12/10/76

SYNTHESIS OF ICEANE AND OXA-ICEANE

A THESIS

PRESENTED FOR THE DEGREE OF

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in

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by

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CONTENTS

Summary

Tetracyclo[5.3.1.$1^{2,6}0^{4,9}$]dodecane (iceane) (1) and an oxygen analogue 3-oxa-tetracyclo[5.3.1.$1^{2,6}0^{4,9}$]dodecane (oxaiceane) (46) have each been synthesized via the same key olefinic ketone (40).

Chapter 2 describes the synthesis of the bromo-cyclopropyl ketone (39) and its successful cleavage by means of a new efficient fragmentation reaction using liquid sodium-potassium alloy to give the olefinic ketone (40), the structure of which was confirmed by independent synthesis.

Chapter 3 details the synthesis of iceane. Because of complications due to intramolecular reactions, the carbon skeleton was developed first, via the diolefin (58), before the functionality necessary to continue the synthesis was introduced. In an attempt to optimize some of the reactions associated with the synthesis, limonene (70) was chosen as a model compound for the diolefin (58). Selective hydroboration of (58) gave the olefinic alcohol (59) which was cyclized using triphenylphosphine in carbon tetrachloride to give a mixture of the epimeric chlorides (83) and (85) of iceane.

Chapter 4 describes the synthesis of oxaiceane (46) and a structural isomer *abeo*-oxaiceane (89) by the oxymercuration-sodium borohydride reduction of the olefinic alcohol (45). The structures

of these cyclic ethers were differentiated by the use of a chiral nmr shift reagent. Sodium-amalgam reduction was used to show that the intermediate mercury compound in the preparation of oxaiceane had a mercury atom in the prow position of a ring in a boat configuration. The mercury salt was isolated and used to investigate the stereospecificity of its reduction with sodium borodeuteride.

Chapter 5 describes an investigation of the products obtained from the acid-catalysed opening of the cyclopropyl ring of tetracyclo[5.3.1.$0^{3,5}0^{4,9}$]undecan-2-one (23) in aqueous acetic acid.

STATEMENT

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

Garry F. Taylor.

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Dr. D.P.G. Hamon whose teaching, guidance and enthusiastic encouragement during the supervision of this work was invaluable.

I would also like to thank my colleagues in the Department for their many rewarding discussions as well as their congenial comradeship.

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

I am indebted to my fiance for her assistance and understanding during the composition of this Thesis and to my mother for her undying patience, sacrifices and encouragement during the course of my studies.

PUBLICATIONS

Part of the work described in this Thesis has been reported in the following publications:

1. "Preparation of Some Bicyclo[3.3.1]nonane Derivatives from Adamantanone", D.P.G. Hamon and G.F. Taylor, J.Org.Chem., 39, 2803 (1974).

2. "A Synthesis of Tetracyclo[5.3.1.$0^{3,5}0^{4,9}$]dodecane (Iceane)", D.P.G. Hamon and G.F. Taylor, Tetrahedron Lett., 155 (1975).

3. "Oxaiceane and *Abeo*-oxaiceane", D.P.G. Hamon, G.F. Taylor and R.N. Young, Tetrahedron Lett., 1623 (1975).

4. "Reactions of γ-Haloketones with Sodium-Potassium Alloy; A New Fragmentation Reaction", D.P.G. Hamon, G.F. Taylor and R.N. Young, "Synthesis", 428 (1975).

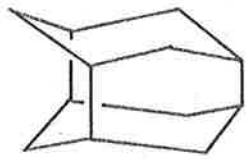
5. "The Synthesis of Tetracyclo[5.3.1.$1^{3,5}0^{4,9}$]undecan-2-one and the Acid Catalysed and Reductive Cleavages of the Cyclopropyl Ring", D.P.G. Hamon and G.F. Taylor, Aust.J.Chem., 28, 2255 (1975).

6. "Mercury and Chloro Groups in the Prow Position of Non-twist Boat Configurations", submitted for publication.

CHAPTER 1

INTRODUCTION

Bridged polycyclic hydrocarbons of high symmetry and unusual structure continue to be a challenging synthetic objective to the organic chemist.[1-11] Tetracyclo[5.3.1.$1^{2,6}0^{4,9}$]dodecane (1)[12] is particularly interesting in this regard.



(1)

This $C_{12}H_{18}$ structure was originally conceived by Muller[13] in 1940. In 1965 Fieser[14] coined the trivial name "iceane" for this molecule because of its superficial similarity to one of the crystalline forms of water. Ganter[15] has since called the molecule "wurtzitane" because of a similarity to the wurtzite structure. The name iceane is the more common however and will be used throughout this thesis.

Iceane is a highly symmetrical (point group D_{3h}) rigid molecule with a carbon skeleton consisting of two chair cyclohexanes connected to each other by three axial bonds. It thus possesses

five six membered rings, two of which exist in chair configurations and three in non-twist boat configurations. Although molecular models indicate that the structure is free of skeletal strain, presumably the molecule has within it severe non-bonded interactions. It was expected therefore that iceane would possess unusual structural parameters and chemical properties as well as presenting a synthetic challenge.*

Because of the six-fold inversion axis of symmetry, there are only three different types of hydrogen atoms, two different types of carbon atoms and two distinct types of C-C bonds in the iceane structure. This high degree of symmetry allows considerable simplification of the synthetic problem.

Retrosynthetic analysis[18] provides two classes of substructure each containing three six-membered rings. Compound (3) is suitably orientated for bond formation between two secondary carbon atoms, however, the formation of (3) would require that its precursor assume an orientation (3a) which is not thermodynamically favoured compared

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* A compound incorporating the iceane structure has recently been reported.[16] Moreover a compound incorporating the iceane structure except that silicon replaces carbon in the 1,3,5,7,9 and 11 positions has recently been isolated[17] from the pyrolysis products of tetramethylsilane.

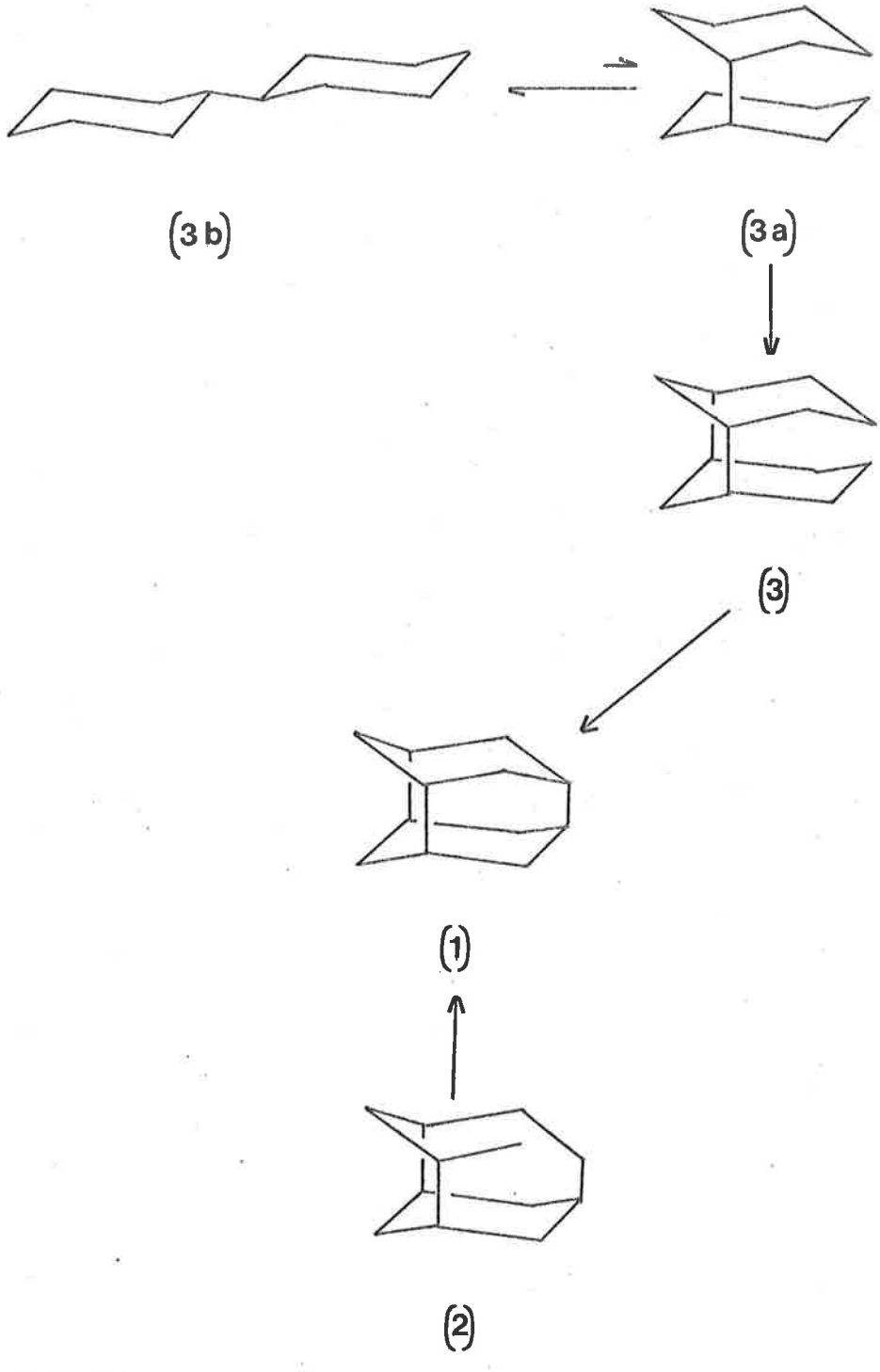


Figure 1

with an alternative orientation (3b). (figure 1). Compound (2) provides for the more facile process of joining a primary to a secondary carbon atom, however, stereochemical factors now become important. Intramolecular alkylation could only proceed provided a methylene carbon atom bearing a leaving group X had the configuration shown in structure (4) (figure 2).

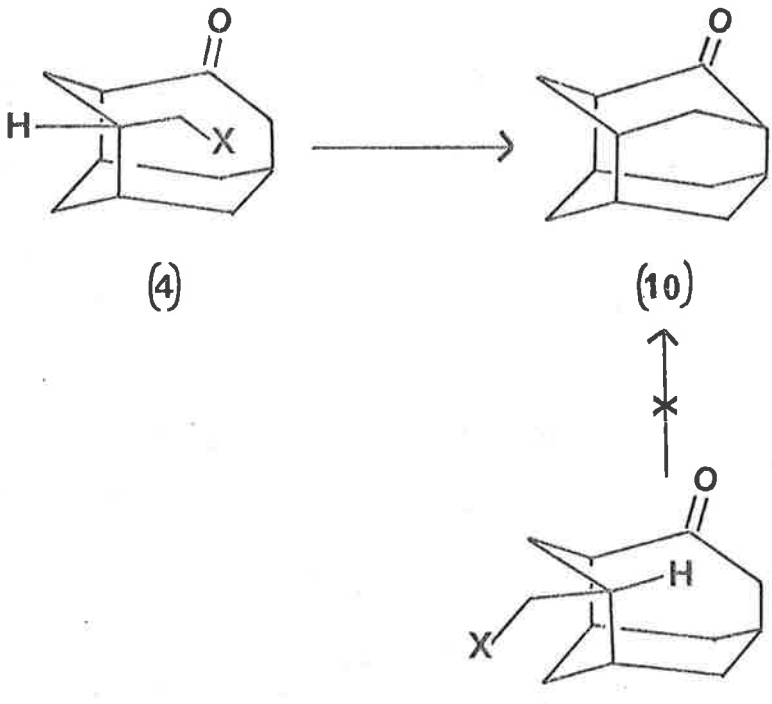


Figure 2

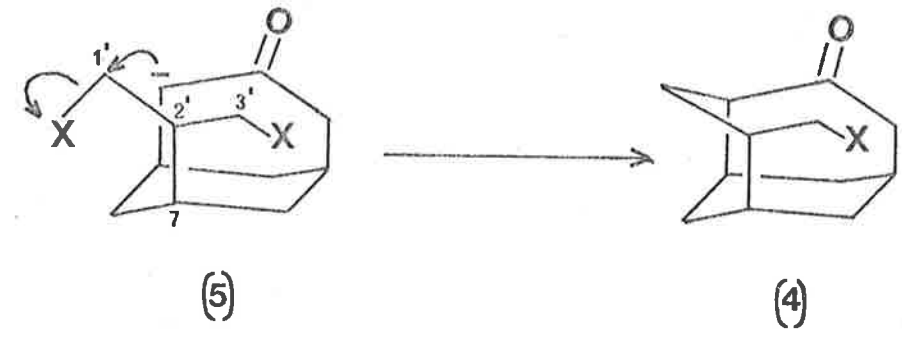
The use of alkylation reactions to form cyclic compounds as postulated in figure 2 has many precedents.[19-21] Consequently at this juncture in the retrosynthetic analysis, the route via

structure (2) seemed the more attractive and methods to overcome problems associated with structure (3) were not considered further.

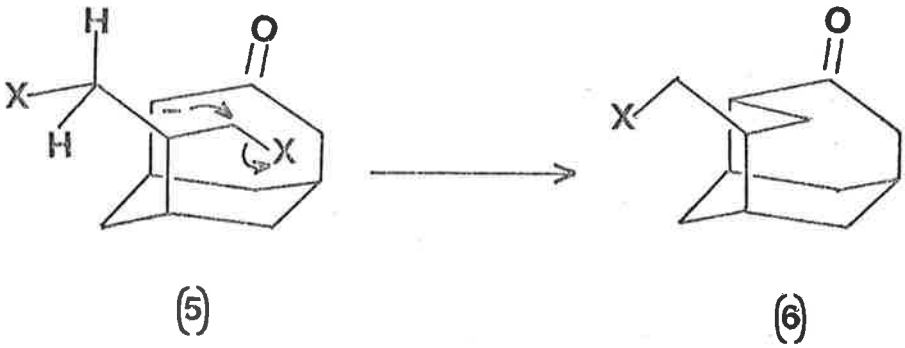
It was conceived that the tricyclic system (4) might be formed in a similar manner to (10) from a compound (5) possessing two leaving groups X. Two problems, however, immediately became apparent. Firstly for any cyclization to occur, it was essential that C2' have the *endo* configuration to allow intramolecular attack. Secondly, because of free rotation about the C2'-C7 bond, ring closure in ketone (5) would probably lead to (6) possessing the incorrect configuration to allow subsequent cyclization. (figure 3).

The second problem could be solved by making C2' a trigonal centre as in ketone (7). Both C2 and C4 in this compound are activated by the carbonyl group to enable the cyclizations to occur. Moreover alkylation could only occur at C1' to give the olefin (8) (or its mirror image). Since a bulky hydroborating agent should approach the double bond from the side of least steric congestion, hydroboration of the olefin (8) followed by oxidation should give the alcohol (9) possessing the correct stereochemistry to allow the second cyclization to occur. (scheme 1)

It was now obvious that the olefinic-ketone (7) had a similar atomic arrangement to the known[22-24] lactone (12) derived from adamantanone[25] (11). Treatment of this lactone with an appropriate

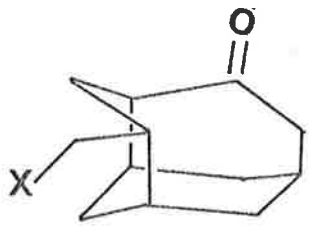


(5) (4)



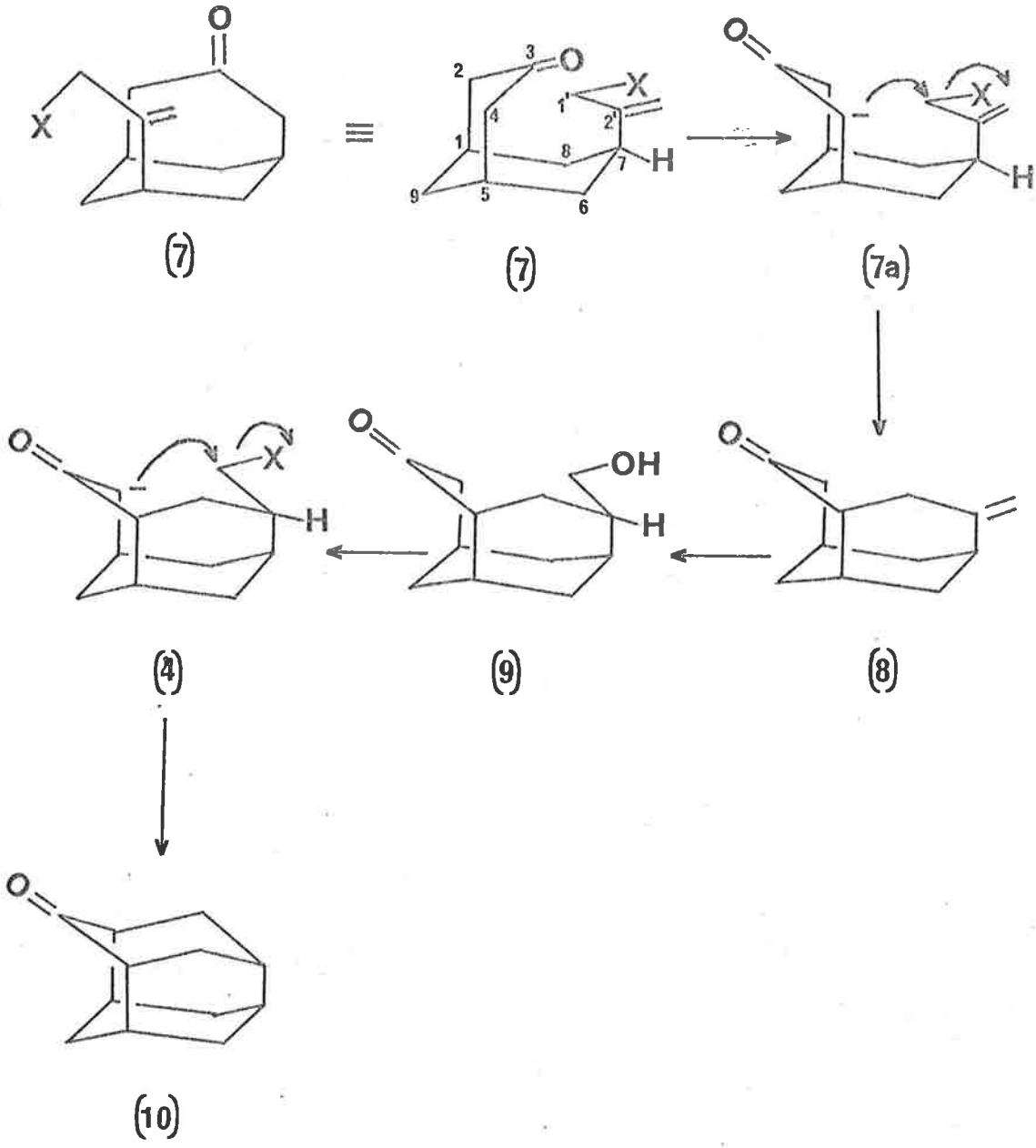
(5) (6)

III



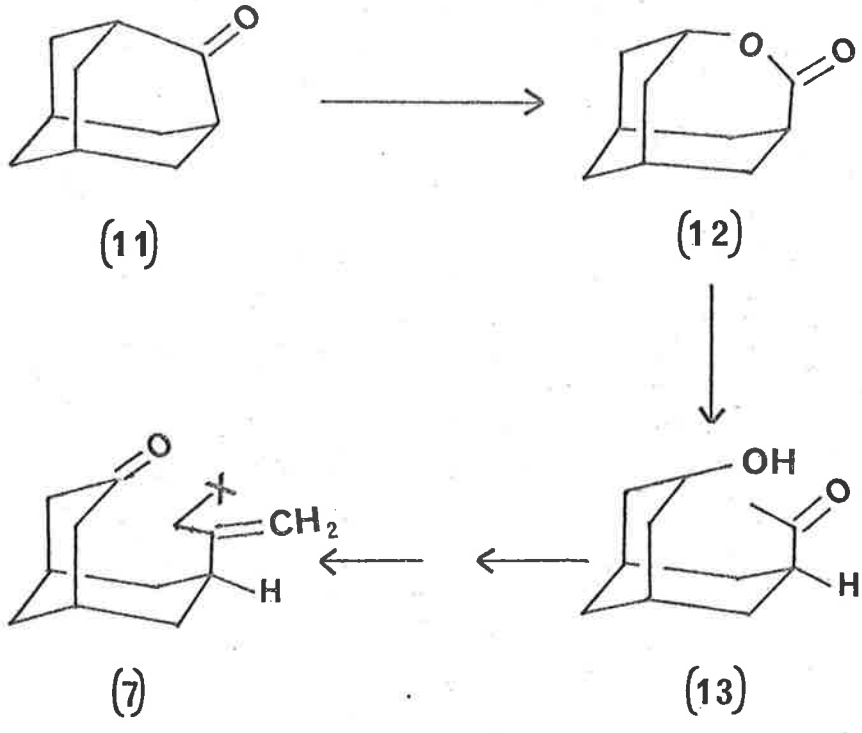
(6)

Figure 3



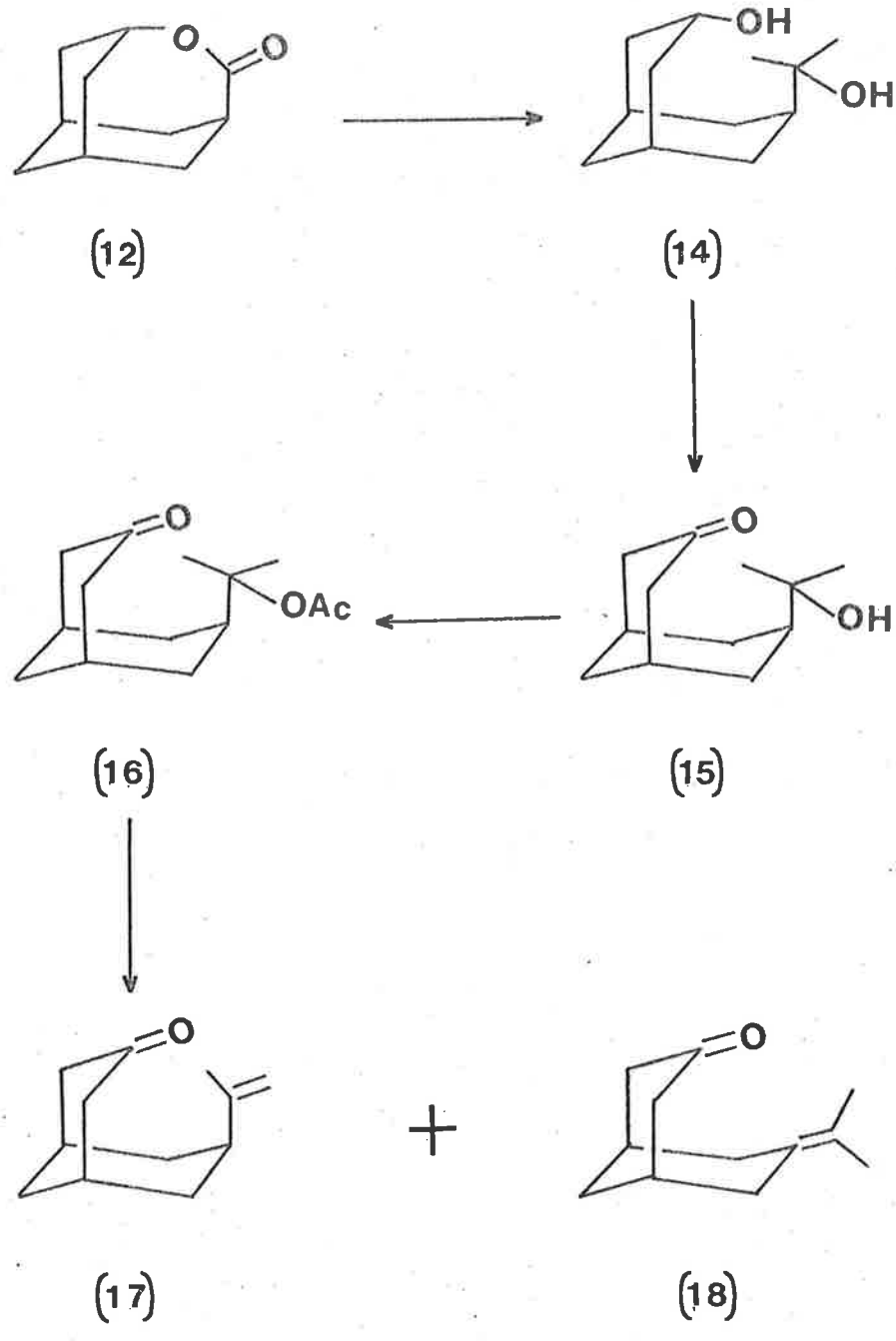
Scheme 1

organo-metallic compound should give the keto-alcohol (13) which appeared to be a suitable precursor to the key intermediate (7) (scheme 2).



Scheme 2

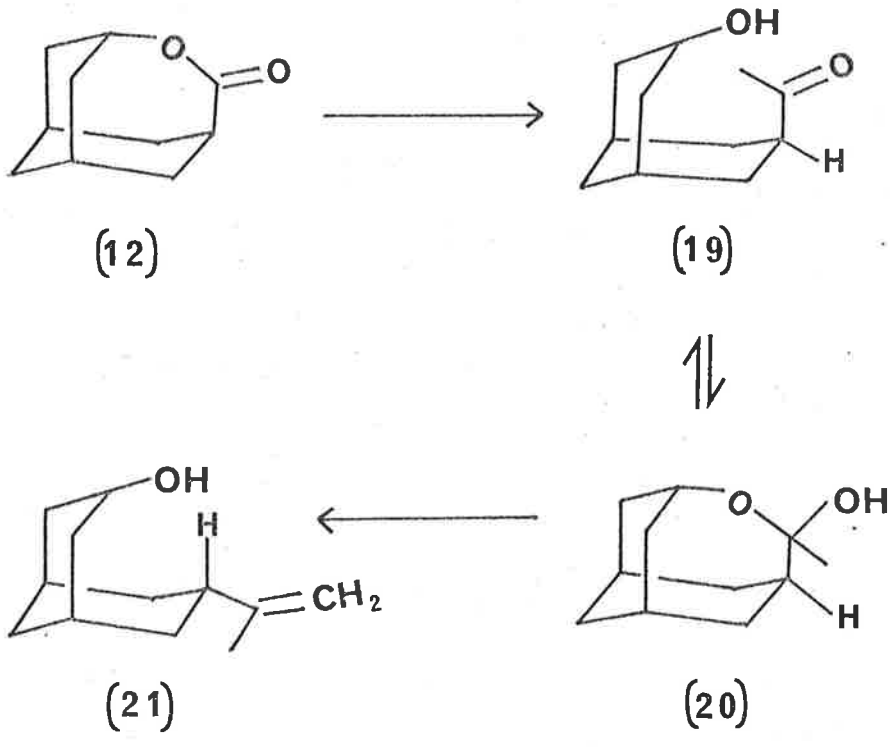
The formation of olefinic-ketone (7) in relation to the synthesis of iceane has been attempted without success by two different routes[26,27] prior to the work reported in this thesis. In the first approach[26] lactone (12) was treated with methyl lithium to give the diol (14) which on oxidation followed by acetylation gave the tertiary acetate (16) (scheme 3). Pyrolysis of the acetate yielded a mixture of the desired olefin (17)



Scheme 3

together with an isomer (18). Although these could be separated by chromatography, the yield of the olefin (17) was low and variable and an alternative route was sought.

In the second approach,[27] attempts were made to introduce the methylene group directly by a Wittig reaction and so bypass the pyrolysis. Addition of one equivalent of methyl magnesium iodide to the lactone (12) gave a monoadduct which existed as the ketol (19) in the crystalline form but which was in equilibrium with the hemiacetal (20) in solution (scheme 4).

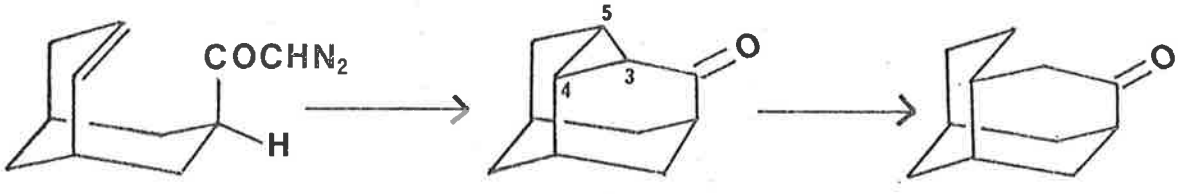


(12) (19) (21) (20)

Scheme 4

As a consequence of this equilibrium, all attempts to protect the secondary hydroxyl group and so expose the carbonyl group were thwarted. Furthermore reaction of the ketol (19) with methylene triphenylphosphorane gave the olefinic alcohol (21) which arose from a Wittig reaction only after prior epimerization of the ketone. Because the essential stereochemistry had been lost, this route was no longer viable.

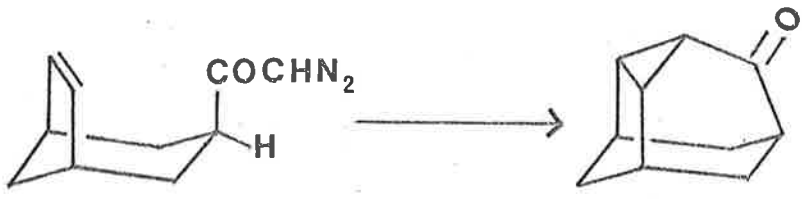
In another early approach[28] to the synthesis of iceane it was conceived that part of the carbon skeleton might be constructed by the intramolecular addition of a keto-carbonoid to a double bond. Obviously regioselective cleavage of the C3-C5 bond in the cyclopropyl ketone (23), derived from diazoketone (22), was necessary in order to produce the required basic skeleton.



(22) (23) (24)

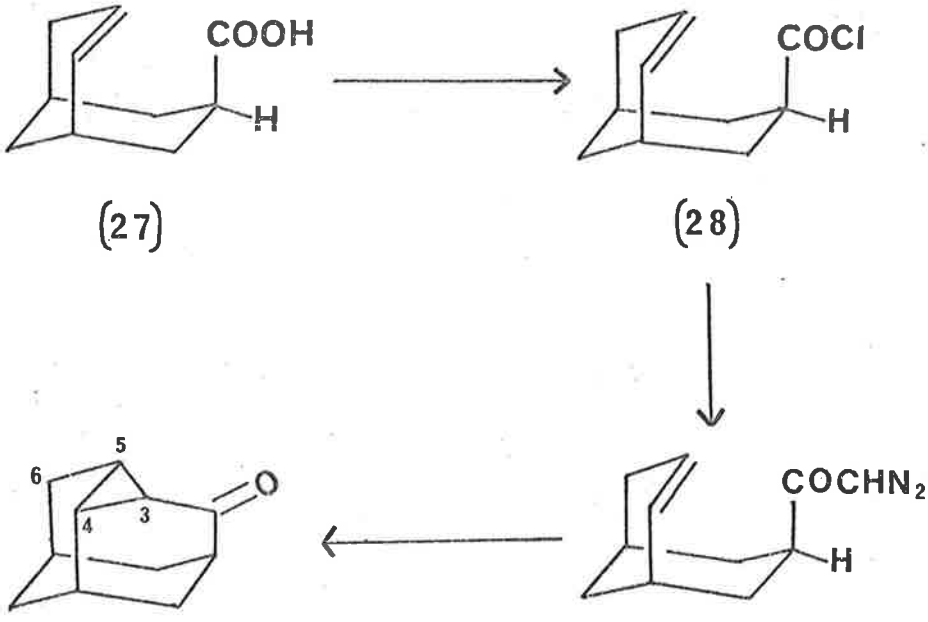
Numerous examples of the use of keto-carbonoid addition reactions have appeared since the original development of this idea,[29] but probably the closest analogy for the present

consideration was the production[30] of 8,9 dehydroadamantanone (26) from the diazoketone (25).



(25) (26)

The cyclopropyl ketone (23) was formed via the olefinic acid (27),[31] its acid chloride (28) and the diazoketone (22)(scheme 5).

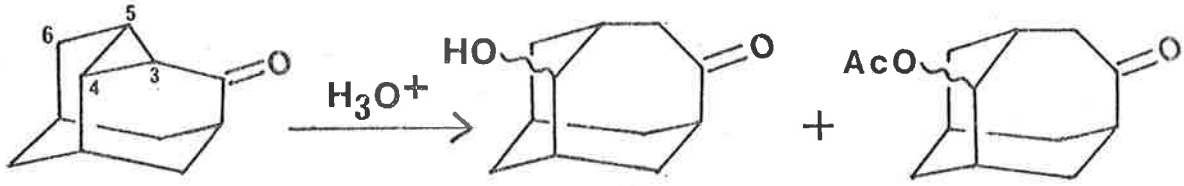


(27) (28) (22) (23)

Scheme 5

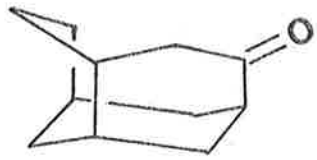
If cleavage of the cyclopropyl ring in ketone (23) was to provide a suitable synthetic route to iceane, not only had rupture of the C3-C5 bond to occur, but it was also necessary that suitable functionality be introduced at C5 and/or C6 in order that the synthesis could be conveniently continued.

Under acidic conditions,[28] cleavage of the C3-C4 bond appeared to give the keto-alcohol (29) and keto-acetate (30) both of which had the undesired homoadamantane[32-36] type carbon skeleton.



(23) (29) (30)

Reduction of the cyclopropyl ketone (23) with lithium in liquid ammonia gave the dihydroketone (24).[28] This compound, however, lacked sufficient functionality for convenient bond formation at C6.



(24)

A major part of the work presented in this thesis follows from these two unsuccessful approaches to iceane. It concerns the synthesis of a cyclopropyl compound which not only showed regio-specific[37] cleavage to give a structure having the desired carbon skeleton, but which also possessed the functionality required for further elaboration to the desired goal. The rationalization behind the predicted mode of cleavage to afford such a key compound will now be presented.

It has been shown[38-41] that in the cleavage of cyclopropyl rings by dissolving metals, stereoelectronic factors play an important role in controlling which bond of the cyclopropyl ring is broken. Usually[40] the bond which ruptures is that which best overlaps with the π system of the carbonyl group,* particularly when, as in the

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* In the case of acid-catalysed cleavage[42-48] one cannot say with certainty which bond of the cyclopropyl ring will break.

case under discussion, the resulting carbanions from the two feasible cleavages are electronically equivalent.* From a study of a model of cyclopropyl ketone (23) it was seen that the C3-C5 bond had the optimal configuration for overlap of its σ orbital with the π orbital of the carbonyl group, whereas the σ orbital of the C3-C4 bond lay effectively in the nodal plane of that system.

The reduction of cyclopropyl ketone (23) was thought to follow the path[53-55] illustrated in figure 4 where X = H. The addition of an electron to the carbonyl group could give the

(31) (32)

Figure 4

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* It has been shown[49-52] however, that in cases where the difference in overlap is marginal, the stability of the incipient carbanion may control the direction of ring scission.

radical anion[56-58,107] (31) which could then undergo fragmentation* to give the incipient carbanion (32) with concomitant protonation by ammonia.

It was thought that it might be possible to trap the intermediate radical anion (32) by the incorporation of a leaving group. For example if X was a halogen atom, elimination to the olefin might occur, particularly in the absence of a proton source.

After the completion of the work for this thesis, it was learned that Le Bel and Liesemer[62] had treated the bromo-ketone (33) with lithium in liquid ammonia and had in fact obtained complete directional control for the cleavage of the C1-C2 bond to give the olefinic ketone (36) (figure 5).

They postulated that the reaction proceeded via the intermediate radical anion (34) which on fragmentation and expulsion of the bromine gave the enolate (35).

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* Although 70% of the unpaired electron density has been shown[59-60] to be located on carbon, recent work[61] has indicated that the fragmentation is anionic and not radical.

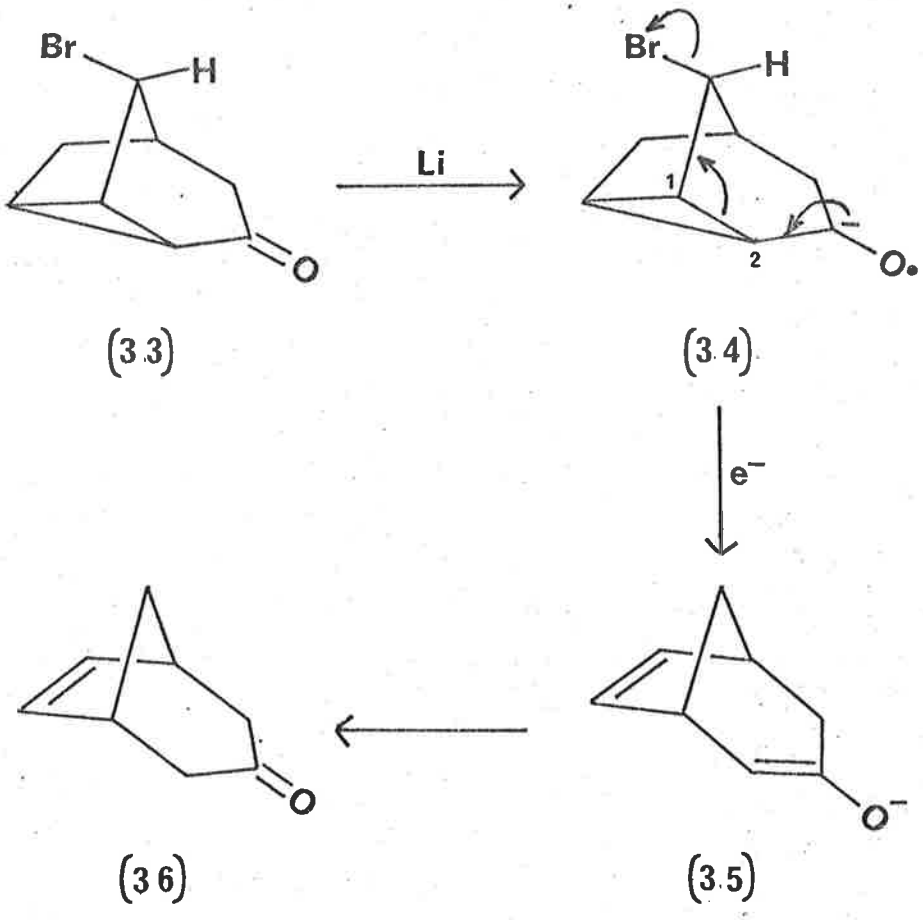
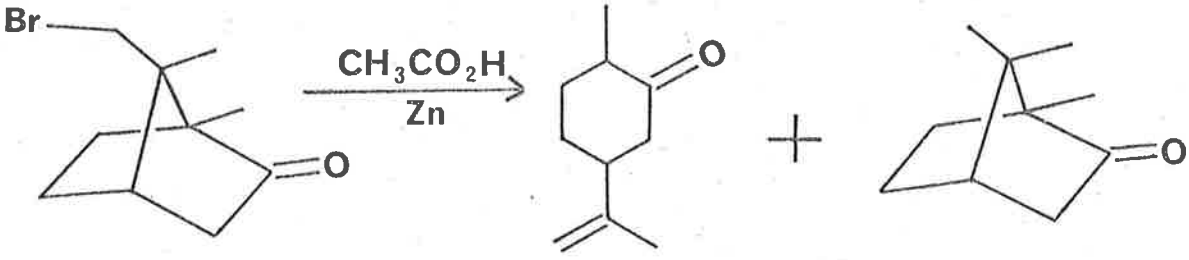


Figure 5

A similar reaction using zinc in acetic acid has also been observed[63] as a minor pathway in the reduction of 9-bromobornan-2-one (37) to dihydrocarvone (38).

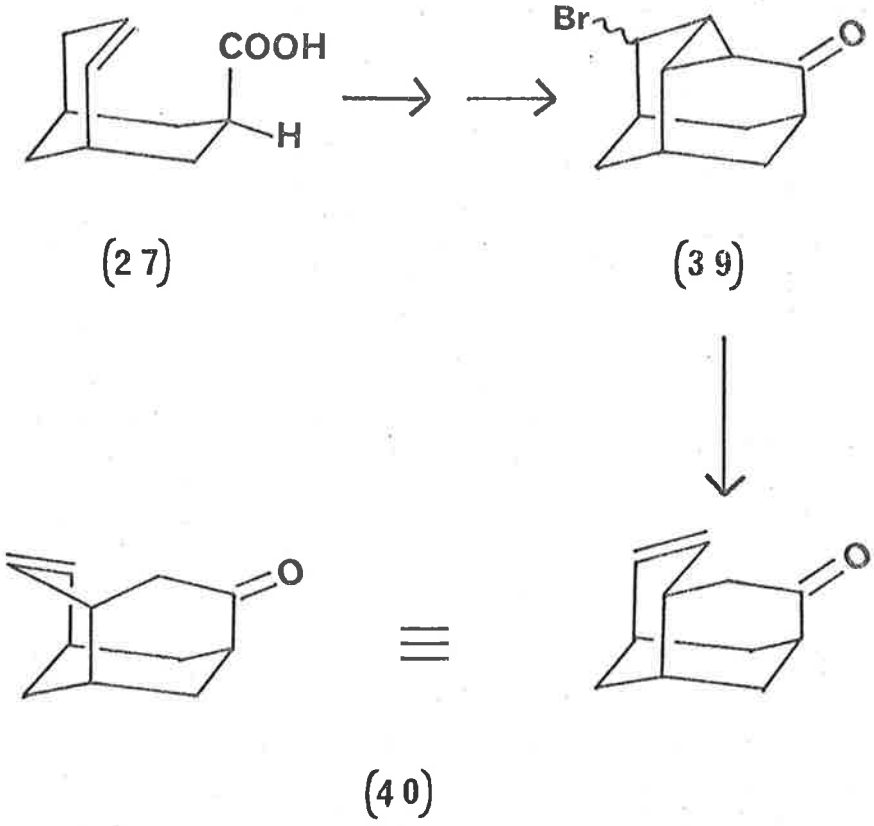
The fact that the reduction potential for carbon-halogen bonds is usually less negative than the potential required to reduce aliphatic ketones,[64-65] suggests that the reduction of



(37) (38) 14%

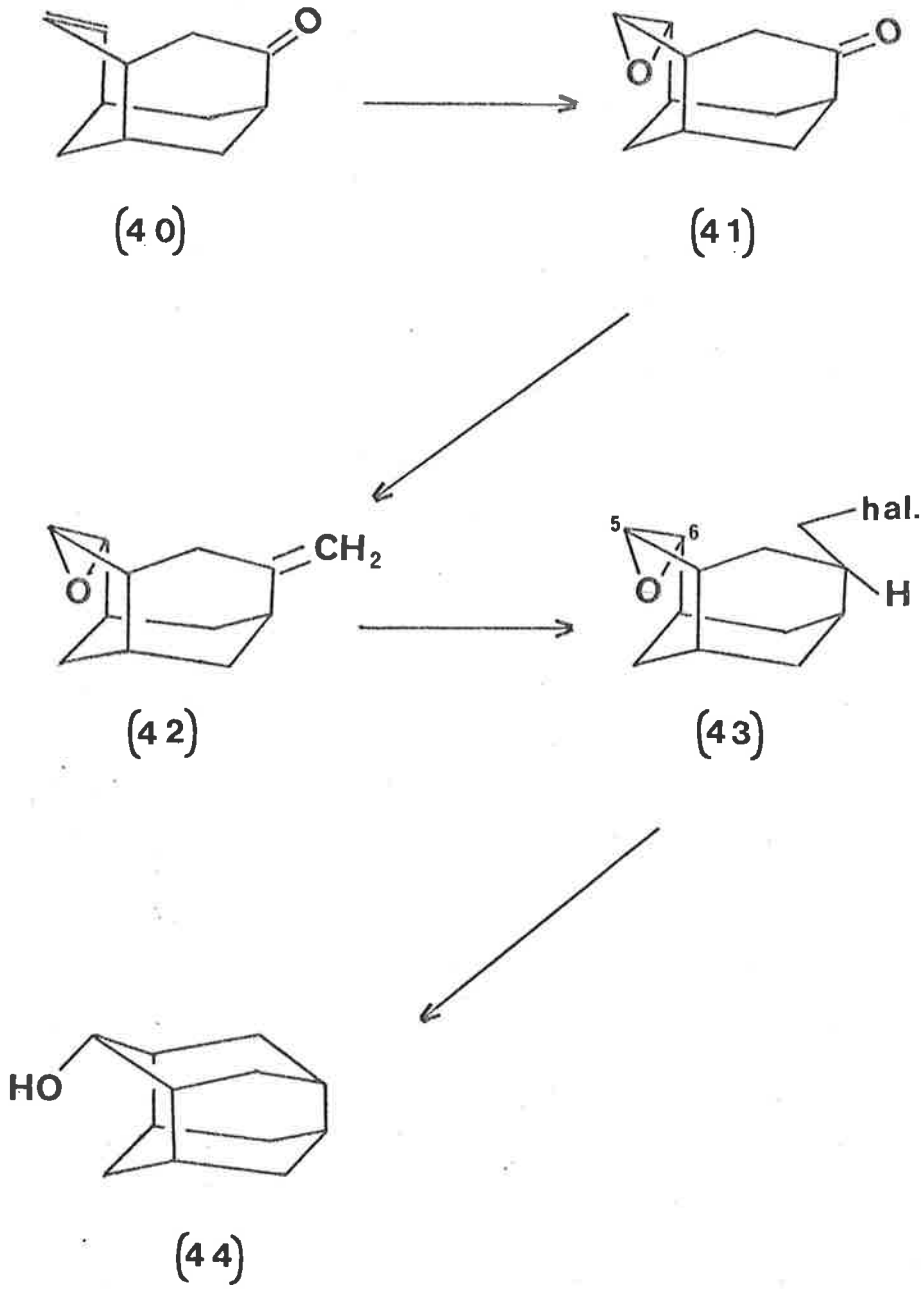
halo-ketones may involve an initial interaction with the carbon halogen bond. So long as the desired cyclopropyl bond is cleaved, however, the actual direction of electron movement is incidental for the purpose in hand.

It was thought that the bromocyclopropyl ketone (39) would be a suitable compound to investigate the above theories. It could possibly be synthesized in the same way[28] as the unbrominated species (23) following allylic bromination of the olefinic acid (27).[31] Ring opening of this compound in the manner described above would give, possibly after oxidation of any alcohol formed by over reduction, the olefinic ketone (40) having the structure required to enable the synthesis to be continued.



(27) (39) (40)

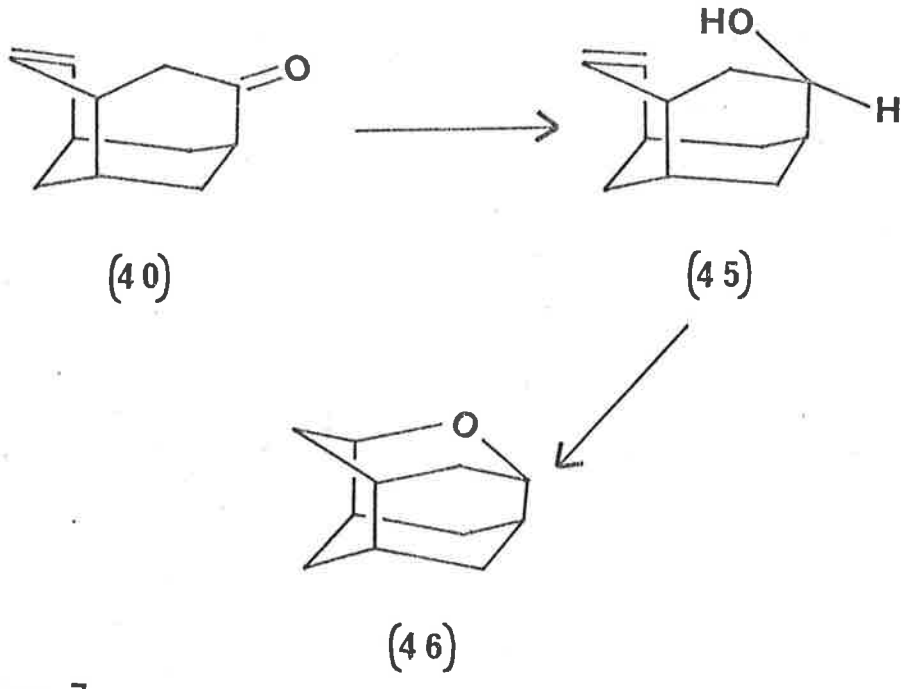
This scheme consequently leads to a different key intermediate to that suggested in schemes 1 and 2. It was conceived that the olefinic ketone (40) could be converted to the keto-epoxide (41) and then by a Wittig reaction to the olefinic-epoxide (42). Hydroboration of the olefin, followed by halogenation, should give the primary halide (43) with the stereochemistry required to allow an intramolecular alkylation in the presence of a metal,[66-68] to give the



Scheme 6

cyclized alcohol (44) (scheme 6). It was thought that diaxial opening[69-71] of the epoxide at C6 should predominate since attack at this position was the less sterically congested.

It was conceived that the key olefinic-ketone (40) could also be used in a synthesis of an oxygen analogue of iceane, namely oxaiceane (46). By analogy with the hydroboration of the olefin (42), metal hydride reduction of the ketone (40) should give the alcohol (45) having the stereochemistry required to allow an oxymercuration-reduction[72-76] reaction to afford the cyclic ether (46) (scheme 7).



(40) (45) (46)

Scheme 7

Chapter 2 of this thesis describes the synthesis of the bromocyclopropyl ketone (39) together with the method which was developed to successfully cleave the C3-C5 bond of the cyclopropane ring and so provide the key keto-olefin (40).

Chapters 3 and 4 describe how the key intermediate (40) was used to successfully synthesize both iceane and oxaiceane together with an oxa-structural isomer, *abeo*-oxaiceane.* In chapter 4 it is shown that the intermediate mercury compound in the preparation of oxaiceane has a mercuri group in the prow-position of a ring in the boat configuration.

In chapter 5 the products obtained from the acid catalysed opening of the unbrominated-cyclopropyl ketone (23)[28] are closely examined. The structure and stereochemistry of these compounds are determined beyond doubt by confirmatory reactions and independent synthesis.

After the work which is presented in this thesis was essentially complete, two other syntheses of iceane[78,79] and one

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* This trivial name is suggested after the nomenclature for steroids.[77]

of oxaiceane[15] appeared in the literature in addition to the preliminary communications[80,81] of our own syntheses.

CHAPTER 2

The synthesis of Tricyclo[5.3.1.$0^{4,9}$]undec-5-en-2-one (40)

The known[31] olefinic acid (27) was brominated in the allylic position to the double bond with N-bromosuccinimide in almost quantitative yield to give the bromo-acid (47) (m.p. 156-158°). However unless rigorously purified[82] N-bromosuccinimide was used and the reaction mixture was allowed to come to reflux without stirring, the known[83] bromo-lactone (48) was the only product observed. It was presumed that with stirring, molecular bromine was present in such an amount as to effect the undesired lactonization via the intermediate bromonium ion (49).[84,85]

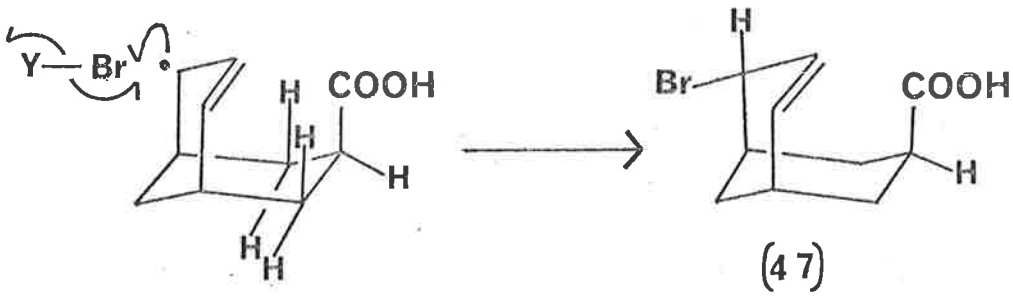
(49) (48)

Alternatively agitation exposed more NBS to interact directly with the double bond whereas bringing slowly to reflux without stirring permitted the radical reaction to afford the allylic bromide.

The bromo-acid (47) was characterized by the following data. Analytical data was consistent with the molecular formula $C_{10}H_{13}O_2Br$.

The infrared spectrum showed carboxylic acid carbonyl absorption at 1685 cm^{-1}. The n.m.r. spectrum showed resonances at δ 5.78 for the olefinic protons and at δ 4.88 for the proton on the carbon adjacent to bromine.

From studies of a model of bromide (47) it can be seen that the side of the double bond on which the carboxyl group is situated is more sterically congested due to the three carbon bridge than is the opposite side. Consequently it would be expected that the brominating species (be it molecular bromine or N-bromosuccinimide)[86-89] approach the less hindered face of the delocalized radical and so give the bromide having the *exo* configuration.



(47)

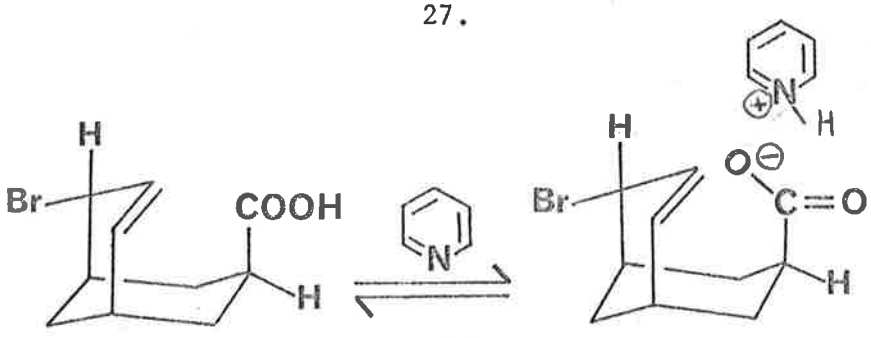
Y = Br or Succinimide

The bromo-acid (47) could be converted to the acid chloride (50) (scheme 8) using the mild conditions of oxalyl chloride in methylene chloride containing pyridine. Pyridine was added to remove liberated hydrogen chloride which may have caused undesired acid-

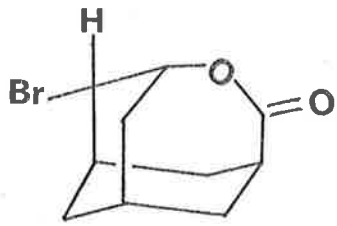
catalysed lactonization. The crude product showed characteristic acyl chloride carbonyl absorption in the infrared spectrum at 1790 cm^{-1} together with a second carbonyl absorption at 1725 cm^{-1} which was subsequently assigned to the bromo-lactone[83] (48). The n.m.r. spectrum of the crude acid chloride showed resonance at δ 5.54 characteristic of vinylic protons and at δ 4.2 for the proton on the carbon atom also bearing bromine. Resonance in the n.m.r. spectrum at δ 4.5 was assigned to the analogous proton in the bromo-lactone (48).

It was felt that the degree of bromo-lactonization might be reduced if the acid was added to oxalyl chloride in methylene chloride containing only one equivalent of pyridine. This resulted in a reduction of lactone when the reaction was attempted on a small scale, but seemed to have little effect on a large scale. One possible explanation was that an equilibrium existed between the acid (47) and its pyridinium salt (51). Sufficient acid remained unionized, however, to allow intramolecular proton transfer and lactonization across the double bond.

The amount of bromo-lactone formed could possibly depend on the length of time which the unreacted acid was dissolved in methylene chloride. This could explain why the small scale reaction, which was complete in 3 hr, returned a smaller amount of lactone than



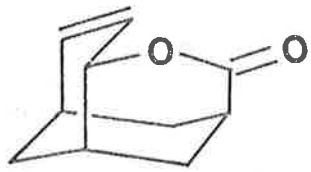
(47) (51)



(48)

the large scale reaction which required 12 hr.

The use of a stronger base than pyridine in the reaction was avoided since it was postulated that ionization of the acid would precede nucleophilic displacement of the bromine to give the olefinic lactone (52).



(52)

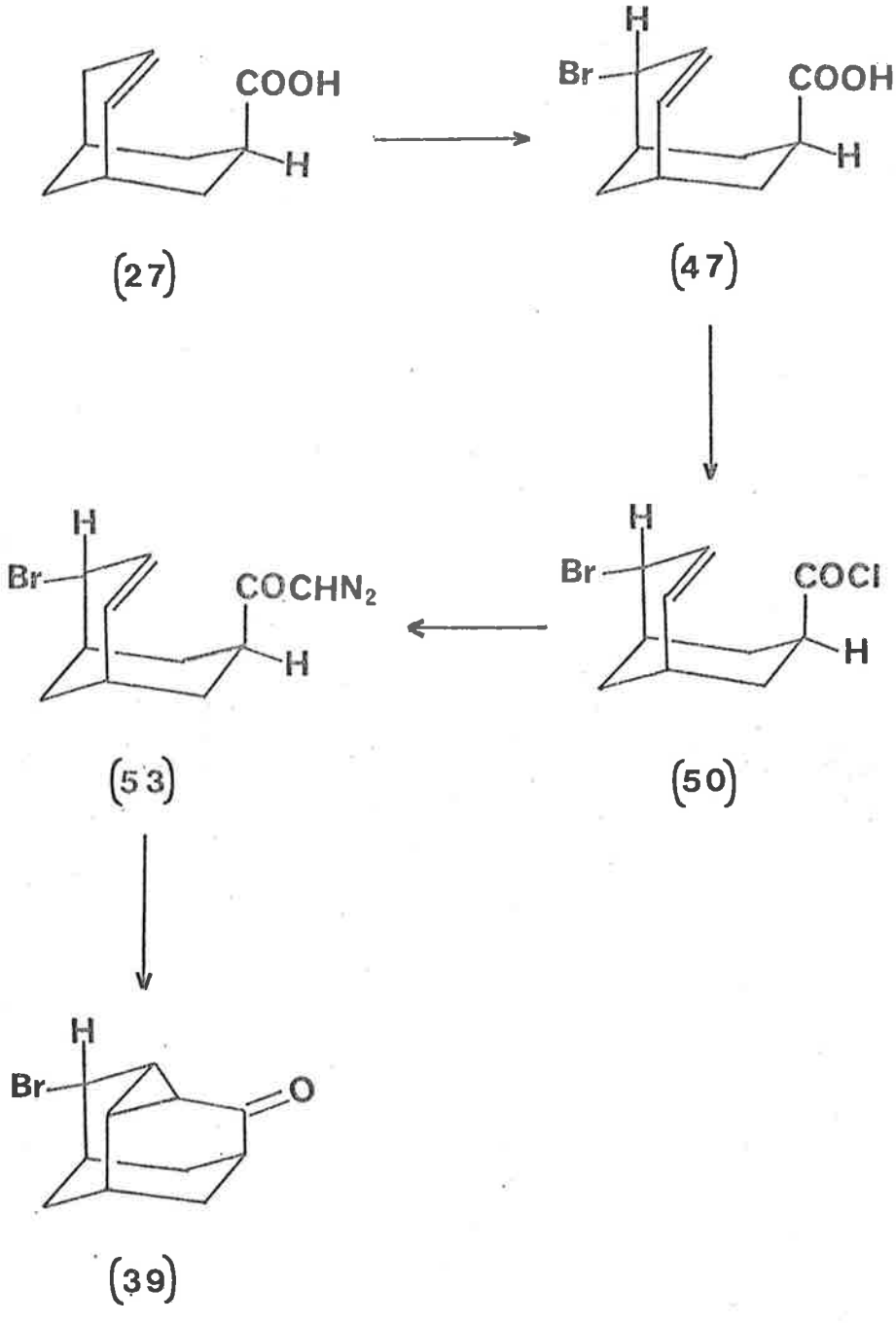
When the crude product mixture from the reaction to form the acid chloride was dissolved in dimethoxyethane, and hydrolysed with 5% sodium bicarbonate solution, the ether-soluble material was a white crystalline solid. The infrared spectrum of this material showed a carbonyl absorption at 1730 cm^{-1}. The n.m.r. spectrum showed a complex multiplet centred at δ 5.9 characteristic of olefinic protons and resonance at δ 4.9 consistent with a proton adjacent to a lactone. Resonance at δ 4.5 was ascribed to the proton on the carbon atom bearing bromine in the bromo-lactone (48) which was formed concurrently with the bromo-acid chloride (50). Thus on basic hydrolysis it appeared as if the bromine had undergone nucleophilic displacement to afford the olefinic lactone (52). The fact that this lactone did form from the acid (47) is further confirmation that the bromine atom has the *exo* configuration since the alternative configuration would not allow the S_N2 displacement to occur.

The crude acid chloride (50) reacted with diazomethane[90,91] in ether to give a diazo compound (53) which also was not purified. The infrared spectrum of the crude material had absorptions at 2100 and 1630 cm^{-1}, consistent with a diazo-ketone. The n.m.r. spectrum showed resonances at δ 5.72 for the olefinic protons, at δ 5.27 for the proton on the carbon bearing the diazo group and at δ 4.83 for the proton on the carbon bearing bromine.

Copper catalysed decomposition of the diazo-ketone (53) in boiling cyclohexane[92-100] yielded, after careful chromatography, 6-bromo-tetracyclo[5.3.1.$0^{3,5}0^{4,9}$]undecan-2-one (39) in 52% overall yield from the bromo-olefinic acid (47). Repeated crystallizations gave a compound melting at 81-82°, however, all attempts to obtain satisfactory analytical data were unsuccessful. In all cases the values obtained for both carbon and hydrogen were too high by 1-2%.

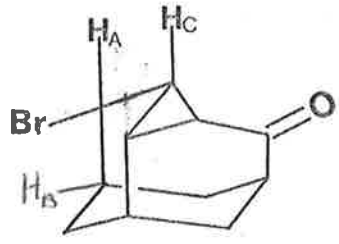
The structure of the bromo-cyclopropyl ketone was established by the following data. Molecular ions at m/e 240 and 242 in the mass spectrum were consistent with the formula $C_{11}H_{13}OBr$. The n.m.r. spectrum showed no vinylic protons but resonance at δ 4.52 for the proton on the carbon bearing bromine. The infrared spectrum had absorptions at 3000 cm^{-1} consistent with the cyclopropyl C-H stretching vibrations and at 1680 cm^{-1} for the carbonyl group.

In the n.m.r. spectrum, the fact that the proton on the



Scheme 8

carbon bearing bromine (H_A) absorbed as a narrow peak ($W_{\frac{1}{2}}$ = 5 Hz), showed that the coupling of this proton to its neighbours was minimal. This is consistent with the *exo* configuration of the bromine atom postulated earlier for the bromo-acid (47) since models indicate that the dihedral angle between H_A and its two neighbouring protons (H_B and H_C) is about 90° for each. Therefore, by the Karplus expression[101-103], the coupling between them should be minimal. In the alternative configuration these protons would be virtually eclipsed and thus a reasonably large coupling would be expected.



(39)

Attempts to improve the yield of the carbenoid addition reaction by refluxing the diazo-ketone in cyclohexane containing activated copper oxide,[104] under irradiation with a 250W tungsten lamp,[105] were unsuccessful in that unchanged starting material was mainly recovered.

Cleavage of the C3-C5 bond of the bromo-cyclopropyl ketone (39) with lithium[64,106-110] in anhydrous ether or dimethoxy-ethane was unsuccessful and mainly unchanged starting material was recovered. This could have been due to a coating of salts on the surface of the metal preventing further reaction.

It was thought that if this was the case, the use of liquid sodium-potassium alloy[111-113] would overcome the problem since during the reaction a fresh metal surface would be continually exposed by the stirring.[112]

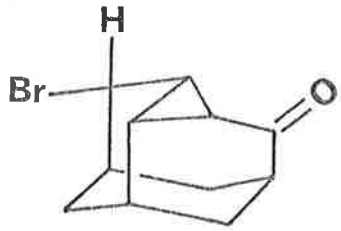
The bromo-cyclopropyl ketone was treated with sodium-potassium alloy in anhydrous ether at 20°. After 30 minutes t.l.c. showed that all starting material had been consumed. Protonation with ethanol diluted with petroleum ether provided a mixture of ketonic and alcoholic products which could be separated by preparative t.l.c.

The ketone (m.p. 258-260°) was shown to be tricyclo[5.3.1.$0^{4,9}$]-undec-5-en-2-one (40) by the following data. Both analytical data and the mass spectrum were consistent with the molecular formula $C_{11}H_{14}O$. The infrared spectrum showed carbonyl absorption at 1710 cm^{-1}. The n.m.r. spectrum showed two complex resonances at δ 6.05 and 5.55 corresponding to the two olefinic protons in an AB-pattern further coupled to adjacent protons.

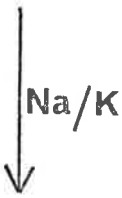
The alcoholic portion of the product mixture could be separated into two components by preparative g.l.c. Each of these gave the above ketone on oxidation with Jones reagent,[114] however, it was observed that the oxidation of one was considerably more sluggish than the other.

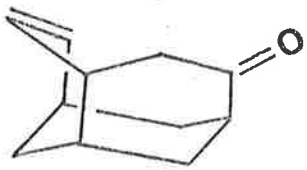
Treatment of the bromo-cyclopropyl ketone (39) with sodium-potassium alloy had thus afforded a mixture of the ketone (40) together with the two epimeric alcohols (45) and (54) through further reduction of the carbonyl group. It was subsequently shown (chapter 4) that reduction of the ketone (40) with sodium borohydride gave exclusively the *endo* alcohol (45) since cyclization of the product from this reduction afforded the ethers (46) and (89). Alcohol (45) was that epimer which showed the slower rate of oxidation with Jones reagent.

It has been shown,[223] however, that in the oxidation of alcohols by Cr^{VI} species, the alcohol with the more hindered hydroxyl group is oxidized more rapidly. This occurs because the decomposition rate of the intermediate chromate ester is accelerated since steric strain is relieved in going from the reactant to the product. In extreme cases, however, the initial esterification step becomes rate limiting in the oxidation.[224] The fact that the *endo* alcohol (45) oxidized at a slower rate than did the *exo* epimer (54) suggests that its hydroxyl group is extremely sterically congested.



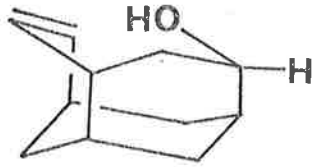
(39)





(40)

+



(45)

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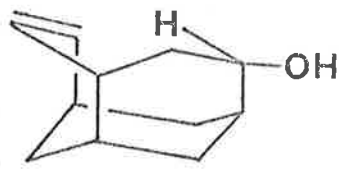
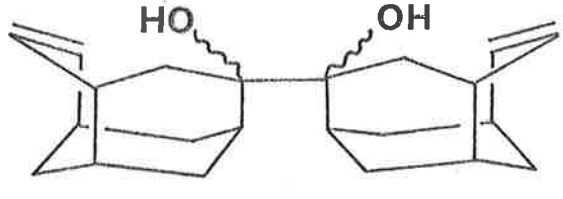


(54)

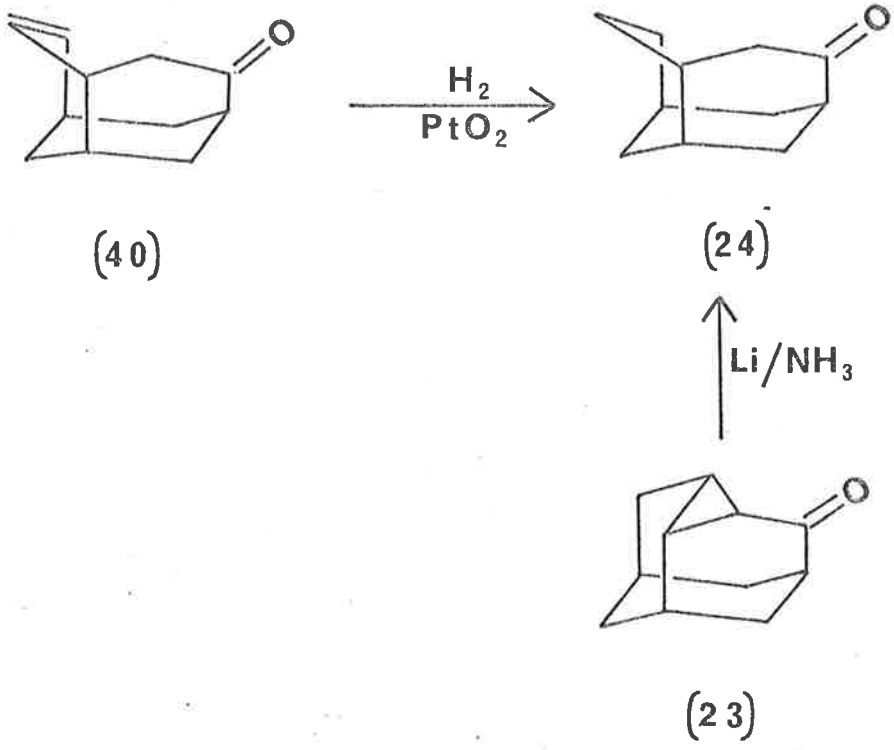
In subsequent reactions the mixture of ketonic and alcoholic products was oxidized directly to give the desired ketone (40) in 91% yield.

When more concentrated ethereal solutions of alloy were used, a small amount of a crystalline material (m.p. 235-239°) was obtained which failed to oxidize with Jones reagent.[114] This material showed a molecular ion in the mass spectrum at m/e 326. The infrared spectrum showed hydroxyl absorption at 3520 cm^{-1}. The n.m.r. spectrum showed a complex multiplet centred at δ 6.2 but lacked resonance for a proton on a carbon atom adjacent to an oxygen atom. It thus appeared that dimerization had occurred by way of a pinacol reaction[115,116] to give a diastereoisomeric mixture of the alcohols (55).



(55)

In an attempt to fully establish the structure of the olefinic ketone (40), it was hydrogenated in the presence of a catalytic amount of platinum oxide.[117,118] The dihydroketone formed was not homoadamantanone [32-36] but was identical in all respects to the compound (24) obtained by lithium in liquid ammonia reduction of the unbrominated cyclopropyl ketone (23).[28]



(40) (24) (23)

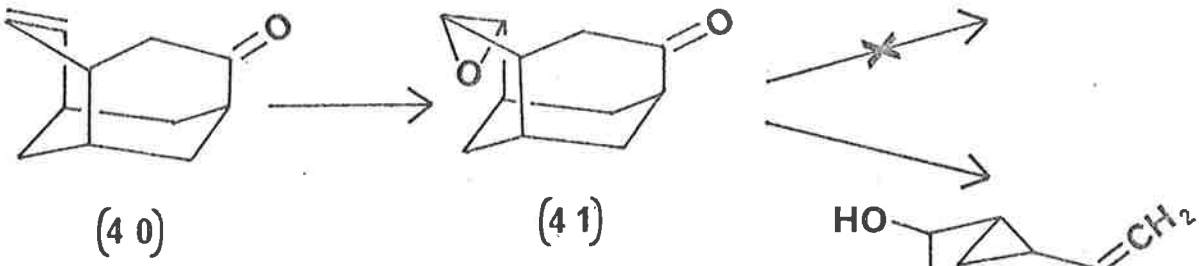
The novel reaction which gave the key keto-olefin (40) has since been developed[113] as a highly efficient fragmentation reaction which should find wide use in organic synthesis.

CHAPTER 3

Synthesis of Iceane

Having obtained the desired keto-olefin (40), it was intended to proceed with scheme 6 (page 20).

Treatment of the keto-olefin (40) with *m*-chloroperbenzoic acid gave the keto-epoxide (41) (m.p. 285-287°) in 76% yield. The infrared spectrum showed carbonyl absorption at 1705 cm^{-1} while the n.m.r. spectrum showed the absence of any resonance due to vinylic protons. All attempts to form the olefinic epoxide (42) however, were unsuccessful. Reaction of the keto-epoxide with methylene triphenylphosphorane at room temperature gave an olefinic alcohol for which was assigned the structure (57).



(40) (41) (42) (57)

In support of structure (57), both analytical data and the mass spectrum were consistent with the molecular formula $C_{12}H_{16}O$. The infrared spectrum had hydroxyl absorption at 3300 cm^{-1} and absorptions at 3050 and 2985 cm^{-1} consistent with methylene and cyclopropyl C-H stretching vibrations respectively. An absorption at 1630 cm^{-1} was consistent with C-C ~~multiple~~ double bond stretching vibrations. The n.m.r. spectrum showed resonances at δ 4.73 for the methylene protons and at δ 3.86 for the proton on the carbon adjacent to the hydroxyl group. There was no direct evidence for the cyclopropyl ring.

The formation of such a compound may be rationalized by the initial enolization of the ketone, followed by intramolecular alkylation of the epoxide[119] to give the cyclopropyl ring, and then subsequent Wittig reaction on the carbonyl group.

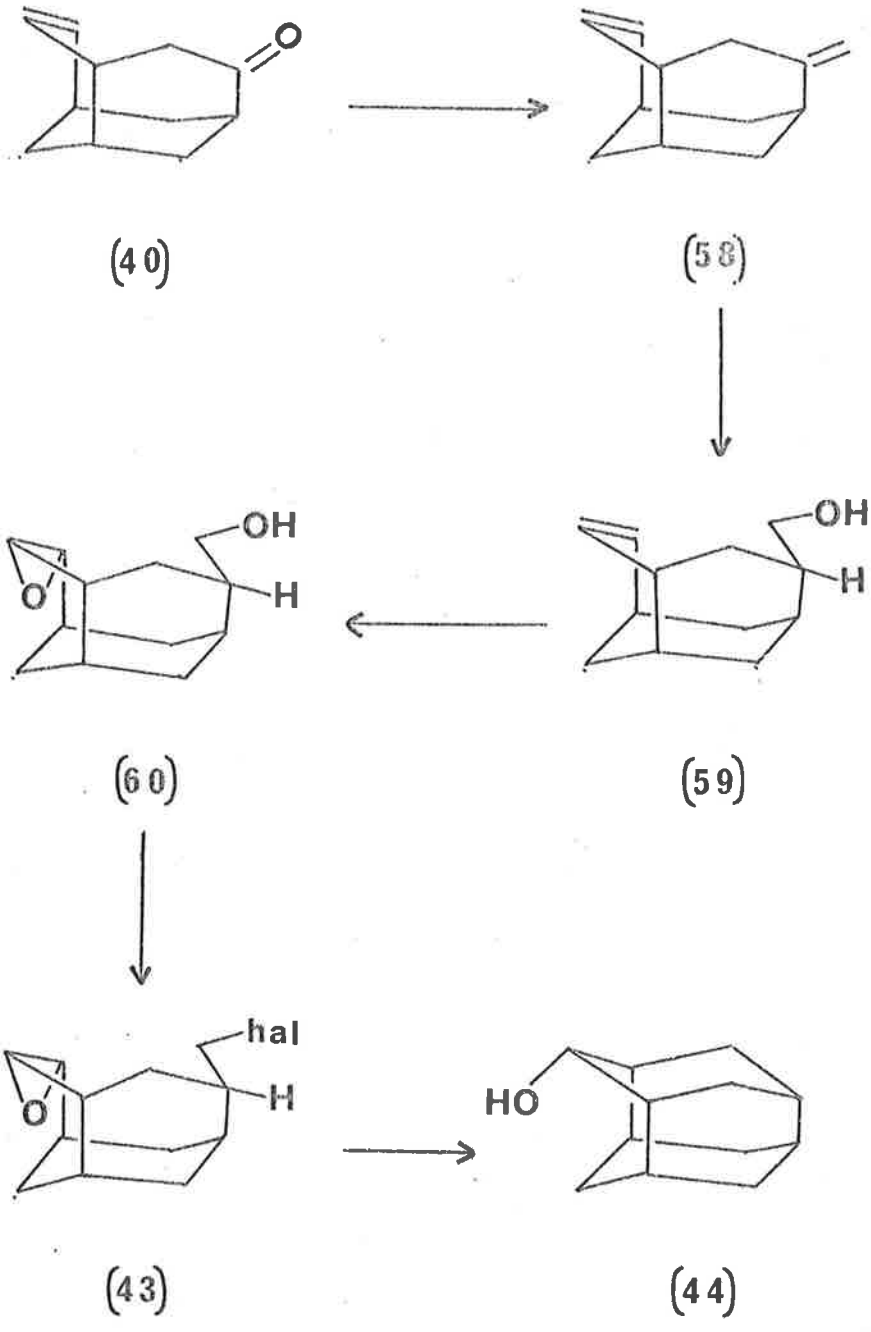
The removal of a proton from the α position of carbonyl compounds by phosphoranes is particularly pronounced with easily enolizable ketones such as cyclohexanone and cyclopentanone.[120] Furthermore if the reaction between the ylid and the carbonyl compound is sterically hindered, enolization becomes the main reaction.[121,122] Because nucleophiles function more successfully as bases at higher temperatures, Wittig reactions with enolizable ketones have been shown[122] to proceed best at low temperatures. However, when the keto-epoxide (41) was treated with methylene triphenylphosphorane for 5 hr at -78°, and then allowed to warm to room temperature over night,

enolization of the carbonyl still occurred and the alcohol (57) was again obtained.

This compound was of no use for the proposed synthesis. The fact that it could form, however, established that the keto-olefin (40) had epoxidized cleanly on the side of the double bond away from the carbonyl group to afford the *exo* epoxide. This was an essential requirement for the proposed subsequent intramolecular alkylation (scheme 6).

An alternative scheme (scheme 9) was conceived in which the carbon skeleton is developed first, by conversion of the olefinic ketone (40) to the diolefin (58). This scheme, however, required a selective hydroboration-oxidation[123-125] reaction at one of the two double bonds to give the olefinic alcohol (59). Subsequent epoxidation of the double bond would give the epoxy-alcohol (60) which could be converted to the epoxy-halide (43) to allow cyclization with lithium using the method of Sauers[66] to give the alcohol (44).

The stages in this scheme at which one might anticipate problems were as follows. Firstly a selective hydroborating reagent would have to be found which reacted with the *exo*-cyclic methylene group but not with the more highly substituted *endo*-cyclic double bond of the diolefin (58). Brown[124] has developed several highly



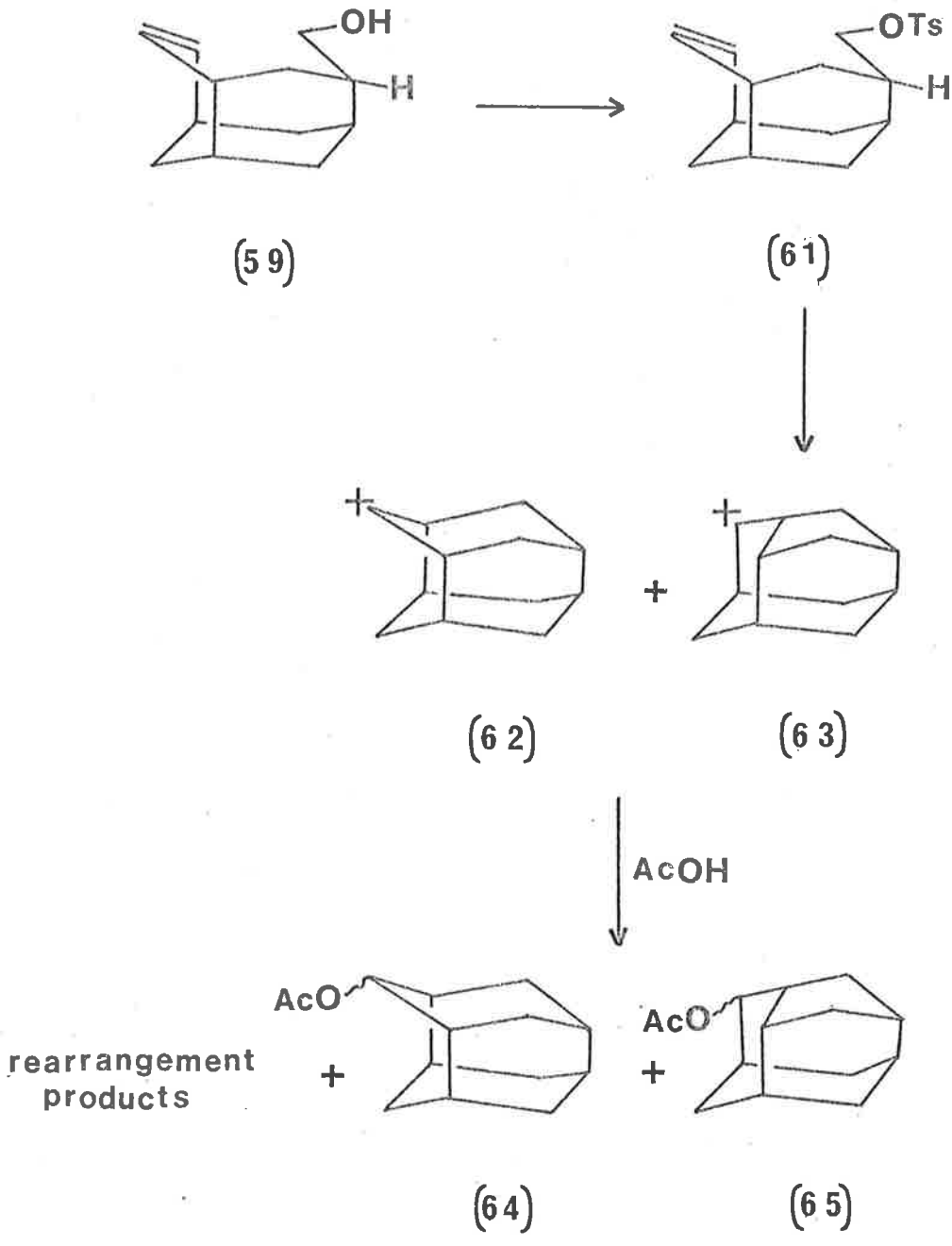
(40) (58) (59) (60) (43) (44)

Scheme 9

selective hydroborating reagents one of which should overcome this problem. Secondly the epoxide had to remain intact while the hydroxyl group was substituted. If problems did arise at this stage, the epoxidation and hydroxyl-substitution steps could possibly be reversed. However, during attempts to chlorinate an alcohol in the presence of a double bond using such reagents as thionyl chloride or phosphorus pentachloride, difficulties could arise with the addition of liberated hydrogen chloride to the olefin.

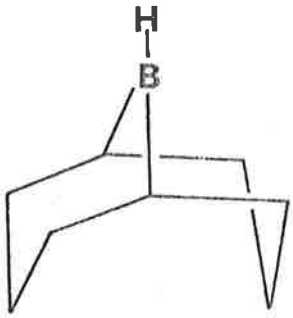
An alternative procedure was to form the tosylate (61) from the alcohol (59) and cyclized by means of a solvolysis reaction. (scheme 10). However, because the reaction would proceed with double bond participation[126-131] through the secondary carbonium ions[132] (62) and (63), not only could both structural isomers (64) and (65) be formed, but the possibility of complex structural rearrangement[133-135,168] was also conceived as a complication.

By the use of methylene triphenylphosphorane in anhydrous ether, the keto-olefin (40) was converted to the diolefin (58) (m.p. 132-135°) in 88% yield. The infrared spectrum of this compound showed olefinic absorptions at 3050, 3020 and 1640 cm^{-1}. The n.m.r. spectrum still showed resonance for the *endo*-cyclic double bond between δ 6.35 and 5.28 while resonance at δ 4.76 was consistent with the newly introduced methylene protons.

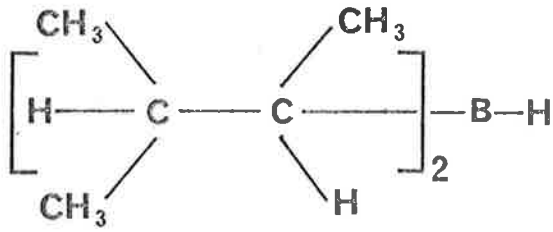

OH
H
OTs
H
(59)
(61)
(62)
(63)
AcOH
AcO
AcO
rearrangement products
(64)
(65)

Scheme 10

Attempts to selectively hydroborate the *exo*-cyclic double bond with 9-boro-bicyclo-nonane (66) according to the method of Brown[123,124,136,137] returned starting diolefin even through the same conditions were shown to reproduce the reactions reported[137] by Brown. However selective hydroboration using three equivalents of disiamyl borane (67)[124,125] in tetrahydrofuran at 0° followed by oxidation with alkaline hydrogen peroxide gave the olefinic alcohol (59) (m.p. 186-187°) in 54% yield.



(66)

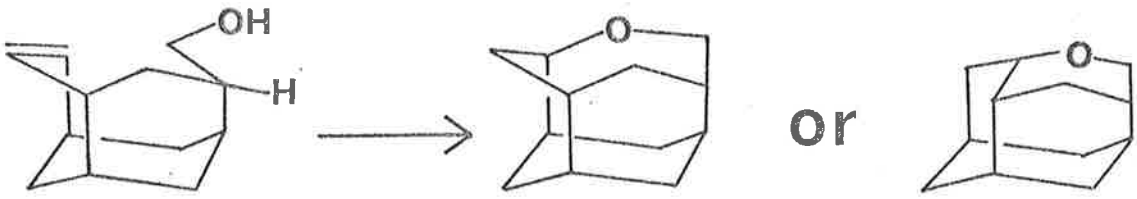


(67)

The infrared spectrum of compound (59) showed alcohol absorption at 3300 cm^{-1}. In the n.m.r. spectrum the vinylic protons were still clearly visible at δ 6.04 and 5.64 but the methylene protons were now absent. Moreover the n.m.r. spectrum showed a complex multiplet between δ 3.35 and 3.90 for the two protons on the carbon atom which also bears the hydroxyl group. This region was not sharpened by exchange of the hydroxyl group with D_2O and is probably complex due to the diastereotopic nature of the hydrogens involved. If the molecule has

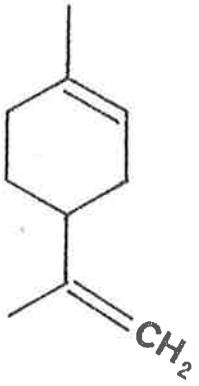
the configuration shown, this intrinsic anisotropy[138,139] may be further complicated by restricted rotation.[140,141] Before proceeding further, it was essential to establish this configuration since it was a key requirement for the subsequent cyclization.

Oxymercuration[76] of the olefinic alcohol (59) using mercuric acetate in tetrahydrofuran, followed by reduction with alkaline sodium borohydride, gave a single crystalline compound (m.p. 275-277°) in 87% yield. This material was more volatile by g.l.c. and less polar by t.l.c. than the starting alcohol. The infrared spectrum showed no acetate or hydroxyl absorption while the n.m.r. spectrum showed no olefinic protons but resonance consistent with three protons on a carbon also bearing oxygen. The mass spectrum revealed that the new compound was isomeric with the starting alcohol. From these data, this new isomer could only be cyclic ether (68) or (69) either of which could have arisen only if the hydroxymethyl group in compound (59) had the desired *endo* configuration.

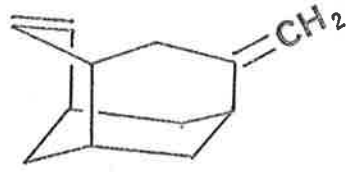


(59) (68) (69)

In an attempt to optimize some of the reactions associated with scheme 9, without consuming valuable material, limonene[142] (70) was chosen as a model compound for the diolefin (58).



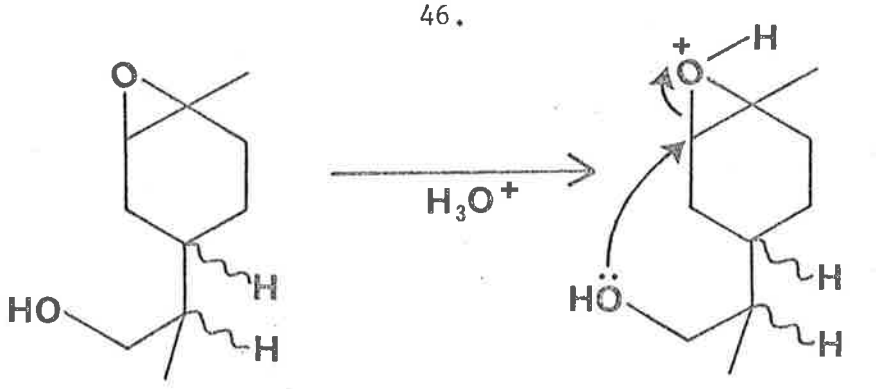
(70)



(58)

By the method of Brown and Zweifel,[143] the *exo*-cyclic methylene group in dl limonene could be selectively hydroborated with disiamyl borane[124,125] and subsequently oxidized with alkaline hydrogen peroxide to afford a diastereoisomeric mixture of the alcohols (71)[144-146] (scheme 11). This could be readily epoxidized with *m*-chloroperbenzoic acid to give a mixture of the hydroxy-epoxides (72).[146] The infrared spectrum showed hydroxyl absorption at 3400 cm^{-1} and absorption at 1040 cm^{-1} consistent with the epoxide. The n.m.r. and mass spectra were also consistent with the structures shown.

Ohloff et al[146] have shown that in the presence of acid, the epoxides (72) cleave to afford the hydroxy-ethers (73).



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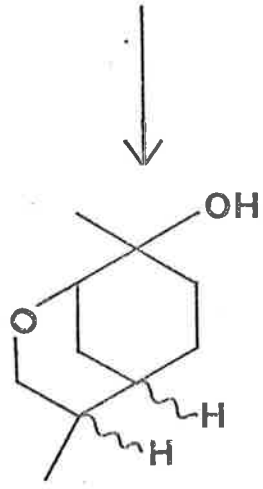
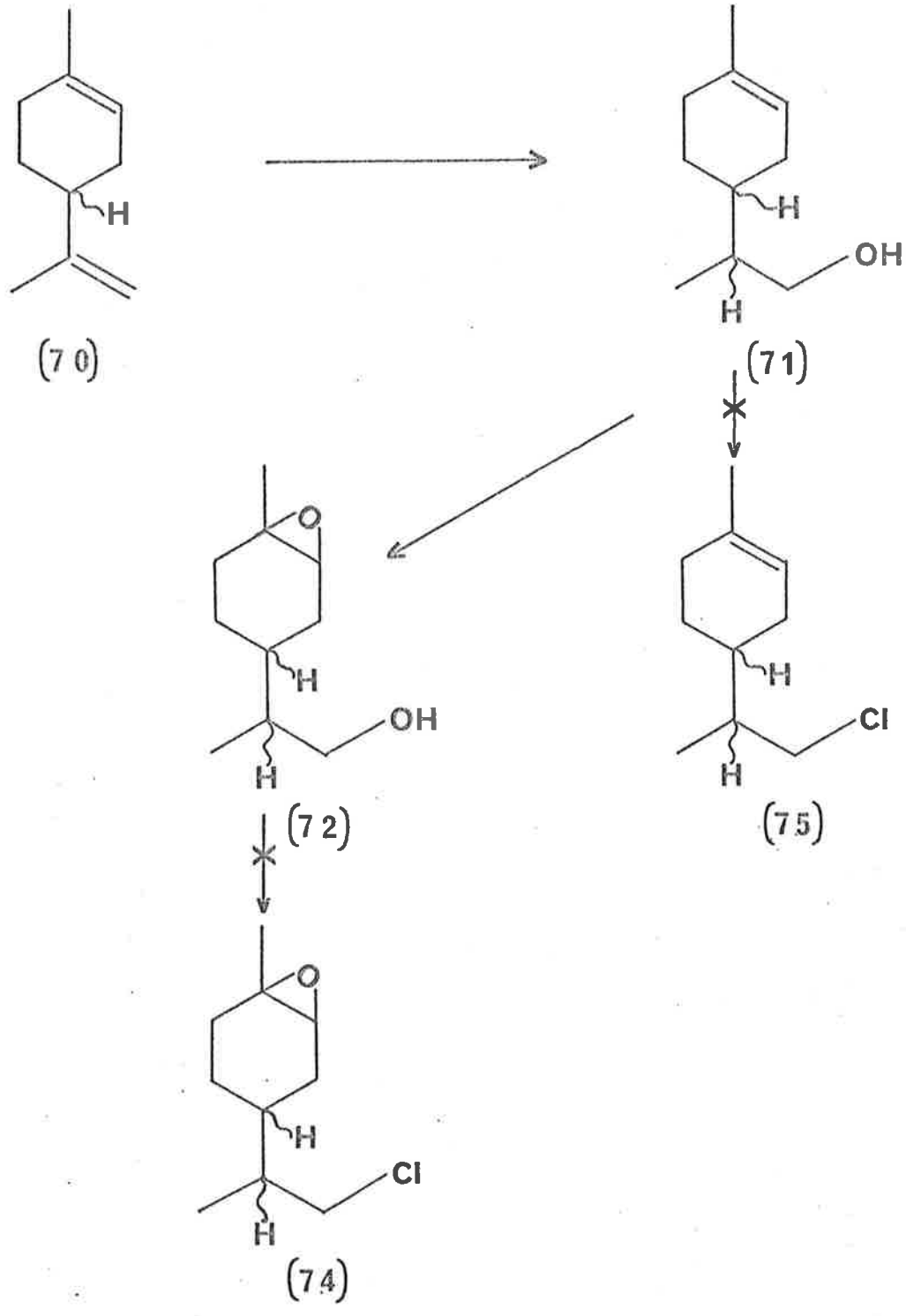


(73)

Therefore misleading results would be obtained during attempts to form the chlorides (74) from the alcohols (72) with such reagents as thionyl chloride or phosphorus pentachloride if these were permitted to liberate hydrogen chloride during the transformation.

When the alcohols (71) were treated with thionyl chloride or with phosphorus pentachloride containing pyridine[147,148] to remove liberated hydrogen chloride, an intractable mixture of products was obtained which was not investigated further.



Scheme 11

It has been shown[148-151] that when the reaction of an alcohol with thionyl chloride is performed in a dilute ether solution, the degree of ionization of the liberated hydrogen chloride is not appreciable, so making it quite inactive. However attempts to form the chlorides (74) from the alcohols (72) with an ethereal solution of thionyl chloride again afforded a complex mixture of products.

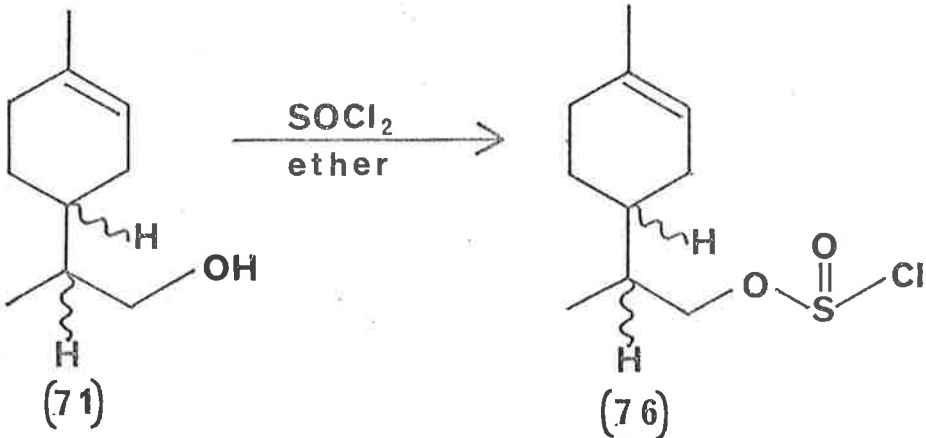
Halogenation of alcohols with either triphenylphosphine in carbon tetrachloride,[152-156] or with N-bromosuccinomide,[157] is known to proceed without the liberation of hydrogen chloride. Attempts to form the halides by these methods, however, were again frustrated by the formation of an intractable mixture of products.

Following the lack of success in forming an epoxy--chloride from the corresponding alcohol, efforts were directed towards the formation of the olefinic chlorides (75) from the alcohols (71) without the addition of hydrogen chloride across the double bond.

It was thought that if thionyl chloride was added to the rapidly stirring alcohols (71) in the absence of any solvent, gaseous hydrogen chloride would possibly be liberated before it could add to the olefin. This clearly was not realized since the n.m.r. spectrum of the major component from the product mixture of such a reaction revealed the absence of any vinylic protons.

When the same reaction was performed in an ethereal solution

of thionyl chloride, the intermediate chlorosulphites (76) were formed.

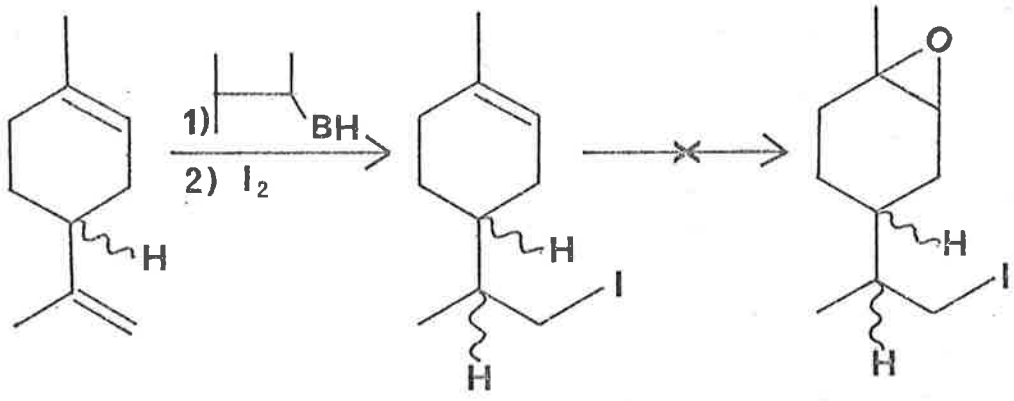


However, these could not be converted to the desired chlorides (75) either by prolonging the reaction time[147] or by increasing the reaction temperature.[158] The chlorosulphites were recovered in each case.

Following a procedure developed by Brown,[159] it was found that the terminal olefin of dl limonene (70) could undergo selective

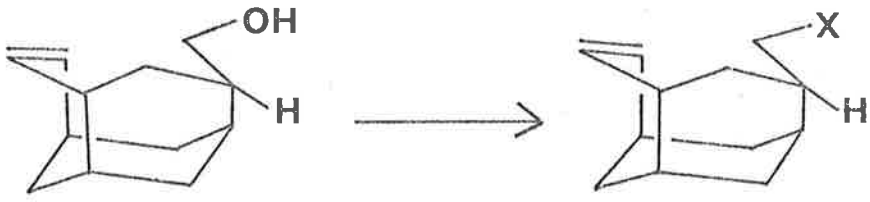
hydroboration with disiamyl borane followed by an *in situ* reaction with iodine in sodium hydroxide solution to give the olefinic iodides (77) in good yield. Both analytical data and the mass spectrum were consistent with the molecular formula $C_{10}H_{17}I$. The n.m.r. spectrum showed a broad resonance at δ 5.35 for the vinylic proton, a doublet at δ 3.22 for the two protons on the carbon bearing iodine and resonances at δ 1.64 and 0.95 for the two methyl groups.

All attempts to epoxidize the olefinic iodides (77) using *m* chloroperbenzoic acid in methylene chloride were accompanied by an immediate evolution of iodine but none of the desired iodo-epoxides (78) was formed. It was conceivable that iodine could be released via a free radical mechanism due to the presence of the peracid. The inclusion[160] of a radical inhibitor, however, failed to stem the iodine release.



(70) (77) (78)

Because the model system was creating more problems than it was solving, it was decided to return to the main system and continue our investigations on the olefinic alcohol (59). Due to the lack of success with thionyl chloride in the model system, its use was avoided in attempts to convert the alcohol (59) to a compound (79) possessing a suitable leaving group X necessary for subsequent cyclization.

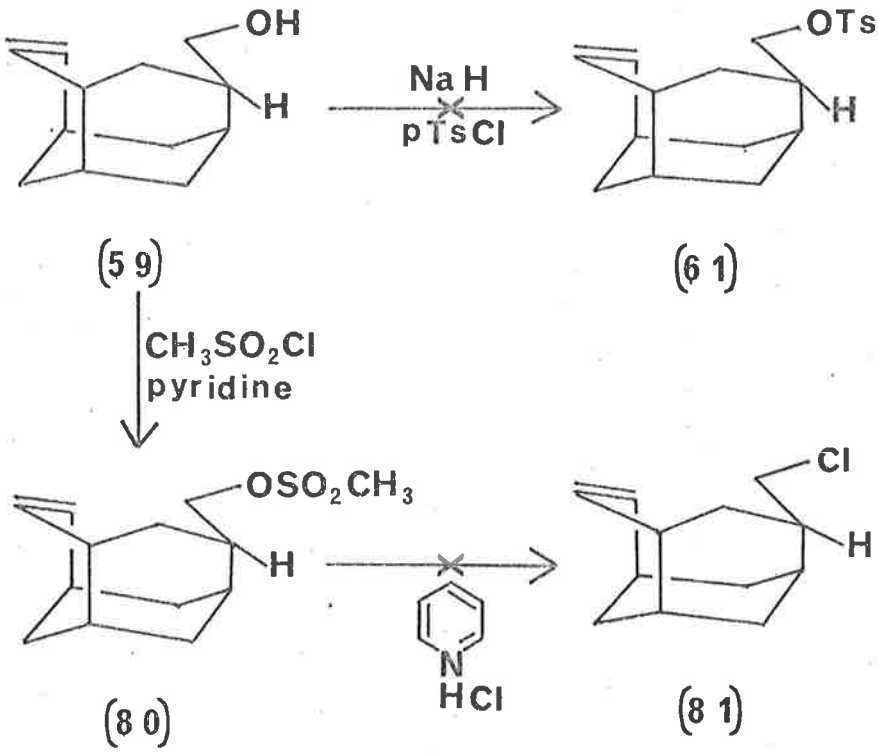


(59) (79)

Treatment of the alcohol (59) with sodium hydride and *p*-toluene-sulphonyl chloride[161,162] failed to produce any of the olefinic tosylate (61) and starting alcohol was always recovered. Probably the cage like structure of the molecule was preventing the tosylate from forming.

When the olefinic alcohol was treated with methanesulphonyl chloride in pyridine,[163] the olefinic mesylate (80) (m.p. 40-41°) was formed. The mass spectrum of this compound was consistent with the molecular formula $C_{13}H_{20}O_3S$. The infrared spectrum showed no

hydroxyl absorption but absorption at 1170 cm^{-1} consistent with the sulphonyl group. The n.m.r. spectrum showed multiplets centred at δ 6.17 and 5.69 for the vinylic protons, a complex multiplet between δ 4.0 and 4.5 for the diastereotopic protons on the carbon atom bearing the mesylate group and a singlet at δ 2.91 for the methyl group.



All attempts to convert the mesylate to the olefinic chloride (81) using pyridine hydrochloride[164] resulted in unchanged starting material always being recovered. Once again

steric congestion due to the cage like structure was probably preventing the back side approach of the chloride anion to the mesylate.

In another approach to the olefinic chloride (81) the alcohol (59) was treated with phosphorus pentachloride in chloroform at -80°C. After the temperature had equlibrated to room temperature, t.l.c. showed that no new compounds had formed. Refluxing the mixture for 24 hr afforded a product (ca. 10%) which was less polar by t.l.c. than the starting alcohol. Because of the low yield and since the n.m.r. spectrum of this component revealed the absence of any vinylic protons, this approach to the olefinic chloride (81) was not investigated further.

On refluxing the olefinic alcohol (59) with triphenylphosphine in carbon tetrachloride,[152-156] the reaction took an unexpected course. A mixture of two compounds was obtained in 55% yield, each of which was shown, by combined g.l.c.-mass spectrometry, to be isomeric with the expected compound (81). The n.m.r. spectrum of the mixture showed no vinylic protons but two resonances at δ 4.82 and 4.00 consistent with protons on carbon bearing chlorine. Since these compounds were isomeric with the olefin (81) but did not have a double bond, they had to contain an extra ring.

The mechanism of the reaction of triphenylphosphine-carbon

tetrachloride with alcohols has been widely discussed.[152,165-167] From a study of models of the case under discussion, it could be seen that the postulated intermediate[167] alkoxy-triphenylphosphorane (82) (figure 6) could interact with either end of the double bond. A chloride anion could then attack the double bond from the *exo* face and so effect cyclization, through displacement of triphenylphosphine oxide, to give a mixture of the *exo*-chloro-skeletal isomers (83) and (84).

Moreover if the cyclization process was concerted, the chlorides formed could possibly undergo S_N2 displacement by chloride anions to afford the epimeric *endo*-chloro-isomers (85) and (86). Thus assuming there was no extensive rearrangement, it seemed likely that substitution had occurred, with double bond participation, to give either both epimers (83) and (85) or epimers (84) and (86) or a mixture of one of each.

The two chloro-isomers could be separated by preparative g.l.c. Initially extensive decomposition of the first eluted isomer was observed to give a ~~less~~ more volatile component which was shown to be isomeric, by g.l.c.-mass spectrometry, with the two chloro-isomers isolated from the reaction. It was conceived that this decomposition product could possibly have been chloro-ethanoadamantane (87) since it has been shown[168] that ethanoadamantane (88) is the most stable

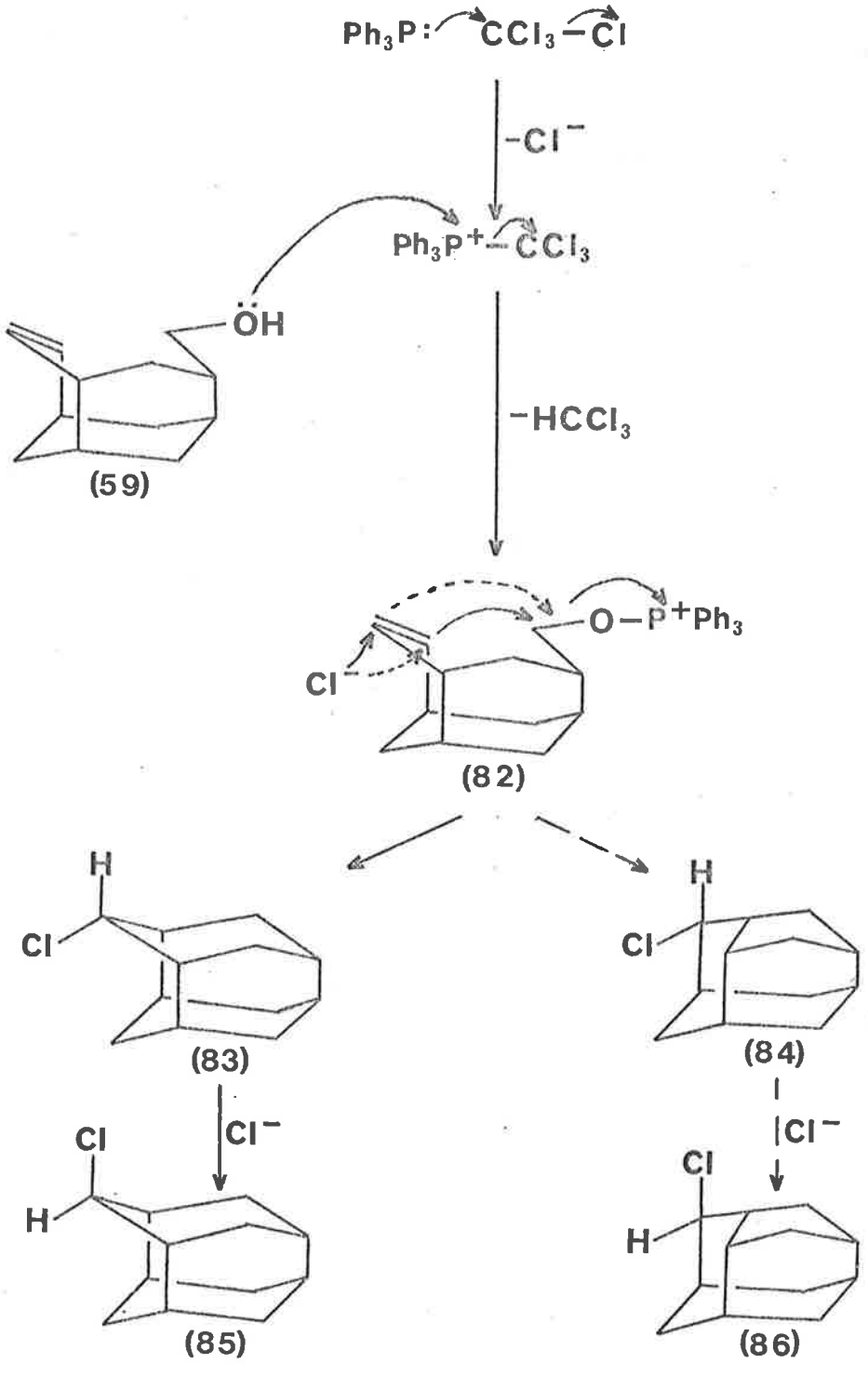
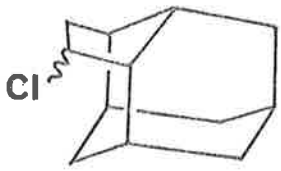
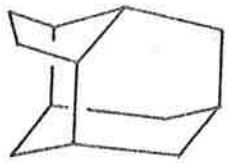

Ph3P: CCl3 Cl
-Cl⁻
Ph3P+ CCl3
OH
(59)
-HCCl3
O-P+Ph3
Cl
(82)
H
Cl
(83)
Cl⁻
Cl
H
(85)
H
Cl
(84)
Cl⁻
Cl
H
(86)

Figure 6

$C_{12}H_{18}$ isomer. Subsequently it was found that this decomposition could be reduced to a minimum if a freshly packed glass column was used for the separation, and metal surfaces in the injector were avoided.



(87)



(88)

The first eluted chloro-isomer (m.p. 215-217°) showed resonance in the n.m.r. spectrum at δ 4.00 for the proton on the carbon bearing chlorine. For the second isomer (m.p. 272-274°) this resonance was seen at δ 4.82.

Each chloride was reduced separately with tri-n-butylstannane[169-171] and both appeared to give the same crystalline compound which was at least isomeric, by mass spectrometry, with iceane. The mixture of chloro-compounds was reduced to yield a crystalline product, which did not melt but, when placed in a sealed tube of small volume sublimed at 325°. This compound was shown to be tetracyclo[5.3.1.$1^{2,6}0^{4,9}$]dodecane (iceane) (1) by the following data.

The analytical data and mass spectrum were consistent with the molecular formula $C_{12}H_{18}$. The p.m.r. spectrum (figure 7) (90 MHz) showed an AM pattern centred at δ 0.94 and 1.90 (J = 12 Hz). This is consistent with the resonance due to the axial and equatorial protons respectively of each methylene group since axial protons normally absorb at higher field than equatorial protons.[172] The difference in chemical shift is probably enhanced by van der Waals deshielding[173,174] of equatorial protons due to their position in rings having a boat configuration. Each of these resonances is broadened by further minimal coupling to the bridgehead protons which absorb as a broad peak at δ 2.18. The integration for each of the three regions was the same.

The $^{13}C-\{^{1}H\}$ n.m.r. spectrum (figure 8) showed only two resonances at δ 28.70 and 31.72 (relative to TMS) integrating for nearly equal areas.

All of these n.m.r. data are consistent with the six fold inversion axis in iceane which results in the molecule having only three distinct hydrogen atoms and two distinct carbon atoms. Furthermore X-ray data* revealed that the molecule must possess a minimum of three-fold symmetry.

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* I am indebted to Dr. M.R. Snow, Department of Physical and Inorganic Chemistry, University of Adelaide, for the X-ray data and its interpretation.

^{1}H nmr 90-MHz spectrum

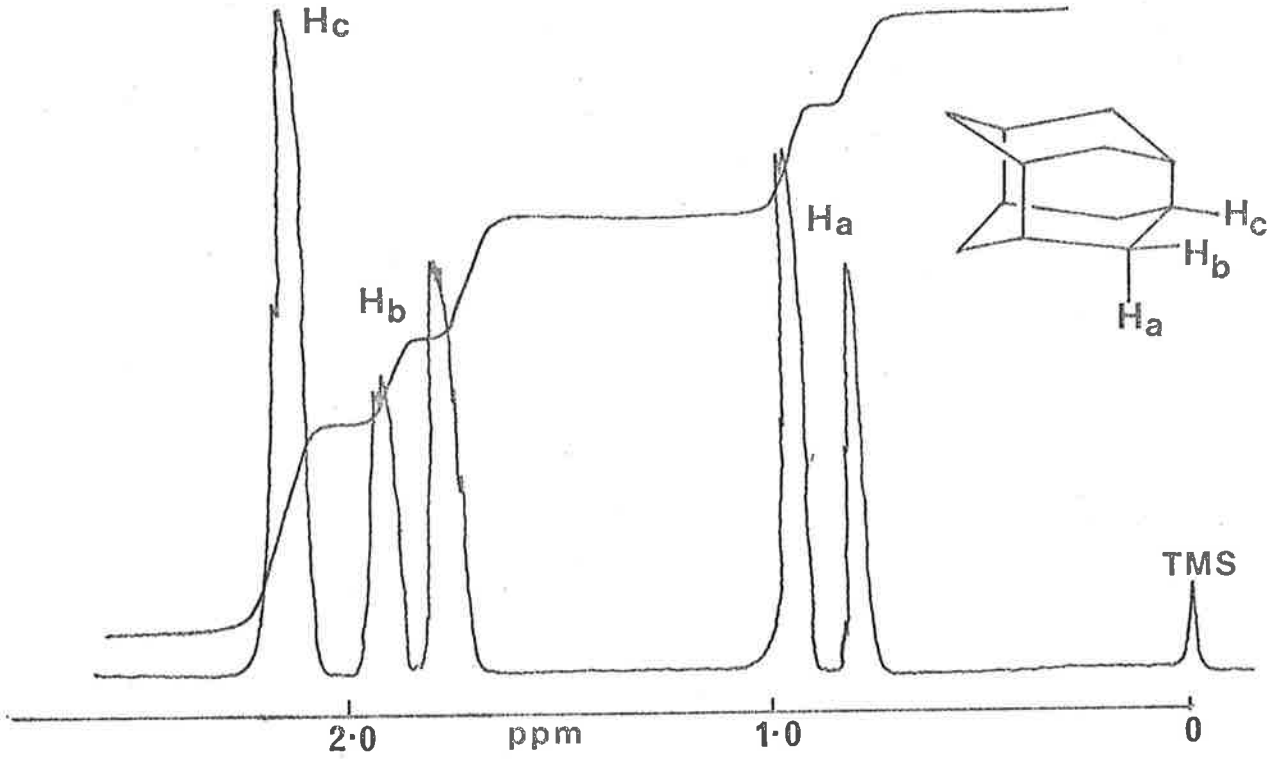


Figure 7

$^{13}C(^{1}H)$ nmr spectrum

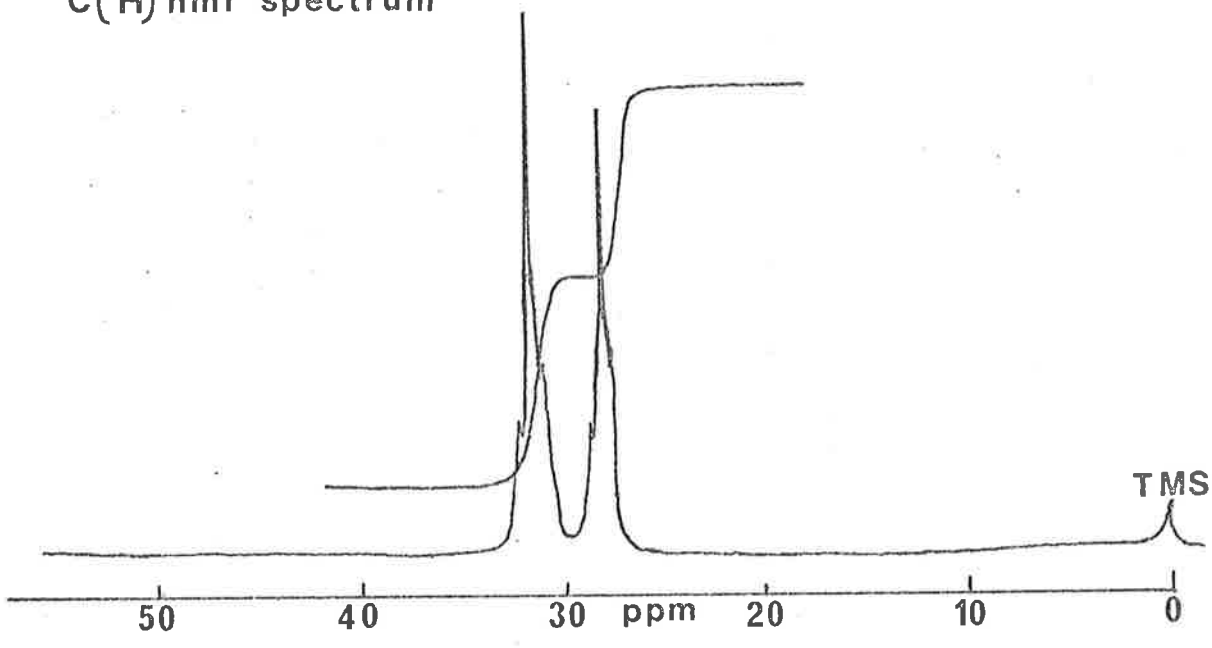
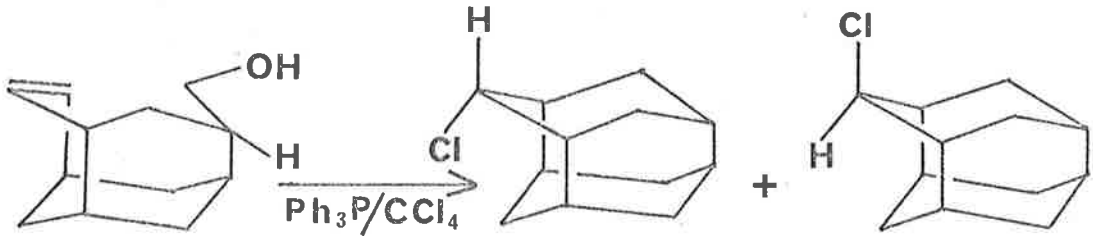
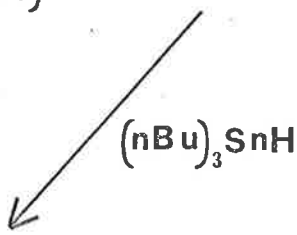


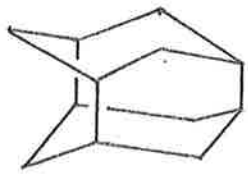
Figure 8

It was now obvious that the cyclization of the olefinic alcohol (59) with triphenylphosphine in carbon tetrachloride had fortuitously produced a mixture of the two epimeric chlorides (83) and (85) of iceane.



(59) (83) (85)





(1)

Differentiation of the structures of the two chlorides followed from the chemical shift of the proton bearing chlorine since axial protons normally absorb at higher field than equatorial protons.[172] The isomer (m.p. 215-217°) which has this

absorption at δ 4.00 must be chloride (83) since the absorption of this proton in the other isomer (m.p. 272-274°), chloride (85), is at δ 4.82. This was consistent with the fact that chloride (83) with the chlorine atom in the prow position of a six-membered ring in a non twist boat configuration was subsequently found to be the less stable isomer.

CHAPTER 4

Synthesis of Oxaiceane and *Abeo*-oxaiceane

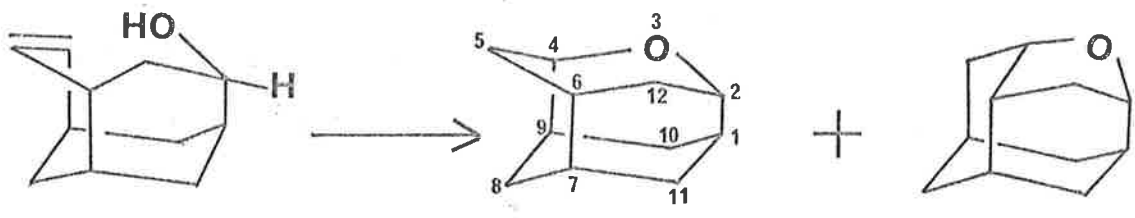
The key intermediate (40) which allowed the synthesis of iceane was also employed in the synthesis of an oxygen analogue, oxaiceane (46) together with a structural isomer, *abeo*-oxaiceane (89).

From a study of models and by analogy with the hydroboration of diolefin (58), it was expected that metal hydride reduction of the olefinic ketone (40) would give an *endo* alcohol with the stereochemistry required for subsequent cyclization. Sodium borohydride reduction gave a single product (m.p. 269-270°) in greater than 95% yield. The infrared spectrum showed alcohol absorption at 3400 cm^{-1} and olefinic stretching vibrations at 3000 (as a shoulder) and 1650 cm^{-1}. The n.m.r. spectrum showed a complex multiplet between δ 6.45 and 5.80 for the vinylic protons and a broad resonance centred at δ 4.12 for the proton on the carbon bearing the hydroxyl group.

This compound was identical to that alcohol obtained from the reaction of sodium-potassium alloy with the bromo-cyclopropyl ketone (39) which showed the slower rate of oxidation with Jones reagent.[114] Since it was assumed that sodium borohydride would approach the carbonyl group from the less hindered face, this alcohol was assigned the structure (45).

Oxymercuration[76] of the olefinic alcohol (45) with mercuric acetate in tetrahydrofuran followed by reduction with sodium

borohydride to remove the mercury gave a mixture of two compounds in *ca.* 1:1 ratio in 80% yield together with regenerated alcohol. It was conceived that oxymercuration had occurred at both ends of the double bond to afford a mixture of the two cyclic ethers (46) and (89).



(45) (46) (89)

Bordwell and Douglas[175] have shown that the addition of sodium acetate to an oxymercuration reaction sometimes increases the yield of one ether over another. However in the case under discussion, the presence of sodium acetate had little effect.

The two new products were isomeric, by mass spectrometry, with the starting alcohol and could be separated by preparative g.l.c. That which eluted first was subsequently shown to be 12-oxa-tetracyclo[5.3.1.$1^{2,5}0^{4,9}$]dodecane (89) (*abeo*-oxaiceane) (m.p. 256-257°) followed closely by 3-oxa-tetracyclo[5.3.1.$1^{2,6}0^{4,9}$] dodecane (46) oxaiceane (m.p. 314-315°).

For each isomer the analytical data and mass spectrum were consistent with the molecular formula $C_{11}H_{16}O$. The infrared spectrum of each showed no hydroxyl or acetate absorption. The resonances in the n.m.r. spectrum of each at δ 4.22 for one isomer and at δ 4.20 for the other were consistent with protons on a carbon atom also bearing oxygen. Thus it was obvious that the two cyclic ethers (46) and (89) had in fact formed. The difficulty lay in distinguishing between the two structures.

It was felt that the two isomers might be differentiated on the basis of symmetry. Oxaiceane has a plane of symmetry whereas the *abeo* isomer is chiral. Consequently one could resolve[176] the starting alcohol, which is also chiral, and determine the optical activity of the products. Differentiation on this particular basis was never tried as the structures were eventually assigned as follows.

In the presence of an n.m.r. shift reagent[177-182,205] oxaiceane, a meso compound, would give one complex whereas *abeo*-oxaiceane, a racemic mixture,[176] would give two. Because the latter are enantiomers they would still appear as only one compound in the n.m.r. spectrum. However, in the presence of a chiral shift reagent,[183-187] the meso compound would give enantiomers,[186,187] which would appear as one compound in the n.m.r. spectrum, while the racemic mixture would give diastereoisomers[176] together with their

mirror images. These would appear as two compounds in the n.m.r. spectrum.

The main feature of the n.m.r. spectrum of each isomer, in the absence of any shift reagent, was the absorption of protons on carbon bearing oxygen. In oxaiceane these protons were equivalent and although each had three neighbours, there was only one significant coupling which produced a symmetrical broadened doublet at δ 4.22 (figure 9a). In *abeo*-oxaiceane, these protons are non equivalent and appeared as an unsymmetrical multiplet centred at δ 4.20 (figure 10a). The remainder of the spectrum of oxaiceane revealed a more symmetrical structure than that of its isomer.

When a chiral n.m.r. shift reagent* was added to a sample of oxaiceane, the two protons on the carbon bearing oxygen were no longer equivalent but diastereotopic, and each one showed an absorption in the n.m.r. spectrum (figure 9b). On addition to the enantiomers of *abeo*-oxaiceane, these two protons became non equivalent in both diastereoisomers so formed and the n.m.r. spectrum was complicated due to coupling (figure 10b). When these protons were

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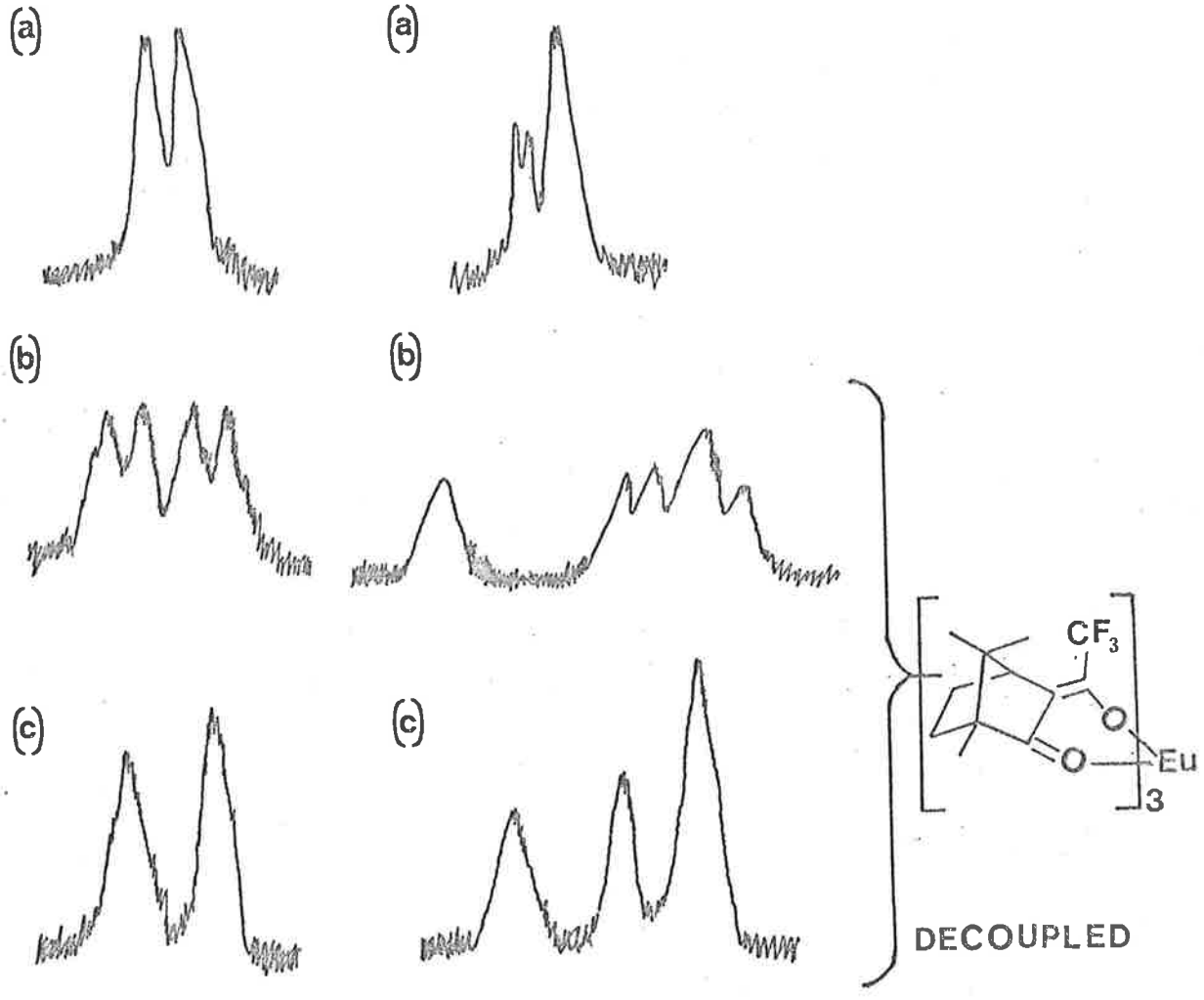
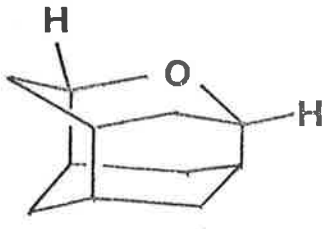
* Eu-Optishift I was purchased from the Willow Brook Labs. Inc., Waukesha, Wisconsin.





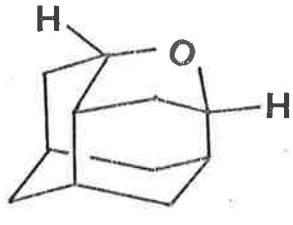


Figure 9

Figure 10

decoupled, oxaiceane clearly showed the presence of two diastereotopic protons (figure 9c) whereas the *abeo*-isomer showed four different protons although two were almost coincident in chemical shift (figure 10c).

The $^{13}C\{^{1}H\}$ n.m.r. spectra (figures 11 and 12) further confirmed the structural assignments. Oxaiceane has seven different carbon atoms. The spectrum showed absorptions (relative to TMS) at δ 69.7 (C2,C4), 31.2 (C5, C12 co-incident with C8, C11), 29.9 (C1, C9), 27.8 two almost superimposed absorptions (C6, C7) and 24.3 (C10) ppm. The off-resonance decoupled spectrum was consistent with the assignments. *Abeo*-oxaiceane showed in its $^{13}C\{^{1}H\}$ spectrum eleven absorptions (unassigned) at δ 76.7, 76.2, 38.4, 36.2, 35.5, 34.6, 34.4, 31.8, 29.7, 29.3 and 26.6 ppm. This is consistent with the eleven non equivalent carbon atoms in this isomer.

In the last chapter it was stated that one of the chloro isomers, chloride (83), obtained from the reaction of triphenylphosphine-carbon tetrachloride with the olefinic alcohol (59), had a chlorine atom at the prow position of a six-membered ring in a non-twist boat configuration. Recently it has been noted[188] that in oxymercuration reactions neighbouring groups give rise to *trans* addition of mercury and that neighbouring group. Moreover it has been shown, for example by Schleyer[189] in the oxymercuration of protoadamantane,[9] that the

$^{13}C(^{1}H)$nmr spectra

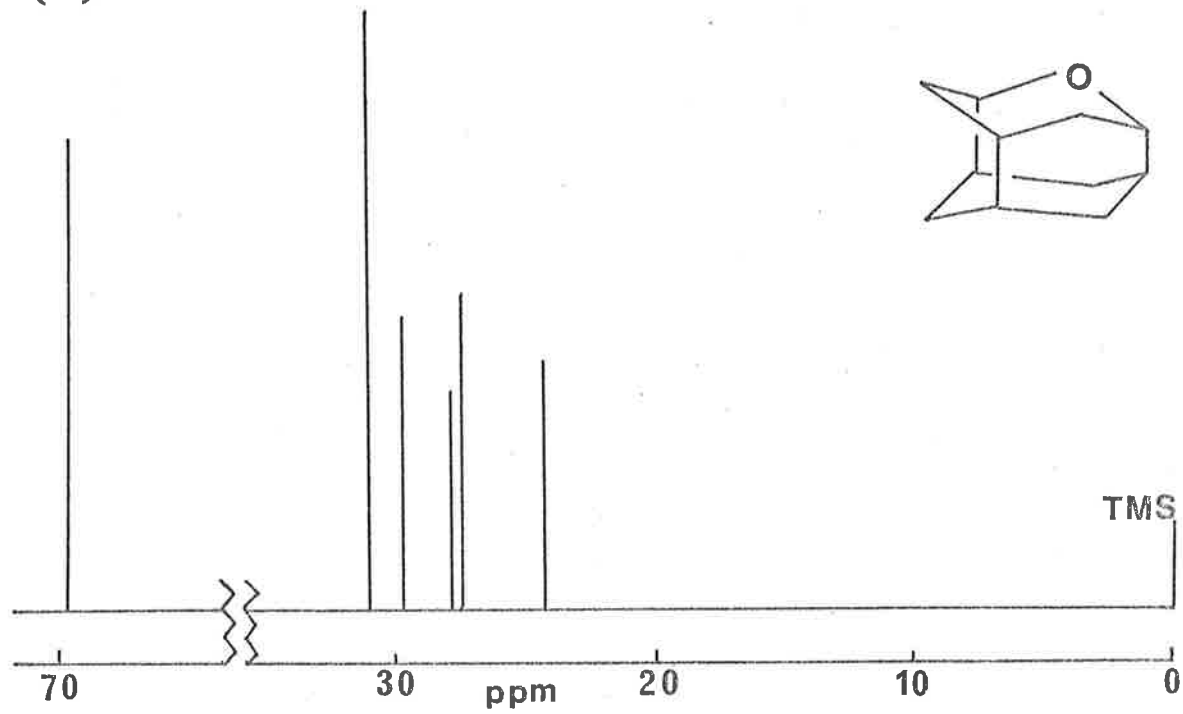


Figure 11

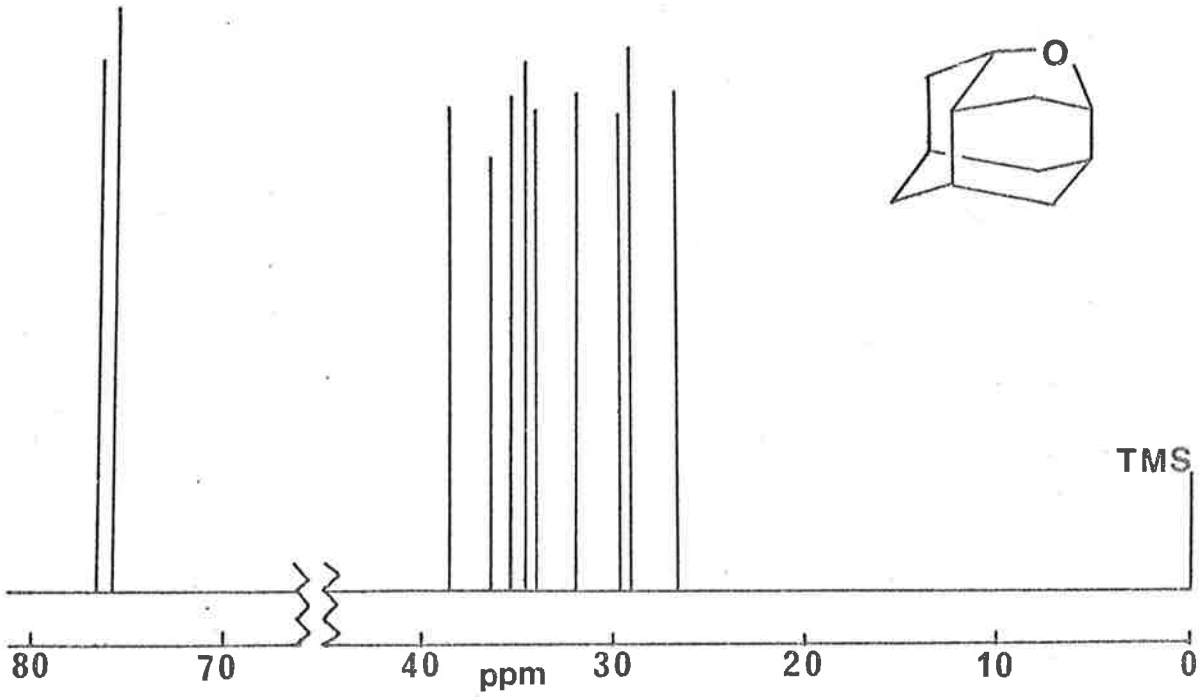


Figure 12

mercury presumably attacks from the less hindered face. If these conditions pertain in the formation of oxaiceane by the oxymercuration of olefinic-alcohol (45), then the intermediate compound (90) would have a large mercury group also at the prow position of a ring in a boat configuration. It was of interest therefore to attempt to define the stereochemistry of the mercury group in that intermediate.

It has been found[190] that halomercuri groups have no preference for an equatorial over an axial conformation; that is the A value[191,192] equals zero. Although the whole basis of 1:3 interactions has been thrown into doubt by the calculations of Allinger and Wertz,[193] the reason for the lack of preference is probably due, at least in part, to the long carbon-mercury bond.[190] Mercuri groups in the axial position of a ring in the boat configuration have previously been reported,[194,195] however no examples have been found which report a similar group in the prow position of a ring in such a configuration.

The reduction of organo-mercury compounds with sodium borohydride has been shown[196-200] to involve radical species and therefore not to be stereospecific as once thought.[175] However it has been shown[188,195,201,202] that sodium amalgam [204,205] reductions of such compounds are stereospecific with retention of configuration.

Reduction of the mercury compounds, formed upon oxymercuration of the olefinic alcohol (45), with $Na/Hg/D_2O$ gave regenerated alcohol

^{1}H nmr 90-MHz spectra

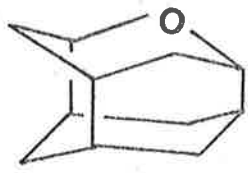


Figure 13

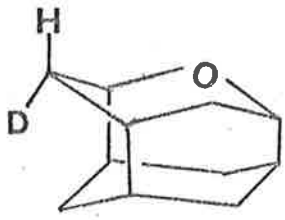


Figure 14

(45), and oxaiceane in a ratio of ca. 4:1 with less than 1% of *abeo*-oxaiceane being formed. The mass spectrum showed that the oxaiceane was greater than 95% a d_1 compound. The problem now was to determine the location of this deuterium.

The 90 MHz n.m.r. spectra (on different scales) of the undeuterated and deuterated oxaiceanes are shown in figures 13 and 14. They are basically the same except that the distorted doublet in oxaiceane centred at δ 1.45 has been replaced by a more complex pattern in the d_1 compound. Furthermore resonance between δ 1.5 and 2.4 in oxaiceane has been reduced in the dueterated species.

In the hope that these n.m.r. spectra could be more easily interpreted, europium shift studies were undertaken. Figure (15) shows the 60 MHz n.m.r. spectra of oxaiceane and d_1 oxaiceane in the presence of $Eu(fod)_3$.[205] The various proton resonances are labelled Ha to Hf for convenience. To aid the interpretation of the spectra a plot was drawn of the change in chemical shift of the various protons against the amount of shift reagent added (figure 16). Protons closest to the site of coordination of the $Eu(fod)_3$ should be shifted at a greater rate than those more distant from it [178,179] and consequently have a greater slope in the graph. By a combination of the results obtained from the graph and by decoupling various

regions of the n.m.r. spectrum (shown by the arrows in figure 15) it was possible to assign all of the protons in oxaiceane with the exception of two tertiary ones.

In the undeuterated spectrum of oxaiceane containing $Eu(fod)_3$, it was obvious that Hh were the protons on the carbon atoms C2 and C4 bearing oxygen. Since they were so far downfield they had to be closest to the site of coordination[178,179] and, furthermore, they were coupled to the tertiary protons He on C1 and C9. Hg and Hb, coupled and integrating for one proton each, were the equatorial and axial protons on C10 immediately below the oxygen atom. The equatorial proton, Hg, would be expected to be further down field and also to be more affected by the shift reagent since it is closer to the site of coordination. All the other peaks in the spectrum, except the one doublet Hf, have retained the same relative arrangement upon the addition of $Eu(fod)_3$. From the graph it can be seen that the protons Hf have moved down field faster than all other protons except those on the carbon bearing oxygen. This is consistent with Hf being the axial protons on C5 and C12 β to the oxygen atom since they would probably be in fairly close proximity to the europium coordinated to the oxygen. Moreover Hf integrates for 2 protons and is geminally coupled to the equatorial protons Hd. Ha and Hc are the remaining axial and equatorial protons respectively on C8 and C11.

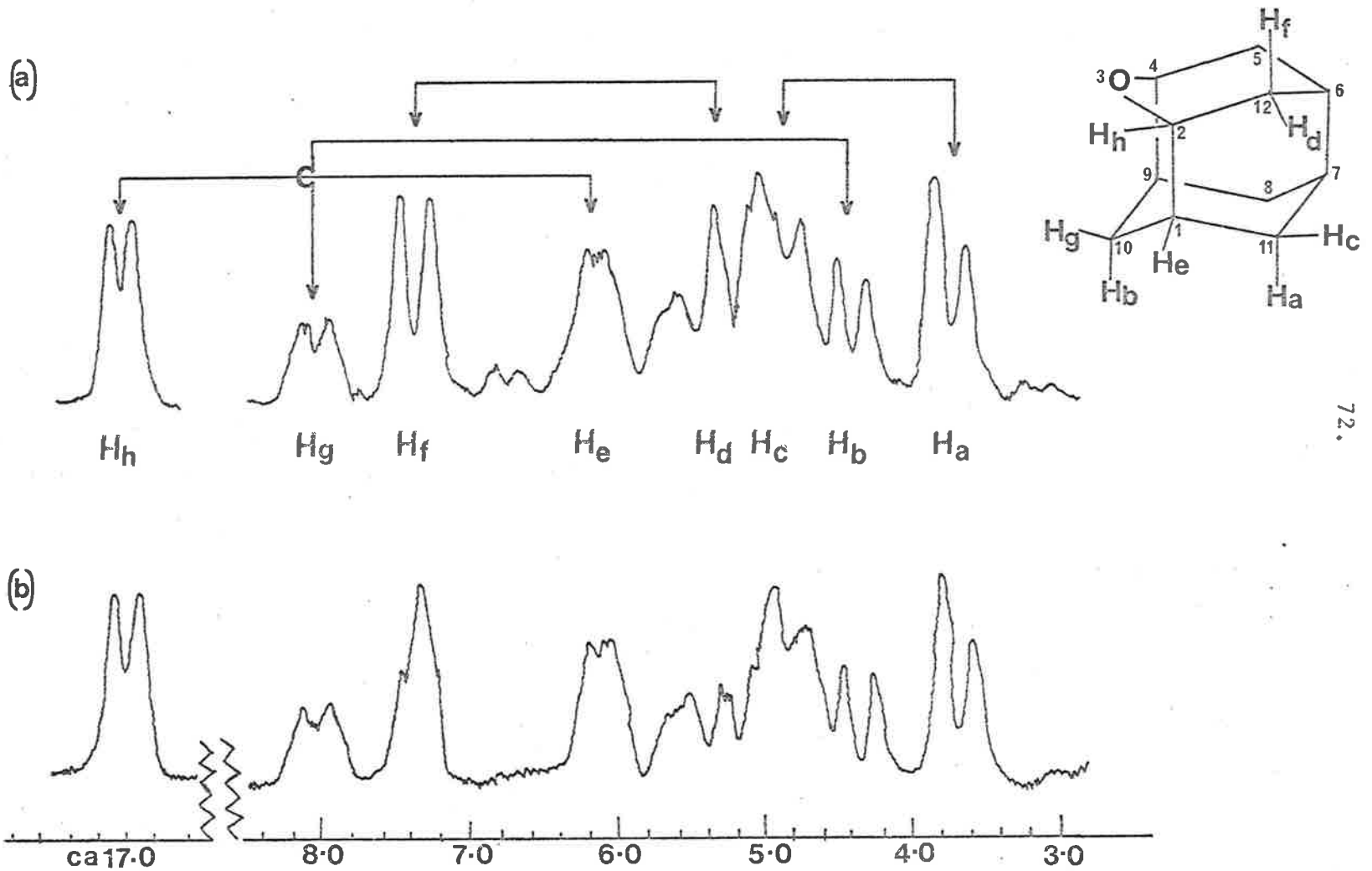

(a)
H_f
3 O
4
5
6
12
H_h
2
H_d
9
8
7
H_g
10
1
11
H_c
He
H_b
H_a
H_h
H_g
H_f
H_e
H_d
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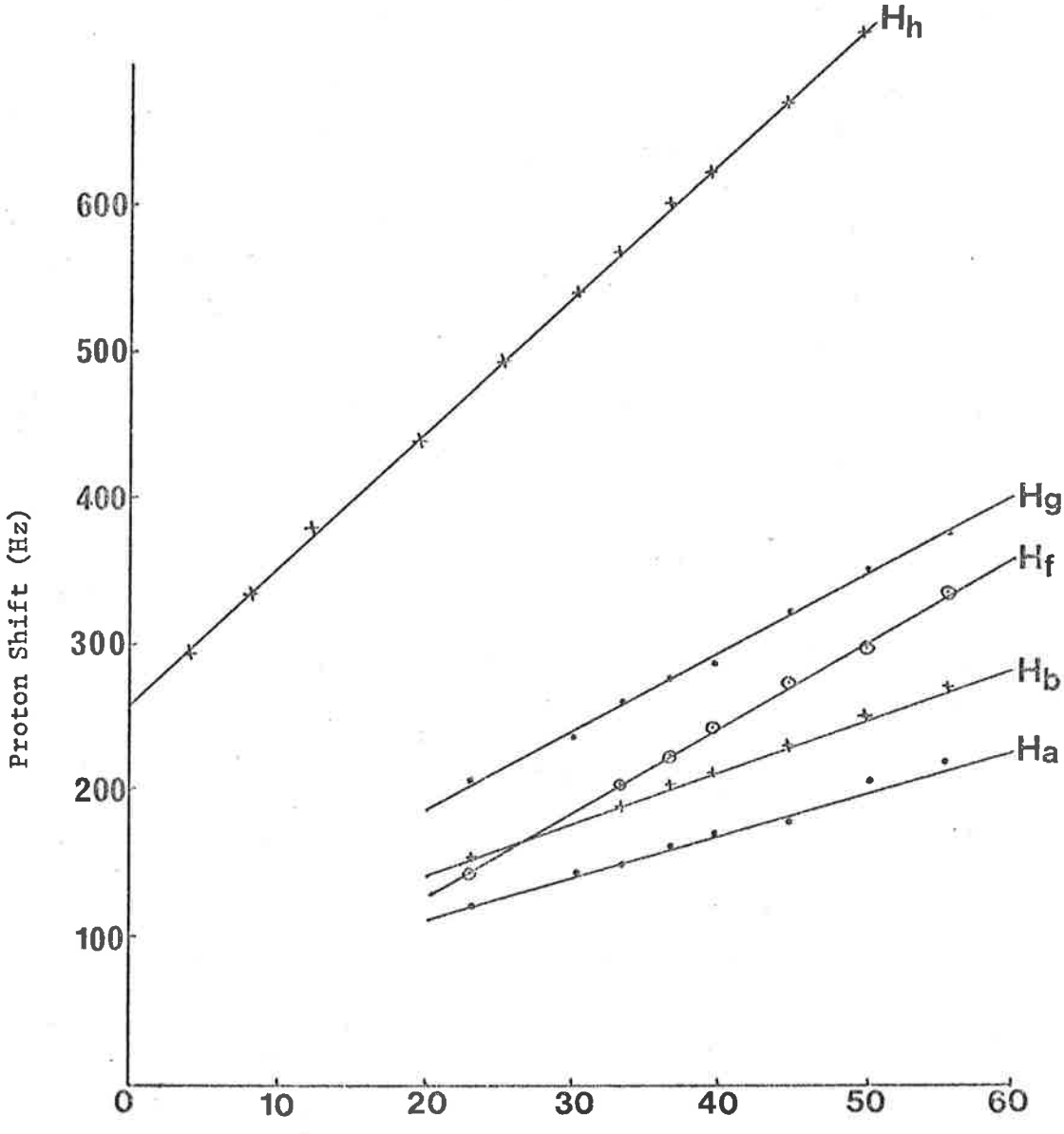
Figure 15



Change in chemical shift versus $Eu(FOD)_3$ for protons assigned in fig. 15a.

Figure 16

In the n.m.r. spectrum of the deuterated oxaiceane (figure 15b) it was seen that the resonance at Hf had changed from a broadened AB doublet to what appeared to be the original doublet (reduced) with an absorption superimposed upon it. The integration for this region was still for two protons (± *ca.* 5%) whereas the integration for the region Hd showed a decrease of one proton. Since the absorption at Hf is due to the axial protons on C5 and C12 in the ring containing the oxygen atom, whereas that at Hd is due to the equatorial protons on C5 and C12 in that same ring, it follows that one of these equatorial protons has been replaced by deuterium. The change in the appearance of the absorption at Hf is due to one of the axial protons remaining unchanged whereas the other experienced reduced geminal coupling to deuterium.

Little is known about the mechanism of sodium amalgam reductions,[195] but clearly there are competing pathways available to intermediates since some products of reductive elimination are usually also obtained.[175] In the present study the mercury compound which gave rise to *abeo*-oxaiceane, upon reduction with sodium borohydride, mainly underwent reductive elimination with sodium amalgam since very little *abeo*-oxaiceane was formed. A model of the supposed intermediate gave no reason to suspect steric hinderance as the cause for this. Calculations[168] on the carbon analogues of oxaiceane and *abeo*-oxaiceane showed that there was a difference in energy of ca. 9 Kcal/

mole between them. Thus it seemed likely that the strain inherent in the intermediate of *abeo*-oxaiceane changed the course of the reaction with sodium amalgam whereas in the case of oxaiceane, electrophilic substitution competed with reductive elimination.

Since it has been shown[188,195,201,202] that when reduction occurs with sodium amalgam, it does so with retention of configuration, the mercuri group in the intermediate (90) must be in the prow-position of a ring in a boat configuration, particularly since the deuterium atom has entered the molecule from the more hindered side. The fact that the deuterium has been located in the sterically congested prow position, emphasizes that the mechanism has not proceeded through a radical intermediate. This example is thus the most severe test to which the sodium amalgam reduction reaction has yet been put (figure 17).

After the completion of this work, Ganter published[15] a similar synthesis of oxaiceane in which the oxymercuration reaction was done in water rather than in tetrahydrofuran. In this report no mention was made of the concomitant formation of *abeo*-oxaiceane. This reaction was repeated in water and found in fact to produce less than 2% *abeo*-oxaiceane.

By using Ganter's method it was possible, after exchange of the ligands, to isolate the crystalline mercuri-chloride (91) (m.p. 255-257°). By reducing some of this compound with sodium-amalgam-D_2O

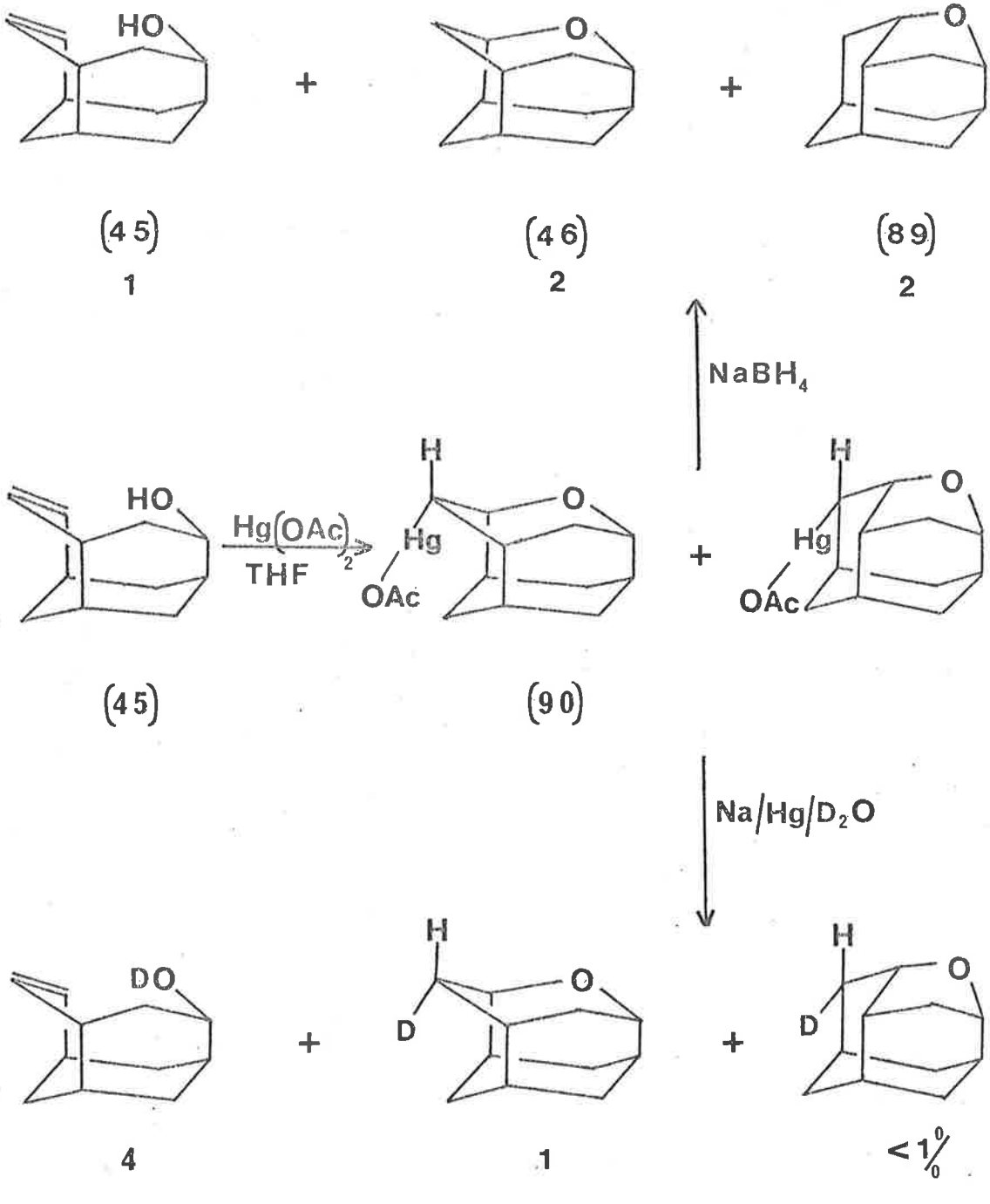
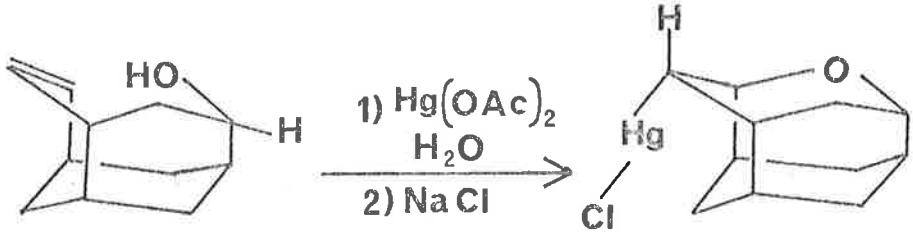

HO
O
O
(45)
1
(46)
2
(89)
2
NaBH4
HO
Hg(OAc)2
THF
H
Hg
OAc
O
H
Hg
OAc
O
(45)
(90)
Na/Hg/D2O
DO
H
D
O
H
D
O
4
1
< 1%

Figure 17

as before, it was shown that the change of solvent had not affected the trans addition and that the mercury substituent was still in the prow position.



(45) (91)

The structure (91) was confirmed by the following data. Both the mass spectrum and analytical data were consistent with the molecular formula $C_{11}H_{15}OHgCl$. The infrared spectrum showed no hydroxyl or acetate absorption. Because of the asymmetry introduced by the mercury atom, the protons on the carbon atoms bearing oxygen were no longer equivalent.[206] In the 90 MHz pulsed Fourier Transformed n.m.r. spectrum they were seen as two overlapping doublets centred at δ 4.42 and 4.27. The proton on the carbon adjacent to the mercury atom was observed as a broad singlet at δ 3.08. No mercury satellites,[206,207] however, for either of these resonances were observed. A sharp singlet at δ 1.61 could not easily be accounted for. It could possibly be attributed to the methyl group of the mercuric acetate (90). Difficulty was encountered in dissolving

sufficient salt into $CDCl_3$ to obtain the n.m.r. spectrum and so, because of its greater solubility, one could in fact be observing the spectrum of the mercuric acetate (90) and not that of the mercuric chloride (91).

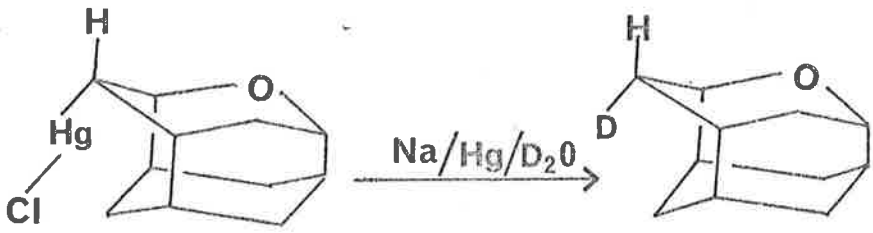
At the time of writing this thesis attempts were being made to grow a crystal of the mercuric chloride (91) suitable to obtain an X-ray structure of the molecule.

Having studied the reduction of the mercuric chloride (91) with $Na/Hg/D_2O$ in some depth, it was of interest to observe the same reaction but using sodium borodeuteride as the reducing agent. Because it was now established that the mercuri group was in an equatorial position in compound (91) it was now possible to determine, by comparison with the product obtained from the sodium-amalgam/D_2O reduction, whether reduction of a mercuric halide with sodium borodeuteride proceeded with or without retention of configuration.

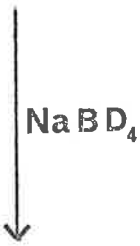
Treatment of the mercuric chloride (91) in ethanol with $NaBD_4$ afforded oxaiceane (26%) which was only 30% a d_1 compound (by mass spectrometry). The low deuterium incorporation could possibly be explained by the abstraction of a hydrogen atom from the ethanolic solvent. When the same reaction was performed in an alkaline solution of tetrahydrofuran the deuterium incorporation was only 21%. The

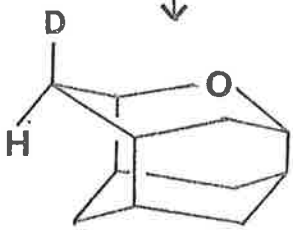
incorporation was marginally increased (50%) when $NaBD_4$ was added to the mercury salt suspended in a 3M solution of sodium hydroxide.

The 90 MHz n.m.r. spectrum of the deuterated compound (30% d_1) showed that the doublet at δ 1.45 due to the axial protons β to the oxygen atom had not partially collapsed as it had in the product from the $Na/Hg/D_2O$ reduction. This implied that there had been no incorporation in an equatorial position. This was substantiated when $Eu(fod)_3$ was added to the n.m.r. sample. The region Hf (figure 15) remained as a doublet ($J \simeq 14$ Hz) but the integration for 2 protons was down by 15%. Since deuterium would have replaced only one of the two axial protons, the actual incorporation must have been 30% d_1 which agrees with the mass spectral data. Moreover the integration for the equatorial protons (region Hd, figure 15) was unchanged ($\pm$ 5%) from the undeuterated species. From this evidence it was obvious that the deuterium had been incorporated into an axial position of the oxaiceane molecule. It was thus concluded that reduction of the mercury salt with sodium borodeuteride had not been stereospecific.



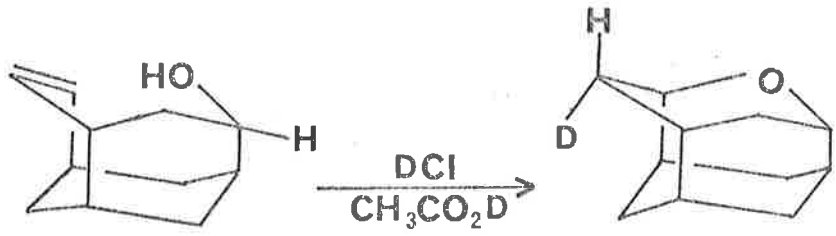
(91)





Cyclization of the olefinic alcohol (45) was also effected using deuterium chloride in deutero-acetic acid. The ratio of oxaiceane to *abeo*-oxaiceane was 3:2 and the mass spectrum of the product mixture indicated almost quantitative incorporation to d_1 compounds. The 90 MHz n.m.r. spectrum of the d_1 oxaiceane (isolated by preparative g.l.c.) was similar to that of the deuterated compound obtained from the $Na/Hg/D_2O$ reduction of the mercury salt (91). The distorted doublet at δ 1.45 in

undeuterated oxaiceane had been replaced by a more complex pattern in the d_1 compound. This implied that the deuterium had been incorporated into an equatorial position during the acid promoted cationic cyclization.



(45)

When the same reaction was performed using perchloric acid in acetic acid,[208] the ratio of oxaiceane to *abeo*-oxaiceane was 1:3. Initially this was rationalized on the basis that the stronger acid was offering the better equilibrating conditions and favoured the formation of the thermodynamic product whereas the weaker acid favoured the kinetic product. This, however, was in direct contrast to the calculations obtained by Schleyer[168] for the hydrocarbon analogues of these compounds.

When oxaiceane, *abeo*-oxaiceane and a mixture of both cyclic ethers were separately treated with perchloric acid in acetic acid at room temperature for 24 hr, no change was observed. It was thus concluded that the different ratios of isomers obtained with

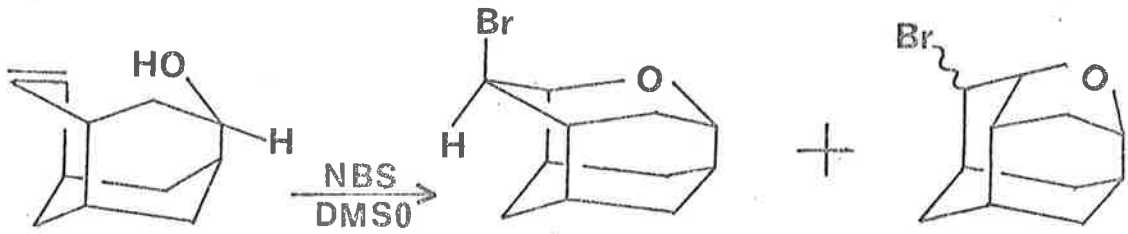
different acidic media was not due to equilibration but was probably a result of the varying degrees of solvation of the secondary carbonium[209] ions in the different media.

Treatment of the olefinic alcohol (45) in dimethyl sulphoxide with N-bromosuccinimide[210-213] gave (by t.l.c.) a single crystalline product. The mass spectrum of this material was consistent with the molecular formula $C_{11}H_{15}OBr$. The infrared spectrum showed no hydroxyl absorption and the n.m.r. spectrum showed no olefinic resonances but a complex multiplet between δ 4.1 and 4.6.

In the n.m.r. spectrum of chloro-iceane (83), the resonance for the axial proton adjacent to the chlorine atom in a prow position of a boat configuration appeared at δ 4.00. The introduction of an electronegative oxygen atom into this system should have the effect of shifting this particular proton further upfield.[212] In the present study, the proton on the carbon bearing bromine is also α to an oxygen atom. Because it resonates in the n.m.r. spectrum between δ 4.1 and 4.6 (i.e. downfield from the axial proton in (83)) it must be in an equatorial position with the bromine atom occupying the axial position. Moreover a bromine substituent does not usually produce as large a downfield shift as a chlorine substituent.

In an attempt to determine the ratio of bromo-oxaiceane (92) to bromo-*abeo*-oxaiceane (93), the product mixture from the cyclization reaction with NBS was treated with lithium aluminium hydride.[215]

After heating under reflux for 60 hr, only starting material was recovered. However reaction of the bromo-compounds with tri-n-butyl stannane[169-171] under reflux in benzene for 4 hr, afforded oxaiceane and *abeo*-oxaiceane in the ratio of 1:4.



(45) (92) (93)

1 : 4

With the idea that an aqueous solvent might direct the bromine atom into the molecule from a different direction and so give a different ratio of products, the olefinic alcohol (45) was treated with N-bromosuccinimide in an aqueous solution[216] of tetrahydrofuran. However the spectral data of the product so formed was identical to that of the product mixture from the previous cyclization with NBS. Moreover on reduction with tri-n-butyl stannane, the same ratio of products was obtained.

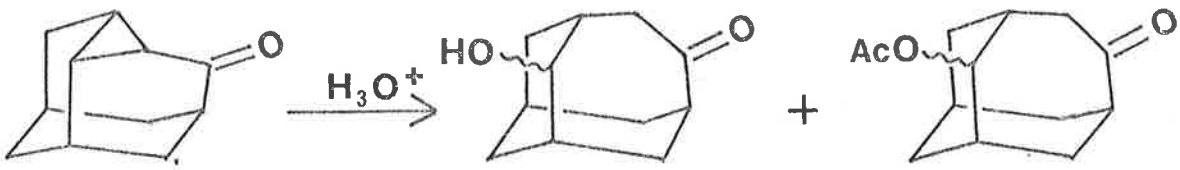
Since the formation of a chloro-oxaiceane isomer would serve as a more direct comparison with chloro-iceane (83) the

same cyclization reaction was attempted with N-chlorosuccinimide prepared according to the procedure of Grob and Schmid.[217] However all attempts to effect such a cyclization under a variety of conditions resulted in the starting olefinic-alcohol (45) always being recovered.

CHAPTER 5

An investigation of the products obtained from the acid catalysed opening of the cyclopropyl ring of ketone (23).

It was stated earlier (page 13) that fragmentation of the cyclopropyl ketone (23) under acidic conditions[28] appeared to give the keto-alcohol (29) and the keto-acetate (30), both of which had the homoadamantane[32-36] type carbon skeleton. In order to establish the structure of these products, deuterium incorporation studies were performed[28] on the corresponding dione. These strongly suggested that the alcohol did have the structure (29) which had arisen from C3-C4 cleavage of the cyclopropyl ketone (23). Because the keto-acetate and ketol were interconvertible, the acetate had also arisen from the same mode of cleavage.



(23) (29) (30)

As the carbon skeleton of keto-alcohol (29) was that of homoadamantonol, conversion of ketol (29) to homoadamantanol would confirm the structure. The ketol was converted to the tosylate derivative (94) m.p. 118-119°, in 73% yield. Reduction of this compound with lithium aluminium hydride in boiling tetrahydrofuran seemed on one occasion to give homoadamantanol (95), after preparative

g.l.c., in very poor yield (figure 18). Only sufficient pure material was available, however, for a mixed melting point with authentic homoadamantanol, prepared by the literature method,[24] and this was undepressed. Attempts to repeat this conversion were even less successful and an intractable mixture of products was obtained. The difficulties[218] inherent in producing penta-coordinate intermediates in the adamantyl series is probably also carried over into the homoadamantyl series and therefore a group susceptible to reduction other than by SN2 processes was sought.

Bromo groups can be reduced from severely restricted sites using organotin hydrides[215] and recently it has been shown that lithium aluminium hydride is also effective.[215] The acid catalysed rearrangement of the cyclopropyl ketone (23), under the same conditions as reported earlier[28] except that the solution was saturated with sodium bromide, produced a new compound, m.p. 190-191° in 30% yield, as well as the keto-acetate (30) and ketol (29) described before. The analytical data and mass spectrum of this new compound were consistent with the molecular formula $C_{11}H_{15}BrO$. The infrared spectrum showed carbonyl absorption at 1685 cm^{-1} and the n.m.r. spectrum showed an absorption at δ 4.45 for the proton on the carbon atom also bearing bromine. Reduction of this bromoketone with lithium aluminium hydride[215] gave homoadamantanol (95)[24] (figure 18).

It followed therefore that the structure of this bromo-ketone

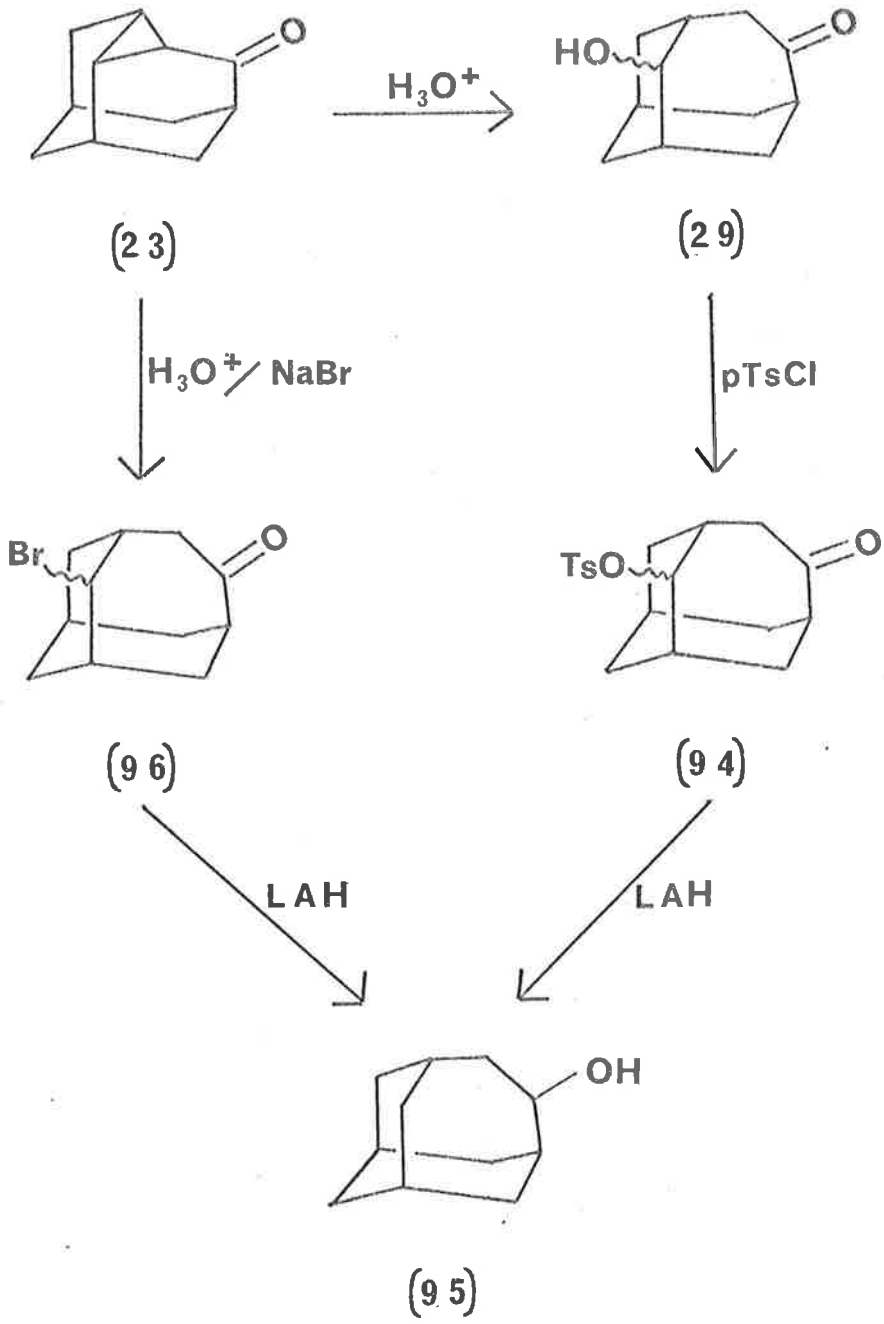
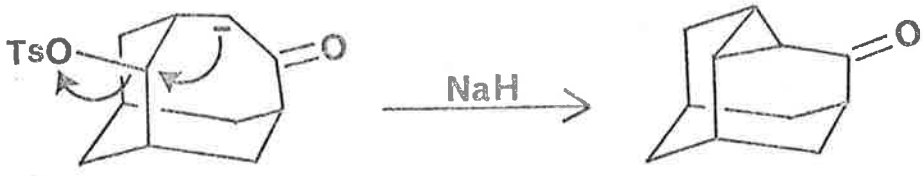


Figure 18

was as shown by (96). Doubt remained, however, as to the stereochemistry of the bromo group. As insufficient material was available to confirm this it was assigned by analogy with that of the ketol (29) which was determined in the following manner. Treatment of the tosylate (94) with sodium hydride in refluxing benzene regenerated the cyclopropyl ketone (23) in 73% yield. In order for the intramolecular alkylation to occur the tosylate, and hence the alcohol (29) and acetate (30) must have the *exo* stereochemistry depicted.



(94) (23)

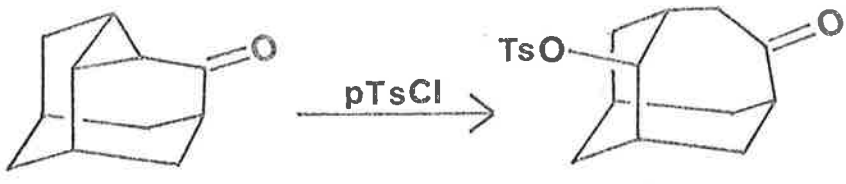
Since the acid catalysed cleavage of the cyclopropyl ring had occurred with high specificity, it seemed reasonable to assign the same stereochemistry to the bromo group in compound (96).

In these rearrangements it was not clear whether or not the thermodynamic product was being formed. Treatment of the ketol (29) under the same reaction conditions (without added bromide) gave a similar ratio of ketol and keto-acetate as found in the rearrangement. This might reflect, however, the position of the equilibrium for the acid-catalysed esterification of the alcohol rather than the products

of ionisation of the carbon-oxygen bond. When the ketol (29) was treated under the reaction conditions in the presence of bromide ion, it appeared from the n.m.r. spectrum that both acetate and bromide were generated. G.l.c. showed a peak with the same retention time as the pure bromoketone (96). This peak did, however, appear to have a shoulder on it which the pure bromide did not. As insufficient material was available, an exact identity could not be made. It is possible that a mixture of bromides could be formed by SN2 processes not involving the generation of an intermediate carbonium ion.

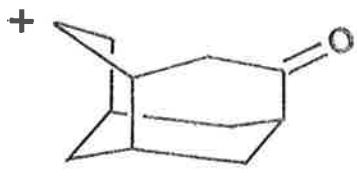
In the acid catalysed rearrangements described, the solvent was an exceptionally good solvating medium and could conceivably have been giving rise to "non vertical" ionisation of the bonds.[219] The alternative mode of ring opening might become favoured under different conditions where solvation effects are minimised. Overlap of the σ bond with the π orbital of the carbonyl group could then become the dominant factor particularly if there is also present a good nucleophile to trap the first formed carbonium ion. Alternatively the course of the reaction, if it involves equilibrating cations, might be diverted in the absence of a good nucleophile, to give an olefin. Because of the limitations expressed by Bredt's rule,[220] this should favour the formation of the olefinic ketone (40).

No new products were formed when the cyclopropyl ketone (23) was treated in benzene with gaseous hydrogen bromide and the starting material was recovered. Treatment of compound (23) with p-toluene-sulphonic acid in benzene gave directly the afore-mentioned tosylate (94).



(23) (94)

It was clear that no change in the direction of ring-opening had resulted and it seemed likely, in the light of previous work,[221] that in fact the first formed carbonium ion had been trapped and that the product had not risen from a rapid Wagner-Meerwein rearrangement of the cation (97).



(97)

CHAPTER 6

EXPERIMENTAL

General:

(1) Melting points were determined in sealed tubes in a Gallenkamp melting point apparatus and were uncorrected.

(2) Infrared spectra were recorded on either a Perkin-Elmer 337, a Unicam SP200 or a Jasco IRA-1 grating infrared spectrophotometer, using the 1603 cm^{-1} band of polystyrene as a reference.

(3) ^{1}H 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, using tetramethylsilane as an internal reference. Data are given in the following order: solvent; chemical shift (δ); multiplicity, s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), dd (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 1Hz, $W_{\frac{1}{2}}$ means peak width at half-height; relative intensity as number of protons (H); assignment. All n.m.r. spectra are interpreted on a first order basis. Centres of doublets are quoted although this is not strictly true for all the doublets recorded.

(4) ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker HX-90-E spectrometer operating at 22.625 MHz using

tetramethylsilane as an internal reference. Sufficient pulse spacing was employed to allow adequate time for the relaxation process.

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

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

(7) Gas chromatographic analyses (G.C.) were performed using Pye Unicam 104 and 105 models. Both instruments were fitted with flame ionization detectors and nitrogen was used as the carrier gas. The columns, constructed of pyrex glass, were (a) FFAP, 20%, 2m x 8mm, (b) OV-101, 15%, 2m x 4mm, and (c) SE52, 20%, 1m x 10mm. Data are given in the following order: column; flow rate; temperature; retention time (min/sec, to the nearest 10 sec). Because detector responses were not determined, product ratios are only approximate.

(8) Analytical and preparative thin layer chromatography (t.l.c.) plates were prepared from 50% Kieselgel G and HF 254 applied to the glass plates as a suspension in water and activated at 120°. Column chromatography was carried out on Sorbsil silica gel or Spence neutral alumina. All elutions employed dry redistilled solvents.

(9) The commonly used anhydrous solvents were purified as follows. Ether and 1,2-dimethoxyethane were dried over calcium

chloride granules for 48 hr, distilled from phosphorus pentoxide and stored over sodium wire. When required further drying was achieved by distillation from lithium aluminium hydride. Reagent grade tetrahydrofuran was distilled from lithium aluminium hydride immediately before use. Benzene was dried by refluxing over a water separator until no more water was collected, then distilled and stored over sodium wire. Petroleum ether, hexane, chloroform and methylene chloride of sufficient dryness were obtained by distillation. Pyridine was heated under reflux over potassium hydroxide pellets for 24 hr, then distilled from fresh potassium hydroxide and stored over 4A° molecular sieves. Acetic anhydride was distilled from calcium carbide.

(10) In this text, petroleum ether refers to the fraction of b.p. 50-65°.

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

(12) Ethereal diazomethane was prepared from N-nitroso-methylurea.[91] It was dried over potassium hydroxide pellets for 3 hr but was not distilled.

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

Chapter 2

exo-8-bromo-tricyclo[3.3.1]non-6-ene-*endo*-3-carboxylic acid (47).

To the olefinic acid (27) (30 g, 0.181 mole) dissolved in carbon tetrachloride (800 ml, spectroscopic grade) was added N-bromosuccinimide (38.63 g, 0.217 mole, recrystallized twice from water[82] and dried at 0.1 mm over phosphorus pentoxide) and azoisobutylronitrile (*ca.* 20 mg). The mixture was heated under reflux, without stirring, for 30 min, during which the heavy precipitate of NBS gave way to a light precipitate of succinimide. The cooled solution was filtered (celite) and evaporated under reduced pressure to afford a white crystalline solid which could be purified by recrystallization from carbon tetrachloride (43.8 g, 98%).

m.p. 156-158°

i.r. (Nujol); 3300-2300 (br. OH), 1685 (C=O) and 1630 cm^{-1} (C=C)

n.m.r. ($CDCl_3$); δ 5.78 (br. s, 2H, HC=CH), δ 4.88 (br. s, 1H, HCBR) and δ 1.2-3.4 (complex).

Mass spectrum; m/e 165 (M^+ calculated for $C_{10}H_{13}O_2Br$-Br = 165).

Analysis; Found C, 48.77; H, 5.49; $C_{10}H_{13}O_2Br$ requires C, 48.98; H, 5.31.

exo-8-bromo-bicyclo[3.3.1]non-6-ene-*endo*-3-carboxylic acid chloride (50)

The bromo-acid (47) (43 g, 0.176 mole) in methylene chloride (800 ml, dried for 12 hr over potassium hydroxide) was added over 2 hr under nitrogen to a stirred solution of oxalyl chloride (37 ml,

0.44 mole) in methylene chloride (300 ml) containing pyridine (14.2 ml, 0.176 mole) at room temperature. After a further 15 hr the solution was evaporated under reduced pressure and the residue was taken up in dry benzene (100 ml). Filtration through celite in a sinter funnel followed by evaporation gave a pale yellow oil which was again dissolved in benzene and evaporated to remove excess oxalyl chloride. This was repeated twice more to afford a viscous pale yellow oil (43.2 g) which was not purified.

i.r. (film); 1790 (C=0) and 1725 cm (C=0 from lactone impurity)

n.m.r. ($CDCl_3$); δ 5.54 (br, s, HC=CH), δ 4.5 (br. s., HCBr, lactone), δ 4.2 (m, HCBr, acid chloride) and δ 1.0-3.2 (complex)

Hydrolysis of bromo-acid chloride (50)

A small portion (1.0 g) of the crude product mixture obtained from the above reaction was dissolved in dimethoxyethane (5 ml) and hydrolysed with 5% sodium bicarbonate solution (5 ml). After 2 hr the solution was extracted with ether (2 x 10 ml) and the combined ethereal extracts were washed with 5% sodium bicarbonate (2 x 10 ml) and water (2 x 10 ml), dried ($MgSO_4$) and evaporated to give a white crystalline solid (0.35 g).

i.r. (Nujol); 1730 cm^{-1} (C=0)

n.m.r. ($CDCl_3$); δ 5.4-6.3 (m, 2H, HC=CH), δ 4.9 (m, 1H, HC=CHCHO), δ 4.3 (m, HCBr from bromo-lactone (48)) and δ 0.9-3.0 (complex).

exo-8-bromo-*endo*-3-diazoacetyl-bicyclo[3.3.1]non-6-ene (53)

The crude acid chloride (50) (42 g, 0.160 mole) in dry ether (200 ml) was added over 30 min to a stirred ice-cold solution of diazomethane[90,91] (*ca.* 0.6 mole) in dry ether (800 ml). The reaction mixture was allowed the warm to room temperature during 18 hr, then heated to 50° to drive off excessive diazomethane. Concentration of the solution gave a yellow oil which crystallized on standing at 0° (38.5 g).

i.r. (film); 3080 (C=C), 2100 ($-N_2$), 1630 (C=O) and 1725 cm^{-1} (C=O from lactone impurity).

n.m.r. ($CDCl_3$); δ 5.72 (m, 2H, HC=CH), δ 5.27 (s, 1H, $COCHN_2$), δ 4.83 (br. s, 1H, CHBr) and δ 1.0-3.3 (complex).

exo-6-bromo-tetracyclo[5.3.1.$0^{3,5}0^{4,9}$]undecan-2-one (39).

The crude diazo-ketone (53) (38.0 g, 0.141 mole) in cyclohexane (350 ml, spectroscopic grade) was added under nitrogen over 2 hr to a stirred suspension of copper powder (30 g, Merck, dried at 110° for 1 hr) in cyclohexane (600 ml) heated under reflux. After a further 2 hr, the reaction mixture was filtered and concen-

centrated under vacuum to give a yellow oil. Purification by column chromatography on Sorbsil (1000 g) eluting with ether-petroleum ether, gave the cyclopropyl ketone (39) as a white crystalline solid (17.67g, 52%). Repeated crystallizations from carbon tetrachloride, ether-petroleum ether and ethanol gave a compound (m.p. 81-82°) which failed on three occasions to provide satisfactory analytical data. In all cases the values obtained for both carbon and hydrogen were too high by 1-2%.

i.r. (Nujol); 3000 (cyclopropyl C-H) and 1680 cm^{-1} (C=O)

n.m.r. ($CDCl_3$); 4.52 (s, HCBr) and δ 0.7-3.0 (complex).

Mass spectrum; m/e 240 and 242 (M^+ calculated for $C_{11}H_{13}OBr$ = 241).

Reaction of bromo-cyclopropyl ketone (39) with lithium.

The bromo-cyclopropyl ketone (39) (70 mg, 0.29 mmole) in dimethoxyethane (1 ml) was added under nitrogen to a stirred suspension of finely cut and beaten lithium (*ca.* 10 mg) in dimethoxyethane (1 ml) heated under reflux. The solution was refluxed for a further 1 hr after which time it was cooled and quenched with water. The aqueous solution was extracted with ether (3 x 5 ml) and the combined ethereal layers were washed with water (2 x 10 ml), dried ($MgSO_4$) and evaporated to afford a semi-crystalline solid (55 mg).

i.r. (Nujol); 3400 (OH), 1700 (C=O) and 1680 cm^{-1} (C=O)

n.m.r. ($CDCl_3$); δ 5.2-6.4 (br., olefinic-protons) and δ 0.7-3.4 (complex)

G.C. FFAP (60 ml/min) (210°) showed 8 components some of which could be attributed to the decomposition of the starting bromocyclopropyl ketone (39) on the v.p.c. column.

The reaction was repeated except that the solvent dimethoxyethane was replaced by ether. The results obtained from this reaction were very similar to those obtained above.

Tricyclo[5.3.1.$0^{4,9}$]undec-5-en-2-one (40)

To a stirred suspension of sodium-potassium alloy[111-113] (2.5 ml, 2.16 g, 0.06 mole) in anhydrous ether (15 ml) under nitrogen, was added dropwise over 20 min a solution of the bromocyclopropyl ketone (39) (3.0 g, 0.013 mole) in anhydrous ether (40 ml). The reaction mixture became dark blue during the addition and remained so during a further 40 min stirring at room temperature. The ethereal layer was removed by filtration under nitrogen. The remaining solids were treated, under nitrogen, with 10% ethanol in petroleum ether with stirring until all excess alloy was destroyed and the blue colour was discharged (1 hr). Water was added and the solution was extracted with ether (3 x 50 ml). The combined ethereal layers were washed with water (2 x 20 ml) dried ($MgSO_4$) and evaporated to give a white crystalline solid which was purified by preparative t.l.c. (ether:petroleum ether = 1:1). The compound of higher Rf was recrystallized (ether/petroleum ether) to give a

white crystalline solid (1.7 g, 81%) m.p. 258-260°. This was shown to be tricyclo[5.3.1.$0^{4,9}$]undec-5-en-2-one (40) by the following data.

i.r. (Nujol); 1710 cm^{-1} (C=O)

n.m.r. ($CDCl_3$); δ 6.1 (dd, 1H, HC=C), 5.6 (dd, 1H, HC=C) and δ 0.7-3.2 (complex).

Mass spectrum; m/e 162 (M^+ calculated for $C_{11}H_{14}O$ = 162)

Analysis; Found C, 81.41; H, 8.91; $C_{11}H_{14}O$ requires C, 81.44; H, 8.70.

G.C. FFAP (60 ml/min) (225°) 09/30.

The lower Rf material consisted of two alcohols which could be separated by preparative g.l.c.

(a) G.C. FFAP (60 ml/min) (225°) 07/30, m.p. 267-269°. This compound had identical spectral data to *endo*-2-hydroxy-tricyclo[5.3.1.$0^{4,9}$]undec-5-ene (45) the synthesis and characterization of which are described in Chapter 4. The mixed melting point was 267-270°.

(b) G.C. FFAP (60 ml/min) (225°) 10/30 was presumed to be *exo*-2-hydroxy-tricyclo[5.3.1.$0^{4,9}$]undec-5-ene (54), m.p. 235-237°.

In subsequent reactions the crude mixture of alcoholic and ketonic products (1.9 g) was dissolved in acetone (50 ml) and treated with Jones reagent[114] until the orange colour persisted. The mixture was poured into water and extracted with ether (3 x 30 ml). The combined ethereal extracts were washed with water (3 x 30 ml) dried

($MgSO_4$) and evaporated to yield pure tricyclo[5.3.1.$0^{4,9}$]undec-5-en-2-one (40) (1.9 g, 91%) m.p. 258-260°.

On one occasion a mixture of equal amounts of each alcohol was oxidized with Jones reagent. V.p.c. revealed that the *endo* alcohol was oxidizing at a much slower rate than the *exo* isomer.

The use of more concentrated ethereal solutions of sodium-potassium alloy during the reaction with bromocyclopropyl ketone (39) gave a small amount of bis-2-*endo*-2-hydroxy-tricyclo[5.3.1.$0^{4,9}$]undec-5-ene (55) as a white crystalline solid m.p. 235-239°.

i.r. (Nujol); 3520 (OH), 1640 cm^{-1} (C=C)

n.m.r. ($CDCl_3$); δ 6.2 (m, HC=CH), δ 2.68 (s, removed with D_2O, OH) and δ 1.0-2.6 (complex).

Mass spectrum; m/e 326 (3%) (M^+ calculated for $C_{22}H_{30}O_2$ = 326). Base peaks at 163 and 164.

Tricyclo[5.3.1.$0^{4,9}$]undecan-2-one (24).

A) A solution of the cyclopropyl-ketone (23) (0.1 g, 0.617 mmole) in anhydrous ether (5 ml) was added dropwise to a stirred solution of lithium (30 mg) in liquid ammonia (25 ml, distilled from sodium) and the solution was allowed to reflux, under a dry ice condenser, for 1 hr. Ammonium chloride (20 ml) was added and the excess ammonia was distilled off. Water (20 ml) and ether (20 ml) were added and the solution was saturated with

sodium chloride. The aqueous layer was separated and extracted with ether (2 x 20 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated to give a white solid. Recrystallization (ether/petroleum ether) gave compound (24) (73 mg, 73%) m.p. 279-281°. Three further recrystallizations did not improve the melting point but analytical data was unsatisfactory. Sublimation of the material gave a compound m.p. 292-293°.

i.r. (Nujol); 1710 cm^{-1} (C=O)

n.m.r. ($CDCl_3$); δ 1.0-2.8 (complex).

Mass spectrum; m/e 164 (M^+ calculated for $C_{11}H_{16}O$ = 164).

Analysis; Found C, 81.04; H, 9.66; $C_{11}H_{16}O$ requires C; 80.48; H, 9.76.

B) The olefinic ketone (40) (20 mg, 0.123 mmole) in ethanol (40 ml) containing platinum oxide (20 mg) was hydrogenated for 3.5 hr at 3 atm. The catalyst was removed by filtration and the ethanol was evaporated to give a white crystalline solid (16 mg). The i.r. spectrum indicated that some reduction of the carbonyl group had occurred. This material was oxidized with Jones reagent[114] according to the usual procedure to give a white crystalline solid (12 mg, 60%) m.p. 279-281°, (after sublimation m.p. 293-294°). The i.r. spectrum was identical to that of the compound prepared in part A and the mixed melting point was 279-281° (before sublimation) and 291-293 (after sublimation).

Chapter 3.

exo-5-epoxy-tricyclo[5.3.1.$0^{4,9}$]undec-2-one (41).

To a stirred solution of the olefinic ketone (40) (0.5 g, 0.0031 mole) in methylene chloride (5 ml) was added a solution of *m* chloroperbenzoic acid (80%, 0.804 g, 0.037 mole) in methylene chloride (5 ml) and stirring was continued at room temperature for a further 20 hr. The precipitated benzoic acid was removed by filtration and the solution was washed with 5% sodium bicarbonate solution (3 x 20 ml), water (20 ml) and finally saturated sodium chloride solution (2 x 20 ml). The organic extract was dried ($MgSO_4$) and evaporated to give a white crystalline solid which was purified by preparative t.l.c. eluting with 40% ether-petroleum ether. The epoxy-ketone (41) was obtained from the major band (0.42 g, 76%). A pure sample (m.p. 285-287°) was obtained after recrystallization from carbon tetrachloride.

i.r. (Nujol); 1705 cm^{-1} (C=O)

n.m.r. ($CDCl_3$); δ 1.0-3.7 (complex).

Mass spectrum; m/e 178 (M^+ calculated for $C_{11}H_{14}O_2$ = 178).

Analysis; Found C, 73.82; H, 7.66. $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92.

6-methylidene-tetracyclo[5.3.1.$0^{3,5}0^{4,9}$]undec-*exo*-2-ol (57)

Methyltriphenylphosphonium iodide (1.12 g, 2.77 mmole),

potassium tertiary-butoxide (0.283 g, 2.53 mmole) and anhydrous ether (10 ml) were stirred together, under nitrogen, at room temperature for 2 hr, during which time the yellow colour of the phosphorane appeared. A solution of the epoxy-ketone (41) (0.15 g, 0.843 mmole) in anhydrous ether (10 ml) was added over 15 min and stirring was continued under nitrogen for a further 24 hr. After this time the reaction mixture was cooled and water (15 ml) was slowly added. The ethereal layer was removed, washed with water (2 x 10 ml), dried ($MgSO_4$) and evaporated to give a viscous oil. The crude product was purified by preparative t.l.c. (ether-petroleum ether = 1:1). The hydroxy-olefin (57) was obtained from the major band as a white crystalline solid (119 mg, 80%). A pure sample (m.p. 104-105°) was obtained after recrystallization from ether/ petroleum ether.

i.r. (Nujol); 3300 (OH), 3050, 2985 (methylene and/or cyclopropyl C-H), 1630 and 890 cm^{-1} ($C=CH_2$).

n.m.r. ($CDCl_3$); δ 4.73 (s, 2H, $C=CH_2$), δ 3.86 (s, 1H, $\underline{H}COH$), δ 1.75 (s, 1H, removed with D_2O, OH) and δ 0.8-2.8 (complex).

Mass spectrum; m/e 176 (M^+ calculated for $C_{12}H_{16}O$ = 176)

Analysis; Found C, 81.54; H, 8.92. $C_{12}H_{16}O$ requires C, 81.77; H, 9.15.

When this reaction was repeated at -78° using the same working up procedure, exactly the same result was obtained.

6-methylidene-tricyclo[5.3.1.$0^{4,9}$]undec-2-ene (58).

Methylene triphenylphosphonium iodide (27.7 g, 0.0686 mole), potassium tertiary-butoxide (7.0 g, 0.0625 mole) and anhydrous ether (100 ml) were stirred together, under nitrogen, at room temperature for 2 hr, during which time the yellow colour of the phosphorane appeared. A solution of the olefinic ketone (40) (3.7 g, 0.0228 mole) in anhydrous ether (60 ml) was added over 1 hr and stirring was continued under nitrogen for a further 18 hr. when t.l.c. (eluting with petroleum-ether) revealed that all starting material had been consumed. The reaction mixture was slowly poured into ice-cold water (100 ml) (to dissolve the precipitated salts), the ethereal layer was removed and the aqueous layer was extracted with ether (3 x 150 ml). The combined ethereal extracts were dried ($MgSO_4$) and the solvent was removed at atmospheric pressure. The residual oil was dissolved in hexane (100 ml) and washed with 75% methanol (2 x 150 ml). The methanol layers were combined and back extracted with hexane (100 ml). The combined hexane layers were washed with 75% methanol (2 x 50 ml), water (2 x 50 ml) and dried ($MgSO_4$). The solvent was removed by distillation at atmospheric pressure until a few ml remained and this was passed down a small column of alumina and eluted with hexane. The solvent was again removed at atmospheric pressure to afford a white crystalline solid (3.2 g, 88%). A pure sample of the diolefin (58) (m.p. 132-135°) was obtained by recrystallization from petroleum ether.

i.r. (Nujol);	3050, 3020 (olefinic C-H), 1640 and 890 cm^{-1} ($C=CH_2$).
n.m.r. ($CDCl_3$);	δ 6.17 (dd, J=8 and 9 Hz, 1H, HC=C), δ 5.50 (dd, J=4 and 9 Hz, 1H, HC=C), δ 4.76 (m, 2H, $C=CH_2$) and δ 1.1-3.1 (complex).
Mass spectrum;	m/e 160 (M^+ calculated for $C_{12}H_{16}$ = 160).
Analysis;	Found C, 89.94; H, 9.86. $C_{12}H_{16}$ requires C, 89.94; H, 10.06.

Attempted hydroboration of diolefin (58) with 9-boro-bicyclo-nonane (66)

9-boro-bicyclo-nonane (66)[123,124,136,137] (54 mg, 0.443 mmole) was added to a stirred solution of the diolefin (58) (70 mg, 0.438 mmole) in anhydrous tetrahydrofuran (5 ml) and stirring was continued at room temperature for a further 2 hr. The solution was cooled and, with stirring, potassium hydroxide solution (3M, 1 ml) was added followed by hydrogen peroxide (30%, 1 ml) and stirring was continued at room temperature for a further 2 hr. Water (10 ml) was added and the solution was extracted with ether (2 x 10 ml). The combined ethereal extracts were washed with sodium carbonate solution (10%, 5 ml), dried ($MgSO_4$) and evaporated. Both t.l.c. and spectroscopic data indicated that starting diolefin had been recovered. Neither using a second equivalent of 9-boro-bicyclo-nonane nor refluxing the reaction mixture for 2 hr prior to work up with alkaline hydrogen peroxide had any effect on this result.

Using the same conditions as employed above with 1 equivalent of 9-boro-bicyclo-nonane at room temperature, hex-1-ene, styrene and 2 methyl-but-2-ene were converted to hex-1-ol, 2 phenyl ethanol and 3 methyl-but-2-ol respectively.

endo-6-hydroxymethyl-tricyclo[5.3.1.$0^{4,9}$]undec-2-ene (59).

2-methyl-but-2-ene (12.53 ml, 0.118 mole) was added dropwise to a stirred solution of diborane (13.86 ml, 0.0394 moles in tetrahydrofuran) cooled to -10° (ice-salt bath), under an atmosphere of nitrogen and stirring was continued at this temperature for a further 2 hr to give disiamyl borane (0.0394 moles). The diolefin (58) (2.1 g, 0.013 mole) in anhydrous tetrahydrofuran (10 ml) was added dropwise over 10 min to the stirred solution and stirring was continued at -10° for a further 1 hr. At the same temperature sodium hydroxide solution (3M, 20 ml) was carefully added to avoid frothing, followed by hydrogen peroxide (30%, 20 ml). After the additions were complete, the solution was allowed to warm to room temperature, saturated sodium chloride solution (30 ml) was added and the aqueous solution was extracted with ether (3 x 15 ml). The combined ethereal extracts were washed with water (2 x 10 ml), dried ($MgSO_4$) and evaporated. The residual colourless oil was chromatographed on silica gel (100 g). Elution with ether-petroleum ether (1:1) gave the olefinic-alchol (59) as a white crystalline solid (1.23 g, 54%). A

pure sample (m.p. 186-187°) was obtained after recrystallization from petroleum ether.

i.r. (Nujol); 3300 (OH), 1640 cm^{-1} (C=C).

n.m.r. ($CDCl_3$) δ 6.04 (dd, J=9 and 7 Hz, 1H, HC=C), δ 5.64 (dd, J=9 and 5 Hz, 1H, HC=C), δ 3.35-3.90 (m, 2H, $-\underline{CH_2}OH$), δ 2.60 (s, 1H, removed with D_2O, OH), and 0.7-2.4 (complex).

Mass spectrum; m/e 178 (M^+ calculated for $C_{12}H_{18}O$ =178).

Analysis; Found C, 80.88; H, 10.19; $C_{12}H_{18}O$ requires C, 80.85; H, 10.18.

Oxymercuration of the olefinic-alcohol (59).

To a stirred solution of mercuric acetate (90 mg, 0.282 mmole) in anhydrous tetrahydrofuran (4 ml) was added the olefinic alcohol (59) (50 mg, 0.282 mmole) in tetrahydrofuran (4 ml) and stirring was continued, at room temperature, for 1 hr. Sodium hydroxide solution (3M, 1 ml) and sodium borohydride (0.5M in 3M NaOH, 1 ml) were added and stirring was continued for 1 hr. The mercury was removed by filtration and the aqueous solution was extracted with ether (2 x 5 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated. Recrystallization from ether-petroleum ether gave a white crystalline solid (43.5 mg, 87%) m.p. 275-277°. This compound was either cyclic ether 4-oxa-tetracyclo[6.3.1.$1^{2,7}0^{5,10}$]tridecane (68) or 4-oxa-tetracyclo[5.3.1.$1^{2,6}1^{5,9}$]tridecane (69).

i.r. (Nujol); complex fingerprint region.

n.m.r. ($CDCl_3$); δ 4.6 (m, 1H, CH-O-), {δ 4.36 (br. d, J=11Hz, 1H), δ 3.81 (d, J=11Hz, 1H), CH_2-O-} and δ 0.7-2.7 (complex).

Mass spectrum; m/e 178 (M^+ calculated for $C_{12}H_{18}O$ = 178)

Analysis; Found C, 81.00; H, 9.92; $C_{12}H_{18}O$ requires C, 80.85; H, 10.18.

Attempts to form *endo*-6-*p*-toluenesulphonoxymethyl-tricyclo[5.3.1.$0^{4,9}$] undec-2-ene (61)

A) To a solution of the olefinic alcohol (59) (60 mg, 0.337 mmole) in anhydrous benzene (3 ml), cooled to 0°, was added sodium hydride (8.1 mg, 0.337 mmole) and *p*-toluenesulphonyl chloride (64.4 mg, 0.337 mmole) and stirring was continued at room temperature for a further 15 hr. Water (5 ml) was added and the aqueous solution was extracted with ether (3 x 5 ml). The combined ethereal extracts were washed with water (2 x 5 ml), dried ($MgSO_4$) and evaporated. T.l.c. on the oily residue obtained showed that mainly starting material had been recovered.

B) *p*-toluenesulphonyl chloride (129 mg, 0.674 mmole) was added to a stirred solution of the olefinic alcohol (59) (60 mg, 0.337 mmole) in pyridine (3 ml) and stirring was continued at room temperature for a further 36 hr. Water (5 ml) was added and the

aqueous solution was extracted with ether (3 x 5 ml). The combined ethereal extracts were washed with hydrochloric acid (10%, 3 x 5 ml), dried ($MgSO_4$) and evaporated. T.l.c. of the oily residue again revealed that mainly starting alcohol had been recovered.

endo-6-methylsulphonoxymethyl-tricyclo[5.3.1.$0^{4,9}$]undec-2-ene (80).

Methylsulphonyl chloride (68 mg, 0.592 mmole) was added to a stirred solution of the olefinic alcohol (30 mg, 0.169 mmole) in pyridine (0.5 ml) and stirring was continued at room temperature for 18 hr. Water (5 ml) was added and the aqueous solution was extracted with ether (3 x 5 ml). The combined ethereal extracts were washed with hydrochloric acid (10%, 4 x 5 ml), dried ($MgSO_4$) and evaporated. Purification of the oily residue by preparative t.l.c. (eluting with ether:petroleum ether = 1:1) afforded a white crystalline solid (20 mg, 46%).

m.p. 40-41°.

i.r. (Nujol); 1170 cm^{-1} (S=O)

n.m.r. ($CDCl_3$); δ 6.17 (dd, J=9 and 7Hz, 1H, HC=C), δ 5.69 (dd, J=9 and 5 Hz, 1H, HC=C), δ 4.0-4.5 (m, 2H, $-CH_2SO_2-$), δ 2.91 (s, 3H, $-SO_2CH_3$) and δ 1.0-2.8 (complex).

Mass spectrum; m/e 256. (M^+ calculated for $C_{13}H_{20}O_3S$ = 256).

Attempts to form *endo*-6-chloromethyl-tricyclo[5.3.1.$0^{4,9}$]undec-2-ene (81)

A) Pyridine hydrochloride (36 mg, 0.312 mmole) was added to

the olefinic mesylate (80) (20 mg, 0.078 mmole) in dimethylformamide (1 ml) and the solution was allowed to stand at room temperature for 18 hr. After this time t.l.c. revealed that no reaction had occurred. After standing for 14 days the result was still the same.

B) The olefinic alcohol (46 mg, 0.258 mmole) in chloroform (1 ml) was added dropwise, under nitrogen, to a solution of phosphorus pentachloride (63 mg, 0.3 mmole) in chloroform (2 ml) cooled to -80°. The temperature was allowed to equilibrate to room temperature over 1 hr at which time t.l.c. revealed that no reaction had occurred. After 3 hr at room temperature, t.l.c. (eluting with petroleum ether) showed a weak band at high Rf in addition to the starting alcohol. This band increased only slightly in intensity after refluxing the solution for 24 hr. Isolation of this band by preparative t.l.c. afforded an oily solid (6 mg, *ca.* 10% of product mixture).

n.m.r. ($CDCl_3$); δ 3.75-4.05 (m) and δ 0.6-3.0 (complex).

exo-3-chloro-tetracyclo[5.3.1.$1^{2,6}0^{4,9}$]dodecane (83) and *endo*-3-chloro-tetracyclo[5.3.1.$1^{2,6}0^{4,9}$]dodecane (85).

Triphenylphosphine (9.43 g, 0.036 mole) in carbon tetrachloride (50 ml, spectroscopic grade) was added, under nitrogen, to a solution of the olefinic alcohol (59) (1.6 g, 0.009 mole) in carbon tetrachloride (50 ml) and the solution was heated under reflux for 5 hr. After this

time t.l.c. showed the absence of any starting alcohol. The precipitated triphenylphosphine oxide was removed by filtration and the solvent was removed by distillation at atmospheric pressure. The residue was redissolved in petroleum ether (5 ml) and chromatographed on silica gel (100 g) eluting with the same solvent. Evaporation of the solvent and subsequent recrystallization of the residue from petroleum ether, gave a mixture of the epimeric chlorides (83) and (85) as a white crystalline solid (0.97 g, 55%). This mixture was not resolved but used directly in the next reaction.

Analysis; Found C, 73.52; H, 8.73; $C_{12}H_{17}Cl$ requires C, 73.28; H, 8.65.

The two epimeric chlorides could be separated by preparative g.l.c.

A) G.C. FFAP (60 ml/min) (190°) ~~86/00~~ was *exo*-3-chloro-tetracyclo[5.3.1.$1^{2,6}0^{4,9}$]dodecane (83) m.p. 215-217°.

i.r. (Nujol); complex fingerprint region.

n.m.r. ($CDCl_3$) (90 MHz); δ 4.00 (br. s, CHCl) and δ 0.7-3.2 (complex).

Mass spectrum; m/e 196 and 198. (M^+ calculated for $C_{12}H_{17}Cl$ = 196 and 198

B) G.C. FFAP (60 ml/min) (190°) ~~86/50~~ was *endo*-3-chloro-tetracyclo[5.3.1.$1^{2,6}0^{4,9}$]dodecane (85) m.p. 272-274°.

i.r. (Nujol); complex fingerprint region.

n.m.r. ($CDCl_3$) (90 MHz); δ 4.82 (br. s, CHCl) and δ 0.6-2.7 (complex).

Mass spectrum; m/e 196 and 198. (M^+ calculated for $C_{12}H_{17}Cl$ = 196 and 198

A third peak in the g.l.c. trace (FFAP (60 ml/min) (190°) 04/45) was shown to arise by decomposition of the chloro-epimer (83). It had the following spectral data.

i.r. (Nujol); complex fingerprint region.

n.m.r. ($CDCl_3$) (90 MHz); δ 4.0 (br. s, HCCl) and δ 0.6-3.4 (complex)

Mass spectrum; m/e 196 and 198. (M^+ calculated for $C_{12}H_{17}Cl$ = 196 and 198

Tetracyclo[5.3.1.$1^{2,6}0^{4,9}$]dodecane (iceane) (1)

The mixture of epimeric chlorides (83) and (85) (375 mg, 1.91 mmole) in anhydrous, benzene (25 ml) was added, under nitrogen to tri-nbutyl-tin hydride (900 mg, 3.1 mmole) containing azobisisobutyronitrile (*ca.* 10 mg), and the solution was heated under reflux for 6 hr. The solution was cooled, carbon tetrachloride (5 ml) was added and refluxing was continued for a further 2 hr. The solvent was removed by distillation at atmospheric pressure. The residue was dissolved in ether (20 ml) and washed with sodium hydroxide solution (10%, 3 x 10 ml). The ethereal layer was dried ($MgSO_4$) and evaporated to give an oily solid which was recrystallized from chloroform to afford iceane (1) as white crystals (249 mg, 81%). This compound would not melt but sublimed at 325° when placed in a sealed tube of small volume.

i.r. (Nujol); 1130, 1065, 905 and 750 cm^{-1}.

^{1}H n.m.r. ($CDCl_3$) (90 MHz); δ 2.18 (br. s, bridgehead protons), δ 1.90 (d, Jgem = 12 Hz, equatorial protons) and δ 0.94 (d, Jgem = 12 Hz, axial protons). (figure 7).

^{13}C-{^{1}H} nmr ($CDCl_3$); δ 31.72 (s, C(3), C(5), C(8), C(10), C(11) and C(12)) and δ 28.70 (s, C(1), C(2), C(4), C(6), C(7) and C(9)). (figure 8)

G.C. FFAP (60 ml/min) (190°) 04/30

Mass spectrum; m/e 162 (M^+ calculated for $C_{12}H_{18}$ = 162).

Crystallography*; hexagonal crystals (from MeOH), cell constants a = 6.60 (1), C = 11.87 (1) A°, ρ = 1.04 g/cc giving FW = 210.5 (Z = 4), space groups $P6_3$ or $P6_{3/m}$ in which iceane must occupy positions of at least threefold symmetry.

Analysis; Found C, 88.99; H, 11.18; $C_{12}H_{18}$ requires C, 88.82; H, 11.18.

* see footnote on page 57.

Work related to the model compound limonene (70)

dl-*p*-menth-1-en-9-ol (71)

These compounds were prepared according to the method of Brown and Zweifel.[143] dl-*p*-menth-1,8-diene (limonene) (70) (5 g, 0.037 mole) gave the alcohols (71) (2.5 g, 43.9%) as a colourless liquid.

i.r. (film); 3300 (OH) and 1040 cm^{-1} (C-O)

n.m.r. ($CDCl_3$); δ 5.35 (br. s, 1H, C=CH), δ 3.75 (s, 1H, removed with D_2O, OH), δ 3.45 (m, 2H, $-CH_2OH$), δ 1.65 (s, 3H, C(1)-CH_3) and δ 0.92 (d, J = 6 Hz, 3H, C(8)-CH_3)

These values are in agreement with those reported for these compounds.[145]

dl-1,2-epoxy-*p*-menthan-9-ol (72)

To a stirred solution of the olefinic alcohols (71) (4.3 g, 0.0279 mole) in methylene chloride (20 ml) was added a solution of *m*-chloroperbenzoic acid (80%, 7.27 g, 0.0336 mole) in methylene chloride (20 ml) and stirring was continued at room temperature for a further 24 hr. The precipitated benzoic acid was removed by filtration and the solution was washed with 5% sodium bicarbonate solution (3 x 25 ml), water (25 ml) and finally saturated sodium chloride solution (2 x 20 ml). The organic layer was dried ($MgSO_4$) and evaporated to afford a colourless liquid (b.p. 100°/0.3 mm).

i.r. (film); 3400 (OH) and 1040 cm^{-1} (C-O-C)

n.m.r. ($CDCl_3$); δ 3.51 (s, 1H, removed with D_2O, OH), δ 3.38 (d, 2H, $CC\underline{H}_2OH$), δ 2.86 (d, J=5Hz, 1H, C-O-CH), δ 1.25 (s, 3H, C(1)-CH_3) and δ 0.80 (d, J = 6 Hz, 3H, C(8)-CH_3).

Mass spectrum; m/e 170 (M^+ calculated for $C_{10}H_{18}O_2$ = 170).

The values are in agreement with those reported for these compounds.[144]

Attempts to form dl-1,2-epoxy-9-chloro-*p*-menthane (74).

(A) With thionyl chloride and pyridine

Thionyl chloride (47.2 mg, 0.4 mmole) was added, under nitrogen, to a stirred solution of the epoxy-alcohols (72) (60 mg, 0.353 mmole) in ether (5 ml) containing pyridine (1 ml) and stirring was continued for 1 hr. The reaction mixture was then evaporated at reduced pressure and the residue was immediately chromatographed on Sorbsil (15 g) eluting with petroleum ether. Evaporation of the solvent gave a colourless liquid (52 mg) which consisted of at least 12 components by t.l.c.

(B) With thionyl chloride in ether

The epoxy-alcohols (72) (60 mg, 0.353 mmole) in anhydrous ether (2 ml) were added, under nitrogen, to a stirred solution of thionyl chloride (47.2 mg, 0.4 mmole) in ether (2 ml), cooled to -80°, and stirring was continued at this temperature for a further 15 min.

After equilibrating to room temperature over 1 hr, the reaction mixture was evaporated at reduced pressure, and the residue was immediately chromatographed on Sorbsil (15 g) eluting with petroleum ether. Evaporation of the solvent gave a yellow oil (40 mg) which was also shown (by t.l.c.) to consist of an intractable mixture of compounds.

(C) With triphenylphosphine in carbon tetrachloride

Triphenylphosphine (1.6 g, 6.11 mmole) in carbon tetrachloride (10 ml) was added dropwise, under nitrogen, to a stirred solution of the epoxy-alcohols (72) (0.2 g, 1.176 mmole) in carbon tetrachloride (10 ml) and stirring was continued at room temperature for 24 hr. The triphenylphosphine oxide was removed by filtration and the solvent was evaporated. The oily residue was placed on a preparative t.l.c. plate and eluted with petroleum ether. Evaporation of the solvent gave a colourless liquid which consisted of at least 5 compounds by t.l.c.

Attempts to form dl-9-chloro-*p*-menth-1-ene (75)

(A) With thionyl chloride

Thionyl chloride (2 ml) was added dropwise to rapidly stirring olefinic alcohols (71) (200 mg, 1.30 mmole). An immediate evolution of gas was observed and the reaction mixture became bright red. After

30 min excess thionyl chloride was removed by distillation at reduced pressure and the residue was purified by preparative t.l.c. (eluting with petroleum-ether). The major band was a colourless liquid (132 mg).

i.r. (film); 3300 (OH), 1200, 970 and 780 cm^{-1}.

n.m.r. ($CDCl_3$); δ 5.04 (br. s, removed with D_2O, OH), δ 3.90 (m, possibly $-CH_2Cl$), δ 3.45 (m, CH_2OH).

(B) With thionyl chloride in ether

The olefinic alcohols (71) (600 mg, 3.90 mmole) in anhydrous ether (20 ml) were added, under nitrogen, to a stirred solution of thionyl chloride (555 mg, 4.70 mmole) cooled to -5° and stirring was continued at this temperature for a further 30 min. After equilibrating to room temperature, the reaction mixture was evaporated at reduced pressure and immediately chromatographed on Sorbsil (100 g) eluting with ether-petroleum ether (1:1). Evaporation of the solvent gave a colourless liquid (510 mg).

b.p. 160°/0.5 mm.

i.r. (film); 1460, 1380, 1210 (S=O), 940 and 760 cm^{-1}.

n.m.r. ($CDCl_3$); δ 5.25 (br. s, HC=C), δ 3.85 (d, J = 5Hz), δ 1.65 (s, C(1)-CH_3) and δ 0.92 (d, J = 6 Hz, C(8)-CH_3).

It appeared that the reaction had stopped at the intermediate chlorosulphite. Attempts to convert this intermediate to the olefinic chlorides (75) included,

(a) standing at room temperature for 24 hr,

(b) refluxing in benzene for 5 hr,

(c) dissolving in ether and adding pyridine,

(d) dissolving in tetrahydrofuran and adding water and

(e) heating to 80° in an oil bath.

In cases (a) - (d) no change occurred. In (e) black polymeric material was recovered.

dl-9-iodo-*p*-menth-1-ene (77)

dl limonene (70) (2.0 g, 0.0147 moles) was added dropwise to a stirred solution of disiamyl borane (0.0206 moles), prepared in the usual manner, and stirring was continued at 25° for 1 hr. The solution was cooled to 0° and to it was added methanol (40 ml), iodine (3.73 gm, 0.0147 moles), all at once, and sodium hydroxide in methanol (5.17 ml, 0.0147 moles) over 5 min. The reaction mixture was then poured into water (75 ml) containing sodium thiosulphate (0.75 g). The aqueous solution was extracted with ether (2 x 50 ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed on Sorbsil (50 g) eluting with petroleum ether. The solvent was removed to give a colourless liquid (1.9 g, 49.0%) b.p. 82°/0.6 mm.

i.r. (film); 1190 and 780 cm^{-1}.

n.m.r. ($CDCl_3$); δ 5.35 (br. s, 1H, -C=CH), δ 3.22 (d, J = 5Hz, 2H, $-CH_2I$), δ 1.64 (s, 3H C(1)-CH_3) and δ 0.95 (d, J = 6 Hz, 3H C(8)-CH_3).

Mass spectrum; m/e 264 (M^+ calculated for $C_{10}H_{17}I$ = 264).

Analysis; Found C, 45.80; H, 6.64; $C_{10}H_{17}I$ requires C, 45.45; H, 6.44.

Attempted formation of dl 1,2 epoxy-9-iodo-*p*-menthane (78)

To a stirred solution of the olefinic iodide (77) (300 mg, 1.14 mmole) in methylene chloride (10 ml) was added a solution of *m*-chloroperbenzoic acid (80%, 300 mg, 1.39 mmole) in methylene chloride (10 ml). Immediately the reaction mixture turned bright red. After stirring for 15 hr, this solution was washed with sodium thiosulphate solution (10 ml), 5% sodium bicarbonate solution (2 x 10 ml), water (25 ml) and finally saturated sodium chloride solution (10 ml). The organic layer was dried ($MgSO_4$) and evaporated to afford a yellow liquid (140 mg), the n.m.r. spectrum of which was not consistent with the epoxy-iodides (78).

Chapter 4.

endo-2-hydroxy-tricyclo[5.3.1.$0^{4,9}$]undec-5-ene (45)

A suspension of sodium borohydride (1.407 g, 0.0370 mole) in ethanol (120 ml) was added dropwise to a stirred solution of the olefinic ketone (40) (3.0 g, 0.0185 mole) in ethanol (120 ml) and stirring was continued, at room temperature, for 3 hr. Saturated ammonium chloride solution (100 ml) was added and the reaction mixture was saturated with sodium chloride. The aqueous solution was extracted with ether (3 x 20 ml) and the combined ethereal extracts were washed with water (2 x 20 ml), dried ($MgSO_4$) and evaporated. Recrystallization of the residue from hexane gave a white crystalline solid (2.9g, 96%) mp 269-270°.

i.r. (Nujol); 3400 (OH), 3000 (olefinic C-H) and 1650 cm^{-1} (C=C).

n.m.r. ($CDCl_3$); δ 5.8-6.45 (m, 2H, HC=CH), δ 3.8-4.4 (m, 1H, HCOH), δ 2.04 (s, removed with D_2O, OH) and δ 1.0-2.9 (complex).

Mass spectrum; m/e 164 (M^+ calculated for $C_{11}H_{16}O$ = 164).

Analysis; Found C, 80.08; H, 9.69; $C_{11}H_{16}O$ requires C, 80.44; H, 9.83.

G.C. FFAP (60 ml/min) (225°) 07/30.

This compound was identical to one of the alcohols obtained from the sodium-potassium alloy reduction of bromo-cyclopropyl ketone (39). The mixed melting point with this compound was 267-270°.

3-oxa-tetracyclo[5.3.1.$1^{2,6}0^{4,9}$]dodecane (oxaiceane) (46) and

12-oxa-tetracyclo[5.3.1.$1^{2,5}0^{4,9}$]dodecane (*abeo*-oxaiceane) (89)

To a stirred solution of mercuric acetate (5.835 g, 0.0183 mole) in anhydrous tetrahydrofuran (100 ml) was added, dropwise and under nitrogen, a solution of the olefinic alcohol (45) (3.0 g, 0.0183 mole) in tetrahydrofuran (100 ml) and stirring was continued, at room temperature, for 1 hr. Sodium hydroxide solution (3M, 100 ml) and sodium borohydride solution (0.5M in 3M NaOH, 100 ml) were added and the reaction mixture was stirred for a further 1 hr, after which time, t.l.c. revealed that no starting alcohol remained. The mercury was removed by filtration and the aqueous solution was extracted with ether (3 x 30 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated to give a white crystalline solid (2.75 g). Regenerated starting olefinic alcohol (45) (0.50 g, 18%) was first removed from the product mixture by column chromatography on Sorbsil (200 g) eluting with ether:petroleum ether (1:1). A mixture of the two cyclic ethers was then eluted from the column with ether and was resolved by preparative g.l.c.

(a) G.C. FFAP (60 ml/min) (210°) 06/00 was 12-oxa-tetracyclo-[5.3.1.$1^{2,5}0^{4,9}$]dodecane (*abeo*-oxaiceane) (89), m.p. 256-257°.

i.r. (Nujol); complex fingerprint region.

^{1}H n.m.r. ($CDCl_3$); δ 4.0-4.4 (m, HCOCH) and δ 0.6-2.8 (complex).

^{13}C-{^{1}H} n.m.r. ($CDCl_3$); δ 76.7, 76.2, 38.4, 36.2, 35.5, 34.6, 34.4

31.8, 29.7, 29.3 and 26.6 (unassigned). (figure 12)

Mass spectrum; m/e 164 (M^+ calculated for $C_{11}H_{16}O$ = 164)

Analysis; Found C, 80.49; H, 9.52; $C_{11}H_{16}O$ requires C, 80.44; H, 9.83.

(b) G.C. FFAP (60 ml/min) (210°), 07/15 was 3-oxa-tetracyclo-[5.3.1.$1^{2,6}0^{4,9}$]dodecane (oxaiceane) (46) m.p. 314-315°.

i.r. (Nujol); complex finger-print region

^{1}H n.m.r. ($CDCl_3$) (90 MHz); δ 4.22 (d, 2H, H-C2 and H-C4, $J_{1,2}=J_{4,9}=$ 10 Hz), δ 1.5-2.4 (complex, 9H), δ 1.45 (d, 2H, C5-H_{exo} and C12-H_{exo}, J_{gem}=14 Hz), δ 1.16 (d, 1H, C10-H_{exo}, J_{gem}=11 Hz) and δ 1.11 (d, 2H, C8-H_{exo} and C11-H_{exo}, J_{gem}=13 Hz) (figure 13)

^{13}C-{^{1}H} n.m.r. ($CDCl_3$); δ 69.7 (C2,C4), 31.2 (C5,C12 co-incident with C8,C11), 29.9 (C1,C9) 27.8 two almost superimposed absorptions (C6,C7) and 24.3 (C10) (figure 11).

^{13}C-{^{1}H} n.m.r. ($CDCl_3$), off-resonance decoupled spectrum; δ 69.7 (d, C2,C4), 31.2 (t, C5,C12 co-incident with C8,C11), 29.9 (d, C1,C9), 27.8 (appeared to be a doublet but presumably two co-incident doublets, C6,C7) and 24.3 (not distinguishable from background noise).

Mass spectrum; m/e=164 (100%), 165 (12%), 166 (0%) (M^+ calculated for $C_{11}H_{16}O$ = 164).

Analysis; Found C, 80.57; H, 9.73; $C_{11}H_{16}O$ requires C, 80.44; H, 9.83.

Oxaiceane (46) in the presence of a chiral shift reagent

The chiral shift reagent Tris(3-(trifluromethylhydroxymethylene)-d-camphorato)europium III (Eu-Optishift I) was added in 10 mg increments to a sample of oxaiceane in $CDCl_3$ containing TMS and the n.m.r. spectra were recorded. After the addition of 70 mg of the shift reagent, the spectrum showed the following resonances,

δ 12.37 (d, J = 10 Hz, 1H, HCO), δ 12.00 (d, J = 10 Hz, 1H, HCO), δ 6.46 (m, 1H, C10-H_{endo}) and δ 0.8-5.4 (complex, unassigned).

When the sample was irradiated at δ 4.9, the two doublets at δ 12.37 and 12.00 collapsed to two singlets. (figure 9c).

Abeo-oxaiceane (89) in the presence of a chiral shift reagent

After the addition of Eu-optishift I (70 mg) to a sample of *abeo*-oxaiceane (89) (*ca.* 30 mg) in $CDCl_3$ containing TMS, the n.m.r. spectrum showed the following resonances,

δ 12.67 (br. s, 1H), δ 11.2-12.1 (m, 3H) and δ 2.0-7.4 (complex).

When the sample was irradiated at δ 4.5, the protons on the carbon atoms bearing oxygen in *abeo*-oxaiceane showed the following resonances.

δ 12.67 (br. s, 1H), 12.17 (br. s, 1H) and 11.83 (br. s, 2H). (figure 10 c).

Oxymercuration of olefinic alcohol (45) and reduction with $Na/Hg/D_2O$.

Mercuric acetate (0.963 g, 3.019 mmole) was added at room temperature to a stirred solution of the olefinic alcohol (45) (0.45 g, 2.744 mmole) in acetone-tetrahydrofuran (1:1, 10 ml) and stirring was continued for 4 hr, after which time t.l.c. revealed that no starting alcohol remained. Water (10 ml), sodium chloride (400 mg) and sodium bicarbonate (560 mg) were added and, after a further 1 hr, the resultant precipitate was removed by filtration. Any further precipitate which settled out at a later time was also collected. The combined filtrates were dried at 60° at 4 mm for 18 hr to give a white crystalline solid (1.0 g). The infrared spectrum of this material showed the absence of any hydroxyl or acetate absorption.

Sodium amalgam (16%, from sodium (1.15 g) and mercury (45 ml)) was added, under nitrogen, to a stirred suspension of the mercuric chloride (1.0 g) in D_2O (5 ml) and stirring was continued, at room

temperature, for 18 hr. The aqueous solution was extracted with ether (2 x 30 ml) and dired ($MgSO_4$) to afford a white crystalline solid (340 mg, 76%) which was purified by preparative t.l.c. (ether:petroleum ether = 1:1). The band of lower Rf was the starting olefinic alcohol (45). The higher Rf band was shown, by g.l.c. to consist of oxaiceane together with less than 1% *abeo*-oxaiceane. It was recrystallized from ether-petroleum ether to afford a white crystalline solid (23 mg, 5%), m.p. 314-315°.

^{1}H n.m.r. ($CDCl_3$) (90 MHz); δ 4.22 (d, 2H, H-C2 and H-C4, $J_{1,2}=J_{4,9}$=10 Hz), δ 1.5-2.4 (complex, 8H), δ 1.45 (more complex than undeuterated sample, 2H, C5-H_{exo} and C12-H_{exo}), δ 1.16 (d, 1H, C10-H_{exo}, J_{gem} = 11 Hz) and δ 1.11 (d, 2H, C8-H_{exo} and C11-H_{exo}, J_{gem} = 13 Hz) (figure 14).

Mass spectrum; m/e 165 (100%), 164 (4%), 166 (7%) (M^+ calculated for $C_{11}H_{15}DO$ = 165)

G.C. FFAP (60 ml/min) (210°), 07/15

Oxaiceane (46) in the presence of $Eu(fod)_3$

The n.m.r. shift reagent Europium III 1,1,1,2,2,3,3 - heptafluoro-7,7-dimethyl-4,6-octanedione ($Eu(fod)_3$) was added in 5 mg increments to a sample of oxaiceane (30 mg) in $CDCl_3$ containing TMS and the n.m.r. spectra (60 MHz) were recorded. After the addition

of 70 mg of the shift reagent, the spectrum showed the following resonances.

δ 16.7 (d, 2H, H-C2 and H-C4, $J_{1,2}=J_{4,9}$ = 10 Hz), δ 7.88 (d, 1H, C10-H_{endo}, J_{gem} = 11 Hz), δ 7.20 (d, 2H, C5-H_{exo} and C12-H_{exo}, J_{gem} = 14 Hz), δ 6.0 (br. s, 2H, C1-H and C9-H), δ 5.4 (br. s, 2H, C6-H and C7-H), δ 5.08 (d, 2H, C5-H_{endo} and C12-H_{endo}, J_{gem} = 14 Hz), δ 4.7 (d, 2H, C8-H_{endo} and C11-H_{endo}, J_{gem} = 13 Hz), δ 4.30 (d, 1H, C10-H_{exo}, J_{gem} = 11 Hz) and δ 3.6 (d, 2H, C8-H_{exo} and C11-H_{exo}, J_{gem} = 13 Hz) (figure 15)

Decoupling; irradiation at δ 7.88, collapsed the doublet at δ 4.30, at δ 7.20, collapsed the doublet at δ 5.08, at δ 6.0, collapsed the doublet at δ 16.7, and at δ 4.7 collapsed the doublet at δ 3.6. These results were checked by irradiation at the alternative positions. The results obtained from the decoupling studies are consistent with the interpretation of the n.m.r. spectra of oxaiceane with and without $Eu(fod)_3$.

d_1-oxaiceane in the presence of $Eu(fod)_3$.

After the addition of $Eu(fod)_3$ (70 mg) to a sample of d_1-oxaiceane (*ca.* 30 mg) in $CDCl_3$ containing TMS, the n.m.r. spectrum was the same as for the undeuterated oxaiceane except for the

following changes.

δ 7.20 (m, superimposed on d, 2H, C5-H_{exo} and C12-H_{exo}) and δ 5.08 (s, 1H, C12-H_{endo}) (figure 15)

Oxymercuration of olefinic alcohol (45) in water.

The oxymercuration of olefinic alcohol (45) was again performed except an aqueous media (as reported by Ganter[15]) replaced the tetrahydrofuran. The olefinic alcohol (45) (40 mg, 0.244 mmole) was added to a vigorously stirred solution of mercuric acetate (86 mg, 0.268 mmole) in water (10 ml) and stirring was continued, at room temperature, for 24 hr. Sodium hydroxide solution (3M, 1 ml) and sodium borohydride solution (0.5M in 3M NaOH, 1 ml) were added and the reaction mixture was stirred for a further 1 hr. The mercury was removed by filtration and the aqueous solution was extracted with ether (3 x 5 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated to give a white crystalline solid (31 mg, 77.5%). V.p.c. showed the following ratio of products; oxaiceane:*abeo*-oxaiceane:olefinic alcohol (45) = 48:1:4.

endo-5-chloromercuri-3-oxa-tetracyclo[5.3.1.$1^{2,6}0^{4,9}$]dodecane (91).

The olefinic alcohol (45) (1.8 g, 0.011 mole) was added to a vigorously stirred solution of mercuric acetate (3.86 g, 0.012 mole)

in water (100 ml) and stirring was continued at room temperature for 24 hr. Sodium chloride (1.5 g) and sodium bicarbonate (1.8 g) were added and, after a further 1 hr, the resultant precipitate was removed by filtration. Any further precipitate which settled out at a later time was also collected. The combined filtrates were dried at 60° at 4 mm for 20 hr to give a white crystalline solid (3.3 g, 94%). Recrystallization from chloroform provided a pure sample m.p. 255-257°.

i.r. (Nujol); complex fingerprint region.

n.m.r. ($CDCl_3$) (90 MHz); δ 4.42 (d, 1H, C4-H, J = 12 Hz), δ 4.27 (d, 1H, C2-H, J = 10 Hz), δ 3.08 (br. s, 1H, C5-H_{exo}), δ 1.61 (s, possibly CH_3, see page and δ 1.06-2.87 (complex).

Mass spectrum; (at high amplification) m/e 396, 397, 398, 399, 400, 401, 402, 403 and 404 (M^+ calculated for $C_{11}H_{15}O\ ^{200}HgCl$ = 400).

Analysis: Found C, 33.08; H, 3.86; $C_{11}H_{15}OHgCl$ requires C, 33.08; H, 3.76.

The reaction of the mercuric chloride (91) with sodium borodeuteride.

(A) in ethanol

The mercuric chloride (91) (200 mg, 0.500 mmole) and sodium borodeuteride (82.8 mg) (1.88 mmole) in ethanol (10 ml) were heated

under reflux for 30 hr. The mercury was removed by filtration, water was added and the aqueous solution was extracted with ether (2 x 15 ml). The combined ethereal extracts were washed with water (2 x 15 ml), dried ($MgSO_4$) and evaporated. Purification of the residue by preparative t.l.c. (ether:petroleum ether = 1:1) gave oxaiceane (21 mg, 26%) m.p. 313-314°.

Mass spectrum; showed *ca.* 30% incorporation of deuterium.

n.m.r. ($CDCl_3$) (90 MHz); was similar to undeuterated oxaiceane. In particular the doublet at δ 1.45 had not collapsed.

n.m.r. ($CDCl_3$) containing $Eu(fod)_3$ (70 mgm) (60 MHz) was the same as for the undeuterated oxaiceane in the presence of $Eu(fod)_3$ (70 mg) except for the following changes:

δ 7.20 (d, J = 14 Hz, 1.7 H) and δ 5.08 (br. m, 2H, C5-H_{endo} and C12-H_{endo}).

(B) in alkaline tetrahydrofuran

A suspension of mercuric chloride (91) (200 mg, 0.50 mmole) and sodium borodeuteride (82.8 mg, 1.88 mmole) in a solution of tetrahydrofuran (10 ml) and sodium hydroxide (3M, 5 ml) were stirred for 30 hr at room temperature. After the reaction had been worked up and purified in the usual manner, mass spectrometry indicated only a 21% incorporation of deuterium into oxaiceane.

(C) in sodium hydroxide solution

To a stirred suspension of the mercuric chloride (91) (150 mg, 0.375 mmole) in sodium hydroxide solution (3M, 10 ml) was added sodium borodeuteride (50 mg, 1.125 mmole). A precipitation of mercury was immediately observed. The reaction mixture was stirred for 1 hr after which time it was worked up and purified in the usual manner. The mass spectrum of the oxaiceane obtained indicated a 50% incorporation of deuterium.

Olefinic alcohol (45) in the presence of acid.

Acetyl chloride (0.5 ml, 0.007 mole) was added to D_2O (0.14 ml, 0.007 mole) and the solution was diluted with deuterated acetic acid (AcOD), (2 ml). The olefinic alcohol (45) (40 mg, 0.245 mmole) was added to this solution which was then stirred at room temperature for 3 hr, after which time, t.l.c. revealed that all starting material had been consumed. Water (2 ml) was added and the aqueous solution was extracted with ether (2 x 5 ml). The combined ethereal extracts were washed with water (2 x 5 ml), dried ($MgSO_4$) and evaporated. The residue (32 mg) consisted of oxaiceane: *abeo* oxaiceane = 3:2. The deuterated oxaiceane was isolated by preparative g.l.c.

Mass spectrum; m/e 165 (100%), 164 (12%), 166 (12%).

n.m.r. ($CDCl_3$) (90 MHz) was very similar to that of the d_1 oxaiceane obtained from the sodium amalgam-D_2O reduction of the mercury salt (91). In particular the doublet at δ 1.4 had collapsed to a more complex multiplet.

The treatment of olefinic alcohol (45) with N-bromosuccinimide.

N-bromosuccinimide (65 mg, 0.366 mmole) was added to a stirred solution of olefinic alcohol (45) (60 mg, 0.366 mmole) in dimethyl sulphoxide (3 ml) and stirring was continued, at room temperature, for 3 hr. After this time t.l.c. showed that all starting material had been consumed. Sodium bicarbonate solution (3 ml) was added and the aqueous solution was extracted with ether (3 x 5 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated to afford a semi-crystalline solid (72 mg), which was purified by preparative t.l.c. (ether:petroleum ether = 1:1). The major band consisted of a white crystalline solid (65 mg).

i.r. (Nujol); complex fingerprint region.

n.m.r. ($CDCl_3$); δ 4.1-4.6 (m, HCBr) and δ 0.6-3.4 (complex).

Mass spectrum; m/e 242 and 244 (M^+ calculated for $C_{11}H_{15}OBr$ = 243).

Reduction of the bromo-ethers with tri-n-butyl stannane.

The mixture of bromo-ethers (20 mg, 0.082 mmole) in anhydrous benzene (2 ml) was added, under nitrogen, to tri-n-butyl stannane

(48 mg, 0.164 mmole) containing azobisisobutyronitrile (*ca.* 1 mg) and the solution was heated under reflux for 4 hr. The solution was cooled, carbon tetrachloride (1 ml) was added and refluxing was continued for a further 2 hr. The solvent was removed at reduced pressure and the residue was dissolved in ether (5 ml) and washed with 5% sodium bicarbonate solution (5 ml). The ethereal layer was dried ($MgSO_4$) and evaporated. The residue was shown, by v.p.c., to consist of oxaiceane:*abeo*-oxaiceane = 1:4.

Chapter 5.

exo-7-acetoxy-tricyclo[4.3.1.$1^{3,8}$]undecan-4-one (30) and *exo*-7-hydroxy-tricyclo[4.3.1.$1^{3,8}$]undecan-4-one (29).

The cyclopropyl ketone (23) (0.45 g, 2.8 mmole) in 45% aqueous acetic acid (v/v) (60 ml) and perchloric acid (72%, 7.5 ml) were heated under reflux for 4 hr. The reaction mixture was then neutralized with sodium bicarbonate and extracted with ether (3 x 20 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated to give a semi crystalline residue which was purified by preparative t.l.c. (ether:chloroform:benzene = 1:3:2). The compound of higher Rf was recrystallized (ether/petroleum ether) to give a white crystalline solid (0.21 g, 33%) m.p. 53-54°.

i.r. (Nujol); 1730 (acetate C=O), 1695 (C=O) and 1245 cm^{-1} (C-O-$COCH_3$).

n.m.r. ($CDCl_3$); δ 4.78 (br. s, -CH-O-), δ 2.5-3.0 (m, 3H, -CH_2-CO-CH-), δ 2.05 (s, CH_3-C=O) and δ 1.0-2.3 (complex).

Mass spectrum; m/e 162 (M^+ calculated for $C_{13}H_{18}O_3$-CH_3CO_2H = 162)

Analysis; Found C, 70.46; H, 8.37; $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16.

The compound of lower Rf was recrystallized (ether/petroleum ether) to give a white crystalline solid (0.22 g, 44%) m.p. 314-316°.

i.r. (Nujol); 3400 (OH) and 1690 cm^{-1} (C=O).

n.m.r. ($CDCl_3$); δ 3.82 (br. s, HC-O-), δ 2.5-3.0 (m, 3H, $-CH_2-CO-CH-$), δ 1.85 (s, removed with D_2O, OH) and δ 1.0-2.5 (complex).

Mass spectrum; m/e 180 (M^+ calculated for $C_{11}H_{16}O_2$ = 180).

Analysis; Found C, 73.66; H, 9.13; $C_{11}H_{16}O_2$ requires C, 73.33; H, 8.89.

exo-7-*p*-toluenesulphonyloxy-tricyclo[4.3.1.$1^{3,8}$]undecan-4-one (94)

(A) *p*-toluenesulphonyl chloride (1.28 g, 6.7 mmole) was added to a stirred solution of the alcohol (29) (0.6 g, 3.3 mmole) in pyridine (15 ml) and stirring was continued for 36 hr at room temperature. Water (20 ml) was added, the aqueous solution was extracted with ether (3 x 15 ml) and the combined ethereal extracts were washed with HCl (10%, 5 x 15 ml), dried ($MgSO_4$) and evaporated. Recrystallization (chloroform/ether) gave a white crystalline solid (0.8 g, 73%), m.p. 118-119°.

i.r. (Nujol); 1690 cm^{-1} (C=O)

n.m.r. ($CDCl_3$); δ 7.8 (d, J = 9 Hz, 2H), δ 7.4 (d, J = 9 Hz, 2H) (aromatic protons), δ 4.57 (br. s, -CH-O-), δ 2.52 (s, CH_3-) and δ 1.2-3.0 (complex).

Mass spectrum; m/e 162 (M^+ calculated for $C_{18}H_{22}O_4S-C_7H_8O_3S$ = 162)

Analysis; Found C, 64.8; H, 6.7; O, 19.0; $C_{18}H_{22}O_4S$ requires C, 64.7; H, 6.6; O, 19.2.

(B) To a solution of the cyclopropyl ketone (23) (0.1 g, 0.62 mmole) in benzene (10 ml) was added *p*-toluenesulphonic acid (180 mg, 0.62 mmole) and the solution was refluxed for 6 hr. The reaction mixture was then washed with water (3 x 10 ml), dried ($MgSO_4$) and evaporated. Purification of the oily residue by preparative t.l.c. and recrystallization (chloroform/ether) gave a white crystalline solid (140 mg, 68%) m.p. 117-118°. The spectral data of this compound was identical to that described in part (A). The mixed melting point with the compound from part (A) was 117-119°.

Determination of the stereochemistry of (94)

The tosylate (94) (200 mg, 0.6 mmole) and sodium hydride (144 mg, 6 mmole) in dry benzene (20 ml) were refluxed under nitrogen for 24 hr. Water (10 ml) was cautiously added to the cooled solution. The organic layer was separated and the aqueous layer was extracted with benzene (2 x 10 ml). The combined benzene layers were washed with water (2 x 10 ml), dried ($MgSO_4$) and evaporated to give a white crystalline solid. Purification by preparative t.l.c. (ether:petroleum ether = 1:1) afforded a white crystalline solid (71 mg, 73%) m.p. 87-89°. The spectral data of this compound was identical to that of cyclopropyl ketone (23) and the mixed melting point was 87-89°.

Reduction of the tosylate (94).

The tosylate (94) (1.8 g, 0.05 mmole) in tetrahydrofuran (2 ml) was added under nitrogen to a stirred solution of lithium aluminium hydride (12 mg, 0.3 mmole) in tetrahydrofuran (3 ml) and the solution was refluxed for 1 hr. The precipitated[222] inorganic salts were removed by filtration and the filtrate was evaporated. Purification by preparative g.l.c. (1m x 10 mm, 20% SE52 column at 150°) gave a small amount of a white crystalline solid which on admixture with an authentic sample of homoadamantanol (m.p. 266-268°), lit. m.p. 269-270°, prepared according to the method of Black and Gill,[24] melted at 265-267°.

exo-7-bromo-tricyclo[4.3.1.1^{3,8}]undecan-4-one (96).

The cyclopropyl ketone (23) (1.5 g, 9.3 mmole) in 45% aqueous acetic acid (v/v) (70 ml) was saturated with sodium bromide. Perchloric acid (8 ml) was added and the mixture was refluxed for 4 hr. The reaction was then neutralized with sodium bicarbonate and extracted with ether (2 x 20 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated to give a semi-crystalline solid which was purified by preparative t.l.c. (ether:chloroform:benzene = 1:3:2). The compound of highest Rf was recrystallized from aqueous ethanol to give a white crystalline solid (0.67 g, 30%) m.p. 190-191°.

i.r. (Nujol); 1685 cm^{-1} (C=O)

n.m.r. ($CDCl_3$); δ 4.45 (br. s, HCBr) and δ 1.2-3.0 (complex).

Mass spectrum; m/e 242 and 244 (M^+ calculated for $C_{11}H_{15}OBr$ = 243).

Analysis; Found C, 54.27; H, 6.15; $C_{11}H_{15}OBr$ requires C, 54.32; H, 6.17.

Acetate (30) (0.51 g, 24%) and alcohol (29) (0.24 g, 14%) were also formed during this reaction.

Reduction of bromo-ketone (96) to homoadamantanol (95).

The bromo-ketone (96) (50 mg, 0.21 mmole) and lithium aluminium hydride (50 mg, 1.3 mmole) in anhydrous tetrahydrofuran (4 ml) were refluxed under nitrogen for 16 hr. Water and sodium hydroxide[222] were cautiously added and the inorganic salts were removed by filtration. Ether (5 ml) was added to the filtrate and the solution was washed with water (5 ml). The aqueous layer was again extracted with ether (5 ml) and the combined ethereal extracts were dried ($MgSO_4$) and evaporated to give a semi-crystalline solid. Recrystallization from aqueous ethanol gave homoadamantanol (28 mg, 88%) m.p. 266-267° (lit. m.p. 269-270°).[24] The infrared spectrum was identical with that of an authentic sample.

Further confirmation of the structure of this compound was

afforded by oxidation with Jones reagent[114] according to the usual procedure to give homoadamantanone m.p. 264-266° (lit. m.p. 266.5-267.5°).[24] The infrared spectrum was identical to that of an authentic sample (m.p. 264-266°) prepared according to the procedure of Black and Gill.[24]

Attempts to equilibrate ketol (29)

(A) Treatment of the ketol (29) (25 mg, 0.14 mmole) with 45% aqueous acetic acid (3.5 ml) and perchloric acid (0.5 ml) under the same conditions as used in its preparation gave a mixture of starting ketol (29) (55%) and the keto-acetate (30) (45%) as determined from the n.m.r. spectrum of the product mixture.

(B) Treatment of the ketol (29) (25 mg, 0.14 mmole) with 45% aqueous acetic acid (3.5 ml), saturated with sodium bromide, and perchloric acid (0.5 ml) under the same conditions gave a mixture of starting ketol (29) (34%), the keto-acetate (30) (44%) and the keto-bromide (96) (22%) as determined from the n.m.r. spectrum of the product mixture. G.l.c. showed peaks of identical retention time to those of authentic (29), (30) and (96) except that the peak corresponding to (96) showed a shoulder.

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A SYNTHESIS OF TETRACYCLO [5.3.1.1^{2,6}0^{4,9}] DODECANE (ICEANE)

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In 1965 Fieser coined the name iceane for the hypothetical hydrocarbon 1.[1] This highly symmetrical molecule (D_{3h}) possesses five six-membered rings of which, because of the rigidity imposed by the carbon skeleton, two exist in chair configurations and three in non twist boat configurations. Although the model is free of skeletal strain, presumably the molecule has within it severe non-bonded interactions. It was expected therefore that iceane would possess unusual structural parameters and chemical properties as well as presenting a synthetic challenge. This communication outlines a route by which iceane has been synthesized.[2]

The olefinic ketone[3] 2 was converted ($Ph_3P{=}CH_2$, ether) to the diolefin 3 (mp 132-135°) (86%) whereupon selective hydroboration (disiamyl borane, THF; H_2O_2, NaOH) gave the olefinic alcohol 4 (mp 127-129°) (55%) ν_{max} 3350 cm^{-1}; nmr (CCl_4) δ6.1 and 5.6 (m, vinylic),[4] 3.7 (m, diastereotopic hydroxymethyl), 2.65 (s, hydroxyl) and 2.8-0.6 (methylene envelope). The configuration of the hydroxymethyl group in compound 4 (predicted to be as shown), was essential to the synthetic route and was established before proceeding. Oxymercuration[5] of the olefinic alcohol 4 gave a compound (mp 165-167°) isomeric with the starting material (mass spec) but showing no hydroxyl absorption (ir). The nmr spectrum showed no vinylic protons but resonances for three protons on carbon atoms bearing oxygen. From these data this new isomer could be only compound 5 or 6 either of which could have arisen only if the hydroxymethyl group in compound 4 had the configuration depicted.

It was intended to convert the compound 4 into a halo-epoxide, via the chloro-olefin 7, with the hope of effecting an intramolecular alkylation reaction.[6] However on refluxing 4 with Ph_3P in CCl_4, the reaction took an unexpected course. A mixture of two compounds was obtained (55%) each of which was shown to be isomeric with the expected compound 7 (glc-mass spec). The nmr spectrum of the mixture showed no vinylic protons but two resonances at δ4.82 and 4.00 consistent with protons on a carbon bearing chlorine. Both these compounds must therefore contain an extra ring. Assuming that there was no extensive rearrangement, it seemed likely that substitution had occurred, with double bond participation to give either both epimers of compound 8, or of compound 9 or a mixture of one of each.[7] A small amount of each chloro isomer was obtained by preparative glc; compound A (first eluted), (mp 215-217°), nmr δ4.00; compound B, (mp 272-274°), nmr δ4.82. Each chloride was reduced separately with tri-n-butylstannane and both appeared to give the same crystalline compound which was at least isomeric (mass spec) with iceane. The mixture of chloro compounds was reduced to yield a crystalline product, which did not melt but sublimed at 318° (sealed tube of small volume) and which was shown to be tetracyclo [5.3.1.$1^{2,6}0^{4,9}$] dodecane 1 by the following data. The analytical data and mass spectrum were consistent with the molecular formula $C_{12}H_{18}$. The pmr spectrum (90 MHz) showed an AM pattern centred at δ0.94 and 1.90 (J = 12 Hz). This is consistent with the resonances due to the axial and equatorial protons respectively[8] of each methylene group. This difference in chemical shift is probably enhanced by van der Waals deshielding of the equatorial protons due to their position in the rings having a boat configuration. Each of these resonances is broadened by further minimal coupling to the bridgehead protons which absorb as a broad peak at δ2.18. The integration for each of the three regions was the same. The $^{13}C-\{^1H\}$ nmr spectrum showed only two resonances at δ28.70 and 31.72 (relative to TMS) integrating[9] for nearly equal areas. All of these nmr data are consistent with the six fold inversion axis in iceane. Furthermore X-ray data[10] revealed that the molecule must possess a minimum of three-fold symmetry.

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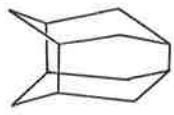

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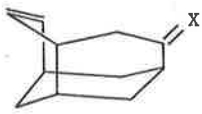

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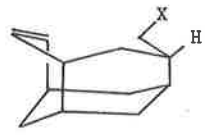
3 X = CH_2



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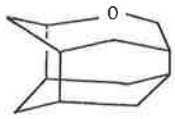
7 X = Cl



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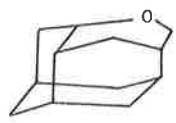

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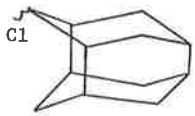

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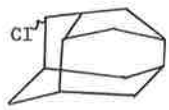

9

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9. Sufficient pulse spacing was employed to allow adequate time for the relaxation process.

10. Hexagonal crystals (from MeOH), cell constants a = 6.60 (1), c = 11.87 (1) A°, ρ = 1.04 g/cc giving FW = 210.5 (Z = 4), space groups $P6_3$ or $P6_{3/m}$ in which iceane must occupy positions of at least threefold symmetry.

Tetrahedron Letters No. 19, pp 1623 - 1626, 1975. Pergamon Press. Printed in Great Britain.

OXAICEANE AND ABEO-OXAICEANE

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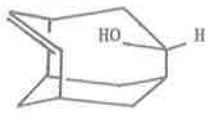
The recent publication[1] of a synthesis of 3-Oxawurtzitane[2] prompts us to report our observations of a parallel synthetic scheme in which the key step, the oxymercuration-reduction reaction of the olefinic alcohol 1,† leads not only to 3-oxa-tetracyclo[5,3,1,$1^{2,6}0^{4,9}$] dodecane 2 (oxaiceane) as reported by the Swiss workers, but also to a structural isomer 12-oxa-tetracyclo[5,3,1,$1^{2,5}0^{4,9}$] dodecane 3 (abeo-oxaiceane).[3] The structures of these isomers are differentiated by the novel use of a chiral nmr shift reagent as well as by ^{13}C nmr. In the light of the recent calculations of Schleyer et al.[4] concerning the carbon analogues, of which only one isomer is known,[5] these two oxa isomers should prove of theoretical interest. The key compound which allowed us to prepare them, and also the hydrocarbon Iceane 4,[5] is the keto-olefin 5, the structure of which was confirmed by independent chemical correlations. Since our route to compound 2 is different from that reported and involves a new fragmentation reaction, we take this opportunity to report it.

The olefinic acid 6[6] was brominated (N-bromosuccinimide in CCl_4) to give the bromoacid 7 (mp 156-8°). Treatment of the crude bromoacid with oxalylchloride and thence with diazomethane gave the diazoketone. This was decomposed with copper powder in refluxing cyclohexane[7] to give the bromocyclopropyl ketone 8[8,9] (mp 78-9°) (43% based on acid 6); ν_{max}^{nujol} 3000 (shoulder) and 1680 cm^{-1}; nmr (CCl_4) no vinylic hydrogens, δ 4.52 br, s (CHBr)[10] and 3.0-0.6 (methylene envelope).

† The oxymercuration was done in THF rather than in water.[1]



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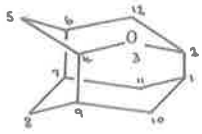

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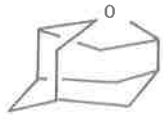

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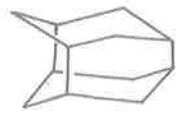

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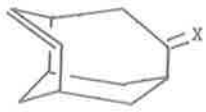
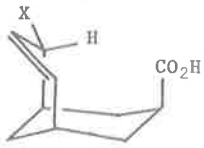
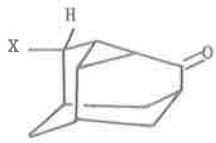


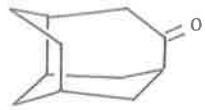
5 X=O
11 X=CH_2



6† X=H
7† X=Br



8† X=Br
10† X=H



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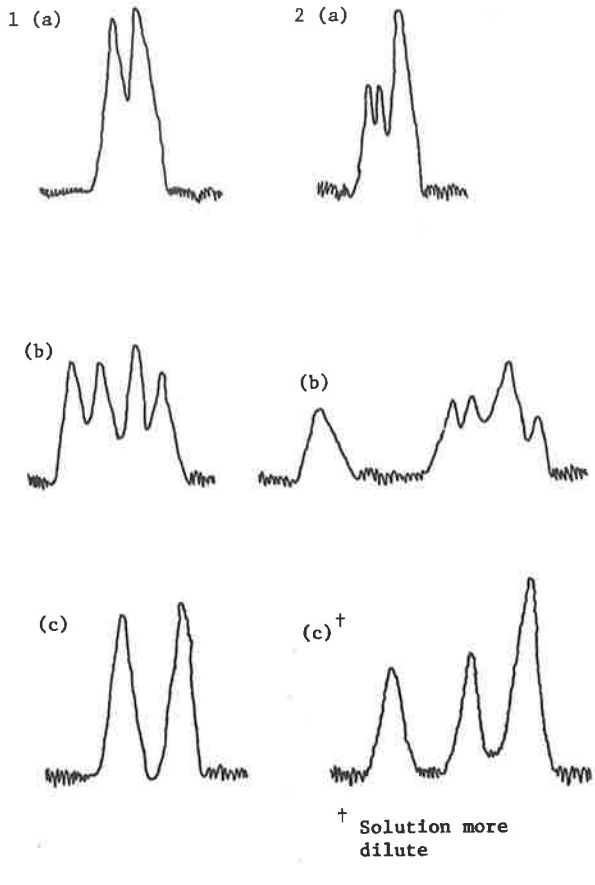
† Enantiomeric series of the (±) compounds shown for clarity.

Treatment of compound 8 with liquid Na-K alloy in anhydrous ether (0.5 hr, 20°) followed by protonation (EtOH: petrol (40°-60°) 1:9) gave a mixture of ketonic and alcoholic products which on oxidation (chromic acid, acetone) afforded the olefinic ketone 5 (mp 258-260°) (90% based on 8); ν_{max}^{nujol} 1710 cm^{-1}; nmr CCl_4 δ 6.1 and 5.5 m (vinylic)[11] and 3.0-0.6 (methylene envelope). This novel metal reaction[12] has considerable general synthetic potential in that it provides a keto-olefin product rather than a diolefin or diketone available from alternative methods.[13] Further work, demonstrating the utility of this procedure, will be reported in the near future. Catalytic hydrogenation of compound 5 gave a dihydroketone 9, which was not homoadamantanone,[14] but which was identical in all respects to a compound obtained by reduction (Li, liq NH_3) of the cyclopropylketone 10.[15]

The alcoholic material obtained from the metal reaction was a mixture of two compounds (glc) both of which gave the ketone 5 on oxidation. Sodium borohydride reduction of ketone 5 gave only one of these alcohols (mp 269-270°) (> 95%); ν_{max}^{nujol} 3400, 3000 (shoulder) 1650 cm^{-1}; nmr ($CDCl_3$) δ 6.4-5.8 complex m (vinylic) 4.1 m (-CHO-) and 2.8-1.2 (methylene envelope and OH). By analogy[5] with the hydroboration of diolefin 11, it was expected that this alcohol would have the stereochemistry shown in structure 1. Indeed, oxymercuration[16] of the olefinic alcohol followed by reduction ($NaBH_4$) gave a mixture of two compounds (ca. 1:1) isomeric with the starting material (glc - ms). These could be separated into two crystalline compounds (prep. glc).[17]

That which eluted first was abeo-oxaiceane (3) (mp 256-7°) followed closely by oxaiceane (2) (mp 314-5°). The structures were assigned on the basis of the following data.



Both gave analytical data and molecular ions consistent with the formula $C_{11}H_{16}O$. The main feature of the pmr spectrum of each isomer was the absorption of the protons on carbon bearing oxygen. That for oxaiceane was a symmetrical broadened doublet at δ 4.22 (fig. 1a) whereas for the isomer this absorption was an unsymmetrical multiplet centred at δ 4.2 (fig. 2a). The remainder of the spectrum of oxaiceane revealed a more symmetrical structure than that of its isomer. The symmetry of oxaiceane and the asymmetry of abeo-oxaiceane were clearly revealed by the use of optically active shift reagent[18] in the nmr samples (fig. 1b and 2b). Figure 2c (the decoupled spectrum of fig. 2b) clearly reveals that there are four different protons present (although clearly two are almost co-incident in chemical shift) as would be expected[18] for diastereoisomeric interactions between enantiomers of compound 3 and the shift reagent. Figure 1c shows that in this sample there are two different protons in this region consistent with diastereotopism[19] induced[18] in the prochiral molecule 2 by the optically active shift reagent.

The $^{13}C\{^1H\}$ nmr spectra further confirmed the structural assignments. Oxaiceane showed absorptions (relative to TMS) at δ 69.7 (C_2, C_4) 31.2 (C_5, C_{12} co-incident with C_8, C_{11}) 29.9 (C_1, C_9) 27.8 two almost superimposed absorptions (C_6, C_7) and 24.3 (C_{10}) ppm. The off-resonance decoupled spectrum was consistent with the assignments. abeo-Oxaiceane showed in its $^{13}C\{^1H\}$

spectrum eleven absorptions (unassigned) at δ 76.7, 76.2, 38.4, 36.2, 35.5, 34.6, 34.4, 31.8, 29.7, 29.3 and 26.6 ppm.

Acknowledgements: G.F.T. acknowledges the receipt of a Commonwealth Postgraduate Scholarship and R.N.Y. the receipt of a University of Adelaide Postdoctoral Fellowship.

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8. We have been unable, as yet, to obtain satisfactory analytical data for this compound.
9. Conversion of 6 to 8 was effected without purification of intermediates.
10. The small coupling constant between this proton and its neighbors is consistent with the configuration depicted since models indicate that in this configuration, but not in the epimer, the dihedral angles between this proton and both of its two neighbors are about 90°.
11. Each multiplet was a doublet of doublets i.e. an AB pattern further split by the neighboring protons.
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