SYNTHETIC APPLICATIONS OF ORGANOBORANES

A Thesis

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by

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CONTENTS

SUMMARY

An investigation of the synthetic utility of organoboranes has been carried out, and this investigation is presented in four parts.

Firstly, a number of novel compounds have been obtained by application of the cyanidation procedure to the products of hydroboration of various unsaturated terpenes. The structures of these products are confirmed herein by synthesis of each product via unambiguous means.

Secondly, an attempt has been made to facilitate the synthesis of secondary carbinols and ketones by application of the cyanidation procedure to dialkylboranes, and borinic acids and esters, respectively. The scope and limitations of such procedures are discussed.

Thirdly, the coupling reaction of organoboranes in the presence of silver (I) salts has been applied to organoboranes derived from dienes, and again the scope and limitations of the reaction are discussed. In the light of products obtained from this investigation, the mechanism of the coupling reaction is re-examined.

Fourthly, an attempt has been made to apply the known ability of optically active dialkylboranes to induce asymmetry in substrates with which they react to a specific synthetic problem. An attempt has also been made to utilize what was formerly an undesirable side-reaction in the hydroboration of allylically substituted olefins to induce asymmetry in a specific substrate. Both of these investigations have also been compared to the more conventional methods of resolution of the optical isomers of asymmetric compounds.

STATEMENT

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

Roger Murphy.

PUBLICATIONS

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

"Annelation of Organoboranes Derived from Geraniol". R. Murphy and R.H. Prager, Aust.J.Chem., 1976, 29, 617.

"Cyclization of Dienes via Hydroboration: Silver Ion Induced Intramolecular Alkyl Coupling". R. Murphy and R.H. Prager, Tet. Letters, 1976, 463.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to Dr. R.H. Prager for his enthusiastic supervision and guidance throughout the course of this work.

My thanks also to Dr. G.E. Gream for many helpful discussions, and to other members of the department, particularly my colleagues in laboratory six, for their advice and encouragement.

Finally, I am indebted to my family and my friends for their patience and support during the course of my candidature.

CHAPTER 1

Synthesis of Products Isolated from the Hydroboration-Cyanidation of Unsaturated Terpenes.

1.1 Introduction.

1.2 Synthesis of Products Derived from Geraniol.

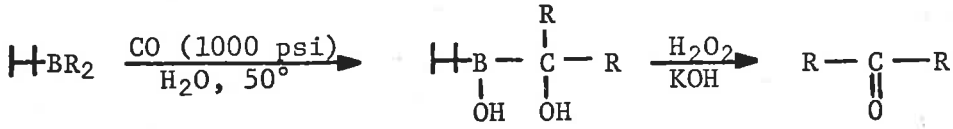
1.3 Synthesis of Products Derived from Linalyl Acetate.

1.4 Synthesis of Products Derived from Myrcene.

1.1 INTRODUCTION

The discovery that diborane in ether solvents reacts practically instantaneously, and quantitatively, with alkenes and related unsaturated carbon compounds, to convert them into the corresponding organoboranes (the hydroboration reaction[1]), created intense interest in the search for new reactions of organoboranes of utility in organic synthesis.[2,3] The synthesis of ketones by carbonylation of organoboranes is of particular interest.

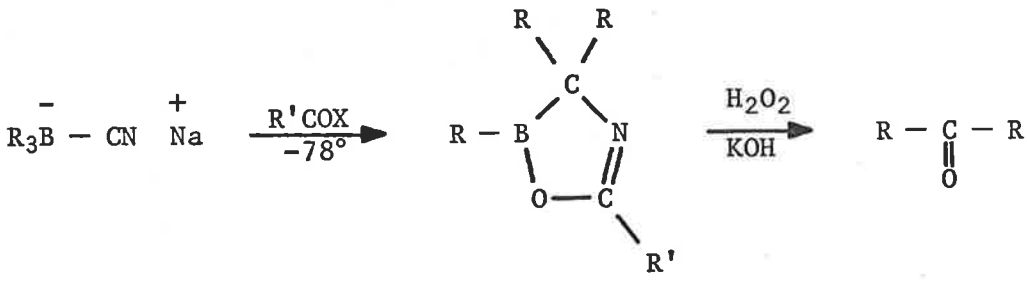
The reaction of trialkylboranes with carbon monoxide in the presence of water[4] provides a convenient synthesis of ketones from olefinic precursors. The process utilizes only two of the alkyl groups on boron and thus is inherently inefficient. Hydroboration of the olefinic substrate with 1,1,2-trimethylpropylborane (thexylborane) overcomes this inefficiency since the bulky thexyl group shows little tendency to migrate[5,6] under the conditions of the reaction (Scheme 1). Unfortunately the conditions



Scheme 1

are more severe than those normally employed with less hindered trialkylboranes. Thus, whilst the carbonylation of thexyldialkylboranes with carbon monoxide provides an excellent general method of ketone generation, relatively labile alkyl groups may suffer unwanted side reactions under the conditions that must be employed.

A milder but equally efficient method of generating ketones employs the rearrangement[7] of trialkylcyanoborates under the influence of an electrophilic reagent (Scheme 2). The problem again



Scheme 2

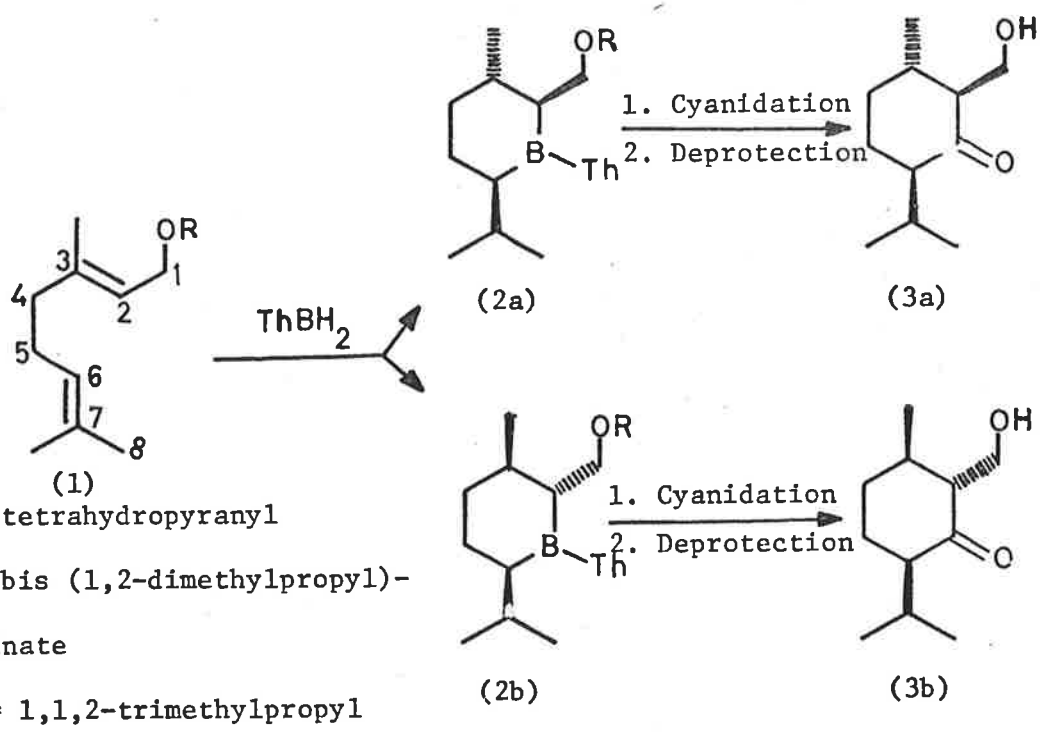
arises of inherent inefficiency in the process since only two of the three available alkyl groups on boron are utilized. The use of thexyldialkylcyanoborates[8] has led to increased efficiency in this "cyanidation process"[9] by avoiding the wastage of one equivalent of olefinic precursor, the thexyl group again showing little tendency to migrate. The results obtained from thexyldialkylcyanoborates

compare very favourably with those obtained via the carbon monoxide insertion method, but, unlike the latter reaction, the bulky thexyl group does not reduce the ease of cyanidation and thus standard reaction conditions may be maintained when dealing with these intermediates. Asymmetric alkyl groups have also been shown to undergo migration with retention of configuration at the chiral centre in both processes.[10,11] Thus cyanidation of thexyldialkylboranes gives comparable results to the carbon monoxide method without the need of subjecting the borane to inconvenient reaction conditions.

Cyanidation of thexyldialkylboranes derived from simple aliphatic and alicyclic olefin precursors gives relatively simple and unambiguous products.[8] Application of the process to more complex boranes, in which the structures of the intermediates may not be known with certainty, often results in the isolation of novel compounds as products.[12,13]

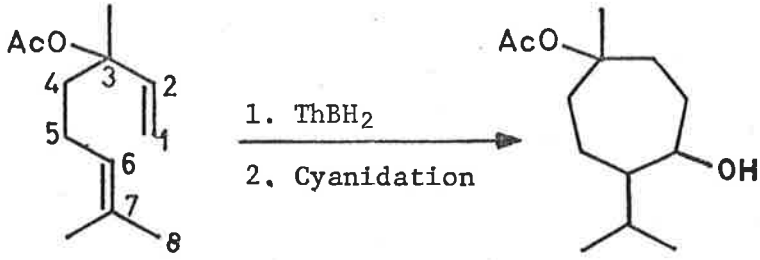
In a preliminary study[14] the author has investigated the nature of the products obtained by hydroboration-cyanidation of some unsaturated terpenes. The hydroboration of various derivatives of geraniol (1) with thexylborane proceeds in a relatively simple manner to give a mixture of isomeric boranes (2a and 2b), which undergo cyanidation in the expected manner. The product isolated is a mixture of the two

isomeric hydroxyketones (3a) and (3b) (Scheme 3). The structure of these products is here confirmed by independent and unambiguous synthesis.

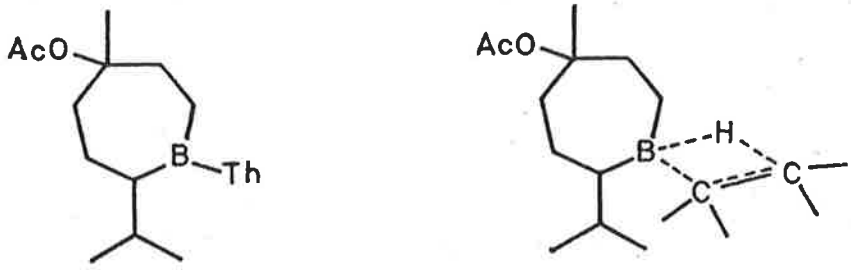


Scheme 3

Linalyl acetate (4) also undergoes hydroboration-cyanidation to give a product (5) with the expected skeletal structure (Scheme 4). The oxidation level of the product, however, is that of an alcohol and not the expected ketone. This behaviour may be explained in terms of the steric compression which may be present in the borane (6). If such steric compression is sufficiently strong then



(4) (5)

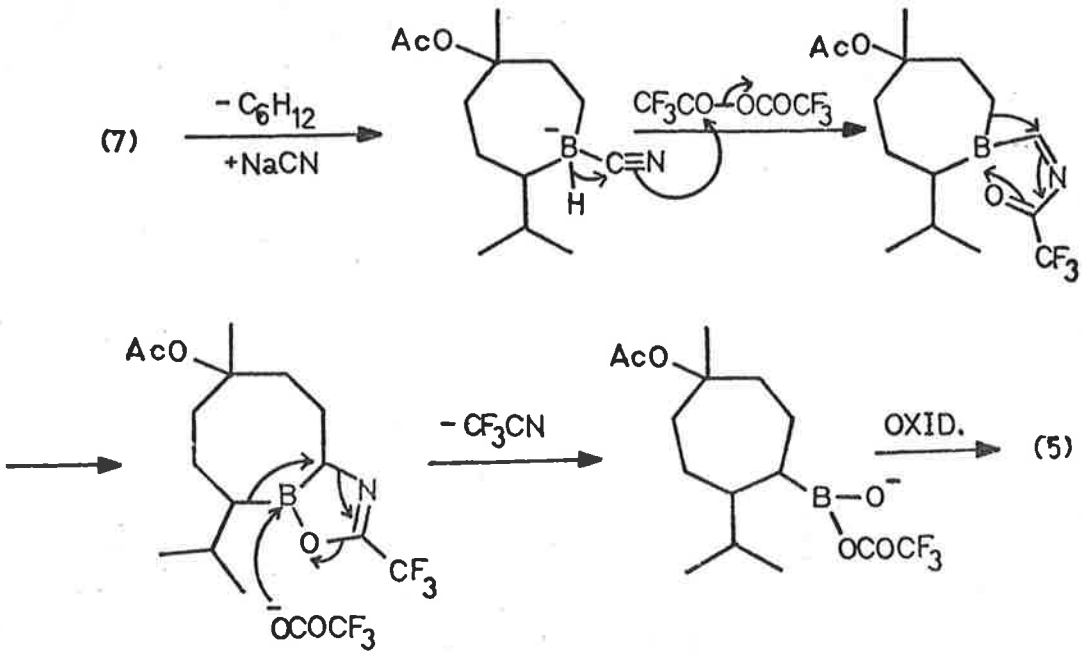


(6) (7)

Scheme 4

elimination of the thexyl group as 2,3-dimethyl-2-butene[14] may become a favourable process, and this would leave a hydrogen atom attached to boron. The same steric compression may also be present in (2a) and (2b), but in these cases the close proximity of the oxygen atom β to the boron may stabilize the intermediate by coordination of oxygen to boron. This would prevent the formation of the four-coordinate transition state necessary for the loss of 2,3-dimethyl-2-butene. There is no such limitation on formation of the transition state (7) for elimination from (6). Subsequent

transfer of the hydrogen† to the carbon atom of the cyanide (i.e. partial reduction) would lead, after transfer of the two alkyl groups on boron, to the isolated product. The transfer of all three groups on boron during cyanidation has previously been observed[8] and it has been noted that the presence of inorganic salts accelerates the process. Thus the transfer of all three groups in the case of linalyl acetate may be explained by the participation of sodium trifluoroacetate (liberated during cyanidation from trifluoroacetic anhydride, the most commonly used electrophilic reagent for this reaction) in inducing migration of the third group (Scheme 5). Once

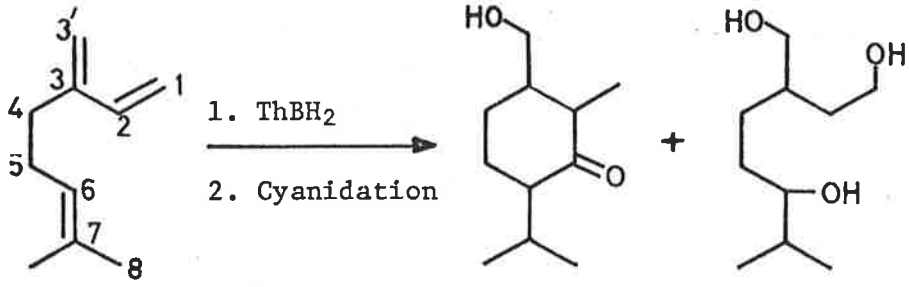


Scheme 5

† Such transfers have not been noted previously and are the subject of the work described in Chapter 2.

again, the structure of the final product is here confirmed by synthesis.

The hydroboration-cyanidation of myrcene (8) gives complex mixtures of products, the composition of which varies with the hydroborating agent. When myrcene is hydroborated with thexylborane in 1:1 molar ratio only two thirds of the substrate is utilized (determined by glc of the reaction mixture), and this indicates that all three double bonds within the molecule are being attacked by the reagent. The two isolated products (9 and 10) also indicate this to be the case (Scheme 6).

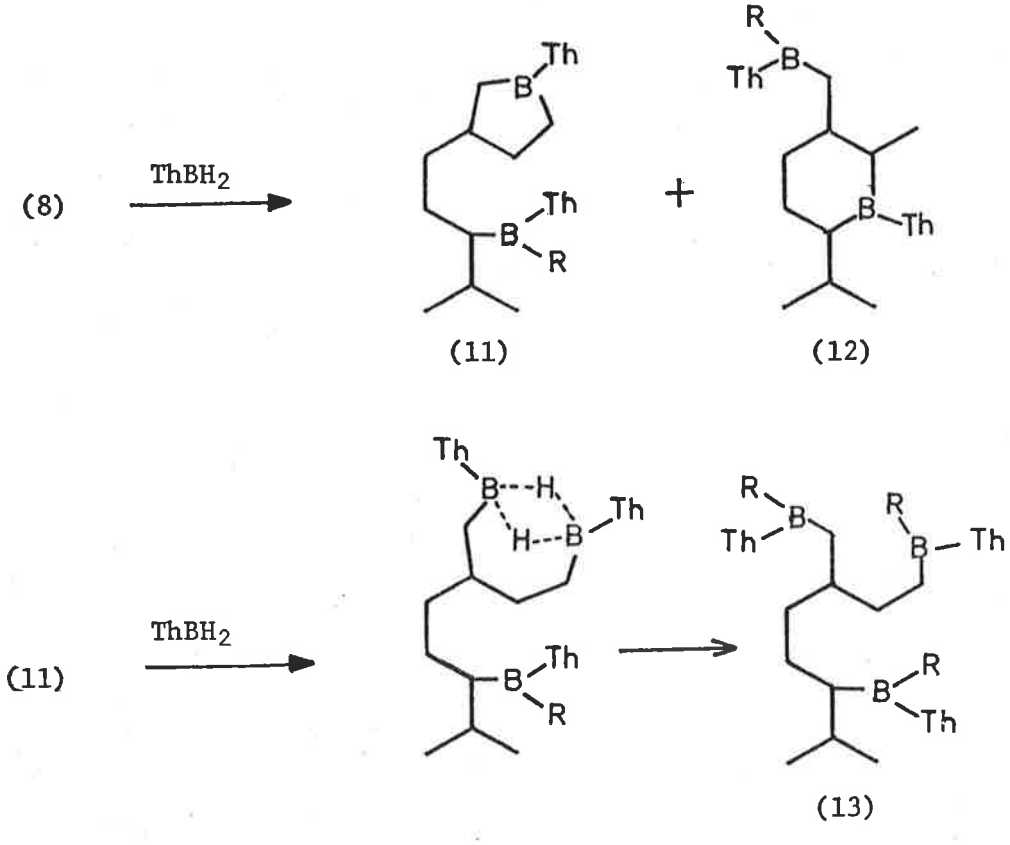


(8) (9) (10)

Scheme 6

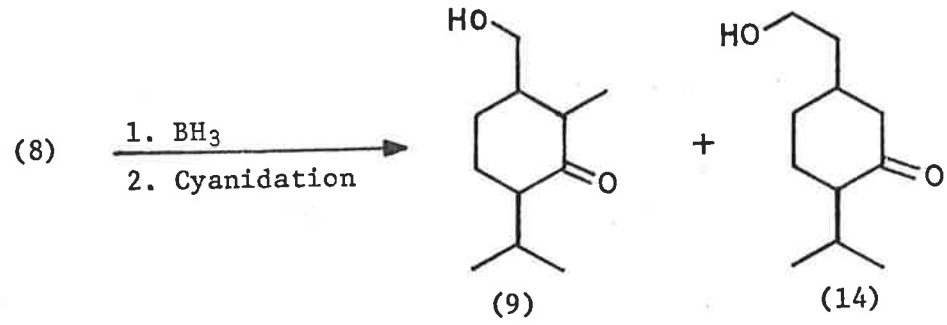
The hydroboration of conjugated dienes such as (8) is a complex process,[15] giving rise to mixtures of cyclic and acyclic boranes. The position of attack of the hydroborating species on the conjugated system of myrcene is determined by the nature of the reagent.[16] Thus thexylborane initially attacks at both the

1- and the 2- positions in the ratio of 1:4. Intramolecular attack may then occur at the 3'- and 6- positions, respectively, giving cyclic products (11) and (12). The borane (11), however, contains a borolane ring, which is very susceptible to further attack by hydroborating species. Thus interaction with thexyl borane opens this ring, giving an acyclic, polymeric borane (13) (Scheme 7). It is this compound (13) which gives rise to (10) since its polymeric nature prevents interaction with sodium cyanide and cyanidation does not occur. The cyclic product (12), however, does undergo cyanidation, giving rise to (9).



Scheme 7

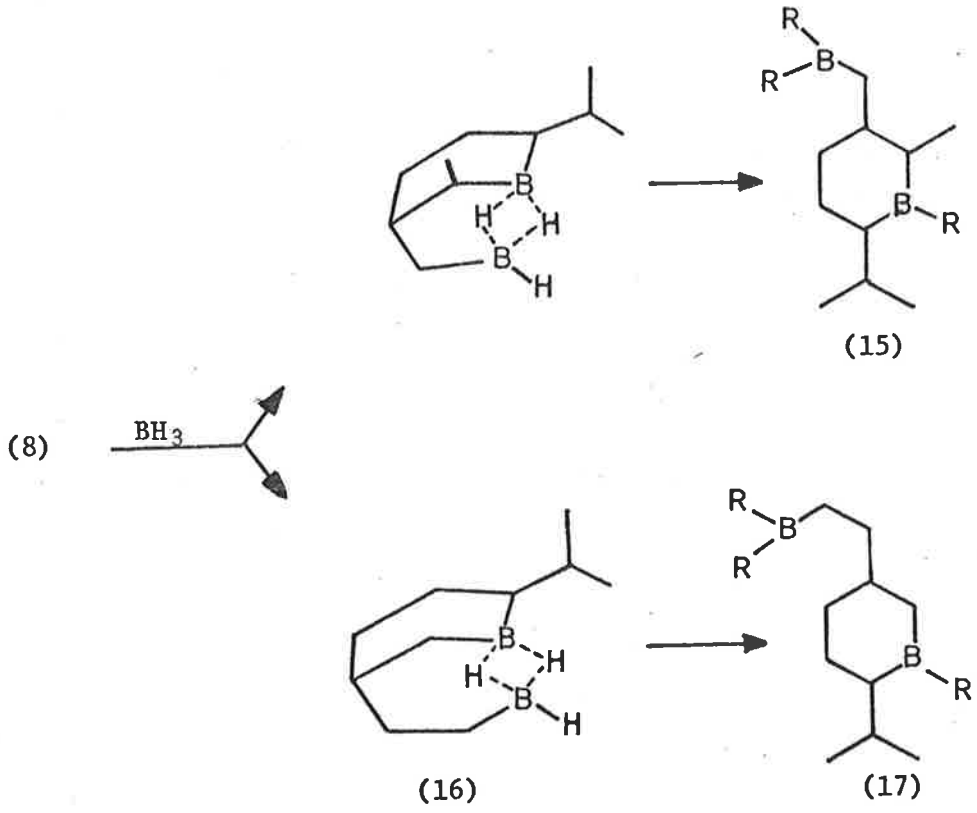
Hydroboration with diborane in 1:1 molar ratio utilizes all available substrate and this indicates that all the double bonds in myrcene undergo hydroboration. The products isolated are two hydroxyketones (9) and (14) with none of the triol (10) present (Scheme 8).



(9) (14)

Scheme 8

Initial hydroboration again occurs at the 1- and 2- positions but in the ratio 3:2. Product (9) can be envisaged as arising from a borane intermediate similar to that observed with thexylborane viz. initial hydroboration at the 2- position, followed by intramolecular attack at the 6- position, to give (15). The other observed product (14) cannot have arisen from interaction of a borolane ring (from hydroboration at the 1- and 3'-positions) with excess of diborane as this would have given rise to the triol (10) previously observed. If, however, attack at the 6-position by diborane occurred simultaneously with attack at the conjugated diene,[17] then an intermediate such as (16) would form (Scheme 9). This molecule now contains a borolane ring. Intramolecular attack

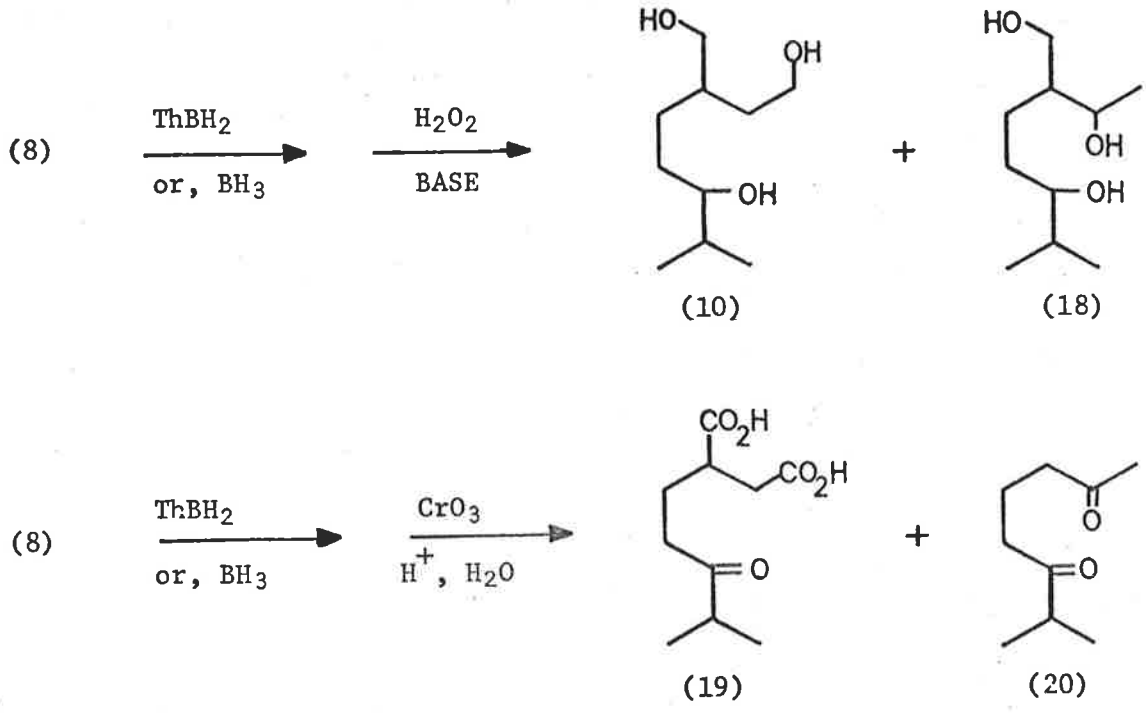


Scheme 9

of the boron hydride on the borolane ring would result in formation of a rearranged borane intermediate (17), which on cyanidation would give the observed product (14).

The complexity of the intermediate boranes resulting from hydroboration of myrcene and their sensitivity to air made it extremely difficult to characterize them directly. Thus the analyses of these intermediates were based on analysis of their oxidation products. Oxidation with alkaline hydrogen peroxide

gave a mixture of the two triols (10) and (18), but these two compounds could not be separated by distillation or chromatography. The trimethylsilyl derivative of the mixture also could not be resolved by glc. Thus analyses of the triol mixture were based solely on the nmr spectroscopic data. Oxidation of the borane intermediates with an acidic aqueous solution of chromium trioxide,[18] however, gave easily separable products, the ketodiacid (19) and the dione (20) (Scheme 10). Thus borane analyses were based almost entirely on the analysis of chromic acid oxidation products.



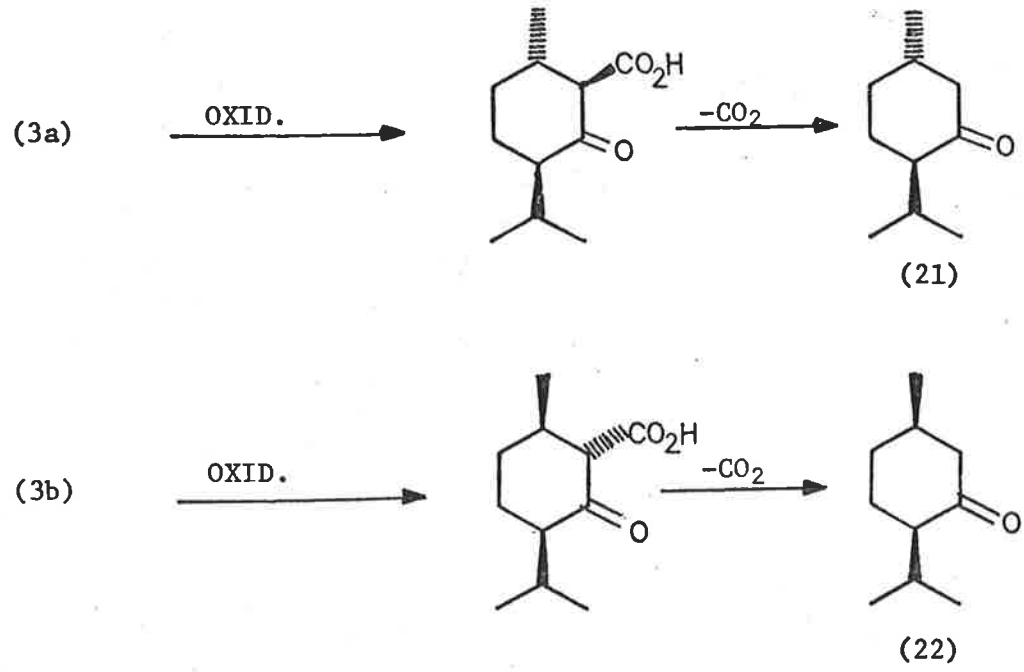
Scheme 10

The structures of the products isolated are here confirmed by independent synthesis.

1.2 SYNTHESIS OF PRODUCTS DERIVED FROM GERANIOL

Stereochemistry of Cyanidation Products

The relative configurations of (3a) and (3b), isolated from the hydroboration-cyanidation of various geraniol derivatives, was established by oxidation, under conditions claimed to be non-equilibrating,[19,20] to a mixture of menthone (21) and isomenthone (22) (Scheme 11). Glc analysis of this mixture showed (21) and

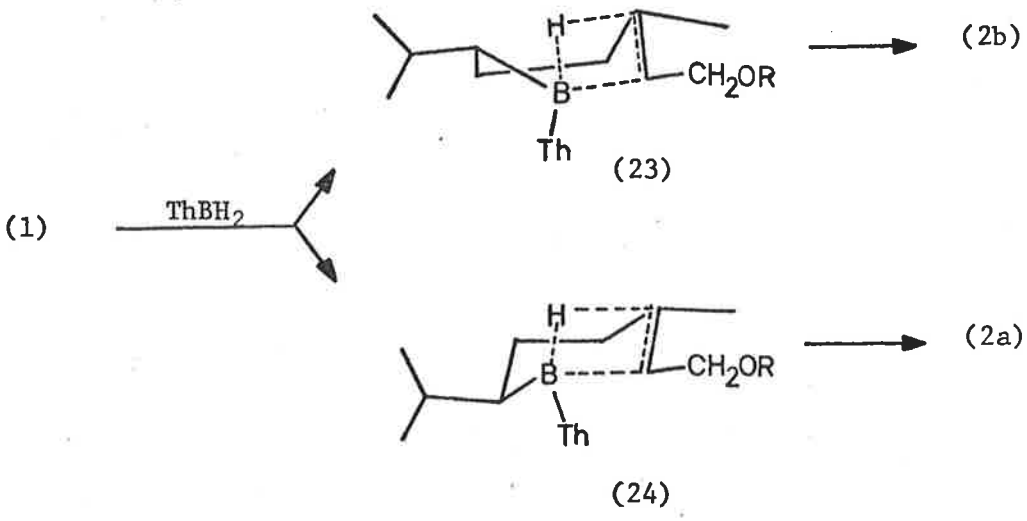


Scheme 11

(22) to be present in the ratio 1:3 after 10 min, but this ratio decreased with time to 1.0:2.1 after 2 h. Thus the ratio of (3a)

and (3b) must also be at least 1:3 and this must reflect the ratio of the intermediate cyclic boranes (2a) and (2b), since cyanidation proceeds with retention of configuration.[11]

An examination of models indicates that this ratio of products must result from the first-formed borane adopting a predominantly pseudo-boat conformation (23) in the transition state for the second hydroboration. This would produce a borinane with the methyl and isopropyl groups in a <u>cis</u> configuration (2b) as observed in the major final product (3b). A pseudo-chair conformation (24) would produce a borinane with the <u>trans</u> configuration (2a) corresponding to the minor product (3a) (Scheme 12). Although

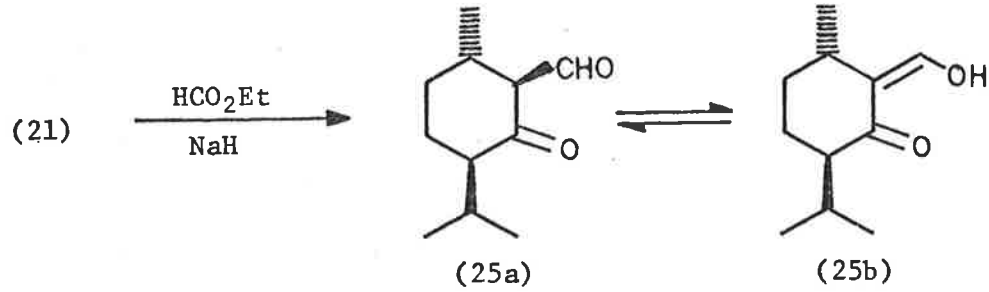


Scheme 12

the pseudo-chair conformation might be expected to be more stable than the pseudo-boat, the bulky thexyl group produces severe Gauche interactions in (24) which are relieved by adopting conformation (23). These considerations hold true whichever double bond is hydroborated first.

Synthetic Confirmation of Structure of Products

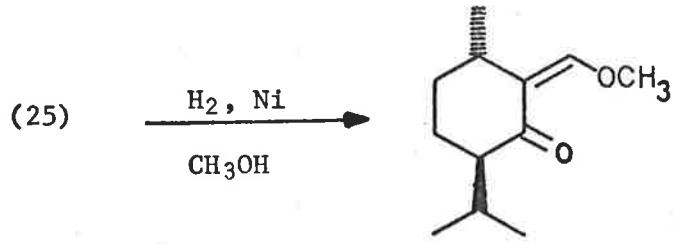
Treatment of menthone (21) with ethylformate in the presence of a strong base (sodium hydride) gave 3-oxo-p-menthane-2-carbaldehyde (25) in 77% yield (Scheme 13).[21] This compound has the same skeletal structure as the target molecules (3a and 3b), but is in a higher oxidation state. Thus a selective reduction of the carboxyaldehyde group was required to complete the synthesis.



Scheme 13

Attempted catalytic hydrogenation of (25) was unsuccessful and in one case gave products (26) from reaction with the solvent

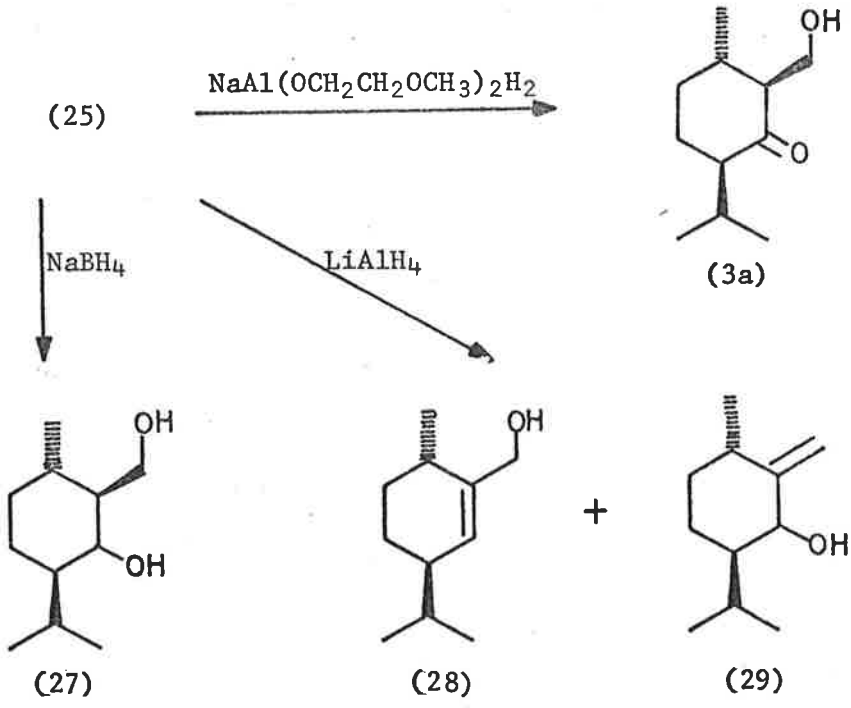
(Scheme 14). Attempts to form various ether derivatives[22] of (25b), in order to investigate the possibility of selective hydrogenation of the enolate, also proved ineffective. The stability of (26) under hydrogenation conditions suggests, however, that selective hydrogenation may not have been a feasible route to the required product.



(26)

Scheme 14

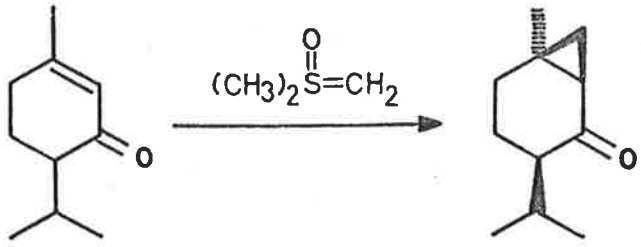
Sodium borohydride reduction[23] of (25) gave the diol (27) in 81% yield, and lithium aluminium hydride[24] gave a mixture of unsaturated alcohols (28) and (29) in the ratio 7:1 by nmr in 92% yield. Reduction with sodium aluminium bis(2-methoxyethoxy)-hydride[25] gave a product, in 66% yield, with glc retention time the same as the minor product (3a) derived from geraniol (Scheme 15). The product did not show (by nmr) any equilibration on treatment with methanolic potassium hydroxide, and this also suggests that it is the more thermodynamically stable isomer, (3a).


(25)
NaAl(OCH2CH2OCH3)2H2
OH
O
(3a)
NaBH4
LiAlH4
OH
OH
(27)
OH
(28)
+
OH
(29)

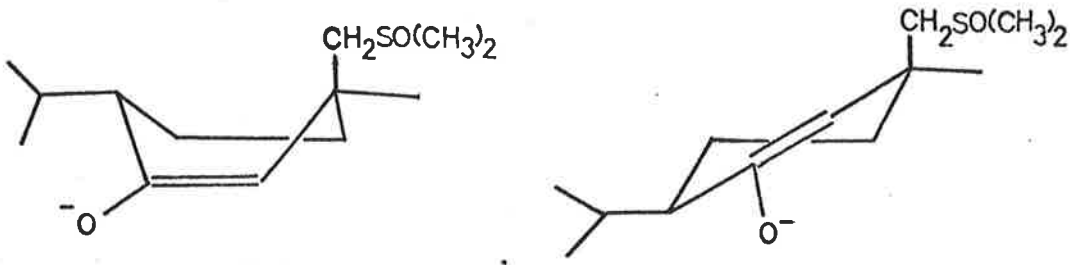
Scheme 15

1.3 SYNTHESIS OF PRODUCTS DERIVED FROM LINALYL ACETATE

Dimethylmethylene oxysulphurane[26] reacted stereospecifically with piperitone (30) to give a homogeneous product, the cyclopropyl-ketone (31) (Scheme 16). Both nmr and glc analysis indicated only one product, the structure of which was assigned on the basis of



(30) (31)



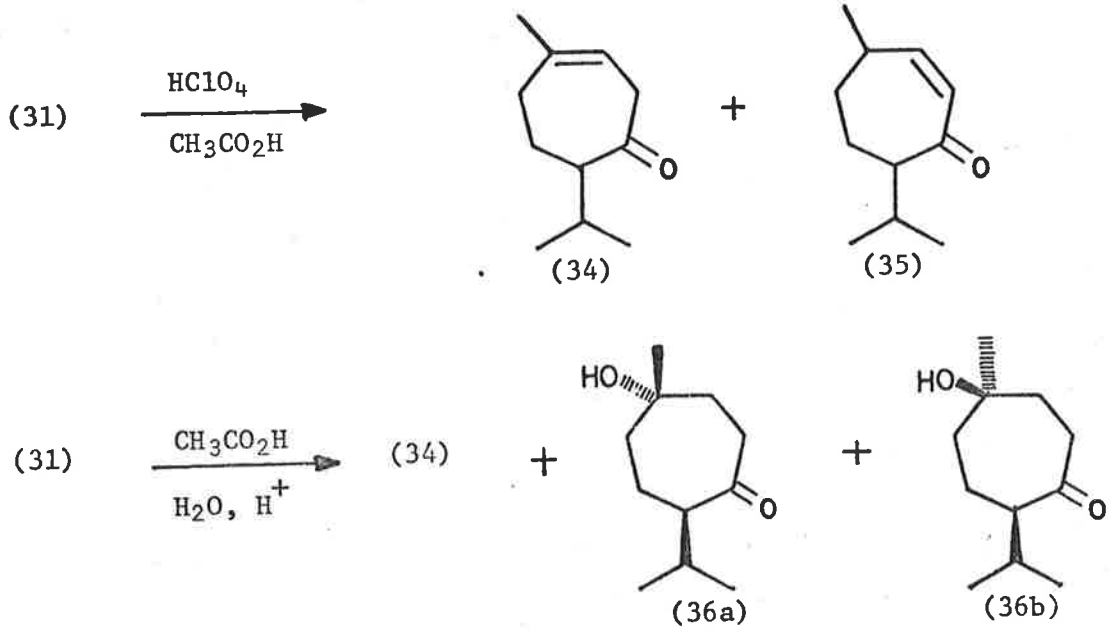
(32) (33)

Scheme 16

the intermediate which is formed first. Addition of the sulphur ylid occurs at the β-carbon atom of the double bond[27] to generate an enolate anion (32 and 33). In this particular case the subsequent attack of the π-system of the enolate anion on the methylene adjacent to sulphur requires the methylene group to adopt a pseudo-axial

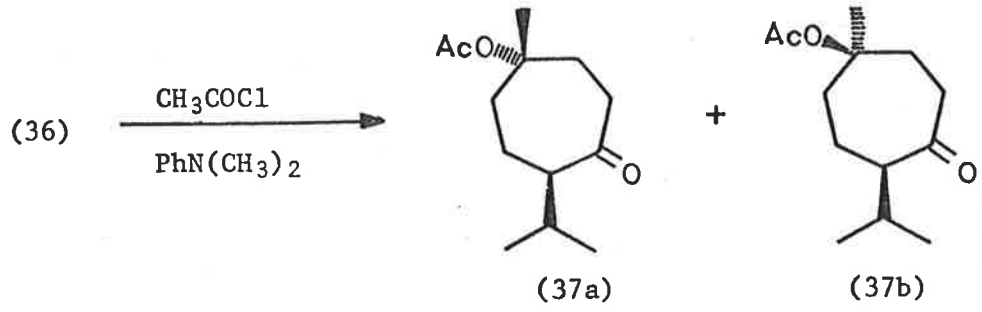
conformation. The enolate (32), however, must adopt a boat conformation whereas (33) can adopt a slightly deformed chair conformation and still retain the dimethylsulphoxymethylene group in a pseudo-axial configuration. Thus (33), the enolate which would give (31), is favoured, and appears to be formed exclusively.

Unfortunately the stereochemical integrity of (31) was lost during the acid catalysed ring opening of the cyclopropyl ring.[28] Perchloric acid, varied over a concentration range of 1-10%, in acetic acid gave inseparable mixtures of the unsaturated ketones (34) and (35) (Scheme 17). Aqueous acetic acid containing a trace of sulphuric acid



Scheme 17

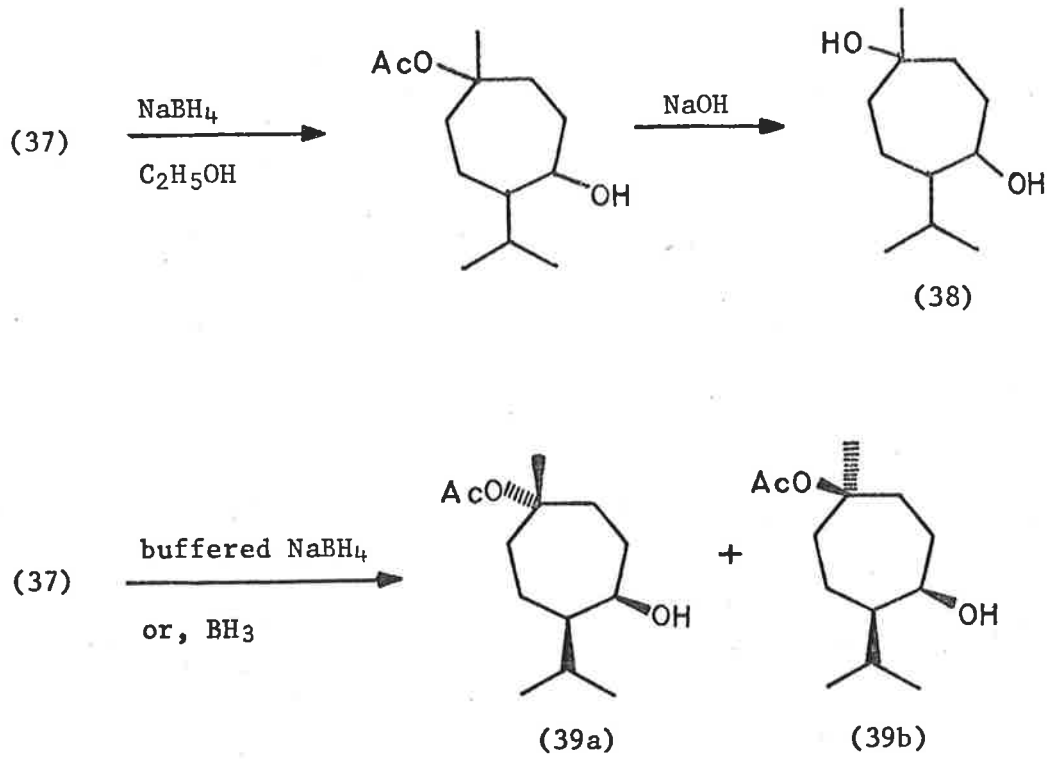
gave (34) in 35% yield, but also gave the required hydroxyketone (36) in 39% yield. The two isomers (36a) and (36b) could not be fully resolved by glc, but the nmr spectrum indicated a 1:1 mixture. This was indicated by the resonances attributed to the methyl protons of the isopropyl group, which showed doublets centred at δ 0.9 and δ 1.0 ppm in the ratio 1:1. Acetylation of the hydroxyketone mixture with acetyl chloride in the presence of N,N-dimethylaniline gave a 1:1 mixture of (37a) and (37b) (again, determined by n.m.r.), in 73% yield (Scheme 18).



(37a) (37b)

Scheme 18

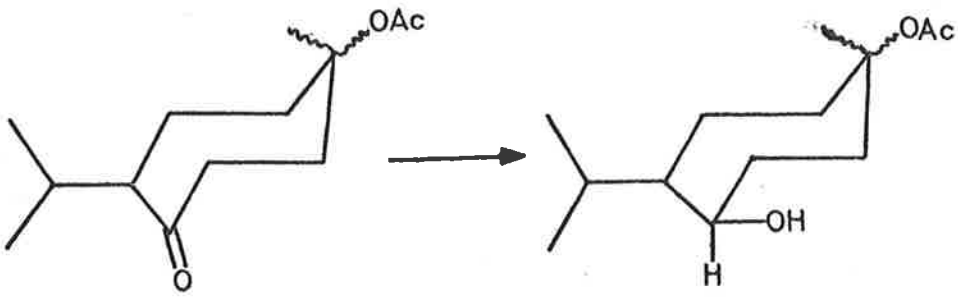
Reduction of (37) by sodium borohydride in ethanol[30] gave a mixture of diols (38) in 98% yield. Repetition of the reduction in buffered medium,[31] or with borane in tetrahydrofuran,[32] gave the desired hydroxyester mixture (39) in 53% and 99% yield respectively. This indicates that the initial observation of ester cleavage with sodium borohydride in ethanol is an artifact caused by hydrolysis of the ester by basic products formed during the reduction (Scheme 19).



Scheme 19

Glc analysis of the product mixture (39) indicated only two isomers in the ratio 1:1. Analysis, under identical conditions, of the product obtained by hydroboration-cyanidation of linalyl acetate[13] showed the presence of the same two isomers but in the ratio 1:2. There was also present a third isomer, which was not found in the synthetic sample. The lack of this third isomer in the synthetic product can be attributed to the stereospecific nature of the reduction of (37) to (39). An examination of models indicates that the isopropyl group adjacent to the ketone moiety severely

hinders approach to the carbonyl group from the upper face of the molecule (i.e. cis to the isopropyl group). This steric hindrance is not present on the lower face of the molecule, and consequently reduction takes place exclusively with hydride attack trans to the isopropyl group (Scheme 20). Hence the isopropyl and hydroxyl groups assume a cis configuration, irrespective of the configuration of the rest of the molecule, and this results in only two isomeric products (39a and 39b).



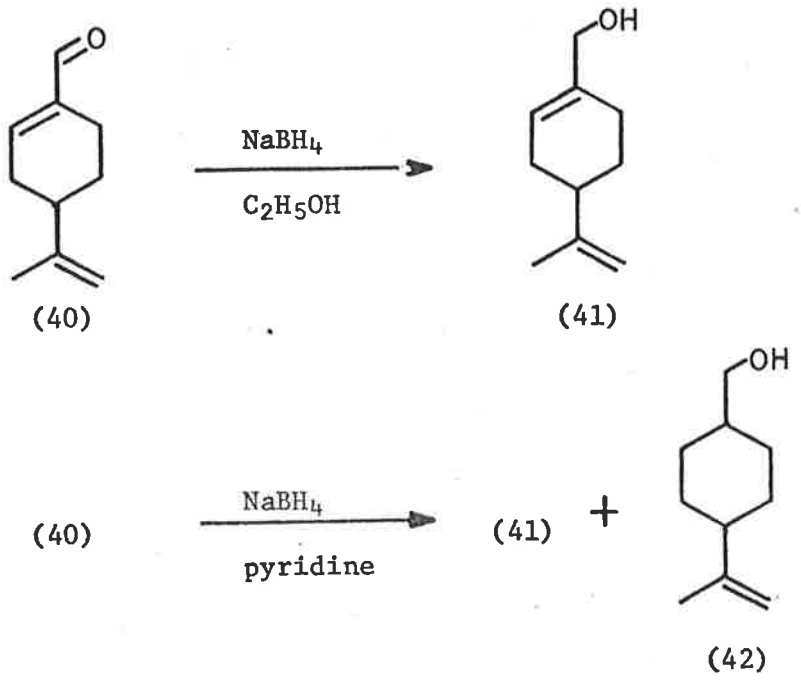
(37) (39)

Scheme 20

1.4 SYNTHESIS OF PRODUCTS DERIVED FROM MYRCENE

2-Methyl-3-oxo-p-menthan-7-ol (9).

The skeletal similarities between the target compound (9) and perillaldehyde (40) made the latter a logical choice as a starting material for this synthetic sequence. The first step of the synthesis required reduction of the conjugated system of (40) to give 4-isopropenyl-1-hydroxymethylcyclohexane (shisool, 42). Reduction using sodium borohydride in ethanol[30] gave only the carbonyl reduction product, the allylic alcohol (41), in 94% yield (Scheme 21).



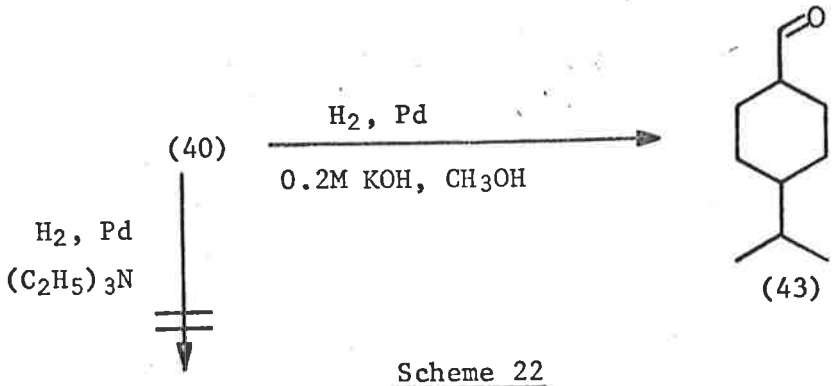
Scheme 21

The reported reduction of conjugated carbonyl systems to the saturated carbonyl analogues by sodium borohydride in pyridine[33] was expected to give the required compound (42). It was found, however, that the product consisted of a mixture of (41) and (42) in the ratio of 1:4 (by nmr, based on resonances at δ 4.7 for $=CH_2$ and δ 5.7 for =CH-). Variation in reaction time (1 h to 3 days) and temperature (0° to 114°) resulted in variations in overall yield but had no effect on the product distribution. Reduction with sodium borohydride in the presence of triphenylphosphine,[34] which is reported to behave in a similar manner to the sodium borohydride-pyridine reagent, gave exactly the same product composition as previously observed, but in much lower yield (10%). Unfortunately (41) and (42) could not be separated by the usual physical methods.

Reduction of (40) with lithium aluminium hydride[35] gave a quantitative yield of (41). Sodium aluminium bis (2-methoxyethoxy)-hydride is reported to be more selective in the reduction of α,β-unsaturated carbonyl compounds,[36] giving either a partially or a wholly reduced product. Unfortunately it also reduced (40) to a single product, (41), in 98% yield.

The hydrogenation of α,β-unsaturated carbonyl systems under basic conditions has been reported[37] to proceed in preference to reduction of an isolated double bond. Thus it was hoped that reduction of perillaldehyde by hydrogenation over pallidium catalyst

under basic conditions may have led to preferential saturation of the conjugated double bond. Two such systems were investigated (Scheme 22). Hydrogenation of (40) in triethylamine resulted in no

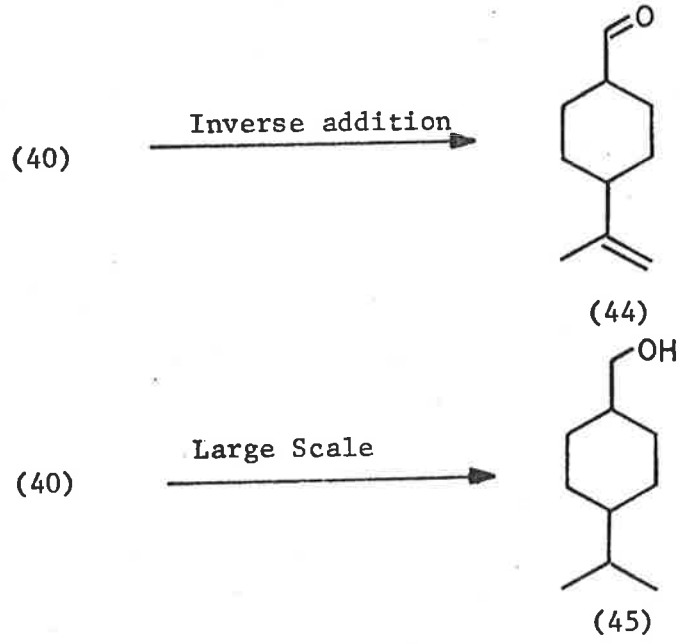


Scheme 22

reduction, unchanged starting material being recovered. Hydrogenation over palladium in methanolic potassium hydroxide solution resulted in non-selective reduction of both double bonds.

Reduction of (40) by sodium in aqueous ammonia reportedly[38] gives (42) in 35% yield. Treatment of (40) with lithium in anhydrous ammonia, in the presence of isopropanol as proton source,[39] gave 97% yield of the reduced product (42). Glc analysis of the product indicated the presence of both cis and trans isomers in the ratio 1:1, but no attempt was made to separate the isomers. The procedure, which involved addition of a solution of (40) in isopropanol and ether to a concentrated solution of lithium in ammonia (the so-called "bronze phase" reduction[40]), proved to be extremely sensitive to impurities in the ammonia. This necessitated distillation of the

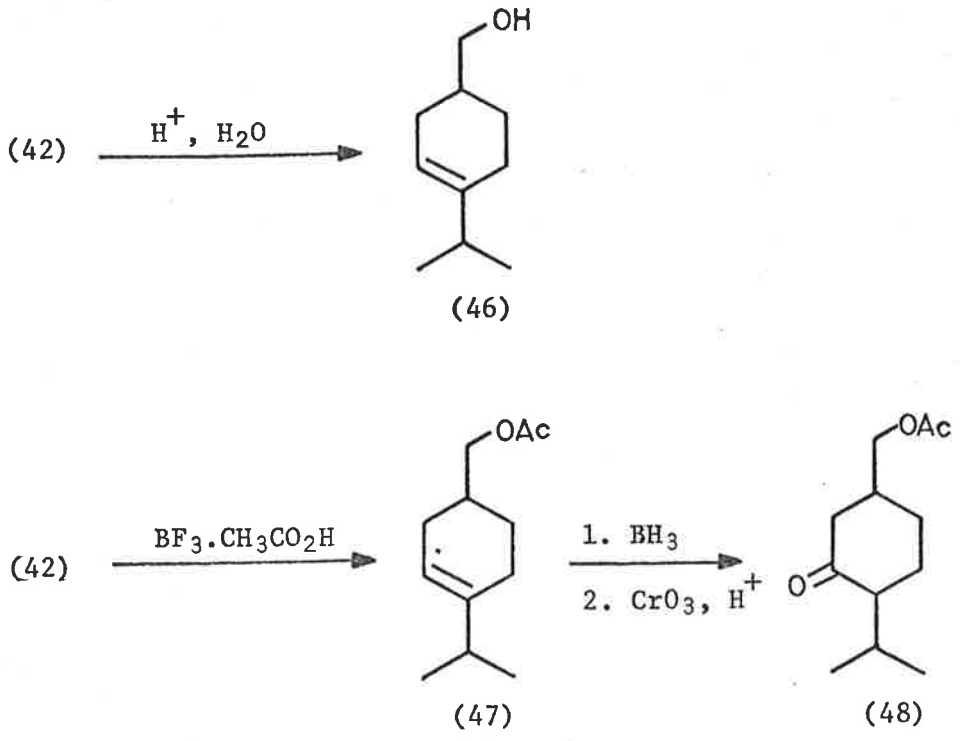
ammonia immediately prior to use. Addition of lithium to a solution of (40) in ammonia,[41] isopropanol and ether ("inverse addition") resulted in reduction of only the double bond of the conjugated system, giving 4-isopropenylcyclohexanecarboxaldehyde (shisoal, 44; cis and trans isomers in the ratio 3:1) in 78% yield (Scheme 23). Reduction of (40) on a large scale (100 mmole) resulted in complete saturation of the compound to give 7-hydroxy-p-menthane (45), as the only product, in 84% yield. The reduction of an isolated double



Scheme 23

bond in a dissolving metal reaction has been reported previously[42] but usually requires prolonged reaction times.

The migration[43,44] of the 8,9-double bond of (42) into the 3,4-position could not be effected with a trace of p-toluenesulphonic acid in benzene,[45] but was accomplished in aqueous sulphuric acid[46] to give (46) in 73% yield. Boron trifluoride-acetic acid complex[47] also induced double bond migration and also acetylated the hydroxyl group giving (47) in 82% yield (Scheme 24). Subsequent hydroboration of (47), followed by in situ oxidation of the borane with chromic

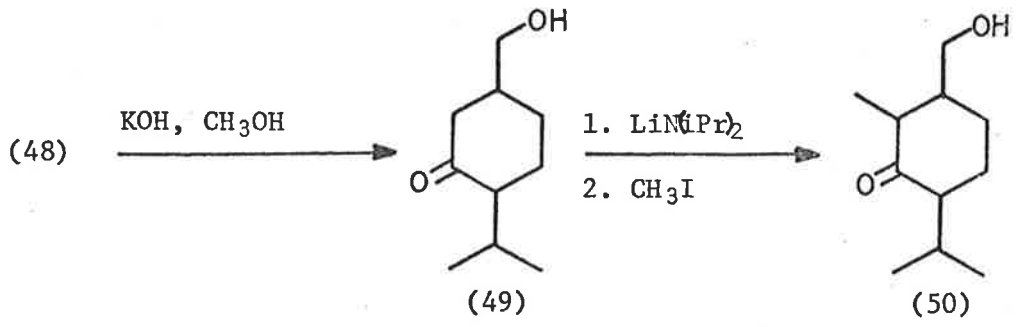


Scheme 24

acid[18,48], gave the ketoester (48) in 89% yield. Glc analysis of the product indicated the presence of both the cis and trans

isomers in the ratio 1:4. No attempt was made to separate these two isomers.

Attempts were made to introduce a formyl group α to the ketone[49] of (48) in order to activate[50] the α-position for methylation. These attempts proved to be unsuccessful under a variety of experimental conditions. The hydroxyketone (49), obtained by the hydrolysis of (48) in methanolic potassium hydroxide,[51] also proved to be resistant to formylation α to the ketone. Treatment of (49) with two equivalents of lithium diisopropylamide in ethereal solution, followed by one equivalent of iodomethane,[52] gave (50) in 91% yield, with no trace of O-alkylated material (Scheme 25).

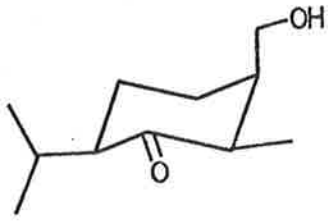


Scheme 25

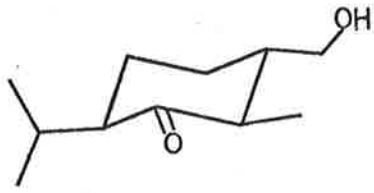
Glc analysis of (50) showed the presence of three isomers in the ratio 1:2:4. Analysis of the product obtained from myrcene[13] had shown the presence of the same three isomers, but in the ratio of 1:2:2. The difference in product distribution may be attributed to the different steric factors affecting the alkylation of (49) and

hydroboration-cyanidation of myrcene, the latter showing less specificity. The two product mixtures do, however, appear to contain the same isomers and thus it may be assumed that (50) and (9) are the same compound.

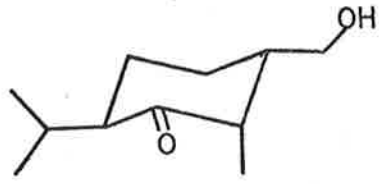
Treatment of (50) with trifluoroacetic acid resulted in a change in the isomer distribution from 1:2:4 to 1:4:0.5. This may reflect the equilibration of structures such as (50a) and (50c) into a compound having structure (50b), which is the thermodynamically



(50a)



(50b)



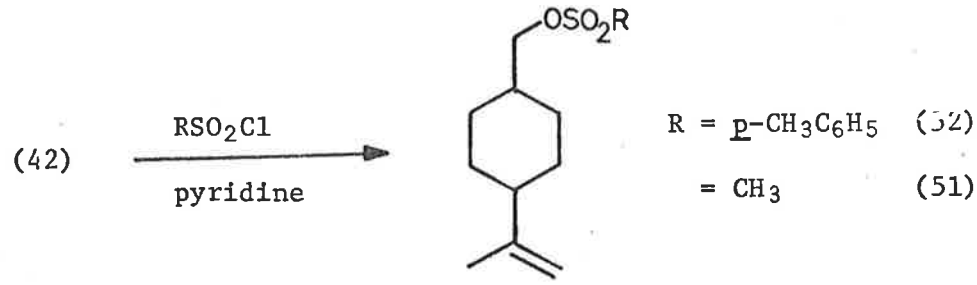
(50c)

most stable configuration for compound (50). Thus it may be assumed that neither the alkylation of (49) nor the hydroboration-cyanidation of myrcene are under purely thermodynamic control.

3-Oxo-7-hydroxymethyl-p-menthane (14).

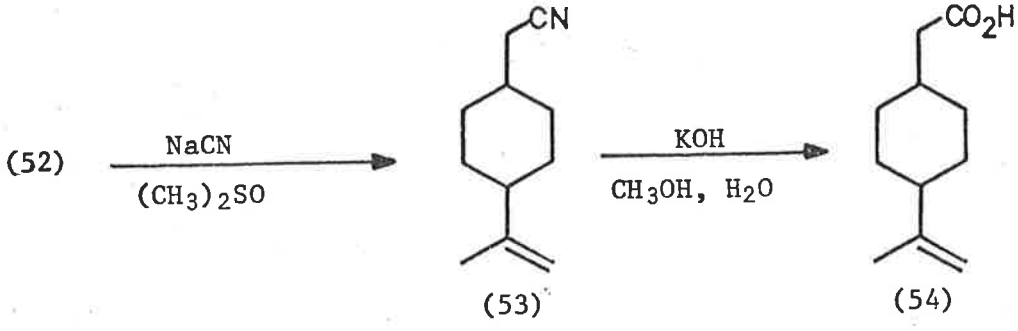
Shisool (42) requires only a one carbon homologation at the C-7 position to give the same skeletal structure as that of the

required product (14). Formation of the methanesulphonate[53] ester (51) of shisool was realized in 52% yield, whilst the p-toluene-sulphonate[54] ester (52) was obtained in 62% yield (Scheme 26). Both (51) and (52) were heat labile and consequently had to be prepared at



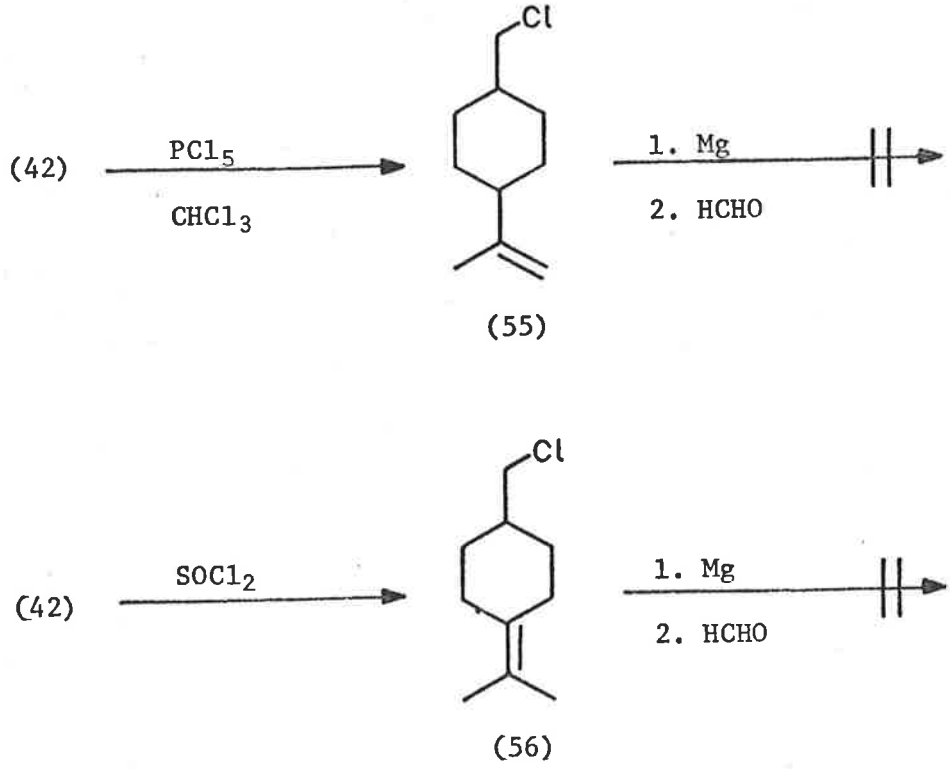
Scheme 26

or below room temperature. The nitrile (53) was obtained in 60% yield by displacement of the sulphonate group of (52) by sodium cyanide in dimethylsulphoxide.[55] Base catalysed hydrolysis of the nitrile[56] gave the expected acid (54) but in only 18% yield. No isomerization of the double bond occurred during the hydrolysis (Scheme 27). The low yield of (54) prompted investigation of alternative pathways to (14).



Scheme 27

Chlorination of shisool with phosphorus pentachloride[57] in chloroform at -15° gave a high yield (89%) of the chloro compound (55). The isomeric chloride (56) was prepared in 73% yield by heating shisool under reflux in an excess of thionyl chloride[58] (Scheme 28). Attempts were made to prepare Grignard derivatives of both (55) and (56), and to subsequently condense these with

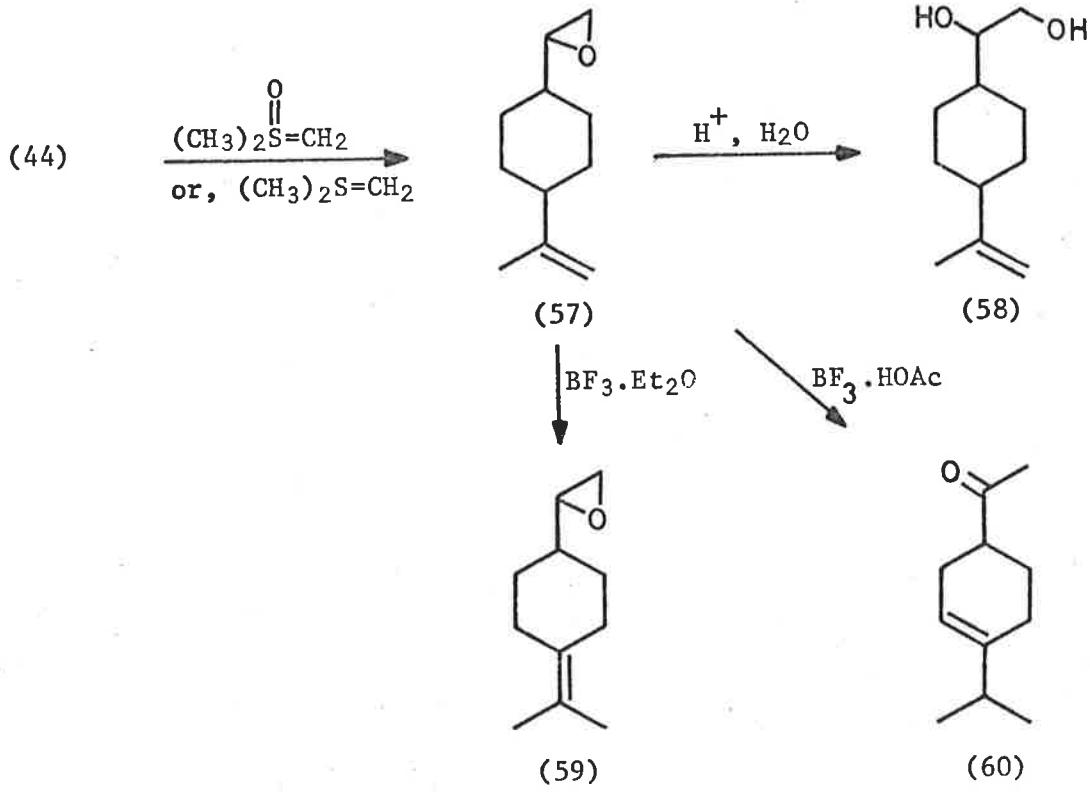


Scheme 28

formaldehyde.[59] Only unchanged chloride was recovered from these reactions, and thus it must be assumed that the Grignard derivative was not forming. Several methods of metallation were attempted,

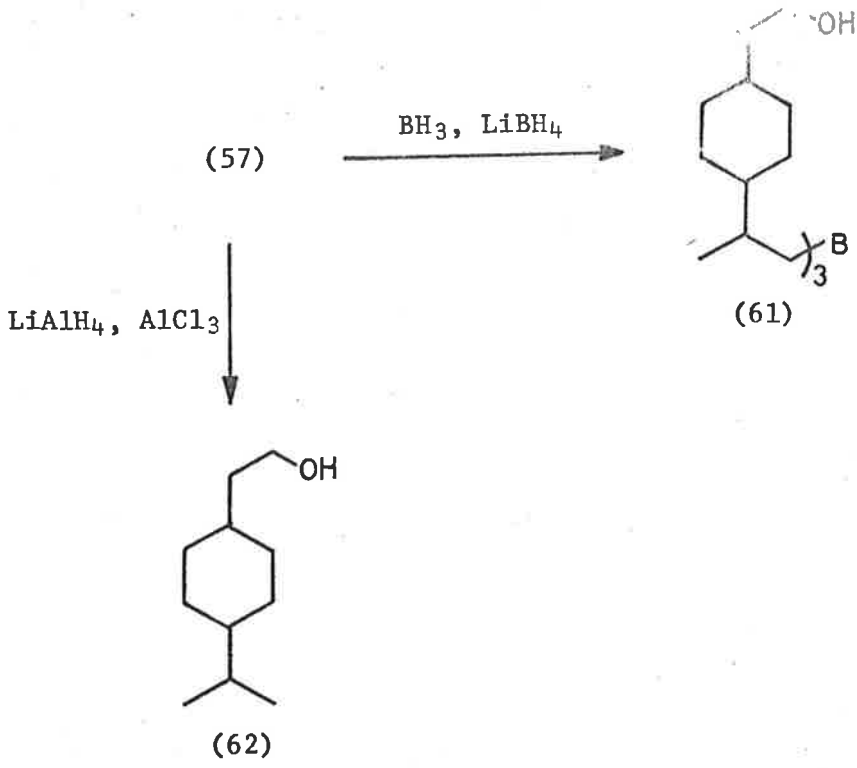
including activation of the reaction with a crystal of iodine[60] and heat.[61] Transmetallation, by the "entrainment" method, from methylmagnesium iodide[62] was also attempted without success. Activated magnesium[63] also did not appear to form the metallated product and the difficulty of formation of these Grignard derivatives remains unexplained.

Reaction of shisoal (44) with either dimethylmethyleneoxysulphurane[26] or dimethylmethylenesulphurane[64] gave the oxirane (57) in 40% and 81% yields respectively (Scheme 29). Attempted isomerization



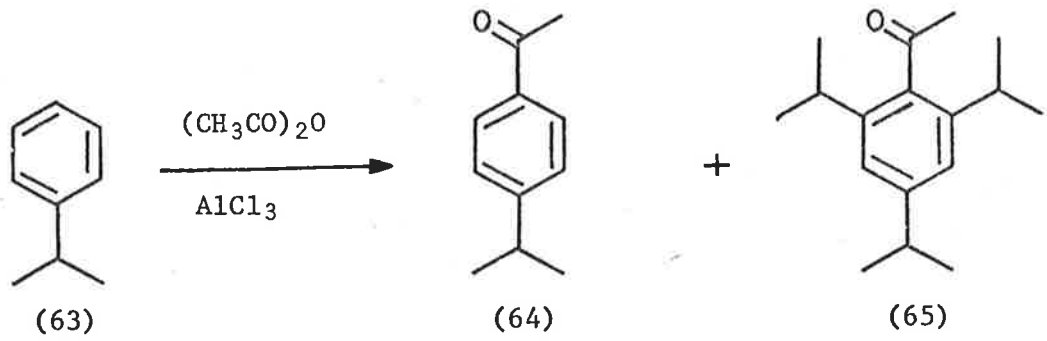
Scheme 29

of the oxirane, to an aldehyde, with aqueous sulphuric acid[65] gave only the diol (58) in 57% yield. Borontrifluoride etherate[26] surprisingly did not effect ring opening of the oxirane, but isomerized the double bond to an exocyclic position to give (59) in 67% yield. Borontrifluoride-acetic acid complex[47] not only induced migration of the double bond into an endocyclic position, but also opened the oxirane ring to give the methyl ketone (60). Reductive cleavage of the oxirane with diborane in the presence of lithium borohydride[66] resulted in opening of the epoxide in the required direction, but also resulted in hydroboration of the olefinic portion of the molecule, giving the trialkylborane (61) in 72% yield. An attempt was made to regenerate the double bond by heating the borane (61) with 1-decene in THF, but glc analysis indicated no displacement of the required molecule from boron. An attempted reductive cleavage with aluminium hydride resulted in unexpected reduction of both the oxirane and the double bond to give the saturated alcohol (62) (Scheme 30). The aluminium hydride was prepared, however, from lithium aluminium hydride and aluminium chloride, and any excess of the latter reagent may have resulted in chlorination of the double bond and subsequent reduction of the chloride thus formed by the hydride reagent.



Scheme 30

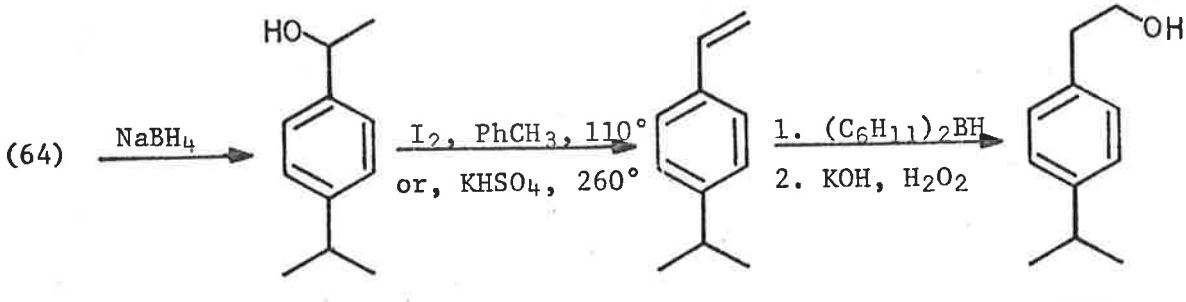
An alternative sequence, which established the carbon skeleton required before introducing the oxygen functions, began with cumene (63). Acylation of cumene with acetic anhydride and aluminium chloride gave 4-isopropylacetophenone (64) in 54% yield. Some disproportionation of cumene was observed during the acylation[67] and this gave rise to the formation of 2,4,6-triisopropylacetophenone (65) in 12% yield (Scheme 31). Reduction of (64) by sodium borohydride in ethanol gave 1-(4-isopropylphenyl)ethanol (66) in 98% yield. Dehydration of this alcohol was attempted by heating, under reflux, a solution of (66)



(63) (64) (65)

Scheme 31

in toluene containing a trace of iodine.[68] This gave only moderate yields of 4-isopropylstyrene (67). Higher yields (89%) of the dehydration product were realized by slow addition of (66) to molten potassium hydrogen sulphate[69] maintained at 260°. Immediate distillation of the product from the reaction mixture prevented any loss by thermal polymerization. Hydroboration of (67) with dicyclohexylborane,[70] followed by <u>in situ</u> oxidation of the resultant organoborane, gave 2-(4-isopropylphenyl)ethanol (68) in 68% yield (Scheme 32).



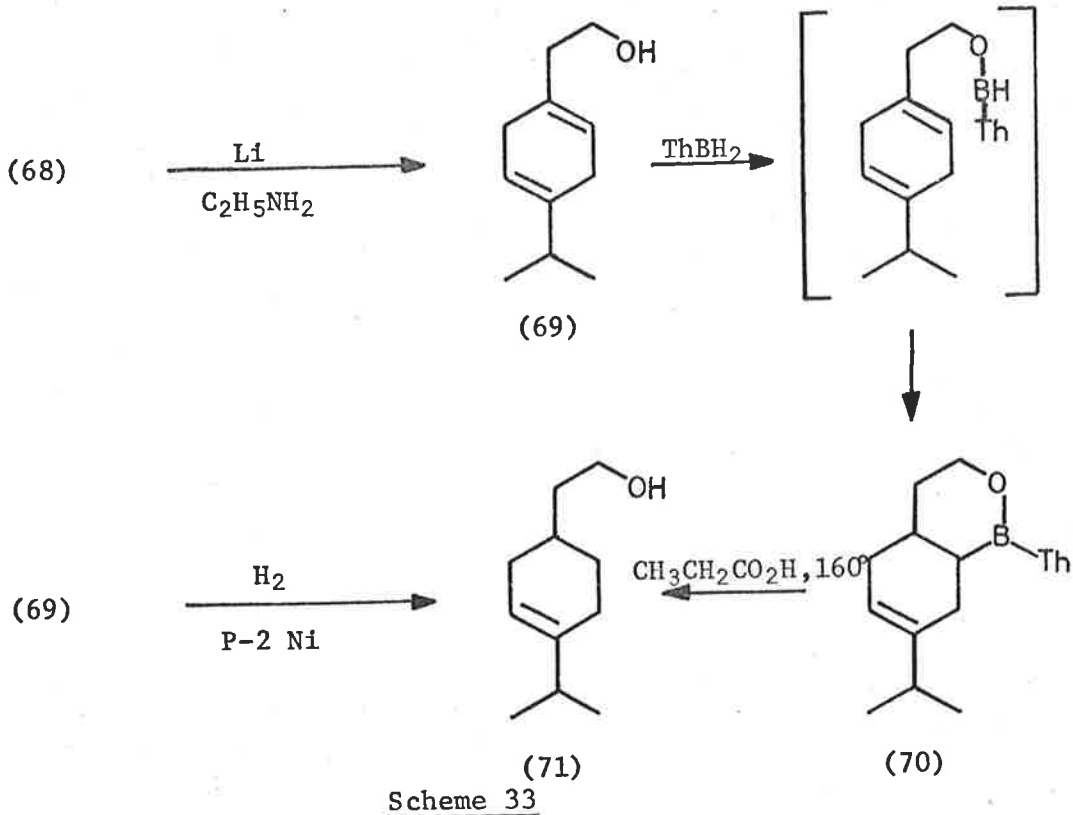
(66) (67) (68)

Scheme 32

Reduction of (68) with lithium in anhydrous ethylamine at -78° over 12 h gave an almost quantitative yield (98%) of 2-(2,5-dihydro-2-isopropylphenyl)ethanol (69). The mass spectrum of this compound showed a molecular ion of m/e 166, and the nmr spectrum showed a broad doublet of doublets at δ 5.4, integrating for two hydrogen atoms.

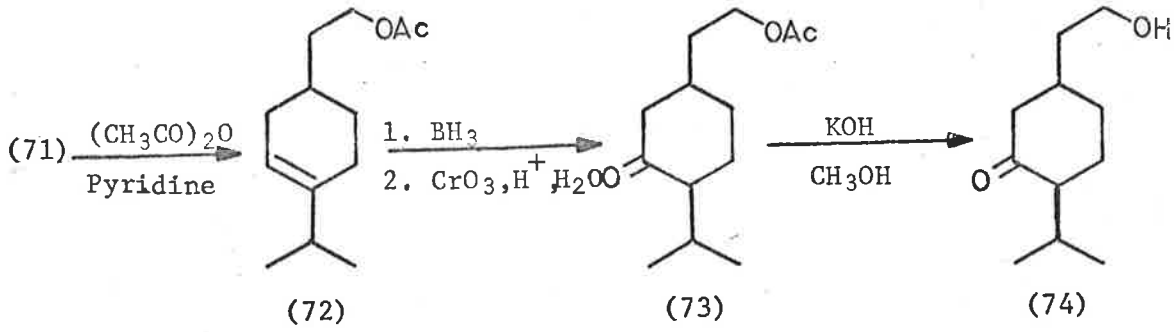
Partial hydrogenation of (69) was directed exclusively at the 1,6-double bond by use of thexylborane[14,71] as the hydrogenating reagent. Reaction of (69) with thexylborane results in the formation of a cyclic oxyborolane (70), which may undergo protonolysis with propionic acid to give the tetrahydroderivative (71) (mass spectrum shows molecular ion at m/e 168, and the nmr resonance at δ 5.4 is now a doublet integrating for only one hydrogen atom). It was also found that P-2 nickel hydrogenation catalyst gave exclusively (71) but in slightly better yield (84% compared to 60% for protonolysis of the borane) and under much milder reaction conditions (Scheme 33). The reported[72] stereospecificity of this catalyst is exemplified here. The steric environment of both double bonds in (69) is very similar, but hydrogenation occurs exclusively at the 1,6 position. It seems unlikely that the difference in size between the isopropyl group and the hydroxyethyl group is sufficient to explain this stereospecificity, but coordination of the hydroxyl group to the catalyst may constrain the molecule such that the 1,6 double bond is much closer to the

active sites of the catalyst than is the 3,4 double bond.



Scheme 33

Acetylation of (71) by acetic anhydride in pyridine[73] gave (72), and hydroboration followed by in situ oxidation with chromic acid solution gave (73) in 78% yield. On standing at room temperature for 24 h in methanolic potassium hydroxide, (73) was converted into the hydroxyketone (74) in 82% yield (Scheme 34).



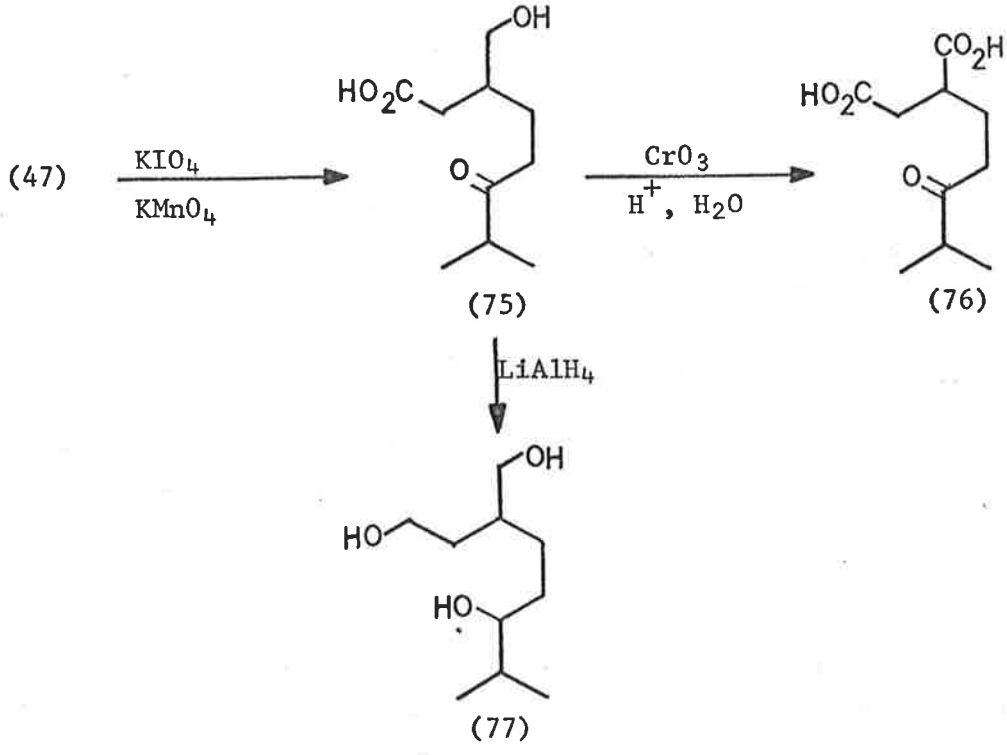
Scheme 34

Glc analysis of (74) indicated the presence of two isomers in the ratio 3:2. These two isomers were also present in the compound (14), isolated from the hydroboration-cyanidation of myrcene,[13] in the ratio (2:1), and glc retention times were identical to those in the synthetic product. Nmr and ir data were identical for the products from each source, and thus it may be assumed that (74) and (14) are identical.

2-Carboxy-6-oxo-7-methyloctanoic acid (19),

Oxidation of p-menth-3-en-7-yl acetate (47) with potassium periodate in the presence of potassium permanganate[74,75] gave 2-hydroxymethyl-6-oxo-7-methyloctanoic acid (75) in 71% yield. It is interesting to note that the oxidation product has undergone hydrolysis of the ester function without oxidation of the alcohol thus generated. Also, even though the molecular geometry of (75)

allows for formation of a γ-lactone, it is the free hydroxyacid that is isolated. Oxidation of (75) with aqueous chromic acid in acetone[76] gave a moderate yield (64%) of compound (76), identical in all respects with (19), the compound isolated from hydroboration-chromic acid oxidation of myrcene (Scheme 35).



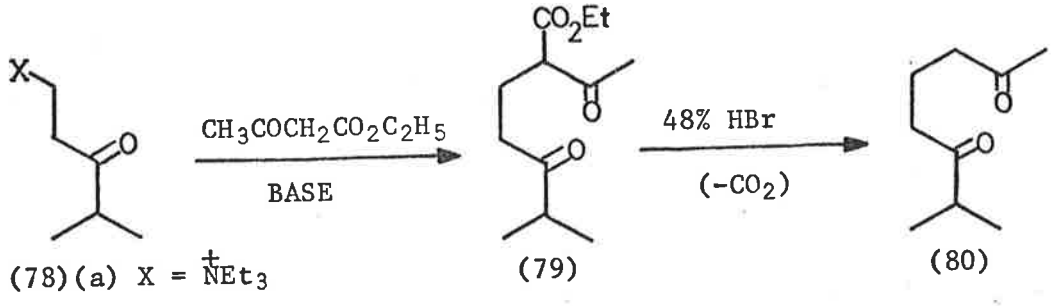
Scheme 35

Reduction of (75) with lithium aluminium hydride gave 3-hydroxymethyl-7-methyl-1,6-octanediol (77) in 46% yield. Nmr and ir spectral data for (77) were identical to those of (10), isolated from the thexylhydroboration-cyanidation of myrcene.

Glc analysis of both (77) and (10) as their respective trimethylsilyl ether derivatives gave, in each case, only one broad peak with no resolution of diastereomers. The retention times for the derivatives of (77) and (10) were the same, and thus they may be assumed to be the same compound.

7-Methyl-2,6-octanedione (20).

The route chosen for the synthesis of (20) is illustrated in Scheme 36.

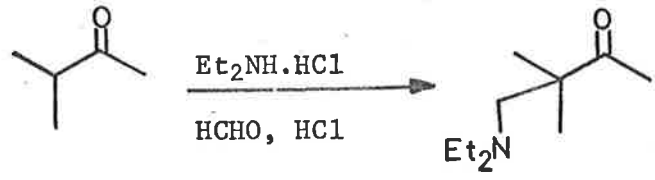


(78)(a) X = $\overset{+}{N}Et_3$ (79) (80)

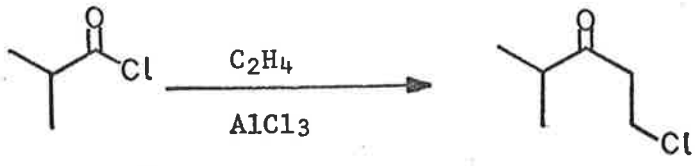
(b) = Cl

Scheme 36

An attempt was made to prepare the precursor amine for (78a) by the reaction of methylisopropylketone with formaldehyde and diethylaminehydrochloride in the presence of hydrochloric acid[77], but the only product isolated was (81) (Scheme 37). The ketone (78b) was prepared by acylation of ethylene with isobutyryl chloride in the presence of aluminium chloride,[78,79] and was isolated in reasonable yield (55%).



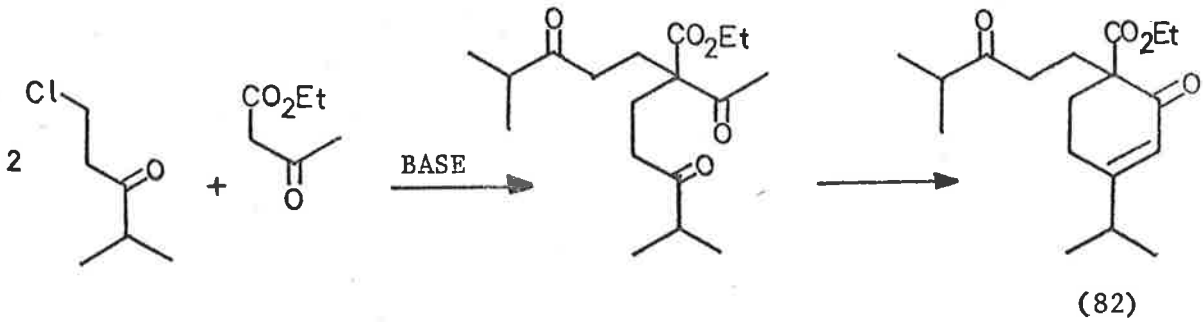
(81)



(78b)

Scheme 37

The reported condensation of (78b) with ethylacetoacetate in the presence of base[79] did not give any detectable amounts of (79). The only product isolated from this condensation was (82). This product may arise from the condensation of one equivalent of ethylacetoacetate with two equivalents of (78b), and then an intramolecular aldol condensation with dehydration would give the observed product (Scheme 38).



(82)

Scheme 38

Variation of the reaction conditions and bases did not affect the product obtained (Table 1).

The condensation was, however, eventually effected by treatment of the two components with potassium t-butoxide in anhydrous THF for relatively short reaction times. Heating the product of the condensation with 48% hydrobromic acid resulted in saponification and decarboxylation to give (80) in 69% yield. This product had the same glc retention time as (20), and also had identical spectral characteristics (nmr, ir, mass spectrum). Thus the two compounds may be assumed to be the same.

Base	Solvent	Reaction Time	Temp.	Product	Yield (%)
Sodium ethoxide	Ethanol	2 h	78°	(82)	40
		6 h	20°	(82)	27
Potassium t-butoxide	t-Butanol	3 h	80°	(82)	59
		16 h	20°	(82)	42
Potassium hydroxide	Methanol	6 h	20°	Unknown	-
Sodium Hydride	THF	3 h	65°	(82)	63
Triethylamine	Ether	18 h	20°	(82)	31
Potassium t-butoxide	THF	15 min	20°	(79)	66

TABLE 1. Base catalysed condensation of ethylacetoacetate with β-chloroethylisopropylketone.

CHAPTER 2

Cyanidation of Dialkylboranes and Borinic Acids and Esters

2.1 Introduction

2.2 Cyanidation of Dialkylboranes

2.3 Cyanidation of Borinic Acids and Esters.

2.1 INTRODUCTION

As has already been mentioned (section 1.1), the hydroboration-cyanidation of linalyl acetate with thexylborane gives rise to a product (5) whose oxidation state is lower than expected. This observation has been rationalized in terms of elimination of 2,3-dimethyl-2-butene from the first formed borane (6) to give a dialkylborane (83).† This may then undergo cyanidation, with transfer of all three groups from boron to the carbon of the cyanide moiety, to give rise to the observed product (5) (Scheme 5).

This interpretation of the reaction pathway leads to a number of possible investigations: (i) confirmation of the intermediacy of a dialkylborane in the pathway; (ii) cyanidation of other dialkylboranes as a general method of synthesis of secondary alcohols; (iii) introduction of a hydride ion into the product of cyanidation of trialkylboranes as a synthetic route to secondary alcohols; (iv) amination of cyanidation intermediates as a possible synthetic method for the production of imines and amines; (v) replacement of the thexyl group with other

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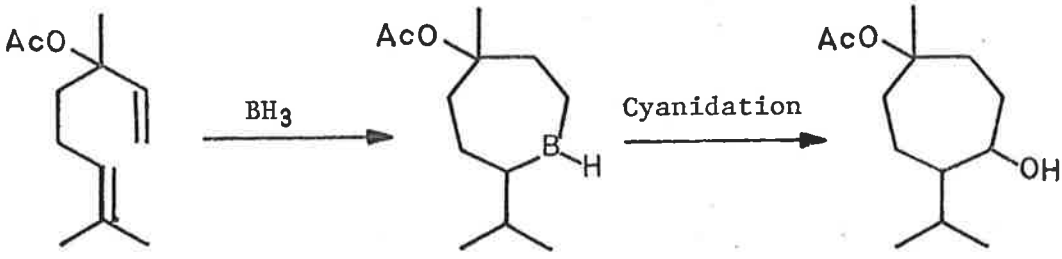
† cf. Schemes 4 and 5. From what follows, the intermediacy of (83) is preferred.

groups showing low migratory tendencies in the cyanidation procedure.

The intermediacy of a dialkylborane (83) in the production of (5) from linalyl acetate (4) may be verified by cyanidation of the organoborane obtained from hydroboration of linalyl acetate with diborane (Scheme 39). Under conditions of high dilution, hydroboration



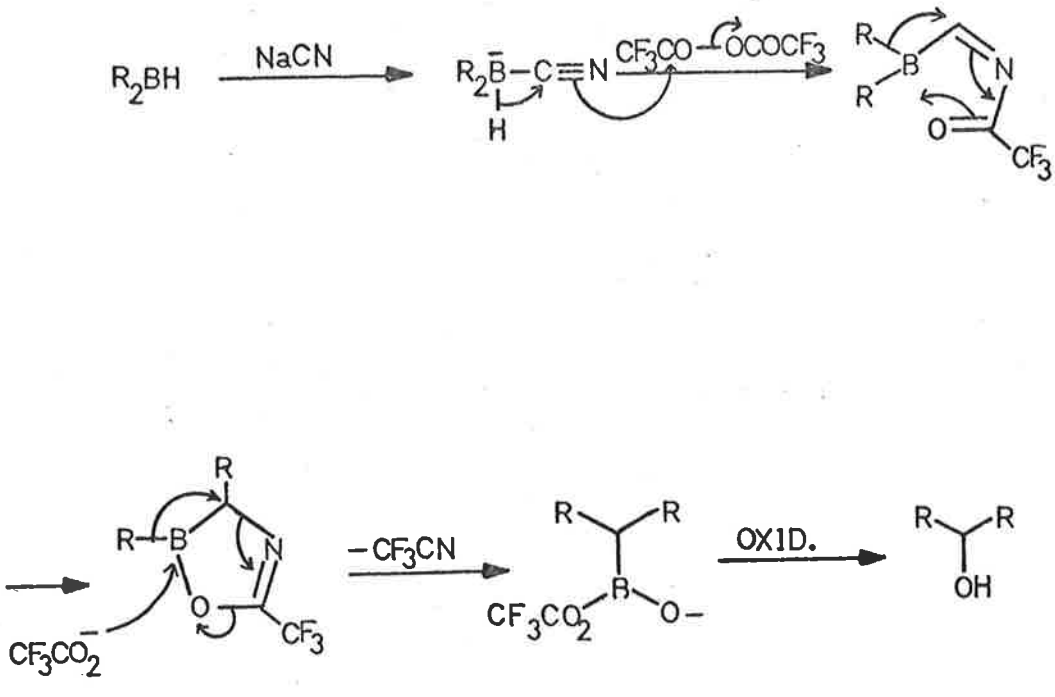
(4) (83) (5)

Scheme 39.

of (4) with diborane should give the cyclic dialkylborane (83), and if this undergoes cyanidation to give (5), then this would be strong evidence in support of the reaction pathway discussed above.

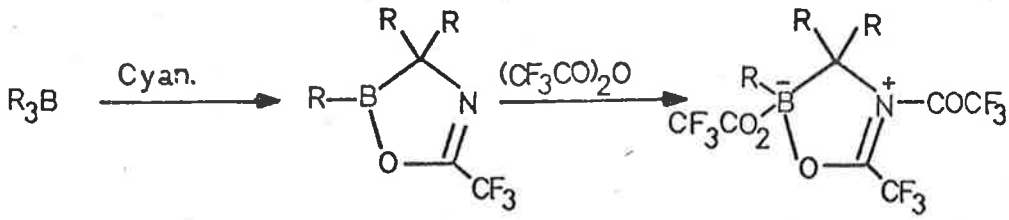
This pathway raises the question of how generally applicable the cyanidation of dialkylboranes may be as a method of synthesis of secondary alcohols. If the interpretation of the reaction pathway is correct, it would suggest that other dialkylboranes, when subjected to the cyanidation procedure, should give rise to products similar to that observed in the case of linalyl acetate. This would provide a

convenient procedure for the synthesis of both symmetrical and unsymmetrical carbinols via hydroboration-cyanidation (Scheme 40), and the stereochemistry of chiral products would be of mechanistic and synthetic interest.

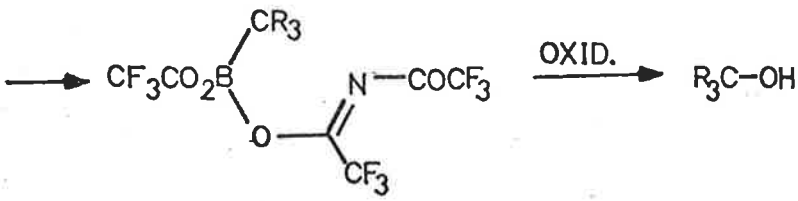


Scheme 40.

This reaction may be considered as an extension of the method of synthesis of trialkylcarbinols by the cyanidation procedure[80] (Scheme 41). The migration of three alkyl groups is



(84)

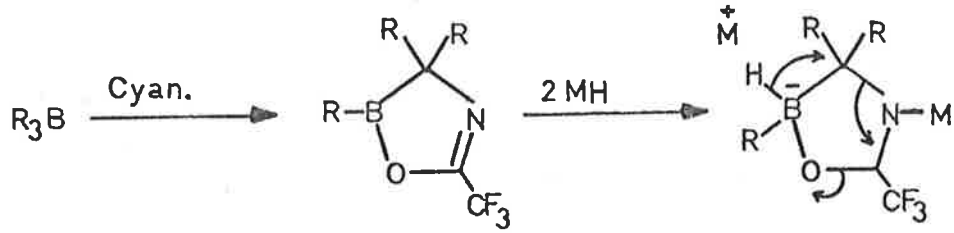


Scheme 41

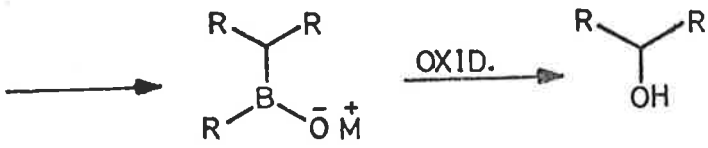
accomplished primarily by the use of trifluoroacetic acid anhydride, but occassionally also requires additional variations in reaction conditions (increased temperature; variation of solvent). It was hoped that a suitably modified cyanidation procedure might also induce migration of the hydrogen atom of dialkylboranes.

A further approach to the synthesis of dialkylcarbinols involved reduction of the cyanidation intermediate (84) of trialkylboranes with a metal hydride (Scheme 42). It was expected that this would give a borate salt (85), in which the substituents appeared to

be in the correct orientation to undergo rearrangement to a borinate salt (86) with concomitant migration of a hydride ion from boron to carbon. Oxidation of (86) with alkaline hydrogen peroxide should then give a dialkylcarbinol.



(84) (85)

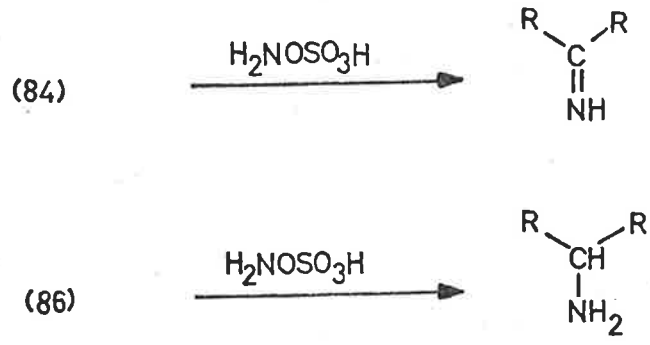


(86)

Scheme 42.

The reported amination of organoboranes by compounds such as chloramine[81] and hydroxylamine-O-sulphonic acid[82] led to the belief that treatment of cyanidation intermediates such as (84) and (86) with these reagents might give imines or amines respectively (Scheme 43), by analogy with the reaction of such intermediates with

hydrogen peroxide. Alkaline hydrolysis of intermediates such as (84) has been reported[83] to give moderate yields of amines and amides, but only under very vigorous conditions (prolonged treatment with concentrated alkali at 100°). It was hoped that the milder conditions employed during treatment with aminating reagents would lead to a more facile method for the synthesis of amines from organoboranes, via the cyanidation reaction.

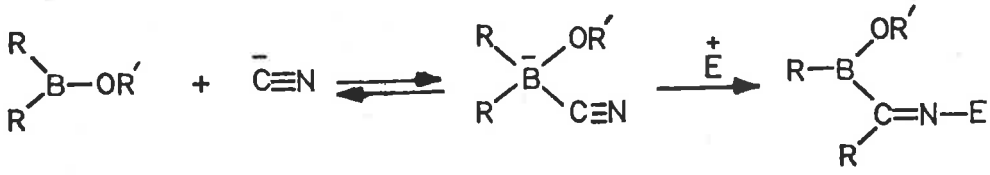


Scheme 43

As has already been stated (section 1.1), thexyldialkylboranes were first used in the cyanidation procedure[8] to improve the efficiency of the procedure by ensuring that only the two alkyl groups required in the final ketone product were involved in migration from boron to carbon. This was made possible by the relatively low migratory aptitude of the thexyl group,[5,6] thus promoting the migration of the other two alkyl groups on boron. It seemed logical, therefore, to investigate the possibility of utili-

zing other substituents, which show little tendency to undergo migration from boron to carbon, in place of the thexyl group.

The high bond energy of the B-O bond (approximately 800 kJ/mole compared to 520 kJ/mole for the B-C bond) suggests that oxygenated derivatives of boranes might show a tendency to undergo alkyl group transfer in preference to oxygen migration from boron to carbon provided that an initial "ate" complex could be formed, or a sufficiently electrophilic reagent (E^+) was used to assist migration (Scheme 44). More specifically, it might be expected that dialkyl-



(87a) R' = H

(87b) R' = CH_3

Scheme 44

borinic acids (87a) and esters (87b) would undergo cyanidation to give ketonic products if two groups migrated, or acidic products if only one group migrated.

2.2 CYANIDATION OF DIALKYLBORANES

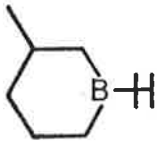
The formation of the compound (5) from the hydroboration-cyanidation of linalyl acetate seems to involve the elimination of 2,3-dimethyl-2-butene from (6) to give a dialkylborane (83) as an intermediate. The intermediacy of such a species may be demonstrated by cyanidation of the product derived from the hydroboration of linalyl acetate with diborane (Scheme 39); such a product should have the same structure as (83). This experiment was not conducted in the preliminary study[13] mentioned previously.

In the event, it was found that cyanidation of (83) gave a product (54%), which was identical in all respects to the product previously isolated after cyanidation of the organoborane obtained from the hydroboration of linalyl acetate with thexylborane. It may thus be concluded that the apparently anomalous product observed from the hydroboration-cyanidation of linalyl acetate does indeed arise through the intermediacy of (83).

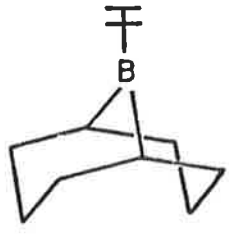
An investigation of the scope of the reaction was carried out by applying the cyanidation procedure to other dialkylboranes. Before this part of the study was begun, however, the dienes to be used were hydroborated with thexylborane and then subjected to the cyanidation procedure. This was to ensure that the dienes chosen

for the investigation did undergo cyanidation under the conditions normally employed for this reaction. The results of this preliminary survey are summarized in Scheme 45.

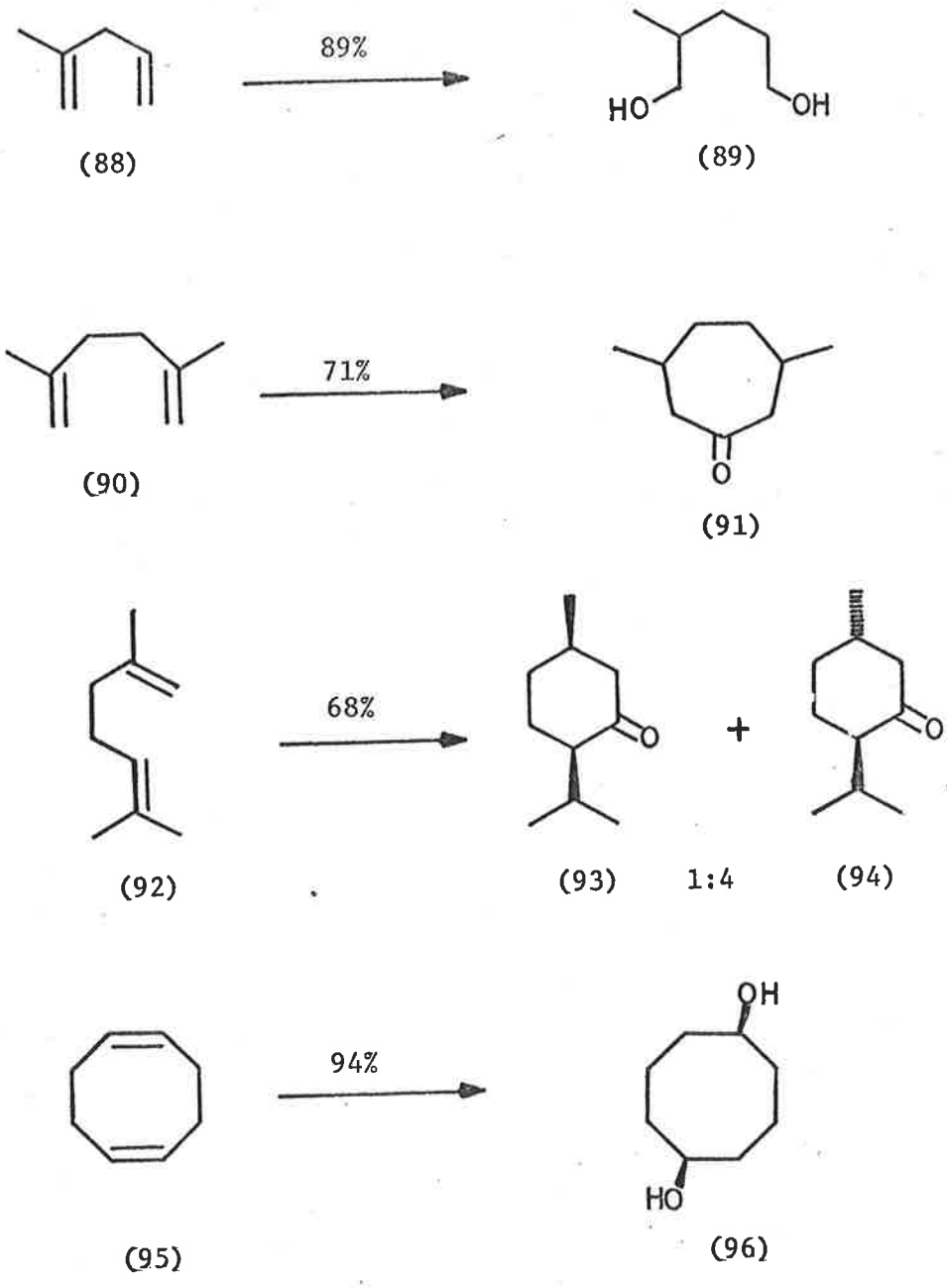
The only product isolated after hydroboration-cyanidation of 2-methyl-1,4-pentadiene (88) with thexylborane was 2-methyl-1,5-pentanediol (89). The lack of carbonylated products may be explained in terms of the tendency of this diene to form polymeric boranes in preference to monomeric, cyclic intermediates, and such polymeric boranes do not undergo cyanidation.[13] The product obtained by hydroboration with thexylborane was heated for varying periods at 65° in an attempt to isomerize[84] the polymeric borane to B-thexyl-3-methylborinane (97); no cyclic ketonic products were isolated, however, after the cyanidation procedure had been applied to the hydroborated product. Both 2,5-dimethyl-1,5-hexadiene (90) and



(97)



(98)



Scheme 45. Hydroboration-Cyanidation of Some Representative Dienes with Thexylborane

2,6-dimethyl-1,5-heptadiene (92)† gave the expected ketones after cyanidation of the product of hydroboration with thexylborane. B-Thexyl-9-borabicyclo-[3,3,1]nonane (98) was generated by hydroboration of 2,3-dimethyl-2-butene with commercially available 9-borabicyclo-[3,3,1]-nonane, but this also failed to undergo carbonylation by the cyanidation procedure; the only product isolated was cis-1,5-cyclo-octanediol (96). B-Thexyl-9-borabicyclo-[3,3,1]-nonane has also been shown to be resistant to carbonylation by the procedure of Brown, using carbon monoxide,[4] and this has been attributed to the severe steric hindrance to approach of the reagents to the molecule.[85] Evidently, the cyanidation reaction is subject to similar steric requirements as is the carbon monoxide reaction.

Although two of the representative dienes chosen for this study failed to undergo carbonylation by the cyanidation method

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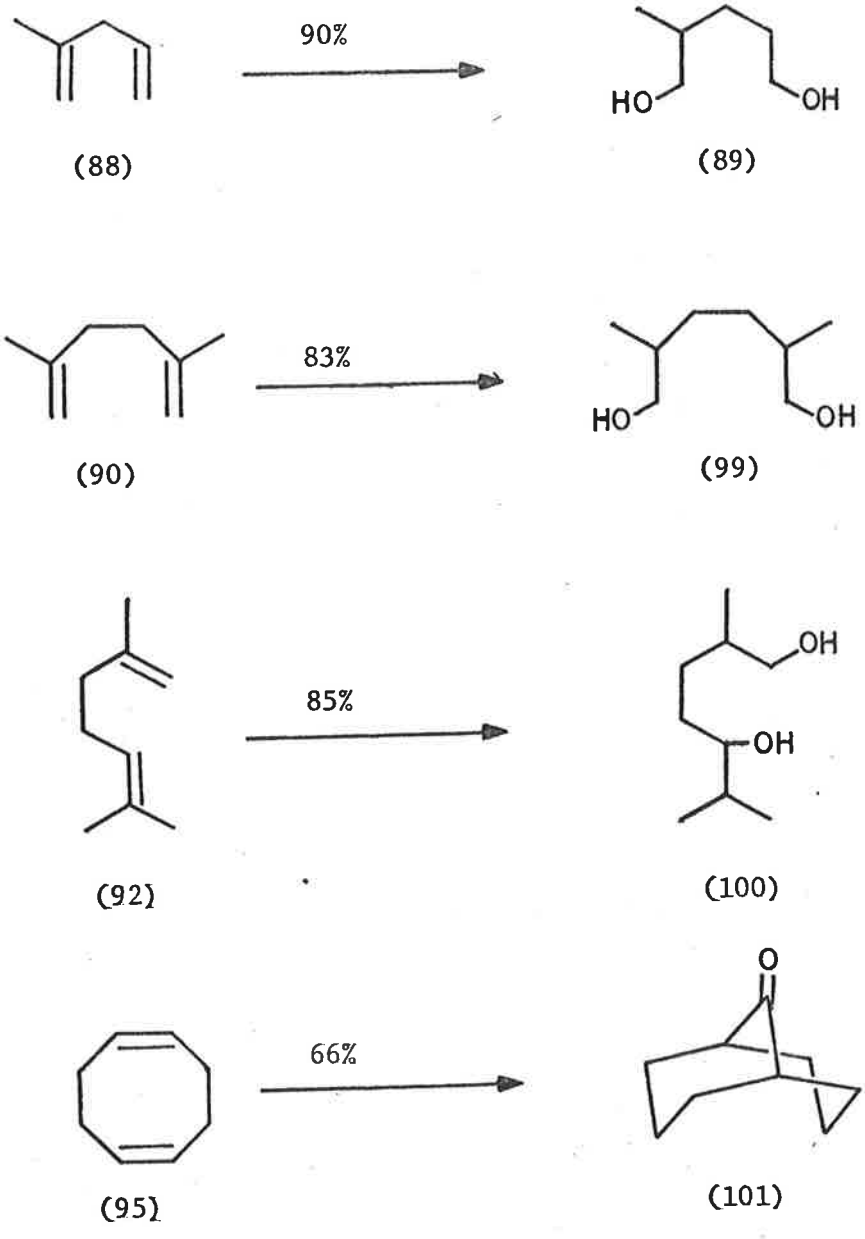
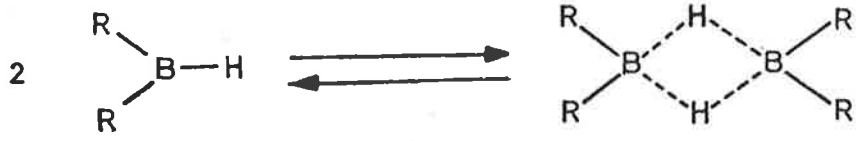
† The ratio of (93):(94) is in direct contrast to the ratio of products previously observed with geraniol derivatives (Scheme 12). The absence of an oxymethylene group in (92) relieves much of the steric strain which causes (23) to predominate over (24), and thus the hydroboration of (92) proceeds via the thermodynamically more favoured chair conformation in the transition state, leading to a predominantly trans-configuration in the product.



Scheme 46. Hydroboration-Cyanidation of some Representative Dienes with Diborane.

after formation of the thexyldialkylborane, it was decided to proceed with the investigation of the effects of the cyanidation procedure on the products of hydroboration of these dienes with diborane. The results of this investigation are summarized in Scheme 46.

With one exception, cyanidation of the hydroborated dienes failed to give any ketonic or alcoholic products derived from cyanoborate intermediates. The only products obtained were those from the oxidation of the hydroborated dienes. This may be rationalized in terms of the structure of the dialkylboranes obtained by reaction of these dienes with diborane. Dialkylboranes (102) exist predominantly as tetraalkyldiboranes (103) at room temperature[2] (Scheme 47).



(102) (103)

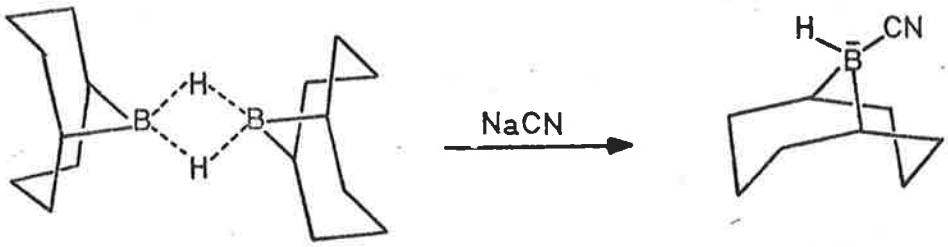
Scheme 47

The formation of the dihydride bridge in (103) involves partial bonding through the vacant orbitals of boron, and this

bridge is stable (heat of dissociation 100-150 kJ/mole[86]) at reaction temperatures used during cyanidation. Thus these orbitals are no longer accessible to the cyanide anion during the cyanidation reaction. Hence the first step of the cyanidation sequence (formation of the cyanoborate) cannot take place and the only products observed are those of oxidation of the tetraalkyldiborane.

Models of the dialkylborane (83), postulated as an intermediate in the hydroboration-cyanidation of linalyl acetate (4), show it to be sterically very hindered, and dimerization to a tetraalkyldiborane may not be favourable. Thus if (83) exists as the monomer, then the vacant orbital of boron will be available for interaction with the cyanide anion, and cyanidation may proceed as described previously (section 1.1).

The carbonylation product formed by cyanidation of 9-borabicyclo-[3,3,1]-nonane is unexpected. The dimeric structure (104), which this compound usually adopts,[87] contains an exceptionally stable dihydride bridge.[88] The compound does, however, adopt the chair-chair conformation of rings as shown, and this allows greater accessibility to the bridge than is normally observed in tetraalkyl-

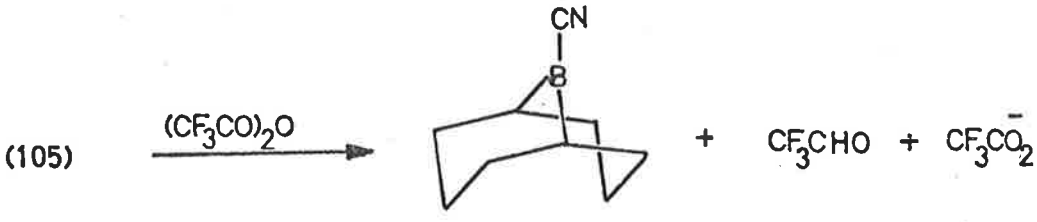


(104) (105)

Scheme 48

diboranes.[87] Thus the cyanide anion may be able to displace one of the hydride ions, and destruction of the dimer may then lead to a cyanoborate such as (105) (Scheme 48).

The high degree of accessibility of the boron atom, and consequently the hydride ion, in (105) may then change the course of the reaction with trifluoroacetic acid anhydride, reduction[89] of the electrophile becoming more favoured than the rearrangement normally observed (Scheme 49).



(106)

Scheme 49

Under the influence of further trifluoroacetic acid anhydride (the cyanidation procedure uses 1.5-3.0 equivalents of the electrophile), (106) may undergo rearrangement to give, after oxidation, the observed carbonylation product. It is to be noted that none of the alcohol corresponding to (101) can be detected, clearly implying that the cyanidated intermediate is not (105).

The inconsistent results of the survey of cyclic boranes prompted a study of the cyanidation of acyclic boranes derived from hydroboration of mono-alkenes with thexylborane or diborane and the results of this study are summarized in Table 2. Both 2-methyl-2-butene (107) and cyclohexene (110) gave ketonic cyanidation products from the thexylborane-derived intermediate boranes, but gave only the oxidation products of the hydroborated alkenes when cyanidation was carried out on the diborane-derived intermediate. These results are in accord with those described for cyclic boranes.† The boranes derived from reaction of (-)-α-pinene (113) with either

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† Product distributions were unaffected by changes in the reaction conditions, such as heating the cyanoborate under reflux in tetrahydrofuran with 3.0 equivalents of trifluoroacetic acid anhydride, or using 10% pyridine in tetrahydrofuran as the reaction solvent.[80]

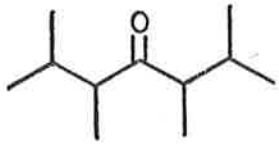
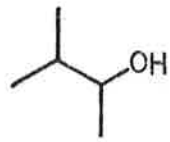
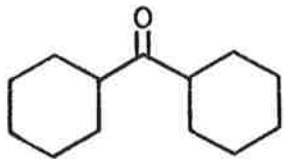
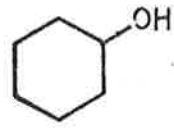
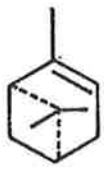
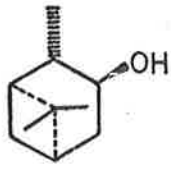
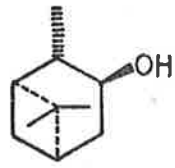
Olefinic Precursor	$ThBH_2$-Cyanidation Product	BH_3-Cyanidation Product
 (107)	 51% (108)	 79% (109)
 (110)	 67% (111)	 82% (112)
 (113)	 83% (114)	 80% (114)

Table 2. Cyanidation of Acyclic Boranes.

thexylborane or diborane showed no tendency to carbonylate under the conditions of the cyanidation procedure, and this may reflect a high degree of steric hindrance to approach of the cyanide anion to the boron atom in these boranes (as was observed with B-thexyl-9-borabicyclo-[3,3,1]-nonane).

Since the stability of the dihydride bridge in compounds such as (103) appeared to be preventing carbonylation of dialkylboranesby the cyanidation method by preventing formation of the cyanoborate salt, or at best allowing only a small concentration of the salt in the equilibrium mixture, insufficient for a practical rate of reaction in the next (bimolecular) step, it was thought that introduction of the hydride at a later stage in the cyanidation of trialkylboranes may overcome this difficulty, but still result in an alcohol as the final product (Scheme 42). In order to investigate this possibility, tri-n-pentyl- and tricyclohexylboranes were subjected to cyanidation, and the products were treated with sodium aluminium bis-(2-methoxyethoxy)hydride for 3 h at 65° prior to oxidation with alkaline hydrogen peroxide. The results of this study are summarized in Table 3.

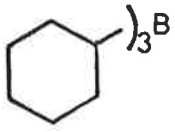
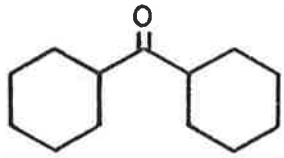
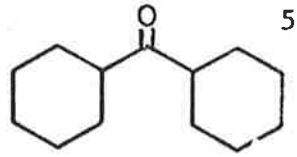
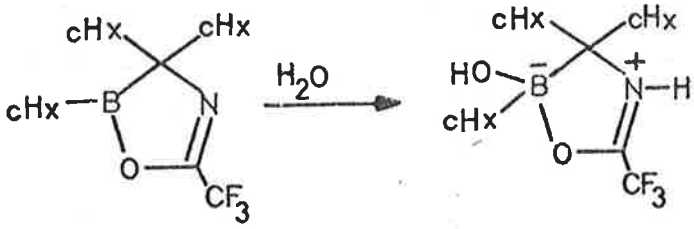
Organoborane Precursor	Normal Cyanidation Product	Cyanidation - MH Product
$(n\text{-}C_5H_{11})_3B$	$(n\text{-}C_5H_{11})_2C{=}O$ 69% (116)	$(n\text{-}C_5H_{11})_2C{=}O$ 58% (116)
	 63% (111)	 59% (111)

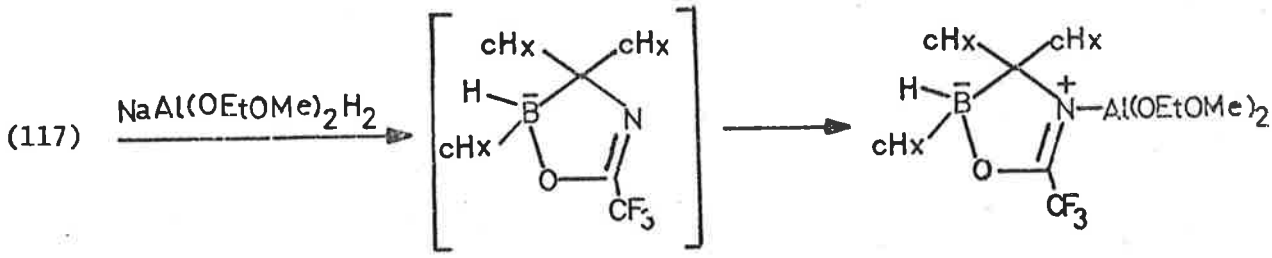
Table 3. Attempted Reduction of Product of Cyanidation of Trialkylboranes with $NaAl(OCH_2CH_2OCH_3)_2H_2$

In the case of tricyclohexylborane, the cyanidation product (117) has been isolated and characterized as its hydrate (118),[83] and so an attempt was made to isolate the presumed reduction product of (117), (120). The mass spectrum of (118) shows a strong molecular ion at m/e 401, corresponding to the hydrate, but the spectrum of the presumably-reduced product shows

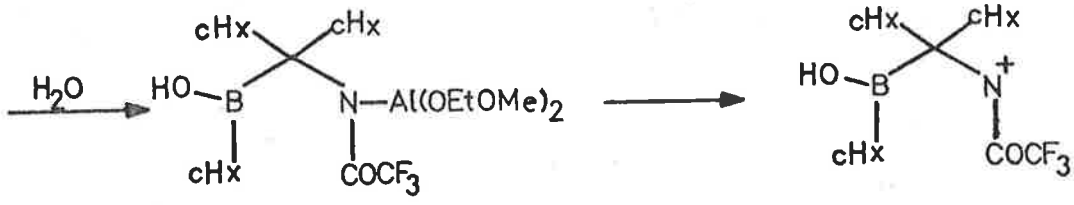
a strong peak at m/e 400. This may correspond to a fragment such as (122), arising from cleavage of the N-Al bond in (121) (Scheme 50).



(117) (118)



(119) (120)



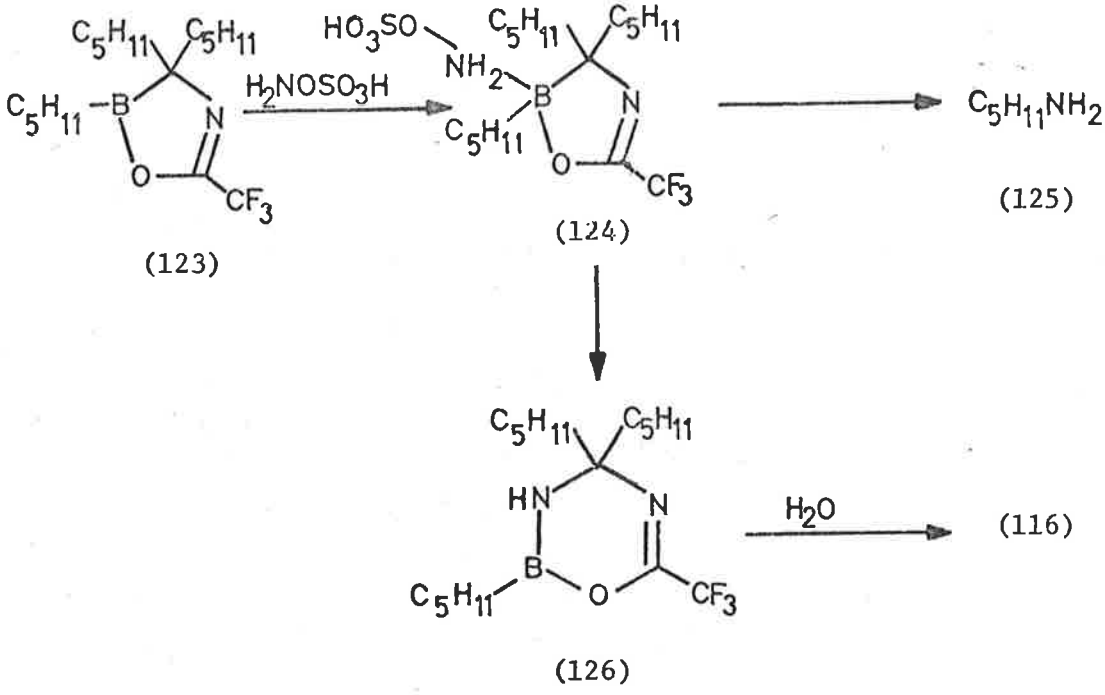
(121) (122)

cHx = 

Scheme 50

It thus appears that the interaction of (117) with the metal hydride results in addition of a hydride ion to boron and binding of the metal to the complex via the nitrogen lone pair electrons to give (120). Subsequent addition of water to the reaction mixture replaces the hydride ion with hydroxide ion, and the product isolated is the ring-opened hydrate (121). Under the conditions of the reaction, the transfer of hydride from boron to carbon and the concomitant rearrangement envisaged in Scheme 42 does not appear to occur, and oxidation of either the normal or reduced cyanidation intermediate gives only carbonylation product.

Since reduced cyanidation intermediates such as (86) were not formed, no attempt could be made to induce aminolysis of such intermediates. Treatment of (123), obtained by cyanidation of tri-n-pentylborane, with hydroxylamine-O-sulphonic acid did, however, give a low yield (35%) of the ketonic product (116) observed after oxidation of the same compound with alkaline hydrogen peroxide (Scheme 51).



Scheme 51

The reaction of (123) with hydroxylamine-O-sulphonic acid is analogous to its reaction with alkaline hydrogen peroxide. The first-formed adduct (124) may undergo rearrangement in either one of two possible ways. The n-pentyl group may migrate from boron to nitrogen to give n-pentylamine (125), but none of this compound was observed. The other possible rearrangement involves migration of the tertiary carbon atom from boron to nitrogen, and since the product observed indicates this to be the reaction that is occurring, it must be assumed that formation of the six-membered cyclic intermediate (126) is the most favourable process for decay of (124).

2.3 CYANIDATION OF BORINIC ACIDS AND ESTERS

It was envisaged that the low migratory aptitude of oxygen substituents on boron would make borinic acids (87a) and esters (87b) suitable substitutes for thexyldialkylboranes in the cyanidation procedure. The two alkyl groups attached to boron in such compounds should migrate to the carbon atom of the cyanide group without migration of the oxygenated substituent. This proposition was investigated by the hydroboration of various dienes† and monoalkenes in the molar ratio sufficient to produce a dialkylborane as an intermediate. This intermediate was then treated with the theoretical amount of water (or methanol) to form the borinic acid (or ester). The results of cyanidation of these compounds are summarized in Scheme 52.

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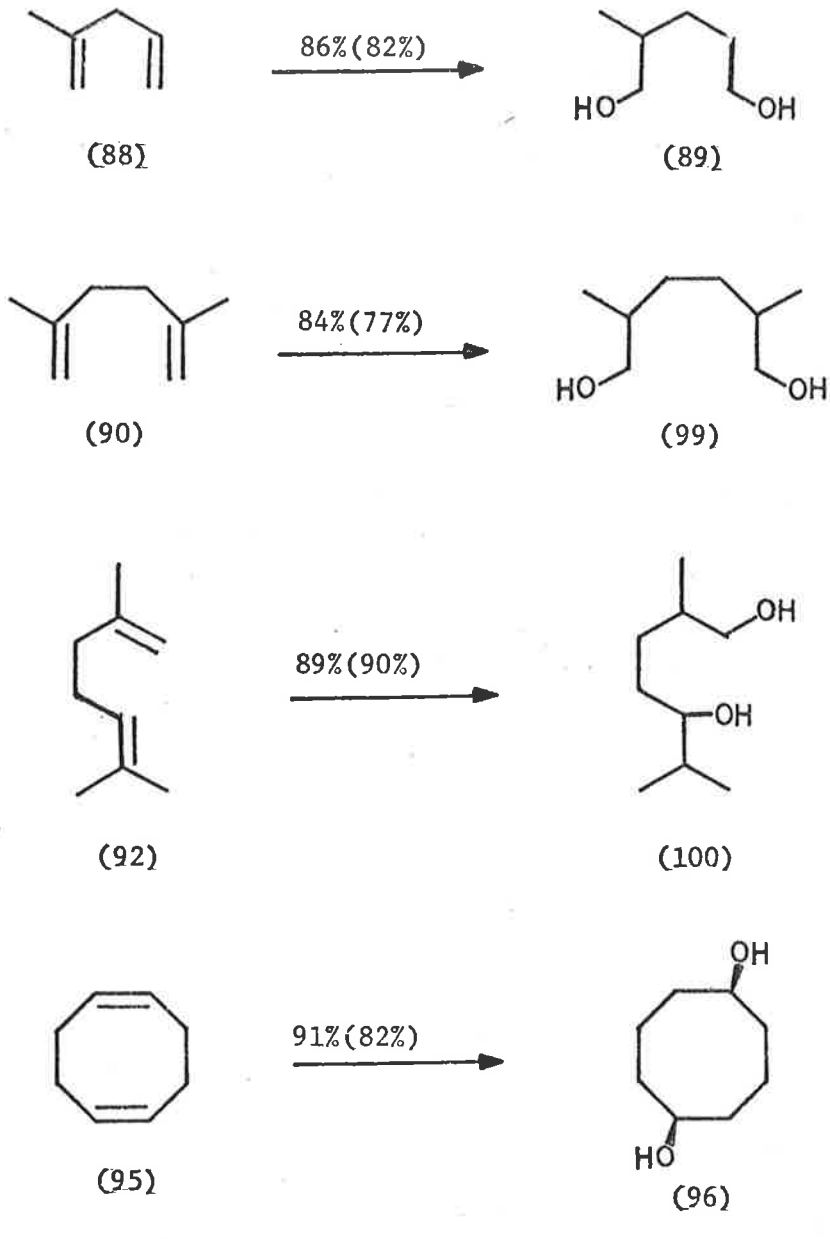
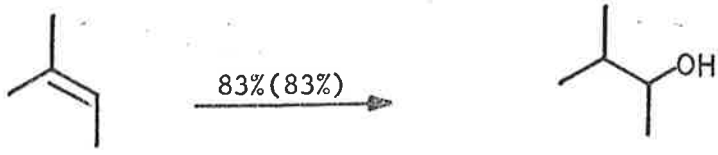
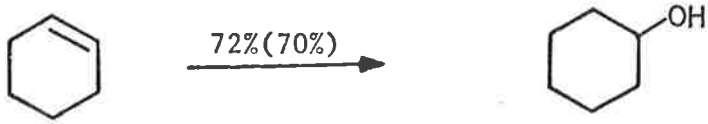
† The products of hydroboration of dienes were heated for 1 h at 65° to ensure that the dialkylboranes obtained were cyclic.



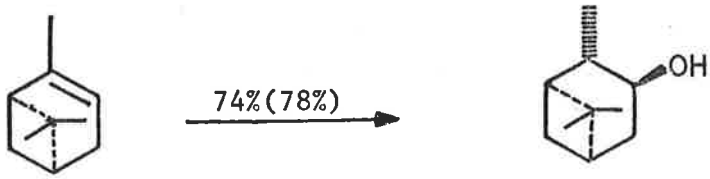
Scheme 52. Cyanidation of some Representative Borinic Acids (and Methyl Esters).



(107) (109)



(110) (112)



(113) (114)

(127a) (127b)

Scheme 52. (cont'd)

None of the substrates investigated showed any carbonylation products after reaction under either the standard cyanidation conditions or forcing conditions (3.0 equivalents of trifluoroacetic acid anhydride at 65°, or 10% pyridine in tetrahydrofuran as the reaction solvent[80]). The only products detected were those from the oxidation of the hydroborated olefins. This may be rationalized in terms of the overlap which may occur in borinic acids and esters between the orbitals on oxygen holding the lone pairs of electrons and the vacant orbital on boron. Such overlap would ensure a significant contribution from (127b) to the real structure of (127), and would thus increase the electron density on boron. This in turn would make formation of the cyanoborate, the first step in the cyanidation procedure, less favourable and cyanidation may not then proceed. Thus the only products observed would be those from the oxidation of the borane intermediates derived from the hydroboration of the olefins. It seems possible that cyanidation of more powerful Lewis acid derivatives would be successful (e.g. $R_2BH + HCl \rightarrow R_2BCl + H_2$; or $R_2BH + CF_3CO_2H \rightarrow R_2BOCOCF_3 + H_2$).

Of these oxidation products, that obtained from 2-methyl-1,4-pentadiene (88) is unusual; only one product, 2-methyl-1,5-

pentanediol (89) was obtained†, and there was no evidence of 1,4-hydroboration. Whilst such specificity may be expected for bulky reagents such as thexylborane, it is not expected when hydroboration is carried out with diborane. Indeed, hydroboration of 1,4-pentadiene with diborane results in predominantly 1,4-attack, with only minor amounts of 1,5-hydroboration occurring.[2] Oxidation of the product of hydroboration of (88) also gave (89) as the only product. This result was consistently repeatable, but remains unexplained.

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† Identified by glc comparison with an authentic sample, and from the compound's ir and nmr spectroscopic data.

CHAPTER 3

Silver (I) Oxidation of Organoboranes

3.1 Introduction

3.2 Cyclization of Dienes via Intramolecular Alkyl Coupling

3.3 Attempted Reduction of Intermediates obtained by Reaction of Organoboranes with Alkaline Silver Nitrate.

3.1 INTRODUCTION

Alkylboronic acids (128), when treated with ammoniacal silver nitrate, give coupled hydrocarbon products,[90,91] and it has been postulated that these arise through the formation and decay of unstable alkylsilver intermediates[92] (Scheme 53). A similar reaction has been observed with trialkylboranes,[93,94]

$$RB(OH)_2 \xrightarrow[NH_3]{AgNO_3} [R\text{-}Ag] \longrightarrow R\text{-}R + Ag$$
(128)

$$R_3B \xrightarrow[NH_3]{AgNO_3} [R\text{-}Ag] \longrightarrow R\text{-}R + Ag$$

Scheme 53

but the experimental conditions required for these reactions suits them more to small scale structural analyses of organoboranes than to hydrocarbon syntheses on a preparative scale.

Silver halides, which are effective coupling agents for Grignard reagents,[95] do not induce coupling of organoboranes.[96] Ammoniacal silver oxide has also failed to produce significant amounts of coupled products from organoboranes.[96] The oxides of silver, gold and platinum, under alkaline conditions, have, however, proved to be very effective coupling agents for

organoboranes,[97-99] and alkaline silver oxide, produced *in situ* from silver nitrate and potassium hydroxide, has proven to be the most promising of the three. The results obtained with this reagent in symmetrical couplings are summarized in Table 4. Coupled products predominate for primary alkylboranes, but as the degree of substitution at the site of attachment of boron increases, then the products tend to be predominantly those of disproportionation.

Mechanistic investigation of the coupling reaction has centred upon what is believed to be the second step in the reaction: the decomposition of an unstable alkylsilver intermediate.

Olefinic Precursor	% Yield of Coupled Products
$R - CH = CH_2$	55 - 70
$R - \underset{\displaystyle R}{\overset{\displaystyle |}{C}} = CH_2$	60 - 80
$R - CH = CH - R$	35 - 40
$R - \underset{\displaystyle R}{\overset{\displaystyle |}{C}} = CH - R$	45
$R - \underset{\displaystyle R}{\overset{\displaystyle |}{C}} = \underset{\displaystyle R}{\overset{\displaystyle |}{C}} - R$	5

TABLE 4. Structural Effects on Symmetrical Coupling with Alkaline Silver Oxide.[96]

Although both radical and non-radical routes[100] have been proposed for the formation of coupled product, the mechanism which has been favoured involves homolytic decomposition of the alkylsilver intermediate to metallic silver and an alkyl radical (Scheme 54).

$$R - Ag \longrightarrow R^{\cdot} + Ag$$

$$2R^{\cdot} \longrightarrow R - R$$

Scheme 54

The radical species thus generated may then undergo the normal reactions, including coupling.

Although there have been extensive studies of the symmetrical coupling of organoboranes,[96] no systematic survey of the reaction of alkaline silver oxide with organoboranes derived from dienes has ever been reported. If the mechanism of coupling discussed above does in fact predominate,† then the proximity of the radical centres generated in this manner from hydroborated dienes should favour intramolecular coupling to give cyclized hydrocarbon products. A preliminary investigation,[13] utilizing

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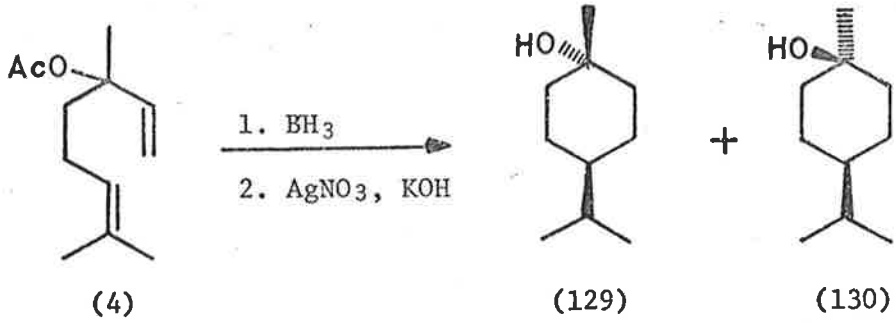
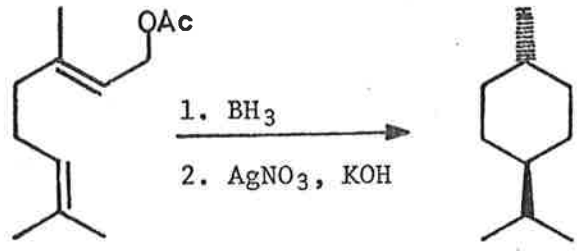
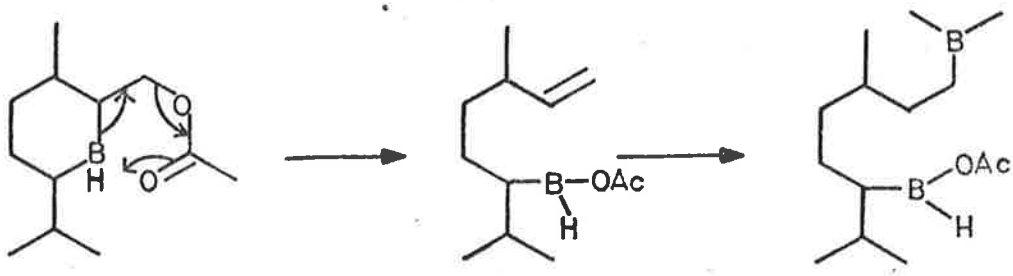
† This mechanism is discussed further in section 3.3.



(4) (129) (130)



(131) (132)



(133) (134) (135)

Scheme 55.

the terpenoid dienes linalyl acetate (4) and geranyl acetate (127), indicated that such cyclizations are favourable (Scheme 55).

Linalyl acetate, after hydroboration and treatment with alkaline silver nitrate, gave a 72% yield of a 1:1 mixture of cis- and trans-1-hydroxy-p-menthane (129 and 130); the acetate presumably is hydrolysed under the basic reaction conditions. Geranyl acetate (131) gave an unexpected product, trans-p-menthane (132), in 83% yield. Formation of this product has been rationalized in terms of a cis elimination[12,101] of boron and acetate in the first formed borane (133) to generate a terminal olefin (134). Further hydroboration of this intermediate would then give a final borane product such as (135). Transalkylation from boron to silver would give a disilver species, which on decomposition may give a coupled (i.e. cyclized) product such as (132).

Consequently, a full investigation of the synthetic utility of such cyclizations has been carried out, and the results of this investigation are discussed herein.

Alkyl radical species are thought to be produced during the autoxidation of organoboranes,[102] and if such autoxidation occurs in the presence of phenyl- or methyldisulphide then the alkyl radical may interact with the disulphide to generate an organic sulphide[103] (Scheme 56).

$$R_3B + O_2 \longrightarrow R_2BO_2^{\bullet} + R^{\bullet}$$

$$R^{\bullet} + CH_3SSCH_3 \longrightarrow RSCH_3 + CH_3S^{\bullet}$$

$$CH_3S^{\bullet} + R_3B \longrightarrow R_2BSCH_3 + R^{\bullet}$$

$$CH_3S^{\bullet} + R_2BSCH_3 \longrightarrow RB(SCH_3)_2 + R^{\bullet}$$

Scheme 56

It was thought that, if organic free radicals were involved in the coupling reaction, then carrying out that reaction in the presence of a radical trap, such as a disulphide or a hydrogen atom donor, should lead to products of reaction with such traps. In particular, interaction with a hydrogen atom donor would presumably give rise to a hydrogenated product. This would provide a very mild method of replacing boron with hydrogen, and such a method would complement the protonolysis method[104,105] of replacing boron with hydrogen.

Consequently, such a study was carried out and the results are discussed in terms of synthetic utility and mechanistic implications.

3.2 CYCLIZATION OF DIENES VIA INTRAMOLECULAR ALKYL COUPLING

Reaction of a diene with diborane in 1:1 molar ratio is capable of giving rise to an organoborane, in which the alkyl group contains two boron substituents at different positions.[106] The dienes chosen for this study of silver (I) induced cyclization were such that the positions of the boron atoms could be varied from 1,2 to 1,8 in the alkyl substituent in order to determine the limits of cyclization. The results of this investigation are summarized in Table 5.

As can be seen from Table 5, the expectation that hydroborated dienes would yield mainly cyclized products on treatment with alkaline silver nitrate has generally been realized. Most of the products observed are those derived from coupling between the two sites of hydroboration within the molecule, and may arise via a radical mechanism.

2-Methyl-2,4-pentadiene (136) failed to undergo the expected cyclization to isopropylcyclopropane (138), but instead gave 2-methyl-2-pentene (142) as the only volatile product (Scheme 57).

This was not consistent with a diradical mechanism; the cyclization of 1,3- diradicals to cyclopropanes has been reported.[107] Oxidation of the product of hydroboration of (136), however, does

Precursor Diene	Product(s)[a]	Yield (%)[b]
2,5-dimethyl-2,4-hexadiene	cis-2,5-dimethyl-3-hexene	89
2-methyl-2,4-pentadiene	2-methyl-2-pentene	63
2,3-dimethyl-1,3-butadiene	trans-1,2-dimethylcyclobutane	79
2-methyl-1,4-pentadiene	methylcyclopentane	85
1,5-hexadiene	cyclohexane	66
	methylcyclopentane	17
2,5-dimethyl-1,5-hexadiene	trans-1,4-dimethylcyclohexane	49
	cis-1,4-dimethylcyclohexane	33
1,6-heptadiene	cycloheptane	67
1,7-octadiene	cyclooctane	42
1,5-cyclooctadiene	cis-bicyclo-[3,3,0]-octane	19
	cis-cyclooctene	19
	cyclooctanone	43
bicyclo-[2,2,1]-heptadiene	polymer[c]	-

TABLE 5. Products of Reaction of Dienes with Diborane Followed by Alkaline Silver Nitrate Oxidation.

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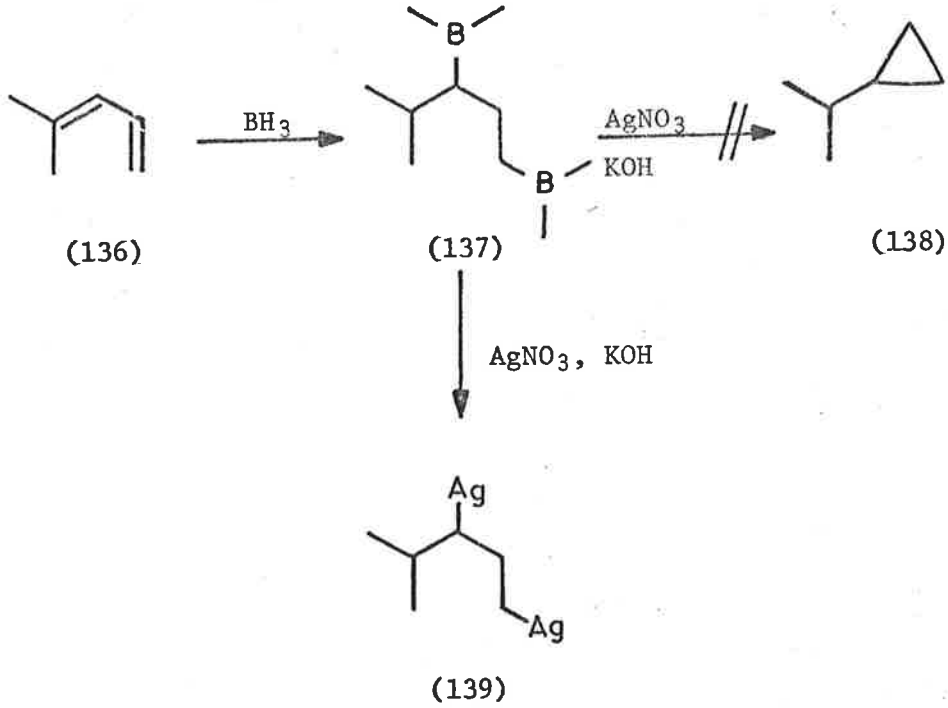
[a] Identified by glc comparison with authentic samples.

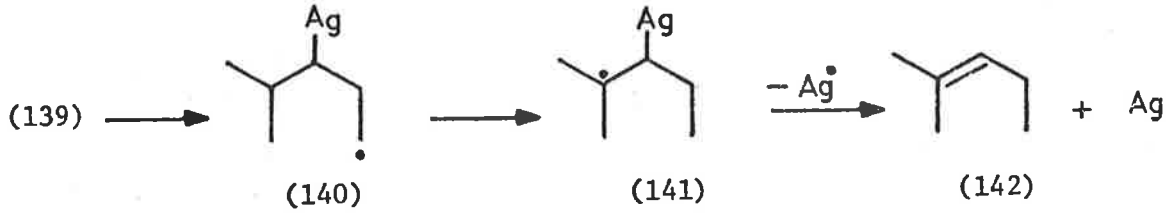
[b] Determined by glc using n-undecane as internal standard.

[c] No volatile hydrocarbons or alcohols.



(136) (137) (138)

(139)

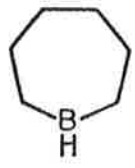


(140) (141) (142)

Scheme 57.

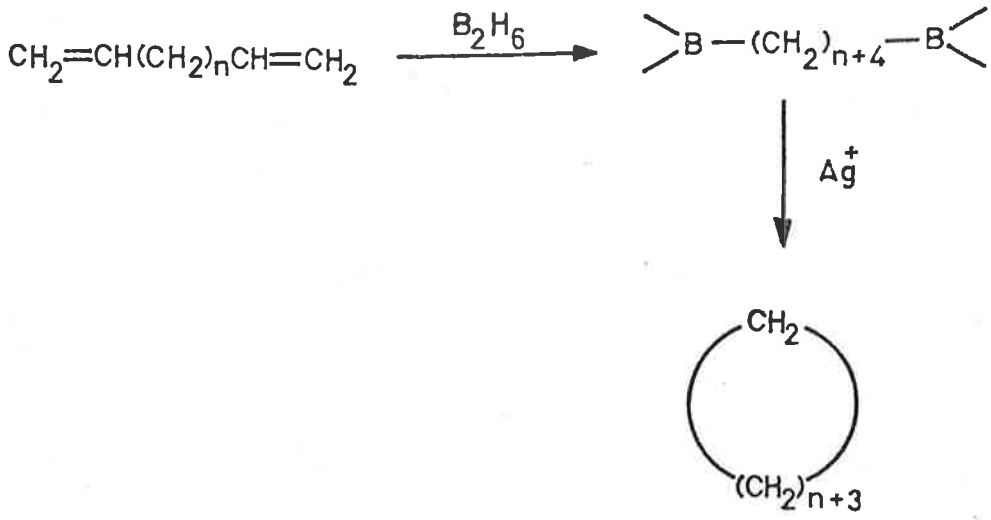
indicate that hydroboration occurs in a 1,3 fashion to give (137). Reaction of (137) with alkaline silver nitrate should then give the disilver species (139). If homolysis of both C-Ag bonds in (139) does not occur simultaneously, then a monosilver radical species such as (140) may arise, and this can undergo a 1,4-hydrogen atom migration[108,109] to give (141). Homolysis of the second C-Ag bond to give a diradical, or homolytic displacement of Ag,[96] will then give (142). All other acyclic dienes used in this study gave the expected cyclized products.

The products obtained from 1,5-hexadiene are of particular interest. Hydroboration of this compound at 0° yields mainly polymeric borane, which slowly rearranges[110] to the seven-membered borepane (143) at 65°. Treatment of the hydroboration product with alkaline silver nitrate either before or after isomerization gives exactly the



(143)

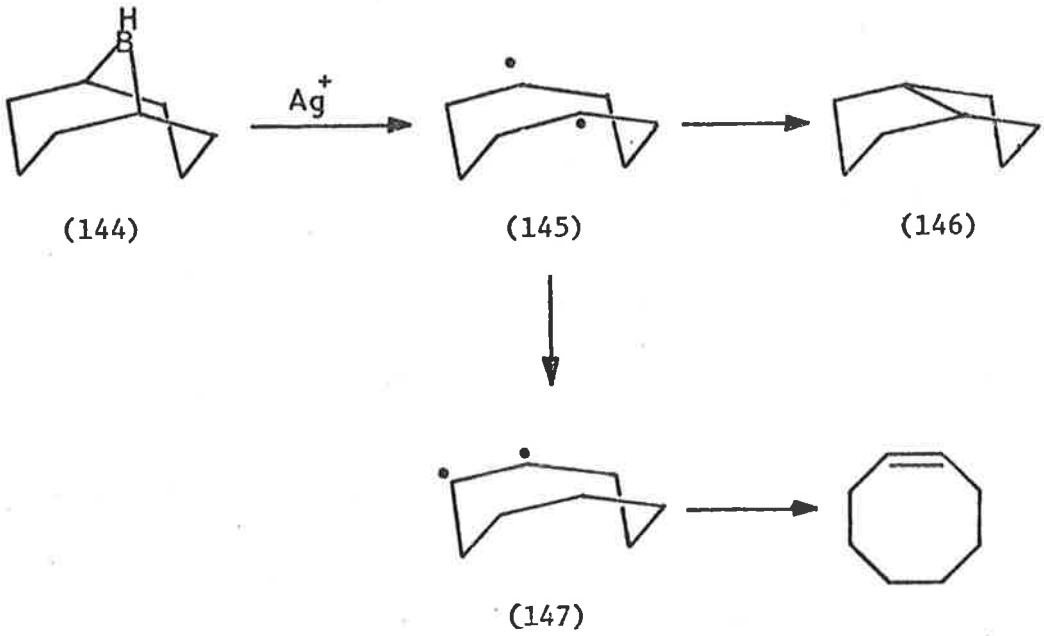
same products, indicating that this reaction has no requirement for the borane to be cyclic. Thus, although boron prefers to form 5,6 and 7-membered rings, this method of cyclization should be capable of extension to larger rings (Scheme 58), and this is illustrated in the products obtained from 1,6-heptadiene and 1,7-octadiene.



Scheme 58

The exclusive terminal cyclization of these two dienes indicates that hydroboration of each double bond occurs essentially independently, and only in cases where cyclic borane formation is thermodynamically favourable will non-terminal cyclization products arise.

The products obtained from hydroboration and silver (I) oxidation of the two cyclic dienes included in the study were not those expected. The hydroboration product of 1,5-cyclooctadiene was heated at 65° for 1 h to ensure complete isomerization to 9-borabicyclo-[3,3,1]-nonane (144)[89] and was then treated with alkaline silver nitrate. The expected product, cis-bicyclo-[3,3,0]-octane (146) was obtained in only 19% yield, the only other volatile products being cis-cyclooctene (19%) and cyclooctanone (43%). The cyclooctene can be envisaged as arising from a trans-annular 1,4-hydrogen atom shift[109,111] in (145) to give (147), which can then give cyclooctene (Scheme 59).

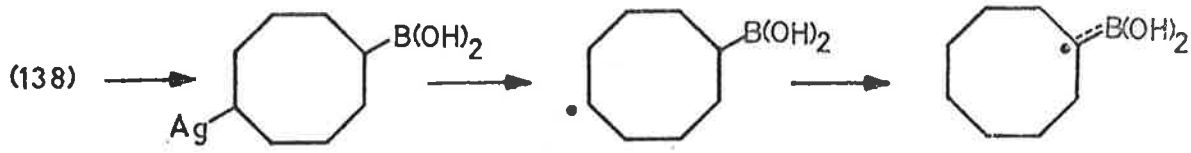


(144) (145) (146)

(147)

Scheme 59

The major product (43%) observed when 9-borabicyclo-[3,3,1]-nonane is treated with alkaline silver nitrate is cyclooctanone, and thic observation has been previously reported by Devaprabhakara.[112] He has explained this behaviour in terms of a sequential oxidation of the two B-C bonds in the molecule (Scheme 60). This requires formation



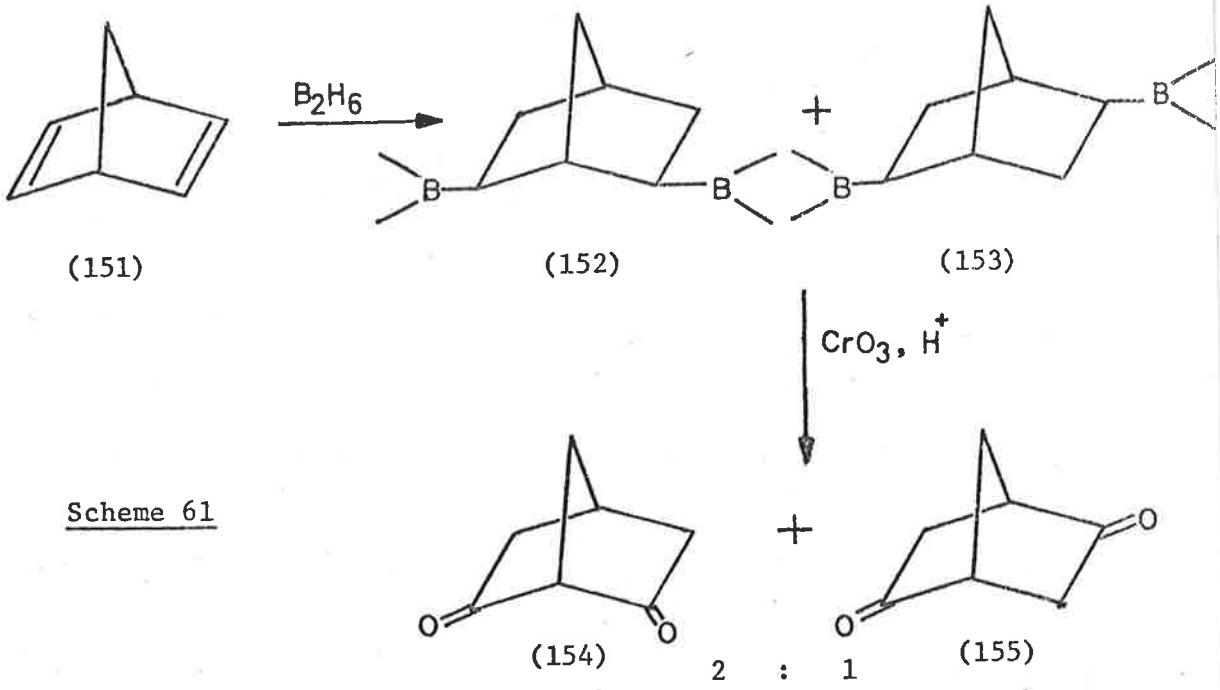
(148) (149) (150)

Scheme 60

of a silver alkyl species such as (148) which may then decompose to give a mono-borono radical (149). Trans-annular 1,5-hydrogen migration would then lead to a radical such as (150), and an intermediate such as this could then proceed by several routes to the observed product, cyclooctanone.

The product of hydroboration of bicyclo-[2,2,1]-heptadiene (151), when treated with alkaline silver nitrate, gave no volatile products. The only product detected was a polymeric material, which was soluble in tetrahydrofuran. Radical species produced from this compound have been shown to be very susceptible to polymerization,[113,114] and thus

it may be assumed that the observed polymeric material arises from the interaction of radical species produced by the oxidation of compounds (152) and (153) with alkaline silver nitrate. The ratio



(151) (152) (153) (154) (155)

Scheme 61

of these two intermediate boranes was determined by oxidation with chromic acid[18] to their respective ketones,[115] (154) and (155) (Scheme 61). The nmr spectra of these two compounds showed distinctive resonances for the bridgehead hydrogen atoms adjacent to the carbonyl groups (δ 4.1 for (154), and δ 3.2 for (155)), and the ratio of peak areas for these resonances indicated that the ratio of (154):(155) was 2:1. This was confirmed by glc analysis.

3.3 ATTEMPTED REDUCTION OF INTERMEDIATES OBTAINED BY REACTION OF ORGANOBORANES WITH ALKALINE SILVER NITRATE.

As mentioned in section 3.1, radicals derived from organoboranes can interact with compounds which act as radical traps, and such interactions can often be synthetically useful reactions.[103,116] Thus an attempt was made to reduce the intermediates produced from the reaction of some representative organoboranes with alkaline silver nitrate by conducting the reaction in the presence of compounds known to be hydrogen atom donors. The results of this investigation are summarized in Table 6.

Olefinic Precursor	Product Yield in absence of H donor[a]	Product Yield in presence of H donor[a]	
	Coupling	Coupling	Reduction
2,5-dimethyl-1,5-hexadiene	73%	65-75%	-
cyclohexene	41%	30-40%	5%[b]
1-hexene	61%	55-65%	5%[b]

TABLE 6. Attempted Hydrogenation of Silver (I) Oxidation Intermediates with Hydrogen Atom Donors.[a]

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[a] Hydrogen atom donors used were: isopropanol, 1-phenylethanol, n-butanethiol, tri-n-butylstannane.

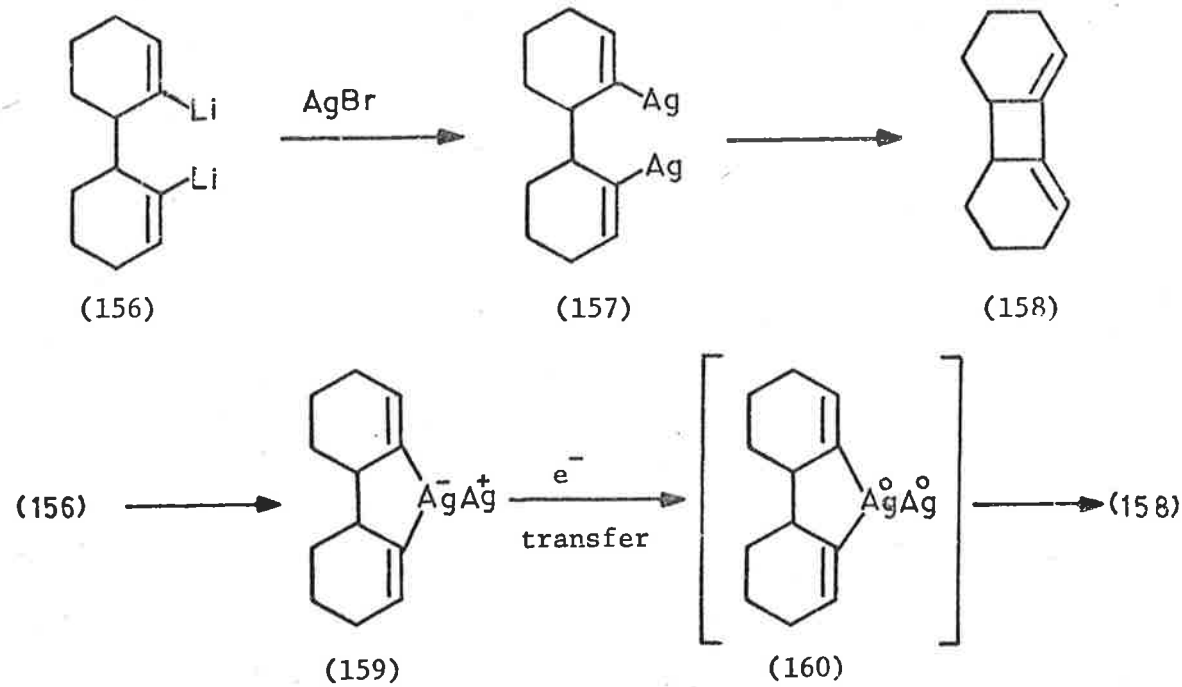
[b] Obtained only in the presence of tri-n-butylstannane.

Only one hydrogen atom donor, tri-n-butylstannane, gave any hydrogenated products at all, and these were obtained in low yields from acyclic organoborane precursors. The lack of any significant interaction between these hydrogen atom donors and the silver (I) oxidation intermediates suggests that these intermediates may not be free radicals and that a reappraisal of the mechanism of this reaction is required.

Since aliphatic free radical couplings proceed in the gas phase with essentially zero free energy of activation,[117] the transition states for these alkyl radical combinations should resemble the reactant radicals. If this is also true of condensed phase reactions, then isomeric product distributions should be essentially unselective for couplings which occur by radical combination. The results reported in section 3.2 do not reflect such randomness. In fact, some olefinic precursors (2,5-dimethyl-2,4-hexadiene, and 2,3-dimethyl-1,3-butadiene) exhibit stereospecificity when the products of hydroboration of these compounds are cyclized by treatment with alkaline silver nitrate. Such total stereospecificity has also been reported for E-1-propenylsilver, which couples to give E,E-3,4-dimethyl-2,4-hexadiene.[118]

Moore[119] has reported a stereospecific cyclization of the disilver compound (157), obtained by transmetallation from 2,2'-dilithio-3,3'-bicyclohexenyl (156), to give tricyclo[6,4,0,$0^{2,7}$]

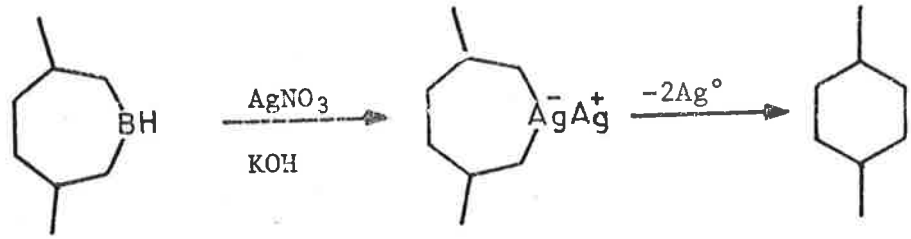
dodeca-2,12-diene (158) (Scheme 62). The stereochemistry of (158)



Scheme 62

is determined by the stereochemistry of (156), meso-(156) giving only cis-(158), and d,l-(156) giving only trans-(158). The stereospecificity of the reaction has been explained in terms of formation of a silver"ate" complex (159), either from (157) or directly from (156). Thus, during cyclization, the new carbon-carbon bond is formed between two ligands attached to a common silver atom, and stretching of the carbon-silver bonds in the sense of a homolytic cleavage would cause an overlap of the carbon orbitals, resulting in bond formation.

Consideration of the cyclization of, for example, 2,5-dimethyl-1,5-hexadiene, in terms of such a silver complex (162) may explain why the cyclization of the silver (I) oxidation intermediate obtained from the hydroborated diene (161) is not affected by radical traps such as hydrogen atom donors (Scheme 63).



(161) (162)

Scheme 63

This mechanism does not, however, appear to be universal for the cyclization reaction as is indicated by some of the examples listed in Table 5 (2-methyl-2,4-pentadiene, bicyclo-[2,2,1]-heptadiene).

Even though the mechanism of the alkaline silver oxide induced coupling is not clear, the specific application of the reaction to the cyclization of dienes offers a convenient and useful synthetic route to alicyclic hydrocarbons.

CHAPTER 4

Asymmetric Induction by Hydroboration with Optically Active Boranes.

4.1 Introduction.

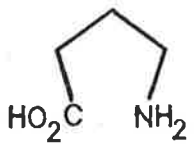
4.2 Attempted Resolution of (±)-4,4,6-Trimethylcaprolactam and (±)-4,6,6-Trimethylcaprolactam.

4.3 Attempted Resolution of (±)-3,5,5-Trimethylcyclohexanone.

4.4 Asymmetric Hydroboration of 6,7-Dihydro-4,6,6-trimethyl-5H-azepinone and 3,5,5-Trimethylcyclohex-2-enone (Isophorone).

4.1 INTRODUCTION

γ-Aminobutyric acid (GABA) (163) is one of a growing number of compounds that have been characterised as neurotransmitter substances in the mammalian central nervous system;[120] in particular it has been shown to have a potent inhibitory action against epileptic seizures.[121] Consequently, a considerable amount of work has been published on the synthesis and activity of GABA analogues.[122-126]



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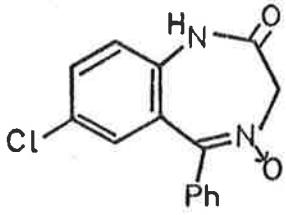

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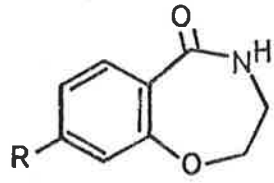

(165)

A number of cyclic amides have been shown to have central nervous system activity, particularly the seven-membered lactams, such as demoxepam (164) and related anticonvulsants and sedatives, and β-adrenergic blocking agents such as (165).[127-130] The widespread industrial usage of caprolactam (166) has led to this compound being subjected to considerable pharmacological scrutiny, and it has been shown that, although the CD_{50}[†] of this compound is relatively high

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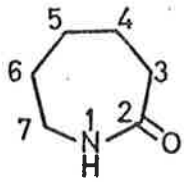
[†] The convulsive dose level (CD_{50}) of a compound is defined as the concentration (in mg of compound per Kg of animal body weight) required to produce convulsions in 50% of the sample animals under standard testing conditions.

(580 mg/Kg of body weight), it does cause epileptic spasms in mice.[131,132]



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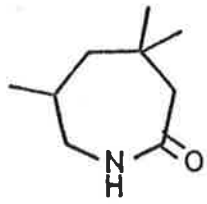

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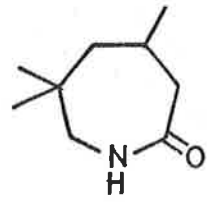


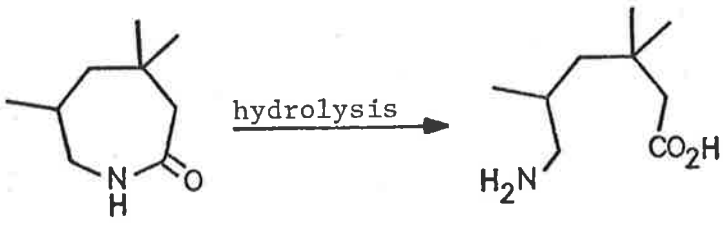
(168)

The lipid solubility of caprolactam is sufficient to allow relatively rapid penetration into the central nervous system, but the lactams of amino acids of longer chain length are more lipid soluble, and are more effective convulsants.[133,134] This has prompted a search for more active derivatives of caprolactam with better lipid solubility; the most active of such derivatives have substituents at the 4 and 6 positions of the ring. Thus 4,4,6-trimethylcaprolactam (167) has a CD_{50} of 9 mg/Kg, and 4,6,6-trimethylcaprolactam (168) has a CD_{50} of 6 mg/Kg.[126]

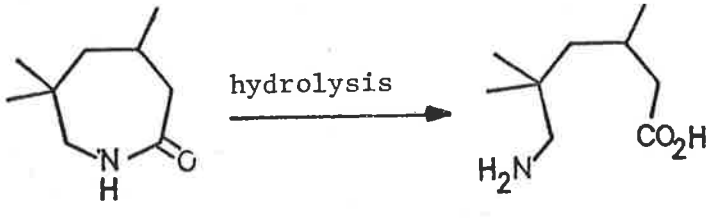
Biologically active chiral molecules generally show enhanced activity of one optical isomer, but the screening of the trimethyl-caprolactams mentioned above has been conducted on racemic mixtures. The aim of the present study was to obtain the pure stereoisomers of (167) and (168), and to examine the effect on the mammalian central nervous system of each of these isomers.

Three approaches were to be adopted in attempting to obtain the pure stereo isomers: (i) resolution of the lactams; (ii) resolution of a chiral, synthetic precursor to the lactams; (iii) induction of an asymmetric centre in either the lactams themselves or a synthetic precursor by means of hydroboration with an optically active borane.

(i) Although (167) and (168) do not contain a "handle" by which resolution of their optical isomers may be readily achieved, it was envisaged that hydrolysis of the amide linkage would give the amino acids (169) and (170) (Scheme 64). These amino acids now each contain two such "handles" by which the isomers may be resolved. It was expected that the diastereomeric salts formed



(167) (169)

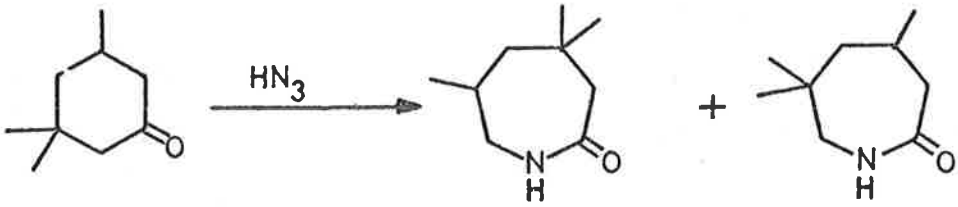


(168) (170)

Scheme 64

by reaction of either the amino or the acid group with an optically active acid or base, respectively, would be separable by classical techniques such as fractional crystallization. Subsequent recyclization of the isomerically pure amino acids would then give optically active lactams.

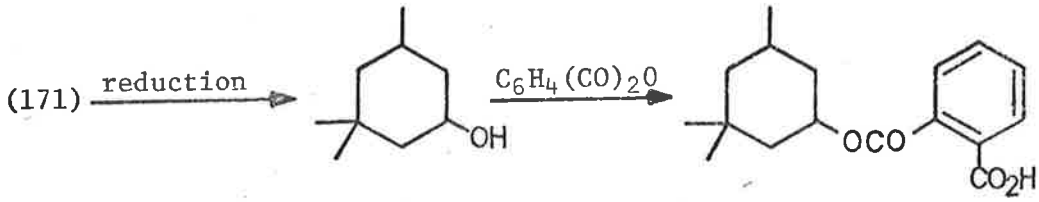
(ii) Both (167) and (168) are obtained by the action of sodium azide on 3,5,5-trimethylcyclohexanone (171) in strongly acidic medium (Schmidt reaction) (Scheme 65).[126,135] The lactams may



(171) (167) (168)

Scheme 65

be separated by fractional crystallization from petroleum, and thus if optically active precursor ketone was employed the products of the reaction will retain this optical activity. It was hoped that resolution of (171) would be achieved via its reduction product, 3,5,5-trimethylcyclohexanol (172). Reaction of (172) with phthalic anhydride was expected to give the hydrogen phthalate ester (173), and this again contains an acid group (Scheme 66). Such a compound will form a mixture of diastereomeric salts upon reaction with an



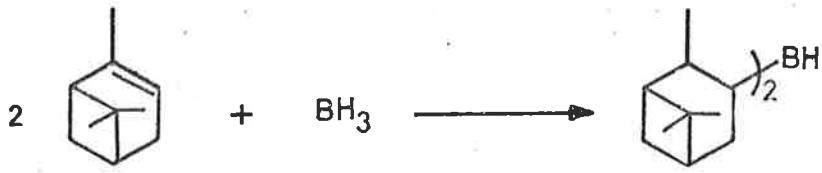
(172) (173)

Scheme 66

optically active base, and these should then be separable by classical techniques. Oxidation of resolved (172) would then give optically active (171), and thus provide a source of the optically active forms of lactams (167) and (168).

(iii) The third approach to be considered was that of inducing asymmetry in (167) and (168) by reduction of a suitable precursor with an optically active organoborane.

The hydroboration of α-pinene (174) with diborane in 2:1 molar ratio proceeds rapidly to give a dialkylborane, diisopinocampheylborane (175), and this reaction is regio and stereospecific; (-)α-pinene gives (+)-diisopinocampheylborane, and (+)α-pinene gives (-)-diisopinocampheylborane[136] (Scheme 67).



(174) (175)

Scheme 67

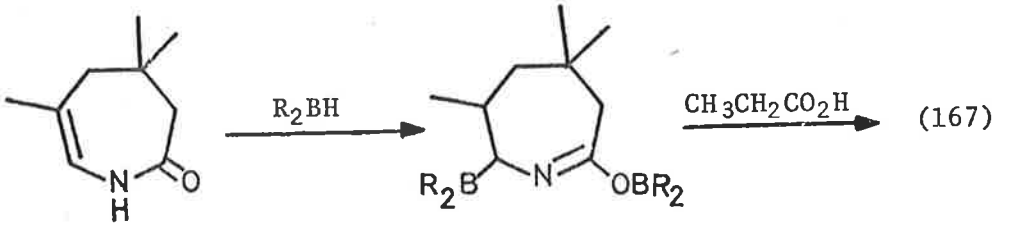
Hydroboration of a racemic olefin with such an optically active dialkylborane gives, after oxidation of the trialkylborane intermediate, an optically active alcohol[137] (Table 7).

Olefin	Alcohol (% yield)	$[\alpha]_D^{20}$	Optical purity (%)
cis-2-Butene	2-Butanol (83)	+11.7°	86
cis-2-Pentene	2-Pentanol (76)	+ 8.6°	82
cis-4-Methyl-2-pentene	4-Methyl-2-pentanol (96)	+16.0°	76
Norbornene	exo-Norborneol (62)	+ 1.95°	68

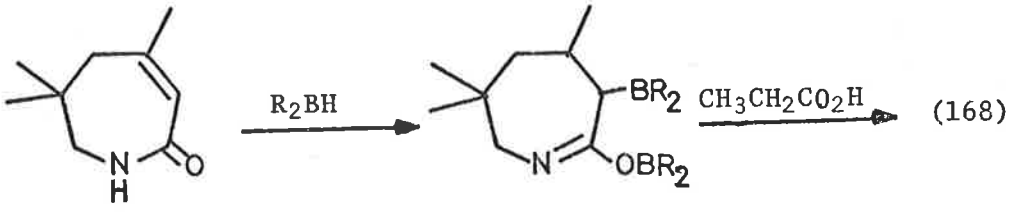
TABLE 7. Preparation of optically active alcohols via hydroboration of racemic olefins with (+)-diisopinocampheylborane.[137]

It was envisaged that hydroboration of the unsaturated lactams (176) and (178), readily available from the Beckmann rearrangement of the syn- and anti-oximes of isophorone (180),[138,139] with optically active diisopinocampheylborane would give, after

protonolysis of the intermediate boranes (177) and (179) with propionic acid,[136] optically active lactams (167) and (168) (Scheme 68).



(176) (177)

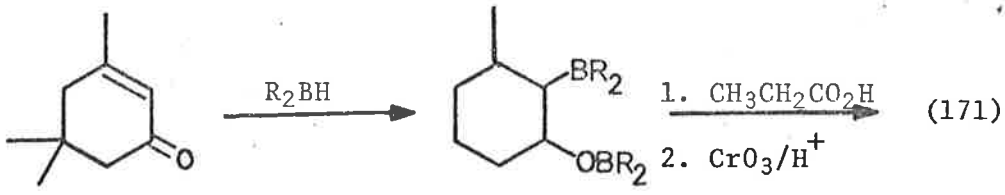


(178) (179)

R = isopinocampheyl

Scheme 68

It was also envisaged that hydroboration of isophorone (180) with this reagent would give, after protonolysis of the intermediate borane (181), and oxidation of the alcohol (172) thus obtained, optically active ketone (171) (Scheme 69). This may then be subjected to the Schmidt reaction as previously described (Scheme 65) to give (167) and (168) in optically active forms.



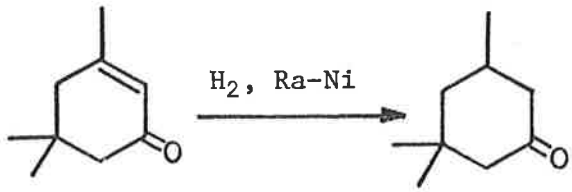
(180) (181)

R = isopinocampheyl

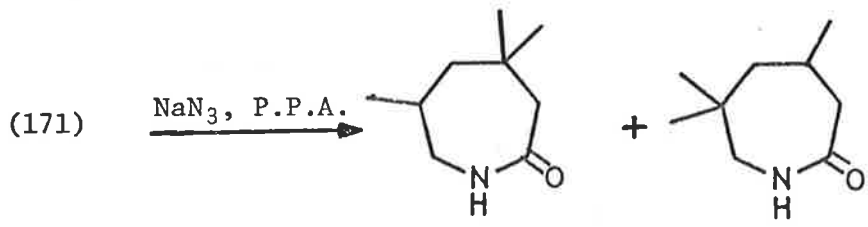
Scheme 69

4.2 ATTEMPTED RESOLUTION OF (±)-4,4,6-TRIMETHYLCAPROLACTAM AND (±)-4,6,6-TRIMETHYLCAPROLACTAM.

Hydrogenation of isophorone (180) over Raney nickel catalyst at 50 psi proceeded smoothly to give 3,5,5-trimethylcyclohexanone (171) (99%). Treatment of (171) with sodium azide in polyphosphoric acid (Schmidt reaction)[126,135] gave 92% of a 1:1 mixture of 4,4,6-trimethylcaprolactam (167) and 4,6,6-trimethylcaprolactam (168) (Scheme 70).



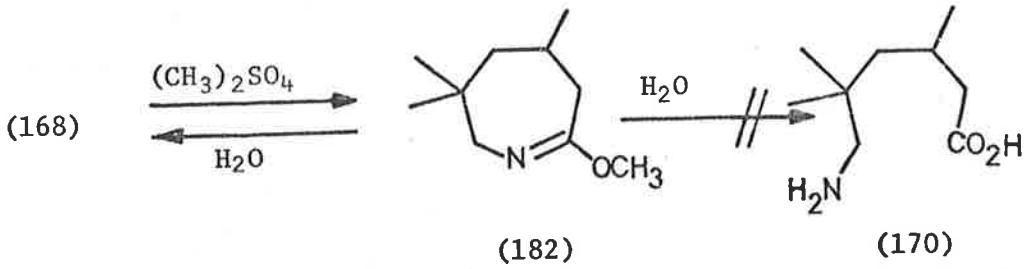
(180) (171)



(167) (168)

Scheme 70

As mentioned previously (section 4.1), the approach to the resolution of the isomers of lactams (167) and (168) involved hydrolysis of the lactams to give their respective amino acids (169) and (170). The hydrolysis was attempted by the method of Benson and Cairns[140] (Scheme 71).

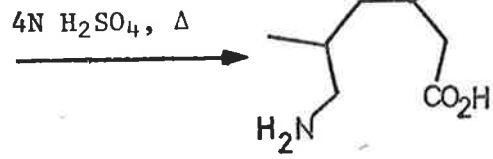


(182) (170)

Scheme 71

Treatment of (168) with dimethylsulphate in anhydrous benzene at 78° for 16 h gave 96% of the lactim (182). Hydrolysis of (182) with water at 100° did not give the expected amino acid (170), but instead gave only the precursor lactam (168).

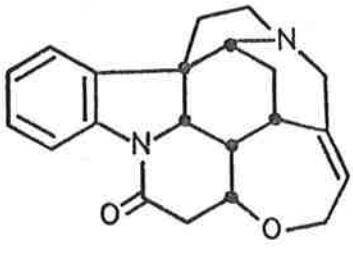
Hydrolysis was accomplished, however, by heating (168) in 4N sulphuric acid for 7 h,[141] and this gave (170) in 67% yield. Similarly, hydrolysis of (167) with 4N sulphuric acid gave 60% of amino acid (169) (Scheme 72).

(167) 

(169)

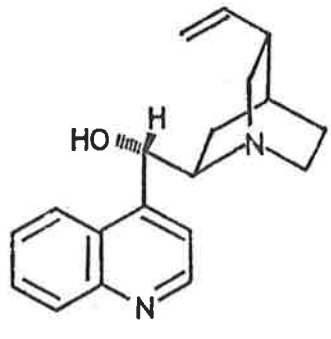
Scheme 72

The strychnine salts of (169) and (170) were prepared by addition of one equivalent of the amino acid to a hot acetone solution of strychnine (183) and allowing the solutions to cool. A small amount of crystalline material was obtained; these salts were decomposed with aqueous ammonium hydroxide and the free amino acids were isolated. These were found to be optically inactive.



(183)

$[\alpha]_D^{20}$ -139.3°



(184)

$[\alpha]_D^{20}$ +229.0°

The above procedure was repeated using various solvents and mixtures of solvents,† but in no case did the free amino acids isolated exhibit any optical activity.

The procedures were repeated using cinchonine (184) as the resolving agent, but again the isolated amino acids proved to be racemic.

Thus resolution of the amino acids, as a method of obtaining optically pure lactams, was abandoned.

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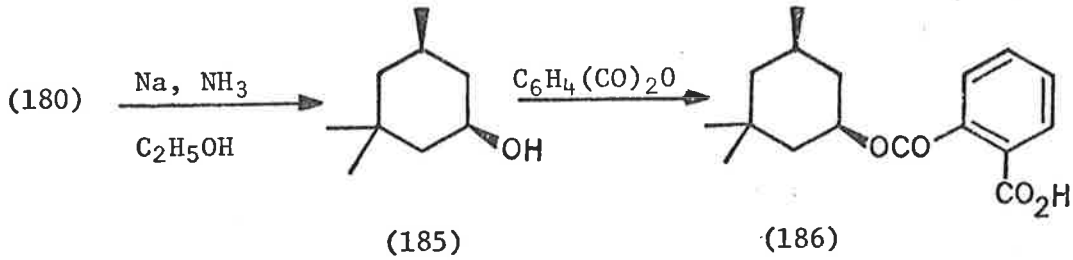
† Solvents used were: ethanol, isopropanol, ether, acetone, ethyl acetate and chloroform.

4.3 ATTEMPTED RESOLUTION OF (±)-3,5,5-TRIMETHYLCYCLOHEXANONE

Reduction of isophorone (180) with sodium in liquid ammonia, in the presence of ethanol, gave exclusively cis-d,l-3,5,5-trimethylcyclohexanol (185)[142] (98%), which when treated with one equivalent of phthalic anhydride in pyridine gave a quantitative yield of the hydrogen phthalate ester (186) (Scheme 73).



(185) (186)

Scheme 73

The strychnine salt of (186) was prepared as described previously (section 4.2) by the addition of one equivalent of the acid to a hot acetone solution of strychnine (183). Upon cooling of the solution, partial crystallization of the salt was observed, but decomposition of this salt showed the free acid thus isolated to be racemic. Fractional crystallization of the salt from various solvents† unfortunately gave no resolution of the optical isomers of (186).

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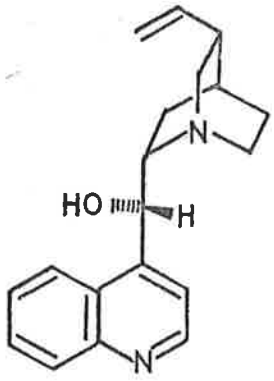
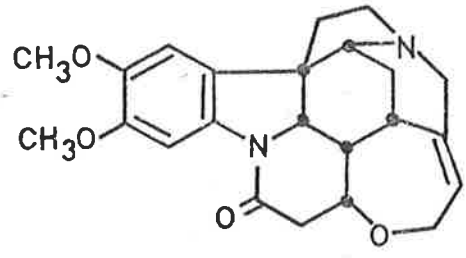
† Solvents used were: ethanol, isopropanol, acetone, ethyl acetate and chloroform, and various mixtures of these solvents.

The salts of other optically active bases (cinchonine (184), quinine (187), brucine (188)) were prepared in a similar manner,



(187)

$[\alpha]_D^{20}$ -145.2°

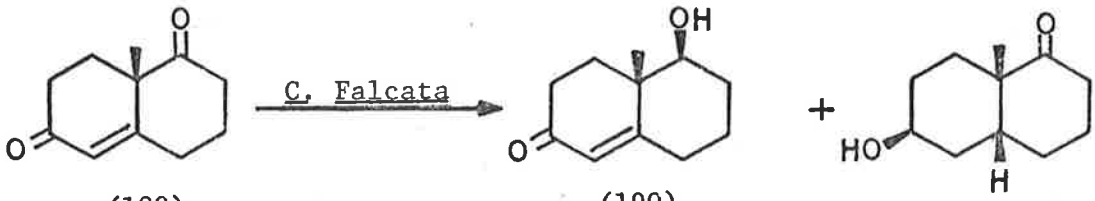


(188)

$[\alpha]_D^{20}$ -120.5°

and attempts were made to separate the diastereomeric salts by fractional crystallization; in no case, however, was resolution of (186) achieved.

The mould Curvularia Falcata has been shown by Prelog[143] to reduce (+)-Δ^4-9(S)-methyloctalin-3,8-dione (189) stereospecifically to a mixture (+)-Δ^4-8(S)-hydroxy-9(S)-methyl-3-octalone (190) and (-)-6(S)-hydroxy-9(S)-methyl-cis-1-decalone (191) (Scheme 74).



(189) (190) (191)

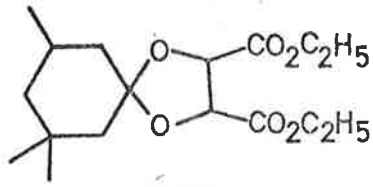
Scheme 74

C.Fulcata exhibits a high degree of product stereospecificity, but only a low degree of substrate stereospecificity, and may thus be capable of reducing isophorone (180), which bears a superficial structural resemblance to (189), stereospecifically to either (+)- or (-)-dihydroisophorol (185). Unfortunately C.Fulcata could not be obtained, but actively fermenting yeast, which was readily available, has been shown to exhibit similar stereospecificity in such reductions.[144,145]

Attempted reduction of isophorone (180) with fermenting yeast, using D(+)-glucose as the fermentation agent, proved unsuccessful; the starting ketone was recovered unchanged.

The resolution of the optical isomers of 3,5,5-trimethyl-cyclohexanone (171) has reportedly been accomplished by preparative glc of the diethyltartrate acetal (192) of the ketone.[146] Thus, this acetal was prepared, in 90% yield, by heating under reflux a mixture of (171) and (+)-diethyltartrate in solution in benzene (containing 10% of N,N-dimethylformamide in the presence of a trace of p-toluenesulphonic acid (Scheme 75).

The separation of the diastereomers of (192) has reportedly been achieved by preparative glc on a 2m column of 15% butanediol succinate on chromosorb W at 200° and with a flow rate of 80 ml/min.[146]

(171) —(+)-diethyltartrate, pTsOH, Δ→ 

(192)

Scheme 75

It was found, however, that these conditions afforded no resolution of (192) and, indeed, no conditions could be found which did afford such resolution using this column. Separation of the diastereomers has also reportedly been accomplished on a column of 30% diethyleneglycol succinate on chromosorb W at 215°, and with a flow rate of 240 ml/min.[146] No attempt was made, however, to repeat this work as the conditions described exceeded those recommended for this particular substrate.†

Various alternative preparative glc columns were tried (columns I, V, IX, X; see section 5.1) and, eventually, partial resolution of the diastereomers was attained on a 6 m column of 20% silicone OV-17 on chromosorb A at 250° with a flow rate of 120 ml/min. Collection of the purest fractions of each diastereomer gave small amounts of compound (192a), having a retention time of

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† The recommended maximum temperature for diethyleneglycol succinate is 150°.[147]

50 min, and compound (192b), having a retention time of 53 mins. Measurement of the optical rotation of each of these compounds showed (192a) to have $[\alpha]_D^{20} = -22.14°$ and (192b) to have $[\alpha]_D^{20} = -9.36°$ (representing 92% and 72%, respectively, of the reported optical rotations[146]).

The free ketones (171a and 171b) were obtained by acid hydrolysis of the acetals with ethanolic hydrochloric acid at room temperature for 48 h; this gave (171a), having $[\alpha]_D^{20} = -8.89°$, and (171b), having $[\alpha]_D^{20} = +7.21°$ (representing 94% and 70% optical purity, respectively), the identity of the ketones being confirmed by glc comparison with racemic (171).

Since it was the purer fraction, (171a) was subjected to analysis by optical rotatory dispersion (ORD), and the results of this study are recorded in Table 7 and Fig. 1.

Application of the octant rule,[148] which relates the sign and amplitude of the Cotton effect[149-152] exhibited by saturated ketones to the disposition of atoms in space about the carbonyl group, to the most probable conformers of the enantiomers of 3,5,5-trimethylcyclohexanone (viz. with the 3-methyl substituent in an equatorial position) suggests that (171a) should exhibit a negative Cotton effect and (171b) a positive Cotton effect (Fig. 2).

Wavelength[a] λ(nm)	Observed Rotation $\alpha°$	Specific Rotation[b] $[\alpha] = \frac{\alpha}{c} \cdot \frac{1800}{\pi}$	Molecular Rotation $[\phi] = \frac{[\alpha].M}{100}$
576.9	-0.34	-111	-156
546.1	-0.38	-124	-174
435.5	-0.66	-216	-302
407.8	-0.81	-265	-371
404.5	-0.81	-265	-371
365.0	-1.03	-337	-472
334.1	-1.36	-445	-623
313.2	-1.32	-432	-604
302.2	-0.68	-222	-311
296.8	-0.48	-157	-220
289.4	-0.44	-144	-202
280.4	-0.42	-137	-192
265.3	-0.41	-134	-188
253.7	-0.39	-128	-179

TABLE 7. Optical Rotatory Dispersion of (-)-3,5,5-Trimethylcyclohexanone.

[a] The wavelengths at which measurements were taken were those of the emission lines of a mercury vapour lamp.

[b] Concentration (c) is expressed in g/100 ml of solution.

[c] M is the molecular weight of the compound under study.

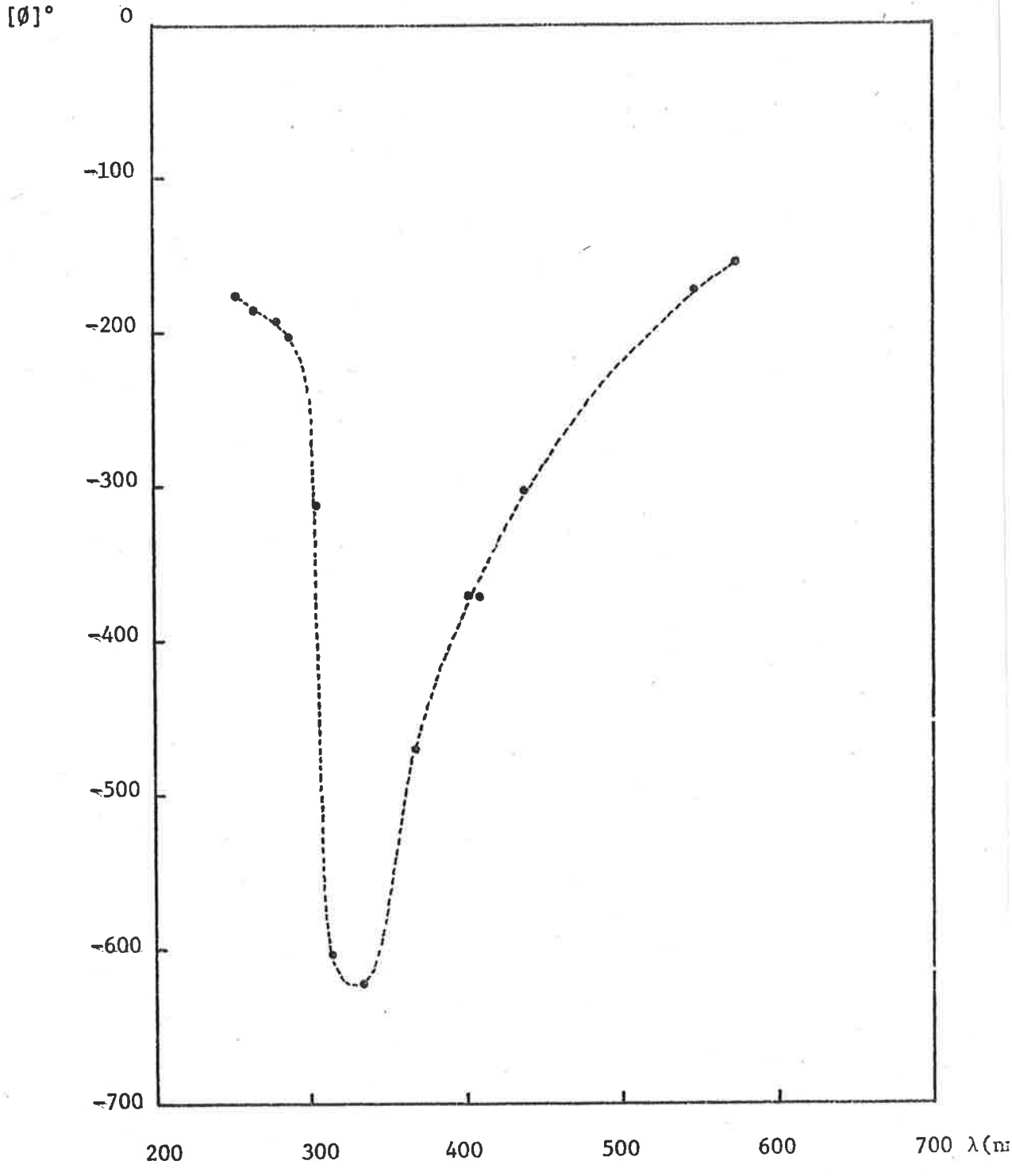
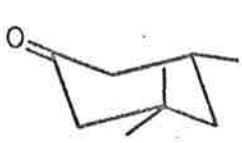
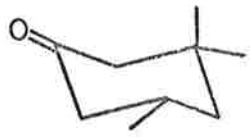


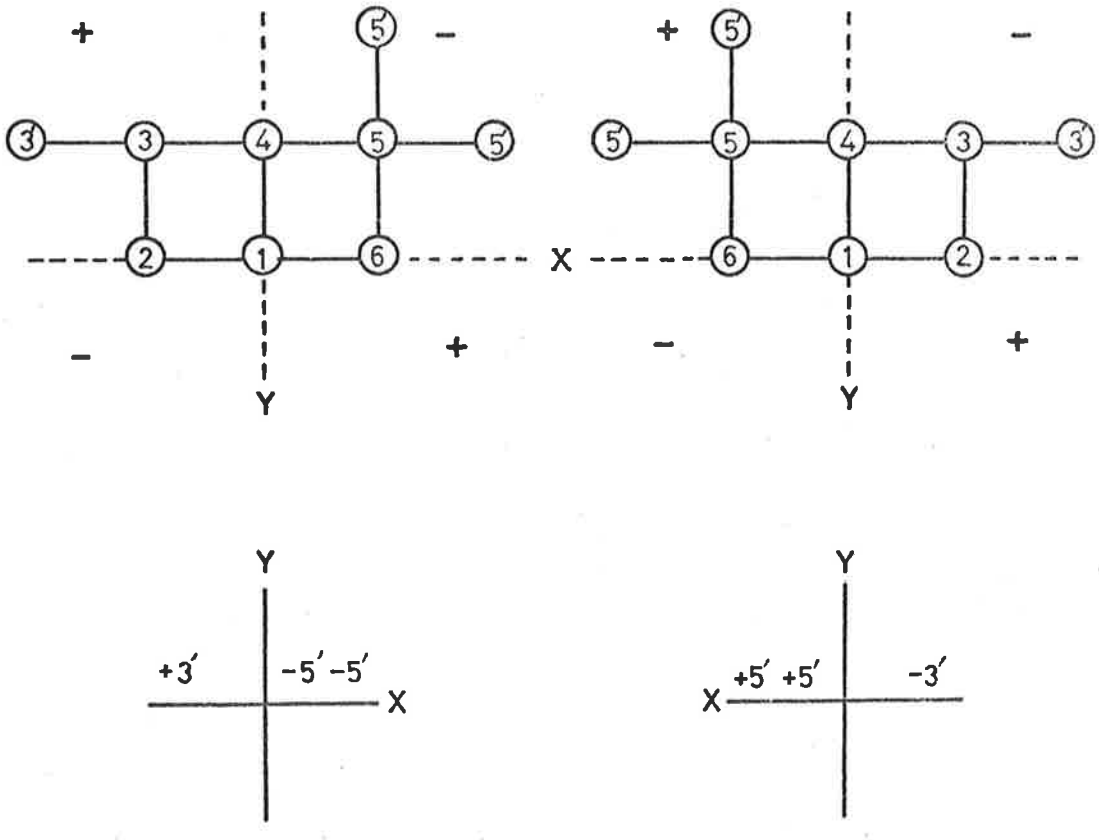
Figure 1. Optical Rotatory Dispersion Curve of (-)-3,5,5-Trimethylcyclohexanone.



(171a)



(171b)



net negative contribution

net positive contribution

Figure 2. Application of the Octant Rule to 3,5,5-Trimethylcyclohexanone.

These Cotton effects are actually associated with the axial 5-methyl group in each of these isomers. The contributions to the anomalous dispersions from the equatorial 3- and 5-methyl substituents are equal and opposite; the entire negative Cotton effect in (171a) is associated with the axial 5-methyl group alone, and similarly the positive Cotton effect in (171b) is associated with this same group.

The Cotton effect observed for (-)-3,5,5-trimethylcyclohexanone is negative (see Fig.1), and this suggests that the structure of this isomer corresponds to (171a); this defines the configuration at C-3 as being R.

The reported[146] configuration at the C-3 position of (-)-3,5,5-trimethylcyclohexanone is S. Although no data are given to substantiate this assignment of configuration, a comparison of this compound with various terpenes is alluded to. The absolute configuration of many terpenes has been assigned on the basis of degradative studies of these compounds, in which they were transformed into compounds of known configuration.[153,154] It appears that the configuration assigned to (-)-3,5,5-trimethylcyclohexanone was chosen by analogy with the configurations assigned to terpenes of similar structure, and it seems from the ORD data collected for this compound that this assignment is incorrect; the correct configurational

assignment should be (-)-3(R),5,5-trimethylcyclohexanone.†

Thus although this method achieved resolution of the enantiomers of the ketone, the small scale which it is limited to makes the method logistically unacceptable as a step in the synthesis of isomerically pure lactams (167) and (168).

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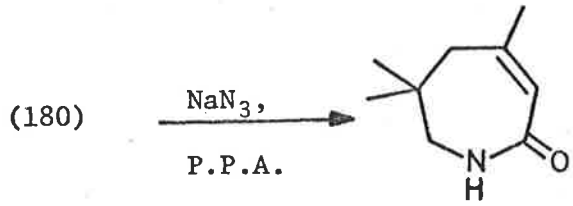
† It was assumed that the (+)-enantiomer of 3,5,5-trimethylcyclohexanone would have the S-configuration at the 3-position.

4.4 ASYMMETRIC HYDROBORATION OF 6,7-DIHYDRO-4,6,6-TRIMETHYL-5H-AZEPINONE AND 3,5,5-TRIMETHYLCYCLOHEX-2-ENONE (ISOPHORONE)

As mentioned in section 4.1, the hydroboration of α-pinene (174) with diborane proceeds stereospecifically to give optically active diisopinocampheylborane (175),[136] and this dialkylborane itself hydroborates other olefins stereospecifically to give optically active products.[137]

Thus an attempt was made to hydroborate 6,7-dihydro-4,6,6-trimethyl-5H-azepinone (178) (prepared in 88% yield by treatment of isophorone (180) with sodium azide in polyphosphoric acid[135] (Scheme 76)) with (+)-diisopinocampheylborane, prepared from (-)α-pinene and diborane.

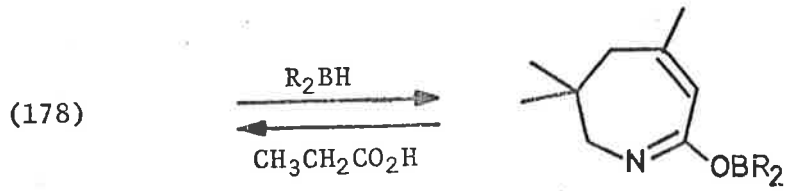


(178)

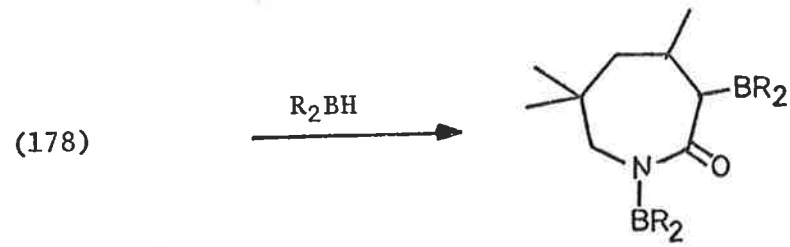
Scheme 76

Treatment of this hydroboration product with propionic acid at 140° for 3 h[136] did not give the desired product (Scheme 68), but instead gave unchanged (178) and an unidentified product, which

appeared to contain boron.†



(193)



(194)

R = isopinocampheyl

Scheme 77

The recovery of unchanged (178) may be due to formation of an intermediate such as (193), and protonolysis of this intermediate with propionic acid can be envisaged as giving the lactam (Scheme 77). The lack of further reaction of (193) with diisopinocampheylborane may be due to two factors: (i) conjugated dienes are known to react with boranes much more slowly than isolated double bonds,[155] and this may

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† This product burnt with the characteristic green flame of boron-containing compounds.

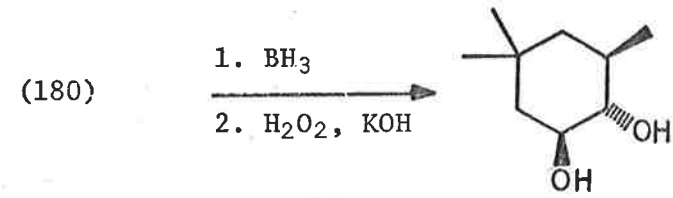
also be true of conjugated imines such as (193); (ii) the steric bulk of the diisopinocampheylborono group attached to the lactam oxygen may prevent approach of another molecule of the borane to the double bond.

The unidentified product from this attempted reduction may have a structure similar to that of (194). The nmr spectrum of this product no longer shows the olefinic resonance (δ 5.8) or the amide proton resonance (δ 7.3) of the starting material, but it does show that the compound contains isopinocampheyl moieties. The approach to the C-B bonds in a compound such as (194) may be sufficiently hindered so as to prevent protonolysis of such an intermediate with propionic acid.

No products were obtained which corresponded to the required lactam (168).

The hydroboration of isophorone (180) is reported[156] to proceed stereospecifically, and oxidation of the borane thus obtained with alkaline hydrogen peroxide gives only one major product, the diol (195) (Scheme 78).

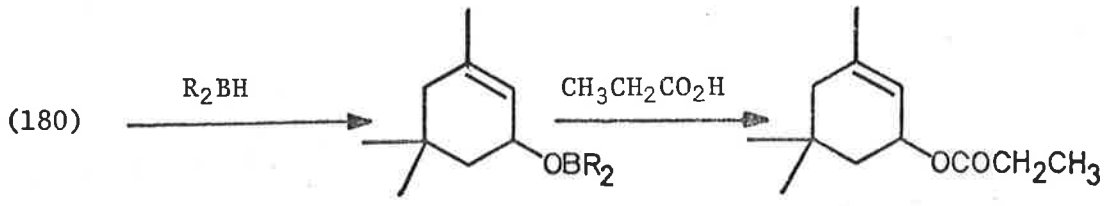
Hydroboration occurs initially at the carbonyl group, and hydroboration of the double bond then appears to proceed preferentially in a trans manner. Thus it was expected that hydroboration of



Scheme 78 (195)

isophorone (180) with an optically active dialkylborane, as envisaged in Scheme 69, would proceed along similar lines to give an optically active borane intermediate (181); protonolysis and oxidation of such an intermediate would then give the ketone (171) in optically active form.

Hydroboration of isophorone (180) with (+)-diisopinocampheylborane (175), followed by protonolysis of the intermediate borane thus obtained with propionic acid at 140° for 3 h, gave isophorylpropionate (197) (83%) as the only product (Scheme 79).



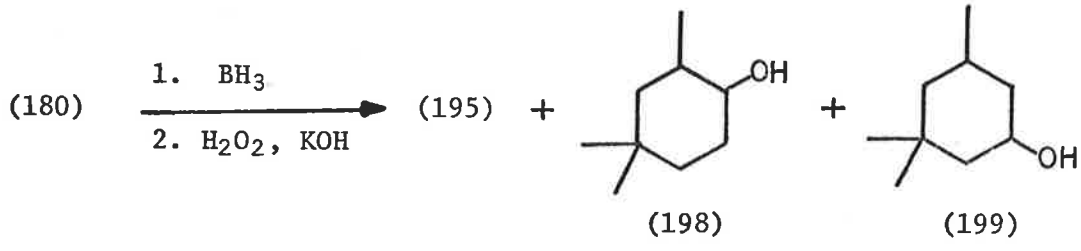
(196) (197)

(R = (+)-isopinocampheyl)

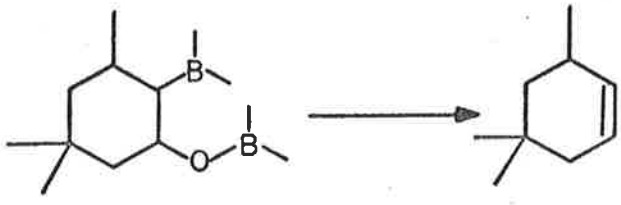
Scheme 79

The lack of any products arising from hydroboration of the double bond suggests that the intermediate (196), formed by initial reduction of the carbonyl group by the hydroborating species, is sufficiently sterically hindered so as to prevent approach of a further molecule of the hydroborating agent to the double bond. Protonolysis of an intermediate such as (196) would give initially an alcohol, which may readily esterify under the conditions of the reaction.

As mentioned above, the hydroboration of isophorone proceeds to give the diol (195) as the only major product, but it also gives a mixture of monoalcohols as minor products[156] (Scheme 80).



(198) (199)



(200) (201)

Scheme 80

These monoalcohols are thought to arise from the hydroboration of the olefin (201), which is formed by a borane-borate elimination from the vicinal diborono intermediate (200). Such eliminations are well known in acyclic systems[101,157] and they tend to occur rapidly and spontaneously, forming the major pathway of reaction.

Elimination, however, plays only a minor role in the hydroboration of isophorone, accounting for only 15% of total products. This is thought to be a result of the preference for the hydroboration of the double bond in isophorone to occur trans to the already-reduced ketone. Thus formation of the four-centre transition state required for this elimination is unfavourable as it results in severe distortion of the ring, and introduces severe Gauche interactions.

Allylic acetates, however, have been shown to undergo hydroboration at the end of the double bond closest to the acetate group, and to undergo cis elimination of an acetoxy borate moiety via a six-membered transition state[101] (section 3.1). An examination of models of isophoryl acetate (202) shows that if hydroboration of this compound occurs at the 2-position then it is possible to form the six-centre transition state required for cis-elimination without distorting the ring, and without inducing unfavourable steric interactions. Indeed, hydroboration of isophoryl acetate has been

shown[156] to give products resulting from such an elimination in significant amounts (total yield of monoalcohols (198) and (199) is 35%).†

It was thought that hydroboration of (202) with an optically active dialkylborane might give an intermediate such as (203) stereospecifically. Elimination of the dialkylacetoxyborate moiety from such an intermediate should generate the olefin (201) without affecting the newly-induced stereochemistry at the 3-position. Rehydroboration with dialkylborane should then favour attack of the borane at the 1-position,[2] and oxidation of the product thus obtained should give optically active products. Such a procedure was attempted using (+)-diisopinocampheylborane (Scheme 81).

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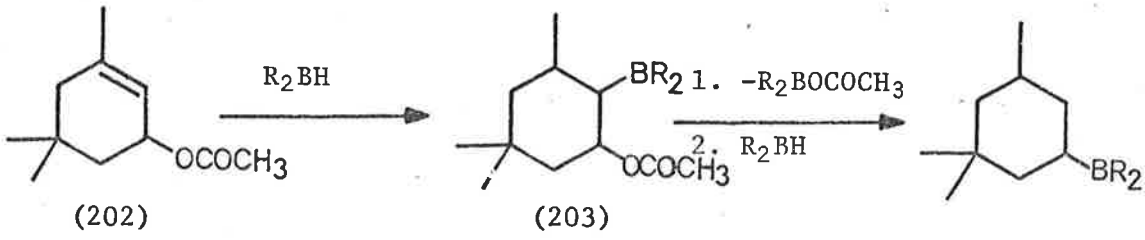
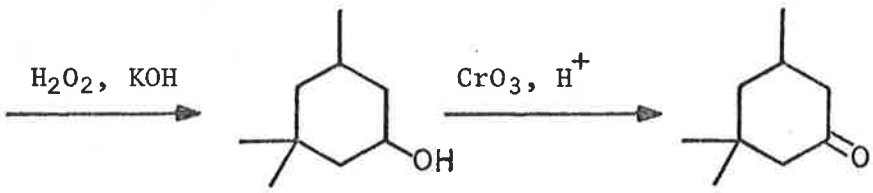
† It should be noted that the acetoxyborate moiety eliminated rapidly utilizes two equivalents of hydride in the reduction of the acetoxy group.[101] The experiment cited above used only sufficient diborane to allow for hydroboration-elimination-hydroboration; use of excess diborane should thus increase yields of elimination products.



(202) (203)

(R = (+)-isopinocampheyl)



(199) (171)

Scheme 81

The alcohol (199) was obtained in only 16% yield,† and it was oxidised directly to the ketone (171) before the optical activity was measured. In the event, (171) was found to have $[\alpha]_D^{20} = +2.3°$, which represents an optical purity of 22%.

Unfortunately, the low yield and low optical purity of the product obtained from this sequence make it unacceptable as a method for obtaining optically pure (171), and thence the optically pure lactams, (167) and (168).

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† Difficulties were encountered in separating (199) from (+)-isopinocampheol.

CHAPTER 5

Experimental

5.1 General

5.2 Work described in chapter 1.

5.3 Work described in chapter 2.

5.4 Work described in chapter 3.

5.5 Work described in chapter 4.

5.1 GENERAL

(i) Melting points (mp) were determined by means of a Kofler hot-stage apparatus and are uncorrected. Boiling points (bp) were determined by micro distillation and are uncorrected.

(ii) Infra-red spectra (ir) were recorded on either a Unicam SP 200 or a Jasco IRA-1 grating infra-red spectrophotometer.

(iii) The ^1H nuclear magnetic resonance spectra (nmr) were determined with a Varian T-60 spectrometer operating at 60 MHz, using tetramethylsilane as an internal standard. Spectra were recorded as solutions in either carbon tetrachloride or deutero-chloroform, and data are given in the following order: multiplicity, s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), e (envelope), exch. means that the signal disappears on shaking the sample with D_2O; relative intensity as number of protons (H); chemical shift (δ); first-order coupling constant (J) expressed in Hz; assignment.

(iv) Mass spectra (ms) were measured with either an Hitachi Perkin-Elmer RMU-7D spectrometer operating at 70 eV, or an AEI MS-30 spectrometer operating at 70 eV. The data are recorded in the following order: m/e value (assignment, relative intensity to base peak (100)).

(v) Gas-liquid chromatographic analyses (glc) were performed on either a Perkin-Elmer 800 or a Pye 104 chromatograph, using nitrogen as carrier gas at a flow rate of 30 ml/min. The columns used were as follows: (I) Carbowax 20M, 20%, 3 m x 1.6 mm, stainless steel; (II) Carbowax 20M, 5%, 2 m x 1.6 mm, glass; (III) FFAP, 5%, 3 m x 1.6 mm, stainless steel; (IV) Silicone GE XE-60, 5%, 3 m x 5 mm, glass; (V) Silicone SE-30. 20%, 3 m x 1.6 mm, stainless steel; (VI) Carbowax 20M, 10%, 3 m x 1.6 mm, stainless steel; (VII) Carbowax 20M, 5%, 3 m x 1.6 mm, stainless steel; (VIII) Butanediol succinate, 20%, 1.5 m x 6 mm, aluminium; (IX) Silicon OV-17, 20%, 6 m x 6 mm, glass; (X) Silicone GE XE-60, 20%, 4 m x 5 mm, glass.

(vi) Optical rotations were measured at the sodium D line at 20°, using a Hilger M412 polarimeter with a shadow angle of 6°.

(vii) Optical rotatory dispersion measurements were made at the mercury emission lines at 20°, using a Perkin-Elmer 141 MC polarimeter.

(viii) Chromatographic adsorbents used were Spence type H alumina, Sorbsil silica gel, and Mallenkrodt silicic acid. Analytical and preparative thin layer chromatography (tlc) was effected using layers containing equal mixtures of Merk Kieselgel G and HF 254.

(ix) All organic solvents were redistilled and the fractions corresponding to their literature boiling points were collected.

Light petroleum refers to the hydrocarbon fraction boiling over the range 40-60°, ether refers to diethylether, and THF refers to tetrahydrofuran. Ether and THF were stored over sodium wire in smoked glass containers, and were redistilled from lithium aluminium hydride immediately prior to use. All organic extracts were dried over anhydrous sodium sulphate prior to removal of the solvents under reduced pressure by means of a rotary evaporator.

(x) Microanalyses were preformed by the Australian Microanalytical Service, Melbourne.

5.2 WORK DESCRIBED IN CHAPTER 1

5.2.1 Oxidation of (3a) and (3b)

Sodium dichromate dihydrate (0.10 g, 0.33 mmol) was dissolved in water (10 ml) and sulphuric acid (97% w/v, 0.136 g) was added. The distilled mixture of (3a) and (3b)[12,13] (0.184 g, 1.0 mmol) was dissolved in ether (10 ml) and added in one portion to the sodium dichromate solution. The mixture was stirred rapidly at room temperature for 2 h. Samples of the organic layer were subjected to glc analysis (column VI, 120°) at 10 min. intervals. Comparison with authentic samples showed the oxidation product to be a mixture of isomenthone and menthone in the initial ratio 3.0:1. This ratio decreased with time to 2.10:1 at 2 h.

5.2.2 3-Oxo-p-menthane-2-carbaldehyde (25).

Compound (25) was prepared by the method of Woodward.[49] Ethylformate (23 ml) was added in a slow stream to a vigorously stirred suspension of sodium hydride (4.0 g) in THF (100 ml) under nitrogen at 0° over 30 min. Menthone (10.0 g) in THF (40 ml) was added dropwise, with cooling in ice, over 1 h. More THF (60 ml) was added and the mixture stirred at room temperature for 18 h. The mixture was diluted with ether and ice-cold aqueous sulphuric acid (10% w/v, 50 ml) and the aqueous layer washed with ether. The

combined organic extracts were washed with ice-cold aqueous Potassium hydroxide (2% w/v, 3 x 100 ml), and the alkaline aqueous extracts were washed with ether and acidified with hydrochloric acid (36% w/v). The mixture was again extracted with ether, the extracts dried, and solvent removed to give 3-oxo-p-menthane-2-carbaldehyde[21] (9.05 g, 77%), $bp_{5.0}$ 110-115° (Found: C, 72.75; H, 10.10. $C_{11}H_{18}O_2$ requires C, 72.49; H, 9.96%). Ir: ν_{max} 1735, 1635 cm^{-1}; nmr: m, 9H, 1.0, CH_3; m, 4H, 1.6, CH_2; m, 3H, 2.5, CH; s, 1H, 8.7, =CH-O; s, exch., 1H, 14.7, OH; ms m/e 182 (M^+, 71%).

5.2.3 Hydrogenation of (25)

Compound (25) (1.82 g, 10 mmol) was hydrogenated at 50° and one atmosphere over Raney nickel in methanol (50 ml) for 40 h. The solution was filtered and diluted with aqueous potassium hydroxide (2% w/v, 50 ml). Extraction with ether gave 2-methoxymethylene-3-oxo-p-menthane (26), $bp_{5.0}$ 93-94° (0.84 g, 40%). Ir: ν_{max} 1700, 1670 cm^{-1}; nmr: m, 9H, 0.9, CH_3; m, 7H, 1.7, CH_2, CH; s, 3H, 3.8, OCH_3; m, 1H, 7.0 =CH-O. The aqueous solution contained unchanged starting material.

5.2.4 Attempted synthesis of enol ethers of (25)

(i) Dihydropyran (10 ml) and (25) (1.82 g, 10 mmol) were

heated under reflux with one crystal of p-toluenesulphonic acid for 3 h.[22] The solution was then diluted with ether and washed successively with aqueous sodium bicarbonate and water. Removal of solvent gave only starting material.

(ii) Triethylorthoformate (10 ml) and (25) (1.82 g, 10 mmol) were heated under reflux with one crystal of p-toluene-sulphonic acid for 3 h.[22] The solution was then diluted with ether and washed successively with aqueous sodium bicarbonate and water. Removal of solvent gave only starting material.

(iii) Trimethylorthoformate (10 ml) and (25) (1.82 g, 10 mmol) were heated under reflux with one crystal of p-toluene-sulphonic acid for 3 h.[22] The solution was then diluted with ether and washed successively with aqueous sodium bicarbonate and water. Removal of solvent gave only starting material.

5.2.5 2-Hydroxymethyl-p-menthan-3-ol (27)

To a solution of (25) (0.182 g, 1 mmol) in methanol (10 ml) was added a solution of sodium borohydride (0.25 g) and sodium hydroxide (0.2 g) in water (5 ml).[23] The solution was stirred at room temperature for 3 h and then poured into ice-cold aqueous sulphuric acid (10% w/v). Extraction with ether yielded 2-hydroxymethyl-p-menthan-3-ol (27) (0.151 g, 81%) as a colourless

viscous oil, $bp_{0.05}$ 84-6°. (Found: C, 70.95; H, 11.60. $C_{11}H_{22}O_2$ requires C, 70.92; H, 11.90%). Ir: ν_{max} 3350 cm^{-1} ; nmr: m, 9H, 0.9, CH_3; e, 8H, 1.2-2.2, CH_2, CH; s, exch., 2H, 3.2, OH; m, 3H, 3.8, CH_2OH, CHOH; ms m/e 168 ($M^+ - H_2O$, 1%).

5.2.6 Reduction of (25) with Lithium Aluminium Hydride

Compound (25) (0.364 g, 2 mmol) in dry ether (10 ml) was added dropwise to a solution of lithium aluminium hydride (0.038 g, 1 mmol) in dry ether (10 ml).[24] The solution was stirred at room temperature for 2 h, after which excess reagent was decomposed by the careful addition of aqueous sulphuric acid (10% w/v). The organic layer was washed with aqueous sodium carbonate, dried and the solvent removed. Nmr analysis of the product indicated a mixture of allylic alcohols (28) and (29) in the ratio of 7:1 (based on resonances at δ 4.2 for $=CH_2$ and δ 4.8 for =CH).

5.2.7 Reduction of (25) with Sodium Aluminium bis(2-methoxyethoxy) hydride

Compound (25) (1.82 g, 10 mmol) was dissolved in dry benzene (30 ml) and sodium aluminium bis(2-methoxyethoxy)hydride[25] (70% w/w in benzene, 2.17 g, 7.5 mmol) in dry benzene (10 ml) was added dropwise with rapid stirring at 0°. The solution was stirred at 0° for

1 h and then poured onto a mixture of ice and sulphuric acid. The mixture was stirred for 10 min and then extracted with ether. Removal of solvent gave 2-hydroxymethyl-p-menthan-3-one (3a) (1.21 g, 66%) $bp_{0.05}$ 80-82°. (Found: C, 71.38; H, 10.77. $C_{11}H_{20}O_2$ requires C, 71.69; H, 10.94%). Ir: ν_{max} 3500, 1700 cm^{-1}; nmr: m, 9H, 1.0, CH_3; d, 4H, 1.6 (3 Hz), CH_2; m, 4H, 1.7-2.2, CH; s, exch., 1H, 3.0, OH; d, 2H, 3.6 (6 Hz), CH_2OH; ms m/e 184 (M^+, 11%). Glc analysis (column IV, 120°) indicated the product was the same as the minor component of the mixture isolated from hydroboration-cyanidation of geraniol.[12]

5.2.8 Trimethyloxosulphonium iodide

Trimethyloxosulphonium iodide was prepared by the method of Kuhn and Trischmann.[158] Dimethylsulphoxide (96 g) and iodomethane (180 ml) were heated under reflux in a nitrogen atmosphere for 5 days. The solution was then cooled, and the solid collected by filtration. After washing with chloroform and drying, the solid (145 g, 53.6%) was recrystallized from water to give large, colourless prisms which decomposed on heating.

5.2.9 Dimethylmethyleneoxysulphurane

Dimethylmethyleneoxysulphurane was prepared, as required, by the method of Corey and Chaykovsky[26] and was used *in situ*.

Sodium hydride (50% w/w oil suspension, 0.96 g, 20 mmol) was washed several times with light petroleum and dried under reduced pressure. Trimethyloxosulphonium iodide (4.40 g, 20 mmol) was added and the system was placed under a nitrogen atmosphere. Dry dimethylsulphoxide (40 ml) was then added slowly, with gentle stirring, from a syringe. The mixture was stirred for 30 min at room temperature and then used immediately.

5.2.10 3-Isopropyl-6-methylbicyclo[4.1.0]heptan-2-one (31)

Piperitone (30) (3.04 g, 20 mmol) in dry dimethylsulphoxide (10 ml) was added to a solution of dimethylmethyleneoxysulphurane (20 mmol), prepared as described above.[26] The solution was stirred at room temperature for 18 h and then poured into water (80 ml). The mixture was extracted with ether and the ether extracts washed thoroughly with water. The extracts were dried and the solvent removed under reduced pressure to give a pale yellow oil. Distillation gave 3-isopropyl-6-methylbicyclo[4.1.0]heptan-2-one (31), $bp_{0.05}$ 38-39°, as a colourless, sweet-smelling oil (2.90 g, 87%). (Found: C, 79.44; H, 10.90. $C_{11}H_{18}O$ requires: C, 79.46; H, 10.92%). Ir: ν_{max} 1680, 1640 cm^{-1}; nmr: d, 2H, 0.7 (7 Hz), cyclopropyl CH_2; d, 6H, 0.9 (7 Hz), CH_3; s, 3H, 1.2, CH_3 on cyclopropyl ring; e, 7H, 1.3-2.6, CH_2, CH; ms m/e 166 (M^+, 9%). Glc analysis (column IV, 100°) indicated the presence of only one isomer.

5.2.11 Perchloric acid catalysed ring cleavage of (31)

A solution of (31) (0.166 g, 1 mmol) in an acetic acid solution of perchloric acid (concentrations varied at 1,5 and 10% w/v; 10 ml) was heated under reflux for 3 h. After cooling, the solution was diluted with water (20 ml) and extracted with ether. The ether extracts were washed successively with water and aqueous sodium carbonate (10% w/v). After drying, removal of solvent gave mixtures of (34) and (35) (in approximate ratio of 1:1 based on nmr resonances at δ 5.4 for =CH- and δ 6.8 for -CH=C-C=O), which could not be separated by tlc or glc (columns I and V).

5.2.12 Sulphuric acid catalysed ring cleavage of (31)

Ketone (31) (3.32 g, 20 mmol) was heated under reflux in aqueous acetic acid (50% v/v, 50 ml) containing two drops of sulphuric acid (96%) for eighteen hours. After cooling, the solution was diluted with water and extracted with ether. The organic extracts were washed with water, saturated aqueous sodium carbonate and saturated aqueous sodium chloride. After drying, removal of solvent gave a pale yellow oil (2.63 g), which upon distillation gave two fractions.

The first fraction (1.16 g, 35%) was 4-methyl-7-isopropyl-

cyclohept-3-enone (34), $bp_{0.06}$ 36-37°. (Found: C, 79.53; H, 11.22. $C_{11}H_{18}O$ requires: C, 79.46; H, 10.92%). Ir: ν_{max} 1700, 1660 cm^{-1}; nmr: d, 6H, 0.9 (7 Hz), CH_3; d, 3H, 1.7 (1 Hz), $=C-CH_3$; e, 8H, 1.4-2.8, CH_2, CH; broad s, 1H, 5.4, =CH; ms m/e 166 (M^+, 37%).

The second fraction (1.29 g, 39%) was 2-isopropyl-5-methyl-5-hydroxy-cycloheptanone (36), $bp_{0.1}$ 57-59°. (Found: C, 71.98; H, 10.83. $C_{11}H_{20}O_2$ requires: C, 71.69; H, 10.94%). Ir: ν_{max} 3390, 1695 cm^{-1}; nmr: dd, 6H, 0.9 (7 Hz), CH_3; s, 3H, 1.2, $O-C-CH_3$; e, 10H, 1.4-2.4, CH_2, CH; s, exch., 1H, 3.7, OH; ms m/e 184 (M^+, 10%). Glc analysis (columns I, III and IV) failed to achieve complete resolution of isomers present. The nmr resonance at δ 0.9 indicated the presence of two isomers in the ratio 1:1.

5.2.13 2-Isopropyl-5-methyl-5-acetoxycycloheptanone (37)

Hydroxyketone (36) (0.368 g, 2 mmol) was dissolved in N,N-dimethylaniline (5 ml) and the solution cooled in ice. Acetyl-chloride (2 ml) was added dropwise with stirring.[29] After completion of the addition the ice bath was removed and the mixture stirred at room temperature for 24 h. The mixture was diluted with light petroleum and transferred to a separating funnel. After washing successively with hydrochloric acid (10% w/v), aqueous sodium

carbonate (10% w/v) and water, the organic extracts were dried and the solvent removed to give 2-isopropyl-5-methyl-5-acetoxy-cycloheptanone (37), $bp_{1.0}$ 68-70° as a yellow oil (0.330 g, 73%). (Found: C, 68.80; H, 9.70. $C_{13}H_{22}O_3$ requires: C, 68.99; H, 9.80%). Ir: ν_{max} 1730, 1700 cm^{-1}; nmr: dd, 6H, 0.9 (7 Hz), CH_3; ds, 3H, 1.3, O-C-CH_3; ds, 3H, 2.0, CO-CH_3; e, 10H, 1.5-2.5, CH_2, CH; ms m/e 166 (M^+-CH_3CO_2H, 5%). Glc analysis (columns I, III and IV) again failed to achieve complete separation of the isomers present, but the nmr spectrum indicated two isomers to be present in the ratio 1:1.

5.2.14 Sodium borohydride reduction of (37)

Ketone (37) (100 mg) in ethanol (2 ml) was added to a stirred suspension of sodium borohydride (100 mg) in ethanol (5 ml) and the mixture was stirred at room temperature for two hours.[30] The solution thus obtained was poured onto a mixture of ice and aqueous sulphuric acid (15% w/v) and stirred for a further 10 min. The mixture was extracted with ether and the organic extracts were washed with aqueous sulphuric acid (15% w/v), aqueous sodium carbonate (10% w/v) and water. After drying removal of the solvent gave a pale yellow oil (80 mg, 98%), which no longer showed any carbonyl absorption in the ir spectrum, and whose spectral properties were consistent with the structure being

2-isopropyl-5-methyl-5-hydroxy-cycloheptanol. Ir: ν_{max} 3400 cm^{-1}; nmr: d, 6H, 1.0 (6 Hz), CH_3; s, 3H, 1.3, O-C-CH_3; e, 10H, 1.5-2.4, CH_2, CH; m, 1H, 3.6, CH-O; s exch., 2H, 5.5, OH; ms m/e 186 (M^+, 7%).

5.2.15 Buffered sodium borohydride reduction of (37)

Ketone (37) (0.226 g, 1 mmol) in ethanol (2 ml) was added to a stirred suspension of sodium borohydride (0.114 g, 3 mmol) in ethanol (5 ml) containing acetic acid (0.180 g, 3 mmol) and the mixture was stirred at room temperature for 30 min.[31] After working up as described above, removal of solvent gave 2-isopropyl-5-methyl-5-acetoxycycloheptanol (39), $bp_{1.0}$ 74-75°, as a colourless oil (0.121 g, 53%). (Found: C, 68.08; H, 10.33. $C_{13}H_{24}O_3$ requires: C, 68.38; H, 10.59%). Ir: ν_{max} 3440, 1730 cm^{-1}; nmr: dd, 6H, 0.9 (6 Hz), CH_3; s, 3H, 1.4, O-C-CH_3; s, 3H, 2.0, CO-CH_3; e, 10H, 1.5-2.2, CH_2,CH; m, 1H, 3.7, CH-O; s, exch., 1H, 4.2, OH; ms m/e 168 (M^+ - CH_3CO_2H, 1%). Glc analysis (column IV, 100°) indicated the presence of two isomers, with retention times of 7.9 and 8.2 min, in the ratio 1:1. These isomers had identical retention times to two of the three isomers obtained from the hydroboration-cyanidation of linalyl acetate.[13]

5.2.16 Diborane reduction of (37)

Ketone (37) (2.26 g, 10 mmol) was dissolved in anhydrous

THF (30 ml) and a solution of diborane in THF (2.6M, 3.85 ml, 10 mmol) was added with rapid stirring.[32] The solution was stirred at room temperature for 30 min and then carefully diluted with aqueous acetic acid (20% v/v). The solution was extracted with ether, and the ether extracts washed with aqueous sulphuric acid (15%, w/v), aqueous sodium carbonate (10% w/v) and water. After drying, removal of the solvent gave a colourless oil (2.26 g, 99%), which was identical in all respects with the product isolated above. Glc analysis also indicated an identical isomer composition as the product isolated above.

5.2.17 7-Hydroxy-p-menthane-1,8-diene (41)

Perillaldehyde (40) (1.50 g, 10 mmol) dissolved in ethanol (10 ml) was added dropwise to a rapidly stirred suspension of sodium borohydride (1.50 g) in ethanol (20 ml), and the resultant mixture stirred for one hour at room temperature.[30] The mixture was then poured onto ice and sulphuric acid (15% w/v), and extracted with ether. After washing with water the extracts were dried and the solvent was removed to give 7-hydroxy-p-menthane-1,8-diene[35] (41), $bp_{3.0}$ 96-97°, as a colourless oil (1.42 g, 93%). Ir: ν_{max} 3350 cm^{-1}; nmr: s, 3H, 1.7, CH_3; m, 5H, 2.0, CH_2, CH; e, 3H, 1.2-2.3, CH_2, OH; s, 2H, 3.9, CH_2-O; broad s, 2H, 4.7, =CH ; broad s, 1H, 5.6, =CH; ms m/e 152 (M^+, 14%). Glc analysis (column IV, 120°)

indicated only one compound present.

5.2.18 Reduction of perillaldehyde by sodium borohydride in pyridine

Sodium borohydride (1.42 g) was added to a solution of perillaldehyde (1.50 g, 10 mmol) in pyridine[33] (30 ml) and the system was placed under a nitrogen atmosphere. The mixture was stirred at room temperature for 18 h and was then poured into a solution of sodium iodate (1.0 g) in water (100 ml). Stirring was continued for 15 min, after which the solution was extracted with light petroleum. The organic extracts were washed with aqueous sulphuric acid (15% w/v), aqueous sodium carbonate (10% w/v) and water. After drying, removal of the solvent gave a colourless oil (1.35 g), which was shown to be a mixture of (41) and 7-hydroxy-8-p-menthene (42) in the ratio 1:4. The product composition was determined by the ratio of resonances at δ 4.7 (for $=CH_2$) and δ 5.7 (for =CH).

The reaction was repeated at 0° and 114°, and the reaction time varied from 1 h to 3 days. In each case the product composition was identical to that found above, and the total yield of product did not vary appreciably.

5.2.19 Reduction of perillaldehyde with sodium borohydride in the presence of triphenylphosphine

Sodium borohydride (1.42 g), perillaldehyde (1.50 g, 10 mmol) and triphenylphosphine[34] (10.5 g) were stirred at room temperature for 3 days in diethylene glycol dimethylether (diglyme) (40 ml). The mixture was then filtered, diluted with water and extracted with ether. After thorough washing with water, the organic extracts were dried, and the solvent removed to give a colourless oil (0.15 g), identical in composition to that described above.

The mixtures of (41) and (42) could not be separated by distillation or thin layer chromatography. The two components were partially resolved by glc (column I, 150°), but preparative glc was impractical for the amounts of compound (42) required.

5.2.20 Reduction of perillaldehyde with lithium aluminium hydride

Lithium aluminium hydride (0.38 g, 10 mmol) was suspended in dry THF under a dry nitrogen atmosphere.[35] Perillaldehyde (0.75 g, 5 mmol) in dry THF was added slowly to the stirred suspension, and the mixture was then heated under reflux for 2 h. After cooling, excess of the reagent was destroyed by the dropwise addition of acetone (3 ml) and the resultant mixture was poured

into ice-cold aqueous sulphuric acid (15% w/v). The mixture was extracted with ether and the extracts washed with aqueous sulphuric acid (15% w/v), and saturated aqueous sodium chloride solution. After drying, removal of the solvent gave (41) as a colourless oil (0.76 g, 100%). The product was pure (glc on column I at 150°) and was identical in all respects to that isolated from the sodium borohydride reduction of perillaldehyde.

5.2.21 Reduction of perillaldehyde with sodium aluminium bis(2-methoxyethoxy)hydride

Perillaldehyde (0.75 g, 5 mmol) was reduced with sodium aluminium bis(2-methoxyethoxy)hydride[36] (70% w/w in benzene, 4.20 g, 11 mmol) under the same conditions as described for lithium aluminium hydride. The resultant product (0.74 g, 98%) again proved to be (41), and was identical in all respects to that isolated above.

5.2.22 Hydrogenation of perillaldehyde in triethylamine

Perillaldehyde (0.75 g, 5 mmol) dissolved in triethylamine (10 ml) was hydrogenated[37] over palladium on carbon at room temperature for 48 h. The catalyst was removed and the solution reduced in volume. Unchanged perillaldehyde (0.73 g) was the only product recovered.

5.2.23 Hydrogenation of perillaldehyde in methanolic potassium hydroxide

Perillaldehyde (1.50 g, 10 mmol) dissolved in a methanolic solution of potassium hydroxide (0.2M, 25 ml) was hydrogenated[37] over palladium on carbon at room temperature until one equivalent of hydrogen had been taken up (approx. 30 h). The catalyst was removed and the solution was diluted with light petroleum. The solution was washed thoroughly with water, dried and the solvent removed. The product isolated (0.75 g), as a yellow oil, was subjected to glc analysis (column IV, 120°) and was shown to consist of a mixture of starting material and 7-oxo-p-menthane in the ratio 1:1.

5.2.24 7-Hydroxy-8-p-menthene (shisool, 42)

Lithium (0.80 g) was dissolved in freshly distilled ammonia (50 ml) over 60 min.[39] A solution of perillaldehyde (1.50 g, 10 mmol) in isopropanol (10 ml) and anhydrous ether (20 ml) was then added over 10 min and the solution stirred for a further 2 h. The solution was then diluted with isopropanol (30 ml) and ether (30 ml), and finally water was added very slowly with vigorous stirring. The mixture was extracted with ether and the ether extracts washed with aqueous sulphuric acid (15% w/v), aqueous sodium carbonate (10% w/v) and water. After drying, removal of the solvent gave 7-

hydroxy-8-p-menthene (42), $bp_{0.4}$ 64-66° (literature[38] $bp_{0.5}$ 65-66°), as a colourless oil (1.49 g, 97%). Ir: ν_{max} 3300, 1640 cm^{-1}; nmr: s, 3H, 1.7 =C-CH_3; e, 10H, 0.9-2.2, CH_2, CH; s, excn., 1H, 2.5 OH; d, 2H, 3.4 (6 Hz), CH_2-O; s, 2H, 4.7, =CH_2; ms m/e 154 (M^+, 19%). Glc analysis (column IV, 120°) indicated the presence of both cis and trans isomers[35] in the ratio 1:1.

Repetition of this reaction on a ten-fold scale resulted in the isolation of a different product (12.7 g, 84%), 7-hydroxy-p-menthane (45), $bp_{0.8}$ 84-85°. (Found: C, 76.81; H, 12.96. $C_{10}H_{20}O$ requires: C, 76.86; H, 12.90%). Ir: ν_{max} 3400 cm^{-1}; nmr: d, 6H, 0.9 (7 Hz), CH_3; e, 11H, 1.0-2.0, CH_2, CH; s, exch., 1H, 2.0, OH; t, 2H, 3.4 (6 Hz), CH_2-O; ms m/e 156 (M^+, 12%).

5.2.25 4-Isopropenylcyclohexanecarbaldehyde (44)

Perillaldehyde (6.0 g, 40 mmol), dissolved in isopropanol (25 ml) and anhydrous ether (100 ml) was added to anhydrous ammonia[41] (200 ml). Lithium wire (6.0 g) was then added over 15 min and the mixture was stirred for a further 90 min after completion of the addition. Saturated aqueous ammonium chloride (100 ml) was then added slowly, and the ammonia was allowed to evaporate. The organic layer of the residue was separated and washed successively with aqueous sulphuric acid (15% w/v) and saturated aqueous sodium chloride solution. After drying, removal of the solvent gave 4-

isopropenylcyclohexanecarbaldehyde (44), $bp_{1.0}$ 74-75°, as a pale straw-coloured oil (4.74 g, 78%). (Characterised as the semicarbazone, mp 162-163°: found: C, 63.06; H, 9.31; N, 20.00. $C_{11}H_{19}N_3O$ requires: C, 63.12; H, 9.15; N, 20.08%). Ir: ν_{max} 1715, 1640 cm^{-1}; nmr: s, 3H, 1.7, $=C-CH_3$; e, 10H, 0.9-2.4, CH_2, CH; s, 2H, 4.7, $=CH_2$; d, 1H, 9.7 (4 Hz), CH=O; ms m/e 152 (M^+, 29%). Glc analysis (column IV, 120°) indicated the presence of both cis and trans isomers in the ratio 3:1.

5.2.26 Attempted double bond isomerization of (42) by p-toluenesulphonic acid

Shisool (42) (100 mg) was heated under reflux in benzene (10 ml) containing a crystal of p-toluenesulphonic acid for 18 h.[45] The solution was then cooled, and anhydrous potassium carbonate (200 mg) was added. After standing for 15 min the mixture was filtered and the solvent removed from the filtrate. Starting material was recovered unchanged.

5.2.27 7-Hydroxy-3-p-menthene (46)

Shisool (42) (1.54 g, 10 mmol) was heated under reflux with aqueous sulphuric acid (15% w/v, 20 ml) for 1 h.[46] After cooling, the solution was extracted with ether and the extracts washed with aqueous sodium carbonate (10% w/v) and water. Removal of the

solvent gave 7-hydroxy-3-p-methene (46), $bp_{0.1}$ 55-57°, as an almost colourless oil (1.13 g, 73%). Ir: ν_{max} 3400 cm^{-1}; nmr: d, 6H, 0.9 (7 Hz), CH_3; e, 8H, 1.2-2.2, CH_2, CH; s, exch., 1H, 2.4 OH; d, 2H, 3.4 (7 Hz), CH_2-OH; s, 1H, 5.3, =CH; ms m/e 154 (M^+, 4%). Glc analysis (column IV, 150°) indicated the compound was pure.

Acetylation of (46) (0.77 g, 5 mmol) in acetic anhydride (20 ml) at room temperature for 18 h gave, after the usual work up procedure, 7-acetoxy-3-p-methene (47) (0.92 g, 94%), $bp_{0.3}$ 57-58°, with spectral characteristics (ir, nmr, ms) identical to those of the compound isolated below.

5.2.28 7-Acetoxy-3-p-menthene (47)

Shisool (42) (1.54 g, 10 mmol) was allowed to stand at room temperature for 18 h in a solution of borontrifluoride-acetic acid complex[47] (0.25 M) in benzene-acetic acid (1:1, v/v, 100 ml). The solution was diluted with ether and washed with water and aqueous sodium carbonate (10% w/v). After drying, removal of solvent gave 7-acetoxy-3-p-menthene (47), $bp_{0.2}$ 54-56°, as a colourless, sweet-smelling oil (1.60 g, 82%). (Found: C, 73.68; H, 10.33. $C_{12}H_{20}O_2$ requires: C, 73.43; H, 10.27.) Ir: 1735 cm^{-1}; nmr: d, 6H, 1.0 (7 Hz), CH_3; s, 3H, 2.0, CO-CH_3; e, 8H, 1.2-2.4, CH_2, CH; d, 2H, 3.9 (5 Hz), CH_2-O-; s, 1H, 5.3, =CH; ms m/e 196 (M^+, 1%). Glc

analysis (column IV, 120°) indicated the compound was pure.

5.2.29 3-Oxo-7-acetoxy-p-menthane (48)

A solution of diborane in anhydrous THF (2.6M, 0.8 ml) was added dropwise to a stirred solution of (47) (0.392 g, 2 mmol) in THF (10 ml) maintained under a nitrogen atmosphere. The solution was stirred for 40 min at room temperature. Chromium trioxide (0.5 g) in aqueous sulphuric acid (50%, 8 ml) was then added,[18,48] and the solution warmed to 65°, and maintained at this temperature for 1 h. After cooling, the solution was extracted with ether and the organic extracts were washed with aqueous sodium carbonate (10%, w/v) and water. After drying, removal of the solvent gave 3-oxo-7-acetoxy-p-menthane (48), $bp_{0.01}$ 49-50°, as a pale yellow oil (0.37 g, 89%). (Found: C, 67.72; H, 9.15. $C_{12}H_{20}O_3$ requires: C, 67.88; H, 9.50). Ir: ν_{max} 1735, 1705 cm^{-1}; nmr: d, 6H, 0.9 (7 Hz), CH_3; e, 9H, 1.2-2.5, CH_2, CH; s, 3H, 2.0, $CO-CH_3$; m, 2H, 3.9, CH_2-O-; ms m/e 152 ($M^+-CH_3CO_2H$, 8%). Glc analysis (column IV, 120°) indicated the presence of two isomers (cis and trans) in the ratio 1:4.

5.2.30 3-Oxo-7-hydroxy-p-menthane (49)

The acetate (48) (2.12 g, 10 mmol) was allowed to stand at room temperature for 18 h in methanolic potassium hydroxide (2M; 20 ml).[51] The solution was then diluted with water and extracted

with ether. The ether extracts were washed with water, dried and the solvent removed to give 3-oxo-7-hydroxy-p-menthane (49), $bp_{0.01}$ 40-41°, as a colourless oil (1.48 g, 87%). (Found: C, 70.86; H, 10.78. $C_{10}H_{18}O_2$ requires: C, 70.54; H, 10.66%). Ir: ν_{max} 3350, 1705 cm^{-1}; nmr: s, exch., 1H, 3.0, OH; m, 2H, 3.5, CH_2-O; ms m/e 152 (M^+-H_2O, 12%). Glc analysis (column IV, 150°) indicated no change in the ratio of isomers present.

5.2.31 Attempted formylation of (48) and (49)

The acetate (48) (2.12 g, 10 mmol) was treated with ethyl formate (0.8 g, 12 mmol) in THF in the presence of sodium hydride[49] (0.24 g, 10 mmol) as described previously for the preparation of (25). The only isolated product was identified as 3-oxo-7-hydroxy-p-menthane (49), (1.60 g, 94%), identical in all respects to that prepared above.

Attempted formylation of (49) under the same conditions using 2 equivalents of sodium hydride gave only unchanged starting material.

5.2.32 2-Methyl-3-oxo-7-hydroxy-p-menthane (50)

Hydroxy ketone (49) (.170 g, 1 mmol) in anhydrous THF (2 ml) was added to a solution of lithium diisopropylamide (2 mmol) in THF, generated from diisopropylamine (0.202g, 2 mmol) in THF (5 ml)

and a solution of n-butyl-lithium in hexane (1M, 2ml), and the resultant solution was maintained under a nitrogen atmosphere at 0° for 20 min.[52] Iodomethane (0.142 g, 1 mmol) was added and the solution stirred at 0° for a further 70 min. The solution was acidified with hydrochloric acid (2M) and the organic layer separated and washed thoroughly with water. After drying, removal of the solvent gave 2-methyl-3-oxo-7-hydroxy-p-menthane, (50), $bp_{0.1}$, 65-66°, as a colourless oil (0.168 g, 91%). (Found: C, 71.97; H, 10.98. $C_{11}H_{20}O_2$ requires: C, 71.69; H, 10.94%). Ir: ν_{max} 3400, 1700 cm^{-1}; nmr: m, 6H, 0.9, CH_3; m, 3H, 1.1, $CO-C-CH_3$; e, 8H, 1.2-2.4, CH_2, CH; s, exch., 1H, 2.3, OH; dd, 2H, 3.3 (6 Hz), CH_2-O; ms m/e 184 (M^+, 2%). Glc analysis (column IV, 150°) indicated the presence of three isomers, with retention times of 5.4, 6.0 and 6.3 min respectively, in the ratio 1:2:4. These were shown to be the same as the isomers present in the product of hydroboration-cyanidation of myrcene.

A small sample of the product was dissolved in trifluoro-acetic acid and allowed to stand at room temperature for 6 h. After dilution with ether the sample was analysed by glc (column IV, 150°) which indicated the presence of the same isomers as previously observed, but in the ratio of 2:8:1.

5.2.33 7-Methanesulphonyl-8-p-menthene (51)

Alcohol (42) (154 mg, 1 mmol) was stirred at room temperature

for 18 h with methanesulphonyl chloride (228 mg, 2 mmol) in anhydrous pyridine (10 ml).[53] The mixture was then poured into aqueous hydrochloric acid (10% w/v, 25 ml) and extracted with ether. The organic extracts were washed with aqueous hydrochloric acid (10% w/v) and water, and then dried. Removal of the solvent gave a yellow oil (120 mg, 52%), which darkened on warming, with spectral properties consistent with 7-methanesulphonyl-8-p-menthene (51). Ir: ν_{max} 1360, 1170 cm^{-1}; nmr: m, 8H, 1.2, CH_2; s, 3H, 1.7, $=C-CH_3$; e, 2H, 1.4-2.0, CH; s, 3H, 3.0, $-SO_2CH_3$; m, 2H, 3.9, $-SO_2OCH_2$; s, 2H, 4.7, $=CH_2$.

5.2.34 7-p-Toluenesulphonyl-8-p-menthene (52)

Alcohol (42) (154 mg, 1 mmol) was treated with p-toluenesulphonyl chloride (285 mg, 1.5 mmol) in anhydrous pyridine (10 ml) as described above.[54] The product isolated after extraction was a light brown oil (190 mg, 62%), which darkened on warming, with spectral properties consistent with 7-p-toluenesulphonyl-8-p-menthene (52). Ir: ν_{max} 1365, 1190, 1175 cm^{-1}; nmr: m, 8H, 1.2, CH_2; s, 3H, 1.7, $=C-CH_3$; e, 2H, 1.4-2.0, CH; s, 3H, 2.4, $Ar-CH_3$; dd, 2H, 3.8 (6 Hz), $-SO_2OCH_2$; s, 2H, 4.6, $=CH_2$; m, 4H, 7.5, Ar-H; ms m/e 308 (M^+, 2%).

5.2.35 7-Cyano-8-p-menthene (53)

Compound (52) (308 mg, 1 mmol) was added to a suspension of sodium cyanide (0.5 g) in dry dimethylsulphoxide, and the mixture was stirred at room temperature for 18 h.[55] The reaction mixture was then diluted with water and extracted with ether. The ether extracts were washed thoroughly with water, dried and the solvent removed to give 7-cyano-8-p-menthene (53), $bp_{1.0}$ 75-77° as a colourless oil (98 mg, 60%). (Found: C, 81.10; H, 10.33. $C_{11}H_{17}N$ requires: C, 80.92; H, 10.50%). Ir: ν_{max} 2250 cm^{-1}; nmr: s, 3H, 1.7, $=C-CH_3$; e, 10H, 1.0-2.0, CH_2, CH; d, 2H, 2.3 (6 Hz), CH_2CN; s, 2H, 4.6, $=CH_2$; ms m/e 163 (M^+, 4%). Glc analysis (columns IV and V, 130°) indicated the presence of two isomers in the ratio 1:1.

5.2.36 7-Carboxy-8-p-menthene (54)

Nitrile (53) (163 mg, 1 mmol) was allowed to stand at room temperature for 18 h in methanolic potassium hydroxide (2M, 10 ml).[56] The solution was then diluted with water and acidified with aqueous hydrochloric acid (35% w/v). Extraction with ether gave 7-carboxy-8-p-menthene (54), mp 177-178°, as a white crystalline solid (33 mg, 18%). (Found: C, 72.34; H, 10.19. $C_{11}H_{18}O_2$ requires: C, 72.49; H, 9.96%). Ir: ν_{max} 2700, 1710 cm^{-1}; nmr: s, 3H, 1.7, $=C-CH_3$; e, 12H, 1.0-2.4, CH_2, CH; s, 2H, 4.7, $=CH_2$; s, exch., 1H, 10.3,

CO_2H; ms m/e 181 (M^+-H, 9%).

5.2.37 7-Chloro-8-p-menthene (55)

Phosphorous pentachloride (2.21 g, 11 mmol) was added in one portion to an ice-cold solution of (42) (1.54 g, 10 mmol) in chloroform (25 ml).[57] The mixture was stirred for 30 min and the loaded onto a short column of silica gel (30 g). Elution with light petroleum gave 7-chloro-8-p-menthene (55), $bp_{0.4}$ 77-79°, as a colourless oil (1.53 g, 89%). (Accurate mass measured at: 172.1016. $C_{10}H_{17}Cl$ requires: 172.1019). Ir: ν_{max} 1640 cm^{-1}; nmr: s, 3H, 1.7, $=C-CH_3$; e, 10H, 1.0-2.0, CH_2, CH; d, 2H, 3.9 (5 Hz), CH_2-Cl; s, 2H, 4.7, $=CH_2$; ms m/e 136 (M^+-HCl, 18%).

5.2.38 7-Chloro-$\Delta^{4,8}$-p-menthene (56)

A solution of (42) (1.54 g, 10 mmol) in thionyl chloride (15 ml) was heated under reflux for 1 h, and then poured slowly onto ice.[58] The mixture was stirred for 15 min and then extracted with ether. The organic extracts were dried and the solvent removed to give 7-chloro-$\Delta^{4,8}$-p-menthene (56), $bp_{0.6}$ 120-121°, as a pale yellow oil (1.26 g, 73%). (Found: C, 69.74; H, 10.46. $C_{10}H_{17}Cl$ requires: C, 69.55; H, 9.92%). Ir: ν_{max} 1670 cm^{-1}; nmr: s, 6H, 1.5, $=C-CH_3$; e, 9H, 0.9-2.3, CH_2, CH; d, 2H, 3.6 (5 Hz), CH_2-Cl; ms m/e 136 (M^+-HCl, 25%).

5.2.39 Attempted condensation of Grignard derivatives of (55) and (56) with formaldehyde

A solution of (55) (172 mg, 1 mmol) in anhydrous ether was added to a stirred suspension of magnesium turnings (46 mg, 2 mmol) in ether containing a small crystal of iodine.[59,60] The mixture was heated under reflux for 30 min and then formaldehyde gas, generated by the thermal decomposition of paraformaldehyde, was bubbled through the solution in a stream of dry nitrogen for 15 min. The mixture was stirred for a further 45 min at room temperature and then poured into ice-cold aqueous sulphuric acid (15% w/v). The mixture was extracted with ether and the organic extracts washed with aqueous sodium carbonate (10% w/v) and water. The extracts were dried and the solvent removed. Analysis of the product (nmr) showed it to be unchanged starting material.

The above procedure was attempted in the presence of iodomethane[62] (142 mg, 1 mmol), but although the magnesium dissolved the only product isolated was unchanged starting material. Activation of the magnesium by the method of Reike and Bales[63] also failed to induce formation of the Grignard derivative of (55).

The isomeric chloride (56) was also subjected to all the above-mentioned procedures without success.

5.2.40 Trimethylsulphonium iodide

Iodomethane (142 g, 1 mol) and sodium sulphide (26 g, 0.33 mol) were allowed to stand at room temperature for 24 h.[158] The resultant product was recrystallized from ethanol to give trimethylsulphonium iodide (167.8 g, 99%) as prismatic needles, mp 186-9°, with decomposition.

5.2.41 Dimethylmethylenesulphurane

Dimethylmethylenesulphurane was prepared by the method of Corey and Chaykovsky[26] from trimethylsulphonium iodide (2.04 g, 10 mmol) and sodium hydride (0.24 g, 10 mmol) in dimethylsulphoxide (10 ml) and anhydrous ether (20 ml). The solution of the sulphurane was used immediately.

5.2.42 7-Epoxymethylene-8-p-menthene (57)

Aldehyde (44) (304 mg, 2 mmol) in dimethylsulphoxide (5 ml) was added to a solution of dimethylmethyleneoxysulphurane[26] (2 mmol), prepared as described above, and the solution was stirred at room temperature for 30 min. Dilution with water and extraction with ether gave, after removal of solvent, 7-epoxymethylene-8-p-menthene (57), $bp_{0.05}$ 75-77°, as a colourless oil (132 mg, 40%). (Found: C, 79.17; H, 10.88. $C_{11}H_{18}O$ requires: C, 79.46; H, 10.92%). Ir: ν_{max} 1640 cm^{-1}; nmr: s, 3H, 1.7, $=C-CH_3$; e, 10H,

0.9-2.0, CH_2, CH; dd, 2H, 2.6 (6 Hz), CH_2-O; m, 1H, 3.4, CH-O; ms m/e 166 (M^+, 7%).

Repetition of the above procedure using (44) (304 mg, 2 mmol) and dimethylmethylene sulphurane[64] (2 mmol) in dimethylsulphoxide and ether[26] gave an identical product (by ir, nmr, ms) to that isolated above, but in improved yield (270 mg, 81%).

5.2.43 7-Hydroxy-7-hydroxymethyl-8-p-menthene (58)

A solution of (57) (166 mg, 1 mmol) in aqueous sulphuric acid (15% w/v, 5 ml) was allowed to stand at room temperature for 2 h.[65] The solution was extracted with ether and the organic extracts washed with aqueous sodium carbonate (10% w/v) and water. After drying of the extracts, removal of the solvent gave 7-hydroxy-7-hydroxymethyl-8-p-menthene (58), $bp_{0.05}$ 75-77°, as a colourless viscous oil (105 mg, 57%). (Found: C, 71.45; H, 11.05. $C_{11}H_{20}O_2$ requires: C, 71.69; H, 10.94%). Ir: ν_{max} 3300 cm^{-1}; nmr: s, 3H, 1.7, =C-CH_3; e, 10H, 0.9-2.0, CH_2, CH; s, exch., 2H, 3.0, OH; m, 3H, 3.5, CH_2-O, CH-O; s, 2H, 4.7, $=CH_2$; ms m/e 166 (M^+-H_2O, 13%).

5.2.44 7-Epoxymethylene-$\Delta^{4,8}$-p-menthene (59)

Boron trifluoride etherate (0.5 ml) was added to a solution of (57) (166 mg, 1 mmol) in ether (5 ml) and the solution was

heated under reflux for 1 h.[26] The solution was then washed with aqueous sodium carbonate (10% w/v) and water, and dried. Removal of the solvent gave 7-epoxymethylene-$\Delta^{4,8}$-p-menthene (59) (111 mg, 67%). Ir: ν_{max} 1680 cm^{-1}; nmr: s, 6H, 1.6, $=C-CH_3$; e, 9H, 0.9-2.0, CH_2, CH; m, 2H, 2.6, CH_2-O; m, 1H, 3.2, CH-O.

5.2.45 4-Acetyl-1-isopropylcyclohexene (60)

Borontrifluoride-acetic acid complex (0.5 ml) was added to a solution of (57) (166 mg, 1 mmol) in acetic acid (5 ml) and the solution was allowed to stand at room temperature for 18 h.[47] It was then diluted with water and extracted with ether. The ether extracts were washed with aqueous sodium carbonate (10% w/v) and water, and dried. Removal of the solvent gave 4-acetyl-1-isopropyl-cyclohexene (60) (120 mg, 72%). Ir: ν_{max} 1710, 1640 cm^{-1}; nmr: d, 6H, 0.9 (7 Hz), CH_3; s, 3H, 2.0, $CO-CH_3$; e, 8H, 1.0-2.2, CH_2, CH; m, 1H, 5.3, =CH; ms m/e 166 (M^+, 7%).

5.2.46 9-Bom-7-hydroxymethyl-p-menthane (61)

Diborane in THF (2.5M, 0.4 ml, 1 mmol) was added to a suspension of lithium borohydride (22 mg, 1 mmol) in THF (5 ml), and to this mixture was added a solution of (57) (166 mg, 1 mmol) in THF (5 ml).[66] The mixture was maintained, with stirring, at 0° for 1 h and then room temperature for 2 h. The mixture was carefully diluted with aqueous sulphuric acid (15% w/v) and

stirred for a further 15 min. The organic layer was separated and washed with aqueous sodium carbonate (10% w/v) and water. After drying, removal of the solvent gave 9-boro-7-hydroxymethyl-p-menthane (61), as a colourless viscous oil (120 mg, 72%). Ir: ν_{max} 3400 cm^{-1}; nmr: e, 16H, 1.0-2.2, CH_3, CH_2, CH; s, exch., 1H, 3.4, OH; t, 2H, 3.6 (6 Hz), CH_2-O; broad d, 2H, 3.9, CH_2-B. Combustion of a small amount of the product gave a green flame, which is also indicative of the presence of boron.

The product was heated under reflux in THF in the presence of 1-decene (280 mg, 2 mmol) and analysed at 30 min intervals by glc (column IV, 150°). After 6 h the only volatile product observed was 1-decene.

5.2.47 7-Hydroxymethyl-p-menthane (62)

To a suspension of lithium aluminium hydride (380 mg, 10 mmol) in ether (10 ml) was added aluminium chloride (1.33 g, 10 mmol), and the mixture was stirred at 4° for 30 min. A solution of (57) (166 mg, 1 mmol) in anhydrous ether (3 ml) was then added, and the mixture stirred and heated under reflux for 3 h. Excess of reagent was then destroyed by the addition of isopropanol and water, and the mixture was acidified with aqueous sulphuric acid (15% w/v). The mixture was extracted with ether and the organic extracts washed with aqueous sodium carbonate

(10% w/v) and water. After drying, removal of the solvent gave 7-hydroxymethyl-p-menthane (62), as a colourless oil (136 mg, 80%). Ir: ν_{max} 3450 cm^{-1}; nmr: dd, 6H, 1.0 (6 Hz), CH_3; e, 13H, 1.3-2.0, CH_2, CH; s, exch., 1H, 2.2, OH; d, 2H, 3.4 (6 Hz), CH_2-O; ms m/e 170 (M^+, 2%).

5.2.48 4-Isopropylacetophenone (64)

Isopropylbenzene (120 g, 1 mol) in n-hexane (200 ml) was added to a stirred suspension of aluminium chloride (267 g, 2 mol) in n-hexane (400 ml), and the mixture was cooled in an ice-salt bath.[67] Acetic anhydride (118 g, 1 mol) was added, with cooling and rapid stirring, over 1 h and the resultant mixture was stirred for a further 3 h. The reaction mixture was then poured onto ice and hydrochloric acid (36% w/v), and extracted with light petroleum. The organic extracts were washed with aqueous sodium bicarbonate solution (5% w/v) and water, and then dried. Removal of the solvent gave a yellow oil, which upon distillation gave two fractions. The first fraction (85 g, 54%) was 4-isopropylacetophenone[69] (64), $bp_{1.0}$ 88-90°. Ir: ν_{max} 1680, 1610 cm^{-1}; nmr: d, 6H, 1.2 (7 Hz), CH_3; s, 3H, 2.5, CO-CH_3; m, 1H, 3.0, CH; m, 4H, 7.5, Ar-H; ms m/e 162 (M^+, 22%). The second fraction (29.5 g, 12%) was 2,4,6-triisopropylacetophenone[67] (65), mp 83-84°. Ir: ν_{max} 1680, 1610 cm^{-1}; nmr: d, 18H, 1.2 (7 Hz), CH_3; s, 3H, 2.5, CO-CH_3; m, 3H, 3.0, CH; s, 2H,

7.3, Ar-H; ms m/e 246 (M^+, 23%).

5.2.49 1-(4-Isopropylphenyl)ethanol (66)

Ketone (64) (50 g, 0.315 mol) in ethanol (100 ml) was added to a stirred suspension of sodium borohydride (13 g, 0.3 mol) in ethanol (100 ml). The mixture was stirred for 1 h and then poured onto ice and sulphuric acid (96%). The mixture was extracted with light petroleum, the extracts dried and the solvent removed. Distillation of the residue gave a colourless oil (50 g, 98%), 1-(4-isopropylphenyl)ethanol[69] (66), $bp_{1.0}$ 95-96°. Ir: ν_{max} 3400 cm^{-1}; nmr: d, 6H, 1.2 (7 Hz), CH_3; d, 3H, 1.3 (6 Hz), CH_3; s, exch., 1H, 2.8, OH; m, 1H, 2.7, CH; q, 1H, 4.6 (6 Hz), CH-O; s, 4H, 7.1, Ar-H; ms m/e 164 (M^+, 34%).

5.2.50 4-Isopropylstyrene (67)

(i) Alcohol (66) (5 g) was heated under reflux in toluene (20 ml), containing a crystal of iodine,[68] for 18 h with azeotropic separation of water. After cooling, the solution was washed thoroughly with aqueous sodium bisulphite (5% w/v) and water, and dried. Distillation of the reaction mixture gave a colourless liquid (1.44 g, 31%), 4-isopropylstyrene[69] (67), $bp_{1.0}$ 44-45°. Ir: ν_{max} 1620 cm^{-1}; nmr: d, 6H, 1.2 (7 Hz), CH_3; m, 1H, 2.8, CH; m, 2H, 5.3, $=CH_2$; m, 1H, 6.6, =CH; m, 4H, 7.2, Ar-H; ms m/e

146 (M^+, 44%).

(ii) Alcohol (66) (10 g) was added dropwise to molten potassium bisulphate (20 g) maintained at 260° and under reduced pressure (80 mm of Hg).[69] Distillate from the reaction mixture was collected and dried, and was identified as 4-isopropylstyrene (67) (7.9 g, 89%), identical in all respects to the product isolated in (i).

5.2.51 2-(4-Isopropylphenyl)ethanol (68)

Olefin (67) (3.75 g, 25 mmol) in anhydrous THF (10 ml) was added to a solution of dicyclohexylborane[70] (25 mmol) in THF at 0° under a nitrogen atmosphere and the solution was maintained at 0° for 15 h. The reaction mixture was then heated to 65° in the presence of aqueous potassium hydroxide (3M, 30 ml) and aqueous hydrogen peroxide (30% w/v, 30 ml), and was maintained at 65° for 3 h. After cooling, the organic layer was separated, washed with water, and dried. Removal of the solvent and distillation of the residue gave a colourless liquid (2.8 g, 68%), 2-(4-isopropylphenyl)-ethanol[70] (68), $bp_{1.0}$ 96-98°. Ir: ν_{max} 3400 cm^{-1}; nmr: d, 6H, 1.2 (7 Hz), CH_3; s, exch., 1H, 1.8, OH; m, 3H, 2.8, CH_2, CH; t, 2H, 3.7 (7 Hz), CH_2-O; s, 4H, 7.1, Ar-H; ms m/e 164 (M^+, 49%).

5.2.52 7-Hydroxymethyl-1,4-p-menthadiene (69)

Alcohol (68) (1.64 g, 10 mmol) in anhydrous ethylamine (20 ml) at -78° under a nitrogen atmosphere was treated with lithium (0.56 g, 0.08 g-atom), added in small pieces over 1 h.[159] The mixture was stirred at -78° for 12 h, and was then allowed to warm to room temperature. The mixture was diluted with water, and then extracted with light petroleum. The extracts were washed thoroughly with water, dried and the solvent removed to give 7-hydroxymethyl-1,4-p-menthadiene (69), $bp_{0.1}$ 80-81°, as a colourless liquid (1.63 g, 98%). Ir: ν_{max} 3380 cm^{-1}; nmr: d, 6H, 1.0 (6 Hz), CH_3; s, exch., 1H, 1.9, OH; m, 3H, 2.2, CH_2, CH; s, 4H, 2.6, ring CH_2; t, 2H, 3.6 (6 Hz), CH_2-O; m, 2H, 5.4, =CH; ms m/e 166 (M^+, 59%).

5.2.53 7-Hydroxymethyl-3-p-menthene (71)

(i) Diene (69) (0.83 g, 5 mmol) in anhydrous THF (10 ml) was added to a stirred solution of thexylborane[14,71] (5 mmol) in THF under a nitrogen atmosphere. The solution was maintained at room temperature for 1 h and then the solvent was removed in vacuo. The residue was dissolved in propionic acid (10 ml) and the solution heated under reflux for 3 h. After cooling, the solution was diluted with water and extracted with ether. The organic extracts were washed with aqueous sodium carbonate (10% w/v) and water, and

then dried. Removal of the solvent gave 7-hydroxymethyl-3-p-menthene (71), $bp_{0.1}$ 78-79°, as a colourless liquid (0.50 g, 60%). Ir: ν_{max} 3400 cm^{-1}; nmr: d, 6H, 1.0 (6 Hz), CH_3; e, 10H, 1.2-2.0, CH_2, CH; s, exch., 1H, 2.2, OH; t, 2H, 3.5 (7 Hz), CH_2-O; m, 1H, 5.5, =CH; ms m/e 168 (M^+, 7%); 3-nitrohydrogenphthalate mp 148-9°. (Found: C, 62.93; H, 6.52; N, 4.10. $C_{19}H_{23}NO_6$ requires: C, 63.14; N, 6.42; H, 3.88%.)

(ii) Diene (69) (0.83 g, 5 mmol) in ethanol (20 ml) was hydrogenated over P-2 nickel catalyst[72] at room temperature and 1 atmosphere until 5 mmoles of hydrogen had been absorbed. The solution was then allowed to stand in air for 15 min and then diluted with water. Extraction with ether gave a colourless oil (0.71 g, 84%) identified as 7-hydroxymethyl-4-p-menthene (71). The spectral characteristics (ir, nmr, ms) of this compound were identical to those of the product isolated in (i).

5.2.54 7-Acetoxymethyl-3-p-menthene (72)

Alcohol (71) (0.84 g, 5 mmol) was dissolved in acetic anhydride (10 ml) and the solution allowed to stand at room temperature for 18 h.[73] It was then carefully diluted with water and extracted with ether. The ether extracts were washed with aqueous sodium carbonate (10% w/v) and water, dried, and the solvent removed to give 7-acetoxymethyl-4-p-menthene (73) (0.96 g, 91%). Ir: ν_{max} 1710 cm^{-1};

nmr: s, 3H, 2.0, CO-CH_3; t, 2H, 4.1 (6 Hz), CH_2-O.

5.2.55 7-Acetoxymethyl-3-oxo-p-menthane (73)

Diborane in THF (1.5 M, 0.70 ml, 1.05 mmol) was added to a stirred solution of (72) (0.21 g, 1 mmol) in anhydrous THF (10 ml) at 0° under a nitrogen atmosphere. The reaction mixture was maintained at 0° for 1 h, and then an aqueous solution of chromic acid[20] (8M, 5 ml) was added, and the mixture was stirred at 0° for a further 24 h. The organic layer was then separated and washed with aqueous sodium carbonate (10% w/v) and water, and then dried. Removal of the solvent gave 7-acetoxymethyl-3-oxo-p-menthane (73), $bp_{0.1}$ 91-92°, as a colourless oil (0.176 g, 78%). (Found: C, 68.69; H, 9.91. $C_{13}H_{22}O_3$ requires: C, 68.99; H, 9.80%). Ir: ν_{max} 1710, 1700 cm^{-1}; nmr: m, 6H, 0.9, CH_3; s, 3H, 2.0, $COCH_3$; e, 11H, 1.2-2.6, CH_2, CH; m, 2H, 4.1, CH_2-O; ms m/e 166 (M^+-CH_3CO_2H, 7%).

5.2.56 7-Hydroxymethyl-3-oxo-p-menthane (74)

Ester (73) (0.226 g, 1 mmol) was allowed to stand in methanolic potassium hydroxide (2M, 3 ml) at room temperature for 18 h. The solution was then diluted with water and extracted with ether. After washing the organic extracts with water, they were dried and the solvent removed to give a colourless oil (0.151 g, 82%), 7-hydroxymethyl-3-oxo-p-menthane (74), $bp_{0.9}$ 77-78°. (Found:

C, 71.65; H, 11.02. $C_{11}H_{20}O_2$ requires: C, 71.69; H, 10.94%) Ir: ν_{max} 3400, 1700 cm^{-1}; nmr: m, 6H, 0.9, CH_3; s, exch., 1H, 1.9, OH; e, 11H, 1.2-2.6, CH_2, CH; m, 2H, 3.4, CH_2-O; ms m/e 184 (M^+, 1%). Glc analysis (columns II and IV, 150°) indicated the presence of two isomers with retention times of 7.8 and 8.4 min, in the ratio 3:2. These products were shown to be identical to those obtained by the hydroboration-cyanidation of myrcene[13] (i.e. compound 14).

5.2.57 3-Hydroxymethyl-6-oxo-7-methyloctanoic acid (75)

Olefin (47) (0.196 g, 1 mmol) in dioxane (20 ml) was added to a stirred solution of potassium periodate (0.75 g), potassium permanganate (0.05 g) and sodium carbonate (0.03 g) in water (20 ml).[74,75] The mixture was stirred at room temperature for 40 h, after which excess reagent was decomposed by the dropwise addition of aqueous hydrogen peroxide (30% w/v, 1 ml). After acidification the mixture was extracted with ether and the organic layer was washed with water and then dried. Removal of the solvent gave a pale yellow oil (0.143 g, 71%), 3-hydroxymethyl-6-oxo-7-methyloctanoic acid (75). (Found: C, 59.29; H, 9.04. $C_{10}H_{18}O_4$ requires: C, 59.38; H, 8.97%) Ir: ν_{max} 2800, 1750, 1710 cm^{-1}; nmr: d, 6H, 0.9 (7 Hz), CH_3; e, 8H, 1.2-2.4, CH_2, CH; broad s, exch., 2H, 3.3, OH, CO_2H; d, 2H, 3.5 (6 Hz), CH_2-O; ms m/e 184 (M^+-H_2O, 7%).

5.2.58 3-Carboxy-6-oxo-7-methyloctanoic acid (76)

Compound (75) (0.202 g, 1 mmol) in acetone (5 ml) was added to an aqueous solution of chromic acid (8M, 5 ml), and the solution was stirred at room temperature for 1 h.[76] Excess reagent was decomposed by the addition of isopropanol (2 ml) and the resultant mixture was diluted with water. Extraction with ether gave a pale yellow syrup (0.137 g, 64%), 3-carboxy-6-oxo-7-methyloctanoic acid (76), $bp_{0.05}$ 128-9° (Found: C, 55.83; H, 7.35. $C_{10}H_{16}O_5$ requires: C, 55.54; H, 7.46%). Ir: ν_{max} 3100, 1760, 1710 cm^{-1}; nmr: d, 6H, 0.9 (7 Hz), CH_3; e, 8H, 1.4-2.4, CH_2, CH; broad s, exch., 2H, 9.1, CO_2H; ms m/e 198 (M^+-H_2O, 1%). These spectral data are identical to those described for compound (19), isolated from the chromic acid oxidation of the hydroboration product of myrcene.[13]

5.2.59 3-Hydroxymethyl-7-methyl-1,6-octanediol (77)

Compound (75) (0.202 g, 1 mmol) in anhydrous ether (5 ml) was added dropwise to a rapidly stirred suspension of lithium aluminium hydride (0.38 g, 10 mmol) in ether (10 ml). After completion of the addition the reaction mixture was refluxed for 1 h, and the excess reagent was destroyed by the dropwise addition of acetone (3 ml). The mixture was acidified with aqueous sulphuric acid (15% w/v) and the organic layer was separated and

washed with water. After drying, the removal of the solvent gave 3-hydroxymethyl-7-methyl-1,6-octanediol (77), as a viscous syrup (0.079 g, 46%), $bp_{0.01}$ 117-120° (Found: C, 63.50; H, 11.55. $C_{10}H_{22}O_3$ requires: C, 63.12; H, 11.65%). Ir: ν_{max} 3400 cm^{-1}; nmr: d, 6H, 0.9 (7 Hz), CH_3; e, 8H, 1.2-2.0, CH_2, CH; broad s, exch., 3H, 2.7, OH; m, 5H, 3.9, CH-O; ms m/e 172 (M^+-H_2O, 3%). Glc analysis (columns III and IV, 100°) of the trimethylsilyl ether of (77) showed it to be identical with compound (10), isolated from the thexyl-hydroboration-cyanidation of myrcene.[13]

5.2.60 1-(N,N-diethylamino)-2,2-dimethylbutan-3-one (81)

A mixture of 3-methylbutan-2-one (8.6 g, 110 mmol), diethylamine hydrochloride (7.95 g, 100 mmol) and aqueous formaldehyde (36% w/v, 77 ml), containing hydrochloric acid (36% w/v, 0.25 ml), was heated under reflux for 3 h, and then cooled and neutralized with aqueous potassium hydroxide (3M).[77] Extraction with ether gave 1-(N,N-diethylamino)-2,2-dimethylbutan-3-one[77] (81), bp_{18} 94-96°, as a colourless liquid (8.9 g, 52%). Ir: ν_{max} 1700 cm^{-1}; nmr: m, 12H, 1.0, CH_3; s, 3H, 2.1, $CO-CH_3$; q, 4H, 2.5 (6 Hz), CH_2-N; ms m/e 171 (M^+, 3%).

5.2.61 1-Chloro-4-methylpentan-3-one (78b)

A suspension of freshly powdered aluminium trichloride

(132 g) in anhydrous dichloromethane (400 ml) was cooled to -15° in an ice-salt bath, and freshly distilled isobutyryl chloride (106.5 g) in dichloromethane (150 ml) was added slowly with rapid stirring.[78,79] The mixture was stirred for 1 h and then ethylene was passed through the mixture for a further 4 h, the temperature being maintained below -10°. The reaction mixture was then poured onto ice and hydrochloric acid (36% w/v) and the organic layer separated and washed thoroughly with water. After drying, removal of the solvent and distillation of the residue gave 1-chloro-4-methylpentan-3-one (78b),[78] bp_{15} 47-50°, as a colourless liquid (73.7 g, 55%). Ir: ν_{max} 1705 cm^{-1}; nmr: d, 6H, 1.1 (7 Hz), CH_3; m, 1H, 2.6, CH; t, 2H, 2.9 (6 Hz), $CO-CH_2$; t, 2H, 3.7 (6 Hz), CH_2-Cl; ms m/e 134/136 (M^+, 9/3%).

5.2.62 Condensation of (78b) with ethylacetoacetate

(i) A solution of ethylacetoacetate (1.56 g, 12 mmol) and sodium (0.23 g, 10 mmol) in ethanol (10 ml) was stirred at room temperature for 15 min.[79] 1-Chloro-4-methylpentan-3-one (78b) (1.06 g, 8 mmol) was then added and the mixture stirred at room temperature for a further 6 h. After acidification with hydrochloric acid (2M), the solution was extracted with ether and the organic extract washed thoroughly with water. The extracts were then dried and the solvent removed to give a yellow oil (0.31 g, 27%), 5-isopropyl-2-carbethoxy-2-(4-methyl-3-oxopentyl)-

cyclohex-5-enone (82), $bp_{0.6}$ 122-123°. (Found: C, 69.78; H, 9.61. $C_{18}H_{28}O_4$ requires: C, 70.10; H, 9.15%). Ir: ν_{max} 1730, 1710, 1670 cm^{-1}; nmr: m, 15H, 1.1, CH_3; e, 10H, 1.3-2.6, CH_2, CH; q, 2H, 4.2 (7 Hz), CH_2-O; s, 1H, 5.8, =CH; ms m/e 308 (M^+, 8%).

Refluxing the reaction mixture for 2 h, instead of allowing it to stand at room temperature for 6 h, gave the same product (ir, nmr) but in higher yield (0.49 g, 40%).

(ii) A solution of ethylacetoacetate (1.30 g, 10 mmol) and potassium t-butoxide (2.24 g, 20 mmol) in t-butanol (40 ml) was stirred for 15 min and then (78b) (1.35 g, 10 mmol) was added and the solution heated under reflux for 3 h. The mixture was acidified with hydrochloric acid and extracted with ether. The organic extracts were washed with water, dried and the solvent removed to give a yellow oil (0.91 g, 59%), identified as (82) (ir, nmr, identical to the product isolated in (i)).

Allowing the solution to stand at room temperature for 16 h, instead of heating under reflux for 3 h, gave the same product (ir, nmr) but in lower yield (0.65 g, 42%).

(iii) Ethylacetoacetate (1.30 g, 10 mmol) and (78b) (1.35 g, 10 mmol) were stirred for 6 h at room temperature in methanolic potassium hydroxide (3M, 20 ml). Acidification and

extraction with ether gave a brown oil, which could not be identified by its ir and nmr spectra.

(iv) Ethylacetoacetate (1.30 g, 10 mmol) was stirred in THF (10 ml) containing a suspension of sodium hydride (0.24 g, 10 mmol) for 15 min, and then (78b) (1.35 g, 10 mmol) was added and the solution was heated under reflux for 3 h. After acidification with hydrochloric acid (2M), the organic layer was separated, washed with water and dried. Removal of the solvent gave a pale yellow oil (0.97 g, 63%) identified as (82). The ir and nmr spectral characteristics were identical to those of the product isolated in (i).

(v) Ethylacetoacetate (1.30 g, 10 mmol), (78b) (1.35 g, 10 mmol) and triethylamine (5 ml) in anhydrous ether (20 ml) were stirred at room temperature for 18 h. The mixture was then acidified with hydrochloric acid (2M), and the organic layer separated, washed with water and dried. Removal of the solvent gave a dark yellow oil (0.48 g, 31%) identified as (82), with spectral characteristics, (ir, nmr) identical to those of the product isolated in (i).

(vi) Chloroketone (78b) (0.135 g, 1 mmol) was added to a stirred solution of ethylacetoacetate (0.130 g, 1 mmol) and potassium t-butoxide (0.112 g, 1 mmol) in dry THF (5 ml). The solution was stirred for 15 min and then acidified with hydrochloric acid. The organic layer was separated, washed with water and dried. Removal

of the solvent gave a colourless oil (0.150 g, 66%), 7-methyl-3-carbethoxy-2,6-octanedione (79), characterized as the bis 2,4-dinitrophenylhydrazone, mp 124-125°. (Found: C, 49.50; H, 4.88; N, 19.85. $C_{24}H_{26}N_8O_{10}$ requires: C, 48.98; H, 4.80; N, 19.04.) Ir: ν_{max} 1730, 1700 cm^{-1}; nmr: d, 6H, 1.0 (7 Hz), CH_3; t, 3H, 1.3 (6 Hz), CH_3; s, 3H, 2.1, CH_3; e, 5H, 1.4-2.6, CH_2, CH; t, 1H, 3.3 (7 Hz), CO-CH-CO; q, 2H, 4.1 (6 Hz), CH_2-O; ms m/e 228 (M^+, 1%). Glc analysis (column VII, 150°) indicated the presence of only one compound with retention time of 6.45 min.

5.2.63 7-Methyl-2,6-octanedione (80)

Compound (79) (0.228 g, 1 mmol) was heated under reflux in hydrobromic acid (48% w/v, 10 ml) for 1 h. The solution was diluted with water and extracted with ether. The organic extracts were washed with water, dried and the solvent removed to give a very pale yellow oil (0.122 g, 79%), 7-methyl-2,6-octanedione (80), $bp_{1.0}$ 64-65°. (Found: C, 69.52; H, 10.28. $C_9H_{16}O_2$ requires: C, 69.19; H, 10.32%). Ir: ν_{max} 1710 cm^{-1}; nmr: d, 6H, 1.0 (7 Hz), CH_3; s, 3H, 2.1, CO-CH_3; e, 7H, 1.2-2.6, CH_2, CH; ms m/e 156 (M^+, 4%). Glc analysis (columns I and IV, 100°) indicated that (80) was the same compound as (20), the product isolated from the chromic acid oxidation of the hydroboration product of myrcene.[13]

5.3 WORK DESCRIBED IN CHAPTER 2

5.3.1 Hydroboration-cyanidation of linalyl acetate (4)

Linalyl acetate (4) (1.96 g, 10 mmol) in dry THF (10 ml) and a solution of diborane in THF (5 ml, 2M, 10 mmol) were added simultaneously over 1 h to dry THF (20 ml) under a dry nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then heated under reflux for a further hour. Sodium cyanide (0.613 g, 12.5 mmol) was then added to the solution, and the mixture was stirred for 1 h at 20°. After the solution had been cooled to -78°, trifluoroacetic acid anhydride (1.71 g, 15 mmol) was introduced and the reaction mixture was allowed to warm to room temperature over 1 h. Oxidation of the product was accomplished by the addition of aqueous potassium hydroxide (10 ml, 3 M) and the subsequent dropwise addition of aqueous hydrogen peroxide (10 ml, 30% w/v). After the mixture had been stirred at 65° for 3 h, the reaction mixture was cooled, and the organic layer was separated. The aqueous phase was extracted with ether (2 x 20 ml) and the combined organic extracts were washed successively with aqueous sodium carbonate (2 x 20 ml, 10% w/v) and saturated aqueous sodium chloride (2 x 20 ml). After drying of the solution, the solvent was removed and the crude product

was distilled to give 2-isopropyl-5-methyl-5-acetoxycycloheptanol (5),[13] $bp_{1.0}$ 74-75°, as a colourless oil (1.23 g, 54%). Ir: ν_{max} 3430, 1730 cm^{-1}; nmr: m, 6H, 0.9, CH_3; s, 3H, 1.4, O-C-CH_3; s, 3H, 2.0, CO-CH_3; e, 10H, 1.5-2.2, CH_2, CH; m, 1H, 3.7, CH-O; s, exch., 1H, 4.0, OH; ms m/e 168 (M^+-CH_3CO_2H, 1%). Glc analysis (column III, 130°; column IV, 100°) indicated the presence of three components with retention times (column IV, 100°) of 7.9, 8.2 and 8.7 min in the ratio 1:2:2. These components had identical retention times to those obtained from the hydroboration-cyanidation of linalyl acetate with thexylborane.[13]

5.3.2 General procedure for the hydroboration-cyanidation of dienes with thexylborane.

A solution of thexylborane in THF[3] (10 ml, 1.0 M, 10 mmol) was added slowly to an ice-cold solution of diene (10 mmol) in dry THF (20 ml) under an atmosphere of dry nitrogen. After completion of the addition, the solution was allowed to stand at room temperature for 1 h and then heated under reflux for a further hour. Sodium cyanide (0.613 g, 12.5 mmol) was then added to the solution, and the mixture was stirred for 1 h at 20°. After the mixture had been cooled to -78°, trifluoroacetic acid anhydride (1.71 g, 15 mmol) was introduced and the reaction mixture was allowed to warm to room temperature over 1 h. Oxidation of the product was accomplished by

the successive addition of aqueous potassium hydroxide (10 ml, 3M) and aqueous hydrogen peroxide (10 ml, 30% w/v). After it was stirred at 65° for 3 h, the reaction mixture was cooled, and the organic layer was separated. The aqueous phase was extracted with ether (2 x 20 ml) and the combined organic extracts were washed successively with aqueous sodium carbonate (2 x 20 ml, 10% w/v) and saturated aqueous sodium chloride (2 x 20 ml). The organic phase was dried, and n-undecane (0.156 g, 1 mmol) was added. The solution was then subjected to analysis by glc, and the reaction products were identified by comparison with authentic samples. Where appropriate, the solvent was removed _in vacuo_ and the crude product was distilled and examined spectroscopically.

(i) 2-Methyl-1,4-pentadiene (88).

Hydroboration-cyanidation of 2-methyl-1,4-pentadiene (88) by the above procedure gave a product, which was not sufficiently volatile for analysis by glc. Removal of solvent and distillation of the crude product gave 2-methyl-1,4-pentanediol[160] (89), bp_{15} 136-138°, as a colourless oil (1.05 g, 89%). Ir: ν_{max} 3400 cm^{-1}; nmr: d, 3H, 0.9 (7 Hz), CH_3; e, 5H, 1.1-1.9, CH_2, CH; s, exch., 2H, 2.7, OH; m, 4H, 3.6, CH_2-O; ms m/e 118 (M^+, 3%). Glc analysis

(column IV) of the trifluoroacetate of (89) showed it to be identical to an authentic sample.

(ii) 2,5-Dimethyl-1,5-hexadiene (90).

Glc analysis (column II, 120°; column IV, 100°) of the product of hydroboration-cyanidation of 2,5-dimethyl-1,5-hexadiene (90) by the procedure described above showed only one product, in 71% yield, identified as 3,6-dimethylcycloheptanone (91) by comparison with an authentic sample.[171]

(iii) 2,6-Dimethyl-1,5-heptadiene (92).

Glc analysis (column IV, 120°) of the product of hydroboration-cyanidation of 2,6-dimethyl-1,5-heptadiene (92) by the procedure described above showed an overall yield of 68% of a 1:4 mixture of isomenthone (93) and menthone (94), the two products being identified by comparison with authentic samples.

(iv) 1,5-Cyclooctadiene (95).

The procedure for (95) was varied slightly. B-Thexyl-9-borabicyclo-[3,3,1]-nonane was prepared by the addition of 2,3-dimethyl-2-butene (0.84 g, 10 mmol) to an ice-cold solution of 9-borabicyclo-[3,3,1]-nonane (1.22 g, 10 mmol) in dry THF (20 ml) under an atmosphere of dry nitrogen. After it had stood at room

temperature for 1 h, the solution was then treated with sodium cyanide (0.613 g, 12.5 mmol), as described above, to give a product which was not sufficiently volatile for analysis by glc. Removal of the solvent gave a viscous oil, which when recrystallized from ether gave colourless needles of cis-1,5-octanediol,[161] mp 74-75° (1.35 g, 94%). Ir: ν_{max} 3380 cm^{-1}; nmr: e, 12H, 1.0-2.0, CH_2; s, exch., 2H, 3.1, OH; m, 2H, 3.8, CH-O; ms m/e 144 (M^+, 9%).

5.3.3 General procedure for the hydroboration-cyanidation of dienes with diborane.

A solution of diborane in THF[3] (5 ml, 2.0M, 10 mmol) was added slowly to an ice-cold solution of diene (10 mmol) in dry THF (20 ml) under an atmosphere of dry nitrogen. After completion of the addition, the solution was allowed to stand at room temperature for 1 h, and then heated under reflux for 1 h. After the solution was cooled to room temperature, cyanidation of the borane intermediates was accomplished as described in section 5.3.2, using sodium cyanide (0.613 g, 12.5 mmol) and trifluoroacetic acid anhydride (1.71 g, 15 mmol).

After oxidation of the cyanidation reaction mixture, small samples (approx. 100 mg) of the products thus obtained were treated with trifluoroacetic acid anhydride (1.0 ml), and then analysed by glc (columns II and IV, 100°).

A modified procedure was also applied to each of the substrates mentioned below, in which excess of trifluoroacetic acid anhydride (3.42 g, 30 mmol) was used, and, after addition of the anhydride, anhydrous pyridine (6.0 ml) was added and the reaction mixture was stirred at 65° for 3 h prior to oxidation. The products obtained by this alternative procedure were in all cases the same as those obtained by the previously described procedure. The yields of products did not vary more than 2% from the stated values, whichever procedure was used.

(i) 2-Methyl-1,4-pentadiene (88) gave 2-methyl-1,4-pentanediol (89) (1.06 g, 90%), identified by glc comparison (columns II, III and IV, 100°) of its trifluoroacetic derivative with that of an authentic sample of the diol.[160]

(ii) 2,5-Dimethyl-1,5-hexadiene (90) gave 2,5-dimethyl-1,6-hexanediol (99), $bp_{1.0}$ 77-79°, as a colourless oil (1.21 g, 83%). Ir: ν_{max} 3450 cm^{-1}; nmr: d, 6H, 0.9 (7Hz), CH_3; e, 6H, 1.2-2.0, CH_2, CH; s, exch., 2H, 3.1, OH; d, 4H, 3.7 (6 Hz), CH_2-O; ms m/e 146 (M^+, 11%). Glc analysis (columns III and IV, 100°) of the trifluoroacetate of (99) showed it to be identical to an authentic sample.[84]

(iii) 2,6-Dimethyl-1,5-heptadiene (92) gave 2,6-dimethyl-1,5-heptanediol (100), $bp_{0.1}$ 88-91°, as a colourless oil (1.36 g, 85%). Ir: ν_{max} 3400 cm^{-1}; nmr: m, 9H, 0.9, CH_3; e, 6H, 1.1-2.1, CH_2, CH; s, exch., 2H, 2.3, OH;

m, 3H, 3.9, CH_2-O, CH-O; ms m/e 160 (M^+, 4%). Glc analysis (columns III and IV, 100°) of the trifluoroacetate of (100) showed it to be identical to an authentic sample.[172]

(iv) 1,5-Cyclooctadiene (95) gave, after recrystallization from pentane, bicyclo-[3,3,1]-nonan-9-one[162] (101), mp 154-156°, as white needles (0.91 g, 66%). Ir: ν_{max} 1695 cm^{-1}; nmr: e, 12H, 1.2-2.2, CH_2; m, 2H, 3.1, CH-CO; ms m/e 138 (M^+, 15%).

5.3.4 General procedure for the hydroboration-cyanidation of olefins with thexylborane.

The procedure followed for monoalkenes was the same as that described in section 5.3.2, except that the diene (10 mmol) was replaced by alkene (20 mmol).

(i) 2-Methyl-2-butene (107) gave 2,3,5,6-tetramethylheptan-4-one (108), $bp_{1.0}$ 57-59°, as a colourless oil (0.87 g, 51%). Ir: ν_{max} 1705 cm^{-1}; nmr: m, 18H, 1.0, CH_3; e, 4H, 1.2-2.3, CH; ms m/e 170 (M^+, 12%). The identity of (108) was further confirmed by glc comparison (column IV, 150°) with an authentic sample.[163]

(ii) Cyclohexene (110) gave dicyclohexylketone (111), $bp_{1.0}$ 101-103°, as a colourless oil (1.30 g, 67%). Ir: ν_{max} 1700 cm^{-1}; nmr: e, 22H, 1.0-2.0, CH_2; m, 2H, 2.4, CH-CO; ms m/e 194 (M^+, 9%). The identity of (111) was further confirmed by glc comparison (column IV, 180°) with

an authentic sample.[164]

(iii) (-)-α-Pinene (113).

Hydroboration-cyanidation of (-)-α-pinene (113) by the above procedure gave (+)-isopinocampheol (114), mp 55-57°, $[\alpha]_D^{20}$ + 30.6° (c, 1 in methanol), as white needles (1.28 g, 83%). The identity of (114) was further confirmed by glc comparison (column IV, 150°) with an authentic sample.[137]

5.3.5 General procedure for the hydroboration-cyanidation of olefins with diborane.

The procedure here was that followed in section 5.3.3, except that the reaction mixture after oxidation was analysed by glc, using n-decane (1 mmol), which was added to the mixture, as an internal standard. Again, alteration of the reaction conditions did not affect the products observed.

(i) 2-Methyl-2-butene (107).

Hydroboration-cyanidation of 2-methyl-2-butene (107) by the above procedure gave 3-methyl-2-butanol (109) (79%), identified by glc comparison (column IV, 100°) with an authentic sample.[3]

(ii) Cyclohexene (110).

Hydroboration-cyanidation of cyclohexene (110) by the above

procedure gave cyclohexanol (112) (82%), identified by glc comparison (column IV, 100°) with an authentic sample.

(iii) (-)-α-Pinene (113).

Hydroboration-cyanidation of (-)-α-pinene (113) by the above procedure gave isopinocampheol (114) (80%), identified by glc comparison (column IV, 150°) with an authentic sample.[137]

5.3.6 General procedure for the cyanidation of trialkylboranes in the absence and presence of sodium aluminium bis-(2-methoxyethoxy)-hydride.

A solution of diborane in THF (2.5 ml, 2.0M, 5 mmol) was added slowly to an ice-cold solution of olefin (15 mmol) in dry THF (10 ml) under an atmosphere of dry nitrogen. After completion of the addition, the solution was allowed to stand at room temperature for 1 h and then subjected to the cyanidation procedure, as described in section 5.3.2, using sodium cyanide (0.32 g, 6.5 mmol) and trifluoroacetic acid anhydride (0.86 g, 7.5 mmol). After oxidation of the reaction mixture with aqueous potassium hydroxide (5 ml, 3M) and aqueous hydrogen peroxide (5 ml, 30% w/v), n-undecane (0.156 g, 1 mmol) was added as an internal standard for glc analysis.

The above procedure was repeated, except that after addition of

the trifluoroacetic acid anhydride, a solution of sodium aluminium bis-(2-methoxyethoxy)hydride (5.05 g, 25 mmol) in dry THF (10 ml) was added, and the solution was heated under reflux for 3 h. Oxidation was then accomplished as above, n-undecane (0.156 g, 1 mmol) was added to the solution, and the reaction mixture was analysed by glc.

(i) Pent-1-ene gave 6-undecanone (116) (69%), identified by glc comparison (column IV, 130°) with an authentic sample.[163] The presence of sodium aluminium bis(2-methoxyethoxy)hydride in the reaction mixture did not change the product distribution, but lowered the yeild to 58%.

(ii) Cyclohexene gave dicyclohexylketone (111) (63%), identified by glc comparison (column IV, 150°) with an authentic sample.[164] The presence of sodium aluminium bis(2-methoxyethoxy)hydride in the reaction mixture did not change the product distribution, but lowered the yield to 59%.

5.3.7 Isolation of cyanidation products from section 5.3.6 (ii).

Hydroboration-cyanidation of cyclohexene was carried out according to the procedure of section 5.3.6, except that instead of oxidation of the reaction mixture, water (2 ml) was added and the solution was diluted with n-pentane (20 ml). The crystalline precipitate thus obtained was removed by filtration and was examined by mass spectrometry.

Analysis of the product obtained in the absence of metal hydride reducing agent gave major mass spectral fragmentation peaks at the following values of m/e:[83] 401, 383, 346, 318, 301, 291, 274, 258, 236, 219, 218, 208, 205, 204.

Analysis of the product obtained in the presence of metal hydride reducing agent gave major mass spectral fragmentation peaks at the following values of m/e: 400, 386, 385, 369, 368, 354, 353, 346, 345, 303, 302, 301, 300, 293, 258, 256, 255, 247, 219, 218, 213, 205, 201.

5.3.8 Aminolysis of cyanidation product from tri-n-pentylborane.

Hydroboration-cyanidation of pent-1-ene was carried out according to the procedure of section 5.3.6, except that instead of oxidation of the reaction mxiture, hydroxylamine-O-sulphonic acid (2.0 g) was added to the mixture as a slurry in dry THF (5 ml). The mixture was heated with stirring at 65° for 16 h and then poured onto ice (40 g). After acidification with hydrochloric acid (35% w/v), the aqueous phase was extracted with ether (2 x 15 ml), n-undecane (0.156 g, 1 mmol) was added to the combined ether extracts, and the solution was analysed by glc (column IV, 130°). 6-Undecanone (116) (35%) was identified, by comparison with an authentic sample,[163] as the only volatile reaction product.

The aqueous extracts were neutralized and extracted with ether (2 x 20 ml), and subjected to analysis by glc (column IV, 200°); no volatile products were found.

5.3.9 General procedure for the cyanidation of borinic acids and methyl esters obtained from dienes.

A solution of diborane in THF (5.0 ml, 2.0M, 10 mmol) was added slowly to an ice-cold solution of diene (10 mmol) in dry THF (20 ml) under an atmosphere of dry nitrogen. After completion of the addition, the solution was allowed to stand at room temperature for 1 h and then heated under reflux for a further hour. After cooling the solution, water (0.18 g, 10 mmol) (or methanol (0.32 g, 10 mmol)) was added and the borinic acid (or methyl ester) thus formed was treated with sodium cyanide (0.613 g, 12.5 mmol) and trifluoroacetic acid anhydride (1.71 g, 15 mmol) as described previously in section 5.3.2. After oxidation of the reaction mixture, the reaction products were examined, as their trifluoroacetate derivatives, by glc (column IV, 100°), and the product identified by comparison with authentic samples. n-Undecane (0.156 g, 1 mmol), added to the total reaction mixture, was used as an internal standard.

(i) 2-Methyl-1,4-pentadiene (88); the borinic acid obtained from 2-methyl-1,4-pentadiene (88) gave 2-methyl-1,4-pentanediol (89) (86%); the methylborinate gave the same product, but in 82% yield.

(ii) 2,5-Dimethyl-1,5-hexadiene (90); the borinic acid obtained from 2,5-dimethyl-1,5-hexadiene (90) gave 2,5-dimethyl-1,6-hexanediol (99) (84%); the methylborinate gave the same product, but in 77% yield.

(iii) 2,6-Dimethyl-1,5-heptadiene (92); the borinic acid obtained from 2,6-dimethyl-1,5-heptadiene (92) gave 2,6-dimethyl-1,5-heptanediol (100) (89%); the methylborinate gave the same product, but in 90% yield.

(iv) 1,5-Cyclooctadiene (95); the borinic acid obtained from 1,5-cyclooctadiene (95) gave cis-1,5-cyclooctanediol (96) (91%); the methylborinate gave the same product, but in 82% yield.

5.3.10 General procedure for the cyanidation of borinic acids and methyl esters obtained from olefins.

A solution of diborane in THF (2.5 ml, 2.0 M, 5 mmol) was added slowly to an ice-cold solution of olefin (10 mmol) in dry THF (10 ml) under an atmosphere of dry nitrogen. After completion of the addition the solution was allowed to stand at room temperature for 1 h. Water (0.09 g, 5 mmol) (or methanol (0.16 g, 5 mmol)) was then added and the

borinic acid (or methyl ester) thus formed was treated with sodium cyanide (0.32 g, 6.5 mmol) and trifluoroacetic acid anhydride (0.86 g, 7.5 mmol), as previously described in section 5.3.2. After oxidation the reaction products were examined by glc (column IV, 130°), and the products identified by comparison with authentic samples. n-Undecane (0.156 g, 1 mmol), added to the total reaction mixture, was used as an internal standard.

(i) 2-Methyl-2-butene (107); the borinic acid obtained from 2-methyl-2-butene (107) gave 3-methyl-2-butanol (109) (83%); the methylborinate gave the same product in identical yield (83%).

(ii) Cyclohexene (110); the borinic acid obtained from cyclohexene (110) gave cyclohexanol (112) (72%); the methyl borinate gave the same product in 70% yield.

(iii) (-)-α-Pinene (113); the borinic acid obtained from (-)-α-pinene (113) gave isopinocampheol (114) (74%); the methylborinate gave the same product in 78% yield.

5.3.11 Cyanidation of borinic acids and esters under forcing conditions.

Each of the reactions described in sections 5.3.9 and 5.3.10 was repeated under the forcing conditions described in section 5.3.3 (viz. using 3.0 equivalents of trifluoroacetic acid anhydride in the

cyanidation procedure, addition of pyridine as a co-solvent for the reaction, and heating the reaction mixture at 65° for 3 h prior to oxidation). In no case did the product distributions alter, and in only one case (α-pinene) did the yield of products vary by more than 2%. (Note: in the case of α-pinene, the yield of isopinocampheol derived from the methylborinate decreased to 69%).

5.4 WORK DESCRIBED IN CHAPTER 3.

5.4.1 General procedure for the hydroboration-silver (I) oxidation of dienes.

Diborane in THF (5 ml, 2.0 M, 10 mmol) was added slowly over 30 min with stirring to an ice-cold solution of the diene (10 mmol) in dry THF (15 ml) under a dry nitrogen atmosphere. The solution was maintained at 0° for 2 h and then allowed to warm to room temperature. Methanolic potassium hydroxide (20 ml, 2M, 50 mmol) was added slowly, followed by aqueous silver nitrate (7.5 ml, 5M, 37.5 mmol). The mixture was stirred for 1 h at room temperature and then filtered. The organic layer was separated and the aqueous phase extracted with THF (2 x 10 ml). n-Undecane (0.156 g, 1 mmol) was added to the combined organic extracts, which were then analysed by glc.

(i) 2,5-Dimethyl-2,4-hexadiene gave cis-2,5-dimethyl-3-hexene (89%), identified by glc comparison (column V, 100°) with an authentic sample.[173]

(ii) 2-Methyl-2,4-pentadiene gave 2-methyl-2-pentene (63%), identified by glc comparison (column V, 60°) with an authentic sample.[174]

(iii) 2,3-Dimethyl-1,3-butadiene gave trans-1,2-dimethylcyclobutane (79%), identified by glc comparison (column IV, 60°) with an authentic

sample.[175]

(iv) 2-Methyl-1,4-pentadiene gave methylcyclopentane (85%), identified by glc comparison (column I, 70°) with an authentic sample.[170]

(v) 1,5-Hexadiene gave cyclohexane (66%) and methylcyclopentane (17%),† identified by glc comparison (column I, 100°) with authentic samples.[170]

(vi) 2,5-Dimethyl-1,5-hexadiene gave trans-1,4-dimethylcyclohexane (49%) and cis-1,4-dimethylcyclohexane (33%), identified by glc comparison (column I, 100°) with authentic samples.[168]

(vii) 1,6-Heptadiene gave cycloheptane (67%), identified by glc comparison (column V, 120°) with an authentic sample.

(viii) 1,7-Octadiene gave cyclooctane (42%), identified by glc comparison (column V, 120°) with an authentic sample.

(ix) 1,5-Cyclooctadiene, which had been thermally isomerized to 9-borabicyclo-[3,3,1]-nonane after hydroboration, gave cis-bicyclo-[3,3,0]-octane (19%), cis-cyclooctene (19%) and cyclooctanone (43%), identified by glc comparison (column IV, 80°) with authentic samples.[176]

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† These product ratios were unaffected by heating the intermediate borane for 1 h at 65° prior to Ag (I) oxidation.

(x) Bicyclo-[2,2,1]-heptadiene gave no volatile products, but gave a polymeric material which was soluble in organic solvents (THF, ether, chloroform).

5.4.2 Determination of positions of hydroboration of bicyclo-[2,2,1]-heptadiene.

Bicyclo-[2,2,1]-heptadiene (151) (0.92 g, 10 mmol) was treated with diborane in THF (5 ml, 2M, 10 mmol) as described in section 5.4.1. The borane thus obtained was subjected to oxidation by the method of Brown and Garg[18] with aqueous chromic acid (30 ml, 1M, 30 mmol). This gave a mixture of bicyclo-[2,2,1]-heptan-2,6-dione (154) and bicyclo-[2,2,1]-heptan-2,5-dione (155), identified by glc comparison (column IV, 120°) with authentic samples. The diones were found to be in the ratio (154):(155) = 2:1, and this was further confirmed by the nmr spectrum of the mixture. The bridgehead hydrogen atoms adjacent to the carbonyl groups resonate at δ = 4.1 for (154) and δ = 3.2 for (155), and these resonances were in the ratio 2:1.

5.4.3 General procedure for the hydroboration-silver (I) oxidation of olefins.

Diborane in THF (2.5 ml, 2.0 M, 5 mmol) was added slowly over 30 min with stirring to an ice-cold solution of the olefin (10 mmol)

in dry THF (10 ml) under a dry nitrogen atmosphere. The solution was maintained at 0° for 2 h and then was allowed to warm to room temperature. Methanolic potassium hydroxide (10 ml, 2M, 20 mmol) was added slowly, followed by aqueous silver nitrate (4 ml, 5M, 20 mmol). The mixture was stirred for 1 h at room temperature and then filtered. The organic layer was separated and the aqueous phase extracted with THF (2 x 5 ml). n-Undecane (0.156 g, 1 mmol) was added to the combined organic extracts, which were then analysed by glc.

(i) Cyclohexene gave dicyclohexyl (41%), identified by glc comparison (column IV, 130°) with an authentic sample.[169]

(ii) 1-Hexene gave n-dodecane (61%), identified by glc comparison (column IV, 150°) with an authentic sample.

5.4.4 Hydroboration-silver (I) oxidation of dienes and olefins in the presence of hydrogen atom donors.

(i) 2,5-Dimethyl-1,5-hexadiene

2,5-Dimethyl-1,5-hexadiene was subjected to the procedure described in section 5.4.1, except that, prior to oxidation with alkaline silver nitrate, hydrogen atom donor† (50 mmol) was added.

† Hydrogen atom donors used were: isopropanol, 1-phenylethanol, n-butanethiol, tri-n-butylstannane.

Glc analysis (columns I and V, 100°) of the reaction mixture indicated the presence of both cis- and trans-1,4-dimethylcyclohexane, consistently in the ratio 2:3, as the only volatile reaction products, and the total yield of volatile products was in the range 65-67%.

(ii) Cyclohexene

Cyclohexene was subjected to the procedure described in section 5.4.3, except that, prior to oxidation with alkaline silver nitrate, hydrogen atom donor† (25 mmol) was added. Glc analysis (column IV, 130°) of the reaction mixture indicated the presence of dicyclohexyl as the only volatile reaction product in yield of 30-40%. In the presence of tri-n-butylstannane, a small yield (5%) of cyclohexane was also observed.

(iii) 1-Hexene

1-Hexene was subjected to the procedure described in section 5.4.3, except that, prior to oxidation with alkaline silver nitrate, hydrogen atom donor† (25 mmol) was added. Glc analysis (column IV, 150°) of the

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† Hydrogen atom donors used were: isopropanol, 1-phenylethanol, n-butanethiol, tri-n-butylstannane.

reaction mixture indicated the presence of n-dodecane as the only volatile reaction product in yields of 55-65%. In the presence of tri-n-butylstannane, a small yield (5%) of n-hexane was also observed.

5.5 WORK DESCRIBED IN CHAPTER 4

5.5.1 3,5,5-Trimethylcyclohexanone (171)

3,5,5-Trimethylcyclohex-2-enone (180) (69 g, 0.5 mole) was hydrogenated at 50 psi over palladium on carbon for 24 h in ethanol (300 ml) to give 3,5,5-trimethylcyclohexanone[166] (171), bp_{30} 93-94°, as a colourless liquid (69.3 g, 99%). Ir: ν_{max} 1705 cm^{-1}; nmr: m, 9H, 1.0, CH_3; s, 2H, 2.0, CH_2-CO; e, 5H, 1.4-2.4, CH_2, CH; ms m/e 140 (M^+, 30%).

5.5.2 4,4,6-Trimethylcaprolactam (167) and 4,6,6-trimethylcaprolactam (168)

Ketone (171) (14.0 g, 0.1 mole) was dissolved in polyphosphoric acid (200 g) and sodium azide (6.8 g, 0.105 mole) was added in small portions over 1 h with slow agitation. The temperature of the reaction mixture was then slowly raised to 50° and was maintained at this level for 16 h. The mixture was then poured onto crushed ice (1 Kg) and was neutralized with solid sodium hydroxide. The mixture was extracted with dichbromethane (3 x 300 ml) and the extracts were washed with saturated aqueous sodium bicarbonate (2 x 400 ml). After drying of the solution, removal of the solvent gave a straw-coloured microcrystalline solid (14.3 g).

Recrystallization of the crude reaction product from light petroleum gave 4,4,6-trimethylcaprolactam[139] (167), m.p. 110-111°, as

colourless prisms (6.80 g, 44%). Ir: ν_{max} 3200, 3070, 1670 cm^{-1}; nmr: m, 9H, 0.9, CH_3; e, 5H, 1.2-2.6, CH_2, CH; dd, 2H, 2.9, CH_2-CO; s, 1H, 8.0, NH; ms m/e 155 (M^+, 17%).

Evaporation of the mother liquors from the above recrystallization gave 4,6,6-trimethylcaprolactam[139] (168), mp 109-110°, as colourless needles (7.40,g, 48%). Ir: ν_{max} 3220, 1665 cm^{-1}; nmr: m, 9H, 0.9, CH_3; e, 7H, 1.2-3.4, CH_2, CH; s, 1H, 7.9, NH; ms m/e 155 (M^+, 12%).

5.5.3 O-Methyl-4,6,6-trimethylcaprolactim (182).

Lactam (168) (1.55 g, 10 mmol) was heated under reflux with dimethylsulphate (1.14 g, 10 mmol) in dry benzene (20 ml) for 16 h. The organic solution was then washed with aqueous sodium carbonate (2 x 20 ml, 10% w/v) and dried. Removal of the solvent gave O-methyl-4,6,6-trimethylcaprolactim (182) as a pale yellow oil (1.60 g, 96%). Ir: ν_{max} 2200 cm^{-1}; nmr: m, 9H, 0.9, CH_3; e, 7H, 1.2-3.3, CH_2, CH; s, 3H, 3.5, OCH_3. The lactim was used in 5.5.4 without further purification.

5.5.4 Hydrolysis of (182).

The lactim (182) (0.835 g, 5 mmol), from 5.5.3 above, was heated under reflux in water (20 ml) for 90 min. The aqueous mixture was then washed with dichloromethane (2 x 15 ml), and the

water removed in vacuo to give a straw-coloured residue (0.08 g), which could not be identified from its spectral (ir, nmr) properties.

Evaporation of the dichloromethane washings gave 4,6,6-trimethylcaprolactam (0.70 g, 90%).

5.5.5 6-Amino-3,5,5-trimethylhexanoic acid (170)

Sulphuric acid (2.94 g, 98% w/v) was added to a solution of lactam (168) (1.55 g, 10 mmol) in water (20 ml) and the solution was heated under reflux for 7 h. After cooling of the solution, barium hydroxide (9.2 g) was added in one portion and the mixture allowed to stand for 18 h at room temperature. After adjusting the pH of the solution to 4-5, the precipitated barium sulphate was removed by filtration and was washed with water (50 ml). The aqueous washings were concentrated in vacuo, and the residue triturated with ether. 6-Amino-3,5,5-trimethylhexanoic acid[139] (170), mp 149-151°, was obtained as a powdery, white solid (1.15 g, 67%). Ir: ν_{max} 3100, 2600, 1710, 1690 cm^{-1}; nmr (D_2O): s, 6H, 0.9, $C(CH_3)_2$; d, 3H, 1.1 (7Hz), $C-CH_3$; m, 3H, 1.8, CH_2, CH; d, 2H, 2.2 (7 Hz), CH_2-CO_2; s, 2H, 2.8, CH_2-N.

5.5.6 6-Amino-3,3,5-trimethylhexanoic acid (169).

Lactam (167) (0.835 g, 5 mmol) was subjected to the procedure described in 5.5.5 to give 6-amino-3,3,5-trimethylhexanoic acid[139]

(169), mp 181-182°, as colourless plates (0.52 g, 60%). Ir: ν_{max} 3150, 2600, 1710, 1695 cm^{-1}; nmr (D_2O): s, 6H, 0.9, $C(CH_3)_2$; d, 3H, 1.0 (6 Hz), $C-CH_3$; m, 3H, 1.7, CH_2, CH; s, 2H, 2.1, CH_2-CO_2; d, 2H, 2.8 (7 Hz), CH_2-N.

5.5.7 Strychnine salts of (169) and (170).

Strychnine (183) (0.334 g, 1 mmol) was dissolved in refluxing acetone, and amino acid (169) (0.173 g, 1 mmol) was added. When all solids had dissolved the solution was allowed to cool, and a precipitate of the strychnine salt of (169) was formed. This precipitate of strychnine removed by filtration. The filtrate was evaporated to dryness to give the amino acid (0.051 g) ($[\alpha]_D^{20} = 0°$, C = 0.51 in methanol).

The procedure was repeated using ethanol, isopropanol, and ethyl acetate, and various mixtures of these solvents with ether and chloroform. In cases where precipitation of the strychnine salt was observed, the amino acid liberated by the above-mentioned procedure was racemic.

This procedure was also attempted with amino acid (170), but again no resolution of the optical isomers was found to occur.

5.5.8 Cinchonine salts of (169) and (170).

The entire procedure described in 5.5.7 was repeated using

cinchonine (184) (0.294 g, 1 mmol) and each of the amino acids (169) and (170) (0.173 g, 1 mmol), but in no case was resolution of the optical isomers of either amino acid observed.

5.5.9 cis-d,l-3,3,5-Trimethylcyclohexanol (185)

3,5,5-Trimethylcyclohex-2-enone (180) (2.0 g, 14.5 mmol), ethanol (30 ml) and dry ether (15 ml) were added to dry, distilled ammonia (150 ml), and sodium (4.6 g, 200 mmol) was then added in small pieces over 30 mins. When the blue colour of the reaction mixture had disappeared the ammonia was allowed to evaporate and the residue was diluted with water (300 ml) and acidified with aqueous hydrochloric acid (35% w/v). Extraction of the residue with ether and distillation of the crude product gave cis-d,l-3,3,5-trimethylcyclohexanol[142] (185), bp_{17} 104-105°, as a colourless liquid which slowly crystallized at room temperature (2.02 g, 98%). Ir: ν_{max} 3350 cm^{-1}; nmr: m, 9H, 0.9, CH_3; s, exch., 1H, 1.5, OH; e, 7H, 1.1-2.1, CH_2, CH; m, 1H, 3.8, CH-O; ms m/e 124 (M^+-H_2O, 10%).

5.5.10 Hydrogen phthalate ester of (185).

The alcohol (185) (2.02 g, 14.2 mmol) was dissolved in dry pyridine (6 ml) and phthalic anhydride (2.12 g, 14.2 mmol) was added to the stirred solution. The mixture was heated at 110° for 40 min

and was then dissolved in an equal volume of acetone. After acidification with aqueous hydrochloric acid (35% w/v), ice was added and the mixture was stirred for 30 min. The precipitated product was collected and recrystallized from hexane to give cis-d,1-3,3,5-trimethylcyclohexylhydrogen phthalate (186), mp 117-119°, as white, crystalline flakes (4.14 g, 100%). Ir: ν_{max} 2700, 1730, 1695 cm^{-1}; nmr: m, 9H, 1.0, CH_3; e, 7H, 1.2-2.3, CH_2, CH; m, 1H, 5.2, CH-OCO; m, 4H, 7.7, Ar-H; s, exch., 1H, 10.3, CO_2H; ms m/e 148 (M^+-$(CH_3)_3C_6H_8OH$, 12%).

5.5.11 Strychnine salt of (186)

Reaction of strychnine (183) (0.334 g, 1 mmol) with the half-ester (186) (0.290 g, 1 mmol), by the procedure described in section 5.5.7, gave a precipitate of the strychnine salt of (186) (0.296 g). This precipitate was dissolved in aqueous hydrochloric acid (10% w/v) to give the hydrogen phthalate (0.101 g) ($[\alpha]_D^{20} = 0°$, C = 0.10 in chloroform).

The procedure was repeated using ethanol, isopropanol, ethyl acetate and various mixtures of these solvents with chloroform. In cases where precipitation of the strychnine salt was observed, the hydrogen phthalate ester liberated by the above-mentioned procedure was found to be racemic.

This procedure was repeated using cinchonine (184), quinine (187) and brucine (188) in place of strychnine, but in no case was resolution of (186) achieved.

5.5.12 Attempted yeast reduction of (180)

To a stirred mixture of actively fermenting yeast (120 g) and glucose (100 g) in water (1 l) at 35° was added, over 2 h, a solution of 3,5,5-trimethylcyclohex-2-enone (6.9 g, 50 mmol) in ethanol (10 ml). After stirring at 35° for 24 h, the mixture was steam distilled and the distillate extracted with dichloromethane. The extracts were dried and the solvent removed to give a colourless liquid (6.5 g), identified as starting material.

5.5.13 3,5,5-Trimethylcyclohexanone diethyltartrate acetal (192)

3,5,5-Trimethylcyclohexanone (171) (14.0 g, 0.1 mole) was added to a solution of diethyl tartrate (20.6 g, 0.1 mole) in benzene (200 ml) containing N,N-dimethylformamide (20 ml) and p-toluenesulphonic acid (0.2 g), and the solution was heated under reflux, with separation of evolved water, for 24 h. The solution was then washed with aqueous sodium carbonate (2 x 100 ml, 10% w/v), dried and the solvent removed. Distillation of the crude product gave 3,5,5-trimethylcyclohexanone diethyltartrate acetal[146] (192), $bp_{1.0}$ 120-125°, as a colourless oil

(29.5 g, 90%). Ir: ν_{max} 1760, 1740 cm^{-1}; nmr: m, 9H, 0.9, CH_3; t, 6H, 1.3 (7 Hz), CH_3-C-OCO; e, 7H, 1.0-2.1, CH_2, CH; q, 4H, 4.3 (7 Hz), CH_2-OCO; apparent d, 2H, 4.8 (3 Hz), O-CH-CO_2; ms m/e 328 (M^+, 6%).

Glc analysis of (192) on columns I, V, IX, and X showed only partial resolution of two components on column IX only. Preparative glc on column IX, with flow rate of 120 ml/min at 250°, gave (192a) (0.131 g), having $[\alpha]_d^{20}$ = -22.14° (C = 1.31, C_2H_5OH), and (192b) (0.094 g), having $[\alpha]_d^{20}$ = 09.36° (C = 0.94, C_2H_5OH).

Each of these products was dissolved in a mixture of ethanol (4 ml) and aqueous hydrochloric acid (4 ml, 2N), and the solutions were allowed to stand at room temperature for 48 h. Extraction of the reaction mixtures with ether gave (171a) (0.035 g), having $[\alpha]_D^{20}$ = -8.89° (C = 1.75, n-hexane), and (171b) (0.019 g), having $[\alpha]_D^{20}$ = +7.21° (C = 1.90, n-hexane). The identity of each product was confirmed by glc comparison (column II, 130°) with racemic (171).

The optical rotatory dispersion data for (171a) are recorded in Table 7 (section 4.3).

5.5.14 6,7-Dihydro-4,6,6-trimethyl-5H-azepinone (178).

3,5,5-Trimethylcyclohex-2-enone (180) (13.8 g, 0.1 mole) was treated with sodium azide (6.8 g, 0.105 mole) in polyphosphoric acid

as described in section 5.5.2, to give a crude product (15.1 g, 99%), which when recrystallized from n-hexane gave pure 6,7-dihydro-4,6,6-trimethyl-5H-azepinone[138] (178), mp 111-112°, as colourless needles (8.7 g, 57%). Ir: ν_{max} 3160, 1660, 1620 cm^{-1}; nmr: s, 6H, 1.0, CH_3; s, 3H, 1.9, =C-CH_3; s, 2H, 2.1, =C-CH_2; d, 2H, 2.9 (6Hz), CH_2-N; s, 1H, 5.8, =CH; s, 1H, 7.3, NH; ms m/e 153 (M^+, 8%).

5.5.15 Hydroboration of (178) with (+)-diisopinocampheylborane (178).

(+)-Diisopinocampheylborane[137] (175) (10 mmol) was prepared in dry THF (10 ml) from (-)-α-pinene (2.72 g, 20 mmol) and diborane in THF (5 ml, 2.0 M, 10 mmol). To this mixture was added a solution of lactam (178) (0.77 g, 5 mmol) in dry THF (5 ml). The solution was allowed to stand at room temperature for 2 h, and the solvent was then removed in vacuo. The residue was heated under reflux in propionic acid (10 ml) under a dry nitrogen atmosphere for 2h. After cooling of the reaction mixture, it was diluted with water (30 ml) and extracted with ether (2 x 15 ml). After washing the ether extracts with water (2 x 20 ml) and saturated aqueous sodium bicarbonate (2 x 20 ml), removal of the solvent gave a sticky residue, which was washed with n-hexane to give an unidentified white, crystalline solid (0.47 g); this product appeared to contain boron (burnt with the characteristic green flame of boron containing compounds).

Evaporation of the hexane washings gave white needles of (178) (0.39 g).

5.5.16 3,5,5-Trimethylcyclohex-2-enol.

Lithium aluminium hydride (3.8 g, 0.10 mole) was suspended in dry ether (100 ml) under an atmosphere of dry nitrogen. 3,5,5-Trimethylcyclohex-2-enone (20.7 g, 0.15 mole) in dry ether (100 ml) was added slowly so as to maintain a gentle reflux of the reaction mixture. After completion of the addition, the mixture was heated under reflux for a further 1 h. Excess of the reagent was decomposed by the cautious addition of water (16 ml), and then aqueous sodium hydroxide (4 ml, 10% w/v). After stirring of the mixture for 10 min., the precipitated lithium salts were removed by filtration, the solution dried and the solvent removed. Distillation of the crude product gave 3,5,5-trimethylcyclohex-2-enol,[167] bp_{10} 92-94°, as a colourless oil (19.3 g, 92%). Ir: ν_{max} 3330, 1670 cm^{-1}; nmr: s, 6H, 0.9, CH_3; s, 3H, 1.7, $=C-CH_3$; s, exch., 1H, 3.2, OH; e, 4H, 1.1-2.1, CH_2, $=C-CH_2$; m, 1H, 4.0, CH-O; m, 1H, 5.4, =CH; ms m/e 140 (M^+, 13%).

5.5.17 3,5,5-Trimethylcyclohex-2-enylpropionate (197)

Alcohol (197) (1.40 g, 10 mmol) was dissolved in dry pyridine

(10 ml) and propionyl chloride (0.93 g, 10 mmol) was added dropwise with stirring. After completion of the addition, the mixture was stirred for 30 min. and then was poured onto ice. Extraction of the mixture with light petroleum gave 3,5,5-trimethylcyclohex-2-enylpropionate (197), bp_{10} 106-107°, as a colourless oil (1.72 g, 87%). Ir: ν_{max} 1720, 1670 cm^{-1}; nmr: m, 9H, 1.0, CH_3; s, 3H, 1.7, $=C-CH_3$; t, 2H, 2.3 (7 Hz), CH_2CO_2; e, 4H, 1.1-2.2, CH_2, $=C-CH_2$; m, 1H, 4.8, CH-OCO; m, 1H, 5.4, =CH; ms m/e 196 (M^+, 2%).

5.5.18 Hydroboration of (180) with (+)-diisocampheylborane (175).

(+)-Diisopinocampheylborane[137] (175) (20 mmol) was prepared in dry THF (20 ml) from (-)-α-pinene (5.44 g, 40 mmol) and diborane in THF (10 ml, 2.0 M, 20 mmol). To this solution was added a solution of ketone (180) (1.38 g, 10 mmol) in dry THF (10 ml). The solution was allowed to stand at room temperature for 2 h, and the solvent was then removed in vacuo. The residue was dissolved in propionic acid (20 ml) and this solution was heated under reflux for 3 h under a nitrogen atmosphere. After it had cooled, the reaction mixture was diluted with water (50 ml) and was extracted with ether (2 x 25 ml). After washing the ether extracts with water (2 x 40 ml) and saturated aqueous sodium bicarbonate (2 x 30 ml), removal of the solvent gave 3,5,5-trimethylcyclohex-2-enyl propionate (197), bp_{10} 106-107°, as a colourless oil (1.64 g, 83%). This product was identical in all

respects to that prepared in section 5.5.17 above.

5.5.19 3,5,5-Trimethylcyclohex-2-enyl acetate (202).

Acetic anhydride (15.4 g, 0.15 mole) was added dropwise with rapid stirring to a solution of 3,5,5-trimethylcyclohex-2-enol (14.0 g, 0.10 mole) in dry pyridine (100 ml), and the resultant solution was stirred at room temperature for 16 h. The reaction mixture was then poured cautiously onto ice and extracted with light petroleum. After washing the organic layer with saturated aqueous sodium bicarbonate solution, the solvent was removed and the crude product distilled to give 3,5,5-trimethylcyclohex-2-enyl acetate[156] (202), bp_{10} 92-94°, as a colourless liquid (15.1 g, 83%). Ir: ν_{max} 1730, 1670 cm^{-1}; nmr: m, 6H, 1.0, CH_3; s, 3H, 1.7, $=C-CH_3$; s, 3H, 2.0, CH_3CO_2; e, 4H, 1.1-2.0, CH_2, $=C-CH_2$; m, 1H, 5.0, CH-OCO; m, 1H, 5.4, =CH; ms m/e 182 (M^+, 3%).

5.5.20 Hydroboration of (202) with (+)-diisopinocampheylborane (175).

(+)-Diisopinocampheylborane[137] (175) (40 mmol) was prepared in dry THF (20 ml) from (-)-α-pinene (0.88 g, 80 mmol) and diborane in THF (20 ml, 2.0 M, 40 mmol). To this solution was added a solution of (202) (1.82 g, 10 mmol) in dry THF (10 ml). The solution was heated under reflux for 12 h under a nitrogen atmosphere, and then

oxidised by the addition of aqueous potassium hydroxide (30 ml, 3M) and aqueous hydrogen peroxide (30 ml, 30% w/v). The organic layer was then separated and the aqueous phase extracted with ether (2 x 30 ml). The combined organic extracts were dried and the solvent was removed. Distillation of the crude product thus obtained gave 3,5,5-trimethylcyclohexanol[142] (199), $bp_{1.0}$ 45-47°, as a colourless, viscous oil (0.224 g, 16%), with spectral data identical to that described for (172). Glc examination (column IV, 130°) indicated the presence of mainly the cis-isomer (90%) with only minor amounts of the trans-isomer (10%).

5.5.21 Oxidation of (199)

The alcohol (199) (0.224 g, 1.58 mmol) was dissolved in ether (5 ml), and to this solution was added an aqueous solution of chromic acid (0.8 ml, 2M, 1.6 mmol). The mixture was stirred for 30 min, and then the organic layer was separated and washed with saturated aqueous sodium bicarbonate solution (3 x 5 ml). Removal of the solvent gave 3,5,5-trimethylcyclohexanone (171) (0.176 g, 80%), having $[\alpha]_D^{20}$ = +2.3° (C = 2.0, chloroform). The spectral data for this product were identical to those of the product obtained in section 5.5.1 above, and glc comparison (columns III and IV, 130°) indicated it to be identical to the racemic ketone.

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CYCLIZATION OF DIENES VIA HYDROBORATION: SILVER ION INDUCED INTRAMOLECULAR ALKYL COUPLING

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The cyclization of dienes or polyenes is a synthetically useful process, and has been achieved in a number of ways, among which the most widely used are thermal rearrangements,[1] cyclizations induced by protic or Lewis acids,[2] transition metals[3] or by radical means.[4] The type of cyclized product depends on the method used. We wish to report a further method of cyclization, based on the silver ion induced oxidation of organoboranes.

The coupling of hydroborated olefins *in situ* by alkaline silver nitrate[5,6] has proved a synthetically valuable procedure for the conversion of branched and unbranched olefins into symmetrical hydrocarbons (Scheme 1). Transalkylation from boron to silver is believed[7] to generate unstable alkyl silver intermediates, which decompose to give radical species. These may then undergo normal radical coupling.

$$R_3B \xrightarrow[\text{Base}]{AgNO_3} [R{-}Ag] \longrightarrow R^{\cdot} \xrightarrow{R^{\cdot}} R{-}R \qquad \text{(Scheme 1)}$$

The proximity of the radical centres generated in this manner from hydroborated dienes should favour intramolecular coupling. Thus it was expected that dienes would yield mainly cyclized products, and these expectations have generally been realized (Table).

TABLE

Products of Reaction of Dienes with Diborane Followed by Alkaline Silver Nitrate

Diene	Cyclic Products[a]	Yield (%)[b]
2,3-Dimethyl-1,3-butadiene	trans-Dimethylcyclobutane[c,d]	79
2-Methyl-1,4-pentadiene	Methyl cyclopentane	85
1,5-Hexadiene	Cyclohexane[e]	66
	Methylcyclopentane[e]	17
2,5-Dimethyl-1,5-hexadiene	1,4-Dimethylcyclohexane, trans	49
	cis	33
1,6-Heptadiene	Cycloheptane	67
1,7-Octadiene	Cyclooctane	42
1,5-Cyclooctadiene[f]	cis-[3,3,0]-Bicyclooctane[c]	19
	Cyclooctene	19
	Cyclooctanone[g]	43
Geranyl acetate	trans-p-Menthane	83
Linalyl acetate	1-Hydroxy-p-menthane, trans	36
	cis	36

[a] Products were identified by g.l.c. comparison (Carbowax 20M; Silicon XE-60) with authentic samples.

[b] Yields were determined by g.l.c. using n-undecane as internal standard.

[c] Characterized by g.l.c.-mass spectrometry.

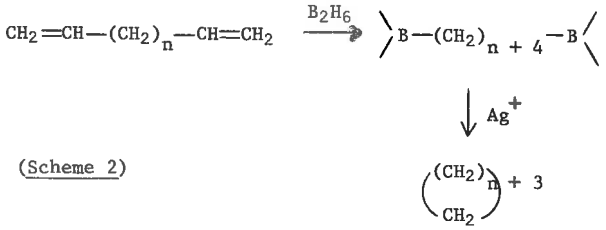
[d] Propylene was identified as a minor product, formed by fragmentation of the diradical intermediate.

[e] Product composition was unaffected by heating the intermediate borane at 65° for 1 h.

[f] The equilibrated hydroboration product, 9-borabicyclo-[3,3,1]-nonane[8] was used.

[g] The origin of this product is under investigation.

Although the hydroboration of dienes is complex, giving rise to mixtures of cyclic and acyclic boranes,[9] there is no requirement in this reaction for the borane to be cyclic. This is shown by the reaction of 1,5-hexadiene (Table). Brown[10] has shown that this yields mainly polymeric borane at 0°, which slowly rearranges to the cyclic borepane at 65°. Treatment of hydroborated 1,5-hexadiene before and after isomerization, however, gives identical products. This suggests that, although boron prefers to form 5,6 and 7-membered rings, the cyclization should be capable of extension to larger rings (Scheme 2).



(Scheme 2)

This is illustrated in the products obtained from 1,6-heptadiene and 1,7-octadiene. The product distributions follow the trends observed for the position of hydroboration of the dienes.[11] We believe the reason for the exclusive terminal cyclization in the case of heptadiene and octadiene is that hydroboration of both double bonds occurs essentially independently, and only in cases where cyclic borane formation is thermodynamically favourable will non-terminal cyclization products arise. The product observed from geranyl acetate arises as a result of cis-elimination[12] within the first-formed cyclic borane.[13] This results in generation of a terminal olefin, which undergoes intramolecular hydroboration to give a seven-membered cyclic borane.

A typical procedure is as follows. The diene (10 mmole) in THF (15 ml) under a nitrogen atmosphere was cooled to 0°. Diborane (10 mmole) in THF was added slowly over 30 min. with vigorous stirring. The solution was maintained at 0° for 2 h and then allowed to warm to room temperature. Methanolic potassium hydroxide (2M, 20 ml) was added slowly, followed by aqueous silver nitrate (5M, 7.5 ml). The mixture was stirred for 1 h at room temperature, centrifuged and the clear supernatant analysed by g.l.c. Products were isolated, where possible, by ether extraction and distillation.

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