] Determined by ^1H NMR integral. The only impurity was shown to be bisketal.

Ethyl 2-diethylphosphono-propanoate (221)



(220) **(226)** **(221)**

Procedure:[93]

To a 3-necked 500 ml flask, fitted with dropping funnel and distillation apparatus, was added triethylphosphite (**220**) (71.4 g, 0.43 moles). The reaction flask was heated to 140 °C and ethyl 2-bromopropionate (**226**) (76.8 g, 0.43 moles) dropped in slowly to the stirring reaction mixture. Ethyl bromide was liberated and collected by distillation. The temperature was maintained between 140-160 °C during the addition (2 hours) and then raised to 190 °C. Heating was continued for a further 2 hours. The clear yellow reaction mixture was distilled to yield the title compound (**226**) (80.2 g, 79%) as a clear oil, b.p. 90-95 °C/0.5mm Hg. (lit.,[129] 93-95 °C/0.85mm Hg) (Found : C 45.1; H, 8.1. $C_9H_{19}O_5P$ requires C, 45.4; H, 8.0%)

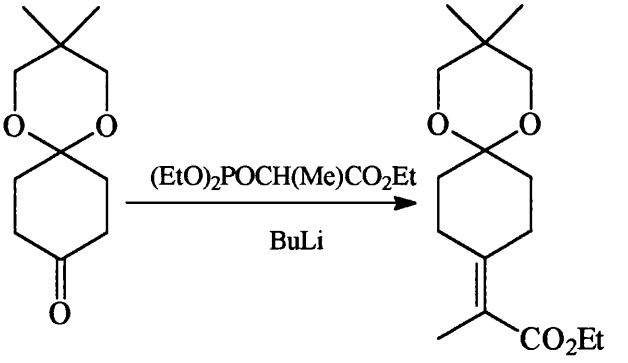
ν_{max}/cm^{-1} 1736 (C=O), 1256 (P=O), 1052 (P-OR).

δ_H 4.02 (6H, m, CH_2-OP and CH_2-OC), 3.04 (1H, dq, $J(^{31}P-^{1}H)$ 23, J 7.3, CH-Me), 1.47 (3H, d, J 7.3, CH-Me), 1.34 (9H, m, Me-CH_2OP and Me-CH_2OC).

δ_C 164.5 (d, $J(^{31}P-^{13}C)$ 3.4, C=O), 62.4 (d, $J(^{31}P-^{13}C)$ 6.2, CH_2-OP), 61.2 (CH_2-OC), 39.1 (d, $J(^{31}P-^{13}C)$ 133.4, CH-Me), 16.2 (d, $J(^{31}P-^{13}C)$ 5.2, Me-CH_2OP), 13.9 (Me-CH_2OC), 11.5 (d, $J(^{31}P-^{13}C)$ 6.2, CH-Me).

[Found : M^+ 238.0979, $C_9H_{19}O_5P$ requires 238.0970] ; m/z 238 (23%, M^+), 193 (66, $C_7H_{14}O_4P$), 165 (44) $C_5H_{10}O_4P$, 138 (49, $C_4H_{11}O_3P$), 109 (100, $C_2H_6O_3P$).

Ethyl 2-(3,3-dimethyl-1,5-dioxa-spiro{5.5}undec-9-ylidene)-propanoate (219)



(218) **(219)**

Procedure:[92,93]

To a flame dried 3-necked 500 ml round bottomed flask fitted with septum and N_2 balloon was added ethyl 2-diethylphosphono-propanoate (**221**) (13.7g, 57.6 mmols) in dry THF (125 ml) *via* cannula. The reaction flask was cooled (-78 °C) and butyl lithium (43 ml, 1.44 M, 62 mmols) added dropwise *via* cannula. The flask was removed from the cooling bath and allowed to stir for 30 minutes. The flask was re-cooled (-78 °C) and 3,3-dimethyl-1,5-dioxa-spiro{5.5}undecan-9-one (**218**) (10.6 g, 53.5 mmols) in dry THF (125 ml) added *via* cannula. The cooling bath was removed and the reaction allowed to stir for a further 5 hours. To the reaction mixture was added MeOH (10 ml) followed by water (100 ml). The product was extracted with ether (3 x 125 ml). The combined organic extracts were washed with saturated aqueous NaCl (3 x 100 ml), dried and solvent removed *in vacuo* to leave the crude product (10.2 g) as a brown oil. Column chromatography with light petroleum-EtOAc (9:1) as the eluent yielded the title compound (**219**) (8.61 g, 85%) as a clear oil, b.p.140 °C/0.5 mm Hg. (R_f 0.55, light petroleum-EtOAc (4:1).

ν_{max}/cm^{-1} 1712 (C=O), 1640 (C=C), 1394, 1364 ($C(Me)_2$), 1100 (C-O-R).

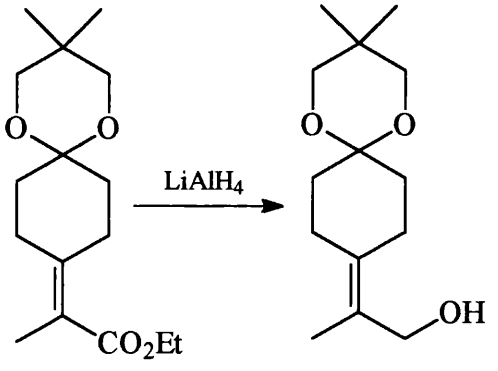
δ_H 4.16 (2H, q, J 7.1Hz, O-$C\underline{H}_2$Me), 3.51,3.48 (4H, ABq, J 11.2Hz, $C(O\text{-}C\underline{H}_2)_2$), 2.51 (2H, t, J 6.1Hz, $C\underline{H}_2$-C=C), 2.29 (2H, t, J 6.5Hz $C\underline{H}_2$-C=C), 1.85 (3H, s, Me-C=C), 1.88-1.82 (4H, m, $C\underline{H}_2$-$C(OR)_2$), 1.27 (3H, t, J 7.1Hz, Me-CH_2), 0.97 (3H, s, $C(\underline{Me})_2$), 0.93 (3H, s, $C(\underline{Me})_2$).

δ_C 170.0 (C=O), 145.4 (C=CMe), 120.8 (C=CMe), 97.0 ($\underline{C}(OR)_2$), 70.0 ($C(O\text{-}\underline{C}H_2)_2$), 60.0 (O-$\underline{C}H_2$-Me), 32.8, 32.3, 27.1, 26.3 ($\underline{C}H_2$-$\underline{C}H_2$), 30.1 ($\underline{C}(Me)_2$), 22.6,

22.5 (C(Me)$_2$), 15.2 (vinyl Me), 14.1 (CH_2-Me).

[Found : M^+ 282.1825, $C_{16}H_{26}O_4$ requires 282.1831] ; m/z 282 (64%, M^+), 253 (24, $C_{14}H_{21}O_4$), 237 (25, $C_{14}H_{21}O_3$), 209 (72, $C_{13}H_{21}O_2$), 128 (100, $C_7H_{12}O_2$).

2-(3,3-Dimethyl-1,5-dioxa-spiro{5.5}undec-9-ylidene)-propan-1-ol (227)



(219) **(227)**

Procedure:[92]

To a flame-dried 3-necked 500 ml round bottom flask, fitted with condenser and N_2 balloon was added $LiAlH_4$ (810 mg, 21.3 mmol). The flask was evacuated and purged with nitrogen before adding dry THF (125 ml) *via* cannula. To the stirred suspension was added ethyl 2-(3,3-dimethyl-1,5-dioxa-spiro{5.5}undec-9-ylidene) propanoate (**219**) (9.66 g, 34.3 mmol) in dry THF (125 ml) *via* cannula. The solution was stirred for 3 hours. To the reaction mixture was cautiously added EtOAc (20 ml). The reaction mixture was then poured into sodium sulphate solution (150 ml) and extracted with ether (3 x 150 ml). The combined organic solutions were washed with saturated aqueous NaCl (3 x 150 ml), dried and solvent removed *in vacuo* to leave the crude product (9 g). Chromatography with light petroleum-EtOAc (1:1) as the eluent yielded the title compound (**227**) (7.75 g, 94%) as a white solid (R_f 0.34, light petroleum-EtOAc (1:1)). The product was purified further by recrystallisation for analytical purposes, m.p. 123-125 °C (from light petroleum-EtOAc). (Found : C 70.1; H, 10.0, $C_{14}H_{28}O_3$ requires C, 70.0; H, 10.0%).

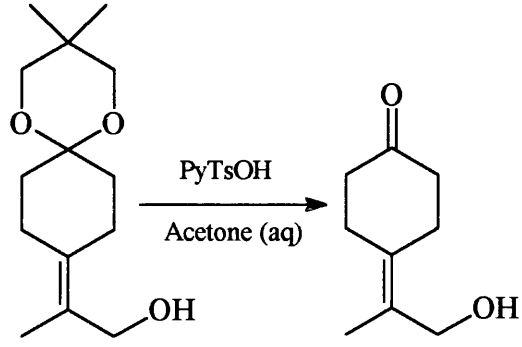
ν_{max}/cm^{-1} ($CHCl_3$) 3613, 3450(br) (OH), 1660 (C=C), 1395, 1367 (C(Me)$_2$), 1102 (C-O-R)

δ_H 4.12 (2H, s, C<u>H</u>$_2$-OH), 3.50 (4H, s, C<u>H</u>$_2$-OR), 2.29 (2H, t, J 6.2, C<u>H</u>$_2$-C=C), 2.23 (2H, t, J 6.4, C<u>H</u>$_2$-C=C), 1.79-1.83 (4H, m, C<u>H</u>$_2$-C(OR)$_2$), 1.77 (3H, s, vinyl <u>Me</u>), 1.21 (1H, br, O<u>H</u>), 0.96 (3H, s, C(<u>Me</u>)$_2$), 0.96 (3H, s, C(<u>Me</u>)$_2$).

δ_C 134.3 (<u>C</u>=CMe), 125.5 (C=<u>C</u>Me), 97.3 (C(OR)$_2$), 69.8 (<u>C</u>H$_2$-OR), 62.6 (<u>C</u>H$_2$-OH), 32.9, 32.6, 25.6, 24.8 (<u>C</u>H$_2$-<u>C</u>H$_2$), 30.0 (<u>C</u>(Me)$_2$), 22.5 (<u>Me</u>), 16.1 (vinyl <u>Me</u>).

[Found : M^+ 240.1742, $C_{14}H_{28}O_3$ requires 240.1726] ; m/z 240 (3%, M^+), 222 (10, $C_{14}H_{22}O_2$), 129 (34, $C_7H_{13}O_2$), 128 (100, $C_7H_{12}O_2$), 69 (73, C_5H_9).

4-(2-Hydroxy-1-methyl-ethylidene)-cyclohexanone (228)



(227) **(228)**

<u>Procedure</u>: [95]

A solution of 2-(3,3-dimethyl-1,5-dioxa-spiro{5.5}undec-9-ylidene)-propan-1-ol (**227**) (7.39 g, 30.8 mmols) and pyridinium tosylate[a] (2.7 g, 10.7 mmols) in wet acetone (150 ml) was refluxed for 16 hours. To the cooled solution was added saturated aqueous $NaHCO_3$ (150 ml) and excess acetone removed *in vacuo*. The aqueous residue was extracted with EtOAc (3 x 100 ml). The organic layers were then washed with brine (3 x 100 ml), dried and solvent removed *in vacuo* to leave the crude product as a brown oil. Chromatography with light petroleum-EtOAc (2:1) yielded a white solid (0.55 g, 8%) which was shown to be identical to starting material (**227**) by NMR and TLC (R_f 0.34, light petroleum-EtOAc (1:1)). Further elution with EtOAc furnished the <u>title compound</u>[97] (**228**) (3.51 g, 74%) as a golden oil (R_f 0.23, light petroleum-EtOAc (1:1)).

ν_{max}/cm^{-1} 3404 (br, OH), 1712 (C=O), 1001 (C-OH).

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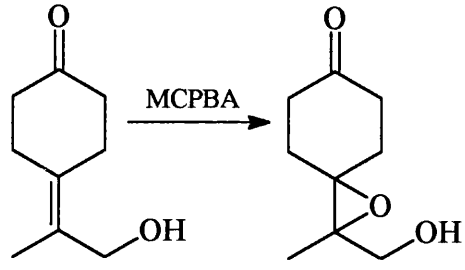
[a] See Appendix 2 for preparation of pyridinium tosylate.

δ_H 4.09 (2H, s, C<u>H</u>$_2$-OH), 3.44 (1H, s, O<u>H</u>), 2.60 (2H, t, J 6.6, ring C<u>H</u>$_2$), 2.52 (2H, t, J 6.8, ring C<u>H</u>$_2$), 2.34-2.41 (4H, m, ring C<u>H</u>$_2$).

δ_C 212.7 (<u>C</u>=O), 130.3, 128.4 (alkene), 62.5 (<u>C</u>H$_2$-OH), 39.8, 39.5, 26.8, 25.9 (ring <u>C</u>H$_2$), 16.0 (<u>Me</u>).

[Found : M^+ 154.0997, $C_9H_{14}O_2$ requires 154.0993] ; m/z 154 (3%, M^+), 136 (61, $C_9H_{12}O$), 123 (8, $C_8H_{11}O$), 79 (100).

2-Hydroxymethyl-2-methyl-1-oxa-spiro{2.5}octan-6-one (229)



(228) **(229)**

<u>Procedure</u>:[96]

To a stirred solution of MCPBA (0.94g, 50-55%, 2.7-3.0 mmols) in $CHCl_3$ (20 ml) at 0 °C was added the 4-(2-hydroxy-1-methyl-ethylidene)-cyclohexanone (**228**) (380 mg, 2.46 mmol) in $CHCl_3$ (10ml) dropwise over 20 minutes. The reaction was stirred for 10 minutes then allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 x 20 ml). The aqueous layer was extracted with EtOAc (3 x 50 ml). The combined organic extracts were dried and concentrated *in vacuo* to give the crude material as a cloudy oil (495 mg). The cloudy oil was purified by flash chromatography to yield the <u>title compound</u>[97] (**229**) (260 mg, 62 %) as a thick clear oil. (R_f 0.36, EtOAc).

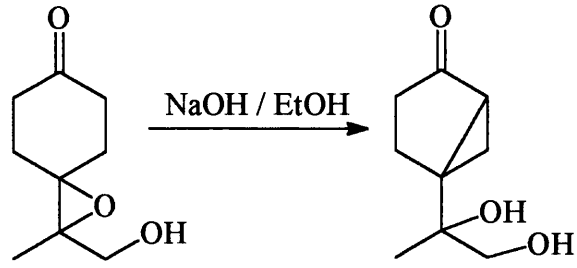
ν_{max}/cm^{-1} 3435 (br, OH), 1711 (C=O), 1036 (C-OH).

δ_H 3.71, 3.65 (2H, ABq, J 11.7, C<u>H</u>$_2$-OH), 2.29-2.57 (4H, m, C<u>H</u>$_2$-C=O), 1.72-2.13 (4H, m, C<u>H</u>$_2$-epoxide), 1.41 (3H, s, <u>Me</u>).

δ_C 210.9 (<u>C</u>=O), 65.7, 64.5 (epoxide <u>C</u>), 64.8 (<u>C</u>H$_2$-OH), 38.2, 29.2, 28.1 (ring <u>C</u>H$_2$), 16.0 (<u>Me</u>).

[Found : M^+ 170.0943, $C_9H_{14}O_3$ requires 170.0943] ; m/z 170 (0.5%, M^+), 139 (6, $C_8H_{11}O_2$), 113 (100, $C_6H_9O_2$), 97 (32, C_6H_9O).

5-(1,2-Dihydroxy-1-methylethyl)-bicyclo{3.1.0}hexan-2-one (230)



(229) (230)

Procedure:[53]

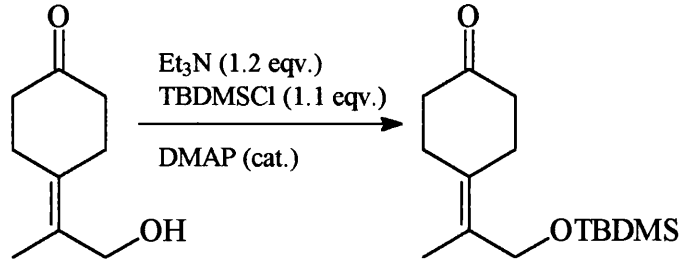
To a solution of the epoxide (**229**) (1.55 g, 10.1 mmols) in EtOH (10 ml) was added aqueous NaOH (10 ml, 2M). The solution was refluxed for 30 minutes. EtOH was removed *in vacuo* and the solution saturated with NaCl. The aqueous solution was extracted with DCM (3 x 50 ml), dried and solvent removed *in vacuo* to leave a crude white solid (0.5 g). Chromatography yielded a white solid which was shown to be the title product[97] (**230**) (150 mg, 10%) as one major diastereomer (R_f 0.53, EtOAc-MeOH (4:1)).

δ_H 3.3 (2H, m, CH_2OH), 0.83-2.55 (9H, m, ring protons and OH), 1.03 (3H, s, Me).

δ_C 218.1 (C=O), 72.6 (C-OH), 68.9 (CH_2-OH), 41.9 (cyclopropyl C), 34.2, 25.1 (cyclopentyl CH_2), 31.8 (cyclopropyl CH), 22.4 (Me), 17.8 (cyclopropyl CH_2).

m/z 170 (0.5%), 139 (38), 97 (51), 95 (11), 79 (12), 67 (11), 43 (100).

4-{2-(*tert*-Butyl-dimethyl-silanoxy)-1-methyl-ethylidene)}-cyclohexanone (334)



(228) (334)

Procedure:[99]

To a flame dried 100 ml 2 necked round bottom flask, fitted with septum and N_2

balloon was added Et_3N (5.3 ml, 38 mmols) followed by TBDMSCl (5.28 g, 35 mmols) and DMAP (260 mg, 2 mmols) in dry DCM (30 ml). To the stirred solution was added 4-(2-hydroxy-1-methyl-ethylidene)-cyclohexanone (**228**) (4.78 g, 31 mmols) in dry DCM (30 ml). The reaction mixture was stirred for 16 hours then diluted with DCM (90 ml), and washed with water (50 ml) and saturated aqueous NaCl (3 x 50 ml). The dried organic layer was concentrated to leave a brown oil. Chromatography with light petroleum-EtOAc (6:1) yielded the title product (**334**) (8.32g, quantitative) as a golden oil, b.p. 140 °C/0.4 mmHg. (R_f 0.56, light petroleum-EtOAc (2:1))

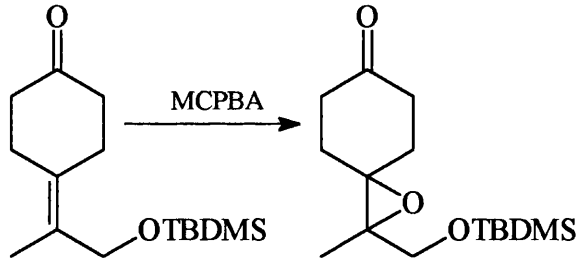
ν_{max}/cm^{-1} ($CHCl_3$) 1711 (C=O), 1064 (C-O-Si), 838 (SiMe),

δ_H 4.12 (2H, s, CH_2-O), 2.44-2.55 (4H, m, CH_2-C=O), 2.28-2.37 (4H, m, CH_2-C=C), 1.68 (3H, s, vinyl Me), 0.83 (9H, s, t-butyl Me), -0.02 (6H, s, -SiMe).

δ_C 212.3 (C=O), 128.9, 128.8 (alkene), 63.2 (CH_2-O), 40.0, 39.7 (CH_2-C=O), 27.1, 26.2 (-CH_2C=C-), 25.8 (t-butyl C), 18.3 (t-butyl Me), 15.7 (vinyl Me), -5.3 (SiMe).

[Found : M^+-tBu 211.1161, $C_{11}H_{19}O_2Si$ requires 211.1164] ; m/z 211 (43%, M^+), 119 (14, C_9H_{11}), 79 (11, C_6H_7O), 75(100 C_2H_7Si).

2-(*tert*-Butyl-dimethyl-silanoxy-methyl)-2-methyl-1-oxa-spiro{2.5}octan-6-one (237)



(**334**) (**237**)

Procedure:[96]

To a 250 ml round bottom flask was added MCPBA (4.5 g, 50-55%; 13-14 mmol) in $CHCl_3$ (75 ml). The solution was cooled to 0 °C and the alkene (**334**) (3.55 g, 13.2 mmol) in $CHCl_3$ (75 ml) added dropwise. The reaction mixture was allowed to stir for 10 minutes before being washed with 10% aqueous sodium bisulphite (75 ml). The organic layer washed with saturated aqueous $NaHCO_3$ (3 x 75 ml), saturated

aqueous NaCl (75 ml) and dried. Solvent was removed *in vacuo* to leave the crude product as a dark brown oil (3.9 g). Kugelrohr distillation (150 °C/0.5 mm Hg) afforded the title product (**237**) (3.36 g, 89%) as a golden oil (R_f 0.37, light petroleum-EtOAc (2:1)).

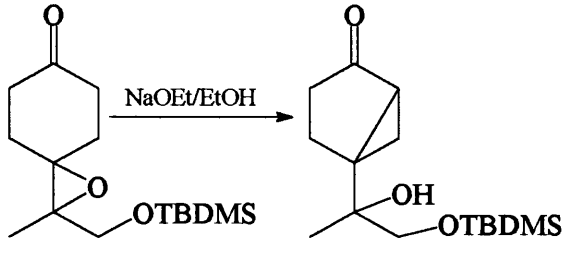
ν_{max}/cm^{-1} ($CHCl_3$) 1716 (C=O), 1156 (C-O-R) 1077 (C-O-Si), 850 ($Si(Me)_2$),

δ_H 3.67, 3.59 (2H, ABq, J 10.7, $C\underline{H_2}$-O), 2.26-2.58 (4H, m, $C\underline{H_2}$-C=O), 1.83-2.06 (4H, m, $C\underline{H_2}$-epoxide), 1.36 (3H, s, vinyl Me), 0.81 (9H, s, t-butyl Me), -0.01 (3H, s, SiMe), -0.03 (3H, s, SiMe).

δ_C 210.1 (C=O), 66.1 ($\underline{C}H_2$-O), 65.4, 64.0 (epoxide C), 38.4 ($\underline{C}H_2C$=O), 29.4, 28.4 (ring $\underline{C}H_2$), 25.6 (t-butyl Me), 18.0 (t-butyl C), 16.0 (Me-epoxide), -5.5 (SiMe), -5.6 (SiMe).

[Found : M^+-tBu 227.1110. $C_{11}H_{19}O_3Si$ requires 227.1103] ; m/z 227 (2%, M^+-tBu), 75 (18, C_2H_7OSi), 74 (64, $C_4H_{10}O$), 59 (100, C_3H_7O).

5-(1-(*tert*-Butyl-dimethyl-silanoxy)-2-hydroxy-*iso*-propyl)-bicyclo{3.1.0.}hexan-2-one (238)



(**237**) (238)

Procedure:[53]

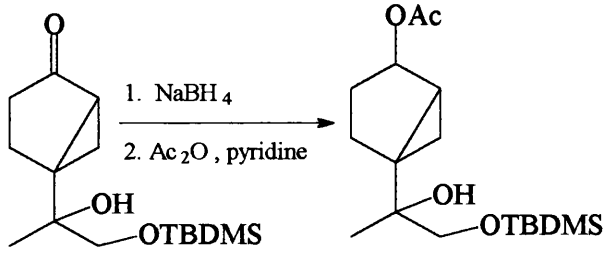
A solution of the epoxide (**237**) (2.9 g, 10.2 mmols) in ethanolic NaOEt (125 ml, 0.45M) was refluxed for 30 minutes. The cooled reaction mixture was neutralised with saturated aqueous NH_4Cl (100 ml). The solution separated into 2 layers and the aqueous layer was extracted with EtOAc (3 x 75 ml). The combined organic layers were washed with saturated aqueous NaCl (3 x 75 ml), dried and solvent removed *in vacuo* to leave the crude product as a dark brown oil. Chromatography with light petroleum-EtOAc (3:1) as the eluent yielded a light brown oil which was shown to be the title compound (238) (2.03 g, 70%) as a mixture of diastereomers (R_f 0.47 light

petroleum-EtOAc (1:1)).

δ_H 3.57, 3.48 (2H, ABq, J 9.7, C<u>H</u>$_2$-O), 3.53, 3.41 (2H, ABq, J 9.7, C<u>H</u>$_2$-O), 2.48 (2x1H, brs, O<u>H</u>), 1.76-2.08 (2x4H, m, cyclopentyl C<u>H</u>$_2$), 1.44-1.60 (2x2H, m, cyclopropyl <u>H</u>), 1.14 (3H, s, <u>Me</u>), 1.12 (3H, s, <u>Me</u>), 0.93 (1H, dd, 4.5, 3.3, cyclopropyl <u>H</u>), 0.85 (9H, s, t-butyl <u>Me</u>), 0.81 (9H, s, t-butyl <u>Me</u>), 0.02 (6H, s, Si<u>Me</u>), 0.00 (6H, s, Si<u>Me</u>).

δ_C 214.9, 214.5 (<u>C</u>=O), 71.0, 70.9 (<u>C</u>-OH), 68.3, 68.2 (<u>C</u>H$_2$-OSi), 39.9, 39.3 (cyclopropyl <u>C</u>), 33.2, 33.1 (cyclopentyl <u>C</u>H$_2$), 31.7, 30.5 (cyclopropyl <u>C</u>H), 25.7 (t-butyl <u>Me</u>), 24.0, 23.7 (cyclopentyl <u>C</u>H$_2$), 22.3, 22.0 (<u>Me</u>), 18.0 (t-butyl <u>C</u>), 17.0, 15.2 (cyclopropyl <u>C</u>H$_2$).

5-(1-(*tert*-Butyl-dimethyl-silanoxy)-2-hydroxy-2-*iso*-propyl) bicyclo{3.1.0.}hexan-2-yl acetate (240)



(238) **(240)**

Procedure:[100,101]

To a solution of the bicyclo-hexanone (**238**) (380 mg, 1.33 mmols) in EtOH (40 ml) was added excess $NaBH_4$ (45 mg, 1.2 mmols) in EtOH (10 ml). The solution was stirred for 16 hours. To the reaction mixture was added saturated aqueous NH_4Cl (30 ml) and excess EtOH was removed *in vacuo*. The aqueous residue was extracted with EtOAc (3 x 30 ml). The organic extracts were washed with saturated aqueous NaCl (3 x 30 ml), dried and solvent removed *in vacuo* to leave a brown oil (390 mg).

The oil was dissolved in dry pyridine-acetic anhydride (15 ml, 4:1) and stirred for 16 hours. The reaction mixture was diluted with saturated aqueous NH_4Cl (20 ml) and extracted with EtOAc (3 x 30 ml). The organic extracts were washed with aqueous $CuSO_4$ (3 x 30 ml) and brine (3 x 30 ml). The dried organic solution was concentrated *in vacuo* to leave the crude product (380 mg) as a brown oil.

Chromatography with light petroleum-EtOAc (4:1) as the eluent yielded a clear oil which was shown to be the title compound (**240**) (361 mg, 82%) as mixture of diastereomers (R_f 0.43, light petroleum-EtOAc (4:1)).

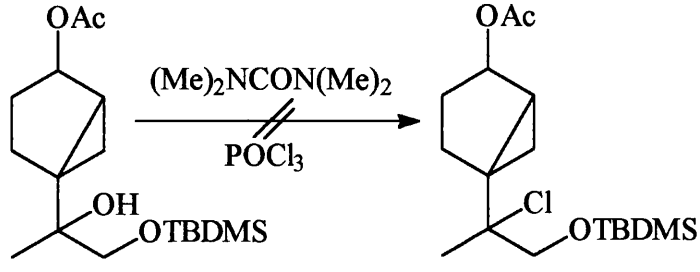
ν_{max}/cm^{-1} 3488 (br, OH), 1736 (C=O), 1374 (acetate C-O), 1252, 838 (SiMe), 1090 (C-O-Si), 1037 (C-OH).

δ_H 5.26 (2x1H, m, C<u>H</u>-O), 3.58, 3.44 (2H, ABq, J 9.5, C<u>H</u>$_2$-O), 3.48, 3.38 (2H, ABq, J 9.5, C<u>H</u>$_2$-O), 2.36 (2x1H, br, O<u>H</u>), 2.02 (2x3H, acetate <u>Me</u>), 1.61-2.05 (2x4H, m, cyclopentyl C<u>H</u>$_2$), 1.21-1.25 (2x1H, m, cyclopropyl <u>H</u>), 1.14 (3H, s, <u>Me</u>), 1.07 (3H, s, <u>Me</u>), 0.89 (9H, s, t-butyl <u>Me</u>), 0.88 (9H, s, t-butyl <u>Me</u>), 0.77-0.87 (2x1H , m, cyclopropyl <u>H</u>), 0.64 (1H, t, J 4.5, cyclopropyl <u>H</u>), 0.58 (1H, t, J 4.4, cyclopropyl <u>H</u>), 0.06 (6H, s, Si<u>Me</u>), 0.05 (6H, s, Si<u>Me</u>).

δ_C 171.2 (<u>C</u>=O), 76.9, 76.7 (<u>C</u>H-OAc), 68.7, 68.5 (<u>C</u>H-OSi), 71.1 (<u>C</u>-OH), 34.2.33.9 (cyclopropyl <u>C</u>), 26.3, 26.3, 26.0, 25.7 (cyclopentyl <u>C</u>H_2), 25.7 (t-butyl <u>Me</u>), 23.2, 22.1 (cyclopropyl <u>C</u>H), 18.1 (t-butyl <u>C</u>), 8.0, 6.6 (cyclopropyl <u>C</u>H_2), -5.6, -5.6, -5.7 (Si<u>Me</u>).

[Found : M^+-tBu 271.1374, $C_{13}H_{23}O_4Si$ requires 271.1368] ; m/z 271 (2%, M^+), 211 (46, $C_{11}H_{19}O_2Si$), 183 (52, $C_{10}H_{15}O_3$), 123 (99, $C_8H_{11}O$), 119 (91, C_9H_{11}), 75 (100, C_2H_7OSi).

Attempted chlorination of tertiary alcohol (240)



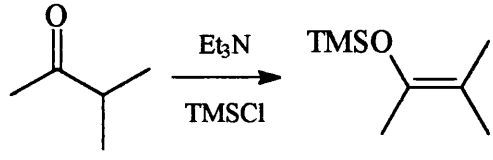
(240) **(241)**

Procedure:[102]

To a flame dried 2-necked 50 ml round bottom flask fitted with septum and N_2 balloon was added tetramethylurea (80 mg, 0.69 mmols) in dry $CHCl_3$ (10 ml). $POCl_3$ (104 mg, 0.62 mmols) was added to the cooled reaction mixture (0 °C). The mixture was allowed to warm to room temperature and stirred for a further hour. The

solution was used immediately without purification. To this mixture was added the alcohol (**240**) (155 mg, 0.47 mmols) in dry $CHCl_3$ (10 ml) and the reaction mixture stirred for 16 hours. The reaction mixture was diluted with $CHCl_3$ (20 ml) and washed with water (3 x 20ml). The dried ($CaCl_2$) solution was concentrated *in vacuo* to leave a light brown oil (190 mg) which on exposure to air decomposed within seconds to a black liquid. All attempts to purify or characterise any component of this mixture proved fruitless.

(1,2-Dimethyl-propenyloxy)-trimethyl-silane (248)



(**247**) (**248**)

Procedure:[103]

To a 2-necked round 100 ml round bottom flask fitted with condenser, septum and N_2 balloon was added DMF (20 ml), Et_3N (17 ml, 120 mmols), TMSCl (7.6 ml, 60 mmols) and the ketone (**247**) (5.4 ml, 50.5 mmols). The reaction mixture was heated at reflux for 50 hours. The cooled reaction mixture was diluted with pentane (50 ml) and washed quickly with ice-cold saturated aqueous $NaHCO_3$ (3 x 50 ml). The aqueous layer was extracted with pentane (3 x 50 ml). The combined organic layers were washed quickly with ice-cold aqueous HCl (2 x 50 ml, 1M) and ice-cold saturated aqueous $NaHCO_3$ (2 x 50 ml). The dried organic solution was concentrated *in vacuo* and the residue distilled with a Kugelrohr apparatus to yield the title compound (**248**) (1.91 g, 24 %) as a clear oil, b.p. 40 °C/15 mm Hg (lit.,[130] 135 °C/760 mm Hg)

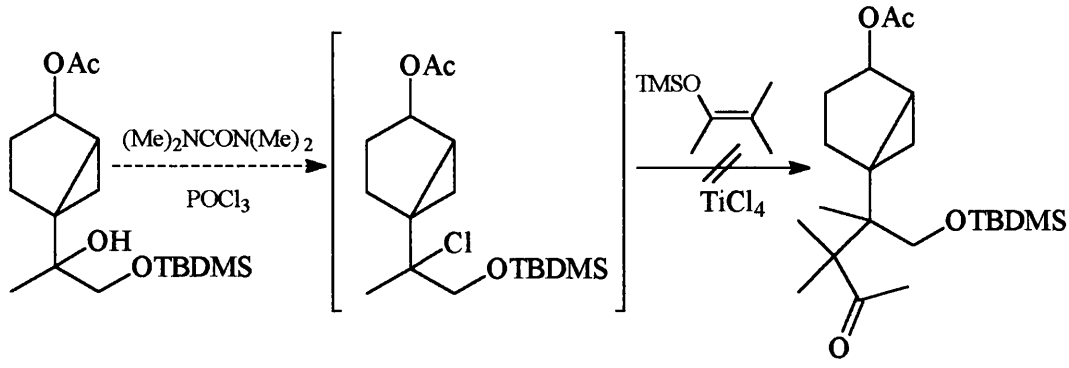
ν_{max}/cm^{-1} 1665 (alkene), 1250, 840 (SiMe), 1188 (C-O-Si).

δ_H 1.71 (3H, s, Me), 1.51 (6H, s, Me), 0.08 (9H, s, SiMe).

δ_C 140.0 (O-C=C), 109.2 (O-C=C), 19.1, 18.7, 18.3 (Me), 0.08 (SiMe).

[Found : M^+ 158.1126. $C_8H_{18}OSi$ requires 158.1127] ; m/z 158 (24%, M^+), 143 (42, $C_7H_{15}OSi$), 75 (100, C_2H_7OSi), 73 (96, C_3H_9Si).

Attempted silyl enol ether coupling



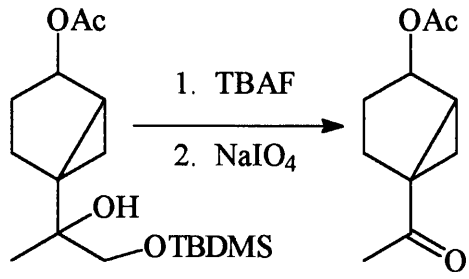
(240) **(241)** **(242)**

Procedure: [90,102]

To a flame dried 2-necked 50 ml round bottom flask fitted with septum and N_2 balloon was added tetramethylurea (253 mg, 2.17 mmols) in dry $CHCl_3$ (10 ml). $POCl_3$ (288 mg, 1.87 mmols) was added to the cooled reaction mixture (0 °C). The mixture was allowed to warm to room temperature and stirred for a further hour. The solution was used immediately without purification. To this mixture was added the alcohol (**240**) (470 mg, 1.43 mmols) in dry $CHCl_3$ (10 ml) and the reaction mixture stirred for 12 hours. The reaction mixture was diluted with $CHCl_3$ (50 ml) and washed with water (3 x 30ml). The dried solution ($CaCl_2$ and molecular sieves 3A°) was concentrated *in vacuo* to leave a light brown oil.

The crude oil was dissolved in dry DCM (20 ml) and transferred to a flame-dried 2 necked 50 ml round bottom flask fitted with septum and N_2 balloon. The solution was cooled (-78 °C) and the silyl enol ether (18) (230 mg, 1.46 mmols) added. To this solution was added $TiCl_4$ (3.1 ml, 0.46 M, 1.43 mmols) dropwise. The solution was stirred for 2 hours at –78 °C then rapidly poured into ice-cold water (70 ml). The aqueous layer was extracted with DCM (3 x 30 ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 x 50 ml) and saturated aqueous NaCl (2 x 50 ml). The dried organic solution was concentrated *in vacuo* to leave a dark brown oil (190 mg) shown to be a mixture of compounds by TLC and NMR. All attempts to purify the mixture were fruitless.

1-Acetylbicyclo{3.1.0.}hex-4-yl acetate (249)



(240) **(249)**

Procedure:[104,105]

To a flame dried 2-necked round bottom flask fitted with a N_2 balloon was added the TBDMS ether (**240**) (228 mg, 0.70 mmols in dry THF (4 ml). To this stirred solution was added TBAF (1.3 ml, 1 M, 1.3 mmols) and the solution stirred for a further 2 hours. The reaction mixture was poured into saturated aqueous NaCl (20 ml). The product was extracted with EtOAc (3 x 20 ml). Solvent was removed *in vacuo* to leave a thick brown oil.

The brown oil was dissolved in water:THF (10 ml, 4:1). Sodium periodate (330 mg, 1.6 mmols) was added and the solution stirred for 2 hours. The reaction mixture was poured into saturated aqueous NaCl (30 ml) and extracted with EtOAc (3 x 20 ml). The organic extracts were washed with saturated aqueous NaCl (3 x 20 ml), dried and solvent removed *in vacuo* to leave a white solid. Dry ether (30 ml) was added to the solid and the mixture stirred for 10 minutes. The filtered solid was washed with dry ether (2 x 10 ml). The combined organic washings were dried and concentrated *in vacuo* to leave a pale yellow oil which was shown to be the title product (**249**) as one major diastereomer (104 mg, 82 %). (R_f 0.3, ether)

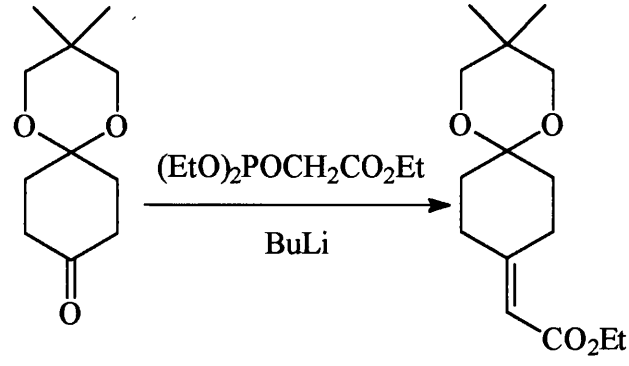
ν_{max}/cm^{-1} 1735 (acetate C=O), 1686 (ketone C=O), 1249 (acetate C-O), 1036 (C-O-C).

δ_H 5.20 (1H, td, J 8.3, 4.7, C<u>H</u>-O), 2.05-2.29 (3H, m, cyclopentyl C<u>H</u>$_2$), 2.00 (3H, s, <u>Me</u>), 1.97 (3H, s, <u>Me</u>), 1.90 (1H, dd, J 8.6, 12.8, cyclopentyl C<u>H</u>$_2$), 1.33 (1H, dd, J 8.7, 5.2, cyclopropyl C<u>H</u>$_2$), 1.23-1.31 (1H, m, cyclopropyl C<u>H</u>), 1.19 (1H, t, J 5.2, cyclopropyl C<u>H</u>$_2$).

δ_C 207.1 (ketone <u>C</u>=O), 171.5 (acetate <u>C</u>=O), 74.9 (<u>C</u>H-O), 39.1 (cyclopropyl <u>C</u>), 31.0 (cyclopropyl <u>C</u>H), 25.9, 24.5 (cyclopentyl <u>C</u>H$_2$), 25.7 (<u>Me</u>-ketone), 21.1 (acetate <u>Me</u>), 15.3 (cyclopropyl <u>C</u>H$_2$).

[Found : M^+ 182.0951. $C_{10}H_{14}O_3$ requires 182.0942] ; m/z 182 (5%, M^+), 139 (7, $C_8H_{11}O_2$), 122 (43, $C_8H_{10}O$), 107 (100, C_7H_7O).

Ethyl 2-(3,3-dimethyl-1,5-dioxa-spiro{5.5}undec-9-ylidene)-acetate (258)



(218) **(258)**

Procedure: [92,93]

To a flame dried 3-necked 500 ml round bottom flask fitted with septum, N_2 balloon and condenser was added triethylphosphonoacetate (12.86 g, 57.4 mmols) in dry THF (125 ml). BuLi (43 ml, 1.4M, 60 mmols) was added to the cooled solution (-78°C) *via* cannula. The solution was allowed to warm to room temperature and stirred for 1 hour. The stirring reaction mixture was recooled (-78 °C) and the monoketal (**218**) (11.08 g, 56.0 mmols) in dry THF (125 ml) added *via* cannula. The reaction was allowed to warm to room temperature and stirred for 3 hours. MeOH (10 ml) was added cautiously, followed by water (100 ml). The product was extracted with ether (3 x 100 ml). The organic extracts were washed with saturated aqueous NaCl (2 x 100 ml), dried and solvent removed *in vacuo* to leave the crude product as a brown oil. Distillation yielded the title compound (**258**) (13.94 g, 93%) as a clear oil, b.p. 120-128 °C/0.4 mm Hg. (lit.[131], 127-132 °C/0.07 mm Hg)

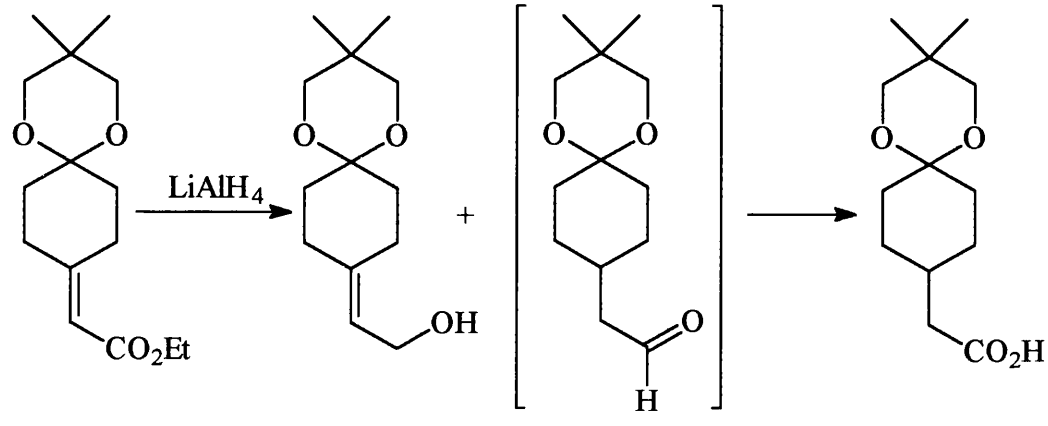
ν_{max}/cm^{-1} 1714 (C=O), 1650 (C=C), 1365, 1398 (CMe_2).

δ_H 5.52 (1H, s, C<u>H</u>=C), 3.48 (4H, ABq, J 11.2, C(O-C<u>H</u>$_2$)$_2$), 4.02 (2H, q, J 7.1, C<u>H</u>$_2$-Me), 2.62 (2H, t, J 6.4, C<u>H</u>$_2$-C=C), 2.17 (2H, t, J 6.4, C<u>H</u>$_2$-C=C), 1.75-1.82 (4H, m, C<u>H</u>$_2$-C(OR)$_2$), 1.14 (3H, t, J 7.1, CH$_2$-<u>Me</u>), 0.86 (3H, s, C(<u>Me</u>)$_2$), 0.84 (3H, s, C(<u>Me</u>)$_2$).

δ_C 166.2 (C=O), 160.6 (C=CH), 113.8 (CH=C), 96.5 ($C(OR)_2$), 69.9 ($C(O-CH_2)_2$), 59.2 (CH_2-Me), 33.1, 33.0, 31.8, 24.5 (ring CH_2), 29.9 ($C(Me)_2$), 22.4, 22.4 ($C(Me)_2$), 14.0 (CH_2-Me).

[Found : M^+ 268.1662. $C_{15}H_{24}O_4$ requires 268.1674] ; m/z 239 (61%, $C_{13}H_{19}O_4$), 223 (30, $C_{13}H_{19}O_3$), 195 (37, $C_{12}H_{19}O_2$), 137 (64, $C_8H_9O_2$), 69 (100, C_5H_9).

2-(3,3-Dimethyl-1,5-dioxa-spiro{5.5}undec-9-ylidene)-ethan-1-ol (259)



(258) **(259)** **(260)** **(261)**

Procedure:[92]

To a flame-dried 3-necked 500 ml round bottom flask, fitted with condenser and N_2 balloon was added $LiAlH_4$ (600 mg, 15.8 mmol). The flask was evacuated and purged with nitrogen before adding dry THF (75 ml) *via* cannula. To the stirred suspension was added ethyl 2-(3,3-dimethyl-1,5-dioxa-spiro{5.5}undec-9-ylidene)-acetate (**258**) (6.80 g, 25.3 mmol) in dry THF (75 ml) *via* cannula. The solution was stirred for 4 hours. To the reaction mixture was cautiously added EtOAc (10 ml). The reaction mixture was then poured into sodium sulphate solution (100 ml) and extracted with ether (3 x 75 ml). The combined organic solutions were washed with saturated aqueous NaCl (3 x 75 ml), dried and solvent removed *in vacuo* to leave the crude product. Chromatography with light petroleum-EtOAc (3:1) as the eluent yielded 2-(3,3-dimethyl-1,5-dioxa-spiro{5.5}undec-9-yl)-acetaldehyde (**260**) (2.09 g, 36%) as a white solid (R_f 0.66, light petroleum-EtOAc (1:1)). The aldehyde (**260**) was unstable in air and readily oxidised over a period of days to 2-(3,3-dimethyl-1,5-

dioxa-spiro{5.5}undec-9-yl)-ethanoic acid (**261**). (R_f 0.13, light petroleum-EtOAc (1:1)).

ν_{max}/cm^{-1} 2400-3300 (OH), 1712 (C=O), 1398, 1365 (CMe_2), 1110 (C-OR).

δ_H 11.3 (br, $CO_2\underline{H}$), 3.50 (2H, s, $C\underline{H}_2$-O), 3.43 (2H, s, $C\underline{H}_2$-O), 2.18-2.24 (4H, m, $C\underline{H}_2$-$C(OR)_2$), 1.76-1.85 (1H, m, C<u>H</u>), 1.62-1.70 (2H, m, $C\underline{H}_2$-CO_2H), 1.17-1.42 (4H, m, $C\underline{H}_2$-CH), 0.92 (6H, s, <u>Me</u>).

δ_C 178.2 (C=O), 97.3 ($\underline{C}(OR)_2$), 69.8, 69.6 ($\underline{C}H_2$-O), 40.6 ($\underline{C}H_2$), 33.6 (<u>C</u>H), 31.4, 28.3 ($\underline{C}H_2$), 30.0 ($\underline{C}(Me)_2$), 22.6 (<u>Me</u>).

[Found : M^+ 242.1516. $C_{13}H_{22}O_4$ requires 242.1518] ; m/z 242 (5%, M^+), 157 (4, $C_8H_{13}O_3$), 141 (100, $C_8H_{13}O_2$), 139 (10, $C_8H_{11}O_2$).

Further elution with EtOAc as the eluent yielded the <u>title compound</u> (**259**) (2.30 g, 41%) as a light yellow oil. (R_f 0.33, light petroleum-EtOAc (1:1)).

ν_{max}/cm^{-1} 3410 (br, OH), 1667 (C=C), 1394, 1362 (CMe_2), 1114 (C-OR), 1019 (C-OH).

δ_H 5.26 (1H, t, J 6.9, C<u>H</u>=C), 3.97 (2H, d, J 6.9, $C\underline{H}_2$-OH), 3.37 (4H, s, $C(C\underline{H}_2$-$OR)_2$), 2.92 (1H, br, O<u>H</u>), 2.01-2.13 (4H, m, $C\underline{H}_2$-C=C), 1.64-1.74 (4H, m, $C\underline{H}_2$-$C(OR)_2$), 0.85 (3H, s, <u>Me</u>), 0.83 (3H, s, <u>Me</u>).

δ_C 140.8 ($\underline{C}$=CH), 121.6 ($\underline{C}$H=C), 69.7 ($\underline{C}H_2$-OH), 58.1 ($\underline{C}H_2$-OR), 32.8, 32.7, 31.9, 23.7 (cyclohexyl $\underline{C}H_2$), 29.9 ($\underline{C}(Me)_2$), 22.5, 22.4 (<u>Me</u>).

[Found : M^+ 226.1558. $C_{13}H_{22}O_3$ requires 226.1569] ; 226 (7%, M^+), 208 (2, $C_{13}H_{20}O_2$), 128 (100, $C_7H_{12}O_2$).

The procedure was followed as above with dry ether as the solvent. Identical work-up yielded a crude product shown to be mostly allylic alcohol[a]. Chromatography with light petroleum-EtOAc (1:1) as the eluent yielded a clear oil which analysed for the <u>title compound</u> (**259**) (89%).

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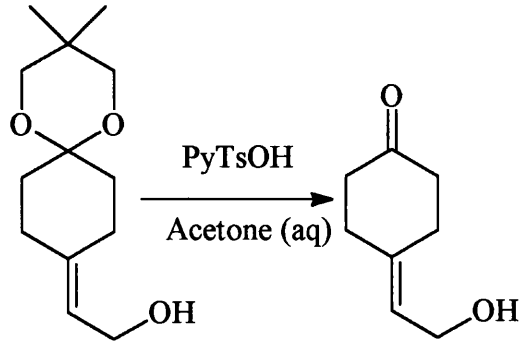
[a]Measurement of the ^1H integral of the crude NMR spectrum showed the desired product to be present as a 12:1 ratio to the aldehyde

4-(2-Hydroxyethylidene)-cyclohexanone (262)



(259) **(262)**

Procedure:[121]

A solution of 2-(3,3-dimethyl-1,5-dioxa-spiro{5.5}undec-9-ylidene)-ethan-1-ol (**259**) (3.90 g, 17.3 mmols) and pyridinium tosylate (1.35 g, 5.4 mmols) in aqueous acetone (150 ml) was refluxed for 16 hours. The cooled solution was diluted with brine (50 ml) and neutralised with aqueous 5% NaOH (5 ml). Excess acetone was removed *in vacuo* and the aqueous residue extracted with EtOAc (3 x 70 ml). The organic extracts were washed with brine (2 x 70 ml), dried and solvent removed *in vacuo* to leave the crude product (2.38 g) as a golden oil. Chromatography with light petroleum-EtOAc (2:1) furnished a light yellow oil (0.54 g, 14%) which was shown to analyse for starting material (**259**). Further elution with EtOAc yielded the title compound[97] (**262**) (2.38 g, 68%) as a clear oil. (R_f 0.13, light petroleum-EtOAc (1:1))

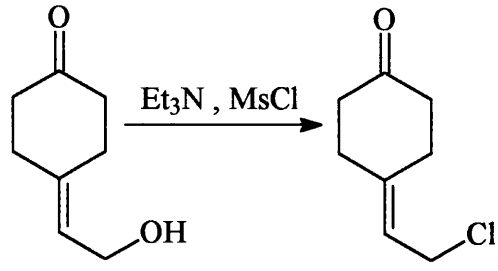
ν_{max}/cm^{-1} 3390 (br, OH), 1710 (C=O), 1020 (C-OH).

δ_H 5.47 (1H, t, J 6.9, C<u>H</u>=C), 4.05 (2H, d, J 6.9, C<u>H</u>$_2$-OH)), 3.33 (br, O<u>H</u>), 2.20-2.47 (8H, m, cyclohexyl C<u>H</u>$_2$).

δ_C 211.7 (<u>C</u>=O), 136.8 (<u>C</u>=CH), 124.1 (<u>C</u>H=C), 70.3 (<u>C</u>H$_2$-OH), 41.0, 40.1, 33.6, 25.8 (cyclohexyl <u>C</u>H$_2$).

[Found : M^+ 140.0835. $C_8H_{12}O_2$ requires 140.0837] ; m/z 140 (3%, M^+), 122 (97, $C_8H_{10}O$), 109 (13, C_7H_9O), 94 (13, $C_7H_{10}O$), 83 (43, C_5H_7O), 80 (67, C_6H_8), 79 (C_6H_7).

4-(2-Chloro-ethylidene)-cyclohexanone (265)



(262) **(265)**

Procedure:[109]

To a flame dried 2-necked 25 ml round bottom flask fitted with septum and N_2 balloon was added successively, alcohol (**262**) (250 mg, 1.79 mmols) in dry DCM (5 ml), Et_3N (0.4 ml, 2.9 mmols) and methane-sulphonyl chloride (0.4 g, 1.82 mmols), at 0 °C. The solution was stirred for 90 minutes, then poured into ice water (10 ml). The aqueous layer was extracted with DCM (3 x 10 ml). The combined organic extracts were washed with ice cold 1M HCl (2 x 10 ml) and saturated aqueous $NaHCO_3$ (3 x 10 ml). The dried organic solution was concentrated *in vacuo* to leave the crude product (250 mg) as a dark brown oil. Chromatography with light petroleum-EtOAc (4:1) as the eluent yielded the title compound as a clear oil (**265**) (165 mg, 59 %). (R_f 0.62, light petroleum-EtOAc (4:1)).

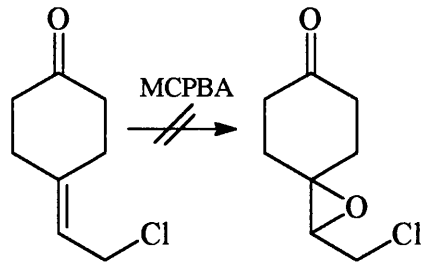
ν_{max}/cm^{-1} 1712 (C=O), 1662 (C=C).

δ_H 5.59 (1H, tt, J 8.0, 1.2, C<u>H</u>=C), 4.05 (2H, d, J 8.0, C<u>H</u>$_2$-Cl), 2.33-2.59 (8H, m, cyclohexyl C<u>H</u>$_2$).

δ_C 210.2 (<u>C</u>=O), 140.7 (<u>C</u>=CH), 120.7 (<u>C</u>H=C), 40.7, 39.9, 39.8, 33.4, 25.6 (<u>C</u>H$_2$).

[Found : M^+ 160.0463, 158.0496. $C_8H_{11}OCl$ requires 160.0469, 158.0498] ; m/z 160, 158 (26%, 86, M^+), 123 (100, $C_8H_{11}O$), 122 (46, $C_8H_{10}O$), 118, 116 (3, 10, C_6H_9Cl).

Attempted epoxidation of 4-(2-chloro-ethylidene)-cyclohexanone (265)

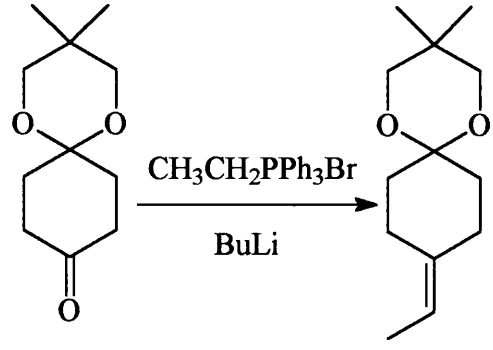


(265) **(266)**

Procedure:[96]

To a solution of 50-60% MCPBA (220 mg, 64-77 mmols) in $CHCl_3$ (5 ml) was added the allyl chloride (**265**) (95 mg, 60 mmols) in $CHCl_3$ (5 ml) at 0 °C. The reaction was stirred for 10 minutes at 0 °C for 10 minutes. The reaction mixture was washed with 10% aqueous sodium bisulphite (5 ml). The organic layer washed with saturated aqueous $NaHCO_3$ (3 x 10 ml), saturated aqueous NaCl (10 ml) and dried. Solvent was removed *in vacuo* to leave a dark brown oil (150 mg), shown to be a mixture of products by TLC and NMR. Column chromatography yielded no identifiable products.

9-Ethylidene-3,3-dimethyl-1,5-dioxa-spiro{5.5}undecane (268)



(218) **(268)**

Procedure:[110]

To a flame-dried 3-necked 1 litre round bottom flask fitted with septum, condenser

and N_2 balloon was added ethyltriphenylphosphonium bromide[a] (54.2 g, 146 mmols). The flask was evacuated and purged with nitrogen. Dry ether (150 ml) was added and the flask cooled to -78°C. To the cooled stirring suspension was added BuLi (100 ml, 1.46M, 146 mmols) *via* cannula. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. To the dark red solution was added 3,3-dimethyl-1,5-dioxa-spiro{5.5}undecan-9-one (**218**) (28.12 g, 142 mmols) in dry ether (250 ml) *via* cannula. The reaction was heated under reflux for 16 hours. The cooled yellow reaction solution was decanted and the residue washed with ether (3 x 50 ml). The combined ethereal solutions were washed with water (200 ml) and saturated aqueous NaCl (3 x 150 ml). The dried organic solution was concentrated *in vacuo* to leave the crude product (33 g) as a brown oil. Distillation yielded the title compound (**268**) (25.30 g, 85 %) as a clear oil, b.p. 96-98 °C/0.6mm Hg. (R_f 0.48, light petroleum-ether (2:1))

ν_{max}/cm^{-1} 1672 (C=C), 1110, 1114 (C-O-R)

δ_H 5.11 (1H, q, J 6.7, C<u>H</u>=C), 3.44 (4H, s, C<u>H</u>$_2$-O), 2.02-2.15 (4H, m, C<u>H</u>$_2$-C=C), 1.69-1.77 (4H, m, C<u>H</u>$_2$-C(OR)$_2$), 1.52 (3H, d, J 6.7, CH<u>Me</u>), 0.91 (3H, s, C(<u>Me</u>)$_2$), 0.88 (3H, s, C(<u>Me</u>)$_2$).

δ_C 137.7 (<u>C</u>=CH), 116.2 (<u>C</u>H=C), 97.7 (<u>C</u>(OR)$_2$), 69.9 (<u>C</u>H$_2$-O), 33.2, 32.7, 32.0, 23.2 (cyclohexyl <u>C</u>H$_2$), 30.1 (s, <u>C</u>(Me)$_2$), 22.7 22.6 (C(<u>Me</u>)$_2$), 12.8 (CH<u>Me</u>).

[Found : M^+ 210.1622, $C_{13}H_{22}O_2$ requires 210.1600] ; m/z 210 (29%, M^+), 125 (11, $C_8H_{13}O$), 124 (12, $C_8H_{12}O$), 128 (100, $C_7H_{12}O_2$), 69 (36, C_5H_9).

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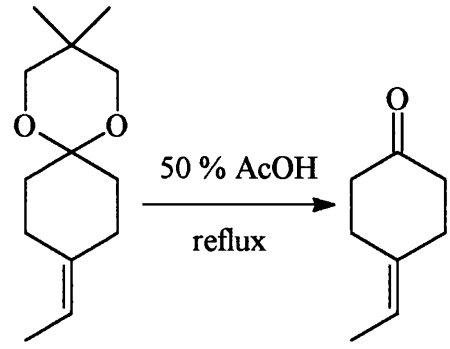
[a] For preparation of Wittig salt see appendix 3.

4-Ethylidene-cyclohexanone (269)



(268) **(269)**

Procedure:[113]

A solution of 9-ethylidene-3,3-dimethyl-1,5-dioxa-spiro{5.5}undecane (**268**) (11.24 g, 53.5 mmols) in 50% acetic acid (150 ml) was refluxed for 2 hours. The cooled (ice-bath) solution was poured into a solution of NaOH (53 g) in ice/water (750 ml) and extracted with ether (3 x 200 ml). The ethereal extracts were washed with saturated aqueous $NaHCO_3$ (3 x 150 ml) and saturated aqueous NaCl (3 x 150 ml), dried and solvent removed *in vacuo* to leave the crude product (7 g) as a brown oil. Chromatography with light petroleum-EtOAc (4:1) as the eluent furnished the title compound (**269**) (5.97 g, 90%) as a clear oil, b.p 78-81 °C/14mm Hg (lit.[132] 78 °C/2 mmHg). (R_f 0.65, light petroleum-EtOAc (1:1))

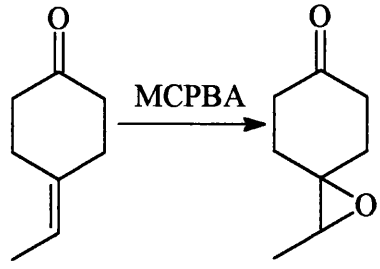
ν_{max}/cm^{-1} 1718 (C=O).

δ_H 5.34 (1H, qt, J 6.8, 1.2, C<u>H</u>=C), 2.26-2.43 (8H, m, C<u>H</u>$_2$), 1.57 (3H, dt, J 6.8, 0.7, <u>Me</u>).

δ_C 211.7 (<u>C</u>=O), 134.3 (<u>C</u>=CH), 119.2 (<u>C</u>H=C), 41.5, 40.5, 33.9, 25.5 (ring <u>C</u>H$_2$), 13.0 (<u>Me</u>).

[Found : M^+ 124.0894, $C_8H_{12}O$ requires 124.0888] ; m/z 124 (100%, M^+), 109 (11, C_7H_9O), 96 (15, C_6H_8O), 95 (22, C_6H_7O), 82 (42, C_6H_{10}), 81 (33, C_6H_9), 67 (91, C_5H_7).

2-Methyl-1-oxa-spiro{2,5}octan-6-one (280)



(269) **(280)**

Procedure:[116]

To a solution of the 2-methyl-1-oxa-spiro{2,5}octan-6-one (**269**) (2.95 g, 23.8 mmols) in DCM (75 ml) at 0 °C was added MCPBA (7.8 g, 50-55%, 23-25 mmols) in DCM (75 ml) dropwise. The reaction mixture was stirred for a further 10 minutes at 0 °C. The reaction mixture was washed with 10% aqueous $NaHSO_3$ (50 ml) and 10% aqueous NaOH (2 x 50 ml). The aqueous washings were extracted with DCM (3 x 75 ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 x 75 ml) and saturated aqueous NaCl (2 x 75 ml), dried and solvent removed *in vacuo* to leave the crude product (2.7 g) as a cloudy oil. Chromatography with light petroleum-EtOAc (2:1) yielded the title compound (**280**) (2.40 g, 73%) as a clear oil, b.p. 72-76 °C/2 mmHg. (R_f 0.38, light petroleum-EtOAc (1:1))

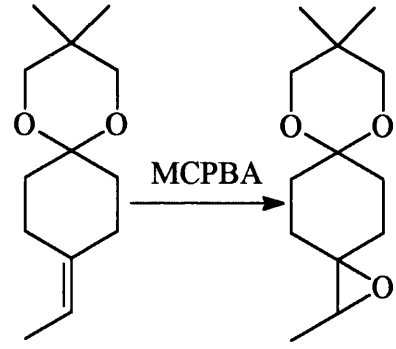
ν_{max}/cm^{-1} 1717 (C=O).

δ_H 2.96 (1H, q, J 5.5, C<u>H</u>-OR), 2.40-2.53 (2H, m, C<u>H</u>$_2$), 2.24-2.34 (2H, m, C<u>H</u>$_2$), 1.88-1.97 (2H, m, C<u>H</u>$_2$), 1.57-1.78 (2H, m, C<u>H</u>$_2$), 1.23 (3H, d, J 5.5, <u>Me</u>).

δ_C 207.1 (C=O), 60.1 (epoxide <u>C</u>), 59.8 (epoxide <u>C</u>H), 38.4, 38.3, 33.3, 26.3 (<u>C</u>H$_2$), 13.7 (<u>Me</u>).

[Found : M^+ 140.0849, $C_8H_{12}O_2$ requires 140.0837] ; m/z 140 (40%, M^+), 112 (23, $C_7H_{12}O$), 111 (22, $C_6H_7O_2$), 98 (30 $C_6H_{10}O$), 84 (33, C_5H_8O), 69 (45, C_5H_9), 67 (60, C_5H_7), 54 (100, C_4H_6).

2,9,9-Trimethyl-1,7,11-trioxa-dispiro{2.2.5.2}tridecane (281)



(268) **(281)**

Procedure:[116]

To a solution of 9-ethylidene-3,3-dimethyl-1,5-dioxa-spiro{5.5}undecane (**268**) (1.00 g, 4.76 mmols) in DCM (30 ml) at 0°C was added MCPBA (1.8 g, 50-55%, 5.2-5.7 mmols) in DCM (30 ml) dropwise. The reaction mixture was stirred for 15 minutes before being washed with 10% aqueous $NaHSO_3$ (20 ml) and 10% aqueous NaOH (2 x 20 ml). DCM was removed *in vacuo* and the residue dissolved light petroleum-ether (30 ml, 1:1). The dried solution was filtered through a pad of celite and concentrated *in vacuo* to leave the title product (**281**) (0.98 g, 91%) as a clear oil. (R_f 0.59, light petroleum-EtOAc (1:1).

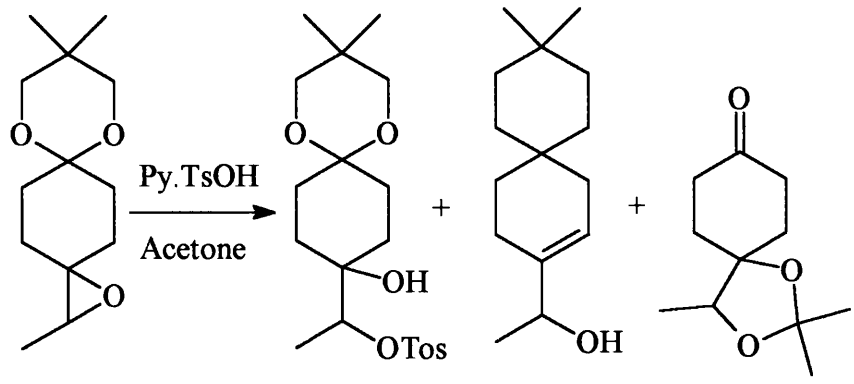
ν_{max}/cm^{-1} 1103, 1120 (C-O-R).

δ_H 3.47 (2H, s, CH_2-O), 3.43 (2H, s, CH_2-O), 2.84 (1H, q, J 5.6, CH-OR), 1.32-1.97 (8H, m, cyclohexyl CH_2), 1.22 (3H, d, J 5.6, CHMe), 0.92 (3H, s, $C(Me_2)$), 0.90 (3H, s, $C(Me)_2$).

δ_C 97.1 ($C(OR)_2$), 70.1 (CH_2-O), 69.9 (CH_2-O), 61.5 (epoxide C), 59.6 (epoxide CH), 30.7, 30.2, 30.1, 24.4 (cyclohexyl CH_2), 30.1 ($C(Me)_2$), 22.5, 22.5 ($C(Me)_2$), 13.5 (q, CHMe).

[Found : M^+ 226.1574, $C_{13}H_{22}O_3$ requires 226.1568] ; m/z 226 (1%, M^+), 208 (5, $C_{13}H_{20}O_2$), 197 (5, $C_{11}H_{17}O_3$), 141 (75, $C_8H_{13}O_2$), 128 (100, $C_7H_{12}O_2$), 69 (86, C_5H_9).

Attempted hydrolysis of the ketal (281)



(281) **(282)** **(283)** **(284)**

Procedure:[95]

A solution of 2,9,9-trimethyl-1,7,11-trioxa-dispiro{2.2.5.2}tridecane (**281**) (490 mg, 2.17 mmols) and pyridinium tosylate[a] (0.5 g, 2 mmols) in aqueous acetone (50 ml) was refluxed for 1 hour. The cooled solution was neutralised with saturated aqueous $NaHCO_3$ (50 ml) and excess acetone removed *in vacuo*. The aqueous residue was extracted with EtOAc (3 x 50 ml). The organic layers were washed with saturated aqueous NaCl (3 x 50 ml), dried and solvent removed *in vacuo* to leave the crude product as a cloudy oil. Chromatography with light petroleum-EtOAc (4:1) furnished a clear oil (102 mg, 21 %) shown to be identical to starting material (**281**). Further elution with light petroleum-EtOAc (2:1) yielded a clear oil shown to contain 2 compounds by TLC. The 2-component mixture was further purified on prep. plates with light petroleum-EtOAc (3:2) to yield 1-(9-hydroxy-3,3-dimethyl-1,5-dioxaspiro{5.5.}undec-9-yl)ethyl *p*-toluenesulphonate (**282**) (295 mg, 34 %)(Rf 0.38, light petroleum-EtOAc (1:1)) and 1-(3,3-dimethyl-1,5-dioxaspiro{5.5.}undec-8-en-9-yl) ethanol (**283**) (125 mg, 26 %)(Rf 0.29, light petroleum-EtOAc (1:1)).

1-(9-hydroxy-3,3-dimethyl-1,5-dioxaspiro{5.5.}undec-9-yl)ethyl *p*-toluenesulphonate (**282**)

δ_H 7.79 (2H, d, J 8.2, Ar H), 7.33 (2H, d, J 8.2, Ar H), 4.47 (1H, q, J 6.5, CH-OTos), 3.51 (2H, s, CH_2-O), 3.41 (2H, s, CH_2-O), 2.43 (3H, s, Ar Me), 1.25-2.17 (8H, m, ring CH_2), 1.18 (3H, d, J 6.5, CHMe), 0.96 (3H, s, $C(Me)_2$), 0.93 (3H, s,

[a] See Appendix 2 for preparation of pyridinium tosylate

C(Me)$_2$).

δ_C 144.5, 134.1 (Ar C), 129.7, 127.5 (Ar CH), 97.1 (C(OR)$_2$), 85.8, (CH-OTos), 72.1 (C-OH), 70.2, 70.0 (CH_2-OH), 30.7 (C(Me)$_2$), 30.1, 28.3, 27.5, 26.6 (ring CH_2), 22.7, 22.6 (C(Me)$_2$), 21.6 (CHMe), 15.1 (Ar Me).

1-(3,3-dimethyl-1,5-dioxaspiro{5.5.}undec-8-en-9-yl) ethanol (**283**)

ν_{max}/cm^{-1} 3603 (OH), 1395, 1365 (CMe_2), 1112 (C-O-R)

δ_H 5.51 (1H, m, CH=C), 4.20 (1H, q, J 6.4, CH-O), 3.59, 3.45 (4H, ABq, J 11.5, CH_2-O), 2.35 (2H, m, allylic CH_2), 1.50-2.13 (4H, m, cyclohexyl ring CH_2), 1.73 (1H, br, OH), 1.24 (3H, d, J 6.4, CHMe), 1.03 (3H, s, C(Me)$_2$), 0.89 (3H, s, C(Me)$_2$).

δ_C 140.8 (C=CH), 117.8 (CH=C), 97.3 (C(OR)$_2$), 71.2 (CH-O), 70.2 (CH_2-O), 34.9, 26.8, 21.8 (cyclohexyl CH_2), 30.2 (C(Me)$_2$), 22.7, 22.4, 21.4 (Me).

[Found : M^+ 226.1557, $C_{13}H_{22}O_3$ requires 226.1569] ; 226 (7%, M^+), 208 (12, $C_{13}H_{20}O_2$), 128 (100, $C_7H_{12}O_2$), 122 (33, $C_8H_{10}O$), 107, (26, C_7H_7O), 79 (28, C_6H_7).

The reaction was repeated as above but with the following changes; 2 hour reflux and stirring for a further 12 hours. The crude product obtained was a dark brown oil. Chromatography with light petroleum-EtOAc (4:1) yielded 2,2,4-trimethyl-1,3-dioxaspiro{4.5.}undecan-8-one (**284**) (26%). Further elution with light petroleum-EtOAc (2:1) yielded 1-(3,3-dimethyl-1,5-dioxaspiro{5.5.}undec-8-en-9-yl) ethanol (**283**) (24%) and 1-(9-hydroxy-3,3-dimethyl-1,5-dioxaspiro{5.5.}undec-9-yl)ethyl *p*-toluenesulphonate (**282**) (trace).

2,2,4-trimethyl-1,3-dioxaspiro{4.5.}undecan-8-one (**284**)

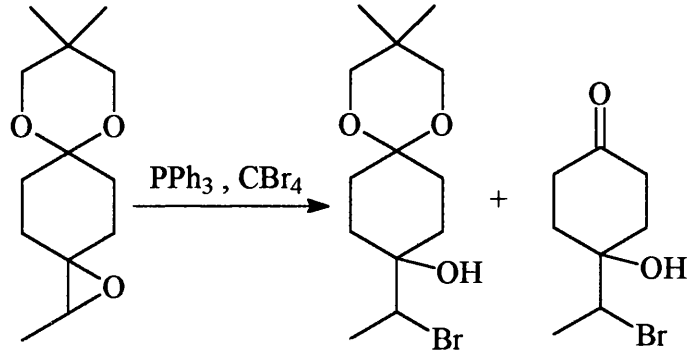
ν_{max}/cm^{-1} ($CHCl_3$) 1718 (C=O), 1101 (C-O-R).

δ_H 3.91 (1H, q, J 6.4, CH-O), 2.68-2.79 (2H, m, cyclohexyl CH_2), 2.24-2.37 (2H, m, cyclohexyl CH_2), 1.93-2.01 (1H, m, cyclohexyl H), 1.82-1.90 (1H, m, cyclohexyl H), 1.75-1.81 (1H, m, cyclohexyl H), 1.56-1.63 (1H, m, cyclohexyl H), 1.46 (3H, s, Me), 1.39 (3H, s, Me), 1.20 (3H, d, J 6.4, CHMe).

δ_C 211.4 (C=O), 107.1 (C(OR)$_2$), 79.5 (C-OR), 77.8 (CH-OR), 37.9, 36.5 (CH_2C=O), 34.5, 30.5 (CH_2C-OR), 28.4, 26.7 (C(Me)$_2$), 13.9 (CHMe).

[Found : M^+ 198.1246, $C_{11}H_{18}O_3$ requires 198.1256] ; m/z 198 (1%, M^+), 183 (70, $C_{10}H_{15}O_2$), 143 (22, $C_8H_{15}O_2$), 141 (50, $C_8H_{13}O_2$), 123 (100, $C_8H_{11}O$), 95 (46, C_7H_{11}).

Attempted ketal removal



(281) **(292)** **(293)**

Procedure:[112]

To a solution of carbon tetrabromide (884 mg, 2.66 mmols) and the ketal (**281**) (300 mg, 1.33 mmols) in acetone (15 ml) was added a solution of triphenylphosphine (698 mg, 2.66 mmols) in acetone (10 ml) dropwise. The reaction mixture was stirred for 1 hour then diluted with light petroleum (75 ml). The resulting precipitate was filtered off and the filtrate concentrated *in vacuo* to give a brown oil (350 mg). Column chromatography with light petroleum:ethyl acetate (2:1) gave 9-(1-bromoethyl)-3,3-dimethyl-9-hydroxy-1,5-dioxaspiro{5.5.}undecane (**292**) as a light brown oil (110 mg, 27 %). (R_f 0.48, light petroleum-EtOAc (3:1)).

δ_H 4.18 (1H, q, J 6.9, C<u>H</u>Br), 3.49 (3H, s, C<u>H</u>$_2$-O), 3.44 (3H, s, C<u>H</u>$_2$-O), 1.56-2.27 (9H, m, cyclohexyl C<u>H</u>$_2$, O<u>H</u>), 1.67 (3H, d, J 6.9, CH<u>Me</u>), 0.92 (3H, s, C(<u>Me</u>)$_2$), 0.91 (3H, s, C(<u>Me</u>)$_2$

δ_C 97.2 (<u>C</u>(OR)$_2$), 72.1 (<u>C</u>-OH), 70.1 (<u>C</u>H$_2$-O), 70.0 (<u>C</u>H$_2$-O), 64.2 (<u>C</u>HBr), 32.5, 28.7, 27.7, 27.5 (cyclohexyl <u>C</u>H$_2$), 30.1 (<u>C</u>(Me)$_2$), 22.6, 22.6 (C(<u>Me</u>)$_2$), 20.8 (CH<u>Me</u>).

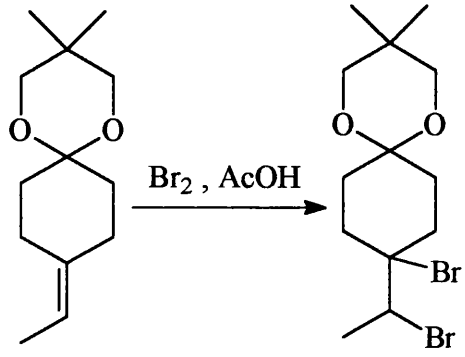
Further elution with light petroleum:ethyl acetate (2:1) gave 4-(1-bromoethyl)-4-hydroxy-cyclohexanone (**293**) (122 mg, 41 %) as light brown oil. (R_f 0.37, light

petroleum-EtOAc (3:1)).

δ_H 4.23 (1H, q, J 6.9, C<u>H</u>Br), 2.60-2.74 (2H, m, cyclohexyl C<u>H</u>$_2$), 2.52 (1H, s, O<u>H</u>) 1.77-2.27 (6H, m, cyclohexyl C<u>H</u>$_2$), 1.71 (3H, d, J 6.9, <u>Me</u>)

δ_C 211.6 (<u>C</u>=O), 71.6 (<u>C</u>-OH), 62.2 (<u>C</u>HBr), 36.6, 36.4, 35.0, 32.3 (cyclohexyl <u>C</u>H$_2$), 20.9 (<u>Me</u>)

9-Bromo-9-(1-bromoethyl)-3,3-dimethyl-1,5-dioxaspiro{5.5.}undecane (296)



(268) **(296)**

<u>Procedure</u>:[119]

To a stirring solution of 9-ethylidene-3,3-dimethyl-1,5-dioxa-spiro{5.5}undecane (**268**) (6.17 g, 29.4 mmols) in ether (60 ml) was added bromine (5.5 g, 34 mmols) in 50 % AcOH (60 ml) dropwise. The bromine solution became colourless as it was added to the solution of the alkene. The solution was allowed to stir for a further 10 minutes before being diluted with water (250 ml). The aqueous layer was separated and extracted with ether (3 x 60 ml). The combined ethereal extracts were washed with 20% aqueous $Na_2S_2O_3$ (30 ml), 10% aqueous NaOH (3 x 30 ml) and saturated aqueous NaCl (2 x 50 ml). The dried solution was concentrated *in vacuo* to leave the crude product as a white solid. The white solid was dissolved in EtOH and the product was precipitated upon addition of water. Filtration afforded a white powder which was dried between filter paper to leave the <u>title product</u> (**296**) (8.82 g, 81 %). (R_f 0.5, light petroleum-ether (4:1))

ν_{max}/cm^{-1} 1377,1396 (CMe_2), 1098 (C-O-R).

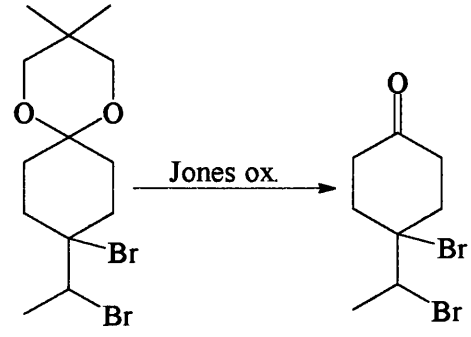
δ_H 4.29 (1H, q, J 6.7, C<u>H</u>Br), 3.51 (2H, s, C<u>H</u>$_2$-O), 3.43 (2H, s, C<u>H</u>$_2$-O), 1.78-2.24

(8H, m, cyclohexyl $C\underline{H}_2$), 1.89 (3H, d, J 6.7, $CH\underline{Me}$), 0.94 (3H, s, $C(\underline{Me})_2$), 0.93 (3H, s, $C(\underline{Me})_2$).

δ_C 96.6 ($\underline{C}(OR)_2$), 76.8 ($\underline{C}Br$), 70.0, 69.7 ($\underline{C}H_2$-O), 59.0 ($\underline{C}HBr$), 36.3, 33.3 ($\underline{C}H_2CBr$), 30.1 ($\underline{C}(Me)_2$), 29.6, 28.9 ($\underline{C}H_2C(OR)_2$), 22.9, 22.6 ($\underline{Me}$).

[Found : M^+-Br 291.0774, 289.0799, $C_{13}H_{22}O_2Br$ requires 291.0784, 289.0804] ; m/z 289,291 (13, 12, $C_{13}H_{22}O_2Br$), 141 (100, $C_8H_{13}O_2$), 128 (23, $C_7H_{12}O_2$).

4-Bromo-4-(1-bromoethyl)-cyclohexanone (297)



(296) **(297)**

Procedure:[120]

To a stirring, cooled (0 °C) solution of the dibromoketal (**296**) (39) (8.60 g, 23.2 mmols) in acetone (120 ml) was added Jones reagent[a] (94 mmols) dropwise. The reaction was stirred at 0 °C for 2 hours. The reaction mixture was poured into 5 % aqueous $Na_2S_2O_3$ (250 ml) and extracted with ether (5 x 100 ml). The ethereal extracts were washed with saturated aqueous $NaHCO_3$ (3 x 50 ml) and saturated aqueous NaCl (3 x 50 ml), dried and solvent removed *in vacuo* to leave the crude product (6 g) as a white solid. Recrystallisation afforded the title compound (**297**) (4.71 g, 71 %) as white crystals, m.p. 80-82 °C (from light petroleum). (R_f 0.59, ether)

$\nu_{max}/cm^{-1}(CHCl_3)$ 1718 (C=O).

δ_H 4.41 (1H, q, J 6.7, $CH\underline{Br}$) 2.67-2.94 (2H, q, $C\underline{H}_2$), 2.12-2.48 (6H, m, $C\underline{H}_2$), 1.94 (3H, d, J 6.7, $\underline{Me}$).

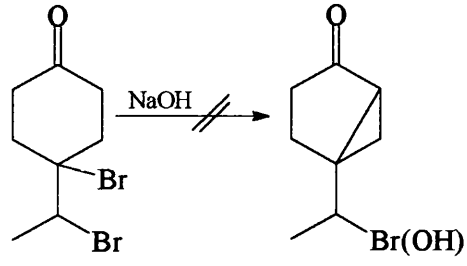
---

[a]Made with CrO_3 (9.4 g) dissolved in conc. H_2SO_4 (8.2 ml), diluted with water (27 ml).

δ_C 208.7 (C=O), 73.6 (CBr), 57.6 (CHBr), 39.6, 38.5, 37.9, 35.1 (ring CH_2), 23.1 (Me).

[Found : M^+ 285.9209, 283.9230, 281.9244, $C_8H_{12}OBr_2$ requires 285.9197 283.9217, 281.9256] ; m/z 286,284,281 (7, 15, 7, M^+), 203,205 (89, 86, $C_8H_{12}OBr$), 123 (100, $C_8H_{11}O$), 95 (74, C_6H_7O), 81 (93, C_6H_9).

Attempted ring closure of 4-bromo-4-(1-bromoethyl)-cyclohexanone (297)

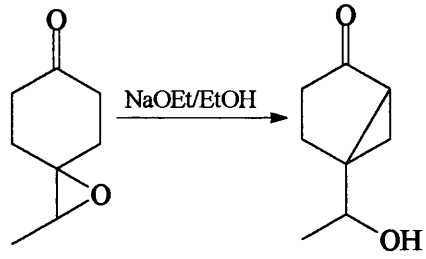


(297) **(298)**

Procedure

To a solution of the dibromoketone (**297**) (306 mg, 1.08 mmols) in DMF-water (10 ml, 3:1) was added powdered NaOH (110 mg, 2.75 mmols). The reaction was stirred for 4 hours. The reaction mixture was poured into saturated aqueous NH_4Cl (30 ml) and extracted with ether (4 x 30 ml). The ethereal extracts were washed with water (2 x 10 ml) and brine (2 x 10 ml), dried and concentrated *in vacuo* to leave the a brown oil (85 mg). All attempts to characterise or purify the crude mixture proved fruitless, as were attempts to extract more organic material from the aqueous layers.

5-(1-Hydroxyethyl)-bicyclo{3.1.0}hexan-2-one (290)



(280) **(290)**

Procedure:[53]

To a 250 ml round bottom flask fitted with condenser was added EtOH (75 ml) followed by sodium wire (1.44 g, 63 mmols). After all the sodium had reacted, the epoxide (**280**) (3.09 g, 22.1 mmol) in EtOH (50 ml) was added. The solution was refluxed for 45 minutes. The cooled reaction mixture was poured into saturated aqueous NH_4Cl (200 ml) and extracted with EtOAc (3 x 150 ml). The organic extracts were washed with aqueous saturated NaCl (3 x 100 ml), dried and solvent removed *in vacuo* to leave the crude product (2.45 g) as a brown oil. Chromatography with light petroleum-EtOAc (2:3) yielded a clear oil which was shown to be the title compound (**290**) (2.35 g, 77 %) as mixture of diastereomers. (R_f 0.41, EtOAc)

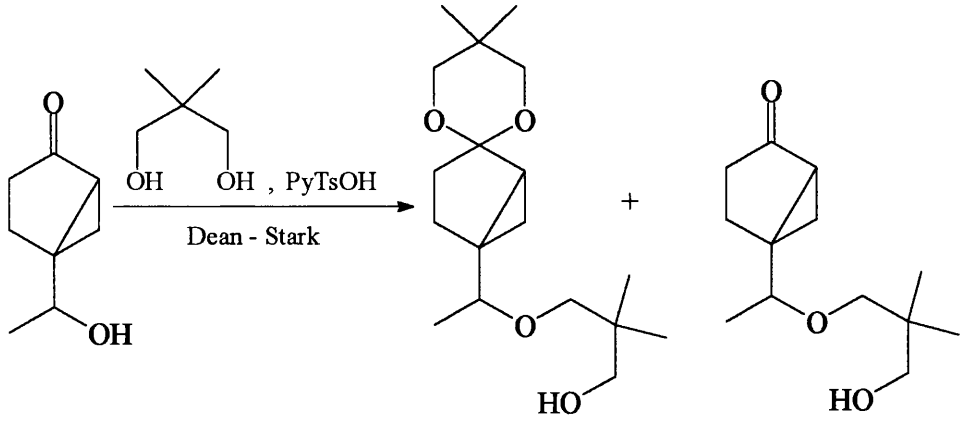
ν_{max}/cm^{-1} 3412 (OH), 1714 (C=O).

δ_H 3.83 (1H, q, J 6.3, C<u>H</u>-OH), 3.49 (1H, q , J 6.4 C<u>H</u>-OH), 3.08 (1H, br, O<u>H</u>), 2.83 (1H, br, O<u>H</u>), 1.92-2.21 (2x4H, m, C<u>H</u>$_2$-C<u>H</u>$_2$), 1.76 (1H, dd, J 9.3, 3.2, cyclopropyl C<u>H</u>), 1.70 (1H, dd, J 9.3, 3.3), 1.37 (1H, dd, J 9.3, 4.6, cyclopropyl C<u>H</u>$_2$), 1.21 (3H, d, J 6.4, <u>Me</u>), 1.18 (3H, d, J 6.3, <u>Me</u>), 1.17-1.22 (1H, m, cyclopropyl C<u>H</u>$_2$), 1.09 (1H, dd, J 4.9,3.3, cyclopropyl C<u>H</u>$_2$), 1.02 (1H, dd, J 4.6, 3.2, cyclopropyl C<u>H</u>$_2$).

δ_C 215.0 (<u>C</u>=O), 69.9, 68.1 (-<u>C</u>HOH), 39.9, 39.6 (cyclopropyl <u>C</u>), 33.3, 31.8 (cyclopropyl <u>C</u>H), 33.1,31.9, 23.7, 21.2 (-<u>C</u>H$_2$<u>C</u>H$_2$-), 20.2, 19.6 (<u>Me</u>), 17.9, 16.7 (cyclopropyl <u>C</u>H$_2$).

[Found : M^+ 140.0838, $C_8H_{12}O_2$ requires 140.0837] ; m/z 140 (14%, M^+), 125 (26, $C_7H_9O_2$), 112 (14, $C_6H_8O_2$), 96 (100, C_6H_8O), 97 (56, C_6H_9O), 83 (70, C_5H_7O), 70 (98, C_4H_6O).

Attempted ketalization of 5-(1-hydroxyethyl)-bicyclo{3.1.0}hexan-2-one (290)



(290) **(302)** **(303)**

Procedure:[121]

A solution of 5-(1-hydroxyethyl)-bicyclo{3.1.0}hexan-2-one (**290**) (860 mg, 6.14 mmols), 2,2-dimethyl-1,3-propane-diol (6 g, 42 mmols) and pyridinium tosylate (550 mg, 2.2 mmols) in toluene (50 ml) was refluxed under Dean-Stark conditions for 30 minutes. The cooled reaction mixture was washed with aqueous saturated $NaHCO_3$ (3 x 50 ml). The aqueous washings were extracted with ether (3 x 60 ml). The combined organic layers were washed with saturated aqueous NaCl (2 x 50 ml), dried and solvent removed *in vacuo* to leave the crude product (1.9 g) as a yellow oil. Chromatography with light petroleum-EtOAc (3:1) as the eluent yielded 4-(1-(1-hydroxy-2,2-dimethylprop-3-oxy)ethyl)-2,2-(2,2-dimethyl-propylene-dioxy)bicyclo{3.1.0}hexane (**302**) (992 mg, 52 %) as a thick oil (two diastereomers) (R_f 0.52, light petroleum-EtOAc (2:1))

ν_{max}/cm^{-1} 3500 (br, OH), 1121 (C-OR), 1058 (C-OH).

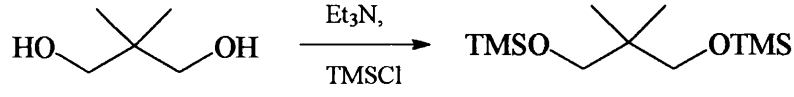
δ_H 3.21-3.61 (2 x 8H, m, C<u>H</u>$_2$-O), 3.14 (1H, q, J 6.3, C<u>H</u>-O), 2.94 (1H, q, J 6.4, C<u>H</u>-O), 1.20-2.55 (2 x 5H, m, C<u>H</u>$_2$C<u>H</u>$_2$ & cyclopropyl C<u>H</u>), 1.11 (3H, q, J 6.4, CH-<u>Me</u>), 1.10 (3H, q, J 6.3, CH-<u>Me</u>), 0.91 (6H, s, <u>Me</u>), 0.89 (3H, s, <u>Me</u>), 0.86 (3H, s, <u>Me</u>), 0.83 (3H, s, <u>Me</u>), 0.83 (3H, s, <u>Me</u>), 0.82 (6H, s, <u>Me</u>), 0.60-0.69 (2H, m, cyclopropyl C<u>H</u>$_2$), 0.51 (1H, dd, J 5.6, 3.8, cyclopropyl CH<u>H</u>), 0.37 (1H, dd, J 8.1, 5.6, cyclopropyl CH<u>H</u>).

δ_C 108.7, 108.7 (<u>C</u>(OR$_2$), 78.7, 78.4 (<u>C</u>H-OR), 78.3, 77.2, 73.0, 73.0, 72.1, 71.4, 71.2, 71.1 (<u>C</u>H$_2$-O), 35.9, 35.9, 30.8, 30.5, 30.2, 30.0 (cyclopropyl <u>C</u> and <u>C</u>(Me)$_2$), 30.3, 29.9, 24.1, 21.9, (<u>C</u>H$_2$-<u>C</u>H$_2$), 27.4, 24.0 (cyclopropyl <u>C</u>H), 22.5, 22.4, 22.3,

22.3, 21.9, 21.4 (C(Me)$_2$), 18.5, 17.4 (CH-Me), 12.3, 9.2 (cyclopropyl CH$_2$).
[Found : M^+ 312.2313, $C_{18}H_{32}O_4$ requires 312.2300] ; m/z 312 (8%, M^+), 225 (17, $C_{13}H_{21}O_3$), 141, (24, $C_8H_{13}O_2$), 128 (91, $C_7H_{12}O_2$), 123 (33, $C_8H_{11}O$), 122 (19, $C_8H_{10}O$), 69 (100, C_5H_9).

Further elution with light petroleum-EtOAc (1:1) as the eluent yielded the 4-(1-(1-hydroxy-2,2-dimethylprop-3-oxy)ethyl) bicyclo{3.1.0}hexan-2-one (**303**) (278 mg, 20 %) as a thick oil (two diastereomers) (R_f 0.28, light petroleum-EtOAc (2:1))
ν_{max}/cm^{-1} 3460 (br, OH), 1718 (C=O), 1108 (C-OR), 1050 (C-OH).
δ_H 2.85-3.31 (2 x 5H, m, CH-O and CH$_2$-O), 1.88-2.11 (2 x 5H, m, CH$_2$-CH$_2$ and OH), 1.71 (1H, dd, J 9.1, 3.4, cyclopropyl CH), 1.65 (1H, dd, J 9.1, 2.8, cyclopropyl CH), 1.16 (3H, d, J 6.4, CH-Me), 1.15 (3H, d, J 6.3, CH-Me), 0.81 (3H, s, Me) , 0.81 (3H, s, Me) , 0.79 (3H, s, Me) , 0.79 (3H, s, Me), 0.97-1.14 (1H + 2H, cyclopropyl CH$_2$), 1.30 (1H, dd, J 9.1, 4.6, cyclopropyl CH$_2$).
δ_C 78.0, 76.8 (CH-OR), 77.8, 77.2, 71.0, 70.6 (CH$_2$-O), 37.0, 36.9, 36.2, 36.1 (cyclopropyl C and C(Me)$_2$), 34.0, 31.0 (cyclopropyl CH), 32.5, 32.5, 23.0, 21.7 (CH$_2$-CH$_2$), 21.7, 21.6 (C(Me)$_2$), 17.7, 17.2 (CH-Me)
[Found : M^+ 140.0831, $C_8H_{12}O_2$ requires 140.0837] ; m/z 140 (31%. M^+), 125 (37, $C_7H_9O_2$), 123 (68, $C_8H_{11}O$), 122 ($C_8H_{10}O$), 97 (46, C_6H_9O), 95 (50, C_7H_{11}), 87 (35, $C_5H_{11}O$), 81 (99, C_6H_9).

2,2-Dimethyl-1,3-bis-trimethylsilanoxy-propane (335)



(294) **(335)**

Procedure:[123]

To a flame dried 2-necked 250 ml round bottom flask fitted with septum and N_2 balloon was added successively 2,2-dimethyl propane-1,3-diol (**294**) (4.87 g, 46.8 mmols) in dry THF (70 ml), Et$_3$N (18 ml, 130 mmols) and TMSCl (15 ml, 120 mmols) *via* syringe. The reaction mixture was stirred for 16 hours. The reaction mixture was diluted with dry pentane (200 ml), filtered through a pad of celite and concentrated *in vacuo* to yield the crude product as a cloudy oil (9 g). Distillation

yielded the title compound (**335**) (7.38 g, 64 %) as a clear oil. b.p. 52-53 °C/2mm Hg. (lit.[133], 73 °C / 11 mmHg)

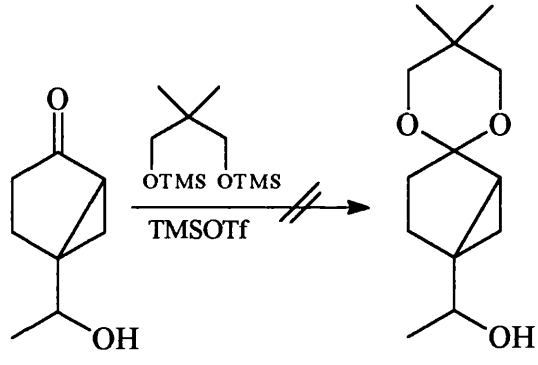
ν_{max}/cm^{-1} 1250 (SiMe), 1085 (C-O), 870, 838 (SiMe).

δ_H 3.29 (4H, s, $C\underline{H}_2$-OSi), 0.79 (6H, s, $C(\underline{Me})_2$), 0.09 (18H, $Si(\underline{Me})_3$).

δ_C 69.8 ($\underline{C}H_2$-OSi), 39.1 ($\underline{C}(Me)_2$), 23.4 ($C(\underline{Me})_2$), 1.5 ($Si(\underline{Me})_3$).

[Found : M^+-Me 233.1401, $C_{10}H_{25}O_2Si_2$ requires 233.1393] ; m/z 233 (2%, M^+-Me), 158 (22, $C_8H_{18}OSi$), 147 (72, $C_5H_{15}OSi_2$), 143 (86, $C_7H_{15}OSi$), 73 (100).

Attempted Lewis acid catalysed ketalization

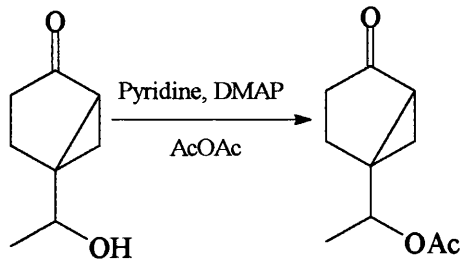


(290) **(309)**

Procedure:[122]

To a flame dried 2 necked 5 ml round bottom flask fitted with septum and N_2 balloon was added successively 2,2-dimethyl-1,3-bis-trimethylsilanoxypropane (**335**) (2.2 g, 8.8 mmols, 3.0 eqv) in dry DCM (1 ml) and TMSOTf (approx. 10 mg, 0.05 mmols). The reaction mixture was cooled (–78 °C) and ketone (**290**) (410 mg, 2.93 mmols) in dry DCM (1 ml) added. The reaction was stirred for 18 hours allowing the temperature to rise to –45 °C. The reaction was quenched with dry pyridine (100 µl) at this temperature, then poured into saturated aqueous $NaHCO_3$ (10 ml). The aqueous layer was extracted with ether (3 x 10 ml). The organic extracts were dried over a 1:1 mixture of Na_2CO_3 and Na_2SO_4 and concentrated *in vacuo* to give a brown oil (250 mg). Chromatography using light petroleum-ether (4:1 increasing to 0:1) then light petroleum-ethyl acetate (4:1 increasing to 0:1) yielded only 4-(1-(1-hydroxy-2,2-dimethyl-prop3-oxy)ethyl) bicyclo{3.1.0}hexan-2-one (**303**) (195 mg, 30 %) shown by NMR and TLC to be identical to material prepared previously.

1-(2-Oxo-bicyclo{3.1.0}hex-5-yl)-ethyl acetate (310)



(290) **(310)**

Procedure:[101,134]

A solution of 5-(1-hydroxyethyl)-bicyclo{3.1.0}hexan-2-one (**290**) (2.35 g, 16.8 mmols) and DMAP (250 mg, 2 mmols) in dry pyridine (40 ml) and acetic anhydride (15 ml) was stirred for 24 hours. The reaction mixture was poured into water (150 ml) and saturated aqueous NH_4Cl (150 ml) added. The aqueous mixture was extracted with EtOAc (3 x 150 ml). The organic extracts were washed with aqueous $CuSO_4$ (5 x 50 ml), aqueous saturated $NaHCO_3$ (3 x 50 ml) and aqueous saturated NaCl (3 x 100 ml). The organic layers were dried and solvent removed *in vacuo* to leave the crude product (3.28 g) as a brown oil. Chromatography with light petroleum-EtOAc (2:1) as the eluent yielded a clear oil which was shown to be the title product (**310**) (2.82 g, 92 %) as a mixture of diastereomers. (Rf 0.62, light petroleum-EtOAc (1:1))

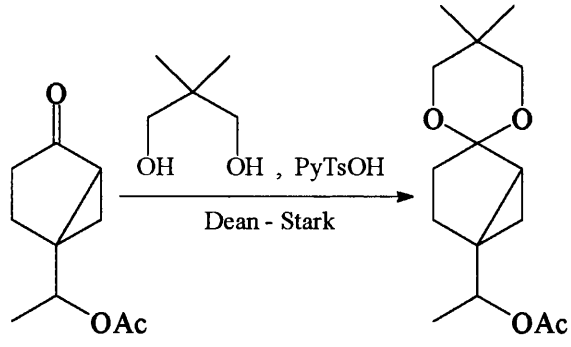
ν_{max}/cm^{-1} 3070 (cyclopropyl CH), 1731 (C=O), 1371 (acetate Me).

δ_H 4.89 (1H, q, J 6.4, C<u>H</u>-OAc), 4.63 (1H, q, J 6.5, C<u>H</u>-OAc), 1.92-2.11 (2 x 4H, m, CH_2-CH_2), 1.96 (3H, s, acetate <u>Me</u>), 1.95 (3H, s, acetate <u>Me</u>), 1.73 (1H, dd, J 9.4, 3.4, cyclopropyl C<u>H</u>), 1.68 (1H, dd, J 9.4, 3.3, cyclopropyl C<u>H</u>), 1.33 (1H, dd, J 9.4, 4.9, cyclopropyl $C\underline{H}_2$), 1.20-1.25 (1H, m, cyclopropyl $C\underline{H}_2$), 1.23 (3H, d, J 6.5, CH-<u>Me</u>), 1.18 (3H, d, J 6.4, CH-<u>Me</u>), 1.07 (1H, dd, J 5.1, 3.4, cyclopropyl $C\underline{H}_2$), 1.04 (1H, dd, J 4.9, 3.3, cyclopropyl $C\underline{H}_2$).

δ_C 212.9, 212.8 (ketone <u>C</u>=O), 169.9, 169.8 (acetate <u>C</u>=O), 72.0, 70.9 (<u>C</u>H-OAc), 36.7, 36.2 (cyclopropyl <u>C</u>), 32.9, 31.7 (cyclopropyl <u>C</u>H), 32.6, 32.3, 23.1, 21.9 ($\underline{C}H_2$-$\underline{C}H_2$), 17.3, 17.3 (cyclopropyl $\underline{C}H_2$), 20.8, 20.7 (CH-<u>Me</u>), 17.1, 17.0 (acetate <u>Me</u>).

[Found : M^+ 182.0942, $C_{10}H_{14}O_3$ requires 182.0943] ; m/z 182 (12%, M^+), 122 (62, $C_8H_{10}O$), 107 (20, C_7H_7O), 96 (22, C_6H_8O), 95 (23, C_7H_{11}), 79 (100, C_6H_7).

1-(2,2-(2,2-dimethyl-propylene-dioxy)bicyclo{3.1.0}hex -5-yl)-ethyl acetate (311)



(310) **(311)**

Procedure:[121]

A solution of the ketone (**310**) (850 mg, 4.67 mmols), 2,2-dimethyl-1,3-propanediol (**294**) (880 mg, 8.5 mmols) and pyridinium tosylate (0.4 g, 1.6 mmols) in toluene (50 ml) was refluxed under Dean-Stark conditions for 1 hour. The cooled reaction mixture was poured into saturated aqueous $NaHCO_3$ (50 ml). The aqueous layer was extracted with EtOAc (3 x 50 ml). The combined organic layers were washed with saturated aqueous NaCl (3 x 50 ml), dried and solvent removed *in vacuo* to leave the crude product as a yellow oil (1.41 g). Chromatography with light petroleum-EtOAc (6:1) yielded a clear oil which was shown to be the title compound (**311**) (485 mg, 39 %) as a mixture of diastereomers. (Rf 0.69 light petroleum-EtOAc (2:1))

ν_{max}/cm^{-1} 1764 (C=O), 1248 (acetate C-O), 1121 (C-OR).

δ_H 4.72 (1H, q, J 6.4, C<u>H</u>-OAc), 4.64 (1H, q, J 6.6, C<u>H</u>-OAc), 3.64, 3.53 (2H, ABq, J 11.4, C<u>H</u>$_2$-O), 3.43, 3.39 (2H, ABqd, J 11.4, 1.8, C<u>H</u>$_2$-O), 3.63, 3.59 (2H, ABq, J 11.1, C<u>H</u>$_2$-O), 3.49, 3.37 (2H, ABqd, J 11.1, 1.8, C<u>H</u>$_2$-O), 2.00 (3H, acetate <u>Me</u>) , 2.00 (3H, acetate <u>Me</u>), 1.64-1.95 (2 x 4H, m, C<u>H</u>$_2$-C<u>H</u>$_2$), 1.26-1.42 (2 x 2H, m, cyclopropyl C<u>H</u>$_2$ & C<u>H</u>), 1.22 (3H, d, J 6.6, CH-<u>Me</u>), 1.21 (3H, d, J 6.4, CH-<u>Me</u>), 1.03 (3H, s, <u>Me</u>), 0.95 (3H, s, <u>Me</u>), 0.94 (3H, s, <u>Me</u>), 0.84 (3H, s, <u>Me</u>), 0.61-0.73 (1 x 2H, m, cyclopropyl C<u>H</u>$_2$).

δ_C 170.7, 170.4 (<u>C</u>=O), 108.5, 108.4 (<u>C</u>(OR)$_2$), 73.3, 73.0 (<u>C</u>H-OAc), 71.1, 71.1 (<u>C</u>H$_2$-OR), 31.6, 30.7 (cyclopropyl <u>C</u>), 31.4, 30.1, 24.0, 23.0 (<u>C</u>H$_2$-<u>C</u>H$_2$), 29.9, 29.9 (<u>C</u>(Me)$_2$), 25.8, 25.3 (cyclopropyl <u>C</u>H), 22.6, 22.4, 22.3, 22.1 (C(<u>Me</u>)$_2$), 17.5, 17.4 (acetate <u>Me</u>), 11.6, 11.0 (cyclopropyl <u>C</u>H$_2$).

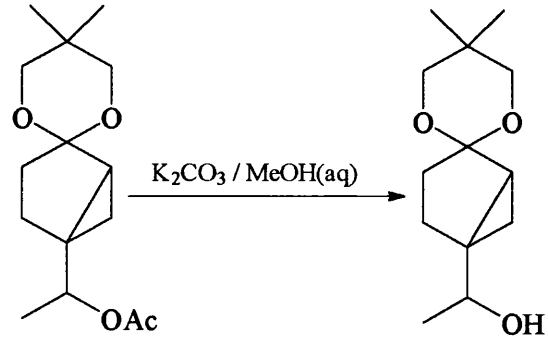
[Found : M^+ 268.1673, $C_{15}H_{24}O_4$ requires 268.1674] ; m/z 268 (5%, M^+), 225 (11,

$C_{13}H_{21}O_3$), 209 (47, $C_{13}H_{21}O_2$), 208 ($C_{13}H_{20}O_2$), 183 (10, $C_{10}H_{15}O_3$), 128 (64, $C_7H_{12}O_2$), 123 (90, $C_8H_{11}O$), 69 (100).

Further elution with light petroleum-EtOAc (2:1) furnished 4-(1-(1-hydroxy-2,2-dimethyl-prop-3-oxy)ethyl)-2,2-(2,2-dimethyl-propylene-dioxy)bicyclo{3.1.0}hexane (**302**) (470 mg, 32 %), which was shown by TLC and NMR to be identical to material prepared previously.

Further elution with EtOAc yielded 4-(1-(1-hydroxy-2,2-dimethyl-prop-3-oxy)ethyl) bicyclo{3.1.0}hexan-2-one (**303**) (27 mg, 3%), which was also shown by TLC and NMR to be identical to material prepared previously.

1-(2,2-(2,2-dimethyl-propylene-dioxy)bicyclo{3.1.0}hex -5-yl)-ethanol (309)



(**311**) (**309**)

Procedure:[88]

A solution of the 1-(2,2-(2,2-dimethyl-propylene-dioxy)bicyclo{3.1.0}hex-5-yl)-ethyl acetate (**311**) (310 mg, 1.16 mmols) and potassium carbonate (0.5 g) in aqueous methanol (30 ml) was stirred for 16 hours. The solution was poured into saturated aqueous NH_4Cl (50 ml) and extracted with EtOAc (3 x 40 ml). The organic extracts were washed with saturated aqueous NaCl (2 x 30 ml), dried and solvent removed *in vacuo* to leave a light brown oil which was shown to be the title compound (**309**) (185 mg, 71 %) as a mixture of diastereomers.

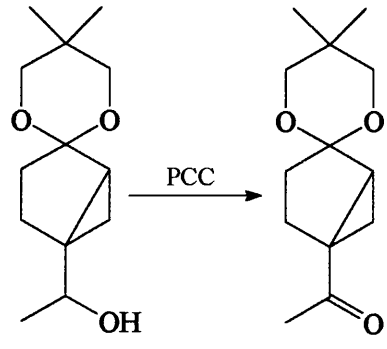
ν_{max}/cm^{-1} 3430 (br, OH).

δ_H 3.36 (2x5H, m, C<u>H</u>$_2$-O & C<u>H</u>-O), 1.55-2.35 (2x5H, m, bicyclohexyl <u>H</u>, O<u>H</u>), 1.20-1.40 (2x1H, m, bicyclohexyl <u>H</u>), 1.15 (2x3H, d, J 6.4, CH<u>Me</u>), 1.00 (3H, s,

Me), 0.95 (3H, s, Me), 0.92 (3H, s, Me), 0.87 (3H, s, Me), 0.54-0.74 (2x2H, m, cyclopropyl CH_2). δ_C 108.8, 108.7 ($C(OR)_2$), 72.8, 72.8, 71.3, 71.2 (CH_2-OR), 71.7, 69.3 (CH-OH), 33.1, 33.1 (cyclopropyl C), 30.1 ($C(Me)_2$), 29.9, 28.4 24.7, 22.6 (CH_2-CH_2), 28.0, 25.2 (cyclopropyl CH), 22.3, 22.3, 22.2, 20.3, 19.8 (Me), 10.7, 10.0 (cyclopropyl CH_2).

[Found : M^+ 226.1552, $C_{13}H_{22}O_3$ requires 226.1569] ; m/z 226 (3%, M^+), 209 (6, $C_{13}H_{21}O_2$), 208 (3, $C_{13}H_{20}O_2$), 141 ($C_8H_{13}O_2$), 128 (100, $C_7H_{12}O_2$).

1-(2,2-(2,2-dimethylpropylenedioxy)bicyclo{3.1.0}hex -5-yl)-ethanone (312)



(309) **(312)**

Procedure:[124]

To a flame dried 2-necked 10 ml round bottom flask fitted with septum and N_2 balloon was added 4°A molecular sieves (0.5 g) , dry celite (0.5 g) and PCC (270 mg, 1.25 mmols). The flask was evacuated and purged with nitrogen. Dry DCM (4 ml) was added *via* syringe. To the stirring mixture was added 1-(2,2-(2,2-dimethyl-propylene-dioxy)bicyclo{3.1.0}hex -5-yl)-ethanol (**309**) (140 mg, 0.62 mmols) in dry DCM (3 ml) *via* syringe. The reaction was stirred for 3 hours. The black reaction mixture was diluted with dry ether (30 ml) and filtered through a pad of silica. The black tarry residue was washed with dry ether (2 x 10 ml). The combined ethereal solutions were concentrated *in vacuo* to leave the title product (**312**) (96 mg, 69 %) as a light brown oil.

ν_{max}/cm^{-1} 3093 (cyclopropyl), 1667 (C=O), 1357, 1332 ($C(Me)_2$), 1113 (C-OR)

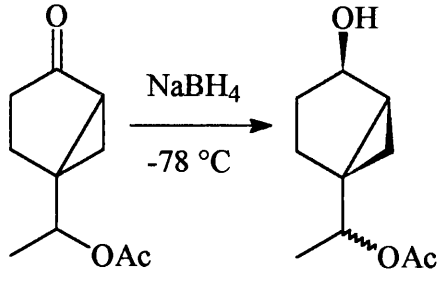
δ_H 3.63 (1H, d, J 11.4, CHH-OR), 3.57 (1H, d, J 11.2, CHH-OR), 3.48 (1H, dd, J11.4, 1.3, CHH-OR), 3.41 (1H, dd, J 11.2, 1.1, CHH-OR), 2.42 (1H, dd, J 5.3, 8.8,

cyclopentyl C<u>H</u>$_2$), 2.26 (1H, td, J 11.9, 8.8, cyclopentyl C<u>H</u>$_2$), 2.07-2.12 (1H, m, cyclopentyl C<u>H</u>$_2$), 2.09 (3H, s, <u>Me</u>C=O), 1.95 (1H, dd, J 12.7, 8.3), 1.39-1.46 (2H, m, cyclopropyl C<u>H</u>$_2$ & C<u>H</u>), 1.06 (1H, t, J 5.1, cyclopropyl <u>C</u>H$_2$), 1.00 (3H, s, C(<u>Me</u>)$_2$), 0.94 (3H, s, C(<u>Me</u>)$_2$).

δ_C 207.3 (<u>C</u>=O), 107.1 (<u>C</u>(OR$_2$), 72.8, 71.2 (<u>C</u>H$_2$-O), 38.1 (cyclopropyl <u>C</u>), 32.5 (cyclopropyl <u>C</u>H), 30.7, 24.0 (<u>C</u>H$_2$-<u>C</u>H$_2$), 29.7 (<u>C</u>(Me)$_2$), 26.2 (<u>Me</u>C=O), 22.2, 22.0 (<u>Me</u>), 16.9 (cyclopropyl <u>C</u>H$_2$).

[Found : M^+ 224.1418, $C_{13}H_{20}O_3$ requires 224.1412] ; m/z 224 (32%, M^+), 139 (22, $C_8H_{11}O$), 128 (100, $C_7H_{12}O_2$), 110 (20, $C_7H_{10}O$), 95 (30, C_6H_7O).

1-(2-hydroxybicyclo{3.1.0}hex-5-yl)ethyl acetate (313)



(310) **(313)**

<u>Procedure</u>:[100]

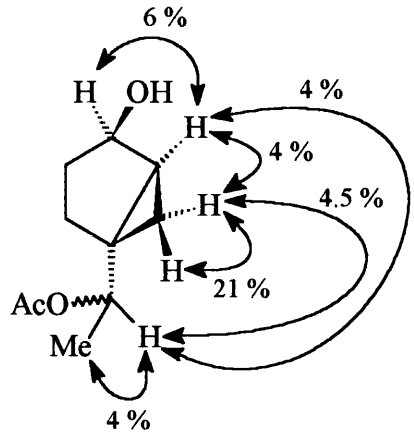
To a solution of the ketone (**310**) (2.68g, 14.7 mmols) in EtOH (140 ml) at -78°C was added $NaBH_4$ (600 mg, 16 mmols, ~4 eqv.) in EtOH (25 ml). The reaction was stirred at -78°C for 8 hours. The reaction mixture was diluted with water (75 ml) then saturated aqueous NH_4Cl (75 ml) and extracted with ethyl acetate (3 x 75 ml). The organic extracts were washed with brine (3 x 75 ml), dried and solvent removed *in vacuo* to leave the crude product (2.33 g) as a cloudy oil. Chromatography yielded the <u>title product</u> (**313**) (2.30 g, 85%) as a mixture of diastereomers shown[a] to be >20:1 selective for the α-isomers. (Rf 0.45, EtOAc).

ν_{max}/cm^{-1} 3402 (-OH), 3070 (cyclopropyl), 2874 (-CH-O-), 1732 (C=O), 1371 (MeC=O), 1246 (C-OAc), 1061 (C-OH)

δ_H α-isomer [A] , α-isomer [B] 4.79[A] (1H, q, J 6.4, C<u>H</u>-OAc), 4.58[B] (1H, q, J 6.5, C<u>H</u>-

OAc) 4.44-4.50^{AB} (2x1H, m, C<u>H</u>-OH), 2.00^{A} (3H, s, acetate <u>Me</u>), 1.99^{B} (3H, s, acetate <u>Me</u>), 1.68-2.00^{AB} (2x3H, m, cyclopentyl C<u>H</u>H and C<u>H</u>$_2$), 1.78^{AB} (2x1H, s, O<u>H</u>), 1.45^{B} (1H, dt, J 8.0 and 4.1, cyclopropyl C<u>H</u>), 1.38^{A} (1H, dt, J 8.1 and 3.9, cyclopropyl C<u>H</u>), 1.19^{B} (1H, d, J 6.5, CH<u>Me</u>), 1.18^{A} (1H, d, J 6.4, CH<u>Me</u>), 1.00-1.18^{AB} (2x1H, m, cyclopentyl CH<u>H</u>), 0.80^{B} (1H, dd, J 5.4 and 4.1, cyclopropyl C<u>H</u>H), 0.78^{A} (1H, dd, J 5.2 and 3.9, cyclopropyl C<u>H</u>H), 0.57^{A} (1H, dd, J 8.0 and 5.2, cyclopropyl CH<u>H</u>), 0.46^{A} (1H, dd, J 8.3 and 5.4, cyclopropyl CH<u>H</u>).

NOE difference (for detailed table of results, see appendix 5)



δ_C 170.7, 170.6 (<u>C</u>=O), 70.8, 70.2, 70.2, 69.6 (<u>C</u>H-O), 28.7, 28.4 (cyclopropyl <u>C</u>), 26.2, 25.7 (<u>C</u>H$_2$), 25.0, 23.8 (cyclopropyl <u>C</u>H), 22.4, 21.4 (<u>C</u>H$_2$), 18.1, 18.0 (<u>Me</u>CO$_2$-), 14.2 (<u>Me</u>CH), 5.5, 5.5 (cyclopropyl -<u>C</u>H$_2$).

[Found M^+ 184.1070, $C_{10}H_{16}O_3$ requires 184.1099] ; m/z 184 (<1%, M^+) 124 (77, $C_8H_{12}O$), 123 (10, $C_8H_{11}O$), 109 (100, C_7H_9), 107 (23, C_8H_{11}), 106 (19, C_8H_{10}).

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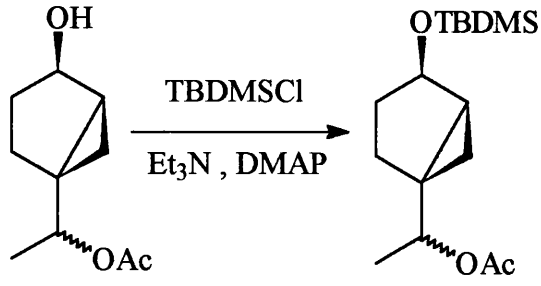
[a]Determined by ^{1}H NMR integral.

1-(2-(*tert*-Butyldimethylsilanoxy)-bicyclo{3.1.0.}hex-5-yl)-ethyl acetate (336).



(313) **(336)**

Procedure:[99]

To a flame dried 2-necked 100 ml round bottom flask fitted with septum and N_2 balloon was added Et_3N (2.7 ml, 15 mmols) *via* syringe. To this was added DMAP (150 mg, 1.2 mmols) and TBDMSCl (2.18 g, 14.5 mmols) in dry DCM (20 ml) *via* syringe. A solution of alcohol (**313**) (1.76 g, 9.57 mmols) in dry DCM (30 ml) was added dropwise to the stirring reaction mixture *via* syringe. The reaction was then allowed to stir for 24 hours. Dry methanol (1 ml) was added to the reaction mixture and stirred for a further 30 minutes. The reaction mixture was diluted with dry pentane (150 ml), filtered and concentrated *in vacuo* to leave the crude product as a dark brown oil. Chromatography with light petroleum-ether (1:1) as the eluent yielded a light brown oil which was shown to be the title compound (**336**) (2.79 g, 98%) as a mixture of diastereomers. (Rf 0.63, light petroleum-ether (1:1))

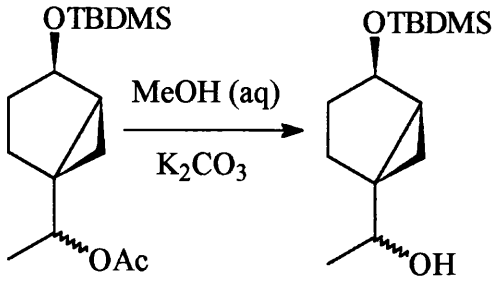
ν_{max}/cm^{-1} 2858 (CH-O-), 1735 (C=O), 1370 (-C(Me)$_3$), 1246 (C-OAc), 1093 (C-O-Si), 864 (Si(Me)$_2$),

δ_H 4.78 (1H, q, J 6.4, CHOAc), 4.58 (1H, q, J 6.5, CHOAc), 4.42-4.48 (2x1H, m, CH-OSi), 2.00 (3H, s, acetate Me), 2.02 (3H, s, acetate Me), 1.63-1.83 (2x3H, m, ring CH_2), 1.33 (1H, dt, J 8.3 and 4.3, cyclopropyl CH), 1.26 (1H, dt, J 8.2 and 4.2, cyclopropyl CH), 1.09-1.22 (2x1H, m, ring CH_2), 1.18 (3H, d, J 6.5, CHMe), 1.17 (3H, d, J 6.4, CHMe), 0.88 (9H, s, C(Me)$_3$), 0.87 (9H, s, C(Me)$_3$), 0.77-0.89 (2x1H, m, cyclopropyl CHH), 0.54 (1H, dd, J 8.2 and 5.2, cyclopropyl CHH), 0.43 (1H, dd, J 8.3 and 5.3), 0.04, 0.04, 0.03, 0.03 (4x3H, s, SiMe).

δ_C 170.8 (C=O) 74.2, 74.0, 74.0, 72.9 (CH-O), 31.5, 31.2 (cyclopropyl C), 29.8, 29.5, 25.3, 24.3 (CH_2-CH_2), 28.2, 27.2 (cyclopropyl CH), 25.9 (C(Me)$_3$), 21.3, 21.2 (acetate Me), 18.2 (C(Me)$_3$), 17.5, 17.4 (CHMe), 8.9, 8.8 (cyclopropyl CH_2), -4.6, -

4.7 (SiMe).

tert-Butyl-(5-(1-hydroxyethyl)-bicyclo{3.1.0.}hex-2-oxy)-dimethyl silane (314)



(336) **(314)**

Procedure:[88]

A solution of the acetate (**336**) (2.79 g, 93.6 mmols) and K_2CO_3 (5.4 g) in aqueous MeOH (150 ml) was stirred for 16 hours. The reaction mixture was neutralised with saturated aqueous NH_4Cl (100 ml) and MeOH removed *in vacuo*. The aqueous residue was extracted with EtOAc (3 x 75 ml). The organic extracts were washed with saturated aqueous NaCl (3 x 75 ml), dried and solvent removed *in vacuo* to leave the crude product (2.75 g) as a yellow oil. Chromatography with light petroleum-ethyl acetate (4:1) furnished a clear oil which was shown to be the title compound (**314**) (2.15 g, 90%) as a mixture of diastereomers. (Rf 0.37, light petroleum-ether (1:1)).

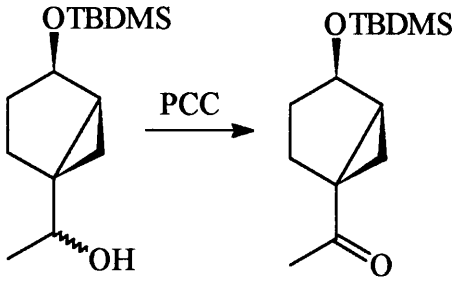
ν/cm^{-1} 3356 (OH), 3065 (cyclopropyl), 2858 (CH-O), 1362 ($C(Me)_3$), 1092 (C-OH), 1043 (C-OH), 859 ($SiMe_2$).

δ_H 4.44-4.54 (2x1H, m, CH-OSi), 3.61 (1H, q, J 6.3, -CHOH), 3.42 (1H, q, 6.4, -CHOH), 1.62-1.79 (2x2H, m, ring CH_2), 1.56 (1H, s, -OH), 1.55 (1H, s, -OH), 1.13-1.32 (2x3H, m, ring CH_2 and cyclopropyl CH), 1.17 (3H, d, J 6.4, MeCH), 1.16 (3H, d, J 6.3, MeCH), 0.88 (2x9H, s, Me_3C), 0.79-0.83 (2x1H, m, cyclopropyl CHH), 0.49 (1H, dd, J 8.4, 5.1, cyclopropyl CHH), 0.39 (1H, dd, J 8.2, 5.2, cyclopropyl CHH), 0.06 (6H, s, Me_2Si), 0.04 (6H, s, Me_2Si).

δC 74.2, 74.1 (CH-OSi), 71.7, 70.4 (CH-OH), 33.9, 33.6 (cyclopropyl C), 29.9, 27.7 24.8, 23.4 (CH_2CH_2), 28.1, 26.8 (cyclopropyl CH), 25.9 (Me_3C), 20.2, 20.0 (MeCH), 18.2 (CMe_3), 8.7, 8.4 (cyclopropyl CH_2), -4.6, -4.7 (SiMe).

[Found : M^+ - tBu 199.1167, $C_{10}H_{19}O_2Si$ requires 199.1155] ; m/z 199 (14%, M^+), 181 (14, $C_{10}H_{17}OSi$), 119 (8, $C_{10}H_{19}O_2Si$), 79 (3, C_6H_7), 75 (100, C_6H_7).

1-(2-(*tert*-Butyldimethylsilanoxy)-bicyclo{3.1.0.}hex-5-yl)-ethanone (315)



(314) **(315)**

Procedure:[124]

To a flame dried 2-necked 10ml round bottom flask fitted with septum and N_2 balloon was added PCC (600 mg, 2.8 mmols). The flask was evacuated and purged with nitrogen. To the oxidant was added dry DCM (2 ml). The alcohol (**314**) (320 mg, 1.26 mmols) in dry DCM (2 ml) was added dropwise. The reaction was allowed to stir for 5 hours before being diluted with dry ether (15 ml) and filtered through a pad of celite. Solvent was removed *in vacuo* to leave a brown oil. Chromatography with light petroleum-ether (3:1) as the eluent yielded the title compound (**315**) (275 mg, 86 %) as a yellow oil. (R_f 0.44, light petroleum-ether (2:1)).

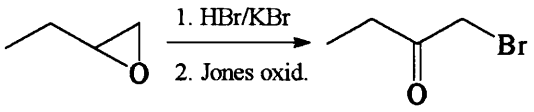
ν_{max}/cm^{-1} 1678 (C=O), 1258, 854 (SiMe), 1096 (C-OSi).

δ_H 4.39-4.48 (1H, m, C<u>H</u>-OSi), 1.77-2.11 (4H, m, bicyclo C<u>H</u>$_2$ and C<u>H</u>), 1.98 (3H, s, <u>Me</u>C=O), 1.13-1.28 (3H, m, bicyclo C<u>H</u>$_2$ & C<u>H</u>), 0.85 (9H, s, t-butyl <u>Me</u>), 0.04 (3H, s, Si<u>Me</u>), 0.02 (3H, s, Si<u>Me</u>).

δ_C 207.9 (C=O), 72.8 (<u>C</u>H-OSi), 38.8 (cyclopropyl <u>C</u>), 34.4 (cyclopropyl <u>C</u>H), 29.6, 24.7 (<u>C</u>H$_2$-<u>C</u>H$_2$), 25.9 (<u>Me</u>C=O), 25.8 (t-butyl <u>Me</u>), 18.1 (t-butyl <u>C</u>), 15.2 (cyclopropyl <u>C</u>H$_2$), -4.7, -4.8 (Si<u>Me</u>).

[Found : M^+ 254.1730, $C_{14}H_{26}O_2Si$ requires 254.1702] ; m/z 254 (1%, M^+), 197 (100, $C_{10}H_{17}O_2Si$), 169 (10, $C_8H_{13}O_2Si$).

1-bromobutan-2-one (321)



(320) **(321)**

Procedure:[120,126]

To a solution of 1,2-epoxy-butane (**320**) (6.50 g, 90.3 mmols) in hydrobromic acid (150 ml, 1.6M) was added KBr (30 g, 220 mmols). The solution was stirred for 1 hour at room temperature. The intermediate bromohydrin was extracted with ether (3 x 150ml). The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ (3 x 100ml) and saturated aqueous NaCl (3 x 100ml). The dried solution was concentrated *in vacuo* to leave a yellow oil (11.6 g) shown by NMR[a] to be mostly the desired regio-isomer (~3:1).

The crude bromohydrin was dissolved in acetone (100 ml). To the stirring solution was added Jones reagent[b] (90 mmols) dropwise at 0°C. The reaction was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was poured into 20% aqueous sodium thiosulphate (100 ml) and extracted with ether (3 x 150ml). The organic layers were washed with aqueous saturated $NaHCO_3$ (5 x 75ml) and saturated aqueous NaCl (3 x 100ml). The dried organic solution was concentrated *in vacuo* to leave the crude product as a light brown oil. Distillation with a Kugelrohr apparatus yielded the title compound (**321**) (4.43 g, 32%) as a clear oil, b.p. 80 °C/23 mm Hg (lit.[135], 68-70 °C/33 mm Hg)

ν/cm^{-1} 1716 (C=O).

δ_H 3.86 (2H, s, $C\underline{H_2}$-Br), 2.63 (2H, q, J 7.3, $C\underline{H_2}Me$), 1.05 (3H, t, J 7.3, Me).

δ_C 202.6 (C=O), 34.0, 33.0 ($\underline{C}H_2$), 7.8 (Me).

[Found : M^+ 151.9635, 149.9692, C_4H_7OBr requires 151.9661 , 149.9681. m/z : 151,149 (3%, 4%, M^+) 123 (3.7, C_2H_2OBr), 121 (3.8, C_2H_2OBr), 95 (6.4, CH_2Br) ,

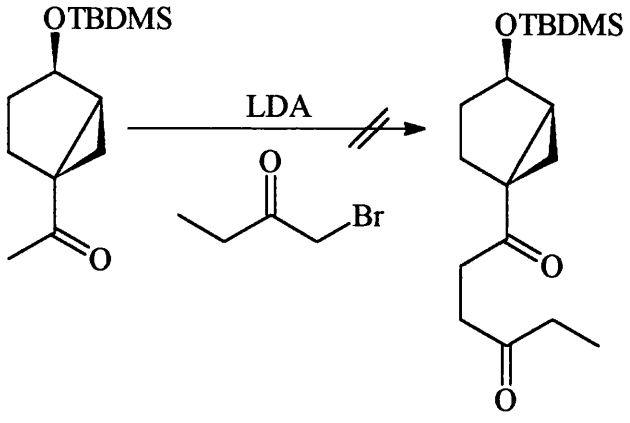
---

[a]1-bromo-propan-2-ol ; δ_H 3.76, (1H, dd, J 10.3, 3.4, $C\underline{H_2}$-Br), 3.73 (1H, dd, J 10.3, 6.9, $C\underline{H_2}Br$), 3.67 (1H, m, $C\underline{H}$-OH), 2.7 (1H, br, O<u>H</u>), 1.57 (2H, m, $C\underline{H_2}Me$), 0.94 (3H, t, J 7.5, Me). 2-bromo-propanol ; δ_H 4.04 (1H, m, $C\underline{H}Br$), 3.72 (2H, m, $C\underline{H_2}$-OH), 2.8 (1H, br, O<u>H</u>), 2.5 (2H, m, $C\underline{H_2}Me$), 1.03 (3H, t, J 7.3 , Me).

[b]Made with CrO_3 (90g) dissolved in conc.H_2SO_4 (8ml), diluted with water (27ml).

93 (7.0, CH_2Br), 57 (100, C_3H_5O).

Attempted coupling of enolate and bromoketone (321)

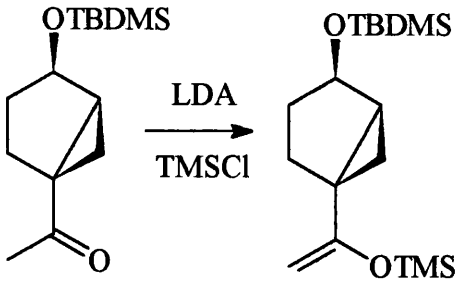


(315) **(316)**

Procedure:

To a flame dried 2-necked 10 ml round bottom flask fitted with septum and N_2 balloon was added diisopropylamine (120 µl, 0.92 mmols) and dry THF (2 ml). The solution was cooled to -78°C and BuLi (0.55 ml, 1.45M, 0.80 mmols) added. The cooling bath was removed and the reaction stirred for 15 minutes. The reaction mixture was re-cooled (-78°C) and the methyl ketone (**315**) (190 mg, 0.75 mmols) in dry THF (2 ml) added. The cooling bath was removed and the reaction stirred for 30 minutes. The flask was re-cooled (-78°C) and the bromomethyl ketone (**321**) (90 µl, 0.88 mmols) added. The cooling bath was removed and the reaction stirred for 8 hours. The reaction mixture was poured into saturated aqueous NH_4Cl (30 ml) and extracted with ether (3 x 30 ml). The organic layers were washed with saturated aqueous NaCl (2 x 30 ml), dried and solvent removed *in vacuo* to leave the crude product (250 mg) as a yellow oil. Chromatography with light petroleum-ether (3:1) yielded unchanged methyl ketone (**315**) (157 mg, 82%).

2-(*tert*-Butyldimethylsilanoxy)-5-(1-trimethylsilanoxyvinyl)-bicyclo{3.1.0.}hexane (322)



(315) **(322)**

Procedure:[127]

To a flame dried 2-necked 10 ml round bottom flask fitted with septum and N_2 balloon was added diisopropylamine (0.28 ml, 21 mmols) and dry THF (1 ml). The reaction flask was cooled to -78°C and BuLi (1.6 ml, 1.33 M, 2.1 mmols) added to the stirring solution. The cooling bath was removed and the reaction stirred for 30 minutes. To the reaction flask was added TMSCl (0.4 ml, 3.2 mmols) and the methyl ketone (**315**) (489 mg, 1.93 mmols) in dry THF (2 ml) *via* syringe. The reaction was stirred for 2 hours. The reaction mixture was diluted with dry pentane (30 ml) and filtered through a pad of celite. Solvent was removed *in vacuo* to leave the crude title product (**322**) as a white waxy solid (575 mg, 91 %).

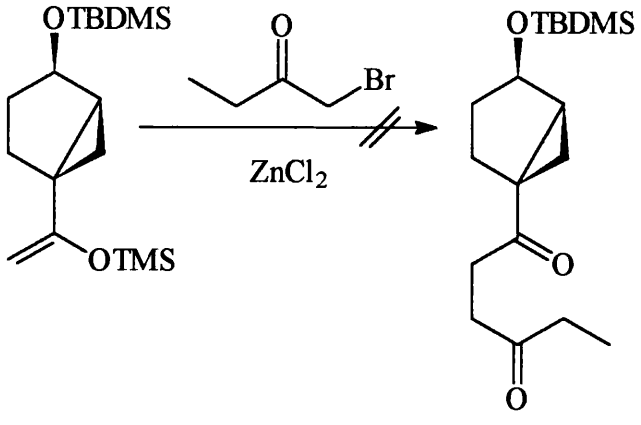
ν_{max}/cm^{-1} 1645 (C=C), 1365 (t-butyl), 1258 (SiMe), 1098 (C-O), 848 (SiMe).

δ_H 4.08, 4.06 (2H, ABq, J 1.3, $C\underline{H}_2$=C), 4.44-4.51 (1H, m, C<u>H</u>-OSi), 0.93- 1.85 (7H, m, bicyclo $C\underline{H}_2$ & C<u>H</u>), 0.89 (9H, s, t-butyl <u>Me</u>), 0.19 (9H, s, Si<u>Me</u>), 0.06 (3H, s, Si<u>Me</u>), 0.05 (3H, s, Si<u>Me</u>).

δ_C 160.2 (<u>C</u>=CH_2), 87.2 (C=<u>C</u>H_2), 73.6 (<u>C</u>H-OSi), 30.9 (cyclopropyl <u>C</u>), 29.9, 26.7 ($\underline{C}H_2$-$\underline{C}H_2$), 29.5 (cyclopropyl $\underline{C}H_2$), 25.9 (t-butyl <u>Me</u>), 18.2 (t-butyl <u>C</u>), 10.1 (cyclopropyl $\underline{C}H_2$), 0.0, -4.6, -4.7 (Si<u>Me</u>).

[Found : M^+ 326.2097, $C_{17}H_{34}O_2Si_2$ requires 326.2098] ; m/z 326 (6%, M^+), 311 (5, $C_{16}H_{31}O_2Si_2$), 269 (29, $C_{13}H_{25}O_2Si_2$), 179 (15, $C_{10}H_{15}OSi$), 147 (81, $C_5H_{15}OSi_2$), 105 (63, C_8H_9), 73 (100).

Attempted coupling of 2-(*tert*-butyldimethylsilanoxy)-5-(1-trimethylsilanoxyvinyl)-bicyclo{3.1.0.}hexane (322) and 1-bromo-butan-2-one (321)

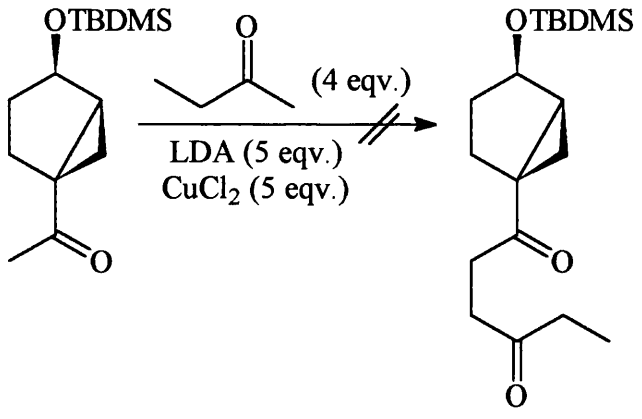


(322) **(316)**

Procedure:[90]

To a flame dried 2 necked 10 ml round bottom flask fitted with septum and N_2 balloon was added $ZnCl_2$ (180 mg, 1.32 mmols). The flask was evacuated and purged with nitrogen. To this was added dry DMF (1ml) *via* syringe. To the stirring solution was added 1-bromobutanone (**321**) (130 µl, 1.27 mmols) and silyl enol ether (**322**) (348 mg, 1.05 mmols) in dry DMF (2ml) *via* syringe. The reaction was stirred for 2 hours, then quenched with water (20 ml). The mixture was extracted with ether (3 x 20 ml). The combined organic extracts were washed with water (2 x 20 ml), saturated NaCl solution (2 x 20 ml), dried and solvent removed *in vacuo* to leave the crude mixture as a yellow oil. Analysis of the crude mixture by NMR and TLC showed only the presence of starting materials (**322** and **321**) and the hydrolysed silyl enol ether (**315**). No attempt was made to recover starting materials.

1-((2-*tert*-Butyl-dimethyl-silanoxy)-bicyclo{3.1.0.}hex-5-yl)-1,4-hexanedione (316).



(315) **(316)**

Procedure:[62]

To a flame dried 2-necked 50 ml round bottom flask fitted with septum and N_2 balloon was added diisopropylamine (2.1 ml, 16 mmols) and dry THF (10 ml). The reaction vessel was cooled to -78°C and BuLi (11 ml, 1.4M, 15.5 mmols) added to the stirring solution. The cooling bath was removed and the reaction stirred for 15 minutes. The reaction vessel was recooled (-78°C) and butanone (0.9 ml, 10 mmols) and methyl ketone (**315**) (580 mg, 2.28 mmols) in dry THF (5 ml) added. The reaction was stirred at -78°C for 30 minutes and anhydrous $CuCl_2$[a] (1.65 g, 12.3 mmols) in dry DMF (18 ml) added. The reaction mixture was stirred for a further 30 minutes at -78°C. The reaction mixture was poured into water (50 ml) and saturated aqueous NH_4Cl (50 ml) added. The aqueous solution was extracted with ether (3 x 75ml). The organic extracts were washed with saturated aqueous NH_4Cl (3 x 50ml) and saturated aqueous NaCl (3 x 50ml), dried and solvent removed *in vacuo* to leave the crude product (1.65 g) as a brown oil. Chromatography with light petroleum-ether (4:1) as the eluent yielded a yellow oil (612 mg). Further purification by column chromatography with hexane-DCM-ether (2:2:1) yielded a golden oil which on analysis was shown to be the title compound (**316**) (390 mg, 53%).

ν_{max}/cm^{-1} 1682, 1712 (C=O), 1255 (SiMe), 1095 (C-O), 854, 837 (SiMe).

δ_H 4.43 (1H, m, C<u>H</u>-OSi), 2.51-2.65 (2H, m, C<u>H</u>$_2$-C=O), 2.43 (2H, q, J 7.3,

---

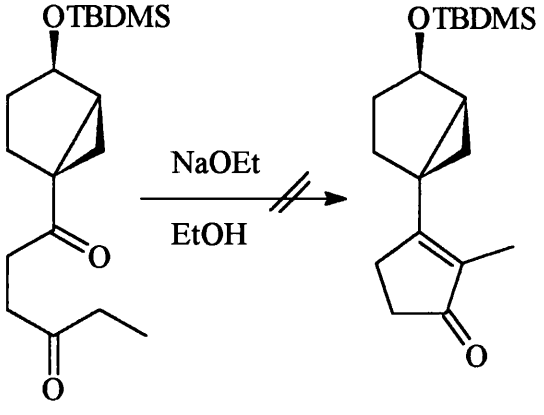
[a] Dried at 100°C in an oven for 3 hours.

CH_2Me), 1.05-2.17 (9H, m, bicyclohexyl H & CH_2-C=O), 0.99 (3H, t, J 7.3, CH_2Me), 0.83 (9H, s, *t*-butyl Me), 0.02 (3H, s, SiMe), 0.00 (3H, s, SiMe).

δ_C 210.1 208.4 (C=O), 72.7 (CH-OSi), 38.2 (cyclopropyl C), 35.9, 35.4, 32.0 (CH_2C=O), 29.5, 24.5 (cyclopentyl CH_2), 34.6 (cyclopropyl C), 25.8 (t-butyl Me), 16.1 (t-butyl C), 15.5 (cyclopropyl CH_2), 7.7 (CH_2Me), -4.7, -4.9 (SiMe).

[Found : M^+ 267.1413, $C_{14}H_{23}O_3Si$ requires 267.1416] ; m/z 267 (7%, M^+), 197 (15, $C_{14}H_{13}O$), 105 (9, C_8H_9), 79 (15, C_6H_7), 75 (100, C_2H_7OSi).

Attempted ring closure



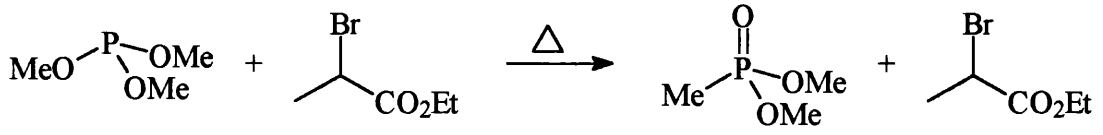
(316) **(317)**

Procedure:[128]

To a solution of sodium (230 mg) in EtOH (10 ml) was added the 1-((2-*tert*-butyl-dimethyl-silanoxy)-bicyclo{3.1.0.}hex-5-yl)-1,4-hexanedione (**316**) (150 mg, 0.56 mmols) (57) in EtOH (10 ml). The solution was heated at reflux for 2 hours. The cooled reaction mixture was poured into dilute HCL (20 ml, 1 M) and extracted with ether (3 x 30ml). The organic extracts were washed with brine (2 x 30 ml), dried and solvent removed *in vacuo* to leave a thick brown oil (85 mg). Purification using prep. plates yielded no identifiable products.

6. Appendix

Appendix 1 – Attempted preparation of ethyl 2-dimethylphosphono-propionate (224)



(223) (226) (224) (226)

To a 50 ml round bottom flask was added trimethyl phosphite (**223**) (7.6 g, 0.06 moles). The flask was heated to 100 °C and ethyl bromopropionate (**226**) (9.8 g, 0.054 moles added dropwise over 25 minutes. The mixture was heated to 120 °C as the bromide was added. The mixture was heated to 170 °C and stirred for 1 hour. The crude mixture was distilled to give two products shown by ^{1}H NMR to be a mixture of methyl dimethylphosphonate (**224**) and ethyl bromopropionate (**226**).

Appendix 2 - Pyridinium *p*-toluene sulphonate

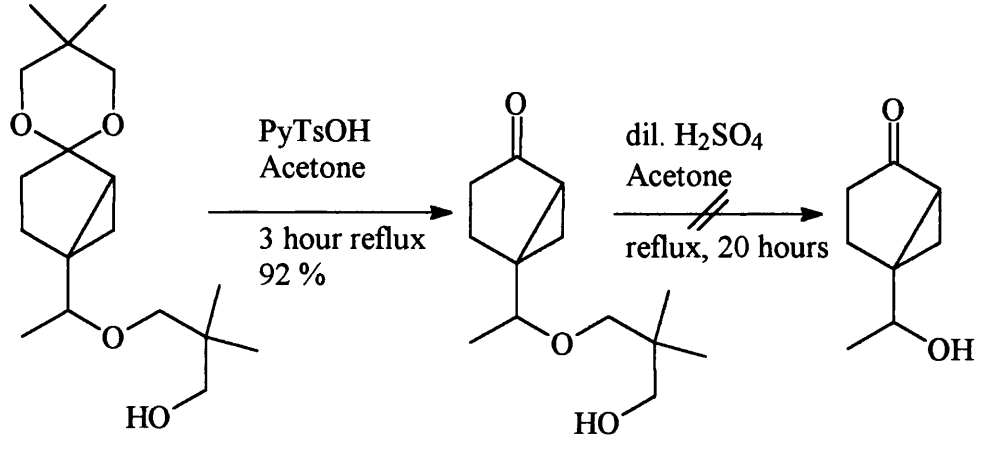
To pyridine (12.1 ml, 150 mmols) was added p-toluene sulphonic acid monohydrate (5.2 g, 30 mmols) with stirring. The solution was stirred at room temperature (slightly exothermic) for 20 minutes. Excess pyridine was removed *in vacuo* to leave a hygroscopic colourless solid. Recrystallisation (from acetone) furnished the title compound (6.63 g, 88 %) as white crystals, m.p. 118-119 °C (lit.[136] 120 °C)

Appendix 3 - Ethyltriphenylphosphonium bromide

To triphenyl phosphine (85 g, 0.32 mols) in dry toluene (100ml) was added ethyl bromide (46.7g, 0.42 mols). The reaction mixture was heated at reflux for 16 hours. The white precipitate was collected from the cooled reaction mixture by filtration, and soxhlet extracted with dry toluene (400ml) for 4 hours. The white product was

dried in a vacuum oven (100 °C) to give the title compound as a white powder, m.p. 208-209.5 °C. (lit.[137], m.p. 202-204 °C)

Appendix 4 – Deprotection of 4-(1-(1-hydroxy-2,2-dimethyl-prop-3-oxy)ethyl)-2,2-(2,2-dimethyl-propylene-dioxy)bicyclo{3.1.0}hexane (302)



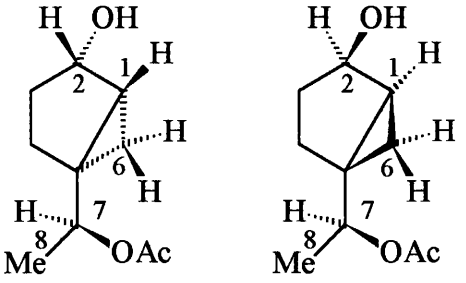
(302) **(303)** **(290)**

To a solution of 4-(1-(1-hydroxy-2,2-dimethyl-prop-3-oxy)ethyl)-2,2-(2,2-dimethyl-propylene-dioxy)bicyclo{3.1.0}hexane (**302**) (350 mg, 1.12 mmols) in acetone/water (50 ml, 9:1) was added pyridinium tosylate (150 mg, 0.6 mmols). The solution was heated at reflux for 3 hours. To the cooled solution was added $NaHCO_3$ (30 ml) and excess acetone removed *in vacuo*. The aqueous residue was extracted with DCM (3 x 30 ml). The dried organic extracts were concentrated *in vacuo* to leave a yellow oil shown by NMR and TLC to be identical to the ketone (**303**) (235mg, 92 %) prepared previously.

The reaction conditions were repeated with ether (**303**) with a longer reflux period (3 days). TLC showed no sign of the alcohol (**290**) so H_2SO_4 (10 ml, 1M) was added and the reaction heated at reflux for 16 hours. Identical workup yielded only crude ether (**303**) with no sign of alcohol (**290**) by ^1H NMR.

The crude ether (**303**) was dissolved in H_2SO_4 (50 ml, 2M) and stirred for 20 hours. TLC showed only ether (**303**) so the reaction mixture was heated under reflux for 16 hours. Identical workup yielded a dark brown oil shown to contain a number of components by TLC and NMR.

Appendix 5 – NOE Difference Results



Relative stereochemistry shown

(313)

Table 5.1. NOE results for both diastereomers

Proton Irradiated	% Nuclear Overhauser enhancement					
	H (1)	H (2)	H (6α)	H (6β)	H (7)	H (8)
H (1)	-	5.7, 5.4	3.3, 3.2	-	4.3, 4.2	-
H (2)	6.9, 6.5	-	-	-	-	-
H (6α)	4.1, 5.2	-	-	20, 22	3.6, 7.5	-
H (6β)	-	-	21, 20	-	-	-
H (7)	4.0, 3.9	-	2.4, 4.3	-	-	3.6, 4.2

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