Synthesis of Compounds of Natural and Unnatural Origin By Intramolecular Alkylations

A Thesis

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by

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Summary

The synthesis of the natural product, crispatanolide was investigated. The bicyclo[3.1.0]hexane moiety in crispatanolie was, for the most part, the subject of study. The 5-alkylbicyclo[3.1.0]hexan-2-ones (with a number of different alkyl groups) were synthesised by an intramolecular alkylation in which an enolate anion displaces a halide ion from a 4-halocyclohexanone. The 4-halocyclohexanones were available from the hydrolysis of the product of the addition of liquid hydrogen chloride to 1-methoxy-4-alkylcyclohexa-1,4-dienes. These enol ethers were available from dissolving metal reduction of the corresponding aryl ethers.

The use of enolate anions to form the bicyclic system was extended to yield an asymmetric synthesis of a bicyclic diol. The synthesis involved a sequential enantioselective (Sharpless) epoxidation and diastereoselective cyclisation reaction which was thought to result from an intramolecular deprotonation of the ketone moiety by the alkoxide moiety. A mixture of diols has been produced which contained 87% of one enantiomer.

The unnatural tetracyclo[5.3.1.$1^{2,6}$.$0^{4,9}$]dodecane ring system was the subject of a previously unfinished project. The cyclisation to form the desired ring system was planned to proceed through the intramolecular alkylation reaction of a dione which possesses two leaving groups. A suitable diketo

dibenzoate has been produced but it did not undergo the cycylisation. An alternative approach to the dione involving the carbonylation of double bonds met with failure.

Statement

This thesis contains no material previously submitted for a degree in any university and to the best of my knowledge and belief, contains no material previously published or written by another person except where due reference is made in the text.

Neil John Shirley.

Acknowledgements

I wish to express my sincere thanks to Dr. D.P.G. Hamon for his advice and encouragement during the supervision of this work. The helpful assistance and suggestions from other members of the Dpartment are also acknowledged.

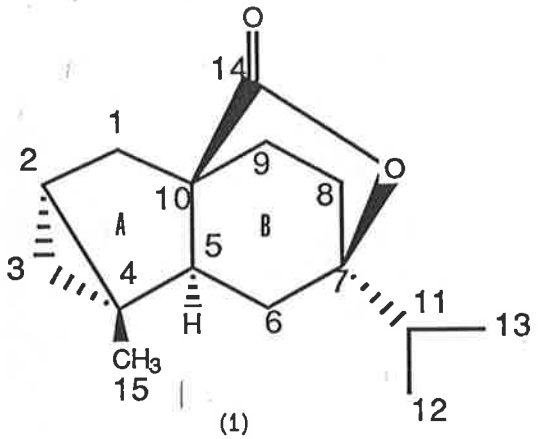
This research was conducted during the tenure of a Commonwealth Postgraduate Award, for which I am grateful.

I am indebted to Mrs. Andrea Hounslow for her assistance with the execution of the 300 MHz NMR experiments and to my parents for their patience, tolerance and care during the course of my studies.

Introduction

Introduction: Work directed towards the synthesis of Crispatanolide

In 1980, Asakawa *et al*[1] isolated a number of terpenoid natural products from liverworts. One of these, crispatanolide (1), was isolated from the liverwort *Makinoa crispata*. An x ray structural analysis has shown the compound has an unprecedented structure, that is, it contains a δ lactone ring between C7 and C14 and a cyclopropane ring contained in the A ring of a eudesmane system.



(1)

The molecule is an attractive synthetic target as it contains a number of structural features that have a defined stereochemical relationship. These main features are the δ lactone moiety which fixes ring B in the boat configuration and the *anti* configuration of the C3 carbon of the cyclopropane and C14 atom. This defines the stereochemistry of the C15 methyl group and the hydrogen on C5 as trans. There is a total of five chiral centres in the molecule. Two are contained in the

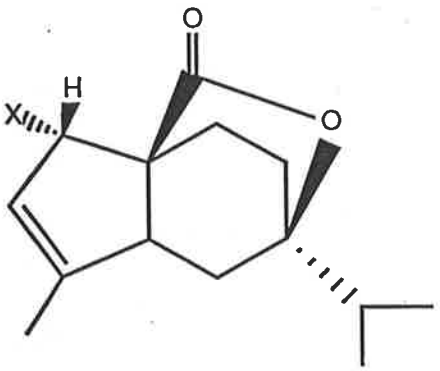
cyclopropane ring and as such their orientations are interrelated by the *cis* nature of the cyclopropane attached to a small ring system. Two more centres are to be found in the lactone ring (C7 & C10) and once again they are interrelated by the lactone bridge. The last centre is at the bridgehead carbon, C5 and is independent of the other pairs.

The synthesis of such a stereochemically rich and compact molecule is likely to be complicated. The same approach to each of the different structural features of the molecule may be invoked at different stages of alternative routes to the natural product. It is intended that this introduction should outline and explain some of these approaches, arrange them in an array of plausible synthetic routes to the natural product from a stereochemically correct precursor and also highlight some areas of chemistry where some chemical precedent is lacking.

Approach to the construction of the cyclopropane ring

If a retrosynthetic scheme is considered in which the need for stereochemical control of the introduction of the structural features is recognised then certain chemical transformations appear less attractive than others as they may generate complex diastereomeric mixtures. The main structural features in crispatanolide (1) must be brought into being with their appropriate relative stereochemistry. Hence, there appear to be two distinct approaches whereby either structural feature is

constructed last, that is, considered first in the retrosynthetic sense. For example, if the cyclopropane moiety is constructed at the final stage, at least two possible subtargets (2) and (3) arise. The cyclopropane could be constructed by the addition of carbenoid species to the double bond in the lactone (2) or by the displacement of a leaving group from the 4- position by an enolate anion derived from the ketone (3).



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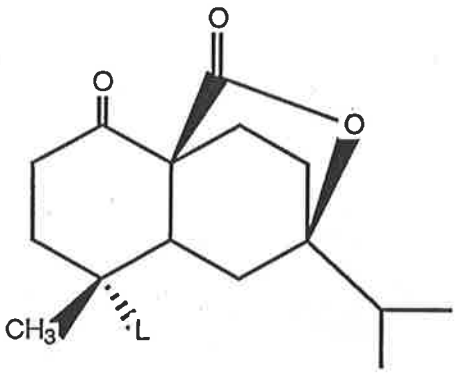
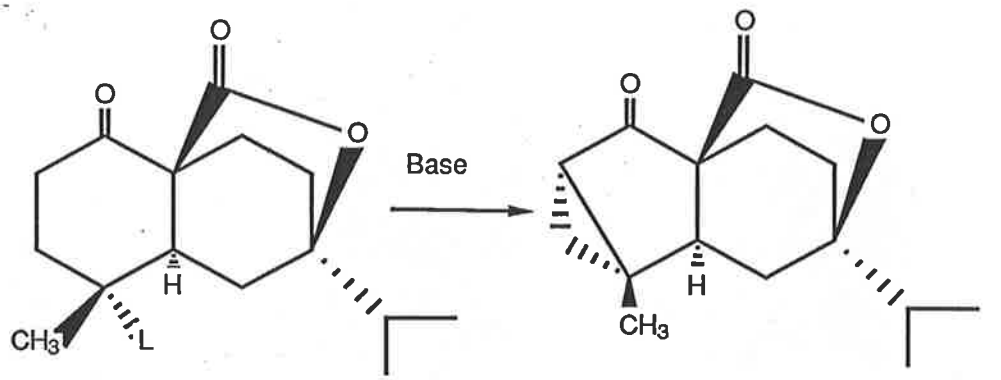


(3)

There are several drawbacks to the approach to crispatanolide (1) through the lactone (2 X=H). The first is the difficulty in the construction of the indene ring system. The second disadvantage is the relatively highly reactive intermediates associated with carbene chemistry which may lead to unpredictable stereochemistry in the product(s). If a Simmons-Smith type cyclopropanation is used to control the side from which the methylene group is added to the indene ring through coordination with a hydroxyl group[2], there is no great ease associated with the synthesis of the alcohol (2 X=OH) containing the appropriate stereochemistry. In contrast, the decalin system in

(3) is synthetically more readily available than the indene system and chemistry involving an Sn2 process submits more easily to stereochemical prediction and control. The loss of the keto group α to the cyclopropyl ring poses no great problem as it may be removed by a Wolff-Kishner reduction. Because of these considerations and the existence of some previous work in the area of 4- substituted cyclohexanones and bicyclo[3.1.0] hexanones[3], the investigation was centered on chemistry associated with the subtarget (3).



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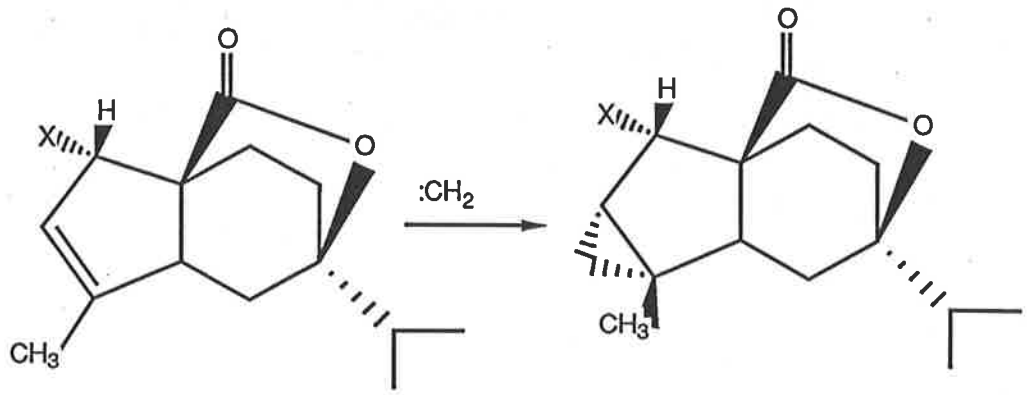
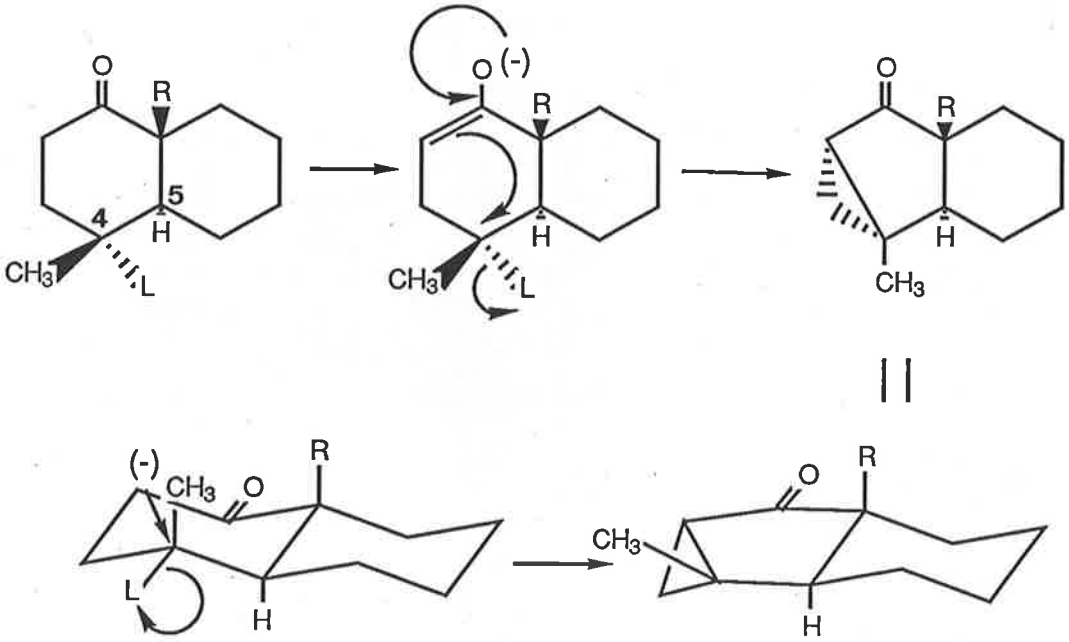


(2) (5)

The orientation in (3) of the leaving group at the 4- position with respect to the hydrogen on the bridge head carbon, C5, will

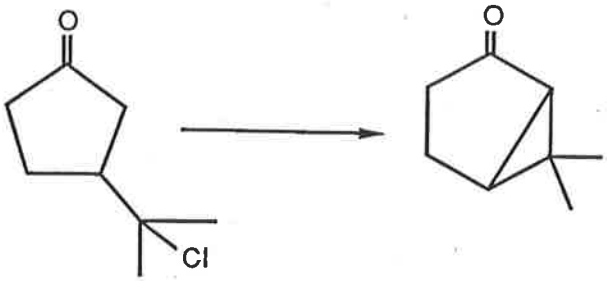
determine the stereochemistry of the cyclopropane with respect to the rest of the molecule. As the enolate anion is presumed to act in an Sn2 manner to displace the leaving group, it must do so following the mechanism of attack from the rear. In the case of crispatanolide, the cyclopropane methylene and the hydrogen on the C5 carbon are *syn*. The leaving group attached to C4 must therefore be *cis* to the hydrogen on C5 for the enolate anion to displace it from the side opposite that of the C5 hydrogen. This would force the methylene of the cyclopropane to be pushed *syn* to the C5 hydrogen. (see diagram below).



The leaving group at the 4- position of a cyclohexanone ring at a tertiary position must fulfil several criteria. Firstly, it must be stable enough not to be prone to elimination from the tertiary centre but must still be able to be displaced by an

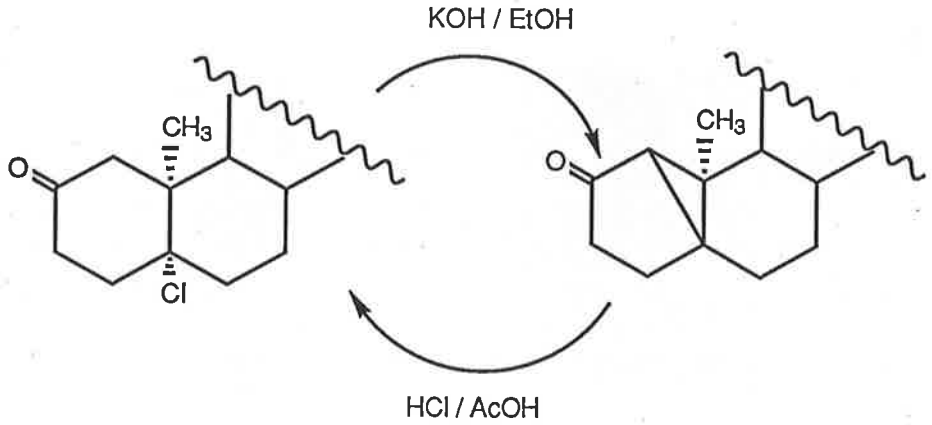
intramolecular nucleophile, in this case, an enolate ion. Leaving groups that have been used to synthesise simple bicyclo[3.1.0]hexanones are tosylate[4] (6 X = OTs) and hydroxyl (6 X = OH)[5] from secondary centres. In one instance, chloride at the tertiary centre in the ketone (7)[6] acted as the leaving group to allow the formation of the bicyclo[3.1.0]hexanone (8). The enolate anion of the ketone (7) was generated by the action of sodium hydride. The ketone (7) is vulnerable to elimination processes both through E1 and E2 mechanisms although the E1 process is not significant in this case. When the enolate anion is generated using kinetic conditions the Sn2 type process gives the bicyclo[3.1.0]hexanone in "satisfactory" yield.

(6)



(7) (8)

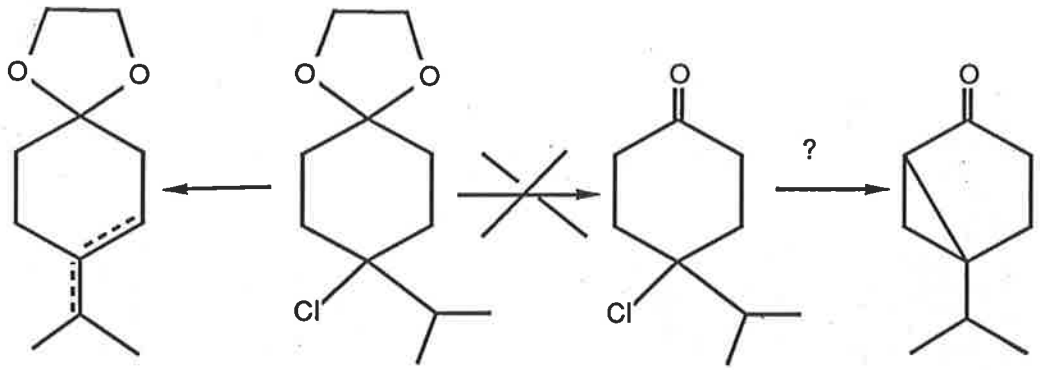
In 1962, Kwei, Shoulders and Gardner[7] reported the synthesis of the chloro steroid (9). They found there to be a rapid and nearly quantitative conversion of the chloro steroid (9) to the bicyclo[3.1.0]hexanone (10) by the action of ethanolic potassium hydroxide. It appeared that in this instance, the chloro group was stable enough not to be eliminated readily from the tertiary position but could be displaced by an enolate anion. Their synthesis of the chloro steriod (9) however involved simply the addition of hydrochloric acid (in acetic acid) across the cyclopropane ring of the bicyclo[3.1.0]hexanone (10) which was initially generated photochemically.



(9) (10)

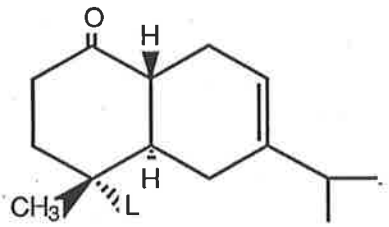
Nelson and Mortimer[4] attempted unsuccessfully to synthesise the chloro ketone (11) which was required for the synthesis of the natural product, sabina ketone (12). These workers were not able to effect the deprotection of the masked carbonyl group of the chloro acetal (13) in the presence of the tertiary chloro group. Under certain conditions, the elimination

reaction occurred which lead to the isolation of the acetals (14) but under others, the chloro acetal (13) was unchanged. The stability of the tertiary leaving group may be dependent on the particular molecule in question and of course, the severity of conditions that are required for its synthesis. The natural product, sabina ketone, being a 5-alkylbicyclo[3.1.0]hexanone, is an ideal model system for the investigation of the chemistry of the cyclopropyl moiety of crispatanolide.



(14) (13) (11) (12)

Should the synthesis of crispatanolide require the cyclopropanation to occur when the carboxylate group that has to be attached (C10 of crispatanolide) is not present, as in the ketone (15), the possibility of mixtures arises. In this case, the kinetic enolate would be expected to yield the desired cyclopropane and the thermodynamic enolate, the other possible cyclopropane. Hamon[8] has shown that the ketone (16), when treated with lithium di*iso*propylamide, produced a mixture consisting of the two possible cyclopropanes (17) and (18). The reaction afforded mainly the less substituted cyclopropane (17).



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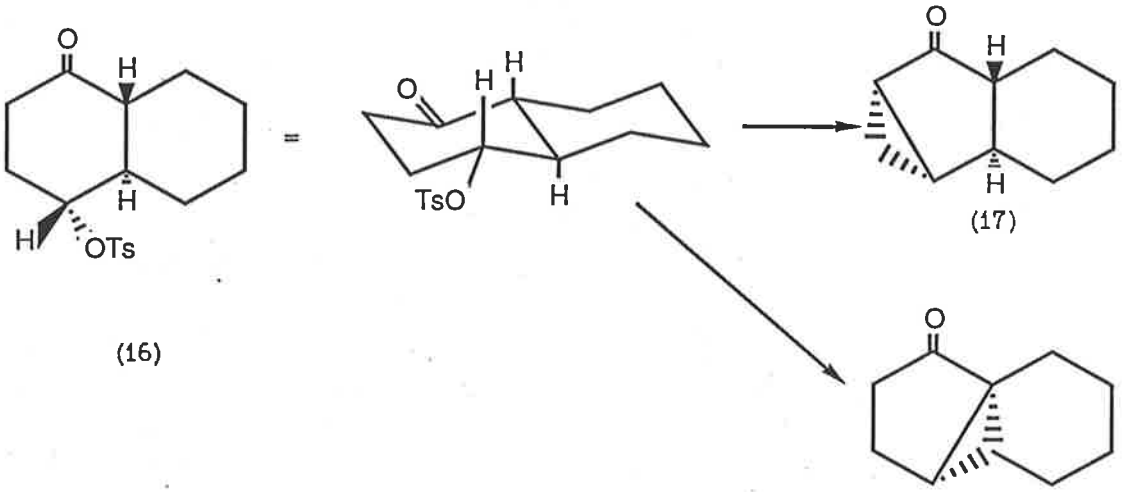


(16)

(17)

(18)

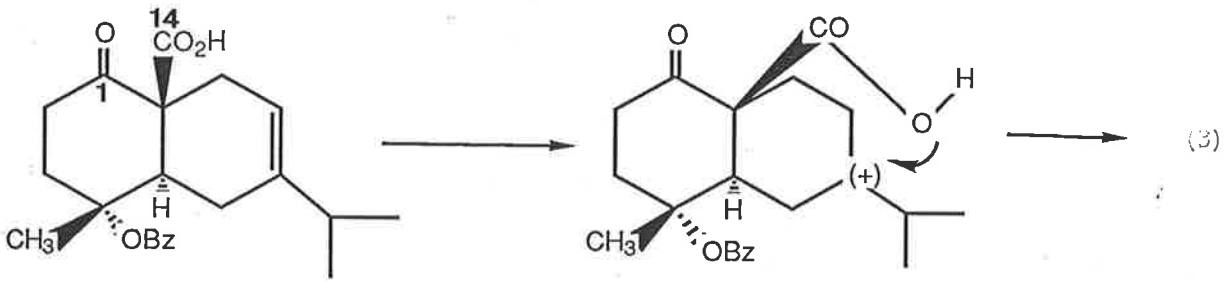
It is hoped that under strictly kinetic conditions, the kinetic product will be formed exclusively from the ketone, (15).

Approaches to the construction of the lactone ring: Lactonisation

In principle, there are two ways in which the lactone ring might be constructed. Firstly, and perhaps more conventionally, it could be constructed by the intramolecular trapping of a carbonium ion by a carboxylic acid. This will be termed the lactonisation approach (scheme i). The carbonium ion may effectively be generated from a double bond as in the enone (19) by treatment with a strong protic acid[9], a Lewis

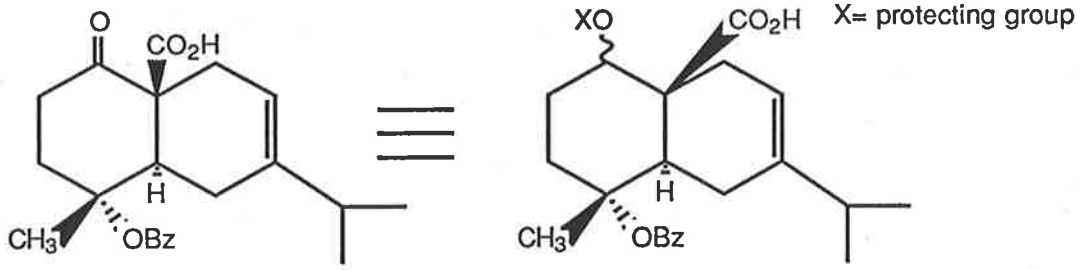
acid[9] or mercuric oxide[10].

Scheme i



(19)

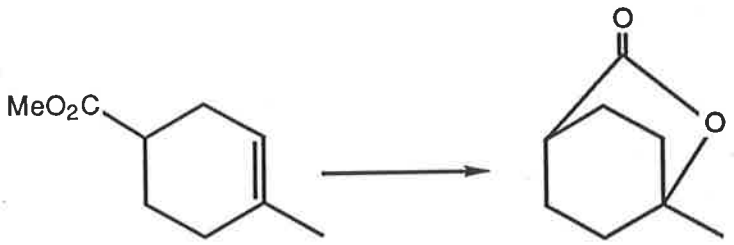
The lactonisation method has some literature precedence[11] but, as outlined, it would require the reaction of a β keto acid in acid solution. The carboxylate group at C14 (crispatanolide numbering) is anticipated to be extremely unstable in the presence of a carbonyl group at C1 as β keto acids readily decarboxylate[12]. This complicating factor might be overcome. The answer may be a protection and deprotection sequence for the carbonyl group at C1 before the lactonisation step. In the lactonisation reaction, care must be exercised in the choice of the Lewis acid or protic acid used so that the loss of the protecting group is avoided.



(19) (20)

Nelsen and Weisman[11] have shown that the ene ester

(21) when treated with aqueous acid gave the δ lactone. In the case of crispatanolide, the same chemistry would lead to the formation of the lactone (22).



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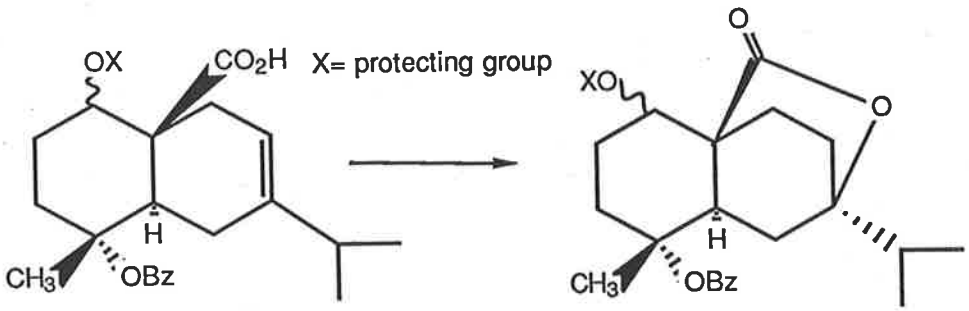


(20) (22)

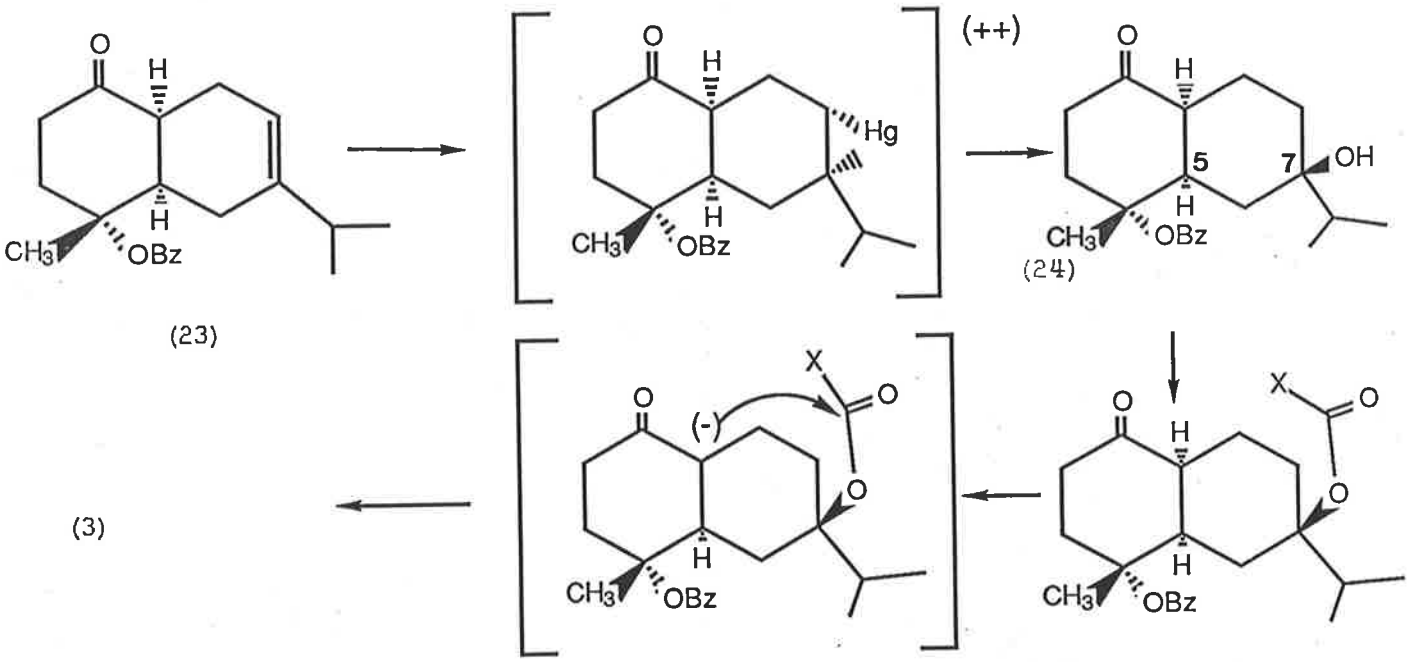
Approaches to construction of the lactone ring: Acylation.

The lactone ring may be constructed in the reverse sense through the use of a stereochemically controlled hydration of the double bond[13] of the enone (23) to give the alcohol (24). The alcohol (24) may be esterified to give the chloro ester (25) or the carbonate (26). This may allow an intramolecular acylation to occur at the bridge head position to give the lactone (3). This will be termed the acylation approach (scheme ii).

The *cis* decalin required for the acylation chemistry is once again available through the use of Diels Alder chemistry.

The *cis* decalin (23) shows significant steric anisotropy at the two faces of the double bond. The face *syn* to the non epimerising bridge head hydrogen is less congested than the other face as the molecule is bowed. For this reason it is anticipated

Scheme ii

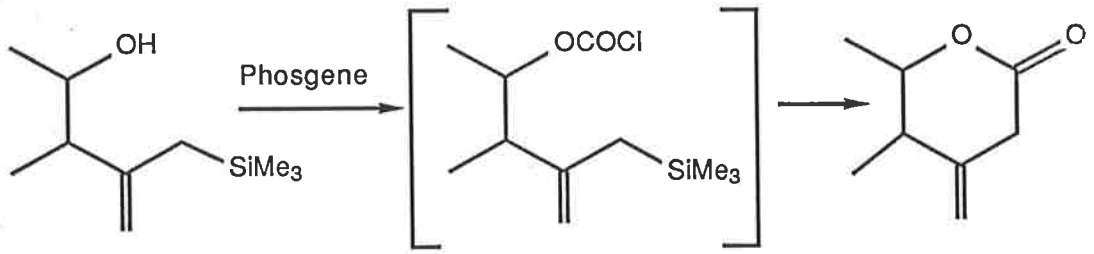


that the large mercury ion would complex to this face preferentially[14]. The resultant mercuronium ion would be hydrolysed in the standard Markownikoff orientation[13] leading to the desired *trans* stereochemistry of the oxygen atom at C7 with respect to the hydrogen atom attached to C5.

Because of the Markownikoff orientation of hydration of the double bond in the ketone (23), it is virtually assured that the

tertiary alcohol will be produced. This, together with the anisotropic considerations above leads to the assumption that the correct stereochemistry for the hydroxyl group at C7 with respect to the hydrogen on C5 will arise.

In 1983, Kocienski *et al*[15] used chemistry that is similar to the proposed acylation chemistry in their synthesis of ethyl pederate. These workers were able to synthesise the δ lactone (27*) from the reaction of the alkoxy chloroformate (28) with tin (iv) chloride. The unstable chloroformate (28) was synthesised from the alcohol (27) by treatment with phosgene in pyridine. In the acylation approach, the enolate anion will be required to displace the leaving group from the formate moiety.



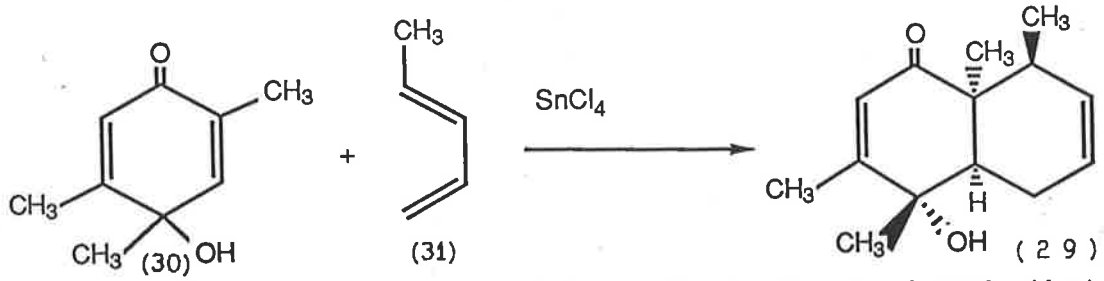
(27) (28) (27*)

Both of the approaches to the lactone problem either through lactonisation (scheme i) or acylation (scheme ii) are worthy of examination. The stereochemical course of the oxymercuration is predictable although the subsequent acylation has little precedence. The acylation method would appear to be more elegant and reqires fewer manipulations than the lactonisation method but

it is more speculative.

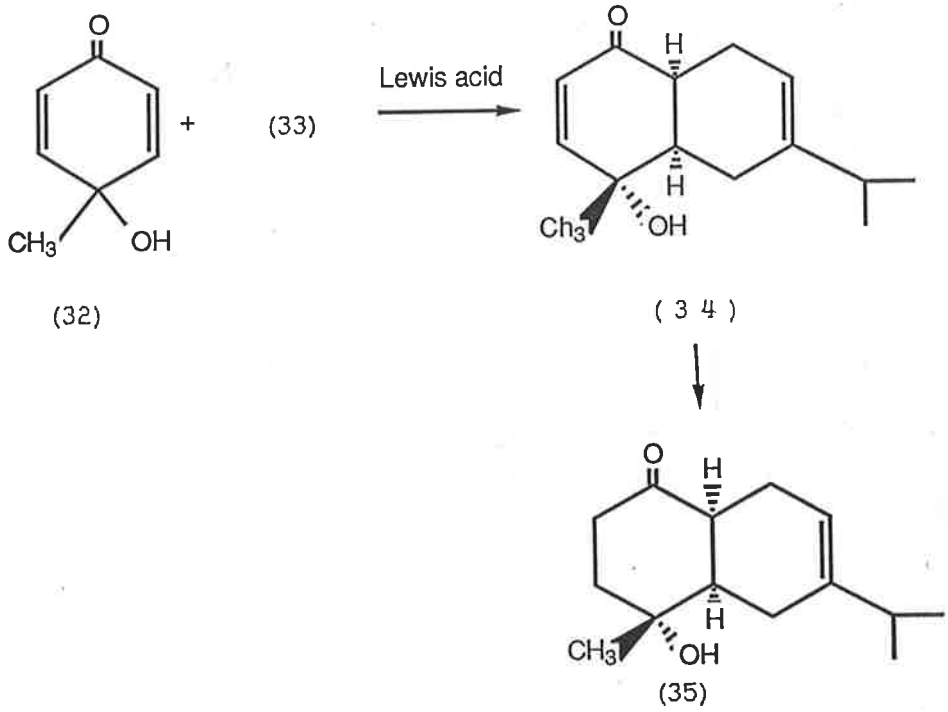
Having decided on several approaches to the construction of the main structural features of the natural product, they must be arranged in an intelligent manner so that the features may be brought into being with their own correct stereochemistry. They must also be arranged with the correct stereochemistry with respect to the rest of the molecule.

Reactions of cyclohexa-2,5-diene-1-ones have been studied by Liotta *et al*[16]. These workers were able to synthesise the diene ketone (29) from the Diels Alder reaction of the cyclohexadienone (30) and the diene (31) in the presence of tin (IV) chloride. Examination of the structure of the diene ketone (29) shows it has the correct *cis* stereochemistry at the hydroxyl group and the hydrogen at the bridge head that is required for the introduction of the cyclopropane ring into crispatanolide with the correct relative stereochemistry. The unconjugated double bond is in the correct place for the lactone forming schemes. The two six membered rings are fused in a *cis* manner as is necessary in the acylation scheme.



For the synthesis of the natural product, it is hoped that 4-hydroxy-4-methylcyclohexadienone (32) will react with 2-

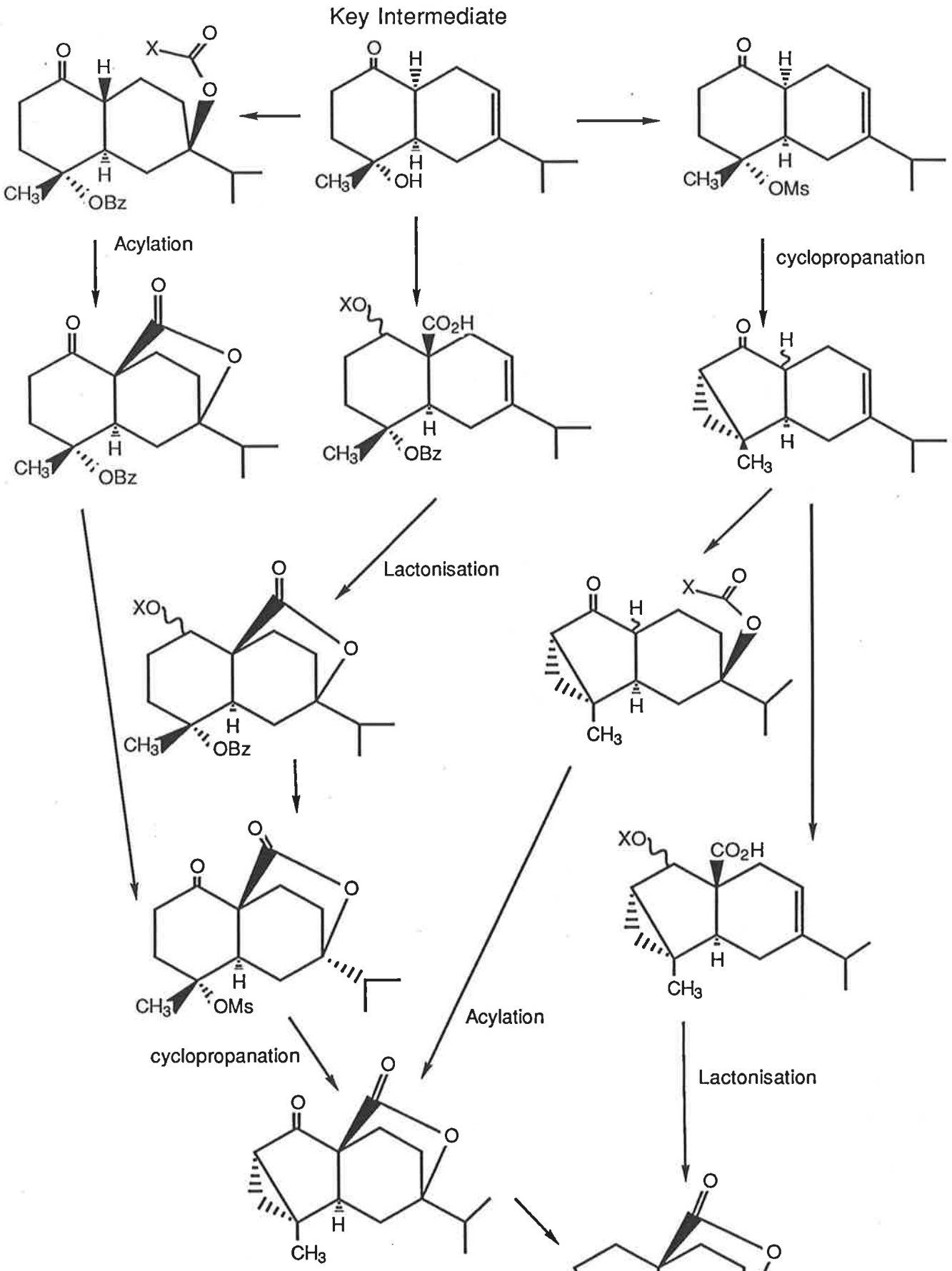
*iso*propylbutadiene (33) in the presence of tin (IV) chloride to give the adduct (34). It is hoped the adduct (34) may be reduced to the enone (35). This compound is vital for this synthesis of crispatanolide as it can be used as the starting material for the schemes discussed.



(32) (34) (35)

From this key compound, (35), cyclopropanation could follow either approach for the lactonisation. Conversely, lactonisation may follow cyclopropanation. The various approaches to the natural product from the enone (35) have been summarised on the next page.

This introduction has outlined the strategies for the synthesis of key features of the natural product, crispatanolide. There are areas of chemistry that have been discussed which are

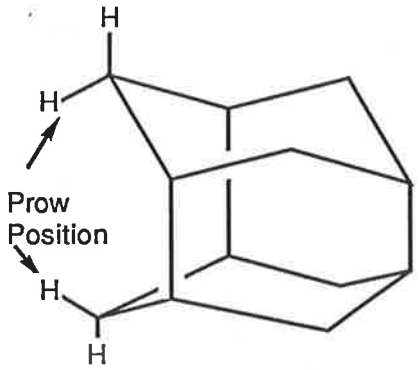


Routes to the natural product, Crispatanolide, from the key Intermediate

of a highly speculative nature. Before a complicated synthesis such as this is embarked upon, these areas must be explored. Questions like the following must be answered. Will 4-hydroxy-4-methylcyclohexa-2,5-dien-1-one react with a diene to give a diene ketone like (34)? Will it possess the correct relative stereochemistry for the synthesis of crispatanolide? Can the adduct of the dienone and 2-*iso*propylbutadiene be used to make the key enone (35)? Even more basic questions exist in the area of the cyclopropane formation. Can 4-alkylbicyclo[3.1.0]hexan-2-ones be synthesised by displacement of a leaving group from the 4- position of a cyclohexanone? How can the cyclohexanones be best made? What type of leaving groups are stable at the tertiary position and which are displaced to form cyclopropanes with ease? Work on the bicyclo[3.1.0]hexanones would appear to be most worthwhile as there are opportunities to apply these insights in other areas of natural product synthesis.

Introduction: Work Towards the Unnatural Hydrocarbon, Iceane

The highly symmetrical hydrocarbon, tetracyclo [5.3.1.$1^{2,6}0^{4,9}$]dodecane[17] (36), has the trivial name, iceane because of its likeness to one of the structures of ice[18].



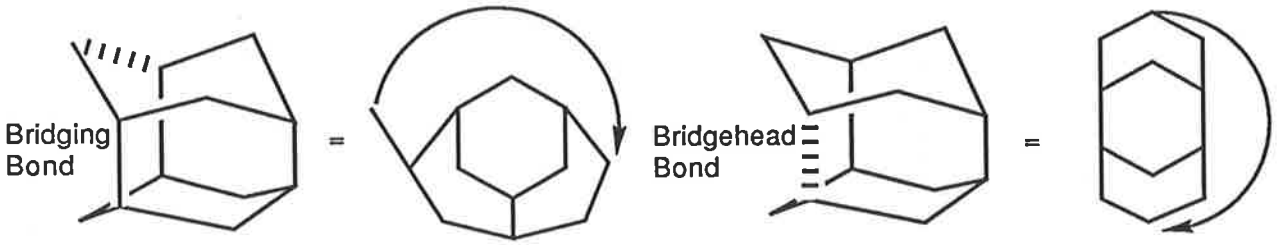
(36)

Examination of the structure shows the molecule contains five six-membered rings, two of which are held in the chair configuration whilst the other three are held in the boat configuration. Molecular models show the structure is not strained although it is anticipated that severe non-bonded interactions would occur between equatorial substituents on the prow positions of the rings in the boat configuration.

It would be interesting to synthesise the skeleton which is functionalised at two prow positions inside the same ring. As the skeleton is rigid, non bonded interactions between substituents on prow positions would be easy to study. There is no complicating flipping of cyclohexyl rings from chair to boat conformers.

Iceane has been synthesised by various workers[19]. The high degree of molecular symmetry in iceane (36) allows, in some cases, a simplification of the retrosynthetic analysis. To summarise an earlier analysis[20], there exist only two types of carbon-carbon bonds in the molecule; those between two bridge – head methine units and those between bridge – head and bridging methylene units. Because of this feature, retrosynthetic analysis which involves the disconnection of only one carbon carbon bond leads to the conclusion that there are only two possible precursors, concepts 1 and 2.

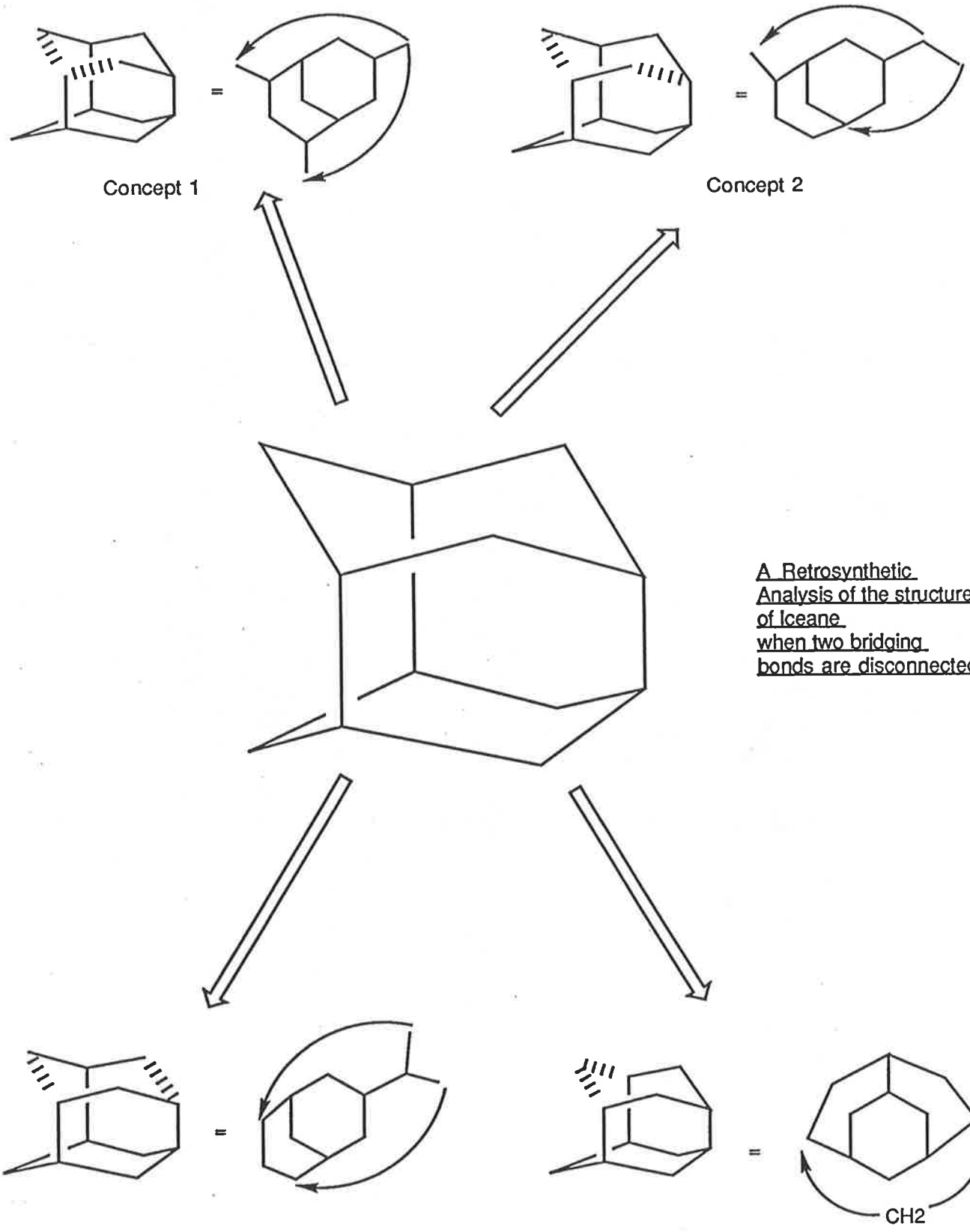
A retrosynthetic analysis of the iceane structure disconnecting a bond



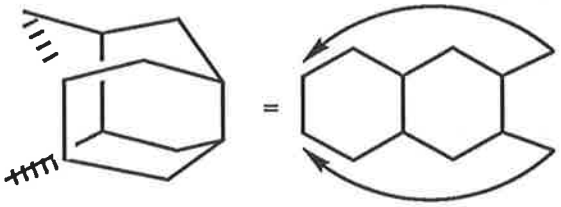
Concept 1 Concept 2

When two bonds are considered in the last step of skeletal assembly, a more extensive range of precursors becomes evident. There are now three types of groups of disconnections; either 2 bridge – head bonds, a bridge – head and a bridging or 2 bridging bonds. The relative ease of constructing bridging bonds over bridge – head bonds (methylenes have fewer substituents to be installed) leads to the consideration of only the last case. (see overleaf)

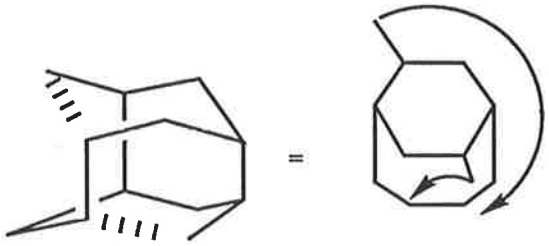
Concept 3 has been exploited by Hamon and Taylor[19a] in



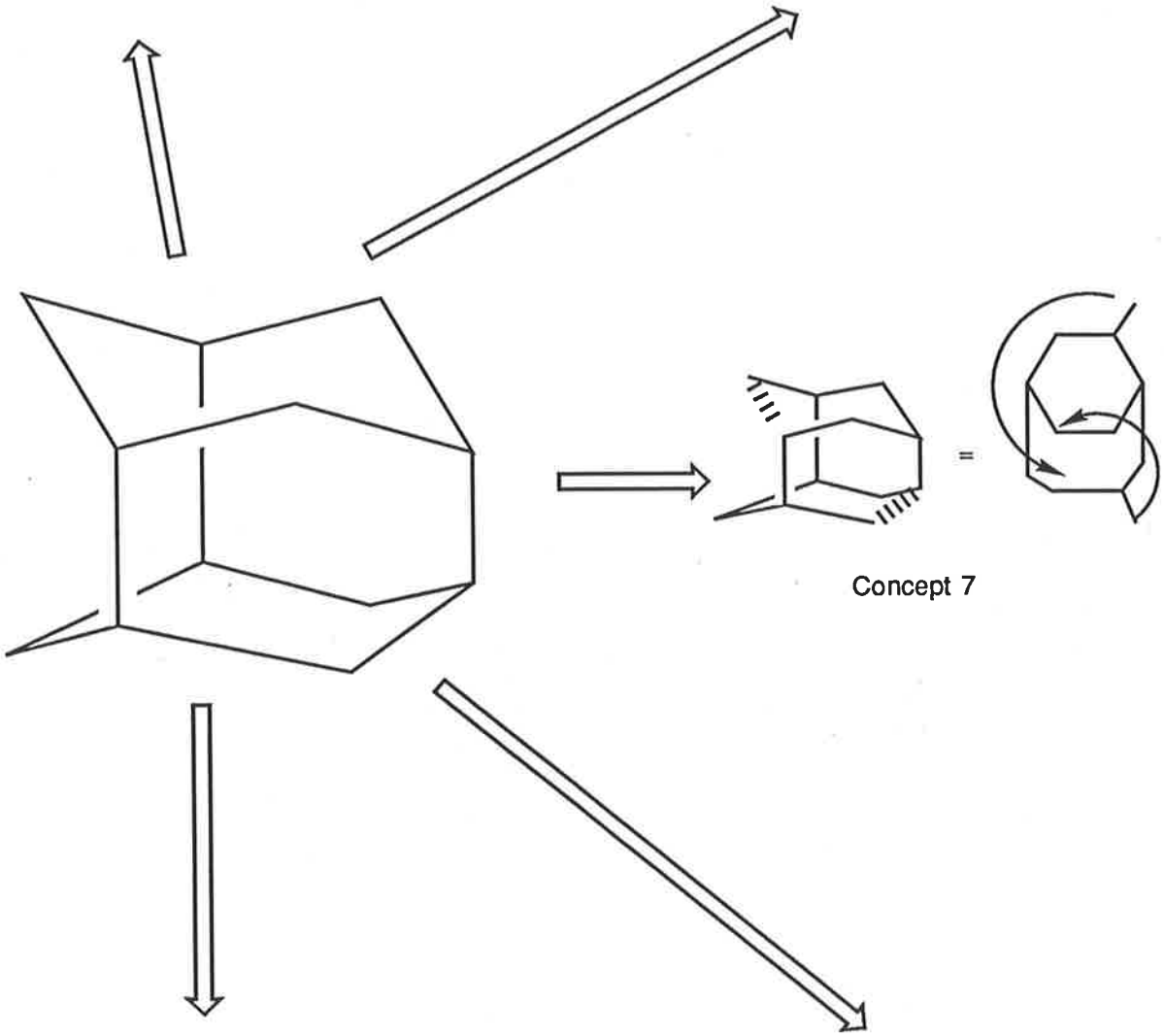
A Retrosynthetic Analysis of the structure of Iceane when two bridging bonds are disconnected



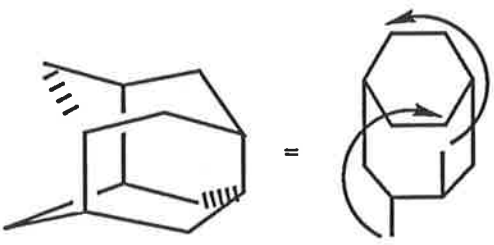
Concept 5



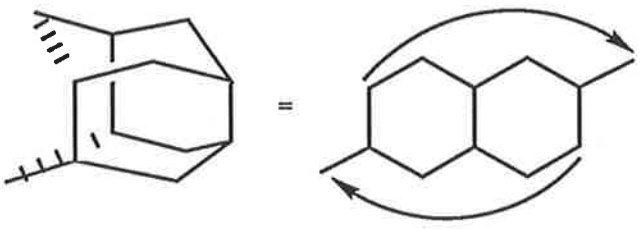
Concept 6



Concept 7

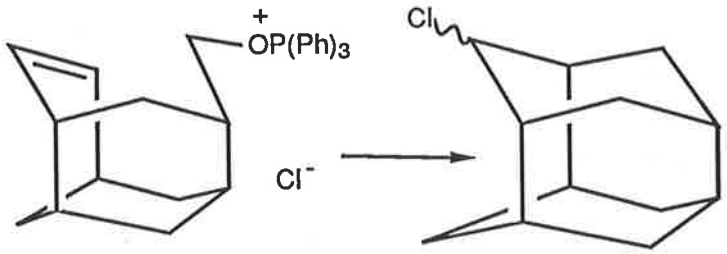


Concept 8



Concept 9

which the two bonds were constructed though not strictly sequentially. The final carbon – carbon bond was formed by a nucleophilic substitution reaction of the intermediate phosphine oxide salt (37). Tobler Klaus and Ganter[19b] used similar chemistry to displace the mesylate group from the ene mesylate (38) to give the alcohol (39).



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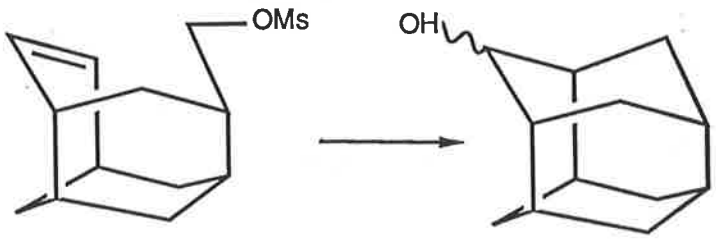
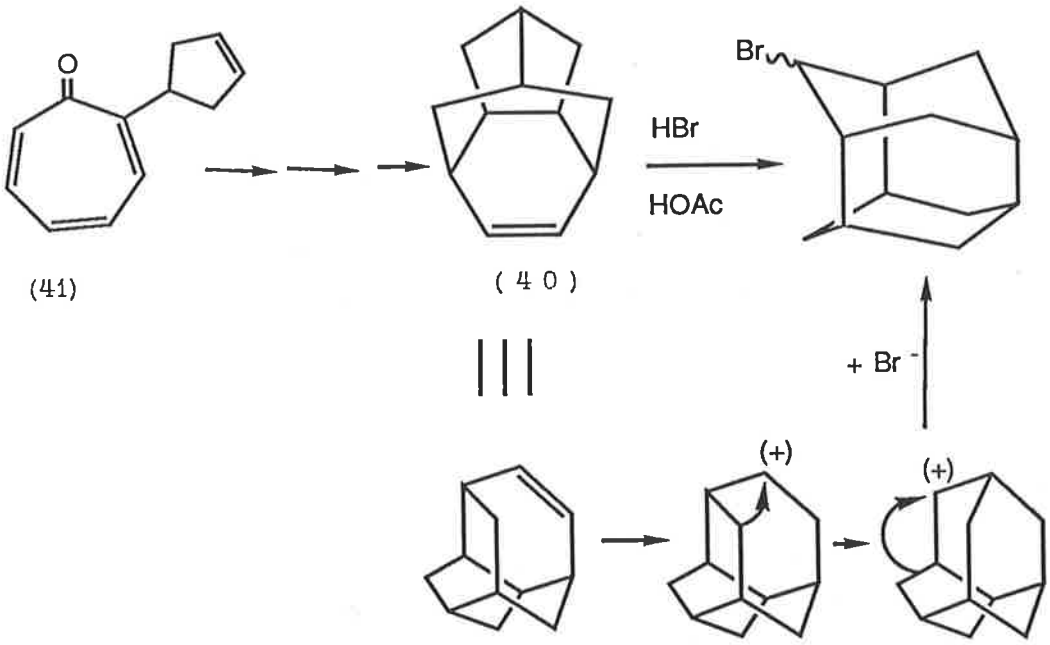


(38) (39)

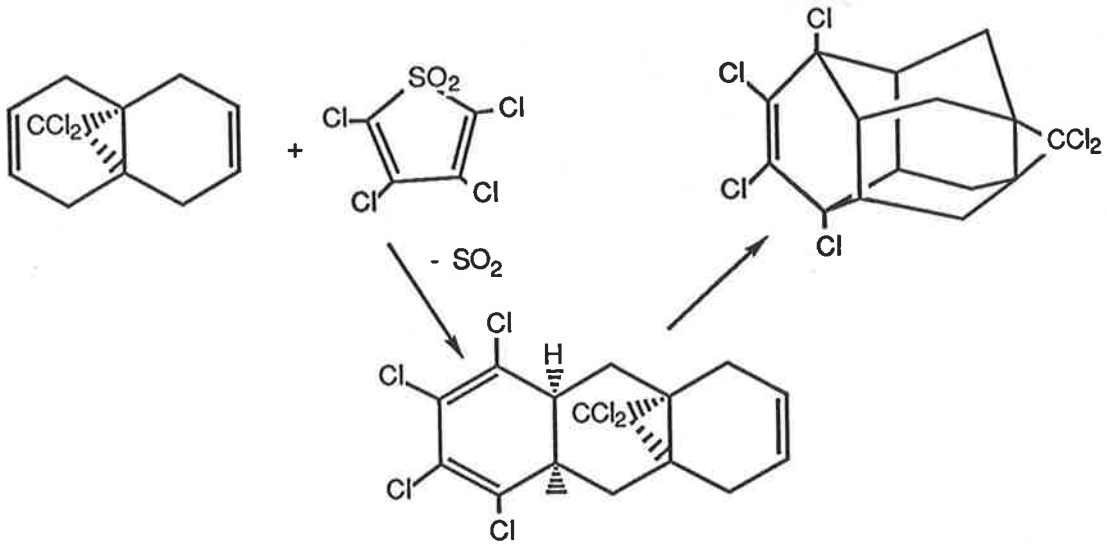
Complex carbonium ion rearrangements have been used to make the bonds that are required for concept 5. Cupas and Hodakowski[19c] used the acid catalysed rearrangement of the alkene (40) derived from the intramolecular Diels Alder reaction of the cyclopentenyl tropone (41).

The approach to be investigated, concept 5, requires an "easily" constructed precursor, a substituted decalin and appears



(41) (4 0)

to have the capacity to generate iceane functionalised at two sites. Iceane derivatives have been synthesised by Spurr[21] using this concept. He used a concerted bond formation process in which the Diels Alder reaction was employed

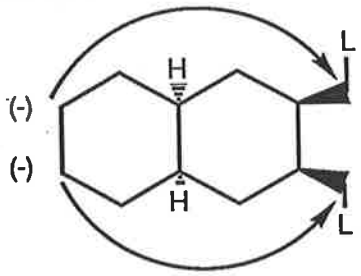


(42)

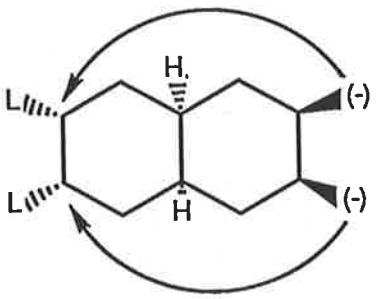
to construct the two bridging bonds in the alkene (42). This is a facile route to the iceane skeleton although the structure bears three extra carbon atoms.

Another method for the construction of the iceane skeleton which makes use of concept 5 involves a stepwise alkylation process. There are two possible alternatives for making the bonds concerned, either (43) or (44).

The required carbanions could be generated adjacent to carbonyl groups which leads to consideration of either (45) or (46). The latter would require the presence of an additional undesired carbon atom.



(43)



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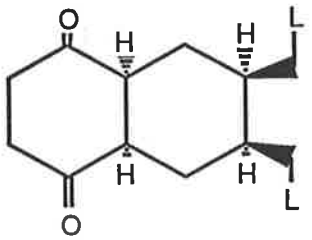
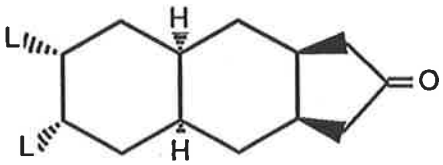


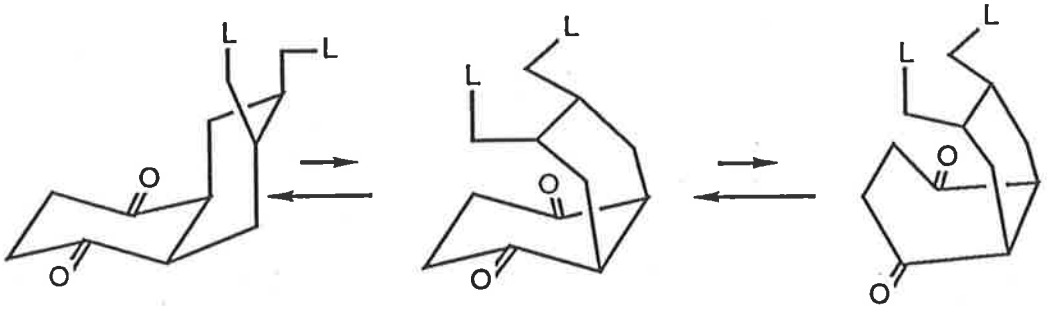
(45)



(46)

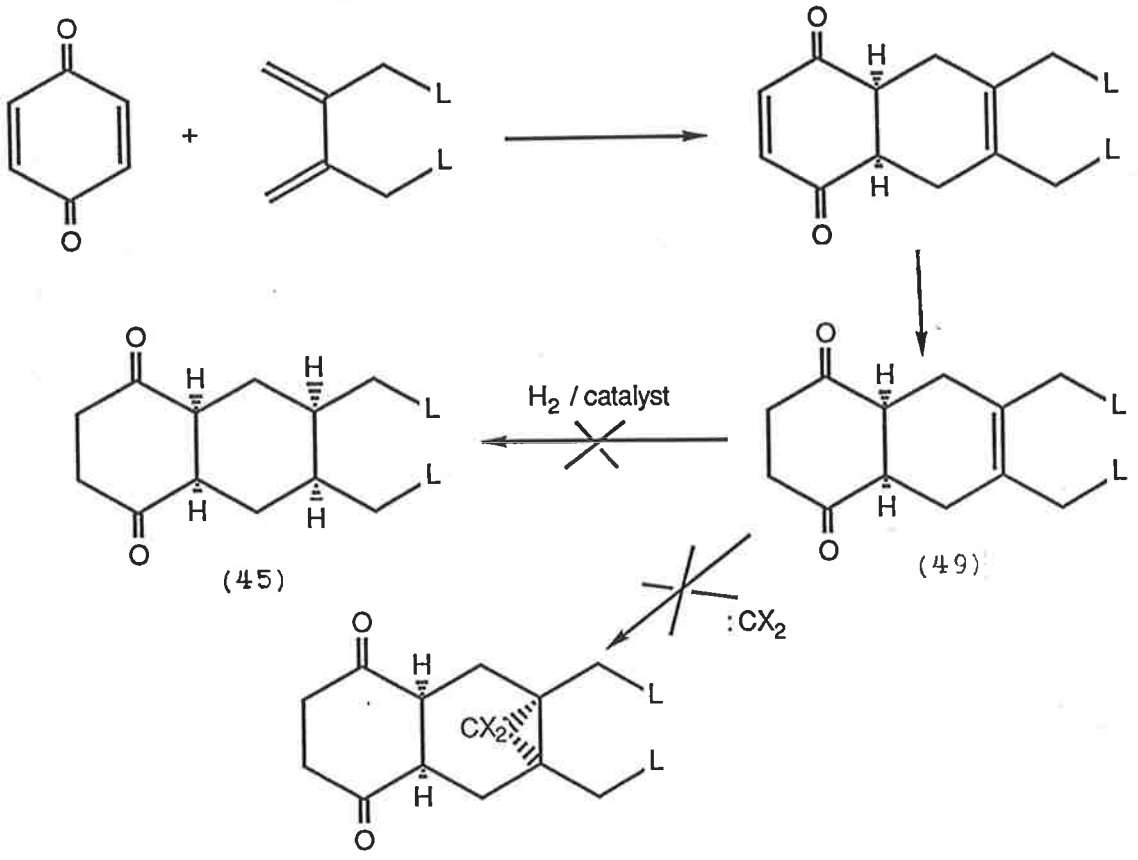
In the cyclisation reaction, the dione (45) must flip from the least energetic chair / chair conformation in (47) to the most energetic boat / boat conformation in (48). It is hoped that the

removal of the highly energetic equilibrium component (48) by an irreversible alkylation would allow the reaction to proceed to completion.



(47) (48)

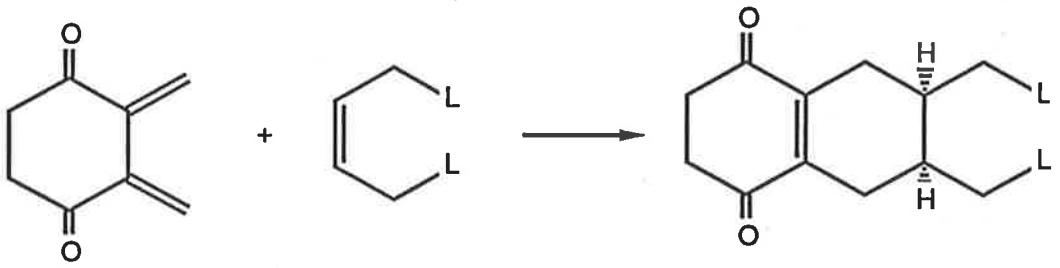
It was conceived that the dione (45) may be available in a small number of steps by the use of a Diels Alder reaction



(45) (49)

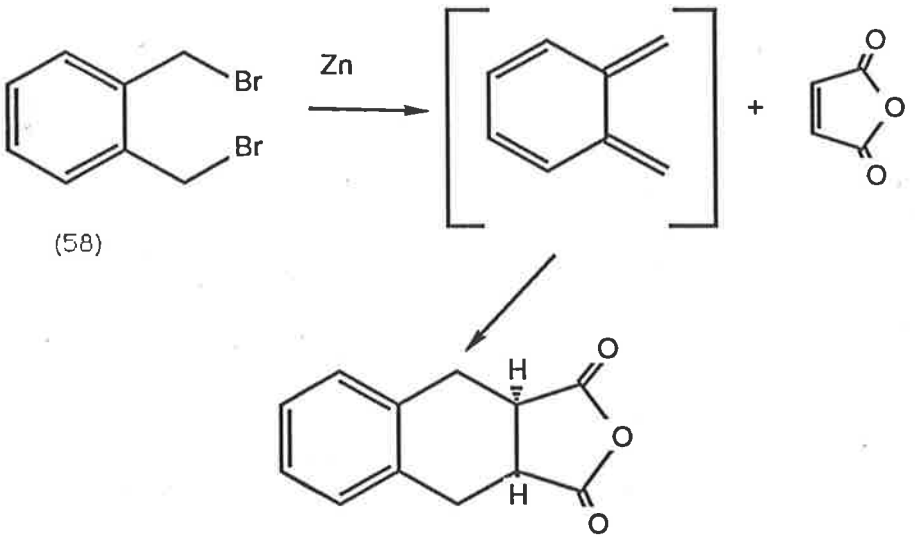
between benzoquinone and a suitably constructed diene. This approach was also investigated by Spurr[22]. It was hoped that the double bond between the carbonyl moieties could be reduced to give the ene dione (49). Unfortunately, treatment of a number of ene diones possessing the general structure of (49) with hydrogen and appropriate catalysts, electrophilic or carbenic reagents, which were to add to the double bond with *cis* stereochemistry, failed to induce a reaction.

To overcome the problem of the removal of the unreactive double bond, Spurr proposed an alternative strategy. In order to obtain the required *cis* stereochemistry, a Diels Alder reaction could still be employed. Whereas previously, the ring containing the dione moiety was used as the dienophile, it was conceived that it could also act as a diene.



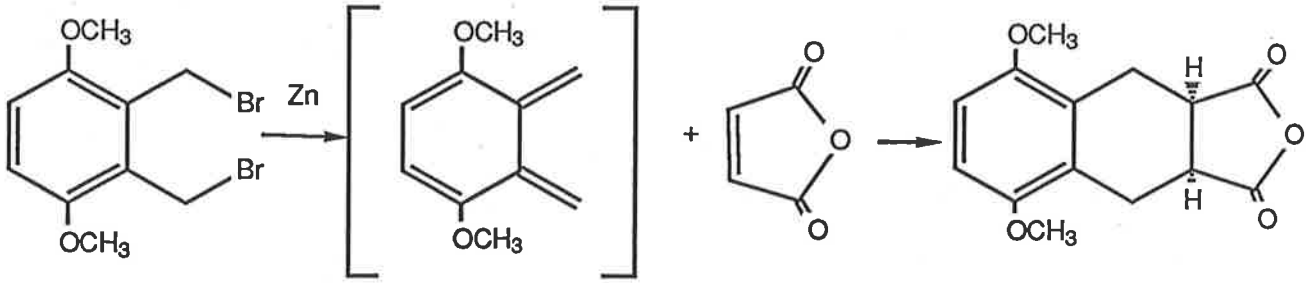
The diene system could be further conjugated as in the "xylylenes". The dibromide (58) forms a very reactive diene when treated with zinc metal. The xylylene has reacted with maleic anhydride in a [4π + 2π] cycloaddition[23]. The adduct possessed the *cis* stereochemistry.

The dibromide (51) has been synthesised in 4 steps[22]



(58)

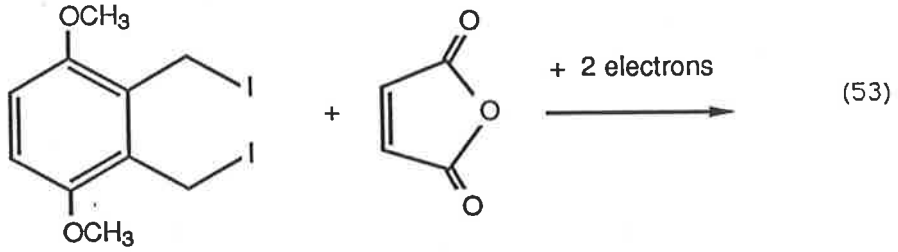
from 1,4-dimethoxybenzene, and reacted with zinc to form the "xylylene" (52). Spurr was able to effect the Diels Alder reaction of the dibromide (51) with maleic anhydride in 65% yield[22].



(51) (52) (53)

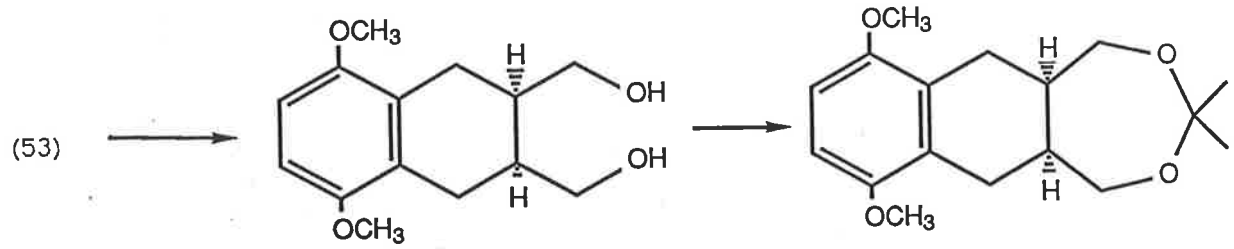
Subsequent repetition of this work failed to give the adduct in the reported yield. However the analogous reaction has been performed in 58% yield with the diiodide (54)[24] and maleic anhydride in a controlled-potential electrochemical reduction[24].

The anhydride group has been reduced with lithium aluminium



(54) (53)

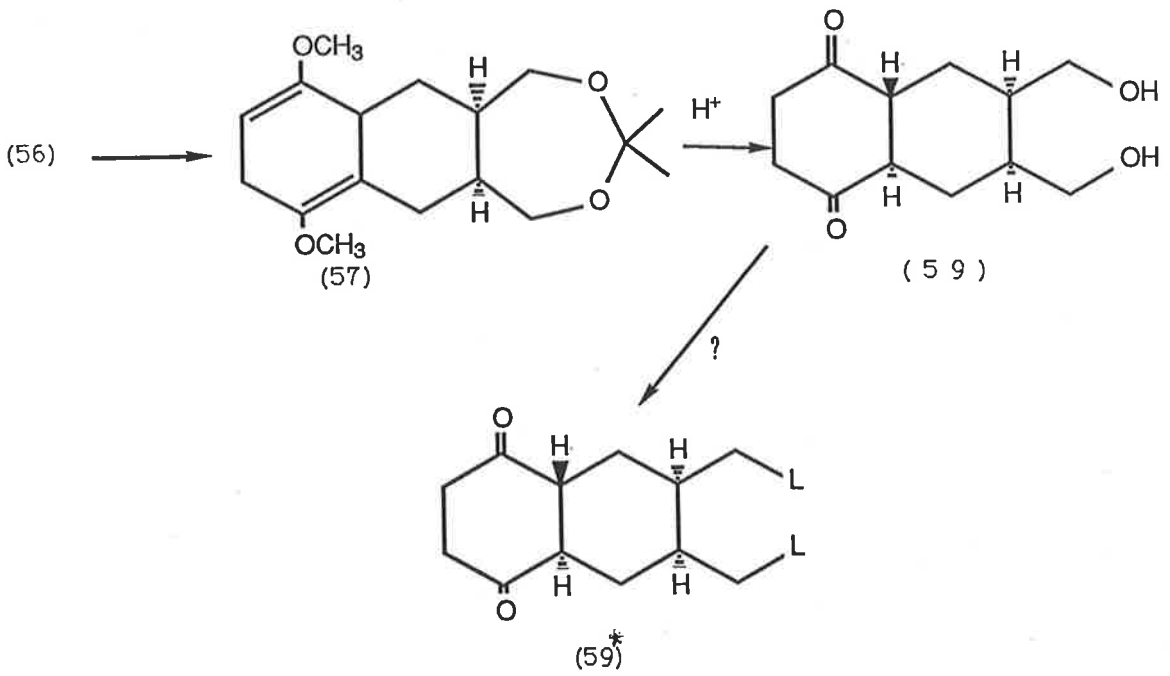
hydride[22] to give the diol (55). The unveiling of the dione moiety has been performed with the use of the dissolving metal reduction after the diol functionality was protected as in the acetal (56)[22].



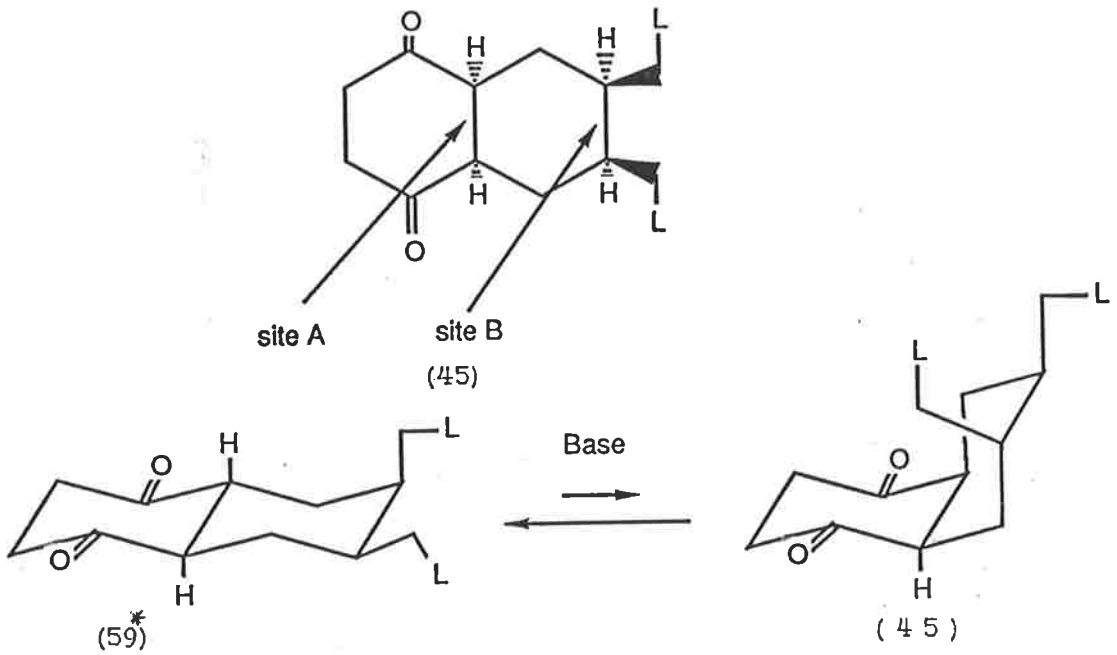
(55) (56)

The di-enol ether (57) has once been hydrolysed to give a mixture containing the dione (59)[24] presumably predominantly in the more stable *trans* configuration at the ring junction, site A. The compound proved difficult to purify. The conversion of the hydroxyl groups to leaving groups was not attempted.

The predominantly *trans* nature of the ring junction was not thought to present a barrier to the cyclisation reaction. Epimerisation could occur at the ring junction during a reaction of the dione (45) with base so that an equilibrium could exist between the *cis* and *trans* isomers of the dione, (45) and



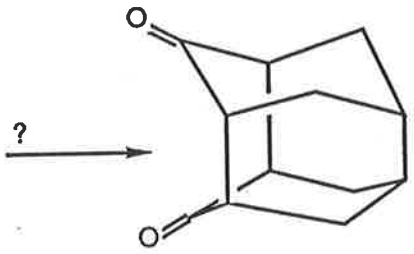
(59*). For this reason the stereochemistry at the ring junction, site A, was considered to be less important to the success of the reaction than the stereochemistry at site B.



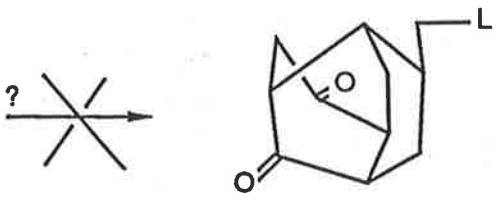
There exists the possibility of the alkylation reaction

occuring to give the seven-membered ring in the dione (17) but it is difficult to justify this concern as when a model of the system is constructed, the compound appears to be somewhat strained. This leads to the assumption that the transition state for this reaction is of a higher energy than that required to form the six-membered ring in the dione (60).

(59)



(60)

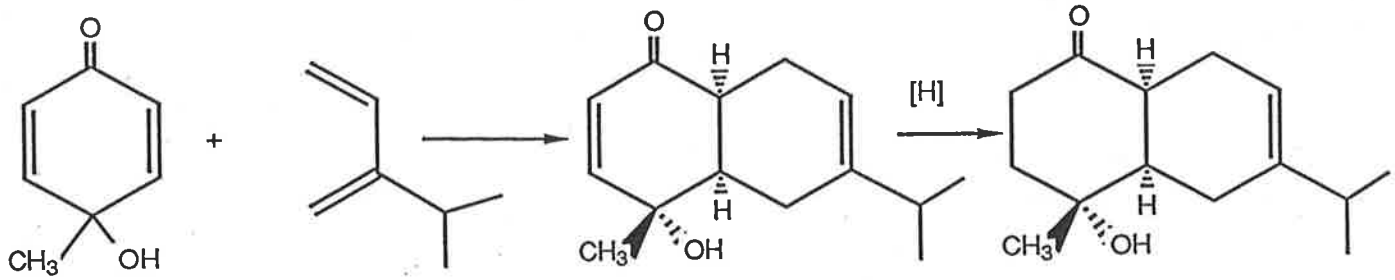


Should the reaction of the key intermediate with base prove fruitful, the iceane skeleton may be available without extra carbon atoms and it will be functionalised at two adjacent prow positions. Previously, only one prow position was available for modification.

Part A

Chapter 1

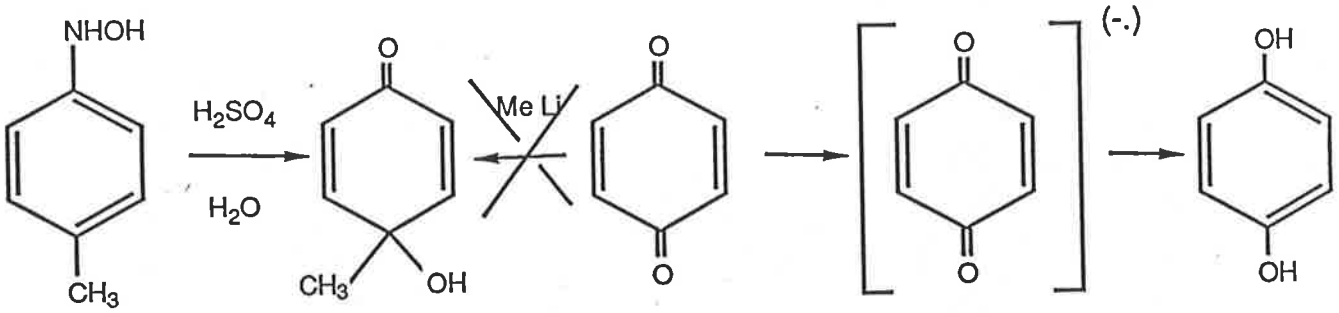
The investigation into the construction of the natural product, crispatanolide (1) commenced with the attempted synthesis of the key intermediate, (35) which was to have been obtained from the reduction of the product of the Diels Alder reaction between the cyclohexadienone (32) and the diene (33).



(32) (33) (35)

The cyclohexadienone (32) has been synthesised in a number of ways[25]. One route involved the treatment of *p*-tolyl hydroxylamine (61) with chilled aqueous acid[26]. This method gave a poor yield of the dienone (32) and was irreproducible. A procedure had been reported for the preparation of the dienone (32) which involved the addition of methyl lithium to benzoquinone in ether at -78^0 [27]. These workers found that a deep blue colour was instantly generated on addition of the alkyl lithium to the quinone. They ascribed this to the formation of the semiquinone radical anion (62) and suggested that this was the source of the trace amounts of hydroquinone normally formed in the reaction. However, on repetition of this work, it was found that only a small amount of the dienone (32) could be detected by NMR spectroscopy and

hydroquinone was the major product. The initially described acidic hydrolysis of tolyl hydroxylamine was used to prepare the cyclohexadienone as it was the more reliable and efficient method. The NMR spectrum of the dienone showed a singlet resonance at δ 1.53 due to the methyl group attached to the tertiary carbon bearing the hydroxyl group and there was an AB quartet which was calculated to be centred at 6.26 and 7.15 from the two groups of protons on the double bonds of the dienone systems.

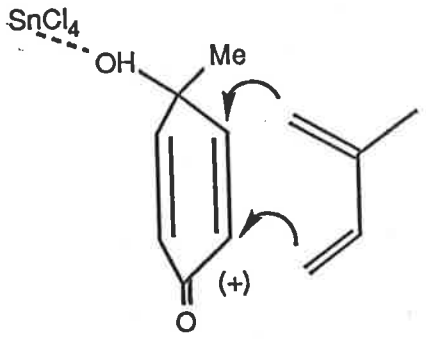


(61) (32) (6 2)

The butadiene (33) has been synthesised in 10% overall yield by Kaempf and Kieffer[28]. Because of the length of the procedure to make the diene (33) which involved 4 steps, isoprene was used as the diene in the development of the Diels Alder reaction between the cyclohexadienone (32) and a diene.

Treatment of the dienone (32) and isoprene in acetonitrile with tin (IV) chloride as a catalyst yielded only the starting material, (32). Limited experimental data were available from the precedent[16] so both the type of catalyst was varied and the ratio of moles of catalyst to moles of dienophile was varied

from 0.9 to 2.0. Liotta[16] referred to complexation of the Lewis acid with the hydroxyl group of (32) which led to the face selectivity observed in the Diels Alder reaction. The bulky tin group forced the diene to approach the dienophile from the less hindered side of the molecule.



The results of the trial Diels Alder reactions between isoprene and the cyclohexadienone (32) are summarised in the table below. In the trials in which the starting material (32) was isolated, isoprene was evaporated *in vacuo* from the crude product.

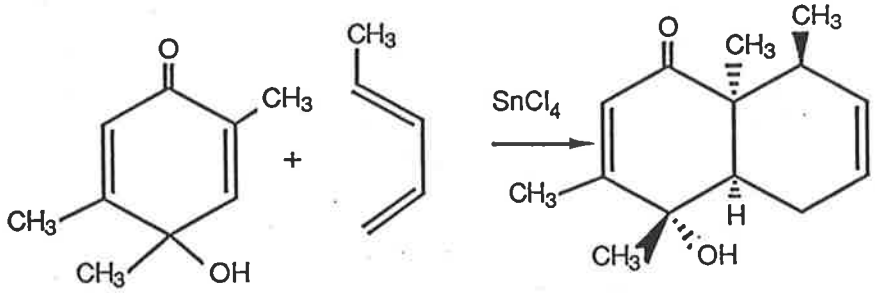
Table of results of the Diels Alder Reaction between the dienone (32) and isoprene

Trial #	Solvent	Conditions			Result
		Lewis acid	acid eq	Time	
1	aceto-nitrile	Tin (IV) chloride	2	12H	starting material

2	aceto-nitrile	Tin (IV) chloride	2	48H	isoprene polymer
3	ether	Boron chloride	2	48H	isoprene polymer
4	aceto-nitrile	Tin (IV) chloride	0.9	24H	isoprene polymer
5	toluene	Aluminium chloride	0.9	12H	starting material
6	toluene	Aluminium chloride	0.9	48H	isoprene polymer
7	aceto-nitrile	Aluminium chloride	0.9	12H	isoprene polymer

It was plain to see that these experiments met with no success. Attempts to vary the time of the reaction, the Lewis acid catalyst and the solvent had an effect on the reaction but obviously not the desired effect. The conditions appeared to be either too severe causing the isoprene to be polymerised or the

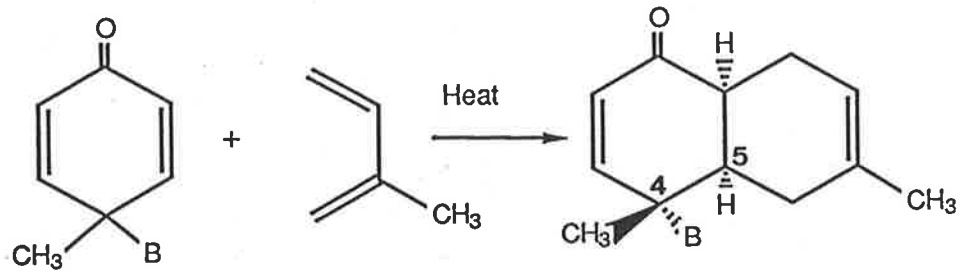
conditions were not strong enough for any reaction to take place. The use of a strong Lewis acid like boron trifluoride etherate in ether resulted in complete polymerisation of the diene. The use of the relatively less acidic aluminium chloride, in trial #5, produced no apparent reaction. In trial #6 for which the reaction time was increased, polymerisation of isoprene took place. This may have been catalysed by a trace of hydrogen chloride generated from adventitious water and aluminium chloride. The relatively mild Lewis acid, tin (iv) chloride which was used by Liotta failed to work in any of the trials. In an attempt to verify the face selectivity described by Liotta, the actual diene that was the subject of the work referred to was used. The reaction between the cyclohexadienone (30) and 1-methylbutadiene (piperylene) (31) when catalysed by tin (iv) chloride was reported to give an adduct but with the dienone (32) the Diels Alder reaction could not be induced to occur in our hands. It produced intractable isoprene polymer. The Diels Alder reaction appeared to be less general than was supposed.



(30) (29)

If Liotta[16] was correct in his assumption that the

relative size of the groups in the 4- position of the dienone controlled the reaction, then a thermal Diels Alder reaction between a butadiene and the dienone (63) (where B is a group possessing much more steric bulk than a methyl group) could yield an adduct (64) which possesses the correct stereochemistry required at C4 and C5 for crispatanolide. If the hydroxyl group of (32) could be for example esterified or silylated, a thermal Diels Alder reaction might yield (64) where B = OOC-R' or $OSi(R')_3$.

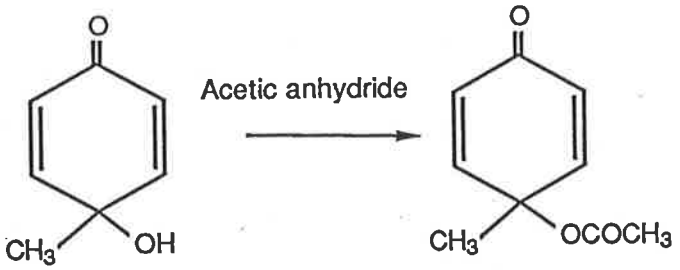


B = Bulky group

(63) (64)

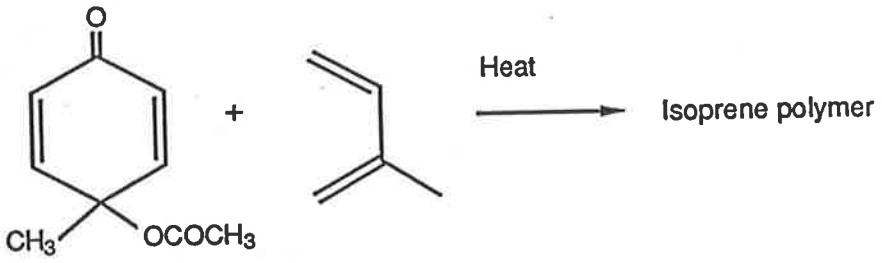
The acetyl cyclohexadienone (65) was prepared in 76% yield by the treatment of the dienone (32) in N,N-dimethylaminopyridine and pyridine with acetic anhydride. It possessed the spectral properties of singlet resonances at δ 1.53 and 2.03 corresponding to the presence of the methyl group attached to a tetrasubstituted carbon and the methyl group of the acetyl ester respectively. This compound was used as the dienophile in some trial Diels Alder reactions. The size difference between the methyl group and the acetyl group was not at all great but the ester (65) was used in an attempt to indicate whether a thermal

Diels Alder reaction was feasible.



(32) (6 5)

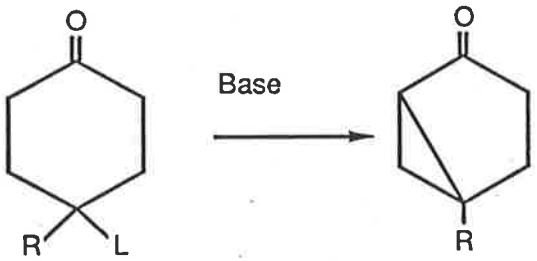
The thermal Diels Alder reaction proved to be fruitless as the adduct could not be detected. When the ester (65), isoprene and toluene were heated in a sealed tube to 140^0 for 12 hours, the ester was isolated unchanged. When the reaction was repeated at 200^0, isoprene polymer was isolated. It seemed that the energy that was required for the Diels Alder reaction might be in excess of that which was required for the polymerisation reaction.



(65)

Because of the failure of the approach to the construction of the basic carbon skeleton of crispatanolide by the use of the Diels Alder reaction, it was decided that attention would be focussed on approaches to the construction of one of the two key

structural features in the natural product target. The synthesis of the bicyclo[3.1.0]hexane ring system was investigated in the hope that it could be used to provide data for the construction of a route to crispatanolide and to other natural products. It was felt that the nature of the most appropriate leaving group, in compounds of the general structure of (66), that could be displaced to give bicyclo[3.1.0]hexanones needed to be determined if a successful synthesis of the ultimate goal was to be achieved.

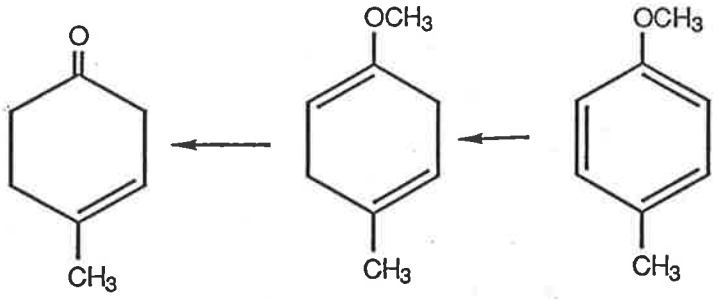


(66) (67)

Work on the cyclopropane moiety had focussed on model compound of the general type (66) where L is a leaving group as it was hoped that treatment of this type of compound with a base would produce the bicyclo[3.1.0]hexanone system (67). The chemistry of 4-methylcyclohex-3-en-1-one (68) appeared, at first, to be most useful as Markownikoff addition of HX to the carbon carbon double bond would in theory, result in a compound with the desired general structure.

The product of the dissolving metal reduction of 4-methylanisole was the enol ether (69) which was obtained in 86%

yield.

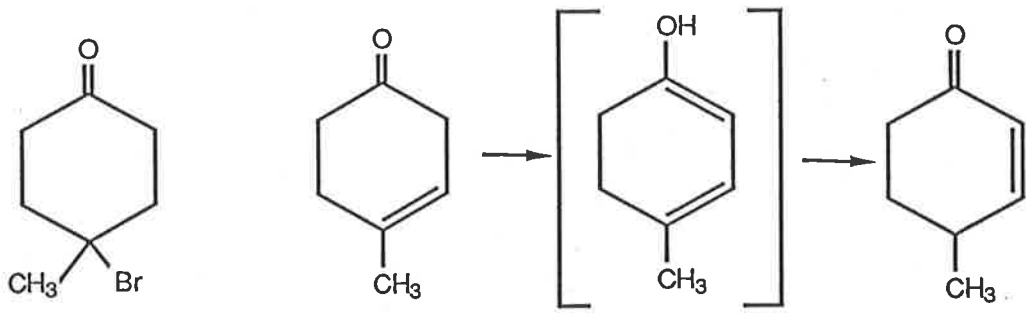


(68) (69)

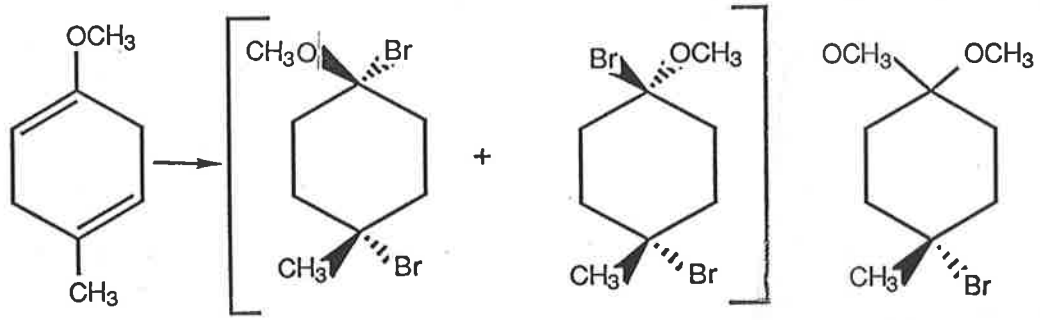
The cyclohexyl bromide (70) might have been available through the addition of hydrogen bromide to the tri-substituted double bond of the enone (68). It is likely however, that under these acidic conditions, the deconjugated double bond would be isomerised to be in conjugation with the carbonyl group. If the acid sensitive ketone functionality were to be masked, as in the enol ether (69), ionic addition of the elements of hydrogen bromide may lead to the formation of the isomeric bromo ethers (71) and (72). Treatment of this mixture with methanol might give the more stable dimethyl acetal (73).

If the potential side reaction like the cleavage of the enol ether moiety is to be eliminated then the reaction must be performed under anhydrous conditions. To avoid a possible demethylation reaction of the methyl enol ether by hydrogen bromide it would be advisable to perform the reaction at a low temperature.

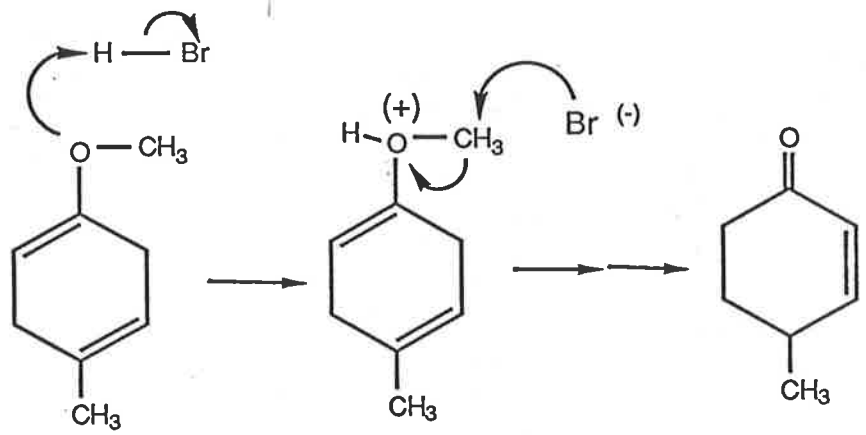
Treatment of the frozen enol ether (69) with liquid hydrogen bromide at -78^0 led to the formation of what was



(70) (68)



(69) (71) (72) (73)



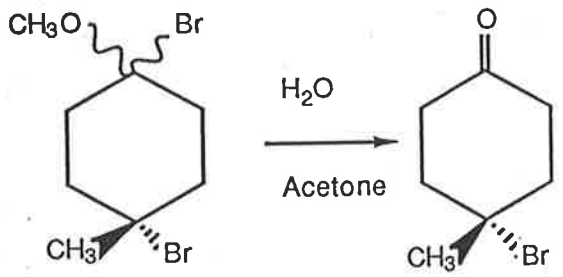
presumed to be a mixture of the bromo ethers (71) and (72) which were too unstable to be characterised. They tended to decompose smoothly and rapidly at room temperature. The compounds were stable enough in solution to record their NMR spectrum. At δ 1.87, a sharp singlet resonance was observed as a result of the presence of the methyl group attached to a carbon atom bearing a bromo atom. A broad singlet resonance was observed at δ 3.43

corresponding to the methoxy group attached to the carbon atom bearing a bromine atom. The rest of the protons in the compounds resonated as a complex set of peaks from δ 1.0-3.0.

The dimethyl acetal (73) was formed from the mixture of the bromo ethers (71) and (72) in quantitative yield by the action of methanol at room temperature. The presence in the NMR spectrum of two singlet resonances at δ 3.10 and 3.17 corresponding to the two methoxy acetal methyl groups helped to confirm the structural assignment. One resonance was thought to be due to the methoxy group on the same side of the cyclohexyl ring as the bromine atom and the other was due to the methoxy group on the side of the ring bearing the methyl group. The mass spectrum of the acetal (73) showed a peak at *m/z* 157 due to the loss of a bromine radical from the molecular ion. The molecular ion was not observed.

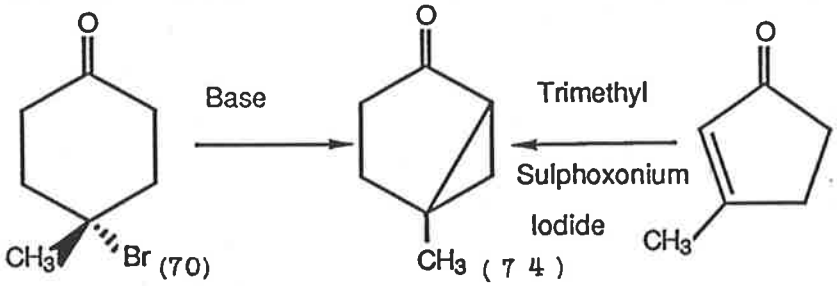
Difficulties were initially encountered in the hydrolysis of the dimethyl acetal (73) as significant amount of elimination occured from the tertiary centre to give complex mixtures. The ketone (70) was successfully prepared in quantitative yield by hydrolysis of the bromo ethers (71) and (72) in wet acetone. The resultant ketone was less stable than the corresponding acetal (73). The bromo ketone (70) lost hydrogen bromide in the liquid state but was more stable in solution. The identity of the unstable bromo ketone (70) was verified by the presence in the infra-red spectrum of a strong absorption at 1710cm^{-1}

which verified the presence of the unconjugated keto group. The mass spectrum of the ketone (70) showed a peak at *m/z* 111 which was consistent with the loss of a bromine radical from the molecular ion.



(71)+(72) (70)

The bromo ketone was treated with sodium ethoxide in ethanol over night in an attempt to form the bicyclic system. A sample of the desired bicyclic ketone (74) was synthesised[29] by the action of trimethylsulphoxonium iodide and sodium hydride in DMF on 3-methylcyclopentenone. Chromatography of the product from the reaction of the bromo ketone (70) with base afforded a compound whose NMR spectrum was identical to that of the bicyclohexanone (74) in 27% yield. The NMR spectrum of the compound exhibited a singlet resonance at δ 1.20 due to the methyl group and 2.03

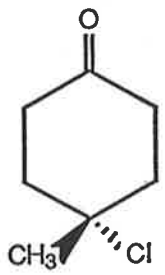


from the two methylene groups of the cyclopentanyl portion of the two rings. This broad singlet resonance at about δ 2.0

proved to be a consistent feature of the 60 MHz NMR spectra of carbon tetrachloride solutions of the 5-alkylbicyclo[3.1.0]hexanones.

Although the bicyclohexanone (67) was available through the bromo ketone (70) by the action of base, because of the instability of the bromo group at the tertiary centre, the reaction would be undesirable in an extended sequence because of the relatively low yield. In general however, halogen appeared to be a potentially useful moiety for the leaving group in the compound (66).

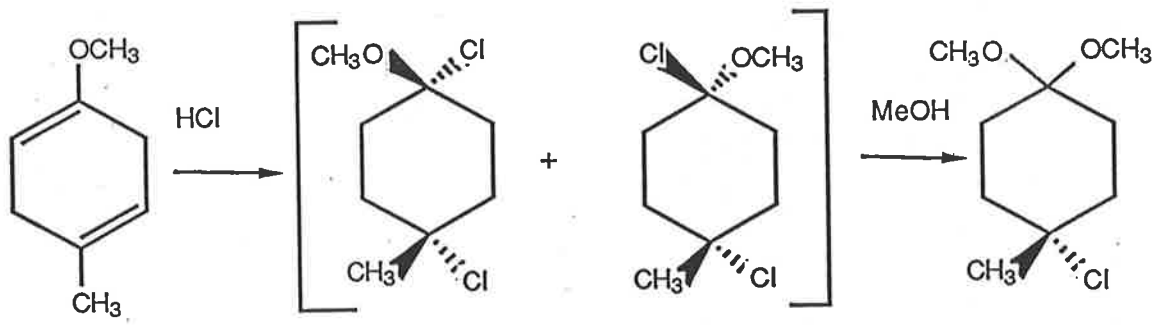
It was thought that replacement of bromine by chloride might result in a better overall yield because of the expected increased stability of the chloro compound (75). The chloride ion is also normally recognised as a good leaving group.



(75)

The enol ether (69) was frozen with liquid nitrogen, liquid hydrogen chloride was condensed onto it and the mixture was slowly allowed to warm to room temperature. The enol ether (69) appeared to react on dissolution in the hydrogen chloride. Upon complete evaporation of the excess hydrogen chloride, what was

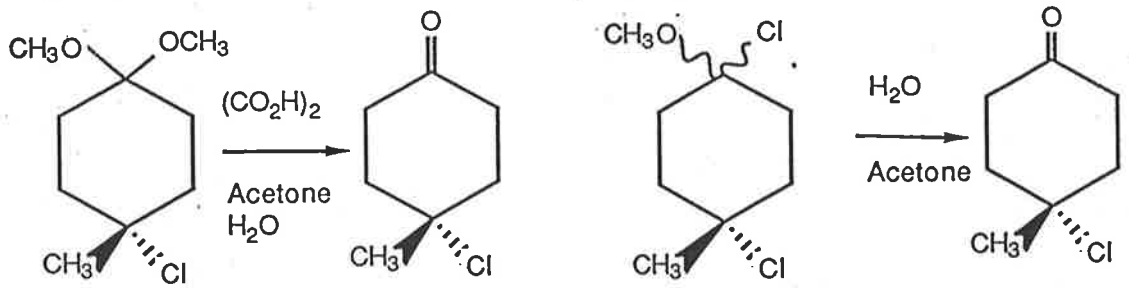
presumed to be a mixture of the chloro methyl ethers (76) remained. These compounds were not purified. Methanol was added to the crude product and the mixture was neutralised with powdered sodium hydrogen carbonate whereupon evaporation of the excess methanol gave the dimethyl acetal (77) in 98% yield. The NMR spectrum of the acetal exhibited two singlet resonances at δ 3.07 and 3.12 for the two methoxy groups, one on the side of the ring bearing the methyl group and the other on the side bearing the chloro group. This parallels the spectrum of the bromo acetal (73).



(69) (76) (77)

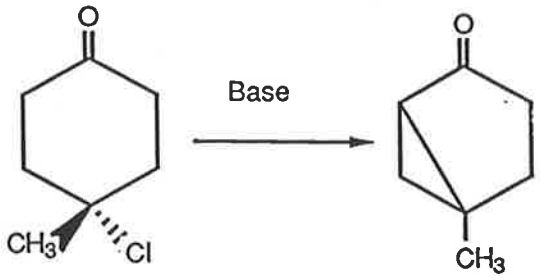
The acetal (77) was hydrolysed with oxalic acid in wet acetone to yield the 4- substituted cyclohexanone (75) in 93% yield. The infra-red spectrum of the chloro ketone (75) showed a carbonyl absorption at 1720 cm^{-1} and the NMR spectrum showed a singlet methyl resonance at δ 2.00 consistent with a methyl group attached to a carbon bearing a chlorine atom. It was assumed that the relative lack of stability of the methanol acetal with respect to the cyclic ethylene glycol acetal (13)

(see introduction) allowed the hydrolysis of the acetal moiety of (73) to occur without concomitant loss of the chloro group. The ketone (75) was also available in 95% yield directly by the action of wet acetone on the chloro ethers (76). This method is generally a more direct and efficient method for the synthesis of the chloro ketone (75) than the hydrolysis of the dimethyl acetal (77).



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

Treatment of the chloro ketone (75) with sodium hydride in benzene gave a brown mixture containing 5-methylbicyclo[3.1.0]-hexan-2-one (74). This was verified by combined gas chromatography / mass spectrometry techniques. The reaction mixture showed a large peak in the GC trace with a mass spectrum consisting of peaks at *m/z* 110 for the molecular ion and at *m/z* 82, 68 and 67. The retention time and the peaks in the

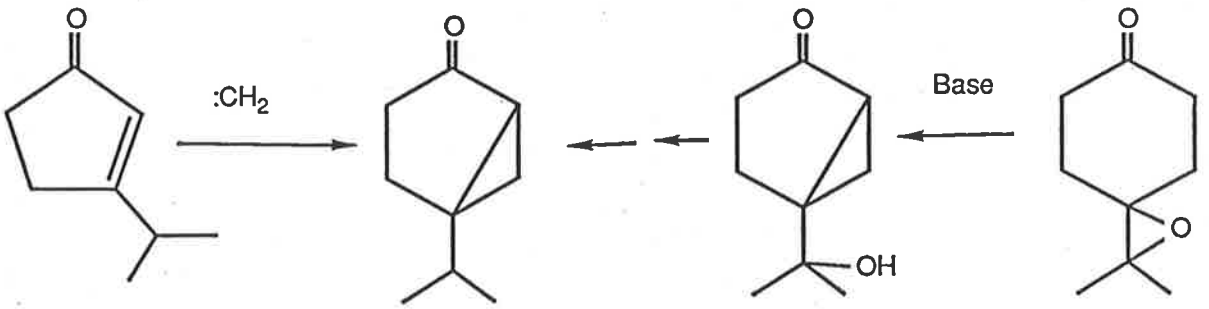


(75) (74)

mass spectrum of the product of the reaction of the chloro ketone (75) were identical to that of the authentic sample of (74).

With potassium t-butoxide in t-butanol the reaction was somewhat cleaner and gave the desired bicyclo[3.1.0]hexanone (74) in 61% yield. When ethanol was used as the solvent and sodium ethoxide as the base, the reaction was largely complete after 15 minutes as shown by GC analysis. The solvent was easily removed and the product was distilled to give a 70% yield of the bicyclohexanone (74).

Sabina Ketone , 5-isopropylbicyclo[3.1.0]hexan-2-one (12) is a natural product which has been isolated from a number of plant sources including lavandin oil[30]. It has been prepared in racemic form[31, 32].

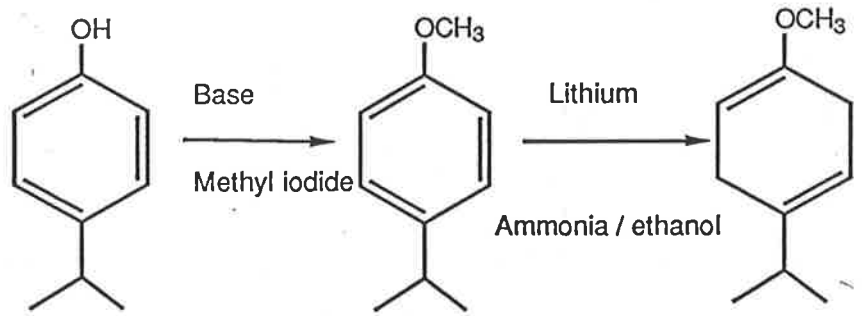


(12)

An approach to the synthesis of this natural product that was to have used the chloroKetone (11) has been reported by Nelson and Mortimer[4] but it was unsuccessful because the chloro Ketone could not be prepared by the route chosen. It was of interest to see if the chemistry which allowed the preparation

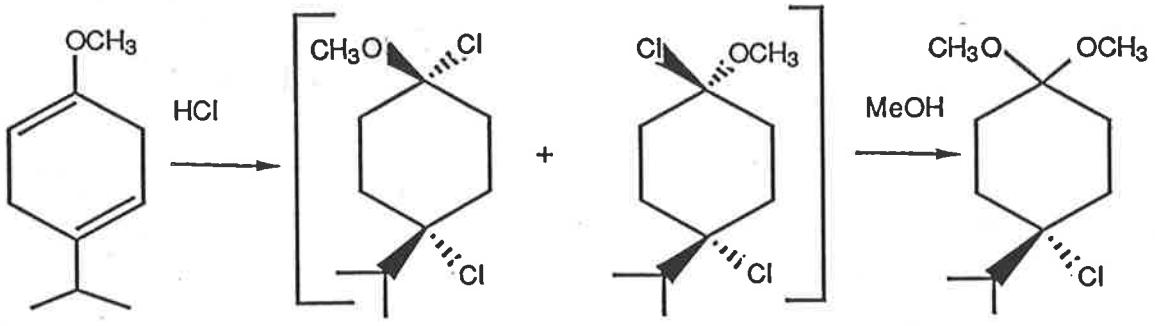
of the bicyclohexanone (74) from the chloro ketone (75) could be developed to give a synthetic route to racemic sabina ketone.

To apply the new procedure for the synthesis of the natural product (12), the isopropyl enol ether (78) must be used. This compound was available as the product of the dissolving metal reduction in 85% yield from the known ether, 4-isopropyl anisole[33] (79).



(80) (79) (78)

Treatment of the frozen enol ether (78) with liquid hydrogen chloride and work up with methanol yielded the dimethyl acetal (81) in 97% yield as a pungent crystalline solid. The NMR spectrum of the acetal (81) contained two singlet resonances at δ 3.05 and 3.11 attributed to the two methoxy groups of

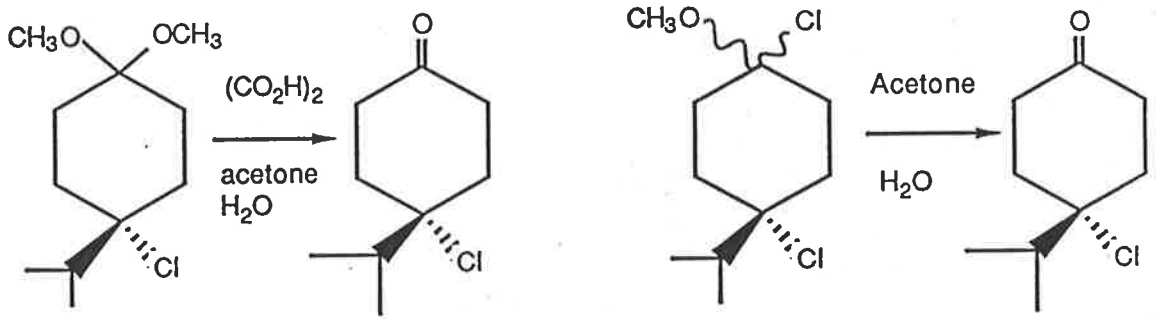


(78) (82) (81)

the acetal on different sides of the ring. The mass spectrum

contained peaks at *m/z* 189 and 191 in the ratio of 3 to 1 attributed to the loss of a methoxy radical from the chlorine containing molecular ions.

Hydrolysis of the acetal (81) in aqueous acetone and oxalic acid for 12 hours afforded the ketone (11) in 98% yield. The infra red spectrum of the ketone showed a strong absorption at 1720 cm^{-1} due to the presence of the carbonyl group. The mass spectrum of the ketone (11) exhibited peaks at *m/z* 176 and 174 in the ratio of 1 to 3 reflecting the relative abundances of the chlorine containing molecular ion.

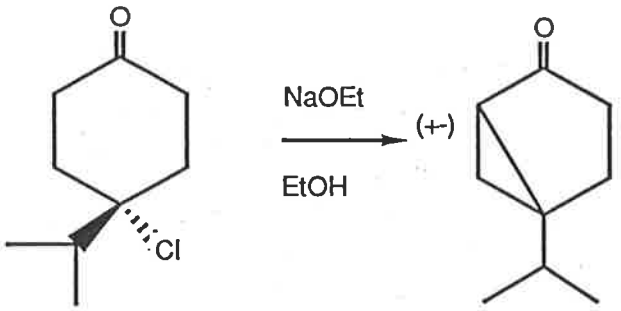


(81) (11) (82) (11)

The chloro ketone (11) was also produced directly from the chloro methyl ethers (82), the intermediates in the formation of the acetal. In a manner analogous to the case of the methyl ketone (75), the chloro methyl ethers (82) were hydrolysed in wet acetone to give the chloro ketone (11) in 99% yield.

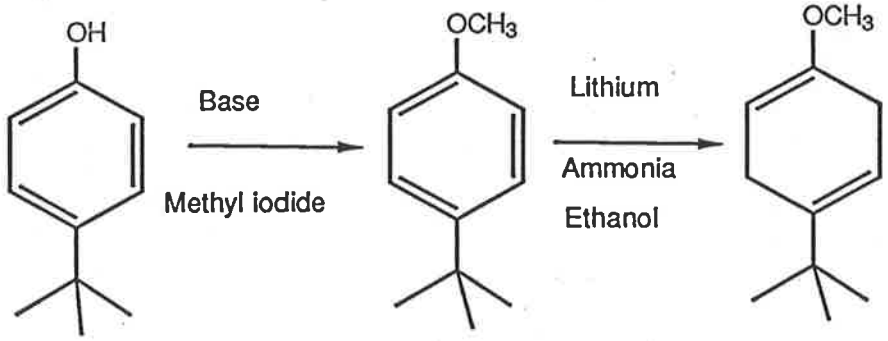
Upon treatment of the chloroketone (11) in ethanol with sodium ethoxide for three hours at room temperature, racemic sabina ketone (12) was obtained in 81% yield. The authenticity of the structure was established by the comparison of the NMR spectrum

of the compound obtained in this manner with the spectrum of sabina ketone (12) published by Gaoni[32].



(11) (1 2)

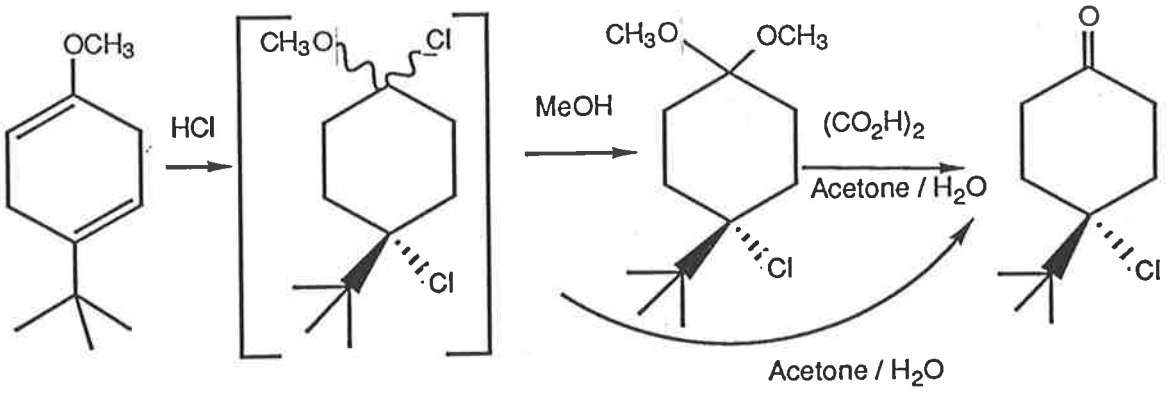
It was decided that the generality of the procedure would be investigated further. 5-*t*-Butylbicyclo[3.1.0]hexan-2-one (83) was sought, and for this, the enol ether (84) was required. This enol ether (84) was obtained in 77% by the dissolving metal reduction of 4-*t*-butyl anisole[34] in the manner described by Kwart and Conley[35].



(84)

Treatment of the frozen enol ether (84) with liquid hydrogen chloride then with methanol yielded the dimethyl acetal (85) in 95% yield whose NMR spectrum contained singlet resonances at δ 3.03 and. 3.10, due to the two different environments for the methoxy groups of the acetal. The treatment of the acetal

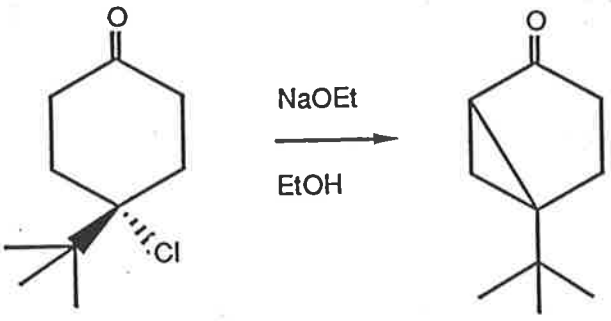
(85) with wet acetone and oxalic acid afforded the chloro ketone



(84) (86) (85) (8 7)

(87) in 95% yield. The assignment of the structure was confirmed by the infra-red spectrum which showed a strong absorption at 1720 cm^{-1} consistent with the presence of the saturated carbonyl group. The mass spectrum of the chloro ketone (87) contained peaks at *m/z* 190 and 188 in the ratio of 1 to 3 due to the chlorine containing molecular ions. The chloro ketone (87) was also prepared in 95% yield directly from the intermediate chloro methyl ethers (86) by the action of wet acetone.

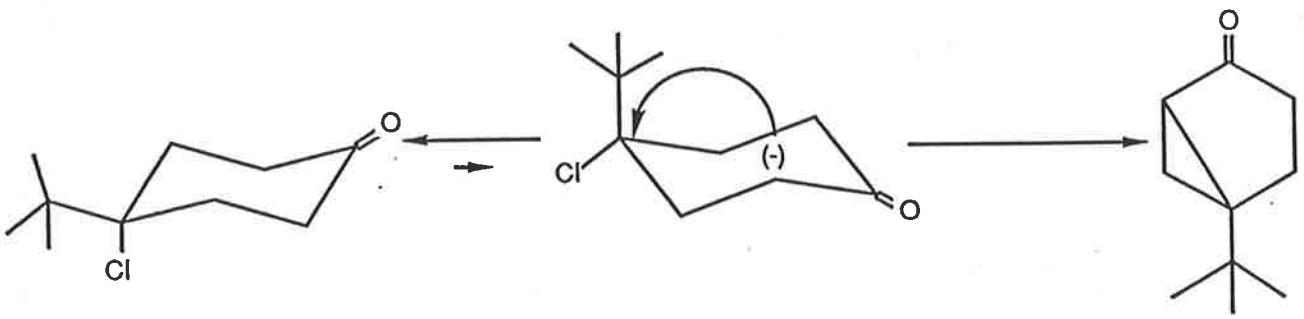
Under conditions which were similar to those described for the preparation of the bicyclohexanone (12), the chloro ketone (87), in ethanol, was treated with sodium ethoxide for 24 hours.



(87) (8 3)

The required bicyclo[3.1.0]hexanone (83) was thus obtained in 50% yield. The mass spectrum of the ketone (83) showed a peak at *m/z* 152 ascribed to the molecular ion. The NMR spectrum of the bicyclohexanone (83) exhibited resonances at δ 0.90 arising from the t-butyl group and 1.97 due to the two methylene groups of the of the cyclopentanyl portion of the bicyclic system. A complex multiplet at δ 1.1-1.9 was assigned to the 3 cyclopropyl protons.

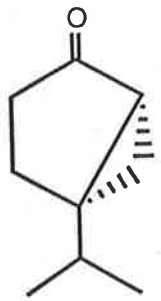
The t-butyl group is a very large and bulky group. In the cyclohexane ring, the preferred conformation is in the equatorial position[36]. The chloro ketone should more accurately be represented as in (88) and (89). Clearly, the chloro group is not in the correct position for the Sn2 displacement by the enolate anion. It is required to be in the equatorial position as in (89). The free energy difference between the two forms is calculated to be at least 3.5 kcal/mol (4 - 0.52 kcal/mol)[36]. This is sufficient to allow a small percentage of the more energetic form of (87), that of (89), to exist at room temperature. It could be for this reason that the



(88) (89) (83)

reaction of the chloro ketone (87) with base to form the bicyclohexanone (11) was significantly slower than either the *iso*propyl case or the methyl case.

The natural product, sabina ketone (12) possesses two chiral centres in the cyclopropane ring. These centres are related by the *cis* nature of the three membered ring and for this reason the molecule can be considered as possessing only two stereoisomers from the point of view of optical isomerism. It was of interest to investigate a possible asymmetric synthesis for sabina ketone through the use of the chloro ketone (11).



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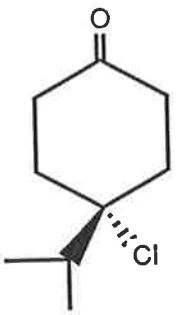

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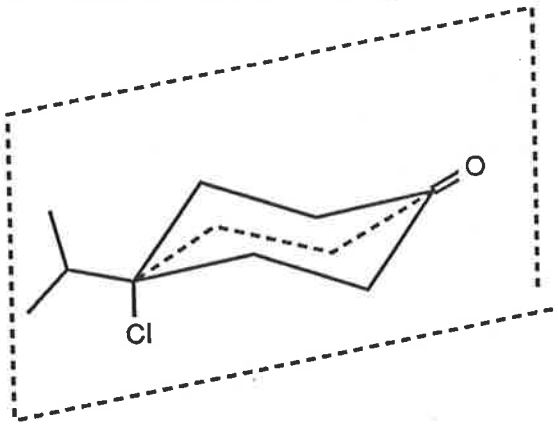
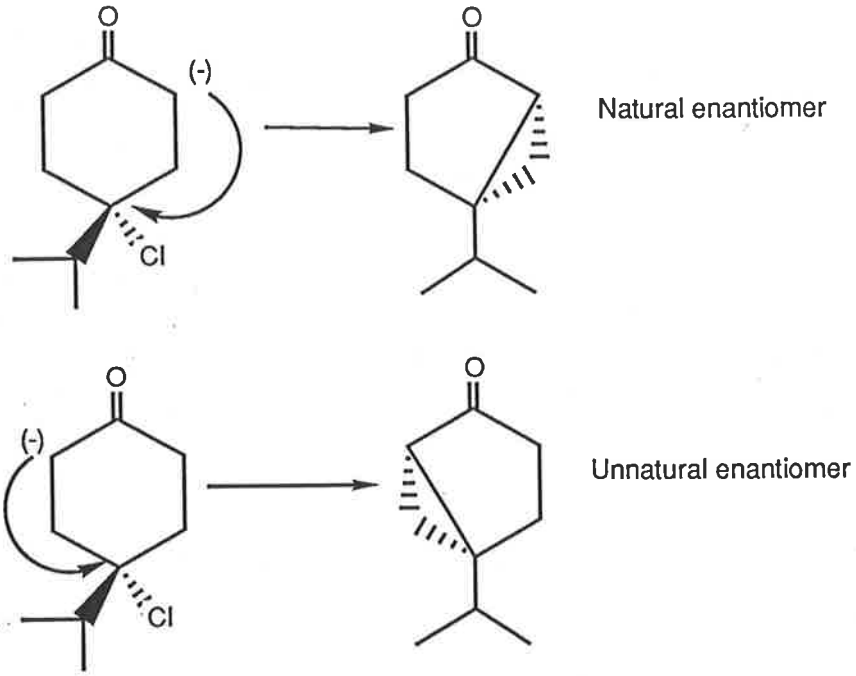
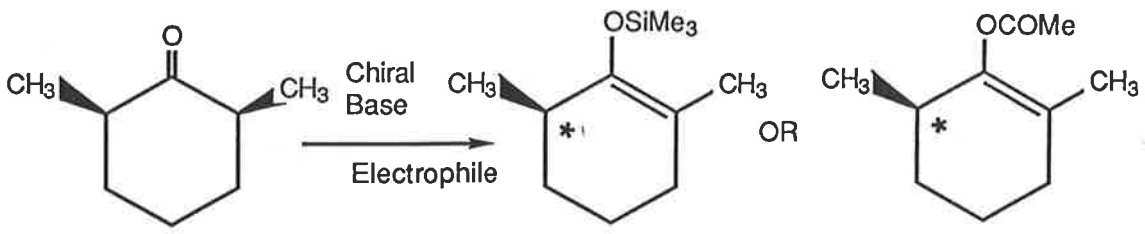


The chloro ketone (11) has no chiral center and possesses a plane of symmetry which runs through the carbonyl and carbon-chlorine bonds. If an asymmetric synthesis of sabina ketone is to be achieved, the two sides of the molecule must be differentiated in some way. If an enolate anion is made exclusively on one side of the molecule and the Sn2 displacement of chloride takes place then one enantiomer of the natural product will be formed. The different methylene groups are enantiotopic whilst the enolate

anions are enantiomeric. Selective formation of only one of these anions requires an asymmetric deprotonation.



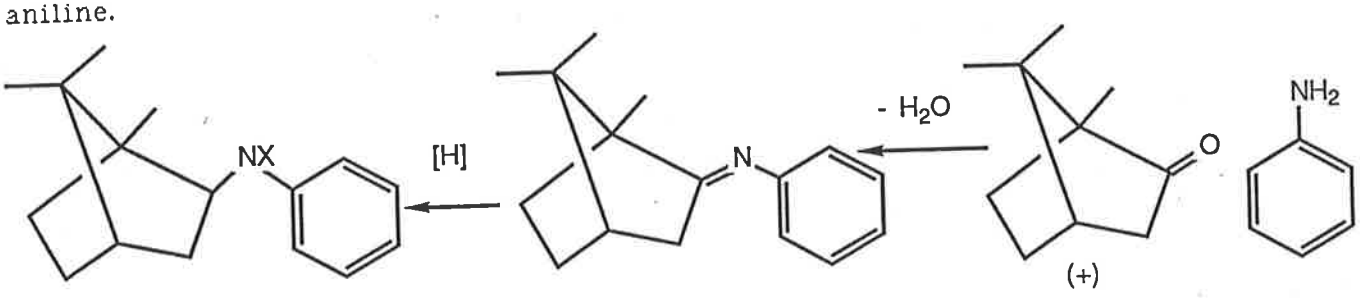
Asymmetric deprotonations have been performed on the ketone (90)[37]. Chiral lithium amide bases were used as the source of asymmetry. The chiral enolate anion of the ketone (90) has been treated with electrophiles to give either the chiral enol silyl ether or the enol acetate. The reaction has been reported to give enantiomeric excesses of up to 74% with



(90)

the symmetrically disubstituted ketone (90). The enantiomeric excess is reported to be not as good in the case of symmetrically substituted ketones without α substituents.

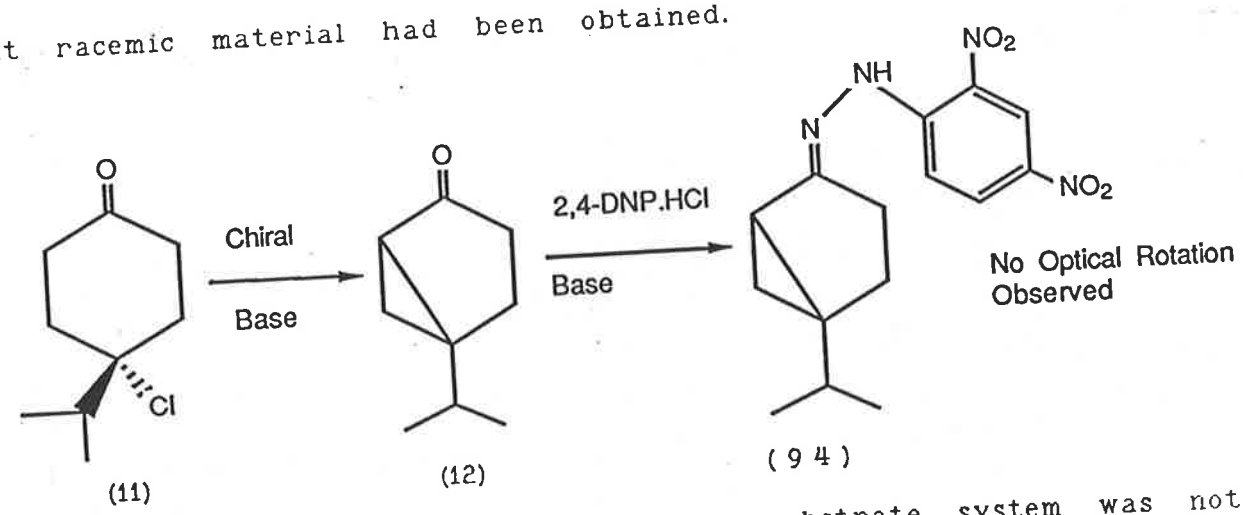
The enantioselective deprotonation of the chloro ketone (11) was attempted with the lithium amide (91) which was the base reported to give the greatest enantiomeric excess in the case above. This amide was prepared from the amine (92) which in turn was the product of the lithium aluminium hydride reduction[38] of the imine (93). The imine was prepared under dehydrating conditions from natural (+) camphor and aniline.



X= Li (91); X= H (92) (93)

The chloro ketone (11) was treated with the chiral amide under the conditions described by Simpkins[37]. The chloro ketone (11) was added to a solution of the chiral amide in dry THF at -78^0 then the mixture was stirred for 8 hours before finally being worked up. Natural sabina ketone is a relatively volatile oil with a specific rotation of -24.4^0 [39]. It was decided because of the small amount of material involved to convert the ketone to its 2,4-dinitrophenyl hydrazone (94). This compound was isolated in 46% yield. The

melting point of the hydrazone was found to be 124^0 and the literature value is 124^0 [39]. This compound is a crystalline stable derivative and the natural enantiomer has a specific rotation of + 135.2^0 [39]. A solution of the 2,4-dinitrophenyl hydrazone (94) from the reaction above did not register any rotation of the plane of polarised light. Because of its strong light absorbing characteristic the hydrazone solution was of a limiting concentration. It appeared that racemic material had been obtained.

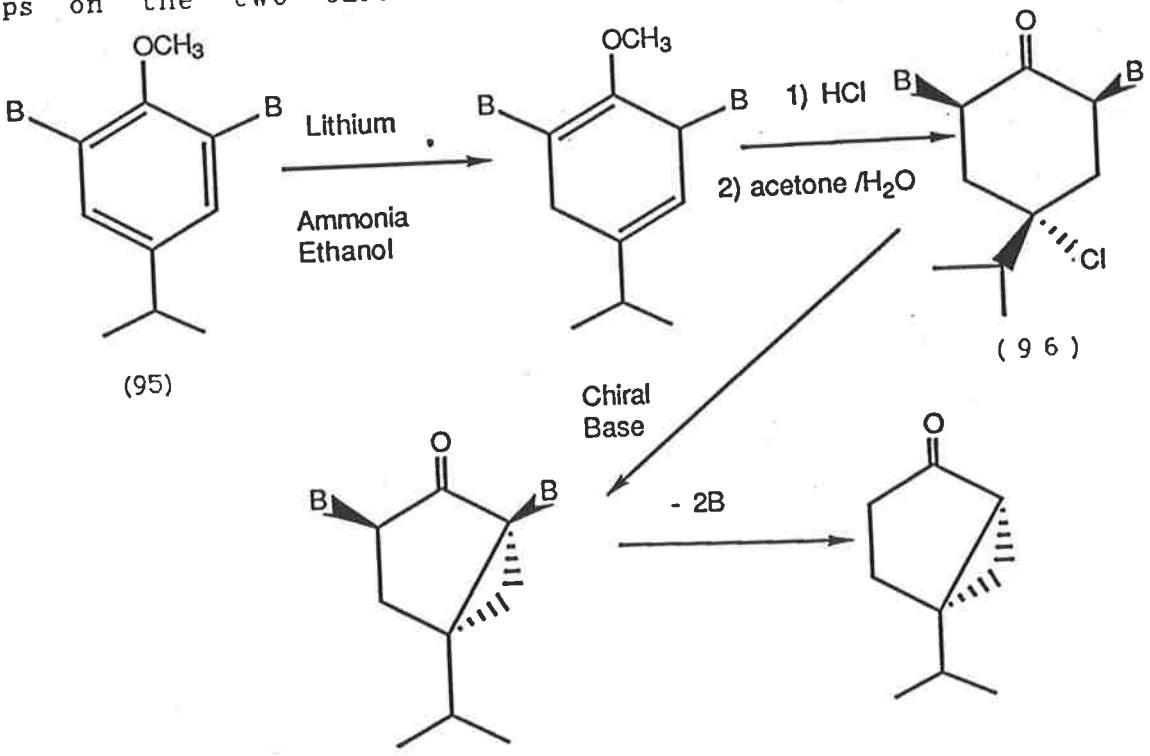


(11) (12) (94)

The deprotonation with the base and substrate system was not selective. If the base acts specifically to remove an α proton which is axial, then the two axial protons in the ketone (11) might not be in sufficiently different steric environments for the chirality of the base to affect the transition state conformation. Furthermore, if the two groups at the 4- position of the chloro ketone (11) are treated as two large groups, then flipping of the cyclohexane ring from one conformer to another would present two different axial protons for the chiral base to

remove (if it acts to remove an axial proton from only 1 side of the carbonyl group as it does in the case of the ketone (90)). The two resultant enolate anions would be enantiomeric and hence the product would be achiral.

In the future, the deprotonation procedure may be improved with the discovery of bases that will react efficiently with symmetrically monosubstituted ketones and may allow a straightforward asymmetric synthesis of sabina ketone to be perfected using the chloro ketone (12). Until that time however, the asymmetric deprotonation could be of use in its present state if the substrate could be modified. If there were two bulky groups on the two carbon atoms α to the carbonyl group then



(95) (96) (12)

the structure would fulfill the requirements of the chiral deprotonation as it stands. If these groups could also be such that they could be removed easily and specifically, then either the natural or unnatural enantiomer of sabina ketone could be available from the chloro ketone (96) in a very few steps. The problem would be to find a group that could easily be installed into the aromatic ether (95), could withstand treatment with liquid hydrogen chloride and could be specifically and cleanly removed.

In conclusion, the construction of most of the crispatanolide skeleton with the correct relative stereochemistry proved to be untenable by either the thermal or Lewis acid catalysed Diels Alder reaction of the cyclohexadienone (32) or its derivative with isoprene. Investigation in the area of the cyclopropyl moiety of crispatanolide met with good success as a general synthesis of 5-alkylbicyclo[3.1.0]hexan-2-ones (such as the natural product sabina ketone (12)) from the 4-alkyl-4-chlorocyclohexan-1-ones has now been realised. These chloro compounds are easily prepared from the appropriate enol ethers. Attempts at an asymmetric synthesis of sabina ketone by asymmetric deprotonation of the chloro ketone (11) were unsuccessful. The question of the asymmetric synthesis of the 5-alkylbicyclo[3.1.0]hexanone system is further explored in the next chapter.

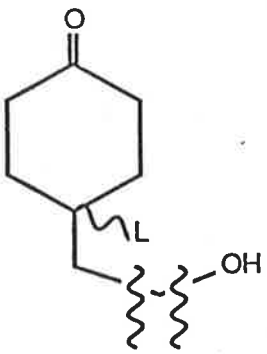
Chapter 2

The challenge of an asymmetric synthesis of sabina ketone (12) was taken up. Work in this area might be expected to lay the foundations for an asymmetric synthesis of the natural product, crispatanolide although it is anticipated that this would be a vastly more complicated problem. The asymmetric synthesis of bicyclo[3.1.0]hexanones may be approached in several different ways. In one approach, Mash and Nelson[40] have shown that chiral acetals of cyclopentenones (among other enones) can be used in chiral coordinated Simmons Smith reactions to afford one enantiomer of bicyclo[3.1.0]hexanone acetals which have been hydrolysed to bicyclo[3.1.0]hexanones.

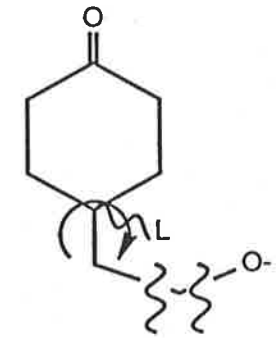
However, as the route to the bicyclo[3.1.0]hexanones by intramolecular alkylation has proved successful, it was considered that extension of this chemistry to include an asymmetric alkylation would be interesting. In the synthesis of racemic sabina ketone (12), the precursor 4- substituted cyclohexanone (11) possesses no chirality. Therefore, when the enolate anion of the ketone (11) was formed with the achiral base, there was no selection between the two enantiotopic groups of acidic protons adjacent to the carbonyl group. For an asymmetric synthesis of the bicyclo[3.1.0]hexyl group, there must be a differentiation between the side of the carbonyl group from which the proton is to be removed. One way this asymmetric deprotonation might be achieved is through the use of a chiral base to perform an asymmetric deprotonation. However, as

described in chapter 2, this approach was not successful.

Alternatively, the problem of preparing one enolate anion in preference to the other might be overcome by the use of an intramolecular base to abstract a proton. As sodium ethoxide was the base in the case of the chloro ketone (11), the use of an alkoxide ion in an intramolecular sense could bring about the cyclisation. If this alkoxide ion were "tethered" to one side of the molecule, it is conceivable that it would react preferentially with one of the methylene groups. If the alkoxide were attached as in (97), this would require that rotation of the side chain with respect to the cyclohexyl ring is precluded. A study of molecular models shows that if the alkoxide base is on

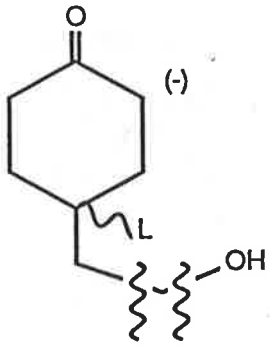


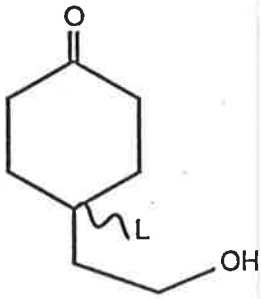
(98)



Restricted rotation of side chain

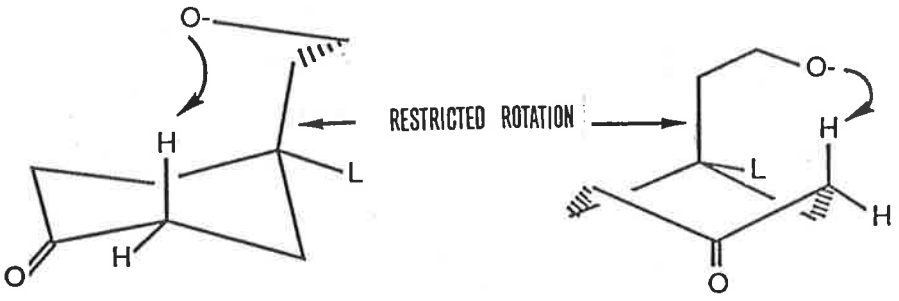
(97)



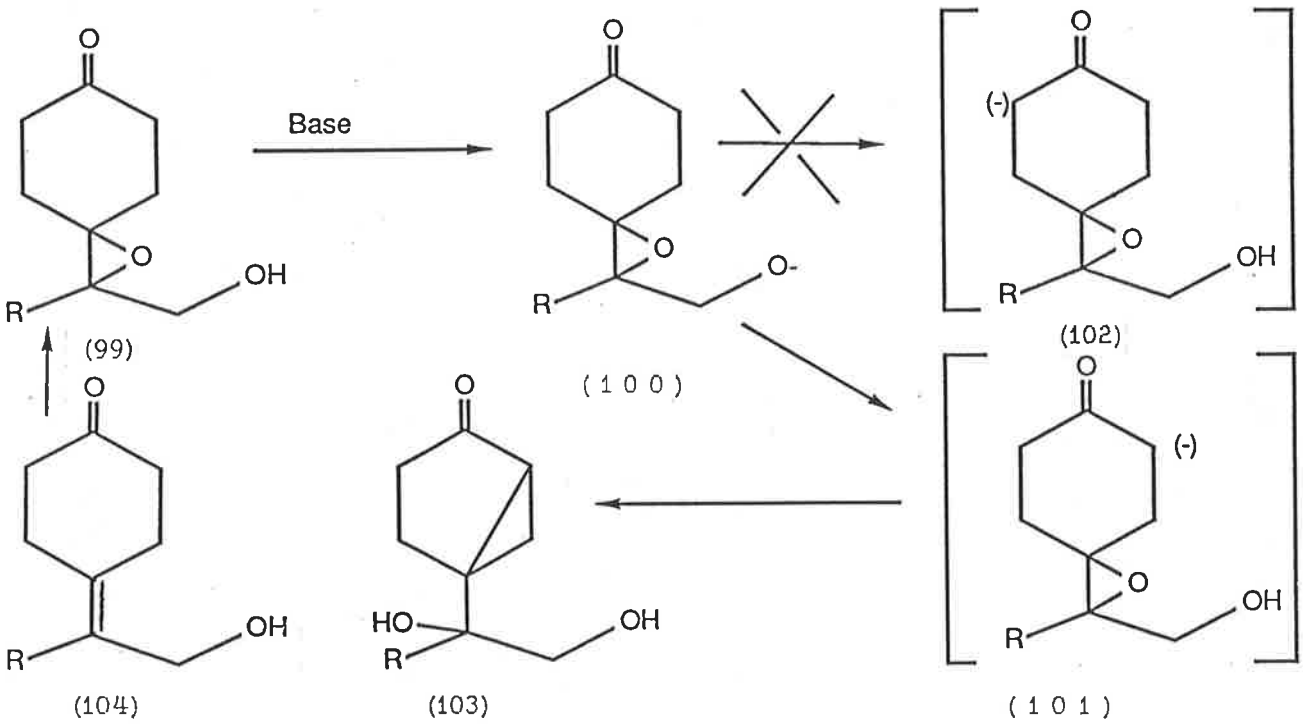


the end of a side chain of two carbon atoms, providing rotation of that group is restricted, it can get closer to one of the methylene groups adjacent to the carbonyl group than to the other. Furthermore, the reaction would proceed through a six membered transition state which should not be unfavourable. The

requirement of restricted rotation introduces chirality into the molecule and an enantioselective synthesis of this substrate would be required if asymmetric sythesis is to be achieved overall.



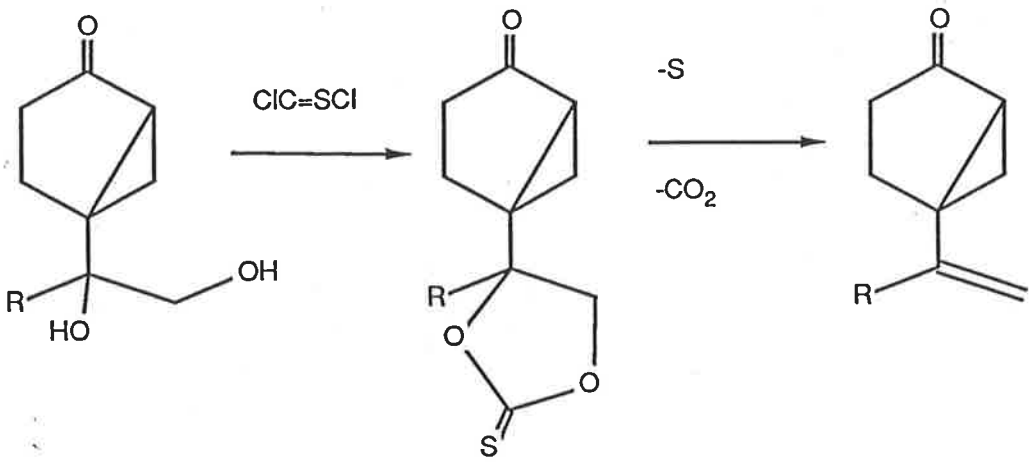
If the epoxidation chemistry of Sharpless[41] is born in mind and also the fact that sabina ketone has been prepared in several steps from an epoxide by Gaoni[32], the plan of attack becomes apparent. The hydroxyl group that is to become the intramolecular alkoxide base in the ketone (98), could also be useful in the Sharpless epoxidation. Epoxidation of an allylic alcohol under Sharpless conditions should yield the epoxide (99) in which the chirality in the side chain is mostly uniform. The rigidity of the epoxide ring would preclude rotation of the side chain with respect to the ring and the epoxide should act as a suitable leaving group. Dependent on which enantiomer of diethyl tartrate is used in the Sharpless epoxidation, either enantiomer of the epoxide (99) could be available. Treatment of the one enantiomer of the epoxy alcohol (99) at infinite dilution with one equivalent of strong base should lead to the alkoxide (100)



which is hoped would allow the formation of the enolate (101) to the exclusion of (102). The enolate (101) should react to form the cyclopropane (103) which would be obtained as one enantiomer. This was termed the epoxide scheme. It should be noted that the stereochemistry at the tertiary alcohol site is retained and its configuration is defined in the Sharpless epoxidation of the allylic alcohol (104).

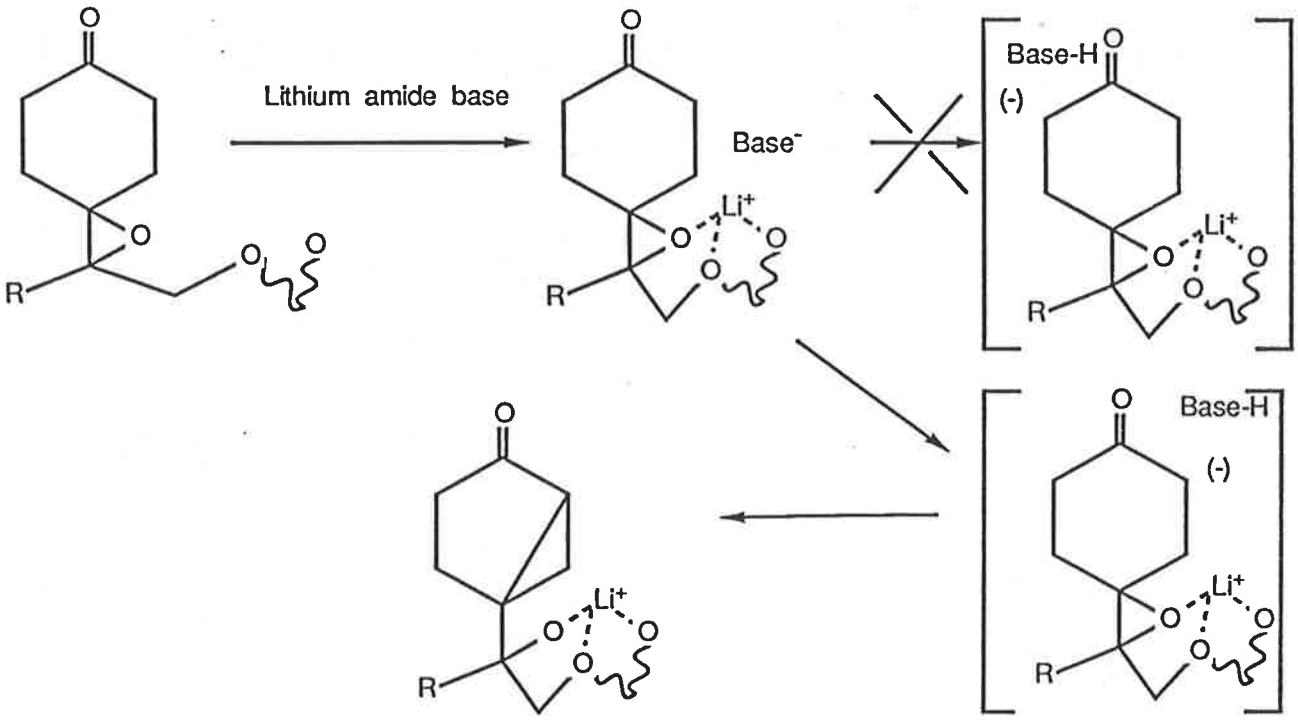
The relationship of the bicyclo[3.1.0]hexanone (103) (R= Methyl) to the simple natural product, sabina ketone (12) is clear. The removal of both hydroxyl groups is required and it was hoped this could be carried out by formation of the enone (105) through the procedure developed by Corey and Winter[42] in which the thionocarbonate derivative is treated with a desulphurising reagent like trimethyl phosphite. The racemic

enone (105) (R= Methyl) has been hydrogenated[32] to afford sabina ketone (12).



(103) (105)

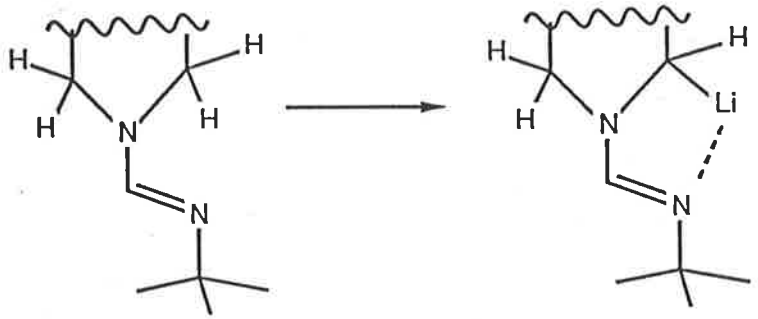
The formation of only one enantiomeric enolate anion in a



system like the epoxide (99) might also be possible through

coordination of a base to one side of the molecule as depicted in the scheme above.

An oxygen rich functionality derived from the hydroxyl group may coordinate the metal cation of a tight metal / base ion pair thereby bringing the base also to bear on that side of the molecule. Meyers[43] has reported regiospecific



(106) (107)

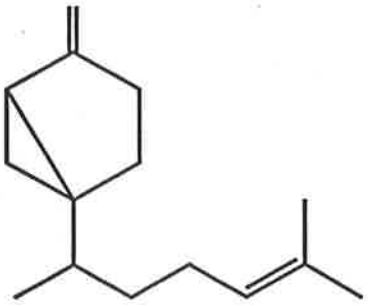
deprotonations with coordinating groups based on the formamidine moiety. The mechanism is believed to proceed through complex formation of the lithium / base and formamidine species (106) to give the kinetic anion (107). The anion is stabilised by the coordination of the lithium metal. The regioselective deprotonation is initially brought about by the regioselective coordination of the base and the amine (106).

The scheme which involves the MOM ether epoxide was termed the base coordination scheme. In both the epoxide and base coordination schemes, it is necessary to remove a proton from only one of the two methylene groups adjacent to the carbonyl group of the epoxide (99).

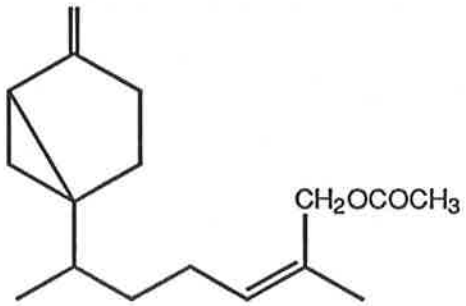
Closer examination of the product of the cyclopropane ring

forming reaction reveals that three chiral centres would be controlled in the reaction. They are the two cyclopropane centres and the chiral center external to the bicyclohexane ring that was installed in the Sharpless epoxidation. It is because this latter centre is controlled that sesquiterpenes containing the bicyclo[3.1.0]hexyl ring might be available through either scheme.

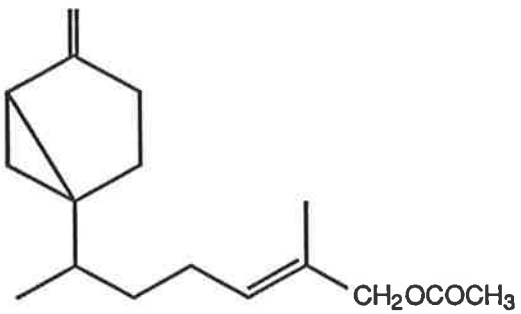
Various sesquiterpene natural products incorporating the bicyclo[3.1.0]hexanone system exist which are related to the sabinene group of terpenes. These include sesquisabinene (109), 12-acetoxysesquisabinene (110), 13-acetoxysesquisabinene (111) and *cis*-sesquisabinene hydrate (112). They have been isolated from *Zingiber* and *Piper* species by Lawrence *et*



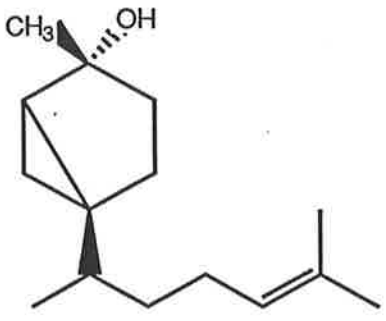
(109)



(110)



(111)



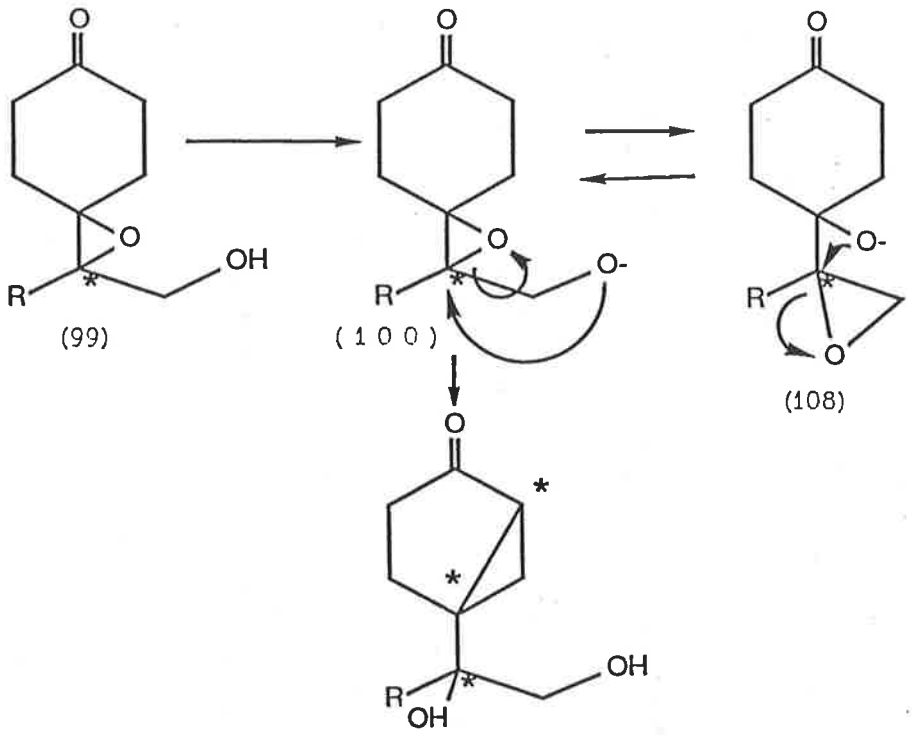
(112)

al[44] and from some *Haplocarpha* species by Bohlmann and Wallmeyer[45].

The sesquiterpenes mirror the mono terpenes with the existence of the two chiral centres in the bicyclo[3.1.0]hexanone ring but with one important addition. They possess an extra chiral centre at the methine group of the side chain. The absolute configuration of the natural products has, to date, not been determined. The stereochemistry of all three of these centres could be controlled in either the epoxide or the base coordination scheme and because of this, the route may provide an asymmetric synthesis for these sesquiterpenes.

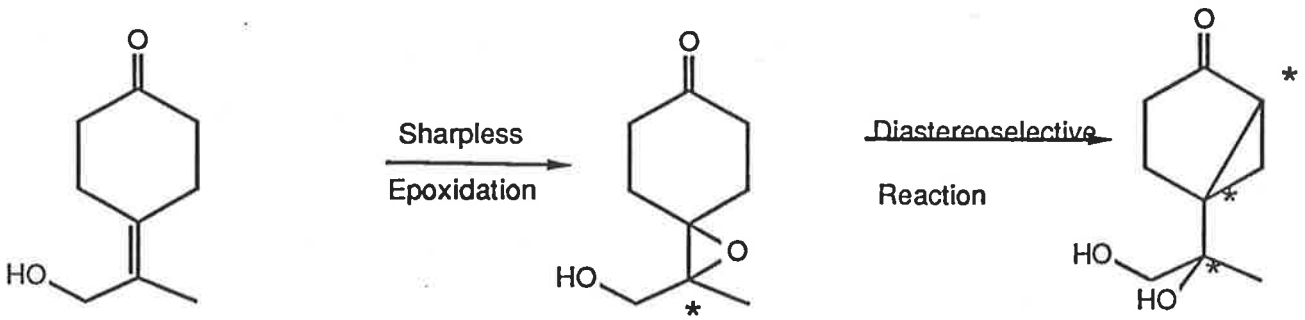
The alkoxide (100) possesses an electrophilic site (the epoxide ring) close to the nucleophilic alkoxide oxygen atom. It is conceivable that the alkoxide anion could attack the carbon of the epoxide ring to give the tertiary alkoxide (108). The stereochemistry at the electrophilic carbon atom is not racemised but is inverted by the reaction. A similar reaction could again occur with the tertiary alkoxide anion attacking the carbon atom of the epoxide ring to regenerate the alkoxide (100). The original stereochemistry has been reinstated and the alkoxides (100) and (108) may be considered as being in equilibrium. This reaction has been refered to as the Payne rearrangement[46]. This equilibrium should not affect the course of the cyclisation although it might affect the rate since the intramolecular reaction which is presumed would be

irreversible should only proceed through the alkoxide (100).



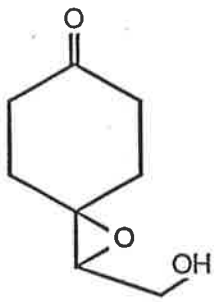
(103)

The asymmetric synthesis depends on the combination of the enantioselective formation of the epoxide (99) and the diastereoselection of the proton removal that should give preferentially one diastereomer (and its mirror image if



preformed with the racemic epoxide). Asymmetric synthesis of one enantiomer of the epoxide would be required for an optically active product (103). However, the diastereoselection can be studied with the racemate of (99) without recourse to optically active products.

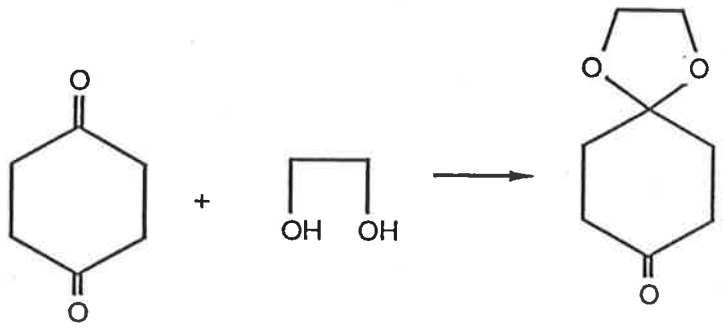
The system (99 R= H) or (113) was chosen for study as it might allow access to the higher sesquiterpenes. It was also necessary to ascertain whether an epoxide when treated with base would indeed give the desired bicyclo[3.1.0]hexanone. The synthesis of this compound has been accomplished in six steps.



(113)

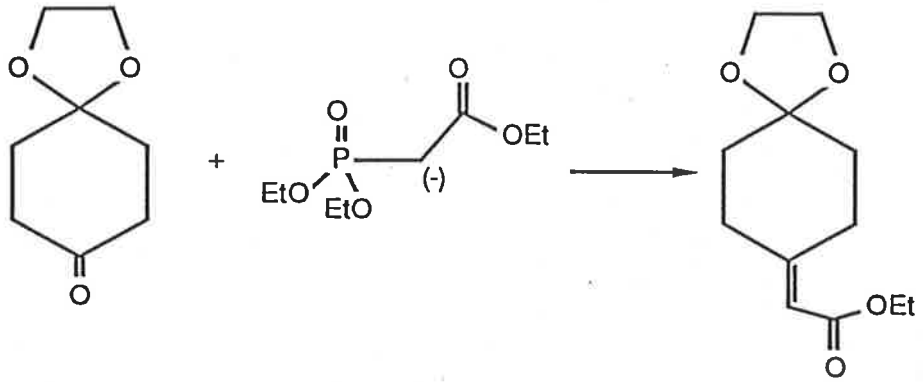
The mono acetal (114) was prepared from cyclohexane -1,4-dione (115) by the method of Courtot[47] in which the dione (115) was treated with 1.2 equivalents of ethylene glycol under dehydrating conditions.

The mono acetal (114) was subjected to the conditions of a Wittig Horner reaction with the readily available triethyl phosphonoacetate (116). The best yield (67%) for this reaction was obtained when the ketone (114) was perfused into 1.5 times



(115) (114)

excess of the sodium salt of the phosphonate in THF over a 6 hour period.

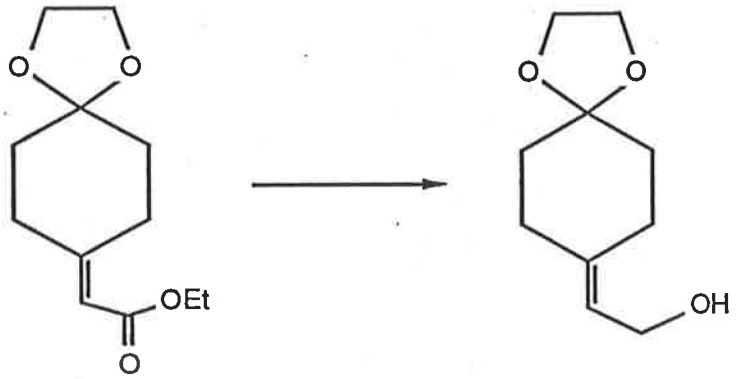


(114) (117)

The spectral characteristics that confirm the structural identity of the unsaturated ester (117) were as follows. The NMR spectrum of the ester (117) showed resonances at δ 1.08 and 4.08, a triplet and a quartet respectively, consistent with the ethoxy group of the ester and a broad singlet resonance, at δ 5.75, was consistent with the vinylic proton on the α carbon of the unsaturated ester. The dioxolane protons, although in principle non-equivalent, resonated as a singlet at δ 3.75. The infra-red spectrum contained a strong absorption at 1700 cm^{-1} due to the unsaturated ester. The double bond of the

enone system was observed to give a weak absorption at 1630 cm^{-1}. The mass spectrum showed a peak corresponding to the molecular ion at *m/z* 226.

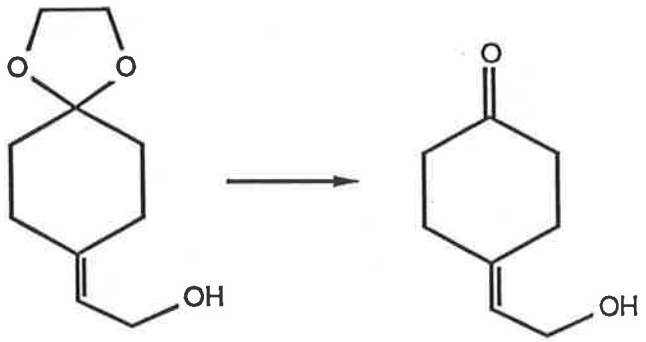
Lithium aluminium hydride reduction of the ester (117) gave the allylic alcohol (118) in 91% yield. The infra-red spectrum of the alcohol (118) showed a strong absorption at 3500 cm^{-1} which confirmed the presence of the hydroxyl group and a weak absorption at 1660 cm^{-1} was consistent with the presence of the double bond. The NMR spectrum exhibited a doublet resonance at δ 4.08 from the allylic methylene bearing the hydroxyl group and a triplet resonance at δ 5.33 from the vinylic methine. The dioxolane protons appeared as a sharp singlet at δ 3.93. A peak that was ascribed to the molecular ion was observed in the mass spectrum at *m/z* 184.



(117) (118)

Acid catalysed deprotection of the carbonyl group of the alcohol (118) was performed by hydrolysis with oxalic acid in wet acetone. The reaction was sluggish and it appeared that after

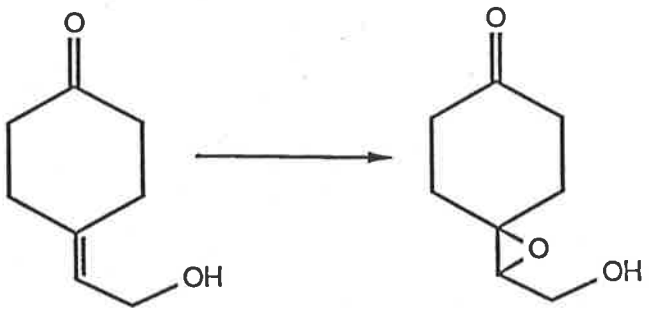
several days, an equilibrium distribution of the ketone (119) and the acetal (118) had been formed with a small amount of the acetal remaining. The two components were separated by chromatography and the keto ol (119) was isolated as a colourless oil in 96% yield. The structural assignment was confirmed by the presence in the infra-red spectrum of a sharp absorption at 1710 cm^{-1} due to the carbonyl group and a broad strong absorption at 3500 cm^{-1} corresponding to the hydroxyl group. The NMR spectrum contained resonances at δ 4.15 as a doublet and at 5.55 as a triplet consistent with the hydroxyethylidene group.



(118) (119)

Because of the trial nature of the investigation of the cyclopropane forming reaction, it was decided that the epoxidation of the allylic alcohol (119) would be performed in an achiral manner so that the diastereoselectivity of the cyclisation could be studied. Thus, the allylic alcohol was treated with 3-chloroperoxybenzoic acid in dichloromethane at low temperature and the epoxide was obtained in 68% yield after

chromatography. The NMR spectrum of the epoxide (113) was not unlike that of the preceeding alcohol (119) except that some of the resonances were shifted upfield. The protons of the methylene group bearing the hydroxyl group appeared as a doublet at 3.83 and a triplet at δ 3.13 was assigned to the epoxy methine proton. The mass spectrum of the epoxide (113) exhibited the molecular ion at *m/z* 156 and a strong peak at *m/z* 157 was thought to be due to the protonated molecular ion. This is sometimes a feature of the mass spectra of alcohols[48].

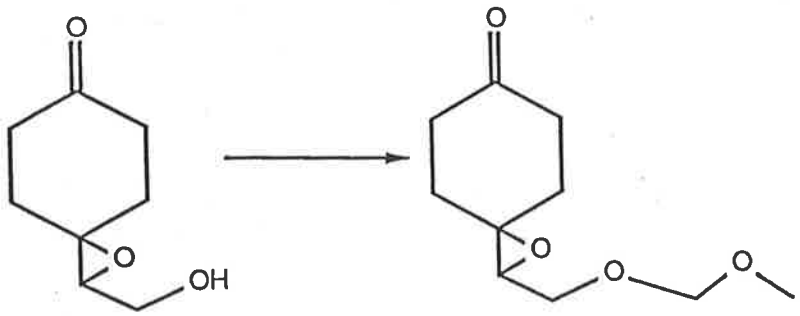


(119) (113)

The epoxide (113) contains three oxygen atoms within a relatively small structure and it was found to be very polar and also water soluble. As a consequence, it was decided to convert the epoxide to a more easily handled and less polar derivative. This presented the opportunity to install a group that could coordinate a metal ion, in order to ascertain if it was stable under the reaction conditions. The oxygen rich methoxymethyl (MOM) or 2-methoxyethoxymethyl (MEM) groups are excellent protecting groups for hydroxyl moieties and can easily be removed

by mild acid treatment[49]. They contain oxygen atoms that could conceivably coordinate a metal cation, a requirement of the base coordination scheme.

The epoxide (113) was converted to its corresponding methoxymethyl ether (120) in 75% yield by treatment with methoxymethyl chloride and di*iso*propylamine in dichloromethane. The spectral characteristics of the ether were as follows. The NMR spectrum showed resonances at δ 3.72 as a doublet which was assigned to the methylene group bearing the ether protecting group. A triplet at δ 3.16 corresponded to the hydrogen atom attached to the epoxide ring. The installation of the MOM group was verified by the presence of singlet resonances at δ 4.65 and 3.37 due to the methylene and methoxy groups of the MOM group respectively.

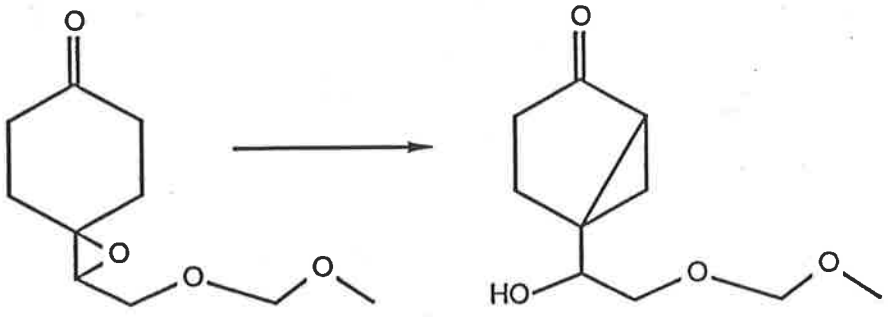


(113) (120)

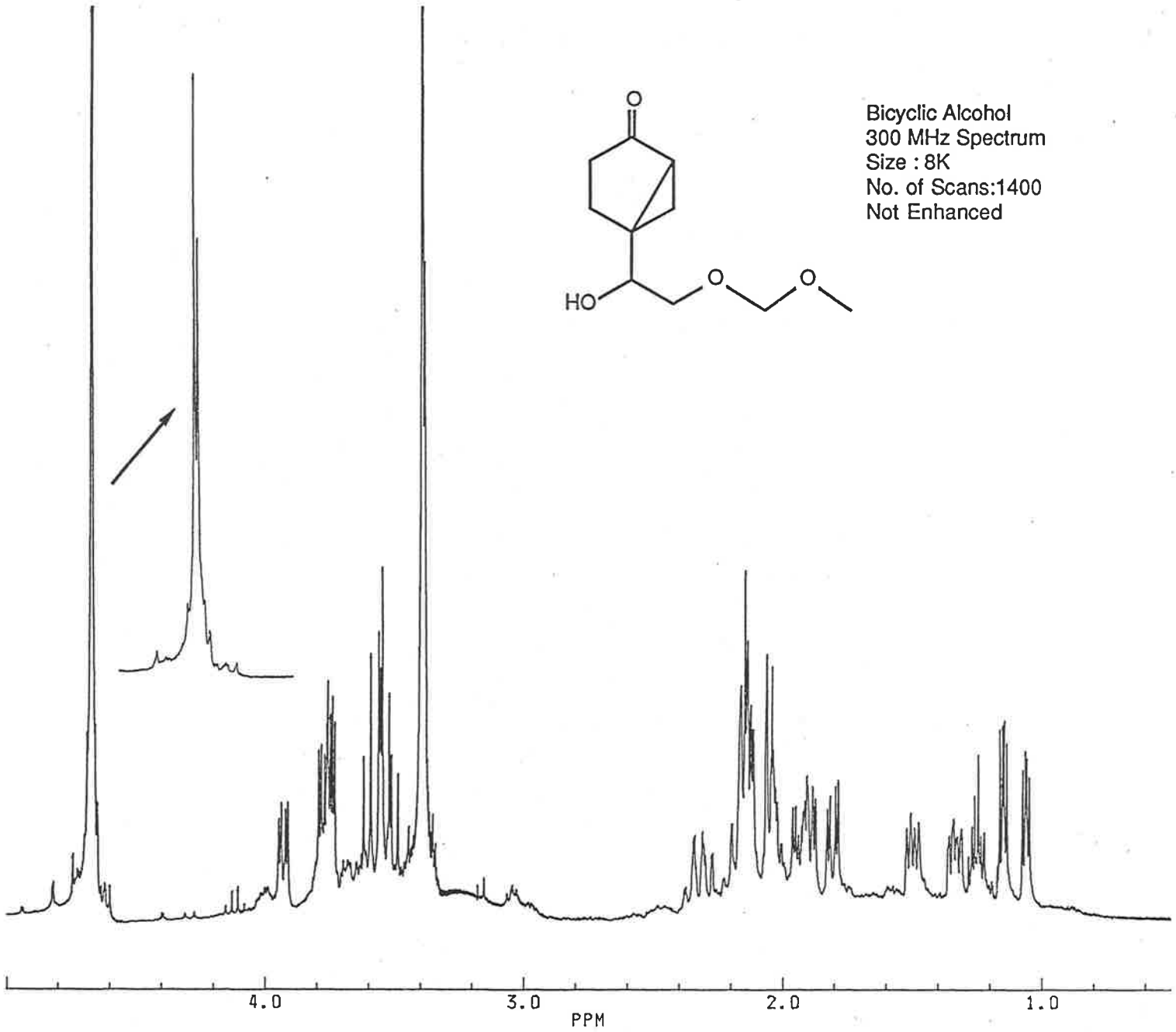
When the epoxide (120) in ethanol was treated with one equivalent of sodium hydride, the bicyclo[3.1.0]hexanone alcohol (121) was isolated by chromatography in 56% yield. Initially, sodium ethoxide (from ethanol and sodium hydride) was used as the

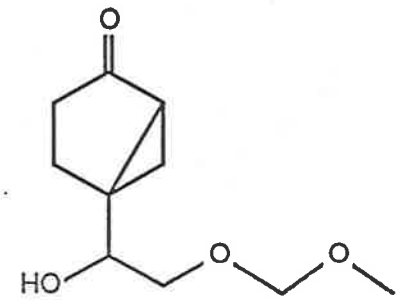
base in expectation that both pairs of diastereomers would be formed since the conditions would allow the equilibration of the first formed enolate anion. With this mixture, it was hoped that suitable analytical procedures could be developed which would allow a measure of the efficiency of the diastereoselection with hopefully more selective bases.

The alcohol (121) was significantly more polar than the epoxide. The 60 MHz NMR spectrum of the product was uninformative but the 300 MHz spectrum revealed a set of complex resonances at δ 1.0-1.5 due to the protons in the cyclopropane ring. A second set of complex resonances was observed at δ 1.6-2.3 which was assigned to the two methylene groups in the cyclopentanone ring of the bicyclic system. Sharp singlets at δ 3.33 and 4.61 indicated that the MOM ether moiety had been retained. A third complex area of resonances were observed between δ 3.3 and 4.0 from the methylene group bearing the MOM ether and the methine now bearing the hydroxyl group. (see spectrum overleaf)

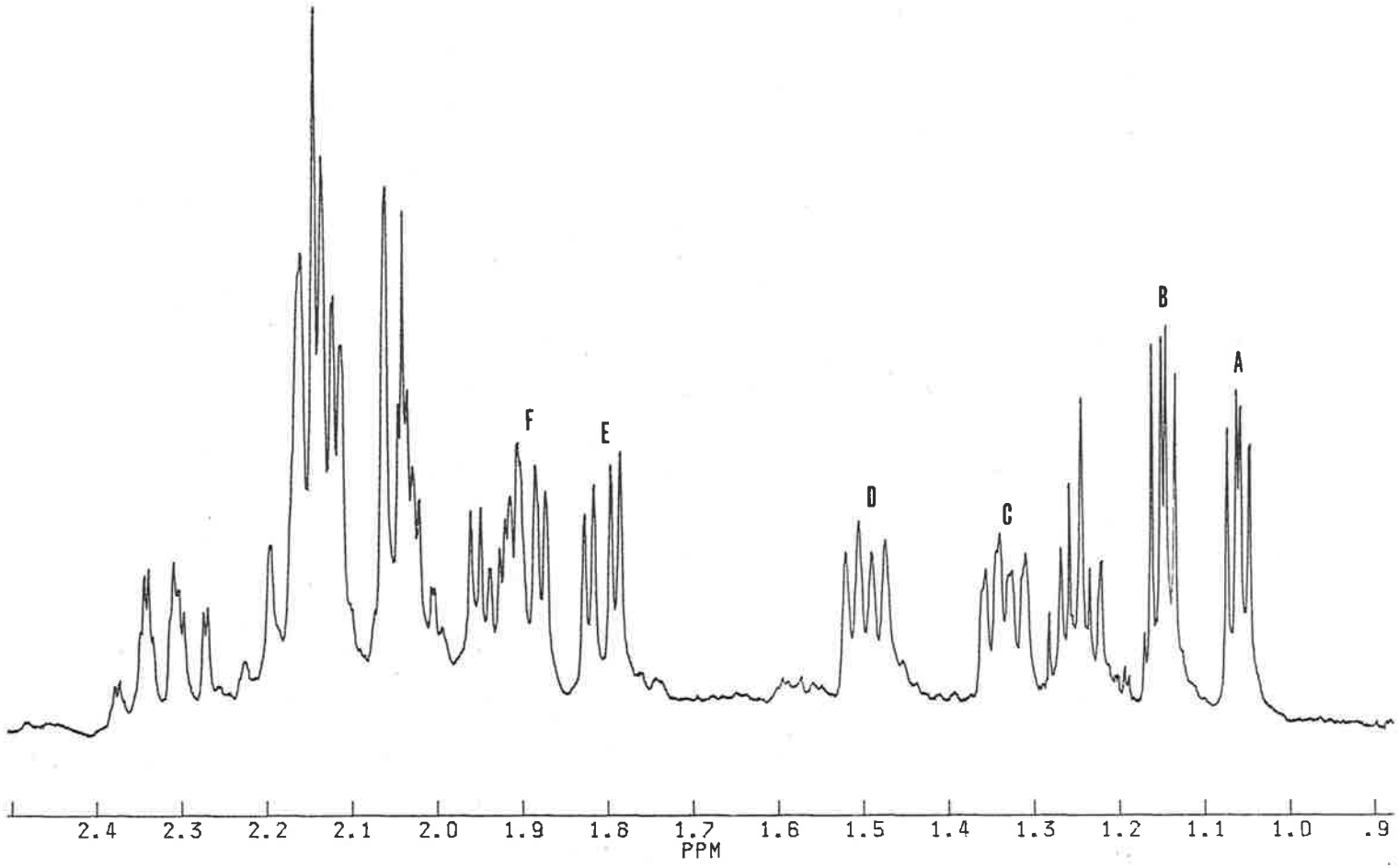


(120) (121)

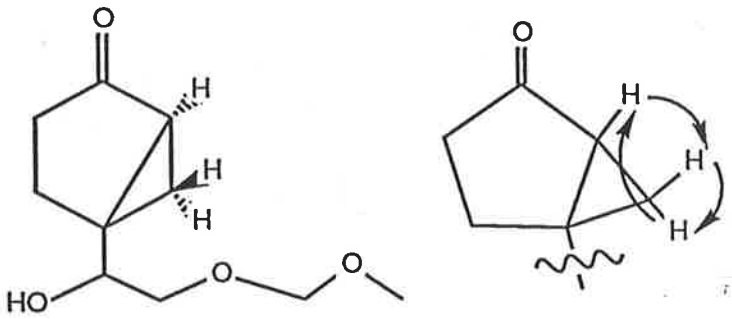

O
HO
O
O
Bicyclic Alcohol
300 MHz Spectrum
Size : 8K
No. of Scans:1400
Not Enhanced
4.0
3.0
2.0
1.0
PPM



Bicyclic Alcohol
300 MHz Spectrum
High Field Region



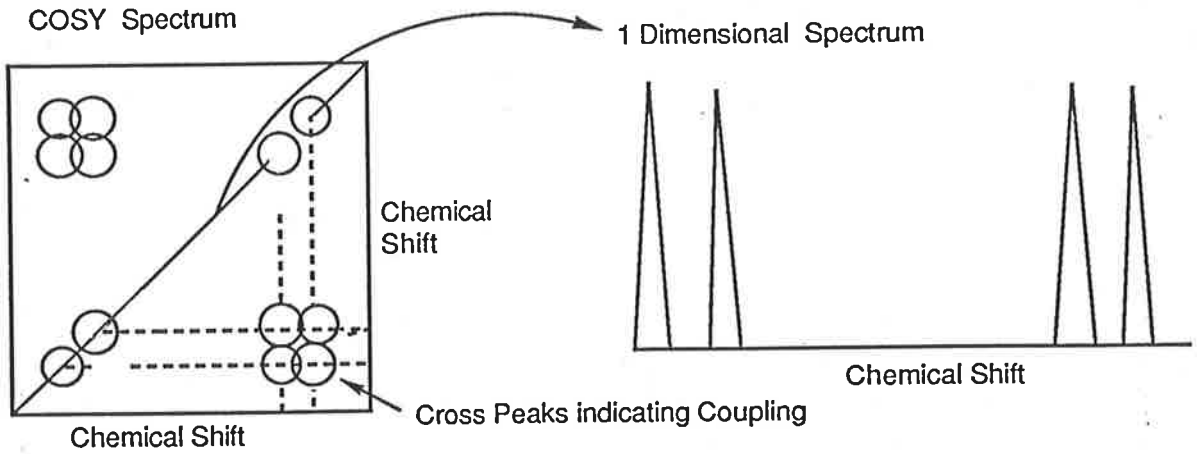
An examination of the expanded spectrum (page 75) revealed that there are 5 groups of resonances at the high field region. Each one of four of these sets of peaks (A to D) is most likely associated with one of the 4 different protons of the methylene groups of the cyclpropane rings in the mixture of diastereomers of the alcohols (121). A fifth peak in this area is possibly due to some degraded material since the alcohol (121) proved to be unstable in chloroform solution even over relatively short periods and the peak increased relatively with time. It is presumed that the degradation is catalysed by small amounts of hydrogen chloride present in the solvent. Both cyclopropyl ketone and MOM ether moieties are sensitive to acid. Each of the 4 major peaks in the high field region consist of 4 peaks which are arrayed in the form of a doublet of doublets. This is consistent with the coupling pattern expected for the cyclopropane protons. Each proton would be expected to be directly coupled only to the two other protons in the three membered ring.



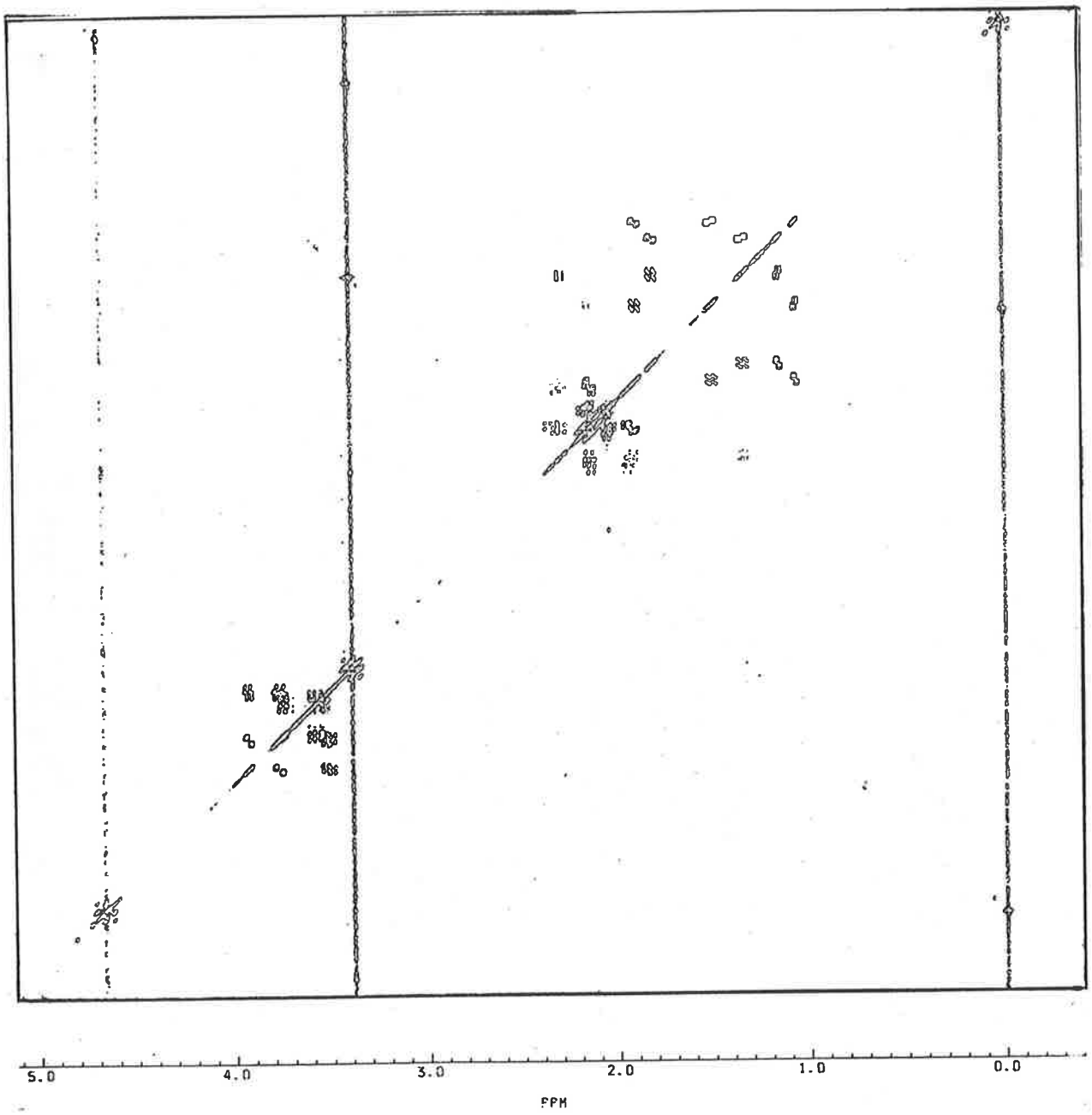
It was assumed that the pairs (A & B) and (C & D) represented signals from the two different diastereomers. Assignment of the

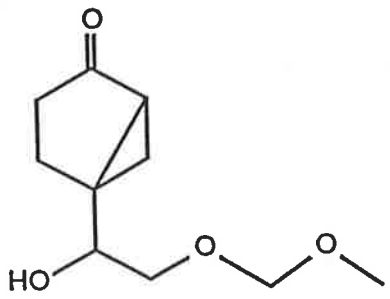
sets of peaks to one diastereomer pair or the other from this spectrum was not unambiguous. In order to monitor the diastereoselective synthesis of one of the diastereomers, an analytical system for the assessment of the relative ratios of stereoisomers was desired. Therefore, it was necessary to assign these peaks. The relative assignment might most easily be achieved by performing a NMR COSY experiment because this should reveal, in one experiment, which resonances are coupled to which. This two-dimensional technique proved to be the best and simplest way to distinguish between the different sets of diastereomers in the roughly equal mixture of all four isomers of the alcohol (121). The technique could not distinguish between the mirror image (enantiomeric) structures of the diastereomeric pairs that must, of necessity, be formed in equal amounts by this procedure.

A COSY (Correlated Spectroscopy) spectrum[50] is a two-dimensional spectrum in which the axes represent chemical shift. The diagonal represents the usual one dimensional spectrum. Peaks that are away from the diagonal arise from cross-coupling between two different resonances. A one-dimensional spectrum consisting of only two doublets would yield two "squares" of four peaks away from the diagonal in a COSY spectrum. Each of the peaks in the "squares" would be as a result of coupling between one of signals from each pair of doublets on the diagonal.

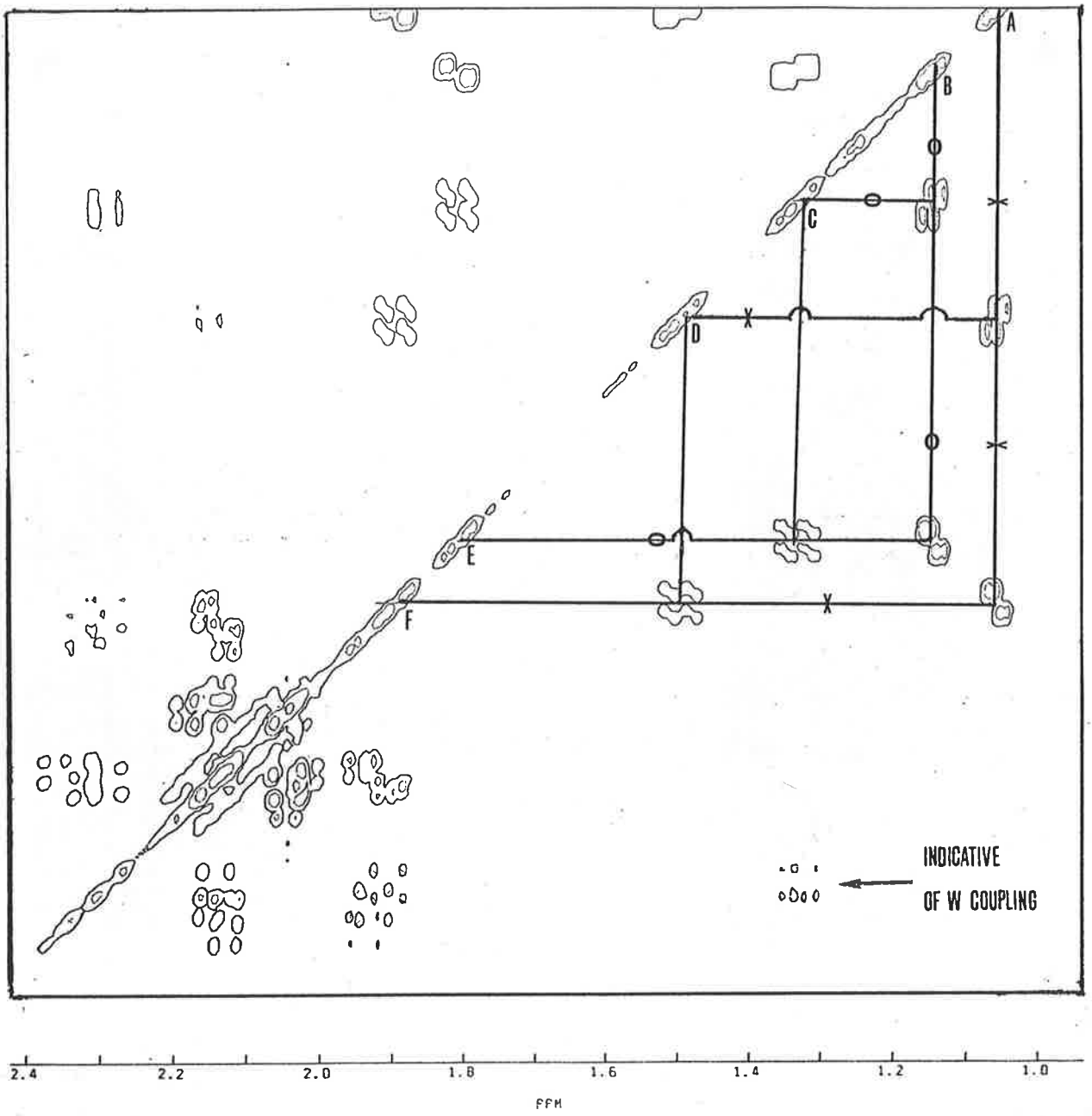


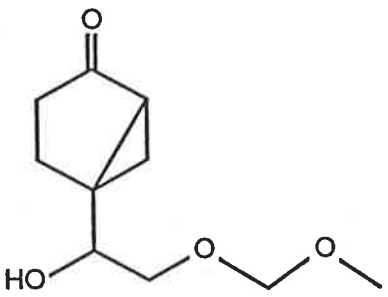
COSY spectra reveal the coupling patterns in complicated spin systems and in this case was of value in the determination of which peaks in the spectrum of the mix of diastereomers of the alcohol (121) belonged to which diasteromer pair. The COSY spectrum of the mixture of diastereomers can be seen overleaf. An expansion of the high field region of the spectrum from δ 1.0-2.4 showed clearly that six sets of peaks formed two separate triads (connected by either crossed or dotted lines). If the peaks are assigned the letters A to F starting at the high field end of the spectrum the peaks A, D & F (crossed line) form a triad as do the peaks B, C & E (dotted line).(see also spectrum on page 75) The coupling constants were measured and the positon on the three membered ring of each proton was determined by the use of chemical shift data[51] and the Karplus equation[51]. A large coupling constant would indicate that the two protons concerned are arrayed at about 0^0 to each other and are *cis* whereas a smaller coupling constant would imply a *trans* arrangement. The diasteromers were distinguished by NMR spectroscopy and their relative ratio could





Bicyclic Alcohol
300 MHz COSYSpectrum
SW :1661 Hz
F1: 512 Zero filled to 1K
F2: 2K
NS: 16
Recycle time : 1.5 sec
Standard Pulse sequence





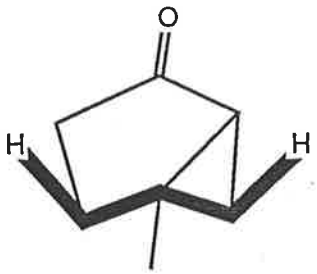
Bicyclic Alcohol
300 MHz COSYSpectrum
High Field Region

be determined by the integration of the peaks in the cyclopropane region.

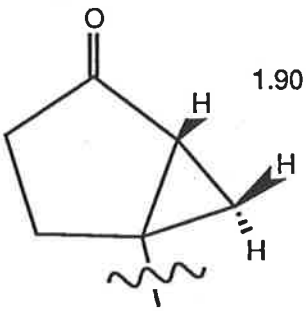
Table of chemical shift and approximate absolute coupling constants for the cyclopropane protons in the mixture of diastereomers of the alcohol (121).

Diastereomer pair #1	Diastereomer pair #2
Peaks A, D & F	Peaks B, C & E
A: δ 1.06	B: δ 1.15
D: δ 1.50	C: δ 1.34
F: δ 1.90	E: δ 1.81
$J_{A,F}$ = 4.5 Hz	$J_{B,C}$ = 3.0 Hz
$J_{A,D}$ = 4.0 Hz	$J_{B,E}$ = 5.0 Hz
$J_{F,D}$ = 10 Hz	$J_{E,C}$ = 11 Hz

N.B. The small residual coupling seen in the peak at δ 1.34 was as a result of long range W coupling[45] as revealed by the cross peaks in the COSY spectrum. (see diagram below)



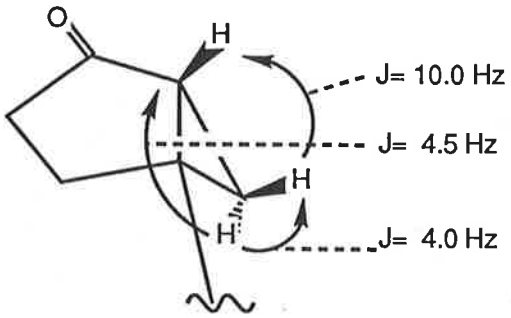
Diastereomer Pair #1



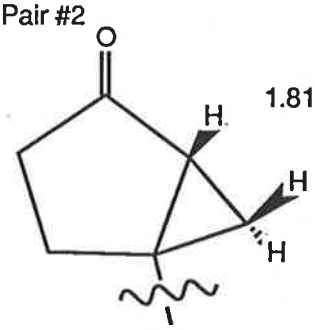
1.90 p.p.m. (F)

1.50 p.p.m. (D)

1.06 p.p.m. (A)



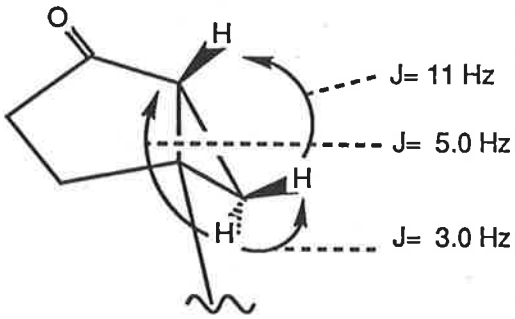
Diastereomer Pair #2



1.81 p.p.m. (E)

1.34 p.p.m. (C)

1.15 p.p.m. (B)



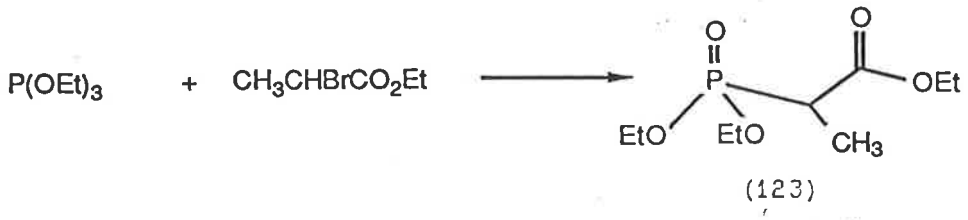
Examination of the expansion of the resonance at δ 4.61 due to the methylene group of the MOM ether moiety showed that there were two distinct peaks corresponding to the two sets of diastereomers. This was found not to be the case on expansion of the methoxy peak at δ 3.33. The shoulder on this peak was too small to represent a diastereomer and was thought to be an impurity. The relative integration of methylene peaks could be

used in addition to the ratio of integration of the cyclopropane peaks to determine the ratio of diastereomers if the base coordination scheme was attempted.

This reaction yielded much information. Firstly, it showed that the cyclopropane forming reaction proceeded in good yield to give the desired bicyclo[3.1.0]hexanone (121). Secondly, the NMR spectrum clearly showed that the different diasteromers of the alcohol (121) could be distinguished. The six cyclopropyl protons of the two different diastereomeric pairs all resonated at different chemical shifts. The MOM group was stable to the conditions and could possibly be a useful metal coordinating group if the epoxide scheme were to fail.

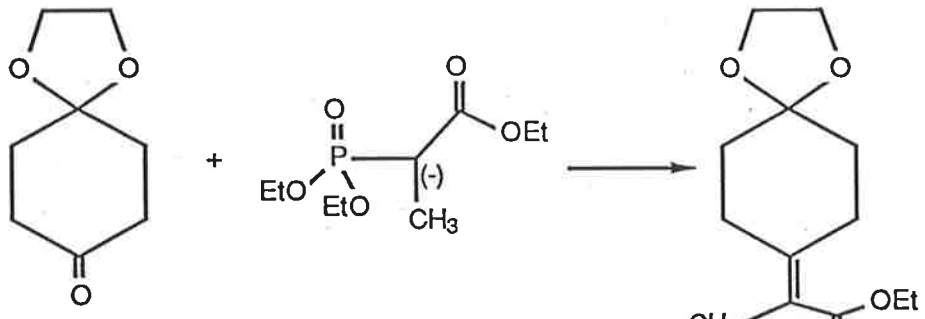
Attention was now turned from the system R = H to R = Methyl, a system that was thought would lead directly to the mononorterpene natural product, sabina ketone (12). The route to the allylic alcohol (122) required for the Sharpless epoxidation needed a simple modification to the synthetic scheme for the model system, (119) R = H.

Fistly, the mono acetal (114) of cyclohexane-1,4-dione was treated with triethyl phosphonopropionate (123). The Wittig Horner reagent (123) was synthesised by the method of Gallagher and Webb[57] by treatment of triethyl phosphite with ethyl



(123)

bromopropionate. The phosphonate was isolated as a colourless oil in 60% yield.

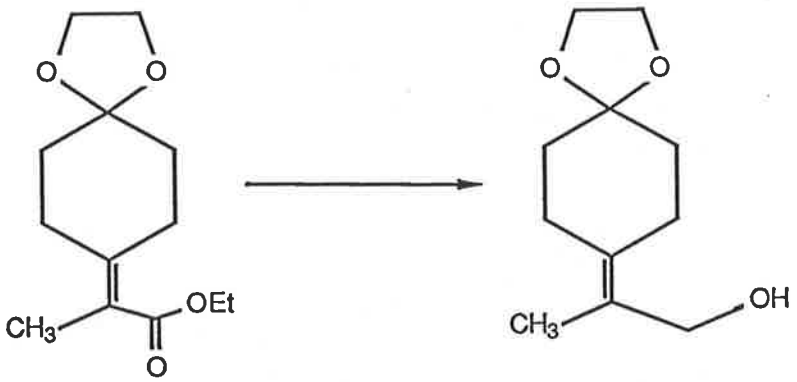


(114) (123) (124)

The ester (124) was obtained in 61% yield from a Wittig Horner reaction in a similar manner as that described for the preparation of the ester (117). The NMR spectrum of the ester (124) consisted of complex alkyl resonances at δ 2.0-2.8 from the cyclohexyl protons. There were triplet and quartet resonances at δ 1.30 and 4.18 associated with the ethoxy group. The singlet at δ 2.03 was assigned to the protons of the methyl group on the α carbon of the enone system. The 1,3-dioxolane protons were ascribed to the large singlet resonance at δ 3.98. The infra red spectrum contained a peak at 1700 cm^{-1} as a result of the absorption of the unsaturated ester carbonyl double bond. The peak recorded at *m/z* 240 in the mass spectrum was consistent with the molecular ion.

Lithium aluminium hydride reduction of the ester (124) proceeded without incident to afford the alcohol (125) in 91% yield. As a colourless oil, the alcohol (125) possessed the

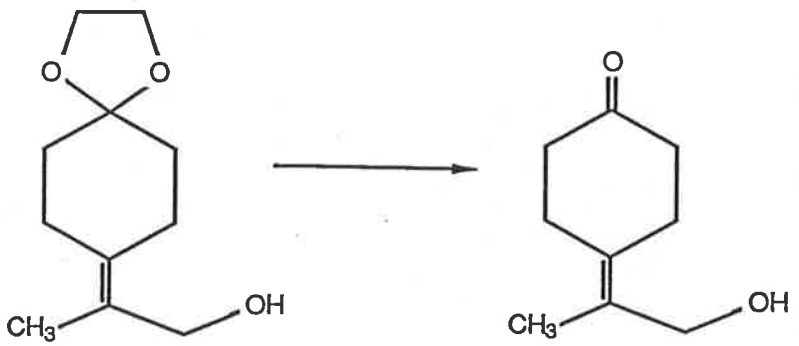
following spectral properties; the infra red spectrum showed an absorption at 3300 cm^{-1} indicative of the presence of a hydroxyl group. The NMR spectrum exhibited singlet resonances at δ 1.76, 3.90 and 4.06 which were assigned in order, to the protons of the methyl group attached to the double bond, the 1,3-dioxolane ring, and the allylic methylene group bearing the hydroxyl moiety. The molecular formula was verified by the presence in the mass spectrum of a peak at *m/z* 198 which was designated as the molecular ion.



(124) (125)

The acetal alcohol (125) was found to be particularly sensitive to acid. Hydrolysis of the acetal protecting group was accomplished over night by the use of wet acetone with oxalic acid. This yielded what was presumed to be an equilibrium mixture of the acetal (125) and the keto ol (122) which were separated by chromatography. The ketone was obtained in 73% yield. The recovered acetal could be resubjected to the hydrolysis conditions. The infra red spectrum of the keto ol (122) included

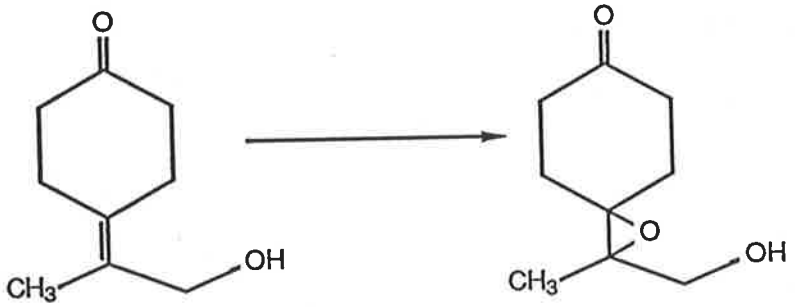
strong absorptions at 3300 cm^{-1} from the hydroxyl group and 1700 cm^{-1} from the keto group. In the NMR spectrum of the keto ol (122) the singlet resonances at δ 1.76 and 4.00 were ascribed to the methyl group attached to the double bond and the methylene group of the allylic alcohol moiety respectively. The mass spectrum contained a very small peak at *m/z* 154 corresponding to the molecular ion. The major peak in the spectrum at *m/z* 136 corresponds to the loss of water from the molecular ion.



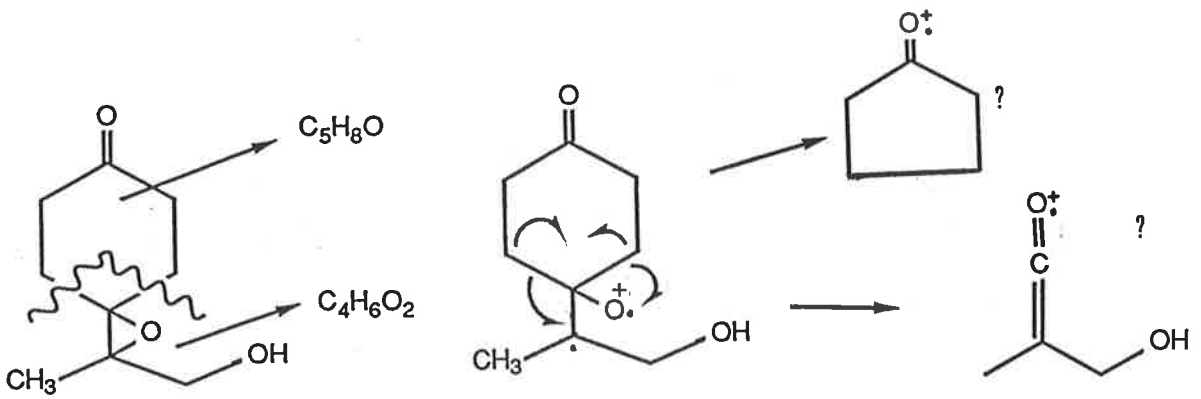
(125) (122)

With the key compound now in hand, trial reactions to find the best conditions to effect diastereoselection for one of the diols were conducted with racemic material. The allylic alcohol (122) was epoxidised with 3-chloro peroxybenzoic acid at low temperature to afford the racemic epoxide (126) in 80% yield. This also served to provide material with which to develop an analytical procedure whereby the determination of the enantiomeric excess obtained in the Sharpless epoxidation could be ascertained. The NMR and mass spectra provided the basis for

confirmation of the identity of the product. A methyl singlet was observed in the NMR spectrum at δ 1.47. The methylene protons that formed part of the hydroxy methyl group gave rise to a singlet resonance at δ 3.68. No peak in the mass spectrum corresponding to the molecular ion was observed. The major peaks that were present in the mass spectrum were at *m/z* 86 and 84 which meant that the molecule must have undergone a complex skeletal rearrangement to give two roughly equally massive daughter ions. They may be due to ions with molecular formulae $C_4H_6O_2$ for *m/z* 86 and C_5H_8O for *m/z* 84 possibly derived as outlined below.



(122) (126)

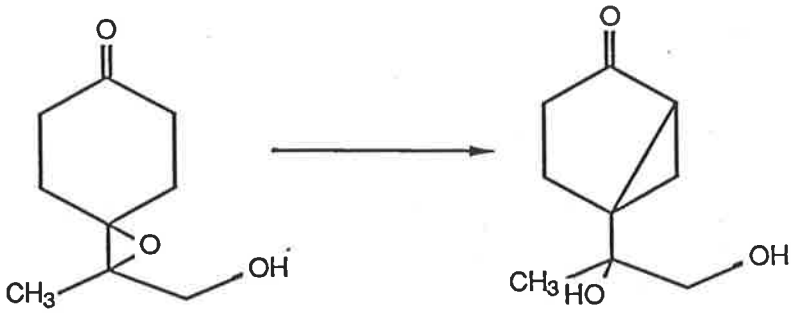


The first priority was to produce the diol (127) from the epoxide (126) without emphasis on diastereoselection. This was in order to show that the reaction actually occurred. The NMR spectrum of an equal mixture of the diastereomers might also show differences in chemical shift between pairs of diastereomers which would allow the relative amounts of the diastereomers to be quantified.

The epoxide (126) was treated with powdered potassium t-butoxide in dry THF at room temperature for 24 hours and afforded the bicyclo[3.1.0]hexanone diol (127) in 12% yield. The compound (127) was found to be extremely water soluble so care was taken to perform the reaction in such a way that the diol could not be fractionated or lost through aqueous washing. When the base was added to the epoxide solution, a brown precipitate was instantly formed. When the reaction was worked up by addition of a small amount of acetic acid, the precipitate instantly dissolved. It was thought that this precipitate was the alkoxide salt (100)(R= Methyl).

The infra red spectrum showed strong absorptions at 3500 cm^{-1} arising from the hydroxyl moieties and at 1710 cm^{-1} arising from the bicyclo[3.1.0]hexanone ring carbonyl group. The mass spectrum showed a small peak at *m/z* 170 corresponding to the molecular ion and also a larger peak at *m/z* 139 corresponding to loss of CH_2OH from the side chain of the molecule.

The poor yield of the diol (127) was disappointing when the relatively high yield for the alcohol methoxymethyl ether (121) was recalled. The diol (127) was isolated from the crude material by chromatography with ethyl acetate as the eluent. Significant amounts of material were not eluted before the elution of the

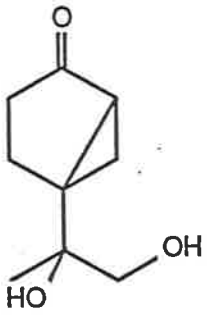


(126) (127)

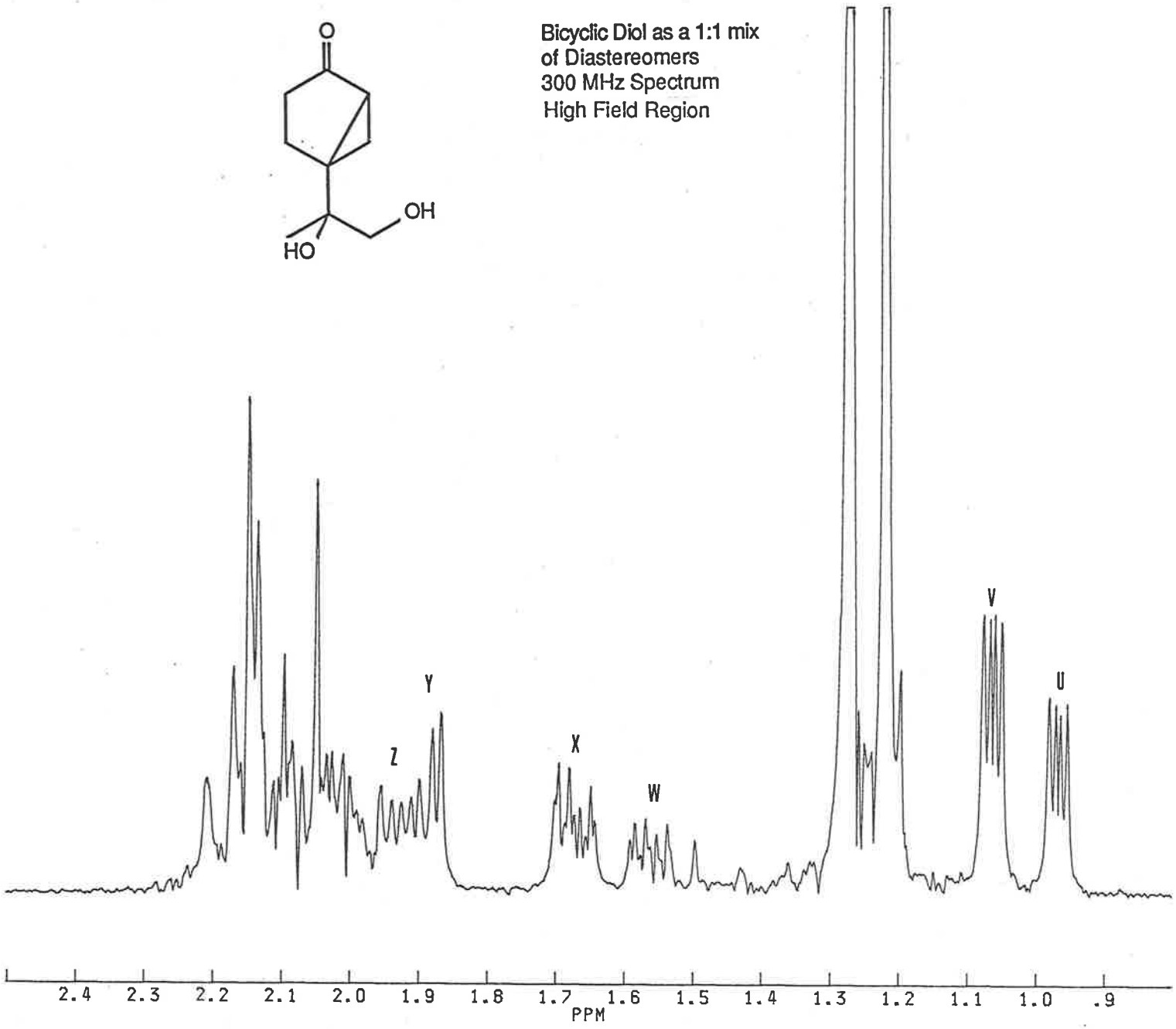
diol (127). It appeared that any byproducts were more polar than the diol and were retained on the column.

The 300 MHz spectrum (see overleaf) of the diol (127) showed similarities to that of the alcohol (121). At least five of the six sets of peaks that corresponded to the cyclopropane protons were clearly discernible. The methyl groups of the two different sets of diasteromers resonated at δ 1.21 and 1.26. The 4 protons that formed a part of the cyclopentanyl ring were assigned to the complex area of resonances at δ 1.8-2.2. The methylene group bearing the hydroxyl moiety was expected to form an AB quartet. The two different diastereomer pairs gave rise to two sets of AB quartets centred firstly at δ 3.50 and 3.61 and secondly at δ 3.54 and 3.70 (vide infra).

The two dimensional COSY spectrum again provided a method to



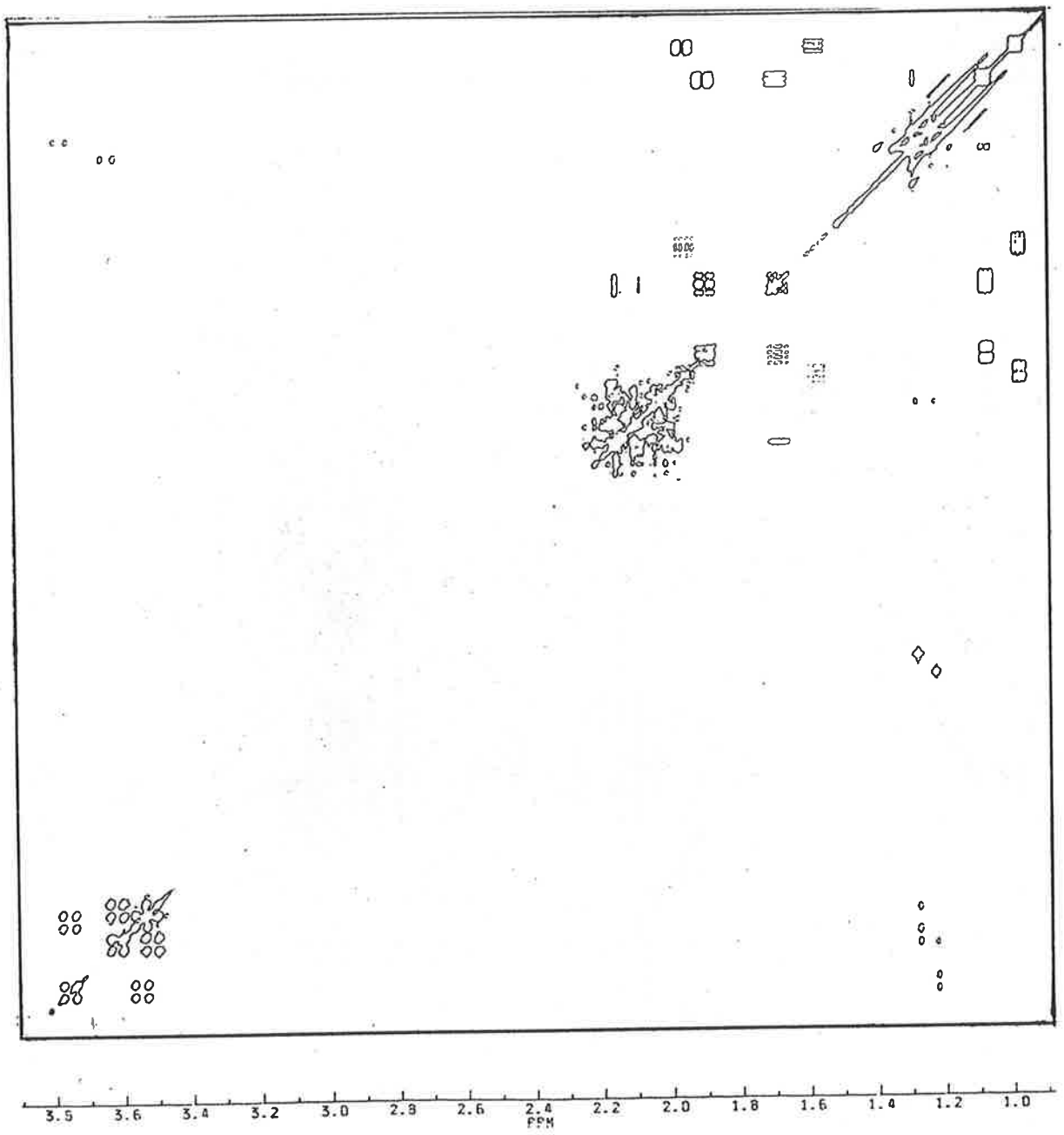
Bicyclic Diol as a 1:1 mix
of Diastereomers
300 MHz Spectrum
Size :16 K
No. of Scans:128
Enhanced

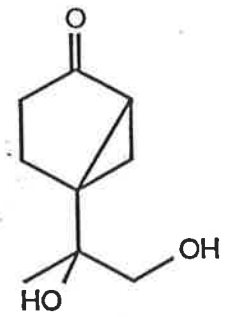

O
OH
HO
Bicyclic Diol as a 1:1 mix
of Diastereomers
300 MHz Spectrum
High Field Region
Z
Y
X
W
V
U
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
.9
PPM

determine which peaks belong to which diastereomer pairs. The COSY spectrum of the mixture of diastereomers of the diol (127) is reproduced on the next page. The peaks at the high field end of the spectrum (disregarding the two methyl singlet peaks) were assigned the letters U to Z. The COSY spectrum showed peaks U, W & Z formed a triad and V, X & Y formed another triad. The two AB quartets at δ 3.5-3.7 were able to be assigned as above (see expansion of the AB quartet region of COSY spectrum). The correlation of a set of AB quartet resonances with a particular set of cyclopropane and methyl protons from a diastereomer pair was determined from the COSY spectrum as each resonance from a methyl group showed some long range coupling to only one of the AB quartets.

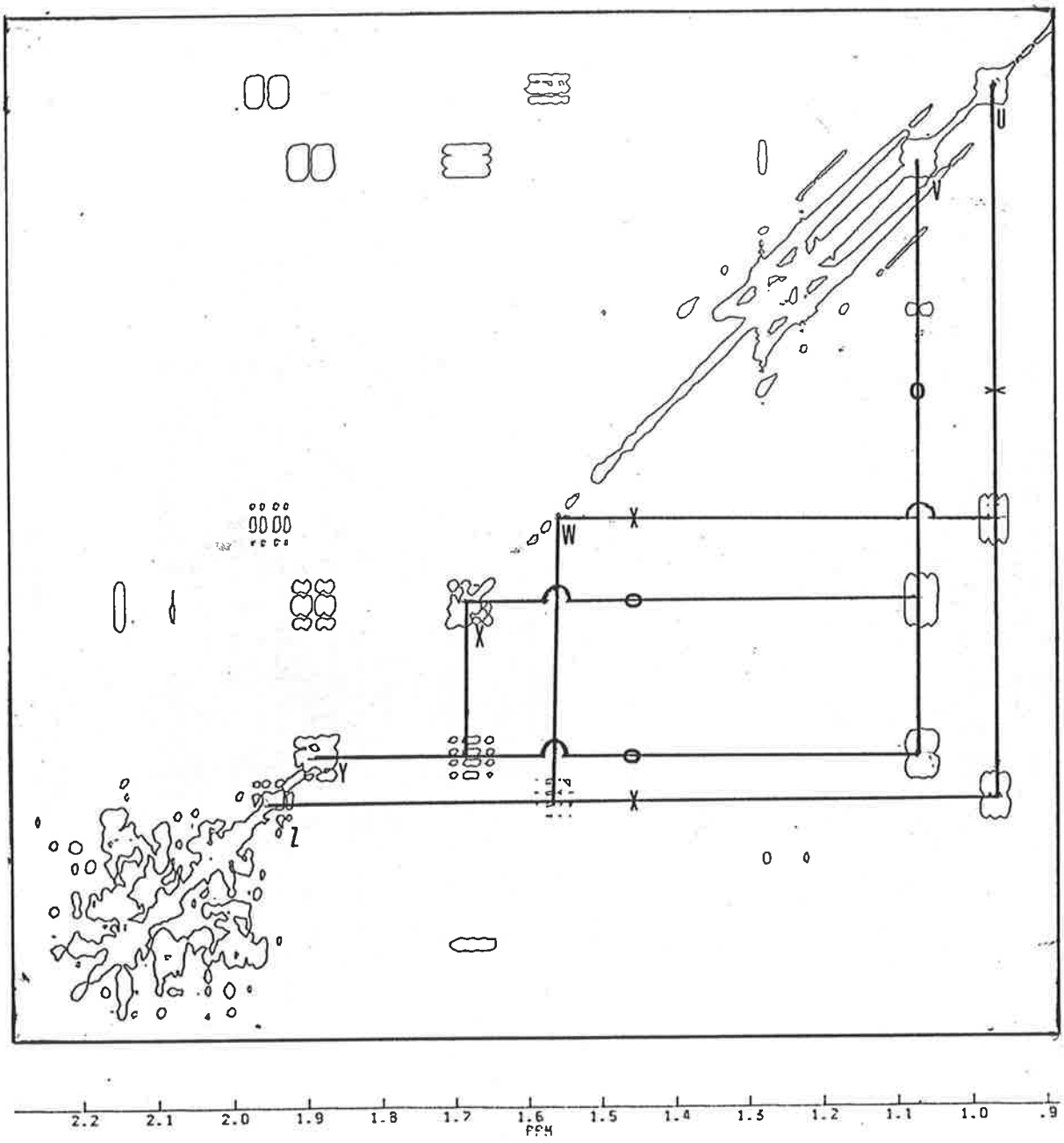
Table of chemical shift and approximate absolute coupling constants for the cyclopropane protons in the mixture of diastereomers of the diol (127).

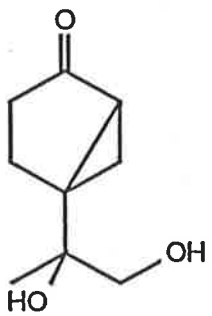
Diastereomer pair #1	Diastereomer pair #2
Peaks U, W & Z	Peaks V, X & Y
U: δ 0.95	V: δ 1.02
W: δ 1.56	X: δ 1.67



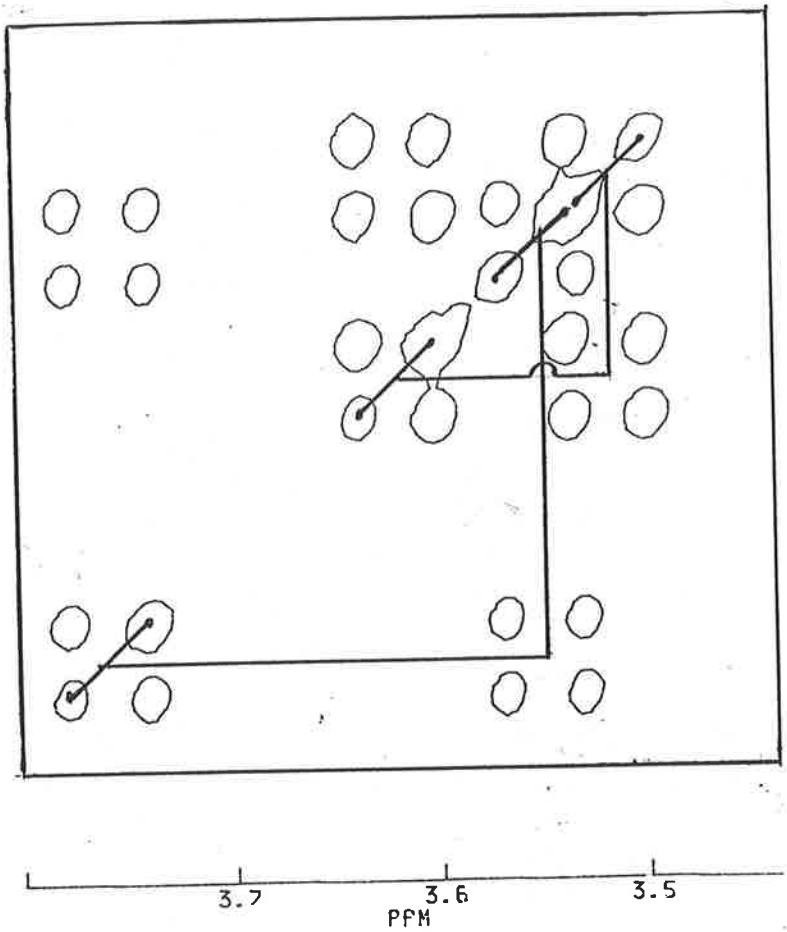


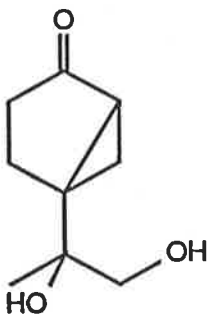
Bicyclic Diol as a 1:1 mix
of Diastereomers
300 MHz COSYSpectrum
SW: 1661 Hz
F1:512 Zero filled to 1K
F2:2K
NS:16
Recycle time :1.5 sec
Standard Pulse Sequence





Bicyclic Diol as a 1:1 mix
of Diastereomers
300 MHz COSYSpectrum
High Field Region



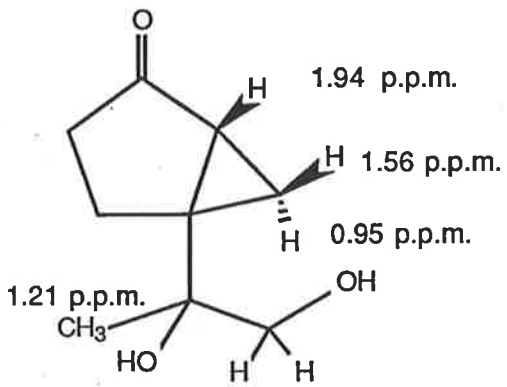


Bicyclic Diol as a 1:1 mix
of Diastereomers
300 MHz COSYSpectrum
AB quartet Region

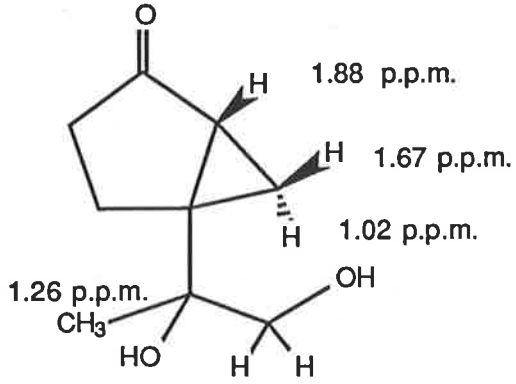
Z: δ 1.94	Y: δ 1.88
methyl δ 1.21	methyl δ 1.26
AB quartet δ 3.54	AB quartet δ 3.50
3.70	3.61
$J_{U,W}$ = 5.0 Hz	$J_{V,X}$ = 5.0 Hz
$J_{W,Z}$ = 9.0 Hz	$J_{X,Y}$ = 9.0 Hz
$J_{U,Z}$ = 3.0 Hz	$J_{V,Y}$ = 3.0 Hz

A 300 MHz NMR spectrum of a mixture of the diastereomers of the diol (127) could be used to determine the ratio of the isomers by comparison of the integration values for the appropriate peaks in the cyclopropyl, methyl and AB quartet areas of the spectrum.

Diastereomer Pair #1 (Minor Diastereomers)



Diastereomer Pair #2 (Major Diastereomers)



It now became of interest to attempt diastereoselectivity for the formation of the bicyclo[3.1.0]hexanones (127). It was

thought that at high dilution, addition of a strong base to the alcohol would allow the alkoxide (100 R = Methyl) to react exclusively in an intramolecular sense. The reaction might require some extra thermal energy above that which it posesses at room temperature to allow the deforming of the molecule into a shape in which the proton transfer may take place with facility. Thus, the first trial reaction (trial #1) was conducted in a similar manner to the reaction described on page 88. There were two modifications. The first was that the reaction was conducted at high dilution and the second was that it was performed at reflux temperature (67^0). The diol was obtained in 15% yield. The 300 MHz NMR spectrum was used to determine the success of the diastereoselection by calculating the integration ratio of the cyclopropane protons U, W & Z versus V, X & Y, the two methyl peaks at 1.2 and the two AB quartets at 3.5.

For the first trial, the diastereomeric ratio was calculated to be 2.2:1 which meant that 69% of the diol mixture was one racemic diastereomer. This was encouraging for it showed that it was possible to influence the diastereomer ratio by modifying the reaction conditions.

The low yield was considered a serious problem and it was thought that the 1 hour reflux could have contributed to the loss of the diol through thermolysis or base catalysed intermolecular condensations so the reaction was repeated in trial #2 but the mixture was refluxed for only 15 minutes. The diol was obtained

in 12% yield and more significantly, the diastereomer ratio was lowered to 1.7:1. The longer period of reflux did not significantly affect the yield. The reaction to form the cyclopropane ring appeared to be rapid.

The base that was thought to be the most appropriate for diastereoselectivity was sodium hydride which was presumed would react quickly and cleanly with the epoxide to form the alkoxide. A solvent with more dissoving ability and hence polarity might dissolve the brown ionic precipitate refered to on page 88. The dissolution of the solid and presumably crystalline alkoxide precipitate might facilitate its uptake of the desired conformation to allow proton transfer to take place. 1,2-Dimethoxyethane was the solvent in trial #3 and pelletised sodium hydride was the base as it was convenient to weigh out and handled. After the reflux period of a day, none of the sodium hydride pellets appeared to have reacted. One equivalent of potassium t-butoxide was added at once in an attempt to force some reaction to take place. The brown precipitate was again formed. The reaction did proceed to yield 17% of the diol mixture in a ratio of 3.1:1.

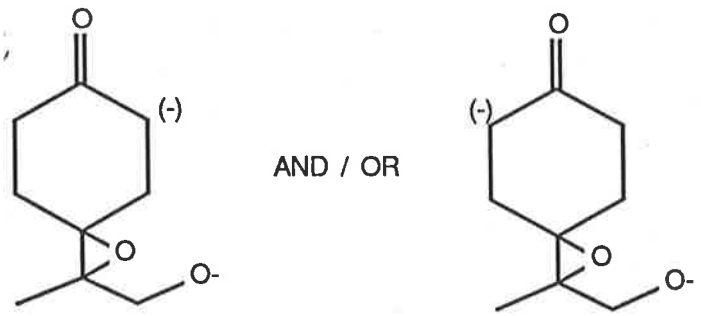
This was an encouraging result but it could not be determined if the relatively good result was influenced by the presence of the sodium hydride or not. The reason for the result of trial #3 needed to be clarified. In trial #4, the solvent was 1,2-dimethoxyethane and the base was powdered sodium hydride. The

powdered form of the base was thought to react more quickly than the pellets as the acid base reaction occurs at the surface of the metal hydride. This trial yielded the diol (127) in a lowly 10% yield with a poor diastereomer ratio of 1.3:1. Evidently, potassium t-butoxide was a more appropriate base than was sodium hydride.

In trial #5, t-butanol was used as the solvent. It was considered that this would be an even better solvent for dissolution of the potassium alkoxide precipitate than was 1,2-dimethoxyethane. The solvent had the possible disadvantage of being a protic solvent, allowing equilibration of anions with the solvent. The epoxide concentration was kept high with respect to the base by perfusing the base into the epoxide solution over a 9 hour period. Under these conditions, a large concentration of the enolate anion can not be formed at any stage. The existence of this large concentration was thought to be responsible for the low yield through aldol reactions. The result was disappointing with a 10% yield of a mixture of 1.5:1 of the diastereomers recovered. These conditions would not favour the base acting in a kinetic manner and the diastereomer rate reflected this.

A change of approach was employed in trial #6 in which the epoxide was perfused into a solution of potassium t-butoxide in 1,2-dimethoxyethane. In this case the epoxide concentration was always low (effectively infinite dilution) with respect to the base concentration. As such, there was a small possibility of

forming a small amount of the alkoxide enolate dianion (128) though at high dilution this was considered unlikely. The trial was not a great success with 12% of the diol (127) being isolated. The diastereomer ratio was found to be 2.0:1.



(128)

Trial #7 was conducted with the aim of keeping the base concentration low with respect to the epoxide concentration for a long period of time as in trial #5. This was done by perfusing the base solution into the large volume of a dilute solution of the epoxide (126). In this case however, the solvent (1,2-dimethoxyethane) was aprotic, precluding the equilibration of anions with the solvent. The yield was 15%, a little higher than most of the other trials but the more important diastereomer ratio was the lowest at 1.1:1. From this result, it was clear that the reaction would have to be be carried out rapidly.

Trial #8 was performed in a similar manner as was the most successful trial, #3. Potassium t-butoxide was added to a dilute solution of the epoxide in 1,2-dimethoxyethane. The initial 30 seconds of stirring of the reaction was not efficient as the stirring bar momentarily ceased to stir. In spite of this, the

diol was recovered in 9% yield but the ratio was an encouraging 2.4:1.

In the last trial, trial #9, special care was taken so that the potassium t-butoxide was thoroughly mixed with the epoxide at the commencement of the reaction. The care was rewarded with a 9% yield of the diol containing 82% of one racemic diastereomer. This corresponded to a ratio of 4.7:1. This result was considered high enough for the procedure to be attempted on the homochiral epoxide (129).

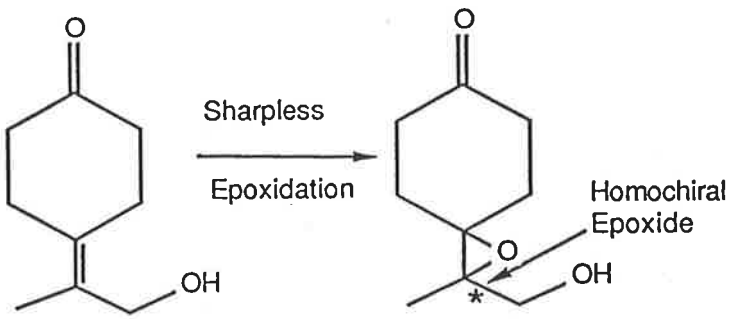
Table of Results for the Diastereoselectivity trials for the diol (127)

Trial No	Solvent	Base	Mode of Addition	% Yield	Isomer ratio
#1	THF	KBuO	base to (126) rapid 1H reflux	15	2.2:1
#2	THF	KBuO	base to (126) rapid 15' reflux	12	1.7:1
#3	DME	NaH+ KBuO	base to (126) rapid 1D reflux	17	3.1:1
#4	DME	NaH	base to (126) rapid 1D reflux	10	1.3:1

#5	BuoH	KBuO	base to (126) perfused 9H	10	1.5:1
#6	DME	KBuO	(126) to base perfused 9H	12	2.0:1
#7	DME	KBuO	base to (126) perfused 9H	15	1.1:1
#8	DME	KBuO	base to (126) rapid poor mixing	9	2.4:1
#9	DME	KBuO	base to (126) rapid good mixing	9	4.7:1

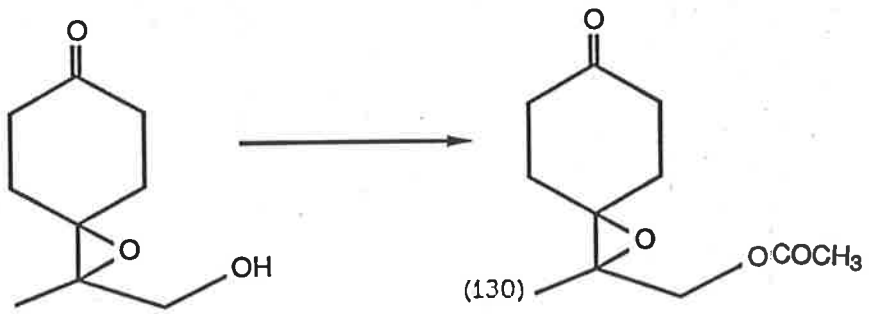
The allylic alcohol (122) was treated with t-butyl hydroperoxide, titanium tetra*iso*propoxide and (+) diethyl tartrate under the conditions described for the Sharpless epoxidation for water soluble epoxides[53]. The epoxide was isolated in 95% yield and the NMR spectrum was identical to that of the racemic material.

In order to determine the enantiomeric excess of the epoxide, a study of the acetate derivative (130) of the epoxide with a



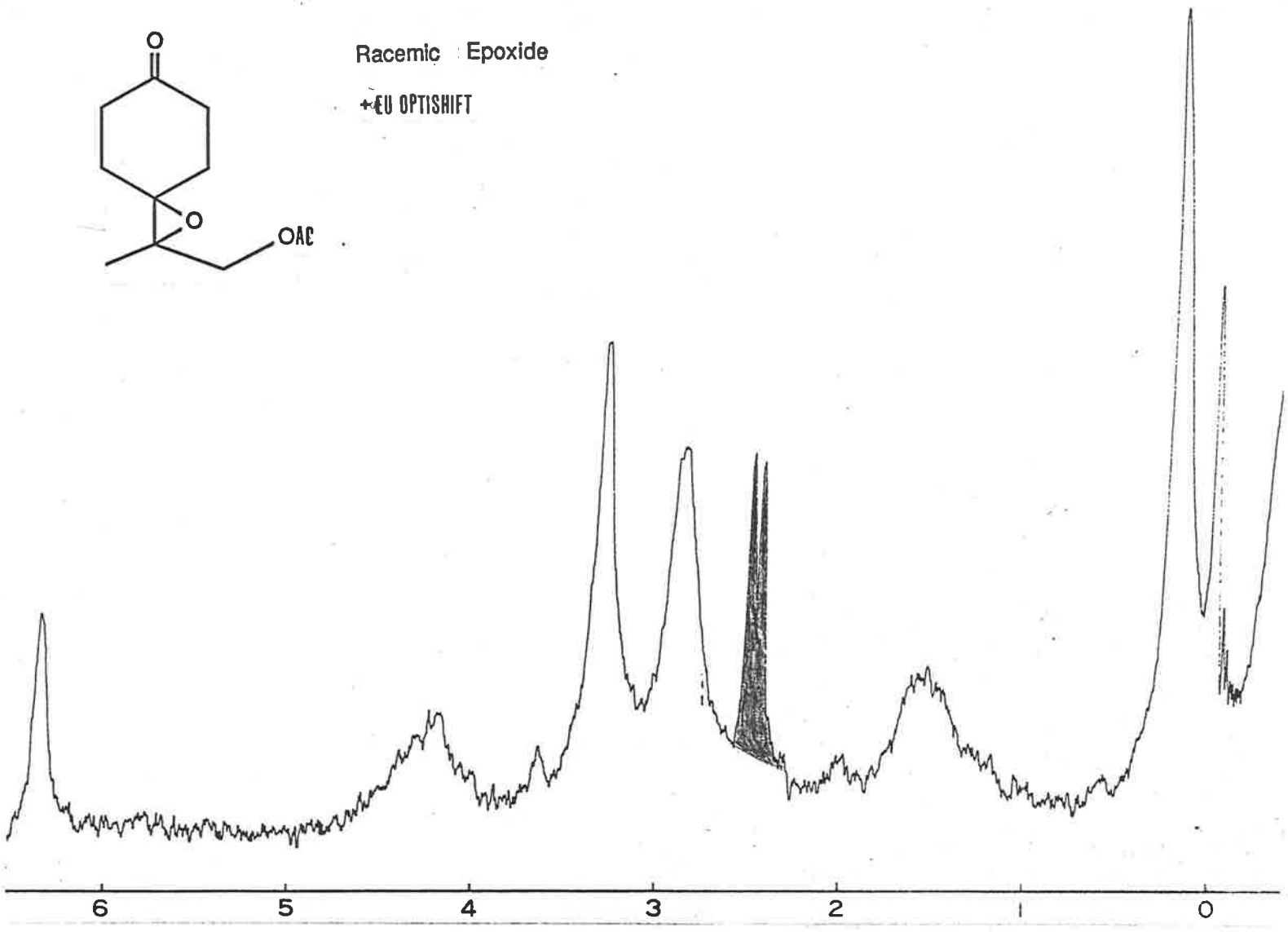
(122) (129)

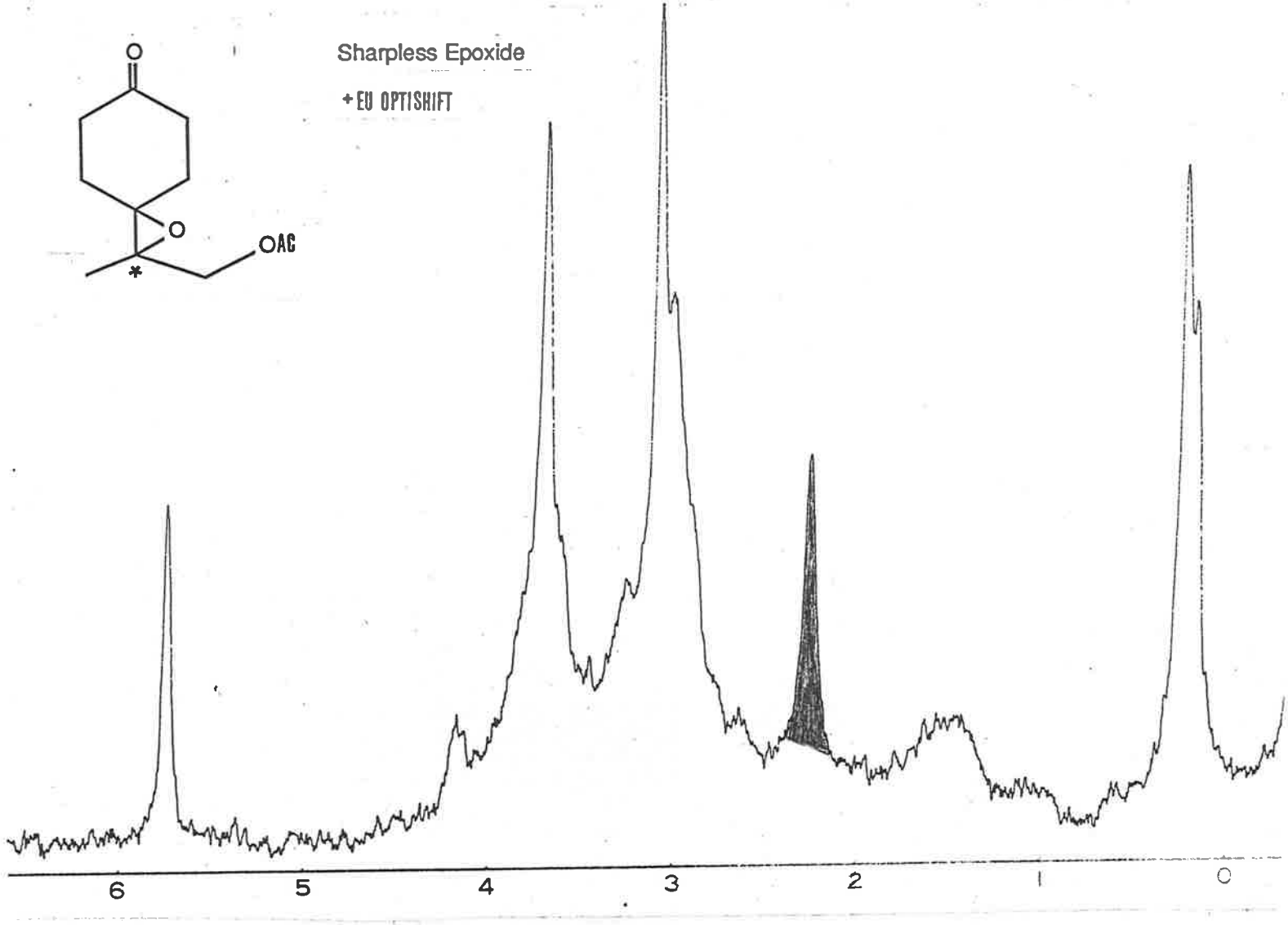
chiral shift reagent was made. With the addition of a chiral shift reagent to solutions of the acetate derivatives from the symmetric and asymmetric epoxidations, two peaks corresponding to the methyl group attached to the epoxide ring were observed in the NMR spectrum of the racemic epoxide (126) whereas essentially one peak was observed in the spectrum of the epoxide from the sharpless epoxidation (see overleaf). However, the chemical shift



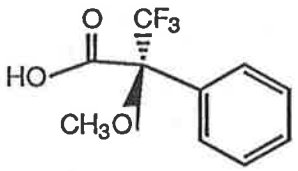
difference between the two diastereomeric methyl groups was too small for a quantitative determination. The peaks could not be separated without the loss of resolution.

The epoxide was converted to its Mosher's acid ester. Mosher's acid[54] (131) is a simple homochiral acid which possesses a trifluoromethyl group. When racemic alcohols are


O
O
OAC
Racemic Epoxide
+EU OPTISHIFT
6
5
4
3
2
1
0

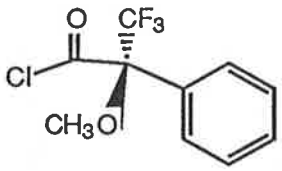

Sharpless Epoxide
+EU OPTISHIFT
O
O
OAc
*
6
5
4
3
2
1
0

esterified with the acid chloride (132) of Mosher's acid, diastereomeric esters are produced. ^{19}F NMR can normally be used to determine the amounts of the diastereomers present as the trifluoromethyl groups in the different diastereomers usually resonate at markedly different chemical shifts.



S - (-) Mosher's Acid

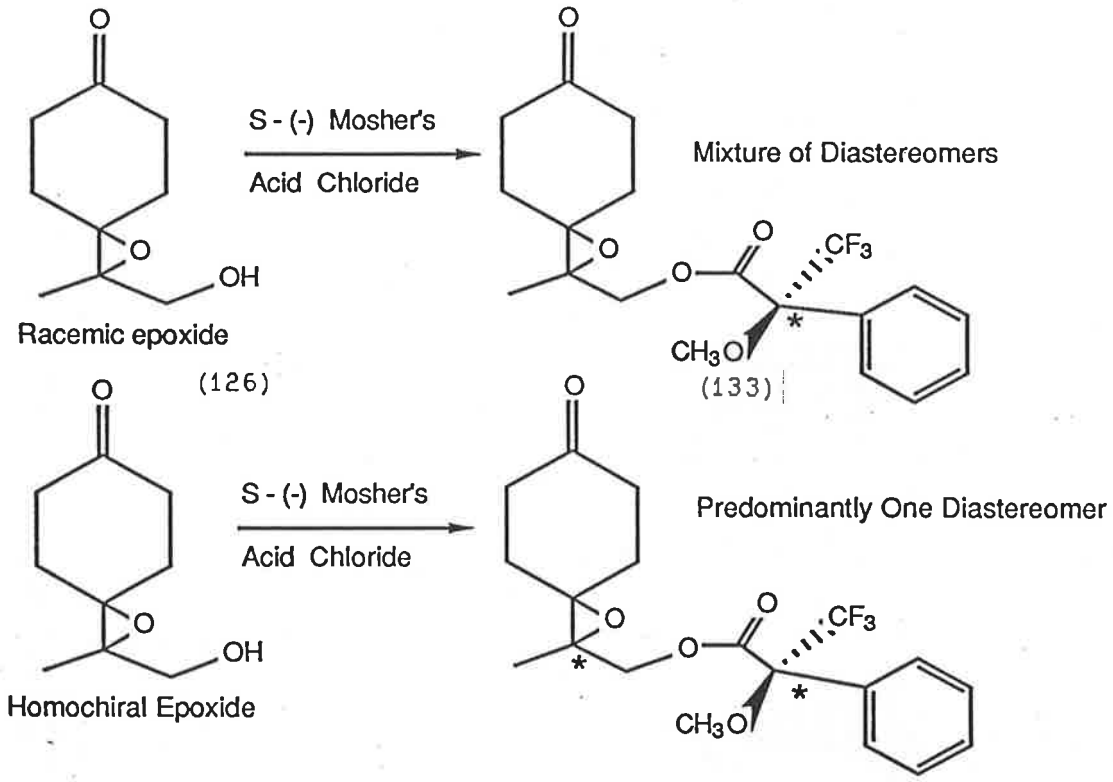
(131)



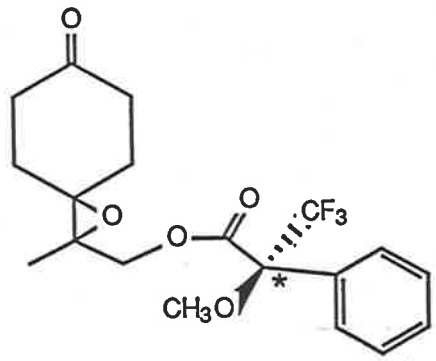
(132)

Both the epoxide (129) from the Sharpless procedure and the racemic epoxide (126) from the achiral 3-chloro peroxybenzoic acid epoxidation were esterified with the acid chloride (132) in the manner described by Dale, Dull and Mosher[54]. The esters (133) were derived from the racemic epoxide (126) and the esters (134) were from the epoxide (129) from the Sharpless enantioselecive epoxidation. The fluorine spectrum of the esters (133) from the racemic epoxide exhibited only a single resonance at 8.53 p.p.m. downfield from trifluoroacetic acid. The esters (134) from the homochiral epoxide had precisely the same ^{19}F NMR spectrum. Fortunately, the ^{1}H spectrum provided the data from wich the enantiomeric excess was calculated.

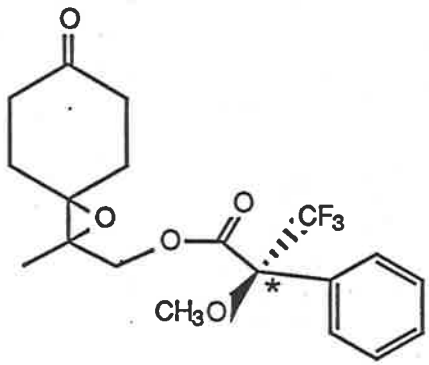
The 300 MHz spectrum of firstly the esters (133) derived from



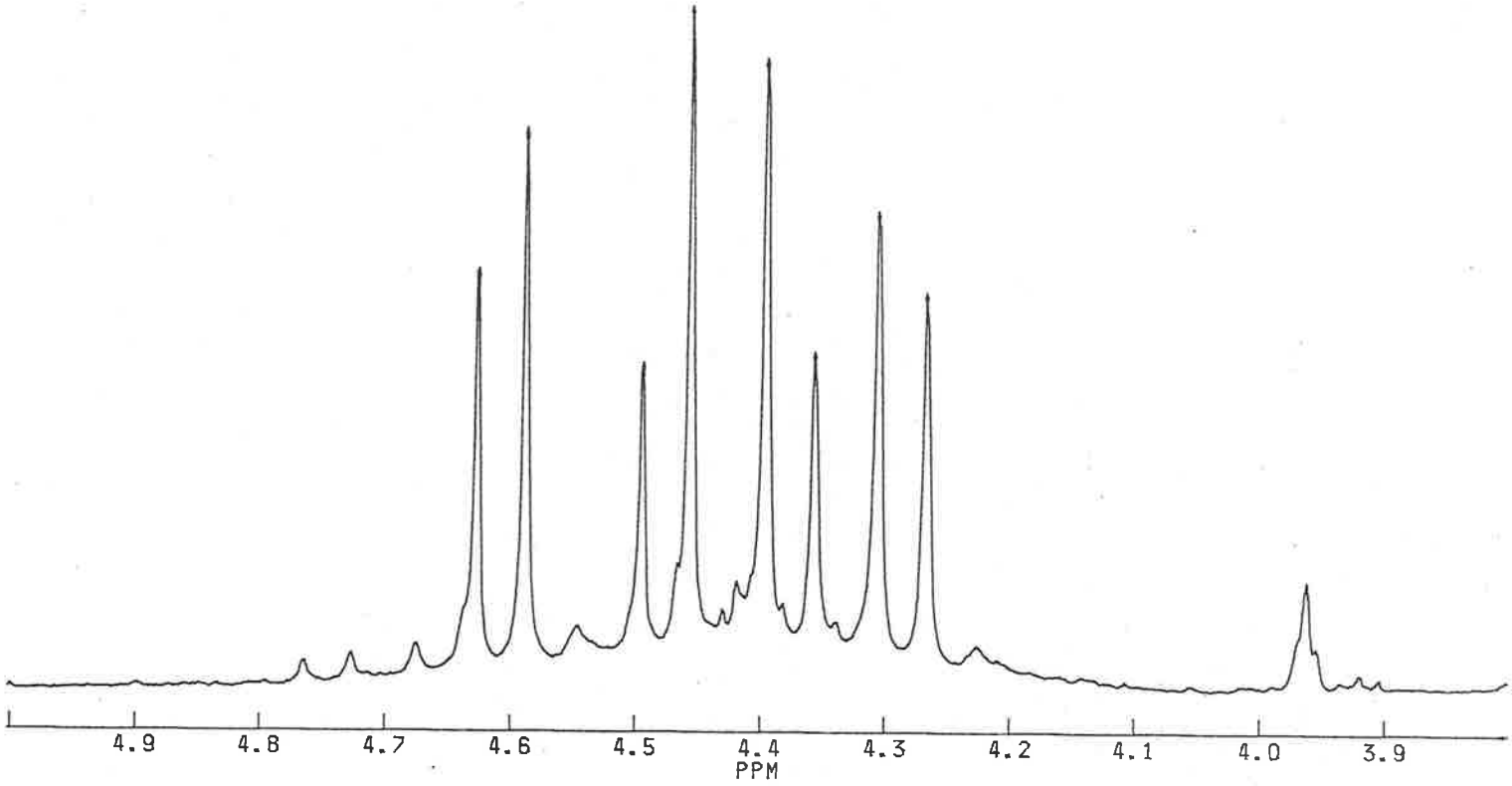
the racemic epoxide and secondly from the homochiral epoxide are reproduced on the following pages. Examination of the first spectrum shows a number of features that can be ascribed to different diastereomers of the same molecule. The two singlet peaks at δ 3.54 and 3.57 correspond to the methoxy groups of the two sets of diastereomers. The two AB quartets centred firstly at δ 4.29 and 4.60 and secondly at 4.38 and 4.47 were due to the methylene group attached to the epoxide which also bore the ester linkage. In the spectrum of the esters (134), the singlet at δ 3.54 and the AB quartet at 4.29 and 4.60 were much larger than the singlet at δ 3.57 and the AB quartet at 4.38 and 4.47. The methyl peak at δ 3.57 could not be

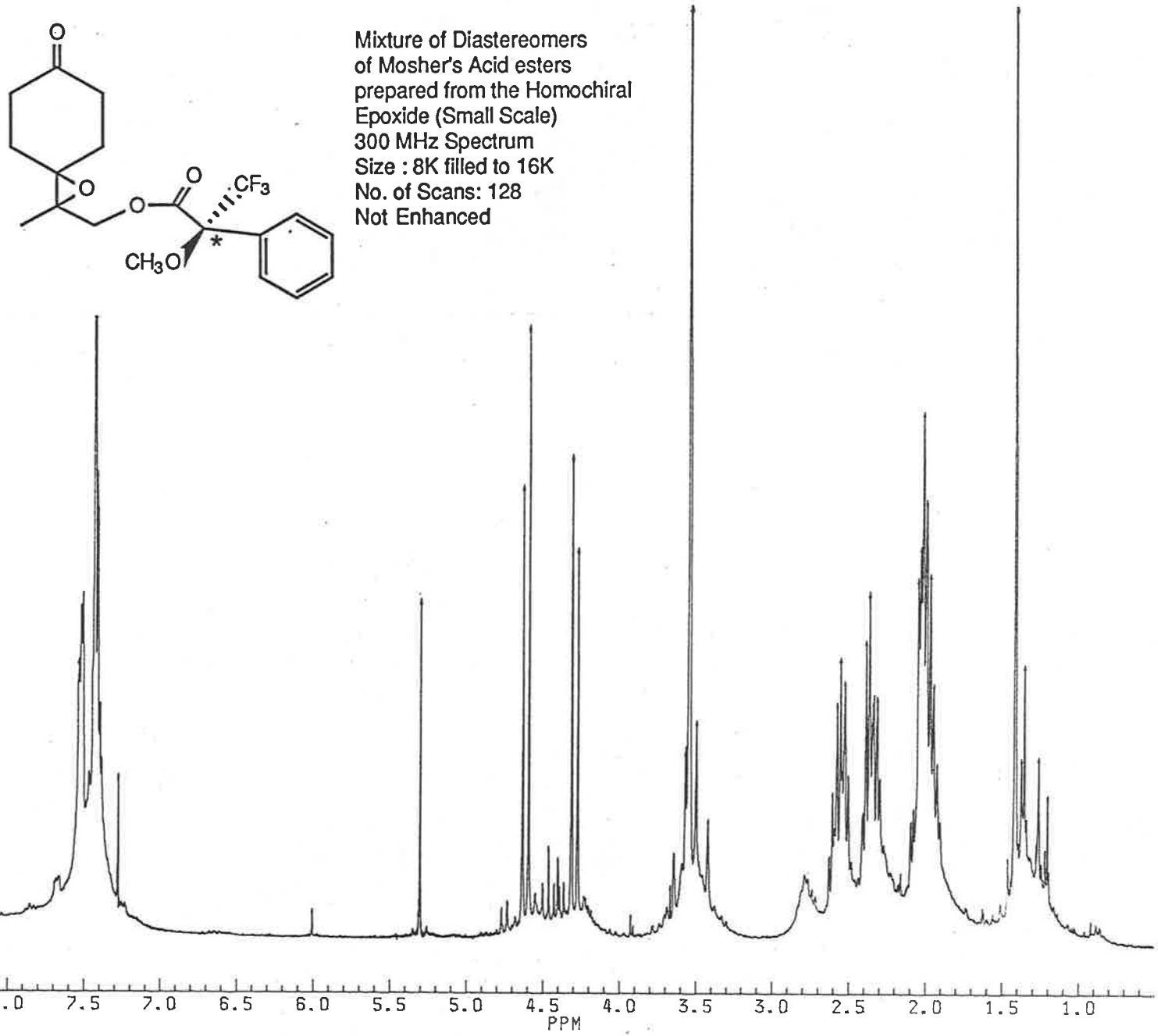


Mixture of Diastereomers
of Mosher's Acid esters
prepared from the Racemic
Epoxide
300 MHz Spectrum
Size : 8K
No. of Scans: 128
Not Enhanced



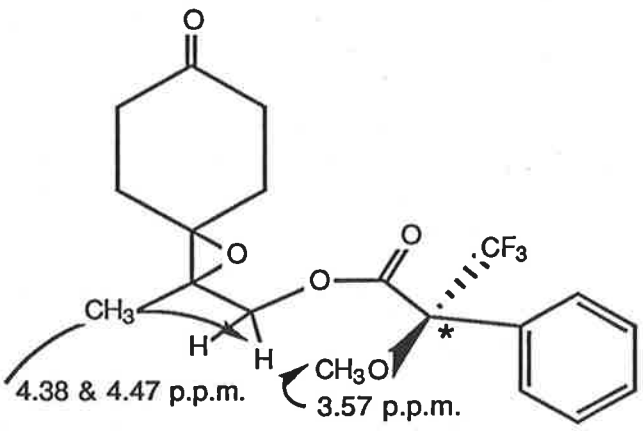
Mixture of Diastereomers
of Mosher's Acid esters
prepared from the Racemic
Epoxide
300 MHz Spectrum
AB quartet Region



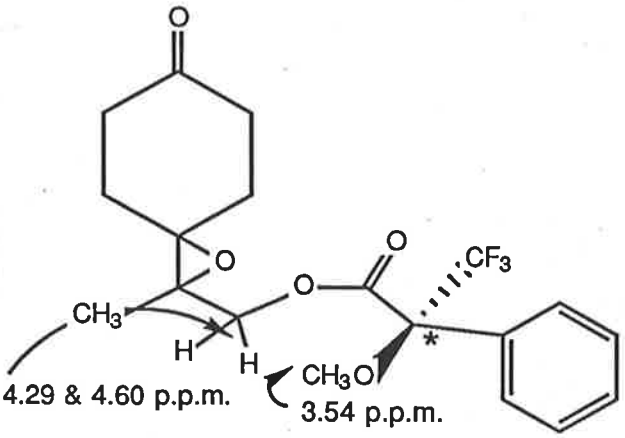

Mixture of Diastereomers
of Mosher's Acid esters
prepared from the Homochiral
Epoxide (Small Scale)
300 MHz Spectrum
Size : 8K filled to 16K
No. of Scans: 128
Not Enhanced
O
O
O
O
CF3
CH3O
*
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
PPM

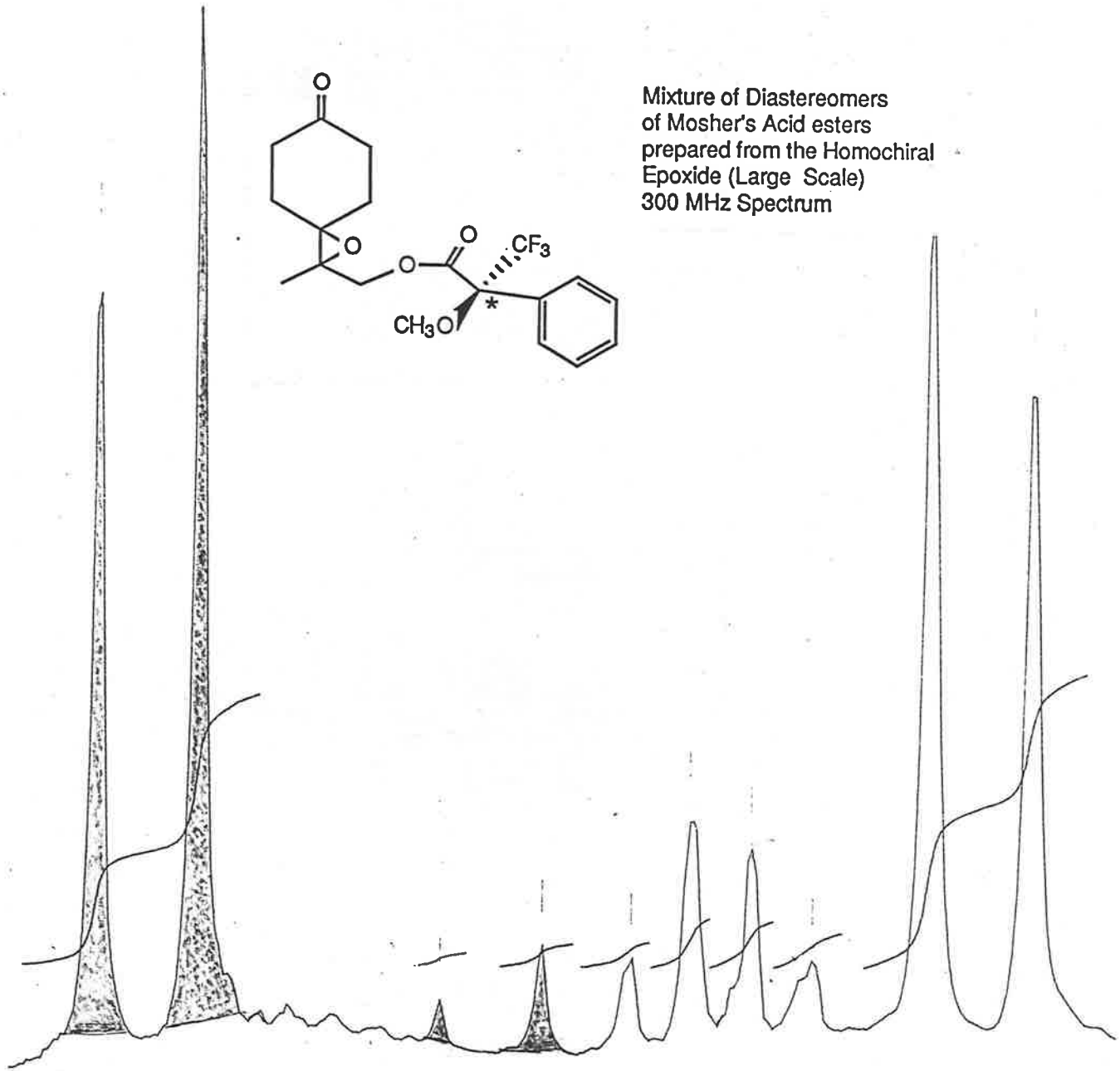
integrated with accuracy because there was an insufficient shift difference from the larger peak. The relative ratio of the two sets of AB quartet peaks was measured at 8.2:1 which meant that 89% of one diastereomer of the ester mixture (134) was present in the solution. Therefore there was 89% of one enantiomer of the epoxide present in the product from the Sharpless epoxidation. This corresponded to an enantiomeric excess of 78%. When the Sharpless epoxidation was attempted for a second time, on a larger scale, the resultant epoxide was esterified to give the mixture of esters (134). The 300 MHz spectrum of the AB quartet region from δ 4.2 to 4.7 is reproduced on the next page. An impurity generated in the small scale esterification obscured the doublet from the AB quartet at δ 4.38 but the other doublet at 4.47 was unobscured. The areas that are marked were carefully cut out and weighed and their relative masses were measured as 593:34 +-1. This corresponded to an enantiomeric excess for the large scale Sharpless epoxidation of 89%.

Minor Diastereomer of Mosher's Acid Ester from Sharpless Epoxide



Major Diastereomer of Mosher's Acid Ester from Sharpless Epoxide



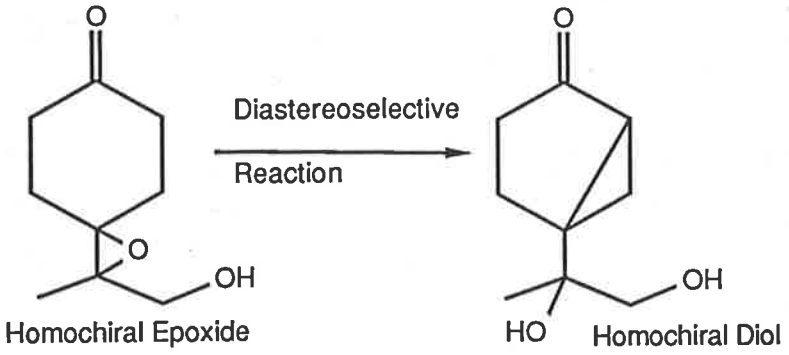


Mixture of Diastereomers
of Mosher's Acid esters
prepared from the Homochiral
Epoxide (Large Scale)
300 MHz Spectrum

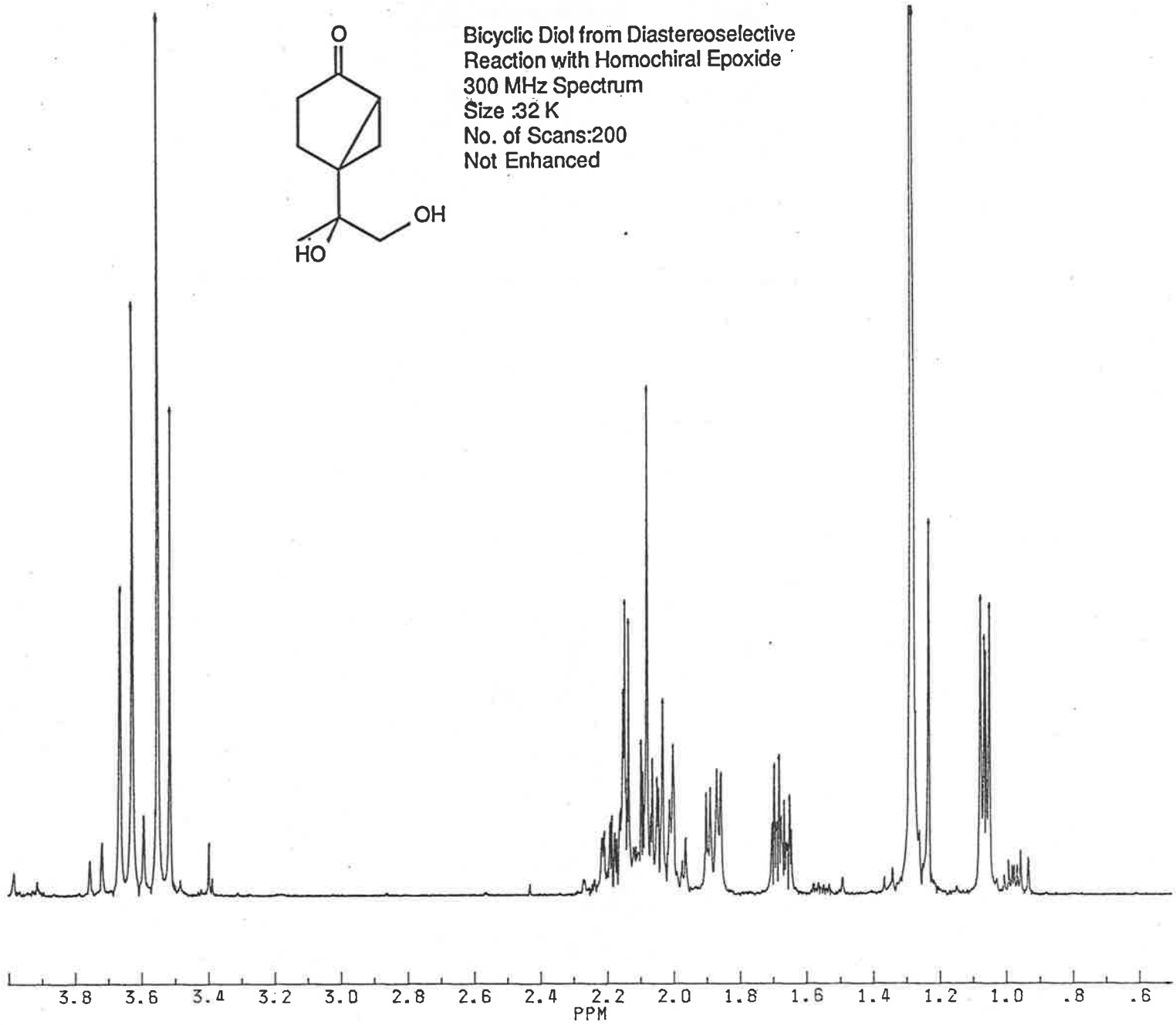
$$\frac{593 - 34}{593 + 34} \times 100 = 89\% \text{ e.e. } (+-1\%)$$

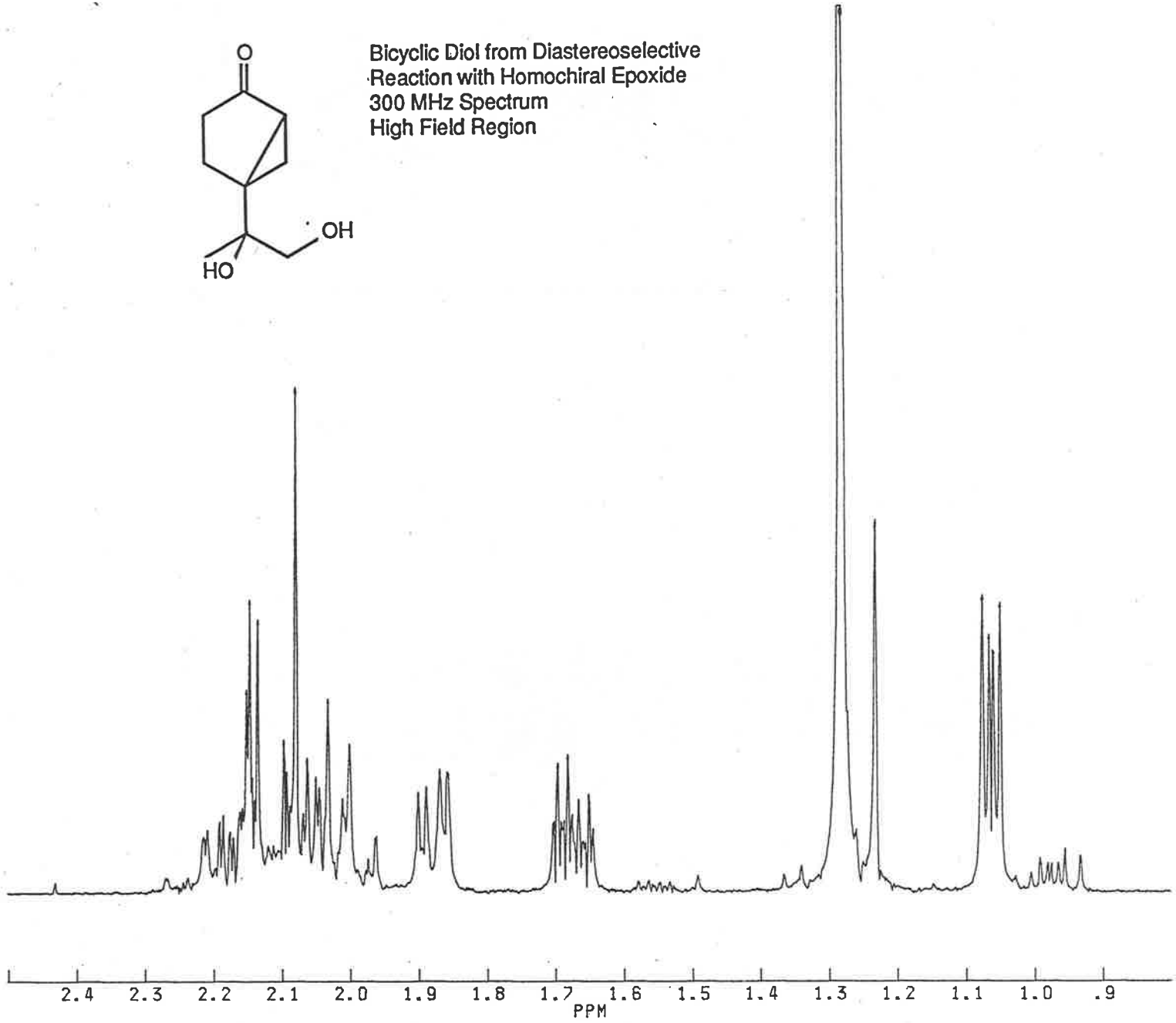
The specific rotation of the epoxide (129) from the large scale epoxidation (89% e.e.) was determined as -2.56. This corresponded to $[\alpha]^{20}_{D}$ -2.87 for the optically pure material.

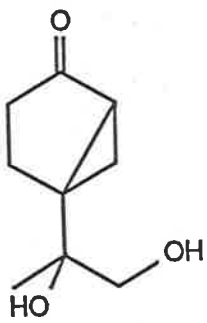
The homochiral epoxide (129) was subjected to the conditions outlined above for the diastereoseletive synthesis of the racemic mixture of the diol (127) (trial 9). This time, the diol (135) was isolated in 14% yield. The 300 MHz NMR spectrum of the diol (135) is reproduced on the following page and clearly showed that the diastereoselection worked well. Interestingly, the chemical shifts of the AB quartets at δ 3.5-3.8 and the methyl groups were shifted slightly downfield (approximately 0.3 p.p.m.) in the



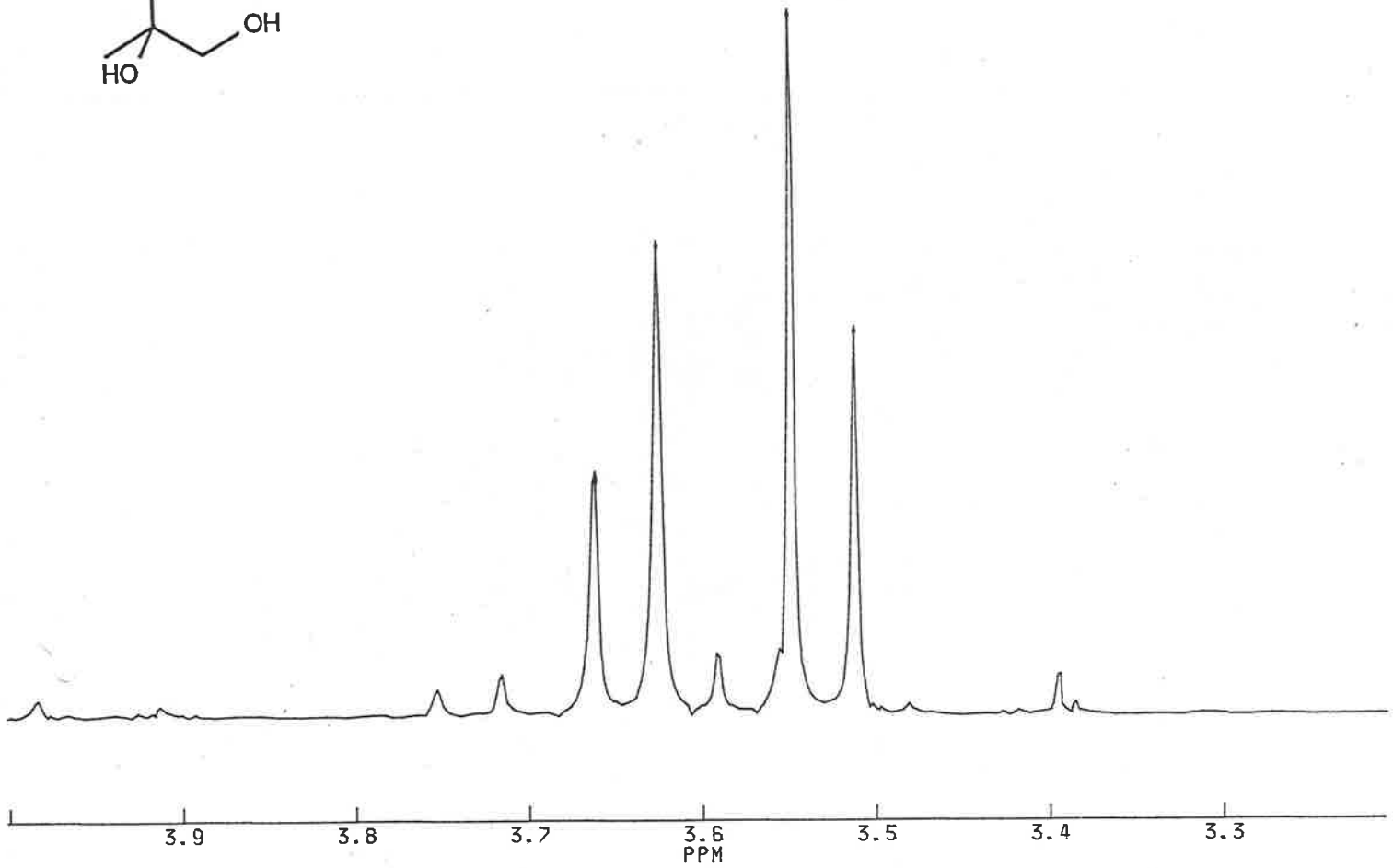
(129) (135)


O
OH
HO
Bicyclic Diol from Diastereoselective
Reaction with Homochiral Epoxide
300 MHz Spectrum
Size :32 K
No. of Scans:200
Not Enhanced
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
.6
PPM


O
OH
HO
Bicyclic Diol from Diastereoselective
Reaction with Homochiral Epoxide
300 MHz Spectrum
High Field Region
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
.9
PPM



Bicyclic Diol from Diastereoselective
Reaction with Homochiral Epoxide
300 MHz Spectrum
Low Field Region



spectrum of the homochiral diol (135) from those of the diol (127). This may be due to a difference in concentration in the solutions used to obtain the spectra of (127) and (135). The protons in the bicyclic ring did not show a change in chemical shift.

The integration values for the methyl resonanes at δ 1.28 and 1.23 for the diol (135) were in the ratio of 13.1:1 and that of the two low field doublets from the two AB quartets at δ 3.53 & 3.64 and 3.57 & 3.74 respectively were in the ratio of 9.3:1. The two doublets from each quartet that resonated at higher field overlapped preventing accurate integration. The cyclopropane protons of the minor diastereomers were too small to give accurate integration data. The average of the two ratios that were obtained was 11:1 which corresponded to 92% +-2% of the major diastereomers by NMR spectroscopy. The variation in the determination of the ratio of diasteromers is to be expected when the ratio is relatively large. The two ratios from the methyl and AB quartet regions correspond to a difference of only 3% in diastereomeric excess.

When the diastereomeric excess was combined with the figure of 89% for the enantiomeric excess from Sharpless enantioselective epoxidation of the material used in the reaction, the mixture of the diol (135) from the above reaction contained 87% of one enantiomer.

89% enantiomeric excess = 95% of one enantiomer of the epoxide

(129)

92% diastereomeric excess for the isomers of the diol (135)

92 * 95 = 87% of one enantiomer of the diol (135) (+-3%)

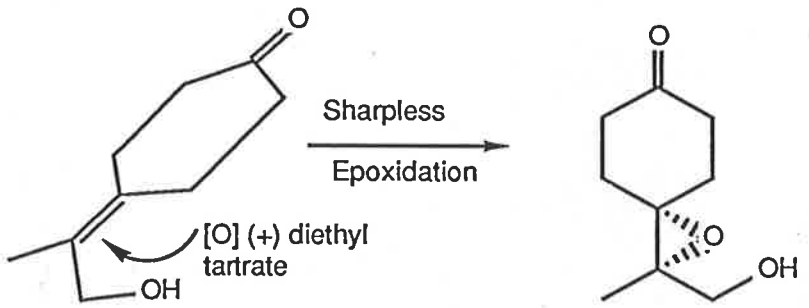
100

The result of the diastereoselection in this critical experiment was higher than expected from the trial reactions possibly because of the larger volume of material used which enabled more accurate measurement of reagent mass. The stirring of this reaction was designed to be particularly efficient as it was thought that good mixing of the reactants at the commencement of the reaction was essential for high diastereoselectivity. This precaution proved fruitful.

The configuration of the enantiomer of the diol produced can be deduced by reference firstly to the work of Sharpless. The enantiomer of the diethyl tartrate that is used in the epoxidation determines the stereochemistry of the product[53]. In the case of the the epoxide (129), (+) diethyl tartrate was used. This means that if the allylic alcohol (122) is drawn as shown below, oxygen would be delivered to the lower face of the double bond so the product (129) would be expected to have the absolute configuration drawn below.

If the diastereoselectivity that exists in the reaction which gives the diol (135) is as a result of the selective

intramolecular deprotonation, as is the contention, the diol



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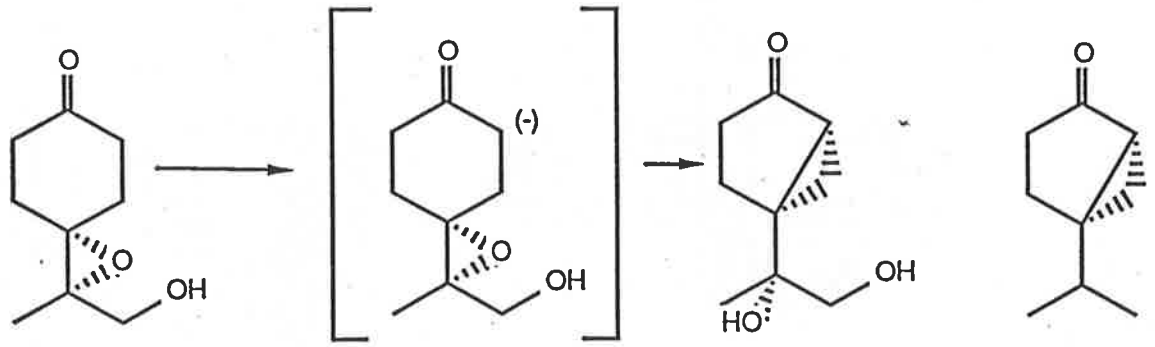
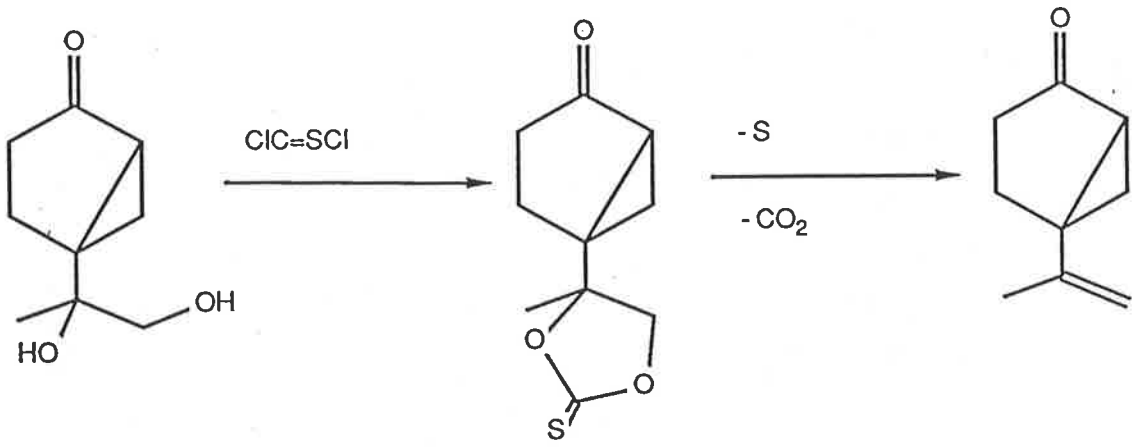


(129) (135) (12)

would have the absolute configuration shown above. This is the correct enantiomer required for the synthesis of natural sabina ketone (12).

To convert the diol (135) to sabina ketone, it is necessary to replace the hydroxyl groups with hydrogens. As outlined before, it was intended to convert the diol to the known alkene (136)[32] by the decomposition of the thionocarbonate derivative.

The diol (135) was converted to the thionocarbonate (137), in 75% yield, by treatment with thiophosgene and triethylamine in

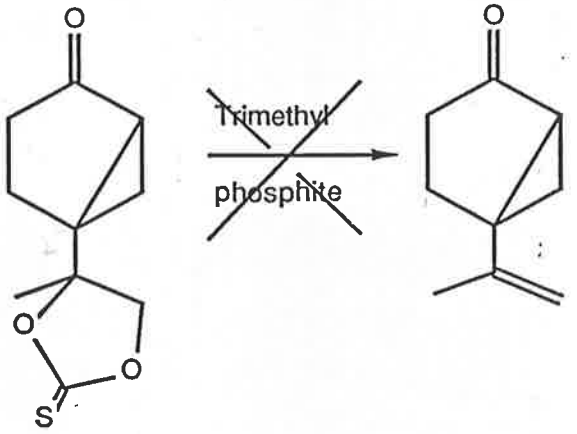


(135) (137) (136)

the presence of a trace of N,N-dimethylaminopyridine as described by Corey and Hopkins[55]. The NMR spectrum of the thionocarbonate (137) contained singlet resonances at δ 1.66 and 1.63 due to the methyl group attached to the thionocarbonate ring of the major and minor diastereomer isomers. These resonances were shifted 0.4 p.p.m. downfield from their postions in the spectrum of the diol (135) and this is consistent with the formation of the thionocarbonate ring. There were two AB quartets observed at δ 4.35 & 4.43 and 4.40 & 4.57 from resonances of the methylene group in the thionocarbonate ring of the major and minor diastereomers. These peaks were shifted an average of 0.8 p.p.m. indicating their proximity to the electron deficient carbon atom in the newly formed ring. The presence of a peak at *m/z* 212 in the mass spectrum assigned to the molecular ion was confirmation of the molecular formula. This compound was found to be unstable when in the solid state and was best kept (for long periods) in dichloromethane solution at low

temperature. This instability is thought to arise from the sensitive trisubstituted thionocarbonate portion of the molecule.

The thionocarbonate was treated with trimethyl phosphite, a reagent known to afford alkenes from thionocarbonates[42]. The thionocarbonate was refluxed with trimethyl phosphite for three days. The known enone (136)[32] possesses singlet resonances in the NMR spectrum at δ 1.74 and 4.92 due to the

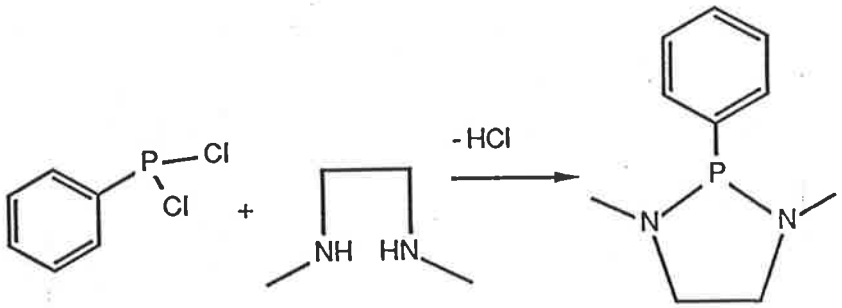


(137) (136)

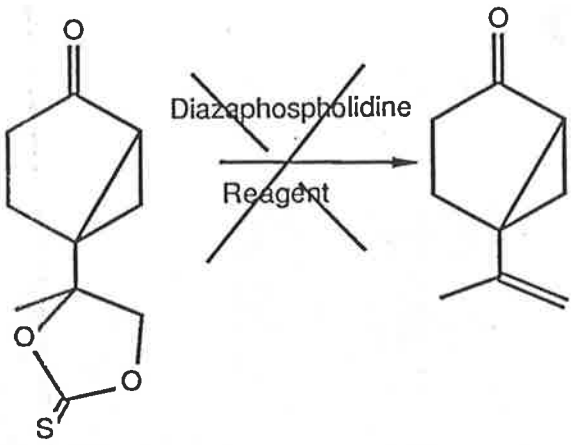
allylic methyl group and the two vinylic protons respectively. No resonances were observed in these areas of the NMR spectrum of the product of the reaction.

The thionocarbonate was treated with a more reactive phosphorus based desulphurising compound, the diazaphospholidine (138) prepared in the manner described by Das and Zuckerman[57]. After the thionocarbonate (137) was treated with excess diazaphospholidine (138) under an atmosphere of argon at room temperature for a week[55], the NMR spectrum of the crude product was found to contain none of the peaks expected

for the enone (136) by NMR spectroscopy.



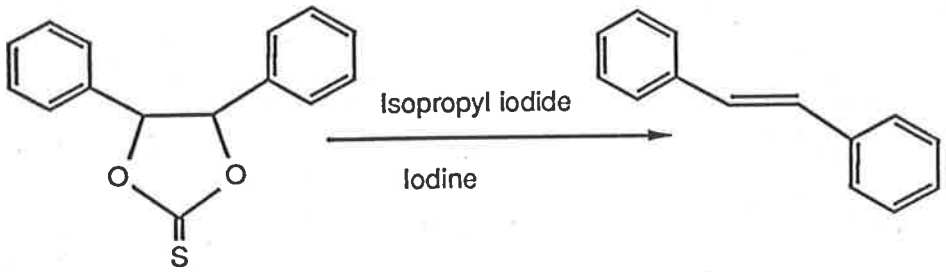
(138)

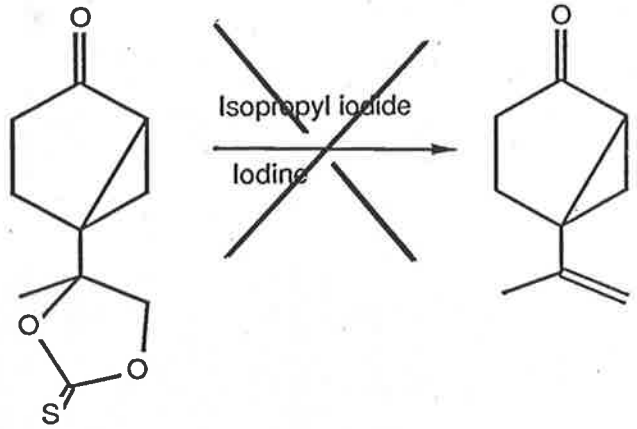


(137) (136)

Vedejs and Wu[58] had reported difficulty with the use of a similar diazaphospholidine and had successfully used *iso*propyl iodide and iodine mixtures to prepare alkenes from thionocarbonates. Unfortunately, when the thionocarbonate (137) was treated with *iso*propyl iodide and iodine under conditions in which, in our hands, stilbene had been formed from the thionocarbonate of *meso* hydrobenzoin, none of the enone (136) was detected by NMR spectroscopy.

The dehydroxylation of the diol (135) appeared to be not viable through the thionocarbonate (137). An alternative strategy





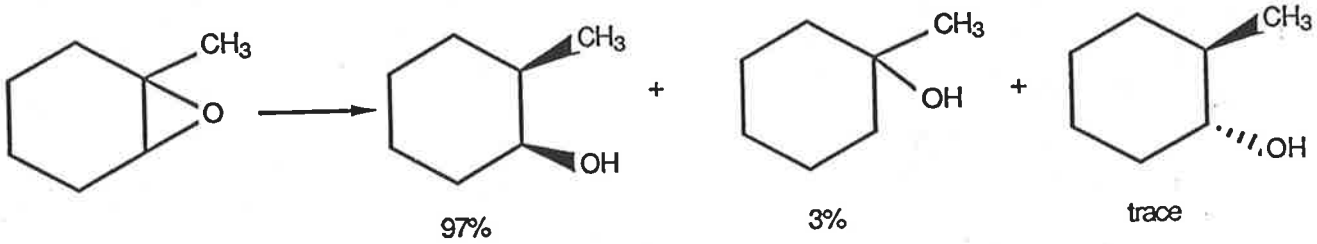
(137) (136)

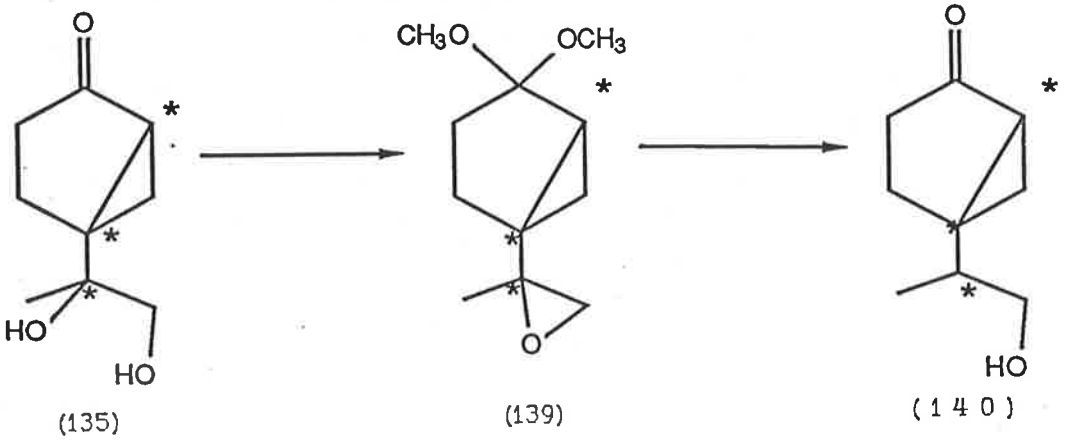
is required but a lack of both time and material has not allowed further investigation. However, it is possible that the following chemistry might achieve the object. If the sesquiterpenes were to be the synthetic target, there must be stereochemical controlled removal of the tertiary hydroxyl group as control of the chirality is crucial to the synthesis. Such a route is hypothetically available. The key step in the process is the regio- and stereoselective reduction of an epoxide under acidic conditions.

If the diol (135) was treated with dimethylformamide dimethyl acetal then the product might be expected to be the epoxide

(139). Neuman[59] has described the mechanism of the formation of epoxides from diols in which the stereochemistry is inverted. Control of the stereochemistry is not lost.

Epoxides may be reduced with sodium cyanoborohydride under anhydrous acidic conditions[60] to give the product in which "hydride" is added to the carbon atom having more carbonium ion stabilising substituents to yield the alcohol (140). Under the reaction conditions described by Huchins *et al*[60], 1-methylcyclohexene epoxide yielded *cis* 2-methylcyclohexan-1-ol (97%) and 1-methylcyclohexan-1-ol (3%) thus high stereoselectivity is found with only a trace of *trans*

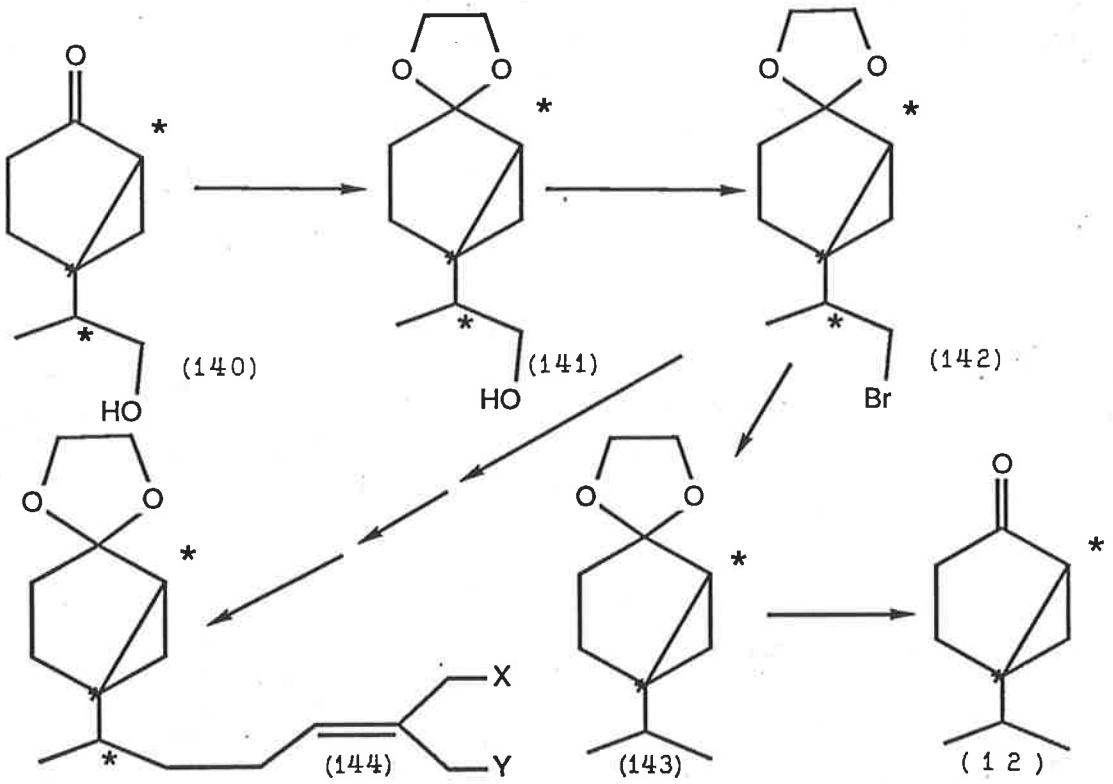




2-methylcyclohexan-1-ol being detected.

The keto ol (140) would be a useful intermediate for the synthesis of either the terpenoids sabina ketone and sabinene or

the sesquisabinene group. Protection of the ketone moiety in (140) as for example the acetal (141) would be advisable before treatment with a mild brominating reagent like triphenylphosphine



dibromide[61] which might yield the bromide (142). The bromo group could be either reduced to give the acetal of sabina ketone (143) or alkylated to give sesqiterpene acetals (144).

It has been shown to be possible to enantioselectively synthesise certain 5-alkylbicyclo[3.10]hexanone structures by the epoxide scheme. It was possible to synthesise the bicyclic compound (135) as an 87% mixture of one enantiomer through the intramolecular regioselective deprotonation by the alkoxide to form the enolate anion in the epoxide (129). It has not proved possible to convert the resultant diol (135) to sabina ketone

(12) through the intermediacy of the thionocarbonate (137) but the synthesis may be successful through the regio and stereoselective reduction of the epoxide (139).

Part B

Chapter 3

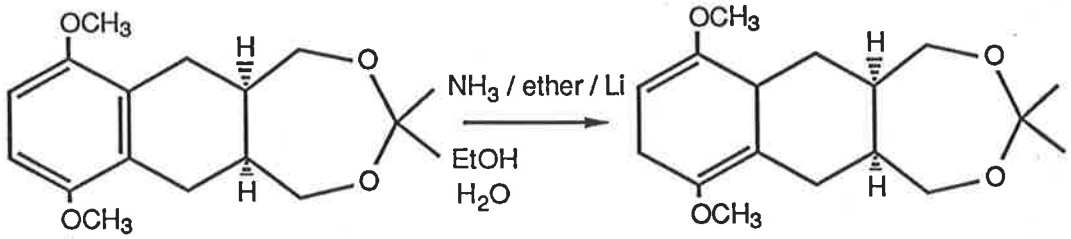
The work towards the synthesis of iceane by the route described in the introduction has been underway for some time. A considerable amount of time had been spent over many years on various approaches to the synthetic problem and the approach that Spurr[22] had devised was thought worthy of examination so that the validity of the original concept for the cyclisation could be established.

Before the commencement of this work, the anhydride (53) had been synthesised by Shirley[24] by the electrochemical reduction of the di iodide (54) to the xylylene which added to maleic anhydride. That anhydride had previously been reduced to the diol and converted to the acetal (56) by Spurr[22]. The acetal (56) had been at least partially reduced to the di enol ether (57) by Shirley. The di enol ether had once been hydrolysed to an intractable mixture containing the diol (58) which could not be obtained pure.

The problems with the route at this stage were twofold. Firstly, it was deemed advantageous to try to improve the reduction of the aromatic acetal (56) so that the di enol ether (57) could be isolated free from any aromatic material. In general, dihydro aromatic compounds of this type are hard to separate from the aromatic material as they sometimes have similar properties[62]. Separation of the two compounds (56) and (57) was not practical. Secondly, there was the more important problem of the purification of the diol (59). Without a

solution to this problem, the cyclisation reaction for the synthesis of the iceane skeleton could not be attempted.

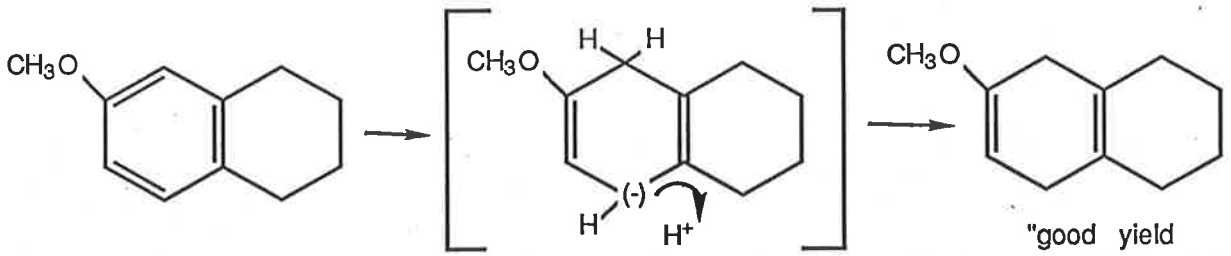
Under the conditions of a dissolving metal reduction, the aromatic acetal (56) did not undergo complete reduction to the di enol ether (57). Usually, 40% of the aromatic material remained. It appeared that it was in the reduction step that the reaction failed rather than any subsequent aerial oxidation of the di-enol ether (57) to the aromatic material (56) during or after work up. When the reaction and work up was carried out in the absence of atmospheric oxygen, the same product to starting material ratio was obtained. The ratio was derived from the relative integration values for the NMR resonances at δ 4.5 due to the vinylic proton in the reduced product (57) and at δ 6.50 due to the aromatic protons in the starting material (56). The ratio of these peaks was found to be 3 to 4 (i.e 60% (57) and 40% (56)).



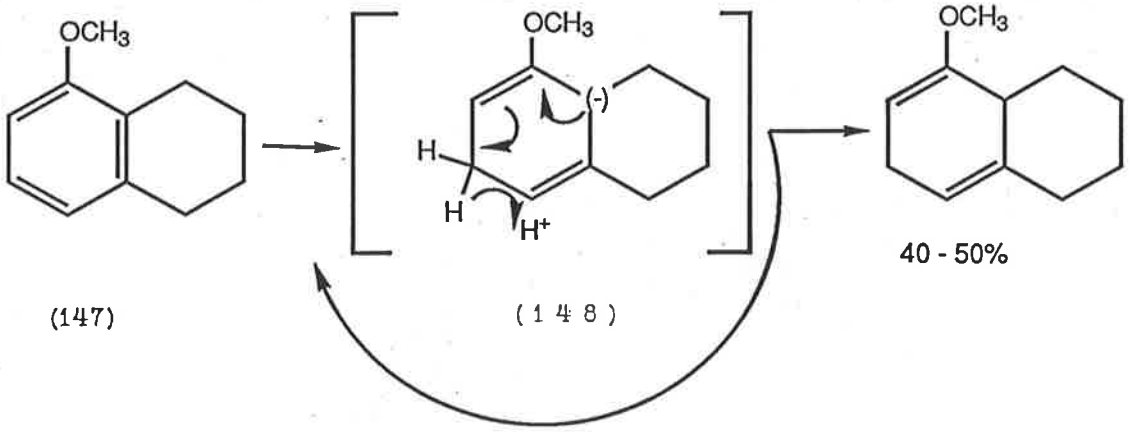
(56) (57)

The phenomenon of incomplete dissolving metal reduction of very electron rich aromatic systems has been noted by Birch[62]. He stated that the aromatic ether (145) was reduced in good yield to give the enol ether (146) but the reduction of the isomeric ether (147) proceeded to the extent of

40-50% with up to 80 equivalents of alkali metal. It was suggested that the intermediate anion (148), produced during the reduction, was not quenched rapidly by a proton source but rearranged at a faster rate with the expulsion of a hydride ion. This is not the case for the anion (149), the intermediate in the reduction of the ether (145). It must be protonated at a faster rate than it loses hydride ion since a good yield of the dihydro product (146) is reported. Hydrogen gas evolution was observed by Birch during the reduction of the ether (147).



(145) (149) (146)

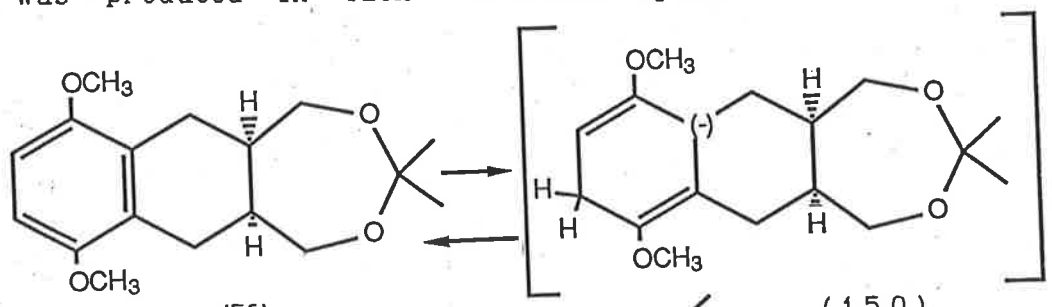


(147) (148)

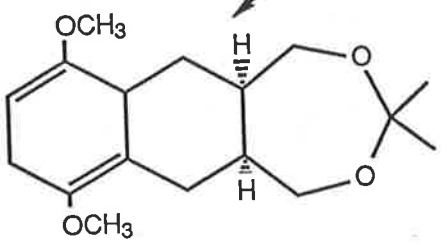
If Birch's postulates are correct, it appeared likely that the same reaction could occur in the aromatic acetal (56). The intermediate anion (150) could possibly extrude a hydride anion

to regenerate the aromatic ring in the aromatic acetal (56).

Birch suggested that the stability of the anions (149) and (148) appeared to determine the success of the reduction. If the anion was "stable", it would eventually be protonated to give the reduced product but if it was not stable, then hydride elimination could take place releasing energy and hydrogen gas. From the results of the reduction of the acetal (56), it appeared that the anion had a "stability" between those of (149) and (148) which led to partial reduction even though the ether was put through up to ten cycles of treatment with lithium metal then quenching with ethanol before finally being worked up. The multiple reduction / protonation sequence was performed in an attempt to accumulate the small percentage of the enol ether (57) that was produced in each reductive cycle.



(56) (150)

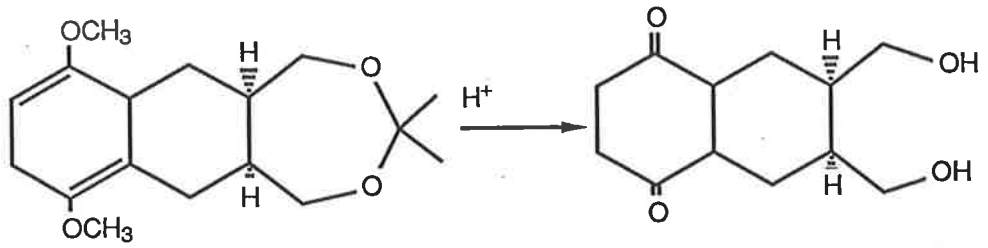


(57)

Hydrolysis of the product of the dissolving metal reduction containing the di-enol ether (57) with 1% aqueous hydrochloric acid gave rise to a mixture which by spectroscopic methods appeared to contain at least some of the desired keto ol (58), possibly as a mixture of stereoisomers. The infra red spectrum of the crude hydrolysate exhibited absorptions at 3500 and 1700 cm^{-1} consistent with the presence of hydroxyl groups and keto groups respectively. The NMR spectrum posessed complex resonances at δ 3.3-4.0 which were assigned to the two hydroxymethylene groups and the two hydroxyl protons present in the keto ol (58). The mixture was difficult to purify by chromatography as the keto ol (58) contained four polar groups and not unexpectedly was found to be water soluble. Spurr[22] reported difficulty with the purification of similar compounds. It was perceived that an indirect method to overcome this problem might be to make a derivative of the hydrolysate. The derivative should be one that was easy to make and purify. Unfortunately this meant that the dissolving metal reduction, the hydrolysis and derivatisation must be completed with purification only after the last step. It would be difficult to expect a good yield of the derivative from such a mixture.

Although the reduction of the acetal did not proceed to completion, the yield was reasonable and there appeared to be no way of circumventing the problem. It was decided that the dissolving metal reduction of the aromatic acetal (56) would be

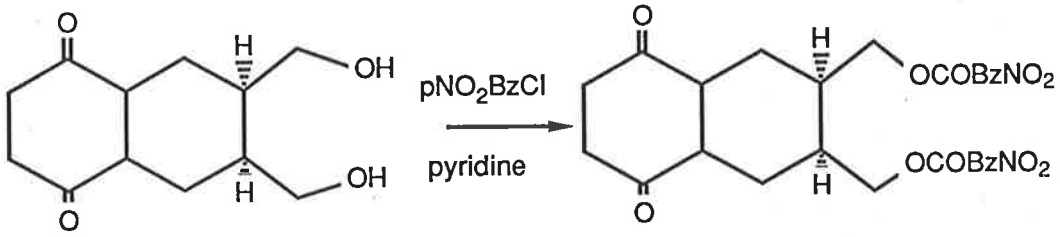
retained in the sequence. The main problem with the sequence lay in the purification of the keto ol (58) and its subsequent functionalisation.



(57) (58)

Treatment of the crude hydrolysate with p-nitrobenzoyl chloride in pyridine yielded what was presumed to be the di benzoate (151) in 11% yield from the di enol ether (57). The crude material was chromatographically purified to yield a white powder. The mass spectrum of the dibenzoate (151) showed a peak at *m/z* 524 although this was of a very low intensity and was only just above background level. This is consistent with the value required for the molecular ion. Attempts to secure a negative ion spectrum of the di ester in order to register a strong molecular ion failed as the spectrum was dominated by the peak due to the NO_2 anion. The infra red spectrum showed a broad absorption at 1720 cm-1 which was assigned to superimposed absorptions of the ester and keto groups. The NMR spectrum of the di ester exhibited resonances at δ 4.3-4.5 due to the two different methylene groups bearing benzoate esters. The existence of an AB quartet centered at δ 8.18 and 8.28 was ascribed to the two p- substituted benzene rings of the

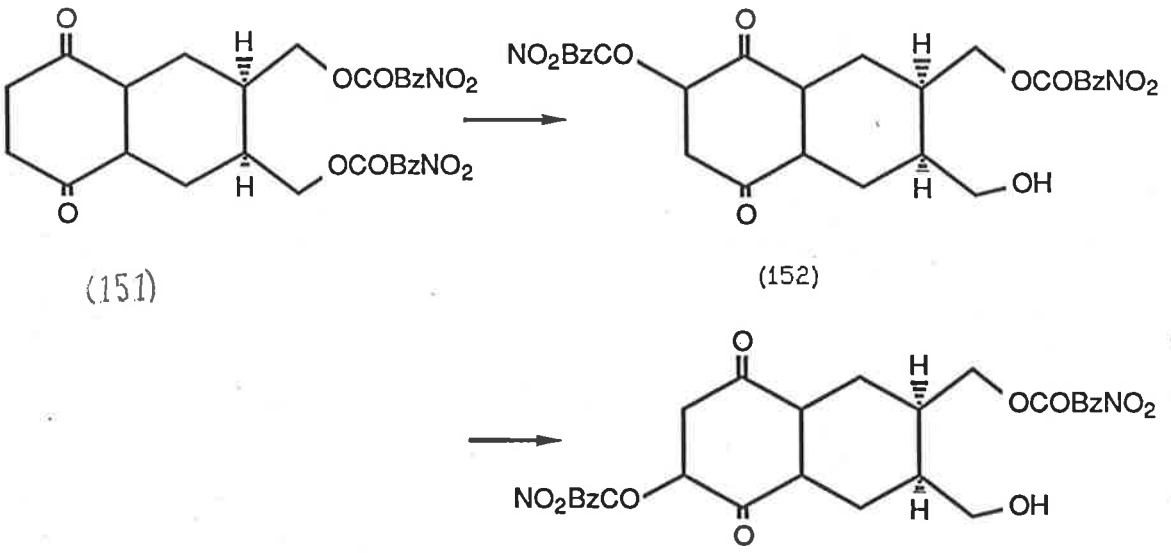
4-nitrobenzoate esters. It should be noted that the stereochemistry at the ring junction site A was assumed to be mainly *trans* as acid catalysed epimerisation at the ring junction could take place during the hydrolysis of the enol ether (57). The stereochemistry at site B, installed in the reaction to form the anhydride (53), was assumed to be unchanged.



(58) (151)

The nitro benzoate group may be a good enough leaving group to be displaced by an enolate anion but there was the possibility of a competing reaction to form the seven membered ring discussed in the introduction. As well as this, at infinite dilution, an intramolecular transacylation reaction could take place to give the triones (152). The electron withdrawing 4-nitro group would favour the leaving group capability of the benzoate group as it effectively lowers electron density in the ring stabilising the negative charge of the anion[63]. This electron withdrawal would also activate the carbonyl bond for nucleophilic attack however the transition state for this reaction is eight centred. It has been shown that the six-membered ring transition state as is required for the formation of the iccane skeleton is generally of a lower energy than that of a seven or eight-membered ring

transition state[64]. For this reason, it was anticipated that these side reactions would not cause any major problems. At least if the nitro benzoate group was not an appropriate leaving group, it was a stable derivative for the purification of the keto ol (58) and should be useful for its elaboration to a compound in which there is a more effective leaving group.

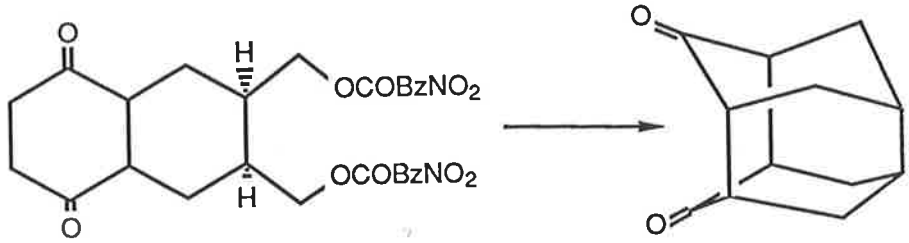


(151) (152)

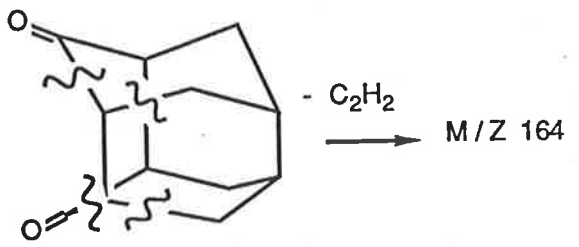
The diester (151), dissolved in a large volume of t-butanol, was treated with two equivalents of potassium t-butoxide and was refluxed for four hours. The product of the reaction was analysed by spectroscopic means. The NMR spectrum of the crude product showed firstly the absence of resonances due to the p-substituted aromatic ring and the methylenes bearing the esters. The spectrum consisted entirely of complex alkyl resonances in the range of δ 0.8 to 2.0. The mass spectrum of the crude product showed peaks at m/z 164 ($M^+ - C_2H_2$?) and 147. The molecular ion might be

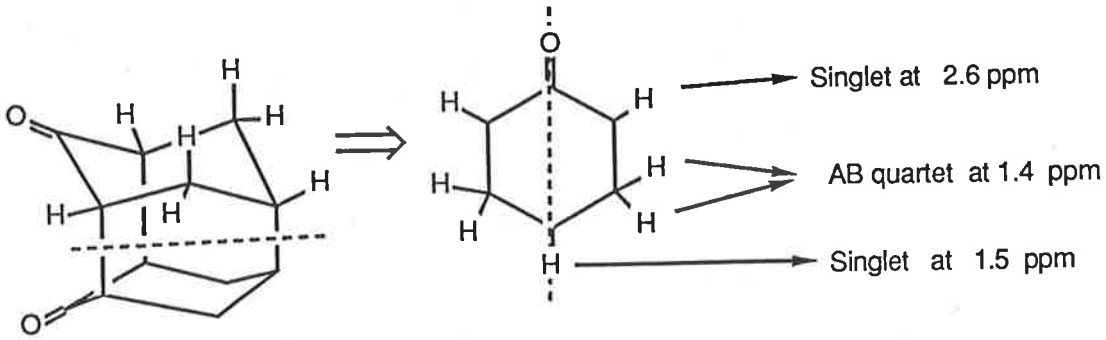
expected because it would require the breaking of two bonds to expel any fragment. Although extrusion of carbon monoxide would not be unusual, the loss of acetylene is more difficult to explain. No peak was observed at *m/z* 190 which would correspond to the molecular ion. Chromatography on silica gel with petroleum ether as the eluent revealed the existence of one major component. This compound was isolated and the 300 MHz NMR spectrum revealed a relativly simple spectrum. At δ 0.85 and at 1.11, there were two small multiplets with a relative integration of 4 in total. There was a large singlet resonance at δ 1.25 with an integration of 7.2 and lastly there was a broad singlet peak at δ 1.59 reminiscent of a hydroxyl resonance. This had a relative integration of 6.3. The spectrum of the desired dione would probably be fairly simple as there are some symmetry elements in the molecule which means that there are only 4 distinct nonequivalent protons. From previous experience[21], it was thought that the NMR spectrum may resemble one in which the two methylene protons of the bridging methylene form an AB quartet at about δ 1.4 and the bridgehead methine would appear as a singlet at δ 1.5 (coupling in similar systems[21] has been shown to be small or nonexistent) and finally, the methines next to the carbonyl group would occur as a singlet at about δ 2.6. It appeared obvious that the compound that was isolated was not the dione (60). The di ester (151) was not appropriate to act as the

Key intermediate but was useful as a device to overcome the problem of the purification of the keto ol (58). Lack of time and material with which to work precluded an investigation into the conversion of the di ester (151) to a more appropriate compound for the key intermediate.



(151) (60)

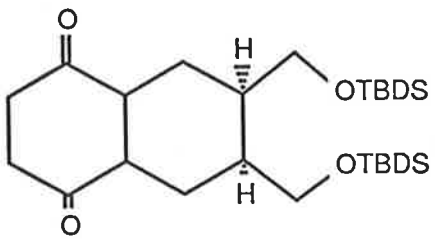




The route to the key intermediate that has been discussed so far has had two problems. The first is obviously the poor performance of the dissolving metal reduction of compound (56) which appeared to be a function of the mechanism of the reduction and the highly electron rich nature of the substrate. For this

reason this defect would be difficult to overcome. The poor performance of the reduction added to the second problem, that of the preparation, handling and purification of the water soluble keto ol (58). At this stage, the purification was only possible through the di ester derivative (151) which itself was synthesised in very poor yield from the hydrolysis mixture of the di enol ether (57). This, combined with the overall length of the synthetic route and the inappropriate nature of the 4-nitrobenzoate group of (151) to function as a leaving group severely limited the amount of material available for further experimentation.

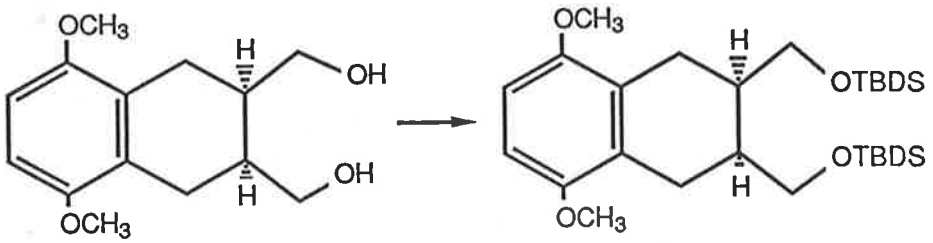
It was decided to try an alternative to the derivatisation procedure. The alternative approach was to unveil the dione functionality separately from the deprotection and associated derivatisation of the diol moiety. This, it was hoped, would avoid the problem of the separation of the highly polar mixtures of compounds resulting from the hydrolysis of the enol ether (57). t-Butyldimethylsilyl ethers are known to be stable to weak acid treatment and can easily be removed by fluoride



(155)

ion[65]. If the di silyl ether (153) could be reduced by a dissolving metal reduction to the di enol ether (154), it might be hydrolysed with mild acid treatment to the di silyl ether dione (155) which may be easy to purify.

When the alcohol (55) was treated with two equivalents of t-butyldimethylsilylchloride, the disilyl ether (153) was obtained in 66% yield. The infra red spectrum of the di ether showed the absence of a strong absorption at 3500 cm^{-1} indicating the hydroxyl groups in the diol (55) were no longer present. The NMR spectrum contained resonances at δ 0.00 and 0.93 in the ratio of 2 to 3 which was consistent with the presence of firstly the two methyl groups attached to silicon and secondly the t-butyl group of the t-butyldimethylsilyloxy group. The presence of a peak at *m/z* 480 which was assigned to the molecular ion in the mass spectum confirmed that the material possesed the correct molecular formula.

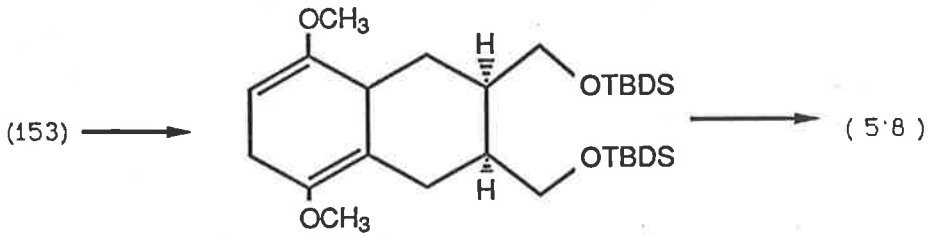


(55) (153)

The di silyl ether (153) underwent partial reduction in a dissolving metal reduction with 52% recovery of crude material. The distribution of product and starting material was approximately 4 to 1. The NMR resonance at δ 4.3 was assigned

to the vinyl enol ether proton and the resonance at δ 6.40 was assigned to the aromatic protons in the starting material, (153). The ratio of the integrations of the peaks were used to determine the extent of the reduction.

The attempted selective hydrolysis of the crude dissolving metal reduction product containing the di enol ether (154) was unsuccessful. When the mixture was treated with aqueous oxalic acid, both the enol ether and t-butyldimethylsilyl groups were hydrolysed. The material that was isolated contained no resonances in the NMR spectrum due to the silyl group and the infra red spectrum showed an absorption at 3500 cm^{-1} and at 1700 cm^{-1} due to the generation of a mixture containing the keto ol (58). The conditions although seemingly mild, were apparently severe enough to allow the hydrolysis of the two t-butyldimethylsilyl protecting groups. This protecting group is not appropriate in this case.

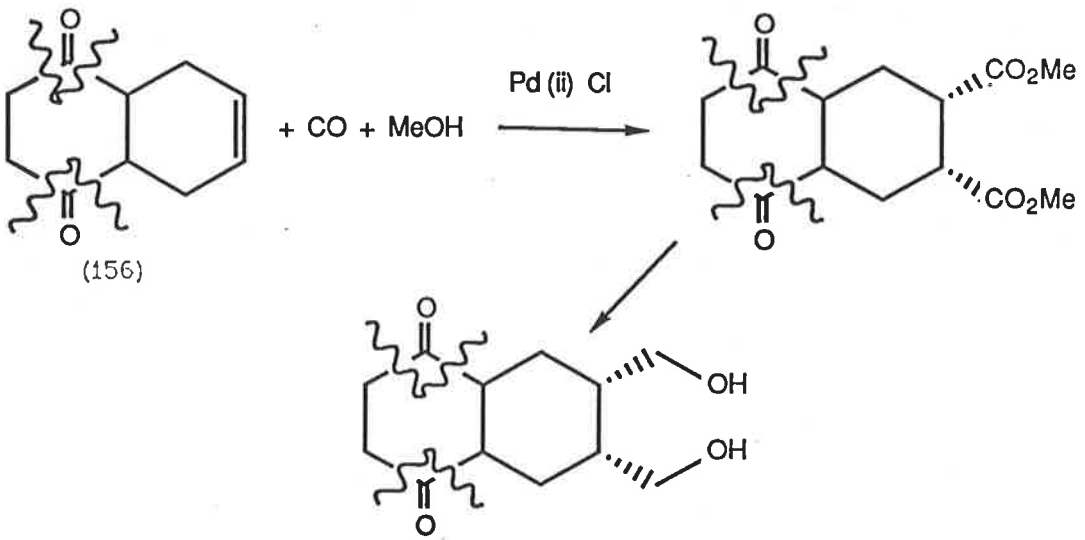


(154)

In conclusion, the most profitable course to take with reference to the purification of the keto ol (58) appeared to be to use the nitrobenzoate (151) as the precursor to the key intermediate as it was clearly not suitable as the key

intermediate itself. Low yields and the production of mixtures in the dissolving metal reduction and subsequent hydrolysis made it difficult to generate large amounts of material with which to experiment. These problems make it prudent to consider an alternative strategy whereby the conversion of the aromatic ring to the dione moiety was not required.

In 1979, Stille and Divakaruni[66] showed that in the presence of palladium (ii) chloride, compounds containing double bonds could be carbonylated with carbon monoxide and methanol to give *cis* 1,4-di esters. Cyclohexene had been treated under mild conditions with carbon monoxide, methanol and palladium (ii) chloride to give *cis* dimethyl 1,2-cyclohexanedicarboxylate. It seemed that this reaction could be used to introduce the

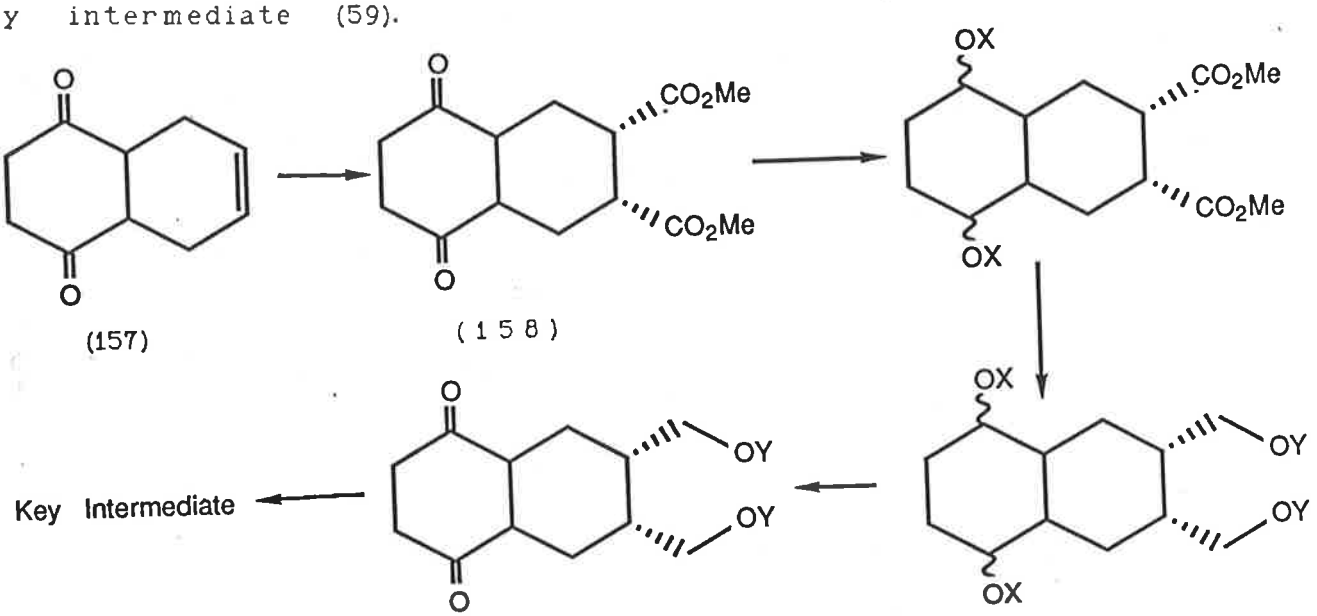


(156)

cis groups at site B into a compound of the general structure (156). These groups could be reduced with a strong reducing agent like lithium aluminium hydride to the *cis* diol

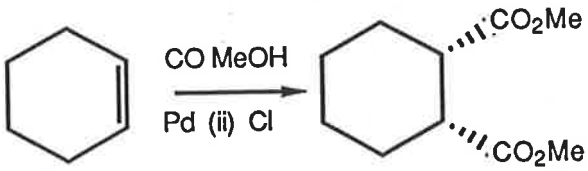
moiety then the hydroxyl groups could be converted to leaving groups.

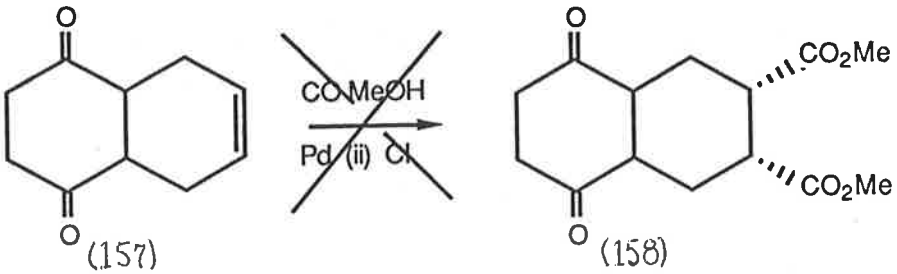
The dione (157) was initially chosen as the substrate. This compound was readily available from the powdered zinc reduction of the Diels Alder adduct of benzoquinone and butadiene[67]. The product of the reaction was expected to be the di ester (158). The chemical transformations that were required to form the Key intermediate were as follows. The two keto groups would need to be reduced to the hydroxyl moieties and be protected in some way. The ester groups would be reduced to the diol moiety and would be protected in a different way. The hydroxyl groups on the ring would then have to be deprotected then oxidised to the dione. Deprotection of the remaining diol and conversion to leaving groups would, in theory, furnish the Key intermediate (59).



Treatment of cyclohexene under the conditions described by

Stille and Divakaruni[66] yielded the di ester in 76% yield however when the dione (157) was used as the substrate, no reaction took place. The reaction was repeated a number of times but none of the desired di ester (158) could be isolated. The pressure of carbon monoxide was increased from three atmospheres as Stille had used, to 14 atmospheres but again, no reaction took place. Stille had used conjugated enones in his carbonylation reactions successfully so it was initiallty thought that the isolated keto groups would not interfere with the reaction. In practice, they might act in some way to poison the palladium. Because of the potential of the carbonylation reaction to provide the key intermediate in relatively few steps, it was decided to pursue the reaction with a different substrate.

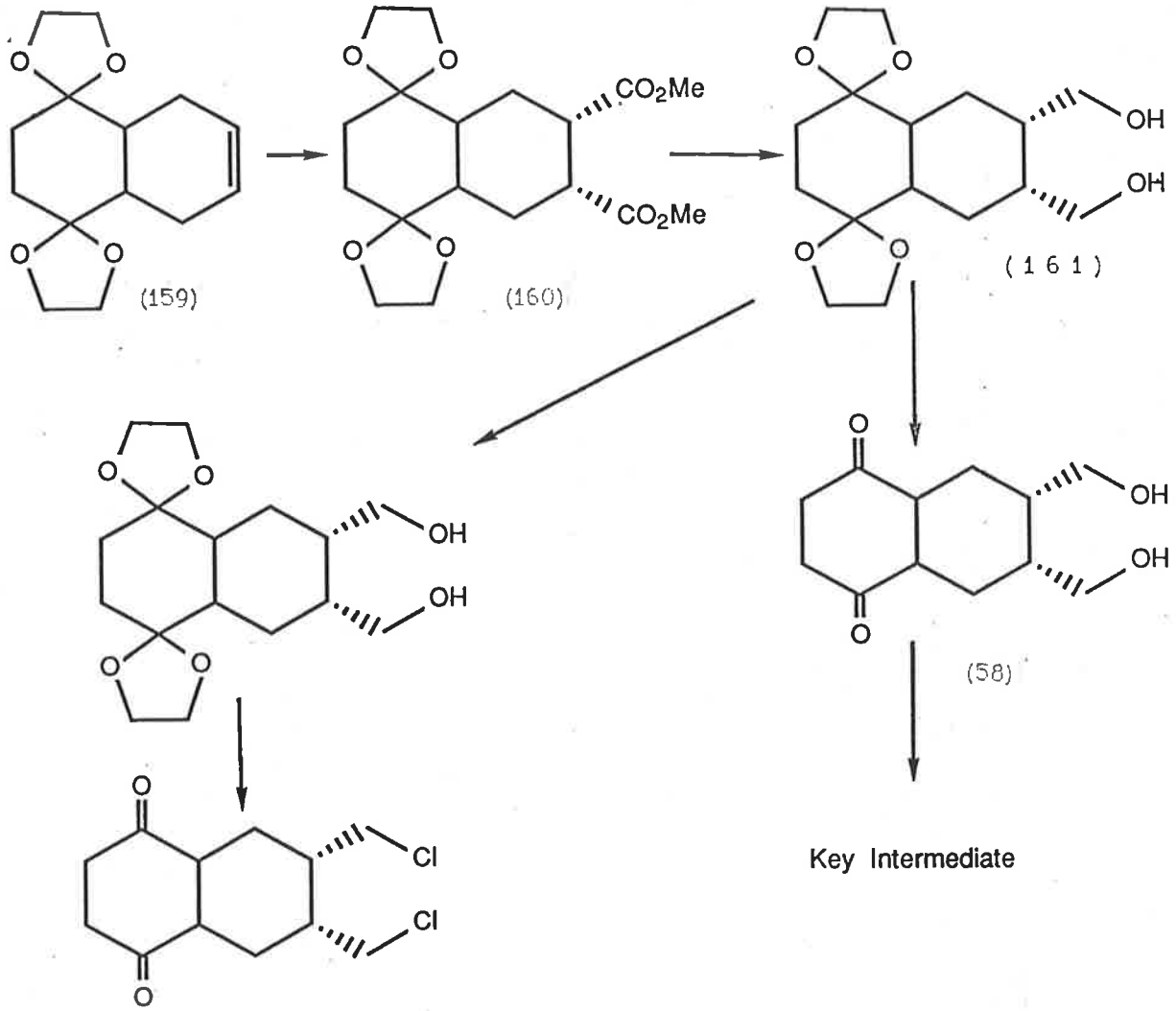




(157) (158)

If the dione moiety of (157) could be protected before the carbonylation reaction, then the benefits would be firstly in the shortening of the route to the key intermediate and secondly in the removal of the keto groups which may have been precluding the

carbonylation reaction. The acetal protecting group was chosen to mask the dione functionality as in the di acetal (159)[68]. It was considered that if the carbonylation reaction proceeded, the di ester ( ) would result. This compound could simply be reduced to the diol (161) and hydrolysis of the acetal would yield the



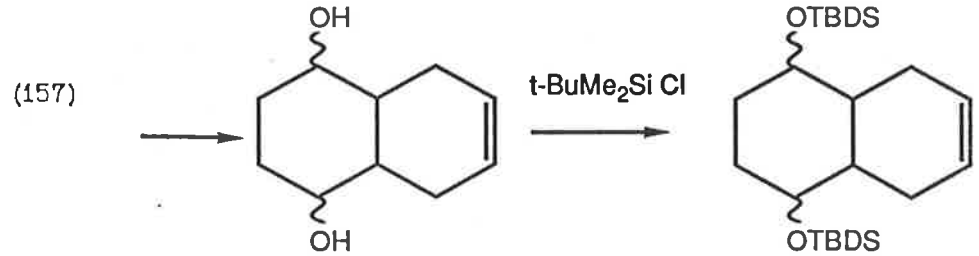
keto ol (58) which could be converted into the key intermediate. Alternatively, the diol (161) could be converted into a compound

with leaving groups that are relatively acid stable like chloro groups. The acetal groups could be removed with mild acid treatment to yield the intermediate once again.

The acetal was formed by treatment of the dione (157) under dehydrating conditions with two equivalents of ethylene glycol in benzene with a trace of acid. Attempts to carbonylate the di acetal (159) met with failure. The product of the reaction was not the di ester but a mixture of the di acetal (159) and the dione (157). Even though the reaction was buffered with sodium butyrate, conditions during the reaction may have been sufficiently acidic for hydrolysis of the acetal protecting groups to occur. Anhydrous potassium carbonate was added to the carbonylation mixture in an attempt to avert the acid generation which was assumed to be the cause of the hydrolysis. The water that may have been generated from the acid base reaction was to have been removed from the reaction by its reaction with trimethyl *ortho*-formate. This carbonylation reaction was fruitless as, in this case, neither the hydrolysis of the acetal groups nor the carbonylation reaction took place. The reason for the failure could be that the extra oxygen atoms in the two acetal groups could be irreversibly coordinating the palladium nucleus during the reaction. For this reason, it was decided to try a protecting group for the hyroxyl moieties that would in effect sterically shield the oxygen atoms to some extent and prevent their interference with the catalyst. This group would

also have to be stable to weak acid.

The dione (157) was reduced with lithium aluminium hydride to the diol (162) where the stereochemistry of the hydroxyl groups is assumed to be *cis*[69] but would appear to be immaterial to the success or failure of the reaction. This compound was converted to the di t-butyldimethyl silyl ether (163). The t-butyldimethyl silyl protecting group for the hydroxyl group fulfilled both the criteria of acid stability and bulk that may shield the oxygen atoms. The di silyl ether structure was confirmed by the presence in the NMR spectrum of singlet resonances at δ 0.00 and 0.90 ascribed to the dimethyl silyl and t-butyl groups respectively. Confirmation of

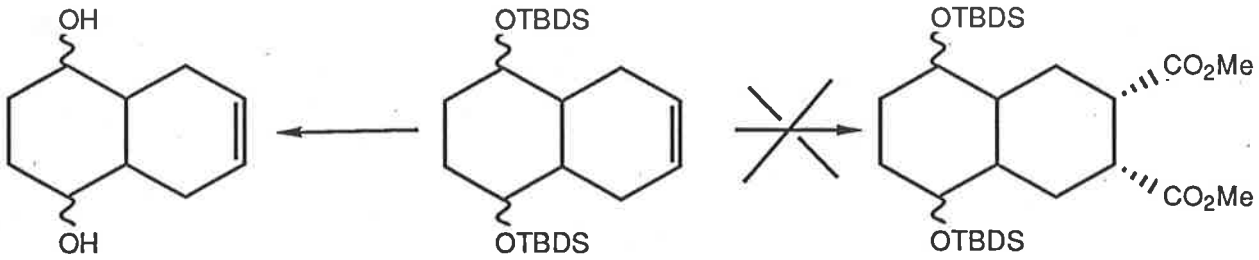


(162) (163)

the molecular formula was provided by the mass spectrum in which the molecular ion was observed at *m/z* 396.

This compound was subjected to the carbonylation reaction with disappointing results. The protecting group that was supposedly stable to weak acid was removed during the course of the reaction and the product was the diol (162). The NMR spectrum of the product exhibited neither of the resonances at δ 0.00 and 0.90 associated with the silyl protecting group nor was there a

sharp singlet resonance at δ 3.7 from any methyl esters. Comparison of the NMR spectra of the diol (162) and the product from the reaction showed they were almost the same. It is not known with any certainty why the silyl group was hydrolysed or why the carbonylation did not take place. It can be assumed that the supposedly robust t-butyldimethylsilyl group was methanolysed in the presence of an acid during the course of the reaction.

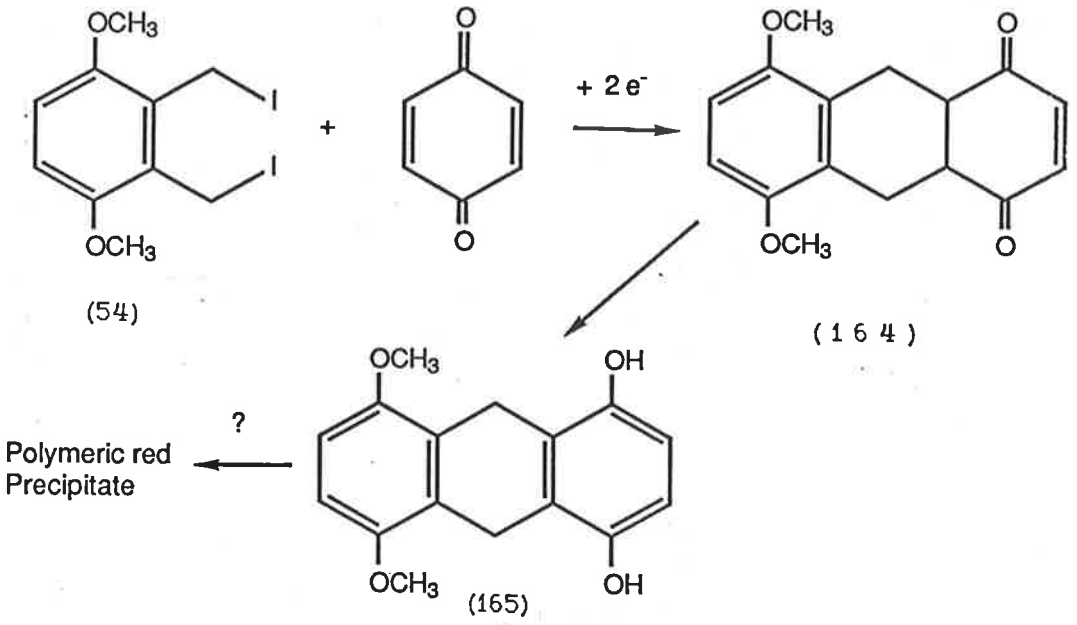


(162) (163)

This approach was abandoned at this time as although the reaction appeared promising, the carbonylation reaction seemed destined to work only on simple compounds that did not bear any extra oxygen rich or acid sensitive functionality. Changes to the carbonylation reaction conditions did not change the course of the reactions.

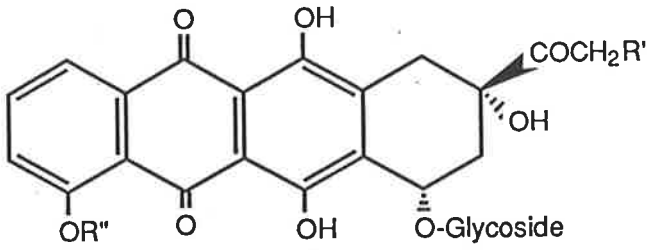
The generality of the electrochemical reduction of the diiodide (54) and subsequent Diels Alder reaction of the "xylylene" has been examined. In theory, providing the half wave potential of the chosen dienophile is more negative than that of the diiodide, ($E_{1/2}$= -0.25 V in 0.1M $N(Bu)_4$ ClO_4 in DMF), the diiodide (54) should be reduced to the

xylylene and the reaction should proceed. For example, benzoquinone, a good dienophile but easily reduced, has been used as the dienophile ($E_{1/2}$= -0.6 V in 0.1M $N(Bu)_4ClO_4$ in DMF) to give the adduct (164) in 42% yield. Under the conditions of the reaction the compound did not isomerise to the hydroquinone (165). The NMR spectrum of the adduct exhibited singlet resonances at δ 6.67 and 6.73 due to the enone vinyl protons and the aromatic protons. It was not possible to determine which resonance was due to which protons. The infra red spectrum showed an absorption at 1670 cm^{-1} due to the ene dione system in (164). The adduct is an analogue of cyclohex-2-en-1,4-dione which rapidly tautomerises in aqueous acid or base solution to hydroquinone. The adduct is similarly sensitive as, after chromatography, when the solvent was removed (with or without heat) a lipstick red precipitate rapidly formed. This



precipitate was found to be insoluble in organic solvents. If the hexenedione (164) isomerised to the hydroquinone (165), a small amount may have been autoxidised with atmospheric oxygen[70] then polymerisation may have ensued. The material showed the same molecular ion as the adduct (164) in the mass spectrum and this lead to the conclusion that it was due in some way to the hydroquinone (165). This compound may polymerise with itself and might also catalyse polymerisation of the dione adduct. For this reason it was not possible to isolate the dione adduct in a solid form that was free of the precipitate. Solutions for spectroscopic analysis could be prepared but required filtration before use. On removal of the solvent, more precipitate was formed.

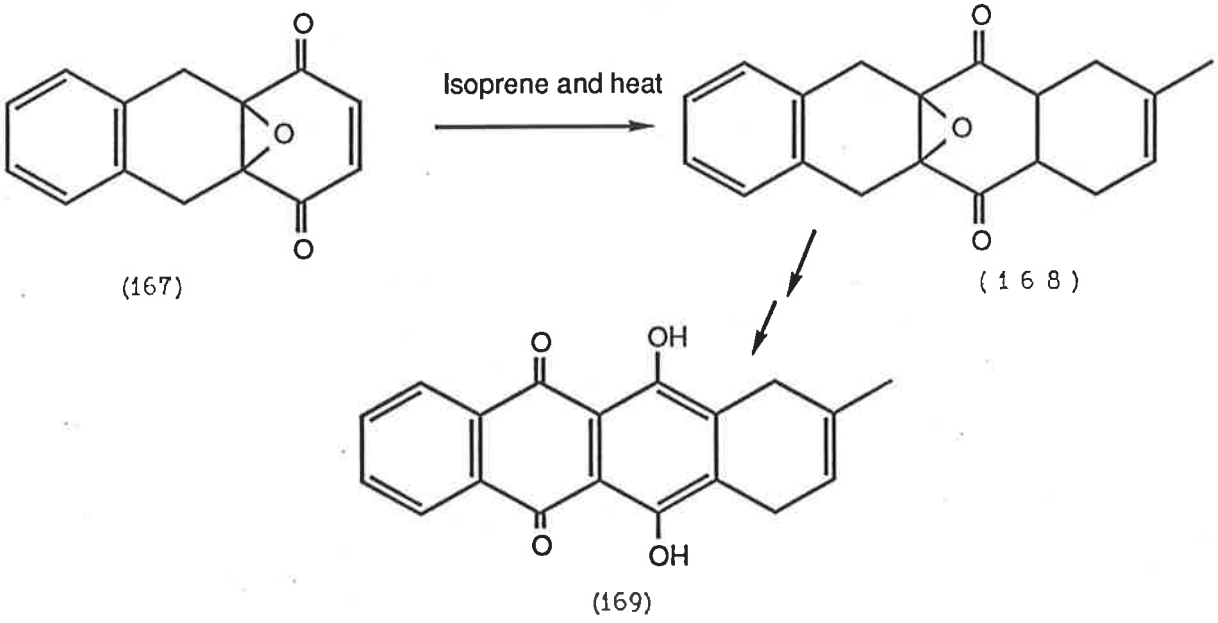
The dione (164) may be useful in the synthesis of anthracyclinone analogues[71] whose general structure is as in (166). It is known that the compound (167) undergoes a Diels Alder reaction with isoprene to give the adduct (168) and subsequently, the quinazerin (169)[72]. Similarly, the dione (164) might react with isoprene and give the adduct (170) which upon selective oxidation[73] could lead to the dimethoxy analogue (171). The di ether (164) could yield analogues of the anthracyclinones that are oxygenated at the 4-position. The naturally occurring anthracyclinones show cytotoxic properties and it is possible that the analogues may also. Unfortunately, because of the particular sensitivity of the dione



R' = OH, H

R" = Me, H

(166)

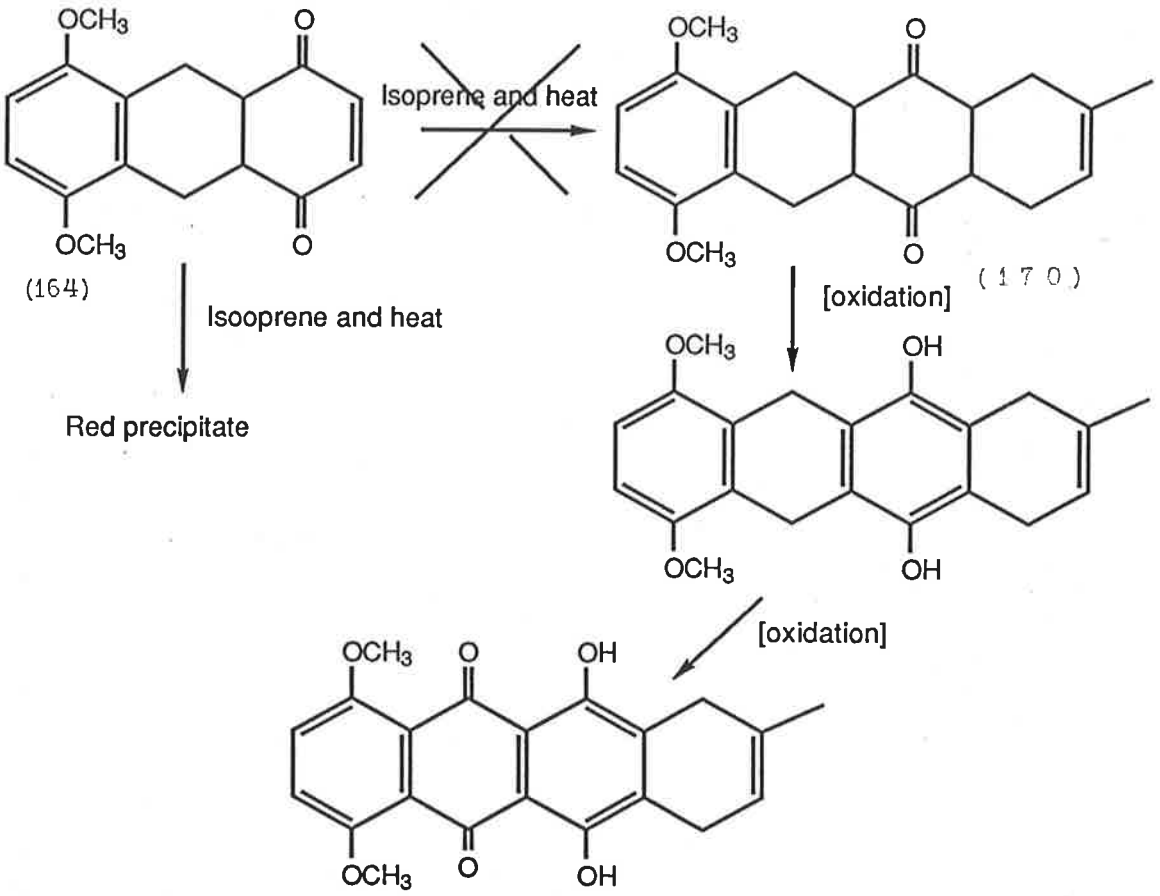


(167) (168)

(169)

adduct (164), it was found to be not useful for the synthesis. Treatment of the dione adduct (164) in toluene with excess isoprene under an atmosphere of nitrogen at reflux (conditions that afforded the dione (168) from the dione (167)) resulted in the formation of the red precipitate.

The investigation into the chemistry of the synthesis of the key intermediate (59) has proved interesing but not simple. With the route first proposed by Spurr involving the "xylelene" chemistry there exists the seemingly insurmountable problem of



(171)

the inability of the dissolving metal reduction to proceed with at least 90% reduction with good recovery of the reduced product. The purification by derivatisation of the keto ol (58) proceeded in very poor yield to give a compound which, although easy to purify, could not be used as the key intermediate and offered only a means of purification. Other chemistry aimed at circumventing the problems by firstly avoiding the formation of the troublesome keto ol (58) using the t-butyldimethylsilyl protecting group met with failure. Selective hydrolysis of enol

ether functionality with mild acid in the presence of the t-butyldimethylsilyl group proved unattainable. Attempts to introduce the *cis* groups at site B through the palladium catalysed carbonylation were also fruitless.

The electrochemistry that was used to synthesise the anhydride (53) was applied in the synthesis of the dione (164). This may eventually yield results in the area of anthracyclinone chemistry if either conditions can be found in which the dione (164) does not degrade rapidly to give the red precipitate.

Experimental

Chapter 4

General

Melting points were determined on a Reichert Hot Stage apparatus and were uncorrected. Microanalyses were performed by the Canadian Microanalytical Service. Petroleum ether refers to a fraction of boiling point 60-70^0. Column chromatography was performed on Sorbsil silica. Drying and purification of other organic solvents was accomplished by standard laboratory procedures[74]. All organic extracts were dried over anhydrous sodium sulphate.

Infrared (I.R.) spectra were recorded on a Jasco IRA-1 grating spectrometer as a neat liquid unless otherwise stated. The 1602 cm^{-1} band of polystyrene was used for calibration. ^1H Nuclear magnetic resonance (N.m.r.) spectra were recorded on a Jeol PMX-60 spectrometer operating at 60 MHz or a Bruker CXP-300 at 300 MHz. Spectral enhancement (where indicated) was carried out by multiplication of the free induction decay by a sine bell curve. Deuterochloroform was used as the solvent unless otherwise specified and tetramethyl silane was used as the internal standard; all chemical shifts are quoted as δ in parts per million and coupling constants are given in Hz. Mass spectra were recorded with an AEI MS 3074 double focussing mass spectrometer or a Zab 2HF double focussing mass spectrometer, both operating at 70eV. Optical rotation measurements were made on a Perkin Elmer model 141 Polarimeter.

Part A

4-Hydroxy-4-methylcylohexa-2,5-dien-1-one (32)

The dienone was synthesised in 20% yield by the method of Goodwin and Witkop[26] in which *p*-tolylhydroxylamine[76] was treated with aqueous dilute sulphuric acid. m.p. 74-76° (Lit.[75] 75-76°). ^{1}H N.m.r. ($CDCl_3$) δ 1.53, s, 3H, CH_3-C-O-; 2.3, s broad, 1H, OH; 6.26, d (ABq), J= 10 Hz, 2H, 2* C=CH-C=O; 7.15, d (ABq), J= 10 Hz, 2H, 2* HC=C-C=O.

N.B. The yield from this reaction was very variable and at no stage was the yield above 33%, the reported yield. The method of Fischer and Henderson[27] (addition of methyl lithium to benzoquinone in ether at -78°) produced mainly hydroquinone and only a small amount of the dienone was detected by NMR.

Attempted synthesis of 4α-hydroxy-4,6-dimethyl-4aα,5,8,8aα-tetrahydronaphthalene-1(2H)-one (34)

Following the general principle outlined by Liotta *et al*[16], the dienone (32) and isoprene were treated with various Lewis acids in various solvents. The solvent and in some trials, unreacted isoprene was removed *in vacuo*.

General Procedure: The dienone (32) (0.15 g 1.2 mMol) in the

solvent indicated (10 ml), freshly distilled isoprene (1 ml) and the appropriate number of molar equivalents of Lewis acid were placed together under nitrogen. After the stated period, the acid complex was hydrolysed in saturated sodium hydrogen carbonate (5 ml) The solution was extracted with dichloromethane (50 ml), dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield the crude product which was analysed by NMR.

Table of results of the Diels Alder Reaction between the dienone (32) and isoprene

Trial #	Solvent	Lewis acid	Equiv. of acid	Time	Result
1	aceto-nitrile	Tin (IV) chloride	2	12H	starting material (32)
2	aceto-nitrile	Tin (IV) chloride	2	48H	isoprene polymer
3	ether	Boron chloride	2	48H	isoprene polymer
4	aceto-nitrile	Tin (IV) chloride	0.9	24H	isoprene polymer

5	toluene	Aluminium chloride	0.9	12H	starting material (32)
6	toluene	Aluminium chloride	0.9	48H	isoprene polymer
7	aceto-nitrile	Aluminium chloride	0.9	12H	isoprene polymer

Reaction of the dienone (32) with 1,3-pentadiene catalysed with tin (iv) chloride.

The dienone (32) (0.15 g 1.2 mMol), toluene (10 ml), freshly distilled 1,3-pentadiene (1 ml) and tin (iv) chloride (0.31 g 1.2 mMol) were placed together under nitrogen. After two days, the acid complex was hydrolysed in saturated sodium hydrogen carbonate (5 ml). The solution was extracted with dichloromethane (50 ml), dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield the crude product which was analysed by NMR. The product appeared to be polymeric material.

Attempted thermal Diels Alder reaction of the dienone (32) with 1,3-pentadiene.

The dienone (32) (0.15 g 1.2 mMol), toluene (10 ml) and freshly distilled 1,3-pentadiene (1 ml) were placed together under nitrogen and heated to reflux temperature. After refluxing for two days, the solvent and any remaining pentadiene were removed from the reaction *in vacuo* to yield the crude product which was analysed by NMR. The product appeared to be polymeric material.

4-Acetyloxy-4-methylcyclohexa-2,5-dien-1-one (65)

The alcohol (32) was treated with acetic anhydride and N,N-dimethylaminopyridine in pyridine under standard conditions to afford the ester (65)[26]. m.p. 40^0 (Lit.[26] 40^0) to afford the ester (65) 0.51 g, 76%. ^1H N.m.r. ($CDCl_3$) δ 1.53, s 3H, CH_3-C-O; 2.03, s, 3H, CH_3-C=O; 6.23, d (ABq), J= 10 Hz, 2H, 2* O=C-CH=C; 6.92, d (ABq), J= 10 Hz, 2H, 2* HC=C-C=O.

Attempted synthesis of acetyl ester (64) (B= acetyloxy) of 4-hydroxy-4,6-dimethyl-4a,5,8,8a-tetrahydronaphthalene-1-one

Trial #1

The ester (65) (0.20 g 1.2 mMol), toluene (10 ml) and freshly

distilled isoprene (0.1 g 1.5 mMol) were placed together under nitrogen in a sealed tube and were heated to 140° for 12 hours. After this time, the solution was cooled and the solvent was removed *in vacuo* to yield the unchanged ester (65) by NMR analysis.

Trial #2

As for Trial #1 but the solution was heated to 200° for 12 hours. The reaction yielded polymeric material by NMR analysis.

1-Methoxy-4-methylcyclohexa-1,4-diene[77] (69)

This compound was prepared in 86% yield by the procedure of Wilds and Nelson[78] from 1-methoxy-4-methylbenzene. ^1H N.m.r. ($CDCl_3$) δ 1.60, s, 3H, CH_3-C=C; 2.62, broad s, 4H, 2* CH_2C=C; 3.43, s, 3H, CH_3O-; 4.50, broad s, 1H, HC=C-O-C; 5.23, broad s, 1H, HC=C-C.

4-Bromo-1,1-dimethoxy-4-methylcyclohexane (73)

Liquid hydrogen bromide (2 ml) was distilled onto the enol ether (69) (1.0 g 8.1 mMol) which was cooled in liquid nitrogen. As the two phase system was allowed to warm slowly, the solid

enol ether gradually dissolved. (Frequent cooling was needed to avoid too rapid a reaction.) After dissolution, the liquid was allowed to warm to room temperature and the remaining hydrogen bromide was removed under reduced pressure to afford a brown liquid, the bromo methyl ethers, (71) and (72) 2.3 g quantitative yield. ^1H N.m.r. ($CDCl_3$) δ 1.0-2.0, complex m, 8H, cyclohexyl ring; 1.87, s, 3H, CH_3-C-Br; 3.43, s, 3H, CH_3O-C-Br.

To this, methanol (3 ml) was added, the solution was allowed to stand for 30 minutes then powdered sodium hydrogen carbonate was added until effervescence ceased, dichloromethane (20 ml) was added, the solution was dried (Na_2SO_4) and the solvent removed in *in vacuo* to yield the bromo ether (73) as a colourless oil which turned brown rapidly 1.90 g, quantitative yield. The compound was too unstable to attempt purification but the crude product was of sufficient purity for use in subsequent synthesis. (Found: 157.1226 M^+ - Br $C_9H_{17}O_2Br$ - Br requires 157.1229) ν_{max} 3550 (weak), 1720 (weak), 1680, 1090, 1050, 890 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.0-2.0, complex m, 8H, cyclohexyl; 1.83, s, 3H, CH_3-C-Br; 3.10, s, 3H, CH_3O-; 3.17, s, 3H, CH_3O-. Mass spectrum *m/z* 157 (M^+ - Br), 122, 105.

Attempted hydrolysis of 4-Bromo-1,1-dimethoxy-4-

methylcyclohexane (73)

The acetal (73) (0.50 g 2.1 mMol), acetone (5 ml), water (0.5 ml) and oxalic acid (0.10 g, 1.1 mmol) were combined, the solution was allowed to stand at room temperature overnight, Dichloromethane (25 ml) was added, the acid was neutralised with anhydrous $NaHCO_3$, the organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to yield a light brown oil 0.23 g. TLC analysis of the oil showed that it consisted of a complex mixture of more than six products which were not separated.

4-Bromo-4-methylcyclohexan-1-one (70)

To the bromo methyl ethers (71) and (72) (2.3 g 8.0 mMol), prepared as above, acetone (5 ml) then water (1 ml) were added. The solution was allowed to stand for 15 minutes, dichloromethane (25 ml) then anhydrous powdered sodium hydrogen carbonate was added until effervescence ceased. The solution was dried (Na_2SO_4) and the solvent was removed *in vacuo*. Care was taken not to heat the material over 50^0. The resultant brown oil which smelt of hydrogen bromide was too unstable for purification and lost hydrogen bromide at a rapid rate 1.54 g quantitative yield. (Found: 111.0795 $M^{+\cdot}$ $C_7H_{11}OBr$ - Br requires

111.0810). ν_{max} 1710, 1260, 740 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.0-3.0, 8H, cyclohexyl; 1.93, s, 3H, CH_3-C-Br. Mass spectrum *m/z* 111 (M^+ - Br), 91, 81.

5-Methyl-bicyclo[3.1.0]hexan-2-one (74) from the bromo ketone (70).

To the bromo ketone (70) (2.0 g 11 mMol) in ethanol (10 ml) under nitrogen, sodium hydride (oil free, 0.40 g 17 mMol) was cautiously added. The solution was left over night, saturated ammonium chloride (2 ml) was added, the solvent was removed *in vacuo*, the wet oil was diluted with dichloromethane (50 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to afford a light brown oil. The compound was distilled (bulb to bulb) 50^0 at 22 mm of Hg. 0.31 g 27%. The compound thus prepared had an NMR spectrum the same as that of the bicyclo[3.1.0]hexan-2-one prepared in an alternative manner[29].

5-Methyl-bicyclo[3.1.0]hexan-2-one (74) from 3-methyl-2-cyclopenten-1-one.

The bicyclohexanone (74) was prepared in 36% yield by the action of the anion of trimethyl sulphoxonium iodide in DMF on

cyclopentanone as described by Bloss, Brook and Ellam[29]. N.m.r. ($CDCl_3$) δ 1.20, s, 3H, CH_3-; 1.0-1.6, m, 3H, cyclopropyl; 2.03, broad s, 4H, cyclopentanyl CH_2CH_2-C=O. Mass spectrum *m/z* 110 ($M^{+\cdot}$) 82, 68, 67.

4-Chloro-1,1-dimethoxy-4-methylcyclohexane (77) from the chloro methyl ethers (76)

Liquid hydrogen chloride (2 ml) was distilled onto the enol ether (69) (1.0 g 8.1 mMol) which was cooled in liquid nitrogen. The two phase system was allowed to warm slowly and the solid enol ether dissolved. Frequent cooling was needed to avoid too rapid a reaction. Upon complete dissolution, the liquid was allowed to warm to room temperature, the remaining hydrogen chloride was removed *in vacuo* affording a colourless liquid, the chloro methyl ethers (76) 1.6 g quantitative yield. ^1H N.m.r. ($CDCl_3$) δ 1.67, s, 3H, CH_3-C-Br; 2.0-2.8, complex m, 8H, CH_2 cyclohexyl; 3.36, s, 3H, CH_3O-C-Cl (1 isomer); 3.47, s, 3H, CH_3O-C-Cl (other isomer).

To this, methanol (3ml) was added. The solution was allowed to stand for 30 minutes, powdered sodium hydrogen carbonate was added until effervescence ceased and dichloromethane (20ml) was added. The solution was dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield the chloro acetal (77)

as a colourless oil, 1.44g, 98%. The compound was of sufficient purity for use in subsequent synthesis. (Found: 161.0733 $M^{+\cdot} - OCH_3$ $C_9H_{17}O_2Cl$ - OCH_3 requires 161.0733). ν_{max} 1080, 1040 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.60, s, 3H, CH_3; 1.2-2.1, m, 8H, cyclohexyl; 3.07, s, 3H, CH_3O-; 3.12, s, 3H, CH_3O-. Mass spectrum *m/z* 161/163 $(M-OCH_3)^+$, 157, 126, 101.

4-chloro-4-methylcyclohexan-1-one (75)

Procedure A:

To the acetal (77) (0.50 g 2.6 mMol) and acetone (5 ml) enough water was added to make the solution just turbid. Acetone was added to just clarify the solution, oxalic acid (0.10 g, 1.1 mmol) was added and the solution was allowed to stand at room temperature overnight. Dichloromethane (25 ml) was added, the acid solution was neutralised with anhydrous $NaHCO_3$ and was dried (Na_2SO_4). The solvent was removed *in vacuo* to yield a light yellow oil 0.35 g, 93%. Although unstable even at 0^0 for long periods, the ketone was of sufficient purity for subsequent work if used within a day. (Found: 146.0502 $M^{+\cdot}$ $C_7H_{11}OCl$ requires 146.0498). ν_{max} 1720, 1190 cm^{-1}. ^1H N.m.r.

(benzene d6) δ 2.00, s, 3H, CH_3-C-Cl; 1.6-3.2, m, 8H, cyclohexyl. Mass spectrum *m/z* 146/148 ($M^{+\cdot}$), 110, 82.

Procedure B:

To the chloro methyl ethers (76) (1.60 g 8.1 mMol), prepared from the enol ether (69), acetone (5ml) and water (1 ml) were added. The solution was allowed to stand for 15 minutes before dichloromethane (25ml) was added and the solution was washed with saturated sodium hydrogen carbonate (3 * 60 ml), dried (Na_2SO_4) and the solvent was removed *in vacuo*. Care was taken not to heat the material over 50^0. The resultant oil had the same properties as that obtained by procedure A, 1.13 g 95%.

5-Methyl-bicyclo[3.1.0]hexan-2-one (74)

Trial #1

To a solution of d6-benzene (0.5 ml) and the chloro ketone (75) (40 mg 2.7μMol) sodium hydride (10 mg 4.2 μMol) was added. The reaction was allowed to stand for 2 days, water was added, the brown solution was dried and the solvent removed *in vacuo*. The mixture thus prepared showed 2 peaks by gas chromatography, one of these (15% OV101 150^0 retention time about

4') had a mass spectrum and retention time identical with that of the bicyclo[3.1.0]hexan-2-one (74) prepared in an alternative manner[29]. Mass spectrum *m/z* 110 ($M^{+\cdot}$) 82, 68, 67.

Trial #2

To a solution of the chloro ketone (75) (200 mg 1.4 mMol) in t-butanol (3 ml) potassium t-butoxide (0.31g 2.8 mMol) was added. After 45 minutes, the solution was diluted with dichloromethane (50 ml), washed with water, dried (Na_2SO_4) and the solvent removed *in vacuo* to yield the crude product which was chromatographed with chloroform (1% ethanol stabilised) to yield the bicyclohexanone (74) 92 mg 61%.

Trial #3

To a solution of the chloro ketone (75) (2.0g 14 mMol) in ethanol (10ml) under nitrogen, oil free sodium hydride (0.5g 2.1 mMol) was cautiously added. The solution was allowed to stand for 3 hours. After that period, saturated ammonium chloride solution (2ml) was added, the mixture was extracted with dichloromethane (50ml, 25ml), the combined organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo* to afford a light brown oil. The bicyclohexanone (74) was purified

by chromatography on silica gel with chloroform as the eluent 1.05 g 70%.

1-Methoxy-4-(1-methylethyl)cyclohexa-1,4-diene[33] (78)

This compound was prepared in 85% yield by the procedure of Wilds and Nelson[78] from the dissolving metal reduction of 1-methoxy-4-(1-methylethyl)benzene (79). (Found: 152.1205 $M^{+\cdot}$ $C_{10}H_{16}O$ requires 152.1201.). ν_{max} 1690, 1660, 1220, 1170, 780 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.04, d, J= 7 Hz, 6H, $CH_3)_2C$-; 2.13, septet, J= 7 Hz, 1H, CH-C=C; 2.73, broad s, 4H, 2* CH_2C=C; 3.51, s, 3H, CH_3O-; 4.60, broad s, 1H, HC=C-O-C; 5.37, s, 1H, HC=C-C-. Mass spectrum *m/z* 152($M^{+\cdot}$), 137.

4-Chloro-1,1-dimethoxy-4-(1-methylethyl)cyclohexane (81)

The chloro ether was prepared in an analogous manner to that described for the chloro acetal (77) in 97% yield from the enol ether (78). The crude product was sufficiently pure for further synthesis. m.p. 39-41^0 (Found: 189.1046 $M^{+\cdot}$-OCH_3 $C_{11}H_{21}O_2Cl$ -OCH_3 requires 189.1046). ν_{max} (nujol) 1240, 1100, 1050, 900 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.01, d, J= 8 Hz,

6H, $CH_3)_2C$-; 1.51-2.17, m, 9H, 8H cyclohexyl + CH-C-Cl; 3.05, s, 3H, CH_3O-; 3.11, s, 3H, CH_3O-. Mass spectrum *m/z* 189/191 $(M-OCH_3)^+$, 153, 102.

4-Chloro-4-(1-methylethyl)cyclohexan-1-one (11)

The chloroketone was prepared from either the acetal (81) in 98% yield or directly from the enol ether (78) in 99% yield in an analogous manner to either of the procedures for the preparation of the chloroketone (75). The chloroketone (11) was recrystallised from light petroleum cooled to -78^0, m.p. $55-57^0$. (Found: C, 61.8; H, 8.3; 174.0811 $M^{+\cdot}$ $C_{10}H_{15}OCl$ requires C, 61.9 % H, 8.7% ; 174.0811). ν_{max} (Nujol) 1720, 820 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.08, d, J= 7 Hz, 6H, $CH_3)_2C$-; 1.68-3.01, m, 9H, 8H cyclohexyl + CH-C-Cl. Mass spectrum *m/z* 174/176 ($M^{+\cdot}$), 84.

+- 5-(1-Methylethyl)bicyclo[3.1.0]hexan-2-one (Sabina ketone) (12)

This compound was prepared in 81% yield in a similar manner to that described for the preparation of the bicyclic ketone (74). The chloroketone (11) was treated with sodium ethoxide in ethanol

for three hours. The compound was purified by bulb to bulb distillation b.p 100^0 at 14 mm Hg (Lit.[31b] $67-70^0$ at 5 mm Hg). The ketone had identical properties in all respects (except for the rotation of the plane of polarised light) to those reported for the natural product[32]. N.m.r. ($CDCl_3$) δ 0.9-1.3, 2*d superimposed (diastereotopic) obscuring cyclopropyl peaks, 8H, $CH_3)_2C-$ + CH_2 cyclopropyl; 1.3-2.0, m, 1H, CH-C=O cyclopropyl; 2.00, s, 4H, CH_2CH_2-C=O.

N-benzyl 1,7,7-trimethylbicyclo[2.2.1]hepan-2-imine (93) from natural (+) Camphor

Natural camphor was condensed with aniline using molecular sieves as a dehydrating agent in 85% yield as described by Roelofsen and Van Bekkum[79]. The imine (93) was distilled at 86^0 at 0.08 mm Hg. (Lit[79] $106-108^0$ at 0,6 mm Hg) 19.3 g 85%. ^1H N.m.r. ($CDCl_3$) δ 0.87, s, 3H, CH_3 (gem); 0.97, s, 3H, CH_3 (gem); 1.10, s, 3H, CH_3 (bridgehead); 1.2-2.2 complex m, 7H, 3* CH_2 + CH; 6.5-7.3, m, 5H, CH aromatic.

Chiral N-benzyl 1,7,7-trimethylbicylo[2.2.1]heptan-2-amine (92)

The imine (93) was reduced with lithium aluminium hydride in THF under standard conditions to afford the amine (92)[38].

To a solution of lithium aluminium hydride (1.00 g 26.3 mMol) in dry THF (50 ml), the imine (93) (4.54 g 20.0 mMol) was added. The mixture was allowed to reflux over night before water (1.0 ml) was added with vigorous stirring. After 15 minutes, 50% sodium hydroxide solution (1.0 ml) was added then after another 15 minutes, water (3.0 ml) was added. The slurry of precipitated lithium and aluminium salts was allowed to stir for 15 minutes before the organic solution was filtered off. The solvent was removed *in vacuo* to yield a colourless viscous oil which was purified by bulb to bulb distillation 100^0 at 0.05 mm Hg to yield the amine (92) as a colourless oil 3.20 g 70%. ^1H N.m.r. ($CDCl_3$) δ 0.83, s, 3H, CH_3; 0.97, s, 3H, CH_3: 1.10, s, 3H, CH_3; 1.3-2.0, complex m, 7H, 3* CH_3 + 3* CH_2 + CH bridgehead; 3.25, t (broad), 1H, CH-N; 3.7, broad s, 1H, HN; 6.5-7.5, m, 5H, CH aromatic.

Attempted asymmetric synthesis of Sabina Ketone 2,4-dinitrophenylhydrazone (94)

The procedure of Simpkins[37] was used as a basis for the reaction.

The chiral lithium amide was synthesised as follows. To the

amine (92) (0.641 g 2.80 mMol) in dry THF under nitrogen at 0^0, n-butyl lithium (2.80 mMol) was added. The solution was allowed to warm to room temperature over 2 hours before being chilled to -78^0.

The ketone (11) (0.500 g 2.800 mMol) in dry THF (5 ml) was added dropwise to the amide solution which was stirred for 8 hours at -78^0 then allowed to warm to room temperature. Saturated ammonium chloride (0.5 ml) was added, the solvent was removed *in vacuo* and the resultant wet oil was taken up in dichloromethane (20 ml), washed with saturated ammomium chloride (2* 20 ml), saturated sodium chloride (2* 20 ml) then water (2* 20 ml), dried (Na_2SO_4) then the solvent was removed *in vacuo* to yield an oil which was purified by chromatography on silica gel with 15% ethyl acetate in petroleum ether as the eluent. The crude ketone (12) was converted to its 2,4-dinitrophenylhydrazone (94) by treatment with 2,4-dinitrophenylhydrazine in ethanol (10 ml) with concentrated hydrochloric acid (2 drops) as described by Vogel[80]. After 3 hours, the solution was filtered, the precipitate collected, washed with ethanol (10 ml) and recrystallised from carbon tetrachloride 0.50 g 46% m.p. 124^0 (Lit.[39] 124^0). The specific rotation of a solution of the hydrazone (94) (0.100 g) in chloroform (10.00 ml) was 0.0^0. This concentration was limiting as at higher concentrations, the absorbtion of the solution was too great for

accurate measurement of the specific rotation. The specific rotation[39] of the 2,4-dinitrophenylhydrazone of natural sabina ketone (11) is $+135.2^0$.

1-Methoxy-4-(1,1-dimethylethyl)cyclohexa-1,4-diene[35] (84)

The enol ether was prepared in 77% yield by the method of Wilds and Nelson[78] by the dissolving metal reduction of 1-methoxy-4-*t*-butylbenzene. ^1H N.m.r. ($CDCl_3$) δ 1.03, s, 9H, t-butyl; 2.65, broad s, 4H, 2* $CH_2C{=}C$; 3.43, s, 3H, CH_3O-; 4.45, broad s, 1H, CH=C-O-C; 5.32, broad s, 1H, CH=C-C-.

4-Chloro-1,1-dimethoxy-4-(1,1-dimethylethyl)cyclohexane (85)

The chloro acetal (85) was prepared in 95% yield from the enol ether (84) in an analogous manner to that described for the preparation of the chloro acetal (77). The crude product was of sufficient purity for further synthesis. (Found: 203.1205 $M^{+\cdot} - OCH_3$ $C_{12}H_{23}O_2Cl - OCH_3$ requires 203.1203). ν_{max} 2800, 1240, 900 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.10, s, 9H, t-bytyl; 1.80, s, 8H, cyclohexyl; 3.03, s, 3H, CH_3O-; 3.10, s, 3H, CH_3O-. Mass spectrum *m/z* 203/205 ($M^{+\cdot}$-

OCH_3), 167, 101.

4-Chloro-4-(1,1-dimethylethyl)cyclohexan-1-one (87)

The chloro ketone was prepared from either the chloro ether (85) in 95% yield or directly from the enol ether (84) in 95% yield in an analogous manner to either of the procedures for the preparation of the chloro ketone (75). The chloro ketone (87) was recrystallised from light petroleum cooled to -78^0, m.p. $69-71^0$. (Found: C, 64.0; H, 9.0; 188.0971 $M^{+\cdot}$ $C_{10}H_{17}OCl$ requires C, 63.7% H, 9.1% ; 188.0968). ν_{max} (Nujol) 1720, 835 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.16, s, 9H, $C(CH_3)_3$; 1.5-2.7, m, 8H, cyclohexyl. Mass spectrum *m/z* 188/190 ($M^{+\cdot}$), 173, 152.

5-(1,1-dimethylethyl)bicyclo[3.1.0]hexan-2-one (83)

This compound was prepared in 50% yield in a similar manner to that described for the preparation of the ketone (74). The chloroKetone (87) was treated with sodium ethoxide in ethanol for 24 hours. The product was purified by chromatography on silica gel with 10% ethyl acetate in petroleum ether as the eluent to yield the bicyclohexanone (83) as a colourless oil. (Found: C, 78.8; H, 10.6; 152.1205 $M^{+\cdot}$ $C_{10}H_{16}O$

requires C, 78.9% H, 10.6% ; 152.1201). ν_{max} 1720, 1360 cm^{-1}. ^1H N.m.r. (CCl_4) δ 0.90, s, 9H, t-butyl; 1.1-1.9, m, 3H, cyclopropyl; 1.97, broad s, 4H, CH_2CH_2-C=O (cyclopentanyl). Mass spectrum *m/z* 152 ($M^{+\cdot}$), 137, 135, 95.

1,4-Dioxaspiro[4.5]decan-8-one (114)

The method of Courtot[47] was employed whereby cyclohexane-1,4-dione (115) was treated with ethylene glycol under dehydrating conditions. ^1H N.m.r. ($CDCl_3$) δ 2.0, complex m, 4H, 2* CH_2C-O; 2.5, complex m, 4H, 2*$CH_2C=O$; 4.00, s, 4H, $-OCH_2CH_2O-$.

(1,4-Dioxaspiro[4.5]dec-8-ylidene)acetic acid ethyl ester (117)

To triethylphosphonoacetate (21.5g 96.0 mMol) in dry THF (75 ml) under nitrogen, sodium hydride (2.3 g 96 mMol) was cautiously added and the solution was allowed to stir until effervescence ceased (about 30 minutes), flushed with nitrogen and sealed with a rubber seal. The mono acetal (114) (10 g, 64 mMol) in dry THF (25 ml) in a 30 ml syringe was perfused into the phosphonate solution over 6 hours. After the reaction had stirred overnight, it was refluxed for 24 hours, diluted with water (100 ml), stirred for 1 hour and was extracted with dichloromethane (2*200 ml). The organic solution was washed with water, dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield a light brown oil which was purified by chromatography on silica gel with 20% ethyl acetate in petroleum ether as the eluent to yield the ester (117) as a colourless oil 9.70g 67%. (Found: C, 63.9; H, 8.0; $C_{12}H_{18}O_4$

requires C, 63.7%, H, 8.0%). ν_{max} 1700, 1630 (weak), 1150, 1070 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.08, t, J= 7 Hz, 3H, CH_3-C-O-; 1.33, m, 4H, 2* CH_2C-O (cyclohexyl); 2.25, m, 2H, CH_2C=C; 2.9, m, 2H, CH_2C=C (possibly *trans* to ester and deshielded); 3.75, s, 4H, -OCH_2CH_2O-; 4.08, q, J= 7 Hz, 2H, -CH_2-OC=O-; 5.75, broad s, 1H, O=C-CH=C. Mass spectrum *m/z* 226 ($M^{+\cdot}$) 197, 181, 153.

8-hydroxyethylidene-1,4-dioxaspiro[4.5]decane (118)

To a solution of lithium aluminium hydride (1.0 g 26 mMol) in dry ether (25 ml), the ester, (117) (4.0 g 18 mMol) in ether (20 ml) was added. The mixture was allowed to reflux over night before water (1.0 ml) was added. After 15 minutes, 50% sodium hydroxide (1.0 ml) was added then after a further 15 minutes, water (3.0 ml) was added. The slurry of salts was allowed to stir for 15 minutes, the solution was filtered off and the solvent was removed *in vacuo* to yield a colourless viscous oil 2.96 g 91%. The alcohol was purified by chromatography on silica gel with ethyl acetate as the eluent. (Found: C, 64.9; H, 8.7; $C_{10}H_{16}O_3$ requires C, 65.2%, H, 8.7%). ν_{max} 3500, 1660 (weak), 900 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.5-1.8, complex m, 4H, 2*CH_2C-O (cyclohexyl); 2.0-2.5, complex m, 5H, 2*CH_2C=C + OH;

3.93, s, 4H, $-OCH_2CH_2O-$; 4.08, d, J= 7 Hz, 2H, $C=CCH_2O-$; 5.33, t (broadened), J= 7 Hz, HC=C. Mass spectrum *m/z* 184 ($M^{+\cdot}$), 182, 171, 156, 127, 99, 89.

4-hydroxyethylidenecyclohexan-1-one (119)

To the acetal (118) (1.0g 5.4 mMol) in acetone (5 ml) enough water was added to make the solution cloudy then enough acetone was added to clarify the solution. Oxalic acid (2.0 g 22 mMol) was added, the solution was allowed to stand over night then solid sodium hydrogen carbonate was added until efffervescence ceased. The mixture was diluted with dichloromethane (50 ml), extracted with water (2* 20 ml), dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield a mixture containing the ketone (119). Chromatography on silica gel with ethyl acetate as the eluent provided the ketone (119) as a colourles oil 0.73 g 96%. (Found: C, 66.2; H, 8.7; 122.0732 $M^{+\cdot} - H_2O$ $C_8H_{12}O_2$ requires C, 68.6%, H, 8.6%; 122.0732). ν_{max} 3500, 1710, 1660 (shoulder on 1710), 1000 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 2.45, *s* (broad $w_{1/2}$ = 4 Hz), 8H, 4* CH_2 cyclohexyl; 4.15, d, J= 6 Hz, 2H, $C=CCH_2-O$; 5.55, t, J= 6 Hz, 1H, HC=C; OH resonance not discernable. Mass spectrum *m/z* 122 ($M^{+\cdot} - H_2O$), 79, 70.

2-hydroxymethyl-1-oxaspiro[2.5]octan-6-one (113)

The allylic alcohol (119) (0.5 g 3.6 mMol) in dichloromethane (10 m) at 3^0 was treated with 3-chloroperoxybenzoic acid (0.8 g 80% 3.7 mMol) in dichloromethane (10 ml) over 3 minutes. The solution was allowed to stand over night, was chilled to -78^0 and filtered. The precipitate was washed with dichloromethane (2* 20 ml) and the combined organic solution was concentrated by evaporation *in vacuo* at room temperature. The crude product was purified by chromatography on silica gel with ethyl acetate as the eluent. The epoxide proved to be very water soluble so aqueous washing was not advisable. 0.38 g 68%. (Found: C, 60.4; H, 7.7; $C_8H_{12}O_3$ requires C, 61.5%, H, 7.7%). ν_{max} 3500, 1700, 790 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.8-3.0 complex m, 9H, 4* CH_2 cyclohexyl + OH; 3.13, t, J= 6 Hz, 1H, HC-O epoxide; 3.83, d, J= 6 Hz, 2H, O-C-CH_2-O-. Mass spectrum *m/z* 157 ($M^{+\cdot}$ +H^+), 156 ($M^{+\cdot}$), 113, 71, 67.

Accurate Mass: Found 156.0777 calculated 156.0786

The methoxymethyl ether (120) of 2-hydroxymethyl-1-oxaspiro [2.5]octan-6-one prepared by the method of Corey, Gras and Ulrich[49]

To the alcohol (113) (5 g 3.2 mMol) in dichloromethane (20 ml) and di*iso*propylethylamine (0.45 g 3.5 mMol) under nitrogen,

methoxymethyl chloride (0.39 g 4.8 mMol) was added in small portions. After 1 hour, the solution was extracted with saturated ammonium chloride, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The methoxymethyl ether (120) was purified by chromatography on silica gel with 40% ethyl acetate in petroleum ether as the eluent as a colourles oil 0.48 g, 75%. (Found: C, 59.1; H, 8.0; 169.0862 ($M^{+\cdot}$ - OCH_3) $C_{10}H_{16}O_4$ requires C, 60.0%, H, 8.0%; 169.0865). ν_{max} 1700, 1150, 920 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.8-2.2, complex m, 4H, 2* CH_2-C-O cyclohexyl; 2.3-2.6, complex m, 4H, 2* CH_2-C=O; 3.16, t, J= 6 Hz, 1H, HC-O epoxide; 3.37, s, 3H, CH_3O-; 3.72, d, J= 6 Hz, 2H, O-C-CH_2O-; 4.65, s, 2H, OCH_2O-. Mass spectrum *m/z* 169 ($M^{+\cdot}$ -CH_2OH), 155, 125.

5-(1',2'-Dihydroxyethyl)-bicyclo[3.1.0]hexan-1-one 2' methoxy-methyl ether (121)

To the ether (120) (0.10 g 0.5 mMol) in ethanol (5 ml) under nitrogen, sodium hydride (0.1 g 4.2 mMol) was added. The solution was allowed to stand for an hour, the solvent was removed *in vacuo* then saturated ammonium chloride (0.5 ml) was added. The slurry was diluted with dichloromethane (50 ml), dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield a brown oil which was purified by chromatography on

silica gel with 75% ethyl acetate in petroleum ether as the eluent to afford the alcohol (121) as a colourles viscous oil 56 mg 56%. (Found: C, 61.1; H, 7.9; $C_{10}H_{16}O_4$ requires C, 60.0%, H, 8.0%). ν_{max} 3500, 1710, 1150, 1040 cm^{-1}. ^1H N.m.r. (see results and discussion for 300 MHz spectrum and COSY spectrum of (121)) ($CDCl_3$) δ 1.0-2.3, complex m, 7H, bicyclo[3.1.0]hexyl; 3.33, s, 3H, CH_3O-; 3.3-4.0, complex m, 4H, HC-O- + OH + O-C-CH_2O-; 4.61, s, 2H, OCH_2O-. Mass spectrum *m/z* 169 (M^+ - OCH_3), 125, 83. Accurate Mass: Found 169.0870 calculated 169.0865

Triethyl 2-phosphonopropionate (123)

The Emmons-Wittig reagent was synthesised in 60% yield following the method of Gallagher and Webb[52] by treatment of triethyl phosphite with ethyl 2-bromopropionate. The resultant oil was distilled (115-118^0 at 4 mm) (Lit.[52] 115-118^0 at 4 mm of Hg). ^1H N.m.r. ($CDCl_3$) δ 1.2-1.8, m, 12H, 3* CH_3 + CH_3-C-P=O; 2.90, d * d, J_{HC-CH}= 7 Hz & J_{HC-P}= 24 Hz, 1H, CH-P=O-; 3.9-4.3, m, 6H, 3*CH_2O-.

2-(1,4-Dioxaspiro[4.5]dec-8-ylidene)propanoic acid ethyl ester (124)

The ester was the product in 61% yield of the reaction of cyclohexane dione mono ethylene glycol acetal (114) and the phosphonate reagent (123) under the conditions described for the preparation of the ester (117). The ester (124) was purified by chromatography on silica gel with 20% ethyl acetate in petroleum ether as the eluent. (Found: C, 65.1; H, 8.3; $C_{13}H_{20}O_4$ requires C, 65.0%, H, 8.4%). ν_{max} 1700, 1360, 1280, 1200 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.30, t, J= 8 Hz, 3H, CH_3-C-O-; 2.0-2.8, complex m, 8H, 4* CH_2 cyclohexyl; 2.03, s, 3H, CH_3-C=C; 3.98, s, 4H, $-OCH_2CH_2O-$; 4.18, q, J= 8 Hz, 2H, $-CH_2$-O-. Mass spectrum *m/z* 240 ($M^{+\cdot}$) 211, 195, 194, 167.

8-(1-Hydroxymethylethylidene)-1,4-dioxaspiro[4.5]decane (125)

The alcohol (125) was the product in 91% yield of the lithium aluminium hydride reduction of the ester (124) in ether under standard conditions. The alcohol was chromatographed on silica with ethyl acetate as the eluent. (Found: C, 66.7; H, 9.2; $C_{11}H_{18}O_3$ requires C, 66.6%, H, 9.2% ;). ν_{max} 3300, 1100 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.6-2.6, complex m, 9H, 4* CH_2 cyclohexyl + OH; 1.76, s, 3H, CH_3C=C; 3.90, s, 4H, -

OCH_2CH_2O-; 4.06, s (broad), 2H, $-CH_2O$.
Mass spectrum *m/z* 198 ($M^{+\cdot}$) 180, 167, 158.

4-(1-Hydroxymethylethylidene)cyclohexan-1-one (122)

The ketone (122) was obtained as the product of the acid catalysed hydrolysis of the acetal (125) in 73% yield by the procedure described for the preparation of the ketone (119). The ketone was purified by chromatography on silica gel with ethyl acetate as the eluent. After the elution of a small amount of the acetal (125) (0.32g), the keto ol (122) was isolated as an oil (1.14g 73%). (Found: C, 68.5; H, 9.2; 154.0999 $M^{+\cdot}$ $C_9H_{14}O_2$ requires C, 70.1%, H, 9.2% ; 154.0994). ν_{max} 3300, 1700, 980 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.76, s, 3H, $CH_3-C=C$; 1.8-2.8, broad s, 9H, 4* CH_2 cyclohexyl + OH; 4.00, s (broad), 2H, $-CH_2O$-. Mass spectrum *m/z* 154 ($M^{+\cdot}$) (weak), 136, 94, 79.

rac- 2-Hydroxymethyl-2-methyl-1-oxaspiro[2.5]octan-6-one (126)

The alcohol (122) was epoxidised in 80% yield by the action of 3-chloroperoxybenzoic acid in dichloromethane by the same procedure in which the epoxide (113) was prepared. The epoxide (122) was chromatographed on silica and eluted with 30% petroleum

ether in ethyl acetate. (Found: C, 62.3; H, 8.5; $C_9H_{14}O_3$ requires C, 63.5%, H, 8.2%). ν_{max} 3300, 1710, 1040 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.47, s, 3H, CH_3-C-O-; 1.8-2.9, complex m, 8H, 4* CH_2 cyclohexyl; 3.68, s, 2H, CH_2O-; OH resonance not observed. Mass spectrum *m/z* 86, 84, 59. Accurate Mass: Found 171.1029 (M+1) calculated 171.1021

1-(1,2-Dihydroxy-1-methylethyl)bicyclo[3.1.0]hexan-4-one (127) as an equal mixture of diasteromers

To the racemic epoxide (126) (0.10 g 0.59 mMol) in dry THF (5 ml) under nitrogen, potassium *t*-butoxide (66 mg 0.59 mMol) was added. The solution was allowed to stir at room temperature for 24 hours. Acetic acid (5 drops) was added, the solvent was removed *in vacuo* to yield a crusty brown mass which contained potassium acetate and the diol (127) which was purified by chromatography on silica gel with ethyl acetate as the eluent. The pure diol (127) (as a mixture of diastereomers) was obtained as an oil which crystallised on standing after a few days 12 mg 12%. N.B. The diol (127) proved to be extremely water soluble hence all experimental manipulations were carried out so as to preclude the possibility of loss of the compound through aqueous washing. m.p. 93-95° (1^{st} melt) 105-110° (total melt). (Found: C, 62.6; H, 8.2; 139.0762 $M^{+\cdot}$ - CH_2OH_2 $C_9H_{14}O_3$

requires C, 63.5%, H, 8.2% ; 139.0759). ν_{max} 3500, 1710, 1190, 1050 cm^{-1}.

N.m.r. ^1H (see results and discussion for 300 MHz COSY spectrum) ($CDCl_3$) (300 MHz) δ

0.95, dd, J= 5 Hz & 3 Hz, 1H, CH cyclopropyl (one diastereomer);

1.02, dd, J= 5 Hz & 3 Hz, 1H, CH cyclopropyl (one diastereomer);

1.21, s, 3H, CH_3-C-O (one diastereomer);

1.26, s, 3H, CH_3-C-O (one diastereomer);

1.56, dd, J= 9 Hz & 5 Hz, 1H, CH cyclopropyl (one diastereomer);

1.67, dd, J= 9 Hz & 5 Hz, 1H, CH cyclopropyl (one diastereomer);

1.8-2.4. complex m, 5H, CH_2CH_2 from bicyclo[3.1.0]hexanone ring + CH-C=O cyclopropyl;

3.50, d (ABq), J= 11 Hz, 1H, CH-O (one diastereomer);

3.54, d (ABq), J= 11 Hz, 1H, CH-O (one diastereomer);

3.61, d (ABq), J= 11 Hz, 1H, CH-O (one diastereomer);

3.70, d (ABq), J= 11 Hz, 1H, CH-O (one diastereomer);

Two hydroxyl resonances not discernable

Mass spectrum *m/z* 170 (M^+ very weak), 139, 97.

Trials for the preparation of one diastereomer of the diol (127)

The trials were carried out on 50 - 100 mg of the racemic epoxide (126). The reactions were worked up by addition of acetic acid (5 drops), the solvent was removed *in vacuo* and the

diastereomer mixtures were isolated from the crude reaction product by chromatography on silica gel with ethyl acetate as the eluent and then were analysed by 300 mHz ^{1}H NMR. The success of the diastereoselection was calculated as the average of the integral ratio of the cyclopropyl peaks at δ {1.02 + 1.67} for one diastereomer pair & {0.95 + 1.56} for the other, the singlet methyl resonances at δ 1.26 for one & 1.21 for the other and the methylene ABq resonances at δ {3.50 + 3.61} for one & {3.54 + 3.70} for the other.

Trial #1

To the epoxide (126) (100 mg 0.59 mMol) in dry THF (100ml) at reflux under nitrogen, anhydrous potassium *t*-butoxide (66 mg 0.59 mMol) was added rapidly. The solution was allowed to reflux for 1 hour before work up. Purification (as above) yielded the diol (127) 15 mg 15%. Average diastereoselection, ratio 2.2:1.

Trial #2

As for trial #1 but the mixture was refluxed for only 15 minutes. Purification yielded the diol (127) 12 mg 12%. Average diastereoselection, ratio 1.7:1.

Trial #3

To the epoxide (126) (50 mg 0.29 mMol) in dry 1,2-dimethoxyethane (100ml) at reflux under nitrogen, pellets of oil free sodium hydride (7 mg 0.29 mMol) were added rapidly. The solution was allowed to reflux for 24 hours. After this time as no reaction appeared to have taKen place, potassium *t*-butoxide (32 mg 0.29 mmol) was added with rapid stirring and the mixture was refluxed for 30 minutes before worK up. Purification yielded the diol (127) 8.5 mg 17%. Average diastereoselection, ratio 3.1:1.

Trial #4

As for trial #3 but the mixture was treated with powdered sodium hydride. In this trial, the sodium hydride did react. Purification yielded the diol (127) 5 mg 10%. Average diastereoselection, ratio 1.3:1.

Trial #5

Into the racemic epoxide (126) (50 mg 0.29 mMol) in dry *t*-butanol (100 ml) at reflux, under nitrogen, potassium *t*-butoxide (32 mg 0.29 mMol) in *t*-butanol (10 ml) was perfused over 9 hours. The solution was allowed to reflux for a further 30 minutes before worK up. Purification yielded the diol (127) 5 mg

10%. Average diastereoselection, ratio 1.5:1.

Trial #6

The racemic epoxide (126) (50 mg 0.29 mMol) in 1,2-dimethoxyethane (10 ml) was perfused into a solution of potassium *t*-butoxide (32 mg 0.29 mMol) in dry 1,2-dimethoxyethane (100 ml) over 9 hours. The solution was allowed to reflux for a further 30 minutes before work up. Purification yielded the diol (127) 6 mg 12%. Average diastereoselection, ratio 2.0:1.

Trial #7

As for trial #5 but the solvent was 1,2-dimethoxyethane. Purification yielded the diol (127) 7.5 mg 15%. Average diastereoselection, ratio 1.1:1.

Trial #8

As for trial #4 but the mixture was treated with anhydrous potassium *t*-butoxide with poor initial stirring. Purification yielded the diol (127) 4.5 mg 9%. Average diastereoselection, ratio 2.4:1.

Trial #9

As for trial #8 but the initial stirring of the powdered potassium *t*-butoxide with the 1,2-dimethoxyethane solution was very efficient. Purification yielded the diol (127) 4.5 mg 9%. Average diastereoselection, ratio 4.7:1.

Asymmetric synthesis of (-) 2-Hydroxymethyl-2-methyl-1-oxaspiro[2.5]octan-6-one (129) by Sharpless Epoxidation[53]

A solution of dichloromethane (30 ml) and titanium tetra*iso*propoxide (0.97 ml 3.3 mMol) under nitrogen cooled to -23^0 (dry ice / carbon tetrachloride) was treated with natural (+) diethyl tartrate (1 equiv.) then was stirred for 5 minutes, the alcohol (122) (0.50 g 3.3 mMol) and finally t-butylhydroperoxide in dichloromethane (1.17g of 41% m/m solution in dichloromethane 6.5 mMol) were added. The solution was placed in the freezer at -23^0 over night. Dimethylsulphide (0.82 g 13 mMol) was added, the solution was stirred for 40 minutes at -23^0, slowly tipped into aqueous 5% sodium fluoride and stirred for 24 hours. The aqueous solution was saturated with sodium chloride, filtered through a celite pad, the aqueous phase was exhaustively extracted with dichloromethane and the combined organic solution was dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield the crude epoxide. The epoxide (129) was purified by chromatography on silica eluting

with 30% petroleum ether in ethyl acetate in 95% yield. The spectral properties were as for the racemic compound (+-) (126).

The epoxide (129) (0.2535 g) was dissolved in chloroform to make a 10.00 ml solution. The rotation of this solution was -0.065^0 +- 0.002.

$$[\alpha] = \frac{r * v}{n * l}$$

r = the observed rotation
v = solution volume in ml
n = no. of grams of solute
l = the length of the cell (dm)

$$= \frac{-0.065 * 10}{0.2535 * 1.0}$$

$$= -2.56^0 \text{ +- } 0.01$$

(89% of the solution rotated the plane of light (89% e.e. vide infra) so divide by enantiomeric excess and multiply by 100)

$$[\alpha]^{20}_D = \frac{-2.56 * 100}{89}$$

$$= -2.87^0 \text{ +- } 0.01$$

2-Hydroxymethyl-2-methyl-1-oxaspiro[2.5]octan-6-one acetate (130) from the racemic epoxide (126)

The racemic epoxy alcohol (126) (0.5g 2.9mMol) was acetylated in the manner described for the preparation of the acetate (65). The acetate was purified by chromatography on silica (flash) with 50% light petroleum in ethyl acetate as the eluent. The ester (805) was obtained as a colourless oil (0.55g 89%). N.m.r. ($CDCl_3$) δ 1.45, s, 3H, CH_3-C-O-; 2.0-3.0, complex m, 8H, 4*CH_2; 2.10, s, 3H, CH_3C=OO-; 4.17, s, 2H, CH_2O-C=O-. The addition of chiral shift reagent (Eu optshift) to an nmr sample of the racemic ester (805) showed that the methyl resonance at δ 1.45 was split into two peaks of equal intenstity. (see chapter 2).

2-Hydroxymethyl-2-methyl-1-oxaspiro[2.5]octan-6-one acetate (130) from the homochiral epoxide (129)

The ester of one enantiomer of the epoxyalcohol (129) from the Sharpless epoxidation was prepared in the same way as was the racemic mixture (see above). It had identical spectral properties to the racemate. The addition of chiral shift reagent (Eu optshift) to an nmr sample of the ester (130) from the asymmetric synthesis showed that the methyl resonance at δ 1.45 was split into two peaks. The peaks could not be further separated by

addition of shift reagent without the loss of resolution.

2-Hydroxymethyl-2-methyl-1-oxaspiro[2.5]octan-6-one (+) (S) 2'-methoxy-2'-trifluoromethylbenzeneacetate (133) (Mosher's acid ester of the racemic epoxide (126))

The procedure of Dale, Dull and Mosher[54] was used to synthesise a small amount of the ester of the racemic epoxide (126) in 88% yield in which the alcohol was treated with the acid chloride of Mosher's acid in carbon tetrachloride. N.m.r. ^{19}F ($CDCl_3$) δ 8.53 p.p.m. from CF_3CO_2H N.m.r. ^1H (300 MHz) ($CDCl_3$) δ 1.41, s, 3H, CH_3-C-O-; 1.8-2.7 complex m, 8H, 4* CH_2 cyclohexyl;
3.54, s, 3H, CH_3O- (one diastereomer);
3.57, s, 3H, CH_3O- (one diastereomer);
4.29, d (ABq), J= 11 Hz, 1H, CH-O-C=O (one diastereomer);
4.38, d (ABq), J= 12 Hz, 1H, CH-O-C=O (one diastereomer);
4.47, d (ABq), J= 12 Hz, 1H, CH-O-C=O (one diastereomer);
4.60, d (ABq), J= 11 Hz, 1H, CH-O-C=O (one diastereomer);
7.2-7.5, complex m, 5H, aromatic.

(-) 2-Hydroxymethyl-2-methyl-1-oxaspiro[2.5]octan-6-one (+) 2-methoxy-2-trifluoromethylbenzeneacetate (134) (Mosher's acid ester of the homochiral epoxide (129))

The procedure described for the preparation of the Mosher's ester (133) of the racemic epoxide (126) was used with the epoxide (129) obtained from the Sharpless asymmetric epoxidation. N.m.r. ^{19}F ($CDCl_3$) δ 8.53 p.p.m. from CF_3CO_2H. N.m.r. ^1H (300 MHz) ($CDCl_3$) δ 1.41, s, 3H, CH_3-C-O-; 1.8-2.7 complex m, 8H, 4*CH_2 cyclohexyl;
3.54, s, 3H, CH_3O- (one diastereomer);
3.57, s, 3H, CH_3O- (one diastereomer as shoulder on singlet at 3.54 unable to be accurately integrated);
4.29, d (ABq), J= 11 Hz, 1H, CH-O-C=O (one diastereomer relative integration 41);
4.38, d (ABq), J= 12 Hz, 1H, CH-O-C=O (one diastereomer relative integration 5);
4.47, d (ABq), J= 12 Hz, 1H, CH-O-C=O (one diastereomer relative integration 5);
4.60, d (ABq), J= 11 Hz, 1H, CH-O-C=O (one diastereomer relative integration 41);
7.2-7.5, complex m, 5H, aromatic.

Results of the small scale trial Sharpless epoxidation of the allylic alcohol (122) (above) showed the enantiomeric excess to be 76% (vide infra). Results of the large scale Sharpless epoxidation of the allylic alcohol (122), performed in the same manner showed the enantiomeric excess to be 89% e.e. (vide

infra).

Relative ratios of peaks for large scale epoxidation:

average major diasteromer relative integration 593

average minor diasteromer relative integration 34

Asymmetric synthesis of the diol (135)

To the homochiral epoxide (129) (0.400 *g* 2.35 mMol) in dry 1,2-dimethoxyethane (400ml) under nitrogen, at reflux, powdered anhydrous potassium *t*-butoxide (0.263 g 2.35 mMol) was added rapidly with vigorous stirring. The mixture was refluxed for a further 15 minutes, glacial acetic acid (20 drops) was added, the clear brown solution was cooled to room temperature, the solvent was removed *in vacuo* and the resultant oil was chromatographed on silica gel with ethyl acetate as the eluent to yield the diol (135) as an oil that crystallised on cooling 56mg 14%. ^1H N.m.r. ($CDCl_3$) (300 MHz) δ

0.95, dd, J= 5 Hz & 3 Hz, 1H, CH cyclopropyl (one diastereomer), too small to be integrated with accuracy;

1.02, dd, J= 5 Hz & 3 Hz, 1H, CH cyclopropyl (one diastereomer),

1.23, s, 3H, CH_3-C-O (one diastereomer), 1.28, s, 3H, CH_3-C-O (one diastereomer), relative ratio 13.1:1

1.56, dd, J= 9 Hz & 5 Hz, 1H, CH cyclopropyl (minor diastereomer),

too small to be integrated accurately;

1.67, dd, J= 9 Hz & 5 Hz, 1H, CH cyclopropyl (major diastereomer);

1.88, dd, J= 9 Hz & 3 Hz, 1H, CH-C=O cyclopropyl (major diastereomer);

1.9-2.4. complex m, 4H, CH_2CH_2 from bicyclo[3.1.0]hexanone ring;

3.53, d (ABq), J= 11 Hz, 1H, CH-O (major diastereomer); partially overlapped by dd at δ 3.54 preventing accurate integration

3.57, d (ABq), J= 11 Hz, 1H, CH-O (minor diastereomer); partially overlapped by dd at δ 3.50 preventing accurate integration

3.64, d (ABq), J= 11 Hz, 1H, CH-O (major diastereomer);

3.74, d (ABq), J= 11 Hz, 1H, CH-O (minor diastereomer);

relative ratio 9.3:1

Two hydroxyl resonances not discernible

Average relative ratio 11:1 92% of the major diastereomer (87% one enantiomer).

1-(4-Methyl-2-thiono-[1,3]dioxolanyl)bicyclo[3.1.0]hexan-4-one (137) prepared by the method of Corey and Hopkins[55].

A solution of the homochiral diol (135) (50 mg 0.29 mMol) and N,N-dimethylaminopyridine (10 mg 82 μMol) in dichloromethane at 0^0 was treated with neat thiophosgene (50 mg 0.43 mMol). After 4 hours, the solvent was removed *in vacuo* and

the product was purified by chromatography on silica gel with 30% ethyl acetate in petroleum ether as the eluent. The thionocarbonate was isolated as a foul smelling semicrystalline mass. 47 mg 75%. This compound could not be further purified as it was thermally unstable when unsolvated. Repeated chromatography resulted not in the purification of this compound but in its degradation. The thionocarbonate was however somewhat more stable in dichloromethane solution at -20^0 for extended periods. (Found: 212.0502 $M^{+\cdot}$ $C_{10}H_{12}O_3S$ requires 212.0507).

ν_{max} (Nujol) 1720, 1310 cm^{-1}.

N.m.r. ^1H ($CDCl_3$) (300 MHz) δ

1.20, dd, J= 5.5 Hz & 3 Hz, 1H, cyclopropyl;

1.49, dd, J= 9.5 Hz & 5.5 Hz, 1H, cyclopropyl;

1.63, s, 3H, CH_3-C-O (minor diastereomer);

1.66, s, 3H, CH_3-C-O (major diastereomer);

2.02, dd, J= 9.5 Hz & 3 Hz, 1H, CH-C=O cyclopropyl;

2.1-2.3, complex m, 4H, CH_2CH_2 from bicyclo[3.1.0]hexanone;

4.35, d (ABq), J= 9 Hz, 1H, CH-O-C=S (major diastereomer);

4.40, d (ABq), J= 9 Hz, 1H, CH-O-C=S (minor diastereomer);

4.43, d (ABq), J= 9 Hz, 1H, CH-O-C=S (major diastereomer);

4.57, d (ABq), J= 9 Hz, 1H, CH-O-C=S (minor diastereomer).

Mass spectrum *m/z* 212 ($M^{+\cdot}$), 196, 152, 134, 109.

Attempted synthesis of homochiral 1-Isopropenyl-bicyclo[3.1.0]hexan-4-one (136)

Trial #1: Treatment with timethylphosphite[56]

The thionocarbonate (137) (5 mg 29 μMol) was dissolved in freshly distilled trimethyl phosphite (1 ml) under nitrogen and was refluxed for 3 days. The solution was cooled to room temperature, the trimethyl phosphite was removed *in vacuo* and the resultant gum analysed by ^1H NMR and mass spectrometry. The known alkene (136)[32] has NMR singlet resonances at δ 1.74 due to the allylic methyl group and δ 4.92 due to the two vinyl protons. No resonances were observed in these areas of the spectrum of the product from this reaction. The mass spectrum of the product exhibited peaks at *m/z* 186 , 155, 91.

1,3-Dimethyl-2-phenyl-1,3-diazaphospholidine (138)

This desulphurising reagent was synthesised in the manner described by Das and Zuckerman[57]. ^1H N.m.r. ($CDCl_3$) δ 2.50, d, J= 14 Hz, 6H, CH_3-N-P; 2.8-3.0, m, 4H, N-CH_2CH_2-N; 7.23, broad s, 5H, CH aromatic.

Trial #2:

The thionocarbonate (137) (10 mg 58 mMol) and diazaphospholidine (138) (0.5 ml) were placed under argon in a sealed in a glass tube. After 5 days at room temperature, the contents were chromatographed on silica gel with 10% ethyl acetate with petroleum ether as the eluent. No material was isolated that resembled the desired product by NMR spectroscopy.

Trial #3:

To the thionocarbonate (137) (5 mg 29 μMol) in isopropyliodide (1 ml) a crystal of iodine was added. The solution was allowed to reflux over night, was cooled to room temperature, granular sodium bisulphite (50 mg) and water (1 drop) were added and the mixture was vigorously shaken until the iodine colour was discharged. The solution was dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield a gum which was analysed by NMR. The NMR spectrum exhibited no resonances at δ 1.74 or 4.92. TLC of the product showed there were many components in the crude product.

Part B

1,4-Dimethoxycyclohexa-1,4-diene

The diene was prepared in 86% yield by the dissolving metal reduction of 1,4-dimethoxybenzene with lithium and ethanol in liquid ammonia as described by Wilds and Nelson[78]. The crude enol ether was used without purification. m.p. 53-54° (Lit.[81] 54°). ^{1}H N.m.r. ($CDCl_3$) δ 2.75, broad s, 4H, 2* CH_2-C=C; 3.48, s, 6H, 2* CH_3O-C=C; 4.48, s broad, 2H, HC=C-O.

Dimethyl 3,6-dimethoxybenzene-1,2-dicarboxylic acid

The ester was prepared by the Diels Alder reaction of 1,4-dimethoxycyclohexa-1,4-diene with dimethyl acetylenedicarboxylate in the presence of a catalytic amount of dichloromaleic anhydride in 69% yield as described by Harland and Hodge[82]. The di ester was recrystallised from, ethanol. m.p. 97-99° (Lit.[22] 102-103°). ^{1}H N.m.r. ($CDCl_3$) δ 3.83, s, 6H, 3.90, s, 6H, 2* CH_3-OAr + 2* CH_3-O-C=O-; 6.93, s, 2H, CH aromatic.

2,3-Bis(hydroxymethyl)-1,4-dimethoxybenzene

Dimethyl 3,6-dimethoxybenzene-1,2-dicarboxylic acid was

reduced to the diol in 96% yield in the manner described by Shirley[24] by the use of lithium aluminium hydride in ether under standard conditions. ^1H N.m.r. ($CDCl_3$) δ 2.8, s (broad), 2H, 2* OH; 3.83, s, 6H, 2* CH_3O-; 4.86, s, 4H, 2* -OCH_2-Ar; 6.86, s, 2H, aromatic.

2,3-Bis(iodomethyl)-1,4-dimethoxybenzene (54)

The di iodide (54) was prepared in the manner described by Shirley[24] in 92% yield by the action of hydroiodic acid on 2,3-bis(hydroxymethyl)-1,4-dimethoxybenzene. The di iodide (54) was recrystallised from ethanol. m.p. 149-50°. (Lit.[24] 149-150°). ^1H N.m.r. ($CDCl_3$) δ 3.90, s, 6H, 2* CH_3O-; 4.63, s, 4H, 2* I-CH_2-Ar; 6.77, s, 2H, aromatic.

cis-5,8-Dimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-c]furan-1,3-dione (53)

The anhydride was prepared by the electrochemical reduction of the di iodide (54) in 58% yield in the presence of maleic anhydride as described by Shirley[24].

Polarographic determination of the half wave potential of the reagents in the reaction below were carried out as for the dione (164).

Electrochemical reductions were conducted in a manner analogous to that used in the preparation of the dione (164). The anhydride (53) was recrystallised from ethyl acetate in petroleum ether. m.p.208-210° (Lit.[22] 210-211°) ^1H N.m.r. ($CDCl_3$) δ 2.5-3.7, complex m, 6H, 2* CH_2-Ar + 2* CH-C=O; 3.76, s, 6H, 2* CH_3-OAr; 6.73, s, 2H, CH aromatic.

cis-2,3-Bis(hydroxymethyl)-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (55)

The diol (55) was prepared in 87% yield by the reduction of the anhydride (53) with lithium aluminium hydride in ether under standard conditions as described by Spurr[22]. ^1H N.m.r. ($CDCl_3$) δ 1.5-3.0, complex m, 8H, 2* CH_2-Ar + 2* CH-C-O + 2* OH; 3.63, broad s, 4H, 2* CH_2-O; 3.76, s, 6H, 2* CH_3O-Ar; 6.66, s, 2H, CH aromatic.

cis-7,10-Dimethoxy-1,5,5a,6,11,11a-hexahydronaphtho[2,3-e][1,3]dioxepin (56)

The acetal (56) was prepared in 65% yield by the anhydrous copper sulphate promoted trans ketalisation of the diol (55) as described by Spurr[22]. ^1H N.m.r. ($CDCl_3$) δ 1.30, s, 3H, CH_3-C-O (acetal); 1.37, s, 3H, CH_3-C-O

(acetal); 1.8-3.0, complex m, 6H, 2* CH_2-Ar + 2* CH-C-O; 3.6, m, 4H, 2* CH_2-O; 3.78, s, 6H, 2* CH_3O-; 6.50, s, 2H, CH aromatic.

cis-7,10-Dimethoxy-3,3-dimethyl-1,5,5a,6,6a,9,11,11a-octahydronaphtho[2,3-e][1,3]dioxepin (57)

The di enol ether (57) was prepared by the dissolving metal reduction of the aromatic acetal (56) in 67% recovery with 60% reduction in the manner described by Shirley[24]. The compound was always obtained as a mixture with the aromatic ether (56). The ratio of reduced product to starting material was found to be 6:4 based on the relative NMR intergation values for the aromatic and vinylic protons. (Found: 294.1847 $M^{+\cdot}$ $C_{17}H_{26}O_4$ requires 294.1831). ν_{max} 1660, 1360, 1200, 1070, 1040 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 1.33, 2* s, 6H, 2* CH_3C-O (acetal); 2.0, complex m, 4H, CH_2 + 2* CH; 2.60, complex m, 5H, 2* CH_2-C=C + CH-C=C; 3.5, complex m, 4H, 2* CH_2O-; 3.55, 2* s, 6H, 2* CH_3O; 4.5, s (broad), 1H, HC=COR. Mass spectrum *m/z* 294 ($M^{+\cdot}$), 236, 147.

The reduction was repeated under the conditions described by Shirley[24] except that ammonia was allowed to evaporate under a constant stream of nitrogen. The same ratio of reduced product to starting material was obtained in this reaction.

Hydrolysis of the enol ether acetal (57) in the preparation of the di 4-nitrobenzoyl ester (151) of *cis*-6,7-hydroxymethyl-2,3,4a,5,6,7,8,8a-octahydronaphthalene-1,4-dione (58)

The enol ether (57) mixture (0.65 g of 60% (58), 1.4 mMol) in acetone (30 ml) was added to 1% aqueous hydrochloric acid (10 ml). The solution was allowed to stand for 20 minutes, was saturated with sodium hydrogen carbonate, diluted with dichloromethane (20 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to yield a brown oil containing the ketone (58) which was not purified 0.20 g. ν_{max} 3500, 1700, 1480, 1250 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 0.9-3.0, complex m, 12H, 2* CH_2-C=O + 2* $-CH_2-$ + 2* CH-C-O + 2* CH-C=O; 3.3-4.0, complex m, 6H, 2* CH_2-O + 2* OH. Mass spectrum *m/z* 226 ($M^{+\cdot}$), 208, 177, 145.

4-Nitrobenzoyl chloride (0.7 g 3.8 mMol) was added to the crude ketone (58) (0.50 g) in pyridine (5 ml). The solution was allowed to stand over night, was diluted with dichloromethane (50 ml), washed with copper sulphate (10* 50 ml) until the dark blue copper pyridine complex was no longer present in the aqueous phase, dried (Na_2SO_4) then the solvent was removed *in vacuo* to yield an oil which was purified by chromatography on silica with 40% ethyl acetate in petroleum ether as the eluent. This afforded the diester (151) 80 mg 11%

from the enol ether (57). ν_{max} ($CDCl_3$) 1720 (broad), 1520, 1260 cm^{-1}. ^1H N.m.r. ($CDCl_3$) (300 MHz) δ 0.9-2.6, complex m, 12H, 2* CH_2-C=O + 2* - CH_2- + 2* CH-C=O + 2* CH-C-O; 4.3-4.5 complex m, 4H, 2* CH_2-OC=O; 8.18, d (ABq) with "inside lines", J= 9 Hz, 4H, CH aromatic *p* disubstituted, 8.28, d (ABq) with "inside lines", J= 9 Hz, 4H, CH aromatic *p* disubstituted. Mass spectrum *m/z* 524 ($M^{+\cdot}$ very small), 326, 272, 159.

Attempted synthesis of the Iceane dione (60)

To the di ester (151) (50 mg 95 μMol) in *t*-butanol (10 ml) under nitrogen, potassium *t*-butoxide (50 mg 0.45 mMol) was added. The solution was refluxed for 4 hours, was cooled and glacial acetic acid (0.1 ml) was added. The solvent was removed *in vacuo*, the resultant oil was taken up in dichloromethane (25 ml), washed with saturated sodium chloride (2* 50 ml), dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield the crude product 40 mg. The product was purified by chromatography with 2% ethyl acetate in petroleum ether as the eluent. N.m.r. (300 MHz) ($CDCl_3$) δ 0.85, complex m, relative integtration 2.5; 1.11, *s* (broadened at the base), relative integration 1.5; 1.25, *s* (broad at the base), relative integration 7.2; 1.59, very broad singlet, relative integration 6.3. Mass spectrum *m/z* 164, 147, 91, 90.

Di(t-butyldimethyl)silyl ether (153) of *cis*-2,3-Dihydroxymethyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene

Triethylamine (3 ml) and N,N-dimethylaminopyridine (50 mg) in dichloromethane (5 ml) and the diol (55) (0.20 g 0.79 mMol) were treated with *t*-butyldimethylsilyl chloride (0.3 g 2.0 mMol). The solution was placed under nitrogen, stoppered and allowed to stand for 2 days. After that time the solvent was removed *in vacuo*, taken up in dichloromethane (50 ml), washed with water (50 ml), 10% hydrochloric acid (50 ml), water (50 ml) then finally with saturated sodium chloride (50 ml). The organic solution was dried (Na_2SO_4), the solvent was removed *in vacuo* to yield an earthy smelling oil which was purified by chromatography on silica gel with 2.5% ethyl acetate in petroleum ether as the eluent to afford the di silyl ether (153) 0.25 g 66%. (Found C, 66.8; H 10.5, 480.3082; $M^{+\cdot}$ $C_{26}H_{48}O_4Si_2$ requires C, 65.0%, H, 10.0% ; 480.3091). ν_{max} 1600, 1490, 1260, 1080, 840, 770 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 0.00, s, 12H, 4* CH_3-Si; 0.93, s, 18H, t-butyl-Si; 1.3-2.8, complex m, 6H, 2* CH_2-Ar + 2*CH-C-O; 3.6, m, 4H, 2* CH_2-OSi; 3.73, s, 6H, 2* CH_3-OAr; 6.40, s, 2H, CH aromatic. Mass spectrum *m/z* 480 ($M^{+\cdot}$), 424, 348, 217.

Di(t-butyldimethyl)silyl ether (154) of *cis*-2,3-Dihydroxymethyl-5,8-dimethoxy-1,2,3,4,5,8-hexahydronaphthalene

The aromatic ether (153) (0.30 g 0.63 mMol) in THF (50 ml) was added to a blue solution of lithium wire (9* excess) in liquid ammonia (250 ml) and THF (50 ml). Enough ethanol then lithium wire was added carefully to allow the colour of the ammonia solution to change from permanently blue to permanently white ten times. When the solution had turned white for the last time, ammonia was allowed to evaporate then dichloromethane (50 ml) and water (50 ml) were added. The aqueous phase was extracted with dichloromethane, the combined organic extract was dried (Na_2SO_4) then the solvent was removed *in vacuo* to afford a light yellow oil, a mixture of the enol ether (154) 80% and the aromatic ether (153) 0.157 g of mixture 52% overall yield. ν_{max} 1670, 1480, 1460, 1260, 840, 780 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 0.00, s, 12H, 4* CH_3-Si; 0.93, s, 18H, t-butyl-Si; 1.3-2.8, complex m, 9H, 2* CH_2-C=C + $-CH_2-$ + 2* CH-C-O + CH-C=C; 3.6, m, 4H, 2* CH_2-OSi; 3.33, s, 6H, 2* CH_3-OC=C; 4.3, s broad, 1H, HC=C-O.

The ratio of reduced product to starting material was found to be 4:1 based on the relative NMR intergation values for the aromatic and vinylic protons. In some cases, the reduction did not occur with aromatic ether (153) being the sole product.

Attempted selective hydrolysis of the enol silyl ether (154).

The enol silyl ether mixture (80%) (154) (50 mg 83 μMol) in acetone (2 ml) was treated with oxalic acid (20 mg 0.22 mMol) Enough water was added to ensure complete solvation. The solution was stirred for 48 hours after which time it was saturated with sodium hydrogen carbonate, diluted with dichloromethane (10 ml), dried (Na_2SO_4), and the solvent was removed *in vacuo* to yield a brown oil 50 mg. TLC analysis (2.5% ethyl acetate in petroleum ether) showed the product was too polar to be the desired di silyl ether (155). The oil was partially separated by chromatography on silica gel with ethyl acetate as the eluent. NMR analysis showed the product had no t-butyldimethylsilyl functionality and resembled the impure dione (58). ν_{max} 3500, 1700 cm^{-1}.

2,3,4a,5,8,8a-Hexahydronapthalene-1,4-dione (157)

The dione (157) was kindly provided by Miss L. Marshallsay and was synthesised by the method of Alder and Stein[67] by the reduction with zinc dust in aqueous acetic acid of the Diels Alder adduct of benzoquinone and butadiene. m.p. 108^0 (Lit.[67] 108^0) ^1H N.m.r. ($CDCl_3$) δ 2.0-2.5, complex m, 4H, 2* CH_2-C=C; 2.63, s, 4H, -

CH_2CH_2-C=O; 2.7-3.0, complex m, 2H, 2* CH-C=O; 5.53, s broad, 2H, HC=CH-C=O.

Attempted synthesis of *cis*-5,8-dioxo-2,3,4a,5,6,7,8,8a-octahydronaphthalene-2,3-dicarboxylic acid dimethyl ester (158)

Trial #1

A solution of anhydrous cupric chloride (9.67 g 71.9 mMol) in methanol (75 ml) was treated sequentially with sodium butyrate (7.92 g 72.0 mMol), the dione (157) (3.00 g 18.3 mMol), trimethyl orthoformate (2.16 g 20.4 mMol) and palladium (II) chloride (0.36 g 2.03 mMol). The mixture was quickly placed in a pressurizable flask, was pressurized to three atmospheres of carbon monoxide, allowed to stir at room temperature, and was repressurized once a day to three atmospheres for a period of three days. The mixture was then filtered, the solvent was removed *in vacuo*, the black oily residue was extracted with hot petroleum ether (4* 50 ml), dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield the crude product which by NMR analysis proved to be the unchanged dione (157) in 83% recovery.

Trial #2

As for trial #1 but the mixture was pressurised to 14

atmospheres for a period of 3 days. The crude product, by NMR analysis, proved to be the unchanged dione (157) in 79% recovery.

cis-1,2-Cyclohexanedicarboxylic acid dimethyl ester

Cyclohexene was treated under conditions described by Stille and Divakaruni[66] to yield the di ester in 76% yield. ν_{max} 1740, 1450, 1240, 1170, 1040 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 0.9-2.3, complex m, 10H, cyclohexyl; 3.53, s, 6H, 2* $CH_3O-C=O$.

2',3',4a',5',8',8a'-Hexahydrodispiro[1,3-dioxolane-2,1'(4'H)-naphthalene-4',2"-[1,3]dioxolane (159).

The di acetal was prepared by the dehydration of a solution of the dione (157), ethylene glycol and *p*-toluenesulphonic acid in benzene in a manner similar to that described by Johnson *et al*[68]. The diacetal (159) was isolated as a white powder 1.32 g 86%. m.p. 116° (Lit.[68] 116.5-117°) ^1H N.m.r. ($CDCl_3$) δ 1.73, s broad, 4H, O-C-CH_2CH_2-C-O in cyclohexyl ring; 2.03, s broad + shoulder on upfield side, 6H, 2* CH_2-C=C + 2* CH-C-O; 3.90, s, 8H, 2* $-OCH_2CH_2O-$; 5.57, s broad, 2H, -HC=CH-.

Attempted carboxylation of the di acetal (159) to form the di ester (160)

Trial #1

The diacetal was treated under the same conditions described for the attempted carboxylation of the dione (157) (vide supra). The crude product, by NMR & Ir spectroscopic analysis, proved to be a mixture of the unchanged di acetal (159) and the dione (157) in 93% recovery.

Trial #2

The diacetal was treated under the same conditions described for the attempted carboxylation of the dione (157). A solution of anhydrous cupric chloride (9.67 g 71.9 mMol) in methanol (75 ml) was sequentially treated with sodium butyrate (7.92 g 72.0 mMol), the diacetal (159) (4.61 g 18.3 mMol), trimethyl orthoformate (2.16 g 20.4 mMol), anhydrous potassium carbonate (2.00 g 14.5 mMol) and palladium (II) chloride (0.36 g 2.0 mMol). The mixture was quickly placed in a pressurizable flask, pressurized to three atmospheres of carbon monoxide, allowed to stir at room temperature and was repressurized once a day to three atmospheres for a period of three days. The mixture was filtered, the solvent was removed *in vacuo*, and the black

residue was extracted with hot petroleum ether (4* 50 ml). The combined petroleum ether extract was dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield the crude product which by H^1 NMR analysis proved to be the unchanged di acetal (159) in 80% recovery.

1,4-dihydroxy-1,2,3,4,4a,5,8,8a-octahydronaphthalene (162)

The dione (157) was reduced with lithium aluminium hydride in THF in 96% yield under standard conditions in a manner similar to that described by Huckel and Waiblinger[69]. m.p. 135-140° (Lit.[69] 138-140°) H^1 N.m.r. ($CDCl_3$) δ 1.0-3.0, very complex area of resonances, 10H, 2* CH_2-C=C + O-C-CH_2CH_2-C-O- +2* CH-C-O; 3.3, broad s, 2H, 2* OH; 3.8, broad s, 2H, 2* CH-O; 5.6, broad s, 2H, -HC=CH-.

Di(t-butyldimethyl)silyl ether (163) of 1,4-dihydroxy-1,2,3,4,4a,5,8,8a-octahydronaphthalene

The diol (163) was treated with 2 equivalents of *t*-butyldimethylsilyl chloride, di*iso*propylethylamine and 4-N,N-dimethylaminopyridine in dichloromethane to afford the di silyl ether (163) in 63% yield as described by Chaudhary and Hernandez[83]. (Found: 339.2162 M^+. -

C_4H_9 $C_{22}H_{44}O_2Si_2$ - C_4H_9 requires 339.2176). ν_{max} 1460, 1250, 1100, 880 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 0.00, 12H, 4* CH_3-Si; 0.90, s, 18H, 2* *t*-butyl-Si; 1.2-2.3, complex m, 10H, 2* CH_2-C=C + -O-C-CH_2CH_2-C-O- + 2* CH-C-O; 3.8, very broad singlet, 2H, 2* CH-O-Si; 5.50, s broad, 2H, -HC=CH-. Mass spectrum *m/z* 396 ($M^{+\cdot}$)(weak), 379, 339, 263, 189.

Attempted carboxylation of the disilyl ether (163)

The di silyl ether (163) was treated under similar conditions described for the attempted carboxylation of the dione (157). The crude product, by NMR and IR spectroscopic and mass spectrometric, analysis consisted of the diol (162).

5,8-Dimethoxy-4a,9,9a,10-tetrahydroanthracene-1,4-dione (164)

The dione (164) was prepared by the electrochemical reduction of the di iodide (54) in the presence of benzoquinone in a similar manner to the procedure described by Shirley[24] for the preparation of the anhydride (54).

Polarographic determination of the half wave potential of the reagents in the reaction below were carried out as follows.

The compound to be studied, (1-2 mg) was dissolved in the

electrolyte solution. The solution was added to a polarographic cell, was degassed and the potential difference between a dropping mercury electrode and a mercury pool cathode was varied from 0 V to -3.0 V relative to a standard calomel reference electrode. The variation of the current across the cell with respect to the potential difference was recorded on a Princeton Applied Research Polarographic Analyser model 174 and an Omnigraphic 2000 chart recorder. The polarographic half wave potential of benzoquinone in 0.1 M tetrabutylammonium perchlorate in DMF was -0.6V. The half wave potential of the di iodide (54) was -0.25V[24].

Electrochemical reductions were conducted in a divided cell with a mercury pool cathode, a graphite anode and a standard calomel reference electrode. A number 3 sinter glass fritt was used as the cell divider. The electrolyte solution (0.1 M tetrabutylammonium perchlorate in DMF about 200 ml) was degassed, placed in the cell compartments. A constant potential of -0.5V relative to the calomel electrode was maintained across the cell until the current fell to 10 mA. The constant potential was then removed from the cell. The di iodide (54) (4.35 g 10.4 mMol) and benzoquinone (2.16 g 20.0 mMol) were added with stirring to the cathode compartment and a constant potential of -0.4 V was applied to the cell and the current increased to 150 mA. The solution was stirred throughout the reaction. During the reduction, the total current which passed through the cell was

measured on an electronic integrator. The reaction was complete after 3 days and the current had fallen to 13 mA and the total integrated current was 90% of the molar amount. The catholyte solution was diluted with water (100 ml), extracted with a mixture of ether and dichloromethane (3:1 500 ml), dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield a red gum that was extracted with boiling ether (200 ml). The ether solution was dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield a semi crystalline mass 2.15 g 76%. Chromatography on silica gel with 30% ethyl acetate in petroleum ether as the eluent afforded the quinone (164) (1.20 g 42%) which was extremely air and heat sensitive producing an insoluble lipstick red precipitate when open to the air. Due to this complication, the quinone was never isolated in a pure form. (Found: 272.1049 M^+. $C_{16}H_{16}O_4$ requires 272.1049).

ν_{max} (nujol) 1670, 1600, 1480, 1260, 1090, 1070 cm^{-1}. ^1H N.m.r. ($CDCl_3$) δ 3-3.7 complex m, 6H, 2* CH-C=O + 2* CH_2-Ar; 3.70, s, 6H, 2* CH_3O-; 6.67 & 6.73, 2* s, 2H + 2H, HC=CH-C=O + 2*CH aromatic. Mass spectrum *m/z* 272 ($M^{+\cdot}$), 255, 241.

Treatment of the dione (164) with isoprene

A solution of freshly distilled isoprene (2 ml) in dry toluene

was placed under an atmosphere of nitrogen & heated to reflux temperature. The dione (164) (100 mg 0.37 mMol) was added to the solution and, it was refluxed for a further hour after which time a crust of the red precipitate of decomposed dione (164) had formed. Evaporation of the solvent and the isoprene yielded the red precipitate which was washed with chloroform (10 ml), dried (Na_2SO_4) and the solvent was removed *in vacuo*. No organic material was isolated from the washing solution. Mass spectrum (of red precipitate) *m/z* 272 ($M^{+\cdot}$) .

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Publications

Part of the work described in this thesis has been reported in the following publication:

"A Convenient Synthesis of 5-Alkylbicyclo[3.1.0]hexanones Including the Natural Product Sabina Ketone", D.P.G. Hamon, Neil J. Shirley, Aust. J. Chem., 1987, 40, 1321.