# SYNTHETIC AND REACTION STUDIES OF STRAINED SMALL RING CARBOCYCLICS

A Thesis

Presented for the Degree of

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in

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by

KEVIN MICHAEL PULLEN, B.Sc.(Hons)

Department of Organic Chemistry

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" There is excitement, adventure and challenge, and there can be great art, in organic synthesis. "

--- R.B. Woodward

CONTENTS

## SUMMARY

1-Methoxy-2,3,3-trimethylcyclopropene, the methyl enol ether of 2,3,3-trimethylcyclopropanone has been synthesized. An improved procedure for the synthesis of 1-methoxy-3,3-dimethyl-2-phenylcyclopropene is also reported. The syntheses of 1-benzyloxy-3,3-dimethyl-2-phenylcyclopropene, 1-methoxy-3,3-dimethylcyclopropene and 1-t-butoxy-2,3,3-triphenylcyclopropene are discussed. The key intermediates for the preparation of the above compounds were the p-toluenesulphonylhydrazones of α-alkoxy-α,β-unsaturated ketones.

An approach towards the synthesis of an enolate anion of cyclopropanone via 1-acetoxy-3,3-dimethyl-2-phenylcyclopropene is described.

The chemistry of both 1-methoxy-2,3,3-trimethylcyclopropene and 1-methoxy-3,3-dimethyl-2-phenylcyclopropene has been studied. Acid hydrolysis of both enol ethers gave products consistent with an intermediate cyclopropanone hemiacetal which underwent ring cleavage to give α-hydroxyketones.

Attempts to convert the above two ethers to bicyclobutanes with a bridgehead oxygen function failed. The addition of methylene carbenes did not give any of the desired products. Both ethers failed to undergo 1,3-dipolarcycloaddition with diazomethane or diphenyldiazomethane.

Approaches towards the synthesis of tricyclo(2.2.0.0 $^{2,5}$) hexane via the key intermediate 2-benzoylbicyclo(1.1.1)pentane are reported. Attempts to convert 2-hydroxy-2-phenylbicyclo(1.1.1)pentane to 2-benzoylbicyclo(1.1.1)pentane via degradation of the aromatic ring with ruthenium tetroxide were thwarted by the instability of the bicyclopentanol. Removal of the hydroxyl function by catalytic hydrogenolysis or Birch reduction were unsuccessful with acyclic products predominating.

The hydroxyl group was successfully protected by conversion to its tetrahydropyranyl ether but conversion of this compound to 2-benzoylbicyclo(1.1.1)pentane has yet to be achieved.

The attempted preparation of 2-benzoylbicyclo(1.1.1)pentane *via* a Wolff rearrangement of 3-diazobicyclo(2.1.1)hexan-2-one or a *quasi*-Favorskii rearrangement of 3-bromobicyclo(2.1.1)hexan-2-one was also unsuccessful due to the low reactivity of bicyclo(2.1.1)hexan-2-one.

STATEMENT

This thesis contains no material previously submitted for a degree or diploma 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.

K.M.Pullen

## ACKNOWLEDGEMENTS

I wish to thank Dr. D.P.G. Hamon for his teaching and guidance during supervision of this work. I would also like to thank Dr. G.E. Gream for his supervision during the year 1977.

I am grateful to my peers and some staff members in the department for their rewarding discussions.

This research was carried out during the tenure of a Commonwealth Postgraduate Award, which I am pleased to acknowledge.

To my wife, I express my thanks for her tacit understanding and also for typing this thesis.

## PUBLICATION

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

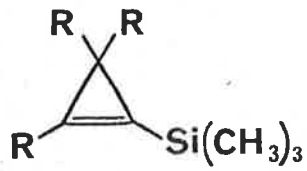
"Synthesis of an Enol-ether of a Cyclopropanone from a Diazoalkenyl-ether; a Novel Class of Compound", D.P.G. Hamon and K.M. Pullen, J. Chem. Soc., Chem. Commun., 459 (1975).

# CHAPTER I

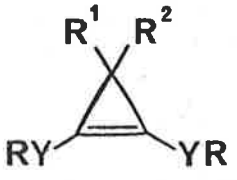
## INTRODUCTION - Part A

A large number of cyclopropene derivatives have been synthesized in recent years.[1-28] The majority of such compounds bear hydrogen, alkyl, aryl or halogen substituents on the double bond.[1,3-11,13-19,25-26] The number of cyclopropenes with other vinylic hetero atoms are few in number.[2,12,20-24,27-28]

Russian workers have reported the synthesis of the silyl derivatives(1).[23] Cyclopropenes, represented by structures (2) and (3), bearing nitrogen[12] and phosphorous[20] substituents respectively on the double bond are also known. The sulphur analogues (4) have only been prepared recently.[27,28]

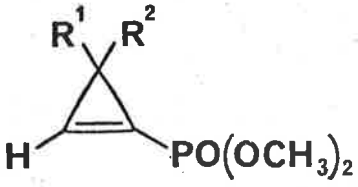



(1)




(2) Y= $NR^3$

(4) Y= S

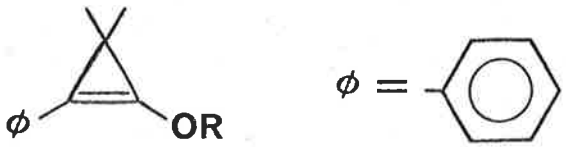



(3)

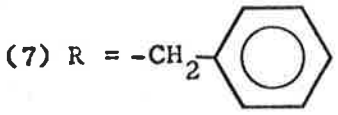
Very little has been reported on cyclopropenes which contain an oxygen atom on the double bond.[2,21,22,24,30] It has been postulated that the cyclopropenyl methyl ether (5) may be an intermediate formed from 1-methoxybut-1-yne under Simmons-Smith conditions which then underwent a further reaction and could not be isolated.[29]


(5)

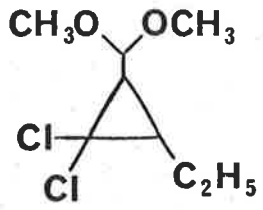
Hamon and Holding reported a synthesis of ethers (6) and (7) but only in very low yield.[2] A brief communication of a new procedure for the preparation of compound (6) appeared later.[22,30]



(6) R = $-CH_3$



Dehydrochlorination of the gem-dichlorocyclopropane (8) unexpectedly gave the cyclopropenol methyl ether (9).[21] The only other known compounds of this type are the fluorinated cyclopropenol methyl ethers (10-12). These have been prepared recently from the reaction between sodium methoxide and perfluorocyclopropene or 1,2-dichloro-3,3-difluorocyclopropene.[24]



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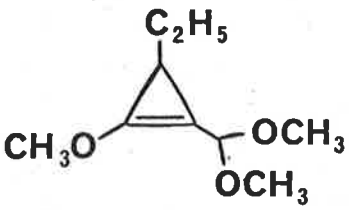

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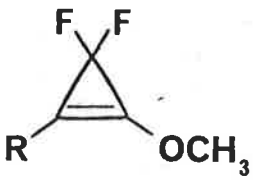


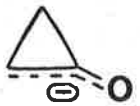
(10) R= F

(11) R= $OCH_3$

(12) R= Cl

Compounds related to cyclopropenol ethers are their corresponding esters (13) of which nothing is known. The synthesis of these ethers and esters was undertaken ~~to enable a~~ in order to study ~~of~~ their chemistry. In particular it was hoped to generate the cyclopropenolate anion (14), for which the two contributing ~~hybrids~~ canonical forms (15) and (16) can be written, in order to compare the alkylation and acylation of such species with those of less strained enolates.

(13)



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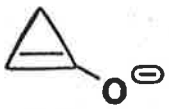

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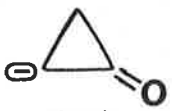
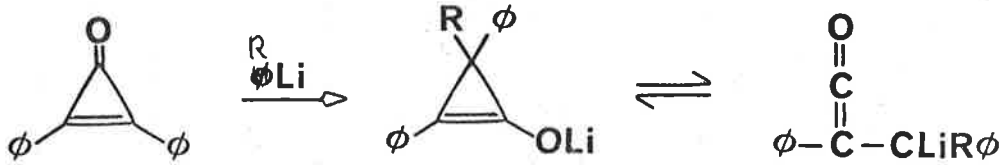


(16)

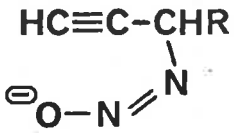
It has been proposed that the cyclopropenolate anion (17) is an intermediate formed on the addition of organolithiums to diphenylcyclopropenone (18) (Figure 1).[31] This enolate anion rearranges to the ketenyl anion (19).[31] It has not been determined whether these anions exist in equilibrium, nor have alkylation or acylation studies been reported.




(18) (17) (19)

FIGURE 1

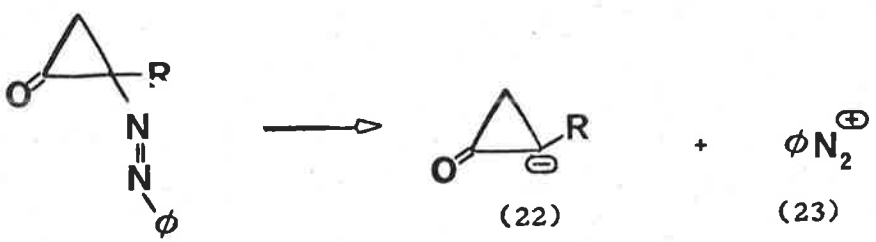
Similarly, the enolate anion of cyclopropanone (20) is a possible intermediate in the intramolecular reactions of propargyl diazotates (21).[32]




(21)


(20)

More recently, it has been postulated that azo cyclopropanones dissociate into the ionic species (22) and (23) (Figure 2).[33] The formulation of the anionic species (22), which is an enolate anion of a cyclopropanone, was purely tentative.



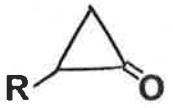

(22) (23)

R= $CH_3$, $CO_2C_2H_5$

FIGURE 2

Normally, alkylation of enolate anions with alkyl halides favours carbon alkylation[34a] although examples of oxygen alkylation are known.[35] It might therefore be anticipated that alkylation of anion (14) would lead to cyclopropanones (24). Acylation favours the formation of O-acyl derivatives rather than C-acylated products.[36,37] A reaction between the anion (14) and anhydrides or acid halides might therefore be expected to give cyclopropenol esters (13).


(14)

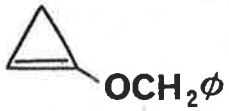



(24)


(13)

The high energy of the cyclopropenolate anion suggested by the rearrangement of anion (17) to the ketenyl anion (19)[31] may change this product distribution. It is conceivable that the stability of the ketenyl anion over that of the cyclopropenolate is partly due to the ability of the phenyl ring to stabilize a negative charge in the ketenyl anion. A cyclopropenolate bearing alkyl groups in the 3-position would destabilize such a carbanion and could possibly prevent the rearrangement.

A number of seperate routes to the cyclopropenolate anion from an enol derivative can be envisaged. It has been shown that sodium-potassium in ligroin cleaves benzyl ethers to toluene and the potassium salts of the corresponding alcohol.[38] If a cyclopropenol benzyl ether (25) could be synthesized it was anticipated that subsequent treatment with the alloy would result in the required anion.

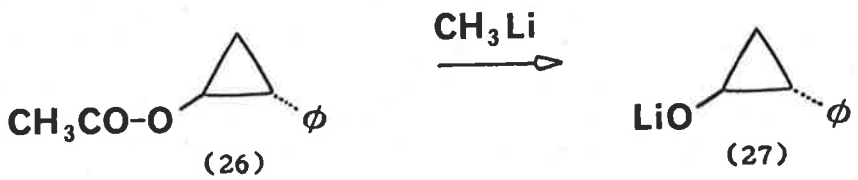



(25)

Since cleavage occurs at elevated temperatures[38] the thermal stability of the ether would be critical. Cyclopropene can only be kept in the condensed phase for prolonged periods at liquid nitrogen temper-

atures.[39] Alkyl substitution at the 3-position enhances the stability of the system.[40a] The most stable cyclopropenes are those in which the hydrogens at C3 have been replaced by alkyl groups.[40a] Neat 3,3-dimethylcyclopropene can be heated in a sealed tube at 100°C for many days without noticeable decomposition.[40a] The presence of one hydrogen atom at C3, as for example in 3-methylcyclopropene, is sufficient to render the compound unstable at room temperature unless other stabilizing substituents are present.[40a] Substitution at the vinyl carbons also has a stabilizing effect on cyclopropene,[41,42] although not as pronounced as is the case with the methylene carbon. As the thermal stability of the cyclopropenol benzyl ether was of extreme importance, the synthesis of a fully substituted analogue was planned.

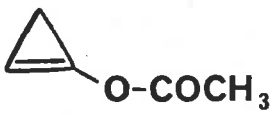
Among methods for generating metal enolates, the reaction of enol acetates with methyllithium appears to be one of the more synthetically useful.[43] The addition of methyllithium to trans-2-phenylcyclopropylacetate (26) resulted in cleavage of the acetate group to give the lithium salt of trans-2- phenylcyclopropanol (27) (Figure 3).[44]




(26) (27)

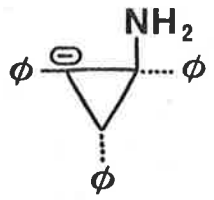
FIGURE 3

If a cyclopropenol acetate (28) could be synthesized then subsequent treatment with methyllithium may lead to a cyclopropenolate anion.




(28)

Nucleophilic addition of methyllithium to the highly strained cyclopropene double bond may be a competing reaction. There are reports where t-butoxide[45] and amide[46] ions, both considered to be poor nucleophiles,[47] add to the double bond. Activation by electron withdrawing groups is usually necessary however, to stabilize a possible carbanion intermediate.[40b] With lithium or sodium amide, the dimerization of 1,2,3-triphenylcyclopropene has been postulated to proceed through the intermediacy of the amide addition product (29).[46] Stabilization by the phenyl substituent is believed to be a major contributing factor.[40c]




(29)

Steric effects also appear to be an important factor. 1,2,3-Triphenyl-3-methylcyclopropene is recovered unchanged after prolonged treatment with potassium amide.[46] Similarly, simple alkylcyclopropenes are usually resistant to nucleophilic attack by alkoxide ions.[48] Therefore, as in the case of the cyclopropenol benzyl ether, the synthesis of a fully substituted cyclopropenol acetate was envisaged.

It was decided to develop a route to the ether of a trisubstituted cyclopropenol and later modify it if possible to give the corresponding acetate. Cyclopropenol ethers other than benzyl would be of use as reference compounds in the proposed alkylation studies.

As cyclopropenol ethers incorporate the cyclopropene skeleton, the methods available for the synthesis of the unsaturated three membered ring were examined. Closs in a review of the synthesis and chemical and physical properties of cyclopropenes divides the routes to these compounds into three classes, namely, β-elimination of cyclo-

propanes, addition of carbenes to acetylenes and ring closure of acyclic precursors.[1]

The thermally induced β-elimination of neutral molecules from suitably substituted cyclopropanes[39,49,50] was avoided. The high temperatures necessary for the elimination may have a detrimental effect on the end product, the stability of which was unknown. The base induced β-elimination of nitrite ion from nitro-substituted cyclopropanes[51] appears to be limited to aryl substituted cyclopropanes where the aryl groups provide the necessary activation to facilitate the elimination.[51,52]

The elimination of β-functionalized silanes (Figure 4) does not easily occur when the alkene to be generated is part of a strained system. Elimination from silylcyclopropanes under acidic or basic conditions only yielded acetylenic products.[53] It was only recently reported that fluoride ion promotes this elimination of β-halosilanes enabling the generation of strained alkenes.[18]

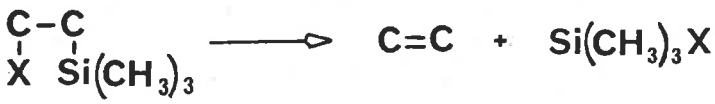
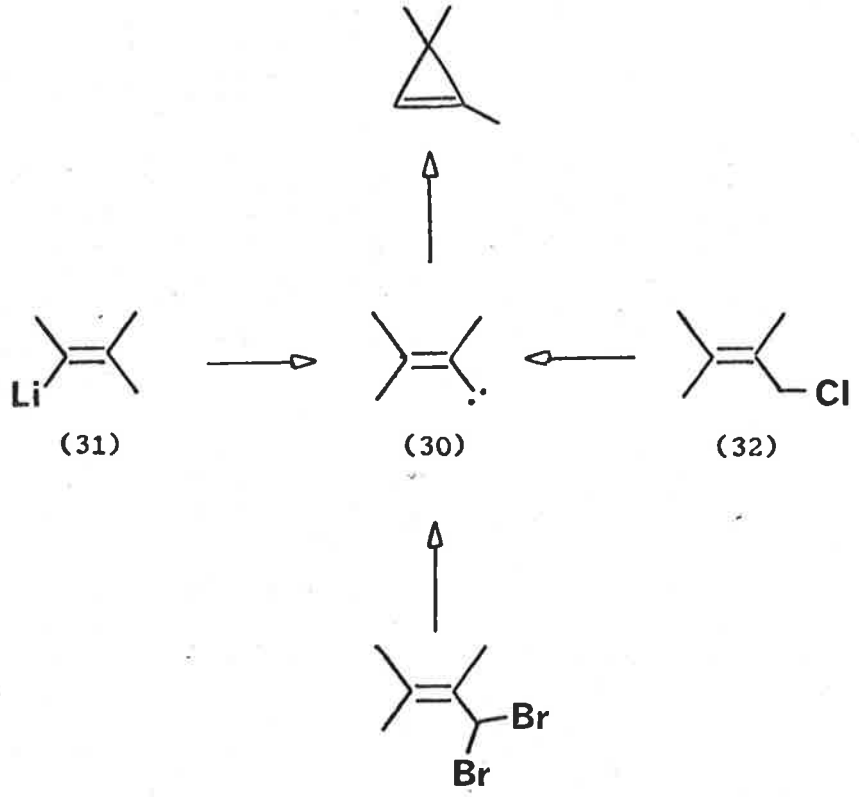


FIGURE 4

The second route to cyclopropenes involves the addition of carbenes to acetylenes.[19a] A severe limitation to this synthetic scheme originates in the tendency of many carbenes to undergo extremely rapid intramolecular rearrangements.[54] In these cases the relatively slow addition to acetylenes constitutes only a minor reaction path and yields are poor. This method was abandoned in favour of a more specific synthesis.

The third general method of synthesis, that of ring closure of acyclic precursors, is thought to proceed through an alkenylcarbene.[55]

The carbene (30) can be generated by several methods (Figure 5).[55] 1,3,3-Trimethylcyclopropene results after the addition of dichloromethane to 2-lithio-3-methylbut-2-ene (31).[55] This same compound is produced by α-dehydrochlorination of 1-chloro-2,3-dimethylbut-2-ene (32)[55] or α-debromination of 1,1-dibromo-2,3-dimethylbut-2-ene (33).[55]




(31) (30) (32)

(33)

FIGURE 5

It has been found that irradiation of 3H-pyrazoles leads to cyclopropene formation, often in good yields.[56] A study of the mechanism indicated that two distinct steps were involved (Figure 6).[56a] 3,3-Dimethyl-5-phenyl-3H-pyrazole (34) initially undergoes ring opening to the diazoalkene (35). Nitrogen is then eliminated to form the alkenylcarbene (36) which cyclizes to the cyclopropene (37).

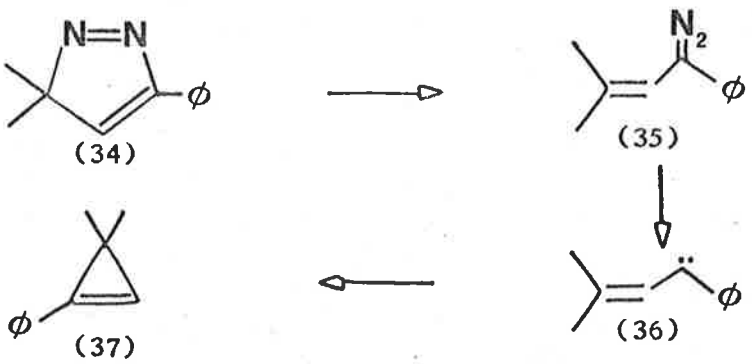
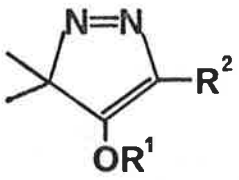
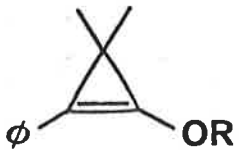



FIGURE 6

As irradiation can be carried out at very low temperatures this method is particularly suited to the preparation of thermally unstable cyclopropenes. The photolysis of compounds of general formula (38) provided a promising route to cyclopropenol ethers and was studied by Hamon and Holding who found that ethers (6) and (7) could be synthesized by this method, but only in very low yield (5-10%).[2]




(38)

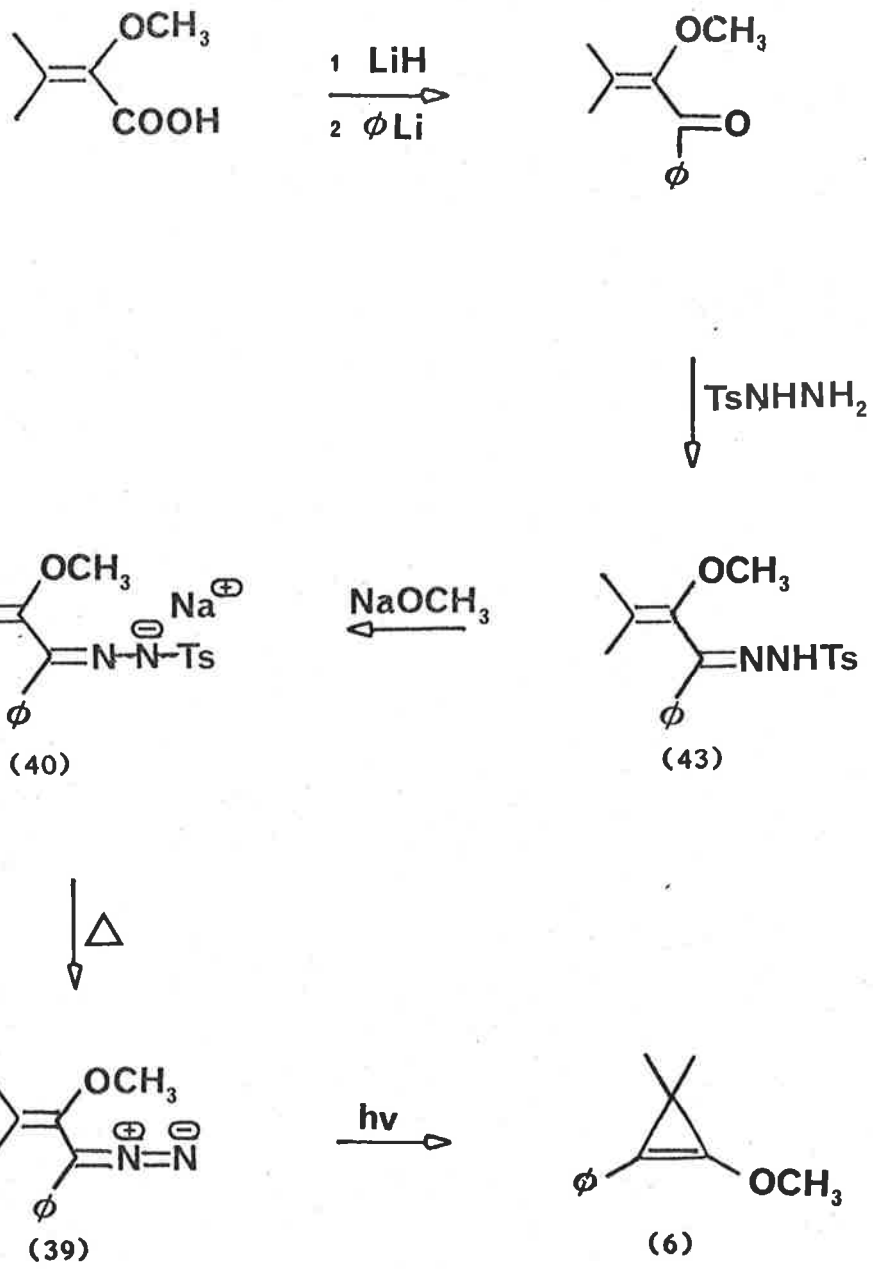



(6) R= $CH_3$

(7) R= $CH_2\phi$

A preliminary study in 1973, illustrated schematically in Figure 7, proved that a more convenient synthesis of the ether (6) was possible from the photolysis of the diazoalkene (39), itself a product from the pyrolysis of the p-toluenesulphonylhydrazone salt (40).[30] This route was based on the work done by Closs who developed a scheme to alkylcyclopropenes by the base induced pyrolysis of tosylhydrazones[+] of α,β-unsaturated aldehydes and ketones (Figure 8).[57] The reaction was thought to proceed via the alkenylcarbene (41) generated from the diazoalkene (42).[57] One important limitation noted by Closs was that

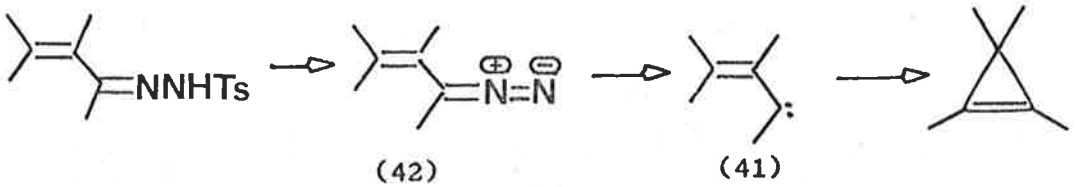
[+]Tosyl is the accepted contracted name for the p-toluenesulphonyl-radical.[58]




Ts = $-SO_2-C_6H_4-CH_3$

FIGURE 7

the α,β-unsaturated carbonyl compound had to be di-alkylated in the β-position, otherwise pyrazole formation became the major reaction pathway.[57]




(42) (41)

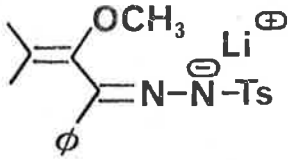
FIGURE 8

Although a specific synthesis of a cyclopropenol ether was now possible, further study was necessary to optimize yields, to determine the generality of the synthesis and to investigate the reactions of the ether (6).

A disadvantage of the synthesis was that incomplete removal of methanol after the formation of the sodium salt (40) from the hydrazone (43) and sodium methoxide in methanol resulted in a reduced yield of the cyclopropenol methyl ether (6) when the diazoalkene (39) was subjected to photolysis.[30] Cyclopropenes are known to react with alcohols under photolytic conditions[9] and it was possible that trace amounts of methanol were participating in a reaction. It has also been reported that metal alcoholates may cause complications in that the alcohols generated in the formation of salts of tosylhydrazones can lead to cationic decomposition of the intermediate diazo compounds.[59]

Extensive literature exists on the base-induced decomposition of tosylhydrazones.[59-93] Kaufman and co-workers found that pyrolysis of dry salts of tosylhydrazones at reduced pressure is often an advantage in effecting their carbenic decomposition to intramolecular products.[59] Furthermore, the decomposition temperatures of lithium salts of hydrazones as solids are lower than those of sodium salts.[93] It was therefore concluded that the pyrolysis of the dry lithium salt (44),

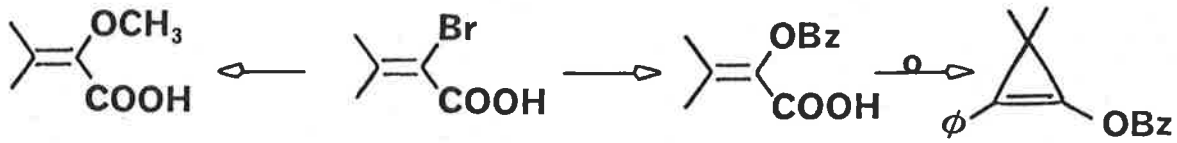
generated from the hydrazone (43) and lithium hydride in an inert solvent, may improve the overall yield of the cyclopropenol methyl ether (6).



(44)

The above synthetic scheme (Figure 7) may provide a general route to cyclopropenol alkyl ethers. Replacing phenyllithium with an alkyllithium should enable an alkyl analogue to be prepared.

The successful synthesis of cyclopropenol methyl ether (6) augered well for the preparation of a benzyl ether needed for cyclopropenolate anion studies. The basic starting material for compound (6) was 2-methoxy-3-methylbut-2-enoic acid (45) synthesized by reaction of sodium methoxide with the corresponding bromoacid (46) (Figure 9).[94] If the alkoxide was the sodium salt of benzyl alcohol then the benzyloxyacid (47) may be the product. An analogous sequence of reactions to that for the preparation of compound (6) should enable the formation of the cyclopropenol benzyl ether (7). Spectral data is available for compound (7),[2] which would assist in its identification by a new synthesis.



(45) (46) (47) (7)

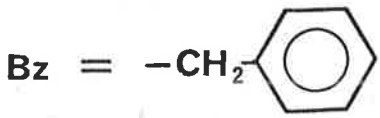
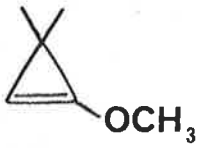


FIGURE 9

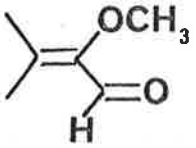
Since it now appeared possible to obtain cyclopropenol ethers with vinyl aryl and alkyl substituents, a compound with hydrogen

bound to the double bond was required to complete the series. This would enable the reactivity of a strained double bond attached directly to an oxygen atom to be examined without the steric and/or electronic influence from any additional group.

It was reported earlier that attempts to prepare the unsubstituted ether (48) were thwarted by the polymerization of the aldehyde (49).[30] An alternative synthesis is proposed based on the work of Regitz.[20]

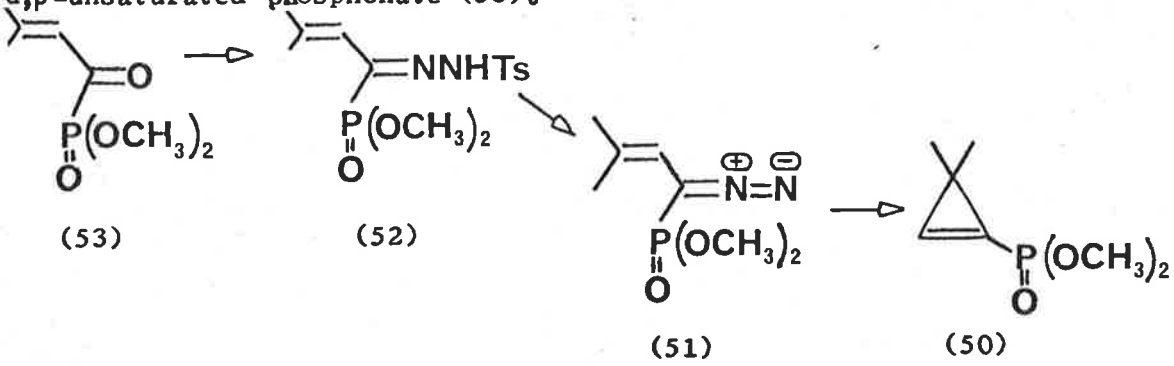


(48)



(49)

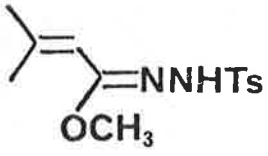
He has shown that a cyclopropene (50) which contains both vinylic hydrogen and hetero atom functionalities can be prepared by the photolysis of the diazophosphonate (51), generated from the tosylhydrazone (52)(Figure 10). The hydrazone (52) was prepared from the corresponding α,β-unsaturated phosphonate (53).



(53) (52) (51) (50)

FIGURE 10

It is conceivable that a hydrazone of type (54) with oxygen as the hetero atom would undergo a similar process to form the less substituted cyclopropenol methyl ether (48).

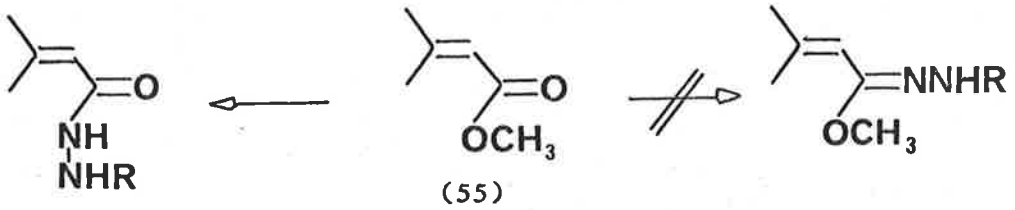


(54)

A direct reaction between methyl dimethylacrylate (55) and tosylhydrazine is unlikely to produce the ester hydrazone (54) as the reaction of an ester with a hydrazine is the standard preparation of acid hydrazides (Figure 11).[95a] A general procedure for ester hydrazone formation has been developed by McDonald and Krueger.[96] They obtained such compounds in good yield from the reaction between tosylhydrazine and the appropriate orthoester. The thermolysis of the salts obtained by the action of sodium hydride on these hydrazones was found to proceed via two major pathways (Figure 12)[96]:

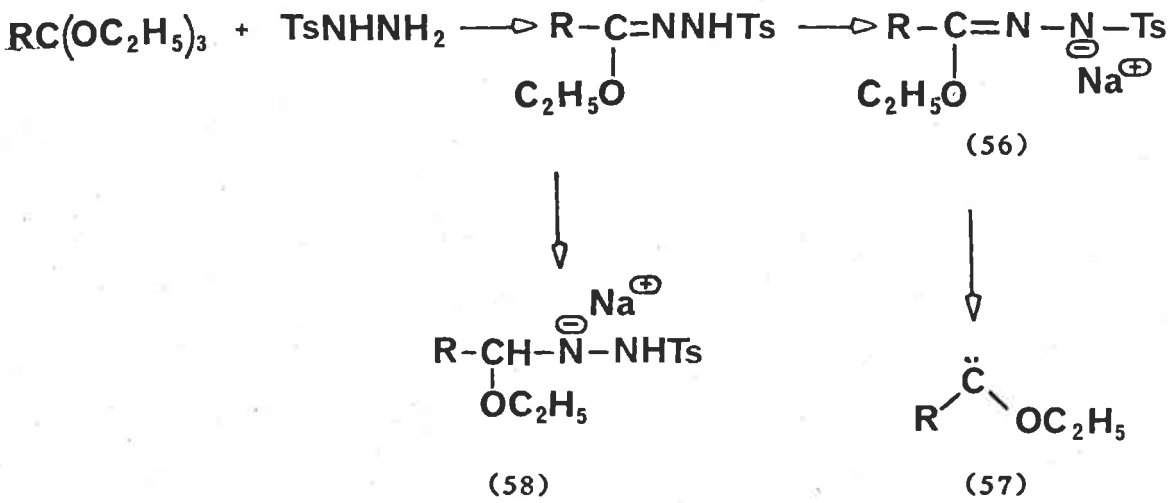
1) salt formation, the expected process (defined as "normal"[96]) to give the salt (56) which on pyrolysis yields an α-alkoxycarbene (57); and

2) nucleophilic attack of hydride at the carbon of the carbon-nitrogen double bond (defined as the "abnormal" process[96]) to yield the salt (58) which subsequently decomposed. The final proof of this unusual mode of attack, by isolating the salt (58) has yet to be accomplished.




(55)

FIGURE 11




(56)

(58) (57)

FIGURE 12

The substituent other than the alkoxy group on the imino carbon is apparently the controlling factor as to which of these two alternatives predominates.[96] If the substituent is hydrogen, nucleophilic attack predominates while if aryl then "normal" salt formation is favoured.[96] When the moiety is methyl a mixture of the two processes occurs.[96] The more bulky the substituent then the less likely is nucleophilic attack.[96] Similarly, nucleophilic attack becomes less probable if the electrophilic character of the carbon atom of the carbon-nitrogen double bond is lowered.[96]

Other workers have studied the reactions of alkoxydiazoalkanes[97] and concluded that tosyl salts decomposed by rapid heating, at low pressure, in closed systems, without solvent, favour clean formation of the desired oxycarbenes.[97b] The hydrazone (54) was expected to allow "normal" salt formation since the trisubstituted alkenyl group could lower the electophilic nature of the imino carbon. It is also quite substantial in size. Pyrolysis of the salt (59) to the diazoalkene (60) followed by photolysis should enable the generation of the carbene (61). Intramolecular insertion of the carbene into the double bond would give the less substituted cyclopropenol methyl ether (48) (Figure 13).

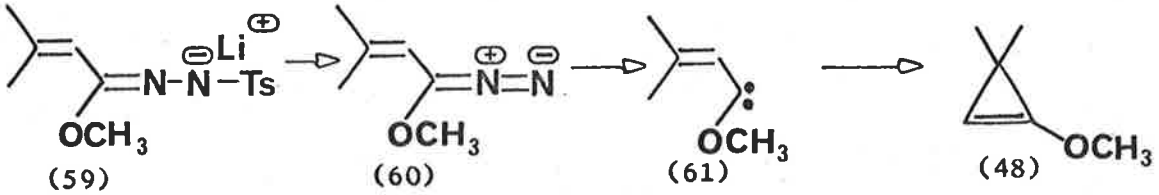
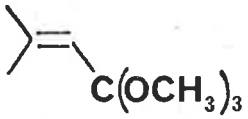
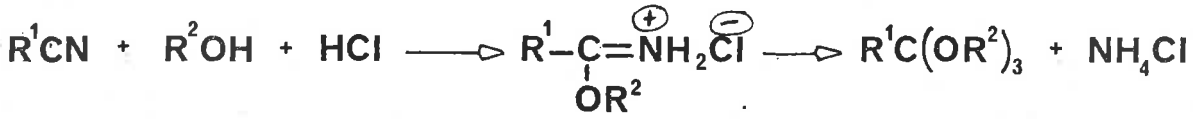



FIGURE 13

If the ester hydrazone synthesis of McDonald and Krueger[96] is to be followed then the unknown orthoester (62) is required. Of all the current procedures available for carboxylic orthoester preparation,[98] the most versatile method involves alcoholysis of imidic ester hydrochlorides (63), which are prepared by the addition of an alcohol to a nitrile in the presence of anhydrous hydrogen chloride (Figure 14).[99]



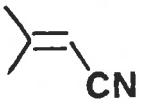
(62)



(63)

FIGURE 14

Dimethylacrylonitrile (64) is a known compound[100] but there is the complication that hydrogen chloride may add across the carbon-carbon double bond.[101]



(64)

Although many orthoesters have been synthesized from their imidic ester hydrochlorides[98] very few have contained a carbon-carbon multiple bond in addition to the nitrile functionality.[102] The conjugation in dimethylacrylonitrile is likely to increase the susceptibility of the carbon-carbon double bond toward attack by hydrogen chloride.[103]

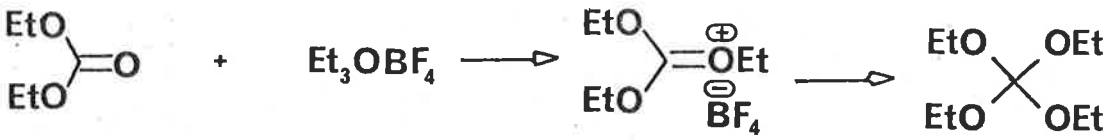
Although the formation of imidic ester hydrochlorides is carried out with ether as co-solvent[98a] which should render hydrogen chloride inactive[104] since a hydrogen-bonded complex forms which shows no appreciable ionization,[105] the lack of literature precedents for the preparation of unsaturated orthoesters by this method motivated one to look for an alternative synthesis.

Trialkyloxonium salts are powerful alkylating agents.[106] Triethyloxonium tetrafluoroborate readily ethylates such compounds as ketones, sulphides, nitriles, esters and amides on oxygen, nitrogen or sulphur

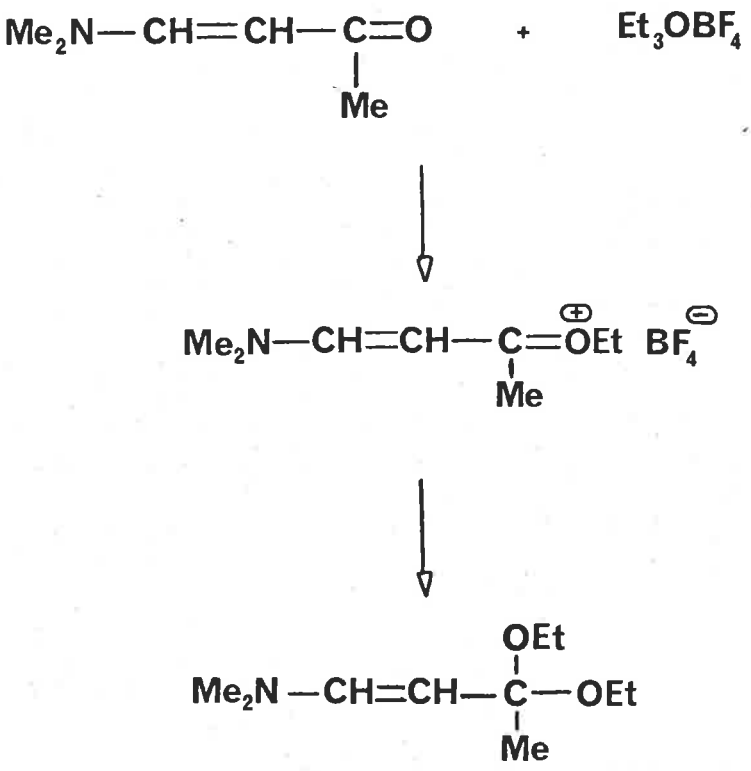
to give onium fluoroborates that can react with nucleophilic reagents.[107] Furthermore, there exist a few reports where alkylation is effected in the presence of a carbon-carbon multiple bond,[108-112] even when conjugated with the reactive site.[108,109] Two examples of the synthetic utility of triethyloxonium tetrafluoroborate are depicted in Figure 15.

Me = $CH_3$

Et = $C_2H_5$



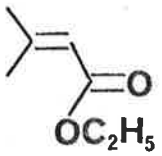
Reference 107a



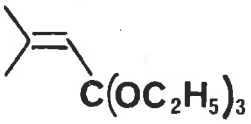
Reference 108

FIGURE 15

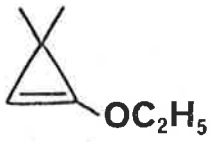
Ethyldimethylacrylate (65)[113] could be expected to give the ethylorthoester (66) under these alkylation conditions. An analogous sequence of reactions to that discussed earlier for the methylorthoester (62) would enable the preparation of the cyclopropenol ethyl ether (67) which contains a vinylic hydrogen atom.



(65)

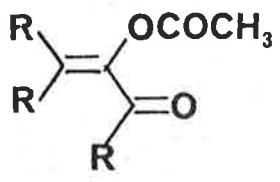


(66)

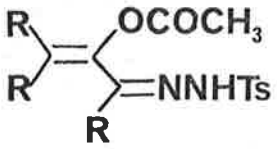


(67)

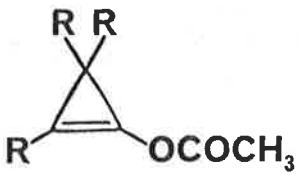
The synthesis of a cyclopropenol acetate by an adaption of the route to the ether (6) required a ketoenolacetate of the type (68). The combination of inductive and mesomeric effects operating in a molecule such as (68) makes it difficult to predict which carbon atom will be the more electrophilic. On the addition of tosylhydrazine a hydrazone of type (69) may form in preference to an acid hydrazide resulting from attack at the ester carbon. A hydrazone of structure (69) would be a suitable precursor for the cyclopropenol acetate (70).



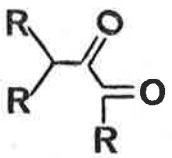
(68)



(69)



(70)

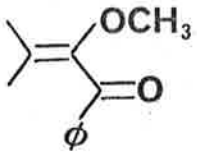


(71)

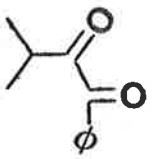
It is known that if an enolate anion is added to an excess of acid chloride or anhydride the O-acylated derivative (an enol ester) is often the major product.[36] The yield of this O-acylated compound may be enhanced by conducting the acylation reaction in a relatively polar solvent with an enolate metal cation (e.g. $Na^+$ or $Li^+$) which does not favour the formation of tightly associated ion pairs.[36b,e,37] An effective

synthesis of an enol acetate (68) would be from an α-diketone (71) and sodium acetate in acetic anhydride.[36e,114]

In particular, isopropylphenyldiketone (72) was chosen for the following reasons. The enol ether ketone (73) was available from the synthesis of the cyclopropenol methyl ether (6)[22] and for expediency, acid hydrolysis should render the α-diketone (72) which can only enolize in one direction and hence can only give a single enol derivative. The diketone is a known compound and could be synthesized later by the more direct route.[115]

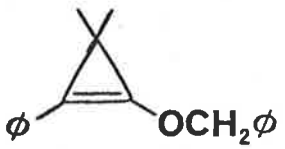


(73)



(72)

In addition, the same enolate anion should be generated from both the cyclopropenol benzyl ether (7) and the acetate (74), thus allowing a direct comparison of their alkylation/acylation reactions. This should reduce the number of authentic compounds that would have to be independently synthesized to confirm the structure of the products obtained from these reactions.



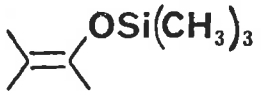
(7)

(74)

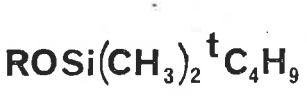
Diketones of the type (71) provide a simple alternative to be pursued if acid hydrazide formation predominates over that of hydrazone when the ketoenolacetate (68) is added to tosylhydrazine.

The use of trimethylsilylenolethers (75) to generate metal enolates when treated with methyllithium is well known.[116] However, the susceptibility of trimethylsilylethers to solvolysis in protic media, in the

presence of either acid or base, prevents them from being broadly useful.[117] The dimethyl-t-butylsilylethers (76) present no such problems since they are stable to aqueous or alcoholic base, hydrogenolysis and mild chemical reduction.[117] They are cleaved rapidly to alcohols with tetra-n-butylammonium fluoride in tetrahydrofuran at 25°C.[117] The synthesis of silylenolethers can be effected from an enolate anion and the appropriate alkylsilylchloride.[116]



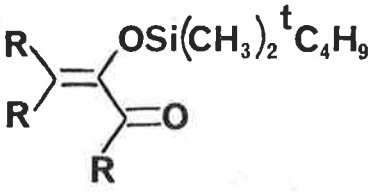
(75)



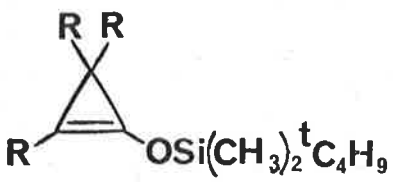
(76)

Thus it is conceivable that the diketones (71) could be converted to the silylenolether ketones (77) and from there to the corresponding cyclopropenol ethers (78) which should be suitable precursors for the enolate anions of cyclopropanones.

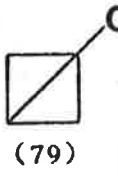
The successful synthesis of the relatively stable cyclopropenol methyl ether (6)[22] prompted a study of its chemistry. It was considered a possible precursor to a bicyclobutane with bridgehead oxygen function (79), a class of compound whose rigorous synthesis and characterization have yet to be reported.



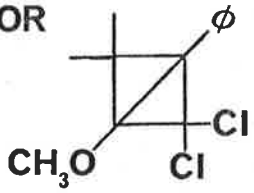
(77)



(78)



(79)

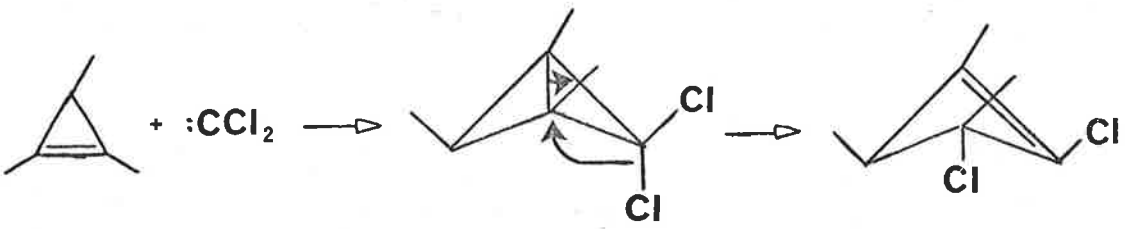


(80)

A few reports have appeared in the literature involving carbenoid additions to cyclopropenes yielding bicyclo(1.1.0)butanes.[118] Dichlorocarbene is probably one of the simplest carbenes to generate and its addition to the cyclopropenol methyl ether (6) may yield the oxygenerated bicyclobutane (80).

A previous attempt to synthesize a bicyclobutane bearing gem-

dichlorides met with failure.[118i] The addition of dichlorocarbene to 1,2,3-trimethylcyclopropene produced 2,3-dichloro-cis-1,3,4-trimethyl-cyclobut-1-ene (Figure 16).[118i] The formation of the cyclobutene was rationalized in terms of an electrocyclic ring expansion of an intermediate bicyclobutane (81).[118i] The instability of compound (81) was attributed to ring strain.[118i] A similar ring expansion may occur in the bicyclobutane (80).




(81)

FIGURE 16

The addition of dichlorocarbene to the cyclopropenol methyl ether (6) is formally the addition of a carbene to an enol ether which has been studied and there exist reports where the resultant cyclopropane ether could[119] or could not[120] be isolated.

According to Skattebøl[120a] when dichlorocarbene is added to enol ethers the oxygen lone pair electrons have the ability to increase the electron density of the cyclopropane ring, thus polarizing the carbon-chlorine bond. The decomposition is depicted as a concerted ring opening with loss of chloride ion to give the cation (82) (Figure 17). Subsequent reaction of this ion leads to the observed products. Thus in the bicyclobutane (80), this polarization together with the additional driving force of relief of ring strain would probably render its isolation impossible.

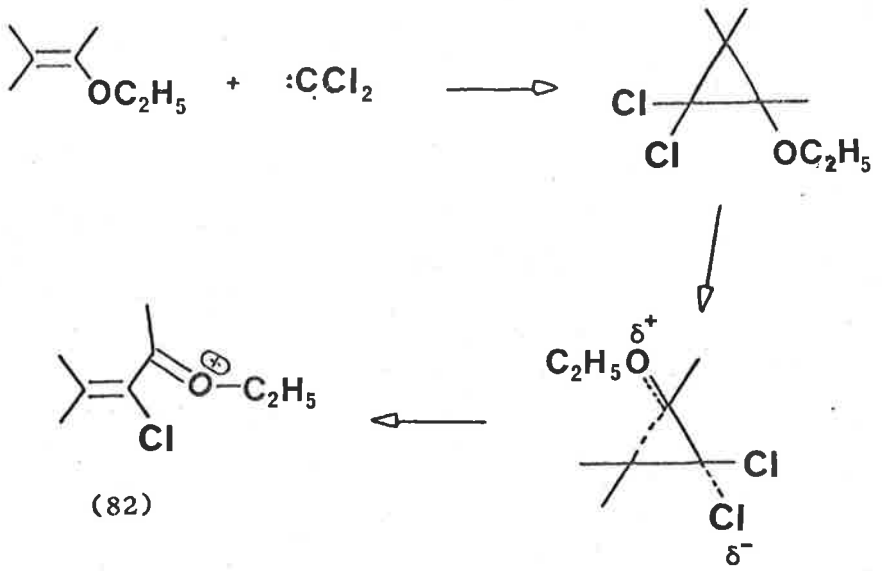



FIGURE 17

The replacement of chlorine with alkyl groups, thus reducing the polarization, may sufficiently stabilize the bicyclobutane. It has been reported that geminal halides on reaction with chromous sulphate generate a carbenoid entity that has the capacity to react with olefins such as 4-hydroxybut-1-ene to give cyclopropanes (Figure 18).[121] Hence 2,2-dibromopropane may give a moderate yield of the fully substituted bicyclobutane with bridgehead oxygen function (83).

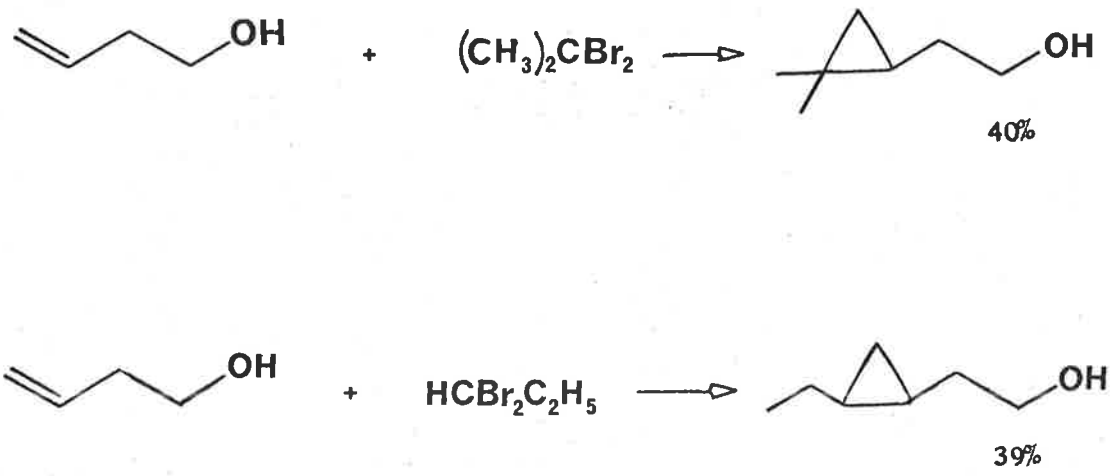
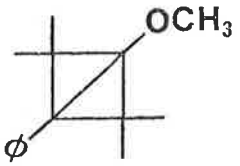



FIGURE 18




(83)

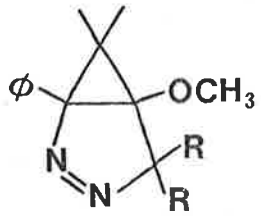
In view of the high strain energy of cyclopropene[122] it might be expected to act as a 1,3-dipolarophile. A few reports of 1,3-dipolar additions to cyclopropenes have appeared in the literature.[39,123,124]

The initial 1,3-dipolar adducts from cyclopropenes should be formed much more exothermally than from unstrained olefins because of the large strain energy release.[124] Any type of conjugation increases the activity of the olefinic dipolarophile.[125] In contrast however, double bonds bearing fluorine or chlorine substituents are especially poor dipolarophiles.[126a] Huisgen has said that the change in electron density of the double bond cannot be the controlling factor and suggested that polarizability contributes to the high dipolarophilic nature of conjugated systems.[126a] The proposed mechanism is a concerted, but not necessarily synchronous, formation of the two sigma bonds.[126a] Unequal progress of bond formation in the transition state leads to partial charges, which may be stabilized by substituents.[126a]

It is impossible to identify unequivocally an electrophilic and nucleophilic centre of a 1,3-dipole, although experimental evidence indicates that the central carbon atom of a diazoalkane is more strongly nucleophilic than the outer nitrogen.[126b] The combined electronic and steric substituent effects, the latter usually being dominant,[126b] are responsible for the orientation of addition of 1,3-dipoles to alkenes.

Thus on both steric and electronic grounds compound (84) would be the preferred adduct from the reaction between a diazoalkane and the cyclopropenol ether (6). This would formally require the development of a partial positive charge alpha to the methoxyl group which should be

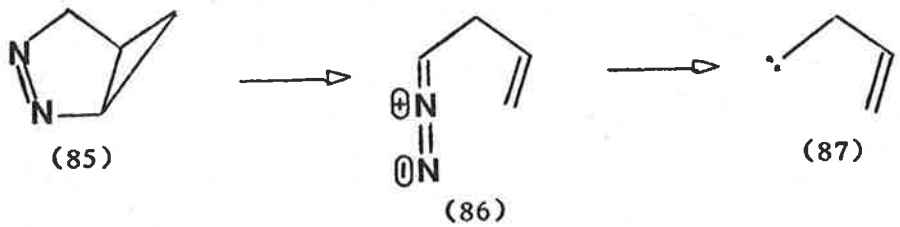
stabilized by the adjacent oxygen and a partial negative charge alpha to the phenyl moiety which should be delocalized over the aromatic ring.



(84)

The favourable electronic interactions and the additional driving force of relief of ring strain were expected to favour dipolar-cycloaddition of the ether (6) with a diazoalkane. It appears that the choice of diazoalkane will decide the decomposition pathway of the adduct.

Hammond et alia reported that photochemical decomposition of 2,3-diazabicyclo(3.1.0)hex-2-ene (85) gave products which were explained in terms of the initial formation of a diazoalkene (86), followed by loss of nitrogen to give the carbene (87) and subsequent rearrangements to yield olefins (Figure 19).[123c]



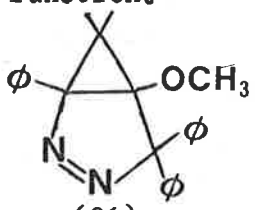
(85) (86) (87)

FIGURE 19

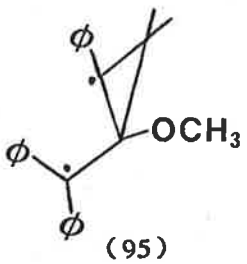
Gassman and Greenlee obtained results which contrasted strongly with those of Hammond.[123d] They found that the photochemical decomposition of derivatives of 2,3-diazabicyclo(3.1.0)hex-2-ene could be changed dramatically by the presence of phenyl substituents.

4,4-Diphenyl-2,3-diazabicyclo(3.1.0)hex-2-ene (88) was prepared by the addition of cyclopropene to diphenyldiazomethane (Figure 20).[123d] The photochemical formation of compounds (89) and (90) were viewed in terms of a process involving initial carbon-nitrogen bond cleavage to yield the diradical (91), followed by loss of nitrogen to (92), or cyclopropyl bond cleavage to produce (93). The diradical (92) cyclized to form the bicyclobutane (89) while the photochemical loss of nitrogen from (93) gave the carbene (94) which accounted for the formation of the olefinic product (90).[123d] Although no explicit explanation for these differences was given one presumes that the radical (91) is sufficiently stabilized by the phenyl rings[127] so that carbon-nitrogen homolysis to generate the diradical (92) is energetically more ~~favourable~~ feasible.

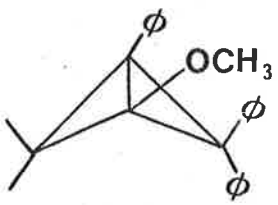
The diradical (95) obtained by homolytic expulsion of nitrogen from the adduct (96), itself prepared from the addition of diphenyldiazomethane to cyclopropenol methyl ether (6), would have both radical centres stabilized by an aromatic ring. This enhanced stabilization may favour the formation of the bicyclobutane (97) with bridgehead oxygen function.



(96)



(95)



(97)

It is interesting to note that the alternative adduct (98), would after homolytic expulsion of nitrogen also generate a diradical (99) which has both centres stabilized. One centre is adjacent to the phenyl substituents while the other can be stabilized by the alpha oxygen atom.[128] Thus even if the energetically unfavourable adduct (98) were to form, photolysis may still yield the bicyclobutane with bridgehead oxygen function (97).

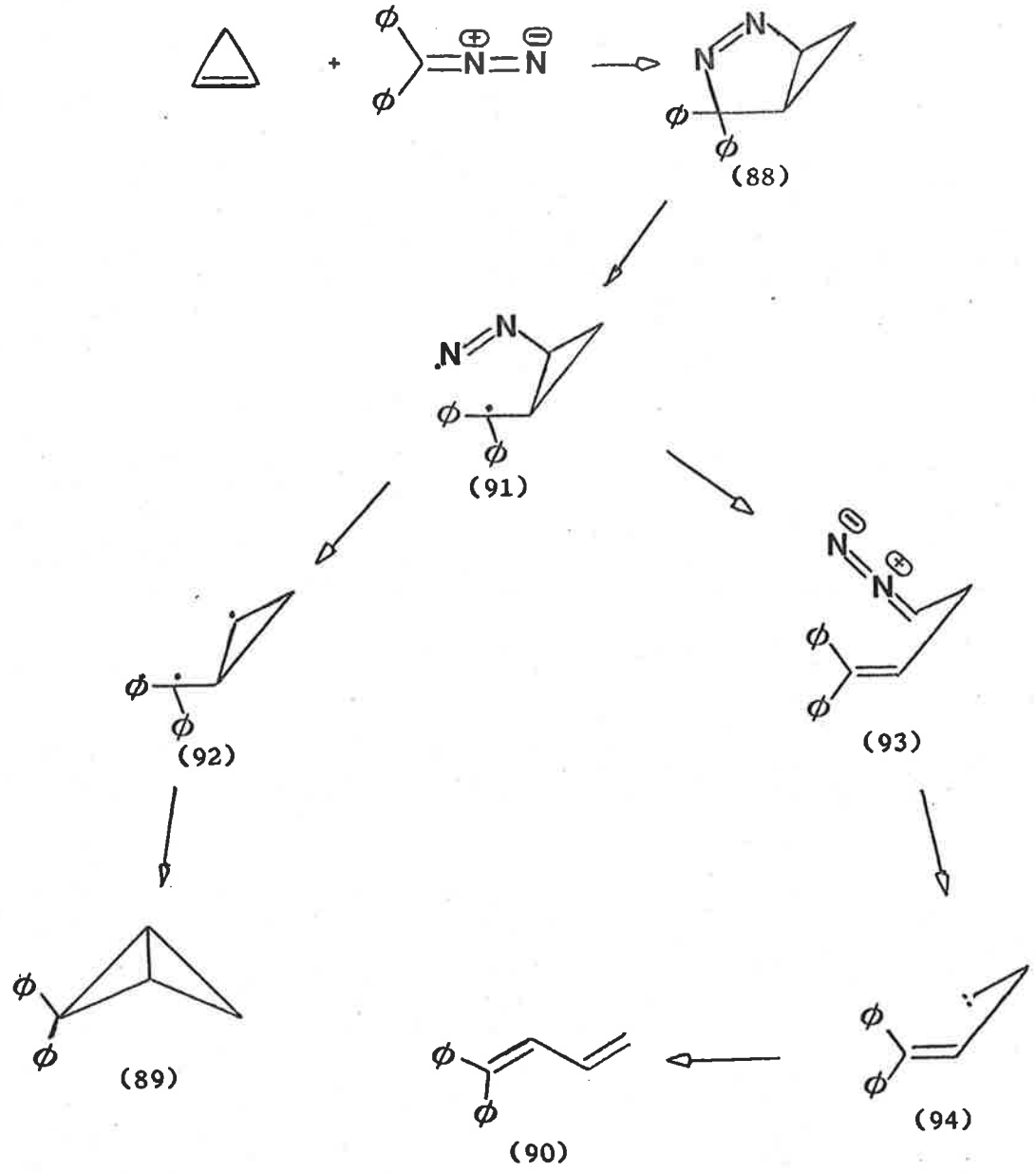
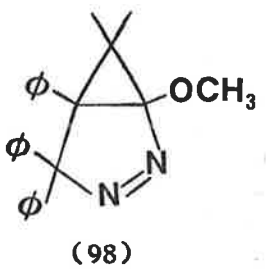
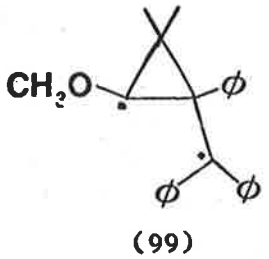



FIGURE 20



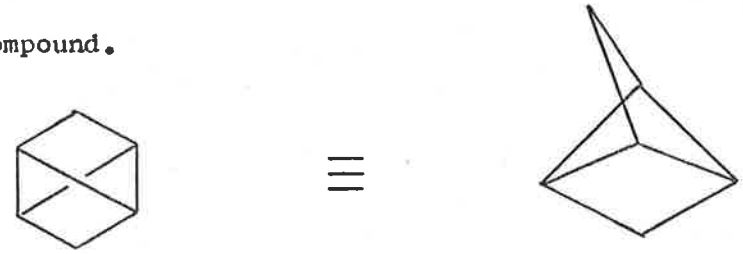

(98)




(99)

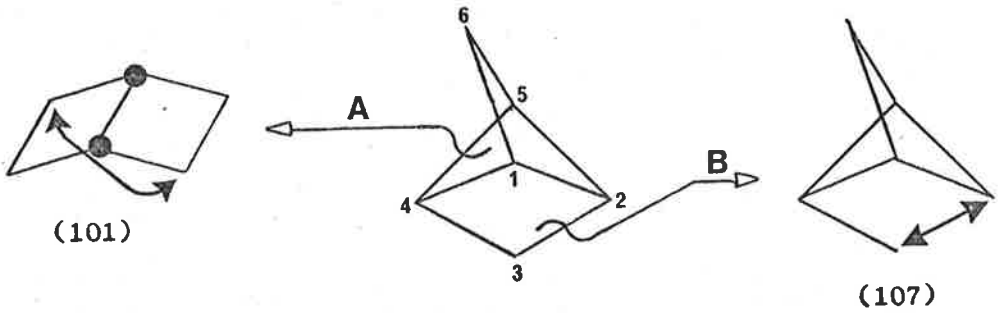
# INTRODUCTION - Part B

Bridged polycyclic hydrocarbons of unusual structure offer a challenging synthetic objective.[129] Tricyclo(2.2.0.$0^{2,5}$)hexane (100) is one such compound.



(100)

This molecule is small enough to allow a complete analysis of the type suggested by Corey[130] in his analytical approach to synthetic problems and first applied to longifolene,[131] caryophyllene[132] and isocaryophyllene.[132]




(101) (107)

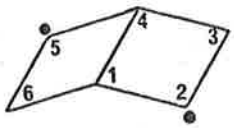
FIGURE 21

If Corey's approach is used, the common atoms (those bound to three or four but not two other carbon atoms[131]) in the tricyclohexane are C1, C2, C4 and C5 (Figure 21).

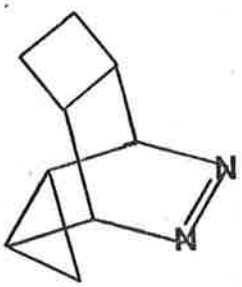
The symmetry of compound (100) creates only two distinct types of carbon-carbon bonds which simplifies the analysis so that there are only two possible structures derived by single bond disconnections.

Following the systematic approach,[131] process A (Figure 21) represents an intermediate derived by breakage of a bond between two common atoms. This produces the bicyclo(2.2.0) framework (101). An intramolecular coupling of the diradical (102) would regenerate compound (100). A structural model of (102) indicates that the orbitals

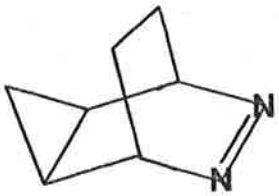
containing the free electrons are virtually orthogonal to the central C1-C4 bond but are nearly co-planar with the C1-C6 and C3-C4 bonds. It is conceivable that participation of these bonds could occur and thus fragment the carbon skeleton. Bond participation is not unknown in strained hydrocarbon fragmentations since Allred, in a study of the thermolysis of azo compounds[133] found that decomposition of compound (103) was accelerated over that of (104) by greater than $10^{14}$. Models of the transition states based on participating cyclopropyl electrons showed aligned overlapping orbitals for the accelerated (103) but orthogonally oriented orbitals with little or no overlap for (104).[133]




(102)

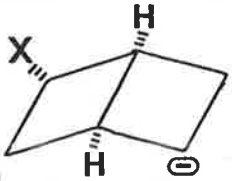



(104)



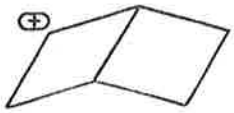

(103)

A $S_N2$ intramolecular displacement of a 1,4-arrangement of an anion and a suitable leaving group in a compound of type (105) would allow the synthesis of the tricyclohexane (100). In addition to the possibility of competing bond participation, the synthesis also requires the incorporation of the correct stereochemistry for the leaving group as indicated in structure (105).




(105)

A $S_N1$ alkylation should be avoided since the bicyclocation (106) is known to rearrange.[134]

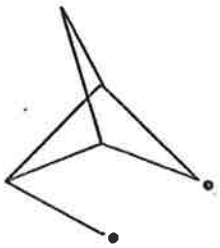


(106)

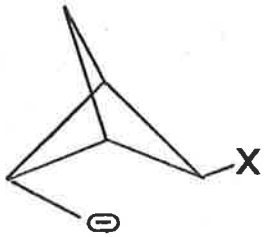
Disconnection of the bond connecting one common and one non-common atom in the tricyclohexane (100) (process B, Figure 21) gives rise to the bicyclo(1.1.1)pentane carbon skeleton (107).

Intramolecular coupling of the diradical (108) would reform the required carbon framework. Once again cleavage with bond participation is a possibility. Intramolecular alkylation of compound (109) requires the introduction of two groups with the correct stereochemistry.

(108)



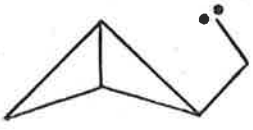
(109)




After exhausting all possible single bond disconnections, one can generate a new series of simpler structures by breaking two bonds of the original network.[131] The four possible processes for compound (100) are depicted in Figure (22).

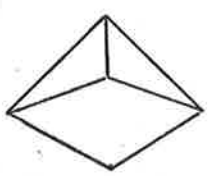
Processes C, D and F derive intermediates which require the simultaneous formation of two bonds from the same carbon atom to restore the tricyclohexane framework.

For process C, the bicyclobutane (110) with an ethyl carbene in the 2-position can be envisaged as a suitable intermediate. Intramolecular insertion of the carbene into the central bond would regenerate the tricyclohexane.



(110)

$:CH_2$



(111)

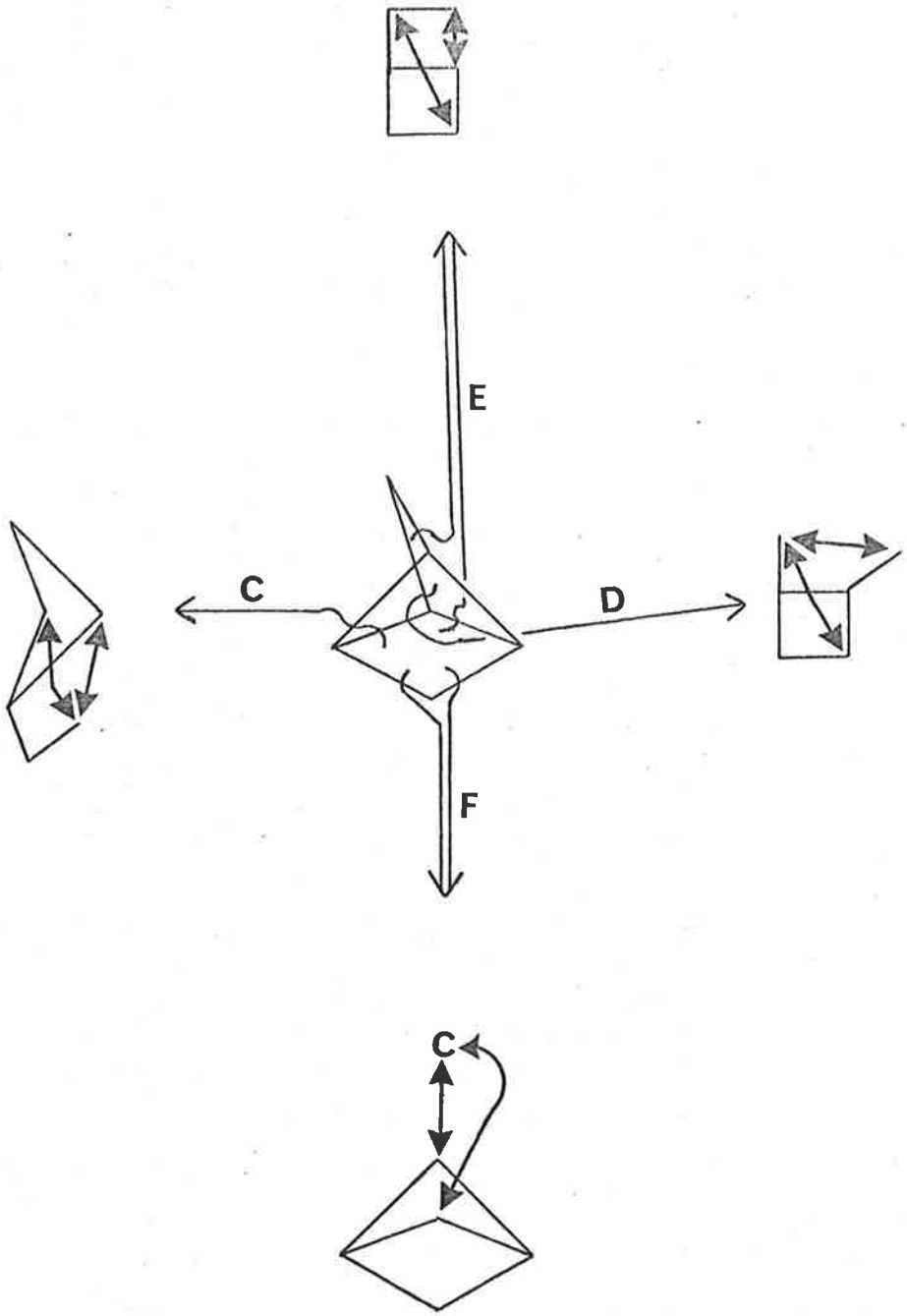
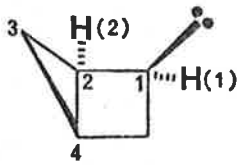



FIGURE 22

The intermolecular insertion of methylene carbene into the tricyclopentane (111), derivatives of which are known,[135] would complete the synthesis and illustrate process F.

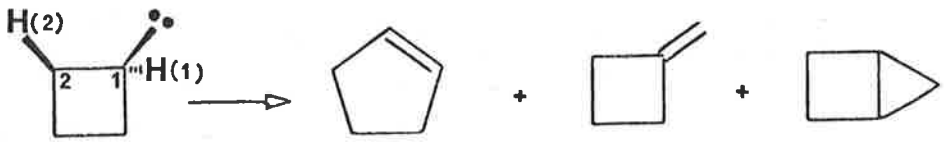
The insertion of carbenes into the central bond of bicyclobutanes has met with very little success, with acyclic products predominating.[136] Thus syntheses based on processes C and F were no longer considered.

To reform the desired carbon skeleton via process D would require the carbene (112) with the stereochemistry indicated. Insertion of the carbene into the cyclopropane C3-C4 bond would give the tricyclohexane (100).




(112)

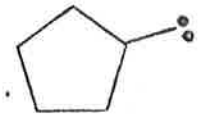
Cycloalkylcarbenes derived from small rings are known to undergo rearrangement with ring expansion.[137] Cyclopentene was the major product formed from C1-C2 insertion of cyclobutylcarbene (113) (Figure 23).[138] Bicyclo(2.1.0)pentane and methylenecyclobutane, from H(2) and H(1) insertion respectively, were the other two major products.[138]



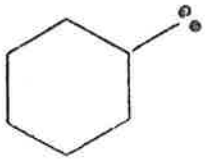

(113)

FIGURE 23

A study of the cyclobutyl (113),[138] cyclopentyl (114)[139] and cyclohexyl (115)[139] carbenes led to the observation that a co-planar arrangement of the divalent carbon, the ring carbon to which it is attached, and the C2-H(2) bond favours insertion of that carbene into the C2-H(2) bond.

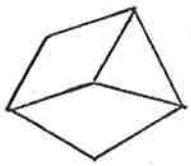


(114)

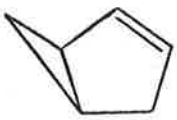


(115)

A structural model of the bicyclo(2.1.0)pentane carbene (112), which can be considered a cyclobutyl carbene with a C2 hydrogen replaced by a carbon-carbon bond, indicates that this C2-C3 bond can obtain the necessary planarity. Thus insertion into this bond (to give the isomeric tricyclohexane (116)) would be favoured over that into the C3-C4 bond. One suspects however, that expansion to bicyclo(3.1.0)-hex-2-ene (117) with its consequent relief of ring strain would be the predominant reaction of the carbene (112). The non-specificity of insertion precluded further consideration of the bicyclo(2.1.0)pentane carbene (112).

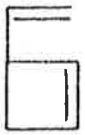


(116)



(117)

A $2\pi + 2\pi$ cycloaddition of the vinyl cyclobutene (118) to the tricyclohexane (100) would illustrate process E. This molecule possesses two $\pi$ moieties bonded to a single saturated carbon atom, an ideal arrangement for a di-$\pi$-methane rearrangement to occur under photolytic conditions.[140] Rearrangements of this type lead to $\pi$-substituted cyclopropanes and formally involve the migration of one $\pi$ moiety bonded to the saturated carbon, C3, to C4 of the other $\pi$ moiety, and concomitant three ring formation between C3 and C5 as depicted in Figure 24.[140] It was noted by Zimmerman and co-workers that the skeletal change in the rearrangement could be accounted for by one basic mechanism (Figure 25).[140] A di-$\pi$-methane rearrangement of the vinylcyclobutene (118) would thus yield the vinylbicyclobutane (119).



(118)

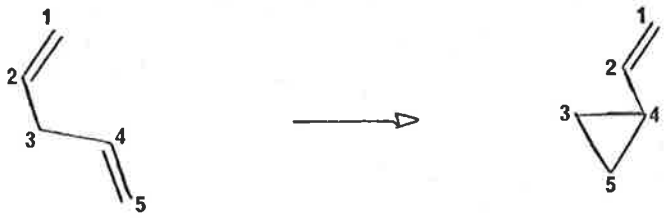



FIGURE 24

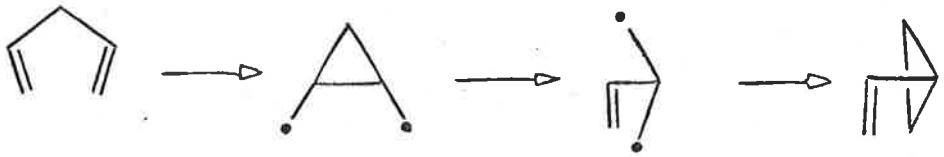
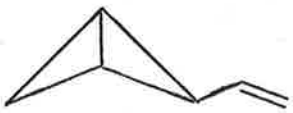


FIGURE 25



(119)

In systems where free rotation about unconstrained π bonds can occur, the triplet energies of dienes are dissipated by cis-trans isomerization pathways and the di-π-methane rearrangements proceed via the singlet excited states.[140]

The vinylcyclobutene (118) contains two isolated double bonds and therefore requires the attachment of an additional chromophore for absorption to occur in the ultraviolet region of the spectrum. The resultant singlet excited state would favour the di-π-methane rearrangement. The alternative, the triplet sensitization of compound (118), would generate the triplet state and thus probably undergo cis-trans isomerization about the unconstrained π bond.[140]

It should be noted that at least one exception exists where a free rotor does not inhibit di-π-methane triplet reactivity. The exception is the singlet and triplet reactivity of 1-phenyl-3-methyl-3-(cis-1-propenyl)cyclohexene (120), summarized in Figure 26.[141] No explanation for this effect has been advanced.

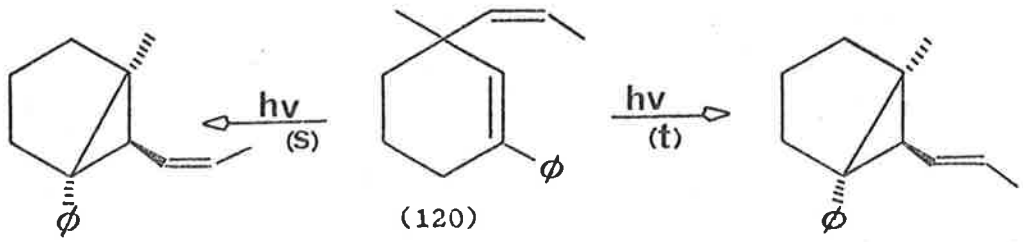



FIGURE 26

The potential problems associated with the photolysis of vinylcyclobutene precluded further study of this compound.

It is known that photolysis of cyclobutylphenylketone yields 2-hydroxy-2-phenylbicyclo(1.1.1)pentane as the major product (Figure 27).[142] The mechanism involves a 1,4-diradical intermediate (121) formed by γ-hydrogen abstraction by the carbonyl $n$-$\pi^*$ excited state.[142,143] This diradical may either disproportionate back to ground state ketone, undergo cleavage or cyclize to the bicyclopentanol (122)(Figure 27).[142]

It was thus conceivable that the benzoylbicyclo(1.1.1)pentane (123), which can be considered a derivative of cyclobutylphenylketone, would undergo a similar photolytic reaction to give 2-phenyltricyclo-(2.2.0.$0^{2,5}$)hexan-2-ol (124), a derivative of the required hydrocarbon (100). The 1,4-diradical (125) would be an intermediate, assuming a similar mechanistic pathway to that for cyclobutylphenylketone. Coupling of this diradical to form the tricyclohexane derivative would illustrate process B (Figure 21).

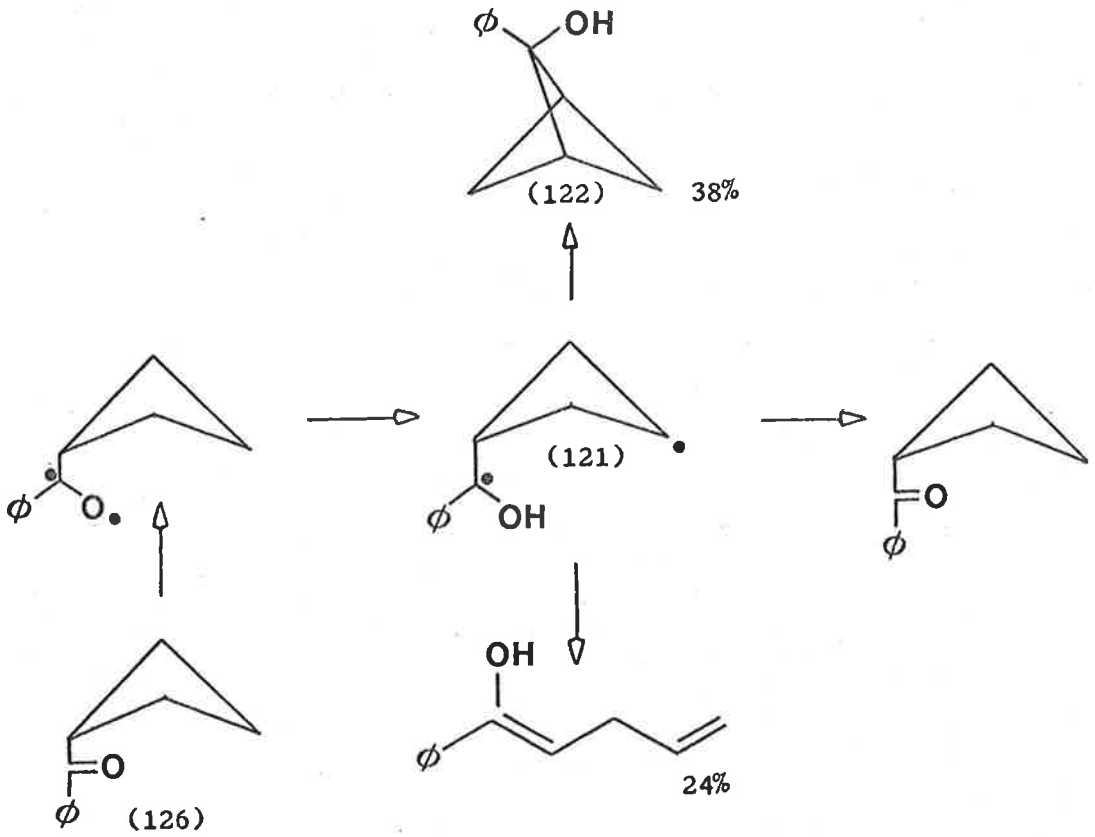
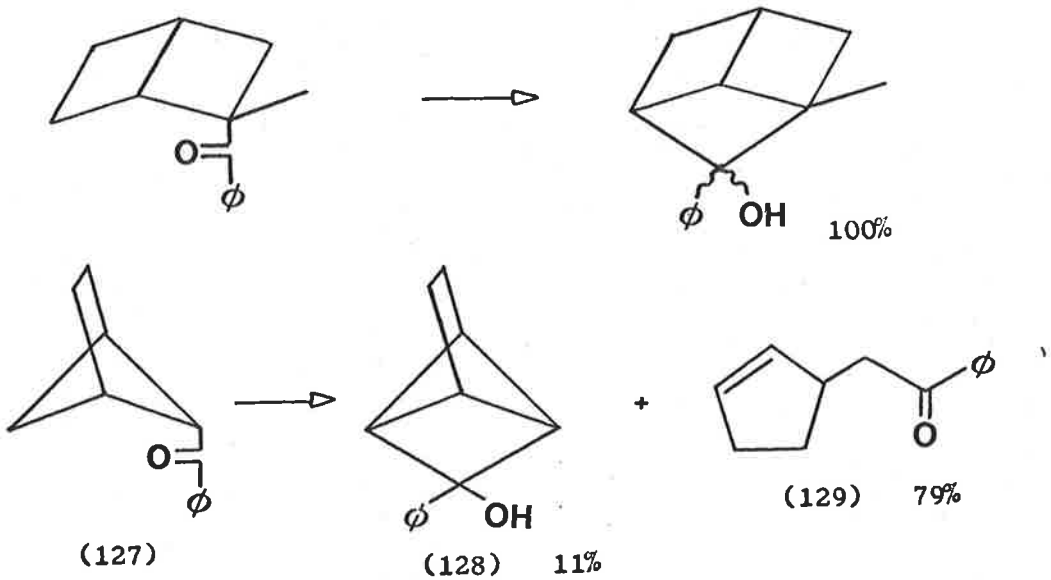



FIGURE 27



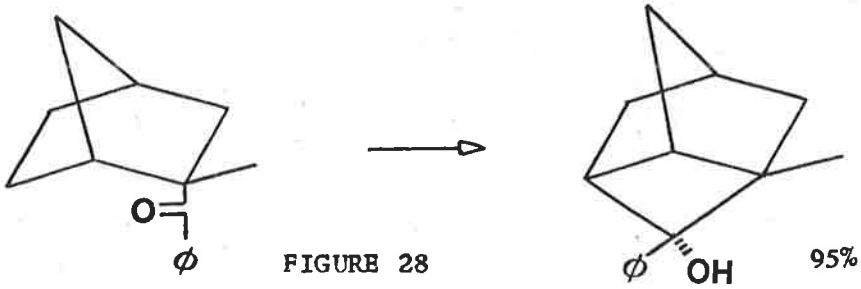
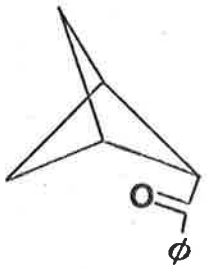
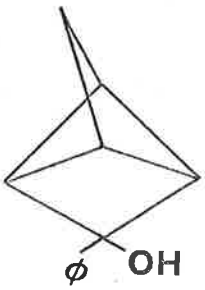
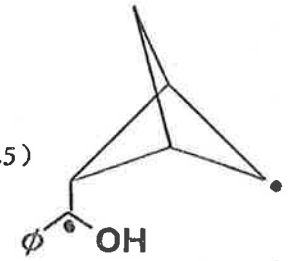




FIGURE 28

(123) 


(124) 


(125) 


The features associated with the photochemistry of cyclobutylphenylketone were the low quantum yield and slow rate of internal hydrogen abstraction.[142,143] Chemical[144] and kinetic[145] evidence accounted for these in terms of the low concentration of its reactive quasi-axial conformer (126).

The geometry of 2-benzoylbicyclo(1.1.1)pentane is such that the benzoyl group is permanently locked into the axial position, a favourable condition for photolytic cyclization to occur. The symmetry of the bicyclo(1.1.1)pentane skeleton results in all methylene positions being stereochemically equivalent so that the synthesis of compound (123) would present no stereochemical problems evident in other potential intermediates discussed earlier.

The alcohols (122) and (124) are examples of highly strained cyclobutanols synthesized by the photocyclization of alkyl aryl ketones that have an accessible γ-hydrogen. The photochemical syntheses of other novel bridged polycyclic cyclobutanols that have been the subject of recent attention[146] are depicted in Figure 28.

Exo-5-benzoylbicyclo(2.1.1)hexane (127) was an appropriate model for the reactive conformer of cyclobutylphenylketone since the benzoyl group was now locked into the axial position.[146c] If the inefficiency of the cyclobutylphenylketone system was totally due to the low population of the reactive conformer then one would expect compound (127) to be more reactive and photoefficient.[146c] The photolysis of ketone (127) produced two major photoisomers, the bridged

cyclobutanol (128) and the cyclopentene derivative (129)(Figure 28)[146c] The quantum yield was found to be lower than expected but the rate of internal hydrogen abstraction was faster than that in the benzoylcyclobutane (126).[144]

The inefficiency of the reaction was attributed to a rapid triplet degradation.[144] In addition the faster reaction rate implied that the inefficiency encountered in its photoreaction could not be ascribed to a low reaction rate as was previously observed with cyclobutylphenylketone.[143]

The diradical produced by transannular hydrogen abstraction from ketone (127) in its excited state preferred fragmentation to ring closure[144,146c] in marked contrast to cyclobutylphenylketone where ring closure predominated.[143]

Other studies[146a,b] revealed the ability of a methyl substituent, alpha to the benzoyl group, to completely suppress this Norrish type II fragmentation[147] in favour of cyclization. An illustration is provided by endo-2-benzoylbicyclo(2.2.0)hexane (130) which yields only the fragmentation product (131), while endo-2-benzoyl-2-methylbicyclo(2.2.0)-hexane (132) is converted quantitatively to a 1:1 mixture of the epimeric tricycloheptanols (133) and (134)(Figure 29).[146a]

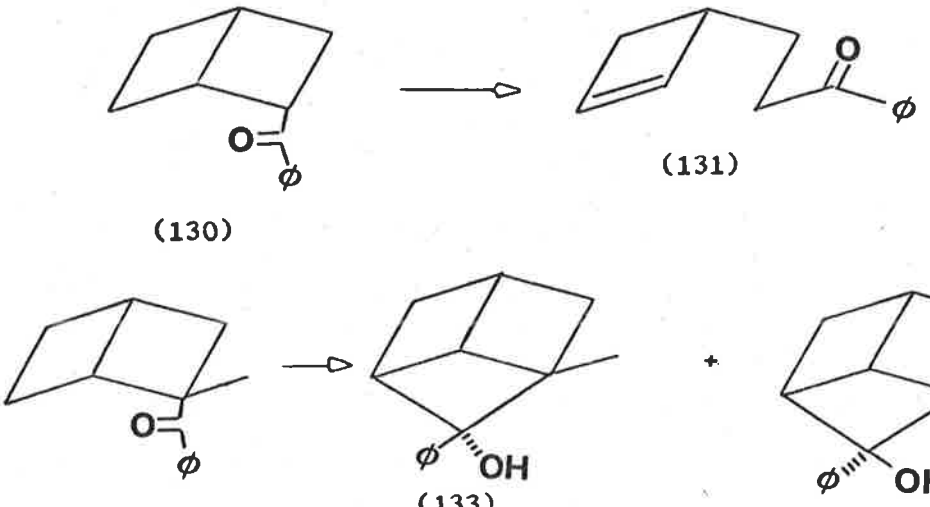
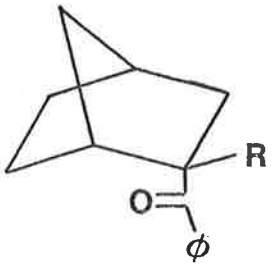



FIGURE 29

Lewis and Ruden previously observed a similar effect with the endo-2-benzoylnorbornanes (135) and (136) and attributed this to a transition state which requires eclipsing of the phenyl and methyl groups for fragmentation while no such eclipsing is evident in the transition state for cyclization.[146b]



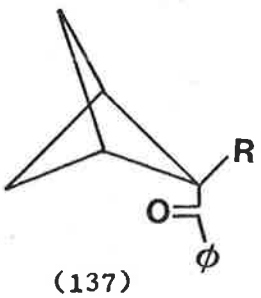

(135) R = H

(136) R = $CH_3$

Mechanistic investigations have confirmed the effect of alpha-methyl substitution to be indicative of steric interference with the bond rotation necessary to bring the diradical into the correct conformation for cleavage.[148]

Recent work has revealed that alpha-fluorines also enhance the efficiency of type II cyclizations.[149] The explanation for alpha-methyl substitution does not account for the effects on product ratios produced by the much smaller fluorine atom.[149] It has been postulated that a hyperconjugative stabilization of the diradical by the fluorine constrains the diradical into a conformation with little of the p-σ overlap required for cleavage.[149]

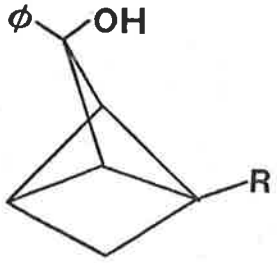
Thus a molecule of type (137) which satisfies both requirements of a benzoyl group in a quasi-axial conformation and either a methyl or fluorine substituent alpha to the benzoyl moiety was expected to produce the cyclobutanol (138), a derivative of the required hydrocarbon (100).




(137)

(a) R = $CH_3$

(b) R = F




(138)

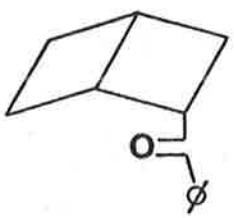
Contrary to common belief, fluorocarbon systems, in general, present no peculiar handling difficulties.[150a] It is possible to replace hydrogen with fluorine in a wide range of hydrocarbons without gross distortion of the geometry of the system.[150a]

Direct fluorination is rarely used because the technique is difficult and fragmentation rapidly increases with increasing complexity of the compound being fluorinated.[150b]

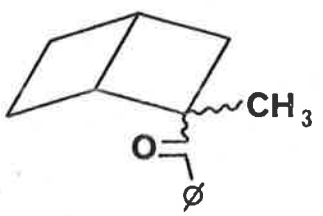
Many compounds containing acidic hydrogen are converted to fluoro-compounds by perchloryl fluoride.[151,152] The mechanism involves nucleophilic attack by carbanions on the fluorine atom in perchloryl fluoride.[152] A disadvantage is that the chloric acid produced as a by-product can give an explosive mixture with organic compounds.[150c]

Metal fluorides introduce fluorine by nucleophilic displacement of a halide.[153,154] The benzoylketone (123) would be a suitable intermediate for the fluoro derivative (137b) since hydrogen atoms alpha to a ketonic function are usually acidic.[155] This would allow fluorination with perchloryl fluoride[151,152] or bromination[156] followed by nucleophilic displacement of the bromide by fluoride ion.[153,154]

In addition, alkylation of the ketone (123) should enable the synthesis of the methyl derivative (137a). An analogy exists in the methylation of endo-2-benzoylbicyclo(2.2.0)hexane (130) with sodium hydride and methyl iodide to give an epimeric mixture of the 2-benzoyl-2-methylbicyclo(2.2.0)hexanes (139).[146a]



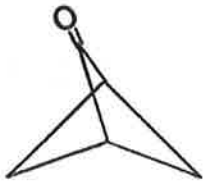

(130)




(139)

The synthesis of the benzoylketone (123) requires the formation of the bicyclo(1.1.1)pentane skeleton. Among the synthetic entries into this ring system,[143,157] the approach involving the photolysis of cyclobutylphenylketone to yield 2-hydroxy-2-phenylbicyclo(1.1.1)pentane (122) and other products (Figure 27)[143] is the most promising since it is amenable to the preparation of sufficient quantities of functionalized material.[145]

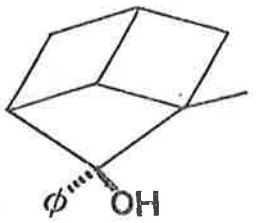
Degradative oxidation of the aryl ring was envisaged for the transformation to the benzoylketone. Caputo and Fuchs discovered that phenylcyclohexane was oxidized to cyclohexane carboxylic acid with ruthenium tetroxide under mild conditions.[158] Later workers observed that oxidation of 1-phenylcyclopentan-1-ol afforded cyclopentanone[159] and that hydrocarbons were inert under these conditions.[160] A similar reaction of compound (122) may yield the interesting bicyclic ketone (140).

(140) 

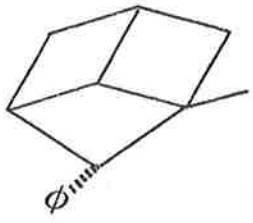
Typically, aqueous sodium periodate is used as a co-oxidant in these oxidations.[161] The phenylalcohol (122) is known to be stable in 30% $D_2O$ - dioxan mixtures for at least 48 hr[162] but it is extremely sensitive to basic media isomerizing rapidly to cyclobutylphenylketone.[162] Under acidic conditions, a less rapid rearrangement to 3-phenyl-3-cyclopenten-1-ol occurs.[162] This potential instability of the hydroxyl function in aqueous media necessitated either its protection or complete removal.

The reductive cleavage of benzyl alcohol derivatives with sodium in liquid ammonia occurs with ease.[163] Meinwald and Mioduski reported the cleavage of the tertiary benzylic tricyclohexanol (134) to the hydrocarbon (141).[146a] A similar cleavage of the alcohol (122)

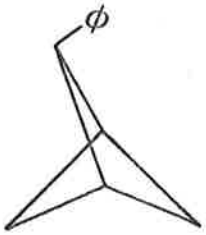
would render the hydrocarbon (142). The possible instability of the bicyclopentanol (122) towards ammonia, a base, required a modification to the scheme.



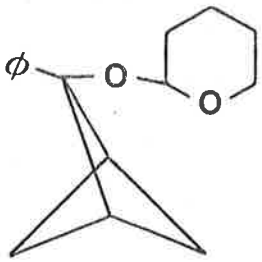

(134)



(141)




(142)

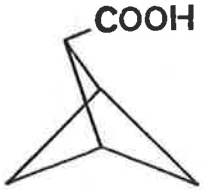



(143)

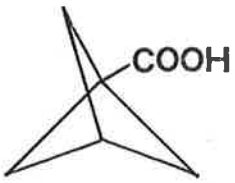
Tetrahydropyranyl ethers can be prepared from their corresponding alcohols and dihydropyran with only a catalytic amount of acid.[164] It should be possible to prepare the ether (143) with minimal presence of acid, thus lowering the tendency for the alcohol (122) to rearrange. Reductive cleavage with sodium in ammonia would give the phenylhydrocarbon (142).

Subsequent oxidation with ruthenium tetroxide should allow the preparation of 2-bicyclo(1.1.1)pentanoic acid (144), a known compound but previously synthesized by an arduous route to give a low yield of product inseparable from its isomer, the bridgehead acid (145).[157b]

(144)



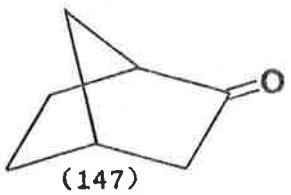

(145)



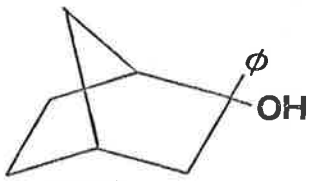

The reaction of organolithium reagents and carboxylic acids constitutes a simple general method for the synthesis of ketones.[165] Thus phenyllithium on the acid (144) should give the required benzoylbicyclo(1.1.1)pentane (123).

The difficulty in obtaining the bicyclopentanol (122)[143] and its instability to acid and base media[162] motivated one to study a model system. Phenylnorbornanol (146), readily accessible from 2-norbornanone (147),[166] is a bridged bicyclocompound containing the 1-phenylcyclopentanol skeleton studied in the ruthenium tetroxide oxidation.[159]

Oxidation should return 2-norbornanone. If successful, it would indicate that a strained hydrocarbon skeleton can survive this oxidative medium.



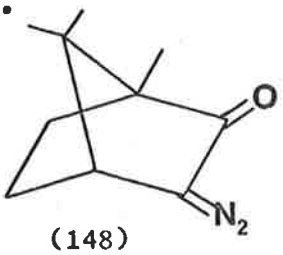

(147)



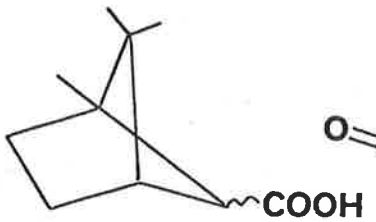

(146)

The low yields in the preparation of the bicyclopentanol (122),[143] its tedious and time consuming purification[143] and the precaution of having an alternative synthesis in the event of insurmountable problems with the proposed plan suggested that alternative schemes for the synthesis were desirable.

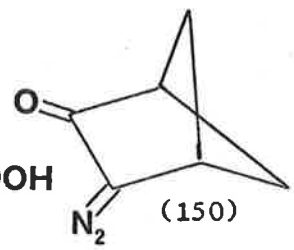
The Wolff rearrangement of α-diazoketones is one of the most widely used syntheses of the bicyclo(2.1.1)hexane skeleton.[167] A typical example is provided by α-diazocamphor (148) which upon irradiation yields the epimeric bicyclo(2.1.1)hexane carboxylic acids (149).[168] A similar rearrangement of the diazoketone (150) would yield the carboxylic acid (144).




(148)

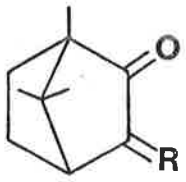



(149)




(150)

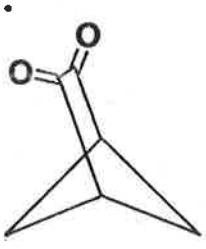
α-Diazoketones can be prepared from their corresponding α-diketones[169] as illustrated with camphorquinone (151) which reacts with tosylhydrazine to form the monohydrazone (152).[169b] Treatment with base effects elimination of the tosyloxy anion with formation of 2-diazo-1-camphorone (148) in good yield.[169b]



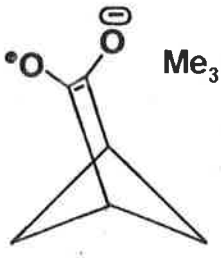

(151) R = O

(152) R = NNHTs

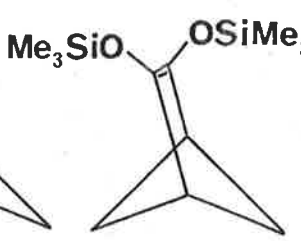
(148) R = $\overset{+}{N}{=}\overset{-}{N}$




(153)

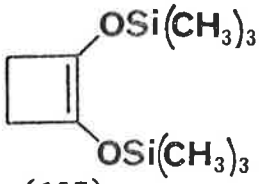



(154)

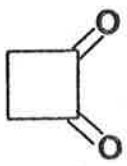



(155)

The generation of diazoketone (150) by the above method would require the diketone (153), an unknown compound. Although the diketone has yet to be synthesized, its radical anion (154) has been prepared from the disilyl ether (155).[170] Bromine oxidation of this ether should afford the diketone (153). Conia has found that 1,2-cyclobutanedione (156) is readily available from bis-(trimethylsiloxy)cyclobutene (157) by this method.[171]



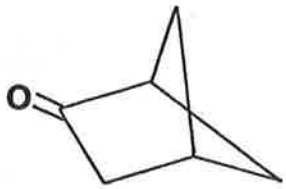

(157)



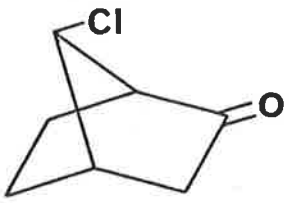

(156)

The multistep sequence[170,172] necessary to synthesize the disilyl enol ether motivated one to look for shorter routes to the diazoketone (150).

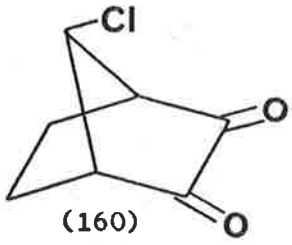
Selenium dioxide oxidation of bicyclo(2.1.1)hexanone (158), a known compound,[173] should directly afford the α-diketone (153) and hence considerably shorten the route to its preparation. A precedent is set by Meinwald who found that oxidation of the bicycloketone (159) gave the corresponding α-diketone (160).[174]




(158)




(159)




(160)

In the steroid field, ring contraction of cycloalkanones to cycloalkane carboxylic acids is possible with hydrogen peroxide and selenium dioxide (Figure 30).[175] These reagents and the bicyclohexanone (158) may enable the preparation of the carboxylic acid (144) obviating the isolation of the α-diketone (153).

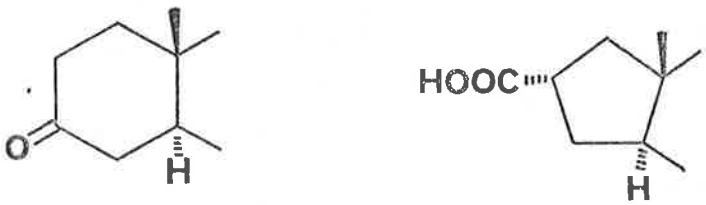



FIGURE 30

Formylation of a carbonyl compound followed by treatment with tosylazide yields an α-diazoketone.[176] A series of diazocycloalkanones have been prepared in this manner.[177]

An alternative synthesis is from the addition of chloramine to α-oximinoketones.[178] The oximinoketones are prepared from the corresponding ketone and an alkylnitrite in the presence of base.[179]

The bicyclohexanone (158) may succumb to similar reactions to generate the diazoketone (150)(Figure 31).

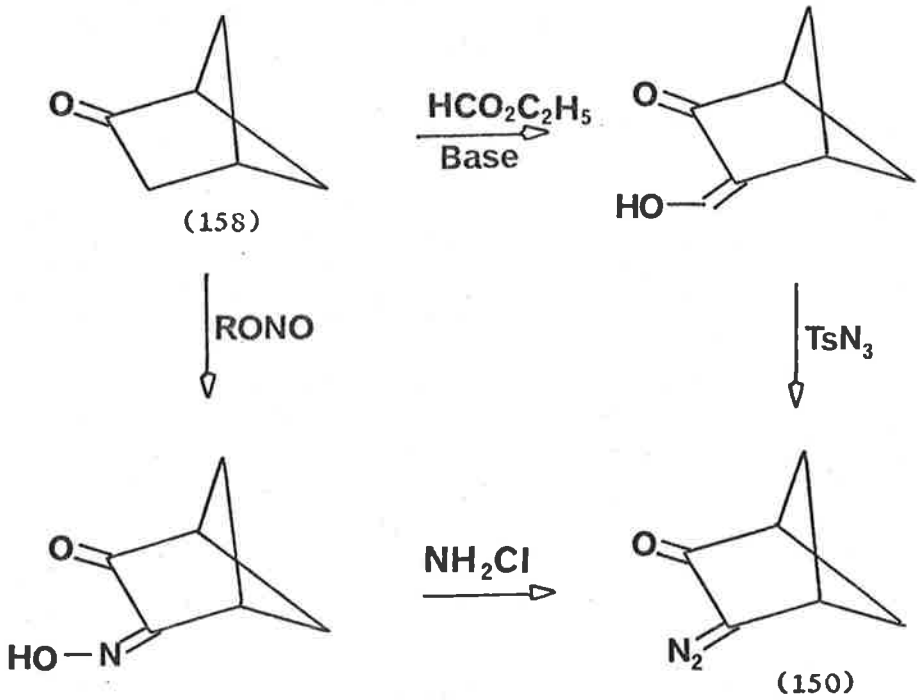
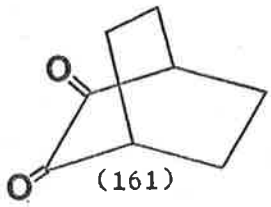


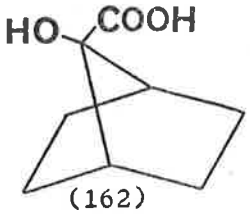

FIGURE 31

Finnish workers reported the benzilic acid rearrangement of the

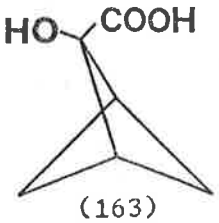
bicyclo(2.2.2)octandione (161) to the ring contracted bicyclo(2.2.1)-heptane derivative (162).[180] A similar rearrangement of the α-diketone (153) would give the α-hydroxycarboxylic acid (163). Although compound (163) contains the desired bicyclo(1.1.1)pentane-2-carboxylic acid skeleton, the basic conditions usually required for benzylic acid rearrangements[181] may destroy the framework since the anion of the hydroxyl function would be formed.



(161)



(162)



(163)

A related rearrangement is the quasi-Favorskii exemplified by the halocycloalkanones.[171,182] The addition of water to α-bromocyclobutanone instigates a ring contraction to cyclopropane carboxylic acid (Figure 32).[171,182d] If water is replaced by methylmagnesiumiodide, cyclopropylmethylketone is the major product(Figure 32).[182c]

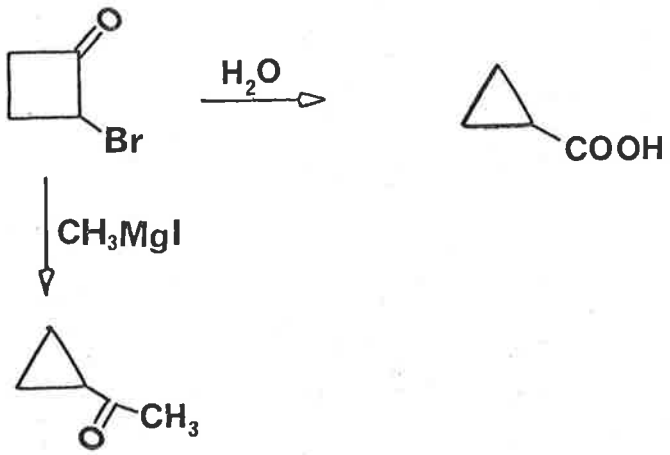
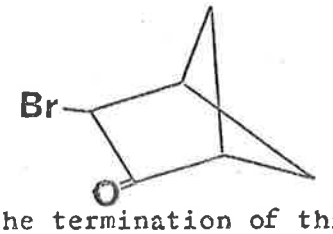


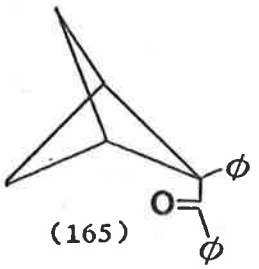

FIGURE 32

Thus bromination of the bicycloketone (158) to the bromoderivative (164) may directly afford the benzoylketone (123) on reaction with phenylmagnesiumbromide.

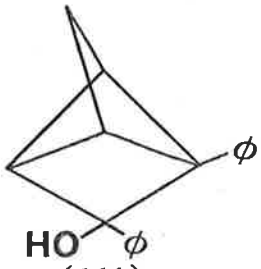
(164)




Just prior to the termination of this work, a photochemical synthesis of a tricyclo(2.2.0.$0^{2,5}$)hexane was reported.[183] Irradiation of 2-phenyl-2-benzoylbicyclo(1.1.1)pentane (165) resulted in a quantitative conversion to 1,2-diphenyltricyclo(2.2.0.$0^{2,5}$)hexan-2-ol (166). This preparation admirably illustrates the single bond disconnection process B in the retrosynthetic analysis of the tricyclohexane structure (100)(Figure 21).



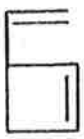

(165)




(166)

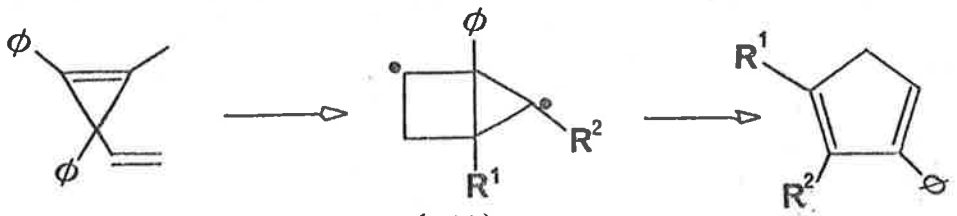
It has been reported recently that insertion of carbenes into the central bond of bicyclobutanes can be achieved in synthetically useful yields.[184] Thus the two-bond disconnection processes C and F (Figure 22) may now provide alternative entries into the tricyclohexane (100) system.

Additional evidence for discounting the photolysis of vinylcyclobutene (118) as a viable preparation of the hydrocarbon is also now available. Padwa has found that subjection of the vinylcyclopropene (167) to photolysis yields the 1,3-cyclopentadienes(168)(Figure 33).[185a] The cyclopropene (167) is a suitable analogy for the vinylcyclobutene (118) since both are 1,4-dienes with one $\pi$ moiety free to rotate with the other constrained in a small ring.



(118)

The proposed mechanistic pathway involved π - π bridging of the exited cyclopropene to give a diradical intermediate (169) which subsequently cleaves to produce the 1,3-cyclopentadiene ring system.[185a] The bridging and formation of the diradical (169) are related to the first two formal steps of a di-π-methane rearrangement.



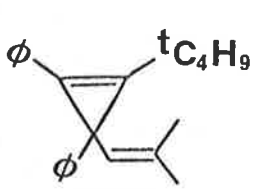
(167) (169) (168)

(a) $R^1 = \phi$, $R^2 = CH_3$

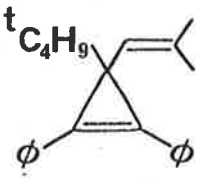
(b) $R^1 = CH_3$, $R^2 = \phi$

FIGURE 33

Zimmerman, simultaneously noted this unusual degenerate di-π-methane rearrangement with the vinylcyclopropene(170).[185b] In addition he also reported that this cyclopropene underwent an incipient di-π-methane rearrangement to give the isomeric cyclopropene (171) which then decomposed via π-π bridging.[185b]

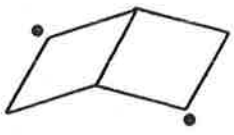


(170)



(171)

Thus π-π bridging of the vinylcyclobutene (118) would give the 1,4-diradical (102) followed by cleavage to 1,4-cyclohexadiene.



(102)

# CHAPTER II

# RESULTS AND DISCUSSION - Part A

It has been found advantageous to form the salt (44) of the tosylhydrazone (43) with lithium hydride in hexane replacing sodium methoxide in methanol (Figure 34).[30] The time for complete salt formation has increased from one hour to approximately twelve, but the subsequent pyrolysis gives improved yields of the diazoalkene (39). To obtain this higher yield it is necessary to keep the pyrolysis time short and maintain a positive flow of nitrogen to assist the product into the cold trap. Longer reaction times result in a mixture of the diazoalkene (39), the cyclopropenol ether (6) and a yellow, viscous oil whose identity remains unknown.

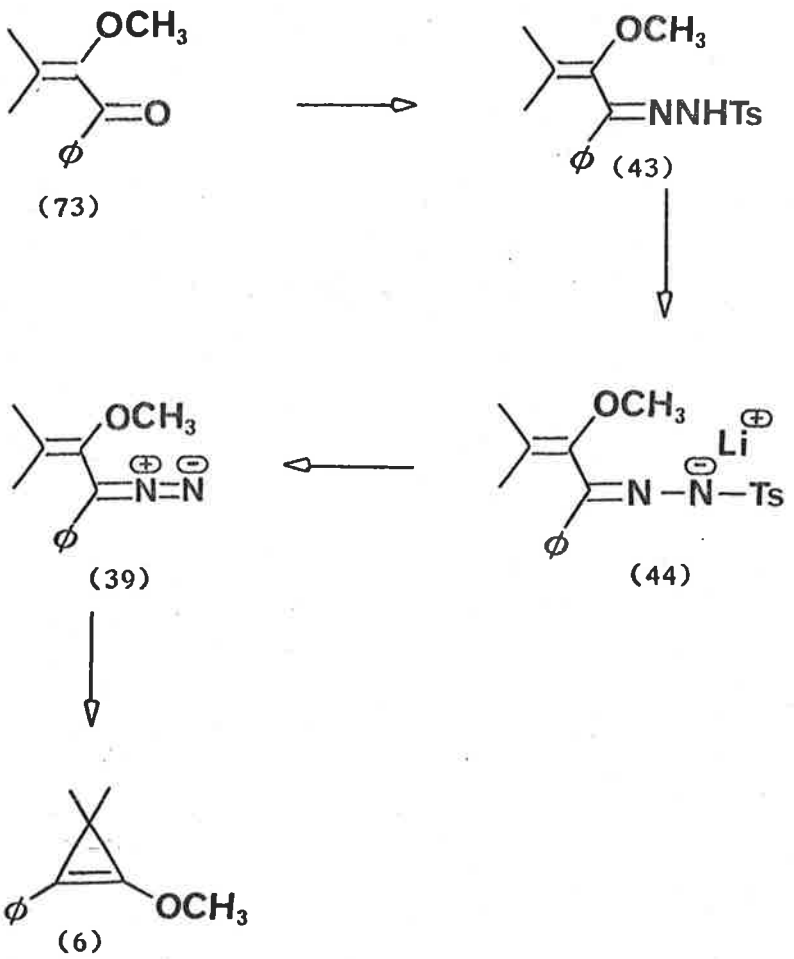



FIGURE 34

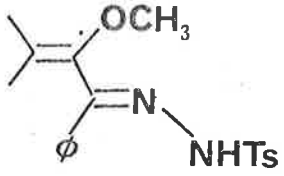
A minor disadvantage of the synthesis was the 14 days necessary for quantitative reaction between the ketone (73) and tosylhydrazine to form the hydrazone (43).[22,30] It was thought that an increase in temperature may reduce this although Closs stipulated[57] that the temperature for unsaturated hydrazone formation must not exceed 50°, only 10° above the current temperature of reaction. Although no reason was stated, one presumes that Closs found decomposition occurring above this temperature. Efforts to decrease the reaction time by increasing the temperature proved unsuccessful. Equimolar quantities of tosylhydrazine and ketone (73) were dissolved in methanol and heated under reflux. After 168 hr thin layer chromatography (t.l.c.) analysis by comparison with authentic materials indicated the presence of the ketone (73), tosylhydrazine and the hydrazone (43). At 192 hr, in addition to the above compounds, there were faint traces of at least six additional products which were in abundance after a further 24 hr when only a very small amount of the required hydrazone (43) was discernible.

Repeating the experiment at the lower temperature of 50° resulted in a similar decomposition.

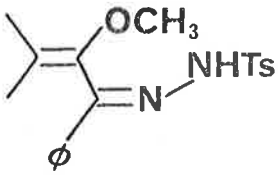
The hydrazone (43) when dissolved in methanol and heated under reflux for 120 hr exhibited an identical decomposition as evident by t.l.c. analysis and it was concluded that the product was unstable at the higher temperatures. No attempt was made to identify these decomposition products. Further experiments designed to reduce the reaction time for formation of the hydrazone were not instituted.

The reaction of ketone (73) with tosylhydrazine usually produced two isomeric compounds, although on one occasion only a single isomer was evident. Since both the mixture and the lone isomer were found to give identical products upon base-induced decomposition, it was

assumed that the E- and Z- structures (172) and (173) respectively, account for the observed differences.




(172)




(173)

Contrary to the earlier report,[30] heating a mixture of the E- and Z- hydrazones does not cause conversion to one isomer, as an analytically pure sample of this isomeric mixture failed to alter its ratio on heating.

It is presumed that the lone isomer is the thermodynamic product since stirring an acid solution of the mixture resulted in complete isomerization to this compound.

The n.m.r. spectra of the mixture and the single isomer were obtained earlier[30] and are now interpreted. The data for each isomer are reproduced in Tables 1 and 2. Table 1 refers to the thermodynamic isomer and Table 2 the kinetic product.

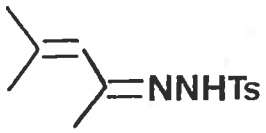
| CHEMICAL SHIFT (p.p.m.) | RELATIVE INTENSITY | MULTIPLICITY | ASSIGNMENT |
|---|---|---|---|
| 8.30 | 1 | broad singlet | N- H |
| 8.07-7.17 | 9 | complex | aromatic protons |
| 3.13 | 3 | singlet | $CH_3$- O |
| 2.40 | 3 | singlet | $CH_3$- Aryl |
| 1.82 | 3 | singlet | $CH_3$- C= C |
| 1.27 | 3 | singlet | $CH_3$- C= C |

TABLE 1

| CHEMICAL SHIFT (p.p.m.) | RELATIVE INTENSITY | MULTIPLICITY | ASSIGNMENT |
|---|---|---|---|
| 8.03-7.10 | 9 | complex | aromatic protons |
| 3.27 | 3 | singlet | $CH_3$- O |
| 2.43 | 3 | singlet | $CH_3$- Ph |
| 1.73 | 3 | singlet | $CH_3$- C= C |
| 1.42 | 3 | singlet | $CH_3$- C= C |

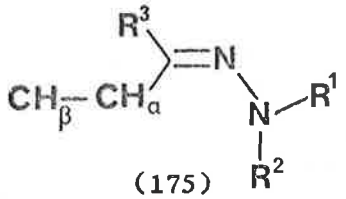
TABLE 2

Closs noted that mesityloxidetosylhydrazone (174) existed as two isomers but no attempt was made to assign the configuration to the compounds.[57] No other direct analogies exist with isomers (172) and (173) for comparison.



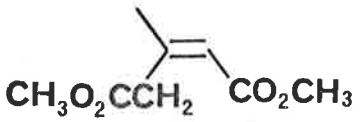

(174)

Extensive literature exists on the study by n.m.r. spectroscopy of the E- and Z- configurations of compounds with general formula (175).[186] The most reliable information in assigning E- and Z- stereochemistry comes from the chemical shift of compounds with $R^3$ a hydrogen atom and/or from compounds with alpha-methine protons.[186k] The least reliable chemical shifts are those of beta-protons and alpha-methylenes.[186k] They depend on the type of compound and quite often on the structure of $R^3$ and $CH_\alpha CH_\beta$.[186k] Unfortunately, hydrazone (43) satisfies none of the above criteria and hence the following assignments of configuration are tentative.

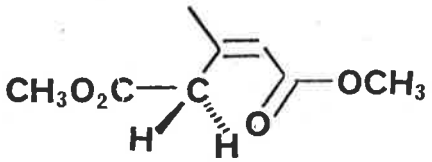


(175)

The chemical shift data for a number of cis-trans pairs of α,β-unsaturated esters reveal that the deshielding of the protons of a β-methyl cis to the alkoxycarbonyl substituent is fairly constant, being of the order of 0.25 p.p.m.[187a] It was noted that the differential shift (0.60p.p.m.) of the β-methylene protons in the β-methylglutaconic esters (176) was much larger than that of the β-methyl protons.[187a] This suggested that the cisoid conformation (177) was heavily populated.[187a]



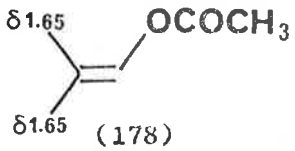
(176)



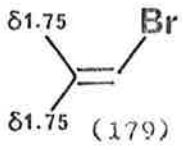
(177)

From a study of models of the cisoid and transoid isomers of compounds (172) and (173) the cisoid conformation appears to possess less steric interactions than the transoid. Since the anisotropic effect of the carbon-nitrogen double bond parallels that of the carbon-oxygen double bond,[186j] it seems likely that in each of these isomers the cis β-methyl substituent will resonate further downfield than the trans β-methyl.

The presence of the methoxyl substituent on the double bond in the hydrazones can be effectively ignored since electron rich substituents, oxygen and bromine for example, have an identical effect on the chemical shift of the cis and trans methyl resonances in compounds such as the enol acetate (178) and the vinylic bromide (179).[187b]

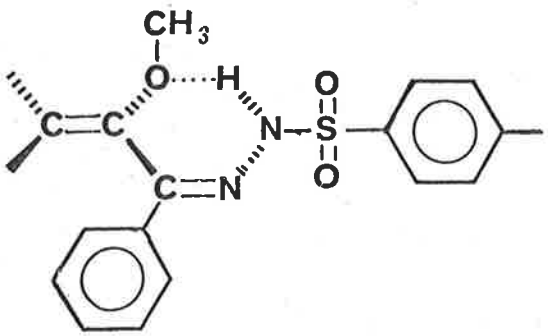



(178)




(179)

A model of the transoid-Z-configuration, depicted in structure (180), reveals the hydrogen on the amino nitrogen to be ideally placed for hydrogen bonding with the methoxyl oxygen to form a six-membered ring. One could expect the lone electron pair on the amino nitrogen, the carbon-nitrogen double bond and the mono-substituted aryl ring to assume a planar arrangement in order to maximize the overlap of the π-orbitals involved. However, this configuration results in a severe interaction between the mono-substituted phenyl ring and the cis-methyl substituent. This would tend to force the aryl ring out of plane with the carbon-nitrogen double bond.

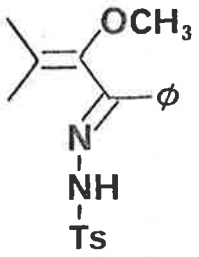



(180)

It is conceivable that N-H hydrogen bonding, if present, could be studied by infrared spectroscopy, intramolecular hydrogen bonding being solvent independent.[188a] Unfortunately, infrared results on N-H hydrogen bonding are not always conclusive and other phenomena can be the controlling factors in frequency shifts.[188b]

The effects operating in a compound such as (43), which are the delocalization of orbitals, hydrogen bonding and steric interactions preclude a definitive answer on the configuration of the thermodynamic product, although the 0.5 p.p.m. difference between the two methyls in

the thermodynamic product suggests that the cisoid conformation is preferred. Steric interactions in this conformation suggest the E-configuration (172a) about the carbon-nitrogen double bond. The 0.3 p.p.m. difference between the two methyls in the kinetic product may indicate heavy population of the transoid conformation.




(172a)

The synthesis has been successfully adapted to the preparation of the cyclopropenol alkyl ether (181)(Figure 35). The trimethylcyclopropenol methyl ether (181) was chosen in particular because it is the methyl enol ether of 2,3,3-trimethylcyclopropanone, a known compound.[189] The acid hydrolysis of compound (181), to be discussed later, was expected to proceed through the intermediate hemi-acetal of this cyclopropanone to give products which are known compounds thus simplifying their identification.

Increased yields of a ketone are generally obtained from an alkyllithium and a carboxylic acid by first generating the lithium carboxylate.[190] The reaction between methyllithium and the lithium carboxylate of acid (45) gave the ketone (182) as a pale yellow liquid. Strong infrared absorptions at 1620 and 1700 $cms^{-1}$ were consistent with a conjugated ketone. The n.m.r. spectrum exhibited singlets at δ3.48, assigned to the methyl attached to oxygen; δ2.17, indicative of a methyl group attached directly to a carbonyl double bond; and two further singlets at δ1.97 and δ1.80, both consistent with methyls on a carbon-carbon double bond. For similar reasons discussed earlier, the methyl group cis to the carbonyl moiety is assigned to the

resonance at δ1.97. Both the mass spectrum of the ketone with a molecular ion at m/e 128 and the elemental analysis were consistent with the molecular formula $C_7H_{12}O_2$.

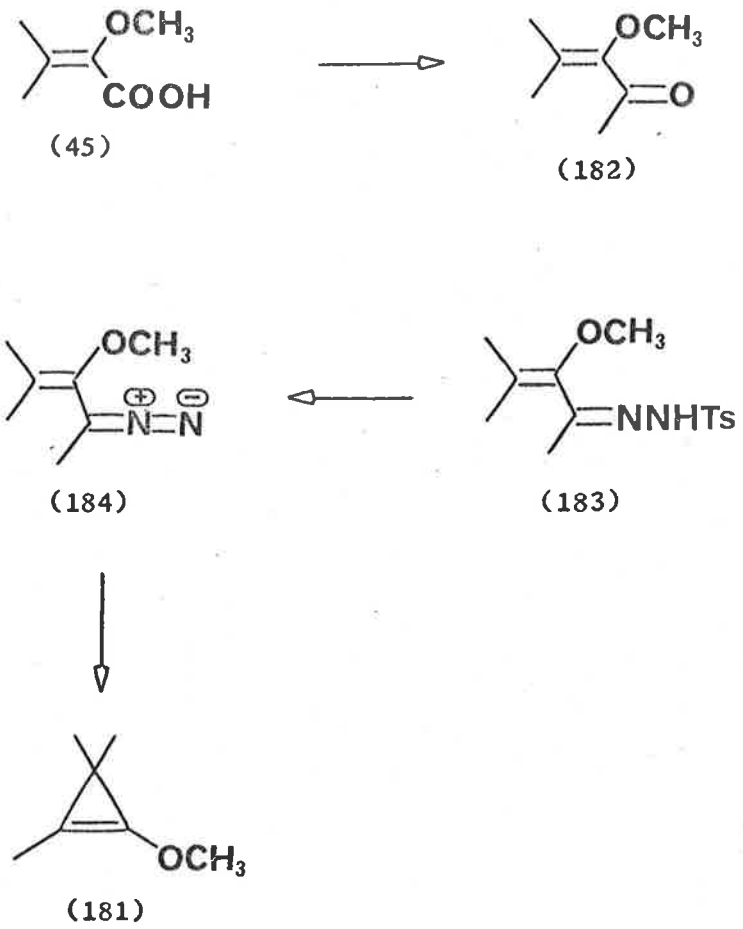



FIGURE 35

The subsequent hydrazone formation was facile only requiring 24 hr for complete reaction between the ketone (182) and tosylhydrazine. The 300 hr difference in reaction times for the formation of the hydrazones (43) and (183) probably reflects the combination of steric and electronic effects operating in these types of molecules.

The analytical data was consistent with the molecular formula $C_{14}H_{18}O_3N_2S$. The mass spectrum did not exhibit a molecular ion but some of the ions known to be produced by sulphonylhydrazones upon electron impact were evident.[191]

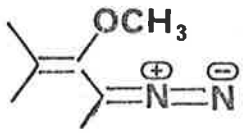
The infrared spectrum exhibited an N-H stretching absorption at 3240 $cm^{-1}$ and an unexpectedly weak broad absorption at 1670 $cm^{-1}$, assumed to be the carbon-carbon and carbon-nitrogen double bonds stretching vibrations. It should be noted that a similar weak absorption in this region was evident in the spectrum of the phenyl derivative (43).

Only one isomer of the hydrazone (183) was evident although on a single occassion the n.m.r. spectrum did reveal a mixture of E- and Z- isomers. Equilibration studies were not undertaken hence no conclusions can be drawn as to the identity of the thermodynamically more stable isomer. The n.m.r. spectrum was consistent with the proposed structure, but for similar reasons to those discussed earlier for the phenyl derivative (43), no configuration assignments were made. The chemical shift data and their probable origin are presented in Table 3.

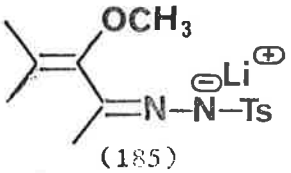
| CHEMICAL SHIFT (p.p.m.) | RELATIVE INTENSITY | MULTIPLICITY | ASSIGNMENT |
|---|---|---|---|
| 7.95-7.28 | 4 | complex | aromatic protons |
| 3.32 | 3 | singlet | $CH_3$- O |
| 2.45 | 3 | singlet | $CH_3$- Ph |
| 1.87 | 3 | singlet | $CH_3$- C= N |
| 1.70 | 3 | singlet | $CH_3$- C= C |
| 1.42 | 3 | singlet | $CH_3$- C= C |

TABLE 3

The diazoalkene (184) was prepared in moderate yield by pyrolysis of the lithium salt (185). A suitable apparatus was arranged to allow the salt to be added a small quantity at a time to a preheated flask and allowing the diazoalkene to collect in a trap before continuing. If this precaution was not carried out and a large sample of the salt was heated *in toto*, extensive decomposition occured to give unidentified products, but very little of the required diazoalkene.



(184)



(185)

The strong infrared absorption at 2050 $cm^{-1}$ was characteristic of the diazo moiety. The n.m.r. spectrum consisted of four lines of equal area whose chemical shift and origin are listed in Table 4.

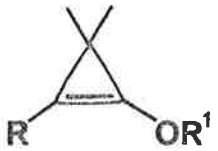
| CHEMICAL SHIFT (p.p.m.) | ASSIGNMENT |
|---|---|
| 3.47 | $CH_3$- O |
| 1.88 | $CH_3$- $CN_2$ |
| 1.70 | $CH_3$- C= C |
| 1.57 | $CH_3$- C= C |

TABLE 4

A solution of the diazoalkene in carbon tetrachloride at $0^o$ when irradiated gave the cyclopropenol methyl ether (181) contaminated with unknown products. These additional compounds are probably a consequence of the instability of the cyclopropenol ether. A 3% solution in carbon tetrachloride at $0^o$ totally decomposed after a few hours whereas the phenyl derivative (6) is stable for at least one year under these conditions.

The progress of the irradiation was followed by n.m.r. spectroscopy. The irradiation was terminated when no resonances attributable

to the diazoalkene (184) were visible. A better yield might be obtained if the irradiation was carried out at a lower temperature. However, facilities for recording low temperature n.m.r. spectra were not readily available.




(6) R = Ø, $R^1$ = $CH_3$

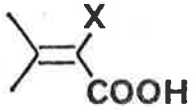
(7) R = Ø, $R^1$ = $CH_2Ø$

(181) R = $R^1$ = $CH_3$

Unsuccessful attempts were made to purify the ether (181). Holding purified the cyclopropenol benzyl ether (7) by passing it down a column of Florosil.[192] The methyl ether (181) decomposed extensively when passed down such a column at $0^{o}$. Similarly, passage down a column of neutral alumina resulted in decomposition and no trace of the ether (181) could be detected.

Although the ether (181) was never obtained pure, it was possible to characterize it from spectral data. The infrared absorption at 1870 $cm^{-1}$ was typical of the ring skeleton vibration of a fully substituted cyclopropene[+] and higher than the phenyl analogue (6) due to the decrease in conjugation. Assignation of the resonances in the n.m.r. spectrum was possible from comparison with the chemical shift data for the cyclopropenol ether (6). The infrared and n.m.r. spectra of the ethers (6) and (181) are reproduced in Figures 36 - 39.

The synthesis of the cyclopropenol benzyl ether (7) has yet to be completed. The initial conversion of the bromoacid (46)[94] to the benzyloxyacid (47) required relatively vigorous conditions. Table 5 lists the reagents and conditions which were unsuccessful. In every case, unchanged starting material was the only compound isolated.




(46) X = Br

(47) X = $OCH_2Ø$

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[+]These are reported to be in the range 1810 to 1880 $cm^{-1}$ for a fully substituted cyclopropene.[193]

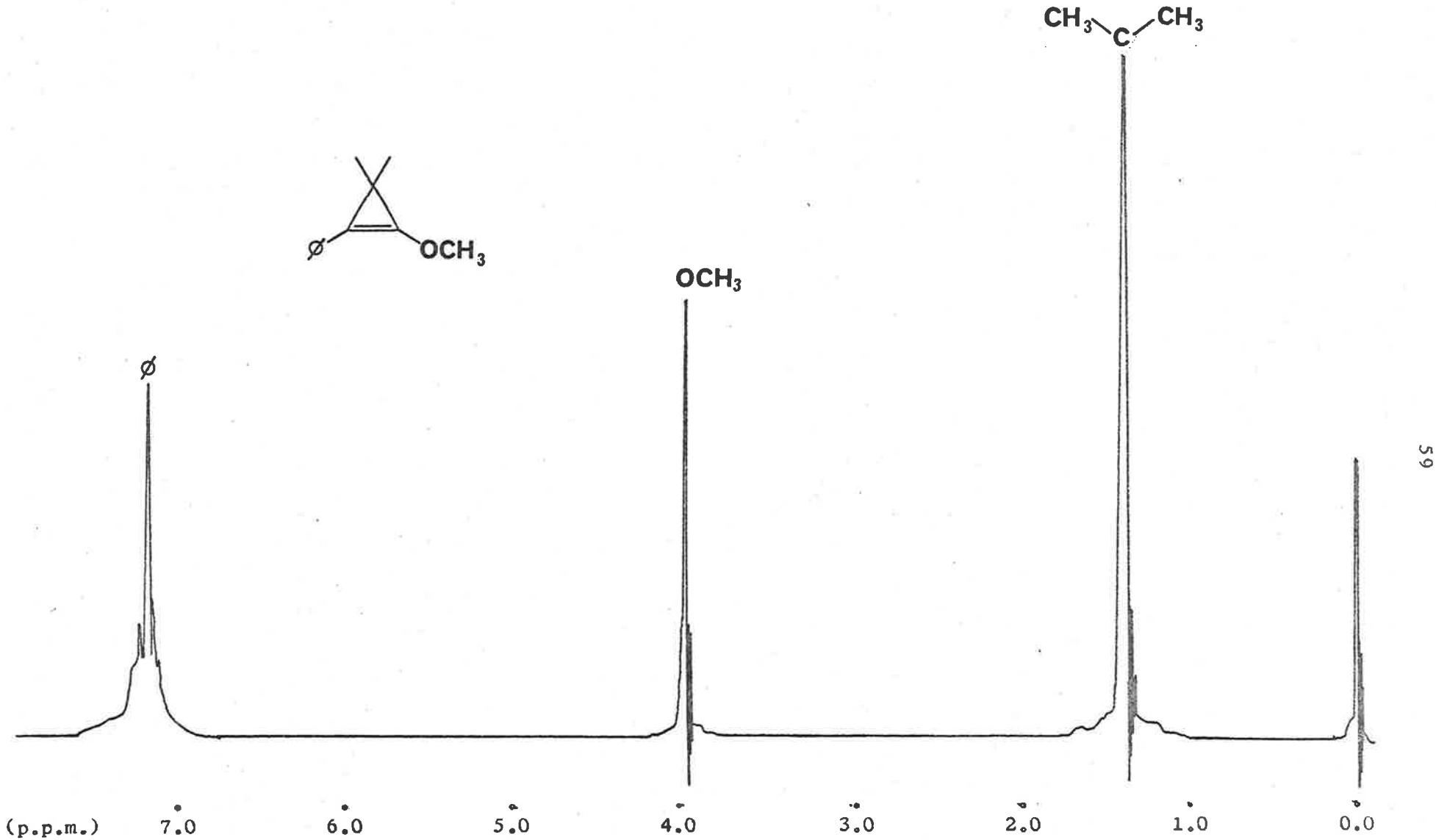



FIGURE 36

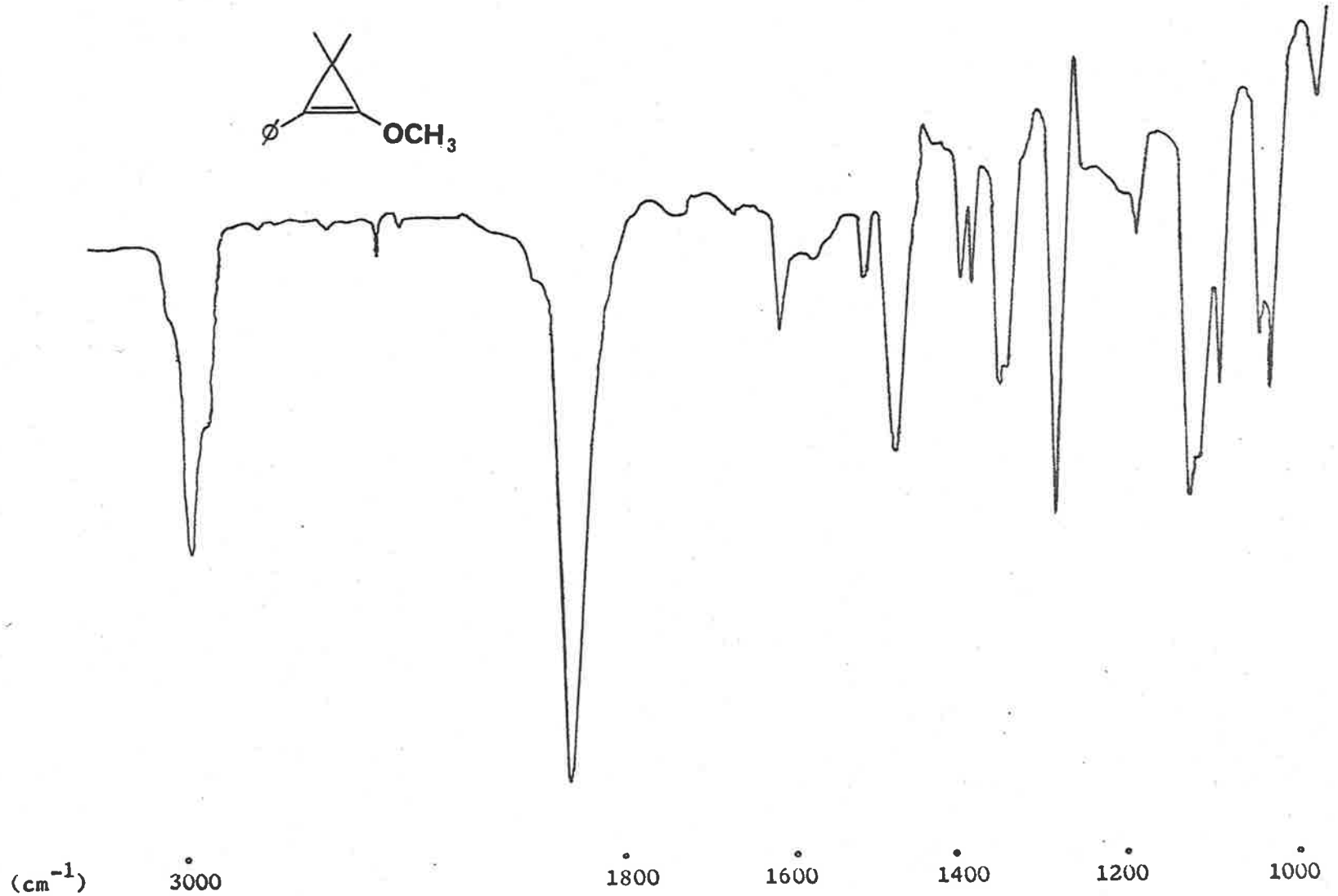



FIGURE 37

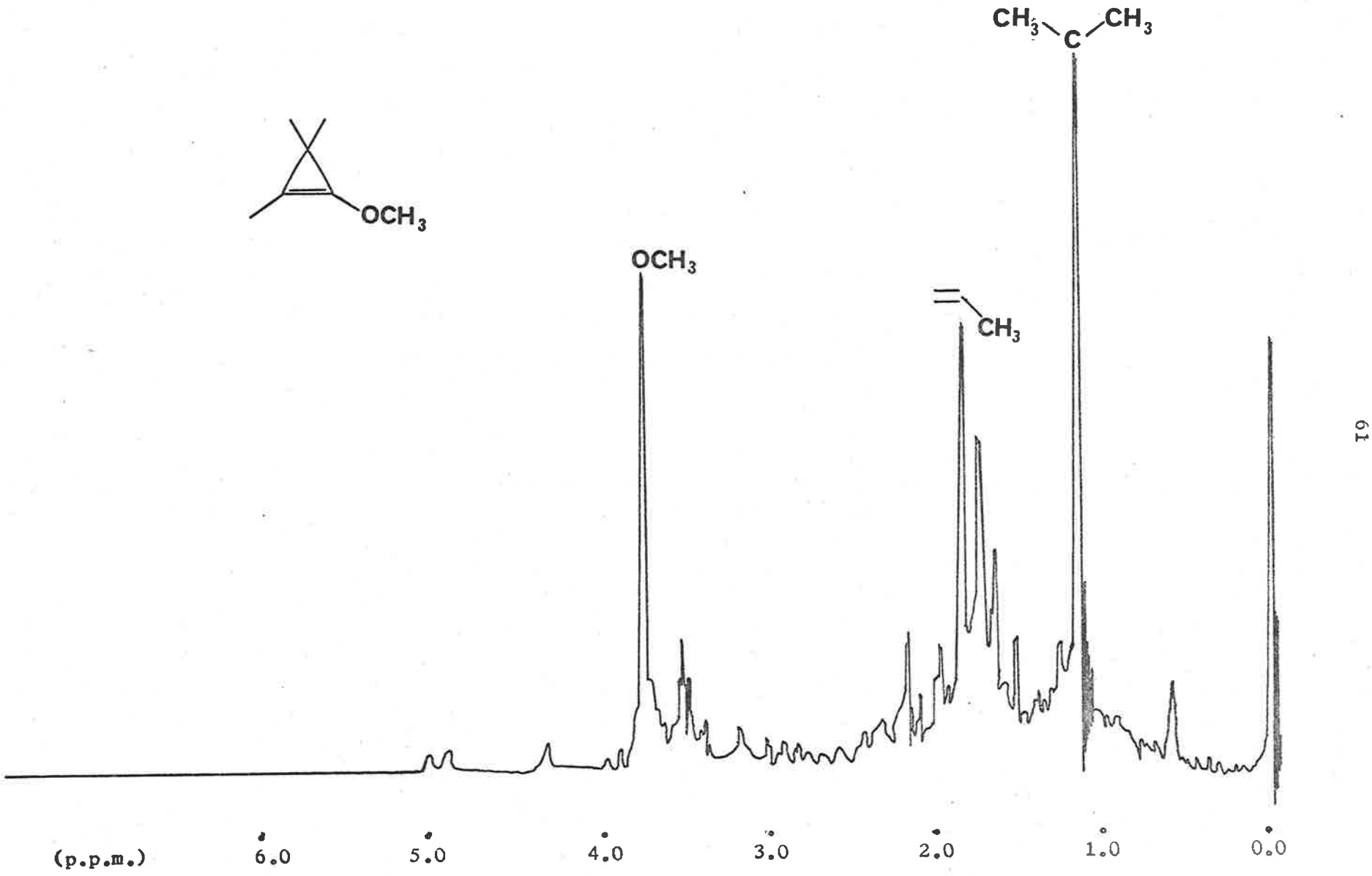



FIGURE 38

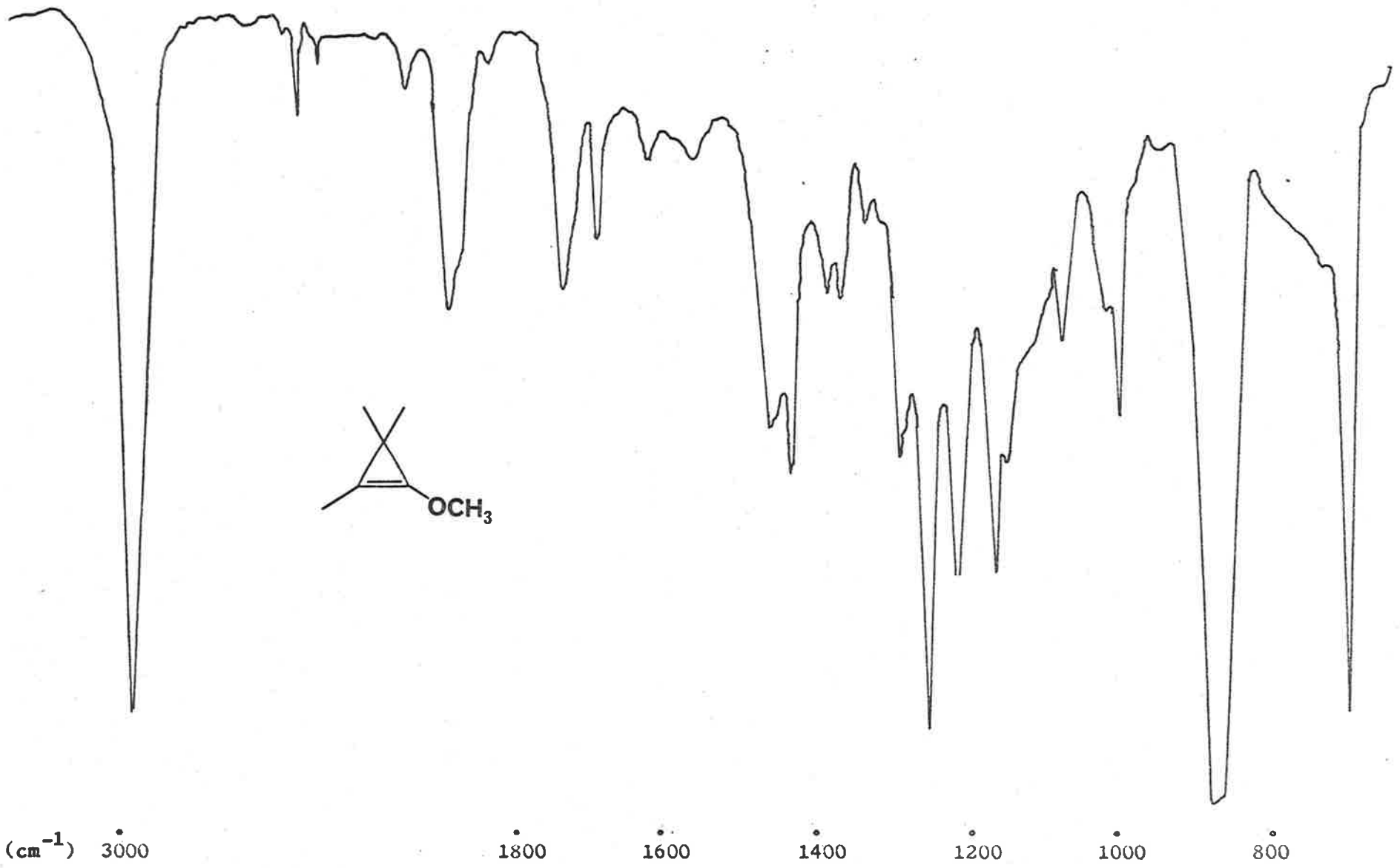



FIGURE 39

| REAGENT | SOLVENT | TEMP. | TIME (hr) |
|---|---|---|---|
| $NaOCH_2\emptyset$ | dimethyl sulphoxide | 70° | 96 |
| $NaOCH_2\emptyset$ | benzene | 80° | 24 |
| $NaOCH_2\emptyset$ | benzene | 80° | 96 |
| $NaOCH_2\emptyset$ | benzene | 80° | 168 |

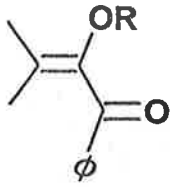
TABLE 5

A successful synthesis of this acid was achieved when the bromoacid (46) was added to three equivalents of sodium dissolved in excess benzylalcohol and then heated at 100° for 72 hr. Upon isolation the benzyloxy acid (47) was obtained as a white solid in 84% yield.

In support of structure (47), the analytical data was consistent with the molecular formula $C_{12}H_{14}O_3$. The mass spectrum exhibited the expected molecular ion at m/e 206. Infrared absorptions at 1625, 1695 $cm^{-1}$ and a broad absorption in the range 3360 - 2380 $cm^{-1}$ were consistent with an α,β-unsaturated acid. The n.m.r. spectrum revealed the aromatic protons as a broad singlet at δ7.67-7.33. A two-proton singlet at δ4.82 was assigned to the methylene protons deshielded by both an aryl ring and an oxygen atom. The methyl groups appeared as two singlets at δ1.88 and δ2.17. The methyl moiety cis to the carboxyl presumably resonates further downfield than the trans methyl as discussed earlier for similar compounds.

The acid has been converted to its phenylketone (186) by stirring a mixture of its lithium carboxylate and phenyllithium in ether, at ambient temperature, under a nitrogen atmosphere, for 96 hr. The infrared spectrum of the crude product was consistent with the unsaturated ketone. There were no bands attributable to the carboxyl function and a broad, strong absorption at 1670 $cm^{-1}$, similar in

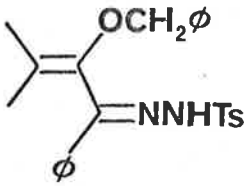
appearance to that in the methoxyketone (73)[30] was assigned to the α,β-unsaturated moiety. Bands at 1580 and 1600 $cm^{-1}$ were indicative of an aryl ring further conjugated with a carbonyl group.



(73) R = $CH_3$

(186) R = $CH_2\phi$

The crude ketone was dissolved in methanol at 40° and an equimolar quantity of tosylhydrazine added. The formation of the hydrazone (187) was followed by t.l.c. analysis and appeared to be only partially complete after 5 weeks. The spectral data of the small quantity of product obtained by preparative chromatography was consistent with the tosylhydrazone (187) contaminated with another compound, possibly an isomer of the hydrazone (187).



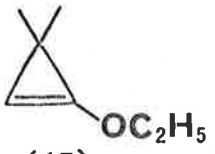
(187)

The n.m.r. spectrum exhibited resonances at δ1.73 and δ1.47, both consistent with methyls on a double bond. The methyl attached to the aromatic ring appeared as a singlet at δ2.40. A sharp singlet at δ4.47 was assumed to be the methylene protons alpha to both an aryl ring and an oxygen atom. The aromatic protons resonated as a complex multiplet in the range δ8.07-6.97. The infrared spectrum showed the loss of the strong carbonyl absorption of the ketone to be replaced by a weak broad absorption at 1670 $cm^{-1}$, a phenomenon which was characteristic of the hydrazones (43) and (183). A broad absorption at 3220 $cm^{-1}$ was consistent with a N- H stretching vibration.

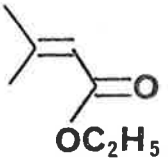
The inordinate length of time in preparing the ketone (186) and its hydrazone (187) prevented their rigorous characterization and the

completion of the synthesis of the cyclopropenol benzyl ether (7).

The synthesis of the lesser substituted cyclopropenol ether (67) has been thwarted by the apparent failure of ethyldimethylacrylate (65) to undergo a reaction with triethyloxonium tetrafluoroborate.




(67)

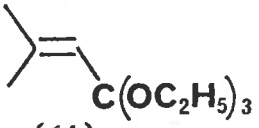



(65)

The unsaturated ester (65) was inert to conditions which successfully enabled the preparation of triethylorthoformate from ethylformate. An equimolar mixture of ethylformate and triethyloxonium tetrafluoroborate at ambient temperature had homogenized after 24 hr. Sodium ethoxide was added to the crude product and stirred for a further 12 hr. Upon isolation, triethylorthoformate was obtained in good yield.

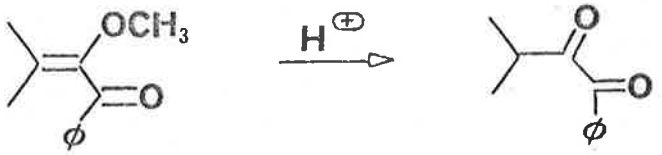
An equimolar mixture of the ester (65) and oxonium salt had not homogenized after several days. Removal of the salt by filtration resulted in a quantitative recovery of the ester (65). A similar recovery was evident when the reaction was repeated at 35°.

The preparation of the unsaturated orthoester (66) via alkylation of ethyldimethylacrylate was abandoned.



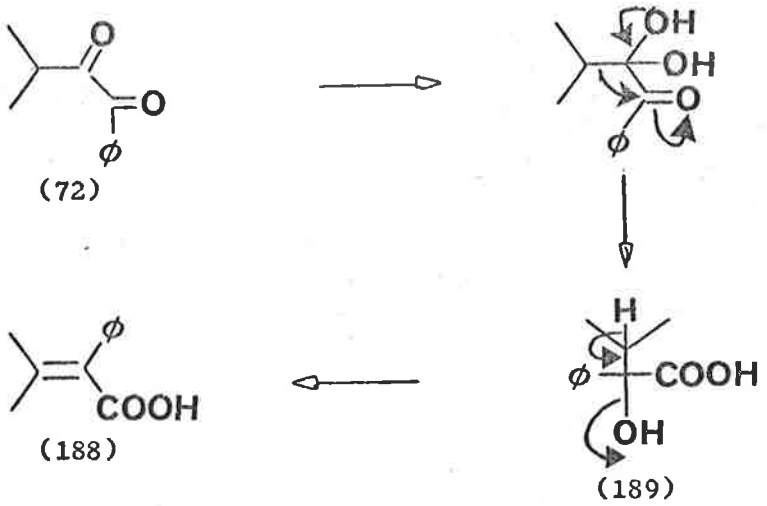

(66)

In order to rapidly obtain a sample of the diketone (72), the enol ether ketone (73) was subjected to acid hydrolysis. The first attempt was successful as evident from the spectral data of the product which were consistent with those reported for the authentic diketone.[194] However, subsequent attempts were irreproducible with none of the diketone detected. The spectral data of the crude reaction mixture were consistent with 3-methyl-2-phenylbut-2-enoic acid (188).



(73) (72)

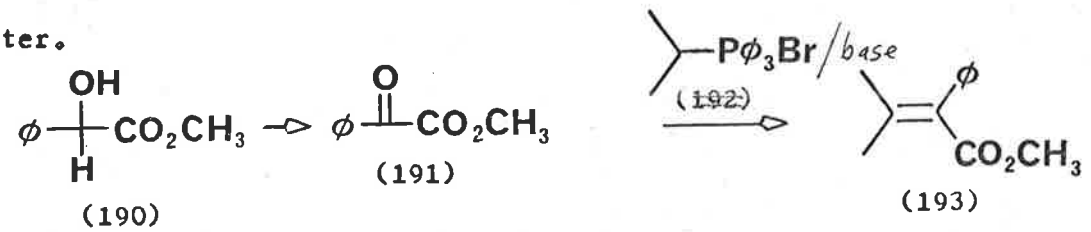
One can envisage an acid catalyzed benzilic acid type rearrangement of the diketone (72) to give the hydroxy acid (189)(Figure 40). Dehydration *in situ* would give the unsaturated acid (188). The structure of acid (188) was confirmed as follows.



(72) (188) (189)

FIGURE 40

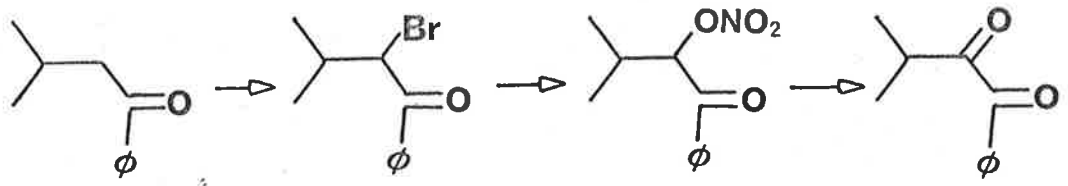
Methylmandelate (190)[195] was oxidized to methylbenzoylformate (191) which underwent a Wittig reaction with *iso*propyltriphenylphosphorane (~~192~~)[196] to give the unsaturated ester (193), according to a literature procedure (Figure 41).[197] Methylation with diazomethane of the crude reaction mixture from the acid catalyzed rearrangement of the enol ether ketone (73) gave a compound identical in every respect to this ester.



(190) (191) (193)

FIGURE 41

Repeated attempts to prepare the diketone (72) by the literature procedure (Figure 42)[115] proved futile. Isovalerophenone (194)[198] was readily brominated[199] to give the α-bromoderivative (195) in moderate yield. Stirring with silver nitrate in acetonitrile as reported[115,200] gave a compound whose b.p. and spectral data were consistent with the nitrite ketone (196). However, the subsequent reaction with piperidine to obtain the diketone (72) after 20 min[115] failed. A prolonged reaction time of 70 hr was equally unsuccessful. Alternative schemes were devised for the synthesis of the diketone (72).




(194) (195) (196) (72)

FIGURE 42

α,β-Epoxyketones on addition of base are known to give enolate anions which on protonation yield α-diketones.[201] An example is depicted in Figure 43. One significant obstacle is the tendency for the diketone to enter a benzilic acid rearrangement under the conditions employed.[201]

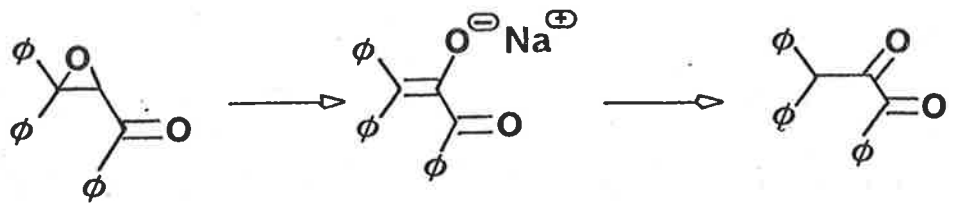
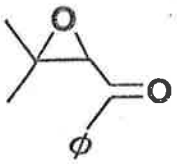


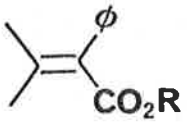

FIGURE 43

The epoxyketone (197) was available[192] and hence might provide an alternative entry to the diketone (72).



(197)

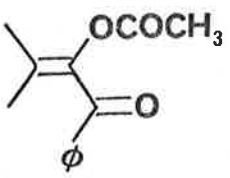
Sodium ethoxide in ethanol was added to the epoxide dissolved in a small amount of ethanol and the colourless solution immediately turned red. After heating under reflux for 1 min, the reaction was quenched with dilute acid. Upon isolation, the product was found to be the dehydrated benzilic acid rearranged compound (188), characterized as its ester (193).



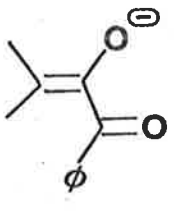
(188) R = H

(193) R = $CH_3$

The reaction was repeated but quenched with acetic anhydride in an attempt to trap the intermediate ion (199) as the enol acetate (198), a compound required for the synthesis of an enolate anion of a cyclopropanone. Surprisingly, unchanged starting epoxide was the only product isolated. It seemed unlikely that the enolate anion (199) would revert to epoxide rather than form the O-acylated product with acetic anhydride. A possible explanation for the above results is that in neither case has the enolate anion (199) been generated and that on the addition of dilute acid it is the epoxide which undergoes a benzilic acid type rearrangement. The red colour of the solution could arise from a very low concentration of the required enolate anion.



(198)



(199)

Further evidence was gained for this hypothesis when the epoxide (197) was found to rearrange in the presence of dilute acid. Methylation of the reaction mixture gave an ester, identical in every respect to methyl-3-methyl-2-phenylbut-2-enoate (193).

Corey and Seebach reported that nucleophilic acylation with benzonitrile of the 2-lithio-1,3-dithiane (200) yielded the diketone-monothioketal (201).[202a] Hydrolysis with N-bromosuccinimide in aqueous acetone gave the α-diketone (202)(Figure 44).[202b] The 2-isopropyl-1,3-dithiane (203) is a known compound[203] and an analogous synthetic scheme was expected to allow the preparation of the diketone (72)(Figure 45).

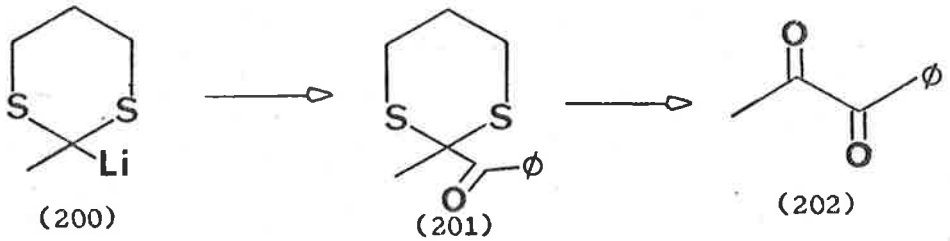



FIGURE 44

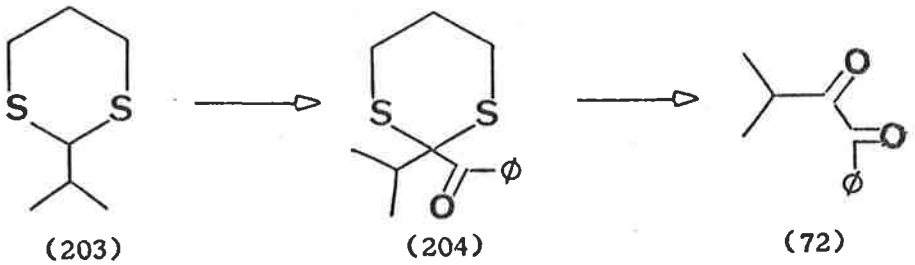



FIGURE 45

1,3-Propanedithiane was prepared according to a literature procedure[204] and by adapting the experimental conditions for the preparation of the ketothioketal (201),[202a,205] the isopropylanalogue (204) was synthesized. The analytical data were consistent with the molecular formula $C_{14}H_{18}S_2O$. The mass spectrum did not reveal a parent ion but only those ions as a consequence of alpha cleavage, characteristic of ketones.[206] An infrared absorption at 1680 $cm^{-1}$ was consistent with an

aryl ketone.

In the n.m.r. spectra of cyclic 1,3-dithianes, axial hydrogens alpha to the sulphur atom resonate at lower field than the equatorial protons, in complete contrast to the generally accepted rule for cyclohexanes.[207] In the n.m.r. spectra of cyclic 1,3-dithianes, in conformations which do not depart appreciably from the chair form, $J_{ax,ax}$ is in the range of 8-13 Hz and $J_{ax,eq}$ is in the range 2-6 Hz. In comparable systems $J_{eq,eq}$ is invariably smaller than $J_{ax,eq}$, the difference being of the order of 1 Hz.[208a] The geminal coupling constants are similar to those for cyclohexane and are in the range -11 to -14 Hz.[208b] These data allow the assignment of each resonance in the n.m.r. spectrum of the 1,3-dithiane (204). The axial protons alpha to the sulphur atoms resonate as an overlapping doublet of doublet of doublets at δ3.53-2.97 (J=4,10,15 Hz). The alpha equatorial protons also resonate as an overlapping doublet of doublet of doublets at δ2.90-2.47 (J= 3,4,15 Hz), superimposed on a complex multiplet assigned to the isopropyl proton. The remaining methylene protons resonate as a complex multiplet at δ2.23-1.83. A six proton doublet at δ1.12 (J=7 Hz) can be assigned to the two equivalent methyl groups.

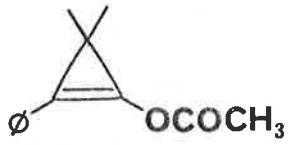
Hydrolysis of the thioketal (204) to the diketone (72) proved extraordinarily difficult. The use of similar conditions to those reported for the methyl analogue (201)[202b] employing N-bromosuccinimide resulted in a pale yellow lachrymatory liquid which rapidly turned brown on standing.

N-Chlorosuccinimide[209] is reported to be effective in cleaving dithianes to diketones.[202b] However, the ketothioketal (204) failed to give any of the desired product. No starting material was evident, but the identity of the product(s) was not determined.

A procedure for thioketal hydrolysis using methyl iodide[210] failed completely, only starting material being recovered after 95 hr.

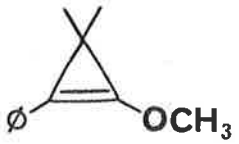
Fujita has reported that thallium trinitrate trihydrate is effective in cleaving dithioacetals to the parent carbonyl compound.[211] The reaction between the thioketal (204) and thallium trinitrate trihydrate gave the diketone (72).

The unexpected delay in obtaining the α-diketone has prevented any further work on the preparation of the cyclopropenol acetate (74).



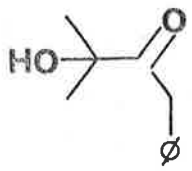

(74)

As expected, the addition of dichlorocarbene to the cyclopropenol methyl ether (6) has met with no success. The carbene was prepared *in situ*[212] by adding potassium *t*-butoxide to the ether dissolved in chloroform at -25°. A vigorous reaction ensued. The mixture was extracted with ether. Careful removal of solvent at low pressure resulted in an intractable gum.




(6)

The attempted addition of dimethylcarbene to the cyclopropenol ether (6) resulted in acyclic products. Upon isolation, g.c. analysis revealed the presence of one major compound. This was collected by preparative gas chromatography. The spectral data were consistent with the hydroxyketone (205), which is one of the two products expected from an acid catalyzed hydrolysis of the cyclopropenol methyl ether (6) which is discussed later. The structure was confirmed subsequently by an independent synthesis.

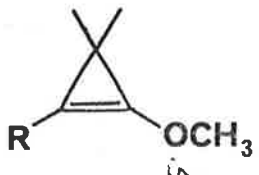


(205)

It is conceivable that zinc ions present in the chromium (II) solution[213] caused a Lewis acid catalyzed rearrangement of the ether (6) to the hydroxyketone (205).

The observed colour change of the solution from blue to green due to the oxidation of chromium (II) to chromium (III) ions indicated that a reduction of some other compound had occured. 2,2-Dibromopropane is known to react with chromium (II) to give a good yield of 2-propanol.[121b] Due to the volatility of this alcohol, it was initially not observed in the g.l.c. analysis of the reaction mixture. However, careful extraction, distillation and analytical procedures proved its presence.

Acid catalyzed hydrolysis of both cyclopropenol ethers (6) and (181) to acyclic products provided additional evidence for their structures. One presumes that the intermediate is a hemi-acetal of a cyclopropanone formed from the acid catalyzed addition of water across the double bond. Subsequent rearrangement of this hemiacetal gives rise to products.



(6) R = Ø

(181) R = $CH_3$

The ring opening of carbonium ion reactions of cyclopropyl derivatives has received widespread attention. The transformation of a cyclopropyl cation to an allyl cation is treated as an electrocyclic ring opening and predicted to be stereospecific and disrotatory.[214a,b] At least partial ring opening is simultaneous with departure of the

leaving group in almost all cases leading to a transition state in which the positive charge is delocalized over all three ring carbon atoms (Figure 46);[214c,d] eventually ring-opened allyl products are produced.[214c,d] DePuy has suggested that the extended Huckel calculations of Woodward and Hoffman predict that the direction of concerted ring opening depends on the stereochemistry of the leaving group.[214e,f] The prediction is that groups trans to the leaving moiety rotate outward and those groups cis rotate inward, all rotations occuring in a disrotatory manner.

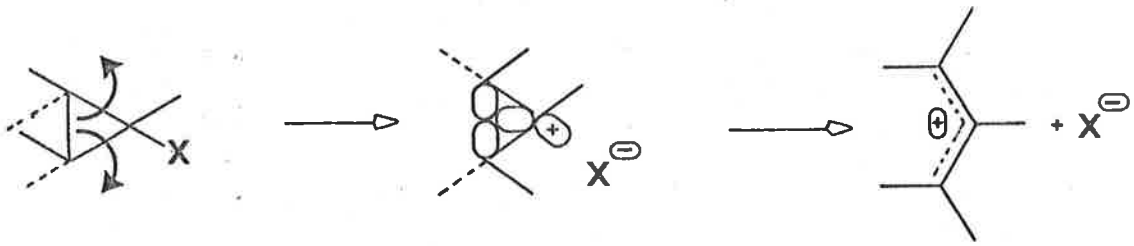
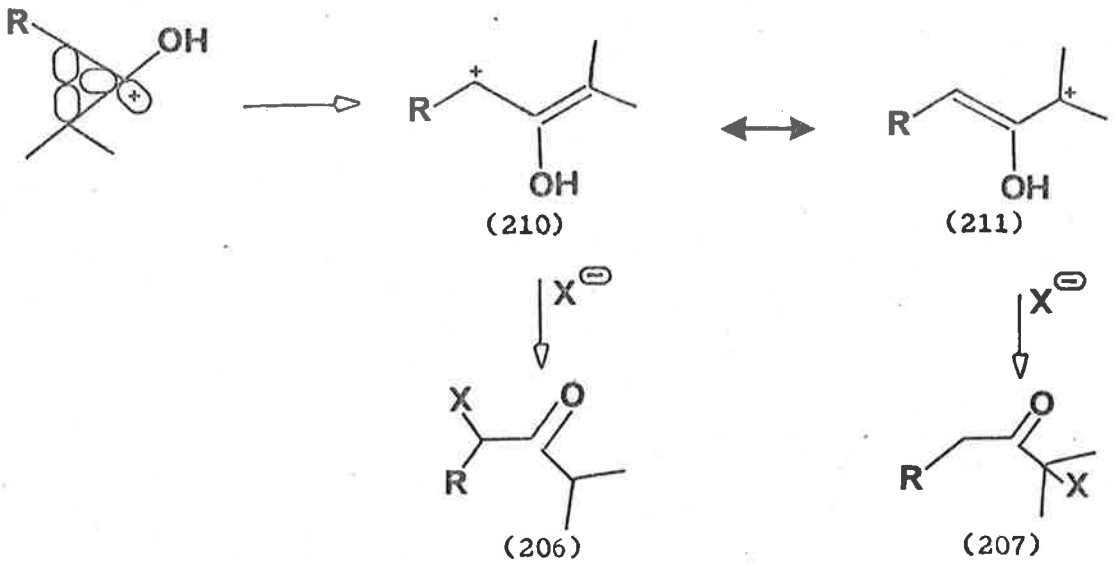


FIGURE 46

This ring cleavage, which is depicted in Figures 47a,b for the hydrolysis of 2,2-dimethylcyclopropanone,[214g] is particularly favoured when the ring carbons are bound to substituents capable of stabilizing the intermediate allyl cation.[214g] The solvolysis of 2,2-dimethylcyclopropanone in dry hydrochloric or in acetic acid, gave the ketones (206a) and (207a) or (206b) and (207b) respectively.[215]

The acid catalyzed hydrolysis of the cyclopropenol ether (6) was expected to give the isomeric hydroxyketones (205) and (208). Compound (208) was known and spectral data were available.[216] The isomeric ketone (205) was unknown.

The ether (6) was dissolved in carbon tetrachloride and a solution of p-toluenesulphonic acid (trace amount) in water was added. The heterogeneous mixture was shaken at ambient temperature and the progress of the reaction was followed by n.m.r. spectroscopy. The




(a) R = H, X = Cl

(b) R = H, X= $OCOCH_3$

(c) R = Ø, X = OH

(d) R = $CH_3$, X = OH

FIGURE 47

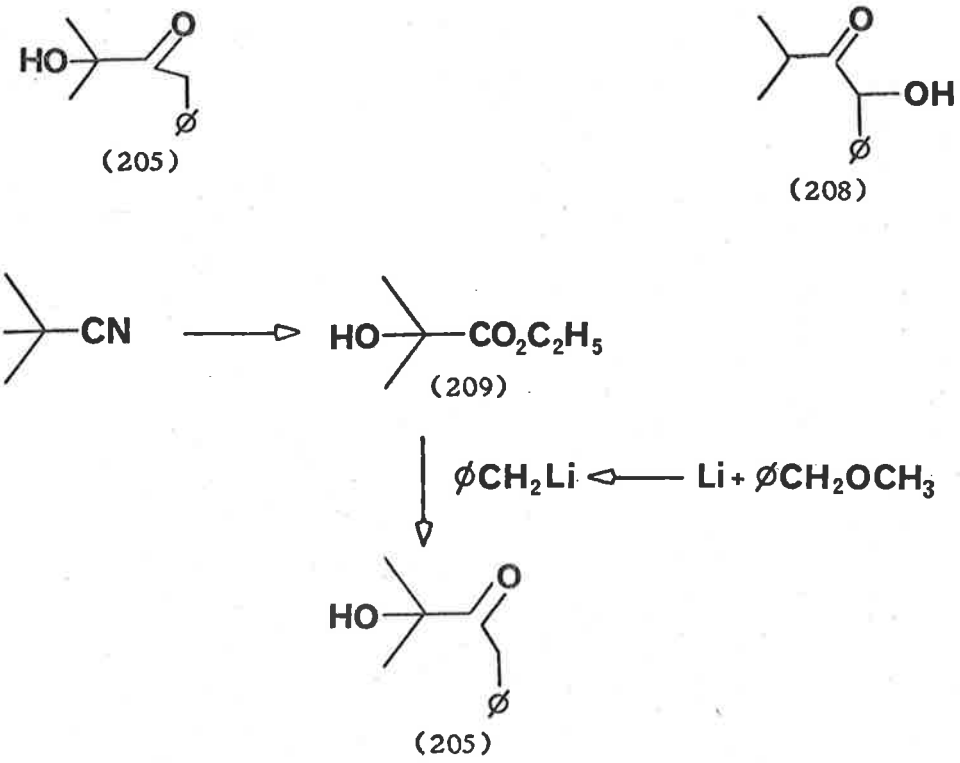



FIGURE 48

reaction was terminated when the resonances attributable to the cyclopropenol ether were no longer visible in the n.m.r. spectrum.

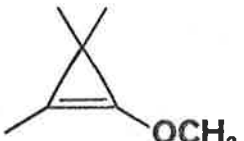
The n.m.r. spectrum of the crude product indicated that the ketone (208) was present as a minor component. Other resonances in the n.m.r. spectrum were consistent with those expected for the isomeric ketone (205). This was confirmed by an independent synthesis (Figure 48).

The hydroxyester (209) was prepared from acetone cyanohydrin according to a published procedure.[217] Two equivalents of benzyllithium[218] (prepared from benzyl methyl ether[219] and lithium) gave the hydroxyketone (205). The analytical data were consistent with the molecular formula $C_{11}H_{14}O_2$. The mass spectrum did not reveal the parent ion but only those ions formed as a consequence of alpha cleavage, which are characteristic of ketones.[206] Infrared absorptions at 1710 and 3160-3680 $cm^{-1}$ were consistent with a hydroxyketone. The n.m.r. spectrum showed absorptions for the aromatic protons as a multiplet at δ7.30-7.00. A singlet absorption at δ3.77 integrating for two protons was assigned to the methylene protons adjacent to both the aryl ring and the carbonyl substituents. The gem-dimethyl moiety resonated as a sharp singlet at δ1.33.

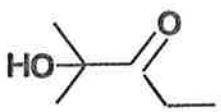
The ketone (205) was the predominant isomer from the hydrolysis of the cyclopropenol ether (6). This may reflect the charge distribution of the intermediate allyl cation represented by the canonical forms (210c) and (211c). Charge distributions in carbonium ions calculated by Molecular Orbital theory indicate that there are differences between the carbon atoms of a conjugated carbonium ion.[220a] The charge distribution in the allyl cation may be near that represented in the canonical structure (211c).

By similar reasoning, it was expected that the acid catalyzed hydrolysis of the cyclopropenol ether (181) would give the hydroxy-

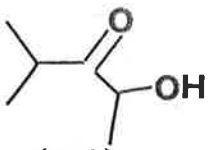
ketones (212) and (213). It was found that the hydrolysis gave only one compound. No other compound could be detected by g.l.c. analysis. The n.m.r. data of this product were not consistent with the isomer (213), a known compound and for which n.m.r. data had been reported.[221] The data were consistent with the isomeric hydroxyketone (212). Although compound (212) had been reported,[222a] a brief and more convenient synthesis (Figure 49) of the diol (217), a precursor of the ketone (212), had been published.[222b] Since all intermediate products were known, it was decided to follow this scheme and to develop the reaction conditions.




(181)

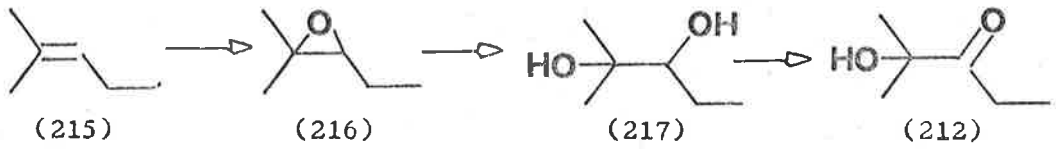



(212)



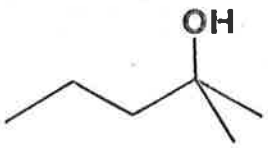

(213)

The reaction of two equivalents of methylmagnesiumiodide with ethylbutyrate gave the tertiary alcohol (214) in good yield.[95b] This alcohol was dehydrated to 2-methylpent-2-ene (215)[223] by use of an acid catalyzed dehydration procedure.[95c] The epoxide (216)[222b] was prepared from the reaction between this olefin and m-chloroperbenzoic acid.[224] The hydrolysis of the epoxide with very dilute acid[222] gave the glycol (217) which upon oxidation with pyridiniumchlorochromate[225] gave the hydroxyketone (212). The ketone (212) was identified by the following spectral data. An infrared absorption at 1705 $cm^{-1}$ was consistent with an aliphatic saturated ketone. A broad band in the range 3150-3700 $cm^{-1}$ indicated the presence of a hydroxyl moiety. The n.m.r. spectrum showed an absorption for the gem-dimethyl groups as a sharp singlet at δ1.37; the methylene protons resonated as a quartet (J=7 Hz) at δ2.56 and a triplet (J=7 Hz) at δ1.08 was assigned to the remaining methyl protons. The hydroxyl proton was evident as a broad absorption at δ3.78.




(215) (216) (217) (212)

FIGURE 49




(214)

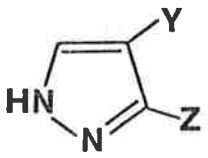
The exclusive formation of the hydroxyketone (212) may reflect a large contribution of the canonical form (211d) to the intermediate allyl cation. A general rule is that progressive alkyl substitution at a carbonium centre stabilizes the ion.[220b] In the canonical form (211d), the charge is stabilized by two methyl groups whereas in the alternative canonical structure (210d), it is stabilized by only one methyl moiety. Thus the hybrid structure would probably be weighted towards the canonical form (211d).

The uncatalyzed addition of diphenyldiazomethane to the cyclopropenol ether (6) failed to occur. Unchanged starting material and benzophenone azine, a decomposition product of diphenyldiazomethane,[226] were the only materials isolated. The less bulky diazomethane also failed to undergo any addition reaction. The methyl substituted ether (181), which presumably offers less steric and electronic influence to cycloaddition, also failed to add either of the above diazoalkanes. The n.m.r. spectral data indicated that decomposition of the ether, which occurs readily, was the only noticeable effect.

The failure of both ethers to undergo 1,3-dipolarcycloaddition prompted a survey of the literature for a possible explanation. Ordinary non-conjugated alkenes are sluggish in their reaction with diazoalkanes when compared with double bonds which are richer in energy

due to strain.[126c] From this observation, one would predict both cyclopropenol ethers to be reactive toward 1,3-dipolarophiles. Since no reaction occurs after 7 days, clearly then, other factors must be considered.

Very little information is available on 1,3-dipolarcycloadditions of compounds with oxygen directly attached to the reactive multiple bond. Holding found that α-methoxystyrene and 1-ethoxypropyne were inert to 1,3-dipolarcycloaddition with diphenyldiazomethane or 2-diazopropane.[192] Ethoxyethyne slowly adds diazomethane to yield 4-ethoxypyrazole (218a).[227] The reaction time is about 14 days at ambient temperature and the yield is 40%.[227] Similarly, 4-isopropoxypyrazole was prepared from isopropoxyethyne and diazomethane in a yield of 45% after 7 weeks.[227] No pyrazole was obtained from 1-methoxybut-1-yne and diazomethane, presumably because the reaction rate was too low.[227] Diazomethane adds to ethylthioethyne in the opposite orientation of its addition to ethoxyethyne to give 3-ethylthiopyrazole (218b).[227] The reaction proceeded more easily than with ethoxyethyne and was complete in 7 days in 60% yield.[227] It was reported in 1947 that when diazomethane and butylvinylether are mixed in the cold, no reaction occurs, but if they are heated for 2 days in a sealed tube at 90-100°, they give 4-butoxypyrazoline in 55% yield.[228]




(218) (a) Z = H, Y = $OC_2H_5$

(b) Z = $SC_2H_5$, Y = H

The orientation of 1,3-dipolarcycloadditions continues to be a major area of discussion. Huisgen favours a concerted mechanism[125,229] whilst Firestone advocates a stepwise-diradical addition.[230,231] A good test case, only recently reported,[231] was the reaction of diazomethane with ethylvinylether, where, according to Firestone, the two theories predict

opposite orientations.

Firestone is of the opinion that diazomethane prefers to react with dipolarophiles D first at carbon, giving an intermediate $DCH_2N_2^{\bullet}$ rather than $^{\bullet}CH_2N_2D$.[231] Therefore, diazomethane and ethylvinylether should give a diradical which leads to 3-ethoxy-1-pyrazoline (Figure 50).[231] The "concerted but not synchronous" mechanism predicts the product to be 4-ethoxy-1-pyrazoline, since ethoxy does not stabilize a partial negative charge.[231]

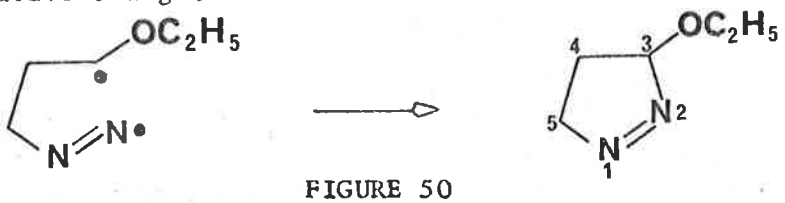
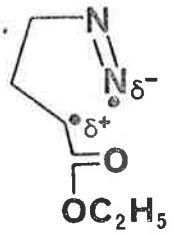


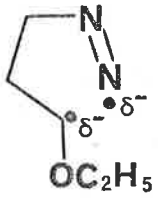

FIGURE 50

The recent investigation by Firestone found the sole product of cycloaddition between diazomethane and ethylvinylether to be 3-ethoxy-1-pyrazoline.[231] The reaction is very slow with the product being obtained in 24% yield after 38 days at ambient temperature.[231]

Whatever the mechanism of the addition, one fact is now clear, and that is the frequent observation that most 1,3-dipoles add faster to electron-poor olefins than to electron-rich ones.[232] Firestone claims this phenomenon to be a result of the partial formal charges of the diradical intermediates.[231] The reaction between ethylacrylate or ethylvinylether with diazomethane provides an example. In diradical (219a), the two radical sites have opposite partial formal charges, but in (219b) the partial charges are of the same sign.[231] Thus (219a) prefers a cycloform while (219b) prefers an extended one, in which repulsion between the like charges is reduced.[231] Firestone has deferred discussing the anomaly of ethoxyacetylene giving 4-ethoxypyrazole to a later paper.



(219a)

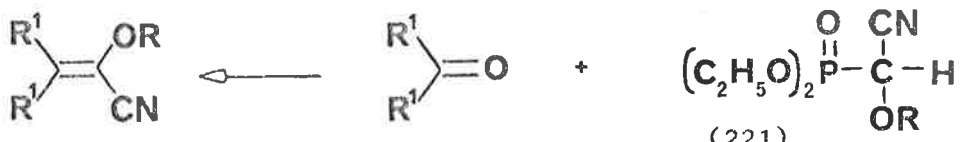


(219b)

Huisgen places his explanation in Molecular Orbital perturbation theory, although he does not deal specifically with ethylvinylether.[229] Cycloadditions are controlled by the HOMO-LUMO interplay which depends on orbital energies.[229] Huisgen finds a correlation between the cycloaddition rates and the nucleophilicity of diazomethane.[229] He modifies his previous assertion that the central carbon atom of a diazoalkane is more strongly nucleophilic than the outer nitrogen[126b] to state that diazoalkanes do in fact possess ambident nucleophilicity.[229] Molecular Orbital perturbation theory explains the nucleophilicity scales as well as the dipolarophilic activity sequences.[229] Huisgen is confident that the Molecular Orbital perturbational treatment will provide a solution in the near future for the outstanding problems in 1,3-dipolarcycloadditions.[229]

One concludes from the above reports that a prolonged contact time between the cyclopropenol ethers (6) and (181) and diazoalkanes may result in a low yield of adduct. Unfortunately, neither ether is sufficiently stable at the temperature necessary for addition. A rigorous explanation for their sluggish reaction with diazoalkanes is still not possible.

The recently reported synthesis of α-alkoxyacrylonitriles (220) from substituted diethylcyanomethylphosphonates (221)(Figure 51)[233] suggests an alternative intermediate in the synthesis of enol ethers of cyclopropanone.

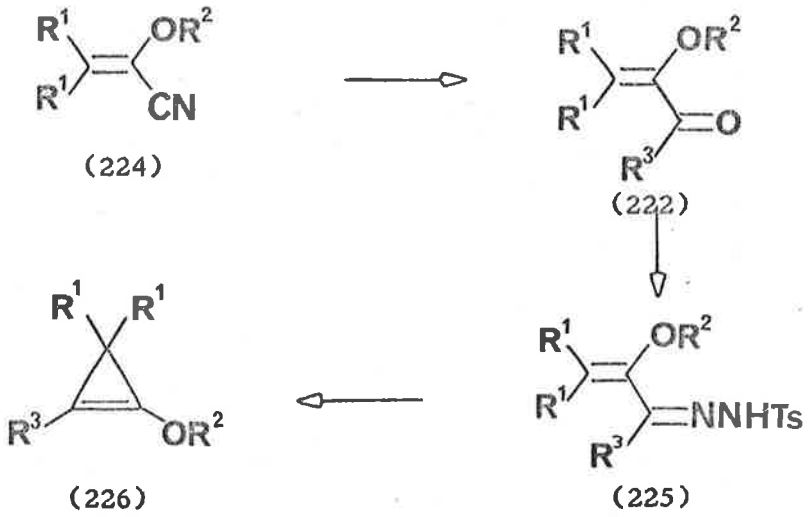


(220) (221) (223) R = t-butoxy

FIGURE 51

The reduction of nitriles with lithium triethoxyaluminohydride[234a,b] or diisobutylaluminium hydride[234c,d] followed by hydrolysis of the intermediate imine salts affords aldehydes.[234] The reaction between Grignard reagents and nitriles enables one to synthesise ketones.[235] With the additional capability of being able to alter both the alkoxy moiety of the phosphonate and the ketone substituents in the preparation of the alkoxyacrylonitrile (220), it should be possible to prepare unsaturated carbonyl compounds of type (222), in which all substituents can be varied. A similar synthetic sequence (Figure 52a) to that described earlier for compounds of type (222) would enable the preparation of enol ethers of cyclopropanones.

A reaction between the phosphonate (223)[236] and benzophenone gave the alkoxyacrylonitrile (224b)(Figure 52b) according to the published report.[233] The conversion of this nitrile to the phenylketone (222b) was achieved in low yield by the addition of phenylmagnesium-bromide. The infrared spectrum revealed the loss of the nitrile absorption and the appearance of a broad band at 1670 $cm^{-1}$. The ketone and tosylhydrazine were dissolved in methanol at 40° and the reaction was followed by t.l.c. analysis. After 14 days there was no indication that the hydrazone (225b) was forming. A possible explanation for the failure of this reaction may lie in the steric hindrance around the carbonyl carbon. The inertness of ketone (222b) toward tosylhydrazine prevented the completion of the preparation of the cyclopropenol ether (226b).




(a) $R_1 = R_2$ = aryl, alkyl

$R_3$ = aryl, alkyl, hydrogen

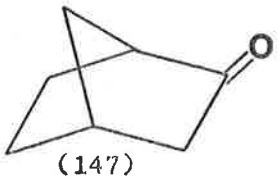
(b) $R_1 = R_3$ = phenyl

$R_2$ = t-butoxy

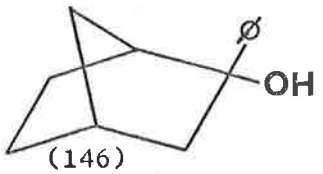
FIGURE 52

# RESULTS AND DISCUSSION - Part B

Phenylnorbornanol (146) was prepared from phenyllithium and 2-norbornanone (147) according to a literature method.[166] By an adaption of the general procedure reported for the oxidation of aryl rings with ruthenium tetroxide,[159] the phenylalcohol (146) was converted to a ketone whose melting point and spectral data were identical to those of authentic 2-norbornanone. This indicated that the strained bicyclic hydrocarbon framework was not degraded under these oxidative conditions.

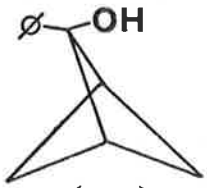



(147)




(146)

Cyclobutylphenylketone, which was needed for the preparation of the bicyclopentanol (122), was initially obtained from cyclobutane carboxylic acid,[237] itself synthesized from the decarboxylation of 1,1-dicarboxycyclobutane.[238] Subsequently, commercial cyclobutylphenylketone, supplied in sealed vials, was used without further purification.

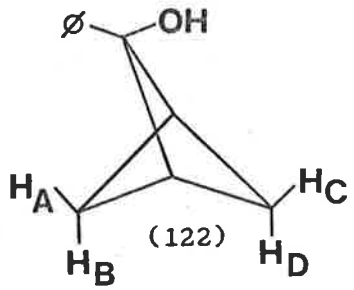



(122)

The formation of the bicyclopentanol (122) by the photolysis of cyclobutylphenylketone was carefully followed by g.l.c. analysis because the reported times for complete reaction vary considerably from 8 hours[142] to 6 days.[239] It was found that a 0.25% (w/v) solution of cyclobutylphenylketone in benzene needed to be irradiated with a 450W UV lamp for approximately 40 hr. The solvent was removed by evaporation and the crude mixture of products distilled through a short Vigreux column. The distillate was further purified by preparative g.l.c. and the alcohol was obtained as a viscous oil which slowly solidified on standing. Sublimation of this solid gave the pure alcohol in 23% yield.

If the crude mixture of products was carefully distilled through an eight inch spinning band column, the crude alcohol (122) could be obtained in 51% yield and of sufficient quality for most further reactions.

The 60 MHz n.m.r. spectrum of the alcohol was consistent with the structure (122) but differed slightly from the reported 100 MHz spectrum[142] which is listed in Table 6. While no differences in the chemical shifts of the respective protons were noted in the 60 MHz spectrum, variations in the multiplicity of protons $H_B$ and $H_C$ were found. Proton $H_B$ appeared as a distorted doublet and proton $H_C$ was more complex than a doublet of doublets. These discrepancies probably arise from the inadequacy of a first order analysis of the spectrum at the lower frequency. In the stronger, 100 MHz field, the pattern simplifies to a first order spectrum.



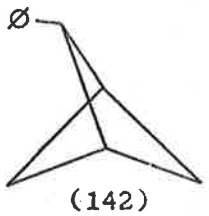

(122)

| CHEMICAL SHIFT (p.p.m.) | MULTIPLICITY (J, in Hz) | ASSIGNMENT |
|---|---|---|
| 2.92 | singlet | bridgehead protons |
| 7.27 | singlet | aromatic protons |
| 1.27 | d of d (10,3) | $H_A$ |
| 1.42 | d (3) | $H_B$ |
| 2.76 | d of d (10,3) | $H_C$ |
| 1.69 | d (3) | $H_D$ |

d = doublet

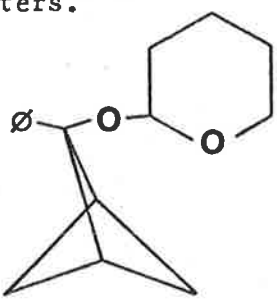
TABLE 6

The sodium-ammonia reduction of the bicyclopentanol (122) to the phenylhydrocarbon (142) was attempted by the use of a procedure reported for the Birch reduction of benzyl alcohol.[240] The product obtained in good yield was cyclobutylphenylcarbinol. The reaction medium is apparently sufficiently basic to cause isomerization of the alcohol to cyclobutylphenylketone which is then reduced in situ. The identity of cyclobutylphenylcarbinol was confirmed by an independent synthesis which involved reduction of cyclobutylphenylketone with lithiumaluminiumhydride according to a literature method.[241]



(142)

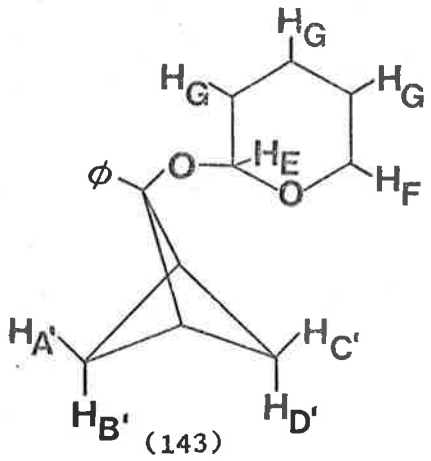
The ether (143) of alcohol (122) was prepared by an adaption of a procedure reported by Robertson for the synthesis of tetrahydropyranyl ethers.[164b] In support of structure (143), the analytical data was consistent with the molecular formula $C_{16}H_{20}O_2$. The mass spectrum did not show a molecular ion but the base peak at m/e 160 was consistent with the parent alcohol molecular ion. It is known that thermal cracking of tetrahydropyranyl ethers to the starting alcohols can occur in the inlet system of mass spectrometers.[242]



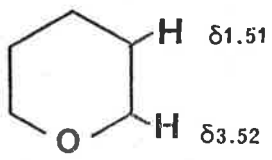
(143)

The infrared spectrum showed no hydroxyl absorption but intense absorptions in the region 1200-970 $cm^{-1}$ were consistent with the carbon-oxygen-carbon stretching vibrations of ethers.[243]

The 60 MHz n.m.r. spectrum was consistent with the proposed structure. The resonances were assigned by comparison with both the known data for the starting alcohol (122)(Table 6) and with pyran (228)[224] whose chemical shift data are depicted in Figure 53.




(143)




(228)

FIGURE 53

The aromatic protons resonated as a singlet at δ7.30. The diastereotopic bridgehead protons appeared as two singlets at δ2.98 and 3.03. The methine proton $H_E$, alpha to two oxygen atoms, resonated as a complex multiplet in the range δ4.38-4.20. The very broad complex multiplet at δ3.93-3.27 integrating for two protons was assigned to the methylene protons $H_F$. Proton $H_{D'}$ resonated as a doublet (J=2 Hz) at δ1.73. The complex doublet of doublets at δ2.88 was consistent with the presence of proton $H_{C'}$. A broad envelope in the range δ1.68-1.25 integrated for 8 protons. Six of these protons were assumed to be the methylene protons $H_G$ in the pyran ring. The remaining protons were assigned as $H_{A'}$ and $H_{B'}$.

Irradiation experiments helped confirm a similar splitting pattern of $H_{A',B',C',D'}$ to that of $H_{A,B,C,D}$ in the starting alcohol (122). Thus irradiating $H_{D'}$ collapsed proton $H_{C'}$ to a less complex doublet. Proton $H_{C'}$ was collapsed to a distinct doublet while irradiating at δ1.50. Thus δ1.50 is probably the centre of the resonance attributable to proton $H_{A'}$.

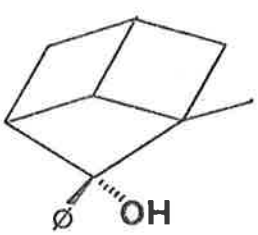
The ether was extraordinarily difficult to purify. The crude product was obtained in good yield by removal of excess dihydropyran by distillation. Attempts to distill the product resulted in extensive polymerization of the ether. The separation of the impurities from the ether on neutral alumina could not be achieved. If the alumina was replaced by silica, decomposition of the ether occured.

For most purposes, ether of sufficient purity could be obtained by using rigorously purified starting materials and isolating the ether by careful removal of excess dihydropyran by distillation. An analytically pure sample was prepared by slow bulb to bulb distillation at reduced pressure although more than half of the material polymerized during this distillation.

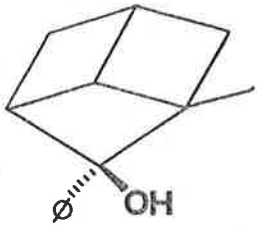
The tetrahydropyranyl ether was unexpectedly inert to metal-ammonia reduction. Under conditions similar to those used for the attempted reduction of the alcohol (122), unchanged starting material was the only recoverable compound. Two frequently encountered problems in the usual procedure for Birch reductions (the addition of sodium to a solution of the aromatic compound and an alcohol in liquid ammonia) have been the insolubility of the aromatic compounds in the reaction medium and the failure of this reaction system to reduce aromatic compounds having electron-donating or bulky substituents.[245a] The ether (143) appeared to be soluble in ammonia so an explanation for the inertness to reduction may lie in the presence of the bulky bicyclo(1.1.1)pentane substituent.

An example where possibly steric factors alter the usual course of a reaction is the reduction of the isomeric phenyl alcohols (133) and (134). The isomer (134) underwent reductive cleavage to give the hydrocarbon (141),[146a] but, possibly as a consequence of the steric congestion around the phenyl ring, the other isomer (133) did not expel the hydroxyl

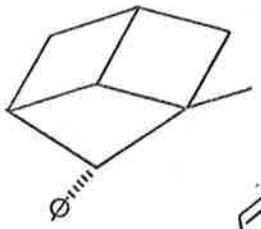
moiety but was reduced to the dihydroderivative (229) instead.[146a] Similar steric hindrance may operate in the ether (143). However, the failure of the aromatic ring to be reduced to its dihydroderivative cannot be explained.



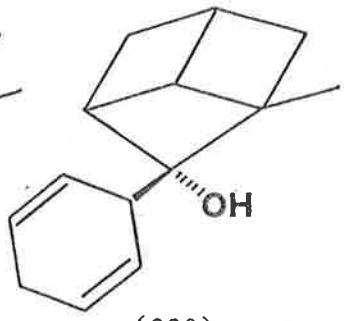

(133)




(134)




(141)

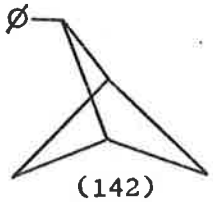



(229)

One reason for the failure of a compound to reduce is that traces of iron, often present in undistilled liquid ammonia, catalyze the unwanted reaction of sodium with alcohol to form hydrogen.[245a] Since only distilled ammonia was used in the attempted reductive cleavage of the ether (143), this reason appears unlikely.

A modification of the usual reduction procedure which has been found to facilitate the reduction of unreactive aromatic systems consists of adding the aromatic compound to a solution of lithium and a non-protonic solvent in liquid ammonia and then adding an alcohol.[245b,c] This procedure has not been attempted on the tetrahydropyranyl ether (143).

Two alternative procedures for the synthesis of the phenylhydrocarbon (142) have been investigated.



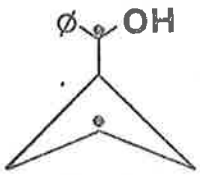

(142)

The alcohol (122) is a substituted benzyl alcohol. Similar benzyl alcohols are known to readily undergo catalytic hydrogenolysis.[163] Palladium on carbon is the preferred catalyst since competing reduction of the aromatic ring occurs only very slowly.[246]

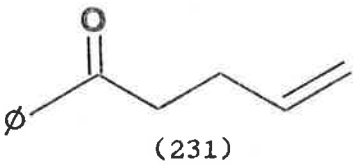
Under these conditions, the bicyclopentanol (122) might be expected to yield the phenylhydrocarbon (142). The hydrogenolysis of the strained carbon-carbon bonds was considered to be a possible competing reaction. Although no experimental value for the strain energy present in bicyclo(1.1.1)pentane exists, calculations[247] indicate that it is higher than that in bicyclobutane which is known to undergo hydrogenolysis.[248] The catalytic hydrogenation of the bicyclopentanol (122) yielded n-butyrophenone as the only product. This was confirmed by comparison with authentic material.

A possible reaction pathway to n-butyrophenone was isomerization of the alcohol to cyclobutylphenylketone followed by hydrogenolysis of the cyclobutyl ring. This seemed improbable as the conditions employed for the hydrogenolysis (palladium on carbon as catalyst, ambient temperature and atmospheric pressure) are usually too mild to affect a cyclobutane.[249] This mechanism could be discounted when it was found that ethylacetate, the solvent for the reaction, failed to isomerize the bicyclopentanol (122) to cyclobutylphenylketone. In addition, when authentic cyclobutylphenylketone was subjected to hydrogenolysis under the above conditions, it was recovered unchanged.

A more plausible pathway involves cleavage of a carbon-carbon bond to give a diradicaloid represented as structure (230) which then rearranges to the $\gamma,\delta$-unsaturated ketone (231), and this, under the reaction conditions, is further reduced. A sample of the authentic unsaturated ketone (231), obtained as a byproduct from the synthesis of bicyclopentanol (122),[142] underwent hydrogenation to give n-butyrophenone when subjected to the above reaction conditions.

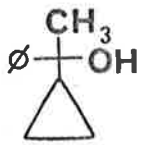


(230)

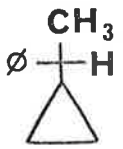


(231)

It has been reported that cyclopropylcarbinols undergo hydrogenolysis to the corresponding hydrocarbons when treated with borane and boron trifluoride.[250] Thus 1-cyclopropyl-1-phenylethanol (232) results in 1-cyclopropyl-1-phenylethane (233) in 75% yield under these conditions.[250] The initial step, formation of an alkoxyborane, is followed by slow heterolysis of the carbon-oxygen bond to give a carbonium ion and then hydride transfer to yield the product.[250] The trapping of the carbonium ion by hydride is reported to be the fast step of the reaction.[250]

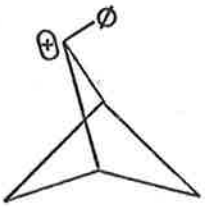


(232)



(233)

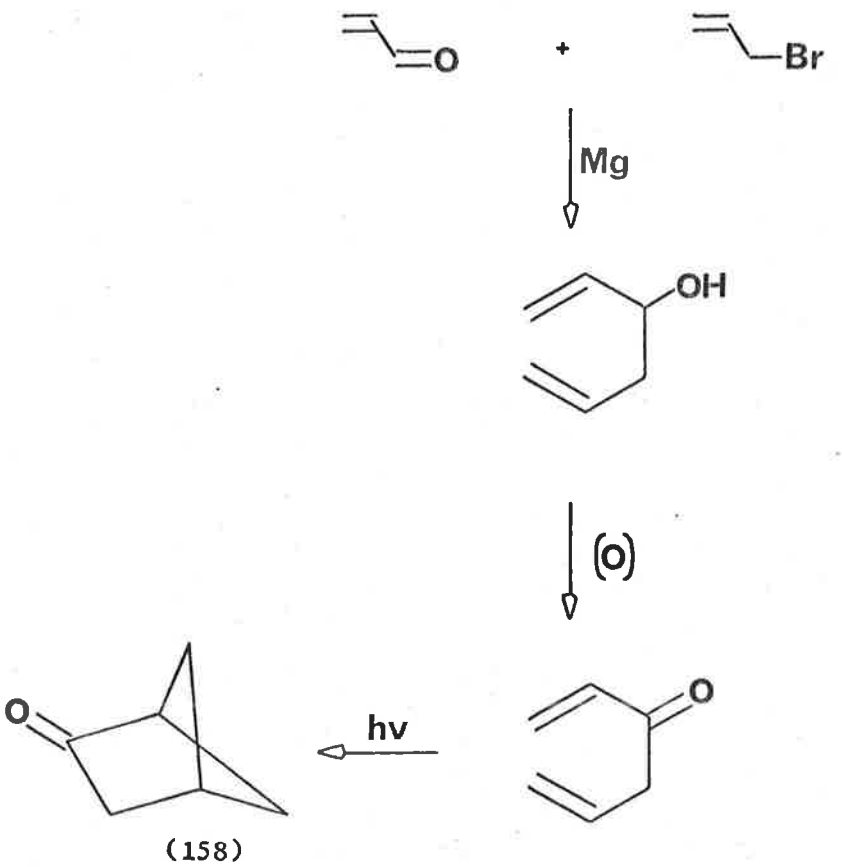
If this trapping of the carbonium ion is sufficiently rapid then the bicyclopentanol (122) might be expected to give the required phenyl-hydrocarbon (142) without undergoing an acid catalyzed rearrangement despite the formation of the incipient carbonium ion (234), which is an intermediate in the protonic acid-catalyzed rearrangement of the alcohol (122).[162]



(234)

Under similar conditions to those reported for the reduction of compound (232),[250] the bicyclopentanol (122) yielded at least two new compounds as was evident by g.l.c. analysis. These were separated, but only in low yield, by preparative gas chromatography. Although no structural assignments were made, the P.F.T. n.m.r. spectra indicated that neither compound was consistent with any of the expected products. This observation together with the inconvenience in obtaining the starting alcohol (122), and the low yield for the reaction, suggested that further study was not warranted.

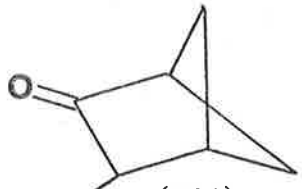
The alternative approach to the synthesis of the tricyclohexane (100) via bicyclo(2.1.1)hexan-2-one has similarly met with no success. The ketone (158) was synthesized by means of a literature procedure which is illustrated schematically in Figure 54.[173b]




(158)

FIGURE 54

The reaction of a ketone with bromine proceeds by the enolation of the ketone and subsequent electrophilic attack on the enol by bromine followed by loss of a proton from an intermediate oxonium ion leading to the bromoketone.[251a] The ketone (158) should enolize in only one direction (Bredt's rule[252]) and bromination was expected to yield the unknown bromoderivative (164). Unchanged starting material was the only compound recovered after prolonged contact with bromine in carbon tetrachloride. No other products could be detected by g.l.c. analysis.




(164)

Copper(II) bromide is an effective bromination agent for ketones.[253] The reaction appears to involve a copper halide catalyzed enolization followed by transfer of a halogen atom from the copper salt to the enolate.[251b]

To avoid wastage of bicyclo(2.1.1)hexan-2-one, camphor was used as a model system since it was readily available commercially, it could only enolize in one direction and it possessed a strained bicyclohydrocarbon skeleton, similar to the ketone under investigation. Camphor was converted to α-bromocamphor in high yield by this method. Its authenticity was verified by comparison with authentic material.[254] However, bicyclo(2.1.1)hexan-2-one failed to undergo any reaction, only unchanged starting material was recovered. G.l.c. analysis indicated no other products to be present.

Similarly an attempt to alpha formylate the ketone with sodium ethoxideand ethyl formate was unsuccessful; starting material was the only compound recovered.

The selenium dioxide oxidation of a methylenic moiety alpha to a carbonyl group frequently affords high yields of α-diketones.[255] The oxidation involves a rapid, concerted reaction of an enol to give a selenium(II) ester of the ketone, which decomposes to products (Figure 55).[256] Unchanged starting material was the only compound isolated, in high yield, from the reaction between selenium dioxide and bicyclo(2.1.1)-hexan-2-one.

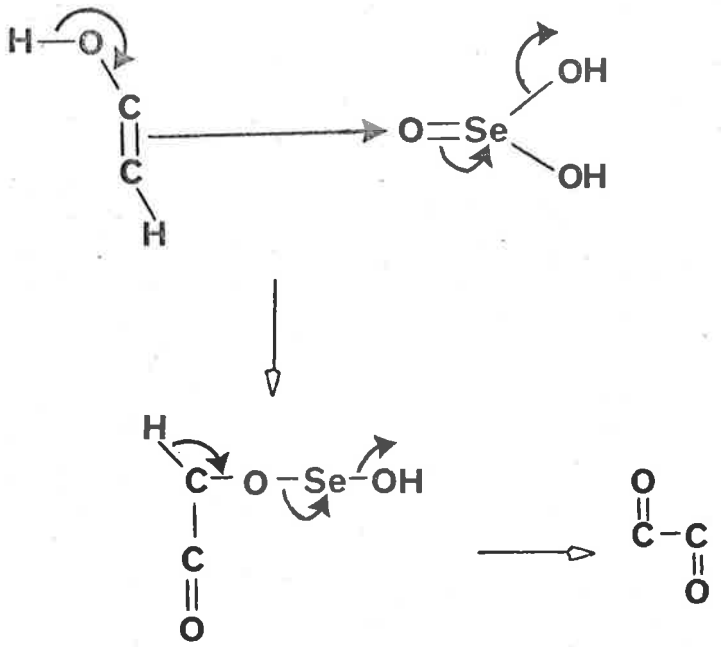


FIGURE 55

The one common requirement for all of the above reactions is the need for the ketone (158) to enolize before reaction can occur. A general phenomenon applicable to the formation of enolates is a stereo-electronic requirement that maximum overlap of the p-orbitals is maintained during the breaking of the carbon-hydrogen bond.[34b] It is conceivable that the angle strain in bicyclo(2.1.1)hexan-2-one makes it difficult to introduce a second $sp^2$ centre into the molecule.

After the above reactions had been attempted, it was found that a study by Tidwell of the base-catalyzed deuterium exchange in bicyclic ketones led to the observation that bicyclo(2.1.1)hexan-2-one had low reactivity.[257] It now seems likely that prolonged reaction times or the use of stronger bases may effect the required transformations but these have yet to be investigated.

# CHAPTER III

# EXPERIMENTAL

GENERAL

(1) Infrared spectra were determined with a Unicam SP200 or a Jasco IRA-1 grating infrared spectrophotometer. The 1603 $cm^{-1}$ band of polystyrene was used as a reference in the calibration of each spectrum and the values are accurate to $\pm$ 5 $cm^{-1}$.

(2) $^1H$ nuclear magnetic resonance spectra were recorded either on a Varian T-60 spectrometer operating at 60 MHz or a Bruker HX-90-E spectrometer operating at 90 MHz, and tetramethylsilane was used as an internal reference. Data are given in the following order: solvent; chemical shift (p.p.m.); multiplicity, s (singlet), br (broad), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets), m (multiplet) removed with $D_2O$ means that the signal disappears on shaking the sample with $D_2O$, complex means that this part of the spectrum could not be interpreted; first-order coupling constant (J) is expressed in Hz to the nearest 1 Hz; relative intensity as number of protons (H); assignment. All n.m.r. spectra could be interpreted on a first-order basis except where otherwise indicated.

(3) Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6D double focusing mass spectrometer operating at 60 eV.

(4) Melting points were determined on a Kofler hot-stage melting point apparatus under a Reichert microscope and are uncorrected.

(5) Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

(6) Gas-liquid chromatography (g.l.c.) analyses were carried out using a Pye 104 gas chromatograph. Preparative g.l.c. was carried out with a Pye 105 model. Both instruments were equipped with flame ionization detectors and nitrogen was used as the carrier gas. The columns, constructed of pyrex glass were packed with:

A. 6% FFAP on Varaport 30 (80/100), 1.0 m x 4.0 mm.

B. 15% FFAP on Varaport 30 (80/100), 2.0 m x 4.0 mm.

C. 10% SE 30 on Chromosorb A (100/120), 1.0 m x 4.0 mm.

D. 15% DEGS on Varaport 30 (80/100), 2.0 m x 6.0 mm.

E. 10% OV 101 on Chromosorb A (100/120), 1.0 m x 6.0 mm.

(7) Analytical and preparative thin layer chromatography (t.l.c.) plates were prepared from 50% Kieselgel G and 50% HF 254 applied to the glass plates as a suspension in water and activated at 120°.

(8) The commonly used anhydrous solvents were purified as follows. Ether was dried over calcium chloride granules for 48 hr, distilled from phosphorous pentoxide and stored over sodium wire. When required, further drying was achieved by distillation from lithium-aluminiumhydride. Benzene was washed successively with concentrated sulphuric acid, dilute sodium hydroxide solution and water and then dried by heating under reflux over a water separator until no more water was collected, distilled and stored over sodium wire. Pyridine was heated under reflux over potassium hydroxide pellets for 24 hr, then distilled from fresh potassium hydroxide and stored over 4 Å molecular sieves. Reagent grade tetrahydrofuran was distilled from lithiumaluminiumhydride immediately before use. Chloroform and methylene chloride were distilled from phosphorous pentoxide. Light petroleum and hexane were washed successively with sulphuric acid, sodium hydroxide solution and water and then dried over calcium chloride granules for 48 hr, followed by distillation and storage over sodium wire. Liquid ammonia was distilled from sodium, at room temperature, directly into the reaction vessel immediately before use. Methanol and ethanol were purified and dried as described by Vogel.[95d]

(9) In this text, light petroleum refers to the fraction of b.p. 60-70°.

(10) All organic extracts were dried over anhydrous magnesium sulphate, unless stated otherwise. Redistilled solvents were used for all extractions.

(11) All glassware for reactions involving metals was flame dried under vacuum.

(12) An ethereal solution of diazomethane was prepared from N-methyl-nitrosourea as described by Vogel.[95e]

# EXPERIMENTAL - Part A

2-Bromo-3-methylbut-2-enoic acid (46)

2-Bromo-3-methylbut-2-enoic acid (46) (m.p. 88-90°; lit.[94] 91.5°) was prepared in an overall yield of 81% from 3-methylbut-2-enoic acid via 2,3-dibromo-3-methylbutanoic acid.[94]

2-Methoxy-3-methylbut-2-enoic acid (45)

The reaction of 2-bromo-3-methylbut-2-enoic acid (46) with sodium methoxide followed by a base-catalyzed isomerization with sodium hydroxide gave 2-methoxy-3-methylbut-2-enoic acid (45) (m.p. 66-67.5°; lit.[94] 70.5°) in 43% yield.[94]

Phenyllithium

A 0.6 M solution of phenyllithium in ether was prepared according to a published procedure.[258]

2-Methoxy-3-methyl-1-phenylbut-2-en-1-one (73)

The ketone (73) (b.p. 76°/1.0 torr) was prepared in 65% yield from the lithium salt of 2-methoxy-3-methylbut-2-enoic acid (45) and phenyllithium by the method reported earlier.[22,30]

Toluene p-sulphonylhydrazine

Toluene p-sulphonylhydrazine (m.p. 108-109°; lit.[259] 109-110°) was prepared in 98% yield from p-toluenesulphonylchloride and hydrazine hydrate as described by Friedman, Litle and Reichle.[259]

2-Methoxy-3-methyl-1-phenylbut-2-en-1-onetoluene-p-sulphonyl-hydrazone (43)

A mixture of the E- and Z- isomers of the above hydrazone (m.p. 111-113° (dec)) was prepared in 98% yield from p-toluene-sulphonylhydrazine and 2-methoxy-3-methyl-1-phenylbut-2-en-1-one (73) as reported previously.[22,30]

1-Diazo-2-methoxy-3-methyl-1-phenylbut-2-ene (39)

A suspension of the hydrazone (43)(180 mg; 0.50 mmol) and lithium hydride (8.0 mg; 1.0 mmol) in dry hexane (3 ml) under a nitrogen atmosphere was stirred at ambient temperature for 12 hr. The hexane was removed by evaporation at reduced pressure, at 15°, under an inert atmosphere, to leave the lithium salt of the hydrazone and unchanged lithium hydride. These salts were placed in a flask connected to a trap cooled to -78°, the whole apparatus being swept continuously with a slow stream of nitrogen. The pressure of the system was reduced to 2.5 torr and the flask containing the salts was submerged in an oil-bath preheated to 160°. The diazoalkene (39) collected in the trap as a red liquid (70 mg; 69%).

The spectral data were identical to those reported earlier.[22,30]

The experiment was reproducible when the scale of the reaction was increased up to three-fold.

1-Methoxy-3,3-dimethyl-2-phenylcyclopropene (6)

A solution of the diazoalkene (39)(150 mg; 0.74 mmol) in carbon tetrachloride (3 ml) was placed in a n.m.r. tube. This tube was inserted into a reactor consisting of a Philips 125-W mercury-quartz medium pressure lamp surrounded by a pyrex water jacket and cooled to 0°. The progress of the irradiation was followed by n.m.r. spectroscopy. After approximately

40 min there were no resonances attributable to the diazoalkene (39), only those consistent with the cyclopropenol methyl ether (6).[22,30] The ether was stored in solution at 0° until immediately before use.

Unsuccessful alternative preparations of 2-methoxy-3-methyl-1-phenylbut-2-en-1-onetoluene-p-sulphonylhydrazone (43)

A: A solution of the ketone (73)(52 mg; 0.27 mmol) and p-toluene-sulphonylhydrazine (55 mg; 0.30 mmol) in methanol (3 ml) was heated under reflux and the progress of the reaction was followed by thin layer chromatography (ether : light petroleum = 1:1). After 192 hr t.l.c. comparison with authentic materials indicated the presence of ketone (73), tosylhydrazine, hydrazone (43) and at least six additional compounds. These additional unidentified products were in abundance after 216 hr with very little of the hydrazone (43) discernible. The reaction was terminated.

B: The above procedure was repeated but with the temperature of reaction lowered to 50°. T.l.c. analysis indicated a similar decomposition.

Decomposition of 2-methoxy-3-methyl-1-phenylbut-2-en-1-onetoluene-p-sulphonylhydrazone (43)

A solution of the hydrazone (43)(20 mg; 0.056 mmol) in methanol (3 ml) was heated under reflux. After 120 hr, t.l.c. analysis indicated that decomposition was occurring. The identical $R_f$ of these decomposition products with those obtained in the attempts to prepare the hydrazone (43) at 50° and 79°, suggested that the hydrazone was unstable at these higher temperatures.

Attempted isomerization of the E- and Z- isomers of 2-methoxy-3-methyl-1-phenylbut-2-en-1-onetoluene-p-sulphonylhydrazone (43) by the application of heat.

A 2:1 mixture of the E- and Z- isomers of the hydrazone (43), compounds (172) and (173) respectively, was heated at 82°/0.5 torr for 114 hr. The n.m.r. spectrum indicated that the initial ratio of isomers had not altered.

Acid isomerization of the E- and Z- isomers of 2-methoxy-3-methyl-1-phenylbut-2-en-1-onetoluene-p-sulphonylhydrazone (43)

A 2:1 mixture of the hydrazones (20 mg; 0.056 mmol) was dissolved in deuterochloroform (0.5 ml) and p-toluenesulphonic acid (trace amount) in $D_2O$ (0.1 ml) was added. The heterogeneous mixture was shaken vigorously at ambient temperature for 24 hr. The mixture was dried and the solvent removed in vacuo. The residue was recrystallized from ether : light petroleum (1:10) to give a white solid (18 mg; 90%)(m.p. 145-146° (dec)). The n.m.r. spectrum revealed that it was a single isomer of the hydrazone (43).

i.r. (nujol): 3150, 1670, 1590 $cm^{-1}$

$^1H$ n.m.r. ($CDCl_3$): δ8.30 (br. s, 1H, N-H); 8.07-7.17 (complex, 9H, aromatic protons); 3.13 (s, 3H, $CH_3$-O); 2.40 (s, 3H, $CH_3$-Aryl); 1.82 (s, 3H, $CH_3$-C=C); 1.27 (s, 3H, $CH_3$-C=C).

Methyllithium

A 1.5M solution of methyllithium in ether was prepared according to a published procedure.[260]

3-Methoxy-4-methylpent-3-en-2-one (182)

A solution of 2-methoxy-3-methylbut-2-enoic acid (45)(1.4 g; 11 mmol) in ether (30 ml) was added dropwise to a stirred suspension of lithium hydride (130 mg; 16 mmol) in ether (10 ml) at 0° under a nitrogen atmosphere, and then after the addition, the stirring was continued at ambient temperature for a further 2 hr. A solution of methyllithium (8.6 ml; 1.5 M; 13 mmol) was added dropwise to the suspension which was then stirred for a further 48 hr. The mixture was slowly pumped under a nitrogen pressure into a vigorously stirred solution of saturated aqueous ammonium chloride (50 ml). The ethereal solution was drawn off and the aqueous layer was saturated with solid sodium chloride and then extracted with ether (3 x 10 ml). The combined organic extracts were dried and evaporated at a reduced pressure with a nitrogen bleed to afford a yellow liquid. This liquid was distilled to give the ketone (182) as a pale yellow liquid (1.1 g; 79%)(b.p. 56-58°/1.0 torr).

i.r. (film): 1620, 1700 $cm^{-1}$

$^1H$ n.m.r. ($CCl_4$): δ3.48 (s, 3H, $CH_3$-O); 2.17 (s, 3H, $CH_3$-C=O); 1.97 (s, 3H, $CH_3$-C=C); 1.80 (s, 3H, $CH_3$-C=C)

mass spectrum: m/e 128 ($M^+$ calculated for $C_7H_{12}O_2$ = 128).

analysis: Found C, 65.74; H, 9.20. $C_7H_{12}O_2$ requires C, 65.59; H, 9.44.

3-Methoxy-4-methylpent-3-en-2-onetoluene-p-sulphonylhydrazone (183)

A solution of the ketone (182)(540 mg; 4.2 mmol) and p-toluenesulphonylhydrazine (860 mg; 4.6 mmol) in methanol (4 ml) was heated at 40° for 24 hr. The solvent was removed by evaporation in vacuo. The residue was crystallized from methanol to give the hydrazone (183) as a white solid (1.0 g; 83%)(m.p. 138-139° (dec)).

i.r. (nujol): 3240, 1670 $cm^{-1}$

$^1H$ n.m.r. ($CDCl_3$): δ7.95-7.28 (complex, 4H, aromatic protons); 3.32 (s, 3H, $CH_3$-O); 2.45 (s, 3H, $CH_3$-Aryl); 1.87 (s, 3H, $CH_3$-C=N); 1.70 (s, 3H, $CH_3$-C=C); 1.42 (s, 3H, $CH_3$-C=C).

mass spectrum: The mass spectrum did not exhibit a molecular ion but ions known to be produced by sulphonylhydrazones upon electron impact were evident[191]: m/e 141, 112, 92, 65.

analysis: Found C, 56.72; H, 6.72; N, 9.14; O, 16.10.

$C_{14}H_{18}O_3N_2S$ requires C,56.74; H, 6.80; N, 9.45; O, 16.20.

The product on one occassion was a mixture of the E- and Z- isomers of the hydrazone (183) as revealed by the n.m.r. spectrum. The resonances attributed to the additional isomer are listed below.

$^1H$ n.m.r. ($CDCl_3$): δ8.17-7.23 (complex, 4H, aromatic protons); 3.18 (s, 3H, $CH_3$-O); 2,47 (s, 3H, $CH_3$-Aryl); 2.02 (s, 3H, $CH_3$-C=N); 1.72 (s, 3H, $CH_3$-C=C); 1.38 (s, 3H, $CH_3$-C=C).

2-Diazo-3-methoxy-4-methylpent-3-ene (184)

A suspension of the hydrazone (183)(130 mg; 0.44 mmol) and lithium hydride (4.2 mg; 0.53 mmol) in dry hexane (3 ml) under a nitrogen atmosphere was stirred at ambient temperature for 12 hr. The solvent was removed by evaporation at reduced pressure, at 15°, under an inert atmosphere, to leave the lithium salt of the hydrazone and unchanged lithium hydride. A suitable apparatus was arranged to allow these salts to be added, a small quantity at a time, to a preheated flask (150°) connected to a trap cooled to -78°. The whole apparatus was swept continuously with a slow stream of nitrogen while maintaining a reduced pressure of 1.0 torr. When no more diazoalkene appeared to be collecting in the receiver a further small quantity of the salts was added to the flask and the product collected. This procedure was repeated until

the total quantity of salts had been subjected to pyrolysis. The diazoalkene (184) collected in the trap as an orange liquid (30 mg; 49%).

i.r. (film): 2050, 1650 $cm^{-1}$

$^1H$ n.m.r. ($CCl_4$): δ3.47 (s, 3H, $CH_3$-O); 1.88 (s, 3H, $CH_3$-C=$\overset{+}{N}$=$\bar{N}$); 1.70 (s, 3H, $CH_3$-C=C); 1.57 (s, 3H, $CH_3$-C=C).

1-Methoxy-2,3,3-trimethylcyclopropene (181)

A solution of the diazoalkene (184) in carbon tetrachloride was subjected to photolysis as described for the preparation of 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6). The reaction was terminated after 25 min. Attempts to purify the ether by column chromatography were unsuccessful. The carbon tetrachloride solution was placed on a column of neutral alumina at 0° and quickly eluted with cold diethylether. Removal of the solvent at reduced pressure at 0° gave an intractable gum. A similar decomposition occurred when the solution was passed down a silica column at 0° and eluted with diethylether. The following spectral analysis was carried out on the crude solution of the ether (181) in carbon tetrachloride.

i.r. ($CCl_4$ soln): 1870 $cm^{-1}$

$^1H$ n.m.r. ($CCl_4$): δ3.75 (s, 3H, $CH_3$-O); 1.83 (s, 3H, $CH_3$-C=C); 1.15 (s, 6H, $(CH_3)_2C$).

In addition to the above resonances attributed to the cyclopropenol ether (181), there were many minor peaks in the range δ1.23-3.57.

Unsuccessful attempts to prepare 2-benzyloxy-3-methylbut-2-enoic acid (47)

For use in the following reactions, the sodium salt of benzyl alcohol was prepared by adding sodium (23 g; 1 mol) in small pieces to benzyl alcohol (160 g; 1.5 mol) at 100° under a nitrogen atmosphere.

After all the sodium had dissolved the excess alcohol was removed by distillation. The solid sodium benzyloxide was stored under nitrogen in a desiccator until use.

A: 2-Bromo-3-methylbut-2-enoic acid (46)(500 mg; 2.8 mmol) and sodium benzyloxide (1.2 g; 9.2 mmol) were dissolved in dimethylsulphoxide (5 ml) under a nitrogen atmosphere and heated at 70° for 96 hr. After it had cooled, the mixture was acidified to pH 2 with 10% hydrochloric acid. The mixture was extracted with ether (3 x 5 ml). The combined organic extracts were washed with cold water (3 x 5 ml), dried and the solvent removed by evaporation. The residue was recrystallized from light petroleum to give unchanged 2-bromo-3-methylbut-2-enoic acid (46)(450 mg; 90%).

B: The bromoacid (46)(500 mg; 2.8 mmol) and sodium benzyloxide (1.2 g; 9.2 mmol) in benzene (5 ml) were heated under reflux for 24 hr. The benzene was removed by evaporation. Sufficient water was added to dissolve the solid residue and the solution was then acidified with 4 N sulphuric acid to pH 2. The solution was extracted with ether (3 x 10 ml). The combined organic extracts were washed with water (2 x 10 ml) and then dried. The ether was removed by evaporation. The unchanged 2-bromo-3-methylbut-2-enoic acid (46) was crystallized from light petroleum (350 mg; 70%).

C: Experimental details are as for part B except that the mixture of bromoacid (46) and sodium benzyloxide in benzene was heated under reflux for 96 hr. Unchanged bromoacid (46) was recovered in 75% yield.

D: Experimental details are as for part B except that the mixture of bromoacid (46) and sodium benzyloxide in benzene was heated under reflux for 168 hr. Unchanged bromoacid (46) was recovered in 82% yield.

2-Benzyloxy-3-methylbut-2-enoic acid (47)

Sodium (660 mg; 29 mmol) in benzyl alcohol (15 ml) was heated at 100° until all of the metal had dissolved. 2-Bromo-3-methylbut-2-enoic acid (46)(1.0 g; 5.6 mmol) was added and the suspension heated at 100° for 72 hr. The slurry was cooled and dissolved in the minimum of water and acidified to pH 2 with 50% sulphuric acid whilst simultaneously extracting with ether (40 ml). The organic layer was separated and the aqueous residue extracted with ether (2 x 10 ml). The combined ethereal extracts were washed with water (2 x 15 ml), dried and the ether removed by evaporation *in vacuo*. The excess benzyl alcohol was removed by distillation at reduced pressure. The residue was recrystallized from light petroleum to give 2-benzyloxy-3-methylbut-2-enoic acid (47) as a white solid (970 mg; 84%)(m.p. 81.5-83°).

i.r. (nujol): 3360-2380, 1695, 1625 $cm^{-1}$

$^1H$ n.m.r. ($CDCl_3$): δ13.33 (br s, removed with $D_2O$, 1H, $CO_2H$); 7.67-7.33 (complex, 5H, aromatic protons); 4.82 (s, 2H, $PhCH_2O$); 2.17 (s, 3H, $CH_3$-C=C); 1.88 (s, 3H, $CH_3$-C=C).

mass spectrum: m/e 206 ($M^+$ calculated for $C_{12}H_{14}O_3$ = 206)

analysis: Found C, 69.89; H, 6.50. $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84.

2-Benzyloxy-3-methyl-1-phenylbut-2-en-1-one (186)

A solution of 2-benzyloxy-3-methylbut-2-enoic acid (47)(1.1 g; 5.3 mmol) in ether (20 ml) was added to a stirred suspension of lithium hydride (64 mg; 8.0 mmol) in ether (10 ml) under a nitrogen atmosphere and stirred at ambient temperature for 10 hr. Phenyllithium solution (0.6 M, 9.7 ml, 5.8 mmol) was added dropwise and the suspension was stirred at ambient temperature for 96 hr. The mixture was pumped slowly under

a nitrogen pressure into a vigoursly stirred solution of saturated aqueous ammonium chloride (50 ml). The ethereal solution was drawn off and the aqueous layer saturated with solid sodium chloride and then extracted with ether (3 x 10 ml). The combined organic extracts were dried and evaporated *in vacuo* to give the crude ketone (186) as a yellow liquid (1.2 g; 85%). The only data recorded for the ketone (186) was the i.r. spectrum.

i.r. (film): 1670, 1600, 1580 $cm^{-1}$

2-Benzyloxy-3-methyl-1-phenylbut-2-en-1-onetoluene-p-sulphonyl-hydrazone (187)

2-Benzyloxy-3-methyl-1-phenylbut-2-en-1-one (186)(1.2 g; 4.5 mmol) and tosylhydrazine (920 mg; 5.0 mmol) were dissolved in methanol (10 ml) and heated at 40°. The progress of the reaction was followed by t.l.c. (ether : light petroleum = 2:3). After 5 weeks, t.l.c. analysis indicated that in addition to the two starting materials there was a faint trace of at least one additional product. This new compound was isolated by preparative t.l.c. in low yield (21 mg; 1%). The spectral data were consistent with the hydrazone (187) contaminated with another compound, possibly an isomer of the hydrazone.

i.r. (nujol): 3220, 1670, 1600 $cm^{-1}$

$^1H$ n.m.r. ($CDCl_3$): δ8.07-6.97 (complex, 14H, aromatic protons); 4.47 (s, 2H, $PhCH_2O$); 2.40 (s, 3H, $CH_3$-Aryl); 1.73 (s, 3H, $CH_3$-C=C); 1.47 (s, 3H, $CH_3$-C=C).

Triethylorthoformate

Ethylformate (1.0 g; 13 mmol) and triethyloxonium tetrafluoroborate[261] (3.1 g; 16 mmol) were stirred at ambient temperature under a

nitrogen atmosphere for 24 hr. A solution of sodium (360 mg; 16 mmol) in ethanol (7 ml) was added to the homogeneous mixture which was then stirred at ambient temperature for a further 12 hr. Saturated sodium carbonate solution (5 ml) was added and the mixture was extracted with ether (3 x 20 ml). The ethereal extracts were combined and dried ($K_2CO_3$). Fractional distillation gave triethylorthoformate (1.4 g; 73%)(b.p. 30-32°/10 torr; lit.[262] 60°/30 torr) which was identified by comparison of its i.r. and n.m.r. spectral data with those of commercially available material.

Ethyl-2-methylbut-2-enate (65)

This ester (b.p. 62-63°/32 torr; lit.[263] 61.5°/30 torr) was prepared in 60% yield by heating 2-methylbut-2-enoic acid and ethanol under reflux in the presence of concentrated sulphuric acid. A standard procedure, recommended by Vogel,[95f] was followed.

Unsuccessful attempts to prepare triethylortho-3-methylbut-2-enate (66) from ethyl-2-methylbut-2-enate (65) and triethyloxonium tetrafluoroborate.

A: Ethyl-2-methylbut-2-enate (65)(2.3 g; 18 mmol) and triethyloxonium tetrafluoroborate (3.8 g; 20 mmol) were mixed together at ambient temperature under a nitrogen atmosphere. The suspension had not homogenized after 4 days. The unchanged oxonium salt was removed by filtration. The liquid was identified as unchanged ester (65) by spectral data.

B: Experimental details are as for part A except that the ester (65) and triethyloxonium tetrafluoroborate were mixed together at 35°. The suspension had not homogenized after 48 hr and unchanged starting materials were the only compounds isolated.

Pyridiniumchlorochromate

Pyridiniumchlorochromate was prepared in 77% yield according to a published procedure.[225]

Methyl 2-hydroxy-2-phenylethanoate (190)

This ester (m.p. 53-53.5°; lit.[195] 55°) was prepared in 88% yield from 2-hydroxy-2-phenylethanoic acid, methanol and concentrated sulphuric acid following the procedure described by Acree.[195]

Methylbenzoylformate (191)

Pyridiniumchlorochromate (8.0 g; 37 mmol) was suspended in methylene chloride (50 ml) and methyl-2-hydroxy-2-phenylethanate (190) (4.0 g; 24 mmol) in methylene chloride (25 ml) was rapidly added at ambient temperature. After 12 hr, the black reaction mixture was diluted with anhydrous ether (350 ml), the solvent was decanted and the black residue was washed with ether (3 x 20 ml). The combined organic extracts were filtered through Florosil and the solvent was evaporated at reduced pressure. Distillation gave methylbenzoylformate (191) as a colourless liquid (3.7 g; 93%)(b.p. 124-125°/10 torr; lit.[263] 250-255°/ 760 torr).

i.r. (film): 1730, 1685, 1590, 1570 $cm^{-1}$

Isopropyltriphenylphosphonium bromide (192)

This phosphonium salt (m.p. 238-239°; lit.[196] 238-239°) was prepared in 96% yield from triphenylphosphine and 2-bromopropane following a published procedure.[196]

Methyl-3-methyl-2-phenylbut-2-enate (193)

Methyl-3-methyl-2-phenylbut-2-enate (193)(b.p. 69-71°/ 0.3 torr; lit.[197] 70-72°/ 0.4 torr) was synthesized in 60% yield from methylbenzoylformate (191) and isopropyltriphenylphosphonium bromide (192) by following a literature method.[197]

Acid catalyzed hydrolysis of 2-methoxy-3-methyl-1-phenylbut-2-en-1-one (73) to isopropylphenyl-1,2-diketone (72)

The ketone (73)(150 mg; 0.79 mmol) was dissolved in acetic acid (3 ml) and perchloric acid (72%, 1 drop) was added. The yellow solution was stood at ambient temperature for 14 hr. The solution was neutralized to pH 7 with 5N sodium hydroxide and then extracted with ether (3 x 10 ml). The combined ethereal extracts were washed with water (2 x 10 ml), dried and the solvent was removed in vacuo to give the yellow diketone (72)(97 mg; 70%). The spectral data were consistent with those reported for the authentic diketone.[194]

i.r. (film): 1705, 1670 $cm^{-1}$

$^1H$ n.m.r. ($CCl_4$): δ8.00-7.43 (complex, 5H, aromatic protons); 3.37 (septet, 7Hz, 1H, $(CH_3)_2\underline{C}H$); 1.18 (d, 7Hz, 6H, $(C\underline{H}_3)_2CH$).

Acid catalyzed hydrolysis of 2-methoxy-3-methyl-1-phenylbut-2-en-1-one (73) to 3-methyl-2-phenylbut-2-enoic acid (188)

The ketone (73)(150 mg; 0.79 mmol) was dissolved in acetic acid (3 ml) and perchloric acid (72%, 1 drop) was added. The yellow solution was stood at ambient temperature for 14 hr. The solution was neutralized to pH 7 with 5N sodium hydroxide and then extracted with ether (3 x 10 ml). The combined ethereal extracts were washed with water (2 x 10 ml) and dried. The dried ethereal solution was cooled to 0° and

added to an excess of diazomethane in ether at 0°. After 2 hr at 0°, the solution was allowed to warm to ambient temperature overnight. The solvents were removed *in vacuo*. The residue was distilled to give methyl-3-methyl-2-phenylbut-2-enate (193) as a colourless liquid (81 mg; 54%)(b.p. 69-70°/ 0.3 torr).

3-Methyl-1-phenylbutan-1-one (194)

3-Methyl-1-phenylbutanone (194)(b.p. 85-87°/ 9.0 torr; lit.[198] 137-138°/ 38 torr) was prepared in 40% yield by a literature procedure which involved the Friedel-Crafts acylation of benzene with 3-methylbutoylchloride.[198]

2-Bromo-3-methyl-1-phenylbutan-1-one (195)

Bromination of 3-methyl-1-phenylbutanone (194), by the method of Kunckell and Stahel[199], gave, in 61% yield, 2-bromo-3-methyl-1-phenylbutanone (195)(m.p. 35-39°; lit.[199] 33-38°).

2-Nitrito-3-methyl-1-phenylbutan-1-one (196)

The reaction between silver nitrate and 2-bromo-3-methyl-1-phenylbutanone (195) gave, in 68% yield, 2-nitrito-3-methyl-1-phenylbutanone (196)(b.p. 103-105°/ 0.2 torr; lit.[115] 105°/ 0.25 torr).

Attempted preparation of isopropylphenyl-1,2-diketone (72) from 2-nitrito-3-methyl-1-phenylbutan-1-one (196)

When the literature procedure[115] was followed none of the required diketone (72) was produced. Unchanged starting material was the

only product isolated. Increasing the reaction time from the recommended 20 min[115] to 70 hr was also unsuccessful.

Attempted preparation of isopropylphenyl-1,2-diketone (72) from 2,3-epoxy-3-methyl-1-phenylbutan-1-one (197)

The epoxyketone (197)[192] (56 mg; 0.32 mmol) was dissolved in ethanol (0.5 ml) and added to a solution of sodium (11 mg; 0.48 mmol) in ethanol (0.5 ml). The mixture was heated under reflux for 1 min and a deep red solution was obtained. The reaction was quenched by the addition of 20% sulphuric acid (0.2 ml) and the mixture shaken until the colour was discharged. The solution was extracted with ether (3 x 1 ml). The combined ethereal extracts were dried, cooled to 0° and then added to an excess of diazomethane in ether at 0°. After remaining at 0° for 2 hr, the solution was allowed to warm to ambient temperature overnight. G.l.c. comparison of the products (column A, 170°) with authentic materials indicated that methyl-3-methyl-2-phenylbut-2-enate (193) was the major product. This was confirmed when the compound was isolated by preparative g.l.c. (column B, 200°) and its spectral data were compared with those of authentic methyl-3-methyl-2-phenylbut-2-enate (193).

Attempted preparation of 2-acetoxy-3-methyl-1-phenylbut-2-en-1-one (198) from 2,3-epoxy-3-methyl-1-phenylbutan -1-one (197)

The epoxyketone (197)[192] (550 mg; 3.1 mmol) was dissolved in ethanol (1.0 ml) and added to a solution of sodium (110 mg; 4.8 mmol) in ethanol (2.0 ml). The mixture was heated under reflux for 1 min when a deep red solution was obtained. The reaction was quenched by the addition of acetic anhydride (440 mg; 4.3 mmol) and the mixture shaken until the colour was discharged. The solution was diluted with ether

(4 ml) and washed with 10% sodium hydroxide solution (2 x 5 ml) and then water (2 x 5 ml). The ethereal solution was dried and the solvent removed by evaporation. The residue was recrystallized from hexane to give unchanged 2,3-epoxy-3-methyl-1-phenylbutanone (197)(520 mg; 95%).

The benzilic-acid type rearrangement of 2,3-epoxy-3-methyl-1-phenylbutan-1-one (197)

The epoxyketone (197)[192](56 mg; 0.32 mmol) was dissolved in ethanol (0.5 ml) and heated under reflux for 1 min. A solution of 20% sulphuric acid (0.2 ml) was added and the mixture was shaken vigorously for 5 min. The solution was extracted with ether (3 x 1 ml). The combined ethereal extracts were dried, cooled to $0^{\circ}$ and added to an excess of diazomethane in ether at $0^{\circ}$. After remaining for 2 hr at $0^{\circ}$, the solution was warmed to ambient temperature overnight. G.l.c. comparison of the products (column A, $170^{\circ}$) with authentic materials indicated methyl-3-methyl-2-phenylbut-2-enate (193) to be the major product. This was confirmed when the compound was isolated by preparative g.l.c. (column B, $200^{\circ}$) and its spectral data were compared with those of the authentic ester (193).

1,3-propanedithiol

1,3-Propanedithiol (b.p. $58-59^{\circ}$/ 12 torr; lit.[204] $57^{\circ}$/ 12 torr) was prepared from 1,3-dibromopropane and thiourea in 54% yield according to a literature method.[204]

2-Methylpropanal-1',3'-propanedithiane (203)

The dithiane (203)(b.p. $134^{\circ}$/ 35 torr; lit.[203] $108-110^{\circ}$/ 5 torr) was prepared in 35% yield from 2-methylpropanal and 1,3-propanedithiol

by a procedure described by Seebach.[203]

3-Methyl-1-phenyl-2-(propane-1',3'-dithiane)butan-1-one (204)

The dithiane (203)(5.0 g; 31 mmol) in tetrahydrofuran (100 ml) was cooled to -30° and n-butyllithium (26 ml; 1.2M; 31 mmol) was added dropwise over 10 min. Stirring was continued at -30° for a further 1.5 hr after which the clear, pale yellow solution was cooled to -78°. Benzonitrile (3.2 g; 31 mmol) was added dropwise over 2 min and the resultant red-orange solution was stirred at -78° for a further 40 min. The cooling bath was removed and the mixture stirred at ambient temperature for 40 min and then poured onto ice (100g). The aqueous solution was extracted with methylene chloride (3 x 50 ml). The combined organic extracts were washed with 2N sodium hydroxide solution (2 x 50 ml) and dried. The solvent was removed by distillation and the residue added to 4% hydrochloric acid (450 ml) and heated at 74° for 2 hr. The aqueous mixture was extracted with methylene chloride (3 x 100 ml). The combined extracts were dried and evaporated in vacuo to give an oil which slowly solidified on standing. 3-Methyl-1-phenyl-2-(propane-1',3'-dithiane)butanone (204) m.p. 129-131° (sealed tube) was obtained as white needles (5.0 g; 61%) by recrystallization from methanol.

i.r. (nujol): 1680, 1590, 1580 $cm^{-1}$

$^1H$ n.m.r. ($CDCl_3$): δ8.13-7.42 (complex, 5H, aromatic protons); 3.53-2.97 (overlapping ddd, (4,10,15 Hz), 2H, $S-CH_{ax}$); 2.90-2.47 (overlapping ddd, (3,4,15 Hz) superimposed on complex multiplet, 3H, $S-CH_{eq}$ + $(CH_3)_2\underline{C}H$); 2.23-1.83 (complex, 2H, $SCH_2\underline{C}H_2CH_2S$); 1.12 (d, 7Hz, $(\underline{C}H_3)_2CH$).

mass spectrum: The mass spectrum showed no parent ion but only those ions which arise from alpha cleavage, which is characteristic of ketones,[206] at m/e 161, 77.

analysis: Found C, 63.25; H, 6.64; S, 23.80. $C_{14}H_{18}S_2O$ requires C, 63.14; H, 6.81; S, 24.03.

N-Chlorosuccinimide

N-Chlorosuccinimide (m.p. 148-149°; lit.[209] 149°) was prepared in 58% yield by passing a stream of chlorine gas into a solution of succinimide in 15% sodium hydroxide solution according to a published procedure.[209]

Unsuccessful attempts to convert 3-methyl-1-phenyl-2-(propane-1',3'-dithiane)butan-1-one (204) to isopropyl-1,2-diketone (72)

A: A solution of N-bromosuccinimide (1.4 g; 8.0 mmol) in 97% aqueous acetone (28 ml) was added to the dithiane (204)(160 mg; 0.60 mmol) dissolved in acetone (3 ml) at -10°. After 2 min, methylene chloride : hexane (1:1)(10 ml) was added followed by 50% sodium bicarbonate solution (10 ml). The organic phase was separated and washed with water (2 x 15 ml). After drying ($Na_2SO_4$), the solvents were removed *in vacuo* to yield a pale yellow lachrymatory liquid which rapidly turned brown on standing. The structure of this compound was not determined.

The experiment was repeated but with reaction times of 10, 30 and 2880 min. A similar result occurred in each case.

B: A solution of the dithiane (204)(100 mg; 0.38 mmol) in acetonitrile (2 ml) was added to a mixture of N-chlorosuccinimide (200 mg; 1.5 mmol), silver nitrate (290 mg; 1.7 mmol), acetonitrile (2 ml) and water (0.3 ml) at 20°. The temperature was raised to 38° for 1 hr. Saturated salt solution (1 ml) was added and the mixture filtered. The

residue was extracted with methylene chloride (3 x 5 ml). The filtrate and organic extracts were combined and dried. The solvents were removed by evaporation to give an intractable mixture.

C: A mixture of the dithiane (204)(100 mg; 0.38 mmol), water (0.1 ml), methyl iodide (270 mg; 1.9 mmol) and sodium carbonate (10 mg; 0.09 mmol) in acetone (2 ml) was heated under reflux. The progress of the reaction was followed by t.l.c. analysis (methylene chloride : light petroleum = 2:5). Only unchanged starting material was present after 95 hr. The reaction was terminated.

Isopropylphenyl-1,2-diketone (72)

A solution of thallium trinitrate trihydrate (530 mg; 1.2 mmol) in methanol (2 ml) was added to a solution of the dithiane (204)(140 mg; 0.54 mmol) in methanol (8 ml) and tetrahydrofuran (1 ml). The mixture was stirred at ambient temperature for 2 hr. The white crystalline precipitate was removed by filtration and the solvents were evaporated. The residue was extracted with chloroform (4 x 5 ml). The combined organic extracts were washed with water (2 x 5 ml) and dried. The solvent was removed *in vacuo* to yield a yellow liquid which was purified by preparative t.l.c. (100% chloroform). The diketone was obtained as a bright yellow liquid (38 mg; 40%). Its spectral data were consistent with those reported.[194]

The addition of dichlorocarbene to 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6)

A solution of 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6) (30 mg; 0.17 mmol) in chloroform (1 ml) was cooled to -25°. A slurry of potassium *t*-butoxide (21 mg; 0.19 mmol) in hexane (1 ml) was added a por-

tion at a time keeping the temperature below -20°. An exothermic reaction ensued. After the addition, stirring was continued at -25° for a further 2 hr. The mixture was rapidly filtered through chilled apparatus. The residue was extracted with cold ether (2 x 2 ml). The filtrate and organic extracts were combined and the solvents removed *in vacuo* at 0° to give an intractable gum.

Chromium(II) sulphate

A 0.5M solution of chromium(II) sulphate in water was prepared according to a published procedure.[213]

Attempted addition of dimethylcarbene to 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6)

2,2-Dibromopropane (100 mg; 0.5 mmol) and 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6)(80 mg; 0.46 mmol) were dissolved in dimethylformamide (2 ml) at 15° under a nitrogen atmosphere. To this was slowly added chromium(II) sulphate solution (2 ml; 0.5M; 1.0 mmol). The mixture was stood at 15° for 24 hr, then it was saturated with solid ammonium sulphate and extracted with ether (3 x 4 ml).

The organic extracts were combined and dried. The dried ethereal solution was divided into two fractions, A and B. G.l.c. analysis of fraction A (column C, 160°) revealed only one major compound. This was collected by preparative g.l.c. (column C, 160°) to give a compound whose spectral data were identical to those of 3-hydroxy-3-methyl-1-phenylbutan-2-one (205). G.l.c. analysis of fraction B (column D, 50°) exhibited a "shoulder" on the edge of the solvent peak. This "shoulder" had a retention time identical to that of 2-propanol. The diethylether was removed from fraction B by careful

distillation through an eight inch spinning band column. The temperature of the distillation pot was raised very slowly until the distillate reached 82°. A small quantity of distillate was obtained whose n.m.r. spectrum was identical to that of authentic 2-propanol.

Ethyl- 2-hydroxy-2-methyl propanate (209)

Ethyl- 2-hydroxy-2-methyl propanate (209)(b.p. 51-53°/28 torr; lit.[217] 48-50°/25 torr) was prepared in 40% yield from acetonecyanohydrin and hydrogen chloride according to a literature method.[217]

Benzylmethylether

Benzylmethylether (b.p. 60-63°/15 torr; lit.[219] 170.5°/760 torr) was prepared in 61% yield following a literature procedure.[219]

3-Hydroxy-3-methyl-1-phenylbutan-2-one (205)

A solution of benzylmethylether (1.5g; 12 mmol) in tetrahydrofuran (25 ml) was added dropwise to finely cut lithium (200 mg; 29 mmol) suspended in tetrahydrofuran (25 ml) cooled to -15° and under a nitrogen atmosphere.[218] After 4 hr at that temperature, a solution of ethyl- 2-hydroxy-2-methyl propanate (209)(660 mg; 5.0 mmol) in tetrahydrofuran (10 ml) was added dropwise over 2 hr. The mixture was allowed to warm to ambient temperature and then heated under reflux for 24 hr. Upon cooling, the mixture was pumped under a nitrogen pressure into a vigorously stirred solution of saturated ammonium chloride (50 ml). The mixture was extracted with ether (3 x 20 ml) and the combined extracts dried ($K_2CO_3$). The solvents were removed by distillation at atmospheric pressure. Distillation of the residue at

reduced pressure gave 3-hydroxy -3-methyl -1-phenylbutan-2-one (205) (530 mg; 59%)(b.p. 130-131°/ 0.7 torr).

i.r. (film): 3680-3160, 1710 $cm^{-1}$

$^1H$ n.m.r. ($CCl_4$): δ7.30-7.00 (complex, 5H, aromatic protons); 3.77 (s, 2H, $-CO-CH_2Ø$); 1.33 (s, 6H, $(CH_3)_2C$)

mass spectrum: The mass spectrum did not show a parent ion but only those ions formed as a consequence of alpha cleavage, which are characteristic of ketones,[206] at m/e: 59, 91, 119

analysis: Found C, 74.59; H, 7.83. $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92.

Acid hydrolysis of 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6)

A mixture of 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6) (30 mg; 0.17 mmol) in carbon tetrachloride (0.5 ml) to which had been added p-toluenesulphonic acid (trace amount) in water (0.25 ml) was shaken vigorously at ambient temperature for 48 hr. The water was separated from the organic layer which was then dried. G.l.c. analysis (column C, 160°) indicated the major compound had a retention time identical to that of 3-hydroxy-3-methyl-1-phenylbutan-2-one (205). The n.m.r. spectrum of the organic layer was a composite of the data reported[216] for 1-hydroxy-3-methyl-1-phenylbutan-2-one (208) and those resonances attributable to 3-hydroxy-3-methyl-1-phenylbutan-2-one (205). The n.m.r. spectrum indicated 3-hydroxy-3-methyl-1-phenylbutan-2-one (205) was the predominant isomer.

2-Hydroxy-2-methylpentane (214)

2-Hydroxy-2-methylpentane (214)(b.p. 117-119°; lit.[95b] 117-120°) was prepared in 62% yield from ethylbutyrate and methylmagnesium iodide following a procedure described by Vogel.[95b]

2-Methylpent-2-ene (215)

2-Methylpent-2-ene (215)(b.p. 65-66°; lit.[223] 67.2-67.5°) was prepared in 59% yield by the dehydration of 2-hydroxy-2-methylpentane (214) using a standard procedure recommended by Vogel.[95c]

2,3-Epoxy-2-methylpentane (216)

A solution of 2-methylpent-2-ene (215)(1.0 g; 12 mmol) in methylene chloride (10 ml) was cooled to 0° and m-chloroperbenzoic acid (2.3 g; 15 mmol), dissolved in methylene chloride (10 ml), was added dropwise and the resultant mixture stirred at 0° for 3 hr. The precipitated m-chlorobenzoic acid was removed by filtration. The filtrate was washed successively with 10% potassium carbonate solution (3 x 5 ml) and water (1 x 5 ml). The organic solution was dried and the solvent was removed by distillation. Distillation of the residue gave 2,3-epoxy-2-methylpentane (216)(840 mg; 70%)(b.p. 128-129°; lit.[222b] 126.5°).

2,3-Dihydroxy-2-methylpentane (217)

A mixture of 2,3-epoxy-2-methylpentane (216)(3.0 g; 30 mmol) and 0.5% sulphuric acid (2.2 ml) was stirred at ambient temperature for 14 hr. The mixture was extracted with ether (6 x 5 ml). The combined organic extracts were dried and the solvent was removed *in vacuo*. Distillation of the residue gave 2,3-dihydroxy-2-methylpentane (217)(b.p. 53°/2.2 torr; lit.[217] 91-92°/25 torr) as a colourless liquid (2.0 g; 56%).

2-Hydroxy-2-methylpentan-3-one (212)

Pyridiniumchlorochromate (3.0 g; 14 mmol) and sodium acetate (trace amount) were suspended in methylene chloride (12 ml) and 2,3-

dihydroxy-2-methylpentane (217)(1.1 g; 9.3 mmol) in methylene chloride (6 ml) was added rapidly at ambient temperature. After 2.5 hr, the black reaction mixture was diluted with anhydrous ether (80 ml), the solvent was decanted and the black residue was washed with ether (4 x 15 ml). The combined organic extracts were filtered through Florisil and the solvent was removed by distillation. Distillation of the residue gave 2-hydroxy-2-methylpentan-3-one (212)(760 mg; 70%)(b.p. 141°; lit.[222a] 140-142°)

i.r. (film): 3700-3150, 1705 $cm^{-1}$

$^1H$ n.m.r. ($CDCl_3$): δ2.56 (q, 7Hz, 2H, $-CO-\underline{CH}_2CH_3$); 1.37 (s, 6H, $(CH_3)_2C$); 1.08 (t, 7Hz, 3H, $-CO-CH_2\underline{CH}_3$); 3.78 (br, removed with $D_2O$, 1H, OH)

Acid catalysed hydrolysis of 1-methoxy-2,3,3-trimethylcyclopropene (181)

A mixture of 1-methoxy-2,3,3-trimethylcyclopropene (181)(35 mg; 0.31 mmol) in carbon tetrachloride (0.5 ml) to which had been added p-toluenesulphonic acid (trace amount) in water (0.25 ml) was shaken vigorously at ambient temperature for 4 hr. The organic layer was separated and dried. G.l.c. analysis (column E, 90°) indicated that the single peak had a retention time identical to that of 2-hydroxy-2-methylpentan-3-one (212). The n.m.r. spectrum of the organic layer was the same as that of the hydroxyketone (212).

Diphenyldiazomethane

Diphenyldiazomethane was prepared in 64% yield by the oxidation of benzophenone hydrazone with mercuric oxide according to a literature procedure.[264]

Attempted reaction of diphenyldiazomethane with 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6)

A solution of diphenyldiazomethane (41 mg; 0.21 mmol) and 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6)(31 mg; 0.18 mmol) in carbon tetrachloride (0.5 ml) was protected from light and stood at 0° for 20 hr. At that time the n.m.r. spectrum indicated no addition had occurred. T.l.c. analysis (ether : light petroleum = 1:10) identified the mixture as diphenyldiazomethane, benzophenone azine and 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6). No other compounds could be detected by t.l.c. analysis.

The experiment was repeated with a reaction time of 24 hr and at a temperature of 19°. An identical result was obtained.

Attempted addition of diazomethane to 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6)

A solution of 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6) (30mg; 0.17 mmol) in carbon tetrachloride (0.5 ml) was added to an excess of diazomethane in ether cooled to 0°. After 7 days at 0°, the solvents were removed at reduced pressure and low temperature. The n.m.r. spectrum of the residue showed the mixture to be unchanged 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6) and acetone azine. No other products could be detected by t.l.c. analysis.

Attempted addition of diphenyldiazomethane or diazomethane to 1-methoxy-2,3,3-trimethylcyclopropene (181)

By the use of similar procedures to those described for 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (6), it was shown that the 1,3-dipolar-

cycloadditions between 1-methoxy-2,3,3-trimethylcyclopropene (181) and diphenyldiazomethane or diazomethane did not occur. N.m.r. and t.l.c. analyses indicated that decomposition of the ether (181), which has been found to occur readily, was the only effect observed.

1-t-Butoxy-1-cyano-2,2-diphenylethane (224b)

1-t-Butoxy-1-cyano-2,2-diphenylethane (224b) was prepared in 70% yield from diethyl-t-butoxy(cyano)methylphosphonate (223)[236] and benzophenone as described by Watt.[233]

2-t-Butoxy-1,3,3-triphenylprop-2-en-1-one (222b)

A mixture of magnesium (86 mg; 3.6 mmol) and bromobenzene (570 mg; 3.6 mmol) in ether (5 ml) was heated under reflux until all of the magnesium had dissolved. A solution of 1-t-butoxy-1-cyano-2,2-diphenylethane (224b) (250 mg; 0.90 mmol) in ether (5 ml) was added dropwise to the cooled Grignard reagent and the mixture stirred at ambient temperature for 16 hr. The mixture was poured onto crushed ice (18 g) and 10% oxalic acid (30 ml) was added. The aqueous solution was isolated and heated under reflux for 4 hr to hydrolyse the imine. The solution was cooled and extracted with ether (4 x 20 ml). The combined organic extracts were dried and the solvent was removed under reduced pressure to leave a yellow oil (crude yield = 20%).

i.r. (film): 1670, 1600 $cm^{-1}$

Attempted preparation of 2-t-butoxy-1,3,3-triphenylprop-2-en-1-one-toluene-p-sulphonylhydrazone (225b)

A solution of the crude 2-t-butoxy-1,3,3-triphenylprop-2-en-1-one

(20 mg; 0.056 mmol) in methanol (2 ml) was heated at 40°. The progress of the reaction was monitored by t.l.c. analysis (ether : light petroleum = 1:1). There was no indication of any new product after 14 days. The reaction was terminated.

# EXPERIMENTAL - Part B

Exo-2-phenyl-endo-2-hydroxybicyclo(2.2.1)heptane (146)

Exo-2-phenyl-endo-2-hydroxybicyclo(2.2.1)heptane (146) (b.p. 90-93°/1.8 torr; lit.[166] 158-168°/17-18 torr) was prepared from phenyllithium and bicyclo(2.2.1)heptan-2-one (147) in 71% yield according to a literature procedure.[166]

Ruthenium tetroxide

Commercial ruthenium tetroxide (300 mg; 1.80 mmol) was dissolved in carbon tetrachloride (10 ml) to give a 0.18M solution. This solution was stored at 0° until use.

Bicyclo(2.2.1)heptan-2-one (147)

Exo-2-phenyl-endo-2-hydroxybicyclo(2.2.1)heptane (146)(100 mg; 0.53 mmol) was dissolved in carbon tetrachloride (2 ml). A solution of sodium periodate (1.5 g; 7.0 mmol) in water (15 ml) was added followed by ruthenium tetroxide in carbon tetrachloride (0.18M, 0.2 ml, 0.036 mmol). The mixture was stirred vigorously at ambient temperature for 72 hr, and then filtered through a celite pad. The aqueous layer was separated, saturated with sodium chloride and extracted with chloroform ( 3 x 5 ml). The celite pad was throughly washed with chloroform (4 x 10 ml). The combined organic extracts were dried and evaporated in vacuo to afford a semi-crystalline solid. Purification by preparative t.l.c. (methylene chloride : light petroleum = 1:10) gave a clear crystalline solid (22 mg; 38%). The i.r. and n.m.r. spectral data of this compound were identical to those of authentic bicyclo(2.2.1)heptan-2-one. Its m.p. and mixed m.p. with 2-norbornanone were 87-89°.

Cyclobutane carboxylic acid

1,1-Cyclobutanedicarboxylic acid was decarboxylated to cyclobutane carboxylic acid (b.p. 192-194° lit.[238] 191-193.5°) in 91% yield as described by Heisig and Stodola.[238]

Cyclobutylphenylketone

This ketone (b.p. 78-80°/0.5 torr; lit.[237] 78-82°/0.7 torr) was prepared in 42% yield from cyclobutane carboxylic acid according to a published procedure.[237]

2-Hydroxy-2-phenylbicyclo(1.1.1)pentane (122)

The following method of preparation is essentially that reported by Padwa.[142] A solution of cyclobutylphenylketone (1.0 g; 6.3 mmol) in benzene (400 ml) under a nitrogen atmosphere was irradiated at ambient temperature with a 450 W mercury lamp inside a Pyrex filter sleeve. The progress of the reaction was monitored by removing aliquots for g.l.c. analysis (column D, 150°). The reaction was complete after approximately 40 hr. The benzene was removed by evaporation under reduced pressure at 15°.

A total of 2.60 g of cyclobutylphenylketone was subjected to photolysis as described above. The combined residues were distilled (65-68°/0.2 torr) through a short column to give a colourless oil. This oil was subjected to preparative g.l.c. (column D, 150°).

The first material to be eluted was 1-phenyl-4-penten-1-one (231) identified by comparing the spectral data with those reported for an authentic sample.[142] Similarly, the second material eluted was shown to be a small quantity of starting material. The third and major product collected was a viscous oil which slowly solidified on standing.

Comparisons of i.r. and n.m.r. data with those reported,[142] identified the compound as 2-hydroxy-2-phenylbicyclo(1.1.1)pentane (122). The alcohol was further purified by sublimation at 55°/0.1 torr to give the alcohol as a white solid (600 mg; 23%)(m.p. 63-64.5°; lit.[142] 64-65°).

It was found that compound of sufficient purity for further reaction could be obtained in higher yield (51%) by distillation of the residues from the photolysis through an eight inch spinning band column, obviating the need for preparative chromatography and sublimation procedures.

Cyclobutylphenylmethanol

Cyclobutylphenylmethanol (b.p. 88-90°/0.8 torr; lit.[241] 121-122/5.0 torr) was prepared in 72% yield from lithium aluminium hydride and cyclobutylphenylketone by a literature method.[241]

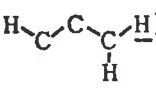
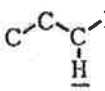
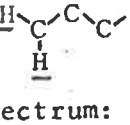
Metal-ammonia reduction of 2-hydroxy-2-phenylbicyclo(1.1.1)pentane (122)

2-Hydroxy-2-phenylbicyclo(1.1.1)pentane (122)(100 mg; 0.63 mmol) and ethanol (0.05 ml; 63 mg; 1.4 mmol) were added to freshly distilled ammonia (3 ml). Sodium (32 mg; 1.4 mmol) was added in small pieces and the blue solution stirred at -78° for 45 min. The ammonia was allowed to evaporate. Brine (5 ml), cooled to 0°, was added to the residue and the resultant solution extracted with ether (2 x 3 ml). The combined organic extracts were dried and the ether was removed by distillation. Distillation of the colourless residue (89-90°/1.0 torr) gave a viscous oil (62 mg; 61%) whose boiling point and i.r. spectrum were identical to those of cyclobutylphenylmethanol.

2-Phenyl-2-O-tetrahydropyranylbicyclo(1.1.1)pentane (143)

2-Hydroxy-2-phenylbicyclo(1.1.1)pentane (122)(59 mg; 0.37 mmol) was dissolved in 2,3-dihydropyran (0.5 ml) and a catalytic amount of p-toluenesulphonic acid was added. The solution was stirred at ambient temperature for 1 hr. Anhydrous potassium carbonate (50 mg) was added and the mixture stirred for a further 16 hr. The salts were separated by filtration and the excess dihydropyran was removed by distillation to give a colourless oil. Careful bulb to bulb distillation ($73^{o}/2.0$ mm) gave the pure ether (30 mg; 33%).

i.r. (film): 1195, 1175, 1145, 1125, 1110, 1070, 1050, 1020, 995, 970 $cm^{-1}$

$^{1}H$ n.m.r. ($CCl_4$): δ7.30 (s, 5H, aromatic protons); 4.38-4.20 (complex, 1H, O-CH-O); 3.93-3.27 (complex, 2H, $-CH_2-O-$); 3.03 (s, 1H, bridgehead proton); 2.98 (s, 1H, bridgehead proton); 2.88 (complex dd, 1H  ); 1.73 (d, 2Hz, 1H,  ); 1.68-1.25 (complex, 8H, $-\underline{CH_2}-\underline{CH_2}-\underline{CH_2}-$ +  ).

mass spectrum: m/e 160. ($M^{+} - C_5H_8O$ calculated for $C_{16}H_{20}O_2$ = 160) Thermal cracking of tetrahydropyranyl ethers to the parent alcohols can occur in the inlet system of mass spectrometers.[242]

analysis: Found C, 79.04; H, 8.27. $C_{16}H_{20}O_2$ requires C, 78.65; H, 8.25.

Attempted metal-ammonia reduction of 2-phenyl-2-O-tetrahydropyranyl-bicyclo(1.1.1)pentane (143)

2-Phenyl-2-O-tetrahydropyranylbicyclo(1.1.1)pentane (143)(59 mg; 0.24 mmol) and ethanol (0.02 ml; 0.53 mmol) were dissolved in freshly distilled ammonia (2 ml). Sodium (12 mg; 0.52 mmol) was added in small

pieces and the blue solution stirred at -78° for 1 hr. The ammonia was allowed to evaporate. Cold water (2 ml) was added and the resultant solution extracted with ether (2 x 5 ml). The combined organic extracts were dried ($K_2CO_3$) and the ether was removed by distillation. The i.r. spectrum of the colourless oil obtained (41 mg; 70%) was identical to that of the starting material (143).

Hydrogenolysis of 2-hydroxy-2-phenylbicyclo(1.1.1)pentane (122)

2-Hydroxy-2-phenylbicyclo(1.1.1)pentane (122)(1.1 g; 6.9 mmol) was dissolved in ethylacetate (3 ml) and a catalytic amount of 5% palladium on carbon added. The mixture was placed under an atmosphere of hydrogen and stirred at ambient temperature for 20 hr by which time one molar equivalent of hydrogen had been absorbed. The catalyst was removed by filtration through a celite pad and the solvent was evaporated. Distillation of the residue gave n-butylphenylketone (830 mg; 74%) (b.p. 75-79°/1.0 torr) which was identified by spectral comparison with authentic material.

Stability of 2-hydroxy-2-phenylbicyclo(1.1.1)pentane (122) in ethylacetate

2-Hydroxy-2-phenylbicyclo(1.1.1)pentane (122)(20 mg; 0.13 mmol) was dissolved in ethylacetate (0.5 ml) and allowed to stand at ambient temperature for 20 hr. The solvent was removed by evaporation to give a viscous oil. Spectral data and g.l.c. analysis (column E, 150°) indicated that the compound was unchanged alcohol (122). The alcohol (122) was recovered in 95% yield.

Attempted hydrogenolysis of cyclobutylphenylketone

Cyclobutylphenylketone (100 mg; 0.63 mmol) was dissolved in ethylacetate (1 ml) and a catalytic amount of 5% palladium on carbon added. The mixture was stirred under an atmosphere of hydrogen at ambient temperature for 20 hr by which time an insignificant quantity of hydrogen had been absorbed. The catalyst was removed by filtration through a celite pad and the solvent was evaporated. Distillation (79-80°/0.5 torr) of the residue gave the unchanged cyclobutylphenylketone (69 mg; 69%).

Hydrogenation of 1-phenyl-4-penten-1-one (231)

1-Phenyl-4-penten-1-one (231)(25 mg; 0.16 mmol) was dissolved in ethylacetate (2 ml) and a catalytic amount of 5% palladium on carbon added. The mixture was placed under an atmosphere of hydrogen and stirred at ambient temperature for 20 hr by which time one molar equivalent of hydrogen had been absorbed. The catalyst was removed by filtration through a celite pad and the solvent was evaporated to give n-butylphenylketone (18 mg; 70%), identified by comparison with authentic material.

The reaction of 2-hydroxy-2-phenylbicyclo(1.1.1)pentane (122) with borane

2-Hydroxy-2-phenylbicyclo(1.1.1)pentane (122)(300 mg; 1.9 mmol) was dissolved in tetrahydrofuran (5 ml) under a nitrogen atmosphere and the solution cooled to 0°. Borane solution (1.57 M; 1.2 ml; 1.9 mmol) was added dropwise over 1 hr. The mixture was stirred for an additional 1 hr while allowing the temperature to rise to 25°. To this was added $BF_3$-etherate (0.03 ml), and the mixture was stirred at ambient temperature

for 15 hr. Water (2 ml) was cautiously added and the resultant aqueous solution extracted with hexane (3 x 5 ml). The combined organic extracts were washed with brine (3 x 10 ml) and then dried. The hexane was removed by distillation to give a yellow oil. The oil was found to consist of at least two compounds by g.l.c. analysis (column D, 150°) which were collected in very low yield by preparative g.l.c. (column D, 150°). Although no structural assignments were made, the P.F.T. n.m.r. spectrum of each indicated that neither of the new compounds had a spectrum consistent with the required 2-phenylbicyclo(1.1.1)pentane (142).

1,5-Hexadien-3-ol

1,5-Hexadien-3-ol (b.p. 64-66°/35 torr; lit.[265] 38-39°/11 torr) was prepared in 65% yield according to a published procedure.[265]

Bicyclo(2.1.1)hexan-2-one (158)

The photolysis of 1,5-hexadien-3-one, prepared by the oxidation of 1,5-hexadien-3-ol,[173b] gave bicyclo(2.1.1)hexan-2-one (158)(b.p.54-56°/17-19 torr; lit.[173b] 56-58°/20 torr) in 10% yield (from 1,5-hexadien-3-ol).[173b]

Attempted bromination of bicyclo(2.1.1)hexan-2-one (158) with free bromine

A solution of bicyclo(2.1.1)hexan-2-one (158)(210 mg; 2.2 mmol) in carbon tetrachloride (2 ml) was cooled to 0° and bromine (440 mg; 2.8 mmol) in carbon tetrachloride (2 ml) was added dropwise. The mixture was allowed to warm to ambient temperature and maintained there for 18 hr. The mixture was washed with sodium thiosulphate solution until the colour

was discharged. The organic layer was dried. G.l.c. analysis (column D, 100°) revealed only one peak whose retention time was identical to that of the ketone (158). The solvent was removed by distillation. Distillation of the residue (b.p. 54-56°/18 torr) gave the unchanged ketone (158)(190 mg; 90 %).

dl-endo-3-bromo-1,7,7-trimethylbicyclo(2.2.1)heptan-2-one

Cupric bromide (11 g; 50 mmol) in ethylacetate (25 ml) was brought to reflux and dl-camphor (4.6 g; 30 mmol) in boiling chloroform (25 ml) was added all at once. The mixture was heated under reflux for 90 hr by which time the black copper salt had turned white and the colour of the solution had changed from green to amber. The salt was removed by filtration and the organic solvents were removed by evaporation. Column chromatography (methylene chloride : light petroleum = 1:1) gave a white solid (3.7 g; 53%) identical in all respects to authentic bromocamphor.[254]

Attempted bromination of bicyclo(2.1.1)hexan-2-one (158) with cupric bromide

Cupric bromide (600 mg; 2.7 mmol) in ethylacetate (1.5 ml) was brought to reflux and bicyclo(2.1.1)hexan-2-one (158)(150 mg; 1.6 mmol) in boiling chloroform (1 ml) was added all at once. The mixture was heated under reflux for 72 hr by which time there had been no colour change either in the salt or solution. The salt was removed by filtration. G.l.c. analysis (column D, 100°) of the organic solution revealed only one peak whose retention time was identical to that of the ketone (158). The solvents were removed by distillation. Evaporative distillation of the residue (54-60°/19 torr) gave the unchanged ketone (158)(130 mg; 87%).

Attempted formylation of bicyclo(2.1.1)hexan-2-one (158)

A mixture of bicyclo(2.1.1)hexan-2-one (158)(400 mg; 4.2 mmol) and ethylformate (630 mg; 8.5 mmol) was added dropwise to a stirred slurry of sodium methoxide (230 mg; 4.3 mmol) in benzene (8 ml) at 0° over a 30 min period. The ice bath was removed and the mixture stirred for 16 hr at ambient temperature. The mixture was extracted with 1 N sodium hydroxide solution (3 x 8 ml). The organic layer was dried and the benzene removed by distillation to give a pale yellow oil whose i.r. spectrum was identical to that of the starting material. The alkaline extract was acidified with 6 N hydrochloric acid and extracted with ether (3 x 10 ml). The combined organic extracts were dried and the ether was removed by distillation to give a small quantity of pale yellow oil. This oil was shown to be unchanged starting material by g.l.c. analysis (column D, 100°).

Attempted oxidation of bicyclo(2.1.1)hexan-2-one (158)

A mixture of bicyclo(2.1.1)hexan-2-one (158)(100 mg; 1.04 mmol) and selenium dioxide (130 mg; 1.2 mmol) in dioxan (5 ml) was cooled to 10° and water (0.060 ml) added. After the addition the mixture was heated under reflux for 6 hr. The mixture was filtered through a celite pad. G.l.c. analysis of the filtrate (column D, 100°) indicated that only unchanged starting material was present. The dioxan was removed by distillation to give a yellow oil. Evaporative distillation (55-57°/20 torr) of the residue gave the unchanged ketone (158)(55 mg; 55%).

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